Stochastic Modelling and Simulation of Ion Transport through Channels

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Abstract
Ion channels are of major interest and form an area of intensive research in the fields of biophysics and medicine, since they control many vital physiological functions. The aim of this work is to propose a fully stochastic model describing the main characteristics of a multiple channel system, in which ion movement is coupled with a Poisson–Nernst–Planck equation. Exclusion forces are considered and different nondimensionalization procedure, supported by numerical simulation, are discussed. Both cases of nano and micro channels are considered.

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I. INTRODUCTION

Ion channels are of major interest and form an area of intensive research in the fields of biophysics and medicine, since they control many vital physiological functions. Since certain aspects of ion channel structure and function are hard or impossible to address in experimental investigations, mathematical models form an useful completion and alternative to these studies.

Ion channels are membrane proteins that catalyze the transfer of ions down their electrochemical gradients across the plasma membrane [25]. They cannot perform thermodynamic work, that is they are not able to move an ion against its electrochemical gradient; as a consequence, the direction of ions travelling through an open channel is solely dependent on the electrochemical gradient. Another characteristic of ion channels is that the rate at which ions move through these proteins is very high; the throughput of an ion channel can be fast up to 100 million ions per second [25]. On a fundamental level, the activity of ion channels can change the membrane potential of the cell or alter the concentrations of ions inside the cell. These processes are basic to the cell physiology; therefore, it is easily imagined that ion channels may be involved, directly or indirectly, in virtually all cellular activities. While the role of some ion channels is known, as for example for calcium or sodium channels, in other cases the physiological role of an ion channel is unknown, and sometimes it is discovered when a disease arises.

The mechanism of ion channels is based on some basic ingredients [25]. We may summarize them as follows.

a. The electrochemical gradient: it determines the direction along which ions will flow through an open ion channel and is a combination of two types of gradients: a concentration gradient and an electrical field gradient. The electrical field gradient takes into account the charge on the ion. The relationship between the electrical potential and the magnitude of the concentration gradient that is created is intuitive: the stronger the electrical potential, the greater the concentration gradient.

b. The current-voltage relationship: current is the movement of charges, and in cells the flow of ions through ion channels can be measured.

c. The anatomy of a typical ion channel: the ion channels are proteins with a hole in their middle [12, 13].

d. The ion selectivity: the capacity of membrane to be permeable to a class of ions. The mechanism by which ion channels pick and choose certain ions is still not fully understood.

e. The ion gating: the opening and closing mechanism of ion channels.

In the present work we do not consider the last two last two mechanism: channels are open and ions may pass through them.

Brownian dynamics represents an attractive computational approach for simulating the permeation process through ion channels over long time-scales without having to treat a system in all atomic details explicitly. The approach consists in the generation of random trajectories of ions as a function of time, by numerically integrating stochastic equations for the motion using some effective potential function to calculate the microscopic forces operating among them [16]. While various approaches for microscopic modelling, either based on equations for the motion with forces accounting for finite sizes [10, 11, 19, 20] or on exclusion processes, have been investigated in detail, there are still open problems in the transition to macroscopic models based on partial differential equations. Some recent literature involves
some heuristic derivations of macroscopic dynamics, \[3, 22\]. Often away from equilibrium standard equations with linear terms are used, whose appropriateness remains unclear. In order to model some exclusion principle, in \[3\] the following modified Poisson–Nernst–Planck equations have been obtained via a heuristic derivation from an exclusion discrete process

\[-\epsilon \Delta V = e \left( \sum_j z_j c_j + f \right)\]

\[\frac{\partial}{\partial t} c_i = \nabla \cdot \left( D_i (1 - \rho) \nabla c_i + c_i \nabla \rho + e z_i \mu_i c_i (1 - \rho) \nabla V \right)\]

where \(c_i\) is the concentration, \(z_i\) is the charge, and \(\mu_i\) the mobility of the ions of type \(i\); \(\rho = \sum_i c_i\) is the total concentration, \(V\) the electrical potential, \(\epsilon\) the permittivity, and \(e\) the elementary charge. In such a way the authors introduce a size exclusion effect. Anyway, the derivation of the continuum model is not completely rigorous, so there still is a lot of work that needs to be done in such a direction.

As mentioned in \([21, 22]\) while macroscopic conservation laws clearly govern the macroscopic behavior of ensembles of channels, their application to a single protein channel able to contain at most one or two ions is questionable. The aim of the present work is first of all to consider a fully stochastic model able to describe the main characteristics of a multiple channel system, in which ion movement in the bath and throughout channels is described via a system of stochastic differential equations, coupled with a Poisson-Nernst-Planck equation, which becomes itself stochastic due to the dependence upon the ion random positions. Exclusion forces are considered and modelled via potential kernels as Pauling and Lennard-Jones potentials. This latter potential is also used in order to model boundary condition in the channels, in particular the reflection of ions at the channel boundary. One of the main problems is to link such completely stochastic model with an average continuum model described by partial differential equations, so widespread in literature \([2, 3, 8, 18, 21, 22]\). It is well known that it is reasonable to consider a continuous model when laws of large numbers may be applied \([4, 5]\), i.e. when the number of ions increases to infinity or the population is large enough that an approximation may be applied. It is clear that this is always the case in the bath, but not always true in the channels. Indeed, as already mentioned, in the case of nano channels the dimension of ions is of the same order that the one of the channel, so that in a channel the description of the system has to remain discrete and stochastic. As a consequence, in the limit of infinite (sufficiently large) number of ions, a problem of coupling their dynamics outside (averaged continuum) and inside (discrete stochastic) channels arises. We may refer to such a model as an hybrid model. The present work means to be a first step in this direction; via a simulation analysis we build up a good discrete stochastic model and understand the role of each parameter. Next step will be to consider a derivation of a model, deterministic or hybrid in the limit of a large number ions in the bath. In order to obtain some insight of the model by means of a numerical analysis, we need to consider an nondimensionalization procedure to catch the main features of the dynamics at the right scale. Since we have many parameters, we discuss also how we may standardize some of them, and the role played by the others. We discuss the role of different rescalings, by comparing the outcome of the dynamics. In particular, we compare two different rescalings, by referring to specific length measures of the channels \([3, 6]\). Both cases of nano and micro channels are considered.
II. THE MODEL

We consider a domain \( \Omega = \Omega_+ \cup \Omega_- \cup \Omega_M \in \mathbb{R}^d \), which consists of two regions of intra- and extra-cellular medium, \( \Omega_+ \) and \( \Omega_- \), divided by the membrane domain \( \Omega_M \), composed of many similar channels; let us denote by \( \Gamma_{D_+} \) and \( \Gamma_{D_-} \) the superior and inferior boundary of the bath, respectively. Typically, for a proper match with the biological case, we consider \( d = 3 \), while in order to reduce the complexity of the study, the simulation domain is such that \( d = 2 \).

![Figure 1: Computational domain in \( \mathbb{R}^2 \), di dimension \( L_1 \times L_2 \) with dimension of the membrane \( \epsilon_2 \times L_1 \).](image)

We suppose that the membrane has dimension \( \epsilon_1 \times \epsilon_2 \times L_1 \in \mathbb{R}^3 \); the dimension of each pore is \( \epsilon_1 \times \epsilon_1 \times \epsilon_2 \in \mathbb{R}^3 \); hence, in the membrane we have \( L_1/\epsilon_1 \in \mathbb{N} \) pores. So we have sketched each channel as a three dimensional parallelepiped with typical dimensions \( \epsilon_1 \) and \( \epsilon_2 \). See Figure 1 for the two-dimensional case.

Ions move freely in the water, treated as a continuum, and their motion through channels is driven by an electrical field, described as gradient of an electrical potential.

We need to describe the ions, their dynamics, the electrical field and the reciprocal interactions.

A. The Variables

*The Ions.* In general, we might suppose that \( K \in \mathbb{N} \) is the total number of types of ions; out of them, the first \( K - 1 \) are free species and the \( K \)-th is a specie confined in the membrane region, which creates the permanent charge of the channels.

As a consequence, in the domain we have a number \( N + J = \sum_{k=1}^{K-1} N^k + J \) of ions, where \( N^k \) is the number of ions of the \( k \)-th species and \( J \) the number of fixed confined ions. The first \( N \) ions are moving in \( \Omega \) and each of them is characterized by its Langevin coordinates, i.e. \( (X^{k,j}(t), V^{k,j}(t)) \in \Omega \times \mathbb{R}^3 \), being, respectively, the location and the velocity of the \( j \)-th ion, of the \( k \)-th species, with \( j = 1, \ldots, N^k(t) \). The latter \( J \) fixed charges are characterized by their position \( Y^j \in \Omega_M \), \( j = 1, \ldots, J \).

By now we consider a simplified model with \( K = 2 \), that is the case where only one population of ions is free of moving in \( \Omega \) and the other one is composed by fixed charges, few in number, located at the upper boundaries of the channels.
Hence, let $N$ be the total number of moving ions in the domain $\Omega \subset \mathbb{R}^3$. Each ion is characterized by its Langevin coordinates, i.e.

$$Z^j = (X^j, V^j) \in \Omega \times \mathbb{R}^3, \quad j = 1, \ldots, N,$$

being respectively the location and the velocity of the $j$-th ion out of $N$. Furthermore, let $Y^j, j = 1, \ldots, J$ be the position of the $j$-th fixed charge out of $J$.

Each ion is also characterized by its occupied volume of order $\tilde{\epsilon}^3$, being $\tilde{\epsilon}$ its diameter. If $\tilde{\epsilon} \sim \epsilon_1$ we are in the case of nano channels, i.e. a finite small number of ions may enter each channel, while if $\tilde{\epsilon} \ll \epsilon_1$ we are in the case of micro channels.

We consider the following counting measure defined on the location-velocity space $\Omega \times \mathbb{R}^3$

$$\mu_Z(t) = \sum_{j=1}^N \epsilon_{Z^j(t)} = \sum_{j=1}^N \epsilon_{(X^j(t), V^j(t))},$$

$$\nu_Y = \sum_{h=1}^J \epsilon_{Y^h}. \quad (1)$$

As a consequence, from (1), the moving ion spatial counting process is given by

$$\nu_X(t) = \mu_Z(t) (\cdot \times \mathbb{R}^3) = \sum_{j=1}^N \epsilon_{X^j(t)} \in \mathcal{M}(\Omega). \quad (3)$$

Finally, we may also consider the following empirical measures

$$X(t) = \frac{1}{N} \nu_X(t) \in \mathcal{M}_P(\Omega);$$

$$Y = \frac{1}{J} \nu_Y \in \mathcal{M}_P(\Omega). \quad (5)$$

In the Equations (3)-(5) $\mathcal{M}(\Omega)$ and $\mathcal{M}_P(\Omega)$ denote the spaces of (discrete) measures and probability measures on $\Omega$, respectively.

**The Electrical Field.** The electrical field $E(t, x)$ (in $V/m$) is described by means of an electrical potential $\Phi(t, x)$ (in $V = \text{kgm}^2/\text{ss}^2\text{C}$), which is a continuous variable on $\Omega_T = [0, T] \times \Omega$.

**B. The Dynamics**

A strong coupling between the variation of the distribution charges and the variation of the electrical potential is shown.

**The Electrical Field.** The electrical potential $\Phi$ is the solution of the Poisson-Nernst-Planck equation

$$- \nabla \cdot (\alpha_w \nabla \Phi(t, x)) = z q \left(K_{\gamma_1} * X(t))(x) + z_F q \left(K_{\gamma_2} * Y)(x),$$

where $\alpha_w$ is the dielectric constant for the water (in $F/m = C/Vm$), $z$ is the valency of the free ions, $z_F$ is the valency of the fixed ions and $q$ is the charge of ions (in $C$). The
smoothing functions $K_i \in C_b^2(\mathbb{R}^3)$, $i = 1, 2$ are such that

$$K_i(x) = \frac{1}{\gamma_i} W_i(x), \quad x \in \Omega,$$

where, for any $i = 1, 2$, the function $W_i \in C_b^2(\mathbb{R}^3)$ has compact support equal to $\gamma_i$, i.e. $\text{supp}(W_i) = \gamma_i$. In such a way, the quantities at the right hand side of (6) has the right dimension of a concentration, i.e. quantity of charge per unite volume. Furthermore the convolution terms in (6) may be seen as an empirical concentration, justifying the dependence on $N$.

For any $t \in [0, T]$, the boundary conditions are given by

$$\Phi(t, x) = \Phi_1, \quad x \in \Gamma_D^+;$$
$$\Phi(t, x) = \Phi_2, \quad x \in \Gamma_D^-;$$
$$\frac{\partial \Phi(t, x)}{\partial \nu} = 0, \quad x \in \partial \Omega \setminus (\Gamma_D^+ \cup \Gamma_D^-).$$

(8)

**The Ions.** Free ions move in the surrounding water along a direction determined by the electrochemical gradient; they interact with each other and with the walls of the membrane. An external source of randomness is introduced in the acceleration field, so that the evolution of the ions state $Z^j(t) = (X^j(t), V^j(t))$, for $j = 1, \ldots, N$ is described by the following Langevin model

$$dX^j(t) = V^j(t)dt,$$
$$mdV^j(t) = -[m \gamma V^j(t) + z q \nabla \Phi(t, X^j(t))]
+F_I \nabla (H_P \ast (\nu_X(t) + \nu_Y)) (X^j(t))
+F_I \nabla H_LJ (d_{\partial \Omega_M}(X^j(t))) \ dt + \sigma dW^j_t.$$

(9)-(10)

In System (9)-(10) $m$ is the effective mass of the ions (in kg), $\gamma$ is the friction coefficient per unit of mass (in s$^{-1}$), describing the effect of the surrounding water molecules; they are related to the diffusion coefficient $D$ (in $m^2/s$) deriving from random collisions with water as shown by the Stokes-Einstein relation [26]

$$m \gamma = \frac{k_B T}{D},$$

(11)

where $k_B$ is the Boltzmann constant ($1.30 \cdot 10^{-23} J/K = 1.30 \cdot 10^{-23} kg m^2/s^2 K$) and $T$ is the absolute temperature (in K).

The stochastic effect is described by a multivariate Wiener process $(W^1_t, \ldots, W^N_t)_{t \geq 0}$ with independent components. The parameter $\sigma$ is the diffusion coefficient (in $kgm/s\sqrt{s}$), acting on $mV^j(t)$, for any $j = 1, \ldots, N$; it must satisfy the following relation with $\gamma$

$$m \gamma = \frac{1}{2k_B T} \sigma^2 = C_{KT} \sigma^2.$$

(12)

Finally, the constant $F_I$ (in N) represents the magnitude of short range forces at contact. One estimate is given in [19] and is of the order $10^{-10} N$.

In System (9)-(10) we also introduced an ion-ion interaction through the Pauling potential
Following [19], we might consider

\[ H_P(r) = \frac{(r_1 + r_2)^{10}}{9r^9}. \]  

(13)

It represents a repulsive potential which arises from the overlap of the electron clouds of the ions, \( r \) is the ion-ion distance and \( r_i, i = 1, 2 \), are the van der Waals radii of ions. Here, since we consider only one single family of ions, \( r_1 = r_2 \). By the operator \( H_P \ast (\nu_Z(t) + \nu_Y)(x) \) we mean

\[ \sum_{k=1}^{N} H_P(|X^k(t) - x|) + \sum_{j=1}^{J} H_P(|Y^j - x|) \]  

(14)

where \(|x|\) is the norm of \( x \) and \(|x - y|\) denotes the distance between \( x, y \in \mathbb{R}^3 \), that is

\[ |x - y| = \sqrt{\sum_{i=1}^{3} (x_i - y_i)^2}. \]

To prevent ions entering the protein of the channels, since the walls of the membrane is made of fixed particles of a repulsive nature with respect to the moving ions. As a consequence a way to include the boundary conditions is via a hard-wall potential, like a truncated shifted Lennard-Jones potential activated when the ions are at fixed distance from the boundary.

In Equation (10) the quantity \( d_{\partial \Omega_M}(x) \) denotes the distance of a point \( x \in \Omega \) from the boundary of the membrane \( \partial \Omega_M \), that is

\[ d_{\partial \Omega_M}(x) = \min_{y \in \partial \Omega_M} |x - y|. \]  

(15)

The truncated shifted Lennard-Jones potentials, as suggested in [24], has the following form

\[ H_{LJ}(r) = \begin{cases} H_{LJ}(r) - \tilde{H}_{LJ}(r_c), & r \leq r_c; \\ 0, & r > r_c, \end{cases} \]  

(16)

where \( r \) is the distance between two particles and \( \tilde{H} \) is the Lennard-Jones potential which includes attraction-repulsion effects

\[ \tilde{H}_{LJ}(r) = \varepsilon_{LJ} \left[ \left( \frac{\tilde{\epsilon}}{r} \right)^{12} - 2 \left( \frac{\tilde{\epsilon}}{r} \right)^6 \right]. \]  

(17)

In [17] \( \varepsilon_{LJ} \) is the well depth (in \( m \)) and a measure of how strongly the two particles attract each other; \( \tilde{\epsilon} \) is the distance at which the intermolecular potential between the two particles is zero; it gives a measurement of how close two nonbonding particles can get and is thus referred to as the van der Waals radius. Here we treat \( \tilde{\epsilon} \) as the diameter of the ions, i.e. it is of same order of the van der Waals radius. Table I shows the size of some families of ions.

If we consider the truncated Lennard-Jones potential [16] with a cutoff \( x_c = \tilde{\epsilon} \), only the repelling part of the potential \( \tilde{H}_{LJ} \) is taken into account; indeed,

\[ \tilde{H}_{LJ}(\tilde{\epsilon}) = -\varepsilon_{LJ}, \]
Table I. Van der Waals radii \( \bar{\epsilon} \) for some families of ions in picometers \((10^{-12}m)\).

| Parameter   | Value    | Measure Units |
|-------------|----------|---------------|
| \( q \)    | 1.6 \times 10^{-19} | C             |
| \( m \)    | 6.5 \times 10^{-26} | Kg            |
| \( D \)    | 1.33 \times 10^{-9} | m^2 s^{-1}   |
| \( \epsilon_1, \epsilon_2 \) | 10^{-9} - 10^{-7} | m             |
| \( F_I \)  | 2 \times 10^{-10} | N             |
| \( K_B \)  | 1.38 \times 10^{-23} | J K^{-1}     |
| \( T \)    | 300      | K             |
| \( \alpha_w \) | 7.08 \times 10^{-10} | C V^{-1} m^{-1} |
| \( \alpha_0 \) | 8.85 \times 10^{-12} | C V^{-1} m^{-1} |

Table II. List of the parameters used in the model. The one related to ions, refer to the case of \( K^+ \).

and (16) becomes

\[
H_{LJ}(r) = \left( \tilde{H}_{LJ}(r) + \epsilon_{LJ} \right) 1_{[0,\bar{\epsilon}]}(r) \tag{18}
\]

\[
= -\epsilon_{LJ} \left\{ 1 - \left( \frac{\bar{\epsilon}}{r} \right)^{12} - 2 \left( \frac{\bar{\epsilon}}{r} \right)^{6} \right\} 1_{[0,\bar{\epsilon}]}(r).
\]

The choice of \( \epsilon_{LJ} \) influences how much the potential \( H_{LJ} \) tends to hard-sphere potential \( H_{hs} \). For the truncated Lennard-Jones potential the choice \( \epsilon_{LJ} = 1 \) describes relatively “soft” molecules; that is, molecules can partially overlap during collisions, whereas if they are closer than \( \bar{\epsilon} \) they start to repel each other. Increasing \( \epsilon_{LJ} \) a hard-sphere behavior is mimicked.

In Table II the value of the model parameters are listed, in the case of \( K^+ \). We observe that their order of magnitude may be very different; in particular, mass \( m \sim O(10^{-26}) \), while the friction term \( m\gamma \sim O(10^{-12}) \), the charge \( q \sim O(10^{-19}) \), the interaction \( \sim O(10^{-10}) \).

It is clear that in order to better manage System (6) and (9)-(10) a nondimensionalization procedure is needed.
III. NONDIMENSIONALIZATION OF THE SYSTEM

We consider the nondimensionalization starting with a time-space rescaling, via some typical scale \((t_0, \epsilon)\).

A. Time, Space, Positions and Velocities

Let \((x_s, t_s)\) be the scaled space-temporal coordinates, such that

\[
t = t_0 t_s, \quad x = \epsilon x_s, \tag{19}
\]

where \(\epsilon\) and \(t_0\) are scaling parameters that will be chosen later on. As a consequence of (19) the time dependent position and velocity are scaled as follows

\[
x_s(t_s) = \epsilon^{-1} x(t_0^{-1} t) \\
v_s(t_s) = \frac{t_0}{\epsilon} v(t_0^{-1} t). \tag{20}
\]

We denote by \(\Omega^s = \Omega^s_+ \cup \Omega^s_- \cup \Omega^s_M\) the rescaled domain with the three different regions, and by \(\Gamma^s_{D+}, \Gamma^s_{D-}\) the superior and inferior boundary of the rescaled bath, respectively.

Given the Langevin coordinate of the moving ions at time \((t_s), \ Z^j_s(t_s) = (X^j_s(t_s), V^j_s(t_s)) \in \Omega^s \times \mathbb{R}^3, \quad j = 1, \ldots, N, \) and the position of the fixed ones \(Y^i_s, \ i = 1, \ldots, J, \) let us denote by \(\nu^s_X(t_s), \nu^s_Y,\) the counting processes at time \(t_s,\) that is

\[
\nu^s_X(t_s) = \sum_{j=1}^N \epsilon X^j_s(t_s), \quad \nu^s_Y = \sum_{i=1}^J \epsilon Y^i_s,
\]

and by \(X^s(t_s), Y^s\) the corresponding empirical measures

\[
X^s(t_s) = \frac{1}{N} \nu^s_X(t_s), \quad Y^s = \frac{1}{J} \nu^s_Y.
\]

B. The Electrical Field

One might obtain a dimensionless equation for the potential \(\Phi\) in several ways. Scaling the electrical potential means to find a scaling parameter \(\tilde{\Phi}\) such that, called \(\Phi^s_s(t_s, x_s)\) the potential field in the new coordinates,

\[
\Phi^s_s(t_s, x_s) = \frac{1}{\tilde{\Phi}} \Phi(t_0 t_s, \epsilon x_s). \tag{21}
\]

As suggested in [6] proper techniques of semiconductor literature can be used for ion channels. A classical literature may be [18]. Indeed being ion channels provided of few fixed charges inside the channels, the applied difference of potential is approximately close to the thermal voltage. This fact may represent a bridge between ion channels literature and the studies on semiconductors [27]. The fundamental hypothesis in [6] is that \(\Phi\) can be scaled
as the following

$$\tilde{\Phi} = \frac{K_BT}{q} \approx 0.39 \text{ J/C}.$$ 

If the variation of $\Phi$ is less than $K_BT/q$, the diffusion prevails, whilst if it is greater than $K_BT/q$ the advection dominates. The chosen scaling corresponds to a limit in which both advection and diffusion are in balance.

C. Rescaling the Equations

We will consider a nondimensionalization of the equations (6) and (9)-(10), based on the transformation proposed in (20)-(21). Details of the nondimensionalization may be found in Appendix A.

a. The Poisson-Nernst-Planck Equation

The scaled Poisson–Nernst–Planck equation is

$$- \text{div}_{x_s}(\alpha_s \nabla_{x_s} \Phi_s(t_s, x_s)) = \lambda^e z \left(V_{\gamma_1}^s * X^s(t_s)\right)(x_s) + \lambda^e z F \left(V_{\gamma_2}^s * Y^s\right)(x_s). \tag{22}$$

In Equation (22), the kernels $K_i^s$, $i = 1, 2$ have been scaled as follows

$$K_i^s(x_s) = \frac{1}{\gamma_i^s} W_i^s(x_s) = \frac{1}{\gamma_i^s} W_i(\epsilon x_s), \tag{23}$$

and the relative electrical permittivity $\alpha_s$ is such that

$$\alpha_w = \alpha_s \alpha_0, \tag{24}$$

where $\alpha_w$ is the typical electrical permittivity of the water, and $\alpha_0$ is the electrical permittivity of the free space. For any $i = 1, 2$ the parameter $\gamma_i^s$ is obtained by the rescaling of the support $\gamma_i$ of $W_i$, that is $\gamma_i^s = \epsilon^3 \gamma_i^s$. See, again, Table II for their physical dimensions.

Finally, the parameter $\lambda^e$ is given by

$$\lambda^e = \frac{q}{\alpha_0 \tilde{\Phi} \epsilon} = \frac{q^2}{\alpha_0 K_B T \epsilon}. \tag{25}$$

Hence, it depends on the scaling length $\epsilon$. Note that, coherently with our purpose, the coefficient $\lambda^e$ is dimensionless, in fact we have

$$\frac{C^2}{m \cdot J K^{-1} K m} = 1. \tag{26}$$
Consistently with (21), in the new reference scale the boundary conditions (8) become

$$\Phi(t_s, x_s) = \Phi_1 \tilde{\Phi} = \frac{q}{K_B T} \Phi_1, \quad x_s \in \Gamma^+_D$$

$$\Phi(t_s, x_s) = \Phi_2 \tilde{\Phi} = \frac{q}{K_B T} \Phi_2, \quad x_s \in \Gamma^-_D$$

$$\frac{\partial \Phi}{\partial \nu}(t_s, x_s) = 0, \quad x_s \in \partial \Omega_{M,s} \setminus (\Gamma^+_D \cup \Gamma^-_D).$$

(27)

b. The Langevin system

The nondimensionalized Langevin system is, for any $j = 1, \ldots, N$,

$$dX^j_s(t_s) = K^j_s(t_s) dt_s,$$

$$m_s d_{t_s} V^j_s(t_{t_s}) = -[\lambda_1 m_s \gamma_s V^j_s(t_s) + \lambda_2 \nabla_{x_s} \Phi_s(t_s, X^j_s(t))$$

$$+ \lambda_3 \nabla_{x_s} H^s_P \ast (\nu^{s}_X(t_s) + \nu^{s}_Y(t_s)) (X^j_s(t)) + \lambda_3 \nabla_{x_s} H^s_{LJ} (d_{t_s} X^j_s(t)))] dt_s$$

$$+ \lambda_4 \sigma_s dW_{t_s}.$$ (28)

In the previous system $m_s, \sigma_s$ and $\gamma_s$ are such that

$$\gamma = \bar{\gamma} \gamma_s, \quad \sigma = \sigma_s \bar{\sigma}, \quad m = M m_s,$$

and

$$\sigma_s = \sqrt{2m_s \gamma_s}, \quad \bar{\sigma} = \sqrt{K_B T M \bar{\gamma}}.$$ (30)

The functions $H^s_P, H^s_{LJ}$ are the scaled Pauling and Lennard-Jones potential.; see (A2) and (A3) in Appendix A for their definitions. Finally, the dimensionless coefficients $\lambda_i, i = 1, \ldots, 4$ in the Langevin system are

$$\lambda_1 = t_0 \bar{\gamma}, \quad \lambda_2 = \frac{t_0^2 K_B T}{M \epsilon^2},$$

$$\lambda_3 = \frac{F_I t_0^2}{M \epsilon}, \quad \lambda_4 = \frac{t_0 \sqrt{K_B T M \bar{\gamma}}}{M \epsilon}.$$ (31)

So the nondimensionalized system has five parameters (25) and (31), depending on the time and space characteristic lengths $t_0$ and $\epsilon$.

D. Reduction of the Parameters

In order to reduce the parameters, first of all we impose $\bar{\gamma} = t_0^{-1}$, so that also $\lambda_1 = 1$. Furthermore, we choose the scaling parameter $t_0$ such that the random term is a Wiener process with diffusion coefficient $\sigma_s$; this is equivalent to impose that is $\lambda_4 = 1$. It follows that

$$t_0 = \epsilon \sqrt{\frac{M}{K_B T}};$$ (32)

as a consequence, $\lambda_2 = 1$. Hence, by (32), we have standardized three of the five parameters.
In conclusion, the nondimensionalized system is given by

\[
\begin{align*}
\frac{dX^j_s(t_s)}{dt_s} &= V^j_s(t_s), \\
\frac{m_s V^j_s(t_s)}{\gamma_s} &= -\left[m_s \gamma_s V^j_s(t_s) + \nabla_{x_s} \Phi_s(t_s, X^j_s(t)) + \lambda_3^\epsilon \nabla_{x_s} H^s_L \Phi_s(T, X^j_s)\right] dt_s \\
&+ \sigma_s dW_{t_s},
\end{align*}
\]

(33)

with

\[
\lambda_3^\epsilon = \frac{F I M^2}{K_B T M^2},
\]

(35)

coupled with the Poisson–Nernst–Planck equation (22)-(25).

**E. The Choice of the Spatial Scale**

Experimental methods for determining the physical dimensions of ion channels have been widely investigated during the last decades [14]. One of the most studied class of channels is the one relative to potassium ions $K^+$, which exhibit common permeability characteristics. A precise description of their structure is presented in [12]. They are mostly composed by a highly selective porous protein located into a lipid bilayer, the total length of the pore is $\epsilon_2 \sim 45\text{Å}$ and its diameter $\epsilon_1$ varies along the channel, assuming its maximum size into a cavity of $\sim 10\text{Å}$ placed in the middle of the membrane. Then the ions $K^+$ move through the pore and remain hydrated. Beside the class of biological channels there exist artificial nanochannels, see [7] and [28], radii and lengths of which range from $100 \cdot 10^{-9}\text{m}$ to $10^{-9}\text{m}$.

As a consequence we may consider two different scaling regimes taking into account the possible real dimension of the pore, i.e. either $\epsilon_1 \sim 10^{-9}$ or $\epsilon_1 \sim 10^{-7}$.

Let us consider now the magnitude of $\lambda^\epsilon$ and $\lambda_3^\epsilon$ in the stochastic system, using the data for a typical ion channel in Table II from (25) and (35), we obtain

\[
\lambda^\epsilon \sim 7 \cdot 10^{-7} \epsilon, \quad \lambda_3^\epsilon \sim 4.8 \cdot 10^{10} \epsilon.
\]

Thus if we nondimensionalise with the typical size of the neck of the channel $\epsilon_1 = O(10^{-9}\text{m})$, i.e. $\epsilon = \epsilon_1$, we obtain

\[
\lambda^\epsilon = \lambda_1^{\epsilon_1} = 7 \cdot 10^2, \quad \lambda_3^\epsilon = \lambda_3^{\epsilon_1} = 4.8 \cdot 10.
\]

(36)

whereas if we nondimensionalise with $\epsilon_1 = O(10^{-7}\text{m})$, the involved parameters become

\[
\lambda^\epsilon = \lambda_1^{\epsilon_1} = 7, \quad \lambda_3^\epsilon = \lambda_3^{\epsilon_1} = 4.8 \cdot 10^3.
\]

(37)

Next step is to compare the two nondimensionalized systems in order to catch the different captured features of the dynamics.
IV. NUMERICAL SIMULATIONS

Simulations of system (22) and (33)-(34) are performed in the MATLAB environment, in which we have simulated explicitly the Langevin system (33)-(34), while we used the package PDETool for the discretization of the Poisson–Nernst–Planck equation (22).

The Computational Domain. As already mentioned, we consider numerical results for \( d = 2 \). Denoted by \( \epsilon_1 \) and \( \epsilon_2 = k \epsilon_1 \), \( k \in \mathbb{N} \) the neck and depth of the channel, respectively, the not rescaled domain, shown in Figure 1, has dimensions given by \( L_1 = 2n_c \epsilon_1 \), and \( L_2 = (2m + 1) \epsilon_2 \), \( m \in \mathbb{N} \). \( n_c \in \mathbb{N} \) is the number of the channels in the membrane.

The rescaled domain after nondimensionalization is shown in Figure 2. The domain has dimension \( L_1^s \times L_2^s = 2n_c \times (2m + 1) \), while the channel has unit base dimension.

We consider an adaptive triangular mesh as in Figure 3.

The Boundary Conditions. We consider the boundary conditions (38), with \( \Phi_1^s = 10^h \), \( h \in \mathbb{N} \), and \( \Phi_2^s = 0 \), that is, for any \( t_s \in \mathbb{R}^+ \),

\[
\begin{align*}
\Phi(t_s, x_s) &= 10^h, \quad x_s \in \Gamma_{D^+}^s; \\
\Phi(t_s, x_s) &= 0, \quad x_s \in \Gamma_{D^-}^s; \\
\frac{\partial \Phi}{\partial \nu}(t_s, x_s) &= 0, \quad x_s \in \partial \Omega^s \setminus \Gamma_{D^-}^s \cup \Gamma_{D^-}^s.
\end{align*}
\]

(38)

The consequent initial electrical field is shown in Figure 4. Toroidal conditions upon \( \partial \Omega \) for the ions are considered in order to simulate infinite reservoir.
The Fixed Ions. Two fixed charges have been located in the upper layer of each channel, in order to simulate the behavior of the receptors present in protein channels. As a consequence, the total number of fixed charges is \( J = 2n_c \).

The Ions Dimensions. We consider two different possible dimensions. The first one refers to a radius of the same scale of the pore, for example \( \tilde{\epsilon} \sim 1.52 \cdot 10^{-10} \), as in the case of \( K^+ \). In general we consider \( \tilde{\epsilon} \sim \epsilon_1/4 \).

In order to simulate possible cases in which the ion dimension is much smaller than the channel one, we consider also the case \( \tilde{\epsilon} \sim \epsilon_1/100 \sim 10^{-8} \), too.

The Initial Conditions. At the initial time \( t = 0 \) a number of \( N \) ions are uniformly distributed in the upper bath \( \Omega^+ \) with normally distributed velocities (see [17]).

Spatial Distribution of Moving Ions. From the definition of the spatial distribution of the moving ions (3), we consider a regularized version via a convolution of the empirical measure (4) by a bivariate normal density \( f \) of zero mean and diagonal covariance matrix, and variances \( \sigma_1^2, \sigma_2^2 \), that is

\[
\tilde{f} \ast X(x) = \frac{1}{N} \sum_{i=1}^{N} f(x_i - x), \quad x \in \Omega. \tag{39}
\]

In the following, we consider \( \sigma_1^2 = \sigma_2^2 = 10^{-1} \).

A. Case 1: dimension of the channel \( \epsilon_1 \sim O(10^{-9} m) \)

We simulate the coupled system (22), (33), and (34), by taking into account the first scaling factor introduced in Section III, that is \( \epsilon = \epsilon_1 = 10^{-9} \). We consider \( N = 10^3 \) free moving ions and boundary conditions (38) with \( h = 4 \). Furthermore, in the membrane we take \( n_c = 10 \) channels. The time increment is \( dt = 10^{-3} \).

Case 1.a. Ion radius \( \tilde{\epsilon} \sim \epsilon_1/4 \). This case is the typical situation of the nano pore. Not many ions may enter into the channel at the same time. Figure 5 shows the initial distribution of the ions and the state of the system at time \( t = 3 \). It is evident that not many ions may enter into a channel at the same time. Figure 6 shows the time evolution of the ion spatial distribution. Since the dynamics its rather fast, after a small time interval at the very beginning of the simulation, the number of ions present in each region is varying but not too much. This is also visualized in Figure
Figure 5: Initial and final ion locations - Case 1.a.

Figure 6: Time evolution of the ion density - Case 1.a.

Ions are rather dispersed outside the membrane, while inside the ion number is small and not varying to much. On the right hand side of Figure 7 the distribution of the time spent by a particle into a channel is shown.

Figure 7: Left: evolution of ion number in $\Omega_+, \Omega_-, \Omega_M$. Right: histogram of the average time spent by ions in $\Omega_M$. Case 1.a.

Case 1.b. Ion radius $\tilde{\epsilon} \sim \epsilon_1 \cdot 10^{-2}$. Here we consider the simulation results in the same conditions with respect to Case 1.a., but the radius of ions, which is here much smaller. This case corresponds more to the case of micro pore. From Figure 9 one may observe that in this case the spatial density of ions in a channel may be significantly greater than zero, a case not observed previously. This is due to fact that here we are reproducing the case in which in each channel may enter a large number of ions at the same time. This may be seen in Figure 10, left, where the number of ions in the membrane is clearly higher. As the time needed for crossing a channel, we see how the distribution is less dispersed and is significantly higher in the mean.(See Table IV).
B. Case 2: dimension of the channel $\epsilon_1 \sim O(10^{-7} m)$

Now we simulate the coupled system for the scaling parameter $\epsilon = \epsilon_1 = 10^{-7}$, i.e. with parameters [37].

Case 2.a. Ion radius $\tilde{\epsilon} \sim \epsilon_1/4$. Again first we consider the case in which not many ions may enter in a channel at the same time, due to the fact that the diameter $\tilde{\epsilon}$ is taken as $\epsilon_1/4$.

Due to the fact that the time rescaling [32] is proportional to $\epsilon_1$, we expect a slower dynamics. This is seen in Figure [13], again the number of ions in the channel region are few, and the velocity of crossing the membrane is smaller. Such dynamics is confirmed by Figure [12].
Figure 11: Initial and final ion locations - Case 2.a.

Figure 12: Time evolution of the ion density - Case 2.a.

Figure 13: Left: evolution of ion number in $\Omega_+, \Omega_-, \Omega_M$. Right: histogram of the average time spent by ions in $\Omega_M$. Case 2.a.

Case 2.b. Ion radius $\epsilon \sim \epsilon_1 \cdot 10^{-2}$. Now again we consider ions much smaller than the channel. Figure 14 shows the initial distribution of the ions and the state of the system at time $t = 3$.

Comparing it with Figure 9, it is evident that again the density in the channel is higher with respect to the case with bigger ions, but, as already mentioned, speed is higher. The qualitative behavior of the time evolution of the number of ions in each region in the bath and in the membrane as shown in Figure 16 is similar to the one of Case 1.b. in Figure 13.
Estimates for the four study cases are shown in Table IV and Table III.

| Case | Mean  | Standard deviation |
|------|-------|--------------------|
| 1.a. | 0.0885| 0.0400             |
| 1.b. | 0.1450| 0.0142             |
| 2.a. | 0.1122| 0.1065             |
| 2.b. | 0.1434| 0.0503             |

Table III. Crossing channel time: mean and standard deviation in the four cases.
Table IV. Estimates of the number of ions in each region: mean and standard deviation (Std) in the four cases.

| Case | $\Omega_+$ | $\Omega_-$ | $\Omega_M$ | Case | $\Omega_+$ | $\Omega_-$ | $\Omega_M$ |
|------|-------------|-------------|-------------|------|-------------|-------------|-------------|
| 1.a. | Mean 498.03 | 414.59 | 87.38 | 2.a. | Mean 692.46 | 206.42 | 101.11 |
| Std 156.97 | 170.99 | 30.13 | Std 109.69 | 20.93 | 53.23 |
| 1.b. | Mean 377.71 | 477.29 | 144.99 | 2.b. | Mean 518.83 | 341.35 | 139.81 |
| Std 312.09 | 334.92 | 103.75 | Std 255.30 | 254.16 | 96.14 |

V. DISCUSSION

We have considered a fully stochastic mathematical model describing the main characteristics of a multiple channel system, in which ion movement in the bath and throughout membrane channels is modelled in terms of a system of stochastic differential equations, coupled with a Poisson-Nernst-Planck equation, which becomes itself stochastic due to the consequent randomness of the ion positions.

By considering real parameters as in Table I and Table II, we have faced the problem of identifying a right scale for the nondimensionalization of the system.

By comparing the simulation results of the rescaled system via typical scales of the channels, we see that a first rescaling by a channel size of order $\epsilon_1 \sim 10^{-10}$ is fast enough to make the dynamics evident. Instead, from Table III we may see that the mean time required to cross the membrane is significantly higher in the case of the second rescaling by $\epsilon_1 \sim 10^{-7}$.

Furthermore, we may notice that with the same rescaling, smaller particles are slower, and a change of velocity is less probable. This is due to the fact that with equal parameters, the smaller the diameter of the ions, the smaller are the forces of Pauling and Lennard-Jones acting on the velocity, since they depend on the ion diameter, as shown by (A2) and (A3).

The second issue we are interested in is the coupling of the dynamics inside and outside the membrane. This is particularly important in the case of nanopores (Cases 1.a. and 2.a). Indeed, as it is well shown in Figure 6, while there is a very high number of ions in the bath region, this is not so in the membrane, since the number of ions within each channel becomes very small.

The interesting mathematical question, which is relevant also for a reduction of the computational costs in the simulations, concerns the coupling of the two scales regarding the dynamics in the bath and within the channels, with respect to the significant difference in the number of ions per unit volume for the two regions.

As mentioned in the introduction, it is well known that it is reasonable to consider a continuous model for the ion concentrations whenever a law of large numbers may be applied, i.e. when the number of ions per unit volume is sufficiently large. On the other hand such laws cannot be applied in each channel, so that the system has to be kept discrete and stochastic.

As a consequence, for a large number of ions in the bath the problem of coupling their dynamics in the bath (averaged continuum), and inside the channels (discrete and stochastic) arises. An interesting issue refers, in particular, to the transition conditions at the membrane boundaries.
Something has already been done, but, to our knowledge, existing literature has not provided a satisfactory answer yet. The present study may be regarded as a first step for further investigation that the authors intend to carry on.

For the time being we propose case 1.a. as a satisfactory rescaling of the system.

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Appendix A: Rescaling the equations

1. Poisson-Nernst-Planck

By considering the rescaling (19) and (21), from Equation (6) we rewrite the rescaled term

$$\nabla \cdot (\alpha_r \nabla \Phi_s (t, x_s))$$

involving the rescaled potential field $\Phi_s(t, x_s)$, where $\alpha_r$ satisfies Equation (24). Then we have the following

$$\nabla \cdot (\alpha_r \nabla \Phi_s (t, x_s)) = -\epsilon^2 \nabla \cdot \left( \frac{\alpha_w \nabla \Phi (t, x)}{\alpha_0} \right)$$

$$= -\epsilon^2 \nabla \cdot (\alpha_w \nabla \Phi (t, x))$$

$$= \epsilon^2 q \alpha_0 \frac{1}{\Phi} \left( \sum_{k=1}^{N} W_1 (x - X_k (t)) + zF \sum_{h=1}^{J} W_2 (x - Y_h (t)) \right)$$

By considering the definition of the interacting kernels (7) and the rescaled ones (23), one obtains

$$\nabla \cdot (\alpha_r \nabla \Phi_s (t, x_s)) = -\epsilon^2 \nabla \cdot \left( \frac{\alpha_w \nabla \Phi (t, x)}{\alpha_0} \right)$$

$$= \frac{\epsilon^2 q}{\alpha_0 \Phi} \left( \sum_{k=1}^{N} W_1^s (x_s - X^k (t)) + zF \sum_{h=1}^{J} W_2^s (x_s - Y^h (t)) \right)$$

So finally the right term becomes,

$$\frac{\epsilon^2 q}{\alpha_0 \Phi} \left( \sum_{k=1}^{N} W_1^s (x_s - X^k (t)) + zF \sum_{h=1}^{J} W_2^s (x_s - Y^h (t)) \right)$$

hence, by the definition (25), we obtain the rescaled Poisson-Nernst-Planck equation (22).
2. The Langevin system

The nondimensionalization of the Langevin equations (9)-(10) has been done as follows. We scale first the location equation, obtaining, for any $j = 1, ..., N$

$$dX^j \sigma (t_s) = \epsilon^{-1} V_j (t_s) dt_s,$$

that is

$$dX^j (t_s) = V_j (t_s) dt_s.$$

Then we scale the equation describing the evolution of the velocity $V_j$, for any $j = 1, ..., N$. From (20) we have that

$$m \sigma V_j (t_s) = \frac{t_0}{M \epsilon} m \sigma V_j (t).$$

Hence, we need to scale the right term in (10). Let us denote by $\gamma$, $\bar{\sigma}$ and $M_S$, the nondimensionalized friction, diffusion coefficient and mass, respectively, such that

$$\gamma = \bar{\gamma} \gamma; \quad \sigma = \sigma \bar{\sigma}; \quad m = M m_s;$$

from the Stokes-Einstein relation and (12) we have

$$m_s \gamma = \frac{K_B T}{D M \gamma}, \quad \sigma = \sqrt{2K_B TM \gamma \gamma_s};$$

hence, $\sigma = \sqrt{2K_B TM \gamma}$. From the definition of the rescaled potential (21), the electrical field becomes

$$\nabla x \phi (t, x) = \frac{K_B T}{q} \frac{1}{\epsilon} \nabla x_s \phi_s (t_s, x_s).$$

The forms of the interacting term are the same as in the dimensionalized term. Indeed, the Pauling potential (13) becomes

$$H_P (r) = \frac{(\epsilon (r_{1,s} + r_{2,s}))^{10}}{(\epsilon r_s)^9} = \frac{\epsilon (r_{1,s} + r_{2,s})^{10}}{(r_s)^9}$$

and

$$\nabla x (H_P * (\nu_X (t) + \nu_Y)) (x) = \nabla x_s \left( \sum_{k=1}^{N} \frac{(r_{1,s} + r_{2,s})^{10}}{|x_s - X_k (t_s)|^9} + \sum_{h=1}^{J} \frac{(r_{1,s} + r_{2,s})^{10}}{|x_s - Y_h|^9} \right)$$

$$= \nabla x_s H_{P}^s * (\nu_X^s (t) + \nu_Y^s) (x),$$

where we have defined the scaled Pauling potential as follows

$$H_{P}^s (r_s) = \frac{(r_{1,s} + r_{2,s})^{10}}{r_s^9},$$

where $r_s$ is a distance in the new coordinate scale.
In a same way it is possible to scale the Lennard-Jones potential (17). For the distance from
the border \( d_{\partial \Omega} \) defined in (15) we have that
\[
d_{\partial \Omega} (\epsilon x_s) = \min_{\epsilon y_s \in \partial \Omega} |\epsilon x_s - \epsilon y_s|
= \epsilon \min_{y_s \in \partial \Omega} |x_s - y_s|
= \epsilon d_{\Omega_s} (x_s),
\]
where \( d_{\Omega_s} (x_s) \) is the distance of the point \( x_s \) from the membrane boundary in the new scale.

The potential \( \tilde{H}_{LJ} \) is scaled as follows
\[
\tilde{H}_{LJ} (\epsilon r_s) = \epsilon \epsilon_{LJ} \left[ \left( \frac{2 R_{vdW}}{r_s} \right)^{\frac{12}{2}} - 2 \left( \frac{2 R_{vdW}}{r_s} \right)^{\frac{6}{2}} \right],
\]
where \( \epsilon_{LJ} \) is the nondimensionalization of the size of \( \epsilon_{LJ} \) which depends on length, and \( R_{vdW} \) is the scaled van der Waals radii. If we define the rescaled truncated shifted Lennard-Jones
potential as
\[
\tilde{H}_{LJ}^s (x_s) = \epsilon \epsilon_{LJ} \left[ \left( \frac{2 R_{vdW}^s}{x_s} \right)^{\frac{12}{2}} - 2 \left( \frac{2 R_{vdW}^s}{x_s} \right)^{\frac{6}{2}} \right],
\]
(A3)

it follows that
\[
\tilde{H}_{LJ} (x) = \epsilon \tilde{H}_{LJ}^s (x_s).
\]

For the random term, we rescaled the Wiener process \( W_i^j \) and obtain \( W_i^j = W_i^j_{t_0 t_s} \sim \sqrt{t_0} W_i^j_{t_s} \),
where \( W_i^j_{t_s} \) is a Wiener process with respect to time \( t_s \).

Finally, by gathering together all the previous terms, from (A1) and (10), we have the
following
\[
m_s d_{t_s} V_s^j (t_s) = - \frac{t_0^2}{M \epsilon} \left[ M m_s \gamma s \epsilon \frac{t_0}{t_0} V_s^j (t_s) + z q f T \nabla x_s \Phi_s (t_s, X_s^j)
+ F_t \nabla x_s H^s (t_s) (d_{\partial \Omega_s} (X_s^j (t_s))) \right] dt_s
+ t_0 \sqrt{t_0} \sqrt{2 K_B T \gamma m_s \gamma s} dW_i^j.
\]

By considering the relation (30) between \( \sigma_s \) and \( \gamma_s \)
\[
m_s d_{t_s} V_s^j (t_s) = - \left[ \gamma t_0 m_s \gamma s V_s^j (t_s) - \frac{t_0 K_B T}{M \epsilon^2} \nabla x_s \Phi_s (t_s, X_s^j)
+ F_t \frac{t_0^2}{M \epsilon} \nabla x_s H^s (t_s) (d_{\partial \Omega_s} (X_s^j (t_s))) \right] dt_s
+ t_0 \sqrt{t_0} \sqrt{K_B T \gamma \sigma_s dW_i^j}.
\]
Thus, we have obtained the Langevin system $\text{(28), (29) and (31)}$. 

[1] T. W. Allen, S. Kuyucak and S. H. Chung. Biophysical Chemistry 86(1): 1–14, 2000.
[2] K. Arning, M. Burger, B. Eisenberg, H. Engl, L. He. PAMM Special Issue, ICIAM 1120801–1120802, 2007.
[3] M. Burger, M. B. Schlake and M. T. Wolfram. Nonlinearity 25(2): 961, 2012.
[4] V. Capasso, D. Morale. Stochastic Analysis and Applications, 27, 3, 574 – 603, 2009.
[5] V. Capasso, D. Morale, G. Pacchetti. BioSystems, 112, 292–297, 2013.
[6] J. Chapman, J. Norbury, C. Please, G. Richardson. http://www.maths-in-medicine.org/uk/2005/ion-channels/.
[7] X. Chen, R. Ji, M. Steinhart, A. Milenin, K. Nielsh, and U. Gösele. Chem. Mater. 19,3–5, 2007.
[8] B. Corry, S. Kuyucak, and S. H. Chung. Biophysical Journal, 78(5): 2364–2381, 2000.
[9] B. Corry, S. Kuyucak, and S. H. Chung. J. Gen. Physiol 114(1–2): 597–599, 1999.
[10] B. Corry, T. W. Allen, S. Kuyucak, and S. H. Chung. Biophysical Journal, 80(1): 195–214, 2001.
[11] C. E. Dangerfield, D. Kay, and K. Burrage. Physical Review E 85 (5), 051907, 2012.
[12] D. A. Doyle et al. Science 280: 69–77, 2008.
[13] B. Eisenberg. Advances in Chemical Physics, 148 (eds S. A. Rice and A.R. Dinner), 2011.
[14] B. Hille. Ionic Channels Excitable Membranes. Sinauer Associates Inc., 3rd Edition, 2001.
[15] W. Im, S. Seefeld, and B. Roux. Biophysical Journal, 79(2): 788–801, 2000.
[16] W. Im, S. Seefeld, and B. Roux. Journal of Chemical Physics, 115(10): 4850–4861, 2001.
[17] D. Marreiro, M. Saraniti, and S. Aboud. Journal of Physics: Condensed Matter, 19(21): 215203, 2007.
[18] P. A. Markowich, C. A. Ringhofer, and C. Schmeiser. Semiconductor Equations, Springer-Verlag, 1990.
[19] G. Moy, B. Corry, S. Kuyucak, and S. H. Chung. Biophysical Journal, 78(5): 2349–2363, 2000.
[20] G. Moy, B. Corry, S. Kuyucak, and S. H. Chung. Chem. Phys. Lett. 320(1): 35–41, 2000.
[21] B. Nadler, Z. Schuss, A. Singer, and R. S. Eisenberg. Nanotechnology, 3: 439–442, 2003.
[22] N. Nadler, Z. Schuss, A. Singer, R. S. Eisenberg. Journal of Physics: Condensed Matter, 16(22): S2153, 2004.
[23] B. Nadler, Z. Schuss, and A. Singer. Phys. Rev. Lett., 94(21): 218101, 2005.
[24] S. V. Nedea, A. J. H. Frijns, A. A. van Steenhoven, A. J. Markvoort, and P. A. J. Hilbers. Physical Review E, 72(1): 016705, 2005.
[25] B. A. Yi and L. Y. Jan. Ion channels in Encyclopedia of the Human Brain, Academic Press, 2002.
[26] P. Ramirez, M. Aguilella–Arzo, A. Alcaraz, J. Cervera, and V. M. Aguilella. Cell biochemistry and biophysics 44(2): 287–312, 2006.
[27] C. Schmeiser. SIAM Journal on Applied Mathematics, 54(1): 175–194, 1994.
[28] I. Vlassiouk, S. Smirnov, and Z. Siwy. Nano Letters 8(7): 1978–1985, 2008.
[29] R. J. Williams, and W. A. Zheng. Annales de l I. H. P., section B, 26(3): 461–488, 1990.