Issued: December 27, 1999

Biomedical Engineering E3500x

Solution to Final Examination:

1. Part i asks for the equations needed to solve for c_1 and c_2. Two differential equations are needed, along with their initial conditions:

$$V_1 \frac{dc_1}{dt} = -P_1 A_1 (c_1 - c_2)$$

$$V_2 \frac{dc_2}{dt} = P_1 A_1 (c_1 - c_2) - P_2 A_2 c_2$$

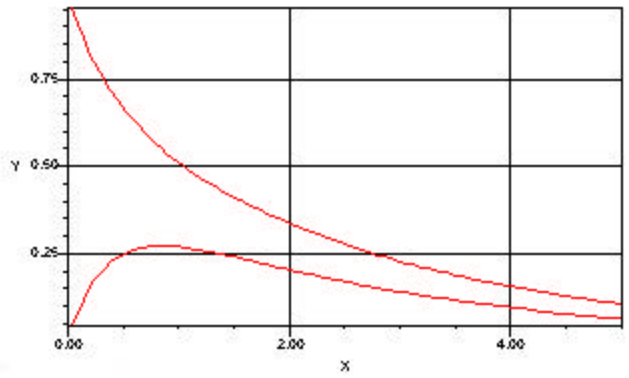
$$c_1(0) = c_1^0; \quad c_2(0) = 0$$

Part ii asks for the rate at which drug is delivered to the body pool. This is just $P_2 A_2 c_2$ because the pool concentration remains at essentially zero. It is <u>not</u> -V dc/dt for either volume 1 or 2.

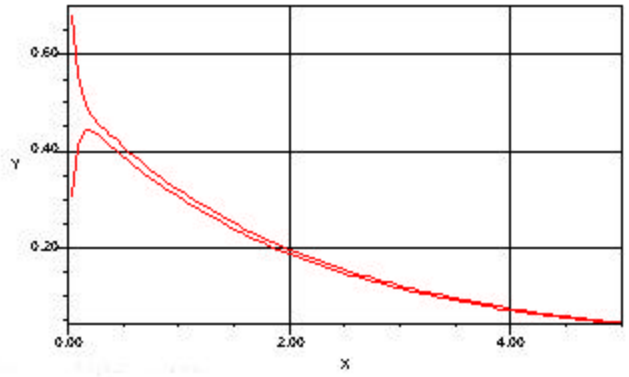
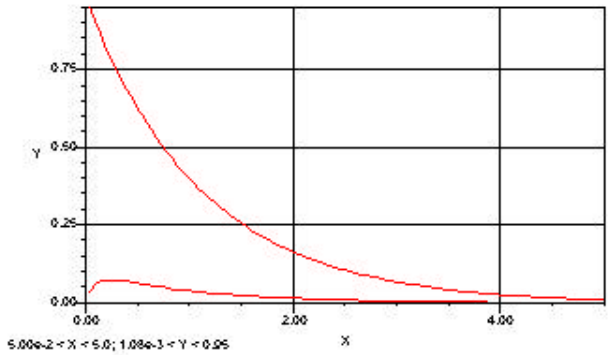
Part iii is given as the <u>lower curve</u> in each of the sketches below. The general case, that shown in the first graph, was the expected answer.

The answer to part iv is given in the legend of the graphs below.

For part v the first equation must be modified: $V_1 \frac{dc_1}{dt} = -P_1 A_1 (\frac{c_1}{k} - c_2)$. It is convenient to modify the equation by defining a "pseudo" concentration for compartment 1, c_1' as 1/k times the real concentration. Then one can write: $kV_1 \frac{dc_1'}{dt} = -P_1 A_1 (c_1' - c_2)$. This equation is just like the first equation so that we can use its solution to predict what will happen in part v <u>as long as we use a pseudo-volume which is k times the actual volume.</u>



Compartment 1 and Compartment 2 time constants (V/PA) equal at a value of 1. <u>In all cases, delivery to the body pool is proportional to concentration in compartment 2.</u> Here c_2 peaks at t=1. Concentrations in the two compartments remain distinctly different.

	Compartment 1 time constant is 0.1. Compartment 2 time constant is 1. Compartments 1 and 2 are nearly in equilibrium. Compartment 2 moves quickly into quasistatic equilibrium with compartment 1.
	Compartment 1 time constant is 1. Compartment 2 time constant is 0.1. Compartment 2 and body pool are nearly in equilibrium., *i.e.* compartment 2 concentration is nearly zero. Compartment 2 moves quickly back toward quasistatic equilibrium with the body pool, c = 0.

2. We represent the overall reaction scheme as:

$$A + E \underset{k_{A-}}{\overset{k_{A+}}{\rightleftharpoons}} EA \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} B + E$$

Later, the k's will be related to k_0 and K of the problem statement. Using the facts that (1) $e_0 = e + ea$, and (2) that the rate of accumulation of complex is negligible (quasi steady state) we can write a balance on *ea* and solve for the fraction of enzyme, ea/e_0, that is complexed:

$$k_{A+} a\, e - k_{A-} ea + k_{B-} b\, e - k_{B+} ea = 0$$

$$\frac{ea}{e} = \frac{k_{A+} a + k_{B-} b}{k_{A-} + k_{B+}} = b; \quad \frac{e}{e_0} = \frac{1}{1+b}; \quad \frac{ea}{e_0} = \frac{b}{1+b}$$

Note that *b* depends only on rate constants and reactant and product concentrations -- not on intermediates. It is defined to keep the algebra more compact but does not appear in the final rate expression.

a. It is now easy to write the reaction rate, either as the net rate of formation of complex from A or the net rate of formation of B from complex. These must be equal:

$$rate = \frac{k_{A+} a - k_{A-} b}{1+b}\, e_0 = \frac{k_{B+} b - k_{B-} b}{1+b}\, e_0$$

The expression can be 'cleaned up' to eliminate b and show explicitly the dependence on the concentrations of a and b:

$$rate = \frac{k_{A+}k_{B+}a - k_{A-}k_{B-}b}{k_{A-} + k_{B+} + k_{A+}a + k_{B-}b}e_0$$

The greatest possible rate of conversion to B is $k_{B+}e_0$; it occurs when b=0 and a >> k_{A-}/k_{A+} and k_{B+}/k_{A+}. This observation establishes k_0 as equal to k_{B+}.

b. The end result in a closed volume is that the rate becomes zero. Since b is composed only of positive factors, this is equivalent to setting the numerator in any of the rate expressions equal to zero. Doing so produces:

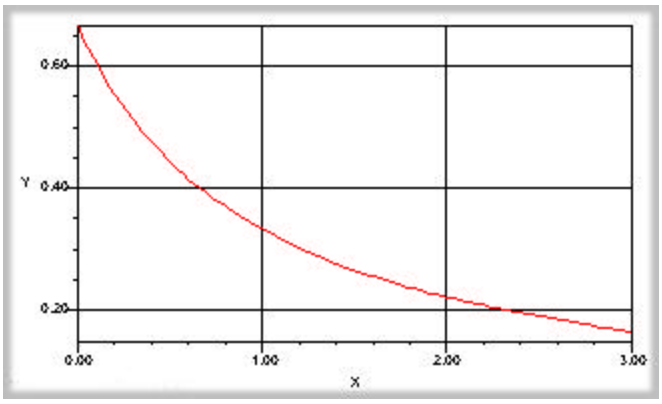
$$\frac{b}{a} = \frac{k_{A+}}{k_{A-}}\frac{k_{B+}}{k_{B-}} = K_{EQ,1}K_{EQ,2} = K$$

(The expression says that the solutes are in equilibrium, the expected final state in a closed system.)

c. The system is at steady state (stated) and $b = a_f - a$ since any of the A fed that is converted will appear as B. Thus the balance is, using V for the volume of the reacting space:

$$q(a_f - a) = V\frac{k_{A+}k_{B+}a - k_{A-}k_{B-}(a_f - a)}{k_{A-} + k_{B+} + k_{A+}a + k_{B-}(a_f - a)}e_0$$

d. It is essential to show that at low flow the concentration of B will be twice that of A or 2/3 of a_f. The plot will look like that shown, with y = b/a_f and x=q, and with the y-intercept located at 2/3. (This is a parametric plot, not a plot of b *vs*. time. The system is at steady state.) The 'interesting' range will be where the maximum reaction rate k_0e_0 (with units of moles/(volume-time) will be comparable to q a_f /V (also with units of moles/(volume-time)). At very high flows, no B can form. At very low flows B and A are in equilibrium.



3. The basic balance is a combination of that for the round tube (geometry) and that for the falling film (gravity, not pressure as the driving force). Leaving out the common term $2pL$:

$$rt_{rz}\Big|_r - rt_{rz}\Big|_{r+\Delta r} = rg_z r\Delta r \text{ with } t_{rz} = 0 \text{ at } r = R_2$$

a. After integration and substitution of the boundary condition, the following stress distribution results:

$$t_{rz} = \frac{r\,g}{2}\left(\frac{R_2^2}{r} - r\right)$$

b. The velocity distribution is gotten, as usual, by inserting Newton's law of viscosity and integrating the resulting first-order differential equation. The velocity equals zero at R_1.

$$v_z = \frac{r\,g_z}{2m}\int_{R_1}^{r}\left[r - \frac{R_2^2}{r}\right]dr = \frac{r\,g_z}{2m}\left(\left[\frac{r^2 - R_1^2}{2}\right] - R_2^2 \ln\left[\frac{r}{R_1}\right]\right)$$

c. It is necessary to integrate one term, 'by parts' to calculate the flow rate. Full credit was given for formulating the answer:

$$Q = \frac{p\,r\,g_z}{m}\int_{R_1}^{R_2}\left(\left[\frac{r^2 - R_1^2}{2}\right] - R_2^2 \ln\left[\frac{r}{R_1}\right]\right)r\,dr$$

as long as the limits and the formulation of *dA* as *2p rdr* were properly specified.

4. a. We reproduce here the data table given in the problem statement with an added column to show the calculated Nernst potentials *(in italics)*:

Ion	Intracellular	Extracellular	V_n
Sodium	15	0.1	*-128.39*
Potassium	28.7	1.0	*-86.02*
Chloride	38	1.3	*+86.48*

Sodium and chloride must be transported inward by active transport mechanisms to overcome the tendency of V_m - V_n to transport them outward. The V_n for K^+ is essentially equal to V_m and there is no active transport.

b. The 'balancing' quantity is $\frac{RT}{z_n F}\ln\left(\frac{c_n^o}{c_n^i}\right)$. This term represents the stored chemical energy at the outside of the membrane minus that at the inside.

5. a. It is first necessary to calculate the Nernst potentials for K+ and Na+. See the *italic entries* in the table below:

Ion	G_n (S/cm^2)	c_n^o/c_n^i	V_n (mV)
K+	37 (10)$^{-5}$	0.05	*- 76.76*
Na+	1 (10)$^{-5}$	9.8	*58.48*
Leakage	30 (10)$^{-5}$	--	-49

We formulate the individual current flows and set them equal to zero:

$$37 * (V_m + 76.76) + 30 * (V_m + 49) + 1 * (V_m - 58.48) = 0$$

The result is V_m = - 62.52 mV.

b. The highest "G" on the graph represents G_K. The middle "G" represents G_L (leakage). The lowest "G" represents G_{Na}.

6. a. The core conductor equation establishes that the total current flow along a core is zero. The internal and external currents balance each other. In the region of an action potential both are finite. Elsewhere both are zero. (37 words)

b. The cable equation shows how the capacitance current must be added to the ionic currents and how this current influences the rate at which an action potential can be propagated down a core. (34 words)

c. (i) The *sodium* and *potassium* conductances are varied. (ii) They are functions of *membrane potential* and *time*. (iii) An action potential originates in a small region where a "suprathreshold" current is applied. This alters V_m, not quite instantaneously because of the capacitative current and the system initially follows the cable model until the alteration in V_m changes G_{Na} and drives V_m toward V_{Na}, the change in *n* being importantly faster than the changes in *m* and *h*. When these changes occur the membrane potential is driven back toward V_K, limiting the duration of the action potential, which, since it is traveling, means that its width is also limited. (90 words in (iii))