In-Vivo Validation of Fully Implantable Multi-Panel Devices for Remote Monitoring of Metabolism

Camilla Baj-Rossi, Andrea Cavallini, Enver G. Kilinc, Francesca Stradolini, Tanja Rezzonico Jost, Michele Proietti, Giovanni De Micheli, *Fellow, IEEE*, Fabio Grassi, Catherine Dehollain, *Member, IEEE*, and Sandro Carrara, *Fellow, IEEE*

***Abstract*—This paper presents the *in-vivo* tests on a Fully Implantable Multi-Panel Devices for Remote Monitoring of endogenous and exogenous analytes. To investigate issues on biocompatibility, three different covers have been designed, realized and tested in mice for 30 days. ATP and neutrophil concentrations have been measured, at the implant site after the device was explanted, to assess the level of biocompatibility of the device. Finally, fully working prototypes of the device were implanted in mice and tested. The implanted devices were used to detect variations in the physiological concentrations of glucose and paracetamol. Data trends on these analytes have been successfully acquired and transmitted to the external base station. Glucose and paracetamol (also named acetaminophen) have been proposed in this research as model molecules for applications to personalized and translational medicine.**

***Index Terms*—Epoxy resin, fully implantable biochip, glucose, packaging, paracetamol, parylene C, polycarbo-nate membrane.**

I. Introduction

HIGHLY integrated and complex monitoring systems are more and more required in advanced health care as well as in translational medicine. In particular, the continuous and simultaneous monitoring of several analytes can be realized with fully implantable multi-panel devices that integrate heterogeneous systems to address different device functions [1]. However, several aspects need attention in this new area of systems integration: coupling nano and biomaterials with CMOS electronics [2], security and privacy constrains [3], new design in power [4] and data transmission [5], and biocompatibility issues [6].

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C. Baj-Rossi, A. Cavallini, F. Stradolini, G. De Micheli, and S. Carrara are with the Laboratory of Integrated Systems, Swiss Federal Institute of Technology (EPFL), 1015 Lausanne, Switzerland (e-mail: sandro.carrara@epfl.ch).

E. G. Kilinc and C. Dehollain are with Radio Frequency IC Group, Swiss Federal Institute of Technology (EPFL), 1015 Lausanne, Switzerland.

T. Rezzonico Jost and M. Proietti are with Institute for Research in Biomedicine, Università della Svizzera Italiana, CH-6500 Bellinzona, Switzerland.

F. Grassi is with the Institute for Research in Biomedicine, Università della Svizzera Italiana, CH-6500 Bellinzona, Switzerland, and also with the Department of Medical Biotechnology and Translational Medicine, Università degli Studi di Milano, Istituto Nazionale Genetica Molecolare, 20134 Milan, Italy.

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To reduce the effects of the foreign body reaction, an external biocompatible packaging is usually required to ensure a correct integration with the surrounding tissue once the device is implanted. Polyurethane, among many other polymers, has been extensively used as an outer membrane to act as a biocompatible interface.

In this paper, we show the realization test of different packagings for an implantable device for continuous monitoring of drugs and endogenous molecules in small animals, which consists of a sensing platform hosting several electrochemical sensors, three *integrated circuits* (ICs) (one as sensors frontend, a microcontroller, and the power/data manager) and a powering antenna. Potential sources of inflammation are attributed to the shapes and size of the device, and to used materials too. *Multi-walled carbon nanotubes* (MWCNTs), used to enhance the sensing signal, were entrapped in a chitosan matrix to prevent toxicity due to their nano-particle nature. Parylene C was employed to prevent the leaking of potential hazardous substances and the corrosion of the electronics from the biological fluids. Two different membranes were used to cover the sensing part of the device. In this paper, we present and discuss three different solutions for the packaging (Fig. 1) and the related biocompatibility tests. The best packaging has been finally chosen to validate the monitoring functions of the device in mice monitoring and the system performance are here reported.

II. Materials and Methods

A. Integrated Device Fabrication and Assembly

The micro-fabrication of the sensing platforms was realized at the EPFL Centre of Micro-nano Technology (CMI). Silicon wafers with 500 nm of native oxide were chosen as substrate. Chip metallization was realized by evaporation of 10 nm of Ti, followed by 100 nm of Pt. Metal passivation was made via atomic layer deposition of Al_2O_3, followed by dry etching with Argon Ion Milling. Further details on the micro-fabrication have been already published and can be found in [7].

Fig. 1(a) shows the photograph of the first implantable device. The passive sensing platform measures 2.2 $\times$ 15 mm, and host five independent Pt working electrodes (WE) with common reference (RE) and counter (CE) electrodes [8].

Fig. 1(b) and (c) show the photographs of the second and third version of the implantable device, respectively. In this second version, the platforms measure 12 $\times$ 11 mm in order

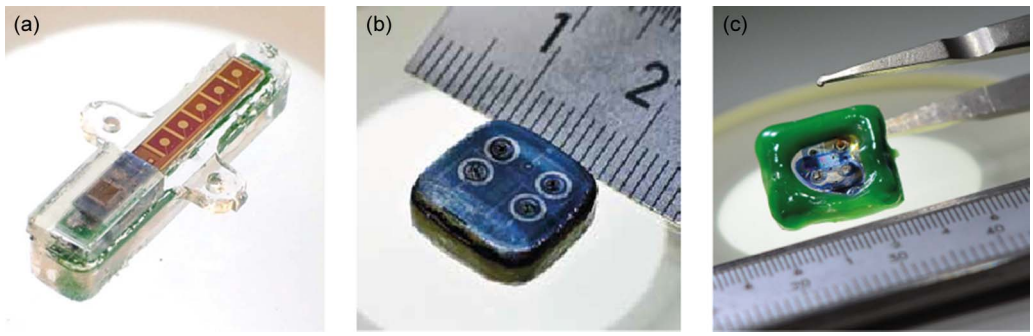

Fig. 1. Photograph of the three versions of the implantable device.

to fit the size of the coil (12 × 12 mm) and allow wire bonding. The platform hosts an array of four independent cells in the more classical three-electrode configuration. A detailed description of the design of this second sensory system has been already published [9]. Again, all the electrodes have been made in Pt. Details related to the Integrated Circuits (IC), designed and realized in UMC 0.18 μm CMOS technology, have been published too [10] as well as all the details related to the remote system used to power the implants [11].

B. Packagings

In the realization of the first packaging, 0.1 μl of a chitosan-MWCNT suspension was manually drop cast on the electrodes, and dried in air, for the sensors nanostructuration. The surface of the biosensors was then protected with a polycarbonate membrane (Cyclopore track etched membrane, cut off 100 nm, Whatman) and sealed with a fast curing medical grade silicone (Med2-4220, Nusil). The sensing platform and the electronic components were glued together using the USP class VI biocompatible glue (Loctite 3211 USP, Loctite). Components interconnection was realized with aluminum wire bonding and protected with a glob top. To further improve adhesion and moisture penetration, the assembled platform was treated with silane A-174 (from Merck) and then coated with 16 μm of parylene C (from Specialty Coating Systems), deposited by chemical vapor deposition using a Comelec C-30-S Parylene deposition system. The outer silicone shell was realized by placing the implant into a Plexiglas mold (realized by micromachining) and by injecting the biocompatible medical-grade silicone (Med-6033 from Nusil). To increase the host comfort, the outer shell was realized 1 mm thick and with rounded corners.

In the second and third version of the packaging, the epoxy adhesive (EP42HT-2Med) system was instead used to assembly the electronic components and the sensing platform. The sensing platform was placed on the top of the PCB containing the ICs and the microprocessor. The interconnections between the pads of the sensing platform and the electronic components were realized with aluminum wire bonding and were protected with a glob top protection of 0.3 mm. In the second version of the implantable device, all the edges of the device were rounded with a milling machine. Two subsequent 5 μm layers of Parylene C were then deposited by chemical vapor deposition using a Comelec C-30-S Parylene Deposition System. Parylene C was used to cover the whole device but not the electrode array that needs to be in contact with body fluids. The electrodes were again functionalized with MWCNTs (same approach previously described for the first packaging). Finally the device was covered with three layers of a biocompatible membrane made by epoxy-enhanced polyurethane. For the biocompatible outer packaging, a homogeneous solution was obtained by mixing 125 mg of an epoxy adhesive (EP42HT-2Med system), purchased by Master Bond (Hackensack, USA) as a certified biocompatible two-components adhesive, 112.5 mg of polyurethane (Sigma Aldrich), 12.5 mg of the surfactant agent polyethylene glycol ether (Brij 30, Sigma Aldrich), for 10 ml of tetrahydrofuran (THF, Sigma Aldrich) used as solvent. Subsequent depositions of the membrane by dip coating were applied at 1 h intervals and then the sensors were stored overnight at room temperature. A fast curing at high temperature (2 h at 80 °C) was needed to ensure the biocompatibility of the resin. After this process the sensors were again kept overnight at room temperature, and then stored in PBS one day for membrane swelling.

For the third version of the implantable device, silicone and epoxy resin have been used together [12]. The usual procedure (described before) has been used for the electrode functionalization with MWCNTs. The edges of the device were not rounded with a milling machine, and two different biocompatible silicone elastomers were used to cover and round the edges and the bottom of the device: a first layer was realized with the Kwik-cast sealant (from World Precision Instruments), and the second more external layer with a certified biocompatible elastomer silicone (Nusil MED2 4220). The sensing part was only covered with the epoxy-enhanced polyurethane to assure a porous membrane. The overall weight and volume of the device are 0.61 g and 0.4 cm^3, respectively.

Fig. 2 reports the scheme with cross-sections of the three different implantable devices with the respective packaging. In all the cases, C57Bl/6 male mice (2 months old) were used for the experiments. The animals were bred and treated in accordance with the Swiss Federal Veterinary Office guidelines and were kept in specific pathogen-free animal facility. Experiments were approved by "Dipartimento della Sanità e Socialità" with authorization numbers TI-19/2010, TI-20/2010 and TI-09/2013. Before implantation, the microchips were accurately cleaned and disinfected with ethanol 70%. Then placed in sterile PBS (Gibco) for 24 h to stabilize the membrane, and further placed under UV light for 1 hour.

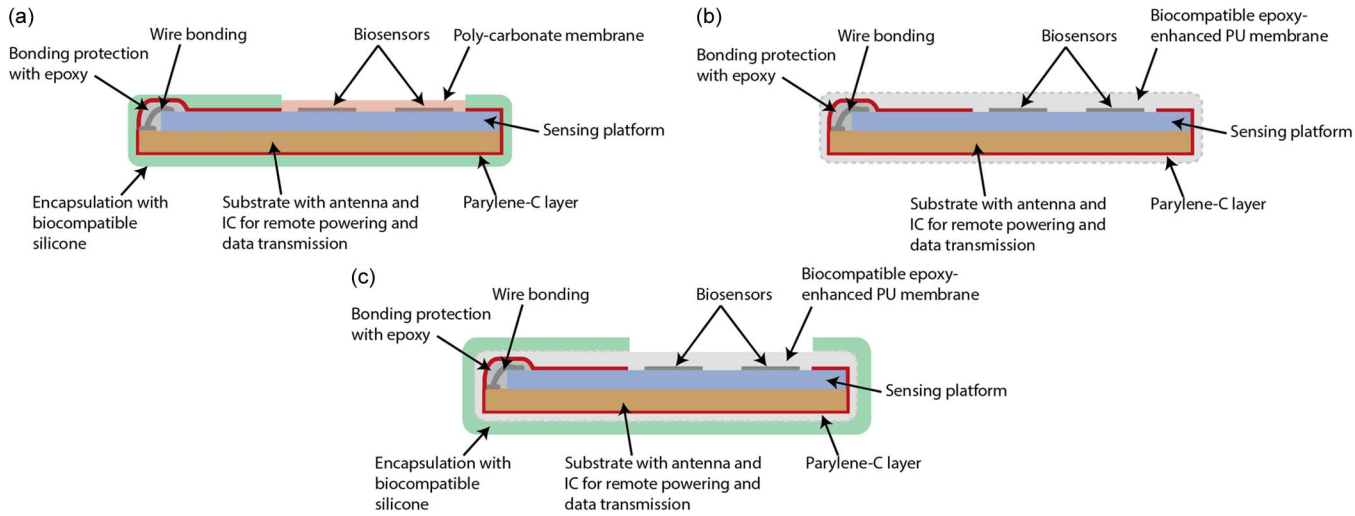

Fig. 2. Schematics of the three implantable devices. (a) The first. (b) The second. (c) The third.

C. In-Vivo Biocompatibility Tests, First and Second Packagings

An *Air Pouch* (AP) was created by subcutaneous injection of sterile air in the back of the mice at day 1 (5 mL) and day 3 (3 mL); this procedure creates a cavity of 1.5 cm diameter and 0.5 cm height. At day 6, mice were anesthetized with isoflurane 4%, shaved and locally sterilized with Betadine Solution; the sterile microchips were implanted and the cavity sutured with Vicryl 6.0 (Provet AG). As a control of local inflammation, *bacterial lipopolysaccharide* (LPS, 50 g/mouse, LabForce AG) was injected daily into the cavity for the last 2 weeks of the 30 days of the experiment. As negative control, APs were generated in absence of any surgical procedure. As further control, commercial chips (DATA MARS) were injected through sterile needle. After 30 days, the microchips were removed, the cavity was rinsed with 0.5 mL of PBS (Gibco) and the liquid collected and centrifuged (7000 rpm for 10′ at 4 °C) for further analysis.

D. In-Vivo Biocompatibility Tests, Third Packaging

The procedures for *in-vivo* tests as well as for the controls have been conducted by following the details described in the previous session but the sterile microchips were here implanted in the peritoneum and the cavity sutured with Vicryl 6.0 (Provet AG). After 30 days, the microchips were removed as well, the peritoneal cavity was rinsed with 0.5 mL of PBS (Gibco) and the liquid was again collected and centrifuged (7000 rpm for 10′ at 4 °C) fur further analysis. In this case, peritoneal wash was performed to mice with absence of any surgical procedure as a further negative control.

E. In-Vivo Biocompatibility Tests: Assessment of the Level of Inflammation

The concentration of ATP was determined in the supernatant of the washing collected liquid with an ATP determination kit (Invitrogen). For polymorphonuclear neutrophils detection, the pellet was re-suspended in 0.2 mL RPMI 10% Fetal Bovine Serum (Gibco) and analyzed at flow cytometer (FACS Canto, Becton Dickinson) with antibodies specific for CD11b and Gr1, labeled with allophycocyanin (APC) and fluorescein isothiocyanate (FITC, BioLegend), respectively.

F. In-Vitro Metabolism Monitoring

We also performed calibrations in chronoamperometry at +650 mV of the sensors towards detection of paracetamol (also known with the name of "acetaminophen" in North America, and proposed here as a model of exogenous analytes) and glucose (here as model of endogenous analytes). For glucose detection, related electrodes in the tested devices were modified by direct drop-cast of 0.2 μl of MWCNTs dissolved in chloroform and 1 μl of Glucose Oxidase in PBS at the concentration of 15 mg/ml. For paracetamol detection, the electrodes were cleaned and used without functionalization. To perform the calibration, the devices were placed inside the cage at a fixed position and the chip was covered with 200 μl of PBS at increasing concentrations of glucose or paracetamol. Calibration lines were calculated from the evaluation of the current steps by measuring the difference between the reached current value and the baseline (corresponding to the current at 0 μM of glucose or paracetamol). Sensitivity and LOD were evaluated in linear regression of data, according to [9].

G. In-Vivo Metabolism Monitoring, Third Packaging

Preliminary *in-vivo* tests with mice were performed in order to understand the main features of the present technology and its main limitations. First, it was necessary to understand if the powering system provides enough energy to the monitoring device once implanted in animals. Even a thin layer of tissue, e.g., the skin of mice, could affect the efficiency of the powering link as it increases the distance between the implanted and the powering coils. Then, the ability of the sensors to measure *in-vivo* both endogenous and exogenous analytes was investigated. As well as for the *in-vitro* tests, the sensing electrodes

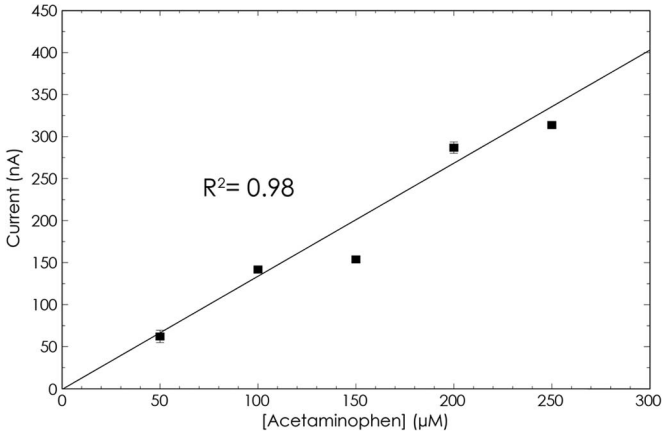

Fig. 3. Calibration curves obtained in chronoamperometry with the autonomous microsystem upon successive injections of acetaminophen.

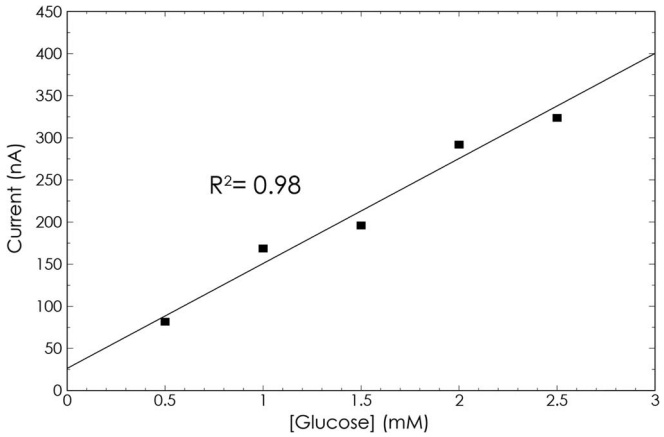

Fig. 4. Calibration curves obtained in chronoamperometry with the autonomous microsystem upon successive injections of glucose.

were functionalized with MWCNTs and the devices were covered with three layers of biocompatible membrane made by epoxy-enhanced polyurethane [9]. For glucose detection, the electrodes were functionalized by drop-cast of MWCNTs in chloroform, followed by the drop-cast of MWCNTs in chitosan, ad by the drop-cast of a solution 15 mg/ml of glucose oxidase and glutaraldehyde 0.25%. In this case, mice were anesthetized with isoflurane, shaved and locally disinfected with Betadine solution; the sterile microchips were implanted in the peritoneum and the cavity sutured with Vicryl 6.0 (Provet AG).

III. Results and Discussion

A. In-Vitro Tests and Calibrations

Measurements for calibrations on paracetamol and glucose were carried out with both the fixed coil and the intelligent moving remote powering systems [11]. Here we report the calibration obtained with the moving powering system. Figs. 3 and 4 show the calibration curves obtained for acetaminophen (also named paracetamol) and glucose, respectively. For glucose we obtained a sensitivity of 38 ± 11 μA/mMcm^2 and a LOD of 0.6 ± 0.3 mM, which is relevant in many clinical applications [13].

Many other human analytes of clinical interest (e.g., lactate, glutamate) can be monitored with our sensing platform, by simply changing the enzyme that is employed for the electrode functionalization. For acetaminophen, we obtained a sensitivity of 66 ± 21 μA/mMcm^2 and a LOD of 34 ± 11 μM, which compare quite well with physiological ranges [14]. Although the calibrations are non perfectly linear, we can conclude that our system can autonomously receive power, actuate the sensors to measure glucose and acetaminophen within the physiological ranges, read the data, and transmit them to the external station.

B. In-Vivo Tests on Biocompatibility

In general, the main features of an implantable device that can be sources of inflammation are the shape, the materials, and the sizes of the device [15]. In this paper, we compare three different packagings realized with different shapes, sizes and with different materials. However, they all share some common features: i) MWCNTs were entrapped in a chitosan matrix to prevent the potential toxicity due to their nano-particle nature; ii) a coating of Parylene C was deposited to prevent the corrosion of electronic components due to the contact with biologic fluids as well as to prevent the leaking of potential hazardous substances [8], [9]; iii) a biocompatible packaging was realized to correct wound healing as well as to ensure prolonged sensor functionality. The main differences between the three systems are: i) the shape of the device; (ii) the shape of the packaging in silicone; (iii) the composition of the membrane that covers the sensors; (iv) the composition of the external packaging. All these differences are well summarized in Fig. 2.

To compare the properties of the different designs, the *in-vivo* biocompatibility of the implantable devices was investigated by subcutaneously implanting the prototypes in mice for 30 days. Moreover, in order to test if the position of the implant influences the final biocompatibility, the first two prototypes were implanted in the back of mice, and the third one was implanted in the peritoneum.

At the end of the period, the implant site was washed with PBS, and levels of ATP and neutrophils in the elution liquid were quantified to follow the local inflammatory response. ATP and neutrophils are both inflammatory mediators as ATP is usually released from endothelial cells during acute inflammations [16].

Data from ATP and neutrophils for the first prototype, depicted in Fig. 5, suggest that the host seems to accept the insert, as verified after 30 days. For the first version of the packaging, further comparison with commercial chips in terms of neutrophil level as well as biocompatibility tests with cell cultures have been also published in [8].

Fig. 6 reports ATP and neutrophil variations in the liquid collected from the implant site for the second version of the packaging. ATP and neutrophil levels were also evaluated for an implanted commercial chip (DATA MARS), for a negative control (mice with AP), and for the case of an artificial inflammation introduced with the injection of bacterial lipopolysaccharides (LPS). As shown in the last column in Fig. 6, the negative control presents a barely detectable concentration of neutrophils, while there is still a small amount of extracellular

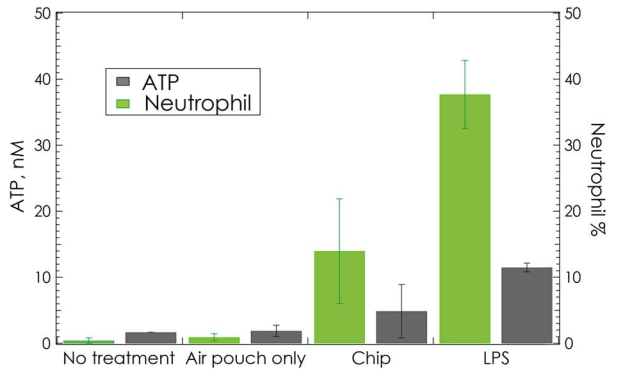

Fig. 5. ATP concentrations (nM) recovered from APs after 30 days from the implant of several prototypes of the first version of the implantable device.

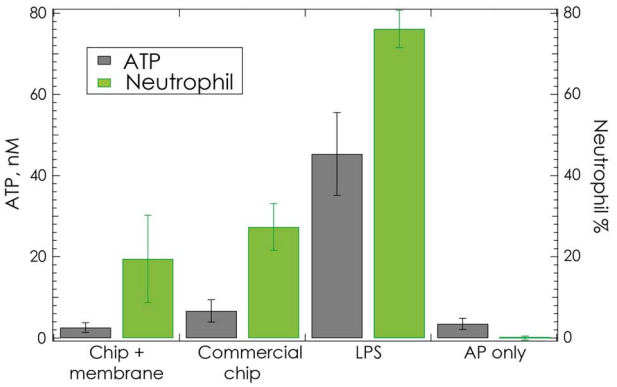

Fig. 6. ATP concentrations (nM) and % of neutrophils recovered from APs after 30 days of several prototypes of the implant of the second version of the implantable device.

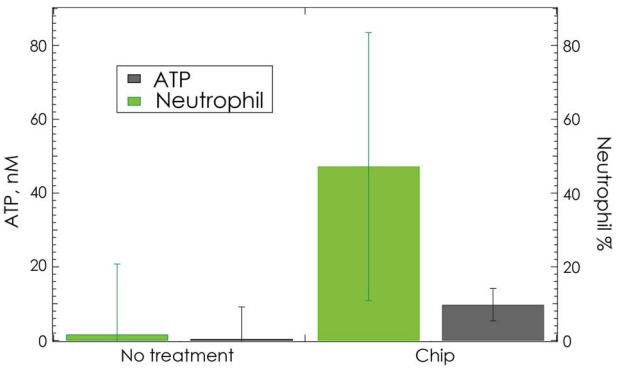

Fig. 7. ATP concentrations (nM) and % of neutrophils recovered from APs after 30 days from the implant of the third version of the implantable device.

ATP due to mechanical stress created during the collection of the fluid. Data from both ATP and neutrophil concentrations suggest that the membrane alone already provides a quite good biocompatible coverage. Furthermore, ATP and neutrophil levels are comparable with the negative control (AP), as well as for the commercial chip, and significantly lower than the positive control (LPS), proving that the host seems to accept the implant, as verified by measures after 30 days by the implantation.

We also performed *in-vivo* biocompatibility tests with the third version of the packaging, made by the epoxy enhanced

Fig. 8. Positioning of the device in the peritoneum of the animal (on the left) and the suture after the surgery (on the right).

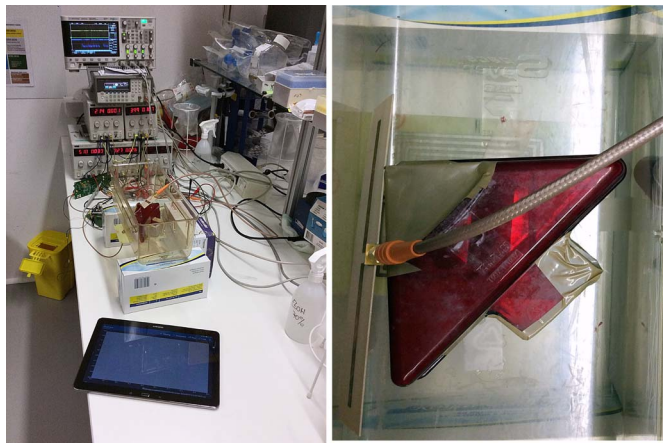

Fig. 9. Experimental setup for *in-vivo* measurements (on the left); the transparent plastic shelter with a red tint, placed inside the cage (on the right).

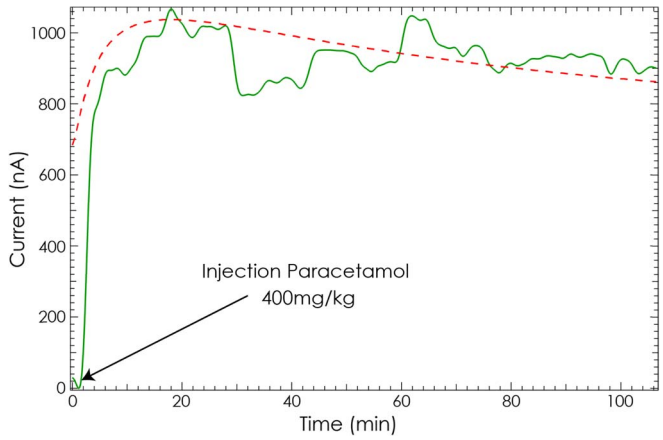

Fig. 10. *In-vivo* monitoring of Paracetamol with the device implanted in mice.

polyurethane membrane and by the biocompatible silicone. Four prototypes were implanted for 30 days in the peritoneum of mice. The values for ATP and neutrophil concentration are reported in Fig. 7. Unfortunately, neutrophils were still high after 30 days compared to the negative control, proving that the host does not tolerate this implant.

C. In-Vivo Validation With the Implantable Device and the Third Packaging

As preliminary tests, measurements were performed few hours after the surgery, to avoid the inflammation due to the foreign body reaction process that could significantly affect

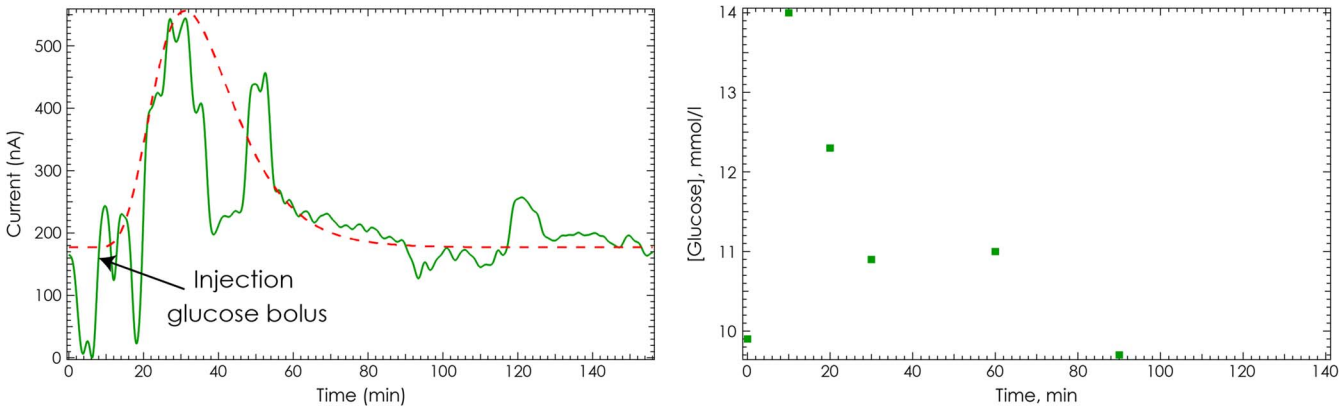

Fig. 11. *In-vivo* monitoring of glucose by the device implanted in mice (on the left), and by external glucometer on mouse' tail blood (on the right).

the measurements, due to an uncontrolled increase of the neutrophils and the release of ATP.

After having acquired some data streams from the implanted devices, 400 mg/kg of paracetamol (previously dissolved in ethanol), or a glucose bolus of 2 mg/kg (accordingly with the mouse weight), were injected in the peritoneum and data were acquired for Paracetamol and glucose for 90′ and 140′, respectively.

After the experiments, the animals were sacrificed and the devices were removed by surgery. Fig. 8 shows the positioning of the device in the peritoneum of the animal (a) and the suture after the surgery (b), while Fig. 9 (on the left) illustrates the experimental setup for the *in-vivo* measurements: three power suppliers, one frequency modulator, a signal generator, an oscilloscope and the PCBs that receive and transmit via Bluetooth the data to a tablet; the plastic shelter is placed in the mouse cage and the tablet displays the measurement. For sake of simplicity, a single coil placed under the cage was used instead of the servo-controlled system [11]. This configuration was selected in order to reduce the sources of noise mainly because, in this preliminary study, the main goal was to validate the transmission of power to the device and reception of data from the device. For that, it was more than sufficient to have the mouse confined in a smaller space. Fig. 9 (on the right) shows the transparent plastic shelter with a red tint normally used in animal laboratories to keep mice calm and avoid stress to animals. As mice do not see red colors but perceive them as being gray or dark, this design is thought to provide a dark shelter for mice. As humans do see red colors, the red transparent material allows inspections of the animals while they are inside the shelter without disturbing them [14].

Fig. 10 shows the *in-vivo* real-time monitoring of the drug paracetamol, after it was injected in the peritoneum of the mouse. The noise from the signal was filtered (with a FIR filter) during data post-processing. Even if the registered noise was quite relevant, typically due to movements of the mouse, a trend can be clearly registered, as roughly highlighted in red in Fig. 10: the signal increases after the injection and it slowly decreases after approximately 30′ of measurements.

As the drug is measured in the peritoneal fluid, we are not expecting to obtain a typical pharmacokinetics curve. In fact, pharmacokinetics curves are obtained from measurements in blood, as reported in this study that shows pharmacokinetics curves after the administration of Paracetamol in mice [17]. In future studies, it would be interesting to associate the paracetamol electrochemical monitoring with another quantitative method, e.g., with HPLC.

Fig. 11 (on the left) shows the *in-vivo* real-time monitoring of the variation in glucose concentration, acquired after that a glucose bolus (2 mg/kg of mouse) was injected in the peritoneum of the mouse. Even if the signal is noisy, a peak of current starting 20′ after the bolus injection can be easily recognized. After the peak, the current start decreasing until it goes back to its original value. The glucose metabolic curve (roughly highlighted in red) is reported in Fig. 11 (on the right) and was obtained by measuring the glucose concentration with an external glucometer, after 10′-20′-30′-60′-90′ the bolus injection. The peak of glucose concentration happens after 10′ the injection. Thus, we can conclude that we had a lag time, of around 20′, by measuring in the peritoneum in comparison with values reported in previous studies on subcutaneous glucose measurements [18].

IV. Conclusion

From these tests we can conclude that the peritoneum is probably not the best place to implant the device. Moreover, data from tests run with the first and second prototypes proved that both the PU-based membrane and the packaging made in silicone elastomer provide a quite good biocompatible coverage. However, fibrous capsules have been observed around the implant after the explant of the packaging realized with the PU-based membrane covering the entire device while this phenomenon has been registered as negligible in the case of the third packaging. Therefore, the membrane in polyurethane represents the best solution as a membrane for the sensing part (as the deposition technique is more reliable and reproducible than the procedure used to fix the polycarbonate membrane) while the best protective and biocompatible packaging for the entire device definitely is the one realized in biocompatible silicone, coherently with other independent tests already published by other authors [12], [19], [20].

The device packed with the silicone elastomer with the polyurethane membrane in front of the biosensors has been

finally successfully tested for continuous monitoring of both endogenous and exogenous analytes in free moving mice demonstrating the working functions of the monitoring system.

The implanted device is fully capable to acquire data in continuous monitoring of glucose and paracetamol, while the remote powering system is not always capable to continuously send the required amount of energy due to the mouse' movements and the related misalignment of the receiving and transmitting coils, as we have had occasion to verify and publish [21].

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Camilla Baj-Rossi received the bachelor's degree and the master's degree in biomedical engineering from Politecnico di Torino, Torino, Italy, in 2008 and 2010, respectively.

Currently, she is working toward the Ph.D. degree in microsystems and microelectronics in the Laboratory of Integrated System (LSI) under the direction of S. Carrara and G. De Micheli. She carried out her master's project with LSI, École Polytechnique Fédérale de Lausanne, working on the design of a multipanel biochip based on P450 and CNT for drugs monitoring in personalized therapy.

Andrea Cavallini received the master's degree in molecular biotechnology from the University of Bologna, Bologna, Italy, and the Bachelor's degree in pharmaceutical biotechnology from the University of Ferrara, Ferrara, Italy.

Currently, he is working toward the Ph.D. degree in microsystems and microelectronics with at École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, under the supervision of Prof. S. Carrara and Prof. G. de Micheli. His research interests include development of implantable biosensor arrays for personalized therapy.

Mr. Cavallini was a recipient of the Best Poster Award at the Nanoeurope Conference in 2009 for his research on P450 biosensors, and the Bronze Leaf Award for his paper at PRIME 2010.

Enver G. Kilinc received the B.Sc. degree in electronics engineering from Istanbul Technical University (ITU), Istanbul, Turkey, in 2008, and the M.Sc. degree in electrical and electronic engineering and the Ph.D. degree in microsystems and microelectronics from École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, in 2010 and 2014, respectively.

In 2010, he joined the Electronics Laboratory, EPFL, as a Research Assistant in the field of RFIC design. He was a Postdoctoral Fellow in the Electronics Laboratory in 2015. Currently, he is a Postdoctoral Fellow in wireless power transmission and implantable biomedical system design with the Advance Digital Systems Laboratory (ADSL), University of Toronto, Toronto, ON, Canada. His research interests include RF CMOS circuit design for wireless sensor systems and biomedical applications.

Francesca Stradolini received the M.Sc. degree in biomedical engineering from the University of Genova, Genova, Italy, in 2015.

She carried out her master's thesis with the École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, working on the development of an Android interface for the wireless and continuous monitoring of metabolites. Moreover, she got the Advanced Studies in Information Technologies and Communication Certificate in 2012. Currently, she is a Doctoral Assistant at the Integrated System Laboratory, EPFL. Her research interests include the development of a non-implantable prototype for the monitoring of multiple anesthesiology drugs in human blood with the total realization of the sensing platform, microfluidics system, and the software development.

Tanja Rezzonico Jost received the master's degree in veterinarian biotechnology sciences from the University of Milano, Milano, Italy.

From 2003 to 2010, she was a Veterinarian Assistant in the Veterinarian Clinic "Acacia" in Lugano, Switzerland. Currently, she is a Research Assistant in the T cell development lab, Institute for Research in Biomedicine, Bellinzona, Switzerland.

Michele Proietti received the master's degree in medicine from the University of Rome, Rome, Italy, in 2001, and the Ph.D. degree in experimental and clinical immunology from the University of Genoa, Genoa, Italy.

From 2001 to 2006, he was Resident with Internal Medicine, University of Rome, Rome, Italy, where he was involved in the management of inpatients and outpatients affected by autoimmune diseases. From 2007 to 2010, he was a Research Fellow with the Center of Excellence for Biomedical Research, University of Genoa. Currently, he is a Postdoctoral Researcher in the T cell development lab, Institute for Research in Biomedicine, Bellinzona, Switzerland. His research interests include various aspects of T cell physiology in inflammation and autoimmunity.

Giovanni De Micheli (F'94) received the Nuclear Engineer degree from Politecnico di Milano, Milano, Italy, in 1979 and the M.S. and Ph.D. degrees in electrical engineering and computer science from the University of California, Berkeley, Berkeley, CA, USA, in 1980 and 1983, respectively.

Currently, he is a Professor and the Director of the Institute of Electrical Engineering and of the Integrated Systems Centre, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland. He is the Program Leader of the Nano-Tera.ch Program. His research interests include several aspects of design technologies for integrated circuits and systems, such as synthesis for emerging technologies, networks on chips, 3-D integration, heterogeneous platform design including electrical components and biosensors, as well as in data processing of biomedical information.

Dr. De Micheli was the recipient of the 2003 IEEE Emanuel Piore Award for his contribution to computer-aided synthesis of digital systems, the Golden Jubilee Medal in 2000 for outstanding contributions to the IEEE CAS Society, the 1987 D. Pederson Award for the Best Paper in the IEEE TRANSACTIONS ON COMPUTER-AIDED DESIGN OF INTEGRATED CIRCUITS AND SYSTEMS, the Best Paper Award at the Design Automation Conference in 1983 and 1993, and the Best Paper Award at the DATE Conference in 2005. He is a Fellow of the ACM and a member of the Academia Europaea.

Fabio Grassi received the master's degree in medicine from the University of Pavia, Pavia, Italy, and the Ph.D. degree in microbiology from the University of Milan, Milan, Italy, in 1985 and 1993, respectively.

He was an Anna Villa Rusconi Fellow with the University of Umeä, Umeä, Sweden, in 1988, a Postdoctoral Fellow with Institut Pasteur, Paris, France, from 1989 to 1993, an Assistant Professor with San Raffaele Scientific Institute, Milan, Italy, from 1994 to 1998, a Marie Curie Fellow with Hôpital Necker, Paris, from 1998 to 2000, and a Special Fellow of the Leukemia and Lymphoma Society with Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, from 2000 to 2002. Currently, he is a Full Professor of biology with the Medical School, University of Milan. In 2002, he joined the Institute for Research in Biomedicine Bellinzona, Switzerland, as the Head of the T cell development lab. His research interests include T cell physiology, including protein and membrane trafficking, signal transduction, control of cell growth and intercellular communications during T cell development, and immunopathological conditions.

Catherine Dehollain (M'93) received the Master's degree in electrical engineering and the Ph.D. degree from École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, in 1982 and 1995, respectively.

From 1982 to 1984, she was a Research Assistant at the Electronics Laboratories (LEG), EPFL. In 1984, she joined the Motorola European Center for Research and Development, Geneva, Switzerland, where she designed integrated circuits applied to telecommunications. In 1990, she joined EPFL as a Senior Assistant at the "Chaire des Circuits et Systemes," where she was involved in impedance broadband matching. Since 1995, she has been responsible for the EPFL-RFIC Group for RF activities. She has been the technical project manager of the European projects, Swiss CTI projects, and the Swiss National Science Foundation projects dedicated to mobile phones, RF wireless micropower sensor networks, and biomedical applications. Since 1998, she has been a Lecturer at EPFL in the area of RF circuits, electric filters, and CMOS analog circuits. From 2006 to 2014, she was a Maitre d'Enseignement et de Recherche (MER) at EPFL. Since 2014, she has been Adjunct Professor at EPFL. She is an author or coauthor of five scientific books and 160 scientific publications. Her research interests include low-power analog circuits, biomedical remotely powered sensors, and electric filters.

Sandro Carrara (F'16) has an outstanding record of accomplishments in the field of design of nanoscale biological CMOS sensors. He is a faculty member (MER) at École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland. His scientific interests are on electrical phenomena of nano-bio-structured films, and include CMOS design of biochips based on proteins and DNA. He has authored seven books, one as author with Springer on Bio/CMOS interfaces and, more recently, *Handbook of Bioelectronics* (Cambridge, U.K.: Cambridge University Press). He has also authored more than 200 scientific papers and 12 patents.

Dr. Carrara is currently Editor-in-Chief (Associate) of the IEEE SENSORS JOURNAL; he is also founder and Editor-in-Chief of the journal *Bio-NanoScience* (Springer), and Associate Editor of IEEE TRANSACTIONS ON BIOMEDICAL CIRCUITS AND SYSTEMS. He is a member of the Board of Governors (BoG) of the IEEE Circuits And Systems Society (CASS). He is member-at-large of the IEEE Sensors Council. He was appointed as IEEE CASS Distinguished Lecturer for 2013–2014. He was the General Chairman of IEEE BioCAS 2014, the premier worldwide international conference in the area of circuits and systems for biomedical applications.