580.439 Midterm Exam Solutions, 1998

Problem 1

Part a) The desired equations are solutions to:

$$I_K = G_K(V - E_K) \qquad \text{where} \qquad G_K = \overline{G}_K\, n^4$$
$$\text{and} \tag{1}$$
$$\frac{\mathrm{dn}}{\mathrm{dt}} = \frac{n_\infty(V_1) - n}{\tau_n(V_1)} \qquad \text{with} \qquad n(0) = n_\infty(V_0)$$

V_0 is the membrane potential before the voltage clamp, V_1 is the potential during the clamp, and the clamp occurs at time 0. The solution to the differential equation is:

$$n(t) = n_\infty(V_0)\, e^{-t/\tau_n(V_1)} + n_\infty(V_1)(1 - e^{-t/\tau_n(V_1)})$$

With the assumption that $n(0^-)=n_\infty(V_R)$ and that $n(t_1^-)=n_\infty(V_1)$, the solution becomes

$$n(t) = \begin{cases} n_\infty(V_R) & t < 0 \\ n_\infty(V_R)\, e^{-t/\tau_n(V_1)} + n_\infty(V_1)(1 - e^{-t/\tau_n(V_1)}) & t \in [0, t_1) \\ n_\infty(V_1)\, e^{-(t-t_1)/\tau_n(V_R)} + n_\infty(V_R)(1 - e^{-(t-t_1)/\tau_n(V_R)}) & t \geq t_1 \end{cases} \tag{2}$$

The potassium current can be computed from Eqns. 1 and 2 together.

Part b) At time t_1, $n=n_\infty(V_1)$. Thus the potassium current is

$$I_K = \overline{G}_K\, n_\infty^4(V_1)\,(V - E_K) \tag{3}$$

Because n does not change instantaneously, its value is the same immediately before t_1 as it is immediately after. Thus all terms in Eqn. 3 are constants except V and the step in V produces an equivalent step in I_K.

Part c) The appropriate equations are

$$\frac{dO}{dt} = \alpha C_3 - 4\beta O \qquad Q = C_3 + O \qquad \text{and} \qquad C_3(0) = 0,\;\; O(0) = Q$$

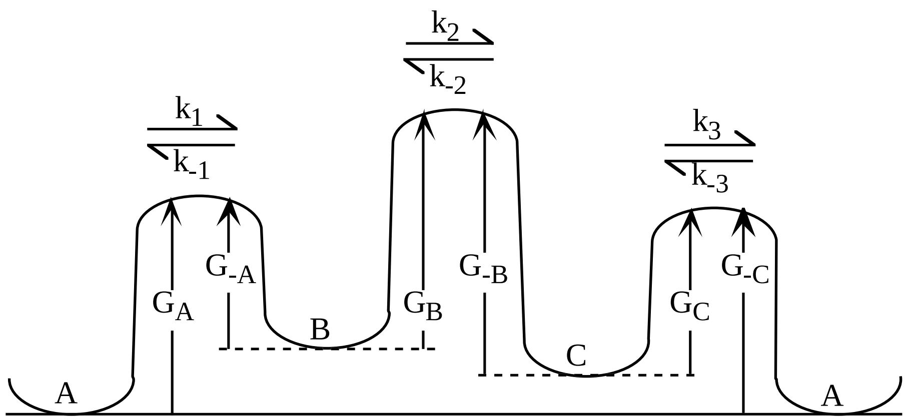
The solution is

$$O(t) = Q\frac{\alpha}{\alpha + 4\beta} + Q\frac{4\beta}{\alpha + 4\beta}\, e^{-(\alpha+4\beta)(t-t_1)} \tag{4}$$

Equation 4 describes the fraction of channels open. The same quantity in Eqn. 2 $n^4(t)$ for $t>t_1$. Inspection of the two equations shows that they quite different in form. In addition to the effects of the fourth power on Eqn. 4, the time constant τ_v is $1/(\alpha+\beta)$ and the n_∞ values is $\alpha/(\alpha+\beta)$. In Eqn. 4, the corresponding values are quite different.

Problem 2

Part a) The barrier system is shown below.



Two *A* states are shown, to account for the fact that the energy diagram is cyclical, like the reaction system; of course, they are the same state and have the same energy level. Writing out the rate constants in terms of barrier energies:

$$
\begin{aligned}
k_1 k_2 k_3 &= (const) e^{-G_A/RT}\ e^{-G_B/RT}\ e^{-G_C/RT} \\
k_{-1} k_{-2} k_{-3} &= (const) e^{-G_{-A}/RT}\ e^{-G_{-B}/RT}\ e^{-G_{-C}/RT}
\end{aligned}
\qquad (5)
$$

taking the ratio $k_1k_2k_3 \,/\, k_{-1}k_{-2}k_{-3}$ gives

$$\frac{k_1 k_2 k_3}{k_{-1} k_{-2} k_{-3}} = e^{-[G_A - G_{-A} + G_B - G_{-B} + G_C - G_{-C}]/RT} \qquad (6)$$

The sum of barrier energies in the exponential of Eqn. 6 is zero, since it begins at the ground state energy of the *A* state and ends up at the same level. Thus, the cyclical nature of the energy diagram forces $k_1k_2k_3 \,/\, k_{-1}k_{-2}k_{-3}$ to be 1.

Part b) The fluxes are given by the three equations below. J_i is the flux leaving the i^{th} state.

$$
\begin{aligned}
J_A &= k_1 A - k_{-1} B \\
J_B &= k_2 B - k_{-2} C \\
J_C &= k_3 C - k_{-3} A
\end{aligned}
\qquad (7)
$$

If the fluxes are zero,

$$
\begin{aligned}
0 = k_1 A - k_{-1} B \quad &\Rightarrow \quad B = \frac{k_1}{k_{-1}} A \\
0 = k_2 B - k_{-2} C \quad &\Rightarrow \quad C = \frac{k_2}{k_{-2}} B \\
0 = k_3 C - k_{-3} A \quad &\Rightarrow \quad A = \frac{k_3}{k_{-3}} C
\end{aligned}
\tag{8}
$$

(Recall that it was discussed in lecture that the right-hand set of equations in Eqn. 8 are equivalent to the usual thermodynamic definition of equilibrium) Now, substituting the right-hand equations in Eqn. 8 into one another gives

$$
A = \frac{k_3}{k_{-3}} C = \frac{k_3}{k_{-3}} \frac{k_2}{k_{-2}} B = \frac{k_3}{k_{-3}} \frac{k_2}{k_{-2}} \frac{k_1}{k_{-1}} A \tag{10}
$$

Because A must equal A, it follows from Eqn. 9 that $k_1 k_2 k_3 / k_{-1} k_{-2} k_{-3} = 1$.

Part c) Using the definitions of fluxes in Eqn. 7, suppose that $J=J_A=J_B=J_C>0$. Recall that, in a steady state, the fluxes in a system like this one must all be equal in order that the concentrations be constant in time. Then, from Eqn. 7,

$$
\begin{aligned}
J = k_1 A - k_{-1} B > 0 \quad &\Rightarrow \quad A > \frac{k_{-1}}{k_1} B \\
J = k_2 B - k_{-2} C > 0 \quad &\Rightarrow \quad B > \frac{k_{-2}}{k_2} C \quad \Rightarrow \quad A > \frac{k_{-1}}{k_1} \frac{k_{-2}}{k_2} C \\
J = k_3 C - k_{-3} A > 0 \quad &\Rightarrow \quad C > \frac{k_{-3}}{k_3} A \quad \Rightarrow \quad A > \frac{k_{-1}}{k_1} \frac{k_{-2}}{k_2} \frac{k_{-3}}{k_3} A
\end{aligned}
\tag{11}
$$

The bottom rightmost equation implies that, in a steady state, $A>A$, which cannot be true, as long as A, B, and C are non-zero. Thus a steady state with non-zero net flux cannot exist in a system like this one.

Problem 3

Part a) The nullclines do not change, since $f_i(\vec{X}) = 0$ is the same as $-f_i(\vec{X}) = 0$.

Part b) The equilibrium points do not move since they are the intersections of the nullclines which do not change. The properties of the system near the equilibrium points do change, however, as described in part d) below.

Part c) All trajectories reverse direction, since the time derivatives of the state vectors change sign. However, the trajectories themselves do not change. That is, if a trajectory passes through a point $\vec{X}_0$, then using $\vec{X}_0$ as the initial value for the normal system gives one half of the trajectory and using $\vec{X}_0$ as the initial value for the time-reversed system gives the other half of the trajectory.

Part d) The Jacobian matrix of the time reversed system is just **–J**, i.e. the negative of the Jacobian of the normal system. This is so because $\partial(-f_i)/\partial X_j = -\partial f/\partial X_j$. Suppose that **J** is the matrix

$$\mathbf{J} = \begin{bmatrix} a & b \\ c & d \end{bmatrix} \tag{12}$$

then the eigenvalues are the roots of

$$(\lambda - a)(\lambda - d) - bc = 0 \quad \text{or} \quad \lambda^2 - (a+d)\lambda + ad - bc = 0 \tag{13}$$

For the time reversed system, the eigenvalues are the roots of

$$(\lambda + a)(\lambda + d) - bc = 0 \quad \text{or} \quad \lambda^2 + (a+d)\lambda + ad - bc = 0 \tag{14}$$

Writing out the roots of the two equations gives

$$\lambda = \begin{cases} \dfrac{(a+d) \pm \sqrt{(a+d)^2 - 4(ad-bc)}}{2} & \text{for the normal system} \\[2ex] \dfrac{-(a+d) \pm \sqrt{(a+d)^2 - 4(ad-bc)}}{2} & \text{for the time - reversed system} \end{cases} \tag{15}$$

Now, if the eigenvalues are complex, the term under the radical is the imaginary part of the eigenvalue and $\pm(a+d)$ is the real part. Thus the real part of a complex conjugate pair of eigenvalues changes sign and an unstable spiral becomes a stable spiral and vice-versa.

Suppose that the eigenvalues are real. Rewriting Eqn. 15:

$$\lambda = \begin{cases} \dfrac{(a+d)}{2}\left[1 \pm \sqrt{\dfrac{1}{4} - \dfrac{ad-bc}{(a+d)^2}}\right] & \text{for the normal system} \\[2ex] -\dfrac{(a+d)}{2}\left[1 \pm \sqrt{\dfrac{1}{4} - \dfrac{ad-bc}{(a+d)^2}}\right] & \text{for the time - reversed system} \end{cases} \tag{16}$$

That is, the sign of each eigenvalue reverses. Thus stable nodes become unstable, unstable nodes become stable, and saddle nodes remain saddles, but with a switch of the stable and unstable manifolds.