

580.439/639 Midterm Exam Solutions 2002

Problem 1

Part a) With the assumption of independence and using the GHK equation, as suggested in the hint, the current becomes:

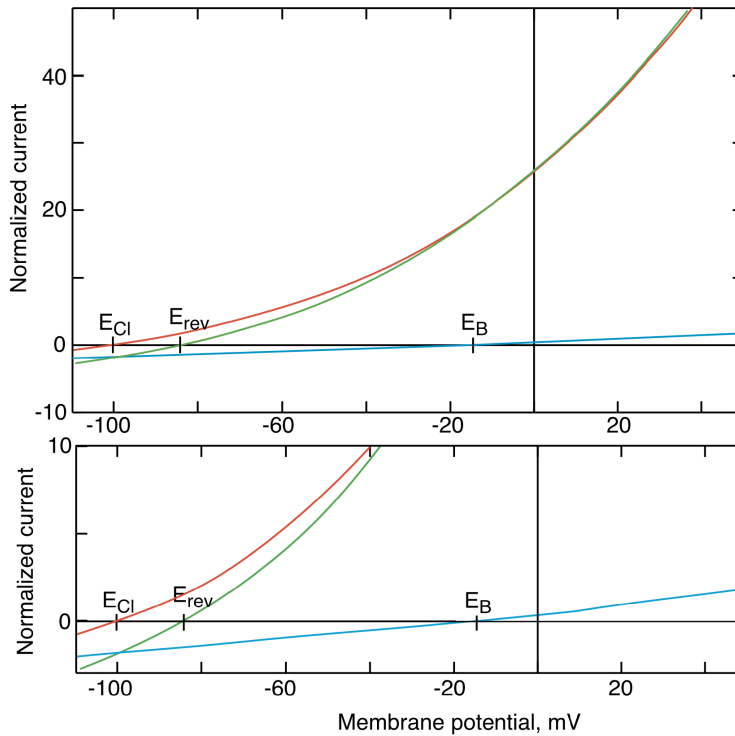
$$I_{GABA} = P_{Cl} V \frac{C_{in} e^{\frac{FV}{RT}} - C_{out}}{e^{\frac{FV}{RT}} - 1} + P_B V \frac{B_{in} e^{\frac{FV}{RT}} - B_{out}}{e^{\frac{FV}{RT}} - 1} \quad (1)$$

where $P_{Cl} = (z_{Cl} F)^2 u_{Cl} / d$ and $P_B = (z_B F)^2 u_B / d$.

Part b) With the parameters given, $E_{Cl} = -26 \ln(C_{out}/C_{in}) = -100$ mV and $E_B = -15$ mV. An exact plot of the two parts of Eqn. (1) and their sum is given below. The equation is plotted in the following form, to avoid dealing with units:

$$\frac{I_{GABA}}{P_{Cl} C_{out}} = V \frac{\frac{C_{in}}{C_{out}} e^{\frac{FV}{RT}} - 1}{e^{\frac{FV}{RT}} - 1} + \frac{P_B}{P_{Cl}} \frac{B_{out}}{C_{out}} V \frac{\frac{B_{in}}{B_{out}} e^{\frac{FV}{RT}} - 1}{e^{\frac{FV}{RT}} - 1} \quad (2)$$

This form of the equation allows one to see that the bicarbonate component of the current is small. The ratios multiplying the second term are $\frac{P_B}{P_{Cl}} * \frac{B_{out}}{C_{out}} = 1 * 0.03 = 0.03$, so the bicarbonate current is likely to be small compared to the chloride current..



However, the voltage terms can distort the conclusion of the previous paragraph. For positive voltages, the current becomes approximately

$$\lim_{V \rightarrow \infty} \frac{I_{GABA}}{P_{Cl} C_{out}} = \frac{P_B}{P_{Cl}} \frac{B_{out}}{C_{out}} V$$

and because $B_{out}/C_{out} \ll 1$, the total current is approximately the same as the chloride current. For negative voltages,

$$\lim_{V \rightarrow -\infty} \frac{I_{GABA}}{P_{Cl} C_{out}} = \frac{C_{in}}{C_{out}} + \frac{P_B}{P_{Cl}} \frac{B_{in}}{C_{out}} V = \frac{3.2}{150} + \frac{P_B}{P_{Cl}} \frac{2.8}{150} V$$

and the chloride and bicarbonate currents are approximately the same.

An adequate sketch in the answer would have included the asymptotes of the two currents, which are proportional to $P \cdot (\text{conc.}) \cdot V$, where “(conc.)” is the appropriate intracellular or extracellular concentration. Given that the permeabilities are the same, the ratios of the slopes of the asymptotes are $C_{in}/B_{in}=1.14$ for negative potentials and $C_{out}/B_{out}=30$ for positive potentials, the same conclusion as in the previous paragraph.

Part c) When the current is zero,

$$0 = P_{Cl} V \frac{C_{in} e^{-FV/RT}}{e^{-FV/RT} - 1} + P_B V \frac{B_{in} e^{-FV/RT}}{e^{-FV/RT} - 1}$$

The terms $V/(e^{-FV/RT} - 1)$ are never zero, so can be cancelled, giving the usual equation:

$$V = \frac{RT}{F} \ln \frac{P_{Cl} C_{in} + P_B B_{in}}{P_{Cl} C_{out} + P_B B_{out}}$$

Note that this equation predicts the correct zero-current potential in the graphs above, -84 mV.

Part d) Clearly the zero-current potential is not at either equilibrium potential and there is a net flow of chloride into the cell ($E_{Cl} = -100$, so there is a positive chloride current at -84 mV, meaning charge out of the cell, meaning chloride into the cell; alternatively, the membrane potential is positive to E_{Cl} so negative ions are driven into the cell) and bicarbonate out of the cell (opposite argument) at the zero-current potential.

Problem 2

This problem assumes a barrier model like the standard one sketched below. The barrier heights are not of concern, only the rate constants. Two sets of rate constants are

needed, one for chloride and one for bicarbonate. These will differ if the barrier heights are different for the different ions, as in the case of the Hille sodium channel model.

The fluxes of chloride J_C and bicarbonate J_B can be handled separately. Using the steady-state assumption that requires the fluxes of both ions to be the same across the two barriers gives

$$J_C = k_{C1} C_1 X \square k_{C1} XC$$

$$J_C = k_{C2} XC \square k_{C2} C_2 X$$

$$J_B = k_{B1} B_1 X \square k_{B1} XB$$

$$J_B = k_{B2} XB \square k_{B2} B_2 X$$

where the variables are defined in the barrier diagram. There are five unknowns in this problem, the fluxes J_C and J_B and the three channel concentrations X , XC , and XB . The fifth equation is the constraint of a fixed number of channels

$$Q = X + XC + XB$$

These equations can be solved in the usual way, giving results similar to Eqn. 15.10 in Hille.

Part b) At low concentrations, in the independence regime, permeation is controlled by the tallest barrier in the model. In this case, if the permeabilities of chloride and bicarbonate are equal, then the barrier peaks should be about equal. Permeabilities at low concentrations tell us little about the binding site in the channel.

Problem 3

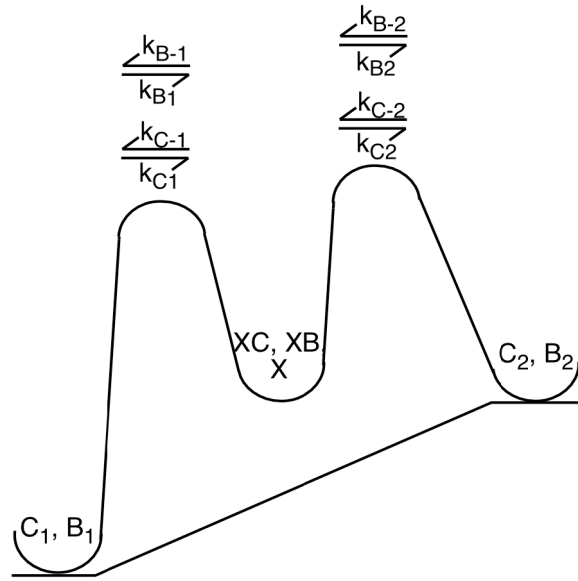
Part a) Using the definitions of state variables suggested in the problem,

$$y_1 = y, \quad y_2 = \frac{1}{\square} \frac{dy}{dt}$$

$$\frac{dy_1}{dt} = \frac{dy}{dt} = \square y_2$$

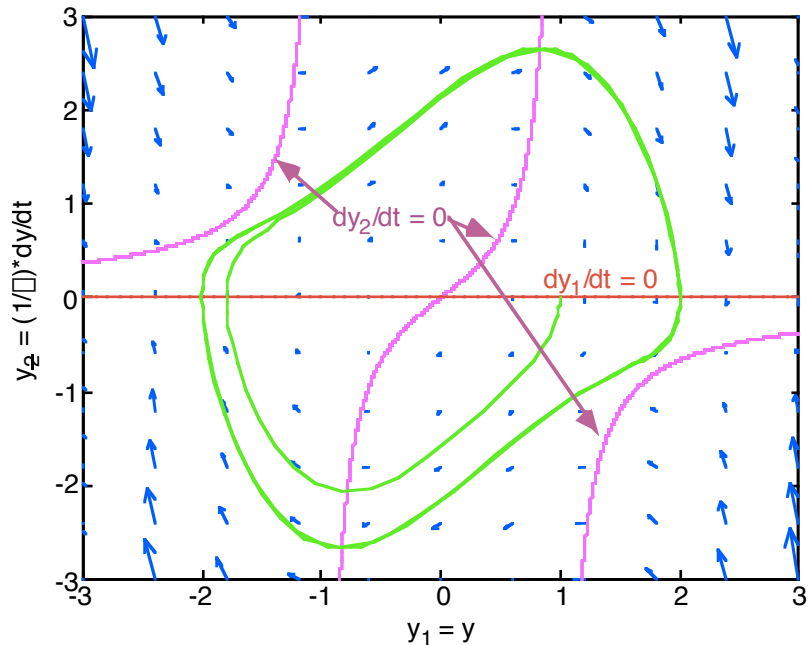
$$\frac{dy_2}{dt} = \frac{1}{\square} \frac{d^2y}{dt^2} = (1 \square y_1^2) \square y_2 \square \frac{1}{\square} y_1$$

Part b) The isoclines are given by the functions



$$\begin{aligned} \frac{dy_1}{dt} = 0 & \quad \square \quad y_2 = 0 \\ \frac{dy_2}{dt} = 0 & \quad \square \quad y_2 = \frac{1}{\square^2} \frac{y_1}{1 \square y_1^2} \end{aligned}$$

These functions are plotted in the phase plane at right for $\square=1$, along with a quiver plot (blue arrows) showing the directions of the trajectories. Six arrows pointing in roughly the correct direction would be sufficient. There is one equilibrium point, at the origin. The green curve is a trajectory from initial value (1,0).



Part c) The Jacobian is found by differentiating the functions above w.r.t. y_1 and y_2 . The Jacobian and its value at the equilibrium point are as follows:

$$J = \begin{bmatrix} 0 & \square \\ 2\square y_1 y_2 & \frac{1}{\square} \square (1 \square y_1^2) \end{bmatrix} \quad J(0,0) = \begin{bmatrix} 0 & \square \\ \square & \square \end{bmatrix}$$

The eigenvalues are

$$\square = \frac{\square \square}{2 \square} \pm \sqrt{1 \square \frac{4}{\square^2} \square}$$

For $\square > 0$, these have a positive real part, so the equilibrium point is unstable.

Part d) Index theory says that a limit cycle would have to encircle the origin. Inspection of the trajectory vectors shows that there is no conflict with a CCW limit cycle that crosses the central limb of the y_2 isocline, but not its outer two legs. However, the existence of a limit cycle cannot be proven.

In fact, a limit cycle exists, as shown by the green trajectory in the figure above. This differential equation has been studied extensively and it is possible to show that it does have a limit cycle, see the discussion in Strogatz.

Part e) In this case, the Poincare Bendixson theorem applies and a limit cycle has to exist.