York University BPHS 4090 (Fall 2014)

Lab 4: Proposal Overview

Overview

The overall purpose of the project is to gain some (deep) insight into your chosen topic, develop a testable hypothesis that you rigorously explore such, and gain practice composing/delivering a poster presentation. More likely than not, you'll quickly come to realize how hard/time-consuming it is to do one thing and do it well. Since a lot of useful notions can be found in the guidelines for the BPHS 3090 Hodgkin-Huxley (HH) project, some of that content is repeated below (in italics) for reference (emphasizing that your 4090 project need not be HH-related!):

More likely than not, you'll quickly come to realize how complex the behavior of the HH system is. As Huxley stated in 1964: "Very often my expectations turned out to be wrong, and an important lesson I learned from these manual computations was the complete inadequacy of one's intuition in trying to deal with a system of this degree of complexity."

Projects can involve almost any of the properties of the Hodgkin-Huxley model. However, to avoid projects whose aims are vague (e.g., 'I would like to understand how the Hodgkin-Huxley model works') the proposed project should be in the form of a specific and testable hypothesis. Projects that involve months of computation should obviously be avoided. The amount of computation time should be explicitly taken into account in planning a project. For example, any project that involves measuring the threshold of occurrence of an action potential for many different parameter values is bound to be very time consuming, because determining the threshold for a single set of parameters itself involves many computations. The task is to choose a physiological property of the excitation of the action potential that is of interest, and then to define a specific, feasible project.

Topics can involve comparing predictions of the Hodgkin-Huxley model with measurements on cells. For example, the text contains data on the effects of many external parameters (e.g., ionic concentrations, cell type) on action potentials. A project might involve reading the original papers that describe such measurements (some were made before the Hodgkin-Huxley model was formulated), and testing the hypothesis that these measurements are (or are not) consistent with the Hodgkin-Huxley model. Similarly, a project might involve examining the effect of some phar?macological substance on measurements of the action potential and testing the hypothesis that the substance produces its effect by changing one or another parameter of the model. These projects will require some reading of original literature which is often difficult and usually time consuming. However, such a project can lead to a very rewarding educational experience. Alternatively, the project might involve a purely theoretical topic in which some property of the model is explained in terms of its underlying structure. This type of project does not necessarily involve reading the original literature.

The Hodgkin-Huxley model is sufficiently complex that investigation of any of the hypotheses will most likely lead to unexpected results. You should pursue these unexpected results and try to understand their bases. For example, you may find that in pursuing some hypothesis you choose to change some parameter of the model that you expect to result in some change in action potential waveform. The resulting

computation might reveal, much to your surprise and chagrin, that no action potential has occurred. Determine why no action potential occurred. The explanation will usually be instructive. Your aim should be not simply to reject or accept the hypothesis but to delve into the topic in sufficient depth so as to a deepen your understanding of the model. One outcome of the project might be to restate your original hypothesis in a new and more sophisticated form.

Beginning with the proposal and extending through the project, you should keep clearly in mind that you are not investigating nerve membrane in these exercises. You are investigating the Hodgkin-Huxley model for nerve membrane. Your explanations of all phenomena must be in terms of the primitive concepts of this model the ionic conductances, ionic concentrations, ionic currents, the capacitance, and the variables m, n, and h. Explanations in terms of molecular channel mechanisms or electrodiffusion of ions in the membrane are irrelevant in so far as they are not contained in the Hodgkin-Huxley model!

Project Components

- Gain a deep understanding of your topic and the associated physics and biology
- Develop a focused and testable hypothesis, as well as a plan of attack to address your hypothesis
- Rigorously pursue your hypothesis via experimental data collection
- Learn to effectively analyze collected data
- Present your finding to the class (via constructing a poster) and effectively answer questions

Timeline

Aside from our normal Wednesday lab session (during which attendance is still expected), additional salient deadlines are:

- 11/11 – Proposals due by end of class. Deliver both a hard copy to the instructor, as well as a soft copy. These proposals will be sent out to the rest of the class. You will then be expected to read all of the other student's proposals and write a short summary (approx. 0.5 page/proposal) of questions/criticisms/requests for clarification. The point is to try to understand what the purpose of the proposed project is and provide constructive feedback.
- 11/12 – Critiques due by 8 PM (lateness penalty will be strictly enforced!). These should be emailed to the instructor (CB). They will be compiled and provided to each proposal writer before the next class.
- 11/13 – Proposals will be discussed for the initial portion of class.
- 12/1 – Drafts of the posters due. A template will be provided well beforehand.
- 12/3 – In-class poster presentations (more details to follow).

Grading – Your proposal will account for 20% of your project grade, 15% based upon your critiques, 10% for in-class participation (including attendance on Wednesdays), 20% for the poster draft (due 12/1), and 35% for the presentation (12/3).

0.1 Proposal

Proposals should consist of three pieces:

Hypothesis – A reasonable hypothesis is the backbone to your proposal and thus is an essential ingredient in success with the project. Formulating the hypothesis should be given considerable thought. You need to be specific about what you are going to test. A hypothesis such as "Changes in the ion concentration will affect the action potential" is too vague. Consider that the number of combinations for concentration changes to test in order to address your hypothesis would be far too large and take up considerably more time than you have. Instead, refine the hypothesis into a single answerable question such as:

"Increasing the extracellular potassium concentration will decrease the minimum current needed to induce an action potential using the Hodgkin-Huxley model".

Specifying with detail which experimental aspects you will focus on and the predicted outcome will produce a decent hypothesis. Ideally you should have a sense ahead of time whether this hypothesis will be viable by loosely testing it well before hand[1].

Background – Also included in your proposal should be the background which explains your reasoning behind the hypothesis. Blindly conducting simulations without a good reason can create an excessive amount of work for you as you try to explain the results without understanding the underlying mechanisms. This is also troublesome for your eventual audience as they try to understand what the reasoning behind the methodology.
Consider the statement: "Changing the extracellular potassium will cause a decrease in current stimulus because the Hodgkin-Huxley model is dependent on it". This fails to explain any possible mechanism as to why potassium concentration would affect it this way. Consider instead: "By increasing the extracellular potassium concentration, the potential across the membrane will depolarize according the Goldman equation $V_m = \frac{RT}{zF} ln\left(\frac{P_K C^o_K + P_{Na} C^o_{Na} + P_{Cl} C^i_{Cl}}{P_K C^o_K + P_{Na} C^o_{Na} + P_{Cl} C^o_{Cl}}\right)$, which will thereby reduce the stimulus size needed to induce an action potential." Though this is an improvement over the last explanation, it certainly still lacks information to explain why the membrane potential affects the stimulus size. An improved background is provided later in the example.

Procedure – The procedure is designed to explain how you might go about testing the hypothesis in a rigorous way. Keeping with the theme of the proposal, the procedure should be very specific about how the data will be obtained. For this, a quantitative description is desirable: what will be the measurement intervals; what will the other, non-changing, salient parameters be set to; how will you quantify your results, etc. Instead of explaining that you will be measuring the "minimum stimuli needed to induce an action potential at various potassium concentrations" , explain as would be done in a scientific paper, i.e. "The extracellular potassium will be increased in intervals of 5 mM starting from 0 mM". **Enough information should be given that someone else could test the hypothesis independently of you.**

Poster Presentation

Logistics – The presentations will take place in class. You will be allowed 11 minutes total: 9 minutes for your presentation and 2 minutes for questions. You will be timed, so it is crucial that you do not

[1] Keep the Huxley quote above in mind!!

exceed your allotted time (otherwise you may be penalized). The posters will be presented electronically (via large flat-panel screen). However, following the presentations, several posters may be selected for printing and hung up in Petrie.