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Deep Learning based algorithm for Detection of Diabetic Retinopathy

Dr. Saranya K S
Assistant Professor II
Bannari Amman Institute of Technology, Sathyamangalam,
saranyaks@bitsathy.ac.in

Lakshmanan N
UG Scholar, CSE
Bannari Amman Institute of Technology, Sathyamangalam,
lakshmanan.cs19@bitsathy.ac.in

Mathivanan S
UG Scholar, CSE
Bannari Amman Institute of Technology, Sathyamangalam,
mathivanan.cs19@bitsathy.ac.in

Logeshwaran M
UG Scholar, CSE
Bannari Amman Institute of Technology, Sathyamangalam,
logeshwaran.cs19@bitsathy.ac.in

***Abstract*—Diabetic retinopathy (DR) is one of the leading causes of avertible blindness worldwide. Early detection of the disease can help to save the vision of diabetic patients. Presence of exudates, hemorrhages, and microaneurysms indicate an unhealthy eye image. Deep learning models have triumphedin image recognition, object detection and biomedical signal classification. Convolution neural network based DR detection techniques are fast evolving and can identify complex features and thus can accurately classify even severe cases. The presented paper investigates the recent work done in diabetic retinopa- thy detection using deep learning and collating the milestones achieved to guide researchers working in this domain to the future trend.**

***Index Terms*—Deep learning, Machine learning, Diabetic retinopathy, Convolutional neural networks, Review**

I. INTRODUCTION

Diabetic retinopathy (DR) is a complication of diabetes, which is currently the leading cause of preventable blindness across the globe. It affects the vision of the subject. Normally DR is common in people with type-2 diabetes (40%) compared to T1D (20%) [1]. The screening/diagnosis of this pathologyis done via visualizing retinal images captured by fundus cameras or OCT imaging systems, capturing either a 2-D fundus retinal image or a 3-D optical coherence tomography (OCT) image respectively. Structures in a fundus image that are relevant to DR are optic disc (OD) or optic nerve head (ONH), retinal vessels, macula, fovea, haemorrhages, micro-vascular lesions and exudates (soft and hard exudates). These are shown in Fig.1 In a fundus image, this is identified by the presenceof hard exudates within 1 optic disc diameter (1ODD) of the fovea. Fig. 2 shows retinal fundus images from each of these different DR categories. Most people affected by DR approacha specialist or ophthalmologist only after the DR status reaches the severe NPDR or PDR stage. This is due to the fact that there are practically no visible clues present at earlier stagesof DR. Different classes of DR are presented in Fig.2

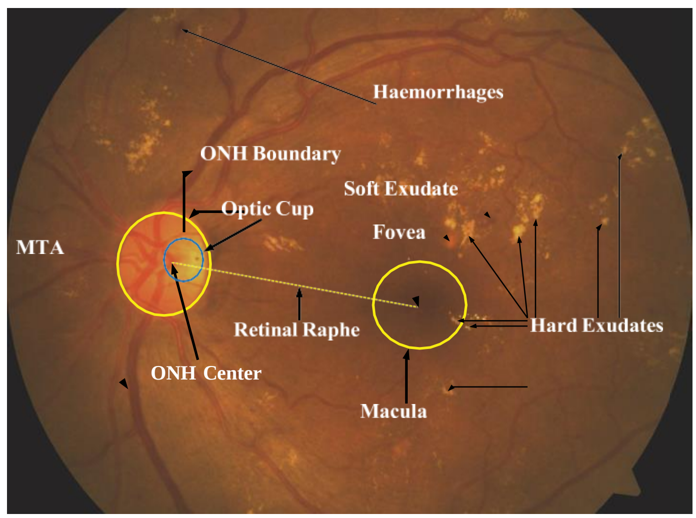

Fig. 1. Structures relevant to DR in a fundus image [2].

Hence it is important to develop automatic screening sys- tems that could easily be accessed to screen the presence of DR at earlier stages. This research area has been widely studied in the past 10 years and many state-of-the-art methods based on various image processing algorithms exist to address this important problem. A vast majority of these methods are based on conventional machine learning concepts that focus on extracting features from the retinal images (both fundus and OCT images) and using certain classifiers, like support vector machines (SVMs), k-nearest neighbours (k-NN) etc, to classify the DR affected retinal images. These methods require image specific information for defining and extracting features. With the success of AlexNet in 2012 ImageNet Large Scale Visual Recognition Challenge.In this paper we discuss the state-of- the-art fundus image based DR classification methods using deep learning approach.The paper is organized as follows: next section details the fundus retinal image databases available for the DR classification problem .

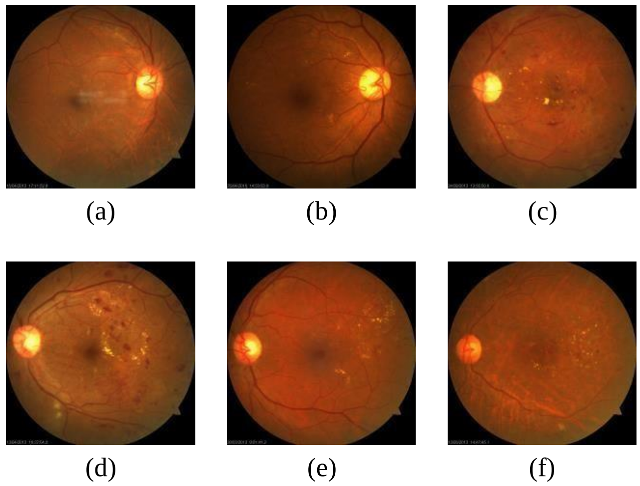

Fig. 2. Stages of DR (a) Mild NPDR (b) Moderate NPDR (c) PDR withNVD and DME (d) PDR with NVD, NVE & DME (e) Severe NPDR (f) Very severe NPDR (images taken from UoA-DR database [3], [4])

Section III discusses various performance metrics used for reporting the performance of various DR classification methods. Section IV gives a brief description about three commonly used convolutional neural network architectures in the field of fundus retinal image processing. Section V provides a detailed review of various state-of-the-artdeep learning based methods used in DR screening. SectionVIconcludes the paper and envisages the future prospects in this field of research.

II. Available Datasets

Deep learning requires the well trained network be exposed to at least thousands of images, else the details which differentiate the weights of the network can't capture the classes. In this paper, we focus on deep learning based DR screening algorithms which use fundus images. Fundus photography captures the back of an eye, also called a fundus. This is done through a specialized camera known as the fundus camera. A fundus image contains macula, optic disc, blood vessels, and other structures as shown in Fig. 1. There are several publicly available datasets with fundus images used for validating automatic DR detection models. In deep learning approaches, the image dataset is split into training and validation; training datasets are used to train a network. After a network is trained, test dataset is employed to evaluate the performance of the network. It is common to use two different datasets for testing and training a deep convolutional neural network (DCNN), and this is usually done to get a better understanding of network performance when previously unseen images are exposed. Not all the images from the dataset are used, some poor-quality images can degrade the trained network, Thus it is always recommended to quantify the quality of the images in the dataset before using it for DR training or testing. Normally, networks perform better after the removal of poor quality images from the training and validation set. This is similar to the data cleaning process in a conventional deep learning domain.

TABLE I
Commonly used Datasets

S.No	Dataset	Number of Images
1	Messidor	1200
2	e-Ophtha-MA	381
3	e-Ophtha-EX	82
4	DIARETDB	219
5	Kaggle	80,000
6	ROC	100

The commonly used datasets in DR detection research areas follow.

A. *Messidor*

The Messidor database is publicly shared with 1200 fundus images and was acquired by three ophthalmologic departments. 800 of these images are obtained with pupil dilation and 400 without [5]. Ground truth marking is not done for this dataset ,instead the dataset comes with an excel file which contains the grading information of each image.

B. *e-Ophtha*

This dataset is majorly used for developing algorithms designed for developing detection of lesions (exudates and microaneurysms) this dataset is divided into two separate datasets, e-Ophtha-EX for exudates and e-Ophtha-MA for microaneurysms [6].

C. *DIARETDB*

DIARETDB is a public database that has been used as a benchmark for automatic diabetic retinopathy detection from fundus. The dataset comes with ground truth marking, microaneurysms, hemorrhages, and exudates areas are labeled [7].

D. *Kaggle*

This dataset was provided as part of Kaggle Diabetic Retinopathy Detection competition. The images in this dataset are not taken in a controlled lab environment, so most of the images are subject to having low contrast. The images in the dataset are scaled by an expert clinician on a scale of 0 to 4.

E. *ROC*

ROC database is a dataset which contains 100 fundus images collected during a DR screening program [8].

TABLE I illustrates the commonly used datasets and their corresponding sizes.

III. PERFORMANCE METRICS

For the detection of DR, the fundus images captured undergo an additional step called pre-processing. Most of the pre-processing steps include contrast enhancement, median filtering, and adaptive histogram equalization. In the applications related to the medical field, the data is frequently

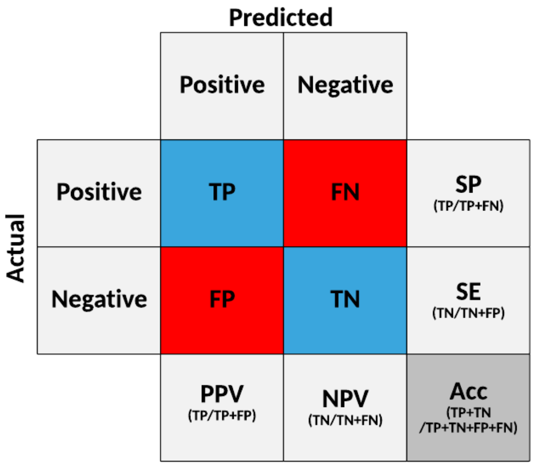

Fig. 3. Confusion Matrix.

divided into two types: healthy and unhealthy, and the same is applicable for DR detection. Deep learning models are usually used for solving classification problems. However, to evaluate a classifier there are only few standard metrics. The correctness of an algorithm is reviewed by analyzing the following metrics:

- True positive (*TP*) = total number of correct identifications as unhealthy
- False positive (*FP*) = total number of incorrect identifications as unhealthy
- True negative (*TN*) = total number of correct identification as healthy
- False negative *FN*) = total number of incorrect identification as healthy

The algorithms reviewed in this paper use performance metrics like sensitivity or true positive rate (SE or TPR) [9] [10], specificity or false positive rate (SP or FPR) [9] [10], and accuracy (Acc) [9] [10], positive predictive value (PPV) [9] [10], negative predictive value (PPV) [9] [10], and area under curve (AUC) characteristic [9] [10]. Some algorithms also preferred the usage of F1-score (F1) [10] as a performance metric over the others.

A classification problem also uses a confusion matrix to understand the classifiers performance. It is a table witha combination of TP, FP, TN, and FN. Formation of the confusion matrix is an easier way of evaluating performance. Values like Acc, PPV, AUC, SP, and SE can be obtained easily. Fig. 3 illustrates an example of the confusion matrix.

The formulas for each of the metric used in detection algorithms are as follows

$$SE/TPR = \frac{TP}{TP + FN} \tag{1}$$

$$SP/FPR = \frac{TN}{TN + FP} \tag{2}$$

$$Acc = \frac{TP + TN}{TP + TN + FP + FN} \tag{3}$$

$$PPV = \frac{TP}{TP + FP} \tag{4}$$

$$NPV = \frac{TN}{TN + FN} \tag{5}$$

$$AUC = \int_{\infty}^{-\infty} TPR(T)FPR(T)dT \tag{6}$$

$$F1 = \frac{2TP}{2TP + FP + FN} \tag{7}$$

IV. Convolutional Neural Networks

In recent years usage of convolution neural networks or CNNs for image classification has become quite popular. The success of LeNet, a CNN used for classifying digits showed that CNNs could be used in solving various vision tasks [11]. Large-scale image recognition tasks were made easy using CNNs [12]. A deep convolutional neural network was trained to classify 1.2 million images present in ImageNet [13],[14]. Also, CNNs computationally have fewer connections as compared to fully connected architectures and thus areeasier and faster to train [12]. To prevent the networks from overfitting, dropout notion was introduced [15] and to address the internal covariate shift,batch normalization was added to the network designing [16], which led to good performing CNNs. CNNs training usually takes a lot of time which can be reduced by using a few high-end GPUs (GraphicsProcessor Units) [17]. The building components of a CNNare the convolutional, subsampling, max pooling, and batch normalization layers. We will explore a few convolutional neural network architectures as transfer learning is becoming quite popular. Transfer learning is where features defined by all layers are intact, but the final few layers are re-trained with minimal problem-specific dataset which reduces both training and network designing time.

A. AlexNet

It was first used in ImageNet competition [13], which triggered the interest of the computer vision community to focus on improving CNN design for image recognition challenges. This architecture had five convolution layers, three pooling, and two fully-connected layers. AlexNet has inspired several CNN architectures, even now it is being used by transfer learning.

B. GoogLeNet/Inception

The GoogLeNet model was first used in [17]. This network architecture is quite complex and deep. It introduced a new layer called Inception. Each Inception layer consists of six convolution and one pooling. Recently GoogLeNet has gained popularity due to its network architecture and usage in several data science challenges. Several versions of GoogLeNet are available and can be used for image classification.

C. VGGNet

A neural network that secured first place in ImageNet competition of 2014 [12]. VGG stands for Visual geometry Group, the structure was designed to find how depth of a network influences it's accuracy. This network could be used for image localization and classification tasks. VGG-M and VGG-VD-16 are products of this research group.

V. Deep learning algorithms for diabetic retinopathy screening - A comprehensive review

Deep learning algorithms are initially considered as a subset of machine learning. However, it has been developed to offer more than what machine learning can do. Deep learningis composed of multiple processing layers which learn data representations; each layer learns different aspects of the data [18]. These multiple processing layers are after naming the network as deep, and this deep architecture is used for solving artificial intelligence problems [19]. Research in deep learning has brought several network architectures like Convolutional Neural Networks (CNNs), Deep Belief Networks (DBNs), Deep Boltzmann Machines (DBMs) and Recurrent Neural Networks (RNNs) [12].

In this paper a systematic review was done on neural networks based algorithms. This sections discusses some key approaches and techniques used for automated DR detection systems.

A. Neural Network Based Detection

Gardner *et al.* in 1996 [20] verified the usage of the neural network over manual grading by an ophthalmologist. This model was utilized to distinguish two classes and was also able to recognize common features in the diseased eye like vessels, exudates, and hemorrhages.

Nayak *et al.* in 2008 [21] also used a neural networkfor three-class classification of DR. The model had three stages image pre-processing, feature extraction followed bya neural network for classification into normal, PDR and NPDR classes. Ting *et al.* in 2017 [22] developed a deep learning system (DLS) consisted of a CNN. The DLS was tested on a multi-ethnic population to generalize the use of an automated system. This model achieved high sensitivityand specificity for identifying diabetic retinopathy, glaucoma, and age-related macular degeneration. Pratt *et al.* in 2016 [23] designed a CNN structure composed of ten convolution layer network, convolution blocks at the start of the layer each have an activation function, batch normalization layerand a max pooling. Drop out is used on dense layers to avoid overfitting. Kaggle dataset served as a primary database for training the model, which was trained on a single GPU. This model achieved lower sensitivity which is quite common fora five-stage classification.

B. Masking Based Detection

Few algorithms enhanced their results by image pre-processing before applying the images to a CNN. Masking techniques are used to strengthen the algorithms. Masking of OD and macula are common, and bright traits like these can degrade images and limit the performance of the classification model. DR classification masking is a standard pre-processing step. Masking of the optic disc is also used frequently to increase the classification performance. Adem, 2018 [24] used canny edge detection and circular Hough transform for masking of OD. OD masked images are trained using a CNN model to classify exudate and non-exudate images. The implemented CNN consisted of three convolution layers with max-pooling. This algorithm attained better results when compared with a CNN-only model for classification and it outperformed the usage of the classical machine learning algorithms fordetection as an alternative. This approach gave better results when it was evaluated as a binary classifier for healthy and unhealthy classification.

C. Multi-stage CNN

Perdomo *et al*. [25] developed an Exudate Detection (ED)-DME classification which is a two-stage classification of DME. This model composed of two CNNs, one for ED and another for DME staging. This model comprises a four-class classifier which can detect the regions related to exudates fromthe input fundus images to classify into no sign, mild, moder- ate and severe DME. A pre-processing step is also included to extract the region of interest from fundus images to prepare forthe ED stage. CNN for ED stage is composed of 8 layers with convolutional, max pooling and fully connected layers whereas the DME detection is based on an AlexNet architecture with 17 learned layers with convolutional, normalization and fully connected network. Training and validation were done using e-Ophtha and Messidor datasets. ED-DME model performed reasonably when compared to a single stage DME model.

D. Pixel-wise Detection

There are some deep learning-based algorithms which use the region or pixel-wise classification. Instead of training a CNN with a whole image, it is only exposed to patches of the images or sometimes each pixel to classify weather it isa diseased pixel/region. The output for these algorithms is a probability map. These algorithms are focused on attaining higher probabilities in identifying diseased prone regions of the fundus image.

Shuang Yu *et al*. in 2017 [26] developed a CNN model for pixel-wise exudate detection. Applying each pixel to CNN for classification is time-consuming so to speed up the process, the potential exudate candidates are selected using an ultimate opening algorithm. Before applying ultimate opening on image patches, on an illuminated green channel image, optic disc is detected and masked out followed by Inpainting of vessels. After obtaining the potential candidates who are referred to as seed points, the local patches of size 64*64 surrounding the seed points are passed on to the CNN model for identification. This model used E-Optha Ex database for its research.

Van Grinsven *et al*. in 2016 [27] also suggested speeding up the training of CNN by selective sampling. While training a CNN, samples that contain more information are selected at

TABLE II
COMPARISION OF VARIOUS DEEP LEARNING ALGORITHMS

Method	Highlights	SP	SE	Acc	AUC	F-1	PPV
Gardner *et al*. 1996 [20]	Binary classification using neural network	88.40%	88.50%	–	–	–	–
Nayak *et al*. 2008 [21]	Three class classifier using Neural network	100%	90%	93%	–	–	–
Ting *et al*. 2017 [22]	Deep learning system	91.10%	100%	–	0.958	–	–
Pratt *et al*. 2016 [23]	Ten-layer convolution network	95%	30%	75%	–	–	–
Adem 2018 [24]	OD masking and CNN	98%	100%	99.18%	–	–	–
Perdomo *et al*. 2016 [25]	Two stage CNN	56.5+/- 27.6%	92.8 +/- 4.5%	93%	–	–	–
Shuang Yu *et al*. 2017 [26]	Pixel-wise detection	100%	90%	93%	–	–	–
van Ginneken *et al*. 2016 [27]	Selective sampling	91.5%	91.5%	–	0.979	–	–
Prentasic. 2016 [28]	Land-mark detection	–	78%	–	–	78%	78%
Lim *et al.* 2014 [29]	Multiscale segmentation	68%	90%	–	–	–	–
Wang *et al.* 2018 [30]	Pre-trained model	–	–	63.23%	–	–	–
Takahashi *et al*. 2017 [31]	Modified GoogLeNet	–	–	96%	–	–	–
Abrmoff *et al*. 2016 [32]	Real time adaptation	90.80%	100%	–	0.989	–	–
Sadek *et al*. 2017 [33]	BovW comparison with deep learning	97%	96.02%	88.17%	–	–	–
Orlando *et al*. 2018 [34]	Feature extraction	–	91.09%	-	0.8932	–	–

each epoch, instead of randomizing the selection process, such that they have higher probabilities of getting selected in the next epoch. In any large dataset, healthy images dominate,so the knowledge held in them is considerably limited as healthy image patches comprise of the repeated patterns whichthe CNN finds unnecessary. The training patches are of size 41*41, and data augmentation is also used while training. The CNN for this model consists of convolutional layers followed by rectified linear units (ReLUs) and max-pooling, and the architecture is based on OxfordNet [12]. The model attained good results on Messidor dataset after eliminating poor images.

Prentai *et al*. in 2016 [28] combined the outputs of anatomical land-mark detection algorithms with that of candidate extraction to improve the execution of exudate classification. A deep neural network was used in this algorithm to generatea viable candidate probability map. Location of bright borders, optic disc, and blood vessels are influential factors as exudates do not appear inside optic disc or blood vessels. The results from the optic disc detection, bright border detection, andblood vessel detection are combined with results from theprobability map generated by CNN to give the final probability map. Lim *et al*. in 2014 [29] utilized the pre-segmentation of input images to obtain a set of potential regions. Segmentation algorithm employed is Multiscale C-MESR Segmentation [35] and then transformed into tiles of fixed size called as Representational Transformation. After these preprocessing steps, the obtained tiles are fed to a CNN to obtain lesion results. Adopting the transformed representation showed improved results with the DIARETDB1 and SiDRP datasets.

E. Pre-trained Neural Networks

Using pre-trained networks is gaining popularity as it demands a considerable amount of time in devising a new network from scratch, networking designing is problem specific and can take much time depending on the complexity of network and size of the dataset to train. There are several state-of-the-art networks available off the shelf which can be used by transfer learning.

Wang, Lu, Wang, & Chen, 2018 [30] utilized transfer learning based approach for the five-stage classification of diabetic retinopathy. Three pre-trained neural networks are chosen. AlexNet, VGG16, and InceptionNet V3. 5-fold cross-validation process is used to test and train all the three classification models. Average cross-validation accuracy was dominated by InceptionNet V3. In Kaggle dataset, only 166 images held for training since the images retrieved from this database were not acquired in a controlled lab environment, moreover different cameras were used to capture these images.

Hidenori Takahashi *et al*. 2017 [31] proposed the use of a modified GoogLeNet for a disease-staging system. They also proposed the use of fundus photographs of four fieldsat 45° since staging of DR require analysis outside the single fundus image. The model was trained simultaneously using four GPUs and achieved K-fold cross-validation accuracy of 0.80. Another advantage of this method is grading the disease into those requiring treatment and not requiring treatment classes, which is a real-time automated DR system.

Abramoff *et al*., 2016 [32] also developed an automated system for real-time detection of DR. At the heart of the model there are two components; one for capturing fundus images and a classifier software for staging. The fundus imagecaptures four images; two from each eye, with centers around optic disc and macula respectively. The CNNs used in this model are also inspired by AlexNet and are hybrid lesiondetectors.

F. Detection by Integration of Machine Learning with CNN

Few models combine capabilities of machine learning with deep learning. Results of a deep learning model mixed with a typical machine learning classifier are considerably better than any single deep learning model. Sadek *et al*. in 2017, [33] compared the performance of several pre-trained networks on different datasets. CNN was used to extract in-depth net- work features and pre-trained networks like GooLeNet, VGG-VD and VGG are used for transferring the characteristics. A nonlinear classifier, support vector machine, is used to classify the retinal images into three classes; normal, exudate, and drusen. Performance analysis was done by comparing this approach with that of a bag of visual words (BovW)approach. This model performed better when compared to BovW approach.Furthermore, GoogLeNet attained the best feature results.

Orlando *et al*. in 2018 [34] also utilized a machine learning classifier. Feature vectors created from the output of CNN and a hand-crafted feature extractor are fed to a random forest classifier to predict the red lesions. Candidate detection is done before creating the feature vectors to extract potential lesion regions in the image. Integration of deep learning extractor with handcrafted features performed significantly better than using a single extractor.

A comparison of all the algorithms based on major metrics is undertaken and the results are depicted in TABLE II.

VI. Conclusion

Automatic screening of DR using fundus imagery is an important approach as manual grading by professional ophthalmologists consumes much time and is quite expensive. Automatic screening techniques are rather economical and can be used as quick augmentation for manual grading.Deep learning is an evolving branch of machine learning and recently a lot of researchers and artificial intelligence enthu- siasts are focusing towards implementing deep learning for image related issues. Novel and complex deep-neural network architectures are being developed to solve various computer vision tasks. The same architectures can be used for bio- medical image processing applications by applying transfer learning, fine-tuning and simple modifications, to avoid re- designing networks from scratch. This paper analyzed promi- nent deep learning based techniques used for screening the DR symptoms. There are several other techniques available, which use conventional machine learning. The current paper only focuses on deep learning techniques and some tech- niques which combine machine learning capabilities with deep learning. Performance analysis from each of the techniques is tabulated. It is indeed difficult to identify the all round best performing algorithm as performance metrics and the computational resources used vary from algorithm to algorithm and are very much data dependent. However, High sensitivity and specificity metrics are mandatory factors when selecting an automated DR screening system and most of the algorithms presented in this paper fall under this category.

High computational facilities like GPUs are required totrain and test the deep networks. Adopting transfer learning based on pre-trained networks does save the training timesignificantly but still does not solve the entire DR classificationproblems. Using supervised learning algorithms to design highperforming CNN architectures is well expected to outperform the existing approaches for network design for bio-medical image classification tasks, like DR screening.

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