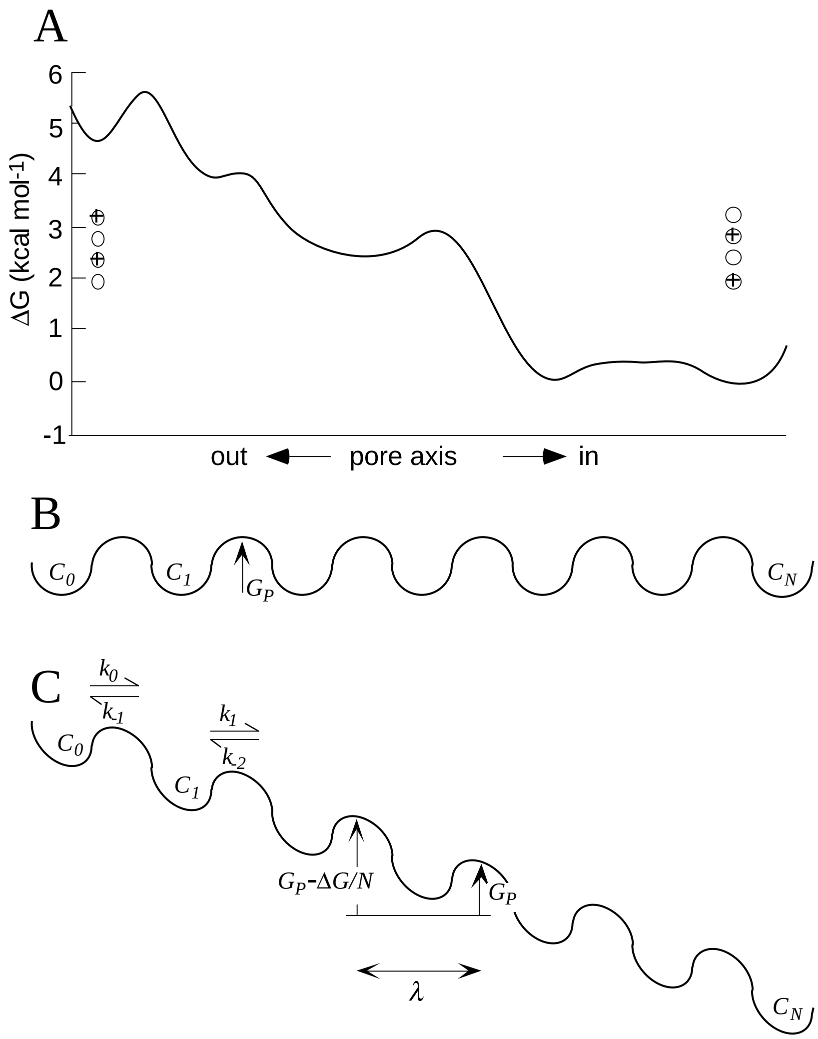
580.439/639 Midterm Exam, 2000

Answer all questions. Closed book except for 2 sheets of paper.

Problem 1



Part A of the figure at right shows the energy barriers computed for permeation through a part of the KcsA channel by Åqvist and Luzhkov (Nature 404: 881, 2000). Instead of a few large energy peaks as is assumed in barrier models, the system consists of many small barriers. This has led to the suggestion that a Nernst-Planck (NP) formulation would be a good model for permeation through such a channel. This problem considers the modifications necessary to adapt the NP equation to this purpose.

Part B of the figure shows a system consisting of a series of small, equally spaced barriers of height G_P. This system was shown in a homework problem to be approximately equivalent to the NP equation, as long as N, the number of barriers, is large and independence holds. The system in B differs from that in A in that there is no net change in the overall energy level, i.e. no tilt of the model. Part C shows the same system as in B except now each energy peak or well is an amount $\Delta G/N$ lower in energy than the previous peak or well, as indicated on the figure (note that ΔG is negative). As in B, the energy barriers are identical, except for the tilt. When a membrane potential ΔV is applied between the N^{th} well and the 0^{th} (i.e. $\Delta V = V_N - V_0$), the potential also divides equally among the barriers, so there is an electrical potential difference $\Delta V/N$ between subsequent peaks or wells. The rate constants k_i and concentrations C_i are defined as shown.

For all the following, use the energy barrier system in C.

pts **Part a)** Write an equation for the net flux J_i across the i^{th} barrier, i.e. between C_{i-1} and C_i. Express this in terms of rate constants and concentrations only. (easy)

pts **Part b)** Show that the system is in steady state if $J_i = J_{i+1}$ for all i. (also easy)

14 pts **Part c)** Write the condition for equilibrium between all energy wells. To do so, compute the potential difference ΔV for equilibrium in terms of C_0, C_N and the parameters of the barrier system. Also compute the concentrations in each energy well in terms of C_0 , C_N, ΔV, and any other parameters necessary. Explain why your result is not the same as the Nernst equation.

4 pts **Part d)** Write the NP equation in discrete-difference form, i.e. making the approximations

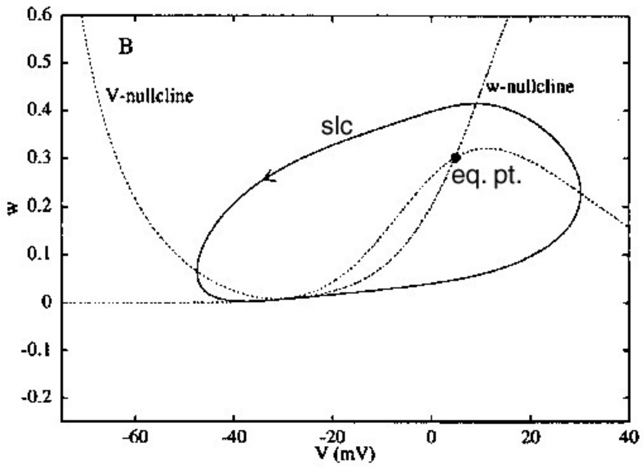
$$\frac{dC}{dx} \approx \frac{C_i - C_{i-1}}{\lambda} \quad \text{and} \quad \frac{dV}{dx} \approx \frac{V_i - V_{i-1}}{\lambda} = \frac{\Delta V}{N\lambda}$$

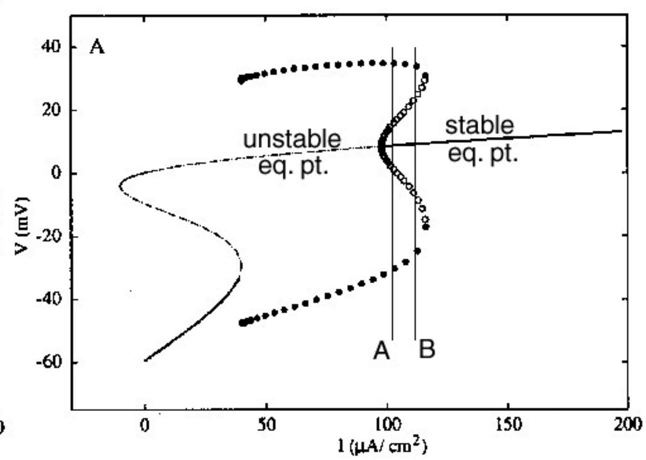
where λ is the distance between adjacent energy wells or peaks, as in the drawing above. Show that, for N large, the NP equation in this form is approximately the same as the flux equation derived in a) above EXCEPT FOR TERMS INVOLVING ΔG which are missing from the NP equation. To do this, it will be necessary to write the rate constants in terms of the barrier parameters and ΔV and to use the approximation $\exp(\varepsilon) \approx 1 + \varepsilon$ for $\varepsilon \ll 1$. What is the mobility in terms of the parameters of this barrier system?

pts **Part e)** Suggest a modified form of the NP equation which includes the effects of the tilt ΔG (hint: $\Delta G/zF$ behaves similarly to ΔV in the flux equation written above).

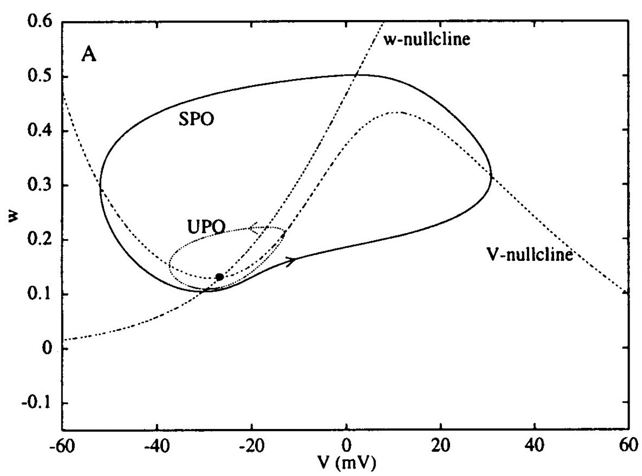
Problem 2 (the figures below are from Rinzel and Ermentrout, chapt. 7 in Koch and Segev, 1998)

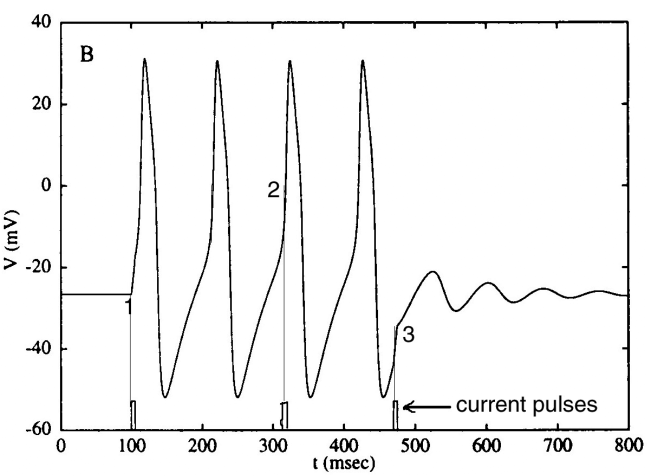
Part a) The figures below show the phase plane for the MLE with parameters that produce three equilibrium points, one stable, one saddle, and one unstable. The phase plane at left is drawn with applied current of 40.76 μ A/cm^2 which is just above the bifurcation point at which the saddle and stable equilibrium points disappear. There is a stable limit cycle (*slc*) and one (unstable) equilib-
20 pts rium point (*eq. pt.*) at this current. The bifurcation diagram for the system is shown at right, with the applied current as parameter. Sketch the phase planes at currents *A* and *B* indicated in the right plot. Show the important changes in the phase plane between I_{ext}=40.76 and currents *A* and *B*; i.e. show what happens to the isoclines, the equilibrium point, and the limit cycles (note that you won't be able to do this exactly, but you should be able to come close).

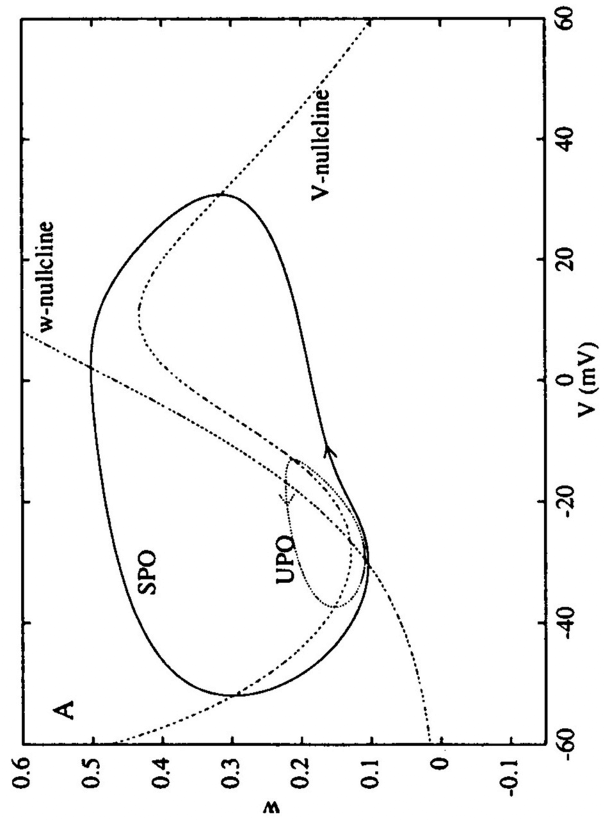


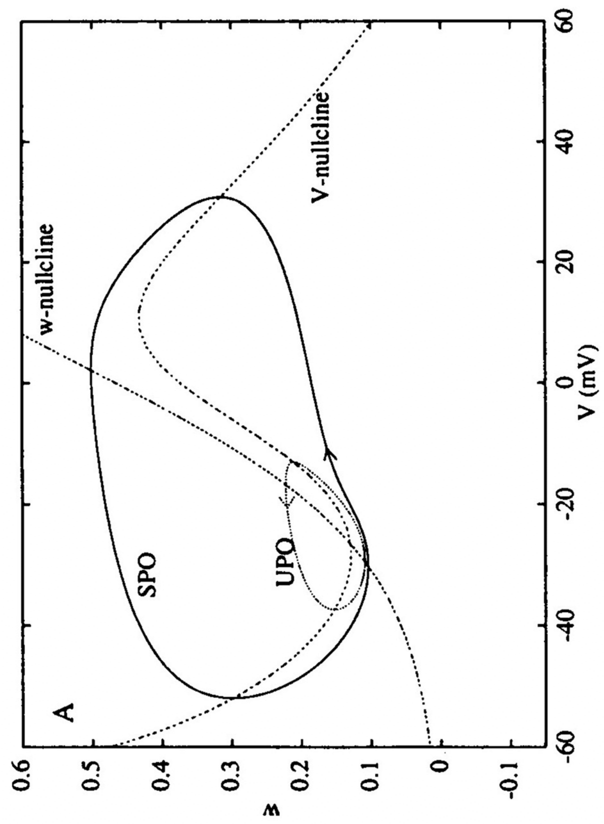


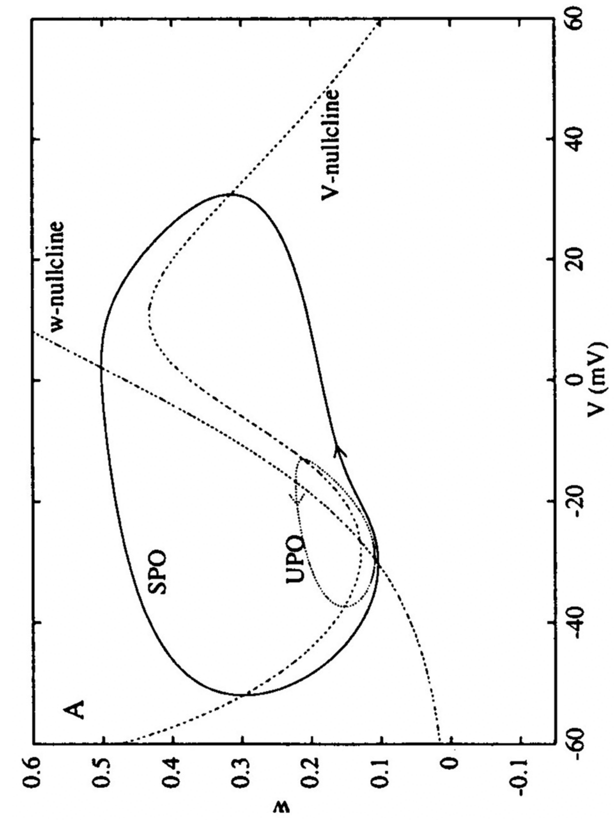
Part b) The figures below show the phase plane for the MLE with parameters that produce one equilibrium point which is stable for the current applied (90 μ A/cm^2). The equilibrium point co-exists with a stable limit cycle (SPO) from which it is separated by an unstable periodic orbit (UPO).
20 pts Consider the time plot at right. Three positive current pulses are applied to the system: the first, at 100 ms starts a train of action potentials; the second just after 300 ms has little or no effect; and the third at 470 ms stops the oscillation. Draw the trajectories for the responses to the three pulses on the phase plane (use the phase planes on the attached page). Label your trajectories with circled numbers corresponding to those on the figure at right below.






A
SPO
UPO
w-nullcline
V-nullcline
w
V (mV)


A
SPO
UPO
w-nullcline
V-nullcline
w
V (mV)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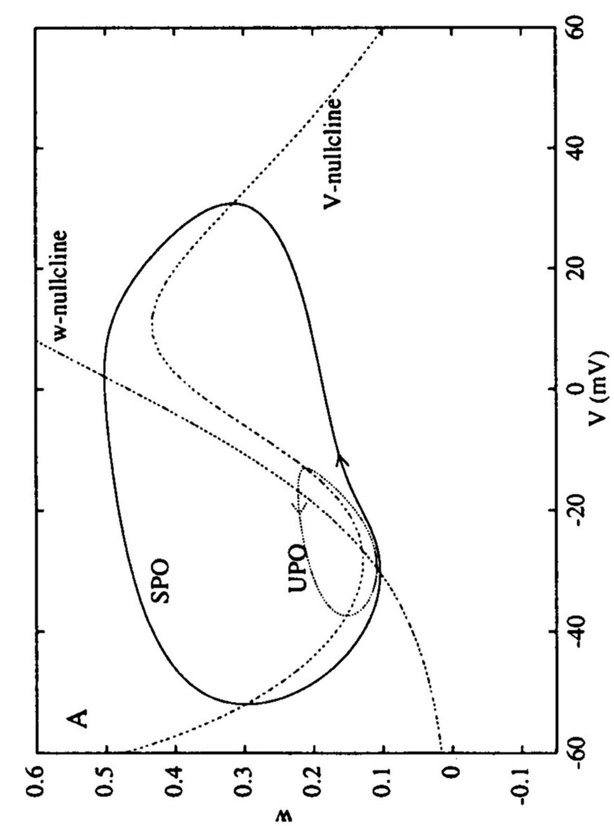
SPO
UPO
w-nullcline
V-nullcline
w
V (mV)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SPO
UPO
w-nullcline
V-nullcline
w
V (mV)