**580.439/639 Final Solutions 2013**

## Problem 1

**Part a)** Inject a current $I_{inj0}$ at point 0, producing a potential $V_0$ at that point and measure a potential $V_1$ at point 1. Then

$$V_0 = I_{inj0}K_{00} = \frac{I_{inj0}}{Y_{00}} = \frac{I_{inj0}}{Y_0 + Y_{0in}} \quad \text{because} \quad Y_{00} = Y_0 + Y_{0in}$$

and, using the transfer impedance

$$V_1 = I_{inj0}K_{01} = V_0 Y_{00} K_{01} \quad \text{so} \quad A_{01} = \frac{V_1}{V_0} = Y_{00}K_{01}$$

If the current is injected at point 1

$$V_0 = I_{inj1}K_{10} = V_1 Y_{11} K_{10} \quad \text{so} \quad A_{10} = \frac{V_0}{V_1} = Y_{11}K_{10}$$

Because of the symmetry of the transfer impedance, $K_{01} = K_{10}$, the ratio of voltage gains is

$$\frac{A_{01}}{A_{10}} = \frac{Y_{00}K_{01}}{Y_{11}K_{10}} = \frac{Y_{00}}{Y_{11}}$$

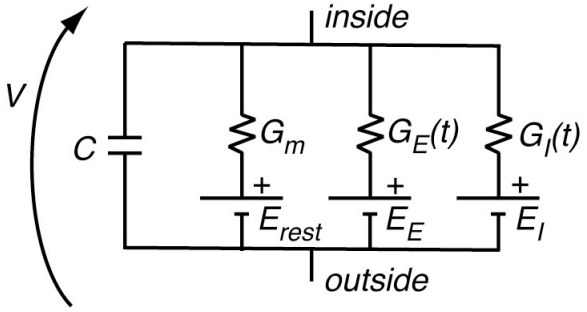
as requested.

Suppose point 0 is near the soma and point 1 is at near of the dendritic tree. Then it is likely that $Y_{11} < Y_{00}$ because the dendritic branches are smaller near the end of the tree. Examples to support this point were given in class. Therefore $A_{01}$ is predicted to be larger than $A_{10}$, consistent with larger soma-fugal spread of potentials.

**Part b)** There is nothing in the answer to part a) that requires a single branch, as long as the measures of $Y_{00}$ and $Y_{11}$ are appropriate.

## Problem 2

**Part a)** At a clamp voltage of V = -70 mV, the membrane potential $V$ is approximately equal to the equilibrium potential $E_I$~-70 mV of the inhibitory synapse, so no current flows through $G_I$ and the only current obtained when the synapses are activated is the inward current through the excitatory synapse equal to $G_E(V\text{-}E_E) = G_E(\text{-}70 - 0)$ which is large and negative. Thus the inward (negative) current in the top trace in the problem figure is the current through the excitatory synapse.




At a clamp voltage of V = 0 mV, the membrane potential is near $E_E$~0 mV and no current flows through the excitatory synapse. The current in this case is $G_I\ (0 - E_I)$ which is large and positive (outward) since $E_I$ ~ -70. Thus the bottom trace in the problem figure is the current through the inhibitory synapse.

**Part b)** When the voltage clamp is applied, the voltage-gated channels in the membrane will change their gating and eventually come to steady state with current (for the $j^{th}$ channel) $I_j = \bar{G}_j\, m_{j\infty}^p(V_{clamp}) h_{j\infty}^q(V_{clamp})(V_{clamp} - E_j)$ for the usual HH model. These channels will conduct a constant current that is compensated by the voltage clamp. As stated in the problem, the horizontal line in the problem figure is the value of this steady current. Because the membrane potential does not change when the synaptic input is applied, this steady current does not change, and the only current deviations from the voltage-clamp baseline are the synaptic currents.

Examples of channels activated at 0 mV are non-inactivating channels like potassium channels. These are outward (positive) currents. An example at -70 mV is the H current, which should be inward. At -70, there are also leak channels and possibly some low-threshold non-inactivating potassium channels.

**Part c)** In NMDA channels there is no current when $V$ is clamped at 0 mV, equal to $E_{NMDA}$, and also no current when $V$=-70 mV, because of the $Mg^{++}$ block of the channel. Of course non-NMDA excitatory channels will be active at -70 mV.

**Part d)** Using the hint, the currents in the problem figure are approximately equal in peak absolute value, implying that the conductances $G_E$ and $G_I$ are approximately equal (although their time courses are somewhat different). Thus the synaptic currents when the synapses are activated will be $G_E(V\text{-}0) + G_I(V+70)$. If $V$ is near -60 mV and the conductances are about equal, the excitatory current (first term) will be larger than the inhibitory current, because it is driven by -60 mV as opposed to 10 mV. Thus the net synaptic current will be inward (negative) and the potential change in the soma will be depolarizing (an EPSP). Of course, because the inhibitory conductance lasts longer, there will be a small hyperpolarizing (inhibitory) tail.

**Problem 3**

**Part a)** $\mathbf{W} = \begin{bmatrix} -1 & w_{12} & w_{13} \\ w_{21} & -1 & w_{23} \\ w_{31} & w_{32} & -1 \end{bmatrix}$, where the state vector is $\vec{x} = \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}$

**Part b)** now the state vector is $\vec{x} = \begin{bmatrix} x_a \\ x_3 \end{bmatrix}$ and $\mathbf{W} = \begin{bmatrix} -(1-w_{12}) & w_{13} \\ 2w_{31} & -1 \end{bmatrix}$

**Part c)** This is a linear system, so the Jacobian is **W**, independent of equilibrium point.

Using the standard approach to finding eigenvalues,

$$\det[\mathbf{W} - \lambda\mathbf{I}] = 0 \quad \text{or} \quad \lambda^2 + (2 - w_{12})\lambda + (1 - w_{12}) - 2w_{13}w_{31} = 0 \ .$$

or

$$\lambda = -\frac{2 - w_{12}}{2}\left[1 \pm \sqrt{1 - 4\frac{(2 - w_{12}) - (1 + 2w_{13}w_{31})}{(2 - w_{12})^2}}\right].$$

**Part d)** To simplify the expression for λ, let $a = 2\text{-}w_{12}$ and $c = 1+2w_{13}w_{31}$. Then

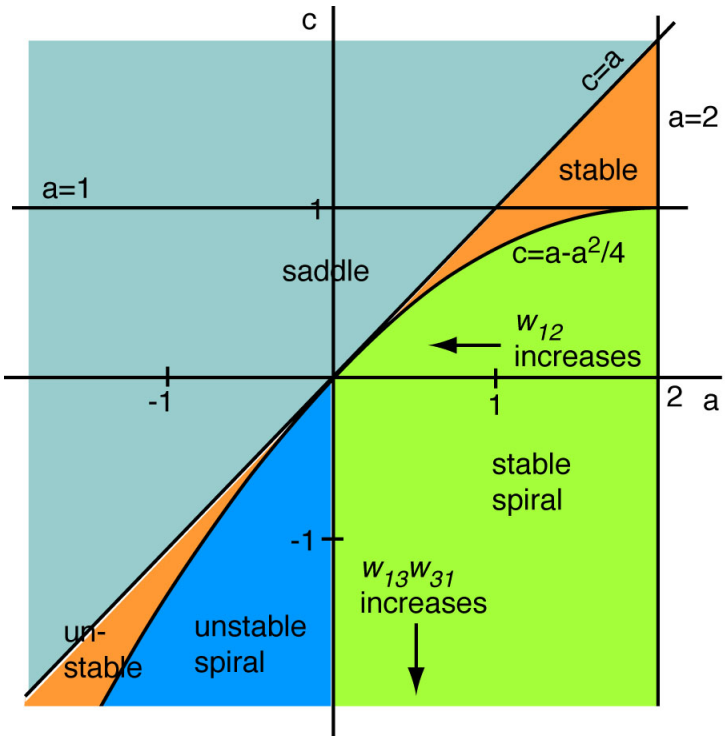
$$\lambda = -\frac{a}{2}\left[1 \pm \sqrt{1 - 4\frac{a-c}{a^2}}\right]$$

It is apparent that if $a\text{-}c = 1\text{-}w_{12}\text{-}2w_{13}w_{31}$ is negative, then the equation under the radical is positive and greater than 1, then the eigenvalues are real with opposite signs, giving a saddle, regardless of $a$. Because the inhibitory gain $w_{13}w_{31}$ is negative by assumption, a saddle occurs with large recurrent feedback $w_{12}$ among the excitatory neurons or small inhibitory feedback gain. These relationships are illustrated in the figure below.

If $a\text{-}c$ is positive with magnitude larger than $a^2/4$ then the equation under the radical is negative and the eigenvalues are a complex conjugate pair. In this case, the pair is stable if a>0 and unstable if a<0. Thus stability requires that $a = 2\text{-}w_{12} > 0$ or $w_{12}<2$. Again increasing the recurrent excitatory gain $w_{12}$ makes the system unstable.

There is a range where $a\text{-}c$ is positive but less than $a^2/4$ where the eigenvalues are both negative, giving a stable ($a>0$) or unstable ($a<0$) system.

Making the inhibitory gain larger in magnitude, which is $w_{13}w_{31}$ always negative, makes $c$ smaller and $a\text{-}c$ positive. It thus pushes the system toward a spiral. However, stability depends on the sign of $a$ and thus the magnitude of $w_{12}$.




This answer is more detailed than was expected for the exam, which is why it was to do last. A full credit answer would be pointing out the role of $a$ in stability and the inhibitory gain in producing spirals.

**Part e)** Now the differential equations are non-linear, so the Jacobian must be derived by differentiating the non-linear equations

$$\frac{dx_a}{dt} = -x_a + S\left(w_{12}x_a + w_{13}x_3\right)$$
$$\frac{dx_3}{dt} = -x_3 + S(2w_{31}x_a)$$

now the Jacobian is

$$\mathbf{W} = \begin{bmatrix} -1 + \left.\frac{dS}{du}\right|_{e.p.} w_{12} & \left.\frac{dS}{du}\right|_{e.p.} w_{13} \\ \left.\frac{dS}{du}\right|_{e.p.} 2w_{31} & -1 \end{bmatrix}$$

In this case, the Jacobian is only meaningful if there is an equilibrium point (*e.p.* in the matrix). The nonlinearity changes the amplitudes of the weights by its slope at the e.p.

**Problem 4**

**Part a)** As stated in the problem, the concentrations and membrane potential must be constant, so

$$\frac{dK_{out}}{dt} = \frac{dK_{in}}{dt} = \frac{dNa_{out}}{dt} = \frac{dNa_{in}}{dt} = \frac{dCl_{out}}{dt} = \frac{dCl_{in}}{dt} = \frac{dV}{dt} = 0 \quad .$$

In order for $dV/dt$=0, it must be true that the net membrane currents are zero, so

$$\sum z_K J_K + \sum z_{Na} J_{Na} + \sum z_{Cl} J_{Cl} = 0 \, .$$

The notation $\sum z_j J_j$ means the sum of all ion currents of ion *j*, active and passive. The total charge flow (current) through the membrane must be 0, but this is guaranteed if the net flux of each ion is zero, so an additional equation is not needed.

**Part b)** For the specific example, the following flux equations define the steady state:

$$\begin{aligned} J_K^p + J_K^{a1} + J_K^{a2} &= 0 \quad \text{for steady state of K} \\ J_{Na}^p + J_{Na}^{a1} &= 0 \qquad \text{for steady state of Na} \\ J_{Cl}^p + J_{Cl}^{a2} &= 0 \qquad \text{for steady state of Cl} \end{aligned}$$

In these equations, the subscripts identify the ion and the superscripts identify the transport mechanism ("p" passive, "a1" active transport by the Na-K ATPase, "a2" active transport by the KCL transporter). As discussed above, an additional equation for charge flow is not needed.

**Part c)** Define the flux of the Na-K ATPase as $J^A$, equal to the number of cycles of the transporter with a sign such that $J_{Na}^{a1} = 3J^A$ and $J_K^{a1} = -2J^A$. Similarly define the flux of the KCl transporter $J^B$ as the flux of KCl into the cell, so that $J_K^{a2} = J_{Cl}^{a2} = -J^B$. Then the currents are equal to the fluxes multiplied by the charge per mole $I_x = -z_x F J_x$, where the minus sign is needed because the direction of flux *J* is opposite that of current *I*. Then the steady state equations can be rewritten in terms of currents as follows (leaving out the common *F* terms).

$$I_K^p = F(-2J^A - J^B)$$
$$I_{Na}^p = F3J^A \qquad (*)$$
$$I_{Cl}^p = FJ^B$$

Now, summing the currents gives

$$I_K^p + I_{Na}^p + I_{Cl}^p = F\left(-2J^A - J^B + 3J^A + J^B\right) = FJ^A \neq 0\,.$$

Thinking about this another way, the sum of the active transports leads to net flow of charge out of the cell ($J_A$<0), because of the 3/2 ratio of the Na-K ATPase (net charge outward) plus the 0 net charge flow in the KCl transporter. Thus the passive transport must counteract the net outward flow of charge from the Na-K transporter by providing an inward flow of current (<0) to make the total charge transfer zero.

**Part d)** The currents in (*) can be made to sum to zero by appropriate scaling, for example

$$1.5\,I_K^p + I_{Na}^p + 1.5\,I_{Cl}^p = -3J^A - 1.5J^B + 3J^A + 1.5J^B = 0\,.$$

Then, substituting the constant-field current equations into this sum of currents gives

$$V = \frac{RT}{F}\ln\frac{1.5u_K K_{outside} + u_{Na}Na_{outside} + 1.5u_{Cl}Cl_{inside}}{1.5u_K K_{inside} + u_{Na}Na_{inside} + 1.5u_{Cl}Cl_{ouftside}}\quad . \qquad (**)$$

The factors of 1.5 show the effect of active transport.

**Part e)** There is now nothing maintaining the concentration differences, so in the steady state

$$Na_{in} = Na_{out}\ ,\ \ K_{in} = K_{out}\,,\ Cl_{in} = Cl_{out}\,,\ \text{and}\ \ V = 0.$$

This is the only steady state that is possible because pump 2, the KCl transporter, has no energy source, so the only force driving ions through the membrane is their electrochemical gradients. Note that this conclusion is consistent with Eqn. (*), with $J^A$=$J^B$=0.

**Part f)** Now, there must be zero net current through the membrane, giving

$$I_K^p + I_{Na}^p + I_{Cl}^p + I_K^{a2} + I_{Cl}^{a2} = 0$$

But the current through the KCl transporter is zero and the Na-K ATPase has been poisoned, so the two transporter terms in the equation above can be eliminated, leaving

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

Thus the membrane potential will revert to the standard GHK equation

$$V = \frac{RT}{F} \ln \frac{u_K K_{outside} + u_{Na} Na_{outside} + u_{Cl} Cl_{inside}}{u_K K_{inside} + u_{Na} Na_{inside} + u_{Cl} Cl_{ouftside}} \qquad (***)$$

The change in potential between equations (**) and (***) is a measure of the effect of active transport. Such changes are observed when ouabain is used to poison membranes.