

## Hodgkin-Huxley Project

This theoretical project is intended to provide an opportunity to learn about the complex behaviors that can be exhibited by the Hodgkin-Huxley model and to compare behaviors of the model with behaviors of electrically excitable cells. We have two simulations. The first models a space-clamped axon. That model 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.

Students are **STRONGLY** encouraged to work in pairs, however, individual projects will be approved if there are extenuating circumstances. If a pair of students collaborate on a project they should submit a single proposal and a single report which identifies both members of the team and gives both email addresses. Proposals should be submitted via the form available on our home page. Proposals will be returned as soon as possible so that students can revise them. Only the final, accepted proposal will be given a grade.

The demonstration project performed in lecture on the effect of temperature cannot be the basis of a student project.

### Practical considerations in the choice of a topic

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.

### Choice of topics

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 pharmacological 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.

## Examples of hypotheses

1. Hypothesis — 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., Mastrorarde, 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.
2. Hypothesis — 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.
3. Hypothesis — Increasing the membrane capacitance will decrease the conduction velocity.
4. Hypothesis — Increasing the membrane conductance (by scaling all the ionic conductances) will increase the conduction velocity.
5. Hypothesis — Increasing the external concentration of sodium will increase the conduction velocity.
6. Hypothesis — Increasing the external concentration of potassium will increase the conduction velocity.
7. Hypothesis — 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.
8. Hypothesis — 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.
9. Hypothesis — The falling phase of the action potential (repolarization) can occur in the absence of a change in potassium conductance.
10. Hypothesis — The initiation of the action potential is independent of the potassium conductance.
11. Hypothesis — 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.
12. Hypothesis — The effect of tetraethylammonium chloride (TEA) on the action potential of the squid giant axon can be modelled 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<sup>+</sup>-induced anomalous 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.
13. Hypothesis — The shape of the action potential in the presence of tetraethylammonium chloride (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<sup>+</sup>-induced anomalous 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.
14. Hypothesis — Increasing the external concentration of potassium will decrease the refractory period; decreasing this concentration will lengthen the refractory period.
  15. Hypothesis — Increasing the external concentration of sodium will decrease the refractory period; decreasing this concentration will lengthen the refractory period.
  16. Hypothesis — Absolute and relative refractory periods are decreased by increasing the rate constants for sodium inactivation and for potassium activation.
  17. Hypothesis — Repolarization cannot occur if the potassium activation rate constant is zero.
  18. Hypothesis — The threshold of the action potential to a brief pulse of current decreases as the external potassium current is increased.
  19. The Hodgkin-Huxley model with default parameters does not exhibit accommodation. Hypothesis — Accommodation occurs if the leakage conductance is increased.
  20. The Hodgkin-Huxley model with default parameters does not exhibit accommodation. Hypothesis — Accommodation occurs if the potassium conductance is increased.
  21. Hypothesis — Increasing the leakage equilibrium potential will block the action potential.
  22. Hypothesis — The effect of the changes in concentration of sodium ions on the action potential 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.
  23. Hypothesis — The threshold membrane potential at which the Hodgkin-Huxley model produces 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.
  24. 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.
  25. 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.
  26. Hypothesis — An increase in the external concentration of potassium increases the threshold potential at which an action potential is elicited.
  27. Hypothesis — Increasing  $K_h$  will result in an increase in the steepness of the repolarization phase of the action potential.

Any of these (or other) hypotheses can be the starting point for a project. Most of the hypotheses given above are simplistic, and a careful investigation will reveal their shortcomings. 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 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!