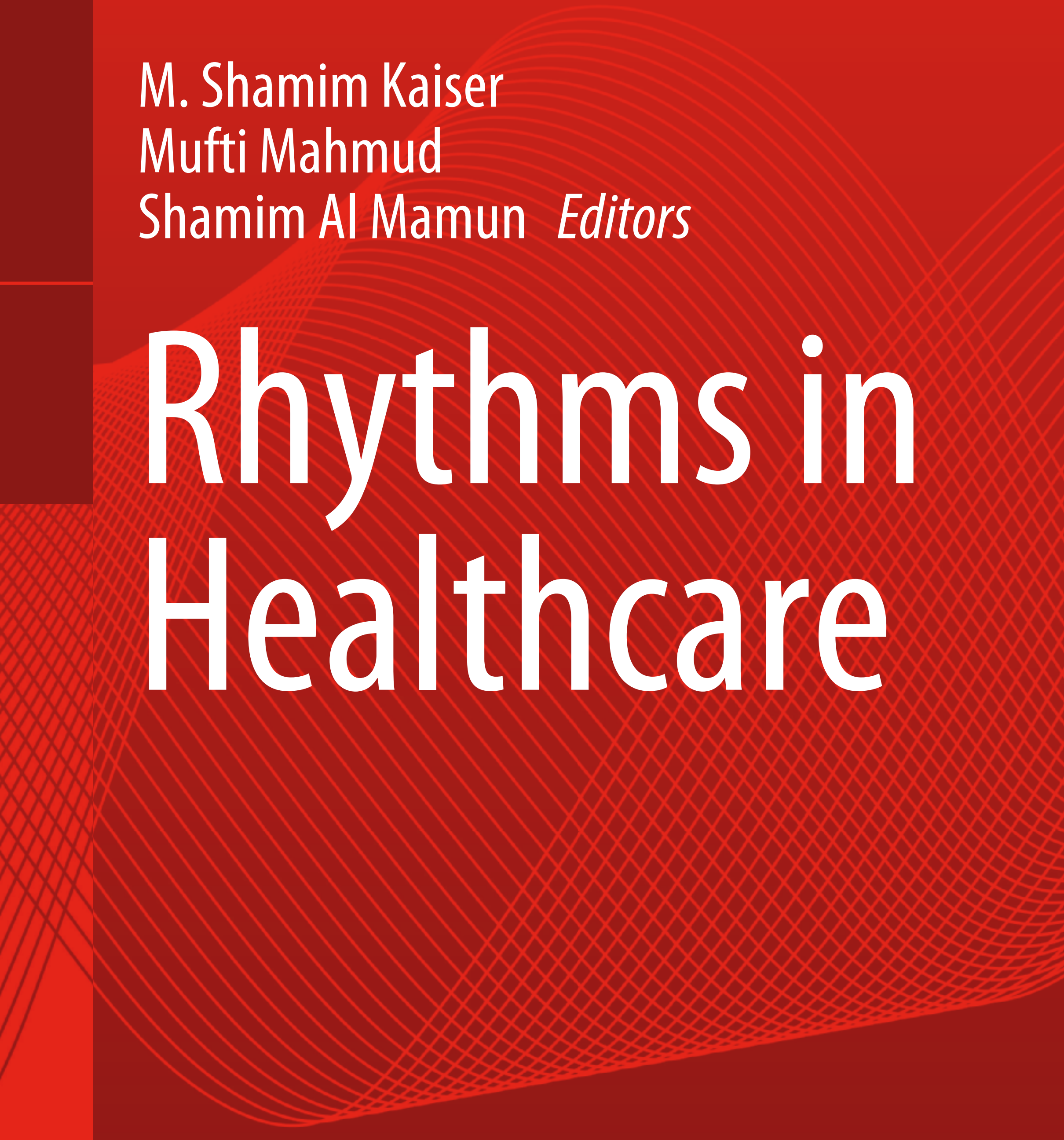
Studies in Rhythm Engineering

M. Shamim Kaiser
Mufti Mahmud
Shamim Al Mamun *Editors*

Rhythms in Healthcare



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Studies in Rhythm Engineering

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M. Shamim Kaiser · Mufti Mahmud ·
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Editors

Rhythms in Healthcare

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Preface

Modern sensing technology enables the acquisition of rhythmic data from the human body and daily activities using a variety of sensors. Technological advancements and a better understanding of machine learning algorithms are catching up with medical practice and research in the field of digital healthcare. The extent to which digital healthcare is actually used is determined by a variety of factors, including the types of diseases and functions that patients suffer from, as well as their age and gender. We can improve the effectiveness of present treatments and the prognosis of patients by adopting new digital technology. This could be cutting-edge technology or an application built on a solid understanding of the basic physiology and anatomy of the human body. Anomaly rhythms can be used to predict any disease-related form using core body temperature, gene expression, and hormone secretion measurements. Sensors embedded in smartphones and other devices can now collect data on physical activity, sleep, and heart rate. As sensors improve, the volume, quality, and variety of data that can be conveniently collected in daily life will increase. As a result, several components of the circadian rhythm can be quantified and analysed.

Implantable devices with a biomedical function (pacemakers, visual prostheses, cochlear implants, neural recording microsystems, and deep brain/sensory stimulators), wearable biosensors (tattoos, gloves, cloths, watches, bracelets, rings, and gloves, as well as glasses and helmets, coats, underwear, and pants), foot and body sensory control devices, wearable patches as well as pulse wave monitoring devices, and other invasive monitoring devices have garnered considerable attention, primarily from the healthcare industry. These devices extract physical signals such as heart rate, blood pressure, skin temperature, respiratory rate, and body motion to extract real-time clinically relevant information from physiological signals. This information is sufficient for determining health status and even for making preliminary medical diagnoses. In the last decade, health informatics has made significant conceptual and methodological improvements. These innovations are explained and how the healthcare system can benefit from them. It synthesizes research from prominent academic and industrial groups in this field, together with computational tools and approaches. It includes in-depth coverage of the most recent conceptual and methodological developments. This volume collates 10 chapters representing the state of the art of biological sensing, intelligent data analytics, and, in many cases, their relationship with biological rhythms. These chapters are authored by experts representing eight countries from a wide geographical location.

In Chap. 1 titled, ‘Is Biological Rhythm Associated with the Mortality of COVID-19?’, Allahyari et al. examined the factors of the COVID-19 death rate in people without an underlying condition who are not taking medication in this study. They analysed data collected from people over the age of 18 who were free of any underlying disease using Artificial Neural Network (ANN). Finally, the clinical, pulmonary symptom, sociodemographic, and biological rhythm parameters influencing COVID-19 death rates were established. The authors concluded that, given the critical nature of biological rhythms and the insignificant relationship between contact with patients and COVID-19 mortality, psychological interventions, exercise programs, and social activities should be implemented on an individual and social level to reduce COVID-19 mortality and severity.

Chapter 2, titled ‘Deep Learning in Biomedical Devices: Perspectives, Applications and Challenges’ by Nova et al., discussed the major components of deep learning in biomedical devices and how they contribute to the analytics of data generated by a variety of sources, including photos, sensors, and signals. The authors holistically analysed the advantages and disadvantages of applications of deep learning in biomedical devices. They also discussed how to integrate technologies and improve decision-making with maximum precision, as well as how to upgrade healthcare components facilitating low-cost investments towards improved service quality and a changing lifestyle. Finally, some potential study directions are highlighted, together with their associated scopes and obstacles.

In Chap. 3, titled ‘Effect of 3D-Multiple Object Tracking Training on Manual Dexterity in Elderly Adults with Dementia and Mild Cognitive Impairment’, Santana-Vargas et al. demonstrated the transfer of cognitive training utilizing the 3-Dimensional Multiple Object Tracking (3D-MOT) technique to two manual dexterity tests administered to two patient groups with moderate cognitive impairment and dementia. Additionally, the minimal number of sessions required to generate a substantial improvement in test scores was found under training settings with a constant and fixed length cognitive stress.

Chapter 4, titled ‘Rhythmic Pattern of EEG for Identifying Schizophrenia’, by Saleh et al. uses electroencephalogram (EEG) signals to identify Schizophrenia (SZ). Using different patterns and variables related to dynamic functional and effective connectivity, they classified the brain connectomes of SZ patients using different convolutional neural networks (CNN) architectures including an extension of dynamic brain connection analysis using recurrent neural networks (RNN). The proposed approach demonstrated an accuracy of 94.12% in detecting SZ and indicated that partial coherence CNN performs similar to support vector machine (SVM) for classifying SZ and control subjects’ EEG connectivity across all feature sets.

In Chap. 5, titled ‘Prior Prediction and Management of Autism in Child Through Behavioral Analysis Using Machine Learning Approach’, Rahman et al. used machine learning (ML) algorithms, such as Decision Trees (DT), Multinomial Naive Bayes (MNB), Random Forests (RF), SVMs, Adaboosts, Multilayer Perceptron

(MLP), K-Nearest Neighbour (KNN), and Logistic Regression (LR), to predict autistic behaviour. They proposed an autism management system based on knowledge fusion of features obtained through mobile apps used by parents to track their children's development. On a dataset of 500 children using a weighted voting strategy, they obtained 97% accuracy outperforming other state-of-the-art classifiers.

Chapter 6 titled, 'DNN and LiDAR Sensor Based Crowd Avoidance Method for Nurse-Following Robot in Healthcare', by Islam et al. details a novel deep neural network (DNN)-based method to track the target individual in the real-world situations. They have validated the method using a robot that can track a target nurse using a colour histogram matching technique and can then follow the target nurse around the room. Using omnidirectional camera and DNN-based posture estimator, they demonstrated that if the nurse is obstructed by pedestrians or a large crowd, the robot can avoid those pedestrians or the large crowd and follow the target nurse once more with minimal effort.

In Chap. 7, titled, 'Investigation on Heart Attack Prediction Based on the Different Machine Learning Approaches', Bokshi et al. reported the outcome of an exploratory study of multiple ML methods such as SVM, LR, RF, NB, DT, and KNN in determining the most effective ones in predicting heart attack using the Cleveland dataset. Along with interpolation-based rectification of missing values, a hyperparameter tuned ANN was also used for the prediction job. The methods were compared and validated using precision, sensitivity, and specificity.

Chapter 8 titled, 'Wearable Devices for Monitoring Vital Rhythm and Earlier Disease Diagnosis of Treatment', by Sultana et al. investigated how wearable vital sign sensing smart sensors can be utilized to diagnose diseases by monitoring those signs. The study found that adopting the appropriate technological solutions could improve early disease identification and control using sensors for continuous vital sign monitoring.

In Chap. 9, titled 'Post-quantum Signature Scheme to Secure Medical Data', Sultana et al. proposed a signature scheme based on Merkle tree and two finalists of SHA-3 (Keccak and Skein) for blockchain technology to secure medical data from quantum attacks. Thanks to the combination of the Merkle tree, Skein and Keccak algorithms, the proposed solution can be readily incorporated into blockchain with improved overall performance that would give a strong security against the quantum threats and fast key creation with authentication process requiring less memory.

Finally, Chap. 10, titled 'Medical Image Analysis using Machine Learning and Deep Learning: A Comprehensive Review', by Nahar et al. provides a relatively short overview of the latest ML and DL approaches for detecting four of the most popular types of brain diseases, including Tuberculosis including lung cancer, pneumonia, and COVID-19.

Focusing on the various aspects of the most recent developments in healthcare domain and approaches for determining health status, the chapters included in this volume are aimed to serve as reference for researchers and students working in the field of health-informatics, health-sciences, and applied computer science.

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Dr. Mahmud Mufti is Senior Lecturer of Computing at the Nottingham Trent University, UK. He received Ph.D. degree in Information Engineering from University of Padova, Italy, in 2011. Recipient of the Marie-Curie postdoctoral fellowship, he served at various positions in the industry and academia in India, Bangladesh, Italy, Belgium, and the UK since 2003. Expert in computational intelligence, data analysis, and big data technologies, Dr. Mahmud has published over 80 peer-reviewed articles and papers in leading journal and conferences. Dr. Mahmud serves as Associate Editor to the cognitive computation, IEEE access, big data analytics, and brain informatics journals. Dr. Mahmud is Senior Member of IEEE and ACM, Professional Member of the British Computer Society, and Fellow of the higher education academy, UK. During the year 2020–2021, he is serving as Vice Chair of the

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Mamun Shamim Al received B.Sc. (Hons.) and M.Sc. (Engg.) degrees in Computer Science and Engineering from Jahangirnagar University (JU) and Bangladesh University of Engineering and Technology (BUET), respectively. He also served Head of the Department of Computer Science in Daffodil International University during 2006–2008. He has received his Ph.D. degree in Graduate School of Science and Engineering, Saitama University, Japan, in 2018. His research interests include an autonomous system, artificial intelligence, and software engineering. He has authored more than 50 research papers in different peer-reviewed international journals and conferences and also worked as Technical Co-chair and Organizing Secretary in ICEEICT and TCCE conference in 2014, 2015, and 2020. Dr. Mamun is also Member of IEEE, USA, and IEICE, Japan.

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Chapter 1
Is Biological Rhythm Associated with the Mortality of COVID-19?

Elahe Allahyari, Seyed Javad Emadi Chashmi, Mufti Mahmud, and Ahmad Ahmadi

1 Introduction

Coronaviruses include a group of viruses that cause respiratory, enteric, hepatic and neurologic diseases. The symptoms of coronaviruses range from mild illness (e.g. common cold symptoms) to severe diseases (such as Middle East Respiratory Syndrome [MERS] and Severe Acute Respiratory Syndrome [SARS]) [1]. In December 2019, a novel variant of the virus, coronavirus disease 2019 (COVID-19), was identified in Wuhan, China [2, 3]. The disease is transmitted through human-to-human direct contact, and its main symptoms include a dry cough, fever and asthma [4–6]. Due to its rapid spread and consequent fatalities, the World Health Organization (WHO) named it a public health emergency and world pandemic in March 2020 [7, 8]. According to statistics published by the WHO (2020), at the beginning

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of the pandemic, Iran had the highest rate of death (total number of deaths) due to COVID-19 after Italy, Spain and China [9].

Nearly 2 years into the coronavirus pandemic in five genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), Gammacoronavirus (gammaCoV) and now the Omicron Variant, COVID-19 cases, hospitalizations and deaths are rising in the world and there is still no certain treatment for it [9]. According to the statistics, COVID-19 mortality rates are estimated to be 3.6 and 5.1% within and without China, respectively [9, 10]. This study also showed that the mortality rate would be even lower due to many patients without/with mild symptoms who have not been tested. Although the mentioned mortality rate seems to be low, it is significant due to the short period of the pandemic [11]. Driven by increasing death rates across the world, strict measures (e.g. home quarantining, spatial distancing, compulsory mask-wearing, banning of large social gatherings) have been taken to prevent the spread of the disease, leading to significant economic loss, global supply chain failure, disruption of travel plans, closures of educational institutions and workplaces, and uncertainty about the future. This has caused increased psychological distress globally [12–17]. Therefore, determining the underlying factors associated with the COVID-19 death rate is a health issue priority.

The high mortality rate of COVID-19 has led to extensive research to determine the factors related to this disease. Studies have shown that COVID-19 mortality rate and its severity are associated with clinical factors such as body temperature and saturation by pulse oximetry, underlying conditions; sociodemographic factors such as age and gender and finally psychological factors [18–20]. Most of these studies investigated the aspects related to the incidence and mortality of the COVID-19 in all patients (with or without underlying disease) which 37.3% of them are at least with one underlying disease [10]. These individuals have different functions compared with ordinary people in the face of the COVID-19 due to the effects of their underlying disease and the inhibitory or aggravating effect of the drugs they receive [18]. Hence, positive PCR people without underlying disease should be given special attention because they represent a better sample for most of the population. However, they have a small proportion of patients with severe conditions or death rates [10]. Since it is more important to control the COVID-19 and its social and economic issues focusing on the majority of the population; in this study, we aimed to investigate the effect of clinical factors, pulmonary complications, sociodemographic factors and biological rhythm on the COVID-19 death rate in the people without an underlying disease who are not receiving medication.

2 Methods

After obtaining the code of ethics (IR.BUMS.REC.1400.251) from Birjand University of Medical Sciences Ethics Committee, the data of all patients of South Khorasan Province who had PCR tests for diagnosis were extracted from the medical care monitoring centre. We limited our study to positive test responses and excluded participants who were either pregnant, younger than 18 years old, had an underlying disease or took medication. People who were still hospitalized at the time of the study or released with personal consent were excluded too.

2.1 Biological Rhythm

Biological rhythm is a hypothetical cycle in physical, emotional or intellectual well-being. These are self-sustaining oscillations of endogenous origin [21]. Bio refers to life, while rhythm is a flow with regular movement. Biological rhythms are reregulated by daylight. There are several types of biological rhythms, including circadian, ultradian, infradian, circaseptan, circalunar and circannual. Synchronized rhythms to waxing and waning of the moon that form a lunar month are called circalunar rhythms. Based on Wilhelm Fliess's theory, our daily lives are affected by biological rhythms with exactly a 23-day physical cycle and a 28-day emotional cycle. Fliess labelled the 23-day rhythm "male" and the 28-day rhythm "female", matching the menstrual cycle. The circalunar biorhythms can influence an individual's ability in various aspects, including mental, physical and emotional activity. These cycles start at birth and oscillate in a steady (sine wave) fashion during the life span. According to Wilhelm Fliess's theory, emotional and physical rhythm cycles are calculated for each day of life as follows in Equation [22]:

$$\text{Physical rhythms} = \sin(2\pi t/23) \tag{1}$$

$$\text{Emotional rhythms} = \sin(2\pi t/28) \tag{2}$$

where t indicates the number of days between birthday and the day for which we are calculating biological rhythm.

These cycles begin at birth and oscillate throughout life in a sine wave fashion. So, there are four points in each cycle including the following:

- Active point: the top of that cycle.
- Passive point: the bottom of that cycle.
- Critical point: where the cycle crosses the zero line from plus to minus.
- Zero point: where the cycle crosses the zero line from minus to plus.

Typically, cycles become synchronized with the solar rhythm of illumination and social Zeitgebers. The primary oscillators lie in the supraoptic chiasmata and ventromedial or lateral nuclei of the hypothalamus [23]. The compression of the working week, use of oral contraceptives and the elimination of seasonal changes in artificial environments disturb circaseptan, circalunar and circa-annual cycles, but there has been little research to examine functional outcomes. Psychological tension and cyclic body physiology changes with the menstrual rhythm are well recognized. Cyclic physiology causes a premenstrual increase of body mass, an increase of fasting blood sugar during menstruation, an increase of habitual daily activity in the postmenstrual phase, a decrease of resting systemic blood pressure at mid-cycle and an increase of resting respiratory minute volume in the luteal phase, adrenaline, lactate [24]. However, not everything in the body operates at the same frequency. There are processes, such as the secretion of insulin or the production of platelets, which follow different rhythms from the conventional 24-hour cycle. Also depending on the time of day-night cycle, our body and some of its organs are programmed to do very different things. In the morning, cortisol is released to wake us up while in the evening melatonin brings us to sleep.

We calculated each participant's emotional and physical rhythms point on admission day. Finally, patient status (death, recovered) were determined by input variables including age, gender, saturation by pulse oximetry (SPO_2), body temperature, duration of disease, duration of hospitalization, cigarette or drug addiction (no, yes), respiratory rate (5 10, 10 14, 14 18, 18 22, 22 28 and >28), direct contact with patients (no, yes), emotional biological rhythm (critical, passive, active, zero point), physical biological rhythm (critical, passive, active, zero point) and having respiratory distress.

2.2 Data Analysis

Machine learning methods are used to identify patterns between data in various sciences. Several mathematical models have been used to predict COVID-19 transmission dynamics, diagnosis and localization of infection, examination of topics and emotions in tweets, diagnosis of disease from chest X-ray images and healthy workplace [25–30]. In the present study, the ANN model simulates the function of the human brain by many information processing systems called neurons or nodes. They can recognize patterns and classify data [31]. Each ANN model would be characterized by its topology, learning algorithm and transfer function [32]. The topology of our study is Multi-layer Perceptron (MLP) as shown in Fig. 1.

MLP identifies complex and nonlinear relationships between the inputs and the output variables by a supervised learning algorithm that learns a function given in Eq. 3:

$$f : R^m \rightarrow R^n \tag{3}$$

where m is the number of dimensions for input and n is the number of dimensions for output. Difference between MLP and logistic regression is that between the input and the output layers in MLP can be one or more nonlinear layers, called hidden layers. We have only one hidden layer in the study. The leftmost and rightmost layers, known as the input and output layers, consist of neurons representing the input and output features, respectively. Each neuron in the hidden layer transforms

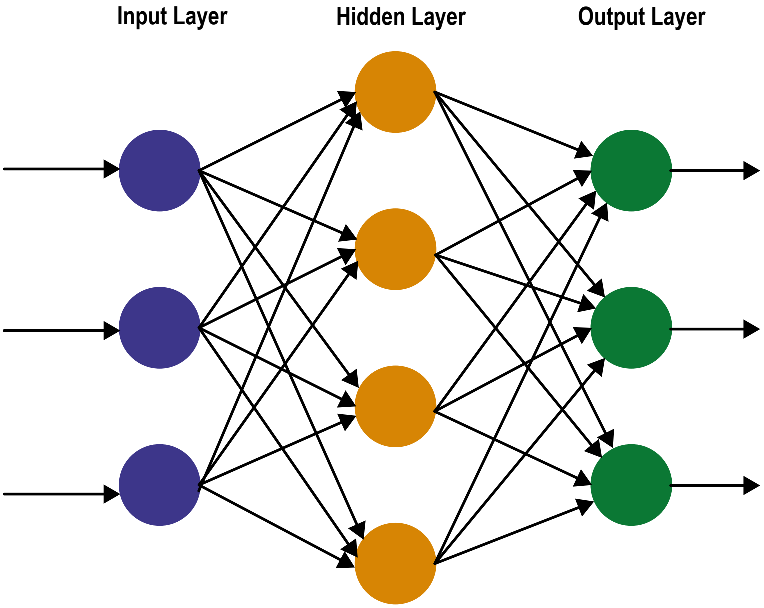

Fig. 1 Architecture of a multi-layer perceptron

the values from the input layer with a weighted linear summation, followed by a nonlinear activation function like the hyperbolic tangent or sigmoid functions. The output layer receives the values from the hidden layer and transforms them into output values with a weighted linear summation, followed by a nonlinear activation function like the linear, SoftMax, hyperbolic tangent or sigmoid functions. MLP requires tuning several hyperparameters such as the number of hidden neurons, layers and iterations. After determining the appropriate function, we examined the model's performance with 2–10 neurons in the hidden layer. We used the online supervised learning method to train 70% data, and the remaining 30% performed the model evaluation stage. The selected model was the one that achieved the best performance on the following evaluation metrics in the testing set [33].

Legends:

T-L: hyperbolic tangent and linear as the transfer function of the hidden and output layers, respectively;

T-So: hyperbolic tangent and softmax as the transfer function of the hidden and output layers, respectively;

T-T: hyperbolic tangent as both transfer functions of the hidden and output layers, respectively; **T-S**: hyperbolic tangent and sigmoid as the transfer function of the hidden and output layers, respectively;

S-L: sigmoid and linear as the transfer function of the hidden and output layers, respectively;

S-So: sigmoid and softmax as the transfer function of the hidden and output layers, respectively;
S-T: sigmoid as both transfer functions of the hidden and output layers, respectively;
S-S: sigmoid as both transfer functions of the hidden and output layers, respectively.

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

$$\text{Recall} = \frac{TP}{(TP + FN)}$$

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

$$F1\ \text{score} = \frac{2(\text{Recall} \times \text{Precision})}{(\text{Recall} + \text{Precision})}$$

where *TP*, *TN*, *FP* and *FN* indicate the True Positive, True Negative, False Positive and False Negative rates, respectively. Each training epoch was repeated three times, avoiding the effect of random assignment of weights and random correlations. Finally, the importance of the input variables was determined in the specification of the patient's status in the final model. All analyses were performed using the Statistical 100 Package for Social Sciences version 26 (SPSS Inc., Chicago, Illinois, USA).

3 Results

The information of 148 recovered and 145 dead subjects were assessed. The mean ages of participants was 56.75 17.22 and 53.77 18.43 years old in recovered and deceased persons, respectively. We first randomly divided data into two parts which include training (70%) and validation (30%). During the training process, the software selected the test set automatically. Different combinations of hyperbolic tangent or sigmoid as the transfer function of the hidden layer and the linear, SoftMax, hyperbolic tangent or sigmoid as the transfer function of the output layer were tested in ANN models with two neurons in the hidden layer. Information from all records was used in the training dataset with Adam optimizer and Initial Lambda, Initial Sigma, Interval Centre, Interval Offset, and Maximum Training Epochs were 5e 7, 5e 5, 0, 0.5 and automatically, respectively. Finally, the accuracy, precision, recall and F1-score were calculated for the validation set in each model. The values of the evaluation metrics from the different transfer functions models are presented

Table 1 Evaluation metrics for different transfer functions

	T-L (%)	T-So (%)	T-T (%)	T-S (%)	S-L (%)	S-So (%)	S-T (%)	S–S (%)
Accuracy	63.20	57.50	60.90	60.90	54	59.80	58.60	58.60
Precision	79.10	55.80	60.50	60.50	60.50	60.50	65.10	53.50
Recall	59.60	57.10	60.50	60.50	53.10	59.10	57.10	59
F1-score	68	56.50	60.50	60.50	56.50	59.80	60.90	56.10

in Table 1. The accuracy, precision and F1-score were the highest when the ANN models had hyperbolic tangent as the transfer function of the hidden layer and linear as the transfer function of the output layer. Therefore, this ANN model fitted the best as it correctly classified most of the dead patients, despite the recall having a slight difference with the transfer functions of hyperbolic tangent or sigmoid in the output layer.

After selecting optimal transfer functions, we changed the number of neurons in the hidden layer between 2 and 10 for the selected function in the model. Increasing the number of nodes in the hidden layer cannot also improve the values of the evaluation metrics (Table 2).

Figure 2 displays that the clinical section (body temperature and saturation by pulse oximetry) had the highest importance in the classification. Although the outcomes in three sections of the pulmonary symptoms (respiratory rate and respiratory distress), sociodemographic (direct contact with the patient, addiction, gender, duration of disease, age and duration of hospitalization) and biological rhythm cycles (physical biological rhythm and emotional biological rhythm) with a slight difference had equal importance. The three variables of body temperature (22.1%), respiratory rate (17.4%) and emotional biological rhythm (13.4%) are the predictors that contribute the most to the classification (Figure 1). Then, saturation by pulse oximetry (9.1%), physical biological rhythm (8.4%) and respiratory distress (7.5%) provide more information for the classification rather than age, duration of disease, duration of hospitalization, gender, direct contact with patients and addiction that contributes very little to the classification of a COVID-19 death rate.

Table 2 Evaluation metrics for different numbers of neurons in the hidden layer

	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)	10 (%)
Accuracy	63.20	59.80	59.80	56.30	58.60	60.90	60.90	56.30	59.80
Precision	79.10	65.10	60.50	62.80	62.80	65.10	58.10	53.50	60.50
Recall	59.60	58.30	59.10	55.10	57.40	59.60	61	56.10	59.10
F1 score	68	61.50	59.80	58.70	60	62.20	59.50	54.80	59.80

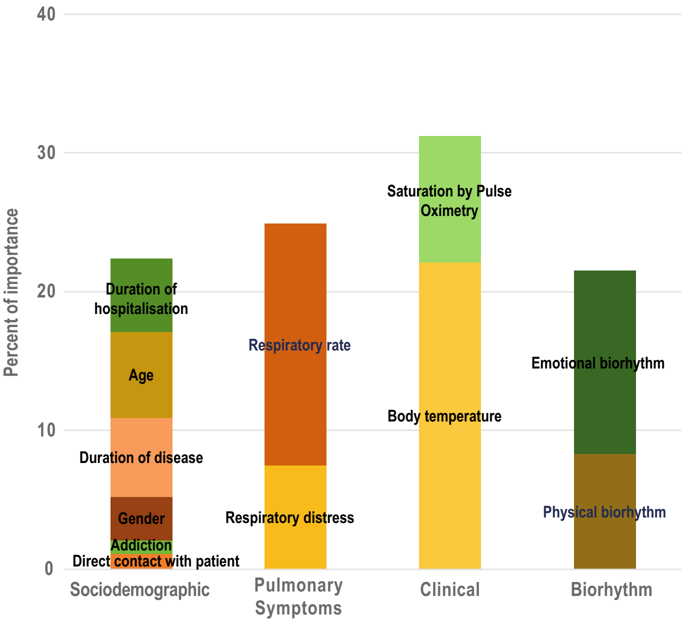

Fig. 2 The factor importance from the selected artificial neural network

4 Discussion

In the present study, we investigated the factors related to the COVID-19 mortality rate. Participants were recruited among people over 18 years old who do not receive any medication. Also, pregnant women and people with underlying diseases were excluded. We found that the most important determinants of mortality in the positive PCR patients are body temperature, respiratory rate and biological rhythm. Respiratory distress, physical biological rhythm and saturation by pulse oximetry were subsequently related to the COVID-19 mortality rate. However, the association between factors such as gender, age, addiction and contact with the patients with the mortality was not statistically significant.

There is an argument regarding the association between factors such as gender and age and COVID-19 mortality. In a meta-analysis examining the effect of obesity on COVID-19 mortality, age over 70 was significantly associated with the COVID-19 death rate [34]. In another study investigating the data from 169 hospitals in 11 Asian, European and North American countries on contract reviews, age over 65 increased the death risk [18]. However, the comparison between patient mortality rates at different age groups before and after the outbreak was insignificant [11]. These researchers believe that the mortality rate of the elderly is high due to old age and various chronic diseases, and the reason for the reported high mortality rate of these people among patients with COVID-19 is the lack of attention to the actual cause of their death in the study [11]. In the present research, the effect of age has been adjusted by limiting the study to the investigation of people without underlying disease. It has become closer to its actual ratio in the population. Therefore, as the study of Goldstein et al. confirmed, there is no significant relationship between age and COVID-19 death rate [11].

Some studies have suggested that the COVID-19 mortality rate is higher among men [10, 18, 19]. However, others argued that the cause of the difference in COVID-19 sex pathogenesis is related to the levels of stress endurance to cope with environmental stressors in men and women, and there is insufficient clinical data on virus entry into the testis and the severity of COVID-19 mortality in men [34, 35]. Moreover, the comparison of mortality rates in men and women before and after the outbreak has also shown that the mortality rate of men after the outbreak has not increased but instead decreased [11]. The probable reason for the decrease in mortality after the COVID-19 outbreak is probably due to the reduction in high-risk activities of men during the quarantine period. Therefore, as Goldstein et al. showed, the significant relationship observed in some studies between sex and the COVID-19 mortality rate is only due to men's higher mortality than women and not due to the destructive effect of COVID-19 disease on men.

Previous studies have also confirmed the effect of body temperature, pulse oximetry and respiratory problems (number of breaths and respiratory distress) [34, 36, 37]. Numerous studies have shown that psychological distress (anxiety, depression and stress) can reduce immune system function and is associated with COVID-19 [38]. Sirignano et al. have also shown that emotional biological rhythms and mood disorders have a similar underlying mechanism related to the brain biological clock and melatonin function [39]. Therefore, low emotional biological rhythms may be associated with mood disorders and can reduce immune system function leading to incidence and intensifying COVID-19. Similarly, the loss of physical strength caused by the passive physical biological rhythm can increase vulnerability to diseases [23].

The present study results showed a significant relationship between biological rhythm and COVID-19 mortality. Moreover, as in other similar studies, the transition of the disease was reduced due to the spread of vaccination [30]. On the other hand, social isolation and loneliness are associated with mortality and have irreparable consequences for country-driven sectors [40, 41]. Therefore, interventions should be done at individual and social levels to reduce the mortality and severity of COVID-19 in the population. In the first place, psychological interventions and exercise programmes can improve mental and physical conditions for individuals, leading to increased immunity and, finally, reducing the severity of COVID-19. On the other hand, due to the psychological consequences of quarantine and social distancing, it is possible to perform social activities under health protocols to reduce the psychological distress caused by social isolation.

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Conflicts of Interest The authors declare that they have no conflict of interest.

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Chapter 2
Deep Learning in Biomedical Devices: Perspectives, Applications, and Challenges

Sifat Nawrin Nova, Md. Sazzadur Rahman, and A. S. M. Sanwar Hosen

1 Introduction

Chronological improvements in healthcare system through the implementations of latter technologies have been diversified significantly. A diligent and continuous effort leading forward to establish a digital heathcare structure for better fidelity and sustainability has always been a challenge. Recently, the Internet of healthcare things (IoHT) is being widely implemented in therapeutic organizations, remote patient monitoring through biomedical sensors, and medical gadgets. By introducing strong connectivity, gathering information beforehand and precise decision-making IoHT and Artificial Intelligence (AI) can carry out a digital health platform ensuring the empowerment of health consumers. Deep Learning (DL) [1] which is a major part of AI and NN has flourished through commendable contributions to the healthcare industry. Understanding biological data and living organisms, communicating to the molecular level was difficult before the AI technology had been discovered. Biological and medical devices are generating a massive volume of data every day in the forms of images, texts, signals, and sequences which comprises the idea of big data [2]. Statistical anticipation shows that almost 30% of the global storage (including cloud) is occupied by medical images in 2011 and which will increase in the following years [3]. On the other hand, to substantiate a better healthcare

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structure with enhanced biotechnology demand for high-quality biomedical devices is increasing exponentially. In the last 5 years, demand for technology in medical science has been dramatically increased. Biomedical devices are complex in both physical and functional characteristics. They can be manufactured in the version of instruments, sensors, signal generators, implants, in vitro reagents, and software for the purpose of the safest prevention of disease, diagnosis even rehabilitation of illness. Thus, they include a vast range of products from surgical tools, ophthalmic instruments, tongue depressors, medical thermometers, clinical syringes, X-ray machines, microchip implants, programmable pacemakers and heart valves, neuroprosthetics, medical robots to many more [4]. In fact, the terminology neuroprosthetics is fledging in the field of Medical AI. Scientists from the 'École Polytechnique Fédérale de Lausanne' (EPFL) in Switzerland has invented a combined model where AI robotics are implemented to amend prosthetic movements [5]. These types of prosthetics can simulate person's nervous system through electrical simulations including cognition, hearing, vision, communication, and hearing skills. This discovery draws a milestone towards prosthetic technology including demands of "brain-computer Interfaces" (BCIs), "deep brain simulators", "spinal cord simulators" (SCS), "bladder control implants", and "cardiac pacemakers" [5]. Thus, in biomedical engineering, medical devices provide a major contribution to process advanced therapy and clinical discipline regarding health diagnosis and treatments. These complex devices generate a massive amount of data that needs to be analyzed for information gathering and future predictions. While biomedical devices are playing a vital role in this field, it is also important to ensure that precise medical attempts are fulfilling the "right treatments to right patients at the right time" by taking account of patients' personalized data such as drug history, biological traits, lifestyle disease management, and electronic health records (EHRs) [6, 7].

Hence, this biological data contains higher dimensions, intrinsic characteristics, and diversified contents. Novel instruments and systems need to be addressed to acquire data robustly with maximum accuracy and fidelity from these devices. Also, the system itself should be reliable, comprehensive, and robust in data acquisition and feature extraction. The latest advancements show that different types of patterns can be achieved from deep learning technologies by providing effective paradigms to complex data. Figure 1a incorporates the recent data studied over deep learning in related research articles. The data are collected from PubMed online database repository. The statistics shows a chronicle uprise of implementation of "deep learning in Medical technology" for the last 11 years. In Fig. 1b, interest in DL in health care is showen from 2016 to 2020, which depicts DL techniques are carrying out a steady domination over the field of medical science and technology for the last few years and the hunger of this implementation will be multiplied in near future. Many approaches have been proposed from time to time over the decade to improve the identification, prediction, classification, and regression of biological data using different AI techniques. The conventional Machine Learning (ML) techniques can be classified into two sub-sets: Supervised learning and Unsupervised learning. S*upervised* learning algorithm learns from a labeled dataset and evaluates the training dataset using that obtained knowledge, whereas *unsupervised* learning algorithm works on

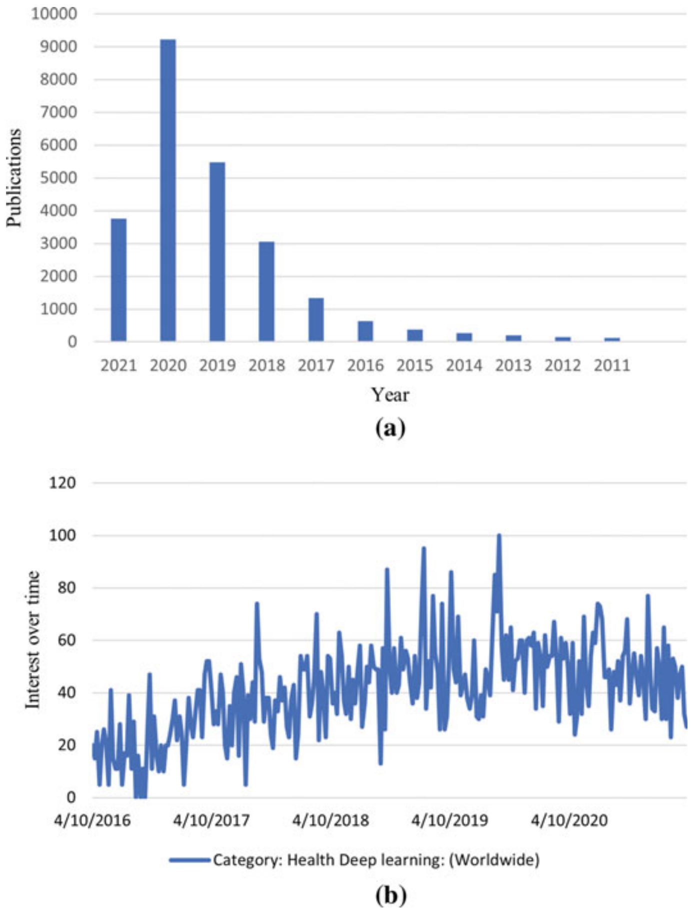

Fig. 1 **a** Publication trends over deep learning techniques in medical science in the last 11 years. The data are obtained by searching "deep learning in medical science" on "PubMed". **b** Research interests on "deep learning in healthcare" between 2016 and 2020. The data are obtained from Google trends by Google Inc

an unknown or unlabeled dataset to extract features or patterns from its own [8]. There is another learning algorithm model which is called *semisupervised* model which predicts features and extracts information from known and unknown datasets, Usually, unknown datasets are larger and more diversified than the known datasets [9]. Currently, this model has started to make a huge impact in the field of health technology because of its flexibility and robustness in data acquisition and analysis. A regular approach to biomedical engineering is having a domain expertise for using the phenotypes in an expedient manner [10]. Supervised learning scales are often limited and thin attributed to extract impactful information. Hence, this is not a feasible measurement to analyze and handle Big Data. Some of the familiar supervised learning approaches are Artificial Neural Network (ANN) [11], Support Vector Machine (SVM) [12], Boltzmann Machines [13], Restricted Boltzmann Machines [14], Bayesian Statistics [15], K-Nearest Neighbors [16], and Hidden Markov Model (HMM) [17]. ANN is an example of ML comprising three layers, input, hidden, and output layers. There is only one hidden layer that remains connected to both the input layer and the output layer. This technique mainly focuses on function approximation by mapping input value to an output value through leveraging the process. However, the concept of single hidden layer has been mitigated by the approach of Deep Neural Network (DNN) which interconnect several hidden layers and is able to process and analyze multiple data, signals, and sequences in the shortest period of time. In fact, DL is a recurrent process pertaining to DNN which is able to process more complex and scalable data. The task-specific algorithms are able to connect with life science and communicate through the molecular level which has been considered to be a huge jump in medical technology for the last decade. Some of the most used unsupervised ML learning algorithms are Autoencoder [18], K-means [19], Fuzzy Clustering [20], Information Bottleneck [21], and Association Rules [22].

As various new technologies have been introduced into our lifestyle, DL is contributing to all of them as one of the game-changing technologies. Some applications of DL include health behavior reaction [23], ophthalmology [24], heart diagnosis [25], cancer treatments [26], natural language processing [27], education [28], patients disease management and detection analysis [28], and drug design [29]. Thus, to curtail the implementation of manual ML and human intervention, DL technologies are widely useful in most of the parts of medical technology.

This chapter provides a conceptual overview of different DL technologies used in healthcare section and biomedical devices for the last few years with a complete overhaul analysis. The exponential growth of health needs, extravagant amount of data generation, and how to keep pace with rampaging changes in technological approaches are also discussed. This chapter also provides a circumstantial delineation over lists of DL technologies used in biomedical engineering to improve the Internet of Healthcare Things (IoHT). With the above aim, discussion over methodologies, existing frameworks, and performance comparisons are mentioned. Towards the end, several research challenges regarding this field and open issues with future challenges are outlined.

This entire chapter is segmented into seven sections. Section 2 describes an overview of IoHT. Section 3 incorporates and explores several approaches of IoHT in Biomedical devices. Section 4 presents a basic concept of DL. Section 5 infers DL contributions to the biomedical device and engineering. Section 6 highlights some open issues and future perspectives in this field, and, finally, Sect. 7 concludes the chapter.

2 Internet of Healthcare Things (IoHT)

In today’s world, where everything is correlated enterprise, data are considered to be assets. Data is the doorway of digitization, a roadmap to plant a digital world with proper health care and lifestyle. Following that, data acquisition, processing, and producing targeted outcomes are the major know-hows nowadays. Electronic health records (EHR), medical devices, associated smartphones, tablets, wearables, physicians, nurses, caregivers, and thousands of patients connected to thousands of things are creating millions of data points each day. These data that every enterprise pertains, are valuable and it needs to be protected from the network it is installed, secrecy needs to be checked, and reliability needs to be promised. With the above scenario, the healthcare industry is emerging with IoHT framework which is basically a catalog of workflow through connectivity. It is an integrated system where sensor-based devices are incorporated with IoT technology to provide healthcare support from scratch. The basic objectives of IoHT are to provide more improved health services, data acquisition in order to make it actionable, the anticipation of data and predict adverse results before they occur, enhance health outcomes, and lower costs. Standing in the era of the twenty-first century, COVID-19 pandemic has swept the globe with its horrifying consequences. After the thrust of this scarcest wave, it is inferred that a subtle deficit of stratagem is still existing in biotechnology and digitization of health care. According to that, IoHT support has been a trend for remote healthcare support [30]. To upgrade the unsustainability of the healthcare system and increased aged population every day, IoHT is introducing new technology trends such as wearables, i.e., wireless health [31]. However, most of the IoHT wireless health care lack a proper framework to maintain the loop of prior identification and consecutive planning for appropriate actions. New approaches through intelligent algorithms are crucial needs for this field. Wireless health services are emerging with health services like remote monitoring, continuous surveillance, diagnosis survey, and personalized Medicare. A fully modeled IoHT system can provide the practitioners with a streamline of personalized healthcare process through customized data-based treatments. “One Health” concept takes shape from this consideration while an unavoidable healthcare ecosystem shows the impact on people’s quality of life and quality of services [32]. Currently, to obtain a real value from IoHT investments, technology departments are investing in IoHT. According to the Accenture 2017 Internet of Health survey, 56% of healthcare organizations claim that their IT departments are leading the IoHT developments, whereas 26% claim that the Research and Development (R&D) departments are directing their IoHT endeavors [33]. Figure 2 depicts a generalized healthcare model based on IoHT. It includes a central connectivity as a base of communication based on the cloud storage which provides sharing of the dataflow. Usually, the architecture of IoHT consists of IoT-integrated smart devices such as wearables or sensors, communication protocol, storage with a cloud database, and end-users [34]. IoHT facilitated healthcare devices which can collect data from heterogeneous resources and environment. In personalized healthcare, these devices are being used in a wide range. A central shared storage with a cloud database is

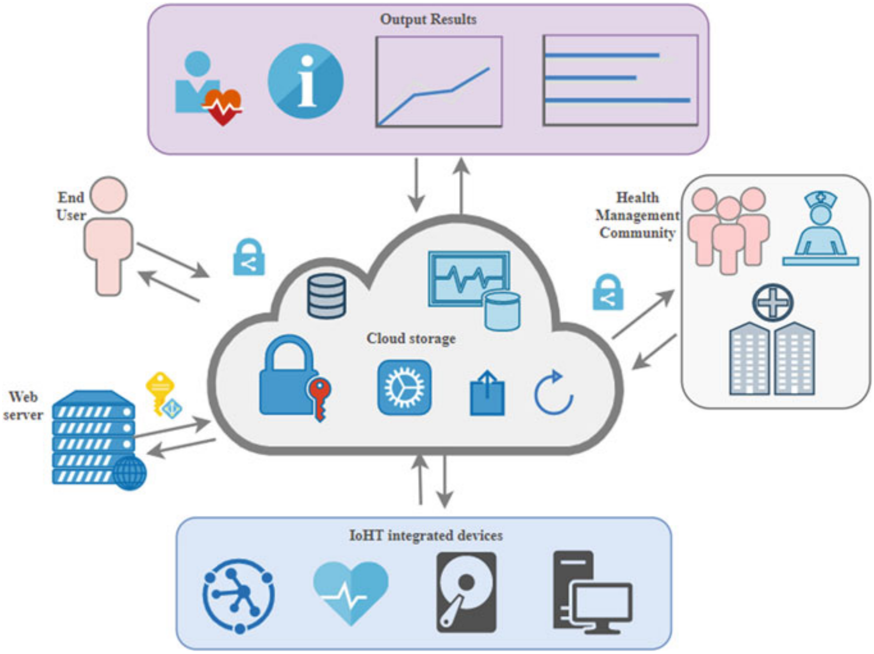

Fig. 2 A general IoHT healthcare model

deployed in the framework. Therefore, the architecture requires authentication, security secrecy, and reliability assurance regarding the data communication. This can be followed by a promising application layer protocol of IoHT. There are several methods available for the application layer protocol of IoHT mentioned in [34]. Some of the common applications of IoHT are Remote Patient Monitoring (RPM), lifestyle disease management, and real-time health surveillance systems [33].

Incorporating IoHT technology in the healthcare field can reduce the cost of health consumers effectively. In recent years, a dramatic reduction in errors has already been observed because of the enhanced manageability of medical devices, drugs, and adherence. However, with all of this imminent and preventive health care, IoHT model still lacks proper data privacy and security management. High amount of data analytics and maintenance is a challenge when the medical infrastructure is extremely large. Though having setbacks, IoHT provides an advanced healthcare database access and potential for the practitioners as well as the consumers to take a full control of the healthcare system.

3 IoHT and Biomedical Devices

The main objective of health and biomedical devices is to ensure that medical devices are able to provide the highest public health benefits within affordable costs for all intended and desired purposes [35]. Technological advancements in all areas including medical field have changed the dimension of the healthcare stratagem. Medical devices mostly include diagnostic and treatment devices with various mechanisms and systemic evaluation. The wide range of complex and multipurpose groups includes cardiovascular valves, optical tools, surgical scalpels, more advanced devices such as X-ray machines, ECG machines, deep brain simulators medical robots, visual prostheses, pacemakers, cochlear implant biomedical sensors, and many more. Implantable biomedical systems are forefront of research and an excrescent interest in both medical and engineering communities [36]. Biomedical devices have different definitions according to different regulatory agencies. The explicit idea of a biomedical device is that it can be an instrument, apparatus, implant, machine, or any other component that is directly related to diagnosis, cure, and prevention of any kind of disease, mitigation and treatments for health support and care. The radical difference between a biomedical device and medicines are the ideas of the action of mechanism they pertain to and the functionality they own. Most of the medicines are designed as “drug” and they interact with the living body at the cell receptor or molecular level [4]. On the other hand, biomedical device has intended functionality of their principal purpose which is obtained by physical, structural, or mechanical means. They also have the capabilities to work on the functionality of medicine by working on the prevention, mitigation, alleviation, and cure of the disease. They can also interact with the body but not at a molecular level in usual way. However, the utmost universality, equity, quality, and safety issues need to be addressed when these types of devices are manufactured. In Fig. 3, a diagram of medical device policies and strategies is depicted from the WHO medical device technical series 2011 [35], where the national health policy and plan are described through the relation between the medical device agenda and the aggregated targeted outcomes of safety, quality, universal coverage, and equity. Manufacturing medical devices are incredibly expensive and regulatory agencies need years to comply with their safety and quality assurance. Nevertheless, nowadays, biomedical devices include AI applications, software simulations, and many other new technological trends but it’s appeared to be a hard task to implement the device itself to the market.

As a matter of hope, increasing health demand doesn’t curtail the need for these device manufacturing although having cost issues. The biomedical device industry is emerging with a new approach to conventional manufacturing with the highest fidelity. In the last decade, investment in this field has increased dramatically by regulatory agencies. China’s medical device industry has bloomed to a 20% rise compared to the last decade [4]. The health industry is taking lead in our lifestyle and in fact the investments are crucial with the interconnected lifestyle. In 2015, the national health expenditure of the United States (US) increased to 3205.6 billion

Fig. 3 A diagram of the relationship between medical devices and expected outputs of safety, quality, equity, and universal coverage [35]

USD which is almost 10% of the surplus GDP [4]. Moreover, 90% of the healthcare expense consumption is going on the proportion of personalized healthcare which is definitely a standpoint of technological renovation.

Biomedical sensors [37, 38] are the fledging trends in the field of biomedical devices. Sensors provide valuable information regarding any physical, chemical, or biological condition of an object. Measurements are entitled based on the quality of the object. They can collect data from the environment and convert non-electric signals to electric signals. Biomedical sensors are specially configured electronic devices or transducers which can convert biological data into measurable electric signals. The main standpoint of the objective of biosensors is to understand and interact with living cells, collect data from the life organs, and intervene the prospectus of them. Thus, medical instruments can derive their instruments from the biosensors which are considered to be a subsection of biomedical sensors. Various types of biosensors have applications in the health industry such as skin sensor devices, wearables, integrated cell molecular detection sensors, contact lenses for detecting blood sugar and drug analysis, and screening sensors [37].

Numerous applications have already gained an impression of implementing biosensors as a major component of biomedical devices. This is a milestone for biomedical engineering as well. It opens a gateway towards an interconnection of

IoHT and biomedical technology to provide a better healthcare infrastructure with reduced healthcare cost and better quality of e-health.

4 Overview of Deep Learning

4.1 Basic Framework

ML is a subsection of AI which is able to determine the relationship among objects without to define them as a priori [39]. The primitive concept of DL is to acquire skills for data representation via increased hidden layers or abstract levels [8]. ANN's learning levels consists of three basic layers: input, hidden, and output layers. In contrast, DL is composed of several hidden layers of neural networks. Converting real data into abstract level is one major task of DL and the variant of transforming level differs in different types of DL algorithms. In each learning approach, layer-wise pre-training allows each level to form a deep structure prior to the input level. Different models are more suited to different data handling based on the given input and expected task performance. The underlying process of each model is to generate an approximated function which can carry out the meaningful output. The interconnected neurons are layered and basically hidden in the mid of input and output layers forming a "deep neural network" architecture. Aiming that, this results in activation sequences through the weighted connection of the neurons pertaining to the input data, which is referred to as Feedforward Neural Networks (FFNNs) [40]. FFNN model is the most primitive model of DL where data keeps passing through layers from input to the output node without having any "state memory": the knowledge of what came before. It refers to be the simplest variant with a densely connected multilayer perceptron. As mentioned earlier, the primary difference between DL and conventional NN is DL can comply with as many as layers it requires, whereas NN composes of maximum of one or two layers. DL is compatible to be trained for both supervised and unsupervised learning, whereas NN is only configured for supervised learning [2].

Several DL methods are overviewed in this section including Convolutional Neural Network (CNN) [41], Recurrent Neural Network (RNN) [42], Autoencoders (AE) [43], Deep Boltzmann Machine (DBM) [44], and Deep Belief Network (DBN) [45]. These hierarchical learning methods can be very powerful as they allow to extract meaning full data directly from the raw input and can be used in many important disciplines for prediction, analysis, and testing purposes [46].

4.2 Convolutional Neural Network (CNN)

CNN [41] is a multilayered neural network which is mostly feedforward in characteristics. Thus, it comprises layers of input, interconnected neural nodes, and outputs. The hidden layers of CNN can be convolutional layers, normalization layers, pooling layers, and fully connected (FC) layers [2]. The concept of CNN is developed based on the idea of connected patterns of neurons in human visual cortex [47]. This network uses a spatial-invariance trick to learn local patterns, most commonly in 2D or 3D images. Often nonlinear layers or filter banks are added after a convolutional layer for convolving with input data in order to pass the outcomes to the activation function (e.g., rectified linear unit (ReLU)) [1]. Many image processing and analysis technologies use convolutional filters (CF). CF can be trained to learn data-driven kernels from the images exploited "stationery" property. Therefore, these neural networks are used where the datasets are comparatively large, such as image detection, classification, object recognition, etc.

4.3 Recurrent Neural Network (RNN)

RNNs [42] have one distinctive difference from CNN, that is, it has "state memory" or cycles. They can be unrolled in time in order to be feedforward networks where the weights are shared. Moreover, RNN uses "time" to share weights, whereas CNN allows "space". Thus, RNNs compute the current state of output based on the previous state of output. As it has memory-like characteristics, it is gaining popularity in many fields involving streaming data. The major setbacks of RNNs include dissipating gradient by long input sequences and erupting gradient problems [48]. To mitigate this drawback, long-short time memory (LSTM) [49] is approached which is amicable in cases where input sequences are comparatively larger, and lags happen between important events.

4.4 Autoencoders (AE)

AEs [43] are an unsupervised type of NN structure taking the encoder–decoder architecture and learning to extract the exact copy of the input data. Basically, this model is designed for feature extraction in a data-driven procedure. As the hidden layers of the connected neurons or the encoded representations are much smaller than the input layer, the model is implied to extract meaningful outputs with low dimensionality. Some major setbacks of AEs are vanishing errors and the requirement of pre-training sets. However, because of its robust feature extraction quality, it has gained huge acceptance in the subject of image denoising as well as unsupervised embedding.

4.5 Deep Boltzmann Machine (DBM)

DBM [44] is one type of stochastic recurrent neural network with symmetrically coupled visible and hidden units. It is a Markov Random Field [50] and usually is used for extracting latent semantic information from larger unstructured and unlabeled data. The original algorithm requires stochastically initialized Markov chains to demonstrate the data-dependent and data-independent expectations in a connected pair [51]. Boltzmann machine with unconstrained connection structure is proven not to be useful enough and the learning process can be time-consuming. Instead, the constrained connection structured BM can be an implantable model for many disciplines [52]. To alleviate the learning efficiency Restricted Boltzmann Machine (RBM) has been discovered where it has no connection between visible units and hidden units, i.e., RBM restricts intralayer connection among the nodes. The main feature of RBM is, after each training process, the activities of its hidden nodes can be used as data for the higher level RBM training. As each layer carries away generative model improvements, the stacking property of RBM helps to form a deep network with efficient strategies and extract meaningful data.

4.6 Deep Belief Network (DBN)

DBN [45] is a generative graphical model and an alternative variant of RBM consists of multiple latent variables of hidden units. This model can be trained with several sets of examples without supervision and learn probabilistic reconstruction of its inputs. The upper levels of DBN remain undirected but the interconnections are usually downwardly directed to its immediate lower level. As it can gain probabilistic reconstruction DBN can be used in feature detection [45] and with learning steps trained to supervised classification [51]. However, practical implementation of DBN can be cost-demanding.

5 Deep Learning in Biomedical Devices

This section elaborates on the implementations of deep learning in health section specifically in biomedical devices to alleviate the healthcare infrastructure. A large number of researches has been categorized in the biomedical engineering field to develop classifiers for the detection and diagnosis of disease, prevention, and cure. The previous section gives a basic familiarization of some of the mostly used DL techniques in medical field. In the last 5 years, these techniques have been majorly used in several fields of biomedical devices such as clinical imaging, biomedical sensors, brain–machine interfaces (BMIs), electronic health records (EHR), drug design, and genomics. This section summarizes some of the applications of DL in these corresponding fields.

Clinical imaging

More than ever, previously unknown information about biology, life science, and diseases has been revealed after the innovation of clinical imaging. Primitively clinical imaging or medical image technology lagged computational and quantitative analysis regarding the development of image acquisition approaches. Currently, after the repeated success of computer vision in other fields, the emerging efforts of the implementation of DL in medical imaging have caught sight. The first application of DL in clinical image was the analysis of brain's "Magnetic Resonance Imaging" (MRI) which scans to predict the Alzheimer disease and its variations by using image processing [53]. Usually, DL algorithms are used in image segmentation, classification, localization, and recognition. Biomedical devices for sensitive organs such as surgical scalpels, injectable implants [54] as deep brain probes, adrenal gland electrodes for stress monitoring, and subcutaneous electronic chips are using DL algorithms for sensing and simulating internal body organs. Some of these devices are enhancing the technology by upgrading to real-time image simulation and surveillance. As numerous recordings and simulation mechanism are required to handle a gigantic volume of information human intervention were impossible in these contexts. Recently, DL techniques in image segmentation and detection have shown higher accuracy in performance. In advanced medical imaging, radio equipment like digital X-ray machines, MRI machines, CT scanners, and ultrasound machines are evolving with increasing needs for high-quality images, unique automation and positioning, and augmented reality. Digitalization has impacted the conventional way of diagnostic imaging. Especially DL has become an important tool for the steps of image processing chain, acquisition, exam planning, and decision support. The major three sections where DL techniques are mostly implemented are:

- Image Classification
- Image Segmentation
- Image Detection

Deep learning has been started to imply in medical imaging along with image classification [55]. In multiclass classification such as Tacked Autoencoder (AE) is used in brain diagnosis and prognosis to achieve better quality image classification. Recently, CNN is widely used in image classification. In the last 5 years, more than 36 papers have been published based on the multiclass classification of CNN [56]. CNN has great potential when it comes to the generation of the image, handling some core limitations of MRI including acquisition speed, image noises, and artifacts.

Segmentation of organs and their substructures have helped improving biological science in most ways. RNN is a useful algorithm in this field of image processing. Many pathology and diagnosis methods now depend on advanced image segmentation processes. Holistically neural networks (HNN) are a new terminology for the segmentation of organs, especially in the segmentation of prostates and brain tumors [57]. NiftyNet [58] is capable of TensorBoard visualization for simultaneous 2D and

3D image reconstruction for medical image analysis. In recent research, patch-based CNNs, end-to-end CNNs, and fully convolutional network (FCN) have been used in semantic segmentation tasks [56].

Detecting image is the primitive process of image segmentation. Moreover, medical image processing requires parsing of 3D volumes of data. Multiple DL methods have been proposed to address 3D information parsing problems. In [59] A sparse adoptive DNN powered by marginal space learning has been proposed to deploy in order to detect the aortic valve in 3D transesophageal echocardiogram. High-dimensional information in medical videos can be characterized by different deep learning models such as DBM, AEs, and GANs, especially LSTM-RNNs. For example, in [60], an LSTM model has been used for detecting fatal standard plane. They have proposed a method of transferring RNN (T-RNN) to understand spatiotemporal feature detection by incorporating hierarchical feature extraction method and temporal modeling. With the increasing aging population, recently, chest disease has become a severe issue. In [61], a CNN-based model is proposed for chest disease diagnosis where the model is pre-trained and pre-tested using different X-ray images containing multiple diseases.

The major limitation of conventional image reconstruction is the compact link between image resolution, signal-to-noise (SNR) ratio, and time acquisition. Apparently, increasing one of the three can negatively affect the harmony of at least one of the two others. However, over the last few years, AI technology has carried away significant improvements over conventional image reconstruction [62, 63]. Especially DL has changed the routine for 2D imaging and proved its potential to lessen the limiting factors of MRI simultaneously in image resolution, SNR ratio, and acquisition speed.

Biomedical Sensors

Biomedical sensors can be classified into three primary categories: physical sensors, chemical sensors, and biosensors or biological sensors. Physical sensors and chemical sensors are the most common sensors in many fields including health care. Biological sensors refer to an analytical device capable of molecule recognition that combines biological component with a “physicochemical” detector [64]. Generally, this type of sensor consists of some enzymes able to detect molecular substances and examine biochemical reactions through specific combinations. These types of sensors are fledging in the field of biomedical devices and some examples are injectable sensors [54], microorganism sensors, DNA sensors, enzyme sensors, tissue sensors, etc. Some electronic sensors, such as cardiac sensors for thermal monitoring or piezoelectric sensors are capable of recording multiple tissue characteristics. All of these feature functions are integrated into a biomedical sensor as a multipurpose tool system for minimum invasion and targeted operation in the human body. Aiming that, DL techniques with successful modeling in physiological sensors and signals are providing better success in this domain compared to traditional ML. Biosensors and signals in healthcare management require a massive volume of sequential medical data with time dependency. Therefore, it is crucial to consider any DL model respective to this domain not only have to consider spatial features but also time factors or temporal features. For example, skin sensitivity sensors, electrocardiogram sensors (ECG), and electroencephalogram (EEG) are these types of spatial–temporal data. RNNs are quite an implementable algorithm for EEG and ECG machines as these can extract features in a sequence of time as well as spatial conditions. DBN and AE are also applied in this domain as well [2]. Several variants of CNN techniques are also used in biosensors for better accuracy purpose. In [65], A model has been proposed to classify sleep stages using complex values CNN variants. In this study, this model is able to extract sleep information and features hidden in EEG signals. Most often data are irregular, noisy, and inconsistent. Multilayered CNN and RNN techniques can ease the preprocessing bottleneck in order to obtain deep residual learning. RNN techniques have been proven to be efficient in mining biological features from wearable sensors. In [66], a deep RNN architecture is proposed to detect human activities. Furthermore, many variants of DL techniques are being used in many other biomedical sensors considering the purpose of the health care structure.

Brain–Machine Interfaces (BMIs)

BMIs [1] are also called “brain-computer interface” (BCI) or “neural control interface” (NCI). It is an external communication path which uses brain modules without having motor involvement for the activation of external devices [67]. Mostly, BMIs are used to facilitate paralyzed patients to communicate with the environment. A distinct variant of DL methods has been applied in BMI technology to access neurophysiology and improve the communication pattern between the environment and the patient. Two familiar BMI signals, electroencephalogram (EEG)and electrocardiogram (ECG) have integrated DL techniques in order to function decoding and anomaly detection purposes [8]. In addition, BMI machines are being distinctively used in stroke motor recovery [67]. This method incorporates in-depth BMI training to learn patients’ brain activities relating to the behavioral intentions for moving the paretic limbs with the contingent sensory feedback of the paretic limb mobility supervised by adaptive devices. Various DL techniques have been used in BMIs including CNNs. CNNs are used in [68] for EEG signal classification. Its methodology includes augmented common spatial pattern features which are covered in different frequency ranges. CNN techniques have also been proposed in [69] to decode hand movements from electromyogram (EMG) signals. Except for CNNs, other variants of different DL methods including RNNs, DBM, RBM, and AE are simultaneously used in many applications of BMIs to improve implantable strategies.

Electronic Health Records (EHRs)

EHRs is a digital chart for patients’ health records which is real time and can provide information instantly to the authorized user. Recently, it has been a vital part of health IT and can be beneficial to ensure structured and systematic personalized health care. EHRs system contains patients’ medical history, medications, treatment plans, diagnoses, test results, routine health checkups, and many more. One of the key features of EHRs is that it is a shared database among authorized organizations, which makes it more efficient, handy, and ready to use in purpose instantly. Important information regarding health can accelerate the treatment process and reduces future damage. Therefore, EHRs is a prominent warehouse of enormous amount of structured and unstructured data. To handle EHRs data, recently, DL methods are widely being used in many healthcare industries.

What deep architecture does here is usually a supervised and predictive clinical task. Several works have already been done in this domain implementing DL methods. Disease prediction techniques by observing patients' clinical status are one of the most prominent applications of DL. Lie et al. [70] have proposed a model consisting of four layers of CNNs where congestive heart failures, attacks, and chronic pulmonary diseases can be detected through longitudinal EHRs. Differently, Pham et al. [71] introduced a DeepCare learning platform which is a dynamic neural network paradigm able to read medical health records and future anticipation. It has been built on LSTM and showed improved modeling and risk prediction accuracy. In [72], RBM is used for suicide risk prediction by analyzing the mental health of patients from embedded EHRs. These methods proved well performance in predictions and provided satisfactory clinical results.

Drug Design and Genomics

DL methods have been applied for the past few years in some of the major areas of computational chemistry. Though allopathy has gained remarkable success in the drug market, marketing survey shows that the experience of drugs from patient to patient can vary differently [73]. The concept of precision medicine is to develop strategies for disease prevention and treatments that take account of every individual personalized drug design. Nonetheless, larger scale molecular data handling is a sophisticated and a crucial problem for drug discovery. To apply the prospect of applying the concept of precision medicine has done dramatic improvements in biological databases (e.g., genome sequence), characterizing patients, and computational hardware and software tools using machine learning for data acquisition [7]. DL is a useful technology for continuously increasing data and automated workflows. A lot of the earlier attempts have been done using DL methods in drug discovery and drug design. Established methods like deep neural networks, CNNs, RNNs, GAN, and AEs are rapidly being used in this domain nowadays. DL architectures can be used in human-engineered architecture like molecule descriptors and drug design. In protein engineering [74] DL methods are applied to study the structural and functional properties of the protein molecules. Recently, some benchmark studies have been published in this domain. Wang et al. [75] used DNN method in the prediction of drug–target interaction, where 2710 ligands and 836 targets have been used as dataset. Their focus feature was molecular descriptors and protein features. To generate focused molecular libraries deep RNNs are used in [76]. By predicting and observing biological activities, molecular graphs can be represented by convolutional neural networks which are proposed in [77].

In high-throughput biology, DL demonstrates advanced acceleration in larger and high-dimensional datasets such as "DNA sequencing", "RNA measurements", etc. Different literature have been proposed in this literature including variant different methods of DL. Zhou et al. [78] proposed a method where CNNs model is used for the chromatin marks prediction from DNA sequences. CNN method is also used in [79] where Basset: an open-source platform used for DNase I hypersensitivity prediction through different cell categories. One of the key features of deep models is that it is capable of high-level feature discovery, improved performances over conventional methods, and increasing interoperability with additional understanding of the biological data.

6 Open Issues and Future Perspectives

Apparently, biomedical devices are a crucial part of diagnoses, assessments, and treatments of various diseases and injuries in human bodies. Over the past 30 years, biomedical devices and apparatus are developing in device design, prototyping, and manufacturing for multidisciplinary applications. In the last few years, AI technologies is playing a vital role in applications like healthcare infrastructure, biomedical engineering, and biological data as well. Research on the application of AI and ML in biomedical science is gaining attention since it reduces human intervention, provides automated, and fastens healthcare routine and better accuracy regarding prediction and decision-making of the results. Overall, it is believed that DL is the advanced subsection of CNN of AI paradigm which is organized as hierarchical processing systems and produces better results than the traditional ML technology. Though since last century, AI is trying to make attempts by adopting and implementing strategies in computers and producing notable outcomes in integrated systems, the overwhelming breakouts of crossing the milestone of AI technology in smart devices have evolved in the last decade. Currently, DL is integrated into any health diagnosis device which requires values or inputs from the real-world environment. The DL-associated devices work in an integrated framework consisting of cloud storage with a shared database, devices deployed within the DL software/hardware tools, i.e., integrated smart medical devices which are capable of collecting raw data from the environments or patients' EHRs and extracting informative features. While every component and individual system are correlated to each framework, it is a very sincere effort to make the workflow fault-tolerant and simultaneous. However, every parameter needs consideration according to maintenance and surveillance of each device other than the whole system may get disrupted because of unwanted interruptions. Though the newest technologies have provided many stratagems regarding the understanding of biomedical and life science, there are conditions where the procedures could face failures, traditional methods may disrupt with functional limitations. Therefore, improvements are required by detecting the limitations and shortcomings of these technologies. This section outlines some key issues of deep learning in biomedical devices and speculates some future perspectives and developments regarding this field.

Analyzing Big data: Deep learning consists of multilayered models with enormous network parameters which need to be estimated accurately. To subordinate with highly intensive data and extract a comprehensive outcome is a major task. As there are no prospective guidelines about specific training dataset range at a time, a rule of thumb is generally followed which is to have at least 10 × the number of samples per network [10]. Moreover, during the learning process parameters are created from the features collected from the neurons to obtain predictions. Deep learning has skillful demonstrations regarding data generation and data acquisition. But healthcare is a different field where a large amount of diversity occurs with each individual patient and adequate diversified patients' data on different biological aspects are rare to create a comprehensive training model. Though tools like natural language processing and computer vision is helping to obtain raw data, it gets complicated when it comes to healthcare rather than speech recognition or image processing. Unlike the other domains, health data have high frequency of diversity, heterogeneity, noise, and multi-structure. Training a model with these characteristics of data needs several processing criteria such as missing values, data sparsity, and redundancy. Therefore, a robust model with effective training from a medical big data perspective would be much more comparative than the other media.

Data representation, transformation, and distribution: Streaming medical data (e.g., biomedical signals, sensor data, genomic data, biomedical imaging) are continuous and very unstructured in nature. They can vary in different formats, i.e., sequences, trees, text data, or a combination of any of these structures. The radical algorithm of DL methods can only interpret input data in numeric format. Qualitative data handling is still critical for DL methods and sometimes can become sophisticated. To understand the changes in data type and convert them into usable formats in Dl needs a lot of computations and encoding for the data representation and transformation phase. Moreover, deep learning models require high computational power and memory additively, it's not worth to apply them in limited or moderate-sized datasets. Thus, a DL architecture which is incorporated with converting multiple data types into workable formats concurrently is necessary to handle practical situations. Moreover, diseases are very nondeterministic in nature and most of the existing deep learning methods simulate static vector-based inputs and handle temporality poorly.

Another challenge in handling continuous medical data by deep learning is data distribution to the authorized streaming community. In near future, upgraded devices may have more challenges such as autoupdated cloud, more dynamic EHRs, sharing information, server–client authorization, security issues, information distribution schemes to the authorized community, etc. Filtering out which data needs to be preserved in the cloud, curtailing redundant data or unnecessary health record history, and updating the storage with produced new feedback and outcomes are some arising challenges for this domain. Many issues arise in data distribution and resource allocation such as authorized community, administration or user identification, and structured schedule algorithms to minimize the deadlocks of the data sharing concurrently.

Security and Secrecy: The key focus of the DL-integrated biomedical device framework is security, secrecy, and privacy. As healthcare contains highly sensitive data it requires intensive security schemes in order to data transmission over a network. Very few of the existing DL methods are compatible with high computational permeability and distributional execution through cloud computing. Moreover, in cloud distribution and parallel computation, data privacy and security are still precarious [80]. Additively, real-time execution capability for handling a massive amount of data is rudimentary [81]. The deployment of DL is already a critical task where fidelity, integrity, and consistency of the network need to be ensured. In the near future, continuous medical data (CMD) and Big data will be merged and the amount of data will be massive. A security procurement is a crucial demand in this case to assure proper fidelity in order to keep valuable information safe and secured. Recently, blockchain is providing a higher degree of privacy to secure health data [82]. It can be applied as a security procurement with DL-associated infrastructure for advanced intelligent healthcare.

To proceed forward mitigating the setbacks the homespun requirement is to develop and improve existing basement theories of DL techniques depending on experimental implants and qualifying performances of individual NN. These models need to be comprehensive and able to assess real-time data streaming within a large volume, individual data type recognition and formatting, trained efficiently to define well-organized parameter tuning strategies, and self-organize based on data-driven policies [8]. A potential solution can make the hierarchical nature of deep learning more useful and robust for further implementations. Above all, an overhaul security protocol needs to be established in order to reduce risks and implement differential privacy standards.

7 Conclusion

Early applications of deep learning technology have shown satisfactory results and effective opportunities in healthcare. Consequently, deep learning can unlock the gateway to the next generation healthcare infrastructure that is more scalable, reliable, robust, standalone yet communicative, fault-tolerant, and automated. Moreover, the huge demand for biomedical devices creates exponential demand for AI technologies in biomedical engineering. The fastest-growing types of data in these devices are mostly EHRs, omics profile and monitor data, heterogeneous, noisy, poorly annotated and unstructured. Thus, DL can provide a holistic manner to organize and sort both hypothesis-driven research and data-driven research and incorporate clinical investigations based on different sources of data. This chapter discusses some major contributions of deep learning in biomedical devices. The discussion focuses on the rudiment learning methods of deep learning. Some methods (e.g., CNN, RNN, AE, DBM, DBN) are also briefly overviewed. A steady rise in deep learning in the field of IoHT has also been observed. Also, a circumstantial IoHT model is streamlined in this chapter with an overview of AI methods involved. Computer technology will eventually dominate through Big Data and machine learning technology. Already technological support has proven to be efficient and promising in healthcare industry more than ever with the newest revolutions. To facilitate more knowledge, biomedical device categories and characteristics are also outlined. This chapter also provides some reviews of the literature on deep learning applications in the diverse field of biomedical field. Statistical results have been shown in this chapter that reveals future applications and trends in DL. The success stories of AI and ML techniques and deep learning architecture include producing intelligent machines, reduction of costs, improved patients' experiences and satisfaction, diagnosis, treatments, prevention, and cure of disease Future predictions by analysis history records as well as EHRs are reducing errors and preventing further clinical damage. Lastly, some major key issues regarding deep learning implementation in biomedical devices have been outlined and some challenges are shown that need to be addressed for further research interests. While the recent bliss in the technological advancements has come out with huge challenge in the healthcare sector, DL provides a glimpse of opportunities to tackle these challenges. With proper adherences to comprehensive framework, DL can be consolidated at all levels including device designing, prototyping, product manufacturing, experimental planning, model building, prediction errors, and risk management. There can be a way found which is more focused on the heterogeneous healthcare pathways by redesigning approaches from both conceptual to methodological conviction by implementing smart IoHT technologies as well.

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Chapter 3
Effect of 3D-Multiple Object Tracking Training on Manual Dexterity in Elderly Adults with Dementia and Mild Cognitive Impairment

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1 Introduction

Grasp and handling objects with hands and fingers making coordinated movements are how we can refer to manual dexterity [1]. Manual skills are acquired with age and are a fundamental part of the skills we require in daily life. With age and as part of normal cognitive aging, manual dexterity and manual skills are deteriorating, along with other functions such as attention, memory, and information processing speed. The pattern in which manual dexterity is affected in healthy aging and cognitive decline is different. Carment et al. [2] found impairment in updating performance in aspects related to short-term memory in cognitive decline, while in healthy aging, impairment was in motor output to sensory cues, interestingly not present in cognitive

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decline. In patients with dementia, the cognitive impairment is broader, and hand manual fine skills are also impaired in different patterns and allow distinguishing between mild, moderate, and severe dementia [3].

Mild cognitive impairment and dementia are increasing every year. It is estimated that around 6–22% of people over 65 have Mild Cognitive Impairment (MCI) or Alzheimer's disease (AD), and 50% of over 85 years have developed AD [4]. Therefore, one of the most pressing challenges to improve the quality of life of older adults is to implement preventive and rehabilitation programs that reduce the rate of morbidity and disability, both physical and mental.

The term mild cognitive impairment is a heterogeneous disorder characterized by cognitive declines, such as memory, complex attention, executive function, and language. The patients present a slight memory impairment beyond what was expected for age but do not affect their daily activities [5]. MCI is considered a transition between the normal state of the brain and dementia. The importance of the detection and timely treatment of MCI lies in its progressive conversion to some type of dementia [4].

Dementia is not a specific disease; it has been defined as any decline in cognition that is significant enough to interfere with independent functioning. It describes many symptoms associated with impaired memory and other thinking skills and encompasses many clinical presentations [6]. Although in mild dementia (MD), patients may still function independently in contrast to more severe forms of dementia where necessary daily life activities are compromised [7], MCI is an important clinical entity to identify. However, there is a controversy about defining and assessing it, MCI criteria are ultimately determined through clinical judgment using information about deficits on objective cognitive tasks and evidence of decline over time on neuropsychological tests.

In recent years, an interest in non-pharmacological interventions for managing MCI or dementia has been promoted, and cognitive training is a valuable tool, given its versatility, the ability to adapt to the user's characteristics, and ease of application [8]. Cognitive training refers to a non-pharmacological intervention designed to improve cognition, regardless of the mechanism of action [9] This kind of tool has been proposed even in cognitively healthy older adults as a preventive measure [10]. Particularly, computerized cognitive training programs have proven to have the same utility as the classic models regardless of the individual's ability to operate a computer. Different computerized cognitive training programs have been applied to older adults and populations with neurodegenerative diseases [9, 11]. These investigations suggest that cognitive stimulation can help improve psychosocial functioning, including depressive symptoms and neurocognitive aspects [12]. All these are under the postulate that the human brain can reorganize and experience functional improvements since neurons are plastic and regenerative. One of the most active areas in visual cognition research has been the study of attention. A perceptual-cognitive task proposed for the first time in 1988 by Pylyshyn and Storm (1988) [13] to study multifocal attention and complex motion information is known as multiple object tracking (MOT). MOT is a visual task where the observer tracks multiple specific objects that move around a space while ignoring other physically indistinguishable objects, called distractors. There is evidence that this task can improve five domains: selective attention, divided attention, sustained attention, inhibition of attention, and speed of information processing [14–16].

2 Materials and Methods

2.1 Participants

Subjects were recruited ($\geq$ 65 years old) from the Neurology and Geriatrics Service of Hospital General de México, Dr. Eduardo Liceaga (HGMDEL), from March to September 2019. Thirty-eight patients participated in this study, of which half were diagnosed with Amnestic MCI using the criteria of the Key Symposium on this topic in 2003, which led to the publication of international criteria for MCI, and the other half with MD due to Alzheimer's disease according to the NIA-AA and the NINDS-AIREN criteria [17, 18].

The participants did not have depressive disorders or other psychiatric conditions. Exclusion criteria included patients with impaired fine or gross motor skills, Parkinson's disease, arthropathies, or amputation of some limb, and patients with severe hearing and visual deprivation. All participants agreed to this study and gave their verbal and written informed consent to participate before the beginning of the first session. The ethics and research committee from HGMDEL revised and approved the protocol, and was conducted following the Declaration of Helsinki.

3 Measures

3.1 Montreal Cognitive Assessment (MoCA Version 7.1)

It consists of a 30-point test administered in 10 minutes. This test evaluates multiple aspects of executive functions such as visual–spatial abilities, attention, concentration, working memory, language, and orientation

3.2 Grooved Pegboard Test (GPT)

This manual dexterity test assesses psychomotor speed and fine motor control. The grooved pegboard apparatus consists of a metal surface (10.1 x 10.1 cm^2) with a five-by-five matrix of keyhole-shaped holes in various orientations where pegs are inserted. The task is to put the 25 pegs into the holes as quickly as possible using the dominant hand. Recently, it has been proposed as an evaluation test of executive functions [19]. It has been validated internationally in elderly populations.

3.3 Minnesota Manual Dexterity Test (MMDT)

The MMDT consists of 60 cylinders per disk painted red on one side and black on the other side that fits in a hole pattern of a black plastic folding board. Each disk must be placed following five different execution modalities or subtests [20, 21]. This test evaluates the fine and coarse manual dexterity, performed with one and two hands, as well as the ability of manual motor speed and speed in hand–eye coordination. The MMDT comprises two subtests: The placing test and the Tuning Test [22].

4 Training Procedure

4.1 3D-Multiple Object Tracking (3D-MOT)

The MOT training program used in this study was NeuroTracker (CogniSensAthletics, Inc., Montreal, Quebec, Canada), where the task is to track a certain number of spheres out of a total of 8 that are observed on a screen through an enlarged 3D virtual visual field [16, 23]. The process is following: At the beginning of the session, eight static spheres positioned arbitrarily are shown on a 3D screen. Next, the number of targets to follow will be indexed for 2 seconds, and immediately, after all, the spheres will begin to move in random directions at a constant speed, bouncing between them and with the walls of a virtual box for 8 seconds. After one trial, if the subject identified the correct indexed spheres, the speed will increase for the next session. If at least one sphere was not correctly identified, the speed will decrease in the following test (one up and one down staircase procedure) and so on until the end of the session. Each session consists of 20 trials, and a speed threshold is obtained (m/s) at the end of it. The initial speed was set at 68 cm per second (cm/s), and object speed increased or decreased by 0.05 log. The size of the 3D volume space was 46 degrees of visual angle at the screen level [15, 16, 24, 25].

All participants completed a total of 36 sessions, divided into four sessions, three times a week. Each 10-minute training session consists of 3 sets of 20 trials in which the subject tracked two spherical targets numbered among six identical distractors.

Functional assessment was performed with the Lawton Instrumental Activities of Daily Living (IADL) Scale and the Barthel Index for Activities of Daily Living. In addition, the geriatric depression scale was used to rule out depression.

5 Statistical Analysis

All statistical analyses were conducted with the IBM program version 19 (Armonk NY: IBM Corp.).The quantitative variables were expressed as mean and standard deviations and the qualitative variables as proportions and percentages. Comparisons for related samples were performed with the Wilcoxon rank-sum test or the t-test; for independent groups, the Mann–Whitney U, or t-test. GPT and MMDT were transformed to a normal distribution with reciprocal transformation. In addition, 2X2 repeated measures analysis of variance (ANOVA) for averaged sessions of 3D-MOT and GPT or MMDT tests as repeated measures, and dementia or MCI as a between-group factor were performed with the first training session 3D-MOT as a covariate.

6 Results

Table 1 shows the demographic characteristics and the results of the functionality scales of the two older adult groups with MCI and MD.

Table 1 Demographics characteristics of the MIC and dementia groups at baseline

	MCI	MD	p-value
Age (years)[a]	74.11 ± 6.5	75.74 ± 6.1	0.461
Gender (female)[a]	14 (73.7%)	16 (84.2%)	0.426
BMI[a]	23.9 ± 3.5	23.5 ± 2.2	0.621
Education (years)[a]	8.95 ± 5.9	4.26 ± 1.4	0.02*
Lawton Brody[a]	8 (5,8) (8,7)	6 (4,8) (7,5)	0.006**
Barthel[b]	90 (75,95) (90,80)	85 (70,95) (90,75)	0.037**
GDS[b]	2 (0,5) (3,0)	3 (0,5) (4,2)	0.08
MMSE[b]	24 (20,30) (25,22)	19 (16,27) (21,17)	0.0001**
MoCA[b]	20 (18,25) (22,19)	15 (7,19) (17,12)	0.0001**

MCI, Mild Cognitive Impairment; MD, Mild Dementia; BMI, body mass index; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Exploration; MoCA, Montreal Cognitive Assessment

[a] Mean ± standard deviation

[b] Median (lower limit, higher limit) (third quartile, first quartile)

* $p < 0.05$ significant t-test for independent groups

** $p < 0.05$, Significant Mann–Whitney U-test for independent groups

The average of the 1st–5th sessions compared to the average of the 6th–10th session was significant for the interaction of session*GPT, F(1,35)=5.233, p=0.028, and for the interaction session*MMDT . F(1,35) = 5.388, p = 0.026. The effect continued from 6th–10th sessions to 11th–15th for sessions*GPT F(1,35) =12.138, p = 0.001 ans was similar for session*MMDT F(1,35) = 12.369, p=0.001. As sessions increase, the effect of training on motor dextery tests decrease; for the interaction sess on*GPT the effect of 3D-MOT was not significant in the 16th–20th sessions F(1,35)=0.023, p=0.880, nor for session*MMDT F(1,35) = 0.033, p = 0.856.

Across sessions, the mean of 3D-MOT was smaller for MCI than MD, and there was a linear increase until the 15th session; from this point and for the 20th session, the increase was quadratic and was no longer significant interaction. Figure 1 shows the progress of training sessions for both groups, with linear and quadratic trends according to Neurotracker scores averaged and normalized for all participants adjusted to the theoretical curve. The session averages are shown in Table 2. Linear and quadratic profile in training was observed in both groups MIC and dementia. The increase in 3D-MOT scores had significant main effects on GPT and MMDT across all training sessions: GPT (5th–10th sessions, F(1,35)=42.904, p < 0.0001; 11th–15th sessions, F(1,35) = 65.973, p < 0.000; 16th–20th sessions, F(1,35)=82.829, p < 0.000; 21st–25th sessions, F(1,35)=78.802 p < 0.0001, and 26th–30th sessions, F(1,35)=82.386, p < 0.0001); and MMDT (5th–10th sessions, F(1,35)= 43.135, p < 0.0001; 11th–15th sessions, F(1,35)=66.226, p < 0.000; 16th–20th sessions, F(1,35)=83.088, p < 0.000; 21st–25th sessions, F(1,35)=779.113 p < 0.0001, and 26th–30th sessions, F(1,35)=82.628, p < 0.0001).

There was a reduction in the time required to complete the GPT and MMDT tests in both MIC and dementia groups. Figure 2 shows the statistical differences in the GPT and MMDT tests for MCI and dementia groups at baseline and after training sessions. GPT pre–post t-tests were significant for MCI p<0.0001 and dementia

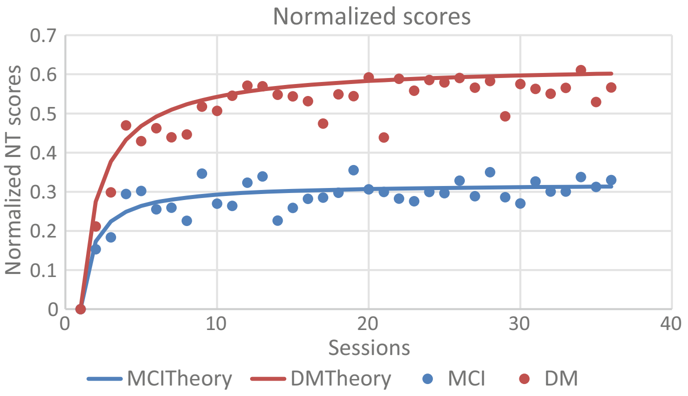

Fig. 1 Normailized 3D-MOT scores of average patient sessions in the MCI (blue dots) and dementia groups (red dots) adjusted to the theoretical curve for each group

Table 2 Average of 3D-MOT sessions across training program and manual dexterity tests at baseline and after 3D-MOT training

Measure	MCI mean ± sd	DEMENTIA mean ± sd	p-value
Initial	0.728 ± 0.7	0.334 ± 0.38	– -
AVG5	1.26 ± 0.7	0.81 ± 0.61	– -
AVG10	1.365 ± 0.65	0.997 ± 0.57	– -
AVG15	1.401 ± 0.58	1.199 ± 0.61	– -
AVG20	1.473 ± 0.61	1.156 ± 0.54	– -
AVG25	1.422 ± 0.69	1.193 ± 0.59	– -
AVG30	1.471 ± 0.61	1.219 ± 0.53	– -
GPT pre	133.91 ± 380.63	176.45 ± 411.82	< 0.001*
GPT post	102.43 ± 334.93	137.38 ± 284.34	< 0.001*
MMDT pre	258.88 ± 1411.66	291.5 ± 1564.05	0.011*
MMDT post	229.36 ± 1508.95	263.87 ± 1279.94	0.01*

AVG, averaged sessions; MCI, Mild Cognitive Impairment; sd, standard deviation; GPT, grooved Pegboard Test; MMDT, Minnesota Manual Dexterity Test

* $p < 0.05$ significant t-test for related samples

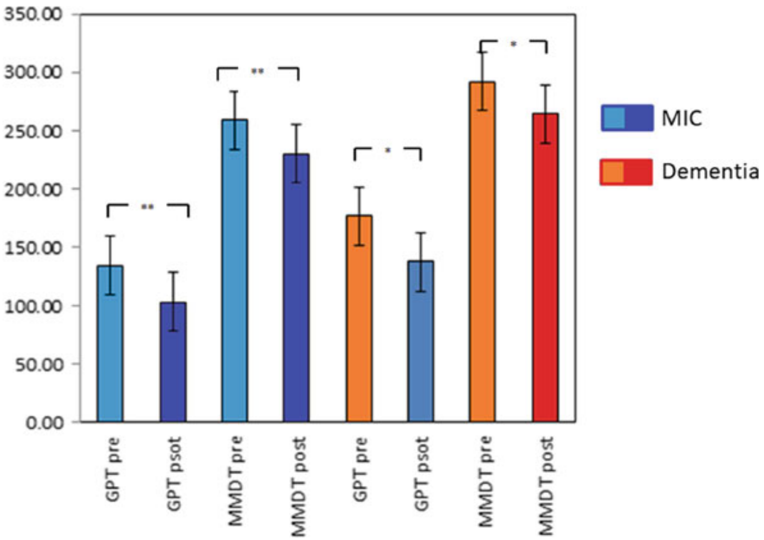

Fig. 2 GPT and MMDT mean scores at baseline and after 36 training sessions with the 3D-MOT for the MCI and MD groups. * $p < 0.05$, significant t-test for related samples. * *$p < 0.001$, significant t-test for related samples

p=0.011, and the same result was observed for the MMDT test; MCI p<0.0001 and dementia p=0.001.

7 Discussion

The 3D-MOT is a perceptual-cognitive training tool effective in improving performance in sports. In other areas such as manual dexterity, the transfer of cognitive skills is less explored. NeuroTracker abilities improved are sustained attention, selective attention, divided inhibition, short-term memory, working memory, and processing speed. The cognitive function that is most transferred after training is the attention and then the working memory (for a systematical review, see Vater, Gray & Holcombe, 2021) [26]. These functions are required, but not specifically in the performance of the GPT and MMDT explored in the present study. The literature reporting the effect of Neuroracker on manual skills is very scarce. Neurotracker has been used in several studies to improve motor skills in older adults. Musteata and colleagues [27] reported improved motor function as part of the Trail Making Test and in the Stroop test as psychomotor speed. In sports, motor improvement was found alone or combined with several motor tasks in badminton athletes [28]. In both studies, transfer to cognitive functions after training with NeuroTracker was reported and was reached partially. There is not always a positive effect on motor skills after training with the NeuroTracker; in children with atypical mild traumatic brain injury, the transfer effect was not observed [29]. After 1 month of training, the improvement on NeuroTracker training sessions is consistent, as shown in GPT and MMDT. Overall, the time requires to perform both manual tasks was reduced significantly. However, this improvement does not imply a transfer effect, although the motor functions are near domain of the cognitive functions improved by the 3D-MOT. We determined the number of sessions required to observe an interaction to improve the second measurement of the manual dexterity test. We found an interaction effect of training and improvement in GPT and MMDT tests, from the first session of training until the 15th session, and after this range of sessions, the interaction effect was lost. However, the training effect continued to the end of the 36-session program. These results show that a two-week program is enough to show an improvement in motor tests, although this is a very short time to consolidate the effect of the NeuroTracker, and also there is the question that if the improvement in manual dexterity tests is permanent or it only occurs while the training sessions are completed. These results are exploratory but show the impact of cognitive training on the improvement of motor abilities in older people and the importance of considering this kind of intervention in the motor functions of older people which can impact favorably in their quality of life.

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Chapter 4
Rhythmic Pattern of EEG for Identifying Schizophrenia

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1 Introduction

Schizophrenia (SZ) is a severe mental disorder characterized by hallucinations, delusions and cognitive deficits [4]. SZ is a challenging brain disorder with no current medical procedure to cure it, however, it can be successfully treated and managed. Early detection of SZ is an important challenge for the psychiatric health services. For this, several attempts of using machine learning methods have been conducted towards a fully automatic detection of SZ.

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The Deep Learning (DL) methods have been proposed for application in the field of biomedical and biometrics include the brain image processing and analysis, such as image detection, image registration, image segmentation and image classification. Various machine learning applications can be formulated as feature representation problems and can thus be solved effectively by using DL methods to find an effective set of features. Investigating brain connectivity networks based on neuroimaging data has become an important tool to understand the structural and functional organization of the human brain in health and disease. In these regard, the analysis of functional characteristics inherent in functional magnetic resonance imaging (fMRI) is playing a core role for brain disease diagnosis or prognosis [13, 37, 38]. Reviews have also shown the functional characteristics in a brain diseases have been studied in two different areas, namely, the effective connectivity [6, 7, 9, 24] that investigates the causal relations between regions where one region exerts over another and the

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functional connectivity [41] measures functional associations between regions by means of temporal coherence or correlation.

There have been limited studies of using DL methods in EEG and fMRI-based brain–computer interface (BCI). The high dimensionality (multichannel and sampling rate) of EEG and fMRI data, channel correlation and presence of artefacts (i.e. movement), and noise make it challenging to design an ideal framework for EEG and fMRI classification using DL. Normally, the preprocessing stage is necessary where the signal is reduced to lower dimensionality or transformed into a new representation without any significant loss in information. The following stage would require the network architecture designed to extract meaningful features from the input before DL methods can be successfully implemented for the classification system. Reference [18] applied CNN framework that takes advantage of the full-resolution 3D spatial structure of resting fMRI data and fits nonlinear predictive models [18]. The CNN by [33] used both temporal and spatial manner: a convolution is first performed on the spatial EEG channels, thus mixing them, and in the next layer, a convolution is performed in time along the temporal samples of the EEG signal. BrainNetCNN architecture of [16] extends CNNs to handle graph-structured data. DL techniques for driver cognitive performance were also applied with Deep Belief Networks (DBNs) and restricted Boltzmann machine on raw representations of the EEG [11, 12]. DL has also been applied in Motor Imaginary MI–EEG (MI-EEG) which manually extracts features from the channels based on FFT and then feed them into a DBN as a classifier and does not interpret the network as a feature learning algorithm.

Reference [32] proposed a parallel MLP and CNN architecture from which the predictions of the networks are joined via averaging. The MLP architecture receives the log energy features of the FBCSP algorithm and the CNN receives a temporal representation of the selected EEG channels and frequencies from the FBCSP algorithm. The temporal representation is the channel-relative instantaneous energy of the envelope of the EEG signal, extracted using the Hilbert transform. Resting-state fMRI (rs-fMRI) has been widely used as one of the major tools to investigate regional associations or brain networks [3, 13].

The rs-fMRI provides insights to explore the brain's functional organization and to examine altered or aberrant functional networks possibly caused by brain disorders such as Alzheimer's disease [10, 23, 38], Mild Cognitive Impairment (MCI) [27], autism spectrum disorder [17], SZ [17, 30] and depression [5]. The above review and references was taken from [13] which provides brain analysis with different types of brain disorder. Their work focuses on the early diagnosis of MCI based on the computational analysis of rs-fMRI. According to [1] Alzheimer's Associations, due to a high rate of progression (approximately 10 to 15%) from MCI to Alzheimer's disease in 1 year, it is of great importance for early detection for diagnosis of MCI and also to be able to seek a proper treatment to prevent from progressing of Alzheimer's disease. Among the brain diseases described above, Schizophrenia (SZ) is considered as a major neuropsychiatric disorder. It's a psychiatric disorder, where most of its characteristic sign is the disintegration of psychological functions resulting in the loss of unity of mind and consciousness. Scientific community has yet to find the biological cause to this disorder. PET studies show abnormalities in the degree of pattern of functional coupling. SZ can be regarded as a dysconnectivity disorder characterized by abnormal structural and functional brain connectivity networks at both microscopic and macroscopic levels. The research carried out by [14] in terms of Functional Connectivity (FC) reveals the statistical dependencies between signals (fMRI or EEG) from spatially distant brain regions regarding dysconnectivity in SZ brain networks especially between the frontal regions. Neuroimaging studies have provided compelling evidences of both structural functional brain abnormalities in SZ. Findings of structural magnetic resonance imaging (MRI) showed consistent decrement of brain tissues especially white matter in SZ patients while fMRI studies show SZ with functional impairment in sensory and frontal brain areas. In addition, disconnection of white matter projection tracts was observed in SZ patients [43] using MRI and Diffusion Tensor Imaging (DTI).

On the other hand, researchers working on electrophysiological studies reported shortened frontal-central distribution of EEG micro-states [20], and abnormalities of Theta and Gamma EEG oscillations related to memory impairment in SZ patients. EEG studies reported SZ-related aberrant synchronization of neural oscillatory at both the low and high frequencies [28, 40]. Research findings reveal differences in FC patterns between SZ and controls are not consistent among fMRI studies [22, 36], with reports of hyperconnectivity and hypoconnectivity (the increased and decreased strength of connections) between the same brain regions. According to Phang's review [30], there are also contradictory findings from EEG studies reporting both increased [39] and reduced [42; 15] Delta/Theta band coherence, and both intact [15, 42] and reduced [26] beta-band connectivity in SZ. CN analysis based on graph theory [31] has also revealed altered topological organization of brain connectome in SZ patients. SZ structural brain networks exhibit higher clustering, diminished overall connectivity strength and reduced global efficiency compared to healthy controls [43].

However, most of the above studies focus more on functional connectivity and disregards to region-to-region activity of the brain signal. However, this paper considers the effective connectivity (directionality) and topological organization of the brain networks using CNN for classification of EEG-based connectivity in SZ, especially on the investigation of the classification performance with a combined low-level effective connectivity measures such as PCOH and the global-level CN measures as input features. The paper is organized as follows: Sect. 1 describes the brain features and its connectivity measures as well as Deep Learning and its application to biomedical engineering. Section 11 describes the EEG connectivity features and the proposed Stack-CNN architectures. Section 3 reports classification performance on a large schizophrenia EEG dataset comparing it with different connectivity features. Section 4 draws the conclusion and Section 5 future work.

The main contributions of this work are summarized as follows:

1. We examine various measures of directed connectivity estimated from EEG to capture disrupted brain network organization in SZ. This includes new feature set PCOH and compared with the time-domain vector autoregressive (VAR) model coefficients, the frequency-domain partial directed coherence (PDC).
2. We extend the work by [30] with new proposed framework static and dynamic CNN stack for classifying EEG-derived altered brain connectivity patterns in SZ.
3. We compare the proposed stack framework with different fusion strategies by [30] in the MDC-CNN in combining CNN classifiers trained on different domains of connectivity features: (1) feature-level fusion by concatenating feature maps of convolutional layers; (2) score-level fusion by concatenating activation outputs of the fully connected layers and (3) decision-level fusion by weighted average of predicted probabilities from independent classifiers trained on the VAR, PDC and CN features, respectively.

2 Methods

Figure 1, shows an overview of the proposed MDC-CNN framework for classifying SZ and Healthy Control (HC) using EEG-based effective brain networks, which consists of two stages: connectivity feature extraction and CNN-based classification. In the first stage, various crafted measures of directed brain connectivity were estimated from multichannel EEG: time-domain VAR coefficients, frequency-domain PDC and PCOH measures. In the second stage, the extracted connectivity features in

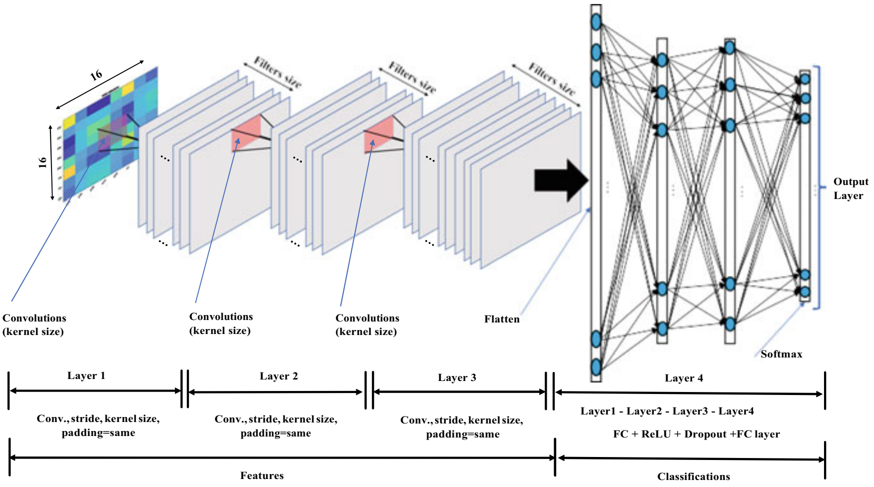

Fig. 1 Show the overview multimodal-CNN framework

different domains were then used as inputs to an ensemble of deep CNN classifiers. The two-dimensional connectivity matrices (i.e. VAR coefficient matrices at L lags and PDC matrices at five main frequency bands) are shaped into a 3D tensor and taken as input to a 2D-CNN model.

The convolution layers of CNN will further learn higher level structural spatial features in the crafted connectivity measures. In the fusion of multiple CNN classifiers, resulting feature maps of different connectivity measures were flattened and combined, followed by fully connected layers and a softmax layer to classify into SZ and HC. An alternative strategy is by weighted average of the decision scores from independent CNNs trained on different feature domains. The proposed new framework is proven in this paper in its applicability to neuropsychiatric disorders SZ with aberrant connectivity patterns and is potentially useful for development of robust computer-aided diagnostic tools in clinical settings.

2.1 Measures of Directed Connectivity

Let $\mathbf{y}_t = \left|[y_{1t}, \ldots, y_{Nt}]'\right., t = 1, \ldots, T$ be N-channels scalp EEG recordings over T time points. A common approach in characterizing effective connectivity between the EEG channels is through a VAR model of order L, VAR(L) on $\mathbf{y}_t$

$$y_t = \sum_{\ell=1}^{L} \Phi(\ell) y_{t-\ell} + \epsilon_t \tag{1}$$

where ϵ_t N(0, ∂) is a white Gaussian noise with mean zero and covariance matrix $\Sigma = E\left(\epsilon_t \epsilon_t'\right)$. The directed connectivity network between different EEG channels at time lag ℓ is quantified by the $N \times N$ coefficient matrix $\Phi(\ell) = \left[\phi_{ij}(\ell)\right]_{1 \le i, j \le N}$. When $\left|\phi_{ij}\right| > 0$, it indicates presence of directed influence in a Granger-causality sense from channel j to channel i with strength of ϕ_{ij}. Denoted by $\beta = [\Phi(1), \ldots, \Phi(L)]'$ the VAR coefficients of all lags, model (1) can be written as a multivariate linear regression

$$\mathrm{Y} = \mathrm{X}\beta + \mathrm{E} \tag{2}$$

where $\mathbf{Y} = \left[\mathrm{y}_{L+1}, \ldots, \mathrm{y}_T\right]'$,$\mathbf{E} = \left[\epsilon_{L+1}, \ldots, \epsilon_T\right]'$ and

$$\mathbf{X} = \begin{pmatrix} \mathbf{y}'_L & \mathbf{y}'_{L-1} & \cdots & \mathbf{y}'_1 \\ \mathbf{y}'_{L+1} & \mathbf{y}'_L & \cdots & \mathbf{y}'_2 \\ \vdots & \vdots & \cdots & \vdots \\ \mathbf{y}'_{T-1} & \mathbf{y}'_{T-2} & \cdots & \mathbf{y}'_{T-L} \end{pmatrix}$$

The estimators of the VAR coefficients can be computed by conditional least-squares (LS) method as $\hat{\beta} = \left(\mathbf{X}'\mathbf{X}\right)^{-1}\mathbf{X}'\mathbf{Y}$ and $\Sigma = (1/(T - L))\left(\mathbf{Y} - \mathbf{X}\hat{\beta}\right)'\left(\mathbf{Y} - \mathbf{X}\hat{\beta}\right)$.

PDC is a frequency-domain measure of effective connectivity which quantifies only the direct dependencies between nodes in a network [34]. Directed connectivity between EEG channels with oscillatory activity at specific frequency can be characterized by PDC matrix $\Pi(f) = \left[\pi_{ij}(f)\right]_{1\leq i,j\leq N}$ with

$$\pi_{ij}(f) = \frac{\left|\Phi_{ij}(f)\right|}{\sqrt{\sum_{k=1}^{N}\left|\Phi_{kj}(f)\right|^2}} \tag{3}$$

where $\Phi(f) = \mathbf{I} - \sum_{\ell=1}^{L}\Phi(\ell)\exp(-i2\pi\ell f/f_s)$ is the Fourier transform of the VAR coefficient matrices with sampling frequency f_s. The PDC $\left|\pi_{ij}(f)\right|^2 \in [0, 1]$ is a normalized measure of the ratio between the outflow of information from channel y_{jt} to y_{it} and the total outflows of all channels from y_{jt} at frequency f.

$$P_{ij}(f) = \frac{\mathrm{M}_{ij}(f)}{\sqrt{M_{ii}\mathrm{M}_{jj}(f)}} \tag{4}$$

For PCOH (4), where Pij is a minor of spectral matrix (matrix of spectra and cross-spectra) with the i-th row and j-th column removed (2).

For each subject, a VAR model (1) was fitted on the EEG signals by which LS and PDCs were computed from the estimated VAR coefficients as in (3). The optimal VAR model order selected by the Bayesian information criterion (BIC) averaged over all subjects was $L = 5$. Band-limited PDC matrices (self-connections excluded) were computed for five main EEG frequency bands (delta (1–4 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (14–30 Hz) and gamma (30–64 Hz).

These resulted to 3D tensor directed connectivity (DC) features (16 × 16 × 5–lags VAR coefficients and 16 × 16 × 5–bands BDCs).

3 Experimental Results

3.1 Dataset

The EEG database was adapted from [25]. Data acquisition was performed in a quite environmental condition. The subjects are asked to recognize whether the picture displayed on the computer screen was the picture selected by each subject as his or her password can be seen in Fig. 2. The experiment was completed with 120 trials (60 trials with the selected password picture and 60 trials with a random picture) for

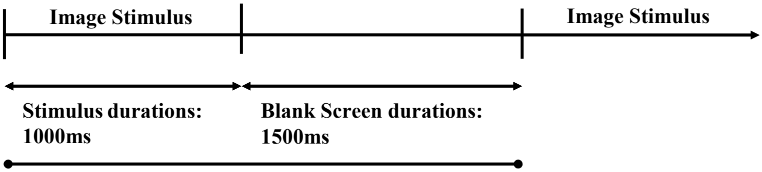

Fig. 2 Show data collection setup with stimulus of 60 trials

each session. The 120 trials were then displayed randomly to the subjects. However, due to the nature of time limitation of this paper, the work conducted here focuses on password datasets of the 60 trails for identification experiments. However, upon inspections of the data, unwanted artefact was removed from the data and the selection of the data was standardized so that each subject would have the same amount of trails (60 trial of passwords, it is reduced down to 54 trial of passwords).

3.2 Comparison of Different Models for Biomedical Application

Table 1 shows the classification performance and standard deviation across subjects of the new proposed CNNs nusing the frequency-domain PCOH. The same performance measures were used which include the classification accuracy, sensitivity, specificity and precision as the measures to evaluate the proposed system. The correct classification due to chance on the test set around 50% due to almost balanced number of subjects assigned to the two classes. Comparison was made between the performances of CNNs with SVM which has shown fairly high accuracy in classifying SZ and HC using features derived from functional connectivity maps in fMRI [19] and EEG [35]. This work is an extension to [30] with an added new feature called PCOH. Comparison was made in terms of classification performance and standard deviation across subjects of the proposed multimodal CNNs using the time-domain VAR, frequency-domain PDC and topological CN features alone in single-domain CNNs. In addition, their works include fusion of these features by weighted average of decision scores in the MM-CNN. The table shows that CNNs clearly outperformed traditional classifier of SVM in classifying SZ and HC EEG connectivity in all feature sets. [30] also evaluated the performance of MM-CNNs under different fusion strategies. The results show that the decision-level fusion by weighted voting outperformed the other fusion schemes, despite with slightly higher computational cost for classification. Among the CNN models, the MMC-CNN based on the weighted averaged fusion shows superior performance over single-domain CNNs trained on individual connectivity features alone, achieving the best accuracy of 91.69% and modified accuracy of 91.81%. It is interesting to see that the new PCOH features performed better than PDC feature, indicating more discriminative information are dispersed in the whole-brain connectivity edges in the frequency domain of the new feature.

Table 1 Performance comparison of the proposed CNNs and LSTM-RNN with SVM using different EEG connectivity features in classifying SZ and HC subjects. Values in parenthesis indicate standard deviations of performance measures

Classifier	Feature	Dimension	Accuracy	Sensitivity	Specificity	Precision	Modified Accuracy
2*Static SVM	Time-domain (VAR)	84, 16, 16, 5(lags)	85.66 (± 9.65)	86.67 (± 12.96)	84.64 (± 9.29)	86.64 (± 8.28)	85.65 (± 9.49)
	Frequency-domain (PDC)	84, 16, 16, 5(bands)	88.01 (± 5.52)	86.67 (± 8.31)	89.64 (± 9.48)	91.36 (± 7.35)	88.15 (± 5.50)
3*Static CNN	Time-domain (VAR)	84, 16, 16, 5(lags)	89.34 (± 8.61)	86.67 (±10.89)	92.50 (±10.00)	93.14 (± 8.59)	89.59 (± 8.61)
	Frequency-domain (PDC)	84, 16, 16, 5(bands)	89.19 (± 6.04)	88.89 (± 9.94)	89.64 (± 9.48)	91.64 (± 7.22)	89.27 (± 5.94)
	*Frequency-domain (PCOH)	84, 16, 16, 5(bands)	85.51 (± 9.45)	86.67 (±21.55)	85 (±12.25)	88.78 (±7.98)	85.83 (±8.21)
3*Dynamic CNN stack	*Time-domain (VAR)	84, 118, 16 × 16, 5(lags)	94.12 (± 6.44)	94.31 (±6.09)	94.31 (±6.09)	95.16(± 5.00)	94.31 (± 6.09)
	*Frequency-domain (PDC)	84, 118, 16 × 16, 5(bands)	86.66 (± 17.18)	6.53 (± 18.40)	86.53 (± 18.40)	87.23 (± 17.28)	86.53 (± 18.40)
	*Frequency-domain (PCOH)	84, 118, 16 × 16, 5(bands)	87.72 (± 16.33	86.25 (± 18.71)	86.25 (± 18.71)	88.43 (± 16.45)	86.25 (± 18.71)
3*Dynamic RNN	Time-domain (VAR)	84, 118, 16 × 16 (5Avglags)	76.25 (±13.83)	80.00 (±14.74)	72.14 (±18.09)	77.44 (±13.82)	76.07 (±13.96)
	Frequency-domain (PDC)	84, 118, 16 × 16 (5Avgbands)	83.38 (± 6.76)	82.22 (± 8.89)	84.64 (± 4.87)	85.83 (± 5.44)	83.43 (± 6.63)
	*Frequency-domain (PCOH)	84, 118, 16 × 16 (5Avgbands)	83.09 (± 12.14)	77.78 (±23.31)	90 (±9.35)	91.28 (±7.74)	83.89n (±16.71)

Using the PCOH features alone achieved accuracy of 85.51% as static CNN and 87.72% as dynamic CNN stack, and 83.09% on dynamic RNN as shown in Table 1. High classification accuracies achieved by the single-domain CNNs suggest that each feature type may capture unique complementary aspects of the brain connectivity networks essential for discriminating HC and SZ.

Table 1 Performance comparison of the proposed CNNs and LSTM-RNN with SVM using different EEG connectivity features in classifying SZ and HC subjects. Values in parenthesis indicate standard deviations of performance measures

Furthermore, the proposed MMC-CNN integrating features from different domains will significantly improve classification beyond the achievable performance from each of these feature domains individually. Nevertheless, use of PCOH on LSTM-RNNs with time-varying connectivity features fails to improve over CNNs with static connectivity features. The same result was obtained with the biometric application which does not improve the performance using dynamic classifier such as RNN. This can be mainly due to the time-varying connectivity metrics estimated based on very short windows of EEG may be less accurate, in contrast to directly learning the spatial patterns of 2D connectivity matrices as in CNNs, the RNNs only take vectorized inputs which neglects the spatial structure and the PCOH across all lags and frequency bands are averaged, which implies loss of frequency-specific information that is crucial in discriminating SZ from HC. The classification performance of CNN for different EEG frequency bands cannot outperform the PDC or the PCOH features in whole bands. In biometric classification using the EEG frequency bands for PDC features, the Gamma band obtained the best result, while the accuracy of CNN using PDC features for biomedical [30] ranged from 72.65% to 86.91% (with modified accuracy ranging from 70.95% to 86.90%), in which the alpha frequency band is more discriminative compared to other frequency bands. This could be explained as the EEG connectivity between the SZ and HC was observed in the low-frequency bands. Since low-frequency bands mainly modulate attention, memory and consciousness, our results indicate schizophrenia patients are at risk on disruption of above mentioned high-order brain functions.

[30] exploit altered patterns in brain connectivity as features for automatic discriminative analysis of neuropsychiatric patients. The same database was used to compare their work with this thesis, where a new feature call PCOH was introduced into the system. The new methods of spatio-temporal analysis provide important tools for characterizing several dynamic aspects of brain oscillations that are reflected in the human scalp-detected EEG. The new feature should be able to identify the dynamic connectivity of brain signals within different frequency bands, in order to uncover the transient cooperation between different brain sites, which converges at the potential of multivariate autoregressive (MVAR) models and their derived parameters. In fact, MVAR parameters provide a coupling measure including PCOH and PDC. These two approaches have been developed to quantify the degree of coupling between different EEG recording positions, with the specific aim to characterize the functional interaction between neural populations within the cortex. The same deep learning methods have been proposed with different architecture based on CNN framework which

was used to classify EEG-derived brain connectome in SZ. To capture complementary aspects of disrupted connectivity in SZ, this paper compared (30] work based on the combination of various connectivity features consisting of time- and frequency-domain metrics of effective connectivity based on vector autoregressive model and partial directed coherence, and partial coherence measures. In order to have a fair comparison, the same novel multimodal connectome CNN (MMC-CNN) based on a parallel ensemble of 1D and 2D CNNs was used in the experiments. This work also considers an extension to dynamic brain connectivity using the RNN. The proposed system shows that PCOH (static)-CNNs have the same accuracy with SVM in classifying SZ and HC EEG connectivity in all feature sets.

Nevertheless, use of LSTM-RNNs with dynamic PCOH connectivity features shows an accuracy of 83.09% fails to improve over CNNs with VAR dynamic CNN stack connectivity features. This may be due to the time-varying connectivity metrics estimated based on very short windows of EEG may be less accurate due to much larger number of parameters to be fitted relative to small sample size. Furthermore, in contrast to directly learning the spatial patterns of 2D connectivity matrices as in CNNs, the RNNs only take vectorized inputs which neglects the spatial structure of the brain networks. Due to the inherent limitation of the RNNs that do not account for the multivariate input patterns, the time-varying VAR and PDCs across all lags and frequency bands were averaged out, which implies loss of frequency-specific information that is crucial in discriminating SZ from HC. In classification, the CNN and MM-CNN models also systematically outperformed the deep RNN, the effective connectivity convolutional network was able to utilize information from multiple different connectivity metrics. Although the best performing approach RNN achieved F1 56.40% less accuracy than the CNN model, it can be argued that the proposed RNN method holds much greater promises than this small performance gain.

4 Discussions

Applications of CNNs to brain connectivity data in classifying spatial maps of functional networks are at its infant stage and dynamic nature of the brain signals would also require DNN architecture such as RNN to handle the temporal signal of the brain. In handling the temporal nature of this type of signal there is need to have proper window length to ensure the better performance of the classification system of SZ in handling the time- and the frequency-domain features. It is to the best of this paper knowledge in this area; researches have not handled this problem with satisfactory results. These are some of the motivation factors for the research carried out in this paper and since the work by [30], regarding DNN uses the same database and the same experiment setup, detailed discussion is provided here related to their work.

In this work, multimodal/multidomain connectome MM-CNN framework was used to classify SZ and Healthy Control (HC) using EEG-based effective brain networks. The framework consists of the connectivity feature extraction and CNN-based classification. The database used in their experiments of EEG dataset of healthy and schizophrenic adolescents was an online database from Lomonosov Moscow State University. The subjects were screened by psychiatrist and grouped into healthy and schizophrenia adolescents, where the total of 84 can be divided as 45 are schizophrenia patients and 39 as healthy subjects. The EEG signals were recorded by 16 electrodes, which are F7, F3, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2. The resting state EEG recording span for one minute with sampling frequency of 128 Hz results in 7680 samples per channel. Several different features were used which include crafted measures of directed brain connectivity estimated from multichannel EEG such as the time-domain VAR coefficients, frequency-domain PDC and PCOH measures. The deep CNN classifiers then used the extracted connectivity features from the different domains as inputs to CNN. The inputs to CNN are properly designed to fit the 2D and 1D CNN model. As an example, the two-dimensional connectivity matrices (i.e. VAR coefficient matrices at L lags and PDC matrices at five main frequency bands) are shaped into a 3D tensor and taken as input to a 2D-CNN model.

The convolution layers of CNN will learn higher level structural spatial features in the crafted connectivity measures. In order to further improve their system performance, fusion of the multiple CNN classifiers was introduced, where feature maps of different connectivity measures are flattened and combined, followed by fully connected layers and a softmax layer to classify into SZ and HC. The weighted average of the decisions from independent CNNs trained on different feature domains was also applied for further improvement of the system performance.

The proposed deep CNN framework for automatic classification of SZ patients using input features based on brain connectivity features derived from EEG seems capable of capturing spatial structure of functional connectivity maps. This provides leverage in information on disrupted neural connectivity patterns in SZ relative to the HC for discriminative analysis at the group level. Their proposed MMC-CNN architecture was designed for multimodal/multidomain connectivity data that can 91 effectively combine complementary information from multiple brain connectivity descriptors of diverse domains and dimensionality for classification purpose. The complementary information from multiple brain connectivity descriptors of diverse domains and dimensionality will include the time- and frequency-domain metrics of effective connectivity as well as complex network measures of network topology. The results on resting state EEG demonstrate that the proposed CNN was able to learn a hierarchy of low- and high-level abstract representation features from the crafted connectivity features to differentiate SZ from HC. The proposed MMC-CNN gave promising classification results on a large SZ EEG dataset, outperforming traditional SVM by a large margin. In addition, the MMC-CNN with combined features also substantially improve the performance over CNNs trained on single-domain features individually, achieving the best accuracy of 91.7% using decision-level fusion.

5 Conclusion

It is interesting to see that the proposed CNN dynamic VAR stacking 94.12% proposed by this work performed better than [30] MDC-CNN based on the weighted averaged fusion with accuracy of 91.69% and modified accuracy of 91.81%. The dynamic CNN stacking PDC proposed by this paper shows an accuracy of 86.66%, while the work by [30] topological CN features alone only achieved accuracy of 80.96% on CN, 89.19% PDC and 88.01% on SVM. High classification accuracies achieved by the single-domain dynamic stack CNNs VAR suggest that this feature type does capture unique complementary aspects of the brain connectivity networks essential for discriminating HC and SZ. Furthermore, the proposed VAR dynamic CNN stack integrating features from different domains does significantly improve classification, with an input of 84 118 256 5 to CNN, compared to [30] feature-domain input 84 16 16 5 of VAR CNN.

6 Future Work

Naturally the proposed deep learning techniques and particularly the suggested CNN and RNN methods in this thesis have several drawbacks. This study has shown that DL with deeper networks takes a longer time to train than traditional shallow neural networks or even with the conventional methods like HMMs. However, top research centres in the world can solve the modern deep learning frameworks and GPU computing of the CNN model trained in sevenfold cross-validation, for example, maybe within an hour. The next difficulty faced by this thesis and others [8, 21] is the selection of hyperparameters of the DL where optimum hyperparameter learning is usually not feasible. This is due to the long training time of these models due to the search of the architectural parameters like the number of filters, the number of different convolutional and fully connected layers, the number of neurons in each layer as well as proper selection of different activation function of the neurons like the sigmoid function. In addition, this DL also requires handling the training parameters like initialization, loss function, learning rate or optimization function which makes it more difficult to handle this system. Reference [29] provide clue that even though the convolutional architectural design can significantly decrease the number of trainable parameters compared to fully connected deep networks, the number of these trainable weights can still be very high compared to the number of samples in the dataset. The paper suggested that careful regularization (i.e. with drop out) is essential to the success of these models, and the effectiveness of their application to datasets with extremely few training examples (i.e. less than a 100 measurements) is debatable. Further suggestion was given on how to improve the performance of the system by combination of different functional connectivity metrics. It was argued, even though using combined inputs naturally increase the number of trainable weights of the model, adding new sources of information might still increase classification performance.

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Chapter 5
Prior Prediction and Management of Autism in Child Through Behavioral Analysis Using Machine Learning Approach

Md. Mahfujur Rahman and Shamim Al Mamun

1 Introduction

Autism spectrum disorder (ASD) is one kind of disability that can cause significant social, behavioral, and communication challenges [1–3]. Their learning, thinking, and problem-solving abilities are very challenging. Autism Spectrum Disorder (ASD) is prevalence in many forms, from very mild ASD to very severe ASD, depending on the severity of the symptoms. Different research stated there is a need for earlier recognition, evaluation, and intervention of Autism Spectrum Disorder [4, 5]. Also stressed the fact that early intervention programs are very beneficial for the overall well-being of a child. We don't realize immediately after the birth of disabled children they are actually what types of problems are facing. It takes too long to find some problems. Parents have to go to the doctor for a screening test to find out what kind of problem and what remedies they have.

Various research articles [6, 7] are applying Machine learning techniques to identify Autism Spectrum Disorder (ASD). Aggarwal et al. [8] published an article where to describe several machine learning algorithms and describe how machine learning works and how can we use a proper way to detect autism in a child. Thabtah et al. [9] published a research work where they work with limited datasets and their mainly focused on the screening methods. It also describes autism disorder factors, symptoms, and types of behavior. The overall objective is to study the various data mining techniques available to predict ASD and to compare them to find the best method of prediction. They proposed new datasets that are related to autism screening in adults. In their datasets, only recorded ten behavioral features with ten characteris-

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tics. Kanad Basu et al. [10] published a research where work with several algorithms (Decision tree, Naïve Bayes, etc.) and prepared a dataset. Here working with the data analysis, data visualization, data exploration, and implementation process, which are more significant ways to find autism. Most of the previous research works, authors work with a few attributes and specific algorithms. We work with several datasets of attributes to better accuracy and we have already near about 72 attributes. We also use several algorithms to find out which algorithm finds the better accuracy.

Nowadays, Machine learning is one of the foremost necessary spaces of analysis [11, 12]. It's a branch of AI supporting the concept that systems will learn from information, establish patterns and build selections with the lowest human intervention. Applying machine learning algorithmic rules we will predict syndrome for obtaining smart success, completely different procedures of machine learning algorithms use different purposes of uses. Here this research approach works for children between the age of 0 and 18 years old and for these, this approach collected real data from autism schools. For this reason, this work will be done with the collected data sets and the attributes of those children and mining this data. Autism is a neuro-developmental delay, if we predict it at an earlier stage then we have a chance to cure it. Finding these we use the attributes where to apply some standard attributes and use many attributes which are collected from doctors and parents with discussion. Through the proposed system, we can easily identify the problem. It saves time and cost, in this process, we can predict autism in an earlier stage when there is a chance to cure it. Patients obtain greater inexpensive and better healthcare services [13–15]. This occurs when a physician uses this application to predict autism before doing the formal screening. It serves the right information and right prediction, so it helps physicians to predict autism in an easy way.

In this paper, we have analyzed the machine learning algorithms to determine a set of conditions that together prove to be predictive of autism disorder. Moreover, this paper proposed an autism management system using knowledge fusion of gathered features from parents monitoring mobile apps. It's mentioned that the quality accuracy measuring method named Confusion Matrix procedure is used for evaluating the results.

The residue of the paper is structured as follows: Sect. 2 describes the prior prognostic of autism, Sect. 3 exhibits the entire methodology. The results are discussed in Sect. 4, the conclusion is discussed in Sect. 5.

2 Prior Prognostic of Autism

2.1 Behavioral Analysis

Autism spectrum disorder (ASD) is a developmental disorder caused by differences in the brain [16]. Scientists could not find out exact reasons for what causes these differences for most people with ASD. However, some people with ASD have a known differences, such as a genetic condition, behavioral features [14, 17].

In this research paper, we categorized 72 questionnaire's into nine categories that used to predict autism in children. We collected data from autism schools and discussing with doctors who treated autistic child and their parents. In the Questionnaire, there are many attributes of a child which represent a child's behavior and developmental issues for that reason it will take less time to predict whether child survived with ASD or not. This research is focused on nine primary research questions which are related to ASD child:

Research Question 1(RQ1): Does a child have an improving delay? Children with ASD may have delays in improving while he/she insists on things at home remaining the same (E.g., furniture staying in the same place, things being kept in certain places, or arranged in certain ways?), he/she insist that aspects of daily routine must remain the same, he/she insist on doing things in a certain way or re-doing things until they are "just right", he/she insist on wearing the same clothes or refuse to wear new clothes. So a lot of things can happen with ASD in improving delays.

Research Question 2 (RQ2): Does a child have a learning delay? Children with ASD may have delays in learning. In this research question's category this research considered the following questions: Does he/she don't speak at all? Is he/she read appropriately for his/her age? Does he/she have difficulty understanding the rules of any work? Does he/she appear to have an unusual memory for details? Does your child look at you when you call his/her name? Does your child point to indicate that he/she wants something? Does he/she can properly respond to others? Does he/she keep a two-way conversation going?

Research Question 3 (RQ3): Does a child have a language problem? How is the nonverbal communication? Each person with ASD communicates in a unique way. Some persons have a good command of the English language. Others are unable to speak at all or only speak a few words. Approximately 40% of children with ASD do not speak at all. Around 25–30% of children with ASD have some words between the ages of 12 and 18 months and subsequently lose them. Others may speak, but not until much later in life. Nonverbal communication difficulties associated with ASD include: Speech and language skills are delayed. Pronouns are reversed (e.g., "you" instead of "I"), and Answers questions in a random order. Doesn't respond to pointing, and doesn't point. Over and over, he repeats the same words or phrases (echolalia), Few or no motions are used (e.g., does not wave goodbye), Talks in a flat, robot-like, or sing-song voice, and does not understand jokes, sarcasm, or teasing.

Research Question 4 (RQ4): Does a child have physical activity? What was the birth weight? Is a child a premature birth? In this research questions, this research focused on lack of eye contact, height, weight, movement right according to age, changes in activity, and spending times a week.

Research Question 5 (RQ5): Does a child have special interests? In this questions categories, this research checked the following questions: Is there anything in particular that piques his attention or fascinates him? (Dolls, trains, road signs, or other items, for example?) Does he or she enjoy looking at things from odd or unconventional perspectives? Is there anything in the smell of persons or stuff that piques his interest? Is he/she particularly interested in how different surfaces feel? Is there anything specific he likes to carry about with him? Does he/she collect or hoard items of any sort? Does she/he Prefer to be alone? Does he/she focus on only a small part of toys or objects? Does he/she play the same music, game, or video, or read the same book repeatedly? Does your child point to share an interest with you?, Does your child pretend? Does your child follow where you're looking?

Research Question 6 (RQ6): Does a child have repetitive behavior? In this questions categories, this research focused on some repetitive behavior such as a. spin himself/herself around and around, b. rock backward and forwards or side to side, either when sitting or when standing c. pace or move around repetitively d. make repetitive hand and/or finger movements e. like to arrange items in rows or patterns f. repetitively fiddle with items.

Research Question 7 (RQ7): Does a child have a lack of maturity? In this questions categories, this research focused on the following: become angry or upset if their daily routine changes, share/talking about emotions and feeling properly, join in playing games with other children easily, come up to you spontaneously for a chat, speaking like 2 years old child.

Research Question 8 (RQ8): Does a child have dangerous behavior? Dangerous behavior is another option for screening autism. This research focused on the following options: harmful for own self, become much angry if anyone interrupts in their work, appear to notice unusual details that others miss.

Research Question 9 (RQ9): Does a child have social interaction delay? In the social interaction delay category, this research focused on the following: social behavior very one-sided and always on his/her own terms, avoids eye contact, avoids or resists physical contact, prefers to play alone, does not respond to name by 12 months of age, has trouble understanding other people's feelings or talking about own feelings (Fig. 1).

2.2 Screening and Diagnosis of Autism Spectrum Disorder

ASD screening and diagnosis is a complex technique because there is no medical test to diagnose the illness, such as a blood test. Doctors make a diagnosis and provide treatment based on the child's history and behavior. That is why it is critical to monitor, screen, evaluate, and diagnose children with ASD in order to ensure that they have a better life.

Monitoring: Monitoring examines how your child grows and changes over time and whether your child meets developmental milestones on RQ1 which is improving, RQ2 which is learning, RQ3 which is language and nonverbal communication, RQ4 which is physical activity, birth weight and premature birth, RQ5 which is special interests, RQ6 which is repetitive behavior, RQ7 which is maturity level, RQ8 which is dangerous behavior, RQ9 which is social interaction. If your child has not met the developmental milestones, we must consult with a specialized doctor right away to discuss your worries. The specialist doctor can also keep track on your children by asking you questions or interacting with them.

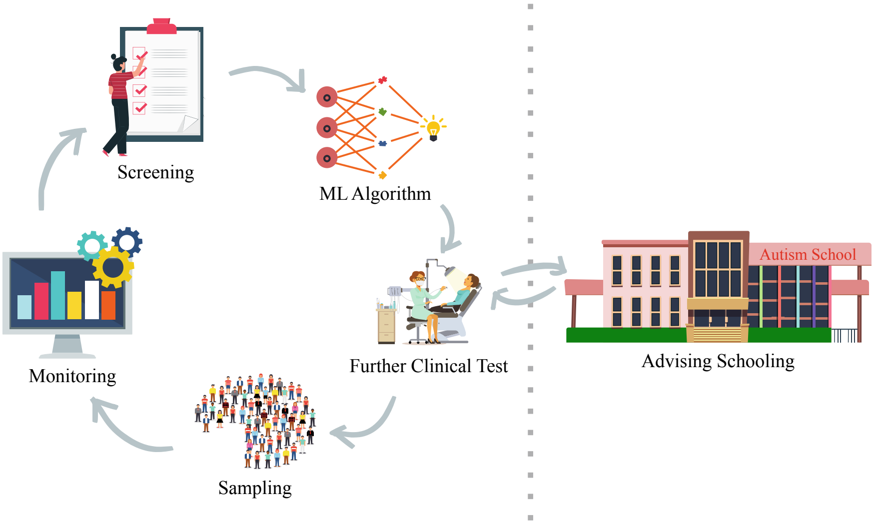

Fig. 1 Behavioral Monitoring of ASD children. The screening takes a closer look at how the child is developing. Moreover, children will get a brief test for behavioral analysis to complete the checklists based on research that ask questions about a child's development, including language, movement, thinking, behavior, interaction, speaking, learning and emotions. Developmental screening can be done by a doctor or nurse, but also by other professionals in healthcare, community, parents, or school settings

Screening: Your child's development is examined more closely during the test. A quick test will be administered to your child, or you will be asked to fill out a questionnaire about your child. Formal questionnaires or checklists that include questions on a child's development, including language, movement, thinking, behavior, interaction, speaking, learning, and emotions, are used for developmental and behavioral screening. A doctor or nurse can perform developmental screening, but it can also be done by other healthcare professionals, community members, parents, or educators. We created a smartphone app to test for ASD as part of this study. A machine learning model for the prior prediction of ASD was also built.

Evaluation: The screening tool is not a perfect method for obtaining a diagnosis, but it is critical in determining if a kid is on track for development or whether a specialist should be consulted. If the screening test raises concerns about a child's ASD, a formal examination may be required. A professional specialist, such as a developmental pediatrician, child psychologist, speech-language pathologist, occupational therapist, or other specialists, performs this formal evaluation.

3 Research Methodology

In this research, machine learning techniques have been proposed and applied voting classifiers to predict autism in children for better prediction. There are several formal screening processes to identify autism disorder in child and it's a very costly process. However, in this research work, a model has been build that can help physicians, doctors, and parents to predict autism in earlier stages avoiding the cost and a long-time process. Moreover, this is a beneficial way because if the prediction of autism is at an earlier stage then physicians, doctors, and parents can take the necessary steps for those children and early treatment can reduce autism. This research work used different machine learning algorithms such as Decision Tree, Random Forest, Gaussian Naive Bayes (NB), SVM, Adaboost, Multilayer Perceptron, Multinomial Naive Bayes algorithms, Logistic Regression. Finally, applied the Weighted Voting Algorithm to aggregate the base algorithms to find the best accuracy.

3.1 Data Collection and Description

In this research work, datasets have been collected from one of the autism schools (Malauri Autism School, Madhupur, Tangail) that are working with autistic children. Moreover, datasets were also collected from the doctor who gives treatment to the autistic child and their parents. We made a well-designed questionnaire for collecting data. We analyzed nearly 500 data of Autism children along with some standard data. These datasets bring 72 questionnaires and these questionnaires are categorized into the following:

1. Improving delay
2. Learning delay
3. Language problems & Nonverbal Communication
4. Physical Movement & Birth Weight & Premature Born
5. Special Interest
6. Repetitive Behavior
7. Lacking of Maturity
8. Dangerous Behavior
9. Social Interaction Delay

In this research work, these datasets have been used to train and evaluate eight machine learning models. Depending on all attributes of questionnaires, scored value is assigned which is shown in Table 1.

To discover our data sets, we used this matrix table to score all of the questions. Behavioral variables and individual characteristics such as Name, Gender, Age, and others (categorical data) are included in the dataset, as well as some numerical data. The variables in the ASD dataset are listed in Table 2.

Table 1 Scoring matrix table

Code	Value
Rare	1
Mild	2
Notable	3
Serious or severe	4

Table 2 List of attributes in autism data set

Attribute	Type	Descriptions
Name	Qualitative	List of name in text format
Age	Qualitative	Age in year
Gender	Qualitative	Male or Female
Living Area	Qualitative	Urban or Rural
Area of House	Qualitative	Small, medium, large
Numbers of family members	Qualitative	Four, Five, Six, Seven, etc.
Family member with PDD	Qualitative	Yes, No
Who is completing the test	Qualitative	Parents, health care provider, others
Improving delay	Numeric	(Q1-Q18), Question based on Survey
Learning Disability	Numeric	(Q19-Q25), Question based on Survey
Speech or other language problem,		
Nonverbal Communication	Numeric	(Q26-Q29), Question based on Survey
Physical Activity, Birth Weight&		
Premature Birth	Numeric	(Q30-Q34), Question based on Survey
Special Interest	Numeric	(Q35-Q46), Question based on Survey
Repetitive Behavior	Numeric	(Q47-Q52), Question based on Survey
lacking of Maturity	Numeric	(Q53-Q61),Question based on Survey
Dangerous Behavior	Numeric	(Q62-Q65), Question based on Survey
Social Interaction Delay	Numeric	(Q66-Q72), Question based on Survey

Legend: PDD—Pervasive Developmental Disorder

3.2 Machine Learning Classifiers and Evaluation Metrics

This subsection provides a brief overview of five alternative machine learning classifiers used to build class complexity predictors. The machine learning classifiers are as follows: (1) Decision Tree, (2) Multinomial Naive Bayes, (3) Random Forest Classifier, (4) Adaboost, (5) Multilayer Perceptron, (6) K-Nearest Neighbor, (7) Support Vector Machines, (8) Logistic Regression, and (9) Weighted Voting Classifier. These classifiers are well-known classifiers in building vulnerability predictors and are used in several similar research. The statistical performance of selected ML classifiers is calculated by performing a confusion matrix technique. Confusion Matrix is a technique for assessing how accurately a predictive model will perform in practice after generating the model. The objective of such an operation is to reduce the variability of the results.

3.3 Implementation

The implementation procedures are illustrated in this section. To carry out the study, Python and Scikit-learn libraries have been used. The models are executed on Google Colab Notebook and ML models are implemented and evaluated using the scikit-learn framework. Pandas and NumPy frameworks are used for loading and cleaning the datasets. Moreover, Matplotlib and Seaborn frameworks are implemented for data visualization (Fig. 2).

Dataset Pre-processing and Visualization The data processing step is categorized into Data Normalization, Mapping data into number & Filling Missing Value. In the collected data sets, the ages range from 1 to 18. Under the circumstances, these predictor variables are in very different ranges. So, normalization of these attributes has been performed. In data sets, there is some attribute in categorical data. Such as Gender, region, and House Area. We have to map these attributes values into 0 to 1. Approximately all machine learning classifier gives better result when data is in numerical value. Hence, the categorical data have been encoded into numerical data using the MAP function of the python library. In the collected data sets, there are some missing value attributes. In this situation, Handled the missing value using the FILLNA function of the Pandas library. After the above procedure, data is explored & visualized using the panda's library.

Feature Extraction It is a process of creating/deriving new features from the features which give more information and are less redundant. Feature Extraction is achieved through Principal component analysis. Improves the algorithm performance by reducing the no of dimensions: The training time of the algorithms reduces significantly with less number of features. Reduces overfitting of data: Overfitting mainly occurs when there are too many variables in the dataset. So, PCA helps in overcoming the overfitting issue by reducing the number of features. Also, PCA is

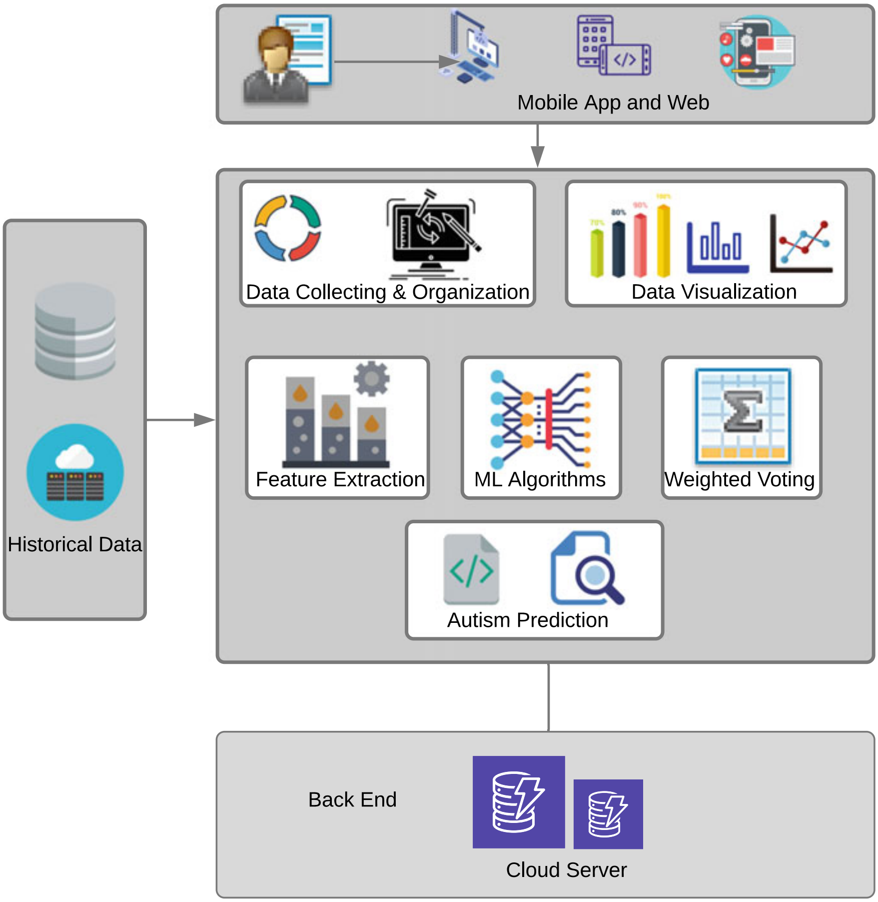

Fig. 2 A functional prototype of the proposed system

to help to figure out which are most important attributes in determining whether an individual has ASD or not (Fig. 3).

Train-Test Splitting Data All categorical variables have been converted into numerical features, and all numerical features have been normalized. As always, we will now split the data (both features and their labels) into training and test sets. 80% of the data will be used for training and 20% for testing.

Train and Fit Model In this step, Dataset has been trained with the training data using eight different classifiers. After doing this procedure, the Fit model is applied.

Aggregating the Outputs of the Base Classifiers: Eventually, using the Weighted Voting Classifier, this step aggregates the outputs of these seven base classifiers for achieving better performance.

Performance Evaluation: The performance of the base classifiers is compared to the performance of the Weighted Voting Classifier in this stage. Different mea-

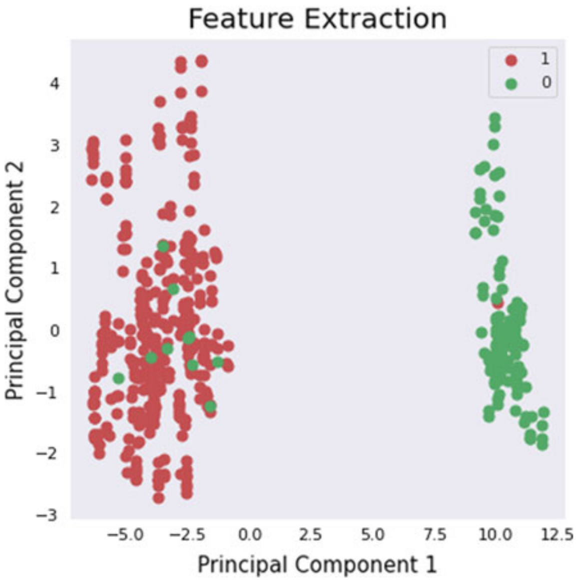

Fig. 3 Feature extraction results of autism dataset

surements are used to evaluate the performance of each base classifier: accuracy, precision, recall, and AUC Score. The number of vulnerable cases returned by a model that is genuinely vulnerable is measured by precision. The higher the precision, the lower the number of false positives. The number of vulnerable examples returned by a model is measured by recall. The lower the false negatives, the higher the recall. The harmonic mean of Precision and Recall is F-Measure. We use a binary classifier in this study, which can create two types of errors: false positive (FP) and false negative (FN). A true positive (TP) is a correctly categorized vulnerable class, while a true negative (TN) is a correctly classed non-vulnerable class (TN).

- True Negative (TN) = The number of classes predicted as low complex, coupled or lack of cohesive which are in actual the same.
- False Positives (FP) = The number of classes predicted as high complex, coupled or lack of cohesive but actually they are not.
- False Negative (FN) = The number of classes predicted as low complex, coupled, or lack of cohesive which turn out to have high.
- True Positives (TP) = The number of classes predicted as high complex, coupled, or lack of cohesive which are in actual the same.

I. **Accuracy** The most intuitive categorization performance parameter is accuracy. As indicated in Eq. 1, it is defined as the ratio of the number of entities accurately predicted to the total number of entities.

$$\text{Accuracy} = \frac{TP + TN}{TP + FP + TN + FN} \tag{1}$$

The ratio in this study refers to the number of classes accurately predicted as complicated versus the total number of classes.

II. **Precision** Precision is an evaluation statistic that measures how accurate the predictions are. It's calculated using Eq. 2 as the ratio of true positives to the sum of true positives and false positives.

$$\text{Precision} = \frac{TP}{TP + FP} \tag{2}$$

In our study, the ration defines how many autism classes are correctly predicted in terms of total number of total autism classes in prediction.

III. **Recall** Another extensively used performance statistic is recall. The ratio of successfully predicted positive entities to all entities is this statistic. Equation 3 gives the formula we apply to calculate recall in our study.

$$\text{Recall} = \frac{TP}{TP + FN} \tag{3}$$

The higher the recall, the fewer entities go undetected. In our investigation, a high recall value is sought so that fewer entries go undetected.

IV. F_1 **Score** Another key performance metric is the F_1 score, which is frequently regarded more valuable than accuracy. This is especially true when class distributions are uneven. It's derived as a weighted average of precision and recall in most cases. Equation 4 shows the formula that we apply to calculate the F_1 score.

$$F\_1\ \text{Score} = 2 \times \frac{\text{Recall}\ \times \text{Precision}}{\text{Recall} + \text{Precision}} \tag{4}$$

Equation 3 is used to compute recall, while Eq. 2 is used to determine precision. On the basis of our dataset, we use this statistic to see if the class distribution makes a difference.

V. **False Positive (FP) Rate** When the goal is to reduce the number of false positives in the confusion matrix, the False Positive Rate as a performance statistic is particularly valuable. One could argue that identifying the highly complicated classes is more significant in this study, even if it means mistakenly classifying some no autism class as autism. We take into account how models are geared toward autism class. Equation 5 is used to compute the FP rate.

$$\text{FP rate} = \frac{FP}{FP + TN} \tag{5}$$

VI. **False Negative (FN) Rate** A high false negative rate, on the other hand, indicates that there is a greater chance of missing high complex class files. It also means that autism class files are mistakenly identified as no autism class, which is quite dangerous. As a result, the FN rate is regarded as a dangerous model measurement. Equation 6 is used to figure out the FN rate.

$$\text{FN rate} = \frac{FN}{TP + FN} \tag{6}$$

In summary, we use these six performance metrics: accuracy, precision, recall, F_1 score, FP, and FN rate to evaluate the selected machine learning classifiers applied in this study.

Final Decision: According to the outcomes of the evaluation metrics, the best classifier for predicting the autism of the children has been selected in this step.

4 Experimental Result and Discussion

To analyze the performances of the executed models, this approach chooses a performance metric 'Accuracy'. The evaluation procedure determined how the model performed in a better way. This study easily calculates the confusion metrics of classifiers. Besides, the scores of Precision, Recall, and F1-score have also been computed. Confusion metrics depend on four basic qualitative model quality indicators, namely, true positive, true negative, false positive, and false negative. The confusion matrix describes the performance of a classifier which is presented in Fig. 4.

The Classification Accuracy, Recall, F-1 Score, Precision, and AUC (Area Under Curve) are shown in Table 3. Here Table IV, this research approach found that the Decision Tree correctly classified instances are 94%, Multinomial Naive Bayes (NB) correctly classified instances are 79%, Random Forest correctly classified instances are 96%, Adaboost correctly classified instances are 96%, Multilayer Perceptron correctly classified instances are 71%, KNN correctly classified instances are 95%, SVM correctly classified instances are 96%, Logistic Regression correctly classified instances are 96%, and Weighted Voting Classifier correctly classified instances are 97%. There are 150 instances in each of our test data sets. The aforesaid algorithms misclassified a few cases, as shown in Table 3, where MLP has the lowest accuracy of 71% and the Weighted Voting Classifier has the best accuracy of 97%.

The Area Under the Curve (AUC) of applied classifiers has also been calculated. When the AUC for a given classifier is 1.0, the classifier is deemed flawless, and when the AUC is 0.5, the classifier is considered worthless. The achieved AUC value for the Weighted Voting Classifier is 98, which is higher than the AUC values of other base classifiers, with the MLP having the lowest AUC value (Fig. 5). The AUC value of MLP is 50.00.

(a) Decision Tree (b) Multinomial Naive Bayes (c) Random Forest

(d) Adaboost (e) Multilayer Perception (f) K-Nearest Neighbor

(g) Support Vector Machine (h) Logistic Regression (i) Weighted Voting Classifier

Fig. 4 Confusion Matrix for different classifiers. **a** Confusion Matrix of Decision Tree **b** Confusion Matrix of Multinomial Naive Bayes, **c** Confusion Matrix of Random Forest **d** Confusion Matrix ofAdaboost **e** Confusion Matrix of Multilayer Perceptron **f** Confusion Matrix of K-Nearest Neighbor **g** Confusion Matrix of Support Vector Machine **h** Confusion Matrix of Logistic Regression **i** Confusion Matrix of Weighted Voting Classifier

5 Conclusions

This study aims to identify the characteristics that are most responsible for ASD. This method aims to find a link between the characteristics that cause ASD. That is, this method identifies the ASD-related characteristics. To discover these ASD characteristics, first train the training data set using various algorithms, then use algorithms to test data sets. The results of the test data sets were then evaluated, and some features that are mostly responsible for ASD were revealed. This research method examines how a weighted vote classifier performs somewhat better than the others algorithm.

Table 3 Measured results of different classifiers for predicting autism

Classifier Name	Accuracy	CL	Precision	Recall	F-1	AUC
Decision Tree	94%	NA	0.87	0.93	0.90	93.73
		A	0.97	0.94	0.96	
Multinomial Naive Bayes	79%	NA	0.64	0.62	0.63	83.44
		A	0.85	0.86	0.85	
Random Forest Classifier	96%	NA	0.96	0.90	0.93	95.73
		A	0.96	0.99	0.97	
AdaBoost	96.00%	NA	0.96	0.90	0.93	96.02
		A	0.96	0.99	0.97	
Multilayer Perceptron	71%	NA	0.00	0.00	0.00	50.00
		A	0.71	1.00	0.83	
K Nearest Neighbor	95.00%	NA	0.93	0.90	0.91	94.63
		A	0.96	0.97	0.97	
Support Vector Machine	96.00%	NA	0.96	0.90	0.93	96
		A	0.96	0.99	0.97	
Logistic Regression	95.00%	NA	0.93	0.90	0.91	93.59
		A	0.96	0.97	0.97	
Weighted Voting Classifier	97.00%	NA	1.00	0.90	0.95	98
		A	0.96	1.00	0.98	

CL—Class; A—Autism; NA—Not Autism

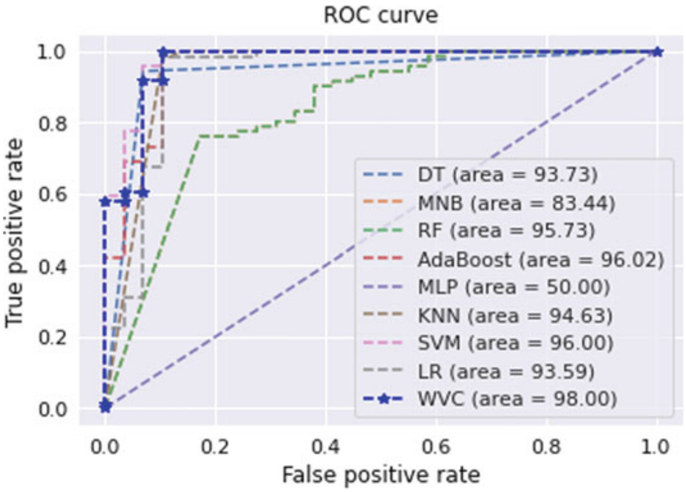

Fig. 5 Area Under the Curve (AUC) for different classifiers

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Chapter 6
DNN and LiDAR Sensor Based Crowd Avoidance Method for Nurse-Following Robot in Healthcare

Md Matiqul Islam, Hisato Fukuda, Yoshinori Kobayashi, and Yoshinori Kuno

1 Introduction

If a robot can follow a target person to give him or her proper support, it is necessary to avoid obstacles, especially humans because supporting robots must work in a crowded environment. For example, shopping malls, airports, hospitals and all the places where helping robot works, environment are crowded. For this reason, a supporting robot must have some functionalities such as manipulation [1, 2], vision [3, 4], and mobility [5, 6]. Especially we focus on avoiding human collision to follow a target person. Many research works have been done for these issues so far [7–14]. Our focus of this chapter is the targeted person-following based robot navigation that can avoid crowded environments.

In [15] the authors actively focused on the person-following mobile robot. We have developed a person-following shopping support robot [16], which helps to carry baggage items in a shopping mall. The main contribution of this work is person-following behavior. We developed a person tracking method based on OpenPose [17] and a color histogram matching algorithm, which is a robust person-following behavior in a crowded environment.

In this paper, we developed an obstacle avoidance method even if the target nurse is temporally lost as shown in Fig. 1.

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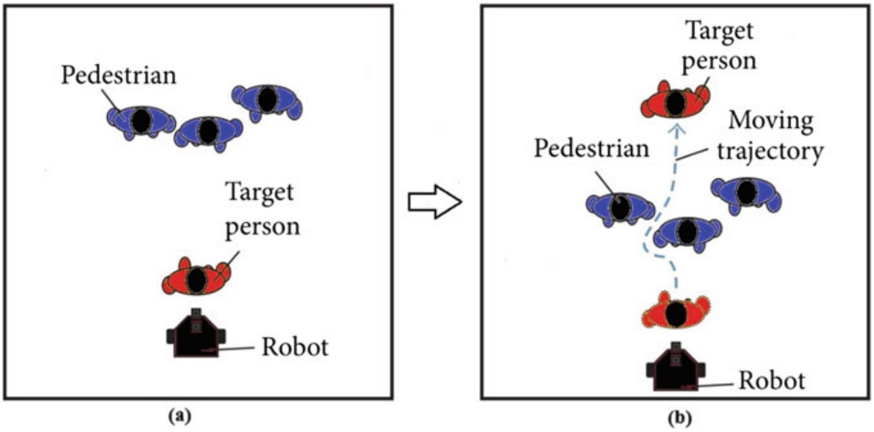


Fig. 1 Our proposed environment

2 Related Work

Early potential research in autonomous navigation for crowded environments was simply detecting the local obstacles and attempting to avoid them. It did not predict the future motion of the target person. In [18], Fox et al. use this type of approach using a dynamic window method. In the dynamic window approach, the robot moves between a start point and a goal point [8]. But the goal of our robot is to navigate following the target person.

Most of the obstacle avoidance techniques grew out of Reynolds' work on flocks and herds [19] and Helbing and Molnar's [20] social forces crowd model. Fiorini and Shiller's [21] velocity-based approach (notably refined by reciprocal velocity obstacles [22]) significantly advanced the field closer to where it is today.

Recent years continue to see improvements in crowd simulation algorithms. Wolinski et al. [23] created extremely precise local obstacle avoidance using probabilistic motion prediction, and Lu et al. [24] improved the performance of potential field-based crowds. Similarly, improvements have been seen with agents that realistically turn corners [25] and show appropriate etiquette when opening doors [26].

Other work focuses on agent-grouping behavior. Schuerman et al.'s work [27] added meta-data to locations in a structure or to a group of agents to avoid agent stalling and maintaining coherent agent groups. Other approaches include Kapadia et al.'s [28] framework focused on multi-agent scenarios.

Our robot can work in both static and dynamic cases because in every frame it can update the targeted and pedestrian person's position or locations and can change the targeted person's following path at any time.

3 The Crowd Avoidance Algorithm

Our robot can follow a target person in crowded environment like shopping malls. According to Fig. 1, the target person passes through the blocking persons. If there is a gap in the crowd, the robot can go through the gap. However, if there is no gap to pass through, the robot should avoid the crowd. The detailed procedure on how to follow our robot as a target person is discussed in [16]. In this paper, we focus on the crowd avoidance procedure. The total working procedure of crowd avoidance is given below:

3.1 Person Tracking

In our system, we use the histogram intersection algorithm to track the target person. From the human pose skeleton data, we crop the body using the left shoulder, right shoulder, left hip and right hip key points as shown in Fig. 2. Then in each frame, we compare each person's body image to the cropped image using the histogram intersection algorithm.

The histogram intersection algorithm was proposed by Swain and Ballard in [18]. Here the author considered two histograms I and M, each containing n bins, and the intersection is defined as,

$$\sum_{j=1}^{n} min\left(I_{j,} M_{j}\right) \tag{1}$$

We get the output of the histogram intersection model with an image histogram as the number of pixels from the model that have corresponding pixels of the same color in the image. The match value is given by,

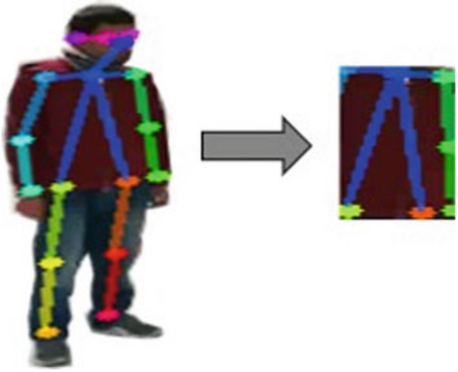


Fig. 2 Cropped image from skeletal key points information

$$\frac{\sum_{j=1}^{n} min\left(I_{j,} M_j\right)}{\sum_{j=1}^{n} M_j} \tag{2}$$

When an unknown object image is given as input, we compute the histogram intersection for all the stored models, the highest value is the best match.

3.2 Locate the Target Nurse and Pedestrian Person in the Space

To locate the target nurse and pedestrian person in the space, we calculate the positional angle value of the target nurse and pedestrian persons based on the 360° wide-angle camera as shown in Fig. 3. However, in practice, we find it sufficient to calibrate the total width of the image to be from 0° to 270° as shown in Fig. 3. Given the width of the image is W and the x coordinate of the person's ankle value is A, then we can easily calculate the person's positional angle value by the following equation,

$$AnkleAngle = \frac{270}{W} * (W - A) \tag{3}$$

After finding the positional angle value of a target nurse and pedestrian person, we input this angle value into the LiDAR sensor. The measuring distance of the LiDAR is from 60 to 2000[mm] and the measuring angle of it is 270° (see Fig. 4a). The LiDAR gets the 1081 data steps at the one scanning (see Fig. 4b), which means that every four data steps represent 1°angle.

When we input our target nurse and pedestrian person's positional angle value in the LiDAR sensor, we can easily get the positional coordinate value and distance.

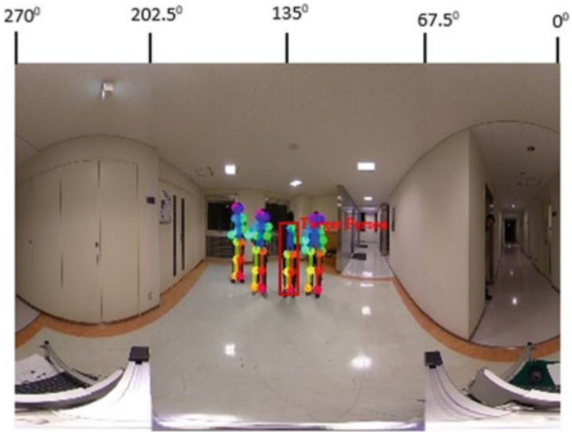


Fig. 3 Calibrating the width of the image 0° to 270° find the positional angle value of a nurse

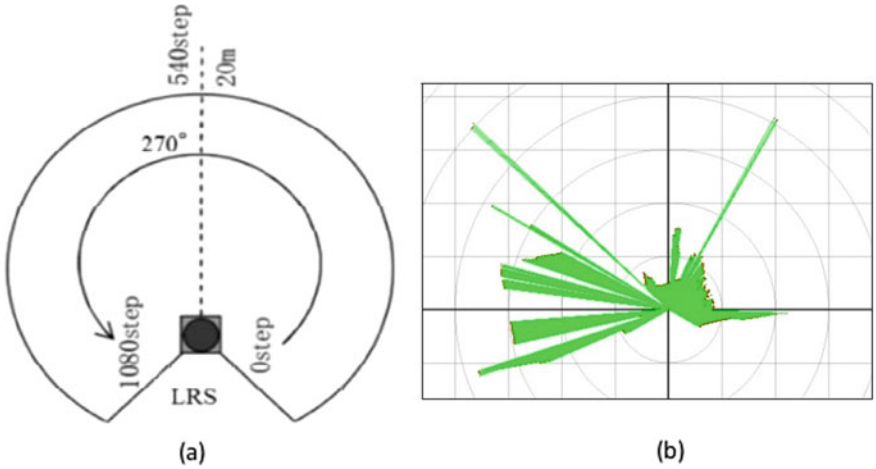


Fig. 4 **a** Measuring area of LiDAR. **b** Display of LiDAR

Figure 5 shows our total procedure for locating the target nurse and pedestrian person in space.

When there is no obstacle between the robot and the target nurse and our robot wants to follow the target nurse, first, our robot checks using the LiDAR sensor whether the target nurse's positional angle value is in the range (100–135)° or not. If not, then our robot rotates an angle θ according to Fig. 5. Now our robot orientation is according to the target nurse. Then it calculates the distance between the robot and the target nurse and follows the person at a certain distance. We calculate the distance using the Euclidean distance as,

$$Distance = \sqrt{(0-x)^2 + (0-y)^2}$$

3.3 Line Following Method

The line-following method is shown in Fig. 6a. Let $\Delta\theta$ [deg] be the angular difference between the robot's moving direction and the line to follow. Let $D1$ [mm] be the distance between the center position of the robot $\left(x_{0,}y_0\right)$ and the line to follow.

Let the equation of the line to follow be $y = mx + c$. Then $D1$ is calculated as follows,

$$D1 = \frac{y_0 - mx_0 - c}{\sqrt{1+m^2}}$$

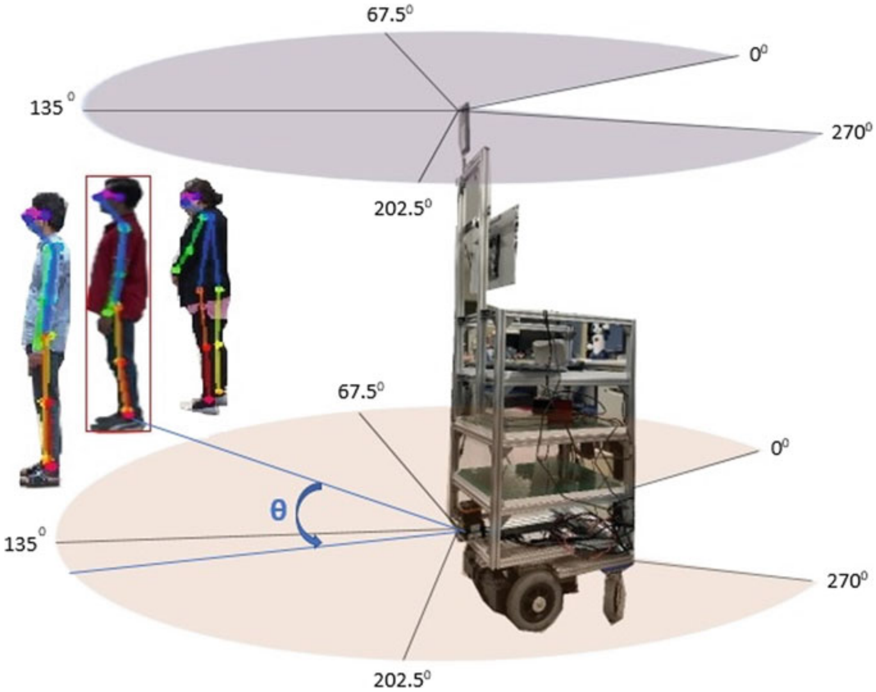
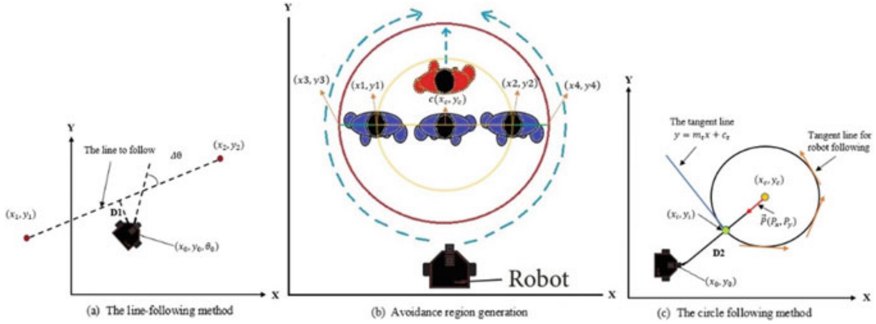


Fig. 5 Location of target nurse and pedestrian person in a space



(a) The line-following method

(b) Avoidance region generation

(c) The circle following method

Fig. 6 Methods for avoiding the crowd

Let, the two points on the line be $(x_{1,} y_1)$ and $(x_{2,} y_2)$. Then the angle of the line θ is

$$\theta = \frac{y_2 - y_1}{x_2 - x_1}$$

Then the angular difference $\Delta\theta$ is calculated using the angle of the robot θ_0 as follows

$$\Delta\Delta = \theta - \theta_0$$

3.4 *Circle Following Method*

Suppose the target nurse walks through the crowd, and the robot is blocked by the crowd. Figure 1b shows our proposed situations. In this situation, we apply the circle following method to avoid the obstacle. Before applying the circle following method, we must generate the avoidance region. We generate the avoidance region as follows:

The generation of the avoidance region is shown in Fig. 6b. First, we take the left most and right most person's positional angle value and pass it to the LiDAR sensor to get the coordinate value $\left(x_{1,}y_1\right)$ and $\left(x_{2,}y_2\right)$ in real space. Then, we calculate the center of these two coordinates as follows:

$$\{x_c, y_c\} = \left[\frac{x_1 + x_2}{2}, \frac{y_1 + y_2}{2}\right]$$

Using this center point and two coordinate values we assume a circle shown in yellow color. To make the collision free avoidance region we add or subtract to the previous coordinate Δx and Δy based on robot size and assume a larger circle shown in red color. The new coordinate values are:

$$\{x_3, y_3\} = [x_1 \pm \Delta x, y_1 \pm \Delta y]$$

$$\{x_4, y_4\} = [x_2 \pm \Delta x, y_2 \pm \Delta y]$$

The radius of the new circle is,

$$r = \frac{\sqrt{(x_4 - x_3)^2 + (y_4 - y_3)^2}}{2}$$

So, the equation of circle with center $\left(x_{c,}y_c\right)$ and radius r units for avoidance region is,

$$(x - x_c)^2 + (y - y_c)^2 = r^2$$

The next task is following a circle as shown in Fig. 6c. The circle following method is the same as the line-following method, where the tangent lines of the circle are used as the lines to follow.

First, consider the line segment between the center of the robot $(x_{0,} y_0)$ and the center of the circle $(x_{c,} y_c)$ and the intersection point of the line and the circle is $(x_{i,} y_i)$.

Let the tangent at $(x_{i,} y_i)$ be $y = m_t x + c_t$. Here, $D[mm]$ is the distance between the robot and the center of the circle, calculated as follows,

$$D2 = \sqrt{(x_c - x_0)^2 + (y_c - y_0)^2}$$

Then, let the vector $\vec{P} = (p_x, p_y)$ be a unit vector having the same direction as the line between the robot and the circle, directing from the circle to the robot. The vector is calculated as

$$\begin{bmatrix} p_x \\ p_y \end{bmatrix} = \begin{bmatrix} \frac{x_c - x_0}{D2} \\ \frac{y_c - y_0}{D2} \end{bmatrix}$$

and the intersection point $(x_{i,} y_i)$ is calculated as

$$\begin{bmatrix} x_i \\ y_i \end{bmatrix} = \begin{bmatrix} x_c + rp_x \\ y_c + rp_y \end{bmatrix}$$

where, r is the radius of the circle. Then the tangent line at the intersection point, $y = m_t x + c_t$, is calculated as follows,

$$m_t = -\frac{x_c - x_0}{y_c - y_0} and c_t = y_c - m_t x_t$$

Then the robot follows the tangent line using the line following method.

Our overall procedure of the crowd avoidance algorithm is as follows.

(1) Track the target nurse using color histogram matching algorithm.

(2) If the target nurse's position is not in the range $(100–135)^0$ rotate the robot θ^0 to Fig. 5. It ensures the robot's movement orientation towards the target nurse and then follows the target nurse if there is no obstacle between the target nurse and the robot.

(3) We set the minimum threshold value for the histogram intersection to track the target nurse. If the histogram intersection value is less than the minimum threshold value, it means that our target nurse is lost to the crowd area.

(4) If the target nurse is lost, our robot calculates the distance of the nearest pedestrian person in the same direction and moves to that person. At the same time, it calculates the angled gap between the nearest pedestrian person and the other pedestrian person. If our robot finds any angle gap greater than or equal to 35^0 our robot moves to that gap and finds the lost target person.

(5) If angle gap is less than 35^0 our robot finds the location coordinate of the left most and right most pedestrian person and assumes a circle that passes to this coordinate and find the collision-free avoidance path according to Fig. 6b.

(6) After avoiding the crowded region, if our robot again finds the target nurse then goes to step (2).

Figure 7 shows the flowchart of our proposed crowd avoidance algorithm.

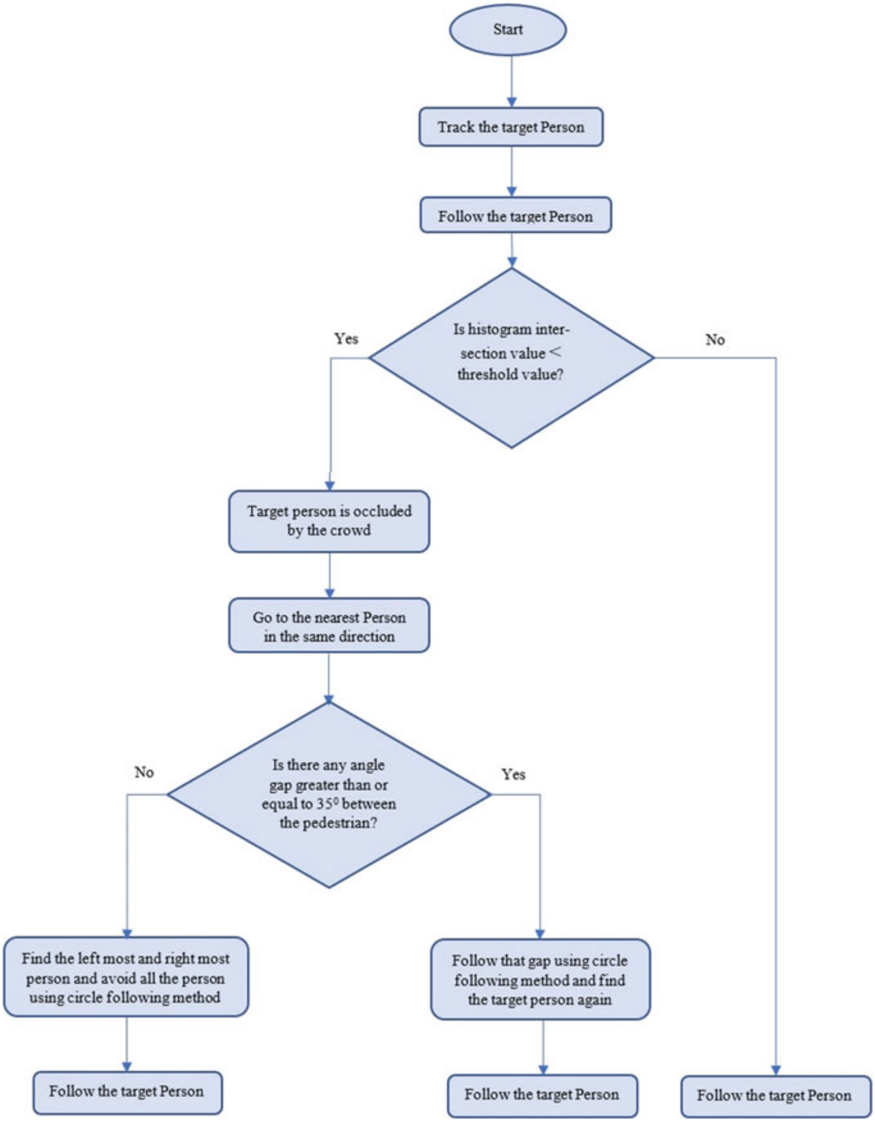


Fig. 7 Flow chart of our proposed crowd avoidance algorithm

4 Experiments of the Crowd Avoidance

To verify that our robot actually could avoid the crowd we experimented with the different patterns as shown in Fig. 9. In the experiment, three-person blocks the robot from a target nurse and the robot moved to avoid the person.

4.1 Hardware

Figure 8 shows the architecture of our mobile robot. Our robot is equipped with one 360° camera at the top and one LiDAR(Hokuyo UTM30-LX) sensor at the bottom. Mini Cart was used as the moving base.

4.2 Experimental Conditions

Figure 9 shows our experimental conditions based on a different pattern. We check patterns 1 to 4 to see that our proposed method worked for a different arrangement

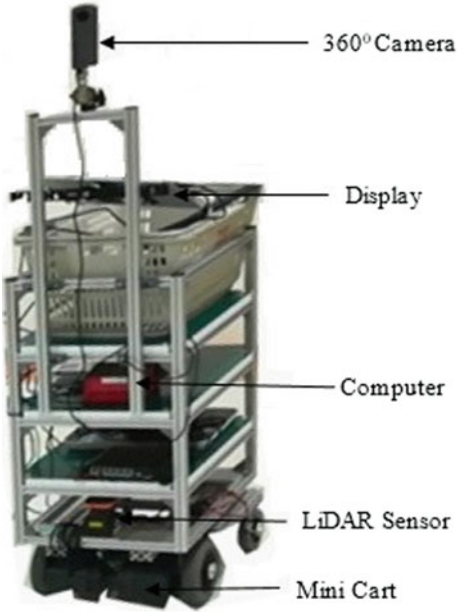


Fig. 8 Our proposed mobile robot

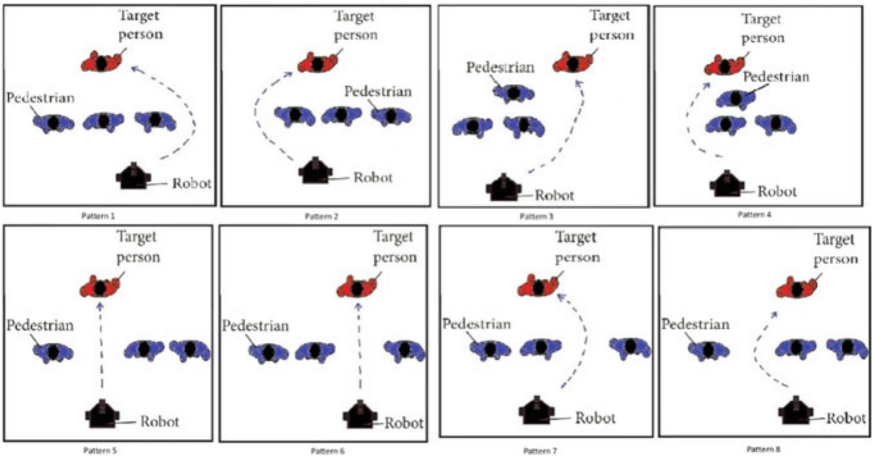


Fig. 9 Pattern of the crowd

of the crowd. Patterns 5 to 8 check if the robot could pass through the crowd when there was a wide gap in the crowd that was enough for the robot to go through.

In our experiment, our robot follows the target person with a minimum 500 mm gap behind the target person.

4.3 *Experimental Results*

Figure 10 shows the robot's camera view using a 360° camera. In this figure, we see that our robot tracks a target person using a color histogram matching algorithm. Figure 11 shows the corresponding location and position of the target nurse and pedestrian persons.

Fig. 10 Robot's 360° camera view

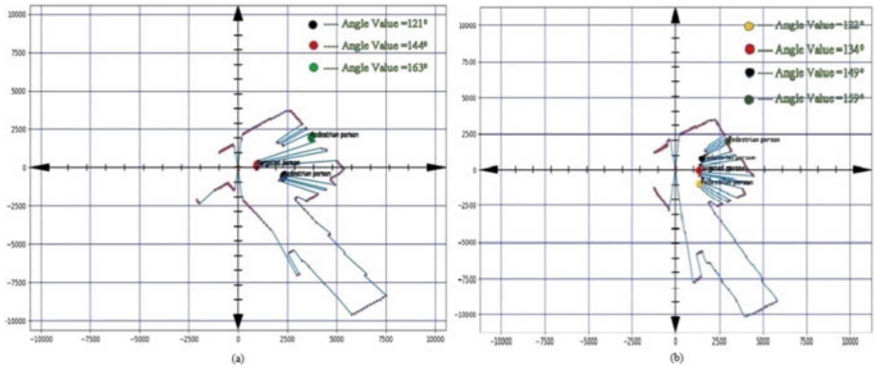


Fig. 11 Location of target person or nurse and pedestrian person in LiDAR sensor

According to Fig. 10a and 11a, we see that our target nurse is the nearest person from the robot's (0,0) position. In this situation, our robot follows the target nurse at a certain distance behind.

In Fig. 10b we see that our target nurse moving in the larger gap between the pedestrians. The corresponding nurse's location and angle value are shown in Fig. 11b.

Figure 12a shows that our target person or nurse is occluded by the pedestrian person. Figure 12b shows that no target nurse is detected by the laser sensor. In this situation, our robot goes to the nearest person in the same direction and finds the large-angle gap between the pedestrian persons. If our robot gets the angled gap between the pedestrians greater or equal to 35° our robot moves in that gap using the circle following method. This pattern is similar to pattern 7 as shown in Fig. 9.

Figure 13 shows the results of a person avoiding a procedure. Figure 13a shows

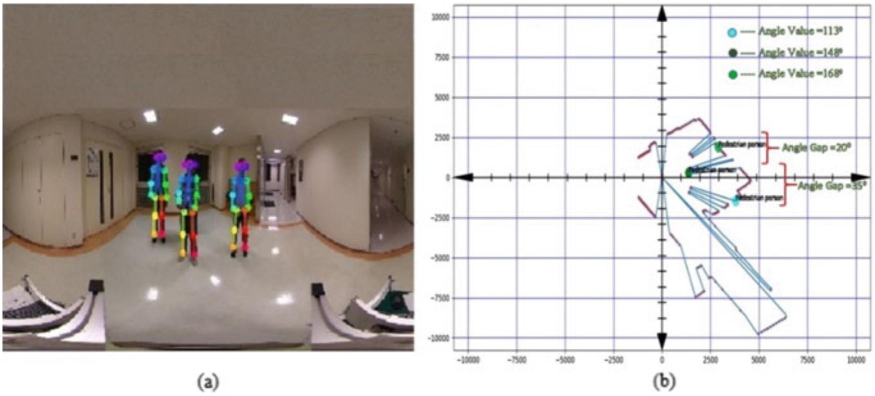


Fig. 12 Find the large angle gap between the pedestrian persons when target person or nurse is absent

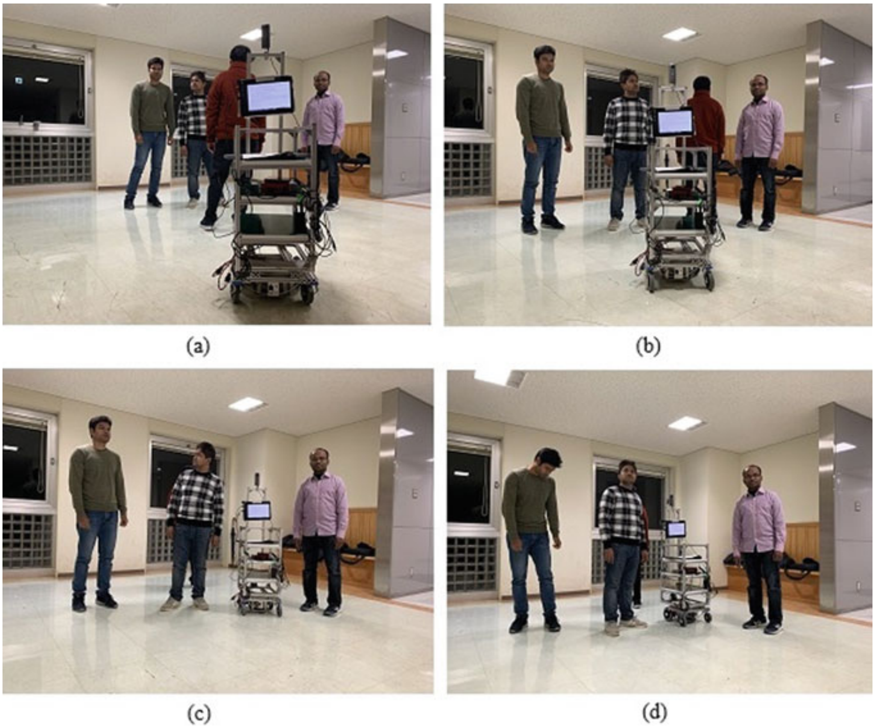

(a) (b) (c) (d)

Fig. 13 Results of obstacle avoiding

that our robot follows a target person. Figure 13b shows that our target person moves the largest angle gap between the pedestrian persons. Figure 13c shows that the target person is occluded by the pedestrian person. In this situation, our robot goes to the nearest pedestrian person and avoids the pedestrian person using the circle following method. Figure 13d shows that our robot again finds the target person and follows him using the line following method.

5 Conclusions and Future Work

In this research, first, we developed a target person or nurse following robot then developed a crowd avoidance method. Using this method, the robot could avoid the crowd even if the person is moving in the crowd. Besides, the robot could pass through the crowd when there was a gap with enough width.

In the experiment, we do not use any map for robot movement. In the future, we will include map generation and shortest path following algorithm to make our robot more efficient.

In the future, we also want to include automatic group detection as it contains sufficient information to allow real-time classification of entities. This classification should improve the realism of group avoidance instead of pedestrian avoidance and will allow modeling of both individual and group behavior and combine them.

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Chapter 7
Investigation on Heart Attack Prediction Based on the Different Machine Learning Approaches

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1 Introduction

Pre-detection of heart attack can not only save lives but also reduces other health related complications that happen subsequently. According to the World Health Organization (WHO), heart diseases are the main cause of death in the twenty-first century. In 2016, 16.5% of the total death happened because of ischaemic heart disease [36]. Among the heart diseases, long lasting Cardiac Ischemia which is also known as a Heart Attack is the lone cause of most of the deaths. Nowadays, modern hospitals maintain a huge amount of patient data which can be used for automated detection of the disease. Moreover, real time data using IoT devices can be acquired, which can help in predicting the disease which the person may encounter in the future. Different machine learning algorithms can be used for classifying heart attacks.

Most of the research that has already happened in this sector is for generalized users all over the world. But the features that contribute to heart disease have different ranges for different parts of the world as it depends much on the weather, food habits, and ethnicity. If a model is proposed which is generalized for people all over the world

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then it might not predict as good as a model which is built solely for some specified ethnicity group.

Machine learning and deep learning can be used in the biomedical field [5–7, 40], automated systems [3, 4, 15], natural language processing [14, 16], pattern recognition [1, 2], and many fields. In heart attack prediction, machine learning and deep learning based approaches have been explored in many researches. Most researchers have used ECG data along with the patient's personal information as features and used data mining techniques for classifying them [45]. Gupta et al. proposed an automated mathematical model of a heart attack detection system. With the help of the fuzzy c-means algorithm, this model can provide accurate information on possible heart attacks [17]. The proposed model is formed on the real time data of the patients. To remove ambiguity and uncertainty, a membership function can be introduced for classification and a Neuro-Fuzzy system can also be used [33]. Gurjar and Sarnaik proposed a system of heart rate monitoring, which continuously monitors the heart rate of a person via some sensors along with the temperature and blood pressure of the patients [18]. Patel et al. proposed a possible heart attack detection system with pulse sensors. An extreme change in the heart rate comparing to the set points will be alerted by a message [37]. An instantly accessible, cloud-based model was proposed by Yahyaie et al. [45]. Majumder et al. proposed a low power communication module and a personalized system for each user for reacting to cardiac arrest [32].

Dutta et al. [11] addressed the class imbalance problem in Coronary Heart Disease (CHD) prediction by implementing a shallow Convolutional Neural Network (CNN). LASSO feature selection technique was used to eliminate features and the majority voting technique was used to obtain dominant features. The dominant features were then homogenized and fed into the convolution layers. The simulated annealing technique was employed in the training process to improve the classification accuracy. The results showed that it could correctly predict the presence of CHD with 77% accuracy.

Wang et al. [44] introduced a data processing algorithm to tackle the challenge of imbalanced data in heart attack forecasting of stroke patients. The under sampling, over sampling and clustering approaches were utilized to propose the under sampling clustering-oversampling (UCO) data processing algorithm. After processing the data by the UCO algorithm, several ML classifiers were deployed to predict the heart attack of stroke patients. The combination of UCO and RF classifier achieved the highest accuracy when compared to all the other classifiers.

Khan et al. [23] proposed a Modified Deep Convolutional Neural Network (MDCNN) to predict heart disease using the IOT framework. A smart watch with a heart monitoring gadget was placed on the heart disease patient's body to collect blood pressure and ECG data for predicting heart disease. It has been reported that the proposed MDCNN achieved a maximum accuracy of 98.2% in predicting heart disease.

Nalluri et al. [35] analyzed the Framingham dataset to forecast the possibility of heart disease in a person using XGBoost and LR algorithms. At first missing values were removed from the dataset and split into train and test parts. Then the XGBoost and LR algorithms were utilized to predict CHD based on various symptoms. The LR algorithm showed better accuracy compared to the XGBoost algorithm. However, XGBoost consumes less time for larger datasets.

Garate-Escamilla et al. [13] utilized the composition of Chi-square and Principal Component Analysis (PCA) feature selectors to predict the heart disease of a person using the UCI heart disease dataset. It has been reported that the pro-posed method with RF classifier achieved the highest performance in predicting heart disease. Ayon et al. [8] presented a comparative study of different artificial intelligence (AI) algorithms to predict coronary artery heart disease using Cleveland and Statlog datasets. Seven AI algorithms were implemented to predict heart disease where the deep neural network achieved the highest accuracy of about 98.15%. Maji and Arora [31] predicted the heart disease of a person using a hybrid approach where the DT algorithm and ANN algorithm were combined to improve the performance. A publicly available heart disease dataset from UCI machine learning repository was used to validate the performance of the proposed hybrid method with the help of tenfold cross validation.

Mohan et al. [34] proposed a Hybrid RF algorithm and Linear Model (HRFLM) algorithm to predict cardiovascular disease utilizing the Cleveland heart disease dataset. Several stages such as data preprocessing, feature selection and classification were involved to predict heart disease. The result showed that the proposed HRFLM method obtained good accuracy in predicting heart disease. Katarya and Meena [22] analyzed the risk factors of cardiovascular disease and found the influence of risk factors on heart disease. Several ML classifiers were employed to predict the cardiovascular disease using the UCI heart disease dataset and the RF classifier showed better accuracy compared to the others.

Magesh and Swarnalatha [30] proposed a Cluster-based Decision Tree Learning (CDTL) technique to predict heart disease using state-of-the-art ML classifiers. The main goal of CDTL was to obtain the optimal feature set for predicting heart disease. The Cleveland heart disease dataset was used to validate the performance of the proposed model. Based on the optimized features obtained by the CDTL method, the RF classifier achieved the highest accuracy.

In this research, a comparative study of different popular ML algorithms was performed and determined which algorithm performs better with the Cleveland dataset. The best combination of ANN was searched and used for the prediction of a heart attack. The performance comparison was not only based on accuracy but also on the F1-score which involves the sensitivity and specificity of a model. Finally, the proposed model was compared with the other heart attack research to establish the supremacy of the model.

2 Machine Learning Algorithms

ML is a sub-division of Artificial intelligence, which is based on the concept of learning a pattern from training data and inferring a class from it. So, it is a two phase system which comprises of finding a pattern from the training dataset and predicting an unseen instance based on that knowledge. ML algorithms can be classified as supervised and unsupervised. In the case of supervised techniques, the training samples are well labeled with specific class names and prediction is a class among them. In unsupervised techniques, the class labels are not in knowledge. Therefore, clustering of data is done [26]. A lot of ML techniques can be found of which the most popular ones are SVM, LR, RF, NB classifier, DT classifier and KNN algorithm. We will use these algorithms to find out which algorithm works better in the context of classifying or predicting heart attacks.

2.1 Support Vector Machine

SVM is a supervised classifier which draws a hyperplane in an N-dimensional plane [42]. It provides an optimal hyperplane which separates two classes. But it can be extended to multiple classes. This algorithm is also used for regression. When data is not linearly separable by a hyperplane, it converts the plane into higher dimensions. This trick is called Kernel. It makes classification possible in nonlinear data. SVM has regularization capability and can handle both linear and nonlinear data. On the other hand, SVM is computationally expensive and it is hard to choose a perfect kernel. It also takes a longer training time. SVM is widely used in medical image processing [21], image classification [43], image interpolation, medical classification, and so on. Figure 1 shows the process of SVM.

2.2 Logistic Regression

LR is a supervised binary classifier where the sigmoid or logistic function is used to model the data and a linear or nonlinear decision boundary is used to predict the

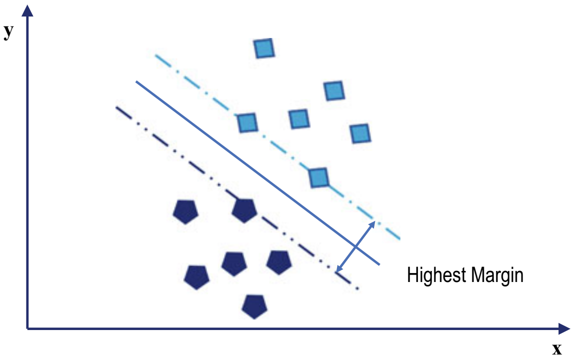

Fig. 1 The working principle of SVM

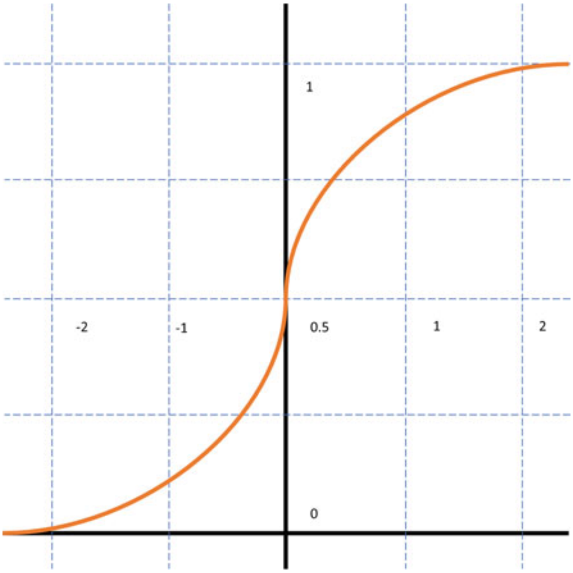

Fig. 2 The working principle of LR

class. It produces a value between 0 and 1. Implementation of logistic regression is quite simple, has a smaller number of parameters and overfitting can be reduced through normalization [25]. It does not perform well when there are too many classes to classify and it does not have a high predictive accuracy.

Logistic function can be described as Eq. (1).

$$g(x) = \frac{1}{1 + e^{-x}} \tag{1}$$

Figure 2 shows the overall process of LR.

2.3 *K-Nearest Neighbor Algorithm*

KNN is one of the simplest classification algorithm which is widely used in pattern recognition, multi-label classification [20], big data analysis, and so on. It is a supervised non parametric classifier which is dependent on feature similarity. In KNN, K refers to the number of neighbor elements in a group or cluster. To determine the neighbor, at a first distance has to be measured between the test data and training data using distance. Any of the following distance functions such as: Euclidean distance, Minkowsky distance, and Chi-Square distance can be used for this purpose. The performance of KNN is largely dependent on the distance function [19]. Then distance is sorted and the lowest k samples are taken and classified into a single class or cluster. The main advantage of KNN is that it is considerably easy to implement

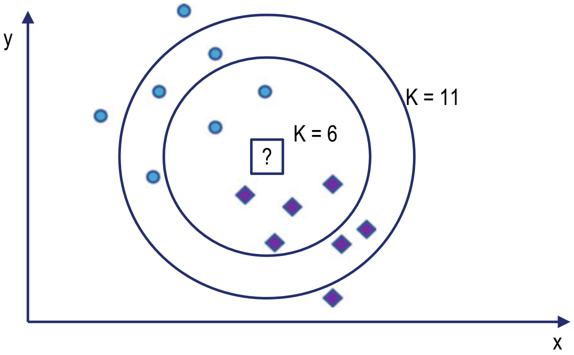

Fig. 3 The working principle of KNN

and no model or parameter tuning is required. It gets slower as the variable increases. Figure 3 shows the process of KNN.

2.4 Random Forest Algorithm

The RF algorithm was proposed by Breiman which is similar to bagging but adds an extra layer for introducing randomness. It constructs each tree with the different bootstrap samples of the training samples but changes the construction procedure of the regression tree. The nodes are divided by the best split among a subset of the data samples chosen randomly. This provides robustness in overcoming overfitting that can be found in algorithms like SVM [28]. Figure 4 shows the process of the RF algorithm.

2.5 Naive Bayes Classifier

In Bayesian classifiers, the class with the highest probability is assigned to the sample instance which is elaborated in the feature vector and assumed that features are not related to the predicted classes. The resulting classifier is known as the Naive Bayes classifier and though its assumptions are quite unrealistic, it sometimes outperforms other ML algorithms and is effectively used in medical diagnosis related scenarios [38]. Here, optimality in terms of classification error is not strictly related to the performance of fitting to the distribution of probability but rather depends on actual and predicted probability distributions given the same output class.

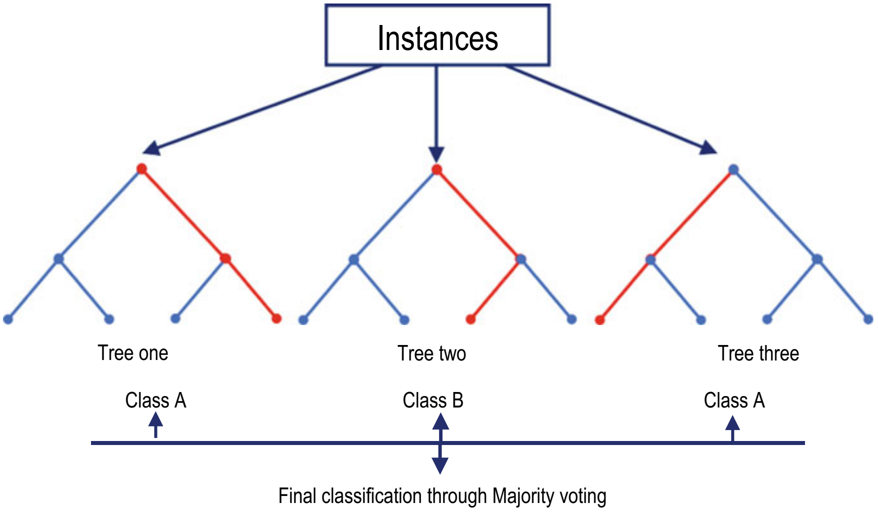

Fig. 4 The working principle of RF

2.6 Decision Tree Classifier

DT algorithms are supervised learning algorithms which can be used for solving both classification and regression problems. This creates a tree where internal nodes represent features and the leaf nodes represent class labels. At first, the training data is considered as a root node and based on the categorical values data samples are distributed recursively [39]. Here, the main challenge is to identify the root node at each level and this selection procedure uses information gain or Gini index. DT algorithms work well with categorical data. Figure 5 depicts the working of the DT algorithm.

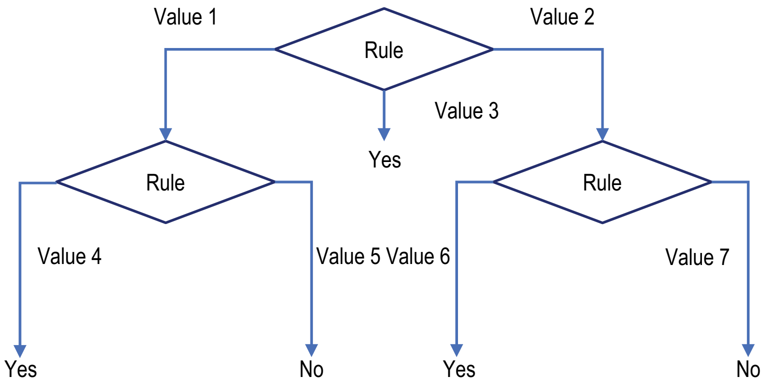

Fig. 5 The working principle of DT

Table 1 Attributes of the dataset

Attribute	Description
Age	Age in years
Sex	1 is male, 0 is female
CP (Chest Pain)	0 is typical angina, 1 is atypical angina, 2 is non angina pain and, 3 is asymptotic
TrestBps	Resting Blood Pressure
Chol	Serum Cholesterol
Fbs	Fasting blood Sugar
RestEcg	Resting electrocardiographic result
ThalaCh	Maximum heart rate achieved
Exang	Exercise induced angina
OldPeak	ST depression induced by exercise relative to rest
Slope	The slope of the peak exercise ST segment
CA	Number of major vessels colored by fluoroscopy
Thal	3 is normal, 6 is fixed defect, 7 is reversible defect
Target	1 is heart attacked, 0 is not heart attacked

3 Dataset

The dataset is provided by Kaggle and the data are collected from four locations-Cleverland Clinic Foundation, Hungarian Institute of Cardiology, V. A. Medical Center and University Hospital Zurich. This dataset has 14 features which are taken from 76 features of the original dataset. The attributes are shown in Table 1.

Then the dataset was fed to the proposed model and features were extracted. The extracted features were used to classify heart attacks. The dataset has 303 instances.

4 Methodology

In this research, the dataset provided by Kaggle has a lot of missing values. Therefore, adjusting the missing values was needed prior to feeding the data to the ML classifiers. Therefore, interpolation was used for the missing values. There were data from 303 patients. The attributes with categorical data were split into new attributes of its parent categories. Then we applied the data to SVM, LR, RF, NB, DT, and KNN classifiers.

We then used the Keras Tuner library to find the best combination of dense layers for the ANN. For the first layer, 50 to 500 neurons were evaluated with a step size of 50. Then the number of dense layers was checked. We have checked for 1 to 20 layers with 50 to 500 neurons. For finding the best model 10 trials were done. The performance of the best models found by this method is given in Table 2.

Table 2 Best ANN models found by the tuning process

1st Dense Layer(Neurons)	Dense Layers (Neurons)	Accuracy (%)
1(250)	1(125)	89.32
1(200)	4(100, 175, 150, 175)	88.34
1(100)	4(75, 175, 50, 50)	88.34
1(100)	4(75, 100, 125, 75)	88.34
1(100)	2(50, 50)	87.37

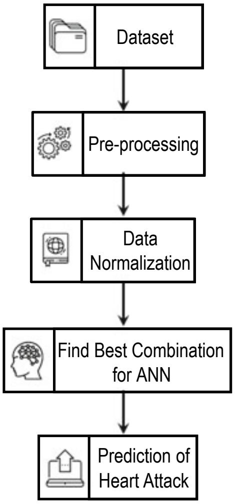

Fig. 6 A flowchart of the methodology followed in this research

We then trained the best model for 1000 epochs with 200 instances and tested the model with 103 instances. We also calculated the sensitivity and specificity of each algorithm. The performance of the ML algorithms and the ANN model were compared. Finally, the performance of the proposed model with the different heart attack prediction studies was also compared. In Fig. 6, the overall methodology is explained. The proposed ANN model is depicted in Fig. 7.

5 Result and Discussion

In this section, the results of the proposed model and the other ML algorithms will be discussed. First of all, the proposed ANN model used 200 records of the patients for training purposes. Here, almost 34% of the data were used for testing purposes. Of the 103 testing instances, the model successfully predicted 93 instances. Only in ten instances, the model provided the wrong result. The model achieved a sensitivity of

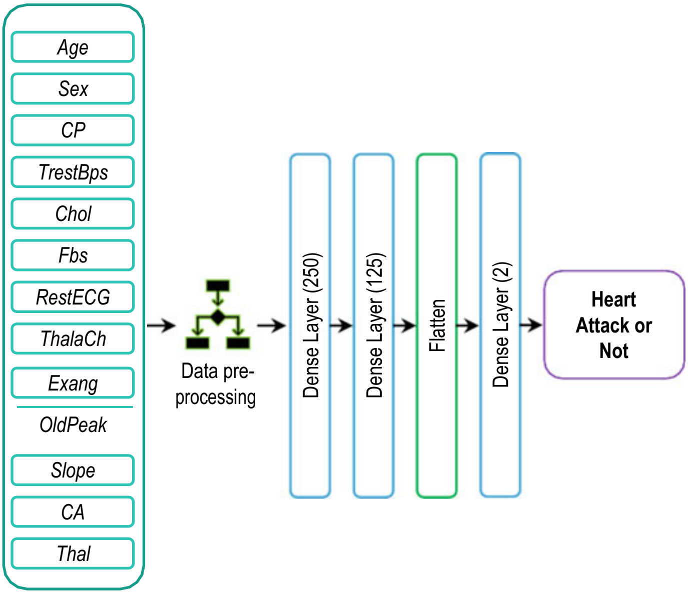

Fig. 7 Architecture of the proposed ANN model

0.9444, and specificity of 0.8571. The positive predictive value was 0.9333 and the negative predictive value was 0.8793. This means that the model's performance is not biased. It can predict both the heart attack and the negative samples. The overall accuracy of this model is 90.29%. Table 3 shows the detailed performance of the model.

The ML algorithms were not a match to the proposed ANN model. Figure 8 shows the comparison of the accuracy and F1-score of the ML models and the proposed model. It can be seen that in terms of the accuracy the RF algorithm and the LR algorithms provided the best performance among the shallow ML algorithms, which is 83.49%. However, the proposed model is at least 7.5% better in terms of accuracy. The NB algorithm provided 82.53% accuracy. The SVM algorithm produced the least accuracy of 56.31%. Due to missing values, the SVM model could not produce a good result.

Table 3 Performance of the proposed ANN model

Metrics	Value
Sensitivity	0.9444
Specificity	0.8571
Positive Predictive Value	0.9333
Negative Predictive Value	0.8793
Accuracy	90.29%

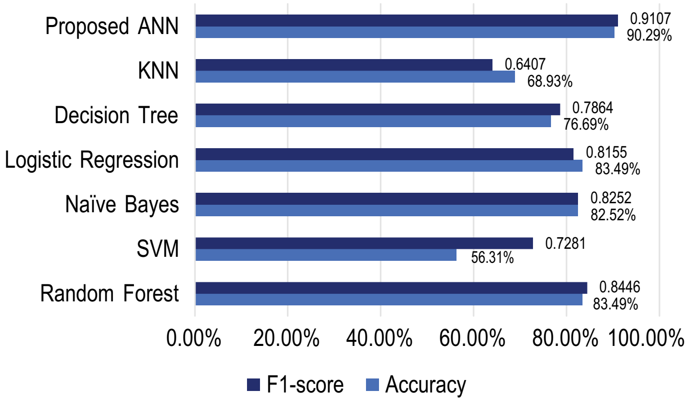

Fig. 8 Performance comparison of the proposed model with the ML models

In terms of F1-score, the RF algorithm produced the highest performance among the ML algorithms, which is 0.8446. The F1-score of the proposed model is 0.9107, which is much higher than the best ML model. The NB algorithm performed better than the RF algorithm in terms of F1-score. The lowest F1- score was achieved by the KNN algorithm, which is 0.6407. The proposed model showed better performance than the other ML algorithms.

In Table 4, the performance of the proposed model was compared with the other studies of heart attack prediction. These researches used algorithms like RF, XGBoost, SVM, backpropagation, and so on. The highest accuracy among these studies was achieved by Khemphila and Boonjing [24]. They achieved 89.56% accuracy with the backpropagation-based multi-layer perceptron (MLP) model. They achieved 89.56% accuracy. In terms of accuracy, our model is slightly better than that model. The proposed model outperformed the other models on the used dataset.

Table 4 Comparison of different studies with the proposed model

References	Dataset	Algorithm	Accuracy (%)
Wang et al. [44]	MIMIC-III	Random Forest	70.29
Nalluri et al. [35]	Framingham	XGBoost	85.86
Soni et al. [41]	Cleveland	Association rules	81.51
Kumari and Godara [27]	Cleveland	SVM	84.12
Khemphila and Boonjing [24]	Cleveland	Backpropagation MLP	89.56
A.K. Dwivedi [12]	Statlog	LR	85.00
Chadha and Mayank [10]	Statlog	DT	88.03
Caliskan and Yuksel [9]	Statlog	DNN	85.20
Long et al. [29]	Statlog	Firefly algorithm	87.20
Proposed Model	Cleveland	ANN	90.29

6 Conclusion

To predict the heart attack of a patient, ML algorithms can be a go to solution. With some changes in these algorithms and modifying hyper parameters, these algorithms can perform better. This study tried to unveil that with combinations of ANN, the performance of the ML algorithms can be improved for detecting heart attack. In the dataset, the target labeled 1 had over 90% chance of having a heart attack and our proposed model performed best in finding these. The database used resting ECG results and ST depression induced by exercise relative to rest. For these parameters, ECG was used. Therefore, a low cost ECG based heart attack pre-detection model can be created, which can use the proposed model as a classifier, which will definitely save many people from a heart attack.

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Chapter 8
Wearable Devices for Monitoring Vital Rhythm and Earlier Disease Diagnosis of Treatment

Ishrat Sultana, Fahiba Farhin, and Fatematuz Zohora

1 Introduction

Different types of automated wearable healthcare technologies have been introduced to work on patients with chronic disease for better management through continuous and real-time monitoring of various vital rhythms. According to World Health Organization (WHO), 75% of all deaths all over the world are responsible for chronic disease [53]. Physiological Diseases, such as Respiratory diseases, Convulsive Seizures, Cardiovascular disease, etc., and neurological disorders [29] such as Alzheimer's disease [40], Parkinson's disease, autism spectrum disorder (ASD), etc. can be effectively diagnosed by manipulating perceived data from wearable sensors placed into different healthcare devices using various machine learning and integrated approaches [7].

The human body has different vital physiological rhythms that can be measured via wearable devices and used to recognize health status for further treatment. Before understanding how the rhythms are received and processed, it is important to understand the main biological facts that contribute to the analysis of human body functioning. Body temperature, Electrocardiogram (ECG), Heart rate, Blood pressure (BP), Respiration Rate, Blood oxygen saturation (SpO2), Blood glucose, Skin perspiration, etc. are the most important biosignals that are used in the disease diagnosis process [9]. With the increasing growth and high availability of Electronic Healthcare Records (EHRs), a few studies have reported the associations between different diseases and vital biological rhythms of the human body. For example, ECG, BP, and

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heart rate are used to analyze cardiovascular disease [45]; Blood Glucose for type 2 diabetes detection [57]; body movement information for Convulsive Seizures [26]; breathing cycle data for respiratory diseases [3, 35]; body temperature for Febrile Neutropenia [48] diagnosis. A disease that involves physiological and behavioral patterns is directly associated with body acceleration, daily activity, and nervous system information [4].

With recent developments in the healthcare field, wearable technology is extensively used to monitor the condition of patients and take immediate action in case of any imbalance of vital rhythms of health. The market was estimated at $16.2 billion till 2021 for wearable medical devices and it is expected to reach $30.1 billion by 2026 at 13.2% [1]. The upward trend of this technology is influenced by the benefit of remote health monitoring systems and real-time interaction with the health service providers. One statistics shows that 70% medical wearable users have given positive feedback about using these devices initially rather than going to the hospital because of the mismanagement of healthcare services. After the pandemic of 2020, the number of adult users of wearable devices has increased from 42 to 54% in the USA [2]. This has intrigued the gadget industry to innovate more wearable devices in the medical field. Fitbit, Amazon, Apple, and Samsung have already invented smartwatches and fitness trackers to monitor the daily rhythms of the users [27]. Besides these, wearable ECG monitor, wearable biosensors are also at the highest priority to develop for the users. This diversification of available devices and biosensors has paved a new era for healthcare services. But the success of this technology depends on the reliability, confidentiality, and interoperability of this whole digital healthcare management system.

This review paper aims to analyze the comprehensive literature on the earlier disease diagnosis based on vital rhythms monitored by wearable devices which will widen the further research scope. The following Research Questions (RQs) have been investigated for this purpose: RQ1. "What is the significance of wearable devices in healthcare monitoring?" RQ2. "How are vital rhythms monitoring integrated into proposed architectures, specifications, and contributions for supporting earlier disease diagnosis?", and RQ3. "What challenges will lead to future research for delivering accurate and reliable disease diagnosis?"

To respond these research questions efficiently, this review paper has explored the technological requirements of wearable devices and the specifications of disease diagnosis. Major contributions of this work are mentioned below:

1. A substantial review of different types of wearable devices by presenting a comparative table of their features.
2. A study on wearable devices and vital sign monitoring on different body locations.
3. To analyze the precedence and pitfalls of the wearable technologies on disease of diagnosis to support the future growth of healthcare with upgraded performance.
4. To identify the current limitations and vital challenges that can pave the path of future research to fill up the gap between knowledge and practical implementation.

The rest of the paper is organized into three sections. Section 2 presents the description of the method and materials of the work. In this part the review strategy of this work is shown and an inspection of different wearable technologies and their projects related to disease diagnosis is given. Section 3 portrays the overview of the outcomes of this review. Section 4 highlights the current limitations and challenges in this particular area of research and the last Sect. 5 presents the closure summary with mentioning future scopes regarding the issue.

2 Methods and Materials

2.1 Review Methodology

In this study, a structured review methodology is followed to adhere to a standard approach to address the formulated RQs. Figure 1 illustrates the review methodology framework that focuses on the motivation of this work derived from previous research and highlights the organization of the review. In the first phase, the RQs are analyzed initially to lead the searching strategy, determine selection and rejection criteria, and data analytics are performed. In the second phase, the right keywords are selected to conduct the search process and the duplicate information is removed. In the third phase, to identify the challenges and review the summary, wearable technologies are explored, vital rhythms monitoring with the wearables are identified, and the disease

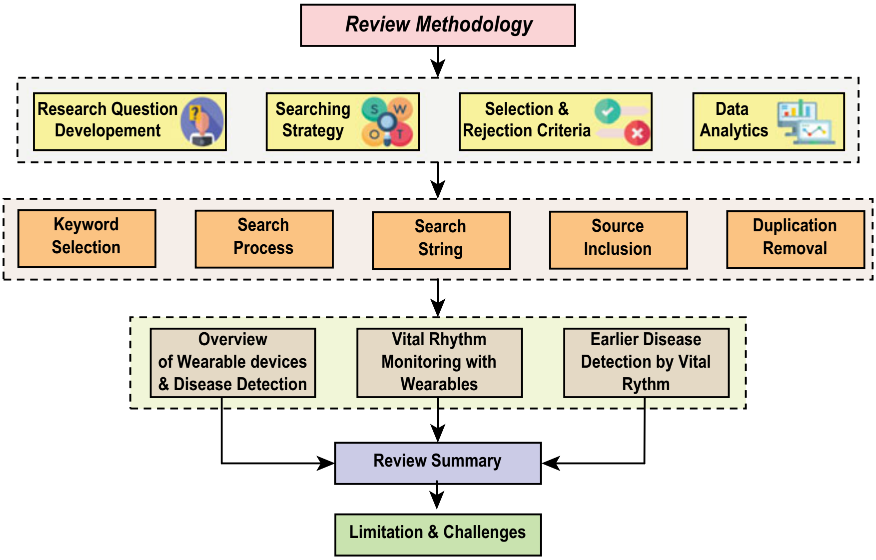

Fig. 1 Review methodology

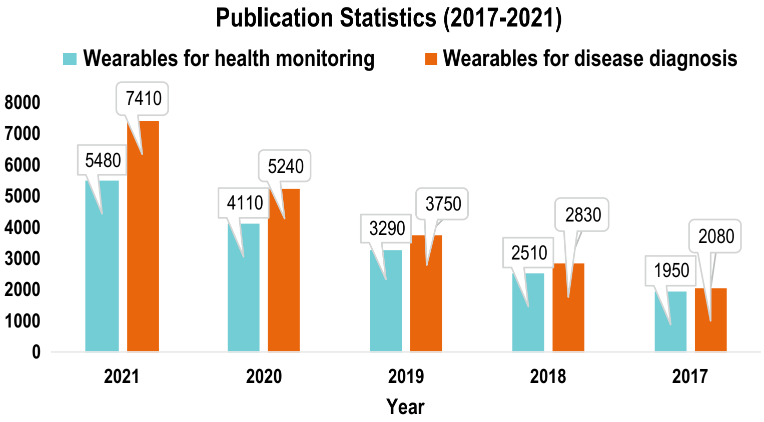

Fig. 2 Publication statistics over 2017–2021 on wearable devices

diagnosis at an earlier stage with the monitored data is analyzed. Different disease diagnosis models with their accuracy are evaluated to better understand the influence of wearable technology on health services.

For the clarification of this review work, the publication statistics have shown in Fig. 2. Published journals and conference papers during the period 2017–2021 have been taken into account to scrutinize the growth of research in this area. After removing the identical publications, reviewing the abstract, and contributions, in total 70 full-text publications are selected and studied in this review. The study of these papers includes their approaches, healthcare specifications, implemented wearable device technologies, their contributions to vital sign monitoring and limitations.

2.2 Wearable Devices

Wearable technology is the most innovational field for the real-time computation of human physiological information. This technology has enhanced the healthcare services with continuous monitoring of vital signs in regular activities with the advantage of remote consultancy and minimizing human interference. Wearable health devices has been introduced in 1990 with the advent of rising awareness of health among the population and improving the healthcare services with the newly invented technology. This is the utmost solution for the remote healthcare services which has been developed more with the integration of IoT cloud services. Figure 4 shows the chronological traditional process of health data handling from wearables which may result in earlier disease prediction or continuous health monitoring.

There are different types of wearable devices that are widely used in the medical sector. A major category is the wireless body area network (WBAN). It connects the nodes (actuators and sensors) through a wireless network that is mainly a star or multihop topology [51]. It can measure most of the biological vital signs such as—body temperature, blood pressure, heart rate, the saturation level of oxygen, electrocardiogram, and blood sugar level. Next, the most prominent sector is the wearable IoT devices and sensors that can be integrated with the cloud and fog platform. These are widely used because of their confidentiality, integrity, security, and real-time monitoring services. These devices transfer the data to the adjacent medical software cloud server [5]. These are then analyzed and processed to identify the information pattern, if it finds any imbalance then the doctors consult according to the patient's severity. Smartwatches, fitness trackers, smart clothing, smart contact lens, intelligent asthma management, and so on are going to make this medical industry in a notable position [2]. Figure 3 portrays the wearable devices on the human body which monitor vital rhythms of health.

In this section, commonly used medical wearable devices have been discussed with the development of technology, many wearables have been implemented in the medical sector but there needs to analyze their infrastructure characteristic and functionality to use them flawlessly as per users' requirements. A large group of devices is related to heart activity, they are mostly working on the principle of the electric waveform. ECG patches, ECG t-shirt devices are the two most common wearables.

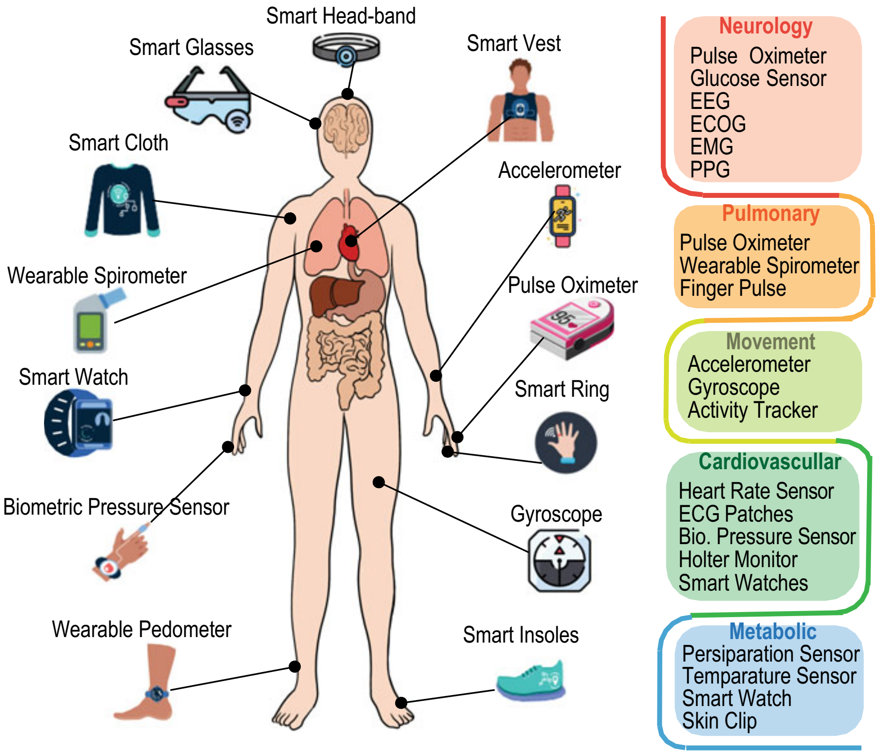

Fig. 3 Overview of wearable devices and the vital rhythms monitored by them on the human body

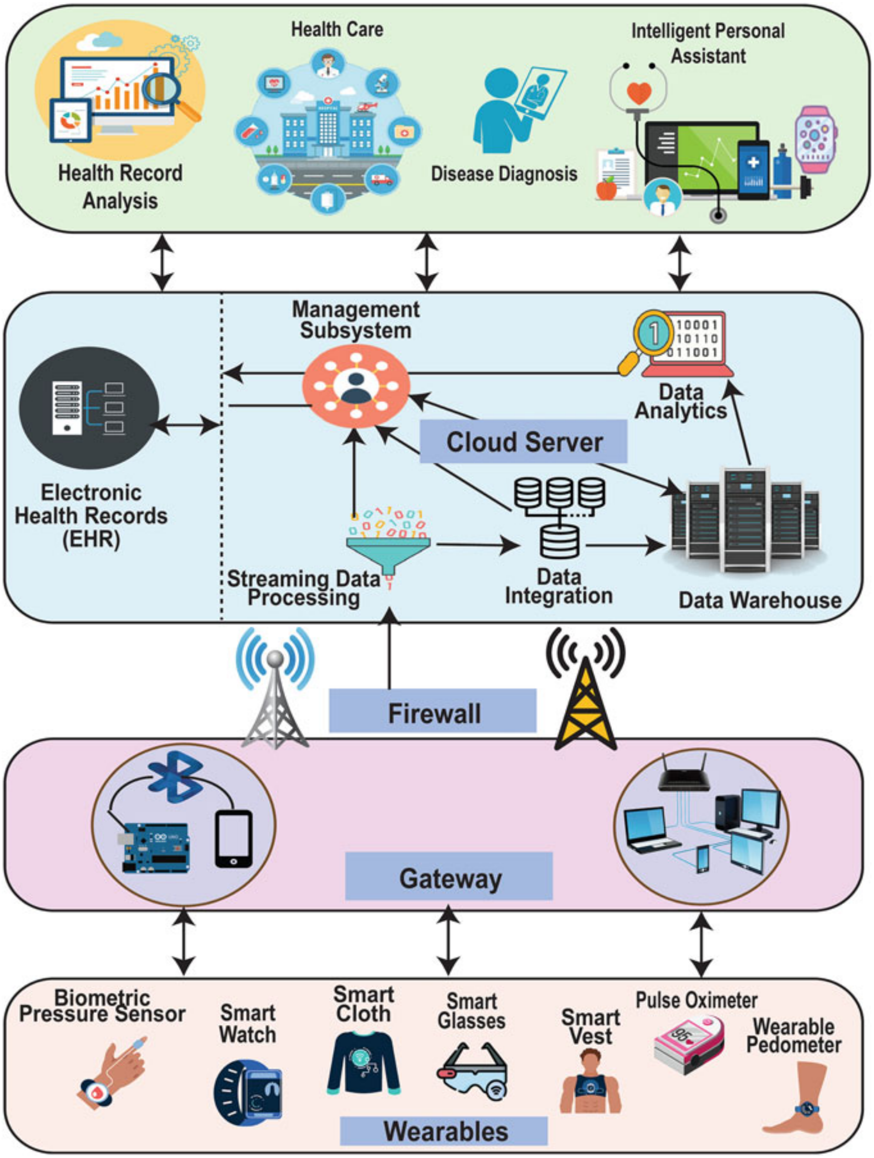

Fig. 4 Flow of data from wearables to health decision-makers for disease diagnosis

To track the movement, rotation, and movement accelerometer and gyroscope are used [13], so they are commonly attached to the wrist, hip, ankle, leg, or thigh as per the requirements. There are also some common wearable devices are mentioned in the summary table. The purpose of all these wearables is to early diagnose any disease and estimate the risk of infectious diseases by continuously monitoring all

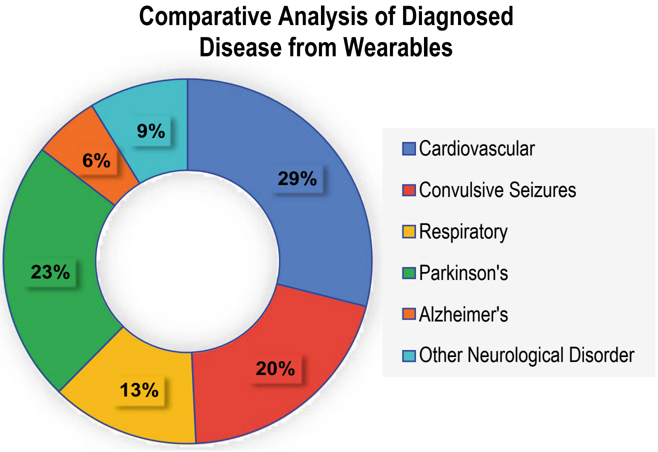

Fig. 5 Comparative analysis of diagnosed disease by considering vital rhythms from wearable devices

physiological information of the human body. Power consumption rate is the barrier to the standard performance of these devices. So the inventors try to maintain the standard of performance with a high signal frequency and low power consumption [8].

In Table 2, we have tried to summarize the case of diseases that have been diagnosed with wearable devices. These devices help in the diagnosis of diseases by observing the value of vital rhythms, and predicting human behavior and repetitive activities. Researchers have developed divergent predicting models [32] with these wearable devices to accurately predict the disease and make a significant impact on healthcare services.

2.3 Vital Rhythm

Vital rhythms are known as the basic measurement of body's functionalities which give the view of basic physiological state of human body [24]. Most wearable devices are designed to monitor and record these vital rhythms to take primary action if anything occurs.

Body temperature: It is the foremost vital rhythm that is checked first if it escalates in case of any infection or viral fever and low temperature is a sign of low blood flow due to circulatory shock. It is measured by a temperature sensor or thermometer by orally or attachment to the skin of body.

Heart rate: It is undoubtedly a major vital rhythm of the human body. Heart is responsible to pump and provide oxygenated blood through the arteries and pull out deoxygenated blood. Heart rate is the counting of heartbeats per minute.

Table 1 Wearable devices summary

Sensor	Human Body Placement	Component	Average Power (mW)	Signal Frequency (Hz)	Functionality	Ref
Temp. Sensor	Skin	T. electric	0.03	dc-0.1	Measuring body temperature	[24]
HR sensor	Sternum	Piezoresistive nanofibers	≤ 1000	0.6 - 2	Counting cardiac rhythm	[28]
Pulse oximeter	Finger	Organic optoelectronic probe	1.5	0.05–30	Measure oxygen level of blood	[6]
Glucose sensor	Arm	E.chemical	0.003	dc-0.1	Measure blood glucose concentration	[26]
ECG patches	Chest	PDMS and printed electrodes	0.0025	0.01–250	Monitoring of cardiac disease	[33]
EEG	forhead	Scalp electrodes	250	dc-150	Detect electrical activity of brain	[55]
ECoG	forhead	Brain surface Electrodes	900	dc-150	Scaling tolerance level of patients for taking therapy	[55]
EMG	Longitudinal midline of muscle	Skin electrodes	0.8	dc-0.01	To diagnosis motor neurons	[38]
Accm	wrist, chest, thigh, hip	7 piezo electric effect	0.004	0.5–0.01	Measure the acceleration of motion of structure	[13]
Gyroscope	Thigh	Optical	0.016	100	Detect the deviation of an object from its desired orientation	[13]

(continued)

Table 1 (continued)

Sensor	Human Body Placement	Component	Average Power (mW)	Signal Frequency (Hz)	Functionality	Ref
Biometric pressure sensor	Arm	Pressure sensitive TFT	0017	dc-50	Detect health problem by measuring blood pressure	[54]
PS	Wrist	Three to four manufactured electrode	0.5 - 5	50	To control the temperature of body by observing sweat	[21]
Holter monitor	Chest	Hardware and software	1200		Diagnosis of heart rhythmic problem	[17]
Wearable spirometer	Chest	Electro chemical	0.01	220	Measure lungs related data	[10]
Smart watch	Wrist	Microprocessor,IC1300	40		Health maintenance and disease prevention	[20]
Activity tracker	Wrist	Mass storage device	1800	48	Tracking orientation, rotation and motion	[21]
PPG	Finger, wrist	Pulsatile (AC) and superimposed (DC) components	0.0434	0.54–0.9	To detect blood volume change in cells	[37]

Legend: *On Sensor Column:* Temp. Sensor—Temperature Sensor; HR Sensor—Heart Rate Sensor; ECG–Electroencephalogram; EEG—Electroencephalogram; ECOG—Electrocorticography; EMG–Electromyography; Accm.—Accelerometer; PS—Perspiration Sensor; PPG–Photoplethysmography. *On Component Column:* T.electric—Thermoelectric.

General rate is 60–100 times in per minute. Many cardiovascular diseases can be early diagnosed by monitoring heart rate basis on the daily activities. Electrocardiography and Plethysmography are the two most powerful technique for measuring heart rate. At present wearable devices such as pulse oximeter, smartwatch, and fitness tracker can easily measure heart rate.

Respiration Rate: This is another significant vital rhythm which indicates the rate of oxygen inhalation and carbon dioxide expulsion from the body’s tissue. Abnormal rate of this vital indicates sleep disorder, asthma, chronic obstructive

Table 2 Review on Wearable Devices

Approach	Wearables	Vital Sign	Outcomes	Ref
1D CNN model for identifying ECG irregularity with time series data	ECG chest sticker (BMD101)	Real time heart rhythm	Accurately classify long-term ECG records from 1D CNN preventing arrhythmia	[22]
Designing minimized mobile device to Record data of tPD and ET patients	Micro-EMG wearable wrist watch	EMG	Quick assessment of disease progression and identification to diagnose tPD or rET patterns	[49]
A ML based smart remote patient monitoring system	Temp. Sensor, oximeter	Temperature, pulse rate	Accurately maintain remote healthcare management system	[47]
Rule mining model on vital sign data	Fitbit	Accm. RHR, sleep measure	Enact outbreak of influenza	[36]
Data prediction model to quantify the movement sequence for PD patients	Accm., PPG sensor	Heart rate, BP	Accurately select the conventional transition strategy for PD patients	[52]
Smart remote patient monitoring model to early diagnosis the AD patients	Smart watch	Heart rate, body temperature, movement tracking	Enhance the diagnosis process of Alzheimer's disease	[25]
Remote infected patient monitoring system using decision tree based algorithm in the cloud platform	Temp. Sensor and PPG sensor	Body temperature, BP	Prevent contagious ebola outbreak with 94% accurate disease diagnosis and 92% resources utilization	[41]
Machine learning based model to detect individual infected pedestrian in a crowdy place	Fiber Bragg Grating (FBG) optical sensor	Temperature, oxygen saturation rate	Reliable way to improve the conventional epidemic situation with a 8% measure error rate	[12]

(continued)

pulmonary disease, and anemia. Sensors can be placed adjacent to the nose or mouth to measure the breathing rate.

Blood Pressure (BP): Blood pressure is the force of blood pushing against the artery wall while pumping of heart. Two most significant value of blood pressure is systolic (maxima) and diastolic (minima). Fluctuation of BP is an indicator of many diseases. High BP is itself is a crucial state called hypertension that requires

Table 2 (continued)

Approach	Wearables	Vital Sign	Outcomes	Ref
Cloud platform-based remote health monitoring system with FCM classifier	Fitness tracker, Temp. Sensor	Temperature, headache, muscle pain, nausea, rash	Generate immediate diagnostic and warning alert according to the user's health condition for identifying CHV infected or uninfected patients	[42]

Legend: *On Approach Column:* 1D—One Dimesion; CNN—Convolutional Neural Network; tPD—Tremor Parkinson Disease; AD—Alzheimer Disease; FCM—Fuzzy C-mean Classifier. *On Wearable Column:* Temp. Sensor—Temperature Sensor. *On Component Column:* T.electric—Thermoelectric. *On Vital Sign Column:* RHR—Resting Heart Rate; BP—Blood Pressure. *On Outcomes Column:* CHV—Chikungunia Virus.

medication. This is a major factor in many diseases like stroke, kidney failure, and heart disease. Generally BP is measured by sphygmomanometers.

Pulse Oxygeneration: The concentration of oxyhemoglobin in the blood is divided by the sum of the proportions of oxy- and deoxyhemoglobin in the blood to determine oxygen saturation or oxygenation. Oxygenation can be classified as tissue oxygenation (StO2), venous oxygenation (SvO2), or peripheral oxygenation (PvO 2), depending on the location and manner of sensing (SpO 2). Because of its noninvasive nature, SpO2 measurement is one of the most common oxygenation measurements. Pulse oxygenation, when combined with a person's pulse, reveals a person's cardiovascular health. Pulse oxygenation needs to be at least 95% in a healthy individual. If it drops too low, under 80%, appropriate organ function is compromised.

Blood Glucose: This is a vital that should be monitored to have an idea of glucose level of the blood. Glucose is known as the energy source of human cells. Value out of its normal range may advisable to take consultancy of physicians. Diabetes which has become a global major health issue is the cause of continuous high glucose level of the blood. Diabetes is the primary factor of many health issues. So monitoring glucose level is important to prevent diabetes and also for the diabetic patients to maintain their medication dose or the eating habit.

2.4 Disease Diagnosis from Vital Rhythm

The death rate due to chronic disease can be reduced significantly by continuous monitoring of the health status of patients. Wearable devices are an effective and affordable solution in this area that can help us to collect various vital indicators data responsible for disease diagnosis and process them through dynamic, intelligent, and comprehensive analysis. This technology also keeps roles in remote monitoring of patients, taking instant treatment decisions, and other functions through cloud services which are getting popular in the disease control process day by day [44].

Respiratory disease and bronchial asthma can threaten lung function and increase mortality. Active monitoring of heart rate, pulse, oxygen saturation, and physical activity on a regular basis and early self-management of acute pulmonary effects can prevent this situation [39]. Along with basic biosignals wearable technologies can also detect cough, breath sounds, and other characteristics that can be used to predict the status of lung functions.

Cardiovascular disease can be monitored via invasive and noninvasive processes. The continuous monitoring of noninvasive ECG is one of the main ways of detecting cardiac functions. ECG electrodes to collect and display the ECG signals in real-time can be placed into a sports vest with close conduct with the human body and monitor data through mobile applications [46].

Diabetes that is caused by a deficiency in insulin secretion can lead to impairment and failure of different organs of the human body like the eyes, kidneys, nerves, heart, and blood vessels. Blood Glucose level Monitoring is one of the major types of equipment to forecast the risk of diabetics among patients that can be effectively implemented in wearable devices. The Gloco Watch [50], a wearable device to monitor glucose level, an optical noninvasive method [34] based on concentration changes in blood glucose characteristics are some examples of sensor-based glucose level monitoring technologies.

Neurodegenerative disorders (NDDs) are nervous system disorders that result in a range of symptoms like paralysis, muscle weakness, poor coordination, loss of sensation, seizures, confusion, pain, and altered levels of perception. Some common NDDs are Alzheimer's disease, Parkinson's disease, Autism Spectrum Disorder, Seizures, and stroke. In 2019, A study by the World Health Organization showed that about 7 million people were affected by Alzheimer's or Parkinson's diseases all around the world. Body movements, velocity, facial expression, close observation over the regular conversation, hyperactivity monitoring is an effective and promising technology in the early detection of NDDs [31, 43].

We tried to represent a brief summary of different diseases that can be remotely monitored and analyzed using wearables, cloud services, integrated technologies, and advanced artificial intelligence in Table 3. Respiratory disease detection using machine learning techniques based on Lung sound auscultation data is described in this work [35]. Another respiratory disease is diagnosed [48] by classifying breathing sound anomalies to detect respiratory disease using hybrid CNN-RNN model on respiratory sound database. A support vector data description (SVDD) model [26] for detecting epileptic seizures using wearable accelerometer device. Early detect fevers [48] in an outpatient through continuous temperature monitoring using a wearable that can reliably estimate body temperature. A voiceprint-based PD is identified by using smartphone application [56]. An approach [30]for training Mendelsohn maneuver using wearable device to strengthen the muscles required for swallowing. This paper [45] represented a continuous ECG monitoring system for wearable devices to prevent cardiovascular disease. A sensor-based patient management approach for Alzheimer's disease is explained [31]. For autistic children, an

Table 3 Disease Diagnosis Summary

Disease	Monitoring	Sensor	Methodology	Output	Ref
Respiratory	Lung sound auscultation	Stethoscope	MCC for feature extraction and CNN for data classification	Ac-90.21%	[35]
Respiratory	Breathing cycle sound	Stethoscope	A deep CNN-RNN model	Ac- 96%	[3]
Convulsive	Seizures	Body movements	Accm. SVDD to classify nonseizure and seizure events	Ac- 86.95%	[26]
Febrile Neutropenia	Temperature	Verily Patch (Temp. Sensor)	K-fold cross-validation	sensitivity 90.2%, specificity 87.8%	[48]
Parkinson's	Voice	Microphone	Customized CNN	Ac- 90.45%	[56]
Aspiration pneumonia	Laryngeal elevation velocity	Stretchable strain sensors	Ward's method hierarchical cluster analysis for data pre-processing and customized algorithm to detect onset and offset times of the laryngeal elevation	Ac- 98.15%	[30]
Cardio	ECG	Dry contact sensors	Proposed a parallel delta modulator model with local maximum and minimum point algorithms	Avg 96%	[45]
Alzheimer's	Velocity, acceleration, sympathetic nervous system activity	Pulse sensor, flex sensor, Accm., gyroscope, magnetometer	Gaussian process, KNN, Threshold based Algorithm, Regression Model	Ac- 83%	[31]
Autism	Location and Hyperactivity	GPS, heartbeat, Accm. and sound sensor	Fuzzy logic based expert system	Ac- 89%	[43]

(continued)

Table 3 (continued)

Disease	Monitoring	Sensor	Methodology	Output	Ref
Neurological Disorder	Movements, facial expressions	Accm., RFID, radar sensor	LSTM for continuous data classification	FD- 93.17%, 61.11% for emotion recognition	[4]

Legend: *On Sensor Column:* Temp. Sensor—Temperature Sensor, GPS—Geographical Positioning System, Accm.—Accelerometer, RFID—Radio Frequency Identification *On Methodology Column:* MCC—Mel-frequency Cepstral Coefficients, CNN—Convolutional Neural Network, RNN—Recurrent Neural Network, SVDD–, KNN—K Nearest Neighbors, LSTM—Long Short-Term Memory. *On Output Column:* Ac—Accuracy, FD—Fall Detection.

assistive system is presented using wearable smartwatch to reduce dependency on the caregiver and parent making them independent [43]. This work proposed an emotion-aware fall monitoring framework using IoT for a senior citizen with a neurological disorder [4].

Here we focused on the disease, the vital rhythms responsible for the cause of the disease, the types of sensors used to detect the biosignals of the human body, used methodology to analyze electronic data, and finally on the outcome of the research.

3 Discussions

According to our study, wearable technology can play a significant role in vital rhythm monitoring and early disease diagnosis. These two issues are the major characteristics of healthcare services. By using this technology, not only the patients will get a conventional idea about health conditions but also will be contented with the healthcare providers. The main purpose of this review is to identify and analyze which wearables are the most eminent for early diagnosis the diseases by monitoring the specified vital rhythms.

Wearable technology is a progressive area with the advancement of the technology industry so at first, we have studied the wearables that are functioning in the healthcare sector. Have started our review by identifying the wearable devices or sensors which are engaged in monitoring the vital rhythms through the daily activities of users. The basic characteristics of these wearables such as the core working mechanism, power consumption of generating the outcome, and the signal frequency are investigated to understand their differences. This will assist to choose the wearables as per the requirements while considering the cost of manufacturing and network [18].

Sequentially next phase of the study has shown the relation between these wearables and the vital rhythms monitoring. Diverse approaches have been studied to understand their impact on the healthcare sector. The most commonly used techniques are Wearable IoT devices and biosensors. As reviewed, they are mostly applicable to preventing the epidemic outbreak through regular monitoring of the vitals and the severity of the disease. They have appreciably contributed to monitoring the patients remotely and giving a real-time diagnosis prescription. In recent studies Hui et al. [22], Sarren et al. [41] have proposed cloud platform-based systems. The critical vital rhythms are monitored for patients are body temperature, heart rate, blood pressure, and glucose level. These are the indicators of any kind of infectious disease or disproportion in health conditions. Fever is one of the most common symptoms of any kind of infection, heart rate provides information about the physiological state, blood pressure value gives us the idea of the cardiovascular condition of the patients. So wearables can be very effective in early diagnosis by monitoring these vitals, especially any infectious disease before it spreads out among all the interacted people of the patients. It is also beneficial for the patients who are treated at home, to be able to get immediate consultancy if any vital irregularity occurs. So the researchers have developed diagnosis models to detect the disease as accurately as possible with the data from the wearables.

The study is distinctive because of the studies of recent works from 2021 to 2017. Works have been searched on various databases such as Springer, Scopus, IEEE Library, MDPI, PubMed, Elsevier, and Google Scholar. The strength of this review is it gives a crystal view of the impact of wearable devices on vital rhythm monitoring for early disease diagnosis in recent studies.

4 Limitations and Challenges

Recently, many research prototypes of wearable sensors and devices have expanded a lot more than in previous times, with the aim of developing in many aspects of healthcare. Our review study has underlined some existing challenges.

- Data confidentiality: Confidentiality maintenance is the highest priority in handling any digital healthcare management system. At first the data collection from all the wearables, then the data transmission through the gateway for storage and processing to the central hub for further instructions execution. Data can be malfunctioned by any kind of intruder or third party [14, 16]. So the whole network should be secured thoroughly without any loopholes. But for any IoT network, it has become a major challenging issue for the increased rate of cyber hacking. Different models have been developed by the researchers to protect the whole IoT network from intruders [15, 23].
- Availability: People will be benefited as much as the devices will be available and accepted by the users. The gadget industry is trying its level best to design upgraded medical wearables with the recent technology, so the manufacturing and implementation of wearable technology are not reasonable yet for all standard people [19].
- Power consumption: The power capability of wearable devices is a crucial characteristic to accurately monitor the vitals for a long period without interruption

[11]. This is related to the functionality of wearable devices and the manufacturing technique. The main challenge here is to balance between designing the power-efficient devices and the product cost.

These are the noteworthy issues on which researchers should investigate more to utilize this wearable technology in the most effective and secure way for wellbeing of human health.

5 Conclusion

Disease diagnosis with a good accuracy level is the primary goal of modern healthcare. Early detection of disease brings efficiency in therapeutic treatment decreasing the premature mortal rate. Advances in wearable electronic technologies along with the high availability of smart devices, wireless systems, cloud computing, and data mining techniques have enabled remote and personalized automatic clinical decision-making to be a promising future in the healthcare sector. In this review, we reported some significant types of sensors that can be placed within comfortable wearable devices along with their characteristics and functionalities. Then we mentioned some recently used wearables that have been approached to diagnose different chronic diseases on the basis of the information processed from various vital biosignals like ECG, heart rate, blood pressure, blood glucose, body temperature, movement tracking, etc. We also listed some physiological and Neurodegenerative diseases information that can be tractable using available wearable technologies along with different proposed methodologies and their performance measures in the area of the disease diagnosis process. Finally, we discussed the technical issues and some existing challenges of wearable devices like limited reliability and data confidentiality, high power consumption, and availability that can be improved using novel materials, and strong data security protocol providing the clinical applications and wearable health monitoring system a prominent future.

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Chapter 9
Post-quantum Signature Scheme to Secure Medical Data

Tania Sultana, Rashed Mazumder, and Chunhua Su

1 Introduction

Several most renowned and largest technology companies around the world have been currently trying to develop the processors of quantum, attempting to be the prior one to achieve quantum dominance. On January 8, 2018, Intel made an announcement about their test chip which was 49-qubit [1], which will let researchers to explore and improve error rectifying methods and imitate mathematical difficulties. On March 5, 2018, one of the most prominent technology companies Google introduced Bristlecone, their quantum processor with brand new 72-qubit, stating that Bristlecone can achieve quantum supremacy and they are prudently optimistic about that [2]. The presence of an omnipotent quantum computer has a significant impact on cryptography: meanwhile in 1994 a scientist named Shor revealed that an adequately strong quantum computer can crack present asymmetric cryptographic algorithms [3], and all of these asymmetric cipher construct the cryptographic bases of the Internet. Between achieving quantum supremacy and destroying RSA, there is a gap, so it is essential to get prepared for an Internet system where quantum computers are a reality; it is the high period to develop post-quantum-safe methods to enhance security and confidentiality. A blockchain is designed to secure data through asymmetric cryptography and hash function. If quantum computing, once advanced enough could threaten the integrity of a blockchain by two quantum algorithms: Grover's and Shor's [4]. Grover's algorithm, it's the main challenge to hashing, which allows to look for an unordered list for a specific term. If $h = H(m)$, then it is impossible to generate the data m from a given h in traditional computer. But in a quantum computer, it is

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possible to find out the value of m from given h with the help of Grover's algorithm. It only takes $O\sqrt{n}$ time to find m in a quantum computer which means finding a preimage is easy in a quantum computer. That advantage of Grover's algorithm leads to a preimage attack or collision. Contrastingly, Shor's algorithm solves prime factor by optimization.

In this research, we are proposing a signature scheme for blockchain technology to secure medical data from quantum attacks. The proposed scheme is based on Merkle tree and two finalists of SHA-3 (Keccak and Skein). Because of the Skein algorithm, this proposed solution can be readily incorporated into the blockchain. Furthermore, the Skein algorithm will aid in improving the overall system's performance. The most essential aspect of this approach is that it would give strong security against the looming quantum threat because of the Keccak algorithm. Furthermore, the Merkle tree will speed up the key creation and authentication process, as well as require less memory.

2 Background and Motivation

The latest cryptographic applications demand both super-speed and strong security. Basically, when sending communications, the senders encrypt them to verify "message security" or to guarantee the consignor's authenticity. The sender can use either the receiver's public key to authenticate message security or his or her own private key to confirm the sender's authenticity. The hashing technique is required to conceal the real data which will be unknown to the outer world. The Secure Hash Algorithm (SHA) was created with the help of the (NIST) and (NSA). SHA was first released in 1993. And that was made into FIPS. Then, in 1995, they obtained a redesigned statement known as "FIPS PUB 180–1", with the acronym SHA-1. It might also be described as a new variant of "MD4". "SHA" accepts input with a length of less than 264 bits and returns a 160-bit result. The word secure is derived from SHA's 2 strengths:

1. No way to derive the original input value.
2. Cannot have same message digest for two input values.

SHA-0 was withdrawn by them within a short time and issued new technique called "SHA-1", which was a new method from the prior one. SHA-1 became vulnerable due to computational flaws in 2005, then a new version of SHA is received. SHA-2 is comparable to the SHA-1 algorithm in that it can prevent all of the assaults that made SHA-1 insecure. However, we must always be prepared for the worst-case scenario, so a new hash function is required. The newest version of the family, SHA-3, was released in 2012. In comparison to previous SHA algorithms, it was an entirely new algorithm. New hash algorithms are intended to alter the complete SHA-2 family, and they should support digest lengths of 224, 256, 384, and 512 bits [5].

As known in today's cryptographic environment, the SHA-2 algorithm is the most commonly utilized algorithm in signature schemes. However, quantum attacks aren't far away from breaking SHA-2. As a result, we must prepare for a secure future in which we can avert the impending threat and keep our technology from collapsing. Landauer's observation is considered as the fundamental basis of quantum computation where all information is ultimately physical. New algorithms and new complexity classes will lead by "quantum parallelism" which was showed by Deutsch [6]. Quantum computers can be built using a wide range of quantum systems, including trapped ions, superconducting qubits, photons, and silicon. Superconducting qubits, in particular, have emerged as a frontrunner for quantum processor infrastructure that is scalable. In 1999, a simplistic qubit for quantum computing was developed. As a result, superconducting computing has advanced rapidly in recent years, with the number of qubits increasing significantly and the reliability of qubits rapidly improving. In 2014, a large constancy 2-qubit system was achieved which used a five-qubit superconducting quantum, paving the way for a surface code method. The remarkable breakthrough, famous as quantum superiority, represents a long-awaited step toward quantum computing and was first described in 2019 dealing a superconducting [7]. Because of the rapid evolution of superconducting QC (quantum computer), the global race to the quantum computer is in high gear. Many companies are vying for a position in QC. All of these advancements and efforts have resulted in a bright future for superconducting QC.

In traditional computing, events are "encoded" in bits, with every bit having a value of 0 or 1. Information in QC is encrypted in qubits. A qubit is a two-level system with two basis qubit states that are typically known as $|0\rangle$ and $|1\rangle$. A qubit can be in state $|0\rangle$, $|1\rangle$ state, or a linear cohesion of those two states. This matter is known as "superposition" [8]. Quantum computer can gain an advantage using two quantum algorithm which is Shor's and Grover's algorithm. Shor explains that QC can factor numbers efficiently. And a quantum computer can utilize "Grover's algorithm" to reduce search time from thousands of years to minutes.

A blockchain is designed to secure data through asymmetric cryptography and hash function. If quantum computing, once advanced enough could threaten the integrity of a blockchain by two quantum algorithms. Grover's algorithm can find the unordered list within the less mathematical computation. The classical computer needs O(N) time to creak a chain whereas the quantum computer only requires $\mathrm{O}\sqrt{N}$ time to crush it. Grover's algorithm, it's the main challenge to hashing. It allows to find a specific item from an unordered list. On the other hand, asymmetric cryptography algorithms depend on prime factors. Finding the prime factors from enormous numbers is next to impossible for classical computers. Shor's algorithm is able to find prime factor optimized way. Shor's algorithm has a polynomial complexity in the input length, making the speed gain roughly exponential. In reality, this means that 4096-bit RSA keys are unbreakable with conventional computation but can be broken using quantum computation [9]. As a result, any part of a blockchain implementation that uses RSA or comparable techniques is vulnerable to a quantum computing attack.

The aforementioned difficulties motivated us to conduct a study on the subject in order to create a blockchain solution to protect sensitive medical data against quantum attacks.

3 Literature Review

Researchers have done a lot of research on this issue. They have proposed different solutions to protect the blockchain from quantum attacks. But no system is ideal, each has its own aspects and limitations. Over time, researchers are showing different solutions for preventing quantum attacks even though the quantum computer is still under construction.

In [10], they present a research initiative on symmetric cryptography that focuses on predicted industrial requirements and stronger post-quantum protection than currently available symmetric algorithms. But there are some limitations. That system requires large hardware and software for its cipher. In [11], they show the previous work of the researchers. In this review, they show the current situation of quantum attacks over blockchain and indicate some future work on this topic. They show the comparison between different proposed systems and their drawbacks. In [12], researchers gave some guidelines to new developers and researchers. Some drawbacks of this review are the large key size and lack of standard security level benchmarks.

In [13], they combine a hash-based single signature technique with Naor-Yung chaining to create a quantum-safe signing scheme for application in blockchain technology. They obtain fewer signatures and improved performance than previous hash-based signature techniques by utilizing the structure and features of a blockchain.

In [14], they proposed a method for smart grid security to prevent the threat of quantum computing attacks. Here, they used the Merkle tree for security purposes. They showed the Merkle tree is much secure than the RSA algorithm. This work motivates us to use the Merkle tree instead of other cryptographic algorithms. In [15], researchers showed the comparison between SHA-2 and SHA-3. After analyzing, they generated a method where they combined both SHA-2 and SHA-3 for confidentiality. But it has some limitations as it requires at least four rounds of iteration to generate the root value.

4 Preliminaries

In our proposed signature scheme, we use two SHA-3 finalists (Keccak and Skein) as well as the Merkle tree. This section provides a basic overview of these methods.

4.1 Keccak

In 2012, Keccak was named the SHA-3 champion, and the competition came to an end. Keccak provides a fantastic set of trade-offs for performance: in software, it is roughly comparable to SHA-2, while in hardware, it gives significantly superior throughput/area performance. Keccak uses a 1600-bit permutation and follows the sponge construction model. All practical hashing functions use finite memory and operate in an iterated manner. Internal collisions may result as a result of this: distinct inputs resulting in the same internal state and, as a result, the same output. Because a random oracle lacks this quality, no hash function with finite memory can behave like one. Applying the sponge construction with a random permutation, on the other hand, produces a so-called random sponge. Except for the consequences generated by finite memory, a random sponge turns out to be as powerful as a random oracle. As a result, random sponges are a good fit for articulating security claims instead of random oracles [16].

Figure 1 shows the two stage of sponge construction: absorbing and squeezing. Sponge function uses two parameter which is capacity c and bit rate r.

$$c = 1600 - r \tag{1}$$

4.2 Skein

Skein is one of the SHA-3 final round finalists. The structure emerges with simplicity, performance, secrecy, a lot of versatility, and easy-to-understand facility.

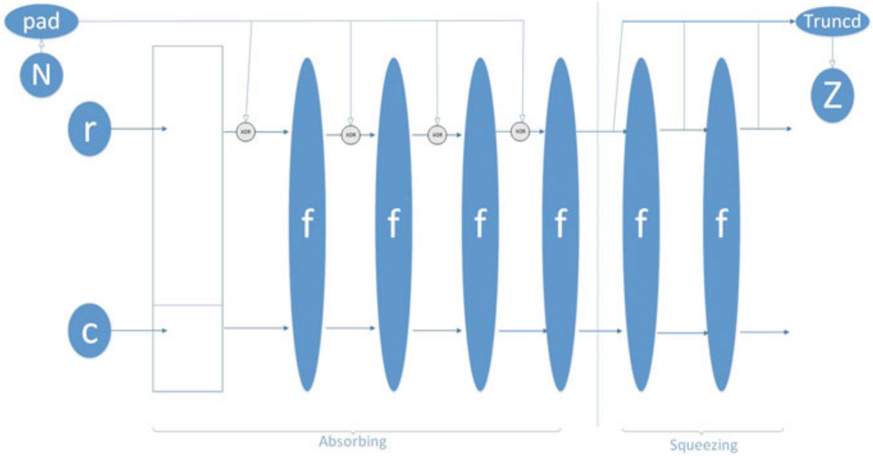

Fig. 1 Sponge Construction [16]

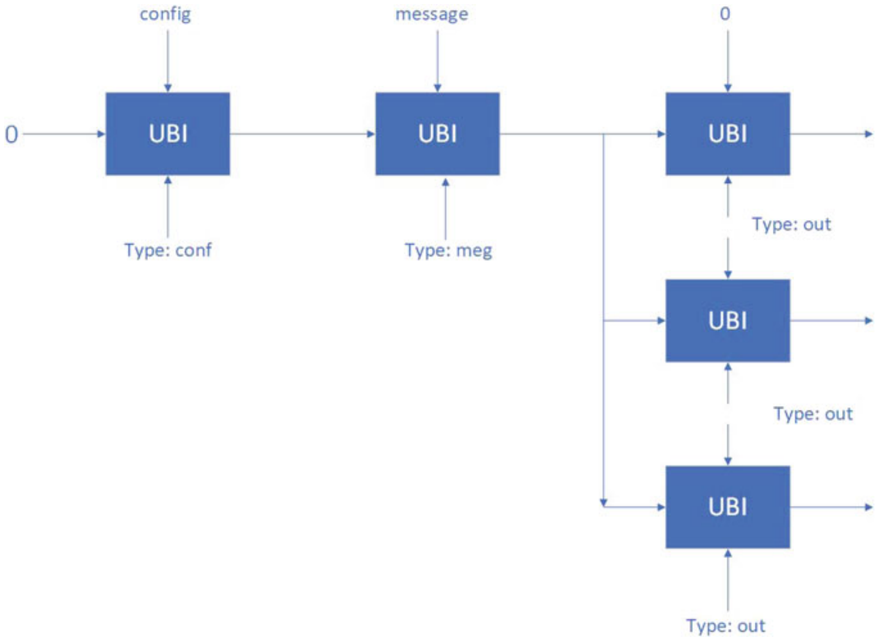

Fig. 2 Skein with large output size [17]

The threefish block cipher is at the heart of its conservative design. On the adjusted Threefish-512, the best attack is with 72 and 35 rounds, with a security parameter of little over 2.0. For comparison, AES experienced an attack in the round of 6 of 10 at the same state in the standardization method, resulting in a safety factor of only 1.7. If one output chunk becomes insufficient, repeat transform as indicated in Fig. 2

Threefish is a big block cipher that can be tweakable. It has three alternative block sizes. Every block required 128 bits tweak value, also the value of the key is similar as the block. Threefish's main design principle is that huge simple rounds are a way to secure from less sophisticated rounds. On current 64-bit CPUs, Threefish performs only three mathematical tasks on 64-bit words: exclusive-or (XOR), addition, and constant rotations. MIX is a basic function that works with two words each with 64 bits. Every MIX function is made up of one addition, a constant rotation, and an XOR. Threefish-512 is built using MIX functions. The 72 rounds of Skein-512 are made up of 4 MIX intimated by a permutation of eight words with each 64 bits. Every four rounds, one subkey will be inserted. Each round has the same permutation for words, "Permute"; the rotation variables are set to maximize diffusion and are repeated every 8 rounds. Another feature of the Skein algorithm is UBI (unique block iteration). The UBI linking techniques provides a fixed-size output by combining an input connecting ratio to an random-sized input string.

4.3 Merkle Tree

A Merkle tree is a binary tree made up of a collection of secret values, with every inside node being a concatenation of the tree's left and right children followed by a hash. Leaf node is the name given to each secret token number of secret leaves, internal node, and height of the tree, respectively, t, i, and h, then

$$t = 2^h \tag{2}$$

$$h = 1 + \text{floor}(\log_2(t)) \tag{3}$$

$$i = (2^h - 1)/(2 - 1) = (2^h - 1) \tag{4}$$

In Fig. 3, we can se, a binary tree with 2^3 leaves. This Merkle tree has 15 internal nodes. In one time signature scheme, for each transaction, it's required to generate a public key which is time-consuming plus it requires large memory space. But, in the Merkle tree, we can generate only one public key for multiple transactions. That great features of the Merkle tree save both time and memory space. In Fig. 3, if we need to verify node Tr_2, then we have to perform only $log_2 t$ transmissions [14]. If we used one time signature scheme, then for authentication, the time complexity will be $O(t)$ but using the Merkle tree reduced the time complexity, which is $O(\log_2 t)$.

Another important feature of the Merkle tree is we cannot alter the root value as it is generated from 2^t secret leaves. Each node is concatenated to generate to root

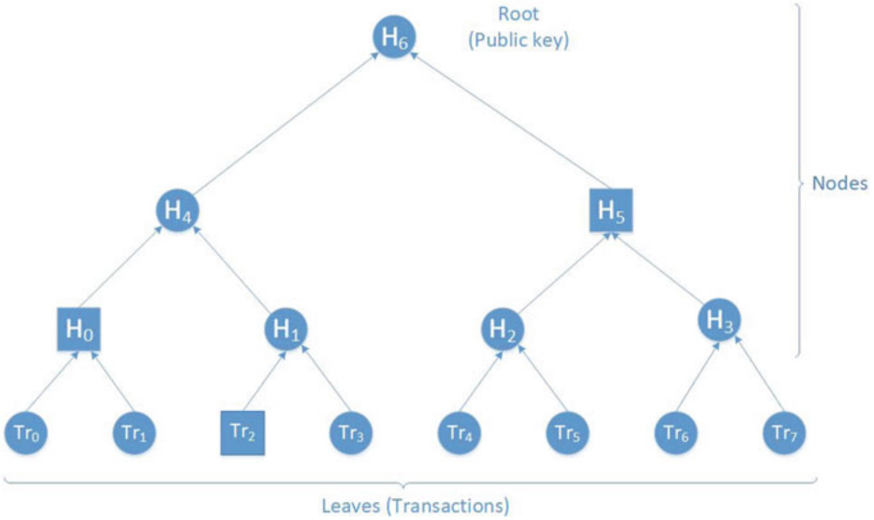

Fig. 3 Merkle tree integrated with 2^3 secret leaves [14]

value which is known as a public key. If anyone wants to alter the root value, they have to alter the whole tree's node value, but this is next to impossible. And this makes the Merkle tree more secure than other cryptographic algorithms.

5 Proposed Signature Scheme

Secure hash function family "MD-5, SHA-0, SHA-1, and SHA-2" all have the same basic structure. There has been an attack against the predecessor of SHA-2 in recent days. SHA-2 has been regarded as secure up to this point. However, quantum computing isn't far away from putting SHA-2 in jeopardy. As a result, we must develop new technology in order to ensure a secure future for sensitive medical data. In [15], researchers showed the comparison between SHA-2 and SHA-3. After analyzing, they generated a method where they combined both SHA-2 and SHA-3 in the Merkle tree for security. However, they continue to use SHA-2, which has the same fundamental structure as SHA-1 and SHA-0. In addition, they demonstrated in their proposal that at least four rounds of iteration are required to generate the root value. Nevertheless, doing that many iterations is time-consuming and will cause the system to slow down when generating the root value. In this research, we proposed an alternate way of creating a safe signature mechanism. We employed two SHA-3 algorithm finalists. The use of the Keccak and Skein algorithms is due to their fundamental structure, which differs from that of SHA-2 and its precursor. Sponge construction is used by Keccak, and Tweakable block cipher (threefish and UBI) is used by Skein. In addition, to create a fast-functioning solution, our proposed scheme requires at least two rounds of iteration to generate the public key (root value). At the lowest level, we used the Skein algorithm because it outperforms Keccak and all other SHA-3 finalists in the java environment in terms of cycles/byte [18], and it is also simple to implement. Because the lower level contains all transactions (leaf nodes), fasting the lower level can improve the overall performance of the proposed scheme. In addition, we used the Keccak for the remaining levels because it claims to be more secure than others.

The Merkle tree is used in this secure signature system. We merged the Merkle tree, Keccak, and Skein algorithm. For key generation, signature generation, and authentication, the Merkle tree is employed. It is critical in blockchain to ensure secrecy and integrity if we utilize the RSA algorithm, which is a factoring-based asymmetric cryptography algorithm. However, Shor's algorithm put RSA in jeopardy. We utilized the Merkle tree as a safe signature mechanism in blockchain to avoid factoring. MMT (modified Merkle tree) is a hash-based binary structure. The value of Merkle tree's child nodes is utilized to calculate the root value (public key).

In this paper, we used four leaves to create a modified Merkle tree with a height of three for understandability. Multiple iterations are required for each height based on the number of leaves or transactions to generate the root value. Figure 4 shows our suggested updated signature system, which employs the Merkle tree, Keccak-512,

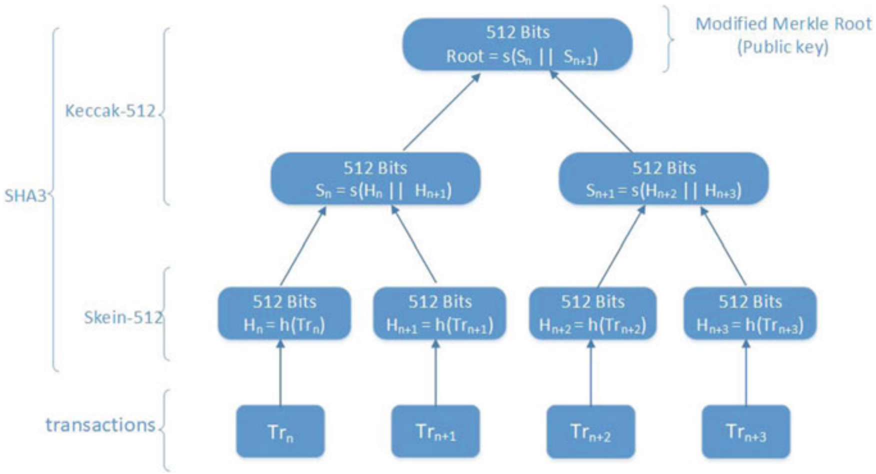

Fig. 4 Proposed signature scheme

and Skein-512 algorithms. Both Keccak and Skein have the capability of producing any length output. The system is more robust because of the properties of these two algorithms.

Because of the Skein and Keccak algorithms, the proposed modified Merkle signature scheme will be secure and fast enough. If all of the SHA family's security claims remain the same, the Skein algorithm performs admirably [19]. Additionally, the SHA-3 competition was won by the Keccak algorithm. Among the other algorithms, the Keccak is the most powerful. This updated signature system will provide the benefits of both security and speed.

5.1 Proposed MMT Signature Scheme for Multiple Transactions

In our proposed scheme, T_r, H, h, S, and s, respectively, represent leaf nodes, the digest of Skein algorithm, Skein hashing function, the digest of Keccak algorithm, and sponge function.

In this signature scheme, we used four transactions (any events related to patients' sensitive medical data that needed to be stored in the blockchain considered as transaction) to generate the root value (public key). The four transactions are as follows: Tr_n, Tr_{n+1}, Tr_{n+2}, and Tr_{n+3} and considered as a sensitive medical data or leaves. From these leaves, the root value is calculated. As there only four transactions, so total number of height of this modified Merkle tree (when multiple transactions in the tree):

$$\text{height} = 1 + \text{floor}(\log_2 4) = 1 + 2 = 3 \tag{5}$$

So, it takes three rounds of iteration to generate the root value of the modified Merkle tree.

Total rounds of iteration = Height of the tree

In Fig. 4, root value calculation for multiple transaction is shown. In this model, we used the Skein algorithm for the first round iteration as this level holds the most number of transactions. Skein algorithm has a great feature that allows great flexibility and fast performance. In this paper, we used Skein-512 to generate 512-bit output as a digest.

First round iteration: calculated the digest value of all transactions using the Skein-512 algorithm.

$$H_n = h(Tr_n) \tag{6}$$

$$H_{n+1} = h(Tr_{n+1}) \tag{7}$$

$$H_{n+2} = h(Tr_{n+2}) \tag{8}$$

$$H_{n+3} = h(Tr_{n+3}) \tag{9}$$

In first iteration, the Skein-512 algorithm is used and it required four calculations to formulate four different digest values. From transaction, digest value is calculated. H_n, H_{n+1}, H_{n+2}, and H_{n+3} are the digest value of "Tr_n, Tr_{n+1}, Tr_{n+2}, and Tr_{n+3}" transactions. For next iteration, H_n, H_{n+1}, H_{n+2}, and H_{n+3} will consider as child node.

Second round iteration: calculated the digest value of child nodes using the Keccak-512 algorithm.

$$S_n = s(H_n || H_{n+1}) \tag{10}$$

$$S_{n+1} = s(H_{n+2} || H_{n+3}) \tag{11}$$

The Keccak-512 algorithm is used in the second iteration as it has half the number of nodes compared to the first level. To generate the digest value, child nodes are concatenated. The sponge function is used to generate new child nodes. After concatenating H_n and H_{n+1} child nodes, S_n digest value is calculated. And H_{n+2} and H_{n+3} child nodes are used to generate S_{n+1} digest value. Both S_n and S_{n+1} are calculated using sponge function. Now S_n and S_{n+1} are considered as new child nodes which will be used in the next round iteration.

Third round iteration: calculated the digest value of internal nodes using the Keccak-512 algorithm.

$$\text{Root} = s(S_n || S_{n+1}) \tag{12}$$

After the third iteration, root value of this modified signature scheme is generated. To generate the root value, the Keccak-512 algorithm is used. Concatenation of S_n and S_{n+1} child nodes produce the root value $Root$.

If the MMT signature scheme has multiple transactions, then the number of iterations will depend on the height of the tree. And the height of this MMT will be calculated as Eq. 3. The first round iteration will be performed using the Skein-512 algorithm, and the subsequent iterations will be performed using the Keccak-512 algorithm.

5.2 *Proposed MMT Signature Scheme for Single Transaction*

Two SHA-3 finalists are used in this proposed scheme. Instead of using just one algorithm, we combined two for security and fast performance. If only one algorithm is used, for a single transaction, it will require only one round iteration to generate the root value. However, in this proposed scheme, at least two rounds of iterations are required to produce the root value for a single transaction.

Tr is the single transaction that needed to be added into the blockchain. Then digest value of the Tr will formulate through Skein-512. After that, the value of Skein-512 hashing function further goes through the Keccak-512 algorithm to generate the new digest value. Sponge function new generates the root value of the tree. In Fig. 5, root value calculation for single transaction is shown.

First round iteration: Digest value is calculated from Skein-512. The value of that digest will be considered as child node for next round iteration.

$$H = h(T_r) \tag{13}$$

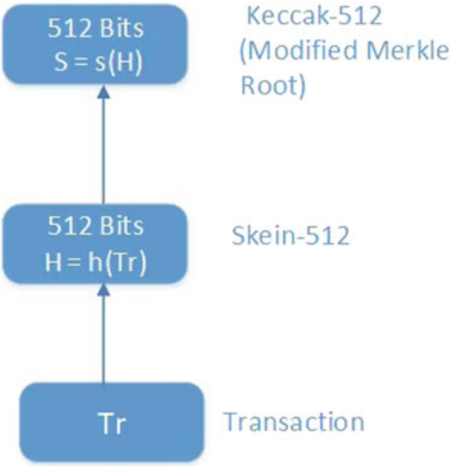

Fig. 5 Proposed MMT for single transaction

Second round iteration: Digest value is calculated from Keccak-512. The value of that digest will be considered as root value or public key.

$$\text{Root} = S = s(H) \tag{14}$$

So, even though there is only one transaction (medical data) needed to add to the blockchain, then at least two rounds of iteration are required for this MMT signature scheme.

5.3 *Proposed Secure Blockchain for Medical Data Using MMT Signature Scheme*

In Fig. 6, blockchain MMT signature scheme is shown. Multiple sensitive medical information are kept in a single block in blockchain, and multiple blocks generate a chain. This stored transaction chain cannot be altered. Because we are using a Merkle tree, only the root value of the tree is stored in the block rather than each transaction's value.

$\text{Root}_n = s(H_{n+2}||H_{n+3})$ is stored in the block. And this block also stored the previous root value $Root_{n-1} = s(H_{n+2}||H_{n+3})$

In Fig. 6, it is demonstrated how each root value is stored in a block. Each block has a block header that includes the previous MMT root value, the nonce, and the Modified Merkle root value (public key).

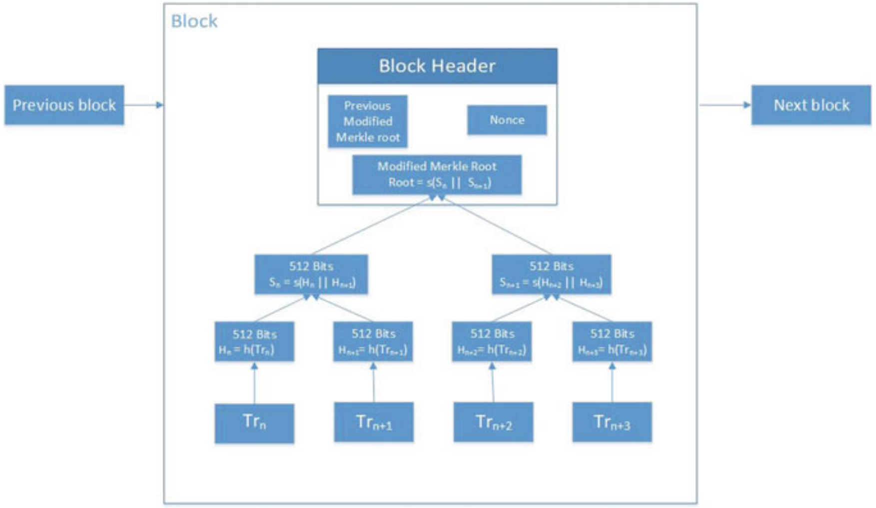

Fig. 6 Proposed Secure Signature Scheme for Medical Data using MMT

If the root value is changed, the modified Merkle tree must be completely rewritten. Because the root value is calculated by adding the values of the leaves and concatenating the internal nodes with the Keccak-512 and Skein-512 algorithm. Changing one value in the modified Merkle tree means changing all of the tree's values, which is not possible.

Each block, on the other hand, stores two root values (the block's own root value and the previous block's root value). It is nearly impossible to change the root value of one block because the next block contains the root value of the previous block.

6 Security and Performance Analysis

We attempted to examine the security strength and performance speed of our proposed model in this section.

6.1 Performance Analysis

In this section, the speed of SHA-2 and SHA-3 families and Keccak and Skein has been analyzed. Table 1 shows the average computational time of SHA-2 and SHA-3. This performance is done in the business laptop (MacBook Pro 13) [15].

Various numbers of loops are used to calculate a single hash. These loops were calculated 30 times, and the average results are shown in the Table 1 [15]. SHA3-256 outperformed the others for various loops. However, when SHA2-512 and SHA3-512 are compared, SHA3-512 outperforms SHA2-512 in two different loop sizes.

Table 2 analyzes the performance of two SHA-3 finalists Keccak and Skein algorithm. Performance investigation was done for two SHA-3 finalists in terms of cycles/byte on the 64-bit JVM (Java virtual machine) [20].

As we can see from Table 2, the Skein algorithm shows great performance in every output size. Based on performance in terms of cycles/byte: $skein < keccak$. Skein algorithm takes 17.2 cycles/byte for both 256 and 512 output size and Keccak takes 21.7 cycles/byte for 256 output size and 40.0 cycles/byte for 512 output size.

Table 1 Summary for a single Hash, average computation time (micro seconds) [15]

Number of loops	SHA2-256	SHA2-512	SHA3-256	SHA3-512
1 k	100,60	91,33	91,00	94,17
10 k	11,93	10,90	9,49	10,23
100 k	2,35	2,54	1,88	2,41
1 M	1,48	1,72	1,06	1,60

Table 2 Summary of SHA-3 two finalists performance analysis in 64-bit JVM [18]

Algorithm-output size	Cycles/byte
Keccak-256	21.7
Skein-256	17.2
Keccak-512	40.0
Skein-512	17.2

Skein performs slightly better than Keccak in 256-bit output size. However, in 512-bit output size, Skein outperforms the Keccak algorithm.

In [19], they showed that the value of cycles/byte (On Java/64-Bit Server, for 1KB input size, Ubuntu 11.10) for Skein-512 algorithm was slightly less than 2000, and the value of cycles/byte for Keccak-512 algorithm was slightly less than 12000. This means that the Skein-512 algorithm is nearly six times faster than the Keccak-512 technique. Furthermore, Skein-512 outperforms the SHA-2 algorithm, which is nearly two times faster. And the value of cycles/byte (On Java/x86, for 1KB input size, Windows 7) for Skein-512 algorithm is almost 2000, and the value of cycles/byte for Keccak-512 algorithm is above the 14000. As a result, the Skein-512 algorithm is nearly 7 times faster than the Keccak-512 method. Furthermore, Skein-512 surpasses the roughly two times quicker than the SHA-2 algorithm.

6.2 Security Analysis

The Merkle-Damgrd architecture is used in the SHA-2 algorithm. Merkle-Damgrd algorithm's compression function does not follow the rules of a random oracle. However, a sponge building is similar to a random oracle. Keccak algorithm's underpinning structure is sponge construction. The sponge function is a compression function for sponge manufacture. The sponge function is similar to a random oracle. Keccak algorithm's properties provide a high level of security. Security claims for SHA-2 algorithm is $2^{n/2}$ and security claims for Keccak algorithm is $2^{c/2}$ and capacity of sponge function $c = 2n$ [8, 21]. That means Keccak provides much security claims than SHA-2.

From Table 3 we can see that SHA3-512 provides greater resistance for second preimage than SHA2-512. Additionally, for generating a single hash value, SHA2-256 and SHA2-512 require 64 and 80 rounds of compression, respectively, whereas SHA3-256 and SHA3-512 require only 24 rounds of compression. This feature also boosts up the overall functionality of the SHA-3 algorithm.

In Table 4, the security level of two SHA-3 (Keccak and Skein) finalists is given. Almost in every parameter, Keccak outperforms Skein algorithm. But in the second preimage, it slightly beats Keccak with 2^{200}–2^{824} range.

Table 3 SHA-2 Vs SHA-3 [15, 22]

Parameters	SHA2-256	SHA2-512	SHA3-256	SHA3-512
Rounds of compression	64	80	24	24
Digest size in bits	256	512	256	512
Average computation time	100,60	91,33	91,00	94,17
Collision	2^{128}	2^{256}	2^{128}	2^{256}
Preimage	2^{256}	2^{512}	2^{256}	2^{512}
Second preimage	$2^{256-L(M)}$	$2^{512-L(M)}$	2^{256}	2^{512}

Table 4 Security of SHA-3 finalists [20]

	Keccak-512	Skein-512
Collision resistance	2^{512}	$> 2^{-265}$
Round of compression	24	32–36
Preimage attack	2^{1590}	2^{105}
Second Preimage attack	$2^{511.5}$	2^{200}-2^{824}
Pseudo preimage	2^{1576}	$2^{511.7}$

6.3 Trade-Off Between Performance and Security

We will provide a theoretical analysis based on Table 2 in this section. In Table 2, we can see the performance of Keccak and Skein algorithm in terms of cycles/byte in the Java environment. Here, we only considered the 512-bit output size that is generated from the 512-bit output size.

Skein algorithm takes 17.2 clock cycles/byte in the compression stage to generate 512-bit output

Keccak algorithm takes 40.0 clock cycles/byte in the compression stage to generate 512-bit output

If we take 2^3 transactions (for understandability) to generate root value, then it needs four rounds of iteration. The first round iteration contains the most number of calculations. The second round requires only half of the calculations compared to the first round. If we move into the next round then, it takes half of the calculation compared to the second round iteration. That means, if we are able to maximize the performance of the first round, then our system will perform fast. Table 5 shows the total cycles/byte calculation for 512-bit input to generate 512-bit output to find out the best performance.

Table 5 Performance analysis for Keccak and Skein in terms of cycles/byte

Algorithm	Cycles/512-bit input
Keccak-512	2560.0
Skein-512	1100.8

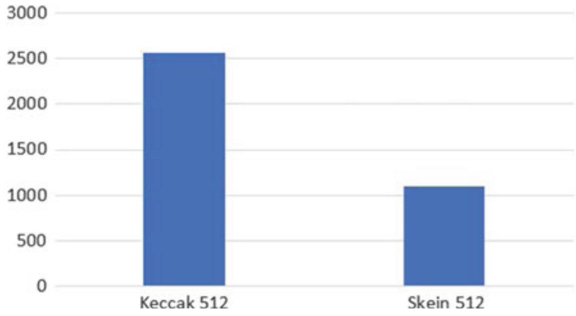

Fig. 7 Cycle/512-bit input calculation for two SHA-3 finalist in 64-bit JVM

Keccak algorithm takes 2560.0 clock cycle for 512-bit input to formulate 512-bit output. Skein algorithm takes 1100.8 clock cycle for 512-bit input to formulate 512-bit output. From Fig. 7, we can see that Skein algorithm shows more than two times greater performance than Keccak algorithm. We used Skein in our proposed scheme solely to achieve high performance. But security claims of Skein are not high enough to beat Keccak algorithm. Keccak algorithm is the strongest among all algorithms and won the NIST competition. So, both of the algorithms are used in the Merkle tree to provide both security and fast performance.

The Skein algorithm is employed in this research, because of its versatility and fast performance. Because of the Skein method, we may utilize this MMT signature scheme in a variety of environments, including the cloud. And incorporated Keccak, which boasts a high level of security.

A combination of the Merkle tree, Keccak algorithm, and Skein algorithm provides strong security and great performance. Furthermore, our proposed signature scheme requires less memory space and less authentication times as it is using the Merkle tree. The Merkle tree only requires $O(log_2 t)$ time complexity for authentication which is less than other cryptographic algorithms, here t is the number of transactions.

7 Conclusion

Quantum computers are thought to have the potential to transform the data security landscape in the near future. Progress in this area has shown us that quantum computers can tackle some computing tasks substantially quicker than ordinary classical computers in recent years. Yet, the alarming fact is that blockchain, the most secure ledger, is currently facing serious privacy and security vulnerabilities. Cryptographic hash is one of the most powerful tools in the cryptographic arena, and it's employed for confidentiality in blockchain applications. Grover and Shor's technique, on the other hand, makes cryptographic hashes breakable under quantum computing. We must progress into post-quantum blockchain to create a secure blockchain for sensitive medical data. In these conditions, the proposed approach is built on a Merkle tree and a combination of two SHA-3 finalists (Keccak-512 and Skein-512) that will be ideal for blockchain technology. Furthermore, the suggested model's design makes it simple to use existing blockchain applications in a cloud context. In Sect. 6, security and performance analysis has been completed for the proposed scheme. The analysis revealed that if we only use the Keccak algorithm, it will be secure enough to withstand a quantum attack but will slow down overall performance speed. That is why we used Skein to boost performance. Using Skein speeds up the entire system based on the clock cycles, and the system is secure for the great Keccak algorithm.

8 Future Work

The priority of this work has been to propose a secure signature scheme for blockchain to secure medical data from quantum attacks. We proposed a modified Merkle tree signature scheme in this paper. Implementing our proposed scheme as a future work could be an option here.

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Chapter 10
Medical Image Analysis Using Machine Learning and Deep Learning: A Comprehensive Review

Nazmun Nahar, Mohammad Shahadat Hossain, and Karl Andersson

1 Introduction

Clinical errors in the diagnosis of a patient may have an impact on the outcome of a therapies [11]. In the incident of a clinical errors, wrong diagnosis may be administered, depriving the patient of necessary medical care. Doctors are frequently confused by features that appear to be relevant at the time, resulting in misdiagnosis [28]. Clinical errors can also be caused by the environment and the tools used for diagnosis [40].

All of the aforementioned attributes could have a notable negative impact on the patient's condition, upsurge overall medical expenses, and end up causing mental harm [9]. Machine learning (ML) methods have been used to support healthcare professionals in making decisions on how to improve health services, such as reducing misdiagnoses and giving patients with appropriate forms of treatment.

Machine learning algorithms are commonly used in medical image analysis studies as effective classification model and clustering techniques. Support vector machines are most popular classification algorithm and most used and effective clustering algorithm is k-means method.

Deep learning (DL) is now widely recognized as an approach for improving the effectiveness of established machine learning approaches. Deep learning, on the other hand, is a general-purpose technique that is disrupting other fields of science

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as well. As a result, medical image analysis investigators must adopt Deep Learning modern technologies wholeheartedly. Medical image processing is a collection of processes used to extract important clinical information from a wide range of imaging techniques, most widely used for diagnostic testing or prognosis. In most cases, the modalities are in vitro cell. The retrieved knowledge could be used to improve treatment and diagnosis based on the needs of the patient. The straightforward utilization of image pixels with machine learning concepts is the main comparison between machine learning with image input, including "deep learning," and machine learning with feature input.

Ml algorithms have the ability to be deeply involved in massive branches of healthcare, from drug development to medical decision-making, which considerably changed the way patients are treated. The current achievement of machine learning techniques at computer vision tasks coincides with the increasing digitization of medical information. As a result, it is suitable for medical image processing to be performed by a machine learning technique that is standardized, reliable, and effective. Deep learning is gaining popularity in nearly every field, particularly medical image classification, and it is supposed to maintain a $300 million healthcare image processing sector by 2021. As a result, it will receive too many funding for healthcare image analysis by 2021 than a whole assessment sector spent in 2016. This is the most powerful and supervised machine learning method. This method employs deep neural network models, which are a modification of Neural Network models but with a greater accurate estimate to the human brain using sophisticated processes than simple neural networks. The utilization of a deep neural network approach is implied by the phrase "deep learning."

The neuron, a notion intrigued by the insights into the human brain, is the basic combinatorial component in a neural network, taking multiple signals as inputs, combining them in linear fashion using weights, and then passing the consolidated signals through non-linear operational processes to produce output signals. In current decades, machine learning (ML) and artificial intelligence (AI) have advanced quickly. Medical image processing, computer-aided diagnosis, image interpretation, image fusion, image registration, image segmentation, image retrieval, and analysis have all benefited from ML and AI. ML retrieves knowledge from image data and successfully and proficiently signifies knowledge. Together, ML and AI can appropriately and rapidly detect and anticipate the threat of diseases, as well as inhibit people in time. These strategies improve physician' and scholars' expertise to recognize how to evaluate gene variants that result in illness. These tools include non-learning algorithms such as Support Vector Machine (SVM), Neural Network (NN), KNN, and others, as well as deep learning algorithms such as Convolutional Neural Network (CNN), Recurrent Neural Network (RNN), Long Short-Term Memory, Extreme Learning Model, and others.

However, the primary goal of this analysis is to deliver a relatively short overview of latest ML and DL approaches for detecting four of the most popular types of brain diseases, including tuberculosis [22], lung cancer, pneumonia, and COVID-19 [3, 4, 36, 39, 46, 55]. A short description of ML and DL is provided in the following section.

2 Medical Imaging Types

Medical imaging comprises techniques and processes to obtain the pictures of the inside of the human body for the purpose of medical diagnosis and treatment of a patient. By doing so medical imaging helps to identify the internal structure of the human body, which is hidden either by skin or bones. This eventually enables diagnosis and treatment of a particular disease. There exists a plethora of techniques which support medical imaging.

These techniques use different technologies, enabling the production of images for various purposes. The integration of Artificial Intelligence (AI) with the common medical imaging techniques enables obtaining more accurate images from the internal of the human body. Various medical imaging approaches including magnetic resonance imaging (MRI), computed tomography (CT), X-ray computed tomography and positron emission tomography (PET), single photon emission computed tomography (SPECT), and many others enable obtaining specific information for a patient to be imaged.

Medical imaging research mainly focuses on extracting salient features of the human body which cannot be investigated by naked eyes. MRI usually consists of a few hundred megabytes while a histology slide comprises an image file of a few megabytes. The less amount of memory in case of histology is due to the fact that it is pre-processed by using certain efficient algorithms, resulting in the use of less memory and less computational time.

3 Overview of Machine Learning and Deep Learning

Machine learning (ML) uses historical data to train a computer or machine, enabling it to formulate a solution to a problem. Because of the availability of cheaper computing power as well as inexpensive memory, the applications of ML have gained tremendous importance. The reason for this is that it allows the solution of a problem faster than humans. Consequently, ML enables the processing and analyzing of huge amounts of data necessary to discover knowledge as well as correlation among the data, which is not possible to notice through human eyes.

However, the intelligence of ML depends on the use of various algorithms, facilitating the abstraction, underpinned on experience. This enables producing appropriate judgments. On the contrary, Deep Learning (DL) is the sub-field of ML, considered as an advanced approach. DL facilitates making decisions based on raw data, which should not be processed further, which is the case with ML. Hence, the imitating power of human thinking and learning is more intuitive in case of DL than from ML [15].

DL consists of a plethora of algorithms which is driven by neural computing, allowing the automatic extraction of features from the raw data. Hence, the learning is carried out automatically by using the features of the raw data. Eventually, such a

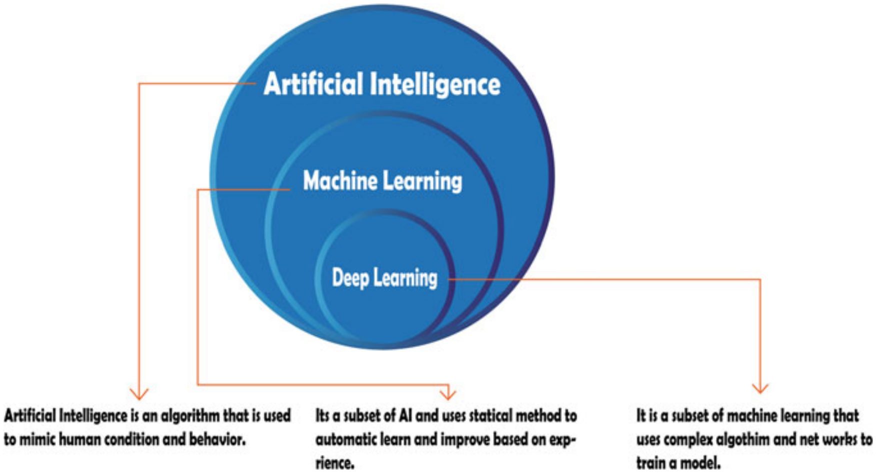

Fig. 1 Difference between AI, ML, and DL

phenomenon of DL increases its prediction accuracy as well as its performance [15]. Figure 1 illustrates the difference among Artificial Intelligence (AI), ML, and DL.

The accuracy of the decision-making process depends upon the selection of appropriate algorithms associated with both ML and DL. There exists a plethora of classification algorithms associated with ML and they are designed for specific classification or regression problems. Although at present the performance of ML is quite satisfactory, they are replaced by DL in most of the classification or regression or prediction applications. The main difference between ML and DL depends on the approaches on how the features are extracted and they depend on the use of the appropriate classifiers. DL uses several non-linear hidden layers while extracting features and hence its performance is better than ML, which depends on handcrafted features. Figure 2 depicts the fundamental difference between ML and DL.

4 Classifier

The raw data which is fed into either ML or DL needs to go through a series of preprocessing steps so that it can be read by the machines. The pre-processed data is then used by the ML or DL to classify features of the raw data. The features are classified based on the characteristics or themes of raw data. The features which are considered should be non-redundant and they should be non-distinguishable. This will allow us to address overfitting and underfitting issues as well as overall computing time.

There exists a plethora of methods to extract features from the raw data. The feature data after the extraction should be labeled. A classifier is a method which is associated in taking decisions on labeling of the data and in this case it is feature

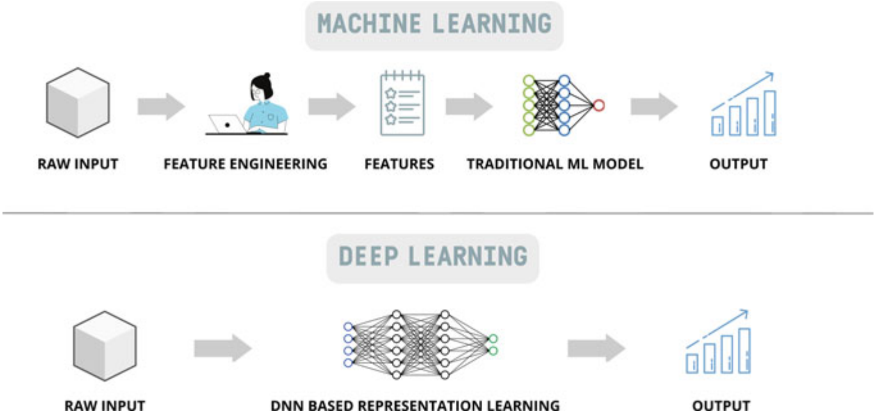

Fig. 2 Machine leaning and deep learning

data. Usually, various classifier algorithms are used to classify or label feature data. The widely used classifiers consist of SVM (support vector machine), RF (random forest), DT (decision tree), NB (Naive Bayes), KNN (K-nearest neighbor), and many others. Dl, on the other hand, by inspiring a biological neural network, accomplishes the overall task of ML by discarding the step-by-step procedures of ML.

ML uses many layers of processing units, which are non-linear in nature. It works by feeding output of one neuron into the next neuron. The DL follows a hierarchical order where the data of the input layer is transformed into a more abstract level to feed into the next level of the hierarchy. The DL uses a plethora of classifiers comprising Recurrent Neural Network (RNN), Convolutional Neural Network (CNN), Boltzmann machine, autoencoders, and Deep Belief Network (DBN). Figure 3 shows the different algorithms of machine learning and deep learning.

5 Performance Metrics

Various performance metrics including accuracy (Acy), sensitivity (Sny)/recall, specificity (Spy), precision (Prn), Area Under Curve (AUC), and F1-score are widely used to measure the accuracy of ML- or DL-based classifiers, which are either used in case of classification or regression problems. It is important to decide the types of performance metrics to be used in case of classification and regression problems. The regression problem involves prediction of an event or phenomenon. The conclusion derived from the result of a performance metric may differ with other performance metrics. For example, a model may give good results in terms of accuracy but it may provide poor results in terms of specificity. The accuracy performance metric is usually used with classification problems. The accuracy can be defined as the ratio of total number of accurate predictions and the total number of predictions which

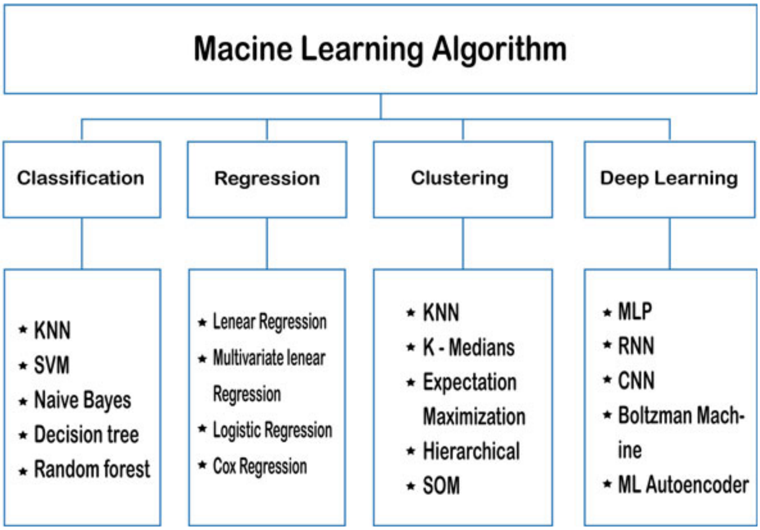

Fig. 3 Machine Leaning and Deep Learning Algorithm

are carried out. Alternatively, we can define accuracy as how close a measured value is to the actual (true) value. Mathematically, accuracy can be written by using the following equation:

$$ACC = \frac{TP + TN}{P + N} \tag{1}$$

Here, TP stands for True Positive that is the test result that correctly indicates the presence of a condition, while TN stands for True Negative that is the test result that indicates the absence of a condition. P stands for the number of real positive cases in the data while N stands for the real number of negative cases in the data. False Positive (FP) states that a test result wrongly indicates that a particular condition is present while False Negative (FN) states that a test result wrongly indicates that a particular condition is absent. It can be seen from Eq. (1) that accuracy involves both positive and negative results. However, the performance of a model in detecting either positive or negative is measured by using metrics like sensitivity/recall and specificity. Equation (2) mathematically defines the sensitivity while Eq. (3) mathematically defines the specificity.

$$\text{Sen} = \frac{TP}{TP + FN} \tag{2}$$

$$\text{Sen} = \frac{TN}{TN + FP} \tag{3}$$

Sensitivity is also referred to as true positive rate while specificity is referred to as true negative rate. The term sensitivity can also be defined as the successful diagnosis number of patients with diseases. The term precision can be defined as the actual diagnosis of the patients who are truly affected by the disease. Equation (4) illustrates the mathematical definition of precision.

$$\text{Sen} = \frac{TP}{TP + FP} \tag{4}$$

Harmonic mean of precision and sensitivity can be defined as F1-score and mathematically this can be defined as

$$\text{Sen} = \frac{2TP}{2TP + FN + FP} \tag{5}$$

6 ML and DL Approaches in Tuberculosis Detection

From January 2016 to 2020, this study looked at articles about computer-aided diagnosis systems for detecting pulmonary tuberculosis (Table 1).

7 ML and DL Approaches in Lung Cancer Detection

Lung cancer is one of the conditions that has obtained a huge amount of attention in the ML and DL publications. Several approaches based on ML and DL have been proposed (Table 2).

8 ML and DL Approaches in COVID-19 Detection

COVID-19 is one of the conditions that has obtained a huge amount of attention in the ML and DL publications. Several approaches based on ML and DL have been proposed (Table 3).

9 ML and DL Approaches in Pneumonia Detection

Pneumonia is one of the conditions that has obtained a huge amount of attention in the ML and DL publications. Several approaches based on ML and DL have been proposed (Table 4).

Table 1 ML and DL approaches in tuberculosis detection

Refs.	Year	Database	Feature extraction	Method	Performance
[44]	2016	Montgomery (MC) and Shenzhen (SZ)	Thoracic Edge Map encoding	Neural Network	ACC-79.23%(MC) –86.36%(SZ)
[43]	2017	Montgomery (MC) and Shenzhen(SZ) Indian (IN)	Texture, Shape, Edge, Symmetry	Bayesian Network, Neural Network	ACC-83%
[38]	2018	MC,SZ, Kenya and IN	Ensemble (Pre-trained CNNS, HOG, SURF)	SVM, Logistic Regression	ACC-93.42%
[18]	2019	Montgomery(MC)	Bag of Features(BoF), SURF	Multilayer Perceptron	ACC-87.4%
[8]	2020	Montgomery (MC) and Shenzhen (SZ)	Ensemble (Pre-trained CNN, Gabor filter)	Logistic Regression, CNN	ACC-93.47%(MC)—97.59%(SZ
[41]	2020	Shenzhen(SZ)	Feature Selection by AEO	CNN	ACC-90.2%
[20]	2020	Montgomery (MC) and Shenzhen (SZ)	Automatic Feature Learning	InceptionV3	ACC-86.8%
[31]	2020	Montgomery (MC) and Shenzhen (SZ) Private (KERH)	Automatic Feature Learning	InceptionV3	Spe = 1.0%, Pre =1.% F1 = 1.0% Recall = 0.99%
[19]	2019	Chest X-ray	Automatic Feature Learning	DenseNet121	AUC-0.965
[24]	2019	NLM Private	Automatic Feature Learning	AlexNet, VGG-16, CapsNet	Acc = 94.56% Sen = 92.83% Spe = 96.06%

10 Discussion

The paper presents an extensive review of applications of machine learning and deep learning to support diagnosis of tuberculosis, lung cancer, pneumonia and COVID-19, especially from Chest X-ray images. The detection of these diseases automatically in the last decade received significant attention resulting in enormous publications having state-of-the-art approaches. Although these studies reported good accuracies, they consist of significant limitations, especially in terms of methods. This can be

Table 2 ML and DL approaches in lung cancer detection

Refs.	Year	Database	Feature extraction	Method	Performance
[25]	2020	Japanese Society of Radiological Technology (JSRT) database	segmentation and rib suppression	multi-resolution patch-based CNNs	ACC-99%
[12]	2020	Dataset of Chest X-Ray and Lung cancer (LIDC-IDRI)	Morphological segmentation	EFT for lung cancer detection	Acc-97.27%
[47]	2020	Database of cancer imaging archive (CIA) dataset	Not Mentioned	DNN and ensemble classifier	Detect cancer with maximum accuracy
[13]	2019	LIDC-IDRI database	Segmentation and normalization	XGBoost and Random Forest Classifier	Acc-84%
[27]	2018	LIDC database	Median filter and Gaussian filter	SVM	Acc-92%
[48]	2019	LIDC database	Convert grayscale image into binary image	MLP, KNN, and SVM	Acc-88.55%
[5]	2017	Kaggle Dataset	Segmentation, normalization and Sampling	3D CNN	ACC-86.6%
[1]	2017	VIA and ELCAP database	Gabor Filter	Marker Controlled Watershed with Masking	Maximum accuracy achieved

considered as a reason for deploying CAD systems in the near future. It has been observed that these studies reported diagnostic accuracy without considering the risk of bias associated with the datasets which are used. On the other hand, the use of CAD systems enables the use of different sets (CXR images) of datasets during training. Hence, the following can be avoided: • Avoiding the use of the same set of CXR images for training and testing. • Testing should be carried out with the CXR images which have not been used for training but belong to the same image subset. Avoiding the use of images with class imbalance. • Avoiding the use of CXR images without annotation. If the above is not followed the accuracy of the diagnosis results in inaccuracy, and hence exaggeration may impact the overall generalization of the system.

Table 3 ML and DL approaches in COVID-19 detection

Refs.	Year	Database	Feature extraction	Method	Performance
[42]	2020	1500 X-ray images	Automatic Feature Extraction	VGG19 Transfer Learning Model	ACC-94.12% Sen-94.12% Spe-92%
[26]	2020	306 X-ray images	Automatic Feature Extraction	GoogleNet	ACC-100%
[37]	2020	11302 X-ray images	Automatic Feature Extraction	Xection and ResNet50V2	Overall Acc-91.4%
[35]	2020	2 databases	Automatic Feature Extraction	DarkNet	Binary Class Acc-98.08% Multiclass Acc-87.02%
[17]	2020	5856 X-ray images	Automatic Feature Extraction	CovXNet	Multiclass Acc-90.02%
[49]	2020	Not Mentioned	Automatics using CNN	ANN, ANFIS, and CNN	CNN compared with ANN and ANFIS
[53]	2020	Publicly available X-ray images	Automatic Feature Extraction	Deep Bayes SqueezeNet	Acc-98.3%
[52]	2020	Publicly available X-ray images	Automatic Feature Extraction	SqueezeNet and MobileNet	Acc-97.27%
[7]	2020	455 X-ray images	Automatic Feature Extraction	CoroNet Deep Learning	Acc-99.18% Sen-97.36%, spe-99.42%
[29]	2020	450 X-ray images	Automatic Feature Extraction	NasNet Deep Learning	Acc-97%

11 Conclusion

This paper presents a comprehensive survey on the use of both machine learning and deep learning on medical image analysis in the light of four important diseases, namely, tuberculosis, pneumonia, lung cancer, and COVID-19. This survey discovers some important issues by taking account of present ML and DL approaches to support medical image analysis. It has been observed that in course of time various classifiers associated with both ML and DL are facing challenging issues especially in identifying and extracting feature data from the medical images. Researchers by publishing state-of-the-art approaches are trying to address these issues. One of such

Table 4 ML and DL approaches in pneumonia detection

Refs.	Year	Database	Feature extraction	Method	Performance
[2]	2020	5528 X-ray images	Automatic Feature Extraction	Deep Siamese Network (DSN)	ACC-96.67%
[6]	2019	5856 X-ray images	Automatic Feature Extraction	Transfer Learning (ResNet50)	Achieved Remarkable Accuracy without overfitting Problem
[54]	2020	5863 X-ray images	Feature Extracted using CNN	CNN-RF	Acc-97%
[21]	2018	JSTR and Montgomery database	Automatic Feature Extraction	Fully Convolutional Networks (FCN)	Acc-80.5% Sen-78.23%
[23]	2020	X-Ray Images	Automatic Feature Extraction	SqueezeNet, Inception-v3	Acc-98.99% Sen-98.80% Spe-99.18%
[51]	2019	5232 X-Ray Images	Automatic Feature Extraction	CNN	Acc-95.3% AUC-94%
[50]	2019	RSNA-PDC database	Automatic Feature Extraction	RetinaNet, Mask R-CNN	Recall-79.3%
[45]	2020	5856 X-ray images	Automatic Feature Extraction	Deep separable residual learning	ACC-98.82% AUC-0.997
[30]	2019	5857 X-ray images	Automatic Feature Extraction	multi-layered capsules (CapsNet)	Acc-95.33%
[16]	2020	5232 X-ray images	Automatic Feature Extraction	Ensemble Method	Acc-96.4% Recall-99.62%

issues includes the improvement of classification accuracy, which depends on the availability of more training data. The more training data you have, the more accurate the result will be. However, the use of hybrid algorithms and the combination of supervised with unsupervised and integration of Ml with DL are considered as promising to get more accurate results. It can be argued that accuracies differ from classifier to classifier. This survey paper also pointed out the limitations of various ML- and DL-based classifiers to diagnose the diseases mentioned before, and hence it brings forward some fundamental research issues. Such research issues consist of transparency and trustworthiness of the results generated by the classifiers associated with both ML and DL since they are black-box type in nature. Due to the opaqueness of the classifiers, decision-makers sometimes become hesitant to make appropriate decisions because such classifiers are unable to identify the features responsible for certain diseases. Therefore, the inclusion of Explainable Artificial Intelligence (XAI) approaches to support medical imaging analysis is crucial since it will enable transparent and trustworthy decisions. In addition from this survey it has been observed that quality of training data and interoperability are the major concerns to develop effective and efficient either ML- or DL-based solutions. The amount of training data should be such that it should not in any way degrade the performance of either ML or DL classifiers. We hope this survey will be a tremendous help to the researchers working in the area of Artificial Intelligence and medical domains. In future, we will survey more research based on disease diagnosis [10, 14, 32–34].

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