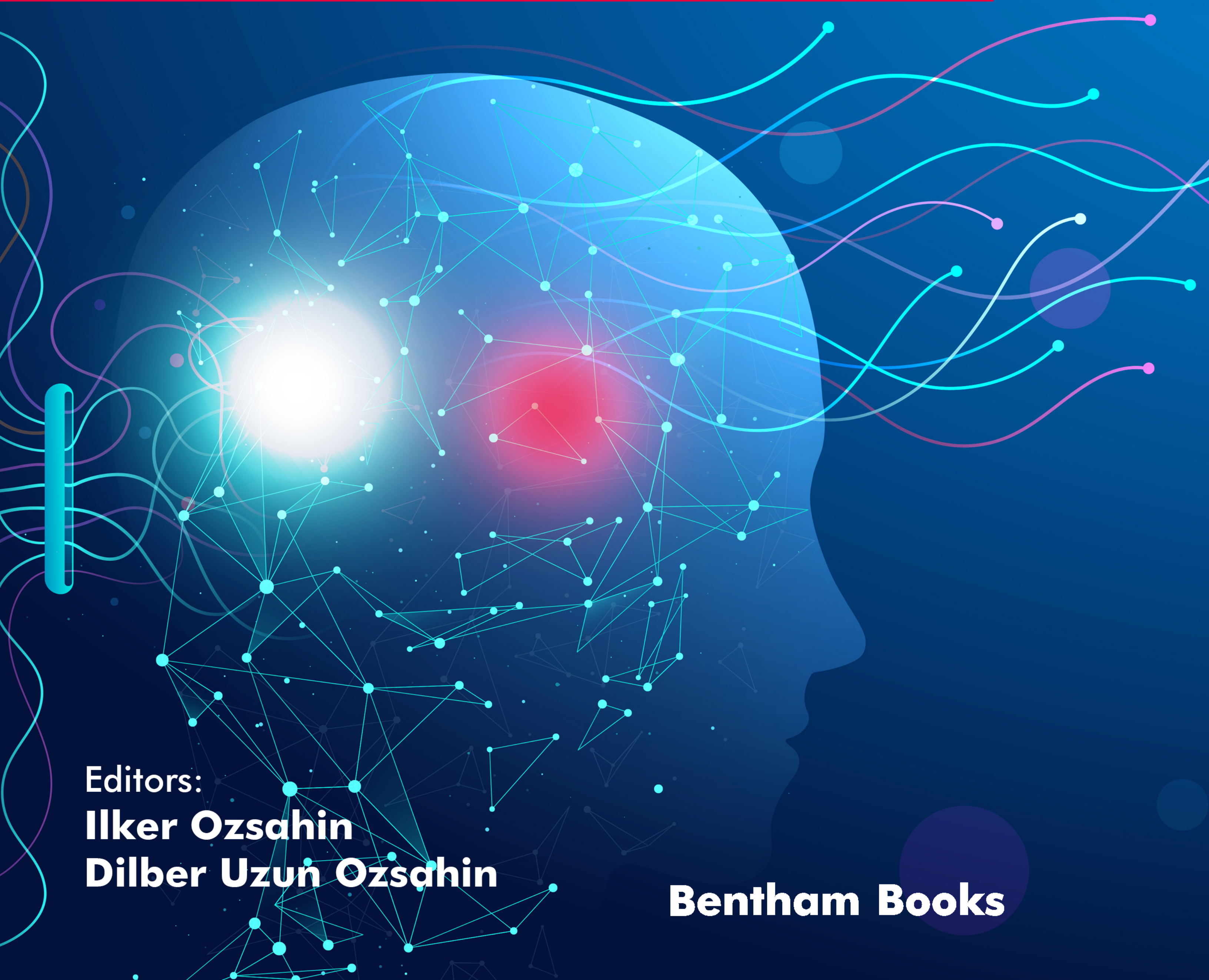
APPLIED MACHINE LEARNING AND MULTI-CRITERIA DECISION-MAKING IN HEALTHCARE



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Applied Machine Learning and Multi-Criteria Decision-Making in Healthcare

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Applied Machine Learning and Multi-criteria Decision-making in Healthcare

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PREFACE

Machine learning in healthcare is a growing area of application of artificial intelligence in medicine. It is used in many areas covering classification and prediction problems. Artificial intelligence can be considered as systems or machines that aim to imitate the cognitive functions of people and improve themselves iteratively with the information they collect. The classification methods in the machine learning field, which is quite popular among artificial intelligence methods, can be used especially for various health data. In general, there are two types of classification approaches. The first is the binary classification approach, which sets the class tags as 0 or 1. The second is the methods that not only identify class labels but also determine class possibilities. The most prominent method for the first approach is the support vector machines method. Artificial neural networks, k-nearest neighbors, decision trees, and logistic regression methods are the methods included in the second approach. The logistic regression method is one of the most prominent methods among these methods. The logistic regression method performs the classification task by determining which class the data belongs to. The fact that this probability is close to 1 indicates that it increases the probability of being included in the related class and that it is close to 0 decreases the probability. The logistic regression method is used for early detection, diagnosis, and treatment in the field of health, from radiology to cancer, from neurology to cardiology, as well as outcome prediction and prognosis evaluation.

Mathematical modeling is used to have a better understanding and sometimes even to predict a pattern and results of the biological studies, and like all others, biological studies are no exception to this fact. Different methods of modeling are used dependent on the study and raw data available. The book will also contain several practical applications of how decision-making theory could be used in solving problems related to the selection of the best alternatives. In addition to machine learning, the book will focus on assisting decision-makers (government, organizations, companies, the general public, etc.) in making the best and most appropriate decision when confronted with multiple alternatives. The purpose of the analytical MCDM techniques is to support decision-makers under uncertainty and conflicting criteria while making a logical decision. Finally, the detail provided in the book will be of great help to the general public in their day-to-day life. The knowledge of the alternatives of the real-life problems, properties of their parameters, and the priority given to the parameters have a great effect on the consequences of the decisions. In this book, the application of MCDM has been provided for the real-life problems that occurred in health and biomedical engineering issues. In addition, the application of MCDM examples will be shown manually to users.

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CHAPTER 1

Introduction

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Abstract: Machine learning (ML) provides computational approaches for an updated knowledge that assists in processing ideas such as data precision. Studies using ML methods are driven by the use of technological approaches to assist the healthcare system. This work reports different significant studies on the applications of machine learning algorithms as alternatives to healthcare challenges. The goal was to identify the research areas concern with possible solutions.

Keywords: Artificial Intelligence, Disease Diagnoses, Machine Learning.

The increase in the number of diseases has brought the high demand in providing improved healthcare service. Thus, improved information and communication technology is advancing in developing artificial intelligence, smart cities, and smart health in establishing a standard healthcare service. Healthcare services such as early disease diagnosis, patient monitoring, and sometimes patient appointments are grinding factors that establish the improvement and design of a tremendous healthcare system.

Machine learning (ML) is an accurate and perhaps regarded as a quick method to predict an outcome. In other words, it is a powerful tool used in healthcare institutions, rendering improved healthcare services. Deep learning and machine learning application in healthcare services are tremendously growing. These processes do not only establish a high connection between medicine and technology, but they give advancement in both health and research.

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Scientists, researchers, institutions, and healthcare are interested in developing "medicine in technology," providing models in computational mathematics and allied with artificial intelligence. This has brought a high level of remedy in both research and healthcare institutions.

Hitherto, diseases such as cancer in its different forms, stroke, high blood pressure, and basic healthcare services were regarded deadly. With the advancement in healthcare technology, these diseases are now managed efficiently by applying different approaches. Among many, the most fascinating of all is the application and imposition of human character, values, language, and even belief in the modeling of human-like technological creatures such as robots. This technology has positively increased the efficient standard of healthcare in both remote and urban human settlements. These robots are built to work like humans, with some of them looking and sounding like humans.

In post anesthesia nursing, a machine learning algorithm is used to identify any disease complications accurately. This process, however, could cause changes in different aspects. Machine learning is now regarded as a tool used to complement and magnify nursing and healthcare instead of replacing the system. Data collection such as research databases, device readings, and genetic tests are used in the technology revolution. Also, the application of machine learning cut across different healthcare services; these include the basic healthcare services using artificial intelligence systems, such as telemedicine, M-health, and maternity healthcare. However, focusing on the pros and cons of this study, one can also be skeptical about using machine learning algorithms for a start. However, weighing on this, it is the easiest and the most advanced treatment method used in healthcare.

Studies have shown that machine learning algorithms are used in the replacement of diagnosticians and nurses. However, machine learning is still regarded as the next generational tool applicable to reduce human interferences and forces such as exhaustion and the inability to compute analysis quickly. Furthermore, machine learning allows data analysis to understand and evaluate other complicated data in healthcare considerably. However, compared to the archaic biostatistics method, machine learning is more advantageous in flexibility and stability, which is more multi-tasking in disease diagnosis.

Diverse data analysis, such as demographic data, doctor's text notes, data imaging, and laboratory findings, can all be analyzed applying the machine learning algorithms method. This analysis can also be incorporated into predicting the appropriate treatments, disease risks, and prognosis. However, machine learning has its unique challenges in proper healthcare delivery, which requires refining clinical complications, model training, and data processing. Thus, other considerations such as ethical and medico-legal implications and doctor's knowledge are highly considered on the use of machine learning tools and data security.

Different studies and research on machine learning as a health monitoring system are recorded. These processes allow physicians and health personnel to monitor patients at a considerable distance taking periodic actions when necessary. These parameters assist the physician in communicating and monitoring the patient transmitting circuit used by the patient and the receiver circuit. In addition, this system assists in identifying doctors or physicians to consult and helps in the prediction of diseases based on machine learning algorithms.

Nowadays, transporting a patient from home to a hospital is challenging due to prevailing obstacles such as queueing for a check-up, the risk of contracting various infections, and the time required. These difficulties necessitated the development of transmittable technologies such as telemedicine, the Internet of Things (IoT), and machine learning to keep patients under the physician's or medical practitioner's supervision. In infectious diseases such as a pandemic, drones are constructed to assist in disinfecting a place exposed to this infection. This system serves as a remote monitoring system that connects the patient with the doctor at the patient's comfort. Machine learning algorithms create platforms that offer efficient medical data that provides the diagnosis, treatment plans, and possible recommendations for the patient.

CONCLUSION

The healthcare industry is stretched with an outgrowing population of patient services. Therefore, there is a need to have spontaneous, efficient, and modern services to cushion the growing difficulties experienced by individuals. Machine learning has, however, revealed its potentials in serving its purpose in the healthcare industry. The application of artificial intelligence and machine learning technologies has enhanced productivity and efficiency in medicine.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

CHAPTER 2

Machine Learning in Health Care

Basil Bartholomew Duwa[1,*], **Dilber Uzun Ozsahin**[1,2,3] and **Ilker Ozsahin**[1,2,4]

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Abstract: Machine learning (ML) as a subset of Artificial intelligence is gradually getting accepted in the healthcare industry. Thousands of data are revealed to be analyzed from different sources in healthcare through machine learning algorithms. ML is unarguably essential in disease diagnoses and a variety of healthcare application services. In this study, the application of ML in healthcare was focused on using artificial intelligence techniques based on different scientific studies. ML is essential in carrying out special, efficient healthcare services with ease for health professionals.

Keywords: Artificial Intelligence, Healthcare, Machine Learning.

Machine learning (ML) is an affiliation or sub-set of artificial intelligence (AI) that mainly focuses on studying computer algorithms applied in building sample data as mathematical models. In other words, ML application enables problems to be solved by machines without literally using computer programming.

Machine Learning ML is applied in various ways, such as email filtering and sometimes computer vision, projecting it (ML) into broader views. ML involves commanding computer-based technology to perform a wanted task without programming. These tasks can include using different approaches, supervised learning, unsupervised learning, and reinforcement learning [1].

Artificial intelligence (AI) in healthcare is regarded as a promising self-learning technique that is taking place globally. The advancement of ML-based artificial

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intelligence has broadened its scope to establish stable and efficient clinical practice worldwide [2].

The history of machine learning can be traced to its etiology, coined by a famous American named Arthur Samuel, who pioneered computer gaming and artificial intelligence [3].

Machine learning is applicable in different facets, including its application in agriculture, banking, bioinformatics, brain-machine interfaces, DNA sequencing, medical diagnosis, economics, speech recognition, *etc* [4].

Table **1** shows the various software used in machine learning. Learning machines are artificial intelligence-based technology centered on using data pattern analysis to understand data rules. These rules are used in diagnosing and predicting outcomes. The ML involves using broad data sets with clinical variables suitable for the program to predict the result. These clinical variables are passed along layers named neural networks [8].

Table 1. Machine Learning Soft Wares [5 - 7].

Name of ML Software	Manufacturer	Date of Manufacture	Application	Outcome	References
1. XGBoost	Tiangi Chen research project	March 27, 2014	Boosting Library app.	Efficient credit	https://en.wikipedia.org/wiki/XGBoost
2. Amazon Web services	Amazon Andy Jassy	March 2006	Cloud-computing services	Standard and efficient service	Amazon Web services (2012)
3. Orange	University of Ljubljana	October 10, 1996	Data visualization, modeling biomedicine, genomicsresearch	Recorded as a great standard app	Orange download May 28, 2018
4. Apache MXNet	Apache Software Foundation	February 21, 2020	Library for machine learning	Globally certified standard	Amazons deep learning frame (2017)
5. Keras	Francois Chollet	March 27, 2015	Designed to enable fast experiment using a deep learning technique	Standard	Keras documentation 2016

MACHINE LEARNING IN HEALTH CARE

Machine learning is a tool used in magnifying and, in other terms complementing knowledge rather than replacing it. Researches' have shown clinical data used in analysis and in collecting data. Clinicians use the genetic testing database to allow machines to examine and predict the type of disease involved. Health care data is regarded as one of the most complicated to handle in the data system. To have useful data, it must be processed before using in machine training [9].

APPLICATION OF MACHINE LEARNING IN HEALTHCARE

ML can be applied in various fields to implement a technological remedy in different systems. Machine learning is a field that expanded from artificial intelligence concerned in designing and developing computer-based algorithms.

Application of ML in Smart Health

Smart health is an integral field that combines e-health and smart cities to consistently solve health issues [10].

S-Health is derived from Smart cities and electronic health (e-Health). In other words, it is a sub-field of e-Health using smart cities to improve basic health care. Smart health uses artificial intelligence (robots) to enhance healthcare in assisting physicians in diagnosing, monitor, detect and treat diseases.

In Fig. (**1**), the improvement of the smart health system is illustrated. The data acquisition is retrieved through self-diagnosis as a result of networking and computing techniques and data privacy and security [11].

Table **2** represents different data sources based on machine learning applications in Smart systems regarding its usage in healthcare management. The first approach by Chai, *et al*. presents a deep learning model for Glaucoma diagnoses using CNN collected from Beijing Tongren Hospital, China. The analysis proposes 81.69% accuracy using the "said" databases. The second approach was based on Zhang *et al*. predicting mini-mental state examination scores (MMSE) in Alzheimer's disease, analyzing the multi-granularity and brain image [12].

CHAPTER 3

Prediction Problems in Healthcare Applications

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Abstract: Artificial intelligence tries to imitate human intelligence with powerful computer skills and aims to solve the problems that people have difficulty solving. Therefore, artificial intelligence and machine learning have begun to be applied thoughtfully in the field of healthcare and other lives. Remarkable results have been obtained in the performed research. These results have paved the way for applications in different healthcare areas and increase the frequency of the studies to achieve even more successful results in the same field. Prediction applications of machine learning are widely applied in healthcare as both class prediction and regression and support doctors and independent decision-making mechanisms. Even if classification studies of these applications have been performed, their diversity and excess numbers make them difficult and cause them to be considered on a subject basis. In this chapter, the usage of the terms “prediction,” “regression,” and “classification” in the literature is explained, and evaluation metrics used in all kinds of problem domains are defined. In addition to these, the problem areas of using machine learning techniques are summarized, and the literature search is performed in three scientific databases. Finally, the number of publications in the considered databases and an overview of the healthcare examples are presented. The data obtained and presented show that the applications using machine learning continue to increase significantly in healthcare and continue to be applied unlimitedly in all healthcare problems.

Keywords: Artificial intelligence, Classification, Evaluation metrics, Healthcare, Literature search, Machine learning algorithms, Machine learning, Prediction applications, Prediction, Regression.

INTRODUCTION

The speed, data processing capacity, and consequently, the storage capacity of computers have increased with the rapid development in electronic technology within a few decades. This era has caused technology to be used almost in all areas of our daily lives, and play a crucial role in both the daily needs of human beings and the field of health. Stored data has led to data sizes that start from

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limited numbers and reach big data in almost every business sector [1]. Creating complicated and massive amounts of data has brought both an advantage and considerable uncertainty for human beings. Experts, who now obtained all the data they want, had the risk of not reaching the required results because of the data complexity or size

Meanwhile, artificial intelligence (AI) and its sub-fields, machine learning (ML) and deep learning (DL) developed in parallel with this technological development and even improved with a more significant acceleration. Therefore, AI tools, and particularly ML, got involved in technology as a leading actor, and this created unlimited opportunities for the researchers by its applicability to every kind of problem [2, 3].

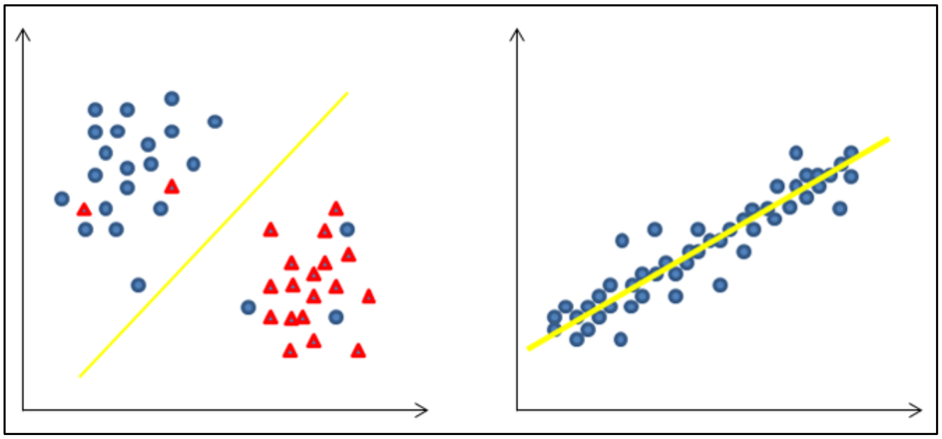
Machine learning differs from basic statistics and explicit programming by self-learning based on experiences and data relationships. Due to this feature of machine learning, it becomes an indispensable element in analyzing data that cannot be analyzed by human beings. Machine learning researcher and applications have been increasing rapidly in almost every field of the healthcare sector, especially in the last decade. Some examples of these research are cancer research, mental disease research, cancer predictions, diabetes disease research, and intensive care predictions.

In this chapter, the prediction and regression applications of ML in healthcare will be discussed in detail. However, before that, the differences between "classification," "prediction," and "regression" will be explained with examples, and the complexity of the terms will be reduced. In addition, evaluation metrics used in applications will be described in detail in a separate section.

The rest of the chapter is organized as follows: Section 2 introduces the readers to the differences between classification, prediction, and regression in ML. Section 3 describes the evaluation metrics used for ML models, and Section 4 summarizes the machine learning algorithms. Section 5 presents the prediction applications in healthcare, and finally, Section 6 concludes the remarks of the chapter.

CLASSIFICATION *VS.* REGRESSION *VS.* PREDICTION

Commonly, ML applications can be divided into two categories as Classification and Prediction. In classification applications, models have a limited number of outputs depending on the application. After the learning process, the untrained examples given to the model are classified into this limited number of classes (labels). However, this process is different in regression applications. Models have one output that can generate an infinite number of values. The new sample tested after learning can produce any value without assigning it to a class. The graphical difference between the classification and prediction is shown in Fig. (**1**).



(a) **(b)**

Fig. (1). Classification *vs.* Regression **(a)** graph for binary classification and **(b)** graph for the regression task.

Although the term "prediction" is commonly used concerning regression applications, it is also used in classification applications. In classification applications, "prediction" means the classification of untrained data into pre-defined classes. However, in regression applications, "prediction" is used to indicate individual outcomes for new data.

In this chapter, "Pr_R" is used to specify prediction applications using regression analysis. Although it is not the main subject of this chapter, "Pr_C" is used to predict classification applications for ease of understanding.

EVALUATION METRICS IN MACHINE LEARNING

Model evaluation methods or metrics in machine learning also differ. The evaluation methods used for Pr_C cannot be used for Pr_R, and those used for Pr_R cannot be used for Pr_C. The following two sections explain the evaluation methods used in Pr_C and Pr_R for comparison.

Model Evaluation Metrics in Prediction of Classes (Pr_C)

Whichever metric is considered in class predictions (Pr_C), true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) values are used

CHAPTER 4

Classification Problems in Healthcare Applications

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Abstract: Health, considered the state of individual physical well-being, is greatly affected by factors, such as the physical environment and everything within an individual. Individuals in poor health require monitoring to be observed in the hospital, home, or anywhere being cared for. Many healthcare applications are being recorded and classified considering the health of humans, using Machine Learning algorithms. The healthcare system has rapidly advanced in technology. Applications in healthcare mainly comprise the IoT (Internet of Things), which are smart mobile devices, and the healthcare applications required for keeping track of individual health status, medical staff prescription, and medical history. In this chapter, modalities of Medical imaging and machine learning methods used in prediction will be studied. The classification in medical applications will also be studied and discussed in detail.

Keywords: Classification, Healthcare, Machine Learning, Medical Imaging, Prediction.

INTRODUCTION

Machine Learning is a sub-section of Artificial Intelligence that can be invested in drug discovery, clinical decision making, and medicine, which helps medical experts in a practical way. Since digital information processing in medical science has increased recently, machine learning algorithms gained importance and success in considering the recorded patient data. According to Hsiao (2014), The use of electronic health records (HER) by physicians has been increasing within the last decade [1]. Medical Images are integrated through the patients' HER and are currently analyzed by radiologists, limited by fatigue, speed, and experience. Training a radiologist is worth time, and financial cost, so accurate and efficient ML algorithms must be used in medical science with image pre-processing tech-

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niques or image analysis [2].

Image Processing and analysis are active research fields in ML. Medical image processing refers to a set of procedures applied to an image to get meaningful clinical information from various imaging modalities, commonly for prognosis and diagnosis. To enhance prognosis or diagnosis, extracted information or data are used further, according to the need of the patient [3].

Types of medical images will be discussed in the next section, including Ultrasound Images, X-Ray Images, Computer Tomography Scans, Magnetic Resonance Imaging, Positron Emission Tomography, Retinal Photography, Histology Slides, and Dermoscopy Images.

MEDICAL IMAGING

Medical imaging modalities are divided into functional imaging, such as Positron Emission Tomography (PET), and anatomical imaging, such as CT or MRI. Furthermore, they can be divided into other types, such as organ-specific or whole-body imaging. The most common medical imaging types are given below.

Ultrasound Images (US)

The widespread clinical use of imaging technology in Ultrasound imaging, transducers, beamforming, pulse compression, harmonic tissue imaging, contrast agents, techniques for measuring blood flow and tissue motion, and three-dimensional imaging are known as the technologies for underpinning. In addition, tissue characterization, image segmentation, micro scanning, intravascular scanning, elasticity imaging, reflex transmission imaging, computed tomography, Doppler tomography, photoacoustics, and thermoacoustics are technologies under specialized emerging technologies [4]. It may also be referred to as a sonogram applied to obtain the image of an unborn baby or aid a surgeon in an operating theater [5]. Fig. (**1**) represents a sample ultrasound image.

X-Ray Images (X-Ray)

The use of clinical applications of X-rays has been started since the discovery of X-rays by Wilhelm Conrad Roentgen in 1895. Since then, diagnostic X-ray equipment has developed considerably, and the imaging quality of X-ray examination has been greatly improved, and the methods have been widely disseminated [6]. X-rays are radiations in electromagnetic forms [7] and are used to capture images dealing with the structure of all types of bones [8]. A sample X-Ray Image is represented in Fig. (**2**).

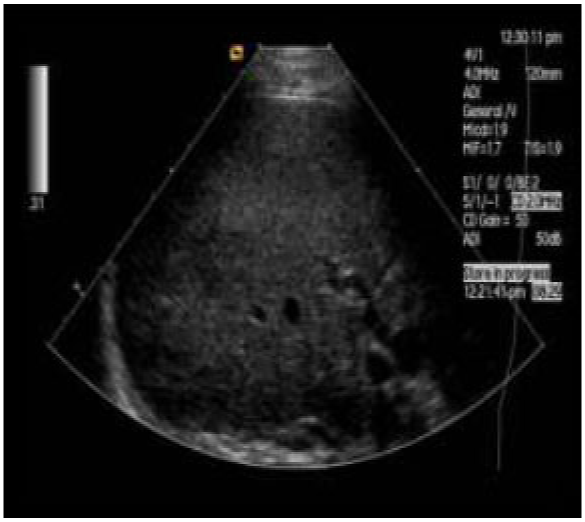

Fig. (1). A sample Ultrasound Image [5].

Fig. (2). A sample X-Ray Image [6].

Computed Tomography Scans (CT)

CT scanning is used for 3D imaging. It is used in various parts of the body such as brain, cardiac, musculoskeletal, and whole-body CT imaging. The images are presented as 3 Dimensional Colored and rendered images. However, radiologists

CHAPTER 5

Logistic Regression as a Classifier in Health Research

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Abstract: In recent years, the use of classification methods in machine learning, which is very popular among artificial intelligence methods, has been increasing due to the increase in the availability of health data. There are several classifier algorithms or methods in both supervised and unsupervised machine learning algorithms. Major unsupervised learning methods can be listed as cluster analysis and principal component analysis. Some notable examples of supervised machine learning algorithms are logistic regression, discriminant analysis, decision trees, nearest neighbor, neural network, naive Bayes, random forest, and support vector machine. In this chapter, binary logistic regression, one of the classification techniques in artificial intelligence, supervised machine learning, and econometrics, is theoretically discussed. In addition, the place and importance of this method in empirical applications in the field of health are briefly mentioned. In this section, an experimental study has also been conducted using the logit model to classify patients living in Adana province in Turkey according to their hospital services preferences. The data used in the study were collected by surveying in Adana. In the study, a binary logit model was used to classify patients and investigate the effects of many factors that may affect patient classification. Also, many tests have been conducted to investigate the classification ability of the model. As a result, the test results show that the model has good performance.

Keywords: Artificial Intelligence, Binary Response, Classifier in Health Research, Consumer Preference, Econometrics, Healthcare, Hospital Preference, Logistic Function, Logistic Regression, Machine Learning, Marginal Effects, Maximum Likelihood Estimator, Microdata, Odds Ratio, Pooled Data, Private Hospital Choice, Sigmoid Function, Statistics, Supervised Machine Learning, Unsupervised Machine Learning.

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INTRODUCTION

Artificial intelligence can be considered systems or machines that aim to imitate the cognitive functions of people and improve themselves iteratively with the information they collect. The classification methods in the machine learning techniques, which are quite popular among artificial intelligence methods, can be used mainly for health data. In general, there are two types of classification approaches. The first is the binary classification approach, which sets the class tags as 0 or 1. The second is the methods that not only identify class labels but also determine class possibilities. The most known method for the first approach is the support vector machines method. Artificial neural networks, decision trees, k-nearest neighbors, and logistic regression methods are included in the second approach. The logistic regression method is one of the most prominent methods among these methods. The logistic regression method performs the classification task by determining which class units belong to. The logistic regression method is used for early detection, diagnosis, and treatment in health, from radiology to cancer, from neurology to cardiology, and prognosis evaluation and outcome prediction.

CLASSIFICATION METHODS

In this section, logistic regression, one of the classification techniques in artificial intelligence, machine learning, and econometrics, will be mentioned. The place and importance of this method in artificial intelligence applications will be summarized first. Recent advances in data collection worldwide have had a significant impact on health research as in other fields in science. The increase in healthcare data and rapid development in big data analytics methods have made it possible to use artificial intelligence in healthcare to become widespread in healthcare services. Artificial Intelligence methods are divided into two main categories. In the first category, machine learning (ML) techniques that can analyze structured data are included. Structured data mentioned here are clinical data, imaging, genetic data, and data obtained with sensors. ML procedures try to cluster patient characteristics or infer the probability of disease outcomes in medical practice [1]. Methods in the second category are used to support and enrich structured medical data. This category includes natural language processing (NLP) methods that extract unstructured data, such as medical text, clinical notes, or medical journals. Here, NLP procedures aim to transform the text into machine-readable structured data, which can then be analyzed with machine learning techniques [2].

Classical Machine Learning methods create analytical algorithms to extract some useful features from medical data. While the inputs in the algorithms are sometimes the basic characteristics of the patients such as age, gender, disease history, they can also include being disease-specific data such as diagnostic images or tests. On the other hand, some medical outcomes are collected in clinical research, such as survival time and disease level. In short, machine learning algorithms need to use inputs and outputs. Machine learning algorithms fell into two main categories: unsupervised learning and supervised learning, depending on whether the outcomes are included or not. In general, unsupervised learning is suitable for dealing with feature extraction, while supervised learning is appropriate to be used in predictive modeling.

There are some classifier algorithms or methods in both supervised and unsupervised machine learning algorithms. The main unsupervised learning methods are clustering analysis and principal component analysis (PCA). Clustering analysis does not use outcome information when grouping subjects with similar patient characteristics into clusters. Clustering algorithms generate cluster tags for patients by maximizing and minimizing the similarity of patients within and between clusters [3]. Some of the leading clustering algorithms are hierarchical clustering, Mean-Shift clustering, k-means clustering, and Gaussian mixture clustering. The principal component analysis is used in dimension reduction in cases where there are many inputs. Thus, it aims to reduce the number of inputs by losing very little information. On the other hand, supervised learninguses both input and output information to determine outputs associated with most closely related inputs to average outcomes. Artificial intelligence applications in healthcare often use supervised learning, as supervised learning provides clinically relevant results than unsupervised learning [3]. Logistic regression, discriminant analysis, decision tree, naive Bayes, nearest neighbor, random forest, neural network, and support vector machine (SVM) are the leading supervised learning techniques used in classification [4]. While SVM and neural networks are the most popular supervised learning techniques in medical practice, Logistic regression analysis is one of the widely used methods among supervised learning methods. Logistic regression analysis is based on logistic function. The Logistic function was first used to analyze biological experiments in a study conducted by Berkson in 1944 [5]. Since then, it has been used in many studies in the field of health. Fig. (**1**) [3] shows the preference rates of various supervised learning techniques in medical practice and the place and importance of Logistic regression analysis.

CHAPTER 6

Deep Learning in Healthcare Applications

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Abstract: The state of individual physical well-being, which is considered as health, can be affected by the physical environment, as well as the factors going on within an individual. Poor health requires continuous monitoring for the individuals, and the process needs monitoring in hospitals or individuals' homes. Furthermore, the recorded health data should be analyzed by specialists to be prepared for further processing, such as artificial intelligence (AI), using the latest environment of technology. Many healthcare applications considering AI have been studied, especially in cancer diagnosis and treatment, in recent years. Deep learning, expressed as the future of healthcare, is driven by increased computational power and huge datasets. In this chapter, an introduction to machine learning (ML), AI, and deep learning in healthcare will be studied.

Keywords: Artificial Intelligence, Convolutional Neural Networks, Deep Learning, Healthcare, Machine Learning.

INTRODUCTION

Recently, the demands for radiology services such as magnetic resonance imaging, computed tomography, and radiographs have increased dramatically [1]. In many countries, medical imaging in healthcare is carried out by radiologists. However, there is a shortage of radiologists due to a lack of recruitment, and many radiologists are approaching retirement age. So, analyzing medical images is becoming a difficult and time-consuming process [2].

Different models matching or exceeding the level of human performance in the field of segmentation, classification, and clustering in biological imaging or health imaging are proposed as computational advances in Convolutional Neural Net-

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works [3 - 5]. In addition, studies have also described the novel CNN-based approaches for the segmentation of nuclei from fluorescence microscopy images [6 - 12].

Artificial Intelligence is a research field that implies the intelligent behavior of human beings by the use of computers [13]. It includes the families of Machine Learning and Deep Learning which is a field of Artificial Intelligence. It is represented by input-hidden-output layers of neurons that model the human brain [14].

A deep learning model has been proposed by Mackay *et al*. used to reduce the amount of experimental cell culture to follow the cell behavior to topographical cue and predict the effects of surface structure on tissue fabrication [15].

Another deep learning application in healthcare systems has been suggested by Zaki G. *et al*. [16]. The authors proposed a computational pipeline system, where it is used to test different nuclear segmentation model architectures systematically and model training strategies by the tuning of parameters to improve the performance of their system and provide computational tools, as well as a framework to improve image segmentation using small annotated biological image datasets.

Pond A. *et al*. suggested a deep learning approach to stage embryonic tissue isolates using small data. The authors trained a CNN-based classifier to stage zebrafish tail buds at four different stages of development using small information-rich datasets. They compared their two and three-dimensional convolutional neural networks to stage developing zebrafish tail buds based on morphological and expression confocal microscopy images [17].

MACHINE LEARNING ALGORITHMS IN HEALTHCARE APPLICATIONS

Machine Learning is a highly sophisticated technological application used in various fields of research. It plays a vital role in various research areas, such as security, finance, or medical science. It is a sub-section of artificial intelligence that uses information available in training data.

Machine Learning is a multi-disciplinary field of science with its roots in statistics, algebra, data processing, and knowledge analytics. These roots make the subject tough, and a novel definition is received [18].

Mishra A. and Shukla A. suggested that machine learning can be split into four sections such as supervised, semi-supervised, unsupervised, and reinforcement learning [19]. Supervised machine learning relates inputs to related outputs considering fundamental algorithms, whereas semi-unsupervised machine learning is used to identify the proper classifier from each unlabelled, as well as labeled information [20]. In Reinforcement Learning, a computer program as a dynamic environment to perform a specific goal has been applied [21]. Finally, unsupervised learning does not use any training data, and they use clustering algorithms such as fuzzy, hierarchical, or K-means with the association rule mining. Fig. (**1**) represents the Machine Learning categories [22].

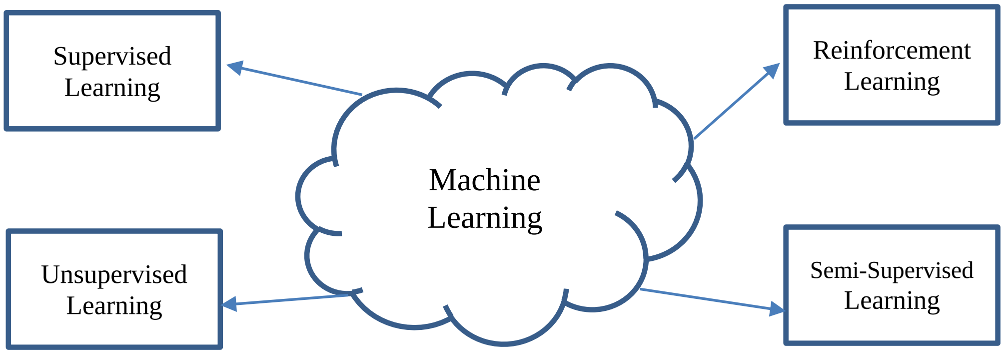

Fig. (1). Machine Learning Categories.

Chan *et al*. Compared deep learning-based methods with conventional methods in lesion detection. They mentioned that applying medical image analysis based on deep learning to computer-aided diagnosis has the potential and provides decision support to medical staff and helps to improve the accuracy, efficiency of varieties of diagnostics and treatment processes. Their goal was to provide reliable, intelligent aids for patient care [23].

Another research has been done by Ali *et al*. [17], which used deep learning to identify Cardiomyocyte Nuclei in Murine Tissue with high precision. They designed an artificial intelligence deep learning model using image segmentation in predicting cardiomyocyte nuclei in mouse heart sections without a nuclear label. They believed that their research is highly sensitive and specifically using cardiomyocyte structural protein immunostaining and a global nuclear stain [24].

Mebel *et al*. proposed an artificial neural network-based computational system for the localization of macromolecular species in cellular cryo-electron tomograms. Their deep learning algorithm leverages and outperforms the template matching algorithm on synthetic datasets. The authors achieved results considering experimental cryo-ET data depicting ribosomes, the localization, and structure resolution. Consistent results were obtained by their approach when compared with those obtained by experts [25].

CHAPTER 7

Comparison of Forecasting Models in the HIV Epidemiology Using Machine Learning Methods

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Abstract: In analyzing the Human immunodeficiency virus (HIV) epidemic dynamics, the biggest problem is uncertainty when planning for the future. In future evaluations, predicting what might happen will make the decisions' results more realistic. Policymakers will have the opportunity to take precautions against any negative changes that may occur. Machine learning methods that produce good and effective predictive results are needed to plan future policies, eliminate the negativities and overcome deciding in an uncertain environment. In this study, seven machine learning models used to make time-series analysis for medical purposes are theoretically explained. Machine learning methods such as Linear Regression, RepTree, Alternating Model Trees, M5, k Nearest Neighbor (kNN), Autoregressive Integrated Moving Average (ARIMA), and Random Forest were used. The dynamics of the HIV epidemic in Turkey have been made stationary time series, considering compliance of the correlation. Then, the time series were preprocessed using the Moving Average technique, and the time series was softened. The time series is divided into 2/3 training and 1/3 test sets. Machine learning methods were trained using these sets, parameter optimization of models was made and tested. Then these models were used to forecast the HIV epidemic Dynamics in Turkey in 3 years between 2019-Q4 and 2022-Q3. The Random Forest method has been successful as the model that produces the least error rate (Mean Absolute Percentage Error, MAPE) among these seven models. According to the estimation results of the Random Forest model, R^2 (the coefficient of determination) value was 82.16%, E (efficiency) value was 0.6268, Slope value was 2.3362, and MAPE value was 5.4132%. The Random Forest model has been observed to give excellent results for the three-year forecast of dynamics of the HIV epidemic in Turkey.

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Keywords: Akaike Information Criterion (AIC), Alternating Model Trees, ARIMA, Autocorrelation Function (ACF), Bayes Information Criterion (BIC), Chi-square, Efficiency, HIV Epidemiology, kNN, Ljung-Box Q-statistic (LBQ).

INTRODUCTION

Decision-making is an integral part of our daily life. Based on our past knowledge and experience, we make predictions to make individual, social or corporate decisions. At the same time, we often find it challenging to make the right decision under uncertain conditions. As the degree of uncertainty increases, the difficulty of estimation increases. Under uncertain situations, future forecasting requires better plans and decisions. Time series analysis is used to make predictions of natural disasters and the situations for investing smartly in the stock market, smart grid applications in the electricity industry, planning the energy consumption supply-demand relationship, planning personnel recruitment in organizations, making decisions to increase the service quality of service providers, and controlling sufficient stock levels.

Time series is created by recording the observed values of a particular situation over time under certain conditions. The analysis methods that allow the change of the characteristics of the data set that make up the time series depending on the time within limits determined by statistical methods and make predictions are generally called time series analysis. Time series analysis is used to conclude to analyze and improve the observed situation or situations and provide recommendations and plans to policymakers by making predictions for the near future for health-related processes and medical applications. In the time series analysis, obtained forecasting graph consists of the centerline of the forecast result, upper and lower confidence intervals control limit. As long as the center graph of the prediction result is between the upper and lower confidence intervals, it is accepted that the predicted process gives results under control.

Time series analysis plays a vital role in decision-making. Therefore, improving the predictive accuracy of machine learning methods has been an exciting area. In order to obtain better prediction accuracy, preprocessing and statistical preparation of the time series, choosing a specific prediction method and model, training the model, optimizing the model's parameter, and testing the model plays an important role.

Predicting the future event of a nonlinear system opens the way for planning and achieving the set goals successfully. However, pattern recognition and predicting future events of nonlinear systems are difficult tasks due to noise and nonstationarity. Therefore, time-series data, which are a series of observations of quantitative characteristics of the individual or collective properties, are taken at regular intervals [1].

Time series data are bulky [2]. Therefore, it is not easy for an expert to make an accurate decision by using/reviewing past data patterns. For example, it is difficult for a stock market specialist to consistently and accurately identify the rise and fall of a stock's price. For this reason, time-series data, also known as historical data, are used to create a model and analyze the nonlinear system under examination [3, 4].

In this study, machine learning models are theoretically explained to perform medical time-series analysis in the field of health. The HIV epidemic in Turkey between the periods of 2019-Q4 and 2022-Q3 was estimated using these models. As a result of the estimation, MAPE values of the machine learning models were obtained. Furthermore, MAPE values of the models were compared, and the machine learning model with the lowest error rate was determined.

MATERIALS AND METHODS

Machine Learning

Machine learning is one of the areas of computer science that aims to enable computers or other devices to gain the ability to learn without being managed externally. Machine learning aims to develop algorithms and methods to learn from data and make predictions according to the data. It focuses on discovering accurate patterns and making predictions using the advantages of many computer science fields that aim to derive meaning from data such as statistics, optimization, data mining, artificial intelligence, evolutionary computing, and artificial neural networks [5].

Today, machine learning combines many disciplines such as statistics, information theory, the theory of algorithms, probability, and functional analysis [6]. Techniques based on machine learning have been successfully applied in various fields, from pattern recognition, spacecraft engineering, finance, entertainment, and computational biology to biomedical and medical applications [7].

Machine learning techniques are divided into two main categories: supervised learning and unsupervised learning, according to the nature of the work and inputs used. In supervised learning, the expected outputs are available in response to each input data, whereas, in unsupervised learning, there are no outputs in response to the input data. The machine learning techniques used in both categories can be listed as Decision trees, association rule mining, artificial neural

CHAPTER 8

Deep Learning and Artificial Intelligence Applications in Dentomaxillofacial Radiology

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Abstract: Artificial intelligence (AI) and Deep Learning (DL) started to play an active role in real-life problem solutions, and they have a rising trend across all medical fields, including dentistry. Since there are advanced improvements in image recognition techniques, a better radiological diagnose, prediction of the prognosis, and clinical decision making with a reduced workload are becoming possible for dentomaxillofacial radiologists. Promising results were obtained regarding dental caries detection, periapical/periodontal lesion detection, anatomical landmark localization, osteoporosis diagnosis, and implant dentistry; nonetheless, AI models do not substitute for most of the conventional processes yet. Further studies should be done to verify the feasibility and reliability of AI and DL applications in clinical practice.

This chapter focuses on artificial intelligence and machine learning applications in dentomaxillofacial radiology.

Keywords: Artificial Intelligence, Dentomaxillofacial Radiology, Dental Radiology, Dentistry, Decision-Making, Digital Dentistry, Diagnostic Systems, Machine Learning.

Artificial intelligence applications, which date back to 1956, come to the agenda with serial developments, especially in diagnosis and radiology in health. In addition, it is considered an application that will serve humanity for a long time to

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cover the whole diagnosis-treatment with clinical trials to make the right decisions in the treatment stage [1, 2].

Considering that machines can do calculations faster than people without interruption, it can be said that the use of artificial intelligence developments in the health sector will be extremely beneficial. Unlike a clinician, machine learning systems can observe and process almost unlimited numbers of data simultaneously. In addition, since these systems can learn from the data of each case, they can learn to evaluate more cases in minutes than a clinician can see over the life of a clinician [3 - 13].

Artificial intelligence is being used in health, such as disease diagnosis, drug development, personalized therapies, and gene regulation. Diagnosing a disease accurately is a challenging process, as every clinician knows, which requires years of medical training and, in some cases requiring very long periods. Machine Learning, especially Deep Learning algorithms, has recently made great progress in automatically diagnosing diseases, making diagnosis cheaper and more accessible [3 - 12, 14].

Since there are many data related to issues like [14, 15]:

- Detection of lung cancer by CT
- Sudden cardiac death due to ECG and cardiac MRI images
- Assessment of the risk of other heart diseases
- Classification of skin lesions in skin images,
- Diagnosis of diabetic retinopathy in orbit images

Artificial intelligence algorithms can be as successful as the experts in diagnosing these situations.

In addition, the algorithms can give fast and accurate results in a few seconds on this type of procedure and will provide the same quality radiological diagnosis all over the world at a much cheaper price [3, 4, 6, 7, 9, 10].

AI can be used to diagnose many diseases in many countries with poor socio-economic status. For example, in countries with a high prevalence of tuberculosis, it is sometimes impossible for patients to be diagnosed due to the small number of radiologists who will evaluate the images of patients. Because artificial intelligence can accurately diagnose pulmonary tuberculosis with 95% sensitivity and 100% specificity, it can be easily diagnosed even in countries where radiologists are available with artificial intelligence by evaluating radiographs to be loaded from health centers [16].

Consider consultation with a physician for a patient with type 2 diabetes. Today, doctors spend a significant amount of time on all procedures, such as evaluating all blood tests, recording and evaluating the patient's history, and patient follow-up. However, using artificial intelligence, changes between blood tests and risky situations can be identified more quickly, and customized treatment protocols can be prepared for the patient instead of stereotyped treatment applications. The research necessary for these “personalized” therapies that will provide the most accurate treatment will be possible only with artificial intelligence systems that can process and summarize huge amounts of medical data quickly and accurately [13, 17].

The use of AI to calculate target areas for head and neck radiotherapy more accurately and faster than a human being is a topic that is being worked on. Interventional radiologists are still responsible for providing treatments, but AI has deeper and more accurate data to protect the patient from harmful radiation [18 - 20].

In addition, as artificial intelligence systems can monitor millions of data simultaneously, they will have an important role in preventive medicine. Artificial intelligence may offer early consultation to specialists as the patient may recognize the risk of developing a particular diabetic complication early [13, 17, 21 - 23].

Artificial Intelligence (AI) can be used for daily clinical problems and is applied across all dentistry departments thanks to machine learning (ML). The accurate diagnosis of deep learning algorithms in radiology and pathology keeps improving with every update, and software is being improved rapidly to be the “person-in-charge” in upcoming days [3, 4, 6, 7, 9, 10].

All departments of dentistry have various applications of AI. For example [3, 4, 6 - 12]:

In Orthodontics

- Prediction of unerupted canines and premolars’ sizes
- Necessity of extractions before orthodontic treatment
- Evaluation of maxillary canines
- Evaluation of lateral cephalograms
- Prediction of mandibular morphology in Class 1-2-3 patients

In Prosthodontics and Restorative Dentistry

- Prediction of the ongevity of dental restorations
- Prediction of color matching

CHAPTER 9

Artificial Neural Networks Approach in Determining Factors of Death Caused by Coronavirus in the World with Unbalanced Panel Data Models

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Abstract: The pandemic, which frightened the whole world, was reported in December 2019 as mass pneumonia cases in Wuhan city of China. The fact that the deadly new type of coronavirus can be transmitted extremely easily from person to person has also increased the spread of the disease. This spread negatively affects social, economic, and demographic life all over the world. This study aimed to identify which chronic and other diseases in combination with COVID-19 caused mortalities around the globe. As a result of the analysis, the appropriateness of the random effect unbalanced panel data model to the research purpose was determined. Coronavirus deaths related to the results of the Wald test used in the Generalized Least Squares (GLS) Technique, cardiovascular, diabetes, hypertension, respiratory disease, cancer, and other diseases are significant. In addition, the hierarchical clustering technique was applied to the meaningful model. According to the Ward Technique results, countries with similar chronic and other diseases for Coronavirus-related deaths were included in the same cluster.

On the other hand, the multi-layered Perceptron (MLP) model, one of the Artificial Neural Network (ANN) methods, was applied to the same model. The aim is to determine which chronic disease has a more significant effect on the Coronavirus-related death factor. Literature research shows that hypertension disease ranks first in Corona-related deaths worldwide. The analysis of the MLP model made for this purpose determined that hypertension disease was in the first place in pandemic deaths.

Keywords: Artificial Neural Networks, Clustering, COVID-19, Panel Model, WHO.

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INTRODUCTION

Coronavirus (COVID-19) appeared in Wuhan, Hubei province of the People's Republic of China, in December 2019. Various animal species are sold in the Huanan seafood market in Wuhan, China. Most of the first COVID-19 cases have been identified in people working or visiting the market. Coronavirus continued to spread rapidly to other cities of China and worldwide in a short time. The World Health Organization (WHO) defines coronavirus as a large family of viruses that can be seen in both humans and animals. It has been determined that the gene sequence of COVID-19 is similar to the ratio of coronavirus causing SARS (Severe Acute Respiratory Syndrome) with 79% and causing MERS (Middle East Respiratory Syndrome) with 50%. Based on these findings, a prediction was made by scientists that COVID-19 was transmitted from bats to humans. Statistics published by Chinese scientists suggest that the deadly coronavirus mainly affects the elderly and those with chronic diseases. The research conducted by Chinese scientists about respiratory viruses is that the immune system's response of most older adults is important. Chinese scientists state that immune cells will cause a cytokine attack by filling the lungs in older people. For this reason, serious diseases such as trachea inflammation, pneumonia, and shortness of breath occur in older adults. Although the mystery of the coronavirus has not been resolved yet in China, the mortality ratio, especially in those with hypertension, diabetes, and heart diseases, is remarkable. The World Health Organization (WHO) declared the COVID-19 pandemic caused by the SARS-CoV-2 virus as a pandemic on March 11. Scientific research about this pandemic, in which the world is caught unprepared, continues. Although scientists have not yet solved the mystery of the virus, the diagnostic and mortality statistics findings provide essential clues to combating the pandemic. Accordingly, global researchers make great efforts to understand the pathology of the disease, slow the rate of its spread, and develop vaccines and drugs.

The primary purpose of this study is to determine chronic and other diseases affecting death in Coronavirus-related deaths in the world with an unbalanced panel data model. The opening section of the study contains information about the novel coronavirus. The second section of the study is an empirical review of the literature. The final section of the paper discusses ways for detecting corona virus-related deaths. These techniques, unbalanced panel data models and prediction techniques, and artificial neural network models are examined. In the fourth part of the study, the methodology and the new Coronavirus pandemic are included. In the fifth section, the analysis and results of the unbalanced panel data model are examined. In the analysis, the GLS technique, cluster analysis, and artificial neural network technique were used. The sixth part of the research consists of conclusions and suggestions.

LITERATURE REVIEW

The subject of the articles scanned for this scientific research is an analysis of balanced and unbalanced panel data models, hierarchical cluster analysis, artificial intelligence, and artificial neural networks, some of the studies on the Coronavirus pandemic. Although the epidemic negatively affected the global supply chain, it increased the demand and housing prices of houses suitable for human health. Therefore, it has been added to the literature in articles on housing demand and housing prices. These are slogans like “Stay at Home” and “Life is at Home” to reduce the spread of healthcare professionals.

Mayda (2005) [1] investigated migration's economic and non-economic changes in 14 major OECD countries between 1980 and 1995. The annual panel dataset used in the migration flow benefited from the time series and the cross-section change. In addition, he estimated the international standard migration model with this study. In another study related to unbalanced panel data, Mouchart and Rombouts (2005) [2] examined panel data clustering models for instantaneous weather estimation with a limited number of random data. Unbalanced panel data models developed for lost data suggest a modeling strategy for instantaneous weather estimation. Selim and Demirbilek (2009) [3] investigated the rental value of housing in Turkey with the hedonic price model and the artificial neural network model for artificial intelligence applications. According to the findings obtained from comparing the two models, the artificial neural network model was a better method for estimating the rental value. Ecer (2014) [4] compared the neural network with the hedonic regression method to predict housing prices in Turkey. According to the findings obtained from the analysis, he found that the artificial neural network model yielded better results than the hedonic model in terms of predictive accuracy. Akay and Yüksel (2017) [5] conducted a mixed variable panel data cluster analysis to investigate aggregated hierarchical algorithms using the k-prototype algorithm and Gower distance. In the study, the performance of the algorithms is shown on mixed (numerical and categorical) variable panel data. In addition, the effectiveness of algorithms was compared in this study. Celik ve Kıral (2018) [6] determined the factors affecting the demand for housing in the provinces of Turkey with hierarchical clustering analysis, balanced and unbalanced panel data analysis techniques. In addition, this research was supported by SWOT analysis. Yılmazel *et al*. (2018) [7] studied artificial neural networks. In the study, they estimated the housing prices for sale in Eskisehir. The findings of the analysis show that artificial neural networks are effective in predicting housing prices. Akay and Yüksel (2019) [8] clustered a mixed variable panel data set containing binary variables and time-invariant. The study's main purpose is to prevent the loss of information without a variable

CHAPTER 10

Dynamics of Two Strain Influenza Model with Vaccine

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Abstract: We consider two strain influenza model with two vaccination in which strain 2 is the mutation of strain 1. A mutation is a significant change in the genetic makeup that arises due to errors during DNA replication or environmental factors. In this case, strain 2 was assumed to have developed due to alterations in the proteins that comprised strain 1. Proper vaccine administration is a critical component of a successful influenza control program. It is a key part of ensuring that vaccination is as safe and effective as possible. Unfortunately, it is easy to make vaccine administration errors. While certain vaccines administered incorrectly may be valid, such errors can leave patients vulnerable to disease. The aim of this chapter is to study the effect of administering strain 1 (V1) vaccine against strain 2 and strain 2 (V2) vaccine against strain.

Keywords: Influenza, Simulation, Stability, Strain, Systems of Differential Equations, Vaccine.

INTRODUCTION

History of Pandemic

Infectious diseases have been recognized since 165-180 AD. These diseases were known as pandemic diseases, such as smallpox or measles. During this time, for example, in Mexico, more than 30 million people were affected by smallpox [1].

In history, very severe cases of infectious diseases are discernible. Between the years 1346-1350, more than 10000 people died in Europe. Between 1665 and 1666 Black Death (bubonic plague) affected one-sixth of the population in London. The highly contagious diseases have always defied human control; therefore, they affected many people worldwide . In 2006 according to World

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Health Organization, approximately 1.5 million people were affected by tuberculosis. Another infectious disease, namely malaria, affected about 40% of the world population in the same year. According to the UNTIL statistic, 25 million people are infected with AIDS globally. As such, the disease should be taken seriously by the government [2].

The influenza pandemic was first recorded in the 20th-century. The 'Spanish Flu' (H1N1) was one of the most serious pandemics that spread in the world quickly, affecting 500 million people, and killing over 30 million people between 1918-1919 [3]. In 1957 and 1968, the flu in Asia (H2N2) and Hong Kong (H3N2) resulted in 69,800 and 33,800 death, respectively [4]. By late 1957, medical practitioners can observe the vaccine reaction in a large number of people. Although they were not catastrophic, they killed millions of people. Following these pandemics, experts discovered that waterfowl was the natural host of all influenza A viruses. Viruses mutated more rapidly in birds than in humans.

In 1977, an influenza outbreak dubbed 'Red Flu' spread out of North-Eastern China and the former Soviet Union. It was discovered that the Red Flu virus's effect is remarkably identical to that of the H1N1 virus. Influenza A virus mutated more rapidly than the latter. Additionally, it has been determined that this disease is exclusive to individuals under the age of 25. However, elderly individuals developed antibodies against a similar virus in 1958 [5].

In 2009, a new pandemic arose from Mexico or the southwestern USA. Again, a type of H1N1 virus transmitted directly from intensively farmed pigs, dubbed "Swine Flu". The virus had spread worldwide, and in most countries, there were infected people. Although the infection symptoms resembled seasonal influenza, it was not as severe as had been feared. This infection is referred to as Swine flu. However, there was insufficient vaccine strain of the virus [6].

Influenza is a disease caused by a virus that affects mainly the nose, throat, bronchi, and sometimes lungs. It is widely referred to as "flu" and is a viral disease that affects humans and many animals. Coughs, sneezes, infected surfaces, and direct contact with infected people are the most common ways of contagion [8].

There are three types of influenza viruses: A, B, and C. Influenza A is the predominant group that infects humans and animals, and it exhibits antigenic diversity, allowing it to evade neutralization by antibodies [9]. Influenza B is a human-specific virus that shows antigenic diversity lesser than influenza A. This feature, however, is uncommon in influenza C; type C influenza is associated with mild illnesses [10]. As a result, influenza A is more dangerous than influenza B, followed by influenza C [11].

Influenza A virus is classified as Hemagglutinin (HA) or neuraminidase (NA) based on the two proteins found on the virus's surface. Hemagglutinin is further classified into 12 subtypes (H1–H12), while neuraminidase is organized into nine subtypes (N1–N9) (WHO, 1980). Additionally, it can be classified into strains; the most prevalent strains detected in humans are the H1N1 and H3N2 viruses [12].

Three critical control strategies against the spread of influenza are antiviral therapy, quarantine, and vaccination. Anti-influenza medications that specifically target influenza neuraminidase have been used to prevent and treat influenza virus infection for many years. For example, the most well-known antiviral therapy for the H1N1 influenza virus is Oseltamivir, better known as Tamiflu [11], because the drug-resistant strain results from amino acid alterations neuraminidase [3]. Ju *et al*. proposed nalidixic acid and dorzolamide as anti-Oseltamivir resistant influenza medicines.

Due to the significant danger of an influenza pandemic and the high number of deaths connected with influenza, it is critical to understand the dynamics of influenza illness spread. The critical theoretical technique used to examine the disease's transmission dynamics is known as Epidemic Dynamics.

MATHEMATICAL MODEL

Mathematical models are critical for comprehending the dynamics of disease. Additionally, it outlines the most effective technique for long-term disease control [13].

Bernoulli devised the first mathematical model for smallpox in 1760 [14]. Hamer later developed a discrete-time model for the transmission of measles in 1906. Ross established the transmission of malaria between humans and mosquitoes in 1911 using the ordinary differential equation. Kermack and McKendrick are credited with inventing compartmentalized models. In 1927, they identified the first SIR epidemic model. They used a compartmental model in which they divided the population into three compartments: S denotes the number of susceptible individuals, I represents the number of infected individuals who were assumed to be infectious and capable of spreading the disease through contact with susceptible individuals, and R denotes the number of individuals who had been infected and were removed. In their model, they assumed that; There is no emigration nor immigration and neither birth nor death in the population, the number of susceptibles who are infected by an infected individual per unit of time, at a time t, is proportional to the total number of susceptibles with the proportional coefficient (transmission rate) β, so that the total number of newly infectives, at time t, is βStI(t); the number removed (recovered) individuals from

CHAPTER 11

Epidemic Influenza Model with Time Delay

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Abstract: In the previous chapter, two different types of vaccine were used for the two strain epidemic model; the results have demonstrated the significance of choosing the right vaccination. This chapter added delay to model (1), which is given in chapter 9. Here delay describes the incubation period. The model consists of four equilibrium points; disease-free equilibrium, endemic based to strain1, endemic with respect to strain2, and endemic with respect to both strains.

The global stability analysis of the equilibrium points was carried out through the use of Lyapunov functions. Two basic reproduction ratios $r_1$and $r_2$are found, and we have shown that if both are less than one, the disease dies out. If one of the ratios is less than one, an epidemic occurs with respect to the other. It was also shown that any strain with the highest basic reproduction ratio would automatically outperform the other strain, thereby eliminating it. Condition for the existence of endemic equilibria was also given.

Numerical simulations were carried out to support the analytic results and show the vaccine's effect for strain1 against strain 2 and the vaccine for strain 2 against strain 1. It is found that the population for infectives to strain 2 increases when the vaccine for strain1 is absent and *vice versa*.

Keywords: Basic Reproduction Ratios, Delay, Global Stability Analysis, Two Strain, Vaccine.

INTRODUCTION

The incubation period of infectious diseases varies [1]. Time delay is one of the important methods that can be used in epidemiology. A more realistic approach includes some of the past histories of the system in the models. The best way to model such processes is by incorporating time delays into the models. An ordinary differential equation should model the system with time delay [2].

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Time delay can be divided into discrete delay (fixed delay) and continuous (distributed) delay. In the fixed delay model, the dynamic behavior of the model at time t also depends on the state at time t-τ, where τ is constant. Time delay can be used to describe;

Latent or Incubation Period

For some diseases, the number of infectives at time t also depends on the number of infectives at a time t-τ, where τ represents the latent period. Some SIR models with latent or incubation periods were studied in recent years [3 - 7]. SVEIR model uses delay for a latent period in which the vaccine class can be infected [8 - 10].

Immunity Period

After recovery from any disease has short or long immunity against re- infectious naturally arise. This time τ represents the immunity period, and after τ time, an individual later loses the immunity [11, 12].

Mutation Period

Some diseases change their structure quickly and gain immunity based on treatment or vaccine. Mutation time is represented by "delay" on the model [13].

Above delay, periods can be mixed in a model, such as two delays for latency and temporary immunity, respectively [14].

In this chapter, in addition to chapter 9, it adds an incubation period for both strains, which makes the model more realistic, and constructed two strain influenza model with two vaccines in which strain 2 is the mutation of strain 1.

The correlation between time delay and mutation is evident on strain 1 (or 2). So, a study on the effect of time delay on vaccine-induced immunity is crucial. This chapter presents a mathematical model to describe the dynamics of a two-strain flu model with two delays. We targeted the effects of the vaccine for strain one instead of strain 2 and the vaccine for strain 2 as opposed to strain 1.

STRUCTURE OF MODEL

The epidemic model constructed in this chapter consists of two strains and two vaccines with two delays (τ_1 and τ_2). Similarly to the previous chapter, the population N(t) is divided into susceptible, immunized with the vaccination for strain 1, immunized with the vaccination for strain 2, infected with strain 1, infected with strain 2, and recovered compartments with S,V_1,V_2,I_1,I_2, and R, respectively.

Assuming that infected at time t-τ_1 and t-τ_2 become infectious τ_1 and τ_2 time later respectively. To be more realistic, it can be assumed that not all those infected will survive after τ_1 (τ_2) times later, because of this reason survival term $e^{\mu\tau i}$ (i = 1, 2) introduced.

There is constant recruitment into susceptible class through birth and immigration, and there is no double infection. The average life expectancy is μ, and d_i (i = 1, 2) are infection death rates of strain 1 and 2, respectively. The average time spent in class I_1 and I_2 become recovery $\frac{1}{\gamma_1}$ and $\frac{1}{\gamma_2}$, respectively. The susceptible individuals are vaccinated with a constant rate r_1 for strain1 and r_2 for strain 2. Strain 2 can also infect the vaccinated individual V_1 at a rate k_1, and strain1 can also infect the vaccinated individual V_2 at a rate k_2. β_1 and β_2 are transmission coefficients of susceptible individuals to strain one and strain 2, respectively. The variables and parameters are positive. With these assumptions, the model is given by a system of 6 ordinary differential equations

$$\frac{dS(t)}{dt} = \Lambda - (\beta_1 I_1(t) + \beta_2 I_2(t) + \lambda)S(t),$$

$$\frac{dV_1(t)}{dt} = r_1 S(t) - (k_1 I_2(t) + \mu)V_1(t),$$

$$\frac{dV_2(t)}{dt} = r_2 S(t) - (k_2 I_1(t) + \mu)V_2(t),$$

$$\frac{dI_1(t)}{dt} = e^{-\mu\tau_1}\big(k_2 V_2(t-\tau_1) + \beta_1 S(t-\tau_1)\big)I_1(t-\tau_1) - \alpha_1 I_1(t), \tag{1}$$

$$\frac{dI_2(t)}{dt} = e^{-\mu\tau_2}\big(k_1 V_1(t-\tau_2) + \beta_2 S(t-\tau_2)\big)I_2(t-\tau_2) - \alpha_2 I_2(t),$$

$$\frac{dR(t)}{dt} = \gamma_1 I_1(t) + \gamma_2 I_2(t) - \mu R(t),$$

where $\lambda = r_1 + r_2 + \mu$, $\alpha_1 = \mu + \nu_1 + \gamma_1$, and $\alpha_2 = \mu + \nu_2 + \gamma_2$,

CHAPTER 12

Mathematical Modeling in Reproduction and Infertility

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Abstract: Infertility is a major concern in health sciences. Many treatment strategies are being developed to overcome this problem. Assisted reproductive technologies (ART) are used in the treatment of infertility. Depending on the cause of infertility, different approaches can be applied in the field of ART treatments. However, since infertility is complex, it may be difficult to select the best treatment strategy for each patient. Mathematical modeling is used to understand better and sometimes even predict a pattern and outcome of biological processes. Thus, developing models help scientists and medical doctors select the best way of treatment and improve pregnancy rates. To date, a number of mathematical model systems have been tested to classify different parameters in infertile patients to develop a model that can predict the chances of becoming pregnant by identifying the behavioral design. In this chapter, several mathematical models are reviewed that corroborate the data obtained from infertile patients and predict the outcome depending on different parameters, including female age, follicle size, and hormonal levels.

Keywords: Assisted Reproductive Technologies (ART), Fuzzy Logic, Hormonal Levels, Infertility, Mathematical Modeling, Prediction in Pregnancy Rate, Pregnancy Calculation, Reproduction.

INTRODUCTION

Reproduction is the biological process that is important for the survival of any organism. Thus, any kind of abnormality that may lead to the inability to reproduce can have severe effects on survival [1]. In addition to the general understanding of reproduction, it is crucial to investigate the underlying molecular and chemical mechanisms [2]. Therefore, studies to apprehend the function of reproductive organs, gametogenesis, the male gametes (sperm) and female game-

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tes (oocytes), implantation, and the survival of the fetus are essential [3]. Many abnormalities in the process of gametogenesis, fertilization, embryo development, and implantation can lead to the incapability of a couple to reproduce or better-called infertility in males or females [4].

Infertility can be explained as not being able to conceive a child for over a year following unprotected intercourse. World Health Organization (WHO) proposes that more than 80 million people are suffering from infertility. It is not only a medical issue but also a social and psychological problem. Studies have shown that in addition to not reproducing, diagnosis with infertility can have severe effects on the couples and cause anxiety, depression, and psychological problems [5]. To date, extensive research studies had been investigated in the field of reproduction and infertility to overcome this issue. There are multiple causes of infertility which can be due to male or female anomalies. Both males and females can carry an abnormality that causes infertility. Approximately in 25% of the cases, the origin of the problem remains unknown. Some of the most common female infertility causes genetic anomalies, malfunction in the formation of the oocytes, which can be a problem in the process of releasing the egg, diseases such as polycystic ovary and hormonal problems, as well as a premature ovarian failure that ovaries stop functioning before the normal age of menopause around 40 years old. Other less common causes are problems during previous surgeries, mucosal problems, and endometriosis [6]. Male infertility can be due to a variety of abnormalities as well, such as genetic anomalies, hormonal abnormalities, undescended testis, semen anomalies, azoospermia, oligospermia, teratozoospermia, infections, and use of drugs [6].

Depending on the cause of infertility, different medical approaches can be offered to the couple to overcome this problem, such as undergoing Assisted Reproductive Technology (ART) procedures. *In vitro* fertilization (IVF), intrauterine insemination (IUI), and intracytoplasmic sperm injection (ICSI) are the most common ART treatments [7]. In all ART treatments, personalized assessment of both partners is crucial. The male partner is evaluated for the semen parameters. The female partner is evaluated for ovarian reserve. The IVF and ICSI cycles involve ovarian stimulation, oocyte pick-up, *in vitro* fertilization, or intracytoplasmic sperm injection that ensures fertilization, culturing of the embryos in the laboratory, and either embryo transfer or vitrification of embryos for future transfers. In every stage of the process, multiple factors affect the outcome of pregnancy. The collection of these data is a great source to evaluate infertility's causes and assess the improvement strategies for pregnancy rates. Data mining has a great potential to evaluate all different kinds of parameters affecting reproduction, infertility, and pregnancy rates. This information is a great supply to predict the patterns and future trends that can be comprehended for patients with similar parameters. Thus, mathematical modeling systems have a great potential to guide both fertility specialists and embryologists to make a better understanding and make better decisions in ART treatments.

INTRODUCTION TO MATHEMATICAL MODELING

Scientists have always been looking towards finding approaches to simplify complex systems and mechanisms in biology; therefore, researchers use different kinds of modeling to understand the study better. However, this approach is not as easy as it sounds due to the vast number of data available and the complexity of reactions and processes going on in a biological system. For example, in a genetic study, researchers must investigate the underlying mechanisms at DNA, RNA, and protein levels solely and the connections available between these different steps of the process. Therefore, providing a model to explain and, more importantly, simplify these steps need experience professional work. These models can be used to illustrate different aspects of a biological system, including structural and functional properties [8]. Apart from the problem with the complexity of these systems, environmental factors such as changes in light, weather, and nutrition must be considered. Mentioned obstacles in modeling a biological system can lead to biological errors that can alter the outcome or lead to misleading results.

Data mining is an important step in modeling systems. This step is critical to extract the predictable information from a large dataset. Thus, one of the crucial steps in these models is the availability of the previous data. Data mining provides the possibility to predict future trends, and thus, it enables modification of the progression of the biological processes. Thus limiting any errors that can lead to misinterpretation must be maintained as much as possible to get a more accurate result [9]. Depending on the types and aims of the investigation, computational or mathematical modeling can be applied.

Our main focus in this chapter is on mathematical modeling and the advantages and disadvantages of using these models in the aspects of evaluating infertility. These can be simply divided into two different frameworks; deterministic mathematical models and stochastic mathematical models. Deterministic models consist of different variables, and the known parameters of the system uniquely describe each. So as far as the set conditions for the system do not change, a model must continue its normal function. However, in real-life systems keeping all variables and conditions constant at all times is impossible. In this kind of modeling, a mathematical equation is constructed [10]. In order to solve the mentioned problem about deterministic modeling, another method known as stochastic modeling is used. This model has a broader look at the process, and it is

CHAPTER 13

Analysis of Retinoblastoma Treatment Techniques with Fuzzy PROMETHEE

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Abstract: Retinoblastoma is the most common primary intraocular malignancy in children (1 in 15.000-20.000 live birth). It involves an uncontrollable growth and division of cells in the retina (neurosensory layer of nerve cells lining the back of the eye). The most common first sign of retinoblastoma is a visible whiteness in the pupil called "cat's eye reflex" or leukocoria. Another sign is strabismus; eyes do not point in the same direction. Children with retinoblastoma may have inherited a gene from their parents that causes this disease. Retinoblastoma is a curable disease with a very low mortality rate; early diagnosis can result in a 95% chance of treatment success and survival of the patient, with a likelihood of saving 70 to 80% of the vision in the affected eye(s). This study aims to shed more light on the parameters that affect the different treatment alternatives of retinoblastoma and how these parameters affect the preference ranking of each technique. In this study, we analyzed and ranked the most common treatment techniques of retinoblastoma using fuzzy PROMETHEE (Preference ranking organization method for enrichment evaluations), a multi-criteria decision-making tool using some parameters. The analysis results based on the parameters, criteria, and weights used suggest that cryotherapy is the most favorable treatment technique for treating retinoblastoma, followed by thermotherapy, chemotherapy, photocoagulation, enucleation, and, finally, radiation therapy. Using fuzzy PROMETHEE allows the decision-maker to change the parameters, criteria, and weights according to the situation and the desired outcome. However, fuzzy PROMETHEE for this application is to aid the decision-maker in arriving at a decision and not be followed blindly without an expert opinion.

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Keywords: Cancer Treatment, Chemotherapy, Children, Cryotherapy, Decision-making, Diagnosis, Enucleation, Eye cancer, Fuzzy logic, Fuzzy PROMETHEE, Multi-criteria, Photocoagulation, Preference ranking, Radiation therapy, Retina, Retinoblastoma, Therapeutic techniques, Thermotherapy.

INTRODUCTION

Retinoblastoma is a cancer type that affects the retina, a neurosensory layer in the inner part of the eye. It occurs when a mutation in both alleles of the Rb1 suppressor gene of the retinoblastoma [1]. Retinoblastoma is one of the most common eye cancer types affecting children, even though it is rarely diagnosed at birth. Children between the ages of 5 and 15 years are the most affected by this cancer type. The growth of these cancerous cells may only affect one eye (unilateral retinoblastoma), both eyes (bilateral retinoblastoma), or, in very rare cases, may spread to other parts of the body like the lymph nodes or bones (trilateral retinoblastoma).

Early diagnosis and treatment of retinoblastoma, like all cancers, greatly increases the chances of survival. Overall, patients diagnosed with retinoblastoma have a 95.5% chance of survival [2]. Patients diagnosed between birth and five years of age generally have a survival chance of 92.3%.

Retinoblastoma is considered one of the potentially curable cancer types, with several therapeutic techniques are applicable based on the stage of cancer and effectiveness of the treatment. The treatment options that are frequently explored as regards retinoblastoma include chemotherapy (systematic, periocular, or intraarterial), enucleation (surgery), radiation therapy (laser therapy), thermotherapy, and cryotherapy. In order to determine the best treatment option to obtain maximum benefits to the patients, a number of factors have to be considered. These factors are likely to affect the outcome of the selected treatment option.

With the millions of children affected yearly by retinoblastoma, it has become necessary to clearly outline the available treatment techniques with their advantages and disadvantages in order to provide the physician and the patient with the information needed to make an informed decision on the treatment technique to embark on that will yield the best results based on the stage of the tumor and health condition of the patient among other factors.

The best-case scenario and most desired outcome in the treatment of retinoblastoma is to retain vision in the affected eye(s) of the patient. This study aims to analyze some important factors of the available treatment techniques to aid in the decision-making that will be suitable for the patient's general health, considering the retainment of vision as the most important factor.

In this chapter, different therapeutic techniques for the treatment of retinoblastoma were presented and analyzed using the fuzzy PROMETHEE method based on certain factors that affect the outcome of the treatment method embarked on, such as chances of blindness, radiation dose (if any), cost of treatment, side effects and treatment period.

MATERIALS AND METHODS

Obtaining crisp data that can be used to make analyses that accurately capture a problem and arrive at an optimum solution has always proved to be a daunting task. Fuzzy PROMETHEE (preference ranking organization method for enrichment evaluations) is a technique that combines the concept of fuzzy logic and that of the PROMETHEE method. Fuzzy logic affords the decision-maker to define the problem using vague but realistic criteria accurately and transform the linguistic variables into mathematical variables. Using PROMETHEE, the decision-maker can compare different fuzzy values. Many studies have been made using fuzzy PROMETHEE in various fields with exceptional and promising results. In a study conducted by Ozsahin *et al*. [3], an analysis and ranking of different nuclear medicine imaging devices were done using fuzzy PROMETHEE and a detailed explanation of the fuzzy PROMETHEE technique was discussed. Ozsahin *et al*. [4] used the fuzzy PROMETHEE method and ranked hadron therapy as the most favorable treatment technique for breast cancer due to its high survival rate, short treatment time, and non-invasive method. In a study, different cancer treatment techniques were analyzed using the fuzzy PROMETHEE method. In the study, hadron therapy emerged as the most favorable cancer treatment technique based on the factors and criteria used for the study. In another study with fuzzy PROMETHEE that evaluated x-ray based medical imaging devices, the x-ray and mammogram had relatively the same ranking due to their minimal dose of radiation when the 'machine's cost was not considered. However, with the cost of machine activated, the mammogram had a slightly higher ranking than the x-ray machine [6]. Results obtained using the fuzzy PROMETHEE method by [7] ranked filtered back-projection as the most favorable algorithm for image reconstruction in nuclear medicine. Preferential ranking for leukemia treatment techniques between radiation therapy, targeted drug therapy, immunotherapy, stem cell transplant, and chemotherapy was carried out by Maisaini *et al*. [8], with radiation therapy emerging as a preferred treatment method due to its relatively low cost of treatment, time per session, cost per session, survival rate and treatment period which were the criteria used for the analysis.

CHAPTER 14

Selection of Hemorrhoid Treatment Techniques using a Multi-Criteria Decision-Making Technique

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Abstract: Hemorrhoids (Piles) are widespread diseases, and they appear in the form of itching, bleeding, and discomfort in the anal area, which are swelling of the veins of the anus and lower part of the rectum. Hemorrhoids may be internal to the rectum or external as they occur under the skin around the anus. It occurs due to increased pressure inside the abdominal cavity and pelvis due to constipation or pressure on veins during pregnancy. Many effective treatment options are available, and most sufferers can relieve symptoms by using home remedies, lifestyle changes after excluding other causes of anal bleeding. Most people over 30 years old have suffered from piles or some symptoms. Many patients do not like to explain that they have an infection in the anus or rectum region. As a result, such patients do internet searches for medications and remedies for this type of condition, which produces a plethora of misleading and superfluous material, as well as wrong information. Also, doctors sometimes cannot decide how to operate when dealing with hemorrhoid removal. For these reasons, we conducted this study to give information about all of the available treatment techniques and compare them using the multi-criteria decision making (MCDM) or multi-criteria decision analysis method fuzzy TOPSIS analysis technique. The treatment techniques discussed in this study are seven nonsurgical techniques (Fiber-diet with water, the enema, ice usage, creams, IR coagulation, rubber band ligation, and sclerotherapy) and three surgical techniques namely stapled hemorrhoidectomy, laser hemorrhoid surgery, open or closed hemorrhoidectomy. Also, the parameters used are (total cost, efficiency, recovery period, survival rate, practicality, comfortability, hospitalization time, and

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procedure time, all gathered from previously recorded information of hospitals, doctors, or patients. This information for each technique is analyzed, ranked, and compared using the previously mentioned TOPSIS MCDM technique.

Keywords: Anal Canal, Fuzzy TOPSIS, Hemorrhoids, Hemorrhoidectomy, Multi-Criteria Decision-Making.

INTRODUCTION

Hemorrhoids are inflamed and swollen veins in the anal area and lower part of the rectum and are caused by a great pressure in this region, which leads to the expansion and bloating of the blood vessels. Although many believe that hot peppers and dazzling foods are responsible for hemorrhoids, there is no scientific evidence for this [1]. There are two types of internal hemorrhoids, and they are inside the lower area of the rectum. Usually, the person does not see or feel them. However, during the process of defecation, pressure and tension may scratch and injure the swollen veins, causing blood and haemorrhoids to exit and drop out of the anus, causing pain. External hemorrhoids are found under the skin surrounding the anus, and when scratched, they may get injured and bleed [2]. When the veins in the lower rectum and anus face pressure, they expand and may swell. Therefore, hemorrhoids occur when the pressure on the veins in the lower part of the rectum rises. Hemorrhoids can last for varying lengths of time; in some people, they resolve on their own after a few days, while in others, they worsen. Whether a person can cope with hemorrhoids depends on the patient, as mild hemorrhoids may go away without any treatment within a few days. On the other hand, large external hemorrhoids may take longer to heal and cause pain [3].

There are various distinct varieties of hemorrhoids, each with its own set of characteristics, and the following list highlights several of them:

Internal hemorrhoids: This type of hemorrhoid appears in the segment of the rectum, as it is often invisible and difficult to notice. It is also noted in most cases of internal hemorrhoids that the patient does not suffer from pain, and the possibility of hemorrhoids disappearing without the need for therapeutic intervention.

Prolapsed hemorrhoids: It is one of the types of hemorrhoids caused by swelling in the internal hemorrhoids, where hemorrhoid becomes prominent from the anus.

External hemorrhoids: It appears on the anus (on the external surface of the anus). Its symptoms are very similar to that of internal hemorrhoids. However, it may cause greater pain or discomfort when sitting due to its location outside the rectal area.

Coagulated hemorrhoid: This type of hemorrhoids contains blood clotting inside, and hemorrhoid appears swollen and inflated around the anal area, in addition to causing severe pain and itching. Hemorrhoids develop in four stages, according to the German “Net Doctor” website. The first stage of the disease means that the enlarged blood vessels have primarily occurred in one area within the anal canal. The second stage means that the enlarged blood vessels suddenly appear during defecation, and then they go back inside alone in the anal canal.

The third stage of the disease means that the enlarged blood vessels protrude outside the anus and do not return alone in the anal canal but can be returned inside by pressing on them.

In the fourth and final stage of hemorrhoids, the swollen blood vessels remain outside the anus indefinitely and are unable to be reintroduced [2, 4].

Dirk Wilhelm, head of general surgery and specific visceral surgery at the right-hand hospital of the Technical University of Munich, told Focus magazine that hemorrhoids and the four stages of the sickness could result in anal bleeding. He said that blood might leak out during the first and second rounds of feces. Locally, these two stages of the disease can be treated using ointments. The third and fourth phases of hemorrhoids will require surgery. According to Dr. Wilhelm, surgical intervention and enlarging the vascular resection prevent the patient from developing hemorrhoids in this region again. However, hemorrhoids can manifest themselves in various sites. According to Wilhelm, hemorrhoids typically manifest themselves in three locations of the anal region. If all of these regions are surgically treated, the patient is almost totally free of hemorrhoids infection [5].

In this study, we will discuss hemorrhoids treatment techniques in detail, as well as the anatomical structure of the pelvic area, including the pelvic bones, pelvic muscles, and pelvic blood vessels, in order to better understand the disease and its causes, which include food consumption, scratching, itching, or increased pressure applied to the anus canal and blood vessels. Then, based on several parameters that affect the disease's treatment techniques, both surgical and nonsurgical, we will compare these hemorrhoid treatment techniques after analyzing using fuzzy TOPSIS the techniques will be listed in order of preference; some require surgery, while others do not, depending on the stage and size of the hemorrhoids.

CHAPTER 15

Mutation Resistant Target Prediction Algorithm in PCR Based Diagnostic Applications

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Abstract: Highly mutable organisms often challenge primer design for diagnostic PCR kit manufacturers due to new mutations occurring in hybridization sites. Novel variants may require reconsideration of the existing PCR primers and even result in misdiagnosis. While conserved sequences are often the main target of primer design algorithms, they often do not consider possible new mutants. We represent a generalizable algorithm for filtration of the sequence to identify conserved sequences and the less likely regions to mutate. Primers selected from the filtered sequences are expected to target regions with lower mutation rates and consecutively act indifferent to more variants of a target pathogen, providing long-lasting primers and less frequent primer redesign.

Keywords: Molecular Evolution, Primer Picking Algorithms, Primer Selection, Sequence Conservation.

INTRODUCTION

In PCR-based diagnosis, sequence specificity is the key to avoid misdiagnosis. For this reason, the primers are designed in a way that they would hybridize only the target sequence at a specific position. Considering the vast number of different organisms and sequence variations, designing a target-specific primer is possible if we know or predict all possible sequences found in a given sample. Owing to scientific advancements of the last two decades, now we have access to sequences of the majority of reference genomes, thus picking primers with specificity for specific target species.

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However, reference genomes still do not represent all variants. The access to the variation information in the sequence is important since it affects the primer picking process, regardless of whether primers are being designed to distinguish between variants or not. To detect all variants of a species, often a conserved sequence is identified using all known variations. However, it could not be guaranteed that all possible variants are known or that no new variants occur. For that reason, a predictive approach is necessary to construct conserved regions including putative variants, or we refer to as "less mutable" sequences. Here we discuss an algorithmic approach to construct such "less mutable" sequences, using evolutionary parameters obtained from a small number of existing variants. The "less mutable" sequences may then be used as input for traditional primer picking tools. We hope this will provide a new perspective in primer design and may be integrated into the primer design process of the diagnostic kit manufacturers Fig. **1**).

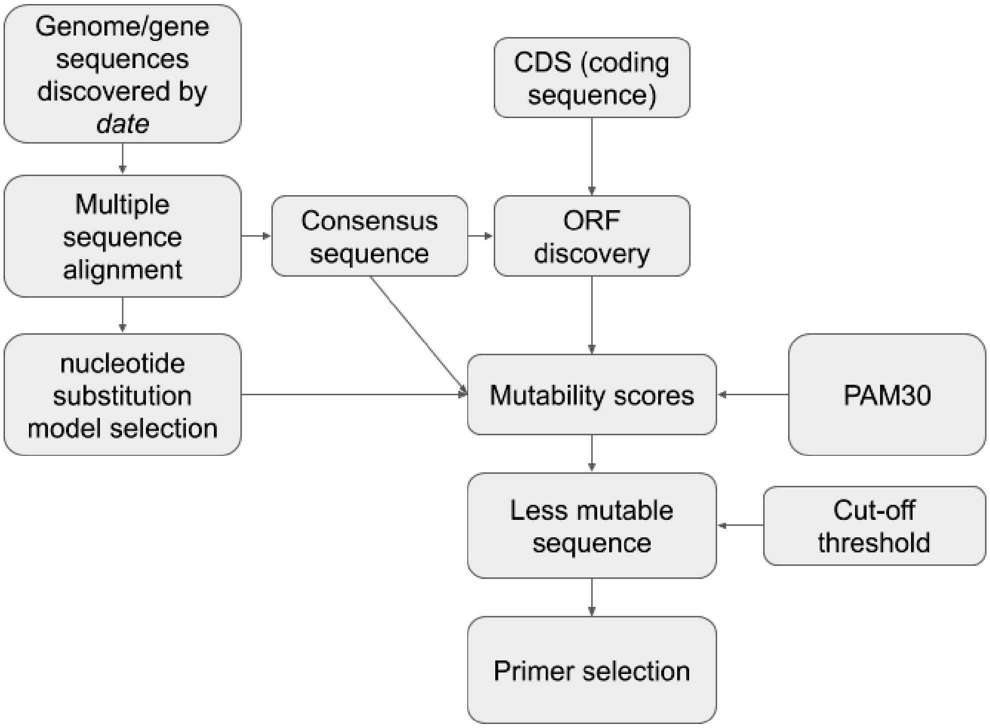

Fig. (1). The process flow chart of the algorithm.

Consensus Extraction

The idea behind the extraction of a consensus is that a sequence with common features may be identified that do not vary from sample to sample. However, there are several obstacles when defining a consensus sequence.

The Error in Sequence Reads

The sequence reads are obtained through next-generation sequencing or Sanger sequencing and are prone to error. While the errors at the ends of the sequence trimming eliminate reads, these errors may also occur at the nucleotide level. Their prevalence in all knowns sequences often filters these errors [1].

Nevertheless, the existence of an error is unavoidable. The best way to eliminate error is often using a higher coverage when it comes to NGS. These errors are often filtered by their prevalence in all known sequences. While the chance of error may be calculated using statistical methods, or a percent of identity at a specific position can be evaluated to decide whether there is an error, no method is definitive enough to reliably regard a nucleotide variation due to error [2].

The Frequency of a Variation

Another issue for extraction of a variation, we are only limited by the samples we have. Considering, in the case of an emergent pandemic, most of the sequencing reads would be coming from high-income countries due to the availability of the sequencing facilities, which in return would have common genetic characteristics. However, without the rest of the sequences of the global gene pool, we would not know for sure whether these genetic characteristics are unique to certain regions or global. Assuming the sequences available on the databases are a complete representation of the whole picture often causes problems. This is one of the main issues when designing PCR primers, especially for genotyping purposes, where PCR primers designed using the sequences obtained from a different region would not work as intended in another due to the prevalence of undiscovered variants target region. The use of ambiguity codes may include variations; however, ambiguity codes alone do not represent prevalence.

Eliminating all variations or putative errors is often the easiest choice with vast genomes. However, that is not the most suitable route for viruses due to the high mutation rate and relatively smaller genomes than bacteria [3].

Problems with Using Consensus Sequence for Primer Selection

While a consensus sequence will represent the genome sections that have not undergone significant change, it does not consider that it is still at the risk of mutation.

CHAPTER 16

Intelligent Learning Systems for the Environmental Factors that Affect the Distribution of Some Leishmaniasis Vectors

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Abstract: Leishmaniasis is a disease that affects humans, canids, rodents, and vertebrates. It is caused by different species of Leishmania protozoa, with tiny sand-fly insects as the incriminated vectors of the disease. Some cases of the diseases require treatment, while in other cases if left untreated, it can lead to the death of the affected victim. The factors that affect the distribution and abundance of these vectors are still not completely known. Therefore, it is of utmost importance to fill in the gaps necessary to fully understand the contributing factors to the abundance and distribution of the vectors and how these factors affect their behavior. Artificial Neural Networks is quite an accomplished problem-solving approach in computing and information technology-oriented devices. In this paper, backpropagation neural networks are applied in recognizing some vectors of leishmaniasis using some environmental factors and how these environmental factors contribute to the distribution and abundance of the vectors analyzed in this study.

Keywords: Artificial Neural Networks, Intelligent System, Leishmaniasis, Sandflies.

INTRODUCTION

Leishmaniasis is a parasitic disease caused by different species of the protozoan

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Leishmania. With about 53 known sand-fly species suspected of spreading the disease, infected female sandflies are the major vectors of the disease. Leishmaniasis does affect not only humans but also canids, rodents, hyraxes, and vertebrates in general. It is known as one of the most common and most severe diseases known to be transmitted by sandflies [1], affecting over 350 million people in 90 countries [2], about 20 different Leishmaniasis species are responsible for causing this disease, and 30 different Phlebotomine sandflies are responsible for its transmission to humans. According to the WHO health report, most people who are infected by leishmaniasis do not show any symptoms in their lifetime; however, in some infected Leishmaniasis cases, people become sick due to their immune systems [3]. This means that the immune response of the host determines the degree of manifestation of the disease. Leishmaniasis is considered a neglected disease and is more common in rural areas. Usually, it has been referred to as a "disease of the poor" due to its dominance in poverty-stricken areas of Asia, East Africa, Southern America, and part of the Mediterranean region. Published health reports show that only malaria has a higher mortality rate than leishmaniasis, especially considering children under 15 years of age [4].

Types of Leishmaniasis

There are three forms of the disease: Cutaneous, Visceral, and Mucocutaneous Leishmaniasis.

Cutaneous Leishmaniasis (CL)

It is also referred to in medical journals as the "Alleppo boil" [5]. It is the most common form of Leishmaniasis, with an estimated 1 million new cases occurring annually worldwide. The symptoms accompanying CL begin with visible areas of abnormal skin tissue with odd discoloration, especially around the face, hands, and feet. When the lesions are removed, a dead skin layer is revealed projecting from beneath a crust [6]. Depending on the immune level of the patient, these lesions and sores can heal over time or may need medication but leave a visible scar afterward. Treatment of CL is species-specific. Though it is widely understood that CL is self-healing, there is a high risk of it escalating into Mucocutaneous leishmaniasis, which is more severe and life-threatening. Several treatments, however, are still under investigation, with some having very undesirable side effects like raised liver enzymes, motion sickness, and headaches, as in the case of "miltefosine". The development and use of antibacterial drugs are also under investigation [7]. Even after successful treatment of CL, there is a high risk of relapse for the patient, and there is usually a permanent scar left on the skin's surface after the ulcers heal.

Mucocutaneous Leishmaniasis (ML)

This is a unique form of leishmaniasis. It is very similar to CL but affects the nasal cavities and pharynx, leading to the destruction of skin tissues of the nose and mouth. This extensive destruction of skin tissue and mucus membrane usually leads to extensive disfiguration and may lead the patient to require reconstructive surgery [8]. It can be an extension of a chronic case of cutaneous leishmaniasis or relapse from CL. ML may occur several years after successful treatment and healing of ulcers from CL and has an incubation period of 1-3months before visible symptoms could present themselves [9]. However, ML can also be caused by improper treatment of cutaneous leishmaniasis, neglected treatment, or failure to treat CL. Unlike CL, ML is not self-healing and would only get severe and subsequently lead to death if left untreated.

The manifestation of symptoms of ML is similar to that of CL. However, the lesions spread to the mucus membrane, causing prolonged nasal congestion, mouth ulcers, bleeding from the ulcers in the nose and mouth usually occurs. It is also worthy of note that ML is not involved with the bone, and all the bleeding and ulcers are strictly restricted to the skin and tissue.

ML that progresses without effective treatment usually ends up being difficult to treat, leading to malnutrition and, in some cases, death. Death due to ML can be caused by suffocation due to blocked airways.

Visceral Leishmaniasis (VL)

It is also referred to as “kala-azar”, Hindu for “black fever” from India, where the disease is very prevalent, with WHO reporting that 90% of cases occur in South Asian Countries.

It is the most severe form of leishmaniasis, with a mortality rate of almost 100% and death occurring within months in untreated cases.

The symptoms of VL are similar to a wide range of common diseases, which makes the diagnosis very difficult. The most common symptoms reported are darkening of the skin, unexplainable weight loss, nausea, and bouts of fever, accompanied by enlargement of the spleen and or liver [10]. As reported by the CDC, a common manifestation of VL is Post kala-azar dermal Leishmaniasis (PKDL), which is characterized by skin lesions during the treatment of VL. In some cases, PKDL heals spontaneously, without the need for treatment [11].

SUBJECT INDEX

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Ilker Ozsahin

I have extensive experience in medical imaging devices such as PET and SPECT. I have been to University of Illinois at Urbana-Champaign, Illinois, the USA, to work on the growth of carbon nanotubes. I worked at Universidad Autonoma de Barcelona in Spain as a Ph.D. student for developing a PET scanner. I worked as a research assistant for six years in the Physics Department at Cukurova University in Adana, Turkey. Then, I worked at Harvard Medical School and Massachusetts General Hospital as a postdoctoral fellow. Also, I worked at the University of Macau as a visiting fellow for multi-pinhole brain and cardiac SPECT collimator design and implementation. Currently, as an Associate Professor in the Department of Biomedical Engineering at Near East University, I am working on the simulation of novel high-sensitivity and high-resolution PET and SPECT scanners, multi-criteria decision-making application on healthcare, as well as deep learning in medical imaging such as Alzheimer’s for high-accuracy classification and early detection.

Dilber Uzun Ozsahin

I graduated from the Department of Physics at Cukurova University in 2006. I have worked at CERN, Geneva, during 2008-2010 for my Master's thesis. I completed my Ph.D. studies in 2014 at Universitat Autonoma de Barcelona, Spain. In 2015, I worked at Gordon Center for Medical Imaging, NMMI Radiology Department, Massachusetts General Hospital & Harvard Medical School as a post-doc. I worked on a new technique called laser-induced optical barriers (LIOB) technique to improve nuclear medicine imaging devices' cost and performance. I have designed a high-performance cardiac SPECT system in a cost-effective manner using the LIOB technique. Recently, I have been working on the application of biomedical instrumentation using artificial intelligence, multi-criteria decision analysis in engineering and healthcare, and artificial intelligence in healthcare. Currently, I am working at the University of Sharjah as an Associate Professor.