Harvard-MIT Division of Health Sciences and Technology
HST.750: Modeling Issues in Speech and Hearing, Spring 2006
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# Problem/Discussion Set for "Theory ↻ Experiment"

1. **Axons and Wires.**

   (a) Compute the length of a segment of 22 gauge copper wire that has the same total resistance as a mammalian nerve fiber 1m in length. Express your answer in A.U.[1]

   (b) Is the propagation of the nerve impulse more closely analogous to the burning of a fuse (e.g., of the combustible type used to detonate explosives) or to the propagation of an electromagnetic wave along a transmission line? Explain your reasoning.

   (c) By limiting the rate at which information can be propagated from point to point within the nervous system, axonal refractory periods impose constraints on neural coding. For this reason, refractory periods might be regarded as a liability to the organism. Are there any more beneficial consequences of refractoriness for neural coding?

2. **Reduction of the HH Equations.** In this problem, you'll examine the behavior of the HH equations in a simple limit. For reference, note that the standard HH equations are summarized at the beginning of Part III of Hodgkin & Huxley (1952d).

   (a) Write out the HH equations assuming that $h$ and $n$ are constants equal to their resting values. When might this be a reasonable approximation? The equations should have the form $dV/dt = f(V, m)$ and $dm/dt = g(V, m)$. These two equations can be combined into a single vector equation:
   $$\frac{dX}{dt} = F(X) \,,$$
   where $X \equiv (V, m)$ and $F \equiv (f, g)$.

   (b) Since these "reduced" HH equations involve only two dynamical variables ($V$ and $m$), the two variables can easily be plotted against one another in "phase space" (i.e., in the $V$-$m$ plane). Assume that the applied current is zero ($I = 0$) and plot the curve in the phase plane for which $dm/dt = 0$ (this curve is known as the $m$-isocline). Also plot the curve for which $dV/dt = 0$ (the $V$-isocline). Locate the points at which the $m$ and $V$ isoclines intersect. At these points, known as "critical points", the system is in equilibrium (the variables $m$ and $V$ are both constant and do not change with time).

   (c) Now you will determine using a linear stability analysis whether the critical points you found are stable or unstable to small perturbations. Expanding the vector equation in a Taylor series about a critical point, $X_c$, yields
   $$\frac{dx}{dt} \approx Ax \,,$$
   where $x \equiv X - X_c$ and the matrix $A$, known as the Jacobian matrix, is defined by
   $$A \equiv \begin{pmatrix} \partial f/\partial V & \partial f/\partial m \\ \partial g/\partial V & \partial g/\partial m \end{pmatrix} \,,$$
   where the partial derivatives are evaluated at the critical point. At each critical point, compute the matrix $A$ and determine its eigenvalues. If all of the eigenvalues have negative real parts, the system is asymptotically stable at the critical point. Why? If one or more of the eigenvalues has a positive real part, the system is unstable at the critical point. Classify the critical points as stable or unstable.

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[1] The following parameters may prove helpful: inside diameter of mammalian nerve fiber $\sim 1\mu$m; resistivity of mammalian axoplasm $\sim 125\Omega$cm; diameter of 22 gauge copper wire $= 0.7112$mm; resistivity of copper $= 1.72 \times 10^{-6}\Omega$cm; A.U.$\equiv$ Angstrom unit ($10^{-8}$ cm) or A.U.$\equiv$ astronomical unit, the mean distance between the earth and the sun ($\approx 1.5 \times 10^{13}$ cm), whichever is more appropriate.

(d) Based on your stability classification, and the locations of the critical points along the $V$ axis, provide an interpretation of each. Show how similar results (3 critical points, 1 of which is unstable) can be obtained from an analysis of Fig. 10 of HH&K (1952).

(e) In his 1972 book, Cole writes

> The [HH] equations are thus a formal and complete presentation of the "Sodium Theory"— essentially replacing the earlier, comparatively qualitative, description of it. Although it should not be necessary, perhaps a more complete descriptive title [for HH1952d] should be on record such as:
>
> > "A Theory that a Sodium Ion Permeability, Controlled by the Membrane Potential, is Responsible for the Impulse Excitation and Propagation of the Squid Axon in Its Normal Environment and Under Normal Conditions, with the Hope and Expectation that the Theory Will Apply to Some Other Excitable Cells and Under Some Other Conditions." (p. 285)

This extended title might be interpreted as implying that potassium permeability, although evidently important for *recovery* from excitation, plays no fundamental role in axon *excitation*. What role, if any, does potassium permeability play in axon excitation? Hint: Show that there would be no unstable critical point in the reduced HH equations (or in Fig. 10 of HH&K) if sodium were the only permeable ion (i.e., if $g_K = 0$).

(f) Extra credit: The HH reduction explored above does not produce action potentials in response to a steady current input. Why? Another simplification of the HH equations that does produce action potentials can be obtained by using the approximations $m \approx m_\infty(V)$ and $n \approx 1 - h$. Write out the HH equations in this approximation. Explain what these approximations mean physically and justify them using information from the H&H papers.

3. **Separating the Ionic Currents.** In this problem you will use the HH model to calculate the total transmembrane current. You will then use HH's (1952a) procedure to separate the total current into its ionic components, comparing the ionic currents you obtain with exact results using the HH model.

(a) The Matlab script `hhvclamp` distributed via email solves the HH equations in voltage clamp. Check over the script to make sure you understand it and to make sure there no insidious errors.

(b) Use the script to obtain records of the total ionic current density versus time with displacement of the membrane potential as parameter (e.g., as in Fig. 3b). Use your records to determine the sodium potential $V_{Na}$ experimentally as "the strength of depolarization which [gives] an ionic current curve which start[s] horizontally" (HH1952a, p. 454). Using the information on p. 455, determine the corresponding internal concentration of sodium.

(c) Use the script to obtain records for the total ionic current density versus time for various voltage steps in a solution containing 10% external sodium. Choose your voltage steps in order to "obtain curves of ionic current against time in the two solutions, with strengths of depolarization which reach the same membrane potential during the voltage clamp" (p. 458). Follow HH and assume that the resting potential "increase[s] on the average by 4 mV when the sea water surrounding the axon [is] replaced by choline sea water" (p. 455).

(d) Use your current records to obtain estimates of $I_{Na}$ and $I_K$ versus time with strength of depolarization as parameter (e.g., Fig. 5 and 6). Use the procedure outlined on pages 457 and 458.

(e) Compare your estimated currents with the exact values computed using the script. Plot the estimated and actual current traces versus time on the same graphs, with strength of depolarization as parameter. Use your results to assess the accuracy of HH's procedure.

4. **Modeling Approaches.** In what way(s) is/are the modeling approach(es) adopted by H&H similar to (and in what way(s) different from) the approach(es) of other authors we've studied in the course? For

example, is the H&H approach basically computational or analytic? forward or inverse? detailed or heuristic? mechanistic or phenomenological? How, in these regards, does the work of H&H compare with other models we've studied? Also, how do you suppose H&H's procedure, logic, and conclusions might have differed had they had access to a modern computer?

5. **The Interplay Between Theory and Experiment.** In 1972 Cole described the space and voltage clamp approach. In his discussion he notes the following:

> Quite aside from the immediate possibilities, this approach has seemed to me to be a beautiful example of the interplay of experiment and theory. Much of the previous progress had been made possible by varied and usually rather elementary theoretical considerations. But a limit had been reached practically at which the appropriate theory was far too difficult—for us at least—to be useful. Since no way could be found to appreciably simplify the theory for existing experiments the impasse could only be broken by very considerably complicating the experiment; placing the axon in a highly nonphysiological situation, for which the theory was almost immeasurably simplified. This is no isolated example of a valuable strategy—if in experimental trouble look at theory and if in theoretical trouble look at experiment.

How does this interplay between theory (modeling) and experiment manifest itself in the work of Hodgkin and Huxley? Describe a problem in auditory science (either from your own work or that of others) where you feel that more conscious application of Cole's strategy might prove beneficial.