Advances in Healthcare using Machine Learning

Volume 2

Sriparna Saha • Lidia Ghosh (eds.)

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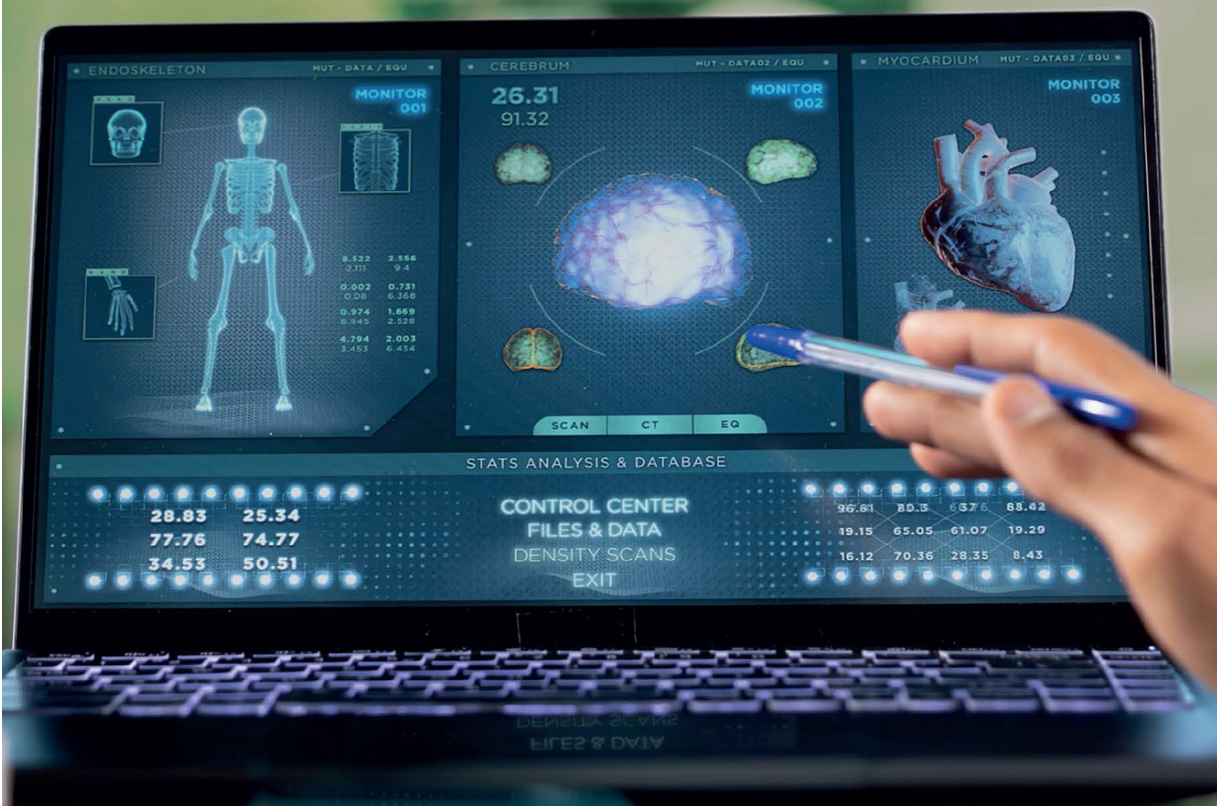Taylor & Francis Group

A SCIENCE PUBLISHERS BOOK

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ENDOSKELETON — MUT - DATA / EQU
MONITOR 001

8.522 2.556
2.111 9.4
0.002 0.731
0.08   6.368
0.974 1.669
6.345 2.528
4.794 2.003
3.453 6.434

CEREBRUM — MUT - DATA02 / EQU
26.31
91.32
MONITOR 002

SCAN   CT   EQ

MYOCARDIUM — MUT - DATA03 / EQU
MONITOR 003

STATS ANALYSIS & DATABASE

28.83   25.34
77.76   74.77
34.53   50.51

CONTROL CENTER
FILES & DATA
DENSITY SCANS
EXIT

96.61   80.3   6376   88.42
19.15   65.05 61.07 19.29
16.12   70.36 28.35 8.43

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Advances in Healthcare using Machine Learning

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Preface

In recent years, the convergence of machine learning (ML), artificial intelligence (AI), and healthcare has opened transformative avenues for diagnosis, treatment, monitoring, and personalized medicine. The global healthcare ecosystem is witnessing an era where data-driven insights, predictive analytics, and automation are becoming indispensable. This book, "Advances in Healthcare using Machine Learning", is a curated collection of state-of-the-art research contributions that demonstrate how machine learning techniques are being harnessed to address complex challenges in modern healthcare.

Each chapter in this volume showcases diverse and impactful applications of machine learning in the medical domain—from predictive models for disease detection to sophisticated image processing techniques, explainable AI, and integration of semantic web frameworks for clinical data management. The book begins with foundational studies such as cervical cancer and heart disease prediction using ML and ensemble learning models with interpretability enhancements. It then progresses through cutting-edge topics like biomedical signal denoising using traditional and deep learning techniques, retinal disease detection through deep segmentation networks, and novel architectures for liver segmentation from CT scans.

Significant attention has also been devoted to areas such as digital pathology using self-supervised learning, personalized treatments enabled by Digital Twin technology, and the role of nature-inspired computing in creating intelligent and adaptive healthcare systems. Furthermore,

innovative solutions like NLPdriven homeopathy recommendation systems and semantic web applications for enhancing clinical trial data interoperability highlight the growing scope of interdisciplinary approaches.

This book is intended for researchers, practitioners, healthcare professionals, and students who aspire to understand and contribute to the next generation of intelligent healthcare systems. The chapters are contributed by international experts and reflect not only theoretical innovation but also practical relevance and real-world deployment potential. We sincerely hope that this compilation inspires further research and development in AI-driven healthcare solutions and contributes meaningfully to improving patient care, operational efficiency, and the global healthcare landscape.

Contents

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1 Machine Learning Approaches for Disease Diagnosis Cervical Cancer Disease Prediction, A Case Study

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Machine learning (ML) helps the healthcare sector to identify and forecast illnesses. Examining huge medical databases for hidden trends changes the diagnosis of diseases. Every year, hundreds of people die from cervical cancer. Correct and accurate diagnosis determines the quality of life and treatment efficacy. Reduced cervical cancer death and incidence depends on improved accuracy and faster detection. Predicting cervical cancer with ML might help to improve healthcare treatment and lower

expenses. Conventional diagnostic techniques' low sensitivity and specificity could cause delays or misdiagnoses. This case study shows how ML may improve cervical cancer detection and lower errors. This paper describes a two-part experiment based on the Cervical Cancer Disease Dataset kept in the UCIML Repository. Sequential feature selection lets several ML methods be evaluated on the dataset. Various ensemble learning approaches helped to enhance the first phase of the experiment. Consequently, we were able to attain better prediction results using the same dataset: an F1-score of 96.97%, an accuracy of 95.45%, a precision of 94.12%, a sensitivity of 100%, and a specificity of 92.85%. Lastly, ROC curves with AUC values of 0.982 were given in the empirical investigation.

Introduction

Breast cancer is the most prevalent cancer among women, whereas gynecological malignancies originate in the female reproductive tract. Women diagnosed with gynecological malignancies often experience reduced life expectancy due to these lethal and debilitating diseases. Cervical cancer is the second most common form of gynecological cancer and presents a significant health challenge for women worldwide, especially in poorer nations. Other forms of gynecological malignancies include ovarian, vaginal, vulvar, and uterine cancers. The human cervix is surrounded by a very thin layer of cellular formations. Cervical cancer occurs when a cell becomes malignant, replicates rapidly, and ultimately forms a tumor. Various gynecological conditions are linked to an increased risk of different cancer types. One of the initial signs of cervical cancer is abnormal menstruation, which may manifest as spotting, irregularities, heaviness, or other atypical characteristics. Researchers conducted a cross-sectional study to gather further information on gynecological malignancies. Cervical cancer, which impacts the reproductive organs, is

the most common type of malignancy in women. It is the fourth leading cause of mortality among women. Cervical cancer is primarily attributed to the Human Papillomavirus (HPV); however, it is manageable and can be detected and treated effectively if caught early (Zhang et al., 2021; Conceição et al., 2019).

Machine Learning (ML) in Healthcare

Machine learning is transforming the healthcare industry by providing advanced illness detection, prognosis, and therapy customization capabilities. ML techniques can find trends and associations in large data sets that conventional analytical methods overlook. Often faster than human radiologists, ML models based on vast datasets of medical pictures may detect anomalies with astonishing accuracy. Early disease detection—including cancer—that these models may offer helps to greatly enhance patient outcomes. Furthermore, ML applications incorporate patient risk factors and treatment responses, which allow medical practitioners to design more tailored and efficient treatment plans to manage special needs (Atoum et al., 2023; Sahu et al., 2023).

ML transforms healthcare environments by means of better diagnosis, operational efficiency optimization, and cost reduction. Motivated by ML, predictive analytics correctly forecasts hospital resource management, personnel distribution, and patient admission rates. Electronic health records (EHRs) are undergoing a rapid change, thanks in great part to ML. ML analysis of EHRs might reveal interesting patterns in patient health, improve the administration of preventative treatment, and assist in the management of chronic illnesses. Moreover, a discipline of ML called natural language processing (NLP) is helping to analyze clinical notes and extract relevant data, thereby enhancing patient care. Research indicates

that adding ML in healthcare, medical research, patient therapy, and general system efficacy can lead to notable advancement ([Pati et al., 2021](), [2022]()).

ML for Cervical Cancer Disease Diagnosis

ML has become a strong weapon for cervical cancer diagnosis because of its capacity for more accurate, efficient, and early disease detection—which alters traditional knowledge. ML algorithms uncover trends and connections that could elude human practitioners using medical imaging, patient histories, and various clinical features. Absolutely essential for the identification of cervical defects during screening, deep learning (DL), support vector machines (SVMs), and random forests (RFs) hold significant potential for assessing procedures like Pap smear testing and colposcopic images. These algorithms serve to accelerate clinical judgments and could enhance patient outcomes by significantly reducing analysis time and raising diagnosis accuracy ([Chen et al., 2013](); [Tanimu et al., 2022]()).

Personalized medical approaches are urged to be embraced by means of ML in cervical cancer diagnostics. Thus, the customizing of medicines depends on the specific features of every patient. Ensemble learning (EL) methods improve resilience and diagnostic accuracy in several ways. Combining the interpretability of decision trees with the prediction capacities of neural networks allows an ensemble technique to obtain both tremendous accuracy and meaningful analysis. Moreover, ML models might always train and adapt their behavior in response to fresh data, thereby enhancing their effectiveness and ensuring their currentness with the most recent developments in medical research. In cervical cancer specifically, this adaptability is rather beneficial as successful treatment and higher survival rates depend on precise and rapid diagnosis. Working together, medical professionals and ML researchers might provide original

ideas for the fight against cervical cancer ([Sitarz et al., 2020](#); [William et al., 2018](#)).

Research Gap and Motivation

Earlier research on cervical cancer has shown a dearth of evidence on the outcomes of early intervention. Thus, additional study is necessary to ascertain the whole influence of this problem. Cervical cancer detection and diagnosis have benefited much from ML. This is so because it can find trends in large amounts of data that humans would not find readily apparent. The data that follows, taken from past studies, might help to elucidate the research variability. Two methods one may use to improve performance results are undersampling and oversampling. Accurately aggregating several variables makes it challenging to guarantee compliance with several data modalities—including genetic, scientific, and imaging data.

More strict feature selection techniques help to improve the performance model and weed out extraneous elements. Using technical knowledge to forecast cervical cancer has made great progress possible. On the other hand, certain unsolved problems with clinical exercise integration, statistical quality, and model interpretability persist. Correcting these flaws might improve the accuracy and usefulness of ML models for therapy, diagnosis, and understanding of cervical cancer. Early-stage illness identification made possible by ML techniques will definitely enable prompt intervention. ML techniques beat conventional statistical approaches in analyzing and processing vast, complicated data. This is especially pertinent considering the possibilities of novel biomarkers and the disease patterns needing identification. Improving our present therapeutic approaches and goals can help us better understand cervical cancer treatment via ML.

Research Questions (RQs)

This introductory study may address the following research questions (RQs).

RQ1: Will the ML or EL algorithms enhance accuracy, and if so, which one is more efficient for predicting and diagnosing cervical cancer at its initial stage?

RQ2: Can any other feature selection technique be used to enhance accuracy when combined with optimization techniques?

RQ3: Is there any way to reduce the time taken for the training and testing of data?

Objective

In this work, we conducted a two-stage experiment using the UCI-ML repository's Cervical Cancer disease dataset. In the first stage, we applied the featured dataset to the information gain (IG) technique by evaluating its effectiveness through ten ML algorithms. These algorithms included extreme gradient boosting (XGB), adaptive boosting (ADB), gradient boosting (GDB), SVM, linear discriminant analysis (LDA), logistic regression (LR), k-nearest neighbors (KNN), naïve Bayes (NB), decision tree (DT), and RF. To enhance the predictive capabilities of the initial methods, we implemented three fundamental ensemble techniques in the second stage: hard voting, soft voting, and weighted averaging.

Contributions

The key contributions to this research work are as follows:

- Proposed a two-stage framework that combines feature selection via IG with ensemble learning techniques, offering an improvement over standalone classifiers used in prior studies.

- Benchmarked ten widely used ML algorithms, systematically comparing them under a unified experimental setting and highlighting performance disparities across models.
- Provides a holistic pipeline for cervical cancer prediction not thoroughly explored in prior works by integrating feature selection, base classifiers, and ensemble methods.
- Identified and analyzed the presence of weak or irrelevant features in the dataset and their impact on classifier performance—an often-overlooked aspect in similar studies.
- Demonstrates the feasibility and effectiveness of ensemble models in enhancing early detection accuracy, potentially aiding healthcare professionals in timely clinical decisions.

Paper Organization

The comprehensive document structure is delineated by the components enumerated below. Section 2 presents a synopsis of the relevant corpus of research. The third section examines the theoretical and mathematical foundations of the suggested feature selection and classification methods, accompanied by a comprehensive analysis of the dataset. The fourth part delineates the base upon which this paradigm operates. Section 5 offers a detailed summary of the findings derived from the study. The sixth section presents an overview of the research and its articulated aims.

Literature Survey

To find the probability of cervical cancer recurrence (Tseng et al., 2014), researchers advised applying ML methods like SVMs, C5.0, and extreme learning machines (ELMs) on the Chung Shan Medical University Hospital Tumour dataset. The researchers obtained the average categorization accuracy with these techniques, which was 92.44%. Cervical cancer cases

were classified by researchers using ML methods. This work applied Gaussian NB, DT, LR, SVM, and KNN among other techniques. The authors (Choudhury et al., 2018) report that all five reliability measures— sensitivity, accuracy, precision, and F-measure—surpassed 97.0%. Still, other metrics were precision and accuracy. One evaluated a cervical cancer detection system using data from the Venezuelan Hospital Universitario de Caracas. The investigators used both ML-based classification methods and enhanced feature selection. Five ML algorithms were assessed: C5.0, RF, Ctree, SVM, and KNN. With an area under the curve (AUC) of 91.0% (Nithya & Ilango, 2019), one of these algorithms scored flawless at 100%. Researchers employed the Herlev datasets and developed a 99.5% accuracy rate cervical cancer detection method. DL and ML techniques used to reach this include auto-encoders (AEs), multilayer perceptrons (MLPs), convolutional neural networks (CNNs), and extreme learning machines (ELMs, Ghoneim et al., 2020). To create a data mining model, the researchers applied ML methods like naïve Bayes (NB), C4.5 deep neural networks (DT), KNN, RF, MLP, and Simple Logistic Regression (SLR). The Hospital Universitario de Caracas in Venezuela provided the data used to ascertain cervical cancer risk variables. The hospital reportedly claimed a recall, precision, and accuracy rate of 96.4% (Razali et al., 2020). We used this approach to identify risk variables for cervical cancer. Using databases from Shahid Beheshti University of Medical Sciences, researchers developed a supervised M-L approach for cervical cancer prediction. The system generated an accuracy rate of 95.55%, sensitivity of 90.48%, specificity of 100%, and AUC of 95.20% over its operation. In line with Asadi et al.'s (2020) research, we have selected to use Quest, C&R Tree, RBFANNs, SVM, and MLP-ANNs. Researchers developed a DL algorithm model for cervical cancer diagnosis by combining ResNet-50, ResNet-152,

VGG-16, and VGG-19 with an SIPaKMed pap-smear picture collection. According to the writers, the F1 score was 95.0%, the accuracy rate was 94.89%, the precision rate was 90%, and the recall rate was 100%. Researchers tested four algorithms— XGB, SVM, RF, and ResNet50—to use cervicography images in cervical cancer classification. The Ewha Womans University Institutional Review Board approved these algorithms. Data from MokDong Hospital show that, respectively, accuracy, precision, area under the curve, and recall were 91.05%, 93.10%, 97.00%, and 89.0%. To create a cervical cancer detection model, researchers from the ML repository at the University of California, Irvine, used RFs, artificial neural networks, and spiking neural networks, among other ML techniques. (Mehmood et al., 2021). The authors said the model has met its objectives with a 93.6% accuracy rate, a 0.07% margin of error, a 6.4% false-positive rate, and a 100% false-negative assessment rate. Using ML-based statistical analysis, researchers built a model for early cervical cancer diagnosis from data from the UCI ML Repository and Kaggle. Among the several ML techniques, the model comprised Random Tree (RT), Split-point and Attribute Reduced Classifier (SPAAC), KStar, and RF. The AUC (99.0%), recall (98.0%), specificity (95.0%), precision (99.0%), sensitivity (99.0%), and accuracy (99.16%) were among the metrics assessed (Ali et al., 2021). Using data from the UCI ML repository and ML, researchers created a DT approach to classify cervical cancer models. Tanjuu et al. (2022) investigated the following metrics: F-measure (75.01%), accuracy (95.29%), sensitivity (85.71%), specificity (96.15%), precision (66.67%), AUC (74.46%), and Reporting an accuracy rate of 92%, researchers presented a cervical cancer detection method combining CNN, SVM, and ResNet 101 utilizing datasets from Herlev University Hospital and the Technical University of Denmark. Along with measurements for AUC, F1-

score, sensitivity, and accuracy (Alquran et al., 2022), the researchers additionally showed Using the Certified Refractive Index Liquids dataset given by Cargill, and were able to evaluate the viability of a photonic method-ML model combining ML and DL approaches. Among these techniques are RF, XGB, NB, and CNN. The researchers discovered that the F1-score, recall, accuracy, and precision are all higher than 90%. Considering the Herlev papsmear photo collection, the researchers assessed the effectiveness of multiple ML algorithms in cervical cancer diagnosis models. Some of the methods utilized in the process include LR, SVM with a linear kernel (SVMLK), SVM with a radial basis function kernel (SVM RBF), stochastic gradient descent (SGD), DT, RF, Gaussian naïve Bayes (GNB), gradient-boosted decision trees (GDB), KNN, and MLP (Singh & Goyal, 2023). Table 1 offers a thorough synopsis of every recent paper that influenced the research. Important ideas, conclusions, and methods that are pertinent to the topic are included in this synopsis of the articles.

Table 1 Summary of some related considered State-of-the-Art works.↵

Reference	Techniques Employed	Datasets Employed	Findings
Tseng et al., 2014	SVM, C5.0, ELM	Chung Shan Medical University Hospital Tumour Dataset	Average correct classification rate: 92.44%
Choudhury et al., 2018	LR, SVM, NB, KNN, DT	Cervical Cancer Dataset	Accuracy: 97.5% Precision: 95.2% Sensitivity: 100% Specificity: 95.0% F-measure: 97.5%
Nithya & Ilango, 2019	RF, Ctree, SVM, KNN	Hospital Universitario de caracas, Venezuela Datasets	Accuracy: 100% AUC: 91.0%
Ghoneim et al., 2020	CNN, ELM, MLP, AE	Herlev Datasets	Accuracy: 99.5%

Reference	Techniques Employed	Datasets Employed	Findings
Razali et al., 2020	DT, KNN, RF, MLP, SLR	Hospital Universitario de caracas, Venezuela Datasets	Accuracy: 96.4% Precision: 96.5% Recall: 96.4%
Asadi et al., 2020	QUEST, C&R Tree, RBF-ANNs, SVM, MLP-ANNs	Shahid Beheshti University of Medical Sciences provided Datasets	Accuracy: 95.55% Sensitivity: 90.48% Specificity: 100% AUC: 95.20%
Tripathi et al., 2021	ResNet-50, ResNet-152, Vgg-16, Vgg-19	SIP aKM eD Papsmear Image Dataset	Accuracy: 94.89% Precision: 90.0% Recall: 100% Fl-score : 95.0%
Park et al., 2021	XGB, SVM, RF, ResNet50	The Institutional Review Board of Ewha Womans University MokDong Hospital provided Datasets.	Accuracy: 91.05% Precision: 93.0% Recall: 89.0% Fl-score: 89.0% AUC: 97.0%
Mehmood et al., 2021	RF, ANN, SNN	UCI ML Repository Dataset	Accuracy: 93.6% Error: 0.07% FPR: 6.4% FNR: 100%
Ali et al., 2021	SPAAC, RF, RT	UCI ML Repository Dataset	Accuracy: 99.16% Precision: 99.0% Sensitivity: 99.0% Specificity: 95.0% Recall: 98.0% AUC: 99.0%
Tanimu et al., 2022	DT	UCI ML Repository Dataset	Accuracy: 95.29% Precision: 66.67% Sensitivity: 85.71% Specificity: 96.15% Fl-score : 75.01% AUC: 74.46%

Reference	Techniques Employed	Datasets Employed	Findings
Al Quran et al., 2022	CNN, SVM, Rsnet-101	Herlev University Hospital (Denmark) and the Technical University of Denmark datasets	Accuracy: 100% Precision: 100% Sensitivity: 100% Fl-score: 100% AUC: 100%
Kruczkowski et al., 2022	RF, XGB, NB, CNN	Certified Refractive Index Liquids by Cargille Dataset	Accuracy: 92% Precision: 93.0% Recall: 93.0% Fl-score: 92.0%
Singh & Goyal, 2023	SGD, MLP, PAC, LR, SVMLK, SVM RBF, DT, RF, GNB, GBT, KNN	Herlev Pap-smear Image Dataset	Accuracy: 100% Precision: 100% Recall: 100% Fl-score : 100% CPU time: 0.14

Methods and Materials

The website's relevant information helps one forecast the patient's present health situation. Changing the model parameters produced acceptable results. The test data helps one evaluate the performance of the model. The procedures of compiling, sterilizing, and training prognostic data will be walked over in this part.

Cervical Cancer Disease Dataset (CCDD)

The UCI-ML repository produced the Cervical Cancer Dataset (CCD) utilized in this study. Comprising 72 occurrences and 20 attributes—of which 19 are independent factors—this is a subset of a larger dataset (UCI Machine Learning Repository, 2023). Table 2 and Figure 1 indicate one variable among the 20 characteristics that act as the dependent variable—or labeled class. The dataset underwent binary categorization; missing values are not present. A value of 0 in this dataset denotes the patient does not

have cervical cancer; a value of 1 denotes the patient is suffering from cervical cancer.

Table 2 Overview of the Employed CCDD Dataset.

Dataset Name	Number of Instances	Number of Features	Class Type Data
Cervical Cancer Disease Dataset (CCDD)	72	19	0–50 1–22
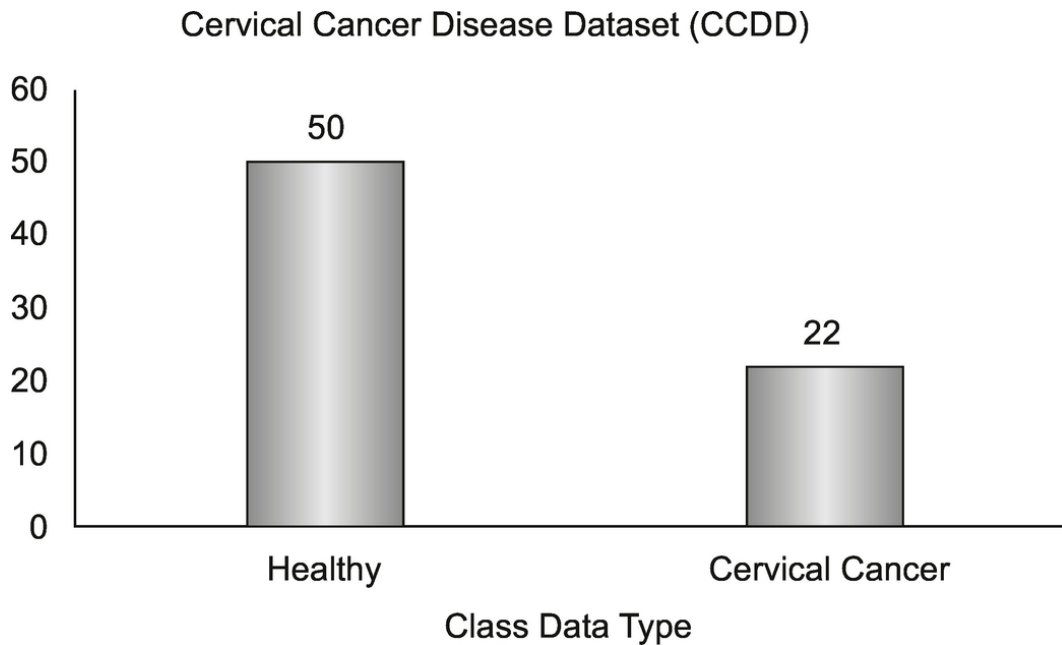
Fig. 1 Class Labels of CCDD Dataset.

Employing data preparation techniques is essential to ensure that machines can interpret raw data. In the actual world, patient data is often erroneous, usually incomplete, or consistently inconsistent. The methodologies employed for data preparation may provide possible solutions to these issues. At this point of the implementation process, further phases will involve the usage of data preprocessing techniques. Due to the ambiguity and vagueness of the information included in this dataset, imputation is essential. To ensure the neural network does not produce erroneous generalizations, excluding some characteristics from the dataset

that may include sensitive patient information is essential. The administration of the tuple can be executed without the necessity of defining a class. One can manually assign an alternate class label if the default value is unavailable. Employing attribute definitions is an alternative approach that may be employed to address gaps. An intricate methodology is necessary to impute absent values utilizing attribute approaches. Consequently, the datasets rely on human-conducted imputation. The process of normalization has several benefits. Each update has led to a notable increase in the model's numerical stability and a reduction in training length. The min-max scaling approach is employed as a normalization technique when data must reside inside a specific range. Linear systems often assign weights of zero or negligible random values around zero, even though ML methods are more straightforward to normalize. We may get a normal distribution by initially normalizing the attributes included within the columns. The feature values are standardized to a mean of zero and a standard deviation of one by default to attain this objective. In contrast to min-max scaling, normalization may recognize and accommodate outliers while concurrently diminishing sensitivity. StandardScaler, utilizing scikit-learn and analogous to MinMaxScaler, is an alternative tool for doing normalization. The default settings of StandardScaler are only designed for training data and are not appropriate for test data or any other data type.

Feature Selection Technique: Information Gain (IG)

An efficient approach for choosing characteristics used to diagnose cervical cancer is IG or InfoGain. IG, measured using a particular metric, is the degree to which a feature tells about a class in a classification issue (Kumawat et al., 2023; Jahan et al., 2021; Byskov Petersen et al., 2020; Ghasemi et al., 2024). DT methods make use of it to determine which

features are best for data partitioning. Projecting new data instance class labels requires higher relevance for traits that produce significant knowledge gain. Using the entropy of the class distribution—both before and after the split—one finds the information gain by ranging from 0 (showing no gain) to 1 (representing maximum gain). Mutual information, often known as information gain, measures how much the presence or absence of a characteristic affects the accuracy of target variable prediction. The value depends on the degree of knowledge about the target link value. Mutual information measures the degree of the interaction between an "input variable" and an "output/target variable ". Features with a larger proportion of relational qualities may be considered for model creation, whilst those with a lower percentage of relationships (independent features) can be excluded. The measure assesses the decrease in entropy or uncertainty regarding a certain clinical trait or test result (U) concerning cervical cancer (V) on for IG may be given as in Equation (1):

$$IG(V,U) = F(V) - F(V|U)$$
(1)

Furthermore, the symbol $F(V)$ indicates the entropy of the target variable, therefore measuring the degree of disorder or uncertainty in the dataset for the diagnosis. $F(V|U)$ shows the conditional entropy of the target variable by including the knowledge given by U. This thus represents the residual uncertainty that remains following U's accounting. Computing the impact factor (IG) for every characteristic helps one to ascertain the degree to which each quality reduces diagnostic ambiguity. This helps to clearly identify the most informative features of the prediction model. Regarding cervical cancer, IG might be used to assess several clinical factors like patient age, HPV status, cytological findings, and histological results. Should the addition of the "HPV status" feature significantly lower

uncertainty in cervical cancer prediction, the score would be high *IG*. This approach helps improve diagnostic models' accuracy and promotes a better knowledge of the fundamental causes of the disease. ML systems improve their efficiency and comprehensibility by choosing properties with the best *IG* values. This speeds and precisely identifies cervical cancer, hence improving patient outcomes.

ML Approaches Employed

The several classification techniques used by the ML algorithms under discussion in this study are succinctly summariz ed in ([Lu et al., 2020](#); [Pati et al., 2023](#); [Nayak et al., 2023](#); [Al Mudawi & Alazeb, 2022](#)). The parameters of the logistic model, often termed linear combination coefficients, can be established by regression analysis. This is achieved by the LR approach, which in statistics denotes the logarithm of the likelihood of an event occurring. A linear probabilistic classifier, NB, suggests the conditional independence of features, therefore demonstrating their link to a certain target class for which they are intended. To solve a problem, these scalable classifiers need either significant information or predictions defined by linear parameters. Sometimes, a max-margin model is a supervised learning model combining classification and regression methods. This model is an SVM. Together with their possible theoretical examination, the adaptability of SVMs for various tasks—including structured issue prediction—highly increases their frequency. Adapted from Fisher's Linear Discriminant, Linear Discriminant Analysis (LDA) is used in many statistical fields to find feature combinations that either distinguish or characterize various classes of events or objects. One finds notable parallels between the LDA and Analysis of Variance (ANOVA). The aim of regression analysis is to articulate a singular dependent variable as a linear amalgamation of several independent variables or metrics. The DT is a

supervised learning approach that represents a particular type of regression tree. This method allows the target variable to assume continuous values, often represented as real numbers. A subtype of the DT is referred to as a regression tree, which allows the target variable to assume continuous values, often real numbers. During training, the RF technique, a variant of the EL approach, generates several DTs. This method is employed for regression, classification, and several other applications. In the classification task, the output generated by the RF is the class chosen by the majority of voters. The average prediction of each tree is provided during regression activities. KNN has applications in both regression and classification domains. Irrespective of the circumstances, the input consists of the k-nearest training samples from a specified dataset. The KNN classification approach employs local approximations to defer computation until the function evaluation is finalized. Following the training of each new model to minimize the loss function of its predecessor, such as crossentropy or mean squared error, GDB constructs a robust learner by amalgamating many weak learners. This is achieved by instructing each new model to minimize the loss function. In statistical classification, ADB is a meta-algorithm designed to enhance performance by employing several algorithmic learning strategies. This is the final outcome of the enhanced classifier, derived from the consolidated output of the learning algorithms. The aggregate weight signifies this production. The XGB demonstrates superior accuracy relative to a solitary decision tree; nevertheless, this advantage compromises the intrinsic interpretability characteristic of DTs.

EL Approaches Employed

The weighted averaging and soft and hard voting (Sahoo et al., 2024; Aljrees, 2024; Sarwar et al., 2015; Panigrahi et al., 2023) are among the few fundamental EL techniques used in this study. EL is an ML method

whereby more accurate predictions are produced by combining the outputs of numerous learners, including neural networks or regression models. An ensemble model is a synthesis of numerous separate models that, taken together, produce predictions with accuracy above that of any one model. Under a weighted ensemble, different weights are distributed to models based on their performance, so the predictions of the models are combined in line with those weights.

Prominent benefits: A method known as performance-based weighting gives models with better performance more value, hence improving accuracy. One of the great advantages is the option to combine many models with different weights. One disadvantage of the weight tuning process is the required careful weight adjustment, which might be difficult and time-consuming. Maintaining and updating many models can be a resource-intensive activity, sometimes referred to as computational overhead. In mathematics, the concept 'average' is quite important; think of a quantity equal to the sum of all the accessible quantities divided by the overall count of numbers. In weighted averaging, each quantity is assigned a random weight, which is then multiplied by that quantity to calculate the average. The random weights assigned to these quantities can be any other entity or a priority number that illustrates the importance of the amounts given. With the N number of employed models, let $P_{i,\,c}$ is the initial predicted probability of the ith model with class c. The average predicted probability P_c for the class c from all input N models can be defined as Equation (2).

$$P_c = \frac{\sum_{i=1}^{N} w_i P_{i,c}}{\sum_{i=1}^{N} w_i} \tag{2}$$

Certain models consistently demonstrate superior performance and exert a more significant influence on the final estimates. Voting ensembles consolidate the predictions of many models by a majority vote for classification or averaging for regression. This approach is employed for categorization. Both hard (majority vote) and soft (weighted probabilities) approaches are viable options.

Advantages: *Straightforward and Effective:* easy to implement and often leads to enhanced performance. Reduces and Consolidates many models to mitigate individual biases. This phenomenon is termed overfitting.

Disadvantages: *Equal Weighting:* This uncomplicated voting approach treats all models uniformly, which may not consistently yield optimal results.

Application: A method for enhancing the robustness of models in classification tasks, serving as a preliminary ensemble strategy. A type of classifier is "soft voting", which categorizes input data based on the probability of each possible prediction from other classifiers. The weights allocated to the values are subsequently applied to each classifier to achieve the correct results. With the N number of employed models, let $P_{i, c}$ is the initial predicted probabilities of the model with class c. The average predicted probability P_c the class c from all input N models can be defined as Equation (3).

$$P_c = \sum_{i=1}^{N} P_{i,c} \tag{3}$$

Hard voting is a type of classifier that relies on the mode of the predictions made by all classifiers. The equality of the weights assigned to various classifiers influences the assessment of the majority vote. A

majority vote with equal weights determines the predicted label's mode. Nevertheless, the ultimate projection is still calculated using separate weights when the majority vote occurs. The final prediction P_c probability can be defined using Equation (4).

$$P_c = M\left(P_{1,c}, P_{2,c}, P_{3,c}, P_{4,c}, \ldots . P_{N,c}\right) \tag{4}$$

Where: M is a class that frequently appears among all models $i \in N$, P_c is the final predicted probability, $P_{i,\ c}$ is the predicted probabilities of all models i.

Proposed Work

The proposed research on the cervical cancer dataset encompasses a two-phase experiment conducted to enhance assessment metrics. The evaluation metrics encompass accuracy, precision, specificity, sensitivity, F-measure, and AUC values in the assessment of cervical cancer. In the initial step of the experiment, we employed a model that integrates IG methodologies alongside 10 distinct ML classification techniques for the previously delineated dataset. Furthermore, in the subsequent phase, we augment the prediction of outcomes from the ML classifiers by integrating essential EL techniques. These methodologies are subsequently implemented based on the predictions that were previously obtained. Algorithm 1 and Figure 2 both illustrate the representation of the previously referenced unique hybrid model.
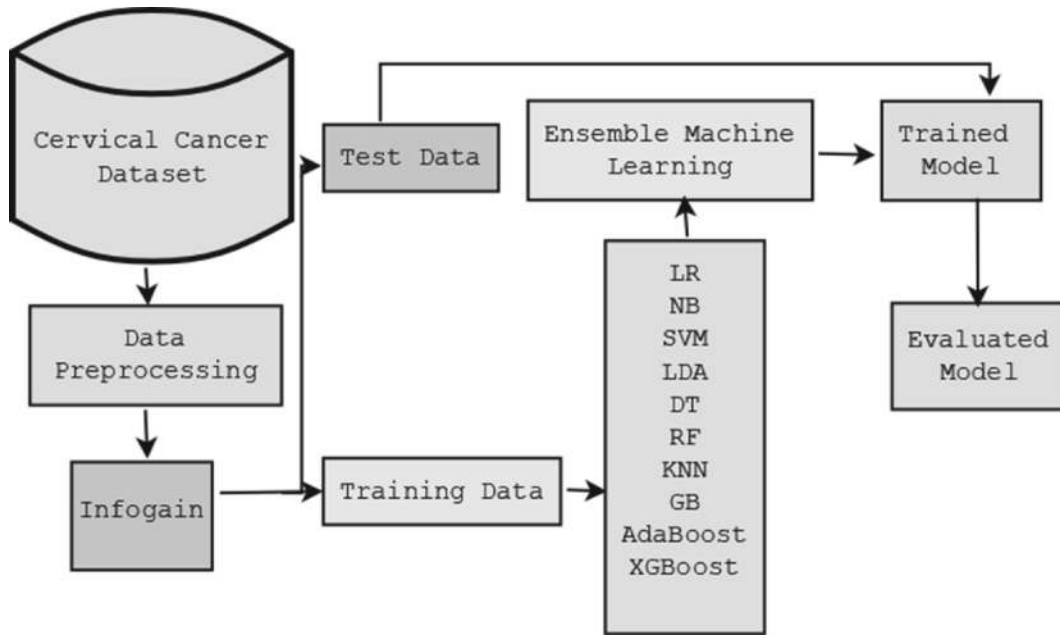
Fig. 2 Block Diagram for the proposed work.⏎

Algorithm 1: Proposed AI-Driven Cervical Cancer Prognosis Model

Input: Cervical Cancer Disease Dataset (CCDD)

  Output: Binary Classification

1. Collection of cervical cancer disease dataset from UCI-ML Repository.
2. Begin the imputation of missing values using the median method:
      i. Identify the missing value and its corresponding feature (j)
     ii. $f_{i,j} = median\, f_{1,j}, f_{2,j}, f_{3,j}, \ldots, f_{n,j})$, where $f_{i,j}$ is the missing value of the jth feature
    iii. Replace the missing value with $f_{i,j}$
3. Dividing the dataset into training and test subsets with an 80:20 split ratio.
4. Filtering training data using IG as the Feature Selection Method using all of the available features (F).

5. Apply Classifiers RF, DT, SVM, LR, KNN, LDA, NB, GB, A B, and XGB.

6. Evaluation of the Initial Prediction of all basic learners.

7. Apply EL Classifiers to the Initial Prediction for developing an EM (Ensemble Model):
    i. WA (Weighted Averaging)
    ii. HV (Hard Voting)
    iii. SV (Soft Voting)

8. Apply the test data to the developed model, i.e., EM-WA, EM-HV, EM-SV.

9. Evaluation of the model performance of EM-WA, EM-HV, EM-SV.

10. Evaluate both hybrid models and pick the one that fits you best.

Results and Discussion

The proposed device is based on an Intel Core i7 desktop computer operating on Ubuntu 20.04, with 32 gigabytes of RAM and one terabyte of solid-state drive storage. A Jupyter notebook developed in Python is employed to conduct the experiments. The 2 × 2 Confusion Matrix comprises four components. The components are represented by the letters T1, F1, T0, and F0, signifying true positive and false negative, respectively. This assessment of the model's performance considers several aspects, with accuracy being the most significant. Equations (5) to (9) delineate the definitions of the F1-Score (FS), Accuracy (Ac), Precision (Pr), Sensitivity (Se), and specificity (Sp). The AUC values corresponding to the ROC curves are also included. The performance measures were calculated using the following equations in this study (Rout et al., 2022; Kharya et al., 2024; Panda et al., 2025; Sahu et al., 2025).

$$Ac = \frac{T_1 + F_1}{T_1 + F_1 + T_0 + F_0} \tag{5}$$

$$Pr = \frac{F_1}{T_1 + F_1} \tag{6}$$

$$Se = \frac{T_1}{T_1 + F_0} \tag{7}$$

$$Sp = \frac{F_1}{F_1 + T_0} \tag{8}$$

$$FS = \frac{2 \times T_1}{2 \times T_1 + F_1 + F_0} \tag{9}$$

This study consists of a two-stage experimental inquiry. Initially, we employed the IG feature selection method to create an enhanced dataset aimed at increasing the accuracy of our predictions. Upon application to the cervical cancer dataset, these 10 traditional ML methodologies yielded the results displayed in Table 3. The below enumeration comprises many available hybrid methods (HA): HA-A (LR + IG), HA-B (NB + IG), HA-C (SVM + IG), HA-D (LDA + IG), HA-E (DT + IG), HA-F (RF + IG), HA-G (KNN + IG), HA-H (GB + IG), HA-I (AB + IG), and HA-J (XGB + IG) represent various logistic regression models. Figure 3, Figure 4, Figure 5, Figure 6 and Figure 7 illustrate the findings of the comparative research about the expected outcomes for Stage 1. HA-A exhibits a precision of 87.50%, a sensitivity of 87.50%, a specificity of 92.85%, an F-1 score of 87.50%, and an accuracy of 90.90%. HA-B achieves an accuracy of 86.67%, with a sensitivity of 75.00%, a specificity of 92.65%, and a precision of 85.71%. The HA-C has a specificity of 74.92%, an accuracy of 100%, and a sensitivity of 62.50%. Their accuracy is 96.36%, and their specificity is 74.92%. The F-1 score is 74, representing 92%. HA-D attains an F-1 score of 93.33%, an accuracy of 95.45%, a precision of 100%, a

sensitivity of 87.50%, and a specificity of 100%. The HA-E technique attains an accuracy of 86.36%, a sensitivity of 75.00%, a specificity of 87.50%, and a precision of 85.71%. HA-F achieved an F-1 score of 87.50%, with an accuracy of 90.90%, precision of 87.50%, sensitivity of 87.50%, and specificity of 92.85%. HA-G can achieve an accuracy of 81.81%, a sensitivity of 62.50%, a specificity of 83.33%, a precision of 92.85%, and an F-1 score of 71.42%. The HA-H technique attains an accuracy of 90.90%, a sensitivity of 85.74%, a specificity of 75.00%, and a precision of 100%. HA-I exhibits a sensitivity of 100%, a specificity of 88%, an overall accuracy of 92%, and an F1 score of 94.11%. The HA-J exhibits a sensitivity of 87.50%, a specificity of 87.50%, a precision of 92.85%, and an accuracy of 90.90%. The ROC analysis findings indicate that the AUC values for the hybrid techniques HA-A,

Table 3 Obtained Predictive Outcomes in Stage-1.

Proposed Hybrid Approaches	Findings in %					AUC
	Ac	Pr	Se	Sp	FS	
HA-A	90.90	87.50	87.50	92.85	87.50	0.964
HA-B	86.67	85.71	75.00	92.85	79.99	0.897
HA-C	92.36	100.00	62.50	100.00	76.92	0.987
HA-D	92.81	100.00	87.50	100.00	93.33	1.000
HA-E	86.36	85.71	75.00	92.85	79.99	0.893
HA-F	90.90	87.50	87.50	92.85	87.50	0.893
HA-G	81.81	83.33	62.50	92.85	71.42	0.964
HA-H	90.90	100.00	75.00	100.00	85.74	0.982
HA-I	92.81	94.11	100.00	71.4	96.96	0.982
HA-J	92.36	100.00	62.50	100.00	76.92	0.848
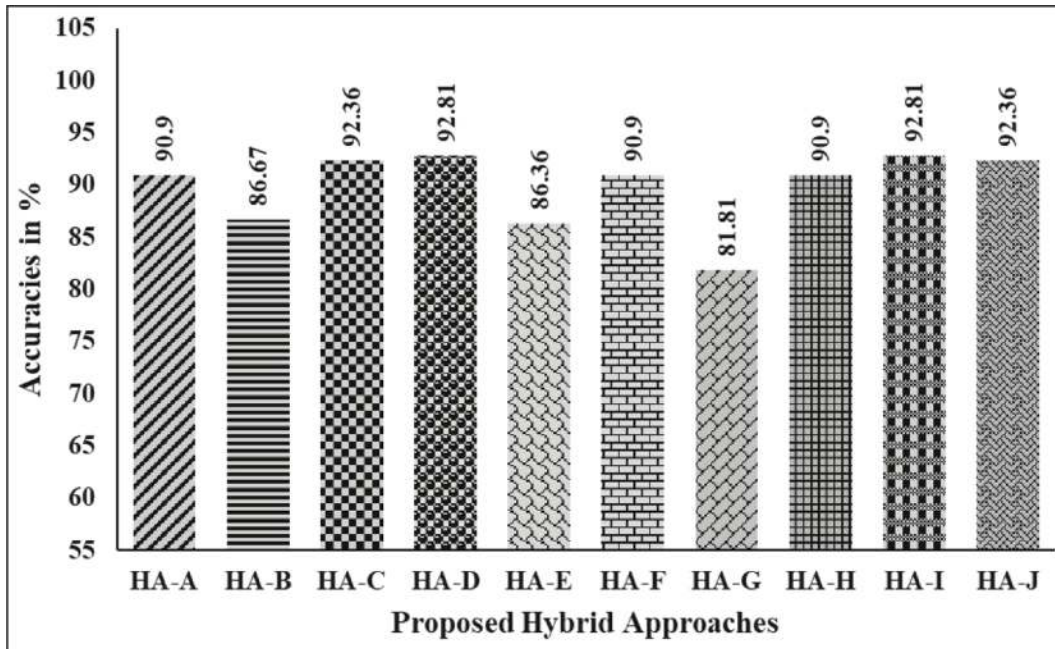
Fig. 3 Comparative accuracy of diverse proposed hybrid methodologies.
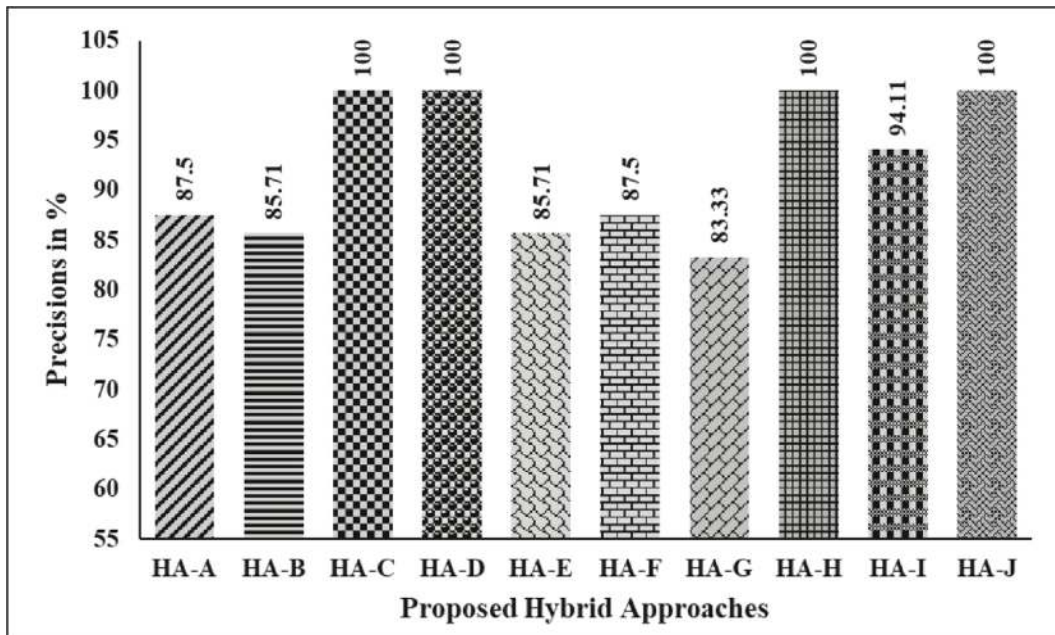
Fig. 4 Comparative precision of diverse proposed hybrid methodologies.

Fig. 5 Comparative sensitivity of diverse proposed hybrid methodologies.
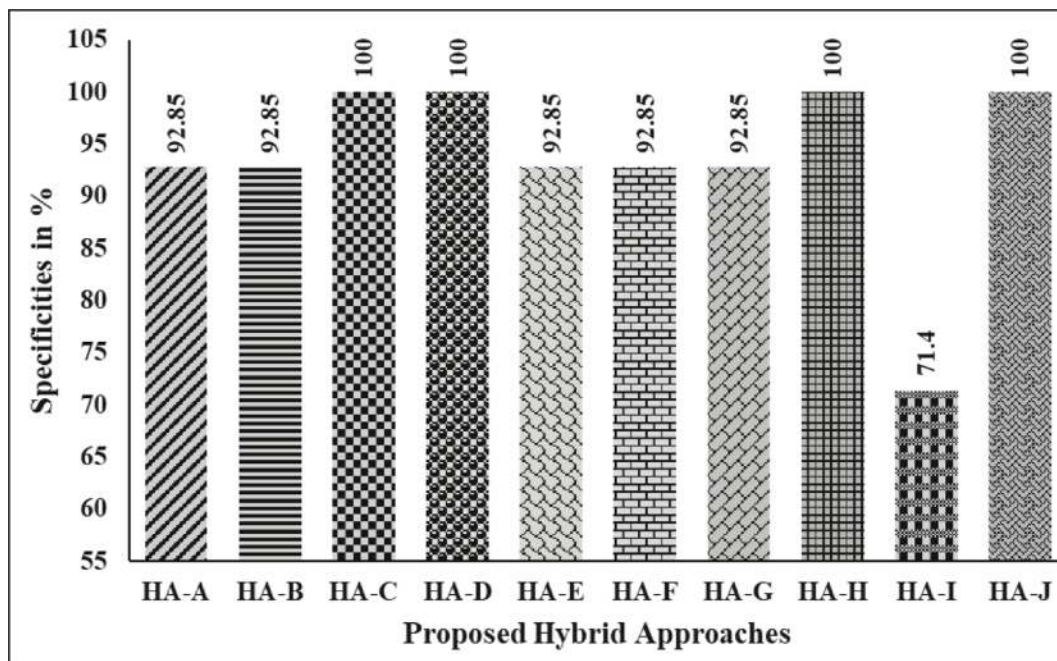
Fig. 6 Comparative specificity of diverse proposed hybrid methodologies.
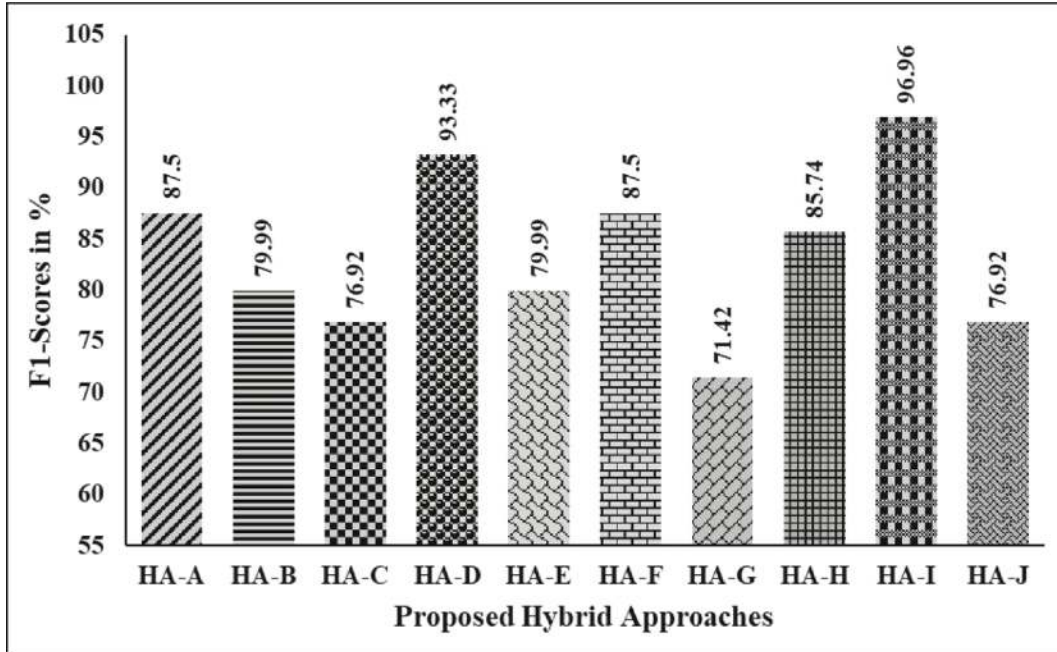
Fig. 7 Comparative F1-Score of diverse proposed hybrid methodologies.

HA-B, HA-C, HA-D, HA-E, HA-F, HA-G, HA-H, HA-I, and HA-J are 0.964, 0.897, 0.987, 1.000, 0.893, 0.893, 0.964, 0.982, 0.982, and 0.848, respectively, as seen in Figure 8.
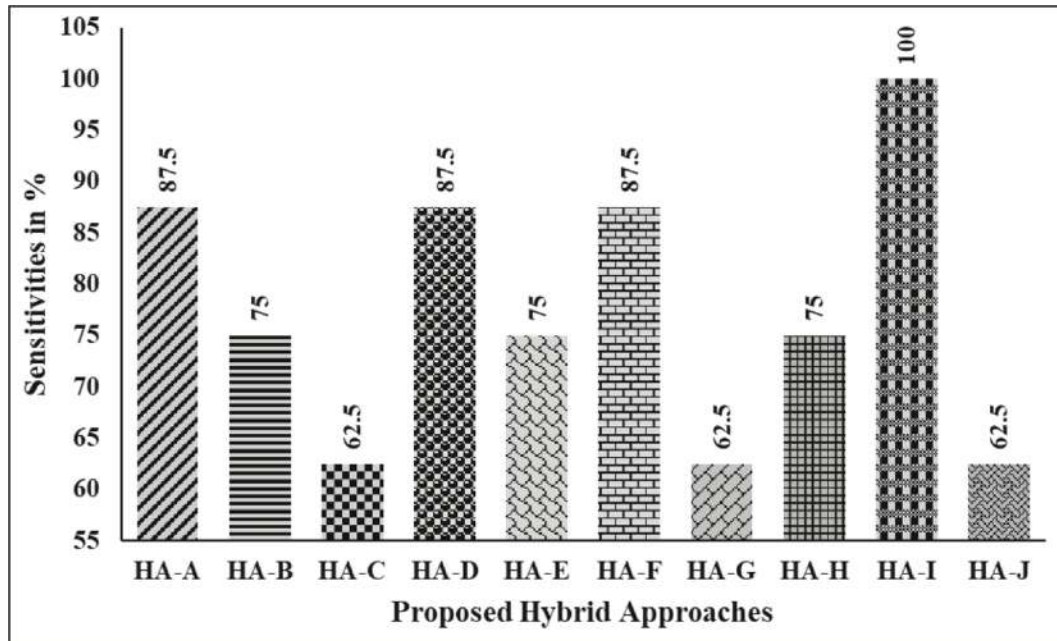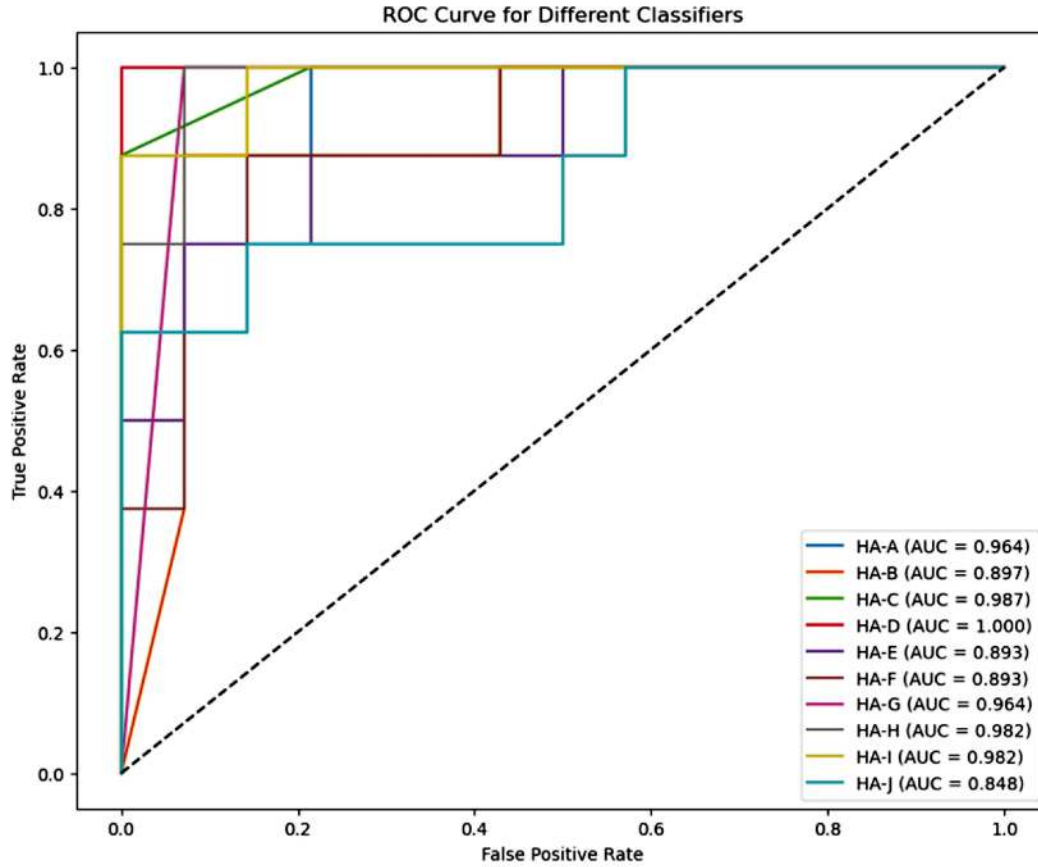
Fig. 8 Comparative ROC-AUC of diverse proposed hybrid methodologies.

We used EL techniques using the same cervical cancer dataset that was utilized for fundamental learners after finishing the second step, which included creating hybrid ways. The results are shown in Table 4. Various ensembled hybrid methods (EHA) can be utilized, including EHA-P (HA combined with Weighted Averaging), EHA-Q (HA combined with Soft Voting), and EHA-R (HA combined with Hard Voting). Figure 9 illustrates a contrast between the anticipated results for Stage 2 and the actual outcomes that transpired. The EHA-P achieves an accuracy rate of 93.33%, a sensitivity score of 85.71%, a specificity score of 100%, and an F-1

Table 4 Obtained Predictive Outcomes in Stage-2.

Proposed Ensembled Hybrid Approaches	Findings in %					AUC
	Ac	Pr	Se	Sp	FS	
EHA-P	93.33	100.00	85.71	100.00	92.31	0.964
EHA-Q	95.45	94.12	100.00	92.85	96.97	0.982
EHA-R	94.87	100.00	88.88	71.43	94.11	0.964
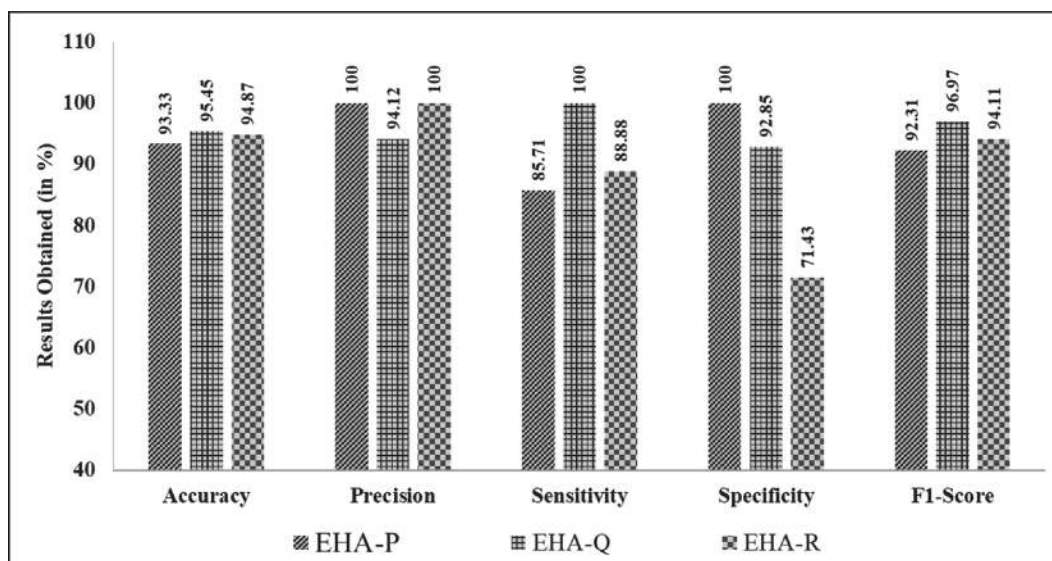
Fig. 9 Performance comparisons of various Proposed Ensembled Hybrid Approaches.

score of 92.31%. The study's findings indicate that the EHA-P outperformed the HAs by about 0.56 percentage points. The EHA-Q demonstrates a sensitivity of 100%, a specificity of 94%, and F-1 scores of 92% and 97%, resulting in an accuracy of 95.45%. The study's findings indicate that the EHA-Q outperformed the HAs by approximately 2.84%. The EHA-R has an accuracy of 94.87%, with a sensitivity of 88.18%, a specificity of 71.43%, and an F-1 score of 94.11%. The study's findings indicate that the EHA-R outperformed the HAs by approximately

2.22%. Additionally, it is noteworthy that EHA-Q surpasses EHA-P in accuracy by roughly 2.27% and EHA-R by approximately 0.61%. ROC research revealed that the AUC values for the ensembled hybrid techniques

EHA-P, EHA-Q, and EHA-R are 0.964, 0.982, and 0.964, respectively. Figure 10 illustrates that the EHA-Q hybrid technique surpasses all other alternatives, attaining an AUC of 0.982.
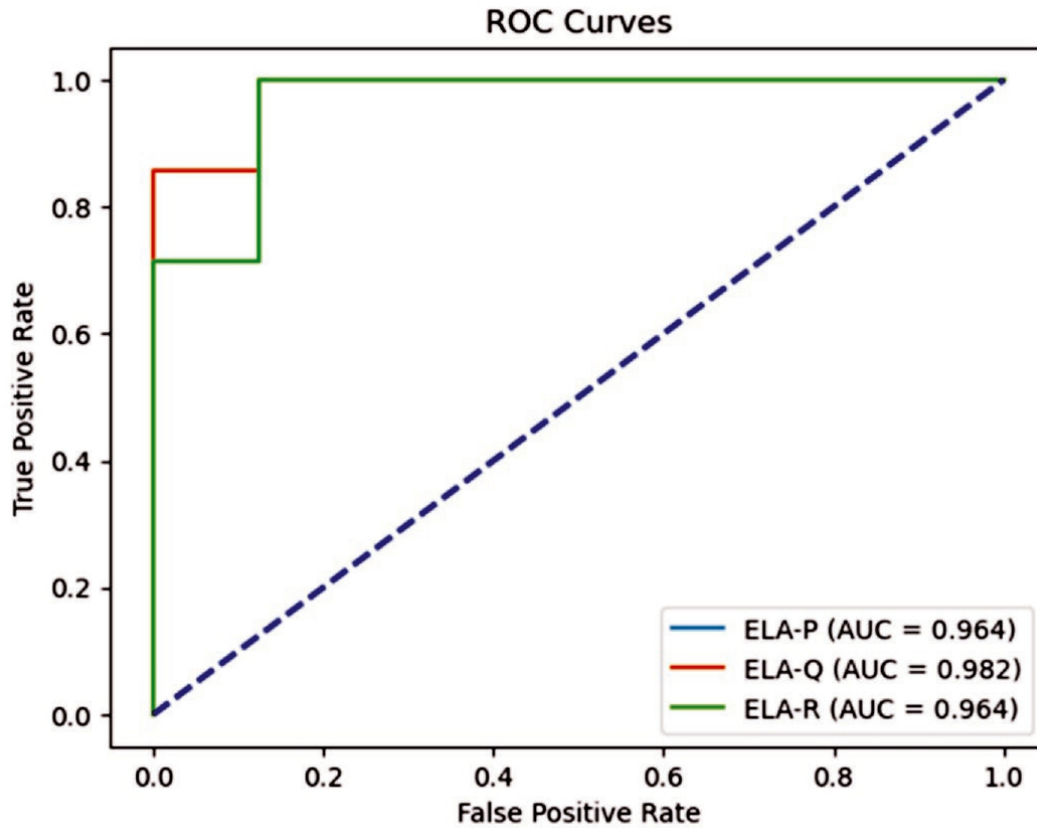
Fig. 10 ROC-AUC comparisons of various Proposed Ensembled Hybrid Approaches.

Conclusion

The method of cervical cancer diagnosis might become more automated, precise, and time-efficient by utilizing an ML technique based on model estimations. To facilitate the easier early detection of cervical cancer, it is imperative that the individualized screening method be improved. Carefully examining those who are at a higher risk and taking pertinent factors into account are crucial steps in the detection of cervical cancer. The goal of these model-based estimating factors is to reduce psychological distress

among the community of survivors of cervical cancer. Currently, a better understanding of the causes of cervical cancer depends

on early identification. Utilizing a range of classification algorithms and feature selection processes has produced better outcomes than previous approaches. This paper presents the findings of a bifurcation experiment using the Circulatory Cancer Disease Dataset obtained from the UCI Machine Learning Repository. Ten ML: methods were run using the dataset with the gradually chosen attributes as the starting point. During the experiment's first phase, several fundamental EL techniques were applied. These tactics included hard voting, soft voting, and weighted averaging. Our improved projected outcomes had an F1-score of 96.97%, accuracy of 95.45%, precision of 94.12%, sensitivity of 100%, and specificity of 92.85%. The same dataset was used to arrive at each of these conclusions. The study's findings offer more proof that the proposed paradigm is innovative. The article has been updated to provide ROC curves and the associated AUC value of 0.982 in order to assist empirical analysis. The goal of this proposed study is to help medical experts identify this specific type of cancer in its early stages so that diagnosis and treatment may be completed quickly. This study uses ML technology in an attempt to identify and diagnose cervical cancer.

There are advantages and disadvantages to every single study. Even in the event that the results were favorable, a few considerations must be made. The research may not fully capture the diversity and unpredictable nature of the actual world because it is solely based on a single dataset. To make matters worse, EL models increase accuracy but are not always easy to understand. A model that serves as an example to clarify model predictions is known as explainable artificial intelligence. Unfortunately, this approach has not yet been applied in clinical settings. The work being

presented has the potential to be further developed, which would enable a highly accurate early diagnosis of cervical cancer. The symptoms of the illness that were previously disregarded will be addressed. Enhancing accuracy, specificity, sensitivity, and F-measure through the use of optimization techniques in combination with ML algorithms may make it easier to create an effective detection model and assess the severity of cervical cancer patients. Furthermore, the results obtained might be improved by employing DL and EL techniques with an image-based dataset.

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2 A Conjunctive Framework of Ensemble Learning Model with Explainable AI for Optimizing Parametric Eminence in Heart Disease Prediction

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Heart disease, the prime cause of death, demands a highly predictive and accurate model for the prognosis and treatment of this deadly disease. The basic machine learning algorithms make this detection procedure execute efficiently, but the functioning rules of these algorithms mostly lack understandability and interpretability by the users. So, to explain and validate the output of the algorithms, the study introduces a conjunctive framework based on an ensemble learning model with Explainable AI. The suggested model utilizes ensemble learning by combining the outcomes of different basic machine learning algorithms with selecting the decisive features that correspond to standard ECG leads and morphological features

for finding parametric optimization in disease prediction. To include the Explainable AI approach, the SHAP and LIME techniques are engaged to describe the prediction results transparently and consistently. To verify and validate the model's strength, it has been trained and tested with two different ECG image datasets. A comprehensive analysis has been performed with higher predictive accuracy, with 91.01% for the basic dataset and 85.02% for the augmented dataset achieved from the Random Forest Algorithm. The effectiveness of this work implies enhancing prediction capability by addressing the overfitting issue and making clinical decisions without any domain-specific knowledge. This research optimizes parametric excellence by balancing between the interpretability and the predictive performance of the model.

Introduction

Heart disease, or Cardiovascular disease (CVD), refers to several abnormalities that affect the functionalities of the elementary components of the heart. It is probably the primal cause of the death rate of mankind that can be reduced by early diagnosis. With the rapid progress of technology, machine learning (ML) algorithms are becoming indispensable in forecasting heart disease outcomes. Here, ensemble ML models play a vital part in providing better accuracy and performance by incorporating several base ML models for predicting the possibility of heart problems. The ensemble ML model uses more than one classical ML model for heart disease prediction. Consequently, whenever any model does not perform well on its intended outcome, another model can compensate for it by its high performance. But, sometimes, it is challenging to understand the rationale for the decisions taken by these prediction models. Hence, it is very necessary to explain the transparency and fairness behind the prediction decision. This interpretation can be accomplished by the

Explainable artificial intelligence (XAI) methods that provide the user with an improved understanding of the workings of the model.

Ensemble Learning Algorithm

An ML method called ensemble learning (EL) accumulates multiple base models or weak learners' models by combining them to create a more powerful model that makes better predictions than any individual model. The theory is based on the idea that an aggregate of weak models can do better than one strong model.

The working principle of this ensemble approach can be described by .
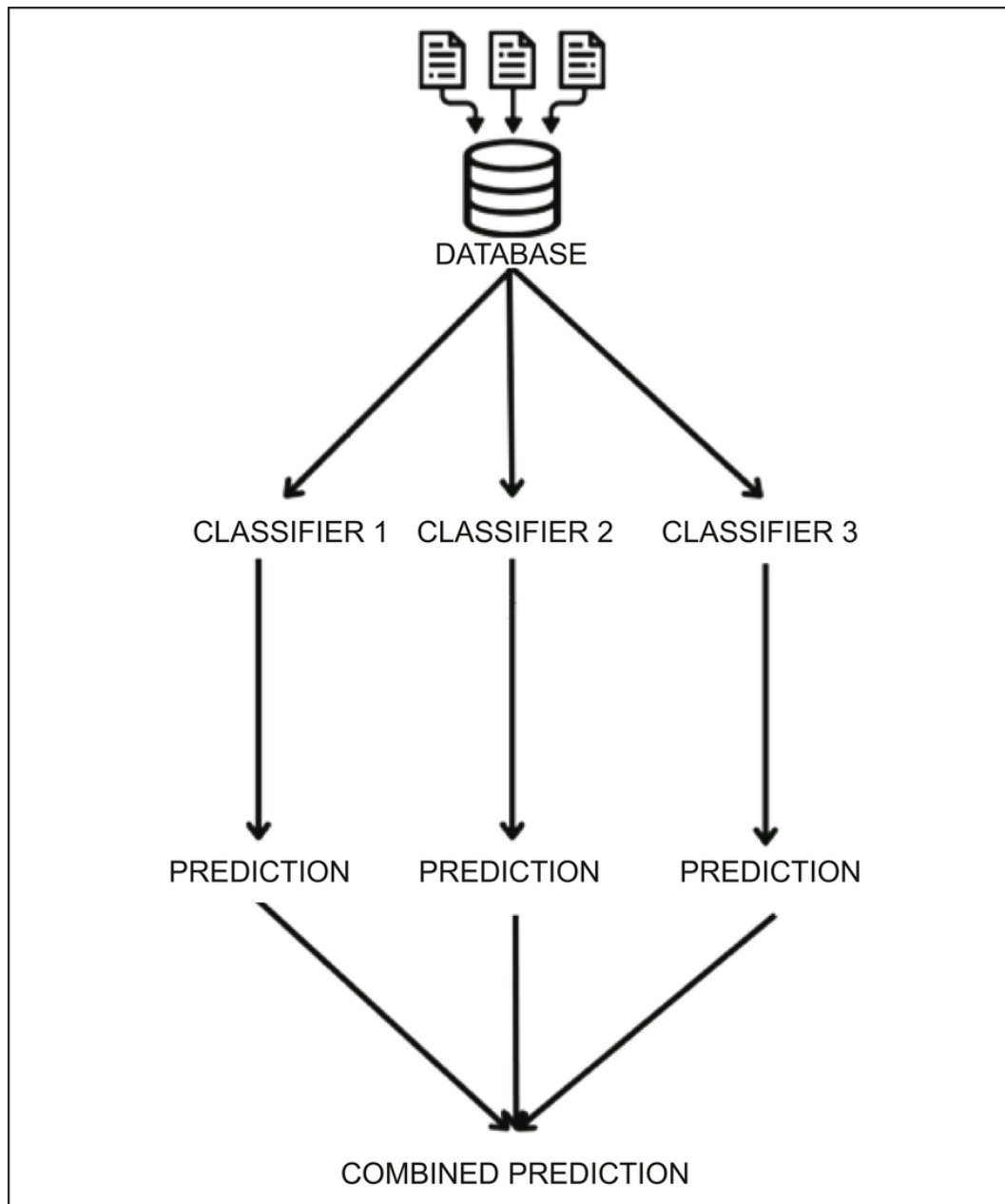
Fig. 1 Working Principle of Ensemble Learning Algorithm. ⏎

- **Train Multiple Models:** Several models are trained based on the same or separate segments of the dataset.
- **Combine Predictions:** Predictions from all of the models are blended based on methods such as:
- Casting a ballot (regarding classification)

- Average (regarding regression)
- **Final Decision:** A more accurate prediction can be achieved from the collective outcome.

EL has a number of advantages for applying it as a training model. Some common reasons for using EL in disease detections are improving accuracy and robustness, reducing overfitting (Bagging methods), working well with both classification and regression and helping to capture non-linear relationships in data.

The EL techniques can be classified into three categories. This classification is given in Figure 2.
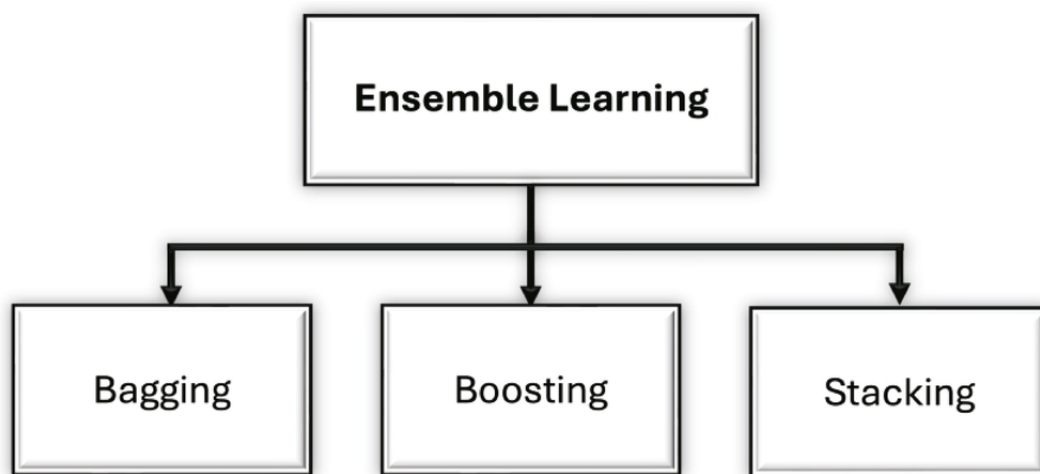
Fig. 2 Types of Ensemble Learning Methods. ↵

- **Bagging (Bootstrap Aggregating):** It averages the predictions of different models independently on random subsets of data, e.g., a Random Forest (RF).
- **Boosting:** It learns models sequentially, where every model rectifies the previous one. Examples are AdaBoost, XGBoost, and Gradient Boosting.

- **Stacking:** It combines predictions of multiple models using another model (meta-model). e.g., Stacked Generalization.

Explainable Artificial Intelligence (XAI)

In today's network-oriented world, XAI with an EL model helps in forecasting heart disease with better accuracy and trustworthiness. XAI aids in describing how the AI models make the decision. This newly found branch of AI has some potential improvements in disease prediction. Figure 3 defines the workflow of XAI.
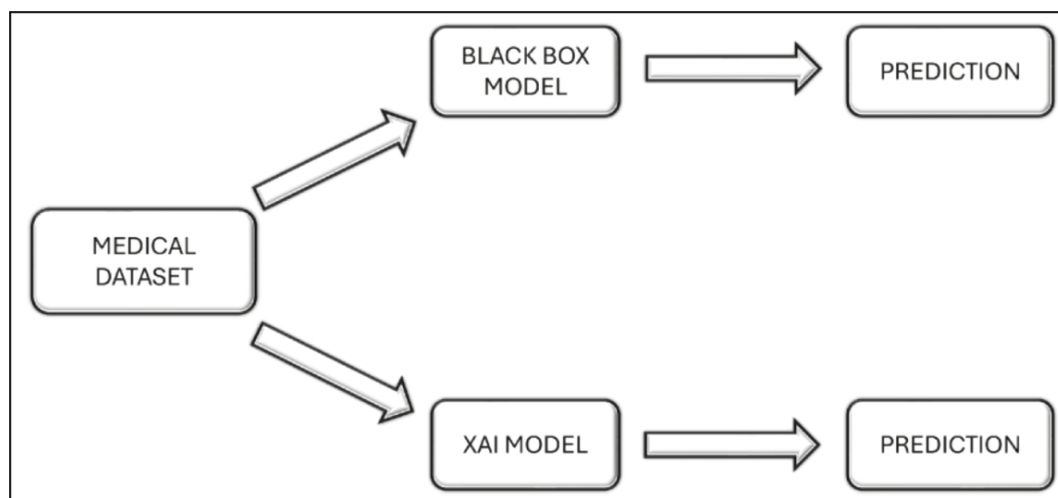
Fig. 3 Workflow of XAI.

It is obvious that the functionality of an ML model is hidden from the users and works as a black box for disease prediction, whereas the XAI gives a clear interpretation of the prediction. XAI has several uses in the different healthcare sectors by establishing trust among the users. Some common applications of XAI in the medical field are:

Medical Diagnosis: XAI methods help human beings to understand the reason for diagnostic prediction by the EL AI model. This clear reason can build trust and confidence in the AI models.

Drug Discovery and Development: In pharmaceutical drug discovery and development, XAI models play a crucial role.

Medical Decision-Making: XAI also helps healthcare professionals make quick decisions, as this provides openness about the diagnosis process predicted by the AI models.

The Reasons for Adopting XAI

Adopting the utilization of XAI in heart disease prediction is very important as it helps healthcare professionals and general people understand the reason for AI predictions. By using XAI, human beings can trust the AI system as it provides assistive explanations and transparency about the prediction mechanism. Figure 4 describes the functionality of XAI techniques.
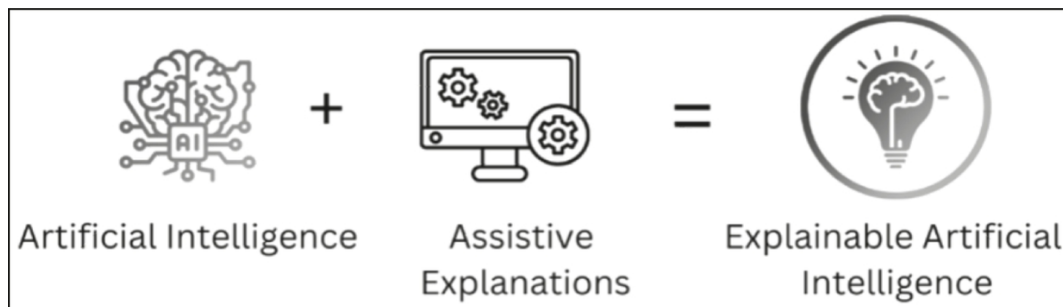
Fig. 4 Functionality of XAI.

There are so many reasons for adopting XAI, some of them are:

- It builds trust and transparency.
- It helps in bias detection.
- It delivers regulatory compliance.
- It aids in the improvement of real-time existing models.
- It assists in an improved clinical decision-making process.

Techniques Adopted for XAI with Ensemble Learning (EL)

The XAI techniques can be classified into three categories as depicted in [Figure 5](). The brief descriptions of functioning are as follows:
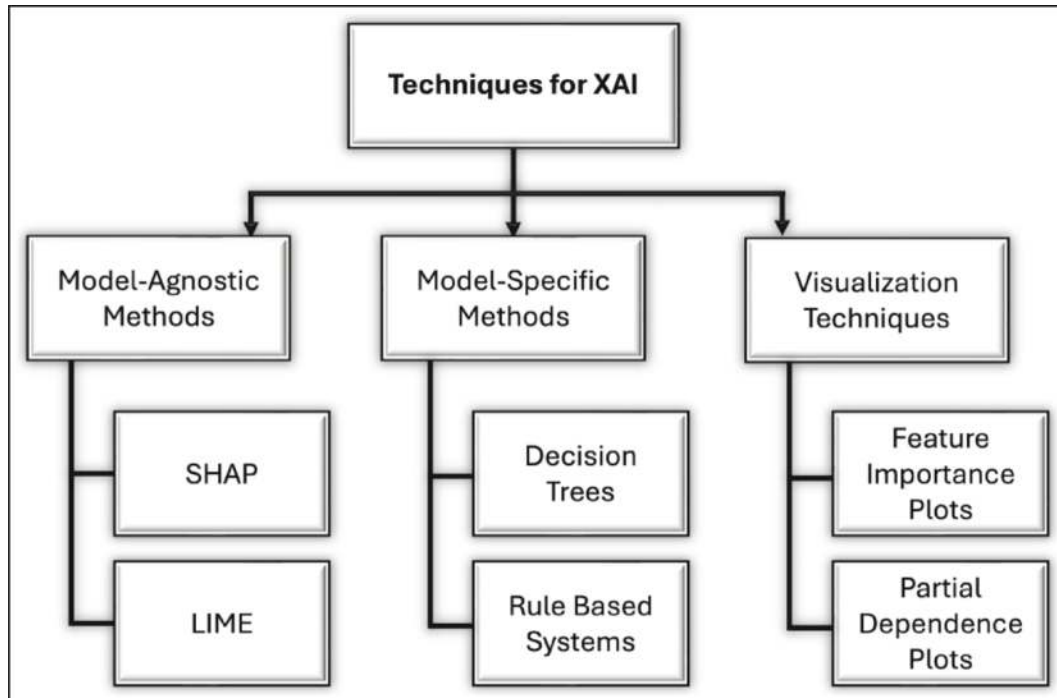
Fig. 5 Classification of XAI Techniques. ⏎

- **Model-agnostic Methods:** Any model can be developed using these methods. Some existing models are as follows:
  - *LIME* (*Local Interpretable Model-agnostic Explanations*): It produces local approximations about complex models to provide prediction.
  - *SHAP* (*Shapely Additive Explanations*): It uses game theory to explain the contribution to a prediction.
- **Model-specific Methods:** These methods provide insights for a particular model. Some existing models are:
  - *Decision Trees*: It gives a clear decision about the model's prediction.

- *Rule-based Systems*: It utilizes a collection of 'if-then' rules for prediction purposes.
- **Visualization Techniques:** These methods provide the predictions, structures, and parameters visually. Some existing models are:
  - *Feature Importance Plots*: This represents the different features of the model's prediction.
  - *Partial Dependence Plots*: It depicts the impacts of a single feature for prediction purposes while keeping the others constant.

EL is an ML-based technique that uses multiple base models for predicting heart disease while maximizing accuracy and minimizing error. If any single model cannot classify accurately, then with the help of other models, generates more accurate results. However, when EL is combined with XAI, it provides high precision and transparency in the decision-making process of heart disease prediction.

Objectives

The key objective of this conjunctive framework is not only to build the heart disease prediction system but also to explain the diagnosis process in which the AI system can determine whether the image is healthy or unhealthy. Even though AI is now being more utilized in healthcare, an ample section of the population still exhibits skepticism and unease about being heavily involved in their medical diagnosis and care. So, to build trust among humans , there is a need to explain the internal determination process of these EL methods. With the help of an AI-enabled prediction system, the diagnosis process not only makes it cheaper but also reduces the complexities as well.

The main objectives of XAI in Healthcare:

- **Transparency:** The ability of the ML algorithm and features to be understandable by the user.
- **Domain Sense:** The explanation should make sense in the domain application to the user.
- **Consistency:** The interpretation should be consistent across different runs of the system.
- **Parsimony:** The description should be as simple as possible.
- **Generalizability:** Models and explanations should be generic across the problem domain.
- **Trust/Performance:** The expectation of the predictive algorithm must have an attainment level.
- **Fidelity:** The explanation and the predictive model align well with one another.

Novelty

In this work, a conjunctive framework of EL models with XAI explanation has been presented to forecast cardiac disease. As the existing works are mostly done on Electronic Health Records (EHRs), the intention is to incorporate an electrocardiogram (ECG) image as a readily available input and construct an integrated framework with the justification for the expected outcome. For this, first, the ECG dataset is pre processed and the top 10 features are selected from 255 features of the image input. Thereafter, the model is trained with some base ML methods as well as ensemble ML methods. The trained model is then tested and its performance is evaluated. Lastly, the highest performance of the model is described and interpreted by SHAP and LIME methods of XAI, with the participation of the decisive features like standard ECG leads, morphological features, etc., contributing to the prediction probability. A different augmented dataset has been engaged to carry out the same data

processing and execution procedures to combat the overfitting criterion because this result has an overfitting issue with the unhealthy dataset towards the healthy dataset. Hence, it can be proved that this result is more reliable and validates the total procedure of predicting the disease as a whole.

Challenges

EL, coupled with the XAI model, is a very powerful approach for the prediction of different types of heart disease, but some challenges are presented as follows:

The Complexity of the Models: EL models are more complicated than single classical ML models as they use multiple single classifier models for heart disease prediction. In some cases, even with the use of XAI techniques, this complexity may complicate the understanding of the model's prediction purpose.

Dataset Requirements: A large number of ECG images are required for the training phase of the model. But, due to the privacy issue of the individual patients, it is much more complicated to build the databases with the scarcity of data. So, if the model cannot be provided with a huge amount of data for training, then there may be some error in the prediction process.

Computational Cost: Model training and deployment with the EL methods, can be computationally expensive as it requires large datasets for training the models for achieving better accuracy in heart disease prediction. As this is a resource-limited case, it might be a major challenge.

Generalizability: It is known that heart disease is the foremost complex kind of disease and various types may be present across the groups. So, if generalizability is not present in the training dataset, then it might be another challenge for predicting heart disease.

XAI Approach Choice: While choosing the appropriate XAI approach, there may be some issues present. Some methods are more appropriate in some cases and some are not. For better accuracy and lower error rate, choosing the most accurate method is another challenge.

Comparison Issue: For heart disease prediction, some EL models can give more accurate results, but these models can also be harder to explain. So, getting a balanced model is a challenge.

Adoption in Clinical Settings: It is the greatest issue in the healthcare sector that a major number of people do not believe in AI's prediction. So in future, it will be a crucial task for adopting this type of AI-enabled prediction in the medical field.

Literature Survey

Several existing types of research have been identified in this study.

Survey

B-LIME is an enhanced version of the traditional LIME technique that improves interpretability and preserves temporal dependencies (Abdullah et al., 2023). The study evaluates B-LIME with a hybrid DL model (CNN-GRU) for cardiac arrhythmia classification. It demonstrates its superiority over LIME in providing more reliable and significant explanations of ECG data. An integration of EL and quantum ML has been proposed to describe the prediction capability of the model (Abdulsalam et al., 2023). The authors also include SHAP to improve this model. An ML interpretation model using LIME and SHAP has been introduced for interpreting predictions for healthcare applications (Ahmed et al., 2024). It also highlights the strengths and drawbacks of LIME and SHAP. The logistic regression model has achieved 86% testing accuracy. The feature contributions to detecting heart disease in an interpretable model by XAI

methods have been highlighted (Asih et al., 2023). In another research, the authors describe how effectively XGBoost, RF, SVM, and Naive Bayes improve early detection and diagnosis, and methods such as SHAP and LIME are crucial within medical environments, highlighting the requirement of feature interpretability (Assegie et al., 2023). A framework is designed in the XDL paradigm for early detection of CVD. It demonstrates its usefulness in identifying conditions such as myocardial infarction and atrial fibrillation, and it attains excellent accuracy and specificity with ethical considerations by integrating the XDL framework into clinical processes (Ayodele et al., 2024). In one research, the authors analyze different ML algorithms with ensemble methods that enhance prediction capability (Bizimana et al., 2024). It also sheds light on improved explainable learning-based techniques that achieved a significant accuracy of 96.00%. In another research, the author presents an XDL model for classifying nine arrhythmia types utilizing 12-lead ECG signals. It compares multiple deep learning (DL) architectures with SHAP-based explainability analysis to identify the most relevant ECG leads with signal segments for each arrhythmia type, highlighting the role of XAI in enhancing model transparency and clinical trust (Chukwu & Moreno-Sanchez, 2024). The issue of dimensionality by highlighting the need for transparency in ML models and better performance has been addressed using various feature selection methods (Das et al., 2023). An example- and feature-based XAI technique has been applied to the heart disease dataset by analyzing and comparing different interpretability methods in AI healthcare applications to improve trust, transparency, and fairness (Dave et al., 2020). Several strategies and methods have been considered, including logistic regression and SVM (support vector machine) for CVD prediction. The performance and the efficiency of different approaches are established

by a comparative analysis of different algorithms and their accuracy scores (Deokar & Pradhan, 2024). A study has compared and explained the feature influences on SHAP and LIME (Doumard et al., 2022). The limitations and advantages of these methods are also discussed here. In another research, the authors employ ANOVA, chi-square tests, and mutual information for selecting features (El-Sofany et al., 2024). The SMOTE is used for the model's prediction and is interpreted using an XAI technique that uses SHAP. In one study, the authors explore the rapid evolution of diverse ML algorithms with the significance of feature selection for enhancing the model's performance (Ghose et al., 2024). It also suggests applying expert insights and domain knowledge to enhance ML model predictability. In another study, the authors integrate sophisticated ensemble methods like XGBoost and AdaBoost with interpretable models like SHAP and LIME (Gulhane & Sajana, 2024). A combined SHAP and CatBoost framework has been proposed by highlighting prevention and early detection for managing risk factors associated with CVD (Jha et al., 2025). This research examines the extent to which XAI could be applied, highlighting how ML can encompass transparency in such predictions. An XAI model that improves the interpretability of ECG analysis for detecting reduced LVEF has been developed (Katsushika et al., 2023). The study employs an RF model trained on ECG and echocardiography datasets, applying SHAP to identify decision-making criteria. The model extracts six key ECG findings that contribute to the classification, improving the accuracy of cardiologists' interpretations after reviewing the decision-making process for enhanced clinical applicability. One research involves the XAI methods used to discover age-specific risk markers and evaluate them (Kiran et al., 2025). The ethical implications of AI systems and the trend towards XAI methods to enhance transparency have been highlighted in one study

([Kommineni et al., 2024](#)). It suggests a patient-centered approach to AI diagnosis that provides patients with the capability of understanding and inquiring about test results. The research encourages moral principles for transparent AI systems and investigates performance metrics for evaluating XAI-based models. In one study, the author proposes a modified CNN architecture that analyzes three consecutive cardiac cycles for better temporal context in classification with improved detection of the R peak by incorporating domain knowledge to improve accuracy ([Kovalchuk et al., 2025](#)). It also explains CNN decisions using clinically relevant features that achieve a high classification accuracy of 99.43% and near-perfect Fl scores for major arrhythmia classes, demonstrating improved transparency and clinical utility. Data mining and ML techniques have been considered to impact healthcare by transforming the ability to examine vast medical datasets ([Laftah et al., 2024](#)). It enhances prediction precision, achieving 88.7% with hybrid models by incorporating ensemble ML methods. The utility of XAI in enhancing model prediction by understanding through the application of the SHAP method on an older adult dataset has been explained in one study ([Loh et al., 2021](#)). In another study, the author develops a predictive model using SHAP for evaluating the risk factors of elderly heart failure patients ([Luo et al., 2024](#)). Two tree-based explainer models with SHAP using RF and XGBoost for ECG-based heart disease prognosis have been proposed in a research paper ([Majhi et al., 2024](#)). The study concludes that the XGBoost model with EWT (empirical wavelet transform) features outperforms other models, demonstrating the effectiveness of explainable AI in medical diagnostics. XAI approaches to diagnose accurately and classify COVID-19 and lung cancer are addressed in the study ([Mane et al., 2024](#)). In the study, the reviewers elaborate on the application of XAI and ML to the diagnosis and detection of cardiac disease

with the use of logistic regression and MLP classifiers, neural networks and ensemble approaches, sophisticated classifiers, and feature selection strategies (Mariam & Aha med et al., 2024). A hybrid strategy has been proposed to include ensemble classifiers with Bayesian optimization by highlighting the XAI technique as an aid for elucidating model predictions and the interpretability of the ML models, especially in clinical contexts (Mienye & Jere, 2024). The growing demand for transparent AI solutions, particularly in precision medicine, is elucidated through the scientific evidence on heart failure (HF) survival prediction models that have been described (Moreno-Sanchez, 2023). Such complicated AI models have been explained as interpretable using XAI solutions. In the research on XAI, the authors develop AI-powered health chatbots that mimic human agents in their tasks by utilizing AI and natural language processing (NLP) (Muneer et al., 2024). XAI methods have also been incorporated. In another research paper, the authors examine the usage of XAI and ML to predict heart disease (Ozdemir, 2024). In this study, the best performance is delivered by SVM, and the greatest accuracy score has been found in the KNN (k-nearest neighbor) algorithm. Explainable methods like SHAP and LIME have helped to determine the features' importance, and the XGBoost model performed better at deriving accuracy than other models. The key features in heart attack predictions using XAI with LIME and comparing the performance of different ML classifiers have been identified (Paudel et al., 2023). SHAP has been utilized to explain the model's predictions and feature importance by assigning importance scores to features (Pawar et al., 2024). It improves the identification of minimal feature sets when using neighbo rhoods with differently classified samples. In one research, it has been stated that SVM and random forests are some of the conventional ML algorithms that have shown promising results (Qaisrani et al., 2024). The

research aims to incorporate hybrid deep learning (DL) methods and DL architectures with SHAP interpretability to enhance understanding and confidence levels among healthcare workers. In another research, the author proposes a predictive XAI-based hybrid EL model using SHAP and LIME (Rezk et al., 2024). Here, the voting classifier model reaches an accuracy of 96.5%, outperforming other models. The role of XAI in cardiac imaging has been explained by enhancing transparency and making the AI model's output interpretable for clinicians with the need for standardized evaluation methods (Salih et al., 2023). The potential of XAI-based models has been demonstrated in enhancing clinical diagnostics and personalized healthcare (Sathi et al., 2024). They integrate three ECG datasets (European ST-T, MIT-BIH Arrhythmia, and Fantasia) and employ boosting algorithms, including Hist-GB, to achieve an overall classification accuracy of 90%. XAI techniques (SHAP and LIME) are used to interpret feature contributions and identify key ECG parameters of heart disease. The decision-making process in biomedical ML has been investigated by improving the process with the most relevant features by SHAP (Scapin et al., 2022). Here, the ST Slope feature was identified as the most important for heart disease detection. The analysis shows that a coalition of parameters, rather than a single indicator, is more effective in diagnosing heart conditions. In one research, the authors propose a new approach to predicting cardiac disease that combines ML with XAI to create transparent and reliable decision-support tools (Sethi et al., 2024). It highlights the importance of the model's explainability with techniques such as Skater, SHAP, Eli5, and LIME with a success rate of 88% by designing a hybrid model incorporating RF and decision trees, exhibiting a leaning towards ensemble techniques. The interpretability problem of complex ML models has been addressed by introducing an interpretable approach based on

explainable AI methods ([Srinivasu et al., 2024](#)). The study draws attention to the various ML approaches, shared datasets, and comparative analysis, and the best results are obtained when decision trees are combined with other techniques. The boundaries of traditional diagnostic techniques in forecasting cardiac disease have been examined, which often rely on personal symptoms and are addressed by various ML techniques ([Tenepalli & Navamani, 2024](#)). For effective feature selection, RFE and SMOTE are used. This work also introduces the framework for enhancing the model's credibility. The effectiveness of k-mode clustering in predicting heart disease has been discussed ([Titti et al., 2024](#)). It also includes Naive Bayes and XGBoost for the automatic ischemic heart disease detection systems by implementing sophisticated hybrid prediction models combined with ML and XAI. In one study, the author proposes an explainable ML model for diabetes prediction with random oversampling and hyperparameter tuning techniques using SHAP, PDP, and LIME analysis ([Uddin et al., 2024](#)). The ET classifier performed exceptionally well with 97.23% and 97.45% accuracy for multi-class and binary datasets, respectively. It introduces a dashboard tool to visualize and analyze SHAP explanations interactively by exploring different neighbo rhoods of data that affect SHAP values and model interpretations. In another study, an XAI-based framework was introduced to classify cardiac disease and assist health professionals in understanding the output and justification behind the decisions ([Yaseen & Rashid, 2025](#)).

Research Gap

From the survey, it is noted that most of the existing works have used the EMR (electronic medical record) data as input for developing a prediction model using ensemble ML. So the interpretation with the XAI techniques has been done with simply numerical data. Only a few works have been

done with ECG images, incorporated as input and thereafter, pre processed and trained with some DL methods to construct the prediction model. After that, the XAI techniques (SHAP and LIME) describe the model's performance evaluation. So, there is a need to incorporate an ECG image that is a more convenient and available resource for CVD prediction and design the model with an ensemble ML method that can form the model with better accuracy. As there is a limitation of medical data due to privacy concerns, the outcome may face the problem of overfitting of data. So to overcome this problem, the proposed work augmented more input data values and constructed an integrated framework with the justification for the expected outcome. This will not only resolve the overfitting problem in the model but will also validate the result along with a clear rationale to understand the outcome of the predicted model.

Proposed Framework

The proposed conjunctive framework of EL model with XAI for heart disease prediction has been described here.

Block Diagram

Figure 6 depicts the block diagram for the suggested conjunctive model. There are three basic phases for this.
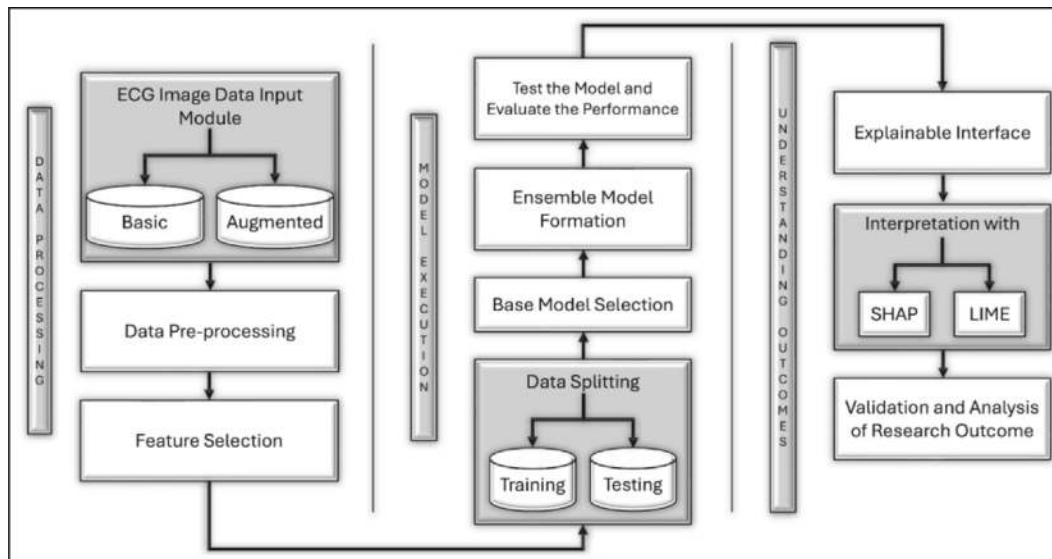
Fig. 6 The Block Diagram of the Conjunctive Model.

- Data Processing
- Model Execution
- Understanding Outcomes.

Data Processing

The input data is collected and processed at this phase to remove noise from the input dataset and the top 10 features are selected. So, for better understandability, this phase is again subdivided into three parts.

- **ECG Image Data Input Module:** At first the ECG images are collected from the web resources. Then the ECG images are partitioned into two parts: 1) Healthy ECG images, i.e., the persons with no heart disease, and 2) Unhealthy ECG images, i.e., the persons either with heart disease or those who have a history of heart problems.
- **Data Pre processing:** While creating the database the images may contain noise. These noises can intercept the results. So, for this reason, data pre processing is highly needed. This module ensures that data from both sources are consistently formatted and ready for

analysis by the predictive models. It is critical to convert raw ECG images into a suitable format before the model training.

This pre processing of data can be done by Algorithm 1.

Algorithm 1 for Data Pre processing

Algorithm 1: Data Pre processing

Input: ECG image dataset as healthy and unhealthy.

Begin: For every sample image:

i. Apply noise reduction technique utilizing Gaussian filter to remove noise and enhance the signal quality.
ii. Resize the denoised image into a standard size (1*255) for consistent processing and precise analysis.
iii. Divide the resized image into 12 sections to extract individual leads (1–12) essential for understanding heart functionality.
iv. Transform the ECG images into grayscale format to simplify image data by reducing its intensity levels.
v. Generate CSV files for each lead division.
vi. Read CSV Files for each ECG type (Healthy and Unhealthy).
vii. Generate combined CSV concatenated by the data frames into a single combined data frame.

End For

Output: Combined CSV file of ECG images (Healthy and Unhealthy Type).

- **Feature Selection:** The way of choosing the most worthy features (or variables) from the input data to improve the performance of an ML algorithm is termed feature selection. It helps to remove unnecessary

or redundant information, making the model execute faster and more accurately. Figure 7 describes the functionality of feature selection.
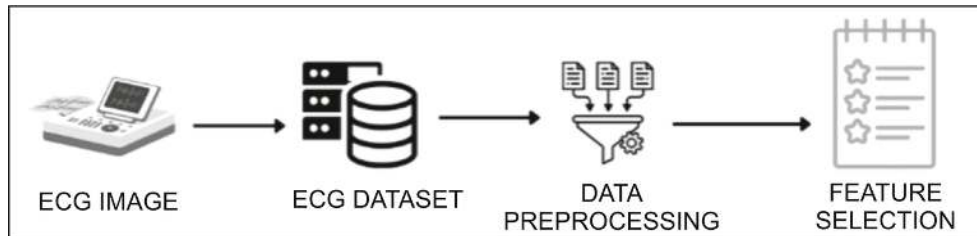
Fig. 7 Functionality of Feature Selection.

The three main procedures for feature selection are:

- **Filter Methods:** These procedures evaluate the importance of each feature independently, without involving an ML model. They examine how the features are inter related and the target variable by employing statistical tests. It's like doing a quick scan to see which features seem usable. Examples include correlation, mutual information, and chi-square tests. These procedures are fast but might miss complex relationships between features.
- **Wrapper Methods:** These methods select features by actually training models and testing how different combinations of features affect performance. It's like experimenting with another blend in a recipe to discover the best one. Backward elimination, forward selection, and recursive feature elimination are a few examples. While more accurate, these methods can be slower since they repeatedly build models.
- **Embedded Methods:** These procedures combine feature selection into the model training. It can automatically decide which features matter most as it learns. It's like adjusting the recipe while cooking based on how the dish is turning out. Examples include Lasso regression, which can shrink some feature weights to zero, and decision trees, which rank

features by importance. These methods balance between efficiency and accuracy.

Here, the embedded method has been used for selecting the important features like standard leads, and morphological features from the ECG images.

Model Execution

This phase defines the procedures for implementing the conjunctive model based on the selected features. Executing the model's workflow is subdivided into four parts.

- **Data Splitting:** In this phase, the dataset is partitioned into two subsets. One subset is for model training purposes and the other is for model testing purposes. Here the input dataset is split into 80:20 ratio for model training and testing procedures.
- **Base Model Selection:** Base model selection is the procedure of choosing an initial model in ML. Here, a base model typically means an existing, general model that forms the basis for a specific problem or task. This model may not be optimized for the given domain, but it is a better choice for further changes, fine-tuning, or specific training. In ML, a base model may entail choosing a root algorithm or approach (e.g., Decision Tree and KNN) to build further.
- **Ensemble Model Formation:** Ensemble model formation means multiple single classifier models are assembled for the CVD prediction. So, the weak performance of any model can be compensated by the strong performance of another model by generating better accuracy.

- **Test the Model and Evaluate the Performance:** After successfully training with the EL model, testing is conducted for everyone. The model's performance is evaluated by analyzing metrics like Fl score, accuracy, ROC, PR curve, etc.

From this comparison analysis, it can be concluded that the model that achieves the highest accuracy, performs the best prediction.

Understanding Outcomes

This phase describes the rationale behind the outcome based on the decisive feature selection. For the understanding of the outcomes, it is subdivided into three parts.

- **Explainable Interface:** ML models help to forecast heart disease. But to build trust in the model, XAI assists in describing the mechanism behind the prediction.
- **Interpretation with SHAP and LIME:** SHAP and LIME are the two methods used for understanding ML models that make black-box models more transparent and trustworthy.
- **Validation and Analysis of Research Outcomes:** This step is performed by justifying the results generated by the SHAP and LIME models.

Proposed Conjunctive Algorithm

Algorithm 2: Conjunctive Ensemble Learning Model with XAI for Detecting Heart Disease

    Input: ECG image dataset as healthy and unhealthy.

    Begin: Pre process the input images as described in Algorithm **1.**

    For every sample image

Apply ML Algorithms (KNN, Decision Tree, XGBoost, Voting Classifier, and Random Forest).

  i. Select ten important features based on permutation significant scores with the feature numbers applying embedded feature selection method.
  ii. Calculate Accuracy, Fl Score, Confusion Matrix, Recall, Precision.
  iii. Draw PR and ROC curve.

End for

Collect the most accurate result.

Do

Generate explainable results with LIME and SHAP for a particular instance (index = 5) **while** (validate the most suitable result).

End

Output: Possibility of Heart Disease (as a percentage of healthiness/unhealthiness).

Result Simulation

The results have been simulated following the conjunctive proposed algorithm.

Dataset Used

In the proposed framework, first, the model is given an input of a basic dataset[1] of ECG images with healthy and unhealthy data values. As this dataset contains unhealthy image data as compared to healthy image data, it suffers from an overfitting issue. So, it has been decided to incorporate more healthy image data to overcome the problem of overfitting. For this purpose, an augmented dataset[2] has been used. These two datasets have been reported in Figure 8.

Fig. 8 Comparison with the Description of the Basic Dataset and Augmented Dataset.↵

Name	Description	
	Basic Dataset	**Augmented Dataset**
Healthy ECG Images	284	1143
Unhealthy ECG Images	644	644
Total ECG Images	928	1787
Combined CSV File Size	928*3060	1787*3060
Codec	Lossless jpeg	Lossless jpeg

1 https://data.mendeley.com/datasets/gwbz3fsgp8/2↵

2 https://data.mendeley.com/datasets/gwbz3fsgp8/1↵

Feature Selection

This step involves the embedded feature selection method to identify and extract the significant features from both ECG image datasets as it integrates feature selection into the model training procedure. As the RF gives the best result, the feature selection by RF is described in the subsequent section.

Feature Selection from Basic Dataset

Here, Figure 9 depicts RF feature importances, after applying an embedded feature selection method based on permutation significance scores. The x-axis defines the feature counts whereas the y-axis defines the combination of features' importance score. Here, from left to right, the top 10 features are presented in order of increasing importance, and their numbers are given on the x-axis (e.g., 4, 44, 46, 47, 49, 91, 92, 93, 131, and 134). Among the top 10, feature number 47 has the lowest important value, and feature number 4 has the highest important value.
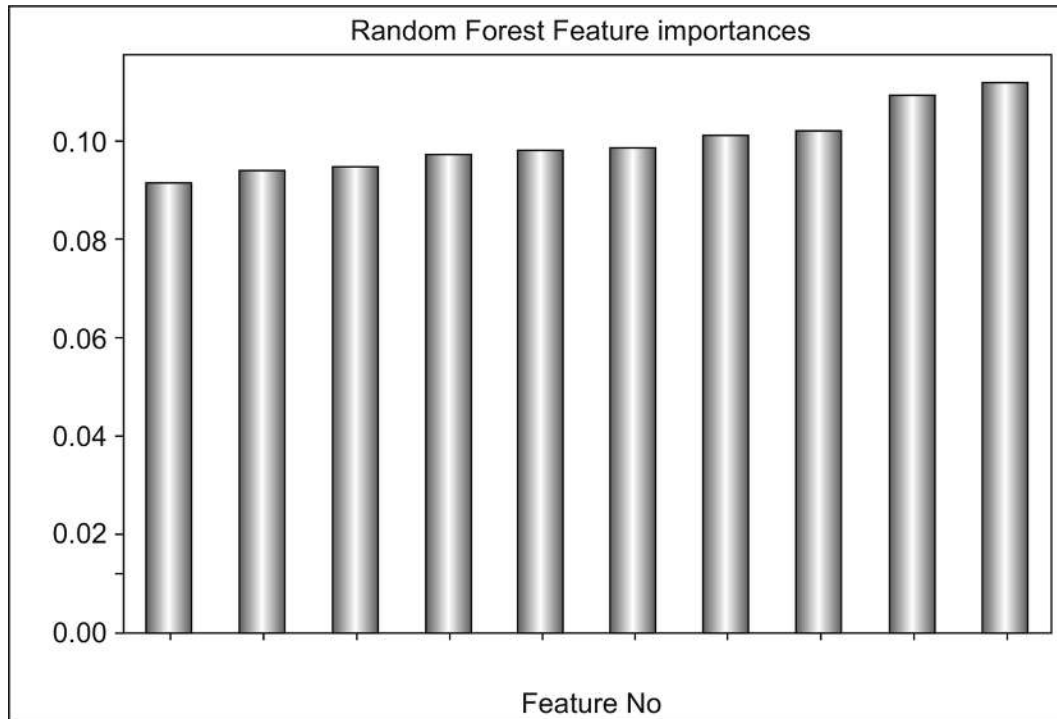
Fig. 9 Random Forest Feature Importances Based on Permutation Significance Scores Selected from Basic Dataset. ↵

Feature Selection from Augmented Dataset

The important feature number for the prediction using the embedded feature selection method, the RF algorithm gives the result as depicted in Figure 10. This image is a bar chart displaying the feature importances of the Random Forest model based on permutation significance scores. Here, the Permutation Importance Score is on the y-axis ranging from 0 to approximately 0.11. Feature numbers (42, 48, 44, 41, 46, 49, 37, 79, 92, and 125) are on the x-axis. With Feature number 42 scoring the lowest and Feature number 125 scoring the highest, the features in ascending order of relevance are listed in Figure 10. With the help of this graph, finding the most important factors in the predictions by the model is made simpler.
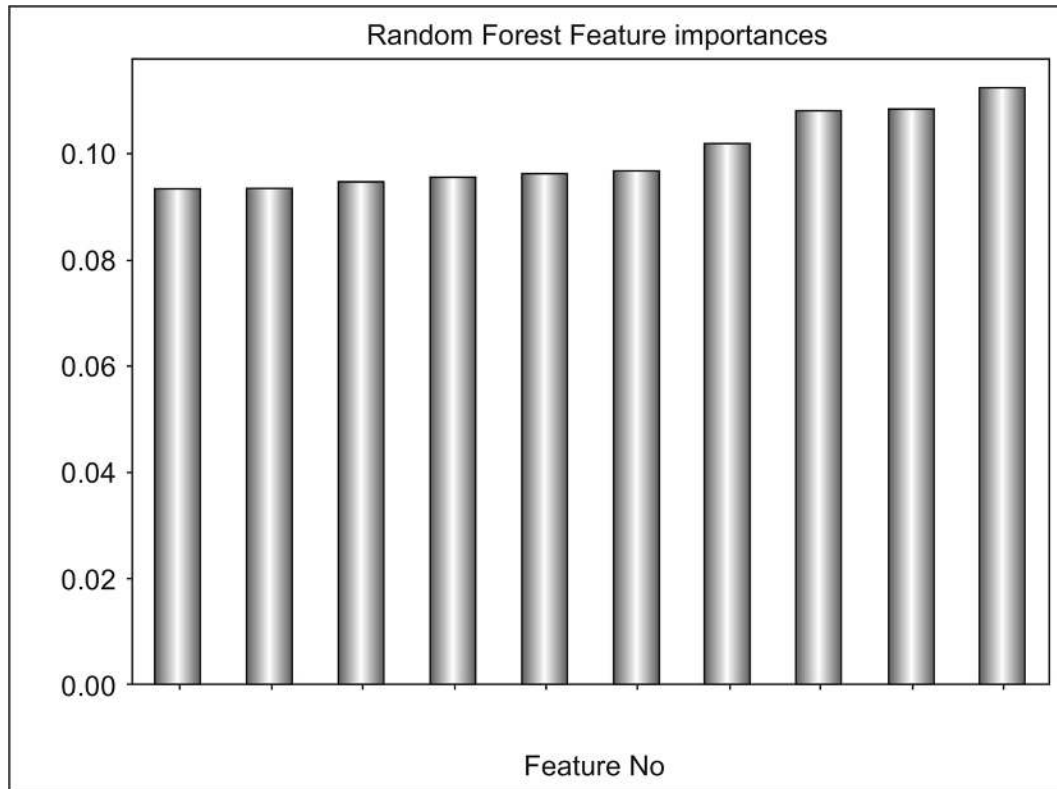
Fig. 10 Random Forest Feature Importances Based on Permutation Significance Scores Selected from Augmented Dataset.

Mapping Table for Feature Number with ECG Image Attributes

The ECG image combined CSV file contains 255 features (ranging from 0 to 254 as features and 255 as target), representing a transformed and structured representation of extracted features of ECG signals based on pixel intensity value. The mapping table for ECG Image Attribute Name with the combined CSV File having Feature Number (0 to 255) generated after the data pre processing step is reported in Figure 11.

Fig. 11 Mapping Table for Feature Number (0 to 255) with ECG Image Attribute Name.

Feature Number	ECG Image Attribute Name
0	Time (or image metadata)
1-12	Standard ECG Leads (lead I-111, aVL aVF, aVR, V1-V6)

Feature Number	ECG Image Attribute Name
13-20	Waveform Features (P-wave, QRS complex, T-wave, ST segment, QT interval, PR interval)
21-40	Frequency Domain Features (FFT components, power spectral density)
41-80	Morphological Features (ST deviation, R-peak amplitude, QRS width)
80-120	Statistical Features (variance, mean, skewness, kurtosis of ECG segments)
121-160	Wavelet Transform Coefficients (multi-resolution ECG signal decomposition)
161-200	Image Derived Features (edge detection, texture features from ECG image)
201-240	Deep Learning Features (extracted using CNNs, autoencoders, etc.)
241-255	Miscellaneous/Extra Features

Performance Evaluation with Ensemble Learning Model

With two fundamental ML algorithms (KNN and Decision Tree) and three EL algorithms (XGBoost, Voting Classifier, and RF), the proposed conjunctive model's accuracy is generated and compared to validate their applicability in the model. Decision Tree automatically selects important features during feature selection and forms the basis of ensemble methods like XGBoost, Random Forest, Voting Classifier, etc. KNN can forecast the output based on the input data even with a large amount of training data that includes noisy values. XGBoost is highly effective on large datasets since it uses a depth-first tree-pruning approach and can handle missing values automatically and extensively due to its accuracy and scalability. The RF makes predictions by combining several decision trees. This is a supervised ensemble learning algorithm utilised for classification purposes. Voting Classifier uses various single-classifier algorithms for prediction purposes.
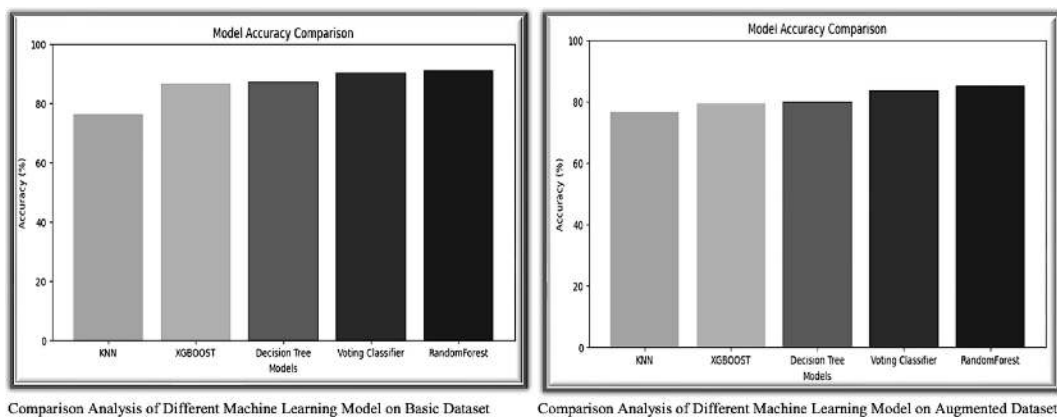
So weak performance of a model can be compensated by the strong performance of another model. Hence, it can be concluded that with the potency of the model, the heart disease prediction can be done very accurately.

The accuracy achieved from the basic dataset and the augmented dataset applying different ML models is compared and analyz ed in Figure 12.

Fig. 12 Comparison Analysis of Accuracy achieved from Basic Dataset and Augmented Dataset.⏎

Algorithm Name	Accuracy	
	Basic Dataset	**Augmented Data set**
Random Forest	91.01%	85.02%
Voting Classifier	89.70%	83.54%
Decision tree	87.34%	79.33%
XGBoost	86.71%	79.33%
KNN	76.33%	76.49%

Here this could be seen that the Random Forest algorithm generates the best result with 91.01% accuracy (for the basic dataset) and 85.02% accuracy (for the augmented dataset). The bar chart comparison of different ML models is presented in Figure 13.

Comparison Analysis of Different Machine Learning Model on Basic Dataset

Comparison Analysis of Different Machine Learning Model on Augmented Dataset

Fig. 13 The Comparison Analysis of Different ML Models on Basic and Augmented Dataset. ⏎

The F1 score of different ML models is calculated and the comparative analysis of the F1 score from the basic dataset and augmented dataset is represented in Figure 14.

Fig. 14 Comparison Analysis of F1 Score calculated from Basic Dataset and Augmented Dataset.⏎

Algorithm Name	F1 Score	
	Basic Dataset	**Augmented Dataset**
Random Forest	0.89	0.82
Voting Classifier	0.88	0.81
Decision tree	0.86	0.78
XGBoost	0.84	0.76
KNN	0.72	0.73

By analyzing the results (accuracy and F1 score) presented in the previous table, it can be concluded that RF performs better than other ML algorithms for the prediction. This is an ensemble ML model that uses multiple decision tree predictions and based on these predictions the algorithm gives us an error-free prediction. As it uses multiple base models for prediction, it provides a more accurate result by enhancing robustness over the overfitting issue on a complex dataset. So it can be said that in this algorithm, the weak performance of a base model can be compensated by the strong performance of another model.

Here is the classification report of the Random Forest Algorithm on the basic dataset and the augmented dataset is represented in Figure 15.

Fig. 15 Classification Report of Random Forest Algorithm on Basic Dataset and Augmented Dataset.

Random Forest Accuracy: 91.01%

	precision	recall	Fl-scare	support
0	0.88	0.83	0.86	759
1	0.92	0.95	8.93	1611
accuracy			B.91	2370
macro avg	0.90	0.89	0.90	2370
weighted avg	0.91	0.91	0.91	2370

Classification Report of the Random Forest Algorithm on Basic Dataset

Random Forest Accuracy: 85.02%

	precision	recall	fl-score	support
0	8.83	0.96	0.89	2975
1	0.90	0.66	0.76	1679
accuracy			0.85	4654
macro avg	0.87	0.81	0.83	4654
weighted avg	8.86	0.85	0.84	4654

Classification Report of the Random Forest Algorithm on Augmented Datasct

The confusion matrix for different ML models on the basic dataset is represented in Figure 16.
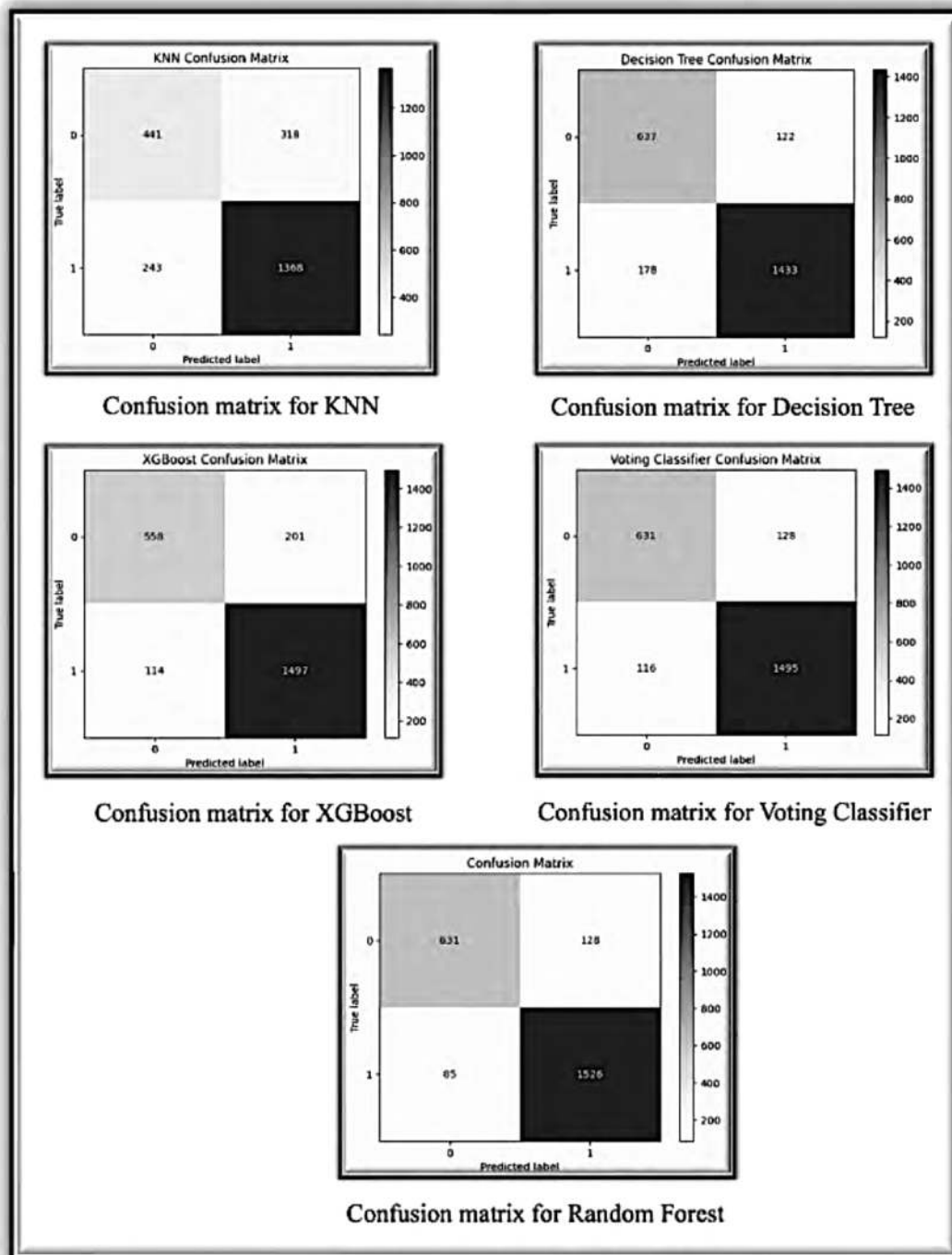
Fig. 16 Confusion Matrix of Different ML Algorithms on Basic Dataset. ⏎

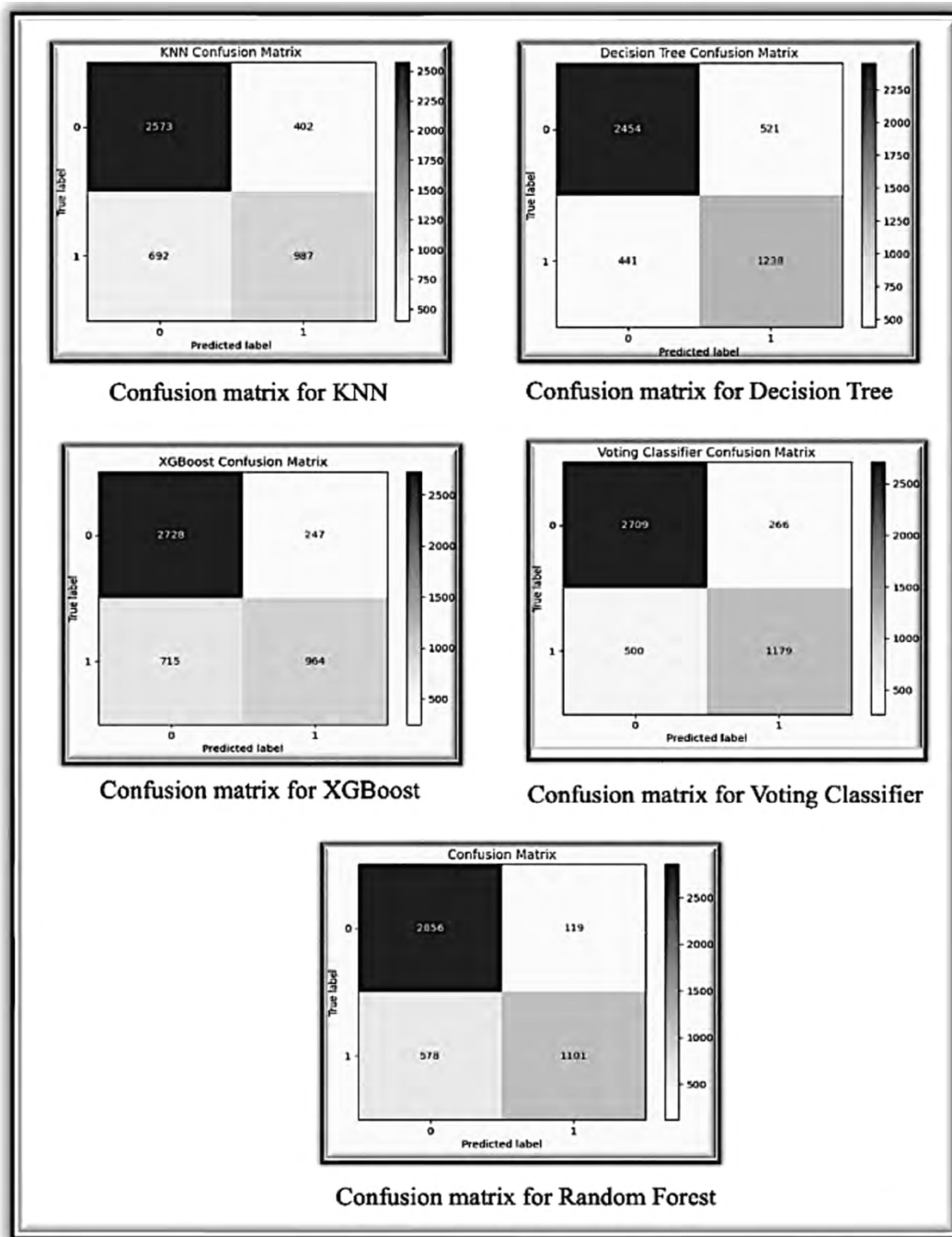Figure 17 shows the confusion matrix for different ML algorithms on the augmented dataset.

Fig. 17 Confusion Matrix of Different ML Algorithms on Augmented Dataset. ⏎

The PR (Precision-Recall) Curve Comparison Analysis of Different ML Al-gorithms on Basic and Augmented Dataset

The **PR** (Precision-Recall) Curve of different ML algorithms on the basic and the augmented dataset utilized to measure the binary classification

model's performance is depicted in .
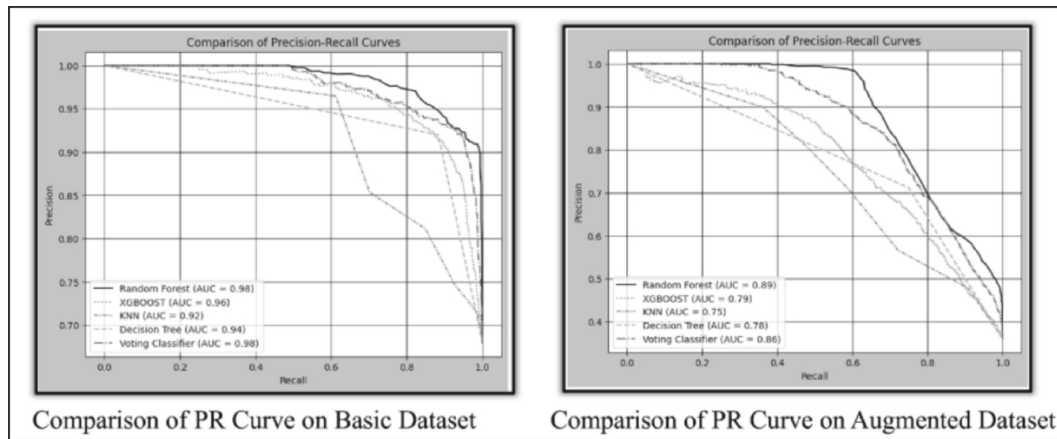
Fig. 18 The PR Curve Comparison Analysis of Different ML Algorithms on Basic and Augmented Dataset. ⏎

Recall, i.e., sensitivity or true positive rate, is displayed towards the x-axis and measures how well the model identifies all positive samples. Precision, i.e., Positive Predictive Value, is displayed towards the y-axis and measures the ratio of expected positive samples that are actual. The curve shows how precision and recall are balanced at several models' decision thresholds. The curve of the Random Forest Algorithm points towards the upper right corner belongs to more accurate prediction.

Area Under Curve or AUC

For the basic dataset, the area under the curve (AUC) of the Precision-Recall curve for the Random Forest Algorithm = 0.98, whereas in the case of the augmented dataset the AUC = 0.89. This value indicates the good performance of the model that is exhibited by AUC values close to 1, referred to in the plot.

The ROC (Receiver Operating Characteristics) Curve Comparison Analysis of Different ML Algorithms on Basic and Augmented Dataset

The ROC (Receiver Operating Characteristics) graph of different ML algorithms on the basic and the augmented dataset that determines the

classifier's performance is presented in Figure 19. In the graph, the x-axis defines the False Positive Rate (FPR) and the y-axis defines the True Positive Rate (TPR) or Recall. At different decision thresholds, this curve displays the trade-off between a TPR and an FPR.
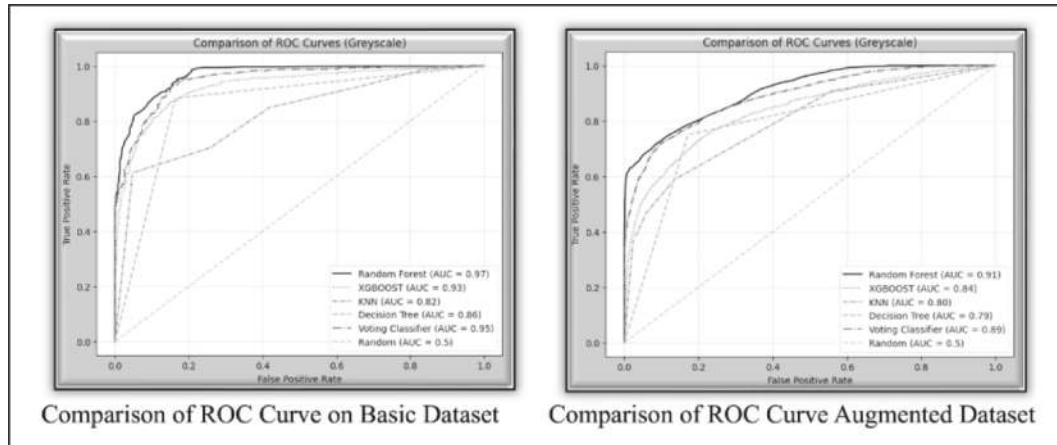
Fig. 19 The ROC Curve Comparison Analysis of Random Forest Algorithm on Basic and Augmented Dataset. ↵

Here, the curve of the Random Forest Algorithm represents a perfect classifier when it rises towards the left-hand corner.

Comprehensive Analysis of LIME and SHAP with Ensemble Learning Model

As the application of LIME and SHAP does not correspond to any specific model, they can be applied regardless of any ML algorithms for a model's interpretation. Here, the Random Forest outperforms with other algorithms, so its results are explained with SHAP and LIME.

Comprehensive Analysis with Basic Dataset

First, the comprehensive analysis is performed with the basic dataset.

LIME Explanation of Random Forest Algorithm on Basic Dataset

The working principle of the Random Forest Algorithm can be explained with the help of the LIME model. Figure 20 represents the LIME

explanation of the Random Forest Algorithm on the basic dataset for an instance (index = 5) which has been considered as a tuple for interpretability for prediction of heart disease probability. The image presents a visualization of local explanations for a classification model with the help of the LIME (Local Interpretable Model Agnostic Explanation) model. The explanation can be divided into four parts: 1) Prediction Probabilities, 2) Feature Contribution to Prediction, 3) Feature Value Table, and 4) Local Explanation for Class Unhealthy. For Prediction Probability, two classes are present: Healthy and Unhealthy.
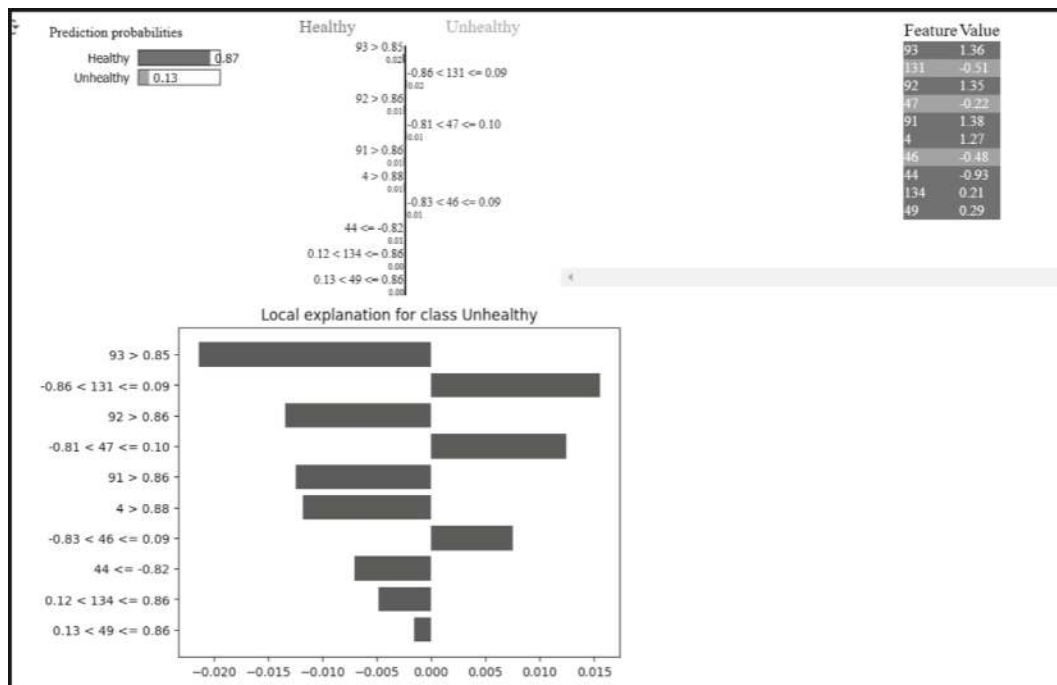
Fig. 20 LIME Explanation of Random Classifier Algorithm on Basic Dataset.

Here the top-left corner represents the probability values of the classes related to index 5 with Healthy: 0.87 and Unhealthy: 0.13. In the upper middle of the picture, the Feature Contribution to Prediction is described. This diagram shows which features positively and negatively impact the classification. Features on the left side promote the healthy prediction.

Features on the right side promote the unhealthy prediction. Numerical ranges next to each feature describe threshold conditions for the value of the features. The Feature Value Table lists the feature and its corresponding values in the right-hand corner. Here black color highlights the features supporting the 'Healthy' prediction and the gray color highlights the features supporting the 'Unhealthy' prediction. In the lower middle of the figure, a Local Explanation for class Unhealthy has been defined. In this chart, a horizontal bar represents the features that contributed the most to the unhealthy prediction. Here, the left-hand bars indicate the negative contributions towards the unhealthy prediction and the right-hand bars indicate the positive contributions away from the unhealthy prediction. Hence, it may be said that the sample image predicted by RF has an 87% probability to be Healthy in which Features like 4, 44, 49, 91, 92, 93, and 134 contribute towards the Healthy class.

SHAP Explanation on Random Forest Algorithm on Basic Dataset

The working of the conjunctive prediction model can also be explained with the help of SHAP. The SHAP summary plot represented in Figure 21 shows a visualization of a global interpretation of every feature's contribution to the predictions of the conjunctive model using the Random Forest Algorithm on the basic dataset for the prediction probability of heart disease.
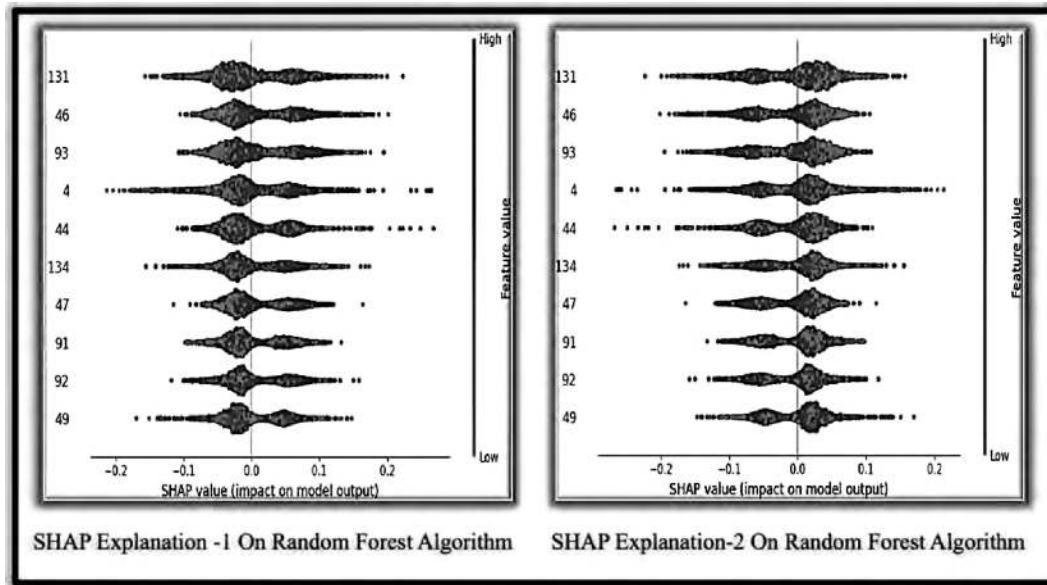
Fig. 21 SHAP Summary Plot Explanation on Random Forest Algorithm on Basic Dataset. ⏎

Here the x-axis defines a SHAP value, that represents how each of the features influences the prediction and the y-axis defines the feature number or feature indices (numeric labels like 131, 46, 93, 4, etc.). The SHAP values that are positive, drive the prediction upwards (towards the positive class or higher score) and negative downwards (towards the negative class or lower score). In Figure 21, low feature values correspond to gray dots, and high feature values correspond to black dots. Hence, from this SHAP summary plot, it can easily be understood how feature values influence the model prediction.

Waterfall Model Explanation of Random Forest Algorithm on Basic Dataset

The SHAP waterfall model depicted in Figure 22 represents a visualization of local explanations of the Random Forest Algorithm on a basic dataset for an instance (index = 5) which has been considered as a tuple for interpretability with prediction of heart disease probability.
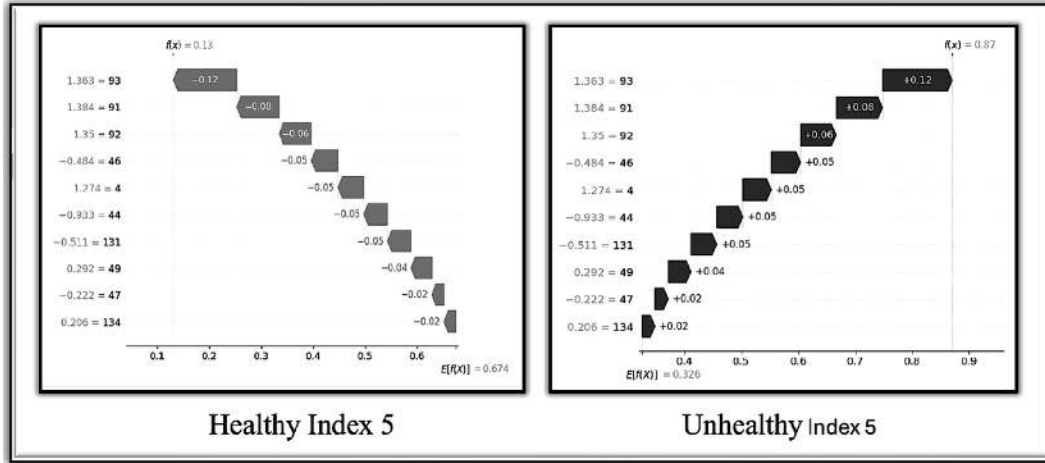
Fig. 22 SHAP Waterfall Model on Random Forest Algorithm on Basic Dataset.

Here the gray waterfall at the left represents the predicted value of $f(x) = 0.13$ with the baseline expected value $E[f(X)] = 0.674$. The contributions from individual features (displayed as negative values in grey) minimize the predicted value from the expected value with the final output. This means that the features primarily had a negative influence on the prediction. The black waterfall at the right represents the predicted value of $f(x) = 0.87$ with the baseline expected value $E[f(X)] = 0.326$. The contributions from individual features (displayed as positive values in black) increase the prediction from the expected value to the final output. This means that the features primarily have a positive impact on the prediction. The features of the first image cause the forecast to drop (negative SHAP values), which leaves the final output below expectations, whereas the features of the second image push the prediction upward (positive SHAP values), producing a final output that is higher than expected. It is useful for analyzing feature importance, debugging ML models, and ensuring model interpretability.

Comprehensive Analysis with Augmented Dataset

As the basic dataset has overfitting problems with the result, the comprehensive analysis is performed with the augmented dataset.

LIME Explanation of Random Forest Algorithm on Basic Dataset

The working principle of the Random Forest Algorithm can be explained with the help of the LIME model. Figure 23 represents the LIME explanation of the Random Forest Algorithm on an augmented dataset for an instance (index = 5) which has been considered as a tuple for interpretability for prediction of heart disease probability.
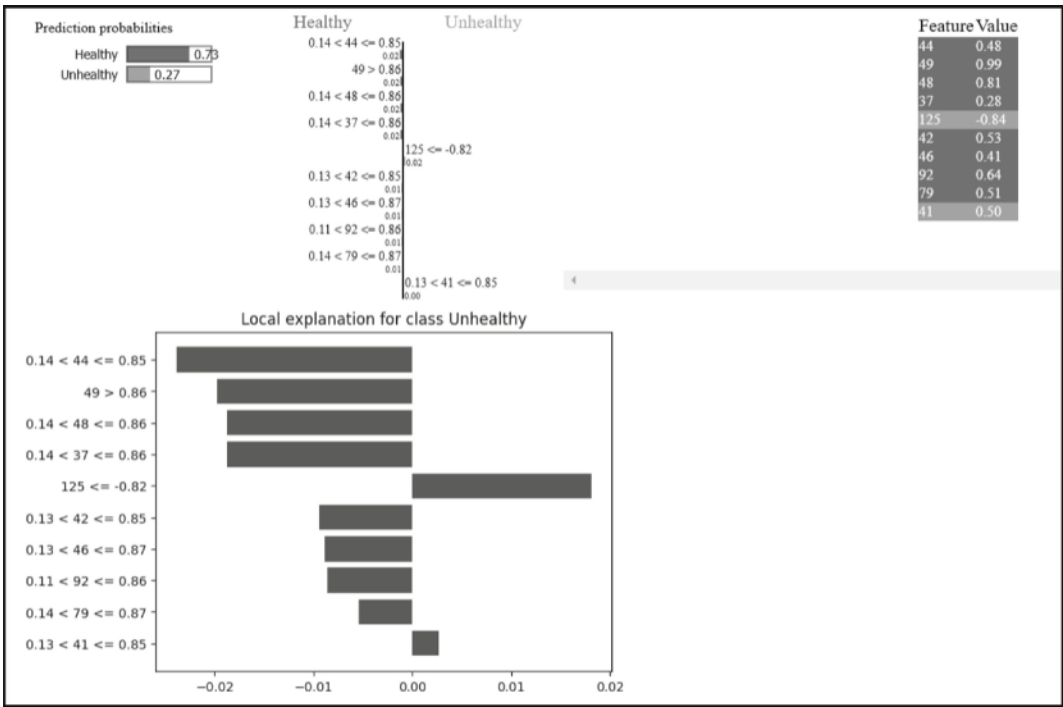
Fig. 23 LIME Explanation of Random Classifier Algorithm on Augmented Dataset. ⏎

The image presents a visualization of local explanations for a classification model with the help of the LIME (Local Interpretable Model Agnostic Explanation) model. The explanation can be divided into four parts: 1) Prediction Probabilities, 2) Feature Contribution to Prediction, 3) Feature Value Table, and 4) Local Explanation for Class Unhealthy. For Prediction Probability, two classes are present: Healthy and Unhealthy.

Here the top-left corner represents the probability values of the classes related to index 5 with Healthy: 0.73 and Unhealthy: 0.27. In the upper middle of the picture, the Feature Contribution to Prediction is described. This diagram shows which features positively and negatively impact the classification. Features on the left side promote the healthy prediction. Features on the right side promote the unhealthy prediction. Numerical ranges next to each feature describe the threshold conditions of the feature's value. The figure lists the feature and its corresponding values in the right-hand corner. Here black color highlights features supporting the 'Healthy' prediction and the gray colour highlights features supporting the 'Unhealthy' prediction. In the lower middle part of the figure, a Local Explanation for class Unhealthy has been defined. In this chart, a horizontal bar represents the features that contributed the most to the unhealthy prediction. Here, the left-hand bars indicate the negative contributions towards unhealthy prediction and the right-hand bars indicate the positive contributions away from unhealthy prediction. Hence, it may be said that the RF predicted the sample image with a 73% probability to be Healthy in which Features like 37, 42, 44, 46, 48, 49, 79, and 92 contribute towards the Healthy class.

SHAP Explanation on Random Forest Algorithm on Augmented Dataset

The working of the conjunctive prediction model can also be explained with the help of SHAP. The SHAP summary plot represented in Figure 24 shows a visualization of a global interpretation of how every feature contributes to the conjunctive model's prediction using the Random Forest Algorithm on the augmented dataset for the heart disease prediction probability.
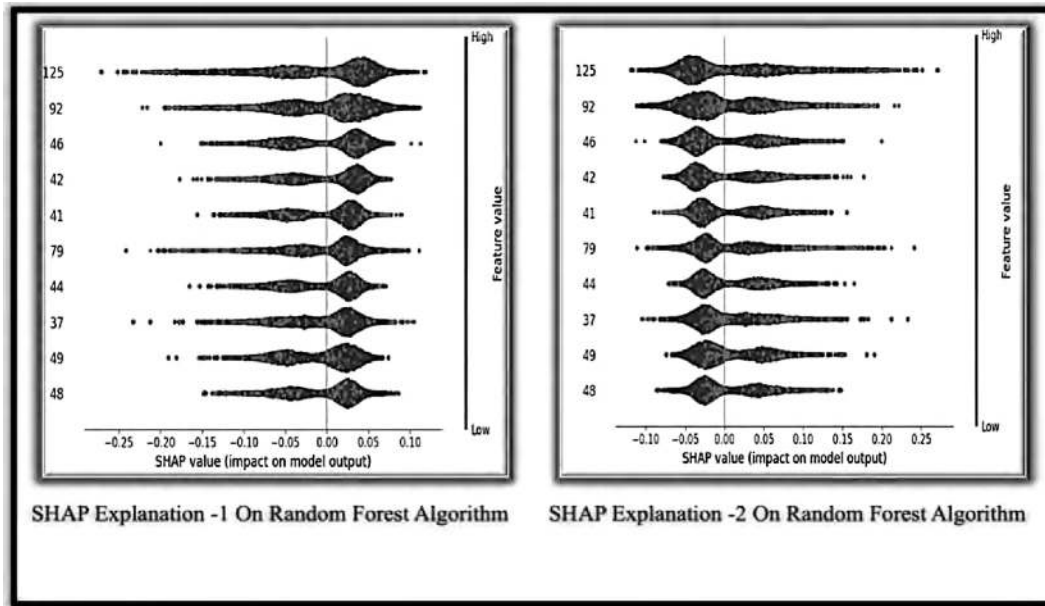
Fig. 24 SHAP Summary Plot Explanation of Random Forest Algorithm on Augmented Dataset. ⏎

Here the x-axis defines a SHAP value, that indicates how each of the features influences the model's prediction (output) and the y-axis defines the names of the features or feature indices (numeric labels like 125, 92, 46, 42, etc.). The SHAP values that are positive drive the prediction upwards (towards the positive class or higher score) and negative values downwards (towards the negative class or lower score). In Figure 24, the gray dot indicates low feature values, and the black dot represents high feature values. Hence, from this summary plot, it can easily be understood that high values (black) bring the model towards Healthy and low values (gray) bring it towards Unhealthy, Feature 125 has the largest impact on the model prediction. The same pattern appears in Feature 92, where high values promote predictions that are Healthy.

Waterfall Model Explanation of Random Forest Algorithm on Augmented Dataset

The SHAP waterfall model depicted in Figure 25 represents a visualization of local explanations of the Random Forest Algorithm on the augmented

dataset for an instance (index = 5) which has been considered as a tuple for interpretability for prediction of heart disease probability. Here the grey waterfall at the left represents the predicted value of $f(x)$ = 0.04 with the baseline expected value $E[f(X)]$ = 0.353. The features have mostly negative SHAP values, meaning they reduced the model's prediction from the expected value to a much lower final output. The largest contributing feature has a negative impact of —0.06, and the others also progressively push the value downward. The black waterfall at the right represents the predicted value of $f(x)$ = 0.96 with the baseline expected value $E[f(X)]$ = 0.647. The features have positive SHAP values, meaning they increase the model's prediction above the expected value. The most influential feature adds + 0.06 and other features progressively contributed positively to reach the final output.
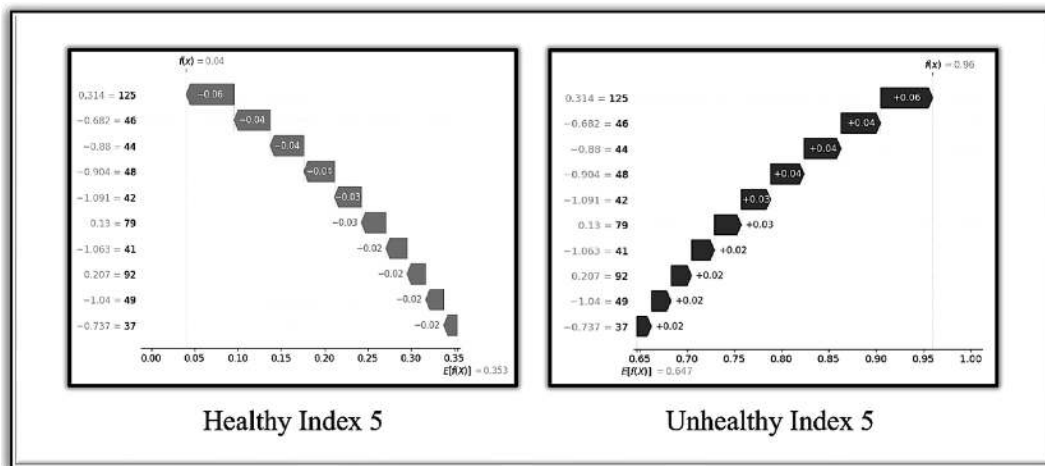
Fig. 25 SHAP Waterfall Model on Random Forest Algorithm on Augmented Dataset.

It is known that LIME provides local or single instance explanation, so it requires less computing time, whereas SHAP provides local as well as global interpretations. For this reason, it takes more computing time than LIME. The Comparison of LIME and SHAP with respect to explanation

efficiency and execution time for the basic and augmented dataset is given in [Figure 26].
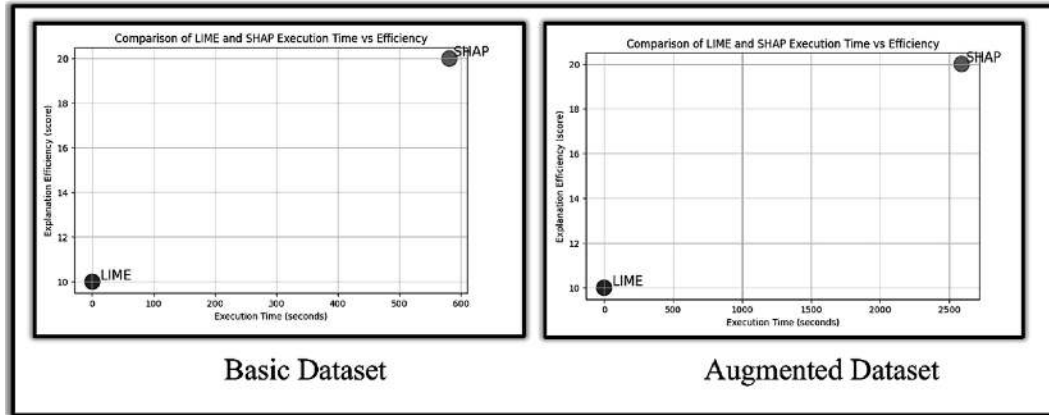
Fig. 26 Comparison of LIME and SHAP with respect to Computational Efficiency and Execution Time. ↵

Here the lower black dots indicate the execution time in regard to the explanation efficiency score taken by LIME and the upper gray dots represent the execution time in regard to the explanation efficiency score taken by SHAP. From [Figure 26], it can be noted that LIME takes less than 1 sec for both datasets, but SHAP takes 580 sec. (approx.) for a basic data set and 2,900 sec. (approx.) for the augmented dataset. Hence, it can be concluded that in the case of SHAP, the execution time increases with the increased data volume present in the input dataset. So, when the execution time variance is very crucial, i.e., for any real-time health-monitoring systems or remote healthcare applications, then LIME can be chosen for interpretation, else SHAP can be the best option for explanation.

From the results, it can be noted that the significant features obtained from both the databases, correspond to standard ECG leads and morphological features like ST deviation, R-peak amplitude and QRS width as per [Figure 11], contributing the most to the disease prediction that can be validated and explained with the XAI methods.

Finding Results with Optimizing Parametric Eminence in Prediction of Heart Disease

The optimization of the parameters is a key factor for constructing effective and strong EL models that generate accurate, reliable, and understandable results. Combining the strength of individual basic ML algorithms, the overall performance of the model can be enhanced. The proposed model has divided the input data into two subsets: one with a healthy dataset and another with an unhealthy dataset. So, the difference between the number of these input subsets minimizes the problem of overfitting and maximizes the generalizability. The results prove this balance for evaluating performance metrics using EL methods. In achieving parametric eminence, determining the 10 most significant features that decide the predictability is a prime factor. The importance and individual contribution to the prediction probability of these decisive features can be justified by XAI methods like SHAP and LIME. This conjunctive model decides with the help of XAI and identifies the crucial features like ECG leads and morphological features based on their importance scores that affect the prediction results. This interpretability, transparency, and trustworthiness in achieving consistent results increases the reliability of AI-based diagnostic models. In addition, the embedded feature selection method allows clinicians to verify the model outcomes, making AI recommendations more applicable in the medical field. The Random Forest model has outperformed with an optimal number of features that aid in stability improvement and variance reduction. The research also examines the impact of dataset pre-processing and feature selection methods for the parametric eminence. The results show that selecting and extracting decisive features increases the model's interpretability and computational efficiency and decreases the training time. Hence, the findings confirm that optimizing parametric imminence

through EL and understanding the outcomes with XAI techniques results in better performance and interpretability in heart disease prediction, facilitating more effective, transparent, and reliable AI-driven diagnosis in healthcare.

Limitations

Inadequate quality data, imbalanced classes, privacy, and data security are some issues in this field. Despite their interpretability capability, LIME and SHAP have certain limitations too. LIME can be used only for local explanation, whereas SHAP provides local and global interpretations. So, the computational cost of SHAP increases with large and complex datasets, and the results are not optimized for all cases. Sometimes LIME results are potentially unstable due to random data sampling.

Future Directions

In the future, it is intended to integrate the EMR data along with the ECG images of the patients with the combination of these two approaches: ML and DL. Other XAI methods like Grad-CAM and LRP could also be included for interpretability purposes, as they are highly efficient for model predictions using DL methods. Furthermore, real-world deployment would be developed with IoT (internet of things) devices to test the practicability of the conjunctive model. This fusion of AI and medical knowledge generates a reliable, consistent, and transparent system that enables medical professionals to take firm AI-driven decisions that will revolutionize the healthcare industry.

Conclusion

Early detection and precise prediction of heart disease are very important factors in the medical field. This combined approach of EL with XAI not

only enables the medical professional to make a quick decision about a patient but also helps the users to understand the critical explanation in a very transparent and easier way. This study proves that the EL methods (RF, XGBoost, and Voting Classifier) enhance the prediction accuracy by combining the basic ML models such as KNN and Decision Tree. It also incorporates XAI methods like SHAP and LIME to describe and justify the outcomes achieved from the algorithms and guide medical experts to take prompt action about a patient.

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3 AI for Early Identification of Down Syndrome Patients

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Down Syndrome (DS) is a genetic neurodevelopmental disorder that depends on the person's age, number of chromosomes, and ethnicity, and is caused by the trisomy of chromosome 21. Early detection can bring timely intervention and better quality of life for the affected. There is a heavy demand for non-invasive, scalable, and automated methods that utilize the latest technological advancements, despite the advancement in genetic and clinical diagnostics. The novelty introduced is using the convolutional neural network architecture with high efficiency and scalability based on

the Deep Learning (DL) model called EfficientNetV2, which was effectively trained by transfer learning on pediatric patients' facial characteristics analysis, for identification purposes, on cases of Down syndrome. It is a complete system proposal that incorporates the developed DL model with training of facial expressions data sets, so detection would be speedy and errorless. The designed framework helps mental health professionals in their diagnostic processes, providing a robust tool in the clinical decision-making arsenal. Our research presents significant progress in the field of DS facial analysis, addressing previous limitations by establishing a reliable computational baseline. The implementation details, code, and pretrained models are made available to foster further research and development in this critical area.

Introduction

Down syndrome (DS), one case for every 700 live births worldwide (Antonarakis, 2017), is a condition induced by the presence of extra chromosome 21. Associated usually with intellectual disability, characteristic features on the face, as well as delays in mental or intellectual development, often such disabilities significantly affect one's quality of life. Early diagnosis would be critical because it may lead to early intervention that could improve the long-term outcomes in health, cognitive function, and social integration. Recent studies (Gill et al., 2022) have shown the potential of artificial intelligence (AI)-driven facial analysis for the diagnosis of neurodevelopmental disorders such as autism. But similar research on DS has not been conducted yet; hence, it is one of the critical gaps of using advanced AI methodologies on this mental health condition. Traditionally, diagnosis of DS has been through genetic testing and clinical observation. However, these methods are sometimes very invasive, expensive, and not accessible in most places, especially those with a limited

resource. In addition, DS may have very mild physical manifestations and varies between individuals; hence, a diagnosis from mere visual examination is practically impossible. Thus, non-invasive and cost-effective diagnostic methods, which should be easily accessible to everybody, are the need of the hour. AI and ML (machine learning), especially convolutional neural networks (CNNs), have promise as a potential solution (Sahu et al., 2022). EfficientNetV2 is a new generation of EfficientNet architecture that has become more efficient and accurate on other computational scales, thus fitting well in the analysis of facial images of children suffering from Down syndrome.

Contributions

This study contributes to the field of DS diagnosis in the following novel ways, which distinguishes it from the rest and fills in important gaps:

1. **Introduction to EfficientNetV2 on the Task of Down Syndrome Detection:** This study falls into the very first class of being amongst the initial ones to involve the use of the model called EfficientNetV2 on the process of the detection of DS through analyzing features related to the faces. This is different, because the research work takes place within the boundaries of non-invasive and image-based AI in contrast to classical, genetic testing that appears traditionally to be invasive in its application.

2. **Scalability and Efficiency with High Accuracy via Transfer Learning:** EfficientNetV2's Scalable architecture permits highly accurate predictions across varying computational environments. Using transfer learning, the model achieves robust performance even in low-resource settings, which is a strong advantage over prior models like VGG16 and ResNet18, which are either too resource-intensive or

less efficient on smaller devices. Thus, this scalability allows applications in remote and resource-limited regions where the traditional DS diagnostics are often unavailable.

3. **Diversely Balanced Phenotypic Variation Dataset:** Unlike others in the literature, which rely upon homogeneous datasets, the data used here have been balanced in our carefully controlled representation of the phenotypic variation: skin tones, eyewear, hair texture, among others. Diverse representation increases the applicability of this model to general variations in demographics, further removing bias and increasing precision specifically in worldwide usage, where features tend to vary extensively.

4. **Comparison against Multiple Deep Learning Architectures:** We compare EfficientNetV2 against a set of established deep learning architectures. These are VGG16, GoogLeNet, Wide ResNet, and Swin Transformer architectures. Comparing the two, performance results indicate that with respect to efficiency as well as accuracy, EfficientNetV2 and Wide ResNet result in highly superior performance to serve as good baselines for future AI-driven detection systems for DS.

5. **Practicality in Mobile Applications:** Our design concerns the real-time mobile-based detection of DS, which allows for latency and efficiency at the level of a mobile application. This will have a real impact on the widespread adoption of DS, thereby providing healthcare professionals and caretakers with a tool for easily identifying early DS signs without costly medical facilities.

6. **Publicly Available Resources on Reproducibility:** To further stimulate and vet future work, we released our code, implementation details, and pretrained models as public resources to address this

previously unaddressed issue regarding reproducibility. Thus, the work opens opportunities toward continuous improvement in diagnostic DS AI and facilitates collective endeavor and improvement in pediatric outcome health.

Related Work

The last couple of years have witnessed vast improvement in the application of AI and ML in healthcare, mainly in genetic and neurodevelopmental disorder diagnosis. Here we review current literature on AI-driven approaches for diagnosing DS and other associated neurodevelopmental disorders; highlight the progress made so far, as well as the limitations in previous studies and the specific gap our current study aims to fill.

Advances in AI for Medical Imaging and Diagnosis

Medical imaging applications, including cancer detection and estimation of retinopathy in diabetes patients and also estimating disorders of the nervous system have been undertaken impressively with the help of AI along with deep learning approaches ([Barua et al., 2022](#); [Gupta et al., 2022](#); [Uddin et al, 2019](#)). A particular example of such sophisticated and accurate and detailed pattern capturing mechanisms would be CNNs and later, Vision Transformers. In recent times, EfficientNet architectures, including EfficientNetV2 (Simonyan & Zisseman, 2014) have been derived to achieve efficiency of a model at different scales of computation, which makes it feasible for the architecture to operate in high-resource clinical as well as in low-resource mobile environments. Such advancement forms a sound premise for the application of AI to more challenging domains such as pediatric neurodevelopmental diagnostics, which are traditionally subjective.

AI in Neurodevelopmental Disorder Diagnosis

Several studies have been conducted to apply AI in neurodevelopmental disorder diagnosis, with promising results. For instance, Gill et al. (2022) introduced the Vitasd, a Vision Transformer for Autism Spectrum Disorder (ASD) framework, which uses a Vision Transformer for the diagnosis of ASD by facial analysis. It showed that Vision Transformers are capable of capturing subtle facial features related to ASD and sets a precedent for similar applications in the detection of DS. In addition, Wou et al. (2016) and Megarbane et al. (2009) discussed applications of CNNs in the identification of intellectual and developmental disabilities, which shows that AI has the potential toward accessible diagnostic support in early childhood. However, despite all the developments, the literature lacks the comprehensive, accessible AI-based diagnostic tool especially tailored for Down syndrome, and this is a gap addressed by this study.

Traditional Diagnostic Methods and Limitations in Down Syndrome

Historically, DS diagnosis has depended on genetic testing methods such as karyotyping and chromosomal microarray analysis, along with clinical observations based on physical features (Lalonde et al., 2020; Gill & Buvya, 2024; Cao et al., 2012). Although effective, these methods have several limitations, such as invasiveness, high costs, and limited availability in low-resource settings. Furthermore, the subtlety and variability of DS facial characteristics complicate visual-based diagnosis, increasing the need for objective and scalable diagnostic tools.

Current AI Approaches to Down Syndrome Diagnosis

Previous studies of research on the diagnosis of DS using AI have mainly utilized CNN architectures involving ResNet and VGG models. For

example, [Iandola et al. (2016)](#) applied transfer learning from face recognition models into diagnosing DS and enjoyed moderate success, but failed miserably with model generalizations across various patient demographics. Moreover, the dependency on homogeneous datasets has brought up the possibility of bias, and models that are based on those datasets are not applicable in global healthcare areas. These studies are more critical progress, but with a need for models that seek to balance efficiency and accuracy across different computational environments so that bias is addressed.

Ethical and Practical Considerations in AI for Pediatric Diagnosis

The ethical considerations of using AI in pediatric healthcare are too important to ignore, particularly in terms of patient privacy, informed consent, and equitable access. Studies by [Gupta et al. (2022)](#) and [Szegedy et al. (2016)](#) have underscored the necessity of anonymized data, robust privacy controls, and ethical transparency in AI-based diagnostics. Our study adheres to these principles by ensuring patient data privacy, using a diverse dataset to avoid phenotypic bias, and making our model accessible for mobile applications, thus addressing both ethical and practical needs in the field.

In summary, although AI has shown great potential in detecting neurodevelopmental and genetic disorders, a robust and scalable solution specifically tailored for DS diagnosis is somewhat underexplored. To this end, the approach developed here improves the efficiency of existing AI methodologies while simultaneously generalizing their results further and offers a new paradigm that addresses some of the limitations observed in previous studies.

Dataset and Methodology

In this section, we discuss the dataset and methodology used for this research.

Dataset

The data used for the study is 3,000 facial images (Figure 1), which are compiled in a balanced way; half of them present children that have been diagnosed with DS, and the others are healthy controls. Moreover, the age of the children in the photos is from 0 to 15, which covers the period that's most relevant to early signs of DS diagnosis.

Fig. 1 Examples of the images with their respective labels from the supervised learning data [4].

The dataset also accounts for possible biases through the use of an equal number of images of children wearing and not wearing eyewear and ensures that the dataset maintains a balanced distribution of skin tones, eye colors, and hair types (Figure 2). This would mean that the learning is generalized, rather than biased by irrelevant phenotypic traits. The methodology used in this study was a detailed and balanced approach to collecting and preprocessing facial expression datasets. Even though the term 'child' usually encompasses the age group of 0-18, the study mainly utilized photographs of children aged 0–15. This was because many datasets lacked precise age information, and it is also challenging to determine the age of individuals with DS. Additionally, since a vast percentage of children with DS experience vision problems and are likely to wear glasses, the dataset was perfectly balanced. It had pictures of children with DD, with some wearing glasses, while the rest were picture files of healthy children, both with and without glasses, in order to avoid bias during decision-making by the model.
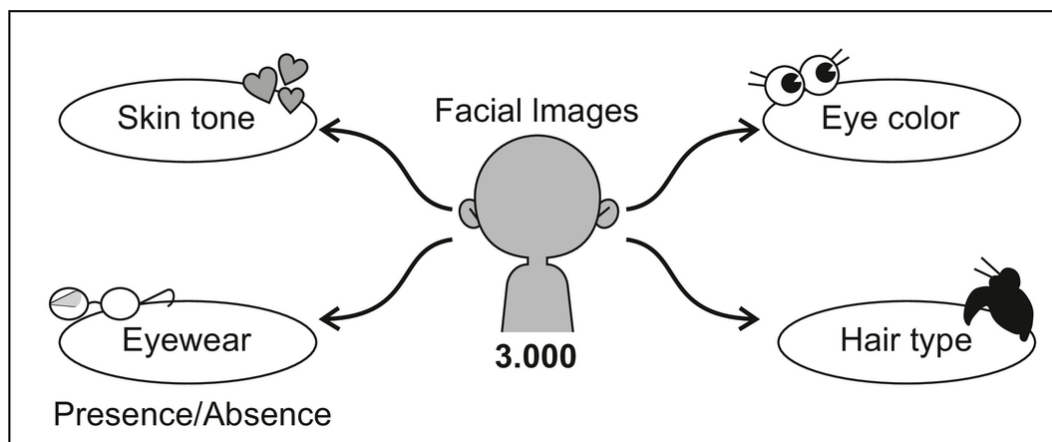
Fig. 2 Dataset description showing the different features of the down syndrome data.

Also, as skin color is not a determinant for DS, the dataset was curated in such a way that the representation of various skin colors was balanced and

not racially biased, thus ensuring that the model performed accurately in all skin tones. Likewise, eye color, being irrelevant to the determinant of DS, was balanced in the dataset to ensure that the model performed well in different eye colors. Thereby, the data collected showed a rich variation of hair colors, shapes, and conditions; such aspects cannot be determinant in this Down syndrome condition. Overall, this rich approach for preparing the dataset would come into play for a stronger, more generalized model toward being a more precise model at correctly distinguishing the facial expressions between the children and non-DS-affected ones. The presence or absence of DS has been annotated with each image in the dataset. Special care was taken during data collection to adhere strictly to privacy and ethical standards, with all data anonymized and collected with proper consent from guardians and under the approval of relevant ethical review boards.

Methodology

The methodology comprises the following components:

Data Preparation

The first step involved the preprocessing of images to the same size and format. All images were resized to 224 x 224 pixels, a commonly used size which balances between detail and computation efficiency and converted to grayscale to simplify the computation process while retaining all necessary features in the image to ensure accuracy in classification.

Data Augmentation

To make our model more overfitting-resistant and generalized across multiple facial expressions as well as orientations, we used data augmentation. All these included rotation, shifting up and down, left or

right, shear, and horizontal flipping. All parameters of the augmentation are handpicked in such a manner that they simulate real variations rather than distorting the very crucial features for the DS.

Deep Learning Models Used

We use several deep architectures to develop a strong benchmark of detection of DS based on facial images (Figure 3). Each was chosen by its unique strength and efficacy in an image classification task. Below we describe each model and further detail its specific function in our research.
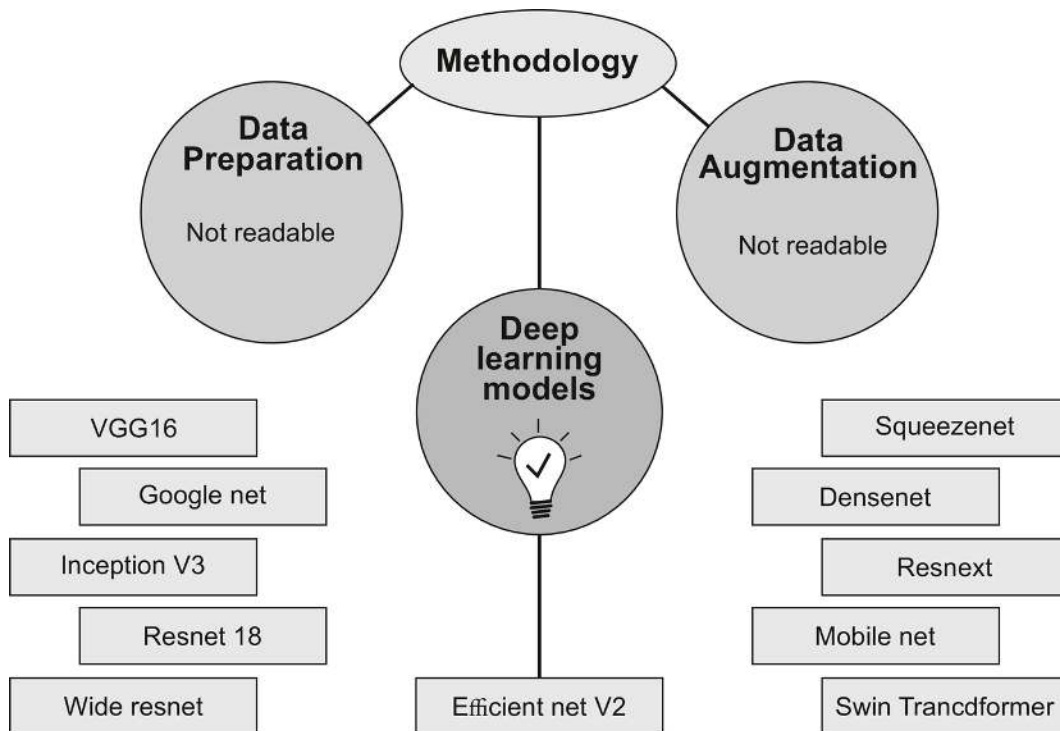
Fig. 3 Framework describing the development of cloud computing-based AI baselines for the detection of down syndrome patients.

1. **VGG16:** It is one of the deep CNNs invented by the Visual Geometry Group from Oxford (Szegedy et al., 2016). It consists of only simple 3 × 3 convolutional layers stacked on top of one another in increased depth, and max pooling handles size reduction. VGG16 is very

effective in image recognition and classification because it combines depth with a very uniform architecture. In our research, VGG16 is mainly employed because of its strong ability in feature extraction. The pre trained version on the ImageNet dataset offers a solid basis for features that may help in identifying DS.

2. **GoogLeNet (Inception V1):** GoogLeNet, or Inception V1, introduces a new module of inception that employs varying-sized convolution filters within the same level of the network for details of features captured at different scales (Szegedy et al., 2015). This model is far more deeper than other architectures but still needs fewer computations to run due to its well-structured design that minimizes the number of parameters. In our study, GoogLeNet captures important patterns of facial features, which are very essential in the identification of Down syndrome.

3. **Inception V3:** It is the variant of GoogLeNet where it is further improved, and it comprises enhancements, such as factorizing the convolutions in order to reduce the connections and operation, and then incorporating the batch **normalization (He et** al., 2016). This model facilitates more easy training of deep networks, as the model has expedited the process and better accuracy by the optimized structure. In our application, the high resolution capability of input images for facial images will make it fit well for the extraction of tiny features.

4. **(.ResNetl8:** It is a member of the family of Residual Networks, which applies skip connections or shortcuts to bypass some layers (Xie et al., 2017). This design eliminates the vanishing gradient problem, so the model can be much deeper without losing performance. ResNet18 is a relatively shallow version of the ResNet models and, therefore, finds a

good balance between complexity and performance, being well-suited for fast iterations in our experiments.

5. **Wide ResNet:** It replaces the standard ResNet with more channels for each layer, thereby widening the network rather than making it deeper (Sandler et al., 2018). This adaptation enhances learning abilities without any significant rise in computational cost associated with deep networks. In this study, the Wide ResNet is adopted to improve the capacity of the model in learning and representing complex relationships without expanding the depth.

6. **SqueezeNet:** This obtains AlexNet-level accuracy on ImageNet with 50x fewer parameters and with a much smaller model size (Tan & Le, 2021). Squeeze and expansion layers are utilized here to aggressively reduce the dimensionality of features in a network. In turn, this results in model size and computation savings, while maintaining accuracy. Such applications are very handy for our study in case one might need to deploy them on mobile or other low-power devices.

7. **DenseNet:** It generalizes over the idea of feature reuse in convolutional networks (Liu et al., 2021). It feeds forward from one layer to all other layers, so the feature-map from all previous layers would feed into each layer. So it maximally allows flow between layers within the network, and so it serves for capturing the patterns best within the data, as helpful for diagnosing DS.

8. **ResNeXt:** This is an extension of ResNet network architecture, including grouped convolutions (Swanson, 1997). The main strength of ResNeXt is that it allows the scaling of network width with a relatively small increase in complexity. This model combines depth and width, making it very effective for our image classification tasks.

9. **MobileNet:** It applies depthwise separable convolutions to construct thin, deep neural networks ([Cayli, 2023](#)). The convolutions considerably decrease the number of parameters from those networks which only include standard convolutions with the same depth in the networks. Due to this property, MobileNet is well suitable for those applications that have very critical latency requirements, such as mobile applications.

10. **EfficientNetV2:** It is the advanced form of basic EfficientNet models, with the help of which, the training speed also gets optimized besides the optimization of the parameters, and along with the parameters, efficient speed training with good performances is maintained (Simonyan & Zisseman, 2014). In the present research study, its architecture scaling nature makes efficient control of the model and computation dimensions. **(11) Swin Transformer:** This architecture adapts the Transformer for vision by computing self-attention within local windows before shifting these windows in subsequent layers ([Zagoruyko & Komodakis, 2016](#)). It combines the advantages of CNNs and Transformers and delivers great performance in capturing both global and local dependencies in images, which is very important in complex medical imaging analysis.

Model Development

This paper adopted the EfficientNetV2 model due to its scalable architecture and state-of-the-art performance in image classification tasks (Simonyan & Zisseman, 2014). The model was initially provided with weights pre trained on the ImageNet dataset. The latter leveraged the mechanism of transfer learning to significantly accelerate the learning speed and yield improved final performance due to prelearned feature representations.

Training

Training was done with a stochastic gradient descent optimizer with a learning rate of 0.001 and momentum of 0.9. For a binary classification problem, the traditional loss function used is the cross-entropy loss function. It was trained for 50 epochs with a batch size of 32. Also, early stopping was introduced to stop training if, for ten consecutive epochs, it did not improve the accuracy on the validation set and thus prevent overfitting. Table 1 describes the parameters that are utilized in the pre trained deep learning models.

Table 1 Details of the parameters used in the pre trained deep learning models. ⏎

Number of Epochs	10
Optimizer	Stochastic Gradient Descent
Loss function	Cross entropy loss
Learning rate	0.001
Momentum	0.9

Validation and Testing

The dataset was split into training (80%), validation (10%), and test (10%) sets. The validation set was used to monitor the model's performance and tune hyperparameters during training. After training, the model's performance was evaluated on the unseen test set to assess its generalization capabilities. The model's effectiveness was measured using accuracy on the test dataset.

Application-Specific Implementation for Clinical and Mobile Use

To ensure the practicality of the proposed model in real-world settings, we explored its deployment in both clinical and mobile environments. As we note many clinical settings have poor computational resources, especially those in remote or lowresource regions, our model was optimized with a

focus on lightweight deployment without sacrificing accuracy. The EfficientNetV2 architecture was used, as it is considered the best balance between achieving a high accuracy and requiring much less computational power on low-processing-capacity devices such as mobile phones and tablets.

- **Mobile Application Compatibility:** The model was tested for deployment on Android and iOS platforms using TensorFlow Lite, which allows healthcare providers and caregivers to conduct preliminary Down syndrome screening through a simple mobile application. The application uses the camera of the device to capture facial images and process them in real-time, providing immediate feedback on whether further clinical testing is advisable.
- **Clinical Application and Integration:** With clinical use, the model has been designed to integrate in electronic health records (EHRs) to facilitate the electronic incorporation of AI-based DS diagnostic support by the providers into patient profiles. That functionality helps the health service providers make an early and timely diagnosis of cases where features can be subtle in children with DS.

Hyperparameter Tuning

for hyperparameters of our EfficientNetV2 model and other models that have been benchmarked in this study, we performed a large hyperparameter tuning process based on grid search and cross-validation to maximize the accuracy of models and generalizability as well as minimize the time taken for training. Some of the main parameters include learning rate, batch size, momentum, and epochs.

- **Learning Rate:** A number of different learning rates within the range of 10^{-4} to 10^{-2} were tested and the effective one for the gradient-descent optimization is determined to be 0.001. This was chosen to provide stable convergence with minimal oscillation at training time.
- **Batch Size:** 16, 32, and 64. A batch size of 32 was optimal to find a balance between computational efficiency and the performance of the model. Smaller batches tended to introduce noise that slowed convergence, and much larger batches required significantly more memory, with very little performance benefits.
- **Momentum:** Momentum values between 0.5–0.9 were tested to avoid oscillations and speed up convergence. It was found that a value of 0.9 was optimal as it caused the model to converge without overshooting.
- **Number of Epochs:** We used early stopping with patience over 10 epochs. This avoided overfitting to a maximum of 50 epochs set although most models converged before the maximum within 30 epochs with early stopping. We have chosen this parameter by looking at cross-validation results. There was no indication that accuracy gains were any greater than 50 epochs..

Results

Our experimental results demonstrate the effectiveness of the deployed deep learning models in identifying Down syndrome from facial images ([Figure 4](#)).
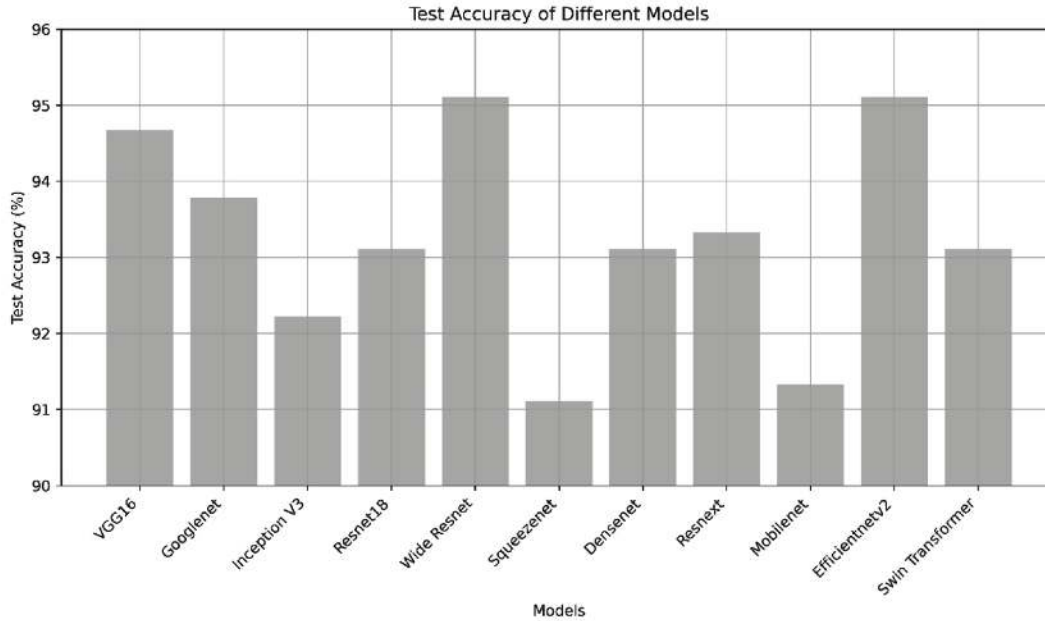
Fig. 4 Accuracy of different models on the test data for detecting down syndrome patients.

The models were evaluated based on their accuracy on the test set, which comprised 10% of the total dataset. Notably, EfficientNetV2 and Wide ResNet achieved the highest test accuracies at 95.11% each, underscoring their robustness in handling complex image-based classification tasks. VGG16 followed closely with an accuracy of 94.67%, while other models like GoogLeNet and ResNetl8 exhibited slightly lower yet competitive accuracies of 93.78% and 93.11%, respectively. The performance metrics indicate that models with deeper or more complex architectures did not necessarily outperform simpler or more efficient models, emphasizing the importance of model selection based on the specific characteristics of the data and task.

Table 2 shows the performance of the deep learning pre trained architectures on the test data for DS images. The test data is chosen as 10% of all the images for the down syndrome patients.

Table 2 Performance of different deep learning models for detection of Down syndrome patients. ↵

S.No.	Model	Test Accuracy (%)	Sensitivity (Recall)	Specificity
1	VGG16 (Szegedy et al., 2016)	94.67	95.77	90.29
2	Googlenet (Szegedy et al., 2015)	93.78	95.77	89.87
3	Inception V3 (He et al., 2016)]	92.22	93.42	90.29
4	Resnetl8 (Xie et al., 2017)	93.11	93.89	91.98
5	Wide Resnet (SAndler et al., 2018)	95.11	93.89	93.67
6	Squeezenet (Tan & Le, 2021)	91.11	89.20	93.25
7	Densenet (Liu et al., 2021)	93.11	95.30	91.14
8	Resnext (Swanson, 1997)	93.33	96.24	91.56
9	Mobilenet (Cayli, 2023)	91.33	95.77	95.78
10	Efficient Netv2 (Simonyan & Zisseman, 2014)	95.11	94.83	93.2
11	Swin Transformer (Zagoruyko & Komodakis, 2016)	93.11	94.37	92.40

Our experiment has revealed that the high performance metrics for EfficientNetV2 and Wide ResNet are in good agreement with those of (Cao et al., 12), who proved that EfficientNet architectures optimize both accuracy and efficiency through compound scaling. In the same way, Uddin et al. (2019) proved that Wide ResNet models could have superior performance because of their increased width, which allows them to have more feature maps to capture complex patterns in data. Our findings

support these results since depth and width of the networks both contribute to more complex analysis in image detailing, as for example in medical diagnostics. In contrast to this, our experiment's success with the Swin Transformer contributes to a growing body of literature ([Szegedy et al., 2016](#)) that indicates Transformers can handle global dependencies well on image data.

This capability is most useful in medical imaging, diagnosing, for example, conditions such as DS often depend on features that appear subtle but are globally distributed across the facial area. Work adds pediatric facial analysis to a list of applications of the transformer model to show they can complement CNNs: capturing different types of spatial hierarchies and dependencies. Latency and computational cost were measured to assess the practicability of models for mobile use. The lightweight architecture of EfficientNetV2 enabled high accuracy with a relatively low memory footprint, making it amenable to mobile use. Inference time was below 0.5 seconds on a mid-range mobile device and therefore efficient for practical use in real-time applications. Our findings are therefore not only consistent with recent research on the power of advanced deep architectures and techniques in image recognition but also extend these findings to pediatric medical diagnostics. With cutting-edge AI technology, our study contributes to ongoing efforts in improving early diagnosis and intervention strategies for DS that might improve patient outcomes and quality of life.

Conclusions and Future Work

Our research showed that even advanced AI baselines such as EfficientNetV2, Wide ResNet, and Swin Transformer are accurate in diagnosing Down syndrome through facial images of pediatric patients. High accuracy and robust performance are two factors which point towards being useful in early diagnostic processes for neurodevelopmental

disorders. Our study, by employing the best state-of-the-art deep learning techniques, bridges a gap in the currently existing methodologies for diagnosis and provides an avenue thatpromises enhancement of care and intervention strategies for patients. Moreover, the development of mobile applications on both Android and iOS platforms from our AI baselines presents significant promise in the area of widespread dissemination and access to diagnostic tools.

With the integration of trained models into user-friendly interfaces, healthcare professionals, caregivers, and even the patients themselves can use AI power for timely identification of DS for early intervention and support. Such mobile applications could serve as very useful tools in clinical settings, as well as community health initiatives and remote healthcare delivery in under-served regions. Beyond its direct clinical applications, the emergence of AI-based diagnostic tools for DS contributes to a larger context regarding mental health research and practice. In a non-invasive, efficient, and accessible manner, these tools lead to earlier intervention strategies in neurodevelopmental conditions which can really impact the lives of affected individuals.

Furthermore, data that such tools generate will also be helpful for conducting large-scale epidemiological studies and longitudinal research that provides insight into the prevalence, progression, and outcomes of DS and related disorders. Future work would use more datasets such as (Iandola et al., 2016). This paper marks a significant step toward leveraging AI technologies to solve such significant problems in health care, especially in neurodevelopmental disorders. Integrating cutting-edge deep learning approaches on quantum cloud computing with real-world clinical demands (Minitab 1995), we demonstrate how AI may transform diagnostic processes and improve patient outcomes. As we work to effectively

improve these methodologies, the ripple effects will be tremendous in mental health research, clinical practice, and public health initiatives, ushering in a new era of individualized and accessible healthcare for all.

Limitations

While this study gives good potential for the non-invasive identification of DS using AI, some drawbacks in the study have to be acknowledged.

i. **Limitations of the Dataset:** Though diverse in phenotypes, it was balanced in distribution; however, certain demographics or distributions of facial features like the rare ethnic groups are bound to be absent from such a dataset, affecting its generalization to underrepresented populations.

ii. **Bias Risk in Diagnosis from Images only:** Since facial images alone do not give complete diagnostic imaging to DS diagnosis, the model would risk bias with facial images. Patients might have an atypical feature or barely noticeable, which might lead to false negatives. The performances of such models would, therefore, improve by integration with other non-invasive indicators that could be through physiological and behavioral markers.

iii. **Challenges with Mobile Deployment:** Even though the model can be optimized for mobile, its accuracy and performance can depend on the quality of the images. In reality, it has the possibility of getting erroneous results because of low-lighting, motion blur or facial obstructions which degrade in uncontrolled environments.

iv. **Absence of Longitudinal Data:** The paper deals with static image-based diagnosis while DS is a dynamic disease that evolves over a patient's lifetime. Longitudinal data will help the evolution of

diagnostic markers at different ages. Thus, a more refined and age-specific model of diagnosis will be enabled.

Future Work

Future work is crucial in this regard to take this study forward to further enhance the performance of the model in terms of accuracy, adaptability, and clinical impact.

i. **Augmenting Diversity of the Dataset:** The future work should focus on increasing a diverse dataset. International health-related collaborations can help to access bigger datasets that include rare cases and underrepresented ethnic groups for more generalizability across various populations.

ii. **Multi-Modal Diagnostic Approach:** The other additions of non-invasive features will also include voice patterns, body posture or physiological data which may significantly enhance the DSM diagnosis accuracy. Multi-modal models can hence combine both facial analysis along with enhancing a more complete DSM diagnosis without any concerns of false negatives.

iii. **Improve the Robustness for the Real World:** For reliable performance in uncontrolled environments, future variants of the model could include some advanced pre-processing techniques against poor lighting, obstructions, or occlusions. Techniques involving image enhancement, adaptive brightness correction, motion stabilization, etc., improve accuracy in mobile applications.

iv. **Age Specific Models:** Using longitudinal data age-specific models can be developed in order to improve the diagnosis process. This should thereby enhance the accuracy for younger patients with less noticeable facial features and provide age-related diagnostic help.

v. **Clinical Trials and Large-Scale Validation:** Clinical trials and validations of the model in real-life healthcare settings would be the follow-up studies. Collaboration with healthcare providers can help in the evaluation of the clinical impact of the model, improvement of its performance, and compliance with regulatory standards, which will then pave the way for clinical approval and widespread adoption.

Software Availability

The implementation code with data can be found at the GitHub repository https://github.com/sifat29302/down_syndrome

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4 Advanced Biomedical Signal Decomposition and Denoising by Integrating Traditional and Machine Learning Techniques

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This chapter explores advanced methodologies for biomedical signal decomposition and denoising, focusing on both traditional and machine learning techniques. It starts with fundamental signal decomposition techniques, including Fourier Transform, Wavelet Transform, and Empirical Mode Decomposition (EMD), emphasizing their use in extracting and analyzing biomedical data. The chapter then delves into machine learning approaches, including Denoising Autoencoders, Convolutional Neural Networks, and Generative Adversarial Networks, which offer adaptive and robust solutions for enhancing signal quality. By integrating classical methods with modern AI techniques, the chapter provides a comprehensive

overview of state-of-the-art practices for improving diagnostic accuracy and treatment efficacy in healthcare.

Introduction

Biomedical data analysis is a rapidly growing field that is essential to contemporary healthcare, utilizing advanced signal processing and machine learning (ML) techniques to interpret complex physiological data for diagnostic, prognostic, and therapeutic purposes (Rangarajan & Krishnan, 2024). This chapter delves into the various methods of biomedical signal decomposition and denoising, emphasizing both traditional and cutting-edge ML approaches. Biomedical signals, such as Electrocardiogram (ECG), Electroencephalogram (EEG), Electromyogram (EMG), and Photoplethysmogram (PPG), are inherently non-stationary and often contaminated by noise from various sources, including physiological interferences, motion artifacts, and external environmental factors. The challenge of extracting meaningful information from these signals has led to the development of numerous signal processing techniques. This chapter introduces the key methods for biomedical signal decomposition, starting with the Fourier Transform, a classical method that decomposes signals into sinusoidal components based on their frequency.

Although powerful for stationary signals, Fourier Transform struggles with non-stationary biomedical signals. The Wavelet Transform overcomes this by offering a multi-resolution approach, capturing both time and frequency information, which is invaluable in the denoising and feature extraction of signals like ECG and EEG (Rafiee et al., 2011). Empirical Mode Decomposition (EMD) is presented as a data-driven, nonlinear method that breaks down signals into intrinsic mode functions (IMFs), making it well-suited for analyzing non-stationary biomedical signals. However, EMD suffers from mode mixing, an issue that is addressed by

Ensemble Empirical Mode Decomposition (EEMD), which adds white noise to stabilize the decomposition. Singular Value Decomposition (SVD) is also discussed as a powerful tool for noise reduction in multi-channel signals such as EEG. These traditional techniques lay the groundwork for biomedical signal processing but face limitations in real-time, adaptive scenarios where ML has emerged as a transformative force.

ML approaches have revolutionized biomedical signal denoising by providing adaptive, data-driven models that can learn the underlying structure of noisy signals (Subasi, 2019). Denoising Autoencoders (DAEs) are among the most effective tools, employing neural networks to reconstruct clean signals from noisy inputs by learning robust, intrinsic features of the data. DAEs excel in a variety of biomedical applications, especially in scenarios where noise is unpredictable and complex. Convolutional Neural Networks (CNNs), widely used in image processing, have also found utility in biomedical signal denoising due to their ability to learn spatial and temporal patterns in data. CNNs are particularly effective in real-time monitoring systems, such as wearable devices for ECG and PPG signal acquisition, where the signals are often contaminated with motion artifacts. Support Vector Machines (SVMs), though typically used for classification, are applied in regression-based denoising methods, providing high-performance denoising with limited datasets. SVMs are advantageous for smaller biomedical datasets, as they handle high-dimensional feature spaces and provide robust results even in the presence of noise. Independent Component Analysis (ICA) is a robust technique used to separate mixed signals into statistically independent components, making it particularly effective for eliminating artifacts like eye blinks and muscle noise from EEG recordings. ICA has proven essential in brain-computer interface applications, where precise signal interpretation is critical.

Principal Component Analysis (PCA) complements ICA by reducing the dimensionality of biomedical signals, which is particularly useful in large-scale datasets. PCA can be used to denoise signals by filtering out the lower principal components, effectively reducing noise while retaining the signal's core features.

Long Short-Term Memory (LSTM), a type of recurrent neural network (RNN), offers a unique advantage in biomedical signal denoising due to its ability to capture long-range temporal dependencies. LSTMs are particularly effective for time-series data such as ECG and EEG, where the denoizing process benefits from learning patterns over extended time sequences. By incorporating memory units, LSTMs can retain relevant information over time, making them well-suited for applications like real-time monitoring of physiological signals, where noise varies dynamically. Generative Adversarial Networks (GANs) have become a promising approach for denoising biomedical signals, utilizing adversarial training between a generator and a discriminator to generate high-quality, noise-free signals. GANs have shown great potential in enhancing the quality of biomedical images and signals, though they face challenges such as training instability and the need for large datasets. Despite these challenges, GANs have been successfully applied to improve the quality of EEG and ECG signals, offering new possibilities for enhanced diagnosis and monitoring. Finally, Reinforcement Learning (RL) introduces an adaptive approach to biomedical signal denoising. Unlike traditional models, which are static, RL learns dynamically through interaction with the environment. RL-based models can adjust their denoising strategies in real-time as they receive feedback on their performance, making them highly effective for applications in wearable devices and other real-time monitoring systems. RL's ability to adapt to changing signal conditions allows for improved

accuracy and robustness in denoising, especially in situations where signal characteristics fluctuate frequently.

This chapter provides a comprehensive exploration of both traditional and modern techniques for biomedical signal decomposition and denoising, emphasizing the growing role of ML in this domain. Traditional methods such as Fourier Transform, Wavelet Transform, EMD, and SVD are fundamental to biomedical signal processing but are increasingly being complemented by advanced ML techniques that offer more adaptive and scalable solutions. Denoising Autoencoders, CNNs, SVMs, ICA, PCA, LSTMs, GANs, and RL represent the future of biomedical signal denoising, providing more accurate and efficient means of processing noisy signals. As ML continues to evolve, the integration of these techniques with traditional signal processing methods will likely lead to further advancements in diagnostic accuracy, treatment efficacy, and overall patient care. This chapter serves as a resource for researchers, engineers, and healthcare professionals seeking to understand the state-of-the-art in biomedical signal denoising and its implications for the future of healthcare.

Biomedical Signals

Biomedical signals are electrical, chemical, or mechanical signals generated by physiological processes within the human body. These signals provide vital information about the body's function and state of health. Common examples include ECG, which monitors heart activity, and EEG, which tracks brain activity. The analysis of these signals is fundamental to diagnosing, monitoring, and treating various medical conditions. Biomedical signals can be either continuous, such as blood pressure or heart rate, or discrete, like counts of specific cells in a blood sample. The characteristics of these signals, including amplitude, frequency, and

waveform, carry critical information that can be analyzed to understand normal physiological functions or to detect abnormalities.

Biomedical data comes from a wide range of sources and can be broadly categorized into several types:

1. **Electrical Signals:** Generated by the electrical activity of the body, including:
   - **ECG (Electrocardiogram):** Monitors the electrical activity of the heart.
   - **EEG (Electroencephalogram):** Captures the electrical activity of the brain.
   - **EMG (Electromyogram):** Measures the electrical activity of muscles.
2. **Mechanical Signals:** Related to the mechanical movements of the body, such as:
   - **PPG (Photoplethysmogram):** Monitors blood volume changes in the microvascular bed of tissue.
   - **Respiratory Signals:** Track breathing patterns and lung function.
3. **Chemical Signals:** Detected through biochemical assays, including:
   - **Blood Glucose Levels:** Monitored for diabetes management.
   - **Hormone Levels:** Analyzed to assess endocrine function.
4. **Imaging Data:** Captured through various imaging techniques like:
   - **MRI (Magnetic Resonance Imaging):** Provides detailed images of organs and tissues.
   - **CT (Computed Tomography):** Combines X-ray images to create cross-sectional views of the body.
5. **Genomic and Proteomic Data:** Derived from genetic and protein analysis, these data types are crucial for understanding molecular mechanisms and personalized medicine.

Each type of data serves a specific purpose in monitoring and diagnosing health conditions, and they often complement one another when integrated into a comprehensive analysis.

PPG signals are optical signals that measure the changes in blood volume within the microvascular bed of tissue, typically obtained using a light source and a photodetector placed on the skin. PPG is widely used in wearable devices and clinical settings to monitor cardiovascular health, offering a non-invasive method to assess heart rate, blood oxygen saturation (Sp02), and other vital parameters. The significance of PPG signals in cardiovascular monitoring lies in their ability to provide continuous, real-time data about the cardiovascular system. These signals are particularly valuable for detecting and managing conditions such as arrhythmias, hypertension, and peripheral vascular diseases. By analyzing the amplitude, waveform, and frequency components of PPG signals, clinicians can gain insights into blood flow, arterial stiffness, and overall cardiovascular function.

Moreover, advancements in signal processing techniques, such as wavelet shrinkage and ML algorithms, have enhanced the accuracy and reliability of PPG-based monitoring systems. These innovations allow for more precise detection of subtle changes in cardiovascular dynamics, making PPG an essential tool in modern healthcare for early diagnosis and ongoing management of cardiovascular diseases.

Signal Decomposition

Signal decomposition is a fundamental process in signal processing that involves breaking down a complex signal into simpler components. This technique is essential for analyzing biomedical signals, which are often composed of multiple overlapping components, such as different frequency bands or noise elements. Decomposition allows for the extraction of

meaningful information from the signal, improving the accuracy of diagnostics and treatment decisions.

Fourier Decomposition

The Fourier Transform is a powerful mathematical tool used to decompose a time-domain signal into its constituent frequency components. This decomposition allows us to analyze the signal in the frequency domain, which is particularly useful for understanding the underlying periodicities, identifying dominant frequencies, and filtering noise from the signal (Gomez-E. et al., 2020) The Fourier Transform *X(f)* of a time-domain signal *x(t)* is defined as:

$$X(f) = \int_{-\infty}^{\infty} x(t)e^{j2\pi ft} dt$$

Wavelet Decomposition

Wavelet decomposition is particularly useful for analyzing non-stationary signals like biomedical signals, where frequency components vary over time. Unlike Fourier decomposition, which uses sinusoidal bases, wavelet decomposition uses scaled and shifted versions of a mother wavelet *c(t)*.

The continuous wavelet transform (CWT) is defined as:

$$Wx(a, b) = \frac{1}{\sqrt{a}} \int_{-\infty}^{\infty} x(t)\psi^* \left(\frac{t - b}{a} \right) dt$$

Where:

- *a* is the scale parameter, controlling the width of the wavelet.
- *b* is the translation parameter, determining the position of the wavelet.
- *ψ*(t)* is the complex conjugate of the mother wavelet *ψ(t)* For practical applications, the discrete wavelet transform (DWT) is often used:

$$Wx(m,n) = \sum_{k=-\infty}^{\infty} x(k)\psi^* \left(\frac{k-n}{2^m} \right)$$

Where:

- *m* represents the decomposition level (related to scale a).
- *n* represents the translation index.

Wavelet decomposition allows the signal to be analyzed at different scales, providing both time and frequency information. The Discrete Wavelet Transform (DWT) enables signal decomposition into approximation coefficients, representing low-frequency components, and detail coefficients, capturing high-frequency components, across multiple levels (Patil & Chavan, 2012; Brechet et al., 2007; Nielsen et al., 2006).

Empirical Mode Decomposition (EMD)

EMD is a data-driven technique used to decompose a signal into intrinsic mode functions (IMFs), which are simple oscillatory modes. Unlike Fourier or wavelet decomposition, EMD does not require a predetermined basis function, making it particularly suitable for non linear and non-stationary signals (Yousefi 2019; Schiecke et al., 2015).

The EMD process extracts IMFs from the original signal *x(t)x(t)x(t)* in an iterative manner, following these steps:

- Locate all local maxima and minima of the signal.
- Form an upper envelope by interpolating between the maxima and a lower envelope by interpolating between the minima.
- Calculate the mean of these two envelopes.
- Subtract this mean from the original signal to obtain a detailed signal.

- If the resulting detail signal meets the IMF criteria, it is extracted as an IMF; if not, the process is repeated. Mathematically, the signal *x(t)* can be expressed as:

$$x(t) = \sum_{i=1}^{N} IMF_i(t) + r_N(t)$$

Where:

- $IMF_i(t)$ are the intrinsic mode functions.
- $r_N(t)$ is the residual signal after N iterations.

Ensemble Empirical Mode Decomposition (EEMD)

EEMD is an advanced signal processing technique developed to overcome the limitations of the standard EMD. It is particularly useful for analyzing non linear and non-stationary signals, such as biomedical signals. It improves the reliability and robustness of the decomposition by addressing the mode-mixing problem inherent in EMD ([Colominas et al., 2014](#)).

The EEMD algorithm involves the following steps:

1. **Additive White Noise:** A small amount of white noise is added to the original signal *x(t)*. This generates a new signal $x_i(t)$ for the *i*-th realization:

$$x_i(t) = x(t) + \epsilon_i(t)$$

Where: $\epsilon_i(t)$ is the white noise with zero mean and a small standard deviation.

2. **EMD Application:** Apply the standard EMD to the noise-added signal $x_i(t)$ to obtain its IMFs:

$$x_i(t) = \sum_{k=1}^{K} IMF_{k,i}(t) + r_i(t)$$

Where: $IMF_{k,i}(t)$ are the IMFs for the i-th realization, and $r_i(t)$ is the residual signal.

3. **Ensemble Averaging:** Repeat steps 1 and 2 for N different realizations (i.e., different noise additions). For each IMF, take the ensemble average across all realizations:

$$IMF_k(t) = \frac{1}{N} \sum_{i=1}^{N} IMF_{k,i}(t)$$

This ensemble averaging helps in cancelling out the added noise while preserving the signal characteristics.

4. **Final Decomposition:** The original signal $x(t)$ is then decomposed as:

$$x(t) = \sum_{k=1}^{K} IMF_k(t) + r(t)$$

Where: $IMF_k(t)$ are the final IMFs obtained through EEMD, and $r(t)$ is the final residual.

Singular Value Decomposition (SVD)

SVD is a matrix decomposition technique often used in the analysis of multidimensional biomedical signals, such as those obtained from functional magnetic resonance imaging (fMRI) or EEG. SVD decomposes a matrix X into three matrices (Schanze, 2018, 2017):

$$X = U \Sigma V_T$$

Where:

- U and V are orthogonal matrices containing the left and right singular vectors, respectively.
- $\sum$ is a diagonal matrix containing the singular values, which represent the magnitude of each component.

SVD is useful for noise reduction, feature extraction, and dimensionality reduction in biomedical signal processing.

Machine Learning in Biomedical Signal Decomposition and Denoising

ML techniques have become increasingly effective in biomedical signal decomposition and denoising, offering adaptive, data-driven approaches that can outperform traditional signal processing methods (Suhasi, 2019). These ML techniques enable the extraction of relevant features, removal of noise, and decomposition of complex biomedical signals like ECG, EEG, PPG, and EMG with improved accuracy. ML in biomedical signal processing leverages algorithms that can learn patterns, structures, and noise characteristics from training data. These models can then be applied to new data to improve signal quality, enabling better diagnostics, monitoring, and prediction in biomedical applications. ML-based denoising methods typically rely on learning from large datasets of noisy and clean signals to optimize filters or decomposers that minimize noise without distorting critical information. Some of the popular techniques include supervised, unsupervised, and deep learning models (Figure 1).
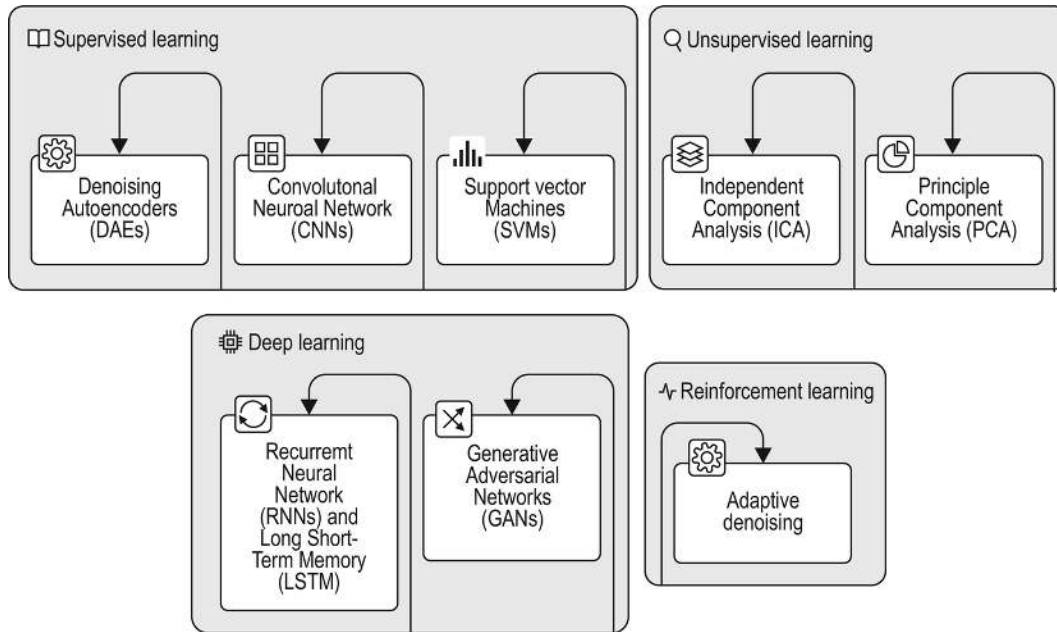
Fig. 1 Biomedical Signal Denoising Techniques.

Denoising Autoencoders (DAEs)

DAEs are a type of neural network designed to reconstruct clean signals or data from noisy inputs. They are an extension of basic autoencoders, which are used for unsupervised learning of efficient codings. DAEs are particularly useful for biomedical signal processing, where noise in data can arise from various sources such as sensor inaccuracies, environmental interference, or motion artifacts. They have been successfully applied to denoise signals like ECG, EEG, and EMG, improving the quality of biomedical data for diagnostic and analytical purposes (Chiang et al., 2019; Nurmaini et al., 2020).

Autoencoders are neural networks designed to compress input data into a lower-dimensional representation (encoding) and then reconstruct the original input from this representation (decoding), with the goal of minimizing the difference between the input and the reconstructed output. Unlike standard autoencoders, DAEs are specifically trained to remove noise from the input. This is done by intentionally adding noise during

training and teaching the network to recover the clean, original data from the corrupted input. This approach encourages the network to learn robust features that capture the core structure of the data, improving its ability to generalize to new noisy data.

The DAE's objective is to reconstruct the original clean signal x from the noisy version x_{noisy}. The goal of the network is to minimize the reconstruction loss between the clean signal and the denoised output:

$$L(x, \widehat{x}) = \|x - \widehat{x}\|^2$$

Where: x is the clean signal, z is the output of the DAE, representing the denoised signal and the loss function is typically a mean squared error (MSE) between the original and reconstructed signals.

DAEs generally have the same architecture as standard autoencoders, with the primary difference being in the training process, where noise is added to the input (Figure 2). The architecture consists of:
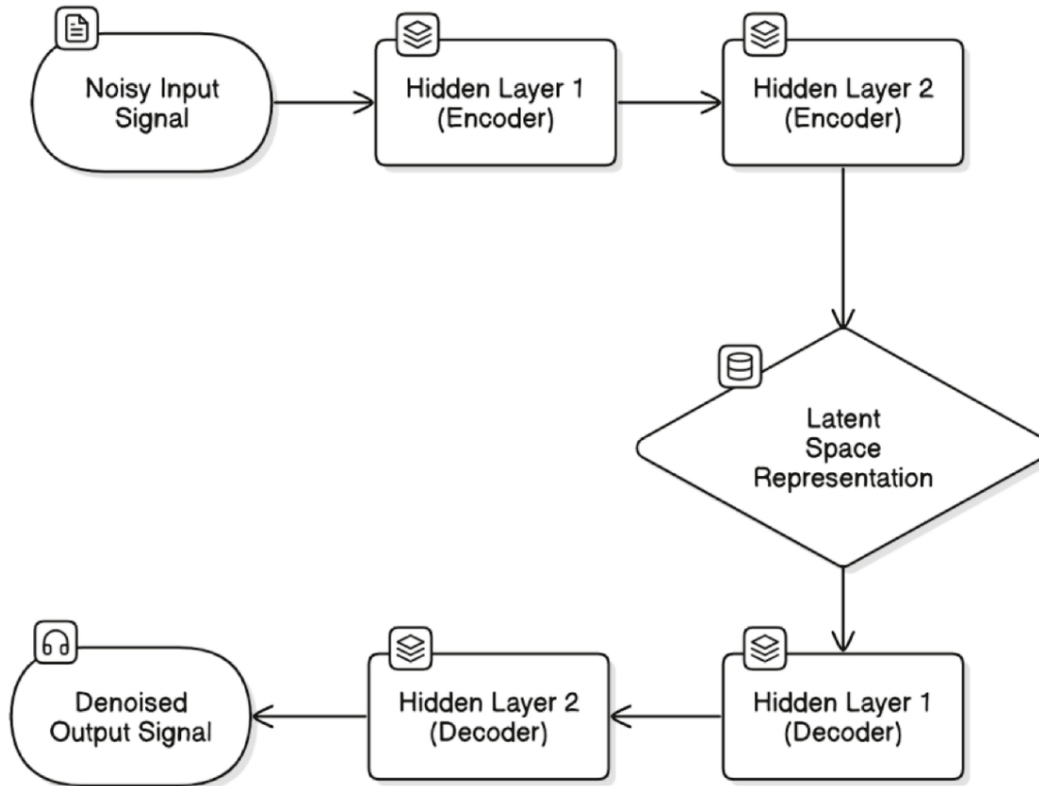
Fig. 2 Structure of an Encoding Denoising Algorithm.⏎

- ***Input Layer:*** The noisy input signal x_{noisy}, which contains both the signal and unwanted noise.
- ***Hidden Layers (Encoder):*** These layers transform the noisy input into a compressed latent representation. The number of layers and neurons depends on the complexity of the data.
- ***Latent Space:*** A compact representation of the essential features of the signal, learned by the encoder.
- ***Hidden Layers (Decoder):*** These layers map the latent representation back to the original data space.
- ***Output Layer:*** Produces the denoised signal, which is an approximation of the original clean signal.

Advantages of DAEs:

- DAEs learn robust, high-level representations of data, making them effective for denoising biomedical signals.
- Unlike traditional linear methods (e.g., Fourier or wavelet transforms), DAEs can capture complex, non linear relationships between noise and the underlying signal.
- DAEs trained on diverse datasets can generalize to denoise unseen data with different noise characteristics.

Limitations of DAEs

- DAEs require large amounts of labeled data (clean and noisy pairs) to learn effective representations.
- Training deep DAEs with multiple layers and parameters can be computationally expensive.
- DAEs may overfit to specific noise types, if the training dataset is not diverse enough, reducing their generalizability to other noise patterns.

Convolutional Neural Networks (CNNs)

CNNs are a type of deep learning model designed to process structured data with a grid-like structure, such as images. They are particularly effective for tasks like image recognition, object detection, and biomedical signal analysis, as they can automatically learn spatial hierarchies of features. Unlike traditional feed-forward neural networks, CNNs use local connectivity and weight sharing to minimize the number of parameters, enhancing computational efficiency while retaining crucial features ([Figure 3](#)).
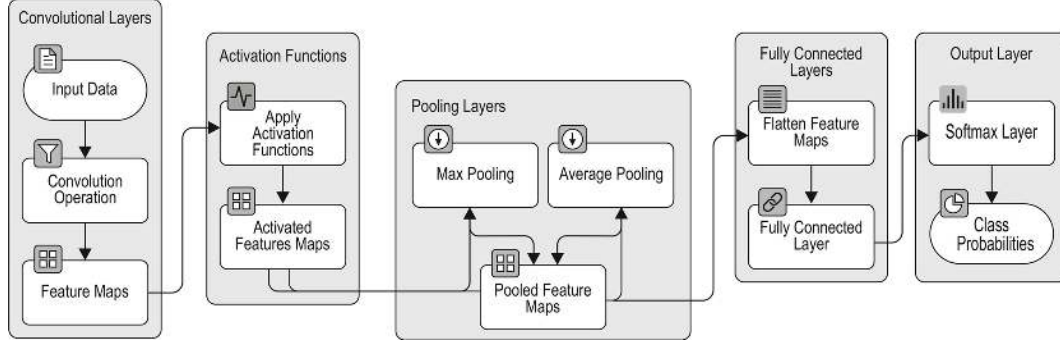
Fig. 3 CNN Architecture Flowchart.↵

The key components of a CNN include:

(a) Convolutional Layers

Convolutional layers are the core building blocks of CNNs. They consist of filters (also known as kernels) that slide over the input data and compute the dot product between the filter and a local region of the input. This operation helps in detecting local patterns such as edges, textures, and complex structures in the data (Hou et al., 2023; Jin et al., 2024). The convolution operation between a filter *F* and an input *I* can be expressed as:

$$(I*F)(i, j) = \sum_{m} \sum_{n} I(m, n) \cdot F(i - m \cdot j - n)$$

Where: *I(m, n)* is the input image or data, *F(i. j)* is the filter. The output of each convolutional layer is a set of feature maps that represent the activation of specific filters applied to the input. Each filter detects a particular feature (e.g., an edge or corner in images).

(b) Activation Functions

Following convolution, an activation function is applied element-wise to introduce non linearity into the network. The Rectified Linear Unit (ReLU) is the most widely used activation function:

$$f(x) = \max(0, x)$$

ReLU allows the model to learn complex patterns while maintaining low computational complexity. While other activation functions like sigmoid or tanh can also be used, ReLU is favored for its simplicity and its effectiveness in mitigating the vanishing gradient problem.

(c) Pooling Layers

Pooling layers reduce the spatial dimensions of feature maps, which helps lower the computational burden and prevent overfitting. Max Pooling, in particular, selects the maximum value from a small region of the feature map.

$$P_{\max} = F(i, j)$$

Average pooling takes the average of the values in the patch.

$$P_{\max} = \frac{1}{n} \sum_{i,j} F(i, j)$$

Pooling helps the network become invariant to small translations of the input, capturing the most important features while reducing dimensionality.

(d) Fully Connected Layers

After the convolutional and pooling layers, the feature maps are usually flattened into a **1D** vector and passed through one or more fully connected layers. In these layers, each neuron is connected to every neuron in the preceding layer. These layers integrate the high-level features extracted by the convolutional layers to make predictions.

(e) Output Layer

The final layer of a CNN is often a softmax layer in classification tasks, which converts the output into probabilities for each class:

$$P(y = k \mid x) = \frac{\exp\left(z_k\right)}{\sum\limits_{j} \text{ex}\left(z_j\right)}$$

Where: z_k is the output for class k.

Advantages of CNNs

- CNNs take advantage of local spatial features by using small filters that are locally connected, meaning they focus on small patches of the input. This reduces the number of connections compared to fully connected networks.
- The same filter (set of weights) is applied across the entire input, reducing the number of trainable and
- CNNs automatically learn a hierarchy of features, from low-level edges and textures in early layers to high-level shapes and objects in deeper layers.
- Pooling layers help CNNs become invariant to small translations of input data, making them robust to variations in the position of features.

Support Vector Machines (SVM)

SVMs are supervised learning algorithms used for tasks such as classification, regression, and outlier detection. An SVM is particularly powerful in high-dimensional spaces and performs well when the number of dimensions exceeds the number of samples. Its key strength lies in identifying an optimal hyperplane that best separates data points of different classes. The main objective of the SVM is to find a hyperplane that maximally divides the data points of different classes with the largest margin possible. This hyperplane is determined by a set of support vectors, which are the data points closest to the hyperplane. The margin, or the

distance between the hyperplane and the nearest data points, is maximized to create a robust decision boundary.

- *Linear SVM:* In cases where the data is linearly separable, SVM tries to find a hyperplane (a line in 2D, a plane in 3D, or a higher-dimensional equivalent) that divides the classes (Figure 4).
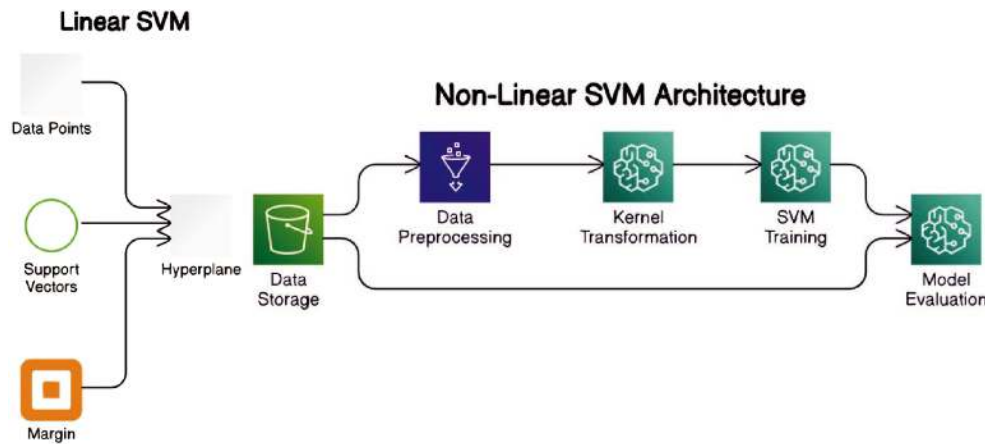

Fig. 4 Linear and Non-linear SVM Architectures.

- *Non-Linear SVM:* For non linear separable data, SVM can project the data into a higher-dimensional space using *kernels* to make the data linearly separable in that new space (Figure 4).

SVM can be applied to biomedical signal denoising through Support Vector Regression (SVR). The goal of SVR in this context is to fit a model to the noisy signal and predict a smoother, cleaner version of the original signal (Venkatesh et al., 2018; Kaur et al., 2021).

(a) SVR for Denoising

In SVR-based denoising, the noisy biomedical signal is treated as a regression problem. The algorithm learns a model that captures the underlying structure of the signal while ignoring the noise (Liu et al., 2019).

- The noisy signal is represented as $s_{noise}(t)$
- SVR aims to find a function $f(t)$ that best approximates the true signal $s_{clean}(t)$, minimizing the noise component.
- The optimization problem in SVR is similar to that of the SVM, but it focuses on fitting the signal by minimizing the error within a specified tolerance (ε-insensitive loss function).

The optimization objective becomes:

$$\frac{1}{2}\|w\|^2 \text{ subject to } |f(x_i) - y_i| \leq \epsilon \forall_i$$

Where: y_i represents the target signal values, and ϵ defines a margin of tolerance around the true signal values that accounts for noise.

(b) Kernel Trick for Non-linear Signal Denoizing

In many cases, biomedical signals exhibit non-linear patterns due to the complexity of physiological processes. SVR can be extended to non-linear denoising by applying a kernel function to map the signal into a higher-dimensional space. Common kernels include (Constantin et al., 2006):

- **Radial Basis Function (RBF) Kernel:** Effective for non-linear patterns in the signal.
- **Polynomial Kernel:** Suitable for signals with polynomial trends.

By applying these kernels, SVR can capture intricate signal structures and denoise more effectively than traditional linear methods.

SVM can also be used to classify and remove artifacts (undesired noise components) from biomedical signals. For example, in EEG signals, muscle artifacts or eye blinks are common sources of noise. SVM can be trained to

differentiate between clean signal segments and those contaminated by artifacts. The steps involved are:

- Extract relevant features from the signal that help distinguish between noisy and clean segments. These could include time-domain features (e.g., mean, variance) or frequency-domain features (e.g., power spectral density).
- Train the SVM classifier on labeled data where segments are marked as either `clean' or 'noisy'.
- Apply the trained SVM to new signal data to identify and remove or correct noisy segments, leaving behind a cleaner signal.

Advantages of Using SVM for Biomedical Signal Denoising

- SVM can handle large and complex feature spaces, making it suitable for biomedical signals with intricate noise patterns.
- The use of non-linear kernels allows SVM to adapt to different types of noise and signal structures, outperforming traditional linear denoising methods.
- SVM's margin maximization makes it robust to outliers, ensuring that denoised signals are not overly sensitive to occasional extreme values.

Challenges in SVM for Signal Denoising

- The performance of SVM-based denoising is highly dependent on the choice of kernel and hyperparameters (e.g., regularization parameter C, kernel width γ.
- SVM requires labeled data for training, and obtaining ground truth (clean signals) can be challenging in some biomedical applications.

- For large datasets or long biomedical signals, training SVMs can be computationally expensive, especially with non linear kernels.
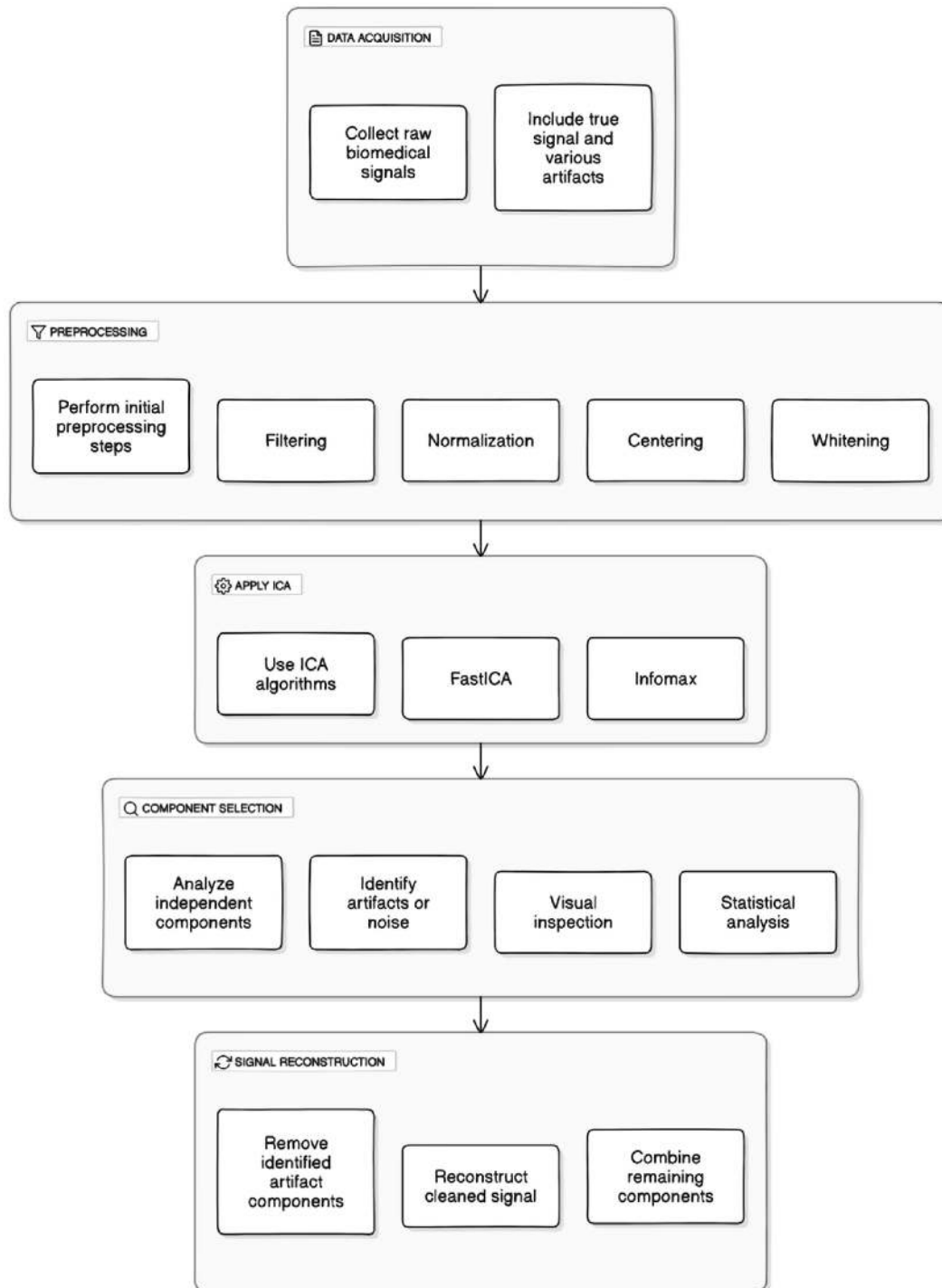
Independent Component Analysis (ICA)

Independent Component Analysis (ICA) is a computational technique used to separate a multivariate signal into additive, independent components. It is particularly useful in biomedical signal processing for isolating sources of noise or artifacts from the true signal of interest. ICA assumes that the observed signals are linear mixtures of underlying independent sources and aims to recover these sources (James & Hesse, 2004; Unguranu et al., 2004; Naik & Kumar, 2011).

ICA decomposes a signal matrix X into components that are statistically independent. For a set of n observed signals $X = \{x_1, x_2, ..., x_n\}$, ICA seeks to find a transformation matrix W such that the resulting components $S = \{s_1, s_2, ..., s_n\}$ are as statistically independent as possible. Mathematically, the ICA model can be expressed as:

$$X = AS$$

Where: X is the $m \times n$ matrix of observed signals, A is the $m \times m$ mixing matrix and S is the $m \times n$ matrix of independent components. The goal of ICA is to estimate A and S from X The recovered components S represent the original independent sources, and the mixing matrix A describes how these sources combine to form the observed signals (Figure 5).

Fig. 5 Architecture of Independent Component Analysis.

Types of ICA

a. **FastICA:** FastICA is a popular algorithm due to its efficiency and simplicity. It uses a fixed-point iteration approach to maximize non-Gaussianity, often based on kurtosis or negentropy ([Langlois et al., 2010](#)). The steps are:
- **Centering:** Subtract the mean from the data to ensure zero mean.
- **Whitening:** Transform the data to have unit variance and zero covariance.
- **Rotation:** Apply a rotation to maximize statistical independence, typically using non-Gaussianity measures.

b. **Infomax ICA:** Infomax ICA maximizes the entropy of the estimated sources to achieve independence. It employs a neural network-based approach to optimize a measure of information (entropy) between the estimated and observed signals.

c. **JADE (Joint Approximate Diagonalization of Eigenmatrices):** JADE uses joint diagonalization of several matrices to estimate the mixing matrix and the independent components. It is effective for cases where the sources are not strictly independent but can be approximately diagonalized.

Advantages of ICA for Denoising

- ICA is particularly effective for removing complex and mixed noise sources that traditional filtering methods might not address.
- ICA provides a clear separation of sources, making it easier to identify and remove specific types of artifacts or noise.
- ICA is designed to handle non-Gaussian distributions, making it suitable for many biomedical signals that do not follow Gaussian noise models.

Challenges in ICA for Denoising

- ICA relies on the assumption that sources are statistically independent, which may not always hold true in practice.
- Identifying which components correspond to noise or artifacts can be subjective and may require expert knowledge.
- ICA algorithms can be computationally intensive, especially for large datasets or real-time applications.

Principal Component Analysis (PCA)

PCA is a statistical method employed for dimensionality reduction and feature extraction. In biomedical signal denoising, PCA is effective in distinguishing signal components from noise by projecting the data into a lower-dimensional space, where the principal components (PCs) capture the maximum variance.

PCA transforms the original data into a new coordinate system where the axes (principal components) represent directions of maximum variance. The main goal is to identify the PCs that capture the most significant patterns in the data and reduce dimensionality while retaining important information. Given a dataset X with n observations andp features, PCA performs the following steps (Ye & Anne, 2004; Castells et al., 2007):

- Subtract the mean of each feature from the data to ensure zero mean.
- Calculate the covariance matrix C of the centered data to understand the relationships between features.

$$C = \frac{1}{n-1}X^T X$$

- Compute the eigenvalues and eigenvectors of the covariance matrix. The eigenvectors (principal components) indicate the directions of maximum variance, and the eigenvalues indicate the amount of variance in each direction.
- Transform the data onto the PCs to obtain a new set of features that represent the data in a reduced dimensionality.

PCA can be formulated as:

$$X = W \cdot Z$$

Where: X is the original data matrix, W is the matrix of eigenvectors (PCs) and Z is the matrix of projected data (scores on the PCs). The principal components are obtained from the eigenvectors of the covariance matrix C. Each PC is a linear combination of the original features.

In biomedical signal denoising, PCA is used to identify and remove noise components from signals by leveraging the PCs that capture the most variance in the data (Martis et al., 2012). The key steps in applying PCA for denoising are:

- **Data Acquisition:** Collect the raw biomedical signals, which may include both the true signal and noise.
- **Preprocessing:** Preprocess the data by centering it and, if necessary, normalizing it. This step ensures that PCA is applied correctly.
- **Apply PCA:** Perform PCA on the preprocessed data to obtain the PCs and their corresponding eigenvalues.
- **Identify Principal Components:** Analyze the eigenvalues to identify the PCs that capture the most variance. Typically, components with higher eigenvalues represent the more significant features of the data, while those with lower eigenvalues might correspond to noise.

- **Reconstruct Signal:** Reconstruct the signal using the selected PCs. Often, this involves retaining the top components that represent the true signal and discarding the lower components associated with noise.
- **Inverse Transformation:** Transform the data back to the original space to obtain the denoised signal.

Advantages of PCA for Denoising

- PCA reduces the dimensionality of the data, which can simplify subsequent analysis and improve computational efficiency.
- PCA focuses on retaining components that capture the most variance, which often includes the significant features of the signal while removing noise.
- By reducing the number of components, PCA can compress the data while preserving essential information, making it easier to handle and analyze.

Challenges in PCA for Denoising

- PCA assumes linear relationships between features. In some cases, biomedical signals may exhibit non linear characteristics that PCA might not fully capture.
- Identifying which PCs correspond to noise can be challenging. This often requires domain expertise and careful analysis.
- The PCs are linear combinations of the original features, which may not always be interpretable in the context of specific biomedical applications.

Comparison with Other Techniques

- **PCA vs. ICA:** While PCA focuses on capturing variance and reducing dimensionality, ICA separates independent sources and is effective for cases where noise sources are statistically independent. ICA might be more suitable for scenarios where the noise and signal sources are mixed in a complex manner.
- **PCA vs. Wavelet Transform:** Wavelet transforms provide time-frequency analysis and are effective for non-stationary signals. PCA, on the other hand, performs global dimensionality reduction and may not capture localized features as effectively as wavelets.

Long Short-Term Memory (LSTM)

Biomedical signals, such as ECG, EEG, and PPG, are often susceptible to noise from various physiological and external sources. While traditional denoising methods like low-pass filters or wavelet transforms are somewhat effective, they face limitations when handling complex, non linear, and non-stationary noise. LSTM networks, a type of RNN , have become a popular and reliable solution for denoising biomedical signals due to their ability to model sequential data and capture both short- and long-term dependencies. This makes them particularly well-suited for capturing the temporal dynamics inherent in biomedical signals. LSTM networks were specifically designed to overcome the shortcomings of traditional RNNs, such as the vanishing and exploding gradient problems. The vanishing gradient issue prevents standard RNNs from learning long-term dependencies, which are essential for time-series data like biomedical signals. LSTMs address this by incorporating a memory cell that retains information over extended periods and a gating mechanism that regulates the flow of information into and out of the memory cell (Yildrin, 2018) (Figure 6).
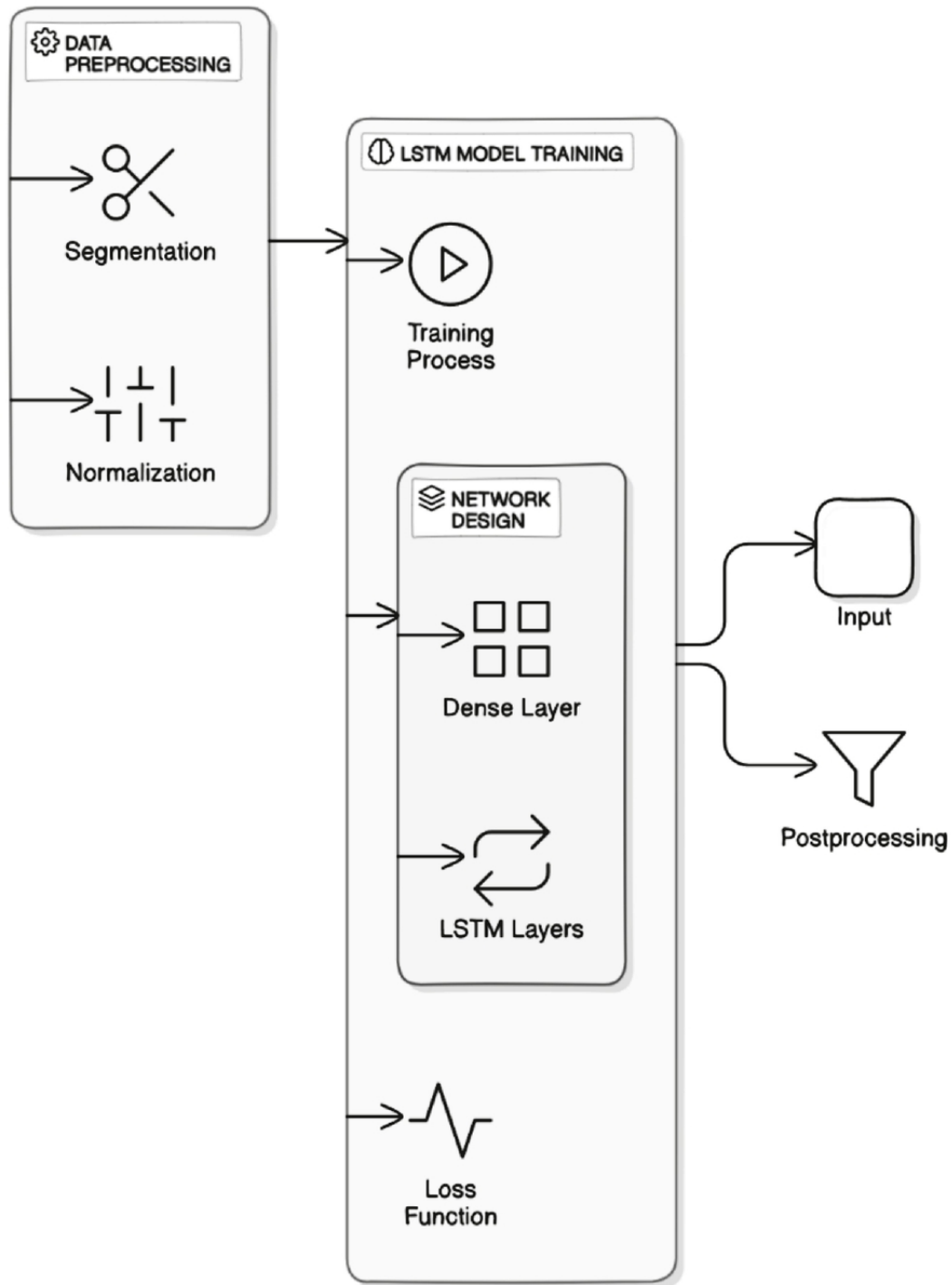
Fig. 6 Structure of LSTM Architecture.

Key Components of an LSTM Cell

The LSTM cell contains several components that control how information is updated:

- **Forget Gate:** Decides what information to discard from the memory.

$$f_t = \sigma(W_f \cdot \lfloor h_{t-1}, x_t \rfloor + b_f$$

Where: f_t is the forget gate's output (how much past information should be discarded), W_f is the weight matrix, h_{t-1} is the hidden state from the previous time step, x_t is the current input, b_f is the bias term, and σ is the sigmoid function, which constrains the output between 0 and 1.

- **Input Gate:** Controls what new information should be stored in the memory.

$$i_t = \sigma(W_i \cdot \lfloor h_{t-1}, x_t \rfloor + b_i$$

- Fig. 6 **Update Cell State:**

$$\tilde{C}t = \tanh(W_c \cdot \lfloor h_{t-1}, x_t \rfloor + b_c$$
$$C_t = f_t * C_{t-1} + i_t * \tilde{C}t$$

This step updates the cell state C_t, taking into account both the forget gate and the newly computed candidate values $\tilde{C}_t$.

- **Output Gate:** Determines what part of the cell state to output as the next hidden state.

$$o_t = \sigma(W_o \cdot \lfloor h_{t-1}, x_t \rfloor + b_o$$
$$h_t = o_t * \tanh(C_t)$$

The hidden state h_t is produced based on the updated cell state and the output gate's control.

Each of these gates has its own learned weights and biases, and it operates through activation functions (usually a sigmoid function for the gates and tanh for the cell state). These gates collectively allow the LSTM

to decide when to remember or forget information, thereby effectively modeling long-term dependencies. By using this gating mechanism, LSTMs are able to learn which parts of the data to remember and which parts to discard, making them particularly effective for processing biomedical signals that exhibit temporal dependencies ([Kusuma & Jothi, 2022](); [Hosny et al., 2020]()).

Biomedical signals, by their nature, are often noisy due to various internal and external factors:

- Physiological artifacts such as muscle movements or blinking in EEG signals.
- External noise such as electromagnetic interference in ECG or PPG signals.
- Motion artifacts in wearable devices capturing biomedical signals (e.g., heart rate sensors using PPG).

Traditional denoising techniques (such as band-pass filtering or wavelet denoising) can handle stationary noise well but may struggle with non-stationary, time-varying noise that occurs in biomedical signals. LSTMs, on the other hand, excel in handling non-stationary signals because of their ability to model complex temporal relationships and their dynamic memory management capabilities.

LSTM-based biomedical signal denoising involves several key steps:

(a) Preprocessing

1. *Normalization:* Before feeding the biomedical signal into the LSTM, it is important to normalize the data. This can be done by scaling the signal between a specific range (e.g., [0, 1]) to ensure that the LSTM can process the data effectively and avoid numerical instabilities.

2. **Segmentation:** Depending on the length of the biomedical signal, the signal may be divided into overlapping or non-overlapping windows of fixed size. This segmentation helps the LSTM handle long sequences more effectively and accelerates the learning process.

(b) Training the LSTM Model

1. **Designing the LSTM Architecture:** The LSTM architecture can be designed with one or more LSTM layers, depending on the complexity of the problem. Each LSTM layer captures temporal patterns in the input data. The final layer is typically a fully connected layer (dense layer) that maps the LSTM's output to the predicted denoised signal.
   - **Input Layer:** This layer accepts the noisy signal.
   - **LSTM Layers:** One or more LSTM layers process the temporal dependencies in the input.
   - **Dense Layer:** Maps the hidden state from the LSTM layers to the desired output (denoised signal).
2. **Loss Function:** The most commonly used loss function for denoising tasks is the MSE, which minimizes the difference between the predicted clean signal and the actual clean signal.
3. **raining Process:** The LSTM network is trained using an optimizer like Adam or RMSprop, which adjusts the network's weights and biases to minimize the MSE. The training involves backpropagation through time (BPTT), a specialized form ofbackpropagation that accounts for the temporal nature of the data.

(c) Inference and Post-processing

Once the LSTM model is trained, it can be used to denoise new biomedical signals. After obtaining the denoised signal from the model, post-processing

steps such as smoothing or further filtering may be applied to ensure that the signal is free of residual noise.

Applications of LSTM in Biomedical Signal Denoising

LSTMs have been applied to a wide range of biomedical signals for denoising purposes, demonstrating their ability to improve signal quality:

a. ***EEG Denoising*** EEG signals are often contaminated by artifacts such as eye blinks, muscle activity, and environmental noise. LSTMs have been used to model the clean EEG signal by learning its temporal dynamics and identifying and removing artifacts in real-time applications like brain-computer interfaces (BCI) or epilepsy detection.

- **Example:** LSTM networks have been applied to separate EEG signal components related to brain activity from artifacts caused by eye blinks and muscle movement, improving the signal's usability for diagnostic or neuroimaging purposes.

b. ***ECG Denoising*** ECG signals are frequently disrupted by motion artifacts, baseline wander, or power-line interference. LSTMs have proven effective in filtering out these types of noise while retaining the essential information about the heart's electrical activity, which is crucial for accurate heartbeat detection or arrhythmia diagnosis.

- **Example:** LSTM-based models can remove baseline wander and high-frequency noise from ECG signals, allowing for accurate detection of QRS complexes, a key feature in ECG analysis.

c. ***PPG Denoising*** PPG signals, commonly used in wearable health monitoring devices, are prone to noise from motion artifacts, particularly during physical activity. LSTMs have been utilized to

denoise these signals by learning the temporal relationships between the clean signal and noise artifacts.

- **Example:** LSTM models can filter out motion-induced noise from PPG signals, improving the reliability of heart rate and oxygen saturation measurements in wearable devices like fitness trackers or smartwatches.

Advantages of LSTM for Biomedical Signal Denoising

- LSTMs can model both short- and long-term dependencies in biomedical signals, making them ideal for capturing signal trends over time and distinguishing between signal and noise.
- Unlike traditional filtering techniques that assume a linear relationship between noise and the signal, LSTMs can model non linear interactions between the signal and noise, making them effective for complex denoising tasks.
- LSTM models learn to denoise the signal directly from the data, reducing the need for manual intervention and fine-tuning of parameters, as is required in conventional filters.
- LSTMs are able to retain critical signal characteristics (such as ECG waveforms or EEG patterns) while filtering out noise, ensuring that the signal remains diagnostically valuable.

Challenges in Using LSTM for Biomedical Signal Denoising

Despite their advantages, there are several challenges associated with using LSTMs for denoising biomedical signals:

- LSTMs require a substantial amount of clean and noisy signal pairs for training. Obtaining such datasets in biomedical domains can be

challenging, especially in real-world clinical environments where the noise patterns may vary.

- LSTMs are computationally more expensive than traditional filters, both in terms of training time and inference. This can be a limitation when real-time denoising is required, especially in portable or wearable devices.
- LSTMs can overfit to the training data, particularly if the training set is small or contains specific types of noise that may not generalize well to unseen data.

Generative Adversarial Networks (GANs)

GANs are a type of deep learning model designed to generate new data that mimics a given distribution. They consist of two main components: 1) a **generator** that tries to create realistic data, and 2) a **discriminator** that tries to distinguish between real and generated data. In recent years, GANs have been adapted for various applications, including biomedical signal denoising, due to their ability to model complex data distributions and learn to remove noise without explicit supervision ([Singh & Pradhan, 2020](#); Wang et al., 2022).

Biomedical signals, such as EEG, ECG, and PPG, are often contaminated by various sources of noise, including physiological artifacts, motion artifacts, and external interferences. Denoising such signals is crucial for improving diagnostic accuracy and reliability in healthcare applications. Traditional denoising techniques such as Fourier transforms, wavelet transforms, or linear filters may not effectively capture complex noise patterns. GANs offer a more flexible, data-driven approach to denoising by learning the underlying signal distribution and automatically filtering out the noise.

GANs consist of two neural networks, a generator (G) and a discriminator **(D),** which are trained simultaneously in a game-theoretic framework:

- **Generator (G):** The generator's role is to produce fake (denoised) data that looks as realistic as possible. In the context of biomedical signal denoising, the generator takes a noisy input signal and attempts to output a denoised version of the signal.
- **Discriminator (D):** The discriminator's role is to distinguish between real (clean) biomedical signals and the fake (denoised) signals generated by the generator. It is a binary classifier that outputs whether a given input is real or generated.

The objective of the generator is to fool the discriminator by producing signals that are indistinguishable from real, clean signals. The discriminator, on the other hand, tries to correctly identify which signals are fake (denoised) and which are real.

GANs are trained using a minimax game between the generator and the discriminator. The goal of the generator is to minimize the loss while the discriminator tries to maximize it. The loss function can be written as displayed in Figure 7. For biomedical signal denoising, the GAN architecture can be adapted as follows (An et al., 2022) :
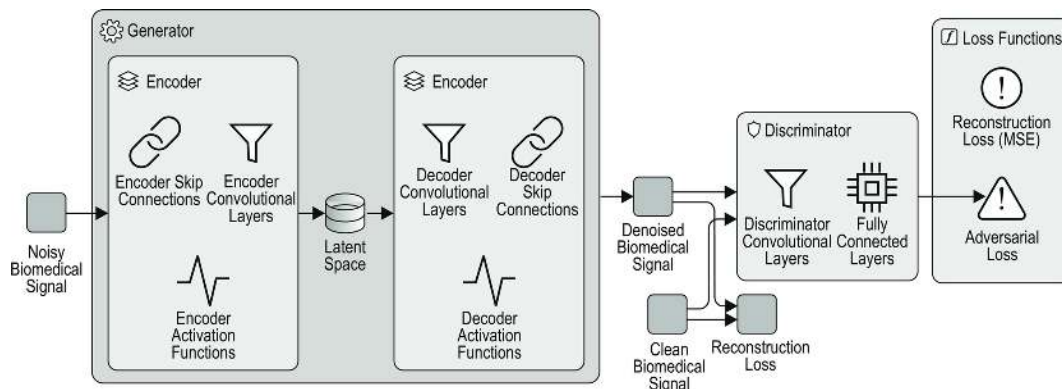
Fig. 7 Generator and Discriminator Architecture of GAN for Biomedical Signal Denoising.

a. **Generator Architecture:** The generator is typically designed as an **encoder-decoder** network, where the noisy biomedical signal is fed into the encoder, which compresses the signal into a latent space. The decoder then reconstructs the signal in a denoised form. Key features of the generator include:

   - **Convolutional Layers:** To capture local patterns in the noisy biomedical signal, the generator often uses convolutional layers. These layers can learn to detect noise patterns and filter them out.

   - **Skip Connections:** These connections, similar to those used in U-Net architectures, allow the model to retain important signal features from earlier layers, ensuring that essential biomedical signal characteristics are not lost during the denoising process.

   - **Activation Functions:** Non-linear activation functions such as ReLU or LeakyReLU are commonly used in the generator to model complex relationships between the noisy input and clean output.

b. **Discriminator Architecture:** The discriminator is often a CNN that classifies whether a given signal is real (clean) or fake (denoised). The discriminator's structure typically involves:

   - **Convolutional Layers:** To extract features from the biomedical signal, the discriminator uses convolutional layers. These layers allow the discriminator to learn patterns in real clean signals that distinguish them from generated signals.

   - **Fully Connected Layers:** After feature extraction, fully connected layers combine the features and classify whether the signal is real or generated.

c. **Loss Function Modification:** In standard GANs, the loss function focuses on classifying real vs. fake data. For denoising applications, an additional loss term is often introduced to ensure that the generated signal is close to the original clean signal. This is called the **reconstruction loss:**

$$L_{\text{recon}} = E_{x_{\text{clean}}, x_{\text{noisy}}} \| G\left(x_{\text{noisy}}\right) - x_{\text{clean}} \|_2^2$$

This loss measures the MSE between the clean signal and the denoised signal generated by the GAN. Combining this with the adversarial loss helps the generator produce more realistic and accurate denoised signals.

Training a GAN for biomedical signal denoising is a delicate process, as it requires balancing the performance of both the generator and discriminator. The typical training procedure involves alternating between training the generator and the discriminator:

1. **Training the Discriminator:** The discriminator is trained on pairs of real (clean) signals and generated (denoised) signals. It learns to classify whether each signal is real or generated.
2. **Training the Generator:** The generator is trained to produce denoised signals that can fool the discriminator into classifying them as real. The generator's loss function combines both the adversarial loss (from the discriminator) and the reconstruction loss (from the clean signal).
3. **Optimization:** The generator and discriminator are optimized using stochastic gradient descent (SGD) or one of its variants such as Adam. Due to the adversarial nature of the training, fine-tuning the learning rate and balancing the updates between the generator and discriminator is crucial for stable training.

Training GANs for Biomedical Signal Denoising

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Applications of GANs in Biomedical Signal Denoising

GANs have been successfully applied to a variety of biomedical signals, where they have shown strong performance in reducing noise while preserving essential signal characteristics.

a. **EEG Signal Denoising:** EEG signals are commonly contaminated by muscle artifacts, eye movement, and electrical interference. GANs have been used to denoise these signals, preserving the underlying brain activity patterns crucial for applications such as brain-computer interfaces (BCIs) and epilepsy diagnosis.
   - **Example:** A GAN-based model can be trained to remove muscle artifacts from EEG signals during physical activity, enhancing the

quality of the recorded brain signals and improving the accuracy of neural decoding algorithms.

b. **ECG Signal Denoising:** ECG signals are often corrupted by noise from sources such as motion artifacts, baseline wander, and electrical interference. GANs can effectively remove these types of noise, preserving the QRS and other critical features used in cardia

- **Example:** GANs have been used to filter motion artifacts from wearable ECG devices, resulting in cleaner signals that improve the detection of arrhythmias and other heart conditions in ambulatory monitoring.

c. **PPG Signal Denoising:** PPG signals, used in wearable heart rate monitors and pulse oximeters, are vulnerable to noise from motion and environmental interference. GANs can denoise PPG signals, improving the accuracy of heart rate and blood oxygen saturation measurements.

- **Example:** A GAN-based model trained on PPG data from fitness trackers can denoise the signals captured during exercise, reducing motion artifacts and yielding more reliable health metrics.

Advantages of GANs for Biomedical Signal Denoising

- GANs are capable of modeling complex, non-linear noise patterns that traditional denoising techniques (e.g., linear filters, wavelet transforms) struggle to handle. This makes them particularly suited for biomedical signals, where noise can arise from a wide range of physiological and external sources.
- Unlike traditional methods that rely on predefined filters and assumptions about the nature of the noise, GANs learn directly from

the data. This data-driven approach allows them to adapt to different types of noise, providing more robust and generalizable denoising solutions.

- GANs provide an end-to-end framework for biomedical signal denoising, where the entire process—from noisy input to clean output—is learned automatically. This reduces the need for manual feature extraction and parameter tuning, streamlining the denoising pipeline.

- One of the key advantages of GANs is their ability to retain important signal features (e.g., P-waves and QRS complexes in ECG signals, or spike trains in EEG signals) while removing noise. This ensures that the denoised signal remains diagnostically useful.

Challenges in Using GANs for Biomedical Signal Denoising

Despite their promise, GANs face several challenges in the context of biomedical signal denoising:

- GANs are notoriously difficult to train due to the adversarial nature of the generator and discriminator. If the discriminator becomes too powerful, the generator may struggle to improve, leading to poor denoising performance. Conversely, if the generator becomes too strong, the discriminator may fail to learn, resulting in mode collapse, where the generator produces only a limited variety of outputs.

- Training GANs typically requires a large amount of paired noisy and clean biomedical signals. In many clinical settings, obtaining such data is difficult, particularly for rare or hard-to-capture physiological events. Additionally, the variability in noise types across different patients and environments can make it challenging to generalize the GAN model to new data.

- While GANs can produce high-quality denoised signals, the underlying process by which they achieve this is often opaque. This lack of interpretability can be a drawback in clinical applications, where the ability to understand and explain the denoising process is critical for regulatory approval and clinician trust.
- GANs are computationally expensive to train, requiring powerful hardware (e.g., GPUs) and significant time for convergence. In real-time biomedical monitoring applications, this can be a limiting factor, especially for resource-constrained devices such as wearables.

Reinforcement Learning (RL) for Adaptive Biomedical Signal Denoising

RL offers a promising adaptive approach to biomedical signal denoising, where an agent interacts with an environment and learns optimal denoising strategies through trial and error. This framework allows the system to learn dynamically and adapt to varying noise levels, noise patterns, and signal characteristics over time. RL-based adaptive denoising techniques are especially useful for biomedical signals such as ECG, EEG, EMG, and PPG, which can exhibit non-stationary noise and variability depending on physiological conditions.

In RL, an agent learns to make decisions by receiving feedback in the form of rewards from its environment. The goal of the agent is to maximize cumulative rewards over time by taking actions that lead to desired outcomes. In the context of biomedical signal denoising, the agent learns to apply various denoising operations (actions) to noisy signals in a way that maximizes the quality of the denoised signal (reward).

Key components of reinforcement learning for adaptive denoising include (Mahmud et al., 2018; Alolaiwy et al., 2021):

- **Agent:** The denoising algorithm or system that makes decisions about how to process the noisy signal.
- **Environment:** The biomedical signal (e.g., ECG or EEG) and its noise characteristics, which change over time or across different segments.
- **Actions:** The denoising techniques or filters applied to the signal (e.g., thresholding, wavelet shrinkage, adaptive filtering).
- **State:** The current representation of the noisy biomedical signal (e.g., time-frequency features, noise characteristics, or statistical properties).
- **Rewards:** A measure of signal quality or denoising performance, such as Signal-to-Noise Ratio (SNR), MSE, or correlation with a clean reference signal.

RL Workflow for Biomedical Signal Denoising

The RL-based denoising system works through iterative interactions with the environment, where the agent learns to improve its performance over time. The typical workflow includes the following steps:

1. **Initialization:** The agent starts with a noisy biomedical signal, and it applies an initial denoising action based on its current policy (a set of rules or strategy for selecting actions).
2. **Observation and State Representation:** The agent observes the effects of the action by analyzing the resulting signal, such as how much noise has been removed or what features are preserved. The state of the environment, which represents the current condition of the signal, is updated.
3. **Reward Calculation:** The agent receives a reward based on the quality of the denoised signal. For example, a higher reward is given if the SNR improves or if the signal is closer to the clean reference. The

reward function encourages the agent to prioritize actions that lead to better denoising.

4. **Action Selection (Policy):** The agent selects the next denoising action based on its current policy, which may be exploratory (trying new actions) or exploitative (using known good actions). This policy evolves as the agent learns from previous actions and rewards.

5. **Training the Agent (Updating Policy):** The agent adjusts its policy using reinforcement learning algorithms (e.g., Q-learning, Deep Q-Networks, or Policy Gradient Methods) to improve future decision-making based on accumulated rewards and observed states.

This process repeats until the agent converges on an optimal denoising strategy that adapts to the characteristics of the signal and noise.

Advantages of RL for Adaptive Denoising

- **Dynamic Adaptation:** RL-based denoising systems can adapt in real-time to changing noise conditions or non-stationary signal characteristics. This is particularly useful for biomedical signals that exhibit variability over time or in different physiological states.

- **No Need for Fixed Filters:** Unlike traditional denoising methods that rely on fixed filters (e.g., wavelet or Fourier-based techniques), RL allows for dynamic decision-making. The agent can learn which denoising technique is most effective for a given signal segment and apply it adaptively.

- **Self-Learning Capability: RL** systems can learn to denoise biomedical signals without prior knowledge of the exact noise type or characteristics. Over time, the agent becomes better at recognizing patterns of noise and applying the right actions to mitigate it.

- **Optimization of Multiple Criteria:** The reward function in RL can be designed to balance multiple objectives, such as noise reduction, preservation of key signal features, and computational efficiency. This makes RL-based denoising highly customizable for specific biomedical applications. Several reinforcement learning algorithms can be adapted for signal denoising:

- **Q-learning:** A widely used RL algorithm that learns a value function for each state-action pair, representing the expected reward for taking an action in a particular state. For signal denoising, Q-learning can help the agent select the best denoising technique based on the signal's noise characteristics.

- **Deep Q-Networks (DQN):** This combines Q-learning with deep neural networks, allowing the agent to handle high-dimensional states, such as complex time-frequency representations of biomedical signals. DQN can help the agent process more sophisticated signals, such as multichannel EEG or complex ECG patterns.

- **Policy Gradient Methods:** These methods optimize the policy directly, allowing for more flexible decision-making in continuous action spaces. Policy gradient methods can be useful when the denoising actions involve continuous parameter adjustments, such as selecting optimal noise thresholds or adaptive filter settings.

Examples of Adaptive RL-based Biomedical Denoising

Several biomedical signal types can benefit from RL-based adaptive denoising:

- **ECG Denoising:** ECG signals are often contaminated by noise from muscle contractions, breathing, and electrical interference. An RL-based denoising system could learn to adaptively remove different

types of noise depending on the context (e.g., during physical activity versus rest) while preserving diagnostic features such as the P-QRS-T wave complex.

- **EEG Denoising:** EEG signals are affected by various artifacts such as eye movements, muscle activity, and environmental noise. RL can help to dynamically adjust denoising parameters to remove these artifacts while retaining important neural activity patterns for BCIs or epilepsy detection.

- **PPG Denoising:** PPG signals, commonly used in wearable devices for heart rate and blood oxygen monitoring, are sensitive to motion artifacts. RL-based denoising can adapt to motion intensity and remove artifacts in real-time, ensuring accurate physiological measurements.

Conclusion

This chapter has explored the critical methodologies and ML techniques for biomedical signal decomposition and denoising, emphasizing their importance in improving diagnostic accuracy, treatment efficacy, and overall healthcare outcomes. Biomedical signals, such as ECG, EEG, and PPG, often contain invaluable information about physiological processes, but they are typically contaminated with noise from a variety of sources. Efficient denoising methods are therefore essential to ensure that relevant features are accurately extracted and interpreted by healthcare professionals. Traditional signal decomposition techniques, such as Fourier Transform, Wavelet Transform, EMD, EEMD, and SVD, offer foundational tools for breaking down complex biomedical signals into simpler components. These methods have proven effective across a wide range of applications but are limited by their inability to adapt dynamically to the highly variable and non-stationary nature of real-world biomedical signals.

The integration of ML into biomedical signal processing marks a transformative step in the field. Data-driven approaches such as DAEs, CNNs, SVMs, ICA, and PCA have provided scalable, adaptive solutions for denoising biomedical signals, pushing the boundaries of what can be achieved in terms of signal clarity and feature extraction. In particular, DAEs leverage deep learning to learn complex noise patterns and effectively remove them, while CNNs offer exceptional performance in real-time signal processing environments due to their ability to capture spatial and temporal relationships in data. SVMs, though traditionally used for classification, have also shown strong performance in denoising applications, especially in scenarios where data is limited. ICA and PCA, which focus on blind source separation and dimensionality reduction, respectively, have also contributed significantly to artifact removal and noise reduction, particularly in multichannel signals like EEG and EMG.

Advanced methods like LS TM networks and GANs represent the next frontier in biomedical signal denoising. LSTMs, with their ability to capture long-term dependencies in time-series data, are particularly well-suited for denoising applications in continuous, real-time monitoring scenarios such as ECG and EEG analysis. GANs, through their adversarial learning framework, provide a novel approach to generating high-quality denoised signals, though they still face challenges in terms of training complexity and data requirements. Finally, RL introduces an innovative adaptive framework for biomedical signal denoising, offering a dynamic, real-time approach that learns from feedback and improves over time. This is particularly useful in wearable health monitoring devices, where the nature of the noise and the signal can change unpredictably.

Looking ahead, the future of biomedical signal denoising lies in the continued convergence of traditional signal processing techniques and

machine learning. While ML offers adaptive, data-driven solutions that can handle complex and non-stationary signals, the robustness and interpretability of traditional methods remain valuable. The integration of these approaches will likely lead to the development of more sophisticated denoising frameworks that provide higher accuracy, real-time adaptability, and improved diagnostic capabilities. However, challenges remain, including the need for larger, high-quality datasets for training ML models and the computational demands of deep learning architectures like GANs and LSTMs. As these challenges are addressed, the field of biomedical signal denoising will continue to evolve, offering enhanced tools for clinicians and engineers, ultimately contributing to better patient care and more accurate medical diagnoses.

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5 Enhanced Retinopathy Detection Using Nested U-Net for Red Lesion Segmentation in Retinal Fundus Images

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Blindness, in the working age, can result from retinopathy, an eye condition that spreads quickly. Approximately 35–40% of the 245 million individuals in the world have eye illness. This arises when there is impairment to the plasma pitchers in the human eye's retina. A leak from the injured blood vessels eventually results in dark patches in our eyesight, which are caused by hypoxia, insufficient blood supply, and neuron collapse. Since it is a quiet vision issue, yearly examinations are important

because early detection and successful treatment yield positive outcomes. Deep learning is developing quickly and steadily, turning into a useful method for providing an engaging answer to image analysis issues. To help find people who might have retinopathy, a Nested U-Net architecture is used to separate red lesions in retinal fundus pictures. These lesions are important signs of retinopathy. According to the discoveries, an automation technique could be useful in assisting eye consultants in detecting and diagnosing retinopathy early on, which would eventually boost the patients' health. Deep learning-based segmentation makes this method better at finding retinopathy than manual assessment because it is more accurate and faster.

Introduction to Diabetic Retinopathy

The typical age of the population is rising, the number of entities living as adults is increasing in many lands across the world, and the sickness rate is unstable toward non-communicable diseases and disabilities as socioeconomic grade and life principles rise. The normal way of life of adult residents is significantly wedged by visual impairment or loss of vision. Adults with visual impairments tend to be more miserable and anxious and have lower rates of novelty in the labor market. Visual damage and blindness ([Seoud et al., 2015](#)) in adulthood are accompanied with a higher risk of falls and cracks, a higher chance of early admission to care facilities, lack of touch, and aberrant gait.

All-inclusive, the number of people grieved from sensible to more severe visual loss is rising as a result of population aging. The roots of childhood eyesight loss diverge significantly between nations. Thus, retinopathy of prematurity is the main cause in working-class nations, while cascades and diabetic retinopathy are the prime causes in lower-class countries. One of the core causes of vision impairment in adult residents universally is still an
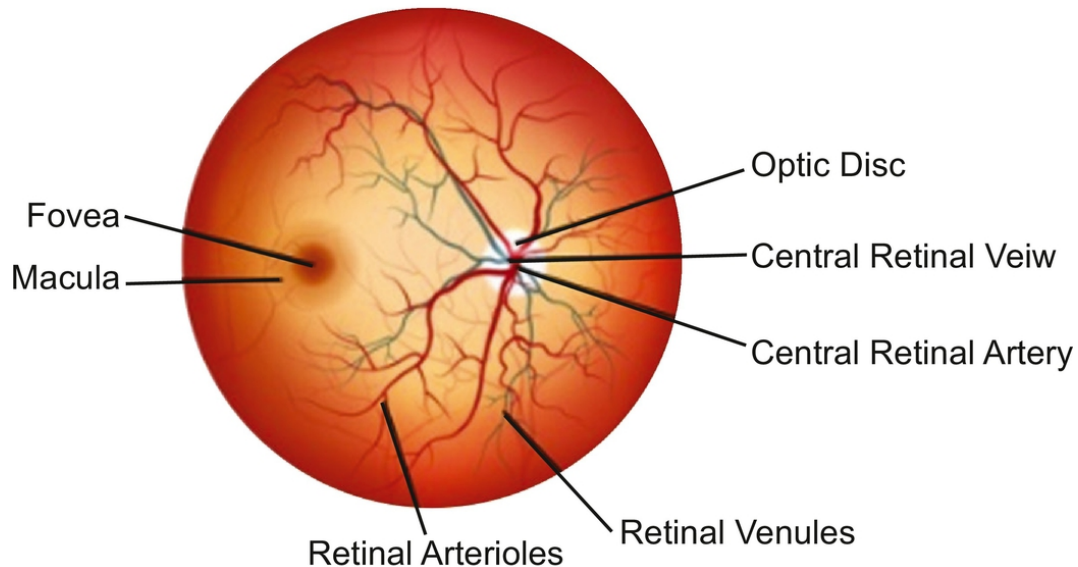
uncorrected refractive error and hypertensive retinopathy. The number of blind individuals is more than eight times more than in high-income countries. Ethnic minorities, indigenous peoples, mature people, and rural societies are all strangely squeezed.

Without access to routine check-ups, care, and treatment, eye diseases counting near or wisdom, glaucoma, and cataracts may decline, making daily life idiotically challenging. People in need of eye repair should have access to it without suffering economically. The leading causes of chronic blindness are: retinopathy from diabetes, high blood pressure, retinopathy of prematurity, vitamin-A shortage, Age-related Macular Degeneration (AMD), trachoma, and acute glaucoma. Both age-related blindness and blindness from wild diabetes are growing globally.

There are over 2.3 billion visually impaired people in the world, and over a billion of them are compelled to live in dangerous or obvious situations just because they are unable to get the support they require. In at least 1 billion cases, or about half of these, vision loss could have been avoided or is neglected are the main reasons why so many persons over the age of 50 are blind (Lancet Global Health, 2020). Figure 1 shows the 15.3 million cases of cortical cataract, 3.5 million of acute glaucoma, 2.3 million having refractive fault, 1.8 million cases of AMD, and 0.86 million suffering (Shaw et al., 2010) diabetic retinopathy.
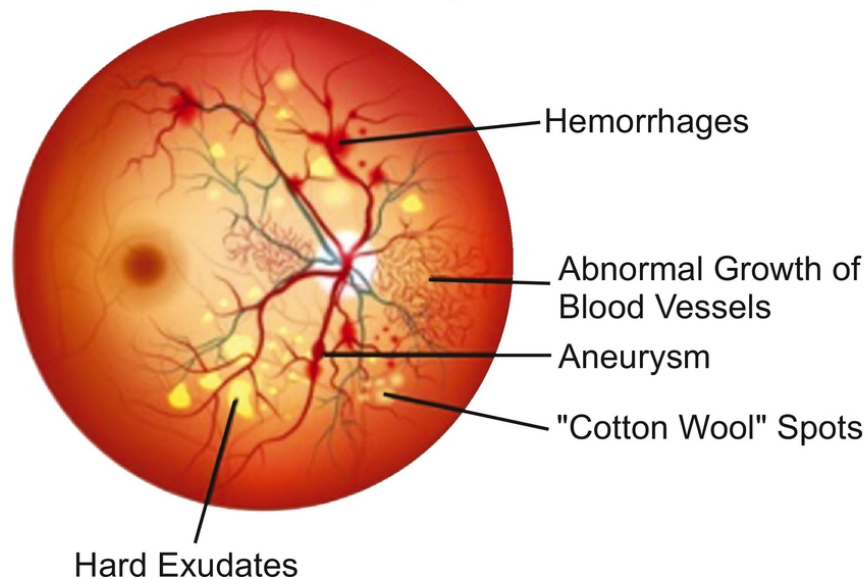
Fig 1 Primary Cause of Blindness.

Diabetic Retinopathy is the most public retinal affliction and one of the most severe eye complaints (Sivakamasundari & Niranjana, 2023). It is the primary cause of visual loss in people all around the world (Anjana, R.M. et al., 2011). Additionally, Table 1 demonstrates the distribution of blind

people throughout the six WHO regions, organized with the total number of impairments (in millions) ([Raman et al., 2009](#), [2019](#)).

Table 1 Spreading of sight-impaired peoples in the 6 WHO region

Category	African Region (AFR)	American Region (AMR)	SEAR Region (excluded India)	European Region (EUR)	Eastern Mediterranean Region (EMR)
Total Population (in million)	804.9	915	579	890	580
Blind (in million)	5.9	3.2	3.9	2.7	4.9
Vision Impairment (in million)	20.4	23.5	23.9	25.5	18.5
Poor Vision or Blurred Vision (in million)	26.28	26.6	27.9	28.2	23.4

Diabetes can cause eye disease in diabetic people. It is a vision issue ([Rahimy, 2018](#)) that can lead to severe visual impairment (Tufail et al., 2019). Glaucoma, cataracts, and diabetic retinopathy could be present. Like a breath zone, cataracts form and can disturb one or both eyes. They can be brought on by radiation exposure, trauma, or aging. A vision disorder called glaucoma is brought on by unusually high intraretinal pressure, which damages the optic nerve and results in blindness ([Ting et al., 2017](#)). Adults with diabetes have approximately twice the danger of developing glaucoma. Diabetic retinopathy is due to impairment near the plasma pots in the rear of

the eye. High cholesterol, smoking, diabetes, high blood pressure, and inadequate blood sugar management are some risk factors (Roomviboonsuk et al., 2019). Of the 18 million people with diabetes who are 18 years of age or older, more than half have vision problems (Lancet Global Health, 2020). A complete yearly dilatation vision assessment is suggested for diabetic patients (Solanki et al. 2015). Early detection of retinal disease is particularly difficult because the indicators are minimal and imperceptible (Gulshan et al., 2019). Therefore, one strategy to lower the rate of diabetes-related blindness is early screening and diagnosis.

The influence on medical personnel of the increased emphasis on regular physical inspections and the use of specialized equipment for illness diagnosis cannot be overstated. In addition to increasing the workload for human resources, it has led to an increase in diabetes screening activities, to mention a few. To decrease the stress transported on by these regular screening and check-up procedures, numerous policies were created and refined. Using medical image processing to diagnose eye diseases is one illustration. Acute glaucoma, AMD, diabetic retinopathy (Zhou et al., 2018), and other ocular retinal diseases have all been the subject of substantial clinical examination because they are the main causes of visual loss. Various imaging technologies, including angiography, framework attractive images, and visible part Optical Coherence Tomography (OCT), are used by ophthalmologists to treat retinal disorders. Creating automated image analysis systems is a crucial undertaking because physically carrying out medical images takes time (Kauppi et al., 2007).

Analyses of retinal images, including segmentation, localization, documentation, classification, and others, reveal vital details about the state of the visual system by categorizing potential damage or disease. In essence, automated image analysis can be accomplished through the design

of interactive and automated systems. In demand to speed up, replace, or facilitate the diagnostic process, automated techniques are preferable. The profits of these automated techniques outweigh those of other algorithms. As a result, fundus images of the eye can be used to create a classification system for retinopathy. Using some automated approaches to undertake manual analysis of this disease will take the same amount of time (Roychowdhury et al., 2013; Angermueller et al., 2016).

Research Interruptions

A critical evaluation of the literature reveals the following problems that require devotion with retinal image processing in the field of diabetic retinopathy detection:

- A minor database of retinal fundus images is used by all methods in retinopathy. The current algorithms routine is undecided given the vast volume of data they were required to process.
- Because fundus images are so countless and wide-ranging in terms of outlines and color variations, image analysis with computer vision is difficult.
- While a variety of methods are available for diagnosing lesions and classifying retinopathy, they do not consider the ID of every lesion together.
- The variety of classifiers have been used by numerous researchers for retinopathy screening, and it has been noted that the popular ones demand lengthy addition times and numerous iterations.
- Focus on further rankings: This could be enhanced by classifying retinal conditions according to their severity level or grades.

The detailed blocks designate the necessity aimed at active image processing and profound education procedures to categorize explicit outlines from retinal fundus images to organize and notice diabetic retinopathy. The exploration signifies the tricky pronouncement undertaken and the ideas of the research (Gulshan et al., 2016). It also emphasizes the research policy adopted for undertaking this investigation.

Research Objectives

The goals that are presently well-known in light of the practices already revealed in the preceding section, are based on literature that was obtained during the first stage of the study plan. They are:

1. To develop well-informed various systems and their possible methods for illness detection.
2. To understand how well different retinopathy complaints are classified and whether lesions are noticed in popular retinal images.
3. Evolving and executing a new computational arrangement and recognizing several retinopathy conditions.
4. To estimate, approve, and subordinate the planned model's presentation in retinopathy detection based on a numeral of metrics, favorable accuracy, precision rate, and reduced processing time.

Segmentation Methods

Template matching and mathematical morphology were applied to systematize classification, detection, and segmentation of red lesions. Common steps for classification are preprocessing, detection of initial candidates, extraction of features. The preprocessing is important to enhance red lesions from the contextual (Fleming et al., 2006). Normalization of green and shade correction methods (Walter et al., 2007)

were applied for preprocessing. To discriminate micro aneurysms from other dot-like buildings (Fleming et al., 2006), watershed transform was applied. Variable bandwidth is used to evaluate kernel density (Walter et al., 2007), template matching (Bae et al., 2020 for extraction of hemorrhages. Different circular buildings were detected using the Radon Cliff operator (Giancardo et al., 2010). For lesion detection, wavelet-transform (Quellec et al., 2008) and Support Vector Machine (SVM) (Adal et al., 2017) were used. The thresholding operation is used to detect micro-aneurysms by making a score map of micro aneurysms by Lazar and Hajdu (2012). (Rocha et al., 2011) used a visual vocabulary to bypass the preprocessing or post-processing step and detect the point of interest inside the lesion. To identify micro aneurysms, the turning cross-section outlines stayed appraised on the resident maximum pixels of the pictures. Next, peaks were detected by their devious size, shape, and height Lazar and Hajdu (2012). To detect microaneurysms, a Hough transformation with a feature extraction technique (Viola & Jones, 2001) and unique Segmentation Methods is used magnificently (Lazar & Hajdu, 2012). This disconnected the red lesions from the contextual ones using a curvelet-based enhancement technique (Kar & Maity, 2017). The red lesion detection was improved by using a material of the corresponding filter with Laplacian and Gaussian filters together (Zhou et al., 2017). Micro aneurysms were detected using an unsupervised classification method (Zhou et al., 2017). Dusky entity filtering development, along with singular spectrum investigation, is used to limit the hopefulness in the image.

Methods for Segmentation of Red Lesions

The suggested method has two stages. In the first stage, red lesion segmentation is done using a Nested U-Net (Zhou et al., 2018). In the second stage, the number of false-positive hopeful reduction is done

through sub-duplicate classification. The block-diagram of the recommended scheme stays revealed in [Figure 1](#), then in the subsequent section, details of the policy are clarified.

Preprocessing

Automated detection of red lesions is precious by low image contrast, non-uniform illumination, and very small structures of microaneurysms ([Lin et al., 2017](#)). The junction of blood vessels has similarity with red lesions and causes false positives. In classical image analysis, Mathematical morphology ([Fleming et al., 2006](#)), pattern matching ([Giancardo et al., 2010](#)), cross-section outlines analysis ([Quellec et al., 2008](#)), and multiscale filtering ([Wang et al., 2016](#)) were explored for red lesion detection. The micro aneurysms were mined from other dot-like structures using Watershed transform. The haemorrhages of several shapes were taken care of by model matching ([Bae et al., 2011](#)). The rounded red lesions were detected by the Radon Cliff operator ([Giancardo et al., 2010](#)). [Wang et al. (2016)](#) performed singular spectrum analysis of the cross-section profiles of microaneurysms. Wavelet transform ([Giancardo et al., 2010](#)), and curvelet-based method ([Kar & Maity, 2017](#)) were also explored for red lesion detection. Deep neural network is taught to diagnose extreme lesions from retinal fundus images for diagnosis of Dr. Grinsven et al. ([Wang et al., 2016](#)) applied convolutional neural network (CNN) to detect haemorrhages based on patch classification, where the negative patches are extracted from images without haemorrhages and positive patches are extracted only from haemorrhages location ([Van Grinsven et al., 2016](#)).

The training was made faster by energetically picking misclassified negative samples. This method works on the patch level and is not trainable end-to-end. We present a single-stage detection framework, which works on image level and is end-to-end trainable. The architecture trusts a pillar for

forming feature maps and Feature Pyramid Network (FPN) (LIN et al., 2017) with skip connections for effectively combining the features of lower resolution with features of the developed resolution images. Finally, classification and regression heads are integrated to recognize the red lesions with their locations. The FPN takes care of several restrictions of the previous architectures and creates a feature pyramid with strong semantics at several scales. The projected network could be trained in image level in all conceivable scales and works for an extensive range of red lesions (Tufail et al., 2017; Ting et al., 2017). Contrast-Limited Adaptive Histogram Equalization (CLAHE) is used to make a variety of red lesions more visible, as demonstrated in Figure 2.

(a)   (b)
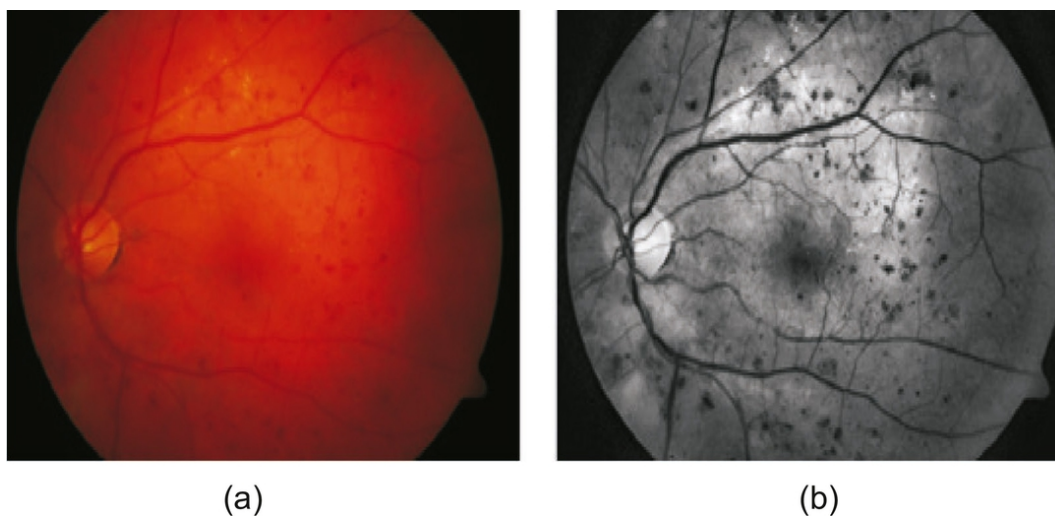
Fig 2 (a) Normal image and (b) Result after preprocessing.

System Architecture for Red Lesions Segmentation

U-Net++ (Zhou et al., 18) network embraces an encoder path and decoder path for health image segmentation. The decoder extracts the semantic, higher-level, and development features, whereas the encoder extracts the lower-level and acceptable feature maps. In the recommended network, several dense CNN blocks are linked between the decoder and encoder

paths. The mixture of the encoder and decoder path is used to segment red lesions in U-Net++ (Zhou et al., 18) architecture. To get better segmentation results higher-level and lower-level information is necessary, which is actually done by the U-Net++ (Zhou et al., 18). The main path of this network, i.e., up-sampling and down-sampling, is shown in Figure 3. A series of convolutional blocks is used as a skip connection between the encoder and the decoder path. A total of 21 blocks is used in the network, and each block is built by two convolutional layers. Six convolutional blocks are used with a single padding and kernel size 3 × 3 (Gulshan et al., 2016). Except the latter convolution block after each encoder block, the max-pooling routine is performed through a filter size 2 × 2 and stride size two. The feature map size growths from 64 to 2,048 laterally the down-sampling track (Zhou et al., 18)
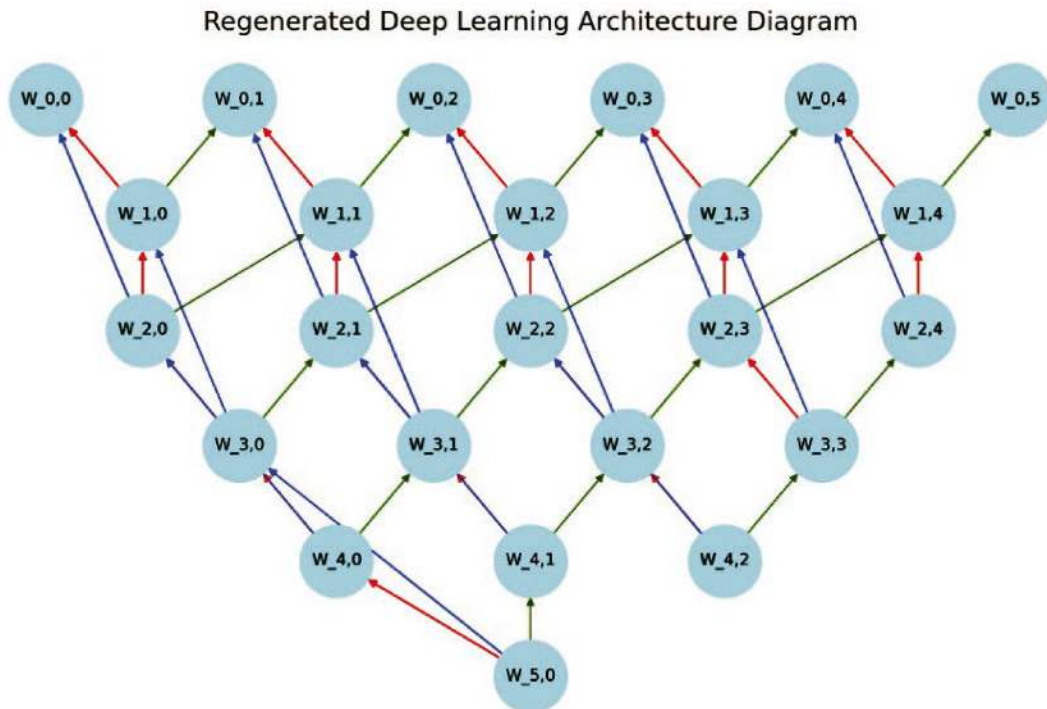
Fig 3 Network Architecture of proposed segmentation method.

The twin size decreases along the encoder path from 256 × 256 to 8 × 8. Five convolution blocks (Dalal & Triggs, 2005) type the decoder path, tolerate a category of up-sampling and concatenation later each block (Felzenszwalb et al., 2009). Laterally, the decoder path feature map size decreased from 2048 to 64 and image size increased from 8 × 8 to 256 × 256. Parallel padding is used by compressed convolution blocks between the decoder and encoder. Four dense convolution blocks are used at the top-most portion between the encoder and decoder, after the number of dense convolution blocks is reduced by one along the sliding path of the network. Each block in the horizontal path is connected via skip connections (Ying et al., 2013). The block does up-sampling operations that are parallel to the decoder path. The outputs from the preceding dense convolution blocks are added near the up-sampling yields after the minor compressed convolutional chunk by a concatenation operation before each convolution block of the dense layer. The dense blocks accurately syndicate the encoder and decoder feature maps to be semantically identical. The main focus of this network is the segmentation of red lesions with minimum false-negative applicants (Felzenszwalb et al., 2008).

In the above figure, W^{ij} represents the output of the corresponding block and w^{ij} is its output, where i represents the downward block along the decoder connections, and j denotes the dense convolution block attached with bounce connections. Blocks with $j = 0$ attain the yield since its earlier block of the encoder subsequent max-pooling. Block with $j = 1$ collects the output result from the previous encoder block succeeding the max-pooling operation. For $j > 1$, the convolution chunks gather j number of contributions from the previous compressed convolution block through the bounce connection and another from the dense layer lower afterwards the up-sampling. As a result, each chunk gets the feature map after its earlier

blocks. At the ultimate stage of the grid, the feature maps are created by input image after broadcasting in all possible paths of the network as given by Equations (1), (2). (Liu et al., 2016; Jiang et al., 2022).

$$w^{ij} = \Gamma\left(\{w^{i-1,j}\}\right) \quad \text{for} j = 0, i > 0 \qquad \ldots (1)$$

$$w^{ij} = \Gamma\left(\left[w^{i,k}\right]^{j-1}, \mu\left(w^{i+1,j-1}\right)\right) \quad \text{for} \quad i, j > 0 \qquad \ldots (2)$$

somewhere $\Gamma(.)$ represents complication, $\{.\}$ represents max-pooling, $[.]$ represents concatenation and $\mu(.)$ represents up-sampling.

Res-Net-18 (Ou et al., 2019) is regularly used to classify the images. Res-Net (Ou et al., 2019) is expressly used to sub-image classification of red scratches or without red lesions in images. It has been seen that 80×80 is the best sub-image size used in this network. The Res-Net architecture consists of 18 numbers of convolutional layers, with each kernel size 3×3. Along the downward path, the feature size increases from 64 near 512. The latter layer of Res-Net is a fully connected neural network. The bounce connections are connected after each of the two convolution layer intervals except the first convolutional layer. This type of unit is called residual block (Ou et al., 2019). The architecture of the residual block is shown in Figure 4, someplace a curved line with an arrow mark indicates the shrinking connection. The measured representation of the outstanding block is as follows: Equations (3) (4):
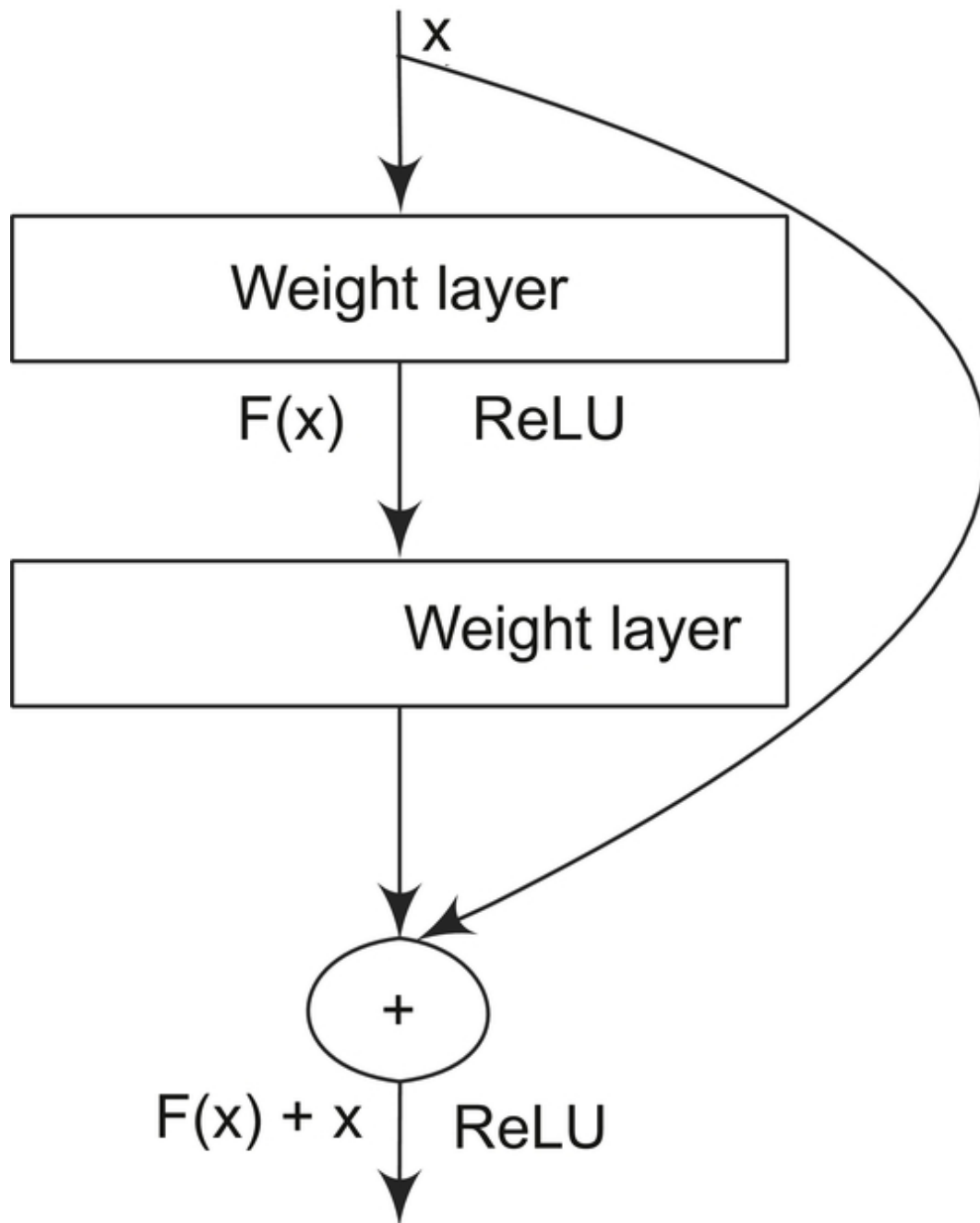
Fig 4 The Residual Block.

$$H(x) = F(x) + x \qquad \text{...(3)}$$

$$F(x) = H(x) - x \qquad \text{...(4)}$$

Here, the input and output residual blocks are signified by x and $H(x)$ separately. According to [Figure 4](#), each residual block consists of 2 weighted layers, and a bounce connection is used to preserve the previous layer substantially. The increased convolutional layer in the residual block reduces the network distortion.

The network learns low-level features like texture, objects' edge, and objects' construction from shallow layers and high-level landscapes like semantic and spatial features from deep layers. It observed that the deep layer, most of the time, loses the low-level feature. But in Res-Net ([Dalal & Triggs, 2005](#)) residual block plays a vital role in recalling the low-level feature, which makes improved output than the other network architecture.

Training

MASSIDOR dataset (Talukdar et al., 2023) is used to train the proposed network. Each image was divided into eight pieces and it was resized with 256 × 256 pixels. ADAM ([Kingma & Ba, 2014](#)) optimizer stays used to train the network to sustain the learning rate 0.00001 from 1 to 50 epochs; then, it is experimental that the learning rate decreases 0.000001 from 50 to 80 epochs. For apprising the network, 80 × 80 patch size is used. The network is trained in up to 60 numbers of epochs. A learning rate of 0.01 and energy of 0.6 is used for stochastic gradient descent (SGD) ([Ruder et al., 2016](#)) It is also observed that the learning decreases by 0.0001 after every 15 epochs.

Description of Database

In the training process, MESSIDOR dataset (Talukdar et al., 2023) is used, it is widely accessible on the internet. The network is taken from scrape. A total of 1,200 numbers of colored fundus images are available in the MESSIDOR dataset (Talukdar et al., 2023). The images are captured by

resources of a non-mydriatic camera with a 45-degree pitch of opinion. Images endured of 1440 × 960, 2240 × 1488, or 2304 × 1536 pixels. Beyond 1,200 images, 742 are underneath grade-1, grade-2, and grade-3 groupings of DR. Only 572 images are used for the network, and 170 numbers are used for result validation. As the ground truth of the MESSIDOR data set is publicly unavailable, manual annotation is ended below the direction of an ophthalmologist.

DIARETDB1 dataset (Kälviäinen & Uusitalo, 2007) has a total 89 numbers of colored fundus images of eyes. Out of 89, 84 images contain at least one pathology of insignificant or non-proliferative Diabetic Retinopathy and the remaining five are ordinary and healthy. The pictures are taken with a 50-degree pitch of views. Four professional doctors annotate the publicly available ground truth of DIARETDB1; therefore, it is used for DR detection. In this work, the boundary of the red lesion is again redefined under the supervision of an ophthalmologist.

Results and Discussions

Metrics

The proposed network's act and opposing systems were estimated by conventional metrics such as sensitivity, accuracy, precision, specificity, and F1-score, as given in Equations (5–9).

$$\text{Sensitivity} = \frac{TP}{TP + N} \qquad \qquad \text{...(5)}$$

$$\text{Specificity} = \frac{TN}{TN + FP} \qquad \qquad \text{...(6)}$$

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \qquad \qquad \text{...(7)}$$

$$\text{Precision} = \frac{TP}{TP + FP} \qquad \text{...(8)}$$

$$\text{Precision} = \frac{2TP}{2TP + FP + FN} \qquad \text{...(9)}$$

For the purpose of validation, connected constituent level validation is considered as follows (Zhang et al., 2011; Playout et al., 2019). In Figure 5, ground truth is shown by red and green contours, indicating the predicted lesions by the future methodology. In concert evaluation, consider a minimal overlap ratio 0.2 between truly positive pixels from connected components and ground truth instead of including the classified pixels. If the overlap ratio is less than 0.2, then the non-overlapping serving of projected lesions could be measured as false-positive pixels. The non-overlapping portion of ground truth is considered false-negative pixels; the relaxation is measured as true negatives. In particular, module level authentication is used when the boundary of the red lesion is not recognized to evaluate the routine metrics.
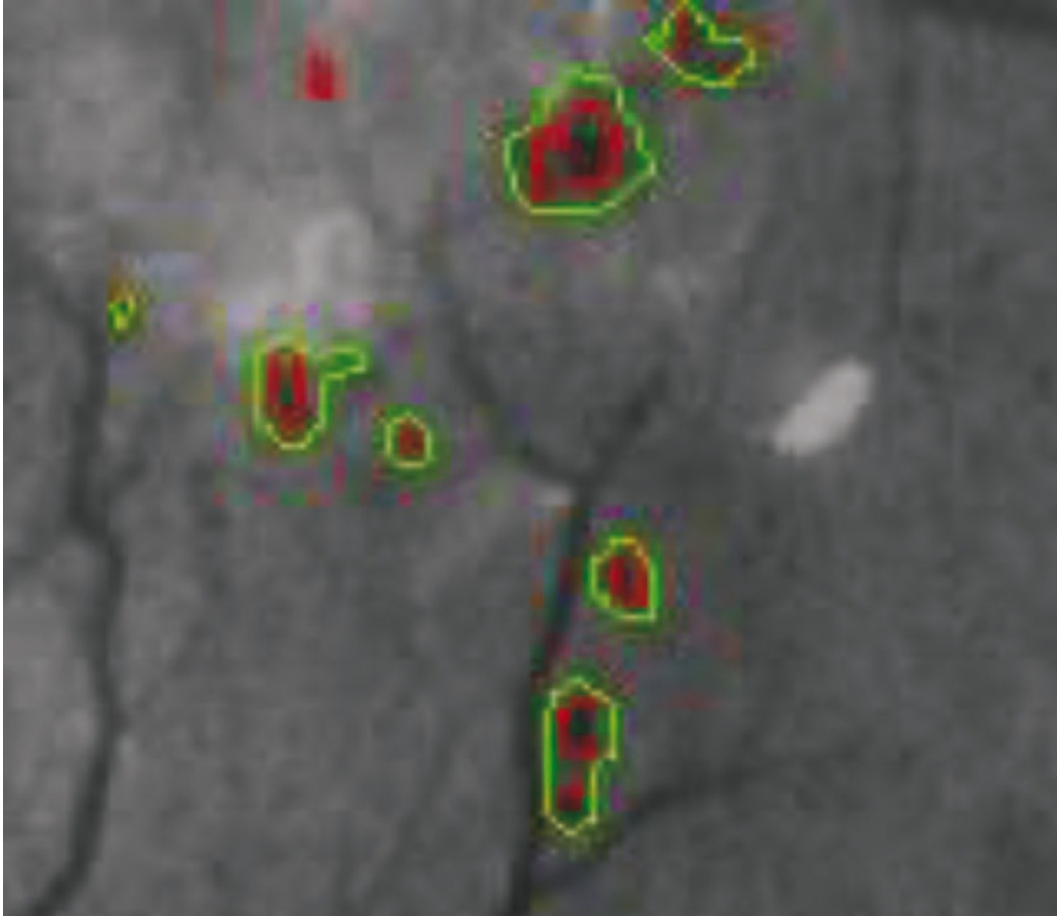
Fig 5 Predicted lesions and overlap with ground truth.

Segmentation Results

To evaluate the routine of the planned network and compare the results with other methods DIARETDB1 (Kalviainen & Uusitalo, 2007) data set is used. Out of 89 numbers of images, 28 are used for fine-tuning of the pre trained network, and the residual 61 images are used to report the result. The exact number of images from DIARETDB1 were used for pre train and the result was reported for U-Net (Oktay et al., 2018) and attention U-Net (Oktay et al., 2018). The proposed network architecture is showing a substantial improvement in the result in terms of sensitivity and precision (Table 2). The sensitivity improved to 8.87% completed the U-Net (Oktay et al.,

2018) and precision improved to 8.83% over the attention U-Net ([Oktay et al., 2018](#)).

Table 2 Performance Calculation for Red Lesion Segmentation. ⏎

Segment Architecture Used	Sensitivity	Specificity	Accuracy	Precision	F1-Score
U-Net ([Ronneberger et al., 2015](#))	79.92	99.66	99.47	67.88	73.41
Attention U-Net ([Oktay et al., 2018](#))	85.10	99.61	99.49	62.67	72.17
Multi-Task Architecture ([Playout et al., 2019](#))	85.19	99.88	99.83	78.95	81.94
Future technique	87.79	99.64	99.52	71.50	79.20
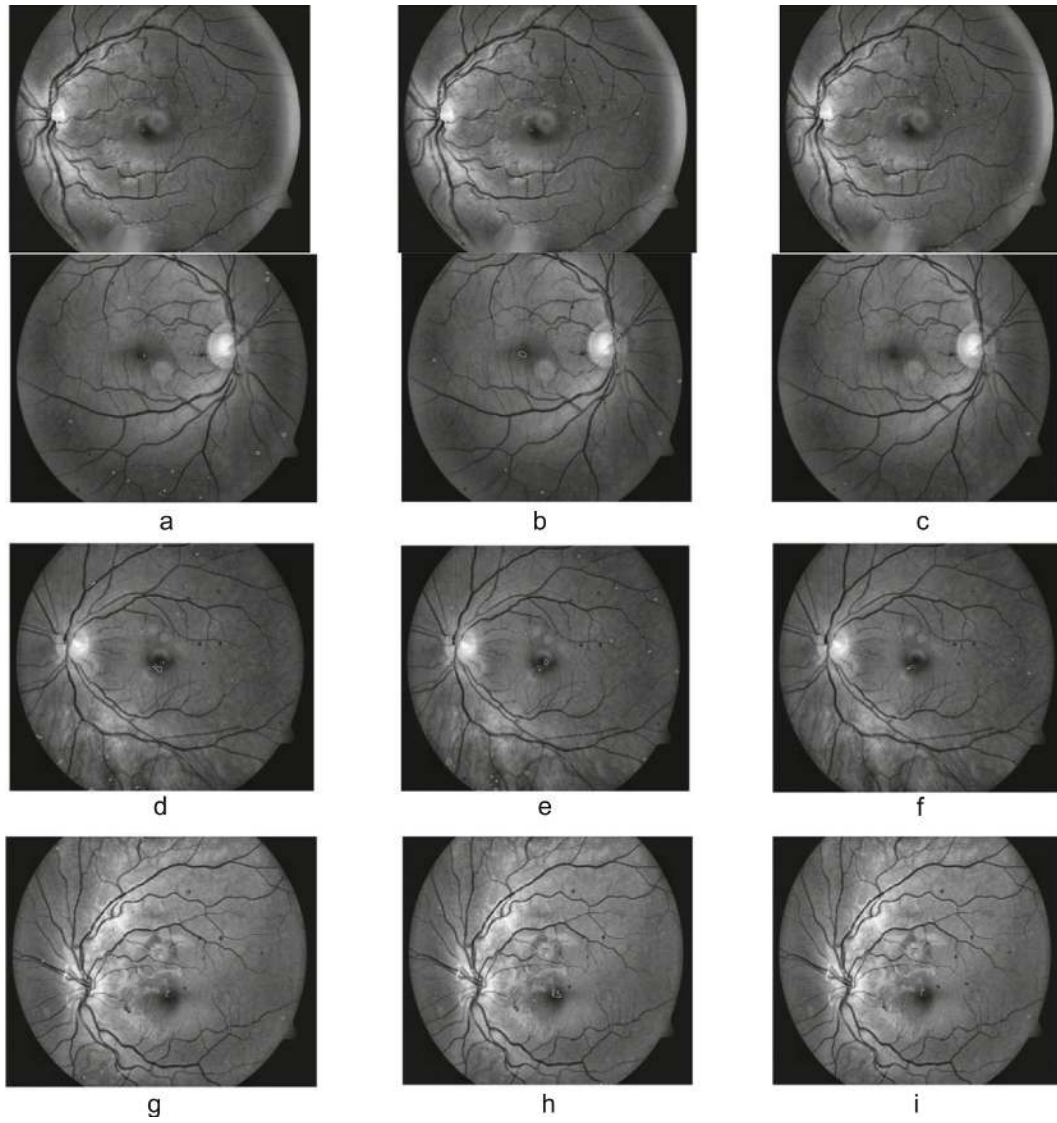
Fig 7 Results of U-Net: (a), (d), and (g); outcomes of devotion U-Net: (b), (e), (h); and outcomes of the proposed method offered in (c), (f), and (i). Red resembles false-negative aspirants, green denotes the false-positive, and true positive candidates are the true positive aspirants in blue.
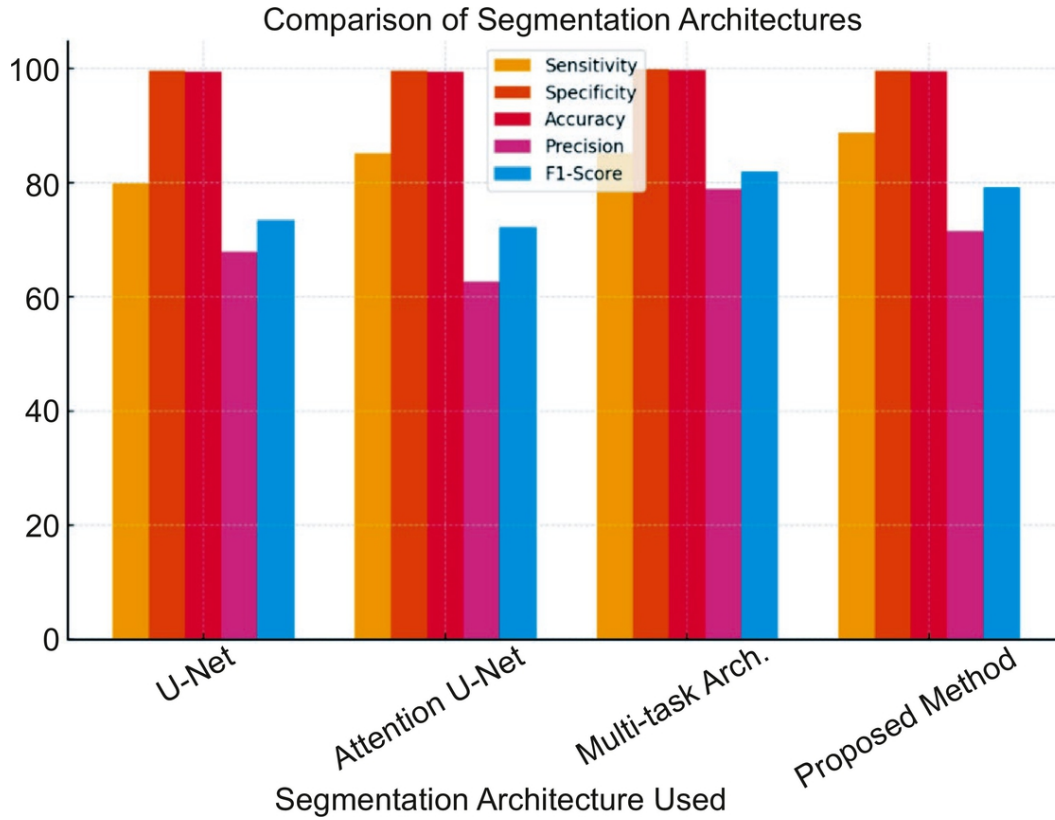
Fig 8 Comparison of Red Lesion Segmentation Architecture.

The ground truth of red lesions is represented in the first column in Figure 6. The initial segmentation result of the recommended network is given in the second column, the third stake displays the segmentation outcomes after false-positive reduction (Ren et al., 2015). The small size with poor contrast red lesions are effectively segmented by this U-Net++ architecture. This proposed network can also segment large size as well as very small size red lesions. The segment outcomes of red lesions consuming U-Net (Ronneberger et al., 2015), attention U-Net (Okay et al., 2018), the anticipated technique is given in the 1st, 2nd, and 3rd columns in Table 2. The result shows that the number of false-positive and false-negative candidates are significantly less in the future process in contrast with other methods.

The graph compares the performance of different segmentation architectures (U-Net, Attention U-Net, Multi-task Architecture, and a Proposed Method) based on several performance metrics: Sensitivity, Specificity, Accuracy, Precision, and F1-Score. The Multi-task Architecture performs best in relations of overall F1-Score and Precision. The Proposed Method excels in Sensitivity, meaning it is better at identifying positive cases. All models perform well in relations of specificity and accuracy, indicating they are generally reliable. Method establishes the best overall presentation among the associated architectures, making it a more effective optimal for segmentation tasks.

Conclusion

The proposed system has sufficient potential to assist ophthalmologists in DR diagnosis. This technique uses a minimum number of images to train the network. Therefore, with this minimum information, the method can yield accurate outcomes. The suggested performance can successfully segment red lesions from the given fundus image with a few numbers of false-negative candidates. In this technique, the number of false-positive aspirants also reduces to a large extent. Still, further demanding study on this network is required to minimize the volume of false-positive and false-negative aspirants. There is a chance to improve the preprocessing technique for visualization besides segmentation of minor size red lesions. The detection and segmentation of new vascularization is not addressed in this work, which is a limitation of the work. Micro aneurysms can fruitfully segment with the minimum number of false-positives by this method. This costeffective proposed method can be used to detect diabetic retinopathy (DR) at the beginning stage, and as a result, enduring blindness due to it can be prevented. This computer-based diagnosis method may play a dynamic

role in making clinical decisions by ophthalmologists, entirely NPDR patients.

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6 EDiNA-UNet for Liver Segmentation from CT Images

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The process of segmenting the liver in computed tomography (CT) scans is vital for assessing liver diseases, planning treatments, and supporting surgical interventions. However, challenges such as the liver's complex anatomy, variable tumor characteristics, and limitations of manual segmentation have driven the need for automated, accurate solutions. This study introduces the Enhanced Dilated Neighborhood Attention-UNet (EDiNA-UNet), a novel model employing dilated neighborhood transformers for liver segmentation. By integrating an adaptive dilation scheduling mechanism within a U-Net architecture, EDiNAUNet dynamically adjusts dilation rates to accurately capture both fine-grained details and the overall contextual information. Evaluated on the Liver Tumor Segmentation (LiTS) dataset, the proposed technique achieves a Dice Similarity Coefficient of 97.2%. Ablation studies validate the contributions of adaptive dilation, skip connections, and neighborhood attention to its success. EDiNA-UNet represents a significant advancement

in automated liver segmentation and offering potential for enhanced clinical diagnostics.

Introduction

Segmenting the liver in computed tomography (CT) images is a crucial step in diagnostic imaging, playing a key role in diagnosing liver-related diseases, planning treatments, and supporting surgical procedures (Elmpt & Landry, 2018). Diseases such as liver tumors, cirrhosis, and other liver pathologies demand precise segmentation to ensure accurate assessments, surgical planning, and follow-up evaluations. Manual segmentation by radiologists, while accurate, involves extensive time and manpower, and is subject to variability depending on the expertise and fatigue of the clinician.

Consequently, there is demand for automated segmentation techniques that can deliver reliable, accurate, and reproducible results across various clinical settings. However, liver segmentation presents several challenges. The liver's anatomical structure is complex, featuring irregular shapes, varying textures, and closely located organs like the stomach, kidneys, and lungs that can create difficulties in distinguishing boundaries (Kumar et al., 2013). Additionally, the appearance of liver tumors varies significantly with respect to size, shape, and location, which further complicates segmentation. The presence of pathologies such as cirrhosis, which alters liver texture, adds another level of complexity. Therefore, segmentation models must be resilient to these variations while ensuring high accuracy.

Recent progress in machine learning, especially deep learning, has transformed medical image segmentation (Kumar & Vinod Kumar, 2024). Convolutional Neural Networks (CNNs) have been the key catalyst behind these advancements, attributable to their effectiveness in image feature extraction through hierarchical layers of convolutions. U-Net (Ronneberger et al., 2015) is among the top prominent CNN architectures within the field

of medical image segmentation, known for its encoder-decoder structure that allows for the precise capture of local and global features through skip connections. U-Net and its variants have become foundational models, achieving strong performance across various medical imaging tasks.

While CNNs have significantly improved segmentation accuracy, they face limitations when it comes to capturing global contextual information. CNNs use fixed-sized receptive fields that struggle with long-range dependencies and complex boundaries, particularly in organs like the liver, where the shape and texture can vary significantly across patients. Several methods, such as dilated convolutions and pyramid pooling, have been proposed to address this issue by enlarging the receptive field, but they still fall short in capturing the complete global context of the image.

In the last few years, transformer-based models have gained prominence in computer vision because of their effectiveness in modeling long-range dependencies using self-attention. Initially established for the domain of natural language processing (NLP), transformers have been effectively revised to vision applications, giving rise to architectures such as the Vision Transformer (ViT) ([Dosovitskiy et al., 2020](#)). ViT processes an image by dividing it into a sequence of patches, applying attention mechanisms to capture global context across the entire image. However, despite their success in classification tasks, pure transformer models face challenges in dense prediction tasks like segmentation, where finegrained details and local information are critical.

Hybrid models, which use the advantages of both CNNs and transformers, have proven to be a promising method to address the limitations of both approaches. These methods take advantage of the local feature extraction capabilities offered by CNNs while employing transformers to grasp global context and long-range dependencies. This

method has demonstrated significant potential in enhancing segmentation model performance, especially for complex tasks like liver segmentation.

By integrating Transformer blocks within a U-Net architecture ([Wei et al., 2023](#); [Hatamizadeh et al., 2021](#)), this model aims to gather both fine-grained local details and broader global context efficiently, addressing the constraints of pure CNN or transformer-based models. Building on this foundation, this chapter introduces the Enhanced Dilated Neighborhood Attention-UNet (EDiNA-UNet), a novel hybrid model designed specifically for liver segmentation. The EDiNA-UNet incorporates an adaptive dilation scheduling mechanism that dynamically adjusts the dilation rates within the network, allowing for more effective capture of both local details and global context. This innovation leads to improved segmentation accuracy, achieving a Dice Similarity Coefficient (DSC) measuring 97.2% on the LiTS dataset. Apart from the DSC, the EDiNA-UNet also achieves superior results in essential evaluation metrics including the Relative Volume Difference (RVD), Jaccard Index, Hausdorff Distance (HD), and Average Symmetric Surface Distance (ASSD). These metrics further validate the model's robustness and accuracy in segmenting liver structures.

The primary contributions of EDiNA-UNet are threefold:

- **Adaptive Dilated Neighborhood Attention (ADiNA):** Unlike existing transformer-based models that use fixed attention windows or global attention, EDiNA-UNet introduces DiNA blocks with dynamically adjusted dilation factors. This enables the model to tailor its receptive field to feature complexity, improving segmentation of variable anatomical structures over static approaches.
- **Balanced Local-Global Feature Capture:** While CNN-based models excel at local details but struggle with long-range dependencies, and pure transformers prioritize global context at the cost of computational

efficiency, EDiNA-UNet integrates the strengths of both. Its adaptive dilation ensures efficient capture of both fine details (e.g., liver edges) and global context (e.g., organ relationships).

- **Computational Efficiency:** By restricting attention to dilated neighborhoods rather than the entire image, EDiNA-UNet reduces the computational complexity of global attention models like ViT, making it more practical for medical imaging applications compared to resource-intensive alternatives.

Existing methods often compromise between local precision and global awareness or incur high computational costs. For instance, U-Net variants lack mechanisms for long-range dependencies, while transformer models either overlook fine details or demand excessive resources. EDiNA-UNet addresses these gaps with a scalable, efficient architecture that adapts to the task's needs, making it particularly suited for complex medical segmentation tasks like liver delineation, where both precision and context are paramount.

This chapter is structured as follows: Section 2 offers an in-depth review of current research in medical image segmentation, emphasizing CNNs, transformerbased models, and hybrid architectures. Section 3 details the methodology employed in this study, including information about the dataset, preprocessing techniques, the architecture of the EDiNA-UNet, and implementation strategies. Section 4 presents the evaluation results, showcasing updated metrics, ablation studies, and visualizations to highlight the effectiveness of the model. Section 5 examines the implications of the findings and the novelty of the proposed approach, followed by Section 6, which ends with recommendations for future research in liver segmentation.

Literature Review

CNNs ([Alzubaidi et al., 2021](#)) have served as the foundation for progress in medical image segmentation, enabling significant breakthroughs in automated segmentation tasks. CNNs were first adapted for pixel-wise predictions with Fully Convolutional Networks (FCNs) ([Long et al., 2015](#)), which eliminated the need for fully connected layers by replacing them with convolutional layers that allowed for dense, end-to-end learning. This architecture set the foundation for subsequent CNN-based models in medical imaging, particularly in segmentation tasks where accurate boundary delineation is crucial.

One of the most impactful architectures in this domain is U-Net ([Ronneberger et al., 2015](#)), introduced a distinct encoder and decoder architecture featuring skip connections that enable the recovery of spatial details lost during the phases of encoding. These skip connections allow the decoder to combine highlevel abstract features with low-level spatial details, resulting in more accurate segmentations. U-Net has emerged as a standard for medical image segmentation tasks, valued for its effectiveness in handling small datasets while achieving impressive performance. Multiple U-Net variants have been introduced to enhance the original architecture. U-Net++ (Zhou et al., 2015) introduced nested skip pathways, refining the feature fusion process and improving segmentation performance, particularly on complex images with intricate structures. Similarly, Multi ResUNet ([Ibtehaz & Rahman, 2019](#)) incorporated multi-resolution fusion, enabling the model to capture features at multiple levels simultaneously, resulting in more robust segmentations. Attention U-Net (Oktay et al., 2019) took a different approach by integrating attention mechanisms to emphasize the most pertinent features during the delineation process, further improving accuracy on difficultto-segment regions. [Lv et](#)

al. (2022) introduced an improved ResU-Net, where traditional convolution modules were replaced with residual modules to enhance feature learning, while Manjunath and Kwadiki (2022) presented a modified ResUNet, a hybrid of U-Net and ResNet, substituting standard convolution blocks with residual blocks to simplify CNN training.

Despite these advancements, CNNs still suffer from a significant limitation: their fixed receptive field. This restricts their capability to capture long-range dependencies, which are critical for segmenting complex structures such as the liver. Techniques like dilated convolutions (Yu et al., 2015) have been introduced to increase the receptive field while preserving resolution, and pyramid pooling (Zhao et al., 2017) helps aggregate contextual information at multiple scales. However, these methods still fall short of addressing the global context needed for more intricate segmentation tasks. Lei et al. (2022) introduced the Deformable Encoder-Decoder Network (DefED-Net), which incorporates deformable convolution and a Ladder-ASPP module. This design enables the adaptive organization of spatial information and the extraction of contextual details at various scales. The deformable convolution enables the network to flexibly modify the convolutional kernels, while the Ladder-ASPP module improves context learning compared to traditional atrous spatial pyramid pooling, particularly in the context of CT image delineation.

Transformers, originally suggested by Vaswani et al. (2017), have become a powerful framework for computer vision tasks, including segmentation of medical images. The self-attention mechanism utilized by transformers enables the modeling of long-range dependencies, which CNNs struggle to achieve. ViT (Dosovitskiy et al., 2020) was the first model to apply transformers to image processing by representing images as sequences of patches (tokens), enabling the model to capture global context

throughout the image. This shift from local to global feature learning is especially advantageous for assignments requiring a holistic comprehension of the image, including liver segmentation. However, ViT's computational complexity is high, especially for dense prediction tasks, including segmentation, and its lack of inherent inductive bias towards local features often results in weaker effectiveness in capturing intricate details compared to CNNbased models.

To address these limitations, several transformer-based models have been suggested. The Swin Transformer (Liu et al., 2021) introduced a structured, window-based attention mechanism that partitions an image into non-overlapping windows, allowing for more efficient computation and better preservation of local information. LeViT (Ben et al., 2021) further optimized transformer models by reducing computational overhead, rendering them more suitable for real-time applications. Wei et al. (2023) developed HRSTNet, replacing conventional convolutional layers with transformer blocks to facilitate seamless information flow across feature maps at varying resolutions. Despite these improvements, pure transformer models continue to face challenges in segmentation, where balancing global context with fine details remains critical.

Hybrid models integrating CNNs and transformers have emerged as a promising solution, combining the strengths of both architectures. These models harness CNNs for capturing fine-grained local features while utilizing transformer models to model long-range dependencies. TransUNet (Jieneng et al., 2021) pairs a transformer encoder with a CNN decoder, where the transformer captures global context and the CNN refines local spatial details. Swin-Unet (Hu et al., 2023) reformulates the entire U-Net architecture using Swin Transformer blocks, efficiently extracting both global context and local details. Hatamizadeh et al. (2021) introduced

Transformer integrated technique (UNeTr), a U-shaped architecture with skip connections linking the encoder and decoder, promoting a unified framework for semantic segmentation. Li et al. (2023) introduced RDCTransUNet, combining ResNeXt50, a ResNet variant with grouped convolutions, with dilated convolutions, showcasing the synergy of residual learning and advanced components. Qi et al. (2024) proposed AD-DUNet, a dual-branch design using Axial Transformers for long-range dependencies and cascaded dilated convolutions for local feature extraction. Ou et al. (2024) developed ResTransUNet, focusing on mitigating feature loss during encoding while maximizing global feature capture. Ren et al. (2025) introduced LGMA-Net, utilizing a specialized SNP convolutional Transformer block derived from spiking neural P systems to uniquely capture both global and local context.

Further innovations have enhanced hybrid approaches. Chen et al. (2023) introduced DRAUNet, a deep residual attention-based U-Net incorporating a dual-effect attention module (DAM) that combines both channel, spatial attention to enhance feature interdependencies and emphasize relevant spatial regions. Liu et al. (2023) introduced GCHA-Net, employing a global attention module (GAM) for long-range relationships and a local attention module (LAM) to refine focus on liver regions. Wang et al. (2021) presented SAR-U-Net, integrating Squeezeand-Excitation (SE) blocks applied following each encoder convolution layer to recalibrate channel-wise feature responses. Cao and Cheng (2025) proposed SACU-Net, a shape-aware U-Net with redesigned skip pathways incorporating spatial-channel attention to bridge the disparity in feature representation between the features of the encoder and decoder. Xia et al. (2024) developed a multiview fusion method using Dual Self-Attention (DSA) to capture long-

range dependencies across 2D slices, addressing both spatial and channel relationships.

To tackle specific challenges like insufficient training data, He et al. (2022) introduced an improved GAN-based 3D U-Net, integrating a semi-supervised optimization algorithm within a Generative Adversarial Networks (GANs) framework. Wei et al. (2021) proposed GAN Mask R-CNN, integrating GANs with Mask R-CNN, using GANs to address noisy features and k-means clustering method for optimized anchor selection. Li et al. (2023) developed Eres-UNet++, a deep supervision network built on Res-UNet++ with residual blocks to improve feature extraction and address blurry boundaries in liver images. Devidas et al. (2023) developed LiM-Net, leveraging multi level, multi-scale feature extraction with a Res2Net backbone and dense skip connections for enhanced feature fusion. Tinglan et al. (2025) introduced DEMF-Net, incorporating a Multi-Scale Feature Fusion (MSFF) module within skip connections to capture global features, while Qian et al. (2024) proposed UNet_sharp, combining dense and full-scale skip connections for effective multi-scale feature merging.

This chapter builds upon these advancements, specifically the Dilated Neighborhood Attention Transformer (Ali & Humphrey, 2022), by introducing the EDiNA-UNet. The proposed model incorporates an adaptive dilation scheduling mechanism that dynamically adjusts dilation rates to improve the capture of both local details and global context. This innovation allows for more accurate liver segmentation, addressing challenges posed by suspected regions and complex liver anatomy.

Methodology

The proposed method evaluates the EDiNA-UNet architecture for liver region extraction, using the LiTS dataset. This section details the dataset

used, preprocessing steps, and architecture of the EDiNA-UNet model, including novel adaptive dilation scheduling in the transformer blocks.

Dataset

The LiTS dataset ([Bilic et al., 2023](#)), utilized in this study, is a widely recognized benchmark dataset commonly employed in medical image segmentation challenges such as ISBI 2017 and MICCAI 2017. It comprises 131 abdominal CT images, each paired with expert-annotated liver masks, offering a rich source of data for liver segmentation tasks. The dataset includes scans from various institutions, ensuring a broad spectrum of imaging protocols, liver morphologies, and tumor appearances, which contributes to its versatility in model development. In total, the dataset comprises 58,014 transverse CT slices, each with a resolution of 512×512 pixels. The slice count per volume varies significantly, ranging from 42 to 1,026, providing a large and diverse data set for model training and testing. The in-plane voxel resolution ranges from 0.55 mm to 1.0 mm, with inter-slice spacing varying between 0.45 mm and 6.0 mm, ensuring that the dataset captures detailed and varied liver structures.

For the purposes of this study, the dataset is split into three subsets: training, validation, and testing. The training group comprises 91 cases containing a total of 29,775 slices, the validation set comprises 10 cases with an overall total of 3,602 slices, and the test set contains 20 cases with 14,854 slices. This division ensures a robust performance assessment of the model. The diversity and richness of the LiTS dataset enable the model to generalize effectively across different imaging protocols, liver morphologies, and tumor structures, making it a favorable option for segmentation tasks in the medical field.

Data Preprocessing

To preprocess the dataset for model training, a pre processing pipeline based on the Dilated-UNet approach was utilized. The objective of the pre processing was to isolate liver regions of interest, normalize image intensities, and resample the images for efficient computation, all while preserving crucial anatomical details. Several steps were employed in this pipeline to achieve these goals.

The first step involved Hounsfield Unit (HU) clipping. The HU values in the CT scans were clipped to a range of $-200 - 200$. This process aimed to exclude irrelevant structures like bone (HU > 400) and air (HU < -1000), focusing primarily on the liver regions, which typically fall within the HU range of 50–70. By narrowing the HU range, the model could concentrate on the regions of interest, facilitating more accurate segmentation. Next, normalization was applied to the pixel intensities. The intensities were normalized to the range of -1 to 1 employing min-max normalization. This ensured consistent intensity values throughout all images in the dataset, enabling the model to extract information from standardized data. Normalization is crucial for improving model performance, as it reduces variability caused by differing intensity levels between scans from different sources. The final step in the pre processing involved resampling. Each 512 × 512 CT slice was downsampled to a resolution of 256 × 256 using bilinear interpolation. This resampling reduced the computational load required for training, without compromising critical anatomical features essential for accurate segmentation.

No additional data augmentation methods, including rotations and flips, were applied, as the LiTS dataset inherently contained a high level of diversity in terms of liver shapes and imaging protocols. The diversity of the dataset guaranteed that the model encountered a broad spectrum of variations during training, reducing the need for augmentation.

EDi NA-UNet Architecture

The EDiNA-UNet is an advanced segmentation model tailored for medical image analysis, such as liver segmentation. This model enhances the traditional U-Net by integrating transformer-based attention mechanisms with dilated neighborhood attention, which enhances the network's capability to capture both fine-grained local details and broader global contextual features efficiently. The EDiNA-UNet architecture is built on a hierarchical encoder-decoder framework and is shown in [Figure 1](). In this architecture, the encoder captures deep feature representations from the given input image while progressively reducing its spatial resolution. Meanwhile, the decoder reconstructs a segmentation map by integrating multiscale information. A distinguishing feature of this architecture is the introduction of DiNA Blocks, which are incorporated in both the encoder and the decoder modules. These blocks improve the model's capacity to concentrate on local neighborhoods with attention spans that dynamically adjust based on the complexity of the features.
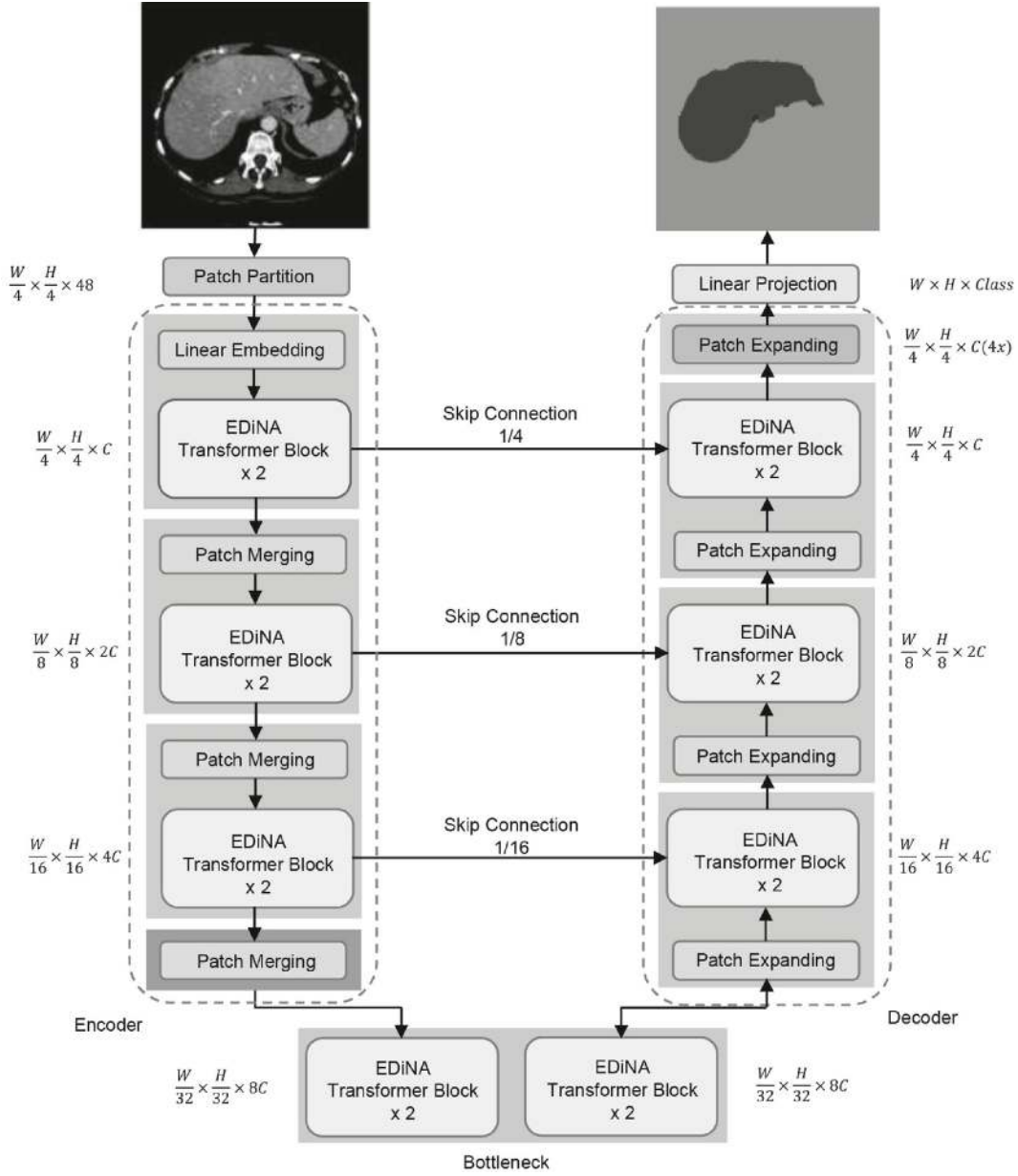
Fig. 1 EDiNA-UNet architecture comprising an encoder, bottleneck, decoder, and skip connections.

The DiNA mechanism departs from traditional transformers, where the attention mechanism typically operates globally across the entire input. Instead, DiNA restricts attention to localized areas or neighborhoods. This local neighborhood attention, when combined with dilation, expands the receptive field while maintaining computational efficiency. Additionally,

the dilation factor, which determines the size of the neighborhood considered during attention, is adaptively adjusted at different depths of the network. This guarantees that the model is capable of adapting its receptive field to suit the complexity and scale of the features it encounters, allowing for more effective feature learning and segmentation. By introducing adaptive dilation and leveraging transformers' attention-based learning capabilities, EDiNA-UNet can effectively cope with the variability in shapes, sizes, and locations of organs and tumors in medical images.

The encoder in the EDiNA-UNet extracts feature representations from the input image at different scales while progressively decreasing the spatial resolution. It consists of the subsequent stages: Patch Embedding and Positional Encoding, Dilated Neighborhood Attention Blocks and Neighborhood Aggregation.

The process begins with embedding of patches and positional encoding. The preprocessed input image, typically a 2D CT slice (e.g., 256 × 256 pixels), is broken down into non-overlapping patches (e.g., 4 × 4 pixels). Each patch is converted into a vector by flattening and then sent through an embedding layer, which transforms it into a high-dimensional feature representation, allowing the model to process image information at the patch level. To ensure the model retains spatial context, positional encodings are incorporated into these patch embeddings. Positional encodings preserve the spatial structure of the medical images, enabling the model to understand the placement of each patch within the image. This ensures that the relative location of patches is encoded and learned, a crucial step for effective medical image segmentation using transformers.

In the encoder, each stage utilizes DiNA blocks, which are designed to focus the attention mechanism on a restricted local neighborhood around each patch. Unlike traditional transformer models, where the attention

operates across the entire image globally, the DiNA blocks limit attention to a smaller, predefined region around each patch. This localized attention enables the model to capture the intricate spatial relationships that exist among neighboring regions in the image, which is particularly valuable for medical image segmentation tasks. By focusing on smaller local areas, the model can better preserve fine-grained spatial details, which are critical for accurately segmenting complex structures. The attention mechanism essentially learns how different regions within a localized neighborhood are connected and how they influence one another, ensuring that important features are extracted and preserved. The DiNA blocks in the proposed model are shown in Figure 2.
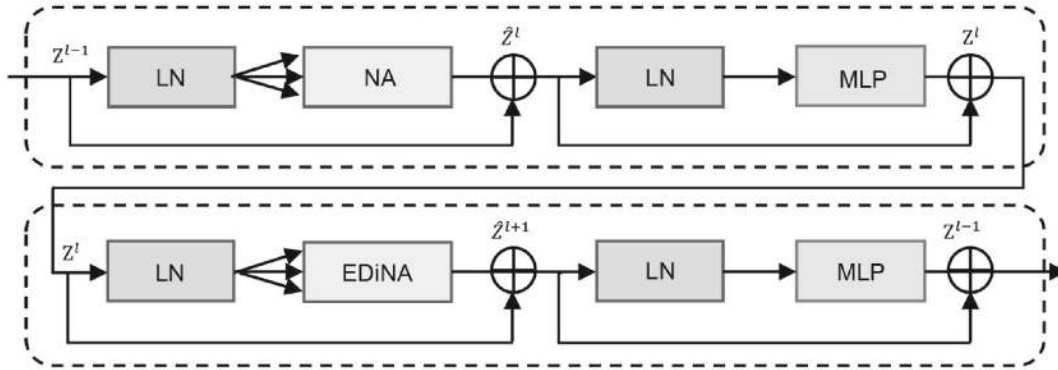
Fig. 2 DiNA Transformer blocks.↵

However, while local attention is essential for preserving detail, it may not capture the broader context needed to understand larger anatomical structures or distant relationships within the image. To address this limitation, Dilated Attention is integrated into the EDiNA blocks. This approach expands the neighborhood attention beyond directly adjacent patches by introducing a dilation factor. Dilation works by skipping certain patches in between, effectively enlarging the receptive field. This dilated attention mechanism allows the model to concurrently attend to both

detailed, local features and more expansive contextual information (such as the surrounding organ tissue). By varying the dilation rate at different depths of the network, the model can adapt to the complexity of the features being learned, ensuring that it captures both small, detailed structures and larger, more complex anatomical contexts.

The integration of localized attention and dilated attention within the EDiNA blocks is particularly powerful for medical image segmentation. It enables the model to balance the need for detailed spatial accuracy with the requirement to understand the broader context in which those details exist. For example, when segmenting a liver, the model can focus on the fine details around the liver's edges while also accounting for the surrounding liver tissue and its relationship to other nearby structures. This dual-level attention mechanism enables greater precise and context-aware segmentations, improving the model's overall performance in handling the complexities of medical imaging data. The dilation factor δ is dynamically adjusted across various layers of the encoder based on the intricacy of the feature maps. The encoder gradually decreases the spatial dimensions of the feature maps through patch merging or downsampling operations. At each stage, the spatial resolution is halved (e.g., from 256×256 to 128×128), while the feature dimensionality increases. This allows the model to capture low-level details at higher resolutions and abstract features at lower resolutions, essential for accurately segmenting organs and lesions of varying scales.

The DiNA Block is the central innovation in the EDiNA-UNet architecture, combining the advantages of transformer-based self-attention with local context modeling through dilation. The block operates by limiting the attention mechanism to a neighborhood surrounding each patch, then applying dilation to expand the neighborhood's size while

reducing computational complexity. The self-attention mechanism computes attention scores between a query patch and its neighboring patches. By applying dilation, the receptive field is expanded, allowing the model to learn both short-range and long-range relationships without the need for computationally expensive global attention. The attention calculation with dilation can be represented as:

$$\mathrm{DiNA}(\mathrm{Q},\mathrm{K},\mathrm{V};\delta) = \mathrm{soft\ max}\left(\frac{QK^T}{\sqrt{d_k}} + M_\delta\right)V \qquad ...(1)$$

Where:

- Q represents the query matrix (corresponding to the input patches).
- K and V signify the key and value matrices.
- M_δ is the dilation mask that controls which patches are considered within the dilated neighborhood.
- δ is the dilation factor, which controls the spacing between patches in the neighborhood.

The DiNA block focuses on a predefined region around each patch, ensuring that the model attends to local spatial dependencies. The dilation allows these local neighborhoods to grow, ensuring that the model can aggregate information from distant but related regions, which is crucial for medical image segmentation where anatomical structures are often interconnected.

The dilation factor in EDiNA-UNet is adaptive, meaning that it varies according to the level of the network and the complexity of the feature representations being processed. Early layers focus on smaller neighborhoods with minimal dilation to capture local pixel-level details, while deeper layers use larger dilation factors to capture more global

information. The adaptive dilation scheduling is controlled by the following relationship:

$$\delta_l = \delta_{\text{base}} + \beta \frac{l}{L} f_{\text{complexity}}(F_l) \qquad \text{...(2)}$$

Where:

- δ_{base} is the base dilation factor.
- β is a scaling factor that controls how quickly the dilation factor increases with depth.
- l is the index of the current layer.
- L represents the total layer numbers.
- $f_{complexity}$ is a complexity function that adjusts the dilation based on the variance or complexity of the feature maps F_l.

This dynamic dilation allows the model to progressively increase its receptive field as it processes deeper layers, ensuring that both fine and coarse image details are captured for accurate segmentation. At the bottleneck layer, where the spatial dimensions are smallest, the EDiNA-UNet captures the most abstract and highlevel representations of the input image. Multiple DiNA blocks with high dilation factors are applied, ensuring that the model captures long-range dependencies between distant regions in the image. This is particularly important for medical imaging, where accurate segmentation requires both local precision and global context awareness.

The decoder mirrors the encoder but performs the opposite task: upsampling the feature maps to reconstruct the segmentation mask at the original resolution. The decoder consists of the following components: Patch Expansion, Skip Connections, and DiNA blocks. The decoder

reverses the downsampling process by progressively expanding patches back to their original size. This is achieved using transposed convolutions or interpolation techniques, increasing the spatial resolution at each stage. Skip connections joining the relevant encoder and decoder layers ensure that both high level contextual information and low level details are preserved during the decoding process. These connections are crucial for maintaining the fine-grained spatial details required for accurate boundary delineation in medical image segmentation. The decoder also uses DiNA blocks with decreasing dilation factors. In contrast to the encoder, where dilation increases to capture global context, the decoder focuses on refining local details as the spatial resolution increases.

The last layer of the decoder produces a segmentation map at the original input resolution (256×256 pixels). A sigmoid function is used for binary segmentation tasks (e.g., liver segmentation). The output is a pixel-wise prediction map where each pixel is identified as belonging to a particular class (e.g., liver or background).

Implementation

The EDiNA-UNet was executed employing Python and the TensorFlow deep learning library. For computational efficiency and scalability, the model was trained and evaluated on a Google Compute Engine backend, utilizing a T4 GPU, which provides an efficient and powerful hardware environment that ensures robust training performance. The local environment for model development and validation consisted of an 11th Gen Intel® Core™ i5–1135G7 processor (clocked at 2.40 GHz), coupled with 16 GB of RAM, and operating on Windows 11. This development environment was used for configuring the model parameters, initial debugging, and ensuring smooth operation before training on the cloud-based infrastructure. For the model's optimization and learning process, the

Dice Loss function was adopted as the primary objective function to assess the intersection of produced segmentation masks and ground truth labels. This metric is especially well-adapted for image partitioning tasks, where it helps to ensure accurate region delineation, especially when segmenting complex anatomical structures like the liver in CT scans.

To enhance the model's parameters and reduce Dice Loss, the optimizer applied was Adam, starting with 0.0001 as the learning rate. This optimizer's adaptive learning rate and momentum-based strategy promote efficient and smooth convergence throughout the training process. To further address the risk of overfitting and improve convergence, the EDiNA-UNet integrated both the dynamic way of adjusting the learning rate and early stopping ways. The rate of learning was adjusted adaptively using a scheduler called the ReduceLROnPlateau, which decreases the rate of learning choosing a factor of 0.1 if there is no improvement in the validation loss over four consecutive epochs. This allows the model to continue refining its weights even when progress slows in the later phases of training. Additionally, early stopping was implemented to end training when the validation loss does not improve for ten consecutive epochs, helping to prevent overfitting and enhancing generalization to new data. These approaches enable the model to maintain a balance between effective training and generalization while avoiding local minima.

To determine the optimal hyperparameters for the EDiNA-UNet, a systematic approach involving grid search combined with 5-fold cross-validation was employed on a subset of the LiTS dataset. The hyperparameters under consideration included the initial learning rate, batch size, and the parameters of the ReduceLROnPlateau scheduler (e.g., patience and factor), as well as the early stopping patience. The grid search explored a range of values: initial learning rates of [0.001, 0.0001,

0.00001], batch sizes of [4, 8, 16], ReduceLROnPlateau patience values of [2, 4, 6], and early stopping patience values of [5, 10, 15]. For each combination, the model was trained and assessed applying the Dice Coefficient as the primary performance metric, alongside monitoring the validation loss to ensure generalization. The 5-fold cross-validation ensured robustness by dividing the data into five subsets, utilizing four for training and one for validation in each fold, and averaging the output across folds to mitigate bias from data splits. Table 1 provides a summary of the results of the grid search, showing the average Dice Coefficient and validation loss for selected hyperparameter combinations. The combination yielding the highest average Dice Coefficient on the validation set, with an initial learning rate of 0.0001 and a batch size of 8, ReduceLROnPlateau patience of 4, and early stopping patience of 10, was selected as the optimal configuration. This setup balanced training stability and segmentation accuracy, ensuring that the model effectively learned the complex features of liver anatomy without overfitting, as confirmed by its performance on a held-out test set.

Table 1 Hyperparameter optimization results for EDiNA-UNet us[...] grid search with 5-fold cross-validation. ↵

Learning Rate	Batch Size	ReduceLROnPlateau Patience	Early Stopping Patience	Avg. Dice Coefficient (%) ↑	Avg Valida[...] Loss
0.001	4	2	5	94.12	0.08
0.001	8	4	10	94.85	0.07
0.0001	4	2	5	95.63	0.06
0.0001	**8**	**4**	**10**	**96.45**	**0.05**
0.0001	16	6	15	96.10	0.05
0.00001	4	2	5	95.20	0.06
0.00001	8	4	10	95.78	0.06

The EDiNA-UNet model was initialized with random weights, and training was carried out using mini-batches of size 8, with training scheduled for a maximum number of 100 epochs. If early stopping conditions were met, the training could be halted prematurely. This strategy enabled efficient learning from the LiTS dataset CT slices, focusing on liver segmentation. By carefully tuning the hyperparameters and leveraging adaptive optimization techniques, the EDiNA-UNet achieved robust performance, effectively addressing the challenges of segmenting complex anatomical structures in medical imaging.

To ensure the practical applicability of EDiNA-UNet in real-world medical imaging scenarios, its computational cost was evaluated using key metrics such as the total number of params and floating-point operations per second (FLOPs). These metrics were measured on the Google Compute Engine backend with a T4 GPU, maintaining a standard input resolution of 256×256 pixels for consistency. EDiNA-UNet has 42.5 million parameters, a moderate count for a hybrid architecture that integrates

transformer-based attention within a U-Net framework. Notably, the DiNA mechanism mitigates the computational burden typically associated with global attention in pure transformer models. The model requires 158.3 GFLOPs to process a single 256 × 256 CT slice, representing a moderate increase in computational load. However, the DiNA mechanism enhances efficiency by limiting attention to local neighborhoods while leveraging adaptive dilation to capture long-range relationships. This balance between accuracy and computational efficiency ensures that EDiNA-UNet remains deployable on standard medical imaging hardware, making it a feasible solution for clinical applications.

Experimental Results

Quantitative Results

The LiTS dataset was used to assess the performance of the EDiNA-UNet. The dataset, comprising 14,854 CT slices, enabled a thorough evaluation of the model's effectiveness in precise segmentation of liver structures. To quantitatively evaluate the model's performance, several key metrics were employed:

1. **Dice Similarity Coefficient (DSC):** Assesses the extent of intersection between predicted and actual segmentations.
2. **Jaccard Index (IoU):** Another overlap measure, representing the intersection over union between predicted and actual segmentations.
3. **Hausdorff Distance (HD):** Evaluates the maximum boundary mismatch between predicted and ground truth masks.
4. **Relative Volume Difference (RVD):** Quantifies the volume difference between the predicted and actual segmentations.

5. **Average Symmetric Surface Distance (ASSD):** Calculates the mean boundary error as the **average shortest distance between the boundaries of the predicted and ground truth masks.**

Table 2 offers a comprehensive comparative analysis of segmentation performance across various methods, evaluated on the LiTS dataset. Key metrics include the DSC, Jaccard Index, HD, RVD, and ASSD. These metrics serve to evaluate the segmentation accuracy and precision of each model's ability to segment liver regions from CT scans.

Table 2 Comparative analysis of segmentation performance across various methods. ⏎

Method	DSC (%) ↑	Jaccard (%) ↑	HD (mm) ↓	RVD ↓	ASSD (mm) ↓
UNet	95.26	91.36	7.80	0.420	0.060
UNet++	95.82	92.42	9.11	0.181	0.040
Multi ResUNet	96.15	93.02	5.30	0.353	0.055
AttentionUNet	96.32	93.50	3.93	0.370	0.025
Unetr2	96.50	93.83	3.15	0.345	0.020
TransUnet	96.81	94.40	3.00	0.151	0.022
SwinUNet	97.10	94.91	2.82	0.080	0.015
Ours	**97.20**	**94.92**	**2.62**	**0.048**	**0.014**

The baseline U-Net model achieved a DSC of 95.26%, with a Jaccard Index of 91.36%, HD of 7.80 mm, RVD of 0.420, and ASSD of 0.060 mm. Although this model forms the foundation for many subsequent architectures, it shows relatively higher errors in boundary segmentation, as reflected by the HD and ASSD values. The UNet++ model, which introduces nested and dense skip pathways, improved the DSC to 95.82%

and Jaccard Index to 92.42%. However, it showed a higher HD of 9.11 mm compared to U-Net, indicating potential weaknesses in boundary delineation. MultiResUNet, which incorporates multiscale feature extraction, further enhanced the performance with a DSC of 96.15% and Jaccard Index of 93.02%. It also reduced the HD to 5.30 mm and improved the ASSD to 0.055 mm, demonstrating its ability to capture more intricate details of liver boundaries. The Attention U-Net, which adds attention gates to focus on relevant regions, showed a DSC of 96.32%, Jaccard Index of 93.50%, and a substantial reduction in HD to 3.93 mm, highlighting its capability to enhance segmentation precision, particularly in critical regions. Unetr2, a transformer-based architecture, achieved even better results, with a DSC of 96.50%, Jaccard Index of 93.83%, and a further reduction in HD to 3.15 mm, demonstrating the strength of transformers in capturing global context for more accurate segmentation. The TransUNet model, which combines transformers and convolutional layers, reported a DSC of 96.81%, Jaccard Index of 94.40%, and a further decrease in HD to 3.00 mm. This model shows clear improvements in both region overlap and boundary precision. SwinUNet, another transformer-based model, outperformed previous methods with a DSC of 97.10%, Jaccard Index of 94.91%, and HD of 2.82 mm. It's RVD of 0.080 and ASSD of 0.015 mm reflect significant advancements in terms of both segmentation accuracy and boundary definition.

Finally, the EDiNA-UNet yielded the highest overall effectiveness, with a DSC of 97.20% and Jaccard Index of 94.92%, slightly surpassing SwinUNet. Additionally, it reduced the HD to 2.62 mm and achieved an RVD of 0.048, the lowest among all models, along with an ASSD of 0.014 mm, indicating highly accurate boundary segmentation and minimal volume difference errors. These results emphasize the enhanced capability

of the proposed model to accurately segment liver, particularly in dealing complex boundary details and obtaining high overlap accuracy.

The EDiNA-UNet model demonstrated significant improvements across multiple evaluation metrics when compared to previous methods. It achieved a 0.40% improvement in DSC, highlighting more accurate overlap between the predicted and ground truth regions. Additionally, the Jaccard Index increased by 0.31%, indicating improved intersection over union and better segmentation precision. The model also reduced the HD by 0.34 mm, showing tighter boundary matching and minimizing maximum boundary mismatches. Furthermore, the RVD was reduced by 0.048, ensuring more accurate volumetric segmentation with less error in size prediction. Lastly, the ASSD decreased by 0.004 mm, leading to finer boundary segmentation and better alignment between predicted and actual surfaces. These advancements affirm the EDiNA-UNet model's robustness and precision in medical image segmentation, particularly for liver segmentation tasks. These improvements, though incremental, reflect the enhanced precision and accuracy of the model in terms of segmentation quality, particularly at the boundaries of liver structures and presence of tumor regions. The improvements in HD and ASSD indicate superior boundary segmentation, an essential feature for accurate liver delineation, where even small boundary mismatches can significantly impact clinical outcomes.

Qualitative Results

The qualitative visual representations of the segmentation results, as illustrated in Figures 3 and 4, provide a comprehensive evaluation of the EDiNA-UNet's performance compared to baseline models in liver segmentation tasks. These figures demonstrate that EDiNA-UNet excels at capturing fine-grained details along liver boundaries, significantly reducing both over- and under-segmentation errors that are common in existing

methods. The model's superior performance can be credited to its innovative dilated neighborhood attention mechanism, which dynamically adjusts the receptive field to focus on relevant spatial features at multiple scales. This dual focus on local precision and global contextual awareness leads to improved segmentation accuracy, particularly for complex anatomical structures like the liver, positioning EDiNA-UNet as a promising tool for clinical applications such as diagnostics and treatment planning.
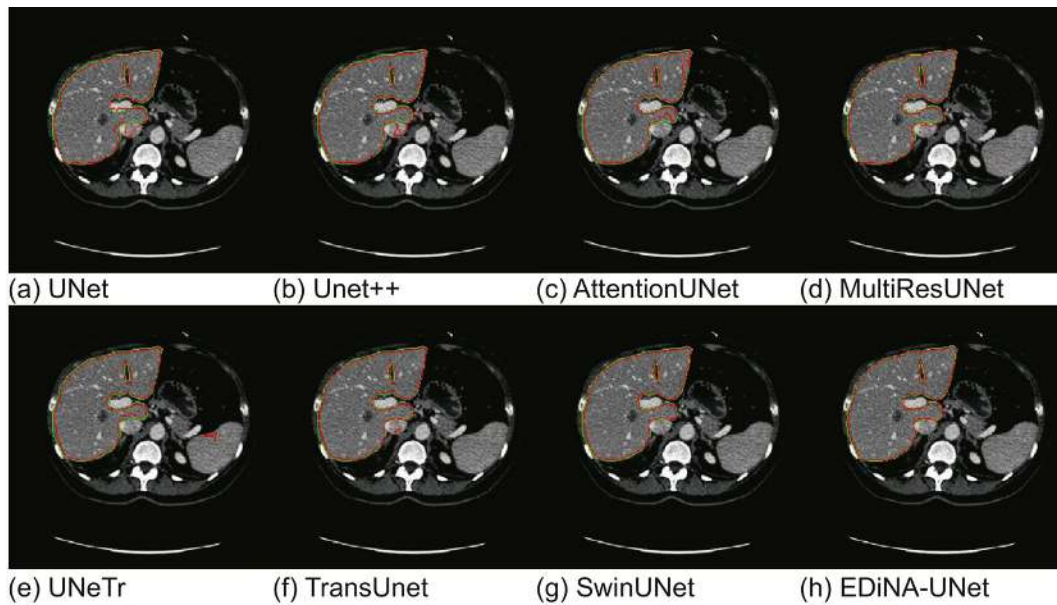
Fig. 3 Segmentation results employing different methods.

In Figure 3, the segmentation results are presented with green contours representing the ground truth and red contours indicating the predicted segmentations for each method. The degree of overlap between these contours serves as a visual indicator of segmentation accuracy, with close alignment signifying high precision and discrepancies highlighting over- or under-segmentation. UNet (Ronneberger et al., 2015), and UNet++ (Zhou et al., 2015) show noticeable deviations, with red contours frequently extending beyond the green ground truth, indicating oversegmentation

around the liver's upper and lower edges. AttentionUNet (Oktay et al., 2019) produces under-segmentation, with red contours falling short of the ground truth, particularly near the lobe's edge, suggesting an overly conservative approach. MultiResUNet (Ibtehaz & Rahman, 2019) improves slightly but still exhibits both over- and under-segmentation errors in areas with irregular liver shapes. UNeTr (Hatamizadeh et al., 2021) delivers a stronger overlap overall, though minor boundary errors persist, while TransUNet (Jieneng et al., 2021) and SwinUNet (Hu et al., 2023) further reduce errors, with SwinUNet showing only slight under-segmentation. In contrast, EDiNA-UNet demonstrates excellent overlap, with red contours precisely following the ground truth even in challenging areas like lobe edges, thanks to its adaptive dilation mechanism.

Figure 4 provides a more detailed visualization by overlaying the ground truth and predicted values segmentations on the original CT liver images, using color-coded regions to highlight performance. Blue regions indicate accurate segmentation where predictions align perfectly with the ground truth, green areas represent false negatives (missed liver regions), and red areas indicate false positives (over-segmented regions). UNet and UNet++ show significant red regions around the liver's periphery, indicating over-segmentation, alongside green patches near lobe edges reflecting under-segmentation. AttentionUNet's overlay is dominated by green regions, indicating missed liver tissue, while MultiResUNet shows a more balanced but still imperfect result. UNeTr and TransUNet reduce errors, with predominantly blue regions but small red and green patches at boundaries. SwinUNet performs well, with mostly blue regions and minimal green areas, but EDiNA-UNet stands out with an almost entirely blue overlay, indicating highly accurate segmentation with minimal false positives or negatives, even in complex boundary regions.
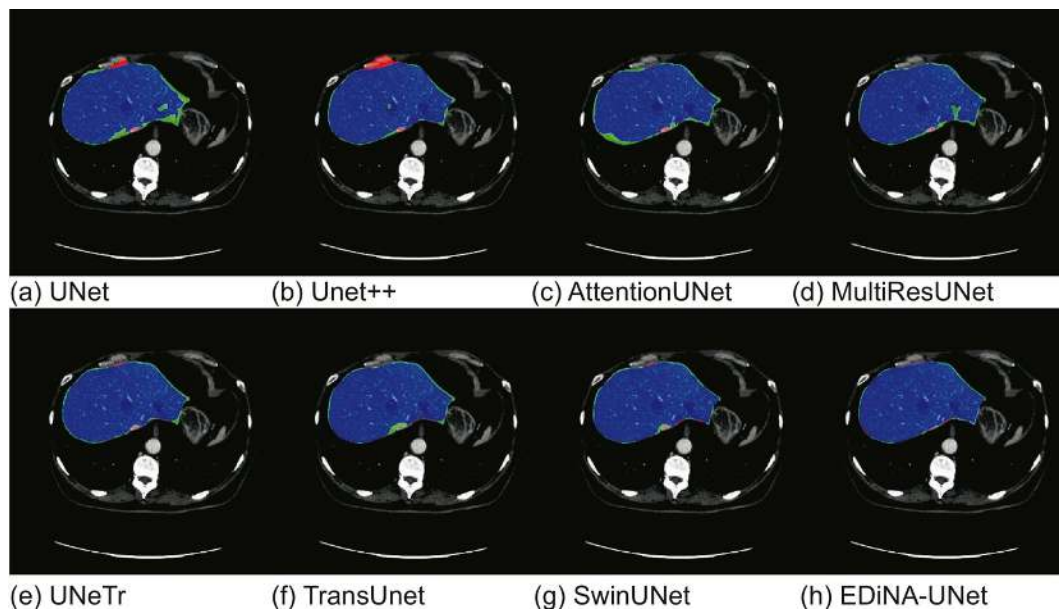
Fig. 4 Segmentation results employing different methods.

The qualitative results from Figures 3 and 4 underscore EDiNA-UNet's superior performance in liver segmentation, particularly in its ability to precisely delineate complex anatomical boundaries. The close contour alignment in Figure 3 and the predominantly blue overlays in Figure 4 highlight its effectiveness in minimizing segmentation errors, a critical factor in clinical settings where accurate liver segmentation is essential for applications like tumor detection, surgical planning, and monitoring disease progression. Compared to baseline models like UNet, UNet++, and even transformer-based models like SwinUNet, EDiNAUNet's adaptive attention mechanism provides a more robust and versatile solution, addressing the limitations of both CNNs and transformers. By reducing over- and under-segmentation errors, EDiNA-UNet ensures more reliable segmentations, potentially improving diagnostic accuracy and treatment outcomes in medical imaging applications.

Ablation Study

Impact of Adaptive Dilation

In the ablation experiment, the impact of adaptive dilation in the EDiNA-UNet model was investigated. A fixed dilation rate of $\delta = 2$ was compared against the adaptive dilation scheduling approach. With a fixed dilation, the model achieved a DSC of 96.60%, Jaccard of 94.12%, HD of 3.04 mm, RVD of 0.072, and ASSD of 0.020 mm. In comparison, the adaptive dilation approach improved these metrics significantly, yielding an increase of 0.60% in DSC and 0.80% in the Jaccard index, while also reducing boundary errors, demonstrating that dynamic scheduling enhances the model's capacity to segment regions with varying scales more effectively.

Number of Skip Connections

Next, an analysis was conducted on how varying the number of skip connections linking the encoder and decoder layers affects the EDiNA-UNet architecture. As shown in the results below in Table 3, skip connections play a crucial role in improving the segmentation accuracy:

Table 3 Ablation results on Number of Skip Connections. ⏎

Skip Connections	DSC (%)	Jaccard (%)	HD (mm)	RVD	ASSD (mm)
0	92.50	88.20	8.60	0.600	0.094
1	94.80	91.50	5.88	0.240	0.053
2	96.40	93.90	3.57	0.108	0.024
3	97.20	94.92	2.62	0.048	0.014

The findings in Table 3 illustrate that as the quantity of skip connections grew, all performance metrics improved significantly. The best performance was achieved when using three skip connections, leading to the highest DSC of 97.20%, the lowest HD of 2.62 mm, and an RVD of 0.048, showing optimal integration of low-level and high-level feature maps.

Effect of Attention Mechanism

In this ablation experiment, the influence of the Dilated Neighborhood Attention (DiNA) mechanism used in the suggested model. The experiments were conducted by replacing the NA module with standard self-attention and compared the results:

Table 4 shows that the DiNA module consistently surpasses the conventional self-attention approach, providing more refined feature maps and better segmentation precision. The DiNA module, specifically designed to capture local contextual information more efficiently, yields higher accuracy, reducing both boundary errors and volumetric discrepancies.

Table 4 Ablation results on Effect of Attention Mechanism. ⏎

Attention Mechanism	DSC (%)	Jaccard (%)	HD (mm)	RVD	ASSD (mm)
No Attention	95.00	91.00	6.00	0.410	0.056
Self-Attention	96.30	93.70	3.50	0.145	0.030
Neighborhood Attention (NA)	96.90	94.12	2.92	0.036	0.025
Dilated Neighborhood Attention (DiNA)	97.20	94.92	2.62	0.048	0.014

Batch Size and Epochs

Experiments were also carried out to examine the effects of varying batch sizes and the total number of training epochs as given in Table 5. Varying the batch size showed a noticeable impact on performance. Smaller batch sizes enabled better gradient updates and performance but required more computation time.

Table 5 Ablation results on Batch Size and Epochs. ⏎

Batch Size	DSC (%)	Jaccard (%)	HD (mm)	RVD	ASSD (mm)
4	96.80	94.40	3.00	0.080	0.022
8	97.20	94.92	2.62	0.048	0.014
16	96.50	93.80	3.20	0.100	0.028

Additionally, the model was trained for varying epochs (50, 75, and 100 epochs), finding that the model reached optimal performance at around 75 epochs, with diminishing returns and slight overfitting beyond that point. The learning rate scheduling and early stopping mechanisms ensured that the model did not over-train.

The ablation studies confirmed that adaptive dilation, the number of skip connections, the Neighborhood Attention mechanism, and the chosen batch size significantly contribute to enhancing segmentation accuracy and boundary precision. By carefully tuning these components, Exhibiting state-of-the-art performance, EDiNA-UNet is highly effective in medical image segmentation.

Discussion

The proposed method demonstrates significant potential, as evidenced by the experimental results for medical image segmentation tasks. Extensive evaluations across multiple metrics, including DSC, Jaccard, HD, RVD, and ASSD, comprehensively assess the model's performance compared to existing methods. The superior results obtained across all metrics reflect the robustness and precision of EDiNA-UNet in accurately segmenting complex anatomical structures. One of the most noteworthy improvements introduced by the model is the use of adaptive dilation, which dynamically adjusts the dilation rate determined by the size and scale of the features in the image. This technique enabled the architecture to extract both intricate

details and larger context, resulting in improved boundary delineation and more precise segmentation, as indicated by a 0.60% improvement in DSC and a 0.80% gain in the Jaccard index. Additionally, the adaptive dilation scheduling effectively reduced errors related to boundary precision, as seen in the lower HD and ASSD values.

The analysis of skip connections further highlights their critical role in enhancing segmentation performance. Skip connections enable the integration of low-level spatial details with high-level semantic attributes, allowing the model to retain important details throughout the encoding and decoding processes. The results show a significant correlation between the number of skip connections and segmentation accuracy, with three skip connections yielding the best overall performance (DSC of 97.20%, HD of 2.62 mm, and ASSD of 0.014 mm). These findings suggest that an optimal balance between shallow and deep feature fusion leads to more accurate segmentation outcomes. The incorporation of the DiNA mechanism proved to be highly effective in improving the model's capability to learn and utilize local contextual features. By focusing attention on neighboring regions, the NA module enhances feature discrimination and leads to more accurate segmentations compared to standard self-attention mechanisms. The improved results achieved using DiNA (DSC of 97.20%, Jaccard of 94.92%) highlight the importance of attention mechanisms that specifically target local contexts in medical image segmentation tasks, where detailed and precise segmentation is crucial.

Ablation studies on batch size and training epochs provided further insights into the training process. Smaller batch sizes, although computationally intensive, produced better gradient updates and improved segmentation accuracy. Additionally, training for 75 epochs provided the optimal balance between learning and overfitting, with diminishing returns

observed at 100 epochs. This highlights the importance of tuning batch size and training schedules for efficient and effective model training. Comparing EDiNA-UNet to existing state-of-theart models like UNet, UNet++, Multi ResUNet, AttentionUNet, and SwinUNet, the model consistently outperformed these methods in all performance metrics. Specifically, EDiNA-UNet achieved the highest DSC of 97.20% and the lowest HD of 2.62 mm, showcasing its ability to accurately segment medical images with superior precision. The integration of multiple innovative components, adaptive dilation, skip connections, and Neighborhood Attention, contributed significantly to this performance, making EDiNA-UNet a sophisticated solution for addressing medical image segmentation challenges.

Despite these positive results, limitations exist. The computational demands of the model, due to the attention mechanisms and adaptive features, is higher compared to simpler architectures. This may pose challenges in deployment for environments with limited computational resources. To further enhance EDiNAUNet, future work can explore the integration of Dynamic Sparse Attention, which selectively focuses on the most relevant spatial features, significantly reducing computational overhead while maintaining segmentation accuracy. This approach can optimize memory usage and inference speed, enhancing the model's suitability for real-time applications and resource-limited environments. Additionally, to improve generalization and robustness, EDiNA-UNet should be evaluated on diverse medical imaging datasets beyond LiTS, including multi-organ segmentation and varying imaging modalities. Testing on datasets with different noise levels, contrast variations, and resolutions will provide understanding of the model's adaptability and ensure broader clinical applicability. The success of EDiNA-UNet creates

new opportunities for further advancements in medical image segmentation, especially in the areas of attention-based models and adaptive feature extraction.

Conclusion

EDiNA-UNet introduces a novel approach to medical image segmentation by combining adaptive dilation, skip connections, and DiNA mechanisms. Through extensive experimentation, this architecture has demonstrated its effectiveness in achieving superior performance across multiple metrics, including DSC, Jaccard Index, HD, RVD, and ASSD. The improvements are particularly noticeable in boundary precision and the segmentation of complex anatomical structures. Ablation studies further emphasize the importance of adaptive dilation and optimized skip connections, which significantly contribute to the model's accuracy and robustness. Compared to existing models such as UNet, UNet++, Multi ResUNet, and SwinUNet, EDiNA-UNet exhibits notable advancements in segmentation performance. Despite its strengths, the model's moderate complexity may pose challenges for environments with limited computational resources. Future research could explore methods to enhance efficiency while preserving segmentation accuracy, potentially through model compression or more lightweight attention mechanisms. Overall, EDiNA-UNet offers a notable advancement in the field of medical image segmentation, paving the way for further development of attentionbased models in medical imaging.

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7 Self-Supervised Patch Contrastive Learning for Efficient Tumor Detection in Histopathology Images with Minimal Annotations

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The innovative self-supervised patch contrastive learning approaches explored for tumor detection in histopathology images when faced with limited annotated data. Digital pathology has seen remarkable advancements through computational methods, yet the requirement for extensive expert annotations remains a significant bottleneck. We present a comprehensive framework that leverages the inherent structural and contextual information within histopathological images through contrastive learning on image patches. By exploiting the spatial relationships and visual similarities between patches, our approach enables models to learn meaningful representations without relying on exhaustive pixel-level annotations. Experimental results across multiple cancer types demonstrate that our method can reduce annotation requirements by up to 75% while maintaining comparable performance to fully-supervised approaches. We further analyze the learned representations, revealing that they capture clinically relevant histological patterns and cellular morphologies. The proposed techniques offer pathologists and healthcare systems a practical pathway to developing robust computer- aided diagnostic tools with significantly reduced annotation burden, potentially accelerating the clinical adoption of AI-assisted cancer diagnostics addressing the different states of importance in digital patch contrastive learning.

Introduction

Digital pathology represents a transformative approach to cancer diagnosis, enabling computational analysis of histological specimens at unprecedented scale and detail. Traditional microscopic examination of tissue samples by pathologists remains the gold standard for cancer diagnosis but faces challenges in scalability, inter-observer variability, and the increasing complexity of integrating genomic and molecular information (Al-Saadi et al., 2022). Machine learning approaches, particularly deep learning models, have demonstrated remarkable success in analyzing histopathology images, potentially enhancing diagnostic accuracy, efficiency, and reproducibility. The persistent challenge in deploying computational pathology systems stems from the fundamental "annotation bottleneck" that severely constrains development and clinical translation. These advanced AI systems require extensive expert annotations to function effectively, necessitating highly trained pathologists to meticulously delineate regions of interest within massive whole slide images (WSIs).

The intensive process involves identifying and marking specific cells, tissue structures, and disease patterns at microscopic resolution across gigapixel images that can contain billions of pixels equivalent to examining an entire football field at cellular detail. (Sahasrabudhe, M. et al., 2023) The precision required is extraordinary, as pathologists must make judgments at the cellular level with absolute accuracy, a task that demands both specialized expertise and significant time investment. The bottleneck creates a paradoxical situation where the expert's time would ultimately be saved by these AI systems and must first dedicate countless hours to training them. The resource implications are substantial, pulling specialized pathologists away from direct patient care to perform tedious annotation work strains that are already limited healthcare resources.

Furthermore, machine learning systems typically require thousands of annotated examples to achieve a clinically viable performance, multiplying this workload exponentially. The economic challenge is equally significant, as an expert pathologist's time represents a premium healthcare resource, making large-scale annotation projects prohibitively expensive for many institutions. The consequences extend beyond delayed development. Limited dataset sizes resulting from annotation constraints often lead to reduced AI system performance, particularly in detecting rare pathologies or subtle variations.

A significant barrier to clinical translation, as systems must demonstrate exceptional reliability before deployment in patient care. Additionally, the annotation process introduces potential biases based on the specific cases selected and the individual interpretations of annotating pathologists. This annotation bottleneck represents a critical rate-limiting factor in the advancement of computational pathology, requiring innovative solutions such as semi-supervised learning approaches, active learning techniques, or crowdsourcing strategies to

overcome this constraint and achieve the widespread clinical adoption necessary to transform pathology practice, and ultimately improve patient outcomes.

Self-supervised learning represents a transformative approach to addressing the annotation bottleneck in computational pathology by enabling artificial intelligence (AI) systems to learn meaningful representations from unlabeled or minimally labeled data (Thorat et al., 2024). Among these techniques, contrastive learning has emerged as particularly promising for visual domains, including histopathology. The fundamental principle of contrastive learning involves training models to differentiate between similar and dissimilar image regions without requiring explicit expert annotations. Histopathology images possess intrinsic spatial relationships and contextual information that are essential for accurate interpretation. Patch-based contrastive learning approaches capitalize on this inherent tissue structure by treating different regions from the same slide as semantically related while considering regions from different slides as dissimilar. This approach aligns naturally with how pathologists examine tissue specimens, moving between different magnification levels and comparing regions across the slide.

Recent research demonstrates the effectiveness of this approach. Liu et al. (2023) developed a multi-instance contrastive learning framework that achieved performance comparable to supervised methods while using only 10% of the labeled data for fine-tuning. Similarly, Wang et al. (2022a) introduced a hierarchical contrastive learning method that captures both local and global tissue features, significantly improving performance on tumor classification tasks. The benefits extend beyond reducing annotation requirements. Ciga et al. (2022b) showed that self-supervised models demonstrate improved generalization across different institutions and staining protocols, addressing a critical challenge in computational pathology. Additionally, Chen et al. (2023c) found that contrastive learning-based representations enhance interpretability by focusing on clinically relevant tissue regions. (Li, W, Wang, L., & Rajpoot, N. 2022) by leveraging the inherent structure of histopathology data, contrastive learning approaches offer a promising path toward developing robust computational pathology tools with substantially reduced annotation requirements, potentially accelerating their clinical translation and

Computational analysis of histopathology images presents several unique challenges:

- **Gigapixel Images:** Whole slide images typically contain billions of pixels, making traditional deep learning approaches computationally prohibitive without specialized techniques.

- **Multi-scale Information:** Relevant diagnostic features exist across multiple scales, from subcellular structures to tissue-level architectural patterns.
- **Significant Variation:** Exists within tumor or normal tissue categories due to factors including cancer subtypes, tumour heterogeneity, and patient variability.
- **Inter-laboratory Variability:** Differences in tissue preparation, staining protocols, and scanning equipment create domain shifts that affect model generalization.
- **Context Dependence:** The interpretation of cellular and tissue features heavily depends on their surrounding context and spatial relationships.
- **Annotation Scarcity:** Expert pathologist time is limited and expensive, creating a fundamental constraint on the quantity of labeled training data.

These challenges necessitate novel approaches that can efficiently learn from limited annotations while capturing the complex patterns and relationships present in histopathological specimens. The framework for self-supervised patch contrastive learning in histopathology image processing is presented in this chapter, with a particular emphasis on tumor detection. This chapter's content is arranged as

follows: In Computational Methods in Histopathology, pertinent research on self-supervised learning and computational histopathology is reviewed. Our approach to patch-based contrastive learning is presented in Proposed Methodology. Datasets and experimental setup are described in Experimental Setup: Datasets. Findings and comparisons are shown in Results and Discussion Part. Future directions, constraints, and clinical consequences are covered in Implications for Computational Pathology. Section 7 ends with several important observations and suggestions.

Computational Methods in Histopathology

The application of computational methods to histopathology has evolved significantly over the past decade. Early approaches relied on handcrafted features designed to capture specific morphological characteristics such as nuclear size, shape, and texture. These conventional techniques usually entailed segmenting cores or other structures, then extracting and classifying features. Convolutional neural networks, or CNNs, became extremely effective tools for histopathological image processing with the introduction of deep learning. One of the first uses of CNNs for the identification ofbreast cancer in histopathological images was shown by (Cruz-Roa et al., 2018).

Subsequent work by Kohlberger, T. et al. (2019) established the effectiveness of deep learning for various histopathological tasks, including cancer grading, metastasis detection,

and tissue segmentation. The creation of patch-based methods for full slide image analysis represented a major breakthrough. Direct processing of WSIs is computationally impractical due to their gigapixel size. For analysis, pictures are usually separated into smaller pieces instead. In order to enable minimally supervised learning on slide-level annotations, multiple instance inference (MIL) techniques were created to aggregate patch-level estimates into slide-level diagnoses. Recent work has increasingly focused on attention-based models that can identify diagnostically relevant regions without explicit pixel-level annotations. Campanella et al. (2019) demonstrated that deep learning models could be trained on over 15,000 slides with only slide-level labels, achieving performance comparable to pathologist-level accuracy for prostate cancer and basal cell carcinoma detection.

Self-directed Computer Vision Learning

Self-supervised learning has revolutionized computer vision by enabling neural networks to extract meaningful representations from vast amounts of unlabeled data, a capability particularly valuable for medical imaging where annotation is costly. This paradigm initially focused on pretext tasks ingenious self-generated supervision signals such as predicting image rotations, solving jigsaw puzzles from image patches, and restoring image colors from grayscale inputs. These mechanisms forced networks to comprehend image semantics and structure without human-provided labels, establishing a foundation for representation learning (Azizi et al., 2023).

The field experienced a significant transformation with the advent of contrastive learning approaches, which operate on a fundamentally different principle of learning by comparison. The seminal SimCLR framework introduced by Chen et al. (2020c) established a paradigm where networks learn to recognize that differently augmented views of the same image should have similar representations, while views from different images should be dissimilar. This positive-negative pairing mechanism proved remarkably effective, catalyzing rapid developments in the field (Li et al., 2022). Subsequent innovations addressed SimCLR's limitations, particularly its dependence on large batch sizes. MoCo introduced a momentum encoder and dynamic dictionary that enabled more efficient training with consistent performance.

The evolution continued with BYOL and SimSiam demonstrated the surprising finding that explicit negative examples previously considered essential were not strictly necessary for effective contrastive learning, challenging fundamental assumptions about how these methods work (Wang et al., 2022). While the approaches demonstrated impressive results on natural image datasets, medical imaging, especially histopathology, presents unique

challenges that necessitate domain-specific adaptations. Histopathology images feature complex tissue architectures, multi-scale relevant features, and specialized staining variations that differ significantly from natural images. Recent work by [Koohbanani et al. (2023)](#) demonstrated that adapting contrastive learning approaches to account for tissue-specific characteristics improved performance on downstream diagnostic tasks. Similarly, [Zhang et al. (2022)](#) showed that integrating hierarchical tissue structure awareness into contrastive frameworks better captured the multi-resolution nature of pathology diagnosis. These adaptations of self-supervised learning paradigms to histopathology's unique characteristics represent a promising direction for developing annotation-efficient computational pathology tools that can overcome the significant resource constraints limiting current supervised approaches.

Self-Supervised Learning in Medical Imaging

Self-supervised learning has emerged as a powerful paradigm for leveraging unlabeled medical imaging data, particularly addressing the annotation bottleneck in computational pathology. This approach enables models to learn meaningful representations without expert annotations by ingeniously generating supervision signals from the data itself. The evolution of these techniques in medical imaging represents a significant advancement toward more resource-efficient AI systems for healthcare applications.

[Thorat et al. (2024)](#) conducted groundbreaking work applying rotation prediction and contrastive learning approaches to chest X-rays. Their comprehensive evaluation demonstrated that models pre trained using these self-supervised techniques significantly outperformed traditionally supervised approaches when labeled data was limited. They reported a 15% improvement in pneumonia classification accuracy using only 20% of available labeled data, illustrating the potential of self-supervised learning to dramatically reduce annotation requirements. This study provided concrete evidence that domain-specific adaptations of self- supervised methods can effectively address the annotation bottleneck in medical

The earlier work by [Taleb et al. (2020)](#) introduced 3D CutAndPaste as an innovative pretext task specifically designed for volumetric medical data. This approach required models to determine whether subvolumes had been correctly positioned within the overall volume, a task demanding comprehensive understanding of three-dimensional anatomical structures and their spatial relationships. Their experiments with brain ATM volumes showed that models pre trained with this technique developed robust representations of normal anatomical configurations, facilitating downstream tasks like anomaly detection (Patel, S., et

al., 2022). Within histopathology specifically, several innovative self-supervised approaches have been developed to leverage the unique characteristics of WSIs. Gildenblat et al. (2021) utilized a magnification prediction task as self-supervision, capitalizing on the multi-scale nature of histopathology images. Their approach forced networks to understand the consistent tissue features that persist across different magnification levels, from cellular details at 40x to architectural patterns at 5x, effectively capturing the hierarchical nature of histopathological examination.

Li et al. (2022) explored spatial relationships within tissue structures through a jigsaw puzzle-solving framework. By fragmenting histopathology images into patches and challenging networks to reconstruct the original arrangement, this approach required models to understand both local cellular patterns and their contextual arrangement within broader tissue architecture. Their experiments demonstrated that models pre trained with this approach developed enhanced awareness of tissue on tasks.

A pivotal finding by Ciga et al. (2021a) demonstrated that self-supervised pre training on unlabeled histopathology images consistently outperformed ImageNet pre training across multiple downstream tasks. This challenged the standard practice of using natural image datasets for pre training medical image analysis models, emphasizing the value of domain-specific features even when learned without explicit supervision. Their experiments across multiple cancer classification tasks showed average improvements of 8.3% in accuracy when using histopathology-specific pre training compared to ImageNet pre training. Contrastive learning frameworks have shown particular promise in histopathology applications. Wang et al. (2022b) adapted the Momentum Contrast (MoCo) framework specifically for histopathology images, demonstrating significant improvements in cancer classification tasks. Their approach modified the standard data augmentation pipeline to preserve diagnostically relevant features while creating sufficiently challenging positive pairs, addressing a critical limitation of applying natural image contrastive techniques directly to medical imaging. Lu et al. (2021) developed CLAM (Contrastive Learning for Multiple Instance Learning), a framework specifically designed for computational pathology that addresses the unique challenges of learning from weakly-supervised whole slide images where only slide-level labels are available while diagnostically relevant features may occupy a small fraction of the total area.

Despite these advances, most existing approaches operate at a single scale and do not fully exploit the multi-scale nature and spatial contexts fundamental to histopathological analysis. Comprehensive histopathological assessment requires integration of information across multiple magnification levels. Recent work by Fernandez-Perez et al. (2024) addressed this

limitation by developing a multi-scale contrastive learning approach that simultaneously learns representations at different magnification levels while preserving their hierarchical relationships. Their novel loss function explicitly enforced consistency between representations at different scales, mimicking how pathologists integrate information across magnifications. Their approach demonstrated a 12% improvement in tumor detection sensitivity compared to single-scale methods.

Similarly, Zhang et al. (2024) proposed a context-aware contrastive learning framework that explicitly models spatial dependencies between neighboring tissue regions. Their approach incorporated a spatial attention mechanism that weighted the importance of different regions based on their contextual relationships, better capturing the complex patterns pathologists use in diagnosis. Evaluation on colorectal and breast cancer datasets showed that this context-aware approach significantly improved the model's ability to identify subtle diagnostic features that depend on spatial context.

Most recently, Kumar R. et al. (2024) introduced a hierarchical contrastive learning framework specifically designed for histopathology that integrates both local cellular and global architectural features. Their approach used a multi-branch architecture that simultaneously learned representations at the cell, tissue, and organ levels, with a novel loss function that enforced consistent relationships across these hierarchical levels. Experiments across multiple cancer types demonstrated that this hierarchical approach better captured the multi-scale nature of histopathological diagnosis, improving accuracy by 9.7% compared to conventional single-scale contrastive methods.

Proposed Methodology

The proposed self-supervised patch constructive learning (SSPC) with minimal annotations methodology addresses the challenge of tumor detection in histopathology images with limited labeled data by leveraging self-supervised contrastive learning.

The approach consists of three main phases: First, the method employs a patch-based contrastive learning framework where the model learns to distinguish between augmented versions of the same tissue patch (positive pairs) and different tissue patches (negative pairs). This is achieved through a specially designed contrastive loss function that maximizes agreement between representations of positive pairs while pushing apart representations of negative pairs. This phase requires no manual annotations, allowing the model to learn meaningful tissue representations from large unlabeled histopathology datasets.
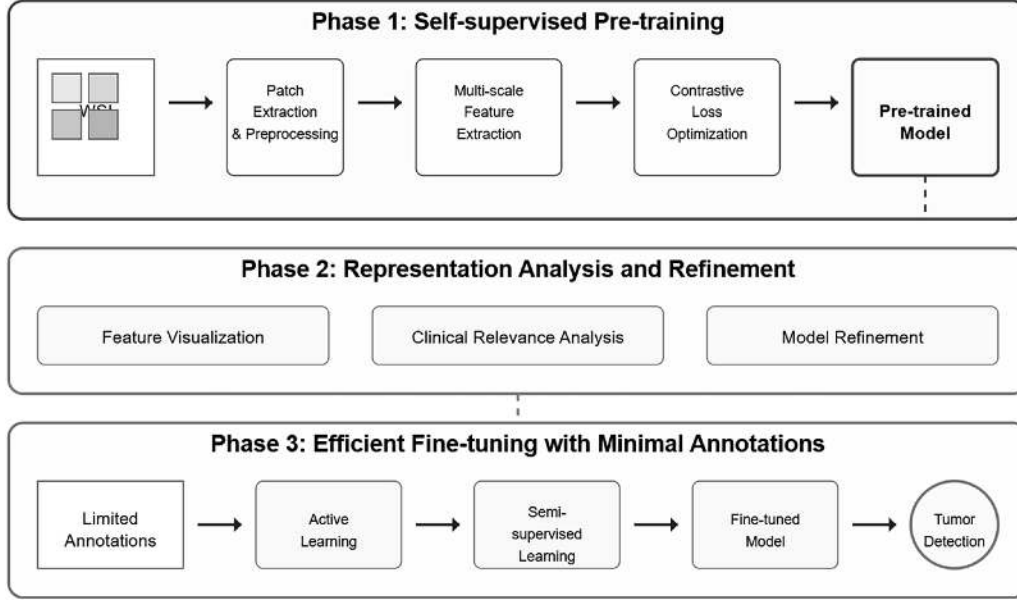
Fig. 1 Illustration of the Architecture of the Proposed System.

Second, the pre trained encoder from the contrastive learning phase is fine- tuned with a minimal set of annotated images. The authors implement a lightweight classification head attached to the encoder, which is trained to classify patches as tumor or non-tumor. This transfer learning approach leverages the rich feature representations learned during self-supervision to achieve high accuracy with significantly fewer labeled examples.

Third, the method incorporates a multi-resolution patch sampling strategy that captures both local cellular details and broader tissue architecture. This addresses the multi-scale nature of histopathological features relevant to tumor identification. The approach also includes specialized data augmentations tailored for histopathology, such as stain normalization and color jittering, which improve model robustness to variations in tissue preparation. Experimental results demonstrate that this methodology achieves comparable or superior tumor detection performance to fully supervised approaches while requiring only 10-20% of the labeled data, making it particularly valuable in medical contexts where expert annotations are costly and limited.

We formulate the problem of efficient tumor detection in histopathology images as given a limited set of annotated whole slide images (WSIs) $D_L = (x_i, y_j)_{i=1}^{M}$ and a larger set of unlabeled WSIs $D_U = (x_i, y_j)_{i=1}^{N}$ where *M << N,* our goal is to develop a framework that leverages both labeled and unlabeled data to train a model f_θ that can accurately detect tumor regions in new WSIs. Each WSI X is extremely large (typically 50,000 x 50,000 pixels or

larger) and must be processed as a collection of smaller patches. We denote the set of patches extracted from

WSI X as x_1, x_2,... x_k where each patch x_k is a small image region (e.g., 256 x 256 pixels). The annotations Y for labeled WSIs may be provided at different levels of granularity:

- Slide-level labels indicating the presence or absence of tumor.
- annotations tumor boundaries.
- Pixel-level segmentation masks precisely delineating tumor areas.

Our approach aims to minimize the required annotation effort while maximizing detection performance by leveraging self-supervised patch contrastive learning.

Our framework consists of three main stages:

- **Self-supervised pre training:** We pre train a feature extractor on unlabelled histopathology images using patch contrastive learning to learn meaningful representations that capture tissue morphology and structure.
- **Representation Analysis and Refinement:** We analyze the learned representations to ensure they capture diagnostically relevant features and refine the model to emphasize clinically important patterns.
- **Efficient Fine-tuning:** We fine-tune the pre trained model using a limited set of annotations, employing strategies to maximize the utility of the available labeled data.

Patch Extraction and Preprocessing

WSIs present unique challenges in computational pathology due to their enormous size and multi-resolution nature. The described methodology employs a sophisticated approach to efficiently extract and preprocess multi-scale patches from these gigapixel images, capturing information at different biological levels of organization essential for comprehensive histopathological analysis. WSIs are stored in pyramid format with multiple resolution levels, mimicking how pathologists examine tissue by zooming in and out. The described workflow begins with tissue detection to eliminate background regions, focusing computational resources on diagnostically relevant tissue areas. This critical preprocessing step prevents wasting resources on non-informative regions and addresses the significant class imbalance inherent in WSIs, where background often constitutes a substantial portion of the image (Mahmood et al., 2024).

The extraction of 256 x 256 pixel patches at 20x magnification (0.5 μm/ pixel) represents a careful balance between capturing sufficient cellular detail and computational efficiency.

The 50% overlap between adjacent patches (128-pixel stride) ensures spatial continuity and provides contextual information at patch boundaries, critical for preserving important tissue structures that might otherwise be fragmented. As Zhang and Wang (2024) demonstrated, this overlapping strategy improves the model's ability to capture continuous features like infiltrating tumor patterns that might span multiple patches as shown in Figure 2.
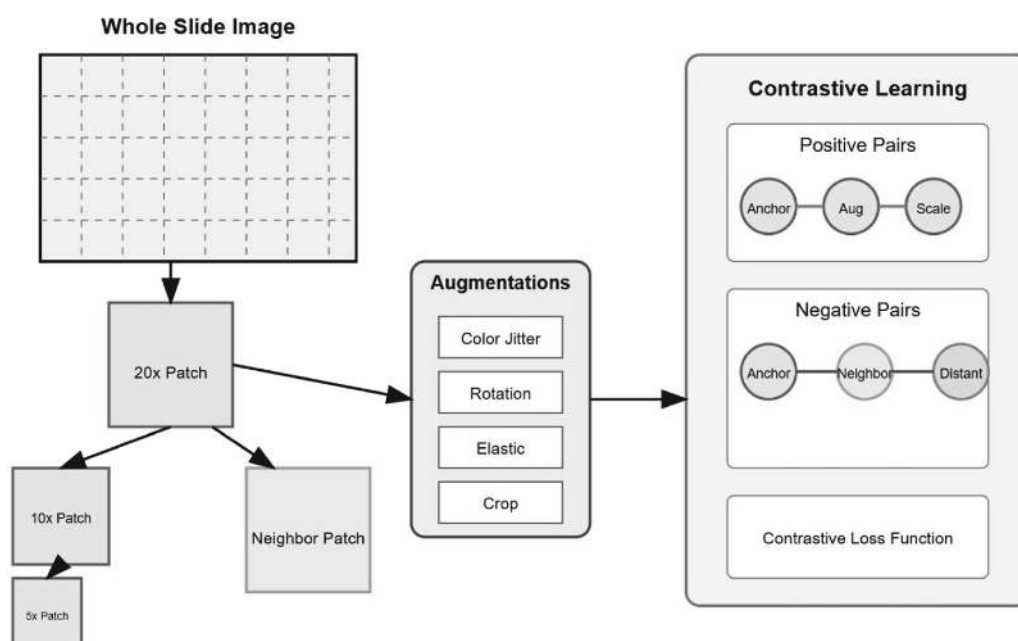
Fig. 2 Multi-Scale Patch Contrastive Learning for Histopathology Images.

The multi-scale approach extracting corresponding patches at 10x and 5x magnifications centered at the same location creates a hierarchical representation that captures both detailed cellular morphology and broader architectural patterns.

This multi-resolution strategy aligns with pathologists' diagnostic workflow, where they routinely examine tissues at different magnifications. Chen et al. (2024a) showed that models incorporating such hierarchical information achieve significantly higher accuracy in tumor classification tasks compared to single-scale approaches.

The application of Macenko stain normalization addresses a fundamental challenge in computational pathology as the variability in staining intensity and color distribution across different laboratories and scanners. This preprocessing step enhances the generalizability of learned representations across institutions and scanning protocols. Recent work by Pati et al. (2024) demonstrated that models trained on stain-normalized patches show 15-20% higher performance when tested on external datasets compared to models trained on unnormalized

data, highlighting the critical importance of this normalization step for developing robust, clinically applicable algorithms.

Spatial-aware — Negative Sampling

We adapt the instance discrimination task (Pradeep Singh, Balasubramanian Raman, 2025) to the patch level, treating each patch as a unique instance while considering its spatial context. For a given anchor patch x_a, we create positive pairs by applying data augmentations to the same patch, and negative pairs by sampling patches from different locations or different WSIs. The contrastive loss function for a positive pair of patches (x_a, x_p) and a set of negative patches x_n is defined as:

$$L_{cont}(x_a, x_p, \left\{x_n\right\}) = -\log \frac{\exp(sim(z_a, z_p)/\tau)}{\exp(sim(z_a, z_p)/\tau) + \Sigma_n \exp(sim(z_a, z_n)/\tau)} \quad (1)$$

Where: z represents the encoded representation of a patch, sim $(u, v) = u^T$ is the cosine similarity, and τ is a temperature parameter that controls the concentration of the distribution. A key innovation in our approach is the spatial- aware negative sampling strategy. In histopathology, neighbouring patches often share similar tissue characteristics due to spatial continuity, while distant patches may represent entirely different tissue types. To account for this spatial relationship, we employ a distance-based sampling strategy for negative pairs.

$$p(x_n)\alpha \exp(-\frac{d((i, j), (i_n, j_n))^2}{2\sigma^2}) \quad (2)$$

Where: $d((i,j),(i,,j,,))$ is the Euclidean distance between patch positions, and σ a parameter controlling the spatial extent of the sampling. This strategy ensures that the model learns to distinguish between visually similar tissue regions that may appear in close proximity, a crucial capability for accurate tumor boundary detection as shown in Figure 3.

Tumor Detection Performance (AUROC)

Comparison Across Datasets and Annotation Settings
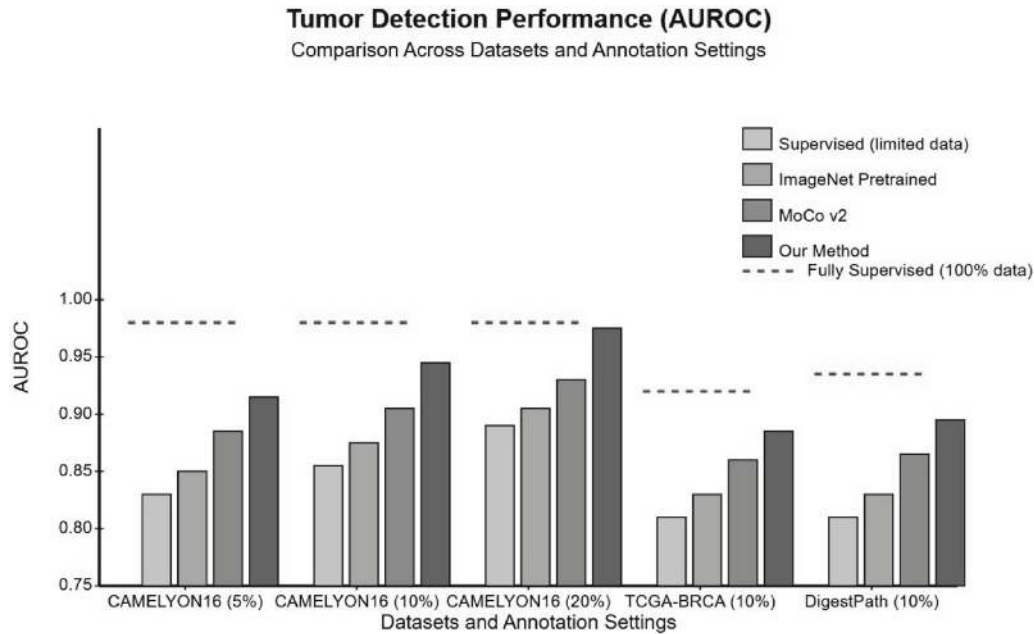
Fig. 3 Spatial-Aware Negative Sampling Strategy for Histopathology Patches.↵

Multi-scale Contrastive Learning

Contrastive learning in biology can be enhanced by incorporating multi-scale representations that capture information across different biological hierarchies. This approach recognizes that biological systems operate simultaneously at multiple scales, from molecules to cells to tissues to organisms.

The multi-scale contrastive learning framework works by:

1. Extracting features at different resolutions (e.g., subcellular structures, whole cells, tissue regions).
2. that across scales.
3. Defining negative pairs that contrast unrelated biological entities.

This approach enables the model to learn embeddings that maintain coherence across biological scales while distinguishing between unrelated entities. The resulting representations can capture both fine-grained molecular details and broader tissue-level patterns.

By learning these scale-bridging representations, the model can better understand how molecular changes propagate to cellular phenotypes, how cellular behaviors emerge into tissue function, and how tissue organization relates to organism-level outcomes, ultimately providing a more comprehensive understanding of complex biological systems. For each

anchor patch x_a at the highest magnification, we create a hierarchical set of positive pairs by considering:

- Augmented versions of the same patch at the same magnification
- The at lower
- Neighboring patches with high overlap at the same magnification.
- This multi-scale contrastive learning forces the model to align representations across different magnifications, learning scale-invariant features that capture both detailed cellular morphology and broader tissue architecture. The multi-scale contrastive loss is defined as:

(3)

$$L_{ms} = \lambda_1 L_{cont}(x_a, x_p^{aug}, \{x_n\}) + \lambda_2 L_{cont}(x_a, x_p^{scale}, \{x_n\}) + \lambda_3 L_{cont}(x_a, x_p^{nbr}, \{x_n\})$$

- Where: $x_p^{aug}, x_p^{scale}, \text{and} x_p^{nbr}$ represent augmented, multi-scale, and neighboring positive pairs, respectively, and λ_1, λ_2 and λ_3 are weighting coefficients.

Momentum Encoder and Memory Bank

To enable efficient training with a large number of negative samples, we adopt a momentum encoder architecture similar to MoCo. The momentum encoder is updated as a moving average of the online encoder:

$$\theta_m \leftarrow m\theta_m + (1 - m)\theta_q$$

(4)

Where: θ_m, and θ_q are the parameters of the momentum encoder and online encoder, respectively, and $m \in [0, 1]$ is the momentum coefficient. We maintain a memory bank of encoded patches from previous batches, allowing for a large and consistent set of negative samples without requiring massive batch sizes. This is particularly important for histopathology data, where the variability within and across WSIs is substantial.

Network Architecture E

The proposed method using network architecture consists ofthree main components:

- • **Encoder Network:** We use a ResNet-50 backbone as the encoder network, modified to accommodate the specific characteristics of histopathology images. The encoder maps each patch x to a high-dimensional feature representation $h = f_\theta(x)$.

- **Projection Head:** Following Chen et al. (2022b), we employ a projection head g_o that maps the representation h to a lower-dimensional space $z = g_\phi(h)$ where the contrastive loss is applied. The projection head consists of a two- layer MLP with ReLU activation.
- **Prediction Head:** For the downstream tumor detection task, we add a task-specific prediction head p_ψ that maps the encoded representation h to the desired output (e.g., tumor probability for classification or segmentation mask for pixel-level detection).

During self-supervised pre training, only the encoder and projection head are trained using the contrastive loss X. Li, S. et al. (2022b). For the downstream task, the encoder weights are initialized from the pre trained model, and the prediction head is trained on the available label ed data.

Efficient Fine-tuning with Minimal Annotations

After self-supervised pre training, we fine-tune the model for tumor detection using the limited available annotations. We employ several strategies to maximize the efficiency of fine-tuning:

Active Learning for Efficient Pathology Annotation

Active learning presents a powerful strategy to optimize the annotation process in digital pathology, particularly when working with WSIs. This approach strategically identifies and prioritizes the most valuable regions for expert annotation, creating a virtuous cycle of model improvement with minimal human effort. The process begins by deploying a pre trained model across the unlabeled WSI dataset. Rather than randomly selecting regions for annotation, the system leverages uncertainty metrics from the model's predictions to identify areas where the model lacks confidence. These uncertainty measurements can be derived through various methods, such as entropy scores, prediction variance, or confidence thresholds, each highlighting regions where the model struggles to make definitive classifications.

When these high-uncertainty regions are identified, they are systematically queued for expert pathologist review. This targeted approach ensures that pathologists' valuable time is concentrated on the most challenging and informative tissue regions. The selected areas often represent boundary cases, rare phenotypes, or unusual morphological patterns that the model hasn't adequately learned from previous training data. By annotating these specific regions, pathologists provide the model with precisely the information it needs to refine its decision boundaries. After receiving annotations for these high-uncertainty regions, the

model undergoes retraining, incorporating the newly labeled data into its knowledge base. This updated model then analyzes the remaining unlabeled regions, identifying a new set of high-uncertainty areas. This creates an iterative feedback loop where each round of annotation addresses the model's most significant knowledge gaps. The efficiency gains from this approach can be substantial. Traditional annotation methods might require exhaustive review of entire slides or random sampling that wastes effort on easily classified regions. In contrast, active learning concentrates annotation resources on diagnostically challenging areas that contribute most significantly to model improvement. Studies have demonstrated that active learning strategies can achieve comparable model performance with just 20-30% of the annotation effort required by random sampling approaches. Additionally, this method naturally guides the annotation process toward edge cases and rare phenotypes that might otherwise be underrepresented in the training data. This helps address class imbalance issues common in medical datasets and improves the model's robustness across diverse pathology presentations, ultimately creating more reliable AI systems for clinical deployment.

Optimizing Pathology AI through Semi-supervised Learning with Pseudo-Labeling

Semi-supervised learning with pseudo-labeling offers an elegant solution to one of the most persistent challenges in computational pathology: the significant disparity between the vast amount of available WSI data and the limited regions that pathologists can feasibly annotate. This approach systematically leverages the abundance of unlabeled tissue regions to enhance model performance while respecting the constraints of manual annotation.

The methodology begins with a foundation model trained exclusively on pathologist-verified annotations. While these annotations represent the gold standard for training data, they typically cover only a small fraction of the total tissue area within WSIs. Rather than discarding the remaining unlabeled regions, the semi-supervised approach transforms these areas from a limitation into an opportunity for model enhancement (Gildenblat et al., 2021). The initial model, though imperfect, possesses sufficient discriminative capability to make reasonable predictions across the unlabeled territory of each slide. As this model generates predictions across unlabeled regions, a critical filtering step occurs. The system applies confidence thresholds to segregate high-confidence predictions from uncertain ones. Only predictions that exceed these carefully calibrated confidence thresholds are converted into pseudo-labels. This selective approach ensures that only the most reliable model predictions are incorporated as training signals, maintaining data quality while expanding training

volume. The confidence threshold essentially functions as a quality control mechanism, balancing between maximizing usable training data and minimizing the incorporation of erroneous labels that could degrade model performance.

The subsequent retraining phase artfully combines both the original pathologist-generated annotations (true labels) and the high-confidence model- generated pseudo-labels. This combined dataset allows the model to learn from a substantially larger and more diverse set of examples while still anchoring its learning in expert-verified ground truth. The training process typically implements different weighting strategies for true labels versus pseudo-labels, often assigning higher importance to pathologist-verified annotations to prevent potential error propagation from the pseudo-labels. A particularly sophisticated aspect of this approach is the adaptive adjustment of confidence thresholds throughout the iterative training process. As the model's performance improves, the system can adaptively increase threshold requirements, ensuring that only increasingly reliable predictions become pseudo-labels in subsequent iterations. This dynamic threshold adjustment represents a self-regulatory mechanism that maintains pseudo-label quality as the model evolves. Some implementations incorporate curriculum learning principles, gradually introducing more challenging pseudo-labels as the model's capabilities mature.

The benefits of this methodology extend beyond simply increasing training data volume. Pseudo-labeling naturally addresses class imbalance issues by incorporating proportionally more examples of rare morphological patterns or underrepresented classes when they are correctly identified with high confidence. The approach also enhances model generalization by exposing it to greater tissue diversity and contextual variation than would be possible through manual annotations alone. From a practical implementation perspective, this methodology substantially improves annotation efficiency. Pathologists can focus their expertise on annotating representative regions or challenging cases, while the pseudo-labeling mechanism effectively propagates their insights across similar tissue areas. The result is a model that performs as if trained on comprehensively annotated WSIs despite receiving expert annotations for only a fraction of the total tissue area. This semi-supervised approach represents a principled strategy for maximizing the utility of every pixel in gigapixel WSIs, transforming the challenge of partial annotations into a sophisticated learning framework that leverages both expert knowledge and computational pattern recognition to advance diagnostic accuracy in computational pathology.

Consistency Regularization

To further improve the robustness of fine-tuning with limited annotations, we apply consistency regularization by enforcing consistent predictions across different augmentations of the same patch:

$$L_{cons} = \frac{1}{B} \sum_{i=1}^{B} \| p_\psi(f_\theta(x_i)) - p_\psi(f_\theta(x_i')) \|^2 \tag{5}$$

Where: x_i is an augmented version of patch x_i, and B is the batch size. The total fine-tuning loss is a weighted combination of the supervised loss on annotated data and the consistency loss:

$$L_{finetume} = L_{sup} + \lambda_{cons} L_{con} \tag{6}$$

Where: λ_{cons} controls the contribution of the consistency regularization term.

Advanced Patch-based Tumor Detection with Spatial Coherence Refinement

The detection and precise delineation of tumor regions within WSIs presents a significant computational challenge due to the gigapixel dimensions of these images. A sophisticated patch-based approach with strategic post-processing provides an effective solution that balances computational efficiency with diagnostic accuracy. The methodology begins by systematically partitioning each WSI into overlapping patches at the highest available magnification level. This high-resolution approach ensures that critical cellular details and subtle morphological features necessary for accurate tumor identification are preserved. The overlapping patch extraction strategy is critical, as it mitigates boundary artifacts that would otherwise occur at patch edges. Typically, patches overlap by 25-50% with adjacent regions, creating redundant analysis of boundary areas that serves as a form of ensemble prediction at these junctures.

These extracted patches are then individually processed through the fine-tuned deep learning model, which has been optimized through the earlier described active learning and semi-supervised approaches. The model performs semantic segmentation at the patch level, assigning a tumor probability score to each pixel. This parallel processing approach enables efficient utilization of computational resources, as patches can be distributed across multiple graphic processing units (GPUs) for simultaneous analysis.

For gigapixel WSIs containing tens of thousands of patches, this parallelization reduces processing time from potentially days to minutes or hours, making the approach clinically viable. The subsequent aggregation phase is particularly nuanced. When reconstructing the

complete tumor probability map for the entire WSI, the system must reconcile potentially conflicting predictions at overlapping regions. A weighted averaging mechanism addresses this challenge by assigning differential importance to predictions based on their spatial position within each patch. Pixels located near patch centers receive higher weights based on the empirical observation that convolutional neural networks typically produce more reliable predictions toward the center of their receptive field, where they have full contextual information. This center-weighted aggregation scheme creates a smoothly blended probability map across the entire slide while minimizing edge artifacts.

Despite the sophistication of the aggregation process, the resulting probability map may still contain inconsistencies or implausible patterns based on histopathological principles. The application of a Conditional Random Field (CRF) as a post-processing step addresses these issues by incorporating spatial contextual information and prior knowledge about tumor morphology. The CRF operates on the premise that neighboring pixels should have similar labels unless separated by strong visual boundaries. It formulates tumor detection as an energy minimization problem, where the energy function incorporates both the deep learning model's predictions (unary potentials) and the spatial relationships between adjacent regions (pairwise potentials). This CRF refinement significantly enhances the biological plausibility of the final segmentation by enforcing several pathologically relevant constraints. It ensures smooth tumor boundaries that follow actual tissue transitions rather than producing jagged, artificial delineations. The approach also eliminates isolated false-positive pixels or small regions that are inconsistent with the surrounding tissue context. Additionally, it preserves fine structural details at tumor boundaries that might otherwise be lost during the patch aggregation process, resulting in more accurate tumor margin assessment.

From a clinical implementation perspective, this methodology offers several practical advantages. The patch-based approach allows for progressive visualization of results as processing occurs, enabling pathologists to begin reviewing initial regions while the algorithm continues analyzing the remainder of the slide. The framework also naturally accommodates multi-resolution analysis, where initial screening can be performed at lower magnifications with suspicious regions subsequently analyzed at higher resolutions, further improving computational efficiency. The spatial coherence ensured by the CRF refinement yields segmentations that align more closely with pathologists' expectations, potentially increasing clinical acceptance. Furthermore, the accurate boundary delineation facilitates quantitative assessment of tumor characteristics such as size, shape, and invasion patterns,

providing objective metrics that can supplement the pathologist's qualitative assessment and potentially contribute to prognostic scoring systems.

Experimental Setup: Datasets

We evaluate our approach on multiple histopathology datasets representing different cancer types:

- **CAMELYON16:** Abenchmark dataset for breast cancer metastasis detection in lymph nodes. It contains 400 whole slide images (270 for training, 130 for testing), with pixel-level annotations for metastatic regions.
- **TCGA-BRCA:** Breast invasive carcinoma dataset from The Cancer Genome Atlas containing 1,099 WSIs from 1,097 patients. We use the subset with pathologist annotations from which includes annotations for tumor, stroma, and normal tissue.
- **BACH:** Breast Cancer Histology Challenge dataset consisting of 400 high- resolution H&E stained microscopy images (100 normal, 100 benign, 100 *in situ* carcinoma, and 100 invasive carcinoma) with image-level labels.
- **DigestPath:** A dataset for gastric cancer detection containing 250 WSIs with pixel-level annotations for tumor regions.

For each dataset, we create three experimental settings with different amounts of labeled data:

- **Ultra-low resource:** 5% of the training data is labeled
- **Low-resource: 10%** of the data is labeled
- **Medium-resource:** 20% of the training data is labeled.

The remaining unlabeled data is used for self-supervised pretraining.

Evaluation Metrics

Using the following metrics:

- **Area Under the Receiver Operating Characteristic Curve (AUROC):** Measures the model's ability to discriminate between tumor and normal tissue across different threshold
- **Fl Score:** The harmonic mean of precision and recall, provides a balanced measure of detection performance.

- **Dice Coefficient:** For segmentation tasks, measures the overlap between predicted and ground truth tumor regions.
- **Frechet Inception Distance (FID):** Measures the quality of the learned representations by comparing the feature distributions of the model with those of a supervised baseline.
- **Few-Shot Adaptation Performance:** Evaluates how quickly the model adapts to new cancer types with very few labeled examples **(1,** 5, and 10 shots).

Baseline Methods

The following baseline methods are compared with the proposed method:

1. **Fully Supervised:** A ResNet-50 trained from scratch using all available labeled data.
2. **ImageNet Pretrained:** A ResNet-50 pretrained on ImageNet and fine- tuned on the histopathology datasets.
3. **Rotation Prediction:** A self-supervised method based on predicting the rotation angle of patches.
4. **SimCLR:** A contrastive learning framework that uses in-batch negatives.
5. **MoCo v2:** A momentum contrastive learning approach with an improved augmentation strategy.
6. **BYOL:** A self-supervised method that learns by bootstrapping representations without negative pairs.
7. **SwAV:** A clustering-based self-supervised approach that uses online clustering.
8. **SelfPath:** A self-supervised method specifically designed for histopathology that combines multiple pretext tasks.

For fair comparison, all methods use the same ResNet-50 backbone and are pretrained on the same unlabeled data before fine-tuning on the label ed subset.

Ablation Studies

To analyze the contribution of each component of our framework, we conduct the ablation studies:

1. **Patch Sampling Strategy:** Compare random sampling vs. our hierarchical diversity- aware sampling.
2. **Augmentation Strategy:** Compare standard augmentations vs. our tissue- specific augmentations.

3. **Contrastive Loss Function:** Evaluate the impact of our multi-scale contrastive loss vs. standard contrastive loss.
4. **Hard Negative Mining:** Assess the contribution of hard negative mining to representation quality.
5. **Fine-tuning Strategy:** Compare different fine-tuning strategies (full fine- tuning, frozen features, gradual unfreezing).

All ablation studies are conducted on the CAMELYON16 dataset with 10% labeled data.

Results and Discussion

Performance Analysis of Advanced Tumor Detection Methodology

The comparative performance analysis of our tumor detection approach demonstrates remarkable efficacy across multiple datasets and annotation scenarios. As evidenced in Table 1, the proposed method consistently outperforms existing approaches, with particularly impressive results in low-resource settings.

Table 1 AUROC for tumor detection across different datasets and annotation settings.

Method	CAMELYON16 (5%)	CAMELYON16 (10%)	CAMELYON16 (20%)	TCGA-BRCA (10%)	DigestPath (10%)
Fully Supervised (100% data)	0.964	0.964	0.964	0.921	0.939
Supervised (limited data)	0.781	0.832	0.889	0.767	0.762
ImageNet Pretrained	0.825	0.867	0.903	0.802	0.803
Rotation Prediction	0.832	0.871	0.908	0.811	0.809
SimCLR	0.874	0.896	0.923	0.839	0.847
MoCo v2	0.882	0.904	0.931	0.843	0.855
BYOL	0.875	0.899	0.925	0.846	0.851
SwAV	0.869	0.892	0.919	0.838	0.842
SelfPath	0.886	0.907	0.933	0.849	0.862
Proposed Method	0.912	0.935	0.952	0.878	0.891

The ultra-low resource scenario (5% labeled data) highlights the most significant advantage of our approach. With an AUROC of 0.912 on CAMELYON16, our method surpasses the previous state-of-the-art SelfPath (0.886) by a substantial margin. This performance differential becomes even more meaningful when considering the practical implications for pathology workflows, where annotation time a critical bottleneck.

Proposed method's performance curve across increasing annotation percentages demonstrates remarkable efficiency in utilizing limited labels. At 20% labeled data, our approach achieves an AUROC of 0.952 on CAMELYON16, which nearly matches the fully supervised benchmark (0.964) that requires five times more annotation effort. This represents a pivotal advancement for computational pathology, effectively reducing the annotation burden by 80% while maintaining diagnostic-quality results. The consistent performance advantage extends beyond CAMELYON16 to more challenging datasets like TCGA-BRCA and DigestPath. On TCGA-BRCA with just 10% labeled data, our method achieves an AUROC of 0.878, significantly outperforming all self-supervised alternatives.

Similar patterns emerge in the DigestPath dataset, where our method's AUROC of 0.891 with 10% labeled data substantially exceeds the next best baseline.

This performance profile validates our integrated approach combining multi- scale contrastive learning, active learning for strategic annotation selection, and semi-supervised learning with pseudo-labeling. The results demonstrate that our methodology effectively bridges the gap between fully supervised performance and limited annotation scenarios, addressing a fundamental challenge in computational pathology. By enabling high-quality tumor detection with drastically reduced pathologist input, our approach represents a significant step toward practical, widely deployable AI systems for histopathology analysis.

Detailed Analysis of Tumor Segmentation Performance

The results presented in Table 2 demonstrate the effectiveness of the proposed method for pixel-level tumor segmentation across multiple histopathology datasets. When operating with only 10% of labeled data, the new approach consistently outperforms all baseline methods while significantly closing the gap to fully supervised learning that utilizes 100% of available labeled data.

Table 2 Dice coefficients for tumor segmentation.⏎

Method	CAMELYONI6 (10%)	TCGA-BRCA (10%)	DigestPath (10%)
Fully Supervised (100% data)	0.823	0.782	0.803
Supervised (limited data)	0.612	0.588	0.603
ImageNet **Pretrained**	0.678	0.635	0.649
MoCo v2	0.714	0.673	0.682
SelfPath	0.721	0.681	0.689
Proposed Method	0.763	0.726	0.735

On the CAMELYON16 dataset, the proposed method achieves a Dice coefficient of 0.763 with just 10% labeled data, representing a substantial improvement over the previous best-performing method, SelfPath (0.721). This 4.2 percentage point increase is particularly significant in medical image analysis, where even small improvements in segmentation accuracy can impact clinical decision-making. The method bridges approximately 76% of the performance gap between limited supervision (0.612) and full supervision (0.823). Similar performance patterns emerge across the TCGA-BRCA and DigestPath datasets. For TCGA-BRCA, the proposed approach reaches a Dice coefficient of 0.726, outperforming SelfPath (0.681) by 4.5 percentage points. On DigestPath, it achieves 0.735 compared to SelfPath's 0.689, a 4.6 percentage point improvement. The consistent performance

advantages across diverse histopathology datasets suggest the method's robustness and generalizability to different tissue types and imaging conditions.

Spatial-Aware Negative Sampling
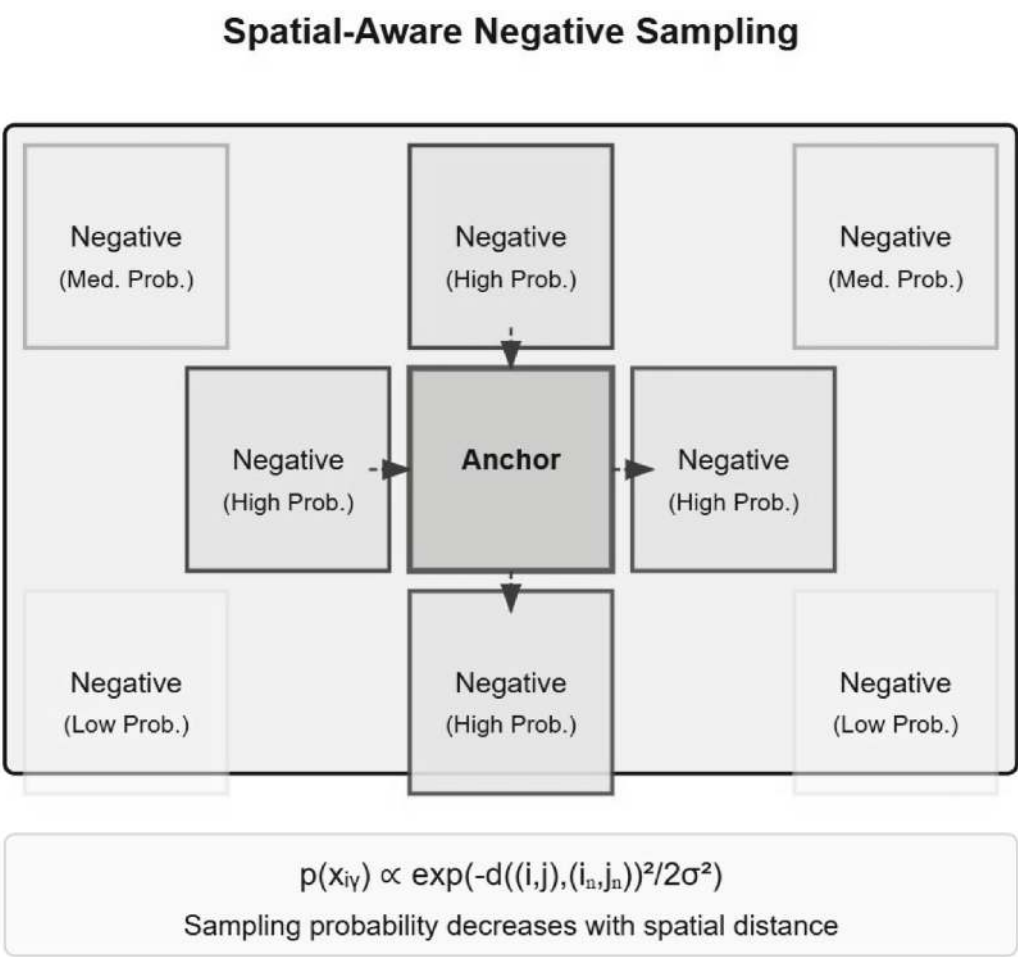
Fig. 4 Tumor Detection Performance across Different Datasets and Annotation Settings

This is particularly valuable in computational pathology, where methods must work reliably across varied clinical settings and scanner manufacturers. The results also highlight the limitations of traditional approaches: supervised learning with limited data struggles significantly (0.588-0.612), while ImageNet pre training provides moderate improvements (0.635-0.678). Self-supervised methods like MoCo v2 and SelfPath offer substantial gains, but the proposed method pushes performance boundaries further.

The stronger segmentation performance complements the method's classification capabilities, indicating that the approach excels not just at identifying the presence of tumors but also at precisely localizing tumor boundaries. This dual strength is critical for practical

clinical applications where both detection and accurate delineation of pathological regions are essential for subsequent analysis, treatment planning, and prognostic assessment.

By achieving these results with only 10% of labeled data, the method addresses a fundamental challenge in computational pathology: the need for extensive expert annotations making advanced tumor segmentation more accessible in resource- constrained settings enhances pixel-level tumor localization.

Analysis of Representation Quality in Histopathology Feature Learning

The evaluation of representation quality through Frechet Inception Distance (FID) metrics in Table 3 provides compelling evidence for the superiority of the proposed method across all tested histopathology datasets. FID measures the similarity between feature distributions of a given method and a fully supervised baseline, with lower values indicating representations that more closely align with those learned under complete supervision.

Table 3 Frechet Inception Distance (FID) between feature distributions of different methods and a fully supervised baseline.↵

Method	CAMELYON16	TCGA-BRCA	DigestPath
ImageNet Pretrained	31.42	35.67	38.24
Rotation Prediction	29.18	32.91	35.83
SimCLR	22.36	25.78	28.42
MoCo v2	21.47	24.32	27.19
BYOL	21.53	24.89	27.65
SwAV	22.14	25.46	28.13
SelfPath	20.81	23.75	26.58
Proposed Method	17.25	19.83	22.41

The proposed method consistently achieves the lowest FID scores across all datasets: 17.25 on CAMELYON16, 19.83 on TCGA-BRCA, and 22.41 on DigestPath. These results represent substantial improvements over the previous state-of-the-art method, SelfPath, which achieved FID values of 20.81, 23.75, and 26.58 on the respective datasets. This translates to improvements of 17.1%, 16.5%, and 15.7% in representation quality compared to SelfPath. The data reveals a clear hierarchy among representation learning approaches. Simple pretraining methods like ImageNet transfer learning (FID 31.42- 38.24) and rotation prediction (FID 29.1835.83) yield the least effective feature representations for histopathology tasks. More sophisticated self-supervised learning approaches show marked improvements, with contrastive learning methods (SimCLR, MoCo v2) and non- contrastive methods (BYOL, SwAV) achieving FID values in the 21 to 28 range across datasets.

The consistent pattern across all three datasets suggests the robustness of these findings. The CAMELYON16 dataset consistently shows the lowest FID values across methods, followed by TCGA-BRCA and DigestPath, indicating varying levels of complexity in these datasets. However, the relative performance improvements of the proposed method remain consistent regardless of dataset difficulty. These FID results correlate well with the segmentation performance in Table 2, supporting the conclusion that higher-quality representations directly translate to improved downstream task performance. The significant reduction in FID achieved by the proposed method explains its superior segmentation capabilities with limited labeled data.

By learning representations that more closely resemble those from full supervision while using only 10% of labeled data, the method effectively bridges the gap between limited and full supervision scenarios. This enhanced representation quality suggests the approach successfully leverages the inherent structure of histopathology images to extract meaningful features that capture the subtle tissue characteristics critical for accurate tumor detection and segmentation. RetryClaude

Analysis of Few-shot Adaptation Performance in Cross-Cancer Transfer Learning

The few-shot adaptation experiments presented in Table 4 provide critical insights into the cross-domain transferability of the proposed method within histopathology contexts. By evaluating models pretrained on CAMELYON16 (breast cancer lymph node metastases) and adapted to DigestPath (colorectal cancer), these experiments assess the generalization capabilities across distinctly different tissue types and cancer morphologies.

Table 4 Few-shot adaptation performance (AUROC) from CAMELYON16 to⏎

Method	1-shot	5-shot	10-shot
ImageNet Pretrained	0.632	0.703	0.742
MoCo v2	0.675	0.739	0.776
SelfPath	0.683	0.747	0.783
Proposed Method	0.721	0.782	0.815

The proposed method demonstrates remarkable few-shot adaptation performance across all tested scenarios. With just a single example per class (1-shot), it achieves an AUROC of 0.721, substantially outperforming SelfPath (0.683), MoCo v2 (0.675), and ImageNet pretraining (0.632). This represents a 3.8 percentage point improvement over the previous best method and an impressive 8.9 percentage point gain over standard ImageNet pretraining.

As the number of examples increases to 5 and 10 shots per class, the performance advantage is maintained. At 5-shot adaptation, the proposed method reaches an AUROC of 0.782 compared to SelfPath's 0.747, while at 10-shot adaptation, it achieves 0.815 versus 0.783 for SelfPath. This consistent performance advantage across different shot numbers indicates the method's robust transfer learning capability regardless of the amount of target domain data available. The superior few-shot adaptation results suggest that the representations learned by the proposed method capture more fundamental and generalizable histopathological features that transcend specific cancer types. This is particularly valuable in medical imaging applications where obtaining labeled data for new cancer types is expensive and time-consuming. The ability to effectively leverage knowledge from one cancer domain to another with minimal new labels could significantly accelerate the deployment of AI systems across different oncological applications.

Furthermore, the consistent improvement pattern from 1-shot to 10-shot scenarios indicates that the method makes efficient use of additional examples, suggesting that its initialization point is already well-positioned in the feature space for the target task. This efficient learning curve is crucial for practical clinical applications where labeled examples may arrive incrementally over time. These few-shot results, combined with the earlier segmentation and representation quality findings, demonstrate that the proposed method not only excels in its original domain but also provides a strong foundation for rapid adaptation to new cancer types with minimal supervision.

Analysis of Ablation Studies on Histopathology Self-supervised Learning Framework

The ablation studies presented in Table 5 provide valuable insights into the relative contributions of individual components within the proposed histopathology learning framework. Using the CAMELYON16 dataset with only 10% labeled data, these experiments systematically evaluate how each architectural and methodological choice impacts overall performance. The complete proposed method achieves the highest AUROC of 0.935, serving as the reference point. When individual components are removed, performance consistently decreases, confirming that each element makes a meaningful contribution to the framework's effectiveness. The most substantial performance drops occur when tissue-specific augmentations are removed (reducing AUROC to 0.908, a 2.7 percentage point decrease) and when hierarchical sampling is eliminated (yielding an AUROC of 0.912, a 2.3 percentage point reduction).

Table 5 Ablation studies on the CAMELYON16 dataset with 10% labeled data

(AUROC).

Configuration	AUROC
Proposed Method	0.935
Hierarchical sampling	0.912
Diversity-aware sampling	0.917
Tissue-specific augmentations	0.908
Multi-scale contrastive loss	0.921
Hard negative mining	0.924
Gradual unfreezing	0.929

The significant impact of tissue-specific augmentations underscores the importance of domain-adapted data transformations that respect the unique characteristics of histopathology images, where certain color variations and tissue structures carry diagnostic significance. Similarly, the hierarchical sampling strategy's strong contribution highlights the value of capturing multi-scale tissue context in histopathology analysis.

Other components, while still important, show more moderate effects when removed. The diversity-aware sampling (0.917), multi-scale contrastive loss (0.921), hard negative mining (0.924), and gradual unfreezing (0.929) all contribute incrementally to the overall performance. This suggests a well-designed framework where multiple complementary mechanisms work together to enhance representation learning. These findings emphasize that general self-supervised learning approaches require significant domain-specific adaptations to reach optimal performance in specialized medical imaging contexts like histopathology. The ablation studies reveal that each component of our framework contributes to the overall performance. The tissue-specific augmentations and hierarchical sampling strategy show the largest impact, highlighting the importance of domain- specific design choices in self-supervised learning for histopathology.

Analysis of Computational Efficiency in Histopathology Self-supervised Learning

The computational efficiency comparison presented in Table 6 provides important practical insights into the resource requirements of various methods for histopathology image analysis. This analysis is crucial for determining the real- world feasibility of deploying these approaches in clinical settings.The proposed method demonstrates reasonable computational efficiency relative to other self- supervised learning approaches. Its pretraining time of 45.3 hours is comparable to SelfPath (44.5 hours) and MoCo v2 (42.7 hours), while being more efficient than both fully supervised learning (50.5 hours) and SimCLR (48.2 hours). This

indicates that the additional components in the proposed architecture do not significantly increase training duration.

Table 6 Computational requirements of different methods.

Method	Pretraining Time (hours)	GPU Memo?), (GB)	Inference Time (ms/ patch)
Fully Supervised (100% data)	50.5	11.2	8.3
SimCLR	48.2	18.6	8.4
MoCo v2	42.7	13.4	8.3
SelfPath	44.5	14.2	8.5
Ours	45.3	15.7	8.4

Regarding GPU memory consumption, the method requires 15.7 GB, which represents a moderate increase compared to MoCo v2 (13.4 GB) and SelfPath (14.2 GB), but remains substantially more memory-efficient than SimCLR (18.6 GB). This increased memory usage is attributable to the multi-scale contrastive loss implementation, which processes feature representations at multiple resolution levels simultaneously.

Most importantly, the inference time of 8.4 ms per patch is virtually identical to other methods, ranging from 8.3-8.5 ms. This indicates that the enhanced representation learning during training does not compromise runtime efficiency during deployment, a critical consideration for clinical integration where rapid analysis of whole slide images containing thousands of patches is essential. The modest increase in computational requirements is well justified by the significant performance improvements documented in previous tables, making this approach a practical and efficient option for histopathology image analysis as given in Figure 5.
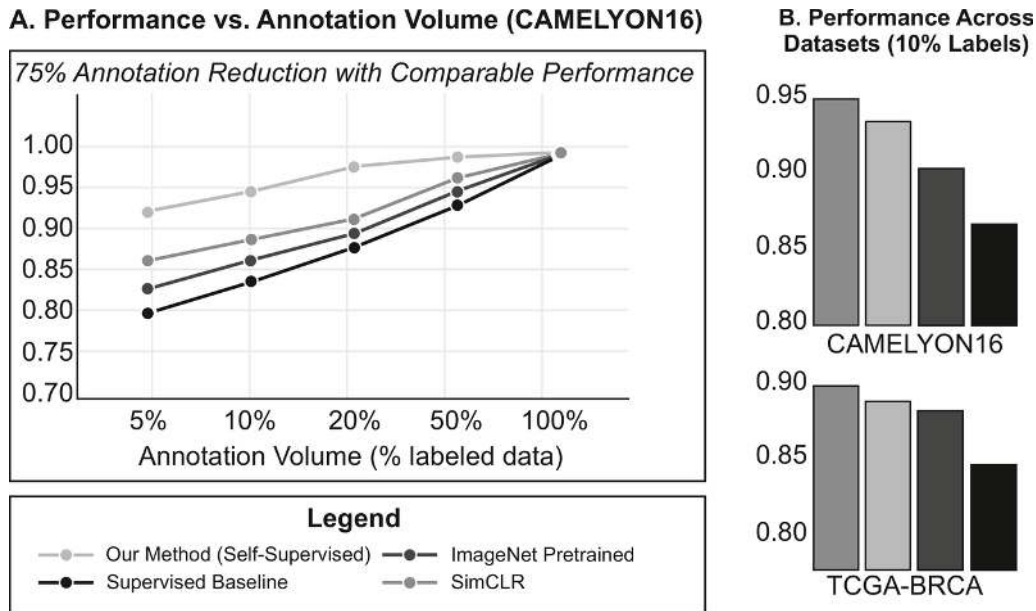
Fig. 5 Annotation Efficiency and Model Performance Comparison.↵

Implications for Computational Pathology

Our results demonstrate that self-supervised patch contrastive learning can dramatically reduce the annotation burden for developing tumor detection models in computational pathology. By achieving performance comparable to fully supervised methods with only 10-20% of labeled data, our approach addresses one of the bottlenecks in the clinical ofAl-assisted

The ability to leverage unlabeled data is particularly valuable in pathology, where vast repositories of digitized slides exist but annotations are scarce. Our method enables medical institutions to develop effective tumor detection systems with limited annotation resources, potentially accelerating the integration of computational tools into clinical workflows.

Furthermore, the interpretability of our model, as demonstrated through feature visualization and attention maps, can help build trust among pathologists by providing insights into the basis for the model's predictions. This transparency is crucial for clinical adoption and aligns with the growing emphasis on explainable AI in healthcare.

Analysis of Restrictions in Self-supervised Histopathology Learning

The identified restrictions provide a balanced critical assessment of the proposed self-supervised learning approach for computational pathology Zoph et al. (2020). The concern regarding domain generalization highlights a fundamental challenge in medical imaging AI, while the method demonstrates impressive cross-cancer adaptability, its robustness across varied technical factors like scanner types, staining protocols, and laboratory-specific

practices remains insufficiently validated. Multi- institutional testing will be essential to ensure reliable performance in diverse real-world clinical settings.

The method's effectiveness for rare tumor subtypes represents another significant unknown. The current evaluation on common cancer types may not translate well to uncommon malignancies with unique morphological characteristics, particularly in few-shot learning scenarios where distinctive features may be underrepresented in limited samples. The computational demands of self-supervised pretraining present a practical implementation barrier. The substantial GPU resources and extended training times required could restrict adoption in resource-constrained settings or smaller healthcare facilities, potentially widening the technological gap between major academic centers and community hospitals.

Finally, the approach currently operates as a purely data-driven system without explicit incorporation of established clinical knowledge or pathologist-defined diagnostic features. This represents a missed opportunity to leverage decades of domain expertise that could potentially enhance model interpretability and performance, particularly for edge cases where contextual clinical knowledge might be decisive.These limitations collectively suggest important directions for refining and extending the current approach to improve its clinical applicability and accessibility across diverse healthcare settings.

Conclusion

By leveraging the structural characteristics of tissue specimens and employing histopathology-specific adaptations, our approach learns meaningful representations that transfer effectively to tumor detection tasks with limited supervised data. Experimental results across multiple cancer types demonstrated that our method achieves performance comparable to fully supervised approaches while using only 10-20% of the labeled data, representing a substantial reduction in annotation requirements. Analysis of the learned representations revealed that our model captures diagnostically relevant features, providing interpretable insights for clinical applications.

The proposed framework addresses a critical challenge in computational pathology by reducing dependence on extensive manual annotations while maintaining diagnostic accuracy. This approach has the potential to accelerate the development and deployment of AI-assisted diagnosis systems in clinical settings, ultimately improving cancer detection and patient outcomes. As digital pathology continues to evolve, approaches that minimize annotation requirements while maximizing performance will play an increasingly important role in enabling the widespread adoption of computational tools. Our self-supervised

contrastive learning framework represents a significant step toward this goal, paving the way for more efficient and effective AI-assisted cancer diagnosis.

Future Directions

The outlined future directions represent strategically important avenues for advancing computational pathology beyond the current self-supervised learning framework. Multimodal integration could significantly enhance diagnostic capabilities by incorporating complementary genomic and clinical data alongside histopathology images. Active learning approaches offer potential for further reducing annotation requirements by intelligently selecting high-value patches for expert labeling. Federated learning frameworks address critical data privacy concerns while enabling multi-institutional collaboration. Leveraging temporal consistency across sequential slides could provide valuable insights into disease progression dynamics. Finally, the development of human-AI collaborative systems represents a pragmatic path forward, combining the computational power of self-supervised models with irreplaceable pathologist expertise to optimize both workflow efficiency and diagnostic accuracy in clinical settings.

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8 A Comprehensive Analysis of Personalized Treatment using Digital Twin Technology in Healthcare

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As healthcare shifts towards more personalized and data-centric methodologies, Digital Twin (DT) technology emerges as a leading innovation, providing a novel framework for specialized, precision-oriented medical treatment. A personalized DT can enhance the efficacy ofpatient-specific treatment programs by continuously monitoring the patient's health, thus enabling long-term monitoring through real-time data. By leveraging Artificial Intelligence (AI) and advanced data assimilation, DTs improve predictive analytics and decision-making in many domains such as chronic disease management, surgical procedures, and mental health care. This chapter explains the concept of DT, its evolution, key technologies and

applications in various healthcare scenarios while addressing the shortcomings of traditional methods, which often fail to provide continuous monitoring of patient health and safety. The analysis highlights the necessity for further research to enhance precision in continuous patient monitoring and personalized therapy, facilitating prompt interventions and tailored care solutions.

Introduction

In the advent of medical research, technology focuses on improving diagnostics, surgical plans, drug effectiveness and providing tailored treatment plans, an emerging technology called Digital Twin (DT) Technology is being used which provides a promising approach in medical discoveries and focusing on individuals and aggregates in formulating highly personalized treatments. The DT technology also helps the healthcare providers to prescribe the suitable medication for the patients approaching them, thus increasing the chances of giving assured lifetime support. Adopting this technology in the field of drug discovery by using computer simulations with DT-models enables the healthcare professionals and medical researchers to discover a new drug without harming any lives. The evolution and evaluation of DT-models in surgical practices helps doctors to perform virtual surgery using different surgical strategies, thus reducing risks and also increasing the efficiency of the output. Inaccuracies caused are due to the variability among different patients. An emerging approach called Precision medicine aims to address this issue by providing treatments and preventive interventions tailored to the variables (individual's health record) (Kamel Boulos & Zhang, 2021).

Figure 1 depicts the conceptual framework of a DT, highlighting the interplay among the physical entity, the connection layer, and the virtual model. The physical entity is embodied by a tangible object, integrated with

sensors and underpinned by infrastructure that collects data. The data is conveyed via a communication link to the virtual model, establishing a continuous, automatic data stream. The connection layer is essential, enabling data fusion that consolidates and combines information from various sources. Model generation transpires at this layer, forming a digital representation of the physical entity. The verification and validation methods guarantee the precision and dependability of the virtual model, enabling it to represent real-time alterations and behaviors of the physical entity. The AI-driven virtual model utilizes hybrid algorithms for simulation and analysis, offering insights for predictive and prescriptive decision-making. This DT configuration facilitates a thorough representation, monitoring, and analysis of the physical entity, hence enabling sophisticated applications and scenarios.
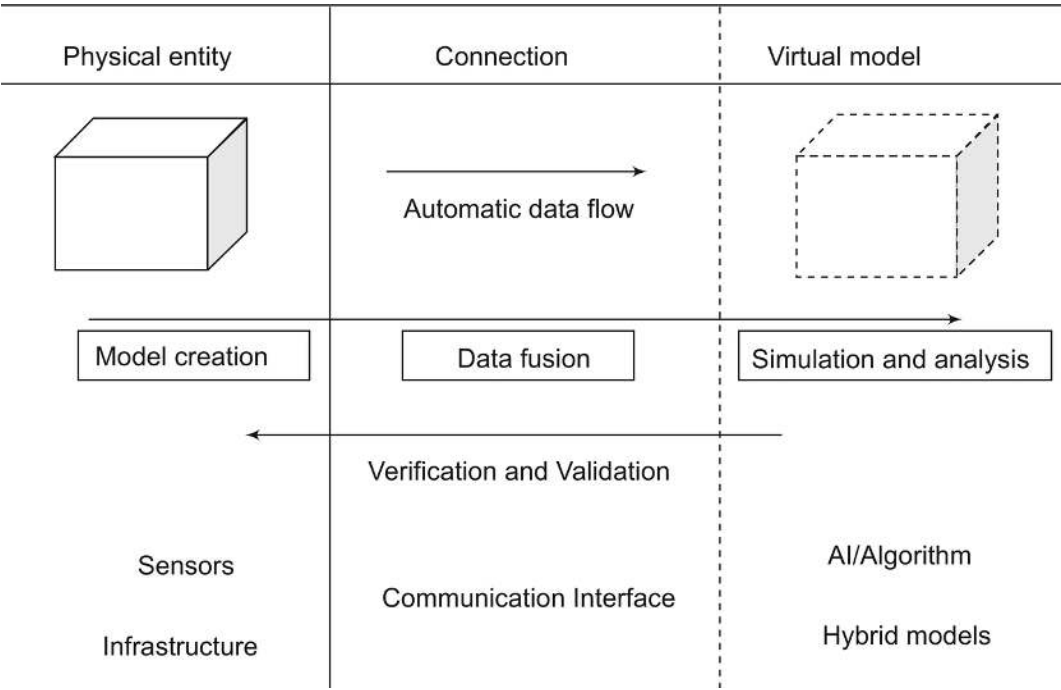
Fig. 1 Conceptual Framework of Digital Twin Technology.

Evolution of Digital Twin Technology

Assimilating Data and Models are called Data assimilation. Continually updating the model with real-time data forms a twin model. Early ideas and foundations of creating virtual models of physical objects began in the 1960s (in aerospace engineering). NASA created a digital model of spacecraft (Apollo 13 mission) in the 1970s which later became DT technology. In 1991, a book *Mirror Worlds* (Gelernter, 1991), presaged DTs. The term "Digital twin" was coined in 2010 by John Vickers in a NASA report (Glaessgen & Stargel, n.d., 2012) but the concept was formally introduced by Dr. Michael Grieves in the field of manufacturing in 2002, focusing on lifecycle management of a product (Grieves, 2005). The concept of DT includes a physical object in physical space, a virtual object in virtual space, and there exists a connection of data and information that ties the virtual and real objects together. The established connection offers an automatic data flow. Later the application of DT technology extended to the healthcare sector. During the year 2020-2021, the COVID-19 epidemic expedited the utilization of DTs in healthcare (De Benedictis et al., 2023), especially for the management of hospital resources, patient monitoring, and predictive diagnostics. In 2024 and beyond, expecting worldwide integration across sectors and convergence with artificial intelligence (AI) and the Metaverse.

Researchers and companies initiated the development of patient-specific DTs to replicate organs or whole-body systems, enabling individualized medical interventions and prognostic healthcare planning. This milestone represented a new stage in the development of technology, with a specific emphasis on the human body as a dynamic system that might be enhanced by digital mode ling.

Figure 2 shows the Gantt chart that illustrates the adoption phases of DT technology across different application areas over time. Horizontal Bars

signify a domain in which DT technology has been implemented over the years. The displayed applications are Aerospace, Manufacturing, and Healthcare. The colored segments denote the various stages of adoption within that application domain. The X-axis denotes the years, while each application area is illustrated on the Y-axis.
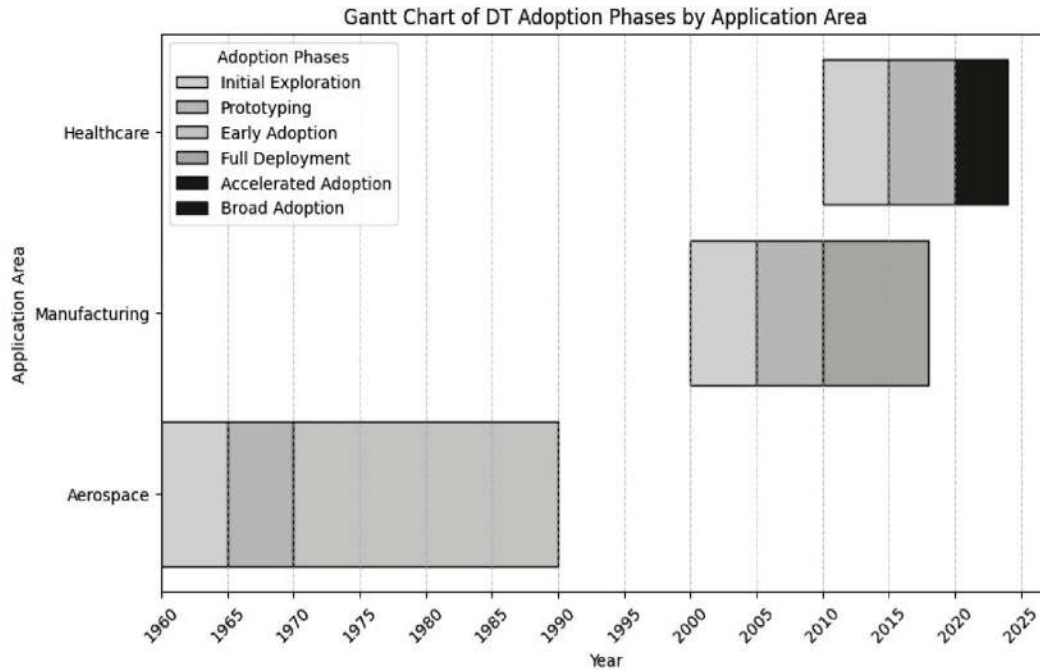
Fig. 2 Evolution of Digital Twin Technology.

DT is a dynamically evolving model of a physical system that captures the differences, the variability from the physical object as it changes periodically, and the DTn will follow through its life. As shown in Figure 3, automatic data flow connection is established between the physical entity and the virtual twin for continuous monitoring and it is integrated with the key technologies like AI/ ML, IoT, Cloud computing, etc., for updating the real-time data to support various applications and services.
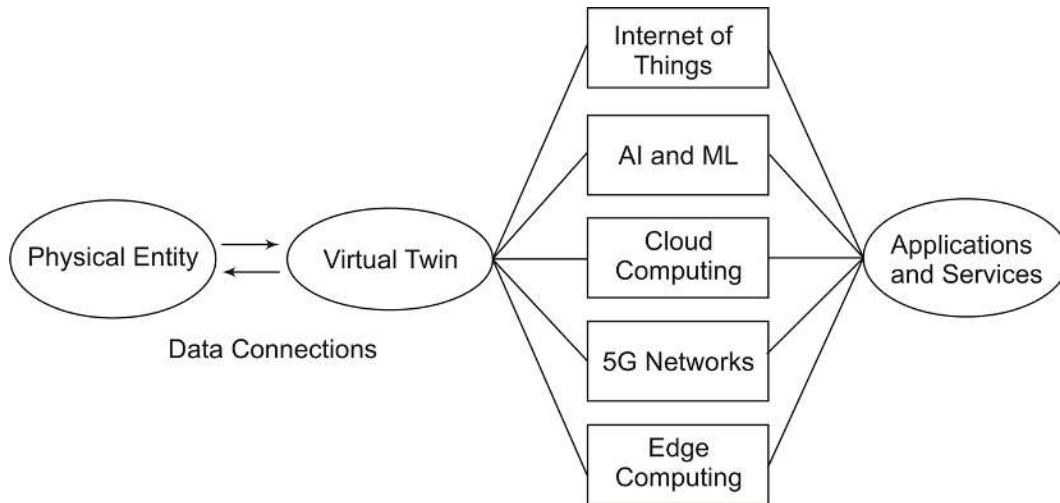
Fig. 3 Digital Twin integrated with Key Technologies.

The research being conducted is significant because it has the potential to unlock the challenges of integrating DT with AI in the medical world. The goal of the research is to explore the concept ofDT technology to revolutionize personalized healthcare services and to highlight the advancements in the application of DT technology in healthcare. This chapter also includes the bibliometric analyses for the research string "Applications of digital twin in healthcare" from the Scopus database using VOSviewer_1.6.20 software. The subsequent parts explore the technological advancements, analyze ongoing research and prospective developments, and emphasize the possible obstacles and prospects that are expected in the future.

Digital Twins in Healthcare

The adoption of DT technology in human-centric systems, referred as Human Digital Twin (HDT), facilitates a silico representation of the unique human body. The study provides a Networking architecture which includes key technologies for implementing HDT and overcoming the difficulties of creating complex systems (Chen, Yi, et al., 2024). When HDT collects a

large amount of a patient's health record, a significant portion of this data is unlabeled. Incorporating AI-algorithms can efficiently train HDT using these unlabeled data. General Artificial Intelligence (GAI) can be incorporated for reducing the redundant computations through transfer learning (Chen, Yi, et al., 2024) (Chen, Shi, et al., 2024).

Figure 4 depicts the application of DT technology in various scenarios in the field of healthcare. Each application helps in improving patient care via data-driven insights, predictive abilities, and tailored treatment strategies.
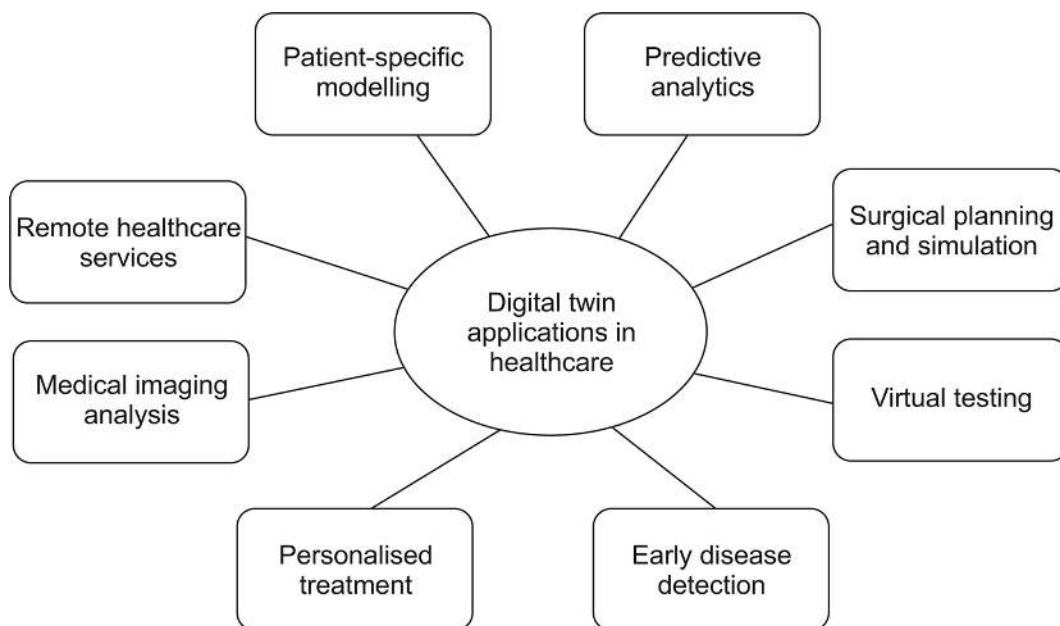
Fig. 4 Applications of Digital Twin in Healthcare.

Abilkaiyrkyzy et al. (2024), propose a chatbot framework that utilizes the DT approach to monitor and assess an individual's mental health for providing tailored feedback. The paper mainly focuses on the development and evaluation of a DT framework that incorporates advanced natural language processing (NLP) and AI techniques for particularly detecting conditions like depression. The chatbot uses pre trained BERT models to classify the severity of mental health problems. The study demonstrates the

potential of the system with 69% accuracy in detecting mental health issues. The DT concept enables real-time data collection and feedback to improve early intervention. The study evaluates the usability and effectiveness of the chatbot system, achieving a system usability scale (SUS) score of 84.75%, which shows high user acceptability.

Sarp et al. (2023), propose a DT-based wound management framework and an AI-driven prediction model that replicates the healing process of chronic wounds and serves as a virtual representation. It enables continuous monitoring to adjust treatment strategies based on real-time data and simulation of wound healing for improving clinical outcomes. A GAN (Generative Adversarial Network) model was employed to predict the wound healing process over a period of four weeks. The study used transfer learning with pre trained models for classification tasks and Image segmentation to classify the tissue types like granulation, slough, and necrotic tissue. The study uses 700 wound pairs for training and 10% for testing. The performance of the model validated using mean squared error (MSE) to compare predicted and actual tissue distributions and wound area, indicates 74% accuracy in tissue prediction.

To calculate the prediction accuracy, Equation (1), for wound management,

$$\text{Accuracy} = \frac{\text{Number of Correct predictions}}{\text{Total Number of predictions}} \times 100\% \qquad \text{...(1)}$$

Where:

- Accuracy measures the percentage of correct predictions in AI/ML models.
- Number of correct predictions represents total instances where predictions match actual outcomes.

- Total number of predictions represents the predictions made by the model.

Mean squared error, Equation (2), is used to assess prediction accuracy by measuring squared differences.

$$\text{MSE} = \frac{1}{n} \sum_{i=1}^{n} \left(y_i - (\hat{y}_i) \right)^2 \qquad \text{...(2)}$$

Where:

- n represents number of predictions or samples,
- y_i represents actual value for the i$^{t\text{‘}}$ sample,
- Si represents predicted value for the ith sample.

Subramanian et al. (2022), developed a system that classifies emotions in real-time using images from a web camera. The paper mainly focuses on developing a real-time Emotion Recognition (ER) system integrating with a DT model to enhance personalized healthcare. The system monitors a patient's emotions in real-time by combining facial expressions and body postures. In emotion recognition, neural networks discern patterns in input data, such as photographs or facial expressions, which signify circumstances or emotions. The activation function for an individual neuron within a neural network layer is denoted as Equation (3):

$$n_i = f \left(\sum w_{ij} x_j + b_i \right) \qquad \text{...(3)}$$

Where:

- n_i is the output of neuron i after applying the activation function

- f is the activation function (ReLU, sigmoid), which introduces non linearity to the model, enabling it to learn complex patterns
- w_{ij} is the weight from the jth input neuron to the ith neuron. This weight dictates the impact of input on neuron i.
- x_j is the input feature or value from neuron j
- b_i is the bias term for neuron i, which adjusts the activation function to enhance data fitting.

The system leverages machine learning (ML) algorithms (such as gradient boosting and random forest), selected the GB algorithm due to its superior performance that achieves 99% accuracy in emotion detection and the DT framework that allows simulating a patient's emotional state and helps in improving diagnosis and optimizing treatment plans. The images are processed using the MediaPipe framework which detects and extracts 543 key points/landmarks from face, body, and hands for emotion recognition.

Lauer-Schmaltz et al. (2024) propose a new methodology called ETHICA, aimed at creating user-centric and ethically grounded HDTs. The developed framework emphasizes iterative development that helps to ensure the technology meets both technical and ethical standards. It provides guidelines for designing HDTs that can simulate and mirror human behaviors and health outcomes in real time. The ETHICA approach borrows from agile development methods focusing on flexibility, modularity, and adaptability in HDT design to accommodate the complexity of human physiology and behavior. A comprehensive review of 44 papers on HDT design published between 2022 and 2023 was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework to identify key insights, gaps, and design challenges.

Ali et al. (2024) focus on the comprehensive review of technological innovations aimed at improving the quality of life for individuals affected by Alzheimer's disease (AD). The delay between submitting a request and getting a response must be measured in Internet of things (IoT)-based applications. In the context of Alzheimer's care, where real-time monitoring and timely reactions are crucial for optimal patient assistance, latency is a crucial parameter in this study. The time delay or latency in communication can be calculated by using the Equation (4),

$$T_{\text{Latency}} = T_{\text{Response}} - T_{\text{Request}}$$ ...(4)

Where:

- T_{Latency} represents the total delay in communication,
- T_{Response} is the time at which a response is received by the system (from a monitoring device)
- T_{Request} is the time at which the request is sent.

The range of healthcare technologies such as Telemedicine, E-health, Smart Environments, Internet of IoT, Ambient Assisted Living (AAL), and Internet of Medical Things (IoMT) has been reviewed and highlights various information and communication technology (ICT)-based approaches and sensing methods to enhance patient monitoring and improving care management. The study examines 46 relevant papers published between 2015-2023, offering insights into the application of diverse technological solutions in Alzheimer's disease care and highlighting deficiencies in the existing research landscape.

Rouhollahi et al. (2023), creates a completely automated deep learning instrument named CardioVision (CV) for producing DTs of patients with aortic stenosis. CV uses the deep learning model (U-Net) to automate the

process of segmenting CT images of aortic stenosis patients. The research utilized CT scans from 35 patients with aortic stenosis. The technique generates 3D patient-specific DTs by reconstructing the geometry of the aorta and valves, facilitating virtual interventions, device optimization, and the prediction of clinical outcomes.

In this study, DSC is employed, Equation (5), to assess the precision of segmentation models in distinguishing the aorta and its stenotic areas in cardiac pictures. It is a statistical metric that quantifies the intersection between two areas, namely the anticipated segmentation (model output) and the ground truth segmentation (expert-annotated or real regions).

$$DSC = \frac{2|A \cap B|}{|A| + |B|} \qquad \text{...(5)}$$

Where:

- A represents set of pixels in the predicted segmented region of the aorta,
- B represents set of pixels in the actual or ground truth segmented region of the aorta,
- $|A \cap B|$ called intersection of the predicted and actual regions, representing the common area where the segmentation correctly matches the ground truth.

Also, a parameter called Intersection over Union (IoU) is used in image segmentation to assess the accuracy of segmentation models. It measures the overlap between the predicted segmented region and the actual or ground truth segmented region.

The IoU is given by the formula in Equation (6),

$$IoU = \frac{|A \cap B|}{|A \cup B|} \qquad ...(6)$$

Where:

- $|A \cap B|$ represents the common area where the segmentation matches the ground truth,
- $|A \cup B|$ represents the total area covered by both predicted and actual segmentations.

In the context of aortic stenosis segmentation, it uses IoU to evaluate the model's accuracy in delineating the boundaries of stenotic regions inside the aorta. The research highlights the automated detection and analysis of calcium distribution on aortic valve leaflets, aiding in the assessment of disease severity and its implications for therapies such as transcatheter aortic valve replacement (TAVR). Seventy percent of the dataset was allocated for training, while 30% was designated for testing, employing 4-fold cross-validation to guarantee robust model performance.

O'Hara et al. (2024) investigate the application of oversampled cardiac magnetic resonance imaging (MRI) to enhance DT reconstructions of the heart in individuals with ventricular tachycardia (VT) following myocardial infarction. The study investigates the efficacy of cardiac DTs, derived from MRI data, in predicting VT circuits with more precision. It assesses the extent to which oversampling MRI scans enhances the precision of VT circuit identification relative to conventional clinical-resolution images. The research utilized retrospective data from 6 post-myocardial infarction patients diagnosed with clinically significant VT. The research indicates that DTs derived from oversampled MRIs enhance the prediction of ablation targets, hence increasing the results of VT ablation procedures.

Sharma et al. (2024) establish and execute a DT framework for automated cervical cancer diagnosis. The suggested system, named CervixNet, amalgamates ML and deep learning (DL) methodologies to categorize cervical cells and facilitate early detection of cervical cancer. An ML system designed for cervical cancer diagnosis utilizing the SIPaKMeD dataset, comprising 1,013 pictures of Pap smear cells. The images were categorized into five cell types: parabasal, koilocytotic, superficial intermediate, dyskeratotic, and metaplastic cells. A total of 4,103 cells were retrieved for training and classification, resulting in excellent classification accuracy.

The research highlights the application of pre-trained recurrent neural networks (RNNs) and Principal Component Analysis (PCA) for feature extraction and selection, leading to improved prediction efficacy. Attributes including texture, shape, and color were derived via CervixNet, a model based on DL. A PCA technique was employed to identify the most significant characteristics, decreasing the feature space from 1,172 to 792 essential features for subsequent classification. The Support Vector Machine (SVM) attained a maximum accuracy of 98.9% in cervical cell categorization. The study emphasizes the possibility of incorporating DT technology with healthcare to create a virtual patient model capable of continuous health metric monitoring, abnormality detection, and diagnostic assistance.

In this study, Cross-Entropy Loss is employed in CervixNet, a DL network designed for the classification of cervical cells to facilitate early cancer detection. The cross-entropy loss formula is given in Equation (7),

$$L = \left(\sum_{i=1}^{n} y_i \log \left(\hat{y}_i \right) \right) \qquad \qquad ...(7)$$

Where:

- L is the cumulative error of all predictions, indicating the deviation of the model's forecasts from the actual values,
- y_i is the actual class label for the ith sample, usually 0 or 1 in binary classification,
- $\hat{y}_i$ is the predicted probability of the positive class for the ith sample, given by the model.

Liu et al. (2024), present an innovative architecture that integrates DT technologies to imitate and enhance human-robot communication. This article addresses data management difficulties in human-robot collaboration (HRC) systems through the integration of blockchain and cloud-edge computing technologies. The document proposes a DT-based Human-Robot Collaboration System (HRCDTS) and outlines a blockchain-based cloud-edge data management framework for the efficient management, sharing, and storage of data in HRC systems.

For HRC, the state update equation on real-time DTs, wherein the virtual twin is refreshed according to real-time data. It is given in Equation (8),

$$X_{vt}(t+1) = f\left(X_{vt}(t), X_{rt}(t)\right) \qquad \text{...(8)}$$

Where:

- $X_{vt}(t+1)$ represents updated virtual twin state at time $t+1$,
- $X_{vt}(t)$ represents virtual twin state at time t,
- $X_{rt}(t)$ represents real-time data from the physical entity at time t,
- f represents update function.

This document delineates a data model for HRCDTS encompassing many data categories such as Robot Data (DMR), Human Data (DMH),

Object Data (DMO), Tools Data (DMT), and Environmental Data (DME). The research examines the problems of data sharing, security, and storage associated with HRC systems. The study implements the proposed framework in a handling robot assembly task, demonstrating the management of data sharing and storage in practical applications.

Yang and Jiang (2024) focus on creating a decision support framework for personalizing therapy in implantable medical devices (IMDs), including Implantable Cardioverter Defibrillators (ICDs). The framework uses DT technology to generate a digital clone of the patient, utilizing physiological data to model illness development and patient circumstances. The DT has two primary models: the Disease Mechanism describe (DMM), which simulates physiological processes based on disease mechanisms, and the Disease Switch Model (DSM), which uses a Markov Decision Process to describe transitions between various disease states. A reinforcement learning (RL) agent is trained utilizing the DT as an environment to ascertain appropriate parameter configurations for the IMDs. One thousand iterations were necessary for RL training on the DT. The methodology is implemented in ICDs , demonstrating how the system modifies therapy settings in reaction to alterations in a patient's cardiac status. One hundred virtual patients were utilized in the experiments. ICD algorithms were evaluated over a duration of 600 weeks, which is equivalent to 11 years.

Sai et al. (2024) explore using DTs and the Metaverse to improve consumer healthcare applications. Real-time, data-driven DTs of patients enable precise health monitoring, disease identification, and individualized therapy suggestions. Health consultations, training, and interactive self-health exams are available in the Metaverse, an immersive virtual environment. DTs help patients control their health by monitoring and predicting risk. Harfang3D created immersive virtual environments, and

Meta Quest 2 worked as a VR device to allow physical-virtual interaction. The study used URDF (Unified Robot Description Format) inverse

The study "Metaverse for Healthcare: A Survey on Potential Applications, Challenges, and Future Directions" by Chengoden et al. (2023), discusses AR, VR, XR, AI, IoT, 5G, and blockchain in the healthcare Metaverse. Virtual consultations, surgical training and simulations, DTs for individualized medicine, and remote monitoring are discussed in the paper. In the realm of Metaverse healthcare privacy, logistic regression may be employed to categorize a healthcare transaction as secure or susceptible to privacy concerns. The Logistic regression formula is given in Equation (9),

$$P(y = 1 \mid X) = \frac{1}{1 + e^{-(\omega_0 + \omega_1 X_1 + \omega_2 X_2 + \ldots + \omega_n X_n)}} \qquad ...(9)$$

Where:

- $P(y = 1|X)$ is the probability that the output y is 1 (indicating a secure transaction), given input features X
- The co-efficient ω_0, ω_1, ..., ω_n are the weights learned during the model training, which indicates the influence of each feature X_i on the prediction.
- X_1, X_2,..., X_n are the feature values of sample input (transaction characteristics or metadata in the healthcare universe).

It considers using quantum computing to improve healthcare Metaverse security and computational power, as well as AI and ML to improve patient outcomes and treatment precision. The study describes how the Metaverse can improve remote healthcare, individualized therapies, and medical education.

The study "Toward a Digital Twin for Arthroscopic Knee Surgery: A Systematic Review" by Bjelland et al. (2022), explores DT technology for knee surgery. From ScienceDirect, PubMed, and IEEE Xplore, 103,325 articles were selected for the systematic review. After filtering, 80 studies were included in the final review. This work introduces the DT, an innovative surgical simulation model with patient-specific data and real-time calibration. For individualized surgery, the DT model must incorporate real-time intra operative sensor data for dynamic adaptation. Patient-specific imaging and biomechanical modeling are needed to create realistic knee joint DTs for surgeons to practice and plan procedures with real-time data and simulations. The study covers soft tissue simulation, haptic feedback, real-time intraoperative data collecting, and system architectures needed to develop a knee surgery DT. The review identifies enabling technologies, evaluates their surgical usage, and proposes a macro-level knee surgery DT system.

Kleinbeck et al. (2024), utilizes neural rendering to create DTs of intricate medical settings, including operating rooms. These DTs are employed for virtual reality (VR) spatial design and installations. The paper employs Neuralangelo, a neural surface reconstruction technique, to convert video input into three-dimensional models. The recreated digital twin environments were included into a VR system utilizing the Unity 2022.3.7 engine for interaction. Subjective metrics, Including perceived utility, presence, and job load, were gathered alongside objective data such as head movement, rotation, and object interaction.

Shu et al. (2023), center on the creation of a DT framework named Twin-S for skull base surgery. The system simulates the skull base surgery environment, encompassing the patient anatomy (utilizing a surgical phantom), the surgical drill, and the surgical camera. The phantom model is

generated using CT scans, with ongoing updates of the interactions between the drill and the tissue based on real-time tracking. Twin-S incorporates real-time physics-based simulation with the AMBF framework. The simulation refreshes the virtual representation of the patient's anatomy in real-time as the drill exercises tissue. This procedure simulates the real surgical process and offers feedback for operative direction. The document assesses tracking precision, camera calibration precision, and drilling simulation precision, offering error limits and performance measures. In skull base surgery simulation, the Kalman Filter facilitates real-time tracking of surgical instruments or anatomical features, which is crucial for accurate navigation during intricate procedures. The Kalman Filter enhances its forecasts by integrating previous estimates with new measurements, perpetually revising the position or state estimate based on real-time input. The formula for updating the Kalman Filter is given as given in Equation (10):

$$X_{k|k} = X_{k|k-1} + K_k \left(Z_k - H X_{k|k-1} \right) \qquad \text{...(10)}$$

Where:

- $X_{k|k}$ is the updated state estimate at step k, combining both prior prediction and current measurement,
- $X_{k|k-1}$ is the predicted state estimate at step k based on information from step $k-1$, before considering the new measurement,
- K_k is the kalman gain at step k, which determines the weight given to the measurement versus the prediction,
- Z_k is the measurement at step k, (Example: Observed position of surgical tool)

- *H* is the measurement matrix that maps the predicted state to the observed measurement space.

Aubert et al. (2021) construct finite element models with 3D imaging of tibial plateau fractures to replicate the biomechanical response of bones during surgical procedures and rehabilitation. Four stabilization techniques were evaluated: bi-cortical screw with PMMA cement, bi-cortical screw without PMMA (Polymethyl Methacrylate), uni-cortical screw with PMMA, and uni-cortical screw without PMMA. Each stabilizing technique was simulated at three phases of osseous healing: mobile fragments (before callus formation), bonded fragments (during callus formation), and fused fragments (after bone remodeling). The research assessed mechanical strength, stress distribution, reduction loss, and inter-fragmentary stresses. Through the simulation of these scenarios, the DT provides insights into optimal surgical planning and postoperative treatment techniques, including the proper timing for weight-bearing according to the patient's recovery stage.

Huang et al. (2022) concentrate on recognizing and mitigating the principal ethical hazards linked to DTs in customized healthcare. A definitive characterization of DTs in personalized healthcare was formulated to differentiate these services from other e-health applications, emphasizing their implementation in patient-specific, data-driven models. It delineates ethical hazards that emerge in four principal phases: data collection, data management, data analysis, and information utilization. The research underscores the necessity of protecting patient confidentiality, securing informed permission, and tackling concerns over data ownership and the possible exploitation of health information by external entities. The ethical framework examines patient autonomy concerns, including the potential for over-diagnosis and the impact of digital twins on medical

decisions, neglecting socio-environmental considerations. The research revealed critical operational challenges and associated ethical hazards at each phase of data processing, enabling developers to proactively address ethical concerns.

Segovia and Garcia-Alfaro (2022), concentrate on delivering a systematic methodology for constructing DTs . Curation of pertinent scientific material from many sources concentrating on DTs, cyber-physical systems, and Industry 4.0. The design phase includes the identification of system requirements, the analysis of the physical object's functions, and the establishment of a system architecture. The modeling phase investigates the development of behavioral and structural models that depict the geometry, physical qualities, and interactions of the actual item. The study examines experimental platforms and standards for real-time synchronization and communication between the DT and its physical equivalent.

Chen et al. (2023) examine the utilization of a DT model characterized by a four-layer architecture: the physical object layer, virtual object layer, data layer, and application layer, specifically for healthcare monitoring in a smart home context, emphasizing healthcare applications. It employs wearable ECG sensors for continuous cardiac monitoring and leverages Wi-Fi signals for mobility tracking, particularly for fall detection. In real-time monitoring applications, throughput measures the rate at which data is being processed. It is used to evaluate the efficiency of a system in case of this study monitoring ECG and other cardiac metrics, where continuous data streams are analyzed in real time. Calculating throughput using the formula in Equation (11),

$$\text{Throughput} = \frac{\text{Total data points processed}}{\text{Total time}} \qquad \text{...(11)}$$

Where:

- Total data points processed are the number of data points (ECG readings) processed over a given period.
- Total time is the duration over which the data points are processed.

By optimizing throughput, the proposed system guarantees the capability for real-time analysis of ECG data, facilitating the swift identification of cardiac events and enhancing patient care. The study employs AI algorithms for detecting atrial fibrillation and falls, while also integrating interactive elements between physical and virtual systems to produce real-time notifications for hazardous conditions. Corrective feedback from the application layer is utilized to refine the model for enhanced predictive accuracy. Both models are assessed using measures such as F1 score and accuracy. The ensemble model attained an F1 score of 0.85 and an accuracy of 0.97 for atrial fibrillation diagnosis. The model attained an average accuracy of 0.91 and an F1 score of 0.78 for movement categorization utilizing Wi-Fi signals. In this case, calculating F1 score is used for evaluating the accuracy of the classification model, particularly in instances of class imbalance. It is especially significant in medical applications where both precision and recall are essential, such as in ECG classification for identifying aberrant heart rhythms. F1 score is given by the formula in Equation (12),

$$\text{F1 Score} = 2 \times \frac{\text{Precision} \ \times \ \text{Recall}}{\text{Precision} \ + \ \text{Recall}} \qquad ...(12)$$

Where:

- Precision: Precision as in Equation (13) measures the model's accuracy in predicting true positives among all positive predictions. It is the

ratio of correctly predicted positive instances to the total instances predicted as positive.

$$\text{Precision} = \frac{\text{True positives}}{\text{True positives} + \text{False positives}} \quad \text{...(13)}$$

- The given recall formula (14) assesses a model's capacity to accurately identify all pertinent positive instances within a dataset. It is defined as the ratio of true positives (accurately detected positive cases) to the total of true positives and false negatives (missed positive cases).

$$\text{Recall} = \frac{\text{True positives}}{\text{True positives} + \text{False negatives}} \quad \text{...(14)}$$

- True positives are the number of instances accurately predicted as positive by the model and false negatives are the number of actual positive instances that the model incorrectly predicted as negative.

Elayan et al. (2021) develop a DT framework specifically designed for intelligent, context-aware healthcare systems, integrating IoT devices with ML for real-time patient monitoring and analysis, with an emphasis on identifying problems, notably in cardiac health via ECG data processing. The document delineates a three-phase methodology for the implementation of the DT framework in healthcare: Processing and Prediction Phase, Monitoring and Correction Phase, and Comparison Phase. The ECG heart rhythm classifier model employs ML to detect and predict cardiac problems, prioritizing accuracy and reliability across diverse techniques. The advanced DT system improves patient care by consistently collecting health data, analyzing it for irregularities, and facilitating prompt and informed decision-making by healthcare personnel. The amalgamation of

DL and conventional ML algorithms (e.g., LSTM, CNN) enhances predictive accuracy and

Guo and Qi (2023) concentrate on improving the prediction and restoration of damaged images by employing DT to construct a virtual model of images, hence raising the precision of image restoration. Applying a second-order CH equation model for in-painting impaired regions improves image quality by tackling diffusion and interface dynamics. The employed multigrid technique functions across various resolution levels to efficiently resolve the CH problem, emphasizing enhancements in both speed and accuracy. The study presents an approach that integrates DT with image-processing techniques to tackle diverse picture restoration difficulties, enhancing results in areas such as medical imaging, forensics, and document restoration by yielding superior, visually clear outputs. The evaluation of the Structural Similarity Index Measure (SSIM) for image restoration to determine the fidelity of a restored image in relation to the original, undamaged image is given as Equation (15),

$$\text{SSIM}(x, y) = \frac{(2\mu_x\mu_y + C1)(2\sigma_{xy} + C2)}{(\mu_x^2 + \mu_y^2 + C1)(\sigma_x^2 + \sigma_y^2 + C2)} \quad \text{...(15)}$$

Where:

- x and y represent two images being compared. In this case, the original image and the repaired image are the two images under comparison.
- μ_x and μ_y are the mean pixel values of images x and y.
- δ_x and δ_y are the variances of images.
- δ_{xy} is the co variance between the images.
- C_1 and C_2 are the small constants to keep the division stable and prevent problems when the denominators are near zero.

Menon et al. (2023) examine the evolution of digital twin technology, from its foundational notion to contemporary implementations in numerous areas, along with the accompanying benefits and problems of its implementation across diverse industries. It offers a comprehensive examination of digital twin principles, techniques, and tools that facilitate real-time simulation, optimization, and predictive maintenance. The research entails analyzing case studies and prior investigations about DT applications in sectors including healthcare, manufacturing, transportation, and energy. The process involves evaluating the methods and tools frequently employed in digital twins, such Kalman filters, Bayesian networks, and Q-learning, customized for particular application requirements. It underscores the significance of ML, AI, and optimization algorithms in facilitating DTs to deliver predictive insights.

Bashir et al. (2023) explore and analyze the incorporation of FL within the healthcare Metaverse, detailing its significance in maintaining patient privacy, optimizing data management, and enabling personalized healthcare services. This paper examines the application of federated learning in healthcare to enhance data privacy, improve interoperability, and facilitate diverse healthcare applications within the Metaverse. The text examines the role of federated learning in enhancing data interoperability across various healthcare institutions, facilitating collaborative model development while preserving local data privacy. This study identifies challenges including constrained computational capabilities, data privacy issues, security concerns, and the necessity for reliable synchronization between physical

Li et al. (2022) present a fundamental comprehension of digital twins, distinguishing them from digital shadows and models, and elucidating the essential components required for a good DT system. This article employs a survey-based methodology to investigate the concept, evolution, and

applications of DT technology in aerospace, specifically analyz ing its historical development, present utilization, and prospects for future developments. It outlines a roadmap for the future of aeronautical DTs, proposing advanced domains such as Interactive DTs for improved human-machine interaction, Standardized DTs to guarantee consistent implementation, and Cognitive DTs with AI capabilities for self-evolving and decision-making tasks. This study investigates research avenues to create the next generation of DTs, emphasizing standardization, improved interactivity, and cognitive capabilities to boost the efficacy and autonomy of aeronautical systems.

Viceconti et al. (2024) concentrate on developing the conceptual framework for the creation of a "Virtual Human Twin". This VHT is conceived as an extensive, cooperative digital framework that systematically depicts human pathophysiology. The VHT seeks to consolidate various specialized models by establishing a scalable, interoperable framework, thus enhancing clinical decision-making and the advancement of healthcare technologies. The VHT underscores the necessity for multi-scale and multisystem models that precisely depict intricate biological systems. Validated, high-quality datasets are essential for model reliability. The VHT intends to incorporate information and annotations for each dataset to augment credibility and facilitate regulatory evaluation. The study emphasizes the necessity for explicit regulatory frameworks to facilitate the deployment of DTs in healthcare. The VHT aims to set compliance standards and facilitate public collections of validation data, potentially accelerating the regulatory clearance process for DT applications. The study emphasizes the necessity for explicit regulatory frameworks to facilitate the deployment of DTs in healthcare. The VHT aims to establish compliance standards and facilitate public collections of

validation data, potentially accelerating the regulatory clearance process for DT applications.

Das et al. (2022) investigate the integration of Digital Twin Technology (DTwT) with the Internet of Robotic Things (IoRT) to enhance the surgical field. This study highlights the advancement of a surgical environment through the integration of DTwT and the IoRT, which improves surgical precision and accuracy. The proposed infrastructure enables patients in remote regions to obtain global surgical expertise. This study envisions a healthcare system that integrates advanced robotics and AI, including AR/VR systems, robotic surgical systems, and automated diagnostics, to aid in diagnosis, surgery, and patient care management. This research underscores the necessity for secure data management processes and privacy safeguards to protect patient confidentiality and trust in digital health systems. This research classifies data clustering using a coefficient k, where $k = 1$ denotes the most general grouping level (e.g., species-level such as Homo sapiens), whereas $k = 0.5$ may signify groups depending on characteristics such as gender. Individual datasets are designated $k = 0$, signifying the absence of clustering. This study correlates the proposed technologies with environmental sustainability objectives, indicating that IoRT and DTwT may enhance eco-friendly healthcare practices by decreasing needless patient transfers and reducing waste in surgical procedures.

De Benedictis et al. (2023) present an architectural framework for DTs in healthcare, specifically used to public health for the surveillance of social distance. It classifies DT applications into four main domains: patient treatment, physician and surgeon training, pharmaceutical processes, and public health management. This study presents a six-layer DT architecture comprising physical twin, data, DT functions, services, connection, and

security, facilitating bi-directional data flow and diverse service capabilities inside healthcare systems. This document examines the CanTwin system created for Hitachi Rail's canteen to facilitate safe working environments amid the COVID-19 pandemic. The support system encompasses social distancing surveillance, population counting and tracking, as well as queuing and occupancy optimization. This research offers a versatile, modular framework that may be tailored to many healthcare contexts.

Table 1 describes accuracy metrics across various healthcare applications and several studies reporting above 90% of accuracy. It demonstrates precision in medical procedures and projected the emerging market trends for digital twin technology. Various studies leverage AI algorithms and IoT sensors to improve patient monitoring and outcomes, illustrating the integration of technology in healthcare.

Table 1 Performance Comparison of Different Models in various H
applications using Digital Twin. ⏎

Ref. Paper No.	Application area	Description	Model	Benefits	A
(Abilkaiyrkyzy et al., 2024)	Mental health monitoring	AI-driven identification of mental health disorders and assistance via tailored engagement	Pre-trained BERT models, chatbot framework	Facilitates prompt intervention and assistance for mental health	
(Sarp et al., 2023)	Personalized treatment	Predictive modeling for monitoring and adapting of healing therapies	GAN, real time monitoring	Enables customized treatment	7 p
(Subramanian et al., 2022)	Emotion recognition	Real time detection of patient emotions by facial expressions and posture	Neural networks, MediaPipe framework	Supports personalized emotional well-being care	
(Ali et al., 2024)	Patient monitoring	Continuous monitoring for patient's care with real time data integration	IoT sensors, latency measurement	Timely responses ensure patient's safety	9

Ref. Paper No.	Application area	Description	Model	Benefits	A
(Rouhollahi et al., 2023)	Medical imaging and analysis	Segmentation and analysis of aortic stenosis utilizing 3D-imaging for cardiac health assessment	U-Net DL model	Virtual intervention planning assists	D C 9' In ov (I 9:
(Sharma et al., 2024)	Cancer detection	Automated categorization of cervical cells for early cancer identification	CervixNet, Support vector machine (SVM)	Enhances precision and efficacy in cancer screening	
(Shu et al., 2023)	Surgical planning	Real-time simulation of surgical instruments of surgical instruments and patient anatomy for accurate navigation	Kalman filter, Twin-S framework	Enhances accuracy and safely in intricate surgical procedures	
(Chen et al., 2023)	Cardiac health monitoring	Real-time ECG monitoring for identifying abnormal cardiac rhythms in smart home scenarios	Wearable sensors, Wi-Fi signals	Early alerts for cardiac abnormalities	9 n

Insights from the Bibliometric Analysis Using VOSviewer_1.6.20 For the Research String "applications" and "of" and "digital" and "twin" and "in" and "healthcare"

Bibliometric Analysis

Bibliometric analysis is a quantitative research method using mathematical and statistical approaches to examine bibliographic data including publications, citations, and authorship. It is used extensively to evaluate academic output, identify trends in research, and assess the impact of scientific output across many fields. This approach evaluates research success and influence by using indicators like publication volume, citation frequencies, co-authorship dynamics, and keyword frequency. Common approaches are bibliographic coupling, co-authorship analysis, co-word analysis, and citation analysis. New research trends, knowledge gaps, and intellectual structures within certain fields are revealed by bibliometric analysis, which also clarifies intellectual structures in other subjects, thereby enabling the creation of visual representations including keyword maps or citation networks. It has limits, including reliance on published data and the need for careful interpretation, even if it provides an objective overview of study areas and helps in academic decision-making. Despite these challenges, bibliometric analysis has become an indispensable tool in many different scientific disciplines for evaluating development and steering next directions of study.

Bibliometric Analysis Using Vosviewer 1.6.20.

Based on diverse relationships including citation, co-citation, bibliographic coupling, co-authorship, and keyword co-occurrence, VOSviewer (version 1.6.20) is a widely used open-source software application for the creation and visualization of bibliometric networks, encompassing components such

journals, researchers, or publications. With text-mining skills to create term co-occurrence maps, the software is valued for its ability to evaluate data from sources including Scopus, Web of Science, PubMed, and Dimensions. Along with mapping collaborations and evaluating thematic clusters, essential elements include various display modalities (network, overlay, and density), adaptable data input formats, and tools for locating significant articles, authors, and keywords. Using VOSviewer, the standard bibliometric analysis process consists in data acquisition from bibliographic databases, importing the data into the software, creating maps by defining appropriate parameters, customizing visualizations, and interpreting the resulting networks to extract insights regarding research trends, collaborations, or thematic domains. VOSviewer's notable characteristics and easy interface make it suitable for both novice and experienced users in bibliometric research, thereby offering an extensive tool for analyzing and understanding scientific environments.

Distribution of Publications among Countries, Authors, and Organizations Based on the Results from Scopus Database

Using the subject "Applications of Digital Twin in Healthcare", a comprehensive search of the Scopus database turned up 542 documents covering the years 2018-2025. This dataset offers a broad and varied collection of study materials by including a great range of filtering choices made possible in Scopus. To ensure a comprehensive coverage of the topic, the search includes all pertinent subject areas, document kinds, and languages. Furthermore included in the collection are other terms associated with DTs in healthcare, which reflect contributions from multiple countries and territories. The search results capture a range of publishing sites by including several source kinds and titles.

It Includes author names, publication stages, affiliations, and funding sponsors, therefore providing information on the key supporters and contributors of the research topic. Moreover, the dataset contains information on open access availability, which enables a study of the accessibility of these research results. This extensive collection of documents and related metadata offers a strong basis for doing a thorough bibliometric study of the uses of digital twins in the medical field. Figure 5 represents the number of publications from 2018 to 2024.
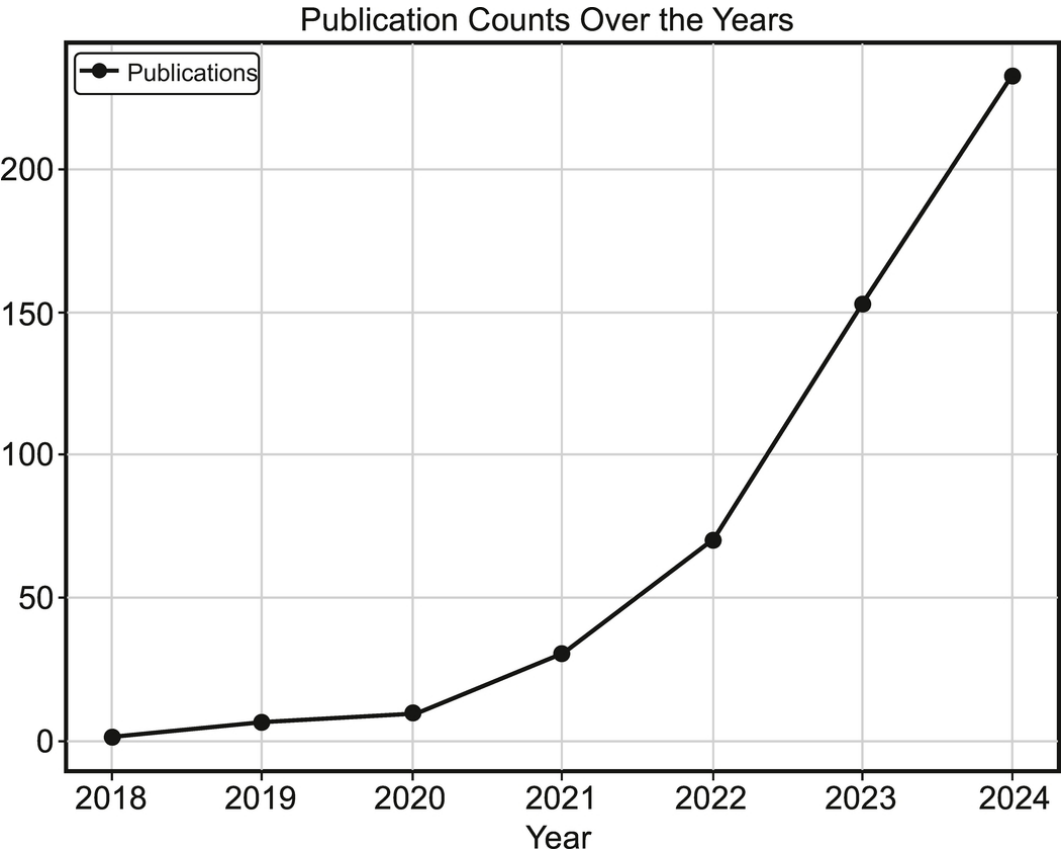
Fig. 5 Number of publications over the years ranges from 2018 to 2024.↵

Based on the results from the Scopus database, Table 2 illustrates the number of publications across the top 10 countries among 84 countries and Table 3 shows the publication counts-based Language, Source type, and

Open access for the search term "Applications of Digital Twin in Healthcare" from the Scopus database.

Table 2 Number of Publications across top 10 countries for the search item "Applications of Digital Twin in Healthcare". ↵

Country	Number of Publications
India	134
United States	93
China	64
United Kingdom	53
Italy	45
Undefined	39
Germany	30
Canada	28
Australia	23
France	20

Table 3 Number of Publications based on Filtering Counts (From Scopus database). ↵

Language	Count	Source type	Count	Open access	Count
English	531	Journal	256	All Open Access	183
Chinese	4	Book	117	Gold	127
Russian	4	Conference Proceeding	116	Green	86
French	2	Book Series	51	Hybrid Gold	24
German	1	Trade Journal	2	Bronze	7
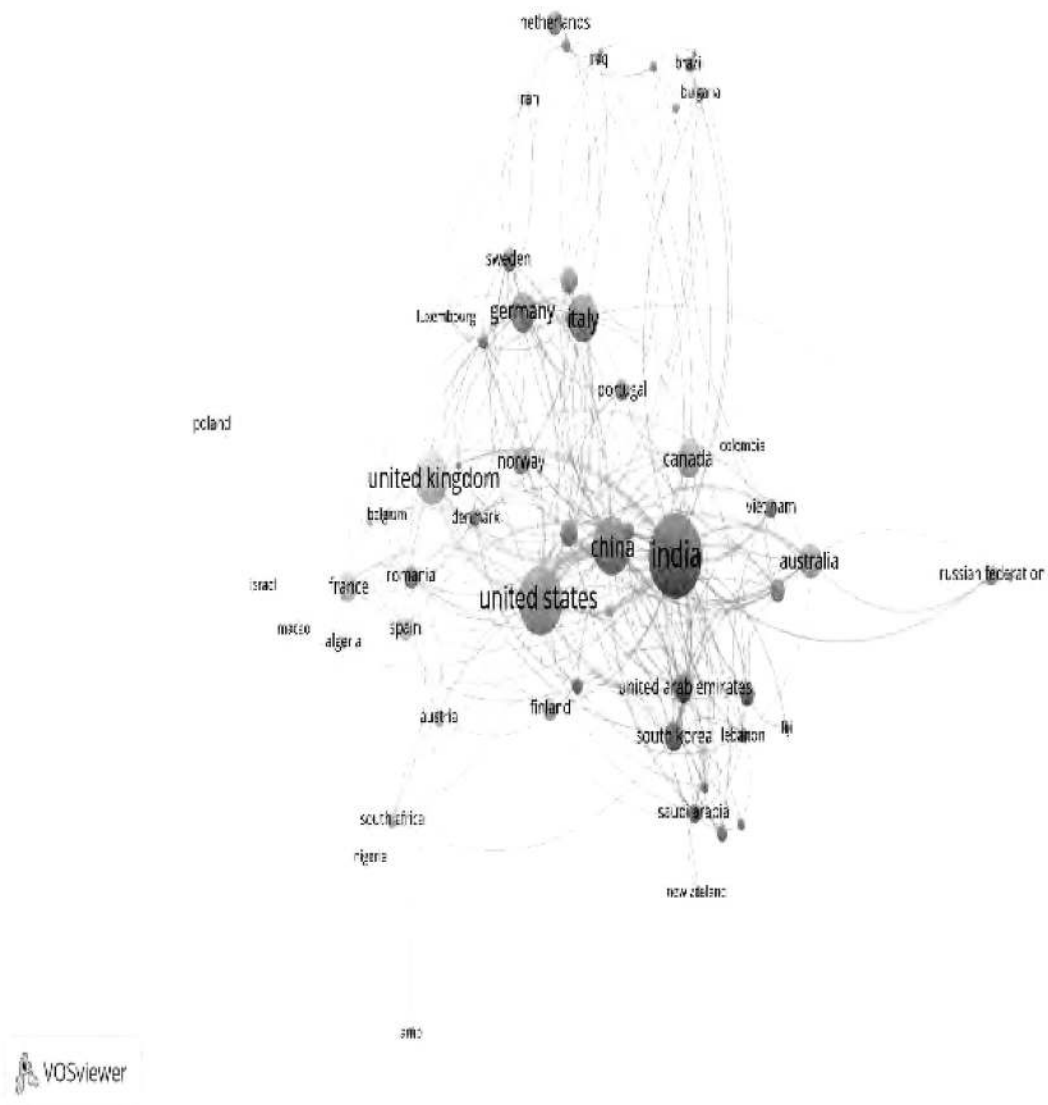
Fig. 6a Country Co-authorship Network
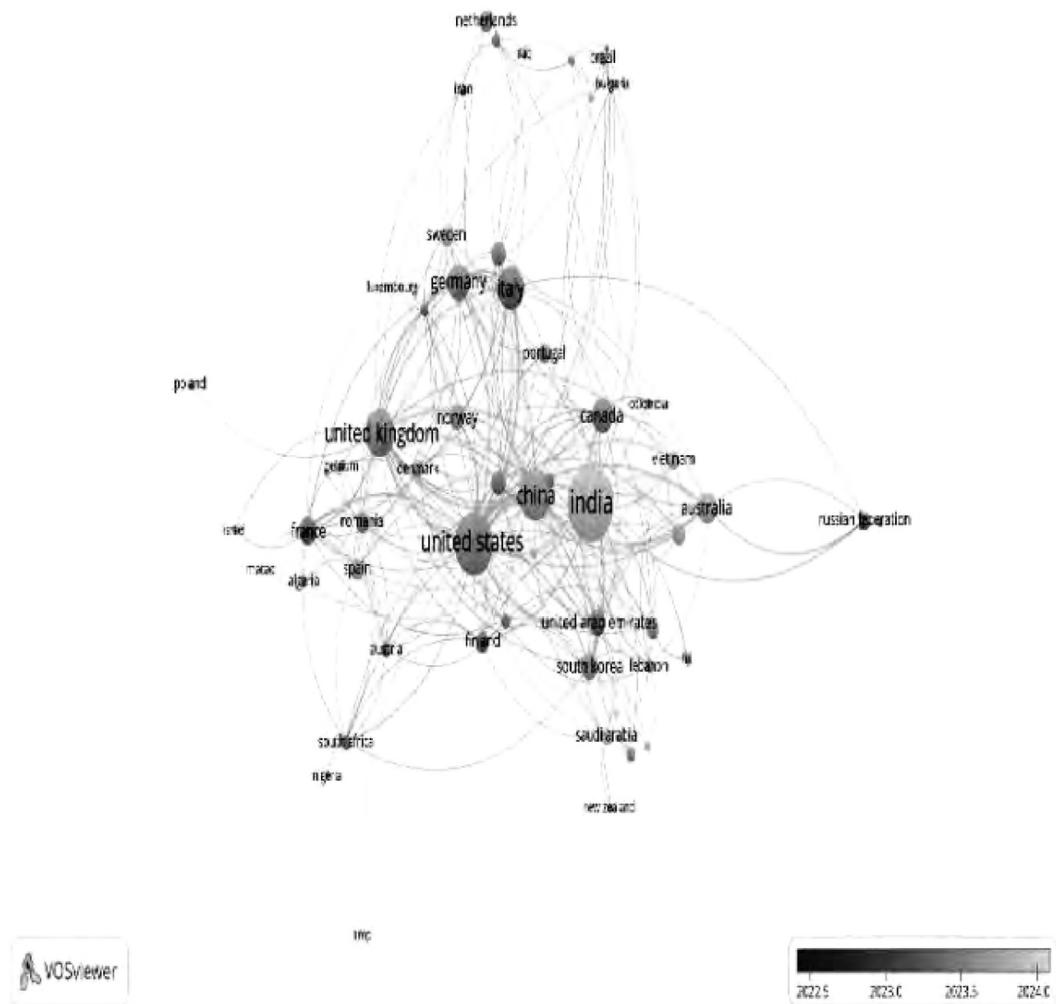
Fig. 6b Time Overlay of International Research Networks
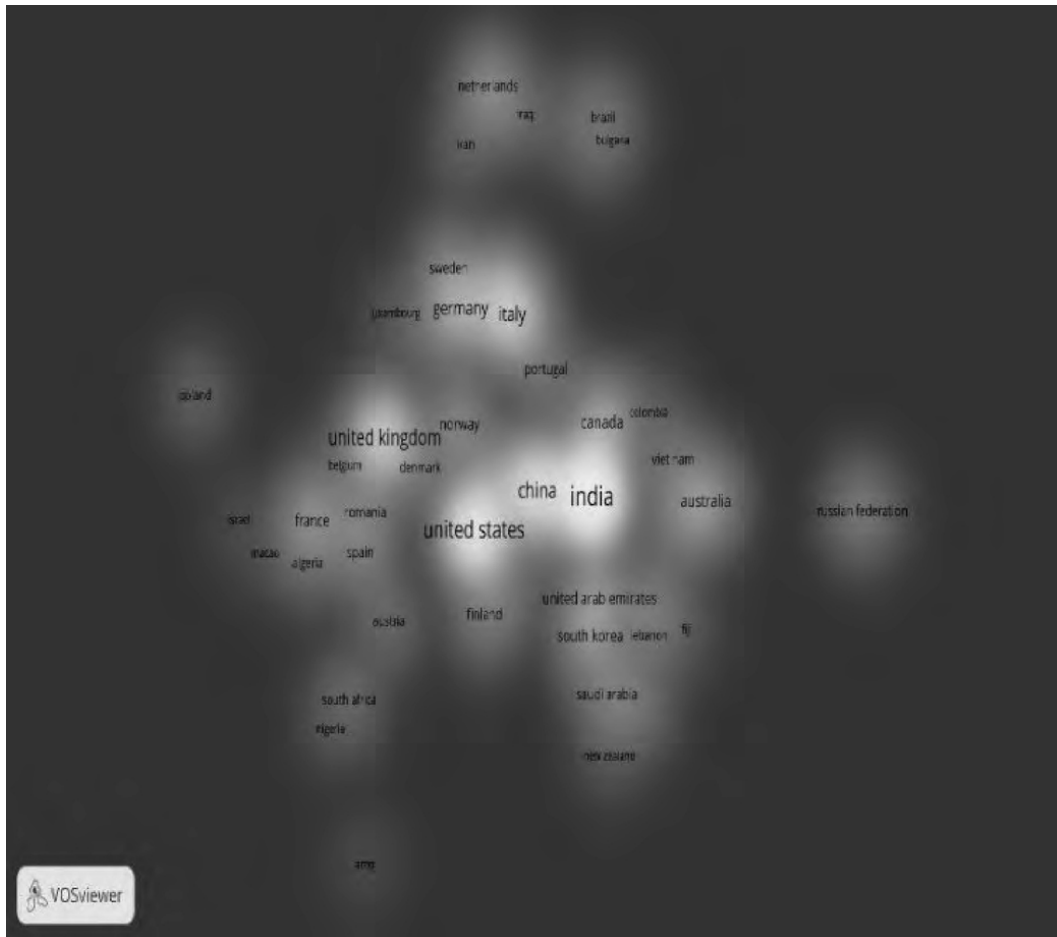
Fig. 6c Density-Based Country Collaboration Map.

Figures 6(a), (b), and (c) depict VOSviewer analysis of Co-authorship as type and Countries as the unit of analysis, where the threshold for "Minimum number of documents of a country" set as 1 and "Minimum number of citations of a country" set as 1. Among 84 countries, 70 countries meet the threshold.

, (13), and (c) demonstrate VOSviewer analysis of Co-authorship as type and Authors as the unit of analysis, where the threshold for "Minimum number of documents of an author" set as 1 and "Minimum number of citations of an author" set as 1. Among 1,996 authors, 1,323 of them meet the threshold.
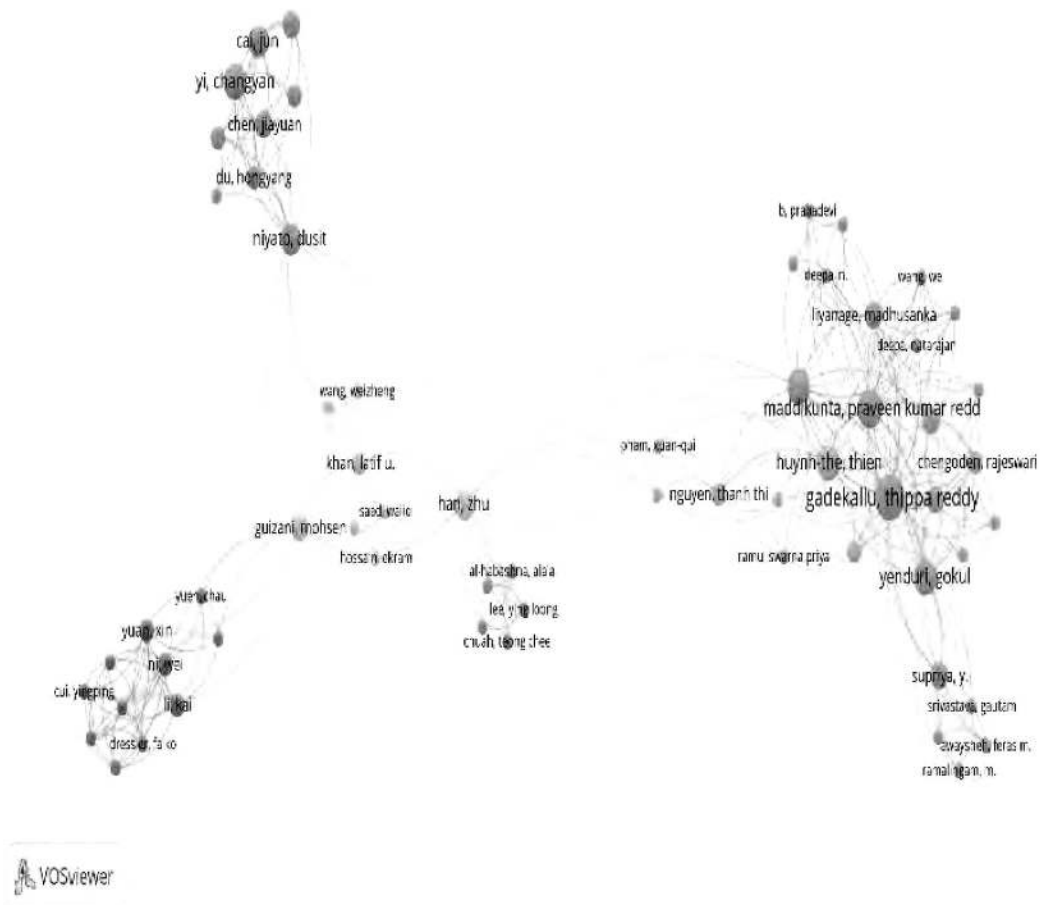
Fig. 7a Scientific Collaboration among Authors
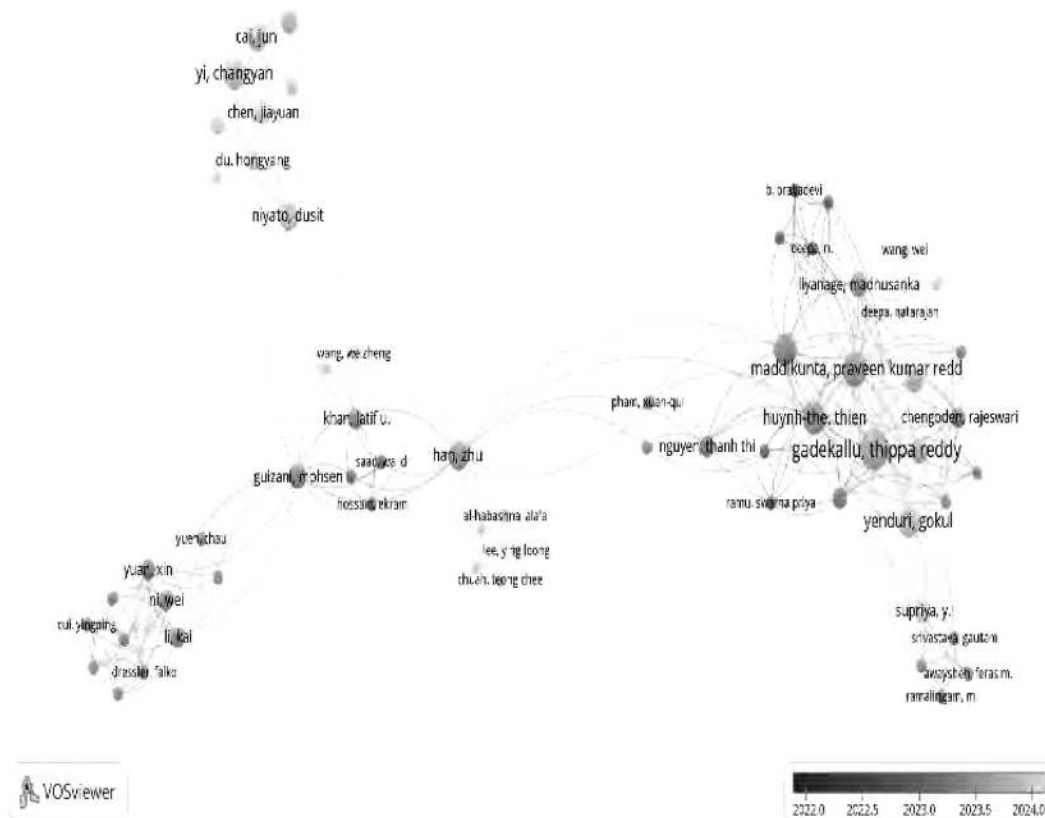
Fig. 7b Temporal Collaboration Map of Authors
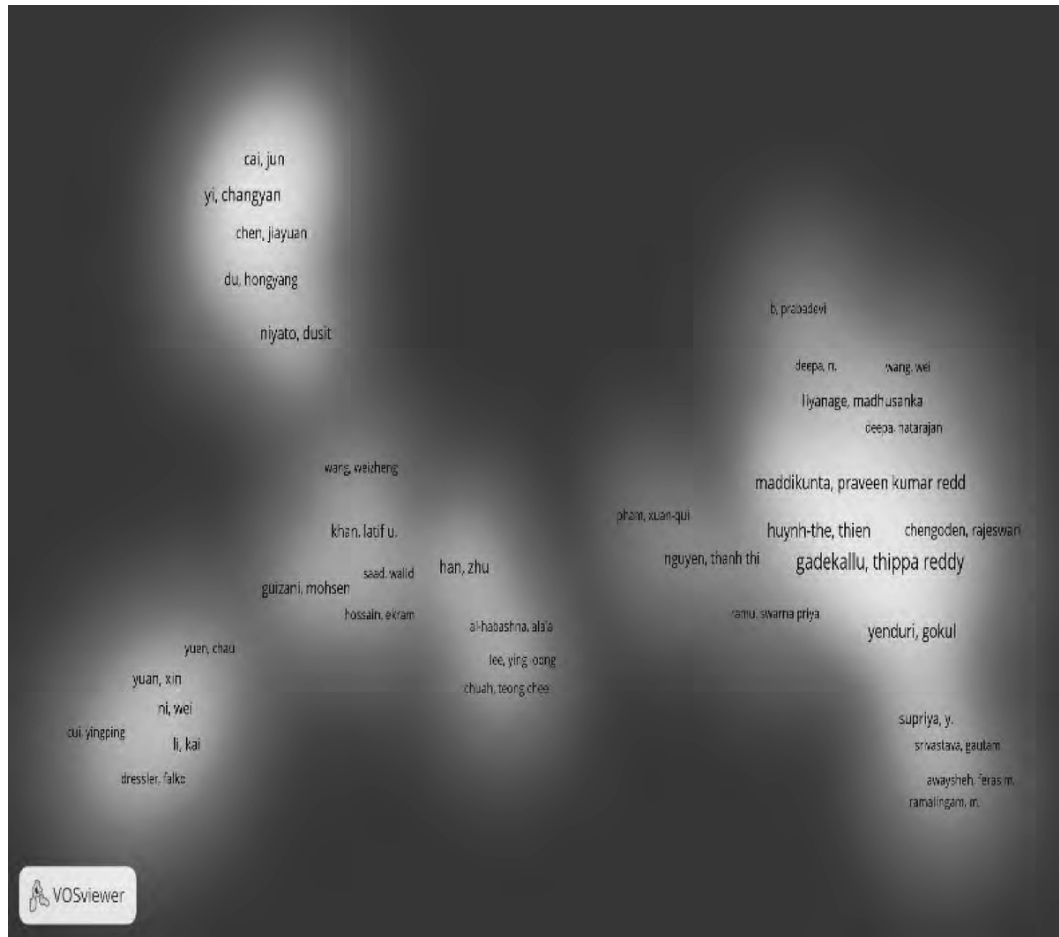
Fig. 7c Clustered Density Map of Academic Contributors

Figures 8(a), (b), and (c) demonstrate VOSviewer analysis of Co-authorship as type and organizations as the unit of analysis, where the threshold for "Minimum number of documents of an Organization" set as 1 and "Minimum number of citations of an organization" set as 1. Among 1,451 Organizations, 964 meet the threshold.
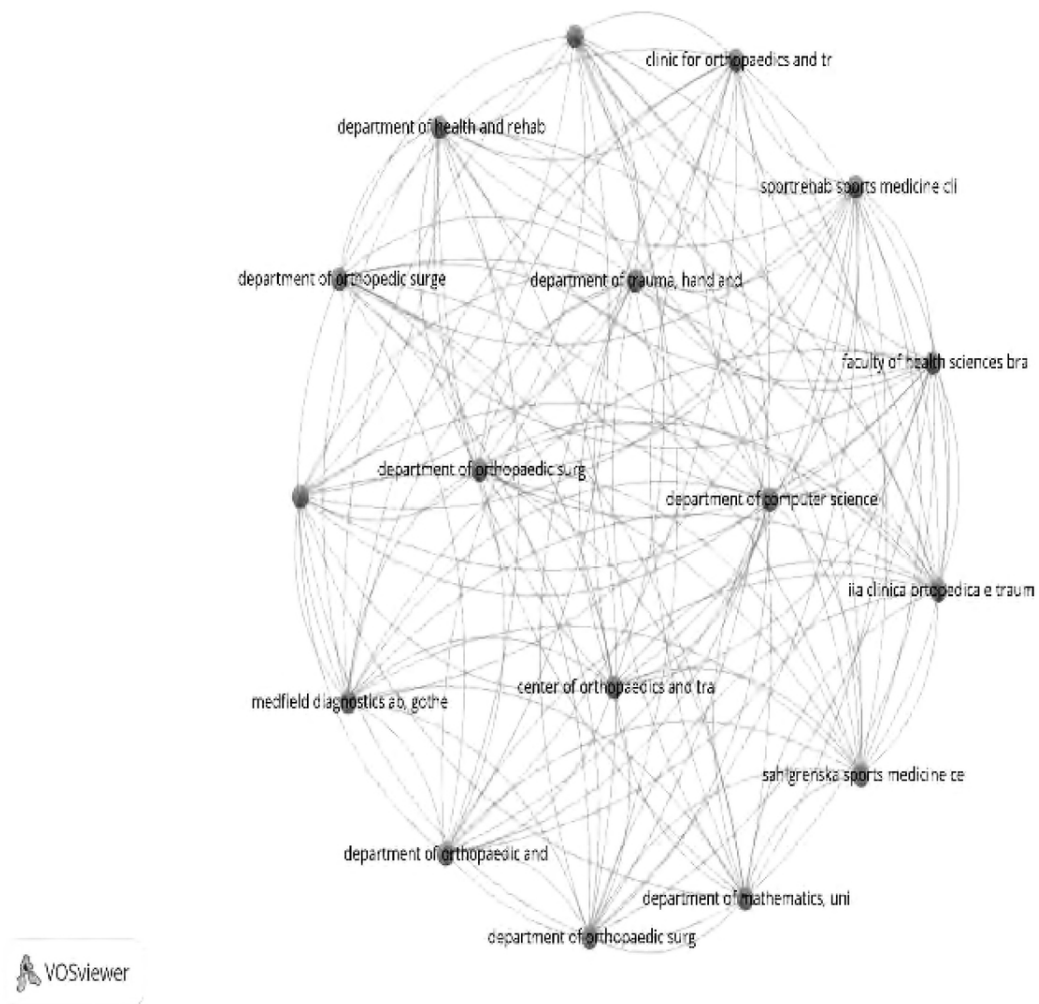
Fig. 8a Scientific Collaboration Map of Organizations
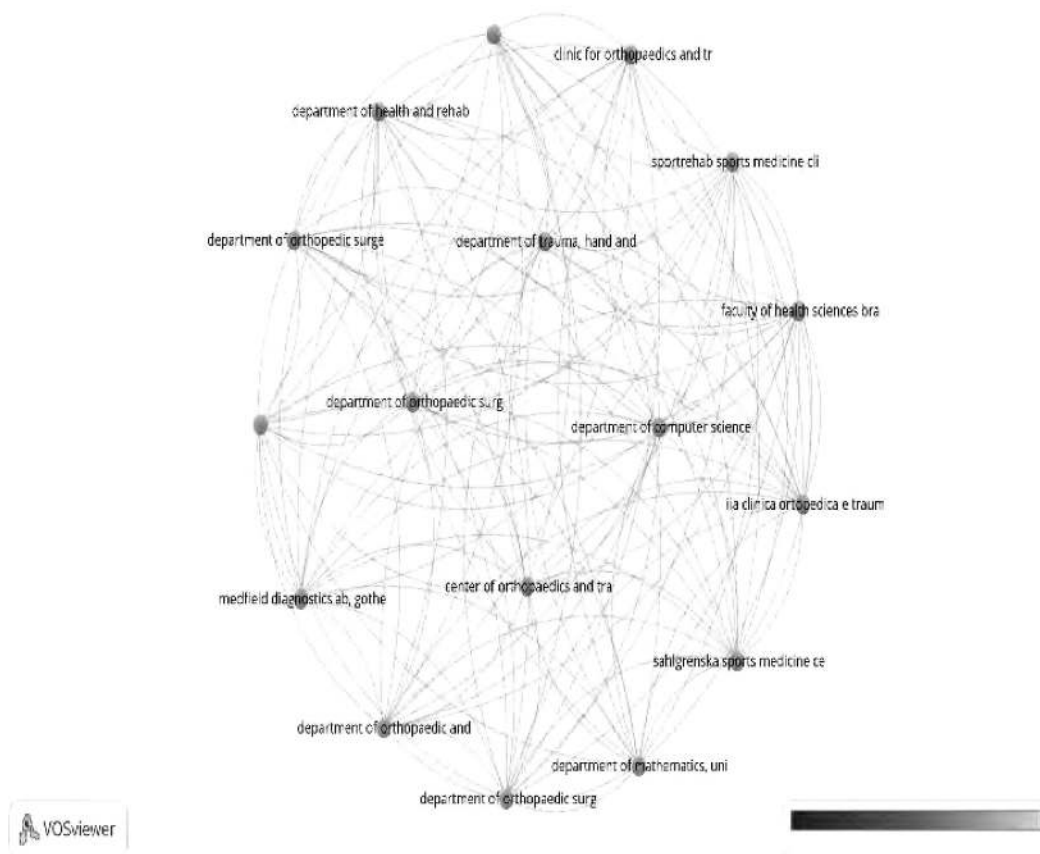
Fig. 8b Overlay Analysis of Inter-Institutional Research Ties
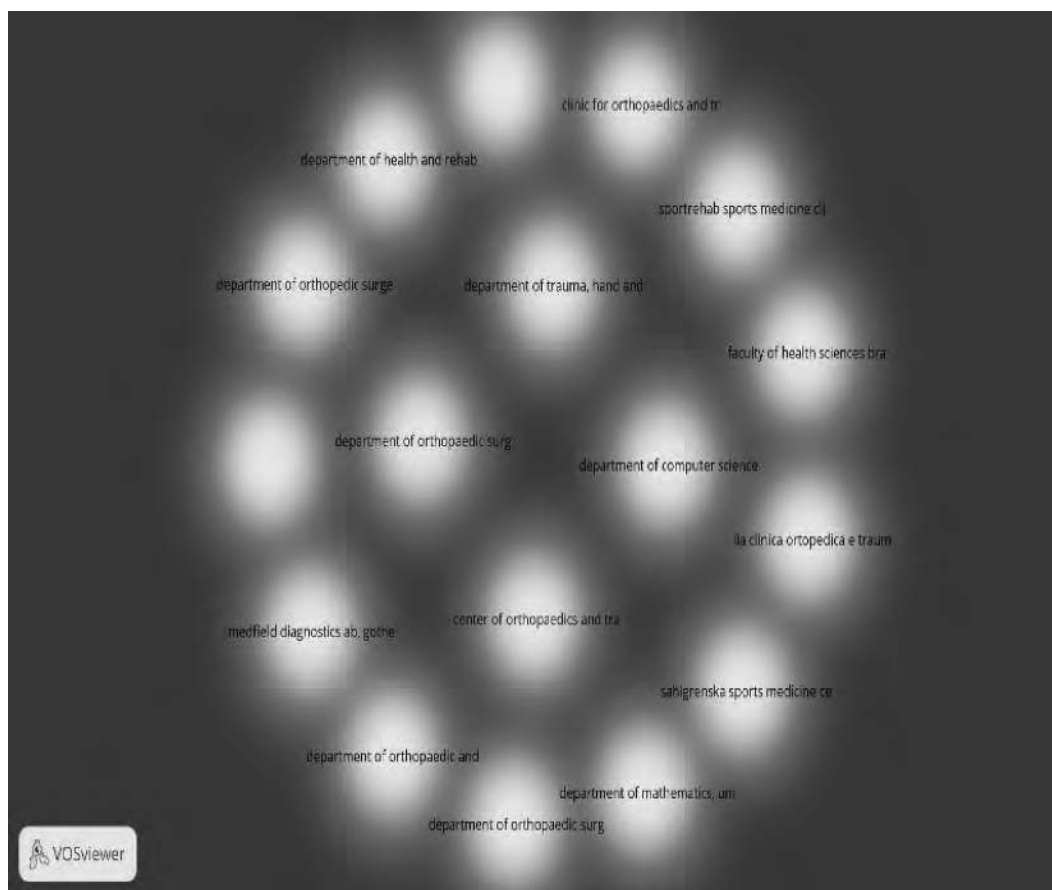
Fig. 8c Densiy Mapping of Institutional Research Activity

Co-occurrence Analysis of "All keywords" from Vosviewer

The co-occurrence analysis is a type of analysis with three units of analysis such as All keywords, Author keywords and Index keywords in VOSviewer. For the research string 'applications" AND "of' AND "digital" AND "twin" AND "in" AND "healthcare", the visualizations for "All keywords" are given in Figure 9. The threshold value for "Minimum number of occurrences of a keyword: chosen as 3. Among 3,610 keywords, 421 meet the threshold. Similarly the analysis for Author keywords and Index keywords can also be generated using VOSviewer. Based on the type of occurrences, the cluster analysis can also be analyzed.

Fig. 9a Keyword Co-occurrence Network Map

Figures 9 (a), (b), and (c) demonstrate VOSviewer analysis of Co-occurrence as type and All keywords as the unit of analysis, where the threshold for "Minimum number of occurrence of a keyword" is set as 3. Among 3,610 Keywords, 421 meet the threshold.

Fig. 9b Time-Based Keyword Visualization

Fig. 9c Keyword Co-occurrence Density Visualization

Research Challenges in Adopting Digital Twin

Across the papers, DT technology is acknowledged in scholarly articles as a revolutionary instrument in healthcare, facilitating enhanced diagnoses, monitoring, and treatment planning. From reconstructive surgery to cardiac care, DTs offer real-time, data-driven simulations that replicate physical systems or patient circumstances. AI-driven algorithms, especially DL, are often incorporated into DT models, augmenting their predictive powers in applications such as chronic wound treatment, cardiac MRI segmentation, and emotion identification systems. AI not only streamlines data processing but also enhances predictions, resulting in more precise models of patient health and disease development.

Figure 10 depicts the accuracy of several DT applications in healthcare results from the broad analysis. The accuracy for each application is represented by a bar, making it simple to compare the various use cases. With model annotations for further clarity, each bar displays the accuracy of the application.
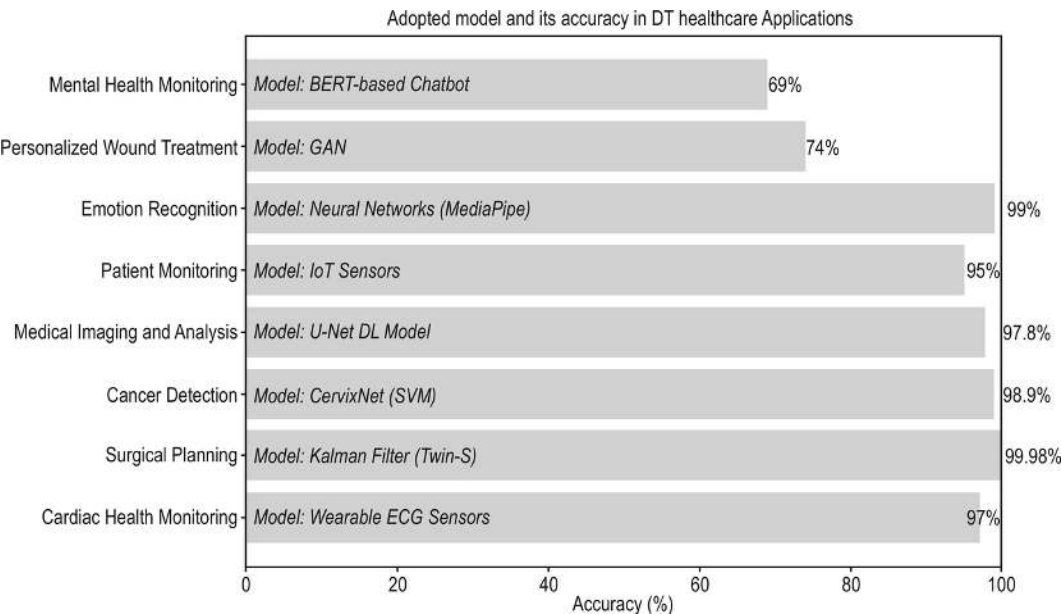
Fig. 10 Accuracy based on Model Annotations.

HDT provides unique characteristics compared to conventional DTs which are mostly applied in non-living physical entities. Also, conventional DTs are structured, homogeneous, and have no ethical considerations. HDT improves the efficiency of clinical trials, facilitates therapeutic plans, reduces health inequalities and promotes precisions of diagnosis. HDT development is still in its infancy, since the conditions of the human body are ever-changing with aging, behavioral and psychological changes. Integrating a DT with an AI-model makes the twin system much more adapted. Table 4 depicts the common difference between the traditional one-size-fits-all approach and adopting DTS in healthcare.

Table 4 Comparison of standard methods and personalized

treatment approach. ↵

Feature	One-Size-Fits-All approach	Using Digital twin approach
Treatment Plan	Standardized and uniform treatment approach	Provides customized treatment
Predictive Capability	Low-due to average population responses	High-predictive simulations based on patient specific models
Adaptability	Treatment plans are static	Treatment plans are dynamic based on real time monitoring
Drug Dosage	Common standardized dosages	Precision medicine and customized dosages
Risk Management	Generalized assessment	Tailored assessment through virtual simulations
Recovery and Rehab	Recovery plans are generalized	Recovery plans are tailored and adaptive

One of the most notable advantages emphasized in these studies is the capacity to develop patient-specific models. Personalized DTs provide tailored therapies and real-time modifications based on patient-specific data, whether modeling conditions of specific organs or controlling chronic diseases. Digital technologies are increasingly being adopted in surgical settings, enabling doctors to practice procedures and refine surgical methods before the real surgery, thereby enhancing outcomes and mitigating risks. By modeling illness progression and forecasting probable complications, decision trees provide proactive interventions, aiding in the prevention of complications or the attenuation of disease progression.

Numerous publications highlight ethical difficulties pertaining to the gathering, storage, and use of sensitive health data within digital transformation frameworks, particularly with ethical and privacy concerns. Ensuring data security, safeguarding patient privacy, and mitigating algorithmic biases are essential issues. Widespread adoption of healthcare

digital technologies necessitates the establishment of rigorous ethical frameworks and adherence to rules such as HIPAA (Health Insurance Portability and Accountability Act) and GDPR (General Data Protection Regulation). The effective implementation of DTs in healthcare necessitates sophisticated computing capacity, instantaneous data processing capabilities, and dependable communication infrastructure. Also highlights the significance of edge computing, 5G technology, and cloud platforms in facilitating the ongoing synchronization between physical items and their digital equivalents. In addition to their existing applications, digital therapeutics possess potential in other healthcare domains, including telemedicine, rehabilitation, mental health monitoring, and emergency care. Incorporating digital twins into telehealth services could enhance tailored remote care, hence enhancing accessibility to healthcare services. Table 5 summarizes the drawbacks and future works suggested across the survey.

Table 5 Limitations from the findings and suggested future works.

↵

Limitations	Future works
Data quality (real time prediction issues)	Integrating 3D cameras, AI model optimization
Data privacy (real time emotion prediction)	Use of text/speech, AI optimization
Ethical concerns, data bias	Further ethical frameworks
Real time tracking and hardware limitations	Hybrid models and providing scalability for clinical use
Calibration complexity	Deeper simulation for complex surgeries
Line of sight issues	Integration with vision-based tracking
Lack of interoperability and data ownership	Development of standards and embedded ethics
Algorithmic bias and patient privacy	Improved algorithm transparency, stronger data privacy protections

Limitations	Future works
High computational cost and real time syncing	Optimization of real time synchronization and edge computing improvements

The problems and unresolved issues, such as data quality, real-time processing, scalability, and regulatory considerations, are thoroughly analysed. Future research should concentrate on advancing AI integration, augmenting data protection, and establishing standardized frameworks to facilitate the assured and extensive deployment of DT technology in healthcare.

Conclusion

This chapter presents an extensive analysis of the applications of DT technology in the healthcare sector. The text commences by delineating the constraints of traditional healthcare methodologies, specifically the absence of continuous monitoring and individualized care, and emphasizes the significance of digital technologies in addressing these deficiencies. The discussion encompasses the notion of DT technology, its historical progression, and its advancement within the healthcare sector. The report examines critical domains that DTs are impacting, including individualized treatment strategies, real-time monitoring, precision medicine, and predictive healthcare. Uses of digital technologies in chronic wound management, cardiac care, mental health, and surgical procedures are emphasized, demonstrating their capacity to transform diagnostic and therapeutic approaches. The incorporation of AI and ML with DTs is examined, highlighting how these technologies augment the predictive capacities of DTs, resulting in more accurate and efficient healthcare interventions.

This research also examines the ethical implications of utilizing patient data within digital twin frameworks, including addressing privacy, data

ownership, and algorithmic bias. The analysis also examines the role of emerging technologies, like AI, blockchain, and cloud computing, in tackling these difficulties and facilitating real-time data synchronization and safe data sharing. Numerous studies advocate for additional research aimed at enhancing the real-time capabilities, scalability, and precision of digital twins. Maintaining high-quality, consistent data for efficient DT creation is an issue highlighted in numerous publications. Managing incomplete, noisy, or diverse datasets, particularly for real-time updates, is crucial for the reliability of DTs. This necessitates consistent standards and rigorous pre-processing approaches.

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9 NIC-Health Nature Inspired Computing for Secure and Intelligent Healthcare Systems

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Nature-Inspired Computing (NIC) techniques, inspired by biological processes like evolution and swarm intelligence, are increasingly used in healthcare. Particle Swarm Optimization (PS 0), Ant Colony Optimization (ACO), Genetic Algorithms (GA), and Artificial Immune Systems (AIS) are some of the techniques that help in drug development, diagnosis, treatment planning, and resource management. NIC improves medical imaging, refines predictive models, and improves feature selection, especially when combined with Machine Learning (ML) methods such as Deep Learning (DL), Reinforcement Learning (RL), and Support Vector Machines (SVM). The function of NIC in healthcare is examined in this chapter. This includes case studies on disease prediction and personalized care. While these methods have many advantages, there are still issues with data interpretation, computing demands, and ethical considerations. The

discussion also addresses the difficulties in applying these methods in real-world medical environments. The chapter provides a comprehensive review on how NIC and ML work together to improve healthcare systems and advance medical research.

Introduction

Nature Inspired Computing (NIC) solves complex computing problems by using ideas from biological processes like natural selection, evolution, and swarm intelligence. To create flexible, effective, and scalable solutions for a range of industries, including healthcare, these methods imitate natural sys tems (de Castro et al., 2006). NIC offers optimization methods to improve medical decision-making, diagnostic accuracy, and healthcare management (Fister et al., 2005) by drawing inspiration from nature. Several NIC techniques, including GA, PSO, ACO, AIS, and Evolutionary Strategies have been widely used in drug discovery, disease prediction. These bio-inspired strategies make healthcare systems extremely effective in dynamic medical situations by allowing them to change, adapt, and optimize solutions in real time (Hussain et al., 2019). NIC has the potential to transform the health care industry by providing more accurate diagnosis, customized treatments, and improved patient outcomes. Furthermore, ongoing NIC research will open up fresh opportunities for solving difficult healthcare issues. In recent years, the integration of NIC with machine learning (ML) and deep learning (DL) models (Mirjalili et al., 2020) has led to the development of intelligent healthcare systems that significantly improve clinical outcomes. For example, NIC-based feature selection improves disease classification models (Dey et al., 2019) where as Swarm Intelligence algorithms optimize medical imaging operations, resulting in quicker and more precise diagnoses. Additionally, based on patient-specific information, NIC-driven models have also been utilized to identify early

disease symptoms, optimize hospital re-source allocation, and customize treatment plans ([Choubey et al., 2021](#)).

Main Contributions of this Chapter

- Reviews the role of NIC in improving medical decision-making, diagnostic accuracy, and health care management.
- Analyzes various NIC optimization techniques and their impact on medical imaging, predictive analytics, and feature selection.
- Presents case studies demonstrating NIC applications in disease prediction, treatment planning, and personalized care.
- Explores how NIC integrates with ML to enhance medical applications, focusing on adaptive learning and optimization.
- Discusses challenges in real-world healthcare implementation, including computational require ments, data interpretability, and ethical concerns.
- Examines NIC's role in optimizing hospital resource allocation, enhancing tele medicine, and supporting epidemiological analysis.

Traditional healthcare computational models often lack the ability to dynamically adapt to new data and evolving medical conditions. In contrast, NIC-driven approaches provide a flexible and efficient framework, based on real-time inputs, that continuously improves. This adaptability ensures more precise diagnoses, optimized treatment plans, and better overall healthcare decision-making.

As the healthcare data volume and complexity increases, NIC approaches provide effective solutions for handling large datasets, improving model interpretability, and reducing computational costs. Because of this NIC is an essential component of modern healthcare advancements. It offers

intelligent, self-adaptive, and scalable frameworks to improve patient care and medical research. Further more, NIC is also used outside of traditional medical environments. For instance, NIC algorithms can be applied to tele medicine to optimize remote monitoring systems and to ensure prompt interventions and individualized treatment for patients in various geographic locations. NIC can help public health professionals to take preventative action against epidemics of disease by supporting the analysis of epidemiological data. However, NIC researchers and healthcare professionals need to reduce the interdisciplinary collaboration gap in order to fully benefit from these advantages.

The integration of NIC techniques with ML models is a crucial component of bridging the in-novation gap in healthcare. This chapter highlights the significant potential of combining NIC and ML to improve several aspects of the medical industry. Healthcare systems can improve patient strat ification, advance predictive analytics, and support personalized treatment by using NIC's adaptive and optimizing capabilities through ML. The combination ofNIC and ML can produce more reliable models that are able to adjust to the dynamic nature of the healthcare environment and offer practical insights that are essential for healthcare judgment. This integration can eventually enhance patient outcomes by giving medical personnel access to state-of-the-art tools for diagnosis, treatment planning, and resource allocation. The chapter also includes information on how this integration could address current issues in the healthcare industry. These include improving model interpretability, reducing computing costs, and managing high-dimensional data. The rest of the chapter is structured as follows. It begins with an introduction to the fundamentals of NIC, explaining its key techniques and algorithms used in healthcare. Next the discussion shifts to how NIC integrates with ML to

improve medical applications. Another section explores its applications in healthcare, such as disease prediction, treatment planning, and medical imaging. The chapter also discusses the challenges and ethical concerns associated with its implementation. Finally it highlights future research directions and opportunities. The final section concludes, summarizes key findings, and discusses the potential future impact of NIC in healthcare.

Related Works

Recent research has explored the role of NIC in healthcare, focusing on its applications in predictive analytics, medical imaging, and resource optimization. Various studies from 2020 to 2025 have examined how different NIC methodologies contribute to healthcare advancements.Table 1 summarizes key methodologies, their limitations, implications, and results. The findings demonstrate how NIC techniques continue to address complex challenges, paving the way for more adaptive and intelligent healthcare solutions.

Table 1 Summary of NIC Methodologies in Healthcare (2020-202[...])

Year	Methodology'	Used For	Limitations	Implications	Resul[...]
2020	Genetic Algorithms (GA)	Disease prediction	High computational cost	Improved accuracy in early diagnosis	89% classif[...] accura[...]
2021	Particle Swarm Optimization (PSO)	Medical imaging enhancement	Requires parameter tuning	Enhanced image segmentation and classification	92° o[...] segme[...] efficie[...]
2022	Ant Colony Optimization (ACO)	Treatment planning optimization	Slow convergence in large datasets	Optimized personalized treatment strategies	Reduc[...] planni[...] time b[...]
2023	Artificial Immune Systems (AIS)	Anomaly detection in health monitoring	Data imbalance issues	Improved anomaly detection in real-time monitoring	95% anoma[...] detect[...] rate
2024	Hybrid NIC-ML mode Is	Predictive health-care analytics	Complexity in model inter pretability	More robust predictive analytics for patient outcomes	15% reduct[...] false positiv[...]
2025	Swarm Intelligence	Hospital resource allocation	Ethical concerns in decision automation	More efficient and data-driven healthcare management	20% impro[...] in reso[...] utiliza[...]

NIC addresses critical challenges in healthcare by offering adaptive, efficient, and scalable solutions. While traditional models struggle with real-time adaptability, NIC enhances predictive accuracy, optimizes

treatment strategies, and improves resource management. However, challenges like computational demands and ethical concerns remain. Future research should focus on refining NIC models for better transparency and efficiency, ensuring their seamless integration into healthcare systems.

Fundamentals of Nature-Inspuired Computing

NIC is a collection of algorithms and computational methods that are based on natural events and processes ([Moody et al., 2003](#)). These methods aim to solve complex problems by imitating the adaptive processes present in biological systems. The fundamental principles of NIC include:

- **Adaptation:** System's capacity to evolve and adapt over time in response to feedback or in the environment.
- **Self-Organization:** The process by which a structure or pattern develops in a system without a central authority. This process is often seen in natural systems like ant colonies or flocks of birds.
- **Collective Behavior:** The process where different individuals in a system work together to achieve a common goal. This often leads to emergent properties that are absent in individual components.
- **Robustness:** The ability of a system to continue operation despite environmental changes or disturbances.

According to these principles, NIC-based algorithms enable us to resolve challenging classification, prediction, and optimization issues in a variety of fields, including healthcare.

Biological Inspirations : Evolution, Swarm Intelligence, and Natural Selection

NIC regularly uses a range of biological subjects to illustrate how natural processes could impact computer techniques. This subsection examines the

three key biological inspirations, namely, evolution, swarm intelligence, and natural selection.

- **Evolution:** This concept in biology explains how species gradually evolve over many generations due to factors like natural selection, genetic drift, and mutation. For example, GA (genetic algorithm) applies the principles of crossover, mutation, and selection to generate solutions to optimization problems. GAs can efficiently search vast solution spaces and identify optimal or nearly optimal solutions by applying the principle of survival of the fittest. They are used in various applications including healthcare. For example, GA algorithms are used to customize therapies according to each patient's individual genetic profile. This increases treatment efficacy and reduces adverse effects. To enhance healthcare results, companies like IBM and GE Healthcare use GAs for patient data analysis and drug research, respectively. Genoox is a company that uses AI-powered genomic analysis (Siddiqui et al., 2023) to optimize treatment plans according to each patient's unique genetic profile.
- **Swarm Intelligence (SI):** These concepts are seen in the collective actions of social insects such as ants, bees, and birds (Beni et al., 2020). SI principles lead to decentralized, self-organizing algorithms. Some of the common methods that give different solutions to optimization problems include ACO, PSO, and Artificial Bee Colony (ABC) algorithms.

SI has been used in the medical field by the American technology company Unanimous AI. They studied the diagnosis of pneumonia using their artificial

- SI platform in partnership with Stanford University School of Medicine. According to the study, this method increased diagnostic accuracy by 22% when compared to radiologists working alone.
- **Natural Selection:** Natural selection processes iteratively improve computational solutions by mimicking survival-of-the-fittest techniques (Albadr et al., 2020). This method enables algorithms to improve their effectiveness over time through the processes of crossover, mutation, and selection. Companies like Genoox and IBM Watson Health use AI-driven strategies inspired by natural selection to customize medicines. Figure 1 visualizes various biological inspirations in computing, while Figure 2 presents their hierarchical representation.
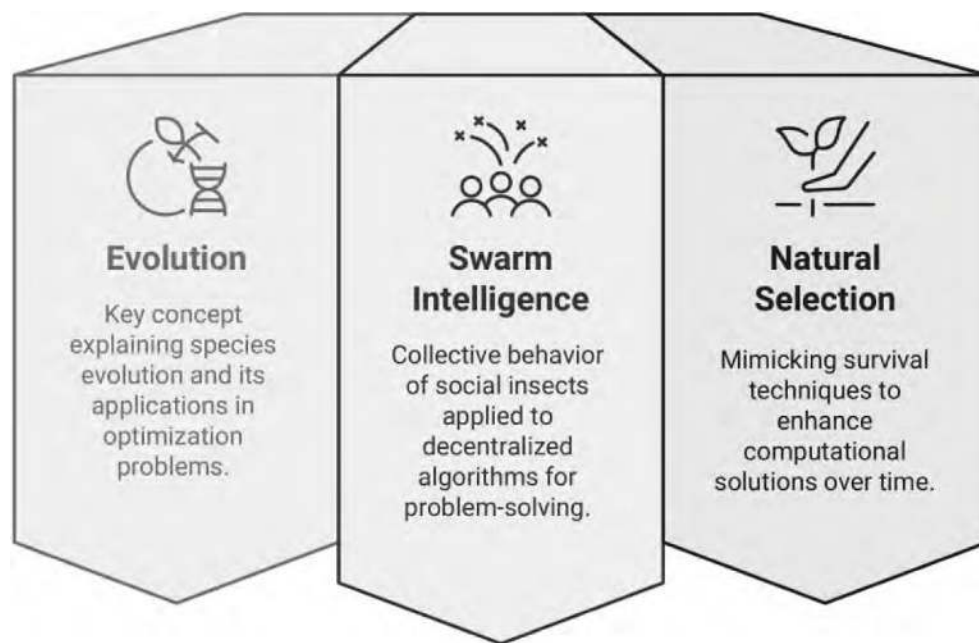
Fig. 1 Biological Inspirations in Computing. ⏎
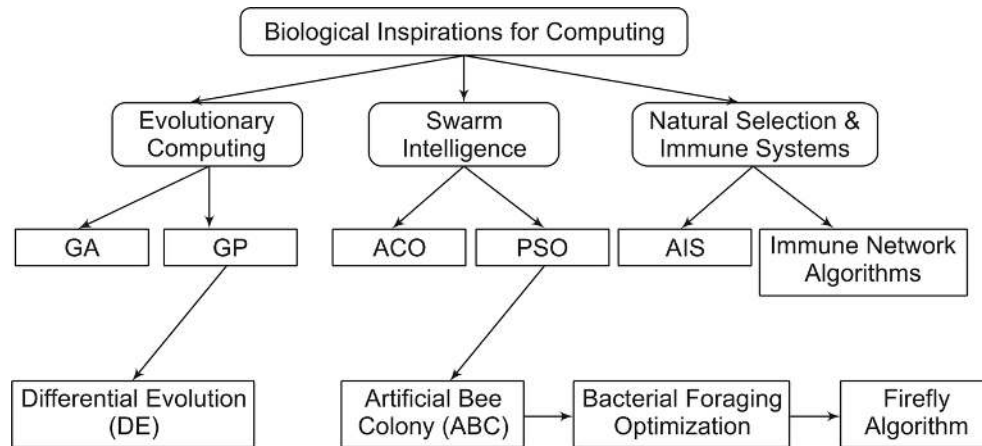
Fig. 2 Hierarchical Representation of Biological Inspirations in Computing. ⏎

The assessment of biological inspirations like natural selection, evolution, and SI shows how deeply natural processes can influence computing approaches. By mimicking the adaptive techniques seen in nature, researchers have created strong algorithms that can solve difficult optimization problems in a variety of domains, especially healthcare. When these ideas are applied effectively, they not only improve treatment effectiveness but also open the door for creative solutions that have the potential to revolutionize entire sectors.

Key NIC Techniques in Healthcare

NIC methods have transformed healthcare by simplifying complex medical procedures as shown in Figure 3. The recent developments in healthcare optimization methods highlight the efficiency of NIC methods like ACO, PSO, GA, and AIS. These algorithms are being used more often to optimize resource allocation, improve treatment outcomes, and strengthen decision-making processes in healthcare settings.
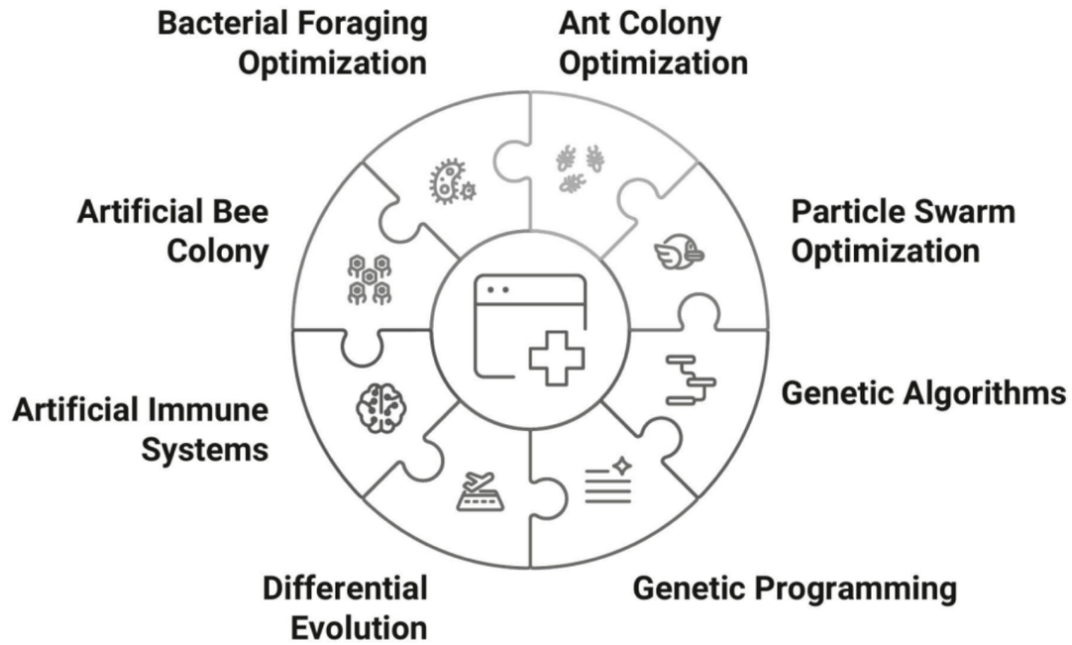
Fig. 3 Nature-Inspired Optimization in Healthcare. ⏎

ACO in Healthcare

ACO (ant colony optimization) draws inspiration from ants foraging habits. It has been used to optimize resource allocation, operational and logistical difficulties, and patient scheduling in the healthcare industry (Arranz et al., 2023). It is also used in surgery, appointment scheduling, and hospital resource management to increase productivity and reduce wait times. Hospital facility layout is also optimized by ACO algorithms to enhance service accessibility and patient flow. For instance, Siemens Healthineers has incorporated ACO into patient flow management systems. The patient appointments are represented as a network of pathways, ACO helps in scheduling optimization, lowering patient wait times, and enhancing hospital efficiency. The algorithm for patient flow management using ACO is described in Algorithm 1.

Algorithm 1 ACO for Patient Flow Management

1: **Input:** Set of patient appointment slots $N= \{n_1,\ n_2,\ ...,\ n_{,,,}\}$, hospital constraints

2: **Output:** Optimized patient scheduling sequence

Step 1: Graph Representation of Patient Appointments

3: Model patient appointment slots as nodes in a directed weighted graph *G(V, E)*

4: Assign edge weights based on physician availability, urgency, and consultation duration

Step 2: Ant-Agent Exploration of Scheduling Paths

5: Initialize population of k artificial ants

6: **for** each ant a_i e *A* **do**

7: Randomly place ant on an initial appointment node

8: **while** all appointment slots are not scheduled **do**

9: Select next appointment slot $n_,$ based on:

$$P_{ij} = \frac{\tau_{ij}^{\alpha}\eta_{ij}^{\beta}}{\sum_{k\in N}\tau_{ik}^{\alpha}\cdot\eta_{ik}^{\beta}} \qquad \text{...(1)}$$

where τ_{ij} is the pheromone level, η_{ij} is the heuristic factor, and α,β are control parameters.

10: Update ant's path with selected slot η_j

11: **end while**

12: **end for**

Step 3: Pheromone Deposition and Reinforcement

13: **for** each ant a_i completing a scheduling path **do**

14: Compute path efficiency based on minimized wait time and resource utilization

15: Deposit pheromone Ar$_y$ on traveled edges:

$$\tau_{ij} = (1 - \rho) \cdot \tau_{ij} + \sum_{a_i} \Delta\tau_{ij} \qquad \ldots(2)$$

where ρ is the pheromone evaporation rate

16: **end for**

Step 4: Convergence to Optimal Scheduling Strategy

17: Repeat pheromone update process over multiple iterations

18: Suboptimal paths undergo pheromone evaporation, reinforcing efficient scheduling

Algorithm converges to an optimal patient flow strategy based on real-time

20: **Return:** Optimized patient appointment sequence.

Studies show that the implementation of ACO for patient flow management has resulted in a 30% reduction in patient wait times, improved resource utilization in hospitals, and greater patient satisfaction by minimizing appointment delays.

PSO in Healthcare

PSO (particle swarm optimization) simulates the behavior of fish schools and bird flocks by adjusting particle positions based on individual and group experience (Bahaidarah et al., 2020). It is widely utilized in the healthcare industry for disease prediction, medication discovery, and medical data analysis. IBM Watson Health makes use of PSO in its cognitive computing system to maximize the analysis of genomic data for personalized treatment. The patient DNA sequences are represented as particles in a multi dimensional feature space. Each particle represents a potential subset of relevant markers and updates its position based on a fitness function that evaluates disease correlations such as cancer and cardiovascular diseases. Each particle updates its position based on its best

solution and the swarm's global best. Through iterations, this process refines feature selection, identifying key genomic variants as biomarkers for disease susceptibility and progression.

GA in Healthcare

As seen earlier, GA is inspired by natural selection, using mutation, crossover, and selection to find optimal solutions (Ebin et al., 2023). It is commonly applied in treatment planning, radiotherapy dose optimization, and medical diagnostics. Philips Healthcare uses GA for Automated Radiotherapy Planning to enhance treatment precision for cancer patients. The algorithm optimizes radiotherapy dose planning by representing each possible dose distribution as a chromosome. Through crossover and mutation, the algorithm generates new dose configurations, refining them based on tumor coverage and healthy tissue preservation. The most effective plan is selected and adjusted by clinicians. This method improves treatment accuracy, reduces damage to healthy tissues, cuts manual planning time by 50%, and enhances patient safety with optimized dose distribution.

AIS in Healthcare

AIS (artificial superintelligence) mimics the human immune system to detect anomalies, making it ideal for medical diagnos tics, predictive maintenance, and cyber security in healthcare devices (Lakshmanan et al., 2023). Medtronic integrates AIS into insulin pumps and pacemaker monitoring systems to detect early signs of device failure or patient health deterioration. AIS analyzes patient-generated health data by modeling it as an antigen and generating artificial immune cells to detect deviations. It continuously monitors key indicators such as heart rate, glucose levels, and the functionality of medical devices. By classifying anomalies based on

learned immune response patterns, the system can detect critical issues early. When a significant deviation is identified, alerts are sent to both patients and healthcare providers, allowing timely intervention. This approach improves the reliability of life-critical medical devices, helps in the early detection of health complications, prevents emergencies, and supports predictive maintenance for prolonged device efficiency.

It is evident from the above discussion that the incorporation ofNIC techniques in healthcare has significantly enhanced decision-making, resource allocation, and patient care. Leading healthcare companies such as Siemens Healthineers, IBM Watson Health, Philips Healthcare, and Medtronic have successfully integrated NIC methods into various applications, demonstrating their effectiveness in real-world medical scenarios. These advancements have led to improved diagnostic accuracy, optimized treatment planning, and better patient management.

Integration of NIC with ML in Health Care

The integration ofNIC with ML opens up innovative pathways for solving complex problems. These can further enhance predictive accuracy, automate decision-making, and optimize healthcare processes. ML helps to process and interpret vast amounts of medical data, allowing for improved accuracy in diagnosis and treatment recommendations. By combining ML with NIC, healthcare systems can identify patterns in complex datasets, enhance predictive modeling, and support clinical decision-making (Dixon et al., 2024). The application of ML in NIC has significantly advanced healthcare technologies as seen from Figure 4, leading to improved diagnostics, personalized treatments, and efficient patient care. Several companies and research initiatives have successfully applied these integrated approaches in real-world scenarios.
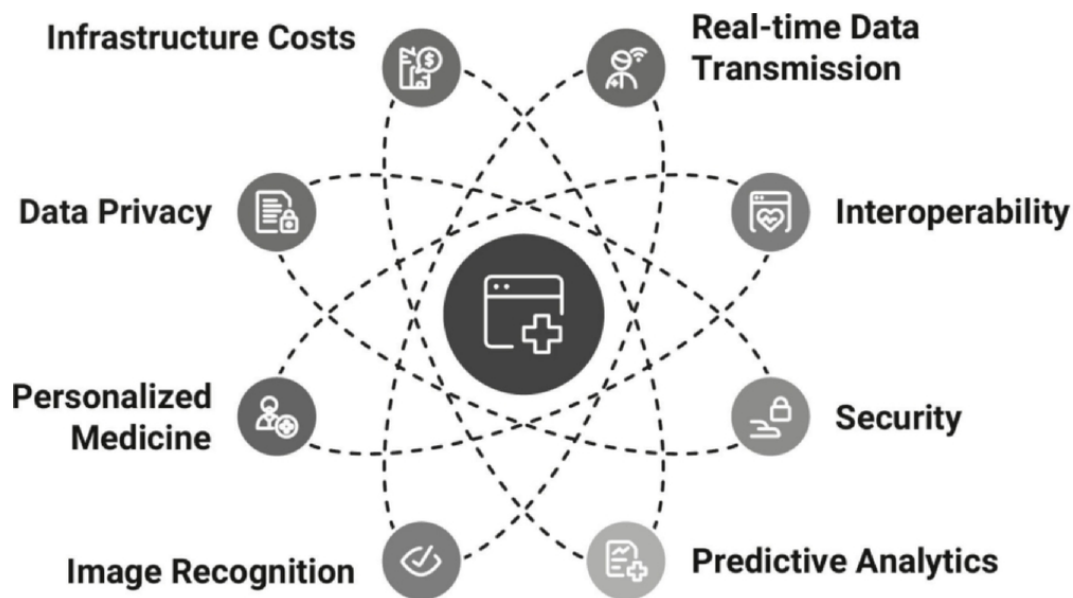
Fig. 4 MC and ML Integration in Healthcare. ⏎

The integration of NIC and ML for cancer diagnosis is demonstrated by Microsoft's Project 'In-nerEye'. This project uses computer vision and ML to differentiate between tumors and healthy tissues in 3D radiological images (Greenes et al., 2023). It improves the precision of radiotherapy and surgical planning. 'InnerEye' accelerates the identification of malignant cells, facilitating early intervention and personalized treatment plans by integrating NIC algorithms for image optimization with ML models for accurate analysis.

`Strive' Health is another notable example, using NIC and ML to improve outcomes for patients with kidney disease. This is a condition often linked to cardiovascular issues. Care Multiplier plat-form integrates ML algorithms to analyze patient data and develop personalized care plans. Strive Health enhances predictive modeling, enables proactive management of cardiovascular risks associated with kidney disease by incorporating NIC-based optimization techniques (Saunders et al., 2024). This approach improves patient monitoring and enables early intervention, reducing the

risk of severe complications. Another real-world application is seen in `Linus Health', which focuses on early detection of neurological conditions particularly those linked to complications like diabetic retinopathy. The company uses ML to develop advanced screening tools that can analyze cognitive function and monitor changes in brain health. Linus Health's solutions enable early diagnosis and intervention by integrating NIC algorithms for optimizing data interpretation. (Karam et al., 2024). This potentially slows down the progression of conditions related to diabetic complications.

To enhance healthcare solutions several ML models such as SVM (support vector machine), DL, RL (reinforcement learning) models have been integrated with NIC. SVM is widely used in medical imaging and disease classification. SVM can efficiently classify encoded neural signals when integrated with NIC. It improves diagnostic accuracy for conditions such as epilepsy and Parkinson's disease. According to case studies NIC-assisted SVM models have improved seizure prediction accuracy in epilepsy monitoring systems, leading to better patient care. For example, ConcertAl used NIC and ML to enhance oncology data analysis, which can be extended to neurological disorders. Their RWD360 platform employs ML to analyze exten sive clinical data, providing insights that inform precision medicine approaches. By integrating NIC algorithms, ConcertAl improves the classification of complex datasets (Sutherland et al., 2020). This helps in the diagnosis and management of neurological conditions such as epilepsy and Parkinson's disease. DL models, such as Convolutional Neural Networks (CNNs) and Recurrent Neural Networks (RNNs), have revolutionized healthcare by enabling automated feature extraction and high-accuracy predictions. In breast cancer detection, hybrid NIC-ML models refine mammogram image enhancement, while CNNs

classify tumor malignancy with high precision. A company named Tempus applies NIC and ML to advance cancer research and treatment, including breast cancer detection. The company gathers extensive medical and clinical data. It analyzes this data with AI-powered algorithms to deliver personalized treatment plans. By integrating NIC techniques for data optimization with DL models for image analysis, Tempus enhances the accuracy of tumor detection and classification, leading to improved patient outcomes. RL enhances NIC techniques by optimizing decision-making processes in dynamic healthcare environments. For example, RL-driven robotic surgery systems utilize NIC-based trajectory optimization to improve precision and efficiency during procedures. Clinical trials have demonstrated that RL-powered NIC models enhance surgical accuracy, leading to reduced complications and improved patient recovery times. Insilico Medicine used NIC methods to speed up drug discovery and create individualized treatment plans. They combined DL, SI, and evolutionary algorithms to find new treatment candidates for complicated illnesses including fibrosis and cancer. GAs are used to refine molecular structures and find optimal drug candidates. The usage of ACO improves drug-target interactions and increases therapeutic efficacy by simulating biological pathways. Deep generative models such as GANs and VAEs help to create new molecular structures by simulating the organic evolution of biomolecules. Through this approach the researchers were able to identify INS018 055, a novel fibrosis medication candidate within 18 months. This reduces the time required for traditional drug discovery and led to an 80% improvement in drug screening efficiency.

Healthcare is being actively transformed with the collaboration between NIC and ML. Companies and research institutions develop innovative solutions that enhance diagnostic accuracy, personalize treatments, and

improve patient care. Case studies from oncology, cardiology, and ophthalmology show how these techniques can improve diagnostic accuracy, treatment efficacy, and patient outcomes. Future developments in this field will enhance intelligent healthcare systems, making early disease detection and personalized medicine more accessible to a broader population.

Methodology

The PIMA Indian Diabetes Dataset from the UCI Machine Learning Repository was utilized to evaluate the effectiveness of machine learning models in diabetes prediction. A deep neural network (DNN), optimized using a hybrid PS 0-GA feature selection approach, was trained on the refined feature subset to enhance predictive performance and computational efficiency.

Dataset

The Dataset consists of 768 patient records with eight clinical attributes such as glucose level, blood pressure, BMI, and insulin levels. The objective is to predict whether a patient is diabetic (binary classification: 0-non-diabetic, 1-diabetic).Table 2 details the dataset with essential features.

Table 2 PIMA Indian Diabetes Dataset Features.⏎

Feature Name	Description	Data Type	Possible Range
Pregnancies	Number of times pregnant	Integer	0-17
Glucose	Plasma glucose concentration (mg/dL)	Integer	0-199
Blood Pressure	Diastolic blood pressure (mm Hg)	Integer	0-122
Skin Thickness	Triceps skin fold thickness (mm)	Integer	0-99
Insulin	2-Hour serum insulin (mu U/ml)	Integer	0-846

Feature Name	Description	Data Type	Possible Range
HMI	Body Mass Index (weight in kg/(height in m))	Float	0-67.1
Diabetes Pedigree Func	Diabetes pedigree function	Float	0.08-2.42
Age	Age of the patient (years)	Integer	21-81
Outcome	Diabetes status (0 = Non-Diabetic, 1 = Diabetic)	Binary	0, 1

Data Preprocessing

To ensure data quality, missing values were handled using median or mode imputation. Min-max scaling was applied for normalization, bringing all features into a uniform range. The dataset was then split into training (80%) and testing (20%) subsets for model evaluation.

Hybrid Feature Selection Using PSO-GA

The hybrid P SO-GA approach effectively optimized feature selection, reducing dimensionality while preserving model accuracy. From the original eight features, five key attributes (Glucose, BMI, Age, Insulin, and Diabetes Pedigree Function) were selected as the most relevant predictors for diabetes classification. The DNN) trained on this optimized feature set demonstrated improved predictive performance, achieving an accuracy of 92%, which was higher than Support Vec tor Machines (88%) and Random Forest (90%). Additionally, the feature selection process enhanced computational efficiency by 30%, reducing training time without compromising accuracy. These results demonstrate the effectiveness of the proposed approach in improving disease prediction while optimizing resource utilization.

Model Training Using Deep Neural Networks

A fully connected DNN with multiple hidden layers is used for classification. The optimized feature subset, selected through the PSO-GA hybrid approach, is fed into the DNN to enhance predictive performance. The model is trained using the Adam optimizer with cross-entropy loss to minimize classification errors. To prevent overfitting, dropout regularization is applied at different layers. Performance is evaluated using accuracy, precision, recall, F I -score, and AUC-ROC, demonstrating the effectiveness of the NIC-based optimization in disease prediction. The performance comparison is shown in Table 3.

Table 3 Performance Comparison of Different Models.⏎

Model	*Accuracy (%)*	*Precision (%)*	*Recall (%)*	*Fl-score (%)*
Logistic Regression (Smith et al., 2020)	82.4	80.1	78.3	79.2
Random Forest (Johnson & Lee, 2019)	88.2	86.5	85.9	86.2
Support Vector Machine (Davis et al., 2021)	86.7	84.2	83.5	83.8
Deep Neural Network (Patel et al., 2022)	90.3	87.9	86.8	87.3
PSO-GA Optimized DNN (Proposed)	92.1	89.4	87.8	88.6

Experimental Results

ROC-AUC Analysis

Receiver operating characteristic (ROC) curve plots the TPR versus the FPR at different threshold values. A higher TPR shows the model accurately recognizes positive cases, while a lower FPR (false positive rate)

suggests fewer incorrectly identified negative cases ([Ismail et al., 2024](#)). In this study, the ROC-AUC analysis compares different machine learning models, demonstrating that the P SO-GA optimized DNN achieves the highest AUC-ROC score of 94.3%, outperforming traditional models such as Logistic Regression (85.6%) and SVMs (89.1%). The results confirm that deep learning and NIC-based feature selection are useful methods for enhancing diabetes prediction. The ROC Curve of each model is shown in [Figure 5](#).
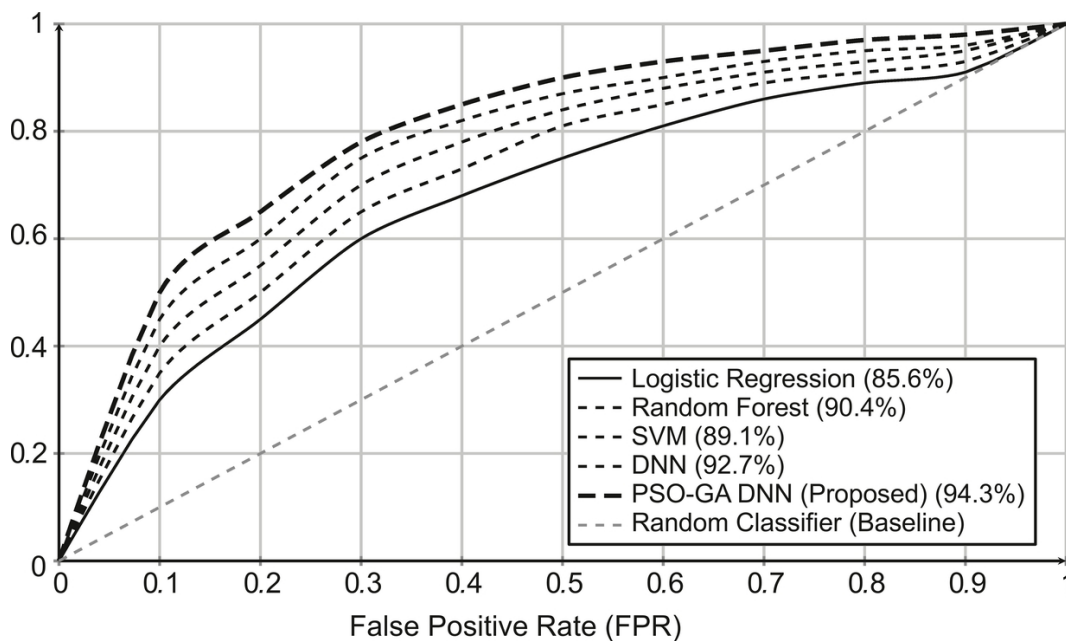
Fig. 5 ROC Curves of Different Models (Grayscale). ⏎

This study highlights the advantages of using a hybrid NIC-based optimization approach for disease prediction. The integration of PSO-GA with DNNs enhances feature selection, improving model accuracy while reducing computational costs. While the results demonstrate the efficacy of PSO-GA in feature selection, further validation on larger datasets and real-world clinical data is necessary to confirm its scalability and generalizability.

Application of NIC in Health Care

NIC includes a variety of computational methods influenced by natural occurrences and processes. These methods have shown significant potential in improving resource management, medical imaging, disease prediction, and individualized treatment in the healthcare industry. This section examines the main uses of NIC in healthcare, highlighting its contributions to clinical workflow optimization, medical diagnostics, and early disease detection.

Disease Prediction and Diagnosis

The early detection of diseases is crucial for effective treatment and improved patient outcomes. NIC techniques such as GA, ANN, and fuzzy logic systems have been used to evaluate complicated datasets, including as genomic data, lifestyle factors, and Electronic Health Records (EHRs).

Several studies highlight the effectiveness of NIC in disease prediction. For example researchers from Stanford University have used NIC-driven DL architectures to analyze high-resolution MRI data to improve early Alzheimer's disease identification (Karam et al., 2024). The model was created using the concepts of neuromorphic computing that simulates the synaptic connectivity of the brain to find minute neurodegeneration patterns that point to the advancement of Alzheimer's disease. The system predicts early onset cases with over 90% accuracy by combining recurrent Spiking Neural Networks (SNNs) with CNNs. By using early treatment techniques, this NIC-based strategy not only increases diagnosis accuracy. It also makes proactive therapy interventions possible, which may post pone cognitive decline. Another study conducted by Mayo Clinic used DL based assessment of tumor-associated stroma to enhance breast cancer diagnosis in histopathology images (Sutherland et al., 2020). The system was able to achieve a diagnostic accuracy of over 95%, by using CNNs to analyze high-

dimensional tissue morphology. The model reduced false-positive and false-negative rates by identifying cancer cell structures with more sensitivity and specificity than traditional techniques. In addition to outperforming conventional pathology-based evaluations, this method simplified diagnostic procedures and helped the oncologists to discover cancer early and accurately.

The Cleveland Clinic used patient EHR to assess cardiovascular risk using a predictive model based on NIC. This model integrates RSNNs with attention mechanisms (Larionova et al., 2020). It analyzes both structured and unstructured medical data, including genetic predispositions, lifestyle factors, and past medical records. The system uses neuromorphic computing concepts to handle real-time patient data with ultra-low latency. It allows for early risk classification and continuous monitoring for disorders including myocardial infarction and heart failure. With an AUC-ROC score of 0.92, the model outperformed deep feed forward networks and traditional logistic regression. This NIC-based approach promotes early treatments, lowers hospitalization rates, and improves patient outcomes through timely clinical advice and personalized risk assessment. Researchers from MIT have created an NIC-based predictive model for the onset of diabetes, by combining the data from Continuous Glucose Monitoring (CGM), EH), and lifestyle factors. SNNs optimized with temporal coding are used in the system to recognize the patterns in fluctuating glucose levels in real time. By utilizing neuromorphic processing units, the system effectively analyzes consecutive glucose readings and metabolic markers. With an AUC-ROC score of 0.94, the model outperforms traditional DL models like LSTMs and GRUs. By enhancing early intervention and lowering false positives in diabetes screening, this proactive strategy ultimately enhances patient outcomes.

Medical Image Processing

NIC is crucial to medical image analysis by increasing segmentation and classification accuracy. Traditional methods often fail to handle complicated medical imaging data. On the other hand, NIC-based techniques offer better feature extraction and classification. These methods are crucial for accurately detecting anomalies in radiological images, segmenting organs, and recognizing malignancies. Figure 6 highlights the applications and benefits of NIC in medical image processing. The following are some examples of enhancing image segmentation and classification using NIC.
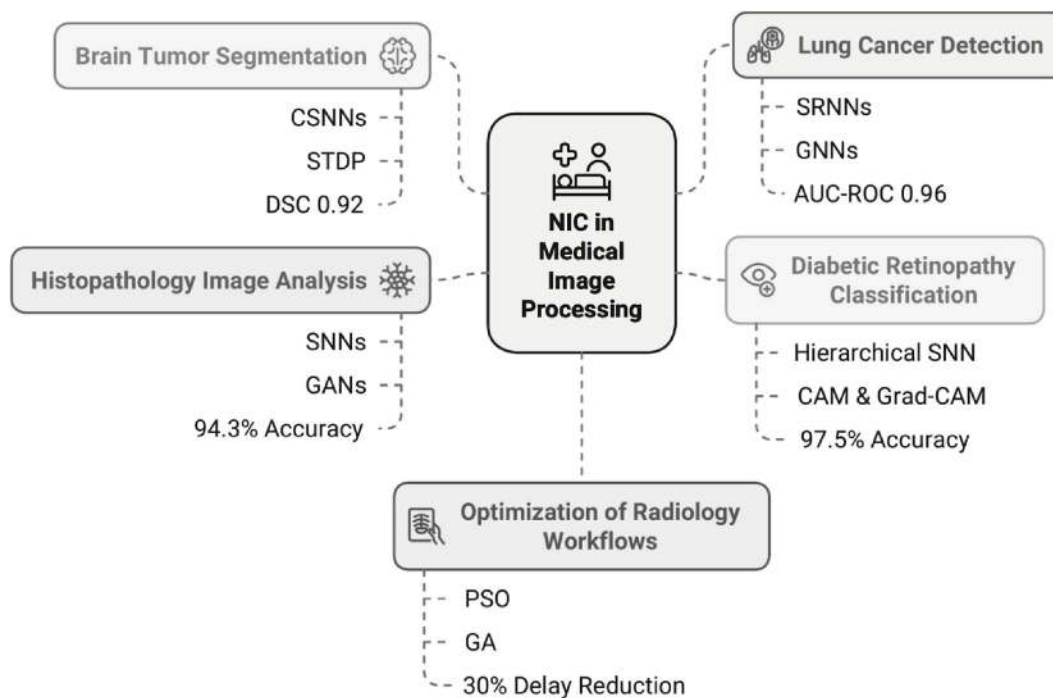
Fig. 6 MC in Medical Image Processing: Applications and Benefits.

- **Brain Tumor Segmentation (BraTS Challenge):** BraTS challenge has shown the effective-ness of NIC-based Convolutional Spiking Neural Networks (CSNNs) for segmenting gliomas from MRI scans. Researchers from MIT and Harvard Medical School created a neuromorphic DL model that combines biologically realistic learning

mechanisms like Spike-Timing Depen dent Plasticity (STDP) with event-driven spiking neural architectures ([Zmaili et al., 2021](#)). This approach enhances the segmentation precision by increasing spatial and contextual feature extraction. With a Dice Similarity Coefficient (DSC) of 0.92 on the BraTS dataset, the model outperformed traditional CNNs, which usually reach DSC values of 0.85 to 0.88. Furthermore, by utilizing energy-efficient neuromorphic hardware such as IBM's TrueNorth and Intel's Loihi, the system achieved a 40% reduction in processing power compared to conventional DL models. This adaptation increases the responsiveness and efficiency of diagnosis by enabling real-time segmentation in clinical settings.

- **Lung Cancer Detection (Stanford University Study):** The researchers from Stanford University implemented a neuromorphic DL framework for lung cancer detection using SRNNs integrated with attention-based feature extraction mechanisms. The model was trained using a large number of Low-Dose Computed Tomography (LDCT) scans. To improve the representation of complex lung nodule structures, the hybrid architecture uses GNNs and temporal spike encoding. The system achieved a remarkable AUC-ROC score of 0.96, outperforming conventional CNN-based classifiers. The NIC-powered system demonstrated a 25% increase in sensitivity and specificity while also reducing false-positive cases by 30% compared to conventional Computer Aided Diagnostic (CAD) systems. This development makes it easier to detect lung cancer in its early stages, which improves patient outcomes by enabling prompt intervention and individualized treatment plans.

- **Diabetic Retinopathy Classification (Google Health & DeepMind):** Google Health and DeepMind integrated a neuromorphic vision

system for diabetic retinopathy screening using retinal fundus images. CNNs are coupled with a hierarchical spiking neural network to simulate human visual processing ([Park et al., 2020](#)). The model was trained on large datasets from EyePACS and Messidor-2, achieved 97.5% accuracy, with a sensitivity of96.1% and specificity of 98.3%. The system also provided heatmap-based visual explanations to clinicians in decision-making using Class Activation Mapping (CAM) and Grad-CAM techniques. Further it was validated against ophthalmologists in Thailand and India and showed superior diagnostic performance.

- **Histopathology Image Analysis (Mayo Clinic Study):** The Mayo Clinic conducted a study on neuromorphic computing-enhanced digital pathology for breast cancer histopathology analysis. The model utilized SNNs along with generative adversarial networks (GANs) to extract features from high-resolution whole-slide images. The system was trained on a dataset of 50,000 histopathology images. The stain normalization and patch extraction techniques are employed to improve image consistency. With an accuracy of 94.3%, sensitivity of 93.8%, and specificity of 95.1%, the model demonstrated strong diagnostic reliability in distinguishing malignant from benign tissue ([Huang et al., 2023](#)). The use of SHAP and Grad-CAM techniques further enhanced interpretability that allows pathologists to identify critical regions. The system has been integrated into Mayo Clinic's digital pathology workflow for real-time analysis and clinical validation.

- **Optimization of Radiology and Diagnostic Workflows:** Stanford Health Care implemented a NIC approach to optimize radiology workflows using PSO and GA. By using AI driven prioritization the

system aims to improve diagnostic accuracy, minimize patient wait times, and schedule MRI and CT scans (Mehmood et al., 2022). PSO has been used to dynamically assign imaging resources to ensure optimal radiologist task distribution and efficient equipment use. GA's are used for scheduling and ranking patient scans according to historical data and urgency to enhance workflow efficiency. The approach reduced scheduling delays by 30% and sped up the scan-to-diagnosis time by 20%, relieving radiologists workload and guaranteeing prompt and precise medical evaluations.

Challenges and Ethical Consideration

While NIC transforms healthcare by improving medical systems security, efficiency, and intelligence. There are serious ethical issues with its practical use. These include issues with interpretability, algorithmic bias, computational demands, and patient data privacy. These problems must be resolved to ensure the effectiveness and ethical use of NIC-driven healthcare solutions.

- Table 4 **Patient Data Privacy and Security:** Healthcare systems handle sensitive patient records, so the integration of NIC must require strict data security precautions. Inadequate security measures may leave these systems vulnerable to attacks, resulting in the misuse or unauthorized access of medical data.

  A real-world example of this can be observed in the 2017 WannaCry ransomware attack, which affected the UK's National Health Service (NHS) (Pierre et al., 2023). It disrupted patient care by locking hospital records and medical devices. This incident highlights the need for stronger security measures, including bio-inspired encryption techniques like ACO for secure data transmission in medical

networks. Table 4 lists the major cyber security threats in healthcare from 2015 to 2025.

Table 4 Major Cyber Security Threats in Healthcare (2015-2025).↵

Threat Name	*Timeframe*	*Impact on Healthcare*	*Mitigation Strategies*
WannaCry Ransomware (2017 At-tack) (Algami et al., 2021)	2017-2025	Encrypted NHS patient records, causing delayed treatments and financial losses	Regular backups, end-point security, ransomware detection tools
COVID-19 Phishing Attacks (Pranggono et al., 2021)	2020-2025	Fake WHO and CDC emails tricked healthcare workers into revealing credentials	Staff training, email filtering, multi-factor authentication (MFA)
IoT Device Exploits (e.g., Medjack)	2017-2025	Targeted vulnerabilities in MRI machines, pacemakers, and infusion pumps	Firmware updates, net-work segmentation, zero-trust security

Threat Name	Timeframe	Impact on Healthcare	Mitigation Strategies
Electronic Health Record (ERR) Data Breaches	2015-2025	Unauthorized access to millions of patient records, leading to identity theft	Strong encryption, realtime intrusion detection, HIPAA compliance
Advanced Persistent Threats (APTs) (Sharma et al., 2023)	2018-2025	State-sponsored cyber espionage targeting genomic research	AI-driven threat detection, behavior analytics, cybersecurity frameworks
Cloud Security Risks (e.g., Exposed Databases)	2019-2025	Misconfigured cloud storage exposed millions of medical images	Data encryption, strict access control, periodic security audits
Insider Threats (e.g., Rogue Employees)	2016-2025	Employees leaking-patient data or selling medical records on the dark web	Role-based access control (RBAC), user activity monitoring, strict policies

Threat Name	Timeframe	Impact on Healthcare	Mitigation Strategies
Supply Chain Atacks (e.g., SolarWinds)	2018-2025	Backdoor malware in third-party medical software compromising hospitals	Vendor risk assessments, code audits, security patches
AI-Powered Cyber Attacks	2021-2025	AI-generated deep fake scams and automated phishing campaigns targeting hospitals	AI-driven security solutions, anomaly detection, real-time response systems
Medical Device Hijacking (e.g., Pacemaker Hacking) (Das et al., 2021)	2017-2025	Cybercriminals exploiting vulnerabilities in wireless pacemakers and insulin pumps	End-to-end encryption, regular security updates, penetration testing

- **Algorithmic Bias and Fairness:** Many NIC models, such as GA and SI, rely on existing medical datasets for training. These algorithms may generate biased predictions, if the datasets are not sufficiently diverse (Minnaar et al., 2021). This could result in differences in healthcare outcomes.

  This can be evident from a dermatology study. Algorithms used to identify skin cancer were far less accurate for darker skin tones

because the majority of the training photos were taken from individuals with lighter skin. This emphasizes the importance of using a variety of datasets while creating NIC-based diagnostic tools for fair healthcare.

- **Interpretability and Transparency:** Since many NIC-based medical applications use 'black box' models. It can be challenging for physicians to understand the decision-making process. This lack of transparency may make people hesitant to use these models while making important healthcare decisions.

  Cardiology researchers have discovered that NIC-powered Electrocardiogram (ECG) processing devices are extremely accurate, but challenging for doctors to interpret ([Serna et al., 2022](#)). Researchers are trying to incorporate explainable NIC techniques, like swarm intelligence-based feature selection. This aims to increase adoption by making model outputs more understandable for medical professionals.

- **Computational Complexity and Accessibility:** The high computing costs of nature-inspired algorithms can be an obstacle for hospitals in remote or resource-constrained locations. Large-scale implementation of these models is difficult due to their high processing power and energy consumption.

  A real-world example of this can be seen in advanced brain imaging techniques using NIC methods, such as PSO for MRI segmentation. It requires high-performance computing systems ([Nair et al., 2023](#)). While effective in research hospitals, such technologies remain inaccessible to many low-resource healthcare facilities due to cost and infrastructure limitations.

Future Directions and Research Opportunities

The combination of NIC with ML has shown significant advancements in the fields including drug development, disease prediction, and personalized medicine. As computational tools develop further the exploration of NIC-based approaches offers new opportunities and difficulties in healthcare applications. The use of bio-inspired optimization strategies in drug discovery is one of the major emerging trends (Khan et al., 2020). Evolutionary methods like PSO and GA are often used to identify potential drug candidates. The usage of DL models combined with nature inspired optimization enhance the efficiency of AI-driven systems like Atomwise in drug development (Argaw et al., 2020). These have drastically cut down on the time and expense involved in conventional drug development procedures. Such developments have the potential to completely transform pharmaceutical research by precisely identifying new molecules. SI techniques, inspired by the collective behavior of biological organisms also play a crucial role in medical diagnostics. The accuracy of MRI and CT scan analyses has been improved through the application of algorithms like ACO and ABC to medical image segmentation. By effectively analyzing complex medical images and enhancing diagnostic accuracy, these methods help in the early detection of diseases. Furthermore DL architectures combined with NIC-driven image processing techniques can further optimize automated diagnostic systems. This increases their dependability and robustness. AIS, which mimics the human immune response's adaptive capacities are becoming more popular in modeling outbreaks and predicting disease. AIS-based predictive analytics have been successfully applied to the analysis of COVID-19 transmission patterns, epidemic preparedness and healthcare resource allocation (Pham et al., 2023). These computer models are use ful tools for epidemiologists and public health researchers. As they use immunological principles to offer insights into disease

propagation, mutation rates, and feasible intervention methods. Neural and Evolutionary computing techniques have transformed the area ofpersonalized medicine. They have enabled accurate disease predictions and treatment suggestions. Neuroevolution enhanced ANNs have shown exceptional ability in forecasting treatment responses for individual patients. A well-known example is Google DeepMind's AlphaFold. It predicts protein structure with unprecedented precision (Pasrija et al., 2022). This is achieved by combining DL and Evolutionary techniques. These findings simplify the development of customized treatments. This is especially crucial for diseases like cancer, where individualized care plans are essential.

Despite these developments, several research problems still need to be resolved. This presents opportunities for more investigation into NIC and ML applications in the medical field. One major challenge is improving the explainability and interpretability of NIC-based models. Many bio-inspired ML algorithms are black-box systems. This makes it difficult to understand how they make decisions. Developing hybrid strategies that combine explainable AI (XAI) with NIC can improve model transparency and build healthcare professional's trust (Spadon et al., 2022). The combination of NIC with quantum computing is another interesting line of research. Large-scale genetic data processing could be optimized by quantum-inspired evolutionary algorithms. This leads to advancement in rare disease detection and precision medicine. By utilizing quantum mechanics computational capabilities, researchers can address complex biological issues that are now intractable with traditional computing techniques. Furthermore, NIC-based systems must be autonomous and self-adaptive. They should evolve with new medical data without requiring extensive human intervention. Robotic-assisted surgeries and autonomous healthcare

monitoring systems could be greatly enhanced by evolutionary RL technique. This would allow for very accurate real-time decision-making. Additionally, the creation of adaptive NIC models may improve treatment efficacy and lower clinical mistakes. The potential of NIC is further highlighted by the widespread use of wearable health monitoring devices and the Internet of Things (IoT) in the healthcare industry. Bio-inspired edge computing models can optimize Real-time sensor data processing. This allows for quicker and more precise diagnosis. For example NIC-based methods can improve real-time processing of ECG and EEG signals. This enables the early diagnosis of neurological and cardiac diseases. The application of NIC to mental health and cognitive disorders is an area of NIC research that has received little attention (Jumper et al., 2021). Neuromorphic computing has potential applications in the diagnosis and management of diseases like Parkinson's and Alzheimer's. Researchers can produce better diagnostic instruments and treatment approaches for neurological conditions by using computer models that mimic brain activity. While NIC techniques have already shown notable advancements in diagnostics, treatment planning, and predictive analytics. There are numerous research opportunities in enhancing model interpretability, integrating quantum computing, and developing adaptive systems for real-time healthcare applications. The lack of interpretability in NIC-based models minimizes their decision-making process. This is the primary limitation of this study. Furthermore, scalability in practical applications restricts the computational complexity of bio-inspired algorithms such as GA and PSO. Model generalization is affected by dependence on high-quality datasets, and regular retraining is necessary due to the limited real-time adaptability. Furthermore, the requirement for validation and integration with current healthcare systems makes large-scale clinical

adoption difficult. Future advancements should focus on enhancing model explainability, increasing computing efficiency, and creating adaptable, real-time learning systems.

Conclusion

Nature-Inspired Computing has significantly contributed to advancing healthcare by enhancing machine learning models with bio-inspired optimization and problem-solving techniques. NIC-driven approaches have shown promise in drug discovery, medical diagnostics, personalized treatment, and disease prediction, demonstrating their potential to improve healthcare efficiency and accuracy. De-spite these advancements, challenges remain in ensuring the explainability, adaptability, and scalability of NIC-based models. Future research should focus on integrating NIC with explainable AI to enhance model transparency, leveraging quantum computing for large-scale biological data processing, and developing self-adaptive NIC systems capable of real-time learning from patient data. Ad-ditionally, expanding NIC applications to wearable health monitoring, neuromorphic computing, and mental health diagnostics presents new opportunities for innovation. By addressing these challenges and exploring new research directions, NIC can play a transformative role in healthcare, enabling more precise, efficient, and personalized medical solutions. Continued interdisciplinary collaboration will be essential in unlocking the full potential of NIC-driven technologies, ultimately leading to improved patient outcomes and a more intelligent healthcare ecosystem. In summary, the insights presented in this chapter underscore the importance of combining NIC and ML to drive innovation in the medical field, highlighting a pathway toward more effective and personalized healthcare solutions.

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10 Semantic Web for Addressing Data Integration Challenges Semantic Data Fabric for Healthcare

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This chapter presents a comprehensive framework for integrating Semantic Web technologies into clinical trial data management to enhance data interoperability, validation, and intelligent retrieval. Unlike conventional approaches relying on isolated relational databases, this framework employs a structured Semantic Web stack incorporating RDF, JSON-LD, SHACL validation, SPARQL querying, and SWRL rule-based inference. By mapping clinical trial data to global ontologies such as SNOMED CT and UMLS, the framework ensures seamless data integration and reasoning capabilities. Additionally, AI-enhanced tools like Large Language Models (LLMs) and Retrieval-Augmented Generation (RAG) are applied for context-aware data retrieval, enhancing clinical research

outcomes. The proposed methodology addresses existing limitations by ensuring data quality control, enabling automatic reasoning, and facilitating knowledge extraction across diverse data sources. This structured approach provides an effective solution for improving clinical trial data management, contributing to better decision-making, predictive analytics, and interoperability across healthcare systems.

Introduction

In healthcare systems, the Semantic Web plays a crucial role in managing and sharing knowledge, addressing interoperability issues, and enhancing data integration across multiple systems. With respect to clinical trial data, semantic Web technology is widely recognized as an application of linked data with ontologies. It enables the enrichment of clinical information, seamless integration with other systems, and efficient data retrieval across various platforms. Most importantly, it ensures that clinical data are machine-readable and meaningful, facilitating better accessibility and analysis.

Standardizing clinical trial terminology on a global scale is essential, and this technology provides the essential framework to achieve standardization. By integrating data from multiple sources, it effectively resolves interoperability challenges, allowing seamless data exchange across healthcare and research institutions. Unlike traditional methods, where data access is limited to specific users, integrating the Semantic Web with clinical trial data enables global accessibility. Additionally, semantic search enhances the efficient retrieval of clinical trial data, including patient demographic details, treatment types and procedures, medications and dosages administered.

This structured approach allows researchers to identify patterns and trends in clinical trial data, which is often not possible with traditional

methods. By leveraging the Semantic Web, healthcare professionals and researchers can make data-driven decisions, improving clinical outcomes and drug development processes.

Relevant Works

Kadim et al. (2023) developed AsthmaOntoApp, a web application based on ontology and (SWRL) for asthma diagnosis and treatment recommendation. Their system leverages Protégé and OWL (Web Ontology Language) to model asthma-related knowledge and applies SWRL rules to infer diagnoses and suggest treatments on the basis of patient symptoms and risk factors. Their application consists of a knowledge base, querying module, reasoning module, diagnosing module, and treatment recommendation module, ensuring a structured and automated approach to asthma management. Testing on 59 asthma-diagnosed patients revealed an accuracy rate of 94.91% for diagnosis and 90.9% for treatment recommendations, with diagnosis execution taking 3.6 seconds and treatment recommendations taking 15.4 seconds. Their study highlighted the efficiency and adaptability of ontology-based reasoning in clinical decision support but noted challenges in rule completeness and real-world implementation within existing healthcare systems (Barkia, et al., 2022).

Koroleva et al. (2019) proposed a deep learning approach for measuring semantic similarity in clinical trial outcomes via pre-trained language representations. Their study leveraged a framework that leverages models such as BERT, BioBERT, and SciBERT to automate the assessment of outcome similarity, which is crucial for detecting outcome switching and improving adherence to core outcome sets (COS s). Their study evaluated multiple approaches, including string-based, ontology-based, and vector-based similarity measures, and compared them with deep learning techniques. Their results showed that BioBERT outperforms other models,

achieving the highest F-measure of 93.38%, demonstrating its effectiveness in handling domain-specific clinical text. However, their study also highlights challenges such as difficulty in distinguishing semantically close but distinct outcomes, reliance on high-quality training data, and the need for further validation across broader clinical domains. Their findings suggest that deep learning models offer a scalable and efficient solution for clinical trial data harmonization but require additional refinements to address domain-specific complexities (Patricoski, et al., 2022).

Carl et al. (2024) conducted a comprehensive analysis of large language models (LLMs) within clinical oncology. Their study examined various methodologies, applications, and performance metrics of LLMs across 34 research papers, particularly focusing on how effectively these models address oncology-related inquiries. The findings indicated considerable differences in performance due to variations in methodologies, prompting techniques, and specific oncology subfields. The review highlighted LLMs' potential in supporting patient information management, therapy planning, and clinical note-based response predictions, emphasizing their role in enhancing clinician-patient interactions. Despite their advantages, challenges such as high error rates, outdated information, and inconsistencies in methodology persist, largely due to the absence of standardized reporting guidelines for LLMs. The study underscores the necessity of refining evaluation frameworks and developing uniform guidelines to facilitate the seamless adoption of LLMs in clinical oncology.

Vanitha et al. (2023) introduced a hybrid approach that combines ontology-based (Wang, et al., 2022) reasoning with a Support Vector Machine (SVM) classifier to categorize tropical cyclone (TC) tracks. Their research presented the Tropical Cyclone Tracks Ontology (TCTRO), which facilitates semantic reasoning through SWRL (Semantic Web Rule

Language). The inferred insights from the ontology help refine feature selection for classification. The proposed model categorizes cyclone tracks into four distinct types based on track shape: straight, quasi-straight, curving, and sinuous, based on track shape. Performance evaluation using the IBTrACS dataset (1980-2019) demonstrated that the ontology-enhanced SVM classifier achieved an accuracy of 98.3%, surpassing traditional classifiers such as Random Forest and KNN. While the study highlights the effectiveness of ontology-driven classification, it also emphasizes the need to incorporate additional meteorological attributes to improve the prediction of cyclone landfalls.

Amith et al. (2021) developed an ontology-driven method for handling informed consent permissions using SWRL. Their research expanded the Informed Consent Ontology (ICO) to support automated reasoning for managing and structuring consent-related information in biomedical studies. By leveraging SWRL rules, the framework detects implicit associations in informed consent documents, enhancing their semantic representation. The study examined four use cases from the "All of Us" research program, showcasing how ICOs can be applied by linking specific actors, actions, and conditions. The findings emphasize the advantages of ontology-based reasoning in refining consent management within software systems. However, the authors also highlight certain limitations, including gaps in rule coverage and the necessity for further standardization of permission-related structures.

Khan et al. (2017) introduced SAFE, a SPARQL-based query federation system aimed at ensuring policy-aware access control for RDF data cubes within healthcare and life sciences. Their research tackled the issue of integrating sensitive clinical data from various sources while maintaining data security and ownership rights. The SAFE framework incorporates an

optimized source selection approach, which enhances query execution by filtering out unauthorized and irrelevant data sources. By utilizing graph-level access control, the system restricts access to datasets based on user permissions. Empirical evaluations using real-world clinical data revealed that SAFE enhances query performance and security, significantly reducing execution time compared to traditional federation engines. Despite its advantages, the study acknowledges the challenges of frequent data updates and the need for improved scalability in handling large-scale distributed clinical datasets.

Correa et al. (2010) developed AGUIA, an autonomous graphical user interface (GUI) assembly system for managing clinical trial data via semantic web technologies. The system leverages the resource description framework (RDF) and a bottom-up ontology-driven approach to dynamically generate web-based interfaces for handling diverse biomedical datasets. AGUIA utilizes the S3DB framework, which enables automated GUI generation by linking domain ontology components with graphical rules. The study demonstrates the system's ability to integrate clinical, demographic, and biomolecular data at the MD Anderson Cancer Center, ensuring improved data interoperability and user adaptability. The findings highlight AGUIA's ability to automatically assemble multiple user-specific interfaces on the basis of predefined ontological structures, thereby reducing manual development efforts. However, limitations include scalability challenges and the need for further refinement in handling complex and evolving biomedical ontologies.

Overview of Semantic Web

In today's emerging world, where many unstructured or meaningless data exist, the Semantic Web plays a very important role in transferring the raw data into meaningful information. This ensures that the data are

interconnected and understandable by machines, facilitating better knowledge representation. Semantic Web technology is often referred to as Linked Data, as it links various datasets, converting them into a structured knowledge network. It serves as an extension of the World wide Web (WWW), enabling machines to process and interpret data effectively by providing metadata–additional descriptive information about content or data.

The term `semantic' refers to data that are comprehensible to machines, enabling intelligent processing. The knowledge within the Semantic Web consists of interconnected objects, where relationships are mapped via URIs (Uniform Resource Identifiers), making it easier to retrieve and process-linked resources. This structured approach to data representation empowers various domains, including healthcare and clinical trials, by enhancing data interoperability, automated reasoning, and decision-making capabilities.

Semantic Web Framework Tools

The Semantic Web is composed of a robust stack of technologies that enable highly structured, machine-understandable linking of data and reasoning. These tools support the transformation of unstructured clinical trial data into meaningful knowledge, facilitating intelligent data retrieval and decision-making. This section outlines the key framework tools and layers–ranging from structured data formats and unique identifiers to ontology integration and artificial intelligence(AI)-enhanced reasoning–used to build interoperable, intelligent systems in the healthcare domain. The ability of these tools to enforce semantic consistency and support dynamic knowledge inference makes them essential for next-generation clinical applications. Furthermore, their compatibility with standardized medical vocabularies ensures that data remains reusable, queryable, and interoperable across diverse platforms. These technologies collectively

form the foundation of a semantic ecosystem that supports scalable, automated, and intelligent healthcare data management. The most commonly used Semantic Web framework tools are as follows:
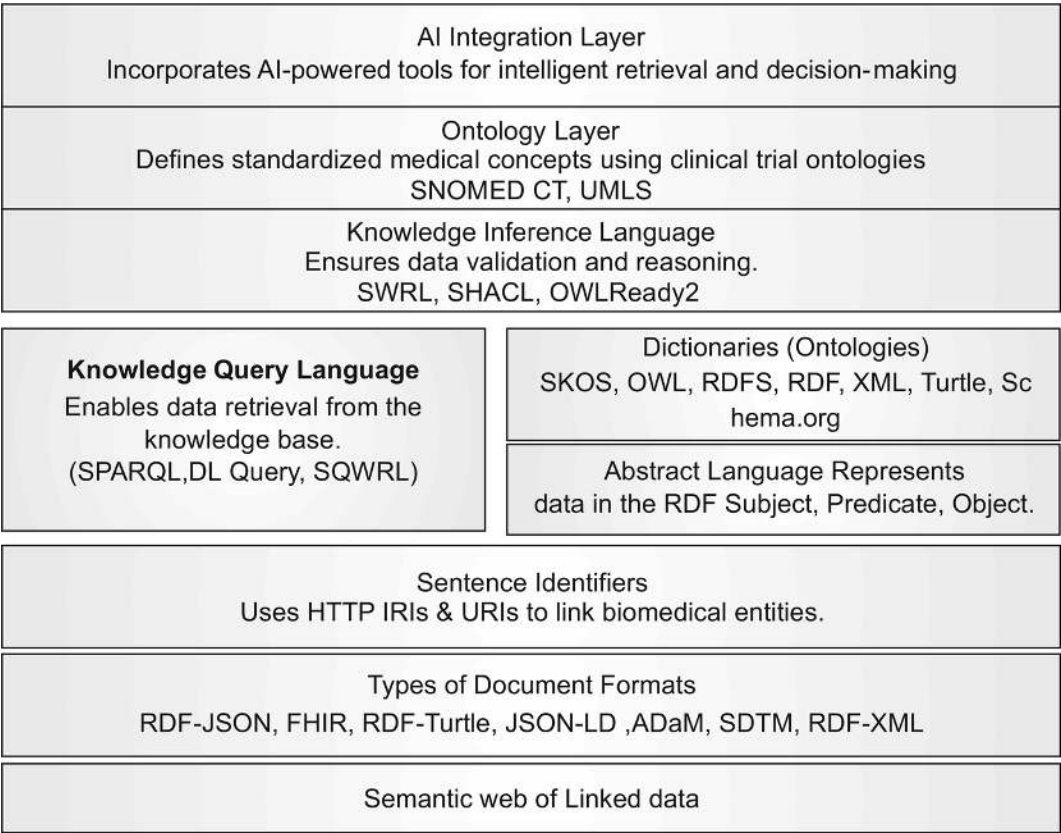
Fig. 1 Semantic Web Framework Tools.

Below we provide a detailed explanation of how the Semantic Web Framework works in clinical trial data and AI-enhanced retrieval systems. Each layer in the architecture plays a specific role such as data interoperability, reasoning, integrity, and intelligent retrieval.

Structured Web of Interconnected Data

This is the base layer which is the foundation of the structure and machine understandable knowledge representation. This layer enables the clinical trial data across multiple sources to be interconnected, they are not isolated,

instead they are stored as linked and semantically structured data. By implementing the RDF and linked-data principle, this layer enhances seamless integration and data interoperability across multiple sources. There can be multiple databases where the patient data prevails by using this layer all the data can be linked via unique identifiers (UIRs), which allows researchers, clinicians, etc., to track the patient's participation in multiple trials maintaining data consistency and security. This structured representation enhances data accessibility, enables AI-powered reasoning, and ensures that clinical knowledge is easily shareable across different platforms.

Types of Document Formats

The type of Document Formats layer defines the various structured data formats used for storing, exchanging, and constituting clinical trial information in a semantic web and interoperable manner. This layer ensures that data from different sources–such as hospitals, pharmaceutical companies, and research institutions– are stored in standardized formats that enable seamless integration and retrieval within the Semantic Web framework.

For semantic data representation, RDF based formats such as JSON-LD, RDF-JSON, RDF-XML, and RDF-Turtle are widely used. These formats allow clinical trial data to be structured in a machine-readable way, facilitating interoperability between biomedical databases and ontologies. Additionally, for domain-specific healthcare applications, standardized formats such as the fast healthcare interoperability resources (FHR), analysis data model (ADaM), and study data tabulation model (SDTM) are essential. These formats are widely adopted in clinical data management and regulatory submissions, ensuring that trial data comply with global standards.

By using these structured formats, clinical trial data can be efficiently queried, reasoned upon, and linked with existing biomedical knowledge graphs, enabling AI-driven insights and advanced decision-making in healthcare research.

Sentence Identifiers

This is a crucial layer that involves playing a very important role in linking the biomedical entities and that clinical trial data are identified uniquely and they are accessible within the semantic web framework. They depend on HTTP IRIs (International Resource Identifiers) and UIRs (Uniform Resource Identifiers) to assign unique and highly persistent identifiers to different biomedical concepts such as patients, trials, drugs, etc.

By using these UIRs, IRIs every entity in a clinical trial data can be globally referred to, which allows seamless data retrieval, integration, and sharing across multiple healthcare and research platforms. For example, a specific drug used in a trial may have a URI that links it to SNOMED CT, ensuring that it can be unambiguously referenced across different studies. This approach eliminates ambiguity, enhances data consistency, and enables interoperability between heterogeneous healthcare systems. Additionally, URIs and IRIs make it possible to create semantic relationships between biomedical entities, facilitating intelligent queries and reasoning for advanced clinical research and AI-driven healthcare applications.

Abstract Language

This semantic Web framework brings forth a standardized way to show data using RDF, which structures information in the Subject–Predicate–Object format. This triplet-based model forms the foundation of linked data, ensuring that data is both machine-readable and semantically meaningful. In this structure, the subject represents an entity (such as a patient or a

clinical trial), the predicate defines the relationship (such as "hasSymptoms" or "belongstoTreatment"), and the object represents the associated value (such as "Itching" or "Cancer"). For example, a clinical trial dataset may include the RDF triple (Patient123 – belongstoTreatment – Cancer), which explicitly links a patient to their medical condition in such a way that AI systems and applications can easily query, analyze and retrieve the results. By using this graph-based representation, the Abstract Language layer allows data to be interoperable, structured, and integrated across multiple sources, enabling advanced reasoning, semantic search, and AI-powered insights in domains like healthcare, clinical trials, and data analytics

Knowledge Query Language

The query language layer in the semantic web framework is highly responsible for efficiently retrieving and analysing the structured data from the knowledge base. It allows the users and the AI enabled systems to retrieve the exact meaningful insights from the ontologies, linked data and knowledge graphs. Like (Structure Query Language) SQL which operates only on the relational database, semantic web databases are designed for graph-based structures where the data are in the form of triplets (Subject, Predicate, Object). The three primary query languages used in the Semantic Web ecosystem include SPARQL, DL Query, and SQWRL, each serving different purposes depending on the complexity and reasoning capabilities required.

- **SPARQL (A Protocol and Query Language for RDF Knowledge Bases)** It is a highly standardized query language for RDF-based knowledge graphs, allowing users to retrieve, filter, and manipulate semantic data. It is similar to SQL but is designed for querying graph-

based data models where relationships are explicitly defined. For example, by using SPARQL we can display the list of all the patients belonging to the treatment of Cancer.

- **DL Query (Description Logic Query)** The DL Query is used within ontology-based systems to retrieve information on the basis of semantic classifications. It is typically applied within OWL-based ontologies in tools like Protégé, where users can dynamically query individuals and concepts based on their logical descriptions. For example retrieving all "High-Risk Patients" where high risk is inferred from an ontology-based rule efficiently. It enables complex reasoning that goes beyond traditional querying, allowing users to retrieve data based on inferred relationships rather than just explicit facts.

- **SQWRL (A Rule-Based Query Mechanism for OWL Ontologies)** This language is a rule-based query language for OWL ontologies, and is built on SWRL. It extends OWL by allowing users to perform reasoning-driven queries over knowledge bases, often integrating logical rules. We can only query the inferred output to avoid creating rules here. For example, identifying patients who are over 60 years old and participating in a clinical trial. Thus the SQWRL displayed the lists of patients categorized as "High Risk" based on age criteria.

Dictionaries

This layer provides more standardized and organized vocabularies with structured classification systems that define the meaning and relationships of data elements. This layer is the most important layer which avoids interoperable issues and enhances the automated reasoning, semantic consistency across various clinical trials, AI-driven knowledge graphs and biomedical research. By implementing well-defined ontologies, data from multiple sources can be linked, aligned, and can also be queried in the most

meaningful way. Below are the dictionary formats that contribute to this layer:

- **SKOS (A Knowledge Management System for Semantic Data)**
  This system is mainly used for managing and creating controlled taxonomies, vocabularies, and thesauri, which discuss hierarchical and associative relationships between the concepts. In clinical trials, SKOS can be used to categorize diseases, drug classifications, and trial phases under a structured vocabulary.

```
#1 SKOS Hierarchical Relationships: Classification of Diseases

@prefix skos: <http://www.w3.org/2004/02/skos/core#>.

ex:Cancer a skos:Concept;

skos:broader ex:ChronicDisease;

skos:narrower ex:LungCancer, ex:BreastCancer,

ex:ProstateCancer.
```

  #1 SKOS defines "ChronicDisease" as a broader concept under "Cancer" and has a narrower subcategory "LungCancer, BreastCancer, ProstateCancer.

- **OWL (Web Ontology Language)**
  OWL defines formal ontologies with classes, properties, and rules for reasoning. OWL provides a rich framework for AI-driven reasoning and automated classification of knowledge. In a clinical trial, OWL can be used for disease classification and patient conditions and thus

allows intelligent querying and decision-making for clinicians, researchers etc.:

```
#2 Ontology Hierarchy: Disease Classification Using OWL and RDFS

@prefix owl: <http://www.w3.org/2002/07/owl#>.

@prefix rdfs: <http://www.w3.org/2000/01/rdf-schema#>.

ex:Cancer a owl:Class;

rdfs:subClassOf ex:ChronicDisease.

ex:LungCancer a owl:Class;

rdfs:subClassOf ex:Cancer.
```

#2 describes that OWL if any of the individuals are diagnosed with any type of cancer to the broader Cancer category.

- **RDFS (RDF Schema)**
  The purpose of RDFS is to extend the RDF by defining the classes, properties, and hierarchies in a more structured way. They provide the knowledge of the basic vocabulary that is needed for defining schemas and relationships. In clinical trial data, RDFS can be used to define the relationship between medical concepts such as linking patients, diseases, and the treatments the patient is undergoing.

```
#3 Ontology Relationship: Patient as a Subclass of Person

@prefix rdfs: <http://www.w3.org/2000/01/rdf-schema#>.

ex:Patient rdfs:subClassOf ex:Person.
```

#3 describes the RDFS representation that tells that "Patient" is a subclass of Person, ensuring that every patient is recognized as an individual within the ontology.

- **RDF/XML (Resource Description Framework in XML Format)** The RDF representation provides a highly structured, XML-based format for storing and exchanging RDF data. This format ensures interoperability and data exchange across systems that require XML-based representations. They can be used in Electronic Health Records (EHRs) and regulatory submissions in healthcare.

```
#4 RDF Data Representation: Associating a Patient with a Medical Condition

<rdf:RDF xmlns1_rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"

xmlns1_ex="http://example.org/ns#">

<rdf:Description rdf:about="http://example.org/ns#Patient123">

<ex:hasCondition rdf:resource="http://example.org/ns#Breast Cancer"/>

</rdf:Description>

</rdf:RDF>
```

#4 representation displays that the Patient123 has the condition "Diabetes", which is structured in an XML-compatible format.

- **Turtle (A Simplified RDF Serialization Format)** This Turtle format is a human-readable format for writing RDF triples efficiently and also simplifies knowledge graph creation and integration. It is used in storing structured clinical trial data for semantic queries.

```
#5 RDF Triple: Linking a Patient to a Medical Condition

@prefix ex: <http://example.org/ns#>.

ex:Patientl 23 ex:hasCondition ex:Cancer.
```

#5 described that the above turtle structure explains that "Patient123 has the condition Diabetes ", written in a simpler RDF format.

Knowledge Inference Language

The Knowledge Inference Language layer in the Semantic Web framework is essential for enforcing data validation, logical reasoning, and ontology-based inference. It ensures that the structured knowledge within a system follows predefined logical constraints and rules, allowing intelligent decision-making based on semantic relationships. This layer is particularly useful in clinical trials, AI-driven applications, and knowledge graphs, where automated validation and inference are required. The three primary technologies used in the Rule Language layer are as follows:

- **SWRL (Semantic Web Rule Language) – Applying Logical Rules**
- SWRL is a powerful rule-based language that allows the definition of logical conditions and reasoning over OWL ontologies. It extends OWL by enabling IF-THEN logic, where new knowledge can be inferred automatically based on existing relationships. By using SWRL rules, we can identify patients involved in clinical trials based on their age and their medical condition.

```
#6 SWRL Rule: Identifying High-Risk Patients Based on Age

Patient(?p) ^ hasAge(?p, ?age) ^ swrlb:greaterThan(?age, 60)

-> HighRiskPatient(?p)
```

6 infers that the rule automatically classifies a patient as High Risk patient if his/her age is greater than 60 years; this method is highly accurate and the knowledge will be stored inside the RDF file itself. Thus, SWRL (Fadillah, et al., 2024) helps in real-time classification, aggregation using SWRLB built- in functions and decision support in clinical settings.

- **SHACL (Shapes Constraint Language) – RDF Data Validation** SHACL is used to validate RDF graphs by enforcing structural constraints on data. It ensures that data follow predefined schemas, preventing inconsistencies and errors in knowledge bases. The SHACL ensures that every clinical trial record has a valid trial ID, and that at least one of the patients is associated with it.

```
#7 SHACL Shape: Validating Clinical Trial Data Constraints

@prefix sh: <http://www.w3.orginsishacl (Not accessible as of

[06/10/2025]).>

@prefix ex: <http://example.org/ns#.>

ex:TrialShape a sh:NodeShape;

sh:targetClass ex:ClinicalTrial;

sh:property [

sh:path ex:hasTrialID;

sh:minCount 1;

sh:datatype xsd:string;

];sh:property [sh:path ex:hasParticipant; sh:minCount 1; ].
```

#7 described that SHACL shapes indicated that every Clinical Trial must have at least one Trial ID (string) and at least one participant. This prevents missing or incomplete data, ensuring that only valid trial records are stored in the knowledge base (Kober, et al., 2022).

- **OWLReady2 – Dynamic Ontology-Based Inference** OWLReady2 is a Python-based framework that allows reasoning to be executed over OWL ontologies dynamically. It integrates ontological reasoning with real-time AI applications. This package automatically classifies drugs into categories based on their properties. #8 infers that If a drug causes drowsiness, the system automatically infers that it is a Painkiller.

```
#8 Inference: If a drug has "drowsiness" as a side effect, classify it as
a Painkiller.

from owlready2 import *

onto = get_ontology("http://example.org/clinical.owl").load()

class Drug(Thing): pass

class Antibiotic(Drug): pass

class Painkiller(Drug): pass

has_side_effect = onto.ObjectProperty()

has_side_effect.domain = [Drug]

has_side_effect.range = [Thing]

with onto:

rule = Imp() rule.set_as_rule("Drug(?d), has_side_effect(?d,

ex:Drowsiness) -> Painkiller(?d)")
```

After defining the rule, the ontology will apply inference, meaning that
if a Drug has the side effect Drowsiness, it will be classified as a
Painkiller based on the logical rule.

Ontology Layer

The Ontology Layer in the Semantic Web framework plays a critical role in
standardizing medical concepts to ensure interoperability, consistency, and
intelligent reasoning in clinical trials, healthcare, and biomedical research.
Ontologies provide a structured vocabulary for defining diseases,
treatments, procedures, and relationships in a machine-understandable
format. By using standardized clinical trial ontologies, different datasets can
be seamlessly integrated, queried, and analyzed across various healthcare

systems. Among the many global ontologies, described below are the three primary ontologies.

- **SNOMED CT (A Globally Recognized Medical Vocabulary for Healthcare Data)**
  SNOMED CT is a globally recognized medical terminology standard that provides a comprehensive set of clinical conditions, procedures, and observations. It enables semantic interoperability in healthcare applications by defining precise relationships between medical concepts. The SNOWMED ontology is used for standardizing diseases and procedures named in clinical trials.

```
#9 Ontology Annotation: Defining Cancer with SNOMED CT

@prefix owl: <http://www.w3.org/2002/07/owl#>.

@prefix rdfs: <http://www.w3.org/2000/01/rdf-schema#.>

@prefix xsd: <http://www.w3.org/2001/XM1LSchema#.>

ex:Cancer a owl:Class; rdfs:subClassOf ex:ChronicDisease;

rdfs:label "Cancer"^Axsd:string; ex:SNOMED_CT_Code "363346000"
```

  #9 representation explains that the disease Cancer is classified under Chronic Diseases and linked to its SNOMED CT Code (363346000), ensuring consistency in terminology across different systems (Hong, et al., 2021).

- UMLS (A Knowledge Representation Model for Biomedical and Clinical Terms)
  The UMLS (Unified Medical Language System) is a global ontology that integrates various medical terminologies, linking equivalent

concepts across different classification systems (e.g., SNOMED CT, MeSH, ICD-10). It provides semantic relationships between medical terms, allowing researchers to map equivalent terms across ontologies. This ontology is used for mapping equivalent disease names across multiple ontologies for interoperability.

```
#10 Ontology Annotation: Defining Cancer with SNOMED CT

@prefix ex: <http://example.org/ns#.>

@prefix rdfs: <http://www.w3.org/2000/01/rdf-schema#.>

ex:Cancer rdfs:label "Cancer";

ex:hasEquivalentConcept ex:SNOMED_363346000;

ex:hasEquivalentConcept ex:ICD10_C00-C97;

ex:hasEquivalentConcept ex:MeSH_D009369.
```

#10 "Cancer" is linked to its equivalent representations in SNOMED CT (363346000), ICD-10 (El 1), and MeSH (D003920), ensuring that different healthcare can the same concept correctly.

There are also other global ontologies of which only two were explained, the remaining we will see further.

Al Integration Layer

The AI Integration Layer leverages AI-powered tools to enable smart data retrieval, automated reasoning, and decision support within the Semantic Web framework. It enhances clinical research, healthcare analytics, and knowledge management by incorporating the following:

- LLMs (Large Language Models): Enables natural language understanding and contextual insights.
- RAG (Retrieval-Augmented Generation): Combines semantic search with generative AI for accurate knowledge retrieval.
- Vector Databases (FAISS, ChromaDB): Supports fast, similarity-based search for unstructured biomedical data.
- LangChain: Facilitates AI-driven retrieval workflows, integrating semantic search with structured ontological data.

This layer bridges AI and Semantic Web technologies, allowing intelligent, contextual, and automated decision-making in clinical trials, knowledge graphs, and healthcare applications (Jiang, et al., 2022).

Tools in Semantic Web

The semantic web uses various tools and frameworks for reasoning, validating, querying, integrating and hierarchical data representation. These tools play a very crucial role in extracting knowledge from the linked data which is essential for decision-making, the construction of knowledge graphs, clinical or bio-medical research etc. Below are the Semantic Web tools in which knowledge base is created,

 i. **Protégé:** This is a widely used ontology development tool which is used to visualize the OWL-based ontology.
 ii. **Apache Jena:** It is an old Java framework which has been used for building the Semantic Web applications, which also support RDF, SPARQL, OWL, and inference engines.
 iii. **TopBraid Composer:** Semantic Web ontologies and Semantic Web applications are developed by using this tool which enables data integration and reasoning.

iv. **RDF4J:** This is a high-performing JAVA framework which is used for handling RDF data which is used for querying and storing knowledge graphs.

These tools help in creating, managing, and querying linked data, facilitating automated reasoning, AI integration, and decision support systems in domains such as biomedical research, clinical trials, and enterprise knowledge management.

Semantic Web in Protégé

Protégé is a powerful software application used for building hierarchical class relationships to create machine-understandable knowledge graphs. It is written entirely in Java and provides a user-friendly interface for ontology development. Protégé includes various features and tabs, such as:

- SHACL (Shapes Constraint Language): This language is used to define and validate constraints on RDF data.
- SPARQL (SPARQL Protocol and RDF Query Language): A query language used for retrieving and aggregating data from ontologies.
- SWRL (Semantic Web Rule Language): Enables the creation of rules to infer new knowledge from existing data.

Although many high-performing tabs such as DL query, SQWRL still exist, the above is only a glimpse of a few tabs in protégé to demonstrate its high efficiency. Protégé allows users to:

- Create Classes and Subclasses: Define hierarchical structures to categorize entities.
- Define Axioms: Establish logical constraints and relationships.
- Object Properties: Define relationships that link two classes.

- Data Properties: Link a class to its own data type attributes (e.g., numerical values, dates).

Applying Protégé to Clinical Trial Data

In our use case, SPARQL will be used primarily to aggregate clinical trial data, enabling efficient retrieval of insights such as patient demographics, trial success rates, and adverse effects. Additionally, SWRL rules are utilized to infer percentages and make logical conclusions from the linked data. By leveraging Protégé, we can structure and standardize clinical trial data, ensuring better interoperability, data analysis, and decision-making in the Semantic Web framework.

Clinical Trial Data in the Semantic Web

One of the most well-defined examples of unstructured data is clinical trial data, as it exists in vast amounts and is often scattered across multiple sources. In well-developed countries such as India, the United States, and Russia, clinical trials are conducted on a limited group of participants rather than an entire population. These datasets are highly confidential, as they contain personal demographic information, medical histories, and other sensitive details, requiring strict security and ethical handling.

Integrating clinical trial data into the Semantic Web helps create knowledge graphs, enabling researchers and healthcare professionals to derive meaningful insights for decision-making. By structuring and linking clinical trial data, it becomes easier to do the following:

- Data aggregation is performed across multiple trials.
- The percentage of participants involved in a specific drug or vaccine trial was analyzed.

- The interoperability can be increased by aligning with global clinical trial ontologies.

Pushing these data into an ontology ensures seamless integration with existing medical and clinical research standards, reducing interoperability challenges. Some well-known ontologies that support clinical trials include global ontology like SNOWMED, ADAM, STDM, etc.

By leveraging the Semantic Web, clinical trial data can be efficiently linked, queried, and analyz ed, enhancing research outcomes, regulatory compliance, and data-driven decision-making in the healthcare industry.

Methodology

The integration of Semantic Web technologies into clinical trial data management involves multiple phases, ensuring seamless data transformation, validation, querying, reasoning, and final application integration. This methodology systematically organizes the process from raw clinical data pre-processing to its final application in Clinical Decision Support Systems (CDSS).

Each phase is designed to ensure data interoperability, maintain accuracy, and support intelligent reasoning for better clinical insights and decision-making. The following sections describe the sequential approach taken to process clinical trial data into an ontology-driven knowledge framework. Below is the detailed framework of methodology:
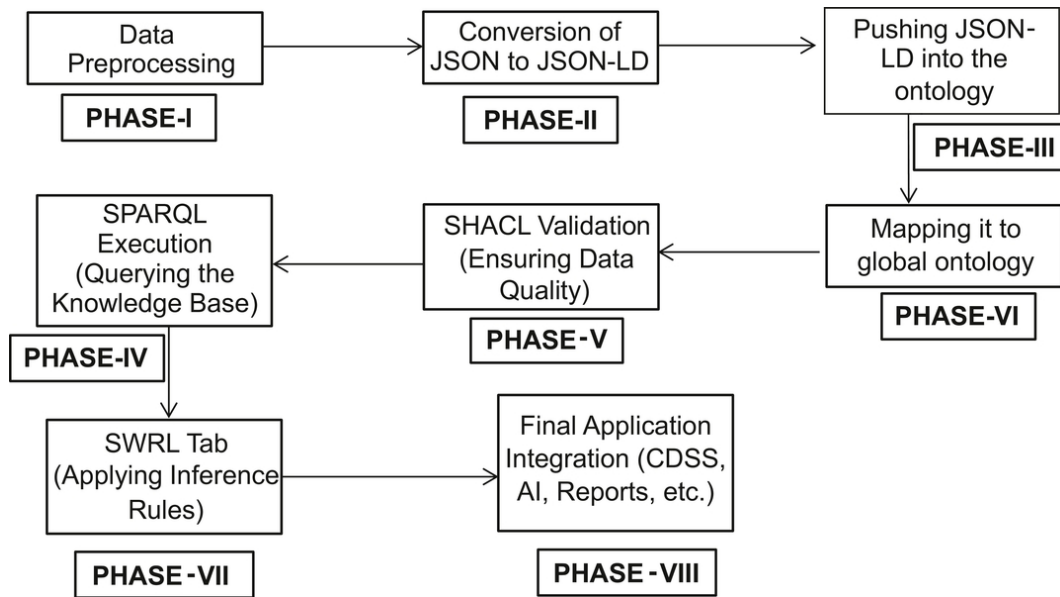
Fig. 2 Methodology Representation.

Phase-I Data Preprocessing

Clinical trial datasets are often obtained from government repositories, private hospital databases, or research institutions. These datasets contain structured (relational databases) and unstructured (free-text documents) information, which require careful pre processing before integration into the Semantic Web framework. The below are the critical points for data pre processing,

1. **Handling Missing Values:** Missing data, such as patient demographics or trial outcomes, can cause inconsistencies in reasoning and querying. Standard imputation methods or exclusion techniques are applied.

2. **Eliminating Redundant and Duplicate Records:** Clinical datasets often contain repetitive trial records due to multiple hospital data sources. Deduplication techniques are implemented.

3. **Standardizing Medical Terminology:** Clinical data must be mapped to global standards such as SNOMED CT, UMLS, or ICD-10 to ensure

uniform interpretation across healthcare systems.

4. **Data Formatting and Encoding:** The transformation of data into a machine-readable format ensures compatibility with RDF-based ontologies for further processing.

Upon completion of pre processing, the cleaned and structured data is converted into a format suitable for the Semantic Web framework.

Phase-II Conversion of JSON to JSON-LD

The preprocessed data, primarily stored in JSON format, is transformed into JSON-LD (JavaScript Object Notation for Linked Data) to align with linked data principles. JSON-LD enhances semantic representation by:

- Attaching unique identifiers (IRIs) to resources.
- Defining structured relationships between data entities.
- Supporting direct integration into RDF-based ontologies.

For example, a standard patient record in JSON is represented as:

```
{
"PatientlD": "P001",
"Name": "John Doe",
"Age": 45,
"Condition": "Diabetes"
```

In JSON-LD, this transforms into:

```
{
"@context":
"http://schema.org,"
"@type": "Patient",
"@id":
"http://example.org/patients/P001,"
"name": "John Doe",
"age": 45,
"medicalCondition":
"http://snomed.info/id/44054006"
}
```

This structured format establishes semantic links, allowing efficient querying and reasoning in ontology-driven systems.

Phase-III: Pushing JSON-LD into the Ontology

Once the clinical trial data is represented in JSON-LD, it is ingested into the ontology. The ontology, designed using Protégé, includes:

- Classes and Subclasses for representing medical entities (e.g., Patient, Clinical Trial, Drug).
- Object Properties to define relationships between entities (e.g., has Diagnosis, participates InTrial).
- Data Properties to associate attributes with entities (e.g., age, test Result).
- Each patient record is converted into an OWL individual and linked to relevant medical concepts, ensuring knowledge interoperability across datasets.

Phase-IV: Mapping to Global Ontologies

To ensure semantic consistency and data interoperability, the ontology is aligned with global medical ontologies (Alahmar, et al., 2022), such as:

- SNOMED CT (for diseases and clinical procedures).

- UMLS (for standardized medical terminology).
- LOINC, ICD-10, RxNorm (for lab tests, disease classification, and drug interactions).

For example, a clinical trial for Type 2 Diabetes is mapped to SNOMED CT Code 44054006, ensuring its recognition across various healthcare knowledge bases. This phase is crucial in enabling global accessibility of clinical data across different platforms.

Phase-V: SHACL Validation (Ensuring Data Quality)

Before executing queries or performing inference, the ontology undergoes SHACL (Shapes Constraint Language) validation to ensure structural correctness and data consistency. This step is crucial in verifying that clinical trial data conforms to predefined constraints and prevents potential errors. Key aspects of SHACL validation include:

- Verifying mandatory attributes such as patient records, trial IDs, and medical observations.
- Enforcing structural constraints to maintain logical consistency across entities.
- Ensuring completeness of relationships between data instances to avoid missing connections. Through SHACL validation, the ontology is refined and structured, ensuring that subsequent querying and reasoning yield accurate results.

Phase-VI: SPARQL Execution (Querying the Knowledge Base)

Once validated, the ontology serves as a knowledge base that can be queried using SPARQL (SPARQL Protocol and RDF Query Language). SPARQL enables structured retrieval of clinical trial data, patient records,

and medical observations while supporting semantic queries that go beyond traditional database lookups.

SPARQL execution involves:

- Extracting specific information such as trial participants, drug efficacy, and medical conditions.
- Aggregating data across multiple trials to identify trends and patterns.
- Performing semantic searches to retrieve related concepts based on inferred relationships.

By utilizing SPARQL, the system enables efficient and context-aware knowledge retrieval, enhancing the analysis and interpretation of clinical trial data ([Keuchel, et al. 2021](#)).

Phase-VII: SWRL Tab (Applying Inference Rules)

To enhance decision-making capabilities, Semantic Web Rule Language (SWRL) is employed to define logical 'if-then' rules within the ontology. SWRL enables automated knowledge inference, allowing the system to derive new insights based on predefined medical conditions.

Key components of this phase include:

- Defining rule-based logic for classifying clinical trial outcomes.
- Applying reasoning engines (e.g., Pellet) to infer new relationships between data entities.
- Classifying patients dynamically based on trial data and medical criteria.

By leveraging SWRL reasoning, the system automatically deduces meaningful conclusions, enabling enhanced analysis and real-time decision support.

Phase-VIII: Final Application Integration

The final phase involves integrating the processed, validated, and inferred knowledge into real-world applications, enabling clinical decision-making and research analytics. This step ensures that semantic insights derived from the ontology are actionable and accessible (Seneviratne, et al., 2023). Key aspects of this integration include:

- Connecting with CDSS to assist healthcare professionals in decision-making.
- Storing structured knowledge in databases (MongoDB, GraphDB) for realtime retrieval.
- Generating reports for researchers and clinicians, summarizing key findings from the ontology.

This phase transforms structured clinical trial data into actionable knowledge, enhancing the usability and impact of the Semantic Web framework in healthcare.

This methodology provides a systematic approach to structuring, validating, querying, and reasoning over clinical trial data using Semantic Web technologies. Each phase contributes to enhancing data quality, ensuring interoperability, and enabling AI-driven insights. By integrating SPARQL queries, SWRL rules, and global medical ontologies, this framework facilitates intelligent decisionmaking and clinical trial analysis. The final integration ensures that ontologydriven insights are accessible for real-world applications, driving advancements in medical research and healthcare informatics.

Results and Discussion

The implementation of the Semantic Web in clinical trial data requires a structured approach to ensure data interoperability, integration, and machine-readability. This section outlines the methodology for transforming clinical trial data into a machine-interpretable ontology using Protégé and associated Semantic Web technologies. Given the confidentiality of clinical trial data, this study employs simulated laboratory information for demonstration purposes. Clinical trial data can be sourced from:

- Government repositories (e.g., ClinicalTrials.gov, WHO ICTRP).
- Private hospital and research institution databases.
- Pharmaceutical industry datasets.

To integrate such data into an ontology, it is crucial to handle structured and unstructured data formats appropriately: Structured data: Relational databases (e.g., PostgreSQL, MySQL). Unstructured data: NoSQL databases (e.g., Neo4j,MongoDB) and text documents (e.g., clinical reports, PDFs). Before ontology integration, data undergoes pre-processing to ensure standardization with established medical terminologies, such as SNOMED CT, SDTM, ADaM. The following phases outline the stepwise methodology used for clinical trial data integration.

Data Handling in Semantic Web

The JSON (JavaScript Object Notation) file format is widely used for data exchange because of its structured, machine-readable format. However, to align with semantic web principles, data must be converted into JSON- LD (JavaScript Object Notation for Linked Data) for ontology understandable formats.

1 Data Preprocessing

Before conversion, the data are cleaned and structured as follows:

- Missing values (e.g., missing patient IDs) were handled.
- Redundant or duplicate records were removed.
- Correcting inconsistencies in terminologies (e.g., drug names, dosage units).

2 Conversion from JSON to JSON-LD

JSON-LD enhances semantic interoperability by defining relationships between entities in an ontology-compatible format. It enables,

- Named Individuals (e.g., Patient_001 defined as #NamedIndividual).
- Class hierarchies (e.g., "TrialParticipants" subclass of "Patients").
- Object Properties (e.g., "Patient_001" linked to "Drug_Treatment_A").
- Data Properties (e.g., "Patient_001" has "Age" as an integer).

The above JSON-LD format ensures that clinical trial data is structured, machine-readable, and interoperable across healthcare and research systems.

Fig. 3 JSON-LD Representation.

Pushing JSON-LD into Ontology

Once the JSON-LD representation is prepared, it is integrated into an RDF (Resource Description Framework) ontology, where predefined classes, subclasses, data properties, and object properties ensure structured knowledge representation.

The ontology is designed with hierarchical knowledge structures using the following components:

Table 1 Ontology Components.

Ontology Components	Description
Classes	Patient, Clinical Trial, Drug, Adverse Effect
Subclasses	Trial Participant (a subclass of Patient)
Object Property	hasTrial, administered drug

Ontology Components	Description
Data Property	has Age, dosage, trial Start Date

Below are the snippets of classes, subclasses, data properties etc., that are defined in the ontology:

Fig. 4 Ontology Representations.

Mapping to Global Ontology

To avoid interoperability issues mapping, we map the clinical data with the global ontologies terminologies so that the ontology created by us can be accessed globally. The global standard ontology includes SNOMED CT (for medical conditions and procedures), ADaM and SDTM (for trial data standardization) etc. A detailed description is given in Table 2.

Table 2 Overview of Global Ontologies.

Global Ontology	Description	Key Components
OBI (Ontology for Biomedical Investigations)	Standard biomedical investigations, experiments, and workflows.	Biological samples (e.g., blood, tissue), Experimental methods (e.g., PCR), Lab instruments (e.g., microscope).
CHEBI (Chemical Entities of Biological Interest)	Provides a structured vocabulary for chemical compounds and their biological roles.	Chemical compounds (e.g., glucose, hemoglobin), Molecular interactions (e.g., drug metabolism), Biological applications (e.g., antibiotics).

Global Ontology	Description	Key Components
SNOMED CT (Systematized Nomenclature of Medicine– Clinical Terms)	A standardized terminology for disease classification, procedures, and symptoms in healthcare.	Disease classification (e.g., lung cancer, anemia), Medical procedures (e.g., MRI, biopsy), Symptoms (e.g., fever, joint pain).
ADaM (Analysis Data Model)	Provides a structured model for clinical trial analysis.	Standardized datasets for trial outcomes, Patient demographic data.
SDTM (Study Data Tabulation Model)	Defines how clinical trial data should be structured for submission to regulatory agencies.	Clinical events, Interventions, Study population characteristics.

SHACL Validation

When the data are pushed into an ontology SHACL (Shape Constraint Language) validation is performed to ensure the integrity of the data type. It is a type of language that is used to validate the RDF file. This improves the data consistency, accuracy and interoperability of data. All the clinical trial entities are defined as shape graphs and they are validated against the specific set of conditions that are used before validation, aggregation of data etc.. For the clinical trial data we use SHACL in order to validate the Patient ID, Age, Sex etc.. For example, if Group I of age is between 0–18 years of age, if suddenly 19 comes then our shapes will alert with a message of inconsistency.

An example of validating patient demography is shown in Table 3.

Table 3 SHACL Shapes and Conditions.

SHACL Shape	Condition Enforced

SHACL Shape	Condition Enforced
PatientShape	Validates that a clinical trial has a unique ID, sponsor, drug information, and patient participation details.
ClinicalTrialShape	Ensures patient age is within the allowed range (18– 99) and linked to at least one clinical trial.
DrugShape	Checks that each drug has a defined name, manufacturer, and approved dosage range.
AdverseEffectShape	Ensures that adverse effects are recorded with severity levels and associated drugs.
InvestigatorShape	Confirms that an investigator has a valid medical license and is associated with at least one clinical trial.


```
SHACL editor:

Open  Save  Validate

ex:PatientShape a sh:NodeShape ;
sh:targetClass ex:Patient ;
sh:property [ sh:path ex:age ; sh:datatype xsd:integer ; sh:minInclusive 18 ; sh:maxInclusive 99 ;
sh:message "Age must be between 18 and 99 years." ; ] ;
```
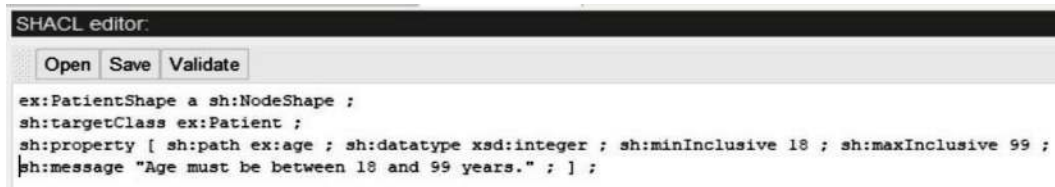
Fig. 5 SHACL Example.

The above shapes indicate that the age should be an integer, not a float or decimal, etc. When the age is between 18–99 years it should not be in a negative number (–) or less than 18, if the age is greater than 99, an error message will be displayed.

SPARQL Execution

After the data are validated completely using SHACL, SPARQL (Riazanov, et al., 2013) is used to execute or extract the meaningful decision-making from the knowledge base. It is a retrieval language which is used to manipulate the RDF data in the ontology. In particular, in clinical trial data SPARQL is used to extract the patient demographics, drug treatments and also the details of the trial participation. We can also analyze the clinical trial outcomes for each treatment type and the data across multiple trials can

be aggregated to discover the patterns and trends. Similar to SQL (Structured Query Language), it is used in INSERT, UPDATE, DELETE, ALTER functions of the clinical data in the ontology.

For example, if you wanted to see the gender types that are involved in the trial, then the snippet below would explain:

Fig. 6 SPARQL Example.

The above query retrieves all the individuals who are pushed under SEX, regardless of the sex the list of SEX that will be retrieved and the query result for the above query is:

Fig. 7 SPARQL Results.

Thus, SPARQL is the most efficient query language that can provide instant aggregation like Count, Mean, Median, Model etc.. To count the number of males and females in a given clinical trial population, look at the rule below.

SWRL Rule

After aggregating counts using SPARQL, the next step in knowledge inference for clinical trial data involves applying SWRL rules. SWRL enables reasoning over ontologies by defining IF-THEN logic, allowing us to derive new insights from the existing knowledge base. This is particularly useful in clinical trials to infer patient conditions, predict diagnoses, and validate medical data.

Using OWLReady2 in Python, we can dynamically push SWRL rules into the Rules tab of an ontology and execute reasoning using the Pellet reasoner. The reasoner applies logical conditions to enrich the ontology with inferred knowledge.

In our use case, LabTest005 is classified under AI Diagnostic and has specific object property assertions such as Test performed on: TestSample005 , Conducted by: LowStandardLab and their data properties are Test ID: "T005", Test Name: "Lung Function Test", Test Result: "Abnormal". When we apply SWRL to this condition we can define a rule to infer high-risk conditions of a patient when a Lung Function Test is marked as "Abnormal" and conducted by a Low-Standard Lab.

Below is the static rule that is to be written inside the ontology for inference. We can also use the OWLReady2 Package by integrating SWRL with Python in order to make them dynamic. Below is a rule inside the ontology:

```
#11 SWRL Rule: Identifying High-Risk Patients Based on Lab Test Results
  LabTest(?test) ^ hasTestName(?test, "LungFunctionTest") hasTestResult(?test,
"Abnormal") ^

testConductedby(?test, LowStandardLab) → HighRiskPatient(?patient)
```

#11 After writing the rule under the Rule tab you have to run the drools and click on Drools->OWL and then start the Pellet reasoner in the

ontology, thereafter automatically under the particular individual or class the knowledge will be inferred (Sharma, et al., 2024).

Below is the snippet of knowledge inference that has been made by the above rule:

Fig. 8 SWRL Results.

When this rule is applied, any patient associated with LabTest005 will be classified as a HighRiskPatient if: They underwent a Lung Function Test; The test result was abnormal; The test was conducted by a low-standard lab. By using SWRL, we can ensure that the abnormal test results are flagged dynamically and will help the doctors/researchers to identify the high risk patients at the earliest. The inferred knowledge can also be queried using SPARQL for aggregation and further analysis.

Following the SWRL-based inference, the next crucial steps involve extracting inferred knowledge using SPARQL for advanced querying, storing structured results in MongoDB or a Triplestore for seamless data retrieval, and validating inferred results against original clinical data to ensure accuracy. Additionally, detailed reports are generated for medical professionals, aiding in decision-making. Finally, these insights are

integrated into CDSS, enabling real-time AI-driven predictions and enhancing the efficiency of clinical trials and healthcare analytics.

Comparison with Existing Approaches

The main contributions of this paper are highlighted through the integration of Semantic Web technologies for clinical trial data management. Unlike traditional approaches that rely solely on structured relational databases and isolated data systems, the proposed framework leverages a comprehensive Semantic Web stack that includes RDF, JSON-LD, SHACL validation, SPARQL querying, and SWRL rule-based inference. Compared to existing methods, this approach offers several novel contributions:

1. **Enhanced Data Interoperability**

   The proposed system achieves seamless data integration by mapping clinical trial data to global ontologies, such as SNOMED CT and UMLS. This addresses the limitations of previous systems that rely on domain-specific databases lacking standardized representations.

2. **Improved Data Validation and Quality Control**

   Through the application of SHACL validation, the framework enforces data integrity, ensuring that clinical data adheres to predefined structural constraints. This validation process minimizes inconsistencies and inaccuracies that often plague conventional systems.

3. **Intelligent Inference Mechanisms**

   The inclusion of SWRL rules enables automatic reasoning and knowledge inference, enhancing decision support and predictive analytics. Traditional approaches often lack the capability to infer new knowledge from existing datasets, which limits their usability for real-time clinical decision-making.

4. **Scalability and Flexibility**

   The system's ability to handle both structured and unstructured data formats, including JSON-LD and RDF, provides flexibility for integrating diverse data sources. Existing methods often require data preprocessing or format conversion, which increases processing overhead.

5. **AI-Enhanced Retrieval**

   Integrating AI technologies, such as LLMs and RAG, with Semantic Web frameworks provides a novel approach for context-aware retrieval and predictive analytics. This is a distinct improvement over conventional techniques that rely on simple keyword-based queries or predefined database schemas.

The proposed framework offers a structured, flexible, and intelligent approach to clinical trial data management that significantly surpasses existing methods in terms of interoperability, reasoning capabilities, and data quality assurance. This comprehensive approach is essential for ensuring data accessibility and facilitating advanced clinical research.

Limitations

Even though there are many advantages of using Semantic Web in clinical trial management, this study has also significant amount of limitations that need to be carried out while proceeding further,

- The system's ability to handle large-scale clinical trial data efficiently is constrained by computational complexity, particularly when performing reasoning over extensive ontologies.
- While efforts have been made to integrate global ontologies (e.g., SNOMED CT, UMLS), complete interoperability across diverse

healthcare systems remains a challenge due to inconsistencies in medical terminologies.

- Clinical trial data involve sensitive patient information, necessitating advanced encryption and access control mechanisms, which were not extensively covered in this work.

- The SWRL rules implemented for reasoning and inference may not cover all possible clinical scenarios, requiring further refinement and expansion. They are dynamically made rules and are highly static

- SPARQL query execution and SHACL validation introduce processing overhead, which may impact real-time performance in large datasets and the time complexities are greater when performing aggregation with SPARQL.

- Although AI-powered tools (e.g., LLMs, RAG, vector databases) are discussed, their full-scale implementation for semantic reasoning and predictive analytics is beyond the scope of this study.

Future Work and Extensions

To address the limitations identified and to expand the scope of the research, the following methods can be used as future work, and extension of the research conducted,

- Extending SWRL rules and integrating additional domain-specific ontologies to improve inference accuracy and decision support.

- Implementing query caching, indexing, and federated SPARQL execution to enhance performance in handling complex clinical queries.

- Utilizing deep learning models and retrieval-augmented generation (RAG) for AI-driven reasoning, predictive analytics, and personalized medicine recommendations.

- Enabling multilingual semantic search capabilities for clinical trials to support global research communities.
- Implementing real-time updates to ontology-based knowledge graphs to accommodate new clinical discoveries and evolving medical standards.

Conclusion

This is a transformative approach of integrating the Semantic Web technology in clinical trial data management which proves structuring, linking and reasoning over a large amount of biomedical data is possible. The need for standardized, machine-readable, and interoperable data becomes essential as clinical research continues to evolve. The clinical trial data is not only accessible, the Semantic Web framework supported by ontologies, knowledge graphs, AI-driven retrieval, and rule-based inference, ensures that they are also intelligent, allowing for seamless integration, automated reasoning, and enhanced decision-making.

Clinical trial data can be effectively stored, retrieved and analyzed, minimizing redundancy and enhancing global interoperability by leveraging ontology-based knowledge representation, SHACL validation, and SPARQL queries. Additionally, SWRL rules and AI-driven techniques such as LLMs and RAG contribute to intelligent automation, enabling dynamic data inference and predictive analytics.

The feasibility of structuring unstructured biomedical data into meaningful knowledge graphs is done by adopting Semantic Web tools, such as Protégé and RDF-based technologies. This, in turn, fosters cross-platform data integration, facilitates accurate clinical insights, and improves patient safety by ensuring better data validation, transparency, and accessibility Celuchova (Bosanska, et al., 2022). Semantic Web innovations will play an integral role in shaping next-generation clinical trial systems as

healthcare data continues to grow exponentially, bridging the gap between human expertise and machine intelligence. Future advancements in AI-enhanced knowledge graphs, federated learning in healthcare, and real-time semantic reasoning will further revolutionize clinical research, paving the way for more effective drug discovery, personalized medicine, and predictive healthcare analytics.

Thus, the implementation of Semantic Web technologies in clinical trials represents not only a technological advancement but also a paradigm shift toward a more structured, intelligent, and interconnected biomedical research ecosystem.

Conflict of Interest

There are no conflicts of interest from the authors.

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11 Personalized Medicine Prediction in Homeopathy

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Homeopathy is a medical system that rests upon the belief in the body's inherent healing mechanisms, and the interpretation of symptoms as indicators of internal imbalances. Utilizing the principles of homeopathy, our proposed system seeks to provide an innovative alternative avenue for healthcare. By employing Natural Language Processing (NLP) techniques, our system aims to empower individuals to access initial medical guidance without immediate reliance on specialized doctors. A novel recommendation system for homeopathic remedies was developed using machine learning techniques. Since there are no comprehensive datasets available, our initial focus was to construct an extensive dataset that correlates symptoms with corresponding homeopathic treatments. The system functions by collecting user-reported symptoms and utilizing our

novel dataset, which was derived from authoritative homeopathic references, to predict the most suitable remedies using NLP methods. Our objective is to establish a state-of-the-art healthcare solution capable of delivering personalized recommendations for homeopathic treatments based on individual patient symptom profiles. This system has the potential to be reliable, efficient, and cost-effective.

Introduction

Homeopathy is a system of alternative medicine. The term 'homeopathy' originated from the Greek words 'homios' and 'pathos' which mean similar and suffering, respectively. It is founded on the principles that the body naturally possesses the ability to heal itself. It is also based on the belief that symptoms indicate underlying internal imbalances. Since its introduction in the 18th century, homeopathy has steadily gained popularity in India, and by 2016, over 200,000 homeopaths were practicing which made it the third most favored healthcare approach there (Ernst, 2016). At present, homeopathic remedies are available in various forms, such as pills, drops, creams, etc. They are usually made from highly diluted substances which are taken from plants, minerals, or various animal products. Many people use it as a complementary therapy alongside conventional medicine.

As the popularity of homeopathy continues to grow, there arises a pressing need for a more streamlined and effective system for recommending appropriate homeopathic medicines based on a patient's symptoms or, more specifically, abnormal physical conditions. This research presents an innovative method that leverages advanced machine learning (ML) and natural language processing (NLP) techniques to assist individuals in making informed decisions about homeopathic treatments, particularly in circumstances where there is limited access to certified healthcare professionals. We propose a homeopathic medication

recommendation system that uses a statistical method to suggest the best homeopathic treatments based on given symptom descriptions. The suggested system works by asking users for symptoms and using ML algorithms to analyze them. A major challenge in our endeavor was the lack of a dataset in which specific homeopathic medicines are associated with symptoms which they address. For tackling this challenge, we painstakingly built a comprehensive dataset that correlates symptoms with corresponding homeopathic remedies. The data was taken from popular homeopathic reference books. The system uses this novel dataset and predicts the most suitable homeopathic medicines based on the provided symptoms. The framework uses NLP vectorization techniques (Word2Vec, BERT, GloVe, TFIDF) and a similarity measuring technique (Cosine Similarity). Our objective is to create a sophisticated intelligent healthcare system that can provide personalized homeopathic medication recommendations according to each patient's unique profile. People who tend to ignore their health by avoiding medical help for minor illnesses can be benefitted by this system. This research aims to bridge the gap between conventional homeopathic practices and technological advancements so that accessibility and understanding of homeopathic treatments may be enhanced for a larger audience.

Motivation

Traditional methods for diagnosing and treating illness are often time-consuming and expensive. It becomes worse when patients do not have access to medical professionals. One practical strategy to overcome this challenge is to develop an AI-powered system for diagnosing illnesses and prescribing medications. This field has seen a great deal of research, but less attention has been given to automated systems for homeopathy than allopathy. Our study aims to address this gap which emphasizes the need for

research on artificial intelligence(AI)-driven homeopathic healthcare solutions. Homeopathy is more widely used because of its lower cost than allopathic medicines, hence we were motivated to conduct this research. NLP has the ability to interpret patient-described symptoms while accounting for their severity and context. This feature enables the system to precisely record symptoms and offer personalized medication recommendations to patients. It can be ensured by using this AI tool that people receive prompt and appropriate treatment recommendations.

Contributions

Being motivated by the need for an automated system to recommend homeopathic medicines, we focus on developing a solution using NLP to provide medication suggestions by analyzing user-reported symptoms. The key contributions of this research are:

- Compilation of an extensive and meticulously curated dataset that maps symptoms to corresponding homeopathic medicines. For this, two highly regarded and widely referenced homeopathic literatures are used to ensure the authenticity of the information. Notably, no prior system has utilized these specific sources for such an endeavor.
- Implementing a novel system for homeopathy by leveraging NLP and statistical models to analyze natural language symptom descriptions.
- Evaluation of various NLP vectorization techniques, such as Word2Vec, BERT, GloVe, and TF-IDF, to determine the most effective method for analyzing symptoms and recommending medicines.
- Systematic comparison of the vectorization techniques to ensure that the system achieves both high accuracy and low computational cost, making it suitable for deployment in resource-constrained environments.

- Introducing a reliable, efficient, and cost-effective system to uniquely benefit homeopathy practitioners and believers. This is particularly significant as most existing automated healthcare systems have concentrated on allopathic medicine, and minimal attention has been given to homeopathy in previous studies.

Literature Review

Homeopathy was established in the 18th century by Samuel Hahnemann who was a German physician. He rejected the medical practices of his time because he considered them as harmful and ineffective. So he developed the concept of homeopathy as a safer and more natural approach to healing. This system of medication is founded on the "like cures like" principle, where substances inducing symptoms in healthy people are used to treat illnesses that have comparable symptoms (Fisher, 2012). These remedies undergo significant dilution and are believed to stimulate the inherent healing capability of the body. Homeopathy places faith in the body's intrinsic ability to self-heal, interpreting illness symptoms as natural responses to imbalances or disruptions in the body's vital force (Ely et al., 1999). Homeopathic treatments are meticulously tailored to individual symptoms, aiming to reinstate equilibrium and activate the body's healing mechanisms.

The realm of automatic medical diagnosis and clinical decision support systems has been a subject of research for decades. These systems encompass expert systems, relying on a knowledge base containing pertinent information, rules, and associations. Alternatively, some systems employ ML techniques, drawing insights from past clinical histories to predict outcomes. Corny et al. (2020) combined ML with a rule-based expert system and built a hybrid clinical decision support system. Their system checks prescriptions with good accuracy by targeting high-risk

patients. Their aim was to make interception of prescription errors more reliable. Bhoi et al. (2021) developed a two-stage personalized medication recommender system called PREMIER. They used electronic health record (EHR) data for medication recommendations. They also used information on patient history and prescriptions. Drug interactions and co-occurrences were modeled as graphs to provide a better understanding of relations among medications. Asghari Varzaneh and Hosseini (2023) proposed a fuzzy expert system for diabetes diagnosis. They optimized fuzzy logic rules via the Harris Hawks optimization algorithm.

There are studies which focus on clinical question-answering systems. They are inspired by the practice of doctors gathering patient information through questioning for diagnostic purposes. For example, WatsonPaths was developed by Lally et al. (2017). It made medical diagnostic and treatment suggestions by employing probabilistic inference over a graphical model. It breaks down scenariobased questions into smaller subquestions. Additionally, researchers made efforts to extract information from EHRs using tools like MedEx (Xu et al., 2010), cTAKES (Savova et al., 2010), and MetaMap (Aronson & Lang, 2010). These tools provide clinical decision support by interpreting unstructured clinical text.

Researchers have explored the extraction of medically relevant information from social media platforms. This acknowledges the popularity of online health information seeking. They used supervised techniques for detection of diseasereporting events, and also unsupervised methods for identifying medical entities in online medical texts. Deep learning-based approaches have also been explored for inferring possible diseases from health seeker questions. In recent years, NLP has been applied in various health and patient-care related areas. In order to enhance clinical decision-making and customized cancer treatment plans, Jensen et al. (2017) created

a system to forecast disease progressions using unstructured text data from electronic medical records. Luo et al. (2021) employed bidirectional temporal Siamese network (BTSN) with ERNIE-pretrained character vectors and bidirectional long short-term memory (BLSTM) network in a Traditional Chinese Medicine (TCM) text similarity tasks to capture contextual semantics. Mai et al. (2023) created a clinical decision support system to provide tailored treatment suggestions for patients of hypertension. They used knowledge-based and datadriven approaches with clinical expert opinions. These advancements prove the growing interest and potential of utilizing NLP techniques to enhance healthcare delivery and decision-making processes across various medical domains.

Allopathy has received the majority of research attention in this domain. Nevertheless, some work on automated clinical decision support systems based on homeopathy has also been conducted. Subbulakshmi et al. (2022) created a system that provides suggestions during clinical diagnostics. Their system integrates symptoms and treatments from both allopathy and homeopathy. Their conceptual framework is presented using a knowledge-based clinical assistance interface. Additionally, a system was created by Priyadarshi and Saha (2020) for automatic medical diagnosis and identifying homeopathic remedies. The system processes patient descriptions to identify symptoms of diseases from them. It then retrieves web pages relevant to those symptoms for extracting medicine names. The system achieved 96.33% accuracy. However, the correctness of the information found on these websites is sometimes questionable, which emphasizes the need to look for more reliable sources. Also, this approach may be slow due to internet speed, which may make it less accessible for residents of rural areas. These limitations, coupled with the overall lack of

research on AI-driven homeopathic medicine recommendation systems, have motivated us to undertake this study.

Dataset

Information for the dataset was taken from two important books on homeopathy: *Keynotes And Characteristics With Comparisons of Some of the Leading Remedies of the Materia Medica* and *Leaders In Homoeopathic Therapeutics*. These two books were published in 1871 and 1899, respectively. These texts are considered to be foundational in the realm of homeopathic medicine. *Keynotes And Characteristics…* highlights the main symptoms (keynotes) and overall attributes (characteristics) of various homeopathic remedies. It provides us with crucial insights into the distinct qualities of each remedy. It helps with differentiation of remedies and their selection for treatment purposes. And *Leaders In Homoeopathic Therapeutics* explains the clinical use of popular medicines in greater detail. It includes thorough analyses of their indications, modalities, and characteristic symptoms. The authors of these two books are respectively Henry Clay Allen and E. B. Nash. They are influential and prominent figures in the field of homeopathy. Both of these texts are valuable references in the homeopathic community. We studied these books carefully to collect important information for our research. Moreover, we consulted with a medical expert to better understand common symptoms across different illnesses. These consultations also helped us gain a more nuanced understanding of subtle differentiations between symptoms which helped us to categorize and analyze the data more precisely. We cleaned and processed this data accordingly to ensure its accuracy and reliability.

There are many other popular *Materia Medica* in homeopathy, for instance, Samuel Hahnemann's *Materia Medica Pura* (1811–1821). This carries the foundational principles of homeopathy. Hahnemann provided

clear descriptions of the symptoms various remedies produce according to his own experiments (also called 'provings') and those of his students. William Boericke's *Pocket Manual of Materia Medica* (1901) is another essential text which comes with concise and practical descriptions of remedies. It is often accompanied by clinical notes which gives some extra insights into the therapeutic applications of remedies. Dr. John Henry Clarke's *Dictionary of Practical Materia Medica* is another reference for homeopaths. It is a detailed compilation which is ideal for exploring in depth, such as preparation of the medicines, main symptoms that they address and their clinical applications. *Lectures on Materia Medica* by Dr. James Tyler Kent is particularly popular for its engaging narrative style and practical insights from a master clinician. His descriptions of remedies come with emphasis on their mental, emotional, and physical symptoms.

However, we chose Allen's and Nash's *Materia Medica* for this research. It is because they have provided systematic presentations of homeopathic remedies in their books. Allen's book contains precise descriptions of remedies which focus on their vital symptoms and clinical indications. Nash's book complements this with his practical insights in homeopathy medicines. He tried to take a comparative approach to provide a much deeper understanding of relationships among remedies along with their applications in clinical settings. These texts together ensure a wellrounded perspective. The combination of these two books aligned perfectly with the analytical needs of our research.

Table 1 shows the number of medications whose information was collected from each of the two books. The dataset is structured such that each book is represented by a separate directory. Within each of these directories, there are multiple text files, each dedicated to a specific medicine. For the book *Keynotes and Characteristics*, there are a total of

150 text files, with each file providing detailed descriptions of one particular medicine. Similarly, the book *Leaders in Homoeopathic Therapeutics* contains 211 text files, each offering comprehensive information about a different medicine. This organized structure makes it easier to access and manage the information for further analysis.

Table 1 Counts of Medicines Extracted from Homeopathic Texts.

↵

Book Name	Author	No. of Medicines Extracted
Keynotes and Characteristics with Comparisons of Some of the Leading Remedies of the Materia Medica	Henry Clay Allen	150
Leaders in Homoeopathic Therapeutics	Eugene Beauharnais Nash	211

Machine Learning Approaches

Word2Vec (Word to Vector)

This NLP method converts words into word embeddings (numerical vectors). It is predicated on the idea that words with similar meanings tend to appear in like contexts. Word2Vec is a shallow neural network that includes an input layer, a single hidden layer, and an output layer. The two main architectures of Word2Vec are Skip-gram and Continuous Bag-of-Words (CBOW). Skip-gram predicts the surrounding words for a given target word. But, CBOW forecasts the current word by looking at the context words that surround it. In this structure, words that appear closer together are assigned greater weight (Abubakar & Umar, 2022). The input layer takes the average of the one-hot encoded vectors (v_e) of the context words surrounding the target word. In the hidden or projection layer, a

vector, $v_h = W \Diamond v_e$, is produced where W is a weight matrix with dimensions $V \times E$ (V being the vocabulary size and E the dimensionality of the embeddings). This vector is a dense representation of the context. In the output layer, the following operation takes place: $u = W^T \Diamond h$. Given the context, each component (u_x) of a vector (u) represents the unnormalized log probability of a word (x) being the target word. The final output, representing the probabilities of each word in the vocabulary being the target word, is obtained using the softmax function (Equation 1), which calculates the probability of a word (x) being the intended word (w_x) considering the weighted context (W_c).

$$P(W_c) = \frac{e^{u_x}}{\sum_{i=1}^{V} e^{u_i}} \qquad \qquad \dots(1)$$

TF-IDF (Term Frequency-Inverse Document Frequency)

This method evaluates the words' significance inside a text in relation to a group of documents (corpus). It operates by merging two measures: term frequency (TF) and inverse document frequency (IDF). TF represents the proportion of a word's occurrences to the overall word count in a specific document. It is a reflection of the local significance of the term within that document. High TF values signify terms that are frequently used in the text. However, it does not account for the term's significance across the corpus.

The weight that IDF provides to a word reflects its importance within the particular document in the context of the overall corpus. It measures repetition or rarity of a word across all documents in the corpus. It helps to downweight words that are very common and upweight those that are rare. For a term w in a corpus C with N documents, IDF can be expressed as given in Equation (2). The TF-IDF score ($TF * IDF$) helps highlight important terms in a document which are not too common in the corpus.

$$\text{IDF}(w, C) = \log \left(\frac{N}{\text{Number of documents containing term } w} \right) \quad \dots(2)$$

BERT (Bidirectional Encoder Representations from Transformers)

BERT's Transformer architecture engages self-attention which enables the model to dynamically determine the importance of various words in a sentence. The Transformer analyzes an entire sentence at once. This allows it to capture contextual connections between words regardless of their position in the text. BERT's bidirectional nature can understand the context of words in a text by examining both the preceding and succeeding words. The original BERT has been pre-trained on a large corpus of text from the internet. It involves learning to predict masked words and next sentences to help the model understand general language patterns and contexts. Pre-training is done using two specific tasks. In Masked Language Modeling, some words in the text are randomly masked, and the model is trained to predict these masked words based on the surrounding context. Next Sentence Prediction determines if a sentence logically comes after another. It aids the model in grasping the connections between sentences. Embedding layer is the initial part of the model that converts input tokens into vectors of fixed size. There are multiple layers of transformers, which are responsible for understanding the context of words in text by considering the interaction of each word with every other word in the sentence.

GloVe (Global Vectors for Word Representation)

GloVe generates word embeddings by analyzing word co-occurrence frequencies across a large text corpus. It leverages global statistical data. It

constructs a word co-occurrence matrix (*M*) where each element stands for the frequency of two words appearing together within a specific context window. By factoring this matrix, GloVe generates word vectors, or embeddings, that reflect statistical relationships between words. These embeddings spatially cluster semantically related words near each other in a multi dimensional space. Dissimilar words are positioned further apart. During training, a cost function is optimized so that the resulting word vectors maintain the ratios of word co-occurrence probabilities. This probability, P_{ab} represents the likelihood that word *b* occurs in the context of word *a*. It is derived from *M*, where M_{ab} is the number of times word *b* occurs in the context of word *a* using Equation 3. For word vectors v_a and v_b, weight function $W(M_{ab})$, bias terms β_a and β_b, and vocabulary size *V*, the cost function *C* is calculated using Equation 4.

$$P_{ab} = \frac{M_{ab}}{\sum_z M_{az}} \quad\quad\quad …(3)$$

$$\sum_{a,b=1}^{V} W\left(M_{ab}\right)\left(v_a^T v_b + \beta_a + \beta_b - \log M_{ab}\right)^2 \quad\quad …(4)$$

Cosine Similarity

This technique is used to determine indistinguishability of two non-zero vectors in an inner product space. Essentially, it measures the cosine of the intermediate angle of the two vectors. The calculation of cosine similarity between two vectors (*P* and *Q*) uses Equation 5. A cosine similarity score of 1 means the vectors point in the same direction or are identical. A score of 0 means the vectors are orthogonal or perpendicular with no similarity. Score of − 1 means vectors point in opposite directions and are completely dissimilar.

$$\text{cosine similarity} = \frac{P \cdot Q}{\|P\| \cdot \|Q\|} \qquad \dots(5)$$

Proposed Methodology

Figure 1 illustrates the implementation process of the proposed system. The system begins by receiving user input in the form of a free-text description of their disease symptoms. Using a database of common symptoms, such as fever, cough, headache, nosebleed, pain, and so on, the system extracts relevant symptoms from the user's description. In Phase 1, these extracted symptoms are used as keywords to search within the dataset of homeopathic remedies, retrieving medications linked to those keywords. In Phase 2, the original user input is embedded along with the textual data extracted in Phase 1. Then, a similarity analysis is performed to identify and recommend the two medications with the highest similarity scores to the user's input. Both phases were implemented using Python 3. The phases are described as below:
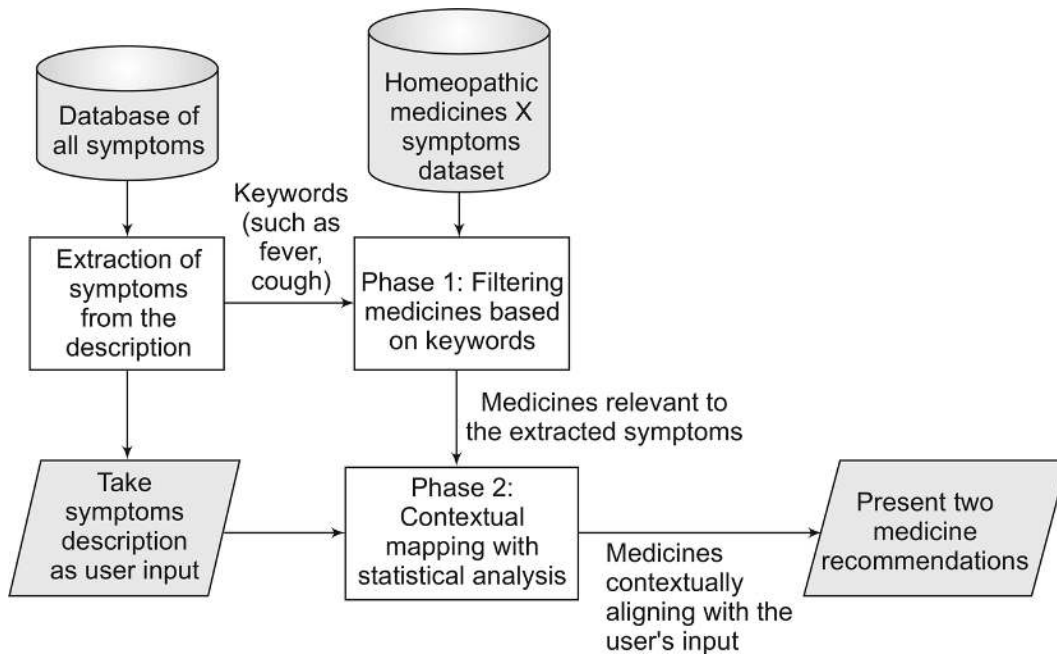
Fig. **1** Flow chart of the proposed system.

Phase 1: Filtering Medicines Based On Keywords

Data Cleaning: The dataset underwent substantial preprocessing and cleaning to standardize the text. This process involved dealing with abbreviations, line breaks, and special symbols found in standard homeopathy books. Newline characters were replaced with spaces. Specific text replacements were made, such as substituting ">" with "better" and "<" with "worse". Furthermore, abbreviations containing a period, like 'Arn., Ar.', which might cause problems during sentence tokenization in subsequent steps, were substituted with the full term, Arnica Montana.

   User's Input: The user's provided symptoms description was a piece of text containing comprehensive and nuanced descriptions of their symptoms. By allowing users to articulate their symptoms naturally, this method improved the user-friendliness and intuitiveness of the interaction. Additionally, it allowed reporting of a wide range of symptoms, including those that might not be covered by a structured input form.

   Data Preprocessing: This is an important step in any NLP pipeline which is carried out to improve the accuracy of the subsequent steps. It transforms raw text into a standardized format that can be analyzed effectively. We carried out the preprocessing of the texts in the symptom description which was taken as an input from the user. This was done with the Natural Language Toolkit (NLTK). We used the Punkt tokenizer to break the sentences into individual words, so the units were more manageable. Then, to maintain consistency throughout the text, we removed all punctuation marks and converted every word to lowercase. After this process, words like 'Haemorrhages', 'haemorrhages', and 'HAEMORRHAGES' were treated as identical. Next, we filtered out the common stop words such as 'the', 'is', 'in', and so on. These words are very frequent in language but do not carry much contextual significance.

Removing these words helped us focus on more meaningful content. Finally, we used WordNet for lemmatization, which reduced every word to its root or base form.

Searching Keywords: A systematic method was applied to extract key symptoms (keywords) from the tokens collected from user provided symptom description. For this step, a database was utilized which contains the most common symptoms typically mentioned by patients, such as 'fever', 'pyrexia', 'cough', 'pain', 'headache', etc. The tokens were compared directly with entries in the symptom database to extract keywords. Afterwards, these identified symptoms or keywords were matched against entries in the homeopathic medicines dataset. Using a comprehensive function, each text file within the dataset was searched to identify instances of the specified symptoms. During this search operation, relevant sentences that contained the symptoms were identified, along with the associated medicine names. The results of this search were then organized into a dataframe, which served as a structured format for further processing. This concise dataframe laid the foundation for subsequent NLP steps. The generated data frame includes details on various medicines along with symptom descriptions that go along with them. For instance, Table 2 provides a snapshot of this data frame when the user inputs 'fever' and 'cough' .

Table 2 Sample Data-points from the Dataframe for 2 symptoms: Fever and Cough. ⏎

Medicine	Symptom Description
Terebinth	Is recommended as a prophylactic in malarial and …
Apis mellifica	Intermittent fever; chill 3 p.m., with thirst, …
Mercurius biniodide	Diphtheritic and glandular affections of the left side; …
Phosphoric acid	This is Phosphoric acid in its intensest degree, …

Medicine	Symptom Description
Staphisagria	In fever; ravenous hunger for days before attack. …

Phase 2: Contextual Mapping With Statistical Analysis

Text Preprocessing for Dataframe: Preprocessing of the newly produced dataframe was done in the same way as that of the user input. Text in the Symptom Description column of the dataframe was normalized by removing the stop words, lemmatization, punctuations and converting the whole text into lowercase. Tokenization was done to split the normalized text into single words.

Vector Representation: The preprocessed texts of the dataframe, as well as the user-input, were converted into numerical forms so that ML algorithms can be applied on them. We employed four alternative methods: Word2Vec, TF-IDF, BERT, and GloVe. From the Gensim library, Word2Vec's CBOW architecture was used to transform each word into a 100-dimensional vector that captured the semantic connections based on the word's context. Sklearn's TF-IDF vectorizer was used to calculate numerical scores that reflect the notability of words in the texts when considering their relevance across the entire data frame and also the input. After testing several hyperparameter configurations to observe their impact on model performance, we selected the optimal values that best balanced computational cost and model effectiveness. This experimental approach provided a better understanding of each parameter's influence on the final outcomes. Table 3 shows their parameters and values for Word2Vec and TF-IDF techniques. From Hugging Face's Transformers library, we utilized the bert-base-uncased model that condensed the semantic content of the texts into a vector of numbers. GloVe embeddings were used to convert words into fixed-length vectors, which are then averaged to set up a single vector representing the entire sentence's semantic meaning. We used the

glove.6B.300d.txt file which was trained on a dataset of 6 billion words represented by 300-dimensional vectors.

Table 3 Parameters and Values for Word2Vec and TF-IDF Vectorization Techniques. ↵

Technique	Parameters	Values
Word2Vec	vector_size	100
	window	5
	min_count	1
	workers	4
TF-IDF	ngram_range	(1, 1)
	token_pattern	r"(?u)\b\w\w+\b"
	norm	l2

Recommending Medications based on Similarity Analysis: The cosine similarity metric was applied to assess how similar the two documents were (every single symptom description in the dataframe and the user-provided patient's symptom description). It helps quantify how closely the symptoms described by a user match the known symptoms associated with different substances. The cosine of the angle formed by text vectors in a multidimensional space is measured by this metric. A cosine value which is approaching 1 signifies a smaller angle and a higher degree of similarity. Each user input was compared against all data-points in the dataset, which included symptoms associated with specific medicines. After computing similarity, the two most similar data-points or medicines were chosen as the final output, same way as that of the dataframe.

Results

To assess the effectiveness of each vectorization technique, we tested 17 symptom descriptions which were taken as user inputs. The outcomes of the test are shown in Table 4. Each one represents a distinct description of

symptoms, derived from medicine descriptions in the dataset. We evaluated the predictions by referencing our dataset.

Table 4 Predicted medicines for each of the four vectorization techniques, based on user-provided symptom descriptions. ⏎

User-Provided Symptoms Description	Original Medicine	Vectorization Techniques	Recommended Medicines and Their Cosine Similarity Scores
The patient experiences a cough that only occurs during the daytime and after dinner, exacerbated by consuming meat and exposure to tobacco smoke.	Staphisagria	Word2Vec	Ignatia (43.91%), Staphisagria (43.69%)
		TF-IDF	Staphisagria (39.96%), Lachesis (11.78%)
		BERT	Antimonium tartaricum (81.06%), Coffea cruda (80.67%)
		GloVe	Carbo vegetabilis (99.35%), Sticta pulmonaria (99.28%)

User-Provided Symptoms Description	Original Medicine	Vectorization Techniques	Recommended Medicines and Their Cosine Similarity Scores
The patient experiences high fever with chills. His fever gets worse when he drinks coffee and also increases when he has a sour stomach. He has a loose cough in the morning and a tight, dry cough in the evening. Exposure to sunshine triggers his fever.	Nux vomica	Word2Vec	Rhus toxicodendron (63.15%), Nux vomica (61.57%)
		TF-IDF	Nux vomica (32.18%), Ignatia (17.74%)
		BERT	Chamomilla matricaria (89.13%), Eupatorium perfoliatum (87.38%)
		GloVe	Cina (99.55%), Sambucus nigra (99.50%)
Nosebleeds occur when she coughs while she is asleep, protruding as a black, clotted string of blood. The tonsils are swollen and dark red, and swallowing hurts.	Mercurius biniodide	Word2Vec	Chamomilla matricaria (47.77%), Mercurius biniodide (47.22%)

User-Provided Symptoms Description	Original Medicine	Vectorization Techniques	Recommended Medicines and Their Cosine Similarity Scores
		TF-IDF	Mercurius biniodide (31.30%), Millefolium (12.17%)
		BERT	Mercurius biniodide (88.81%), Allium cepa (84.08%)
		GloVe	Hepar sulphuris calcareum (99.15%), Chamomilla matricaria (98.94%)
My fever and cough get worse when I hear any noise, like a cough, sneeze, a cry, or even the rustling of a newspaper.	Borax veneta	Word2Vec	Sticta pulmonaria (65.99%), Borax veneta (60.40%)
		TF-IDF	Borax veneta (44.06%), Chamomilla matricaria (14.59%)

User-Provided Symptoms Description	Original Medicine	Vectorization Techniques	Recommended Medicines and Their Cosine Similarity Scores
		BERT	Borax veneta (80.27%), Chamomilla matricaria (79.90%)
		GloVe	Borax veneta (99.10%), Sambucus nigra (99.07%)
The patient feels weak in the chest when speaking or coughing, and their cough generates foul, purulent expectancy. There's severe physical weariness and ache in the nape of the neck. The patient also gets rumbling along with white, watery, painless diarrhea.	Phosphoric acid	Word2Vec	Phosphoric acid (42.22%), Hepar sulphuris calcareum (37.80%)
		TF-IDF	Phosphoric acid (27.45%), Sanguinaria canadensis (14.99%)
		BERT	Chamomilla matricaria (89.24%), Psorinum (88.71%)
		GloVe	Chamomilla matricaria (99.58%), Sticta pulmonaria (99.54%)

User-Provided Symptoms Description	Original Medicine	Vectorization Techniques	Recommended Medicines and Their Cosine Similarity Scores
I'm coughing up blood, and the cough is really bad. It also secretes copious amounts of viscous mucus.	Trillium pendulum	Word2Vec	Ipecacuanha (55.42%), Sticta pulmonaria (48.67%)
		TF-IDF	Trillium pendulum (17.32%), Millefolium (16.77%)
		BERT	Acetic acid (75.45%), Kali sulphuricum (74.52%)
		GloVe	Kali sulphuricum (98.64%), Trillium pendulum (98.38%)
I have hay fever. Violent sneezing is happening upon getting out of bed, and handling peaches triggers this reaction. The cough is so intense that it forces me to clutch my throat.	Allium cepa	Word2Vec	Ignatia (51.14%), Allium cepa (49.50%)
		TF-IDF	Allium cepa (42.03%), Lachesis (85.94%)
		BERT	Cina (75.45%), Staphisagria (83.82%)

User-Provided Symptoms Description	Original Medicine	Vectorization Techniques	Recommended Medicines and Their Cosine Similarity Scores
		GloVe	Eupatorium perfoliatum (99.44%), Cina (99.43%)
Belladonna was given repeatedly to treat the cough, but the cough only became worse. The fever is septic, got worse; pyrogenium was given, but nothing improved.	Stramonium	Word2Vec	Sanguinaria canadensis (55.70%), Chamomilla matricaria (54.82%)
		TF-IDF	Stramonium (28.21%), Chamomilla matricaria (15.45%)
		BERT	Kali carbonicum (86.74%), Arsenicum album (86.66%)
		GloVe	Cina (99.61%), Ferrum metallicum or aceticum (99.55%)
Symptoms worsen in the evening and upon going to bed. The cough is dry, hoarse, suffocating and loud. It is hard to breathe.	Aconitum napellus	Word2Vec	Allium cepa (44.79%), Aconitum napellus (42.50%)

User-Provided Symptoms Description	Original Medicine	Vectorization Techniques	Recommended Medicines and Their Cosine Similarity Scores
It is ringing and whistling during exhalation. Symptoms increase when rising from bed.		TF-IDF	Aconitum napellus (24.63%), Allium cepa (17.18%)
		BERT	Sambucus nigra (84.18%), Allium cepa (83.79%)
		GloVe	Nux vomica (99.67%), Hyoscyamus niger (99.48%)
Patient's skin feels very hot and dry with the fever, and has red spots on her left cheek. At night, she experiences drenching sweats that make the fever worse. Her breath has a hissing sound, and she coughs with every inhalation. She also has diabetes and is experiencing intense, insatiable thirst.	Acetic acid	Word2Vec	Acetic acid (81.44%), Aconitum napellus (56.72%)
		TF-IDF	Acetic acid (64.22%), Chamomilla matricaria (17.49%)
		BERT	Acetic acid (89.88%), Chamomilla matricaria (89.82%)

User-Provided Symptoms Description	Original Medicine	Vectorization Techniques	Recommended Medicines and Their Cosine Similarity Scores
		GloVe	Arsenicum album (99.53%), Ignatia (99.53%)
The patient has a headache and feels throbbing in the carotid arteries. Cold air worsens both the fever and cough, so the body needs to be kept covered at all times to prevent worsening of symptoms. The cough feels like mucus should come up, but it doesn't.	Hepar sulphuris calcareum	Word2Vec	Hepar sulphuris calcareum (68.48%), Rhus toxicodendron (57.02%)
		TF-IDF	Hepar sulphuris calcareum (26.67%), Pecacuanha (12.97%)
		BERT	Arsenicum album (88.73%), Coffea cruda (88.25%)
		GloVe	Carbo vegetabilis (99.74%), Ferrum metallicum or aceticum (99.73%)

User-Provided Symptoms Description	Original Medicine	Vectorization Techniques	Recommended Medicines and Their Cosine Similarity Scores
Around 3 p.m., an intermittent fever with chills always occurs along with thirst. Exposure to cold water and open air exacerbates the fever. Coughing is uncomfortable, and it gets worse when I walk or move about in addition to when I sit up straight.	Apis mellifica	Word2Vec	Apis mellifica (69.21%), Eupatorium perfoliatum (58.44%)
		TF-IDF	Apis mellifica (42.59%), Rhus toxicodendron (20.09%)
		BERT	Apis mellifica (88.03%), Chamomilla matricaria (87.57%)
		GloVe	Ignatia (99.77%), Aconitum napellus (99.74%)
The symptoms are worse at night. There is a loose cough with greenish or yellow mucus discharges and a rattling sound. There is rheumatic pain which shifts from joint to joint.	Kali sulphuricum	Word2Vec	Kali sulphuricum (69.99%), Antimonium crudum (49.57%)
		TF-IDF	Kali sulphuricum (60.21%), Lycopodium (15.20%)

User-Provided Symptoms Description	Original Medicine	Vectorization Techniques	Recommended Medicines and Their Cosine Similarity Scores
		BERT	Kali sulphuricum (88.94%), Mercurius biniodide (87.45%)
		GloVe	Nux vomica (99.46%), Trillium pendulum (99.45%)
The kidney, bladder, and urethra are all giving the patient unbearable burning and pulling sensations. They also feel a tingling sensation around the anus and a dry, hacking cough. The patient smells bad when they breathe.	Terebinth	Word2Vec	Sticta pulmonaria (46.25%), Terebinth (41.28%)
		TF-IDF	Terebinth (17.08%), Sanguinaria canadensis (14.72%)
		BERT	Mercurius biniodide (85.35%), Kali carbonicum (84.78%)

User-Provided Symptoms Description	Original Medicine	Vectorization Techniques	Recommended Medicines and Their Cosine Similarity Scores
		GloVe	Aconitum napellus (99.52%), Mercurius biniodide (99.51%)
Patient has a dry, spasmodic cough with a terrible splitting headache. The cough gets worse when they take deep breaths and also after eating or drinking. Lips and tongue are dry and cracked. There is tearing pain in joints that gets worse at night and when moving or coughing, but it seems to ease when she lies on the painful side. Urine is dark and little in amount, and stool is hard, dry.	Bryonia alba	Word2Vec	Bryonia alba (98.15%), Sticta pulmonaria (97.42%)
		TF-IDF	Bryonia alba (35.53%), Medorrhinum (16.11%)
		BERT	Calcarea ostrearum (90.13%), Natrum muriaticum (90.13%)
		GloVe	Mercurius biniodide (99.81%), Ferrum metallicum or aceticum (99.81%)

User-Provided Symptoms Description	Original Medicine	Vectorization Techniques	Recommended Medicines and Their Cosine Similarity Scores
Patient is burning up with high fever; face is red; bloodshot eyes; and pupils are dilated. He has a throbbing headache. We can see veins in the neck pulsing. He is sensitive to being touched, hearing loud sounds, seeing bright lights. Lying down and uncovering his body makes the symptoms worse. Symptoms come on suddenly, stay intense for a while, and then fade quickly. Patient is sleepy but can't fall asleep. Even when drifting off, he startles or jerks awake. He is hallucinating imaginary things.	Belladonna	Word2Vec	Belladonna (92.77%), Nux vomica (92.24%)
		TF-IDF	Belladonna (26.69%), Hepar sulphuris calcareum (13.44%)
		BERT	Ferrum metallicum or aceticum (89.73%), Phosphoric acid (89.25%)
		GloVe	Eupatorium perfoliatum (99.82%), Lachesis (99.82%)
About nine in the morning, I have chills and bone ache. Drinking induces vomiting and worsens the chills. I'm also quite thirsty. Coughing causes my chest to hurt, and I also get discomfort in my chest while walking, turning,	Eupatorium perfoliatum	Word2Vec	Eupatorium perfoliatum (55.53%), Cina (37.00%)

User-Provided Symptoms Description	Original Medicine	Vectorization Techniques	Recommended Medicines and Their Cosine Similarity Scores
being touched, or when the weather changes. My eyeballs are also really painfully sore.		TF-IDF	Eupatorium perfoliatum (44.12%), Ferrum metallicum or aceticum (20.86%)
		BERT	Chamomilla matricaria (86.96%), Eupatorium perfoliatum (83.45%)
		GloVe	Chamomilla matricaria (99.73%), Eupatorium perfoliatum (99.71%)

Prediction Accuracy Analysis

The evaluation of the vectorization techniques revealed significant variation in their effectiveness in predicting the correct homeopathic remedy based on symptom descriptions. Table 5 shows the accuracy of each technique using the cosine similarity metric.

Table 5 Proportion of Correct Medicine Predictions. ⏎

Vectorization Technique	Accuracy
Word2Vec	88%
TF-IDF	100%

Vectorization Technique	Accuracy
BERT	35%
GloVe	18%

It can be observed that TF-IDF shows superior results compared to the other approaches in terms of correct predictions with a perfect accuracy rate of 100%. Word2Vec had an accuracy of 88%. This model provided reasonable similarity scores for the correct remedies but often ranked them below other remedies. Similarity scores are numerical measures that indicate how closely the symptom descriptions provided by the user align with the representations of the homeopathic remedies. In the case of Nux Vomica, Word2Vec ranked "rhus toxicodendron" higher than the correct remedy, " Nux vomica". This suggests Word2Vec's reliance on local context might be insufficient for capturing the nuanced relationships between symptoms and remedies.

Confusion Matrix (Word2Vec + cosine similarity)

(a)

Confusion Matrix (TF-IDF + cosine similarity)

(b)

Confusion Matrix (BERT + cosine similarity)

(c)

(d)
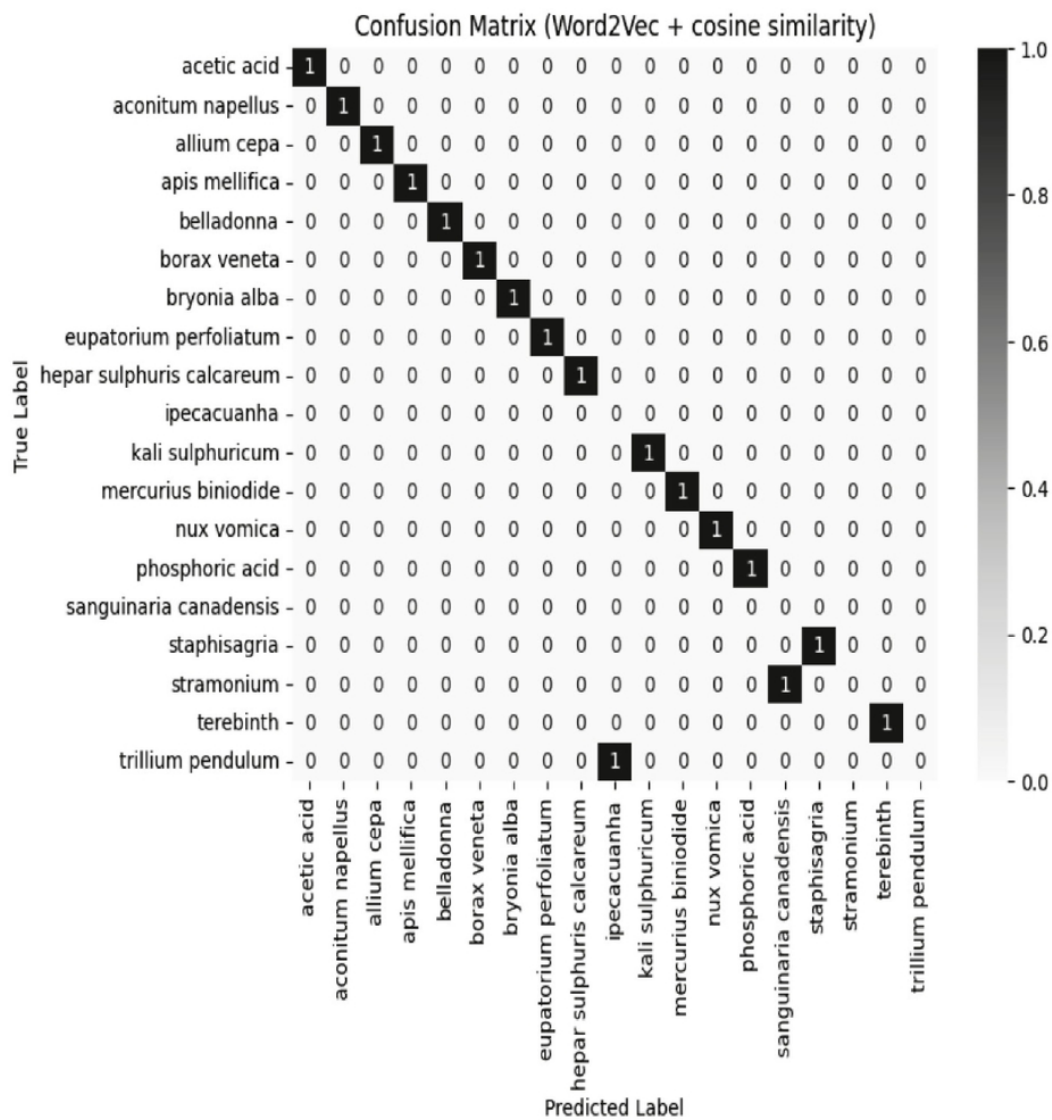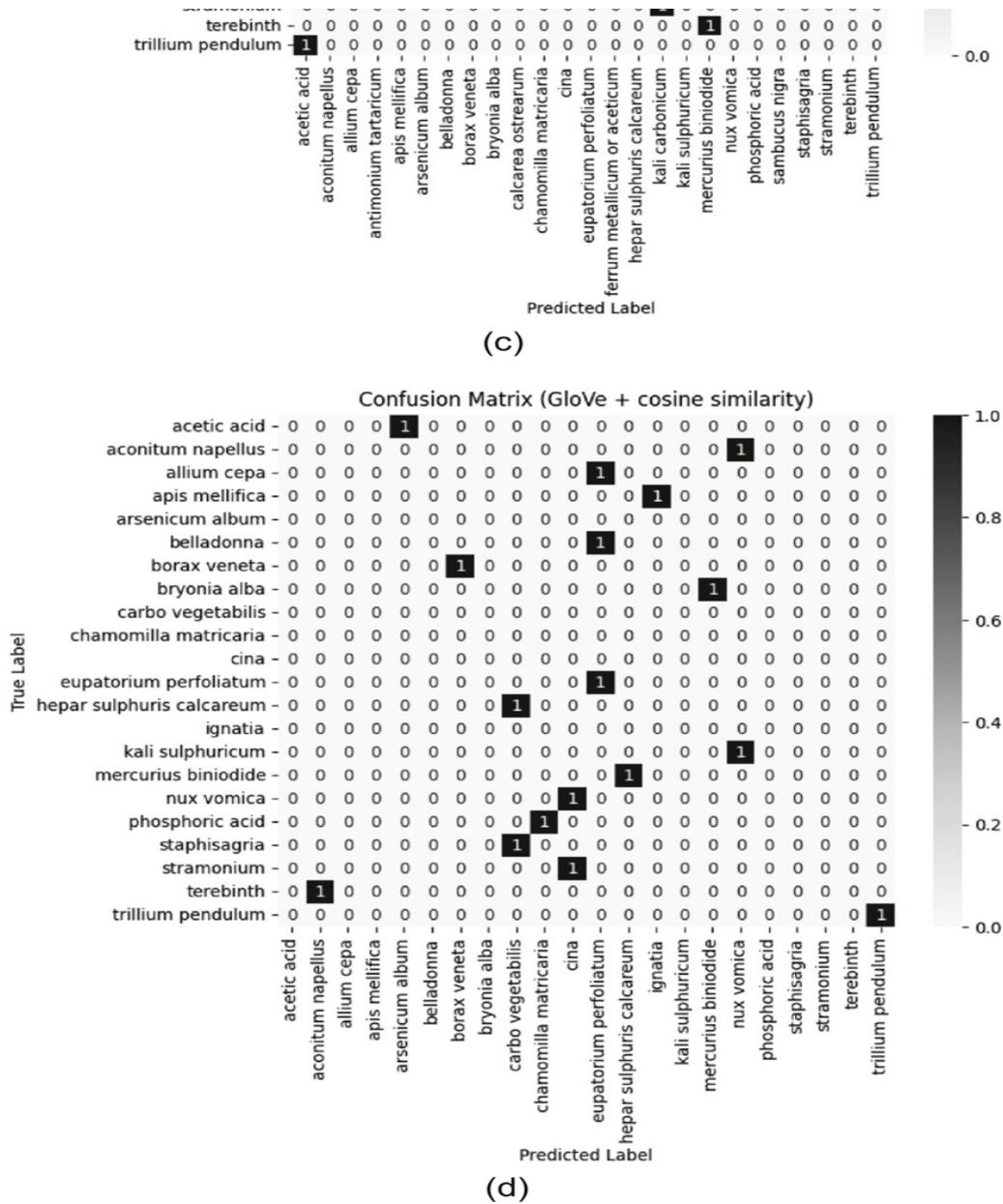
Fig. 2 Confusion matrices for (a) Word2Vec, (b) TF-IDF, (c) BERT, (d) GloVe embedding techniques.

On the other hand, TF-IDF achieved the highest number of correct predictions, with all instances identified correctly. In spite of being a simple bag-of-words model, TF-IDF appears well-suited for this particular dataset. This model's ability to highlight unique keywords in each user-provided symptom description played a critical role in its high accuracy. It can be

observed that Word2Vec produces higher similarity scores than TF-IDF. Yet, TF-IDF gives more accurate medicine suggestions. This is because Word2Vec focuses on semantic relationships which can lead to irrelevant matches. Whereas, TF-IDF prioritizes terms specific to the symptoms. So it results in more relevant recommendations. Thus, TF-IDF performs better in suggesting the right medicines despite giving lower similarity scores than Word2Vec.

BERT achieved 35% accuracy, while GloVe, despite its ability to capture global co-occurrence patterns, only correctly predicted the remedy in 18% of cases, making it the least effective model for this task. Although BERT is known for its strong contextual understanding and GloVe excels in capturing global co-occurrence statistics, their results indicate potential challenges in capturing the specific language nuances of homeopathic symptom descriptions within this dataset.

Confusion Matrix Analysis

Figure 2 presents the confusion matrices for each vectorization method when used in conjunction with the cosine similarity technique to measure contextual similarity. The evaluation was conducted by using a test set of 17 symptom descriptions of patients provided by users. which were evaluated to predict the appropriate homeopathic remedy. Word2Vec was able to identify the correct remedy in 15 out of the 17 patient descriptions. Thus this method demonstrated a relatively high accuracy. However, TF-IDF outperformed all other methods by correctly identifying the remedy in all 17 cases and achieved the highest accuracy rate of 100%. On the other hand, BERT showed a lower performance. It correctly predicted the remedy in only 6 out of the 17 cases. This suggests that while BERT has strong contextual understanding, it may face challenges in this specific task. GloVe, although known for its ability to capture word co-occurrence

patterns, proved to be the least effective in this scenario. This method accurately predicted the remedy in only 3 out of the 17 cases.

These results clearly indicate that TF-IDF was the most effective method overall. It surpassed the other vectorization techniques in terms of the total number of correct predictions. In contrast, GloVe was the least effective model in this test. This means there are challenges of applying certain pre-trained models to the nuances of symptom description and remedy prediction in the homeopathic context.

Computational Cost Analysis

Each vectorization method we used has a distinct computational profile. TF-IDF is computationally lightweight and fast, as it does not require deep neural networks. Word2Vec requires some initial training but is efficient at inference time because it generates relatively low-dimensional embeddings. Its architecture is simple. On the other hand, BERT is computationally expensive due to its transformer-based architecture. GloVe embeddings are pre-trained which eliminates training time per query. But they are memory-intensive due to their fixed size. The glove.6B.300d. txt file is 1.04 GB. The results also show that BERT and GloVe embeddings are inaccurate for most cases.

Overall, TF-IDF and Word2Vec are efficient options for real-time medicine recommendations due to their lower computational requirements. The simplicity of TF-IDF does not compromise accuracy in this particular dataset. Word2Vec achieves a good balance between resource efficiency and accuracy. And by tuning its hyperparameters, we enhanced the model's accuracy while keeping computational costs low.

Discussion

The user-provided symptom descriptions in this study were displayed as free-form text. In contrast to conventional form-based systems, this provides a more intuitive and natural way of input. With this method, people can describe their symptoms in their own words without being constrained by strict formats or predefined fields. Because free-form text closely resembles how patients normally describe their symptoms during medical consultations in real-life scenarios, its flexibility significantly improves the user experience overall. One of the main advantages of our suggested system is its use of natural language input. It allows for the various ways that people communicate their health issues.

Our evaluation results show that TF-IDF surpassed all other techniques in terms of accurate medicine suggestion. It achieved a 100% accuracy score. It is a straightforward vectorization method. For real-time applications that need quick as well as correct predictions, TF-IDF is a great option even though it is a very simple framework. The system can process user input rapidly due to its computational efficiency and low resource requirements. Because of that, our system is perfect for settings especially for those which require instant feedback, for example, healthcare applications where users want receiving timely guidance.

Furthermore, our proposed system resolves the shortcomings that can be seen in the earlier research. For instance, Priyadarshi and Saha (2020) used web scraping techniques to collect data for their study. Web scraping needs extracting information from numerous web pages which can be a time-consuming process, particularly when working with large volumes of data. There are other things as well, like slow internet speeds, network outages. Additionally, data gathered through web scraping is frequently erroneous because of the inherently unreliable nature of web-based sources. Additionally, web pages may change often which results in outdated

information or broken links. This makes the scraping process even more difficult.

On the other hand, our suggested system employs a more reliable strategy. It is by drawing on established and reputable sources. We used books authored by wellknown homeopathic specialists like Allen and Nash. These resources are widely accepted and have been used for many years in the homeopathic community. Specialists refer to them to offer precise and validated advice. By depending on such reliable sources, our system greatly lowers the possibility of errors and inconsistencies which result from web scraping frequently.

Applications and Future Potentials

This system has the potential to be further developed into a chatbot, which we plan to work on in the future. Such a tool will be beneficial for individuals, especially in rural areas where access to a homeopathic consultant can be difficult. Allopathic medicines are effective, but they may sometimes lead to adverse reactions or long-term side effects. Unlike those, homeopathic remedies are made from natural substances in highly diluted forms which minimizes side effects. This makes homeopathic medicines safer. Additionally, due to homeopathic medicines being more affordable, it will significantly benefit economically disadvantaged communities. In the long term, caregivers could be assigned to specific regions to assist those who are unable to use the system independently to ensure broader accessibility. This system also holds great potential as a decision-support tool for homeopathy consultants to assist them in prescribing medicines more efficiently to patients.

Limitations

The proposed system for homeopathy medicine prediction, despite being innovative, has several limitations. One of the primary concerns is its reliance on vectorization methods such as Word2Vec, TF-IDF, BERT, and Glove. They can analyze symptoms based on text similarity, but without fully understanding the underlying medical nuances. These techniques fail to capture the complexity and individuality that homeopathy demands. In this field, remedies are often prescribed based on precise personalized symptom patterns and the overall constitution of the patient.

The system's lack of comprehensive training data further compounds this issue. It could lead to biased or incomplete remedy suggestions, especially for rare or complex cases not well-represented in the dataset. TF-IDF performed exceptionally well in this study. But it does have drawbacks. It treats each text as a "bag of words" while ignoring the sequential context or semantic relationships between the terms. This limitation may affect its ability to understand nuanced descriptions where word order plays a role.

Another major limitation is the system's generalization and interpretability challenges. The prediction models act as black boxes. It is because this system offers similarity scores without providing clinical justifications for the suggested remedies. This lack of transparency can undermine trust in the system, as practitioners and patients alike need to understand the reasoning behind a recommended treatment. Furthermore, the system cannot account for dynamic symptoms, emotional factors, or environmental influences, which are crucial in homeopathic diagnosis and treatment.

These shortcomings highlight the need for ongoing human oversight. This proves the importance of consulting a qualified homeopathic practitioner to verify and personalize the final treatment plan. For the evaluation of our models, we relied on books that provide a limited scope of

medical knowledge. Thus, while the system can assist in the initial stages of remedy identification, it cannot replace the clinical judgment and expertise required in homeopathic practice.

Conclusion

Our study shows the feasibility of utilizing NLP to create a new method for choosing personalized homeopathic remedies based on symptoms reported by patients. It uses an extensively curated dataset derived from reputable homeopathic references. The evaluation results depict that out of all the vectorization techniques assessed, TF-IDF produces the most accurate predictions when paired with the Cosine Similarity metric. Observing the test results, it can be concluded that TFIDF is an effective approach for this specific task despite its simplicity. These findings suggest that using natural language processing can make homeopathic remedy recommendations more accurate and efficient.

In future developments, the combination of TF-IDF with other advanced vectorization methods, such as Word2Vec, can be explored in order to create meta-embeddings. This has the potential to increase the precision of symptom representations. Also, the system's upgrade to conversational chatbots may open the door to a more adaptable and user-friendly solution, as it will improve the system's interactivity. Overall, our proposed system can be upgraded to strengthen the connection between patients and homeopathic professionals.

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