

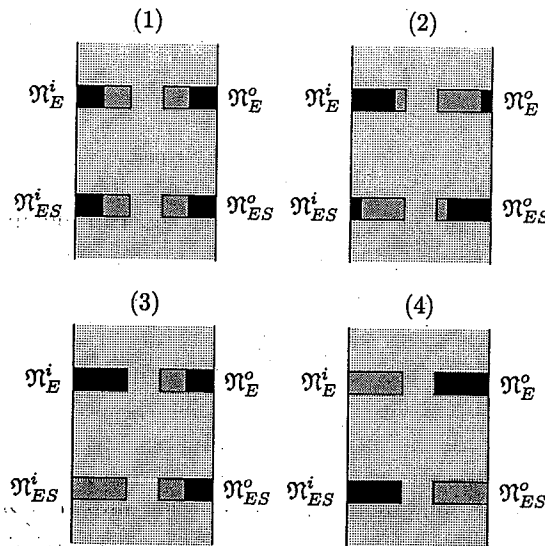
10/4/06

Recitation 8

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Quantitative Physiology: Cells and Tissues
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Exercise pr1.6.17. 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 \mathcal{N}_E^i , \mathcal{N}_E^o , \mathcal{N}_{ES}^i , and \mathcal{N}_{ES}^o mol/cm²; the total enzyme density is $\mathcal{N}_{ET} = \mathcal{N}_E^i + \mathcal{N}_E^o + \mathcal{N}_{ES}^i + \mathcal{N}_{ES}^o$. The state of the enzyme system is depicted schematically for four different conditions in the following figure.



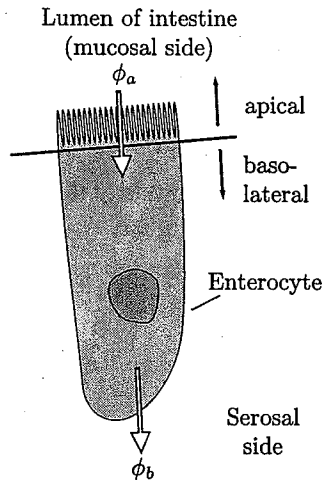
The length of the darker part of the box representing each state is proportional to the fraction of enzyme in that state.

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 ?

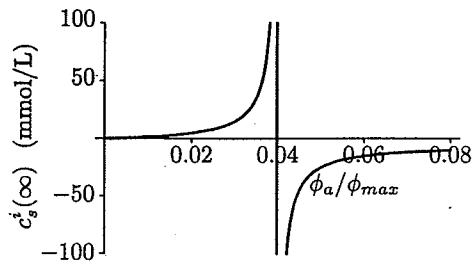
Exercise pr1.6.14. Glucose is transported “into” the body by enterocytes, which are absorptive epithelial cells that line the small intestine. The following figure shows a schematic representation of an enterocyte.



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.

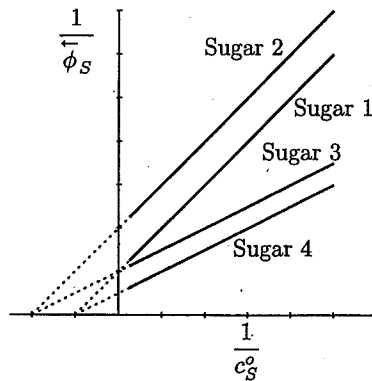
Transport through the apical part of the cell membrane, which faces the lumen of the small intestine, is coupled to the transport of Na^+ . Transport through the basolateral membrane of the cell, which faces the serosal side, is via a glucose carrier. Assume that the glucose carrier in the basolateral 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 \mathcal{V} represent the volume of the cell. Assume that A_a , A_b , and \mathcal{V} are constant with respect to time. Assume that glucose is not produced, consumed, or bound by any intracellular mechanism.

- 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.
- 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.
- 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 ϕ_a , ϕ_{max} , K , A_a , and A_b .
- $c_s^i(\infty)$ is plotted versus ϕ_a/ϕ_{max} for $c_s^o = 0$, $K = 5 \text{ mmol/L}$ 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?

Exercise pr1.6.3. The unidirectional transport of sugar molecules into red blood cells of badgers, $\overleftarrow{\phi}_s$, is measured by means of radioactive tracers as a function of the external concentration of the sugar molecules, c_s^o . The results for 4 different types of sugar molecules are plotted in Figure 1. It



Sugar Species	K (mmol/L)	$(\overleftarrow{\phi}_s)_{max}$ ($\mu\text{mol}/\text{cm}^2\cdot\text{s}$)
A	20	20
B	20	80
C	40	40
D	40	80
E	40	40
F	20	10
G	10	40
H	20	5
I	10	20
1	20	40

Table 1: Parameters of carrier model.

Figure 1: Flux versus concentration in reciprocal coordinates. The straight lines were fit to the measurements (not shown).

is known that the transport of 10 types of sugar molecules through badger red-cell membranes can be described by a simple, symmetric, four-state carrier model. The values for the parameters K and $(\overleftarrow{\phi}_s)_{max}$ for these sugars are given in Table 1 including the value for Sugar 1. Determine the identity of the three measured sugars (2,3 and 4) among those (A-I) in the table.

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Exercise pr1.6.17.

- a. **True.** This is a basic assumption of the simple, symmetric four-state carrier model and guarantees that the carrier does not leave the membrane.
- b. **Ans. ii.** Note $K = c_S^i n_E^i / n_{ES}^i$. With $n_E^i = n_{ES}^i$ (as shown) $K = c_S^i$.
- c. **True.** States E^o and ES^o do not change. The change from state (1) to state (3) could have been achieved by changing c_S^i from $c_S^i = K$ as in (1) to $c_S^i = 0$ as in (3).
- d. **False.** Note that $n_{ES}^i < n_{ES}^o$ which implies that $n_E^i / n_{ES}^i > 1$ which implies that $K / c_S^i > 1$ which implies that $c_S^i < K$. Also $n_{ES}^o > n_E^o$, so that $c_S^o > K$ which implies that $c_S^o > c_S^i$ which implies that $\phi_S < 0$.
- e. **True.** $n_E^i = n_{ES}^i$ which implies that $c_S^i = K$. $n_E^o = n_{ES}^o$ which implies that $c_S^o = K$. Therefore, $c_S^i = c_S^o$ and $\phi_S = 0$.
- f. **True.** $n_{ES}^i = 0$ and $n_E^i > 0$ implies that $c_A^i n_E^i / K = 0$ which implies that for K bounded $c_A^i = 0$.
- g. **False.** Changing K changes both $c_S^i n_E^i / n_{ES}^i$ and $c_S^o n_E^o / n_{ES}^o$. But n_E^o / n_{ES}^o doesn't change.
- h. **Ans. (4).** $n_E^i = 0$ implies that $c_S^i \gg K$, and $n_{ES}^o = 0$ implies that $c_S^o = 0$. In general,

$$\phi_S = (\phi_S)_{max} \left(\frac{c_S^i}{c_S^i + K} - \frac{c_S^o}{c_S^o + K} \right).$$

The first term is maximized when $c_S^i \gg K$ and the second term is minimized when $c_S^o = 0$. For these conditions, $\phi_S = (\phi_S)_{max}$.

Exercise pr1.6.14.

- a. If the concentration of glucose in the enterocyte is constant then the net rate of influx of glucose must be zero. Therefore, $A_a\phi_a = A_b\phi_b$.
- b. Since the transport of glucose through the basolateral membrane can be represented by a simple, symmetric, four-state carrier model, the relation of efflux to concentration is

$$\phi_b = \phi_{max} \left(\frac{c_s^i}{c_s^i + K} - \frac{c_s^o}{c_s^o + K} \right)$$

- c. For $c_s^o = 0$, combining expressions yields

$$A_a\phi_a = A_b\phi_{max} \left(\frac{c_s^i}{c_s^i + K} \right)$$

To solve for c_s^i , it is easiest to divide both sides of the equation by $A_b\phi_{max}$, invert both sides of the equation and solve for $1/c_s^i$ and then take the reciprocal to obtain

$$c_s^i = K \frac{(A_a\phi_a/A_b\phi_{max})}{1 - (A_a\phi_a/A_b\phi_{max})}$$

- d.
 - i. Note when $\phi_a = 0$, $c_s^i(\infty) = 0$. This is apparent from the results of part c and is consistent with the plot shown in the problem. The physical explanation is that when the apical flux is zero, the basolateral flux is zero. Hence, for zero glucose flux through the basolateral membrane, the intracellular concentration must equal the extracellular concentration of glucose which is zero.
 - ii. In steady state, as the total rate of influx of glucose in the apical region $A_a\phi_a$ increases, the efflux through the basolateral region increases to equal the influx. A higher efflux in the basolateral membrane occurs at higher intracellular concentrations of glucose. As the efflux is driven toward saturation, a small increment in efflux requires a large increment in intracellular glucose concentration. A steady-state solution exists provided the influx through the apical membrane is less than the maximum efflux through the basolateral membrane $A_b\phi_{max}$.
 - iii. When the influx exceeds the maximum efflux, i.e., when $A_a\phi_a > A_b\phi_{max}$, the enterocyte can no longer transport glucose out of the basolateral membrane fast enough to match the rate of influx through the apical membrane. Hence, no steady state is possible for $\phi_a/\phi_{max} > A_b/A_a = 1/25$. This accounts for the unphysical result in this region, which is that the equations are satisfied only for negative values of the intracellular concentration.