

An Implantable Bio-Micro-system for Drug Monitoring

Sara Ghoreishizadeh*, Enver G. Kilinc†, Camilla Baj-Rossi*,
Catherine Dehollain†, Sandro Carrara*, and Giovanni De Micheli*
EPFL, * LSI †RFIC, Lausanne - Switzerland

Abstract—Multi-target and continuous monitoring by wireless implantable devices is of increasing interest for personalized therapy. In this work an implantable system is presented which is capable of measuring different drugs with *Cyclic Voltammetry* (CV) method. The wireless microsystem consists of four modules, namely (i) The inductive coil; (ii) Power management IC; (iii) Readout and control IC; (iv) Biosensor array. The power management IC provides 1.8 V with as high as 2 mW power for the readout IC. The configurable readout IC is able to control the biosensor array and measure the sensor current in CV method. CV experiments performed with this microsystem well agree with a commercial equipment for two well known anti-cancer drugs, Etoposide and Mitoxantrone, detection.

Index Terms—Cyclic voltammetry measurement; Drug detection; Power management; Inductive coil; Readout circuit; Integrated circuit.

I. INTRODUCTION

The development of new implantable devices for wireless and continuous monitoring of the metabolism of drugs in the human body is required for personalized therapy [1]. Typically when a group of patients having the same disease receive the same treatment, the therapeutic output is usually quite different from patient to patient. This explains the low success rates obtained in several pharmacological therapies [2].

The design of the implantable monitoring system for long-term duration has many challenges. First, a multi-target biosensor containing several sensing sites has to be developed in order to detect several drugs at the same time. The most common structure of the sensing site has three electrodes: *working electrode* (WE), *counter electrode* (CE) and *reference electrode* (RE) [3], where the WE of each sensing site is functionalized to selectively detect a single target drug. Second, in order to assess biocompatibility by reducing the size and the weight of the overall implantable system, the biochip should be batteryless. In addition, the batteries have a limited lifetime and need to be changed end of their lifetime which increases the number of surgery operations. In a previous study [4], a short-range remote powering system is proposed to track the freely moving animal in a living space and deliver the sufficient power to the batteryless implanted system.

In this work, we implemented an autonomous microsystem for *Cyclic voltammetry* (CV) measurements on anti-cancer drugs. The implantable microsystem consists of three main building blocks (i) An inductive coil; (ii) A power management IC dealing with the energy source of the implantable microsystem to provide power; (iii) An interface IC to control

and readout the biosensor; (iv) The biosensor. The power management unit together with the measurement IC and the biosensor array are implemented to realize an implantable and wireless platform to measure multi-target three-electrode biosensors. Some examples of wireless implantable devices can be found in literature [5-7], but they are limited to the monitoring of endogenous molecules detection (i.e. glucose, lactate) by chronoamperometry.

The quality of the measurement depends on the compatibility between the biosensor and the interface electronics as well as the sufficiency and stability of the supply power during the measurements. To test the full chain of measurement and data acquisition, as well as the functionality of each block, we perform CV measurement on two anti-cancer drugs and compare the voltammograms with the measurements with a commercial equipment.

The three main building blocks of the wireless implantable microsystem are presented in Section II; Section III presents the measurement method and results on two anti-cancer drugs based on the CV method by using the integrated circuit.

II. SYSTEM DESIGN

Fig. 1 shows the block diagram of the batteryless implantable bio-chip system for drug monitoring. The detailed description of the three main building blocks are presented in the following subsections.

A. Inductive link and power management IC

The implantable system is remotely powered via an optimized inductive link at 13.56 MHz [8]. The power efficiency of the overall system is dominated by the power transfer efficiency of the inductive link. Therefore, the link has been optimized to obtain a good coupling between the coils and quality factors.

A class-E power amplifier with high drain efficiency is designed to drive the external coil. To drive the transistor in the class-E power amplifier, an off-chip oscillator is used. The induced voltage at the implanted device is proportional to the frequency. If the frequency increases, the voltage at the input of the rectifier also increases [8]. On the other hand, the penetration of the body tissues decrease by the increase of the frequency [9]. According to the aforementioned trade-offs, and among the allowed frequency band for inductive applications introduces in [10], the frequency band of 13.56 MHz is chosen. Moreover this band allows higher magnetic

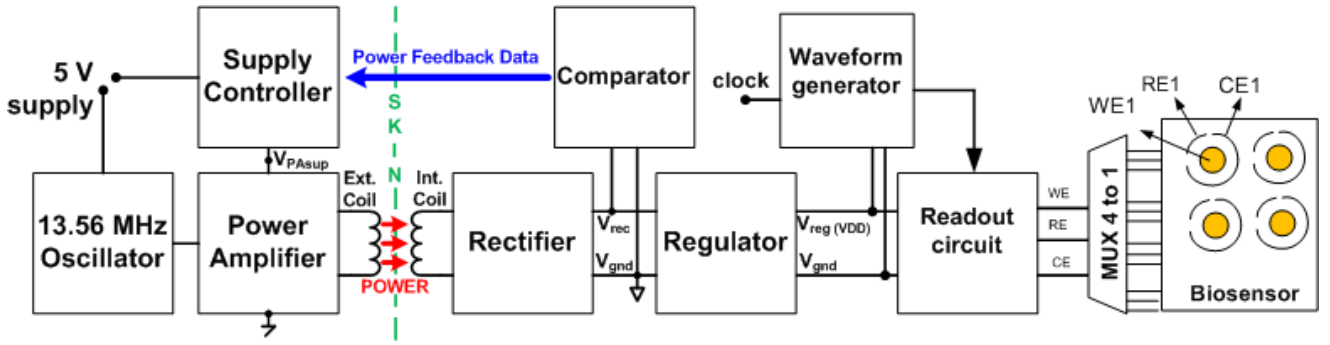


Fig. 1. Block diagram view of the implantable biochip with the inductive link

field strength, higher data bandwidth, and less interference compared to the other standard bands [11].

The induced AC voltage in the internal coil is converted to DC voltage by an efficient full-wave passive rectifier. The schematic view of the rectifier is shown in Fig. 2. The measured power efficiency of the rectifier is 80 % for 2 mW load.

A low-drop out (LDO) voltage regulator is implemented to create a clean and stable 1.8 V supply voltage for the biochip system. The high-speed voltage regulator is designed to suppress the ripples at the remote powering frequency. The details of the LDO design can be found in [12]. Fig. 3 shows the *Power supply rejection* (PSR) value of the regulator. It shows that the regulator has more than 65dB line regulation and more than 60dB at 27.12 MHz.

The power level of the implantable biosensor system needs to be monitored to provide sufficient power for different load conditions. Also, the coupling between the coils may changes during the measurement. The transferred power needs to be adapted dynamically to different load and also coupling conditions. To this purpose, a feedback mechanism is implemented in which the rectifier voltage (V_{rec}) is followed and compared with a certain voltage in order to keep the voltage V_{rec} at sufficient level regardless of the load [4]. The output of the comparator is transmitted to the external base station, as a power feedback data, to control the supply voltage of the power amplifier (V_{PAsup} in Fig. 1) [12].

Fig. 4 shows the power feedback system to control the delivered power to the implant by adjusting the power amplifier supply voltage. When the implant power is insufficient, *Power Low* data is transmitted to the external base station. As a result, V_{PAsup} increases by charging the C_{PAsup} and the transmitted power level is also increased. On the other hand, if V_{rec} in the implantable system is higher than necessary, *Power High* is transmitted to protect the implant from breakdown. Therefore, the delivered power is reduced by adapting the supply voltage of the power amplifier.

Fig. 5 shows the measured output waveform at the output of rectifier, regulator and the power feedback data when the inductive link is used for sending power to the IC.

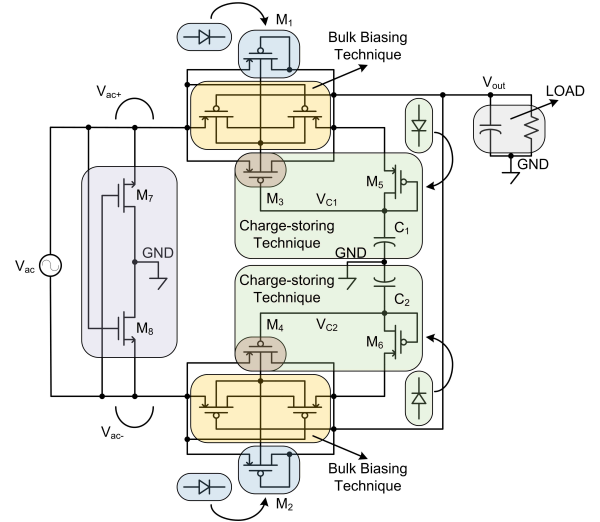


Fig. 2. The schematic view of the Rectifier circuit.

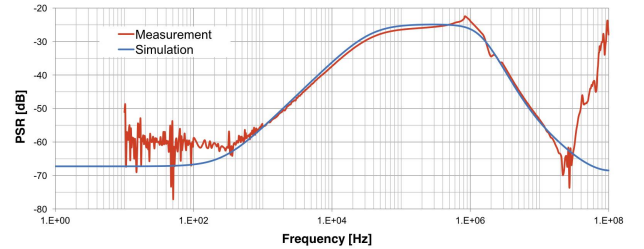


Fig. 3. The (simulated and measured) PSR of the regulator. The regulator has more than 65dB line regulation and more than 60dB at 27.12 MHz.

B. Control and readout electronics

To control the biosensor in CV measurement, the applied voltage between the WE and the RE is swept very slowly from negative voltages to positive voltages, forward and backward. The resulting current is measured and plotted versus the applied voltage. To implement the control and readout circuit for the CV measurement, a triangular waveform generator and a readout circuit is implemented in $0.18\mu\text{m}$ which are described in details in the following subsections.

1) *Ramp generator*: A *Direct Digital Synthesizer* (DDS) is designed to generate a very slow triangular waveform from a 5 kHz clock. The waveform generator is realized by mixed-mode design methods which consists of a digital up/down counter

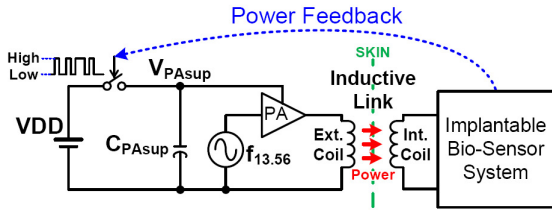


Fig. 4. The schematic view of the power feedback circuit.

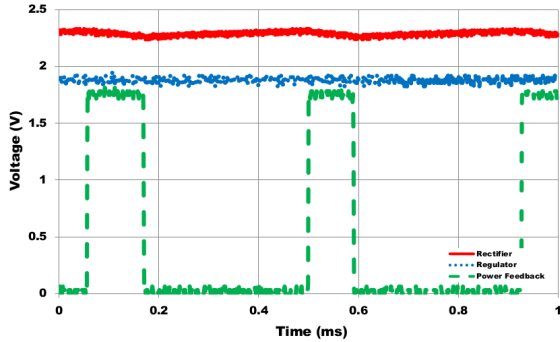


Fig. 5. The measured output waveform of the rectifier, regulator and the power feedback module when the inductive link is used for powering the system.

and a 9-bit DAC implemented in a resistor ladder scheme. The conceptual diagram of the ramp generator is shown in Fig. 6. The generated waveform sweeps the voltage between 200 mV and 1.6 V [13]. The generated waveform goes through a voltage buffer which acts as a low-pass filter. Using a low pass filter softens the voltage and reduces the noise.

2) *Readout circuit*: To control the sensor in CV measurement, a fixed voltage can be applied to the RE through the potentiostat while the triangular waveform is applied to the corresponding WE, thereby the differential voltage sweeps between negative and positive voltages with 1.4 V peak-to-peak voltage. The bidirectional current readout is realized through a transimpedance amplifier [13].

The output of the readout circuit is converted to digital data by a microcontroller. The digitized data is transmitted by an on-off keying transmitter to the external base-station.

C. Biosensor array design

The microfabricated electrodes made on Silicon substrate where realized at the centre of Micronano technology of EPFL. The biosensor size is 30x16.4 mm and consist of an array of four independent sensors, with WEs of 1.2mm diameter, REs of 0.41mm² area and CEs of 2.2mm² area. The main advantage behind the design of an array of independent sensors is the possibility to perform multiplexed measurements of drugs. More details on the microfabrication and biosensor design can be found in [14].

III. MEASUREMENTS AND DISCUSSIONS

A. Materials and methods

Milli-Q water (18 MΩ/cm) was used to prepare all aqueous solutions. All experiments were carried out in a 100 mM

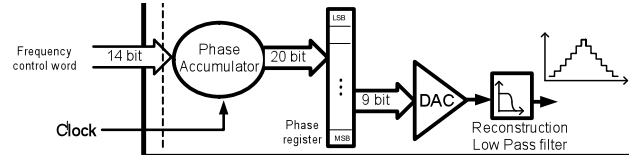


Fig. 6. The block diagram view of the integrated waveform generator.

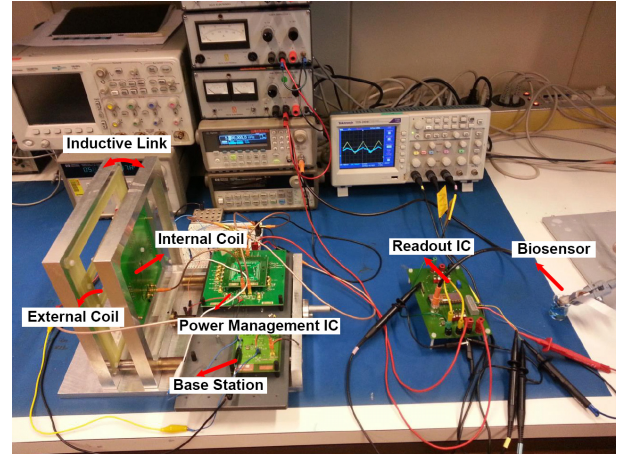


Fig. 7. The measurement setup.

Phosphate Buffer Solution (PBS, pH 7.4) as supporting electrolyte. Etoposide, and Mitoxantrone, two well known antineoplastic agents, were purchased as a powder from Sigma-Aldrich. Due to their low solubility in water, both Etoposide, and Mitoxantrone solutions at different concentration were prepared by dissolving them in Dimethyl sulfoxide (DMSO, from Sigma Aldrich) before storing at room temperature. The biosensor was dip into 10 ml PBS (100 mM, pH 7.4) and drug samples were added at the right concentration.

B. Measurement results

Fig. 7 shows the measurement setup. The measured voltage waveform at the output of the rectifier, regulator and the waveform generator are shown in Fig. 8 when the power management unit (and the inductive link) is used as the supply voltage of the waveform generator and readout IC.

The electrochemical response of the biosensor was investigated by cyclic voltammetry at room temperature under aerobic conditions by applying the triangular waveform with the slope of 82 mV/sec to the WE and a fixed voltage to the RE. The measurements were done both with or without the power management unit. When the power management unit is not in use, the measurement IC is connected to the supply voltage of 1.8 V. Fig. 9 shows the acquired voltammograms for positive applied voltages without the power management IC. The oxidation current peak is located at voltages 495 mV and 535 mV for Mitoxantrone and Etoposide, respectively.

CV measurements were also performed using an Auto-lab PGSTAT128N electrochemical workstation (Metrohm) for comparison. The same triangular waveform slope and range is applied to the sensors. The main oxidation peak position and its location (in voltage) for both measurements are summarized

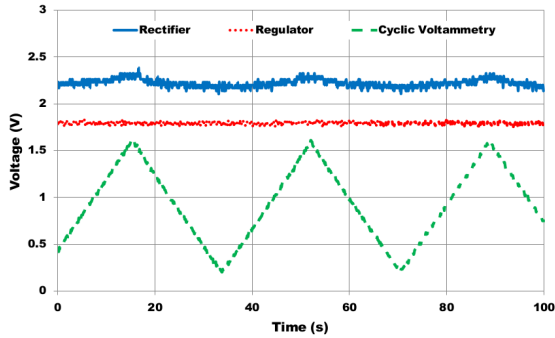


Fig. 8. The measured output waveform of the rectifier, regulator and the waveform generator for cyclic voltammetry when the inductive link is used for powering the system.

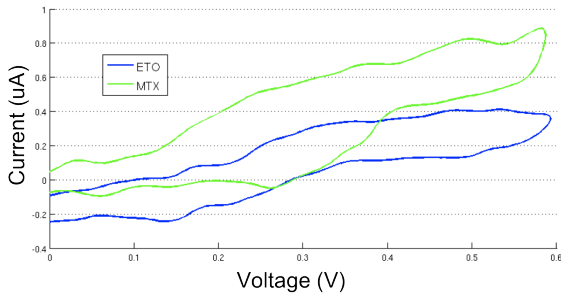


Fig. 9. The measured voltammograms during the detection of Mitoxantrone (MTX) and Etoposide (ETO) using the readout IC.

in Table I. The measured oxidation current peak location and value has less than 7% discrepancy between our microsystem and the Autolab potentiostat. The peak positions are consistent with the literature [15], [16].

IV. CONCLUSIONS

In this work an implantable microsystem has been designed and tested to perform drugs measurement in a wireless mode. The system consists of (i) Inductive link at 13.56 MHz; (ii) An integrated circuit implementing the rectifier and the regulator to empower the measurement circuit; (iii) An integrated circuit to implement triangular waveform generator with sub-Hertz frequency to control the biosensor in CV measurement, and readout circuit to measure the sensor current; (iv) A biosensor array for multi-target detection. The integrated circuits have been implemented in $0.18\mu\text{m}$ technology and tested successfully. The power efficiency of the full wave passive rectifier is 80% for 2 mW load. The system has been used to measure two well known anti-cancer drugs (Mitoxantrone and Etoposide) with CV method. The redox peaks corresponding to the two compounds were estimated in terms of maximum current (coding the drugs concentration) and the voltage position (coding the type of drugs) are measured with less than 7% discrepancy compare to the commercial equipment. The next step as the future work would be to complete the integration of the communication part and perform in-vivo test with mice. This new development opens the possibility to use implantable microsystems in personalized chemotherapy.

TABLE I

COMPARISON OF THE MAIN OXIDATION PEAK MEASURED WITH THE COMMERCIAL EQUIPMENT AND THE IMPLEMENTED MICROSYSTEM. DISCREPANCY IS LESS THAN 7%.

Biomolecule	Autolab		Microsystem	
	Voltage (mV)	Current (μA)	Voltage (mV)	Current (μA)
Etoposide	495	0.45	495	0.43
Mitoxantrone	535	0.81	513	0.86

V. ACKNOWLEDGEMENT

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