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Universal Signal Conditioning System for Amperometric Sensors

David-George Cristea[1,4], Mihai Emanuel Basch[1], Hadar Ben-Yoav[2],
Virgil Tiponut[1], Yosi Shacham-Diamand[3]
[1]*Politehnica University of Timişoara, Applied Electronics Department, 300223, Romania*
[2]*University of Maryland, Electrical and Computer Engineering (ECE), 20742, USA*
[3]*Tel Aviv University, Faculty of Engineering, 69978, ISRAEL*
[4]*Technion-Israel Institute of Technology, Department of Electrical Engineering, 32000, ISRAEL*
cristea.david@gmail.com

***Abstract*—In this article the research for developing whole-cell biochips has been presented using both bioluminescent and electrochemical methods. The research was on integrating an electrode cell with both electrochemical and bioluminescent detection using a single VLSI chip. The authors have investigated the signal conditioning system that can work with any kind of amperometric and bioluminescent sensor. During this research the authors focused on the analog front-end unit. The work includes investigating the electronic model for simulation for an electrochemical cell and conceiving a fully integrated 8X8 electrochemical sensor array. The authors are focusing on signal conditioning system and its functionality. The main concern for the authors was to maintain the complexity and the number of electronic devices as low as possible.**

***Index Terms*—amperometric systems, electrochemical and bioluminescent cells, labonchip, sensory system, universal signal conditioning system.**

I. INTRODUCTION

This Integration of living organisms on chip has become a field of great interest in the last decade. The development in genetics and bio technology makes it easy to integrate a large number of cells in a smaller and smaller volume. Also the advances in materials and electronics fields makes it possible to collect and analyze electric signals that have been impossible to detect until now. The universal presence of biological and chemical terrorism threats forced governments to invest huge amounts of money in security devices such as E-NOSE, lab on chip devices, E-THONGUE etc. We have used with bacteria and microbes. They are living on and inside our bodies. They can be friends or worst enemies. Our device works with living genetically modified Ecoli bacteria that detect toxicants in the water, air, soil etc. In literature there are several models to signal conditioning systems that work either with bioluminescent sensors either with electrochemical cells. The main problem of these two types of sensors is that one inject current into the circuit and one subtracts current from the circuit but due to the duality of this sensors, it is desirable to have a system that can work with both kinds of sensors. Another problem that needed to be overcome was the large excursion of currents, from 2 nano Amps to 100 micro Amps.

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II. TARGETED SENSORS

There are few methods to detect the generated signal from the microbial cells, e.g. optical, electrochemical, electrical and mechanical.

Electrochemical biosensors are based on a bio-interaction process, where electrochemical species are consumed or generated producing a measurable electrochemical signal. Electrochemical measurements detect only the electrical properties of the analyte species undergoing redox reactions; therefore, they are limited to sensing electro-active species. Electrochemical detection usually uses amperometry, potentiometry or conductometry [1].

Chemiluminescence (CL) is the generation of light due to the release of energy during a chemical reaction. When this emission originates from living organisms or from chemical systems derived from them it is named bioluminescence (BL) [4]-[8]. The analyte concentration can be determined by measuring the CL emission intensity, because it is a function of the concentration of the chemical species involved in the CL reaction. The CL method is a superior detection method for microfluidic systems due to the simple instrumentation and high sensitivity involved. The optical system used requires no external light source, which not only simplifies the instrumentation but also reduces noise, which in turn lowers the detection limit [2][3].

III. PROPOSED SENSORS ARRAY

The system was designed to work with both types of amperometric sensors, the sensors that inject and subtract currents from the circuit, in general and for electrochemical and bioluminescent sensors in particular. We have focused our attention on electrochemical sensor array due to the fact that currents produced by electrochemical sensors are much smaller than current injected by the bioluminescent sensors. We have designed an electronic equivalent model for both electrochemical single cell and for electrochemical sensor array as seen in [4][5]. Because of different fields combined, the necessity of equivalent circuits for simulation is obvious. In Fig. 1, we present our proposed model. This model is based on our needs and has been developed having in mind

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the simplicity needed in simulation and at the same time all the factors that affect the behavior of the sensor. For this design, the values have been chosen for our purpose and system applications and the model is included in an array of sensors. The used electrochemical methods were Cyclic Voltammetry (CV) and Electrochemical Impedance Spectroscopy (EIS). The main characteristic to establish by EIS is electron (charge) transfer resistance, CTR, in protecting film presence.

For small polarization

$$\Delta E = \left| E - E_0 \right| \tag{1}$$

, charge transfer resistance

$$R_{ct} = \Delta E / I = RT / nFI_o \tag{2}$$

– actually "ohmic" entity – may be defined. This makes possible to approach the electrode dynamic properties by equivalent scheme, presented in Fig. 4, in which, in addition to Rct, the electrolyte resistance Rel, interfacial double layer capacitance Cdl, and diffusion impedance W are also involved (provided that low amplitude sinusoidal potential is applied). Such Randles' circuit well simulates AC response of Au or Pt in Fe2/Fe3 solution.

For (3),

$$\mathrm{Re}\, l + (Cdl\ /(Rct + W)) \tag{3}$$

circuit, EIS spectrum in Nyquist plot, imaginary Zim vs. real Zre impedance parts, in which lower impedance corresponds to higher frequencies f, presents a semicircle continued by straight line with 45° slope. Diameter of the semicircle is interpreted just as Rct.

The resistance of the electrolyte (Rel) is always of the order of magnitude of several Ohm. However, if WE has its own high internal resistance (being, for example, semiconductor, or very thin metal film), Rel may increase up to tens kOhm. Rct depends on reaction rate and electro-active material concentration. With moderately (10 mM) concentrated and fast reacting material (as Fe2/Fe3), "specific" Rct may be as low as several Ohm·cm2. However, for slow reactions and low concentrations it may reach MOhm·cm2. Cdl in electrolytes on metals is always in the range of 5 to 50μF/cm2. The Warburg impedance usually dominates at low frequencies (~1 rad/sec) [4], so that, for example, for

$$Co - CR = 10^{-5}\ mol/cm^3\ (10.mM) \tag{4}$$

and n = 1, /W/ is about 10 Ohm·cm2. Impedance of single electrode (WE) is measured with 3-electrode scheme. With this scheme, current I flows through WE, electrolyte and CE. RE electrode serves for WE potential measurement (with respect to RE).

We have simulated the circuit maintaining a 300mV constant potential between counter electrode CE and reference electrode RE, in the same time measuring the current flow between working electrode WE and ground.

Rct have a varying value between 1 Ohm and several kilo Ohms while Rel=1-10 ohm and Cdl ~0.65uF.[4].

The simulations ware realized in CAD tools and the experimental results were obtained from Tel Aviv University laboratories under Prof. Yosi Shacham supervision.

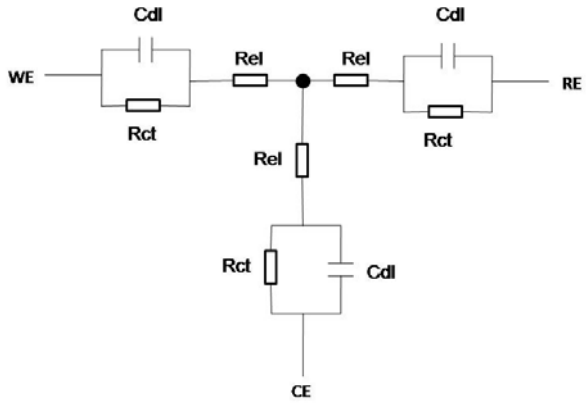

Figure 1. Equivalent electronic model for electrochemical cell [4].

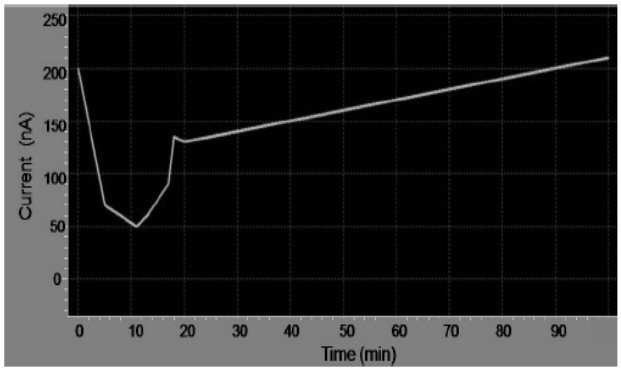

Figure 2. Simulation results for electrochemical cell model [4].

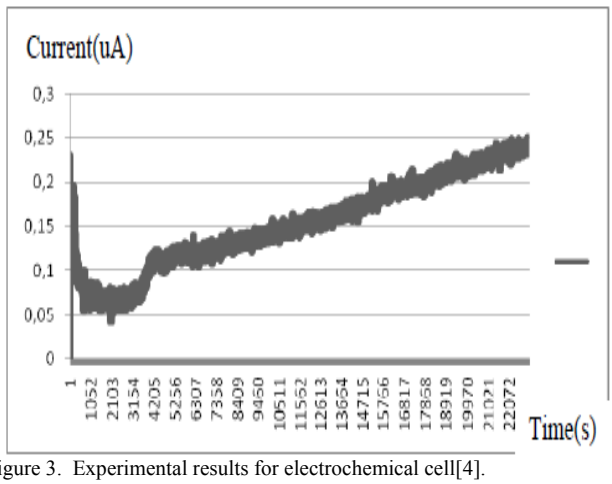

Figure 3. Experimental results for electrochemical cell[4].

Each cell in the array, for the simulation has the design shown in Fig. 1. The matrix of sensors consists of 64 cells, each cell being able to perform both as electrochemical and bioluminescent sensors, one at a time. The selection of sensors in the array and the type of sensor that we want to read will be made by the selection circuit that will be presented. The selection circuit will select one of the 64 cells that can perform as both types of sensors so the selection will be made out of the 128 sensors. The selection circuit has 2 roles, to multiplex and to control the circuit.

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The multiplexing part consist in 9 regular multiplexers and the controlling part is a well known shift register. The decision was made to use in this part simple circuits because being well known, one can predict their behavior in almost all conditions.

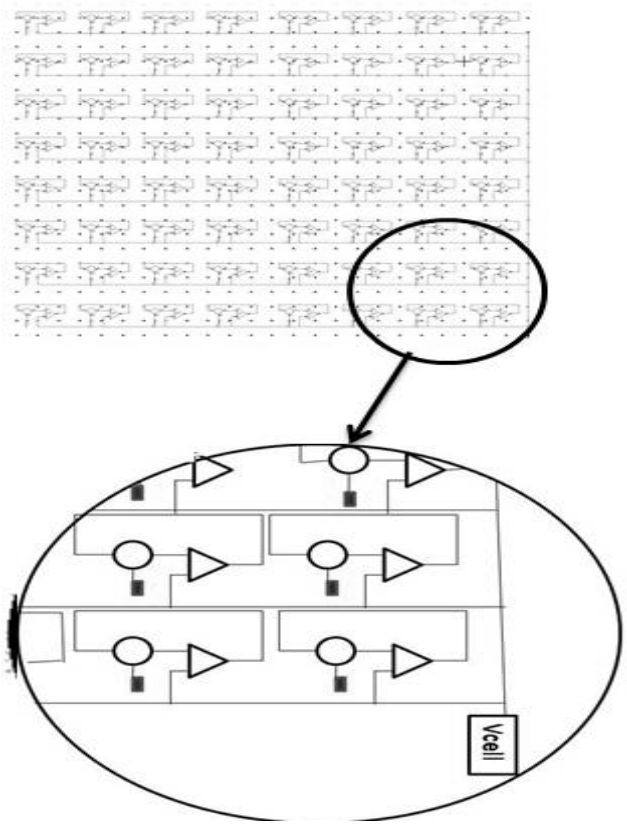

Figure 4. Proposed sensor array [5].

These 8 multiplexers will be controlled by one multiplexer with enable block and by a shift register. We modeled each 8 to 1 regular multiplexer so we obtain the minimum of complexity for the greatest accuracy. At the entrance of the circuit, the 8X8 sensors array will be kept at a constant potential of 300 mV, while at the exit of the matrix, the multiplexers will read each of the 64 cells. The 8 to 1 multiplexer enable circuit will dictate which of the 8 simple multiplexers will be active and what cell in the array will be read.

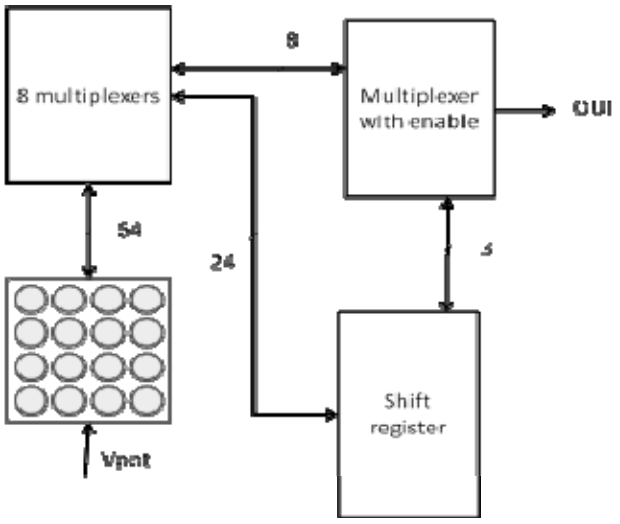

Figure 5. Multiplexing circuit diagram[4].

After one of the 8 multiplexers has been selected, it will start to read the output currents from the cells in the matrix[6]. The electronic equivalent circuit for electrochemical sensors was validated through experimental results, as seen in [2] and [3].

We have obtained signals that approximate very closely the behavior of a real life electrochemical sensor, both in transitory and in stable functionality.

The main novelty of this sensor array is the number of sensors that will be integrated on the same chip and the fact that the array incorporate two types of sensors that produce 2 different types of responses for the same toxic agent. This method increase the safety of the system. Having in mind that the system is based on living organisms no one can predict its behavior in all infield conditions. Also the life expectancy of living material must be taken in consideration.

We have used a complex multiplexer to measure one sensor at a time from a matrix of 64 cells, each cell can be used as 2 types of sensors, in this case we are using 128 actual sensors from a 64 cell matrix. Each cell will have 1 square millimeter on the final chip. We want to design low cost, disposable, single use cell matrix. Here we present a matrix of 3 electrode cells and we present the principle for the command circuit, as future work. The frequency is not very important here, we use a slow circuit because we wanted to avoid complexity and in this way the raising of the chip price. The frequency is low, in Hz-KHz range because the signals are varying very slow. A fast circuit is usually a complex and expensive one because we need to overcome a lot of noise on high frequencies etc.

Another decision that we had to make was the number and style of potentiostats. Here we have to choose from a number of possibilities:

1. One potentiostat for each individual cell,
2. One potentiostat for each row or column in the matrix
3. Only one potentiostat for all the array of potentiostats
4. Somewhere in the middle

The first approach, one potentiostat for each individual cell in the matrix it is the simplest from the electronically point of view but it is inefficient from the cost point of view. Using a potentiostat for each cell is uneconomical tacking a lot of space on chip so increasing the cost of the system.

The second approach is promising and presents some advantages, but also has drawbacks because of the command circuitry that are complicated and more circuitry mean more errors which need to be compensated, so increasing the chip area, increases the design cost, too.

The third approach is the most radical approach because it uses only one potentiostatic device. Being the most radical it has the biggest problems because it is quite a challenge to create an ideal current multiplexer and also presents a lot of drawbacks from command circuit point of view.

We decided to use the forth style, somewhere in the middle. Actually we decided to split the potentiostat in its component blocks[4].

The first operational amplifier of the potentiostat have the only role to maintain a fixed potential regardless currents that flow in or out from the cell. Each cell will have its own operational amplifier to maintain its fixed potential. The second operational amplifier in the potentiostat has the role

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to measure the current generated by the bacteria. There is only one operational amplifier to measure currents from all cells in the array [4].

IV. SIGNAL CONDITIONING SYSTEM

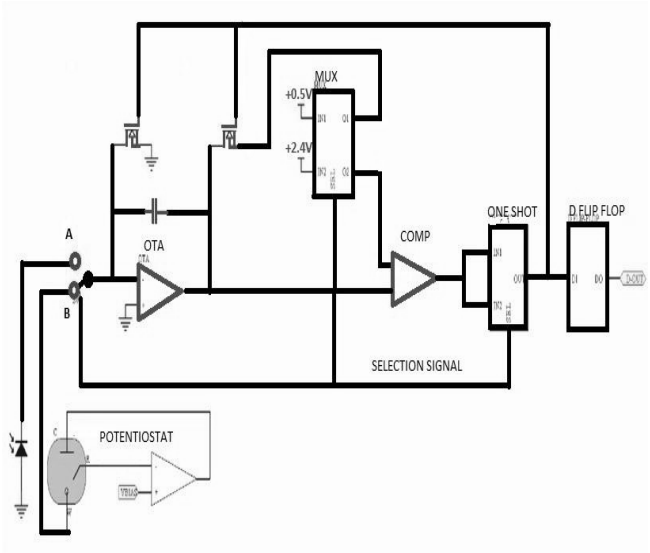

Figure 6. Universal Signal conditioning system block diagram [3].

The simplified signal conditioning system is presented. The Point A and B will be the exit points of the sensor array and the MUX multiplexer will make the selection between operational transducer OTA 0.5 V and at one entrance of the the two types of sensors that can be activated in each cell. First, we assume that point A is connected. In this case, the multiplexor MUX will send at the entrance of the comparator COMP 2.4 V.

The current from the sensor will start to charge the 1 pF capacitor, until the voltage will reach 2.4 V.

When this value is obtained, the comparator will send a signal to the ONESHOT circuit. The role of this circuit is to amplify the signal enough to reset the two keys of the circuit discharging the capacitor to 0.5 V and bringing 2.4 V at the entrance of the comparator COMP. The same impulse will be send to the D Flip-Flop circuit that transforms the impulses into the OUT signal of the design. More toxic agent into the water will be translated into more light, a bigger input current which will charge the capacitor faster, so the comparator will fire faster to the One-Shot circuit, which will reset faster the circuit so the frequency of the signal will increase proportionally with the concentration of pollutants. In the other case, the entrance of the circuit is on point B, at the exit of the electrochemical sensor. In this case, the OTA integrates the signal downwards, from 2.4V to 0.5 V. The MUX will provide 2.4 V to the entrance of the OTA, charging the capacitor, and, 0.5 V to the entrance of comparator COMP. The current from the electrochemical sensor will start to discharge the capacitor until it will reach 0.5 V. In this moment, the comparator will send a signal to ONE SHOT. This signal, which resets the keys, is also the output signal of the circuit.

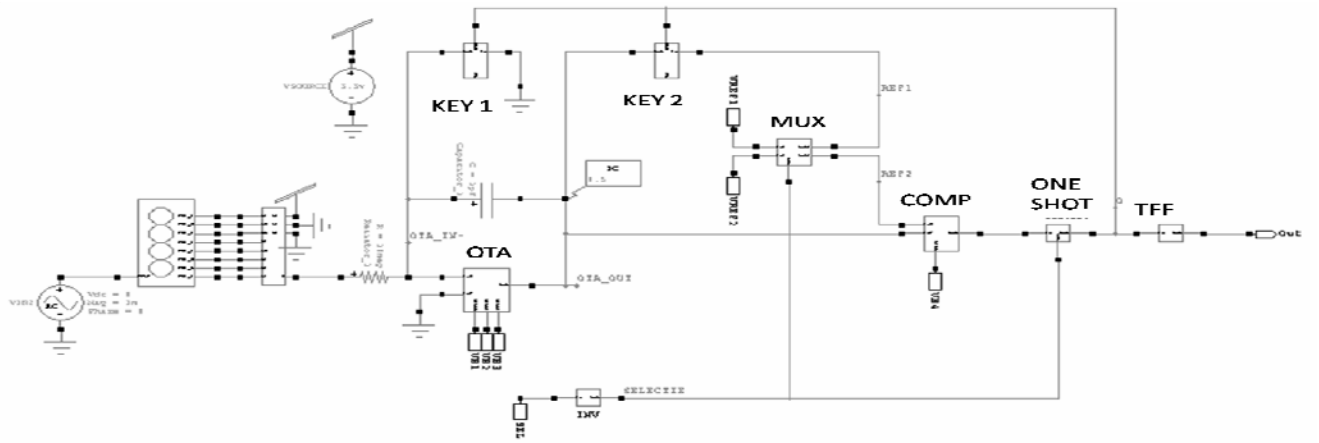

Figure 7. Universal signal conditioning system with control circuit.

In the control circuit we needed to use 2 clock signals.

CLKS is the clock that moves the information from the first flip-flop circuit to the last. The Shift Register consists of 26 groups. CLKP is the clock that acts when all the flip-flops circuits are charged. When all the flip-flops circuits are charged, the dates will be transferred to each exit point from P0-P26. The buffers act as compensator to compensate the delay that is inserted by the flip-flops circuits.

V. TEMPERATURE COMPENSATION BLOCK

If The sensory system functionality is affected by the temperature variation mainly at smaller currents so for bioluminescent sensors case due to the fact that this type of sensors have a lower current range compared to electrochemical sensors. Thus, there are cases when electrochemical sensors provide smaller currents than usual so the compensation will work in both cases. The viability of the temperature compensation block is proved trough comparison between results with and without compensation block.

As a temperature sensor, the compensation block is using 3 diodes in series connection which can be easily implemented in the CMOS technology by using p-type diffusion in an N-Well and through them a constant current from a current source is flowing. It is well known that when a diode is in conduction area, the voltage on the diode- the forward voltage-FV is temperature dependent. This voltage

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has been used to control the capacitor battery realized by capacitor-coupled PMOS transistors, the drain coupled with the drain. The controlling is made trough a repertory circuit coupled operational amplifier, as seen in Fig. 8.

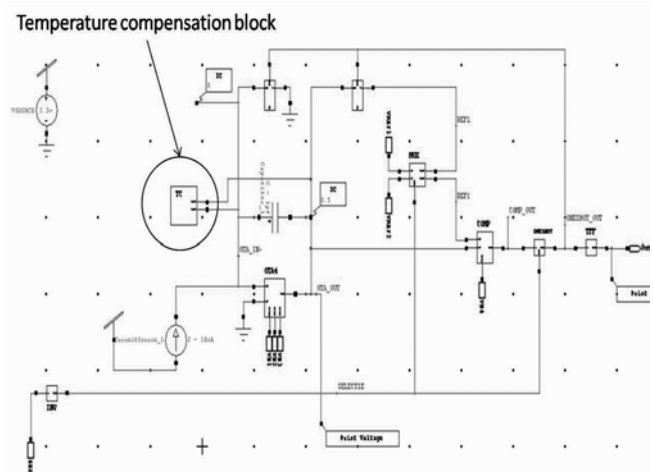

Figure 8. Signal conditioning system with temperature compensation block.

A temperature raising will provoke an decreasing of Vctrl voltage and, as a consequence, the input capacity is raising and so, a temperature decreasing will lead to an increase of the Vctrl voltage and so to a decreasing of the capacitance used for signal integration at the OTA entrance[10], [11]. The integration on chip of another block might be seen as a disadvantage due to the limitations imposed by chip area price but overall, even if it takes some space from the sensors area, the advantages provided by the compensation made it a good decision. Also, an outside sensor would increase further more the final price of the design and also would require integrated circuits at the entrance of the circuit, ESD protection, compensation of errors and so on[12]-[15]. The sensor integration, was, from author point of view the best choice for the temperature compensation issue.

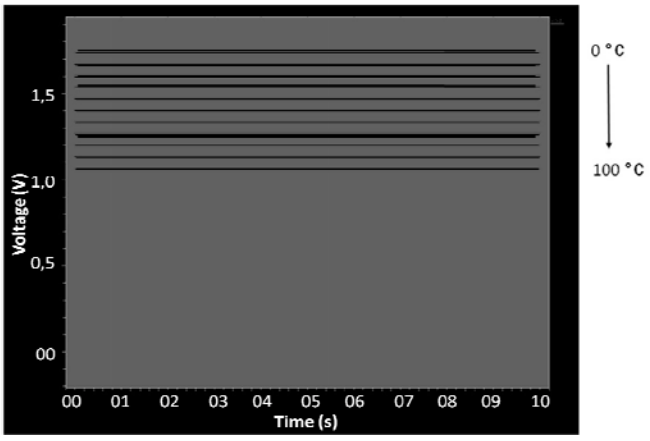

Figure 9. Variation of the voltage control (Vctrl) with temperature.

As one can see, the Vctrl voltage has a good variation for temperature variation and the temperature effects are compensated as seen in Fig. 10. In Fig. 11 and Fig. 12 the functionality of the compensation block is proved. The simulations ware made in all important corners of technology, Slow, Fast, Typical and combinations that can result in fabrication of the chip. In all cases the behavior of the system was improved, especially in small currents cases. These cases correspond to electrochemical sensors so this study was very important for the research.

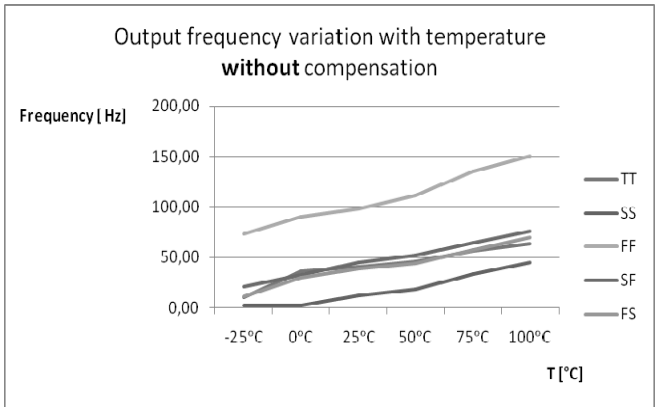

Figure 10. Output Frequency variation with temperature without compensation.

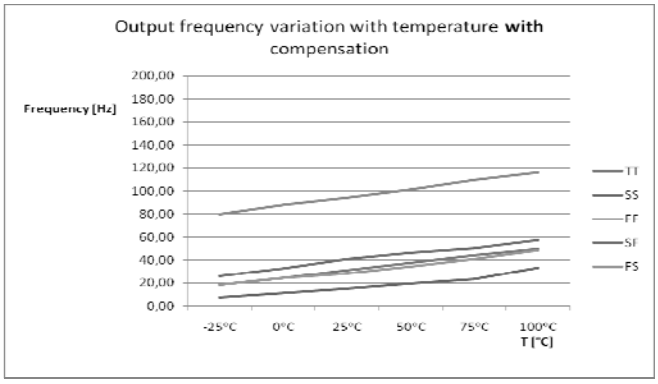

Figure 11. Output Frequency variation with temperature, with compensation.

As one can see, as stated before, the compensation is more obvious for smaller currents. The stability obtained is better for this sensory system comparing it to other designs present in literature.

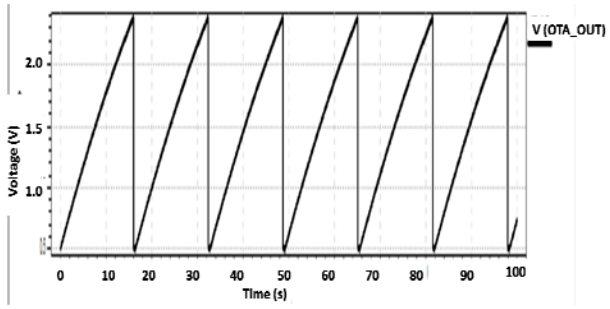

Figure 12. Output of OTA circuit.

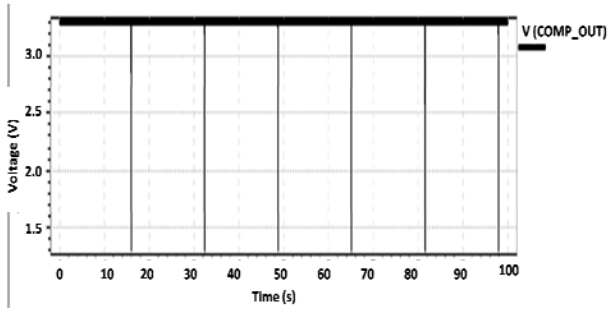

Figure 13. Output signal of Comparator.

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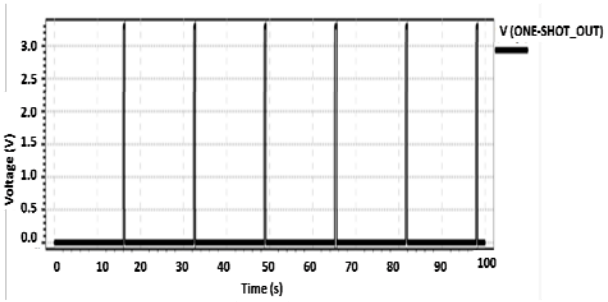

Figure 14. Output of One shot circuit.

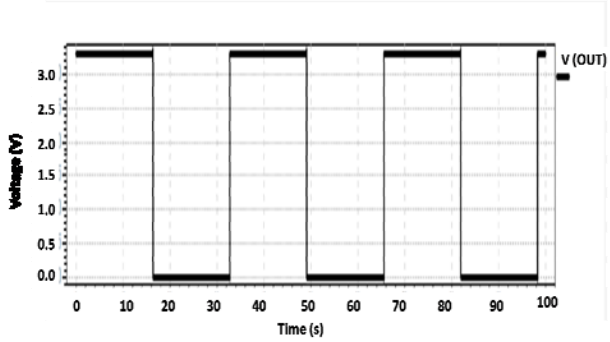

Figure 15. Output of the system.

The simulations ware made on a 4X1 sensor array because the complexity of the signals for more than 4 sensors increase and the concept can be illustrated better in a 4 sensors array. As one can see, the obtained signals are relatively clean and the system has a big noise tolerance. We also performed simulations at different temperatures, varying from minus 25°C to 100°C, for different corners of technology and the result was a linear characteristic for all the input current spectrum. The temperature range is theoretical, E coli bacteria are surviving between 2°C and 75°C. For theoretical simulations, simulations were made using 25um Generic CMOS technology.

VI. CONCLUSIONS

We managed to design a new and functional system capable to work with both electrochemical and bioluminescent sensors, amperometric sensors in general. We have used, where it was possible, well known blocks for the advantages they present. Common blocks are well known with their limitation and strong points so we were able to predict their behavior on different frequencies, temperatures and other different conditions that the system may encounter in the field. Also, the system was simulated on a large scale of temperatures between -25°C and +100°C theoretical range and behaved well. In practice, the range of temperature will be between 3°C and +74°C, outside this range, E coli bacteria that we use will die or slow their metabolism.

The long-term goal of this work is expand the system to a > 106 array where each pixel includes a single cell detector, i.e. microbe or mammalian cells.

Such system will be a breakthrough in investigating large number of single cells in parallel in real time applications. It will serve both basic biological research of cellular activity and also as whole cell biosensors for functional detecting of acute and genetic toxicity in both water and air.

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