580.439/639 Midterm solutions

Problem 1

Part a) No net transport of ions implies that

$$I_K^a + I_K^p = 0 \qquad I_{Na}^a + I_{Na}^p = 0 \qquad I_{Cl}^p = 0,$$

where a means active transport and p is passive transport. There is no active transport of chloride, so passive transport of chloride must be zero, most likely chloride is at equilibrium.

In addition, because of the fixed flux ratio in the active transport and the fact that sodium and potassium are transported in opposite directions,

$$r \, I_K^a = -I_{Na}^a \qquad \Rightarrow \qquad r \, I_K^p = -I_{Na}^p . \tag{*}$$

Zero net charge transfer follows from the equations above and does not require another equation. Formally, it could be written

$$I_K^a + I_K^p + I_{Na}^a + I_{Na}^p + I_{Cl}^p = 0 .$$

Note that positive currents are outward charge movement as usual. Thus if the active transport current is positive (as for sodium) the passive current must be negative.

Part b) The following current-voltage equation was worked out from NP theory:

$$I_i = P_i \frac{C_{in} e^{z_i F \Delta V / RT} - C_{out}}{F(\Delta V)}, \tag{**}$$

where the function $F(\Delta V)$ is a function of membrane potential and perhaps other factors that vary with the assumptions. For the constant field assumption, $F(\Delta V) = d \left(e^{z_i F \Delta V / RT} - 1 \right) / \left(z_i F \Delta V / RT \right)$, where d is the thickness of the membrane.

Substituting the current-voltage equation (**) into Eqn. (*) gives

$$rP_K \frac{K_{in} e^{F \Delta V / RT} - K_{out}}{F(\Delta V)} + P_{Na} \frac{Na_{in} e^{F \Delta V / RT} - Na_{out}}{F(\Delta V)} = 0 .$$

Assuming that $F(\Delta V) \neq 0$, this can be solved to give the GHK equation without its chloride terms:

$$\Delta V = \frac{RT}{F} \ln \frac{rP_K K_{out} + P_{Na} Na_{out}}{rP_K K_{in} + P_{Na} Na_{in}} . \tag{***}$$

It is not necessary to make the constant-field assumption here, because Cl⁻ doesn't enter into the steady-state assumption and because of the assumption that $F(\Delta V) \neq 0$, justified on the grounds that this term is non-zero for cases where it can be evaluated.

Part c) The concentrations need to be low enough that the saturation terms in the denominator of the current-voltage equation can be ignored. Then the equation takes the form of Eqn. (**) and we must assume that $F_K(\Delta V) = A F_{Na}(\Delta V)$ for some constant A. This is true for the constant field assumption, and is sometimes true for the barrier model considered in class, as considered in a homework problem.

Part d) Immediately after ouabain, the steady state of zero charge transfer requires that

$$I_K^p + I_{Na}^p + I_{Cl}^p = 0 \,.$$

Because $F(\Delta V)$ is not the same for Cl⁻ as for Na⁺ and K⁺, it is necessary to use the constant field assumption. Substituting the appropriate current-voltage equations in the steady-state equation above gives the usual GHK equation:

$$\Delta V = \frac{RT}{F} \ln \frac{P_K K_{out} + P_{Na} Na_{out} + P_{Cl} Cl_{in}}{P_K K_{in} + P_{Na} Na_{in} + P_{Cl} Cl_{out}} \,. \qquad (****)$$

Note that if the pump is turned off instantaneously, chloride will be out of equilibrium because the new resting potential will be different from the value derived in part b), unless $r=1$ which is not true for Na-K-ATPase. Thus chloride must be included in the steady state equation as above.

Part e) There are several ways to get this answer:

1) Notice that the pump transfers net charge in the outward direction (3 Na out for 2 K in), so killing the pump should depolarize the cell.

2) Comparing Eqns. (***) and (****) can in principle be used to compute the change in resting potential; however, this requires knowing some parameters that were not given.

3) The currents in the vicinity of the equilibrium point with the pump turned on are sketched at right; these are linear approximations valid near the equilibrium point. By differentiating the current-voltage equations above one can show that the slopes of I_K^0, I_{NA}^p, and I_{Cl}^p are all positive as drawn. Furthermore, $I_{Cl}^p=0$ at the equilibrium point. The gray line shows the presumed I-V relationship for the pump, which is irrelevant to this answer, except that the current must be positive at the equilibrium point to make the overall sum of currents zero. Thus, when the pump current disappears, the sum of the other three
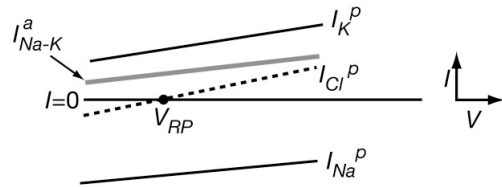
currents will be negative at the equilibrium point, depolarizing the cell. Moreover, given the positive slopes of the I-V relationships, a new equilibrium point will appear at a potential positive to the old one.

Problem 2

Part a) Voltage-gated channels have, usually, 4 subunits each of which contains a gate. Thus if the gating variable m is the probability of one subunit having an open gate, then n^4 is the probability of all 4 being open, assuming independence.

Part b) The currents through the two versions of the leakage channel are as follows:

$$I_{L1} = G_L(V - E_L) \quad \text{and} \quad I_{L2} = G_{Na}(V - E_{Na}) + G_K(V - E_K).$$

If the models are equivalent, then for all V, the currents should be equal

$$I_{L1} = G_L(V - E_L) = I_{L2} = G_{Na}(V - E_{Na}) + G_K(V - E_K)$$

Setting $V=E_{Na}$ and $V=E_K$ gives

$$G_L(E_{Na} - E_L) = G_K(E_{Na} - E_K) \quad \text{and} \quad G_L(E_K - E_L) = G_{Na}(E_K - E_{Na}),$$

so that

$$G_K = \frac{G_L(E_{Na} - E_L)}{(E_{Na} - E_K)} \quad \text{and} \quad G_{Na} = \frac{G_L(E_K - E_L)}{(E_K - E_{Na})}.$$

This could also be done by making the two models Thevenin equivalents.

Part c) Two bifurcations:

1) Hopf – real parts of a complex conjugate pair of eigenvalues change sign with a non-zero imaginary part.

2) Saddle node – A stable node (real negative eigenvalue) meets a saddle node at a point where nullclines are tangent (in a 2nd order system). The eigenvalues disappear.

Part d) There are two mechanisms: 1) During the action potential, voltage dependent potassium conductances increase in response to the depolarization. Because their time constants are long, the increased G_K outlasts the action potential, hyperpolarizing the membrane. 2) Calcium-dependent potassium conductances increase in response to elevated intracellular calcium due to voltage-gated calcium channels that open during the action potential.

Part e) The membrane potential differential equation for this cell is

$$C\frac{dV}{dt} = -\bar{G}_{Nap}m(V - E_{Na}) - \bar{G}_K m(V - E_K) + \text{ other terms } .$$

Isolating just the two terms of interest, their contribution to the membrane potential derivative is

$$C\frac{dV}{dt} = -m\left[(\bar{G}_{Nap} + \bar{G}_K)V - (\bar{G}_{Nap}E_{Na} + \bar{G}_K E_K)\right]$$

$$= -\left(\bar{G}_{Nap} + \bar{G}_K\right)m\left[V - \frac{\bar{G}_{Nap}E_{Na} + \bar{G}_K E_K}{\bar{G}_{Nap} + \bar{G}_K}\right] \qquad (*****)$$

That is, giving two channels the same gating variable makes them one channel with a conductance equal to the sum of their conductances and a reversal potential V_0 where

$$V_0 = \frac{\bar{G}_{Nap}E_{Na} + \bar{G}_K E_K}{\bar{G}_{Nap} + \bar{G}_K}.$$

The effect of the two channels is thus depolarizing at potentials less than V_0 and hyperpolarizing at more positive potentials.

Problem 3

Part a) The eigenvalue equation for **J** is

$$\det[\mathbf{J} - \lambda\mathbf{I}] = \det\begin{bmatrix} a - \lambda & b \\ c & d - \lambda \end{bmatrix} = 0$$

$$\lambda^2 - (a + d)\lambda + (ad - bc) = 0 \qquad .$$

$$\lambda^2 - \text{trace}[\mathbf{J}]\lambda + \det[\mathbf{J}] = 0$$

The eigenvalues are given by the quadratic formula:

$$\lambda = \frac{\text{trace} \pm \sqrt{(\text{trace})^2 - 4\det}}{2}.$$

Now working through the usual possibilities:

trace < 0		negative real part
trace^2-4 det > 0		real radical
det > 0	stable node	both λs negative
det < 0	saddle	one negative, one positive
trace^2-4 det < 0	stable spiral	negative radical
trace > 0		positive real part
trace^2-4 det > 0		real radical
det > 0	unstable node	both λs positive
det < 0	saddle	one negative, one positive
trace^2-4 det < 0	unstable spiral	negative radical

Plotted in the two dimensional display mentioned in the problem set (see Fig. 4.15 in E.M. Izhikevich *Dynamical systems in Neuroscience* MIT Press, 2007)
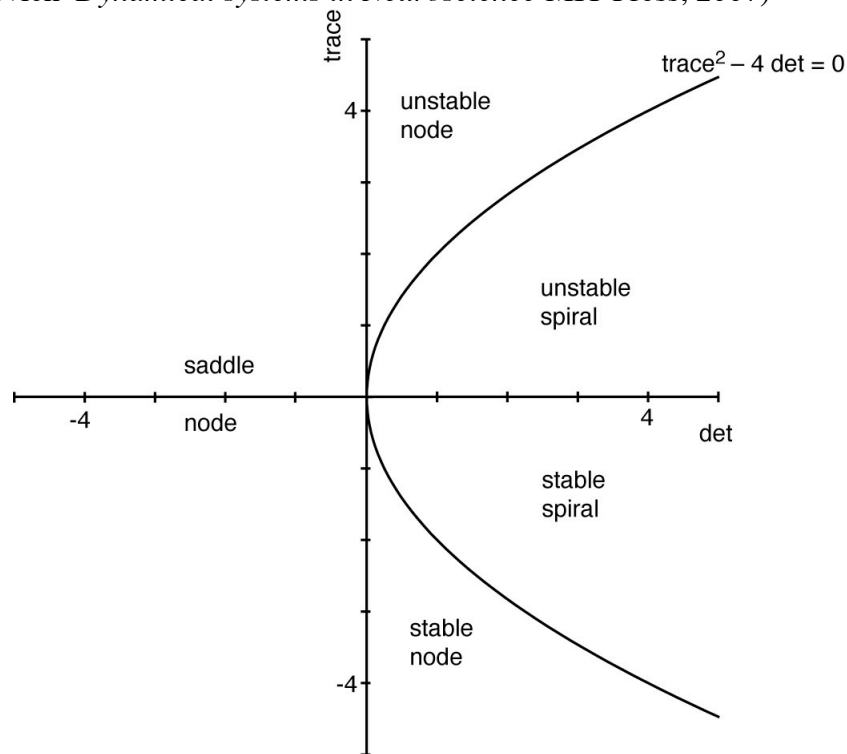
Part b) A Hopf bifurcation occurs when a stable spiral becomes unstable. This boundary is where *trace* = 0 in the plot above. This can also be seen from the quadratic formula above, where a zero real part of the eigenvalues requires that *trace*=0. There is no Hopf bifurcation on the negative abscissa of the plot because the eigenvalues are real for *det* < 0.

A saddle node bifurcation occurs when one eigenvalue of a real pair of eigenvalues is zero. From both the graph and the quadratic formula, it is evident that this occurs when *det*=0, i.e. on the ordinate of the plot above.