ABSTRACT
A ±1.2V / 350µW integrated front-end architecture for a true/false in-vivo subcutaneous detection device is presented. The detection is focused on using three electrodes amperometric sensors. The powering and AM transcutaneous communication are based on an inductively coupled link working at 13.56 MHz. A prototype device (5.5 mm x 29.5 mm) has been implemented and fully validated.

KEY WORDS
Implantable Device, Front-End architecture, Bioelectronics, Microelectronics Design, Biosensors.

1. Introduction

The integration of medicine and electronic technologies allows the development of biomedical devices able to diagnose and/or treat pathologies by detecting and/or monitoring pathogens, multiple ions, pH changes, and so on. Moreover, the advances in different areas such as microelectronics, microfluidics, microsensors and biocompatible materials open the door to develop human body Lab-on-Chip implantable devices and Point-of-Care in vitro devices. Two main problems should be overcome to obtain implantable devices. The first one resides in the way to transfer enough energy to power the devices, whereas the second one consists on the integration of the necessary instrumentation and communication electronics to control the sensors and to send the information through human skin.

An inductive coupling power harvesting is a growing alternative method for transmitting energy to the implanted device, substituting the use of batteries or wires. Furthermore, this mechanism permits to establish a bidirectional communication between the implanted device and an external interface. Some implantable telemetry circuits based on inductively coupling can be found in the literature like [1-3]. On the other hand, several works have developed integrable electronics for in-vivo monitoring like in [4] or in [5] where a signal-processing unit based on current to frequency converter and a communication protocol is presented. Although, a lot of works are focused on the development of robust electronics for in-vivo monitoring, continuously sensing, recording and data transmission, not all the in-vivo applications need these electronics. There are other less studied applications more focused on the detection of presence or absence of a certain levels of proteins, antibodies, ions, oxygen, glucose, etc. These in-vivo detection circuits or True/False applications [4] work as an alarm; when the analyzed concentration level exceed, under or over, a threshold value or the system detects the presence of zero-tolerance pathogens like salmonella [4] the systems send to an external reader a signal indicating the fault or showing the value as in some pregnancy tests. For instance, in the case of glucose monitoring, the detection of a threshold decrease in the glucose level it is mandatory to avoid critic situations like the hypoglycemia [6].

This work propose a generic implantable front-end architecture based on inductive coupling for in-vivo presence or absence detection of pathogens, ions, oxygen concentration, etc, for a generic amperometric biosensor application. The proposed architecture includes the on-chip biasing, the potentiostat to drive the sensor, and the modulation and communication block. Two full custom IC’s and an antenna of 5.5 mm X 14.5 mm tuned at 13,56MHz have been designed to validate the proposal.

2. Architecture

The proposed generic implantable architecture is presented on Fig. 1.a. It is comprised of a BioSensor, an antenna and eight electronic modules. Three electrodes amperometric biosensor has been utilized to explain and develop the system. Anyway, it is easy to adapt the topology for any kind of sensor by simply modifying two modules: the Sensor Control and the Sensor Conditioning (Fig. 1.a). The three electrodes that compound the sensor
are: a) the working electrode (W) which serves as a surface on where the electrochemical reaction takes place; b) the reference electrode (R), used to measure the potential at the W electrode, and c) the auxiliary or counter electrode (A/C), which supplies the needed current required for the electrochemical reaction at the W electrode.

The system is conceived as an active RFID Tag [7-8] where the inductively coupled link, generated by the implantable and by the external antenna, is able to supply the enough energy to power all the system and, to provide a wireless bidirectional communication link through the human skin.

As a detector of absence or presence of any substance the system works as follows: when the inductive link delivers enough energy and the on-chip voltage regulators work properly, a power-on signal activates the electronics. At this point the Sensor Control module drives the amperometric BioSensor with the voltage provided by the Vin Generator. When this voltage is applied between the R and W sensor electrodes the reaction takes place and the sensor starts to generate a current proportional to the reaction. This current is measured and conditioned by the Sensor Conditioning module and the signal is forwarded to the Modulation / Data Processing module. In this block, the absence/presence detection takes place as well as the modulation process to send the information to the external reader using a backscattering method through the inductive link. In this way, the external reader can be quickly advised every time the desired substance exceeds the programmed threshold level or levels. The role of each module and the selected implementation are stated below:

2.1 Antenna

The antenna is used as a wireless communication link and power energy source. It should produce enough energy to supply the electronics and should have enough communication range to send and receive data through the human skin. To design an implantable antenna several possibilities could be explored. It is possible to use a small coiled antenna with extremely small size like those used in some RFID human or animal identifiers by Verichip® Corp. Also it is doable to integrate an antenna using a MEMS CMOS compatible process or using a modern organic technology like in [3].

A planar rectangular coil of 5.5 mm x 14.5 mm with a thickness of 0.5 mm has been designed. It has seven turns, a conductor width of 0.2 mm, inductance of 400 nH and a series resistance of 340 mΩ. It is tuned to work at the RFID frequency of 13.56 MHz. A minimum energy loss due to the skin absorption could be achieved working at this range of frequency [9], but other frequency could also be used. The commercial Texas Instrument® TRF7960 is used as external reader. It transmits the power to the integrated antenna and it receives the data from it.

2.2 AC/DC and Regulation Module

An AC voltage is produced by the coupled antenna, for that, one AC/DC rectifier is necessary to generate an unregulated DC voltage. Immediately after, a regulation block produces a regulated DC voltage to drive all the electronics. A bipolar power scheme able to supply a regulated differential voltage of ±1.2 V and a maximum current of ±1.5 mA implemented. The AC/DC block is based on a half-bridge NMOS rectified [10] with a bulk control voltage. This circuit maintains the bulk voltage at the highest potential to avoid parasitic conductance. The regulation block is based on the use of two low dropout regulators, Fig 1.b.

Figure 2.b presents the on chip voltage generated at various air coupling distances. The desired on-chip voltages are obtained for a distance up to 20 mm on air coupling conditions. A more accurate study with human tissue is beyond the scope of this work [11].

2.3 Vin Generation Module

This block is used to generate the voltages to be applied to the sensor. In function of the performance of the integrated BioSensor and how it works, the block can generate a DC or AC signal. This module could be programmed by the external reader in order to add more
functionality to the system. Three fixed internal voltages of 0.6 V, -0.6 V, and 0.5 V can be selected through S1 and S2. Fig. 1.b. Furthermore, an external off-chip DC or AC voltage could be selected.

2.4 Sensor Control Module

A specific electronic circuit is used to control the voltage applied to the sensor. This circuitry applies the voltage provided by the Vin Generation Module –Vin- between the Sensor Cell Electrodes. The topology of the circuitry should be selected in function of the used type of sensor. For three electrodes amperometric sensors, it is useful to work with potentiostat amplifiers. In this work, the adopted architecture is based on three operational amplifiers, OP1, 2, and 3, Fig. 1.b. This architecture controls the voltage at the Working (W) and Reference (R) electrodes such that, Vin = -VR where, VR is the voltage at the Reference electrode. In order to keep this condition, the current at the R electrode should be ideally zero and no current should flow through it. OP3 is used to ensure a minimal current flow and to sense the voltage difference between the R and W electrodes, that is, between the R and a virtual ground (section II.F). This difference is used by OP2 and compared with the desired Vin voltage, producing a voltage variation at the Auxiliar electrode and defining a current trough the cell in such a way that the voltage difference between the R and W electrodes follows the defined Vin signal that polarizes the sensitive cell. The designed potentiostat [12] can work with signals from DC up to 2 kHz and with Vin voltages up to +/-1.2V.

2.5 Conditioning Module

This block detects the signal generated by the BioSensor and adapts it to be treated by the subsequent module. In an amperometric sensor a current proportional to the anodic electrochemical reaction is generated at the working electrode. For that reason, a current to voltage converter based on a transimpedance amplifier –TIA- has been implemented. Moreover, the voltage at the working electrode is grounded through the virtual ground of the TIA. Its DC input resistance is 1 GΩ allowing a current detection up to 1 nA. The current-to-voltage conversion is defined by \( VTIA = -IW \times RTRANS \), where IW is the current through the working electrode and RTRANS is the externally selected gain resistance. A second gain stage based on an inverter configuration follows the TIA and adapts the voltage values for the next stage. The gain of this inverter configuration is defined by RG2 and is externally configured. Fig. 1.b presents the TIA, OP4, and the inverter gain, OP5.

2.6 Modulation and Data Processing Module

The data generated by the sensor and adapted by the Conditioning Module is then analyzed and emitted to the external reader through this module. For an integrated detector, the use of comparators is a smart solution to detect one or several points with medical interest.

In the implemented approach a comparators block able to detect three different threshold voltages (Fig. 1.b, Vth1, Vth2 and Vth3) has been designed. All three voltages are on-chip generated and programmed externally using S3 and S4. In function of the comparators response a modulation circuitry, based on monostables and a digital logic, activates the backscattering communication. This method consists in changing the impedance of the integrated antenna, in this way; the external antenna can detect this variation. A DC modulation [3] is used implementing a PMOS (W/L = 3000 μm / 2 μm) transistor connected directly behind the rectifier. This modulation presents a higher Q-factor modulation than the AC [3].

A low-power AM modulation protocol has been integrated as follows [12] to validate the communication: when there is enough voltage, start-up time, a Power-On-Reset signal activates the circuitry and the antenna starts to transmit continuously a series of ones. When the first threshold level is achieved the system transmits one zero (Tth1), if the second is reached two zeros are transmitted (Tth2) and when the third is achieved a series of three zeros are sent (Tth3). A zero time slot interval is defined as 250 ms (Tth1 = 250 ms). This time is controlled by an external capacitor, CPRG, Fig. 1.b.

3. Results

All modules of the architecture have been designed in 0.13μm technology from STMicroelectronics®. The first designed implantable prototype is presented on Fig. 2.a with dimensions of 5.5 mm x 29.5 mm. It is composed by two IC’s, one for powering [10] and communications and the other one with the instrumentation, one antenna, a sensor connection and the external capacitors and resistors. The Texas Instrument® TRF7960 is used as external reader with a maximum emission power of 200 mW at 13.56MHz. A commercial sensor AC1.W1.R1 form BVT Technologies® is used to validate the detection architecture.

The recovered voltage in the implantable device has been studied in function of the XY misalignments and in function of the distance (Z Axis) between the reader and the implantable. Figure 2.b presents the Z axis dependence of the rectified voltage obtaining a maximum working distance of 20 mm. In that point, the rectified voltage (Vrec) is not enough to generate the on-chip regulated voltages (±1.2 V). This is also the maximum allowable distance to transmit properly information to the external reader. The recovered power is in the range of 1.1 mW to 800 µW from 1 mm to 20 mm respectively. Figure 2.c depicts the rectified voltage (Vrec) distribution in function of the XY misalignment for Z distances of 10, 15, and 20 mm. The voltages obtained in the (0,0) position are equal to those presented in Fig. 2.b for all Z
distances so, it can be stated that the farther the antenna is placed from the center lower the rectified voltage is. At that point, it is defined a Safety Operation Area (SOA) where the implanted device can be positioned freely and still working properly. The SOA reduces its size if the Z axis distance increases. This effect is presented in the XY plane view in Fig. 2.d where it is compared the rectified voltage (Vrec) distribution with the total available area of the external reader (orange rectangle). For a distance of 10 mm the SOA area is close to the maximum area available. On the other hand, the SOA reduces till a minimum area of 20 mm x 10 mm for the highest Z = 20 mm (red zone). This situation is also illustrated in Fig. 2.a where it is depicted the External Reader Area (orange rectangle) of the TRF7960 and the obtained SOA for Z = 10 mm.

The detection instrumentation and communication mechanism is validated using several concentrations of K4[Fe(CN)]6 in PBS and a commercial sensor AC1.W1.R1. First of all, a cyclic voltammetry [13] from -1 V to 1 V at 0.05 V/s has been carried out to verify the Control and Conditioning modules. Figure 3.a depicts the voltammograms obtained for 1 and 4 mM of K4[Fe(CN)]6. The results are compared with the ones obtained with the commercial instrument CH 1232A (CHInstruments®). The reduction and oxidation potentials are located around the same voltages of 0.170 V and 0.240 V. Moreover, the shape of the voltammogram is almost equal in both instruments with a maximum difference in the peak amplitude of 5 µA respect the commercial one. Then, an amperometric analysis [13] is performed as is depicted in Fig. 3.b obtaining a similar response between the commercial and the full-custom instrument. The current picks during the transitions are filtered using a 4th-order OTA filter in the modulation module to avoid false detections.

The communication mechanism is configured to detect three different threshold values (Vth1, Vth2, Vth3, Fig. 3.b) as it is explained in II.F. Figure 3.c depicts the waveforms of the internal and external antennas when Vth3 is achieved for the worst case of a separation of 20 mm between antennas. A 10% AM modulation amplitude is achieved at the external reader, enough to detect the transmitted zeros. In that case, the time slot is around 750 ms, which corresponds of transmitting three zeros of 250 ms each one. Finally, Table I summarizes the most important features of the implantable device.

### 4. Conclusion

In this paper, the design and results of a front-end architecture detection system for in-vivo implanted devices is presented. With respect to other works where the modules are validated independently, this solution combines in the same implantable package the communication circuit and antenna, power and sensor instrumentation modules, all of them fabricated in CMOS.
technology.
The implemented instrument is designed to be inserted under the human skin. It is oriented to work with three electrodes amperometric sensors thanks to the low-power biopotentiostat amplifier, which is able to detect a minimum current of +/-1 nA. The electronics presents a low-power consumption of 340 µW @ +/- 1.2 V in order to avoid local heating dots. The maximum current that can be supplied through the inductive link, on air coupling, is ±1.5 mA @ +/- 1.2 V for a distance up to 15 mm. The power link has been studied in function of XYZ axis misalignments to define the Safety Operation Area (SOA) for the implanted device.
The instrument detection capability is validated using a commercial sensor and several concentrations of K4[Fe(CN)]6. Some voltammograms are carried out and compared with the ones obtained with a commercial instrument CH 1232A. Then, an amperometric configuration has been used to validate the threshold detection mechanism and the AM communication. In that way, the implantable detection architecture is experimentally fully validated.

References