

*Master in Photonics*

MASTER THESIS WORK

**STUDY OF NON INVASIVE OPTICAL  
GLUCOSE MONITORING DEVICE**

**Igor D. Blanco Núñez**

Supervised by Dr. Turgut Durduran, ICFO

Presented on date 10<sup>th</sup> September 2010

Registered at

**ETSETB** Escola Tècnica Superior  
d'Enginyeria de Telecomunicació de Barcelona

# Evaluation of a Non-Invasive Optical Glucose Monitoring Device

**Igor D. Blanco Núñez**

ICFO-Institut de Ciències Fotoniques, Mediterranean Technology Park, 08860  
Castelldefels (Barcelona), Spain

E-mail: [iblanco@icfo.es](mailto:iblanco@icfo.es)

**Abstract.** A non invasive optical glucose monitoring device based on a commercial pulse oximeter has been the object of this study. The fundamental principles of the technology and the proprietary algorithm were studied. The results of a prior clinical trial were analyzed with advanced biostatistical tools. Finally, a preliminary optical set-up was designed and utilized to study the potential of additional wavelengths to improve the device/algorithm performance.

**Keywords:** Clarke's Error Grid Analysis, Spectrometer, pulse-oximetry, diffuse optics, diabetes, glucose.

## 1. Introduction

Millions of people with Type-1 diabetes self-monitor their glucose levels to assess glycemia. As time goes by, people with this pathology suffer a slow but continuous general deterioration [1] [2] of their life conditions which affect the immune system, develop eye cataracts [3], suffer from obesity and other problems. Currently, the glycemic self-controls are being carried out through traditional methods of finger prick blood extraction. The extracted blood is then deposited in a special stripe where an estimation of glucose is produced via a series of chemical processes. Through this process, diabetic people used to be exposed daily to small injuries and often these injuries get infected and take time to heal. Furthermore, as the diabetes progresses extremities suffer from hypoperfusion making this process difficult.

As a consequence, a significant amount of research effort is dedicated to develop different non-invasive technologies [4] in the past two decades. Some of these are based on Raman Spectroscopy, Polarization changes, Fluorescence or Optical Coherence Tomography. Unfortunately, none has been able to replace the finger prick test due to problems in reliability, user-friendliness and patient compliance. Main limitations cover many different factors like instability in the laser wavelength and intensity, interference related to other compounds rather than glucose, sensitiveness to scattering processes, etc..

This project is a collaborative work between the Medical-Optics (PI: Dr Durduran) at ICFO and a small company, SabirMedical ([www.sabirmedical.com](http://www.sabirmedical.com)) in Barcelona. SabirMedical has developed and patented [5] an algorithm that utilizes the output from a pulse-oximeter to infer the glucose concentration in blood. They have carried out a pilot clinical study to compare their results to that of a blood test (considered as a gold-standard). We were asked to evaluate their findings to see if there were any factors that have introduced the observed systematic errors (to be discussed below) that could be eliminated by better opto-electronics and/or with a better understanding of the physics behind the problem. Since they were using a device that is made

for a different purpose, i.e. to calculate the blood oxygen saturation in the arterial component, it is probable that a new design based on, for example, a better selection of the wavelengths could improve the outcome.

We have undertaken this study from a bio-statistics and physics perspective. After an initial bibliography study about various attempts to measure the glucose concentration, non-invasively using optics, it was clear that this was a relatively new approach without a solid physics understanding. Instead, it is a systems approach based on biological modelling and complex numerical approaches. The systematic errors in the results could be attributed to the shortcomings of the pulse-oximeter design. For example, the choice of wavelengths that are optimized to differentiate the hemoglobins may not be providing the optimal, glucose level dependent variations in the pulse-shape. Another potential component comes from the inherently poor quantization of a commercial pulse-oximeter. They are designed to raise alarms when oxygenation falls below a certain threshold or to follow-up trends rather than to provide accurate values. For example, it does not take the finger diameter into account. Therefore, we have hypothesized that by studying the existing clinical data from a bio-statistical viewpoint, we should be able to identify whether any physical properties such as the finger circumference effects the results. The second hypothesis was that by designing a set-up that allows us to explore a wide-range of wavelengths, we can identify the potential for other wavelengths and pave the way to the development of a better physical model and/or a better device that is optimized for this purpose.

## 2. Further details of the system

The system to be evaluated in this study basically consists of a pulse oximeter that is connected to a computer. A custom software analyzes the signal and creates an estimation of the glucose level. The system basically establishes a physiological model of the pulse wave and its energy being correlated with the metabolic function of glucose to generate a fixed-length vector containing the values of the foregoing model. This is combined with other variables related to the user such as, for example, age, sex, height, weight, etc. This fixed-length vector is then utilised to feed a function-estimating system based on “random forests” for the calculation of the glucose concentration. It is beyond the scope of this report and my research project to get into the details of this patented algorithm.

In order to fully understand how it works it is important to review the concept of general photon propagation in tissues and pulse-oximetry.

### 2.1 Pulse oximeter

In most tissues it was found [6] that there is a spectral window where absorption of water and hemoglobin (main absorbers in tissues) is relatively small (mean absorption length  $>1\text{cm}$ ) and light scattering large (mean scattering length  $<1\text{mm}$ ).

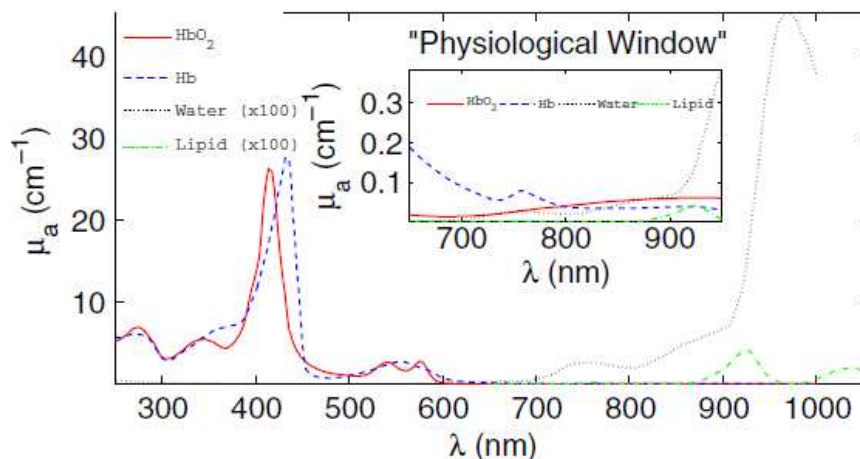


Figure 1: Physiological Window

This region is called ‘‘Physiological Window’’ (fig1) and is located in the near infrared (650-950nm).As a result, light can penetrate deeper in tissue in a process similar to heat diffusion, called *photon diffusion*, where light scattering dominates the photon propagation.

Even though absorption in the near-infrared is relatively small, the spectra of oxy- and deoxy-hemoglobin and water, differ significantly. Under these conditions a physical model was built in order to quantitatively separate tissue scattering from tissue absorption.

Within the context of light scattering, two length scales are important. A short ‘‘scattering length’’ which corresponds to the typical distance the photons travel before they scatter and a longer ‘‘random walk step’’ which corresponds to the typical distance traveled by photons before their direction is randomized. The reduced scattering coefficient is the reciprocal of the random walk step and it is wavelength dependent and denoted by  $\mu_s(\lambda)$ . On the other hand, there is also

a wavelength dependent absorption path in tissue that corresponds to the typical distance traveled by a photon before it is absorbed. The absorption coefficient is the reciprocal of this distance and it is denoted by  $\mu_a(\lambda)$ . Having clarified this, a pulse oximeter [7] is a device based on the Beer-Lambert Law, which relates the absorption of light to the properties of the material through which the light is travelling. In other words, for a particular wavelength we have that  $I_o/I_i = 10^{-(\epsilon C)L}$ . Where  $I_o$  is the output light intensity,  $I_i$  the input light intensity,  $\epsilon$  the extinction coefficient for this wavelength,  $C$  the concentration of the absorber and  $L$  is the path length travelled by the light.

The pulse oximeter is a device that applies this concept to the absorption of light by the oxy and deoxy-hemoglobin at 660nm and 910 nm. Current pulse oximeters are basically composed by two LEDs that emit in those wavelengths and two detectors as shown in fig2.

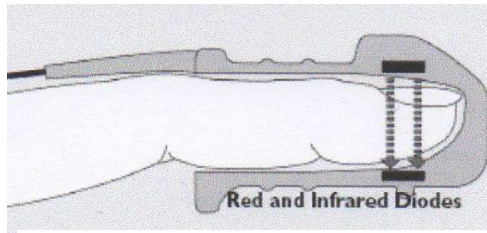


Figure 2: Pulse-Oximeter

As consequence, if we refer  $\lambda_1$  to 660nm and  $\lambda_2$  to 910nm and we apply Lambert-Beer’s Law for both wavelengths, we obtain:

$$\frac{I_o^{\lambda_k}}{I_i^{\lambda_k}} = 10^{-(\epsilon_{HbO_2}^{\lambda_k} \cdot [HbO_2] + \epsilon_{Hb}^{\lambda_k} \cdot [Hb]) \cdot L}$$

Where  $I_i$  and  $I_o$  are the input/output light intensities;  $k$  are the two different wavelengths;  $[HbO_2]$  is the concentration of oxy-hemoglobin;  $[Hb]$  the concentration of deoxy-hemoglobin;  $[TH]$  the total concentration of Hemoglobin;  $\epsilon_{HbO_2}^{\lambda_k}$  the extinction coefficients of oxy-hemoglobin for a given  $k$ ;  $\epsilon_{Hb}^{\lambda_k}$  the extinction coefficients of deoxy-hemoglobin for a given  $k$  and  $L$  the path length i.e finger’s thickness;

On the other hand, for any given wavelength, the optical density is defined as:

$$D_k = -\log\left(\frac{I_o^k}{I_i^k}\right) = [\epsilon_{HbO_2}^k \cdot [HbO_2] + \epsilon_{Hb}^k \cdot [Hb]] \cdot L$$

It can be then easy found that the oxygen saturation in blood is given by:

$$SpO_2 = \frac{[HbO_2]}{[TH]} = \left[ \frac{\epsilon_{Hb}^{\lambda_1}}{(\epsilon_{Hb}^{\lambda_1} - \epsilon_{HbO_2}^{\lambda_2})} \cdot \frac{1}{D_{\lambda_1}} \right] \cdot D_{\lambda_2} - \left( \frac{\epsilon_{Hb}^{\lambda_2}}{(\epsilon_{Hb}^{\lambda_2} - \epsilon_{HbO_2}^{\lambda_2})} \right)$$

However, in mid 1970 **Takuo Aogayi** [8] (Nihon Kohden Corporation) discovered that there is a pattern of pulsatile absorption due to the arterial pulse. Pulsatile expansion of the arteriolar bed produces an increase in the path length therefore increasing absorption [8]. All pulse oximeters assume that the only pulsatile absorbance is that of arterial blood (AC).

## 2.2 A new approach

The device under evaluation is based on the correlation between the characteristics of the previous pulses and the percentage of glucose in blood. The reason behind sits on the complex mechanisms of the endocrine system [10].

One of these functions is the auto regulation of glucose through the production of insulin in the pancreas.

As any biological complex system, there are several interconnected processes that are related to the concentration of glucose in blood and one of them affects the elasticity of the capillaries.

There is a direct link between the concentration of glucose and the concentration of collagens proteins that regulate the elasticity of these capillaries. Therefore, if the elasticity is altered, the absorption pattern will also change.

The AC pulses present two differentiated phases. A “raise up” phase which is related with the systolic pulsation of the heart and a “fall down” phase which is related to the diastolic one and the reflexions suffered by this wave in the periphery of the circulatory system.

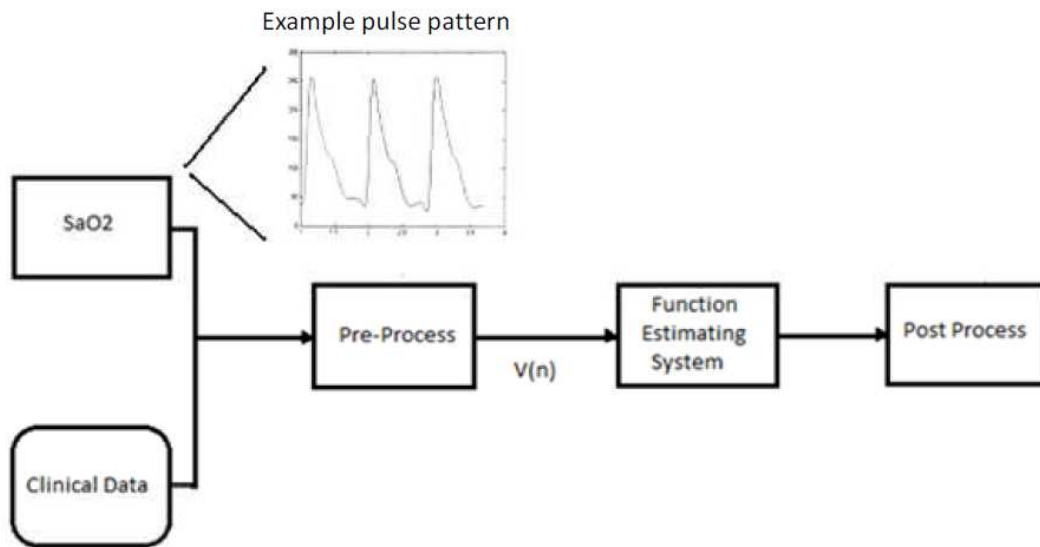


Figure 3: Glucose Estimation Process

The device uses the shape of these pulses and their energy to produce an estimation of glucose level in blood. There are several steps in the process.

Initially, the system establishes a physiological model using the previous parameters to generate a fixed-length vector containing the values of the foregoing model together with other variables relating to the user such as, for example, age, sex, height, weight, etc.

The fixed-vector  $V(n)$  is obtained in this part of the pre-process through the application of the stochastic model ARMA [11] and its application over the Tiger-Kaiser operator.

This vector is utilized to feed a function-estimating system based on “random forests” for the calculation of the variable of interest. The principal advantage of this parameter-estimating system stems from the fact that it does not impose any a priori restriction on the function to be estimated, being moreover highly robust in relation to heterogeneous data, such as the case of the present invention.

## 3. Clarke’s Error Grid Analysis (EGA)

It is customary to evaluate glucose measurement devices using an EGA.

The original EGA [12] was developed in 1970s to quantify the clinical accuracy of patient estimates of their current blood glucose (BG) as compared to BG value obtained in their meter.

It was then used to quantify clinical accuracy of BG estimates generated by meters as compared to a reference value.

A description of the EGA appeared in Diabetes Care in 1987 [13] and it became one “Gold Standard” for determining the accuracy of blood glucose meters.

It uses the Beckham analyzer as the reference and it consists in a grid divided in five zones:  
These five zones are defined as following:

- ZONE A:** Clinically Accurate.
- ZONE B:** Acceptable results.
- ZONE C:** Overcorrected. Unnecessary corrections that could lead to a poor outcome.
- ZONE D:** Dangerous Failure to detect.
- ZONE E:** Erroneous treatment.

The device was used to obtain in a preliminary clinical trial some data from 598 patients at hospital. The 5.5% of the data belong to the hypoglycemic range (<70mg/dl) versus 56% belonging to the hyperglycemic (>110mg/dl) one. About 38.5% were located between them.

As we can see in figure 4, for low reference concentration of glucose, there is a clear overestimation of the readings of the device (y axis) and, on the other hand there is an underestimation for high concentrations.

According to the definition of the different zones of the EGA, we got that 90.5% of the points belong to the zones A and B (safe zones), 0.3% of total belong to C zone and 9.2% of total belong to D zone. There are no points in E zones.

### 3.1 Clinical Data Analysis

In order to confirm the data distribution of previous EGA diagram, a Bland-Altman [14] analysis was done.

This type of analysis makes the point that two methods that are designed to measure the same parameter (or property) will have a good correlation when a set of samples are chosen such that the property to be determined varies a lot between them.

A high correlation for any two methods designed to measure the same property is thus in itself just a sign that one has chosen a wide spread sample. A high correlation does not automatically imply that there is good agreement between the two methods. In our particular case, for concentration below 150mg/dl most of the points are located between the *limits of agreement* i.e between the minus or plus 1.96 the standard deviation of the difference range.

However, we see a clear group of points out of range for concentration higher than 160mg/dl. The location of these points under the lower boundary of the limit of agreement indicates a clear underestimation of the readings in this range.

Summarizing, the inaccuracy in the system readings is located within the ranges of hypo and hyperglycemia, but according to the Bland-Altman analysis, we have a higher dispersion of the points in the hyperglycemia area.

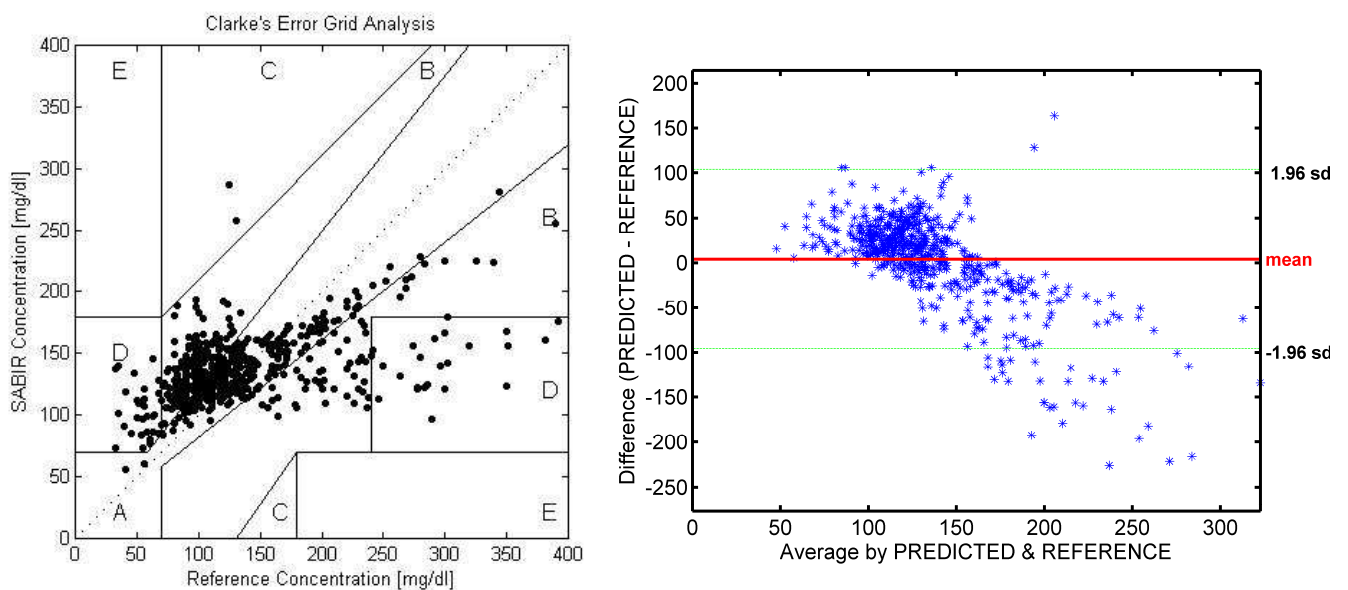


Figure 4: EGA & Bland-Altman diagrams



3.2 A statistical Solution through CHAID

We have clearly identified the device’s difficulty to process properly some readings, especially when the reference concentration is higher than a particular threshold (150mg/dl) but as well within the hypoglycemic range (<70mg/dl).

Within the first range, the dispersion of the points increases significantly, being some of them at the right D zone of EGA.

One way to approach this problem would be to know the common characteristics of the people that fell into this particular cluster and to produce an algorithm that easily identifies them.

In order to identify the characteristics of these clusters a tree decision technique CHAID [15] was applied. This technique detects interaction between variables in a data set where it is possible to establish relationships between a ‘dependent variable’ – in our case a variable called “Newmarker” that label our points depending on which zone of the EGA diagram are located – and other explanatory independent variables such as age, weight, height, heart rate etc. CHAID does this by identifying discrete groups of respondents and, by taking their responses to explanatory variables, seeks to predict what the impact will be on the dependent variable.

With purpose of establishing possible discriminators in our data set, we initially apply the algorithm one by one to the following set of independent variables: SpO2 (Saturation of Oxygen), HR (Heart Rate), BMI (Body Mass Index), Age, Gender and Reference (Glucose concentration used as reference).

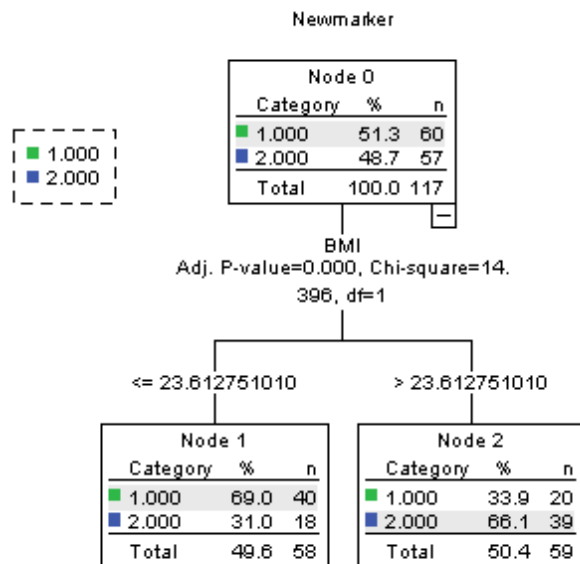


Figure 5: Chaid Tree Example

about 65% of the population located in both D zones having as a common characteristic that BMI value is higher 23.1 Kg/m<sup>2</sup>.

The remaining 35% have a BMI less than 23 Kg/m<sup>2</sup>. Bearing in mind that the BMI range for a healthy persons goes from 18.5 to 25 Kg/m<sup>2</sup>, an initial conclusion is that the device has problems is accurately obtaining readings in the segment of the population that goes from normal to obese people.

It makes sense to think that the thickness of the finger and the concentration of lipids are affecting the prediction and the accuracy of the algorithm.

In fact, this was one of our hypotheses.

The second draw reflects that among the group of people (goods and bads) that share this characteristic, the 63% of them are class D whilst 37% of them are “good” points. Therefore, here it is our first discriminate variable.

On the other hand, the second plot is related to the reference concentration of glucose.

There are now two different boundaries, one covering the points with Reference value less than 86.1 mmg/dl and another one for values higher than 138 mmg/dl.

However, the number of “bad points” – points located in the zone D of Clarke’s EGA- was significantly less than the “good points” i.e zones A and B of EGA, respectively. As consequence, we randomly produced five sub-sets of 60 “good” points that were merged with the 57 “bad” points of the original dataset. We then ran the algorithm over these new five sub-datasets and the results were averaged. A larger dataset would enable us to increase the precision of this technique.

We found no correlation for any parameter but for the BMI and the Reference.

The results reflected in figure 6, show two interesting conclusions.

The first one is related to the BMI.

The first draw in the first plot shows that

Within the first range (ref<86.1) we see that only 55% of total bad points share this characteristic whilst among of the total good and bad with ref<86.1 the 80% of them are "bad" points.

These results fit with the previous conclusions we obtained through the observation of the EGA: lack of accuracy within the hypoglycemic range, being now the boundary moved from 70mmg/dl to 86.1 mmg/dl.

On the other hand if we pay attention at the second range of this plot (ref>138mmg/dl) we see that 39% of total bad points share the characteristics of having a reference value higher than 138 mmd/dl. If we check all the points among this range, we find that 57% of them are zone D points i.e "bad" points.

If we merge both regions, we see that 94% of total bad points have as a common characteristics that they are either located in areas where Ref<86.1 or Ref>138. If we look at the total number of good and bad points located within this new range, we have found that 69% of them are "bad" points.

We can therefore conclude that there is a clear inaccuracy in the readings of the device among the hypo and hyperglycemic regions.

The reasons of this conclusion might sit on malfunction of the device predictive algorithm when it faces extreme hypo and hyperglycemic scenarios. Another reason can be the insufficient data within these ranges data for a pretrial analysis.

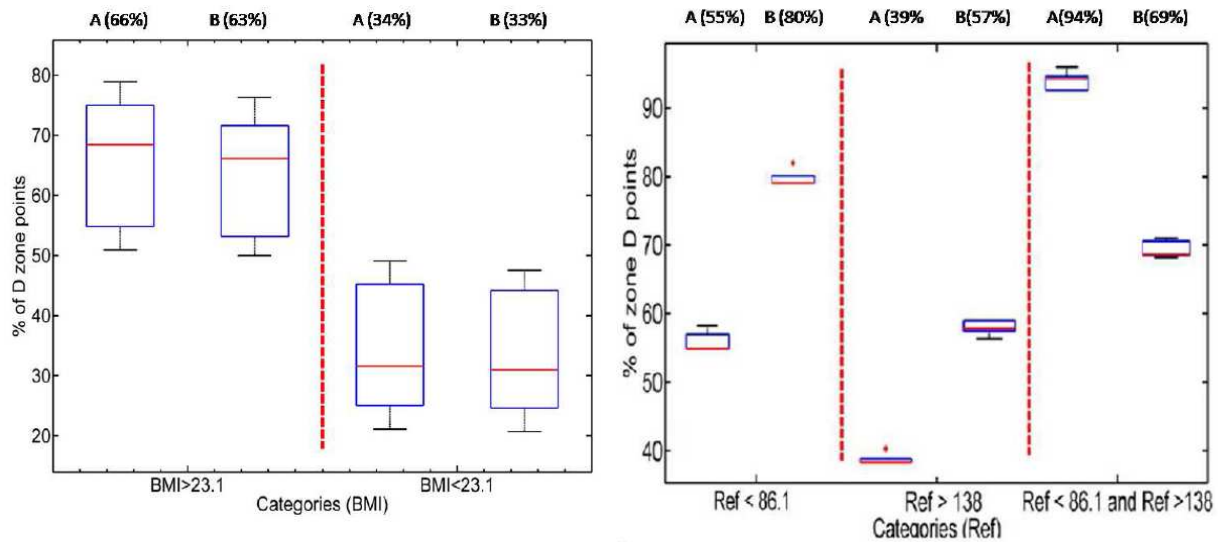


Figure 6: BMI & Reference Box-Plots

#### 4. Technology limitations and solutions proposed

The device is technologically limited by the use of a pulse oximeter as it was created for a different purpose. A pulse-oximeter is optimized to obtain the arterial oxygen saturation.

The choice of wavelengths, the sampling rate and the probe are all designed accordingly.

One of the goals of my project was to consider improved technologies that are based on a better understanding of the physics of the problem.

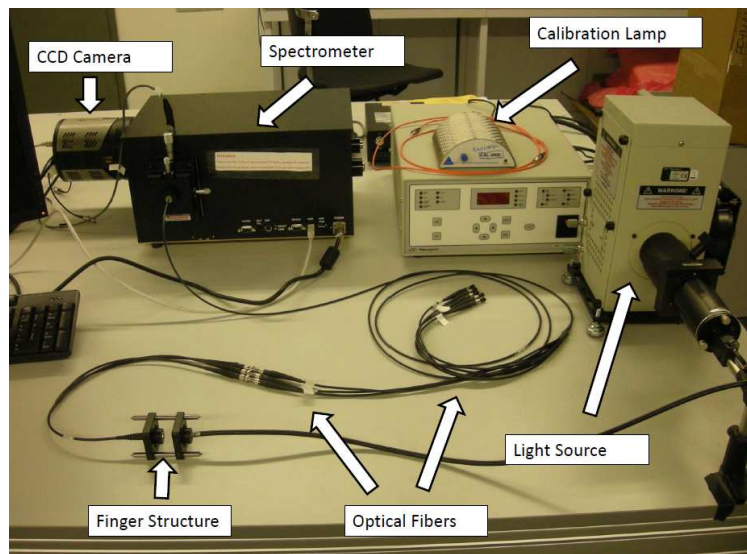
##### 4.1 New set-up

An experiment was then proposed with the aim of proving heart pulsations can be found in many different wavelengths. For this new set up I use a white light source, one spectrometer-CCD camera system (Pixus 400), some optical fibers and a special platform built to fix the finger. A main optical fiber (600um) was then connected to the light source.

In order to avoid skin burns one optical filter was put on the output of the lamp to get rid of wavelengths below 400nm. This fiber was connected in the other side to a platform where the finger was fixed.



On the other side of this structure, a similar fiber was located and it collected the light intensity transmitted through the finger. This fiber was then split in three (200um each) and these new fibers delivered their respective signals into the CCD camera-spectrometer system. The purpose of splitting the signal in three was to averaging them later.



**Figure 7: New Set-Up**

#### *4.2 Experimental results*

I collected data for two different individuals at 15.6Hz for 20 seconds obtaining 300 frames. The acquisition time plus the read out time of my set up was up to 64ms. Once, I centered the grating of the spectrometer at 800nm, the dispersion was about 19.09 nm/mm, the resolution with 200/240 um fiber was from 4.6 to 5nm and the wavelength range from 540nm to 1055nm. Before data collection, I registered the BMI and heart rate of two individuals being respectively 1.2Hz and 20Kg/m<sup>2</sup> per individual 1 and 0.9Hz and 25Kg/m<sup>2</sup> per individual 2.

I obtained then three different light intensities for any wavelengths with a total number of different wavelengths recorded up to 1043, ranging from 540nm to 1054nm. Once the data was collected I averaged the three intensities.

Heart's pulsations were found for all the wavelength range for both individuals.

In order to reduce this wavelength range, I also averaged the intensities over plus or minus 5nm around each center wavelength, obtaining a single light intensity for the following wavelengths: 600, 650, 700, 750, 800, 850, 900, 950, 1000 and 1050 nm.

With the aim of checking if the frequency of the pulsations matched the heart rate of the individuals registered before a Fourier Transform Analysis was applied and the frequency of the pulsations matched the expected values of 1.2 and 0.9 Hz respectively.

A high pass digital filter was also applied to the signal to get rid of low frequencies.

These results are reflected in figure 8, where two examples of the PSD (Power Spectral Density) per individual show the frequency of the pulsations at 0.9Hz and 1.2Hz for 750nm and 900nm, as we expected.

We can also see that for different wavelength we obtain a different value in the peaks of the PSD. This confirms that absorption is wavelength dependent.

In order to check if there was a particular wavelength where the absorption was higher, we compared the values of the PSD for both individuals along the same wavelength range (fig 9).

We have found that both absorption profiles differ and the reason could be related to the different BMI value of the individuals. As we can see in figure 9, individual 1 shows an initial maximum of absorption located at 660 nm, (where hemoglobin absorption is maximum in this spectral window) whilst this maximum is located in 700nm for individual 2.

On the other hand, the absolute maximum absorption value for individual 1 is located at 1050nm whilst this value was not significant for individual 2.

The reason might sit of the physiological differences between both individuals, reflected on this study through the BMI parameter as a discriminate variable.

In one side we have a slim person with BMI about 20 Kg/m<sup>2</sup> and on the other side a robust person with BMI value of 25 Kg/m<sup>2</sup>. Both constitutions differ also significantly in size.

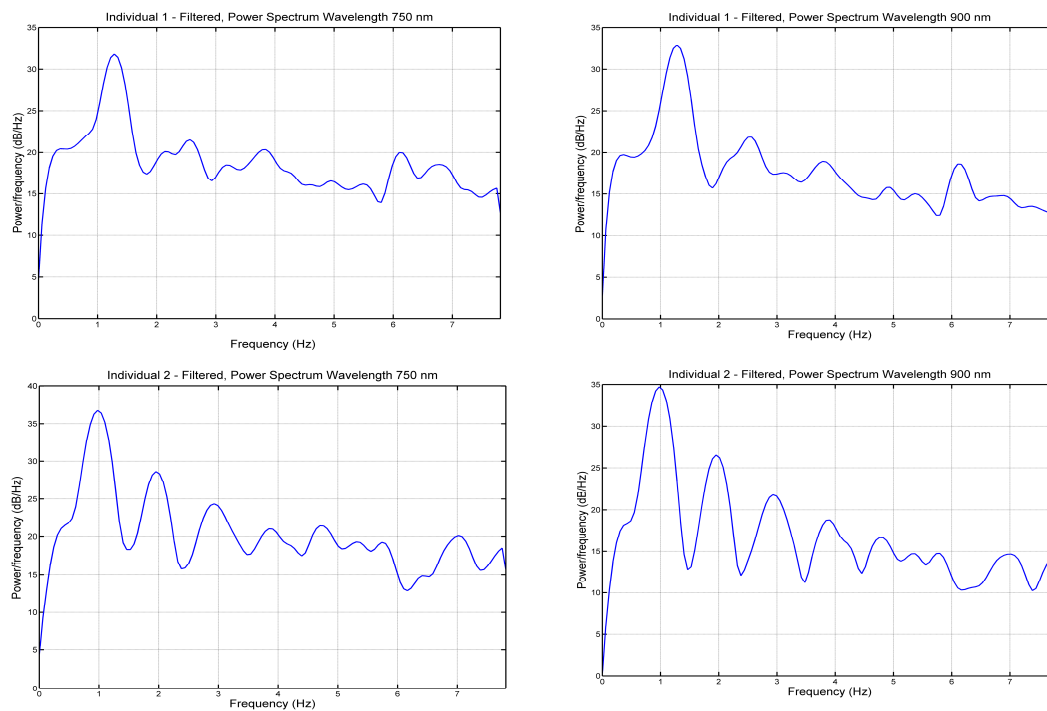
As consequence, light at 1050nm was not able to cross the finger of individual 2 so good as it did for individual one.

On the other hand, it is easy to think that higher concentration of lipids in individual 2 have distorted somehow its absorption pattern if we compared it with the individual 1.

## 5. Conclusions

I have evaluated the existing clinical trial data from SabirMedical that uses a novel algorithm to extract the blood glucose concentration from the output of a commercial pulse-oximeter. I have shown that the instrument systematically over/under-estimates the "gold-standard" values for BMI values higher than 23 Kg/m<sup>2</sup> and for true glucose levels lower than 86.1mm/dl and higher than 138mmg/dl. These could be due to shortcomings in the training of the analysis algorithm due to the small data set, possible complications due to the extremes in the patient physiology and, perhaps, in the most relevant manner to this work due to the shortcomings of the usage of a device optimized to extract the arterial oxygen saturation. Given this information, I have put together a bench-top set-up that has enabled me to observe the pulsatile signals in a wide-range of wavelengths and observed that the results depend on the chosen wavelength. The next steps in this project would be to develop a physical model to explain this wavelength dependence and try to improve the analysis algorithm.

During this work I have gained substantial knowledge in data analysis, basics of diffuse optics, pulse-oximetry, the set-up and usage of a white-light optical system using a CCD based spectrophotometer and I have learned the basics of biostatistics.



**Figure 8: Filtered PSD reflecting heart's pulsation**

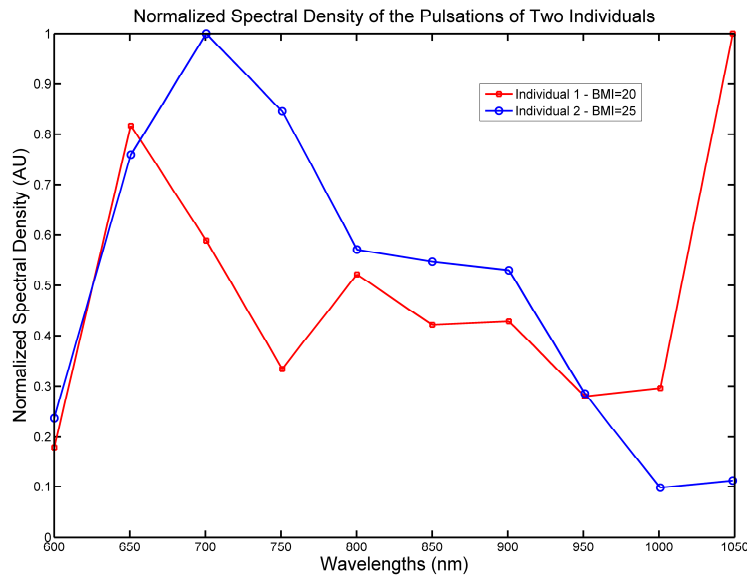


Figure 9: Normalized PSD of pulsations for 2 individuals

## 6. Acknowledgments

I would like to express gratitude to Prof. Dr. Turgut Durduran for supervising my work and I would also like to thank my colleagues at the Medical Optics group for their assistance during my research period at Ico. I would also like to thank SabirMedical for all their help and support. Finally I want to acknowledge the Fundació Cellex Barcelona for its funding support.

## References

- [1] Shehadeh A, Regan T.J 1995 Cardiac consequences of diabetes mellitus *Clinical Cardiology* **18** 301–305
- [2] Geerlings S.E, Hoepelman A 1999 Immune dysfunction in patients with diabetes mellitus (DM) *Immunology & Medical Microbiology* **26** 259–265
- [3] Klein B.E, Klein R, Moss S.E, 1985 Prevalence of cataracts in a population-based study of persons with diabetes mellitus *Ophthalmology* **92** 1191-6
- [4] Tura A, Maran A and Pacini G 2007 Non-invasive glucose monitoring: Assessment of technologies and devices according to quantitative criteria *Diabetes Research and Clinical Practice*. **77** 16-40
- [5] [http://v3.espacenet.com/publicationDetails/biblio?DB=EPODOC&adjacent=true&locale=en\\_EP&FT=D&date=20100514&CC=WO&NR=2010052354A1&KC=A1](http://v3.espacenet.com/publicationDetails/biblio?DB=EPODOC&adjacent=true&locale=en_EP&FT=D&date=20100514&CC=WO&NR=2010052354A1&KC=A1)
- [6] Jöbsis-vanderVliet F F 1999 Discovery of the near-infrared window into the body and the early development of near-infrared spectroscopy *J. Biomed. Opt.* **4** 392
- [7] Millikan G.A 1942 The Oximeter, an Instrument for Measuring Continuously the Oxygen Saturation of Arterial Blood in Man *Rev. Sci. Instrum.* **13** 434-444
- [8] Severinghaus, JW 2007 Takuo Aoyagi: Discovery of Pulse Oximetry *Anesthesia & Analgesia* **105** Suppl. S1-S4
- [9] Yelderman M, New W 1983 Evaluation of pulse oximetry *Anesthesiology*. **59** 349-351
- [10] Keener J, Sneyd J 1998 Mathematical Physiology Interdisciplinary *Applied Mathematics* **8** 355-376, 579-611
- [11] Sheng Lu 2001 A new algorithm for linear and non linear ARMA model parameter estimation using affine geometry **48** 1116-1124
- [12] Clarke W.L 2005 The Original Clarke Error Grid Analysis (EGA) *Diabetes Technology & Therapeutics* **7(5)** 776-779
- [13] Clarke W.L, Cox D, Gonder-Frederick L.A, Carter W, Pohl S.L 1987 Evaluating clinical accuracy of systems for self-monitoring of blood glucose *Diabetes Care* **10** 622-628
- [14] Altman D.G, Bland J.M 1983 Measurement in Medicine: The Analysis of Method Comparison Studies *The Statistician* **32** 307-317
- [15] Kass G.V 1980 An Exploratory Technique for Investigating Large Quantities of Categorical Data *Applied Statistics* **29** 119-127