580.439/639 Midterm Solutions, 2000

Problem 1

Part a) The net flux J_i is the difference of two unidirectional fluxes:

$$J_i = k_{i-1}C_{i-1} - k_{-i}C_i$$

Part b) In steady state, $dC_i/dt = 0$ for all i. From the flux equations

$$\begin{aligned}\frac{dC_i}{dt} &= k_{i-1}C_{i-1} - k_{-i}C_i - k_iC_i + k_{-(i+1)}C_{i+1} \\ &= \left[k_{i-1}C_{i-1} - k_{-i}C_i\right] - \left[k_iC_i - k_{-(i+1)}C_{i+1}\right] = J_i - J_{i+1}\end{aligned}$$

Thus, $dC_i/dt = 0$ iff $J_i = J_{i+1}$ and all the fluxes must be equal, as usual.

Part c) At equilibrium, the electrochemical potential is equal in all wells. The problem can be done this way, but it is easier to consider the condition under which the fluxes are zero.

$$J_i = 0 \quad \Rightarrow \quad k_{i-1}C_{i-1} = k_{-i}\,C_i$$

Plugging in for the rate constants:

$$k_{i-1} = (\text{const})\exp\left[-\frac{G_P + \frac{\Delta G}{2N} + \frac{zF\Delta V}{2N}}{RT}\right] \quad \text{and} \quad k_{-i} = (\text{const})\exp\left[-\frac{G_P - \frac{\Delta G}{2N} - \frac{zF\Delta V}{2N}}{RT}\right]$$

Combining the previous two equations:

$$\frac{C_{i-1}}{C_i} = \frac{k_{-i}}{k_{i-1}} = \exp\left[\frac{zF\Delta V}{NRT} + \frac{\Delta G}{NRT}\right]$$

Thus, at equilibrium the potential difference between adjacent wells is

$$\frac{\Delta V}{N} = -\frac{\Delta G}{NzF} + \frac{RT}{zF}\ln\frac{C_{i-1}}{C_i}$$

This equation is true for all i because of the assumption that the potential divides equally among the potential wells. Thus the concentration ratios C_{i-1}/C_i are the same for all subsequent pairs of wells. Adding the equations for C_0/C_1, C_1/C_2 . . . . and C_{N-1}/C_N gives the usual Nernst equation plus a term for the tilt of the energy system:

$$\Delta V = -\frac{\Delta G}{zF} + \frac{RT}{zF}\ln\left[\frac{C_0}{C_1}\frac{C_1}{C_2}\cdots\frac{C_{N-1}}{C_N}\right] = -\frac{\Delta G}{zF} + \frac{RT}{zF}\ln\frac{C_0}{C_N}$$

This equation is different from the Nernst equation because there is a net chemical potential difference ΔG across the whole system. Usually C_0 and C_N are at the same potential in the absence of an electrical potential difference. In this system, the electrical potential has to counteract the effect of ΔG at equilibrium.

Part d) The NP equation in differential and discrete-difference forms is as follows:

$$J = -uC\left[RT\frac{d\ln C}{dx} + zF\frac{dV}{dx}\right] = -u\left[RT\frac{dC}{dx} + zF\,C\frac{dV}{dx}\right]$$

$$\approx -u\left[RT\frac{C_i - C_{i-1}}{\lambda} + zF\,C\frac{V_i - V_{i-1}}{\lambda}\right]$$

$$= -u\left[RT\frac{C_i - C_{i-1}}{\lambda} + zF\,C\frac{\Delta V}{N\lambda}\right] \qquad (*)$$

Where use has been made of the fact that the potential difference between two wells V_i-V_{i-1} is $\Delta V/N$. The concentration term C multiplying the voltage differential is well-defined only in the limit of λ small. An approximation that is useful later is that $C \approx (C_{i-1}+C_i)/2$.

The flux equation can be written as follows:

$$J = k_{i-1}C_{i-1} - k_{-i}C_i$$

$$= (\text{const})\left[\exp\left(-\frac{G_P + \frac{\Delta G}{2N} + \frac{zF\Delta V}{2N}}{RT}\right)C_{i-1} - \exp\left(-\frac{G_P - \frac{\Delta G}{2N} - \frac{zF\Delta V}{2N}}{RT}\right)C_i\right]$$

$$= (\text{const})e^{-G_P/RT}\left[\exp\left(-\frac{\frac{\Delta G}{2N} + \frac{zF\Delta V}{2N}}{RT}\right)C_{i-1} - \exp\left(\frac{\frac{\Delta G}{2N} + \frac{zF\Delta V}{2N}}{RT}\right)C_i\right]$$

Assuming that N is sufficiently large that the exponents are small and using the approximation exp(ε)≈1+ε gives

$$J \approx (\text{const})e^{-G_P/RT}\left[\left(1 - \frac{\Delta G}{2NRT} - \frac{zF\Delta V}{2NRT}\right)C_{i-1} - \left(1 + \frac{\Delta G}{2NRT} + \frac{zF\Delta V}{2NRT}\right)C_i\right]$$

$$= \frac{(\text{const})e^{-G_P/RT}}{RT}\left[RT\left(C_{i-1} - C_i\right) - zF\frac{\Delta V}{N}\frac{C_{i-1}+C_i}{2} - \frac{\Delta G}{N}\frac{C_{i-1}+C_i}{2}\right] \qquad (**)$$

Eqns (*) and (**) have similar form if

$$u = \frac{\lambda\,(\text{const})\,e^{-G_P/RT}}{RT}$$

With this substitution, Eqn. (**) becomes

$$J = -u\left[RT\frac{(C_i - C_{i-1})}{\lambda} + zF\frac{\Delta V}{N\lambda}\frac{C_{i-1}+C_i}{2} + \frac{\Delta G}{N\lambda}\frac{C_{i-1}+C_i}{2}\right] \qquad (***)$$

The first two terms of Eqns. (*) and (***) have the same form, with the proviso that $C \approx (C_{i-1}+C_i)/2$. The third term in Eqn. (***) is not present in Eqn. (*).

Part e) Note that the form of the third term in Eqn. (***) is the same as the voltage differential, suggesting that the modified NP equation should be

$$J = -uC\left[RT\frac{d\ln C}{dx} + zF\frac{dV}{dx} + \frac{dG}{dx}\right] = -u\left[RT\frac{dC}{dx} + zF\,C\frac{dV}{dx} + C\frac{dG}{dx}\right]$$

G in this equation represents an additional potential energy term which varies with position in the permeation pathway. For the KcsA channel, *G* is the function shown in part A of the figure in the problem set. Recalculation of Eqn. (**) using this augmented NP equation verifies that the term gives the same behavior as the barrier model. Note that this same equation could be derived by beginning with a definition of electrochemical potential that includes an energy of interaction *G* with the channel, so that

$$\mu = \mu^0 + RT\ln C + zF\,V + G$$

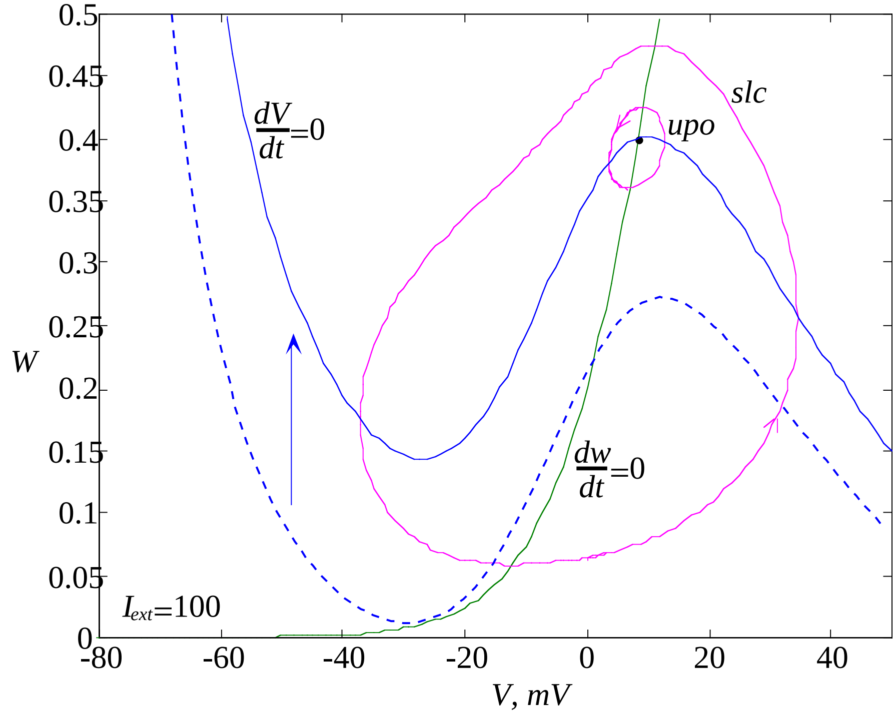
and then writing the NP equation as $J=-uC\,d\mu/dx$.

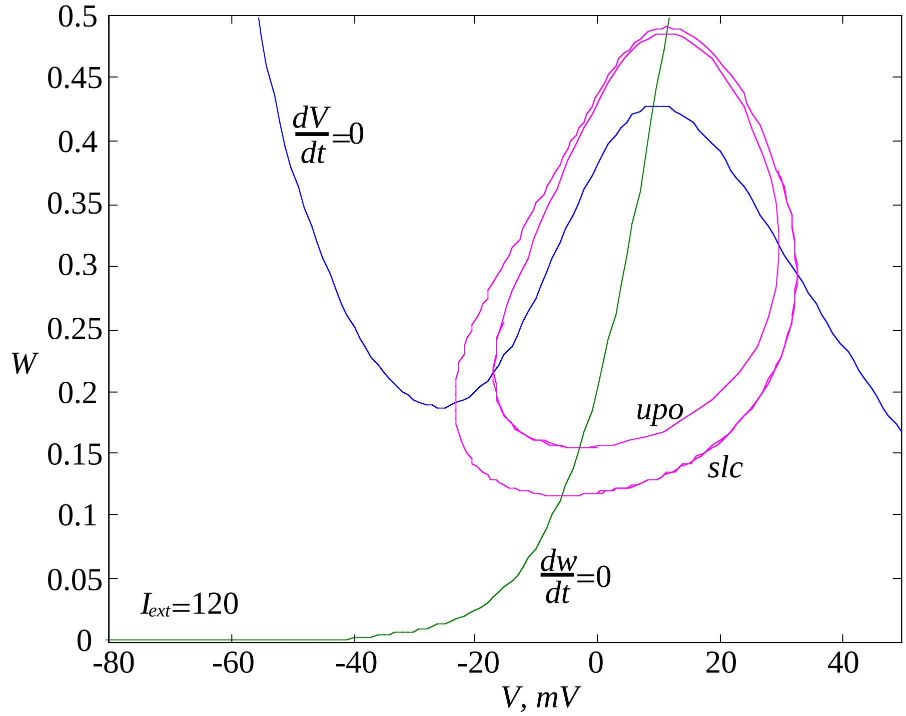
Problem 2

Part a) From the bifurcation diagram it is evident that at currents *A* and *B* there is a stable limit cycle, an unstable limit cycle, and a stable equilibrium point. The MLE isoclines do not change shape as external current is changed, but the *V* isocline moves vertically as current increases. The main difference between currents *A* and *B* should be a vertical movement of the *dV*/*dt* isocline and an increase in the size of the unstable limit cycle. Thus the phase planes should look something like those drawn below.

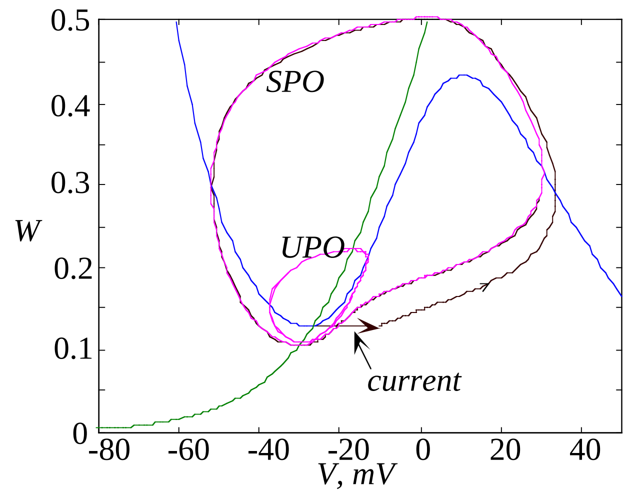
The first phase plane is for I_{ext}=100 μA/cm^2, which is approximately current *A*. The *dV*/*dt* isocline has moved vertically from its value at the saddle bifurcation (blue arrow). The two limit cycles are shown in magenta and labeled *upo* and *slc*. The stable equilibrium point is shown with the black dot. In this case, the *UPO* is small and located close to the equilibrium point.

The second phase plane below is for I_{ext}=120 μA/cm^2, corresponding to current *B*. The *dV*/*dt* isocline has moved vertically again, slightly. The main difference between *A* and *B* is that the unstable limit cycle (*upo*) has expanded. As the current is increased further, the *upo* and *slc* coalesce and the limit cycles disappear, as shown in the bifurcation diagram, just to the right of *B*.

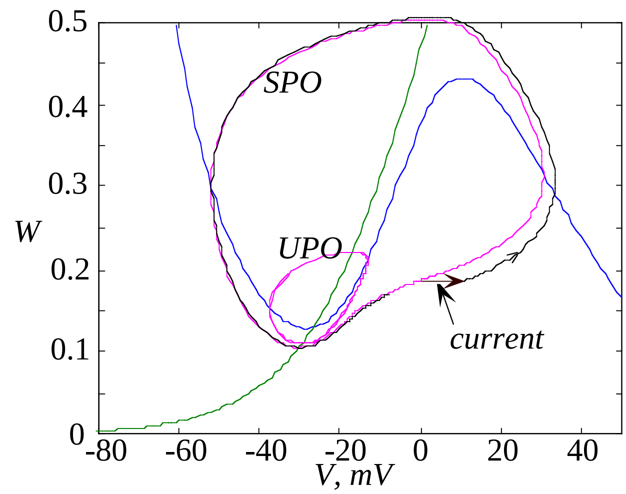




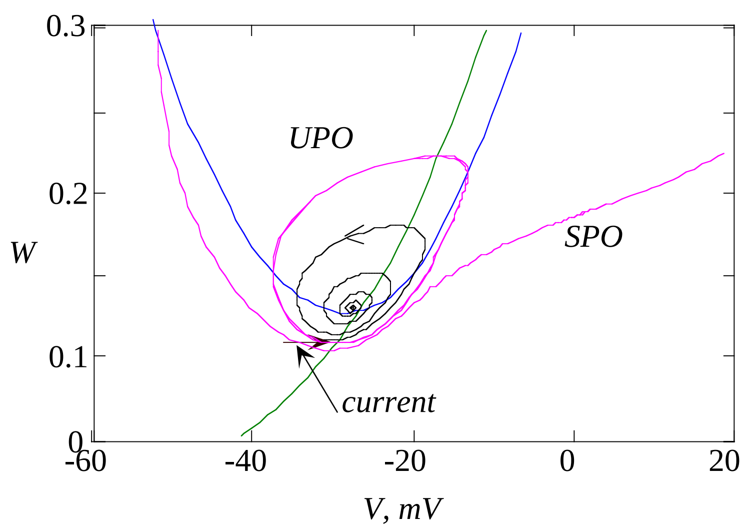
Part b) The effect of current pulses is to displace the membrane potential *V* by dumping charge on the membrane capacitance. Because the change in membrane potential is fast, no change in *w* occurs during the transition, so the effect of the current is to displace the state variables horizontally in the phase plane. The current amplitude, and therefore the amplitude of the voltage change, was not specified in the problem statement, but the qualitative nature of the result is not strongly dependent on the amplitude of the current shift, as long as the state variables are carried past the separatrixes in the phase plane.



Current 1 occurs with the system sitting at its equilibrium potential, and therefore at the one equilibrium point in the phase plane. The arrow at right shows the effect of the current in displacing the membrane potential to the right. There are two attractors in the phase plane, one inside the unstable limit cycle (*UPO)* at the equilibrium point and the other outside of *UPO*, which is the stable limit cycle (*SPO*). The current in this case carries the system out of the *UPO* so that it is captured by the *SPO*.



Current 2 has almost no effect on the limit cycle. From the membrane potential at the time current 2 is applied (near 0 mV on the upsweep of the action potential), the horizontal step can be understood to be like the one drawn at right. The displacement moves the system away from the limit cycle. However because the *SLC* is the attractor everywhere outside the *UPO*, the trajectory rapidly converges back to the *SLC*.



Current 3 stops the limit cycle. As drawn at right, in this case the trajectory is carried into the *UPO*, so that the system is captured by the stable equilibrium point. The eigenvalues at the equilibrium point are complex in this case, so the trajectory spirals around the equilibrium point as drawn.