Research Article
Identification of Diabetic Retinopathy through Machine Learning

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1. Introduction
Diabetes mellitus (DM) comprises a group of metabolic disorders that share the phenotype of hyperglycemia, caused by an absolute or relative deficit in insulin production or action. Chronic hyperglycemia is associated with damage, dysfunction, or failure of organs and tissues, including retina, kidney, nervous system, heart, and blood vessels [1]. Diabetic retinopathy is present in both type 1 and type 2 diabetes, especially in patients with long-term disease and poor glycemic control [2]. The pathogenesis is multifactorial, being related to the metabolic effects of chronic hyperglycemia. Among the main factors involved in the genesis of diabetic retinopathy are the biochemical (earlier), hemodynamic, and endocrine factors, which interact with each other, leading to nonenzymatic protein glycation, oxidative stress, accumulation of polyols, and activation of protein kinase C [3]. The need for the early detection of DR has encouraged the search for more effective alternative screening methods. Automatic retinal image analysis models are options that aim at reducing physicians’ workload and providing a practical and cost-effective method [4]. The automatic image analysis software, in general, uses artificial intelligence based on machine learning (machine learning), and some more advanced ones, on deep learning (deep learning), a recent advance in artificial neural networks, which allows to improve the classification of images gross [5].

Given the current scenario of research on alternative screening methods for diabetic retinopathy, we proposed to carry out this study, considering that the automatic models of image analysis, optimum-path forest (OPF) and restricted Boltzmann machines (RBM), can be used together, combining the practicality and low operational cost of OPF with the reduction of the computational load that the RBM allows, in situations that require many input variables for image recognition, as in diabetic retinopathy. Studies using OPF and RBM to identify diabetic retinopathy are rare, and the personal and social burden of blindness caused by diabetic retinopathy encourages the search for new forms of
screening that have similar accuracy to the gold standard, which is the analysis of photograph by the specialist.

2. Material and Methods

2.1. Type of Study. This study is a transverse study.

2.2. Study Location. The study was conducted at the Department of Ophthalmology, Otorhinolaryngology and Head and Neck Surgery, University of Baghdad, Baghdad, Iraq.

2.3. Ethical Analysis. The research project was approved by the Research Ethics Committee of the Faculty of Medicine of University of Baghdad, Baghdad, Iraq.

2.4. Study Population. Participants who signed an informed consent form were evaluated for inclusion and exclusion criteria.

2.5. Inclusion Criteria. Individuals over 18 years of age with a diagnosis of type I or II diabetes mellitus and suspected diabetic retinopathy, regardless of gender and race, were included. We considered as suspicion of retinopathy diabetic patients with prolonged evolution time (>5 years for type I diabetes and >10 years for type II) and/or complaints related to low vision.

2.6. Exclusion Criteria. The following were excluded from the study:

   (i) Diabetic individuals with media opacities that prevented the fundus from being performed
   (ii) Diabetic individuals with causes of low vision other than diabetic retinopathy
   (iii) Diabetic individuals undergoing previous treatments for diabetic retinopathy (laser, anti-angiogenic injections, vitrectomy)

2.7. Ophthalmological Evaluation. All patients underwent an eye examination with the following:

   (i) Measurement of visual acuity
   (ii) Applanation tonometry
   (iii) Biomicroscopy with retinal assessment
   (iv) Indirect binocular ophthalmoscopy
   (v) Color photograph
   (vi) Retinography analysis was performed by a masked retina specialist for ophthalmological evaluation data; when any sign of diabetic retinopathy was detected, the classification used was that of the WHO guidelines

   Based on this classification, the specialist separated the photos into four classes:

   (i) Absence of diabetic retinopathy
   (ii) Mild diabetic retinopathy
   (iii) Moderate/severe diabetic retinopathy
   (iv) Proliferative diabetic retinopathy

2.8. Techniques Used in Ophthalmological Evaluation

2.8.1. Visual Acuity. Verification of visual acuity was performed with better optical correction when used by the patient, using an optotype table from the Early Treatment Diabetic Retinopathy Study (ETDRS) [5]. To analyze the level of visual impairment (low vision and blindness) of the patients, the WHO parameters were used [6].

2.8.2. Biomicroscopy. Biomicroscopic examination was performed using slit lamps from the FMB retinal outpatient clinic, evaluating the conjunctiva, cornea, anterior chamber, iris, pupil, lens, vitreous, and retina, with the aid of a 78-diopter lens (Volk Optical Inc., Mentor, USA).

2.8.3. Applanation Tonometry. The measurement of intraocular pressure was performed with the patient in the sitting position, after topical anaesthesia with 1 drop of eye drops prepared with 5 mg of 0.5% proxymetacaine hydrochloride (Merck, Germany) and 15 drops of sodium fluorescein eye drops (Sigma-Aldrich), using a Goldmann-type applanation tonometer, model R-900 (Haag-Streit AG., Bern, Switzerland), coupled to a lamp crack.

2.8.4. Pupillary Dilation. For the biomicroscopy of the lens, vitreous, and retina, as well as for fundus examination, the individuals underwent pupillary dilation with threeinstillations, spaced five minutes apart, of a drop of 1% tropicamide eye drops (Mydriacyl® 1%, Sigma-Aldrich).

2.8.5. Fundoscopy. Fundus examination was performed with an indirect binocular ophthalmoscope, model H-OI (Neitz Instruments Co. Ltd., Tokyo, Japan), and a 20-diopter lens (Nikon Corporation, Tokyo, Japan), with the patient in the supine position and the pupil dilated.

2.8.6. Retinography. Retinography was performed using a Visucam retinograph (Carl Zeiss Meditec, Inc., Dublin, USA), with the recording of the retina and optic disc.

2.9. Evaluation of Images by Machine Learning: The Evaluation of the Images Was Carried Out at the Department of Computing, Faculty of Sciences

2.9.1. Optimum-Path Forest (OPF)

   (i) Training: before the OPF was applied to the patients included in the study, a training set of the system was assembled, using photographic images of other diabetic patients with and without diabetic retinopathy, taken by the same Visucam retinal imager,
2.9.2. **Restricted Boltzmann Machine (RBM) and Deep Belief Networks (DBNs).** The extraction of features used in the OPF was done by RBM/DBN [6, 7].

### 1 Experimental Setup.

Before performing the classification, the dataset was preprocessed as follows: all images were resized to 200 × 200 pixels, and the RGB images (red, green, blue) were converted to gray scale with pixel intensities in the interval [0; 1].

Table 1 describes six different models employed to solve the classification problem. Such models vary in the number of hidden layers and hidden neurons. Also, it is important to note that the “Norm.” (normalized) setting employs a naive (native) RBM architecture as it employs a different preprocessing approach, which was only effective for a hidden layer (single RBM).

Considering a sample image $x_i \in X$, where $X$ represents the entire dataset, the aforementioned preprocessing for the “Norm.” was a simple “statistical trick” to improve the quality of the gray scale of $x_i$, which corresponds to the following formula:

$$\bar{x}_i = \frac{(x_i - \bar{x}_X)}{\sigma(x_i)} \quad (1)$$

where $\bar{x}_i$ represents the normalized image, $\bar{x}_X$ represents the average pixel values of the image $x$, and $\sigma(x_i)$ represents the standard deviations of $x_i$ pixels. Then, the entire dataset was normalized using a Gaussian distribution with a mean of zero and a unity standard deviation. This fact allowed us to make use of the well-known Gaussian–Bernoulli RBM, a variant of the RBM that samples the visible values of a Gaussian distribution, given the latent binary space. It is important to explain that only one model was chosen to use visible Gaussian units, since preliminary experiments with more than one hidden layer did not show good convergence. After the end of the RBM learning process, the datasets composed of resources extracted from the hidden layer units fed the supervised learning algorithm (OPF). Four models were considered to extract features and classify the images:

#### Table 1: Different configurations.

<table>
<thead>
<tr>
<th>Model</th>
<th>DBN templates</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>i:1000:1000:4</td>
</tr>
<tr>
<td>M2</td>
<td>i:1000:500:4</td>
</tr>
<tr>
<td>M3</td>
<td>i:1000:500:4</td>
</tr>
<tr>
<td>M4</td>
<td>i:1000:500:4</td>
</tr>
<tr>
<td>M5</td>
<td>i:1000:1000:4</td>
</tr>
<tr>
<td>M6</td>
<td>i:1000:1000:4</td>
</tr>
<tr>
<td>Standard</td>
<td>i:1000:4</td>
</tr>
</tbody>
</table>

DBN: deep belief network and $i$: number of neurons in the input layer.

#### 2.10. Statistical Analysis.

To analyze the results, the Wilcoxon test was used to compare whether the position measures of two samples are equal in the case where the samples are dependent. Sensitivity and specificity values were calculated for the algorithms used to evaluate the images. The hypothesis that the probability of error was less than 5% ($p < 0.05$) was assumed as true.

### 3. Results

#### 3.1. General Characterization of the Sample.

A total of 73 patients (122 eyes) were evaluated, 50.7% men and 49.3% women. Age ranged from 36 to 79 years, with an average of 59.7 years. Most patients classified themselves as “white” (86%). Seventy patients had type 2 DM, and only three had type 1. The insulin treatment regimen occurred in 53.4% of the patients. Among the diseases associated with DM, the main one was systemic arterial hypertension (70%). The association with smoking and alcoholism was small, corresponding to 12.3% and 4.3% of patients, respectively (Table 2). The main complaint of patients was poor vision, both near (93.1%) and far (91.8%), even among users of optical correction (63.1%). Table 3 shows the level of visual impairment in the 122 eyes studied. As for ocular history, the three most mentioned were cataract (10.9%), glaucoma (6.8%), and previous surgeries (9.6%).

#### 3.2. Ophthalmological Evaluation.

The specialist’s evaluation of 122 retinographies revealed the absence of diabetic retinopathy (DR) in 17 eyes (Figure 1) and the presence of DR in 105 eyes (86%), classified as follows:

- (i) Mild diabetic retinopathy: 19 (18.1%)
- (ii) Moderate/severe diabetic retinopathy: 77 (73.3%)
- (iii) Proliferative diabetic retinopathy: 9 (8.6%)
3.3. Image Evaluation. The set of images evaluated contained 259 photographic images (137 from the training set, used for learning the system, and 122 new ones, from 73 patients included in the study, used in the tests).

Fifteen sets of experiments were performed with a repetition of 30 cycles in each set, varying the ratio of training/test sets at random, in each repetition of each set (80% for training and 20% for tests). Thus, all samples participated in the tests (in each execution different groups of 20% were used for training, totaling 100% of the samples). After the execution of the 15 series, the results presented in Table 4 were obtained.

Tables 5 and 6 show the average performance of the 15 series of experiments with RBM-500 and RBM-1000, considering four classes (no DR, mild DR, moderate/severe DR, and proliferative DR). Table 7 shows the average performance of the 15 experiment series with OPF-500 and OPF-1000.

Considering only the presence or absence of the disease (diabetic retinopathy), Tables 8 and 9 show the performance of RBM (500 and 1000) and OPF (500 and 1000).

Sensitivity measured the model’s ability to correctly identify individuals who had diabetic retinopathy, whereas specificity measured those who did not (Table 9). Sensitivity values for the RBM were high, especially for the RBM-500 (100%) versus 95.7% for the RBM-1000 (Table 8). The OPF-500 had higher sensitivity values (95.5%) than the OPF-1000 (86.4%). As for specificity, both RBM-1000 and OPF-1000 presented 100%; that is, they correctly identified all images that did not have DR. This capacity was lower in the RBM-500 (64.3%) and OPF-500 (87.5%) (Table 10).

4. Discussion

Early screening is one of the pillars of the prevention of blindness in diabetics, since retinopathy can be asymptomatic in the beginning and vision loss can only be noticed when the disease is advanced (51). The results of two large studies on diabetic retinopathy, the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS), showed that early and effective treatment can prevent severe vision loss and reduce the risk of blindness from the disease in about 50% (52–54).

Machine learning automatic disease detection models provide a quick and practical means of screening for diabetic patients still undiagnosed with retinopathy, especially those living in remote communities without access to specialized services (41).

This study used two image classifiers with different characteristics, the OPF (optimum-path forest) and the RBM (restricted Boltzmann machine). The metrics used to assess the classifiers in this research were accuracy, sensitivity, and specificity.

The results obtained showed that the RBM, which used 1000 characteristics extracted from the analyzed photographic images, had the best overall performance in terms of diagnostic accuracy (89.5%); that is, it was the model that had the greatest ability to correctly differentiate images with and without DR signals after 15 sets of experiments.
As for sensitivity, the four models analyzed (RBM-500 and RBM-1000 and OPF-500 and OPF-1000) presented performance above 80%, considered ideal for imaging screening tests (55). The RBM-500 achieved 100% accuracy when the RD was present, followed by the RBM-1000 (95.7%). The OPF-500 had a sensitivity of 95.5%, whereas the OPF-1000 had a sensitivity of 86.4%.

Regarding specificity, the RBM-1000 and OPF-1000 classifiers showed the best results (100% correctness when there was no disease). The OPF-500 had the lowest performance (87.5%), but still above 80%, whereas the RBM-500 had the worst performance of the four models, with 64.3%.

Results similar to those of the present study were found in a systematic review of 2019 [8], which evaluated deep learning detection models for DR image classification. The sensitivity values of eight studies evaluated ranged from 80 to 100% and specificity values from 84 to 90%, indicating the
potential of using automatic methods of artificial intelligence as screening tools [9].

Regarding the performance of the RBM and OPF algorithms in differentiating the severity of diabetic retinopathy, the results of the present study showed better performance of the classifiers in identifying signs of proliferative retinopathy (100% correctness in the four models) and worse performance in detecting initial or mild, with no obvious signs of the disease. These results do not compromise the use of algorithms in DR screening, since the focus of current international screening programs is the early identification of the so-called “referential diabetic retinopathy,” which presents signs of advanced disease and indication for immediate treatment [10].

Following this line of conduct, Nagasawa et al. [11] used a deep learning model to identify only the untreated proliferative form, due to the importance of indicating immediate treatment, and obtained a sensitivity of 94.7% and a specificity of 97.2% [12]. Other studies using artificial intelligence medical devices have shown good results, especially in the moderate and severe forms of DR and with the identification of specific signs of these forms, such as the presence of exudates [13].

The present study had some limitations. The number of retinographs analyzed was lower than planned due to technical problems with the retinograph, which led to the loss of a portion of the images already stored. There was also variation in the number of images evaluated in each class, but the imbalance was artificially compensated by the generation of synthetic images by the algorithms. Furthermore, it was not possible to use an external image bank to train the classifier system within the research schedule, which would help in the external validation process of the analyzed algorithms. According to Gulshan et al., access to a large database of high-quality international images facilitates the validation of deep learning models, as they contain data from populations with different ethnic characteristics [11].

A relevant issue in Iraq, due to the high miscegenation of the population, is the wide variation in retinal color, a detail that becomes positive as it provides more information to the algorithms and facilitates the differentiation between the natural components of the fundus and the signs of DR [10, 12]. In the present study, 96% of the participants declared themselves “white,” which would minimize the effect of potential chromatic variations in the retinal imaging.

### Table 7: Average performance of the 15 series of experiments with OPF-500 and OPF-1000, considering four classes (no DR, light DR, mod/severe, and proliferative).

<table>
<thead>
<tr>
<th>OPF-500</th>
<th>Without DR</th>
<th>With DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialist Machine learning</td>
<td>Absence</td>
<td>Light</td>
</tr>
<tr>
<td>Without DR</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>With DR</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>OPF-1000</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>With DR</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

RD: diabetic retinopathy, mod: moderate, and OPF: optimum-path forest.

### Table 8: Average performance of the 15 series of experiments with RBM-500 and RBM-1000 (considering disease versus nondisease).

<table>
<thead>
<tr>
<th>RBM-500</th>
<th>Without DR</th>
<th>With DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialist Machine learning</td>
<td>Absence</td>
<td>Light</td>
</tr>
<tr>
<td>Without DR</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>With DR</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>RBM-1000</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>With DR</td>
<td>1</td>
<td>22</td>
</tr>
</tbody>
</table>

RBM: restricted Boltzmann machine.

### Table 9: Average performance of the 15 series of experiments with OPF-500 and OPF-1000 (considering disease versus nondisease).

<table>
<thead>
<tr>
<th>OPF-500</th>
<th>Without DR</th>
<th>With DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialist Machine learning</td>
<td>Absence</td>
<td>Light</td>
</tr>
<tr>
<td>Without DR</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>With DR</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>OPF-1000</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>With DR</td>
<td>3</td>
<td>18</td>
</tr>
</tbody>
</table>

### Table 10: Sensitivity and specificity values of the RBM (500 and 1000) and OPF (500 and 1000) in identifying disease versus nondisease and their respective 95% confidence intervals.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>95% CI</th>
<th>Specificity (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBM-500</td>
<td>100</td>
<td>82.8%–100%</td>
<td>64.30</td>
<td>35.6%–86.0%</td>
</tr>
<tr>
<td>RBM-1000</td>
<td>95.70</td>
<td>76%–99.8%</td>
<td>100</td>
<td>76.2%–100%</td>
</tr>
<tr>
<td>OPF-500</td>
<td>95.50</td>
<td>75.1%–97.8%</td>
<td>87.50</td>
<td>46.7%–99.3%</td>
</tr>
<tr>
<td>OPF-1000</td>
<td>86.40</td>
<td>64%–96.4%</td>
<td>100</td>
<td>59.8%–100%</td>
</tr>
</tbody>
</table>

The sensitivity of RBM-500 is 100%, and the sensitivity of OPF-500 is 95.50%, which are indicated in bold.
of this factor. However, self-declaration does not exclude the possibility of miscegenation. Most validated deep learning systems used public external image banks that mostly make available images of a single ethnicity [11]. To verify the influence of the background color factor, Li et al. studied four ethnic groups with diabetic retinopathy (Chinese, Malay, Caucasian Australian, and Indigenous Australian) with different degrees of physiological retinal pigmentation and concluded that this factor did not affect the performance of the tested deep learning algorithm. According to the authors, this result could be extrapolated to most populations in the world [5]. Although the results obtained in this study are promising, there are still challenges to be overcome before the use of automatic disease detection models through machine learning becomes a reality in clinical practice. One of them is the capture of good quality retinal images, which enable the correct classification of DR by algorithms. Difficulties are manifold: inadequate pupillary dilation, opacity of the eye’s transparent media, problems with contrast and focus, poor technique, or inexperience of the retina camera operator. Imaging rates with low quality and without classification conditions reach 25% in some studies [4, 14]. However, scientific evidence has shown that artificial intelligence itself may solve this problem in the near future. A study achieved good results by adapting a deep neural network to correct the quality of retinal images through reprocessing [6]. The authors suggest that the proposed system has the potential to be implemented in the healthcare network. Another important issue that must be considered is how AI models can fit into the healthcare network. For their use to be effective in preventing blindness by DR, a restructuring involving implementation costs, management logistics, health policies, and acceptance by health professionals and patients would be necessary.

The algorithms would be incorporated into the computer system of the primary care point of patients with suspected DR, which would be equipped with a traditional retinograph or a portable retinal image capture device. Another option would be the development of mobile applications with the algorithms, which could be made available to health professionals far from specialized retina centers. With the system in place, automated screening would be easy and fast and the results known at the time of screening. A pilot study carried out in Australia compared the use of an automated screening model, where a deep learning algorithm provided real-time reporting of results, with a manual model in which retinal images were transferred to a specialized classification center and the results transferred to the patient only two weeks after the evaluation. Findings showed that 96% of participants said they were satisfied or very satisfied with the automated screening model and about 80% reported preferring the automated screening model over the manual model, suggesting a good level of acceptance of this system [2–4].

Machine learning identification of diabetic retinopathy represents an important technology, offering great potential to improve the efficiency and accessibility of DR screening programs, particularly in developing countries where the number and location of specialist physicians are poor and patient identification needing faster care to avoid a major and debilitating visual loss is imperative.

The novelty of the present study was the comparison of two different image analysis models (OPF and RBM) for the automatic detection of DR, through accuracy, sensitivity, and specificity, and the demonstration that the RBM performed better than the OPF, especially in sensitivity, which is important for clinical diagnosis. The present study also demonstrated that the combination of algorithms can be a strategy to improve the performance of DR screening by artificial intelligence.

For future research, it is proposed to use a larger database and the generation of synthetic images to improve the training process, using deep neural networks such as GANs (generative adversarial nets), already used in some studies with retinal vessels [5, 8], which are capable of generating as many synthetic images as the user requires, with good quality. The development of a mobile app is also being planned as the next step in this line of research.

5. Conclusions

Given the results obtained and under the experimental conditions of this study, we can conclude that

(a) The RBM-1000 performed best in terms of diagnostic accuracy (89.47 ± 2.64) in the overall analysis
(b) The RBM-500 was superior in the automatic detection of signs of diabetic retinopathy on photographic images (100% sensitivity)
(c) As for specificity, both RBM-1000 and OPF-1000 presented 100%; that is, they correctly identified all images without diabetic retinopathy
(d) Machine learning automatic disease detection models, especially the RBM, showed good diagnostic accuracy and high sensitivity and have potential for use in screening for diabetic retinopathy

Data Availability

The data used to support the findings of this study are included within the article.

Disclosure

This study was performed as a part of the Employment of Institutions.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this article.

Acknowledgments

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References


