# 580.439/639 Midterm Exam, Solutions

## Problem 1

**Part a)** See the drawings in the course notes and Hille. The selectivity filter on the external side of the membrane and the gating structure on the cytoplasmic side should be in the drawing.

**Part b)** Toxin binding sites are predicted to be in various locations based on the structure of the molecule. Presuming that the structure of KcsA is similar to that of other potassium channels, which seems to be true, these sites should be similar in the voltage-gated potassium channels that have been studied with toxins. Toxin binding sites should be exposed to the external or cytoplasmic solutions, as found in experimental studies. In the case of KcsA, some binding sites were found inside the channel's pore, explaining why they were only available for binding with the channel open.

**Part c)** The single-file behavior of potassium channels (i.e. the necessity for 3-4 $K^+$ ions to move through the channel in single file) is not observed in Na and Ca channels. In the case of $Ca^{++}$ channels, the channel is occupied by a $Ca^{++}$ ion at all times to block permeation by other ions. Thus the selectivity filter in these channels will differ from that in the $K^+$ channel, for example by not being long and narrow and by having different occupancy properties.

**Part d)** $B$ is the gate-open state because gate opening experimentally occurs when the membrane is depolarized and depolarization (inside more positive) will favor state $B$.

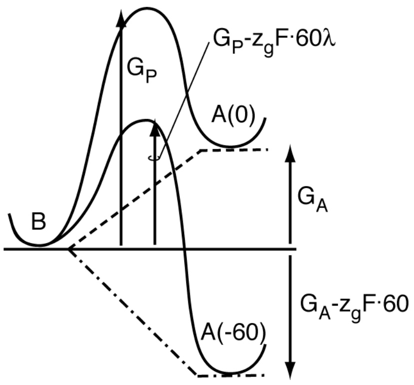
**Part e)** One charge translates half the way through the membrane and the second translates 3/4 of the way. Thus the gating charge movement associated with one paddle is $1.25q_E$. The charge movement for the channel is four times this or $5q_E$.

**Part f)** As in the model of the HH $n$ variable developed in a homework, the probability $B$ of being in the open state obeys the following equations:

$$\frac{dB}{dt} = k_1 A - k_{-1} B = k_1 (1 - B) - k_{-1} B$$

$$\frac{dB}{dt} = 0 \qquad \Rightarrow \qquad B = \frac{k_1}{k_1 + k_{-1}}$$

where $k_1$ and $k_{-1}$ are forward ($A$ to $B$) and reverse ($B$ to $A$) rate constants. The rate constants can be worked out in terms of a barrier model like the one at right. Consider first the $A$ and $B$ states. These states differ by an energy $G_A$ which is the difference in free energy of the molecule in the two configurations plus an energy due to electrical effects $z_g F \Delta V$ where $z_g$ is the gating charge from part e), computed as the equivalent charge that translates fully through the membrane.



At the barrier peak, there is an energy $G_P$ due to non-electrical effects plus $z_g F\Delta V\lambda$, i.e. a fraction $\lambda$ of the membrane potential. The details of the barrier height will not matter, because they will cancel. Substituting for the rate constants in the equation for $B$ above:

$$B(\Delta V)=\frac{k_1}{k_1+k_{-1}}=\frac{\alpha e^{-(G_P-G_A-z_gF\Delta V(1-\lambda))/RT}}{\alpha e^{-(G_P-G_A-z_gF\Delta V(1-\lambda))/RT}+\alpha e^{-(G_P+z_gF\Delta V\lambda)/RT}}=\frac{e^{(G_A+z_gF\Delta V)/RT}}{1+e^{(G_A+z_gF\Delta V)/RT}}$$

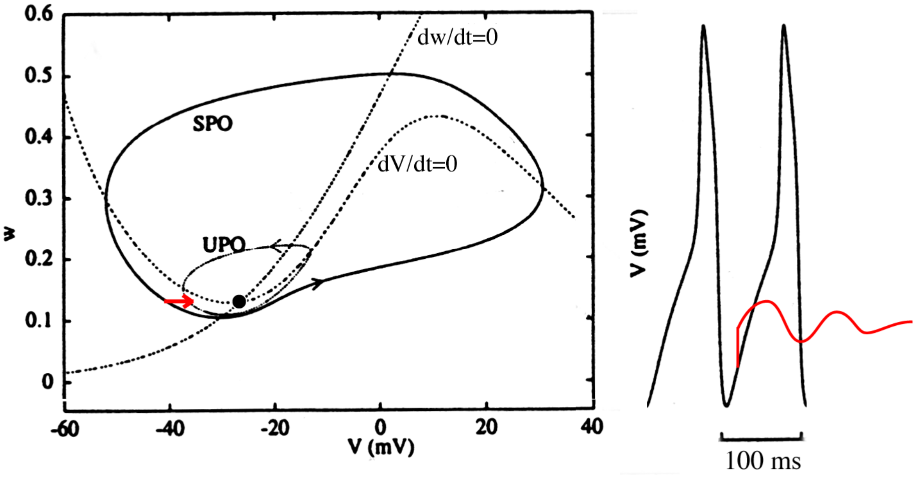
This result makes intuitive sense in that as $\Delta V \rightarrow \infty$ $B \rightarrow 1$ and as $\Delta V \rightarrow -\infty$ $B \rightarrow 0$, as expected from the effect of membrane potential on the charged part of the paddle. Now the ratio requested in the problem statement is

$$\frac{B(0)}{B(-60)}=\frac{\dfrac{e^{G_A/RT}}{1+e^{G_A/RT}}}{\dfrac{e^{(G_A-z_gF60)/RT}}{1+e^{(G_A-z_gF60)/RT}}}=\frac{1+e^{(G_A-z_gF60)/RT}}{1+e^{G_A/RT}}e^{z_gF60/RT}$$

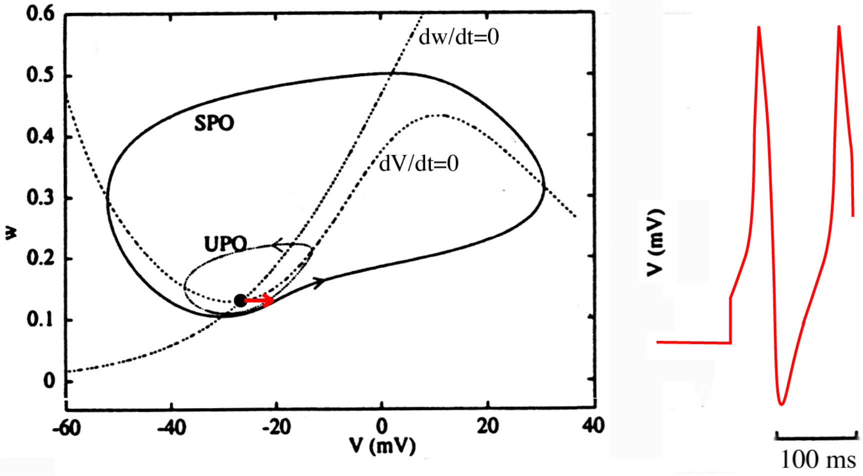
This is not the intuitively expected result, that the difference should depend only on $\exp(z_gF\Delta V/RT)$.

**Problem 2**

More details on these manipulations can be found in the Rinzel and Ermentrout chapter. Answers are shown as red lines below.

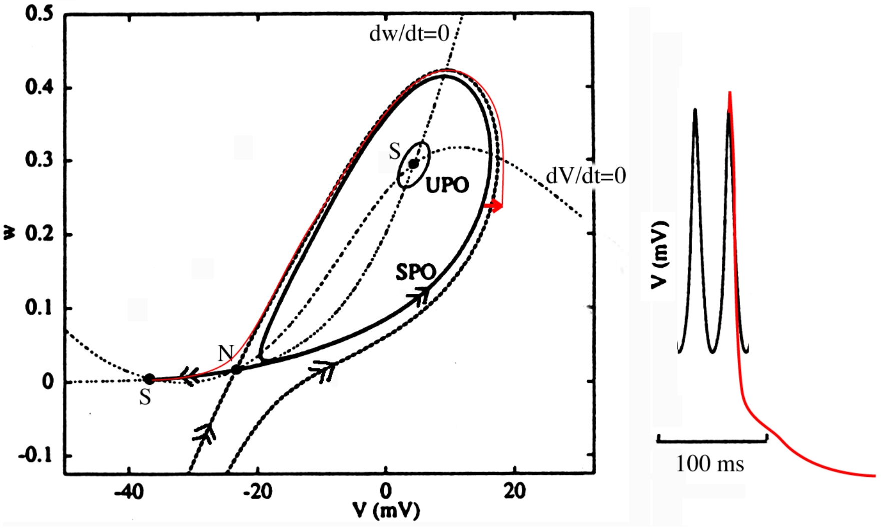


**Part a)** The depolarizing pulse should be applied as shown to move the trajectory across the UPO, which serves to separate the stable equilibrium point from the limit cycle. The ringing is caused by the fact that the equilibrium point is a stable spiral in this case. (The ringing is not a necessary part of the answer since you had no way of knowing about it.)

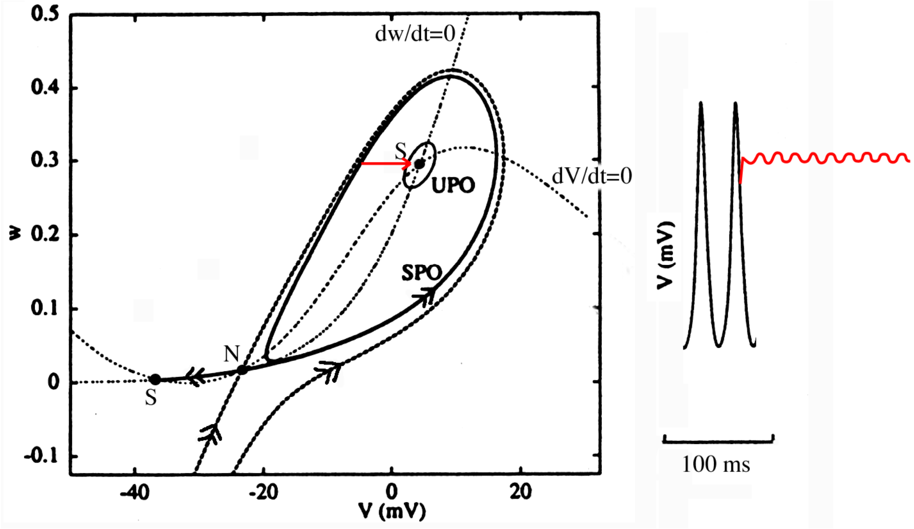


**Part b)** In this case, the voltage trajectory must carry across the UPO into the region of the limit cycle.

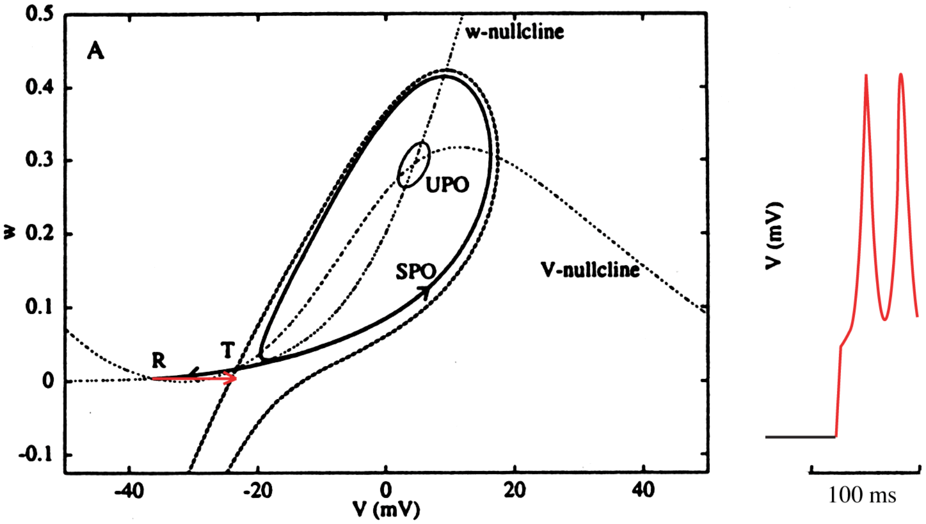
**Part c)** The voltage step can be placed at many points along the right side of the limit cycle. Its goal is to move the trajectory across the stable manifold of the saddle node, which moves the trajectory into the region of attraction of the resting potential. One such trajectory is shown in the phase plane at right along with the accompanying voltage waveform. Notice that only a very small voltage displacement is necessary (arrow in the phase plane).



**Part d)** This case is essentially the same as part a), where the voltage step is applied so as to transfer the trajectory across the UPO into the vicinity of the high-voltage equilibrium point. Again, the equilibrium point is a spiral, so the trajectory oscillates after the transfer.



**Part e)** In this case, the goal is to move the trajectory across the stable manifold of the saddle node.



**Part f)** A depolarizing pulse can only make transfers like that shown in part e) above. At small currents (smaller than used in part e), the trajectory will return to rest; larger currents, like the one in e), put the trajectory into the limit cycle (SPO); larger current pulses that transfer the trajectory across both stable manifolds produce an action potential followed by a return of the trajectory to rest. So, it is not possible to transfer from the resting potential directly to the upper equilibrium point with a single depolarizing pulse.

From the upper equilibrium point, a depolarizing pulse which moves the trajectory across the UPO, the SPO, and the stable manifold (to a point similar to the endpoint of the arrow in part c) would produce an action potential followed by a return to the rest potential. Thus a transfer to the upper equilibrium point to the resting potential is possible with a single pulse.