ON THE USE OF DEEP LEARNING METHODS ON MEDICAL IMAGES

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ABSTRACT: Deep Learning algorithms have recently been reported to be successful in the analysis of images and voice. These algorithms, specifically Convolutional Neural Network (CNN), have also proven themselves to be highly promising on images produced by medical imaging technologies, as well. By use of deep learning algorithms, researchers have accomplished several tasks in this field including image classification, object and lesion detection and segmentation of different tissues in a medical image. Researchers mostly focused on medical images of neurons, retina, lungs, digital pathology, breast, heart, abdomen and skeleton system to take advantage of the Deep Learning approach. This study reviews literature studies of recent years that utilized Deep Learning algorithms on medical images in order to present a general picture of the relevant literature.

Keywords: Deep Learning, medical images, CNN

INTRODUCTION

Medical images, produced by highly specific equipment, can also be stored on a computer in the digitized form which provides an opportunity to analyze these images by use of computer programs. Early systems to process and analyze these images were rule-based expert systems that could only work with low-resolution images. These expert systems were called GOFAI [1].

Introduction of machine learning based intelligent systems to the field was not too late and they quickly became widespread. The quality of these systems mainly depended on extracting meaningful features from the given image. Extracting good features, namely feature engineering, is a vital task in every machine learning process and still an important research topic among the machine learning community. Deep Learning (DL), actually a subset of machine learning algorithms, has improved learning systems that required good features to be manually picked by researchers out of the dataset usually by trial-and-error to a more automatic system in which good features are extracted from the dataset automatically by the algorithm itself. Convolutional Neural Network (CNN) is one of the most popular DL algorithms that is capable of extracting features from the given images without user intervention [9].

The very first studies that used CNN were published in late 70s [2] while one of the first study that applied CNN over medical images was accomplished by Lo et al. [3] roughly 2 decades later in 1995. First reported successful DL application was LeNet [4] which was designed to recognize handwritten characters. Time elapsed from the first introduction of CNN to a successful application was unexpectedly long because DL in general required advanced hardware and software systems to function properly. The study of Krizhevsky et al. [5], namely ImageNet, published in December, 2012 has been a milestone for both DL algorithms and specifically CNN. In the following years, more advancements have been obtained by using deeper learning structures [6].

A more recent CNN architecture called AlexNet has now been considered as the state-of-art algorithm in the relevant literature to accomplish classification tasks on image data. AlexNet has utilized many techniques to be able to extract good features from the image automatically. Bengio et al. have reviewed these techniques in their paper [7]. Ravi et al. [8] considered AlexNet along with other DL studies for their use in the field of health, especially on medical images. A specific research to study DL on medical images was conducted by Shen et al. [10]. In their paper, they reviewed a lot of articles from the relevant literature but did not mention some of the prominent studies in the field such as studies applied DL to analyze retinal images.

It is very hard to extract features from an MRI image to feed a traditional artificial neural network (ANN). Thus, DL is advantageous over classical ANN because it provides automatic feature extraction [11, 12]. With CNN, more complex features can be extracted in a hierarchical manner. Studies that applied CNN to medical image analysis, for instance, to classify lung diseases by using Computer Tomography (CT) images [13], to detect tuberculose in X-ray images [14], to classify neurons [15], to detect bleeding in the color retinal images [16] and to anatomically classify specific organs or body parts in CT images [17].

This study aims to deliver a view of DL applications in the field of medical imaging analysis. To this end, relevant studies in the literature, with a focus on the most recent ones, are considered and summarized through the paper. Through this analysis, the advantages of and the problem related to the DL approach when used on medical images will also be discussed as well. Therefore, the study aims to provide a general picture of DL application in the field that covers general trends, advantages, disadvantages, problematic aspects of these applications so that researchers who want to conduct a study in the field may benefit.

1. An Overview of Deep Learning

Even though, DL is considered as a subset of machine learning algorithms and shares many common aspects with it, it has some differences that diverge it from the traditional machine learning approach. The most significant difference is that machine learning algorithms require the features to be picked manually to feed the algorithm whereas in DL these features are detected automatically by the algorithm. Furthermore, DL adopts a hierarchical learning methodology. After high-scale data sources and more advanced hardware/software opportunities required for DL have been available to public, DL has increasingly been used for medical image analysis, as well. In this section, RNN and CNN, mostly used DL architectures for medical image analysis, will be explained shortly.

1.1. Convolutional Neural Network (CNN)

CNNs are designed to process data types that inherently consist of multiple dimensions such as two dimensional images. Their architecture has some elements inspired from the visual cortex of a human in which there is a hierarchy of simple and complex cells [18]. Simple cells in the cortex respond to simple patterns in the lower regions of the visual receptors whereas complex ones combines information acquired from the simple cells to recognize more complex patterns [19].

The basic CNN architecture consists of convolution layer, non-linear layers and a pooling layer (See Figure 1).

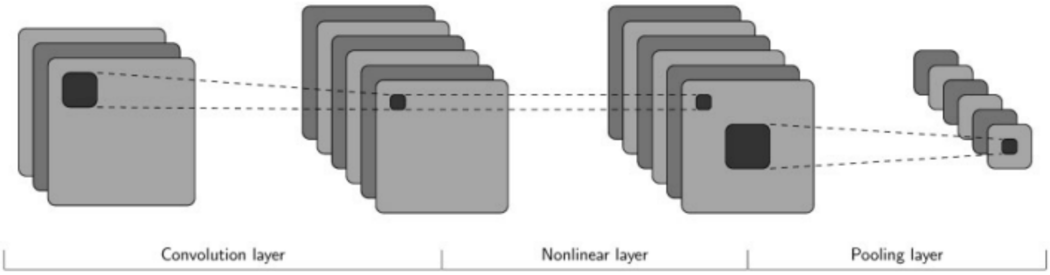

Figure 1. Basic building blocks of a CNN [20]

Even though traditional ANN (e.g., Multi-layer perceptron) and CNN have common properties, there are two main differences between them. Firstly, CNN, as the name suggests, does convolution operation over the given images in a way that features of the object in the image can be learned through each convolution transformation. More formally, all convolution layers does a transformation via parameters $W = W_1, W_2, \ldots., W_K$ with bias $B = \{b_1, \ldots., b_K\}$. Then the feature map X is obtained via the non-linear transformation function σ (·) [9]:

$$X_k^l = \sigma(W_k^{l-1} * X^{l-1} + b_k^{l-1}) \qquad (1)$$

The second difference between MLP and CNN is that CNN has special layers called pooling layers through which weights are shared across layers. At the end of a CNN pipeline, there is generally a fully-connected layer which resembles the classic MLP structure (See Figure 2).

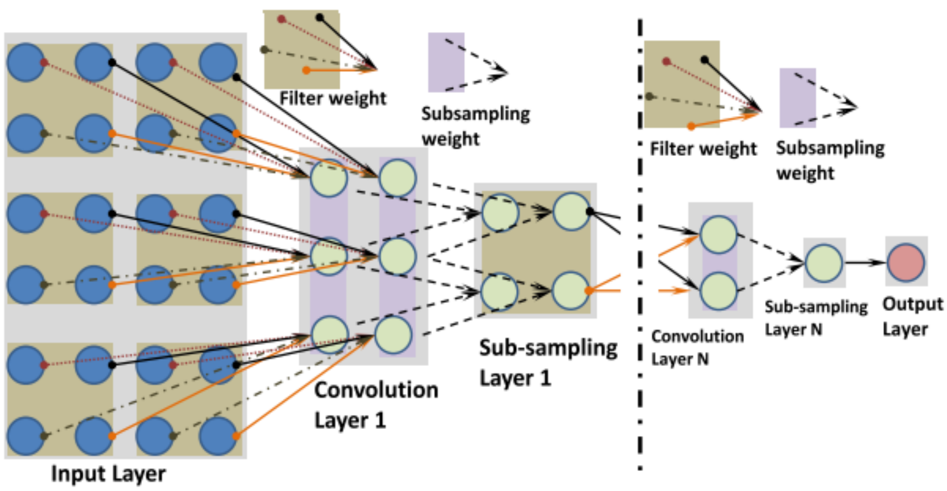

Figure 2. CNN architecture [8]

The model developed by Fukushima in 1980 to mimic human visual system (Neocognitron) can be considered as a simple version of CNN [21]. LeNet, a more successful CNN model developed by Le Cun et al. [22], was utilized to recognize handwritten digits with an architecture made up of 1 input, 3 hidden and 1 output layers.

1.2. Recurrent Neural Network

Recurrent Neural Network (RNN) is a model that was mainly developed for the task of analyzing discrete arrays of data. Moreover, it can be considered as a generalization of MLPs because both input and output values may be of different lengths [9]. Designed to process sequential data, RNNs have a structure of circular connected nodes (See Figure 3). Unlike the feed-forward ANNs, RNNs can use the output of the network as an input to process sequential data [23]. Past output data is stored on some hidden neurons called the state vectors and next output is calculated with the consideration of inputs from these neurons [24].

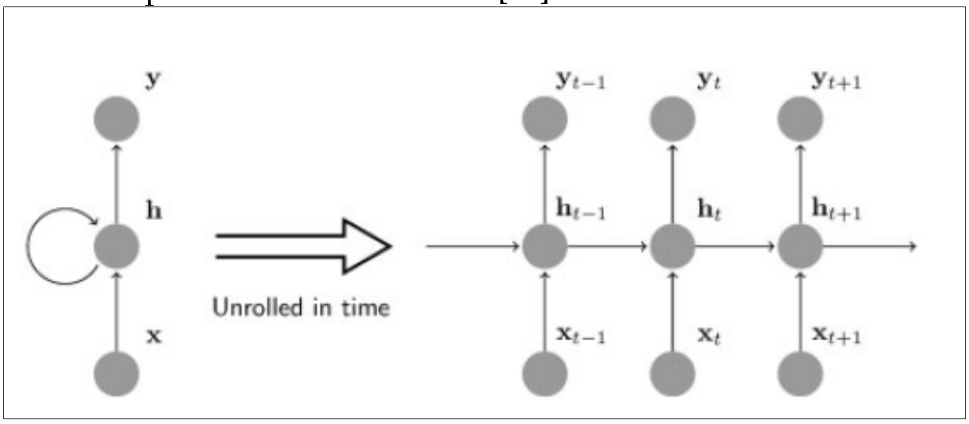

Figure 3. Basic structure of an RNN with an input unit x, a hidden unit h and an output unit y [24]

As past and future input values can be used in various ways to affect the value of the output, new recurrent architectures as an improvement to the original RNN are also introduced in the literature. Bidirectional Recurrent Neural Network (BRNN) [25] is one of the most popular of these new additions and has gained widespread use in the relevant literature (See Figure 4).

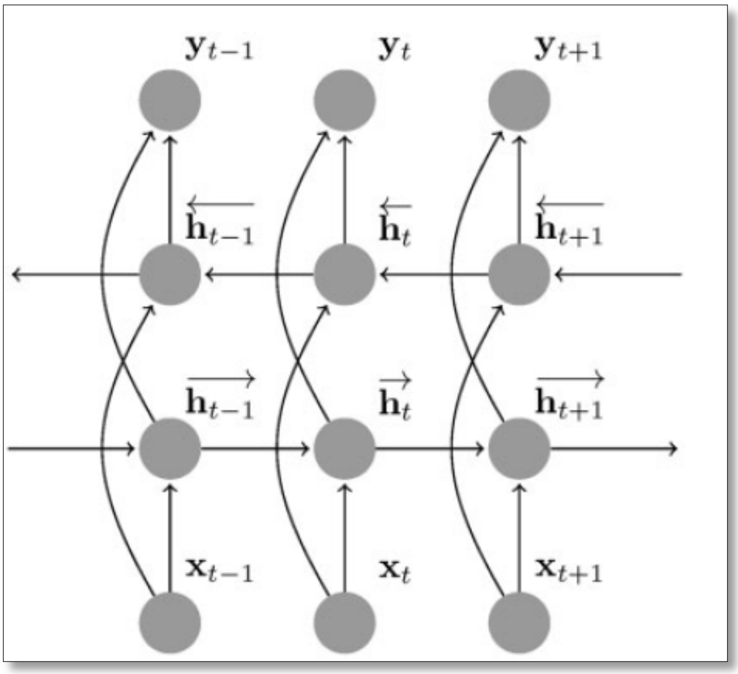

Figure 4. Basic structure of a BRNN [25].

Rather than being sequential, images are generally considered as a kind of data containing inner correlations and spatial information about pixels. Therefore studies that take biomedical images as non-sequential data more often utilized DNN or CNN instead of RNN [19]. By using improved versions of RNN, researchers have recently paid increased attention to RNN for the purpose of image based recognition. For instance, Multidimensional Recurrent Neural Network (MDRNN) [26] has been applied to three dimensional images. Furthermore, Stollenga et al. [27] implemented a MDRNN based solution to segment neural structures in MRI and three dimensional electron microscope images.

Biomedical signals are inherently sequential data and hence RNNs, an appropriate DL structure to process sequential data, are expected to produce promising results with biomedical signal data. In this sense, brain code deciphering [28] and anomaly classification studies [29, 30] have been conducted. Additionally, Petrosian et al. [29] performed feature extraction from raw EEG signals by using wavelet decomposition method and fed a RNN with this input data to detect sudden disease seizures.

2. Types of Medical Images

There are various imaging modalities in the medical field and use of these technologies have been increasing continuously. Henceforth the amount of data produced by these equipment has also been on the rise, as well. Thus processing medical images by using DL, as an approach requiring great amount of data to operate more successfully, has been gaining more attention as the amount of data increases continuously.

Smith-Bindman et al. [31] has investigated the use of medical imaging technologies over the data of top six health systems in the USA that contained 30,9 million medical images collected and viewed between 1996 and 2010. According to their report, CT,

MRI and PET use has been increased in the mentioned period of time by 7.8%, 10 and 57 respectively.
Digital medical imaging modalities include but not limited to ultrasound (US), X-ray, computerized tomography (CT) scans, magnetic resonance imaging (MRI), positron emission tomography (PET) scans, retina photography, histology slides and dermoscopic images. Figure 5 presents some of the images taken by these technologies [32].

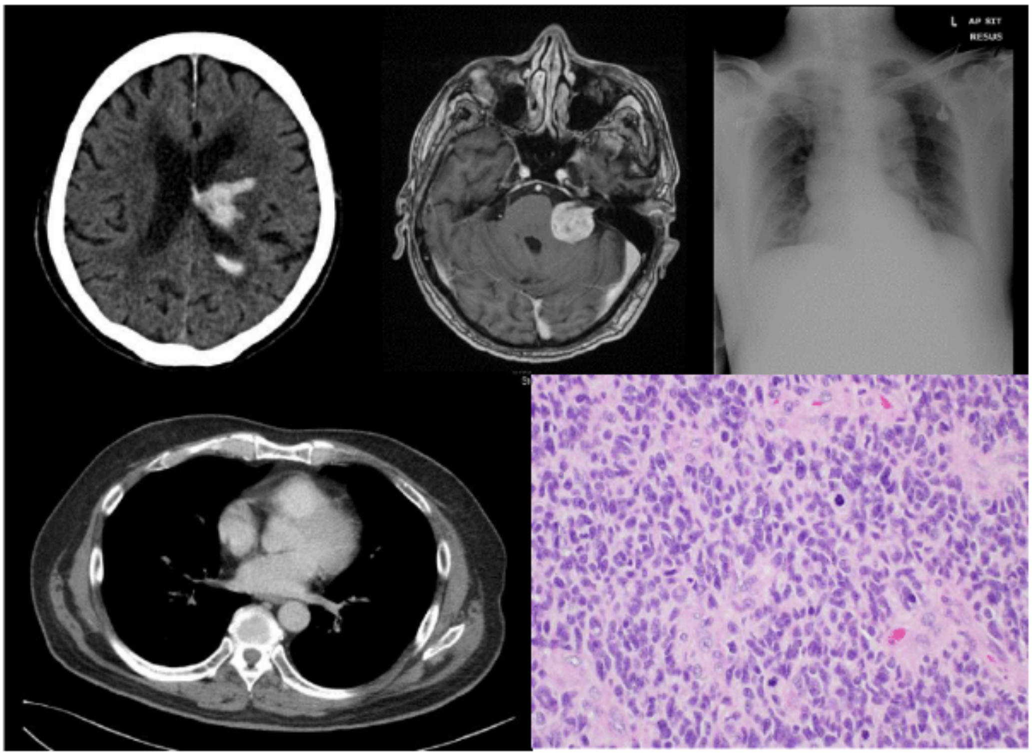

Figure 5. Images from some medical imaging modalities [32].

Some modalities are used to capture a specific organ (e.g., retina and dermoscopic photography) while some others can analyze multiple organs at once (e.g. CT and MRI). Expectedly, the amount of data produced by each imaging technology differs significantly, e.g., a histology slide is an image up to a few megabytes in size whereas an MRI file may occupy a few hundreds of megabytes of disk space.

3. Deep Learning Applications on Medical Images

CNNs are in general used for the tasks of classification, localization, detection, segmentation and registration over medical images.

3.1. Classification

The classification task is also known as Computer Aided Detection (CAD). Lo et al. [33] used CNN to detect lung nodules in breast X-ray photographs. In order to detect whether there is a lung nodule in a region or not, they used a CNN with two hidden layers that was trained by using 55 X-ray photographs. As a result, they reported that DL helped to achieve improved classification rate for this task.

Rajkomar et al. [34], classified 1850 breast X-ray photographs by a CNN trained with 150.000 training samples. The direction of the image was predicted with a nearly perfect accuracy by a modified version of GoogleNet CNN [35].

Pneumonia or breast infection, is a globally widespread health problem. Rajpurkar et al. [36], has successfully classified 14 different diseases in breast X-ray photographs. They trained the network with 112.000 samples taken from the ChestXRay [37] dataset. Their network, namely CheXNet, contained 121 convolutional layers and was actually a modified version of DenseNet [38].

Hosseini-Asl et al. [39], detected the patients with Alzheimer's disease at an accuracy of %99. They used several of 3D CNNs connected in an autoencoder architecture predefined in the CADDementia dataset to map the general structure of the brain.

Korolev et al. [40], proposed two different neural network architectures to evaluate their performance on Alzheimer’s disease data. The first method, VoxCNN, shared a similar architecture with VggNet [41] while the second one, VoxResNet, a ResNet architecture, was a Residual Neural Network. Samples from Alzheimer’s Disease Neuroimaging Initiative (ADNI) database were used to classify diseased and normal MRI scans. Even though the reported performance was lower than that of some literature methods, such as study of Hosseini-Asl, Korolev algorithm had advantages like being simple to apply and not requiring manual fine-tuning of parameters.

Diabetic retinopathy (DR) is another disease that could be successfully diagnosed by use of CNNs. In the study of Pratt et al. [43], a CNN consisting of 10 convolutional and 3 fully-connected layers, was trained using nearly 90.000 digital eye fundus photographs to detect the eye problem. In addition to that study, Abramoff et al. [44] evaluated the commercial device IDx-DR version X2.1 to detect DR. With this device, they have been inspired by AlexNet and VggNet to analyze 1.2 millions DR images. As a result, they reported an accuracy of 98%.

The methods mentioned so far are all supervised learning methods. Another major machine learning approach, unsupervised learning, is also an active research topic in the context of medical image analysis by use of DL. For instance, Plis et al. [45], employed Deep Belief Networks (DBN) to extract useful features from MRI images of patients having Huntington disease and schizophrenia. Likewise, Suk et al. [46] used Restricted Boltzmann Machines (RBM) to reveal relationships among different parts of the brain in fMRI images so that patients with Mild Cognitive Impairment (MCI) could be detected.

Lastly, Kumar et al. [47], evaluated performances of state-of-art CNN architectures, AlexNet and VggNet, by using Bag of Visual Words (BOVV) and Local Binary Patterns (LBP). The BOVV technique was observed to be the best in classifying histopathologic images into 20 different tissue types.

3.2. Detection

Accurately detecting a lesion in a scan (e.g., MRI scan) is utterly important both for the patient and the clinician. In the relevant literature, studies aiming at detecting this kind of anomaly are sometimes called as Computer Aided Detection (CADE) methods. The well-known Kaggle Data Science competition in 2017 [48] called for competitors to detect malignant lung nodules in CT scan images. All competing algorithms was run against a dataset including nearly 2000 CT scans and eventually Liao et al. [49] won the prize. In order to detect the nodules, they adopted an approach of primarily isolating local regions by use of a 3D CNN, which was inspired by the architecture of U-NET [50].

Shin et al. [51], evaluated five well-known CNN architectures for the task of detecting lymph nodes and cancerous lung tissues in scan images. Detecting abnormal lymph nodes is important because they may be sign of infection or a cancer. They emphasized the benefits of transfer learning and concluded that high number of layers may improve accuracy which appears to be in contrast with the norm of preferring lower number of layers in medical image analysis.

Overfeat [52] is the CNN architecture that won the ILSVRC 2013 localization competition. Ciompi et al. [53] utilized Overfeat to estimate the presence of nodules in two dimensional CT scans of lung fissures. Additionally, Esteva et al. [54], utilized another proven CNN, namely GoogleNet Inception V3, on 130.000 dermatologic and dermoscopic photographs in order to detect skin diseases.

There are also numerous studies on the use of CNN with histopathologic images. Ciresan et al. [55], employed a CNN of 11 to 13 layers in order to recognize mitotic figures in a collection of 50 breast histology images taken from the MITOS dataset. Moreover, Yang et al. [56], utilized a CNN consisting of 5-7 layers to classify whether histopathologic images contain a tumor or not, and achieved an accuracy of 97% at this task. Sirinukunwattana et al. [57], used CNN to determine the cell nucleus in a total of 100 colorectal adenocarcinoma histology images. Similarly, Xu et al. [58], implement a method based on Stacked Sparse Auto-Encoders (SSAE) to detect the nucleus in breast cancer histologic slides. In this context, some researchers like Albarquoni et al. [59] discussed lack of insufficient labeling of medical images.

3.3. Localization

Yan et al. [60], considered widthwise CT scan slices and implemented a two-phase CNN architecture that in the first phase defines the local parts and determines several body organs in the second phase. The proposed CNN architecture was reported to outperform standard CNN structures. Rath et al.[61] utilized almost 4000 widthwise CT scans to distinguish 5 categories of body parts (neck, lung, liver, pelvis and legs) from each other by use of a CNN that consists of 5 conventional layers. Shin et al. [62], has successfully found localization of liver, heart, kidney and spleen from 78 high-contrast MRI images by use of Stacked Auto Encoders (SAE). They reported that the proposed scheme learned spatial and temporal features automatically and resulted in an accuracy ranging between 62% and 70% depending on the organ.

3.4. Segmentation

Even though segmentation oriented studies considered several organs such as liver and prostat, the relevant literature generally focused on performing brain segmentation. Automatic segmentation is a vital task because determining borders of a segment in the image, such as boundaries of a tumor, is crucial in planning the surgery and preventing surgical resection. Akkus et al. [63] evaluated several CNN architectures and performance metrics for the task of segmenting brain in MRI images. Moeskops et al. [64], utilized 3 CNNs, each of which has different two dimensional input patches, in order to classify and segment different tissues such as white matter, gray matter and cerebrospinal fluid in the MRI images of 22 premature babies and 35 adults.

Preira et al. [65], focused on deeper CNN architectures with 11 layers. In order to prevent common problems with deepers networks such as overfitting, they used small filters of 3x3 size. Havaei et al. [66], considered gliomas and evaluated performances of two-dimensional CNN architectures over BRATS 2013 dataset. Chen et al. [67] proposed to use up-sampling filters, atrous spatial pyramid pooling and conditional random fields (CRFs) in order to enhance the performance of CNN for medical image analysis. Casamitjana et al. [68], compared several three dimensional CNN architectures. Brosh et al. [69], utilized a multi-scale architecture to segment brain lesions in the MRI images.

3.5. Registration

Image registration is the task of aligning multiple medical images of a patient from different times or of different patients or of a patient from different modalities. Aligning different medical images serves as a tool to ease the clinical decision making. El-Gamal et al. [70] evaluated current available methods in image registration and discussed their effectiveness and use in appropriate clinical environments. In the relevant literature, image registration task is generally considered as an optimization problem where the task is to minimize a cost function which depends on a metric that measures the similarity of images to be aligned. Use of DL or even ANNs is relatively new to this field. Yang et al. [71] utilized a SAE with convolutional layers to predict the final configuration of an input pixel in the alignment. They proposed to use the Large deformation diffeomorphic metric mapping technique in order to reduce the computational burden and speed-up the process. Moreover, Miao et al. [72], stored 3D models of some equipment such as knee and hand implants onto 2D X-ray images, and attempted to predict the final position of the equipment by use of a 5-layered CNN.

CONCLUSION

This study aims to provide a general view of DL applications in the field of medical image analysis. Up to recently, traditional machine learning methods have suffered from the lack of large amount of labeled data to properly train and test learning algorithms. Sun et al. [73], utilized a dataset of 300 million images obtained from

Google and observed that more data improves the performance of the algorithms. In the field of medical image analysis, there is in general a deficiency of public and carefully labeled data. Cho et al. [77], focused on the matter and discussed how much data may suffice to properly train an algorithm for the purpose of medical image analysis. Some generative models such as Variational Autoencoders (VAEs) and Generative Adversarial Networks (GANs) attempt to generate artificial medical data in order to overcome the problem. Guibas and Virdi [78] utilized the artificial data population methods and implemented a two-phase segmentation method that was reported to be successful in generating retinal fundus images. Likewise, Costa et al. [79], utilized GANs to generate artificial retinal fundus images. In addition to generating artificial data, GANs are used by Moeskops et al. [80], Kamnitsas et al. [81] and Alex et al. [82] for other purposes such as MRI segmentation.

As a result, if recent studies are considered, the performance of machine learning methods specifically DL is observed to be satisfactorily good and sometimes even superior to human performance in image analysis tasks. And medical image analysis, as a sub-field, also benefits from this advantage, as well.

In the future, research in the medical image analysis field is expected to continue with tasks of prediction [84], content-based image acquisition [85, 86], image reports or subtitle generation [87, 88], manipulation of physical objects [89, 90] and surgical robots [91, 92].

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