Computer Simulation of Biological Ion Channels

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This thesis is my own original work, however it incorporates material which has been previously published in scientific papers of which I am a joint author (see the list of publications). My main role in the collaborative project which this thesis describes was the design, implementation, and testing of the algorithms for solving Poisson's equation. Thus I am primarily responsible for the work described in chapters 3, 4, and 6, except for the derivation of the analytical solution described in section 4.1, for which Serdar Kuyucak is primarily responsible. I participated in all aspects of the project, including making improvements to the Brownian dynamics techniques described in chapter 5, designing the model channels, and helping to analyze and understand the results described in chapters 5, 7, and 8, for instance by developing the technique for generating multi-ion energy profiles. Chapters 1, 2, and 9, as well as the discussion sections in chapters 5, 7, and 8, are newly written for this thesis. They represent my own interpretation of the results of the simulations, and my own views on the aims and significance of the project and possible future directions.

Matthew Hoyles

To my parents

Acknowledgments

Thanks to my supervisors, Serdar Kuyucak and Shin-Ho Chung, for their patience and understanding. Thanks to my other collaborators, Toby Allen and Sandy Li, for helping to make the project a success. Thanks to Janey Wood for helping to prepare the figures for this thesis. Thanks to my brother, Daniel Hoyles, and Arrow Consulting, for paying me a retainer when the money ran out. And finally, thanks to my parents, for their unfailing support over the years. This thesis is dedicated to them.

Abstract

This thesis describes a project in which algorithms are developed for the rapid and accurate solution of Poisson's equation in the presence of a dielectric boundary and multiple point charges. These algorithms are then used to perform Brownian dynamics simulations on realistic models of biological ion channels. An iterative method of solution, in which the dielectric boundary is tiled with variable sized surface charge sectors, provides the flexibility to deal with arbitrarily shaped boundaries, but is too slow to perform Brownian dynamics. An analytical solution is derived, which is faster and more accurate, but only works for a toroidal boundary. Finally, a method is developed of pre-calculating solutions to Poisson's equation and storing them in tables. The solution for a particular configuration of ions in the channel can then be assembled by interpolation from the tables and application of the principle of superposition. This algorithm combines the flexibility of the iterative method with greater speed even than the analytical method, and is fast enough that channel conductance can be predicted. The results of simulations for a model single-ion channel, based on the acetylcholine receptor channel, show that the narrow pore through the low dielectric strength medium of the protein creates an energy barrier which restricts the permeation of ions. They further show that this barrier can be removed by dipoles in the neck of the channel, but that the barrier is not removed by shielding by counter-ions. The results of simulations for a model multi-ion channel, based on a bacterial potassium channel, show that the model channel has conductance characteristics similar to those of real potassium channels. Ions appear to move through the model multi-ion channel via rapid transitions between a series of semi-stable states. This observation suggests a possible physical basis for the reaction rate theory of channel conductance, and opens up an avenue for future research.

List of Publications

Hoyles, M., S. Kuyucak, and S.-H. Chung. 1996. Energy barrier presented to ions by the vestibule of the biological membrane channel. *Biophys. J.* 70:1628–1642.

Kuyucak, S., M. Hoyles, and S.-H. Chung. 1998. Analytical solutions of Poisson's equation for realistic geometrical shapes of membrane ion channels. *Biophys. J.* 74:22–36.

Li, S. C., M. Hoyles, S. Kuyucak and S.-H. Chung. 1998. Brownian dynamics study of ion transport in the vestibule of membrane channels. *Biophys. J.* 74:37–47.

Hoyles, M., S. Kuyucak, and S.-H. Chung. 1998a. Computer simulation of ion conductance in membrane channels. *Phys. Rev. E.* 58:3654–3661.

Hoyles, M., S. Kuyucak, and S.-H. Chung. 1998b. Solutions of Poisson's equation in channel-like geometries. *Computer Phys. Commun.* 115:45–68.

Chung, S.-H., M. Hoyles, T. W. Allen, and S. Kuyucak. 1998. Study of ionic currents across a model membrane channel using Brownian dynamics. *Biophys. J.* 75:793–809.

Chung, S.-H., T. W. Allen, M. Hoyles, and S. Kuyucak. 1999. Permeation of ions across the potassium channel: Brownian dynamics studies. *Biophys. J.* 77:2517–2533.

Allen, T. W., M. Hoyles and S. Kuyucak, and S.-H. Chung. 1999. Molecular and Brownian dynamics study of ion selectivity and conductivity in the potassium channel. *Chem. Phys. Lett.* 313:358-365.

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