York University BPHS 3090 (Winter 2015) - "Project"

Due Date: Apr. 17, 2015 9:30 AM

1 To do

- Get the software via SoftCell working on your computer so to be able to simulate various aspects of the Hodgkin-Huxley equations (see appendix)[1]. A potentially useful reference is

  `http://ocw.mit.edu/courses/electrical-engineering-and-computer-science/6-021j-quantitative-physiology-cells-and-tissues-fall-2004/tools/manual5.pdf`.

- From the appendix, choose one of the listed hypotheses. With this in hand, carefully create a proposal (as outlined in the appendix)[2].

- Write a short report (3–4 pages) the summarizes your key findings, providing clear quantitative support (e.g., figures from your simulations) to argue for or against the hypothesis. Make sure to clearly explain unexpected finding[3].

[1] Tip: Do not underestimate the time this will take. It's unlikely things will work right off the bat and will require some tweaking. Expect at least 1–2 hours just to get things up and running.

[2] Tip: Do not underestimate the time this will take. You should plan for at least 3–4 hours to preliminary explore the numerical framework and develop a reasonable take on things to create your proposal. Also, students who have previously taken BPHS 3090 must choose a different hypothesis than the one chosen in the previous year.

[3] Tip: Do not underestimate the time this will take. With your proposal already in hand, you should plan for at least 3–4 hours to delve into the numerical simulations, and a similar amount of time to produce your report.

2 Appendix

A useful piece of advice: 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.'

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!

2.1 SoftCell

There are two HH simulation modes. The first models a space-clamped axon, which generates membrane action potentials. The second models an axon without space-clamp (although the second model can simulate a space clamp since the longitudinal resistances can be set to zero). The second model can produce propagated action potentials. The second model can be used to explore a wider range of phenomena than the first. The first model is faster and simpler than the second. Thus both models are useful, and your project can use either or both of the models.

2.2 Possible hypotheses

1. The conduction velocity of a propagated action potential produced by the HH model will increase as temperature increases.

2. Lowering G_k causes forward-propagating self-sustaining 'train' of APs. This effect is due to an increase in resting membrane potential and thereby a decrease in threshold for firing. The combination of these two is eventually significant enough for an overshoot in membrane potential returning to its resting value from the undershoot (after the peak of the AP) to fire off an additional AP.

3. The effect of temperature on the conduction velocity of the squid giant axon can be fit by the Hodgkin-Huxley model. Articles in the literature should be consulted for this project:

- Chapman, R. A. (1967). Dependence on temperature of the conduction velocity of the action potential of the squid giant axon. J. Physiol. 213:1143-1144.
- Easton, D. M. and Swenberg, C. E. (1975). Temperature and impulse velocity in giant axon of squid loligo pealei. Am. J. Physiol. 229:1249-1253.

4. When two action potentials are elicited, one just after another, the velocity of the second is slower than the velocity of the first action potential. This phenomenon is predicted by the Hodgkin-Huxley model. Articles in the literature should be consulted for this project:

    - George, S. A., Mastronarde, D. N., and Dubin, M. W. (1984). Prior activity influences the velocity of impulses in frog and cat optic nerve fibers. Brain Res. 304:121-126.

5. The threshold current for eliciting an action potential with an intracellular electrode is higher for a space-clamped than for an unclamped model of an axon.

6. Increasing the membrane capacitance will decrease the conduction velocity.

7. Increasing the membrane conductance (by scaling all the ionic conductances) will increase the conduction velocity.

8. Increasing the external concentration of sodium will increase the conduction velocity.

9. Increasing the external concentration of potassium will increase the conduc? tion velocity.

10. Increasing the external concentration of calcium will increase the conduction velocity.

11. Increasing the temperature will increase the conduction velocity.

12. The difference in waveform of the action potential of a frog node of Ranvier and of a squid giant axon (Figure 1.9 in volume 2 of the text) can be reproduced by the Hodgkin-Huxley model of a squid giant axon by a change in temperature.

13. The membrane capacitance determines the time course of the rising phase of the action potential. Increasing the membrane capacitance decreases the rate of increase of the rising phase of the action potential.

14. The falling phase of the action potential (repolarization) can occur in the absence of a change in potassium conductance.

15. Increasing the temperature sufficiently blocks the occurrence of the action potential because the membrane time constant limits the rate at which the membrane vari? ables can change and prevents the difference in time course of the sodium and potassium activation which is responsible for initiation of the action potential.

16. The initiation of the action potential is independent of the potassium conduc? tance.

17. The prolonged plateau of the cardiac muscle action potential can be accounted for by the Hodgkin-Huxley model with a potassium conductance that has a slow activation.

18. The effect of tetraethylammonium chloride (TEA) on the action potential of the squid giant axon can be modeled with the Hodgkin Huxley model by decreasing K_n and increasing K_h. Articles in the literature should be consulted for this project:

- Armstrong, C. M. (1966). Time course of TEA+-induced anamalous rectification in squid giant axons. J. Gen. Physiol. 50:491-503.
- Armstrong, C. M. and Binstock, L. (1965). Anomalous rectification in the squid giant axon injected with tetraethylammonium chloride. J. Gen. Physiol. 48:859-872.
- Tasaki, I. and Hagiwara, S. (1957). Demonstration of two stable potential states in the squid giant axon under tetraethylammonium chloride. J. Gen. Physiol. 40:859-885.

19. Theshapeoftheactionpotentialinthepresenceoftetraethylammoniumchlo? ride (TEA) can be accounted for by the Hodgkin-Huxley model with a reduced maximum value of the potassium conductance. Articles in the literature should be consulted for this project:

    - Armstrong, C. M. (1966). Time course of TEA+-induced anamalous rectification in squid giant axons. J. Gen. Physiol. 50:491-503.
    - Armstrong, C. M. and Binstock, L. (1965). Anomalous rectification in the squid giant axon injected with tetraethylammonium chloride. J. Gen. Physiol. 48:859-872.
    - Tasaki, I. and Hagiwara, S. (1957). Demonstration of two stable potential states in the squid giant axon under tetraethylammonium chloride. J. Gen. Physiol. 40:859-885.

20. Increasing the external calcium concentration will block the occurrence of the action potential because this will reduce the difference in the time constant of sodium and potassium activation which is responsible for the initiation of the action potential.

21. Increasing the external concentration of potassium will decrease the refractory period; decreasing this concentration will lengthen the refractory period.

22. Increasing the external concentration of sodium will decrease the refractory period; decreasing this concentration will lengthen the refractory period.

23. Absolute and relative refractory periods are decreased by increasing the rate constants for sodium inactivation and for potassium activation.

24. Repolarization cannot occur if the potassium activation rate constant is zero.

25. The threshold of the action potential to a brief pulse of current decreases as the external potassium current is increased.

26. The Hodgkin-Huxley model with default parameters does not exhibit accommodation. Hy? pothesis Accommodation occurs if the leakage conductance is increased.

27. The Hodgkin-Huxley model with default parameters does not exhibit accommodation. Hy? pothesis Accommodation occurs if the potassium conductance is increased.

28. Increasing the leakage equilibrium potential will block the action potential.

29. The effect of the changes in concentration of sodium ions on the action po? tential of the giant axon of the squid can be accounted for by the Hodgkin-Huxley model. Articles in the literature should be consulted for this project:

    - Hodgkin A. L. and Katz, B. (1949). The effect of sodium ions on the electrical activity of the giant axon of the squid. J. Physiol. 108:37-77.

- Baker, P. F., Hodgkin, A. L., and Shaw, T. I. (1961). Replacement of the protoplasm of a giant nerve fibre with artificial solutions. Nature 190:885-887.

30. In response to rectangular pulses of current, the rheobase of the strength- duration relation increases as temperature increases.

31. An increase in temperature results in a decrease in the duration of the refrac? tory period.

32. The threshold membrane potential at which the Hodgkin-Huxley model pro? duces an action potential in response to a brief pulse of current is equal to the membrane potential for which the linearized Hodgkin-Huxley equations have unstable eigenvalues.

33. Application of a long-duration constant current to the Hodgkin-Huxley model produces a train of action potentials. Hypothesis: The frequency of the action potentials increases with increasing current amplitude.

34. Application of a long-duration constant current to the Hodgkin-Huxley model produces a train of action potentials. Hypothesis: The frequency of action potential increases as the parameter K_n is increased.

35. Application of a long-duration constant current to the Hodgkin-Huxley model produces a train of action potentials. Hypothesis: The frequency of action potential increases as the temperature is increased.

36. An increase in the external concentration of potassium increases the threshold potential at which an action potential is elicited.

37. Increasing K_h will result in an increase in the steepness of the repolarization phase of the action potential.

2.3 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 parameter(s) will be changed 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 before hand[4].

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

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 tounderstand what the reasoning behind the simulations.
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 $V_m = \frac{RT}{zF} ln\left(\frac{P_K C_K^o + P_{Na} C_{Na}^o + P_{Cl} C_{Cl}^i}{P_K C_K^o + P_{Na} C_{Na}^o + P_{Cl} C_{Cl}^o}\right)$, 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.**

2.3.1 Proposal Example I

Hypothesis: By increasing the extracellular potassium concentration, there will be a increase in the threshold required to induce an action potential using the Hodgkin-Huxley model.

Background: By increasing the extracellular potassium concentration, the potential across the resting membrane will depolarize according the Goldman equation $V_m = \frac{RT}{zF} ln\left(\frac{P_K C_K^o + P_{Na} C_{Na}^o + P_{Cl} C_{Cl}^i}{P_K C_K^o + P_{Na} C_{Na}^o + P_{Cl} C_{Cl}^i}\right)$. The rate constant α increases as the difference between the membrane potential and resting potential increases and β decreases exponentially with the difference (α is the rate constant for the open channel while β is the constant for when it is closed). By increasing the resting potential, the difference between the potentials will be smaller, causing β to increase thereby reducing the number of channels open and by extension reducing the conductance (as conductance is positively correlated with the number of channels open). Therefore, to induce an action potential in a poorly conducting membrane will require a larger stimulus than in a highly conductive membrane

Procedure: The program's default parameters for the conductance and concentrations (other than the external potassium concentration) will be maintained throughout the procedure (constant values listed at end). The initial concentration for extracellular potassium will be initially set to 0 and steps of 5 mM will be used. The current stimulus will begin with a duration of 0.5 ms, zero slope and an amplitude of 10 $\mu A/cm^2$, and the amplitude will be decreased or increased accordingly by steps of 2 $\mu A/cm^2$. We will define an action potential to be a membrane voltage $V_m > 0$. To ensure the rate constant are the cause, plots of α, β, m and h will collected to see if there are variances between trials.
Constants: $G_{Na} = 120$ mS/cm^2, $G_K = 36$ mS/cm^2, $C_{Na}^o = 491$ mM, $, C_{Na}^i = 50$ mM, $C_K^i = 400$ mM, $, C_{Ca}^o = 44$ mM, $, C_{Ca}^i = 0.0001$ mM

2.3.2 Proposal Example II

Hypothesis: The conduction velocity of a propagated action potential produced by the HH model will increase as temperature increases.

Background: According to the software manual (Equations 5.14 to 5.20), the rate constants for the Hodgkin Huxley model increase exponentially with temperature. Hence, we expect that the time course for m, n, and h will be faster at higher temperatures. Since these factors determine the sodium and potassium conductances that generate the action potentials, increasing temperature should increase the speed of action potentials.

Procedure: We will perform simulations at different temperatures starting at 0 degrees (freezing point of water) and incrementing by 10 degrees up to 50 degrees (half way to the boiling point). For each simulation, we will determine how long it takes the peak of the action potential to travel 1 cm. The time for the peak to reach a point 1 cm from the stimulus electrode will be determined by plotting membrane potential versus time at the 1 cm place. The time to reach a point 2 cm from the stimulus electrode will be determined from a similar plot at the 2 cm place. The velocity will be computed by dividing 1 cm by the difference in times. In addition to showing a plot of velocity versus temperature, we will also show plots of m, n, and h to show that our reasoning is correct.