Title
Particle dynamics in nanopore systems

Permalink
https://escholarship.org/uc/item/035178cn

Author
Krems, Matthew A.

Publication Date
2011

Peer reviewed|Thesis/dissertation
UNIVERSITY OF CALIFORNIA, SAN DIEGO

Particle Dynamics in Nanopore Systems

A dissertation submitted in partial satisfaction of the requirements for the degree
Doctor of Philosophy

in

Physics

by

Matthew A. Krems

Committee in charge:

Professor Massimiliano Di Ventra, Chair
Professor Prabhakar Bandaru
Professor Olga Dudko
Professor Clifford Kubiak
Professor Oleg Shpyrko

2011
Copyright
Matthew A. Krems, 2011
All rights reserved.
The dissertation of Matthew A. Krems is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

Chair

University of California, San Diego

2011
DEDICATION

To my mom
Live as if you were to die tomorrow, learn as if you were to live forever.
—Gandhi
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature Page</td>
<td>iii</td>
</tr>
<tr>
<td>Dedication</td>
<td>iv</td>
</tr>
<tr>
<td>Epigraph</td>
<td>v</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>vi</td>
</tr>
<tr>
<td>List of Figures</td>
<td>viii</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>x</td>
</tr>
<tr>
<td>Vita and Publications</td>
<td>xi</td>
</tr>
<tr>
<td>Abstract of the Dissertation</td>
<td>xii</td>
</tr>
<tr>
<td><strong>Chapter 1</strong>              Introduction</td>
<td>1</td>
</tr>
<tr>
<td><strong>Chapter 2</strong>              Nanopores and Electrolytic Solutions</td>
<td>5</td>
</tr>
<tr>
<td>2.1 Biological Nanopores</td>
<td>7</td>
</tr>
<tr>
<td>2.2 Synthetic Nanopores</td>
<td>8</td>
</tr>
<tr>
<td>2.3 Electrolytic Solutions</td>
<td>9</td>
</tr>
<tr>
<td><strong>Chapter 3</strong>              Molecular Dynamics</td>
<td>17</td>
</tr>
<tr>
<td>3.1 The Force Field</td>
<td>18</td>
</tr>
<tr>
<td>3.1.1 Non-bonded Interactions</td>
<td>18</td>
</tr>
<tr>
<td>3.1.2 Bonded Interactions</td>
<td>20</td>
</tr>
<tr>
<td>3.1.3 Force Field Parameters and NAMD Files</td>
<td>21</td>
</tr>
<tr>
<td>3.2 Anatomy of a Nanopore for Molecular Dynamics Simulations</td>
<td>23</td>
</tr>
<tr>
<td>3.3 Profile of a NAMD Run</td>
<td>30</td>
</tr>
<tr>
<td>3.3.1 Minimization</td>
<td>31</td>
</tr>
<tr>
<td>3.3.2 Equilibration</td>
<td>31</td>
</tr>
<tr>
<td>3.3.3 Simulations with an External Electric Field</td>
<td>32</td>
</tr>
<tr>
<td><strong>Chapter 4</strong>              Scattering Approach to Electronic Transport</td>
<td>34</td>
</tr>
<tr>
<td>4.1 Landauer Transport</td>
<td>35</td>
</tr>
<tr>
<td><strong>Chapter 5</strong>              Effect of Noise on DNA Sequencing via Transverse Electronic Transport</td>
<td>39</td>
</tr>
<tr>
<td>5.1 Setup and Methods</td>
<td>42</td>
</tr>
<tr>
<td>5.1.1 Noise</td>
<td>47</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2.1</td>
<td>Model of an α-hemolysin nanopore</td>
</tr>
<tr>
<td>2.2</td>
<td>Potential drop across a nanopore</td>
</tr>
<tr>
<td>2.3</td>
<td>The time-averaged density of water molecules in a 7 Å radius cylindrical nanopore under the influence of the electric field</td>
</tr>
<tr>
<td>2.4</td>
<td>Relationship between ionic conductance and temperature for nanopore systems and those without nanopores</td>
</tr>
<tr>
<td>3.1</td>
<td>The Leonard-Jones potential</td>
</tr>
<tr>
<td>3.2</td>
<td>Bonded interactions</td>
</tr>
<tr>
<td>3.3</td>
<td>Unit cell of $\beta$-Si$_3$N$_4$</td>
</tr>
<tr>
<td>3.4</td>
<td>A top down view of the unit cell of $\beta$-Si$_3$N$_4$ replicated five times in each direction</td>
</tr>
<tr>
<td>3.5</td>
<td>Si$_3$N$_4$ crystal cut for use with periodic boundary conditions and with a nanopore</td>
</tr>
<tr>
<td>3.6</td>
<td>Side view of conical pore used in molecular dynamics simulations</td>
</tr>
<tr>
<td>3.7</td>
<td>View of double-stranded DNA</td>
</tr>
<tr>
<td>3.8</td>
<td>The volume of the cell during equilibration</td>
</tr>
<tr>
<td>4.1</td>
<td>A schematic view of the transport problem</td>
</tr>
<tr>
<td>5.1</td>
<td>Schematic representation of ss-DNA translocating through a nanopore while the transverse electronic current is collected</td>
</tr>
<tr>
<td>5.2</td>
<td>Currents as a function of time across two pairs of perpendicularly placed electrodes for poly(C)$_{15}$ with one base originally aligned parallel to a pair of opposite electrodes</td>
</tr>
<tr>
<td>5.3</td>
<td>Transverse current versus time for poly(A)$_{15}$ at a transverse bias voltage of 1.0 V</td>
</tr>
<tr>
<td>5.4</td>
<td>Probability distributions for poly(A)$_{15}$ with various noise timescales for a transverse bias voltage of 1.0 V</td>
</tr>
<tr>
<td>5.5</td>
<td>Current distributions of a model system for the Adenine nucleotide represented by a single energy level</td>
</tr>
<tr>
<td>5.6</td>
<td>Normalized current distributions for the four nucleotides at a transverse bias voltage of 1.0 V and 0.1 V</td>
</tr>
<tr>
<td>5.7</td>
<td>Current distributions and associated error</td>
</tr>
<tr>
<td>6.1</td>
<td>A snapshot of the molecular dynamics geometry at a time when a buildup of charges of the opposite sign on each side of the nanopore is observed due to a finite electric field along with a simplified equivalent circuit model</td>
</tr>
<tr>
<td>6.2</td>
<td>Net charge on the surface of the nanopore and voltage across the nanopore plotted as a function of time</td>
</tr>
</tbody>
</table>
Figure 6.3: Net charge of the positively charged side of the capacitor vs. time when a constant 20 V applied voltage responsible for the accumulation of the charges on the surface of the pore is turned off ................................. 66
Figure 6.4: Net charge versus a periodic voltage of amplitude $V_0 = 1$ V and different frequencies along with the capacitance versus the voltage 68
Figure 6.5: Memcapacitive effects due to ionic transport across the pore . . 70
Figure 6.6: The predicted current of the model versus the actual current we obtain from our molecular dynamics simulations .......................... 72
Figure 7.1: Schematic for ionic Coulomb blockade and density plot ....... 76
Figure 7.2: Current as a function of concentration and voltage from a rate equation model ............................................................... 80
Figure 7.3: Current as a function of concentration from molecular dynamics 82
Figure 7.4: Current as a function of voltage from molecular dynamics . . 82
Figure 7.5: Residence times for K$^+$ and Cl$^-$ ions ............................ 83
ACKNOWLEDGEMENTS

First of all, I want to thank my advisor, Professor Massimiliano Di Ventra. From the very beginning, he has pushed me to achieve my best, and the lessons from this will carry on for the rest of my life.

I would also like to thank my collaborators, Mike Zwolak and Yuriy Pershin, who have been a great pleasure to work with. Many thanks also go to fellow group members, past and present, Neil Bushong, Johan Lagerqvist, and Jim Wilson.

I feel truly lucky to have had such great officemates over the years, who have not only helped me to broaden and deepen my knowledge of physics, but also have become great friends. I want to thank Yonatan Dubi, Heiko Appel and Alexander Stotland.

Thanks go to JJ, John and Mary Jane, who have been, in every sense of the words, my San Diego family. Also, I want to thank my friends Jonathan, Alex, Tyler, and Chris who have helped to make my time in San Diego more enjoyable than it otherwise would have been.

Finally, I want to thank my mother, Deborah, and friend, Stephanie. The two of them have always been there for me and believed in me even when I did not believe in myself. Their support and encouragement has helped me to get to where I am today.

Chapter 5 is in part a reprint of the material as it appears in Matt Krems, Yuriy V. Pershin, Mike Zwolak, and Massimiliano Di Ventra, “Effect of Noise on DNA Sequencing via Transverse Electronic Transport,” Biophysical Journal 97, 1990 (2009). The dissertation author was the primary investigator of this paper.

Chapter 6 is in part a reprint of the material as it appears in Matt Krems, Yuriy V. Pershin, and Massimiliano Di Ventra, “Ionic Memcapacitive Effects in Nanopores”, Nano Letters 10 2674 (2010). The dissertation author was the primary investigator of this paper.

Chapter 7 is in part a reprint of the material as it appears in Matt Krems and Massimiliano Di Ventra, “Ionic Coulomb Blockade in Nanopores”, in preparation (2011). The dissertation author was the primary investigator of this paper.
VITA

2005 B. S. in Physics, *summa cum laude*, University of Missouri, Rolla (now Missouri University of Science and Technology)

2006-2007 Teaching Assistant, Department of Physics, University of California, San Diego

2007 M. S. in Physics, University of California, San Diego

2007-2011 Research Assistant, Department of Physics, University of California, San Diego

2011 Ph. D. in Physics, University of California, San Diego

PUBLICATIONS


ABSTRACT OF THE DISSERTATION

Particle Dynamics in Nanopore Systems

by

Matthew A. Krems

Doctor of Philosophy in Physics

University of California, San Diego, 2011

Professor Massimiliano Di Ventra, Chair

In this dissertation, I discuss various aspects of the dynamics of charged particles in nanopore systems. In recent years, there have been numerous studies of organic and inorganic nanopores. Nonetheless, there is still much to be understood about these systems. I begin by summarizing some of the important literature on nanopore systems as well as the dynamics of ions in aqueous solutions. An important tool for studying these systems at the nanoscopic level has been molecular dynamics. Some of the techniques and methods of molecular dynamics will be discussed. Additionally, theoretical calculations of electronic transport have been demonstrated to be potentially useful for predicting the conductivity of a DNA base between two electrodes in a nanopore. These electronic current calculations will be discussed.
I continue by discussing the effect of noise on DNA sequencing via transverse electronic transport. Although previous theoretical studies have shown that measuring the transverse current across DNA strands while they translocate through a nanopore or channel may provide a statistically distinguishable signature of the DNA bases, and may thus allow for rapid DNA sequencing, fluctuations of the environment, such as ionic and DNA motion, introduce important scattering processes that may affect the viability of this approach. Theoretical calculations and modeling are used to address this issue.

Next, I will present a study of the dynamics of ions in a nanopore system under an alternating electric field. In this case, a nanopore in ionic solution acts as a capacitor with memory (memcapacitor) at various frequencies and strengths of the electric field. Most importantly, the hysteresis loop of this memcapacitor shows both negative and diverging capacitance as a function of the voltage. Molecular dynamics simulations and a simple, physically motivated model is presented to explore this phenomenon.

Finally, I will discuss an aspect of ionic conduction in nanopores. Making an analogy to classical Coulomb blockade, where the electrostatic interactions of electrons causes an increased resistance of a device with a tunnel junction, I discuss the buildup of ions at the neck of a nanopore and the effect of this on ionic conduction. Molecular dynamics simulations and a rate model will be employed to study this effect.
Chapter 1

Introduction

We are entering an age of a new technological revolution. Technological revolutions in the past have had great consequences for humanity. The industrial revolution changed the way people work, manufacture products, and organize their social structure, moving from farms to cities. The computer revolution again changed the way people work and the way information is shared and distributed throughout the world. The world’s economies and social structures have become globalized. Now, we are at the beginning of a new revolution: the bio revolution. Recently, research in biological physics, chemistry, neuroscience, and other related fields has rapidly progressed and over the next century surely will bring about new advances which will have enormous implications for humanity. One of these advances in the past few years has been the ability to sequence an entire human genome.

Genes, which make up a genome, are segments of deoxyribonucleic acid (DNA) molecules which consist of a linear sequence of subunits called nucleotides. Each nucleotide has three components: a phosphate group, a sugar, and a base, either adenine (A), thymine (T), guanine (G), or cytosine (C). The sequence of these four bases are the unique signature of a gene.

DNA is normally found as a double stranded molecule, with the two strands wound around each other in a double helix arrangement, connecting so called base pairs with hydrogen bonds. While these bonds are very weak, the combined effect of millions of base pairs is strong enough to keep the two strands together. The now
conventional methods of DNA sequencing based on the Sanger method \cite{1, 2} using gel electrophoresis, or the process of sorting by size charged molecules through a viscous gel by an electric field, chain termination techniques, and optical readout measurements will potentially be replaced by much faster and much cheaper methods. This is the goal of obtaining the $1000$ genome. There are many new ideas for DNA sequencing \cite{1}, but perhaps, one of the most promising methods of reaching this goal are methods using nanopores.

I will begin in Chapter 2 by discussing some of the most important experiments with nanopores and the reasons for nanopores being considered as a potential sequencing platform. There are numerous important techniques involved in the fabrication, characterization, and implementation of nanopores in experimental systems, and I will provide a brief overview of these methods. Additionally, I will discuss some general features of ionic conductance in electrolytic solutions.

Molecular dynamics simulations have proved to provide many fruitful results for studies related to nanopores and many other phenomena in molecular biology. In Chapter 3, I will introduce the theory and techniques of molecular dynamics (MD), particularly in relation to the molecular dynamics code, NAMD \cite{3}, which is used for a wide variety of problems in molecular biology, and is the code I have used for all of the molecular dynamics calculations presented in this work. A general overview of MD will be presented, but additionally, I will make an effort to elucidate some of the more detailed aspects of what it takes to make a practical MD simulation. I will discuss the general form of the force equation and the force field parameters associated with simulations involving water, organic material (DNA), in addition to synthetic compounds, like silicon nitride (Si$_3$N$_4$). I will also discuss some of the steps to generate nanopore geometries and present a general profile of a molecular dynamics simulation run.

In Chapter 4, I will provide an overview of an approach to calculating currents in quantum mechanical systems. The approach is based on quantum mechanical scattering methods and a basic understanding of these methods will help to reader to better understand some of the calculations in the next chapter.

Chapter 5 will deal specifically with one approach to DNA sequencing us-
ing nanopores. In particular, the effect of noise on DNA sequencing via transverse electronic transport will be discussed. Previous theoretical studies have shown that measuring the transverse current across DNA strands while they translocate through a nanopore or channel may provide a statistically distinguishable signature of the DNA bases, and may thus allow for rapid DNA sequencing. However, fluctuations of the environment, such as ionic and DNA motion, introduce important scattering processes that may affect the viability of this approach to sequencing. To understand this issue, a simple model that captures the role of this complex environment in electronic dephasing and its ability to remove charge carriers from current-carrying states is analyzed. It is found that these effects do not strongly influence the current distributions due to the off-resonant nature of tunneling through the nucleotides - a result expected to be a common feature of transport in molecular junctions. In particular, only large scattering strengths, as compared to the energetic gap between the molecular states and the Fermi level, significantly alter the form of the current distributions. Since this gap itself is quite large, the current distributions remain protected from this type of noise, further supporting the possibility of using transverse electronic transport measurements for DNA sequencing.

Chapter 6 will deal with another aspect of charged particle dynamics of nanopores. When subject to a periodic external electric field, a nanopore in ionic solution acts as a capacitor with memory (memcapacitor) at various frequencies and strengths of the electric field. Most importantly, the hysteresis loop of this memcapacitor shows both negative and diverging capacitance as a function of the voltage. The origin of this effect stems from the slow polarizability of the ionic solution due to the finite mobility of ions in water. A microscopic quantitative model is developed which captures the main features observed in the simulations and suggest experimental tests of the predictions. A possible memory mechanism due to the transport of ions through the nanopore itself is suggested, which may be observed at small frequencies. These effects may be important in both DNA sequencing proposals using nanopores and possibly in the dynamics of action potentials in neurons.
Finally, in Chapter 7, we show both analytically and by means of molecular dynamics simulations that ion-ion interactions in nanopores lead to the phenomenon of ionic Coulomb blockade, namely the build-up of ions inside a nanopore with specific capacitance impeding the flow of additional ions due to Coulomb repulsion. This is the classical counterpart of electronic Coulomb blockade observed in mesoscopic systems. We discuss the analogies and differences with the electronic case as well as experimental situations in which this phenomenon could be detected.
While ion-selective pores have been studied for several decades in neurons and other systems, the first experiments to suggest that a nanopore, or nanoscale hole in an insulating membrane, could be used as a more general measurement device were those of Kasianowicz and his collaborators in 1996 [4]. In their seminal work, they were able to pull a single-stranded polynucleotide through a biological nanopore, α-heomolysin, embedded in a lipid bilayer, by applying an external voltage to the system. The applied voltage coupled with the charged backbone of the polynucleotide caused it to translocate through the nanopore. This translocation was detected with the measurement of a blockade current, as the polymer partially blocks the pore. What they noticed in their current versus time trace was that there were two distinct levels of ionic current. These two levels were attributed to an open-pore current, one in which there was no polynucleotide in the nanopore, and that of a blockade current, a drop in the ionic current due to the polynucleotide being in the nanopore. This work inspired numerous other nanopore studies [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19].

There are several different explanations for why there is a blockade current and what causes its exact properties [1]. It is natural to think of this difference being a result of a volume-exclusion effect. The polymer’s finite size fills the pore partially which allows fewer current carrying ions to pass from one side of the pore
Figure 2.1: Model of an α-hemolysin nanopore. This self-assembled structure has a small cylindrical neck, which is about 5 nm long, at the bottom of the structure. The width of the neck varies along the structure and is anywhere from 1.4 nm to 2.0 nm. Given the width of ssDNA, the width of the pore is perfectly suited for measuring blockade currents with DNA, but the length of it may make it impossible to discriminate single nucleotides. Downloaded at http://en.wikipedia.org/wiki/File:7ahl_opm.gif and used under the GNU Free Documentation License.
to the other. However, this is far from a complete view. There are additional effects such as hydration as the charged backbone of the polynucleotide causes the highly polarizable water molecules to form layers surrounding it. Additionally, the pore walls may play a significant role in the dynamics of the polymer and ions. Needless to say, the water-ion-polymer-nanopore environment is a complex one. There are various other effects which will be important for understanding the dynamics of nanopore systems, and these will be discussed later.

In nanopore experiments, measurements of translocation events and their translocation time have provided a way to obtain information on the polynucleotide such as its length and composition. However, the translocation time is only a small amount of information for a very complicated system, that of a fluctuating water-ion environment with a nanopore and charged polynucleotide. Estimates of the length or composition of a polynucleotide from the translocation time alone is far from providing a complete picture of the polynucleotide dynamics. Among other things, it is important to have a good characterization of the nanopore itself. There are two main types of nanopores used in experiments today: biological (organic) and synthetic (inorganic) nanopores [20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30].

2.1 Biological Nanopores

The self-assembled biological nanopores spontaneously self insert themselves into a lipid bilayer membrane. Because of this, the experimenter has little control over the detailed characteristics of the nanopore. Nonetheless, due to the robust nature of these steps, the pores tend to have pretty consistent characteristics. It has been shown that α-hemolysin pores, in particular, are very stable [31]. However, the lipid bilayer support on which the nanopore rests is not as stable and can be difficult to set up [19].

So far, while many fruitful experiments have been done with α-hemolysin pores, no one has been able to demonstrate single nucleotide resolution for any type of measurements. From Fig. 2.1, one can see that the length of the stem of α-hemolysin is about 5 nm long [32]. For comparison, in the case of double-
stranded DNA (dsDNA), the distance between base-pairs is about 3.4 Å [1]. When dsDNA is denatured, or separated, typically by heating the dsDNA, into single-stranded DNA molecules, the distance between individual bases can vary much more greatly as the individual bases have much more freedom to move around. Nonetheless, the spacing between bases in ssDNA is still very small and a pore such as α-hemolysin may not be the best candidate. Another biological pore, mycobacterium smegmatis porin A (MspA), due to its geometry which is more suited for single-nucleotide resolution may be more promising for use in DNA sequencing [33]. The 1.2 nm width and 2 nm length of the stem may provide better resolution for sequencing techniques than other biological pores [34]. Despite the utility and potential of biological nanopores, synthetic nanopores offer many advantages over their biological counterparts.

2.2 Synthetic Nanopores

Synthetic nanopores, such as those made of Si$_3$N$_4$, provide the experimentalist with much more control over the specific dimensions and properties of the pore, at least in principle. Rather than relying on a robust self-assembly process as in biological nanopores, the synthetic nanopore sculptor can fine tune their fabrication steps to make pores of various sizes and shapes. Although biological nanopores seem to have much more consistent properties, one is limited to what nature produces. Thus, constructing synthetic nanopores is a much more involved process than constructing biological pores, and much research still needs to be done to perfect techniques for their construction. However, as more and more research is done on synthetic nanopore construction, synthetic nanopores are becoming better characterized and more consistently developed. One of the first techniques to construct them was developed by Golovchenko et al. and is called ion-beam sculpting [20].

The first step is to make a through hole using a focused ion beam (FIB). The through hole is significantly larger, at around 100 nm or so, than the desired dimensions of the nanopore. The next step involves one of three techniques, broad
area ion exposure, transmission electron microscope, or FIB exposure, to close and sculpt the hole until the desired size of the hole is reached, down to 1 - 10 nm. Golovchenko’s group uses the broad area ion exposure technique by exposing the large-diameter pore to an Ar\(^+\) beam which activates a diffusion process that causes the pore to close. The Ar\(^+\) current is proportional to the pore area, so by measuring this, one can have an idea of the size of the pore. However, the microscopic details of the pore itself are not known.

Although the precise composition and geometry of a synthetic nanopore are hard to know exactly, they also allow for the integration of electrodes inside the pore which can measure electronic currents inside the pore itself. This is not possible with biological pores. This possibility may turn out to be very important for DNA sequencing applications with nanopores or nanochannels and because of this, all of the work presented in this dissertation will focus on synthetic nanopores. It will next be important to know how to theoretically characterize and study these synthetic pores. The tool for this will be molecular dynamics (MD), and this will be the focus of a later chapter.

One of the interesting things about synthetic nanopores, in particular, is that the potential drop occurs almost entirely across the pore. By performing molecular dynamics simulations with nanopores and looking at the potential profile in the z-coordinate, the axis along the direction of the pore, we can see this effect (see Fig. 2.2).

### 2.3 Electrolytic Solutions

A nanopore immersed in ionic solution is a very complex environment, and it is important to understand the dynamics of the electrolytic solution in which a nanopore is immersed in addition to being able to characterize the nanopore itself. There are many interesting phenomena due to the interaction of fully dissociated ions and water, even without the presence of a nanopore or polynucleotide. These interactions play a role in the ion dynamics of systems and, as will be shown in future chapters, potentially lead to several other important interactions when a
Figure 2.2: Here we show the applied potential (dashed line) and the corresponding calculated potential (dots) across a nanopore system. The calculated potential was generated using the PMEPot plugin for VMD and averaged over slices in the z direction. Due to the periodic boundary conditions used in this simulation, the calculated potential must be the same at both ends as seen here. One can notice that the entire 20 V potential drops across the pore (indicated by the shaded area). The actual potential in the system is more like the solid line which is the sum of the calculated and applied potentials.
nanopore is immersed in an electrolytic solution. Electrolytic solutions may consist of molecular units, ions, or a combination of the two. For the purposes of DNA sequencing and nanopore research, I will specifically focus on effects in electrolytic solutions with strong electrolytes, or electrolytes consisting of ions only.

An ion immersed in solution rarely exists entirely on its own. Due to the positive or negative charge, and easily polarizable water, there are always tightly bound hydration layers surrounding the ion. These hydration have numerous effects on the conduction of ions in an aqueous environment. For instance, the ion with its hydration shell form a “quasi-particle” like structure with an increased effective mass and radius from a bare ion. This increased radius leads to enhanced interactions with a constriction such as a nanopore as well as a smaller drift velocity due to the increased mass.

As an example, in Ref. [35, 36], it was shown that the shedding of water molecules in the hydration layers of an ion as it passes through a nanopore leads to a quantization of the ionic conductance. Estimates of the energy barrier associated with removing these hydration layers have been made [35, 36, 37], and have been shown to lead to non-Ohmic behavior in the conductance through a restricted opening. In addition to the hydration layers formed around an ion, there also may be hydration effects on the inner walls of a nanopore. Studies suggest that at neutral pH levels, there is a small, but non-trivial surface charge on Si$_3$N$_4$ pores. By looking at the time-averaged density of the location of the oxygen atom in a water molecule (see Fig. 2.3), one can see a clear structure in the water, even under the presence of an applied electric field.

They hydration layers surrounding an ion also lead to other non-ideal behaviors of ions in electrolyte solutions. For example, it was noticed in molecular dynamics simulations that increasing the temperature also increases the conductance. This was an unexpected result. If one assumes that the velocity of an ion is

$$v_{tot}(r, t) = v_{th}(r, t) + v_{elec}(r, t)$$  \hspace{1cm} (2.1)

where the total velocity, $v_{tot}$, is a function of the position and time and can be seen as the sum of a random thermal component as well as a component due to an
Figure 2.3: Here we look at the time-averaged density of water molecules in a 7 Å radius cylindrical nanopore under the influence of an electric field. This plot was constructed by doing a normalized cylindrical time averaging of the position of the oxygen atom in a water molecule. Blue means there is no concentrated and static water density there, while brighter colors show there is an increased density in that region. The numbers refer to the dimension of the pore in Å. We only look at a slice through the pore and expect this effect to be cylindrically symmetric. By looking inside the pore and at the surface of the pore, one can see what look like “standing waves” of water density. This interesting structure of water molecules is present over time. This is due to effects of the charged pore walls and the highly polarizable nature of water.
electric field. If one were to look at an individual ion, it would follow a directed Brownian path in the direction of the force due to the electric field. However, when looking at macroscopic quantities such as the total current or ionic conductance, the thermal component should average out to zero. Thus, since current is directly related to the ionic velocity, one would naively expect that the current should not depend on temperature.

Nonetheless, this naive assumption is wrong. By looking at Fig. 2.4, we can see the linear increase in total current with temperature for nanopores of various radii and the case of just the electrolyte solution with no pore. While it was initially suspected this could be an artifact in the MD simulations by using the wrong thermodynamic ensemble, it turned out to be that the hydration layers surrounding the ion play a role here. The work of Kuyucak et al. (see [37]) showed that the effective radius and mass of a dressed ion, or an ion with surrounding hydration layers, depends on the temperature. In particular, they state that the radius of an ion-water quasi-particle is equal to the radius of the bare ion plus a term proportional to the cube root of a Boltzman factor, which depends on temperature. They also say that the mass is proportional to the bare mass plus a term proportional to the Boltzman factor. Due to the Boltzman factor, as the temperature increases, the numbers of water molecules associated with the ion decreases which decreases the mass of the quasi-particle. As a result, even at a fixed electric field, the conductivity increases with temperature.

An additional explanation has also been suggested to explain increasing conductance with temperature [38]. In this work, they suggest that the formation of cation-anion pairs plays a role. At certain concentrations, ions of opposite charge will pair up. However, the lifetime of these pairs depends on the temperature as random “kicks” due to an increased temperature will break them up. At low temperatures, their lifetime is long which does not allow either ion to be in a current carrying state due to the neutral charge of the composite pair. However, as the temperature increases, the ion pair receives more of these “kicks” due to the temperature, and the pairs have a much shorter lifetime, allowing more ions to be in current carry states. From both of the explanations for the temperature
Figure 2.4: Top panel: By looking at the total current as a function of temperature at fixed bias and concentration, we can see there is a close to linear relationship between temperature and total current for various radii of a cylindrical pore. Bottom panel: This effect is also seen in situations with no pore so the increase of ionic conductance with temperature is seen as a general feature of electrolytic solutions.
dependence, it is clear that interactions among ions will play an important role in the conductance characteristics of an electrolytic solution.

It is clear that the hydration shells and interaction of water with ions and the pore surface play an important role in the ionic conductance, but there are also further effects due to the Coulomb interaction of the ions. An important concept is that of an ionic atmosphere [39]. Under ideal conditions, ionic conduction would simply be linear with an increase in molar concentration, but in practice, this is not the case [39].

Peter Debye and Erich Huckel were, in particular, interested in how ionic conduction would be affected by considering the electrostatic interaction of an ion with other ions in solution. In an electrolytic solution, there are always a balance of positive and negative ions to make the overall charge of the system neutral. In the particular systems that are discussed in this thesis, we have a equal amount of potassium (K+) and chlorine (Cl−) ions which are fully dissociated and dissolved in water. In the Debye-Huckel theory, oppositely charged ions will form an ionic atmosphere around an ion. At equilibrium, this is assumed to be spherically symmetric, although in practice this cannot be the case as the ions are charges with a finite size surrounding the central oppositely charge ion.

The ionic atmosphere is employed in the use of the Debye-Huckel equation which aims to describe the conductivity behavior of electrolytic solutions. The ionic atmosphere describes a region around a central ion in which ions of the opposite charge are attracted electrostatically. Without an external electric field, the ionic atmosphere is symmetric about the central ion. With an electric field, however, the ionic atmosphere becomes a dynamic entity. As the central ion moves through solution, the ionic atmosphere has to build up in front of the moving ion and decay behind it. Since it takes a finite time to build up the atmosphere in front of the ion, an asymmetry may develop in its shape. This is called the relaxation effect, with a relaxation time, \(\tau\), associated with rate constants for the build up and decay of the atmosphere. If the relaxation time at a given concentration is much faster than the time it takes an ion to move a comparable distance in the solution, the ionic atmosphere will be an important effect. However, for fields typically use in
DNA sequencing applications and other experiments with nanopores [1], the time scale to move a distance similar to the extent of the ionic atmosphere is typically much faster than the relaxation time [39]. This is the so-called Wien effect. At such high fields, the ionic atmosphere simply does not have time to form.

I hope the previous paragraphs have convinced you that nanopore systems are complex environments with many important phenomena to consider. In a later chapter, I will discuss in more detail the potential to use a nanopore to sequence DNA via tunneling currents. Recently, experimenters have demonstrated the feasibility of the approach to use electronic tunneling currents to distinguish DNA [40, 41, 42]. One approach [40] uses a break junction to produce distributions of the nucleotides similar to the technique discussed in a later chapter. The other [41, 42] uses a scanning tunneling microscope (STM) in a tunneling gap. While these are far away from being practical production devices, these recent works show just how much promise measuring tunneling currents have for DNA sequencing, and the potential nanopores have to play a role in these efforts.
Chapter 3

Molecular Dynamics

Molecular dynamics simulations provide a unique way to look at the detailed dynamics of biological systems as well as other systems involving inorganic materials. These systems of interest involve the interaction of potentially thousands and even hundreds of thousands of atoms. Ideally, one could perform a first-principles quantum mechanical calculation to describe the dynamics of these systems. However, even in the effective single-particle picture of density functional theory, one can look at only a few hundred atoms for timescales on the order of only hundreds of femtoseconds. Biological systems consist of many more atoms and have much longer timescales. It will be necessary to resort to a classical equation of motion with a force field which aims to phenomenologically include many of the quantum effects while still maintaining computational efficiency.

The basis for classical molecular dynamics is Newton’s second law,

\[ m_i \ddot{r}_i = - \frac{\partial}{\partial r_i} U_{\text{total}}(r_1, r_2, \ldots, r_N), \quad i = 1, 2, \ldots, N, \quad (3.1) \]

where \( m_i \) is the mass of atom \( i \), \( r_i \) is its position, and \( U_{\text{total}} \) is the total potential energy of the system. We note that, while in the full quantum mechanical problem, one would consider the interaction of the electrons as well as the nuclei separately, here we only consider atomic details. While this equation is very simple, much of the complexity and richness is hidden in the potential function, \( U_{\text{total}} \), which is represented by the MD force field. The force field is the most important part of an MD simulation and will be discussed in more detail in the following section.
3.1 The Force Field

When performing an all-atom MD simulation, one assumes that every atom feels a force, as in Eq. 3.1, specified by a force field accounting for the interaction of that atom with the rest of the system. This is represented by the potential function, $U_{\text{total}}$, which is a true many body potential that contains, at least in principle, all two, three, and up to N-body interactions, where N is the number of atoms in the system. It is approximated by a simpler form containing pairwise-additive two-body interactions for non-bonded interactions and certain two-, three-, and four-body interactions for bonded interactions. The program, NAMD\(^1\) [3], which is used for all of the MD simulations in this dissertation, employs a force field defined as follows,

$$U_{\text{total}} = U_{\text{bond}} + U_{\text{angle}} + U_{\text{dihedral}} + U_{\text{vdW}} + U_{\text{Coulomb}}, \quad (3.2)$$

where the bond, angle, and dihedral terms contain the bonded interactions and the vdW and Coulomb terms contain the non-bonded interactions.

3.1.1 Non-bonded Interactions

At the quantum mechanical level, only the Coulomb interaction plays a role between two particles. However, to describe this classically, one must split this up into different separate interactions.

The vdW term in $U_{\text{total}}$ represents the van der Waals interaction which is approximated by a Leonard-Jones 6-12 potential. This is a mathematically simple phenomenological model which describes the interaction between a pair of atoms. In general, the Leonard-Jones potential takes the form,

$$U_{\text{vdW}} = \sum_i \sum_{j>i} 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right], \quad (3.3)$$

where $\epsilon_{ij}$ represents the potential well between two atoms, $i$ and $j$, $\sigma_{ij}$ represents the distance between two particles in which their potential is zero, and $r_{ij}$ rep-

\(^1\)Not (just) Another Molecular Dynamics
Figure 3.1: The Leonard-Jones potential. Note the strongly repulsive part of the potential as the radial distance between two atoms approaches zero. The Leonard-Jones interaction, like the Coulomb interaction, extends to infinity, but in practice, for MD simulations, one employs a cut-off of the interaction for large enough radial distances. In nearly every aspect of MD, one is constantly trying to find the right balance of accuracy and computational efficiency.

represents the distance between the two particles\(^2\). The form of the Leonard-Jones potential is due to the fact that the parameters, \(\epsilon_{ij}\) and \(\sigma_{ij}\), can be fitted to reproduce experimental data and accurate quantum chemistry calculations. In particular, the \(r^{-12}\) term describes the Pauli repulsion at short ranges due to overlapping electron orbitals and the \(r^{-6}\) term describes the London dispersion force, or induced dipole-dipole forces. The Leonard-Jones potential is shown in Fig. 3.1.

The Coulomb term represents the long-range electrostatic interaction between two particles and takes the form,

\[
U_{\text{Coulomb}} = \sum_i \sum_{j>i} \frac{q_i q_j}{4\pi \epsilon_0 r_{ij}^6},
\]

(3.4)

where \(q_i\) and \(q_j\) represent the charge of the atoms\(^3\), \(\epsilon_0\) is the permittivity of free

\(^2\)In principle, every different atom combination has different values of the parameters \(\epsilon_{ij}\) and \(\sigma_{ij}\).

\(^3\)An important part of the parameterization of the force is assigning partial charges to the atoms of a molecule which best represent the physical interaction. Thus, these numbers are not always whole number multiples of the fundamental charge, \(e\).
space, and \( r_{ij} \) is again the distance between the two atoms. Depending on the boundary conditions of the simulation cell in a NAMD molecular dynamics simulation, there are a couple of ways in which one can compute the Coulomb term. It is simply too computationally demanding to compute directly the sums in Eq. 3.4 every time step so one may employ a cut-off scheme or use an efficient particle-mesh Ewald summation scheme [3] with periodic boundary conditions.

### 3.1.2 Bonded Interactions

Two atoms connected with a covalent chemical bond behave much like a harmonic oscillator for small deviations from their equilibrium bond length. Therefore, the bond term in \( U_{\text{total}} \) is represented by,

\[
U_{\text{bond}} = \sum_{\text{bond } i} k_{\text{bond}}^i (r_i - r_{0i})^2 ,
\]

(3.5)

where \( k_{\text{bond}}^i \) is the force constant, \( r_i \) is the current length of the bond, and \( r_{0i} \) is the equilibrium bond length. It is also necessary to describe an interaction due to the directionality of bonds. This is incorporated through the angle term which embodies harmonic angular vibrations between three atoms (two bonds) and is described by,

\[
U_{\text{angle}} = \sum_{\text{angles } i} k_{\text{angle}}^i (\theta_i - \theta_{0i}) ,
\]

(3.6)

where \( k_{\text{angle}}^i \) is the force constant parameter, \( \theta_i \) is the current angle of the two bonds between the three atoms, and \( \theta_{0i} \) is the equilibrium angle. The dihedral term describes atom pairs separated by three covalent bonds with the central bond having a torsion angle. This term is represented by,

\[
U_{\text{dihedral}} = \sum_{\text{dihedral } i} k_{\text{dihedral}}^i [1 + \cos (n_i \phi_i - \delta_i)] ,
\]

(3.7)

where \( k_{\text{dihedral}}^i \) is the force constant, \( n_i \) is a “multiplicity” factor, \( \phi_i \) is the torsion angle, and \( \delta_i \) is a phase shift for the dihedral\(^4\). See Fig. 3.2 for a schematic picture of the different bond types.

---

\(^4\)There may also be an improper dihedral angle interaction which keeps molecules from flipping over to their mirror image.
3.1.3 Force Field Parameters and NAMD Files

After having outlined the various components of the force field, including bonded and non-bonded interactions, one must define which atoms are involved in each bonded interaction, as well as define all of the previously mentioned parameters for both the bonded and non-bonded forces. While there are many potential ways to do this, I will focus here on the essential components that NAMD uses for a molecular dynamics simulation.

First of all, one must define a so-called .pdb file, which corresponds to the Protein Data Bank, a repository for 3D structural data of large biomolecules, such as proteins or nucleic acids. The primary purpose of the .pdb file is to store all of the individual atom names with their initially defined coordinates in xyz-space. The .pdb file may store other identifying information but the names and positions of the atoms are the most important.

One next needs a file which contains other necessary information about the atoms such as the charge, mass, and other atoms in which an atom is bonded to. This information is stored in a .psf file, standing for Protein Structure File. The generation of this file is quite a bit more complicated than generating a .pdb file.
and will involve the use of a topology file, provided by, for example, the CHARMM force field.

NAMD is capable of using two types of general force fields, CHARMM [43, 44] and AMBER [45], as well as additional user-defined parameters. CHARMM parameters are used in all of the simulations discussed in this thesis, so I will discuss the CHARMM force field briefly.

The CHARMM force field characterizes various proteins, lipids, and nucleic acids, as well as their interaction with an explicit water and ion environment. Determining the force field is a significant undertaking and is the result of numerous quantum mechanical calculations and experimental results. The parameters are adjusted to reflect these findings and tested for accuracy in reproducing structural, dynamic, and thermodynamic properties of well studied small molecules. Additionally, bulk properties of the water and ion environment should be accurate. The parameters may be empirically adjusted if discrepancies are found.

A force field is, by no means, a definitive list of parameters. It seems to be very much an art to find a force field which is accurate for a small set of systems and equally applicable to other systems. In reality, one must hope that their force field works well for other, more complicated systems. Nonetheless, the main purpose of molecular dynamics simulations has been to sample phase space and not to provide quantitative results. With this in mind, MD is a useful tool, but should only be used for the right types of problems.

When trying to use the CHARMM force field for a practical simulation in NAMD, there are two important types of files needed, the topology file and parameter file. These two files are typically bundled together when one acquires the CHARMM force field files. The topology file contains all the information needed to generate the .psf file needed for the simulation. Thus, the topology file itself is not needed during the simulation, but only in the creation of the .psf file. The .psf files contains information for each individual atom, such as mass and charge, but must also define how each atom is bonded to the other atoms with a list of bonds, angles, dihedrals, and other bonded lists. The topology file is used to define these lists of bonded atoms in a .psf file for the particular atoms of the .pdb
file. The topology file also is used to generate the information in a .psf file for the water molecules and ions, as well as filling in “best-guesses” for where hydrogen atoms are in the protein, lipid, or nucleic acid.

In addition to the CHARMM force field, other specifications or user-defined models may be used. For example, in the MD simulations for this thesis, the Universal Force Field (UFF) [46] parameters are used to specify the Si$_3$N$_4$ atoms. In Chapter 5, the silicon and nitrogen atoms are held fixed and have zero charge, but have van der Waal’s parameters specified. In Chapters 6 and 7, the silicon and nitrogen atoms are allowed to move with a harmonic confining potential in such a way that gives the correct dielectric properties of the material, have partial charges defined for each of the atoms of the material, and have bonds defined within the Si$_3$N$_4$ material.

Once one has a correctly defined .pdb file and .psf file (constructed with the aid of the CHARMM topology file and perhaps user defined models), one is almost ready to run the MD simulation. The other part of the CHARMM force field is the parameter file which contains all of the numerical constants to calculate the forces and energies, given a .psf and .pdb file. The CHARMM parameter file, with perhaps user defined additional parameters, coupled with the .pdb file and .psf file are the essential ingredients to running a simulation.

3.2 Anatomy of a Nanopore for Molecular Dynamics Simulations

Ultimately, one wants to use molecular dynamics to simulate some physical system. While the Protein Data Bank contains thousands of geometries for various molecules, and the companion program to NAMD, Visual Molecular Dynamics (VMD), contains various utilities for solvating one of these geometries in a water box as well as adding ions and generating the protein structure files, we are specifi-
Figure 3.3: Unit cell of $\beta$-Si$_3$N$_4$ generated from VMD. The silicon atoms are represented by yellow balls and the nitrogen atoms are blue. The relevant bonds are indicated by sticks connecting the atoms. Here, I use the CPK coloring scheme inspired by the work outlined in Ref. [50, 51]

...ually interesting in using molecular dynamics to study synthetic nanopores, which up until recently\(^7\), no standard tools were available for doing this. Nonetheless, it is important to understand the process of going from a unit cell of a structure to a realistic nanopore in solution. We follow Ref. [14, 47] for our preparation of the Si$_3$N$_4$ nanopore.

First, a unit cell of a Si$_3$N$_4$ crystal in the $\beta$-phase was constructed according to the x-ray crystallography of Ref. [48]. The unit cell has unit cell vectors [49]:

\[
\begin{align*}
a &= 7.595 \text{ Å} \times [1, 0, 0] \\
\mathbf{b} &= 7.596 \text{ Å} \times [1/2, \sqrt{3}/2, 0] \\
c &= 2.902 \text{ Å} \times [0, 0, 1]
\end{align*}
\]

The unit cell is shown in Fig. 3.3

\(^7\)Recently, an “Inorganic Builder” plugin was developed for VMD (http://www.ks.uiuc.edu/Research/vmd/plugins/inorganicbuilder/).
Figure 3.4: A top down view of the unit cell of $\beta-\text{Si}_3\text{N}_4$ replicated five times in each direction. Notice how it has a rhombus-like shape due to the nature of the unit cell. This would not be a convenient shape for doing simulations with periodic boundary conditions. Also, since we plan to drill a hole in the center of the crystal structure, we would not want to waste computational effort on the parts far away from the hole. It will be more convenient to have a more symmetric figure around a central hole.

direction. This is done with a script written in the Tcl programming language$^8$. In Fig. 3.4, you can see the result of replicating the unit cell a certain number of times.

Once one has the slab of Si$_3$N$_4$ material, it must be cut into a more reasonable shape for molecular dynamics. A nanopore will be drilled through the center, and this will be the primary region of interest, so it would also waste computational cycles to keep all of the areas far away from the center. One can see in Fig. 3.6 the hexagonal shape for the Si$_3$N$_4$ membrane which turns out to be convenient for periodic boundary conditions. In another part of this thesis, we do simulations with spherical boundary conditions, and in this case, we use a circular piece of Si$_3$N$_4$ material.

Next, we must drill the pore. In the case of Fig. 3.5, we just use a simple cylindrical pore, although in practice, at the atomic level, it is never really a perfect

$^8$The Tcl programming language has extensions for VMD and these are useful for doing various types of operations with the .pdb and trajectory files generated during simulations as well as other files used in molecular dynamics.
Figure 3.5: The shape in Fig. 3.4 must be cut into a more convenient form to apply periodic boundary conditions. It turns out that cutting a Si$_3$N$_4$ crystal into a hexagonal shape is convenient for this. As a next step, we can cut a hole down the center of the crystal to produce a pore, in this case a 4 Å radius hole. Notice that, in this case, it is not perfectly circular because at these length scales, we are dealing with specific atoms. This may lead to various effects in nanopores such as dangling atoms and surface charges.

shape as can be seen in the figure. For example, in a following chapter, we want to drill cone-shaped pores with a specified angle, $\theta$, relative to the bottom surface of the pore and neck radius. This involves another Tcl script with the exclusion of all atoms with the following conditions

$$x^2 + y^2 < \left( r + \left( \frac{2l}{\tan(\theta)} \right) \left( z + \frac{l}{2} \right) \right)^2$$

(3.11)

where $l$ is half the length of the nanopore along the direction of the hole as we set $z=0$ as the middle of the pore, $r$ is the desired neck radius at the bottom of the pore, and $x, y, z$ are the coordinates of the atom. To make a cylindrical pore, one can just set $\theta$ to 90°.

Once the pore is generated, a .psf file must be generated for it. The parameters for this are found in the Universal Force Field (UFF) parameter list from Ref. [46]. A Tcl script which sets up this .psf file “by hand” is used for this. This script produces the bond list for bulk atoms as well as surface atoms and modifies the charges of the atoms to provide a more accurate description of their interaction. In a later step, all of the atoms of the Si$_3$N$_4$ crystal are harmonically confined with
Here we show a side view slice of a conical pore which is a typical shape in experiments and will be a useful design to demonstrate the phenomenon of ionic Coulomb blockade in a later chapter. For this plot, we use the vdW display scheme which shows the approximate extent of the van der Waal’s interaction for each atom.

a spring constant that reproduces the experimentally measured dielectric constant of Si$_3$N$_4$.

Optional Step: Adding DNA to the System

For some of the simulations discussed in this thesis, a single or double strand of DNA will also be part of the simulation cell. This can be done in a variety of ways, but I use a program called the Nucleic Acid Builder$^{10}$ (NAB) to generate the double-stranded DNA (dsDNA) .pdb and .psf file (see Fig. 3.7 for a visualization of this). This can then be separated into a single-stranded DNA (ssDNA) molecule and then implemented into the nanopore geometry.

One can use the built-in VMD utility, PSFGen$^{11}$ to combine the two geometries, i.e. the .pdb and .psf of the ssDNA or dsDNA with the .pdb and .psf

---

$^9$One can see once again that molecular dynamics is in some ways an “art” as one tries to reproduce some experimental situation as close as possible. Nothing guarantees that this description of the physics will hold under different conditions, but this is the best we can do for systems with thousands and even hundreds of thousands of atoms at this point.

$^{10}$http://casegroup.rutgers.edu/

$^{11}$http://www.ks.uiuc.edu/Research/vmd/plugins/psfgen/
Figure 3.7: An example of a dsDNA molecule generated from the Nucleic Acid Builder (NAB). Here, for example, we produce a 15 base pair strand containing adenine and thymine. The NAB allows you to specify what you want each base to be in a single strand and then produces the second strand of the double helix with the corresponding complimentary base pairs. Here I use the “Licorice” visualization scheme in VMD.
file of the nanopore. At this point, one would have a nanopore with a DNA strand sticking out of it (depending on exactly where you place it) in a .pdb file and the .psf describing the interactions. The built-in VMD programs to solvate the system and add ions will automatically recognize whether the DNA is there or not and add the water and ions appropriately.

**Anatomy of a Nanopore continued...**

After this, the nanopore must be solvated in a water box. Fortunately, VMD has a built-in utility to do this called “Add Solvation Box.” It is very easy to use and can be scripted so one does not have to use the graphical user interface (GUI) in VMD to generate the water. The plugin puts the nanopore in a rectangular shape of pre-equilibrated TIP3 water molecules. The TIP3 water model is typical for molecular dynamics simulations as it has a good compromise between computational efficiency and accuracy. It has three interaction sites corresponding to the three atoms of the water molecules and uses Leonard-Jones parameters for all the atoms including the hydrogens. The charges are unmodified [52].

Depending on the boundary conditions, whether periodic or spherical, one needs to cut the water to fit their desired simulation box. In the spherical boundary conditions case, one can just remove the specified atoms a certain radius, \( r \), from the center greater than the desired size of the simulation volume. For the hexagonal shape with periodic boundary conditions, one should cut it into a hexagonal shape which can be done by removing all atoms that have greater \((x, y)\) coordinates than any of the atoms in the \( \text{Si}_3\text{N}_4 \) membrane.

Next, we can use the built-in and scriptable “Autoionize”\(^{12}\) plugin to add ions to the system. One can choose sodium (\( \text{Na}^+ \)) and chlorine (\( \text{Cl}^- \)) ions or potassium (\( \text{K}^+ \)) and chlorine ions to add to the system. We use \( \text{K}^+ \) and \( \text{Cl}^- \) atoms as these are typically used in nanopore experiments, especially those involving DNA sequencing. One can also add other types of ions, such as \( \text{Mg}^{2+} \), just as long as the system has an overall neutral charge. In particular, for periodic systems using full electrostatics such as Particle Mesh Ewald (PME) methods for calculating

\(^{12}\)http://www.ks.uiuc.edu/Research/vmd/plugins/autoionize/
the Coulomb interaction, with a finite charge for the system, the method will not converge [3].

The Autoionize plugin automatically randomly places a specified molarity of ions in the system by removing water molecules and making sure a certain distance exists between water and ions (which will aid in the minimization procedure). If the system is not electrically neutral, it will automatically add extra (or less) ions of one type to make the system electrically neutral.

At this point, one should have a Si$_3$N$_4$ membrane with a nanopore of a specified geometry, solvated in a user-defined water box with ions and with or without DNA depending on what one wants. All of these steps will generate .pdb and .psf files along the way. This is one example of this type of workflow for generating synthetic nanopore geometries, but it is typically easy to make changes such as a different membrane material (such as SiO$_2$), different solvents (such as some type of alcohol perhaps), or different ions. A combination of the plugins available for VMD with user written Tcl scripts makes all of these operations possible to be done reasonably quickly and efficiently.

### 3.3 Profile of a NAMD Run

After constructing a suitable geometry .pdb file and its corresponding .psf file to describe the interaction of all the atoms, we can finally simulate some biological systems. The molecular dynamics simulations done in this thesis typically consists of three primary stages: minimization, equilibration, and dynamics. Ultimately, we are interested in nanopore systems experiencing an applied voltage, which constitutes the dynamics part, but without the first two steps of minimization and equilibration, the dynamics stage will either be unstable or produce poor results. I am going to discuss each stage briefly and outline some of the numerical techniques required.
3.3.1 Minimization

It is necessary to find some kind of stable point or minimum in the potential energy landscape before the equilibration stage. At a minimum on the potential energy surface, the net force on each atom will vanish. However, for complicated systems such as those typically studied with molecular dynamics, there will likely be multiple local minima in addition to the one true absolute minimum. Typically, one searches for a minimum with a specified tolerance since it is unlikely to find, at least in a reasonable amount of time, a minimum where all the forces are zero.

The .pdb coordinates provide a starting guess for the minimization procedure. In the initial stage of the minimization procedure, the gradient can be used to obtain an initial direction and magnitude for the change in coordinates to approach a minimum. Specifically, NAMD employs a conjugate gradient \cite{53} and line search method.

3.3.2 Equilibration

After the minimization stage, one is ready to actually solve Newton’s equations of motion for the system. By propagating Eq. 3.1 in time, the trajectory of all of the atoms in the simulation can be obtained. While minimization is done at zero temperature, at this point, one can explicitly give the system a temperature by assigning velocities according to a Maxwell-Boltzmann velocity distribution,

\begin{equation}
    f(\mathbf{v}) = \left(\frac{m}{2\pi kT}\right)^\frac{3}{2} e^{-mv\cdot\mathbf{v}/2kT},
\end{equation}

where $m$ is the mass of the atom, $k$ is Boltzmann’s constant, $T$ is the temperature, and $\mathbf{v}$ is the velocity of the particle. The velocities are distributed such that the system has the appropriate temperature (typically room temperature) and a zero center-of-mass velocity. The direction of the velocity is applied randomly to the atoms. In using the term “temperature”, it becomes necessary to talk about the statistical ensemble we are in. One can use the NPT (constant particle number, pressure, and temperature) ensemble for equilibration, which means the volume and total energy of the system are not constant. It is important to use this ensemble
Figure 3.8: Using the built-in VMD plotting tool, NAMDPlot (http://www.ks.uiuc.edu/Research/vmd/plugins/namdplot/), we can automatically parse the output from an equilibration run and plot it. Here, we can see that the system quickly adjusts its volume in the constant-pressure simulation and fluctuates about a mean value.

because equilibration requires that the volume fluctuate around a mean value. One can see in Fig. 3.8 how this looks.

It is easy enough to imagine that particle number does not change. Simply do not add new particles to the system. To keep the temperature and pressure fixed takes a little bit more work. For an NPT ensemble, the pressure in molecular dynamics is controlled by constantly adjusting the size of the simulation box and rescaling all the coordinates of the atoms during this process. For the constant-pressure equilibration simulations described in this thesis, the Nose-Hoover Langevin piston method [54, 55] is applied in NAMD to fix the pressure and temperature of the system.

3.3.3 Simulations with an External Electric Field

For most of the simulations discussed in this thesis, after an initial minimization and equilibration phase, we want to apply a global electric field of the system. This is applied in an NVT (constant particle number, volume, and tem-
perature) ensemble. We must have a constant volume simulation or otherwise the electric field will distort the geometry. NAMD implements the external electric field simply by adding an extra term to Eq. 3.1. The force due to an external electric field is simply

\[ \mathbf{F} = q \mathbf{E} \tag{3.13} \]

where \( q \) is the charge of the particle and \( \mathbf{E} \) is the electric field. In this thesis, we use both constant and alternating electric fields. NAMD allows one to specify each component of the electric field vector and allows one to set the frequency and phase if one wants an alternating electric field. If \( \mathbf{E}_0 = (E_x, E_y, E_z) \) are the components of the electric field, NAMD implements an alternating field as

\[ \mathbf{E} = \mathbf{E}_0 \cos(\omega t - \phi). \tag{3.14} \]

NAMD also allows you to change the electric field by hand by specifying it for a given period of time and then changing it for a different period of time. Since NAMD implements external fields as a force, it is not a perfect correlation to how an experimental voltage would affect a biotechnological system as the ones described in this thesis. However, it is a reasonable approximation and the best we can do at the moment. To apply a specified voltage to the system, one can divide the desired voltage, \( V \), by the length of the system along the pore axis, \( l_z \), which one can obtain at the end of the NPT equilibration run. Since during the electric field phase, a constant volume ensemble is used, the calculated voltage from the applied electric force will be fixed. At this time, NAMD does not allow you to spatially vary the electric field.
Chapter 4

Scattering Approach to Electronic Transport

In a later chapter, a technique for sequencing DNA using transverse electronic transport via embedded electrodes in a synthetic nanopore will be outlined. An electronic transport approach to DNA sequencing in a nanopore will sensitively depend on the electronic structure of the different nucleotides as well as the pore geometry and surrounding environment. Therefore, understanding the electronic properties of DNA is essential for the characterization of DNA using transverse electronic current techniques.

In Ref. [1], the projected density of states (DOS) for the different nucleotides placed between two gold electrodes is presented and shows they have a similar electronic structure, with molecular states very near the Fermi energy. Most of the DOS was shown to have have been contributed by the DNA backbone and will also sensitively depend on the nucleotide geometry and orientation. One can find a Hamiltonian for a nucleotide in solution with electrodes and use a technique developed from scattering theory for calculating electronic currents. Before I discuss the particular current calculations for DNA, it will be necessary to introduce Landauer transport theory. While I do not aim to give a complete description of the method, I will sketch the derivations to arrive at the equations used for the calculations discussed in the following chapter.
4.1 Landauer Transport

For the current calculations outlined in the next chapter, the Landauer approach to electronic transport is used. There are many assumptions which go into formulating the problem, and I will refer to [56] for an outline of these assumptions as well as for the details of the calculations and development of the Landauer transport equations below. Fig. 4.1 is a schematic view of the transport problem.

It is important to point out that this is a single-particle approach (i.e. no electron-electron interactions) and static (no time dependence of the Hamiltonian). As a general rule, one should think of the Landauer approach to transport as a viewpoint or method based on scattering, not a fundamental approach to the problem. Nonetheless, the approach proves to be useful in a wide variety of problems in mesoscopic and nano physics, and its validity as a technique is justified in its ability to reproduce the quantum of conductance [56], $G_0$:

$$G_0 = \frac{2e^2}{h},$$  \hspace{1cm} (4.1)

where $e$ is the electron charge, $h$ is Planck’s constant, and the factor of 2 accounts for up and down spins. This conductance value corresponds to a fully transmitted wave in a ballistic transport system. One might ask why there would any resistance at all in an ideal system. This is a result of the fact that there is a contact resistance resulting from the large reservoirs injecting electrons into a narrow constriction.

For ideal and identical leads, electrons that are free to travel only in the $x$-direction along the nanojunction are considered. The Hamiltonian of the system, $H_S$, must satisfy the asymptotic conditions derived from the time-independent Schrödinger equation:

$$\lim_{x \to \pm \infty} H_S = -\frac{\hbar^2}{2m} \nabla^2 + V_L(r_\perp) \equiv H_L$$ \hspace{1cm} (4.2)

$$\lim_{x \to \pm \infty} H_S = -\frac{\hbar^2}{2m} \nabla^2 + V_R(r_\perp) \equiv H_R$$ \hspace{1cm} (4.3)

where the $H_L$ and $H_R$ refer to the Hamiltonians of the left and right leads respectively, $m$ is the electron mass, and $V_i(r_\perp)$ is a single-particle potential which confines electrons in the $y$-$z$ plane in the $L$ or $R$ electrode. The eigenstates of the
Figure 4.1: A schematic view of the transport problem at hand. A central nanojunction, which is the system of interest and in our case, a DNA nucleotide immersed in water, is weakly coupled to two ideal leads which have associated chemical potentials, $\mu_L$ and $\mu_R$. This difference in chemical potentials gives rise to a potential difference, $V$, across the nanojunction. The reservoirs supply as many electrons as needed to the leads from infinity in order to maintain the potential difference.

Electrodes can be split up into longitudinal (i.e. in the x-direction) and transverse (i.e. the y-z plane) parts, and the total solutions, $\psi_{ak}$, can be written as products of the longitudinal and transverse eigenstates as

$$\psi_{ak} = \sqrt{\frac{1}{L_x}} u_a(r_\perp) e^{ikx},$$  \hspace{1cm} (4.4)

where $a$ is the quantum number associated with the general normalized transverse solutions, $u_a(r_\perp)$, $k$ is the wave number of the plane wave states in the x-direction, and $L_x$ is a normalization length. Now we know the general solutions at the boundaries. The solutions of the full system asymptotically merge with the states of the left and right leads, and we can write these as

$$\Psi_{ik_i}(r) \rightarrow \psi_{ik_i}(r) + \sum_{f=1}^{N_L} R_{if} \psi_{fk_j}(r)$$  \hspace{1cm} (4.5)

for the left lead and

$$\Psi_{ik_i}(r) \rightarrow \sum_{f=1}^{N_R} T_{if} \psi_{fk_f}(r)$$  \hspace{1cm} (4.6)

for the right lead, with $T$ and $R$ transmission and reflection coefficients, and $N_{L(R)}$ are the number of possible reflected waves and the energy given by $\hbar k_f$. So far, the general framework is essentially identical with the scattering at a boundary type
problems one does in an undergraduate quantum mechanics course. We further develop this framework by now looking at a current. We use the current density operator, \( \hat{j} = 1/(2m) \sum_i \{ \delta(\mathbf{r} - \mathbf{r}_i), \hat{p}_i \} \), with \( \hat{p} \) the momentum operator, to find the total current at each energy. At this point, one can integrate over all of the energies, multiplying by the density of states to get an expression for the total current. After some further operations (please see Ref. [56]), one can arrive at the equation

\[
I = \frac{e}{\pi \hbar} \int_{-\infty}^{\infty} dE \left[ f_L(E) - f_R(E) \right] T(E)
\]  

(4.7)

where the \( f_{L(R)} \) are the Fermi-Dirac distributions for the left and right electrodes respectively and \( T \) is the transmission probability for a given energy. The Fermi-Dirac functions are constructed from the given voltage bias across the DNA-water solution, \( V = (\mu_L - \mu_R)/e \), where \( \mu_{L(R)} \) is the chemical potential and \( e \) is the electron charge.

The transmission function \( T \) is what characterizes the nanojunction system itself. We must next develop a general way to find \( T \). Let’s look at our nanojunction/electrode setup in Fig. 4.1 again. One can define a Hamiltonian for the system, assuming decoupled (i.e. non-interacting) electrodes with

\[
\hat{H}_S = \hat{H}_L + \hat{H}_R + \hat{H}_C + \hat{V}_{LC} + \hat{V}_{CR} + \hat{V}_{CR}^T
\]

(4.8)

where \( \hat{H}_L \) is the Hamiltonian of the left electrode, \( \hat{H}_R \) of the right electrode, and \( \hat{H}_C \) of the central nanosystem of interest (DNA-water solution). The term \( \hat{V}_{LC} \) represents the interaction of the left with the central system and \( \hat{V}_{RC} \) the interaction with the left electrode. One can write the Schrödinger equation in matrix form as

\[
\begin{bmatrix}
\hat{H}_L & \hat{V}_{LC} & 0 \\
\hat{V}_{LC}^T & \hat{H}_C & \hat{V}_{CR}^T \\
0 & \hat{V}_{CR} & \hat{H}_R
\end{bmatrix}
\begin{bmatrix}
|\phi_L\rangle \\
|\phi_C\rangle \\
|\phi_R\rangle
\end{bmatrix} = E
\begin{bmatrix}
|\phi_L\rangle \\
|\phi_C\rangle \\
|\phi_R\rangle
\end{bmatrix}
\]

(4.9)

where the \( \phi \)'s are the single particle wave functions of the three regions. We can solve this system for the DNA-water region, \( \phi_C \) to get

\[
\left[ E - \hat{H}_C - \hat{\Sigma}_L(z) - \hat{\Sigma}_R(z) \right] |\phi_C\rangle = 0
\]

(4.10)
where

\[
\hat{\Sigma}_L(z) \equiv \hat{V}_{LC}^\dagger \hat{G}_L(z) \hat{V}_{LC} \\
\hat{\Sigma}_R(z) \equiv \hat{V}_{RC}^\dagger \hat{G}_R(z) \hat{V}_{RC}
\]

are the self energy operators and

\[
\hat{G}(z) = \frac{1}{E - \hat{H}_C - \hat{\Sigma}_L(z) - \hat{\Sigma}_R(z)}
\]

is a single particle Green's function with \( z = E \pm i\epsilon \) for the retarded and advanced versions for either the left or right electrode or the central system. One can connect the Green's function formalism to the transmission probability, \( T \), mentioned above [56] with the equations

\[
T(E) = \text{Tr} \left\{ \hat{\Gamma}_R \hat{G} \hat{\Gamma}_L \hat{G}^\dagger \right\}
\]

where \( \hat{\Gamma}_{L,R} = i \left( \Sigma_{L,R} - \Sigma_{L,R}^\dagger \right) \) and \( \hat{G} \) is the retarded Green's function. With our new expression for the transmission, \( T \), we can now find the total current of the system from Eq. 4.7.

This formalism will be useful for the calculations done in the next chapter and will allow us to calculate thousands of currents for various geometries of a DNA-nanopore solution.
Chapter 5

Effect of Noise on DNA Sequencing via Transverse Electronic Transport

The prospect of sequencing an entire human genome for less than $1000 USD in a matter of hours is becoming closer to reality [1, 57, 19]. The original DNA-nanopore experiments of Kasianowicz et al. [4] showed polynucleotides can be pulled through nanoscale pores and their translocation detected by measuring the consequent blockage of the ionic current through the pore. Since then, numerous experimental studies have been performed using biological [5, 7, 9, 58, 59, 28] and synthetic nanopores [12, 15, 60, 16, 61, 62] which probe various physical properties of translocating polynucleotides. This has fueled an enormous amount of research into novel sequencing proposals based on nanopores or nanochannels [1, 57, 19].

One sequencing idea suggests detecting transverse electron currents as single-stranded DNA (ss-DNA) translocates through a pore [29, 64, 65, 66]. Previous theoretical work showed the four DNA nucleotides possess statistically distinguishable electronic signatures [29, 64] in the form of current distributions when accounting for structural distortions and partial control of the DNA dynamics (i.e., by a transverse field) [64, 65, 66]. These results indicate DNA sequencing is, in principle, possible via transverse current measurements. However, such studies have neglected scattering processes, such as fluctuations of the environment, which in-
Figure 5.1: Schematic representation of ss-DNA translocating through a pore while the transverse electronic current is collected. The light (purple) atoms are the silicon nitride pore and the dark (black) atoms represent the electrode surfaces within our molecular dynamics simulations. The single strand of DNA translocates through the pore pulled by a longitudinal electric field, $E_{\parallel}$, and the nucleotides also experience a transverse electric field, $E_{\perp}$. The white arrows around the DNA base indicate an acoustic phonon-like motion which contributes to the noise. The visualization was made with VMD [63].
roduce electronic noise, and may thus affect the ability to distinguish the bases.

Recently, experimentalists have successfully embedded electrodes into solid state nanopores and nanochannels [67, 68, 69, 70] and are getting closer to measuring electronic currents with single nucleotides present in the gap between the electrodes. When the latter is achieved, one question which will arise is how does the noise induced by the environment - noise which is beyond that due to “static” structural distortions of the nucleotides - affects the nucleotides’ electronic signatures, i.e., the current distributions. The environment is composed of ionic and water fluctuations and other excitations which may drastically affect the electron dynamics, and thus the current [56]. To complicate matters, the liquid environment can scatter electrons out of their current-carrying states by absorbing them into the solution and allowing the longitudinal field (that pulls the DNA through the pore) to carry them away. The influence of these and related factors can be very important, as seen in previous studies of electronic transport through DNA [71, 72, 73], and so far no study has examined such effects in detail.

In this chapter, we address these issues theoretically. Clearly, a fully time-dependent calculation with inclusion of all these types of scattering processes would be ideal [56]. However, the complexity of the problem we consider, both in the number of atoms involved and the type of scattering processes to take into account, makes this type of dynamical calculation unrealistic at present. Instead, we use a simplified model to capture some of the physics we deem important and leave a time-dependent treatment for future investigation.

In general, one expects any type of electronic noise to eventually destroy the capability to distinguish the DNA bases once its strength is sufficiently large. Indeed, we do find this type of behavior. However, the noise strength at which the electronic transport is negatively influenced is very large, beyond the strength one would expect in realistic experimental situations. This is due to the off-resonant nature of tunneling through the nucleotides, and we thus expect this result to be a common feature of molecular junctions. In other words, the separation of the energy levels of the nucleotides from the equilibrium Fermi level “protects” the electronic signature of the bases. The present study will thus help researchers
understand future experimental data, and provides further support to the viability of DNA sequencing via transverse electronic transport.

## 5.1 Setup and Methods

As our starting point, we employ molecular dynamics simulations performed with NAMD2 [3] to pull homogeneous ss-DNA through a Si$_3$N$_4$ nanopore with embedded gold electrodes. Our basic setup is shown in Fig. 5.1 and is the same as that used in previous work [64, 65], except the new trajectories here correspond to longer simulation times. These trajectories give us the real-time atomistic structure of ss-DNA as it propagates through the pore. With these structures, we calculate the electronic transport in the transverse direction across the pore. In the latter calculations, we include the effect of noise as discussed below.

The details of the simulations are as follows. The pore is made of 2.4 nm thick silicon nitride material in the β-phase. The nanopore hole has a double conical shape with a minimum diameter of 1.4 nm located at the center of the membrane and an outer diameter of 2.5 nm (see Fig. 5.1). The inner diameter is chosen wide enough such that ss-DNA is able to pass through but narrow enough that an appreciable tunneling current can be detected. The nanopore is then solvated in a TIP3 water sphere of 6.0 nm radius with spherical boundary conditions in an NVT ensemble and with a 1 M solution of potassium and chlorine ions. The CHARMM27 force field [43, 44] is used for the interaction of DNA, water, and ions, while UFF [46] parameters are used for the interaction of the Si$_3$N$_4$ membrane and other atoms. The Si$_3$N$_4$ atoms are assumed to be fixed during the simulation (this does not affect the conclusions). A 1 fs timestep is used and the system temperature is kept at room temperature with a Langevin dampening parameter of 0.2 ps$^{-1}$ in the equations of motion [14]. The van der Waals interactions are gradually cut off starting at 10 Å from the atom until reaching zero interaction 12 Å away. The energy was initially minimized in 1000 time steps.

A single strand of DNA is constructed by removing one strand from a helical, double-stranded polynucleotide created using the Nucleic Acid Builder of
the AmberTools package [74]. At the initial time of the simulation, the ss-DNA is placed parallel to the pore axis with the first base just inside the pore. The ss-DNA is driven through the pore with a global electric field of 6 kcal/(mol Åe) to achieve reasonable simulation times. In the calculation of the electronic transport, the longitudinal pulling field is turned off and a transverse field (of the same magnitude as that driving the current) is turned on at a moment when a base is between the electrodes. This approximates the situation when the transverse field is much larger than the longitudinal field. We envision this as the typical operating regime for a sequencing device as it allows for the suppression of a significant amount of structural distortion [64]. The particular time to stop the translocation is chosen by visual inspection. This stopping time is not particularly important because it generally takes on the order of hundreds ps for the transverse field, $E_\perp$, to align the nucleotide with the electrodes [65]. Single-stranded DNA differs from double-stranded DNA in that the persistence length of the polynucleotide is much shorter. This, in particular, allows for the base to quickly align with the perpendicular electric field. An example of this is reported in Fig. 5.2 where poly(C)$_{15}$ is such that a single C base is aligned parallel to a pair of opposite electrodes. A bias of 1 V oriented perpendicular to the base plane is then turned on. From the figure it is clear that, for this particular polynucleotide and initial condition, the base and backbone reorient themselves towards the field within about 800 ps. This is also confirmed by the currents as a function of time across two pairs of perpendicularly placed electrodes. At $t = 0$ the largest current is from the pair of electrodes parallel to the plane of the base, while after 800 ps, the largest current is from the opposite pair of electrodes. It is also evident from the figure that the rotation does not occur uniformly in time but it proceeds by fast rotations, followed by periods of time in which the system is temporarily trapped in a local energy minimum. Faster rotations have been observed with other initial conditions, transverse voltages and nucleotide strands [65], but we cannot exclude the possibility that, for other initial conditions, longer times would be needed for a complete rotation of the bases.

The current calculations are performed within a single-particle scattering approach using a tight-binding Hamiltonian (see, e.g., Ref. [56]). These calcula-
Figure 5.2: Currents as a function of time across two pairs of perpendicularly placed electrodes for poly(C)$_{15}$ with one base originally aligned parallel to a pair of opposite electrodes (see inset). The black current trace corresponds to the current from the black electrodes, and likewise the gray current trace corresponds to the gray electrodes. At time $t = 0$, a bias of 1 V oriented perpendicular to the base plane is switched on. The corresponding field aligns the base and backbone with the gray pair of electrodes (as shown in the inset), with a corresponding increase in the current across that pair of electrodes.
ctions include water, although, within our approach, water has little direct effect on the current [65]. “Snapshots” of the atomistic structure of ss-DNA between the gold electrodes are taken from the molecular dynamics at regular time intervals. These coordinate snapshots are used to obtain the tight-binding Hamiltonian. For each carbon, nitrogen, oxygen, and phosphorous atoms, \( s, p_x, p_y, p_z \) orbitals are used, whereas for gold and hydrogen only \( s \) orbitals are employed. The Fermi level is taken to be that of bulk gold \(^1\).

To obtain the current across the ss-DNA, we use the retarded Green’s function,

\[
G_{\text{DNA}}(E) = \frac{1}{ES_{\text{DNA}} - H_{\text{DNA}} - \Sigma_t - \Sigma_b - \Sigma_n},
\]

where \( E \) is the energy, \( S_{\text{DNA}} \) and \( H_{\text{DNA}} \) are the overlap and Hamiltonian matrices, respectively, of the contents of the gap between the electrodes (we will call it electronic junction), \( \Sigma_{t(b)} \) are the self-energy terms associated with the interaction between the electrodes and the junction contents, and \( \Sigma_n \) is the self-energy associated with the noise. The Green’s function for gold needed to calculate \( \Sigma_{t(b)} \) is approximated as in Ref. [75]. We use a white-noise term, which corresponds to a noise timescale via

\[
\tau_n = -\frac{\hbar}{\text{Im}\{\Sigma_n\}},
\]

and we also take \( \text{Re}\{\Sigma_n\} = 0 \) (see discussion below). This timescale sets a decay time due to interaction with the environment. The latter can be thought of as a noise probe that interacts with the contents of the junction [76, 56].

If we were to follow this type of reasoning we would then set the current in the probe to be zero and calculate the total transmission coefficient as

\[
T(E) = T_{tb}(E) + T_p(E),
\]

where

\[
T_{tb}(E) = \text{Tr} \left[ \Gamma_t G_{\text{DNA}} \Gamma_b G_{\text{DNA}}^\dagger \right]
\]

is the transmission coefficient that directly couples electrodes that measure the current in the presence of the noise probe with \( \Gamma_{t(b)} = i \left( \Sigma_{t(b)} - \Sigma_{t(b)}^\dagger \right) \). This

\(^1\)The tight-binding Hamiltonian is constructed at every snapshot using the YAEHMOP package (http://yaehmop.sourceforge.net/), with the Fermi level also consistently calculated using this method.
transmission contribution includes only elastic processes, as we discuss in more
detail below. The other term is

\[ T_p(E) = \frac{T_{tn}T_{nb}}{T_{tn} + T_{nb}} \]  

(5.5)

where

\[ T_{\mu\nu}(E) = \text{Tr} \left[ \Gamma_\mu G_{DNA} \Gamma_\nu G_{DNA}^\dagger \right] \]  

(5.6)

is instead the transmission from reservoir \( \mu \) to \( \nu \), namely it takes into account
processes that can drive electrons out of the electrodes into the noise probe and
vice versa.

The current is then given by

\[ I = \frac{2e}{\hbar} \int_{-\infty}^{\infty} dE T(E) \left[ f_t(E) - f_b(E) \right], \]  

(5.7)

where \( f_t(b) \) is the Fermi-Dirac function of the top (bottom) electrode [56]. The
current distribution for a nucleotide is the distribution obtained from the various
snapshots while the nucleotide fluctuates between the electrodes.

We will later make a microscopic connection to the above transmission
probability by starting with a Hamiltonian for independent electrons coherently
coupled to a phonon environment. However, this analysis leads us to conclude that
in the complex liquid environment the term in Eq. 5.5 cannot correctly represent
the physical situation at hand. In fact, retention of such term would give rise
to unrealistically large currents (several orders of magnitude larger than what we
present here). While this result would naively suggest that such currents could in
fact be observed in the present case, it is unlikely that the nanopore environment
would allow for the coherent coupling between the electrons and excitations that
gives this increased current. Furthermore, it is likely that due to the presence of
the longitudinal field that drives the DNA through the pore the electrons scatter
out of their current-carrying states. In this work we will then assume that current-
carrying electrons can be scattered into the complex liquid environment and retain
only the first term \( T_{ib} \) in the transmission probability of Eq. 5.3, and analyze its
effect as a function of the timescale strength \( \tau_n \). This is equivalent to assuming that
the liquid environment is represented by two probes connected to the junction, and
the probes’ electrochemical potentials are adjusted so that the combined current from the two probes into either electrode is zero. ²

5.1.1 Noise

As stated above, previous theoretical studies have shown the current distributions caused by DNA static structural distortions are statistically distinguishable [29, 64, 65, 66]. These studies, however, have not included the effects of external noise. We focus specifically on noise given by Eq. 5.2 because it represents many processes which happen in an experiment. These include fast processes, such as electronic interactions with bound waters or charges on the pore walls, and also slow processes, such as the dynamic movement of the DNA bases and ions. From visual inspection of the molecular dynamics simulations, we observe that the bases fluctuate in a way reminiscent of acoustic phonons, i.e., we observe only

²This condition entails that $I_1 + I_2 = 0$, where 1 and 2 are the two probes. This together with current conservation, $I_t + I_b + I_1 + I_2 = 0$, yields $I_t = -I_b$, which is the current calculated in this chapter.
low-energy excitations. An example of these excitations is represented in Fig. 5.1, where these slow oscillations, while not periodic, are mostly in the longitudinal direction. No oscillations where the bases are, e.g., in a “breathing mode”, that is where the base itself is expanding and contracting, causing large energy relaxation, were observed. At low bias, these are also unlikely to be excited by the electrical current itself, so that we expect a low exchange of energy with the current-carrying electrons [77, 78]. Furthermore, we assume the timescale for noise, Eq. 5.2, is a constant for all molecular states in the junction. In certain cases, this most likely overestimates the effect of the noise, but, on the other hand, it misses “colored noise” effects, where, for instance, the noise has a strong component at a particular frequency. In the absence of a physical model for such noise which is supported by experiments, its effect is only speculative at this stage, and we thus defer its study for future research.

5.2 Results and Discussion

We have performed current calculations for representative noise timescales [79]:

\[ \tau_n = \infty, 10^{-13}, 10^{-14}, 10^{-15}, 10^{-16} \text{ s} \]

The timescale of \(10^{-16} \text{ s}\) is a particularly fast and unphysical timescale but was used to show the onset of major differences in the current and current distributions.

For weak noise, \((\tau_n = 10^{-13} \text{ s} - 10^{-14} \text{ s})\), the average current itself is essentially unchanged as well as the distributions. The average percent change of an individual current value for \(\tau_n = 10^{-13} \text{ s}\) is only about 0.1 %. For \(\tau_n = 10^{-14} \text{ s}\), it is 1.5 %. However, for a single current count, the current may vary by orders of magnitude due to the noise, further strengthening the argument that a single base measurement is likely not enough to distinguish the bases [64]. From Figs. 5.3 and 5.4, \(\tau_n = 10^{-15} \text{ s}\) lowers the current on average and slightly alters the distributions. There is an average current reduction of about 30 %. At the unphysical fast timescale of \(10^{-16} \text{ s}\), the current is significantly lowered and the distributions are pushed into an unmeasurable regime. However, we are not aware of a physical process that may cause such strong noise under the experimental conditions.
Figure 5.4: Probability distributions for poly(A)$_{15}$ with various noise timescales for a transverse bias voltage of 1.0 V. The very light dashed lines correspond to the bins used to produce the current distributions. The solid lines are interpolated from the dashed ones. Like the current itself, only with very fast noise, $\tau_n = 10^{-16}$ s, does the distribution change and shift appreciably. At $\tau_n = 10^{-15}$ s, the distribution’s mean shifts slightly and it broadens somewhat.
envisioned in this work.

We have found above that even relatively strong noise does not negatively impact the current distributions. This may seem an unexpected result, and it will be helpful for future experimental and theoretical efforts to understand the reason for such an effect. We thus develop a model system to understand this behavior, as well as the noise processes we are including. Our starting point is based on our previous work on transverse transport through DNA [29, 64, 65, 66]. In an ideal configuration of a nucleotide between electrodes, the LUMO level of the base is closest to the gold Fermi level [1, 29] and also couples well to both electrodes. Thus, it is reasonable to treat a nucleotide in the electronic junction as a single energy level, $E_0$.

At this point we may consider a model Hamiltonian representing this level interacting with a bosonic environment $^3$

$$H = E_0 \hat{d} \dagger \hat{d} + H_{de} + \hat{d} \dagger \hat{d} \sum_k g_k (\hat{b} \dagger_k + \hat{b}_k) + \sum_k \omega_k \hat{b} \dagger_k \hat{b}_k,$$  \hspace{1cm} (5.8)

where $\hat{d} \dagger \hat{d}$ represents the occupation of the DNA LUMO level, $H_{de}$ is the DNA-electrode interactions, and $H_e$ is the electrodes’ Hamiltonian. The two remaining terms represent an interaction with a bosonic environment in the junction with interaction strength $g_k$ to each mode $k$. To get a tractable model, we make a few additional assumptions. First, we assume the junction DNA energy level is equally coupled to all levels of both electrodes and that we are at low enough bias and temperature (compared with electronic energies) that the electrodes bandwidth is effectively infinite. Second, we assume that the bosonic environment does not generate electronic correlations in the electrodes, which is reasonable for the small electrode coupling that we have here. Within these approximations, the real-time retarded Green’s function, Eq. 5.1, becomes [80, 81]

$$G_{DNA}(t) = -i \Theta(t) e^{-i \tilde{E}_0 t} e^{-\gamma t} e^{-\phi(t)}.$$

(5.9)

This Green’s function includes the coupling to the electrodes through the factor $e^{-\gamma t}$, where $\gamma$ is the coupling strength to both electrodes, and includes the coupling

$^3$For simplicity, we set $\hbar = 1$ in Eqs. 5.8-5.14.
to the bosons through the factor $e^{-\phi(t)}$ and the renormalized energy $\tilde{E}_0$. The bosonic term is
\begin{equation}
\phi(t) = \sum_k \frac{|g_k|^2}{\omega_k^2} \left[ n_k \left( 1 - e^{i\omega_k t} \right) + (n_k + 1) \left( 1 - e^{-i\omega_k t} \right) \right],
\end{equation}
where $n_k = 1/\left(\exp(\beta\omega_k) - 1\right)$ is the equilibrium occupation of mode $k$ at inverse temperature $\beta$. So long as the temperature is large compared to the boson cutoff frequency, $\omega_c$, then $n_k \approx 1/\beta\omega_k$ and $n_k \approx n_k + 1$, thus
\begin{equation}
\phi(t) \approx \sum_k \frac{2|g_k|^2}{\beta\omega_k^3} (1 - \cos \omega_k t).
\end{equation}
In terms of the spectral function, $J(\omega) = \sum_k |g_k|^2 \delta(\omega - \omega_k)$,
\begin{equation}
\phi \approx \int_0^{\omega_c} \frac{2J(\omega)}{\beta\omega^3} (1 - \cos \omega t) d\omega.
\end{equation}
Similarly, the renormalized energy state is
\begin{equation}
\tilde{E}_0 = E_0 + \int_0^{\omega_c} \frac{J(\omega)}{\omega} d\omega.
\end{equation}
For an ohmic boson bath [82], $J(\omega) = \alpha\omega$ for $\omega < \omega_c$. At high temperature with respect to its cutoff frequency, $\phi(t) \approx \eta t$, where $\eta = \alpha\pi/\beta$, and $\tilde{E}_0 = E_0 + \alpha\omega_c$.

Generally $\omega_c$ is quite small compared to molecular energies, we thus ignore the energy shift, which is valid except when the noise strength is very large. This gives
\begin{equation}
G_{DNA}(E) = \frac{1}{E - E_0 + i\gamma + i\eta},
\end{equation}
for the retarded Green’s function. In this work, $\eta = \hbar/\tau_n = 0, 6.6 \times 10^{-3}, 6.6 \times 10^{-2}, 6.6 \times 10^{-1}, 6.6$ eV for the timescales considered. For an interacting junction as given by the Hamiltonian in Eq. 5.8, the current is given by (using Eq. 4.114 in Ref. [56])
\begin{equation}
I(\eta) = \frac{2e^2V}{\hbar} \left[ \frac{\gamma^2}{E_0^2 + (\gamma + \eta)^2} + \frac{\eta\gamma}{E_0^2 + (\gamma + \eta)^2} \right].
\end{equation}
The first and second terms represent precisely the first and second contribution in Eq. 5.3, respectively. However, as we have previously discussed, within this model calculation, the liquid environment is allowed to form coherent interactions
Figure 5.5: Current distributions of a model system for the Adenine nucleotide represented by a single energy level $E_0$. The current distribution on a logarithmic scale is taken to be Gaussian in similarity to Fig. 5.4 for no noise. As noise is turned on, at first the distribution does not change at all, but around $\eta \approx E_0$, where $\eta = h/\tau_n$ measures the strength of the noise, the distribution starts to shift. At larger $\eta$, the peak of distribution shifts to lower values as $\eta^{-2}$. The off-resonant tunneling, indicated by large $E_0$ as measured from the Fermi level, “protects” the current distributions from noise.
with the current-carrying electrons inside the junction. This results in the second term giving rise to orders of magnitude increase in the total current to values that are unlikely in the present setting. In the junction, one has to consider also that the bosonic environment scatters the current-carrying electrons in all directions, including along the pore channel where they can be collected into the liquid. This effect is exacerbated by the fact that the environment both carries some longitudinal momentum and can act as a sink for electrons as well, due to the longitudinal bias. Therefore, on physical grounds, we assume that such processes occur which provide only the first contribution to the current in Eq. 5.3. Again, this is equivalent to assuming a two-probe noise model, as we have discussed previously. Under this assumption and for $\gamma \ll E_0$, the expression in Eq. 5.15 becomes
\[
I(\eta) \approx \frac{2e^2V}{\hbar} \frac{\gamma^2}{E_0^2 + \eta^2},
\]
(5.16)
i.e., the current for just a single structural distortion for linear response and weak coupling, and in the absence of inelastic processes that enhance the current. Note, that irrespective of this approximation, our main conclusions would be qualitatively unchanged.

We know from above that the current acquires a distribution when structural distortions of the DNA are taken into account. Under the assumptions that went into Eq. 5.14 we can introduce these structural distortions by allowing $E_0$ or $\gamma$ to acquire distributions. From Fig. 5.4, it is clear that the current distributions on a logarithmic scale can be approximated as a Gaussian when no noise is present, which indicates that the coupling to the electrodes is controlling these distributions, as only the coupling fluctuates on an exponential scale. By assuming the coupling to both electrodes is identical, we miss structural distortions which bring the base into closer proximity to one electrode and farther from the other. However, this is unlikely to affect the essential physics.

Now, let us calculate the distribution of $\gamma$’s using the curve in Fig. 5.4 with no noise. Using the fact that the current distribution on a logarithmic scale is approximately a Gaussian, and that we are in a weak coupling regime ($\gamma \ll E_0$), $\ln \gamma/\gamma_m$, where $\gamma_m$ is the maximum likelihood coupling strength, should also follow
a Gaussian distribution,

$$p(\ln \gamma / \gamma_m) = \frac{1}{\sqrt{2\pi \sigma_\gamma^2}} \exp \left\{ -\frac{(\ln \gamma / \gamma_m)^2}{2\sigma_\gamma^2} \right\},$$

(5.17)

with the standard deviation $\sigma_\gamma = \sigma_I/2 \approx 0.45$, where $\sigma_I$ is the standard deviation of $\ln I/I_m$ with $\eta = 0$ and $I_m$ the maximum value. (Note that the relatively small standard deviation of the current distributions $\ln I/I_m$, as seen in Figs. 5.4 and 5.6, is a result of the control exerted by the transverse field [64, 65].) The maximum, $\gamma_m$, appears at $6.8 \times 10^{-4}$ eV, when $E_0 = 1$ eV, which is approximately the energy separation of Adenine’s LUMO from gold’s Fermi level [1]. We assume that the standard deviation of $\ln \gamma / \gamma_m$ does not change when we turn on the noise. The resulting current distributions are plotted in Fig. 5.5.

Although we assume in our model that the distributions stay Gaussian with the same standard deviation no matter what the noise strength, our model explains the key features found in our numerical simulations. The fact that the molecular energy levels are far away from the electrode Fermi level “protects” the distributions from this type of noise. This is represented by the term $(E_0^2 + \eta^2)^{-1}$ in the current (Eq. 5.16). The other features that appear, such as increased broadening and eventual multiple peak development, are not explained by our simple model. These are due to multiple energy levels, $E_i$, of the fluctuating nucleotide junction, contributing to transport. The contribution from each reaches its turning point, $\eta \approx E_i$, at a different value of $\eta$ and thus the single peak broadens and develops into multiple peaks.

We now examine the role of transverse bias on the distributions for two different noise strengths (i.e., no noise and a timescale of $\tau_n = 10^{-15}$ s). The results for the cases of 0.1 V and 1.0 V transverse biases are presented in Fig. 5.6. Previous work has shown that the transverse bias has a nonlinear effect on the mean of the distribution [65]. This is due to both a pulling effect of the backbone toward one electrode as the field is increased with consequent alignment of the base toward the other electrode, and the steric effect of the alignment of the backbone with one of the electrodes. Therefore, while one can expect the mean current to be
Figure 5.6: Normalized current distributions for the four nucleotides at a transverse bias voltage of 1.0 V (top) and 0.1 V (bottom). The solid lines correspond to an infinite noise timescale (no noise) and the dark dashed lines represent the distributions for $\tau_n = 10^{-15}$ s, with the light dashed lines representing the bins used to produce the distributions.
shifted to lower values with lower bias, the degree to which this occurs is not easy to determine a priori. This is especially true with the smaller base T. For this base, one cannot always expect perfect alignment at all times with the electrodes even in the presence of a stabilizing transverse field, further emphasizing the statistical nature of this problem. These effects can be seen in Fig. 5.6. In addition, one can see that all of the distributions are shifted slightly to lower current values due to noise, corresponding to an overall lowering of the current magnitude. However, the distributions themselves are very similar to the case of an infinite timescale (zero noise).

Finally, given these distributions and the accuracy with which we want to sequence DNA, we can answer the question of how many independent electrical current measurements one needs to do in order to sequence DNA within that accuracy. The number of current measurements will dictate how fast we can sequence. We can estimate this speed from the distributions of Fig. 5.6 by calculating the statistical likelihood for all configurations of a given base in the junction region and multiplying it by the probability that we can tell this base from all other bases for the value of the current at that specific configuration. The average probability that we can correctly sequence a base after $N$ measurements is then given by

$$<P> = \sum_{X=A,C,G,T} \frac{1}{4} \sum_{\{I_n\}} \prod_{n=1}^{N} P^m_X$$

where $A$, $C$, $G$ and $T$ are the distributions for the four bases. $P^m_X$ is the probability that a base is $X$ considering only the current for measurement $n$, which can be found by comparing the ratios of the four distributions. The sum over $\{I_n\}$ is a sum over all possible sets of measurements of size $N$. The inset of Fig. 5.7 shows $1 - <P>$, the exponentially decaying ratio of falsely identified bases versus number of independent counts (measurements) of the current averaged over the four bases, where the ensemble average is performed using multiple realizations of current sets, $\{I_n\}$.

We can see that if, for instance, we want to sequence DNA with an error
Figure 5.7: We show here again the distributions for the four bases under a transverse bias of 1.0 V. We can use Eq. 5.18 to find the error percentage given a number of measurements. This is plotted in the inset. Due to the distinguishability of the distributions, it will take only about 35 measurements to obtain a 0.1% error rate. This leads to a sequence time for an entire human genome of about 3 hours under ideal conditions.

of 0.1%, we need about 35 electrical current measurements to distinguish the four bases. If we are able to collect, say, $10^7$ measurements of the current per second (a typical rate of electrical current measurements), we can sequence the whole genome in less than three hours without parallelization. This is the case with or without the introduction of electronic noise. These estimates may vary with different device structures but are representative of the speeds attainable with this sequencing method.

5.3 Conclusion

In conclusion, we have presented results combining molecular dynamics simulations with quantum mechanical current calculations including a model of noise generated by the complex liquid environment in which the DNA translocation and interrogation takes place. We have shown that for reasonable timescales, e.g., down
to $10^{-15}$ s, the noise considered here will likely not affect the distinguishability of the current distributions obtained from measuring the transverse electronic current of the different DNA nucleotides. At extremely fast timescales, below $10^{-15}$ s, the distributions are significantly altered, but this is beyond physically reasonable times for the experimental system we are considering. We have also proposed a simple model system which provides insight into the physical mechanisms of noise and why the current distributions are protected. This is due to the off-resonant nature of tunneling through the nucleotides and thus it is likely to be a general property of transport in organic molecules. While the distributions are only mildly affected, we have shown that the type of noise we consider can potentially alter a single current count significantly, further supporting the notion that only a statistical study of the transverse currents can potentially distinguish the nucleotides. We finally note that while our study is done for a nanopore geometry, the results are applicable to other types of sequencing devices as well, such as the nanochannels of Refs. [69, 70] used in transverse electronic measurements.
ACKNOWLEDGEMENTS

We thank Yonatan Dubi and Johan Lagerqvist for useful discussions. This research is supported by the NIH-National Human Genome Research Institute and by the U.S. Department of Energy through the LANL/LDRD Program.

Chapter 5 is in part a reprint of the material as it appears in Matt Krems, Yuriy V. Pershin, Mike Zwolak, and Massimiliano Di Ventra, “Effect of Noise on DNA Sequencing via Transverse Electronic Transport,” Biophysical Journal 97, 1990 (2009). The dissertation author was the primary investigator of this paper.
Chapter 6

Ionic Memcapacitive Effects in Nanopores

As discussed in a previous chapter, a nanopore is an aperture of nanoscale dimensions across an insulating membrane. This way, if immersed in an ionic solution, ions can enter the nanopore, and if subject to an electric field of given strength, they may enter it from one side of the opening and emerge on the other side. The membrane can be made of either biological or solid-state materials. Nanopores are ubiquitous in biological systems as they regulate the flow of ions across cell membranes (of, e.g., neurons). At present, they are also actively investigated for potential applications in DNA sequencing [1, 19]. Despite its apparent simplicity, ion dynamics in nanopores is far from trivial. An example of this is provided by the recently predicted phenomenon of “quantized ionic conductance”, namely the presence of current steps occurring at effective pore radii that match the radii of the water hydration layers that form around the ions [35].

Here, we predict another intriguing property of ion dynamics in nanopores, when the latter are subject to a periodic external electric field. In particular, we show that the electric field forces ions to accumulate at the two surfaces of the nanopore membrane, creating an effective capacitor. However, this capacitor shows interesting features as a function of the frequency of the field, namely a hysteresis loop of the capacitance (memory-capacitance or \textit{memcapacitance} for short [83]) as a function of voltage which diverges at zero voltage and displays
negative-capacitance properties. Memcapacitors have been theoretically formulated in Ref. [83] and belong to the wider class of memory-circuit elements, which includes also memristors and meminductors, namely resistors and inductors with memory. Following Ref. [83] we define a voltage-controlled memcapacitive system by the set of equations

\[
Q(t) = C(x,V,t)V(t) \tag{6.1}
\]

\[
\dot{x} = f(x,V,t) \tag{6.2}
\]

where \(Q(t)\) is the charge on the capacitor at time \(t\), \(V(t)\) is the voltage across it, and \(C\) is the time-dependent memcapacitance which depends on the internal state of the system described by a set of \(n\) state variables \(x\), with \(f\) a continuous \(n\)-dimensional vector function. Using all-atom molecular dynamics (MD) simulations, we indeed demonstrate that memory characteristics of nanopores in solution originate from the finite mobility of ions in water with consequent slow polarizability of the ionic solution. We also develop a simple microscopic model that captures the main properties observed in the simulations and allows us to extend our results to regimes beyond the reach of MD simulations. Additionally, we use an equivalent circuit formulation to discuss how ionic transport through the nanopore itself may lead to an additional memory mechanism. We also propose ways our predictions could be tested with available experimental capabilities.

### 6.1 Ionic memcapacitors

In order to show that a nanopore in solution indeed acts as a memcapacitive system (Eqs. (6.1) and (6.2)), let us be more specific and consider the experimental situation as depicted in Fig. 6.1 which we suggest as a way to observe the effects predicted here. An external (time-dependent) voltage \(V(t)\) is applied to electrodes which form an effective capacitor with the ionic solution and the nanopore at its interior. In this chapter, we consider a typical setup for, e.g., DNA sequencing devices [64, 65, 84] with KCl ionic solution and a Si₃N₄ nanopore 25 Å thick and 88 Å wide with a 7 Å radius cylindrical hole drilled through the center of the
Figure 6.1: Left: a snapshot of the molecular dynamics geometry at a time when a buildup of charges of the opposite sign on each side of the nanopore is observed due to a finite electric field $E$. The nanopore membrane is located at the center (represented by the red lines) and water is not visible. Top and bottom horizontal red lines represent electrodes (holding plate charges $\pm Q(t)$) of the suggested experimental set-up needed to observe the predicted memcapacitive effects. Right: simplified equivalent circuit model.
membrane. However, the specific dimensions of the pore are irrelevant for the overall conclusions of this work and similar considerations would apply also to biological pores. When a global time-dependent bias is applied to the system, the ionic solution is polarized and ions are forced to accumulate at the surfaces of the pore (see Fig. 6.1). First, we consider relatively short time scales when ion transport across the nanopore is not significant. (We will discuss towards the end of the chapter the effect of ion transport across the pore at longer times.) This implies that the same (and opposite in sign) charge, \( Q(t) \), that accumulates on the surfaces of the pore also accumulates on the plates of the capacitor.

In the simplest approximation, the electrical properties of the total nanopore system can be approximated by an equivalent circuit model as shown in Fig. 6.1, where capacitors and resistors (generally, non-linear) represent different parts of the system. Here, \( C_{e-s} \) denotes the external electrode-solution capacitance, \( R_s \) is the resistance of the solution, \( R_{ss} (\gg R_s) \) is the resistance of the ion current through the pore, and \( C_{ss} \) is the capacitance of the membrane. The total voltage drop is then given by

\[
2 \frac{Q}{C_{e-s}} + 2R_s \frac{dQ}{dt} + \frac{Q}{C_{ss}} = V(t). \tag{6.3}
\]

Since we are interested in the properties of the pore and solution only, we envision the experimental set-up so that \( C_{e-s} \gg C_{ss} \). The equation for the charge then takes the form

\[
\frac{dQ}{dt} = \frac{V(t)}{2R_s} - \frac{Q}{2R_s C_{ss}}. \tag{6.4}
\]

Eq. (6.4) describes a relaxation of \( Q \) towards \( V(t)/(2R_s) \) with a relaxation time \( 2R_s C_{ss} \). Generally, due to the finite mobility of ions in water, the charge on the external plates - and hence on the pore - is slow to respond to changes of the bias upon varying \( V(t) \). This means that \( V(t) \) may be zero when \( Q(t) \) is finite and vice versa. Therefore, the capacitance of this whole system, \( C = Q(t)/V(t) \), depends on the applied voltage history, shows divergences and acquires negative values at specific times, similar to what has been recently predicted in some solid-state memcapacitors [85]. Since these memory effects can be viewed as originating from the history-dependent permittivity of the ionic solution, following the defi-
nition of Ref. [83] (Eqs. (6.1) and (6.2)), a nanopore in ionic solution is indeed a memcapacitive system.

6.2 Results and Discussion

Let us now demonstrate these memcapacitive effects from a microscopic point of view. For this we employ all-atom MD simulations using NAMD2 [3] and investigate the response of the system to external ac- and dc-electric fields. According to our previous discussion, in order to calculate the total capacitance of the system we only need the net charge that accumulates at the nanopore surface. We then employ periodic boundary conditions in both the direction perpendicular and parallel to the external field. On each side of the pore, we place a 50 Å long section of water with a 1 M solution of a homogenous, random distribution of potassium and chlorine ions. The CHARMM27 force field [43, 44] is used for the interaction of water and ions while quantum mechanical parameters [46] are used for the $\text{Si}_3\text{N}_4$ pore $^1$.

We have performed extensive MD simulations of the process of polarization of the ionic solution in proximity to the nanopore membrane. As a general observation, within the parameters used, a delay between the formation of ionic polarization and both the external ac-electric field and the voltage across the pore has been observed. This is evident in Fig. 6.2 where the net charge of ions on one side of the nanopore is plotted as function of time together with the voltage drop across the membrane. The latter is obtained by doing a full electrostatics calculation from MD simulations [86]. At this point we remark that in all our simulations we have found that the net charge induced by the external field is always located within 10 Å from the membrane surface and that the voltage drop across the membrane is very close in value to the external applied voltage, what-

$^1$The $\text{Si}_3\text{N}_4$ atoms are harmonically confined in order to mimic the dielectric properties of $\text{Si}_3\text{N}_4$. A 1 fs time step is used and the system temperature is kept at room temperature with a Langevin dampening parameter of 0.2 ps$^{-1}$ in the equations of motion [14]. The van der Waals interactions are gradually cut off starting at 10 Å from the atom until reaching zero interaction 12 Å away. The energy was initially minimized in 1000 time steps and then equilibrated for 1 ns with a zero electric field.
Figure 6.2: Net charge on the surface of the nanopore (equal to system’s plate charge) and voltage across the nanopore (which is very close to the external voltage, solid line) plotted as a function of time. The solid line for the charge corresponds to the model we discuss in the text. One can clearly see that the net charge lags behind in time with respect to both the external voltage and the voltage at the pore.
Figure 6.3: Net charge of the positively charged side of the capacitor vs. time when a constant 20 V applied voltage responsible for the accumulation of charges on the surface of the pore is turned off. A decay timescale of 75 ps is obtained by fitting the simulation results with an exponential decay curve, i.e., \( Q(t) = Q_{\text{max}} e^{-t/\tau} \). Due to the nearly equal mobilities of \( K^+ \) and \( Cl^- \) [87], we find similar results for the negatively charged side and different field strengths as well. This is shown in the inset with initial voltage of 5 V.

ever the strength and frequency of the latter. This last observation is consistent with previous studies [1].

Next, we fit these MD simulation results employing the equivalent circuit model given by Eq. (6.4). Using microscopic parameters, Eq. (6.4) can be rewritten as

\[
\frac{dQ(t)}{dt} = 2e A \mu n E(t) - \frac{Q(t)}{\tau},
\]

where \( A \) is the area of the membrane surface, \( \mu \) is the ion mobility which is similar for both types of ions and we take to be \( 7.12 \times 10^{-8} \, m^2V^{-1}s^{-1} \) [87], \( e \) the ion charge, \( n \) the density of ions in the bulk, and \( \tau = 2R_sC_{ss} \) is the relaxation time. The factor of 2 takes into account the conductivity of both channels (\( K^+ \) and \( Cl^- \)). Using dc-field simulations, we were able to extract \( \tau \). We do this by first applying a constant electric field (with the same magnitude as the amplitude of our ac-field simulations) which forces ions to accumulate in the vicinity of the membrane as it is shown in Fig. 6.1. The total net charge within 10 Å from the nanopore
surface is integrated to obtain the capacitor charge. Then, we turn off the field and monitor the decay of this charge back into the bulk (see Fig. 6.3). From this we obtain the relaxation time \( \tau \). We find that this time is slightly dependent on the amplitude of the initially applied electric field, becoming slightly longer as the applied field decreases. For voltages as low as 5 V across the membrane we get from our simulations a relaxation time \( \tau \sim 75\text{ps} \).

Solving Eq. (6.5) for \( Q(t) \) with an ac electric field \( E(t) = E_0 \sin(\omega t) \) of amplitude \( E_0 \) and angular frequency \( \omega = 2\pi f \), we obtain the long-time limit solution:

\[
Q(t) \underset{t \to \infty}{\to} \frac{2A\mu enE_0 \sin(\omega t)}{(1 + \frac{1}{\omega^2\tau^2}) \omega^2 \tau} - \frac{2A\mu enE_0 \cos(\omega t)}{(1 + \frac{1}{\omega^2\tau^2}) \omega} \quad (6.6)
\]

which amounts to a sine function with a phase shift, namely \( Q(t) = Q_0 \sin(\omega t - \delta) \), where

\[
Q_0 = \left[ \left( \frac{2A\mu enE_0}{(1 + \frac{1}{\omega^2\tau^2}) \omega} \right)^2 + \left( \frac{2A\mu enE_0}{(1 + \frac{1}{\omega^2\tau^2}) \omega^2 \tau} \right)^2 \right]^{1/2} \quad (6.7)
\]

and \( \delta = \tan^{-1}(\omega\tau) \). Using the appropriate values of \( A \), \( n \), and \( \tau \) as obtained from the numerical simulations, this model agrees very well with the results of our MD simulations as it is evident from Fig. 6.2. In particular, it is clear that the net charge and voltage on the capacitor are phase shifted by the amount \( \delta \). This means that when the voltage is zero the charge on the capacitor is not necessarily zero, and vice versa. This is shown in Fig. 6.4(a) where the net charge is plotted as a function of the voltage across the capacitor. This gives rise to diverging and negative values of capacitance.

To see this, we write the external voltage across the whole system as \( V(t) = V_0 \sin(\omega t) \), with \( V_0 = -E_0d \) where \( d \) is the size of the simulation cell along the direction of the electric field. From \( C = Q(t)/V(t) \) and (6.6) we then obtain the long-time limit of the capacitance:

\[
C(t) \underset{t \to \infty}{\to} \frac{2A\mu en}{(1 + \frac{1}{\omega^2\tau^2}) \omega^2 \tau d} - \frac{2A\mu en}{(1 + \frac{1}{\omega^2\tau^2}) \omega d} \cot(\omega t), \quad (6.8)
\]

\(^2\)Here, we do not consider possible protonation of water which may cause the number of mobile charges to increase and thus change the number of charges that buildup on the pore, effectively increasing the ionic concentration.

\(^3\)Smaller voltages give rise to a very noisy net charge, and it is thus difficult to extract a relaxation time from them.
Figure 6.4: Upper panel: net charge $Q$ versus a periodic voltage of amplitude $V_0 = 1$ V and different frequencies as obtained from Eq. 6.6. The inset shows the same quantity for $2$ GHz and $V_0 = 20$ V compared with the charge obtained directly from our MD simulations. Lower panel: capacitance versus a periodic voltage of frequency $f = 10$ MHz and amplitude $V_0 = 1$ V as obtained from Eq. 6.8. In the inset we show the same quantity for $f = 2$ GHz and $V_0 = 20$ V compared with the capacitance obtained directly from our MD simulations. It is seen that $C$ can be both negative and diverges as the voltage approaches zero. The arrows indicate the direction the voltage is swept in time and the numbers show the order in which the trace is generated.
This represents the main result of this work. It shows that the capacitance of the whole nanopore system is history-dependent, diverges when the voltage crosses its zero value, and acquires negative values within a certain voltage range. This is plotted in Fig. 6.4 where both the charge on the capacitor and the capacitance are plotted as a function of voltage across the capacitor. From Fig. 6.4 it is evident that at low frequencies, this ionic memcapacitor behaves almost like a regular capacitor. At higher frequencies, memory effects in the capacitance manifest in a hysteresis loop characteristic of memcapacitors. However, unlike typical memcapacitors that show a pinched hysteretic loop [83], ionic memcapacitors have a non-vanishing (diverging) zero-bias capacitance.

Memory at small frequencies — At small enough frequencies, there will be enough ion transport through the pore to play a role in the dynamics. In fact, it is no longer correct to assume that the charge associated with \( C_{e-s} \) is the same as the charge associated with \( C_{ss} \). Using Kirchoff’s loop rule, we get an equation similar to Eq. (6.3):

\[
2 \frac{Q_{e-s}}{C_{e-s}} + 2R_s \frac{dQ_{e-s}}{dt} + \frac{Q_{ss}}{C_{ss}} = V(t). \tag{6.9}
\]

except now we differentiate between the two charges, \( Q_{e-s} \) (on the external plates) and \( Q_{ss} \) (on the pore). Applying Kirchoff’s junction rule we then get

\[
\frac{dQ_{e-s}}{dt} = \frac{dQ_{ss}}{dt} + \frac{V_{ss}}{R_{ss}}. \tag{6.10}
\]

where due to \( C_{ss} \) and \( R_{ss} \) being in parallel, \( V_{ss} \) is simply the voltage on the \( C_{ss} \) capacitor, \( Q_{ss}/C_{ss} \), and we can approximate the conductance across the pore as \( 1/R_{ss} = 2A_p\epsilon n\mu/L_p \) where \( A_p = \pi r_p^2 \), with \( r_p \) the pore radius, \( \epsilon \) the electronic charge, \( n \) the ion density, \( \mu \) the ion mobility, and \( L_p \) the length of the nanopore. We approximate \( C_{ss} \) as that of a parallel plate capacitor, i.e., \( C_{ss} = \epsilon A/L_p \) with \( \epsilon \) the permittivity of Si\textsubscript{3}N\textsubscript{4}, and \( A \) is again the area of the membrane surface. We can solve Eq. 6.9 for \( Q_{ss} \) and plug it into Eq. 6.10 to arrive at the following second order equation for \( Q_{e-s} \).
Figure 6.5: Memcapacitive effects due to ionic transport across the pore. Main panel shows the charge on the external capacitor plates plotted versus the voltage across it for various frequencies of the electric field with $V_0 = 1.0 \, V$, $A = 10 \, \mu m^2$, $L_p = 25 \, \AA$, $r_p = 7 \, \AA$, $\epsilon = 7.5\epsilon_0$, $C_{ss} = \epsilon A/L_p$, and $C_{e-s} = 10C_{ss}$ for a 1 M concentration of ions. The inset shows the capacitance plotted versus the voltage for the same frequencies. Memory effects due to ionic transport across the pore occur at much lower frequencies than those due to the polarization of the ionic solution.

\[
2R_sC_{ss} \frac{d^2Q_{e-s}}{dt^2} + \left( 1 + 2 \frac{C_{ss}}{C_{e-s}} + 2 \frac{R_s}{R_{ss}} \right) \frac{dQ_{e-s}}{dt} + 2 \frac{Q_{e-s}}{R_{ss}C_{e-s}} = \frac{V(t)}{R_{ss}} + C_{ss} \frac{dV(t)}{dt} \quad (6.11)
\]

For an ac field, this equation can be solved analytically but the solution is a bit involved. We then just plot it for different frequencies in Fig. 6.5. As anticipated, we see that direct transport across the pore leads to an additional memory mechanism at specific frequencies, much smaller than the ones due to the polarization of the ionic solution.
6.3 Experimental Test

The results presented in this chapter show that there are two very distinct memory regimes for nanopores in solution. To observe the first memory mechanism due to the polarization of the ionic solution, ideally, one would need high frequencies (on the order of 1GHz). On the other hand, much smaller frequencies (on the order of 1KHz) are necessary to observe the additional memory effect due to transport through the pore. This indicates that the second memory mechanism would be the easiest one to detect. However, in both cases we have shown that the capacitance acquires diverging (and also negative) values. This result appears to hold also at frequencies that are relatively smaller than those required to observe the first memory regime, namely at frequencies that are on the order of tens of MHz or less (see Fig. 6.4). Therefore, with appropriate control of the external circuit, at these frequencies one should at least be able to observe non-trivial changes (manifested, e.g., in fast jumps between positive and negative values) of the capacitance when the bias crosses its zero value. We thus expect that by simultaneously measuring the electric charge on the external electrodes as shown in Fig. 6.1 (or, equivalently, the current at the electrodes) in the presence of an applied time-dependent voltage should allow a direct verification of our predictions for both types of memory.

As an additional suggestion to experimenters, one should be able to see memcapacitance behavior by looking at the lag of the current in the overall system with the applied external voltage. We see our nanopore system as an effective parallel RC circuit, where the hole in the pore itself acts as a resistor and the nanopore as the capacitor. From geometrical considerations, these two would clearly have the same voltage, thus being in parallel. In a RC parallel circuit with fixed R and fixed C (i.e. non-memcapacitive behavior), we would expect a 90 degree lag of the total current with the voltage, but now we have an extra effect due to the fact that the capacitance depends on time (see Eq. 6.8):

$$I = \frac{V}{R} + C \frac{dV}{dt} + V \frac{dC}{dt}$$

(6.12)

using Kirchoff’s junction rule. Without the extra term $\left(V \frac{dC}{dt}\right)$, one would have a
Figure 6.6: We can plot the predicted current of the model versus the actual current we obtain from our molecular dynamics simulations. We ignore the initial transient current in the plot. One can see there is a very good agreement between the model and the simulations.

lag of 90 degrees of the total current with the voltage, but this extra term causes a deviation from this. Using Eq. 6.8, our model gives for the total current, $I$:

$$I = \frac{V_0}{R} \sin(\omega t) + Q_0 \omega \cos(\omega t - \delta)$$  \hspace{1cm} (6.13)

where we take $R$ to be infinity, which is a good approximation as very few ions go through the pore compared to buildup of charge on the capacitor in the high frequency regime.

By measuring the lag, $\delta$, in the total current vs. the applied voltage, we can see if there is a memcapacitive effect. To emphasize the memcapacitive effect (and for the sake of speed), the voltage we use in our simulations is much higher than what would be used in experiments. Nonetheless, we can use our model which is fitted for voltages we use in our simulations to predict memcapacitive behavior in systems with more reasonable external voltages. Ultimately, what leads to memcapacitive effects is that the ions take a certain time, $\tau$ to react to the changing voltage. If $\tau \ll 1/\omega$, then one would expect that the time for the ions to follow the field would be negligible and we would be in the regime of a
normal capacitor. We use the same parameters for our model as in the previous calculations except now, we used a frequency of 10 MHz and an external voltage of 1.0 V with the same decay timescale. For most of the voltage range, it looks like we have a normal capacitor, but at small voltages we see the infinite capacitance effects (see Fig. 6.4 inset). This leads to a potentially measurable lag in the current as discussed above, or one can measure the capacitance directly from the charge and the voltage, which may be a harder measurement to make.

6.4 Conclusions

We have shown, using molecular dynamics simulations, that a nanopore sequencing setup acts as a memcapacitor, namely a capacitor with memory [83]. The latter is due to two types of effects, and thus arises at very different frequencies of the external bias. At high frequencies the finite mobility of ions in water and hence the slow polarizability of the ionic solution give rise to one type of memory. Memcapacitive effects, however, may also occur as a result of the ion transport through the pore at very low frequencies. These processes occur internally in the system and, from the point of view of an external circuit, the whole system behaves as an unusual capacitor. These effects may potentially play a role in nanopore DNA sequencing proposals, especially those based on ac-electric fields [88], as well as in other nanopore sensing applications. Moreover, the effect of the charge buildup on the nanopore surface may influence DNA translocation and its structure in proximity to the pore. Finally, due to the ubiquitous nature of nanopores in biological processes, these results may be relevant to specific ion dynamics when time-dependent fields are of importance, such as in the action potential formation and propagation during neuronal activity. We thus hope this work will motivate studies in this direction.
ACKNOWLEDGEMENTS

We thank Heiko Appel for useful discussions. Financial support from the NIH-National Human Genome Research Institute is gratefully acknowledged.

Chapter 6 is in part a reprint of the material as it appears in Matt Krems, Yuriy V. Pershin, and Massimilian Di Ventra, “Ionic Memcapacitive Effects in Nanopores”, *Nano Letters* **10** 2674 (2010). The dissertation author was the primary investigator of this paper.
Chapter 7

Ionic Coulomb Blockade in Nanopores

Recently, there has been a surge of interest in nanopores due to their potential in several technological applications, the most notable being DNA sequencing and detection [1, 19]. In addition, nanopores offer unprecedented opportunities to study several fundamental physical processes related to ionic transport in confined geometries. For example, due to the tightly bound hydration layers surrounding an ion, it may be possible to observe steps in the conductance due to the shedding of water molecules in the individual layers as the ion-water “quasi-particle” passes through the pore opening [35, 36]. This can be viewed as the classical analog of the electron conductance quantization in nanoscopic/mesoscopic systems (see, e.g., Ref. [89, 90]).

In this chapter, we discuss another fundamental physical process which may occur in nanopores due to screened ion-ion interactions. This many-body effect originates when ions flow under the effect of an electric (or pressure) field and build up in nanopores of specific capacitances, so that the flow of additional ions is hindered. To be specific, Fig. 7.1 shows a typical pore geometry we have in mind with an opening wider than the other so that ions of one polarity can easily accumulate inside the pore, while ions of opposite polarity will accumulate outside the narrow opening of the pore. This effect is similar to the Coulomb blockade phenomenon experienced by electrons transporting through a quantum dot weakly
Figure 7.1: Right panel: a snapshot of a molecular dynamics simulation of 1M KCl solution subject to an electric field and translocating through a cone-shaped Si$_3$N$_4$ pore (indicated by the yellow and blue atoms) at a pore slope angle of 45° with a bottom opening of 7 Å radius and thickness of 25 Å. Cl$^-$ ions and K$^+$ ions are colored aqua and brown respectively. The symbols $\gamma_t$ and $\gamma_b$ indicate the rates of ion transfer at the bottom and top openings, respectively. The field used to generate this figure is 5.0 kcal/(molÅe) which allows an easier visualization of the ions build-up. Left panel: the net charge density corresponding to the right panel configuration. It is clear that in this case there is an accumulation of Cl$^-$ ions inside the pore while the K$^+$ ions are located mostly outside the pore.
coupled to two electrodes - in the sense that the tunneling resistance between the electrodes and the dot is much larger than the quantum of resistance [91]. Like the quantum case, we also expect ionic Coulomb blockade to occur when the nanopore is “weakly coupled” to at least one ion reservoir. In this case, this means that the average time it takes an ion to “cross” the weak contact link is much longer than the average time it takes the same ion to propagate unhindered by the pore. In other words, the “contact” ionic resistance of the pore with at least one reservoir has to be much larger than the resistance offered to ion flow without the pore. From previous work [35, 36] we know that such a situation may be realized when the pore opening is in the “quantum” regime, namely when the pore radius is small enough that an ion has to shed part of its hydration layers to cross the pore aperture.

The analogy with the electron case seems therefore complete safe for a notable exception. In the ionic case, Pauli exclusion principle need not be satisfied: we can fit as many ions inside the pore as its capacitance allows without hindrances from Fermi statistics. We thus expect ionic Coulomb blockade to occur as a function of the ionic concentration - which could be thought of as controlled by a “gate voltage” - but not as a function of bias, namely we expect the current to show a strongly non-linear behavior as a function of molarity - within the limits of ion precipitation - at fixed voltage, and essentially linear behavior with bias - for values below electrolysis - at fixed molarity\(^1\).

Note also that the phenomenon we consider here is fundamentally different from other nonlinear ionic transport effects that have been considered previously in the literature [39, 92, 35, 37, 93]. For instance, ions in solution can form an “ionic atmosphere”, namely a region around a given ion in which ions of opposite charge are attracted electrostatically [39]. However, the ionic atmosphere is a dynamic phenomenon with typical lifetimes on the order of \(10^{-8}\) s and it can be easily destroyed at field strengths of \(10^4\) V/cm [39]. Therefore, for the voltages and molarities we consider in this work the ionic atmosphere is not relevant [39].

Another deviation from Ohmic behavior has been observed experimentally

\(^1\)Some non-linearities with bias may arise because of the different energies of the various hydration layers (see Refs. [35, 36]).
in Ref. [92]. In this work, addition of a small amount of divalent cations to an ionic solution, leads to current oscillations and negative-incremental resistance. The phenomenon has been explained as due to the transient formation and breakup of nano-precipitates [92]. The nano-precipitates temporarily block the ionic current through the pore thus causing current oscillations. The phenomenon we consider here is instead due to the interaction of like-charged ions in the pore and is thus radically different from the effects discussed above. Finally, nanopores as those shown in Fig. 7.1 can be easily fabricated [1]. We thus expect our predictions to be readily accessible experimentally.

7.1 Results and Discussion

Let us then start by presenting first a simple analytical model that captures the main physics of ionic Coulomb blockade. We will later corroborate these results with all-atom classical molecular dynamics simulations. Like the electronic Coulomb blockade case (see, e.g., [94]), we can model the dynamics of ionic conduction using a rate equation approach by calculating the transition probabilities for the pore to accommodate a certain amount of charges in addition to the background charge. Referring again to Fig. 7.1 we consider the rates of conduction in and out of the wide opening of the pore (“top opening”) and the neck of the pore (“bottom opening”), as indicated by $\gamma_t$ and $\gamma_b$, respectively. For clarity, we refer to the ions with the charge sign that favors accumulation inside the pore. In the case of Fig. 7.1 these are Cl$^-$ ions, as also demonstrated by the density profile on the left panel of the same figure. The opposite-charge ions accumulate on the outskirts of the pore entrance (see Fig. 7.1) and the current blockade occurs when ions from the reservoir adjacent to the neck of the pore attempt to enter it. The considerations we make below would then be similar, but clearly with different values of the parameters and the direction of ion motion. If we reversed the bias direction we would obtain similar results but with the opposite charge sign accumulation inside and outside the pore.

We assume that the rate through the bottom opening is related to the top
one by
\[ \gamma_b = \alpha \gamma_t \quad 0 < \alpha < 1, \tag{7.1} \]
and
\[ \gamma_t = A_t \mu n_0 E \tag{7.2} \]

where \( A_t \) is the top area of the pore, \( \mu \) is the ionic mobility, \( n_0 \) is the ionic density, and \( E = V/d \) is the electric field, where \( V \) is the voltage and \( d \) is the length of the pore [56]. The parameter \( \alpha \) takes into account the difference in the two rates due to the partial shedding of the hydration layers around the ions when they cross the bottom neck, and the fact that the radius of the pore opening is smaller at the neck than at the top.

In order to be able to solve the rate equations analytically we assume only two possible “ionic states”. The first state with transition probability \( P_0 \) corresponds to only the background charge in the pore, namely to \( \lfloor n_0 \Omega_p \rfloor \) ions, where \( n_0 \) is the background density, \( \Omega_p \) is the volume of the pore, and the symbol \( \lfloor \cdots \rfloor \) represents the floor function which will make the product \( n_0 \Omega_p \) an integer. The second state with probability \( P_1 \) is that of the background charge plus one single extra ion, namely \( \lfloor n_0 \Omega_p \rfloor + 1 \) ions in the pore. While this may seem like an oversimplified situation it actually captures the main trends observed with the molecular dynamics simulations as we show below. The Markovian equation for the transition probability \( P_0 \) is then
\[ \frac{dP_0}{dt} = \Gamma_{1 \rightarrow 0} P_1 - \Gamma_{0 \rightarrow 1} P_0, \tag{7.3} \]
where \( \Gamma_{0 \rightarrow 1} \) is the transition rate of going from state 0 to state 1, and \( \Gamma_{1 \rightarrow 0} \) is the reverse process. The equation of motion for \( P_1 \) is easily obtained by interchanging 0 with 1 in Eq. 7.3.

The transition rate \( \Gamma_{0 \rightarrow 1} \) contains the capacitive barrier experienced by an ion entering the pore already occupied by \( \lfloor n_0 \Omega_p \rfloor \) ions. Using the steady-state Nernst-Planck equation it can then be written as [36]
\[ \Gamma_{0 \rightarrow 1} = \gamma_t \exp (-\epsilon_C/kT), \tag{7.4} \]
Figure 7.2: Current as a function of the ion concentration at a fixed voltage of $V = 1.0$ V from Eq. (7.10). The inset shows the current, at a concentration of 1.0 M, as a function of bias. See text for all other parameters.

where $\epsilon_C$ is a single-particle capacitive energy barrier, $k$ the Boltzmann constant, and $T$ the temperature. We can write the single-particle capacitive energy as [94]

$$\epsilon_C = e^2 \left( \frac{2[n_0 \Omega_p]}{2C} + 1 \right)$$

(7.5)

where $e$ is the elementary charge and $C$ is the capacitance of the pore. Since the capacitance of the pore is linearly related to the ratio of the surface areas of the top and bottom openings, it must vary according the parameter $\alpha$ we have introduced in Eq. (7.1). We then assume $C = \alpha C_0$ with $C_0$ some reasonable experimental value for the capacitance. The rate $\Gamma_{1\rightarrow 0}$ is instead simply

$$\Gamma_{1\rightarrow 0} = \gamma_b,$$

(7.6)

because there is no capacitive barrier for this process. We also note that, in principle, there is a finite rate for an ion to move in the direction opposite to that determined by the electric field. This rate would contribute to both $\Gamma_{0\rightarrow 1}$ and $\Gamma_{1\rightarrow 0}$. However, this process is exponentially suppressed for the biases we consider here, and we can thus safely ignore it.
At steady state, \( dP/dt = 0 \), and from Eq. (7.3) - and the equivalent equation for \( P_1 \) - we obtain the steady-state probabilities

\[
P_0 = \frac{\Gamma_{1 \to 0}}{\Gamma_{0 \to 1} + \Gamma_{1 \to 0}} = \frac{\gamma_t \exp(-\epsilon_C/kT)}{\gamma_t \exp(-\epsilon_C/kT) + \gamma_b} \quad (7.7)
\]

\[
P_1 = \frac{\Gamma_{0 \to 1}}{\Gamma_{0 \to 1} + \Gamma_{1 \to 0}} = \frac{\gamma_t \exp(-\epsilon_C/kT)}{\gamma_t \exp(-\epsilon_C/kT) + \gamma_b} \quad (7.8)
\]

Finally, the current at steady state is the same everywhere and we evaluate it across the neck of the pore

\[
I_b = e \left( \Gamma_{1 \to 0}^b P_1 - \Gamma_{0 \to 1}^b P_0 \right), \quad (7.9)
\]

where the superscript \( b \) indicates that we retain only the terms corresponding to the bottom part of the transition rates. In the present case, this gives

\[
I_b = e \alpha \gamma_t \left( \frac{\exp(-\epsilon_C/kT)}{\exp(-\epsilon_C/kT) + \alpha} \right), \quad (7.10)
\]

with \( \gamma_t \) and \( \epsilon_C \) given by Eqs. (7.2) and (7.5), respectively. This equation shows indeed what we were expecting: the current is linearly dependent on bias (via the parameter \( \gamma_t \)) for a fixed ion concentration, and it saturates - and eventually decreases - with increasing concentration according to the difference between the top and bottom openings (parameter \( \alpha \)). This is shown in Fig. 7.2 where we have used the parameters \( A_t = 7.8 \text{ nm}^2, d = 25 \text{ Å}, \mu = 7 \times 10^{-8} \text{ m}^2\text{V}^{-1}\text{s}^{-1}, C/\alpha = 1.0 \text{ fF}, \text{ and } T = 295 \text{ K}. \)

We now show that this model indeed captures the main physics of this phenomenon by performing all-atom molecular dynamics simulations using NAMD2 [3]. The pores we consider are made of 25 Å thick silicon nitride material in the \( \beta \)-phase and they have a conical shape with a slope angle of 45° (see Fig. 7.1). We vary the bottom opening from a radius \( r = 5 \text{ Å} \) to a radius \( r = 10 \text{ Å} \). We then introduce a given concentration of KCl while keeping the temperature fixed at 295 K. By introducing an external constant electric field we can then probe the ionic conductance. Other details of the simulations are reported in Ref. [95].

The results of these simulations are plotted in Fig. 7.3 and Fig. 7.4. As predicted by Eq. (7.10), our calculations show an almost linear behavior of the
Figure 7.3: Current as a function of KCl molarity for various neck radii and at a fixed bias of 1.0 V. For relevant experimental molarities, we observe an almost linear increase of the current for a radius $r = 10 \text{ Å}$ and a non-linear behavior approaching a saturation at a given molarity for smaller radii. The current saturation and decrease is shown explicitly in the inset for a 7 Å neck radius pore.

Figure 7.4: We can also look at the current as a function of voltage from the molecular dynamics simulations. Here, we use a 7 Å radius pore and go up to voltages which are much higher than those used in experiments in order to compare with the results of the model. It is clear that the dependence is qualitatively similar to the model in that the current is nearly linear with the voltage.
Figure 7.5: We can look at the distributions of residence times in the pore for Cl\(^-\) ions which transport from the top to the bottom (the “right” way given the direction of the applied electric field). We can do the same for the K\(^+\) ions, where now going from the bottom to the top of the pore is the “right” way. One can see that the average dwell time is greater than the timescale \(e/I\) which implies there is an ionic blockade in the pore.

current as a function of bias, and for a fixed bias a saturation of the current as a function of ion concentration which is more pronounced for pores with smaller neck radius. In the inset of Fig. 7.3 we also show explicitly current saturation and decrease for a 7 Å neck radius pore, which has to be compared with the results reported in Fig. 7.2. Note, however, that current saturation and decrease occur at molarities well above the ionic precipitation limit of KCl of about 3.5 M. We thus expect these two features not to be directly visible for this configuration.

Additionally, we can compare the average residence time, \(\tau_{res}\) for a Cl\(^-\) ion in the pore to the average time it takes for conduction, i.e. \(e/I_{avg}\). To further support the fact that there is a blockade effect due to like-signed charges in the pore, we can check to see if, on average, \(\tau_{res} > e/I_{avg}\). We see this to be the case whenever the system is in the blockade region. No matter what the system, though, there is a wide spread of residence times for a given configuration as can be seen in Fig. 7.5.
Finally, we discuss conditions under which the phenomenon of ionic Coulomb blockade may be better resolved. It is definitely true that nanopores of a V-shape as that shown in Fig. 7.1 can be easily fabricated [1]. However, the amount of surface charges on the internal walls of the pore is not so straightforward to control. Nevertheless, surface charges are beneficial to the observation of this effect. Indeed, if a certain amount of, say, positive charges are present at the surface of the pore walls, more Cl\(^-\) ions would accumulate inside the pore even without the need of an electric field. Everything else being equal, the predicted non-linearities as a function of molarity would then occur at lower concentrations. Better yet would be if these surface charges could be modified electrically. This has been recently achieved experimentally by placing electrodes inside nanopores of a shape similar to the one considered in this work [96, 97, 98]. The predicted phenomenon is therefore within reach of these experiments. Note also that the same phenomenon would occur in the case of a straight-wall (e.g., cylindrical) pore provided the openings are small enough that the hydration layers need to be partly shed. In this case, using molecular dynamics simulations we have also observed ion current blockade as a function of molarity (not reported here). Here, however, we expect the pore wall charges to play a much more important role than in the case of V-shaped pores. In this respect, experiments with more well-controlled synthetic pores, e.g., nanotube pores [99] may be particularly suitable to verify this phenomenon. We leave all these studies for future work.

7.2 Conclusions

In conclusion, we have predicted that ionic Coulomb blockade effects should be observable in nanopores of specific geometries, when ions accumulate in the pore thus impeding the flow of like-charge ions. We have corroborated these predictions with all-atom molecular dynamics simulations. The ensuing non-linearities as a function of ion concentration are within reach of experimental verification. This phenomenon parallels the one observed in electronic transport across quantum dots weakly coupled to two electrodes. These effects may play a significant role in vari-
ous applications of nanopores presently pursued, and is of fundamental importance for understanding ionic conduction in confined geometries.
ACKNOWLEDGEMENTS

We thank Jim Wilson and Alexander Stotland for useful discussions. Financial support from the NIH-National Human Genome Research Institute is gratefully acknowledged.

Chapter 7 is in part a reprint of the material as it appears in Matt Krems and Massimiliano Di Ventra, “ Ionic Coulomb Blockade in Nanopores”, in preparation (2011). The dissertation author was the primary investigator of this paper.
Bibliography


