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Coarse grained model for exploring voltage dependent ion channels ☆

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ABSTRACT

The relationship between the membrane voltage and the gating of voltage activated ion channels and other systems have been a problem of great current interest. Unfortunately, reliable molecular simulations of external voltage effects present a major challenge, since meaningful converging microscopic simulations are not yet available and macroscopic treatments involve major uncertainties in terms of the dielectric used and other key features. This work extends our coarse grained (CG) model to simulations of membrane/protein systems under external potential. Special attention is devoted to a consistent modeling of the effect of external potential due to the electrodes, emphasizing semimacroscopic description of the electrolytes in the solution regions between the membranes and the electrodes, as well as the coupling between the combined potential from the electrodes plus the electrolytes and the protein ionized groups. We also provide a clear connection to microscopic treatment of the electrolytes and thus can explore possible conceptual problems that are hard to resolve by other current approaches. For example, we obtain a clear description of the charge distribution in the entire electrolyte system, including near the electrodes in membrane/electrodes systems (where continuum models do not seem to provide the relevant results). Furthermore, the present treatment provides an insight on the distribution of the electrolyte charges before and after equilibration across the membrane, and thus on the nature of the gating charge. The different aspects of the model have been carefully validated by considering problems ranging for the simple Debye–Huckel, and the Gouy–Chapman models to the evaluation of the electrolyte distribution between two electrodes, as well as the effect of extending the simulation system by periodic replicas. Overall the clear connection to microscopic descriptions combined with the power of the CG modeling seems to offer a powerful tool for exploring the balance between the protein conformational energy and the interaction with the external potential in voltage activated channels. To illustrate these features we present a preliminary study of the gating charge in the voltage activated Kv1.2 channel, using the actual change in the electrolyte charge distribution rather than the conventional macroscopic estimate. We also discuss other special features of the model, which include the ability to capture the effect of changes in the protonation states of the protein residues during the close to open voltage induced transition. This article is part of a Special Issue entitled: Membrane protein structure and function.

1. Introduction

The detailed relationship between the external voltage and the gating of voltage activated ion channels is a problem of great current interest [1–8]. Unfortunately, despite great progress in structural and biophysical studies [1–3,9,10], we still do not have a clear picture of the corresponding structure–function correlation. Furthermore, although there has been a significant progress in computational modeling of ion channels and even some understanding of ion selectivity [11–19], the understanding of the gating process has been limited. Not only that the exact structural changes have not been elucidated but also the energetics of the conformational transition and the coupling to the external voltage are far from being understood. In fact, despite several attempts to analyze these issues by molecular simulations [20–22] we still do not have clear understanding about the nature of the gating and the corresponding energy balance. That is, the simulation time does not allow for sufficient convergence of the free energy associated with very large conformational changes in such a large protein membrane system. Thus the system does not render itself to conclusive brute force simulations. We believe that at present the best option is to use coarse grained (CG) modeling that uses effective surfaces with much fewer minima and traps than the fully atomistic surface and can capture properly the interplay between the external voltage and the ion channel.

A part of the problem of modeling voltage activated ion channels involves the modeling of the effect of the change of the protein conformation on the ion current. Macroscopic models have studied the

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nature of the ion current in the open channel, but the corresponding relationship to the actual protein structure has not been completely clear. Attempts to do so with microscopic models have resulted in free energy profiles for a single ion transfer and some information on multiple ion transfer [14–16]. However, the overall selectivity current has not been reproduced by any microscopic model and the nature of the selectivity has not been properly evaluated. At present it seems to us that semimacroscopic studies with a realistic electrostatic treatment have provided arguably the most effective way for exploring multi-ion current [17] and providing a probable explanation for the origin of the observed selectivity (attributing it in part to the change in the effective ion–ion repulsion) see [11]. As far as the effect of moving to the closed structure is concerned, to the best of our knowledge the first calculation of the energetics of ion transfer in the closed channel has been reported in the semimacroscopic model of [17] (who has noted that the profile for the KcsA channel corresponds to a closed channel).

Now, despite the relative progress in modeling ion current, the situation is much less promising in studies of the effect of the external potential. That is, there has been interesting Poisson–Boltzmann (PB) macroscopic studies that evaluated the gating charges [23], but the results reflect a macroscopic perspective that may lead to traps as was the case in early studies of electrostatic effects in proteins (see review in [24]). Furthermore, although there are recent microscopic attempts [20], they are either based on assuming a linear potential in the protein membrane region, or on free energy calculations that are unlikely to provide fully convergent results due both to the challenge of obtaining stable solvation free energies in protein interiors and the difficulties in capturing the response of the ionic atmosphere by microscopic simulations (see discussion in Section 3).

As stated above, another major challenge in the field is the evaluation of the energetics of the conformational changes of the channel upon voltage activation. Here the application of brute force microscopic simulations is unlikely to provide converging results of the relevant potential of mean force (PMF) in the near future.

In view of the above challenges it seems to us that CG models provide one of the best option for progressing in this field. Thus we have developed and refined in this work a CG model for simulations of membrane proteins in the presence of external potential (electrodes) and electrolyte solution. This includes the development of a semimacroscopic way for modeling the electrolyte solution between the membrane and the electrodes. Special emphasis is dedicated to a consistent modeling of the effect of external potential, focusing on a realistic description of the electrolytes in the solution regions between the membrane and the electrodes, as well as the coupling between the combined potential from the electrodes plus the electrolyte and the protein ionized groups. The model provides a clear connection to the fully microscopic treatment of the electrolytes and thus allows us to explore possible conceptual problems that are hard to resolve by other approaches. This includes the ability to obtain a clear description of the electrolyte charge distribution in systems that contains the membrane and electrodes (including near the electrodes, where continuum models do not seem to provide the relevant result). Furthermore, the model allows us to evaluate the distribution of the electrolytes before and after the equilibration between both sides of the membrane, and thus the nature of the gating current. The clear connection to the microscopic description, combined with the power of the CG modeling, offers a powerful tool for exploring the balance between the protein conformational energy and the interaction with the external potential in voltage activated channels. This tool is validated here on several levels and is also used to explore some key features of the Kv1.2 voltage activated channel.

2. Methods

Our general strategy involves refinement of our recently developed CG model and the extension of this model to incorporate the electrodes/electrolytes components in the simulation of the protein/membrane system. The main features of the model are described below.

2.1. General features of the coarse grained (CG) model

The present work uses a CG model that describes the main chains by an explicit model and the side chains by a simplified united atom model. This CG model, which is a modified version of the model used in our recent works [25–27], provides a more advanced treatment of the electrostatic effects than most current CG models. Our model expresses the overall free energy (in kcal/mol) as:

$$\Delta G_{total} = \Delta G_{main} + \Delta G_{main,side} + \Delta G_{side}. \quad (1)$$

The main chain atoms are represented explicitly with implicit solvent treatment, while the main-side interaction involves van der Waals and screened electrostatic terms [26]. The major and most relevant part of our CG treatment comes from the ΔG_{side} term, which is given by:

$$\Delta G_{side} = \Delta G_{side}^{vdw} + \Delta G_{side}^{elec} + \Delta G_{side}^{hyd} \quad (2)$$

where the first term describes the effective van der Waals interactions between simplified side chains and is described in details in ref. [26]. The second term represents the electrostatic interactions between the ionizable residues (see below) and the last term represents the hydrophobic contributions which are not included implicitly in the first term (see below). The ΔG_{side}^{elec} term is given by:

$$\Delta G_{side}^{elec} = -2.3RT \sum_i Q_i \left(pK_{a,i}^{w} - pH \right) + \Delta G_{QQ} + \Delta G^{self,ion} + \Delta G_p^{self} \quad (3)$$

where i runs over the protein ionized residues, $pK_{a,i}^{w}$ is the pK_a of the ith residue in water and Q_i is the charge of the ith residue in the given ionization state. Here "ion" and "p" designate, respectively, ionized and polar residues, where each residue can have only one of these two contributions (note that the polar term has not been used in our previous works). The ΔG_{QQ} term represents the charge–charge interaction free energy, which is given by:

$$\Delta G_{QQ} = 332 \sum_{i<j} \frac{Q_i Q_j}{r_{ij} \varepsilon_{eff}} \quad (4)$$

where the free energy is given in kcal/mol, the charge–charge distances (r) in Å and the charges (Q) in electronic charge units. ε_{eff} is the effective dielectric for charge–charge interaction, which reflects the idea established in many of our earlier works (e.g. refs. [28,29]) that the optimal value of ε_{eff} is large even in protein interiors (namely $\varepsilon_{eff} > 20$). This type of dielectric has been found recently to provide very powerful insight in studies of protein stability (see refs. [28,30]). The ionization state of the protein residues were determined by a Monte Carlo approach of ref. [26] for the given pH.

A key element in our approach is the treatment of the self energy, $\Delta G^{self,ion}$, associated with charging each ionized group in its specific environment. This term is given by

$$\Delta G^{self,ion} = \sum_i \left(U_{np}^{self,ion}\left(N_{np}^i\right) + U_p^{self,ion}\left(N_p^i\right) + U_{mem}^{self,ion}\left(N_{mem}^i\right) \right) \quad (5)$$

where U designates an effective potential and i runs over all ionized residues (designated by "ion"). $U_{np}^{self,ion}$, $U_p^{self,ion}$ and $U_{mem}^{self,ion}$ are the contributions to the self-energy from nonpolar residues, polar residues and membrane grid points, respectively. Here, N_{np}^i, N_p^i and N_{mem}^i are, respectively, the effective number of nonpolar residues, polar residues and membrane atoms in the neighborhood of the ith residue. Note that the nonpolar contribution for the membrane is