580.639

Second Project Assignment, 2010

The second project assignment is to find an interesting neural system and ask a question about it that involves analyzing a model. The essence of the project is asking an answerable question. It is important that there be data that can be used to test the model, or data that the model is attempting to duplicate. The model can deal with "what if" questions, as long as there are real neural systems somewhere in view. To enforce the connection between modeling and data, project proposals that do not refer to data papers will be rejected. Suggestions as to possible proposals are given at the end of this document. Additional ideas can be gotten by browsing through recent issues of journals such as the *Journal of Neurophysiology, Journal of Neuroscience, Journal of Physiology, Biophysical Journal, Biological Cybernetics, Neural Computation, Journal of Computational Neuroscience,* etc. Ideas can also be obtained from papers referenced in the course reading material. Modeling work in the literature varies in quality; one reliable source of interesting projects are papers written by John Rinzel and his colleagues.

This project should solidify and extend your understanding of material discussed in this course. Thus it should address models of neurons (not cardiac cells) at the level of membrane dynamics, dendritic tree properties, or network models. If you are doing modeling for your research, please propose a project different from your research topic. Remember that this is a course project, not a PhD thesis, so propose something reasonable, something that can be accomplished in a month. In the past, some students have attempted modeling that is too ambitious, in the sense that very large computational resources are needed or too many aims are included. I will try to identify and head off such efforts through the project proposal, but I can’t catch everything. Another warning is to pick a paper that is primarily aimed at modeling, not theory. In other words, make sure you understand how the contents of the paper can be reduced to a model that you can study successfully.

This project is required for graduate students and all students taking 580.639 and is optional for undergraduates and students taking 580.439. Whereas graduate students can chose any paper as the basis for the project, undergraduates must chose an acceptable paper, from the list at the end of this document or another paper approved by the instructor. If undergraduates do the project, it will be used to improve their final grade as long as the project grade > final grade, in which case the grade will be computed as for graduate students. If the project grade does not exceed the final grade, it will not be used.

Work on this project must be independent. You may discuss your project with classmates and instructors, but the actual programming, simulations, data interpretation, and writing must be your own individual effort.

A **project proposal** (≤2 pages) containing a brief review of the background for the project, a succinct statement of the question(s) to be answered by the project, and a short bibliography (1-5 papers) is due in class or electronically on **Monday, November 14**. The proposal should specify the computational methods that will be used, i.e. what simulation package (remember that if you want help from the T.A. or from me, you need to pick a package with which we have familiarity; basically this means Matlab). Please also include with the proposal an electronic copy of the most important reference paper for the proposed work. The purpose of the project proposals is to make sure that the planned projects are feasible and interesting. The project must be completed and handed in by **Monday, December 19 at 5:00 P.M,** by email to eyoung@jhu.edu; it must be a .ps or .pdf file. Word processor files will not be accepted.

The evaluation of the final project will be based on four components: 1) degree of difficulty of the model and the project; 2) quality of the modeling (i.e. does the model duplicate the model or data in the reference paper); 3) creativity in asking a new question with the model (i.e. a question that goes beyond what is in the reference paper); and 4) quality of the write-up (clarity, completeness, use of references, presentation of results, use of proper English, etc.).

The final project description should be written like a scientific paper. In particular, references to the literature should be used to document all ideas and facts that are not your own and that don’t derive from your modeling work described in the writeup. **Plagiarism, such as copying segments of the text from the primary reference paper or other papers must not be done; if short segments of text are copied, they must be set off in quotes (“ “) and attributed with proper references. The final project writeup must be done using proper English grammar and spelling. A copy of the primary reference paper and a copy of all programs must be handed in with the project writeup.** Although the reference papers are included with the writeup, the writeup must stand alone as a description of the model and the work done. That is, it should not be necessary to refer to the reference papers to understand what was done.

It is preferable if the programs handed in are arranged according to the figures, i.e. there is a Matlab script *figure1.m* that does the calculations for figure 1 in your writeup, etc. This is not required, but it makes evaluating the project easier and more accurate.

In previous years some students have been unable to get their model programs to run. In some cases, this failure can be traced to a failure to adjust parameter values to have proper dimensions. The set of units chosen must be self-consistent. The simplest self-consistent set of units is the MKS, in which

voltage - volts
current - amps
time - seconds
area, volume - m^2, m^3
conduct. - Siemens
capacitance - Farads
charge - coulombs
concentration - moles/m^3
rate constants - sec^{-1}
etc.

These units require the use of absurdly large or small numbers when applied to neurons, so are usually changed to more appropriate units like mV, pA, ms, μ^2, nS, etc. However these changes cannot be done arbitrarily. If voltage is measured in mV and conductance in nS, then current has to be measured in pA in order that Ohm’s law, $I = G*V$, still be quantitatively valid. Similarly, the impedance equation $I = C*dV/dt$ forces capacitance to be in certain units, once units for current, voltage, and time are chosen (and the same units must be chosen for I and V in both equations). Usually it is a good idea to choose units so that the numbers in the simulation are of order 1. If your insist on using Amp/cm^2, for example, your currents will be very small numbers and you will have to be careful to set the tolerances carefully so that the ODE solvers compute all the variables accurately. Make sure you understand what AbsTol and RelTol control.

When you set up your model, it is your responsibility to get the units right; papers frequently give parameters in inconsistent unit sets. You should check the units of every equation in your model and make sure that you make the decision about what units various values have. If you find that you are unsure about the units of a variable, then you probably have made a mistake in your program. It is important to note that these errors are severe; for example, if you decide to measure current in nA and voltage in mV and then specify conductances in your program as nS, then your actual conductances are 1000 times larger than you think.

A second caveat is that parameters are sometimes wrong in papers in the literature. Authors of the papers are usually cooperative about providing corrections, so if you are confident that your program exactly duplicates the model given in a paper and you still can't duplicate the results in the paper, try looking on the authors' website for corrections or, failing that, emailing the authors and asking for any known corrections. Please remember when you do this that you represent the JHU and all your colleagues here, so 1) make sure you have debugged your program before you start emailing people and 2) be polite. I would prefer that you go over your program with an instructor before you conclude that the parameters are wrong.

A third piece of advice is to start simple with your model. Don't try to get the whole thing working at once. For example, if you're going to model a dendritic cable containing active channels and spines, start out with a passive model, get the conductance and capacitance parameters right, and then add the active channels. It is much more difficult to debug everything at once in a complex model. Debugging a complex model is an art and it behooves you to learn it now. If you need help with developing a systematic approach to debugging, see an instructor.

The list below provides examples of projects and reference papers to get you started. These have accumulated over the years and more recent works may be available for some of them.

Most of the papers below are membrane-patch models based on Hodgkin-Huxley style modeling. Interesting projects on network models, i.e. models of populations of interconnected neurons with simpler properties than membrane-patch neurons, are also possible and provide a change from the HH modeling done in Project 1. Two suggestions are offered below, Izhikevich 2007 and Wang and Rinzel 1992. You can find additional examples by looking at the papers that cite these (look these up in Google Scholar and click on the "cited by" link).

Undergraduate project suggestions:

1. Reward learning in a network. (Izhikevich, E.M. Solving the distal reward problem through linkage of STDP and dopamine signaling. Cerebral Cortex 17:2443--2452 2007). As written, this paper probably requires more computer speed than you will have available, but a reduced network can be run, with some effort toward efficient programming.

2. Rhythmic discharge under the control of chloride. (Marchetti C, et al. Modeling spontaneous activity in the developing spinal cord using activity-dependent variations of intracellular chloride. J Neurosci. 25:3601-12, 2005).

3. Dendritic oscillation in dopamine neurons. This paper contains some incorrect parameters, well known to the instructors, and a part of doing the project is discovering those parameter

errors. (Li Y-X et al. Modeling N-methyl-D-aspartate-induced bursting in dopamine neurons. Neuroscience 71:397-410, 1996).

(NOTE: there is a paper on dopamine neurons by Kuznetzov and colleagues that is not recommended because of errors in the parameter values.)

4. Computation possibilities of rebound from inhibition. Dodla et al. Well-timed brief inhibition can promote spiking: postinhibitory facilitation. J. Neurophysiol. 95:2664-2677 (2006).

5. Low threshold channels and neural computation (Svirskis and Rinzel. *Network: Comp. Neural Syst*. 14:137, 2003; also Svirskis, G, Kotak, V, Sanes DH, and Rinzel J *J. Neuroscienc*e 22:11019–11025 2002).

Graduate project suggestions:

1. Dendrites and coincidence detection in neurons with high temporal precision. (Agmon-Snir H, Carr CE, Rinzel J. The role of dendrites in auditory coincidence detection. *Nature* 393: 268-272 (1998); VK Dasika, JA White, HS Colburn. Simple models show the general advantages of dendrites in coincidence detection. *J. Neurophysiol*. 97:3449-3459 (2007)). Another possible source is V Grau-Serrat, C.E. Carr, J.Z. Simon. Modeling coincidence detection in nucleus laminaris. Biol. Cybern. 89:388-396 2003.

3. Bursting properties of single pancreatic beta cells and networks of those cells (Smolen et al., *Biophys J*. 64:1668-1680, 1993). There is a large literature on this subject, especially from P. Smolen, A. Sherman, and J. Rinzel with many interesting possibilities for projects. If you are tempted to implement the model of Chay and Keizer (*Bioph. J*. 42:181, 1983), please use the version in Sherman et al. (*Bioph. J*. 54:411, 1988) which works better.

5. Bistable properties of thalamocortical neurons (Destexhe et al., *Bioph. J*.65:1538 (1993).

6. Action potential initiation in the dendritic trees of olfactory-bulb mitral cells (Davison AP, Feng J, Brown D.A *Brain Res Bull*. 51:393-9 (2000). Shen GY, Chen WR, Midtgaard J, Shepherd GM, Hines ML *J Neurophysiol*. 82:3006-20 (1999)).

7. Back-propagation of action potentials and K-A channels (Migliore, J. Comp. Neurosci. 7:5-15 (1999)).

8. Oscillations of multiple cells coupled through gap junctions. (Manor et al. J. Neurophysiol 77:2736 (1997)). Another nice paper showing synchronized oscillation through inhibitory synapses is Wang, XJ and Rinzel, J. *Neural Computation* 4: 84-97 (1992). Note that the Manor paper was used in project #1, so if you use this paper, you must focus on the multi-neuron aspects.

9. Threshold behavior in phasic neurons. Yan Gai, Brent Doiron, Vibhakar Kotak, and John Rinzel (2009) Noise-Gated Encoding of Slow Inputs by Auditory Brain Stem Neurons With a Low-Threshold K+ Current. J Neurophysiol 102 3447-3460.

10. A classical paper on network computation. JL Elman Finding structure in time. *Cognitive Science* 14:179-211 (1990). Be careful of recent papers on extensions of this model. Some of them are too complicated for their own good.

11. How do rhythmic EEG potentials arise from sparse firing in interconnected neural networks? N Brunel and X-J Wang What Determines the Frequency of Fast Network Oscillations With Irregular Neural Discharges? I. Synaptic Dynamics and Excitation-Inhibition Balance. J. Neurophysiol. 90:415-430 (2002).

12. Nature of the threshold: slope sensitivity in neurons. C Gutierrez, CL Cox, J Rinzel, M Sherman. Dynamics of Low-Threshold Spike Activation in Relay Neurons of the Cat Lateral Geniculate Nucleus. J Neuroscience 21:1022-1032 (2001). Ferragamo MJ, Oertel D (2002) Octopus cells of the mammalian ventral cochlear nucleus sense the rate of depolarization. J Neurophysiol 87:2262-2270.

13. Role of potassium currents in controlling the spiking behavior of neurons. JS Rothman, PB Manis *J. Neurophysiol.* 89:3097-3113 (2003).

14. Models of shunting inhibition. SA Prescott, Y DeKoninck. Gain control of firing rate by shunting inhibition: Roles of synaptic noise and dendritic saturation. PNAS 100:2076–2081 (2003). B Doiron, A Longtin, N Berman L Maler. Subtractive and Divisive Inhibition: Effect of Voltage-Dependent Inhibitory Conductances and Noise. *Neural Computation* 13, 227–248 (2000). C Ly, B Doiron (2009) Divisive Gain Modulation with Dynamic Stimuli in Integrate-and-Fire Neurons. *PLoS Comput Biol* 5: e1000365. doi:10.1371/ journal. pcbi.1000365. GR Holt and C Koch. Shunting Inhibition Does Not Have a Divisive Effect on Firing Rates. *Neural Computation* 9:1001–1013 (1997). NOTE: be careful with these models, they are computationally complex and may require simplification to make them practical for this project. The Ly and Doiron paper is the simplest.