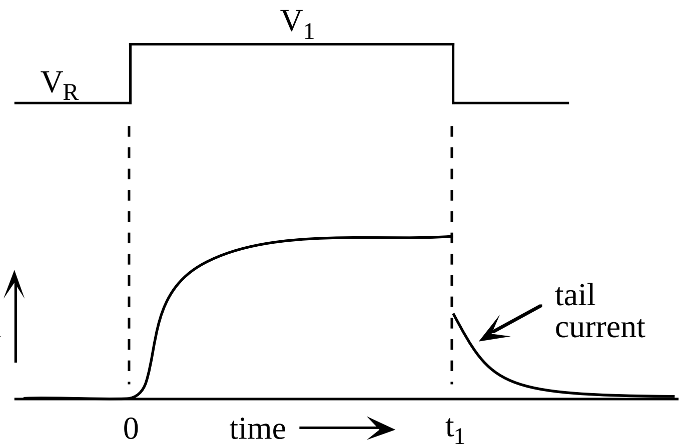
580.439 Midterm Exam 1998

1.5 hour, closed book except for two 8.5”x11” sheets of paper. There are two problems marked **; <u>do only one of them</u>.

Problem 1

A common tool used in voltage clamp analysis is *tail currents*, meaning the currents which flow when a channel is deactivated at the trailing edge of a voltage clamp protocol. The figure at right shows an example for the squid giant axon delayed rectifier channel. The top trace shows a voltage clamp protocol, where V_R is the resting potential and V_1 is some suitable depolarized potential. The bottom trace shows the resulting potassium current.



14 pts

Part a) Write equations for the current during the voltage clamp and after it, i.e. for all time >0. These should be written in terms of the parameters of the Hodgkin-Huxley model for the squid giant axon delayed rectifier potassium channel (such as $n_\infty(V)$, $\tau_n(V)$, etc). Assume that the system is held at V_R for t<0 and at V_1 for $t<t_1$ long enough to allow all gating transients to disappear.

14 pts

Part b) Explain why there is a discontinuity in the potassium current at the offset of the voltage clamp (at time t_1).

15 pts

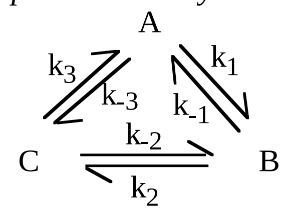
**** Part c)** An alternate way of expressing the Hodgkin-Huxley potassium channel model is in terms of a four-state diagram like the one below.

$$C_0 \rightleftharpoons C_1 \rightleftharpoons C_2 \rightleftharpoons C_3 \underset{4\beta}{\overset{\alpha}{\rightleftharpoons}} O$$

Write a differential equation for the fraction of channels in the open state O in terms of the parameters of this model. Solve this equation for $O(t)$, for $t>t_1$, that is during the time of the tail currents. ASSUME that there is a fixed number of channels Q, that 100% of the channels are in the O state at time t_1 and consider only states C_3 and O. Is this result the same as the one you got in part a)? Should it be?

Problem 2

An important rule for kinetic models is that the product of the rate constants going clockwise around any loop must equal the product of the rate constants going counter-clockwise. Thus for the simple 3-state model at right, $k_1 k_2 k_3 = k_{-1} k_{-2} k_{-3}$. This rule is called *microscopic reversibility*.



14 pts. **Part a)** Draw an energy barrier model for the example system and show from that diagram that microscopic reversibility must hold. In doing this, IGNORE THE EFFECTS OF ELECTRICAL POTENTIALS. This assumption doesn't change the conclusion, it just makes it simpler.

15 pts. **Part b)** Another way to prove microscopic reversibility is to demand that, at equilibrium, there should be zero net flux through the system (*principle of detailed balance*). Write equations for the three fluxes in this system and show that if the three net fluxes are zero at equilibrium, then microscopic reversibility must hold.

15 pts **** Part c)** Consider whether a steady-state of flux could occur in such a system. That is, could there be a non-zero net flux around the system in either the clockwise or counterclockwise direction in steady state? Apply the usual steady-state condition to the fluxes in the model and argue that microscopic reversibility implies that there cannot be such a flux. (Hint: assume that the net flux is from A to B to C to A, etc.; what conditions must hold for each of these net fluxes to occur? Can you find a paradox?)

Problem 3

A useful technique for calculating some features of phase planes is to run the system backward in time. That is, if $\vec{X} = \vec{F}(\vec{X})$ is the system, then running it backward in time means computing solutions to $\vec{X} = -\vec{F}(\vec{X})$. Explain what happens to the following features of the phase plane when the system is run backward. Give a brief justification of each answer.

7 pts. each part

Part a) Nullclines

Part b) Equilibrium points

Part c) Trajectories

Part d) Eigenvalues of the linearized system at an equilibrium point