ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

A wearable and Non-Invasive Glucose Monitoring Device based on NIR Absorption

Elia Tomé (GM), Simon Romanski (EL), Nicolas Freundler (SV), Vithooban Thavapalan (SV)
Group 18

Under the supervision of Professor Stéphanie Lacour and Florent-Valéry Coen

Lausanne, December 2017

I. Summary

Half a billion people are living with diabetes today. With the increase of the accessibility to food, obesity and without action of the public health system, the number will rise in the next years. [1].

Insulin is a key molecule, signaling cells to absorb glucose from their surroundings. Diabetes is characterized by the inability of having a normal range of glucose level in the blood, which is between 70 and 120 mg/dl before a meal [2]. Type I Diabetes is due to insufficient insulin production and Type II to a decreased sensitivity of cells to insulin. To overcome the negative effects of Type I Diabetes, a patient can take artificial insulin at a specific time (after a meal for instance) to mimic the natural behaviour of the body. However, to know when is the right time or how much insulin he has to take, the patient needs to measure his glucose level in the blood (to prevent a high take of insulin).

This document describes in a first part the existing devices for blood glucose concentration measurement. These devices imply electrochemical measurement, which make them invasive and often unable to work continuously. The goal of this project is to develop a wearable non-invasive device, that can take measures without interfering with the patient, continuously, with wireless communication to a smartphone (to enable alerts if the levels of glucose are not normal) and is easy to calibrate.

In a next step, the measurement method that we use is assessed: a non-invasive detection based on the light scattering property of the skin and its changes referring to blood glucose concentration change. The device is a band that is attached around the ankle.

More specifically, the materials and the electronic parts that are used are described. For substrate and encapsulation of the electronics, PDMS is chosen because of its convenient flexibility and transparency. As rigid thick parts are integrated (such as a LED and a photodiode), the device will need a different flexibility (ideally null) where these parts are embedded in the substrate, else the connections will break. Hence, rigid islands in the substrate are required.

The process flow is then given step by step. After a list of companies where the materials can be bought, the document concludes with considerations about the use of our device for diabetes patients and about the points where difficulty is still encountered in its approval by international organizations.

II. State of the art review

To prevent long term complications due to low or high blood glucose level, the patient has to monitor it several times a day. The usual glucose monitoring systems are the glucose meters, which are based on the Clark electrode. They have been have developed by different companies, from Abbott to Roche [3].

After having washed his hands, the patient has to prick the middle of his finger and deposit the resulting blood droplet (0.3 to 1 µl) on the lecture site of a disposable stripe. This site has microfluidic channels that will suck the droplet to the electrode. There an enzyme (the Glucose

Oxidase) is immobilized and will react with the blood sample. The enzyme is then oxidized using an intermediate (like the Ferricyanide ion ($Fe(CN)_6^{3-}$), which will finally be reoxidized at the electrode, which will trigger an electric current. Thus this current will be proportional to the glucose level. The stripe will then be put on a glucometer and the result is usually displayed in [mg/ml]. This is the oldest technology for monitoring, as it is on the market since the 1970s, yet also the most accurate one for a home use. The main drawbacks being the invasive approach, the discrete measurements (with this kind of device, we cannot obviously monitor the glucose level continuously) and the price. Often, the glucose meter is free, but the stripes cost between 0.35 and 1 dollar each. Scaled to a year, a patient that makes the test five times a day has an overall cost of 638.75 to more than 1,900 dollars.

An alternative, that can monitor continuously the glucose level and that is also available on the market is the *FreeStyle Libre* of Abbott [4]. It is a disposable patch, a rigid implant with an electrode that is put under the skin. It measures the glucose level in the interstitial fluid (more details about its mechanism are unknown, as it is a currently marketed device). As it has a RFID chip, the electrical consumption is almost null. The energy needed for the data transfer to the smartphone comes from this one, when we swipe the phone in front of it. Therefore, apart from its continuous monitoring, the main advantages of this device are that it is almost invisible, can be used for more than a week and therefore gives a good historical trend and the direction in which the glucose level is going. The price is 65 CHF for the scanning device and 65 CHF also for each captor, meaning in the best case (2 captors used every month) the cost is of 1,625 CHF per year. The major drawbacks of this technology are the measurement of the interstitial fluid, which is less accurate because its level is lagging compared to the blood level, and its use for maximum two weeks (often less, because the device does not stick to the skin).

Another more advanced device is the *Dexcom continuous glucose monitoring* [5]. It follows the same principle as the *FreeStyle Libre*, but has a transmitter that can send data to a smartphone, to know how the glucose level is varying or to emit an alarm when it is too low or too high. We will use this idea for the comfort of the patient.

In 1975 the search for a noninvasive glucose monitoring system begun without much success until now, even though the urge for the 3C is increasing (Cost, Comfort and Convenience) and the number of patents increased linearly [6]. Several techniques are currently in research area: smart lens, Near and Mid Infrared measurement, using the saliva and much more. But for now, none gave satisfactory results. Indeed, in the NIR range, glucose and many others sugar-like molecules share similar curve of absorbance. As these molecules can vary proportionally or inversely or randomly with the concentration of glucose, finding a correlation between the absorbance and the glucose level is stochastic.

Despite its limitations, we were inspired by the paper of Yadav *et al* [7], which seems to have good results with NIR absorption. A 940 nm wavelength is used to assess the level of glucose in the blood with the use of a LED and a photodiode put on the arm of a subject. This specific wavelength was used, as it is more specific to glucose than for other sugar-like molecule. We will keep the basic components for our device and assemble them using the methods that we have learned during the course. To overcome the defaults of the NIR measurements, we had the idea to use several samples of the patient's blood with different concentration of glucose for the calibration in order to get measurements as accurate as possible.

III. Product

As assessed before, we want to develop a non-invasive and easy to use glucose monitoring device. It will take the form of a discrete ankle bracelet that can be worn underwear and coming in different sizes to adapt to the morphology of the patient. Using NIR detection method, it will be pain free and energetically cheap as it will emit discrete pulses of light. Yet this allows what can be considered as a continuous monitoring as the glucose level does not change dramatically in a few moments and as our device works day and night. Finally it will send data to a smartphone, in order to let the patient control the evolution of his glucose level or alert him if these levels are extrem.

We will now examine in detail how our device works:

A) <u>Glucose detection:</u>

Our device is based on an optical method, measuring light intensity difference when it passes across the tissue. The main phenomena in our application are light absorption and scattering. When a beam of light going through a molecule, this molecule keeps numerous incoming photons because their energy corresponds to an excited energy level of the molecule. These photons are totally turned into another form of energy (e.g. heat). The light decrease through a thin slice is proportional to the quantity of molecules in this slice (divided by the cross section area A of the beam) and to the intensity itself. I is the intensity, C the molar concentration, m a coefficient, V the volume and l the length.

$$dI = -mIdN/A = -mId(CV)/A = -mICd(Al)/A = -mICdl$$

In all practical case, the sample is thick, then considered as a sum of thinner slices. This consideration leads to the following integral (I_0 and I being respectively intensities of incoming and transmitted light):

$$I = I_0 e^{-mCl}$$

The second main phenomenon is scattering. Scattering is when the photon molecule interaction leads to a deviation of the photon trajectory and possibly in a wavelength shift instead of absorption. Practically, the consequences in the calculation of transmitted intensity is that absorption coefficient m is corrected in m_{eff} and leads to the equation

$$I = I_0 e^{-m_{eff}Cl}$$

These coefficients depend on the wavelength of incoming light, and they can be different for different species. These relations are absorption spectra, sort of “identity cards”. If we know the wavelength and the intensity of the emitting LED, we can assess the concentration of glucose based on how much light is transmitted. Glucose absorption spectrum has several peaks. We are aiming for peaks as they correspond to maximum of sensor sensitivity. However, blood contains a lot of different chemical species with their own optical features and one must be aware not to choose a value which these species are also sensitive to. 940 nanometers is a good trade off [7].

As the sensor is placed on the skin 4 millimeters away the emitting LED, we will not collect the whole light passing through the tissue but only a small part. Skin is a scattering tissue, there is consequently always a part of the light that can go in any direction. The more glucose there is, the

more light is absorbed and therefore not scattered. Thus overall scattering property of skin is reduced. This allows us to put the sensor so near the LED and not necessarily at the opposite side of the ankle. In fact, this display measures directly the loss of scattering quality of the skin. The downside of this approach is that the computation of the output/input intensities ratio becomes quite complicated. The equation previously described can only hold as a coarse estimation of absorption. The skin is divided in three layers, going from the outside into the inside: epidermis (up to 100 µm), the dermis (1 to 4 mm) and the adipose tissue (1 to 12 mm). This value concern the forearm and the wrist, but they should be similar for the ankle concentrated in the dermis. Most blood tissue in the skin is concentrated in the dermis and represents 8% of the dermis volume [8].

In short, a portion of light is able to reach the sensor when it is near the LED light source thanks to scattering. Glucose absorbed the incoming light and reduces scattering property of skin. The output intensity therefore decreases as glucose concentration decreases.

B) <u>Electrical Part/Components:</u>

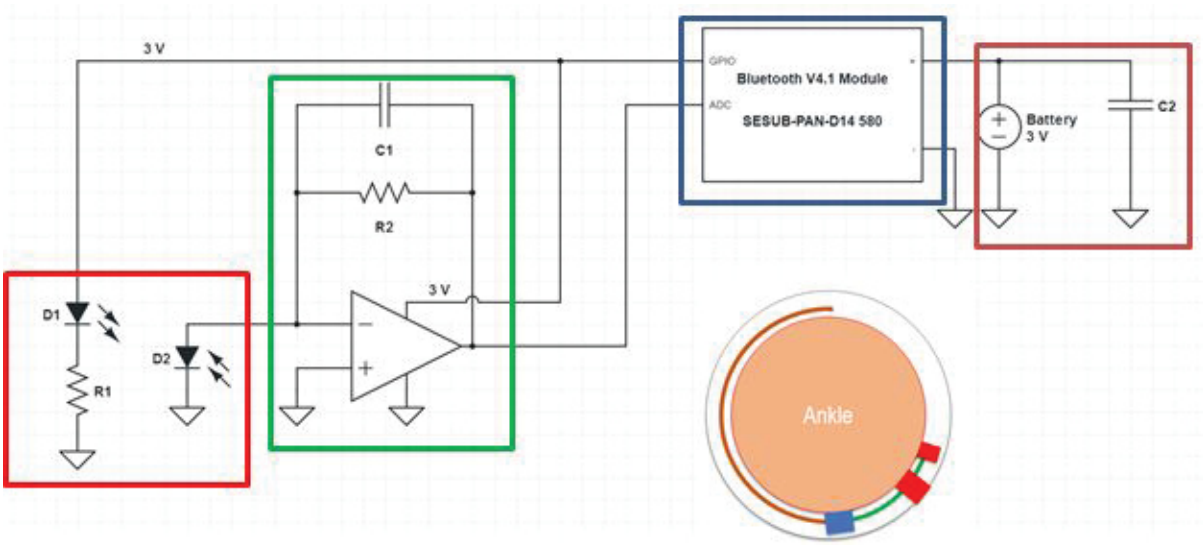

Figure 1 : Circuit layout

The electric circuit layout can be seen in **Figure 1** and consists of four main modules of the circuit:

The sensor section, the amplification and filter section, the Bluetooth module and the battery. One can see the approximate corresponding positions in the overview in bottom right corner which is not to scale.

Sensor module:

The sensor module consists of two parts. For emitting light at 940nm there is an LED (Lumiled LI1IZ940) with a resistor (R1 = 1 Ω) to provide the required forward current of 1000mA for the LED. For sensing the scattered light we use a photodiode (OSI Optoelectronics PIN-3CDP). It is crucial to have enough optical power in order to detect the scattered light which is why we chose the high power LED with a typical radiometric power of 1150 mW. This is more than an order of a

magnitude higher than the radiometric power of the LED that was used for [7]. Therefore, it is reasonable to assume that we can use the presented measurement technique outside of laboratory conditions.

Amplification and Filtering

The output signal of the sensor is amplified by an operational amplifier and filtered with a low pass filter at the same time as suggested in the data sheet of the photodiode. This is achieved by coupling the inverted amplifier layout with a capacitor. The capacitor (C1 = 16 pF) and the resistor (R2 = 500 MΩ) are chosen in a way that a cutoff frequency of 20 Hz is reached. Technically the frequency could be even lower as blood glucose levels change slowly. The frequency is chosen as we try to minimize the requirements for the resistor and capacitor but still cut off the noise at 50 Hz.
Note that the operational amplifier can be both implemented as a fully integrated circuit or as rigid external component depending on the preference of the manufacturer.

Bluetooth module

For transmitting the data from our device to a mobile device via Bluetooth we chose the TDK Sesub-Pan D14580 due to its small size and low power consumption. Furthermore it has a built-in programmable microchip and ADCs that allow us to process the data from analog signals to the Bluetooth protocol standards.
Additionally, it has a sleep mode that allows us to use the LED only for pulses of 60 mA to prevent overheating of the device and enhance the charging cycle of the battery drastically.

Battery

We chose a Lithium-Polymer battery (BV-454523-35ST) due to its thickness of only 0.45 mm and its flexibility. It has a capacity of 35mAh and as it is a Lithium-Polymer battery it can usually provide a current of up to 20 C but as we only use it for a 60 ms pulse, we can potentially achieve much higher currents of about 1A as needed. This also allows operating the battery without a cooling as we usually only send the pulse once in 15 minutes. The 1 A input current is reached due to the small resistor. As the resistance of the human body is significantly higher, the current will be much lower as we have a voltage source.

The 60 ms pulses every 15 minutes are applied to the sensor part only due to its high current. The Bluetooth module will be active for 500 ms to enable sending the data. A battery charging cycle estimation can be found in the appendix. According to our calculation the battery would have to be recharged every 18 days which is a longer charging cycle than any commercially available continuous glucose monitor provides to the best knowledge of the authors.

Not that we use a capacitor (C2 = 100 nF) as a decoupling capacitor to maintain the required voltage.

Overview of the parts

The complete list of parts and datasheets can be found in the appendix.

C) <u>Materials and Process flow:</u>

The electrical circuit is going to be embedded in flexible material in order to have a compliant structure for each user. It should be noted that using already commercialized NIR LED for glucose measurements has some constraints in terms of materials we are going to use. As polyimide is generally used for thin substrate applications, the 0.7 mm thick LED has led us to use PDMS (both for the substrate and the encapsulation).

Thick metal film, typically 500 nm thick layers of gold is going to be used for the interconnections between the different rigid electrical components. Considering the power required by our LED, the resistance of your metal track will be way too high. Therefore, we need a thick layer of metal. Naturally, this also means we will lose the micro cracked properties of gold cited by Prof. Lacour S. in her work on e-dura [9] which confers high stretchability. However our application is not affected by that as we don't actually need stretchability. Also, we want to make sure that the interconnections are putting up with really low strain therefore they are going to be placed at the neutral plane (at 800µm).

Nevertheless, it should be noted that because of high thicknesses of the electrical components used the stress at bending could possibly make the interconnections pop out. Indeed according to the study of P. I. Hsu et al. [10] hard materials cannot be expanded elastically or plastically to almost 5% strain without failure. The same study claims that patterning the stiff device materials into islands onto the compliant substrate will prevent the strain in the substrate of being transferred to the islands. P. I. Hsu and colleagues show that the strains are pinned to low values in the island and the nearby substrate by the high Young's modulus of the island, but increase farther from the island and deep underneath it.

We therefore decided to add SU8 epoxy based photoresist to support every rigid electrical component in order to recreate the same island technique. Taking P.I. Hsu's study as a reference, we decided to have:

- Island thickness : 3% of the substrate thickness (25µm)
- Island sizes : 20% longer and wider than the electrical components

The general design of an island is shown in the following picture (**Figure 2**):

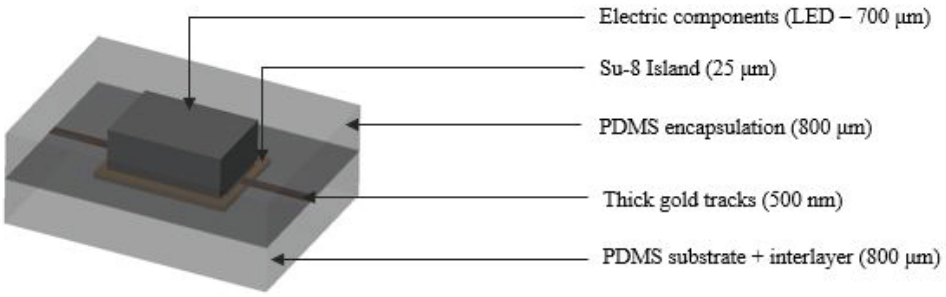

Figure 2 : General design and dimensions of an island (example of the LED)

In order to present our process flow is going to be divided in two subparts:

- The fabrication of the substrate with the SU8 islands and the gold deposition.
- The fabrication of the encapsulation with the rigid existing electronics

The scheme of our process can be found in the *Appendix*.

The first step is to create a patterned SU-8 mold in order to cast our PDMS onto it. The 755µm PDMS substrate is then going to be prepared by mixing the silicone gel with cross linker in a 10:1 weight ratio, casted into the master and cured for 4 hours at 75°C. As we don't want to deteriorate the PDMS when peeling it off from the mold, we will use silanization which is a process intended to produce a passivation of the surfaces to aid release from PDMS and prevents the PDMS form adhering to the master. Using 2 or 3 drop of the silanizing agent and putting the wafer under vacuum for one hour is enough [11]. Then, the SU-8 islands are going to be placed with a pick and place machine and a 45µm layer of PDMS will be casted onto them and baked, trapping the islands inside. We will then use a 50µm polyimide foil made to adhere to PDMS membrane as a shadow mask, prior to metal evaporation. Lastly, we will carry out one run of successive electron beam evaporation to deposit a 20nm thick adhesion interlayer of chromium and the 500nm of gold layer [12].

For the second subpart, we will first deposit silver paste onto the gold interconnections to ensure electrical contact between our tracks and the components. It will be applied via screen printing, by using a laser cut PET sheet as mask. Then the rigid electrical components are going to be placed with a pick and place machine and stuck to our tracks.. Their positioning will be very important as they have to be onto the islands. Furthermore, the PDMS encapsulation will be then casted on the electric components, having a 1.6mm thick output, to finish our workflow, Finally, thanks to the salinization process, the PDMS will be peeled off carefully form the master without deteriorating it.

IV. Feasibility assessment

In order to build our prototype we are going to buy materials through specialized commercial websites:

- the PDMS will be prepared via the Sylgard 184 elastomer kit from Dow Corning [13]
- the SU-8 islands will be delivered via *mircochem.com*
- The NIR LED and photodiode which are optoelectronic components are going to be delivered by Everlight which offers really thin fabrications (0.7mm thin LED *IR92-01C/L491/2R*)
- The different rigid electrical components are going to be bought through the electronic components distributor, *Mouser*

We are thinking of implementing the production flow with the help of EPFL microfabrication labs like LMIS or even the LBIS having different electrical and electromechanical characterization facilities and specific production machines.

Of course it is possible that we encounter some difficulties throughout the development of our device, especially for the precise measurement of glucose concentration. More precisely, the first hardware failure we can easily encounter is light scattering. Indeed, optical measurement of glucose concentration is not as direct as sticking your finger. A considerable amount of light will have to get from the LED to the sensor. Therefore, we will need a high amount of power in order for the NIR to adopt the path between the LED and the sensor.

Furthermore high power means also high current: in our case an input current of 1 A. Yet, knowing that 10 mA is a safety reference especially for wearable devices, high current could also

mean having difficulties in the approval of our device. It is important to note that we use a voltage source and not a current source. We achieve 1 A at the LED because we have a small resistor. However, the resistance of the human body is significantly higher. Ultimately one would get the same current through the body as when holding a usual 3 V battery touching both poles. Additionally, we have a reliable electrical isolation through PDMS.

Nevertheless, we should also consider software failure as we want to have substantial results on whether the concentration of glucose is getting crucial for the patient or not, regarding the light transmission signal. We want to ensure the there is no software is bug regarding this analysis. Free and reliable, formal verification-based techniques are commonly used. With these techniques, the software will be tested for a wide range of input values for which the output, given back by the system, is analyzed.

Finally, having created the prototype is only a small percentage of what, Food and Drug Administration (FDA) or European certification (CE) approval prerequisites can be. In fact the next step would be to assign our device to one of the three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device and to follow the regulations listed for this class. It is important to distinguish as those are different categories handled by different divisions of the FDA.

Now according to the FDA [14] devices with a high complexity and risk, which for example monitor vital functions of the human body, are categorized in class 3. This highest -risk class of medical devices require usually Premarket Approval (PMA) by the FDA and a certain amount of clinical data to assure the safety and efficacy of the device. Therefore, it is important for us the keep in mind the long process of approval according to the FDA, and try to optimize some hardware/software points mentioned above.

V. Conclusion

Diabetes is a common illness and its prevalence will only increase in the future years. It has big impact on the everyday life of people, yet it is easy to control through invasive monitoring.

The device presented in this work is non-invasive, discrete and does not interfere significantly with the everyday life of the patients as it is controlled remotely via Bluetooth through mobile devices.

To the best knowledge of the authors, this is the first time the scattering property of light is presented for the use of glucose detection in a portable device. A detailed examination of the measurement technique, the circuit design and signal processing, and a potential manufacturing process has been given.

Due to the limited amount of time for the project this works only presents a concept and a feasibility study for the glucose measurement device. In-depth island simulation can be used in order to assess the best size and thickness. Furthermore, the construction of a prototype could proof the usability and of our device.

References

[1] IDF Diabetes Atlas, 7th edition

[2] Federation Francaise des diabétiques, *Ma glycémie* [online] Available at : *https://www.federationdesdiabetiques.org/diabete/glycemie*

[3] Baxter Healthcare Corporation (2016), *Liste des marques et fabricants de glucomètres propres au pays* [online] Available at : *http://www.glucosesafety.com/ca/fr/downloads/Country_Specific_Glucose_Monitor_List_fr_102014.pdf*

[4] Abbott Diabetes Care Inc (2016) , *Pourquoi piquer lorsqu'on peut scanner ?* [online] Available at : *http://www.freestylelibre.ch/fr_CH/*

[5] Dexcom, Inc. (2017) , *Continuous Glucose Monitoring*, [online] Available at : *https://www.dexcom.com/fr-CH?gclid=EAIaIQobChMI4u7Hw4-X2AIVBzobCh3LBANWEAAYASAAEgI8x_D_BwE*

[6] Smith, J. L.(2017), *The Pursuit of Noninvasive Glucose 5th Edition* [online] Available at : *https://www.researchgate.net/publication/317267760_The_Pursuit_of_Noninvasive_Glucose_5th_Edition*

[7] *Near-infrared LED based non-invasive blood glucose sensor*, J. Yadav, A. Rani, V. Singh, B. M. Murai, in Signal Processing and Integrated Networks, February 2014

[8] *Quantifying the Composition of Human Skin for Glucose Sensor Development*, W.Groenendaal, G.van Basum, K. A. Schmidt, P. A. J. Hilbers and N. A. W. van Riel, in Journal of Diabetes Science and Technology, September 2010

[9] Electronic dura mater for long-term multimodal neural interfaces. Ivan R. Minev et al., *Science 347,* 159 (2015)

[10] P. I. Hsu et al. *Spherical deformation of compliant substrates with semiconductor device islands*

[11] Microfluidics/Microfabrication Facility Saenz, C., *HMS Procedure for silanization of SU -8/silicon master*, Octobre 2015

[12] Lacour et al., Stretchable interconnects for elastic electronic surfaces, *Proceedings of the IEEE, vol. 93, no. 8*, August 2005

[13] Dow Corning Corporation, *Sylgard® 184 silicone elastomer kit* (last updated 2017) [online] Available at : http://www.dowcorning.com/applications/search/products/details.aspx?prod=01064291

[14] U.S. Food and Drug Administration, *Medical Devices* (last updated November 2017) [online] Available at : https://www.fda.gov/MedicalDevices/