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# Hierarchical electrochemical modeling and simulation of bio-hybrid interfaces

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**Abstract**

In this article we propose and investigate a hierarchy of mathematical models based on partial differential equations (PDE) and ordinary differential equations (ODE) for the simulation of the biophysical phenomena occurring in the electrolyte fluid that connects a biological component (a single cell or a system of cells) and a solid-state device (a single silicon transistor or an array of transistors). The three members of the hierarchy, ordered by decreasing complexity, are: (i) a 3D Poisson–Nernst–Planck (PNP) PDE system for ion concentrations and electric potential; (ii) a 2D reduced PNP system for the same dependent variables as in (i); (iii) a 2D area-contact PDE system for electric potential coupled with a system of ODEs for ion concentrations. The backward Euler method is adopted for temporal semi-discretization and a fixed-point iteration based on Gummel's map is used to decouple system equations. Spatial discretization is performed using piecewise linear triangular finite elements stabilized via edge-based exponential fitting. Extensively conducted simulation results are in excellent agreement with existing analytical solutions of the PNP problem in radial coordinates and experimental and simulated data using simplified lumped parameter models.


*Keywords:* Bio-hybrid systems; Neuro-electronic interfaces; Multiscale models; Electrodiffusion of ions; Functional iterations; Numerical simulation

## 1. Introduction and motivation

In this article we address the study of a class of problems arising in the context of Bioelectronics, a recently emerged discipline at the crossroad among Nanotechnology, Solid-State Electronics, Biology and Neuroscience. The focus of our investigation is on the mathematical and computational modeling of bioelectronic interfaces (see [1,2] for a review and [3–6] for a selection of significant applications). Bioelectronic interfaces are bio-hybrid structures

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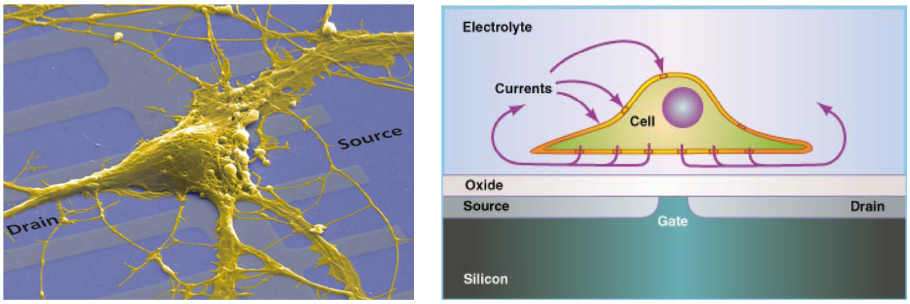


(a) Rat neuron on electronic substrate. (b) Neuro-chip.

Fig. 1. Left: rat neuron grown on an EOSFET. Right: schematics of a neuro-chip.
*Source:* (Left) Image reprinted from [7]. (Right) Image reprinted from [8].

constituted by living cells attached to an electronic substrate and surrounded by an electrolyte bath. An example can be seen in Fig. 1(a) which shows an electronmicrograph of hippocampal neuron cultured on an electrolyte–oxide–silicon field-effect transistor (EOSFET) [7]. Fig. 1(b) reports a schematic cross-section view of a neuro-chip, which allows to identify the main parts of the bio-hybrid system: the cell, the extracellular bath, the thin interstitial cleft separating the cell and the electronic substrate, the protective oxide layer deposited on the top of the substrate, and the source-to-drain transistor structure.

In the basic function mode of the EOSFET, as a consequence of the cellular activity elicited by the application of an external stimulus, ionic current flows through the adhering cell membrane and along the cleft. The resulting extracellular voltage turns out to play the role of the gate voltage which controls electrical charge flow in the substrate and, ultimately, the current flowing out from the drain terminal of the device.

The interface contact in the scheme illustrated in Fig. 1 is realized by the thin conductive electrolyte separating the two subsystems, whose amplitude is smaller than the cell radius by about three orders of magnitude. Therefore, the cell–chip junction forms a planar electrical core-coat conductor and the main physical phenomena (ion electrodiffusion and gate voltage modulation) take place in this three-dimensional region whose vertical thickness is much smaller than the two-dimensional area where the cell adheres to the substrate.

The above description indicates that a sound mathematical picture of a bioelectronic interface requires the adoption of a genuine multiscale perspective. For this reason, in this article we continue our analysis started off in [9] and numerically investigated in [10] and propose a hierarchy of models based on PDEs and ODEs for the simulation of the biophysical phenomena occurring in the 3D interface contact described above. The hierarchy includes the following three members, ordered by decreasing level of complexity: (i) a 3D Poisson–Nernst–Planck (PNP) PDE system for ion electrodiffusion and electric potential dynamics [11]; (ii) a 2D reduced PNP system for the same dependent variables and phenomena as in (i); (iii) a 2D area-contact PDE system for electric potential dynamics coupled with a system of ODEs for ion dynamics. This last member of the hierarchy is a variant of the area-contact model proposed and studied in [12].

Model (i) is the most accurate in the hierarchy but, of course, requires a considerable amount of computational effort for its numerical simulation. Model (ii) is obtained by averaging the 3D PNP equations in the direction $z$ perpendicular to the electrolyte cleft. This model reduction procedure leads to a modified PNP system to be solved in a 2D plane $x$–$y$ parallel to the substrate. Model (iii) is a further reduction of (ii) obtained by neglecting spatial dependence of ion concentrations in the electrolyte cleft. This leads to a time-dependent 2D Poisson equation for electric potential coupled with electrolyte cleft ion dynamics described by a system of ODEs as done in [12]. In all members of the hierarchy, iono-electric coupling between substrate and electrolyte is accounted for by "lumped" transmission conditions expressing continuity of dielectric and ionic fluxes across the interfaces. Electrodiffusive ionic coupling between cell(s) and electrolyte is described through a variety of transmembrane currents including the Goldman–Hodgkin–Katz (GHK) and Hodgkin–Huxley (HH) models [13,6].

The backward Euler method is adopted for temporal semi-discretization and a fixed-point iteration based on Gummel's map [14] is used to decouple system equations. Spatial discretization is performed using a generalization to axisymmetric cylindrical coordinates of the piecewise linear triangular finite element scheme stabilized via edge-based exponential fitting proposed and analyzed in [15].