

A first experimental model for a characterisation biodevice with epinephrine solution

Cristian RAVARIU¹, Ala BONDARCIUC²,
Florina RAVARIU³, Elena MANEA³, Cecilia PODARU³

¹*Politehnica* University of Bucharest, Faculty of Electronics
and Telecommunications, Bucharest, Romania

E-mail: cravariu@arh.pub.ro

²*Colentina* Hospital, Neurology Research Department,
Bucharest, Romania

³National Institute for Research and Development
in Microtechnologies (IMT Bucharest), Romania

Abstract. The electrical properties of the chemical mediators at synapses level could be investigated in vitro, with some test biodevices. One of neurotransmitters, like epinephrine, placed on an insulator support and contacted with metal electrodes, provides a Biomaterials On Insulators - BOI-type, test architecture. The test device is inspired from the pseudo-MOS technique, frequently used in the Silicon On Insulator characterisation. The DC regime study allows some polarography experiments. A behavior like a Field Effect Transistor was also investigated in DC regime, biasing a third terminal – the gate and monitoring the drain-source current. A dependence of the current – gate voltage is expected. It is still linear, emphasizing none inversion layer of the ionic charge. The AC regime measurements of the BOI device provided some conductometry results like resistivity. The current is a variable of time due to the oxidation / reduction rate at the electrode surface. This parameter is extracted from the switch regime of the biodevice.

1. Introduction

This paper proposes a biodevice based on the structure Biomaterial On Insulator BOI, working as epinephrine characterization device, another scope versus the common biosensor function.

In a previous work some test biodevices with two terminals, using the electrochemical cell: Sn/bioliquids/Sn [1], beside to Au/epinephrine/Diamond/Au chain [2], was studied by polarography.

Starting from a generalization of the Silicon On Insulator SOI concept, [3] and inspiring from the pseudo-MOS transistor technique, [4], [5] - a dedicated test device for the electrical characterization of the Si-film placed between two contacts probes - now a Bioliquid On Insulator device is created.

This epinephrine biodevice provides non-linear characteristics in DC regime, being depicted by the polarography's laws. The transistor effect was investigated, applying a transversal electric field on the longitudinal current flow, using a third terminal as a gate. On the other hand, the neurotransmitter solution presents hysteresis that proves the memory property of this kind of biomaterial. In the industry fields these studies offer alternative candidates instead of semiconductor diode with non-linear characteristics or intelligent devices that fill an increasing/decreasing voltage applied to them. In AC regime, corresponding to the conductometry in electrochemistry, the epinephrine solution resistivity is comparable with usual semiconductors resistivities. The switch regime study offers useful data in the neuroelectrophysiology understanding. At synapses level, the electrical conduction with a threshold voltage is ensured by these kinds of neurotransmitters. Hence, a parallel study with a threshold electronic devices, like pseudo-MOS transistor can be valuable in the biologic modelling.

2. Measurements Description

The biodevice architecture was inspired from the pseudo-MOS transistor, also named Ψ -MOSFET. This inherent device on all SOI structures is ad-hoc constructed for the electrical characterization of the wafer: the source and drain are two probes placed directly on the top of the Si-film, [5].

As is shown in Fig. 1, instead of the Silicon film, in this paper was used a drop of bioliquid and diverse metallic electrodes (in-oxidable steel INOX, Sn, Au).

The substrate was a Silicon wafer 200 μm thickness, p-type with a 10^{15}cm^{-3} Boron concentration, square shape 1 cm \times 1 cm. On this substrate, an oxide layer with 150 nm thickness was thermal grown.

In order to make comparisons, a physiological NaCl serum with the same concentration as epinephrine $c_i = 1 \text{ mg/ml}$, was sometimes used as a reference bioliquid. The bioliquid is dropped onto the oxide surface. The pH was constantly maintained closed to the bloodstream by a buffer system, being monitored with an EUTECH INSTRUMENTS EC-PH-10/01N pH-meter. The electrical characteristics of the biodevice were tested using a buffer solution, containing 122 mM NaCl, 4.7 mM KCl, 5 mM K_2HPO_4 and 0.5 KH_2PO_4 (pH 7.5). The solution was 5% saturated in Oxygen at 37°C.

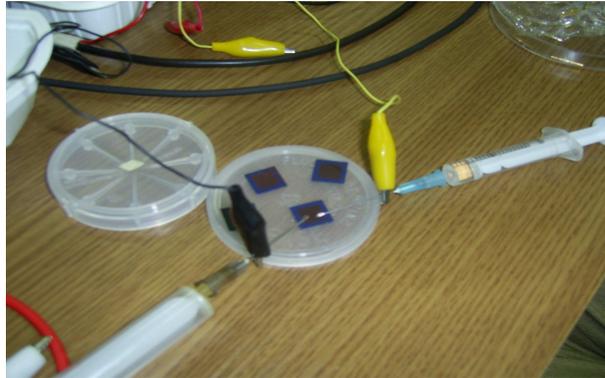


Fig. 1. A drop of bioliquid on insulator, contacted with two INOX steel electrodes.

All bioliquids contacted with two electrodes were tested using a simple circuit with a high resistance in series with the BOI device and biased at a DC power supply. The electrical characteristic were measured for a three terminal bio-device with epinephrine, acquired from Sicomed-SA. Also named adrenaline, it has $C_9H_{13}NO_3$ formula, being a catecholamine [6].

Using the third electrode as Gate, this contact represents also the reference electrode; the source is the counter electrode and the drain is the work electrode in the electrochemistry terms.

Making a parallel with the pseudo-MOS transistor could be observed the following resemblances:

1. two electrodes performing: a first contact Metal/Bioliquid – source contact, and a second contact Bioliquid/Metal – drain contact, as for the pseudo-MOS transistor, ensuring the longitudinal current flow;
2. either contact develops a double layer as is usually named in electrochemistry or a space charge region at the metal/semiconductor interface in microelectronics devices, being the key factor in both cases for the exponential law that depicts the current over-voltage dependence;
3. a semi-conducting layer between source and drain contacts with an electronic conduction in the pseudo-MOS case and an electrolyte liquid with ionic conduction in the biodevice case;
4. the semi-conducting layer is placed on an insulator support in both cases;
5. grace to this insulator support, on the back side of the device can be attached a third terminal as a bottom contact, named gate.

The molecular part of the proposed biodevice consists in polar molecules of epinephrine, or hydrate ions of Na^+ , Cl^- . The biodevices from Fig. 2a, in series with a high value resistance, $R = 110\text{ k}\Omega \dots 1.7\text{ M}\Omega$ was connected to a DC or AC power supply

Hameg HM 8012, Fig. 2b. The U_S , U_R voltages were measured with a Hameg HM 8001-2 voltmeter. The current value results from the Ohm's law: $I_D = U_R/R$ and the potential drop over biodevice is: $U_{BOI} = U_S - U_R$.

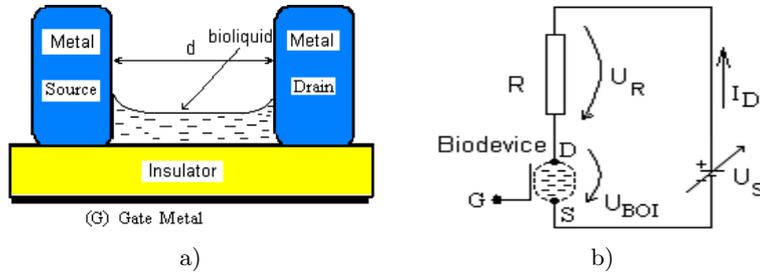


Fig. 2. a) The biodevice; b) the experimental circuit.

3. The DC Regime Analysis

The kinetic of reaction from electrochemistry was studied by polarography, [1]. This means a DC regime study of the current-voltage static characteristics, in micro-electronics terms. There a redox reaction of epinephrine was established. In order to reduce the negative differential resistance zones (e.g. between peak 1 and peak 2 on Adr. $R = 110\text{ k}\Omega$ curve) of the I-V characteristics, a higher series resistance $R = 1.7\text{ M}\Omega$ was used now. The polarographic I_D-U_{BOI} curves for epinephrine and NaCl solution, placed between two tin contacts, are available in Fig. 3 with classical notations from electrochemistry: current I versus ε as overvoltage.

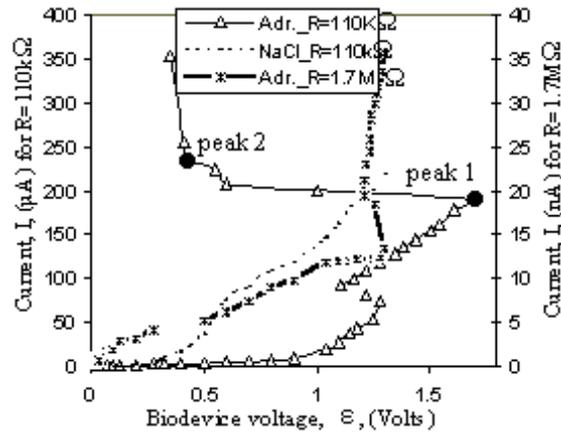


Fig. 3. The current-voltage dependence in DC regime for epinephrine and NaCl solutions with $R = 1.7\text{ M}\Omega$ or $110\text{ k}\Omega$.

The difficulties in experiments were: (1) due to the adhesion forces, identical shapes of the drop between both electrodes didn't occur; (2) the current is a variable

of time due to the generation-recombination rate of the ionic charges in the bioliquid solution. Hence, the time waiting between two consecutive voltages, was 100ms. This relaxation time was suggested by the following switch regime study.

Consequently, the $I_D - U_{BOI}$ characteristics exhibit high non-linearity: for epinephrine solution a low region with negative slope at $U_{BOI} = 1.3$ V appears for $R = 1.7$ M Ω , Fig. 3, and higher for $R = 110$ k Ω , Fig. 4.

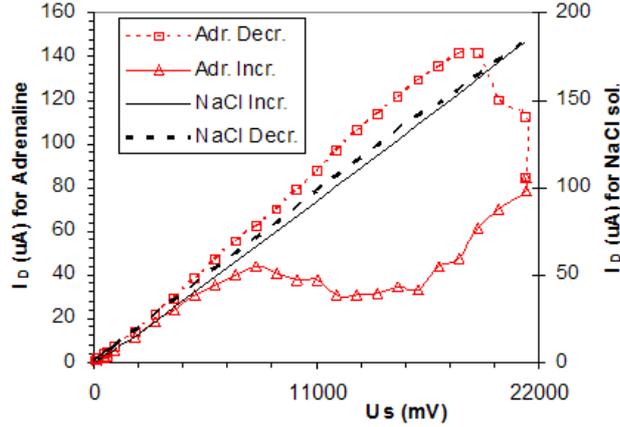


Fig. 4. The voltammograms for hydrophilic solutions and $R = 110$ k Ω ; I_D is the source-drain current and U_S is the external voltage.

Figure 4 comparatively presents the behavior of epinephrine and NaCl aq. solutions, both with the concentration 1 mg/ml, in the case of Sn electrodes and $R = 110$ k Ω . The U_S potential has increased from 0 V to 100 mV with 10 mV/5 sec, from 100 mV to 1 V with 0.1 V/5 sec, from 1 V to 21 V with 1 V/5 sec; then back decreased with similar rates. The first negative differential resistance region is starting for adrenaline at the value, $U_{BOI} = 1.3$ V (Fig.3, Fig.4) that proof a stable value for this point. In this way is reinforced the prior supposition, [1] that this behavior corresponds to an oxidation reaction kinetics: till 1.3V the adrenaline is oxidized in adrenalinequinone, then the reverse sense reaction occurs.

The first cycle of the voltammograms proves a hysteresis for $I_D - U_S$ epinephrine biodevice, in agreement with that for dopamine, another catecholamine, [7]. The internal feed-back redox reaction from our biodevice could be modeled by the Butler-Volmer exponential dependence, in analogy with a biased np junction:

$$I(U_{BOI}) \cong I_{ox}^0 \cdot \exp \left[\frac{\alpha \cdot z \cdot F \cdot U_{BOI}}{RT} \right], \quad (1)$$

$$\text{with } I_{ox}^0 \cong zF \cdot k_{ox} \cdot c_i, \quad (2)$$

where $\alpha \in (0,1)$ is the transfer coefficient, T is the temperature, R is the gases constant, F is the Faraday constant, z is the number of exchanged electrons, k_{ox} is the rate for the adrenaline oxidation, c_i is the ions concentration of oxidized species.

If the proposed biodevice works as biosensor, the second equation provides the analyte concentration, c_i from the experimental representation of the first equation: $\ln I_D - U_{BOI}$.

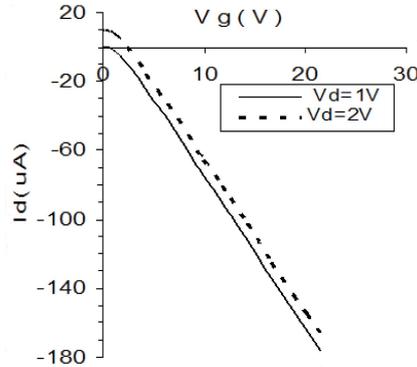


Fig. 5. The I_D - V_G curves for two drain voltages and INOX steel electrodes.

From a second DC power supply, the gate terminal was biased in order to study the back gate control on the source-drain current. Figure 5 presents two distinct I_D - V_G characteristics for $V_{D1} = 1$ V and $V_{D2} = 2$ V. In measurements, the leakage current through the biodevice gate was in the range 4–8 μ A. Probably this is the main cause of the weak I_D - V_G dependence in Fig. 5. The transversal electric field produced by the gate terminal, can only induce a separation of ions through bioliquid as an electrophoresis effect. The poor differentiation of the characteristics from Fig. 5 for $V_d = 1$ V and $V_d = 2$ V proofs rather the invalidation of the Field Effect Transistor hypothesis for our test biodevice, as was expected to happen in analogy with the pseudo-MOS transistor case.

4. The AC Regime Analysis

For AC stimulation a sinusoidal signal with $f = 10$ kHz was used from a Hameg 8018 Function Generator.

The conductometry curve in AC regime for the epinephrine bio-device provides the impedance: $Z = 930 \Omega$, extracted from the $I_D - U_{BOI}$ slope, Fig. 6. Writing the current density in two ways, yields:

$$j = c_i \cdot \frac{zF}{A} \cdot \mu_i \cdot \frac{u}{d} = \frac{u}{d} \cdot \sigma, \quad (3)$$

where j is the current density, σ is the conductivity, A is the source/drain surface, d is the source-drain distance, F is the Faraday constant, z is the number of exchanged electrons, u is the applied AC voltage, c_i is the ions concentration of oxidized species, μ_i is the ion mobility, [8].

The following parameters were used since to estimate the conductivity/resistivity: the area is $A = 1 \text{ mm}^2$, the distance drain-source is $d = 3 \text{ mm}$, the ions mobility is Hence the resistivity of epinephrine with $1 \text{ mg}/1 \text{ ml}$ aq. solution concentration is $10 \text{ } \Omega\text{cm}$, very close to that of a Si semiconductor value. Hence, this biomaterial is a suitable candidate for the organic semiconductors.

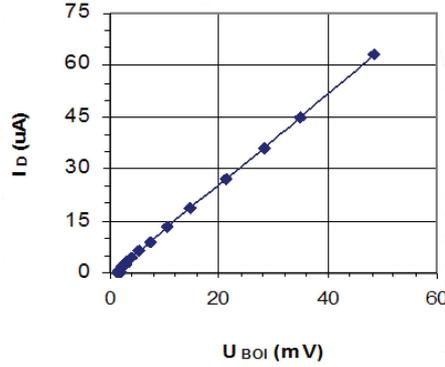


Fig. 6. Conductometry curve in AC regime for adrenaline biodevice.

5. The Switch Regime Analysis

In switch regime the response of adrenaline was more sensitive versus NaCl aq. solution with Sn electrodes, Fig. 7.

When the external voltage U_S increases from 0 to 2 V (at $t = 0 \text{ s}$), I_D decreases from $0 \text{ } \mu\text{A}$ to $-2,5 \text{ } \mu\text{A}$ for adrenaline biodevice, while I_D decreases from $0,4 \text{ } \mu\text{A}$ to $-0,1 \text{ } \mu\text{A}$ for salt solution, Fig. 7. On the other hand, this is an experimental demonstration that our adrenaline biodevice comes into damped oscillations. In order to avoid this unstable regime during the DC measurements, was selected a 100 s time waiting between two adjacent steps. Taking into account that the current produced by the ions transport can be written:

$$I = zq \cdot v \cdot A \cdot c_i, \quad (4)$$

where $q = 1,6 \times 10^{-19} \text{ C}$, v is the ion velocity, A is the electrode area, z is the electrons number exchanged in reaction and c_i is the ion concentration in g/dm^3 . For a period of time the external voltage is constant, hence the velocity is constant. By derivation in time yields:

$$\frac{dI}{dt} = zqvA \cdot k_{ox}, \quad (5)$$

where $k_{ox} = \frac{dc_i}{dt}$ represents the oxidation reaction rate.

In this way, the slope of the current - time function, experimentally extracted from Fig. 7 express the oxidation rate evolution in time. From electronically point of view the ionic charge concentration variation in time, dc_i/dt represents the generation-recombination equivalent term. However, the switch regime depicts very well the time evolution of the ions concentration.

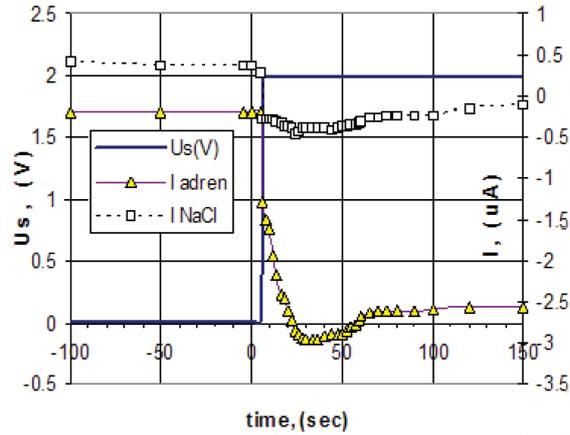


Fig. 7. The biodevice behavior in switch regime for U_S increasing from 0 V to 2 V at $t = 0$.

From the slopes, $dI/dt = 150$ mA/s for epinephrine, Fig. 7, and $z = 2$, $v = 10^{-5}$ m/s, $A = 1$ mm², accordingly with (5) the oxidation rates results: $k_{ox} = 0.2$ nl/s for the epinephrine biodevice.

6. Parallel with Synapsis

The synaptic space size varies from 12 nm ... 20 nm to 100 nm, existing high fluctuations in time due to the adaptation phenomenon. The number of contacts among neurons has elevated variations in the central nervous system: from an isolated one to ten hundreds. The maximum synapses number reaches 10 000–20 000. The synapses densities on the neuron surface could be 15–20/100 μm^2 .

The neuronal fasciculus can transmit 1 000 signals per seconds. One vesicle exocytosed in the synaptic space contains 15 000 molecules of catecholamine and can be 1 000 vesicles released at one nervous pulse. Therefore the total number of adrenaline molecules dispersed in the synaptic space can be roughly 10^7 . The epinephrine chemical formula, $\text{C}_9\text{H}_{13}\text{NO}_3$, provides the molar mass $M_{Adr} = 183$ g/mol. The epinephrine concentration c_{Adr} provides the molecules density expressed in molecules per μm^3 , from the transport under electric field in biodevice:

$$c_{mb} = \frac{c_{Adr} \cdot N_A}{M_{Adr}} \text{ and } c_{ms} = \frac{N_S}{A_s \cdot x_s}, \quad (6)$$

where c_{mb} and c_{ms} are the molecules densities in biodevice and synapse, N_A is the Avogadro number, x_s is the synaptic distance. From (3) results the molecules density in biodevice $c_{mb} = 0.3 \times 10^7$ molec/ μm^3 and $c_{ms} = 2 \times 10^7$ molec/ μm^3 in synapse. These closes values encourage to propose this test biodevice as an alternative tool in the synapses investigation.

7. Conclusion

Bioliquids could be alternative candidates for organic semiconductors, if they present non-linear electrical conduction. In this case, possible new applications could be offered by bio-devices, like: diode functions, oscillators, gate-controlled devices.

A poor dependence of the I_{DS} current versus the V_G voltage was experimentally demonstrated, but the transistor effect isn't still reached as non-linearity.

The polarographic experiments and cyclic voltammograms express the measured current versus the external voltage U_S . Some negative differential resistance zones occurred in the case of hydrophilic substances. The reason is related to some chemical reaction: forward and reverse oxidation of adrenaline in adrenaaliquinone. However the I_D values were instable in time, probably due to the same cause. This was confirming by some measurements in switch regime. A method to monitor the ionic charge concentration variation in time was proposed. The switch regime study is important because in the nervous system this regime prevails and there are implied a lot of catecholamines.

The molecules density in biodevice and synapses are comparable. Therefore, the biodevice proposed in this paper is suitable as a first order experimental model for a parallel study of synapses.

In fact, a second aim of this paper is fulfilled by presenting as close as possible the duals phenomenon from biology and microelectronics, searching a common language.

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