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Rashmi Panda
Niladri B. Puhan
Aparna Rao
Bappaditya Mandal
Debananda Padhy
Ganapati Panda

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Rashmi Panda,^{a,*} Niladri B. Puhan,^a Aparna Rao,^b Bappaditya Mandal,^c Debananda Padhy,^b and Ganapati Panda^a

^aIIT Bhubaneswar, School of Electrical Sciences, Bhubaneswar, India

^bL. V. Prasad Eye Institute, Glaucoma Diagnostic Services, Bhubaneswar, India

^cKeele University, School of Computing and Mathematics, Faculty of Natural Sciences, Staffordshire, United Kingdom

Abstract. Glaucoma is a progressive optic neuropathy characterized by peripheral visual field loss, which is caused by degeneration of retinal nerve fibers. The peripheral vision loss due to glaucoma is asymptomatic. If not detected and treated at an early stage, it leads to complete blindness, which is irreversible in nature. The retinal nerve fiber layer defect (RNFLD) provides an earliest objective evidence of glaucoma. In this regard, we explore cost-effective redfree fundus imaging for RNFLD detection to be practically useful for computer-assisted early glaucoma risk assessment. RNFLD appears as a wedge shaped arcuate structure radiating from the optic disc. The very low contrast between RNFLD and background makes its visual detection quite challenging even by medical experts. In our study, we formulate a deep convolutional neural network (CNN) based patch classification strategy for RNFLD boundary localization. A large number of RNFLD and background image patches train the deep CNN model, which extracts sufficient discriminative information from the patches and results in accurate RNFLD boundary pixel classification. The proposed approach is found to achieve enhanced RNFLD detection performance with sensitivity of 0.8205 and false positive per image of 0.2000 on a newly created early glaucomatous fundus image database. © 2018 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.5.4.044003]

Keywords: retinal nerve fiber layer; glaucoma; fundus image; deep learning; convolution neural network; patch classification.

Paper 18095RR received May 7, 2018; accepted for publication Oct. 2, 2018; published online Oct. 30, 2018.

1 Introduction

Glaucoma is the second leading cause of blindness and around 80 million people would be suffering from this disorder by 2020.¹ The vision loss due to glaucoma is asymptomatic in early stages and its irreversible nature of blindness in later stages makes the early detection quite important to prevent any further damage.^{2,3} In this regard, the degeneration of retinal nerve fiber layer (RNFL) provides the earliest evidence of glaucoma much before the actual visual field defect begins.⁴ The detection of RNFL defect (RNFLD) in fundus images is a cost effective technique as compared to optical coherence tomography (OCT) or GDx, which require skilled technician to acquire the images. Thus, RNFLD detection in fundus imaging can be used for mass screening in a suburban or peripheral environment.

RNFLD is a peripapillary glaucoma indicator that appears as a wedge shaped arcuate structure radiating from the optic disc (OD). The visibility of the RNFLD region is prominent near OD as compared to other background regions. Figure 1 illustrates a sectorial RNFLD region in color and red-free images. The width of the arcuate RNFLD region increases with the progression of glaucoma;⁵ hence, it can be used as a glaucoma progression indicator. The RNFLD detection in fundus images is a challenging task as the intensity difference between RNFLD and background is very subtle. Moreover, the presence of blood vessels and macula makes the detection task more challenging as they are associated with similar intensity ranges as RNFLD regions.

A limited number of methods are available in the literature for the detection of RNFLD in fundus images towards early glaucoma detection. In the work of Kolar et al.⁶ and Odstreilik et al.,⁷ the thickness of RNFL from fundus image patches is predicted by estimating the correlation coefficient between fundus image patch features and corresponding OCT image patch thickness using regression models. The main limitation of both methods is the additional requirement of the OCT images for OCT-RNFL thickness mapping. Joshi et al.⁸ and Lamani et al.⁹ followed a binary classification strategy to decide whether a selected fundus image patch contains RNFLD or not. Joshi et al.⁸ explored the intensity-based dissimilarity features along with k-NN and nearest mean scaled classifiers. Texture and fractal descriptors followed by the SVM classifier are used by Lamani et al.⁹ for RNFLD patch classification purposes.

Oh et al.¹⁰ applied Canny's edge operator followed by Hough transform-based line detection to obtain the RNFLD boundaries. Among the detected lines, the false positives (FPs) are further reduced by applying the conditional decision rules. Muramatsu et al.¹¹ detected RNFLD boundary pixels as a function of mean and standard deviation of neighborhood intensities. Later, the FPs are reduced by applying the popular artificial neural network classifier. The main limitation observed in Refs. 10 and 11 is that both methods produce several FPs in boundary detection. Panda et al.¹² proposed a recurrent neural network and random forest¹³-based learning strategies for RNFLD boundary detection by designing handcrafted features.

*Address all correspondence to: Rashmi Panda, E-mail: rp14@iitbbs.ac.in

Fig. 1 (a) Color fundus image having RNFLD. (b) Redfree fundus image having very faint RNFLD region, radiating from OD, is marked between arrows with blood vessel passing through it.

In this paper, we propose a deep learning approach by employing fully connected neural network architecture for RNFLD boundary detection using redfree fundus images. In the first step, a region of interest (RoI) is selected around the OD after blood vessel inpainting, contrast enhancement, and OD localization. Then, the initial set of RNFLD boundary pixels is obtained by analyzing the one-dimensional (1-D) intensity profiles on concentric circles around the OD. Next, the true boundary pixels are retained by designing a convolutional neural network (CNN), which is trained with a large number of image patches big enough to include the important discriminatory information around each pixel. Finally, to compute the angular width of the RNFLD region to be used as glaucoma progression indicator, random sample consensus (RANSAC)-based line fitting algorithm is applied on the detected RNFLD boundary pixels.

The organization of the paper is as follows: Sec. 2 describes the proposed method explaining the deep learning approach for RNFLD detection. Experimental results are presented in Sec. 3. Finally, Sec. 4 mentions some conclusions of the proposed work.

2 Proposed Method

2.1 Preprocessing

2.1.1 Image enhancement

The RNFLD region in the redfree image is often found around the OD, but the intensity difference between the RNFLD region and the background is very subtle. Moreover, the blood vessels passing through/near RNFLD acts as obstruction in the

detection process. In the preprocessing step, the extracted blood vessels^{14–16} are removed through the inpainting process.¹⁷ The visibility of RNFLD region is further enhanced by contrast-limited adaptive histogram equalization (CLAHE).¹⁸ The result of the image enhancement procedure is shown using a test image in Fig. 2.

2.1.2 RNFLD candidate pixel selection

To reduce the search space in achieving low computational complexity, a RoI around the OD is selected and the candidate RNFLD boundary pixels are obtained by analyzing the 1-D intensity profiles on concentric circles around the OD.¹³ The candidate boundary pixels are detected by identifying the prominent minimas in the 1-D intensity profile and applying peak and width analysis of the minimas¹⁹ (Fig. 3). The maximum radius of the concentric circles is empirically determined to be 2.5 times the OD radius by using the images in the training set such that all the candidate RNFLD boundary pixels could be detected. However, the threshold value remains same for the testing set.

2.2 Deep Learning-Based RNFLD Boundary Pixel Classification

The deep learning approach has recently gained a lot of attention in the field of visual pattern recognition, which has been introduced with the objective of moving machine learning closer to artificial intelligence.²⁰ In this regard, the CNNs have extremely good learning ability from the abstract level of input visual

Fig. 2 (a) Redfree fundus image having RNFLD [Fig. 1(b)]. (b) Enhanced image after blood vessel inpainting and CLAHE-based contrast enhancement.

Fig. 3 (a) RoI around the OD from the preprocessed redfree fundus image. (b) Illustration of 1-D intensity profile on a circle around the OD as shown in (a). (c) Smoothed 1-D intensity profile and prominent local minimas are marked. (d) Candidate RNFLD boundary pixels obtained on the circle shown. (e) All detected candidate RNFLD boundary pixels.

data.²¹ However, the limited number of images in medical image databases poses significant difficulty in training a deep CNN. Thus, we have followed a deep patch-based training strategy in our application.

The RoI image is normalized and the intensity range is scaled to (0–1) prior to supplying as input to the network. Then, a large number of $N \times N$ patches are randomly extracted from the red-free RoI image, which include both background and RNFLD boundary patches. The extracted patches reflecting the image content and the corresponding class label of the patches (background/RNFLD boundary) are considered as input to the CNN for training.

A typical CNN architecture constitutes several convolutional layers along with max-pooling, up-sampling and fully connected layers. The convolutional layer consists of a set of learnable filters. When the input patch passes through the convolutional layer, the activation map is generated.²¹ A nonlinear activation function, such as rectified linear unit (ReLU) layers, is applied immediately after the convolutional layer, which enables the network to train faster. The max-pooling layer reduces the resolution of the activation map with respect to the previous layer. Finally, the last layer in CNN is a fully connected layer associated with a softmax layer that generates a probability of belongingness of a patch to a particular class.

2.2.1 Proposed architecture

The CNN architecture followed in the proposed work has the layer organization, as shown in Fig. 4. The network architecture consists of a total of seven convolutional layers with each

convolutional layer followed by the ReLU unit with a dropout of probability 0.25.²² The image patch $I_p(N \times N)$ is supplied as input to the proposed network. The first and second convolutional layers (Conv1 and Conv2) contain a stack of 32 filters with kernel size 3×3 . The third layer is a max-pooling layer (MP1) of window size 2×2 . The max-pooling layer is followed by three convolution layers (Conv3, Conv4, and Conv5) with a stack of 64 filters and two more convolutional layers (Conv6 and Conv7) with a stack of 32 filters. Our patch-based model is designed to capture large intraclass variations that would appear in the RNFLD boundary. The final layer of the architecture is a fully connected layer (FC₂) with softmax unit and contains two output neurons resulting in probability of the two-class classification. Then, a binary decision about the RNFLD boundary pixel is reached by passing the RNFLD boundary probability values through a sigmoid unit of threshold 0.01. The threshold is empirically determined to maximize the detection performance. Once it is determined, it remains unchanged for every test image in during RNFLD detection. The formulation of the network model can be represented as follows:

$$\begin{aligned} \Phi_{\text{proposed}} &\equiv I_p(28 \times 28 \times 1) \rightarrow \text{Conv1}(3 \times 3 \times 32) \\ &\rightarrow \text{Conv2}(3 \times 3 \times 32) \rightarrow \text{MP1}(2,2) \rightarrow \text{Conv3}(3 \times 3 \times 64) \\ &\rightarrow \text{Conv4}(3 \times 3 \times 64) \rightarrow \text{Conv5}(3 \times 3 \times 64) \\ &\rightarrow \text{Conv6}(3 \times 3 \times 32) \rightarrow \text{Conv7}(3 \times 3 \times 32) \rightarrow \text{FC}_2. \quad (1) \end{aligned}$$

In the proposed CNN architecture, a large number of input patches (I_p) of dimension 28×28 pixels with the

Fig. 4 The proposed deep patch-based CNN architecture for RNFLD boundary pixel classification in redfree fundus images.

corresponding class label (background/RNFLD boundary) are given as input to train the network. The cross-entropy function is considered as the cost function, which is defined as follows:

$$J_{\text{CEL}}(\mathbf{y}, \hat{\mathbf{y}}) = -\sum_i [y_i \log \hat{y}_i + (1 - y_i) \log(1 - \hat{y}_i)], \quad (2)$$

where y_i and $\hat{y}_i$ are the groundtruth and prediction values at the output node.

A single iteration of learning in the network involves presenting the inputs to the network, propagation of the excitations through the network until it reaches the output layer and computation of the cost function at output, which is again backpropagated through the network. The change in the weight is a function of the cost function as follows:

$$\Delta w_i = \frac{\partial J_{\text{CEL}}}{\partial w_i}. \quad (3)$$

The backpropagated errors committed by particular units are accumulated and the weights are updated when a batch is complete:

$$w_{i+1} = w_i - \eta \sum_{i \in \text{Batch}} \Delta w_i. \quad (4)$$

The result of deep CNN-based RNFLD patch classification is shown for the test image in Fig. 5(a).

2.3 Postprocessing and RNFLD Angular Width Computation

After detecting the boundary pixels using the deep learning technique with the proposed CNN architecture [Fig. 5(a)], random sample consensus (RANSAC) algorithm is used to fit lines to the detected RNFLD boundary pixels.²³ Prior to that, the closely situated large pixel clusters are grouped. A threshold (T_{cluster}) for cluster size as a function of maximum cluster size is chosen to eliminate very small pixel clusters and the result is given in Fig. 5(b). After line fitting, it is observed that the fitted lines lie very close to the groundtruth RNFLD boundaries, which are manually labeled by the ophthalmologists. Finally, the RNFLD angular width (θ_{RNFLD}) is determined by using the slope information of the fitted lines to the RNFLD boundaries [Fig. 5(c)]. The RANSAC model of a straight line passing through two randomly selected points (x_1, y_1) and (x_2, y_2) from a cluster is given by

$$aX + bY + c = 0, \quad (5)$$

$$(y_1 - y_2)X + (x_2 - x_1)Y + x_1y_2 - x_2y_1 = 0, \quad (6)$$

where a , b , and c are the model parameters. Then, the angle of each fitted boundary line is obtained as follows:

$$\theta_L = \arctan(-a/b). \quad (7)$$

RNFLD angular width is then determined as the difference of angles of the boundary lines:

Fig. 5 (a) Detected boundary pixels after CNN-based patch classification. (b) Final clustered RNFLD boundary pixels using slope similarity criterion. (c) RANSAC line fitting on the boundary pixels overlapped with the groundtruth (red: groundtruth manually labeled by expert, green: detected).

$$\theta_{\text{RNFLD}} = \theta_{L_1} - \theta_{L_2}. \quad (8)$$

For example, in Fig. 5, the angular width of the RNFLD region after RANSAC line fitting is computed to be $\theta_{\text{RNFLDdetected}} = 14.44$ deg, which is very close to the ground-truth ($\theta_{\text{RNFLDgt}} = 13.6$ deg). In case of multiple RNFLD boundary detection, the operator is required to identify correct pair of lines. Then, the RNFLD angular width is quantified automatically.

3 Results and Discussion

The proposed method is evaluated on a newly created glaucomatic fundus image database obtained from Glaucoma Diagnostic Services, L. V. Prasad Eye Institute, Bhubaneswar, India. The fundus images are acquired using a Visupac version 4.4.4 camera (FF 450 plus IR Carl Zeiss Ltd., USA) with $5\times$ magnification and 20 deg, 30 deg, and 50 deg field of views (FoV). The original images are in JPEG format and have pixel resolutions of 1958×2588 , 1934×1960 , and 1934×2576 . The database includes a total of 68 fundus images, which are divided into training (13 images containing 20 RNFLD regions) and testing (55 images) sets. The testing set comprises 29 images having RNFLD and 26 images without RNFLD. A total of 39 RNFLD regions are present in the testing set, which are associated with 78 RNFLD boundaries. All the images are analyzed by an ophthalmologist blinded to the clinical details of the patient. For comparison with the diagnostic performance of our method, the ophthalmologist's findings are taken as the gold standard.

The images are scaled down by a factor 3 and the RoI of size 301×301 pixels is selected in the implementation of the proposed algorithm. The CNN is trained with 50,000, (28×28) randomly selected patches belonging to the background and RNFLD boundary from the training set that constitutes 13 full size fundus images containing a total of 20 RNFLD regions.

Fig. 7 Comparison of FROC curves for different RNFLD boundary detection algorithms.

The network is trained and the weights are updated in batches; the batch size in our approach is set to 64 and number of epochs as 100. A stochastic gradient decent approach, i.e., RMSProp (root mean square propagation) method is explored for learning the parameters in the network and the learning rate is set at 1×10^{-4} . The proposed network is implemented on Keras (Theano framework). The experiments are conducted on the desktop computer having Intel Core i7 – 6700K CPU with four NVIDIA TITANX graphics cards.

For quantitative evaluation, sensitivity (SN), false positives per image (FPI), and area under the curve (AUC) are computed. The SN reflects the ability of the proposed method to detect true RNFLD boundary:

Fig. 6 (a)–(f) RNFLD boundary detection results [red: groundtruth, green: truly detected RNFLD (TP), blue: falsely detected RNFLD (FP)].

Table 1 RNFLD angular width estimation and localization accuracy.

Image No.	θ_{RNFLD} (deg)			E_{Dmean} (pixels)	
	Groundtruth	Panda et al. ¹³	Proposed	Panda et al. ¹³	Proposed
1	16.4	17.9	17.36	7.5	5.1
2	11	9.4	10.7	3.6	4.83
3	18	21	20.6	3.6	4.2
4	20.9	24.9	23.2	5.8	5.7
5	23.2	25.6	25.7	3.5	7.2
	178.87	Both boundaries missing	Both boundaries missing		
6	16.4	13.2	14.8	6.6	3.5
7	20.1	16.4	18.4	4.9	5.8
8	33.9	8.4	24.3	10.1	3.75
9	17.5	21.5	20.3	5.9	4.7
10	13.6	18.3	14.44	4.4	4.3
11	19.4	23.5	23.4	4.7	4.0
12	6.5	9.7	8.1	6.2	8.8
	18	16.7	20.9		
13	20.6	Both boundaries missing	Both boundaries missing	4.5	3.8
	24.1	19.8	One boundary missing		
	21.5	25	23.1		
14	26	26.13	24.3	5.02	6.5
	45	Both boundaries missing	Both boundaries missing		
15	24	23.2	22.5	4.56	5.3
	40.9	One boundary missing	Both boundaries missing		
16	31.42	27.24	One boundary missing	7.36	3.7
17	24.59	23.23	23.64	1.74	2.1
18	28.20	25.61	One boundary missing	8.70	3.3
19	31.55	28.22	29.7	3.61	5.2
20	28.94	29.22	26.8	3.80	5.13

Table 1 (Continued).

Image No.	θ_{RNFLD} (deg)			E_{Dmean} (pixels)	
	Groundtruth	Panda et al. ¹³	Proposed	Panda et al. ¹³	Proposed
21	30.02	34.14	31.7	6.80	4.8
	42.43	One boundary missing	39.87		
22	19.23	17.82	17.29	5.36	6.48
23	19.4	15.18	21.5	4.09	3.93
24	13.93	One boundary missing	14.3	2.96	5.4
	24.91	Both boundaries missing	27.5		
25	26.56	20.92	23.7	10.87	5.6
	25.05	21.07	One boundary missing		
26	18.55	19.30	16.8	2.3	7.05
27	25.14	22.84	23.5	2.47	5.36
28	24.91	Both boundaries missing	22.14	—	4.2
29	30.57	Both boundaries missing	27.61	—	4.16
	43.49	Both boundaries missing	Both boundaries missing		
				Average = 5.2, Median = 4.7	Average = 4.96, Median = 4.83

$$\text{SN} = \frac{\text{TP}}{\text{TP} + \text{FN}}, \quad (9)$$

$$\text{FPI} = \frac{\text{FP}}{\text{Total number of images}}, \quad (10)$$

where true positive (TP) represents the number of correctly detected RNFLD boundary lines; false negative (FN) is the incorrect detection of RNFLD boundary lines as background; FP represents number of boundary lines in the background detected as RNFLD. The AUC is computed as the area under the free response receiver operating characteristics (FROC) curve.

Out of 78 RNFLD boundaries present in 29 test images, the proposed method could correctly detect 64 with nine FPs. Out of 26 test images without having RNFLD, two FP cases are detected. Thus, the total number of FPs becomes 11 for the testing images. More examples of RNFLD boundary detection by

using the proposed architecture are shown in Fig. 6. The FN cases arise due to the very minute difference of intensities between the RNFLD and background. The macular sheath, which is a dark strip from OD to macula, if present in the fundus images results in FPs. The FROC curve is plotted in Fig. 7 by varying the threshold for cluster size ($T_{cluster}$). The AUC is computed from the FROC curve to be 0.89. The optimal value of the SN of RNFLD boundary detection is found to be 0.8205 with FPI of 0.2000.

To quantify the localization accuracy of the proposed RNFLD boundary detection method, the mean Euclidean distance (E_{Dmean}) between the detected RNFLD boundary and the groundtruth boundary is also computed for each image. The E_{Dmean} of detected RNFLD boundaries in the images of test set is provided in Table 1. The average value of E_{Dmean} for the whole database is found out to be 4.96 pixels, which indicates better agreement of the detected boundaries by the proposed method with the groundtruths. The RNFLD angular width computed using Eqs. (7) and (8) is provided in Table 1. The angular width could not be determined in such cases, where at least one boundary line is not detected by the proposed method. The θ_{RNFLD} and E_{Dmean} values of the proposed method are also compared with the existing method in Ref. 13. The average E_{Dmean} of proposed method is 4.96 pixels, which is better than that of Ref. 13 (5.20 pixels).

The proposed method is compared with existing RNFLD boundary detection algorithms (Oh et al.¹⁰ and Panda et al.^{12,13}). We also compare the performance of the SVM classifier in combination with the handcrafted features of Refs. 12 and 13. The comparison of FROC curves for the aforementioned algorithms is shown in Fig. 7. It can be observed from Table 2 and Fig. 7 that the proposed method achieves more enhanced performance than the existing methods in terms of quantitative measures, such as SN, FPI, and AUC. Oh et al.¹⁰ reported an overall accuracy of 86% SN on their private database; yet when compared on the training images of the database, the performance of the method lags as compared to our proposed method (Table 2). In Fig. 7, it can be observed from the FROC curve that most of the SN values obtained by Oh et al.¹⁰ is found to be less than 0.5. Thus, the AUC value for this method did not exceed 0.5. It is observed during the implementation of the existing method in Ref. 11 that it is somewhat challenging to optimally fine-tune its intensity-dependent parameters for the test cases. The advantage of the proposed architecture is that it learns the patch features directly from a large number of image patches unlike the methods in Refs. 12 and 13, where the classifiers learn from several handcrafted features.

Table 2 Performance comparison of RNFLD boundary detection.

Method	SN	FPI	AUC
Oh et al. ¹⁰	0.5513	0.7818	0.45
Panda et al. ¹²	0.5513	0.3636	0.67
Panda et al. ¹³	0.7051	0.2727	0.87
Features of Ref. 13 + SVM	0.6154	0.5455	0.63
Proposed (CNN)	0.8205	0.2000	0.89

4 Conclusion

An automated deep learning-based RNFLD boundary detection is proposed in this paper, which could be helpful in computer-aided large-scale early glaucoma risk assessment. After obtaining the candidate RNFLD boundary pixels in the preprocessing step, the true boundary pixels are detected using the proposed deep patch-based CNN architecture. The CNN architecture is trained with a large number of RNFLD and background patches and the trained network accurately detects the RNFLD boundary. The classified RNFLD boundary pixels are line fitted to extract the angular width of the RNFLD region, which acts as a glaucoma progression indicator. The proposed RNFLD boundary detection method achieves the potential to accurately detect RNFLD boundaries with an improved performance SN of 0.8205 with FPI of 0.2000 on a newly created fundus image database. The RNFLD region widens with the progression of glaucoma; hence, the proposed method can be useful for progression monitoring of early glaucoma in mass screening.

Disclosures

The authors do not have any conflicts of interest with other people or organizations that could inappropriately influence their work.

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Rashmi Panda received her MTech degree from NIT Rourkela. She is currently pursuing her PhD degree with the School of Electrical Sciences, IIT Bhubaneswar. Her fields of research interest include biomedical image analysis, image processing, and pattern recognition.

Niladri B. Puhan received his ME degree in signal processing from Indian Institute of Science, Bangalore, and his PhD degree from Nanyang Technological University, Singapore, in 2007. He is currently an assistant professor with the School of Electrical Sciences, IIT Bhubaneswar. His fields of research interest include signal and

image processing, computer vision, biometrics, and biomedical image analysis.

Aparna Rao completed her basic medical education with Maharashtra, followed by a diploma in ophthalmology from Guru Nanak Eye Center, Maulana Azad Medical College, New Delhi, and a MD (DNB) from ICARE Eye Hospital and Glaucoma Research Institute, Noida, Uttar Pradesh. She further did a postdoctoral research fellowship in glaucoma at the Rajendra Prasad Center for Ophthalmic Sciences, AIIMS, New Delhi, where she also worked as research associate (ICMR, Delhi) for a couple of years. She then did a glaucoma fellowship at LVPEI, Hyderabad, before joining LVPEI, Bhubaneswar. She now is completing her PhD at KSBT, KIIT, Bhubaneswar, with a focus on glaucoma and trabecular meshwork. Her areas of interest are research on pseudoexfoliation, trabecular meshwork, congenital glaucoma, and stem cells.

Bappaditya Mandal received his BTech degree in electrical engineering from Indian Institute of Technology (IIT), Roorkee, India, and his PhD degree in electrical and electronic engineering from Nanyang Technological University (NTU), Singapore, in 2003 and 2008, respectively. He is currently a lecturer in computer science, School of Computing and Mathematics, Keele University, United Kingdom. His research interests include subspace learning, feature extraction and evaluation, computer vision, image and signal analysis, and machine learning.

Debananda Padhy received his MOptom degree in optometry from Chitkara University, Chandigarh, in 2017. He is currently an assistant optometrist in L. V. Prasad Eye Institute, Bhubaneswar. His fields of research interests include optics and refraction, binocular single vision, and glaucoma imaging analysis.

Ganapati Panda received his PhD degree in electronics and communication engineering from IIT Kharagpur, India, in 1982. He is currently a professor of electrical sciences with the IIT Bhubaneswar. His research interests include digital signal processing, soft computing, and distributed signal processing. He is a fellow of the National Academy of Engineering India, the National Academy of Science India, the Institution of Engineering and Technology, United Kingdom, and the IETE.