Automatic Detection of Genetic Diseases in Pediatric Age Using Pupillometry

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Abstract- Severe vision impairments in children are caused by inherited retinal disorders. As a result of these illnesses, many children go blind in childhood. Diagnosing this type of sickness can be difficult, given the variety of clinical and genetic factors involved (with over 200 causative genes). Chromatic Pupillometry, a method increasingly utilized to measure outer and inner retinal functioning, offers a distinct approach. Using a specific medical device (pupillometer) and a proprietary machine learning decision support system, a hybrid solution is suggested. Features collected from pupillometric data are classified by means of two Support Vector Machines (SVMs), one for each eye Retinitis Pigmentosa in paediatric patients has been diagnosed using the CDSS. By merging two SVMs into an ensemble model, the system achieves 0.846 accuracy, 0.937 sensitivity, and 0.786 specificity, which are excellent results. Using pupillometric data, this is the first study to apply machine learning in order to identify a hereditary illness in children under the age of 18.

Keywords— Man-made reasoning, clinical choice emotionally supportive networks, AI, pupillometry, python, uncommon sicknesses, retinitis pigmentosa, retinopathy, support vector machine.

I. INTRODUCTION

. Retinal disorders are the primary reason for blindness in children with acute vision problems. In established market economies (1/3000 persons), they are a common cause of blindness in childhood. It can be classified into illnesses of the outer retina, namely photoreceptor degenerations, and diseases of the inner retina, especially retinal ganglion cell degenerations (e.g. congenital glaucoma, dominant optic atrophy, Leber hereditary optic neuropathy). Over 200 causal genes have been discovered to far, which represents a tremendous hurdle to a quick and efficient diagnosis, especially when considered that the same gene might produce distinct and diverse clinical presentations in different individuals with the disease.

A. Modern Techniques OF Therapeutic Assessment

Infants and young children should not be subjected to an array of clinical tests, particularly invasive ones, that are not always appropriate for the evaluation of IRD. As an example, electrophysiological testing, which represents the most useful clinical inquiry for the identification of inner and outer retinal disorders, sometimes requires sedation of the children in order to be carried out. There is a significant expense associated with sedation since it alters the retinal response and needs a sophisticated healthcare setting (e.g., operating room; paediatric; anesthesiologist; specialised instruments). Diagnostics are therefore difficult and need the use of specialist institutes. This means that young patients and their families have to wait a long time for a thorough and accurate test. As a result, in many situations, the electrophysiological responses are below the noise level (for example, an extinguished scotopic electroretinogram response confirms a correct diagnosis for this disease). Therefore, these reactions are not ideal for monitoring changes in visual functioning, which are essential for evaluating disease progression and therapeutic efficacy [1].

B. Pupillometry

A innovative technique to help the diagnosis of IRDs would be valuable. To this end, chromatic pupillometry has been presented as a very sensitive and objective test to assess the function of distinct light-sensitive retinal cells and, thus, it has been demonstrated useful to identify the retinal dysfunction\scaused by IRDs as detailed in the following [2-6]. Photosensing Retinal Ganglion (ipRGC) cells display a slower temporal dynamics and induce a prolonged pupillary constriction in response to light, continuing even after the light is turned off [2]. PLR (Pupillary Light Reflex) has been studied by altering the properties of large-field (90) flash stimuli and adaption circumstances (light vs. dark). Red flashes with a high brightness are delivered in a rod suppressing field, and the PLR response is largely cone-mediated, whereas blue flashes with a low luminance are shown to the dark-adapted eye and the PLR response is predominantly rod-mediated. An initial transient pupil constriction (cone- and rod-mediated) occurs when high-luminance, short-wavelength stimuli are given to the darkadapted eye, followed by a melanopsin-mediated persistent constriction lasting for more than 30s following stimulus offset. As part of clinical procedures, prolonged melanopsin-mediated constriction has been employed to test inner-retina function. The use of chromatic pupil responses may be a unique method to detect and monitor illnesses affecting the outer or inner retina [2]. On the basis of this findings, a clinical decision support system (CDSS) may be built to help the diagnosis of IRDs. As part of a research effort, we developed excellent procedures and systems for early diagnosis and monitoring using chromatic pupillometry. University of Florence, Campania Luigi Vanvitelli Eye Clinics, and the University of Milan. An innovative CDSS for the diagnosis of Retinitis igmentosa (RP) in paediatric patients was developed by this team. The following activities were included in the research:

(1) A pupillometric procedure has been developed [7]. Researchers focused on participants with RP (one of the IRDs with the greatest frequency) aged eight to 16 years old in the first phase of the research.
(2) The operating unit of Florence designed and developed a cloud-based web-platform for information technology (IT). It has been used by other operating units to communicate findings and data acquired in partner institutions [8], [9].
(3) Machine Learning (ML) methods, which might be useful in the development of the CDSS, are being analysed.
(4) It is also possible to integrate the entire web application into a single project [10-21].

II. RELATEDWORKS

"Clinical decision support system", "eye illnesses", "rare eye diseases, "CDSS, "DSS, "pupillometry, "retinitis pigmentosa, "machine learning," and "retinitis pigmentosa" were used as keywords in the literature search. It was not possible to find any articles that had all of these keywords in one article. No paper identified uses combined pupillometry and machine learning methods. This page contains a list of publications that mention "clinical decision support system" and "machine learning" In the case of "rare illnesses", "retinitis pigmentosa" and "pupillometry", the number of studies is smaller. As a result, the following seven articles have been selected for their relevance and diversity. The interactions with eye disorders are described in detail. On the other hand, Brancati and colleagues [22] used machine learning to detect pigment signals on fundus pictures obtained with an intraretinal camera to investigate individuals who had RP. A recent study by Gao et al. [23] used ML random forest to detect intact choriocapillaris in OCT images in order to assist the diagnosis of choroideremia.

Four additional publications use comparable supervised ML algorithms to age-related macular degenerations [24], [25] diabetic retinopathy [26] and glaucoma. In a new study, Gargeya et al. [28] used deep learning to support diabetic retinopathy diagnosis.

III. PROPOSED SYSTEM

In compliance with the Declaration of Helsinki, this study was authorised by the local ethics committees of the clinical centres involved (University of Campania and University of Milan). The research procedure was explained in detail to all participants, who signed a permission form before the measurement sessions began. 20 patients affected by RP and 18 control subjects, characterized by the absence of any ocular diseases and an absolute refraction error lower than 5 dioptres, were enrolled in the present multi-centric research study. Medical, Surgical, and Dental Sciences (University of Campania Luigi Vanvitelli in Naples) and Department of Clinical Sciences and Community Health of the University of Milan were responsible for recruiting and evaluating the individuals. Subjects underwent a standardized evaluation of pupillary response to chromatic stimulation, carried out with a customized DP-2000 binocular pupillometer (NeurOptics, US) showed in Fig.1.

FIGURE 1. DP-2000 binocular pupillometer(NeurOptics, US).

In addition, the system facilitates the automated identification of the pupil contour and video monitoring of its dynamic response to red (= 622 nm), green (= 528 nm), blue (= 462 nm) and white light stimuli, as well as the simultaneous imaging and assessment of both eyes. Videos were taken at a frame rate of 30 frames per second, with a grey-level resolution of 8 bits and a spatial resolution of 0.05 millimetres, according to the researchers. As a result, a standard procedure was established across the participating institutions in order to provide a homogenous collection of pupillometric data. Manufacturer customised original firmware in order to accommodate the indicated stimulation sequence. After a 10-minute initial acclimation to darkness, six distinct stimulation patterns are delivered to both eyes three times each. Each pupil has 18 traces, i.e. 36 signals, for each topic. On a dark background, rod function was tested using low intensity impulses. Impulses of high strength were used to test the function of intrinsically photosensitive retinal ganglion cells (ipRGCs). We also applied high-intensity stimulation on a blue backdrop to test cone function. It took 1 second to respond to each light stimulation. Fig. 2 summarises the steps of the procedure.

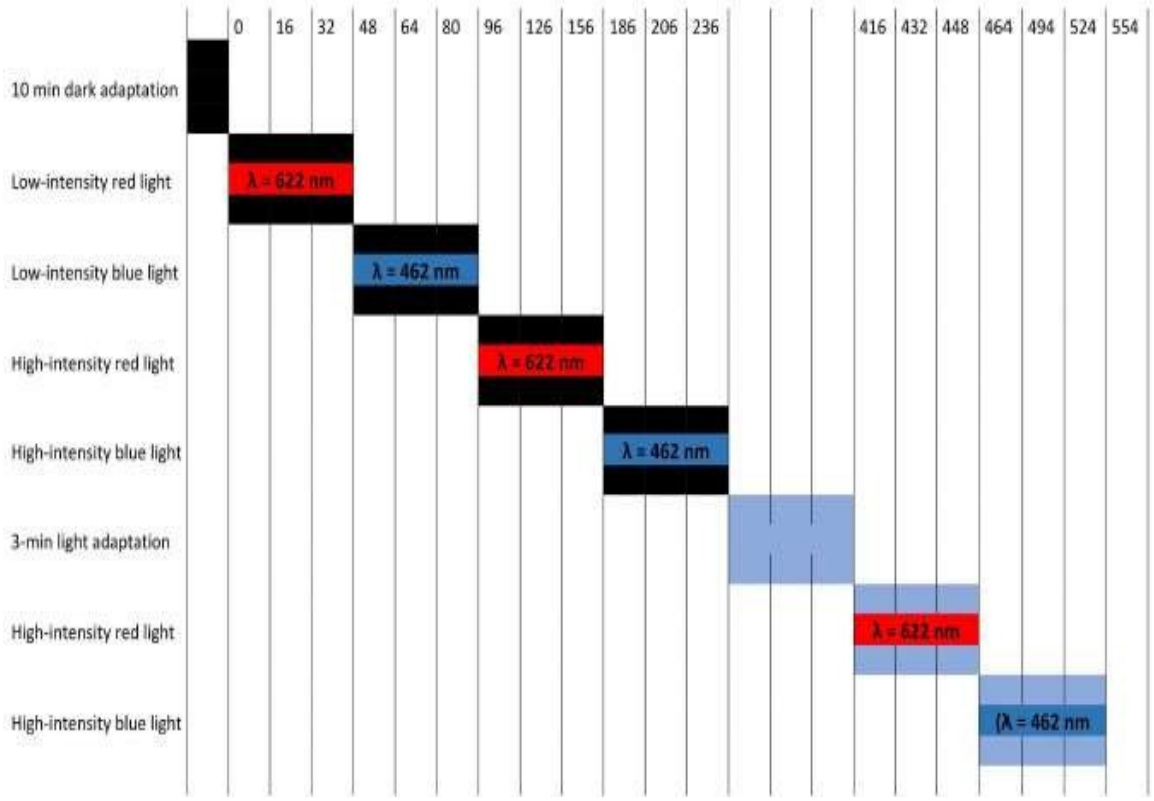

FIGURE 2. Phases of pupillometric protocol, central color is the light one and the side color represent background; numbers in the central part are the intensity of the light stimuli and on top of the scheme there is time express in seconds.

We found that 8 out of 38 test participants had signals that were considerably distorted and eliminated them from the research. Indeed, pupillometric Blinking or eye movements might impact the measurement of pupil diameters, affecting the accuracy of the measurement. Despite the fact that the system is capable of detecting blinking, this feature was not included in this first research. Impossible measurements can be corrected by stimulating the brain. Naples and Milan clinical partners assessed the quality of the remaining 30 test individuals. The main stages for the implementation of the RP classifier are shown in Fig. 3, namely: import and pre-processing of the pupillary diameter signals, pupillary feature extraction and reduction, hyperparameters optimization and, finally, training of the supervised classifier. These stages are discussed in the following paragraphs.

(1) Signal processing

After each measurement, a binocular pupillometer produces a raw les that must be analysed in order to export the appropriate data. These signals are utilised to extract therapeutically motivated characteristics of pupillary reactivity and to generate an input dataset for an unsupervised classifier. This means that, before extracting the feature set, the raw pupillometric data must be cleaned of noise and corrected for eye blink artefacts. An involuntary eye blinking during video recording is in fact connected with sudden false spikes, which might contaminate the ensuing traces of the pupil diameter, thereby decreasing their trustworthiness. Pupilometric signals are not substantially distorted by this FIR filter. Blink-related artefacts are then identified with values exceeding a suitably designed maximum threshold (0.2mm) and eliminated appropriately.

(2) Feature Extraction

From the following literature [3], [4] [5], [6] and [29], we chose the best predictive characteristics. This 8-element vector of characteristics is extracted from each pupillometric signal after pre-processing**.**

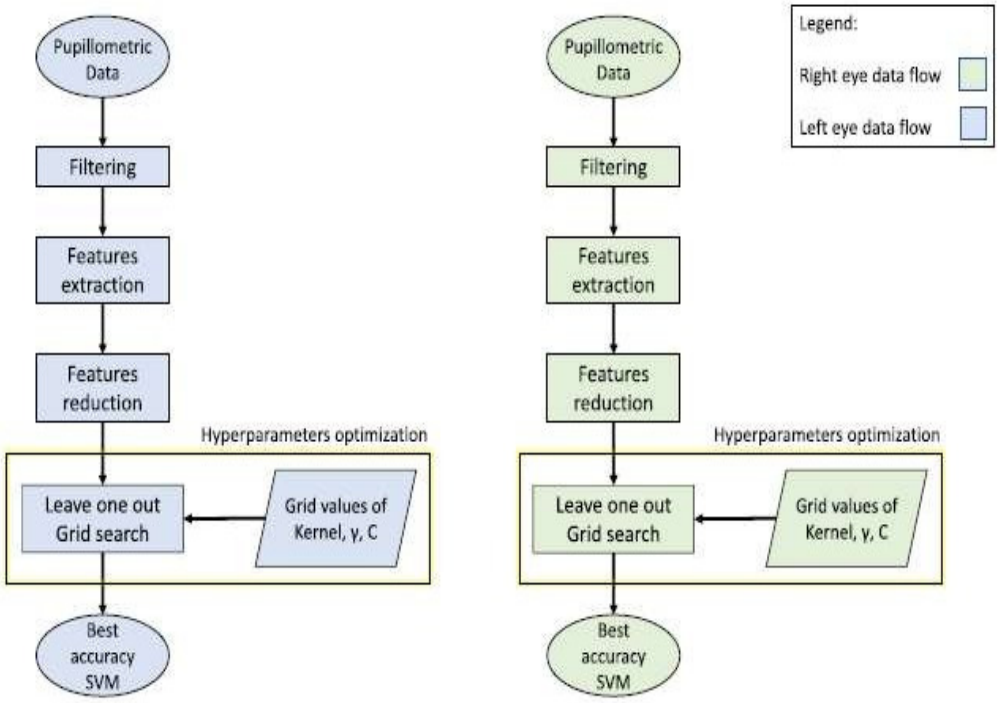

FIGURE 3. Data analysis, selection of features and optimization of the SVM parameters.

(3) Support vector Machines

First proposed byVapnik [39], support vector machines (SVMs) are supervised linear binary classifiers. Formally, SVMs are defined in terms of an optimum hyperplane. Practical classification problems, however, frequently do not allow for the separation of input datasets by a linear border. So-called soft-margin SVMs enable certain examples to reside either within or outside a given decision hyperplane during training.

(4) Feature reduction

"Results and Discussion section" explains the measuring methodology that was used to extract 288 characteristics from the 36 pupillary reactivity signals available for each participant to be classified. In order to minimise overfitting of the training dataset, feature reduction was a critical pre-processing procedure.

(5) SVM Training and Classification

Fig. 4 shows the general design of the CDSS. A subject's RP status is determined by the presence of a "Pathologic" label in one or both eyes (thus improving the global sensitivity of the CDSS). Because the artefacts may not be evenly distributed between the two eyes, this option is made. If, for example, a patient often blinks the left eye, the contralateral eye would produce a clearer signal. Because of its demonstrated solidity and flexibility, an SVM was used as supervised (eye) classification method [30]. SVM classifiers were trained by analysing the pupillometric feature vectors of 30 of the individuals.

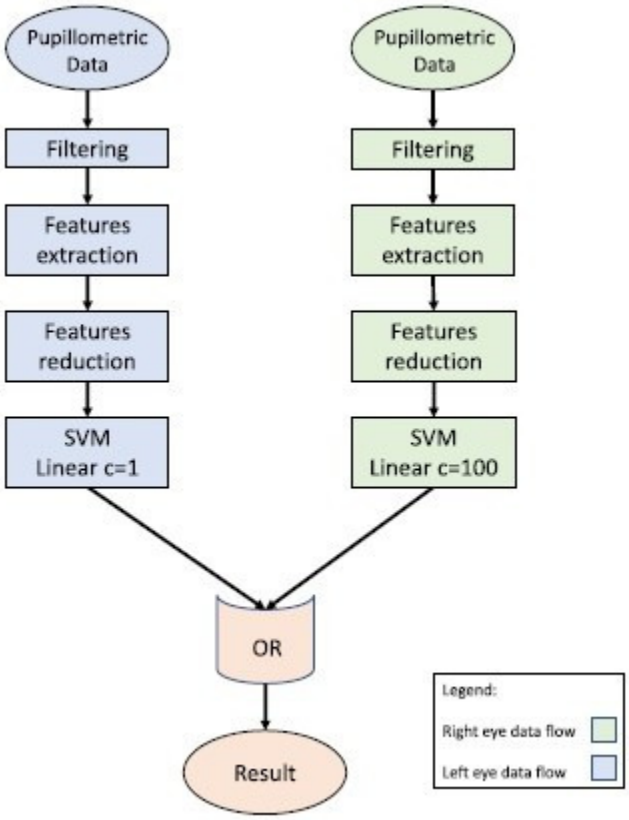

Fig. 4. Decision support process.

IV. RESULTS AND DISCUSSION

On finds in Tables 1 and 2 a combination of SVM hyper-parameters that is optimum, as determined by the data-driven tuning procedure, together with the corresponding classification accuracy for the 30 subjects. Tables 3 and 4 summarize sensitivity, specificity and accuracy for the final ensemble model . In details, these performance scores were derived by comparing the actual class of the subject - as assigned by the physician - with the class obtained by applying an OR logical operation to the two labels separately returned by the tuned SVMs for each eye. As expected, this strategy determines an increase in the overall sensitivity of the CDSS. It is worth to specifying that only one table is reported because both the linear and RBF kernel functions gave the same results in the ensemble logic.

Eye	Kernel	C	Accuracy
Right	Linear	100	86.7%
Left	Linear	1	83%

TABLE 1. Best parameters for left and right eye features with linear kernel.

Eye	Kernel	C	γ	Accuracy
Right	RBF	1000	0.001	80%
Left	RBF	1	0.1	90%

TABLE 2. Best parameters for left and right eye features with RBF kernel.

Accuracy	Sensitivity	Specificity
86.7%	93.7%	78.6%

TABLE 3. Leave-one-out validation of the ensemble model: performance.

	Pathologic	Healthy
Pathologic	15	1
Healthy	3	11

TABLE 4. Leave-one-out validation of the ensemble model: confusion matrix.

IRDs are degenerative diseases that affect the eye starting from the first years of life. Accurate diagnosis of inherited retinal disease is a relevant clinical issue. In clinical practice, the diagnosis relies on invasive test, particularly electroretinogram, which requires sedation in children/noncollaborative patients. This aspect brings the necessity of a non-invasive and accurate system to make fast diagnoses in pediatric age. 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 speci fic patient preparations with drugs or collyriums. If compared with other standard diagnostic techniques, particularly, electrorheological test, in this case no electrodes need to be placed on the patient skin: this is particularly convenient when dealing with pediatric patients. Particularly, in younger children the electrophysiological testing are usually performed in sedation, thus requiring a more complex clinical setting (i.e. availability of operating theater together with anesthesiologist).

V. FUTURE SCOPE AND CONCLUSION

This paper describes 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 a 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 so as 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. Moreover, considering the duration of the whole acquisition protocol, the procedure would benefit of some systems to capture the attention of the young patient (and his/her sight).

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