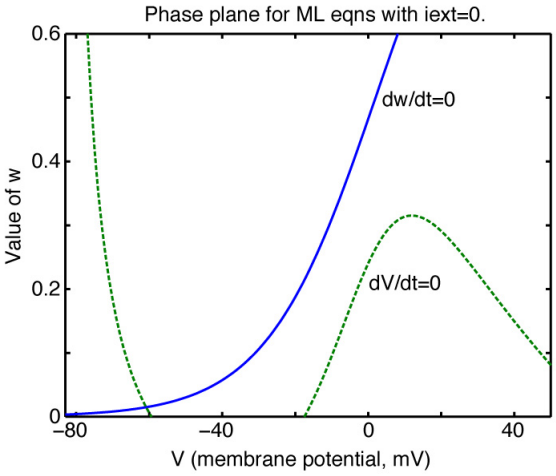
580.439/639 Midterm Exam, 2012

1.25 hour, closed book except for 1-page cheat sheet, do all problems.

Problem 1 (short answers)



Part a) Consider the MLE model as discussed in class. For one parameter set, the model has nullclines like those drawn at right. The potassium gating function $w_\infty(V)$ depends on the particular subunits that make up the potassium channel. By substituting a so-called KvS subunit for one of the usual four subunits in the potassium channel, the $w_\infty(V)$ function can be shifted by V_0 mV to the right (toward higher membrane potentials), so that $w_{new}(V) = w_\infty(V\text{-}V_0)$. What effect will this have on

i) . . . the nullclines?

ii) . . . the equilibrium point or points, including the number of equilibrium points.

iii) Sketch the shape of a bifurcation diagram showing equilibrium point(s) on the ordinate and the value of V_0 on the abscissa. You will not be able to compute the stability of the equilibrium point(s), so just show the shape of the equilibrium point plot.

In each case show sketches of the phase plane to explain your answer.

Part b) Draw a sketch of the pore of a voltage-gated potassium channel and explain what part of the channel is important for ion selectivity and for the single-file nature of permeation through this channel (i.e. the fact that potassium ions pass through in groups of 2-3). It may help to point out where this channel is different from the sodium channels whose structure is currently known. Also show what part of the channel is the activation gate and how voltage sensitivity is achieved.

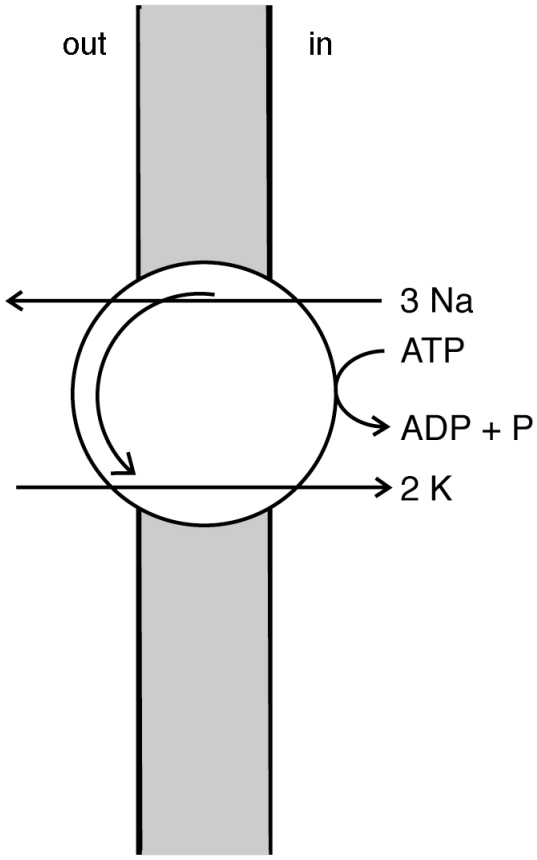
Part c) Suppose that a certain channel is blocked by the binding of an ion within the pore of the channel. Assume the binding is a single-step process like

$$Ch + X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ChX \quad ,$$

where *Ch* is channel, *X* is the relevant concentration of the blocker, and *ChX* is the blocked channel. Draw a single-barrier model for this process and specify the minimum number of variables needed to account for 1) the kinetics of the binding, i.e. the rate constants; 2) the concentration of the blocker *X* at which half the channel is blocked; and 3) the effects of membrane potential on the block. Write equations for the rate constants and the half block concentration of *X*. These should include the effect of membrane potential. It may be easiest to start with a differential equation for d*ChX*/dt.

Problem 2

The Na-K ATPase pump works as summarized at right. In each cycle, 2 K ions are pumped into the cell, 3 Na ions are pumped out, and an ATP molecule is hydrolyzed to ADP and P inside the cell. (Important: in this problem, remember that steady states of zero charge transfer across the membrane are established very fast compared to steady states of ion concentration).



Part a) Write a condition for thermodynamic equilibrium of this pump.

Part b) Suppose J is the flux of the pump, in units of moles of ATP consumed per second per square cm of membrane. Write an equation for the current produced by the pump, in units of coulombs/(cm^2 s).

Part c) Consider a membrane with a capacitance, HH-like Na and K channels, Na-K ATPase, and leakage channels. All other ion conduction mechanisms are negligible. Write equations that have to be solved to find the steady-state membrane potential V_{rest}. Just write these in terms of currents, i.e. I_{Kv} and I_{Nav} for the voltage-gated channels and J for the Na-K current, as in part b). Assume that the leakage current is part potassium (fraction f_K) and the rest sodium. Is the Na-K pump at equilibrium at V_{rest}? Why or why not?

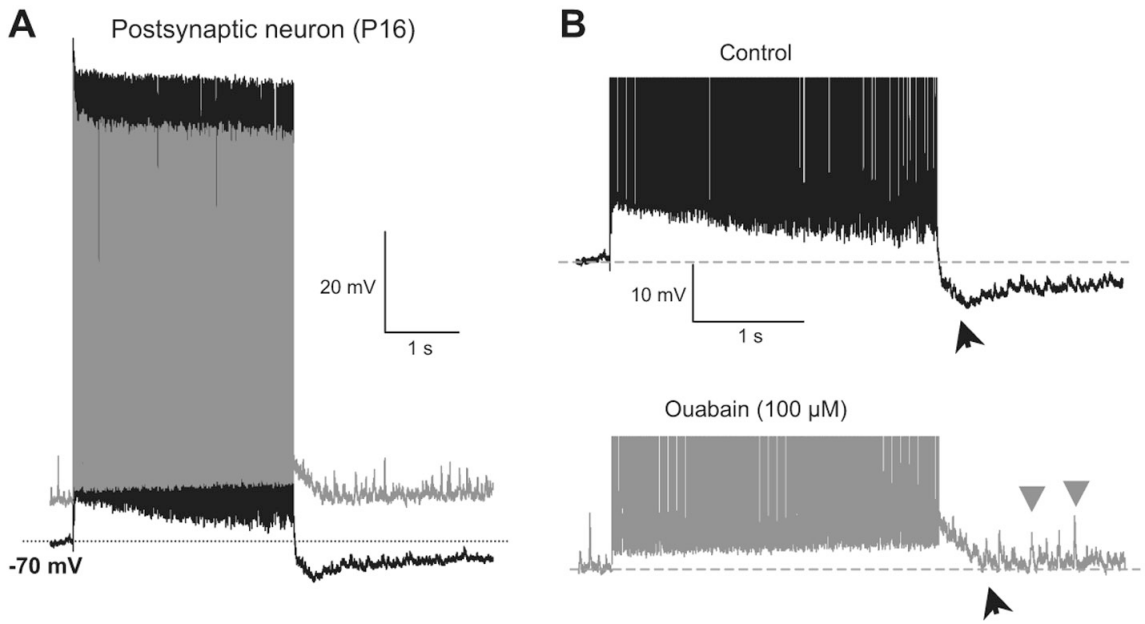
Part d) Ouabain blocks the Na-K ATPase completely. Suppose a membrane is in steady state at V_{rest} and a blocking concentration of oabain is applied as a step at time 0. How will the membrane potential change from V_{rest} (depolarize or hyperpolarize).

Part e) Write an equation for the membrane potential in the new steady state of zero-charge transfer after the ouabain is applied. Assume that the ion concentrations change very slowly after the ouabain is applied. There are a couple of possibilities here.

Part f) The potential of part e) will change steadily with time. Explain why and tell what the ultimate true steady state is.

Part g) The figure below shows the deviation from steady-state of a system like the one discussed above. In this case, a neuron's membrane potential is being recorded (black traces) and the plots show membrane potential versus time. Initially the resting potential is -70 mV, and the system is in steady state at this resting potential. A high frequency burst of spikes is induced by stimulation (100 Hz for 3 s duration). The spikes are plotted on a compressed time scale so that individual spikes cannot be resolved, but the solid black region shows this steady high-frequency spiking. Note that the baseline potential of the spikes, i.e. the minimum membrane potential during the maintained spiking) decreases steadily during the burst. Also, after the burst the resting potential is

hyperpolarized. The authors of this paper (Kim and von Gersdorff, *J. Neuroph*. 108:1924 2012) suspected that the Na-K pump was involved so they repeated the experiment in the same neuron after a blocking concentration of ouabain was applied. The result was the gray spike train record overlaid on the black record in A. The black (no ouabain) and gray (ouabain) records are shown separately in B to allow comparison. In B, the tops of the spikes have been cut off.



Explain what is happening in this experiment. In particular

1. Why is there a slow hyperpolarizing trend of the minimum spike voltage and a hyperpolarization after the spiking stops (black traces)?
2. What is the new (apparent) steady state after the spiking stops? Note that it is decaying slowly to the original resting potential (-70 mV), explain why.
3. Why is the resting potential depolarized with ouabain and why are none of the changes in 1) and 2) above seen with ouabain (gray traces)?
4. In fact there is a (slight) depolarization during the spike train in the gray traces. Explain why.