

## Wireless In vivo Biofuel Cell Monitoring

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# Wireless In vivo Biofuel Cell Monitoring

L. Di Trocchio, C. Carucci, K.R. Sindhu, C. Morel, J.-L. Lachaud, S. Bichon, S. Gounel, N. Mano, C. Boiziau, C. Dejous, A. Kuhn, and S. Hemour, *Senior Member, IEEE* 



The novel wireless *in vivo* biofuel cell monitoring setup. The animal, wearing a special design jacket embedding an RFID wearable antenna, is free to move inside the cage, while the open circuit voltage delivered by an implanted glucose/ $O_2$  biofuel cell is continuously, wirelessly monitored.

#### **Take-Home Messages**

- This work presents a light, batteryless, and wireless strategy to continuously monitor a biofuel cell implanted in a laboratory rodent using a Frequency Identification (RFID) link.
- The proposed telemetry system successfully monitored a glucose/O2 biofuel cell continuously *in vitro* and *in vivo* over a 24-hour cycle (one day and night).
- The targeted biological application is the study of an implanted glucose/O2 biofuel cell in a real-case scenario involving a living laboratory rodent.
- The main breakthrough of this work is that the passive and lightweight wearable telemetry system allows the monitoring of the biofuel cell while keeping the animal free to move inside its cage, allowing long term measurement.
- A very good agreement between the *in vitro* and *in vivo* measurements was observed, evidencing the resilience of our system to the animal typical behavior.

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*Abstract* Enzymatic reactions involving glucose hold the potential for building implantable biosensors and embedded power generators for various medical applications. While Biofuel cells (BFCs) such as enzymatic glucose/ $O_2$  are ensured to benefit from abundant chemical resources that can be harvested in the immediate environment of the human body, the highly critical *in vivo* kinetics of biofuel cell is not yet fully understood. Unfortunately, existing solutions for real-time monitoring of the reaction on rodents are not possible today, or too bulky, which has a biasing impact on the animal behavior. This work presents a light, battery-less, and wireless strategy to continuously monitor a BFC implanted in a laboratory rat using a Frequency Identification (RFID) link. An extremely lightweight and flexible tag antenna of footprint lower than 10 cm<sup>2</sup> is presented with communication capability above 60 cm in field environment. The operational capabilities are demonstrated with a 24-hour continuous monitoring of an enzymatic glucose/ $O_2$  reaction, both *in vitro* and *in vivo*.

#### Keywords - RFID tags, biofuel cell, wearable sensors, in vitro, in vivo.

#### I. INTRODUCTION<sup>1</sup>

HE research of a suitable alternative to bulky L batteries to power Electronic Medical Devices (EMDs) is nowadays one of the most important research topic in bioelectronics, in particular to power Implanted Medical Devices (IMDs) [1-5]. Batteries are energy inefficient, unsustainable and need to be recharged/replaced, demanding surgery in case of implants. Moreover, batteries often occupy a larger volume than the sensor itself, limiting the device miniaturization, critical to place the implant at the right location of the body with minimum biological tissue displacement [6]. A possible solution consists in transferring the power wirelessly from a source placed outside of the body, commonly using optical [7, 8], ultrasonic [9, 10] or Radio Frequency (RF) [11-15] links. However, these systems need the constant presence of an external power source, which has to be coupled to the implant, implying permanent additional stress for the patient. To avoid the continuous presence of the transmitter,

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C. Carucci and A. Kuhn are with ISM, Univ. Bordeaux, CNRS, Bordeaux INP, UMR 5255, 33600, Pessac, France (e-mail: cristina.carucci@unica.it, kuhn@enscbp.fr).

S. Bichon, S. Gounel, N. Mano are with CRPP, Univ. Bordeaux, CNRS, UMR 5031, 33600, Pessac, France (e-mail: <u>sabrina.bichon@crpp.cnrs.fr</u>, nicolas.mano@crpp.cnrs.fr).

K.R. Sindhu C. Morel, and C. Boiziau are with Inserm, Univ. Bordeaux, U1026, Laboratory for the Bioengineering of Tissues, F-33000 Bordeaux, France (e-mail: <u>sindkr@gmail.com</u>, chloe.morel77@gmail.com, <u>claudine.boiziau@inserm.fr</u>). autonomous powering approaches can be suitable alternatives. By harvesting the energy from the ambient environment in many different ways [3, 4] those microsystems may provide an attractive alternative to batteries.

Biofuel Cells (BFCs) offer one of the most interesting powering approaches, converting biochemical fuels into electricity thanks to biochemical reactions [16, 17]. In particular enzymatic glucose/O<sub>2</sub> BFCs harvest energy directly from living organisms, using often specially designed enzymes [16, 18, 19] coated on the anode and cathode of the BFC.

Since glucose and water are abundant in biological environment, e.g. in the human body, the IMDs could be powered by the body's own resources, in a fully renewable way [20]. The design of BFCs is also flexible, since the electrodes can be shaped as required by the designer [20-23]. Some BFCs could power wireless electronic circuits, [24-26], but they were too bulky to be implanted. For a given electrode volume, porous surfaces can increase the output power. For example, 3D porous gold electrodes with controllable and defined pore sizes and thicknesses [27-29], have reached power densities above 100 µW/cm<sup>2</sup> [20, 30, 31]. Moreover, due to the dependence of the output power of the glucose biofuel cells on glucose concentration [20], the enzymatic reaction can be used as a sensor, to monitor the glucose concentration in the organism [20, 32-34]. Unfortunately, the limited lifetime of these devices and the possible long-term biocompatibility issues are important challenges that have to be faced to improve BFCs capable to successfully power an IMD [35]. Toward progress in reliability and lifetime, continuous monitoring of the BFC output is of high importance to get a better understanding of the kinetics of the reaction. This must be done in a real application context, i.e. in vivo, and without affecting or impeding the patient with wires.

BFCs have been studied *in vivo*, in several animal species [36, 37], mostly in laboratory rodents, like rats [38, 39]. In most cases, the monitoring was done by using wires, and

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the animal was kept under anesthesia or put in a small cage, to prevent or limit any movement. Some efforts have been made to improve the animal comfort and enable measurement in real living conditions with a wireless link. A BFC implanted in a rabbit was monitored for two months, using a Bluetooth radio [40], but it required batteries and led to impairment in usual activities of the animal due to the bulkiness of this kind of power source.

Alternatively, Ultra High Frequency (UHF) Radio Frequency Identification (RFID) technology appears as an elegant way for monitoring signals, as the telemetry circuit is wirelessly powered. The RFID Integrated Circuit (IC) can embed Analog-to-Digital Converter (ADC), sensors capabilities and/or external sensor interfaces, which allow the data processing directly in the RFID tag [41]. This technology permits incredible flexibility to the tags and countless applications, having the sensed data independent from the path. It has been deployed in numerous applications (e.g. body temperature monitoring [41-43], sometimes with on-chip temperature sensors [44, 45], vital signs monitoring systems like ECG [46] or EEG [47], relative plantar pressure [48], bed-regress tracking in elderly people [49], breath monitoring [50], pH skin sensor [51], etc.)

The only constraint of such systems is that the sensor tag has to be within the Reading Range (RR) of the remote telemetry reader [52]. A minimum necessary power to turnon the circuit has to be provided, limiting the RR. This is especially critical when dedicated energy is needed for power-hungry functions such as ADC or sensors data processing. As a matter of fact, the wearable antenna plays a critical role in the tradeoff: (i) reading range vs. (ii) unaffected animal behavior. Reading range is addressed by maximizing the realized gain, by matching the complex input impedance of the antenna to the one of the chip, and optimizing the radiation characteristics of the antenna. However unaffected animal behavior (also called "wearability" or "comfortable wearing") is mainly obtained by reducing the overall size of the antenna.

As a path towards solving this tradeoff, the epidermal electronics concept brings radical change to the wearable antenna design process, by prioritizing extra lightweight electronic payload, to ensure long-term (weeks) wearability [53, 54]. This category of devices consists in very thin, single-layer foldable antennas, attached to the skin at a maximum of one millimeter from it, by means of a flexible (and sometimes elastic [54]) substrate. Typical realized gain of such antenna [42] is in the order of -15 dB taking into account a homogeneous human model ( $\varepsilon_r = 41.2$ ,  $\sigma = 0.95$  S/m), which is very low, as compared to ordinary antennas, mainly because of the presence of human tissues.

This work presents, for the first time, a passive RFID telemetry system for BFC *in vivo* monitoring. A special care is given to the high dielectric constant and the dielectric losses of the rat tissues, which influence the input impedance and limit the radiation characteristics of the antenna. The proposed monitoring system is illustrated in Fig. 1: After having performed the surgery to implant subcutaneously the two BFC electrodes, the rat, placed



Fig. 1. Setup of the proposed telemetry system.

inside the cage, wears a jacket, embedding the RFID sensor tag. On the top of the cage, the RFID reader antenna powers and interrogates the tag. Thanks to this setup, the animal is continuously monitored while it is free to move inside the cage. A cover (of non-conductive material) may be used to secure the rat inside the cage.

The article is organized as following: in Sec. II the designed antennas are presented, and the RFID link is validated. The *in vitro* and *in vivo* characterizations of the BFC-antenna setup are then described in Sec. III and the achieved results are reported in Sec. IV.

#### II. RFID TAG-BASED MONITORING SETUP

#### A. Tag antenna design

To monitor and record the energy produced by the implanted BFC, an ADC-embedded silicon RFID IC (AMS-SL900A) was selected [44]. This IC has two analogical inputs that can be used to connect the electrodes. Moreover, it has a built-in temperature sensor, which may allow the monitoring of the animal temperature during the experiment (not implemented in this study), all without any external battery. The chip input impedance is  $Z_c=123$ -j303  $\Omega$  at UHF-RFID frequencies and has a sensitivity  $p_{min} = -6.9$  dBm in battery-less mode. Moreover, the ADC is capable of converting voltages between 310 and 620 mV, covering thus most of the voltage range of a BFC [55].

Since the SL900A IC has an unbalanced RF configuration, dipole-like structures generally employed [56, 57] are sub- optimal. Therefore, a folded monopole structure was designed, which is represented on Fig. 2a. The antenna was terminated by a loop, to enhance the inductive behavior required, and the width of the far-end side was increased, to improve the tag bandwidth. Additionally, a lumped inductor was inserted, to ease the impedance matching of the chip. Soldering pads for the IC and the electrode connector were inserted onto the ground, minimizing the discontinuities of the surface current (Fig.2a), allowing the connection of the BFC electrodes with minimum tag dimensions. Finally, a lumped capacitor  $(2.2 \ \mu F)$  was implemented at the output of charge pump's rectifier to allow stable ADC operation and enhance the RR [44].

To insure high wearability, a flexible and low-weight 40  $\mu$ m thick Kapton® ( $\epsilon_r = 2.94$ , tan $\delta = 0.0012$ ) was



Fig. 2. The wearable monopole antenna: Antenna shape and surface current density (a) and the simulation box (b). Antenna #2 position and radiation pattern is given for the two vertical central planes in (c) and (d).

selected as substrate and 30  $\mu m$  copper was used as metal.

The resulting structure, as on Fig. 2a, has been optimized using the HFFS (Ansoft, Pittsburgh, PA) simulation tool. The rat was modelled as a parallelepiped, having dimensions 19x8x8 cm<sup>3</sup>, with rounded edges (Fig. 2b). The material used was defined as a balanced average of all body tissues at 900 MHz ( $\varepsilon_r = 55.03$ ,  $\sigma = 1.01$  S/m) [58], located in the midrange of the UHF-RFID band (860-960 MHz). Since the dielectric characteristics of biological tissues are almost constant over this band [59], the material values were kept constant as a function of frequency.

The flexible antenna is specified for two different cases. The first one, "Ant1" (Fig 2b) is the classical epidermal electronic case, the antenna is placed at a distance of 1 mm from the skin to insure high-wearability. In simulations,  $\varepsilon_r = 1$  was used as relative permittivity of the medium between the antenna and the rat. In the second case, in order to simulate a real-case scenario, ("Ant2") (Fig 2c, d), a patch made of bio-silicone ( $\varepsilon_r = 2.2$ ,  $\sigma = 0.005$  S/m), 3 mm thick, was placed between the antenna and the rat. This is because sticking the antenna directly on the skin of the animal can cause skin inflammation [60]. For the sake of completeness, Fig. 2c and 2d show the resulting far-field radiation patterns of Ant2 (the antenna is being operated in mid-field and far-field). Table I shows the dimensions in mm for the two antennas. The two selected inductors were 8.2 nH and 16 nH for Ant1 and Ant2 respectively.

Fig. 3 shows the simulated reflection coefficient of the two antennas, taking into account the chip impedance as reference, and the maximum realized gain. This parameter is defined as  $G_r^{\text{max}} \cdot \tau$  where  $G_r^{\text{max}}$  is the maximum value of the antenna gain and  $\tau$  is the power transmission coefficient. The two antennas were designed to operate in the 915 MHz band. As Fig. 3 shows, the antennas resonate at this frequency, they have a -10 dB bandwidth of 64.3 and

TABLE I The dimensions (in MM) of the designed antennas

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Case	$A_1$	$A_2$	$A_3$	$W_s$	$W_1$	$W_2$	$W_3$	$L_s$
Ant1	2	1	0.5	25	18.4	18.8	45	43.5
Ant2	2	1	0.5	21.5	17.2	14.7	42	41
Case	$L_1$	$L_2$	L <sub>3</sub>	$L_4$	$L_5$	L <sub>6</sub>	$L_7$	$L_8$
Ant1	12	5	17	8	6	4.9	3.95	10.1
Ant2	9.5	5	14.5	8	6	4.9	3.95	10.1

65.8 MHz, for Ant1 and Ant2, respectively, and a -3 dB bandwidth that covers all the UHF-RFID spectrum, thanks to tissue losses.

Fig. 3 also shows the behavior of the maximum realized antenna gain with respect to the frequency. As a result, for both structures, the gain is quite flat over the antenna bandwidth, with values of the order of -15 dB, similar to other epidermal electronic antennas. Thanks to the longer separation between the structure and the biological tissues, Ant2 offers a gain slightly higher than Ant1, while being smaller, as Table I evidences. This is important because the design priority was put on the miniaturization of the structures, while keeping a gain that insures a RR large enough to monitor a rat in its cage.

As a final remark, since the horizontal segments of the antennas are not participating in the radiation process, the antennas can be easily adapted to resonate at all the worldwide UHF-RFID bandwidths, by adjusting its overall width, without changing the radiation characteristics.

Starting from the simulation, the resulting RR is obtained by implementing the following expression [61]:

$$RR = \frac{\lambda_0}{4\pi} \sqrt{\frac{EIRP \cdot G_r \cdot \tau}{p_{\min}}},$$
 (1)

where  $G_r$  is the gain of the receiver tag antenna,  $\tau = 1 - |S_{11}|^2$ is the tag power transmission coefficient,  $p_{min}$  is the sensitivity of the RFID chip and *EIRP* is the equivalent isotropic radiated power. By assuming the maximum allowed radiated power in the US (EIRP = 4 W), the resulting maximum RR is RR<sub>1</sub> = 63 cm and RR<sub>2</sub> = 65 cm for Ant1 and Ant2 respectively, large enough to allow the rat monitoring.

#### B. RFID link validation

The tag Ant2 was built by chemical etching of copper on Kapton® substrate. The full structure, including the components, has a weight of only 0.6 g. The RFID setup was completed with a 5 dB gain circularly polarized antenna (Abracon APAES915R80C16-T) and a reader (AMS Radon), emitting 1 W. The reader was also programmed to measure the voltage delivered by the BFC.

The maximum tag RR was estimated by fixing the receiver position and increasing the reader-antenna distance in different conditions until ADC reading failed to be wirelessly recovered. The resulting RR was above 60 cm, in agreement with the simulation.

In order to verify the complete coverage of a surface equivalent to a typical rat cage, a specifically designed measurement setup was defined. A half PET bottle, 0.5 mm thick, was filled with minced bovine meat, at room



Fig. 3. Simulated reflection coefficient and maximum realized gain for the two designed structures, with respect to the frequency.

temperature (21-23 °C), to simulate the animal body tissue. On its side, the tag antenna was placed. Moreover, a 3 mm silicone patch was placed between the bottle and the antenna, to emulate the real case scenario. A grid, having the external dimension of  $40x28 \text{ cm}^2$ , typical of a rat cage, was drawn and the bottle position was swept in order to verify the communication between the tag and the reader. The reader antenna was placed on the top of the grid, at a distance of 40 cm from the cage bottom.

Two rat positions were taken into account, with the bottle axis parallel and perpendicular to the ground, in order to mimic the two assumed most frequent positions of the rodent inside its cage. For the perpendicular position, the tag antenna was always oriented facing the reader. Fig. 4 illustrates the measurement setup and the detected points. As a result, for all measurement points, for both antenna positions, the RFID link was established. Therefore, the rat should be detectable in the whole cage and in any position.

#### III. IN VITRO AND IN VIVO BIOFUEL CELL MONITORING

Glucose/O<sub>2</sub> biofuel cells take advantage of the oxidation of glucose and reduction of molecular oxygen to water in order to produce electrons, as follows:

Anode side: 
$$C_6H_{12}O_6 \rightarrow C_6H_{10}O_6 + 2H^+ + 2e^-$$

Cathode side:  $O_2 + 4H^+ + 4e^- \rightarrow 2H_2O$ 

Global reaction: 
$$2C_6H_{12}O_6 + O_2 \rightarrow 2C_6H_{10}O_6 + H_2O$$

At the anode side, the glucose  $(C_6H_{12}O_6)$  is electrooxidized, producing gluconolactone  $(C_6H_{10}O_6)$ , two hydrogen ions and two electrons. These electrons flow towards the cathode side, where they combine with oxygen and hydrogen ions to produce water by a reduction process. The produced electron flow, passing through a load, generates the energy needed to power the IMD. Glucose oxidase is the most commonly used anodic enzyme [62] while Bilirubin Oxidase is preferentially used on the cathodic side because of its high tolerance to chloride ions and stability near neutral pH [63]. To properly connect the redox centers of enzymes to the electrode surface, dedicated redox polymers are used if needed as a shuttle of electrons



Fig. 4. RFID link validation: wireless sensor telemetry has been tested for two antenna configurations (parallel and perpendicular to the Patch antenna) while mounted on a PET bottle filled with ground beef. Red and black scatter show where readings have been validated (total coverage of the surface corresponding to the cage).

to improve the electron transfer [64].

After having validated the link and the measurement capability, the continuous monitoring of the BFC was performed *in vitro* and *in vivo* and the resulting voltage values were compared. The following section presents the performed measurements, including the BFC preparation with macroporous electrodes and the enzyme immobilization.

#### A. Electrodes and enzyme preparation

#### 1) Fabrication of macroporous gold electrodes

Cylindrical macroporous gold electrodes were prepared using a procedure described in previous work [65]. In brief, a colloidal template made out of silica beads (d = 1170 nm) was first generated at the gold wire surface by following a reported procedure. Subsequently metallic gold is electrodeposited in the void space between the silica beads. After dissolution of the template a porous matrix is obtained. The thickness of the electrodes can be controlled by the number of macroporous layers that are deposited. This is achieved by following the periodic current oscillations during the potentiostatic deposition of the metal. Macroporous gold electrodes of 11 half layers thickness were used for all the experiments *in vitro* and *in vivo*.

*2) Immobilization of enzymes in the macroporous electrodes* 

Bilirubin Oxidase (BOD) from *Magnaporthe oryzae* is able to undergo Direct Electron Transfer because the active redox center of the enzyme is close enough to the outer surface of its protein shell. In this case, electrons can directly be transferred from the electrode to the enzyme. To improve the interaction between the enzyme and the gold surface, and thus increase the rate of electrons transfer, we designed and produced a mutant of this enzyme bearing a cysteine residue, well known to strongly attach to gold surfaces [66]. The mutant BOD has then been directly immobilized onto the porous electrode by a coating process previously described [67]. On the contrary, Glucose Oxidase (GOx) is not able to promote direct electron



Fig. 5. In vitro measurement setup (a), a plastic bottle partially filled with water simulates the body tissue to match the antenna, and the *in vivo* BFC monitoring setup (b). The chip is connected to the two electrodes subcutaneously implanted (c). X rays images of the rat just after the implantation (d). Cathode is red (left implanted electrode); Anode is blue (right implanted electrode).

transfer because its active centers are deeply buried within the protein. In that case, a redox mediator is needed to shuttle electrons between the active centers of the GOx and the electrode surface. Polycationic osmium based-redox polymers are one of the most efficient redox mediators allowing the connection of the redox centers of GOx to the electrode surface while immobilizing the enzyme on the electrode. The immobilization is achieved by mixing GOx, which is polyanionic at neutral pH, with the polycationic osmium based redox polymer in the presence of a chemical cross-linker (poly (ethyleneglycol) diglycidyl ether, PEGDGE) to further strengthen the formed hydrogel [68, 69]. As a result, the GOx molecules are surrounded by osmium complexes that shuttle the electrons exchanged during the oxydo-reduction of the substrate to the electrode surface, regardless of the orientation of the enzymes. The anodic redox polymer used in this work was an osmium based redox polymer with a redox potential of -20 mV/AgAgCl. The anodic hydrogel was composed of 35 wt% of GOx from Aspergillus niger, 60 wt% of PolyVinylPyridine-Os[(1,1-dimethyl-2,2'biimidazole)2-2-[6 methylpyrid-2yl] imidazole]<sup>2+/3+</sup> and 5 wt% PEGDGE. Once realized, the hydrogel was deposited on the porous electrode surface and let cured for 18 h at 4 °C. Full details on the polymer synthesis, enzyme production/purification and adduct preparation can be found in our earlier works [70, 71].

#### B. In vitro measurements setup

Before implementing the *in vivo*, real-case scenario monitoring, the BFC was wirelessly monitored *in vitro*. Fig. 5a shows the measurement setup. In continuity with the link mapping, the circularly polarized antenna was connected to the RFID reader, emitting 1 W of power. The wearable antenna (Ant2) was placed on a bottle half-filled with Phosphate-Buffered Saline solution (PBS-137 mM NaCl, 2.7 mM KCl, 10 mM Na<sub>2</sub>HPO<sub>4</sub>, 1.8 mM KH<sub>2</sub>PO<sub>4</sub>, pH 7.2), in order to mimic the animal. A 3 mm thick patch of silicone was placed between the antenna and the bottle.

The BFC electrodes were placed in a temperaturecontrolled oxygenated PBS solution, at  $37^{\circ}$  C, to mimic the natural body temperature. 5 mM of glucose were added to the solution, which is the normal glucose concentration in a rat [72].

Finally, the electrodes were connected to the 1 M $\Omega$  input of the embedded ADC (1 mV resolution), and the voltage of the cell was sampled every 10 seconds to monitor the enzymatic reaction. It was recorded until it reached the minimum detectable value, i.e. 310 mV.

#### C. In vivo measurement setup

In order to achieve the *in vivo* monitoring of the BFC, a pair of modified macroporous gold electrodes was implanted sub-cutaneously in the back of a 12-16 weeks-old Sprague Dawley female rat. Once the implantation was achieved, electrodes were connected to the inputs of the SL900A chip by means of the electrode connector. As for the *in vitro* study, Ant2 was used for the experiment. It was glued on a bio-silicone patch and placed on the animal using a commercial jacket for rats (Harvard Apparatus) (Fig.5c).

After surgery, X-ray imaging was performed to confirm the correct position of the electrodes (Fig. 5d). Then the rat was placed inside its cage to recover from the anesthesia and to perform the monitoring. Fig.5b shows the measurement setup. The reader antenna was placed on the cage, at a distance of about 30-35 cm from the animal. The RFID setup presented in Sec. II.B was used. To monitor the rat movement, a camera was also placed on the top of the cage, alongside the reader antenna.

The open circuit voltage of the BFC was recorded from the end of the surgery (about one hour after the end of the implantation), until the minimum detectable value was reached. The recording time was about 24 hours, recording one measurement every 10 seconds, similarly to the *in vitro* study. During the whole recording, the animal, inside its cage, was placed in a temperature and humidity controlled room, with the day/night time automatically regulated and food and water *ad libitum*.



Fig. 6. The in vitro (red curve) and in vivo (black curve) open circuit voltage of the BFC recorded wirelessly.

#### IV. RESULTS AND DISCUSSION

Fig. 6 shows the resulting open circuit voltage of the BFC recorded *in vivo* (black curve), compared to the *in vitro* one (red curve). No data were recorded during the first 2 hours because the voltage values were above the working range of the ADC.

Firstly, the *in vitro* analysis (red curve) shows a regular decrease with two different slopes. A fast voltage decrease is observed between 2 and 4 hours after measurement. Then, the slope is reduced after 4 hours and the voltage decreases regularly until it reaches the minimum detectable value about 20 hours after the *in vitro* experiment beginning. This overall decay of the open circuit potential may be attributed to  $O_2$  depletion in the medium and/or to the denaturation/loss of the enzymes. This question has to be addressed in future studies.

The same general behavior is observed in the *in vivo* case (black curve). The signal was monitored continuously during the whole experiment duration, validating the wireless measurement setup. The absence of data from about 4.5 to 5.5 and from 20 to 21 hours after the implantation corresponds to the moment when the rat was removed from the cage to perform X-rays and check the position of the electrodes (shown in fig. 5c). Moreover, videos using the camera were recorded during the experiment, for further study of the rat's behavior. A short video in supplementary material (Suppl. S1) shows that the rat was able to move freely.

Interestingly, the *in vivo* analysis shows a highly comparable behavior, despite more signal noise than the *in vitro* experiment. The two curves evolve in a very analog way, except late at night and the first two hours of daytime. We hypothesize that the rapid voltage changes might be due to rat micro-movements and/or to electrodes displacement. Regarding the voltage increase about 16 hours after implantation, this is not observed *in vitro*, and might be due to circadian rhythm modifications of different parameters.

Rats are nocturnal rodents especially active during the night, and are feeding mostly in this period [73]. Modifications of the BFC activity could be also induced by changes in body temperature, glucose concentration or oxygen pressure. According to bibliography, the body temperature is higher during the night and drops at the late night, from 38.5 to 37°C [74]; glucose concentration peaks at the beginning of the night (7 mM), slowly decreases during the night (6 mM) and goes up again just before dusk [75]; in reference [76] it is shown that oxygen concentration in tissues peaks during the night, and gradually declines at the end of the night and during daytime. This shows that the recorded signal is not directly associated with a single physiological parameter. However, the unexpected parallel decline of voltage in vitro and in vivo may be an indication that the inflammatory reaction induced by BFC implantation is moderate and does not impair BFC functionality.

Our monitoring system, associated with video monitoring will therefore be a great help to correlate the measured voltage with the rat behavior during the night.

#### V. CONCLUSION

A monopole RFID wearable tag antenna, implementing the SL900A IC, is proposed. Having lightweight (0.6 g) and compact dimensions ( $42x21.5 \text{ mm}^2$  regarding Ant2), this passive system has a RR of more than 60 mm, allowing the wireless monitoring of a laboratory rat.

The telemetry system successfully monitored a glucose/ $O_2$  biofuel cell continuously *in vitro* and *in vivo*. Very good agreement between the two measurements was observed, evidencing good consistency of the BFC signal between the *in vitro* ideal case, and the *in vivo* real case scenario.

The proposed battery-less, flexible and lightweight system is thus a first important step towards an alternative to wired telemetry for monitoring a BFC *in vivo*.

#### ETHICAL APPROVAL

All applicable international, national, and institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted (animal experimentation permission APAFIS# 16443-2018072016398155).

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