Effects of Exogenous Electromagnetic Fields on a Simplified Ion Channel Model

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Abstract In this paper, we calculate the effect of an exogenous perturbation (an electromagnetic field [EMF] oscillating in the range of microwave frequencies in the range of 1 GHz) on the flux of two ion species through a cylindrical ion channel, implementing a continuous model, the Poisson–Smoluchowski system of equations, to study the dynamics of charged particle density inside the channel. The method was validated through comparison with Brownian dynamics simulations, supposed to be more accurate but computationally more demanding, obtaining a very good agreement. No EMF effects were observed for low field intensities below the level for thermal effects, as the highly viscous regime and the simplicity of the channel do not exhibit resonance phenomena. For high intensities of the external field ($>10^5$ V/m), we observed slightly different behavior of ion concentration oscillations and ion currents as a function of EMF orientation with respect to the channel axis.

Keywords Ion channel modeling · Electromagnetic field effects · Poisson–Smoluchowski equations · I – V curves

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1 Introduction

The existence of nonthermal mechanisms of interaction between electromagnetic fields (EMF) and biological systems represents an open and controversial question. It is generally accepted that a possible biological target for EMF interaction might be the cell membrane, in particular the ion channels, either through an influence on the channel dynamics (e.g., altering the opening probability) or directly on ion fluxes through the channels [1–3]. The characterization of ion fluxes inside membrane pores and channel proteins is a true challenge by itself, e.g., explaining properties like the selectivity to different ion species [4, 7]. Some attempts have been made to characterize the ion currents inside channels in case of equilibrium situations [9, 10, 13], but to study the EMF effects, an approach is required that allows treatment of time-dependent perturbations (see [11] for a different approach to this topic). For this purpose, we implemented a system of equations that describes ion diffusion in the continuous and high-friction limit—the so-called Smoluchowski equation [12]—together with a characterization of the electric forces generated by the partial charges on the channel surface and the moving ions themselves, described by the Poisson equation. Hereon, we refer to this model as the Poisson–Smoluchowski (PS) model. Despite the fact that we do not expect from our model a detailed description of interactions at the single-ion level (like ion selectivity as shown in [13]), we obtained sufficiently good agreement with more refined models in terms of voltage–current dependency and ion concentration inside the pore. Moreover, even if our model was too simple to elicit resonance phenomena, it allowed the observation of different responses to EMF with different orientations with respect to the ion channel main axis. This result could be, in principle, useful in the design of experiments aiming at studying the effects of EMF in real cells (e.g., by means of patch clamp technique for the recording of cellular electrical activity), even if such effects are probably too weak to be detected.

2 The Model

2.1 The PS Model

We implemented a continuum approximation of ion density distribution in a high friction regime, as in [7, 9], taking into account the critical remarks that have been made about these models (see for example [10]). We consider a very simple model of ion channel, similar to a gramicidin pore, and only a plane section of the channel is simulated, due to the almost cylindrical symmetry of the ion channels we are interested in. The PS system of equations is less computationally demanding than Brownian dynamics (BD), but it shows very good agreement with the results coming from such Models by considering appropriate boundary conditions on the channel walls and introducing a term—the *Born energy*—to take into account the effective force inside the channel due to a different value in the dielectric constant outside and inside the channel. The PS model allows simulations for time intervals of the order of tens of nanoseconds, allowing the study of EMF perturbations in the range of gigahertz for several periods of oscillation.

Considering an ion channel/pore and N different ion species with charge $q_i = ez_i$, the evolution of ion densities can be written as follows:

$$\frac{\partial c_i(\vec{x}, t)}{\partial t} = D[-\beta \vec{\nabla} \cdot \vec{F}_i + \nabla^2]c_i(\vec{x}, t) \quad (1)$$

where $c_i(\vec{x}, t)$ is the i -th ion concentration, $\beta = 1/KT$, $D = 1/\beta m \gamma$ is the diffusion constant, γ the friction coefficient, and m the ion mass. $\vec{F}_i$ is the force acting on the i -th ion concentration, resulting from several terms: (1) electrostatic interactions F_{EL} , (2) dielectric barrier F_B , (3) transmembrane potential V , (4) repulsive forces in the channel walls (boundary conditions). Throughout the paper, we consider two monovalent ions: Na^+ and Cl^- . The charge density that produces the electric potential ϕ ($\vec{F}_{EL}(i) = -q_i \vec{\nabla} \phi$) comes from two terms: the fixed charge density found on the channel walls ρ_f and the mobile ion densities $\rho_m = \sum_{i=1}^N q_i c_i$. The resulting Poisson equation for ϕ is:

$$\nabla \cdot (\epsilon \nabla \phi(\vec{x}, t)) = -[\rho_f(\vec{x}) + \rho_m(\vec{x}, t)]; \quad (2)$$

where ϵ is the dielectric constant. The membrane potential V produces a uniform electric field, directed along the channel axis (see Fig. 1). The simultaneous implementation of (1) and (2) for the considered ion species constitutes the PS system of equations.

To solve the PS equations, we discretized the system onto a $210 \cdot 210$ lattice grid with $\Delta = 0.5 \text{ \AA}$. The time interval was fixed at $\Delta_t = 20$ ps, to satisfy the stability constraints imposed on the equations due to numerical diffusion (see [Appendix](#) for details of the numerical implementation).

Fig. 1 The simplified ion channel/pore; 1 unit = 1 $\text{\AA}$. *White regions*: upper and lower ion reservoirs. *Light gray region*: inner channel. *Dark gray regions*: protein walls. Throughout the simulations, ion density is sampled at the points labeled from 1 to 10. The *four large dots* on the channel walls represent the position of the partial charges

2.2 Boundary Conditions

We consider two ion reservoirs outside the channel, kept at constant values in time, in which the relative dielectric constant is the same as for water ($\epsilon_w \simeq 80$). As in real ion channels, the ions cannot pass through the channel walls; we introduced a repulsive potential on the walls of our channel model. It should be ideally infinite, but due to the stability constraints imposed by the equation-solving method, it was set equal to $1.1 \cdot 10^{-20}$ J. A tunneling effect is thus present, but this phenomenon is not presumed to alter significantly our results, as only a small fraction of ion concentration is found outside the channel walls (around 10% of the concentration found inside the channel, see Fig. 2), and the ion reservoirs replace the lost ion density throughout the simulations.

2.3 Dielectric Barrier—Born Energy

Recently, the importance of the dielectric barrier has been stressed when considering ions that enter a protein channel or pore. The value of the dielectric constant inside channels (as well as the friction coefficient) is an open question in the study of ion channels. There is no direct experimental information on this value, but recent molecular dynamics simulations suggest that, in channels with small radii, like the potassium channel [5], it could be much lower than in the bulk. This is justified by the fact that almost no water molecules should be found inside the channel and, also, the entering ions must lose part of their hydration shell [4]. This introduces, for each ion species, an energy barrier between the channel and the outside medium, the Born energy ΔG_i :

$$\Delta G_i = \frac{q_i^2 N_A}{8\pi r \epsilon_0} \left(\frac{1}{\epsilon_c} - \frac{1}{\epsilon_w} \right) \quad (3)$$

Fig. 2 Charge (Na^+) concentration in a section transverse to the channel axis. Dashed lines indicate the position of the channel walls

Fig. 3 Energy profile inside the ion channel. *Solid line* shows transmembrane potential. *Dotted line* shows transmembrane potential plus dielectric barrier. *Dashed line* shows energy profile with transmembrane potential, dielectric barrier, and electric potential due to the fixed charges on the channel walls

where q_i is the ion's charge, r its radius, ϵ_c the dielectric constant inside the channel, ϵ_w the dielectric constant of water solution, and N_A is Avogadro's number. We implemented a smooth version of (3) with the term:

$$E_{\text{born}} = \left(\Delta G - \alpha \cdot (y - y_0)^2 \right) \cdot e^{-|y - y_0|/\lambda} \quad (4)$$

where α is a tuning parameter that allows the barrier to become zero outside the channel, λ controls the smoothing term, $y - y_0$ is the position along the channel axis with respect to its center. For the considered ions, the Born energy (Fig. 3) was assumed to be 10^{-21} J (see [10]), and this adds a force acting on the charges $\vec{F}_B(i) = -\vec{\nabla}(\Delta G_i)$. This value was chosen to be smaller than boundary repulsive forces along the channel walls (by a factor of 10) but to be able to reproduce the main conductance properties of the channel as obtained with other simulation methods (see Section 2.5).

2.4 Selectivity

Ion channels usually display excess charges in the protein walls that help permeation of some types of ions while discouraging the counterions from entering the channel (see [7] for a recent review). We considered the case of a cation-selective channel by placing negative charges in the walls near the channel ends (Fig. 1). Four partial charges with a value of $q_p = -0.09e$ (e is the positive elementary electric charge) are located near the channel entrances. The effect of these charges on the potential profile of a Na^+ ion is to cancel the barrier due to Born energy in a bare channel. For negative ions Cl^- , the opposite happens, and the barrier is roughly doubled (Fig. 3).

2.5 PS Model Validation

The results obtained with the PS model of a simplified channel were compared with the results from other models known in the literature. We compared, at the

equilibrium, the ion density distributions and the values of the currents passing through the channel as a function of membrane voltage (referred as I – V curves) obtained with different models: Poisson–Nernst–Planck (PNP) [9], BD [10], and PS. BD results should be taken as the most accurate, especially regarding properties such as channel selectivity to different ion species. Given the ion density distribution along the channel for each ion species, the corresponding ion flux $\vec{J}$ can be calculated, for a given transmembrane potential, by means of the Nernst–Planck equation [6]:

$$\vec{J} = \vec{J}_{\text{drift}} + \vec{J}_{\text{diff}} = -\mu z c \vec{\nabla} V - D \vec{\nabla} c. \quad (5)$$

In our case, the ion flux is directed along the channel axis: $J = J_y$ (see Fig. 1). The I – V can thus be obtained for specified values of V : $i(V) = S \cdot J_y(V)$, where S is the section of the channel.

PS simulations were performed by considering $\Delta t = 8 \cdot 10^{-13} \text{ s}$, taking into account the stability conditions of the system. We considered a cylindrical channel with radius $r = 4 \text{ \AA}$, fixed charges on its walls as previously described, ion concentrations equal to 0.3 M both in the intracellular and extracellular reservoirs, and a transmembrane

Fig. 4 Cationic (*top*) and anionic (*bottom*) concentration profiles along the channel, in the presence of fixed charges on the channel walls. *Bars* show BD (adapted from [7]), *arrows* show PNP (adapted from [7]), *dotted line* shows PS

Fig. 5 I – V curve plots for both ion species. Dots show PS, squares show BD (adapted from [10]), triangles show PNP (adapted from [10])

potential set to 105 mV, as in [10]. The system approaches a steady state (equilibrium) after 50,000 iterations, corresponding to a transient time $t = 4 \cdot 10^{-8}$ s. Ion density distributions inside the channel are shown in Fig. 4. Our results appear in good agreement with BD results, even if we are considering only a bidimensional section of the channel. Comparing our results to those of PNP [9], the role of the dielectric barrier appears crucial to obtain a low anionic concentration inside the channel. Selectivity is found also in the I – V curves: For PS and BD, the negative ion current is almost negligible for each considered transmembrane potential, as shown in Fig. 5.

3 Introduction of an External Time-Dependent EM Field

Our main goal is to simulate the effect of an external EMF on a ion channel embedded in a cell membrane, so we modify the parameters used for validation (ion concentrations outside the channel and transmembrane potential) introducing more biologically plausible ones. Starting from the Langevin equations for the motion of

a single ion under the influence of a time-dependent EMF, we obtain the following Smoluchowski equation:

$$\begin{aligned} \frac{\partial c_i}{\partial t} = & \frac{\partial [-C_1(F_x + eE_x) + C_2(F_y + eE_y)]c_i}{\partial x} + \\ & - \frac{\partial [C_1(F_y + eE_y) + C_2(F_x + eE_x)]c_i}{\partial y} + \\ & + KT(C_1 - C_2)\frac{\partial^2 c_i}{\partial x^2} + KT(C_1 + C_2)\frac{\partial^2 c_i}{\partial y^2} \end{aligned}$$

where $\vec{F} = \vec{F}(x, y)$ as in Section 2, $\vec{E} = \vec{E}(x, y, t)$ is the external electric field, $\vec{B} = \vec{B}(x, y, t)$ is the external magnetic field (always directed along the z axis), $C_1 = m\gamma / [(m\gamma)^2 + (eB_z)^2]$, and $C_2 = eB_z / [(m\gamma)^2 + (eB_z)^2]$. We remark that $|eB| \ll m\gamma$, as $|eB| = 5.33 \cdot 10^{-26}$ kg/s, and $m\gamma = 4.32 \cdot 10^{-13}$ kg/s. The magnetic field can thus be neglected in the calculations. Ion concentrations in the reservoirs were kept at 0.5 M (intracellular) and 0.1 M (extracellular), and transmembrane potential was set to 150 mV, corresponding to a constant electrostatic field of 10^7 V/m. Several simulations were performed with six different values of the EMF, oscillating with a frequency of 1 GHz: Starting from a value of 100 V/m, it was eventually increased 10, 100, 1,000, 5,000 and 10,000 times. Two groups of simulations were performed, with the same parameters as above. In the first case, the electric component of the EMF

Fig. 6 Time evolution of ion density as a function of EMF of different intensity directed along the channel axis

was directed along the channel axis; in the second case, it was set perpendicular to the channel axis.

Starting from the equilibrium state, obtained for the same transmembrane potential and ion concentrations in the reservoirs, we observed the changes in ion densities due to the switching on of the external EMF, up to its successive switching off. The value of ion density was sampled at each time interval in ten different points placed in the middle of the channel and close to its walls, as shown in Fig. 1, to check how the interaction of ion density with the channel walls could change the effect of the EMF perturbation. The total density distribution inside the channel was sampled at different iteration values.

As can be seen in Fig. 6, the ion concentration oscillations are negligible for field values smaller than 1,000 V/m, and thus no phenomena are observed that could be related to the so-called nonthermal effects of EMF in biological materials. The oscillations follow the EMF waveform with no sign of distortion and decay immediately after the EMF is switched off, showing that the EMF superimposes linearly to the random motion of the ions due to thermal noise. This was expected, as in our model, there are no sources of nonlinearity in the interaction, for example voltage-dependent conductance, as observed in some real channels. We also remark that, as we are considering a continuous ion density distribution, a more complex channel structure would not produce relevant effects; that instead can be necessary to explain some features of ion selectivity and channel blocking due to different ion species [7].

In the case of the electric field directed perpendicularly to the channel axis, some differences could be observed in the current amplitude I versus field intensity E . The current decreased linearly as a function of E for both ion species, while it remained

Fig. 7 Plot of the ionic currents inside the pore as a function of external electric field E . Circles shows $E = E_y$ (along the pore axis), diamonds shows $E = E_x$ (perpendicular to the pore axis)

unchanged when the electric field was directed along the channel axis (see Fig. 7). In the case of $E = 10^6$ V/m, the current decrease is on the order of 1% (from $2.078 \cdot 10^{-11}$ to $2.057 \cdot 10^{-11}$ A).

4 Conclusion

We implemented a system of equations, the PS equations, that allowed us to study the dynamics of the concentration of different ion species inside a channel protein subjected to time-dependent perturbations. The implementation of the PS model on an idealized ion channel, similar to a gramicidin pore, was in good agreement with simulations performed with BD, considered very reliable, in terms of ion density distribution inside the channel and the relative I - V curves. We studied the effect of an exogenous EMF, in the range of radiofrequencies, applied to the ion channel. No effects of signal amplification (like parametric or stochastic resonance) were observed in these simulations that could justify the presence of nonthermal effects, and this can be explained by high friction regime and by the absence of sources of nonlinearity in our channel model (e.g., the absence of a gating mechanism and the complete stiffness of the channel walls). Moreover, we are aware of the possibility that some mechanism of interaction of weak EMF with a small number of ions and water molecules in a limited space could be missed by a continuum model like ours, but a very fine tuning of parameters (like dielectric constant inside a channel) must be supplied to produce realistic simulations in such a particular situation (see, for example, [14] for questions related to ion motion in a quasi-ballistic regime). We were able nonetheless to observe some differences in the response to external EMF as a function of its orientation with respect to the channel axis. Such differences were more marked at increasing field intensities, thus far above the thermal energy threshold: for the maximum EMF applied, the difference in ion current was on the order of 1%, for both ion species considered in the simulation. This result could be, in principle, useful for the lineup of electrophysiological experiments (e.g., by the patch clamp recording technique) aiming at studying the effect of EMF inside real ion channels or in artificial membranes with embedded pores or channels, even if it appears as a very weak effect and could be masked by measurement noise.

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Appendix

The Smoluchowski operator in two dimensions for the ion concentration c is (we omit the index for notation simplicity):

$$\frac{\partial c(x, y, t)}{\partial t} = \frac{1}{m\gamma} [-\nabla F(x, y) + \kappa T \nabla^2] c(x, y, t). \quad (6)$$

It can be divided into two parts: a diffusion operator U_1 :

$$\frac{\partial c(x, y, t)}{\partial t} = D \nabla^2 c(x, y, t). \quad (7)$$

where D is the diffusion constant as derived by Einstein (η = viscosity, a = radius of the particles): $D = KT/m\gamma = KT/(6\pi\eta a)$, and a drift operator U_2 :

$$\frac{\partial c(x, y, t)}{\partial t} = -\frac{1}{m\gamma} \nabla(F(x, y)c(x, y, t)). \quad (8)$$

To be numerically implemented, Smoluchowski equation is discretized in time and space: $x_j = x_0 + j\Delta_x$, $y_l = y_0 + l\Delta_y$, and $t_n = t_0 + n\Delta_t$, with j , l , and n integers. We define c_{jl}^n for $c(x_j, y_l, t_n)$.

U_1 has been implemented with a mixed implicit–explicit method, the Crank–Nicholson method [13], that, in two dimensions, reads:

$$c_{jl}^{n+1} = c_{jl}^n + \frac{D\Delta_t}{2\Delta^2} \left(\delta_x^2 c_{jl}^{n+1} + \delta_x^2 c_{jl}^n + \delta_y^2 c_{jl}^{n+1} + \delta_y^2 c_{jl}^n \right) \quad (9)$$

with $\Delta \equiv \Delta_x = \Delta_y$, $\delta_x^2 c_{jl}^n = c_{j+1,l}^n - 2c_{jl}^n + c_{j-1,l}^n$, and $\delta_y^2 c_{jl}^n = c_{j,l+1}^n - 2c_{jl}^n + c_{j,l-1}^n$, and in which c_{jl}^{n+1} are the unknowns. This system can be solved by the alternating-direction implicit method [8], for which the sparse system (9) is split into two linear tridiagonal systems. The stability of the solution for this system was estimated following von Neumann stability analysis [8]. The solutions, supposed stationary or slowly varying, are expanded over the eigenmodes of the solutions of the system: $c_j^n = \xi^n e^{ikj\Delta_x}$, and the stability criterion is $|\xi(\kappa)| \leq 1$ for each κ . It can be shown that the Crank–Nicholson method is always stable for every chosen Δ_t .

The U_2 term is a flux-conservative equation:

$$\frac{\partial c(x, y, t)}{\partial t} = -v \nabla g(x, y, t), \quad (10)$$

where $v = 1/(m\gamma)$ and $g(x, y, t) = F(x, y)c(x, y, t)$. Its solution is implemented with the Relaxation Method [8], with c_{jl}^n replaced by an average over its first spatial neighbours. After discretization ($g_{lj}^n = F_{lj}c_{lj}^n$) we obtain:

$$c_{j,l}^{n+1} = \frac{1}{4} [c_{j+1,l}^n + c_{j-1,l}^n + c_{j,l+1}^n + c_{j,l-1}^n] + \frac{v\Delta_t}{2\Delta} [g_{x,j+1,l}^n - g_{x,j-1,l}^n] - \frac{v\Delta_t}{2\Delta} [g_{y,j,l+1}^n - g_{y,j,l-1}^n]. \quad (11)$$

In this case the stability conditions are:

$$\frac{|v|\sqrt{2}\sqrt{F_x^2 + F_y^2}\Delta_t}{\Delta} \leq 1. \quad (12)$$

The relaxation method introduces an additional diffusive term to (10), called numerical diffusion. If we want its contribution to be negligible, an additional constraint is introduced:

$$|v|\Delta_t \gg \frac{(\Delta_x)}{2} \frac{|\nabla^2 c|}{|\nabla c|}. \quad (13)$$

The Poisson equation in two dimensions reads:

$$\frac{\partial^2 \phi(x, y)}{\partial x^2} + \frac{\partial^2 \phi(x, y)}{\partial y^2} = -\rho(x, y), \quad (14)$$

or, in operator form, $\mathcal{L}\phi = \rho$. $\rho(x, y)$ is the charge density in space, and $\phi(x, y)$ the electric potential. Its solution can be seen as the equilibrium solution of a diffusion equation of the form:

$$\frac{\partial \phi}{\partial t} = \mathcal{L}\phi - \rho \quad (15)$$

and can be solved by the Gauss–Seidel method [8], for which

$$c_{jl}^{n+1} = c_{jl}^n + \frac{\Delta_t}{\Delta^2} (c_{j+1l}^n + c_{j-1l}^{n+1} + c_{jl+1}^n + c_{jl-1}^{n+1}) - \frac{\Delta^2}{4} \rho_{jl}. \quad (16)$$

The stability condition is $\Delta_t/\Delta \leq 1/4$. Considering $\Delta_t = \Delta^2/4$, we get

$$c_{jl}^{n+1} = \frac{1}{4} (c_{j+1l}^n + c_{j-1l}^{n+1} + c_{jl+1}^n + c_{jl-1}^{n+1}) - \frac{\Delta^2}{4} \rho_{jl}. \quad (17)$$

The Gauss–Seidel Method can be made to converge faster: it is the Successive Over-Relaxation Method (SOR [8]), that we used for the implementation of our model.

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