

372f Probing Ion Energetics in the Gramicidin A Channel Using Non-Additive Force Fields

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The quantitative prediction of ionic conductance through simple model ion channels, and in particular, single ion channels such as the bacterial Gramicidin A potassium channel, has proven elusive via the use of molecular simulation methodologies, such as fully atomistic molecular dynamics simulations coupled to continuum transport theories. Recently, Allen and coworkers (1) computed the maximum potassium ion conductance for Gramicidin A to be 0.8 pS, roughly one-third of the experimental value of 21 pS. Fundamentally, this conductance is governed, in part, to the underlying free energy surface for the passage of the ion from bulk solution, through the channel, and into the cytoplasmic milieu. The authors claim, as well as authors of other recent studies(2), that perhaps a more physical picture of the interactions governing the dynamics of ion and water passage through the channel would allow a more quantitative description of the macroscopic transport. In essence, it has been suggested that accounting for the differing environments encountered by ion and water along this passage, as described by polarization effects, for instance, may be sufficient to yield accurate free energy profiles leading to quantitative predictions of ion energetics.

In this talk, we will discuss our efforts in validating and applying polarizable, non-additive, force fields to membrane and membrane-protein systems. Our singular focus will be on the Gramicidin A channel. We will present results of calculations of the free energy profile, or equivalently, the potential of mean force, for potassium ion translocation through the channel. Our model systems allow for polarization of the solvent (based on the TIP4P-FQ model of Rick et al (3)) and the protein (based on a fluctuating charge model developed in our lab, Patel et al (4)). The results suggest a lowering of the internal free energy barrier by roughly 2 kcal/mol, leading to a higher conductance.

Finally, we will discuss properties of the membrane, solvent, and protein resulting from the use of a polarizable force field allows and which are not necessarily observed with conventional fixed-charge force fields widely used today.

References:

(1) T. W. Allen, O. S. Andersen, and B. Roux. PNAS, 101, #1, 2004. pp. 117-122. (2) T. W. Allen, T. Bastug, S. Kuyucak, and S. H. Chung. Biophys. J. 84, 2003. pp. 2159 – 2168. (3) S. W. Rick, S. J. Stuart, B. J. Berne. J. Chem. Phys. 101(7), 1994. pp. 6141-6156. (4) S. Patel and C. L. Brooks, III. J. Comp. Chem. 25, 2004. pp. 1-15.