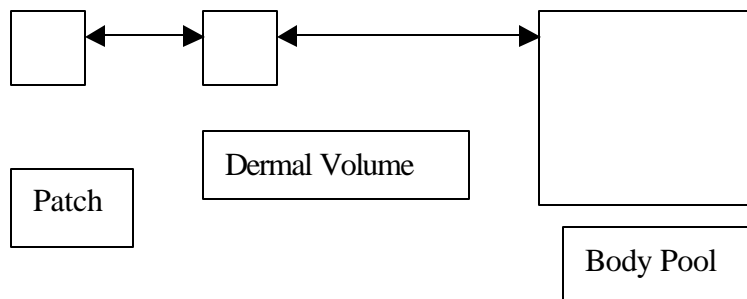


**Biomedical Engineering E3500x**

Final Examination: No books or notes are allowed. A calculator may be used. Keep all other materials brought into the examination room closed and at floor level. Three hours are allowed.

1. A 'skin patch' is a packet containing a gel in which a drug is dissolved. You are asked to model drug delivery into the body of a patient wearing such a patch. The patch has an active volume  $V_1$  in which drug is dissolved at an initial concentration  $c_1^0$ . All boundaries of this volume are impermeable except for an area  $A_1$  that is next to the skin. This area has a permeability for the drug equal to  $P_1$ . Drug that passes through the area  $A_1$  is assumed to enter a second 'dermal' volume  $V_2$ . The concentration in this volume is  $c_2$ , initially zero. Drug enters the body 'pool' from  $V_2$  through an area  $A_2$  which has a permeability  $P_2$ . The body pool for this drug is much larger than  $V_1$  or  $V_2$  so that its concentration is always effectively zero.



It is desired to calculate the rate at which drug enters the body pool as a function of time elapsed after placement of the patch on the skin surface. Assume for parts i. -- iv. that the activity of drug in each of the volumes is identical, *i.e.* at equilibrium the concentration of drug in each volume would be the same.

- i. Write equations that are sufficient to solve for  $c_1$  and  $c_2$ , assuming the volumes,  $V$ , and permeabilities,  $P$ , are fixed and known.
- ii. Indicate, assuming you have solved for  $c_1$  and  $c_2$ , an expression for the rate at which drug enters the body pool. (This expression should be directly applicable to the solution for  $c_1$  and  $c_2$ , to yield an expression for the rate at which drug enters the body pool.)
- iii. Sketch the rate at which drug enters the body pool versus time.
- iv. There are two ways in which volume  $V_2$  can behave quasistatically. Identify in a physical sense, these two different ways. Indicate, for each, the parameter relationships which are necessary to achieve that quasistatic behavior.
- v. Repeat part i. for the situation in which the concentration of drug in the patch is, at equilibrium,  $k$  times that found in the dermal volume and the body pool. Such a situation occurs if the affinity of the drug for the solvent in the patch

is  $k$  times higher than it is for the (presumably aqueous) medium of the dermal and body pool volumes.

2. A metabolite A is converted by an enzyme E to a product B. At equilibrium, the ratio  $b/a$  is  $K$ . (Lower-case letters represent the concentrations of the substances involved in the reaction.) Assume quasistatic behavior for all intermediates. Assume that the maximum rate of conversion of A to B is given by  $k_0e_0$  where  $e_0$  is the total concentration of enzyme.

- a. Solve, using a process that can be followed for grading, for the rate of conversion of A to B when  $a$ ,  $b$  and  $e_0$ , are known.
- b. Demonstrate that your result will give the correct end-result for the concentrations of A and B when enzyme is used to conduct this reaction in a closed volume where the original concentrations of A and B are  $a(0)$  and  $b(0)$ .
- c. Write (do not solve) the equation(s) that give the steady-state concentrations of A and B in a volume containing enzyme at a concentration  $e_0$  when that volume is fed with a stream flowing at the rate  $q$ , and containing only A at a concentration  $a_f$ .
- d. For a value of  $K$  equal to 2.0, sketch  $b$  (y-axis) vs.  $q$  (x-axis). Estimate the algebraic value of  $q$  for which  $b$  changes most with  $q$  in terms of other quantities specified for this problem. This is an "interesting" value of  $q$ . Explain why this value is interesting even if you cannot make the algebraic estimate

3. Blood flows down the outside of a vertical rod of diameter  $R_1$ . The outer diameter of the flowing annulus of blood is  $R_2$ . Blood at this diameter is in contact with air, which may be assumed to have a viscosity of zero. Designating Newtonian viscosity and mass density as  $\mu$  and  $\rho$ , respectively obtain expressions for:

- a. The shear stress distribution  $\tau_{rz}(r)$ , with  $R_1 < r < R_2$ .
- b. The velocity distribution  $v_z(r)$  over the same range of  $r$ .
- c. The volumetric flow rate of blood.

4. In this problem you may use the macroscopic equations for steady-state electrodiffusion through a homogeneous membrane:

$$J_n = G_n (V_m - V_n); \quad V_n = \frac{RT}{z_n F} \ln \left( \frac{c_n^o}{c_n^i} \right); \quad V_m = \mathcal{Y}_{in} - \mathcal{Y}_{out}$$

and  $J_n$  is taken to be positive when the flux is outward. At a temperature of 24 C,  $V_n$  can

be expressed as  $\frac{59}{z_n} \log_{10} \left( \frac{c_n^o}{c_n^i} \right) [mV]$

a. A cell exhibits a steady potential difference of -86 mV with respect to the fluid surrounding it. Compositions, in mmol/L, of the following ions are also steady in time, both within the cell and in the medium, as shown:

Ion	Intracellular	Extracellular
Sodium	15	0.1
Potassium	28.7	1.0
Chloride	38	1.3

There is no coupling of either active or passive transport of the ions through the membrane. For each ion, determine if that ion is transported across the membrane by an active transport mechanism and, if so, in which direction across the membrane (inward or outward) it is transported.

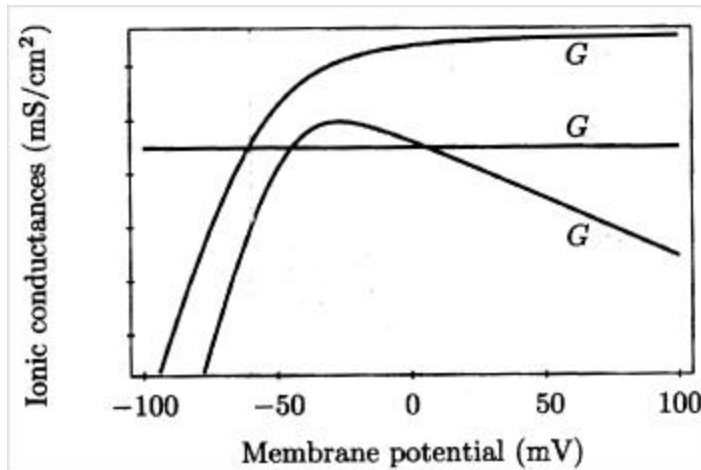
b. The quantity  $z_n F (\mathcal{Y}_i - \mathcal{Y}_o)$  represents the stored electrostatic energy per mole at the inside of the membrane minus that at the outside. Electrodiffusive equilibrium is defined by the equality of this term to another term. Write the other term and explain in a few words what it represents.

5. The following table gives the resting values of ionic conductances and concentrations in the giant axon of the squid:

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

a. Calculate the resting potential for the axon.

b. Sketch the following drawing in your answer book (question sheets will not be examined). Indicate by a vertical line on your sketch the location of the normal resting potential and identify which curve corresponds to  $G_K$ , which to  $G_L$ , and which to  $G_{Na}$ .



6. The propagation of action potentials occurs in 'large' cells. You are asked to write explain the essential role of three parts of the theory of how these potential are propagated, within the indicated word limits.

- a. (50 words) What is the essential fact established by the core conductor equation? This equation is proposed for a simpler situation than that treated in the whole Hodgkin-Huxley model. Is the essential fact still strictly observed in the whole model?
- b. (50 words) What is the essential phenomenon, beyond what appears in the core conductor model, that is introduced by the cable equation? What are the principal factors (in words, not symbols) that determine the rate of propagation of an action potential according to this equation?
- c. The full Hodgkin-Huxley model introduces non-linearities in the form of conductances that are not constant. Carefully answer, in order, labeled, the following questions:
  - i. Which conductances are varied?
  - ii. What variable(s) determine the value of these conductances?
  - iii. In not more than 100 words describe how the Hodgkin-Huxley model 'works' to allow the propagation of an action potential. How do the non-linearities interact with the phenomena demonstrated by the core conductor and cable equations to yield the observed propagation?

-end-