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Computational modeling and simulation of complex systems in bio-electronics

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Abstract In this article, we discuss the mathematical and computational framework required to develop a general-purpose simulation tool for bio-electronic applications. Electrochemical and fluid-mechanical transport of substances, chemical reactions and electrical transduction of biological signals are described through the coupled use of systems of partial and ordinary differential equations (PDEs and ODEs). Functional iteration techniques for system decoupling and mixed-hybridized finite element discretization methods are proposed and validated in the simulation of realistic problems in Electrophysiology and Biochemistry.

Keywords Nanotechnology · Hybrid bio-artificial systems · Electrophysiology · Ionic-electrical coupling · Ionic channels · Mathematical modeling · Numerical simulation

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1 Introduction and motivation

The development of a general-purpose simulation tool for bio-electronic applications requires a mathematical model accounting for the electrical, fluid-mechanical and biochemical phenomena that simultaneously occur in complex bio-electronic systems like bio-chips or bio-reactors [4, 12, 14]. To this purpose:

- *electro-chemical and fluid-mechanical* transport of substances throughout the cellular environment can be described by the velocity-extended Poisson-Nernst-Planck/Navier-Stokes (PNP_{ext}/NS) coupled system of PDEs [8–10];
- *chemical reactions* in cellular metabolism can be treated by coupling the PNP/NS system with generation/reaction zero-order terms [5, 6];
- *electrical transduction* of biological-driven signals, operated by solid-state integrated circuits (as in bio-chips) or more classical measurement tools (as in patch-clamp techniques), can be handled by integrating the sole PNP system with systems of ODEs characterized by suitably computed lumped electrical equivalent parameters [6, 11].

In the following sections, we describe the coupled system of PDEs that constitutes the multi-physics mathematical model of the problem at hand, the appropriate functional iteration techniques for system decoupling and linearization, and the discretization methods for an accurate and stable numerical approximation. Simulation results of realistic test cases are included to validate models and computational tools.

2 The PNP$_{ext}$/NS model

The PNP$_{ext}$/NS coupled model reads:

$$\begin{cases} z_i \dfrac{\partial n_i}{\partial t} + \vartheta_i \operatorname{div} \boldsymbol{J}_i = z_i R_i \\ \lambda^2 \operatorname{div} \boldsymbol{E} = \displaystyle\sum_{i=1}^{M} z_i n_i + d \\ \boldsymbol{J}_i = \boldsymbol{J}_i^{DD} + \boldsymbol{J}_i^{adv} \\ \boldsymbol{J}_i^{DD} = z_i \ (\mu_i \boldsymbol{E} z_i n_i - \mu_i \nabla n_i) \\ \boldsymbol{J}_i^{adv} = \boxed{z_i \kappa_1 \boldsymbol{u} n_i} \\ \boldsymbol{E} = -\nabla \varphi, \end{cases} \tag{1}$$

$$\begin{cases} \operatorname{div} \boldsymbol{u} = 0 \\ \dfrac{\partial \boldsymbol{u}}{\partial t} + \operatorname{div}(\boldsymbol{u} \otimes \boldsymbol{u}) - \operatorname{div} \underline{\underline{\sigma}}(\boldsymbol{u}, \pi) = \boxed{\kappa_2 \displaystyle\sum_{i=1}^{M} z_i n_i \boldsymbol{E}} \\ \underline{\underline{\sigma}}(\boldsymbol{u}, \pi) = \dfrac{2}{\mathrm{Re}} \underline{\underline{\varepsilon}}(\boldsymbol{u}) - \pi \underline{\underline{\delta}} \\ \underline{\underline{\varepsilon}}(\boldsymbol{u}) = \dfrac{1}{2}(\nabla \boldsymbol{u} + (\nabla \boldsymbol{u})^T). \end{cases} \tag{2}$$

System (1) is the velocity-extended version of the system analyzed in [8], and is coupled with (2) through the boxed terms in $(1)_5$ and $(2)_2$, κ_1, κ_2 being positive parameters. The dependent variables in (1) are the concentration n_i of the i-th ionic species, $i = 1, \ldots, M$, z_i being the electronic affinity, and the electric potential φ. The dependent variables in (2) are the velocity $\boldsymbol{u}$ and pressure π of the electrolyte fluid. The quantities λ, θ_i are singular perturbation parameters, μ_i is the mobility of the i-th ionic species, $R_i = R_i(n_1, \ldots, n_M)$ are bio-chemical reaction rates, and d is a given function representing the distribution of a permanent ionic charge. Finally, $\boldsymbol{J}_i$, $\boldsymbol{E}$ and $\underline{\underline{\sigma}}$ are the current density associated with $z_i n_i$, the electric field and the electrolyte stress tensor, respectively, Re denoting the Reynolds number associated with the fluid part of the model. The coupled system (1)–(2) is to be solved in a given domain $\Omega \subset \mathbf{R}^m$, $m = 2, 3$, supplied with proper boundary and initial conditions (see [9, 10], for details).

3 A staggered algorithm

The staggered algorithm for the successive solution of the PNP$_{ext}$ and NS subsystems is depicted in Fig. 1. For each time level, a PNP$_{ext}$ system with a given velocity field $\boldsymbol{u}^{(k)}$ is solved using the Gummel Map typically employed in semiconductor device simulation [7]. This provides in output the updated densities $n_i^{(k+1)}$ and electric field $\boldsymbol{E}^{(k+1)}$. Then, the

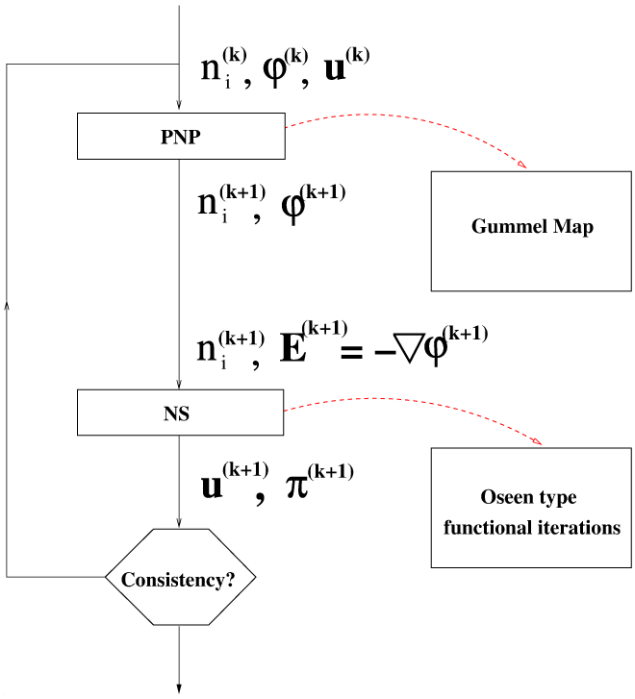

Fig. 1 Staggered algorithm for the solution of the PNP/NS system

NS system is solved using a fixed point iteration based on Oseen subproblems [13]. This provides in output the updated velocity $\boldsymbol{u}^{(k+1)}$ and pressure $\pi^{(k+1)}$. The process is repeated until self-consistency is achieved for the solution at the considered time level.

4 Finite element approximation

The required properties on the solution of both linearized PNP and NS subsystems are (i) same computational accuracy for scalar and vector/tensor-valued unknowns; (ii) local conservation and self-equilibrium; and (iii) nonnegativity of the scalar variable in the case where it has the physical meaning of a concentration. To satisfy these constraints, dual-mixed hybridized finite element formulations are adopted (see [2]). In the case of the continuity equations in the linearized PNP$_{ext}$ system, exponential fitting is included in the scheme to deal with the presence of highly dominating advective terms (see [1]). In the case of the momentum balance equation in the linearized NS system, a Discontinuous Galerkin upwind treatment is introduced for stabilization (see [3]).

5 Simulation examples

The first two examples deal with the numerical characterization of a voltage operated ionic channel (VOC) where K^+

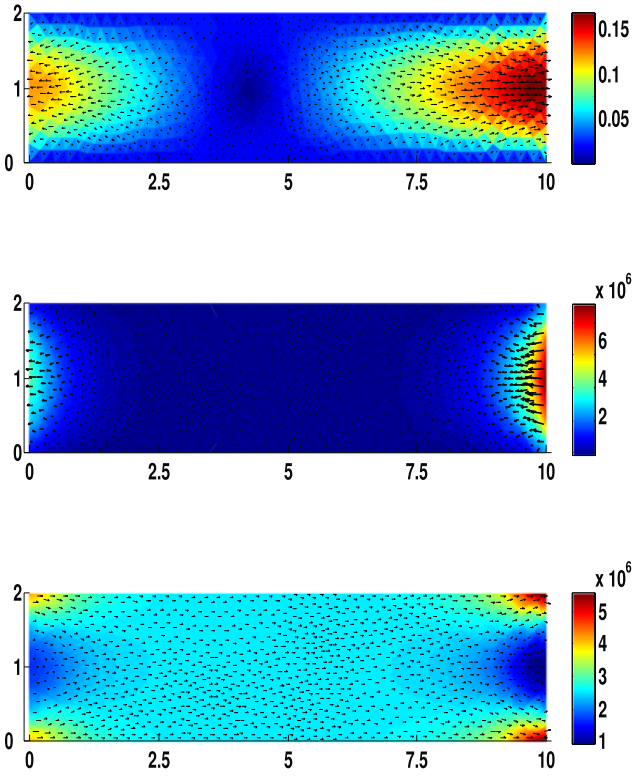

Fig. 2 Computed fluid velocity and current density fields. Spatial dimensions are in nm units

and Cl^- ions are flowing. The channel geometry is a rectangle of 2×10 nm size, and the unstructured finite element triangulation used in the computations has an average mesh size $h \simeq 0.25$ nm.

In the first set of simulations, the PNP$_{ext}$/NS system is solved in stationary conditions by enforcing a parabolic fluid velocity profile on the top and bottom of the channel to simulate the effect of a mechanical contraction of the membrane, and a bias of -50 mV across the channel. The approximate fluid velocity $\boldsymbol{u}_h$ (m s^{-1}) is depicted on top of Fig. 2, while the *total* approximate current densities $\boldsymbol{J}_h^{adv}$ and $\boldsymbol{J}_h^{DD}$ (A m^{-2}) are depicted in the middle and bottom of Fig. 2, respectively. The results indicate that the fluid contribution is relevant at the inlet/outlet sections of the channel, while current flow in the interior of the channel is mainly due to electrochemical phenomena.

Concerning the computational complexity, we mention that the simulation is run using `Matlab` 7 on a standard PC (AMD Athlon XP 2600, clock 2140 MHz and RAM of 512 MByte). The convergence history of the staggered iteration is reported in Table 1, where $\mathtt{it}_{PNP}^{(k)}$ and $\mathtt{it}_{NS}^{(k)}$ are the number of iterations required for the inner loops on the PNP$_{ext}$ and NS subsystems to reach convergence at each k-th iteration of the staggered loop,

Table 1 Convergence history of the staggered iteration

k	$\mathtt{it}_{PNP}^{(k)}$	$\mathtt{it}_{NS}^{(k)}$	$\mathtt{err}^{(k)}$
1	15	2	7.986×10^{-1}
2	13	2	4.124×10^{-2}
3	9	1	3.919×10^{-3}
4	4	1	5.637×10^{-4}
5	2	1	5.238×10^{-5}
6	1	1	8.332×10^{-6}

and

$$\mathtt{err}^{(k)} \equiv \max\Big\{ \big\| \boldsymbol{u}_h^{(k+1)} - \boldsymbol{u}_h^{(k)} \big\|_{(L^\infty(\Omega))^2}, \big\| \varphi_h^{(k+1)} - \varphi_h^{(k)} \big\|_{L^\infty(\Omega)}, \big\| \chi_{i,h}^{(k+1)} - \chi_{i,h}^{(k)} \big\|_{L^\infty(\Omega)} \Big\},$$

$\| \cdot \|_{L^\infty(\Omega)}$ denoting the norm in the function space $L^\infty(\Omega)$ and χ_i denoting the scaled electrochemical potential for the i-th species, having set the exit tolerance of the staggered iteration equal to 10^{-5}. The obtained results display a monotone reduction of the iteration error and clearly indicate that the convergence of the staggered algorithm is substantially limited by the electrochemical phenomena, this agreeing with the fact that, in the present case, the fluid-dynamical problem is moderately convection-driven. The very reduced elapsed time of the PNP$_{ext}$/NS simulation (order of minutes), compared with Molecular Dynamics computational techniques, makes it affordable to characterize with a reasonable accuracy also the transient performance of biological systems, as discussed below.

In the second set of simulations, the solution of the sole PNP model is compared to the reduced-order model provided by the Goldman-Hodgkin-Katz (GHK) relation [5, 6]. The two approaches are tested in the study of the channel current transient in a realistic voltage clamp experiment, including a series resistance R_e and a membrane capacitance C_m. Such experiment consists in the application of two successive voltage steps of 100 and 50 mV, starting from an initial applied bias of -100 mV. The results are shown in Fig. 3, having set $R_e = 1$ MΩ and $C_m = 0.1$ pF, with the dashed and solid lines corresponding to the GHK and PNP models, respectively. The small absolute value of the current indicates that the transient is determined by the time constant $\tau = R_e C_m$. This conclusion would be quite different if a (more realistic) multi-channel simulation were performed, as documented in [11]. We also notice that the computed steady-state currents are in good agreement in the case of negative bias, while they exhibit a spread of the order of 30 percent if a positive bias is applied, this latter result being probably ascribed to the more markedly nonlinear behaviour of the electric potential computed by the PNP simulation.

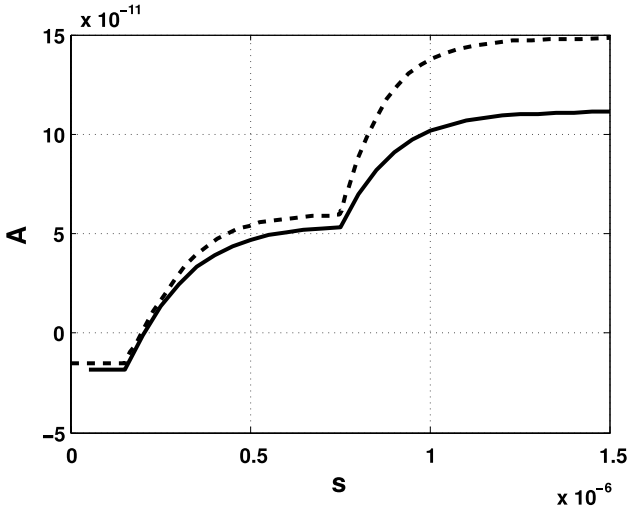

Fig. 3 Current transient in a K^+–Cl^- VOC

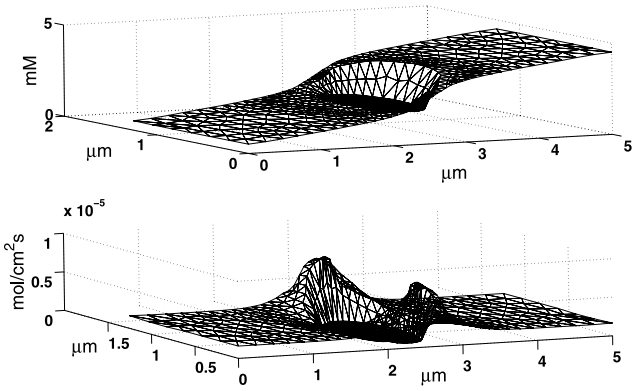

Fig. 4 Diffusion and osmosis of glucose throughout a membrane

The concluding example deals with the study of nonlinear diffusion and osmosis of glucose throughout a membrane located at the center of a rectangular biological environment. The general PNP/NS system is solved in a reduced form which accounts for the sole diffusion of glucose and rate-saturated chemical reactions to describe glucose consumption into the cell [6]. Figure 4 shows the computed glucose concentration (top) and current density modulus (bottom). Notice the presence of a finite jump of the concentration across the membrane and of a strong variation of current density modulus due to membrane resistance to the flow.

6 Conclusions

Multi-physics and multiscale models and advanced computational techniques were discussed for the simulation of complex bio-electric systems. Numerical examples on realistic data were included to validate the proposed methodologies. Future research activities will be devoted to:

- devising a mathematical model of the cellular membrane accounting for its dielectric and mechanical properties;
- investigating the impact of a moving electrolyte on electrophysiological measurements through a full PNP/NS simulation;
- investigating appropriate models for membrane permeability to account for the gating mechanisms that govern aperture and closure of VOCs ionic channels [5].

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