Sub-mW Reconfigurable Interface IC for Electrochemical Sensing

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***Abstract*—The IronIC project has the aim of developing a fully implantable and remotely powered platform for the real-time monitoring of human metabolites. In this paper we present a mixed-signal interface IC for the electrochemical sensing data acquisition chain. The IC controls and reads out up to five biomolecular sensors, by receiving commands from a standard interface to conduct *chronoamperometry* (CA) and *cyclic voltammetry* (CV). Different voltage profiles are generated by using a single fully on-chip reconfigurable waveform generator, while the measured data are digitized. The IC is realized in 0.18 μm CMOS technology. Electrical measurements show that the linear readout current range is $\pm$1650 nA with 8-bit resolution. The cyclic voltammetry of potassium ferricyanide and the chronoamperometry of hydrogen peroxide have been successfully performed with the interface. The IC consumes 0.92 mW from 1.8 V supply voltage, making it suitable for remotely powered and implantable applications.**

***Index Terms*—Interface IC, Electrochemical sensing Control and Readout, Cyclic Voltammetry, Chronoamperometry.**

I. Introduction

Fully implantable devices for the monitoring of human metabolism require high level of miniaturization and integration. The electrochemical detection of the target molecules can definitely solve the issue of small and minimally-invasive implants. The IronIC project has the aim of developing a fully implantable and remotely powered platform for the real-time monitoring of human metabolites. The target molecules are principally but not limited to glucose, lactate, ATP, arachidonic acid, and bilirubin. The project is quite ambitious and presents several challenges:

- the continuous monitoring of multiple metabolites
- the integration of heterogeneous systems and technologies on the same platform
- the biocompatibility
- the remote powering through the skin.

The final system consists of three devices: a fully implantable sensors array for the metabolite detection, a wearable patch for the remote powering and data acquisition, and an interface dedicated to display the measurements on tablets and smartphones. A conceptual sketch is depicted in Fig. 1.

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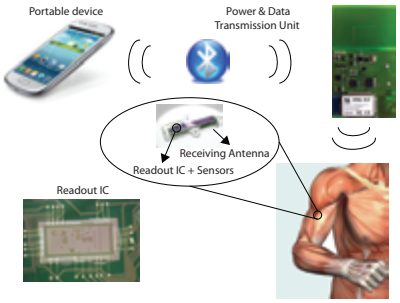

Fig. 1. Conceptual sketch of the final system for the IronIC project.

Based on the fact that the chemical detection is transduced in an electrical signal, the implantable platform requires a control unit and a readout electronics to perform the detection. The multi-target detection needs the integration of different detection methods within the readout IC. *Chronoamperometry* (CA) and *cyclic voltammetry* (CV) are the two most common electrochemical techniques used to measure the concentration of endogenous (i.e. glucose, lactate) and exogeneous (i.e. drugs) molecules in the human body [1–3].

Low power interface ICs for glucose and neurotransmitters detection through CA were presented in [4–7]. Interface ICs for CV, instead, include only the sensor readout, while using external waveform generators for the sensor control [8–12] . Li *et al.* reported an interface IC including all CA and CV control and readout parts. However it consumes about 20 mW, which make it not suitable for remote powering and implantable applications [13]. A fully-integrated and low-power readout IC to perform both CA and CV control and readout has not been introduced in literature, to the best of our knowledge.

In this paper we present a new reconfigurable sub-mW interface IC, controlling and reading out five bimolecular sensors in both CA and CV techniques with a fully digital output. The interface IC controls also a pH and a temperature for sensor calibration. It works with a 1.8 V supply voltage and has a single readout circuit for both CV and CA. The reconfigurable sensor control part is implemented fully on-chip without any need of external clock or bias generator. The measured signal of all the electrochemical sensors is digitized through a fully-on chip sigma-delta *analog to digital converter* (ADC). The IC configures the sensor array and performs CV or CA based on the received commands, and streams out the measured current. To validate the interface IC, CV and CA

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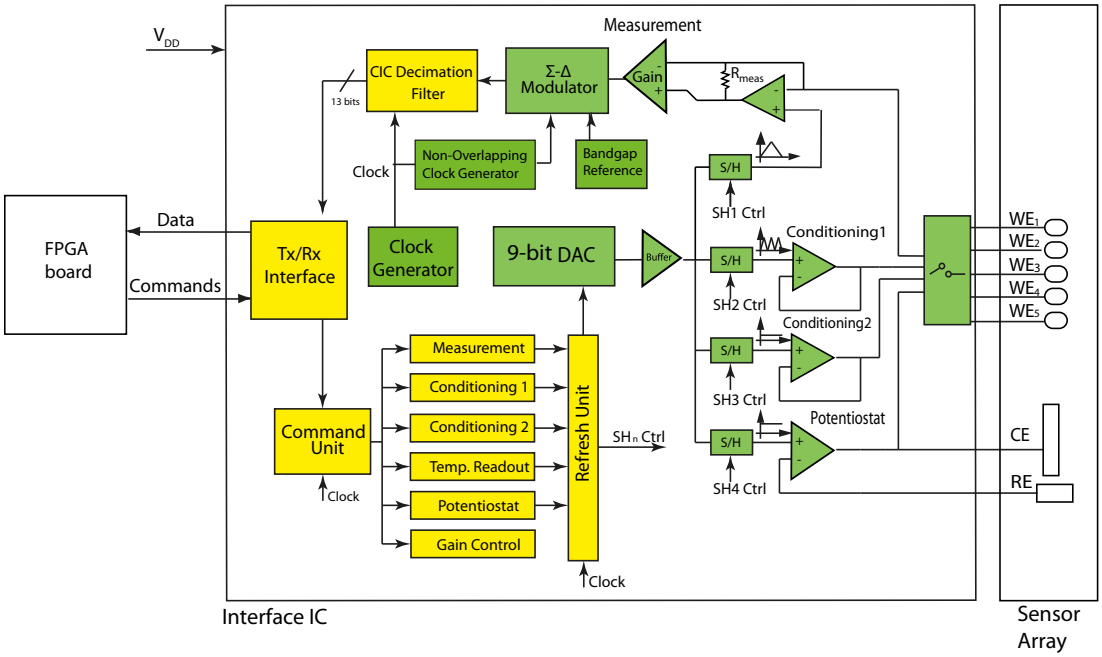

Fig. 2. The schematic view of the interface IC. The blocks in green and yellow are implemented in full-custom analog and semi-custom digital, respectively.

measurements are performed on the electrochemical sensors by using potassium ferricyanide and hydrogen peroxide as models of target molecules.

The design of the interface IC is presented in the following section. The electrical measurement are presented in Section III. Both CA and CV measurements are reported in Section IV. The summary and conclusions are given in Section V.

II. Interface IC

The block diagram of the mixed-mode interface IC is shown in Fig. 2, where the analog and the digital blocks are shown in green and yellow, respectively. The IC is in contact with five bio-molecular sensors. The interface IC is configured for a measurement according to the *Commands*, and it streams the results out on the *Data* pin. In this section we explain three main parts of the interface IC: (i) the electrochemical sensor control and readout circuit, (ii) the *Commands*, and (iii) the *Data* transmission.

A. Electrochemical Sensor Control and Readout

The electrochemical control and readout block performs both CV and CA measurements on the selected bio-molecular sensor. The control and readout is achieved through a chain of analog and digital blocks. A fixed or triangular voltage waveform is generated internally by a direct digital synthesizer (DDS). The DDS includes the digital *Refresh Unit* and a 9-bit *digital to analog converter* (DAC). This voltage waveform is applied to the sensor selected by the multiplexer. The sensor current is converted to voltage through a transimpedance amplifier and later amplified by the *Gain* stage.

The output of the *Gain* stage goes through a sigma-delta modulator and a *cascaded integrator-comb* (CIC) filter to be digitized. A second order sigma-delta modulator is designed to work with an oversampling ratio of 256 and the signal bandwidth of 1 kHz to achieve 13 bits dynamic range. The required clock and reference voltages are generated on-chip by the clock generator and the bandgap reference circuit, respectively. The 13 bit output of the CIC filter is given to the *Tx/Rx interface* to prepare for transmission.

To reduce the power consumption and the area of the IC, the DDS is shared among different circuits to generate three different voltage profiles: (i) triangular waveform for CV; (ii) fixed voltage for CA; (iii) triangular voltage for electrode conditioning. The *sample and hold* (SH) circuits are used to enable DDS sharing when different voltage profiles are needed at the same time. More information about the design and simulation of the analog circuits in the readout chain can be found in [15].

B. Commands

The instruction set of the interface IC consists of three main commands, each having a length of two bytes: (i) *Configuration*; (ii) *Execution*; and (iii) *Read*. The *Tx/Rx Interface* unit samples the voltage on the *Commands* pin to extract the commands.

The instruction *Configuration* is used to define the measurement parameters. Two types of measurements can be performed by the biosensor array: CA and CV. *Configuration*[13:10] selects the measurement type and the parameter to set. The parameter is set to *Configuration*[8:0]. In case of CV measurement, four parameters can be set: the maximum voltage, the minim voltage, the scan rate, and the number of periods of the triangular waveform applied to the WE. In case of CA measurement, the applied voltage to the WE can be set. The circuits Conditioning 1 and Conditioning 2 are used

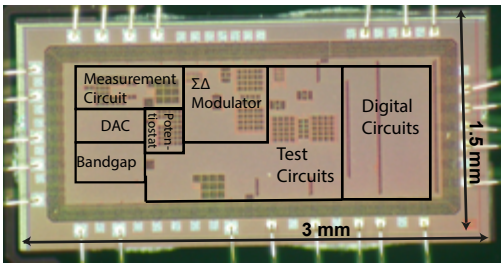

Fig. 3. The microphotograph of the interface IC.

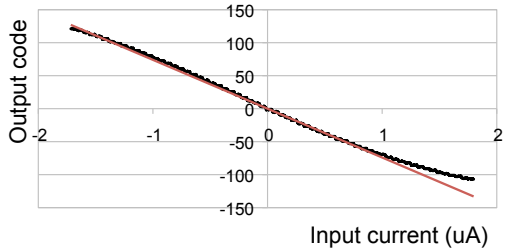

Fig. 4. Input-output characteristics of the current readout chain which includes the transimpedance amplifier, the gain stage, and the sigma-delta ADC.

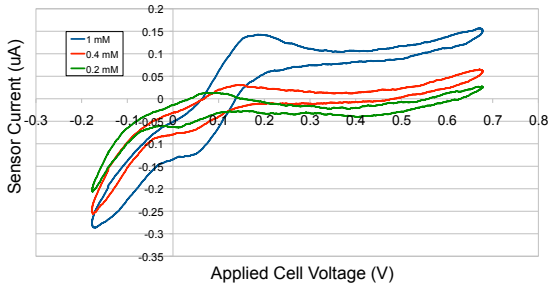

Fig. 5. Cyclic voltammetry of potassium ferricyanide at different concentrations with the IC commanded by the FPGA board.

to condition the electrodes when used for the first time and they can be configured in either CA or CV with configurable parameters. The connection of the five WEs and the RE with the measurement circuit and the conditioning circuits is also determined by the *Configuration* command. The *command unit* writes the parameters into the dedicated registers. The *Refresh unit* generates the digital data for the DAC as well as for the SH control signals.

The instruction *Execution* is used to begin/stop a CV, CA, or conditioning by applying/removing the appropriate voltage profile to the sensor. The stop command turns also off the sigma-delta modulator and the CIC filter. The instruction *Read* requests the readout IC to send back a certain number of measured data.

C. Data Transmission

If a *Read* command is received, the IC sends out the requested number of data. In case of CA or CV measurement, *Data*[12:0] contains the output of the sigma-delta ADC (i.e. the sensor current), while *Data*[15:13] of four consequent *Data* gives the 9-bit applied voltage (to the selected WE) preceded by a 3-bit starting pattern. An 8b/10b channel encoding is used in the *Tx/Rx unit* to convert the *Data* in order to achieve DC-balancing and avoid long sequences of the same logic value.

III. Electrical Measurements

The interface IC is implemented in 0.18 μm CMOS technology. Its microphotograph is shown in Fig. 3. A FPGA board (Xilinx Virtex-5) is used to send the commands to the interface IC, and receive the data back from the IC. The Data bitstream is 8b/10b decoded by the FPGA to extract the current and voltage values. Any fixed or triangular waveform with a slope larger than 2 V/S is generated by commanding the IC to work in CA or CV modes, respectively. To generate the triangular waveform with a slope smaller than 2 V/S, the IC is commanded to work in the CA mode, and the slow triangular voltage is generated by sending a configuration command to the IC that changes the voltage of the WE, for every step in the voltage. The electrochemical readout circuit is characterized by configuring the IC for CV measurement. The proper *Configuration* commands are sent to the IC to generate and apply a triangular voltage waveform to WE1 with a maximum of 1.5 V, minimum of 0.5 V, and slope of 4.5 V/s. The circuit is electrically characterized by using a resistor (267 kΩ) instead of the sensor between WE1 and a fixed voltage of 900 mV. The input-output characteristics of the readout chain is shown in Fig. 4. The current readout chain includes the transimpedance amplifier, the gain stage, and the sigma-delta ADC. Measurements show that the 1-dB compression point in the current readout chain is at $\pm$1650 nA, while the readout resolution is 8 bits within this range. The measured power consumption of the IC is 0.92 mW from 1.8 V supply voltage.

IV. Electrochemical Measurements

The interface IC is validated on the electrochemical sensors described in [16]. The same FPGA board is used with a different set of commands to address CA and CV measurements. Potassium ferricyanide ($K_4Fe(CN)_6$) and hydrogen peroxide (H_2O_2) are chosen as target molecules. The first compound is chosen because it has a well-defined response and highly reversible electrochemistry [3]. Therefore, it is a valid benchmark for cyclic voltammetry. The hydrogen peroxide, instead, is selected because it is an extremely significant molecule in the biomedical field. Many analytes can be detected by using oxidases. These enzymes usually promote a redox reaction, where the H_2O_2 is the main by-product [17]. Then, since hydrogen peroxide is an electrochemically active molecule, it can be directly detected through amperometric measurements.

A. Validation of the cyclic voltammetry

For each measurement, a drop of buffer saline solution with different concentration of potassium ferricyanide is placed on top of the WE, as well as the RE and the CE. A triangular voltage waveform with a maximum of 1.5 V, minimum of 0.5 V, and the slope of 10 mV/sec is applied to WE1 while 0.7 V is applied to RE. CV performed by the interface IC in the

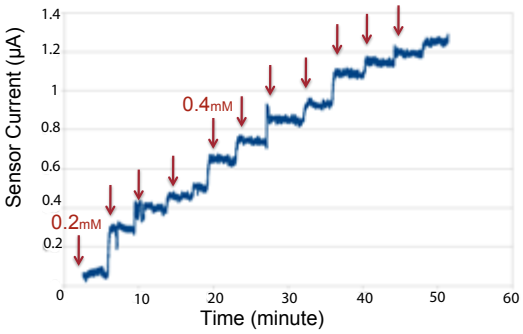

Fig. 6. Chronoamperometry of hydrogen peroxide using the proposed IC. Successively injections of 0.2 mM and 0.4 mM of H_2O_2 show that the IC is able to correctly readout the current.

TABLE I
MEASURED SPECIFICATIONS OF INTERFACE IC

Parameter	*Value*
Current consumption of analog part	462 μA
Current consumption of digital part	56 μA
Minimum control voltage step	3.5 mV
Linear sensor current range	$\pm$1650 nA
Current resolution	13 nA

presence of potassium ferricyanide at different concentrations is plotted in Fig. 5. The measured sensor current is calculated from the output code of the readout IC and the measured characteristics of the IC in Fig. 4. A low pass filter is used to reduce the noise. The places of the peaks agree well with literature [18].

B. Validation of the chronoamperometry

The CA of H_2O_2 at +650 mV is reported in Fig. 6. The sensor current is measured in time while the concentration of the H_2O_2 is increased in steps of 0.2 mM or 0.4 mM. Since the CV and CA readout circuits are exactly the same, the IC output code in CA is converted to current using the same characteristics shown in Fig. 4. Table I summarizes the measurement results.

V. CONCLUSION

We presented a mixed signal interface IC for an electrochemical sensing data acquisition chain. The IC controls and reads out up to five biomolecular sensors. The IC supports both CA and CV measurements. Different voltage profiles are generated to control CV and CA by using a single fully on-chip waveform generator. The waveform generator is commanded by a standard interface for CA or CV with slope larger than 2 V/s or by voltage steps for CV with slope smaller than 2 V/s. The IC reads out the electrochemical sensors and streams out the digitized measured data. The interface IC is implemented in 0.18 μm CMOS technology and consumes 0.92 mW from 1.8 V supply voltage. The measured linear current readout range is $\pm$1650 nA with 8-bit resolution. Electrochemical measurements including CA and CV measurement have been successfully performed on H_2O_2 and potassium ferricyanide, respectively. The encouraging results obtained from the IC make it ready to be integrated on the sensing platform.

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