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TRANSDUCTION MECHANISMS FROM BIOLOGICAL MEMBRANES TO SILICON SENSORS : MODELLING AND COMPUTER SIMULATIONS

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Abstract A hybrid system consisting of a biological membrane (including an enzyme complex) in proximity (1 -10nm) to an ISFET is modelled. The response of the microelectronic device to a H^+ production, resulting from the enzyme-mediated transduction of a chemical signal, is simulated. Both steady and transient conditions are considered. Finally, hypothetical chemical mechanisms resulting in output switching phenomena are briefly discussed.

I.INTRODUCTION

In recent years, a cross - fertilization process involving microelectronics and biology has started, resulting in a fruitful comparison between strategies devised within the framework of semiconductor technologies for information transduction and processing and strategies naturally developed by biological systems. A specific example of interpenetration between biology and microelectronics is given by hybrid systems incorporating semiconductor - based microdevices in intimate contact with biological structures.

Such systems are of interest for several research fields, including microelectronic biosensors and molecular biology. Moreover, the characterization (at the nm level) of the functional coupling between biological and semiconductor structures represents a kind of "preliminary exercise", based on already existing technologies, which could be, in our opinion, very useful to the design of "truly molecular" devices.

II ELECTROLYTE - BIOLOGICAL MEMBRANE - ELECTROLYTE - INSULATOR - SEMICONDUCTOR (EBEIS) STRUCTURE.

An Electrolyte - Biological membrane - Electrolyte - Insulator - Semiconductor structure (from now on indicated simply with the acronym EBEIS) can be regarded as an extension of an EIS (Electrolyte - Insulator - Semiconductor) structure, (a well - known model for the study of FET - based pH sensors[1]), and it can be considered as the "heart" of any FET - based biosensor.

A detailed sketch of the EBEIS structure is given in Fig. 1A. It consists of a reference electrode, a "bulk" electrolyte solution ($\geq 1\mu l$), a biological membrane a few nm thick, a thin (1-10 nm) layer of "local" electrolyte solution (0.004-0.04 pl), a layer (100nm thickness, 20μm length, 200μm width) of insulator (e.g., Si_3N_4 or Al_2O_3) and a semiconductor (e.g., p - type silicon) bulk. In the following we shall consider only those structures where the thickness of the biological component (membrane) and its distance from the insulator are both in the nm range.[2,3]

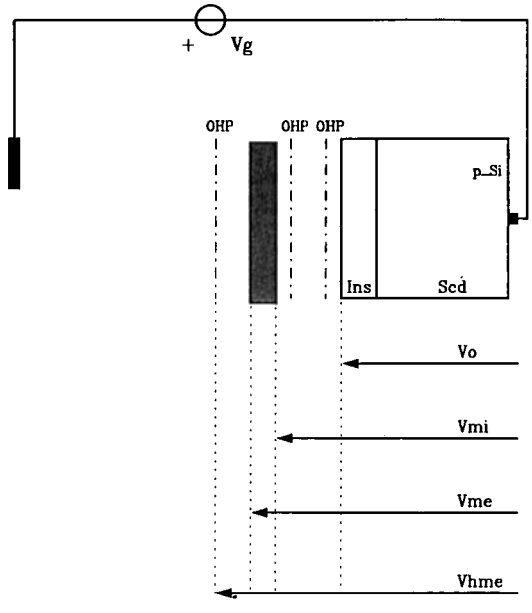

FIGURE 1A EBEIS structure. OHP is the Outer Helmholtz Plane.

An equivalent circuit of the EBEIS structure is shown in Fig. 1B.

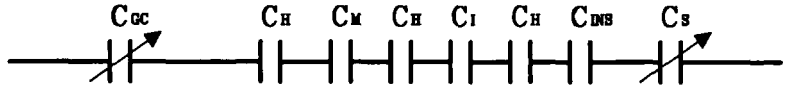

FIGURE 1B Equivalent circuit of the EBEIS structure.

Figure 2 shows a schematic representation of the chain of transduction mechanisms : a chemical signal *S* originated in the bulk solution is detected by a functional group at the biological membrane. As a result, protons are generated in the electrolyte bounded between the membrane and the insulator, and then transduced into an electrical signal. The (passive) capacitor - like electronic component can be transformed into an (active) FET - like component (ISFET).[1]

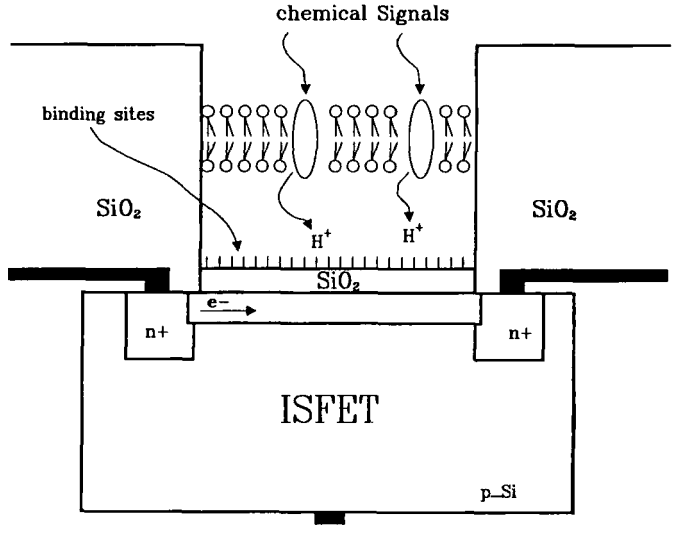

FIGURE 2 Chain of transduction mechanisms from a chemical signal (top) to the corresponding current in the ISFET channel (bottom).

III EQUATIONS DESCRIBING THE SIGNAL TRANSDUCTION CHAIN

It is assumed that, when a chemical signal S (substrate) reaches the membrane from the bulk electrolyte, a Michaelis - Menten - type enzyme reaction takes place, resulting in the production of protons in the local (buffered) electrolyte compartment; these transduction mechanisms are described by the following relations :

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} E + P \tag{1}$$

$$\frac{dS}{dt} = \frac{k_2 E_o S}{k_m + S} \tag{2}$$

$$E_o = ES + E \tag{3}$$

$$k_m = \frac{k_{-1} + k_2}{k_1} \tag{4}$$

where S is the substrate concentration, E is the enzyme concentration in free form, E_o is the total concentration of the enzyme (defined as the sum of the concentrations in free and complexed forms, see Eq. (3)), ES is the intermediate enzyme - substrate complex concentration, P is the product concentration, k_1 and k_{-1} are the forward and backward rate constants for complex formation, k_2 is the rate constant for complex decomposition into product, and k_m is the Michaelis constant.

It is also assumed that the "local" electrolyte compartment constitutes a microenviroment bounded by the membrane on one side and by the insulator on the other side. Protons interact with the insulator according to site - binding theory. As anticipated, the electronic component of the system is described as an ISFET. [1,4] As a result, the threshold voltage V_{th} of the ISFET[1] depends on the $[H^+]$ concentration in a Nernstian way (i. e. , 50mV/pH at room temperature).

The electrical potential in the bulk electrolyte is assumed to be described by the Gouy - Chapman - Stern model[5] . Thus

$$V_g = V_{hme} + \frac{2kT}{q}\sinh^{-1}\left[\frac{C_H(V_{hme} - V_{me})}{\sqrt{8\varepsilon_w kT c_\infty}}\right] \quad (5)$$

where ε_w is the water permittivity of the solution, C_H is the capacitance of the Helmholtz layer, and c_∞ is the ion concentration in the bulk electrolyte solution.

As a simplifying condition, a linear drop in potential is assumed to occur inside the thin rim of the local electrolyte compartment.

The proton concentration at the insulator surface, $[H^+]_s$, is assumed to be related through a Boltzmann distribution to its concentration just outside the membrane $[H^+]_m$:

$$[H^+]_s = [H^+]_m \exp\left[\frac{-q(V_o - V_{mi})}{kT}\right] \quad (6)$$

The meaning of the voltage drops in Eqs. (5) and (6) follows immediately from Fig. 1A.

At any interface, the dielectric permittivity of water, ε_w, is modelled with a maximum of three compartments: a first layer of fully oriented dipoles (thickness = 0.2nm; ε_w=6); two layers of quasi - oriented dipoles (thickness=0.4nm; ε_w=32) and a bulk compartment (ε_w =80).

IV SIMULATION RESULTS

A version of the circuit simulation program SPICE, developed to model ISFET devices[1], was further modified to include the equations provided in the previous section, and then used to simulate the EBEIS behaviour under different operating conditions.

Figure 3 shows the result of the system output simulation under steady - state conditions; this result was obtained by letting the reaction products diffuse outside the local compartment, according to the standard description of FET - based enzymatic biosensors (ENFET).[5,6] This situation represents the typical operating condition of an ENFET.[6]

As expected, a large region of linear response to the substrate *S* is obtained [6].

The system behaviour changes under the drastic assumption of no leakage from the local compartment, that is, if a perfect adhesion of the membrane to the lateral edges of the device (see Fig. 2) is assumed.

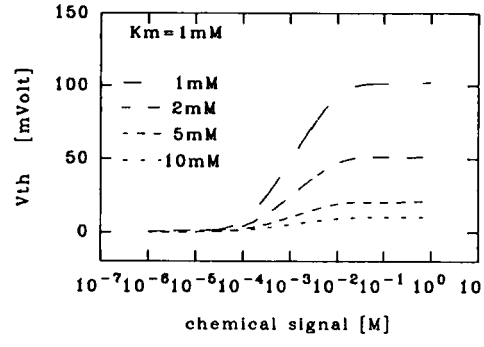

FIGURE 3 Chemical signal detection under steady - state conditions.

The transient output of the system under these conditions as a function of the membrane - to - device insulator distance is shown in Fig. 4A.

Poisoning effects, induced on the enzyme by the pH decrease in the local (sealed) volume are simulated in Fig. 4B. These effects were simulated by making the constant k_2 of the enzyme-product reaction dependent on the pH in the inner compartment via the exponential relationship

$$k_2^* = k_2 \exp\left[\frac{-|\Delta pH|}{\alpha}\right] \tag{7}$$

where α is a damping constant.

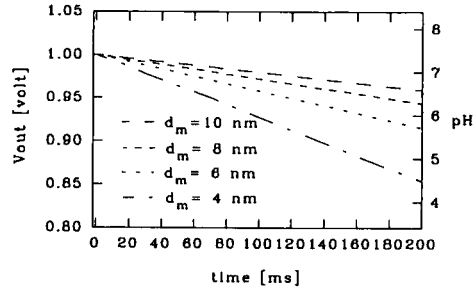

FIGURE 4A Transient output of the system under the "sealed" condition.

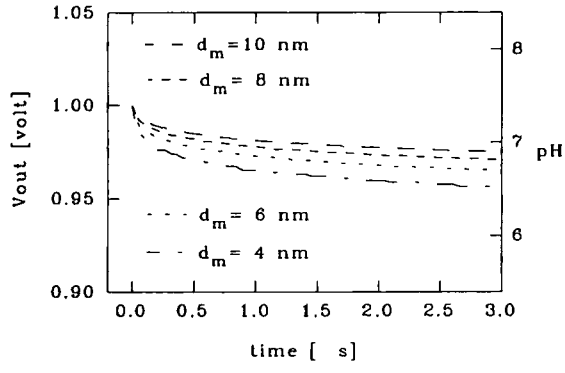

FIGURE 4B Same as in Fig. 4A but with an acidification - induced reduction in the efficiency of the enzyme reaction.

Such effects should be taken into account when considering sub - pl volumes with inefficient diffusion processes.

Finally, a (highly speculative) flow system, with H^+ - producing enzymes and OH^- - producing enzymes embedded inside the membrane, is shown in Fig. 5.

The chemical signal S_1 (H^+production) generates a low pH value in the local volume. If a sealed condition is assumed (i.e., if diffusion phenomena are to be neglected), then this value remains stable in time, even in the absence of S_1 (it is "memorized").

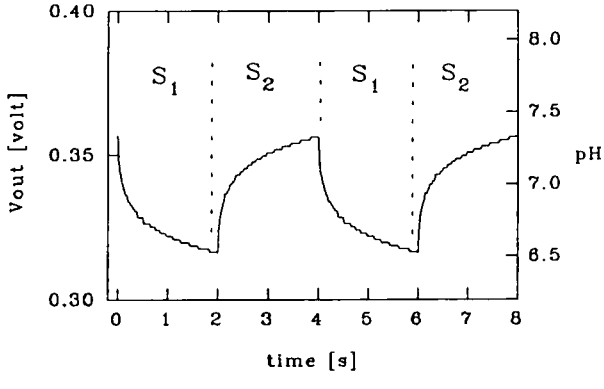

FIGURE 5 Simulated switching output of the ISFET driven by two alternating chemical signals.

It can then be "erased" by the chemical signal S_2 (OH^- production), which sets the pH to the original value, making the device ready for a new measurement. The system output can then be switched in time between two values by acting on S_1 and S_2.

V PROSPECTS

Transduction mechanisms in biological macromolecules represent a valuable paradigm for future molecular devices. Hybrid devices, that functionally couple biological macromolecules to microelectronic structures, can be used to better characterize such mechanisms and to compare them directly with the mechanisms utilized in microelectronic devices.

The description given in this paper can be considered as a first step toward the analysis of these bio/electronic structures at molecular level.

The proposed approach migth be of some use in the molecular electronics field, especially as far as a description of biochemical phenomena in terms of information processing is concerned. In addition, we believe that this approach can be useful for a better design of present - day microelectronic biosensors, based on CAD simulation programs. It should also be noted that standard "bulk" physico - chemical descriptions could not seem appropriate enough to describe sub - pl volumes confined between thin biological layers and micron - size electronic devices.

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