

580.432 Solutions to the Midterm

Problem 1

Part a) The charge Q on the membrane capacitance C is $Q=CV$, where $V=0.1$ volt. The capacitance is given by

$$C = 1 \mu\text{fd}/\text{cm}^2 \cdot 4\pi r^2 \text{ cm}^2 = 1 \mu\text{fd}/\text{cm}^2 \cdot 4\pi (10^{-3} \text{ cm})^2 = 12.6 \text{ pfd}$$

so the charge is 1.26 pCoul.

The charge can be converted to chemical units by dividing by $F = 9.648 \times 10^4$ Coul/mole, so the charge on the membrane capacitance is $13.0 \text{ aMole} = 1.30 \times 10^{-17}$ moles.

The total charge in the cell in chemical units is the total number of moles of K^+ and Cl^- in the cell:

$$\begin{aligned} Q_{\text{cell}} &= (\text{cell volume}) \times (\text{conc. of } \text{K}^+ + \text{conc. of } \text{Cl}^-) \\ &= \frac{4}{3}\pi(10^{-3} \text{ cm})^3 \times (2 \times 0.14 \text{ moles/liter} / 10^3 \text{ cm}^3/\text{liter}) = 1.173 \times 10^{-12} \text{ moles} \end{aligned}$$

So the result is that the fraction of the total charge in the cell that is needed to charge the membrane is $1.30 \times 10^{-17} / 1.173 \times 10^{-12} = 1.1 \times 10^{-5}$. The amount of charge needed to produce a 100 mV membrane potential is a negligible fraction of the total charge in the cell.

Part b) Potassium and chloride will both be at equilibrium when

$$V = E_{\text{K}} = \frac{RT}{F} \ln \frac{K_{\text{out}}}{K_{\text{in}}} = E_{\text{Cl}} = \frac{RT}{F} \ln \frac{Cl_{\text{in}}}{Cl_{\text{out}}}$$

Thus the condition for simultaneous equilibrium reduces to the so-called Donnan condition: $K_{\text{out}}Cl_{\text{out}}=K_{\text{in}} \cdot Cl_{\text{in}}$. With the electroneutrality conditions $K_{\text{in}}=Cl_{\text{in}}+N$, this gives us two equations in two unknowns (K_{in} and Cl_{in}). These are solved by using the Donnan condition to eliminate Cl_{in} from the electroneutrality equation:

$$K_{\text{in}} = \frac{K_{\text{out}}Cl_{\text{out}}}{K_{\text{in}}} + N$$

$$K_{\text{in}}^2 - NK_{\text{in}} - K_{\text{out}}Cl_{\text{out}} = 0$$

$$K_{\text{in}} = \frac{N \pm \sqrt{N^2 + 4K_{\text{out}}Cl_{\text{out}}}}{2} \quad \text{and} \quad Cl_{\text{in}} = \frac{-N \pm \sqrt{N^2 + 4K_{\text{out}}Cl_{\text{out}}}}{2}$$

Because $\sqrt{N^2 + 4K_{\text{out}}Cl_{\text{out}}} > N$, the \pm s in the equation above should be + in order that both K_{in} and Cl_{in} are positive.

Part c) An equilibrium means that potassium and chloride are in thermodynamic equilibrium across the membrane, i.e. that the molar free energies μ_K and μ_{Cl} are the same on both sides of the membrane. As a consequence of the equilibrium, there is no net potassium or chloride flux across the membrane. A steady state means, for this system, that concentrations and the membrane potential are steady in time; components may or may not be at equilibrium, but in general are not. In the model of part b), a steady state requires that K_{in} and Cl_{in} are constant in time. If they are not at equilibrium then active transport mechanisms must be added so that the passive flux through the membrane is exactly balanced by active fluxes, giving no net flux.

Problem 2

Part a) The flux across the two barriers is given by

$$\begin{aligned} J_{1 \rightarrow XS} &= k_1 S_1 X - k_{-1} XS \\ J_{XS \rightarrow 2} &= k_2 XS - k_{-2} S_2 X \end{aligned}$$

where X is the concentration of free (unblocked) channels and XS is the concentration of blocked channels. In steady state, $J = J_{1 \rightarrow XS} = J_{XS \rightarrow 2}$. Using this fact and the fact that the total amount of channel is fixed, so $Q = X + XS$, the flux equations can be rewritten and solved for XS as

$$\begin{aligned} k_1 S_1 X - k_{-1} XS &= J = k_2 XS - k_{-2} S_2 X \\ k_1 S_1 (Q - XS) - k_{-1} XS &= J = k_2 XS - k_{-2} S_2 (Q - XS) \\ XS &= Q \frac{k_1 S_1 + k_{-2} S_2}{k_{-1} + k_1 S_1 + k_2 + k_{-2} S_2} \end{aligned} \quad (1)$$

This is the usual saturating relationship.

Part b) Intuitively, models in which the barrier between the inside of the cell and the channel is high should be less sensitive to pH inside the cell than models with a low barrier there. Thus the likely answer is models B and E.

To verify this, consider the rate constants in Eqn. (1).

$$\begin{aligned} k_1 &= \alpha e^{-(h_1 + \lambda_1 v)} & k_{-1} &= \beta e^{-[h_1 - h^* + (\lambda_1 - \lambda^*)v]} \\ k_2 &= \beta e^{-[h_2 - h^* + (\lambda_2 - \lambda^*)v]} & k_{-2} &= \alpha e^{-(h_2 + \lambda_2 v)} \end{aligned}$$

where $h_i = G_i/RT$ and $v = F \cdot \Delta V/RT$ are the dimensionless energy factors and α and β are constants.

α and β differ because the dimensions of the second-order rate coefficients k_1 and k_{-2} are different than for the first-order rate coefficients k_{-1} and k_2 . This subtlety was ignored in the lecture on barrier models, but does not change any of the ultimate results. For models B and E in which $h_2 > h_1$, the rate constants for the second barrier will be small, i.e.

$$k_1 \gg k_{-2} \quad \text{and} \quad k_{-1} \gg k_2 \quad \text{because} \quad e^{-h_1} \gg e^{-h_2}$$

Thus, the following approximation can be written for Eqn. (1), as long as $S_1 \gg S_2$:

$$XS \approx Q \frac{k_1 S_1}{k_{-1} + k_1 S_1} = Q \frac{S_1}{\frac{k_{-1}}{k_1} + S_1} = Q \frac{S_1}{\frac{\beta}{\alpha} e^{h^* + \lambda^* v} + S_1} \quad (2)$$

That is, to the extent that $e^{-h_1} \gg e^{-h_2}$, the fraction of blocked channels depends only on the $[H^+]$ in the extracellular solution. Note that Eqn. (2) is the same as the equilibrium fraction of channels blocked, when H^+ ions are at equilibrium between the external solution and the channel site. The reason for this is that the flux across the second barrier is essentially zero, so that the steady state reduces to a zero flux equilibrium.

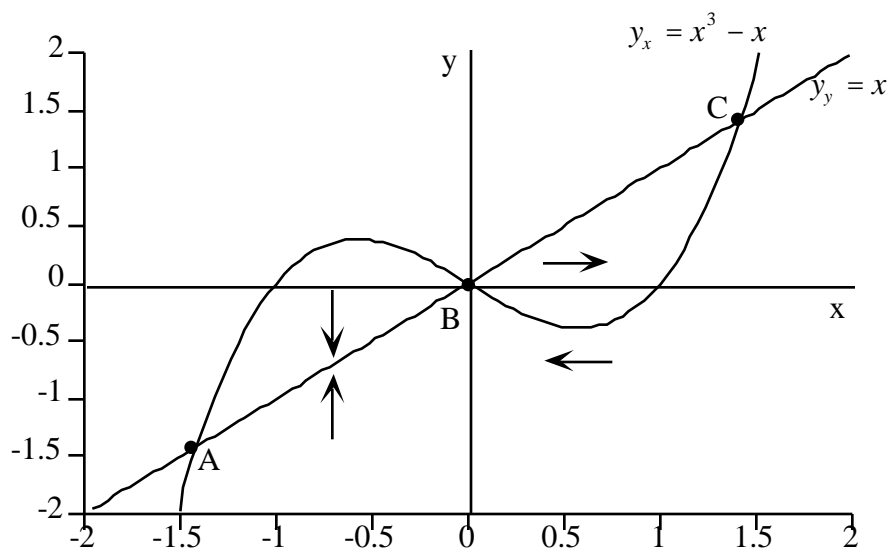
Part c) The difference between the vertical pairs of models is the extent to which block should be dependent on membrane potential. From Eqn. (2), the $[H^+]$ at which 50% of channels are blocked is $\beta e^{h^* + \lambda^* v} / \alpha$, which depends on membrane potential as $e^{\lambda^* v}$. Note that λ^* differs between the vertical pairs of models: λ^* is about 0.5 for models A, B, and C and is near 0 or 1 for models D, E, and F. For the particular case of models B and E, which are favored by the arguments of part b), model B should produce a strongly voltage-dependent block, i.e. the fraction of channels blocked should vary as $e^{0.5v}$ at fixed pH, whereas model E should be only weakly voltage dependent, since $\lambda^* \approx 0$ in model E.

Problem 3

The nullclines are given by the points where $\dot{x} = 0$ and $\dot{y} = 0$. For this system,

$$\begin{aligned} \dot{x} = 0 & \quad y_x(x) = x^3 - x \\ \dot{y} = 0 & \quad y_y(x) = x \end{aligned}$$

These are plotted at right in the phase plane. The arrows show the directions of flow above and below the nullclines. There are three equilibrium points, A at $(-\sqrt{2}, -\sqrt{2})$, B at $(0,0)$, and C at $(\sqrt{2}, \sqrt{2})$.



The Jacobian for this system is the matrix

$$\begin{matrix} \partial \dot{x} / \partial x & \partial \dot{x} / \partial y & -3x^2 + 1 & 1 \\ \partial \dot{y} / \partial x & \partial \dot{y} / \partial y & 1 & -1 \end{matrix} =$$

The Jacobians at the three equilibrium points and their eigenvalues are listed below. The eigenvalues were obtained in the usual way, by solving $\det[\lambda\mathbf{I} - \mathbf{A}] = 0$

$$\begin{array}{l} \text{at A :} \\ \begin{array}{cc} -5 & 1 \\ 1 & -1 \end{array} & \lambda = -3 + \sqrt{5} \text{ and } -3 - \sqrt{5} \\ \\ \text{at B:} \\ \begin{array}{cc} 1 & 1 \\ 1 & 1 \end{array} & \lambda = \sqrt{2} \text{ and } -\sqrt{2} \\ \\ \text{at C:} \\ \begin{array}{cc} -5 & 1 \\ 1 & -1 \end{array} & \lambda = -3 + \sqrt{5} \text{ and } -3 - \sqrt{5} \end{array}$$

Based on the eigenvalues, A and C are stable equilibrium points and B is a saddle node.

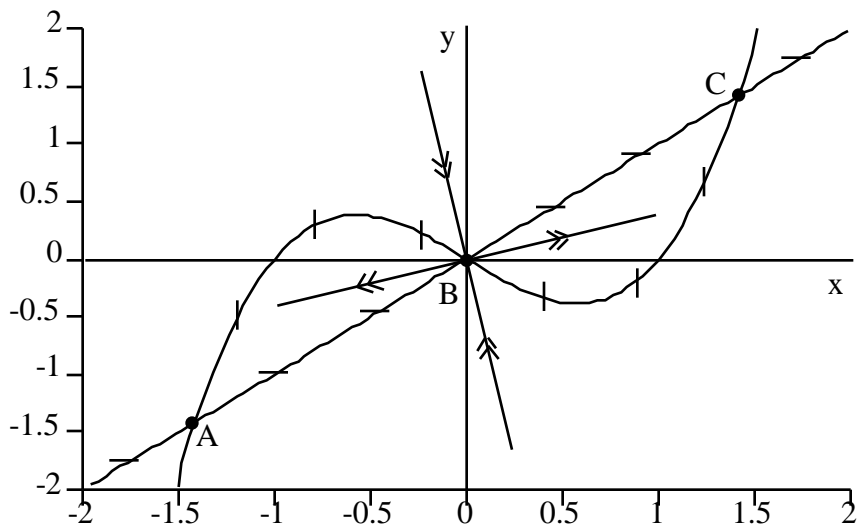
The flow field is strongly determined by the manifolds of the saddle node. Their direction can be determined from the eigenvectors of the eigenvalues at B:

$$\begin{array}{ccc} 1 & 1 & 1 \\ 1 & -1 & \sqrt{2} - 1 \end{array} = \sqrt{2} \begin{array}{c} 1 \\ \sqrt{2} - 1 \end{array}$$

and

$$\begin{array}{ccc} 1 & 1 & 1 \\ 1 & -1 & -\sqrt{2} - 1 \end{array} = -\sqrt{2} \begin{array}{c} 1 \\ -\sqrt{2} - 1 \end{array}$$

The directions of these eigenvectors are plotted on the phase plane at right. These are, of course, only accurate near the saddle node and the unstable manifolds curve around to end in equilibrium points A and C, as mentioned in the problem statement. The stable manifolds project off the plane, as drawn. The horizontal and vertical lines drawn on the nullclines remind us the direction that the trajectories must take in crossing those curves. From this information and the direction arrows in the first phase plane plot above, the overall trajectories can be seen to flow as sketched in the phase plane at right below.



Clearly this system cannot have a limit cycle. In order that its index be -1, it would have to enclose all three equilibrium points or either point A or point C. Consideration of the direction of flow at the nullclines through these points shows that such a closed contour is not possible, because in either case it would have to cross a manifold of the saddle node (equilibrium point B).