Deep Learning for Medical Image Processing: Overview, Challenges and the Future

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Abstract The health care sector is totally different from any other industry. It is a high priority sector and consumers expect the highest level of care and services regardless of cost. The health care sector has not achieved society's expectations, even though the sector consumes a huge percentage of national budgets. Mostly, the interpretations of medical data are analyzed by medical experts. In terms of a medical expert interpreting images, this is quite limited due to its subjectivity and the complexity of the images; extensive variations exist between experts and fatigue sets in due to their heavy workload. Following the success of deep learning in other real-world applications, it is seen as also providing exciting and accurate solutions for medical imaging, and is seen as a key method for future applications in the health care sector. In this chapter, we discuss state-of-the-art deep learning architecture and its optimization when used for medical image segmentation and classification. The chapter closes with a discussion of the challenges of deep learning methods with regard to medical imaging and open research issue.

Keywords Deep learning · Medical image analysis · Image analysis

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1 Introduction

Gone are the days when health care databases were small. Due to the tremendous advancement in image acquisition devices, the increase in throughput and the installation of bio-medical data collection devices have led to an unprecedented amount of data. This data is high dimension (CT, MRI, etc.), rich in variables and collected from many (often incompatible) data platforms. It makes medical data challenging and of great interest for analysis, especially images. This rapid growth in medical images requires extensive and tedious effort from medical experts—work that is subjective, prone to human error and that may have large variations from expert to expert. An alternative solution is to use machine learning techniques to automate the process of diagnosis; however, traditional machine learning methods are not sufficient to deal with such complex problems. A happy marriage of high-performance computing with machine learning promises the capacity to access big medical image data for accurate and efficient diagnosis. Deep learning will not only help to select and extract features, but also construct new ones; furthermore, it not only diagnoses a disease, but also measures the predictive target and provides actionable prediction models to aid physicians to develop effective treatment plans (Fig. 1).

Machine learning (ML) and artificial intelligence (AI) have progressed rapidly in recent years. ML and AI techniques have played an important role in the medical field, supporting such activities as medical image processing, computer-aided diagnosis, image interpretation, image fusion, image registration, image segmentation, image-guided therapy, image retrieval and analysis. ML techniques extract information from the images and present information efficiently in an effectively form. ML and AI facilitate and assist doctors in diagnosing and predicting the risk of diseases accurately and more rapidly, allowing them to be detected earlier. These techniques enhance the abilities of doctors and researchers to understand how to analyze the generic variations which will lead to disease. These techniques comprise conventional algorithms without learning such as support vector machines (SVMs), neural networks (NNs), k-nearest neighbor (KNN) and so forth, and deep learning algorithms such as convolutional neural networks (CNNs), recurrent neural networks (RNNs), long short-term memory (LSTM), extreme learning models (ELMs) and generative adversarial networks (GANs). The SVM, NN, KNN and similar algorithms are limited in terms of processing images in their raw form;

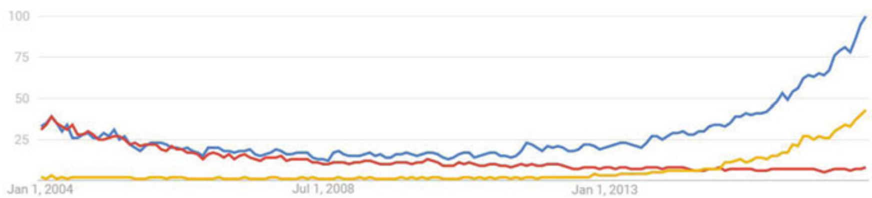

Fig. 1 Trends: deep learning vs machine learning vs pattern recognition

this is time-consuming, based on expert knowledge and requires considerable time to tune the features. The CNNs, RNNs, LSTM, ELMs and GANs algorithms can be fed with raw data, have automatic features and are able to learn rapidly. These algorithms try to learn multiple levels of abstraction, representation and information automatically from a large set of images that exhibits the desired behavior of data. Although automated detection of diseases based on conventional methods in medical imaging has shown significant accuracy for decades, new advances in machine learning techniques have ignited a boom in deep learning. Deep learning-based algorithms have shown promising performance as well speed in different domains such as speech recognition, text recognition, lip-reading, computer-aided diagnosis, face recognition and drug discovery.

The purpose of this chapter is to provide a comprehensive review of deep learning-based algorithms in relation to medical image analysis problems not only in terms of current work, but also with regard to the future direction of this methodology. This chapter provides fundamental knowledge and the state-of-the-art approaches concerning deep learning in the domain of medical image processing and analysis.

2 Why Deep Learning Over Machine Learning?

Accurate diagnoses of disease depend upon image acquisition and image interpretation. Image acquisition devices have improved substantially in recent years; X-Ray technology, and CT and MRI scans are able to provide radio-logical images with much higher resolution. However, we have only just begun to reap the benefits of automated image interpretation. One of the best machine learning applications is computer vision, though traditional machine learning algorithms for image interpretation rely heavily on expert crafted features; for example, the detection of tumors in lungs requires structural features to be extracted. Due to the extensive variation of data from patient to patient, traditional learning methods are not reliable. Machine learning has evolved over the last few years, gaining the ability to sift through big and complex data.

Deep learning is of great interest to each and every scientific field, especially in medical image analysis; it is expected that medical imaging markets will hold a value of $300 million by 2021. Thus, by 2021, medical imaging alone will receive more investment than the entire analysis industry spent in 2016. It is the most effective and supervised machine learning approach. This approach uses models of deep neural networks, which are a variation of neural networks, but with considerable equivalence to the human brain, using advanced mechanisms as compared with simple neural networks. The term “deep learning” implies the use of a deep neural network model. The basic computational unit in a neural network is the neuron, a concept inspired by the study of the human brain. The neural network takes multiple signals as inputs, combines them linearly using weights, and then passes the combined signals through non-linear operations to generate output signals.

2.1 Neural Networks and Deep Learning Architecture

Artificial neural networks (ANNs) were structurally and conceptually inspired by the human biological nervous system. The perceptron is one of the earliest neural networks based on the human brain system. It consists of an input layer that is directly connected to an output layer, and was good at classifying linearly separable patterns. To solve more complex patterns, a neural network was introduced that has a layered architecture; that is, an input layer, an output layer and one or more hidden layers. A neural network consists of interconnected neurons that take input and perform certain processing actions on the input data, finally forwarding the current layer output to the subsequent layer. The general architecture of a neural network is shown in Fig. 2.

Each neuron in the network sums up the input data and applies the activation function to the summed data, finally providing the output to be propagated to the next layer. Thus, adding more hidden layers allows a system to deal with complex problems, as the hidden layers can capture non-linear relationships. These neural networks are known as deep neural networks (DNNs). Deep learning provides a new cost-effective means by which to train DNNs, which were slow to learn the weights. Extra layers in DNNs enable the composition of features from lower layers to the upper layer by giving the potential to model complex data.

Deep learning is the growing trend for the development of automated applications and was termed in ten breakthrough technologies of 2013. Today, several deep learning-based computer vision applications are performing even better than humans; that is, they are able to identify indicators for cancer in blood and tumors in MRI scans. It is the improvement of artificial neural networks that consist of more hidden layers that permits this higher level of abstraction and improved image

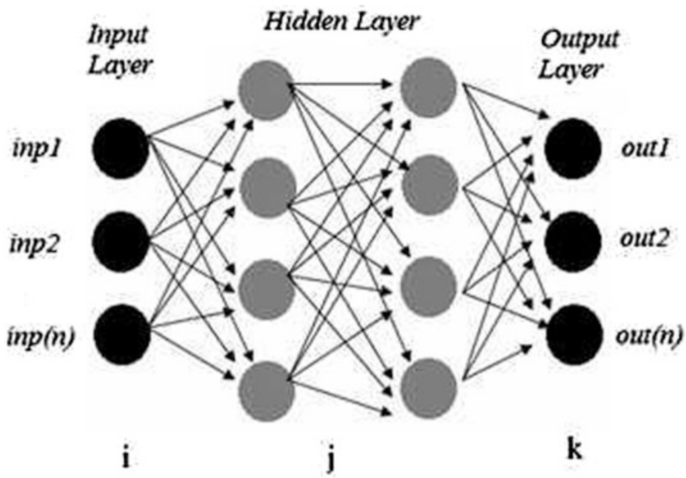

Fig. 2 Neural network architecture

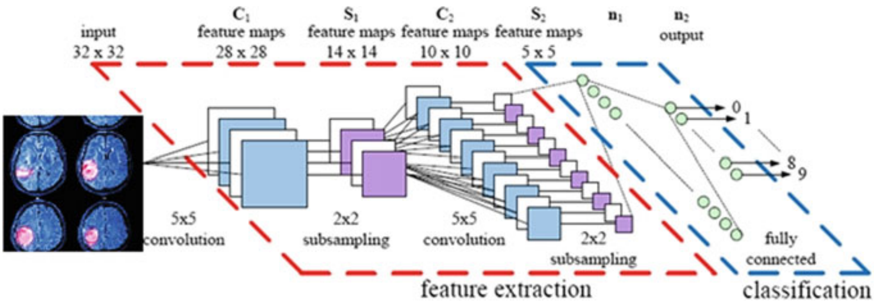

Fig. 3 Conventional neural network architecture

analysis. It has become an extensively applied method due to its recent unparalleled results in several applications: object detection, speech recognition, face recognition and medical imaging.

A deep neural network hierarchically stacks multiple layers of neurons, forming a hierarchical feature representation. The number of layers now extends to over 1000! With such a gigantic modeling capacity, a deep network can essentially "memorize" all possible mappings after successful training with a sufficiently large knowledge database and make "intelligent" predictions; for example, interpolations and/or extrapolations for unseen cases. Thus, deep learning is generating a major impact on computer vision and medical imaging. In fact, similar impact is happening in domains such as text recognition, speech recognition, lip-reading, computer-aided diagnosis, face recognition and so on. Various types of deep learning algorithms are in use in research: CNNs, DNNs, DBNs, dAs, DBMs, deep conventional extreme machine learning (DC-ELM), RNNs and their variants such as BLSTM and MDLATM (as illustrated with their pros and cons in Table 1.

The CNN model is the subject of considerable interest in digital image processing and vision. Several studies have showed that it extracts highly variable features and patterns without any preprocessing. The CNN has the properties of shared weights and replicated filters on each layer with local connectivity. These properties improve how the models learn. There are two types of layers: feature extractors (having filters and sub-sampling, alternatively) and trainable classifier. There different types of CNN architecture: Alexnet[1] (as shown in Fig. 4), Lenet,[2] faster R-CNN,[3] googleNEt,[4] ResNet,[5] VGGNet,[6] ZFnet and so on.

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[1]https://github.com/BVLC/caffe/tree/master/models/bvlcalexnet

[2]http://deeplearning.net/tutorial/lenet.html

[3]https://github.com/ShaoqingRen/fasterrcnn

[4]https://github.com/BVLC/caffe/tree/master/models/bvlcgooglenet

[5]https://github.com/gcr/torch-residual-networks

[6]http://www.robots.ox.ac.uk/vgg/research/verydeep/

Table 1 Comparison of different architectures of deep learning

Types of network	Detail of networks	Pros	Cons
Deep neural network (DNN)	There are more than two layers, which allow complex non-linear relationships. It is used for classification as well for regression. The architecture is shown in Fig. 5	It is widely used with great accuracy	The training process is not trivial because the error is propagated back to the previous individual layers and they become very small. The learning process of the model is also much too slow
Convolutional neural network (CNN)	This network is very good for two-dimensional data. It consists of convolutional filters which transform 2D into 3D. The architecture is shown in Fig. 3	Very good performance, model learns rapidly	It needs a great deal of labeled data for classification
Recurrent neural network (RNN)	It has the capability to learn sequences. The weights are shared across all steps and neurons	Learn sequential events, can model time dependencies, there are many variation: LSTM, BLSTM, MDL-STM, HLSTM These provide state-of-the-art accuracy in speech recognition, character recognition and many other NLP related tasks	There many issues due to a vanishing gradient and the need for big datasets
Deep conventional extreme learning machine (DC-ELM)	For sampling of local connections, this network uses a Gaussian probability function, as shown in Fig. 5	It is widely used and has great accuracy It is computationally efficient and fast training mechanism. It is good for random distortion	Initialization can possibly be effective if the learning function is very simple and the amount of labeled data is small
Deep Boltz-mann machine (DBM)	This model is based on the family of Boltzmann machines. It consists of unidirectional connections between all hidden Layers, as shown in Fig. 6	The top-down feed-back incorporates ambiguous data for more robust inference	Optimization of parameters is not possible for big datasets
Deep belief network (DBN)	DBN has unidirectional connection and is used in both supervised and unsupervised machine learning. The hidden layers of each sub-network serves as visible layer for the next layer. The architecture is shown in Fig. 7	The greedy strategy (used in each layer) and the inference tractable maximize directly the likelihood	The initialization makes the training process computationally expensive

(continued)

Table 1 (continued)

Types of network	Detail of networks	Pros	Cons
Deep Autoencoder (dA)	It is used in un-supervised learning and it is designed mainly for extraction and reduction of the dimensionality of features. The number of input is equal to number of output. It is shown in Fig. 8	It does not need labeled data. There are different variations: Sparse Autoencoder, De-noising Autoencoder, Conventional Auto-Encoder for greater robustness	It needs a pre-training step. Its training may disappear

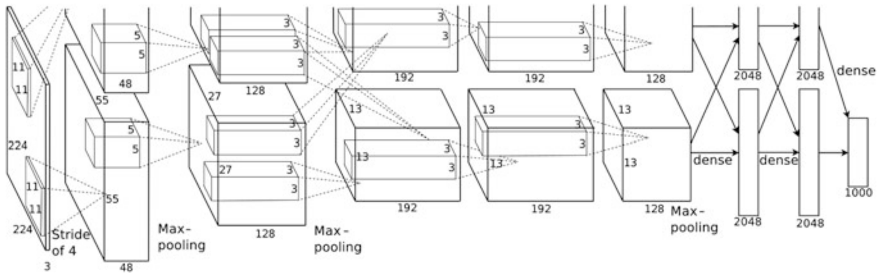

Fig. 4 Type of architecture of CNN: AlexNet

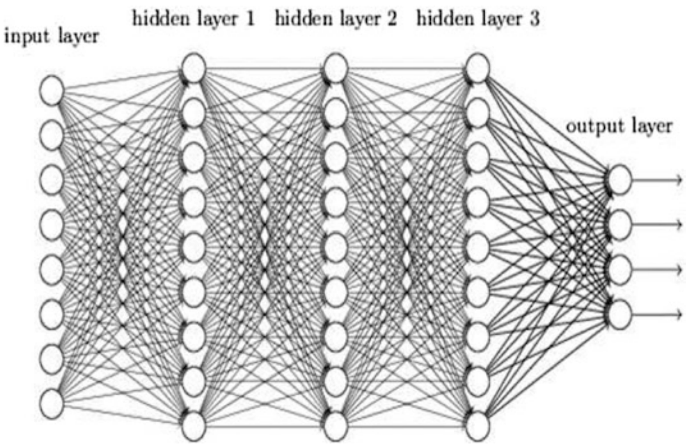

Fig. 5 Deep neural network

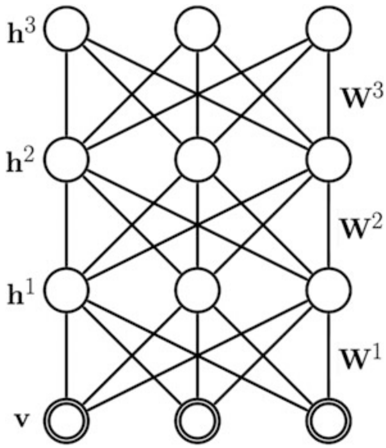

Fig. 6 Deep Boltzmann machine (DBM)

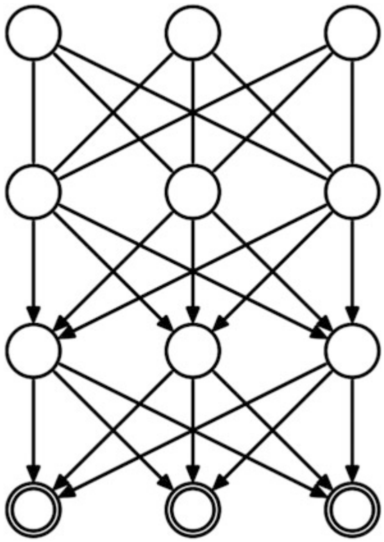

Fig. 7 Deep belief network (BDN)

3 Deep Learning: The not-so-Near Future in Medical Imaging

Deep learning technology applied to medical imaging may become the most disruptive technology radiology has seen since the advent of digital imaging. Most researchers believe that within the next 15 years, deep learning-based applications will take over from humans, and that not only most of the diagnosis will be performed by intelligent machines, but that they will also help to predict disease, prescribe medicine and guide in treatment. Of the medical field will be the first to be

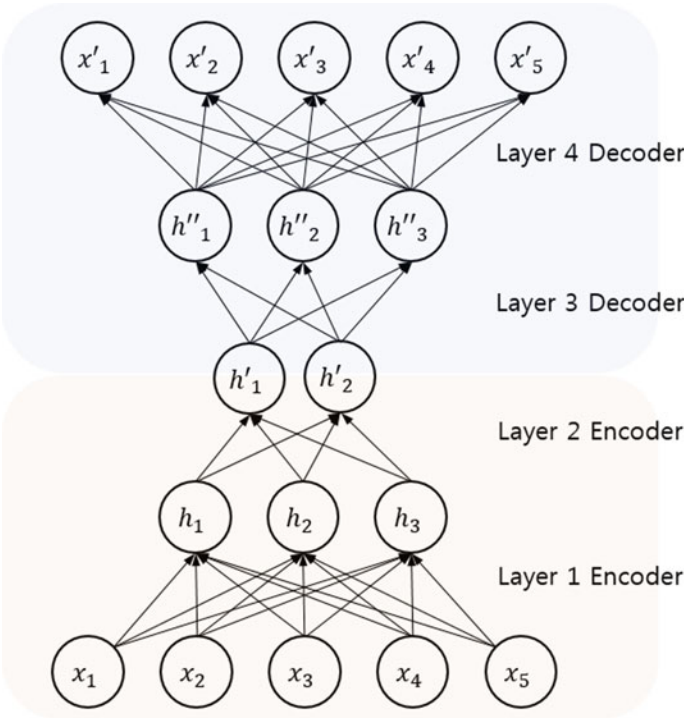

Fig. 8 Deep autoencoder (dA)

revolutionized by deep learning: ophthalmology, pathology, cancer detection, radiology or prediction and personalized medicine? Ophthalmology will be the first field to be revolutionized in health care; however, pathology and the diagnosis of cancer has received more attention and, currently, we have an application with acceptable accuracy. Google DeepMind Health is working with the National Health Service, UK: a five-year agreement has been signed to process the medical data of up to one million patients. Even in the early days of this project, Deepmind already has high hopes for the proposal.

The researchers and vendors in the medical sector who are moving this field forward have a bold recommendation. IBM Watson recently boosted itself through a US$1 billion entry into the imaging arena by the acquisition of Merge; imaging and Google DeepMind Health is another big investment. Even though there has been huge investment and there is considerable interest, the future of deep learning in medical imaging is not as near as that of other imaging applications due to the complexities involved in this field. The notion of applying deep learning-based algorithms to medical imaging data is a fascinating and growing research area; however, there are several barriers that slow down its progress. These challenges include the unavailability of datasets, privacy and legal issues, dedicated medical experts, non-standard data machine learning algorithms.

3.1 Dataset

Deep learning requires immense training datasets to establish the accuracy of deep learning classifiers; the lack suitable datasets is one of the biggest barriers to the success of deep learning in medical imaging. On the other hand, the development of large medical imaging data is quite challenging, as annotation requires extensive input from medical experts; in particular, multiple expert opinions are required to overcome the problem of human error. Furthermore, annotation may not be possible due to a lack of qualified experts or the unavailability of sufficient cases dealing with a rare disease. Another major issue is the unbalanced nature of data, which is very common in the health sector: rare diseases, by virtue of being rare, are underrepresented in the datasets. If not accounted for properly, class imbalance ensues.

3.2 Privacy and Legal Issues

It is much more complicated and difficult to share medical data as compared with real-world images. There are both sociological and technical elements to data privacy, which must be addressed jointly from both perspectives. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) comes to mind when privacy is discussed in the health sector. It provides legal rights to patients regarding their personally identifiable information and establishes obligations for health care providers to protect and restrict the use or disclosure of such information. With the rise of health care data, data analytics researchers see big challenges with regard to anonymizing patient information to prevent its use or disclosure. Discarding such information as a patient's social security number, medical record number, name and age make it complicated to link the data up to a unique individual. But, even so, a hacker could still possibly identify a patient by means of association. An alternative route is differential privacy, which restricts the data to an organization based on the nature of the data required. These privacy challenges are factors that can lead to situations where a data analytics model can be impacted negatively from both legal and ethical perspectives.

The main privacy challenges associated with health care data analytics, overrunning the privacy concerns of "traditional" data processing include addressing how to share sensitive data while limiting its disclosure and sharing by ensuring sufficient data utility. For example, the year of birth, 3-digit Zip code and gender) are unique for 0.04% of the US population, while the date of birth, 5-digit Zip code and gender) are unique for 87% of the US population. Limited access to data, unfortunately, also reduces information content that could be very important. In addition, data are not static. Data volume is increasing over time, thus none of the current methods result in making data secure.

3.3 Data Interoperability and Data Standards

Data interoperability and data standards present one of the major barriers. Currently, the nature of data differs from hardware to hardware, thus there exists a large variation in images due to sensors and other factors. Furthermore, the breadth of any applications the medical sector requires combine several different datasets to enable better algorithms for learning and accuracy. Interoperability is the backbone of critical improvements in health sector and yet has to become a reality. Similar to the concept of an asynchronous transfer mode network, health data should be standardized and shared between providers. To achieve the appropriate level of interoperability, the HIPAA, HL7, HITECH and other health standardization bodies have defined certain standards and guidelines. How does an organization know whether it meets interoperability and security standards? An authorized testing and certifying body provides an independent, third-party opinion on electronic health records. Two types of certification are used to evaluate the system: Certification Commission for Healthcare Information Technology (CCHIT) and The American Recovery and Reinvestment Act (ARRA). Review processes include standardized test scripts and the exchange test of standardized data.

3.4 Black Box and Deep Learning

Medical imaging broke paradigms when it first began more than 100 years ago and deep learning algorithms gave new birth to medical imaging applications and opened up new possibilities. Medical imaging solves problems previously thought to be unsolvable by machine learning algorithms; however, deep learning is not free from problems. One of the major issues is the black-box problem. Although the mathematics used to construct a neural network is straightforward, but how the output is reached is exceedingly complicated. Machine learning algorithms are fed immense amounts of data as input, identify patterns and build predictive models; however, the issue is more one of understanding how a model works. The deep learning model is continuous and most of the researchers using it without knowing the working process or why it provides better results.

4 Deep Learning in Medical Imaging

Many image diagnosis tasks require an initial search to identify abnormalities, and to quantify measurements and changes over time. Automated image analysis tools based on machine learning algorithms are the key enablers to improve the quality of image diagnosis and its interpretation by facilitating efficient identification. Deep learning is an extensively applied technique that provides state-of-the-art accuracy.

It has opened new doors in medical image analysis. Applications of deep learning in health care cover a broad range of problems ranging from cancer screening and disease monitoring to personalized treatment suggestions. Various sources of data today: radiological imaging (X-ray, CT and MRI scans), pathology imaging and, recently, genomic sequences have put an immense amount of data at the physician's disposal. However, we are still short of tools with which to convert all this data into useful information. In the discussion that follows, we highlight state-of-the-art applications of deep learning in medical image analysis. Although the list is by no means complete, it does provide an indication of the far-ranging impact of deep learning in the medical imaging industry today.

4.1 Diabetic Retinopathy (DR)

The detection of diabetic retinopathy (DR) manually is a difficult and time-consuming process at present due to the unavailability of equipment and expertise. This disease shows hardly any symptoms in the early stages and a clinician needs to examine the colored fundus image of the retina, which leads to delay in treatment, miscommunication and loss of follow-up. The automated detection of DR based on deep learning models has been proven to offer optimized and better accuracy. In this section, we present research work undertaken using deep learning approaches.

Gulshan et al. [1] applied a deep convolutional neural network (DCNN) on an eye picture archive communication system (EyePACS-1) dataset and a Messidor-2 dataset for the classification and detection of moderate and worse referable cases. The EyePACS-1 dataset consists of approximately 10,000 retinal images and the Messidor-2 dataset consists of 1700 images collected from 874 patients. The authors claimed 97.5% sensitivity and 93.4% specificity on EyePACS-1, and 96.1% sensitivity and 93.9% specificity on Messidor-2. Kathirvel [2] trained a DCNN with dropout layer techniques and tested this on the publicly available datasets Kaggle fundus, DRIVE and STARE for the classification of fundus. The reported accuracy value rose to 94–96%. Pratt et al. [3] employed a NVIDIA CUDA DCNN library on a Kaggle dataset consisting of over 80,000 digital fundus images. They also validated the network on 5000 images. The images were resized to 512 $\times$ 512 pixels and then sharpened the obtained images. Finally, the features vector was fed into Cu-DCNN. The images were sorted into five classes using features such as exudates, hemorrhages and micro-aneurysms, and achieved up to 95% specificity, 30% sensitivity and 75% accuracy.

Haloi [4] implemented a five-layer CNN with a dropout mechanism for the detection of early-stage DR on Retinopathy Online Challenge (ROC) and Massidor datasets. The Maddissor dataset gave a sensitivity value of 97%, specificity of 96%, accuracy of 96% and area under the curve (AUC) up to0.988 on; the ROC dataset gave an AUC of up to 0.98. Alban and Gilligan [5] denoised the EyePACS angiograph images and then applied CNNs to detect DR. They diagnosed five classes of severity and the system provided 79% AUC and 45% accuracy. Lim et al. [6] extracted features from identified regions using a method proposed in San et al. [7] and then passed the features vector to a DCNN for classification. They realized the model on DIARETDB1 and SiDRP datasets. All these works are summarized in Table 1.

4.2 Detection of Histological and Microscopical Elements

Histological analysis is the study of cells, groups of cells and tissues. When different changes occur at cellular and tissue level, then microscopic changes, characteristics and features can be detected through microscopic image technology and stains (colored chemicals) [8, 10]. This technique involves a number of steps: fixation, sectioning, staining and optical microscopic imaging. It can be used in the management of various skin diseases, especially squamous cell carcinoma, and melanoma; other diseases such as gastric carcinoma, gastric epithelial metaplasia, breast carcinoma, malaria, intestinal parasites and tuberculosis. Plasmodium is a genus of parasite that is the main reason for malaria. Microscopical imaging is the standard method for the detection of parasites in a stained blood smear sample. The mycobacterium in sputum is the main cause for tuberculosis. Smear microscopy and a fluorescent auramine-rhodamine stain or Ziehl-Neelsen stain are the gold standards for the detection of tuberculosis.

Recently, in the Histo Phenotypes dataset Sirinukunwattana et al. [11] applied a DCNN classifier for the diagnosis of the nuclei of cells responsible for colon cancer using stained histological images. Bayramoglu and Heikkila [12] conducted two studies for the detection of thoraco-abdominal lymph node and interstitial lung disease using the transfer learning (fine tuning) approach with a CNN model. Due to limited histological data, in Sirinukunwattana et al. [11] the features vector was extracted using facial images [13] and natural images from ImageNet [14] using a source CNN and then transferred to the object CNN model for classification. The CNN classifier employed for grading gastric cancer analyzed signet ring cells in tissues and epithelial layers of tissue. They also counted the mitotic figures for breast cancer [15] (Fig. 9).

In Quinn et al. [16], the authors employed shape features such as moment and morphological to predict malaria, tuberculosis and hookworm from blood, sputum and stool samples. Automatic microscopic image analysis performed using a DCNN model as a classifier reported an AUC of 100% for malaria, and 99% for tuberculosis and hookworm. A DCNN was also applied for the diagnosis of malaria in Quinn et al. [16] and intestinal parasites in Peixinho et al. [17]. Fully CNN deep learning was used in Xie et al. [18] for automatic cell counting. Qiu et al. [19] also employed a DCNN for the detection of leukemia in metaphase. Malaria detection is a crucial and important area of research. In 2015, 438,000 people died due to malaria according to the World Health Organization. Dong and Bryan [20] developed four systems for the detection infected and non-infected cells by malaria

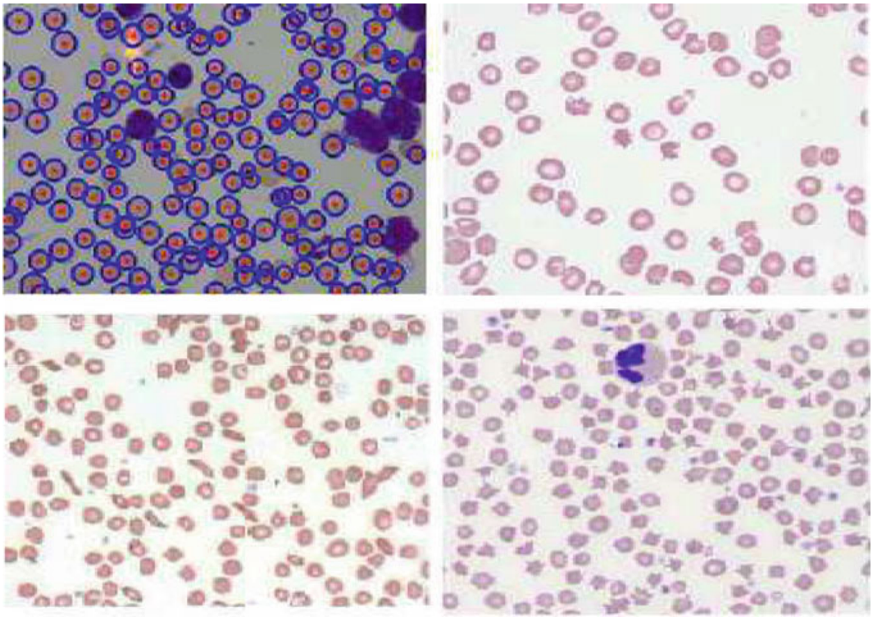

Fig. 9 Microscopic blood smear images

Table 2 Summary of deep learning (DL) for diabetic retinopathy (DR)

Authors	Model	Data set	Accuracy: acc or sensitivity: sensi or specificity: spec (%)
Gulshan et al.	Deep convolutional neural network	EyePACS-1 Messidor-2	97.5% sensi & 93.4% spec 96.1% sensi & 93.9% spec
Kathirvel	CNN with dropout layer	Kaggle-fundus, DRIVE and STARE	94–96%
Pratt et al.	Cu-DCNN library	Kaggle	75% acc
Haloi et al.	Five layers CNN	Massidor ROC	98% AUC 97% AUC
Alban et al.	DCNN	EyePACS	45% acc
Lim et al.	DCNN	DIARETDB1 SiDRP	–

using CNN models and SVM. Three CNN architectures—GoogLeNet, LeNet-5 and AlexNet—were used for automatic feature extraction and classification, and reported 98.13, 96.18 and 95.79%, respectively. An SVM-based system achieved the lowest accuracy of up to 91.66%. A summary of these studies is given in Table 2.

4.3 Detection of Gastrointestinal Diseases (GI)

Gastrointestinal (GI) diseases affect all organs involved in the digestion of food, the absorption of nutrients and the excretion of waste products. The digestive tract begins at the mouth and terminates at the anus. The organs are the esophagus, stomach, large intestine (colon or large bowel) and small intestine (small bowel). GI tract may also be divided into the upper GI tract and lower GI tract. The upper GI tract consists of the esophagus, stomach and duodenum (part of the small bowel), and the lower GI tract consists mainly of the small intestine (jejunam and jilium) and large intestine. The digestion and absorption of food is affected by a variety of ailments and diseases such as inflammation, bleeding, infections and cancer in the GI tract [21]. Ulcers cause bleeding in the upper GI tract. Polyps, cancer or diverticulitis cause bleeding from the colon. The small intestine suffers from diseases such as celiac disease, Crohn's disease, malignant and benign tumors, intestinal obstruction, duodenal ulcers, irritable bowel syndrome and bleeding due to abnormal blood vessels (arteriovenous malformations—angiodysplasias or angioectasias).

Image processing and machine learning play a vital role in diagnosing and analyzing these diseases, helping doctors make swift treatment decisions efficiently and accurately. Due to advances in computer-aided diagnosis (CAD) systems, various kind of imaging tests are used in practice for the detection and classification of diseased in digestive systems. These imaging tests are wireless capsule endoscopy (WCE), endoscopy and enteroscopy, colonoscopy or sigmoidoscopy, radio-opaque dyes and X-ray studies, deep small bowel enteroscopy, intra-operative enteroscopy, computed tomography and magnetic resonance imaging (MRI).

Jia and Meng [22] employed a DCNN for the detection of bleeding in GI disease in 10,000 WCE images. The WCE is a non-invasive video-imaging method for the examination of disease in the small bowel. They claimed an F-measure of approximately 99%. Pei et al. [23] focused mainly on the evaluation of the frequency of bowel contractions by investigating diameter patterns and the length of the bowel by measuring temporal information. The authors implemented fully convolutional networks (FCNs) and stacked an FCN with LSTM using small and massive datasets. An FCN-LSTM trained on a small dataset consisted of five cine-MRI sequences without labeling and the FCN system was realized on massive dataset consisting of 50 raw cine-MRI sequences with labeling. Wimmer et al. [24] learned features from an ImageNet dataset; then, the learned feature vector was fed to CNN SoftMax for the classification and detection of celiac disease using endoscopic images of duodenums [25].

A popular approach for automatic feature extraction from endoscopy im-ages was adopted by Zhu et al. [26] using a CNN. Then, the features vector was fed to the SVM for the classification and detection of GI lesions. The proposed system was realized on 180 images of lesion detection and an accuracy of 80% was reported. Similarly, a hybrid approach was used by Georgakopoulos et al. [27]. Fast features extraction using a CNN was applied and then the extracted features were passed to an SVM for the detection of inflammatory GI disease in WCE videos. The experiments were conducted on 337 annotated inflammatory images and 599 non-inflammatory images of the GI tract of the KID training set, containing 200 normal and 200 abnormal images; the test dataset contained 27 normal and 27 abnormal images. They obtained an overall accuracy of up to 90%.

The work involved in the detection of polyps in colonoscopy videos using representation of the image in three ways [28]. A number of CNN models were trained on isolated features such as texture, shape, color and temporal information in multiple scales which enhance the accurate localization of a polyp and then combined the results for the final decision. They claimed that their polyp dataset is the largest annotated dataset and that they decrease the latency of the detection of polyps compare with state-of-the-art techniques. Ribeiro et al. [29] also conducted three experiments using different CNNs. They applied normalization (see details in A. Coates and Ng [30]. The size of the dataset increased using data augmentation by making different variations of images. Ribeiro and Häfner [31] presend a further pixel and CNN-based work for the prognosis of polyp tumor staging using colonic mucosa as a target attribute. The work available on GI disease is summarized in Table 3.

4.4 Cardiac Imaging

Deep learning has provided extremely promising results for cardiac imaging, es-pecially for the quantification of calcium scores. Various diverse applications have been developed: CT and MRI scans are the most frequently used imaging modalities where the most common targets for image segmentation are the left ventricle. Manual identification of the Coronary Artery Calcium (CAC) in cardiac CT requires substantial expert interaction, which makes it time-consuming and in-feasible for large-scale or epidemiological studies. To overcome these limitations, (semi)-automatic calcium scoring methods have been proposed for CSCT. Recent work on cardiac images has focused on CT angiographic image-based CAC computation using DCNNs, as shown in Fig. 10.

4.5 Tumor Detection

When the cells in any part of the body have abnormal growth and make a mass, this is called a tumor or neoplasm. There are two types of tumor: non-cancerous (a benign tumor) and the other is cancerous (a malignant tumor). A benign tumor is not a significant danger as it is remains attached to one part of the body and does not spread to other part of the body. A malignant tumor is very harmful as it spreads to other parts of the body. When it spreads to other parts of the body, then it is difficult to treat and prognoses also become very poor (Table 6).

Table 3 Summary of deep learning (DL) for histological and microscopical elements detection

Authors	Model	Data set	Accuracy: acc or sensitivity: sensi or specificity: spec (%)
Bayramogl and Heikkil	Transfer approach with CNN	ImageNet (source for features) HistoPheno—types dataset	–
Quinn et al.	DCNN and shaped features like moment and morphological	Microscopic image	100% for Malaria; 90% for tuberculosis and hookworm
Qiu et al.	DCNN	–	–
Dong et al.	GoogLeNet, LeNet-5, and AlexNet		98.66, 96.18 and 95.79% acc

Table 4 Summary of deep learning (DL) for GI

Authors	Model	Data set	Accuracy: acc or sensitivity: sensi or specificity: spec (%)
Bayramogl and Heikkil	Transfer approach with CNN	Image Net (source for features) HistoPheno—types dataset	
Qiu et al.	DCNN and shaped features like moment and morphological	Microscopic image	100% for malaria: 99% for tuberculosis and hookworm
Qiu et al.	DCNN	–	–
Dong et al.	GoogLeNet, LeNet-5, and A lex Net		98.66, 96.18 and 95.70% acc

Table 5 Summary of deep learning (DL) for tumor detection

Authors	Model	Data set	Accuracy: acc or sensitivity: sensi or specificity: spec (%)
Bayramogl and Heikkil	Transfer approach with CNN	Image Net (source for features) HistoPheno—types dataset	–
Quinn et al.	DCNN and shaped features like moment and morphological	Microscopic image	100% for malaria; 99% for tuberculosis and hookworm
Qiu et al.	DCNN	–	–
Dong et al.	GoogLeNet, LeNet-5, and A lex Net		98.66, 96.18 and 95.79% acc

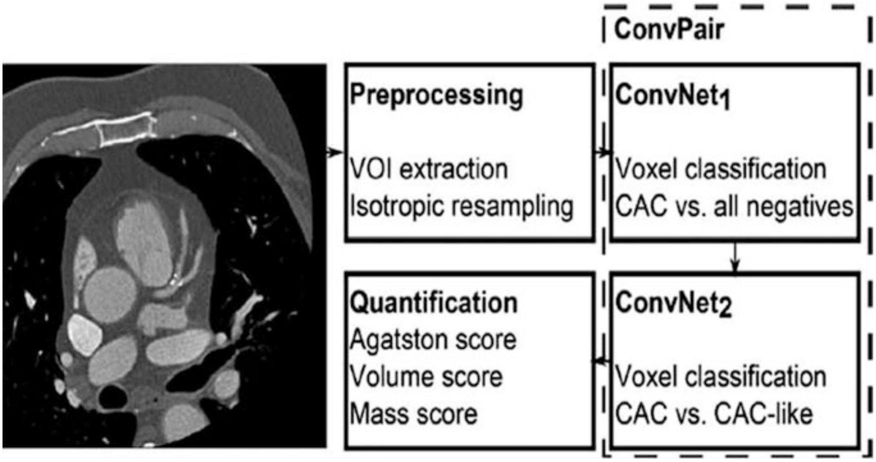

Fig. 10 Calcium score classification. *Source* Wolterink et al. [32]

Table 6 Summary of deep learning (DL) for alzheimer disease detection

Authors	Model	Data set	Accuracy: acc or sensitivity: sensi or specificity: spec (%)
Bayramogl and Heikkil	Transfer approach with CNN	Image Net (source for features) HistoPheno—types dataset	–
Quinn et al.	DCNN and shaped features like moment and morphological	Microscopic image	100% for malaria; 99% for tuberculosis and hookworm
Qiu et al.	DCNN	–	–
Dong et al.	GoogLeNet-, LeNet-5, and A lexNet		98.66, 96.18 and 95.79% acc

Wang and Qu [33] used 482 mammographic images of women aged between 32 and 70. Of these images, 246 were affected by tumor. The images were first denoised using a median filter and then the images of the breast tumor were segmented using region growth, morphological operations and modified wavelet transformation. Next, morphological and textural features were passed to an ELM and an SVM for classification and the detection of a breast tumor. The total error rate of the ELM was 84 and of the SVM 96. Kooi and den Heeten [34] have a limited dataset of malignant masses and benign solitary cysts. A CNN model needs a large number of training images to enable its capacity to find cysts and masses. Therefore, a CNN fed by different variations of images reported an AUC of up to 87% (Fig. 11).

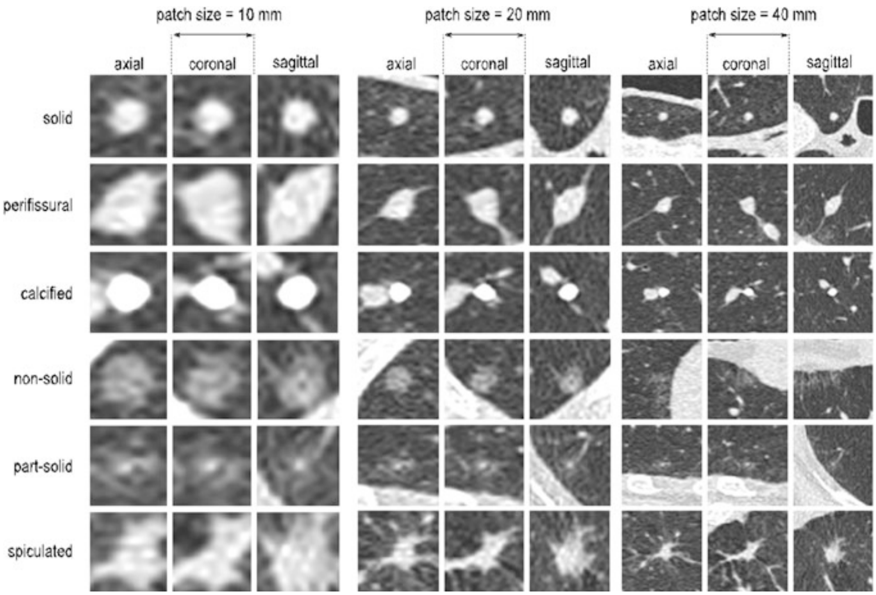

Fig. 11 Lung nodule segmentation. *Source* Cui et al. [35]

4.6 *Detection of Alzheimer's Disease and Parkinson's Disease*

Arevalo et al. [36] conducted an experiment on a benchmark dataset of 736 mediolateral oblique and craniocaudal mammographic views from 344 cancerous patients. They segmented the images manually into 310 malignant and 426 benign lesions. First, the images were enhanced and then were fed into the CNN to train it for the identification of benign and malignant lesions. They reported an AUC of 82.6%. Huynh and Giger [37] used CNN for feature learning on breast ultrasound images with 2393 regions of interest from 1125 patients. They performed two experiments. In the first experiment, an SVM model classified the extracted features into malignant, benign and cystic, obtaining a satisfactory result. In the second experiment, an SVM classified handcrafted features.

The AUC of the CNN features was 88% and the AUC of the handcrafted features was 85%. An SVM was used for classification and a CNN was used for feature extraction in Huynh and Giger [38]. They obtained an AUC of 86% on a dataset containing 219 lesions in 607 breast images. Antropova and Giger [39] investigated a CNN for the transfer learning of features from an ImageNet dataset (non-medical) and an SVM applied on 4096 extracted features for the classification of breast lesions as malignant or benign using 551 MRI images consisting of 194 benign tumors and 357 malignant tumors. An AUC of up to 85% was reported.

In Samala et al. [40], the frozen approach of transfer learning was used. A DCNN trained on mammographic images with dropout and jittering approaches reported an AUC of 99% which was then validated on device tree blob images with an AUC of 90% after transfer learning. The datasets consisted of 2282 digitized film and digital mammograms [41], and 324 device tree blob volumes [42]. The training set comprised 2282 images with 2461 lesions and 230 device tree blob views with 228 masses. The remaining images were used for an independent test. Shin et al. [43] conducted the finetuning approach of transfer learning on ImageNet using a CNN. Next, the CNN model was applied as a classifier for the detection of lesions in thoraco-abdominal lymph nodes and interstitial lung disease. The authors achieved a sensitivity of up to 83 and 85% and an AUC up to 94 and 95%, respectively. A brief summary of the published work is given in Table 4.

Parkinson's disease is a neurological disorder associated with a pro-gressive decline in motor precision and sensor motor integration stemming, presumably, from a disorder of the basal ganglia [44]. Parkinson's disease is associated with the breaking up or the death of dopaminergic neurons. Neurological testing such as MMSE [45, 46] and brain scans are routinely used to determine the diagnosis of Alzheimer's disease association [47]. The scale and shift in variant-based features—such as the shape of data, and the mean and standard deviation—using a CNN model (LeNet-5) carried out classification on functional MRI 4D in the work of Sarraf et al. [48]. The proposed system trained on 270,900 images, and was validated and tested on 90,300 images in functional MRI. The authors obtained 96.86% accuracy for the detection of brains affected by Alzheimer's disease (Table 7).

Suk et al. [61] employed a DBM for feature extraction and the detection of abnormalities from 3D patches of MRI and PET images. The results were validated on an Alzheimer's Disease Neuroimaging Initiative (ADNI) Dataset [62] comprising PET, MRI and a combination of PET and MRI, obtaining accuracies up to 92.38, 92.20 and 95.35%. Hosseini-Asl and El-Baz [63] also explored a 3D-CNN for the diagnosis of Alzheimer's disease and extracted generic features using a CADDementia MRI dataset. The authors then finetuned a fully connected three-layer CNN for the classification of Alzheimer's disease using the ADNI dataset. Sarraf et al. [43] diagnosed Alzheimer's disease in adults (over 75 years old) using functional MRI and MRI images. The authors conducted studies based on research and clinical applications. The CNN model employed for the detection of healthy brains or brains affected by Alzheimer's disease reported 99.9% for the functional MRI data and 98.84% for the MRI data. They then performed classification at subject level and then the decision making-based algorithm was applied. The final accuracy improved up to 97.77% for the functional MRI and 100% for the MRI subjects. In Payan and Montana [64], a sparse autoencoder (a neural network) was used for the extraction of features and then a 3D-CNN was applied as a classifier on an ADNI dataset consisting of neuron images. The dataset was divided into a training set (1731 samples), a validation set (306 samples) and a test set (228 samples). Performance of up to 95.39% was achieved for Alzheimer's disease.

Liu et al. also used a sparse autoencoder for the extraction of generic features and then applied a CNN softmax for the classification of brains affected by Alzheimer's disease, or by the prodromal stage or mild stage of Alzheimer's

Table 7 Summary of some deep learning based medical imaging

Application area	Input data	Deep learning method
Cardiac CAC	CT	CNN Wolterink et al. [49], Lessmann et al. [32], Wolterink et al. [50]
Lungs cancer	MRI	CNN Sakamoto and Nakano [51]
Lungs cancer	CT	DNN Ciompi et al. [52], Paul et al. [53]
Diabetic retinopathy	Fundus image	CNN Pratt et al. [1], Gulshan et al. [3]
Blood analysis	Microscopic	CNN Razzak and Alhaqbani [8], Xie et al. [18]
Blood analysis	Microscopic	DBN Duggal et al. [54]
Blood vessel	Fundus	DNN Liskowski and Krawiec [55]
Blood vessel	Fundus	CNN Ngo and Han [56]
Brain lesion segmentation	MRI	CNN Kamnitsas et al. [35], Cui et al. [57], Kleesiek et al. [58]
Polyp recognition	Endoscopy	CNN Yuan and Meng [59], Segu et al. [25], Wimmer et al. [60]
Alzheimer's disease	PET	CNN Sarraf et al. [43]

disease. They achieved an accuracy of up to 87.76% on binary images of MRI and PET for the detection of the early stages of Alzheimer's disease. All methods are summarized in Table 5.

5 Open Research Issues and Future Directions

Three trends that drive the deep learning revolution are the availability of big data, recent deep learning algorithms modeled on the human brain and processing power. While the potential benefits of deep learning are extremely significant, so are the initial efforts and costs. Big companies such as Google DeepMind, IBS Watson, research labs together with leading hospitals and vendors are coming together and working towards the optimal solution to big medical imaging. Siemens, Philips, Hitachi and GE Healthcare have already made significant investments. Similarly, research laboratories such as Google and IBM are also investing in the delivery of efficient imaging applications; IBM Watson is working with more than 15 health care providers to learn how deep learning could work in real-world applications. Similarly, Google DeepMind is collaborating with the NHS, UK, to apply deep learning to various health care applications (e.g., anonymized eye scans analysis could help to find the signs of diseases that could lead to blindness) on dataset of 1.6 million patients. The GE Healthcare partnership with Boston Children's Hospital is working to create smart imaging technology to detect pediatric brain disorders. Furthermore, GE Healthcare and the University of California, San Francisco, have also announced a three-year partnership to develop a set of algorithms to differentiate between normal results and results that require further attention by an expert.

5.1 Requires Extensive Inter-organization Collaboration

Despite great effort from big stakeholders and their predictions about the growth of deep learning and medical imaging, there will be a debate on replacing humans with machines; however, deep learning has potential benefits for disease diagnosis and treatment. However, there are several issues that need to be resolved in order that it may come about sooner. Extensive collaboration is required between hospital providers, vendors and machine learning scientists to stimulate and empower this extremely beneficial solution for improving the quality of health. This collaboration will resolve the issue of the lack of available data for the machine learning researcher. One of the major challenge is the need of sophisticated techniques to deal with the extensive amount of health care data, especially in future as health care industry is transferring to body sensor network based monitoring.

5.2 Need to Capitalize Big Image Data

Deep learning applications rely on extremely large datasets; however, annotated data is not readily available compared with other imaging areas. It is very simple to annotate real-world data; that is, annotation of a group of men and woman, annotation of objects in a real-world image. However, annotation of medical data is expensive, tedious and time-consuming, as it requires extensive time from experts (especially due the sensitivity of the domain, the annotation required and the fact that different experts will have different opinions on the same data). Furthermore, annotation may not be available in rare cases. Thus, sharing data resources with different health care service providers will help to overcome this issue.

5.3 Advancement in Deep Learning Methods

The majority of deep learning methods focus on supervised deep learning; however, the annotation of medical data—especially image data—are not always possible; that is, in the case of rare diseases or the unavailability of a qualified expert. To overcome the unavailability of big data, the supervised deep learning field is required to shift from supervised to unsupervised or semi-supervised systems. Thus, the efficiency of unsupervised and semi-supervised approaches in medicine will be compromised. Also, there is the highly sensitive question of how we can move from supervised systems to transform learning without affecting the accuracy of health care systems. Despite current best efforts, deep learning theories have not yet provided complete solutions and many questions remain unanswered, despite the unlimited opportunity for improvement that are yet to be explored.

5.4 *Black-Boxes and Their Acceptance by Health Professionals*

Health professionals are wary as many questions are still unanswered and deep learning theories have not yet provided a complete solution. Unlike health professionals, machine learning researchers argue that inter-operability is less of an issue than a reality. Humans are not concerned with all the parameters and make complex decisions; it is just a matter of human trust. Acceptance of deep learning in the health sector needs proof from other fields. Medical experts are hoping to see its success in other critical areas of real-world life; for example, autonomous cars, robots and so on. Even though the deep learning-based method has achieved great success, a solid theory regarding deep learning algorithms is still absent. Embarrassment due to this absence is well-recognized by the machine learning community. Black-boxes could be another of the main challenges; the legal implications of black box functionality could be a barrier as health care experts would be reluctant to rely on it. Who would be responsible if results were incorrect? Due to the sensitivity of this subject, hospitals may not be comfortable with black-boxes; that is, how a particular result could be traced to the ophthalmologist. The unlocking of black-boxes is a major research issue and deep learning scientists are making strenuous efforts to find the key (Fig. 12).

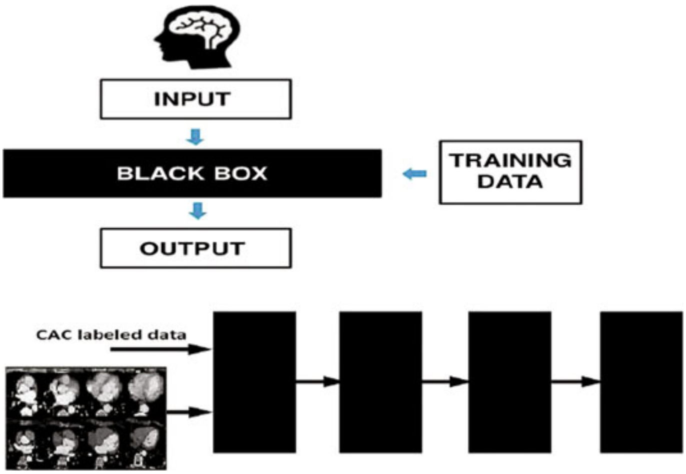

Fig. 12 Deep learning: a black box

5.5 Privacy and Legal Issues

Data privacy is affected by issues, both sociological and technical, that need to be addressed jointly from both sociological and technical perspectives. The HIPAA comes to mind when privacy is discussed in the health sector. It provides legal rights to patients regarding their personally identifiable information and establishes obligations for health care providers to protect and restrict its use or disclosure. With the increase of health care data, anonymizing patient information to prevent its use or disclosure presents a major challenge for researchers. Unfortunately, restricted access to data also reduces the information content, which could be very important. Furthermore, real data is not static; its volume is constantly increasing and changing over time, meaning that current methods are not sufficient for its proper handling.

6 Conclusion

During recent years, deep learning has gained a central position with regard to the automation of our daily life and has delivered considerable improvements in comparison with traditional machine learning algorithms. Based on their tremendous performance, most researchers believe that, within next 15 years, deep learning-based applications will take over from humans in certain roles and that most daily activities will be performed by autonomous machines. However, the penetration of deep learning into health care, especially in medical imaging, is taking place slowly compared with other real-world problems. In this chapter, we have highlighted the barriers that are reducing the growth of deep learning in the health care sector. In the final section, we highlighted state-of-the-art applications of deep learning in medical image analysis. Although the list is by no means complete, it provides an indication of deep learning's far-ranging impact in the medical imaging industry today. Finally, we highlighted the open research issues.

Many big research organizations are working on deep learning-based solutions that encourage the application of deep learning on medical images. Looking to the brighter side of machine learning, we are hoping that humans will soon be replaced in most medical applications, especially diagnosis. However, we should not consider it as the only solution; there are several challenges reducing the expansion of deep learning. One of the major barriers is the unavailability of annotated datasets. Thus, it remains to be seen whether we will be able to obtain enough training data, without which the performance of deep learning algorithms will be affected. Recent developments on other applications have shown that the bigger the data, the better the result; however, how much big data could be used in health care.

So far, deep learning-based applications have provided positive feedback. However, due to the sensitivity of health care data and a variety of challenges, we should look at more sophisticated deep learning methods that can deal with complex health care data efficiently. We conclude that there are unlimited opportunities for the improvement of the health care system through the use of deep learning-based systems.

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