Computer Simulation of Biological Ion Channels

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A thesis submitted for the degree of Doctor of Philosophy of The Australian National University
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

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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


# Contents

1 Ion Channels .......................... 1
   1.1 The Role of Ion Channels .......... 4
   1.2 Ion Channel Function ............. 7
   1.3 Ion Channel Structure ............ 10

2 Conductance Theories ................. 15
   2.1 Reaction Rate Theory ............. 16
   2.2 Molecular Dynamics ............... 20
   2.3 Ab Initio Molecular Dynamics ...... 22
   2.4 Poisson-Nernst-Planck Theory ...... 23
   2.5 Brownian Dynamics ............... 27

3 Iterative Method ...................... 31
   3.1 Macroscopic Theory of Electrostatics ........ 32
      3.1.1 Poisson’s Equation .......... 32
      3.1.2 Born Energy ................. 35
      3.1.3 Induced Surface Charge ...... 36
      3.1.4 Limitations of Macroscopic Electrostatics .... 37
   3.2 Outline Generation ................ 40
   3.3 Tiling the Boundary .............. 43
      3.3.1 Sector Spacing .............. 47
      3.3.2 Ring Generation .............. 48
      3.3.3 Sector Generation .......... 51
   3.4 Iterative Algorithm .............. 51
      3.4.1 Basic Algorithm ............ 51
      3.4.2 Convergence ................. 53
      3.4.3 Pre-Calculation of Interactions .... 53
   3.5 Curvature Compensation .......... 54
   3.6 Testing and Performance .......... 58

4 Analytical Method .................... 63
   4.1 Analytical Solution .............. 63
      4.1.1 Toroidal Coordinates ...... 63
## CONTENTS

4.1.2 Solutions of Laplace’s and Poisson’s Equations .... 66  
4.1.3 Solution of the Difference Equation ............ 69  
4.1.4 Application of External Electric Field .......... 71  
4.1.5 Calculation of Force and Potential Energy ....... 72  
4.2 Algorithm .................................. 72  
4.2.1 Legendre Functions .................... 73  
4.2.2 Boundary ............................. 74  
4.2.3 Charges .......................... 75  
4.2.4 Potentials ............................ 76  
4.2.5 Conversion of Derivatives ................ 77  
4.2.6 Charges Inside the Boundary .............. 77  
4.3 Testing ..................................... 77  

5 Brownian Dynamics ........................................ 83  
5.1 Model ................................ .......... 83  
5.1.1 Shape of the Channel .................. 83  
5.1.2 Water as a Continuum ................. 84  
5.1.3 Smooth Water-Protein Interface .......... 84  
5.1.4 Dipole Rings .......................... 85  
5.1.5 Applied Electric Field ................. 85  
5.2 Theory .......................................... 86  
5.2.1 Langevin Equation .................... 86  
5.3 Methods .......................................... 88  
5.3.1 Algorithm ................................. 88  
5.3.2 Reflective Boundaries ................ 89  
5.3.3 Physical Parameters .................... 89  
5.3.4 Testing .......................... 90  
5.4 Results .......................................... 93  
5.4.1 Repulsive Dielectric Force ............. 93  
5.4.2 Dipoles in the Transmembrane Segment ...... 96  
5.4.3 Permeation of Ion Through the Channel ...... 96  
5.4.4 Trajectory of Ions .................... 99  
5.5 Discussion .................................... 99  

6 Lookup Table Method .................................... 103  
6.1 Components of the Potential .................... 103  
6.2 Generalized Coordinates ...................... 104  
6.3 Lookup Algorithm ............................. 105  
6.4 Testing .......................................... 106  
6.5 Performance .............................. 107
CONTENTS

7 Single-Ion Channel 113

7.1 Model .................................. 113
  7.1.1 Shape of the Channel ................. 113
  7.1.2 Dipoles in the Protein Wall ............ 113
  7.1.3 Energy Barrier in the Transmembrane Segment .... 115
  7.1.4 Applied Electric Field ................. 115

7.2 Theory ................................ 116
  7.2.1 Pöschl-Teller Function ................. 116
  7.2.2 Michaelis-Menten Equation .............. 116

7.3 Methods .............................. 117
  7.3.1 Stochastic Boundaries .................. 117
  7.3.2 Short Timestep Algorithm ............... 117
  7.3.3 Procedure for Calculating Conductance .......... 119

7.4 Results ............................... 119
  7.4.1 Dipoles in the Channel ................. 119
  7.4.2 Ionic Concentrations in the Channel ...... 121
  7.4.3 Current-Voltage Relationships .......... 125
  7.4.4 Conductance-Concentration Curve .......... 129

7.5 Discussion ............................ 131

8 Multi-Ion Channel 133

8.1 Model .................................. 135
  8.1.1 Shape of the Channel ................. 136
  8.1.2 Dipoles ............................ 137
  8.1.3 Brownian Dynamics .................... 138
  8.1.4 Dielectric Constant ................... 139

8.2 Methods .............................. 140
  8.2.1 Energy Profiles ....................... 140

8.3 Results ............................... 140
  8.3.1 Dipoles and Energy Profiles ............. 140
  8.3.2 Dependence of Conductance on Dipole Strengths ... 143
  8.3.3 Effects of Dielectric Constant and Diffusion Coefficient on Currents .... 146
  8.3.4 Current-Voltage Relationships .......... 149
  8.3.5 Ions in the channel .................... 153
  8.3.6 Conductance-Concentration Relationships .... 155

8.4 Discussion ............................ 157

9 Conclusion 163

Bibliography 167
## List of Figures

3.1 Channel outlines .............................................. 41
3.2 Catenary and bicone parameters ............................... 44
3.3 Torus and cylinder parameters .................................. 45
3.4 Effect of changing channel parameters .......................... 46
3.5 Sector spacing for a catenary channel ........................... 50
3.6 Centreline potential energy profiles .............................. 59
3.7 Offset potential energy and force profiles ....................... 60

4.1 Toroidal coordinate system ...................................... 64
4.2 Accuracy of the analytical method ................................. 79
4.3 Accuracy of the iterative method ................................ 80

5.1 Test of the Brownian dynamics algorithm: mean-square dis-
placements .............................................................. 91
5.2 Test of the Brownian dynamics algorithm: velocity functions 92
5.3 Ejection of ions from the vestibule ............................... 94
5.4 Repulsive dielectric force and applied electric field ......... 95
5.5 Cancellation of repulsive force by dipoles ....................... 97
5.6 Permeation of sodium ions across the channel .................. 98
5.7 The path of ions ...................................................... 100

6.1 Testing of the lookup table method: parallel trajectory .......... 108
6.2 Testing of the lookup table method: radial trajectory, $z = 0$ . 109
6.3 Testing of the lookup table method: radial trajectory, $z = 30$ . 110

7.1 Idealized biological ion channel ................................ 114
7.2 Changes in the potential profile with dipole strength .......... 120
7.3 Channel conductance as a function of dipole strength ........... 122
7.4 Concentrations of sodium and chloride ions in the channel ... 123
7.5 Concentrations of sodium and chloride ions in the channel in 
the presence of a membrane potential $E$ .......................... 124
7.6 Concentrations of sodium and chloride ions in the channel in 
the presence of two dipole rings .................................. 126
7.7 Concentrations of sodium and chloride ions in the presence of
dipoles and an applied electric field .............................. 127
LIST OF FIGURES

7.8 Current-voltage relationships obtained with symmetrical solutions ........................................... 128
7.9 Conductance-concentration curve .......................................................... 130

8.1 Idealized potassium channel ................................................................. 136
8.2 Electrostatic energy profile of a potassium ion traversing the channel ..................................... 141
8.3 Changes in channel conductance with the strength of carbonyl groups .................................... 144
8.4 Changes in channel conductance with the strength of mouth dipoles and helix dipoles .......... 145
8.5 Effects of the effective dielectric constant on conductance .................................................... 147
8.6 Effects of the diffusion coefficient on conductance ............................................................. 148
8.7 The current-voltage relationships: symmetrical solutions ...................................................... 150
8.8 The current-voltage relationships: asymmetric solutions ....................................................... 151
8.9 Concentrations of potassium ions in the channel ............................................................... 154
8.10 The conductance-concentration curves .................................................................................. 156