A Population Firing Rate Model of Reverberatory Activity in Neuronal Networks

Zofia Koscielniak, Carnegie Mellon University
Mentor: Dr. G. Bard Ermentrout, University of Pittsburgh

Introduction:

The field of mathematics has made tremendous impact on the study of neuroscience. The electrochemical activity of neurons is precisely timed and executed, and thus ideal for mathematical modeling. Mathematicians are able to model neural activity that can be experimentally confirmed with startling accuracy. Mathematical models also give insight into how certain factors can affect neural activity. As computer technology improves and computation time decreases, mathematicians are able to construct more complicated and realistic models. Today, various approaches to modeling the activity of the nervous system exist. They include investigating electrical and chemical activity inside an individual neuron as well as a network of cells. All these models provide valuable insight into how the nervous system functions.

The structure of a neuron is specifically designed to propagate the fast spread of chemical signals. At the resting state, the cytoplasm inside the neuron has a slightly negative charge. When the cell receives a signal of sufficient strength from another cell, they it depolarized enough to allow a signal to travel down the axon, causing the neuron to fire. The electrical potential difference travels down the length of the axon, and causes the synaptic vesicles to release a neurotransmitter signal, and potentially exciting the dendrites of an adjacent neuron (3).

A stated before, the potential inside a neuron has to be sufficiently increased before a signal can propagate down the axon. This initial depolarization is caused by the neurotransmitter signal form another neuron. These signals come in short bursts and the

depolarization is reverted back to resting state quickly. Another kind of signal, called asynchronous synaptic transmission, has been shown to elevate the potential of the cell slightly, and take a much longer time to return to resting state then the regular neurotransmitter signal (5). This signal raises the potential of the cell more than the regular signal would by itself, and can cause the cell to reach the depolarization threshold. The cell then fires an action potential that it would not have without asynchronous synaptic transmission. There in addition to sources of excitation, there are also negative feedback mechanisms which prevent "run-away" activity in networks. In my research, I plan on developing a neural firing rate population model that explores two such sources, spike frequency adaptation, synaptic depression, and whether these, in combination with asynchronous release are sufficient to explain synchronous population bursts in cell culture networks.

Methods: Population Firing Rate Model

A population firing rate model is based on determining a function for the firing rate of a group of neurons given their inputs. This function meant to characterize the probability of action potentials (4). The basic model begins with a designated set of times, t_1 to t_n (representing the spike times of a neuron), and an empirically-determined α-function that represents the responses of post-synaptic cells to pre-synaptic spikes. The total response of the post-synaptic cell at a time t becomes $\alpha(t-t_1)+\ldots$

$+\alpha(t-t_n)=\sum_{j=1}^{n}\alpha(t-t_j)$. Let $\mu(t)$ equal the firing rate of the system such that at any t_i.

The total response of the system becomes the integral

$\Phi(t) = \int_0^t \alpha(t-s)(\sum_{j=1}^{n} pr(s = t_j))ds$ where $pr(s = t_j)$ is the probability that $s = t_j$. In a population model, however, that probability equals the firing rate because it represents the potential of a typical neuron receiving a re-synaptic spike, so this integral can be written as $\Phi(t) = \int_0^t \alpha(t-s)\mu(s)ds$. In any particular synapse, the firing rate of the post-synaptic cell is determined by the firing patterns of the pre-synaptic cell.

Thus, $\mu_{post}(t) = F(\Phi_{post}(t)) = F(\int_0^t \alpha(t-s)\mu_{pre}(s)ds)$, where the firing rate of a post-synaptic cell is a non-linear function of the response of that cell based on the inputs it encounters. One of the fundamental assumptions of a population model is that the firing rates of all neurons are the same, thus $\mu_{pre} = \mu_{post}$, and the firing rate can be written as $\mu(t) = F\left(\int_0^t \alpha(t-s)\mu(s)ds\right)$. All population models use this basic problem structure, but vary in the selection of the α function.

Methods: A Population Firing Rate Model of Spike Frequency Adaptation

My first model of reverberatory activity will be based on spike frequency adaptation. Spike frequency adaptation is the gradual reduction of firing frequency of a neuron with continuous inputs (1). Instead of one response function Φ, I will now have three, representing responses to regular, fast signals, asynchronous synaptic transmission, and spike frequency adaptation. The firing rate now becomes $\mu(t) = F(A\Phi_{fast} + B\Phi_{slow} - C\Phi_{adap})$,

where $\Phi_{fast} = \int_0^t \alpha_{fast}(t-s)\mu(s)ds$, $\Phi_{slow} = \int_0^t \alpha_{slow}(t-s)\mu(s)ds$, and

$\Phi_{adap} = \int_0^t \alpha_{adap}(t-s)\mu(s)ds$, F is a nonlinear function of inputs to the cell, and A,B, and C are the maximum magnitudes of corresponding responses. Since this model will represent a gradual decrease in firing frequency, it makes sense for the α functions to be decaying exponentially. Thus, $\alpha_{fast} = \frac{e^{\frac{-t}{\tau_{fast}}}}{\tau_{fast}}$, $\alpha_{slow} = \frac{e^{\frac{-t}{\tau_{slow}}}}{\tau_{slow}}$, and $\alpha_{adap} = \frac{e^{\frac{-t}{\tau_{adap}}}}{\tau_{adap}}$, where τ_{fast}, $\tau_{slow,}$ and τ_{adap} are time constants determined from empirical data. The first fundamental theorem of calculus can be used to determine the first derivatives of the response functions. The derivatives become: $\frac{d\Phi_{fast}}{dt} = \frac{-\Phi_{fast} + \mu(t)}{\tau_{fast}}$, $\frac{d\Phi_{slow}}{dt} = \frac{-\Phi_{slow} + \mu(t)}{\tau_{slow}}$, and $\frac{d\Phi_{adap}}{dt} = \frac{-\Phi_{adap} + \mu(t)}{\tau_{adap}}$. As previously stated, $\mu(t) = F(A\Phi_{fast} + B\Phi_{slow} - C\Phi_{adap})$, so these functions become

$$\frac{d\Phi_{fast}}{dt} = \frac{-\Phi_{fast} + F(A\Phi_{fast} + B\Phi_{slow} - C\Phi_{adap})}{\tau_{fast}},$$

$$\frac{d\Phi_{slow}}{dt} = \frac{-\Phi_{slow} + F(A\Phi_{fast} + B\Phi_{slow} - C\Phi_{adap})}{\tau_{slow}}, \text{ and}$$

$$\frac{d\Phi_{adap}}{dt} = \frac{-\Phi_{adap} + F(A\Phi_{fast} + B\Phi_{slow} - C\Phi_{adap})}{\tau_{adap}}.$$

Thus, this system can be described with three first-order differential equations. My research will include a full analysis of this system.

Methods: A Population Firing Rate Model of Synaptic Depression

The synaptic depression model is characterized by many components of the spike frequency adaptation model. Short-term synaptic depression refers to the observation that, as a cell fires at some rate μ(t), it does not have enough time afterwards to fully recover to the neurotransmitter level it had before (2). Letting σ represent the amount of exhaustible resources in the cell at any time, and f be the fraction of those resources after every fire that is lost, change in σ(t) becomes $\frac{d\sigma}{dt} = \frac{1-\sigma}{\tau_{dep}} - f\mu(t)\sigma$, where τ_{dep} is a time constant determined empirically. Assuming that synaptic depression only affects the fast reaction, and not asynchronous synaptic transmission, μ(t) becomes $\mu(t) = F(A\sigma\Phi_{fast} + B\Phi_{slow})$, reducing the system to three differential equations:

$$\frac{d\Phi_{fast}}{dt} = \frac{-\Phi_{fast} + F(A\Phi_{fast} + B\Phi_{slow} - C\Phi_{adap})}{\tau_{fast}},$$

$$\frac{d\Phi_{slow}}{dt} = \frac{-\Phi_{slow} + F(A\Phi_{fast} + B\Phi_{slow} - C\Phi_{adap})}{\tau_{slow}}, \text{ and}$$

$$\frac{d\sigma}{dt} = \frac{1-\sigma}{\tau_{dep}} - fF(A\Phi_{fast} + B\Phi_{slow} - C\Phi_{adap})\sigma.$$

Methods: Analyzing Systems of Differential Equations

The first step in analyzing either of these systems is solving them. From there, it is necessary to find parameters that cause the system to exhibit the oscillating behavior seen experimentally. From there, I plan on performing a bifurcation analysis on time constants (τ), maximum reaction constants (A, B, C), and the depression constant (f). A bifurcation analysis involves examining the consequences of varying parameters on the

stability and steady states of a system (3). Finally, I plan to couple these systems together and study how spike frequency adaptation and synaptic depression affect each other in the population model. A mathematical model of reverberatory activity in neural networks will provide powerful insights into the function of the system.

References

1. Benda, Jan, Longtin Andre, and Len Maler. "Spike-Frequency Adaptation Separates Transient Communication Signals From Background Oscillations." The Journal of Neuroscience 25 (2005): 2312-2321.
2. De La Rocha, Jaime, and Nestor Parga. "Short-Term Synaptic Depression Causes a Non-Monotonic Response to Correlated Stimuli." The Journal of Neuroscience 25 (2005): 8416-8431.
3. Edelstein-Keshet, Leah. Mathematical Models in Biology. 1st ed. New York: The Random House/Birkhauser Mathematics Series, 1988.
4. Ermentrout, G. Bard. "Neural Networks as Spatio-Terminal Pattern-Forming Systems." Reports on Progress in Physics 61 (1998): 353-430.
5. Lau, Pak-Ming, and Guo-Qiang Bi. "Synaptic Mechanisms of Persistent Reverberatory Activity in Neuronal Networks." Proceedings of the National Academy of Sciences of the United States of America 102 (2005): 10333-10338.