Remote System for Monitoring Animal Models With Single-Metabolite Bio-Nano-Sensors

Sandro Carrara, Léandre Bolomey, Cristina Boero, Andrea Cavallini, Eric Meurville, Giovanni De Micheli, Tanja Rezzonico Jost, Michele Proietti, and Fabio Grassi

***Abstract*— A novel system for remote monitoring of metabolism in an animal model is proposed in this paper. The system is obtained by integrating bio-nano-sensors to detect single-metabolites, an electrochemical front-end made with off-the-shelf components, a radio frequency communication sub-system, and an antenna of new design. The system has been calibrated and tested for continuous monitoring of four different metabolites: glucose, lactate, glutamate, and adenosine triphosphate. Tests using animal models (mice) have been conducted to investigate tissue inflammation induced by the implanted bio-nano-sensors. These tests confirm that our system is suitable and reliable for remote monitoring of single-metabolites in experiments with animal models.**

***Index Terms*— Animal monitoring, body sensor node, carbon nanotubes, implantable, SYST.**

I. Introduction

GENETICALLY engineered mice are highly useful models for emulating human diseases and studying disease mechanisms as well as for testing therapeutic strategies [1]. Remote monitoring during the experiments assures continuous acquisition of data on soluble mediators in animal model. Remote monitoring of blood pressure in mice has been already demonstrated including remote powering of the system [2]. Although many other physiological parameters, e.g. the viscosity [3], may be monitored by telemetry, the big challenge is the monitoring of the animal model at molecular level. Thus, it is so important to follow in time the biomarkers trend related to the disease under investigation. Continuous monitoring of humans is already in the market for glucose [4] as well as for lactate. The reliability of the technology for glucose remote monitoring has been validated up to 8 month in mice [5], [6] and up to one year in pigs [7]. The next step will be the extension of the technology to other relevant metabolites like, for example, glutamate and ATP. Glutamate is an important neurotransmitter usually associated with brain damages [8] while ATP has been very recently associated to regulation of adaptive immune responses [9]. Several nano-materials have been proposed to improve devices performance including conductive polymers [10], nano-particles [11], graphene [12], and carbon nanotubes [13]. Recently, carbon nanotubes have been demonstrated to enhance the sensitivity for both exogenous [14] and endogenous [15] metabolites. The aim of the present paper is to propose the first telemetry system based on Bio-Nano-Sensors and reliable for remote and continuous single-metabolite monitoring of glucose, lactate, glutamate, and ATP in mouse models.

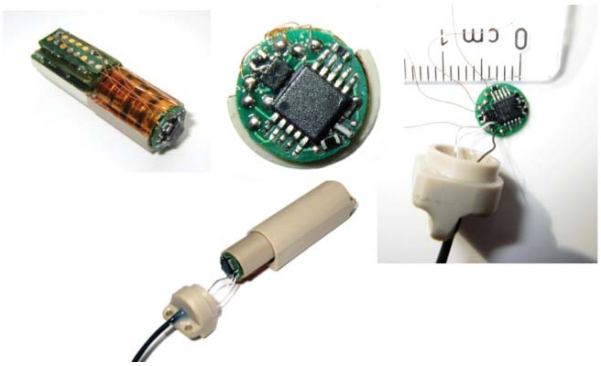

Fig. 1. System for remote acquisitions with single-metabolite bio-nano-sensors.

II. Remote Monitoring System

A. Wireless Implantable System

A wireless electrochemical monitoring system has been realized to assess the sensor *in-vivo*, as shown in Fig.1. This embedded system responds to the constraints linked to implants in animals. The materials used to build the packaging are biocompatible and support chemical sterilization process such as ethylene oxide gas or chlorine bleach. The wireless link allows us to perform measurements at distance with a laptop computer that can be easily brought into the operation room.

B. Implantable Body Sensor Node

The telemetry system is based on an implantable Body Sensor Node (BSN) for rheology monitoring, which architecture has been already described in [3], [16], [17].

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C. Electrochemical Front-End

The novelty proposed in this paper for the remote monitoring system is in the electrochemical frontend. VLSI design provides fully customized solutions for also addressing multi channels chip [18] with detection of femptoampere currents [19], even including differential configurations [20]. However, the system proposed here does not require complex architectures. Therefore, our frontend to interface the BSN to the electrochemical Nano-Bio-Sensor was realized with a simple potentiostat following [21]. It is based on the commercial IC MAX4039 (manufactured by Maxim integrated products – biggest IC in the board of Fig. 1) that integrates two operational amplifiers and one voltage reference (1.2 V). The IC is powered by the 3 V battery and consumes only 9 μW. The potentiostat is mounted on a circular Printed Circuit Board (PCB) of 7 mm in diameter (photo on the right of Fig. 1), which is placed at the end of the BSN, just after the batteries. The potentiostat output is connected to the DSP analogue-to-digital converter (smallest IC in the board of Fig. 1). Then the signal is low-pass filtered and the data are directly sent to the base station. A computer connected to the base station can display the data in real-time and save them for further analysis.

The computer can also set the measurement by remotely enabling and disabling the BSN. With the embedded non-rechargeable batteries exhibiting a total energy of 600 J, the system can be powered in stand-by for over 9 years. Then, the Bio-Nano-Sensor (see Section III) is connected to a biocompatible cable in polyurethane with silver coated wires that goes through the BSN housing to the potentiostat.

III. Single-Metabolite Bio-Nano-Sensors

A. Chemicals

Multi-Walled Carbon Nanotubes (MWCNT) were purchased in powder (90% purity) from Dropsens (Spain). Glucose oxidase from *Aspergillus Niger* (GOD, EC 1.1.3.4, 129.9 units/mg solid) lactate oxidase from *Pediococcus species* (LOD, EC 1.13.12.4, $\geq$ 20 units/mg solid), hexokinase (HEX) type 3 from *Baker Yeast*, D-(+)-glucose, lithium L-lactate, and L-glutamic acid were purchased from Sigma-Aldrich (Switzerland) as lyophilized powder. Glutamate oxidase from *Streptomyces species* (GlOD, EC 1.4.3.11, 25 units) was supplied from Yamasa Co. (Japan). All the proteins were dissolved in Phosphate Buffer Solution (PBS) 0.01 M at pH 7.4, while the other reagents were dissolved in Milli-Q.

B. Screen-Printed Electrodes

Experiments were carried out using screen-printed electrodes (SPE) from Dropsens (Spain). Working and counter electrodes are made of graphite, while the reference electrode is in Ag/AgCl. The total area of the cell is around 22 mm^2, with a working electrode of 4 mm in diameter.

C. Preparation of the Bio-Nano-Sensors

A 40 μl volume of the MWCNT-chloroform solution was deposited by drop casting (5 μl each time) onto the working electrode and dried. Then, 20 μl of the enzyme probe were dropped onto the working electrode and stored overnight at $+4$ ºC, in order to allow the adsorption of the proteins onto the electrode surface. Glucose and lactate oxidases were prepared at concentrations of 15 mg/ml, and of 125 mg/ml, respectively [22], [23]. The glutamate oxidase was prepared at the concentration of 250 units/ml. For the measure of the ATP, instead, GOD and HEX were mixed in a 1:1 ratio to obtain a solution at pH 7.4 with 15 mg/ml of each protein [24]. 20 μl of the solution were then drop cast onto the working electrode, and let dry at 4 ºC overnight. The electrodes were rinsed out with Milli-Q the day after the deposition and conditioned for 10 minutes at constant potential ($+650$ mV) before the first use.

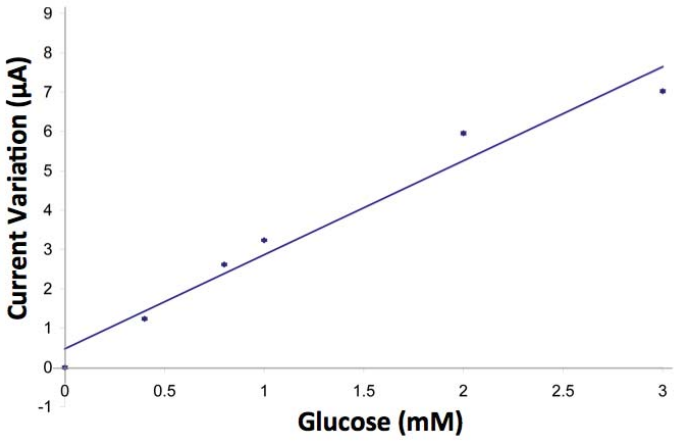

Fig. 2. Calibration curve for Glucose detection in 0 to 2 mM concentration range.

D. Calibration Curves and Telemetry Acquisitions

For calibration and investigation of the detection limit, electrodes were dipped into the PBS with a volume of 25 ml under stirring conditions. The electrochemical response of electrodes is investigated by chronoamperometries under aerobic conditions. The Bio-Nano-Sensors calibration has been done with the lab-electrochemical-station Versastat 3 potentiostat (Princeton Applied Technologies). After calibration, the same Bio-Nano-Sensors have been used for remote acquisitions in order to test the telemetry system described in the previous section.

IV. In-Vitro and In-Vivo Tests

A. Calibration for Glucose, Lactate, and Glutamate

Oxidases are enzymes that catalyze the transformation of metabolite (X) in metabolism product (X_p) by following the well-known equation:

$$X + O_2 \xrightarrow{XOD} X_P + H_2O_2. \quad (1)$$

The metabolite X is glucose, lactate, and glutamate, which are catalyzed by the glucose-oxidase (GOD), the lactate-oxidase (LOD), and the glutamate-oxidase (GLOD), respectively.

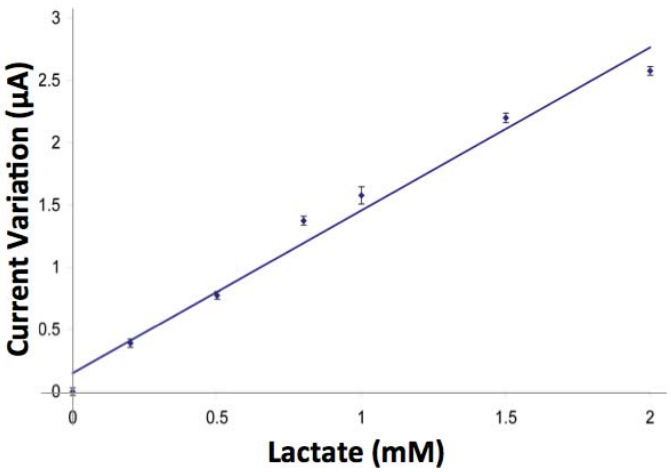

Fig. 3. Calibration curve for Lactate detection in the 0 to 1.4 mM concentration range.

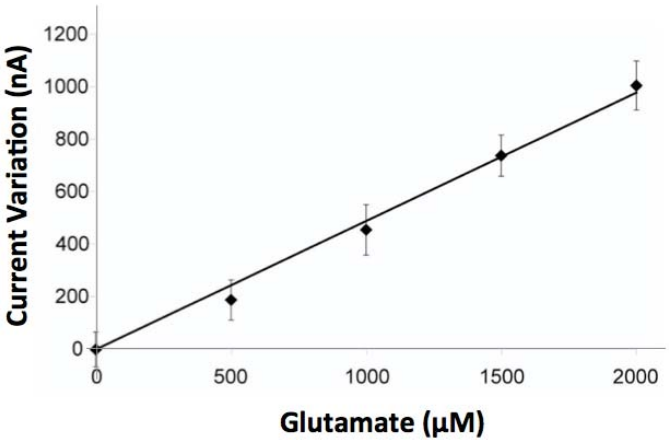

Fig. 4. Calibration curve for Glutamate detection in 0 to 2 mM concentration range.

The reaction (1) produces the hydrogen peroxide (H_2O_2) that may be oxidized:

$$2H_2O_2 \overset{+650mV}{\longrightarrow} O_2^+ + 2H_2O + 4e^- \tag{2}$$

or reduced:

$$H_2O_2 + 2H^+ + 2e^- \overset{+1540mV}{\longrightarrow} 2H_2O \tag{3}$$

at the interface with our electrodes. Equations (2) and (3) are two different redox reactions, the first enabled at the electrodes interface with a typical potential of + 650 mV, while the second with typical potential of + 1540 mV.

Of course, these potentials also depend on the metal of the electrodes. In presence of oxygen, reaction (2) is the most common used. So, for our Bio-Nano-Sensors we worked at +650 mV by following the redox of equation (2). Figs. 2–4 report the calibration curves for three different metabolites. The obtained sensitivities and the ranges of concentration are reported in Table I.

B. Calibration for ATP

In the case of the ATP monitoring, our Bio-Nano-Sensor consists of two co-immobilized enzymes: glucose oxidase and hexokinase. Both enzymes are sensitive to glucose, but with a different catalytic mechanism [24]:

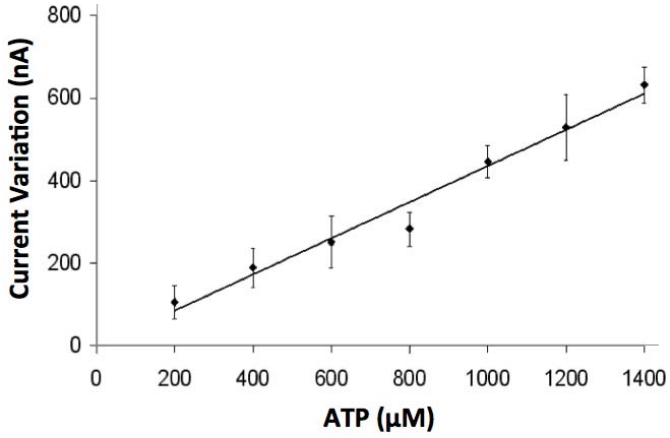

Fig. 5. Calibration curve for ATP detection in the 0 to 1.4 mM concentration range.

TABLE I
SENSITIVITY AND RANGE OF THE BIO-NANO-SENSORS

Metabolite	Sensitivity	Range
Glucose	299 nA/μM mm^2	0.5–4 mM
Lactate	446 nA/μM mm^2	0.5–2.5 mM
Glutamate	40 nA/μM mm^2	0.5–2 mM
ATP	34 pA/μM mm^2	200–1400 μM

$$D - Glucose + O_2 \overset{GOD}{\longrightarrow} D - Gluconic\,Acid + H_2O_2. \tag{4}$$

$$D - Glucose + ATP \overset{HEX}{\longrightarrow} D - Glucose - 6 - P + ADP. \tag{5}$$

In presence of ATP, the hexokinase competes with the glucose oxidase for the substrate, and the quantity of hydrogen peroxide produced in the reaction (4) is proportionally decreased by the glucose consumption in the reaction (5). Therefore, the ATP is detected by a decreasing of the current registered in the redox reaction (2). Fig. 5 reports the obtained calibration curve for the ATP detection The obtained sensitivity is reported in in table I, too.

C. Telemetry Acquisitions

The metabolite is kept by the enzymes, transformed, and then released in all the reactions involving oxidases and hexokinase. This feature of reactions (1), (4), and (5) enables continuous monitoring and acquisition over time of current variation as proportionally related to the concentration of the monitored metabolites. Fig. 6 shows the continuous monitoring of glucose over a time frame of 35 minutes, while Fig. 7 shows the continuous monitoring over a time frame of 16 minutes in the case of Lactate. Similarly, continuous monitoring of glutamate and ATP is acquired, as shown in Figs. 8 and 9. Figs. 8 and 9 clearly show that raw signals acquired on each single Bio-Nano-Sensor are typically very noisy. Noise rejection is done by averaging on 20 data points and moving this average along the entire data stream. Figs. 6 and 7 show signals after such filtering.

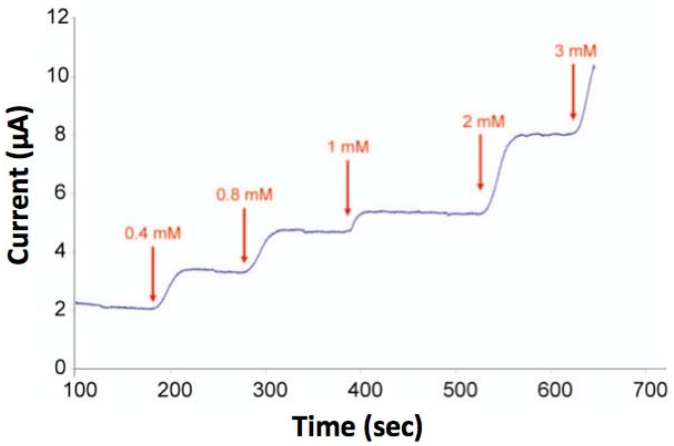

Fig. 6. Continuous monitoring with the single-metabolite remote system and a glucose bio-nano-sensor.

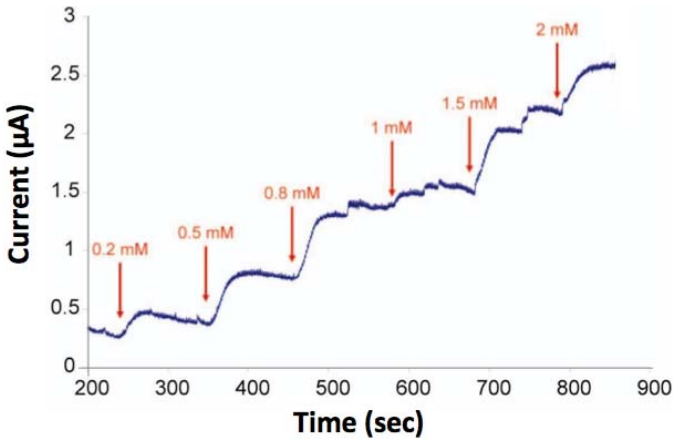

Fig. 7. Continuous monitoring with the single-metabolite remote system and a lactate bio-nano-sensor.

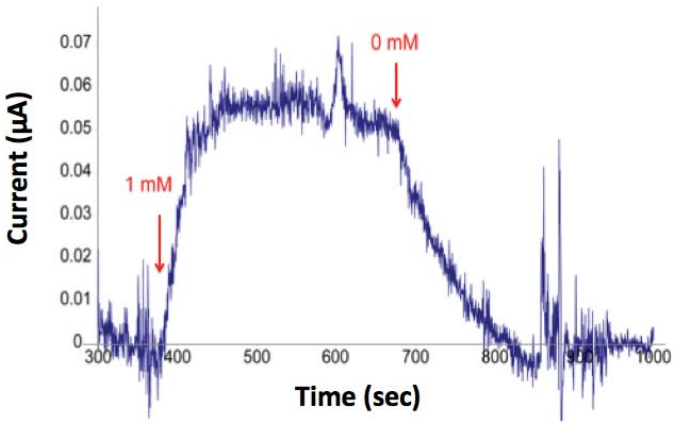

Fig. 8. Continuous monitoring with a glutamate bio-nano-sensor.

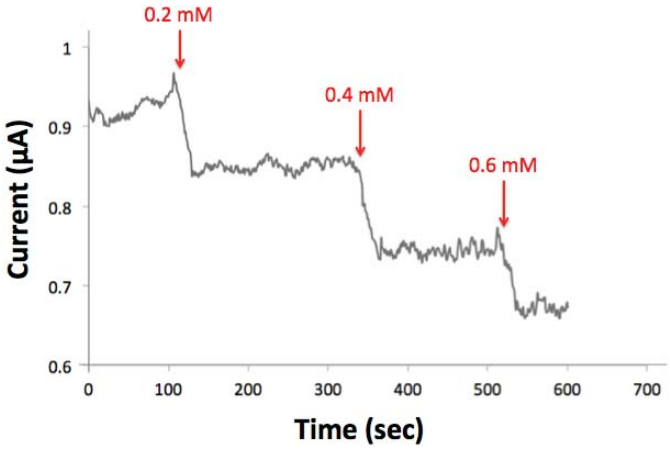

Fig. 9. Continuous monitoring with an ATP bio-nano-sensor.

Fig. 10. Air pouch model in mice used in this paper to test the inflammatory behavior of the monitoring implants.

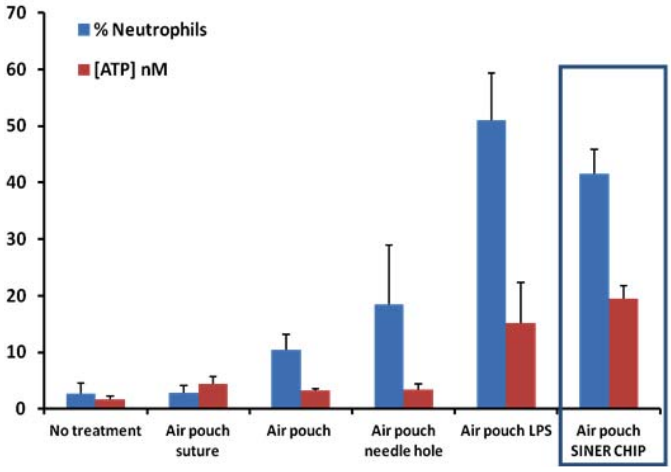

Fig. 11. Tests of inflammation in the mouse induced by the implanted bio-nano-sensor and the wear remote system.

D. Tests With Animal Models

To check whether the Nano-Bio-Sensor has any influence on tissue homeostasis at the site of implantation, we monitored inflammatory reaction *in vivo* in air pouches in mice (see Fig. 10) in which the Nano-Bio-Sensors were implanted. The air pouch is generated by subcutaneous injection of sterile air into the back of a mouse. The resulting subcutaneous cavity has a diameter of around 1.5 cm and a height of 0.5 cm.

The air pouch does not induce any relevant reaction of the tissue and provides an environment in which studying localized inflammatory phenomena by different stimuli, including the introduction of a Bio-Nano-Sensor. To study the impact of the implant, we inserted the sensor into the air pouch and analyzed the ATP concentration and neutrophils infiltration at day 7 after implantation. ATP is the source of energy for the cell. It is present at high concentration inside cells

but virtually absent in extracellular fluids. Cell damage, such as the one taking place at inflammatory sites, determines the efflux of ATP from the cells and its appearance in the extracellular fluid, making it a so-called danger-associated molecular pattern. Neutrophils constitute around 50–70% of our circulating white blood cells and extravasate from blood vessels at inflammatory sites. Therefore, their presence and number is an important parameter to score inflammatory reactions. We analyzed these two parameters of inflammation in different experimental conditions. The ATP concentration in the subcutaneous microenvironment is not affected by suture. Some increase in neutrophils infiltration is detected by more invasive procedures such as performing the hole for implanting the biochip or the implantation of our Nano-Bio-Sensors.

ATP levels and neutrophils increased to a similar extent by LPS (bacterial lipopolysaccharide) injection, confirming the limited inflammation associated with sensor implantation (Fig. 11). Nevertheless, the level of ATP induced by the implant (from 20 to 60 nM depending on different implanted sensors) is largely below the targeted range of hundreds of μM for ATP concentrations found in cell signaling [9] and relevant for anticancer treatments [25].

V. Conclusion

A novel system for remote monitoring of metabolism at molecular level in translational research made with animal models has been proposed in the paper. The new proposed system integrates Bio-Nano-Sensors with electrochemical front-end for the detection, a proper transceiver, battery for the powering, and a novel antenna. The Bio-Nano-Sensors are suitable for continuous monitoring of glucose, lactate, glutamate, and ATP (four highly relevant molecules of the human metabolism). Good sensitivities were provided by carbon nanotubes used as enhancers of the electrons transfer between the probe proteins and the sensors electrode.

The electrochemical front-end has been built by using out-of-the-shelf components. The low-power transceiver and the antenna were especially designed for prolongation of the implantation. The tests for continuous monitoring, wireless communications, and biocompatibility demonstrated the feasibility of this technology for translational research in biomedical field with mouse models. Our *in-vivo* tests demonstrated mild pro-inflammatory potential at implantation site, enabling the exploitation of the proposed system for *in-vivo* monitoring.

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Leandre Bolomey was born in 1980 at Morges, Switzerland. He received the Masters and Ph.D. degrees in electrical sciences, with thesis entitled "Generic implantable Body Sensor Node," from the École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, in 2003 and 2010, respectively.

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Her current research interests include electrochemical biosensors for the detection of metabolites in stem cell cultures, with an aim to develop a fully integrated chip to detect such metabolites in real-time in Petri dishes, functionalization of electrodes with nanostructures, such as carbon nanotubes, and the interaction between proteins and nanostructures.

Ms. Boero was a recipient of the Gold Leaf Award at PRIME in 2009.

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His current research interests include development of implantable biosensor arrays for personalized therapy.

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