Review Article

A Review on Machine Learning Methods in Diabetic Retinopathy Detection

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Abstract

Ocular disorders have a broad spectrum. Some of them, such as Diabetic Retinopathy, are more common in low-income or low-resource countries. Diabetic Retinopathy is a cause related to vision loss and ocular impairment in the world. By identifying the symptoms in the early stages, it is possible to prevent the progress of the disease and also reach blindness. Considering the prevalence of different branches of Artificial Intelligence in many fields, including medicine, and the significant progress achieved in the use of big data to investigate ocular impairments, the potential of Artificial Intelligence algorithms to process and analyze Fundus images was used to identify symptoms associated with Diabetic Retinopathy. Under the studies, the proposed models for transformers provide better interpretability for doctors and scientists. Artificial Intelligence algorithms are also helpful in anticipating future health issues after appraising premature cases of the ailment. Especially in ophthalmology, a trustworthy diagnosis of visual outcomes helps physicians in advising disease and clinical decision-making while reducing health management costs.
Keywords: Artificial Intelligence; Diabetic Retinopathy; Deep Learning; Fundus Images; Machine Learning.

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Introduction

Globally, the number of people living with diabetes will be reached 600 million by 2040 [1]. This statistic demonstrates the growing eye diseases related to diabetes in the coming years. Also, this shows the need to diagnose eye disorders such as Diabetic Retinopathy (DR) in the early stages and even before the clinical symptoms appear.

With Artificial Intelligence (AI) coming and its branches such as Machine Learning (ML) and Deep Learning (DL), the availability of the huge amount of data, high-speed, and also cheap hardware, it has been possible to benefit from it in many industries such as medicine [2–7]. Ophthalmology has a remarkable potential in benefiting from AI in disease diagnostic such as diabetic eye complications. With the help of AI algorithms, it is possible to predict Ocular diseases in the early stages and even before the appearance of initial clinical symptoms; this prevents blindness and vision impairment. DR includes five stages, which are: 1- no Diabetic Retinopathy - 2- Mild Diabetic Retinopathy - 3- Mediate Diabetic Retinopathy - 4- Serious Diabetic Retinopathy and - 5- Proliferative Diabetic Retinopathy (PDR) [8–10]. Accurate diagnosis of different stages of DR requires highly skilled doctors. But even conversant doctors make mistakes in the exact classification of DR. Since the correct categorization of cases and early disclosure of signs can hinder vision deficit, the potential of ML and DL algorithms for the correct type of ailment stages has accepted much concentration in recent years [11].

The data required for AI algorithms are produced in clinical examinations performed by ophthalmologists. This data can include multifocal ocular images and other measures such as Visual Acuity (VA) and Intraocular Pressure (IoP). According to the type of data available, the use of ML and DL algorithms to identify or predict eye impairments such as Diabetic Retinopathy, Age-related Macular Degeneration (AMD) [12], Glaucoma, and many eye-related disorders are a concern to many health institutions located all over the world [13–19].

Therefore, improving AI algorithms for ophthalmology has increased inmates' access to monitoring and clinical interpretation, as well as diminished healthcare costs, particularly in countries with low income and insufficient resources [20, 21]. In addition, by employing AI algorithms for Optical Coherence Tomography (OCT) and Fundus images [22, 23], they are possibly used to identify ailment aspects, disease advancement, and the treatment response of retinal disorders such as DR in the early stages [24].

Many screening programs for DR detection using OCT and Fundus images, with the aim of timely referring the patient to ophthalmologists for timely treatment and prevention of decreased vision, are being implemented around the world [25, 26]. In this article, an attempt has been made to review the most recent articles associated with DR categorization. In the following, first, a definition of Diabetic Retinopathy is provided. Then, an introduction to Artificial Intelligence and its most widely used techniques, Machine Learning and Deep Learning are described. After that, the datasets used in developing proposed AI algorithms in the field of ophthalmology are provided. Finally, a revision of the current claims of ML and DL algorithms in ophthalmology and DR-accompanying disorders has been done.

Diabetic Retinopathy

Diabetic Retinopathy is the leading cause of Ocular impairment in patients with diabetes under 50 years of age [27]. DR occurs

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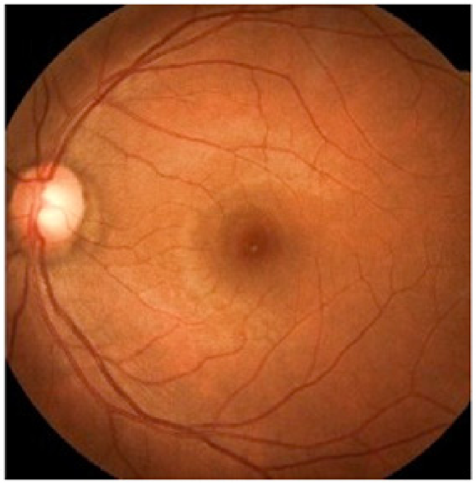
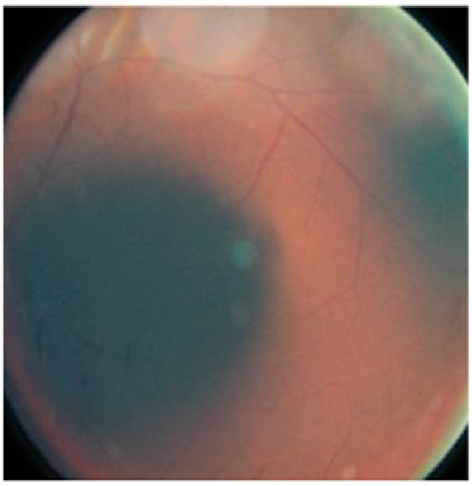


a



b

Figure 1: a- Human retinal without Diabetic Retinopathy, b- Human retinal in PDR stage(29)

due to microvascular damage to the retinal capillaries. There is evidence that retinal nerve dysfunction may occur before vascular changes are observed [10, 27]. DR is one of the central vision problems related to diabetes, which accounts for 2.6 % of sightlessness globally [28]. In this condition, Glucose that is not digested by the pancreas can block the blood vessels of the eye. This can cause eye damage due to swelling and leakage of blood vessels in the eye.

DR is detached into two typical phases, Non-Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR) (Figure 1a, 1b).

The NPDR stage, known as the early stage of DR, is characterized by less than five microaneurysms, retinal hemorrhages, and hard exudates [8–10]. Microaneurysms and retinal hemorrhages usually appear as red lesions. While the stage of PDR, the most common type of sight-threatening lesion in type 1 diabetes, is defined by the detection of retinal neovascularization. Therefore, identifying the early symptoms can help speed up the treatment process and prevent the disease from becoming acute [30].

Artificial Intelligence background

Any system that can perform independently and intelligently has benefited from Artificial Intelligence techniques [31]. Considering the breadth of this field of computer science, Machine Learning is a particular subfield of AI used in many areas (Figure 1a, 1b). ML refers to a set of algorithms that can learn from a large amount of data. The dataset consists of samples with a specific topic, such as eye impairments. These samples are characterized by variables associated with the ailment and involve dispassionate details such as age, gender, or Intraocular Pressure. Samples are categorized into groups noted as classes [32].

Also, Deep Learning is a subgroup of ML methods. Their engineering is inspired by biological neural networks. DL algorithms can engineer features automatically. The most common DL algorithm usual in ophthalmology is noted as Neural Network (NN) [33, 34]. Neural networks (Figure 2) contain various layers of

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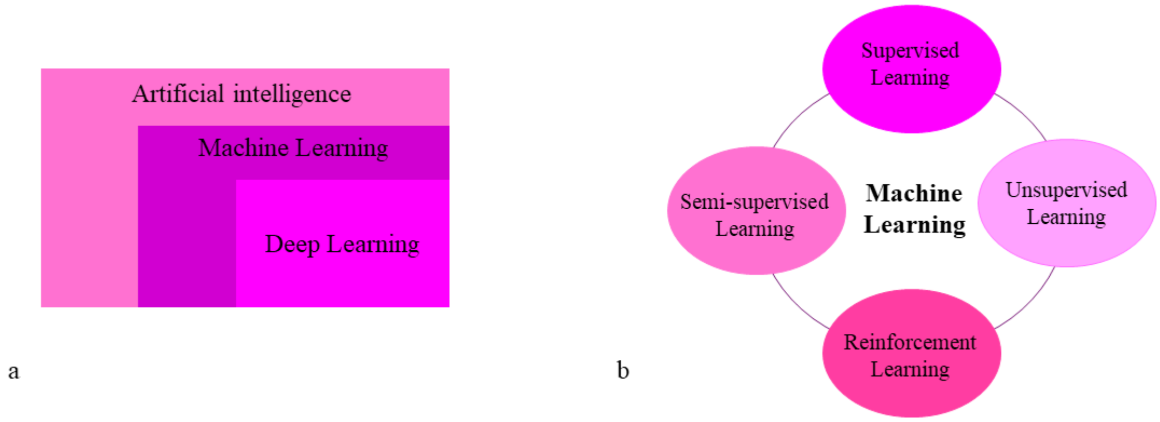

Figure 2: a- AI and its subsets, b- Machine Learning categorization

nodes termed neurons. Neurons of the first layer are displayed by unique variables for a sample. Each neuron in the algorithm is affiliated to the whole set of neurons in the next layer.

These connections have variable weight. So that each neuron of the first layer increases or diminishes the value of each neuron in the second layer. Therefore, the value of each neuron in the second layer is contingent upon the total of the weighted values of all the neurons in the first layer. Finally, the output layer concludes predefined classes in the dataset (such as DR vs. normal). When a dataset is trained with accompanying samples of known classes through NN, the variables of each instance lead to an output that illustrates a particular class.

The algorithm indicates an error when it makes an incorrect class prediction. Then, it determines which weighted connections to change in the NN to ensure it selects the correct class [35]. After the algorithm has altered its internal weighted connections, the NN is retrained, accompanying the dataset. This process is accomplished iteratively, and the algorithm persists in regulating its internal programming just before it can dependably categorize samples into the correct classes. Finally, the developing NN is tested on an entirely new dataset of samples accompanying known classes, noted as the validation dataset. This tests the algorithm's capability to categorize new samples correctly. Using the results of the validation dataset, metrics such as sensitivity and precision are possibly driven. Success in correctly predicting classes in ML and DL relies on classification algorithms. There are different classification algorithms for various purposes in ML. Some commonly used classifiers are Support Vector Machine (SVM), Random Forest (RF), Logistic Regression (LR), Decision Tree (DT), Naïve Bayes (NB), and K-Nearest Neighbor (KNN). It can be said that the main difference between ML and DL is the feature extraction technique that the classification algorithm works on. In DL, features are extracted using multiple nonlinear hidden layers. This issue causes DL classification algorithms to perform better than classification algorithms in ML. Because feature extraction in ML algorithms relies on their non-automatic extraction. There are different types of classifiers in DL, some of which are: Recurrent Neural Network (RNN), Convolutional Neural Network (CNN), Boltzmann Machine (BM), AutoEncoder (AE), and Deep Belief Network (DBN) [36].

From the mentioned DL algorithms, CNN [33, 37] is the best regular in image processing topics

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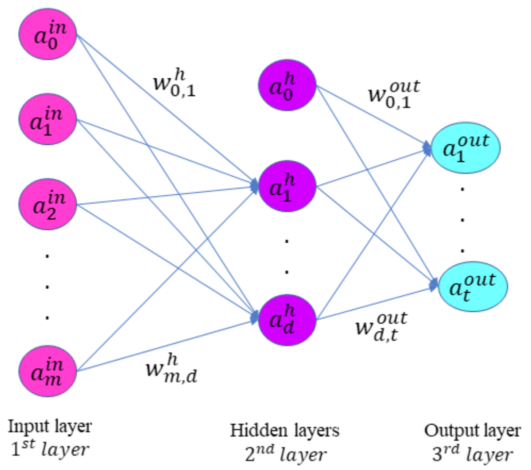

Figure 3: A fully connected Artificial Neural Network. The input layer represents variables. Weights must be between 0 and 1.0. the output layer indicates the predicted class

in the way that image processing for DR disclosure. In CNN, the engineering of the layers is specific that it avoids the dilemma of image processing in the form of part refining that was ordinary in NNs. CNN can recognize patterns in images. Specifically, the layers of CNN assist the network to learn various features of an image. Indiscriminate, the architecture of a CNN subsists of an input layer, an output layer, and various hidden layers. In each hidden layer, the weight of the neurons and the bias values are unchanging. But the network invariably amends the weights of the neurons all the while training. Updating the weights of the neurons in the hidden layers means that the neurons are detecting particular features. Three transcendent coarse layers that lie between the input and output layers are pooling, convolution, and ReLU, which transform data to learn distinguishing features. The convolution layer applies a set of filters on the input images that activate definite features of the images. The ReLU activation function acknowledges tighter training. Because of the consistency of positive values and mapping negative values to zero, it transfers only the activated features to the next layer. By operating sampling, the pooling layer reduces the dimensions of the features, and thus, the number of parameters that the network must learn and the number of computations aspiring decreased. The last layer, which is a sufficiently connected layer, resides in a vector accompanying k length which is the number of classes into that the CNN commits to categorize the data. On this layer, the SoftMax activation function is enforced to label images. Figure 4 illustrates a simple concept of CNN. The most influential models of CNN that have been used apathetic types of research aims are AlexNet, GoogLeNet, ZFNet, LeNet, and ResNet.

A point that concedes the possibility be acclaimed in AI studies, particularly studies related to image processing, is that it is mainly to illustrate the community at which point the DL method was advanced and tested. Reporting dataset attributes such as principal population representing data substrates in the way that visibility and reference standard are outstanding in ophthalmology. Especially DL methods can anticipate extra features that cannot be discovered by non-automated inspection. In ophthalmology, the reference standards are generally ophthalmologists, graders, or optometrists. In terms of test procedures, they may be executed as clinical examinations or image-based examinations.

Datasets

The set of images used in training ML and DL algorithms available in public form are Messidor [38], IDRiD [39], DRIVE [40], DIARETDB [41, 42], ODIR [43], DDR [44], STARE [45], EyePACKS [46], and APTOS [47]. Table 1 represents the general information of these

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Table 1: Some datasets were utilized to train DL and ML models for DR detection. The number of labels is associated with DR stages (N, DR, MDR, SDR, PDR)

Dataset	Number of images	Image size (pixel)	Number of labels	Train+ validation, Test
EyePACS 2015(46)	88,702	433×289 ~ 5184×3456	25810, 2443, 5292, 873, 708	35126, 53576
APTOS 2019(47)	3,660	-	-	-
Messidor(38)	1,200	1440×960 ~ 2304×1536	-	-
Messidor-2(38)	1,748	1440×960 ~ 2304×1536	-	-
IDiRD(39)	516	4288×2848	-	413, 103
DRIVE(40)	40	565×584	33, 7	20, 20
DIARETDB0(42)	130	1500×1152	20, 110	-
DIARETDB1(41)	89	1500×1152	5, 84	28, 61
ODIR(43)	10,000	-	1620, 8380	9000, 1000
DDR(44)	13,673	-	6266, 6256	9568, 4105
STARE(45)	~ 400	-	-	-

datasets.

These datasets are used to compare different classification methods of DR. To check the accuracy of the model trained on these datasets, the clinical datasets collected from the participating laboratories are used. Among the mentioned datasets, Messidor is used to train DL and ML models.

Developed algorithms for the diagnosis of DR Fundus cameras are used to examine the eyes of patients for DR. The resulting images are then graded to identify and assess the severity of DR; several AI-based systems have been developed by different groups using retinal fundus images to diagnose DR. Our review paper investigates DR classification using AI methods. We divided the investigation results into three groups Supervised [48], Self-Supervised [49], and Transformers [50], and two subgroups are binary and multiple classifications.

Supervised

1-Binary classification

Pao et al. [51] determined a model that uses the deterioration of each Fundus image to recognize the lesion and generate important areas for feature extraction by a binary classification algorithm. This model reached 87.37 % accuracy. In this study, the ROC curve was used as the main accomplishment sign, however the inequality in the Fundus data. Hua et al. [52] developed a model based on ResNet-101 for image classification called RFA-BNET. Although this model achieved less accuracy than the ensemble models, it was considered due to the method used. They reported accuracy, specificity, sensitivity, and Area Under the Receiver Operating characteristic Curve (AUROC) to 95.1 %, 97.4 %, 79.32 %, and 0.9732 respectively.

Paisan et al. [20], to evaluate the performance

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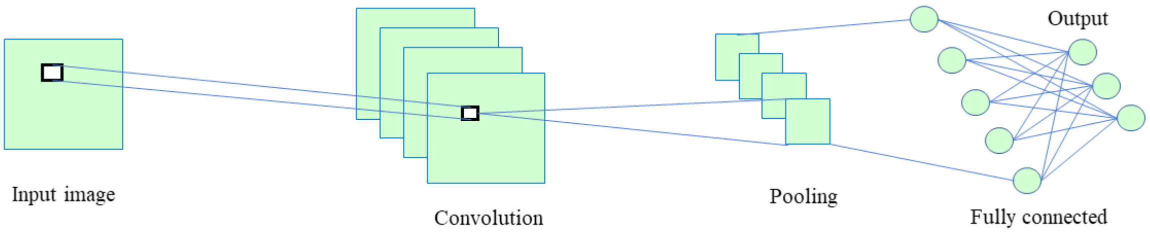

Figure 4: A simple conception of CNN with Convolution, Pooling, and a Fully connected layer

of AI-based systems in the real world, experimented with Thailand's health system. The DL algorithm investigated in this study achieved accuracy over 94 %, specificity equal to 95.4 %, and sensitivity was 91.4 %. Pragati et al. [53] developed an integrated ML approach that used SVM, Principal Component Analysis (PCA), and optimization techniques. In this study, DR datasets were applied to DT, SVM, RF, and NB Machine Learning algorithms. The SVM algorithm performed nearly 76 % better than the other algorithms. Also, in this study, found that only the RF algorithm using PCA performed better. For the mentioned combination of RF and PCA, accuracy, specificity, sensitivity, precision, recall, and F1_score had been reported to be 67.09 %, 67.6 %, 66.3 %, 67 %, 67 %, and 67 % respectively. Also, to improve the performance of SVM and PCA, they used the optimization method known as butterfly flame. The result of this approach was an 85.61 % performance improvement. Also, the measured six mentioned evaluation metrics were 86.3 %, 75.2 %, 94.2 %, and specificity, sensitivity, and F1_score were equal to 86 %. Garcia et al. [54] used the AlexNet and VGGnet16 frameworks to develop a new method to investigate the left and right eyes separately. VGG16 achieved 83.68 % accuracy without a fully bonded layer. Also, AUROC for the proposed method was 0.996. But the different stages of DR were not classified.

2- Multiple classifications

Zago et al. [55, 56] conducted a study using VGG16 and CNN. DIARETDB1 dataset was used to train the model. They used images with dimensions of 65 x 65 pixels. These images are obtained using the mentioned frames with five layers of two-dimensional convolution. They used Messidor-2, Kaggle, DDR, Messidor, IDRiD, and DIARETDB0 datasets to test and classify DR. The reported sensitivity and AUROC for the proposed method were 0.94 and 0.916 respectively [56].

Prabha et al. [57] developed a classification algorithm based on CNN to diagnose DR in the early stages. They extracted the required data, which were fundus images, to train the algorithm from the STARE and DRIVE datasets. In this method, image thresholding using the repeated selection method was used for image segmentation. The proposed system achieved high accuracy of 95 % and sensitivity of 94.7 %.

Keel et al. [58, 59] developed two CNN-based DL systems, one of which was for diagnosing DR. In this algorithm, regions of the image that were distinct in terms of time were identified. After this step, a thermal map of the areas necessary for early disease diagnosis was prepared. Among the most critical areas for the early prediction of the disease, which is 96 %

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of cases, that cause a true positive referral of DR, were the areas that suffered from retinal bleeding.

Of course, the study of Abramoff et al. [60, 61] was the first time that an advanced DL algorithm based on CNN was used for the automatic diagnosis of DR. Messidor-2 dataset was used to train this algorithm. The sensitivity and specificity of this algorithm were reported 87.2 % and 90.7 % respectively.

Wang et al. [62] used a classical BP Neural Network algorithm to diagnose retinopathy. They used the Levenberg-Marquardt method as the training function. Ophthalmologists used 80 datasets to evaluate it. The accuracy result was satisfactory. Dota et al. [63] to solve the problem related to the Garcia et al. study, used the Kaggle DR dataset to apply to three DL models: Deep Neural Network (DNN), Fully connected Neural Network (FNN), and CNN. After the preprocessing steps, the DNN achieved an accuracy of nearly 90 %.

Xu et al. [64] Developed a DL architecture in which they categorized the Fundus images using CNN and a Stochastic Gradient Descent optimizer. The proposed model trained on the Kaggle and EyePACS datasets, which were images of Fundus retinopathy. The model's architecture was such that out of 8 two-dimensional convolutional layers, included four max-pooling layers, followed by two convolutional layers. Finally, it was related to two layers utterly related to a softmax activation function. The model saw the identified features such as hard transpiration, microaneurysms, blood vessels, and red lesions. They compared the method of feeding the trees with the extracted features to CNN. Gradient Boosting Machine (GBM) hyper-parameters are then used for the number of classes. The proposed model achieved an accuracy of over 94 %.

Self-Supervised

1-Binary classification

In the model developed by Lu et al. [65] appointed SFCN, trained on 25 images from the DRIVE dataset, an accuracy of 87.6 % and Area Under Curve (AUC) equal to 0.85 had been recorded. In comparison, Hua et al. [52] RFA-BNET utilized 20 images accompanying thorough augmentations and reached an accuracy of 95.1 %. Also, other metrics such as sensitivity, specificity, and AUROC have been reported to be 79.32 %, 97.41 %, and 97.32 % respectively. Kanagasinget et al. [66] developed a DL algorithm using data from DiaRetDB1, EyePACS, and the Australian Eye DR Database. The desired algorithm achieved a specificity of 92 % on 193 patients in an Australian clinic.

2-Multiple-classification

He et al. [67] trained CABNet on the EyePACS dataset. This block makes it easier for the model and parts of the Fundus images to be embedded. This makes the model superior and acceptable. CABNet also reached 85.69 % accuracy and 0.8542 was reported for kappa.

In a study conducted in 2018 by Hemanth et al. [68], they developed Hopfield's Neural Networks (HNN) to classify retinal images. This network can adjust the weight and output together. The weights are dynamic in the proposed method. The proposed algorithm called MHNN achieved 99 % accuracy, sensitivity, and specificity of nearly 99 %. This algorithm was evaluated better than many neural networks and HNN methods for DR diagnosing.

Transformers

1-Binary classification

Panwar et al. [69] attended a study utilizing

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a CNN trained to accompany a transfer model. The model was trained by extracting a feature vector from the test set of images. This vector forges the capability to categorize new images accompanying extreme accuracy in other classifiers. This study showed that a DL architecture using transfer learning can precisely classify spots in fundus images. Sun et al. [70] proposed a transformer model, which was based on a pixel relational encoder and a decoder. The developed model uses only image labels. This model compensated for the gap between the grading of DR and the diagnosis of the lesion.

In another study by Papadopoulos et al. [71], a transformer model was developed that uses the attention mechanism to devise heat maps. This procedure extracts the required information by combining various four-sided sections accompanying an attention form concentrated on the domains of the eye that have spots. The model was evaluated on Messidor-2 and Kaggle datasets. Also, AUC, sensitivity, and specificity for evaluation on the Kaggle dataset were 0.957, 95.1 %, and 75.3 % for high sensitivity points respectively. But, for the high specificity points, the reported specificity was 84.3 % and sensitivity was equal to 95.1 %. On the other hand, AUC, sensitivity, and specificity for the evaluation by Messidor-2 were 0.976, 95.4 %, and 84.5 % on the high sensitivity points respectively. While the reported sensitivity on the high specificity points was equal to 85.6 % and specificity was 95.1 %.

2- Multiple-classification

MIL-VT is a similar model to MIL that uses the same approach as Vanilla ViT [72, 73]. Using the APTOS dataset, 85.5 % accuracy was reached in the DR image classifying. The elite of this proposed model achieved higher accuracy compared to GREEN-SE-ResNext50.

Recent advances and the use of AI algorithms in ophthalmology have provided more accessible access to screening systems that lead to more accessible and more accurate diagnosis, and classification of DR. Of course, inexpensive smartphone-based fundus cameras such as DIYretcam, T3retcam, MIIretcam, JaizRetcam, and Hopescope provide rapid image analysis [74]. Thus, in a study conducted by Sosale et al., Medios AI evaluated the Remidio Fundus phone. The sensitivity and specificity for it were higher than 92 % [74].

Conclusion

In this article, 23 papers have been investigated to review the proposed methods for diagnosing Diabetic Retinopathy in the early stages. 13 articles related to supervised methods, six articles for self-supervised methods, and four selected papers suggested methods with transformers reviewed. This article lets researchers be aware of the advances in Artificial Intelligence algorithms for Diabetic Retinopathy detection.

Since Machine Learning and Deep Learning methods have entered the mainstream of medicine, Diabetic Retinopathy can be diagnosed in the early stages using these techniques. This way, the statistics of blindness and vision loss caused by Diabetic Retinopathy going to reduce. According to the studies, the proposed models for transformers provide better interpretability for doctors and researchers. In addition, more rigorous scientific evidence on safety, validity, usability, patient, and physician satisfaction is necessary before using AI-based systems. On the other hand, AI algorithms are valuable in anticipating future health consequences after evaluating former cases of the ailment. In ophthalmology, the reliable prophecy of visual

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issues assists physicians in ailment counseling and clinical administration while reducing healthcare costs. But there are still questions regarding using these systems in medicine and ophthalmology. For instance, if a patient is misdiagnosed using AI-based technologies, who will be responsible? Therefore, future research should try to address such questions.

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Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present manuscript.

Abbreviations

DR: Diabetic Retinopathy
AI: Artificial intelligence
ML: Machine Learning
DL: Deep Learning
VA: Visual Acuity
IoP: Intraocular Pressure
AMD: Age-related Macular Degeneration
OCT: Optical Coherence Tomography
NPDR: Non-Proliferative Diabetic Retinopathy
PDR: Proliferative Diabetic Retinopathy
NN: Neural Network
SVM: Support Vector Machine
RF: Random Forest
LR: Logistic Regression
DT: Decision Tree
NB: Naïve Bayes

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KNN: K-Nearest Neighbor
RNN: Recurrent Neural Network
CNN: Convolutional Neural Network
BM: Boltzmann Machine
AE: AutoEncoder
DBN: Deep Belief Network
PCA: Principal Component Analysis
AUROC: Area Under the Receiver Operating characteristic Curve
AUC: Area Under Curve

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