Increased Nanopore Event Detection Speed Using Transient Analysis

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1 Abstract

In an attempt for simplicty we approxiamte our nanopore setup as a RC network and show the response of our model. By then looking at the response of our amplifier circuitry we are able to acheive a model similar to that of our collected data. We then proceed to view the differences between models of different enzymes bound to ssDNA and unbound ssDNA and come to the conclusion that only the resistance of the channel created by our pore changes for different enzymes. From this observation we come to the conclusion that differences in our transients are due primarily to the difference in type of enzyme bound to ssDNA.

2 Introduction

Over the last decade, research in the use of nanometer scale pores to detect many biological events has been heavily explored. This paper attempts to explain a new technique for detecting different events of single-stranded DNA (ssDNA) binding to enzymes.

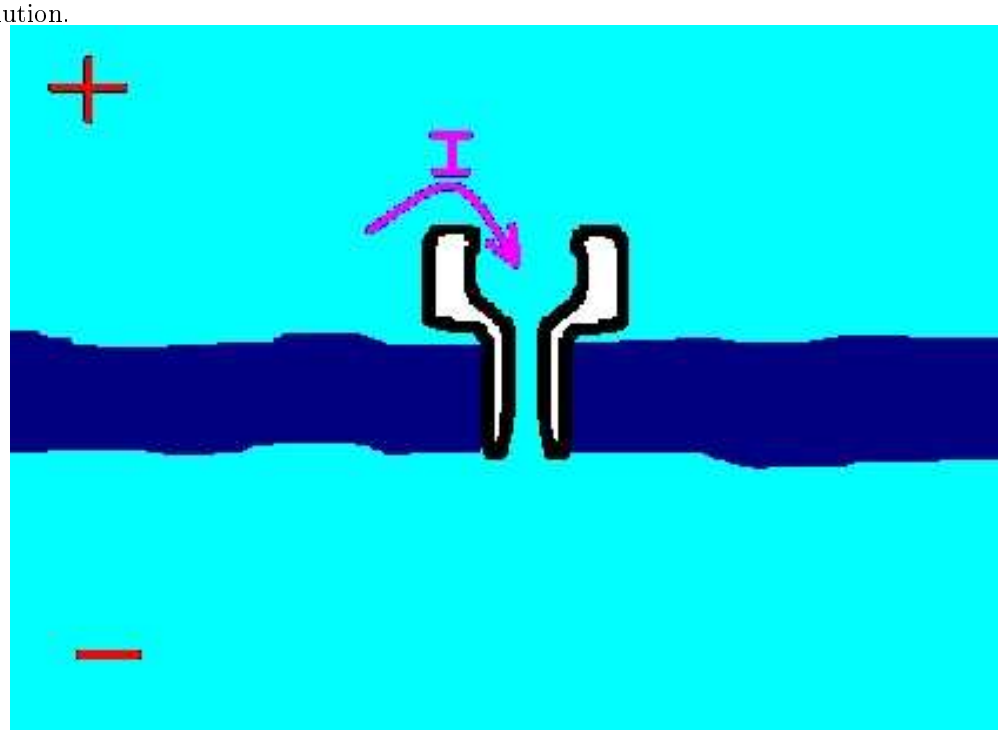
3 Creating a Model

We begin by viewing the physical properties of our nanopore system and then create the linear-network equivalent of the system.

3.1 Nanopore Setup and Physical Operation

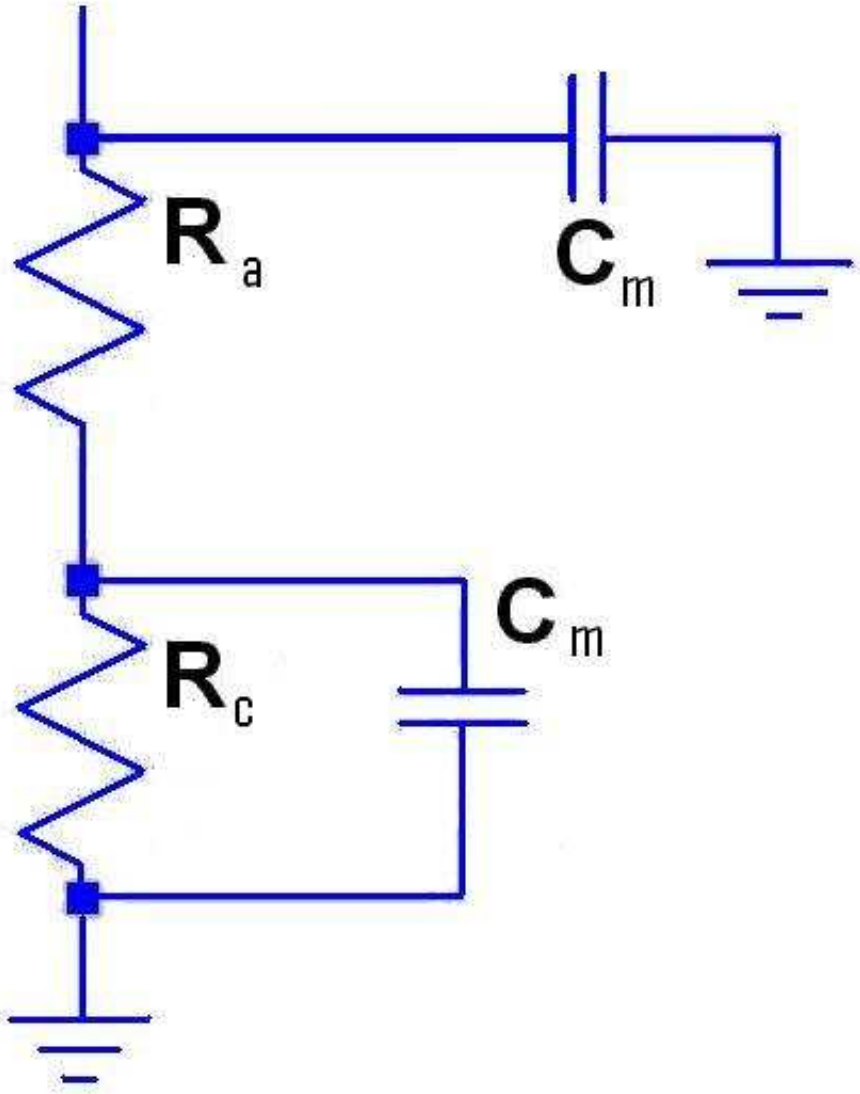
Our nanaopore system is composed of a salt solution and some physical barriers which resemble cirucit elements. Ion flow through the nanopore forms ionic current which is believed to be proportional to the current data collected via a voltage divider circuit as is explained later. Salt ions flow through the pore which is inserted into a membrane. The ion flow is due to a voltage applied by

the user and causes charge to build up on the membrane like a capacitor. The size of our pore restricts ion flow in a way we believe to be directly proportional to voltage. There is also a small resistance due to the flow of ions within the solution.



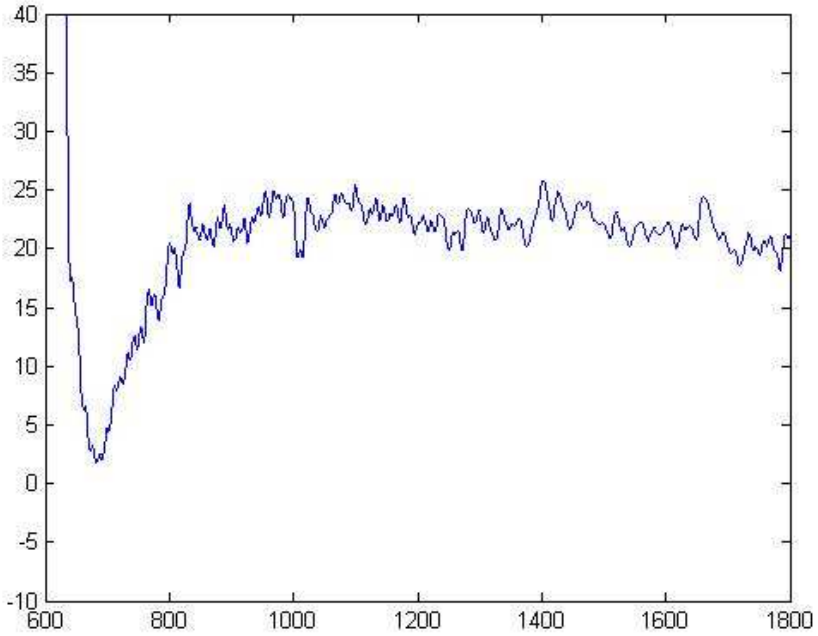
3.2 MOdeling with a Linear Network

From our description we can notice some real circuit elements emerge and some elements that resemble fluid analogies to circuit elements. We can start by noting that the membrane is a capacitor. It acts as a wall separating two fluids with charge. We apply a voltage across the membrane and charge will build up against it, but can not pass through it. We also note that the size of our pore restricts the flow of ions from the higher potential region to the lower in a somewhat linear fashion and hence we model it as a resistor. The same applies for the movement of ions within the solution. We note that our system has other walls separating the solutions and other capacitive effects and hence add a capactior to model parasitics. We end up with the following RC network to describe our system.



4 Circuit Model Analysis

Now that we have acheived a basic linear circuit approximation for our sytem we need to verify that our model does give a response similar to that observed experimentally.



This graphic shows the time-domain response of our system directly following a voltage step. After falling from a very large peak, we see an overshoot and then a transient response to the steady-state current level.

We must first decide what model we want to use to power the network. As a first-order approximation, an ideal voltage source with a step at t=0 from 0V to $V_p$will be used. Our RC network can now be modeled with the following equations:

$$i_p = \frac{dV_p}{dt}C_p + \frac{V_p - V_m}{R_a}$$

$$\frac{dV_m}{dt} = \frac{V_p - V_m}{R_a C_m} + \frac{V_m}{R_c C_m}$$

where $V_m$is the voltage at the node between R_a and R_c.

The second equation can be solved analytically as a first-order differential equation, where V_p is represented by a Heaviside function.

$$V_m(t) = \frac{R_c V_p}{R_a + R_c}\left(1 - e^{-\left(\frac{1}{R_c C_m} + \frac{1}{R_a C_m}\right)t}\right)$$

Substituting this solution into our first equation we can solve for i_p.

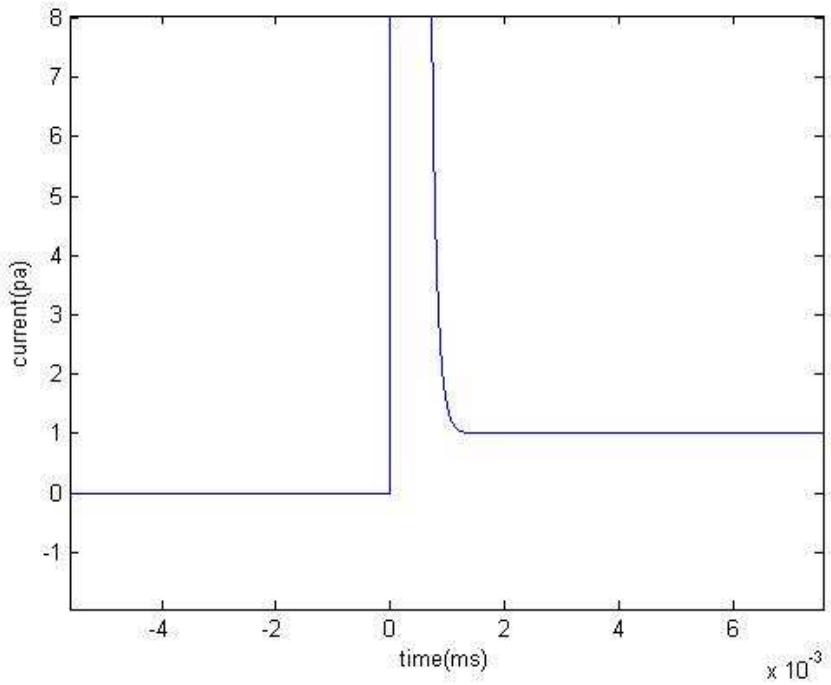
$$i_p = \delta(0)C_p + \frac{V_p - V_m}{R_a}$$

Our analytic solution will include a delta function at zero, and hence, can not be handeled by most computers for numerically solving. Instead of using a delta function, we will make a discrete step function and numerically differentiate to avoid this complication. The spike we get will be very large compared to the rest of our signal and hence will still appear infinite, minimizing error in the numerical solution.

In solving these equations we will use the following component values, which

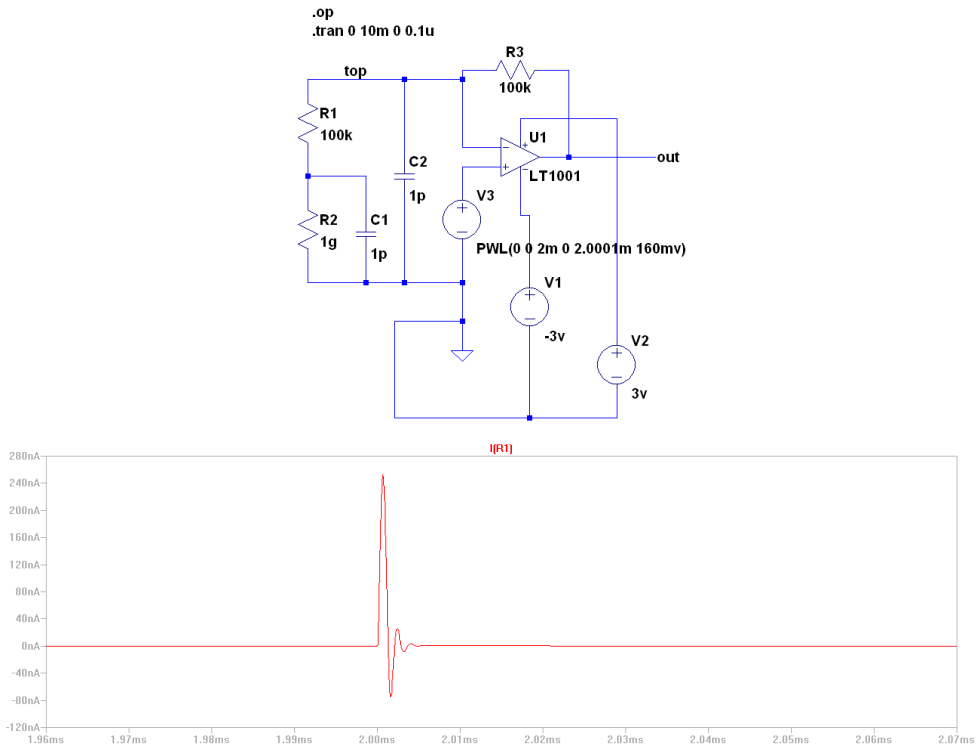
are experimentally obtained approximations.
$R_a := 10^{-4}\text{G}\Omega$
$R_c := 1\text{G}\Omega$
$C_p := 1\text{pF}$
$C_m := 1\text{pF}$

We arrive at the numerical solution shown here.



This solution closely matches that shown by R. Smeets et al. in the paper *Noise in solid-state nanopores (2007)*. The time scaling issues in this model are likely due to inaccurate component values to within an order of magnitude. However, this model does not fit the experimental data very well.

If instead of viewing the voltage input as an ideal voltage source, we model it by an operational amplifier with a resistive feedback, the model starts to look more like the experimental data containing some oscillatory signal.



This oscillation in the signal could be due to the signal being outside of the frequency range of the amplifier. If this truly is the case, then the above diagram would be a beginning explanation for the oscialltions. To better model the data, a more accurate SPICE model of the amplifier would need to be found or constructed.

5 Conclusion and Next Steps

At this point our model closely fits those found by other research groups. If circuit values similar to those used in solid-state nanaopores replace the ones in our model, the osciallatory behavior, likely due to the op amp, subsides and a signal similar to our model is acheieved, indicating that this model is a decent fit to our nanopore system and that our much smaller biological nanopore has frequency components outside of the amplifiers range, hence we get an oscillatory resopnse with the transient.

There will be two major next steps necessary to acheive a more accurate model. First a better model for the amplifier will need to be put together. Once this model is made, a better analysis determinig if the effects seen on the signal can actually be attributed to the amplifier or if there might still be other components contributing to the signal. In addition, more accurate approximations for

component values (order of magnitude) will need to be determined and then either system identification or some other fitting method can be used to refine these values to give a best fit to the experimental data.