

# Towards a reliable model of ion channels: three-dimensional simulation of ionic solutions

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## ABSTRACT

Ion channels play a crucial role in the physiology of complex biological systems because of their influence on the electrical equilibrium between the cells and their environment. From an engineering viewpoint, ion channels will be the key components of the design and the production of a new generation of biosensors integrating the selectivity of ion channels with the processing capabilities of modern microelectronics.

The aim of this contribution is to review the state-of-the-art simulative approaches used for the modeling of the ion channel environment. A self-consistent approach will be presented, based on the coupling of Poisson/Coulomb/Langevin solvers, and aimed to model the dynamics of ionic solutions. Simulation results will be shown as well.

**Keywords:** Aqueous solutions, molecular dynamics, Brownian dynamics, ion channels.

## 1 INTRODUCTION

Particle-based methods [1] can describe aqueous ionic solutions in which most of life occurs. Water can be described as a continuous dielectric, with dielectric constant appropriate for the salt composition of the solution [2], that stochastically interacts with the ionic dynamics through a friction coefficient and a random force. This Brownian approach based on the Langevin equation [3] is well suited for the simulation of bulk solutions, and can be used to model a computationally efficient “ion bath”.

Any approach aimed at the simulation of aqueous solutions must fully account for the electrostatic nature of the ion-ion and ion-water interactions. Furthermore, the recent availability of reliable and accurate experimental data requires the implementation of realistic “computer experiments”, which must be able to fully reproduce the features related to the experimental set-up.

In this paper, we will first recall the concept of self-consistency in particle-based simulations, we will then discuss the main algorithmic components of the simulation tools. Finally, some simulation results will be presented for a NaCl electrolytic solution.

## 2 SELF-CONSISTENT MODELING

A crucial aspect of particle-based simulative methods is the coupling of the dynamics of charge carriers with the field of forces generated by *external* boundary conditions and by *internal* carrier-carrier electrostatic interaction. The research described in this document adopts the so-called self-consistent approach that has been successfully employed for more than three decades in plasma simulations [4].

The adjective *self-consistent* refers in this case to the fact that the forces due to the electrostatic interactions of the system components strictly depend on the spatial configuration of the components themselves, and must be continuously updated as the dynamics of the system evolves.

Self-consistency is achieved by periodically “freezing” the simulation of the dynamics, and by updating the force distribution. The dynamics evolution is then resumed in the “updated” field of forces, which is assumed to be constant for a time  $\Delta t$  which is usually of the order of a tenth of a femtosecond. At the end of  $\Delta t$  a new field is computed from the new charge distribution. The alternating computation of forces and charge displacements allows the successful simulation of the transient behavior of plasmas in highly non-linear regimes, such as the ultrafast response of photo-generated electron-hole pairs in semiconductors when high electric fields are externally imposed [5].

## 3 ALGORITHMIC COMPONENTS

This section is devoted to the description of the main algorithmic choices done in order to implement a self-consistent simulation tool for ionic solutions.

### 3.1 Ionic Dynamics

The modern theory of ionic solutions [6], [7] represents ionic solutions as suspensions of spheres in a solvent. The simplest representation of the solvent water, as a uniform dielectric, with dielectric constant of the ionic solution, does remarkably well in these theories, derived under conditions of thermodynamic equilibrium, i.e., zero flux of all species in all regions, however small the region or short the time. Here we develop a stochas-

tic extension of this theory. Ions are treated as Brownian particles, by implementing a dynamics simulation engine based on the well known Langevin's equation [3] that describes the forces acting on a suspended particle with position  $\mathbf{r}$  at time  $t$ :

$$m\dot{\mathbf{v}}(\mathbf{t}) + \beta\mathbf{v}(\mathbf{t}) - \mathbf{F}(\mathbf{r}) = \sqrt{2\beta k_B T}\dot{w}, \quad (1)$$

where  $m$  is the ion mass,  $\mathbf{v}$  its velocity,  $\mathbf{F}$  the force on the ion due to the internal interactions and to the externally imposed boundary conditions, and  $\beta$  is the friction constant, which depends on the ion radius and on the viscosity of the medium. Also,  $k_B$  is Boltzmann's constant,  $T$  the absolute temperature of the system, and  $\dot{w}$  is an uncorrelated random force expressing the effect of the molecular fluctuations exerted on the ion by the surrounding water.

Langevin's equation is then solved for each ion every  $\Delta t$  seconds by means of a standard Euler scheme as follows:

$$\mathbf{v}(t + \Delta t) = \mathbf{v}(t) - \left[ \gamma\mathbf{v}(t) - \frac{\mathbf{F}}{m} - \sqrt{\frac{2\gamma k_B T}{m}} N(0, \Delta t) \right] \Delta t. \quad (2)$$

where  $\gamma = \frac{\beta}{m}$  is related to the diffusion coefficient  $D$  by the well known Einstein relation [8]

$$D = \frac{k_B T}{m\gamma}, \quad (3)$$

and  $N(0, \Delta t)$  is a random number with normal distribution, zero mean, and variance  $\Delta t$ , describing the properties of the random force  $\dot{w}$ .

### 3.2 Boundary conditions

The aim of the research shown here is to be able to reproduce in a realistic way the transport of charge in aqueous solutions. The typical simulated systems are cubic cells with a side length of a micrometer or smaller, and two "electrodes" facing each other on two opposite sides of the cube. Both the electrodes keep a local electrostatic equilibrium by injecting or extracting ions from the solution in order to maintain a predetermined equilibrium concentration in the electrode region.

The other surfaces are reflectors, i.e. ions bouncing off them have the sign of the normal component of the momentum changed, while the parallel components are conserved.

Electrostatic boundary conditions are implemented in the particle-mesh force solver (see section 3.4) in such a way that a constant potential is applied to the electrodes (Dirichlet condition), while the normal component of the electric field is kept zero on all other surfaces (Neumann condition).

### 3.3 Force calculation, the P<sup>3</sup>M scheme

Any particle-based, full phase-space simulation of the dynamics of a system of charges must account for the instantaneous distribution of the forces acting on the charged particles [1]. In other words, each simulated ion continuously senses a field of forces due to its position and to the position of all other components of the simulated population. This requires a self-consistent coupling of the ion dynamics with the electric field generated by the ions themselves, and by the conditions imposed at the boundaries of the computational domain.

Furthermore, finite-size effects must be accounted for in order to correctly model the thermodynamic behavior of the solute, and to model macroscopic measurable quantities such as the free energy per mole [9] and the transport coefficients [10].

To summarize, three main requirements must be satisfied in order to adequately perform the force calculation in an ionic solution simulator: (a) the method must include long-range interactions with collective plasma modes and with the boundary conditions as described in section 3.2, (b) the method must account for short-range ion-ion interaction, and, (c) ion finite-size effects must be modeled as well. Finally, whatever algorithmic combination is chosen, efficiency must be pursued, for the high frequency of the force calculations requires an highly efficient approach to achieve realistic simulation times.

Following several works [1], [11] in plasma simulation, we have chosen to represent the force  $\mathbf{F}_i$  on the  $i$ -th ion as the sum of two components:

$$\mathbf{F}_i = \mathbf{F}_i^m + \mathbf{F}_i^{sr}, \quad (4)$$

where  $\mathbf{F}_i^m$  represents the long-range *mesh force* accounting for the boundary conditions and for the collective electrostatic behavior of the plasma, and  $\mathbf{F}_i^{sr}$  is the short-range inter-particle force, describing the interactions between close ions. This decomposition of the force is based on two well known [1] approaches, the particle-mesh (PM) one, which computes the electric field intensity on the nodes of a discretization grid, and the particle-particle (PP) method, based on the equation of Coulomb for interacting charges. The resulting hybrid scheme for the force calculation was initially proposed by Hockney [1], and is referred to as the *Particle-Particle-Mesh* (P<sup>3</sup>M) method.

Details on the approaches adopted for the calculation of the two components of  $\mathbf{F}_i$  are given in the two following sections.

### 3.4 Particle-Mesh interaction

As its name suggests, the mesh force is computed on the nodes of a discretization grid, in this case a non-

uniform three-dimensional tensor product grid. To resolve the spatial variations of potential due to the ion distribution, the mesh spacing has been chosen to be smaller or equal to the Debye length, expressed as

$$L_D = \sqrt{\frac{\epsilon\epsilon_0 k_B T}{q^2 n_{ion}}}, \quad (5)$$

where  $\epsilon$  is the dielectric constant of the medium,  $\epsilon_0$  is the permittivity of vacuum,  $q$  the elementary charge, and  $n_{ion}$  is the concentration of ions expressed in  $m^{-3}$ . Equation 5 gives values of  $6.5 \text{ \AA}$  and  $20 \text{ \AA}$  for 1 and 0.1 molar concentrations of NaCl, respectively.

The high frequency of solutions required by the self-consistent scheme allows us to safely assume that two consecutive solutions of the field equations differ only slightly, and any solution is an excellent initial guess for the successive one. This fact promotes the use of an iterative solver, rather than a direct one.

The method of choice for this work is to compute the mesh force as the negative gradient of the electrostatic potential obtained by solving Poisson's equation. This choice allows an easy and accurate implementation of complex boundary conditions and different dielectrics within the simulation domain. The method used for the solution of Poisson's equation is the iterative version of the multi-grid approach [12], which is successfully employed in the simulation of semiconductor devices [13]. Besides its extreme efficiency, the multi-grid method allows the implementation of robust solvers, especially when non-uniform grids are used.

A theoretical analysis of the multi-grid approach for the simulation of complex domains can be found in literature, both in the two- and three-dimensional case [13], and it is beyond the scope of this document.

### 3.5 Particle-Particle interaction

The starting point for the computation of the short-range component of the force on the  $i$ -th ion due to the  $j$ -th ion is Coulomb's law corrected with a rapidly varying component that accounts for the finite-size effect [14]:

$$\mathbf{F}_{ij}^{coul} = \frac{q_i q_j}{4\pi\epsilon r_{ij}^2} \left[ 1 + \text{sgn}(q_i q_j) \left( \frac{s_i + s_j}{r_{ij}} \right)^p \right] \mathbf{a}_{r_{ij}}, \quad (6)$$

where  $q_i$  is the charge of the  $i$ -th ion,  $\epsilon$  is the dielectric constant,  $r_{ij}$  is the interaction distance,  $s_i$  is the ion "size", and it is proportional to the ionic radius. Finally,  $p$  is a parameter that determines the "hardness" of the repulsion between ions, as indicated by Pauling in [14].

Following [1], the calculation of the short-range force  $\mathbf{F}_i^{sr}$  on the  $i$ -th ion is performed by only considering the contributions of the ions inside a *short-range* spherical region  $\Omega_i^{sr}$  centered around the  $i$ -th ion:

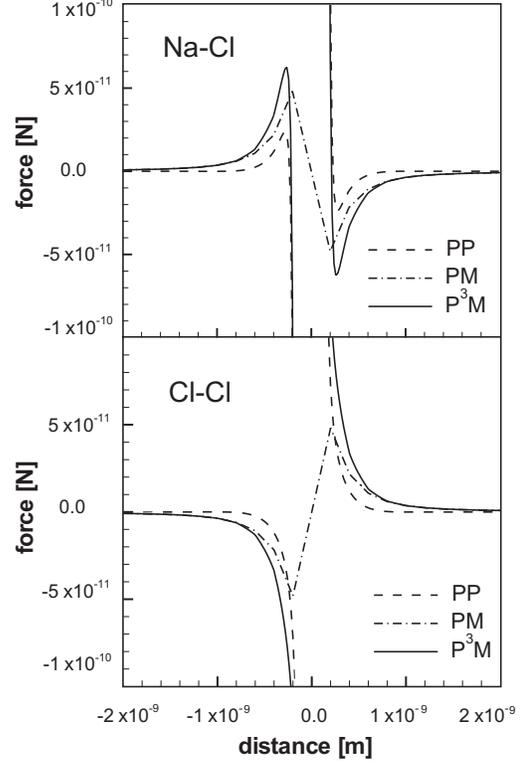


Figure 1: Electrostatic force between ions as a function of the interaction distance. The curves represent the models used for the computation: particle-particle (PP), particle-mesh (PM), and particle-particle-particle-mesh ( $P^3M$ ).

$$\mathbf{F}_i^{sr} = \sum_{\substack{j \in \Omega_i^{sr} \\ j \neq i}} \mathbf{F}_{ij}^{coul} + \mathbf{R}_{ij}, \quad (7)$$

where  $\mathbf{R}_{ij}$  is the so-called *reference force* [1], that is a correction that accounts for the charge double-counting arising by the overlap between the short-range domain and the whole simulated region [11].

The reference force  $\mathbf{R}_{ij}$  is a function of the interaction distance  $r_{ij}$  and of the radius  $r^{sr}$  of the short range region  $\Omega_i^{sr}$ . The extension of the short-range region has been chosen such that its radius  $r^{sr}$  spans at least two grid cells. It should be noted that the irregular nature of the grid implies a short-range radius which is not constant over the simulated domain.

Figure 1 shows the different components of the force between a  $\text{Na}^+$  and a  $\text{Cl}^-$  ion as a function of distance (upper plot), as well as the force between two  $\text{Na}^+$  ions (lower plot). The different contributions of the PM and PP solver are evident, as well as the repulsion of the electronic shells at very short ranges.

## 4 SIMULATION RESULTS

It is well known that thermal transport coefficient can be extracted from the simulation data by the time-

correlation function formalism [8]. An alternative route is provided by the Einstein relation, which is formally equivalent to the integration of the time correlation function [15].

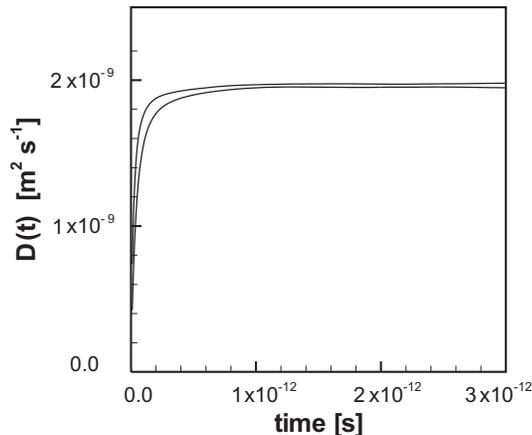


Figure 2: The diffusion coefficient for  $\text{Na}^+$  and  $\text{Cl}^-$  ions as a function of time as expressed in Eq. 9.

Indeed, for any dynamic variable  $G(t)$ , the following identities hold for a stationary process in three dimensions:

$$\begin{aligned} \theta &= \frac{3}{2t} \langle (G(t_0 + t) - G(t_0))^2 \rangle \\ &\approx \frac{3}{2} \frac{d}{dt} \langle (G(t_0 + t) - G(t_0))^2 \rangle \\ &= 3 \int_0^t \langle (\dot{G}(t_0 + t) \dot{G}(t_0)) \rangle dt'. \end{aligned} \quad (8)$$

The identities in Eq. 8 can be applied to the velocity by substituting  $\dot{G}(t)$  with  $\mathbf{v}(t)$ , and obtaining the following equation for the diffusion coefficient [10]

$$D(t) = \frac{3}{t} \langle (\mathbf{r}(t_0 + t) - \mathbf{r}(t_0))^2 \rangle \quad (9)$$

where it is understood that the infinite time limit is to be taken. Figure 2 shows the diffusion coefficient for a 0.1 molar concentration of  $\text{Na}^+$  and  $\text{Cl}^-$  as a function of time, as expressed by Eq. 9. The friction coefficient used in the simulation gives for  $D(t = \infty)$  the expected value of  $2 \times 10^{-9} \text{ [m}^2\text{s}^{-1}\text{]}$  (see Eq. 3) which is recovered by the statistical analysis of the ion dynamics, as shown in Fig. 2.

## 5 CONCLUSIONS

A self-consistent approach has been discussed for the particle-based simulation of ionic solutions. A P<sup>3</sup>M solver for the force equations has been coupled with a Brownian dynamics simulation engine for a fully three-dimensional solution cell with realistic boundary conditions.

## 6 ACKNOWLEDGMENTS

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