

Computational Analysis of Segmenting Retinal Blood Vessels Using Fuzzy C-Means

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ABSTRACT

Segmentation is a critical phase of the image processing system as it excerpts the objects of one's interest. The image segmentation results in vigorous and high grade of accuracy and is very much helpful in analyzing diverse image modalities. In diabetic retinopathy, the segmentation is conducted on the blood vessels of the retinal images which assists in classifying the retinal images as benign or malignant. The images have been obtained from the Digital Retinal Images for Vessel Extraction retinal dataset. The dataset comprises 20 retinal images. The research paper proposes a hybrid segmentation technique using Fuzzy C-Means and Haar feature extraction. The input retinal images are enhanced using a Gaussian filter and exposed to Fuzzy C-Means for segmentation. The Haar feature extraction is applied to the segmented retinal image to extract the blood vessels. The conducted segmentation has been analyzed by obtaining the readings for the 8 performance evaluation parameters. The proposed segmentation technique achieved an average specificity of 94.965% with an average accuracy of 85.77% and a Negative Predictive Value of 94.197%.

Keywords – Blood vessels, DRIVE dataset, Fuzzy C-Means, Haar feature extraction, segmentation

I. INTRODUCTION

Segmentation is intended to extract the complex structure of the blood vessels from the retinal images. Segmentation partitions the retinal images into several regions and extracts the important ones. Retinal images show the blood vessels, the optical nerves, and the retina which transmits information to the brain. The morphology of the blood vessels within retinal images is a critical indicator of diabetic retinopathy, glaucoma, and hypertension. The degree of accuracy achieved during segmentation is utilized for the diagnosis methods. The enhancement of contrast is an important step in the segmentation of retinal blood vessels. The dependability of the segmentation depends on the stability of the contrast over the image. Segmentation of the vessel segmentation is a critical task for the computational analysis of retinal fundus images. Segmentation acts as a stepping stone for advanced applications such as analysis of the flow of blood, assessment of image quality, registration of retinal image, and artery/vein ratio evaluation. Preliminary methodologies for retinal vessel segmentation were completely unsupervised and depended on traditional image processing processes such as morphological or edge detection operations. The primary motive behind such methods was to emphasize the intensities of the retinal vessels by preprocessing the images. The research work has been going on advanced filtering methods over recent years but these methods failed to achieve competitive performance levels on the recognized benchmarks because of their incapability to handle images with pathological structures and generalize them to diverse forms and purposes. Retinal image segmentation aids in the early detection and prevention of eye diseases. By identifying subtle changes or abnormalities in the retinal structures, such as microaneurysms or drusen deposits, segmentation algorithms can assist in detecting diseases at their earliest stages, facilitating timely interventions and preventing vision loss. Accurate segmentation of retinal features provides valuable information for treatment planning and surgical guidance. By precisely delineating the boundaries of lesions, tumors, or anatomical structures, retinal

segmentation allows surgeons to localize target areas, plan interventions, and perform surgeries with increased precision and safety. Segmentation of retinal images is essential in clinical trials and medical research focused on developing new therapies or studying disease progression. Accurate segmentation provides quantitative measurements and biomarkers that can be used as endpoints for evaluating treatment efficacy, conducting population studies, or investigating novel imaging techniques.

A. Methods

The research paper proposes a method for conducting on the retinal images from the DRIVE dataset. The proposed technique makes use of Green Channel Complement, Gaussian filter, Fuzzy C-Means (FCM), and Haar feature extraction briefed below.

Green Channel Complement - The complement of the green channel is computed. This is achieved by subtracting each pixel value in the green channel from the maximum value (usually 255 for an 8-bit image) to obtain the complementary intensity. The GCC technique helps in highlighting retinal blood vessels by suppressing other non-vascular structures and background information present in the retinal image. It takes advantage of the fact that the green channel provides good contrast for vessels, and the complement operation enhances the visibility of vessels by increasing their intensity relative to the background. The resulting complement of the green channel image is often used to enhance the visualization of retinal blood vessels. The blood vessels appear brighter and more prominent in the GCC image, making it easier to analyze and segment vascular structures.

Gaussian filter - The Gaussian filter is a commonly used image filtering technique in retinal image processing. It is based on the Gaussian distribution and is employed to smooth or blur an image, reduce noise, and enhance certain features. Retinal images can suffer from various types of noise, such as Gaussian noise, salt-and-pepper noise, or speckle noise. The Gaussian filter is effective in reducing these noise types by convolving the image with a Gaussian kernel. The filter attenuates high-frequency components, which are often associated with noise while preserving the essential details and structures in the image. By removing noise and reducing image irregularities, the Gaussian filter can enhance the quality of the retinal image, facilitating more accurate and robust segmentation results. Gaussian filtering is employed as a preprocessing step in vessel extraction algorithms. The Gaussian filter can be used for image enhancement in retinal images. By adjusting the parameters of the filter, such as the kernel size or standard deviation, it is possible to control the amount of smoothing or blurring applied to the image. This can help emphasize certain image features, improve contrast, or enhance the visibility of subtle details in the retinal structures

Fuzzy C-Means - FCM can be used to partition an image into distinct regions or segments based on pixel intensities. By assigning membership values to each pixel indicating its degree of association with different clusters, FCM allows for soft boundaries between segments, capturing gradual transitions and overlapping regions in the image. FCM can be employed in edge detection by considering the gradient or intensity differences between pixels. By defining appropriate distance metrics and applying FCM, edges can be detected as regions with high membership values, indicating a rapid change in intensity or gradient. FCM is useful for segmenting images based on texture features. By considering local texture properties, such as the co-occurrence matrix or Gabor filter responses, FCM can identify regions with similar textures. This approach is particularly effective in distinguishing different texture patterns in medical imaging, such as identifying tumor boundaries in MRI images. FCM has found extensive applications in segmenting biomedical images, including retinal images, MRI scans, histopathological images, and ultrasound images. In retinal image segmentation, for example, FCM can be employed to identify blood vessels, optic disc, macula, and various retinal lesions. FCM allows for precise delineation of these structures by assigning membership values that reflect the likelihood of pixels belonging to each structure. FCM is utilized in segmenting multispectral and hyperspectral images, which contain multiple bands of information for each pixel. By considering spectral signatures, FCM can capture the spectral variations and assign membership values to pixels based on their spectral similarities. This approach enables the identification of different materials or objects within the image based on their spectral characteristics.

The fuzzy C-Means algorithm operates by conveying membership to each data point corresponding to each cluster center based on the distance between the data point and the cluster center. The sum of the membership of each data point should be equal to one. Fuzzy C-Means is an unsupervised clustering algorithm that allows the building of a fuzzy partition from data. The working of the algorithm allows the construction of a fuzzy partition from the data. The functioning of the algorithm depends on the parameter m corresponding to the degree of fuzziness of the solution. The greater m values blur the classes and the elements behave to belong to all the clusters. The optimized solutions to the problems depend on the value of m .

HAAR feature extraction - In 1909 Alfred Haar proposed a sequence of rescaled square shape functions designated as Haar features. Haar features are very similar to convolution kernels as in CNN (Convolution Neural Networks). Haar features are demarcated by precise patterns of black and white pixels in a convinced area. The algorithm even works on grayscale images using thresholds. Haar's feature works on the difference between the means of light and dark areas and checks for a certain threshold and classifies them as black and white.

HAAR (Haar-like) feature extraction is a technique used in computer vision and image processing for object

detection. HAAR features are rectangular regions within an image that capture local intensity variations. They are computed by subtracting the sum of pixel intensities in one region of the image from the sum of pixel intensities in another region. HAAR features are defined as the difference between the sum of pixel intensities in two rectangular regions, often referred to as the "white" and "black" regions. These features capture variations in brightness and texture within an image. To efficiently compute HAAR features, an integral image is constructed from the original image. The integral image allows fast computation of the sum of pixel intensities within any rectangular region of the image. Each pixel in the integral image is the sum of all the pixels above and to the left of it in the original image. A set of HAAR-like features is defined based on different sizes, positions, and shapes of rectangular regions. These features can capture various patterns such as edges, corners, and texture variations. Feature selection is usually performed using machine learning techniques to identify the most discriminative features for object detection.

The research paper is framed in multiple sections. Section II elaborates on the conducted literature review on the segmentation of retinal images. Section III mentions the proposed methodology for conducting segmentation on retinal images from the DRIVE dataset using flowcharts and pseudocode. Section IV elaborates on executing an instance on the retinal image illustrating the step-wise intermediate stages with images before accomplishing the final segmentation of the retinal images. Section V concludes the research paper.

B. Performance Evaluation Parameters

Performance evaluation parameters are intended to analyze the strengths and weaknesses of the methods or techniques under study. The matrix shown in Fig. 1 shows the four different combinations which define different performance metrics. The predicted values are predicted by the model and the actual values are the true dataset values.

		Predicted	
		1	0
Actual	1	True Positive (TP)	False Negative (FN)
	0	False Positive (FP)	True Negative (TN)

Fig. 1. Combinations matrix

Different performance evaluation parameters considered in the research work are mentioned below.

- Specificity – The tendency to label a person who is not suffering from a disease as negative is referred to as specificity.

$$\text{Specificity} = TN / (TN + FP)$$

- Accuracy – The nearness of the given set of measurements to their true values is referred to as accuracy.

$$\text{Accuracy} = TP + TN / (TP + TN + FP + FN)$$

- Negative Predictive Value (NPV) – The possibility of a person with a negative test being free of disease is referred to as NPV.

$$NPV = 100 * TN / (FN + TN)$$

- False Negative Rate (FNR) - The ratio of positives yielding negative outcomes is referred to as FNR.

$$FNR = FN / (TP + FN)$$

- False Positive Rate (FPR) – The ratio of negatives yielding positive outcomes is referred to as FPR.

$$FPR = FP / (FP + TN)$$

- False Omission Rate (FOR) – The proportion of false negatives which are incorrectly rejected is referred to as FOR.

$$FOR = FN / (FN + TN)$$

- False Discovery Rate (FDR) – The rate that signifies the features called truly null is referred to as FDR. The aggregate rejections of the null comprise both FPs and TPs.

$$FDR = FP / (FP + TP)$$

- F1-Score – F1-score is an accuracy metric that computes the number of times the model has made a precise prediction across the whole dataset.

$$F1 - score = TP / TP + \frac{1}{2} (FP + FN)$$

II. STATE-OF-THE-ART

State-of-the-art research and development push the boundaries of knowledge and understanding in a field. It represents the culmination of scientific progress and serves as a benchmark for future advancements. By striving for the state-of-the-art, researchers, and practitioners contribute to the overall growth and evolution of their respective domains. Table I shows the conducted summarized literature review performed in context with the research work.

Table I. Literature Review

Citations	Techniques / Methods	Data sets	Performance metrics	Result
N. Wang et al., 2023 [1]	U-Net, FCB	CHASE DRIVE	Accuracy, Specificity, Sensitivity, F1 score, Precision	DRIVE (Accuracy – 94.03%, Specificity – 73.80%, Sensitivity – 97.03%) STARE (Accuracy – 95.04%, Specificity – 97.20%, Sensitivity – 74.13%)
I. Mehidi et al., 2023 [2]	Fuzzy C-Means clustering and Vessel segmentation	DRIVE CHASE STARE IDRiD	Accuracy, Specificity, Sensitivity, F1 score, Precision	STARE (FCM Accuracy – 95.11%) DRIVE (FCM Accuracy – 95.04%)
S. Alqahtani Saeed et al., 2023	Coherence, Anisotropic diffusion filtering	CHASE DRIVE	Accuracy Specificity Sensitivity	STARE (Accuracy – 95.40%, Specificity – 95.91%, Sensitivity – 81.10%) DRIVE (Accuracy – 96.10%, Specificity – 96.20%, Sensitivity – 82.10%)
S. Mahapatra et al., 2022 [3]	Frangi filter, AWSFCM(Adaptive Weighted Spatial Fuzzy C-Means) ELPSO (Enhanced Leader Particle Swarm Optimization)	DRIVE STARE	Accuracy, Specificity, Sensitivity, Precision	DRIVE (Accuracy- 96.05%) STARE (Accuracy- 96.01%)
Z. Li et al., 2021	U-Net, Dense Net	DRIVE	Accuracy, Specificity, Sensitivity, PPV, AUC	Accuracy – 96.98% Specificity – 98.96% Sensitivity – 79.31%
N. Tamim et al., 2020	Multi-Layer Perceptron, Neural Networks, Edge detection	DRIVE CHASE STARE	Accuracy, Specificity, Sensitivity, F1-score, PPV, NPV	DRIVE (Accuracy – 96.07%, Sensitivity – 75.42%, Specificity – 75.42%) STARE (Accuracy – 96.32%, Sensitivity – 78.06%, Specificity – 98.25%) CHASE (Accuracy – 95.77%, Sensitivity – 75.85%, Specificity – 98.46%)
F. Orujov et al., 2020	HE (Histogram equalization), CLAHE,	DRIVE, STARE,	Sensitivity, Specificity,	STARE (Accuracy – 86.5%),

	Edge detection, Contour-based Applications, STEAR algorithm	CHASE	Accuracy, Dice, Jaccard	DRIVE (Accuracy – 93.9%), CHASE (Accuracy – 88%)
L. Ngo et al., 2020	Neural Network, Optical Coherence, Tomography	OCT images	RMSE, DSC (Dice similarity coefficient)	DSC values for segmentation - 0.966 ± 0.011 , Absolute pixel distances between the manual and segmented boundaries - 0.612 ± 0.162
R. Sundaram et al., 2019	Hybrid segmentation algorithm, Morphological Operations, Bottom Hat Transform, MSVE (Multi-Scale Vessel Enhancement)	DRIVE, CHASE, HRF (High-Resolution Fundus)	Sensitivity, Specificity, Accuracy	HRF Dataset gave better results in CHASE dataset images
Y. Jiang et al., 2019	FCNN (Fully Convolutional Neural Networks)	DRIVE, STARE, CHASE	Sensitivity, Specificity, Accuracy, AUC, F1 Score	DRIVE (Accuracy – 97.06%, Specificity – 98.48%, Sensitivity – 81.96%, F1-score – 82.86%)
N. Memari et al., 2019	Fuzzy C-Means, Clustering, Frangi filter, Gabor filter, Matched filtering	DRIVE, STARE, CHASE	Accuracy, Specificity, Sensitivity	DRIVE (Sensitivity – 76.10%, Specificity – 98.10%) STARE (Sensitivity – 78.20%, Specificity – 96.50%) CHASE (Sensitivity – 73.80%, Specificity – 96.80%)
J. Almotiri et al., 2018	Fuzzy C-Means, Mathematical Morphology, Vessel tracking	STARE, DRIVE	Accuracy, Precision, Sensitivity, Specificity	DRIVE (Accuracy - 95%, Precision - 77%) STARE Accuracy- 95.88%)

III. RESEARCH METHODOLOGY

This section elaborates on the proposed segmentation method via flowchart and detailed pseudo code. The flowchart depicting the adopted methodology is shown in Fig. 2 below.

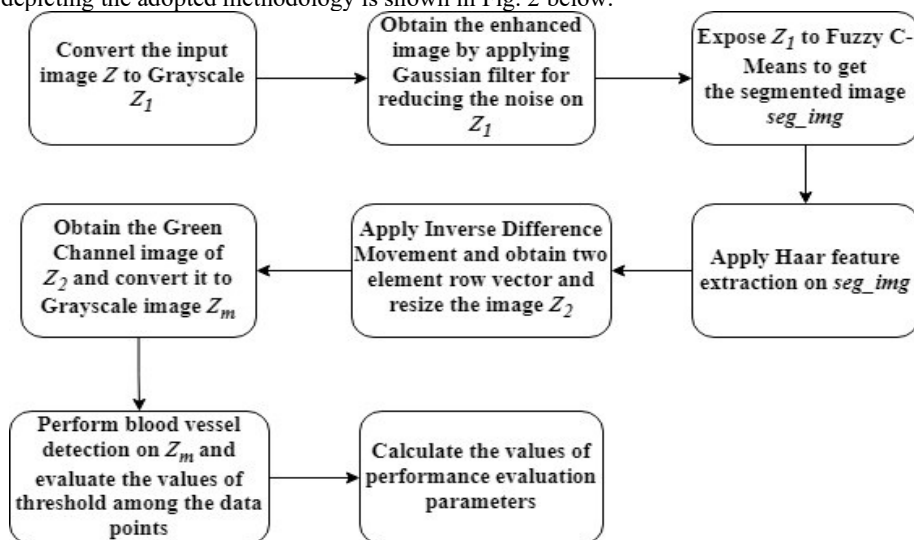


Fig. 2. Flowchart depicting research methodology

The pseudocode for the adopted research methodology is mentioned as under.

1. Obtain the retinal image Z as input and proceed with its conversion to Grayscale image Z_1 .
2. Enhance image Z_1 using a Gaussian filter.
3. Perform segmentation on image Z_1 using Fuzzy C-Means and obtain the image seg_img .
4. Let the seg_img undergo Haar feature extraction.
5. Apply Inverse Difference Movement and obtain a two-element row vector.
6. *Resize image Z_1 to obtain image Z_2 .*
7. Apply Green Channel Complement on image Z_2 and obtain its Grayscale image Z_m .
8. Accomplish blood vessel detection on Z_m .
9. Evaluate the values of the threshold among the data points.
10. Perform calculations applying multiple formulas to obtain the values of performance evaluation parameters.

IV. RESULTS

This section illustrates the implemented research methodology on the retinal images from the DRIVE dataset. The retinal image *36_training.tif* has been provided as an input image to the proposed method. Fig. 2 shows the different intermediate stages of segmentation through which the input image undergoes.

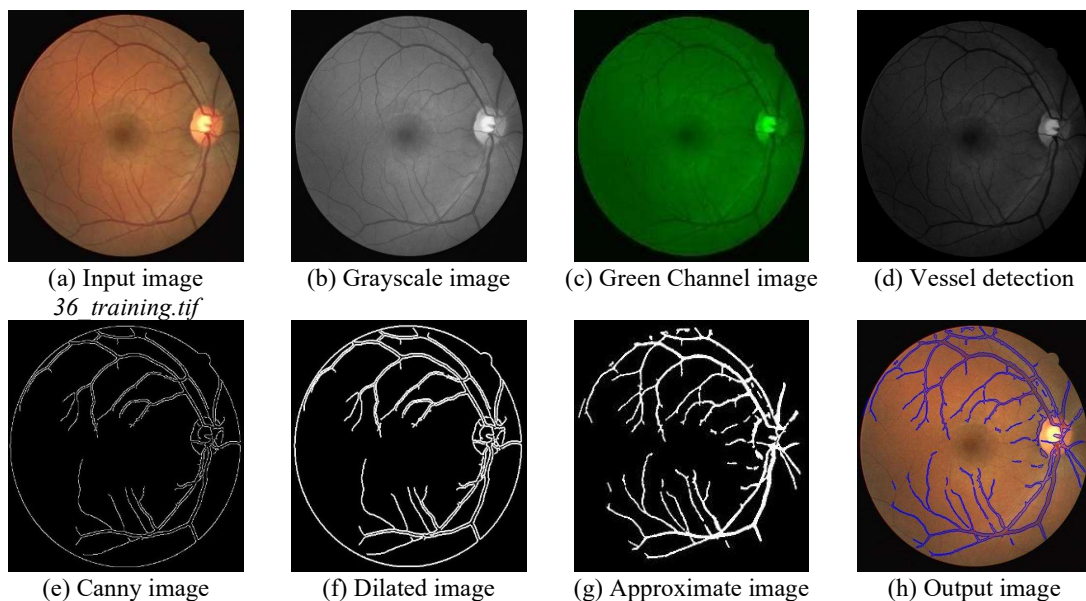


Fig. 3 (a) is an input image (*36_training.tif*) provided to the proposed system. Fig. 3(b) shows the grayscale conversion of Fig. 3(a).

Table II shows the obtained values of performance evaluation parameters after executing the proposed methodology on the entire DRIVE dataset comprising 20 retinal images.

Table II. Readings of Performance metrics for the DRIVE dataset

Images (*.tif)	Specificity	Accuracy	NPV	FNR	FPR	FOR	FDR	F1-Score
21 training	0.9823	0.9271	0.9426	0.9480	0.0177	0.8433	0.0574	0.0781
22 training	0.9690	0.9147	0.9420	0.9449	0.0310	0.8991	0.0580	0.0713
23 training	0.7491	0.7153	0.9353	0.8204	0.2509	0.9568	0.0647	0.0697
24 training	0.8980	0.8485	0.9384	0.9343	0.1020	0.9609	0.0616	0.0490
25 training	0.9797	0.9254	0.9431	0.9356	0.0203	0.8329	0.0569	0.0930
26 training	0.9505	0.8986	0.9422	0.9238	0.0495	0.9114	0.0578	0.0819
27 training	0.9564	0.9031	0.9415	0.9409	0.0436	0.9212	0.0585	0.0675
28 training	0.9803	0.9260	0.9432	0.9346	0.0197	0.8268	0.0568	0.0950
29 training	0.9357	0.8840	0.9407	0.9345	0.0643	0.9396	0.0593	0.0628
30 training	0.9410	0.8894	0.9414	0.9283	0.0590	0.9287	0.0586	0.0715
31 training	0.9431	0.8905	0.9406	0.9426	0.0569	0.9401	0.0594	0.0586
32 training	0.9880	0.9331	0.9435	0.9374	0.0120	0.7519	0.0565	0.0999
33 training	0.9767	0.9224	0.9429	0.9365	0.0233	0.8533	0.0571	0.0866
34 training	0.9379	0.8896	0.9444	0.8750	0.0621	0.8872	0.0556	0.1186
35 training	0.9887	0.9336	0.9434	0.9394	0.0113	0.7469	0.0566	0.0978

36 training	0.9821	0.9285	0.9441	0.9207	0.0179	0.7812	0.0559	0.1164
37 training	0.9585	0.9057	0.9422	0.9314	0.0415	0.9055	0.0578	0.0795
38 training	0.9581	0.9055	0.9424	0.9274	0.0419	0.9014	0.0576	0.0836
39 training	0.9677	0.1148	0.9433	0.9220	0.0323	0.8677	0.0567	0.0981
40 training	0.9502	0.8983	0.9422	0.9234	0.0498	0.9114	0.0578	0.0822

Table III shows the average values of the different performance evaluation parameters calculated on the 20 retinal images of the DRIVE dataset.

Table III. Average values of performance evaluation parameters

Performance Metric	Average Value
Specificity	0.94965
Accuracy	0.857705
NPV	0.94197
FNR	0.925055
FPR	0.05035
FOR	0.878365
FDR	0.05803
F1-Score	0.083055

V. CONCLUSION

The research paper proposed a segmentation technique to extract the blood vessels of the retinal images from the DRIVE dataset using FCM and Haar feature extraction. The adopted research methodology has been detailed using a flowchart and pseudocode. Five instances comprising the retinal images from the DRIVE dataset have been exposed to the implementation and the intermediary states of the input images before accomplishing the final output have been shown in each of the five instances. The results have been obtained for all 20 retinal images of the DRIVE dataset. The average values of 8 performance evaluation parameters have been calculated. The proposed segmentation technique achieved a specificity of 94.965% and an accuracy of 85.77%. The average NPV has been computed at 94.19% with average FNR and average FPR of 92.50% and 5.03% respectively. The average FOR has been calculated at 87.83% with an average FDR of 5.80%.

REFERENCES

- [1]. M. M. Fraz *et al.*, "Blood vessel segmentation methodologies in retinal images - A survey," *Comput. Methods Programs Biomed.*, vol. 108, no. 1, pp. 407–433, 2012, doi: 10.1016/j.cmpb.2012.03.009.
- [2]. Z. Yavuz and C. Köse, "Blood Vessel Extraction in Color Retinal Fundus Images with Enhancement Filtering and Unsupervised Classification," *J. Healthc. Eng.*, vol. 2017, 2017, doi: 10.1155/2017/4897258.
- [3]. N. Shaukat, J. Amin, M. I. Sharif, M. I. Sharif, S. Kadry, and L. Sevcik, "Classification and Segmentation of Diabetic Retinopathy: A Systemic Review," *Appl. Sci.*, vol. 13, no. 5, 2023, doi: 10.3390/app13053108.
- [4]. N. Wang, K. Li, G. Zhang, Z. Zhu, and P. Wang, "Improvement of Retinal Vessel Segmentation Method Based on U-Net," *Electron.*, vol. 12, no. 2, 2023, doi: 10.3390/electronics12020262.
- [5]. I. Mehidi, D. E. C. Belkhiat, and D. Jabri, "Comparative analysis of improved FCM algorithms for the segmentation of retinal blood vessels," *Soft Comput.*, vol. 27, no. 4, pp. 2109–2123, 2023, doi: 10.1007/s00500-022-07531-9.
- [6]. S. Alqahtani Saeed *et al.*, "Impact of Retinal Vessel Image Coherence on Retinal Blood Vessel Segmentation," *Electron.*, vol. 12, no. 2, pp. 1–20, 2023, doi: 10.3390/electronics12020396.
- [7]. S. Mahapatra, S. Agrawal, P. K. Mishro, and R. B. Pachori, "A novel framework for retinal vessel segmentation using optimal improved frangi filter and adaptive weighted spatial FCM," *Comput. Biol. Med.*, vol. 147, no. June, 2022, doi: 10.1016/j.compbiomed.2022.105770.
- [8]. Z. Li, M. Jia, X. Yang, and M. Xu, "Blood vessel segmentation of retinal image based on dense-U-net network," *Micromachines*, vol. 12, no. 12, 2021, doi: 10.3390/mi12121478.
- [9]. N. Tamim, M. Elshrkawey, G. A. Azim, and H. Nassar, "Retinal blood vessel segmentation using hybrid features and multi-layer perceptron neural networks," *Symmetry (Basel)*, vol. 12, no. 6, 2020, doi: 10.3390/SYM12060894.
- [10]. F. Orujov, R. Maskeliūnas, R. Damaševičius, and W. Wei, "Fuzzy based image edge detection algorithm for blood vessel detection in retinal images," *Appl. Soft Comput. J.*, vol. 94, 2020, doi: 10.1016/j.asoc.2020.106452.
- [11]. L. Ngo, J. Cha, and J. H. Han, "Deep Neural Network Regression for Automated Retinal Layer Segmentation in Optical Coherence Tomography Images," *IEEE Trans. Image Process.*, vol. 29, no. c, pp. 303–312, 2020, doi: 10.1109/TIP.2019.2931461.
- [12]. R. Sundaram, K. S. Ravichandran, P. Jayaraman, and B. Venkatraman, "Extraction of blood vessels in fundus

- images of retina through hybrid segmentation approach,” *Mathematics*, vol. 7, no. 2, pp. 1–17, 2019, doi: 10.3390/math7020169.
- [13]. Y. Jiang, H. Zhang, N. Tan, and L. Chen, “Automatic Retinal Blood Vessel Segmentation Based on Fully Convolutional Neural Networks,” *Symmetry (Basel)*, vol. 11, no. 9, p. 1112, Sep. 2019, doi: 10.3390/sym11091112.
- [14]. N. Memari, A. R. Ramli, M. I. Bin Saripan, S. Mashohor, and M. Moghbel, “Retinal Blood Vessel Segmentation by Using Matched Filtering and Fuzzy C-means Clustering with Integrated Level Set Method for Diabetic Retinopathy Assessment,” *J. Med. Biol. Eng.*, vol. 39, no. 5, pp. 713–731, Oct. 2019, doi: 10.1007/s40846-018-0454-2.
- [15]. J. Almotiri, K. Elleithy, and A. Elleithy, “Retinal vessels segmentation techniques and algorithms: A survey,” *Appl. Sci.*, vol. 8, no. 2, 2018, doi: 10.3390/app8020155.