York University BPHS 3090 (Winter 2015) - HW 3

Due Date: Feb. 4, 2015 9:30 AM

Questions

1. A cell in a bath is subjected to changes in extracellular osmolarity the flux of the volume can be described by the equation $\phi = \mathcal{L}_V RT(C^o_\Sigma - C^i_\Sigma)$. A step change in the osmolarity of the bath produces a change in the normalized volume of the cell shown in the waveform $v(t)$ depicted below in Figure 1a. In Figure 1b, there are twelve possible normalized concentration waveforms $c(t)$.

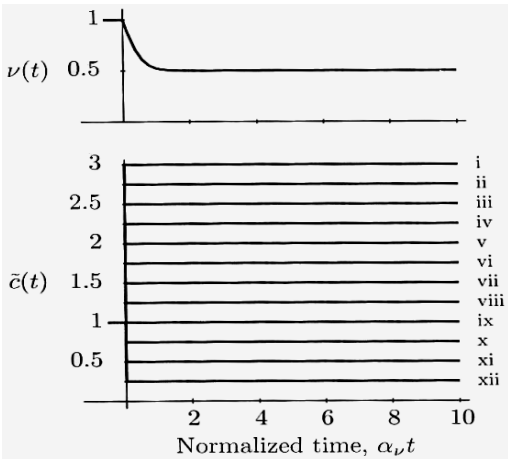


Figure 1a & b: Change in normalized volume (upper panel) in response to a change in normalized external solute concentration (lower panel) (Exercise 4.18). The normalized volume is $\nu(t) = \mathcal{V}^i(t)/\mathcal{V}^{in}$, where $\mathcal{V}^i(t)$ and $\mathcal{V}^{in}$ are the cell water volume and its isotonic value. The normalized extracellular concentration is $\tilde{c}(t) = C^o_\Sigma(t)/C^{on}_\Sigma$, where $C^o_\Sigma(t)$ and C^{on}_Σ are the total extracellular solute concentration and its isotonic value.

Assume that all solutes are impermeant and that the cell acts as an ideal osmometer such that $\mathcal{V}_c = \frac{N^i_\Sigma}{C^o_\Sigma} + \mathcal{V}'_c$, where $\mathcal{V}'_c$ represents the osmotically inactive portion of the total cell volume $\mathcal{V}_c$; it can be assumed that the active portion of the total cell volume is greater than the osmotically inactive portion.

a) From Figure 1b, which of the twelve concentration waveforms can describe the change of the normalized volume waveform in Figure 1a? Explain the choices made and the assumptions involved.

b) If the temperature of the cell and bath system was decreased by 10° C, determine mathematically if the initial slope of the normalized volume, $\frac{dv(t)}{dt}$ at $t = 0^+$, and the final value of the normalized volume $v(\infty)$ are either increasing, staying the same, or decreasing; ensure to explain the reasoning behind the solution

2. A spherical cell is subjected to four different aqueous solutions of impermeant solutes and its equilibrium radius is measured as shown in Figure 1. The isotonic radius is 80 μm.

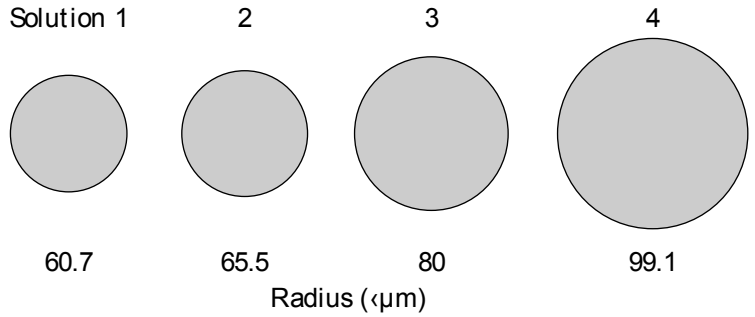


Figure 1: A spherical cell placed in four different solutions of impermeant solutes. The circles represent cross-sectional diagrams of the cell, and the numbers below the circles indicate the measured radii.

The four solutions are: 150 mmol/L NaCl, 200 mmol/L $CaCl_2$, 800 mmol/L sucrose, and 150 mmol/L xylose. The latter two solutes are sugars. You may assume that the intracellular quantity of solute does not change during these measurements.

a) Determine the compositions of Solutions 1-4

b) Find the total quantity of intracellular solute.

c) What fraction of the isotonic volume of the cell is due to osmotically active water?

3. Consider the simple, symmetric, four-state carrier model. For each of the following conditions, find $\mathfrak{N}_E^i, \mathfrak{N}_E^o, \mathfrak{N}_{ES}^i, \mathfrak{N}_{ES}^o,$ and ϕ_S. Explain the physical significance of each of your answers.

a) $\alpha = 0$

b) $\beta = 0$

c) $K = 0$

4. For each of the following statements indicate whether it is true or false and briefly explain your reasons.

a) Insulin regulates the transmembrane transport of glucose in erythrocytes.

b) Insulin regulates the transmembrane transport of glucose in skeletal muscle cells.

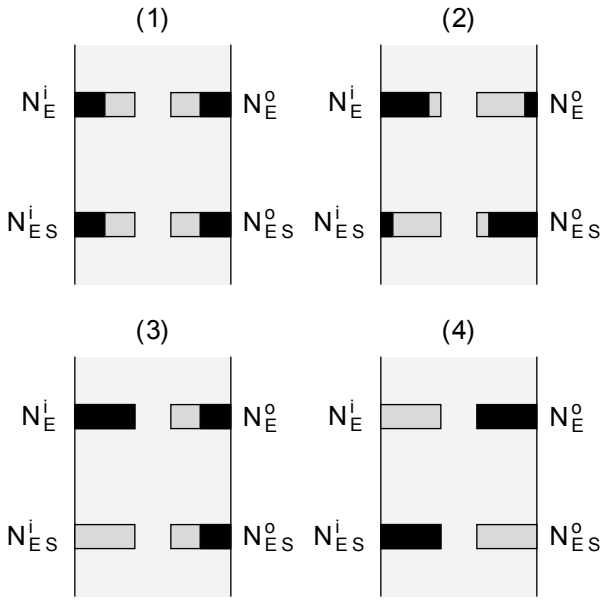
c) During fasting the liver secretes glucose into the circulatory system.

d) During fasting muscle cells secrete glucose into the circulatory system.

e) Insulin acts on insulin-dependent cells by increasing the glucose transport through individual glucose transporters.

f) Insulin is secreted into the circulatory system by the -cells in the islets of Langerhans of the pancreas.

5. Solute *S* is transported through a membrane by the simple, symmetric, four-state carrier model. The enzyme can be found in four different states: unbound to solute at either the inside or outside faces of the membrane or bound to solute at either face. The steady-state densities of enzymes in these four states are $\mathfrak{N}_E^i, \mathfrak{N}_E^o, \mathfrak{N}_{ES}^i,$ and $\mathfrak{N}_{ES}^o$ mol/cm^2; the total enzyme density is $\mathfrak{N}_{ET} = \mathfrak{N}_E^i + \mathfrak{N}_E^o + \mathfrak{N}_{ES}^i + \mathfrak{N}_{ES}^o$. The state of the enzyme system is depicted schematically for four different conditions in the following figure.



The length of the darker part of the box representing each state is proportional to the fraction of enzyme in that state.

Answer question a-h and give brief explanations for your choice.

a) **True or False:** For all four conditions (1)-(4), $\phi_E = -\phi_{ES}$

b) **Multiple Choice:** Which of the following statements applies to (1):

i) $c_s^i > K$
ii) $c_s^i = K$
iii) $c_s^i < K$

c) **True or False:** The transition from (1) to (3) can be achieved by changing c_s^i only.

d) **True or False:** In (2), $\phi_s > 0$

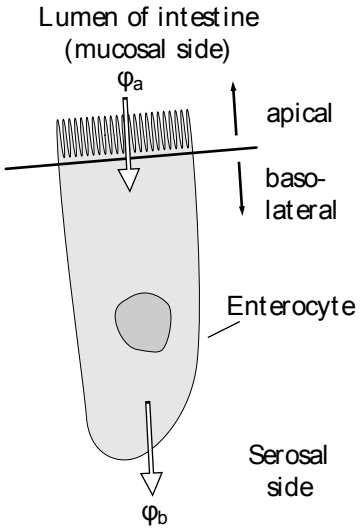
e) **True or False:** In (1), $\phi_s = 0$

f) **True or False:** In (3), $c_s^i = 0$

g) **True or False:** The transition from (1) to (3) can be achieved by changing *K* only.

h) For which of the conditions (1) to (4), is the magnitude of the flux of *S* equal to the maximum flux possible for any concentration of *S*?

6. Glucose is transported into the body by enterocytes, which are absorptive epithelial cells that line the small intestine. The following figure shows a schematic representation of an enterocyte.



The cell membrane has an apical part that separates the interior of the cell from the lumen of the intestine and a basal part that separates the interior of the cell from extracellular space on the serosal side. ϕ_a represents the flux of glucose from the lumen of the intestine through the apical part of the cell membrane and into the cell. ϕ_b represents the flux of glucose from the cell through the basal part of the cell membrane and into the extracellular serosal space.

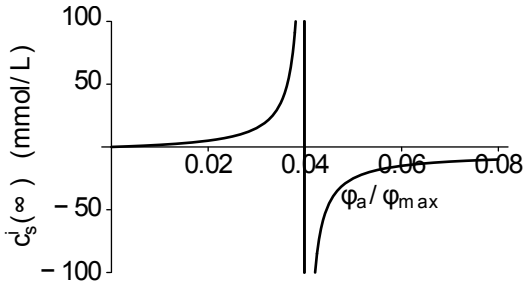
Transport through the apical part of the cell membrane, which faces the lumen of the small intestine, is coupled to the transport of Na^+. Transport through the basolateral membrane of the cell, which faces the serosal side, is via a glucose carrier. Assume that the glucose carrier in the basolateral part of the cell can be represented by the simple, symmetric four-state carrier model. Let K represent the dissociation constant for the binding of glucose to the carrier, and let ϕ_{max} represent the maximum flux through the carriers in the basolateral part of the membrane. Let A_a and A_b represent the areas of the apical and basolateral membranes, respectively. Let V represent the volume of the cell. Assume that $A_a, A_b,$ and V are constant with respect to time. Assume that glucose is not produced, consumed, or bound by any intracellular mechanism.

a) In the steady-state the concentration of glucose in the cell is constant. Determine a relation that ϕ_a and ϕ_b must satisfy in the steady state.

b) Determine a relation between ϕ_b and c_s^i and c_s^o dictated by the transport properties of the basolateral membrane, where c_s^o is the extracellular concentration of glucose on the serosal side of the membrane.

c) Assume that the flux ϕ_a from the lumen of the intestine into the cell is constant and that the concentration of glucose on the serosal side is zero, $c_s^o = 0$. Using the results of parts a) and b), determine an expression for $c_s^i(\infty)$ in terms of $\phi_a, \phi_{max}, K, A_a,$ and A_b.

d) $c_s^i(\infty)$ is plotted versus ϕ_a/ϕ_{max} for $c_s^o = 0, K = 5$ mmol/L and for $A_a/A_b = 25$ in the following figure.

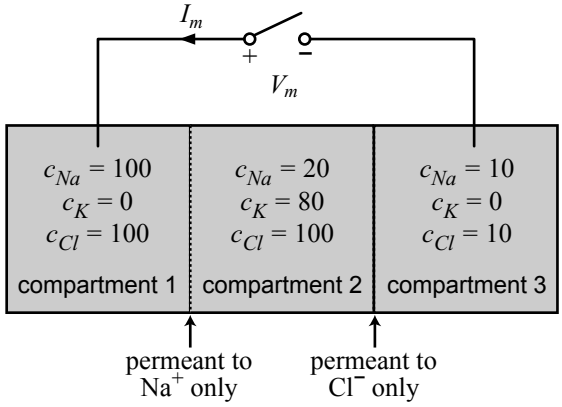


i) Explain the *physical significance* of the value of $c_s^i(\infty)$ when $\phi_a = 0$.

ii) Note from the figure that $c_s^i(\infty)$ increases rapidly as ϕ_a/ϕ_{max} increases from 0 to 0.04. Give a *physical interpretation* for this result.

iii) For $\phi_a/\phi_{max} > 0.04, c_s^i(\infty) < 0$. What is the *physical significance* of this result?

7. Three compartments are separated from each other by semi-permeable membranes, as illustrated in the following figure.



Each compartment contains well-stirred solutions of sodium, potassium, and chloride ions, with concentrations indicated in the figure (in mmol/L). The membrane between compartment 1 and 2 is permeant to sodium ions only, and its specific electrical conductivity G_{Na} is 5 mS/cm^2. The membrane between compartment 2 and 3 is permeant to chloride ions only, and its specific electrical conductivity G_{Cl} is 2 mS/cm^2. Both membranes have areas $A = 10$ cm^2.The temperature *T* is such that *RT /(F log e)* = 60 mV.

a) Sketch an electrical circuit that represents the steady-state relation between current and voltage for the three compartments. Label the nodes that correspond to compartments 1, 2, and 3. Include the switch in your sketch. Label I_m, V_m and the conductances.

b) Let V_1 and V_2 represent the steady-state potentials in compartments 1 and 2 with reference to compartment 3 when the switch is open. Calculate numerical values for V_1 and V_2

c) Compute the steady-state value of the current I_m when the switch is closed.

8. In biochemistry, Michaelis–Menten kinetics, named after biochemist Leonor Michaelis and physician Maud Menten, is one of most common models used to describe enzyme kinetics. The model is in the form of an equation describing the rate of enzymatic reactions by relating reaction rate to the concentration of a substrate S.

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} E + P$$

a) Determine the differential equations associated with the changes in enzyme and enzyme substrate concentrations; ensure to explain all assumptions made, and to list the units associated with each term in the differential equation

b) Two common assumptions made are that the substrate concentration is much greater in comparison to that of the enzyme, and that the E + S to ES equilibrium is established before the reaction is being watched (implying that the ES concentration is constant). Given these assumptions, solve the equation for the ES complex concentration; what does the numerator and denominator of the [ES] equation represent?

c) The Michaelis-Menton equation must be modified when there are inhibitors of the enzymes added to the reaction of the substrate. These interactions can be either reversible or irreversible. List the three types of inhibitor types and, assuming reversible reactions, create a kinetic scheme (similar to the figure above) for each reversible enzyme inhibitor reaction (ensure that the appropriate rate constants are added and described where necessary)

9. The following is going to require the Macroscopic Diffusion Module of SoftCell.

a. With the module lauched, ensure the impulse profile (indicated by an up arrow) is pressed on the "MD Initial concentration profile" panel. Next click the "Parameters" button and ensure the diffusion constant is 10^{-5} and the impulse has an area of 100 μmol/cm^2 and positioned at 0.5 cm. Next, change "Marker 1" position to 0.3 cm and "Marker 2" to 0.7 cm and hit the "Update" button, the markers will appear as green triangles along the position axis. Click the "1-step" button on the "Control" panel and view the output on the "Plots vs position".

i. What is the shape of new concentration and why?

ii. Reset the concentration profile and change the "# steps" to 100. Now click the start button and look at the "Plots vs time" graph. Make the flux and concentration profiles for both markers visible. Noting the symmetry of the marker position, is the concentration profiles for each marker what is expected? Are they identical? Now look at the flux for each marker, are they identical to each other? If not, explain why they are not?

b. Now change the profile to a sinusoid and make sure to click the ”Update” button. Note on the ”Plots vs position” plot make visible the concentration and flux profiles. What shape is the flux’s profile and why?

c. Next we will superimpose sinusoids. Click the ”Parameters” tab and change the first sinusoid to 1 cycles/sec and amplitude to 1, and for the second sinusoid make the frequency 10 cycles/sec with an amplitude of 1 (make sure to hit the update button when done). Run the simulation for 100 steps.

i. Which sinusoid appears to attentuate first? Why?

ii. Can you think of a way to roughly approximate the ratio of the amplitude attenuation of the two frequencies? Run a simulation to test your approximation (make sure you record what you did and why).