Automatic Classification of Diabetic Retinopathy Through Segmentation Using CNN

Saif Hameed Abbood[1,2](✉), Haza Nuzly Abdull Hamed[1], and Mohd Shafry Mohd Rahim[1]

[1] School of Computing, Faculty of Engineering, University Technology Malaysia (UTM), 81310 Johor, Malaysia
saifhameed.it@gmail.com, {haza,shafry}@utm.my
[2] Information Technology, Wasit Health Directorate, Iraqi Ministry of Health, 52001 Wasit, Iraq

Abstract. The process division of Diabetes Retinopathy (DR) has been considered as a significant step in diabetic retinopathy assessment and treatment. Different levels of microstructures like microaneurysm, rough exudates as well as neovascularization could take place on the retina area due to disruption to the retinal blood vessels triggered by elevated blood glucose levels. This is one of the primary causes of the prevalent visual impairment/blindness due to diabetes. Image segmentation, region merging, and Convolutional Neural Network (CNN) used in the paper for automated classification of high-resolution photographs of the retinal fundus in five stages of the DR. High heterogeneity is a significant problem for fundus image recognition for diabetic retinopathy, whereby new blood vessel proliferation including retinal detachment occurs. Therefore, careful examination of the retinal vessels is important to obtain accurate results which, through retinal segmentation could be achieved. We also highlight the difficulties in the development and learning of powerful, efficient, and reliable deep learning models for different DR diagnostic problems. The system was able to classify various DR stages with an average accuracy of around 94.2%, a sensitivity of 97%, and a specificity of 96%. There appears to be a genuine necessity for a steady interpretable classification system for DR and diabetic macular edema supported with solid confirmation. The suggested interpretable categorization systems allow diabetic retinopathy and macular edema to be properly classified. These technologies are expected to be beneficial in increasing diabetes screening and communication and discussion among those who care for these patients.

Keywords: Diabetic retinopathy · Computer vision · Image classification · Deep learning · Artificial intelligence

1 Introduction

Diabetic retinopathy (DR) is the leading cause of avoidable visual loss in people of working age in developed countries. The disease's global prevalence is estimated to rise at an exponential rate, reaching 529 million by 2030 [1]. As the number of persons diagnosed with diabetes rises, so does the number of people who get retinopathy.

S. Spinsante et al. (Eds.): HealthyIoT 2021, LNICST 432, pp. 99–112, 2022.
https://doi.org/10.1007/978-3-030-99197-5_9

This is concerning for worldwide national health care, as it affects people's ability to work, putting the economy in jeopardy. As a result, it is vital to provide a cost-effective and successful method of screening patients, which, when combined with collaborative treatment, has been credited with lowering the incidence of legal blindness in the working-age population [2].

The retina, which is spherical in shape, consists of a small membrane in the back of the eye. The purpose of the retina is to pass light into the neuronal signals as well as to communicate the sensory visual input with the brain 1. The retina is located next to the optic nerve, as well as a dark circular section present in the central region of the retina is known as the macula. The fovea is a key component of the macula that offers a clear sight [4].

Diabetic retinopathy (DR) is a diabetes complication that swells and drains fluids and blood from the veins of the retina [5]. If diabetic retinopathy, shifts to an advanced stage it can lead to vision loss. DR causes 2.6% of blindness worldwide [6]. In diabetic patients with a long-term illness, the risk of diabetes retinopathy rises. Normal retinal screening is critical for the diagnosis and early treatment of DR in patients with diabetes to prevent blindness [7]. The presence of various forms of lesions in a retina picture is determined by diabetic retinopathy. These lesions are soft and hard Exudates (EXs), Hemorrhages (HMs), and Microaneurysms (MAs) [8, 9].

The presence of excessive blood glucose in the blood develops diabetic retinopathy and affects minute blood vessels within the retina. These tiny blood vessels will leak fluids and blood into the retina, which will form characteristics such as hemorrhages, micro-aneurysms, spots of cotton wool, rough exudates, vein loops, macula swelling, and thickening [10]. Moreover, as blood flow is being supplied, the retina begins to develop several new abnormally fragile blood vessels called Intraretinal Microvascular Abnormalities IrMAs [11]. Non-Proliferative DR (NPDR) and Proliferative DR can be commonly called (PDR) [5]. The phases of DR may be graded depending on the appearance of characteristic features on the retinal fundus.

The elevated pressure in the eye could cause late-stage damage to the optic nerve. Therefore, DR can be indicated momentarily as a lack of vision (which in this situation is irreversible) due to symptoms of diabetes of retinal blood vessels. Exudates [12] are a crucial symptom of diabetic retinopathy that can be bagged in a picture of the retinal fundus and is the evidence for the production or development of the DR in the patient. Retinal testing for weakened eyes at the early stages is a potential solution for diagnosis (Fig. 1) [13].

Early detection of diabetic retinopathy can minimize vision acuity, visual impairment, and related morbidity [15]. Early diagnosis may lower the risks of DR. The most prevalent vision-threatening lesions in Type 1 diabetes are the Proliferative Diabetic Retinopathy (PDR) as well as the most prominent Type 2 disorder is Diabetic Macular Edema (DME) which significantly result in mild visual losses. The retinal fundus tests allow the retinal vasculature as well as underlying anatomy to be specifically visualized. Retinal vasculature disruption is largely due to the pathogenicity and clinical characteristics of DR. In the early stages the DR identification may also help in the diagnosis of developing lesions through retinal fundus images [16].

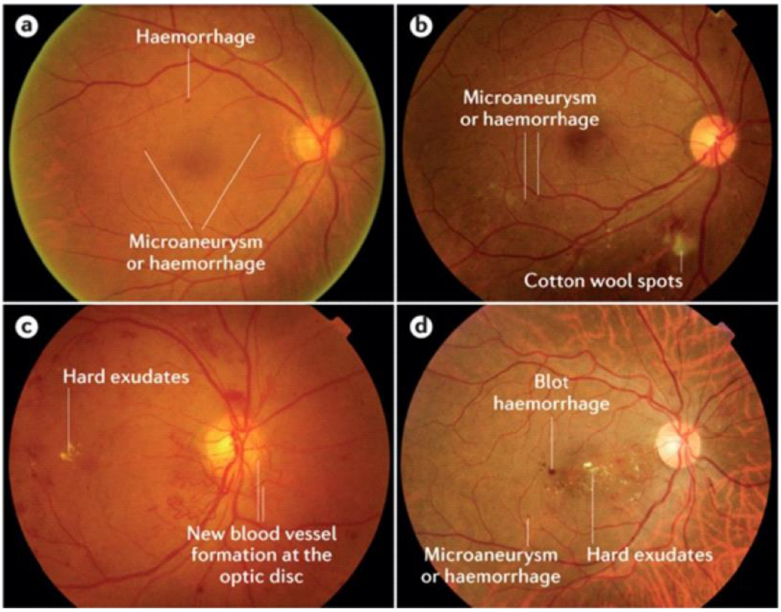

Fig. 1. Fundus images showing various DR developments (a–d) (Source: Nature Reviews/Disease Primers) [14]

Various approaches could be adopted to diagnose diabetic retinopathy. Usually, the retinal fundus is examined by an ophthalmologist with a pupil dilatation, whether with an indirect ophthalmoscope or slit-light biomicroscope [17]. Put another way, a dilated pupil assists in taking photographs of the fundus, and afterward, these images can be investigated by an ophthalmologist. The state-of-the-art in diabetic retinopathic diagnosis is the Early Treatment of Diabetic Retinopathy Study (ETDRS), performed by professional photograms and skilled ophthalmologists, using 30°, 7 standard field stereoscopy 35 mm (7F-ETDRS) color slides or with the help of fundus fluorescein angiography (FFA) [18].

Telemedicine is increasingly used to diagnose diabetic retinopathy and, in particular, to scan for the DR on basis of digital images from retinal fundus compressed (or otherwise), processed and sent to a distant ophthalmologist for further evaluations [19]. Through the extraction and classification of characteristics, segmentation may be utilized in medical research to separate various tissues from one another [20, 21].

The purpose and contribution of this work are achieving a high accuracy classification of five diabetic retinopathy stages as an aim to simulate the clinical diagnosis of the expert ophthalmologists.

2 Literature Review

The current medical imaging literature review provides promising outcomes in various modalities of medical scanning and imagery [22]. Salehinejad et al. [23] suggested the development of X-rays for the identification of chest Disorders by a Convolutionary Generative Adversarial Networks (DC-GAN). They demonstrated that artificial data is better than the actual unbalanced and balanced data sets as well as it improves the detection performances and accuracies.

Rad A. E. [24] devised a methodology for analyzing dental x-ray pictures and diagnosing caries problems in teeth Enhancement was used to increase the quality of the X-ray pictures, and the Thresholding approach was used to make the pictures simpler. The individual tooth was extracted using the integral projection approach, and a feature map of the tooth surface was created for the analysis and detection procedure.

Mazhar J. Awan [25] presented a method for Knee Anterior Cruciate Ligament from Magnetic Resonance Imaging by combining class balance and data augmentation, a 14-layer ResNet-14 convolutional neural network (CNN) architecture with six alternative orientations.

The relevance and viability of diabetic retinopathy diagnosis telemedicine were assessed by Vaziri et al. [26], as a predictor, with a standard statistical consensus value (κ statistics). The goal of this analysis was to evaluate the telemedicine and classification precision within the full scope of DR and Diabetic Macular Edema (DME) in comparison to today's gold standards.

The previous research in the identification of different phases of diabetic retinopathy focused on the systematic extraction of features as well as classification of features using different techniques of computer vision & machine learning-based classification models. Rahim et al. [27] published a 2016 approach for the use of blurred picture treatment for diabetic retinopathy. Method focused on the different lesions of the retinal tract including the hemorrhages, exudates, micro-aneurysms, blood vessels, etc.

A method to automatically diagnose non-proliferative DR was suggested by Al-Jarrah and Shatnawi in [28]. The approach was based upon the identification of MAs and HAs by extracting essential features including the optic disks, fovea as well as blood vessels to accurately segment the lesions of the dark spot.

Yi-Peng Liu [29] WP-CNN was presented, which was motivated by ensemble learning. Backpropagation is used to optimize various path weight coefficients, and the output features are averaged for redundancy reduction and fast convergence in WP-CNN.

An ensemble for classifying the retinal image suggested by Balazs Harangi [30] that combines a convolutional neural network (CNN) with traditional hand-crafted features into a single design. To offer a final forecast, this method combines CNN training with fine-tuning of the weights of handcrafted characteristics. This solution is focused on automatically classifying fundus images based on the severity of DR and DME.

Gautami ghan [31] suggested a model to diagnose DR from digital anatomical structure images, the methodology uses the R-CNN (Regional Convolutional Neural Network) approach. The complete image is segmented in the suggested method, and the regions of interest are extracted for further processing. The suggested method employs four layers of convolutional neural networks to train 130 anatomical features and is then tested on 100 photos. All of the photographs are divided into two categories: those with DR and those without.

Iyyanar P [32] presented a CNN approach for automatic classification of diabetic retinopathy through spatial analysis, The proposed approach is to create a more efficient and effective way to identify images using minimal pre-processing procedures.

These methods perform slightly worse than earlier methods, owing to the failure of the neural network to learn critical aspects such as the proliferation of new blood vessels and retinal detachment that occur during the lateral phases of diabetic retinopathy with a high severity level.

According to our study of the previous work, some limitations are noticed in that approached such as the methods which were used in some works are not achieved high accuracies [29–31], in addition, some works such as [26–28] are not detected all lesions of diabetic retinopathy such us neovascular of the retina that's mean not all stages of diabetic retinopathy are detected, this shows the necessity of more researches in the field to achieve high accuracies to simulate the clinical diagnosis of disease.

We utilized U-Net segmentation in this work with region merging and a Convolutional Neural Network to detect the various phases of Diabetic Retinopathy. The technique of automatically detecting the borders of blood vessels within the retina is known as retinal segmentation. This helps the classifier to pick up on essential characteristics like retinal growth and separation. Through region merging, losing data is very expected in the segmentation stage owing to the incorporation of retinal segmentation. This technique exceeds previous approaches by a factor of 94.2% ACC, furthermore, for each class, we create important score pixel-maps to assist experienced ophthalmologists to deduce as well as comprehend the outcomes.

3 Methodology

Fundus photography is an imaging technique widely applied to record the scope of disease in medical diagnostic settings and clinical trials. The picture of the fundus consists of 3 channels: red, green, and blue (RGB). Moreover, the retinal fundus images contain three types: color fundus, red-free, and stereo fundus. The DR characteristics, including intra-retinal hemorrhagenic structures, microaneurysms, wedged cotton-wool spots, virulence beading, extensive growth of blood vessels, and Intra-retinal Microvascular Abnormalities (IrMA) have been described by seven standard color fundus images. Digital retinal fundus images are a fast-imaging technique that can be accessed in a highly availability, non-invasively, and well-tolerated fashion.

High variability, particularly for proliferative DR within which, the retinal spread of new blood vessels including retinal separation occurs, is an important problem in the diagnosis of fundus photos. The method of automated identification of blood vessel boundaries is known as retinal segmentation. Therefore, we must locate the position and emergence of the new blood vessel to calculate the retinal feature extraction through image segmentation (Fig. 2 and Fig. 3). The correct examination of the retinal blood vessels is important to obtain the exact results, that could be accomplished by retinal segmentation. As mentioned, retinal segmentation is an automated blood vessel boundary detection mechanism.

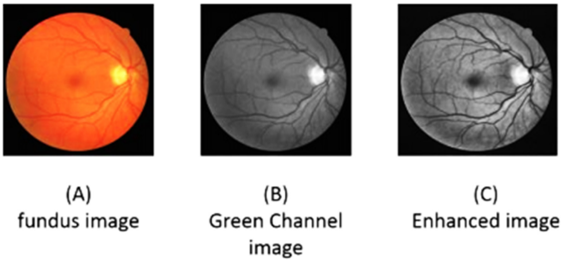

Fig. 2. Fundus image pre-processing and enhancement [33] (Color figure online)

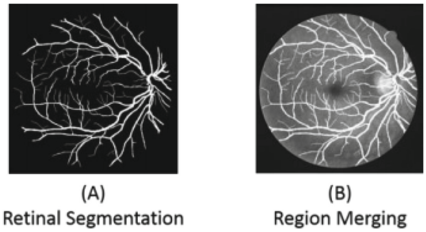

Fig. 3. Fundus image segmentation [33]

3.1 Proposed Method

The approach presented in this paper intends at the detection of the different phases of DR via retinal segmentations with U-Net along with the merging of the region & using convolutional neural networks. Retina segmentation is the mechanism by which the blood vessel boundary inside the retina is automatically detected. This helps classificatory predictors to learn essential features like the proliferation of retina as well as retinal detachments. The data lost in the event of segmentation of the retinal image is restored using region merging (Fig. 4).

The U-net Framework is an encoding-decoding paradigm that has some skip interfaces between the decoder and the encoder modules. This architectural design's key benefit is that it can take a broader context into consideration when planning for a pixel-based predictor.

Preprocessing, Retinal Segmentation, and Classifier are the three stages of the approach proposed in this paper. In Fig. 4, the proposed method's flowchart is depicted. The database comprises high-resolution retina fundus photographs with a large black boundary. As shown in Fig. 2(A), we started by removing the majority of the black borders and then resizing the photos to 480 × 480 pixels. Data augmentation is the most effective way to avoid overfitting. Image transformations such as color augmentation, translation, rotation, flipping, stretching, are used in the augmentation step. The training set is increased by an element of two thanks to the data augmentation. The network suffers from significant overfitting without data augmentation. The fundus picture has three channels: red, green, and blue. To calculate the segmentation of the retina, we must monitor the location of the blood vessels. When compared to a brighter background, the darker blood vessels contrast refines substantially. As seen in Fig. 2(B), the stronger

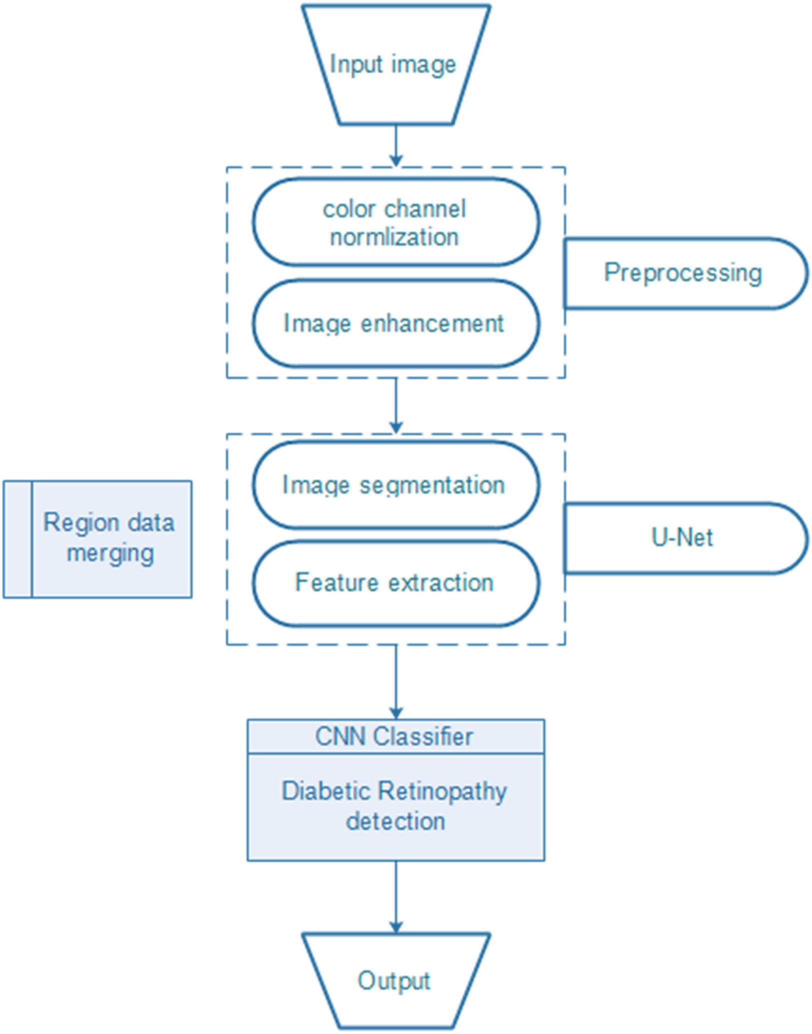

Fig. 4. Process for automatic DR detection

green portion enhanced the contrast of the retinal image, resulting in the best outcome. As an outcome, we chose the green channel of an image and sent it to be preprocessed further, after enhancement, these images are fed into U-net, which performs retinal segmentation. Figure 2(C) depicts the outcome of picture enhancement.

The technique of automatically detecting the borders of blood vessels within the retina is known as retinal segmentation. This enables the classifier to pick up on critical characteristics like retinal detachment and retinal proliferation. These characteristics play a crucial role in the characterization of diabetic retinopathy and considerably increase accuracy. The retinal segmentation was done with the use of a neural network. The U-Net is a Convolutional Neuron network with an imminent and advancing path in its architecture. The approaching path captures context and is symmetric, whereas the advancing path allows for exact localize. This is the best way way to do retinal segmentation. Figure 3(A) shows the result of retinal segmentation. As illustrated in Fig. 3(B), to recover data lost during retinal segmentation, the U-output Net is subsequently subjected to region merging with its input image. The classifier is a convolutional neural network that learns features of pictures produced after retinal segmentation with region merging and uses them to classify diabetic retinopathy into five stages based on severity.

3.2 Deep Learning

Deep Learning (DL) techniques [34] in several automated classification-based problems have already been employed commonly over the past few years. For image classification, the normal method involves extraction of the essential characteristics from a collection of convolutionary layers, which is followed by a final grading by a group of fully convolution layers with those characteristic attributes. The parametric values are modified in the training process while utilizing a gradient-based optimization approach, that reduces a predetermined loss function to a minimum [35]. After the classification model has been trained (the parameters of model layers are adjusted), particularly in comparison with the correct "true" values contained in a labeled dataset where classification quality determines the performance quality. These data are regarded as the gold standard, preferably based on the expertise of a human specialist's panel. Further, the image mapping enables multi-dimensional items to be grouped into a smaller number of classes.

Classification of Diabetic Retinopathy
The proposed model estimates the probability P(K|I) since C belongs to the potential class of production and I to the retina. Using a SoftMax method [36] as a final layer upon the given values following the final linear combination of selected features. This can be determined as the probability function:

$$P(K/I)_i = e^{Z_i} / \sum_{j=1}^{C} e^{Z_j} \tag{1}$$

Before using SoftMax, let us consider the final value of any output neuron, which is for instance calculated as ZK for the Class K ranking. To measure the likelihood of all groups, we need a normalization function from SoftMax, however, in this event, we just want to test SoftMax within the context of argmax (SoftMax), since argmax (Zi) = argmax (SoftMax (Zi)). Therefore, we ignore SoftMax from within the assessment of class definition.

Dataset
The data collection consisted of the retinal fundus downloaded from Kaggle (containing about 67k images) for the training/testing of diabetic retinopathy. Other patient information (demographic profile) was not used in the present data sets. In each of the images, various DR stages, as well as severeness of the symptoms, were measured. In this paper, the International Clinical Diabetic Retinopathy (ICDR) scores were used for the classification and grading of DR using retinal fundus images [37], which indicates no/normal

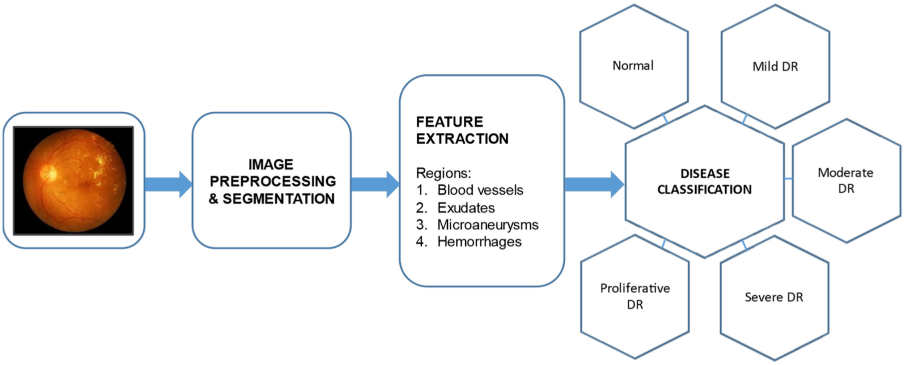

Fig. 5. Model for classification of DR stages

DR (0), moderate DR (1), mild DR (2), severe DR (3) and proliferative DR (4). Figure 5 represents the model for the classification of DR stages.

Consequently, around 207 retinal fundus images from the EyePACS database collection of Kaggle were collected for this analysis. For the training and validation algorithm, 70% maculation-centered images from the dataset were used (referred to as development set, divided into training (~68%) and tuning set (~2%)). We also used 30% of the dataset as test data to measure the algorithm's output to determine the performance of the algorithm.

Convolutional Neural Network (CNN)
Convolutional Neural Network CNNs are more effective algorithmically and in computational integrity than full connected networks. Therefore, CNNs are perfect to take advantage of the general high-local image correlations and the pixel mapping.

4 Results

The output of the model was found to predict various stages of diabetic retinopathy based on hemorrhages, exudates/hard exudates, proliferative blood vessels, microaneurysm, cotton wool spots, etc. Table 1 shows the outputs of the present classification model for diabetic retinopathy. The findings reveal that the classification model makes the precise estimation of the unspecified class efficiently with about 85% accuracy. It was able to accurately forecast severe DR (3), moderate DR (2), mild DR (1), as well as Proliferative DR (4) up, to 86%, 81%, 92.04%, and 88.72%, respectively. The classification model reported an 82% sensitivity, an 86% accuracy as well as up to 95% high prediction efficiency. Figure 6 and Fig. 7 show classification results of DR predictions. Figure 8 represents the plotting curve for training and testing via model.

Table 1. DR classification results

Stage (class)	Training dataset	Testing dataset	Correct classification (%)
Normal (0)	41	8	84.43
Mild DR (1)	50	10	81
Moderate DR (2)	49	8	92.04
Severe DR (3)	53	10	86
PDR (4)	41	8	88.72
Mean			86.74

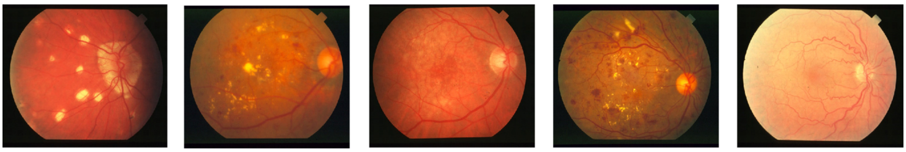

Fig. 6. Classification of DR (Test 1)

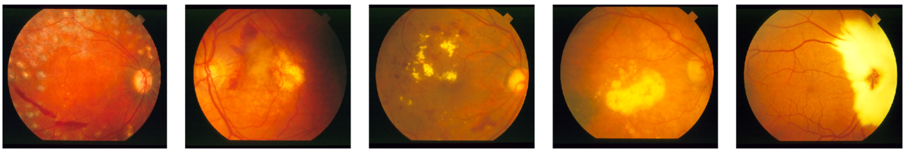

Fig. 7. Classification of DR stages (Test 2)

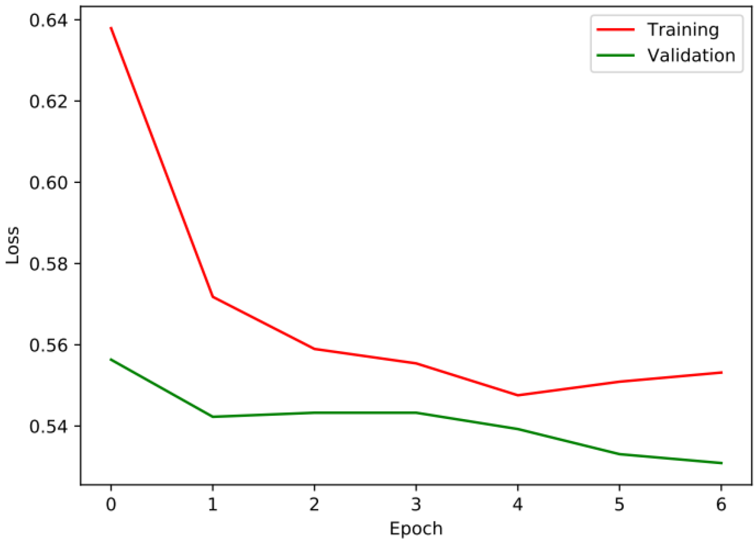

Fig. 8. Plotting training and validation through model

Table 2 below, represents a salient comparison among previous works based on method, accuracy, sensitivity, and specificity.

Table 2. Comparison of previous works

Reference	Classes	Method	Accuracy (%)	Sensitivity (%)	Specificity (%)
[12]	3	Blood vessels, exudates, and texture	93.6	90.3	100
[15]	2	Decision support system	–	100	63
[26]	5	Higher order spectra	82	82.5	88.9
[27]	4	Area of blood vessels, exudates	84	91.7	100
[34]	2	Hemorrhages, blood vessels, microaneurysms, exudates	–	74.8	82.7
[30]	5	Hemorrhages, exudates, blood vessels, microaneurysms,	90.07		
[31]	5	Hemorrhages, exudates, blood vessels, microaneurysms,	93		
[32]	5	Hemorrhages, exudates, blood vessels, microaneurysms,	90		
Proposed work	5	Hemorrhages, exudates, blood vessels, microaneurysms,	94.2	97	96

According to the comparison Table 2 between the previous models with current U-Net, the methods [12, 15, 26, 27] which achieved good results have not detected all features of five stages of diabetic retinopathy such as [12] extracted 3 classes only with 93.6% ACC, as well as [27], while the methods [30–32, 34] detected all features, however, it couldn't achieve high results in comparison with the current work which is achieved high results and all features detection, are achieved 90.07%, 93%, 90%, respectively. The proposed regional model has a higher level of accuracy. This is because

DR lesions were extracted from regional features. U-Net assists in the extraction of additional useful features for classification.

Among all the networks on the test set, the proposed U-Net technique has the best accuracy rate of 94.2%. We also look at the sensitivity and specificity indexes for the prediction result to see how well the model performs on the referable diabetic retinopathy identification task. The identification system threshold in clinical diagnosis can be modified according to the diagnosis requirement for expected sensitivity and specificity. As a result, because it indicates the prediction confidence degree, which shows the model generalization power, it is an important quantitative statistic in practical application. The best result is achieved by our U-Net model, showing that the suggested network has greater classification performance and confidence.

5 Conclusion and Future Work

The paper proposed an optimal model for Diabetic Retinopathy detection, we used U-Net approach to design this model. It was also observed that preprocessing of DR images is very essential to get proper features. In the case of noisy images, the chances of getting poor data will lead to lower accuracies. Additionally, we applied the model with image pre-processing for an interpretable DR classifier, achieving more than 94% of accuracy for the detection of various classes of diabetic retinopathy. The system was able to classify various DR stages with an average accuracy of around 94.2%, a sensitivity of 97%, and a specificity of 96%. The proposed framework not only allows retinal fundus images to be classified in 5 ICDR standardized DR grades, but it can also produce significant score pixel-maps for each class to allow professional ophthalmologists to deduce as well as perceive the results. Automated tools have the potential to improve the quality of DR screening, increase access to health care, and lower the cost of screening. Early detection and therapy may assist to avoid the beginning of the disease or slow the progression of the condition. In the future, the automated network design based on feature amalgamation will receive increasing attention, also we are trying to use a generative adversarial network to solve the lack and imbalance of data and try to train the networks using a limited amount of data.

References

1. Qureshi, I., Ma, J., Abbas, Q.: Recent development on detection methods for the diagnosis of diabetic retinopathy. Symmetry **11**, 749, (2019)
2. Liew, G., Michaelides, M., Bunce, C.: A comparison of the causes of blindness certifications in England and Wales in working-age adults (16–64 years), 1999–2000 with 2009–2010. BMJ Open **4**, e004015 (2014)
3. Fenner, B.J., Wong, R.L., Lam, W.C., Tan, G.S., Cheung, G.C.: Advances in retinal imaging and applications in diabetic retinopathy screening: a review. Ophthalmol. Therapy **7**(2), 333–346 (2018)
4. Li, X., Li, X.: The antidepressant effect of light therapy from retinal projections. Neurosci. Bull. **34**(2), 359–368 (2018)
5. Shi, L., Wu, H., Dong, J., Jiang, K., Lu, X., Shi, J.: Telemedicine for detecting diabetic retinopathy: a systematic review and meta-analysis. Br. J. Ophthalmol. **99**(6), 823–831 (2015)

6. Bourne, R.R., et al.: Causes of vision loss worldwide, 1990–2010: a systematic analysis. Lancet Glob. Health **1**(6), 339–349 (2013)
7. Chakrabarti, R., Harper, C.A., Keeffe, J.E.: Diabetic retinopathy management guidelines. Exp. Rev. Ophthal. **7**(5), 417–439 (2012)
8. Salz, D.A., Witkin, A.J.: Imaging in diabetic retinopathy. Middle East Afr. J. Ophthalmol. **22**(2), 145 (2015)
9. Bawankar, P., et al.: Sensitivity and specificity of automated analysis of single-field non-mydriatic fundus photographs by Bosch DR algorithm—comparison with mydriatic fundus photography (ETDRS) for screening in undiagnosed diabetic retinopathy. PLoS ONE **12**(12), e0189854 (2017)
10. Vo, H.H., Verma, A.: Discriminant color texture descriptors for diabetic retinopathy recognition. In: 2016 IEEE 12th International Conference on Intelligent Computer Communication and Processing (ICCP) 8 September 2016, pp. 309–315. IEEE (2016)
11. Gupta, G., Kulasekaran, S., Ram, K., Joshi, N., Sivaprakasam, M., Gandhi, R.: Local characterization of neovascularization and identification of proliferative diabetic retinopathy in retinal fundus images. Comput. Med. Imaging Graph. **55**, 124–132 (2017)
12. Patil, P., Shettar, P., Narayankar, P., Patil, M.: An efficient method of detecting exudates in diabetic retinopathy: using texture edge features. In: 2016 International Conference on Advances in Computing, Communications, and Informatics (ICACCI), pp. 1188–1191 (2016)
13. Prasad, D.K., Vibha, L, Venugopal, K.R.: Early detection of diabetic retinopathy from digital retinal fundus images. In 2015 IEEE Recent Advances in Intelligent Computational Systems (RAICS), 240–245 (2015)
14. Wong Ty, C.C., Larsen, M.: Sharma, S., Simo, R.: Diabetic retinopathy. Nat. Rev. Dis. Primers **2,** 16012 (2016)
15. Xu, K., Feng, D., Mi, H.: Deep convolutional neural network-based early automated detection of diabetic retinopathy using fundus image. Molecules **22**(12), 2054 (2017)
16. Winder, R.J., Morrow, P.J., McRitchie, I.N., Bailie, J.R., Hart, P.M.: Algorithms for digital image processing in diabetic retinopathy. Comput. Med. Imaging Graph. **33**(8), 608–622 (2009)
17. Wat, N., Wong, R.L., Wong, I.Y.: Associations between diabetic retinopathy and systemic risk factors. Hong Kong Med J. **22**(6), 589–599 (2016)
18. Chui, T.Y., et al.: Longitudinal imaging of microvascular remodeling in proliferative diabetic retinopathy using adaptive optics scanning light ophthalmoscopy. Ophthalmic Physiol. Opt. **36**(3), 290–302 (2016)
19. Cheloni, R., Gandolfi, S.A., Signorelli, C., Odone, A.: Global prevalence of diabetic retinopathy: protocol for a systematic review and meta-analysis. BMJ Open **9**(3), e022188 (2019)
20. Norouzi, A., et al.: Medical image segmentation methods, algorithms, and applications. IETE Tech. Rev. **31**(3), 199–213 (2014)
21. Sami, A.S., Rahim, M.S.M., Ahmed, F.Y.H., Sulong, G.B.: A review study of methods utilized for identifying and segmenting the brain tumor from MR imageries (2019)
22. Norouzi, A., et al.: Medical image segmentation methods, algorithms, and applications. IETE Tech. Rev. **31(**3), 199–213 (2014)
23. Salehinejad, H., Colak, E., Dowdell, T., Barfett, J., Valaee, S.: Synthesizing chest x-ray pathology for training deep convolutional neural networks. IEEE Trans. Med. Imaging **38**(5), 1197–1206 (2018)
24. Rad, A.E., Amin, I.B.M., Rahim, M.S.M., Kolivand, H.: Computer-aided dental caries detection system from X-ray images. In: Phon-Amnuaisuk, S., Au, T.W. (eds.) Computational Intelligence in Information Systems. AISC, vol. 331, pp. 233–243. Springer, Cham (2015). https://doi.org/10.1007/978-3-319-13153-5_23

25. Awan, M.J., Rahim, M.S.M., Salim, N., Mohammed, M.A., Garcia-Zapirain, B., Abdulkareem, K.H.: Efficient detection of knee anterior cruciate ligament from magnetic resonance imaging using deep learning approach. Diagnostics (Basel) **11**(1), 105 (2021)
26. Vaziri, K., Moshfeghi, D.M., Moshfeghi, A.A.: Feasibility of telemedicine in detecting diabetic retinopathy and age-related macular degeneration. In Seminars in ophthalmology. Inf. Healthcare **30**(2), 81–95 (2015)
27. Rahim, S.S., Palade, V., Shuttleworth, J., Jayne, C.: Automatic screening and classification of diabetic retinopathy and maculopathy using fuzzy image processing. Brain Inform. **3**(4), 249–267 (2016). https://doi.org/10.1007/s40708-016-0045-3
28. Al-Jarrah, M.A., Shatnawi, H.: Non-proliferative diabetic retinopathy symptoms detection and classification using neural network. J. Med. Eng. Technol. **41**(6), 498–505 (2017)
29. Liu, Y.P, Li, Z., Xu, C., Li, J., Liang, R.: Referable diabetic retinopathy identification from eye fundus images with weighted path for convolutional neural network. Artif. Intell. Med. **99**, 101694 (2019)
30. Harangi, B., Toth, J., Baran, A., Hajdu, A.: Automatic screening of fundus images using a combination of convolutional neural network and hand-crafted features. In: 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), pp. 2699–2702 (2019)
31. Ghan, G., Chavan, S., Chaudhari, A.: Diabetic retinopathy classification using deep learning. In: Fourth International Conference on Inventive Systems and Control (ICISC), 2020, pp. 761–765 (2020)
32. Iyyanar, P., Parthasarathy, J.: Diabetic retinopathy classification using deep learning framework. J. Crit. Rev. **7**(14), 2683–2689 (2020)
33. Adapa, D., Joseph Raj, A.N., Alisetti, S.N., Zhuang, Z., Naik, G.: A supervised blood vessel segmentation technique for digital Fundus images using Zernike Moment based features. PLoS ONE **15**(3), e0229831 (2020)
34. Cao, P., Ren, F., Wan, C., Yang, J., Zaiane, O.: Efficient multi-kernel multi-instance learning using weakly supervised and imbalanced data for diabetic retinopathy diagnosis. Comput. Med. Imaging Graph. **1**(69), 112–124 (2018)
35. Scanlon, P.H.: The English national screening program for diabetic retinopathy 2003–2016. Acta Diabetol. **54**(6), 515–525 (2017)
36. Nwankpa, C., et al., Activation Functions: Comparison of trends in Practice and Research for Deep Learning. In: 2nd International Conference on Computational Sciences and Technology (INCCST) (2020)
37. Sahlsten, J., et al.: Deep learning fundus image analysis for diabetic retinopathy and macular edema grading. Sci. Rep. **9**(1), 1–1 (2019)