Current Research in Translational Medicine 68 (2020) 245–251

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State of the art

Machine learning and artificial intelligence in the service of medicine: Necessity or potentiality?

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ARTICLE INFO

Article history:
Received 25 October 2019
Accepted 18 January 2020
Available online 3 February 2020

Keywords:
Artificial intelligence
Machine learning
Medical applications

ABSTRACT

Motivation: As a result of the worldwide health care system digitalization trend, the produced healthcare data is estimated to reach as much as 2314 Exabytes of new data generated in 2020.
The ongoing development of intelligent systems aims to provide better reasoning and to more efficiently use the data collected. This use is not restricted retrospective interpretation, that is, to provide diagnostic conclusions. It can also be extended to prospective interpretation providing early prognosis. That said, physicians who could be assisted by these systems find themselves standing in the gap between clinical case and deep technical reviews. What they lack is a clear starting point from which to approach the world of machine learning in medicine.
Methodology and Main Structure: This article aims at providing interested physicians with an easy-to-follow insight of Artificial Intelligence (AI) and Machine Learning (ML) use in the medical field, primarily over the last few years.
To this end, we first discuss the general developmental paths concerning AI and ML concept usage in healthcare systems. We then list fields where these technologies are already being put to the test or even applied such as in Hematology, Neurology, Cardiology, Oncology, Radiology, Ophthalmology, Cell Biology and Cell Therapy.

Introduction

The introduction of information technology in the field of healthcare has provided improvements on numerous aspects [1], starting from digitization of patient data in electronic health records (EHR) [2] to providing clinical decision making [3]

As a result of the worldwide health care system digitalization trend, the produced healthcare data in 2011 have been estimated to be 150 Exabytes 150 * 10^18, and it is estimated to have 2314 Exabytes of newly produced data in 2020 [4,5]. However, processing these data efficiently so that useful information and new knowledge can be extracted remains a real challenge. In fact, the ever-increasing amount of collected data withstands the ability of current data analysis systems. As a result, healthcare systems are increasingly burdened. This is called the “Data Rich/Information Poor (DRIP)” syndrome [6]. DRIP means that we are collecting more data than we can analyze. Fortunately, with the latest advancements in data analysis and decision-making systems, overcoming this challenge seems to finally be feasible.

Collected medical data can be analyzed by different means and at different levels. The first level is acquiring individual patient data where conventional alerting systems can help in raising attention when values are out of the normal range, as in heart electrocardiography (ECG) monitors.

At the second level, the different data sources are gathered, fused and processed in such a way that the result can be used as an input to another sort of system that provides suggested differential diagnosis and conclusions based on a set of rules. By moving into a tree-like hierarchy using the provided data, these systems can help in reaching a plausible explanation of the entered symptoms. These rule-based systems are called “Expert Systems”. Expert Systems learn from experience to emulate the decision-making abilities of human experts. These systems are often capable of responding to questions beginning with "What" rather than "How" and, simultaneously, explaining the reasoning behind their

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http://dx.doi.org/10.1016/j.retram.2020.01.002
2452-3186/

decisions. Another essential feature of these systems is that they integrate new experiences, hence enriching and enhancing their knowledge base. This, in turn, improves their decision-making abilities. An early example of such systems is the "MYCIN" system [7].

These systems are based on a data transformation process that helps in providing diagnosis and conclusions which rely on the well-established "data-information-knowledge-wisdom" model [8] (see Fig. 1).

The current ongoing enhancement of intelligent systems aims to provide better reasoning and efficient use of collected data. The objective is to enable decision systems to run prospectively and provide early prognosis (as opposed to the retrospective approach where systems only provide diagnosis and conclusions).

These technical achievements have been well documented [9]; however, a simplified tutorial for physicians seeking to understand the actual state of this technology and potential further uses proves essential. To this end, in this state-of-the-art review, we offer physicians an insight into Artificial Intelligence (AI) use in the medical field. While not seeking to achieve an exhaustive review of all medical applications for AI, this paper offers easy-to-understand insights that can make AI-Medicine exchanges more meaningful, which could lead to a constructive debate about how to reduce the gap between the two disciplines.

Thus, we will try to clarify some basic definitions and to elaborate a brief discussion about the general lines of development in the use of machine learning and artificial intelligence concepts in healthcare systems. Then we will list some fields and examples where these technologies are already put to the test or even applied, as summarized in Table 1.

Basic definitions

Intelligence is among the terms that withstand any definition attempt. Simple navigation on the web can lead us to hundreds of definitions that vary according to individual perspectives (philosophy, biology, psychology, mathematics, computer science). However, for the sake of this state-of-the-art, we will try to compile many definitions found in the literature.

Intelligence is the ability to make consistent designs, solve problems or create products that are valued in a particular culture or a business field. It uses association, memorization, reasoning, understanding, abstraction, conceptualization, approximation, systemization and logical inference. These elements are used to derive new knowledge from known facts [10–12]

Artificial Intelligence, on the other hand, refers to the system's ability to interpret external data correctly, to learn from such data, and to use those learnings to achieve specific goals and tasks using flexible adaptation [13].

The main component of AI is **Machine Learning** (ML), as shown in Fig. 2. Machine learning is when computers are used to apply statistical models to data. It is a sub-discipline of AI, where computer programs (algorithms) learn the relationships between input and output data. We can distinguish between three categories of ML algorithms: Supervised Learning, Unsupervised Learning and Reinforcement Learning.

In **Supervised Learning**, computer programs learn associations through analyzing data samples defined by a supervisor (typically a human expert) in a process called Training. Once associations have been learnt, they can be used to predict future examples in a process called Testing [14].

In **Unsupervised Learning**, computer programs learn associations in the data without an external definition of associations. It is often used for clustering i.e. extracting undiscovered correlations in the input data in such a way to form data subsets which share common features.

In **Reinforcement Learning**, the system learns how to behave based on a scalar reward/punishment signal. Punishment can be considered as a negative reward signal that reinforces an action that avoids its delivery [15].

It is worth mentioning that there is a particular field of ML that is often used for large data processing sets called **Deep Learning** (DL). DL is a neural based computational system that determines correlations between the data by evolutionary tests to reduce a cost function. Deep learning starts with random values (initial states) until reaching the correct weights that best minimize a predefined cost function. It means that the system is continually dashing through predictions and adjusting the way it predicts according to the input data [16].

Deep learning is a powerful tool for learning complex cognitive problems [17,18]. However, data issues such as low data volume, high sparsity and poor data quality can limit the efficacy of deep learning methods [19–24].

Finally, it should be emphasized that ML use goes beyond decision-making systems and can be used in many medical applications such as Nanobots (miniscule robots used to perform specific tasks such as drug delivery [25] and in the assistance of impaired patients. These applications, while interesting, lie outside the scope of this work.

In the next section, after a small introduction about the patient data acquiring process, we will explore the following medical fields where AI technologies are already applied: Patient Intake; Radiology, Hematology, Neurology, Oncology, Cell Biology and Cell Therapy, Cardiology, Ophthalmology.

Patient Intake: obtaining initial patient data

The Clinical Process, actions carried out by health-care professionals in order to assess and improve the health of a patient, has a starting point (an appointment, emergency visit, etc.), procedures, and an expected clinical outcome. In ordinary cases, the process starts with retrieving and acquiring the anamneses, AKA, the case history. This involves a predefined set of questions that the health-care professional should ask during the patient appointment. Since the 1960s, this step has been partially digitized [26] The digitization especially included data storage and retrieval. That said, data collection is still done by residents or nurses, as it is difficult to rely on an automated system to collect this information. The point is that a human being can determine how to convert the informal story told by the patient into a more formal list of separated potential causes, symptoms (and their temporal evolution), patient medical history, and other useful notes. For instance, if a patient says, "I think I have diabetes," a human physician would realize this is purely the patient's perception which would not be medically considered as "diabetes mellitus" until there was a whole story with symptoms and tests to confirm it. Imagine, however, if the patient was entering these

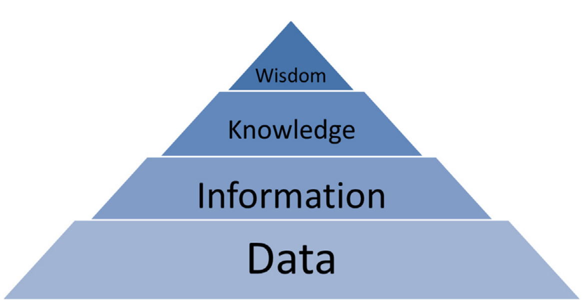

Fig. 1. Representing the classical pyramid of (date-information-knowledge-wisdom).

Table 1
Summary of some important examples of the artificial intelligence techniques applications in precise medicine.

Author	Journal, Year	Domain	Technique	Technology	Topic
Wu et al.	Breast Cancer Res Treat, 2019	Radiology	Ultrasound	Logistic regression	Breast cancer
Moradi et al.	Medical Imaging, Computer-Aided Diagnosis SPIE 2019	Radiology	X ray	ML	Chest
Uthoff et al	Med Phys. 2019	Radiology	CT	ML	Lungs
Yang et al.	Medical imaging, Computer-Aided Diagnosis SPIE 2019	Radiology	MRI	ML	Brain
Diamond et al.	Int J Biomed Comput 94	hematology	Flow cytometry	AI	Leukemia
Diamond et al.	Cytometry 94	hematology	Flow cytometry	AI	Leukemia
Nguyen et al.	J Clin Pathol 97	hematology	Flow cytometry	AI	Leukemia
Gunčar et al.	Sci Rep 2018	Hematology	Laboratory	ML	Biological hematology
Arai et al.	Blood Adv 2019	Hematology	HSCT	ML	aGVHD
d'Onofrio et al.	Oxford: Butterworth Heinemann; 1998	Hematology	Hemoglobin disorder	NN	Laser cytometry and integrated isovolumetric
Zini et al.	Hematology 2005	Hematology	Hemoglobin disorder	NN	Laser cytometry and integrated isovolumetric
d'Onofrio et al.	Hematologica 1998	Hematology	AML	AI	cytometry
Kantardzic et al.	Comput Ind Eng 2002	Hematology	PV	DM	Laboratory findings
Shouval et al.	J Clin Oncol 2015	Hematology	HSCT	ML	ALL post-HSCT
Shouval et al.	Plos One 2016	Hematology	HSCT	ML	ALL post-HSCT
Subasi et al.	Neural Comput Appl. 2019	Neurology	Epilepsy	ML	Seizure detection
Avcu et al.	IEEE, ICASSP 2019	Neurology	Epilepsy	NN	Seizure detection
Ahmadi Rastegar	Npj Park Dis. 2019	Neurology	Parkinson's disease	ML	Progression prediction
Thompson et al.	Radiother Oncol. 2018	Oncology	radiotherapy	AI	Radiotherapy
Londhe et al.	Drug Discov Today 2019	Oncology	radiotherapy	AI	Radiotherapy
Araújo et al	PLOS ONE. 2017	Oncology	Histology	NN	Classification
de Ridder et al.	Brief Bioinform. 2013	Cell biology	Laboratory	ML	Detection by fluorescence
Oei et al.	PLOS ONE. 2019	Cell biology	Laboratory	NN	Microscope images
Sugimoto et al.	Cytotherapy. 2019	Cell therapy	Laboratory	ML	CAR-T
Lee et al.	Immunology, 2019	Cell biology	Immunology	DL	Tracking of immunological synapses
Yaseen et al.	Appl Sci. 2018	Cardiology	Heart Sound Signal	AI	Classification
Alfaras et al.	Front Phys 2019	Cardiology	ECG	ML	Arrhythmia
Sayres et al.	Ophthalmology. 2019	Ophthalmology	Diabetic Retinopathy	DL	Grading
Li et al.	IEEE Trans Med Imaging	Ophthalmology	Glaucoma	NN	Detection

Abbreviations: AI: artificial intelligence; ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; CAR-T: chimeric antigen receptor T- cells; DL: deep learning; DM: Data mining; ECG: electrocardiogram; HSCT: hematopoietic stem cell transplant; ML: machine learning; NN: neural networks; PV: polycythemia Vera.

details into a computer system. How would the system interpret this input?

Although we have had tremendous advancements in natural language processing, no system can so far derive medical terms directly from the patient's input. After data has been collected, the clinical Text Analysis and Knowledge Extraction System [27] can be used to extract useful information from unstructured electronic health records. This structured information can then be used in various ways to elaborate on the case or even provide predictive modeling on the patient's future based on current medical health records [24,28].

Once the patient's information is entered, health care professionals can proceed to the medical examination. Medical examination results may lead to a decision that lab tests or medical imaging are needed, two fields where ML tools can assist the physician. In the following paragraphs, we elaborate on AI and ML applications in specific medical fields.

Radiology

Whether the performed medical imaging was Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI), AI techniques can provide guidance and assistance to the physician in extracting useful insights from the image.

In general, a physician will enter the medical image as an input to the system, then the system will extract the characteristics of the

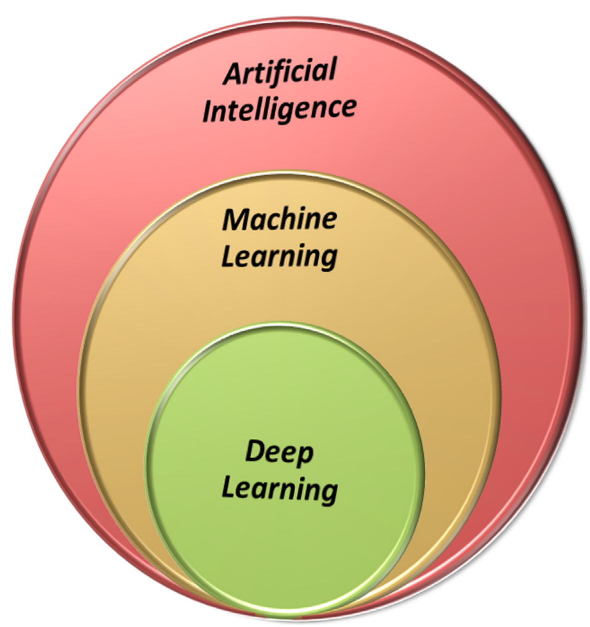

Fig. 2. Representing the inclusive relations between artificial intelligence, machine learning and deep learning.

image. Based on the values of these characteristics (aka Features), a prediction can be made about the image. These predictions can take the following forms [29]:

- Segmentation: drawing borders around the elements in the image.
- Labeling: identifying the elements in the image.
- Detection and diagnosis: detecting a specific disease and predicting its stage.
- Help dictating the final radiology report.

Starting with the simplest and commonly used medical imaging technique, ultrasound, a system was recently presented by Wu and colleagues [30] that uses logistic regression to classify triple-negative (TN) breast cancer on ultrasound images with a sensitivity of 86.96 % and a specificity of 82.91 %.

Another example is a recent work that used DL to identify which x-ray images indicate a healthy chest [31]. In this example, though health specialist expertise is still required, using this system would identify 50 % of the healthy chest cases, thus reducing the number of cases that need to be classified by the specialist.

Computerized Tomography (CT) images could also be classified using deep learning techniques. In their work on distinguishing malignant and benign lung nodules, Uthoff et al. [32] used a ML-based system that uses the features in CT images taken from the parenchyma around lung nodules to classify the nodules. They reported a sensitivity of 100 % and a specificity of 96 %.

As for MRI, Yang et al. [19] presented a system based on machine learning to predict the grade of Glioblastoma using MRI images. They achieved an accuracy of 92 %.

Hematology

The serious application of AI in hematology can be considered as relatively recent.

Cell diagnostic identification is one of the most seriously expedited areas. In this field, three major works have yielded three remarkable put-to-use systems for the following: flow cytometry immunophenotyping, bone marrow analysis, and peripheral blood analysis.

The three systems interact with each other and relate medical history with lab results contained in databases. When evaluating 100 leukemia patients, these three systems came to an agreement in 94 cases on the final diagnosis and, with the physician's interpretation, in 99 cases [33–35].

Machine learning methods were tested more recently for the diagnosis of sole hematological disorders depending only on laboratory findings. Two approaches were applied, one used all the available blood tests and the other used only a limited set more habitually measured during patient intake, obtaining respective prediction accuracies of 88 % and 86 % when considering the list of the five most likely diseases and 59 % and 57 % when considering only the most likely disease [36].

Using ML, Arai et al. analyzed a Japanese cohort of 26,695 patients to predict the risk of acute graft versus host disease (aGVHD), the alternating decision tree (ADTree) ML algorithm was applied to develop models using the training cohort, and 15 factors were chosen to comprise the final model. The article shows that aGVHD predication scores also demonstrated the link between the risk of GVHD and overall survival after HSCT. In short, the algorithms produced clinically reasonable and robust risk stratification scores [37].

Another area was the use of neural networks in the service of peripheral blood analysis, where two remarkable approaches are to be noted. The first one concerns hemoglobin disorder diagnosis through laser cytometry with an integrated isovolumetric sphering system, which proved itself accurate in almost all cases of HbE, HbE associated with b-thalassemia trait, IDA associated to b-thalassemia trait, and IDA associated to a-thalassemia [38,39].

The second is an AI model based on cytometry depending on the light assessment of white blood cell volume and peroxidase activity in the perox channel and nuclear density in the baso channel to differentiate, according to FAB classification, between acute myeloblastic leukemia samples. When tested on pathological samples, this system reached a 91 % diagnostic efficiency [40].

Another worthy application is a data-mining model that enhances Polycythemia Vera (PV) diagnosis based on eight parameters from the PV Study Group (PVSG) criteria, plus gender and hematocrit value (Hct). This system has been put to the test and no significant differences were observed in this model diagnostic classification results versus PVSG diagnostic criteria (98.1 %). Furthermore, the system demonstrated the same accuracy rate using only 4 parameters (Hematocrit, Platelet count, Spleen, and WBC) [41].

In the same field, the European Group Blood and Marrow Transplant (EBMT) conducted a data-mining study on a cohort of 28,236 patients. In this work, a model based on ten selected variables was used in order to evaluate and predict overall mortality at 100 days after the allo-HSCT. This model proved to be more efficient for this purpose than the EBMT score (area under the receiver operating characteristics curve of 0.701 vs. 0.646; $P < .001$) [42].

Another study done by the EBMT with a cohort of acute leukemia patients has shown that only a few variables, such as conditioning regimen, donor type, and disease stage, carry the weight of treatment-related mortality and that being on the cutting edge in this field will likely require additional types of input [43].

Finally, gene profiling seems to be an useful field for classifying certain pathologies. Coupling AI models with the DNA microarray approach has helped create new pathological classes and even analyze stem cells using unsupervised and supervised learning. Unsupervised learning has been used in class discovery such as classifying multiple myeloma into 5 subtypes using translocation oncogene and cyclin expression [44]. Supervised learning has been used for class prediction, as in the case of acute myeloblastic leukemia. The later method is probably to be applied in order to help differentiate stem cells into specific lines using basic genetic profiling [45].

Neurology

One useful diagnostic tool in neurology is Electroencephalography (EEG) readings which provide an idea about the electrical activity of the brain. Many ML techniques have been implemented to analyze these signals and provide a prediction. In 2017, Subasi et al. [46] proposed an algorithm to detect epileptic seizures in EEG records using two machine learning techniques named SVMs (Support Vector Machines) and GAs (Genetic Algorithms) which proved an accuracy of 99.38 % on the EEG dataset used. However, in a recent publication, Avcu et al. [47] presented another ML technique called CNNs (Convolutional Neural Networks) that can detect seizures using only two channels with an accuracy of 93.3 %.

To see the other ways ML techniques have been assisting neurologists, we will take for an example the case of Parkinson's disease (PD). Starting from the early prognosis of PD, a recent work by Prashanth et al. [48] presented an ML system that can accurately predict PD with an accuracy of 96.40 %. The method uses non-motor features and olfactory loss in addition to Cerebrospinal Fluid (CSF) measurements and data from dopaminergic imaging markers. Now, after the disease has been diagnosed, another ML system can be used to predict disease progression. The system presented by Rastegar et al. [49] used serum cytokines from one time point (baseline); then, after one year, to predict the outcome for two years.

Oncology

The use of AI and ML in the fight against cancer has predominantly been considered as an attractive approach in the era of small molecule inhibitors, gene therapy, and engineered biotherapies. These techniques are currently used in the field of radiation oncology in image segmentation and radiotherapy dose optimization where AI and ML have adequately met conventional standards and proved to be more efficient than manual planning in most situations [50].

Nanobot development is one example of a physical application of AI in oncology. Nanobots are used for handling the following: 1) the problem of hypopermeation and lack of diffusion of target therapeutic agents at the application site; 2) targeting tumors deficit in vascularity but showing active proliferation [51].

For patients undergoing gastrectomy, one specific ML technique has proven to be the best at individualizing and specifying risk-based stratification concerning survival predictions [52].

A Google Research DL pathology algorithm has been trained, using images, to identify the spread of breast cancer to neighboring lymph nodes. This algorithm obtained a localization score of 89 % vs. 73 % accuracy rate for pathologists [53].

CNNs are the most common form of supervised learning; their application was explored in measuring and tracking brain tumors, glioma, and liver tumors in 2D as in 3D images, with interesting accuracy results in many experiments in comparison with Semi-automated RECIST-based methods [54–56].

Cell biology and cell therapy

In cell biology and cell therapy, there are large numbers of cell types and image screening and analysis techniques. Consequently, it was essential to use ML to identify the best image screening and analysis technique/cell type combinations so that we can differentiate between cell lines. Thus, many advancements in this field have been made. For instance, some currently commercialized ML automated microscopes can analyze more than 100,000 cell images per day [57] Bioimaging technology can effectively perform specific image analysis tasks, such as object detection, motion analysis, and morphometric feature measurements [58].

Machine learning uses experience instead of manual adjustment of parameters to identify cells and objects. It is more potent than conventional processing tools when it comes to accomplishing complex multi-dimensional data analysis tasks [59–61].

A significant task of ML in cell biology is determining whether an experimental perturbation (e.g. genetic modification) leads to a specific cellular phenotype (detection by fluorescence) [62]. One ML method was recently evaluated on actin-labeled fluorescence microscopy images of one epithelial cell line of a normal human breast and two lines of human breast cancer with different levels of aggression. The study showed that the technique performed better on the cell classification task compared to a human expert [63].

Such technology may be used to create and enhance new production and quality control methods of cell therapies such as chimeric antigen receptor- T (CAR-T) cells, an approach that has been applied and that has efficiently shown the features of clinically active CAR-T (e.g. glycolysis status, early memory phenotype, and low profile exhaustion) [64,65].

ML could also be used for stem cell therapy, an approach that was recently tested showing the high variability in cell identities that can be caused naturally by alterations in regulatory dynamics. This technique proved to be more powerful in understanding individual cell biology, and the collective dynamics of cell lines, communities and environments [66].

Cardiology

The main diagnostic keys available to cardiologists are the heart's electrical signals Electrocardiography ECG and heart auscultation. ML tools have assisted signal analysis and classification for both the former and later.

The cardiologist would normally perform cardiac auscultation using their stethoscope. A digital stethoscope, a phonocardiogram (PCG), could also record these signals, which could then be processed using ML techniques to detect abnormal sounds. In 2018, Yassen et al. [67] presented a an ML-based system that classifies heart signals and diagnoses heart disorders with 97 % accuracy.

To add to the above, ECG signals that cardiologists read on paper can actually be entered into computers in the form of values representing line amplitude at each timestamp. These values can be used as an input to the algorithm/structure that can analyze the signal patten and then classify it.

Earlier this year, Alfaras et al. [68] presented an ML model that can classify ECG signals and detect arrhythmia using a single lead, while cardiologists normally need to read the set of 12 leads to make a complete reading of the ECG record. This model achieved a sensitivity of 92.7 % and a positive predictive value of 86.1 % for ventricular ectopic beats, using the lead II, and a sensitivity of 95. 7 % and positive predictive value of 75.1 % when using the lead V1.

Ophthalmology

Be it vision abnormality or a disease affecting the eye, the delicate field of ophthalmology has received a fair share of ML applications [69,70].

Ophthalmologists already us machines to quickly and efficiently identify sight abnormalities. When it comes to other diseases, complaints concern the complications from diabetes mellitus on the eyes, mainly diabetic retinopathy (DR). Sayers et al. [71] have shown how using a deep learning algorithm can help specialists grade DR faster and with greater accuracy.

In addition, Li et al. [72] have recently presented a CNN model that detects glaucoma using the attention-based approach which outperforms state-of-the-art methods.

Whether it is a sight abnormality or a affecting the eye, the delicate field of ophthalmology has received a fair share of ML applications

Ophthalmologists are already using machines to identify any sight abnormalities quickly and efficiently. When it comes to other diseases, a lot of complaints are concerning the complications of diabetes mellitus on the eyes, mainly diabetic retinopathy (DR). Sayers and colleagues showed how using a deep learning algorithm can help specialists grade DR faster and more accurately.

On the other hand, Li and al. have recently presented a convolutional neural network model that can detect glaucoma using the attention-based approach in a better way than the state-of-the-art methods.

Conclusion

From the standpoint of physicians reviewing the current stage of ML and AI in healthcare, the question is now are we ready to completely adopt the assistance of this technology in our profession? The answer is that there are still many limitations to fully incorporate these systems in the field of healthcare. These include the need for legal and ethical guidelines and frameworks that deal with critical cases. Multi-level training which would provide physicians with the proper background concerning this technology is imperative. And then there is the question of how to integrate it safely and compassionately into daily clinical practice. And what is the proper infrastructure to implement these systems? To add to this, financial burden is equally a matter to be considered, at least in the set-up phase [73]. Looking to the positive, such systems would help physicians save time and effort and would assist physicians in the decision-making process. Given the enormous number of examples these systems are trained with, their observations exceed what any physician alone has witnessed throughout their career and can be of great benefit [74]. AI alone or in partnership with ML seems to be an effective solution for enhancing the quality of personalized medicine and for accelerating the rhythm of evolution for complex diagnostic and therapeutic techniques such as in the field of genetics, small molecule, and super target therapies.

In our opinion, digital transformation in the service of medicine must be based both on clinical expertise—to guarantee maximum effectiveness—and on precise IT guidance in order to overcome limitations.

Declaration of Competing Interest

The authors declare no conflict of interest for this manuscript.

Acknowledgments

The authors would like to thank William Stowe and Rachel Tipton for the proofreading of this manuscript.

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