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An Extensive Analysis on Diabetic Retinopathy Prediction Using Deep Learning Approaches

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Abstract- Diabetic Retinopathy leads to loss of vision leads to diabetic mellitus complications. The analysis with computer-aided diagnosis over retinal fundus images is an effectual way for predicting the disease in earlier stage and assists the physicians. There are diverse Machine Learning approaches that are adopted for predicting the complications; however, it leads to computational complexities while performing feature extraction separately. This drawback came be overcome with the utilization of deep learning (DL) approaches as it performs feature extraction and classification concurrently for enhancing the prediction accuracy. This work provides an extensive analysis and reviews on approaches used for DR prediction. There are various challenges that are identified and needs to be addressed using the emergent DL approaches. These approaches are extremely robust, and efficient to predict DR by handling all the learning challenges and provides the direction for further analysis.

Keywords- Diabetic Retinopathy, deep learning, computational complexity, feature extraction, and classification

1. Introduction

Diabetic Retinopathy (DR) is the preliminary source of blindness due to diabetic’s mellitus. It is a major complication related to diabetes and the primary issue related to DR. It is extremely complex when it reaches the advanced stages and therefore the earlier prediction of the disease is extremely essential. Moreover, it leads to significant complexities over the healthcare system owing to huge amount of patients and the number of technical experts. It motivates to model an automated diagnostic system for assisting in prior DR diagnosis. There are various attempts that have been made in this direction and various techniques based on feature extraction and provide promising solution in predicting DR regions from the retinal fundus images.

The conventional machine-learning (ML) uses hand-engineered features are generally utilized for DR prediction. Some extensive analyses are reviewed with these conventional approaches. For instance, author et al. [1] classifies DR diagnosis based on various approaches like clustering-based models, mathematical morphology, deformable and thresholding models, retinal lesion tracking, hybrid models and matched filtering approaches. Author et al. [2] analyses various approaches that haul out lesion features from provided images like texture, blood vessel area, micro-aneurysms, exudes, and haemorrhages. Author et al. [3] performs extensive research on the prediction of exudates. Some algorithmic are

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constructed for segmenting retinal vessels. Author et al. [4] models various approaches for glaucoma prediction and optic disc segmentation. Moreover, some expert knowledge is needed for handling this hand-engineered features and selecting appropriate features required severe examination of diverse ways and tiresome parameter evaluations. However, some approaches are relies on hand-crafted features do not simplify it.

Recently, there are enormous dataset and remarkable computing power provided by graphical processing units which motivates the research area over deep-learning approaches. These approaches show outstanding recital in diverse computer vision tasks and attained better decision-making over conventional hand-crafted feature selection approaches [5]. Various learning approaches are designed for diverse tasks to examine the retinal images and to design automatic computer-aided diagnosis model. This work examines present DL approaches utilized for predicting that highlights the importance and challenges need to be addressed by recent research ideas. Initially, an extensive analysis is done with diverse DL models and examines DL-based approaches for DR prediction. At last, this work summarizes the research gaps, challenges need to be addressed, and future research direction while modelling and training the traditional learning approaches for DR prediction. Fig 1a to Fig 1f depicts the retinal image for eye detection.

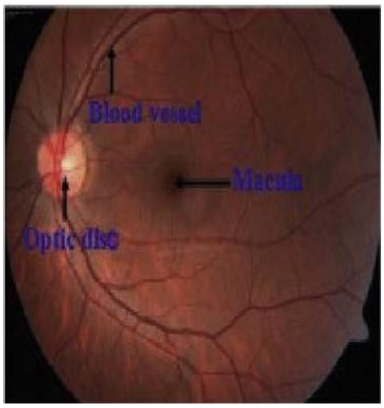

Fig 1a. Normal retina

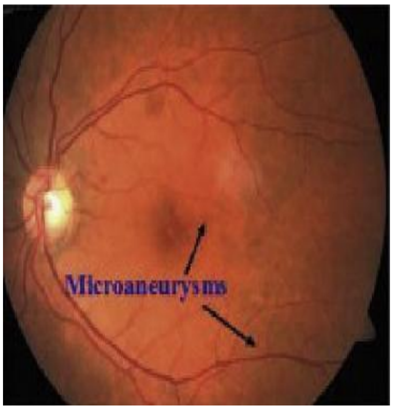

Fig 1b. Mild DR

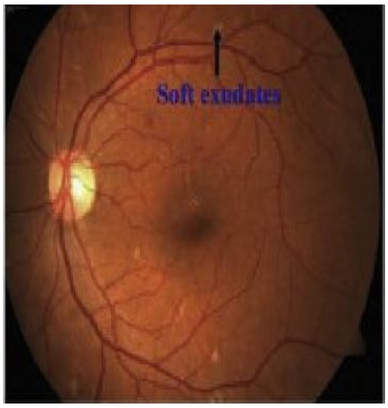

Fig 1c. Moderate DR

Fig 1d. severe DR

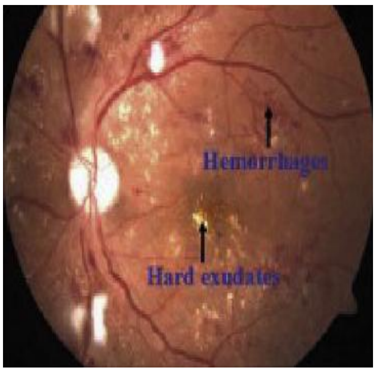

Fig 1e. Proliferative DR

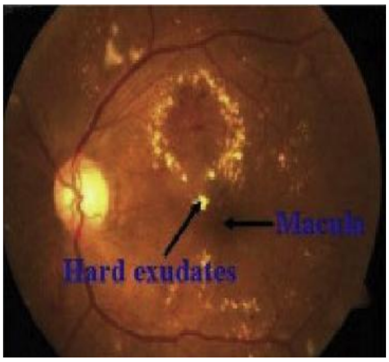

Fig 1f. Macular edema

2. Reviews on DR datasets

Joshi et al. [6] discusses a dataset known as Singapore epidemiology of eye diseases (SEED) which is tranquil of 236 images with the concentration of examining the major eye disease that includes cataract, glaucoma, refractive errors, AMD and DR. The images possess OC and OD regions with trained grade functions as ground truth value for segmenting purposes.

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In [7] discusses digital images for optical nerve dataset for segmenting optic nerve and corresponding pathologies. It is interpreted with independent experts where the image centres are based on optic nerve and preserved in slide format. Work [8] concentrates on automated retinal image analyzer which is gathered from tracing the blood vessels, fovea and OD locations. It is used for diagnosing DR and AMD with fundus camera and Zeiss FF450 camera. Sivaswamy [9] discusses retinal image database for evaluating nerve and modelled for predicting glaucoma and composed of 169 optic nerve regions cropped manually from provided images. Kaggle dataset [10] is composed of high-resolution retinal images acquired from various circumstances and offered by expert ophthalmologists and images are allocated with grading scale of 0-4 as $0 \rightarrow no\ risk; 1 \rightarrow mild; 2 \rightarrow moderate; 3 \rightarrow severe\ and\ 4 \rightarrow PDR$. E-ophtha dataset [11] discusses digital retinal images for extracting vessels and collected from DR screening. It is composed of 40 fundus images and chosen randomly in which 33 images does not show any DR sign and 7 images show mild DR prediction. It is partitioned into training and testing sets and composed of 20 images. It gives pixel-level annotation. Hoover et al. [12] discusses the funded program of U.S. health institute known as structured analysis of retina composed of 13 infected images related to human eye. It offers disease code list and image names. The optic nerve and blood vessels have pixel level annotation without any grading. It performs manual segmentation by labelling the pixels of image vessels. It deals with challenging OD detection problem owing to the retinal disease appearance. Kal et al. [13] discusses a dataset composed of 90 color fundus images where the image annotation is done by independent experts. It is also known as 'calibration of level_1 fundus image. It is partitioned as 28 training and 61 testing images. Chase dataset [14] constructed the diabetic retinopathy image database to get rid of various shortcomings in grading and constraint amount of observers. Images are chosen by the experts with visible fragile vessels. The images are computed by five diverse experts. The annotated images include the soft EX, HMs, MAs, blood vessels, macula and ODs. Zhang et al. [15] models the online fundus image database for analysing glaucoma. It is an online repository with ground truth values for sharing the retinal image analysis and appropriate diagnosis. The images are acquired for 3 years and specifically concentrate on optic cup and OD segmentation for predicting glaucoma. NIH fund for generated for develop under-eye age-based eye disease [16] which is a long-term multi-centre with 595 participants and modelled to evaluate the clinical courses. The participant's illness was analyzed for graded long-term with reading centre, ophthalmologic evaluation, and visual acuity.

The computing and informatics department of Lincoln University designed a retinal vessel image dataset [17] for width estimation. It is composed of 193 annotated segments and 16 mydriatic images. It includes 5066 profiles with three independent experts. It evaluates the precision and accuracy of vessel width measurement and it includes partitioning of 16 images into four sections: kick-point image (2 images), central light reflex image set (2 images), vascular disease image set (4 images), and high resolution image set (8 images). Eyepacs dataset [18] discusses eye picture archive and communication systems for modelling telemedicine system and flexible protocol for screening DR in collaboration with the physicians. The fundus images are uploaded easily to the EyePACS web. It computes the severity and presence of discrete retinal lesions related to DR. It uses canon CR-1 non-mydriatic cameras which are accessed over the EyePACS website. It is graded as HMs, MAs, wool spots, intra-retinal micro-vascular abnormalities, venous beading, without/with MA, pre-retinal HE and HM, vitreous HM and fibrous proliferation. It also deals with the occurrence of laser scars. Images are provided on the online grading template that records the lesion type with yes (present), no (absent), or cannot grade.

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3. Reviews on automatic retinopathy detection

This section discusses the DR lesions type, DR stages, DR grading, and detection framework. There are some research directions that need to be examined and addressed. In [19], the author discusses the earlier stage of DR and retinal damage due to the internal elastic lamina disruption. It diminishes the vision owing to the endothelial barrier function loss that causes retinal edema and leakage. MA is extremely smaller and shows red spot and sharp margins. The bot and dot haemorrhages occur due to retinal layer. The damaged capillary leakage leads to exudates and appears in irregular shape and seems to be yellow in color. There are two diverse types of exudates (EX): hard and soft exudates. The former exudates are grey cloud that occurs in arteriole and the latter model possesses sharp margins. It is composed of circular rings and blocks. Ex is different with bright and dark lesions. The diameter variations are termed as venous bleeding with advanced non-proliferative diabetic retinopathy stages. Patz et al. [20] discusses intra-retinal micro-vascular abnormalities that specify actual blood vessels growth or pre-existing capillaries. The retinal vessels grow towards the vitreous and known as neo-vascularization. It leads to hard exudates and retina thickening with one diameter disk and fovea is for central vision. The foremost objects act as a primary role in DR prediction that classifies highest contrast among circular-shaped regions. It is utilized as a reference frame for predicting severe eye pathologies like disc drusen, glaucoma, and optic disc pit to verify disc neo-vascularization. Also, OD is utilized to pinpoint some structures like fovea. For normal retina, the OD edges are well-defined and clear. Fig 2 depicts the flow diagram for retinal disease prediction.

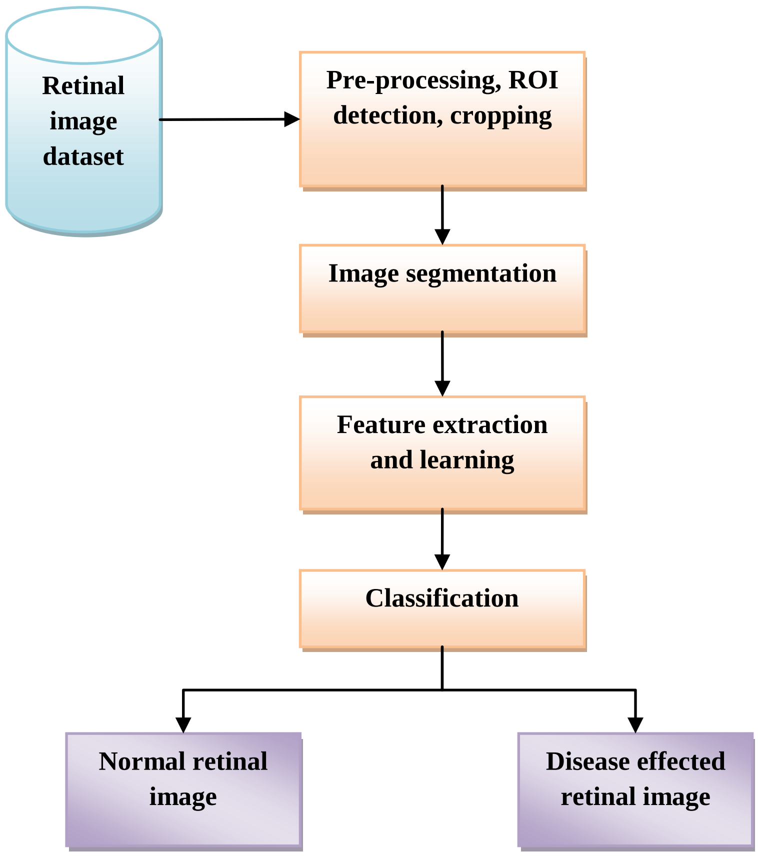

Fig 2 Flow diagram for retinal disease prediction

Fleming et al. [21] discusses the stages and classes of severity as proliferative and non-proliferative models. The later model is considered as the earlier stage when diabetes initiates

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to spoils retinal blood vessels. It is frequent among the diabetes people. The vessels initiate to discharge blood or fluid that causes the retina to swell. When time passes, edema makes retinal thickening with indistinct vision. The features include hard EX with or without haemorrhage. The prediction of DR is the superior stage that leads to growth on blood vessels. It is considered as proliferation of abnormal vascular with vitreous cavity. The blood vessels bleed with vitreous cavity and crucial visual loss owing to haemorrhage. In [22], the author performs screening and examining retina using ophthalmoscopy and needs dilated pupils to classify and grade pathology. The grading process is a crucial activity during DR screening programme for predicting retinal disease. Grading is done with well-trained technicians to carry out a necessary task for recovering blinding eye conditions for potential blinding eye recovery like diabetic eye disease and age-based mascular degradation. The higher level of DR prediction is classified into two tasks like image and lesions-based detection. The former model concentrates on the evaluation of image levels during screening process as it computes DR signs. The latter model includes two phases: lesion classification and lesion segmentation or detection. The detection process performs potential ROI; however, it includes false positive. It is utilized for eliminating false positive. It is a screening task that categorizes image as normal or DR signs.

The DR detection framework includes pre-processing steps, segmentation, feature extraction and appropriate classification process. It is divided into two processes: supervised and unsupervised learning. The former model is a system with labelled data for infer-functional mapping; while the later is to identify the hidden patterns with its own properties of unlabeled samples with similarity. Using the hand-crafted feature extraction process, the DL approaches are integrated with automatic learning process and unified framework. The training is done in an E2E manner. Table 1 depicts the comparison of grading process.

Table 1 Comparison of grading process

Grade	Features	Description
$R0 \rightarrow no\ DR$	No abnormalities	12 month re-screening
$R1 \rightarrow mild\ DR$	Only MA	12 month re-screening
$R2 \rightarrow moderate\ DR$	Venous beading in two quadrant	6 month re-screening
$R3 \rightarrow severe\ DR$	Intra-retinal micro vascular abnormalities	Re-screening
$R4 \rightarrow PDR$	New vessels at OD	Re-screening
$M0 \rightarrow no\ ME$	No retinal thickening	12 month re-screening
$M1 \rightarrow mild\ ME$	Retinal thickening at posterior pole	6 month re-screening
$M2 \rightarrow moderate\ ME$	Similar mild ME signs	Laser treatment
$M3 \rightarrow severe\ ME$	Retinal thickening that affects fovea centre	Laser treatment

4. Reviews on performance evaluation

Some metrics are done for evaluating DR prediction algorithm. They are: precision, sensitivity, specificity, accuracy, ROC curve, F-score, dice similarity coefficient (DSC), overlapping error, log loss, IOU, and boundary based computation.

1) Accuracy: It is depicted as the proportion of appropriately classified samples over total instances. It is depicted as in Eq. (1):

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$$Accuracy = \frac{TP+TN}{TP+TN+FP+FN} \tag{1}$$

Here, $TP \rightarrow true\, positive$ is number of positive samples with DR that are properly categorized; $TN \rightarrow true\, negative$ is the number of negative samples are appropriately classified; $FP \rightarrow\ false\, positive$ is the number of positive instances that are inappropriately categorized and $FN \rightarrow false\, negative$ is the number of negative samples that are inappropriately categorized.

2) Sensitivity: It is known as the TPR (true positive rate) or recall. It is the fraction of properly classified positive samples;

3) Specificity: It is also known as TNR (true negative rate). It is the fraction of properly classified negative samples;

4) Precision: It is known as positive prediction value. It is a measure of fraction of positive samples that are properly categorized. It is mathematically shown as in Eq. (2), Eq. (3), Eq. (4), and Eq. (5):

$$Sensitivity\ (recall) = \frac{TP}{TP+TN} \tag{2}$$

$$Specificity = \frac{TN}{TN+FP} \tag{3}$$

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

$$F = 2 * \frac{Precision * Recall}{Precision + Recall} \tag{5}$$

5) Logarithmic loss: It specifies accuracy by penalization of false classification. For predicting the loss, classifier needs to allocate probability of every class. It is expressed as in Eq. (6):

$$Log\ loss = -\frac{1}{N}\sum_{i=1}^{N}\sum_{j=1}^{M} Y_{ij}\log P_{ij} \tag{6}$$

Here, $'N'$ is number of samples; $'M'$ is number of labels; y_{ij} is the binary specifies where label $'j'$ is proper classification for instances, P_{ij} is the probability of allocated label to some instances. Some metrics are utilized for evaluating the segmentation performance that includes intersection over union, overlapping error, DSC, and boundary-based evaluation. Intersection over union (IOU), overlapping error is expressed as in Eq. (7), Eq. (8):

$$IOU = \frac{Area\ (A\ \cap G)}{Area\ (A\ \cup\ G)} \tag{7}$$

$$E = 1 - IOU \tag{8}$$

Here, $'A'$ is segmentation output and $'G'$ specifies the manual segmentation of ground truth value. Boundary-based evaluation is depicted as absolute point-wise localization error attained by evaluating distance among the closed boundary curves. The distances among the curves are expressed as in Eq. (9):

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$$B = \frac{1}{n}\sum_{\theta=1}^{\theta_n}\sqrt{\left(d_g^{\theta}\right)^2 - \left(d_a^{\theta}\right)^2} \tag{9}$$

Here, d_g^{θ} and d_a^{θ} are distance from curve centroid to points; $'n'$ is total amount of angular samples. The distance among ground truth and boundaries are ideally nearer to zero. DSC is mathematically expressed as in Eq. (10):

$$DSC = \frac{2TP}{2TP + FP + FN} \tag{10}$$

DSC values ranges from 0 and 1; the DSC value is closer to 1 with superior segmentation outcomes. Region-based Precision Recall is utilized to evaluate boundary or edge detection on overlapped region. It projects the quality segmentation with precision recall space.

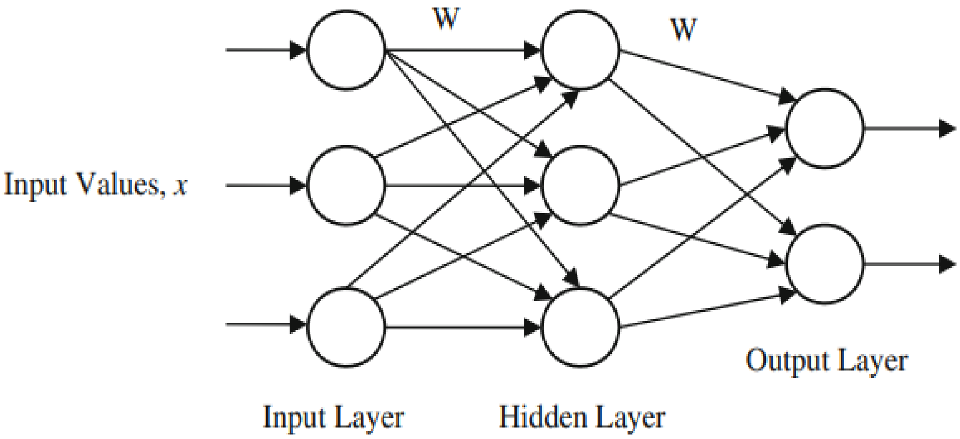

Fig 3 ANN architecture

5. Reviews on deep learning

There are various DL approaches that includes convolutional neural networks (CNNs), deep belief networks (DBN), auto-encoders (AE), and recurrent neural networks (RNN). These learning architectures are explained below and the graphical representations are shown in Fig 4 to Fig 8.

a. Convolutional Neural Networks (CNNs)

CNN model replicate the human visual system and extensively utilized for diverse computer vision tasks. It is significantly composed of three diverse layers: convolutional, pooling and fully connected layers. Initially layer uses convolution to encode spatial data and FC layers are used for encoding the global information. Some CNN model includes ResNet, VGGNet, AlexNet, and GoogLeNet. The features are automatically learned and outcomes in superior performance. CNN models like Alexnet and LeNet composed of few layers. Lim et al. [23] elaborates deep CNN model known as VGGNet with 19 layers, deeper for superior performance. The deeper model includes ResNet, Inception, and GoogLeNet with various computer vision tasks. Usually, the model specifies the input and provides output. The process of learning CNN model needs expensive huge amount of data to get rid of over-fitting issues and fulfils faster convergence; however, huge amount of data are not accessible over medical domain. Transfer learning is utilized for CNN pre-training as feature extractor and fine-tuning CNN with data for appropriate region. FCN is an extended CNN version

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where FC layers are transformed into convolutional and deconvolution layers are attained with output mapping as the input image. Generally, it is utilized for segmentation.

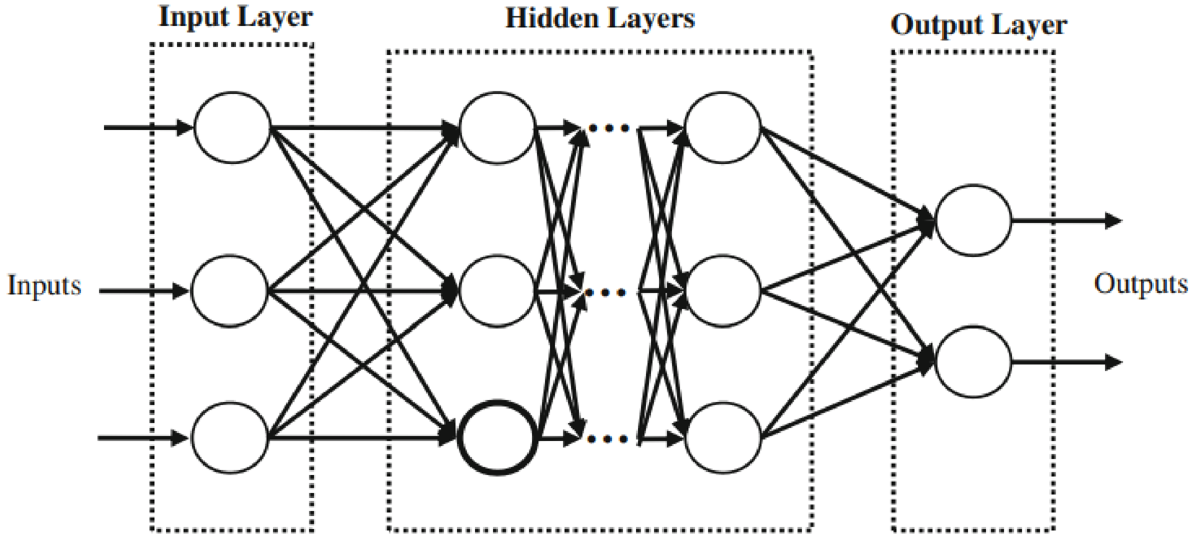

Fig 4 Deep Neural Networks

Guo et al. [24] adopts CNN model for segmenting vessel and non-vessel pixels. It is composed of two FC and three convolutional layers. Sevas et al. [25] anticipates pixel-wise supervised segmentation approach is trained with provided images and pre-processing is done with global contrast normalization, zero-phase whitening, gamma corrections, and augmented with geometric transformations. This model is forceful against vessel reflex and sensitive over vessels. Zilly et al. [26] performs retinal blood vessel segmentation as regression tasks that are applied for VGG pre-training with modified FC layers and integrated with convolutionl layers before performing layer pooling. Convolutional layers are upsampled to similar image size, concatenated and trained over the volume. Zhang et al. [27] performs discriminative features with CN and uses k-NN for performing principle component analysis for estimating local structure distribution employed for generalized probabilistic tracking model for segmenting the blood vessels. Fu et al. [28] uses FCN merged with structured detection to segment blood vessels with multi-label inference. The layered-CNN model is utilized for segmenting the blood vessels and fovea. After colored image normalization, the author formulates the segmentation issues as a classification issue related with the classes of blood vessels. It is extremely time consuming as the pixels are independently classified with number of pixels.

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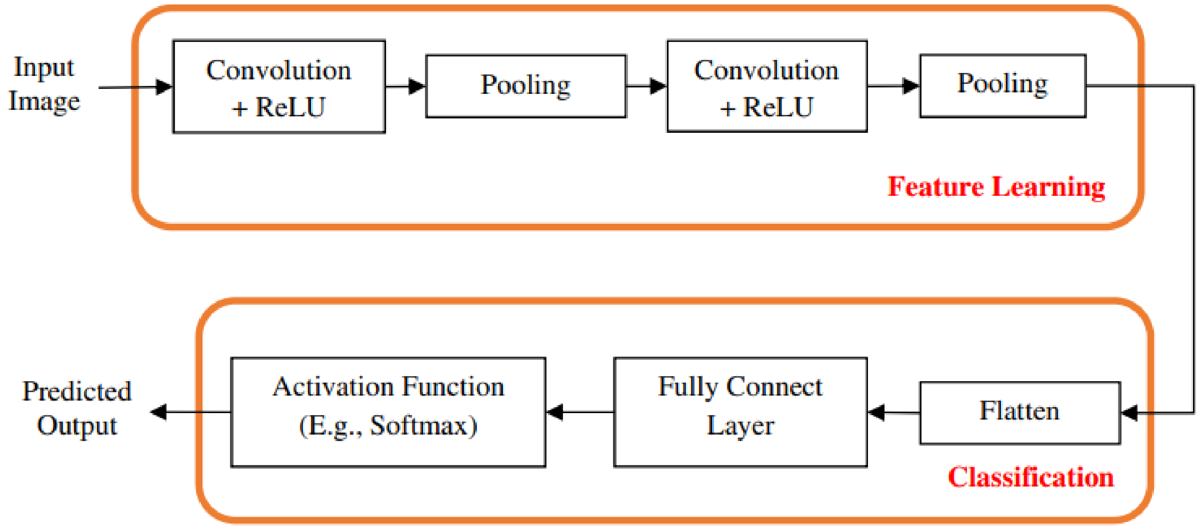

Fig 5 Convolutional Neural Networks

b. Auto-encoder

Maji et al. [29] discusses auto-encoder with hidden layer neural networks with input and output. It is utilized for constructing the stacked auto-encoder. The training of this model is composed of two phases: fine tuning and pre-training. During pre-training, SAE is trained in an unsupervised manner. It is fine-tuned with back propagation and gradient descent model. There are two diverse auto-encoder types known as sparse and de-noising. It is an auto-encoder type that intends to sparse feature extraction from the raw data. The sparsity representation is attained by direct output penalization of hidden unit activations or penalization of hidden unit biases. Roy et al. [30] discusses denoising auto-encoders for DR prediction. It works in a robust manner by recovering corrupted input and induces the model for capturing the appropriate version.

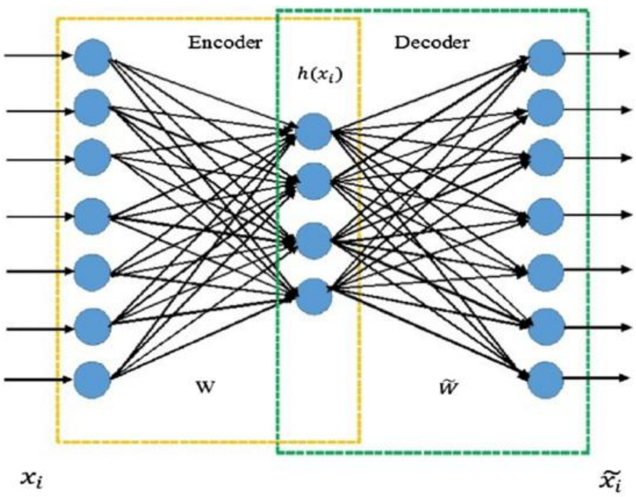

Fig 6 Auto-encoder representation

c. Recurrent neural networks

Mikolov et al. [31] discusses about a neural network type that learns context from the provided input patters. The outputs are learned from the prior iterations and merge it with given input for yielding the output. It includes various parameter set to the hidden weights, output weights, and input weights.

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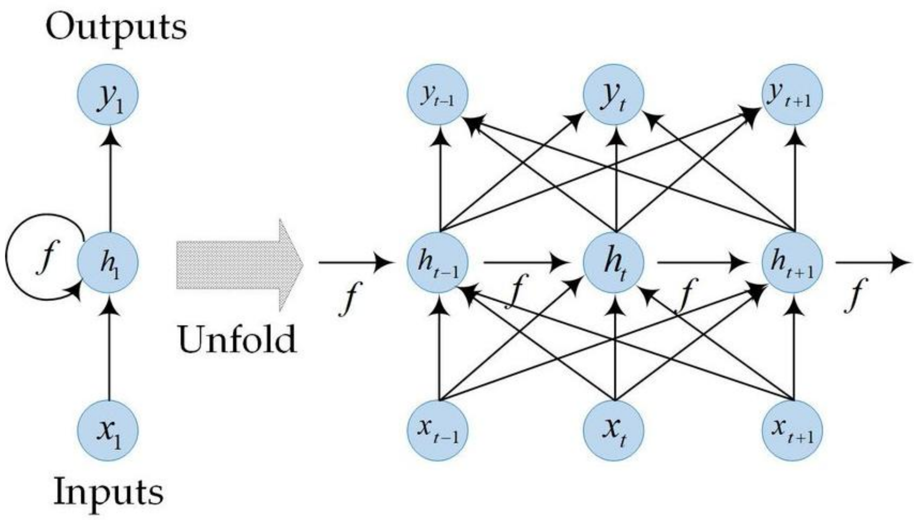

Fig 7 Recurrent Neural Network representation

d. Deep belief networks

Vinyals et al. [32] elaborates this network model with the designed with the cascading restricted Boltzmann machines. It performs divergence algorithm for maximizing the similarity among the input and projections. The probability measure shows the similarity among the de-generated solutions and offers a probabilistic model. Initially, it is pre-trained in an unsupervised manner with greedy learning approach. It is fine-tuned with back propagation and gradient descent algorithms.

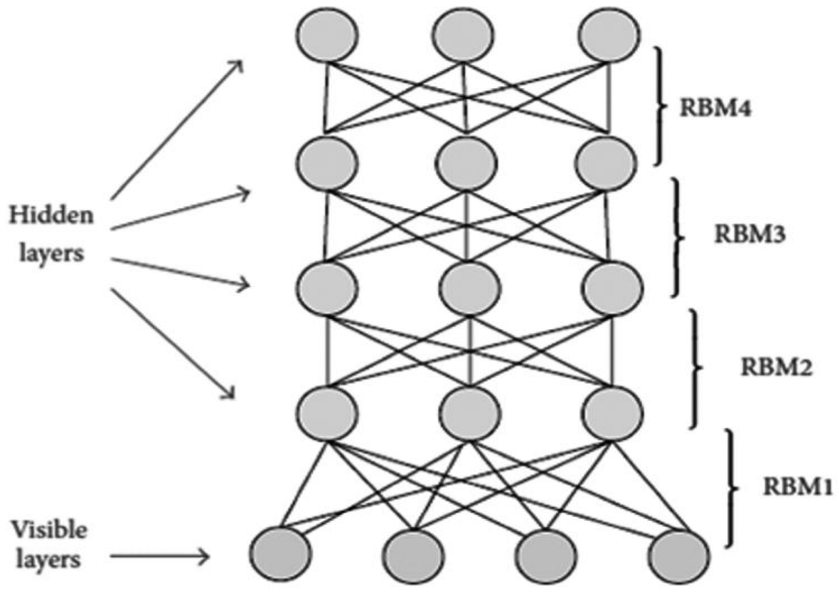

Fig 8 Deep belief network

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Table 2 Comparison of various deep learning approaches

Learning approaches	Description	Benefits	Disadvantages
Deep Neural Networks	It is extremely simple for learning approaches with more hidden layers. It is useful for various applications that are related to regression and classification	It is extensively utilized for superior performance and finest accuracy	Huge time is needed for training process
Convolutional Neural Networks	It is extremely superior for image-based applications	It is completely faster and superior with better performance	Training labels are required for data in classification associated applications
Recurrent Neural Networks	It is completely useful for handling the sequence format. The network weights are shared with network nodes	It is operated in a sequential manner and provides better accuracy	It needs huge sized dataset for superior performance
Deep Belief Network	It is completely utilized for supervised learning process. The hidden layer of every network is accessible for successive sub-network	Greedy norms are utilized in every layer to superior prediction	It requires superior higher computational complexity during training process
Deep auto-encoder	It is utilized for dimensional reduction of image features. The input and output size is same	Not labelled input data and diverse applications like sparse auto-encoder, de-noising, auto-encoder. It provides flexible robustness to input data.	Needs pre-trained process while using it
Deep Boltzmann machine	It functions over uni-directional manner and boltzmann	With appropriate interference and functions for discrete predicted value	It needs huge dataset for analysis, utilization, optimization of parameters

6. Limitations and future research directions

There are various learning approaches that are adopted for predicting the eye disease which is caused due to diabetes mellitus. Some of the limitations are listed below:

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1) Some methods are analyzed over the real-time dataset; however, it leads to lesser standardization with the traditional models.

2) Some retinal image database is extensively utilized by various approaches. The significance of the prevailing approaches is not satisfactory while implementing over the large-sized database.

3) There is no proper standardization for computing disc ratio in various prevailing approaches.
4) There are very techniques that are accessible using learning approaches for eye disease prediction.

In future, there are some research directions that need to be concentrated.

1) Modelling various approaches based on deep learning approach for eye disease prediction.

2) Modelling an efficient method that is utilized for various sizes of retinal image dataset.

3) The standardization of the approach needs to be improved with execution steps requires accuracy for eye disease detection.

7. Conclusion

This work provides an extensive review on various deep learning approaches that includes the prediction of diabetic retinopathy, reviews on DR dataset, performance metrics, and so on. This work describes various learning approaches utilized for predicting eye disease with available retinal images. Recently, there is enormous research work that intends to resolve various research challenges and it needs to be addressed with learning process. The investigators pretend to enhance the performance of disease detection with extensive analysis. Hence, the performance of these models does not meet the standardization of the model which is considered to be a challenging task for various research works. Also, it is obvious that some works are carried out for eye disease with deep learning approaches. Therefore, it is considered as an open research direction for predicting the eye disease with deep learning frameworks.

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