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# Three-dimensional simulation of biological ion channels under mechanical, thermal and fluid forces

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ABSTRACT

In this article we address the three-dimensional modeling and simulation of biological ion channels using a continuum-based approach. Our multi-physics formulation self-consistently combines, to the best of our knowledge for the first time, ion electrodiffusion, channel fluid motion, thermal self-heating and mechanical deformation. The resulting system of nonlinearly coupled partial differential equations in conservation form is discretized using the Galerkin Finite Element Method. The validation of the proposed computational model is carried out with the simulation of two ion nanochannels. The first is a voltage operated channel with $K^+$ and $Na^+$ ions, and the second is the sodium-potassium pump in which also chlorine ($Cl^-$) and bicarbonate ($HCO_3^-$) ions are considered. In the first case study, we investigate the coupling between electrochemical and fluid-dynamical effects. Then, we enrich the modeling picture by investigating the influence of a thermal gradient. Finally, we add a mechanical stress responsible for channel deformation and investigate its effect on the functional response of the channel. Results show that fluid and thermal fields have no influence in absence of mechanical deformation whereas ion distributions and channel functional response are significantly modified if mechanical stress is included in the model. These predictions agree with biophysical conjectures on the importance of protein conformation in the modulation of channel electrochemical properties. In the second case study, we exploit our multiphysical mathematical formulation to investigate the effect of permanent surface charge on the function of the sodium-potassium pump. In particular, we consider the biophysical application in which the pump actively participates to the process of aqueous humor production across the transepithelial membrane in the ciliary body of the eye. In this study we are motivated by the fact that several data are available to verify the accuracy of model predictions and that the role of surface charge has not yet been mathematically analyzed in the specific context at hand. Results show that the model is able to predict in a very accurate manner the correct aqueous humor flow direction, the magnitude of aqueous velocity and the experimentally measured transepithelial membrane potential only if the (negative) surface permanent charge is larger than a limiting value, whereas if the charge is below this value, fluid inversion occurs.



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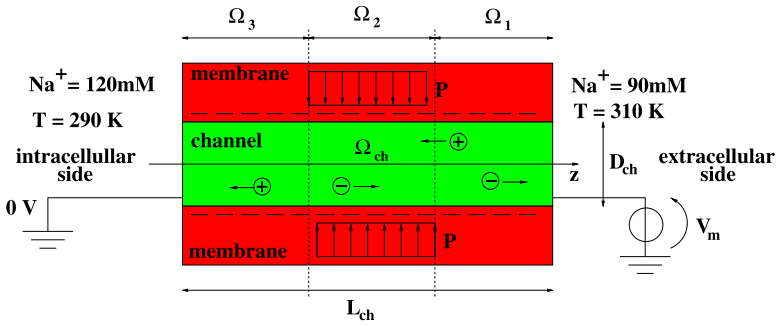


**Fig. 1.** Two-dimensional cross-sectional scheme of the general physical problem. The computational domain of interest in the present article is, in the general case, the union of three subdomains, the parallelepipeds $\Omega_1$, $\Omega_2$ and $\Omega_3$, in which the ionic channel, the parallelepiped $\Omega_{ch}$, is embedded. The red regions are the lipid membrane bilayer whereas the green region is the transmembrane channel. The solid black dashed lines at the interface between membrane and channel represent negatively charged fixed ions localized along the channel wall. $P$ denotes a mechanical pressure that may deform a portion of the channel surface whereas $V_m$ is an external voltage source. The intracellular side is set at ground potential. Thermal and chemical external gradients are also applied to the system as a result of the different values of ion concentration and temperature in the intracellular and extracellular sides.

## 1. Introduction and motivation

Ion channels connect the intracellular environment and the surrounding biological medium, allowing the dynamical exchange of the chemical species that supervise the functions of every cell in the human body. Ion channels control electrical signal transmission among excitable cells, notably, muscle cells and/or neurons, and because of their fundamental role they have been subject to biophysical and mathematical investigation for a long time.

The most commonly used approach to ion channel modeling is based on the representation of the cell membrane lipid bilayer as an equivalent electrical circuit including capacitive and conductive elements, these latter being in general described by a nonlinear current-voltage characteristic. The resulting formulation is constituted by a nonlinear system of ordinary differential equations (ODEs) whose best known example is the Hodgkin–Huxley (HH) model [1,2]. We refer to [3,4] for a detailed treatment of ODE-based differential models and their application to relevant problems in Computational Biology.

ODE differential models are widely used because of their limited computational cost and ease of implementation. However, their biophysical accuracy is limited and often allows to characterize only basic properties of the cellular system under investigation, such as the homeostatic Nernst potential [5], and/or to reproduce simple experiments in Electrophysiology, such as the transmembrane current in voltage clamp conditions [6,7].

To analyze the fundamental mechanisms that govern ion transport across a membrane channel, a higher model complexity is required. With this aim, a system of partial differential equations (PDEs) expressing the balance of mass and of linear momentum for each ion species can be adopted to describe the dynamical balance of electro-diffusion forces acting on chemicals flowing across the cell membrane bilayer. The resulting formulation is represented by the Poisson–Nernst–Planck (PNP) model for ion electro-diffusion. We refer to [8–11], for a detailed illustration of the PNP differential system and a discussion of its mathematical and numerical properties.

In the present work we address the three-dimensional (3D) study of a generalized version of the PNP model, modified by including the effect of electrolyte fluid convective transport, a thermal gradient and mechanical forces. The extension of the PNP system accounting for fluid velocity is well-known as the *velocity-extended* PNP model and has been the object of extensive mathematical and numerical investigation in [12–16]. In these pages we adopt a wider vision of ion transport as schematically depicted in Fig. 1 where the region in which simulations are conducted is an open bounded domain composed by several subregions, representing the bio-physical system that includes the ions in motion through a physiological fluid under the action of several externally applied forces: electrical, thermal, chemical and mechanical. Each of these external forces contributes to determining ion flow in the medium according to the effect of the following vector fields:

1. Electric field;
2. Concentration gradient;
3. Thermal gradient;
4. Electrolyte fluid.

The inclusion of thermal and mechanical forces makes the mathematical formulation proposed and investigated in the present article a significant extension of the model studied in [17]. In typical applications of Electrophysiology and Cellular Biology the electric field may be the result of the application to the cell of an external voltage drop such as in a patch clamp experiment [18–20], and/or the presence of fixed charged ions embedded in the portion of lipid bilayer surrounding a transmembrane channel [5,21]. The ion concentration gradient may be the result of the administration of a substance such as a drug or a toxin [22–25], whereas the thermal gradient may be the result of the activation of heat-sensitive thermo-transient receptor potential (thermo-TRP) cation channels exposed to capsaicin, a natural ingredient of spicy foods such as red hot chili peppers and of cold-sensitive TRP channels exposed to menthol [26,27]. Ion motion can also be