Original Article

Automatic Cataract Detection Using the Convolutional Neural Network and Digital Camera Images

Alireza Meshkin [1,*], PhD; Farjam Azizi [1], MS; Khosro Goudarzi [1], MS

1 Department of Computer Engineering, Damavand Branch, Islamic Azad University, Damavand, Iran.

***Corresponding Author:** Alireza Meshkin
E-mail: alireza.meshkin@iau.ac.ir

Abstract

Background: The cataract is the most prevalent cause of blindness worldwide and is responsible for more than 51 % of blindness cases. As the treatment process is becoming smart and the burden of ophthalmologists is reducing, many existing systems have adopted machine-learning-based cataract classification methods with manual extraction of data features. However, the manual extraction of retinal features is generally time-consuming and exhausting and requires skilled ophthalmologists.
Material and Methods: Convolutional neural network (CNN) is a highly common automatic feature extraction model which, compared to machine learning approaches, requires much larger datasets to avoid overfitting issues. This article designs a deep convolutional network for automatic cataract recognition in healthy eyes. The algorithm consists of four convolution layers and a fully connected layer for hierarchical feature learning and training.
Results: The proposed approach was tested on collected images and indicated an 90.88 % accuracy on testing data. The keras model provides a function that evaluates the model, which is equal to the value of 84.14 %, the model can be further developed and improved to be applied for the automatic recognition and treatment of ocular diseases.
Conclusion: This study presented a deep learning algorithm for the automatic recognition of healthy eyes from cataractous ones. The results suggest that the proposed scheme outperforms other conventional methods and can be regarded as a reference for other retinal disorders.

Keywords: Cataract; Deep Learning; Convolutional Neural Network; Image Processing.

Article Notes: Received: Jan. 02, 2021; Received in revised form: Jan. 31, 2021; Accepted: Feb. 13, 2021; Available Online: Jun. 22, 2021.

How to cite this article: Meshkin A, Azizi F, Goudarzi K. Automatic Cataract Detection Using the Convolutional Neural Network and Digital Camera Images. Journal of Ophthalmic and Optometric Sciences . 2021;5(3): 25-36.

Introduction

A cataract is an opaque area in the lens of the eyes that negatively impact vision. Most cataracts are caused due to aging. Around 40 years of age, the eye lens proteins begin to undergo degradation and aggregation, resulting in a foggy region in the lens known as a cataract. The situation usually exacerbates with time, constantly darkens most of the lens, and worsens the vision. The most common symptoms of cataracts include blurred vision, dark vision, and reduced color sensitivity. Cataracts are often treatable with surgery. While an optometrist is not qualified to perform cataract surgery, he can make a cataract diagnosis and refer the patient to an ophthalmologist to perform this procedure. During cataract surgery, the surgeon creates a small hole in the eye, breaks and removes the old lens, and replaces it with a new artificial lens [1].

The World Health Organization (WHO) estimates that 314 million people globally suffer from visual impairments [2]. Visual impairment and blindness are the chief health challenges in rural and remote communities in developing countries [3]. Visual impairment refers to reduced visual acuity, and its correction may require further interventions, whereas blindness refers to total loss of vision, which generally may be irreversible [4]. Computer-aided interventions hold the potential to enhance the surgeon's capabilities through a combination of clinical information, better visualization, and navigation [5]. With this interpretation, finding an effective method for automatically detecting and classifying cataracts can contribute to their inexpensive and timely diagnosis [6]. The fast and automatic recognition of ocular diseases is significant and essential to lessen the workload of ophthalmologists, prevent damage to the patients, and consequently lower treatment costs.

The traditional methods of cataract classification involve machine-learning algorithms to manually extract the features of existing components [7]. The efficiency of these methods depends largely on the manually identified features from the existing initial components, such as wavelet features, texture, color, histogram of oriented gradients (HoG), and the graph [8]. The manual feature extraction and selection is time-consuming and requires proficient ophthalmologists with long experiences in this specific field. Thus, a convolutional neural network, as a widely applied deep learning algorithm, seems to be a viable option to overcome these challenges [9].

This paper is organized as follows: Section 2 describes the related work. In section 3, tested data is evaluated, and the artificial network is analyzed. Section 4 presents the considered network architecture and the proposed method. Section 5 will discuss the results, and finally, conclusions are drawn in section 6.

Related work

Computer-assisted recognition and diagnosis have offered considerable performance improvement in medical imaging. While many past studies have addressed cataract detection and grading using retinal images, most have concentrated on manual features and traditional machine learning-based strategies. Zhang et al. applied a deep convolutional neural network (DCNN) for four-class cataract classification [10]. A deeper network based on a combination of DCNN and random forests (RF) algorithm was developed by Ron et al. for six-level cataract classification [11]. Using CNN and deconvolution network (DN), Xu et al. presented a local (a small group of pixels)-global (the whole image) feature representation model [12]. Feature extraction was first done using CNN, followed by layer-by-layer classification of cataracts using DN.

Li et al. exploited deep learning (DL) models to classify cataracts in retinal images [13]. The local and global features were extracted from the gray level co-occurrence matrix (GLCM) and pre-trained residual network (ResNet), respectively, and inputted into a support vector machine (SVM) for automatic cataract classification [14]. Zhu et al. applied discrete state transitions (DST) and exponential discrete state transitions (EDSTs) along with multilayer perceptron (MLP) to classify cataracts [15]. Improved Haar features (IFN) and visible structure features (VSF) were combined as datasets. In the proposed method, DST-MLP and EDST-MLP prevent overfitting, decrease storage memory during network training and achieve ideal accuracy under different weights and settings.

Imran et al. introduced an innovative combination of Self-Organizing Map (SOM) and Radial Basis Function neural network (RBFNN) to classify the cataract [16]. Initially, SOM is used for center initialization, and cataract classification is then performed using RBF neural network. SOM-RBF neural network yields a 91.7 % accuracy for four-class cataract classification. Pratap and Kokil applied transfer learning to detect cataracts. A pre-trained CNN was employed for automatic feature extraction, and an SVM classifier was used for four-stage cataract classification. Tests were made on collected datasets for which the image quality selection module was involved to accept or reject images based on the naturalness image quality evaluator (NIQE) and perceptron image quality evaluator (PIQE). The proposed method achieved a 92.91 % accuracy [17].

Moreover, Imran et al. designed a deep convolutional neural network-based cataract classifier. The authors implemented novel data augmentation techniques, such as Gaussian scale-space theory (GST) and general data augmentation setting to tackle unbalanced dataset issues. In addition, they utilized the basic CNN method for automatic feature extraction and classification. Based on their results, the developed method with the augmented dataset resulted in an accuracy score of 96.61 % for cataract recognition and 93.97 % for its classification [18]. Although deep learning models have provided a desirable performance regarding cataract recognition and classification, their training with the study's working graph is challenging, and their performance hugely depends on the large retinal dataset. Imran et al. resolved this issue by integrating the transfer learning concept with the SVM algorithm for four-class cataract classification. DCNN classifier was implemented for fingerprint detection with an overall prediction accuracy of 98.5 percent [19].

Materials and Methods

Image datasets

The dataset used in this study for model testing and evaluation was extracted from a structured ophthalmology database of 5000 patients, which contains their age, color fundus images from their left and right eyes, and doctor's diagnostic keywords from skilled physicians (briefly ODIR-5K). This dataset provides "real life" patient information collected by the Shanggong medical technology company from different Chinese hospitals and medical centers. In these institutes, the fundus images were taken using various market-available cameras, including Canon, Zeiss, and Kowa, with varying picture resolutions. After eliminating the patient's identification data,

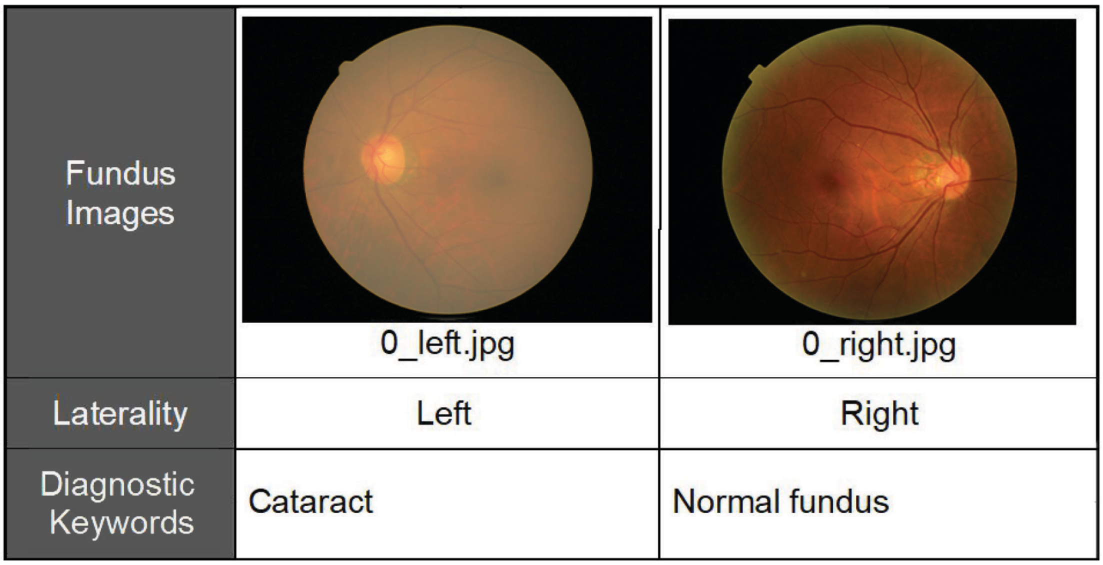

Figure 1: A schematic of the recorded images from the considered dataset

trained human readers labeled the annotations with quality control management. Eight labels were assigned to each patient, including normal (N), diabetes (D), glaucoma (G), cataract (C), age-related macular degeneration (AMD) (A), hypertension (H), pathological myopia (M) and other diseases/abnormalities (O). The classification was based on images of both eyes and the patient's age[20]Lingling</author> <author>Wang, Ting</author> <author>Wu, Zhonghua</author><author>Wang, Jianwu</author> <author>Wang, Ming</author> <author>Cui, Zequn</author> <author>Ji, Shaobo</author> <author>Cai, Jianfei</author> <author>Xu, Chuanlai</author><author>Chen, Xiaodong</author > </authors> </contributors> <titles> <title> Portable food-freshness prediction platform based on colorimetric barcode combinatorics and deep convolutional neural networks</title><secondary-title>Advanced Materials</secondary-title></titles><periodical > <full-title> Advanced Materials</full-title> </periodical> <pages> 2004805</pages> <volume> 32 </volume> <number> 45</number> <dates> <year> 2020 </year> </dates> <isbn> 0935-9648 </isbn> <urls> </urls> </record> </Cite> </EndNote>.

It should be kept in mind that due to the drawbacks of deep learning, which requires a large amount of data for training, an additional dataset was utilized here to enhance the accuracy. This 601-image dataset from the Kaggle website is related to the challenge of ocular disease recognition using computer-vision techniques [21].

Artificial neural network (ANN)

As a type of machine learning model, artificial networks are emerged as a powerful competitor for conventional statistical and regression models in terms of utility and based on data analysis factors, including processing speed, latency, error tolerance, performance, volume, convergence accuracy, and scalability. Artificial neural networks offer a good potential to provide high-speed processing in a massive parallel implementation, underlining the need for further study in this area. The artificial networks can be extended to be used in natural language processing, image recognition, and worldwide function

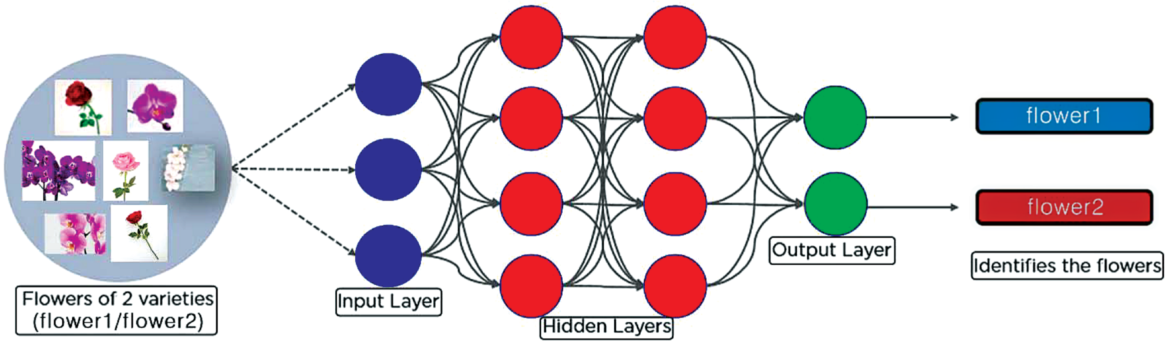

Figure 2: A schematic of artificial neural network

approximation in numerical paradigms. The data analysis outputs have proved artificial neural networks' effectiveness, efficiency, and success in solving non-complex and complex problems in different areas of life. Three groups of layers exist in a neural network: the input layer, hidden layer, and output layer. The input layer includes all input parameters. The data are calculated in the hidden layer while the output layer calculates the output vector. Three major steps to implementing artificial networks involve the selection of input and output parameters, training, and testing. The input and output parameter data are generally normalized in a specified range [22].

Convolutional neural network

Convolutional neural networks are a group of deep neural networks (DNNs), and similar to ANNs, belong to the fully-supervised learning algorithms primarily utilized for image classification. These networks have been shown to effectively recognize large-scale objects, which requires a large number of training images. While ANNs attempt to solve the complex image data, the CNNS are the predominant multilayer network for complex image recognition and receive patterns mimicking the human visual recognition fields as their inputs. CNNs are capable of learning via the self-optimizing process and are swiftly adapted to various spectral inputs. Additionally, they are generalizable beyond training data.

Recognition uses weights, basically the filters that are mathematically convolved with the considered image. A convolution is a linear operation that multiplies a set of weights with the input. It involves performing the dot product between an array of input data and a two-dimensional array of weights. The output of each CNN's convolutional layer is exactly connected to small regions of the input data. Prior knowledge is the primary benefit of these networks. With an approach similar to human learning behavior, CNN has a relatively lower preprocessing than other image classification algorithms[23]. A artificial neural network example is depicted in figure (2).

In general, a convolutional network comprises three fundamental layers: convolutional, pooling, and fully connected (FC). Additional layers, such as random dropout and batch normalization, can be incorporated to prevent overfitting. In neural networks, each layer is followed by an activation function. A brief description of these layers and functions is provided in the following.

Convolutional layer: This layer involves filters that operate on image pixels. A kernel is a matrix that applies the expected operation to the image of interest. This layer performs the convolution process on the input images using the kernel. The convolution output is known

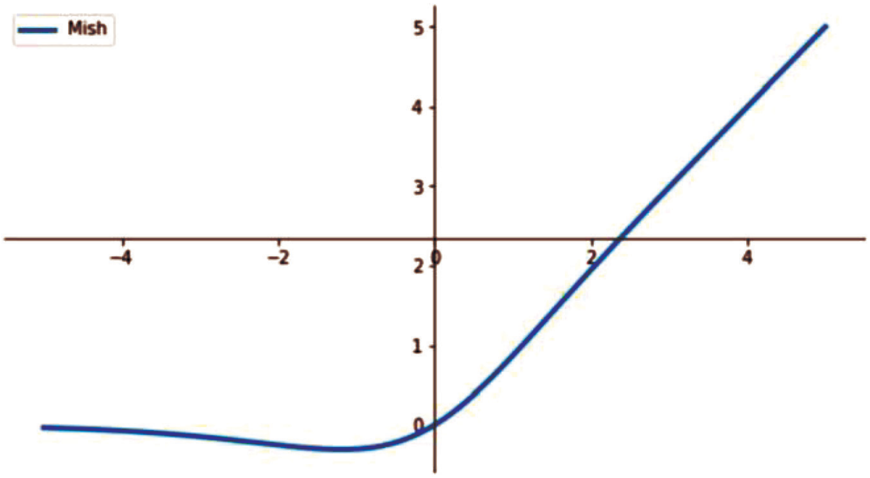

Figure 3: A schematic of the Mish activation function

as a feature map. The convolution operator is described in equation (1):

$$y_k = \sum_{n=0}^{N-1} x_n h_{k-n} \quad (1)$$

Where x represents the image and h is the filter. N denotes the number of elements in x, and y is the output vector.

Pooling layer: In this layer, also known as the down-sampling layer, the dimensions of output neurons from the convolution layer will decline, thereby reducing computations and preventing overfitting. The max-pooling layer is applied in this study which only selects the maxima in each feature map and causes a reduction in the number of output neurons.

FC layer: This layer is fully connected to all activators in the preceding layer.

Random dropout layer: It is added to prevent overfitting. In this layer, each neuron can be dropped out of the network with a certain probability at each training stage so that a reduced network will remain eventually.

Batch normalization layer: The role of this layer is to normalize data inside the network. Applying different calculations to input data will change the data distribution. By minimizing the internal covariance variation, this layer improves the network training speed and accelerates convergence. Equation (2) gives the batch normalization layer conversion:

$$\mu_B = \frac{1}{n}\sum_{i=1}^{n} y_i^{(l-1)} \qquad (2)$$

$$\sigma_B^2 = \frac{1}{n}\sum_{i=1}^{n} (y_i^{(l-1)} - \mu_B)^2$$

$$\hat{y}^{(l-1)} = \frac{y^{(l-1)} - \mu_B}{\sqrt{(\sigma_B^2 + \varepsilon)}}$$

$$z^{(l)} = \gamma^{(l)}\hat{y}^{(l-1)} + \beta^{(l)}$$

In the above relations, and are the batch mean and variance, respectively. is an infinitesimal constant for numerical stabilization. is the number of layers, and represents the input vector to the normalizer layer. is the corresponding normal output vector of each neuron. Finally, and are the scale and learning rate tuning parameters, respectively.

Activation function: One activation function will follow each convolutional layer. It is, in fact, an operator which maps the output to a set or group of inputs and is considered for non-linearization of the network structure.

In this study, the Mish activation function is employed in convolutional layers. Unlike other activation function operators like Relu, Mish lacks a uniform nature, meaning it is not entirely ascending or descending. As shown by figure (3), it is a non-uniform function that starts to descend after reaching zero but will follow an ascending trend again.

Similar to Relu, Mish has an infinite upper bound, meaning that for extremely large values, the outputs fail to saturate to the maximum. Thus, the gradient will not become zero for any value, making the learning more powerful. Mish is lower bounded, meaning the output will approach a constant value as the input approaches negative infinity. Initially, it is imperative to overcome negative values as much as possible. With this strength, Mish forgets the substantial negative value, which is nothing other than deactivation. This property of Mish introduces regularization into the model[24], which is described in relation (3):

$$f(x) = x.\tanh\big(\mathrm{C}(x)\big) \qquad (3)$$

$$where\ \mathrm{C}(x) = \ln(1 + e^{x})$$

Softmax function: This probability distribution function calculates the output classes. The softmax function is applied in the last FC layer to predict the class of the input image as healthy or cataract-affected and follows the form in equation (4):

$$\rho_i = \frac{e^{x_j}}{\sum_1^k e^{x_k}} \qquad for\ j = 1, \dots, k \quad (4)$$

In this relation, x is the network input. The output values vary between 0 and 1, the sum of which equals one.

Proposed method

This section delineates the proposed method of this study. Figure (4) and Figure (5) illustrate the overall structure of the presented scheme.

This study employed the Keras library in Python programming language to implement the convolutional network. The architecture of the deep neural network was chosen to have four convolutional layers along with the Mish activation function. It also contained dropout and batch normalization layers, two max-pooling layers, and finally, Flatten layer and Softmax layer, through which the results were displayed. It should be noted that in training a neural network, the inputs are broken into equally sized small batches rather than being submitted as a whole, which will result in a more comprehensive model. In this study, the batch size was set to 26. The network requires a back-and-forth propagation or the so-called epoch to be applied to the input. In order to implement and train the network, whose size was 43 in this study, the architecture output will be connected to a two-dimensional (2D) matrix. As can be observed from Table 1, an FC layer is used to provide access to the output layer.

A total of 26354 parameters existed in this model. The designed architecture initially consisted of two 2D convolutional layers, with other settings being a filter size of 16 and a Kernel size of 3. Additionally, the initial size of the input images was considered 256×192. A Mish activation function was then applied, followed by batch normalization and 2D max-pooling layers. This structure was repeated a second time, after which the dropout layer was added. Finally, the selected feature vector was fed into two FC layers, followed by a Softmax function to automatically recognize and classify the images into either cataract-affected or healthy normal eyes.

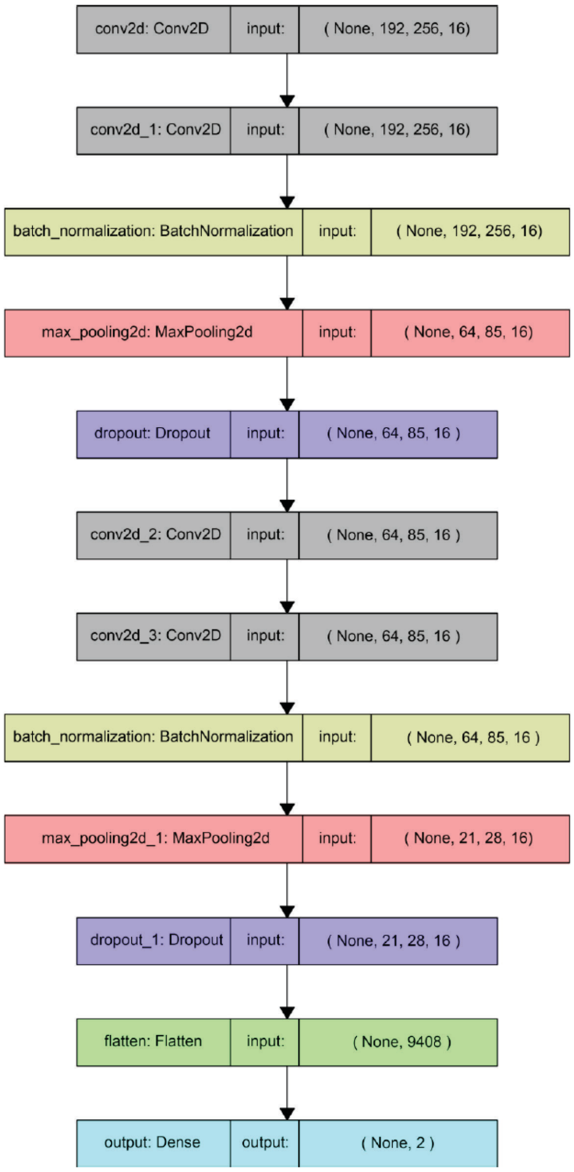

Figure 4: A schematic of the neural network architecture

Training and evaluation of the proposed deep network

A trial and error approach was adopted to determine and compute the cloud of parameters of the proposed network. Given the comparative analysis of the testing outputs, the cross entropy objective function and Adam optimizer were applied. The two data environments were divided into training, testing, and validation sets to evaluate the considered system.

Results and discussion

All study simulations were carried out on a computer with AMD Ryzen 7 5800H CPU, 3.20 GHz processor, and 16 GB RAM. Figure (6) depicts the accuracy plot, which describes the overall model performance in all classes. Accuracy is a useful criterion when all classes have the same significance and is calculated as the ratio between the number of correct predictions and the total number of predictions and also figure (6) indicates the prediction accuracy after training and its accuracy on new data for validation. The model accuracy on new data for validation is equal to 83.78 percent. As shown in Figure (7), the loss function is a criterion for assessing how a deep learning model matches training data. In other words, it evaluates the model error in the training set. It should be noted that the training set is a part of the dataset used for initial model training. From a computational perspective, the training loss function is calculated considering the sum of errors of each instance in the training set. More importantly, the training loss is measured after each batch and is usually visualized by plotting the training loss graph. The validation loss function is a criterion to evaluate the performance of a deep learning model in the validation set. The validation set is a portion of the dataset reserved for model performance validation. Similar to training loss, validation loss is obtained from the sum of errors of each sample in the validation set. Additionally, the validation loss is measured after each epoch to determine whether the model needs tuning or further adjustments. For this purpose, a learning curve is usually plotted for validation loss.

Conclusion

This article presented a deep learning algorithm for the automatic recognition of

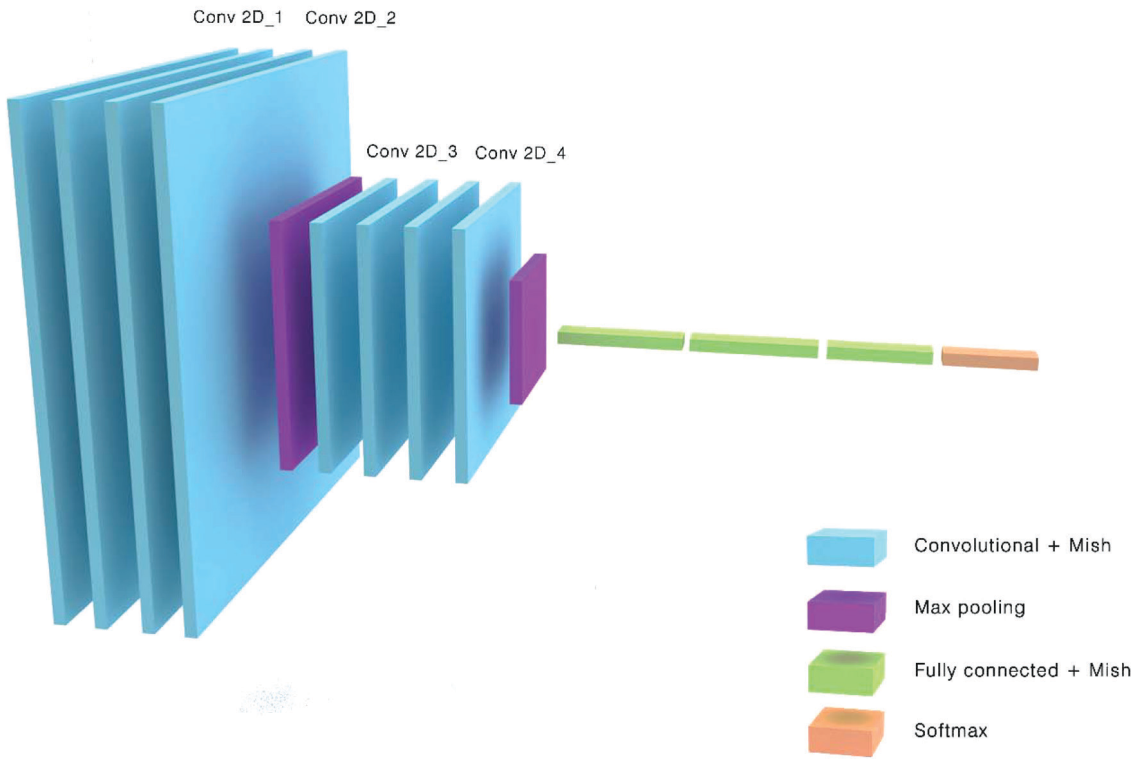

Figure 5: A schematic of the convolutional neural network architecture

healthy eyes from cataractous ones. In the proposed approach, the considered dataset images were used to discriminate the healthy and unhealthy eyes. The features were extracted hierarchically using the designed convolutional network. As the results suggested, the proposed model could select the features producing the highest distinction between classes. The algorithm provided a 2-class classification for different ocular statuses, including being healthy or cataract-affected. Given the acceptable accuracy of the model in the environment allocated to the testing data, which is equal to 90.88 %, using the method and concept of evaluation, the process that occurs during model development to check whether the model is appropriate for the given problem and the relevant data, the keras model provides a function that evaluates the model, which is equal to the value of 84.14 %, the model can be further developed and improved to be applied for the automatic recognition and treatment of ocular diseases.

Authors ORCIDs

Alireza Meshkin:
https://orcid.org/0000-0002-7046-4404

Table 1: The details of convolutional network layers and the number of parameters at each layer

Model: "sequential"		
Layer (type)	Output Shape	Param #
conv2d (Conv2D)	(None, 192, 256, 16)	448
conv2d_1 (Conv2D)	(None, 192, 256, 16)	2320
batch_normalization (BatchNo	(None, 192, 256, 16)	64
max_pooling2d (MaxPooling2D)	(None, 64, 85, 16)	0
dropout (Dropout)	(None, 64, 85, 16)	0
conv2d_2 (Conv2D)	(None, 64, 85, 16)	2320
conv2d_3 (Conv2D)	(None, 64, 85, 16)	2320
batch_normalization_1 (Batch	(None, 64, 85, 16)	64
max_pooling2d_1 (MaxPooling2	(None, 21, 28, 16)	0
dropout_1 (Dropout)	(None, 21, 28, 16)	0
flatten (Flatten)	(None, 9408)	0
dense (Dense)	(None, 2)	18818
Total params: 26,354 Trainable params: 26,290 Non-trainable params: 64		

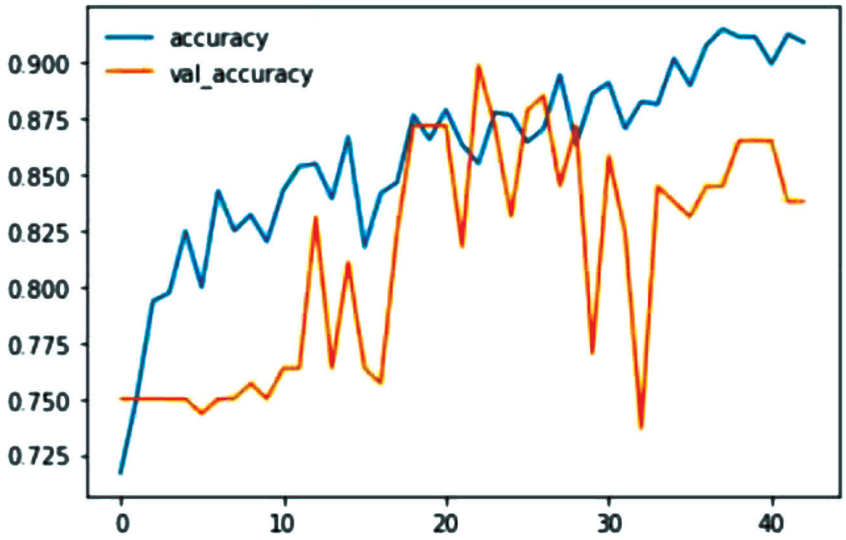

Figure 6: A schematic view of the accuracy criterion for the deep convolutional network

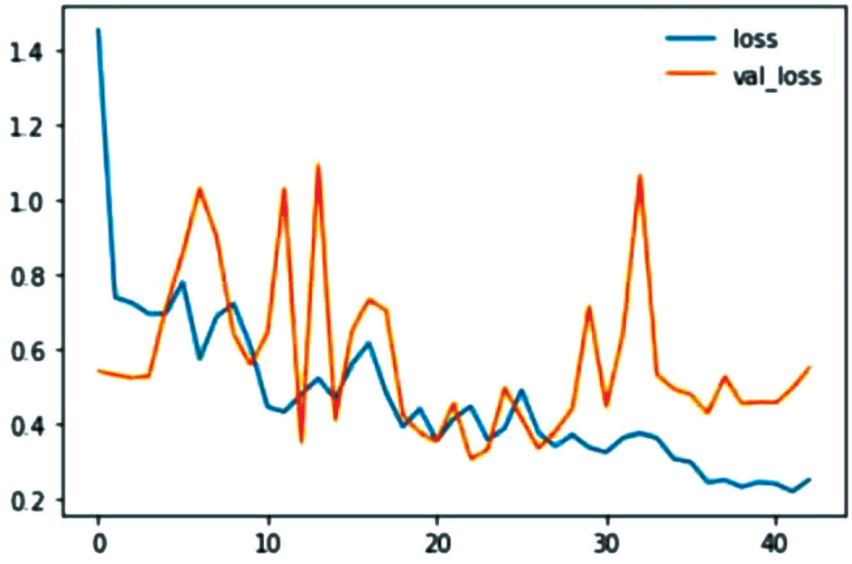

Figure 7: A schematic view of the accuracy criterion for the deep convolutional network

References

1. Khoza LB, Nunu WN, Ndou ND, Makgopa J, Ramakuela NG, Manganye BS, et al. Barriers related to the provision of cataract surgery and care in Limpopo province, South Africa: Professional ophthalmic service providers' perspective. Scientific African. 2020;9:e00479.

2. Imran A, Li J, Pei Y, Akhtar F, Yang J-J, Dang Y. Automated identification of cataract severity using retinal fundus images. Computer Methods in Biomechanics and Biomedical Engineering: Imaging & Visualization. 2020;8(6):691-8.

3. Ntsoane MD, Mpolokeng BL, Oduntan OA. Utilisation of public eye care services by the rural community residents in the Capricorn district, Limpopo Province, South Africa. African Journal of Primary Health Care and Family Medicine. 2012;4(1):1-7.

4. Tielsch JM, Sommer A, Witt K, Katz J, Royall RM. Blindness and visual impairment in an American urban population: the Baltimore Eye Survey. Archives of ophthalmology. 1990;108(2):286-90.

5. Maier-Hein L, Vedula SS, Speidel S, Navab N, Kikinis R, Park A, et al. Surgical data science for next-generation interventions. Nature Biomedical Engineering. 2017;1(9):691-6.

6. Zhang L, Li J, Han H, Liu B, Yang J, Wang Q, editors. Automatic cataract detection and grading using deep convolutional neural network. 2017 IEEE 14th international conference on networking, sensing and control (ICNSC); 2017: IEEE.

7. Qian X, Patton EW, Swaney J, Xing Q, Zeng T, editors. Machine learning on cataracts classification using SqueezeNet. 2018 4th international conference on universal village (UV); 2018: IEEE.

8. Buvana M, Muthumayil K, Jayasankar T. Content-based image retrieval based on hybrid feature extraction and feature selection technique pigeon inspired based optimization. Annals of the Romanian Society for Cell Biology. 2021:424-43.

9. Singh LK, Garg H, Khanna M, Bhadoria RS. An enhanced deep image model for glaucoma diagnosis using feature-based detection in retinal fundus. Medical & Biological

Engineering & Computing. 2021;59:333-53.
10. Ran J, Niu K, He Z, Zhang H, Song H, editors. Cataract detection and grading based on combination of deep convolutional neural network and random forests. 2018 international conference on network infrastructure and digital content (IC-NIDC); 2018: IEEE.
11. Xu X, Zhang L, Li J, Guan Y, Zhang L. A hybrid global-local representation CNN model for automatic cataract grading. IEEE journal of biomedical and health informatics. 2019;24(2):556-67.
12. Li J, Xu X, Guan Y, Imran A, Liu B, Zhang L, et al., editors. Automatic cataract diagnosis by image-based interpretability. 2018 IEEE international conference on systems, man, and cybernetics (SMC); 2018: IEEE.
13. Xiong Y, He Z, Niu K, Zhang H, Song H, editors. Automatic cataract classification based on multi-feature fusion and SVM. 2018 IEEE 4th International Conference on Computer and Communications (ICCC); 2018: IEEE.
14. Zhou Y, Li G, Li H. Automatic cataract classification using deep neural network with discrete state transition. IEEE transactions on medical imaging. 2019;39(2):436-46.
15. Imran A, Li J, Pei Y, Akhtar F, Yang J-J, Wang Q, editors. Cataract detection and grading with retinal images using SOM-RBF neural network. 2019 IEEE Symposium Series on Computational Intelligence (SSCI); 2019: IEEE.
16. Pratap T, Kokil P. Computer-aided diagnosis of cataract using deep transfer learning. Biomedical Signal Processing and Control. 2019;53:101533.
17. Imran A, Li J, Pei Y, Mokbal FM, Yang J-J, Wang Q, editors. Enhanced intelligence using collective data augmentation for CNN based cataract detection. Frontier Computing: Theory, Technologies and Applications (FC 2019) 8; 2020: Springer.
18. Imran A, Li J, Pei Y, Yang J-J, Wang Q. Comparative analysis of vessel segmentation techniques in retinal images. IEEE Access. 2019;7:114862-87.
19. Corbilla C. Reconeixement intel·ligent de malalties oculars mitjançant arquitectures d'aprenentatge profund. Universitat Oberta de Catalunya 2019;http://hdl.handle.net/10609/113126
20. Guo L, Wang T, Wu Z, Wang J, Wang M, Cui Z, et al. Portable food-freshness prediction platform based on colorimetric barcode combinatorics and deep convolutional neural networks. Advanced Materials. 2020;32(45):2004805.
21. Bhati A, Gour N, Khanna P, Ojha A. Discriminative kernel convolution network for multi-label ophthalmic disease detection on imbalanced fundus image dataset. Computers in Biology and Medicine. 2023:106519.
22. Jr2ngb. Cataract and normal eye image dataset for cataract detection, Version 2. https://wwwkagglecom/datasets/jr2ngb/cataractdataset. 2019.
23. Bhagya Raj G, Dash KK. Comprehensive study on applications of artificial neural network in food process modeling. Critical reviews in food science and nutrition. 2022;62(10):2756-83.
24. Dubey S, Singh S, Chaudhuri B. A comprehensive survey and performance analysis of activation functions in deep learning. arXiv 2021. arXiv preprint arXiv:210914545.

Footnotes and Financial Disclosures

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