In this paper, the design of an Integrated Circuit (IC) for the measurement of tissue impedance is presented. The chip is intended to be used in monitoring biomedical parameters in living bodies. Tissue impedance is one of these parameters which allows ischemia monitoring. The designed IC is used in a four-electrode based set-up in order to minimize the effect of electrode-electrolyte interface impedance. A needle shaped probe which contains the four electrodes for the impedance measurement and Integrated Circuits (ICs) required for excitation and measurement purpose have been designed, fabricated and tested in-vivo. The IC has been fabricated in a 0.8 µm CMOS process, working at 3V of power supply. Test results have shown the circuit feasibility.

I. INTRODUCTION

Tissue impedance is one of the parameters that allows ischemia monitoring in living bodies. When ischemia is produced, the tissue impedance suffers large changes both in magnitude and phase [1,2]. Here we propose a new fully-integrated impedance measurement system that allows to acquire and process data in-situ. Output data are received by a computer in order to be post-processed. Figure 1 describes the basic principle for the impedance measurement. A silicon probe that contains the four-electrodes and the ICs required for excitation and measurement purposes have been designed, fabricated and tested in-vivo. This paper is organized as follows. Section II describes the fabrication, characterization and test process for the integrated four probes needle. Circuit model extraction for each electrode-tissue interface is obtained. Compatible circuits with this models, medical limitations and processing algorithms have been designed and tested. Its specifications and limitations are described in section III. In Section IV an exhaustive set of measurement has been presented, which are performed over fabricated needles, integrated circuits, and whole system both in lab and in-vivo conditions. In Section V conclusions are resumed.

II. THE NEEDLE

The bio-impedance probes developed for this work consist of four platinum electrodes (300 µm X 300 µm) on a needle shape silicon substrate [3]. The fabrication of the bio-impedance probes was carried out at the IMB-CNMI facilities. The clean room process consists of two photolithographic steps starting from a thermal oxidation to grow a thick field layer (800 nm) on four-inches P-type <100> Si wafers with a nominal thickness of 525 µm. The first photoresist layer is applied and patterned on the wafer surface in order to pattern a double Ti/Pt layer (30 + 150 nm) by using the so-called lift-off technique. Then, two LPCVD layers of SiO₂ and Si₃N₄ (300 + 700 nm) acting as passivation layer are deposited and patterned using the second photolithographic level in order to open the electrodes and the bonding pads. After the clean
room processes, the wafer is sawed by successive parallel and oblique cuts which result in a significant amount (>500) of needle shaped probes as the one shown in Fig. 2.

The electrode-tissue, or electrode-electrolyte, interface impedance determines the performance of any tissue impedance measuring system, specially at low frequencies [3]. This undesired impedance causes measurement errors that could be understood as noise or signal distortion. In order to minimize these artifacts, the electrode-tissue impedances should be reduced and matched as much as possible. Since the conductance of these interfaces is directly related to the area, the most evident way to reduce their impedance is to enlarge the electrode surface. This can be achieved by enlarging the apparent area (silicon area occupied by the electrodes) or by enlarging the effective area by increasing the surface roughness, which is the interesting choice. In this work, the platinization process was used [4]. At low frequencies, this method can reduce the interface impedance ten or more times. However, the resulting black platinum surface is fragile and becomes easily detached when the electrode is inserted into the tissue. For that reason, an intensive insertion test is performed after the platization and before the probes are used.

The characterization of the probes was performed by using a commercial impedance analysis system (SI 1260, Solartron Analytical from The Roxboro Group plc, Cambridge, UK). We performed dry inter-electrode impedance measurements to obtain parasite capacitances and dry electrode-pad impedance measurements to obtain parasite resistances. The interface impedance was analyzed from the measurements performed while the probe was immersed in a NaCl 0.9% solution (resistivity at 298K = 71.3Ω.cm). The results from the characterization are summarized in Table 1 and Fig. 3. This information was used to elaborate an electric model of the electrodes for the IC design.

As it is common for most bioelectrode systems, the small-signal electrode-electrolyte interface impedance can be modeled as a pseudo capacitive element, \( Z = K j\omega^\beta \) [5]. In this particular case, \( \beta = 0.9 \) and \( K \) is around \( 2.5 \times 10^5 \).

The electrode-electrolyte interface impedance becomes very important at frequencies below 100Hz (Fig. 3) and that can involve important tissue impedance measurement errors. On the other hand, at frequencies beyond 100kHz, the capacitive coupling of the wires (including the coaxial wires from the probes to the instrumentation) is strongly manifested. Therefore, the useful frequency band is limited between 100Hz and 100kHz.

![Impedance probe after wafer sawing. The dimensions are expressed in µm](image)

**Fig. 2** Impedance probe after wafer sawing. The dimensions are expressed in µm

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cond.</th>
<th>Min.</th>
<th>Typ.</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>electrode-pad resistance: ( T_A = 298K )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( I^+ )</td>
<td>1050 Ω</td>
<td>1200 Ω</td>
<td>1300 Ω</td>
<td></td>
</tr>
<tr>
<td>( V^+ )</td>
<td>900 Ω</td>
<td>1000 Ω</td>
<td>1100 Ω</td>
<td></td>
</tr>
<tr>
<td>( V^- )</td>
<td>850 Ω</td>
<td>1000 Ω</td>
<td>1050 Ω</td>
<td></td>
</tr>
<tr>
<td>( I^- )</td>
<td>600 Ω</td>
<td>700 Ω</td>
<td>800 Ω</td>
<td></td>
</tr>
<tr>
<td>inter-electrode capacitance</td>
<td>( T_A = 298K )</td>
<td>5 pF</td>
<td>6 pF</td>
<td></td>
</tr>
<tr>
<td>inter-electrode impedance module in saline solution</td>
<td>( T_A = 298K )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( V_{OSC} = 100mV )</td>
<td>( 0.9% ) NaCl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( 100mV_p )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 Hz</td>
<td>5 kΩ</td>
<td>8 kΩ</td>
<td>25 kΩ</td>
</tr>
<tr>
<td></td>
<td>100 Hz</td>
<td>3.5 kΩ</td>
<td>5 kΩ</td>
<td>7 kΩ</td>
</tr>
<tr>
<td></td>
<td>1 kHz</td>
<td>3.6 kΩ</td>
<td>3.8 kΩ</td>
<td>4 kΩ</td>
</tr>
<tr>
<td></td>
<td>10 kHz</td>
<td>3.4 kΩ</td>
<td>3.5 kΩ</td>
<td>3.6 kΩ</td>
</tr>
<tr>
<td></td>
<td>100 kHz</td>
<td>3.2 kΩ</td>
<td>3.3 kΩ</td>
<td>3.4 kΩ</td>
</tr>
<tr>
<td>cell constant ( k = \rho R )</td>
<td>( T_A = 298K )</td>
<td>0.32 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( R = ) measured resistance</td>
<td>( 0.9% ) NaCl</td>
<td>( V_{OSC} = 100mV_p )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \rho = ) resistivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>spatial resolution</td>
<td>error &lt; 1%</td>
<td>4 mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
When a pair of electrodes is inserted in an electrolytic solution a DC voltage is created between them. This voltage depends on many factors (materials, sizes, temperatures, polarization currents...) and almost random signals are detected. In this particular case, using buffers with high input impedances, voltage drops up to 400mV have been measured in saline solution.

III. CHIP DESCRIPTION

The proposed measurement system is shown in Fig. 4. It is based on a four-electrodes system (Z₁ to Z₄), the external electrodes (Z₁, Z₄) are employed to inject the current into the tissue sample (SUT) of unknown impedance Zₓ, and the two inner (Z₂, Z₃) take its response. The excitation part consists of a VCO giving a sinusoidal current, while a signal acquisition circuitry (IA, demodulators and A/D) processes the SUT response [13-14]. Sinusoidal excitation currents (I) is generated for three different frequencies. For signal acquisition and processing, an Instrumentation Amplifier (IA), two demodulators and two Analog-to-Digital converters (A/D) are used. The final outputs of the circuit are two digital signals corresponding to the real and imaginary parts of the tissue complex impedance, Zₓ.

Accurate methods for impedance measurements have been developed [6-8]. We use the two-phase reference coherent demodulation method [8], which gives simultaneously the real (Re[Zₓ]) and imaginary (Im[Zₓ]) component of a complex impedance Zₓ.

\[ Z_{E2} = \frac{1}{g_{m}} \]

\[ I \]

\[ Z_{E1} \]

\[ V \]

\[ V_{o} \]

\[ V_{cap} \]

\[ V_{L} \]

\[ V_{I} \]

\[ V_{H} \]

\[ V_{L} \]

\[ V_{o} \]

\[ i_{o+} \]

\[ i_{o-} \]

\[ S \]

\[ f_{osc} = \frac{G_{ml} \cdot V_{I}}{2(V_{H} - V_{L})C_{I}} \] (1)

where \( V_{I} \) is a constant voltage generated on-chip, \( G_{ml} \) is the transconductance of the OTA used in the integrator, \( C_{I} \) the integrating capacitor, and \( (V_{H} - V_{L}) \) the voltage swing for the integrator output. Input \( S \) is a digital control signal that can select three different values for \( C_{p} \), making possible the generation of three different frequencies. The OTA has been designed to work in weak inversion, saturation region to fulfill the circuit specifications with low power consumption and moderated capacitor area [9].

The output buffer avoids coupling effects derived from the electrodes. As can be noticed in Fig. 3, the electrode impedance is frequency dependent, having its magnitude a high value for low frequencies. This is incompatible with a high output impedance for the current source, being necessary to avoid any current offset. The buffer we use here reduces the high impedance for low frequencies, limiting it to the inverse of a transconductance \( g_{m}^{-1} \) of an OTA, that can be controlled by design. Classical approximations introduce discrete highpass RC networks for this proposal [10]. The electrodes have a very high DC impedance and hence, any offset at \( I \) current signals will destroy the input range for the instrumentation amplifier.

![Fig. 4 Blocks involved on the real and imaginary impedance measurement system.](image)

**A: The signal excitation circuit.** This circuit drives a sinusoidal current to the SUT. The objective is to generate a voltage response when it passes through the load, in this case, the tissue. The current must keep below 5µA RMS, over a load range of 100Ω to 10kΩ which means that the output resistance of the VCO must be high enough to reduce load effects inside the specifications. The phase is in the range of \( [0, 30^\circ] \). These specifications must be inside the 2% of magnitude error and 1° of phase error. The VCO circuit diagram is shown in Fig. 5. It uses a ramp integrator tuned to a bandpass filter, both implemented as in [9]. The oscillation frequencies are given by,

\[ f_{osc} = \frac{G_{ml} \cdot V_{I}}{2(V_{H} - V_{L})C_{I}} \]

B. The amplifier: Specifications for the instrumentation amplifier are specially strong due to the input levels derived from the electrode model. The contact potential in the interface electrode-tissue, \( E_{rev} \) will cause a high swing input common-mode voltage, and even a large differential DC voltage level. DC levels imposed by contact potentials are in the ±400mV range, and are significantly larger than the signals to be amplified (from 0.5mV to 50mV as maximum). The gain of the amplifier is 20dB, with a dynamic range of 74dB. The CMRR required is of 109.54dB. The circuit we have employed as amplifier is based on the proposed in [11], and its schematic is shown in Fig. 6. It is based on V-I and I-V conversion using linearization circuits at input and output stages. It has a bandpass transfer function to filter low
frequency noise and also, to eliminate the DC differential level from the electrode model.

Lowpass filtering is performed by $Z_s$, while the highpass function is implemented by feedback with $H_{lowpass}$ function. This fact will relax the CMRR specification at DC.

### C. The impedance measurement circuit

From the IA a sinusoidal waveform with amplitude and phase proportional to the impedance of the tissue is obtained. For decoding this information, two phase reference coherent demodulation method is employed [6-8]. This is illustrated in Fig. 7, where two in-quadrature clocks signals must be used to perform the multiplier operator. The excitation circuit has a bandpass filter based on a $TTB$ that implements simultaneously BP and LP functions, both in 90° phase shift [6]. These signals are used to generate clocks for demodulation purpose: the in-phase and in-quadrature clocks. This is done by means of two differential comparators placed in each filter output (LP and BP). For a given phase shift $\alpha$ between $I$ and $V_x$, when the multiplication has been performed, the DC levels obtained at the demodulator outputs are proportional to the $\cos(\alpha)$ and $\sin(\alpha)$ functions, being these the real and imaginary parts of $Z_x$. A four order lowpass filter, with very low cutoff frequency (about 200Hz) is necessary to select these DC signals. This filter has been implemented by cascading two $TTB$ circuits, with input pair transistors working in weak inversion. In order to reduce the capacitor area, bias currents of $2nA$ have been used to obtain low transconductance to capacitance ratios.

### IV. Experimental Results

A test chip has been fabricated in a 0.8µm CMOS process. A 3V supply voltage has been chosen in order to be battery powered. The layout is shown in Fig. 8. The core area is 6.95mm². Test results are shown for the whole chip for several types of loads: 1) Resistive ($R$). 2) Passive ($RC$), and saline solution (NaCl) with the needle. Another set of measurement was performed in-vivo conditions with kidney rats. In the Fig. 9 are shown the magnitude and phase response measured when the load is resistive. It can be appreciated the how magnitude changes are correctly sensed by the circuit. The phase is shift increase with the frequency. This could be produce by the phase response of the amplifier in its bandpass. Figures 10 (a) and (b) represent the real and imaginary parts. The magnitude and phase derived from them for several RC loads are in Figures 10 (c) and (d). For the parallel RC load, two capacitors (10 and 100nF) and a range of $[100Ω-10kΩ]$ for resistances are used. It can be observed the expected maximum for the real part between 1kHz and 1.5kHz. The measurements have been calibrated in order to eliminate the set-up response of the output and the offset in the measurements. Results show a good agreement with the expected data, being possible to detect changes in both magnitude and phase. Measures has been taken using the fabricated needle and 0.9% NaCl saline solution as load. In Fig. 11 are shown the magnitude and phase response for this load, using 1:1 to 1:40 concentrations. The magnitude is nearly constant, while the phase go down when frequency increases. This means that there is a load influence over the phase response that can be due to changes on electrode-solution model. The total current consumption is 700µA.
After performing electrical and in-vitro tests, an in-vivo test was carried out in a rat kidney subjected to acute ischemia. The study was conducted under the supervision of the IIBB ethics commission and conformed to the EU guidelines for handling and care of laboratory animals. A male Wistar rat (Ifa Credo, Spain) weighting 250g was anaesthetised with sodium pentobarbital (50mg/kg). A tracheotomy was performed, the trachea was intubated by using polyethylene tubing (PE-240), and ventilation was maintained using a Harvard animal respirator. PaCO2 values were kept between 4.7 and 5.4 by ventilatory control while PaO2 was controlled between 14 and 20kPa by adequate oxygen-air mixture control. The abdominal area was covered with saline soaked gauze at 310K (37°C) and a plastic cover to minimize dehydration of exposed tissues. The animal was permanently exposed to radiant heat, maintaining abdominal and kidney surface temperature at 309K. To induce kidney ischemia and reperfusion, laparotomy was performed and left renal pedicle
was dissected and occluded with a non-traumatic microvascular clamp. The kidney rat was subjected to 60 min. ischemia followed by 40 min. reperfusion. The impedance probe was orthogonally inserted into the kidney by direct puncture. The penetration depth of the center of the electrode array was 5 mm. The probe was kept into the tissue by its own shape and no bleeding was appreciated. Fig. 12 shows the magnitude and phase responses measured in this experiment. The impedance module increases according to the severity of the ischemic insult while the phase decreases. Both results are agree with the expected ones, and proves that the IC proposed forecast the same evolution than magnitude and phase impedance measured with conventional instrumentation [15].

![Phase](image1)

![Magnitude](image2)

**Fig. 12** Magnitude and phase obtained in-vivo test.

### V. CONCLUSIONS

An IC for myocardium impedance measurements including the excitation and the data acquisition circuitry has been designed and tested. It is part of a wireless system to be used during heart surgery. The chip has been designed for 3V battery power supply, taking into account the strong specifications given by the impedance range to be measured and by the electrical electrode model used in the four wires measurement system. Experimental results have been obtained in the lab and in-vivo experimentation, showing the feasibility of the IC.

### VI. ACKNOWLEDGE

We would be grateful for the experimental work to G. Hotter and her team at the Instituto de Investigaciones Biomedicas (CSIC). Also for the support received from the EC project “Si-Based Multifunctional Microsystems Needle for myocardial ischemia monitoring: MicroCard”. ESPRIT (N° 33485).

### REFERENCES