Towards Glaucoma Detection Using Intraocular Pressure Monitoring

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***Abstract*—Diagnosing the glaucoma is a very difficult task for healthcare professionals. High intraocular pressure (IOP) remains the main treatable symptom of this degenerative disease which leads to blindness. Nowadays, new types of wearable sensors, such as the contact lens sensor Triggerfish®, provide an automated recording of 24-hour profile of ocular dimensional changes related to IOP. Through several clinical studies, more and more IOP-related profiles have been recorded by those sensors and made available for elaborating data-driven experiments. The objective of such experiments is to analyse and detect IOP pattern differences between ill and healthy subjects. The potential is to provide medical doctors with analysis and detection tools allowing them to better diagnose and treat glaucoma. In this paper we present the methodologies, signal processing and machine learning algorithms elaborated in the task of automated detection of glaucomatous IOP-related profiles within a set of 100 24-hour recordings. As first convincing results, we obtained a classification ROC AUC of 81.5%.**

***Keywords*-Glaucoma diagnosis; biomedical signal processing; machine learning;**

I. Introduction

According to the World Health Organization (WHO), glaucoma is the second most frequent cause of blindness in the world. More than 80 million people worldwide suffer from this asymptomatic and painless disease of the eye. Development of glaucoma usually comes along with an increase of intraocular pressure (IOP) which gradually damages the optic nerve at the back of the eye. This leads to a progressive and irreversible loss of vision for affected patients. Thus, a high IOP is a major risk factor of glaucoma.

However, IOP is subject to variations depending on individuals' body circadian cycles and activities, such as physical activity, food intake, stress, emotions and sleep periods throughout day and night. Measuring it punctually with usual tonometers is not sufficient to capture its continuous changes throughout a 24 hour cycle. Understanding how IOP evolves and detecting patterns that truly characterize a glaucomatous profile has become a necessity for healthcare professionals to detect glaucoma early and prevent the loss of vision. The contact lens sensor (CLS) Triggerfish®, developed by the swiss company Sensimed [1], is a sensor that provides such an automated recording of 24-hour profile of ocular dimensional changes related to IOP. This company is now leading clinical studies over the world to record IOP-related profiles and build a growing database dedicated to research on glaucoma.

In this paper, we report on a research work done in collaboration with Sensimed for the application of signal analysis and machine learning techniques on 24-hour profiles data recorded from healthy and ill subjects suffering from glaucoma. This paper is organized as follows. Section II gives an overview of the existing related work. Section III gives a description of the data acquisition system, i.e. the CLS Triggerfish® and the constituted database of IOP-related profiles. Section IV presents the statistical and physiological features which were extracted. In Section V, we presents the machine learning techniques as well as the evaluation protocol that were applied to perform the automated detection of glaucomatous profiles. Finally, in Section VI, we present and discuss the obtained results.

II. Related Work

Machine learning (ML) applied to medical data for diagnosis diseases is not a new topic. Different pattern recognition techniques have been applied for the detection of various diseases like Alzheimer's, Parkinson's, diabetes, just to name a few. Cruz *et al.* [2] made a survey on ML

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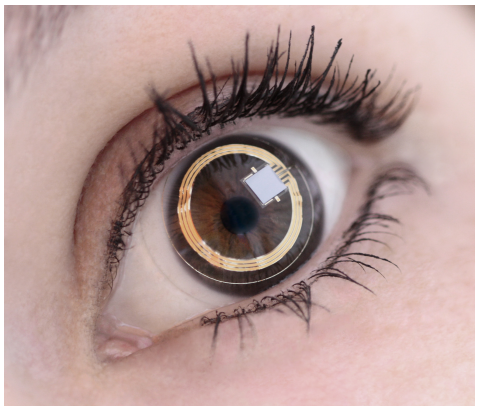

Figure 1. The contact lens sensor Triggerfish® set up in the eye.

methods (naive Bayes, k-NN, SVM, ANN, decision trees, genetic algorithms) and their applications in cancer prediction and prognosis. Gayathri *et al.* [3] made a survey of 47 articles published between 2005 and 2013 and related to ML approaches applied for the diagnosis of many categories of heart diseases. In particular, Salem *et al.* [4] made a consequent survey on ML approaches to electrocardiogram (ECG) classification for the diagnosis of cardiovascular diseases (CVD), evaluating them in terms of classifiers used (SVM, HMM, ANN, fuzzy and hybrid approaches), features extracted, types of CVD and classification accuracy. Analysis and feature extraction on ECG and IOP-related profiles are rather analog as they call on the same signal processing techniques.

Some other works, more focusing on glaucoma detection and using ML techniques, can be mentioned. Goldbaum *et al.* [5] trained and tested by cross-validation three classifiers (MLP, SVM and GMM) on the task of diagnosing glaucoma from standard automated perimetry[1] of 189 normal eyes and 156 glaucomatous eyes. GMM gave the best ROC AUC of 92%. Sample *et al.* [6] compared two ML classifiers (GMM and SVM) to predict development of abnormal fields at follow-up in ocular hypertensive eyes that had normal visual fields in baseline examination. They obtained a specificity of 96% for both classifiers using data from 94 eyes. Goldbaum *et al.* [7] applied unsupervised ML techniques (clustering) to identify patterns of glaucomatous visual field loss in sita fields automatically identified using variational bayesian-independent component analysis. Their best model yielded three clusters corresponding to classes *normal field*, *mildly abnormal field* and *severely abnormal field*, with an average sensitivity of 88.9% for the two last. These results are quite good because classifications were based on the visual field whose loss is a consequence of the glaucoma, unlike the IOP whose rise can be a direct cause. So, glaucoma detection from IOP changes might lead to glaucoma prediction.

Continuous monitoring of ocular dimensional changes related to IOP, analysing the resulting patterns and applying ML techniques on this kind of medical data is quite new, mainly because the patented used technology is recent and profile data have just began to populate the database for research.

[1] *Perimetry* is obtained by measuring the visual field and allows to define the extent and progression of glaucoma.

III. Data Acquisition

Acquisition of data was supervised by Sensimed throughout clinical studies performed over the world. The company has developed a new technology of wearable contact lens sensors and started to populate a growing database with patient IOP-related profiles.

As the intraocular pressure varies with time, the contact lens sensor (CLS) Triggerfish® (Fig. 1) provides an automated recording of continuous ocular dimensional changes over 24 hours. Measurements are obtained in millivolts (mV) proportional to the circumferential deformation of the strain gauge (Fig. 2). A correlation between IOP changes in common mmHg and CLS-obtained mV has previously been shown [8]. The current CLS version records these changes during continuous periods of 30 seconds every 5 minutes. These short acquisition periods are called *bursts*. The CLS has a sampling frequency of 10 Hz, yielding 300 points per burst [9][10]. Therefore, recorded IOP-related profiles consist of series of bursts. To observe the general shape of a profile, we compute the median of each burst (i.e. all points it contains) and plot the series of all obtained burst medians of the profile (Fig. 4, top panel).

The CLS system is sensitive, safe and non-invasive. Its installation and removal on the patient is simple and executed by a healthcare professional. The patient wears the device up to 24 hours during which he keeps doing usual activities (including sleeping). The system works as follows. The soft disposable silicone CLS embeds a micro-sensor which measures spontaneous circumferential variations at the corneoscleral area. Placed around the eye, an adhesive antenna receives the data from the CLS over the air. The data is then transmitted to the wearable recorder (Fig. 3). The recorder stores the acquired data during the monitoring session. At the end of the recording, the data is transferred via Bluetooth to the dedicated software installed on the practitioners computer. Finally, the data is sent via Internet to Sensimed for statistical analysis and modelling.

After pooling of data from clinical studies in several countries, a database of 100 selected IOP-related profiles was built up and ready for the feature extraction.

A. Tools Used

A Java utility software was developed to visualize the profiles and manage the data, the feature extraction and the glaucomatous profile classification (Fig. 4).

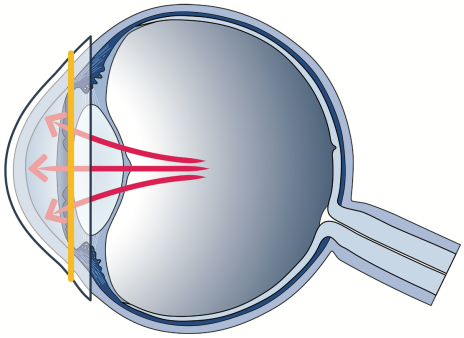

Figure 2. As IOP fluctuates, circumferential dimensional changes in the area of the corneoscleral junction of the eye are captured by the highly sensitive strain gauge of the contact lens sensor Triggerfish®.

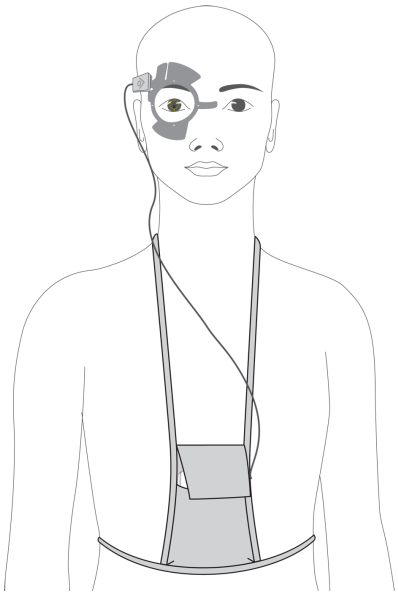

Figure 3. The Triggerfish® full equipement is composed of the contact lens sensor, the adhesive antenna and the wearable recorder.

IV. Feature Extraction

The feature extraction is an essential stage of any machine learning process. For the classification to be efficient, powerful and meaningful features had to be extracted from the profile raw data. A challenge was to find out new features without having any a priori knowledge on the information potentially contained in the IOP-related profiles. Glaucoma is still a mystery for medical doctors and this kind of data is quite new and never used before.

A. Statistical Features

As first features, we computed several statistical values from the burst medians of each profile: the minimum, the maximum, the amplitude, the mean, the median, the standard deviation and difference between the first and last (profile curves would seem to go up or down throughout the recording period). Then, in order to model the shape

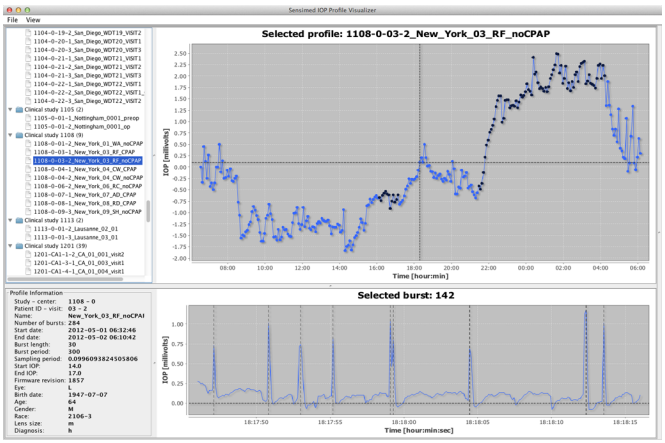

Figure 4. The Java tool developed to visualize profiles, extract features and perform classification

of each profile curve, we computed some polynomial fitted curves [11] and took their various polynomial coefficients as features. Finally, a frequency analysis was done: raw frequency values as well as filter banks were taken as features.

B. Physiological Features

As second features, we extracted several physiological values from the profiles. This is certainly the most interesting and important part for medical doctors, because in the case where the automated classification of glaucomatous profiles works well, the latter shall know why by getting physiological reasons corresponding to these features. By observing the profile signal, three physiological phenomena can be identified:

1) Eye blinks, appearing during wake periods (Fig. 5)
2) The ocular pulse, which appears particularly well during sleep periods (when there are no blinks) and is the manifestation of the heart beating (Fig. 6)
3) The slope of the curve, which seems to be different at the start and the end of the sleep period, depending on the subject diagnosis (Fig. 4)

C. Implemented Algorithms

To compute these physiological features, the following algorithms needed to be implemented.

1) Eye Blink Detection: A blink can be characterized as a sequence of three successive and continuous local extrema in the signal: first a local minimum (the start point), then a local maximum (the peak) and finally a local minimum again (the end point). All burst points are chronologically parsed. Each point may potentially be the peak of a new blink. A given candidate point can be the peak of a blink only if the sequences of nearby points toward the left and the right are strictly monotonically decreasing until reaching a local minimum, namely the blink start and end points. When such

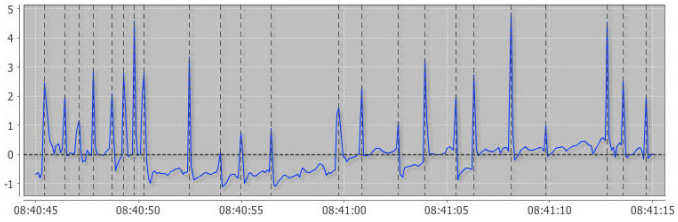

Figure 5. Example of the blink detection in a burst.

points have been found, the difference between the peak and the start as well as the end point is computed. When these differences are significantly greater than the mean amplitude of all bursts of the profile, a blink is detected. As soon as we have detected blinks with this algorithm, we are able to perform various measures and statistics over the recorded patient profiles. The blink rate is measured in blinks/minute and corresponds to the number of blinks occurring during a certain period. The blink duration is measured in seconds and corresponds to time difference between the start point and the end point of a blink. The inter-blink interval, also measured in seconds, corresponds to the time difference between the end point of a blink and the start point of the following blink. Finally, the blink amplitude is defined as the extent of signal rise from the mean of the start and end points of the blink to the peak blink signal. Blinks provide useful features but can also be considered as noise in the IOP signal variation during the wake time. Being able to detect them, and particularly their start and end points, enables deletion of these from the signal of the profile bursts. A simple linear interpolation is then applied to fill in the resulting gaps (Fig. 5).

2) Sleep and Wake Period Detection: Blinks occur mostly during the wake time and can be used to detect sleep and wake periods. During the sleep, there are no blinks, patients are asleep, the signal is more stable and reveal different phenomena that can be extracted and used as features. Three sleep period detection methods were developed.

0BIB (Zero Blink In Bursts) – As part of the proposed blink detection algorithm, efforts were made to detect bursts with an absence of blinks in a given profile. It was estimated that the probability of these periods corresponding to a subjects sleep would be high. There are, however, potential drawbacks to this method. The absence of blinks in bursts does not ensure that a subject is sleeping, nor that his eyes are closed. For instance, prolonged fixation at an object for the entire burst duration can take place in the absence of blinking. Moreover, the blink detection algorithm itself can be subject to errors, especially type II errors, when highly varying IOP patterns are detected as blinks. Such patterns can occur during the rapid eye movement (REM) stage of sleep, when eye movements occur with closed eyelids. A single false positive signal in a burst during sleep would label that period as *awake*, causing a gap to appear in the surrounding sleep period.

BMLT1 (Blink Mean Less Than One) – This method was developed to avoid some shortcomings of the *0BIB method*. All bursts in a profile are scanned and the mean numbers of blinks over N consecutive bursts are computed. If an obtained mean value over N bursts is less than 1, the subject is assumed to be asleep for the duration of those bursts. By taking the blink mean, the context of the nearby bursts is taken into consideration, which avoids detecting a short wake period (type II error) of 1 or 2 bursts during a known sleep period. This method is assumed to produce more consistent results and more homogenous detected wake and sleep periods. However, this second method still has the drawback of depending on blinks, whose absence does not ensure a sleep state.

BLAM (Burst Local Amplitude Medians) – This method is based on the shape of the burst and does not depend on blink detection. First, in every burst of a given profile, a sliding window (i.e. a considered portion of the burst) is shifted. At each step of the shift, the amplitude of the signal is computed inside the window. Hence for each burst, a vector of *local amplitudes* is yield. Then, the median of the computed vector is compared with a dynamical threshold proportional to the mean of the global amplitudes of all bursts in the profile. This global mean burst amplitude strongly depends on the eye activity during the wake time (e.g. the blinking) and hence is largely bigger than local amplitudes computed on portions of the signal containing most of the time no eye activity. Looking at the IOP signal in bursts, it appears that the amplitude at a blink peak is about 8 times bigger than the one at an inter blink. Finally, a constraint ensuring that a sleep period contains at least 5 bursts stated as *asleep* was added to the algorithm.

To evaluate the elaborated sleep and wake period detection methods, a ground truth was required for comparing with the obtained results. Therefore, wake and sleep periods of all profiles were visually parsed and manually annotated by an experienced examiner. The resulting annotations were compared with the patient-reported sleep times from the diary when available. The accuracy of the methods was subsequently computed by comparing each burst result with its corresponding burst annotation. The best result was obtained by combining both BMLT1 and BLAM with an accuracy of $95.2 \pm 0.5\%$. Then, considering the detected wake periods of the whole profile set, we obtained a mean blink rate of 29.8 ± 1.9, a mean blink duration of 0.26 ± 0.03 sec., a mean inter-blink interval of 1.91 ± 0.25 sec. and mean blink amplitude of 116.0 ± 69.0 mV.

3) Ocular Pulse Detection: Ocular pulse is obtained by measuring the heart rate transmitted into the eye via the perfusion of the optique nerve. Characterised by its frequency, duration and amplitude, the ocular pulse can be typically observed in bursts during sleep periods (Fig. 6).

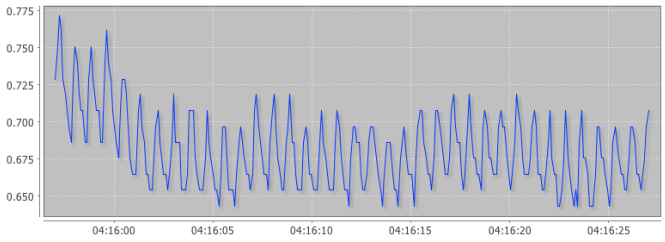

Figure 6. Example of burst captured during a sleep period. The ocular pulse, caused by the beating heart, is visible within the IOP recorded signal.

The ocular pulse detection algorithm works as follows. In a given profile, a sliding window is shifted over each burst in order to identify IOP signal parts which are suitable enough to detect ocular pulses. Such parts must contain no eye blink and no hole. In every frame, the continuous component of the signal is removed to avoid side effects in the frequency analysis. Furthermore, to increase the frequency precision of the Fast Fourier Transform output, signal frames were zero-padded to reach a length of 8192 (2^{13}). Then, a maximum (peak) is searched in the frequency band which is related to the heart rate, namely between 0.8 Hz (48 beats/min.) and 1.8 Hz (108 beats/min.). The maximum found corresponds to the ocular pulse whose amplitude and frequency values are then retrieved. However, the signal sometimes contains some considerable noise (due to several possible artefacts) potentially leading to lots of unwanted noisy frequencies within the ocular pulse frequency band. In that case, the maximum found will be too weak relatively to its neighbourhood to ensure that the computed ocular pulse is reliable and relevant. Therefore a quality rate value QR has been elaborated to measure the prominence strength of that maximum. Let $\sum_{amp1}$ be the sum of amplitudes of all frequency values within a 4 Hz wide neighbourhood of the maximum (2 Hz on the left and 2 Hz on the right), and let $\sum_{amp2}$ be the sum of amplitudes of all remaining frequency values within the ocular pulse frequency band. The QR value has been defined as: $QR = \sum_{amp1} / \sum_{amp2}{}^2$ Empirical verifications on various IOP profiles shown that if $QR > 3.7$ the ocular pulse found can be considered as reliable and relevant.

The mean ocular pulse frequency computed on all profiles was equal to 60.4±3.9 beats/min. during sleep periods and 71.1±8 beats/min. during wake periods. The mean ocular pulse amplitude during the same periods was equal to 0.057±0.017 mV and 0.075±0.024 mV.

4) Smooth Curve Slope Computation: Some medical doctors having observed many profiles supposed the slope of the curve at the start and the end of the sleep period to be potentially a discriminating feature. To obtain them, we simply computed the slope of the smoothed profile curve at these places. In order to smooth the curve, we applied the Loess regression algorithm [12].

V. Glaucomatous Profile Detection

Once the feature extraction was done, we could at last tackle the problem of detection of glaucomatous profiles, i.e. the IOP-related profiles recorded from patients having an established glaucoma. This detection problem is in fact a classification task consisting in separating the glaucomatous profiles from the healthy in a given set. Hence, a machine learning algorithm and an evaluation protocol had to be set.

A. Selected Machine Learning Algorithms

Two machine learning algorithms were tested: Gaussian Mixture Models (GMM) and Support Vector Machines (SVM). As GMM performed worse than SVM in this binary classification task, they were put aside. SVM is a recent algorithm that finds the optimal hyperplane, namely the one which maximizes the margin between the 2 classes (e.g. glaucomatous and healthy profiles), by mapping the samples to a higher dimensional space where they are linearly separable. We used *LIBSVM*, which is a well known and efficient Java library for Support Vector Machines [13].

B. Evaluation Protocol

Much classification tests were done on various training and test sets composed of randomly selected IOP-related profiles. Among these tests, we used a classical data mining approach composed of a training and a test sets where the data used for testing have not been used to train the classifier. The training set was balanced in terms of number of healthy and glaucomatous profiles. However, the results could vary a lot, depending on the train and test composition. For instance, we noticed that if profiles coming from the same clinical study were contained in the same train set, the efficiency of the classification of profiles coming from other studies in the test set would fall down. Indeed, every clinical study has its own characteristic subject population (e.g. some studies may have only healthy subjects or patient suffering from a particular type of glaucoma).

Therefore we set a protocol in order to evaluate the performance of our classification algorithms. We decided to do a k-fold cross-validation [14], where $k = 10$. All profiles were mixed and randomly partitioned into $k = 10$ balanced homogenous subsets. By homogenous we mean that the folds had to contain profiles coming from different clinical studies. The cross-validation process consisted then in taking successively each of the k-folds for testing and the remaining $k - 1$ ones (i.e. 9) for the training. At last, the k obtained accuracies, ROC AUC, etc. were averaged to give unique estimations.

VI. Results and Discussion

After having tested all feature combinations, the one with all features has come out to be the best. Knowing that SVM have precisely the quality to deal with all features to find the most discriminating hyperplane, it was not surprising.

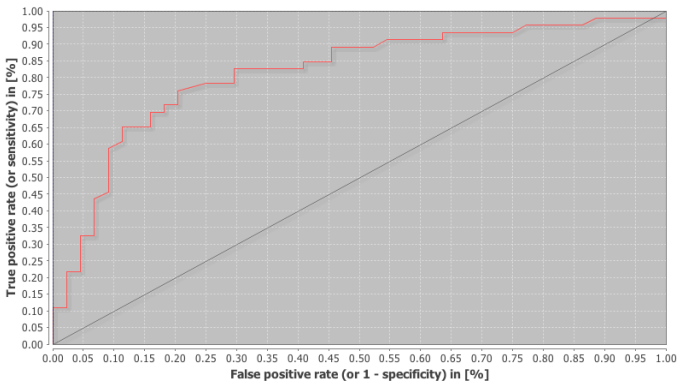

Figure 7. Best ROC CURVE obtained with SVM for the classification of glaucomatous IOP-related profiles (ROC AUC = 81.5%±7.6%)

Finally, having tuned our SVM [15] and found the best parameters C and γ for the RBF (gaussian) kernel, we got as glaucomatous IOP-related profile classification an accuracy of 76.7±8.2%, a precision of 74.5±8.5%, a recall of 82.6±7.4% and a ROC AUC of 81.5±7.6% (Fig. 7).

At the time we run our tests, the number of available valid profiles were still too small for the machine learning part to provide stable results. The growing IOP-related profile database provided by Sensimed pushes us to go on with this research, improve our algorithms and get better results and knowledge on glaucoma in order to provide healthcare professional with efficient diagnosing and even predicting tools. However, getting more data is not sufficient. As in any machine learning problem, we have to be sure that the available data covers the statistical distribution of the system to model.

VII. Conclusion

In this paper, we reported on a research work done in collaboration with the company Sensimed in the task of detecting glaucoma from IOP-related profiles. The data were acquired with CLS Triggerfish®. At first, we put efforts in the extraction of statistical and physiological features. Algorithms for detecting eye blinks, sleep periods as well as ocular pulse were developed and evaluated. At last, we presented the machine learning techniques used, the evaluation protocol elaborated and the results obtained for the detection of glaucomatous profiles.

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