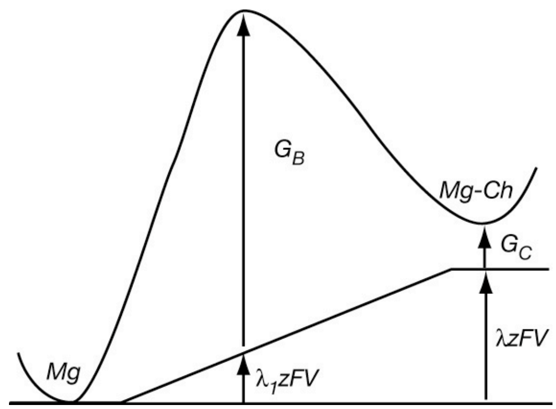
580.439/639 Midterm Solutions, 2006

Problem 1

Part a) An adequate barrier model for this question is shown at right. The barrier heights G_B and G_C and the fraction of the membrane potential at the barrier peak λ_1 are needed. The rate constants are given by the usual expressions:

$$k_1 = \alpha e^{-(G_B + \lambda_1 zFV)/RT}$$

$$k_{-1} = \beta e^{-(G_B - G_C + (\lambda_1 - \lambda) zFV)/RT} \quad .$$



Part b) The equation for $Mg\text{-}Ch$ is as follows. As suggested in the problem statement, the state of the channel (Ch) is explicitly included.

$$\frac{d\,Mg-Ch}{dt} = k_1\, Mg \cdot Ch - k_{-1}\, Mg - Ch \quad ,$$

where Mg is the magnesium concentration in the extracellular space, $Mg\text{-}Ch$ is the channel with magnesium bound and Ch is the free channel. Using the fact that there is a finite total amount of channel, $Q = Ch + Mg\text{-}Ch$,

$$\begin{aligned} \frac{d\,Mg-Ch}{dt} &= k_1\, Mg\,(Q - Mg - Ch) - k_{-1}\, Mg - Ch \\ &= k_1\, Mg \cdot Q - (k_1\, Mg + k_{-1})\, Mg - Ch \end{aligned} \quad .$$

Part c) At equilibrium, $d\,Mg\text{-}Ch/dt = 0$, so

$$Mg - Ch = \frac{k_1 \cdot Mg \cdot Q}{k_1 \cdot Mg + k_{-1}} \quad .$$

To get the equilibrium fraction of unbound channel f_{Ch}

$$f_{Ch} = 1 - \frac{Mg - Ch}{Q} = 1 - \frac{k_1 \cdot Mg}{k_1 \cdot Mg + k_{-1}} = \frac{1}{1 + \dfrac{k_1}{k_{-1}} Mg} \quad .$$

This is the fraction of channels that are **not blocked** by magnesium. The ratio k_1/k_{-1} can be written as follows, after substituting the expressions for rate constants from Part a).

$$\frac{k_1}{k_{-1}} = \frac{\alpha\, e^{-(G_B + \lambda_1 zFV)/RT}}{\beta\, e^{-(G_B - G_C + (\lambda_1 - \lambda) zFV)/RT}} = \frac{\alpha}{\beta} e^{-G_C/RT} e^{-\lambda zFV/RT} = const \cdot e^{-\lambda zFV/RT} \ .$$

Part d) The current through the NMDA channels is

$$I_{NMDA} = G_{NMDA}(V - E_{NMDA}) = g_{NMDA} f_{Ch}(V - E_{NMDA}) \ \ ,$$

where G_{NMDA} is the conductance of NMDA channels, assumed equal to a constant g_{NMDA} multiplied by the fraction of unblocked channels. Substituting for f_{Ch} the fraction of open channels from Part c) gives the result in the the problem statement (Eqn. (*) of the problems), with

$$G_{NMDA} = g_{NMDA}, \qquad q = \frac{RT}{\lambda zF}, \qquad K_{MG} = \frac{\beta}{\alpha} e^{G_C/RT}$$

Problem 2

Part a) The differential equation for membrane potential takes the usual form:

$$C_m \frac{dV}{dt} = -I_{NMDA} - I_{pump} - G_L(V - E_L) \ .$$

The differential equation for *Na* is as given in the problem statement:

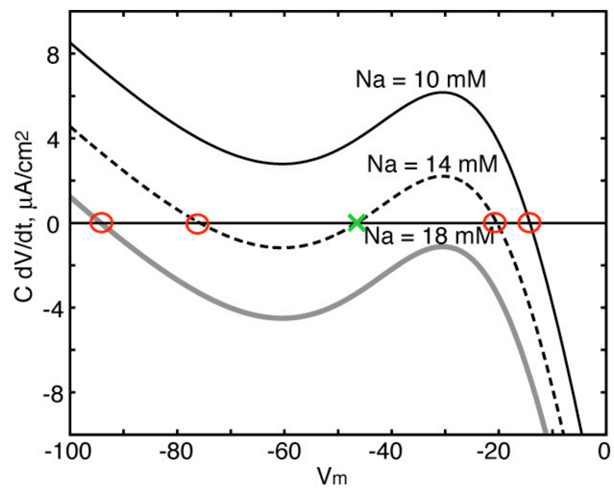
$$\frac{dNa}{dt} = a\left[-I_{Na,NMDA} - b \cdot I_{pump}\right] \ .$$

The first term is the flux of sodium into the cytoplasm through the NMDA channel. It is negative because of the usual convention that such currents are outward. The constant a converts current in μA/cm^2 to the time derivative of Na. It should consist of the following: 1) division by F to convert coulombs to moles; 2) multiplication by the *Area* of the cell, to get total outward flux; 3) division by the *Volume* of the Na-containing compartment, to convert flux to concentration change. Thus the units are

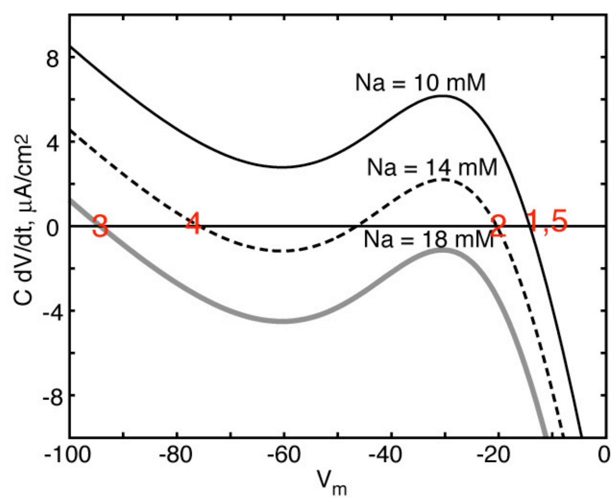
Moles/(m^3 s) = *Area* (m^2)/(*Volume* (m^3) F (coul/Mole)) $\cdot$ coul/(m^2 s)

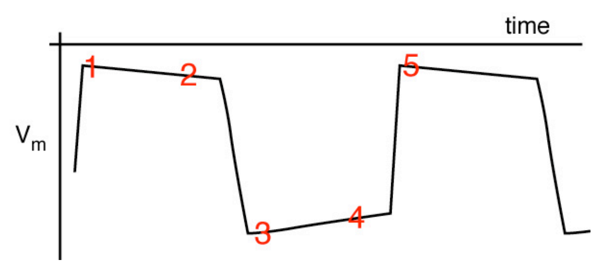
The remaining constant b = 3 to convert the pump current to sodium current. The pump moves 3 Na ions out of the cell for each 2 K ions moved into the cell. The the Na flux is three times the charge flux I_{pump}.

Part b) For the 1D system, the equilibrium points are where dV/dt=0, marked with red circles (stable) and green Xs (unstable) in the phase plane at right. The stability of these points can be seen intuitively by considering what happens if the system is started a small distance from an equilibrium point. For the stable equilibrium points the sign of dV/dt is such that V moves toward the equilibrium point; for the unstable equilibrium the sign is such that V moves away. More formally, the Jacobian of the system is the slope of the phase plane plots at the equilibrium point. For a 1D Jacobian, the eigenvalue is just the Jacobian, so a negative eigenvalue corresponds to a negative slope.



The idea of the second part of this question is that the system will follow the equilibrium points as Na changes slowly. With the assumption about dNa/dt given in the problem statement, the sequence of equilibrium points is given by the numbers on the phase plane at right and a sketch of the resulting membrane potential is shown below. Between points 1 and 2, $[Na]_{inside}$ is increasing and between 3 and 4, $[Na]_{inside}$ is decreasing. Of course the changes in sodium are not predicted by the phase plane, but rather by the differential equation for Na.





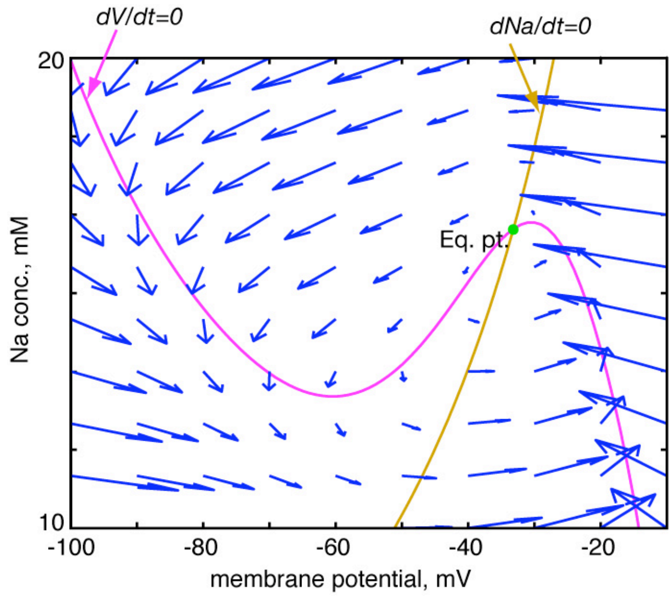
Part c)

$$\frac{dNa}{dt} = 0 \quad \Rightarrow \quad I_{Na,NMDA} = -3I_{pump}$$

$$\frac{dV}{dt} = 0 \quad \Rightarrow \quad I_{NMDA} + I_{pump} + G_L(V - E_L) = 0$$

If G_{NMDA}=$G_{Na,NMDA}$= 0, then I_{NMDA} = $I_{Na,NMDA}$ = 0, so the first isocline equation requires that I_{pump}=0 and the second isocline equation requires that $G_L(V\text{-}E_L)$=0, or V(eq. pt.)=E_L. If I_{pump}=0, then Na(eq. pt.)=Na_{eq}.

Part d) From the 1D phase plane above, it is clear that, for fixed Na, the V isocline can have three equilibrium points. This is possible for the solid (magenta) line, but not for the dashed (brown) line, thus identifying which isocline is which. The fully labeled phase plane is shown at right. Of course the arrow plot was not expected as part of the answer, but it was possible to infer the directions of the arrows on the two sides of each isocline qualitatively from the differential equations in Part a).



Part e) There can be a limit cycle, if it includes the equilibrium point, but since the point is stable, the Poincare-Bendixson theorem doesn't apply. Thus the existence or non-existence of a limit cycle can't be proven. The actual limit cycle is shown at right. It is possible to guess the shape of this limit cycle based on the statement in the problem that $|dNa/dt| << |dV/dt|$.