Development of a Smartphone-based Pupillometer for Neuro-ophthalmological Diseases Screening

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Abstract: Over the last two decades pupillometry gained a renewed interest, due to the discovery of intrinsically photosensitive retinal ganglion cells (ipRGCs) and their function in pupil light reflex (PLR). This technique is usually used to assess patient's neurological state and has been researched as a screening tool for neuro-ophthalmological diseases. Several automated pupillometers have been developed, as they allow a quantitative measure of PLR, but most of them are expensive and not portable, which reduces their possibility to be a widespread screening tool. Taking advantage of low price and accessible smartphone technology, a smartphone-based pupillometer was developed in this work. An Android application was developed that allows pupil's dynamic video recording and its processing for pupil detection. The preliminary tests made to validate the application and the algorithms have shown that the proposed system is a promising tool for a simple, inexpensive and portable pupillometry.

1 INTRODUCTION

Pupil light reflex (PLR) has been widely used to assess the patient's consciousness in both qualitative and quantitative ways. Over the last 20 years, due to the discovery of intrinsically photosensitive retinal ganglion cells (ipRGCs) and their function in pupil response to light (Hattar et al., 2002; Lucas et al., 2001), pupillometry gained a new interest. Particularly because these cells discovery and research showed that pupil light reflex is not only pursued by rods and cones, but also by ipRGCs, as they are sensitive to the absorption of blue light (Gamlin et al., 2007). This renewed interest in pupillometry research also lead to an increase in its potential to be applied to neuro-ophthalmological diseases screening and detection, such as Parkinson (Giza et al., 2011; Wang et al., 2016), Alzheimer (Granholm et al., 2017) or Glaucoma (Rukmini et al., 2019; Rukmini et al., 2015; Gracitelli et al., 2014)

Usually known as pupillometry, this technique allows an objective measurement of pupil's dynamic to a certain stimulus when automated. Pupillometry is non-invasive and allows a functional assessment of the pupil light reflex. With ipRGCs discovery, chromatic pupillometry also gained an important role as it allows to study different types of damage to rod, cones and ipRGCs, measuring pupil responses to red or blue light stimuli (Rukmini et al., 2019). This technique using red or blue stimuli has been studied and applied for the previously mentioned neuro-ophthalmological diseases screening.

Several types of pupillometers have been developed over the years based in infrared video acquisition, first established by Loewenstein et al. (Lowenstein and Loewenfel, 1958) with the construction of a photoelectric pupillograph in 1947. Technology improvements over the last decades allowed continuous video recording of the pupil and automatic computer data analysis, leading to a large upgrade in pupillometry technique. Since Loewenstein et al. (Lowenstein and Loewenfel, 1958) work, pupillometry has

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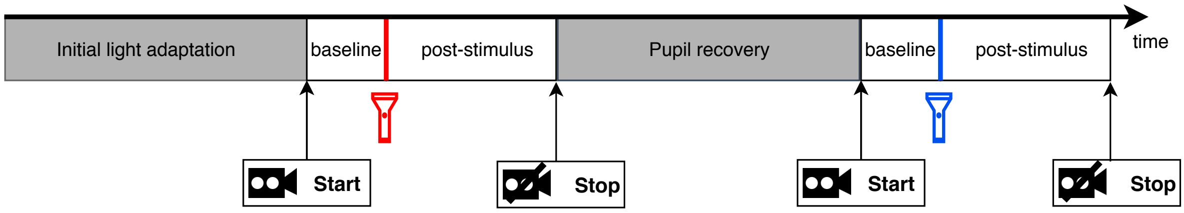

Figure 1: Chromatic pupillometry protocol schema.

been infrared camera based, which allows a proper image contrast and the environment light does not have an impact in pupil size. These type of systems, with infrared cameras, are highly effective and provide precise measurements of the pupil. However, they are also expensive, not portable and usually require some trained operator, which is a restriction for its widespread use.

Mobile smartphones industry exponential increase has brought a new interest for medicine applications, as they overcome those previously referred limitations, such as price, portability and accessibility. As smartphones are present in everyones daily routines, they could lead, in the limit, to a self-diagnosis tool easily widespread over the population. The usage of smartphones for pupillometry has started in 2013, by Kim et al. (Kim and Youn, 2013), with the development of a smartphone-based infrared video pupillometer. This device included an optical apparatus attached to the camera, with four infrared light emitting diodes (LEDs), one white LED to work as the stimuli, one infrared cut-off filter and one microcontroller. Tight occlusion around the eye was also taken care to protect the eye from environment light, to reduce its influence in PLR. All the acquired data was transfered to a laptop and the analysis was made using a proposed algorithm processed in MATLAB® (Mathworks Inc., Natick, MA).

Another smartphone app has been developed in 2016 by Shin et al. (Shin et al., 2016) used only to acquire five steady images of the eye in different stages: one before the flash, another one during the light stimuli and the remaining three photos after the flash. The acquired images were then analyzed by a clinician and compared the measurements with a penlight measurement. In this research study, no automated neither computerized algorithm was used to analyze pupil's size variations with the stimuli. The results showed that pupil size measurements with a smartphone application were similar to the ones made by a trained clinician.

More recently, McAnany et al. (McAnany et al., 2018) have developed an iPhone-based pupillometer, which uses the rear camera to capture a high speed video, its flash as a white stimulus and processes real time measurements. The major difference from this research study to the other two mentioned is the completely software based system, without the need to any external optic apparatus, and the full process being taken care by the iPhone. The algorithm used to analyze the acquired data uses a ratio between pupil diameter and iris diameter. The measurements with this system were then compared to ones acquired with an infrared pupillometer and the results were in agreement.

Although these studies show an increased potential in smartphone-based pupillometry, apart from McAnany et al. (McAnany et al., 2018) system, they do not provide a low-cost, real-time, accessible and portable device for pupillometry. The iPhone project can be considered low cost when comparing to the industrial pupillometers, but comparing to other smartphones is a high range one. It is also important to notice that the referred studies using smartphones do not specifically target chromatic pupillometry, which has been studied as a proper neuro-ophthalmological diseases screening method (Rukmini et al., 2019).

The present study aims to describe an all-in-one smartphone-based chromatic pupillometer using a medium range Android device. All-in-one indicates that the smartphone is used to acquire and process the pupillometry data, running image processing algorithms through the Android application, without the need of high computing machines. The main goal of this study was to show Android capability to perform chromatic pupillometry measures and to run pupil detection algorithms in real-time.

2 METHODS

Given the state-of-the-art of mobile pupillometers, it is intended to develop a low cost system using a medium range Android smartphone, with a camera to allow pupil recording, a flash to work as a stimulus and with enough capability to run image processing algorithms. The system should also allow chromatic pupillometry, using both blue and red stimuli in order to be used to screen neuro-ophthalmological diseases according to the recent findings and protocols.

The acquisition protocol should start with a period for the eye to adapt to the environmental light conditions, then the recording period with some initial time to acquire pupil's baseline, then a short colored light stimulus flash followed by a post-stimulus period. Before a new acquisition a pause should be made for pupil recovery and the process should then be repeated with change of light stimulus color. A representation schema of this type of protocol is shown in Figure 1. Each of the protocol periods duration should be tested and optimized in future work, particularly to be applied to neuro-ophthalmological pathologies such as Alzheimer, Dementia, Glaucoma or Parkinson.

Essentially, the main goal is to develop a system with all these characteristics, that could be, in the future, used in any Android device as a tool spread through the population for neuro-ophthalmological diseases early screening.

2.1 System Architecture

The system proposed in this work consists only in a smartphone that allows acquiring and processing the pupillometric data. Development was made using a Nokia 7 Plus (Nokia Corporation, HMD Global, Finland) which is an Android One device, with Android 9 Pie operating system (Android sdk 28). The application was developed in Java programming language using Android Studio (IntelliJ® Platform). Video and image processing was made using OpenCV library (Open Source Computer Vision Library) with Java Native Interface (JNI) framework, which allows Java to run C or C++ code, being then incorporated in the Java Android application.

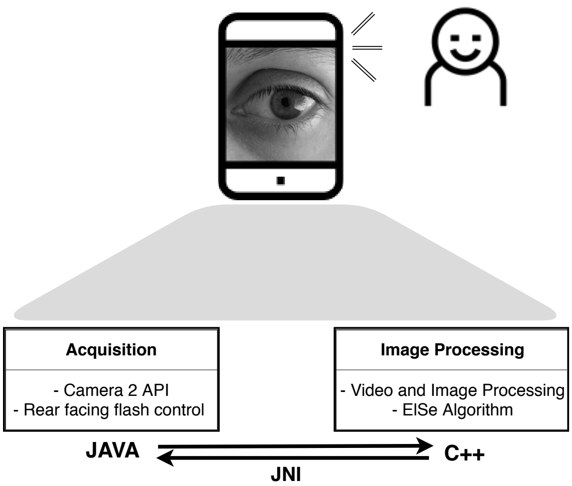

Figure 2: Proposed system architecture.

For the acquisition part of the application Android's Camera2 API was used, which provides an interface to individual camera devices available in the smartphone and proper adjustments of the recording and image characteristics. In this case, Nokia 7 Plus has one front camera and two rear cameras. The rear-cameras are considered as one logical camera by Camera2 API, which means that it is not possible to access each of the physical rear cameras, they work as one, so when changing recording characteristics the result comes from both physical cameras combined in one image.

Camera2 API also allows to control rear-facing flash light, which was used as light stimuli for pupillometry measures. The spectral emission of the rear-facing flash of the Nokia smartphone was measured using a spectrometer (AvaSpec - Mini2048CL - UVI25 by Avantes, Netherlands) and the average resultant of three acquisitions made is shown in Figure 3.

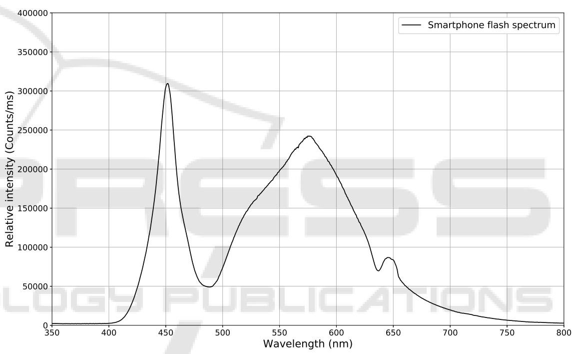

Figure 3: Spectral emission characteristics of the rear-facing camera flash of the Nokia 7 Plus.

To allow chromatic pupillometry, a simple filter made with standard grade cellophane paper, with blue or red colors, was placed in front of the rear-facing flash. In this way the color of the flash gets filtered to get blue or red flash lights, whose spectra, which was also acquired with Avantes spectrometer, are shown in Figure 4. This low cost and easy solution to get colored stimuli allows to get the proper wavelength light stimuli (red and blue), according to literature.

2.2 Video and Image Processing

After video acquisition, the second main part of the proposed smartphone application is the video and image processing algorithm. Using OpenCV for Android and C++ language, as previously referred, the acquired video is then processed, converted to frames and pupil is detected in each frame through a proper algorithm.

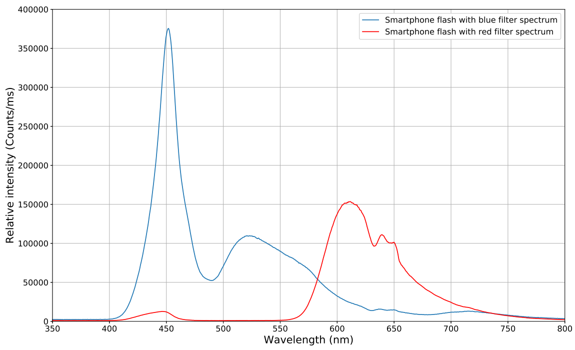

Figure 4: Spectral emission characteristics of the rear-facing camera flash of the Nokia 7 Plus with red and blue filters.

The acquired video does not contain only the eye, but also some part of subject's face, due to the distance to the smartphone to allow proper image focus. To overcome this and to reduce non relevant information in the image for the application of pupil detection algorithm, an eye detection algorithm is applied. OpenCV offers a pre-trained Haar cascade algorithm for face and eye detection, based in Viola and Jones Haar cascade object detection algorithm (Viola and Jones, 2001).

In this work, OpenCV Haar cascade eye detection was applied to each frame,and was then cropped in the obtained location. This algorithm sometimes fails and considers some other part of the image to be an eye; these detections with smaller size were automatically discarded.

After eye detection, a process was made as summarized in Figure 5 in order to detect the pupil. Contrast Limited Adaptive Histogram and ElSe Algorithm are going to be further explained in 2.2.1 and 2.2.2.

2.2.1 Contrast Limited Adaptive Histogram

One of the problems of images acquired with non infrared cameras or in non ideal lightning conditions is the low contrast ratio between iris and pupil, particularly in dark colored iris. To overcome this situation, a contrast enhancement of the image increases pupil's visibility.

Histogram equalization distributes the intensities on the histogram, leading to an increase in the global contrast of an image. It is highly efficient and simple, however it can produce "washed out" effect or can destroy the brightness of the image.

Adaptive Histogram Equalization allows locally enhancement of the contrast, as it perform histogram equalization in different sections of the image redistributing the lightness values of the image. One of the main problems of this technique is the high computational complexity, not being favorable for real-time applications.

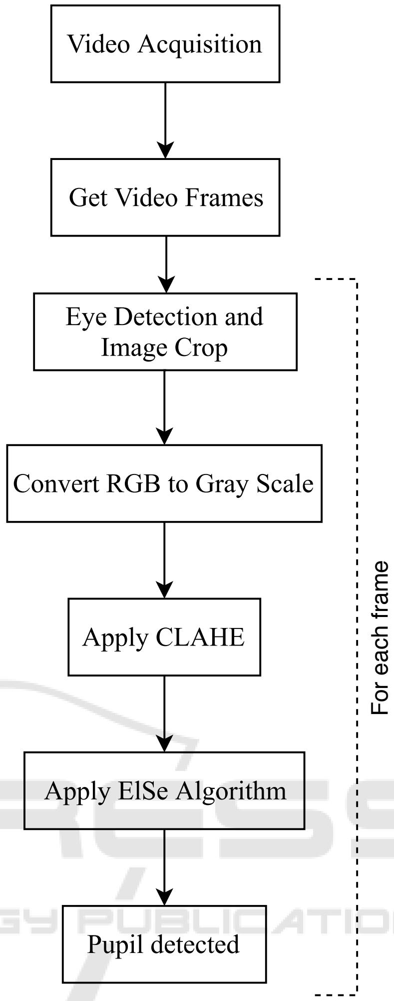

Figure 5: Flowchart of the image processing algorithms.

An extended case of adaptive histogram equalization is Contrast Limited Adaptive Histogram Equalization (CLAHE), which performs an histogram clipping at some threshold and redistributes the image using the maximum values. It has a lower computational complexity and prevents over-amplification of noise signals.

According to Hassan et al. (Hassan et al., 2017), CLAHE algorithm outperforms a simple histogram equalization or an adaptive histogram equalization for iris recognition. Taking these results into consideration, in this work CLAHE was tested and applied to video frames before running the pupil detection algorithm, using the OpenCV CLAHE function with cut limit = 4.

2.2.2 Pupil Detection Algorithm

After image acquisition and eye detection, the concern rests in pupil detection algorithms as one of the main parts in automated pupillometry systems. It is important to clarify that pupil detection refers to finding its center and size (area or diameter) in the image, either in pixels or converted to some unit of measure. There are some difficulties regarding achieving this, that can go from low contrast images, blur, illumination issues and many others.

With the increasing interest in automated pupillometry has also increased the need to have better and more precise pupil detection algorithms. Particularly, as the applications of pupillometry are being studied to be in real-world environments and not only under laboratory and controlled conditions.

One of those is ElSe algorithm, developed by Fuhl et al. (Fuhl et al., 2015), based on ellipse evaluation of a filtered edge image thought to be applied in real-world scenarios, such as in-door environments or during driving. In a state-of-the-art review published in 2016 (Fuhl et al., 2016) that compared several pupil detection algorithms behavior has considered ElSe algorithm as a gold standard for pupil detection. This is an open source algorithm which is the one chosen to be used in the system proposed in this work, due to its easy access and it is targeted for real world environments, which is what having a smartphone-based pupillometer pursues.

The input is a gray scale image and in a very summarized way the algorithm tries to find an ellipse that could most likely be the pupil. First applies a Canny filter to have the image edges, then they are filtered using straightening patterns, the straight lines are removed and the best ellipse is selected through least square ellipse fitting. The final step is the ellipse evaluation, excluding those that are unlikely to be pupils. If this first process fails there is a second approach that the algorithm tries through coarse positioning. This second analysis is made by downscaling and convolving the image with two different filters: a surface difference filter and a mean filter. The results of both convolutions are multiplied and the maximum value is the starting point to be refined. The surrounding pixels of this point is verified, and the new pupil position is the center of mass of the pixels under this threshold.

Even though ElSe algorithm was developed to real-world scenarios it is important to notice that it was tested and validated in datasets acquired with infrared cameras, which in most of the cases have a very evident pupil. In the present work, this algorithm was applied to images acquired using Nokia 7 Plus smartphone camera, without any optical apparatus, as a preliminary test and validation of the proposed solution. Some of Fuhl et al. (Fuhl et al., 2015) datasets possess eye images where the pupil is hidden, sideways or even more far-fetched scenarios. In this preliminary study, ElSe algorithm was only applied to images where the pupil is normal, with subject looking straight forward and the pupil is not occluded by eyelashes for example.

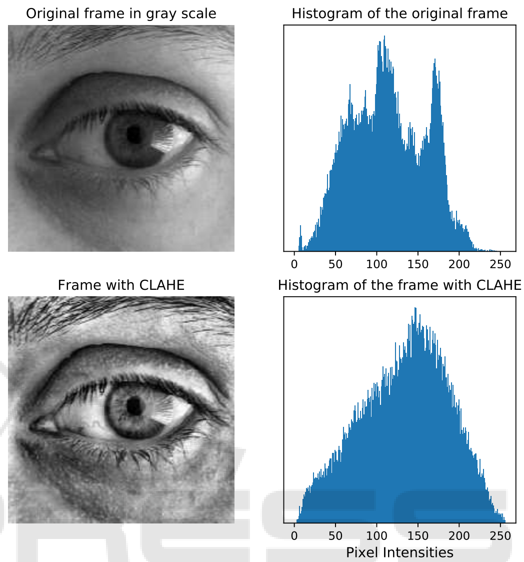

Figure 6: Original video frame in gray scale with and without CLAHE with respective histograms.

3 PRELIMINARY RESULTS

First, pupil detection algorithm running in the Android application was validate with eye images datasets published by Fuhl et al. (Fuhl et al., 2015). As expected, pupil center and size were the same as Fuhl research group has labeled. This simple test was just to guarantee that ElSe algorithm was properly running in the Android application, considering the system architecture and the linkage between programming languages.

Preliminary tests were made using the developed smartphone application to acquire videos of the eye and apply the processing algorithms to get the pupil. ElSe algorithm was tested in frames with and without CLAHE. An example of the same frame with and without CLAHE is shown in Figure 6 with the respective histograms.

The image processing algorithms proposed in this work for each frame are exemplified in Figures 7 and 8 with a frame from a video acquired with the developed smartphone application.

Table 1: Pupil parameters mean values obtained for 41 images with and without CLAHE. Unit of measure: pixels.

Pupil parameter	Original Image	Image with CLAHE
Center	$(124 \pm 6,\ 106 \pm 5)$	$(124 \pm 6,\ 106 \pm 5)$
Height	20 ± 8	21 ± 7
Width	19 ± 7	19 ± 6
Angle	108 ± 32	105 ± 36

The pupil detection algorithm with and without CLAHE was also applied to 41 frames from the same acquisition made with the same person. The average results for these 41 images are summarized in Table 1 for both CLAHE and non CLAHE algorithms. From this test it is possible to verify that the results are similar in terms of center, height and width, being the angle the most different value, in average, and with higher standard deviation.

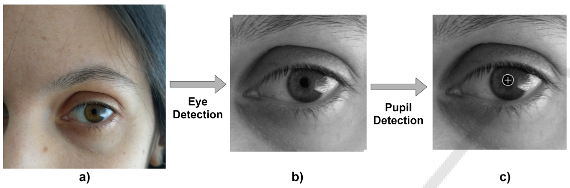

Figure 7: Image Process Schema. a) Frame from the video acquired using the smartphone-bases pupillometer with Nokia 7 Plus; b) Cropped image around the eye obtained through eye detection algorithm; c) Eye image with pupil detected.

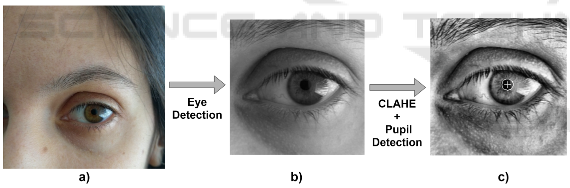

Figure 8: Image Process Schema with CLAHE. a) Frame from the video acquired using the smartphone-bases pupillometer with Nokia 7 Plus; b) Cropped image around the eye obtained through eye detection algorithm; c) Eye image with CLAHE and pupil detected.

With the images acquired in these preliminary tests this algorithm seems promising to deal with images acquired with this smartphone camera without any optical apparatus and further tests should be made to better validate the proposed algorithm.

4 CONCLUSION

Using low-cost, portable and accessible technology for medical applications, particularly for screening and monitoring diseases, is gaining interest and market all over the world. The usage of a smartphone for this purpose is a smart and easy way to spread early screening and make it more available and accessible to everyone and all over the world. This work proposes a solution for pupillometry measurements with a smartphone, which overcomes the main problems with the existing pupillometers to spread this technique into medical and screening usage. The preliminary tests made with the proposed prototype indicate a great potential of this solution, particularly due to its low price, easy accessibility and portability. Another advantage of the proposed system is that it only needs the smartphone, diminishing the requisites of high range technology and apparatus. To perform chromatic pupillometry it needs a standard grade cellophane paper, which, in the future in a commercial solution, can be available as a kit to complement the smartphone application.

Further work is to improve the algorithms for pupil detection and make more validation tests. It is also relevant to test this solution in different light conditions and make some adjustments in the camera recording characteristics in order to get a more efficient and precise pupillometer application.

After these improvements and algorithm validations, the next step should be validating this smartphone-based pupillometer for neuro-ophthalmological diseases screening, using the colored filters to apply colored stimuli allowing to do chromatic pupillometry. With these colored stimuli, should be tested different acquisition protocols that could early screen pathologies as Alzheimer, Dementia, Glaucoma or Parkinson in a portable and accessible way.

In general, a smartphone-based pupillometer seems to be the future of pupillometry to lower the gap between academic research and clinical application. The preliminary tests made with the proposed system show its potential to be used as a pupillometer and, in the future, to screen and monitor neuro-ophthalmological diseases.

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