

Enhanced AI-Powered Diabetic Retinopathy Screening for Vision Protection Utilizing Machine Learning Models

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Abstract- Diabetic retinopathy is a prevalent ocular condition characterized by the deterioration of retinal blood vessels, leading to visual impairment. The increasing prevalence of this condition can be attributed to its strong association with diabetes. Diabetic retinopathy, a medical condition, possesses the capacity to lead to total vision loss, thereby emphasizing the utmost significance of timely detection for the purpose of minimizing the likelihood of visual impairment and its related complications. Currently, the assessment and diagnosis of ocular conditions heavily rely on the visual inspection of fundus images. The implementation of this methodology requires the utilisation of expensive ophthalmic imaging technology and involves a meticulous analytical procedure. The objective of this project is to facilitate a substantial overhaul of the screening procedure for diabetic retinopathy. The objective of this study is to develop a machine learning model that exhibits intuitive characteristics and demonstrates consistent accuracy in predicting the presence of diabetic retinopathy. This prediction will be based on the analysis of pre-recorded digital fundus images. The methodology employed in this study involves the retrieval of annotated fundus photographs from publicly available repositories. Two powerful machine learning techniques, namely support vector machine (SVM) and deep neural network (DNN), are utilised in the analysis. The support vector machine (SVM) model exhibited a noteworthy average area under the receiver operating characteristic curve (AUC) of 97.11% during the evaluation process conducted on the test dataset. In contrast, the deep neural network (DNN) model demonstrated significantly higher performance, as evidenced by an average area under the curve (AUC) of 99.15%. The results of this study demonstrate a promising methodology for the screening of diabetic retinopathy that exhibits notable attributes of efficiency, accuracy, and cost-effectiveness.

Index Terms—GLCM, Diabetic Retinopathy, Support Vector Machine and Deep Neural Network.

I. INTRODUCTION

Diabetes, a chronic condition that can be effectively controlled, is distinguished by either insufficient insulin synthesis by the pancreas or the body's diminished capacity to effectively utilize the insulin it generates. The hormone insulin plays a crucial role in the regulation of blood glucose levels, as prolonged elevation of blood glucose can lead to the gradual deterioration of essential physiological processes. Diabetes is recognized for its association with a diverse array of enduring and consequential outcomes. These include the development of diabetic nephropathy, a condition that detrimentally impacts renal function, as well as strokes, heart attacks, neuropathy leading to nerve impairment, diabetic foot ulcers, and diabetic retinopathy (DR) [1]. Diabetic retinopathy (DR) predominantly affects the retina, a photosensitive layer situated in the posterior segment of the ocular globe. The condition described above is caused by vascular dysfunction in the retinal area, resulting in initial symptoms of mild visual impairments. If left untreated, these impairments may eventually lead to total blindness. The

preliminary stage of diabetic retinopathy (DR) is commonly known as non-proliferative diabetic retinopathy (NPDR). Non-proliferative diabetic retinopathy (NPDR) is characterized by the presence of microaneurysms, which are minute outpouchings in the retinal blood vessels that facilitate the extravasation of blood into the retinal tissue [2–4]. According to data provided by the International Diabetes Federation (IDF), diabetic retinopathy (DR) has been identified as the leading cause of visual impairment among individuals aged 20 to 65. This particular medical condition impacts approximately 33% of individuals diagnosed with diabetes, with approximately 10% of these cases progressing to a more severe form of the disease that poses a significant risk to visual health. The International Diabetes Federation (IDF) has observed a notable rise of 16% in reported instances of diabetes on a global scale, resulting in a supplementary 74 million individuals being impacted by the condition. As a result, it is noteworthy to mention that the cumulative prevalence of diabetes has escalated to an astonishing figure of 537 million, as reported by reputable

sources [5,6]. The escalating prevalence of diabetes underscores the growing importance of diabetic retinopathy (DR), positioning it as a prospective primary contributor to visual impairment or blindness in the forthcoming years. Routine ocular examinations play a critical role in the effective management of diabetes, as they enable the timely identification of diabetic retinopathy, thereby facilitating prompt intervention to mitigate the risk of vision impairment.

Machine learning (ML) and artificial intelligence (AI) have demonstrated their efficacy in addressing complex problems in diverse fields, underscoring their increasing importance in the field of medicine [7–9]. The healthcare sector holds significant promise for the application of machine learning (ML) and artificial intelligence (AI) due to their potential to facilitate the development of personalized treatment strategies tailored to the distinct requirements of individual patients. In the context of our study, we employed machine learning algorithms to perform estimations of diabetic retinopathy (DR) through the analysis of retinal images. The process of identifying essential characteristics in fundus images was successfully achieved through the application of grey-level co-occurrence matrix (GLCM) analysis. Subsequently, we undertook the development of two machine learning classifier models, specifically the Support Vector Machine (SVM) and Deep Neural Network (DNN). The models in question employ features obtained through the analysis of fundus images using the Gray-Level Co-occurrence Matrix (GLCM) method. A thorough investigation was conducted to identify the optimal classifier for accurately distinguishing between retinal scans displaying normal health and those indicating the presence of Diabetic Retinopathy (DR).

The subsequent sections of this paper provide additional insights and perspectives pertaining to our research endeavor. Section 2 of this research paper offers a thorough exploration of the contextual framework surrounding the topic under investigation. Additionally, it presents a critical analysis of current scholarly publications that are relevant to the subject matter. Section 3 of this study offers a thorough analysis of the materials and methodologies utilised throughout the research process. The experimental findings are reported in Section 4, which is subsequently succeeded by the concluding remarks in Section 5.

The ocular apparatus is an intricately structured and fragile organ that serves as a fundamental component of the human visual system. The spherical and irregular design of the object facilitates the reception and conversion of reflected light rays from the surrounding environment into coherent visual representations, as stated in reference [10]. Figure 1 illustrates the anatomical composition of the eye, incorporating essential components [11]. The cornea, a transparent and curved structure positioned at the front of the eye, functions as a safeguarding layer for the iris, the pigmented component of the eye responsible for regulating the entry of light. Situated in close proximity to the iris, the lens, which is transparent in nature, plays a crucial role in the process of converging incoming light

onto the retina. The previously mentioned essential layer is accountable for the transformation of light into electrical signals, which are subsequently transmitted through the optic nerve situated in the posterior region of the eye, to the brain for subsequent analysis and processing.

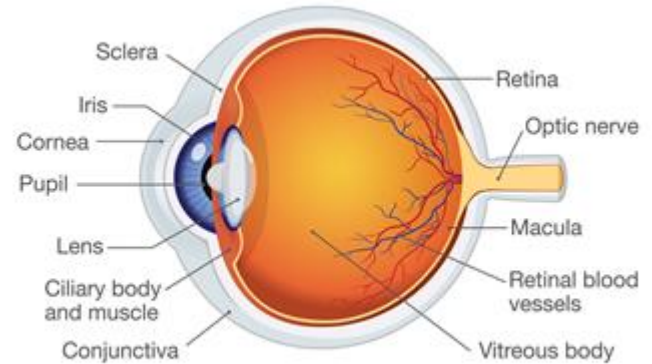


Figure 1: Eye's Anatomy

Individuals diagnosed with diabetes experience a variety of consequences, one of which is the development of Diabetic Retinopathy (DR). This condition is particularly concerning for individuals who struggle with effectively managing their elevated blood glucose levels [13]. Diabetic retinopathy (DR) is a pathological manifestation commonly observed in individuals with diabetes, characterised by the detrimental impact on the blood vessels located in the posterior segment of the eye. If left undetected and untreated, Diabetic Retinopathy (DR) has the potential to result in visual impairment and eventual blindness, as indicated by various studies [3-5]. This condition presents itself through two primary manifestations, specifically proliferative retinopathy and macular edema. Proliferative retinopathy is a pathological condition that occurs as a direct consequence of vascular disease. This vascular disease disrupts the normal integrity of the ocular blood vessels, leading to the infiltration of blood into the central region of the eye. Consequently, individuals affected by proliferative retinopathy experience visual impairment, which is characterised by the presence of blurred vision. In contrast, macular edema is indicative of an advanced stage characterised by the infiltration of fluid into the central region of the macula, which can result in the manifestation of partial or complete vision impairment [3–5]. The comprehensive evaluation of these disorders requires meticulous ocular examinations, including a comprehensive assessment of visual acuity to measure visual clarity at various distances, along with a thorough examination of the dilated eye. The subsequent technique entails the dilation of the pupils to facilitate the examination of the retina and optic nerve, and is executed by an ophthalmologist utilising a magnifying lens. Specialised instruments are employed to conduct tonometry examinations for the purpose of quantifying intraocular pressure [14]. An identifiable characteristic of diabetic retinopathy (DR) is the presence of hard exudates, which are discrete deposits with well-defined boundaries located within the outer retinal

layers [13]. The presence of exudates in retinal scans is readily discernible, thereby facilitating precise diagnoses by medical practitioners. Currently, there exist a number of retinal imaging systems that are capable of producing digital retinal images of exceptionally high quality [13].

II. LITERATURE REVIEW

A number of recent research studies have been conducted to explore the detection and diagnosis of diabetic retinopathy (DR) through the utilisation of fundus images and machine learning methodologies [15–19]. Throughout the duration of these experiments, researchers made distinct choices regarding the utilisation of binary fundus image datasets or multiclass datasets. The core elements of disaster recovery (DR) prediction algorithms consist of preprocessing, feature extraction, and classification methodologies. Several preprocessing techniques have been utilised to enhance the quality of input photographs. These techniques include Convolutional Neural Network (CNN), Grey Level Co-occurrence Matrix (GLCM), and Local Binary Patterns (LBP). CNN (Convolutional Neural Network) and GLCM (Gray-Level Co-occurrence Matrix) have gained significant traction as prominent feature extraction methodologies within the research community. The research studies predominantly employed Convolutional Neural Networks (CNNs) as the chosen method for feature extraction. The convolutional neural networks (CNNs) utilised in this study were trained using binary datasets that involved the categorization of retinal images into two distinct classes: those depicting a healthy state and those indicative of symptoms associated with Diabetic Retinopathy (DR).

In their study, Ahmad Z. et al. (2018) proposed the development of a discriminative regression (DR) classifier. The classifier utilised the gray-level co-occurrence matrix (GLCM) as a method for feature extraction. The binary classifier employed a Support Vector Machine (SVM) with various kernel functions, such as quadratic, linear, Gaussian, and polynomial. The polynomial kernel function exhibited the highest level of accuracy, achieving a rate of 90.91% as documented in reference [15].

Xu et al. (2019) conducted a research study wherein they utilised a Convolutional Neural Network (CNN) model to automatically classify a dataset consisting of 1000 retinal photographs obtained from the Kaggle dataset. The objective of the study was to categorise the retinal images into two distinct groups: healthy images and images portraying Diabetic Retinopathy (DR). After the initial step of resizing the photos to dimensions of $224 \times 224 \times 3$, further image enhancement techniques were applied. The study employed a convolutional neural network (CNN) architecture consisting of eight convolutional layers, four max-pooling layers, and two fully connected layers. The study culminated in the utilisation of a SoftMax function within the network architecture for the purpose of classification. This approach yielded a commendable accuracy rate of 94.5% [16].

The study conducted by Dhiravidachelvi et al. (2019) introduced a novel methodology aimed at the detection and classification of microaneurysms observed in fundus scans of patients diagnosed with diabetic retinopathy. The researchers utilised a methodology that involved an initial preprocessing step for the data. This preprocessing step consisted of applying a median filter and contrast-constrained adaptive histogram equalisation (CLAHE) technique. Following that, feature extraction was conducted utilising the gray-level co-occurrence matrix (GLCM) methodology. The classification task was ultimately performed by employing a k-nearest neighbour (KNN) binary classifier. The model demonstrated a maximum accuracy of 93%, along with a maximum sensitivity of 95.7% and a maximum specificity of 90.56% [17].

Elveny et al. (2020) conducted a study wherein they proposed an innovative methodology that involved the application of a probabilistic neural network (PNN) machine learning classifier. The primary objective of this approach was to accurately detect and classify cases of diabetic retinopathy by analysing fundus images. The researchers implemented a methodology that involved a sequence of preprocessing procedures, which included scaling, isolating the green channel, and contrast stretching. Following the initial phase, the process of feature extraction was carried out utilising the GLCM (Gray-Level Co-occurrence Matrix) technique. Based on the findings of the study, it was determined that the model exhibited a detection accuracy rate of 86.8% in correctly identifying instances of diabetic retinopathy [18].

The research conducted by Ramzi A. et al. (2021) introduced a novel machine learning technique with the objective of identifying and categorising cases of diabetic retinopathy (DR). The researchers utilised the local binary patterns (LBP) technique to extract features from the data. They then assessed the efficacy of various state-of-the-art pre-trained deep learning models for the purpose of classification. The ResNet model exhibited remarkable performance, achieving an accuracy rate of 96.35% as reported in the referenced source [19].

While the aforementioned research has made significant contributions, it is imperative to acknowledge the existence of certain limitations. A considerable proportion of individuals tend to disproportionately prioritise accuracy as the sole metric, thereby neglecting the essential evaluation of sensitivity and specificity when assessing the effectiveness of models. Moreover, the complex structural design and computationally intensive nature of models like ResNet require significant computational resources. Furthermore, it is noteworthy to mention that a significant aspect overlooked in these studies is the absence of cross-validation for their models.

The primary objective of our research is to design and develop machine learning models that possess a lightweight architecture, with the intention of enhancing the classification of diabetic retinopathy (DR). This, in turn, will lead to improved levels of accuracy, sensitivity, and specificity in the classification process. To achieve the stated objective, we have employed a fundus image segmentation technique that exhibits a reduced level of

complexity while retaining a high degree of effectiveness. Furthermore, we have extended the feature extraction procedure to incorporate ten significant Gray-Level Co-occurrence Matrix (GLCM) attributes. In addition, an assessment was conducted to compare the performance of Support Vector Machines (SVM) and Deep Neural Networks (DNN) in order to determine the most suitable model for the classification of Diabetic Retinopathy (DR).

III. METHODOLOGY

The primary objective of our research is to develop an advanced screening system for diabetic retinopathy (DR) that incorporates machine learning models, leveraging the capabilities of artificial intelligence (AI). The current methodology has been specifically designed to enhance the accuracy, effectiveness, and cost-effectiveness of diabetic retinopathy detection. The core methodologies employed within our system can be concisely delineated as follows:

A. Dataset

To procure a comprehensive dataset for the proposed classifier aimed at detecting diabetic retinopathy (DR), we acquired pre-existing fundus images of both normal and retinopathic cases from esteemed public data repositories. The findings from Kaggle [20] indicate that... Table 1 provides a comprehensive summary of the key characteristics of the photographs incorporated in our research investigation. The dataset consists of a comprehensive compilation of 560 photographs, meticulously categorized into two distinct classes: normal and DR. Each category is comprised of a total of 280 photographs. Figure 2 depicts a visual representation of two exemplary image samples, each belonging to one of the two distinct classes under consideration.

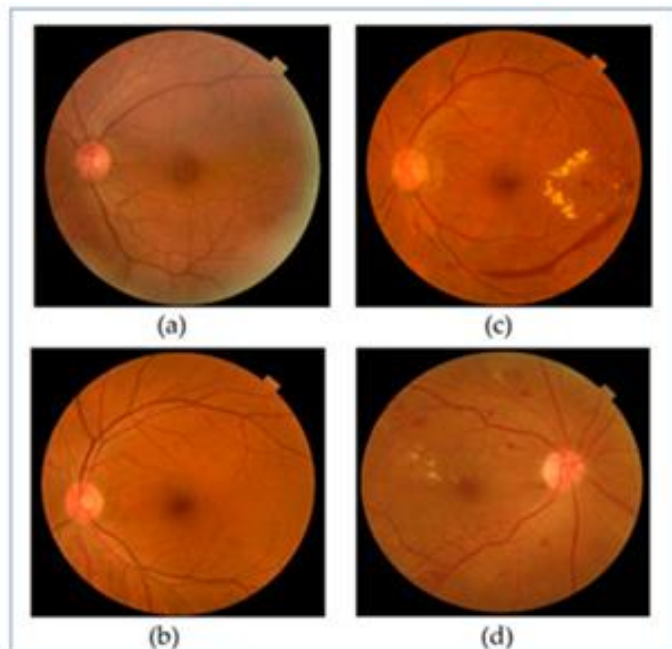


Figure 2: Samples of Normal & DR Images

Table 1: Dataset Description

Image Dataset	No of Images	Total Images
Kaggle	327 Normal Images 288 DR Images	615 Images

B. Pre-processing

An in-depth analysis of the proposed dimensionality reduction (DR) classifier uncovers a set of systematic methodologies, each fulfilling a distinct objective in the development of a sophisticated and accurate categorization framework. The research methodology commences with the initial preprocessing stage, followed by the subsequent segmentation phase, and culminates in the extraction of Gray-Level Co-occurrence Matrix (GLCM) features. The data is then partitioned, and predictions are generated using a two-class machine learning classifier.

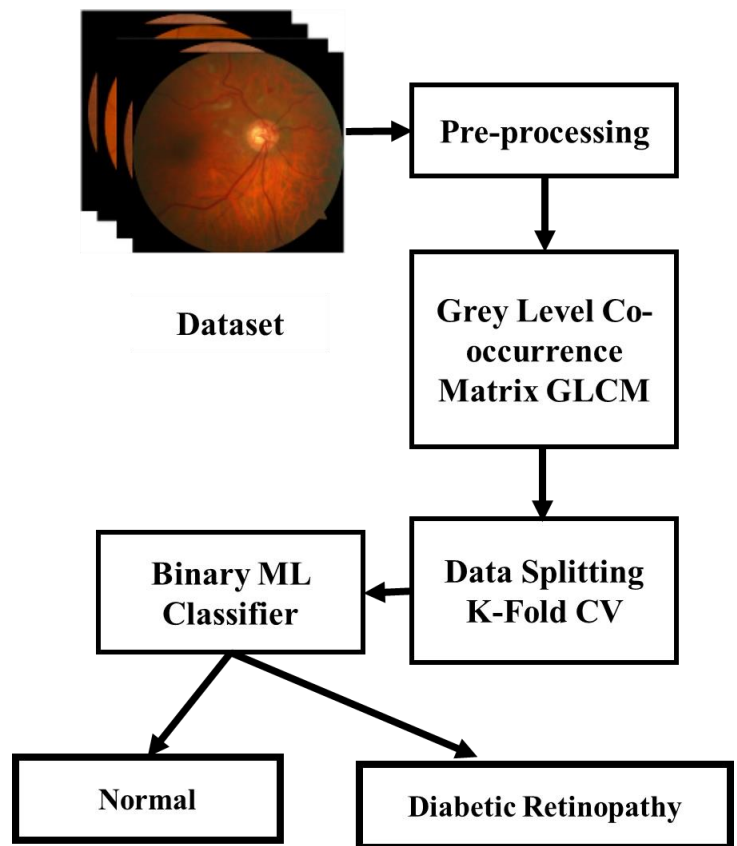


Figure 3: Methodology Block Diagram

The initial stage of the research process encompasses the conversion of the unprocessed fundus photographs into a uniform and standardised format. The process involves the adjustment of each image's dimensions to a standardised size of 512×512 pixels, thereby establishing uniformity across all images. The objective of this step is to appropriately preprocess the images in order to facilitate subsequent analysis utilising machine learning techniques. The expedition's progression is characterised by a shift in visual representations from a coloured

format to grayscale, which serves to preserve the fundamental elements while simultaneously enhancing computational efficiency. Histogram equalisation is a widely utilised technique in the field of image processing due to its significant impact on enhancing contrasts and improving edge definition. This technique effectively highlights the detailed outlines of blood vessels, exudates, and microaneurysms, when they are present in the image. The ongoing endeavour to establish a universally applicable threshold for image processing is currently underway. This involves converting a grayscale image into binary representations, where shadows below the predetermined threshold are represented as black, while those surpassing it are depicted as white. The aforementioned process gives rise to a compelling dynamic between the presence of illumination and the absence of clarity. The investigation into the technique of thresholding reaches its apex when combined with the utilisation of noise reduction, a method that effectively eliminates clusters of pixels containing 50 or fewer white pixels in a meticulous manner. This process significantly enhances the overall clarity of the finished composition.

The complement operation is a crucial step in the transformation process as it effectively reverses the colours, converting black to white and white to black. The present procedure successfully elucidates the intrinsic characteristics of blood vessels in contrast to a white backdrop. The pinnacle of artistic expression is achieved through the technique of overlaying a mirrored image onto a canvas that has been meticulously rendered in shades of grey. The moment of revelation showcases segmented digital retinal (DR) images, wherein the narratives pertaining to blood vessels, exudates, and microaneurysms are effectively communicated through a visually captivating arrangement. The aforementioned methodology extends beyond the domain of image processing, infusing the essence of diabetic retinopathy screening with vitality, thereby transforming it into a visually captivating symphony that enhances its core objective.

C. Extraction of Grey level Co-occurrence Matrix GLCM

Texture analysis is a highly engaging and intriguing area of study within the realm of digital images. Among the various methodologies that have been developed, the Grey-Level Co-occurrence Matrix (GLCM) stands out as a particularly noteworthy choice. The methodology described above facilitates the analysis of nuanced differences in grey levels among adjacent pixels, regardless of their orientation. The outcome of this process yields the creation of a square matrix that encompasses the frequency of occurrence of specific pairings of grey levels, denoted as $G(i, j)$, across the entirety of the image or a designated section of the image. The study employs a comprehensive approach by examining the horizontal, vertical, and diagonal orientations to facilitate an in-depth analysis of the fluctuations in intensity at the designated pixel of interest [26,27]. The GLCM algorithm is visually depicted in Figure 4. In this analysis, we will investigate a 9x9 image patch that encompasses a range of grey levels from 0 to 3, as illustrated in Figure 4a. The primary focus of our research inquiry revolves

around the reference pixel, which is strategically located at the central position. The reference pixel's Gray-Level Co-occurrence Matrix (GLCM) is depicted in Figure 4b, showcasing the standard directions. Through a comprehensive analysis of the Gray-Level Co-occurrence Matrix (GLCM), valuable insights can be obtained regarding the patterns of occurrence of pixel pairings. Figure 4c visually presents the frequent co-occurrence of pixel pairs $\{(3, 2), (2, 3), (3, 1), (2, 0), (0, 1), (1, 3), (2, 1), (1, 2)\}$. This observation is expected to elicit curiosity. In order to achieve simplicity, the process of scaling each individual element within the Gray-Level Co-occurrence Matrix (GLCM) involves dividing said element by the sum of all elements present within the GLCM. The outcome of this procedure yields a normalised Gray-Level Co-occurrence Matrix (GLCM), wherein the values of each element are confined within the numerical interval of 0 to 1. This procedure facilitates the extraction of salient textural attributes and the discernment of intricate patterns within digital images.

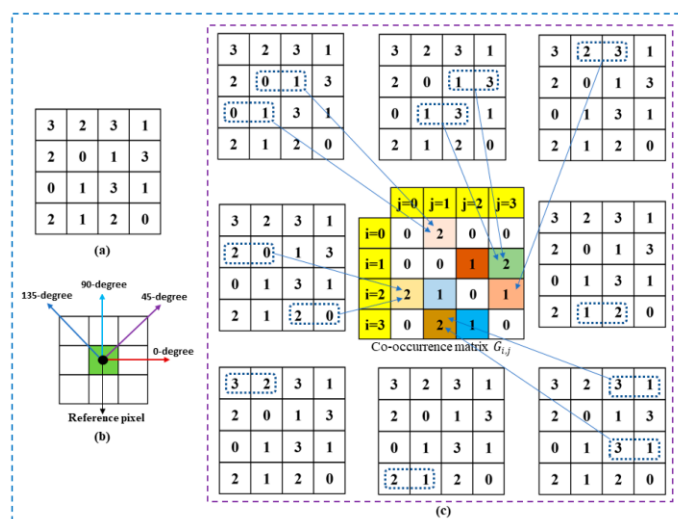


Figure 4: Utilizing a Patch Image to Determine GLCM Features

D. Data Separation Using K-Fold CV

In the context of machine learning model development, a pivotal phase entails the intentional partitioning of data into two distinct categories: the training set and the test set. The training set serves as the foundational framework through which a previously empty model acquires and improves its capabilities. In contrast, the test set serves the purpose of an evaluative entity, tasked with appraising the precision and efficacy of the model. The prevailing methodology employed for partitioning data, referred to as the 70:30 random data split technique, entails the random assignment of 70% of the data to the training cohort, while reserving the remaining 30% for the test subset. However, it is important to acknowledge that this particular methodology does have certain limitations, particularly when it is employed with datasets that are relatively small in size. These limitations can potentially lead to the occurrence of overfitting. To address the aforementioned limitations and improve the robustness of our model, we have opted to utilise a stratified k-fold cross-validation methodology.

The proposed methodology involves the division of the entire dataset into k segments, where k is an integer greater than one. During each iteration of the experiment, a total of k-1 segments are utilised for training purposes, while the remaining segment is exclusively allocated for comprehensive testing. This distribution of segments can be observed in Figure 5. By implementing the aforementioned methodology for a total of ten iterations, with a fixed value of k set to 10, and utilising ten distinct training and test datasets, we calculate the mean scores of the model. The utilisation of this particular methodology ensures a heightened degree of precision and consistency in the evaluation of the model's performance, thereby enhancing the reliability of the ratings and providing a robust assessment of the model's quality.

Training Cycle	Segment 1	Segment 2	Segment 9	Segment 10	Score
n=1	Test	Training					Score 1
n=2	Training	Test	Training				Score 2
.....
n=3	Test	Training	Score 9
n=10	Training					Test	Score 10
Mean Score							$\frac{1}{10} \sum_{n=1}^{10} Score_n$

Figure 5: Dataset Splitting

E. Machine Learning Classifier

1. Support Vector Machine

The core of our model is a binary machine learning classifier. This classifier makes the final prediction by using our test data's unique properties. To find the best machine learning classifier algorithms, we investigated many choices. We chose the SVM and the strong Deep Neural Network (DNN) as our final selections. We'll examine these two popular algorithms in the next sections. We'll now examine the Support Vector Machine (SVM), a key component of supervised machine learning. The method excels at data categorization and prediction, distinguishing between linearly divided data classes. Imagine a graphical representation of a set of data points scattered across a surface with numerous hyperplanes trying to cluster the linearly separable data. Figure 6a illustrates the representation. The Support Vector Machine (SVM) searches for an ideal hyperplane methodically. The hyperplane is used to maximise the margin between influential support vectors. These support vectors are a subset of data points near the hyperplane that represent both classes. Figure 6b (references 30, 31, and 32) shows the Support Vector Machine (SVM)'s discernment. A protocol must be followed while using the Support Vector Machine (SVM) classifier. This protocol involves feature scaling to keep values between +1 and -1. This data standardisation makes SVM processing uniform and dependable. Support vector machine (SVM) machine learning algorithms produce continuous output. The output oscillates between positive and negative numbers, indicating the SVM's position relative to the decision border [27]. Measure the spatial gap between a data point and the hyperplane to calculate classification confidence. In this setting, data points farther from the hyperplane are classified more accurately. The hinge loss function, a well-known cost function, underpins the classifier under study. Equation (1) uses the function to calculate

cost by carefully examining the hyperplane margin. Equation (2) explains how the weight matrix W, bias b, and feature inputs X synergistically coordinate classification. Support Vector Machines (SVMs) are notable for their adaptability.

$$L(y) = \max(0, 1 - p.t) \tag{Eqtn 1}$$

$$p = w^T X + b \tag{Eqtn 2}$$

Kernels allow Support Vector Machines (SVMs) to handle non-linear datasets. Kernels translate two-dimensional data into higher-dimensional spaces [33,34]. Support Vector Machines (SVMs) can overcome linear model constraints because of their versatility. SVM kernel selection involves a deep understanding of the dataset's properties and requirements. A deliberate technique improves categorization accuracy in this process. Thus, SVM kernel selection is a hyperparameter [33]. The SVM classifier, a popular machine learning technique, relies on two key hyperparameters: the regularization coefficient C and the influential gamma component γ [34]. Adding the regularization parameter C prevents overfitting by regulating its magnitude within a 0.1 to 100 range. When the regularization parameter C is reduced, the regularization term affects the objective function more. Thus, to optimize margins, the suggested approach allows certain misclassification mistakes. In contrast, the illusive γ component, crucial for determining decision boundary curvature in non-linear circumstances, has a wide range of values, often 0.0001 to 10. The gamma distribution can handle a wide range of similarities, when each category has a large data set. A significant gamma value increase indicates a strong effort to improve categorization accuracy. To ensure group membership, data points must cluster closely like people with comparable traits. Support Vector Machines (SVM) require careful parameter C tuning for linear classifiers to achieve high precision. However, nonlinear classifiers necessitate careful calibration of the regularization parameter C and kernel coefficient γ for optimal accuracy and precision.

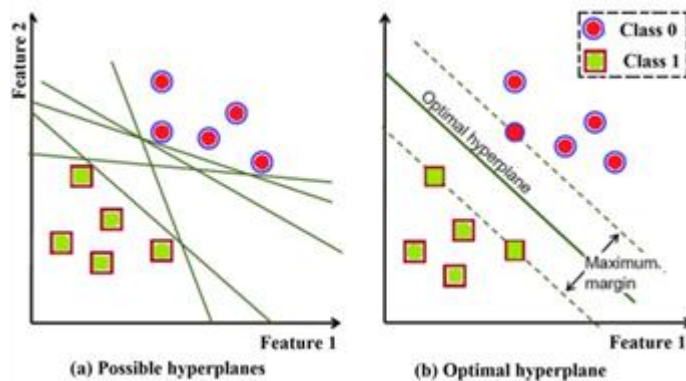


Figure 6: Combining SVM with Optimal Hyperplane Fitting to Find the Best Hyperplane

2. Deep Neural Network DNN

A Deep Neural Network (DNN) is a type of artificial neural network that is specifically designed to perform forward propagation. The system comprises a multitude of artificial neurons, each meticulously engineered to replicate the functionality of an actual neuron, as visually depicted in Figure 8a [35, 36]. The artificial neurons under investigation are designed to receive a set of N inputs (X_i) for the purpose of data collection. The provided inputs are subsequently processed through a summation and activation function, leading to the production of an output (Y) as per Equation (15). The determination of the output variable Y is contingent upon the summation of the weighted inputs, denoted as the product of the weights W_i and their respective inputs X_i , in addition to the bias B . The aforementioned summation is subsequently subjected to an activation function ϕ , resulting in the ultimate output Y . The careful consideration of the activation function is of utmost importance, as it exerts a significant influence on both the capabilities and performance of the neural network. The activation functions frequently employed in neural networks encompass the sigmoid function, the hyperbolic tangent function (\tanh), and the rectified linear unit (ReLU). The conventional architecture of a deep neural network (DNN) is depicted in Figure 8b. It comprises an initial layer responsible for input, multiple intermediate layers for generating hidden representations, and a final layer dedicated to output. The input layer of a neural network is tasked with receiving and accepting data features, which are subsequently processed through the hidden layers of the network. This processing ultimately leads to the generation of an output at the output layer. The learnable parameters of the neural network encompass the weights W_i and the bias B , which undergo updates throughout the training cycles [38]. To achieve optimal performance of the model, it is crucial to optimise various hyperparameters. These include the number of neurons, the selection of activation function, the number of hidden layers, the choice of optimizer, the learning rate, the batch size, and the number of epochs.

The schematic representation of the proposed deep neural network (DNN) classifier is illustrated in Table 2. The proposed architecture comprises an initial input layer that receives a set of ten Gray-Level Co-occurrence Matrix (GLCM) features. Subsequently, these features are passed through a sequence of five hidden layers. Finally, the output is obtained from a binary classifier layer. In the field of architecture, it is common practise to incorporate a series of layers in a concealed manner. This sequence typically begins with a dense layer, which is subsequently followed by a dropout layer, and ultimately concludes with a batch normalisation layer. Table 2 provides a comprehensive overview of the output dimensions and the corresponding number of parameters for each layer. The incorporation of dropout layers within the dense layers is implemented with the purpose of alleviating the potential issue of overfitting. Overfitting refers to the situation where the model excessively adapts to the training data, resulting in subpar performance when presented with unseen data. In contrast, the inclusion of batch normalisation layers serves to enhance the regularisation of the model, thereby mitigating the risk of overfitting and enhancing the overall generalisation

performance. For the purpose of model training, the following hyperparameters were determined to be optimal: the activation function was selected as Rectified Linear Unit (ReLU), the dropout rate was established at 0.5, the momentum was set to 0.95, the epsilon value was assigned as 0.001, the optimizer employed was Adam, the batch size was configured as 32, the number of epochs was designated as 100, and the learning rate was defined as 0.001. The procedure of model training involved the utilisation of the training dataset to generate accuracy and loss curves. After completing the training phase, the subsequent step involved evaluating the efficacy of the deep neural network (DNN) model that was trained. This was accomplished by utilising the test dataset. Furthermore, a visual depiction of the receiver operating characteristic (ROC) curve was generated, and the model scores were calculated. The methodology employed in this study involved the utilisation of the Python programming language on the Google Colaboratory platform. Additionally, the data utilised in this research was stored on Google Drive. The experimental procedure was additionally executed on a Dell XPS 15 9500 laptop, featuring an Intel(R) Core(TM) i7-10750H processor operating at a frequency of 2.60 GHz. The laptop is equipped with a hexa-core processor configuration, consisting of six physical cores and twelve logical processors. The execution was conducted at the United States Corporate Headquarters, situated at 1 Dell Way, Round Rock, Texas 78664.

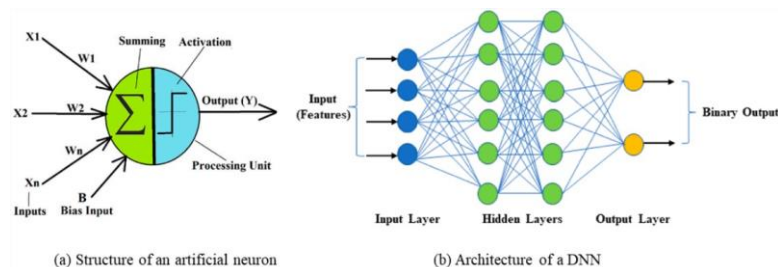


Figure 7: Deep Neural Network Structure

The model scores were evaluated using several metrics, including Sensitivity, Specificity, Precision, F1 Score, and Accuracy.

IV. RESULTS

The proposed methodology encompasses several crucial stages, namely the extraction of GLCM features, data partitioning, and the training and testing of Support Vector Machine (SVM) and Deep Neural Network (DNN) models. In the initial phase, GLCM features were extracted from a comprehensive dataset comprising 560 photographs that were categorized into two distinct classes. The extracted features were subsequently stored in an Excel spreadsheet and employed for the purpose of training and assessing machine learning algorithms. To optimize the dependability and precision of the training and evaluation procedure, a stratified k-fold cross-validation methodology was employed. The value of the hyperparameter k was empirically determined to be 10, leading to the generation of a training

dataset with dimensions of 504 rows and 11 columns. Similarly, a separate testing dataset was created with dimensions of 56 rows and 11 columns. The data subsets were partitioned into distinct sets of feature columns and target columns, yielding two distinct sets of features denoted as x-train and x-test, as well as two arrays of target values denoted as y-train and y-test. The arrays x-train and y-train were utilized in the training process of the model, while the arrays x-test and y-test were employed for the purpose of evaluating the performance of the trained models. The Support Vector Machine (SVM) model was trained using pre-determined hyperparameter configurations. These configurations involved the use of a polynomial kernel with a C value of 1 and a γ value of 1. Subsequently, the model was subjected to a training process utilizing the designated training dataset, and its efficacy was evaluated on the test dataset, with the documentation of model scores. As mentioned earlier, the initial phase involved the segmentation of the entire collection of retinal images within the dataset. The figures presented in Figure 8 illustrate various stages of the segmentation process.

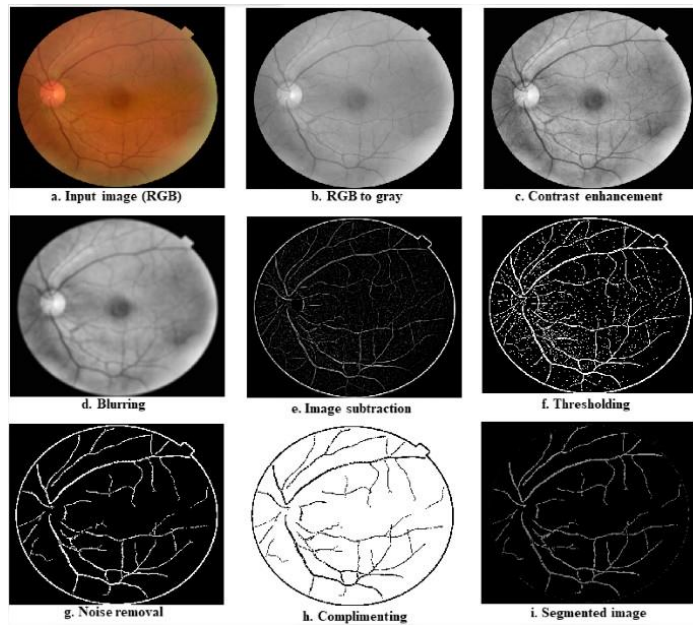


Figure 8: Segmentation algorithm iterations using normal fundus image transformations.

The process commences with the utilization of an image from the healthy class, serving as an exemplary representation (Figure 8). Subsequently, a sequence of transformations is undertaken. The image undergoes a series of transformations in order to achieve the desired outcome. These transformations encompass converting the image to grayscale, enhancing contrast, averaging, subtracting, thresholding, removing noise, complementing, and ultimately generating the final segmented image as depicted in Figure 8. Moreover, Figure 9 a-i showcases an illustrative depiction of diabetic retinopathy (DR) alongside its corresponding alterations observed at various stages of the segmentation technique.

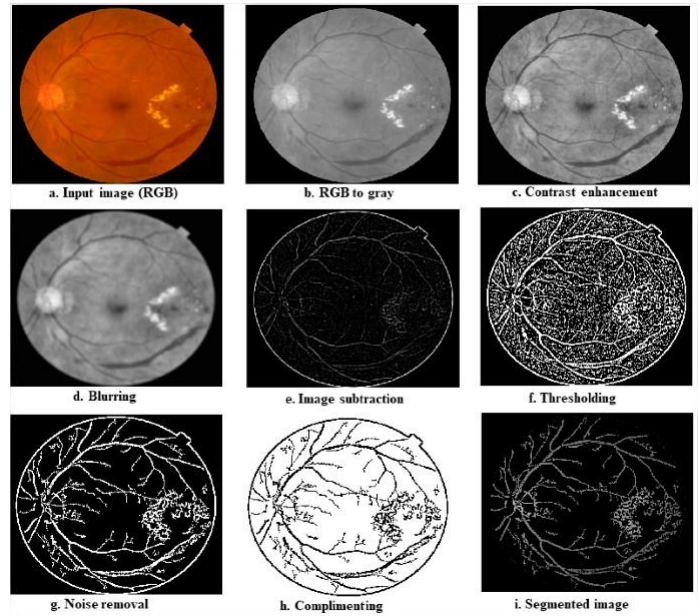


Figure 9: Segmentation algorithm iterations using Diabetic Retinopathy fundus image transformations.

In the third phase of the study, the data partitioning process was conducted to separate the GLCM features into distinct training and test sets. To ensure a comprehensive and robust evaluation of the model, a total of ten iterations were conducted. The experimental procedure employed in this study consisted of conducting ten iterations, each of which involved the use of distinct training and test sets. This approach allowed for the implementation of a ten-fold cross-validation technique. Table 3 provides a comprehensive depiction of the performance indicators for both models, encompassing the average scores and their corresponding standard deviations (SD).

Table III

Performance evaluation parameters

Model	AUC	F1 Score	Precision	Specificity	Sensitivity	Accuracy
DNN	99.15	93.72	93.10	95.17	95.02	95.77
SVM	97.11	91.88	90.28	95.13	93.65	94.59

The Support Vector Machine (SVM) model exhibited exceptional performance during the process of cross-validation, attaining outstanding scores across a range of metrics. The findings of this study reveal several key performance metrics for the evaluated model. The accuracy rate achieved was 94.59%, indicating the overall correctness of the model's predictions. The sensitivity rate, measuring the model's ability to correctly identify positive instances, was found to be 93.65%. Conversely, the specificity rate, which assesses the model's ability to correctly identify negative instances, was determined to be 95.13%. Furthermore, the precision rate, representing the proportion of correctly predicted positive instances out of all predicted positive instances, was calculated to be 90.28%. The F1 score, a measure that combines precision and sensitivity, was

determined to be 91.88%, indicating a balanced performance between these two metrics. Lastly, the Area Under the Curve (AUC) value, which assesses the model's overall discriminatory power, was found to be 97.11%. This metric provides an indication of the model's ability to distinguish between positive and negative instances across various classification thresholds. Figure 10 provides a visually compelling representation that effectively illustrates the dynamic evolution of the Deep Neural Network (DNN) model across the various stages of training, validation, and testing.

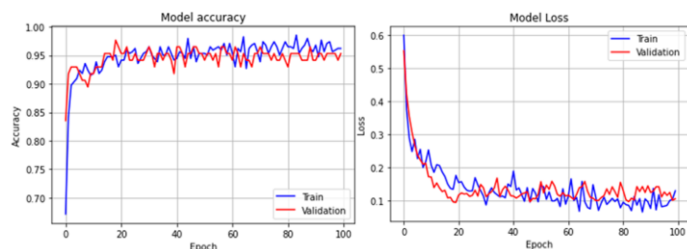


Figure 10: DNN Accuracy Vs Loss Plot

The analysis of the graphical narrative reveals that the deep neural network (DNN) model initiated its convergence phase around epoch 40, ultimately achieving its peak performance by epoch 63. The deep neural network (DNN) model exhibits outstanding performance across a wide range of performance metrics, as indicated by their mean values. The metrics obtained from the analysis encompass a range of performance indicators. These include an accuracy rate of 95.77%, indicating the proportion of correctly classified instances. The sensitivity, or true positive rate, stands at 95.02%, reflecting the ability of the model to accurately identify positive instances. The specificity, or true negative rate, is calculated at 95.17%, representing the model's proficiency in correctly identifying negative instances. The precision, or positive predictive value, is determined to be 93.10%, signifying the proportion of correctly classified positive instances out of all instances classified as positive. The F1-score, a measure that combines precision and sensitivity, is computed to be 93.72%, indicating the overall balance between precision and recall. Lastly, the mean AUC (Area Under the Curve) is an impressive 99.15%, suggesting the model's strong discriminatory power in distinguishing between positive and negative instances. The aforementioned accomplishments are illustrated in Figure 11, a visually captivating representation that displays the Receiver Operating Characteristic (ROC) plots, the mean ROC plot, Area Under the Curve (AUC) scores, and the average AUC score for both models.

V. Discussion

Diabetic Retinopathy (DR) is a chronic and progressive ocular disorder that arises as a complication of diabetes mellitus. If left

untreated, this condition can result in significant visual impairment or complete loss of vision. Conducting a timely examination is widely regarded as the most efficacious measure for mitigating the detrimental effects associated with a particular phenomenon. The gold standard for diagnosing diabetic retinopathy is a comprehensive dilated eye examination. This procedure involves the use of an ophthalmoscope by an eye specialist to carefully examine the eye for any abnormalities, particularly blood vessel damage, in order to make an accurate diagnosis. In addition, it is worth noting that there exist dedicated imaging devices that are capable of capturing fundus images, which play a crucial role in assisting eye specialists during their manual evaluation of the specific ailment. However, it should be noted that the process of manually assessing DR is inherently subjective, making it susceptible to errors and often requiring a significant amount of time. The objective of this study is to investigate the capabilities of machine learning algorithms in detecting diabetic retinopathy (DR), with a focus on utilizing digital fundus images to improve the efficiency of DR diagnosis. By utilizing Gray-Level Co-occurrence Matrix (GLCM) features extracted from a dataset comprising 560 fundus images, two distinct classification models were constructed: Support Vector Machine (SVM) and Deep Neural Network (DNN). The training process involved the utilization of a dataset consisting of 504 images to train the models under investigation. Subsequently, a meticulous evaluation was conducted on 56 images to evaluate the performance of these models. The results demonstrate that the deep neural network (DNN) classifier exhibited superior performance compared to the support vector machine (SVM) classifier across all performance metrics. Notably, the DNN classifier achieved a remarkable mean area under the curve (AUC) of 99.15%, surpassing the SVM classifier's AUC of 97.11%.

The deep neural network (DNN) model exhibits a high level of intricacy and encompasses a significant number of trainable parameters, specifically 711,553 out of a total of 715,521 parameters. This surpasses the current state-of-the-art ResNet model in terms of density, while also offering the advantage of being considerably more lightweight. On the other hand, the Support Vector Machine (SVM) exhibits a concise and uncomplicated implementation, necessitating minimal adjustment of hyperparameters. This characteristic makes it well-suited for deployment, even on computing systems with limited capabilities. The Support Vector Machine (SVM) demonstrates remarkable efficiency, as evidenced by its ability to complete ten rounds of training and testing within a mere 5 seconds. This stands in stark contrast to the Deep Neural Network (DNN) model, which took 196 seconds to accomplish the same task. The task of comparing with previous studies is complex due to the discrepancies in the characteristics of the datasets used. These disparities include variations in the number and quality of training and test images, as well as differences in the techniques and evaluation metrics utilized. The balanced composition of our dataset, which includes an equal number of normal and DR images, is of utmost significance as it guarantees unbiased predictions. The evaluation criteria employed in this study encompassed several key factors,

including accuracy, area under the curve (AUC), sensitivity, specificity, and the training time of the models. The GLCM-SVM model developed in this study demonstrated superior performance compared to a previously published GLCM-SVM model. The accuracy of our model was measured at 94.59%, surpassing the previous model's accuracy of 82.35%. Additionally, our model achieved an AUC of 97.11%, indicating excellent discriminative ability. In terms of sensitivity, our model achieved a value of 93.65%, outperforming the previous model's sensitivity of 76.92%. Similarly, our model exhibited a higher specificity of 95.13% compared to the previous model's specificity of 72.58%. These results highlight the improved performance and robustness of our GLCM-SVM model in accurately classifying the target variable. The deep neural network (DNN) utilized in our study demonstrated exceptional performance in classifying diabetic retinopathy (DR). The classifier achieved an accuracy score of 95.77%, indicating its ability to accurately classify DR cases. Additionally, the area under the receiver operating characteristic curve (AUC) was measured at 99.15%, further validating the classifier's discriminative power. Sensitivity, representing the ability to correctly identify positive cases, was determined to be 95.02%, while specificity, reflecting the ability to correctly identify negative cases, was measured at 95.17%. These performance metrics were obtained through a rigorous ten-fold cross-validation procedure, ensuring the reliability and generalizability of the results. Remarkably, the training process of our deep neural network (DNN) model was successfully accomplished within a mere 121 seconds, exhibiting a noteworthy speed advantage of approximately 16 times compared to the ResNet model. This finding highlights the appropriateness of our deep neural network (DNN) model for clinical use cases, where predictive scores that surpass the threshold of 95% are considered satisfactory. It is postulated that the proposed approach has the potential to greatly aid ophthalmologists in expeditious and precise diagnoses, thereby facilitating the rapid screening of fundus images within a matter of seconds.

Table IV. Comparison with the Existing Literature

Author	Methods	Dataset Size	Accuracy	Sensitivity	Specificity
[16]	GLCM, SVM	Train: 27 Test: 17	82.35	76.92	72.58
[19]	GLCM, Prob. NN.	Normal: 470 DR: 555	86.80	N.A.	N.A.
[20]	LBP, CNN-ResNet	Train: 3662 Test: 1928	96.35	N.A.	N.A.
Developed	GLCM, SVM	280 Normal	94.59	93.65	95.13

Method - 1					
Developed	GLCM	Normal	95.77	95.02	95.17
Method - 2	. DNN	DR:			
		DR:			
		DR:			

However, it is important to acknowledge that our proposed models do possess certain limitations. Although our technique demonstrates exceptional proficiency in identifying the existence of diabetic retinopathy (DR), as substantiated by the area under the receiver operating characteristic curve (AUC) surpassing 99%, it does not furnish insights into the severity of the ailment. Moreover, the financial burden associated with fundus imaging poses a significant obstacle for individuals who have limited financial means. Our forthcoming initiatives encompass the advancement of a cost-effective retinal imaging apparatus, which integrates a smartphone, a lens, and a machine learning algorithm. This amalgamation empowers patients to conduct retinal screenings in the comfort of their own homes and promptly seek appropriate referrals if deemed necessary.

VI. Conclusion

The present research study introduces two separate machine learning approaches that have been specifically designed for the purpose of detecting and diagnosing diabetic retinopathy (DR) through the analysis of pre-existing color retinal images. The core components of these techniques encompass the processes of picture segmentation, feature extraction, and classification. The present study uses segmentation algorithms to discern distinct areas within retinal pictures that are pertinent to the condition of diabetic retinopathy (DR). Afterwards, relevant characteristics are derived from these selected locations through the utilization of the Gray-Level Co-occurrence Matrix (GLCM) technique. The study's findings involve the development of two distinct models, specifically a Support Vector Machine (SVM) and a Deep Neural Network (DNN). The evaluation of the DNN model on the test data reveals its exceptional performance in comparison to both the proposed SVM model and the currently prevailing state-of-the-art models. The diabetic retinopathy (DR) classifier, which is based on a deep neural network (DNN), has effective performance in delivering timely diagnostic results for retinal pictures, often requiring a minimal amount of time for analysis, often just a few seconds. Furthermore, the primary objective of this work is to conceive the potential development of a user-centric demand response (DR) classifier that is specifically tailored for home use. The present study introduces a novel approach that involves the utilization of a cost-effective equipment for acquiring fundus images, which integrates a lens and a smartphone. This technology allows users to independently and conveniently conduct screenings for diabetic retinopathy (DR) in the comfort of their own homes.

REFERENCES

- [1] Regier, E.E.; Venkat, M.V.; Close, K.L. *Journal of Diabetes News*. *J. Diabetes* 2015, *7*, 437–441.
- [2] Ninel, Z.; Gregori, M.D. Diabetic Retinopathy: Causes, Symptoms, Treatment. Available online: <https://www.aao.org/eye-health/diseases/what-is-diabetic-retinopathy>.
- [3] Duh, E.J.; Sun, J.K.; Stitt, A.W. Diabetic retinopathy: Current understanding, mechanisms, and treatment strategies. *JCI Insight* 2017, *2*, e93751.
- [4] Sidey-Gibbons, J.A.M.; Sidey-Gibbons, C.J. Machine learning in medicine: A practical introduction. *BMC Med Res. Methodol.* 2019, *19*, 64.
- [5] Deo, R.C. Machine Learning in Medicine. *Circulation* 2015, *132*, 1920–1930.
- [6] Eye from Front: Anatomy: The Eyes Have It. Available online: <http://kellogg.umich.edu/theeyeshaveit/anatomy/external-eye.html>.
- [7] Seid, M.A.; Ambelu, A.; Diress, M.; Yeshaw, Y.; Akalu, Y.; Dagnew, B. Visual impairment and its predictors among people living with type 2 diabetes mellitus at Dessie town hospitals, Northeast Ethiopia: Institution-based cross-sectional study. *BMC Ophthalmol.* 2022, *22*, 52.
- [8] Foady, Z.; Novitasari, D.C.R.; Asyhar, A.H.; Firmansjah, M. Automated Diagnosis System of Diabetic Retinopathy Using GLCM Method and SVM Classifier. In Proceedings of the 2018 5th International Conference on Electrical Engineering, Computer Science and Informatics (EECSI), Malang, Indonesia, 16–18 October 2018; pp. 154–160.
- [9] Dhiravidhelvi, E.; Rajamani, V.; Manimegalai, C. GLCM-based detection and classification of microaneurysm in diabetic retinopathy fundus images. *Int. J. Adv. Intell. Paradig.* 2019, *14*, 55.
- [10] Adrimana, R.; Muchtara, K.; Maulina, N. Performance Evaluation of Binary Classification of Diabetic Retinopathy through Deep Learning Techniques using Texture Feature. *Procedia Comput. Sci.* 2021, *179*, 88–94.
- [11] Benítez, V.E.C.; Matto, I.C.; Román, J.C.M.; Noguera, J.L.V.; García-Torres, M.; Ayala, J.; Pinto-Roa, D.P.; Gardel-Sotomayor, P.E.; Facon, J.; Grillo, S.A. Dataset from Fundus Images for the Study of Diabetic Retinopathy (0.1). Zenodo. 2021. Available online: <https://zenodo.org/record/4532361#.YyAk9bRBxPY>.
- [12] Xie, Y.; Ning, L.; Wang, M.; Li, C. Image Enhancement Based on Histogram Equalization. *J. Phys. Conf. Ser.* 2019, *1314*, 012161.
- [13] Ridler, T.W.; Calvard, S. Picture thresholding using an iterative selection method. *IEEE Trans. Syst. Man Cybern.* 1978, *8*, 630–632.
- [14] Hall-Beyer, M. GLCM Texture: A Tutorial v. 1.0 Through 2.7. 2007. Available online: <http://www.ucalgary.ca/UofC/nasdev/mhallbey/research.htm>.
- [15] Mujeeb Rahman, K.K.; Monica Subashini, M. A Deep Neural Network-Based Model for Screening Autism Spectrum Disorder Using the Quantitative Checklist for Autism in Toddlers (QCHAT). *J. Autism Dev. Disord.* 2022, *52*, 2732–2746.
- [16] Jun, Z. The Development and Application of Support Vector Machine. *J. Phys. Conf. Ser.* 2021, *1748*, 052006.
- [17] Roman, I.; Santana, R.; Mendiburu, A.; Lozano, J.A. In-depth analysis of SVM kernel learning and its components. *Neural Comput. Appl.* 2020, *33*, 6575–6594.
- [18] Hastie, T.; Rosset, S.; Tibshirani, R.; Zhu, J. The Entire Regularization Path for the Support Vector Machine. *J. Mach. Learn. Res.* 2004, *17*, 1–24. Available online: https://hastie.su.domains/Papers/svmpath_jmlr.pdf (accessed on 8 September 2022).
- [19] Kanhirakadavath, M.R.; Chandran, M.S.M. Investigation of Eye-Tracking Scan Path as a Biomarker for Autism Screening Using Machine Learning Algorithms. *Diagnostics* 2022, *12*, 518.
- [20] Mujeeb Rahman, K.K.; Subashini, M.M. Identification of Autism in Children Using Static Facial Features and Deep Neural Networks. *Brain Sci.* 2022, *12*, 94.
- [21] Shabani, F.; Kumar, L.; Ahmadi, M. Assessing accuracy methods of species distribution models: AUC, specificity, sensitivity and the true skill statistic. *Glob. J. Hum. Soc. Sci.* 2018, *18*, 6–18.
- [22] NHS. Overview—Diabetic Retinopathy. Available online: <https://www.nhs.uk/conditions/diabetic-retinopathy/#:~:text=Diabetic%20retinopathy%20is%20a%20complication,it%20could%20threaten%20your%20sight>
- [23] Prajapati, R.; Khatri, U.; Kwon, G.R. An efficient deep neural network binary classifier for Alzheimer's disease classification. In Proceedings of the 2021 International Conference on Artificial Intelligence in Information and Communication (ICAIIIC), Jeju Island, Korea, 13–16 April 2021; pp. 231–234.
- [24] Schmidhuber, J. Deep Learning in Neural Networks: An Overview. *Neural Netw.* 2015, *61*, 85–117.
- [25] Tharwat, A. Parameter investigation of support vector machine classifier with kernel functions. *Knowl. Inf. Syst.* 2019, *61*, 1269–1302.
- [26] Yu, W.; Liu, T.; Valdez, R.; Gwinn, M.; Khoury, M.J. Application of support vector machine modeling for prediction of common diseases: The case of diabetes and pre-diabetes. *BMC Med. Inform. Decis. Mak.* 2010, *10*, 16.
- [27] Huang, S.; Cai, N.; Pacheco, P.P.; Narrandes, S.; Wang, Y.; Xu, W. Applications of Support Vector Machine (SVM) Learning in Cancer Genomics. *Cancer Genom. Proteom.* 2018, *15*, 41–51.
- [28] Jafarpour, S.; Sedghi, Z.; Amirani, M.C. A robust brain MRI classification with GLCM features. *Int. J. Comput. Appl.* 2012, *37*, 1–5.
- [29] Bakti, L.D.; Imran, B.; Wahyudi, E.; Arwidiyarti, D.; Suryadi, E.; Multazam, M. Maspaeni Data extraction of the gray level Co-occurrence matrix (GLCM) Feature on the fingerprints of parents and children in Lombok Island, Indonesia. *Data Brief* 2021, *36*, 107067.
- [30] Ningsih, D.R. Improving retinal image quality using the contrast stretching, histogram equalization, and CLAHE methods with median filters. *Int. J. Image Graph. Signal Process.* 2020, *10*, 30.
- [31] Datta, Parul, "Classification_features_DR_dataset", Mendeley Data, V2, 22 August 2020. Available online: <https://data.mendeley.com/datasets/77wffjyxdc>
- [32] Dataset for Diabetic Retinopathy Detection. 2015. Available online: <https://www.kaggle.com/competitions/diabetic-retinopathy-detection/data>.
- [33] Elveny, M.; Anjulina, T.; Siregar, B.; Syah, R. Identification of Diabetic Retinopathy with Retinal Fundus Imagery Using Probabilistic Neural Network. *J. Phys. Conf. Ser.* 2020, *1641*, 012055. Available online: <https://iopscience.iop.org/article/10.1088/1742-6596/1641/1/012055/meta>.
- [34] Xu, K.; Feng, D.; Mi, H. Deep Convolutional Neural Network-Based Early Automated Detection of Diabetic Retinopathy Using Fundus Image. *Molecules* 2017, *22*, 2054.
- [35] Steven Ferrucci, O.D.; FAAO. Standard Tools and Tests for Diagnosing Diabetic Retinopathy. Available online: <https://modernod.com/articles/2019-june/a-new-ally-in-the-diagnosis-andmanagement-of-diabetic-retinopathy?c4src=article:infinite-scroll>.
- [36] NVISION. Eye Centers, Understanding Aqueous Humor and Vitreous Humor (The Differences). Available online: <https://www.nvisioncenters.com/education/aqueous-and-vitreous/>.
- [37] Diabetes Now Affects One in 10 Adults Worldwide. Available online: <https://www.idf.org/news/240:diabetes-now-affects-one-in-10-adults-worldwide.html>.
- [38] The Eyes (Human Anatomy): Diagram, Function, Definition, and Eye Problems, WebMD. Available online: <https://www.webmd.com/eye-health/picture-of-the-eyes>.
- [39] May, M. Eight ways machine learning is assisting medicine. *Nat. Med.* 2021, *27*, 2–3.
- [40] Wang, W.; Lo, A.C.Y. Diabetic Retinopathy: Pathophysiology and Treatments. *Int. J. Mol. Sci.* 2018, *19*, 1816.