

## STOCHASTICAL LANGEVIN-LORENTZ-POISSON MODELLING OF ION FLOW THROUGH MEMBRANE IONIC CHANNELS

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### Abstract.

In this paper a stochastic Langevin-Lorentz-Poisson modelling of ion flow through membrane ionic channels is presented. In the model the spatial charge effects are modelled assuming stationary conditions and the spatial ionic distributions is described by a coupled system of equations, a dynamic Langevin-Lorentz equation and a Poisson equation. The numerical solution of the coupled problem is performed by using an iterative method. The ion displacements are determined by time integrating the Langevin-Lorentz equation in the absence of the thermal noise, obtaining the deterministic ion position and velocity. A Fokker-Planck analysis is then performed in order to estimate the effective ion position and velocity. A typical Ca<sup>++</sup> channel is examined and the simulation results are expressed in terms of number ion exits from the channel versus the transmembrane potential.

*Keywords:* cellular ionic channels; ion flow; Langevin-Lorentz-Poisson model; stochastic ion injection

### 1. Introduction

Various critical cellular functions, including differentiation, apoptosis, etc, are governed by the exchange of signals between living cells, which occurs mainly through the cellular membrane, a selective permeable barrier between the cell and the extra cellular environment. In particular, among interesting substances ions play a role of paramount importance, since the activation of several critical signalling pathways depends on ionic concentrations. For these reasons, the ion transport across cell membranes, which occurs through ionic channels (hydrophobic regions having a size of the order of few Angstrom), have a fundamental role in biological systems.<sup>4</sup> Recently experimental results have gained insight on the mechanism of ion flow across ionic channels. The currents flowing through a single channel under controlled experimental conditions have been examined by using the patch-clamp technique. Moreover several attempts have been made to build coherent representations of ion flow across ionic channels in accordance with experimental measurements [2][3]. However the simulation of this mechanism is a very complicated task, for

a number of reasons including the lack of accurate descriptions of the channel structure, the difficulty of modelling the behaviour of the protein chains constituting the channel walls, the very high number of atoms, the very short time scale of the involved dynamical phenomena, etc. In literature several approaches have been followed for this purpose, among which the most used are continuum model such as Poisson-Nernst-Planck (PNP) and particle models such as Molecular Dynamic (MD), Brownian Dynamic (BD) and Langevin-Lorentz-Poisson (LLP). The PNP model is based on the electro-diffusion theory that describes the average ionic flux due to gradients of ion concentrations and electric fields and allow to build the transmembrane voltage/current relationship, although the ionic channel environment is described as a continuum. The MD is based on the atomic model of macromolecular systems. The motion of all the particles (atoms and ions) in the system is obtained by integrating Newton classical equations, in such a way to deduce the macroscopic properties from microscopic observations. The drawback of MD is the huge computational effort, which prevents MD application to complete simulation of ion transport across ionic channels. The BD and LLP are stochastic computational methods well suited for the analysis of the ion permeation process in the long time scale (ns). Their main hypothesis is that the solvent molecules are not dealt with explicitly and are represented as a continuous dielectric. Moreover they consider integration of stochastic equations of ion motion, treating in a different way the ion-ion and ion-channel interactions. In this paper, a novel stochastic Langevin-Lorentz-Poisson model for the analysis of ion permeation across a ionic channel is presented. In the model the spatial ionic distributions inside the membrane channel is described by a coupled system of equations: a dynamic Langevin-Lorentz equation, and a Poisson equation. The numerical solution of the coupled problem is performed by using an iterative method, which at each step alternates the solution of a Poisson problem with the integration of Langevin equation. In addition in order to carry out a simulation more adherent to reality a novel stochastic mechanism of ion arrival is adopted, which allows us to describe the fluctuation in time of the total number of particles inside the simulation region. In the analysis a typical  $\text{Ca}^{++}$  channel of cylindrical shape is considered and the results expressed in terms of number of ions crossing the channel show good agreement with experimental data. The paper is structured as follows: in Section II the numerical solution of mathematical model is presented; in Section III a simulation of the  $\text{Ca}^{++}$  ion flow across a typical calcium channel and the novel stochastic injection mechanism is illustrated. [da spostare i reffs, 8, 3, 7, 1, 25](#)

## 2. Numerical Solution of the Langevin-Lorentz-Poisson Problem

The behaviour of ions inside cellular membrane ionic channels is governed by a system of coupled equations consisting of a Langevin-Lorentz equation for the motion of ions and a Poisson problem for the electrical scalar potential  $\phi$  (Langevin-Lorentz-Poisson problem):

$$(1) \quad m \frac{d\mathbf{v}}{dt} = -h\mathbf{v} + q(\mathbf{E}_T + \mathbf{v} \times \mathbf{E}_T) + N(t)$$

$$(2) \quad \nabla^2 \varphi + q \int \int \int_{\Omega} f(P) d\Omega = 0$$

$$(3) \quad \mathbf{E}_T = -\nabla \varphi + \mathbf{E}_{ESO}$$

where  $m$  is the generic ion mass,  $\mathbf{v}$  is its velocity,  $h$  is a viscous friction coefficient, modeling ion interactions with water molecules,  $q$  is ion charge,  $\mathbf{E}_T$  and  $\mathbf{B}_T$  (if any) are the total electric and magnetic field respectively,  $N(t)$  is a Langevin force that take into account the thermal noise. In the Poisson equation [2](#)  $\Omega$  indicates the domain of analysis for the ionic channel and  $f(P)$  is the space particle distribution function. The total electric field  $\mathbf{E}_T$  consist of two terms: the first is due to the scalar potential  $(-\nabla\phi)$ , the second,  $E_{ESO}$ , takes into account exogenous electric forces, if any, influencing the ion in the cell environment. In our approach the numerical solution of the above coupled electromagnetic-motional problem is performed according to a self-consistent scheme in which the numerical solution of the 3-D Poisson problem alternates with the time-domain integration of the ion motion equations. In particular for each time step the solution of a Poisson problem is calculated by using a point to point method, that is the electric field is computed by adding the contributions due to each ion, assuming a stationary ion flow. The contributions of the environment are summarized by the exogenous electric field. This total electrical field [3](#) is used to determine the ion displacements by a time-integration of the Langevin-Lorentz equation [1](#), in the absence of thermal noise. In this way the deterministic ion displacement are obtained. At this point in order to consider the statistical parameters of ion motion, a Fokker-Planck analysis of the dynamical equation is performed to estimate the expected deviation values for the ion displacement. Finally, the effective ion position and velocity values are obtained by adding the two contributions.

### 3. LLP Analysis of a $\text{Ca}^{++}$ Ionic Channel and stochastic injection mechanism

In order to show the application of the LLP model, the analysis of the ionic flow across a typical  $\text{Ca}^{++}$  channel is illustrated hereafter. For the description of  $\text{Ca}^{++}$  channel, we assume a commonly used schematisation, in which only the channel region is considered; it consists of a cylinder, with an height of 10 Angstrom and a radius of 5 Angstrom and the cylinder axis coincident with the  $z$  axis. A schematic representation of the  $\text{Ca}^{++}$  channel is shown in fig. [1](#).

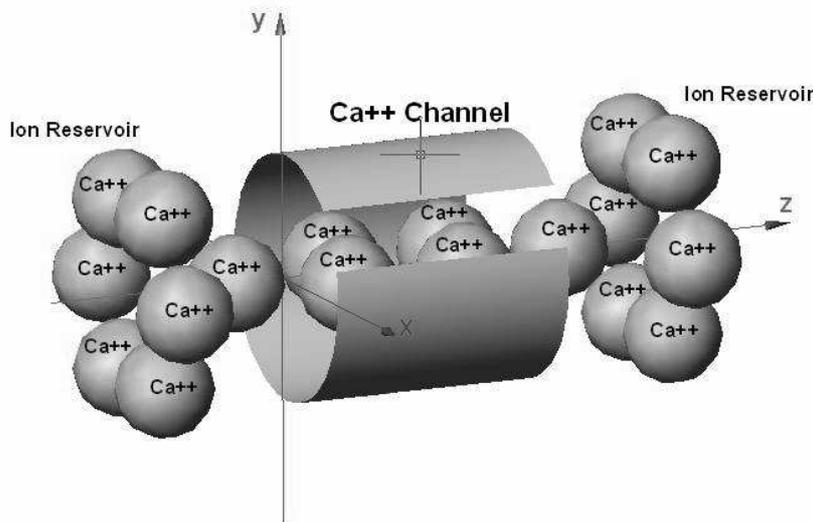


Fig. 1. Ionic channel geometry schematisation

The channel walls, made of polypeptide chains, are assumed fixed and their influence on the ion permeation is modelled by adding to the exogenous field  $E_{ESO}$  a contribution along the radial direction. This field forces the ions advancing in proximities of the cylinder surface to move forward the cylinder axis. Being the channel a non-isolated system, some ion populations in the close proximities of channel extremities, called reservoirs, are considered, ready to access or leave the channel region. The behaviour of reservoirs is approximated by resorting to fixed point charge configurations placed in the neighbourhood of the channel extremities. Even the contributions of these charges is accounted for by means of the exogenous field  $E_{ESO}$ . The aim of this analysis is to study the ion flow through open protein channels of biological membranes, in such a way to build a I/V relationship. In particular, the influence of membrane voltage on the number of the ion escapes from the Ca++ channel is investigated. Assuming that the typical transit time of a ion is of the order of 1 ns, the simulation time interval was chosen greater than this typical transit time. In order to make the analysis compatible with the hypothesized stationary conditions the integration time step was chosen of the order of 1 fs. In the simulation it has been assumed that the channel is initially empty and is filled by ions injected following a stochastic mechanism. In order to evaluate the arrival process from the two baths into the channel region we consider the following assumption: the ionic motions in the solution are independent diffusion processes; the bath is in stationary conditions; a fixed number of particles is considered and distributed in an finite region of the bath. This number of particles follow the Poisson distribution and the initial positions of the particles are random variables. Under all the above hypothesis it has been shown in literature<sup>6</sup> that the first arrival and inter-arrival time follow an exponential distribution function and the latter arrival depends only on the elapsed time since the precedent arrival. Thus the arrival process is a memoryless Poisson process. Based on this observations, the stochastic ions injection model has been set up. In the initial configuration the channel is empty, the simulation time is fixed and the entering of the ions into the channel is governed by a exponentially distributed process for the arrival time from each side of the channel (assumed equal to 60 ps). Under these assumptions several runs have been performed; in figure 2 the number of the Ca++ ions crossing the channel versus the transmembrane voltage are shown; in particular it is worth noticing the quasi-linear increase of the average number of ions crossing the channel as the membrane voltage increases, which is in good agreement with results obtained by using the PNP model and with experimental data. Figure 3 shows that the ionic flow is not affected significantly, when considering values of friction coefficient greater than a threshold.

#### 4. Conclusions

The stochastic LLP model presented is able to described faithfully experimental observations about ion flow across membrane channels. The stochastic mechanism of ion arrival has revealed successful to properly take into account the fluctuation in time of the total number of particles inside the channel region. The simulation performed for different values of transmembrane voltages correctly reproduces the behaviour of the gating mechanism of cellular membrane.

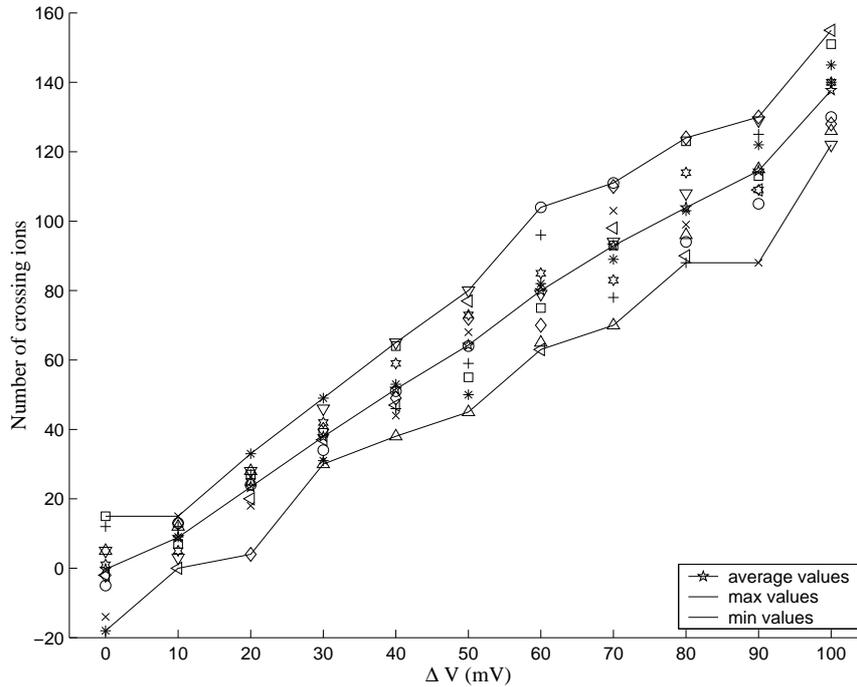


Fig. 2. Number of ions exiting the channel versus transmembrane voltage (stochastic injection)

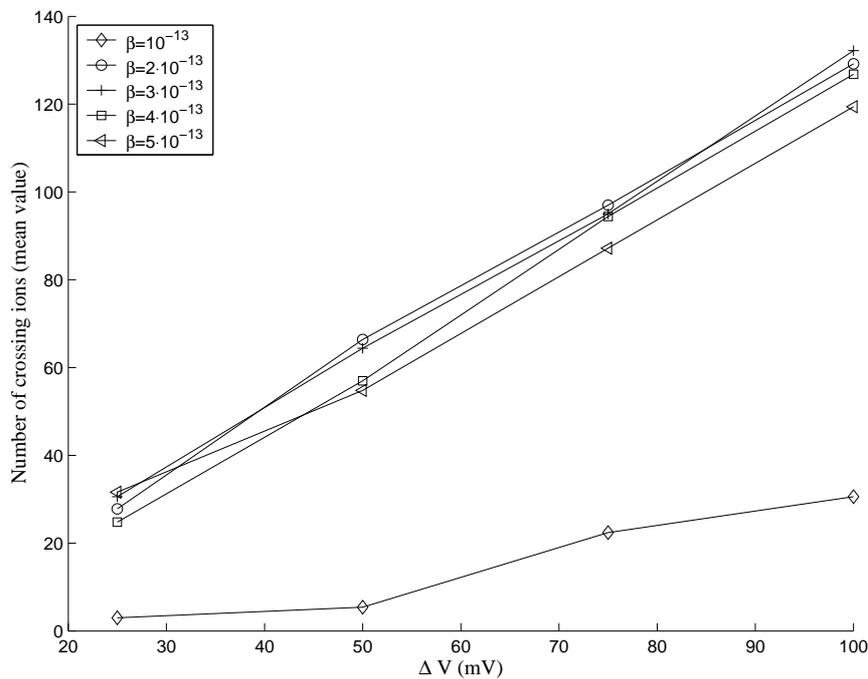


Fig. 3. Number of ions exiting the channel versus transmembrane voltage for different values of friction coefficient

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