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Synopsis Of

Detection and Extraction of Clinical Features in Retinal Images and Severity Grading in Diabetic Macular Edema

A Thesis

To be submitted by

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For the award of the degree

Of

DOCTOR OF PHILOSOPHY

1 Abstract

The retinal components such as optic disc, macula and fovea are significant in ophthalmology and information extracted from the components is valuable for various aspects of eye health assessment. The information on optic disc region can help in (i) identifying signs of retinal diseases like hard exudates in diabetic retinopathy (DR) and diabetic macular edema (DME). Hard exudates are lipid deposits in the retina. (ii) It acts as a reference point to locate macula and fovea. High-acuity vision and detailed visual tasks rely on the macula and fovea. It is situated in the center of the retina and in charge of central vision. Recognizing the importance of the macula, its health, and proper functioning are critical to overall visual health. Diabetic macular edema are such conditions that can seriously impair central vision and cause visual loss. (iii) The diameter of the optic disc is a key parameter in assessing and grading diabetic macular edema. The presence, distribution, and extent of hard exudates contribute to the assessment of DME severity. The distribution of hard exudates near the macula can interfere with vision and is associated with more advanced stages of DME.

The World Health Organization (WHO) disclosed in its global vision report that over 2.2 billion people have blindness or visual impairment, and over one billion of those people have a reasonable chance of receiving treatment. DME impacts twenty-one million people worldwide. In patients affected by DR, DME is likely the most common cause of vision loss. The evaluation of retinal disorders received much attention in computer-aided system due to following reasons: (i) Lessening of human participation (ii) Helps early detection (iii) Second opinion (iv) Medical malpractice reduction. The segmentation of the optic disc is crucial in retinal imaging, and its accurate recognition is essential for the advancement of automatic screening systems. In our proposed work, segmentation of optic disc is performed in two stages. In the first stage, an unsupervised algorithm extracts the region of interest containing optic disc. It can be viewed as a pre-segmentation stage which removes the outliers. The second stage involves the segmentation of optic disc at three levels. The objective of this approach is to enhance the intensity of the optic disc region in comparison to the surrounding areas in the image.

Hard Exudates are one of the biomarkers in diabetic retinopathy and basic cause of diabetic macular edema. The optic disc or a portion of it, as well as hard exudates, may exhibit similar intensity levels. Prior information of optic disc helps in segmentation of hard exudates. In this work, we propose an unsupervised approach for the segmentation of hard exudates. The RGB fundus image undergoes partitioning into three mutually exclusive regions, providing flexibility for adapting multiple approaches in different regions for extracting exudates regions. The exudates from one region are segmented using luminance, A-axis component, and adaptive threshold, while the exudates from other regions are detected using a multistage edge detection approach that includes morphological operation and contour feature. It outperforms existing methods under various illumination conditions, considering different shapes, sizes, and positions of exudates.

Ophthalmologists and other medical experts can determine the approximate location of the macula within the retina by knowing the location of the optic disc. We propose an automatic pixel based approach for the localization of optic disc, macula, and fovea. It

generates the motions in all four directions and extract global flow feature of optic disc utilizing optic flow techniques. The global octet flow feature is converted into its image intensity representation. The boundary outliers are removed utilizing the flow feature of masked image. The adaptive threshold technique followed by contours extracts the precise bounding box enclosing optic disc. Further, the approach utilizes both the A-axis and luminance component to compute the optic disc center. The macula is situated at a distance from the optic disc center of about 2.5 times the optic disc diameters. Utilizing this information , the localization of macula is performed in two stages. The first stage entails extracting the region of interest that contains the macula. This stage sense the direction of macula relative to optic disc and extracts the arc segment having macula. This approach ensures the inclusion of the macula in the region of interest and eliminates localization errors associated with the optic disc center. The second stage includes the construction of global octet flow feature, image intensity representation, removal of boundary outliers to extract the macula region. The macula is avascular dark region and it is distinguishable in green component of macula region. Further, the approach smooths the macula region, extracts the dark region utilizing global thresholding technique, and compute the center of macula through first order contour moments. A smaller Euclidean distance between the predicted and ground truth centers of the optic disc and macula signifies superior performance of the approach compared to existing methods.

In our continued efforts, we propose two methods for grading the severity of diabetic macular edema. The first approach integrates knowledge from the optic disc, macula, and hard exudates regions. The second approach develops a deep learning model to grade the severity of diabetic macular edema. In this approach, we propose an ensemble dual-path EfficientNet model with augmentation having residual convolution blocks. The model is structured with two paths, both utilizing EfficientNet as the foundational backbone. The proposed model demonstrates superior performance compared to existing models.

2 Objectives

The objectives of this work is to develop an automatic system that can detect the retinal components such as optic disc region and its location, macula, hard exudates (one of the biomarkers in diabetic retinopathy) and evaluates the severity grading of diabetic macular edema using color fundus images. Thus, the research work is carried out to address the following objectives.

(a) Implementation of a segmentation and detection model for optic disc.

(b) Implementation of a segmentation model for hard exudates.

(c) Implementation of a localization model for optic disc.

(d) Implementation of a localization model for macula and fovea.

(e) Implementation of a three-class diabetic macular edema classification model for eye fundus image.

3 Existing Gaps Which Were Bridged

The proposed work mainly focused on the implementation of extraction of retinal components and severity classification of diabetic macular edema models. The proposed works focus on the following issues.

(a) Performance: Accurate diagnoses are fundamental for initiating appropriate and timely treatment plans. Accurate diagnosis guarantees that patients get the most effective treatments attainable for their individual medical conditions.

(b) Handle diverse imaging conditions: The eye fundus image is very rich in information. The retinal components like optic disc, macula, and fovea have different structural and intensity properties. Optic disc is circular or ellipse in shape and orange to pink in color. The macula is a dark avascular region. Hard exudates have random shapes and positions. The performance of the model can be influenced by diverse imaging conditions, including variations in illumination.

4 Most Important Contributions

4.1 Three Level Automatic segmentation of Optic Disc using LAB color space Contours and Morphological Operation

The main challenge of optic disc segmentation is the differentiation of its perimeter from other retinal components. The proposed approach involves (a) Unsupervised extraction of the region of interest, which contains the optic disc, is performed to reduce the presence of outliers. A new image is constructed using luminance and A- axis component which highlights the optic disc region, followed by an unsupervised K-means clustering approach to partition the fundus image into mutual exclusive regions. (b) Segmentation of the optic disc at three levels. (i) In Level 1, the maximum intensity levels are observed specifically in the optic disc region. (ii) Level 2 involves the optic disc region and its immediate surroundings, exhibiting high intensity levels. (iii) In level 3, the optic disc area and most of its surroundings show similar intensity levels. Table 1 illustrates the proposed approach outperforms the state of art techniques.

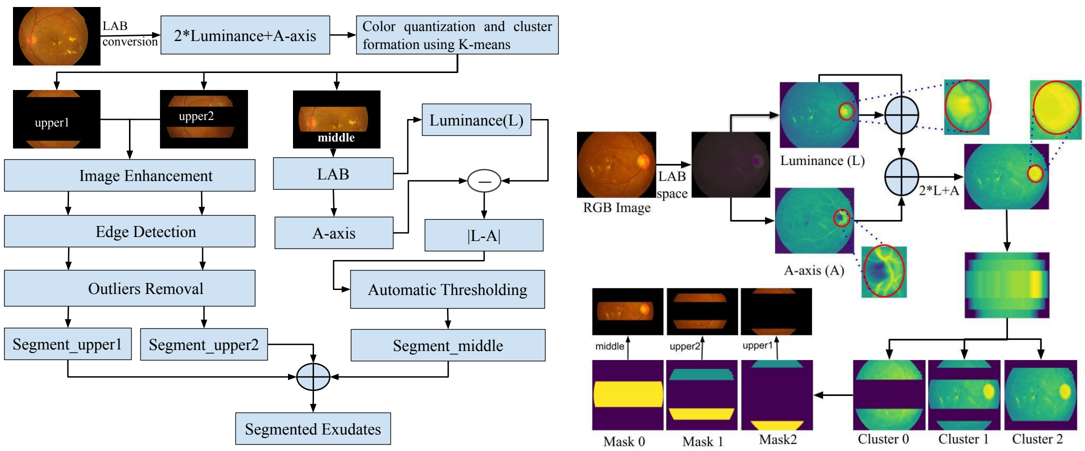
Table 1: Performance comparison with state-of-the-art techniques

Dataset	Methodology	Recall	Precision	IoU	DC	Accuracy
IDRiD (Porwal *et al.* (2020))	Maiti *et al.* (2022)	0.952	-	0.936	0.92	0.997
	Porwal *et al.* (2020)	-	-	0.933	0.94	-
	Wang *et al.* (2022)	0.938	0.922	0.869	0.93	0.997
	Kumar and Bindu (2021)	-	-	0.976	0.95	-
	Hasan *et al.* (2021)	0.899	0.912	0.845	-	0.998
	Proposed	**0.973**	**0.945**	**0.996**	**0.96**	0.997
DRISTI-GS (Sivaswamy *et al.* (2014))	Wang *et al.* (2022)	0.960	0.94	0.91	0.95	-
	Hasan *et al.* (2021)	0.960	-	0.933	-	0.998
	Li *et al.* (2023)	-	-	0.941	0.97	-
	Khan *et al.* (2020)	0.9649	-	0.9179	-	0.996
	Xiong *et al.* (2022)	0.980	-	0.895	0.94	0.997
	Proposed	0.977	**0.952**	**0.997**	**0.97**	0.996
SYSU (Lin *et al.* (2020))	**Proposed**	**0.965**	**0.979**	**0.994**	**0.98**	0.997

Note: Bold value represent the improved performance metric over the state-of-art techniques. The symbol (-) indicates that the metrics is not reported in the paper

4.2 Automatic Segmentation of Hard Exudates using LAB color space Contours Edge detection and Morphological Operation

The proposed block diagram shown in Figure 1 (a) depicts the work flow of the segmentation of hard exudates. The proposed approach is broadly divided into two parts. (a) Unsupervised approach is utilized for the partition of RGB fundus image as shown in Figure 1 (b). (b) This makes the system flexible to implement different approaches on the partitioned fundus RGB image. Luminance and A-axis component highlights the exudates from its environs and adaptive threshold is utilized to segment the exudates from one region, while multistage edge detection method followed by morphological operation and contour feature detects the exudates in other regions. Table 2 presents a



(a) Proposed block diagram for the segmentation of hard exudates

(b) Unsupervised approach partition the image into disjoint and mutually exclusive region

Figure 1: Proposed block diagram for the segmentation of hard exudates and partitioning the image into disjoint and mutually exclusive region

comparison of performance metrics for the segmentation of hard exudates with existing techniques. Our proposed algorithm is superior in terms of Recall, Precision, Dice coefficient, and IoU values.

Table 2: Performance comparison with state-of-the-art techniques.

Dataset	Methodology	Performance metrics					
		Recall	Precision	Specificity	Dice coefficient	IoU	Accuracy
IDRiD (Porwal *et al.* (2020))	Garifullin *et al.* (2021)	0.767	0.753	0.997	-	-	-
	Zhang *et al.* (2022)	0.6939	-	-	0.7255	0.5693	0.8596
	Guo *et al.* (2019)	0.7803	-	-	0.7815	-	-
	Hamad *et al.* (2021)	0.81	-	0.992	-	-	0.9920
	Proposed	**0.913**	0.8108	0.981	**0.850**	**0.750**	0.9750
E-Ophtha (Decenciere *et al.* (2013))	Zhang *et al.* (2022)	0.578	-	-	0.5296	0.3603	0.8442
	Hamad *et al.* (2021)	0.79	-	0.989	-	-	-
	Proposed	**0.901**	**0.854**	0.987	**0.875**	**0.778**	0.996

Note: Bold value represent the improved performance metric over the state-of-art techniques. The symbol (-) indicates that the metrics is not reported in the paper

4.3 A Pixel based Approach for Localization of Optic Disc and Macula using Image Translation and Global Octet Optical Flow Feature

4.3.1 Localization of Optic Disc

The proposed approach (Figure 2) generates the global motion of optic disc in four directions. An pixel based octet flow feature and its image intensity representation is constructed for each image. Outliers are removed using flow feature and adaptive thresholding is performed to extract optic disc region in X and Y directions respectively. The approach extracts the contours to compute exact bounding box enclosing optic disc. Further, the methodology computes the center of optic disc using luminance and A axis component.

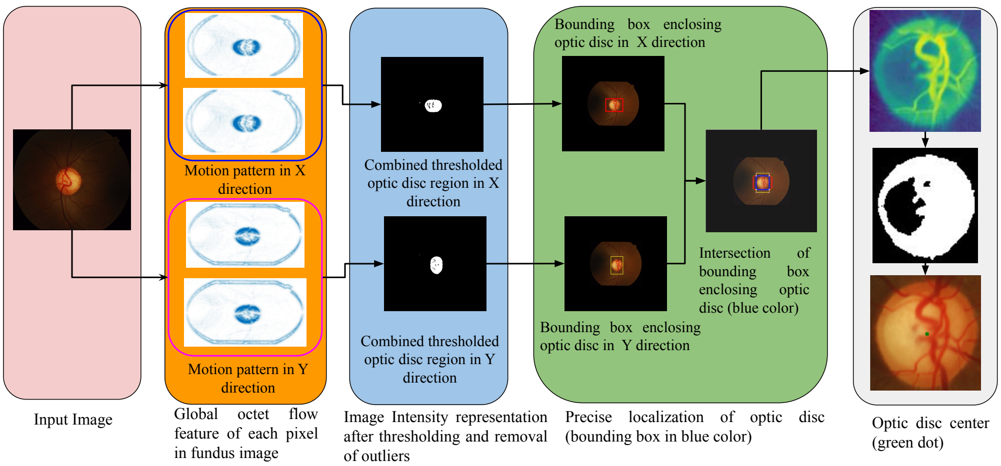


Figure 2: Proposed block diagram for the localization of optic disc

Table 3 illustrates that the proposed approach performs superior to its state-of-the-art (SOTA) algorithms as it achieves a lower Euclidean distance.

Table 3: Performance comparison with state-of-the-art techniques.

Dataset	Methodology	Performance (Euclidean Distance (pixels))
Drishti-GS (Sivaswamy *et al.* (2014))	Panda *et al.* (2017)	38.04
	Proposed	**4.32**
IDRiD (Porwal *et al.* (2020))	Zhao *et al.* (2023)	17.995
	Li *et al.* (2018)	32.6
	Song *et al.* (2020)	14.21
	Porwal *et al.* (2020)	21.072
	Hasan *et al.* (2021)	20.23
	Proposed	**10.23**

4.3.2 Localization of Macula using Global Octet Optical Flow Feature

We propose an automatic pixel-based method for efficient macula localization (Figure 3) through the utilization of image translation, global optic flow, contours, morphological operations and adaptive threshold techniques. Our approach senses the direction of the macula relative to optic disc using morphological operation, medial axis transform, and connected component analysis. In the next stage, we extract the region of interest containing macula. The approach extracts the region of interest utilizing the computed optic disc center information.

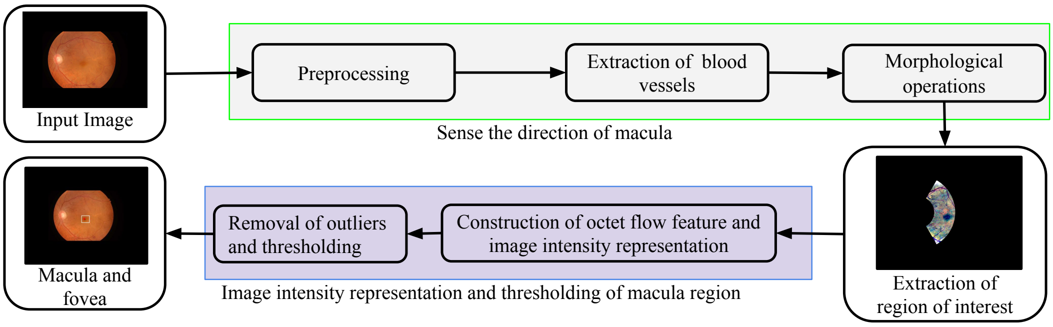


Figure 3: Proposed block diagram for localization of macula and fovea

Our approach ensures a system that is free from optic disc localization errors. It efficiently generates the global motion of an arc segment containing macula in four directions and constructs a pixel-based octet flow feature along with its corresponding image intensity representation for each arc image. Outliers are identified and removed using the flow feature of masked arc image, followed by an adaptive thresholding to extract the macula regions. In the next step, we smooth the macula region, and extract the center of avascular dark region. Table 4 illustrates that the proposed approach performs superior to its state-of-the-art (SOTA) algorithms as it achieves a lower Euclidean distance.

Table 4: Performance comparison with state-of-the-art techniques on IDRiD dataset.

Methodology	Performance (Euclidean Distance (pixels))
Hasan *et al.* (2021)	41.87
Porwal *et al.* (2020)	57.133
Li *et al.* (2018)	52
Zhao *et al.* (2023)	39.446
Fu *et al.* (2022)	25.02
Proposed	**11.34**

4.4 Severity Grading of Diabetic Macular Edema

We propose two approaches for assessing the severity of diabetic macular edema. The first approach (Figure 4) incorporates information from the optic disc, macula, and hard exudates regions. The second approach employs a deep learning model to evaluate the severity of diabetic macular edema as shown in Figure 5.

4.4.1 Proposed Method 1

The proposed unsupervised approach is divided into two stages.

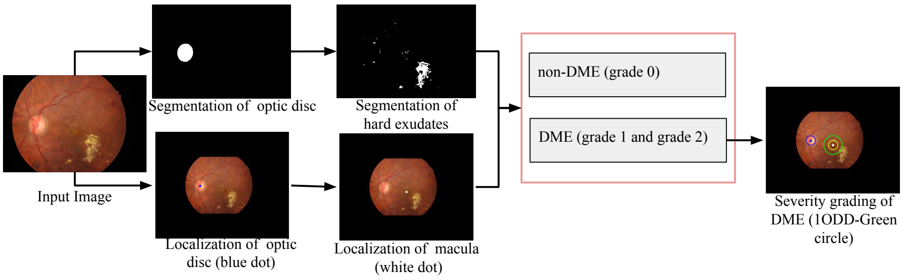


Figure 4: Proposed block diagram for the automatic diabetic macular grading system

(i) In the first stage, we classify the fundus image as non-DME (Grade 0) and DME (Grade 1, Grade 2) using hard exudates information. The presence of hard exudates classifies the image as having DME condition while the absence of hard exudates indicates non-DME condition. Hard exudates exhibit variability in their shape, size, and placement. Consequently, intensity based entropy feature and color moments features are utilized in this work.

(ii) Grading between NCSME (Grade 1) and CSME (Grade 2) is carried out in the second stage, utilizing optic disc and center of macula information.

4.4.2 Proposed Method 2

We proposed an automatic effective method named as EDEA (Ensembled dual Path EfficientNet with Augmentation) for DME severity grading. An ensemble module is

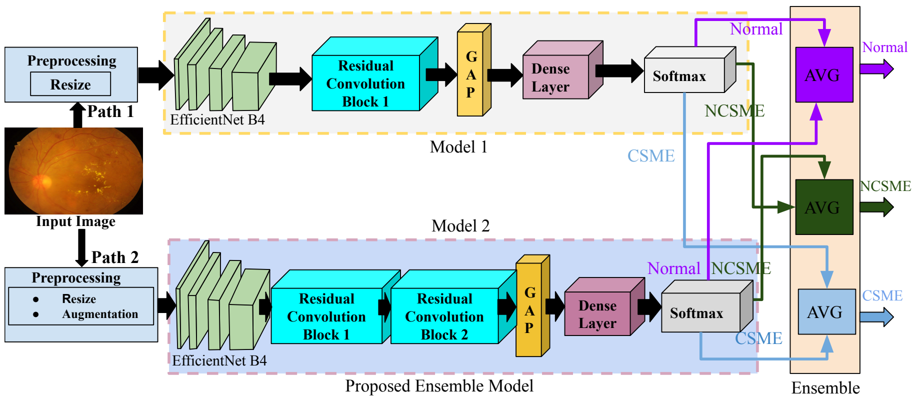


Figure 5: Proposed ensembled dual path with augmentation DME grading system

proposed for automatic learning of features using deep neural network and residual convolution blocks followed by global average pooling to finetune the features as shown in Figure 5. It consists of two paths with EfficientNet as the backbone model. One residual convolution block has included after EfficientNet in the model 1 (path 1). On the other hand, two residual convolution blocks have been used in the model 2 (path 2) to improve the representation of previous layer. Each model utilizes global average pooling, dense, and softmax layers after residual convolution to produce three outputs. These outputs are ensembled using the averaging approach to produce final class probabilities. To ensure that our suggested model is accurate, we have computed gradient-weighted class activation map. It highlights the correct feature for the DME severity grading. The proposed approach performs better than the existing approaches outlined in Table 5 for determining the severity of DME, with an accuracy of 0.94 and 0.961, respectively.

Table 5: Performance comparison with state-of-the-art techniques on IDRiD dataset.

Author	Approach	Accuracy
Proposed Method 1	EDEA (Ensembled dual-path EfficientNet4 with augmentation)	**0.94**
Proposed Method 2	Positional constraints utilizing optic disc, macula, and hard exudates	**0.961**
Sulaiman *et al.* (2020)	DLCNN	0.68
Carvalho *et al.* (2020)	ResNet50	0.911
Li *et al.* (2019)	DSAM and DDAM	0.924
Tu *et al.* (2020)	SUNet	0.8155
Reddy and Gurrala (2022)	DLCNN-MGWO-VW	0.932

5 Conclusions

The detection and localization of retinal components namely the optic disc, macula, and fovea in fundus images is a challenging task and plays a key role in assessment of retinal diseases such as severity grading of diabetic macular edema. We proposed two methods for the severity grading of diabetic macular edema. The first method adopts an unsupervised approach that utilizes grading scales by assessing the extent and distribution of hard exudates in the macula. This approach integrates the retinal components information namely the optic disc, macula, fovea, and one biomarker of diabetic retinopathy named hard exudates. The task becomes harder in the presence of retinal abnormalities, varying illumination conditions, and retinal artifacts. We have discussed the retinal components and clinical features of diabetic macular edema in very detail.

We have proposed an efficient and robust approach for the segmentation of optic disc utilizing LAB color space, contours, information content and morphological operations. The proposed methodology is divided into two stages (i) unsupervised extraction of region of interest: (ii) segmentation of optic disc at three levels. The method aims to maximize the brightness difference between the optic disc and surrounding regions. We have demonstrated that the proposed method is robust and works well in different illumination conditions. The information pertaining to the optic disc region is utilized and removed from the segmentation results of hard exudates. Additionally, segmentation of hard exudates poses challenges due to the unknown characteristics of their shape, size, and position within RGB fundus images. We have proposed an unsupervised approach for the segmentation of hard exudates. It partitions the image into three mutually exclusive and exhaustive regions namely upper1, upper2, and middle region. This approach makes the system flexible to adapt different methodologies to segment the exudates from different regions. The exudates from upper 1 and upper 2 regions are extracted using a multistage canny edge filter, while from the middle region, an absolute difference of luminance and A- axis is computed followed by an automatic thresholding technique. The proposed approach excels in diverse illumination conditions, adeptly extracting irregularly shaped hard exudates from any position.

Further, we proposed a global octet flow feature for the localization of optic disc. The proposed method generates the global motion of the optic disc in four directions. It constructs a pixel-based octet flow feature and represents it using image intensity for each image. It extracts the precise bounding box enclosing the optic disc and appearance-based approach computes the center of the optic disc. The positional relation between the center of the optic disc and macula is utilized to extract the center of macula. The proposed approach senses the orientation of macula with respect to optic disc. The advantage of this approach is that it is independent of the localization error of optic disc and does not require accurate blood vessels information. Further, we generate the global octet flow feature of arc segment and extracts the center of macula.

The detection and grading of diabetic macular edema are conducted through a two-stage approach (proposed method 1). In the first stage, we detect whether DME is present or not. The presence or absence of hard exudates identifies that it is non-DME (Grade 0) or DME (Grade 1 and Grade 2). In this stage, positional constraints information of macula and optic disc are not required. In the second stage, the grading of DME images involves assessing whether hard exudates or portions of hard exudates lie inside or outside of a region within one optic disc diameter, centered at the macula. A supervised three-class DME grading system is proposed utilizing an ensemble dual-path EfficientNet model with augmentation (proposed method 2). Model 1 (path 1) incorporates one residual convolution block after EfficientNet, while Model 2 (path 2) includes two residual convolution blocks to enhance the representation of the preceding layer. Both models employ global average pooling, dense, and softmax layers after residual convolution to generate three outputs. The final class probabilities are obtained by ensemble averaging of these outputs.

Future Scope

The proposed research work mainly focuses on extraction of retinal components and severity grading of diabetic macular edema.

- In our work, the optic disc information is utilized for the segmentation of hard exudates and localize the macula. In future we will utilized the optic disc information in ophthalmology and healthcare for the screening of coloboma and glaucoma disease.
- The macula information is valuable for evaluating retinal diseases such as age-related macular degeneration.
- The proposed global octet flow feature has the potential to be extended for the segmentation and evaluation of plant diseases.
- In conjunction with these efforts, we will focus on refining and enhancing the proposed approaches to boost their performance.
- In the future, the integration of computer vision and artificial intelligence methodologies will be utilized in creating a smartphone-based system for automated retinal image analysis.

6 Organization of the Thesis

The proposed outline of the thesis is as follows:

(a) Chapter 1: Introduction

(b) Chapter 2: Literature Survey

(c) Chapter 3: Three Level Automatic Segmentation of Optic Disc using LAB color space Contours and Morphological Operation

(d) Chapter 4: Automatic Segmentation of Hard Exudates using LAB color space Contours Edge detection and Morphological Operation

(e) Chapter 5: A Pixel based Approach for Localization of Optic Disc and Macula using Image Translation and Global Octet Optical Flow Feature

(f) Chapter 6: Severity Grading of Diabetic Macular Edema

(g) Chapter 7: Conclusions and Future Scope

7 List of Publications

(I) REFEREED JOURNALS BASED ON THE THESIS

1. Shree Prakash and Jagadeesh Kakarla, "Three Level Automatic Segmentation of Optic Disc using LAB color space Contours and Morphological Operation", *International Journal of Imaging Systems and Technology*, Wiley (SCI, IF: 3.3), Volume 33, 1796-1813, (2023).
2. Shree Prakash and Jagadeesh Kakarla, "A Pixel based Approach for Localization of Optic Disc using Image Translation and Global Octet Optical Flow Feature", *International Journal of Imaging Systems and Technology (Under Review).*
3. Shree Prakash, Jagadeesh Kakarla, and B Venkateswarlu Isunuri, "Automatic Grading of Diabetic Macular Edema using Ensembled dual Path EfficientNet with Augmentation", *Expert Systems (Under Review).*

(II) PRESENTATIONS/PUBLICATIONS IN CONFERENCES BASED ON THE THESIS

1. Shree Prakash and Jagadeesh Kakarla, "Automatic Segmentation of Hard Exudates using LAB color space Contours Edge detection and Morphological Operation", *8th International Conference on Computer Vision & Image Processing (CVIP)*, (2023).

(III) PRESENTATIONS/PUBLICATIONS IN CONFERENCES (Others)

1. IB Venkateswarlu, J Kakarla, S Prakash "Face mask detection using MobileNet and Global Pooling Block", *IEEE 4th Conference on Information & Communication Technology (CICT)*, 1-5, (2020).

References

1. **Carvalho, C.**, **J. Pedrosa**, **C. Maia**, **S. Penas**, **A. Carneiro**, **L. Mendoncca**, **A. M. Mendonca**, and **A. Campilho** (2020). A multi-dataset approach for dme risk detection in eye fundus images. *International Conference on Image Analysis and Recognition*, **12132**, 285–298.

2. **Decenciere, E.**, **G. Cazuguel**, **X. Zhang**, **G. Thibault**, **J. C. Klein**, **F. Meyer**, **B. Marcotegui**, **G. Quellec**, **M. Lamard**, **R. Danno**, *et al.* (2013). Teleophta: Machine learning and image processing methods for teleophthalmology. *Irbm*, **34**(2), 196–203.

3. **Fu, Y.**, **G. Zhang**, **J. Li**, **D. Pan**, **Y. Wang**, and **D. Zhang** (2022). Fovea localization by blood vessel vector in abnormal fundus images. *Pattern Recognition*, **129**, 108711.

4. **Garifullin, A.**, **L. Lensu**, and **H. Uusitalo** (2021). Deep bayesian baseline for segmenting diabetic retinopathy lesions: Advances and challenges. *Computers in Biology and Medicine*, **136**, 104725.

5. **Guo, S.**, **T. Li**, **K. Wang**, **C. Zhang**, and **H. Kang** (2019). A lightweight neural network for hard exudate segmentation of fundus image. *Artificial Neural Networks and Machine Learning, Springer*, **11729**, 189–199.

6. **Hamad, H.**, **T. Dwickat**, **D. Tegolo**, and **C. Valenti** (2021). Exudates as landmarks identified through fcm clustering in retinal images. *Applied Sciences*, **11**(1), 142.

7. **Hasan, M. K.**, **M. A. Alam**, **M. T. E. Elahi**, **S. Roy**, and **R. Marti** (2021). Drnet: Segmentation and localization of optic disc and fovea from diabetic retinopathy image. *Artificial Intelligence in Medicine*, **111**, 102001.

8. **Khan, T. M.**, **M. Mehmood**, **S. S. Naqvi**, and **M. F. U. Butt** (2020). A region growing and local adaptive thresholding-based optic disc detection. *Plos one*, **15**(1), e0227566.

9. **Kumar, E. S.** and **C. S. Bindu** (2021). Two-stage framework for optic disc segmentation and estimation of cup-to-disc ratio using deep learning technique. *Journal of Ambient Intelligence and Humanized Computing*, 1–13.

10. **Li, F.**, **W. Xiang**, **L. Zhang**, **W. Pan**, **X. Zhang**, **M. Jiang**, and **H. Zou** (2023). Joint optic disk and cup segmentation for glaucoma screening using a region-based deep learning network. *Eye*, **37**(6), 1080–1087.

11. **Li, X.**, **X. Hu**, **L. Yu**, **L. Zhu**, **C.-W. Fu**, and **P.-A. Heng** (2019). Canet: cross-disease attention network for joint diabetic retinopathy and diabetic macular edema grading. *IEEE transactions on medical imaging*, **39**(5), 1483–1493.

12. **Li, X.**, **L. Shen**, and **J. Duan** (2018). Optic disc and fovea detection using multi-stage region-based convolutional neural network. *International symposium on image computing and digital medicine*, 7–11.

13. **Lin, L.**, **M. Li**, **Y. Huang**, **P. Cheng**, **H. Xia**, **K. Wang**, **J. Yuan**, and **X. Tang** (2020). The sustech-sysu dataset for automated exudate detection and diabetic retinopathy grading. *Scientific Data*, **7**(1), 1–10.

14. **Maiti, S.**, **D. Maji**, **A. K. Dhara**, and **G. Sarkar** (2022). Automatic detection and segmentation of optic disc using a modified convolution network. *Biomedical Signal Processing and Control*, **76**, 103633.

15. **Panda, R.**, **N. Puhan**, and **G. Panda** (2017). Robust and accurate optic disk localization using vessel symmetry line measure in fundus images. *Biocybernetics and Biomedical Engineering*, **37**(3), 466–476.

16. **Porwal, P.**, **S. Pachade**, **M. Kokare**, **G. Deshmukh**, **J. Son**, **W. Bae**, **L. Liu**, **J. Wang**, **X. Liu**, **L. Gao**, *et al.* (2020). Idrid: Diabetic retinopathy–segmentation and grading challenge. *Medical image analysis*, **59**, 101561.

17. **Reddy, V. P. C.** and **K. K. Gurrala** (2022). Joint dr-dme classification using deep learning-cnn based modified grey-wolf optimizer with variable weights. *Biomedical Signal Processing and Control*, **73**, 103439.

18. **Sivaswamy, J.**, **S. Krishnadas**, **G. D. Joshi**, **M. Jain**, and **A. U. S. Tabish** (2014). Drishti-gs: Retinal image dataset for optic nerve head (onh) segmentation. *International symposium on biomedical imaging (ISBI)*, 53–56.

19. **Song, W.**, **Y. Liang**, **K. Wang**, and **L. He** (2020). T-net: A template-supervised network for task-specific feature extraction in biomedical image analysis. *ArXiv*, **2002.08406**.

20. **Sulaiman, T.**, **J. Angel Arul Jothi**, and **S. Bengani** (2020). Automated grading of diabetic macular edema using deep learning techniques. *International Conference on Modelling, Simulation and Intelligent Computing*, 264–272.

21. **Tu, Z.**, **S. Gao**, **K. Zhou**, **X. Chen**, **H. Fu**, **Z. Gu**, **J. Cheng**, **Z. Yu**, and **J. Liu** (2020). Sunet: A lesion regularized model for simultaneous diabetic retinopathy and diabetic macular edema grading. *IEEE 17th International Symposium on Biomedical Imaging (ISBI)*, 1378–1382.

22. **Wang, Y.**, **X. Yu**, and **C. Wu** (2022). Optic disc detection based on fully convolutional neural network and structured matrix decomposition. *Multimedia Tools and Applications*, **81**(8), 10797–10817.

23. **Xiong, H.**, **S. Liu**, **R. V. Sharan**, **E. Coiera**, and **S. Berkovsky** (2022). Weak label based bayesian u-net for optic disc segmentation in fundus images. *Artificial Intelligence in Medicine*, **126**, 102261.

24. **Zhang, J.**, **X. Chen**, **Z. Qiu**, **M. Yang**, **Y. Hu**, and **J. Liu** (2022). Hard exudate segmentation supplemented by super-resolution with multi-scale attention fusion module. *IEEE International Conference on Bioinformatics and Biomedicine*, 1375–1380.

25. **Zhao, W.**, **Z. Zhang**, **Z. Wang**, **Y. Guo**, **J. Xie**, and **X. Xu** (2023). Eclnet: Center localization of eye structures based on adaptive gaussian ellipse heatmap. *Computers in Biology and Medicine*, **153**, 106485.