

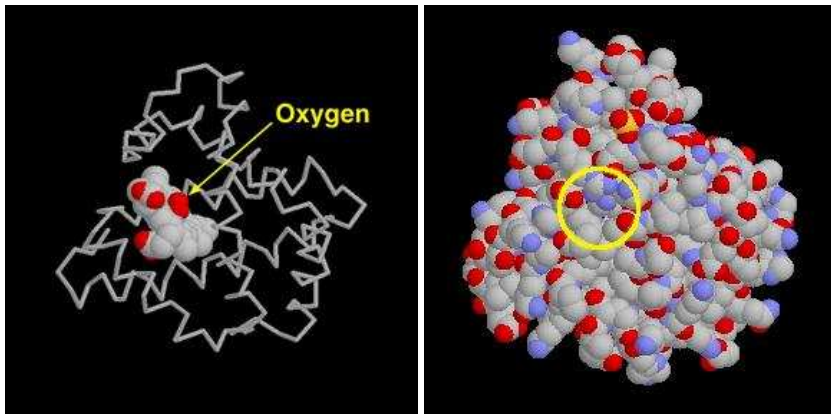
# Rutgers 642:613 - Fall 2003

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Sections 2.3-2.5, Membrane Diffusion & Transport

<http://www.math.rutgers.edu/~sontag/613.html>

## facilitated diffusion: myoglobin



(from Protein Data Bank, PDB, <http://www.rcsb.org/pdb/molecules/mb3.html>)

“myoglobin is where the science of protein structure really began...John Kendrew and his coworkers determined the atomic structure of myoglobin, laying the foundation for an era of biological understanding”

“The iron atom at the center of the heme group holds the oxygen molecule tightly. Compare the two pictures. The first shows only a set of thin tubes to represent the protein chain, and the oxygen is easily seen. But when all of the atoms in the protein are shown in the second picture, the oxygen disappears, buried inside the protein.”

“So how does the oxygen get in and out, if it is totally surrounded by protein? In reality, myoglobin (and all other proteins) are constantly in motion, performing small flexing and breathing motions. Temporary openings constantly appear and disappear, allowing oxygen in and out. The structure in the PDB is merely one snapshot of the protein, caught when it is in a tightly-closed form”

## “Ohm’s law” for diffusion

suppose on opposite sides of membrane have chemical at constant concentrations  $c_e$  and  $c_i$  (“external” and “internal”) and membrane has thickness  $L$

$$c(0, t) \equiv c_e \quad \begin{array}{c} \text{no flux} \\ \downarrow \\ \boxed{c_t = D\nabla^2 c} \\ \uparrow \\ \text{no flux} \end{array} \quad c(L, t) \equiv c_i$$

(membrane drawn horizontally)

assuming no diffusion along membrane itself, so model as 1-d problem (same math as adding Neumann conds)

could find time-dependent solution, given initial conds (using separation of variables), but just steady-state here:

$$c'' = 0 \Rightarrow \text{line; and boundary conds} \Rightarrow c(x) = c_e + (c_i - c_e)\frac{x}{L}$$

$$\text{so } J = -Dc' = \frac{D}{L}(c_e - c_i) \text{ (constant), or } c_e - c_i = J\frac{L}{D}$$

analogous to Ohm’s law  $V = IR$

(potential difference proportional to difference of charges & flux=current)

## facilitated diffusion

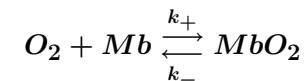
when a reaction *facilitates* diffusion; example:

oxygen in muscle fibers binds to myoglobin  $\rightsquigarrow$  oxymyoglobin which results in enhanced transport

seems counterintuitive because Mb much larger than O (500 times larger), so diffuses slower!

model will show enhancement; later, we’ll interpret

$$s(0, t) \equiv s_0 \quad \boxed{s = O_2, e = Mb, c = MbO_2} \quad s(L, t) \equiv s_L \ll s_0$$



$$\frac{\partial s}{\partial t} = D_s \frac{\partial^2 s}{\partial x^2} + k_- c - k_+ s e$$

$$\frac{\partial e}{\partial t} = D_e \frac{\partial^2 e}{\partial x^2} + k_- c - k_+ s e$$

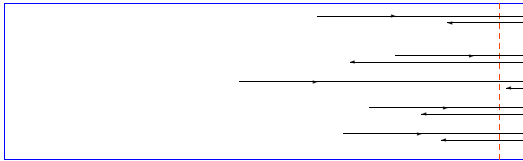
$$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} - k_- c + k_+ s e \quad (\text{and assume: } D_e = D_c)$$

assume also zero-flux of Mb & MbO<sub>2</sub> at boundary

i.e.,

$$\frac{\partial e}{\partial x} = \frac{\partial c}{\partial x} \equiv 0 \quad \text{at } x = 0, L$$

if you have never thought of such boundary conditions, you may wish to interpret them as follows: think of a narrow strip (of very small width  $\varepsilon$ ): most particles bounce back far into region, so the net flux at  $x = L - \varepsilon$  is  $\approx 0$



so quasi-steady state approx  $\Rightarrow c = e_0 \frac{s}{K + s}$  ( $K = k_-/k_+$ )

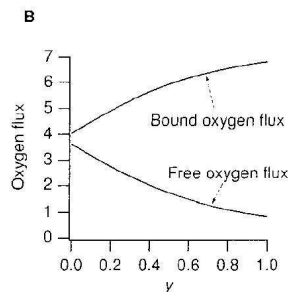
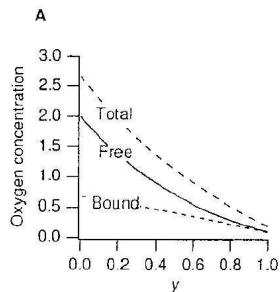
now substitute into  $J = D_s(s_0 - s_L) + D_c(c_0 - c_L)$  to get:

$$J = \frac{D_s}{L}(1 + \mu\rho)(s_0 - s_L) \quad (\rho = \frac{D_c e_0}{D_s K}, \mu = \frac{K^2}{(s_0 + K)(s_L + K)})$$

expression for flux  $J \sim$  “Ohm’s Law”;

factor  $1 + \mu\rho$  enhances – e.g.  $\rho \approx 500$

now substitute expression for  $J$ , &  $c$  as function of  $s$  (q-s-s), into  $D_s s_x + D_c c_x = -J$ ; next integrate from 0 to  $x$  (any  $x$ , not just  $L$ ), & get soln for  $s$  (or  $\sigma$ ) – see book for details



steady-state analysis:

$$D_s s_{xx} + k_- c - k_+ s e = D_c e_{xx} + k_- c - k_+ s e = D_c c_{xx} - k_- c + k_+ s e = 0$$

$(e + c)_{xx} \equiv 0$  (linear) &  $(e + c)_x \equiv 0$  at  $\partial \Rightarrow e + c \equiv “e_0”$  also,

$$(D_s s_x + D_c c_x)_x = D_s s_{xx} + D_c c_{xx} = 0$$

means that  $D_s s_x + D_c c_x = \text{constant}$ , call it “ $-J$ ” because it is the sum of the two fluxes, i.e. *it is the total flux of oxygen* (bound or not)

integrate:  $f' = -J \Rightarrow f(0) - f(L) = JL$ , so:

$$J = D_s(s_0 - s_L) + D_c(c_0 - c_L)$$

(where we know  $s_0, s_L$  but not  $c_0, c_L$ )

we had:

$$D_s s_{xx} + k_- c - k_+ s(e_0 - c) = D_c c_{xx} - k_- c + k_+ s(e_0 - c) = 0$$

now let  $\sigma = (k_+/k_-)s$ ,  $u = c/e_0$ ,  $x = Ly$ ,

$$\varepsilon_1 = D_s/(e_0 k_+ L^2) \approx 10^{-7}, \varepsilon_2 = D_c/(k_- L^2) \approx 10^{-4} \rightsquigarrow$$

$$\varepsilon_1 \sigma_{yy} = \sigma(1 - u) - u = -\varepsilon_2 u_{yy}$$

interpretations

may also write:

$$J = \frac{D_s}{L}(s_0 - s_L) + \frac{D_c}{L}e_0 \left( \frac{s_0}{K + s_0} - \frac{s_L}{K + s_L} \right)$$

(second term  $> 0$  since  $s/(K + s)$  is increasing)

and this exhibits flux as sum of “Ohm” term

plus term that depends on diffusion constant  $D_c$

one intuition:

by binding to Mb, there would be less free O<sub>2</sub> near left end

but boundary conditions say that one has  $s_0$  there

so more must flow in (diffusion tends to equalize!)

while at other end, opposite happens, and more flows out

**a related example: muscle respiration**

consider problem of getting O<sub>2</sub> to center of muscle  
 muscle fiber thought of as cylinder  $0 \leq r \leq a$   
 radial diffusion, ignoring longitudinal diffusion now

recall Laplacian in polar coordinates, 2-dim case:  
 write  $f(r, \varphi, t) = c(r \cos \varphi, r \sin \varphi, t)$ ; then (some calculus):

$$(\nabla^2 c)(r \cos \varphi, r \sin \varphi, t) = \frac{\partial^2 f}{\partial r^2} + \frac{1}{r} \frac{\partial f}{\partial r} + \frac{1}{r^2} \frac{\partial^2 f}{\partial \varphi^2}$$

(all terms on the RHS evaluated at  $r, \varphi, t$ )  
 so Laplacian for radially symmetric  $c$  (write “ $f$ ” as “ $c$ ”):

$$\frac{D}{r} \frac{\partial}{\partial r} \left( r \frac{\partial c}{\partial r} \right)$$

(for spherically symmetric  $c$  in 3-d,  $\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \frac{\partial c}{\partial r})$ )

so integrate:  $y(\varepsilon_1 \sigma + \varepsilon_2 u)_y = A + \gamma y^2/2$   
 $\Rightarrow (\varepsilon_1 \sigma + \varepsilon_2 u)_y = A/y + \gamma y/2$ , and integrate again:

$$\varepsilon_1 \sigma + \varepsilon_2 u = A \ln y + \gamma y^2/4 + B$$

but soln not well-defined at  $y = 0$  unless  $A = 0$ , so  $A = 0$

at boundary  $y = 1$ :  $\varepsilon_1 \sigma(1) + \varepsilon_2 u(1) = \gamma/4 + B$

what  $\sigma(1) = \sigma_1$  is so that  $s(0)=u(0)=0$  (“just enough” O<sub>2</sub>)?

evaluate above at zero  $\Rightarrow B = 0$  too, so, using also

$$\frac{1}{y} \varepsilon_1 (y \sigma_y)_y = \sigma(1 - u) - u$$

and q-s-s approx, substitute  $u$  as function of  $\sigma$  to obtain:

$$\sigma_1 + \rho \frac{\sigma_1}{1 + \sigma_1} = \frac{\gamma}{4\varepsilon_1}$$

where  $\rho = \varepsilon_2/\varepsilon_1$ , so can solve for  $\sigma_1(\gamma)$  ( $\gamma \sim$  consumption  $g$ )  
 — note that it is an increasing function

so steady-state equation (same variables as before):

$$\frac{D_s}{r} \frac{\partial}{\partial r} \left( r \frac{\partial s}{\partial r} \right) + k_- c - k_+ s e - g = 0$$

$$\frac{D_c}{r} \frac{\partial}{\partial r} \left( r \frac{\partial c}{\partial r} \right) - k_- c + k_+ s e = 0$$

where  $g =$  constant consumption of oxygen in muscle

we impose boundary conditions:

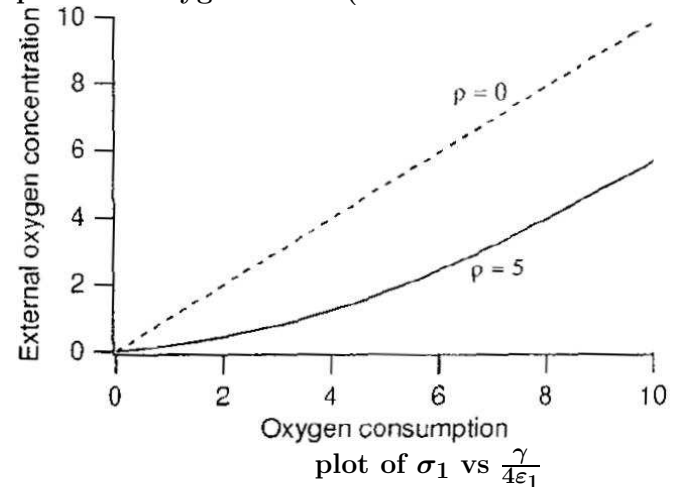
$$s(a) = s_a, \quad \frac{dc}{dr}(a) = 0, \quad \frac{ds}{dr}(0) = 0, \quad \frac{dc}{dr}(0) = 0$$

(at  $r = 0$ : if continuing in same direction, even function, so derivative zero at that point, or think of small circle around zero: balance of flows in/out is zero)

with  $\varepsilon_1 = D_s/(e_0 k_+ a^2)$ ,  $\varepsilon_2 = D_c/(k_- a^2)$ ,  $\gamma = g/k_-$ ,  
 $\sigma = (k_+/k_-)s$ ,  $u = c/e_0$ ,  $r = ay$ ,  $\rightsquigarrow$

$$\left( y (\varepsilon_1 \sigma + \varepsilon_2 u)_y \right)_y = \gamma y$$

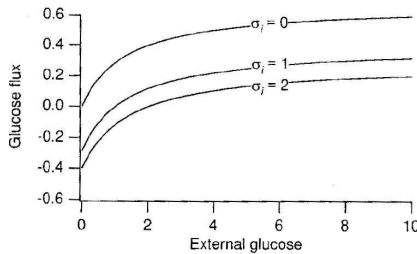
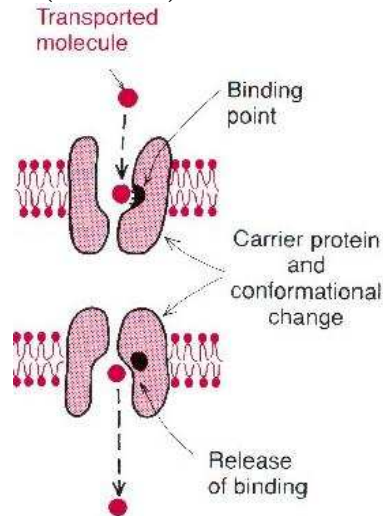
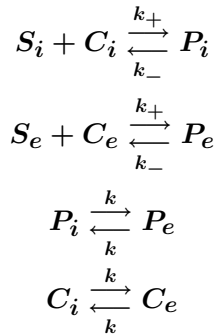
Mb helps diminish the minimal concentration  $\sigma_1$  needed to prevent “oxygen debt” (concentration at center falls to 0)



$\varepsilon_1 = D_s/(e_0 k_+ a^2)$  small if  $k_+$  (binding constant) large,  
 $\varepsilon_2 = D_c/(k_- a^2)$  large if  $k_-$  small (unbinding),  
 so  $\rho$  large if high affinity

## Uniport, e.g. Glucose Transport

$S_i$  ( $S_e$ ) = glucose inside (external),  
 $C_i$  ( $C_e$ ) = carrier protein, open to inside (external),  
 $P_i$  ( $P_e$ ) = complex, open to inside (external)



horiz axis  $s_e$ , vertical  $J$ , different  $s_i$ 's (non-dimensionalized)

variations: *symport* in which two go in simultaneously  
 sodium outside cell is high compared to inside  
 (due to Na/K pump)  
 so gradient provides energy for transport  
 (but no additional energy required)

or *antiport*, where exchange inside/outside

assume also that  $\xrightarrow{J_1} S_e$  and  $S_i \xrightarrow{J_2} 0$   
 (constant supply rate outside & removal rate inside)

$$\begin{aligned}
 \dot{s}_i &= k_- p_i - k_+ s_i c_i - J_i \\
 \dot{s}_e &= k_- p_e - k_+ s_e c_e + J_e \\
 \dot{p}_i &= k p_e - k p_i + k_+ s_i c_i - k_- p_i \\
 \dot{p}_e &= k p_i - k p_e + k_+ s_e c_e - k_- p_e \\
 \dot{c}_i &= k c_e - k c_i - k_+ s_i c_i + k_- p_i \\
 \dot{c}_e &= k c_i - k c_e - k_+ s_e c_e + k_- p_e
 \end{aligned}$$

at steady state:

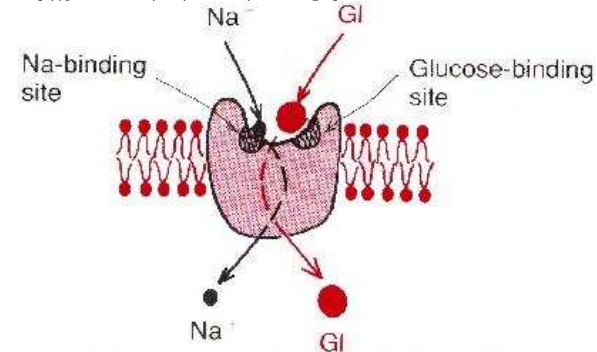
$0 = d/dt(s_i + s_e + p_i + p_e) = J_e - J_i$ , so  $J_i = J_e = J$   
 note that  $p_i + p_e + c_i + c_e = \text{total amount of receptors "c}_0$ "  
 use rhs's for  $s_e, p_i, p_e, c_i$  plus  $p_i + p_e + c_i + c_e = c_0$  to solve  
 for  $J$  in terms of  $s_e, s_i$  (seen as parameters when solving  
 for rest)  $\rightsquigarrow$

$$J = ac_0 \frac{s_e - s_i}{(s_i + K_1)(s_e + K_2) - K_3}$$

for suitable constants (see book)

e.g. *symport*: when both sodium and glucose are attached,  
 conformational change in protein molecule happens,  
 and both are transported to inside cell

[http://jmswan.com/237/channels/channel\\_graphics.htm](http://jmswan.com/237/channels/channel_graphics.htm)



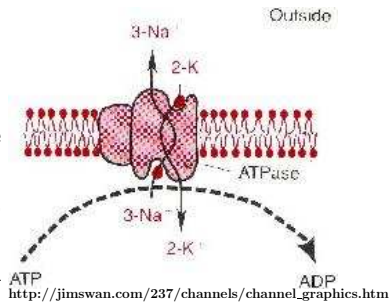
(skip equations - similar to uniport, but exponents appear, as in cooperativity)

active transport: e.g.: electrogenic Na<sup>+</sup>-K<sup>+</sup> pump

three sites for Na<sup>+</sup> attachment on inside surface of carrier, and two for K<sup>+</sup> outside

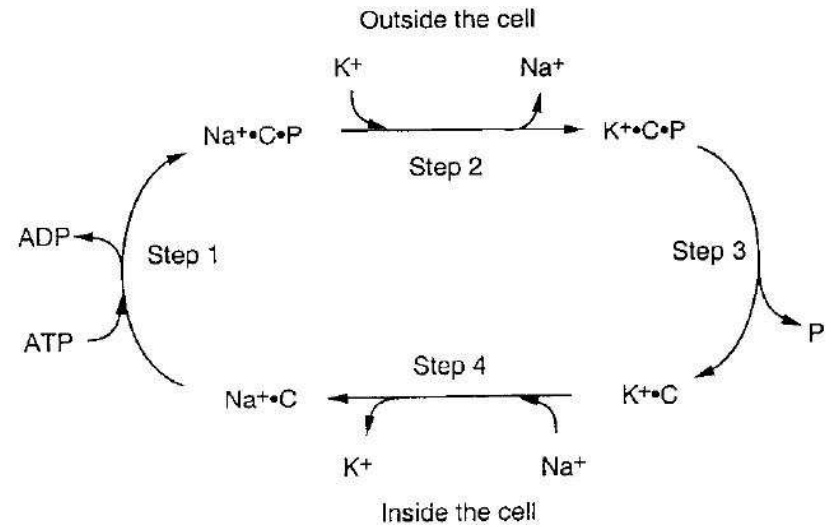
ATPase on intracellular surface hydrolyzes ATP, releasing energy that causes carrier conformational change

this pumps the 3 Na<sup>+</sup> ions out and then potassium attaches and 2 K<sup>+</sup> ions are pumped in



on balance, more +’s pumped out, but on the other hand negative (other) ions are not permeable - this creates a polarization across the membrane

see book for details (skipping - no time...)



We apply the law of mass action to these kinetics, assume that intracellular sodium and extracellular potassium are supplied at the constant rate  $J$  and that intracellular potassium and extracellular sodium are also removed at the constant rate  $J$ , and then find that in steady state the flow of ions through the pump is given by

$$J = C_0 \frac{[Na_i^+][K_e^+][K_1]K_2 - [Na_e^+][K_i^+][K_{-1}]K_{-2}[P]}{([K_e^+][K_2 + [K_i^+][K_{-2}])K_n + ([Na_i^+][K_1 + [Na_e^+][K_{-1}])K_k} \quad (2.52)$$

where  $K_1 = k_1k_2k_p$ ,  $K_{-1} = k_{-1}k_{-2}k_{-p}$ ,  $K_2 = k_3k_4k_5$ ,  $K_{-2} = k_{-3}k_{-4}k_{-5}$ ,  $K_n = k_{-1}k_p + k_2k_{-1} + k_7k_p$ , and  $K_k = k_{-3}k_{-4}[P] + k_{-3}k_5 + k_4k_5$ . The rate constants  $k_p$  and  $k_{-p}$  are the forward and backward rate constants for the hydrolysis of ATP. As before, the total concentration of carrier molecule is denoted by  $C_0$ .

Because ATP is much more energetic than ADP, we expect the reverse reaction rate  $k_{-p}$  to be small compared to the forward reaction rate  $k_p$ . If we ignore the reverse reaction (take  $K_{-1} = 0$ ), we find

$$J = C_0K_1K_2 \frac{[Na_i^+][K_e^+]}{([K_e^+][K_2 + [K_i^+][K_{-2}])K_n + [Na_i^+][K_1]K_k} \quad (2.53)$$

which is independent of the extracellular sodium concentration.