Biophysics I (BPHS 4080)

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Website: http://www.yorku.ca/cberge/4080W2018.html

York University
Winter 2018
Lecture 9

Reference/Acknowledgement:
- TF Weiss (Cellular Biophysics)
- D Freeman

Simple, Symmetric Four-State Model

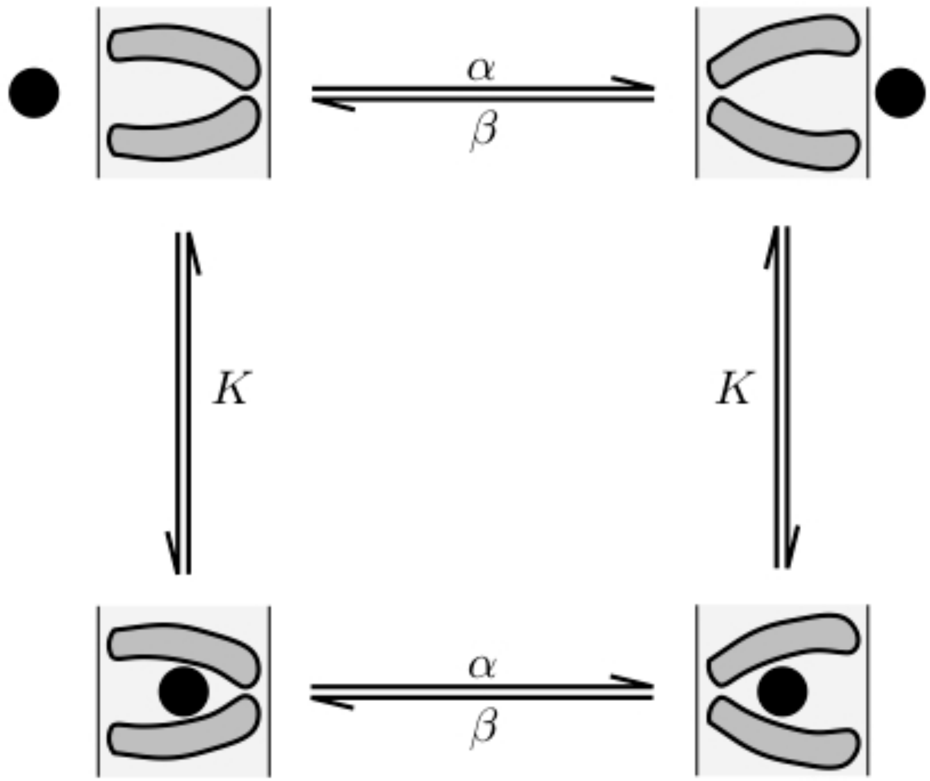


Figure 6.20

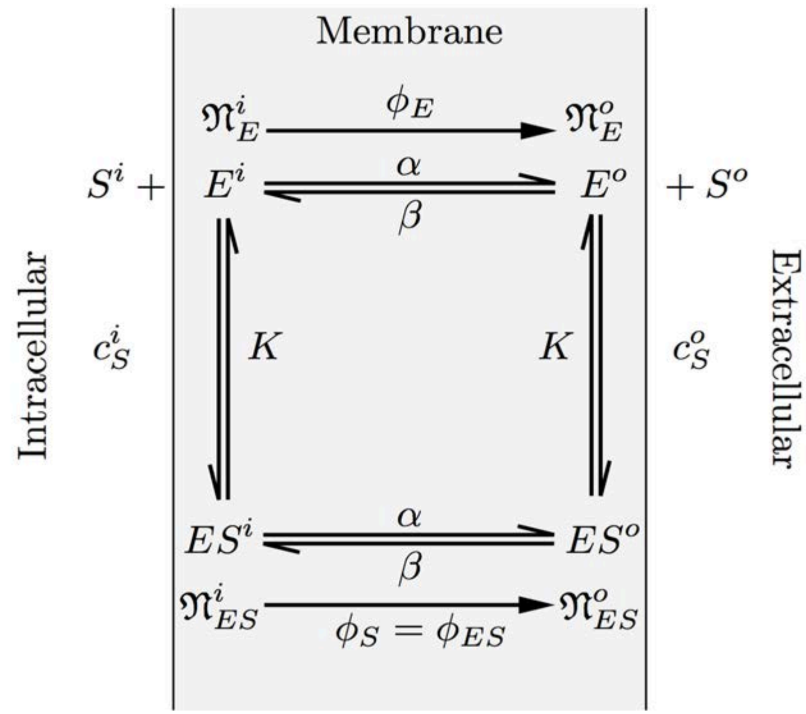


Figure 6.21

Assumption: Steady-state

(i.e., carrier densities are independent of time)

Simple, Symmetric Four-State Model

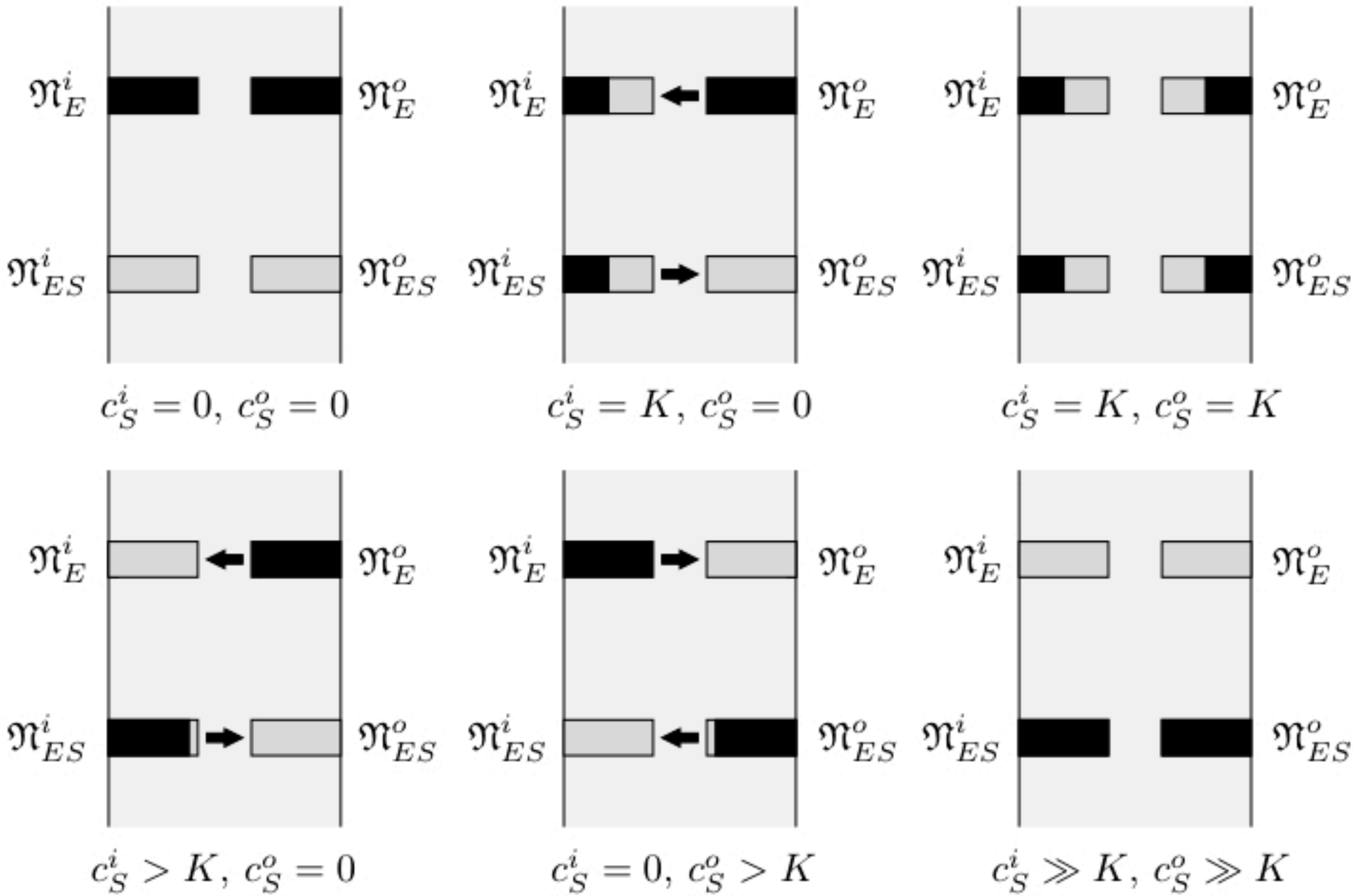


Figure 6.23

Simple, Symmetric Four-State Model

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

Total flux

$$(\phi_S)_{max} = \frac{\alpha\beta}{\alpha + \beta}\mathfrak{N}_{ET}$$

$$\overleftarrow{\phi}_S = (\phi_S)_{max}\left(\frac{c_S^o}{c_S^o + K}\right)$$

Influx

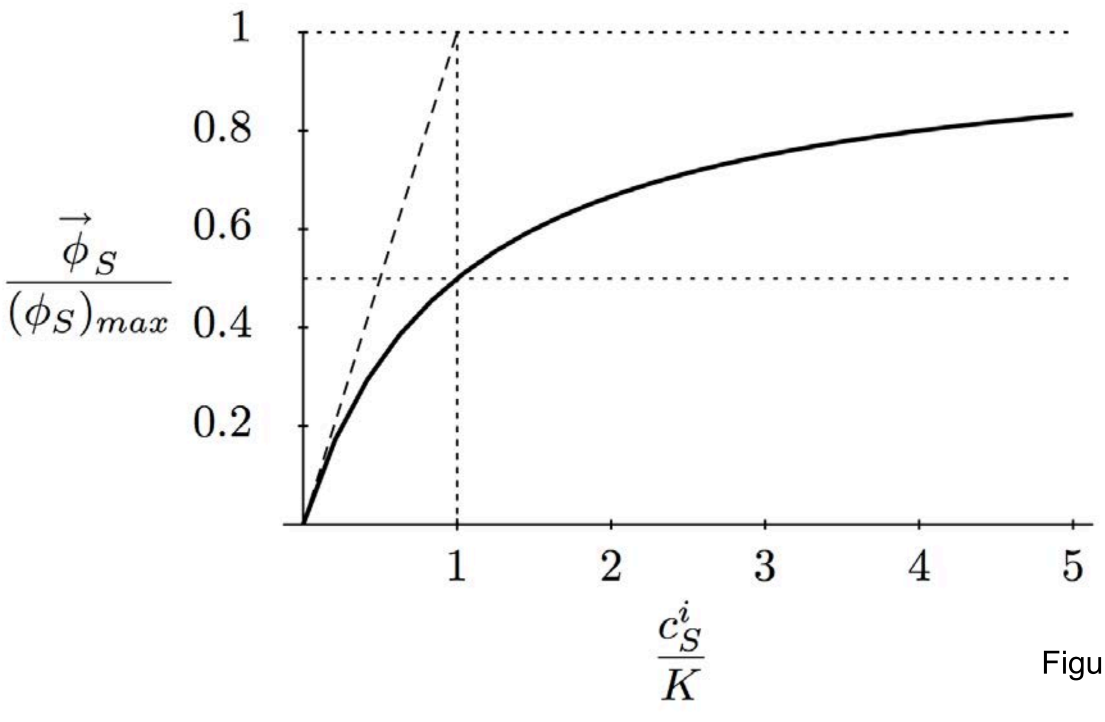


Figure 6.25

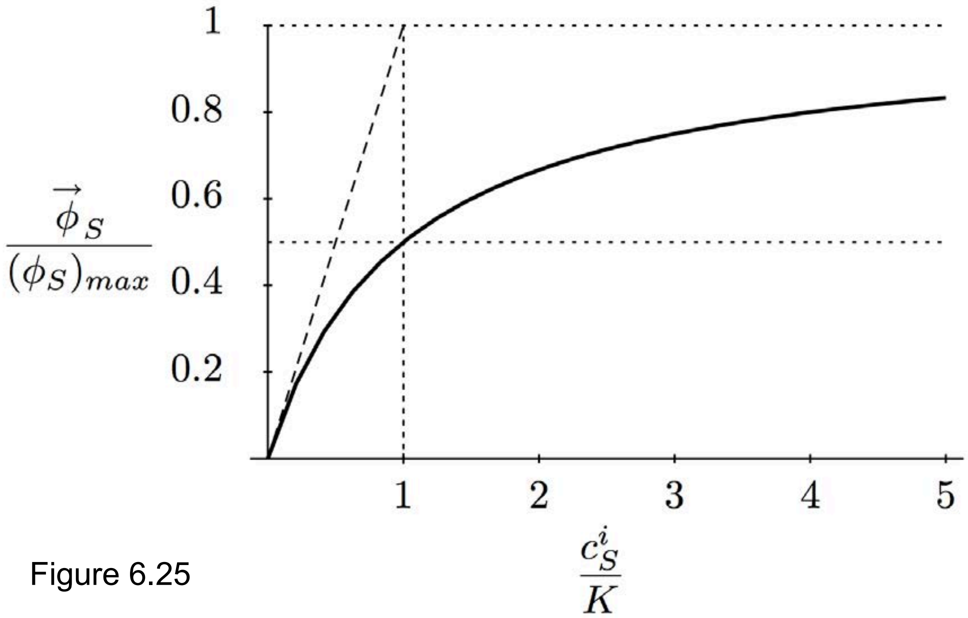


Figure 6.25

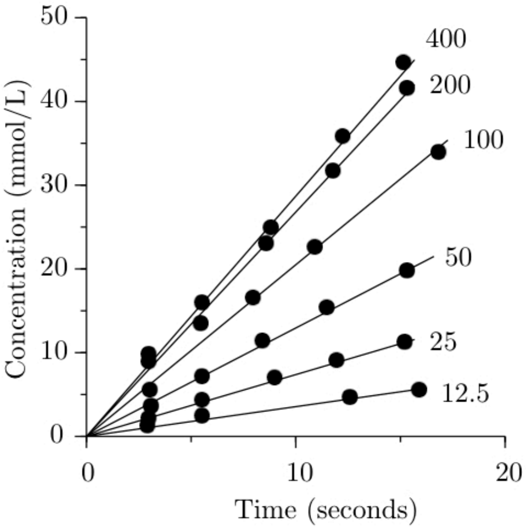


Figure 6.1

→ Carrier model qualitatively explains the data that D&D could not!

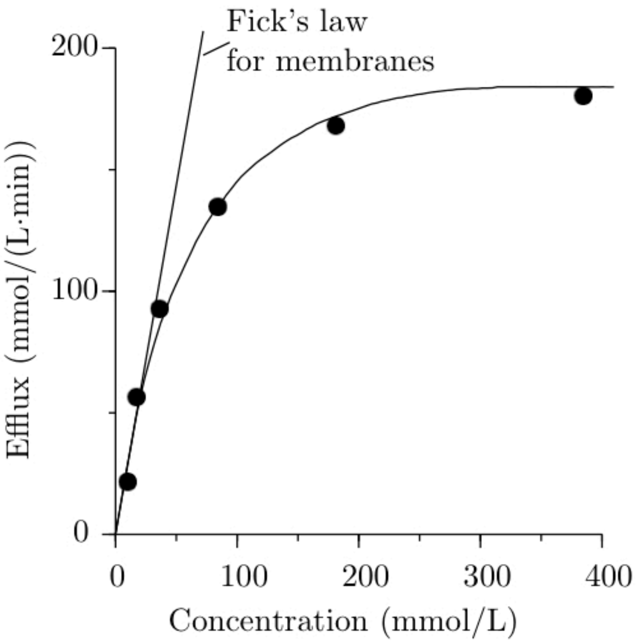


Figure 6.2

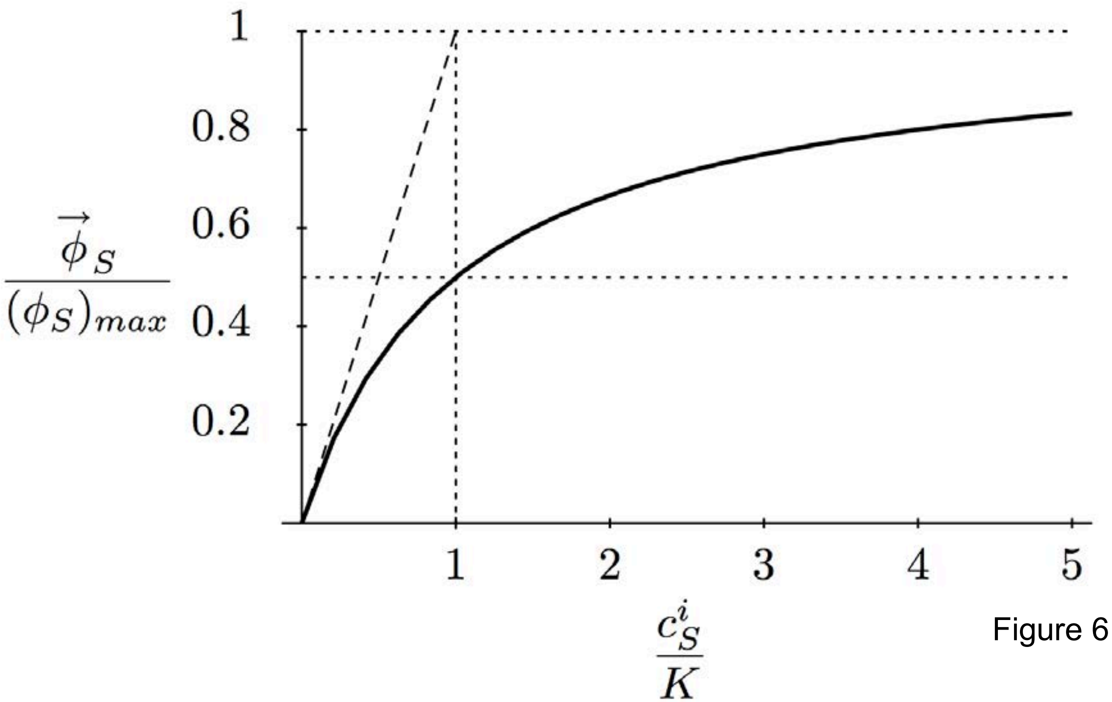


Figure 6.25

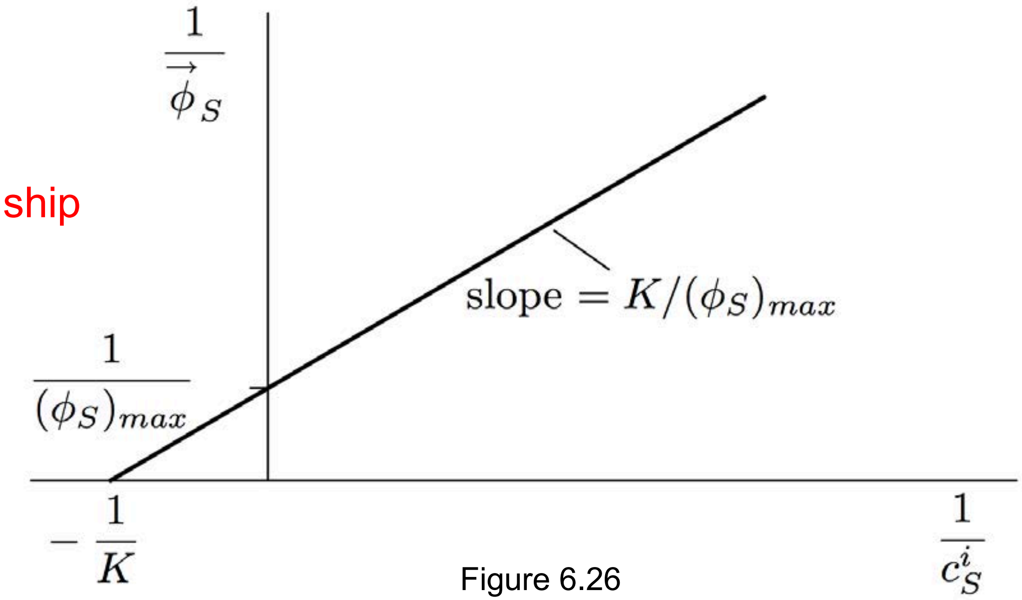


Figure 6.26

→ Linear way to plot nonlinear relationship

(e.g., Lineweaver-Burk plot)

Passive Transport: More than diffusion? → Carrier-Mediated Transport

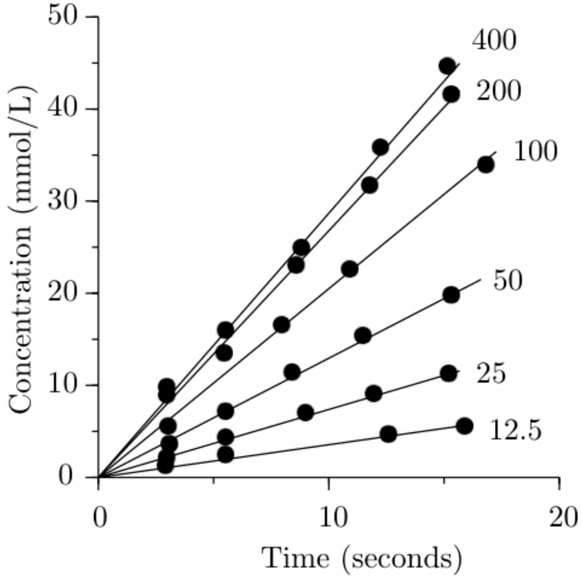


Figure 6.1

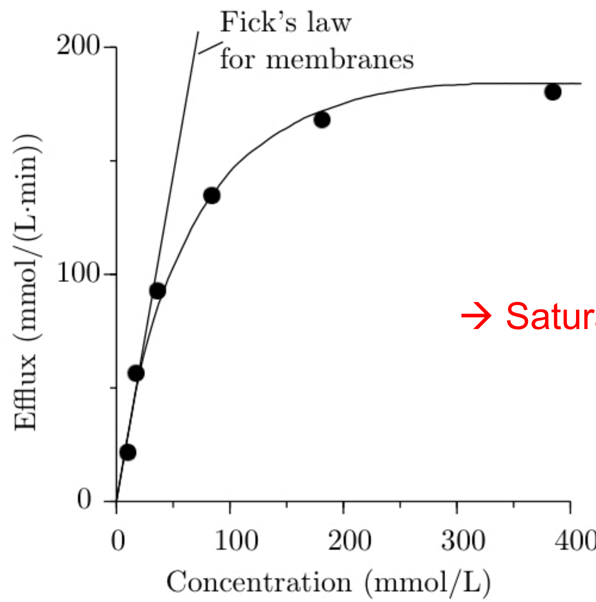
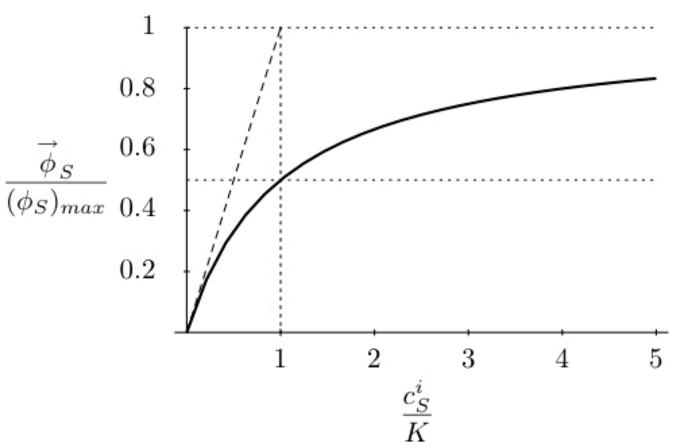
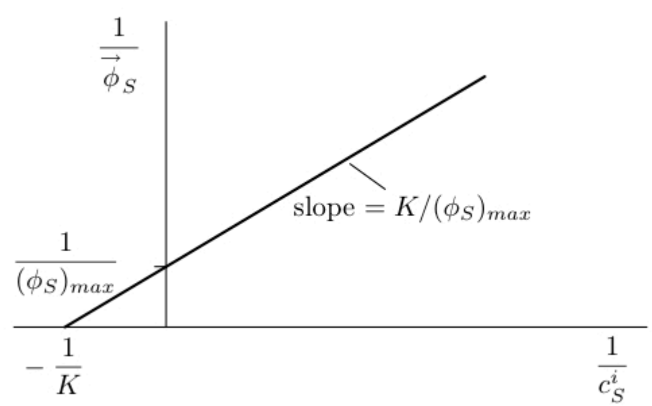


Figure 6.2

→ Saturation

Simple Symetric 4-State Carrier Model





Carrier-Mediated Transport: glucose transporter as example

Distinguishing characteristics of glucose transport:

- facilitated -- i.e., faster than dissolve and diffuse
- structure specific -- different rates for even closely related sugars
- passive -- given a single solute, flow is down concentration gradient
- transport saturates -- solute-solute interactions
- transport can be inhibited -- solute-other interactions
- pharmacology (cytochalasin B)
- hormonal control (insulin)

similar to water channels
(Hg, vasopressin)

<u>Glucose transport → Important to understand re insulin (e.g., diabetes)</u>

Insulin
backbone

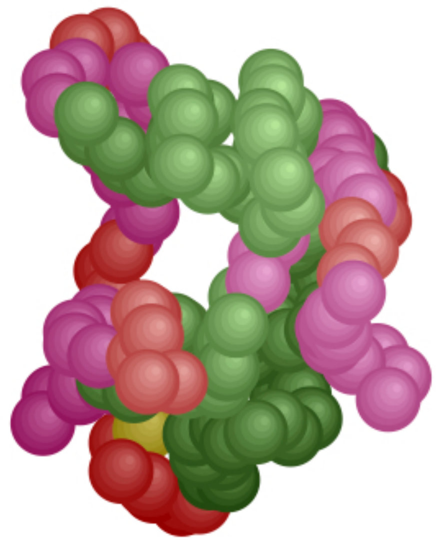


Figure 1.19

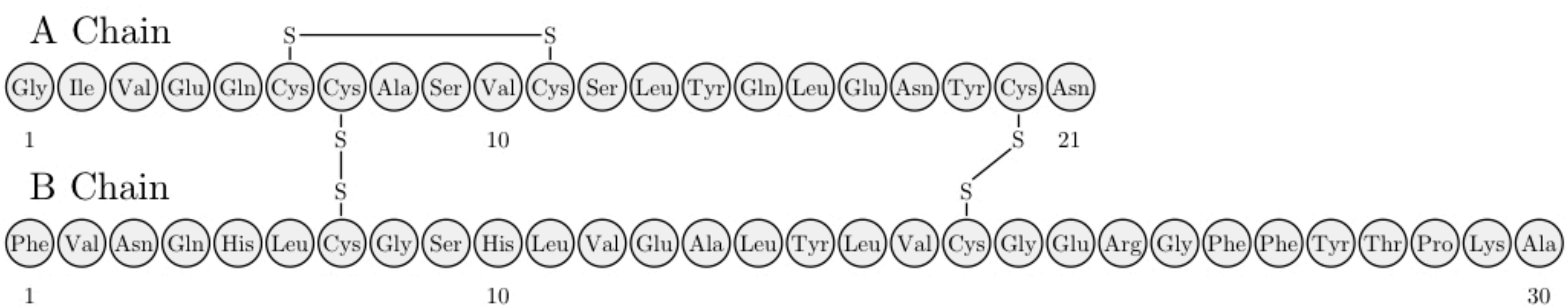


Figure 1.18

Distinguishing characteristics of glucose transport
– are they also characteristic of the simple symmetric 4-state model?

- facilitated: √ solute doesn't need to dissolve in membrane
- structure specific: √ parameters are structure specific
- passive: √ given a single solute, flow is down concentration gradient
- transport saturates: √ rectangular hyperbola
- transport can be inhibited: × need more states
- pharmacology (cytochalasin B): √ similar to inhibition
- hormonal control?

(Selective) Inhibition

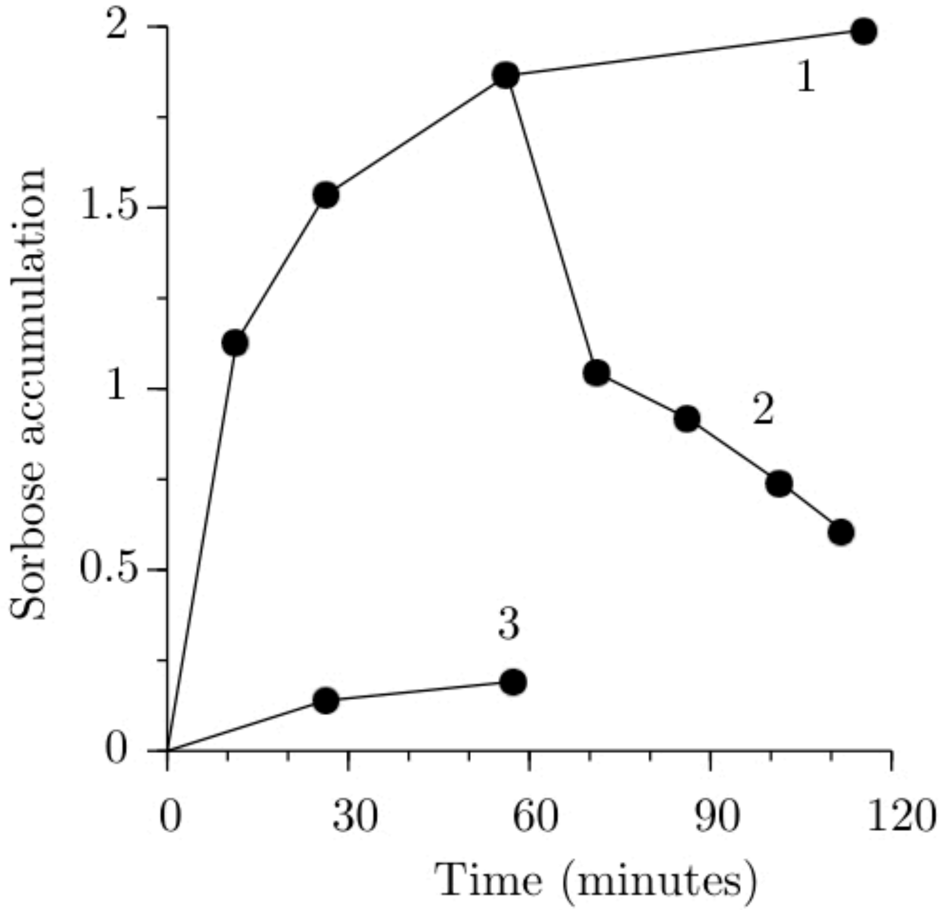


Figure 6.3

→ Glucose inhibits sorbose transport

<u>Two solutes</u>

(competition, both transported)

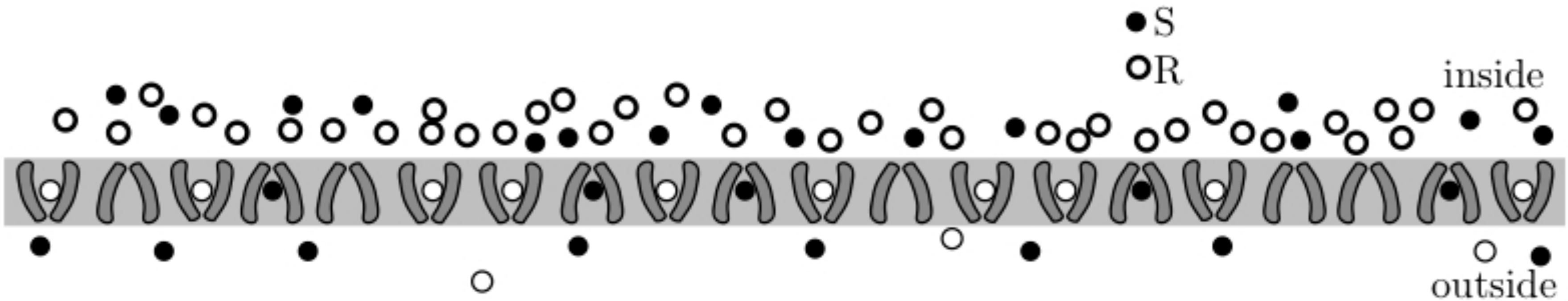


Figure 6.31

Two solutes
(competition, both transported)

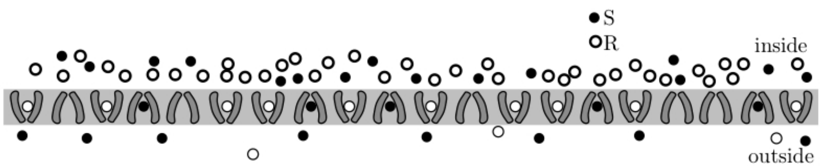
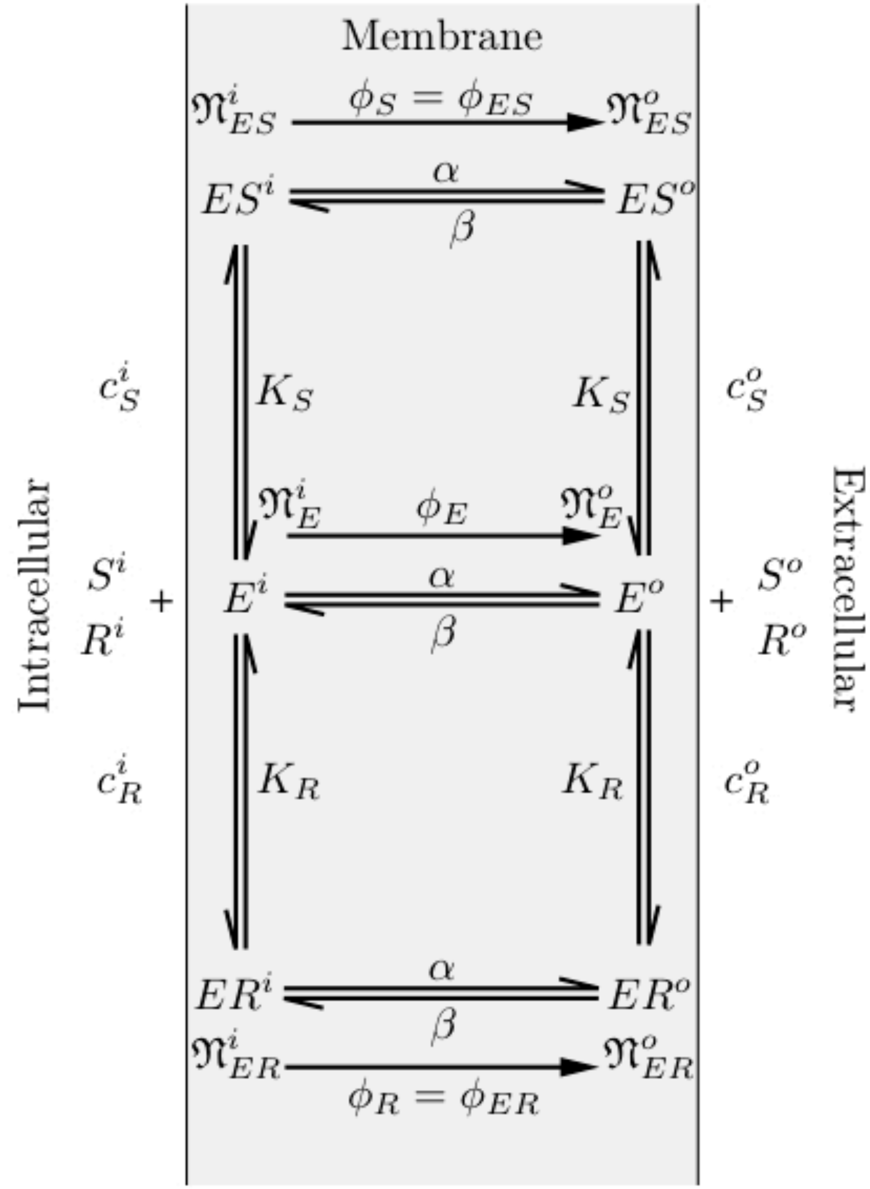
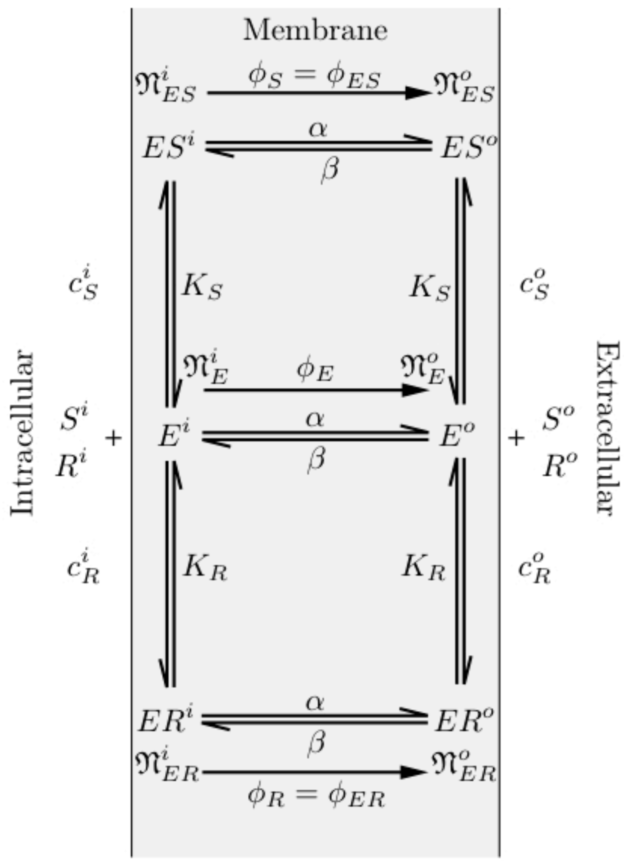
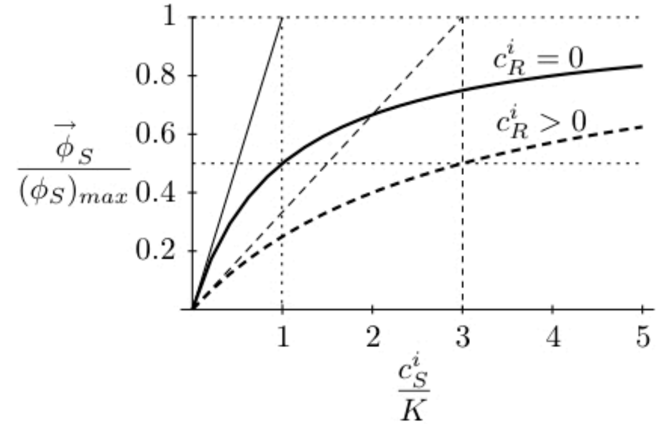


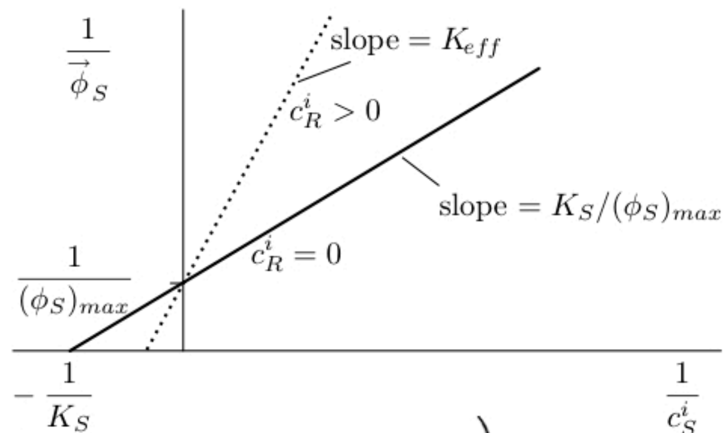
Figure 6.31



2 Solutes





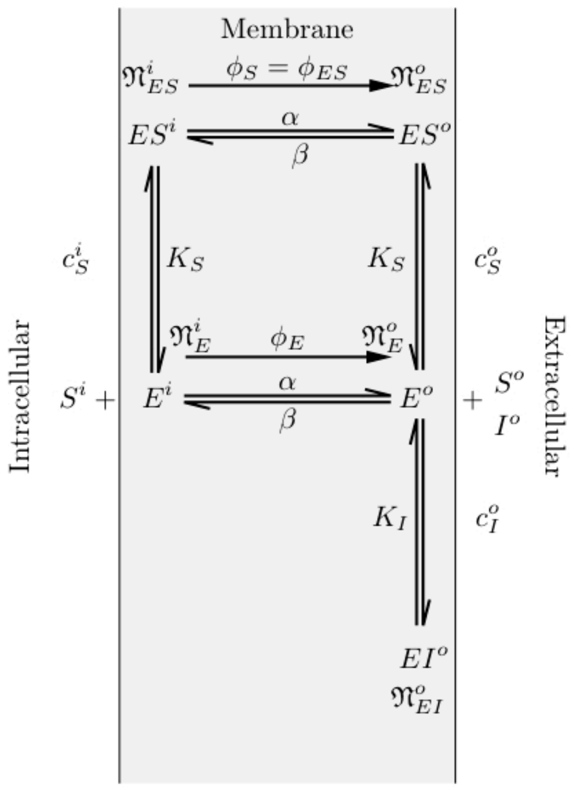


$$\phi_S = (\phi_S)_{max}\left(\frac{c^i_S}{c^i_S + K_S(1+\frac{c^i_R}{K_R})} - \frac{c^o_S}{c^o_S + K_S(1+\frac{c^o_R}{K_R})}\right)$$

$$\overleftarrow{\phi}_S = (\phi_S)_{max}\left(\frac{c^o_S}{c^o_S + K_S\left(1+\frac{c^o_R}{K_R}\right)}\right) = (\phi_S)_{max}\left(\frac{c^o_S}{c^o_S + K_{eff}}\right)$$

$$K_{eff} = K_S\left(1+\frac{c^o_R}{K_R}\right)$$

1 Solute + 1 Competitive Inhibitor

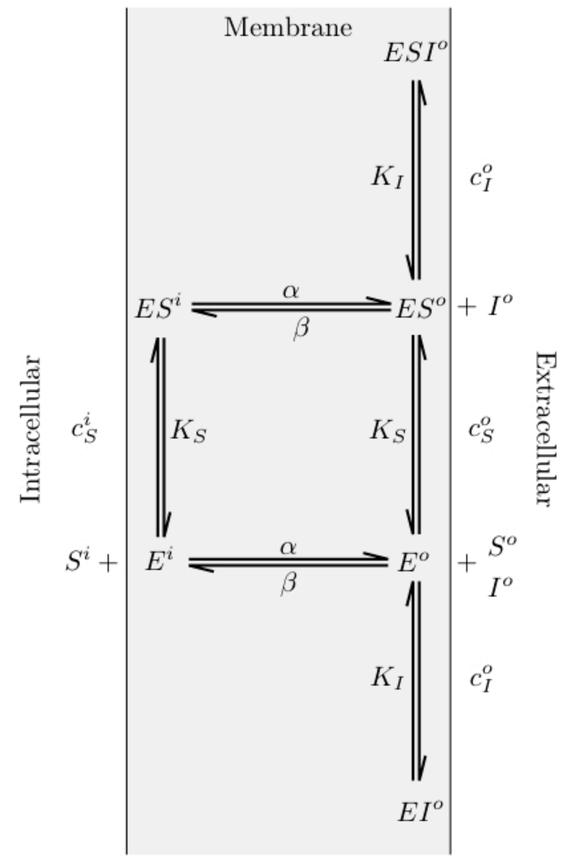


$$\overleftarrow{\phi}_S = (\phi_S)_{max}\left(\frac{c^o_S}{c^o_S + K_S\left(1 + \frac{\alpha}{\alpha+\beta}\frac{c^o_I}{K_I}\right)}\right)$$

$$\overleftarrow{\phi}_S = (\phi_S)_{max}\left(\frac{c^o_S}{c^o_S + K_{eff}}\right)$$

$$K_{eff} = K_S\left(1 + \frac{\alpha}{\alpha+\beta}\frac{c^o_I}{K_I}\right)$$

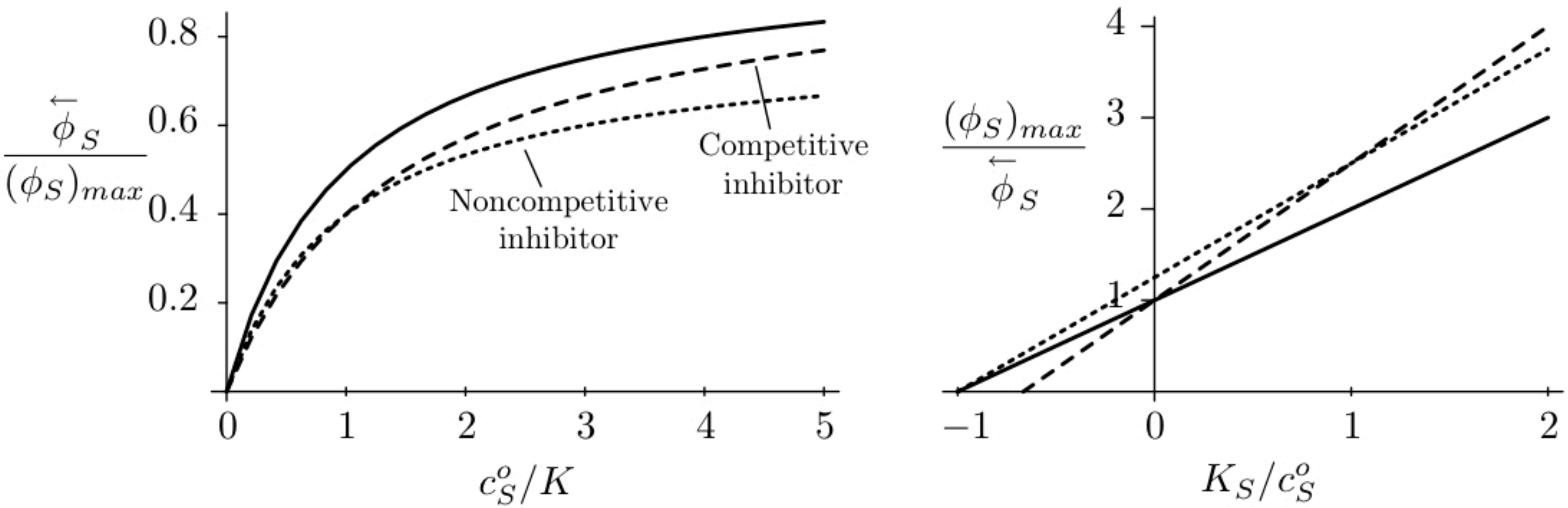
1 Solute + 1 Noncompetitive Inhibitor



$$\overleftarrow{\phi}_S = \mathfrak{N}_{ET}\left(\frac{\alpha\beta}{\alpha(\frac{c^o_I}{K_I}+1)+\beta}\right)\left(\frac{c^o_S}{c^o_S + K_S}\right)$$

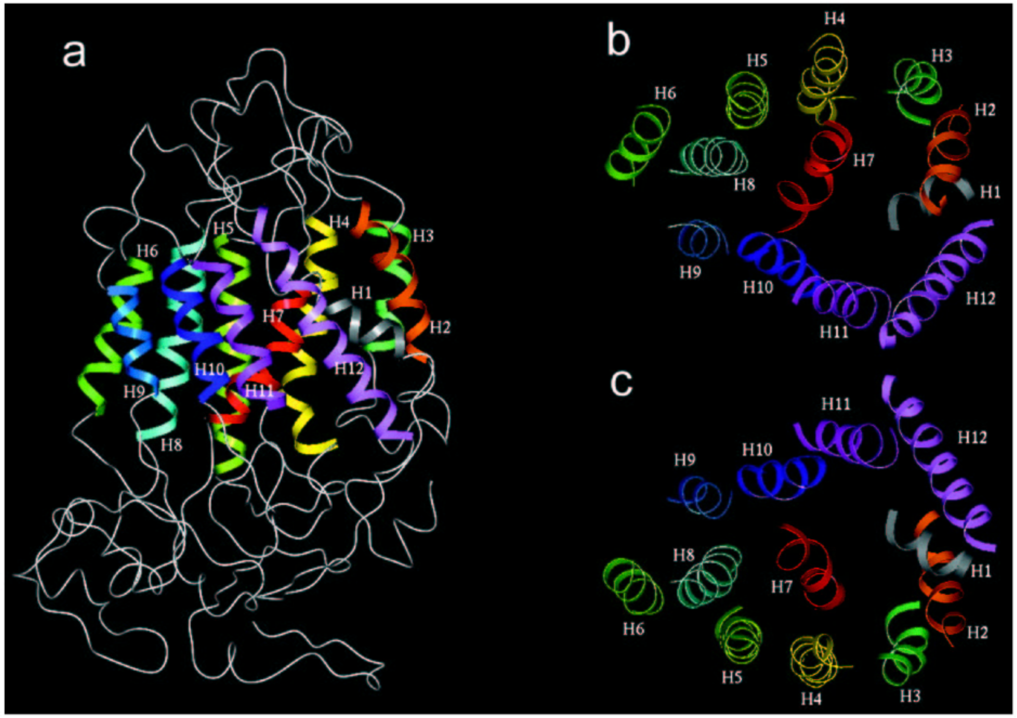
$$\overleftarrow{\phi}_S = (\phi_S)^{eff}_{max}\left(\frac{c^o_S}{c^o_S + K_S}\right)$$

$$(\phi_S)^{eff}_{max} = \mathfrak{N}_{ET}\left(\frac{\alpha\beta}{\alpha(\frac{c^o_I}{K_I}+1)+\beta}\right)$$

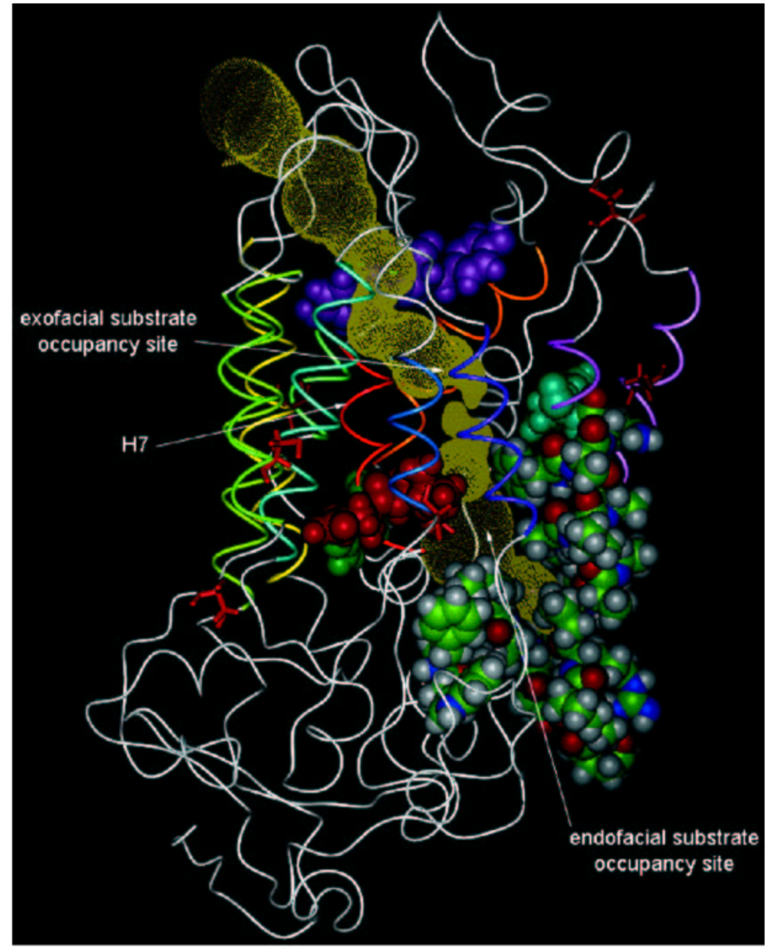


→ Model can be adapted to describe a wide array of behaviors

Molecular biology to identify glucose transporter



Zuniga, Shi, Haller, Rubashkin, Flynn, Iserovick, and Fischbarg (Nov. 2001)
J. Biological Chemistry 48: 44970-44975.



Zuniga, Shi, Haller, Rubashkin, Flynn, Iserovick, and Fischbarg (Nov. 2001)
J. Biological Chemistry 48: 44970-44975.

Glucose transport → Are all the bases covered?

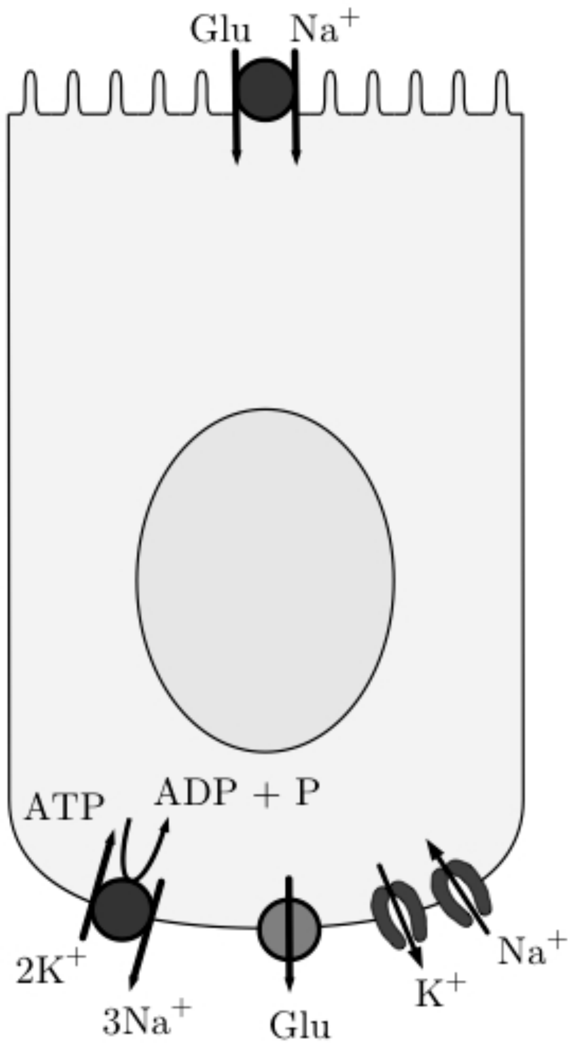
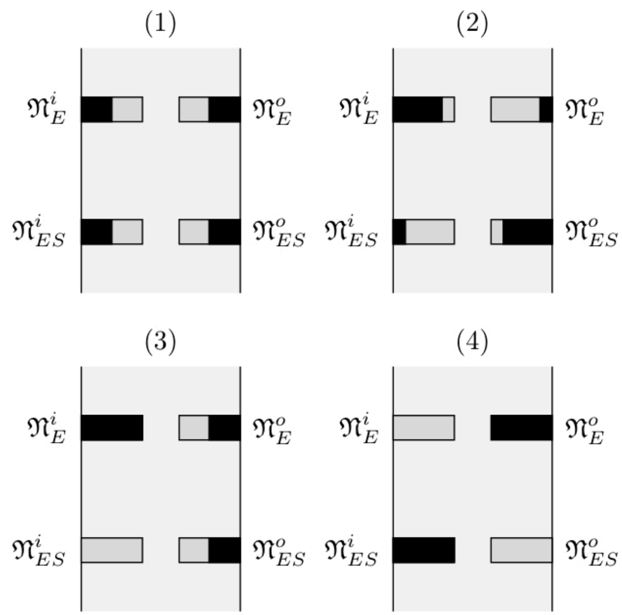


Figure 2.15

→ Need to consider additional aspects (e.g., electrical charge)

Problem

Problem 1. 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), $\phi_E = -\phi_{ES}$.

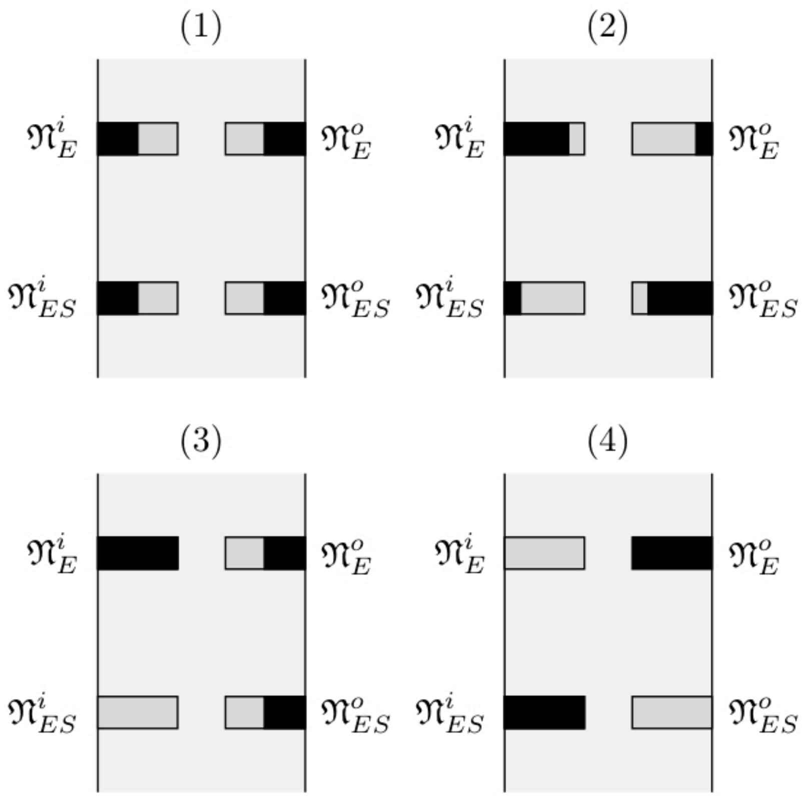
b) **Multiple choice:** Which of the following statements applies to (1):

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), $\phi_S > 0$.

Problem



Simple Symetric 4-State Carrier Model

$$\mathfrak{N}_{ES}^i = \left(\frac{\beta}{\alpha+\beta}\right)\left(\frac{c_S^i}{c_S^i+K}\right)\mathfrak{N}_{ET}$$

$$\mathfrak{N}_E^i = \left(\frac{\beta}{\alpha+\beta}\right)\left(\frac{K}{c_S^i+K}\right)\mathfrak{N}_{ET}$$

$$\mathfrak{N}_{ES}^o = \left(\frac{\alpha}{\alpha+\beta}\right)\left(\frac{c_S^o}{c_S^o+K}\right)\mathfrak{N}_{ET}$$

$$\mathfrak{N}_E^o = \left(\frac{\alpha}{\alpha+\beta}\right)\left(\frac{K}{c_S^o+K}\right)\mathfrak{N}_{ET}$$

$$\phi_S = \left(\frac{\alpha\beta}{\alpha+\beta}\right)\mathfrak{N}_{ET}\left(\frac{c_S^i}{c_S^i+K} - \frac{c_S^o}{c_S^o+K}\right)$$

Problem

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

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

i) $c_S^i > K$.

ii) $c_S^i = K$. → ii

iii) $c_S^i < K$.

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

d) **True or False:** In (2), $\phi_S > 0$. → False