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Rollable and Implantable Intraocular Pressure Sensor for the Continuous Adaptive Management of Glaucoma

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Abstract — **We designed and tested a new rollable and implantable medical device to directly and continuously measure intraocular pressure. Since high intraocular pressure is a leading risk factor for glaucoma, such a system could solve the difficulties encountered in the management of this condition. In fact, glaucoma is one among those pathologies that could most benefit of an adaptive patient-specific medicine device. The presented prototype was realized with standard industrial microelectronic technologies (Flip-Chip on Kapton flexible PCB) and off-the-shelf IC components. Detailed system description and measurements, obtained during in-vitro and laboratory characterizations, are reported.**

I. Introduction

Glaucoma refers to a group of diseases providing gradual, irreversible loss of vision and, if untreated, can lead to blindness. Glaucoma is acknowledged to be the leading cause of irreversible blindness in the world. According to the most recent studies [1], one out of two glaucoma cases are undiagnosed while one of three patients does not receive adequate treatment. Its prevalence is 2-4% of the population above 40 years and it is estimated that up to 70 million patients worldwide may have glaucoma.

The inability to adequately manage this condition is tight to the difficulty to identify the onset of the degenerative process and to optimize the medical therapy. High intraocular pressure (IOP) is considered a leading risk factor for glaucoma, and lowering IOP continues to be the only evidence-based treatment for preventing the development of glaucoma or reducing the rate of its progression [2, 3].

Contemporary office-based measurements are not sufficient to discover daily changes and spikes, nor do they demonstrate the effect of medication or the patients' compliance to the prescribed therapy [4]. The detection of the IOP's variation due to circadian rhythm was confirmed to be a more valuable parameter than the standard static measure (Figure 1). Continuous 24h measurements enable the analysis of the IOP trend and detect high pressure peaks, the actual sight-threatening event in the most common forms of glaucoma [5]. A dedicated device able to directly, precisely and continuously measure IOP and its variations could actually revolutionize the management of glaucomatous condition.

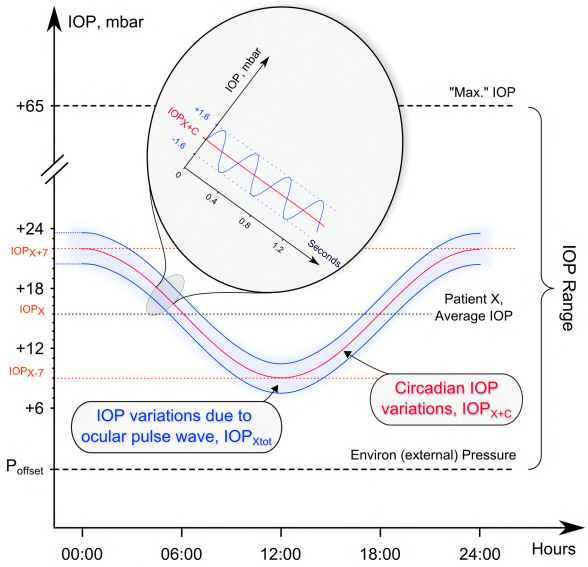

Figure 1. Typical circadian intraocular pressure signal (IOP). Even though in the ophthalmology field IOP is commonly expressed in term of mmHg, we preferred to use bar (1 mbar = 100 Pa ~ 0.75 mmHg)

Different types of non-invasive or minimal invasive IOP monitoring solutions have been studied and developed during the last decade. Many of these systems have very interesting diagnostic features such as patient-directed care, self-tonometry and continuous IOP measurements [6, 7]. Nevertheless, despite of the various solutions proposed there is no device on the market that simultaneously allows patients to directly, precisely and continuously perform IOP measurements. Companies have focused their developments on non-invasive or minimal invasive solutions at the expense of other important characteristics and functions such as direct IOP measurements (less IOP calculation difficulties and inaccuracies), true continuous monitoring in normal life conditions (patient not restrain or affected by the measurements) and chance to assist patients in their daily

treatment. Therefore, it is becoming clear that to revolutionize the management of glaucomatous condition a minimal invasive device will be insufficient.

We propose the development of an implantable medical device which allows to gather continuous and direct IOP measurements without the need of recurrent calibration and specialized operators dramatically improving the management of glaucomatous condition. The implantation of the medical device relies on standard microsurgical procedures and will not require dedicated surgical gestures. The communication with the implanted device will be ensured by an external antenna embedded, for example, in a dedicated glass frame. Data collection and data analysis will not require any action by the patient which will be warn only if daily drug consumption needs to be modified. Since glaucoma is a condition common in the elderly population (>60 years old) this last characteristic is of particular importance. From the patient prospective, the system needs to be as "invisible" as possible.

The goal of this study was to validate the system's rationale, technology and measurement strategy in order to schedule a more precise development plan. The entire developed system comprises: (i) a RFID reader and acquisition software (Figure 2), (ii) the implantable medical device and (iii) a pressure chamber with a reference pressure sensor to test and validate the measurements acquired with our system (Figure 3).

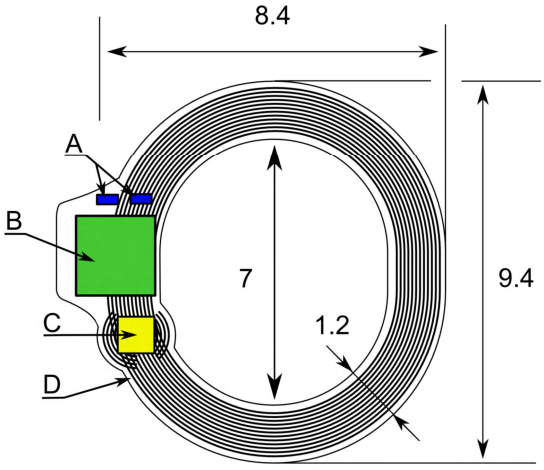

Figure 2. In scale drawing with typical dimensions and layout of the implantable device. (A) Capacitances (B) Off-the-shelf telemetry IC provided by Melexis – 2.47x2.57 mm, (C) pressure sensor 1x1 mm, (D) The substrate, flexible printed circuit. All the dimensions are expressed in mm.

The present paper is organized as follows. Section II describes the system architecture and the measurement protocols. Section III describes the experimental results. Finally, Section IV presents the conclusion and the future work for this project.

II. System Architecture

The implantable medical device was realized with standard off-the-shelf components. We designed, manufactured, assembled and coated the medical device just by exploiting the most sophisticated but still standard manufacturing and assembly techniques used for industrial production. The focus was to realize a first proof of concept, to obtain valuable information on the effective industrial technological gap existing for such a system and to find out the critical issues that still need to be solved.

We report hereunder the main components and the manufacturing and assembly procedures.

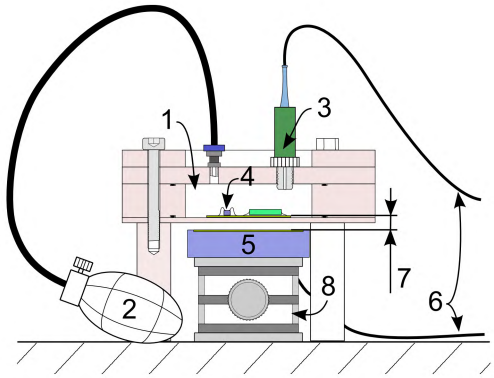

Figure 3. Pressure sensor measurement setup. (1) Pressure chamber, (2) bulb filler with valve to drive the pressure inside the chamber, (3) reference pressure sensor, (4) medical device, (5) RFID reader, (6) USB cables, (7) Distance between reader's and device's antenna, (8) Metric lab jack used to define the RFID reading distance (7).

A. *The RFID transceiver*

The RFID transceiver operates at 13.56 MHz and is powered by the electromagnetic (EM) signals sent by the RFID reader. Once the transceiver's embedded antenna pick up an interrogating EM signal (energy, commands and data) the transceiver exploits the electrical signal to supply itself and the pressure sensor. In addition, it process the received data and sends back to the reader the data gathered from the sensor.

We selected the transceiver manufactured by Melexis (MLX90129) which was the smallest RFID transceiver present on the market having the needed characteristics to interface piezo-resistive pressure sensors.

B. *The substrate*

The printed circuit board (PCB), which we called "the substrate", comprises the RFID tuned antenna and the electrical connection between the different ICs (RFID transceiver, pressure sensor IC and coupling capacitance). In addition to the track resistive requirements (in the mΩ/□ range), needed to obtain an acceptable resonator quality factor, the substrate has to fulfill tight mechanical constrains. Actually, to comply with the standard microsurgical implantation procedure, the transponder needs to be rolled-up and implanted thorough a syringe's bore with a diameter ranging between 1.4 - 2.5 mm. Once delivered, the medical device has to unfold itself to regain its original flat form.

Simple mechanical calculation reveals that the rolling and the subsequent elastic unrolling procedure is a critical task, especially for the conductive metallic layers (Figure 4).

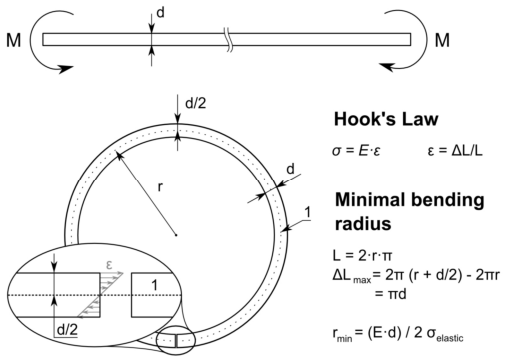

Figure 4. Calculation of the minimal ring radius (r_{min}) when a straight beam is bent in to a ring shape, and plastic deformation needs to be avoided. (M) Applied moment, (d) thickness of the beam, (r) ring radius, (ε) relative beam deformation, (1) neutral axis, (E) tensile modulus, (σ) stress, (σelastic) yield point at 3%.

In the light of these considerations, the studied substrate was manufactured in collaboration with GS Swiss PCB AG with standard manufacturing technology and the following characteristics: flexible Kapton® substrate with a thickness of 12µm (DuPont™ Pyralux®, AP-7164E), 12µm copper track thickness, 50µm/50µm Trace/space and 25µm of solder mask (NPR-80). The solder mask was added to allow the plating (Nickel-Gold) of the IC's landing pads. Gold plated pads are needed for the Flip-Chip assembly technology.

C. *The pressure sensor*

After having taken into account the different technologies and force/pressure sensing principles, we decided to focus on piezo-resistive sensors. The requirements for the analog readout electronics, the technology reliability and the small thermal excursion inside the eye are among the major parameters that drove the selection. The pressure sensor must have high sensitivity (1.3 mbar) but, at the same time, be as small as possible. The sensor plays also a relevant role for the RFID reading distance. The quality factor of the resonator is highly dependent on the energy dissipated in the medical device's circuitry. In our case, the sensor resistive load (~5kΩ) might play a major role for the RFID energy range. Taking into account all these considerations, we selected the pressure sensor SE101 from BCM which has an absolute pressure range of 0-1.5 bars.

D. *The assembly*

Assembly reliability is important because it can dramatically influence the functionality of the whole system. In particular, the assembly of the pressure sensor is a critical task since the sensitive membrane has to be left uncontaminated and clean. The assembly of all the components was performed in collaboration with Hybrid SA. Thermo compression flip-chip technology, gold stud bumps and non-conductive adhesive (Hysol® FP5001™) were tested in this first proof of concept. In addition, to further reinforce the bounding point and have a better match of the different thermal expansion coefficients, a globe top layer was deposited on the external perimeter of the pressure sensor (Hysol® EO1016) and an under fill was deposited under the RFID transceiver. For the passive components (capacitances), standard reflow soldering technology was used (SAC).

E. *The coating*

The coating and/or the materials at the interface with the environment have to be biocompatible and biostable. In our case, the coating has to fulfill another important function, the reduction/elimination of sharp edges and corners. This feature is particularly useful during the implantation procedure in order to reduce the risk of tissue injury and facilitate the folding and unfolding procedure. Parylene C coating was selected for its conformal, pin-hole free, biostable and biocompatible characteristics. Parylene is FDA approved for various medical applications.

Parylene is deposited by chemical vapor deposition and is characterized by conformal and uniform deposition over all the exposed surfaces. In the results section, we will briefly discuss the effect of Parylene C coating (thickeness of the coting layer ~5µm) on the sensitivity of the pressure sensor.

III. Experimental Results

A. *Selection of the pressure sensor*

A preliminary study was conducted to evaluate and select the best piezo-resistive pressure sensor with respect to linearity, sensitivity and reproducibility. An evaluation board (EVB) was designed to test both the short listed piezo-resistive pressure sensors (BCM SE101, GE P1602 and Melexis MLX90268CA) and some basic electronic elements composing the medical device (Figure 5).

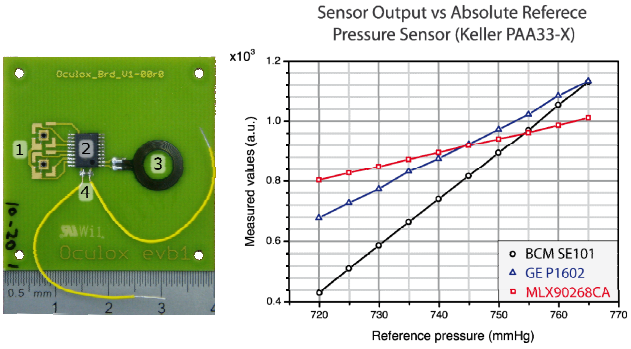

Figure 5. Preliminary evaluation board and pressure sensor sensitivity characterization. EVB's photo: (1) Pressure sensors under test wire bounded to the FR-4 board, (2) MLX90129 - TSSOP packaged RFID transceiver, (3) Tuned RFID antenna, (4) Decoupling capacitance hundreds of nF EIA0201.

In order to evaluate the performance of the selected pressure sensor, the EVB was positioned in the pressure chamber (Figure 3) and together with the Melexis' RFID development kit (DVK90129), the measured values were retrieved and compared with the value provided by a reference pressure sensor (Keller PAA33-X). During the measurements, the temperature was maintained constant at 22°C and the sensor output (16-bit) was encoded in 11-bit. By looking at the results, the best sensor was the BCM SE101, with an approximate sensitivity of 0.1mbar.

B. *Measurements using the medical device*

The manufacturing and assembly of our medical device was successful even if the yield of functioning devices was only 50%. The poor yield is attributable to some minor issues encountered during the assembly phase. The same issues have also a major contribution (~ 60%) in the reduction of the sensors' sensitivity (Figure 6). The observed sensor's sensitivity reduction, which is attributable to the conformal Parylene C coating, is ~ 20%.

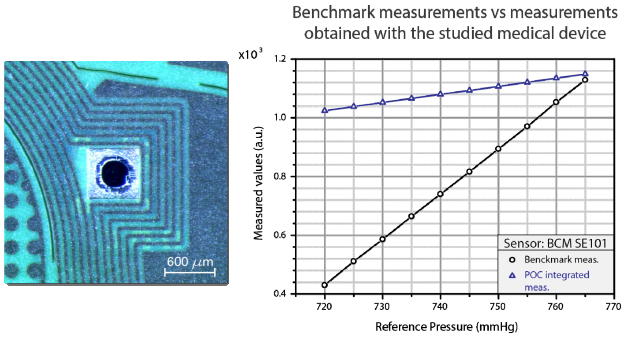

Figure 6. Comparison pressure measurements to evaluate the pressure sensor sensitivity changes of the fully integrated medical device respect to benchmark. The photo on the left depicts the encountered assembly issue (sensor membrane contamination)

The substrate presented the calculated electrical characteristics: antenna resistance 11±1 Ω, inductance 1.7±0.05 μH. Preliminary rolling and unrolling mechanical tests show that the substrate still has to be improved since plastic deformation occurs already when the curvature radius is smaller than ~2.5 mm.

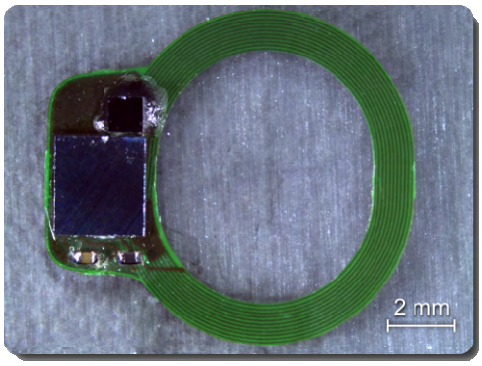

Figure 7. Developed implantable medical device

The energy range of the medical device, assessed using the standard reader provided with the development kit (DVK90129), is limited to ~20 mm.

IV. Conclusions and Future Work

The results obtained with the presented medical device (Figure 7) are consistent with the theoretical calculation and the forecast. Several different ideas sprung from the performed analysis and tests (e.g. exploit the polymer used for intraocular lenses as substrate, modify the structure of the pressure sensor to facilitate the assembly procedure). Simultaneously different new technologies which may fit perfectly in our concept became commercially available (e.g. specific and innovative metal deposition technology, new assembly techniques).

The design and manufacture of an application-specific transceiver in order to substantially reduce the current IC area and implement a low-power transmission protocol (currently we rely on the ISO15693) are under development. We are also developing our own piezo-resisitve pressure sensor which will present high sensitivity, adapted Wheatstone bridge resistance and a dedicated MEMS structure to dramatically facilitate the assembly procedure. A specific reader with an optimized antenna and an optimized output power will also be developed. Preliminary theoretical calculations on radio frequency exposure (varying magnetic field) show that the system will comply to the IEEE Std C95.1a concerning the basic restriction and maximal permissible human tissue exposure. In addition, we are evaluating new technologies to manufacture an implantable substrate simultaneously characterized with the sufficient electrical resistivity but enhanced mechanical properties (Figure 8).

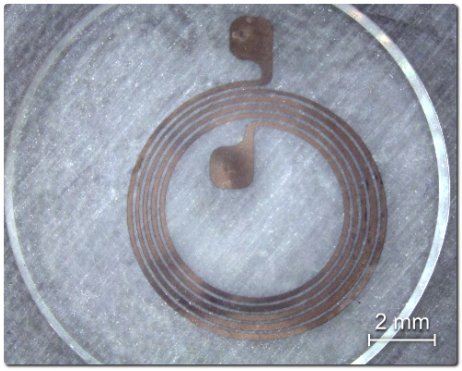

Figure 8. Deposition of dedicated circuits on FDA approved polymer. The same polymer is used to manufacture intraocular lenses.

V. References

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