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Automatic Detection of Genetic Diseases in Pediatric Age Using Pupillometry

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ABSTRACT
Children with inherited retinal disorders have substantial vision impairment. They are divided into outer and inner retina illnesses, and they frequently result in infant blindness. Given the vast range of clinical and genetic symptoms associated with this type of sickness, the diagnosis might be difficult. causes (with more than 200 causal genes). It is frequently based on a complicated network of clinical tests, including invasive ones that are not necessarily suitable for newborns or young children. Thus, a new strategy is required that makes use of chromatic pupillometry, a method that is increasingly being employed to evaluate the inner and outer retinal functions. To assist in the detection of inherited retinal illnesses in pediatric children, this research offers a unique Clinical Decision Support System (CDSS) based on Machine Learning and employing Chromatic Pupillometry. The employment of specialized medical equipment (pupillometer) in conjunction with a specially created custom machine learning decision support system is suggested as a method that blends hardware and software. The features retrieved from the pupillometric data are classified using two separate Support Vector Machines (SVMs), one for each eye. Retinitis pigmentosa in children has been diagnosed using the specified CDSS. The system performed satisfactorily, as evidenced by the results of integrating the two SVMs into an ensemble model, which showed 91.176 accuracy, 1.0 sensitivity, and 0.0 specificity. This study is the first to use pupillometric data to apply machine learning.

INTRODUCTION
Inherited Retinal Diseases (IRDs) represent a significant cause of severe visual deficits in children. They frequently are cause of blindness in childhood in Established Market Economies (1/3000 individuals). IRDs can be divided into diseases of the outer retina, namely photoreceptor degenerations and diseases of the inner retina, mainly retinal ganglion cell degeneration The unusually high genetic heterogeneity of both diseases more than 200 causal genes have been found as of yet represents a tremendous barrier to a timely and accurate diagnosis, especially in light of the possibility that the same gene can result in a variety of clinical presentations. To diagnose inner and outer retinal illnesses, the most informative clinical inquiry is electrophysiological testing, which frequently necessitates sedating the children. This complex pattern of clinical tests is widely used in the clinical examination of IRDs. Sedation alters the retinal response and necessitates a sophisticated medical setting. A novel approach to support the diagnosis of IRDs would be this pupillometry. To this regard, chromatic pupillometry has been proposed as a highly sensitive and objective test to quantify the function of different light-sensitive retinal cells and, therefore, it has been shown helpful to detect the retinal dysfunction caused by IRDs.

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SVM, CNN, and ML are the techniques employed in this project. SVM, CNN, and ML are the techniques employed in this project. ML tools have been proven as very effective in supporting the decision process, indeed in previous works the authors successfully used ML for creating CDSSs dedicated to chronic diseases such as congestive heart failure or chronic obstructive pulmonary disease. Support vector machine (SVM) algorithm, has established itself as a high-performance supervised machine learning method in the field of medical decision making due to its classification problem solving capability. convolutional neural networks (CNNs) have made many breakthroughs in the field of medical image processing, which have rigid features and high resolution.

PROBLEM STATEMENT

When a gene has a fault with its code and this results in a health issue, the condition is referred to as a genetic disorder. The current diagnostic techniques for pediatric patients with genetic illnesses frequently include lengthy, intrusive procedures that may not be appropriate for young children. The automatic diagnosis of genetic disorders in pediatric patients is therefore in need of a non-invasive and effective approach. Inherited retinal diseases (IRDs) encompass a wide range of genetic disorders that result in substantial vision impairment and can lead to blindness in pediatric patients. Each IRD is caused by at least one gene that is not working as it should.

LITERATURE REVIEW

Article Reference	Algorithm	Dataset	Performance Evaluation	Input	Results
Brancati et al. (2018) [22]	AdaBoost.M1	RIPS dataset (120 images from four patients duplicated in two subsets G1 and G2 classified by specialists)	Hold out	Fundus images	On G1: Accuracy: 99.35% Sensitivity: 79.40% Specificity: 99.51% Precision: 58.92% F-measure: 62.48% On G2: Accuracy: 99.35% Sensitivity: 75.66% Specificity: 99.57% Precision: 63.50% F-measure: 63.70%
Gao et al. (2017) [23]	Random forest	30 images from 19 participants	10 images for training 20 images for test	OCT images	Jaccard index: 0.81±0.12
Garcia-Floriano et al. (2017) [24]	SVM	27 healthy 24 with drusen	Leave-one-out	Fundus images	Accuracy: 92.16% Precision: 93.20% Recall: 92.20% F-measure: 92.10%
Khalid et al. (2017) [25]	SVM	1447 healthy 40 central serious chorioretinopathy 650 retinal edema 752 age-related macular degeneration	40 training 2819 validation	OCT images	Accuracy: 99.92% Sensitivity: 100.00% Specificity: 99.86%
Piri et al. (2017) [26]	Custom ensemble algorithm	>1.4 million diabetic patients from the Cerner Corporation's Health Facts data warehouse	the exact partition for training and validation set are not specified	Blood test results and demographic data	Accuracy: 92.76% Sensitivity: 90.22% Specificity: 95.30% AUC: 97.90%

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A study of the state of the art was developed at the beginning of the activity. The search for previous articles in the literature was done on Scopus, IEEE Xplore and PubMED, using the following keywords: ‘‘clinical decision support system’’, ‘‘eye diseases’’, ‘‘rare eye diseases’’, ‘‘CDSS’’, ‘‘DSS’’, ‘‘pupillometry’’, ‘‘retinitis pigmentosa’’ and ‘‘machine learning’’.

PROPOSED SYSTEM

Module 1 – Data Collection & Filtering:

As detailed in the following, the field diagnosis is used to label the subjects and their related data during the training process of the ML system, whereas the above diameter signals are used to extract clinically motivated features of the pupillary reactivity and for building the input dataset of the supervised classifier. However, before the extraction of the feature set, the raw pupillometric signals must be properly processed to attenuate noisy components and, particularly, to cope with potential eye-blink artefacts. Involuntary eye blinking during video capture is indeed associated with abrupt spurious spikes, which might significantly corrupt the resultant traces of the pupil diameter, thus reducing the reliability of the features of interest. In detail, the pre-processing module first involves the application of a Savitzky-Golay (SG) of a third-order smoothing filter [33] and window span of 55 samples. This FIR filter generally improves the original SNR levels without greatly distorting the underlying pupillometric signal. Afterwards, the residual between the original data and the SG-smoothed signal is computed: blink related artefacts are then identified with values exceeding a properly tailored maximum threshold (0.2 mm) and removed accordingly. Finally, possible gaps produced by the above operation are filled by means of a cubic interpolation, and the resulting trace is once again filtered by a low-pass filter to give final smoothness to the pupillary trace. A sample filtered signal is shown in Fig.

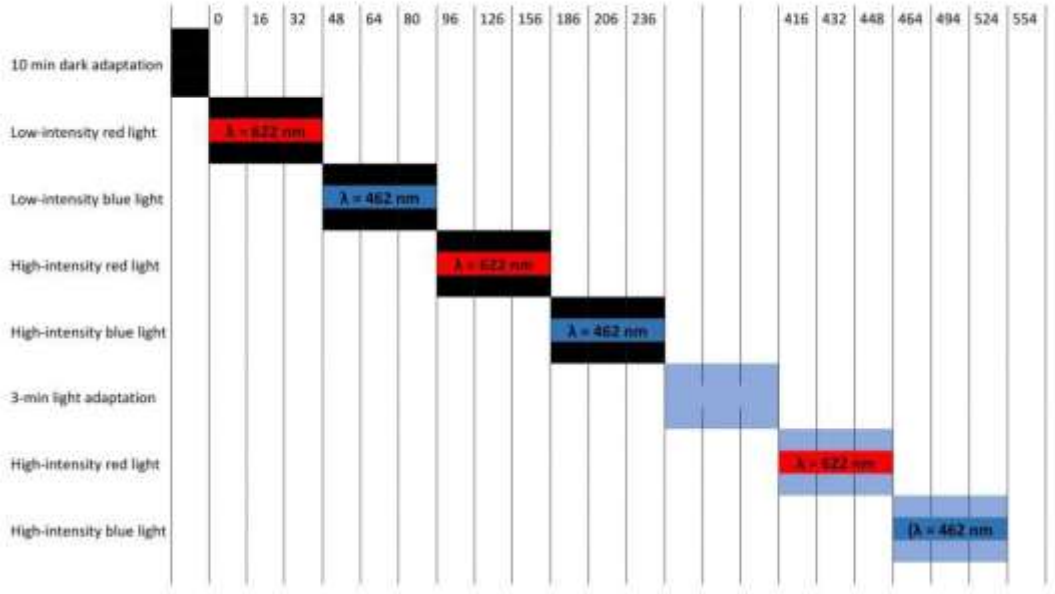

Fig.1. Phases of pupillometric protocol, central color is the light one and the side color represent background; numbers in the central part are the intensity of the light stimuli and on top of the scheme there is time express in seconds.

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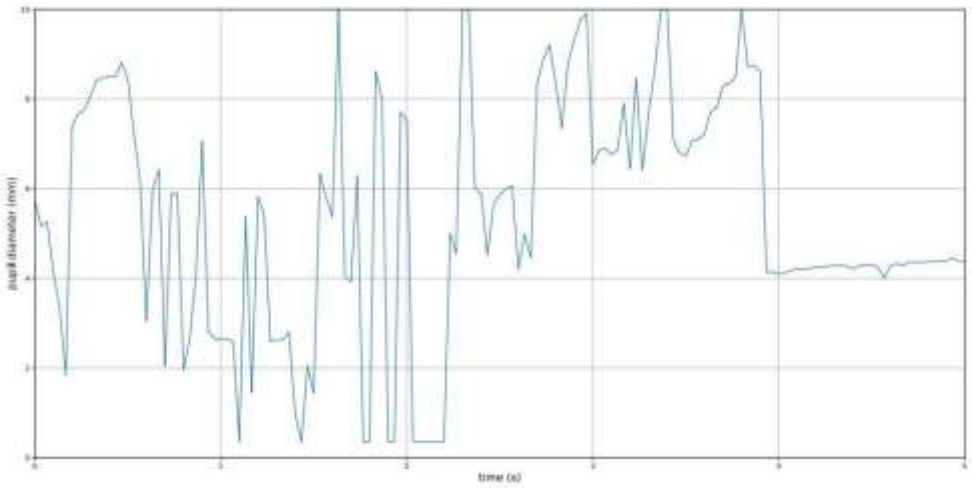

Fig.2. Example of irrecoverable signal, the quantity and size of the spikes and artefacts makes it impossible to extract features.

SOFTWARE DESIGN

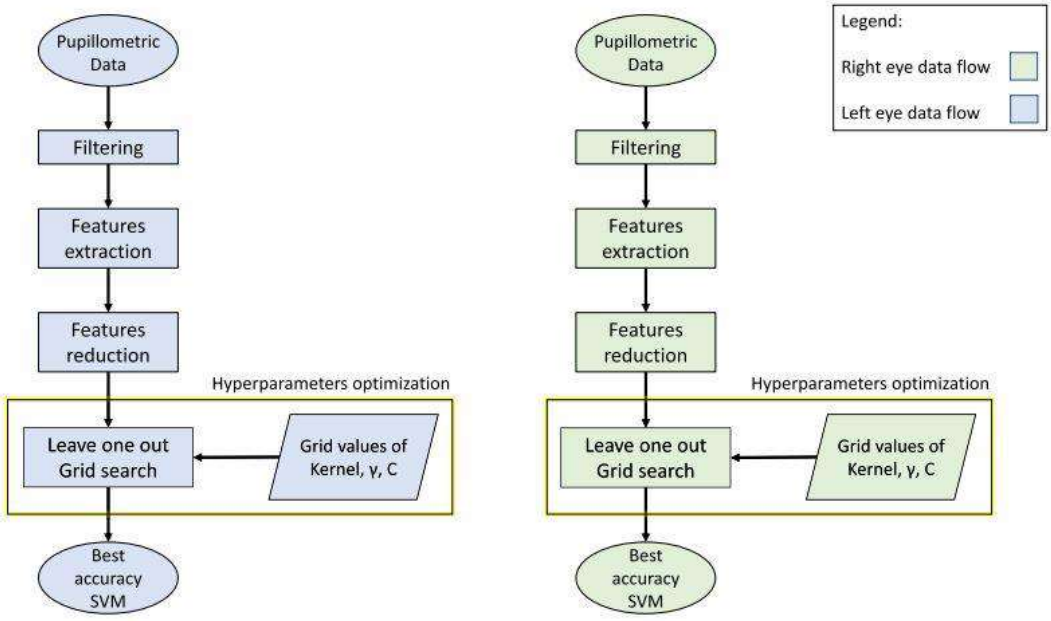

Fig.3. Data analysis, selection of features and optimization of the SVM parameters.

Module 2 – Features Extraction, Reduction, Right Eye, Left Eye Features:

Extraction:

We selected the most predictive features based on the following literature [3], [4] [5], [6] [34]. After the pre-processing stage, the following 8-elements vector of features is extracted from each pupillometric signal:

• MAX: maximum pupil diameter at baseline;
• MIN: minimum diameter in correspondence with the peak constriction;
• DELTA: absolute difference between the above values;
• CH: percentage maximum constriction (with respect to the pupillary diameter at rest);
• LATENCY: delay between the light stimulus and the onset of the pupillary constriction;

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• MCV: mean constriction velocity;
• MDV: mean dilation velocity;
• CV max: maximum constriction velocity.

According to the literature on pupillometry in various diseases and in biometric authentication, the eight features listed above, which were calculated on the filtered signal, were selected. The same features are offered by the equipment itself in its output files and are frequently used by the physicians working in this study. By computing MAX and LATENCY in the first second and the others using a 5-s window, the time span utilized to derive the a for mentioned features were correctly constrained to reduce the chance of erroneous values.

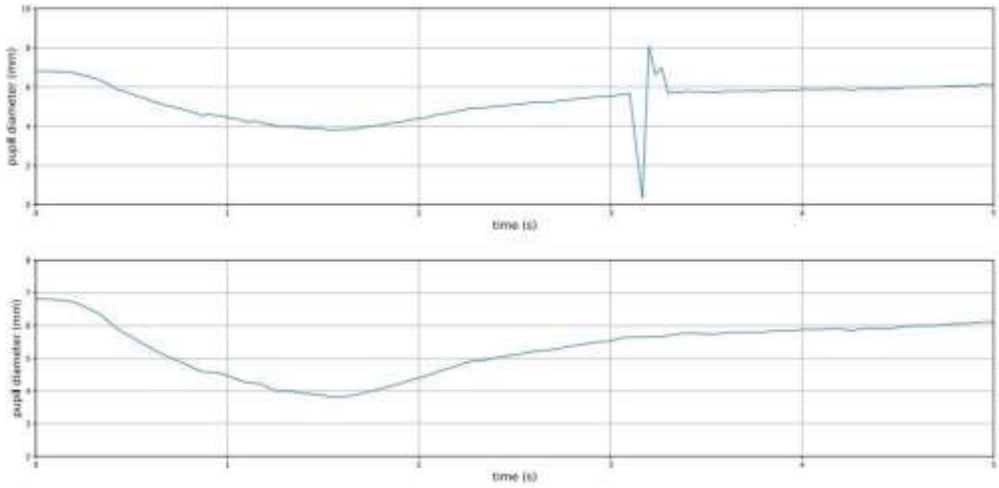

Fig.4. Feature Extraction

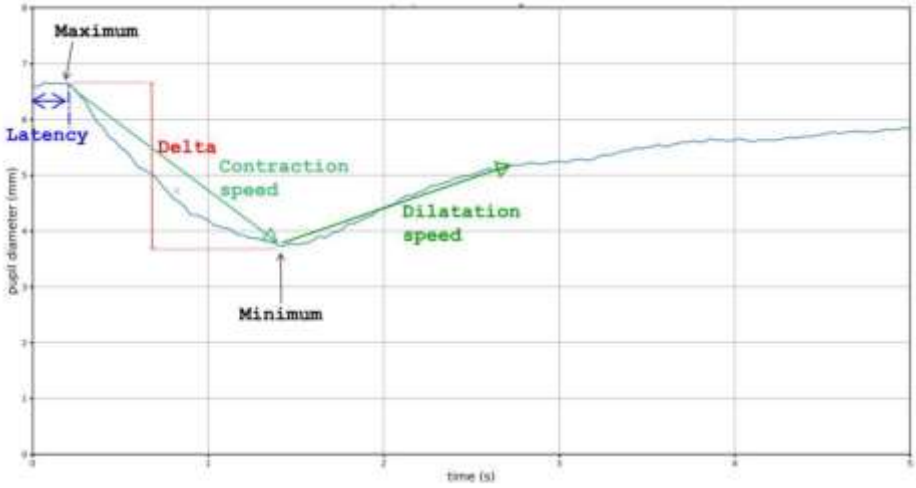

Fig.5. Graphic Representation of Features

Reduction:

Feature reduction was a crucial first step that was used to prevent the training dataset from becoming overfit because to the comparatively high number of features. A basic guideline for ML applications is to limit the dimension of the input feature space to less than one fifth of the entire number of observations, or the best subjects. The set of features used in this investigation was taken from the findings of a recent study [34], which found a subset of pupillary features with superior discriminant potential for the clinical diagnosis of RP.

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Stimuli	Feature	Operation on consecutive stimuli
(1, 2)	Delta	Min
(3, 4)	Min	Max
(5, 6)	Delta	Min

Table.1. Strategy for Feature Reduction

Module 3 – Graph Metrics & Disease Prediction

We propose the adoption of chromatic pupillometry to support the screening and we achieved an excellent sensitivity 93.7 % (due to one false negative) with a satisfactory specificity (78.6 %). We privileged the sensitivity over the specificity because this novel technique will be, at least in these first stages, mostly applied for screening purposes. It is planned to test the accuracy of the method in a successive study on a larger sample of pediatric patients, which should undergo electroretinogram to confirm
the diagnosis. The non-invasiveness is granted by adopting the proposed pupillometric method, which requires no specific patient preparations with drugs or collyriums. If compared with other standard diagnostic techniques.

RESULT

Fig.6. Uploading data

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Fig.7. Filtering the data

Fig.8. Feature Extraction

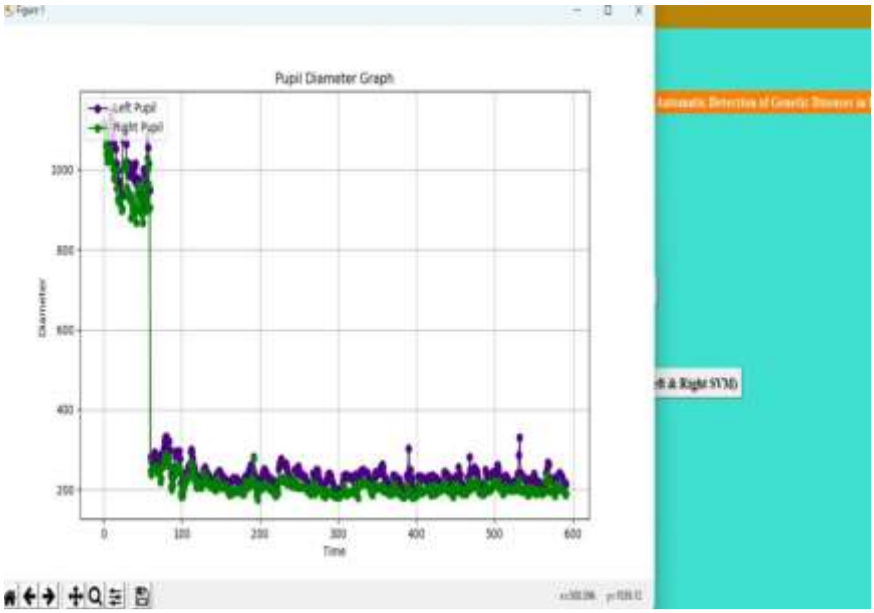

Fig.9. Feature Reduction

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Fig.10. Applying SVM on Right Eye Features

Fig.11. Applying SVM on Left Eye Features

Fig.12. Applying SVM on Both Right & Left Eye

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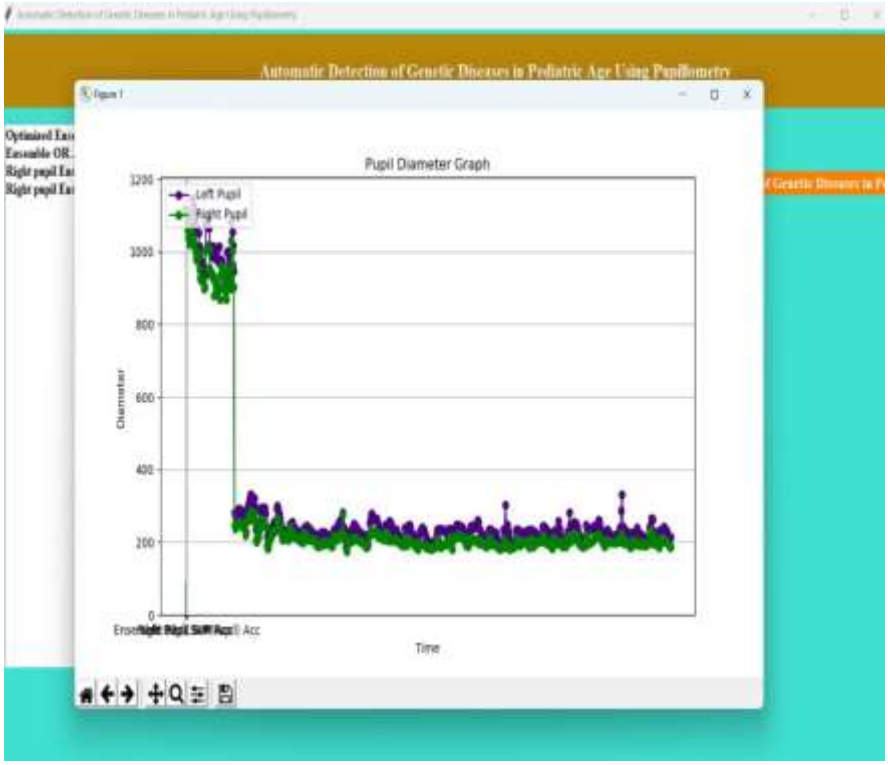

Fig.13. Applying SVM on Both Right & Left Eye

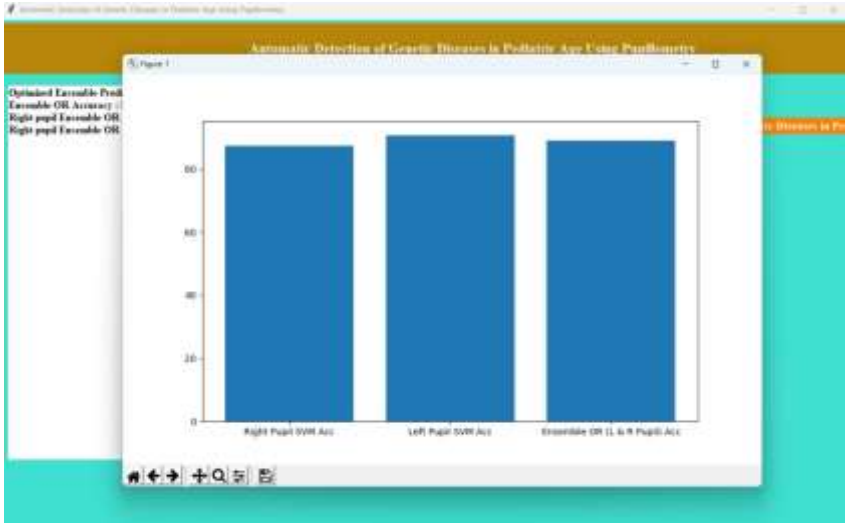

Fig.14. Accuracy Graph with Metrics

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Fig.15. Testing the Model

CONCLUSION

A new approach for supporting clinical decision for diagnosis of retinitis pigmentosa starting from analysis of pupil response to chromatic light stimuli in pediatric patients. The system was developed to clean artefacts, extract features and help the diagnosis of RP using an ML approach based on an ensemble model of two fine-tuned SVMs. Performances were evaluated with a leave-one-out cross-validation, also used to identify the best combination of internal parameters of the SVM, separately for both the left and right eyes. The class assigned to each eye were combined in the end with an OR-like approach to maximize the overall sensitivity of the CDSS; the ensemble system achieved 84.6% accuracy, 93.7% sensitivity and 78.6% specificity. The small amount of data available for this work, calls for further tests with a larger data pool for validating the performance of the system. Future scope includes testing the same approach with different devices. A problem that came out with great evidence, at the signal acquisition stage, is the frequent presence of movement artifacts. This is due to the particular shape of the device, together with the young age of the enrolled patients. Devices with different frame, including also systems based on smartphones, are going to be investigated.

FUTURE SCOPE

The future scope of this research includes testing the described approach with different devices, particularly those with alternative frames such as smartphone-based systems. Additionally, incorporating attention-capturing techniques for young patients and validating the system's performance with a larger dataset are important areas of focus to enhance the clinical decision support system for diagnosing retinitis pigmentosa.

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