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Lecture 5
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Exercise 5.1: Deriving the Hodgkin-Huxley Model

The Hodgkin-Huxley model is a scientific model that describes how action potentials in neurons are initiated and propagated. It is a set of nonlinear ordinary differential equations that approximates the electrical characteristics of excitable cells. This is the Hodgkin-Huxley model for generation of an action potential:

$$I_{ionic} = \underbrace{g_L(V_m - E_L)}_{I_L} + \underbrace{\overline{g_K} \cdot n^4 \cdot (V_m - E_K)}_{I_K} + \underbrace{\overline{g_{Na}} \cdot m^3 h \cdot (V_m - E_{Na})}_{I_{Na}}$$

The membrane of a neuron has a negative potential at rest, that results from ion flow. The current for each ion depends on the conductance of the membrane, and on how far from the reversal potential the membrane potential is:

$$I_{ion} = g_{ion} \cdot (V_m - E_{ion})$$

For several ions, the conductance (g_{ion}) is not constant, and can thus be written in terms of a maximal conductance ($\overline{g_{ion}}$) multiplied by a gating variable:

$$g_{ion} = \overline{g_{ion}} \cdot n_{ion}$$

We consider only ions flowing through channels (the constant currents are typically grouped into a single term called the leakage current,I_L, the first term in the model). Consider the scenario that the flow of ions through channels is modulated by a physical gate present on the channels which can be opened or closed with a certain probability. In this case, n_{ion} can be interpreted as the probability for one of these channels to be open and represents the proportion of the maximum conductance.

(a) What are the lower and upper bound for n_{ion}?

(b) Suppose now that each channel has several gates in series (let's say x gates), all of which need to be open to permit the specific ions to pass through the channel. If the probability of a single gate to be open is n, what is the probability that all the x gates are open?

(c) Each gate can move from a open state to a closed state and vice-versa. If the probability that a gate in a closed state becomes open is α_n, and the probability that an open gate closes itself is β_n, how does the proportion of open gates n vary? $dn/dt = \ldots$

(d) In the steady state, n does not change anymore implying $dn/dt = 0$. How large is the gating variable n in steady state: $n_\infty = \ldots$ in terms of α_n and β_n?

(e) Do you think α_n and β_n should be voltage dependent?

(f) Hodgkin & Huxley found that a model with 4 gates in series produces a good fit to the S-shaped curve of the potassium current (I_K) during the action potential. Having read the previous points explain the second term, I_K, of the model.

(g) Sodium channels open only transiently when the membrane potential is depolarized. Therefore Hodgkin & Huxley introduced another variable that can be interpreted as "blocking an open channel". The probability that an open channel is not blocked is denoted by h. Can you explain the expression for I_{Na}, last term of the model?

(h) Draw schematically the evolution of m, h and n as function of time during an action potential.

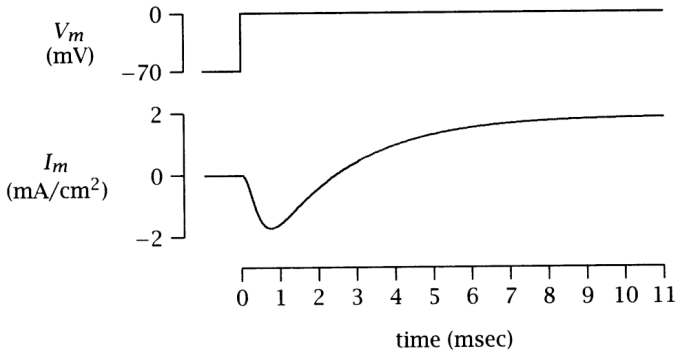

Figure 1: Voltage clamp experiment

Exercise 5.2: Voltage-Clamp

When a normal, healthy squid axon is voltage-clamped in artificial sea water, one obtains the membrane current I_m record shown in Fig. 1, in response to a step change in membrane potential from $V_m = -70$ mV to $V_m = 0$ mV. Draw similar plots of I_m vs. t (V_m is stepped from -70 mV to 0 mV) when the recordings are made under each of the following experimental conditions. For each of your plots, explain in one or two sentences how and why your graph differs from Fig. 1.

1. Tetrodotoxin (blocks Na^+ channels) is added to the bath surrounding the axon.
2. TEA (blocks K^+ channels) is added to the interior of the axon.
3. $[Na^+]_{out}$ is adjusted such that $[Na^+]_{out} = [Na^+]_{in}$.
4. $[K^+]_{out}$ is adjusted such that $[K^+]_{out} = [K^+]_{in}$.
5. Ouabain, a specific inhibitor of the Na^+-K^+ pump, is added to the bath five minutes before the experiment.

Exercise 5.3: I-V Curve

In Fig. 2 you see the momentary I-V relation of the squid giant axon ($I_i = I_{Na} + I_K$):

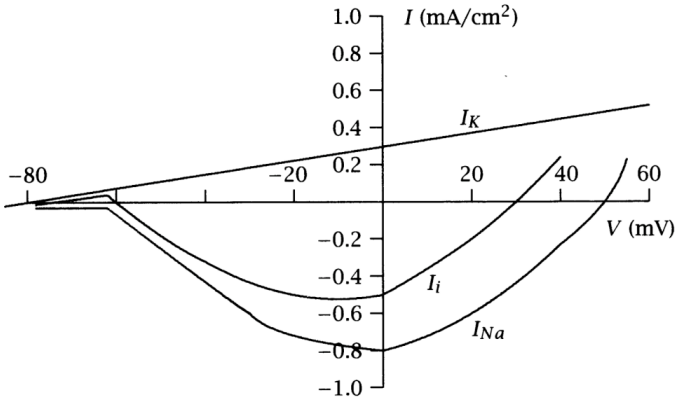

Figure 2: I-V Curve in Squid Axon

1. Why can you tell with this graph that the K^+ conductance g_K does not depend on the voltage V?
2. Draw I_{Na}, I_K, I_i for the case that g_K is twice as large.
3. Draw I_{Na}, I_K, I_i for the case that g_{Na} is voltage independent.

Exercise 5.4: A Historical Figure

In Fig. 3 you see the original figure from one of the famous 1952 Hodgkin & Huxley papers. On the vertical axis n_∞ (range: 0 to 1) is plotted versus the membrane voltage on the horizontal axis. The reference used by Hodgkin & Huxley to evaluate the membrane voltage was infact the resting potential and with an opposite sign as compared to contemporary convention. In other words, an abscissa of 0 in Fig. 3 refers to the resting potential and a negative value on the abscissa indicates depolarization.

Using their data, calculate the steady-state K^+ current $I_{K\infty}$ after the axon is stepped from the resting potential of –60mV to 0 mV (voltage clamp). Here, $\overline{g_K}$ is given to be $36\frac{\text{mS}}{\text{cm}^2}$, and the equilibrium potential of K^+ is $E_K = -72$ mV. All voltages in the text are according to the modern convention, *i.e.* referred to the extra-cellular space.

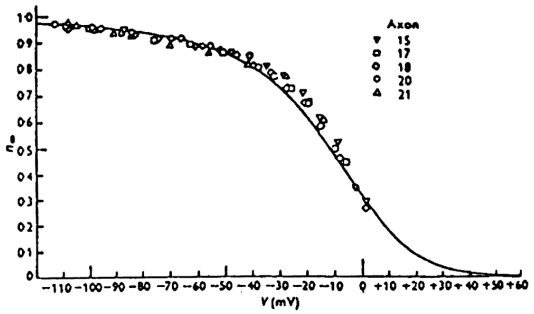

Figure 3: Abscissa: membrane potential minus resting potential. Ordinate: n_∞ calculated from experimental measurements of the steady state potassium conductance $I_{K\infty}$ in the squid giant axon in sea water.