

Simulating ion channel inhibition in drug discovery

Master thesis proposal

Jan-Frederik Pietschmann Anna-Karin Tornberg

Ozan Öktem Lars Carlsson

1 Introduction

An important step in drug discovery is to predict/asses whether a compound inhibits an ion channel or not. This can either be part of the desired effect, but it can also be associated with side effects whose severeness depends on the ion channel that is inhibited. Such an inhibition can be assessed experimentally. On the other hand, a typical drug discovery project may involve a large number of compounds that will have to be tested against large number of ion channels, so a purely experimental approach quickly becomes unfeasible.

An alternative approach is to simulate the ion channel inhibition caused by a compound. This is currently part of predictive chemistry and the usual approach is based on Quantitative Structure–Activity Relationship (QSAR) which is purely data driven in the sense that one learns a model relating the compound properties to inhibition properties from experimental data using techniques from statistical learning. Such an approach does not explicitly take into consideration the physics governing the inhibition. Model learnt from data associated with a ion channel results in poor predictions when applied to other ion channels, so such a data driven approach requires a substantial amount of data, one data set for each type of ion channel. One can also consider simulating the inhibition based on first principles. This leads to molecular dynamics based approaches where one has to simulate large quantum mechanical systems for long time frames. Current approaches are neither computationally feasible nor are they accurate enough. Furthermore, such an approach requires an atomic model for the ion channel, which is rarely available.

The idea that underlies this masters thesis is to simulate ion channel inhibition based on a mesoscopic model. The model is phenomenological but it does abide by physics based principles that apply to the situation at hand. Another advantage with this approach is that it does not require an atomic model for the ion channel. Instead, the channel only needs to be described roughly.

2 The organization

The project is a collaboration between Anna-Karin Tornberg at the Numerical Analysis group, Department of Mathematics, KTH, Jan-Frederik Pietschmann at the Numerical Analysis and Scientific Computing group, Department of

Mathematics, Darmstadt University of Technology, Ozan Öktem at the Center for Industrial and Applied Mathematics, Department of Mathematics, KTH and Lars Carlsson at AstraZeneca.

Tornberg and Pietschmann will advise on numerical analysis related issues, Öktem will provide input on relating the simulation model to future inverse modeling attempts (not part of this master thesis project), and Carlsson will provide expertise on the chemistry, data pre-processing (compound docking), validation and experimental data for validation. The work will be pursued from KTH, but the person has the possibility to visit Pietschmann and Carlsson.

3 The model

The model is based on a class of partial differential equations that are used to describe the flow of ions through an ion channel. The most popular variant is the Poisson–Nernst–Planck (PNP) model which has originally been introduced in the context of electro-diffusion in semiconductors, cf. [5, 6, 4].

The basic idea is that the motion of ions is governed by a combination of diffusion (Brownian motion) and drift, the latter due to the electrostatic field generated by all charges present in the system. A more detailed derivation in the context of ion channels can be found for example in [8]. We consider two different types of ions c_1 and c_2 , with c_1 positively and c_2 negatively charged. The corresponding concentrations $c_i = c_i(x, t)$, $i = 1, 2$ at position x and time t under an electrostatic potential $V = V(x, t)$ can be modeled by the (scaled) classical PNP model

$$\partial_t c_1 = \nabla \cdot (D_1(\nabla c_1 - c_1 \nabla V)), \quad (1a)$$

$$\partial_t c_2 = \nabla \cdot (D_2(\nabla c_2 + c_2 \nabla V)), \quad (1b)$$

$$-\Delta V = -c_1 + c_2 + c_{\text{perm}}. \quad (1c)$$

Here D_i denotes the diffusion coefficients and c_{perm} is a given function modeling permanent charges in the channel. This model does not account for finite volume effect which can occur when the density inside the narrow channel becomes very high. To this end, a non-linear variant has been derived and analyzed, cf. [2, 3]

$$\partial_t c_1 = \nabla \cdot (D_1((1 - \rho)\nabla c_1 + c_1 \nabla \rho - c_1(1 - \rho)\nabla V)), \quad (2a)$$

$$\partial_t c_2 = \nabla \cdot (D_2((1 - \rho)\nabla c_2 + c_2 \nabla \rho + c_2(1 - \rho)\nabla V)), \quad (2b)$$

$$-\Delta V = -c_1 + c_2 + c_{\text{perm}}, \quad (2c)$$

with $\rho = c_1 + c_2$. Both models are supplemented with mixed boundary conditions consisting of a Dirichlet and a no-flux part, i.e.

$$\begin{aligned} c_i(x) &= c_i^D, & \text{on } \Gamma_D, \\ V(x) &= V^D, & \text{on } \Gamma_D, \\ \partial_n c_i &= \partial_n V = 0, & \text{on } \partial\Omega \setminus \Gamma_D \end{aligned}$$

The goal of both models is to predict the flux, either given by

$$j_{\text{PNP}} := \sum_{i=1,2} \int_{\Gamma_D} D_i(\partial_n c_i - c_i \partial_n V), \quad (3)$$

or, for the non-linear model by

$$j_{\text{NPNP}} := \sum_{i=1,2} \int_{\Gamma_D} D_i ((1 - \rho) \partial_n c_i + c_i \partial_n \rho - c_i (1 - \rho) \partial_n V). \quad (4)$$

4 Thesis topics

Depending on the background of the student, a combination of these topics could be covered in the thesis.

4.1 Implementation of numerical schemes

In the literature, several discretization schemes of (1) are proposed, see [5]. One possibility is to apply a Newton scheme to the complete system (1) or (2), respectively. To facilitate the solution of the resulting linear system, various block iteration algorithms have been proposed. Most often, so-called Gummel-type methods are used. In two space dimension, so-called exponential fitting methods can be used as well, cf. [1].

4.2 Convergence

In [7], a convergence proof for two different finite element discretization of (1) is given. The discretization is based on an Entropy functional which decreases during the evolution of the PNP system. It would be interesting to see whether this analysis can be used to prove converge for the nonlinear system (2). To make this problem more accessible, one could start with a given potential (e.g. neglect the Poisson equation) and one species which yields

$$\partial_t c_1 = \Delta c_1 + \nabla \cdot (c_1 (1 - c_1) \nabla V).$$

4.3 Numerical study of the flux dependence on the area function $a(x)$

For possible applications in drug discovery, it is of interest to study how the flux measurements (3) or (4), respectively, are influenced by the geometry of the domain Ω . To this end, one has to scale the equations appropriately to account for the dimensions of the hERG ion channel that is of interest for AstraZeneca. The simplest approach is to start with a reduced one dimensional model given by, cf. [3],

$$\partial_t c_1 = \partial_x (D_1 a(x) (\partial_x c_1 - c_1 \partial_x V)), \quad (5a)$$

$$\partial_t c_2 = \partial_x (D_2 a(x) (\partial_x c_2 + c_2 \partial_x V)), \quad (5b)$$

$$-\partial_x (a(x) \partial_x V) = a(x) (c_1 + c_2 + c_{\text{perm}}). \quad (5c)$$

This can be derived from the 3d model if the domain is cylindric. Here the so-called area function $a = a(x)$ accounts for the area of the three-dimensional cylinder. The idea is to use the numerical codes to empirically study the dependence of the flux j on the function a . From AstraZeneca flux measurements for an empty, open channel are available and could be used to estimate parameters in the model (e.g. permanent charge, area). This could be done for both the linear and non-linear model.

References

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