580.439/639 Midterm Exam

October 20, 2004

1.5 hours, do all problems, closed book except for a single sheet of paper.

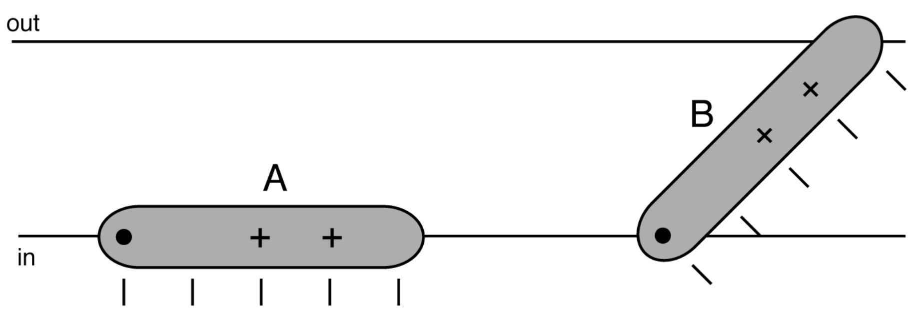
Problem 1

Part a) Sketch the structure of the KcsA channel, showing its relationship to the cell membrane. In particular, show the parts important for ion selectivity and gating.

Part b) Explain how toxin binding sites in potassium channels can be used to validate the structure of the KcsA channel.

Part c) How is ion permeation through Na or Ca channels different from that of K channels and what does this imply about the structure of the channel molecules?

Consider the model below for the gating paddle in the potassium channel. This is similar to the gating movement proposed by Jiang et al. (2003) based on their structural studies of the Kv potassium channel's S1-S4 segments. The S4 segment occupies two positions, similar to *A* and *B* below. Gating of one subunit of the potassium channel means transitions between the *A* and *B* states of the paddle.



Part d) Given the normal behavior of the voltage-gated potassium channel in voltage clamp experiments, which state (*A* or *B*) corresponds to the gate *open* and why.

Part e) What is the gating charge associated with a potassium channel whose subunits have paddles like that drawn above? Assume that the full membrane potential is developed between the horizontal lines marking the inside and outside boundaries of the membrane. The ticks next to the gating paddle are evenly spaced, the black dot is the center of rotation of the paddle which is at the inside boundary of the membrane, and the *B* state has the paddle at a 45˚ angle. The "+" signs correspond to single elementary charges on amino acid residues, arginines in the actual molecule. Express the answer in terms of q_E, the charge in coulombs of one elementary charge or one mole of charges. (NOTE: for simplicity, some liberties have been taken with the number of gating charges, actually 4, and the exact geometry of the S4 segment.)

Part f) Write an equation for the ratio $n_\infty(0)/n_\infty(-60)$, which is the steady-state ratio between the probabilities that a subunit gate is open at 0 mV and at –60 mV membrane potentials. A barrier diagram is needed here.

Problem 2

By passing a brief current pulse into the MLE (Morris-Lecar Equations) through I_{ext}, it is possible to change the membrane potential V without changing the potassium activation w. This corresponds to the biological experiment of injecting a current pulse into a cell, changing its membrane potential, without changing channel gating. The model (or cell) is then allowed to evolve according to the relevant differential equations. In this problem, you will draw arrows to show the effects of such a current injection in the phase plane, where the current injection is designed to start or stop a limit cycle. The phase planes are taken directly from Rinzel and Ermentrout's chapter.

In each of the examples on the next page, a phase plane is shown with isoclines, equilibrium points, stable (SPO) and unstable (UPO) limit cycles, etc. In each case show where, along the trajectories in the phase plane, a depolarizing voltage step could be applied to accomplish the goal stated at left. Your answer has three parts:

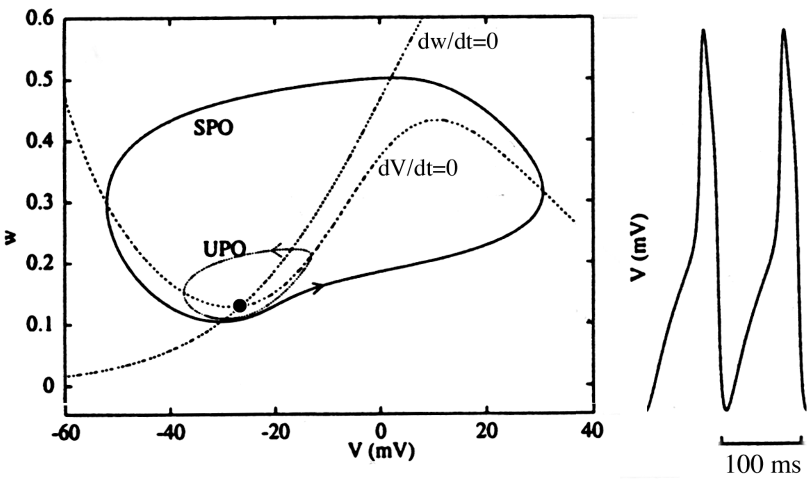
(1) Draw an arrow on the phase plane to show the trajectory corresponding to the voltage step. The arrow should show the (approximately) smallest voltage change possible. The arrow should start on the trajectory specified and end at a point that would accomplish the goal specified.

(2) Write a sentence describing what is necessary to achieve the goal (e.g. "cross the stable manifold").

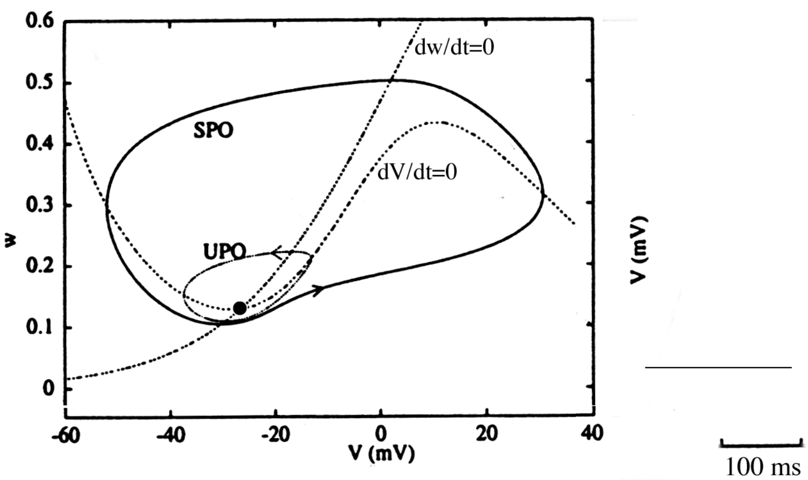
(3) On the voltage vs. time plots at right, show the trajectory that results from the voltage step. The voltage plots show a short segment of the voltage-time plot preceding the voltage step (e.g. a limit cycle or a constant voltage at the equilibrium point) and do not necessarily end at the time point at which the voltage step must be applied. Your plot should start somewhere along the voltage plot and should correspond to the arrow in the phase plane and the trajectory that will follow it.

Draw your answers to Problem 3 on this and the next page and hand them in as part of the test. Equilibrium points are identified as: S – stable; N – saddle node; U – unstable.

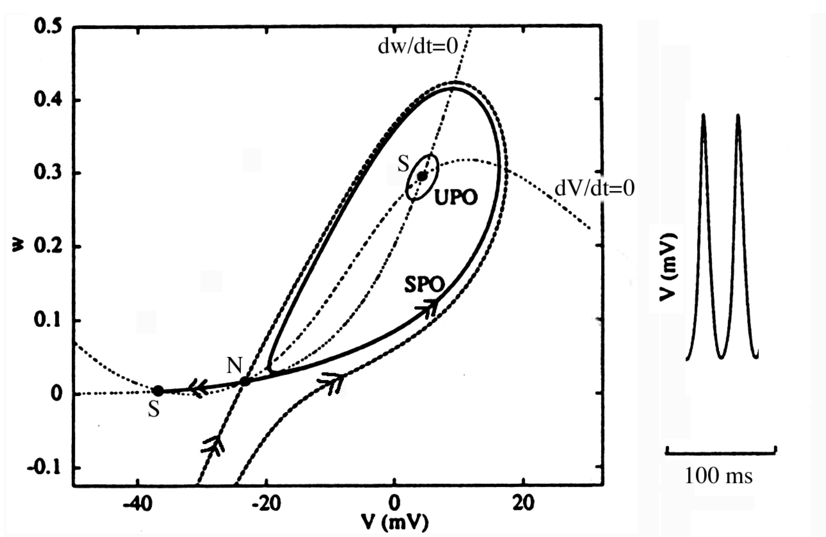
Part a) Stop the limit cycle, returning the system to its stable equilibrium point (black dot)



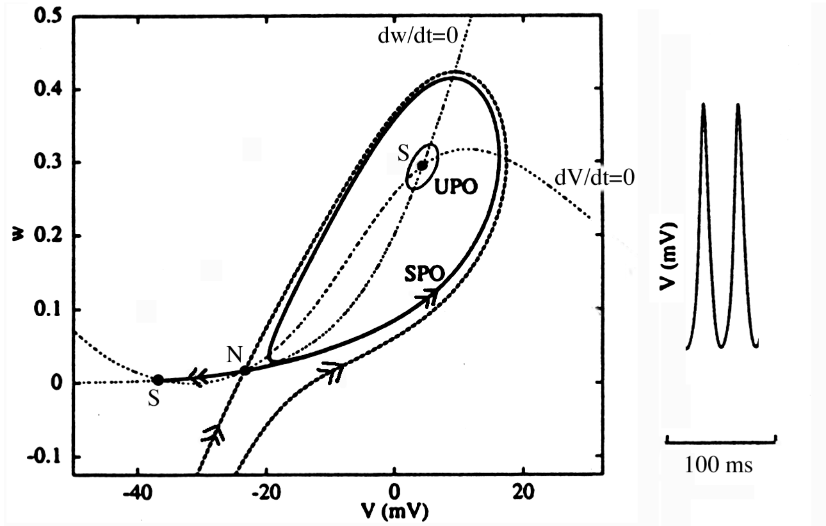
Part b) Initiate the limit cycle beginning with the system at its stable equilibrium point (black dot).



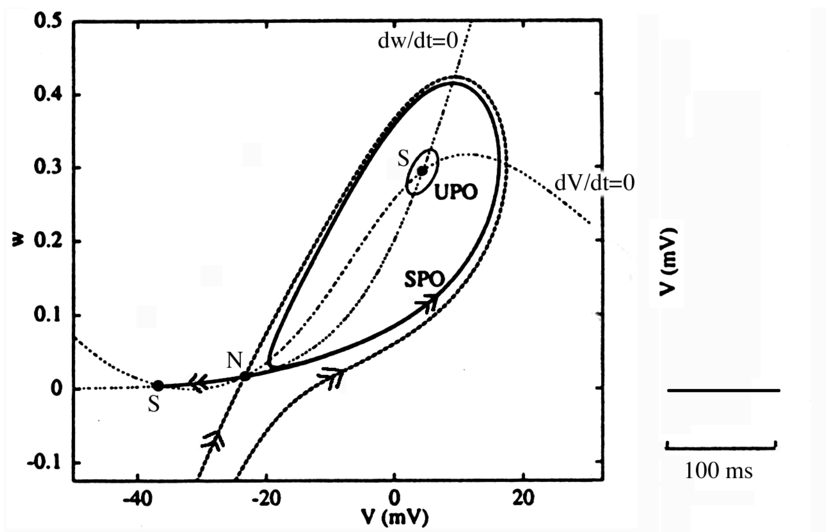
Part c) Stop the limit cycle (SPO) and transfer the system to the resting potential (S, near –35 mV).



Part d) Stop the limit cycle (SPO) and transfer the system to the upper equilibrium point (S, near +5 mV).



Part e) Beginning at the resting potential (S near –35 mV), transfer the system to the limit cycle.



Part f) Is it possible to transfer the system between the two stable equilibrium points with depolarizing voltage pulses? If so, show the arrows on the phase plane below. If not, tell why not. Consider both directions, from rest near –35 mV to S near +5 mV and vice-versa.