

MODELING THE NEURAL PATHOLOGY OF PARKINSON'S DISEASE

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Acknowledgments

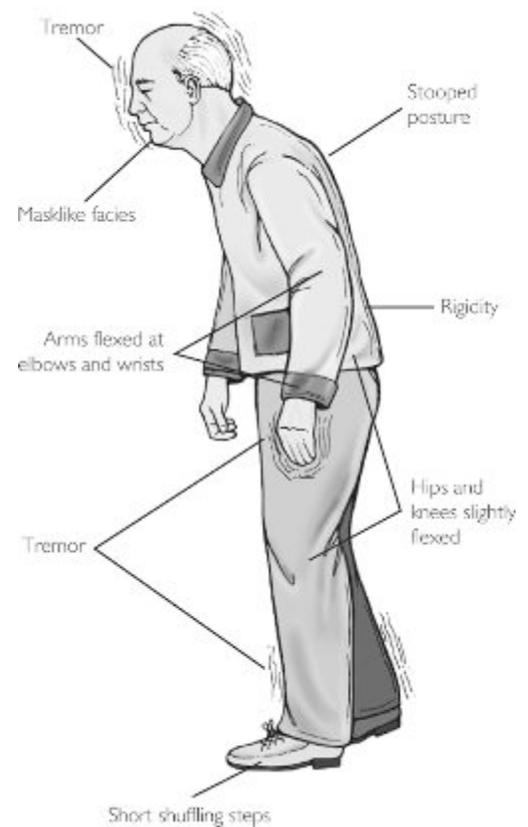
In producing the simulator this thesis describes, I worked considerably with Dr. Richard Murrow, a neurologist at UNC Hospitals, Dr. Oleg Favorov, a professor of biomedical engineering at UNC, and my advisor Dr. Greg Welch. I am indebted to each of them for their guidance and wisdom.

Abstract

This thesis describes a simulator that models the groups of neurons, the constituent elements of the brain, hypothesized to be involved in Parkinson's disease. In other words, this thesis describes a simulator for the neural pathology of Parkinson's disease. The thesis first describes Parkinson's disease, wades into the biological background of neurons, clarifies the equations used to simulate interactions between neurons, describes the basic structure of the Matlab file and C library involved, and showcases the resulting output and how that matches with real-life readings.

Introduction

Parkinson's disease "is a progressive disorder of the nervous system that affects movement" (Mayo Clinic Staff). It can manifest itself in tremors, slow movement, stiff muscles, poor balance, and changes in speech, making life very frustrating for people who have it (Parkinson's Disease Foundation). The image to the right shows where such symptoms may show ("Parkinson's Disease Nursing Care Plan"). Although it can appear at any age, Parkinson's is most likely to show up in the elderly or those who are over fifty years old (BSDPF). Indeed, about one million Americans have Parkinson's, with about 60,000 Americans being "diagnosed with Parkinson's disease each year"



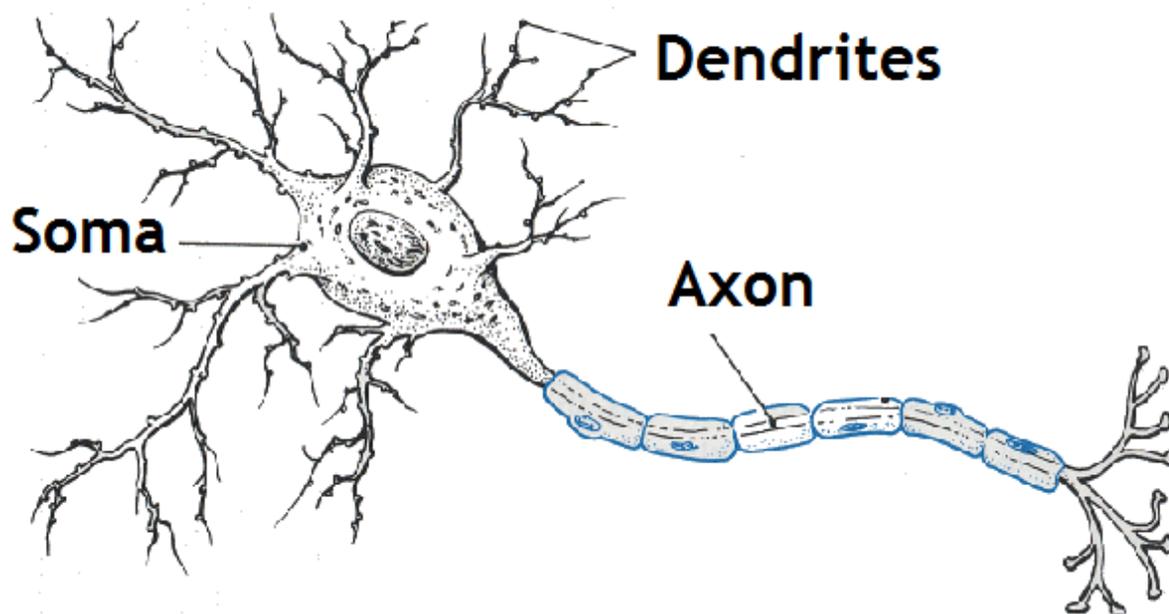
(Parkinson's Disease Foundation). Unfortunately, because it is a progressive and chronic disease, it only becomes worse and worse.

There are treatments to Parkinson's that are effective in varying degrees. The "most common" one is medication that addresses "the shortage of the brain chemical (neurotransmitter) dopamine" which is said to cause the symptoms of Parkinson's." When medication does not work, brain surgery is an option. The safest, least harmful method of surgery is Deep Brain Stimulation, a.k.a. DBS. This entails sending "electrical impulses" into target regions through electrodes inserted into the brain (Mayo Clinic Staff).

Dr. Richard Murrow, a neurologist at UNC hospitals, uses DBS systems to treat some of his patients who have Parkinson's. His desire to better understand and teach how the constituent elements of the brain interact with each other in Parkinson's disease spurred the development of the simulator described in this thesis. No one is sure what the exact mechanisms behind Parkinson's are. In this thesis, I explore one hypothesized mechanism. In doing so, I needed to develop a model to simulate the building blocks of the brain, neurons.

There is a vast body of literature in the modeling of the brain and its elements. People have developed a variety of models. Even as all of these models are greatly simplified versions of biological neurons, some exhibit higher degrees of complexity than others (Abbott et. al). On the lower end of complexity is the Integrate and Fire neuron, which is computationally efficient but not as biologically accurate. Another sort of neuron, the FitzHugh-Nagumo neuron, is both moderately costly and effective. For the purposes of designing a simulator for Dr. Murrow, I opted to use a Hodgkin-Huxley sort of neuron, which is very computationally expensive but very plausible biologically as well (Brunel). Experimenting with using a simpler neuron model did not

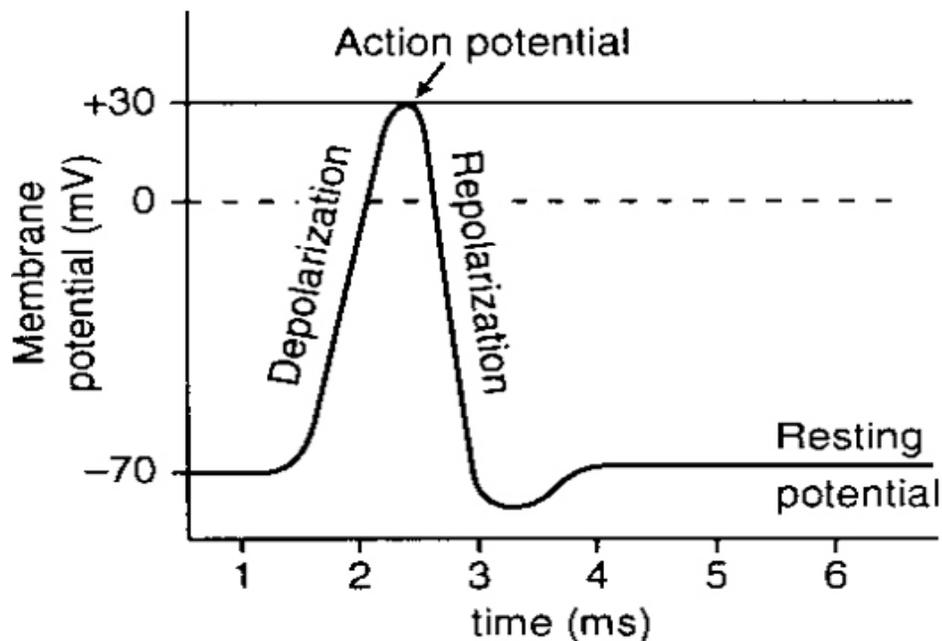
result in good results. The Hodgkin-Huxley style of implementing a neuron is very flexible. One can add/remove different features of the neurons easily, adjusting them to the sort of neuron being modeled. As I designed my model of an individual neuron before meeting with Dr. Murrow and Dr. Favorov to work on the larger simulator, I was selective in choosing and modifying neural features so that the model would produce appropriate behavior. Consequently, this thesis spells out a new model for neurons.



The figure above portrays the building block of the nervous system, the neuron (“Neuron Basics”). A neuron consists of *dendrites*, a *soma*, and an *axon*. Neurons receive signals from other neurons; the input devices that receive these signals are called dendrites. In a computer, they would be the keyboard and the mouse. Analogously, the soma is the main processing unit; when received signals pass a threshold, the soma creates an output signal. Furthermore, the axon can be thought of an output device that goes about delivering the resulting signal to other devices

(other neurons). Finally, the junction between any two neurons is called the synapse; this can be thought of as a connection between two devices, i.e. a USB wire.

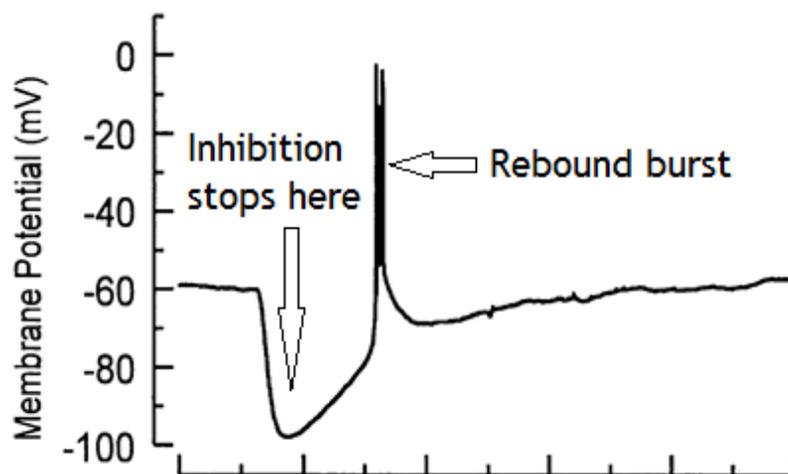
The electrical charge outside the membrane of a neuron is positive, while the charge within the membrane is negative. The difference between these two charges is the *membrane potential* of the neuron (Gerstner and Kistler). In the model described in this report, I simulate the changing membrane potentials of neurons as they interact with each other.



The figure above shows how the membrane potential of a neuron changes as it receives inputs (“Action Potential”). Without any inputs, the neuron is resting at some constant potential. However, an incoming input changes its membrane potential. In the figure above, the neuron is receiving inputs in the time period between 1 and 2 seconds, causing its membrane potential to increase. At about 2.5 seconds, the membrane potential passes a certain threshold, causing the neuron to release an action potential.

In order for this to make more sense, think about a person who has anger issues but is trying to contain himself. As others slight him through the day, he gets more and more frustrated, but he does not act on his building resentment. Then, someone upsets him and he deems the offense his final straw – he explodes. Analogously, the neuron will have to receive many inputs before it releases its output, an action potential. It is an all or nothing event. After a neuron “spikes,” or releases an action potential, it returns back to resting potential.

In the figure above, the neuron receives inputs that cause a positive change in the membrane potential. This means that the synapse connecting this receiving neuron to the outputting neuron is *excitatory*. Interestingly, certain inputs can cause a negative change. If this happens, the synapse is said to be *inhibitory* (Gerstner and Kistler). In the above figure, the neuron spikes when it receives many excitatory inputs. Even as that mechanism describes a good deal of how neurons spike, literature also showed us that there are a variety of other ways to cause a neuron to spike – a professor at Indiana University noted that there were “20 ways to spike your neuron” (Yaeger). Out of these, two ways particularly caught our attention, namely the

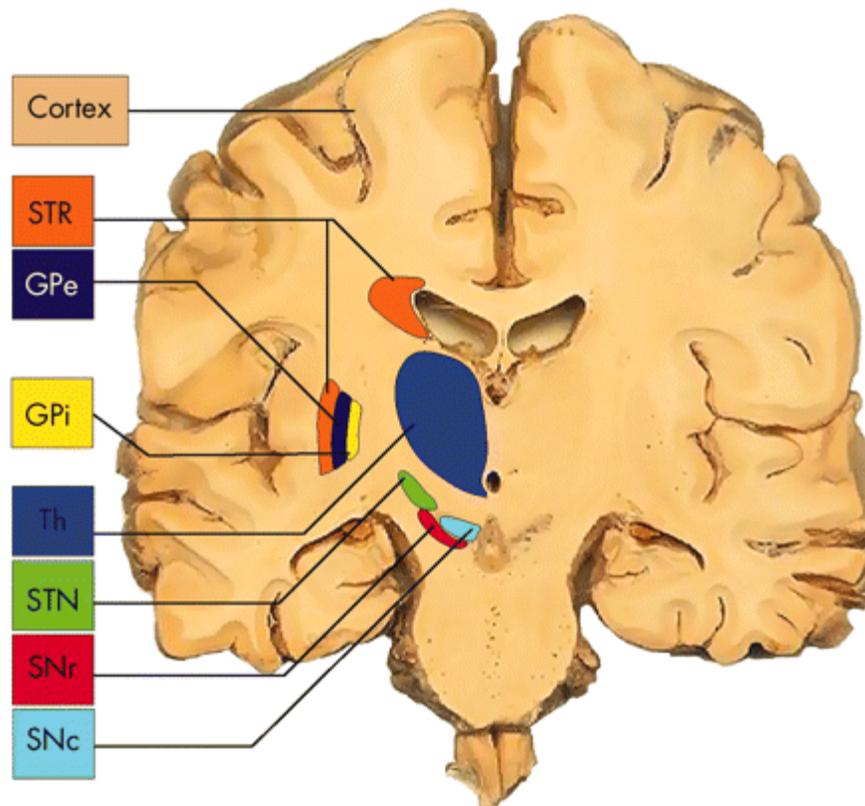


“Rebound Spike,” which is a “spike upon release from inhibitory inputs” and the “Rebound Burst,” which is a “burst of spikes upon release from inhibitory inputs,” as portrayed in the

figure above (Yaeger). Consider the angry man again. Say he is receiving a constant stream of compliments (inhibiting inputs), as opposed to insults (excitatory inputs). As he encounters kindness, his frustration levels continue to decrease. When the nice words suddenly stop however, he becomes so shocked and confused that he immediately becomes angry and releases his rage. Analogously, when an inhibiting current “is suddenly turned off” it results “in an overshoot of the membrane potential, triggering one or more action potentials.” We can refer to these action potentials produced as “low-threshold spikes” (Destexhe et al). This name captures the fact that the *low-threshold calcium current* (I_t or I_{pir}) is the chief player in post-inhibitory rebound, “a major characteristic” of the neurons hypothesized to be involved in Parkinson’s disease (Modolo et al).

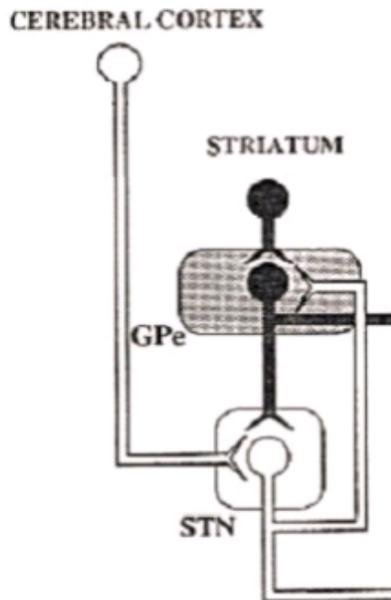
Model

As I indicated earlier, no one is certain what the causes of Parkinson's are. With the help of Dr. Murrow and Dr. Favorov, I have designed a simulator for the interactions between certain groups of neurons in the brain that are hypothesized to be crucial in Parkinson's.



The figure above is a view of the brain that shows regions that are all likely players in Parkinson's (Aziz and Pereira). In order to be computationally efficient, I only modeled the *Subthalamic Nucleus (STN)*, *Cortex*, *Striatum (STR)*, and the *External Globus Pallidus (GPe)*. The hypothesis I model involves a loop between neurons in two sections of the brain, the STN and the GPe. Referring to the “powerful reciprocal loop between the STN and Gpe,” Wilson and

Bevan write, “This nominates the STN and GPe as a likely source of persistent activity in the basal ganglia, and particularly oscillations” and that the “emergence of rhythmic bursting in the STN and its targets in Parkinson’s disease” has “raised much interest in the potential importance of” this “network in the pathophysiology of that disease.”



Consequently, my program implements a model of STN and GPe neurons. There are multiple parameters that can be manipulated to produce different results. In the schema to the left¹, the white synapses reflect excitatory connections, while as the black synapses reflect inhibitory connections. Thus there are: excitatory connections from the STN to the GPe, inhibitory connections from the GPe to the STN, and excitatory connections from the Cerebral Cortex to the STN. While as all other connections in our model are simulated through modeling action potentials and synapses, we model the cerebral cortex

input by a simple injection of current; this is for simplicity purposes. In addition to what is reflected in the schema, we model inhibitory connections within the neurons in the GPe and excitatory connections within the neurons in the STN. Finally, there is an option to add a constant injection of inhibitory current from the Striatum.

Parameters

It is computationally expensive to simulate every nanosecond of time. Consequently, the model updates all the neurons in the model on a reasonably sized time interval dt . The default

¹ Schema provided by Dr. Murrow

value is 0.05 milliseconds. The smaller the value, the more accurate the results of numerically integrating the differential equations in the model. (I use Euler's method.) However, decreasing dt will increase the completion time of the simulation by a linear factor.

A very important parameter is the *input scaling factor* of the low threshold calcium current. In effect, increasing the value of this will mean increase the impact of post-inhibitory rebound (the spiking of a neuron after being released from inhibitory inputs). When Dr. Oleg Favorov and Dr. Murrow were experimenting with the model, they increased this parameter as research suggested, and we immediately saw output that very closely resembled real life readings recorded in the operating room. Other parameters include the sparsity of connections between the STN and the GPE, as well as a scaling factor for the constant input received from the cerebral cortex, $I_{appliedStimulus}$.

Currents Modeled

Designing how to model the neurons in the STN and GPE entails a tradeoff. Increased realism necessitates waiting longer for the simulation to finish. Because a less realistic model resulted in output that did not smoothly correspond with real life readings, I settled on using more biologically realistic models of neurons. Below are the currents modeled and the respective equations:

- 1) The equations responsible for changing membrane potential:

$$d(V)/dt = (I_{syn} - I_{internal})/C$$

$$I_{internal} = I_l + inputScalingFactor * I_{pir} + I_K + I_{Na}$$

Where I_{syn} , I_l , I_{pir} , I_K , and I_{Na} are as follows.

- 2) The sodium (Na⁺) current (Shaikh et al): This is responsible for causing rapid increase of the membrane potential once the voltage of a neuron passes a threshold.

$$I_{Na} = g_{Na} * (m^2) * h * (V - V_{Na})$$

$$dh/dt = a_h * (1 - h) - b_h * h$$

$$dm/dt = a_m * (1 - m) - b_m * m$$

- 3) The potassium (K⁺) current (Pospischil et al): This is responsible for the decreasing of a neuron's membrane potential once an action potential is fired.

$$I_K = g_K * n^4 * (V - V_k);$$

$$dn/dt = a_n * (1 - n) - b_n * n$$

- 4) The low threshold calcium current, also known as the I_{pir} current: This is responsible for causing post-inhibitory rebound, which is the physiological phenomenon that describes a neuron firing after being released from inhibiting inputs.

$$\begin{aligned}
I_{piv} &= g_T * (m_{It}^3) * h_{It} * f_{It} * (V - V_{piv}) \\
d(d_{It})/dt &= b_2 * (1 - h_{It} - d_{It}) - a_2 * d_{It} \\
d(h_{It})/dt &= a_1 * (1 - h_{It} - d_{It}) - b_1 * h_{It} \\
d(m_{It})/dt &= (m_{Steady_{It}} - m_{It}) / \tau_m \\
m_{Steady_{It}} &= 1 / (1 + \exp(-1 * (V + V_s + 63) / 7.8)) \\
\tau_m &= .2 * (1.7 + \exp(-1 * (V + V_s + 28.8) / 13.5)) / (1 + \exp(-1 * (V + V_s + 63) / 7.8)) \\
a_1 &= (1 / .33) * \exp(-1 * (V + V_s + 160.3) / 17.8) \\
K &= ((.25 + \exp((V + V_s + 83.5) / 6.3))^{.5}) - .5 \\
b_1 &= a_1 * K \quad a_2 = 1 / (r_2 * (1 + K)) \quad b_2 = K * a_2 \\
r_2 &= .33 * 240 / (1 + \exp((V + V_s + 37.4) / 30)) \\
\text{if } V < \text{Resting}, d(f_{It})/dt &= (V_1 - V) * (1/65) * (2/\sqrt{\pi i}) * \exp(1 * ((f_{It} - 2.08)^2)) \\
\text{if } V > \text{Resting}, d(f_{It})/dt &= (V_1 - V) * (1/20) * (2/\sqrt{\pi i}) * \exp(-1 * ((f_{It} - 1.87)^2)) \\
\text{where } 0 \leq f_{It} \leq 1 &
\end{aligned}$$

Note: The variable f_{It} is an addition of mine. Even as literature was very helpful in learning about the transient calcium current and other important features of post-inhibitory rebound, there were holes in the literature. Models that were presented comprehensively either were not accurate given other features of the model or did not specify enough parameters to work appropriately. In one model, post inhibitory rebound would not occur unless the neuron had been inhibited for a long time, much more than necessary. Another model's internal variables would be activated and inactivated almost immediately, creating for interesting situations such as: (a) a perpetual burst phase, and (b) depolarization before being released from inhibition (Models: Shakik vs. Wang, et al). Consequently, I had to modify existing models.

With other literature in mind, I created a fatigue factor for the I_{pir} circuit so as to prevent perpetual bursting. While the equations are not experimentally determined, the idea behind the fatigue factor is not arbitrary. Literature shows that a half-center neuron exhibits adaptation properties which contribute to fatigue, which manifests itself in increased spacing between action potentials as is shown in the results (Enoka pg. 277). In any case, the fatigue factor primarily controls for the number of spikes in one burst, and does not really impact the other voltage-dependent aspects of the transient calcium current. Moreover, other researches have used a fatigue factor in modeling neurons (Perkel, Mulloney).

- 5) The leakage current, which is responsible for slowly dragging the membrane potential back to the resting potential of the neuron. In the angry man analogy, this corresponds with a person cooling down over time.

$$I_l = g_l * (V - V_l)$$

- 6) The Synaptic Currents: These currents describe the synapse, and how incoming inputs are translated into changes in membrane potential.

$$I_{syn} = I_{appliedStimulus} - (I_{Nmda} + I_{Ampa} + I_{GABAa} + I_{GABAb})$$

$$I_{Ampa} = g_{Ampa} * R_{Ampa} * (V - E_{Ampa})$$

$$I_{Nmda} = g_{Nmda} * R_{Nmda} * B_{Nmda} * (V - E_{Nmda})$$

$$B_{Nmda} = 1 / (1 + .28 * e^{(-.62 * V)})$$

$$I_{GABAa} = g_{GABAa} * R_{GABAa} * (V - E_{GABAa})$$

$$I_{GABAb} = g_{GABAb} * R_{GABAb} * (V - E_{GABAb})$$

For all the 4 above currents, the R corresponds to number of channels open, and is modeled via a differential equation. In this equation, C turns from 0 to 1mM when there is an action potential in a presynaptic neuron. C retains this value for a duration of 1 ms for the GABA_A and AMPA currents. For the GABA_B current, C retains this value for 84 ms. Finally, Dr. Murrow and Dr. Favorov asked me to retain the C value for 20 ms for the NMDA current. For simplicity purposes, this model assumes that an action potential has occurred when the voltages passes 0 mV.

$$dR/dt = aC(1 - R) - bR$$

Simulator

My simulator is a Matlab program where the user enters in his desired parameters. Because Matlab is very slow, I have split up the actual computational part of the program into a C library which Matlab calls.

C Library

When the Matlab program runs, it calls the function “mexFunction” which initializes the simulator, loads the appropriate parameters from Matlab, runs the simulation and returns the results of the simulator to Matlab. When the simulator runs, it generates connections between neurons using a random number generator. Crucially, the seed used is always the same, so that when we compare the results of the simulation we know that changes in the output display are a result of changes in parameters, not changes in random number sequences that permeate through the simulation. The neurons and the connections having been initialized, the program enters into a ‘for’ loop where the increment is delta t. At each time step, the program simulates each neuron.

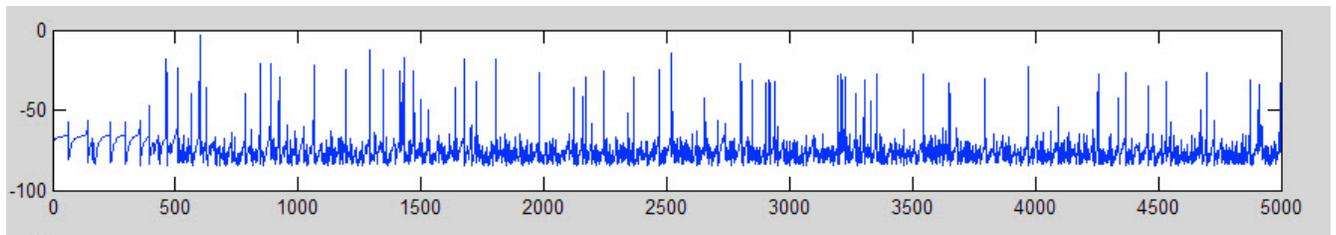
My C Library is very object oriented in that I have classes representing neurons and their connections. In particular, I have two object classes – neuron and synapse. The synapse object keeps track of the parameters of that particular synapse. Namely, it records the strength of the synapse, the scaling factors of the different synaptic currents, whether it receives a constant injection of current or a stream of action potentials as its input, pointers to the outputting neuron and the receiving neuron, and the time duration in which the synapse is active. Most importantly, the neuron object keeps track of the many variables that listed above in the currents modeled section. When the program simulates the neuron, it calls its “updateNeuron” function with time and delta time arguments. The updateNeuron function is basically an implementation of the

Euler's method in simulating the dV/dt function. Once the simulator finishes simulating every time step, it calculates a weighted average of the membrane potentials of the different neurons in the model. By weighting different neurons differently, I simulate a real-life reading where an electrode is able to pick up the membrane potentials of close neurons really well but farther away neurons less so. These graphs are supposed to match up with Dr. Murrow sees on his screen in the hospital when recorded as described below. When the simulator finishes it produces several graphs showing different weighted averages of the same network of neurons. The different weights simulate placing the electrodes in different parts of the intended region of the brain.

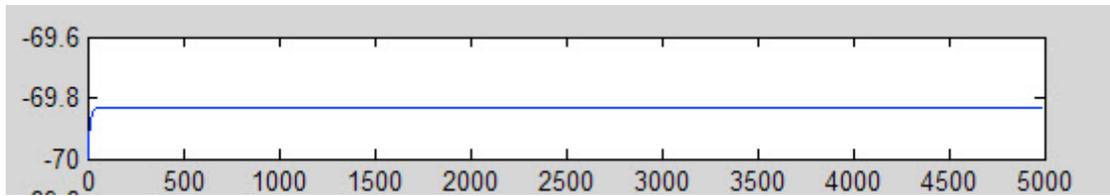
In addition to these graphs, my program has an option to simulate the sound of the readings. In order to achieve this, I scale the membrane potential graph and send it to an audio output function. Both Dr. Murrow and Dr. Favorov were impressed at how this sound resembled many features of the sounds that they hear in the hospital when they are working with patients with Parkinson's. According to Dr. Murrow, even more so than the visuals, the sound can be used to get a feel for the pathological oscillations in Parkinson's.

Experiments

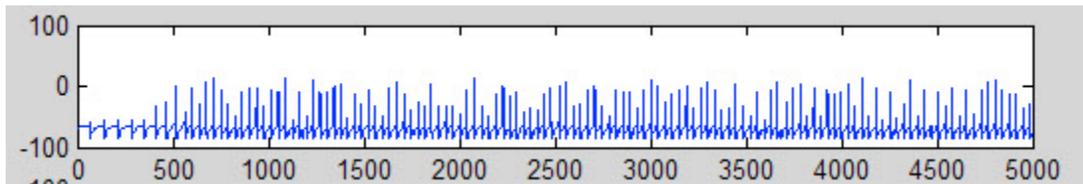
When Dr. Murrow works with patients with Parkinson's, he sometimes inserts an electrode into their brains and takes readings of the voltage potentials there. Below is a screenshot that one of the graphs my model produces in comparison to a real-life reading of a patient with Parkinson's. When comparing my graph to his, consider only the top half of his reading, as the top half of his reading is a mirror of its bottom counterpart. According to Dr. Murrow, this graph does a good job reflecting what he sees in the hospital. For instance, the graph shows valleys of low activity interspersed by semi-chaotic bursting, something that he also sees in patients with Parkinson's:



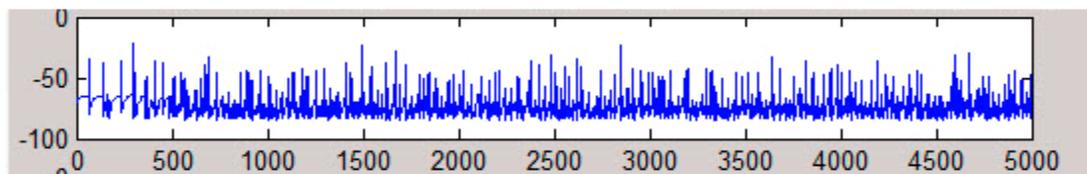
One of the primary motivations behind creating a simulator for the pathology of Parkinson's was to experiment with changing parameters and seeing what the results would like. When the input from the cerebral cortex is turned off, activity comes to a halt, as shown below:



This is expected as the cerebral cortex plays an important part of the loop I modeled. In addition, when the ability of GPe neurons to inhibit each other is turned off, the simulator produces non-oscillatory activity, as shown below:



This may indicate that the degree of GPe neurons inhibiting each other plays a significant role in producing tremor. Furthermore, when we set nmda, an excitatory current, to 0, we get the below graph:



According to Dr. Murrow, this is not a result that reflects activity in a patient with Parkinson's. Because changing the nmda current to 0 did not result in Parkinsonian behavior, this indicates that the nmda current may play a necessary role in producing Parkinson's.

Conclusion

Parkinson's disease negatively impacts millions of individuals; resulting tremor and other symptoms makes life very difficult. Often medication is not effective, compelling those suffering with Parkinson's to try the expensive surgery that is Deep Brain Stimulation (DBS). Even as DBS produces improvement in symptoms, why and how exactly it works is still difficult to understand and quantify. In describing a model for the neural pathology of that disease in this thesis, I hope to help Dr. Murrow and others better grasp the internal neural dynamics behind Parkinson's and consequently lay some of the foundations for improving DBS in the future. As for future steps, if someone were to expand on this research, they could further investigate why manipulating certain parameters results in behavior that looks or does not look Parkinsonian. Moreover, someone can try to map the activity produced in these graphs to actual tremor movement activity, and thus further connect this simulator with real-life behavior. Finally, someone can expand the model with more networks of neurons, and try to match it up with the attributes of both healthy and Parkinsonian brains. That would be a long, challenging endeavor, but one that may promise much fruit for patients with Parkinson's.

Bibliography

Abbott L, Kepler T, Garrido Luis. Statistical Mechanics of Neural Networks. Springer Berlin / Heidelberg. 5.

“Action Potential.” 5/11/2012 < <http://www.answers.com/topic/action-potential>>.

Aziz TC, Pereira EAC. "Parkinson's Disease and Primate Research: Past, Present, and Future." Postgraduate Medical Journal 82.1039 (2006): 293.

Bachmann-Strauss Dystonia & Parkinson Foundation (BSDPF). "What is Parkinson's?" 5/11/2012 <http://www.dystonia-parkinsons.org/index.cfm?fuseaction=home.viewPage&page_id=22A9BBC7-9228-A9D1-5F731EA5606F7856>.

Brunel, Nicolas. "From Hodgkin-Huxley to Integrate-and-Fire." 5/11/2012 <<http://www.neurophys.biomedicale.univ-paris5.fr/~brunel/tutorial.pdf>>.

Destexhe A, Neubig M, Ulrich D, Huguenard J. "Dendritic Low-Threshold Calcium Currents in Thalamic Relay Cells." 18.10 (1998): 3574.

Enoka, Roger M., 1949-. Neuromechanics of Human Movement. Champaign, IL: Human Kinetics, 2008. SearchUNC. <<http://search.lib.unc.edu?R=UNCb5744706>>.

Gerstner W, Kistler W. "Spiking Neuron Models Single Neurons, Populations, Plasticity " 5/11/2012 <<http://icwww.epfl.ch/~gerstner/SPNM/SPNM.html>>.

Mayo Clinic Staff, "Parkinson's disease - MayoClinic.com." 5/11/2012 <<http://www.mayoclinic.com/health/parkinsons-disease/DS00295>>.

McIntyre CC, Grill WM, Sherman DL, Thakor NV. Cellular effects of deep brain stimulation: model based analysis of activation and inhibition. *Journal of Neurophysiology*.

2004;91(4):1457–1469.

Modolo J, Henry J, Beuter A. "Dynamics of the Subthalamo-Pallidal Complex in Parkinson's Disease during Deep Brain Stimulation." *Journal of Biological Physics* 34.3-4 (2008): 251.

"Neuron Basics." 5/11/2012 <<http://www.mindcreators.com/NeuronBasics.htm>>.

Parkinson's Disease Foundation. "What is Parkinson's Disease?" 5/11/2012

<http://www.pdf.org/en/about_pd?gclid=CI6QuZeF4q8CFZNV7AodxCCK_Q>.

Perkel DH, Mulloney B (1974) Motor pattern production in reciprocally inhibitory neurons exhibiting postinhibitory rebound. *Science* 185:181–183

Pospischil M, Piwkowska Z, Rudolph M, Bal T, Destexhe A: Minimal Hodgkin-Huxley type models for different classes of cortical and thalamic neurons. *Biological Cybernetics* 2008, 99:427-441.

Shaikh AG, Kiura K, Optican LM, Ramat S, Tripp RM, Zee DS. Hypothetical membrane mechanisms in essential tremor. *J Transl Med*. 2008;6(1):68

Ulrich D, Huguenard J. R. "Gamma-Aminobutyric Acid Type B Receptor-Dependent Burst-Firing in Thalamic Neurons: A Dynamic Clamp Study." *Proceedings - National Academy of Sciences USA* 93.23 (1996): 13245.

Wang X-J, Rinzal J (1992) Alternating and synchronous rhythms in reciprocally inhibitory model neurons. *Neural Comput* 4:84–97

Wang X.-J., Rinzal J., Rogawski M. (1991) A model of the T-type calcium current and the low threshold spike in thalamic neurons. *J. Neurophysiol*

Wilson, C. J., and M. D. Bevan. "Intrinsic Dynamics and Synaptic Inputs Control the Activity Patterns of Subthalamic Nucleus Neurons in Health and in Parkinson's Disease."

Neuroscience 198.0 (2011): 54-68. . ScienceDirect.

Yaeger, Larry. "Neural Networks Pt. 4 Spiking Neuron Models." 5/11/2012

<<http://informatics.indiana.edu/larry/al4ai/lectures/09.NN4-SpikingNeuronModels.pdf>>.