Bio-Systems Modeling and Control

Lecture 18

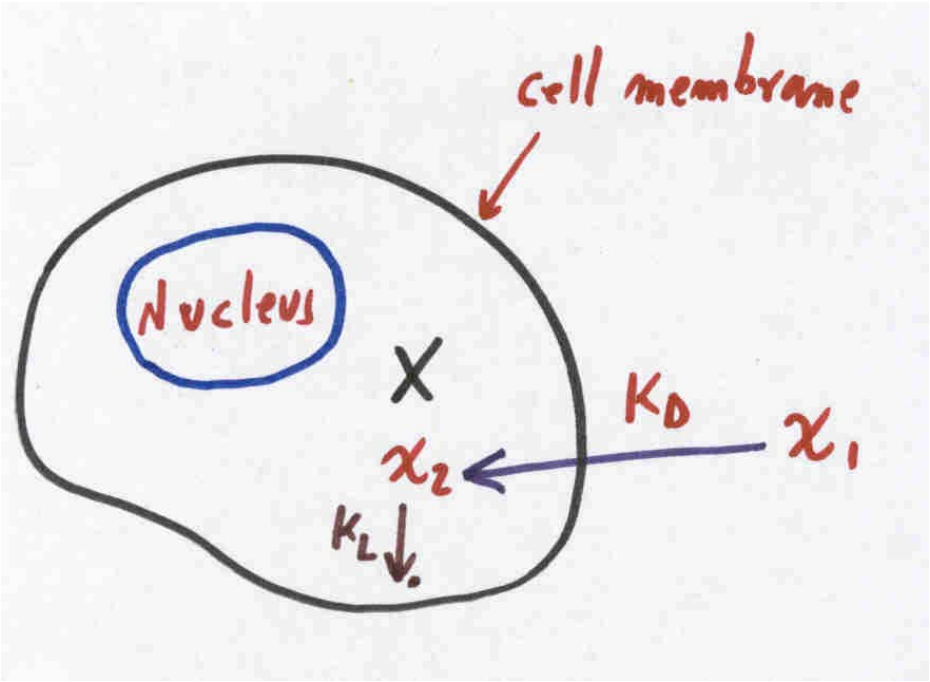
Diffusion

Diffusion combined with Law of Mass Action – Simple Cellular Linear Model Examples

References:

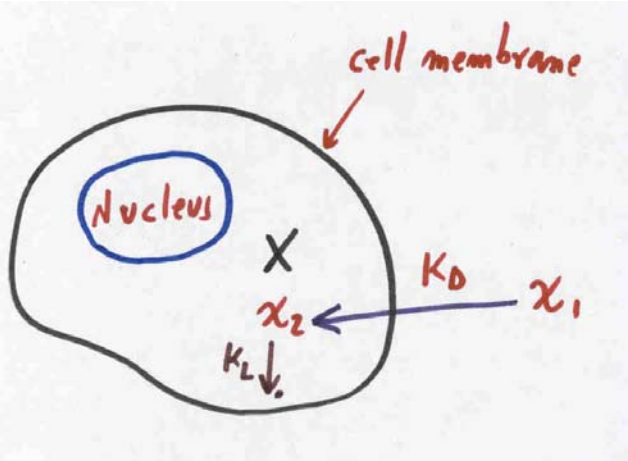
- Robert B. Northrop “Endogenous and Exogenous Regulation and Control of Physiological Systems”, CRC Press 2000.
- Michael Khoo “Physiological Control Systems” Wiley / IEEE Press 1999.
- Dr. Khoo’s PowerPoint slides (USC, Biomedical Engineering Dept)

Example: Simple Cellular Diffusion



- Assume that the regulated variable is the concentration x_2 [μgram/liter] of a certain substance X inside a cell.
- X is also present outside the cell in concentration $x_1 > x_2$.

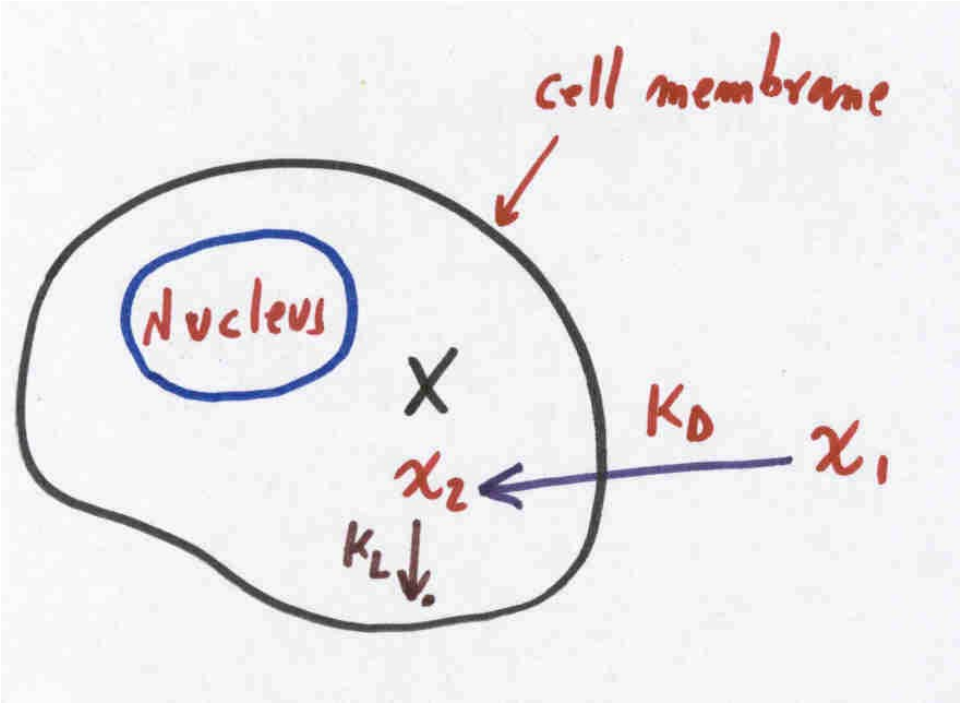
Simple Cellular Diffusion Model Assumption



- X diffuses passively into the cell, according to Fick's Law ←→ Flow is proportional to concentrations differences, across cell's membrane.
- X is metabolized inside the cell at a rate proportional to x_2.

Simple Cellular Diffusion Model parameters and equation

$$V\frac{dx_2}{dt} = K_D(x_1 - x_2) - K_L x_2$$



K_D=diffusion rate constant

K_L=Loss rate constant

V=cell volume

Simple Cellular Diffusion Model is First-Order Linear System

$$V\frac{dx_2}{dt} = K_D(x_1 - x_2) - K_L x_2 \Rightarrow$$

$$\Rightarrow \frac{dx_2}{dt} = -\frac{K_D + K_L}{V}x_2 + \frac{K_D}{V}x_1$$

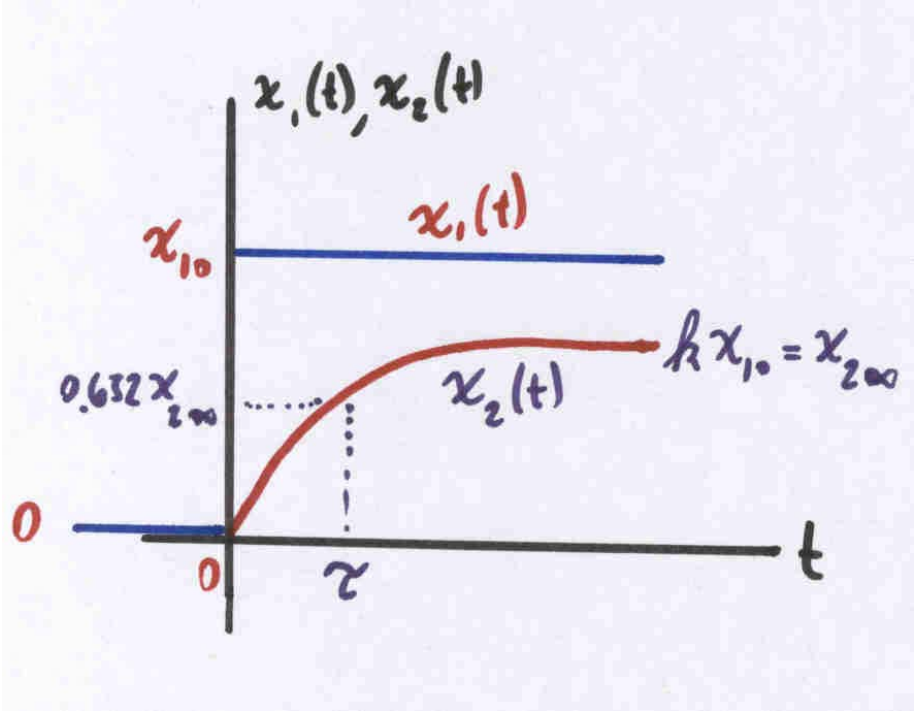
$$\boxed{\frac{X_2(s)}{X_1(s)}} = \frac{\frac{K_D}{V}}{s + \frac{K_D + K_L}{V}} = \boxed{\frac{k}{1 + \tau \cdot s}} \qquad k = \frac{K_D}{K_D + K_L} \qquad \tau = \frac{V}{K_D + K_L}$$

Parameters: k=gain, τ=time constant

Simple Cellular Diffusion Model Step Response

$$\frac{X_2(s)}{X_1(s)} = \frac{\frac{K_D}{V}}{s + \frac{K_D + K_L}{V}} = \frac{k}{1 + \tau \cdot s}$$

$$k = \frac{K_D}{K_D + K_L} \qquad \tau = \frac{V}{K_D + K_L}$$



A bit of relevant Linear Systems Theory: Laplace Transform, Transfer Function

- We take Laplace Transform of both sides of the linear differential equation, using s as a differentiation operator (in place of d/dt). Use $X_1(s)$ as the Laplace transform of $x_1(t)$, and $X_2(s)$ for $x_2(t)$.
- The resulting Laplace transformed variables ratio $X_2(s)/X_1(s)$ is called a <u>Transfer Function</u>. It is in general a rational function of s (i.e. ratio of polynomials of s)

More Linear Systems Theory: Poles and Zeros

- In general, the numerator roots of $X_2(s)/X_1(s)$ are called zeros, and the denominator roots of $X_2(s)/X_1(s)$ are called poles.
- Here (in the simple diffusion example), the transfer function has no zeros and it has one pole, at $s= -1/\tau$ ←→ see inverse relationship between pole location and time constant: The faster time constant the farther to the left (of the complex s-plane) pole is.

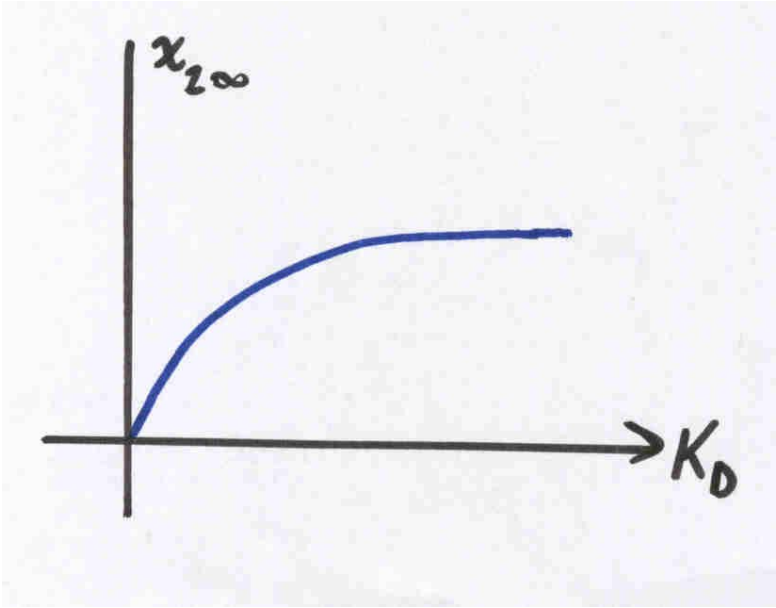
More Linear Theory: Stability and Steady-state

- A linear system is stable if <u>all its poles have negative real parts</u>.
- We can apply the <u>final-value theorem</u> to any signal that becomes constant at steady state. Here:

$$\lim_{t\to\infty}[x_2(t)] = \lim_{s\to 0}[sX_2(s)] = \lim_{s\to 0}[sX_1(s)\frac{X_2(s)}{X_1(s)}] =$$

$$= \lim_{s\to 0}[s\cdot\frac{x_{10}}{s}\cdot\frac{k}{1+s\tau}] = x_{10}k = x_{10}\frac{K_D}{K_D+K_L}$$

Open-Loop Parametric Control of x_2 by K_D



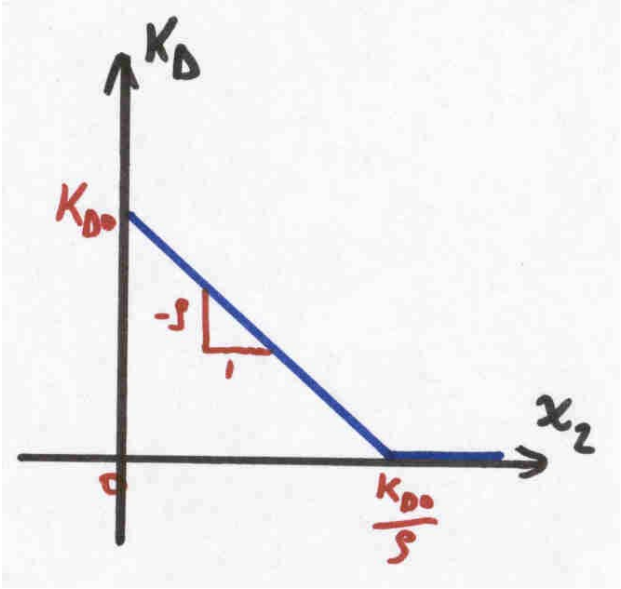
- If somehow we can control the diffusion coefficient K_D, we can make (in open loop) the final value of x_2 dependent on x_1.
- If x_1 varies, so does x_2.

Closed-Loop Parametric Control of x_2 by K_D

$$K_D = K_{D0} - \rho x_2 \quad ____ \quad 0 \le x_2 \le \frac{K_{D0}}{\rho}$$

$$K_D = 0 \quad _____ \quad x_2 > \frac{K_{D0}}{\rho}$$

$$x_{2\infty} = \frac{x_{10}}{1 + \dfrac{K_L}{K_{D0} - \rho x_{2\infty}}} \Rightarrow x_{2\infty} \approx \frac{K_{D0}}{\rho}$$



If somehow we can make the diffusion coefficient K_D to decrease as x_2 increases , and we need x_2 to reach a specific level, we can make the final value of x_2 less dependent on x_1, if ρ is large.

What is Diffusion? - 1

- On a microscopic scale, all physiological systems contain cells, as well as molecules and ions suspended or dissolved in physiological fluids.
- Molecules and ions are in constant random motion, due to their internal thermal energy. These collide with walls of their containers, and with each other.

What is Diffusion? -2

- In Physiological systems, Fick's Diffusion Law describes the average movement of molecules or ions, in response to concentration gradients.
- Physiological diffusion generally occurs through cell membranes.
- Molecules pass through the membrane at specific discrete sites, through protein receptors.

What is Physiological Diffusion? -3

- Specific receptors suit specific molecules that need to pass through it.
- If the receptor combine (chemically or physically) with the diffusing molecules, the process is called facilitated diffusion or carrier-mediated diffusion.
- Sometimes, another molecule can modify the permeability of the pore. This is called Ligand-gated diffusion.

What is Physiological Diffusion? - 4

- Example to Ligand-gated diffusion: The hormone insulin increases the diffusion of glucose molecules at glucose pore sites.
- In insulin-sensitive cells, the presence of insulin raises the permeability for glucose, allowing glucose to flow more easily from higher extra-cellular concentration to a lower intracellular concentration.

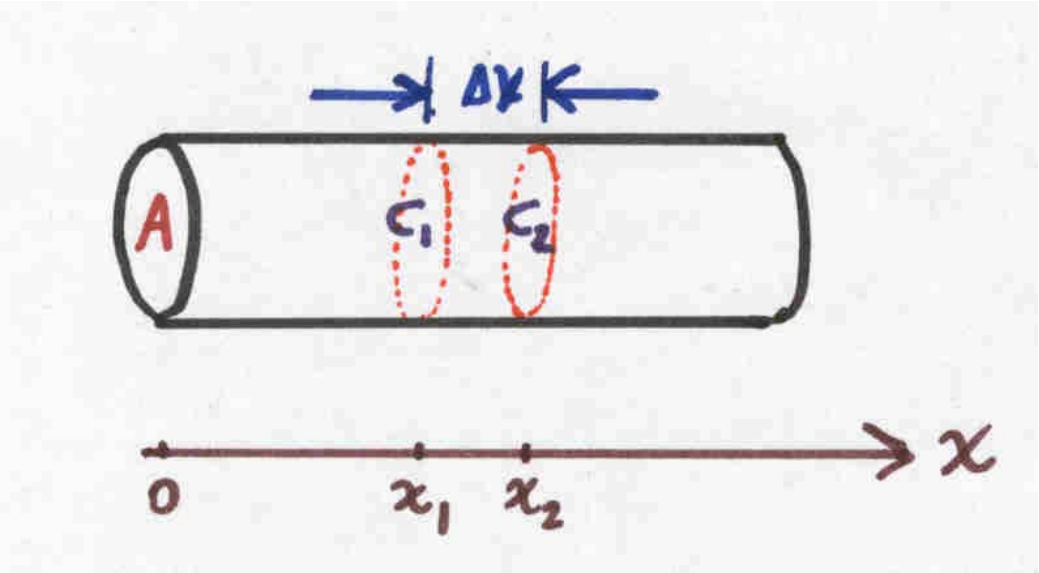
What is Physiological Diffusion? - 5

- Some pore sites are opened by a change in the trans-membrane potential difference. This is called voltage-gated diffusion.
- Voltage-gated diffusion is involved in the generation of nerve impulses, or in their inhibition. It also occurs in the triggering of muscle contractions.

What is Phyiological Diffusion? -6

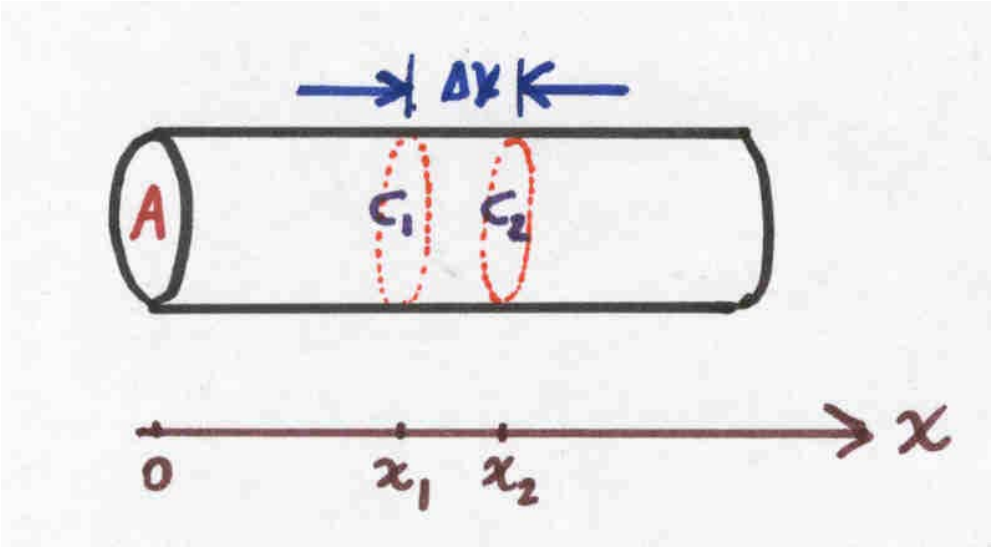
- The larger the concentration difference across the membrane the faster is diffusion flow (measured typically in [μg or ng per minute per μm^2).
- Flow saturates above a certain critical level due to either finite number of pore sites, or configuration change to the receptor, if too many molecules bind to it.

1D version of Fick's Law – definition of parameters



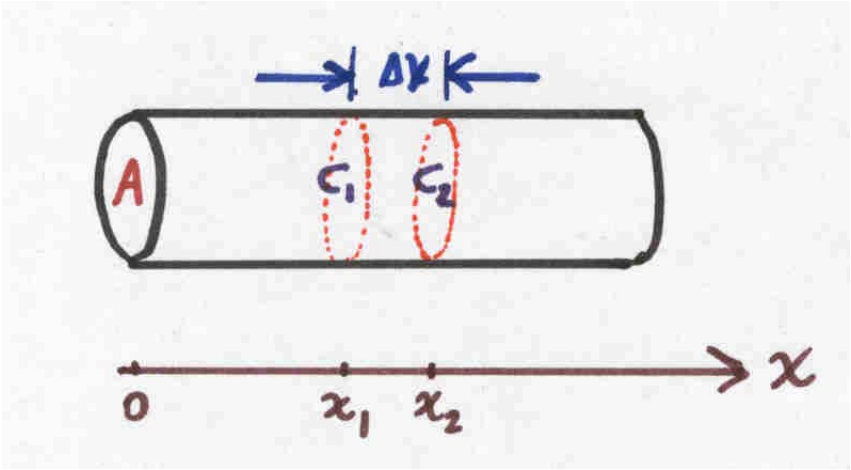
- Consider a tube with cross section area of A.
- Let the concentration at $x=x_1$ be C_1, and at $x=x_2=x_1+\Delta x$ be C_2.
- Assume that $C_1>C_2$.

1D version of Fick's Law – model assumptions



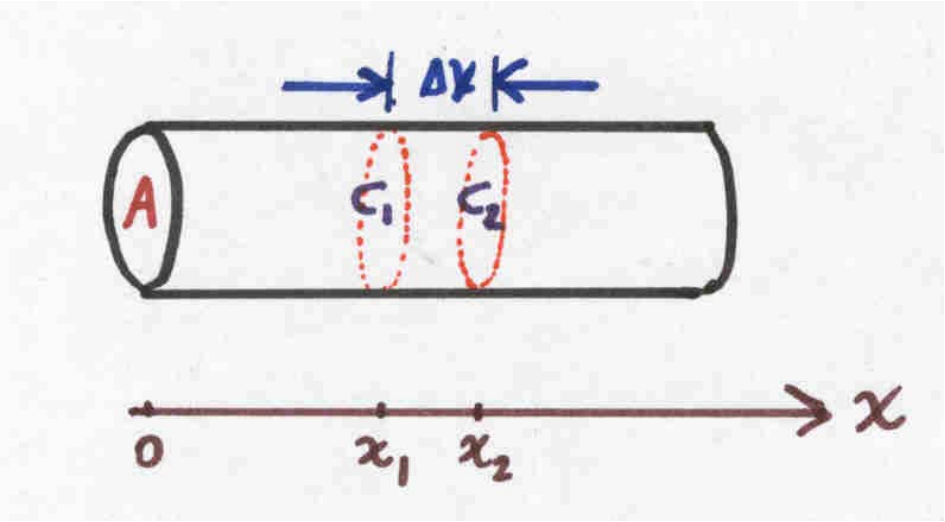
- Assume that each molecule can jump in +x or –x directions with equal probability.
- Average molecules transfer per time from plane 1 in the direction of plane 2, is proportional to the concentration profile dC_A/dx .

1D version of Fick's Law – model assumptions (cont'd)



- Likewise, average molecules transfer per time from plane 2 in the direction of plane 1, is proportional to the concentration profile dC_2/dx .
- Concentration transfer rate is proportional to A and inversely proportional to Δx.

1D Fick's Law Derivation



$$\frac{\Delta C_1}{\Delta t} = \frac{kA}{\Delta x} \cdot \frac{d}{dx}(C_1(x) - C_2(x))$$

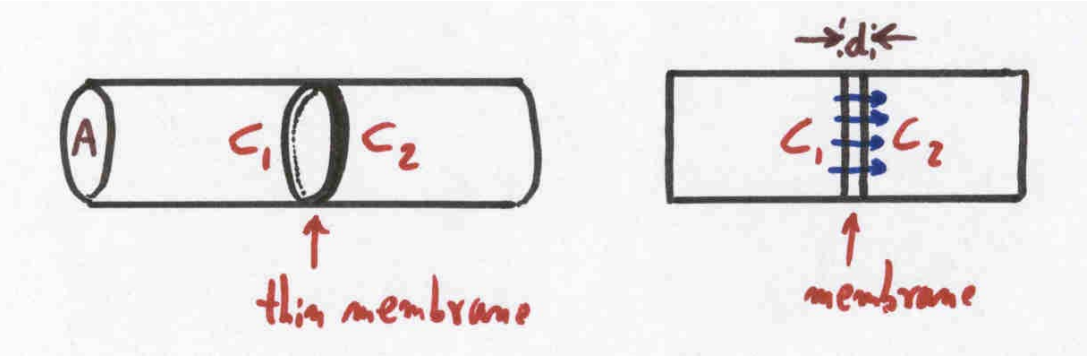
At the limit, as Δx→0 and Δt→0, we observe:

$$\frac{\Delta C_1}{\Delta t} = \frac{kA}{\Delta x} \cdot \frac{d}{dx}(C_1 - C_2) \Rightarrow \boxed{\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}}$$

- Partial derivative of C_1 w.r.t time is the concentration rate at x, in the positive direction of x. [Denote C(x)=c]
- Concentration profile = Partial derivative of c w.r.t. x, in the positive direction of x.
- Rate of mass transfer is proportional to the second partial derivative of c w.r.t. x.
- Diffusion coefficient = D=kA ; [D]=[(μm)^2/min]

1D version of Fick's Law (applied to flow through a thin membrane)

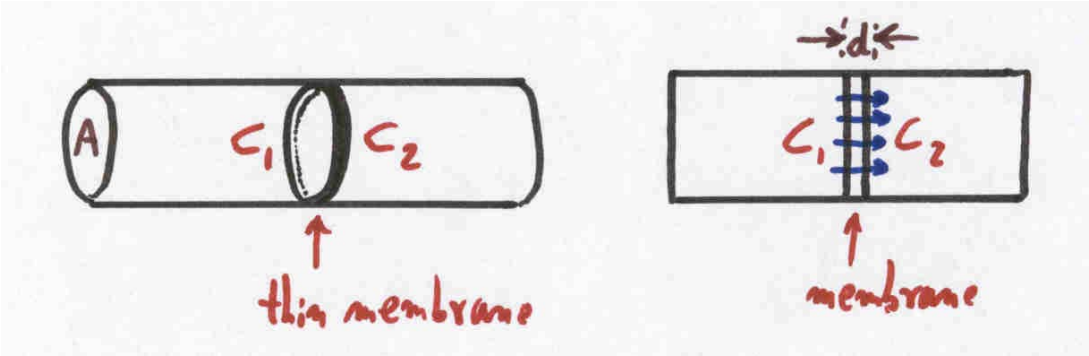
$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}$$



- Assume a thin membrane of thickness d: Concentration is C_1 on the left and $C_2<C_1$ on the right.
- Let x=0 be at the left hand side of the membrane, and x=d at the right side of the membrane.
- Boundary conditions: $c(0)=C_1$ and $c(d)=C_2$.

1D version of Fick's Law (applied to flow through a thin membrane) -2

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}$$

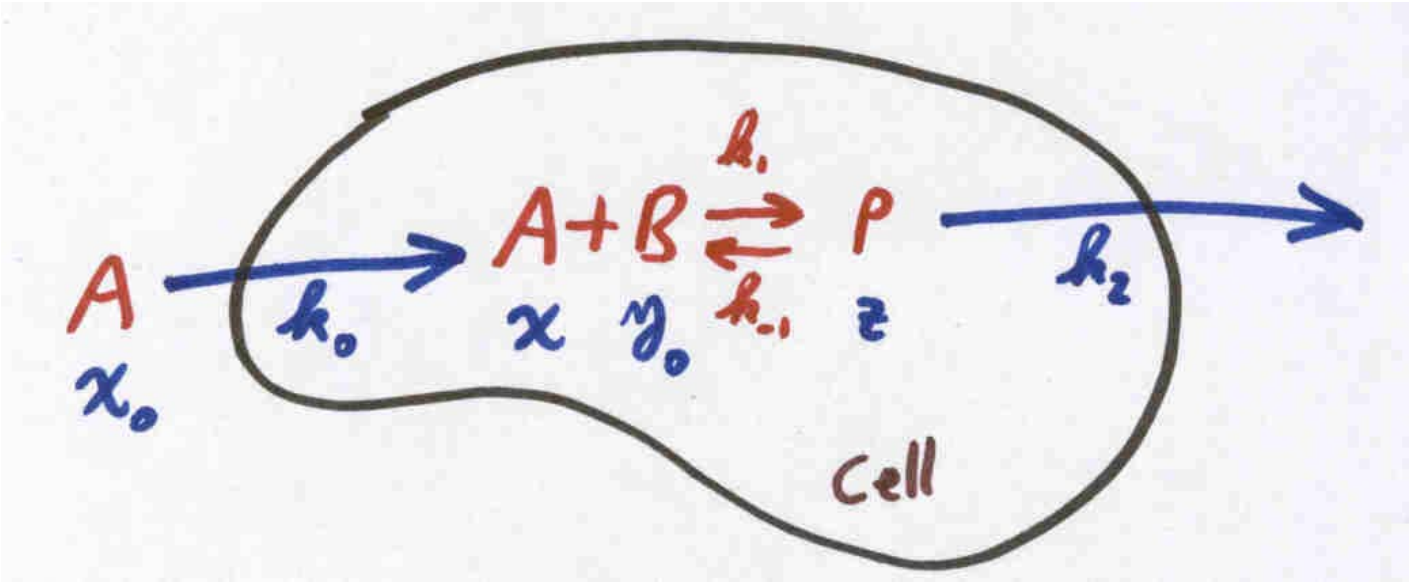


- Let's look at steady-state: $\partial c/\partial t=0$
- A solution for $D\partial^2 c/\partial x^2=0$ is $c(x)=ax+b$. When we substitute the boundary conditions $c(0)=C_1, c(d)=C_2$, we obtain $c(x)=C_1-(C_1-C_2)x/d$
- Molecules transfer rate through membrane is constant : $dc/dt=(D/d)(C_1-C_2)$. Mass flows until $C_2=C_1$.

Diffusion through a thin membrane

- Concentration rate through membrane: $dc/dt=(D/d)(C_1-C_2)$
- D/d is the membrane's permeability.
- Diffusion Flow=$\Phi=(D/d)(C_1-C_2)$←→ "Ohm's Law" format.
- Membrane Permeability (Diffusivity, conductance) = D/d = 1/R, where R is diffusion resistance.

Example: Diffusion and Mass-Action Combined

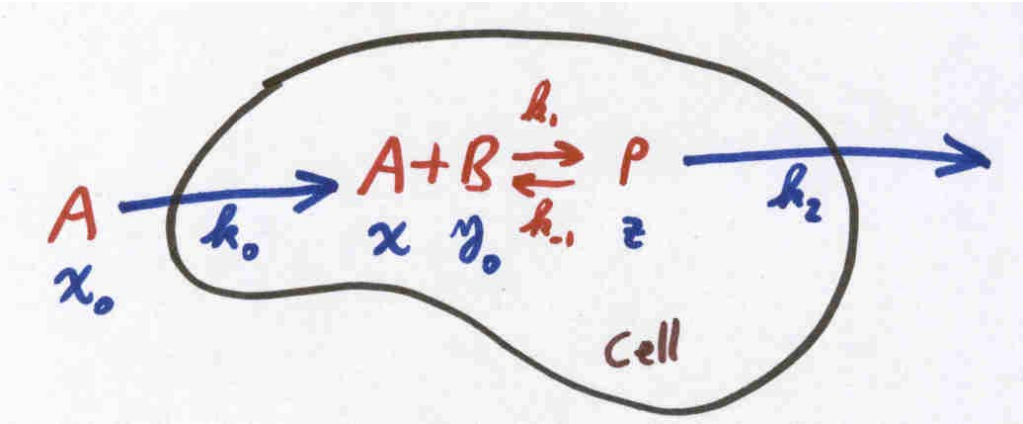


- Reactants A and B combine reversibly to form a compound P inside a cell. P diffuses out of the cell. Outside concentration of P is 0.
- B has constant concentration y_0 inside the cell.
- A diffuses to cell from outside (concentration=x_0)

Model equations expressed in terms of substances concentrations

$$\frac{dx}{dt} = k_0(x_0 - x) - k_1 y_0 x + k_{-1} z$$

$$\frac{dz}{dt} = -k_2 z + k_1 y_0 x - k_{-1} z$$

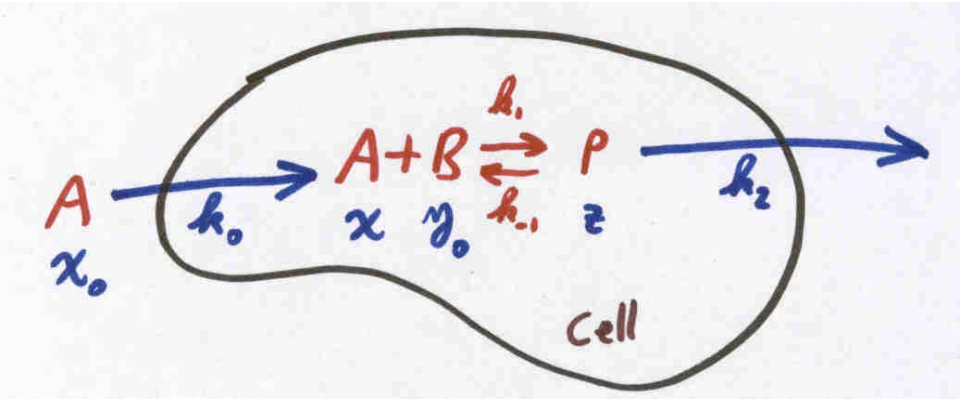


Equivalent diffusion-related coefficients: k_0 for inflow of A, and k_2 for outflow of P.

Model equations – Is system linear?

$$\frac{dx}{dt} = k_0(x_0 - x) - k_1 y_0 x + k_{-1} z$$

$$\frac{dz}{dt} = -k_2 z + k_1 y_0 x - k_{-1} z$$



System is linear only because concentration of B is kept constant at the level of y_0

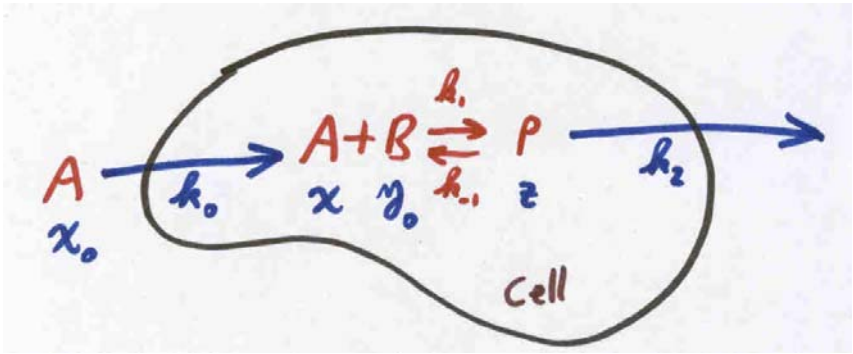
Model equations – Steady state conditions

$$\frac{dx}{dt} = 0 = k_0(x_0 - x_{ss}) - k_1 y_0 x_{ss} + k_{-1} z_{ss}$$

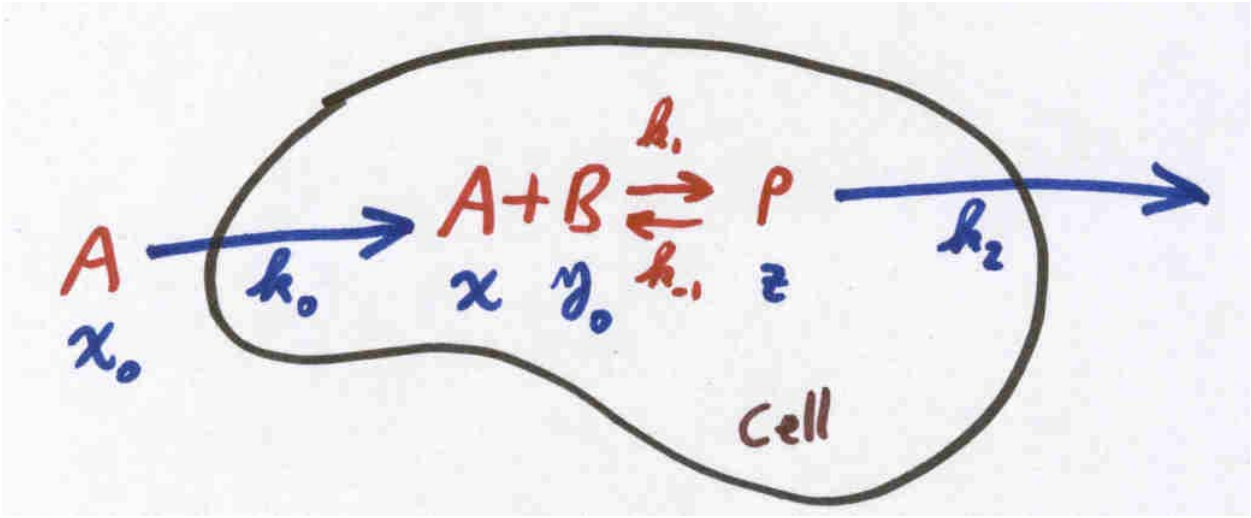
$$\frac{dz}{dt} = 0 = -k_2 z_{ss} + k_1 y_0 x_{ss} - k_{-1} z_{ss}$$

$$\Rightarrow z_{ss} = \frac{k_1 y_0}{k_{-1} + k_2} x_{ss}$$

$$x_{ss} = \frac{x_0}{1 + \frac{k_1 k_2}{k_0 k_{-1} + k_0 k_2} y_0}$$

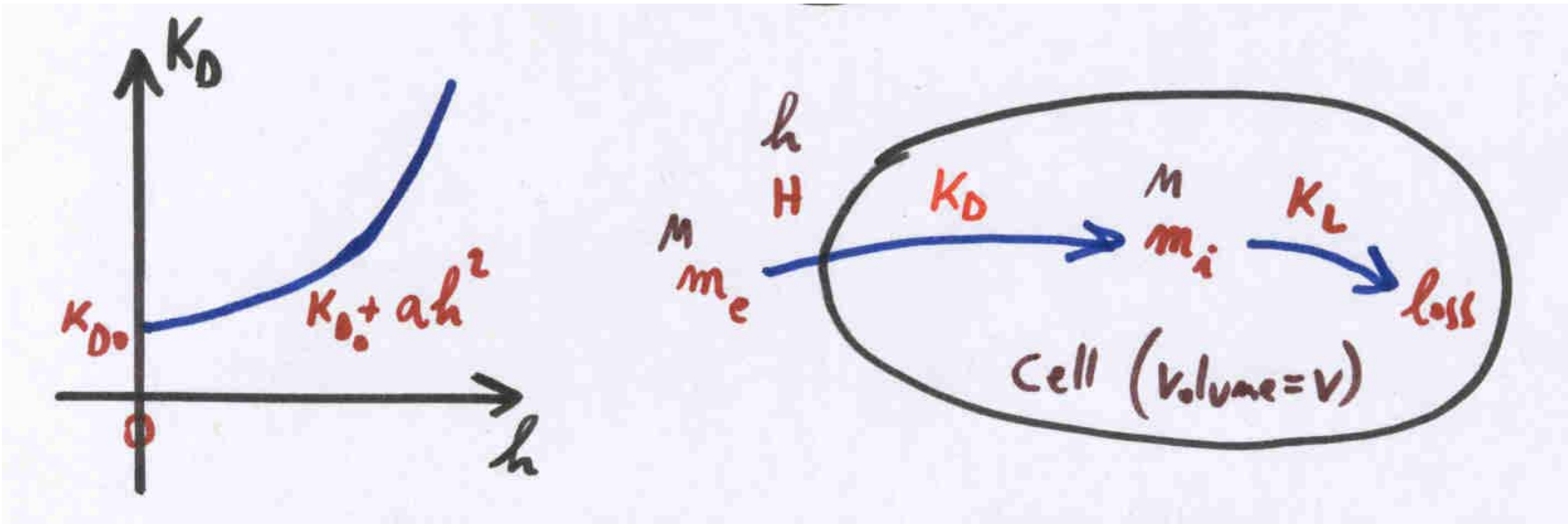


Follow-up example:



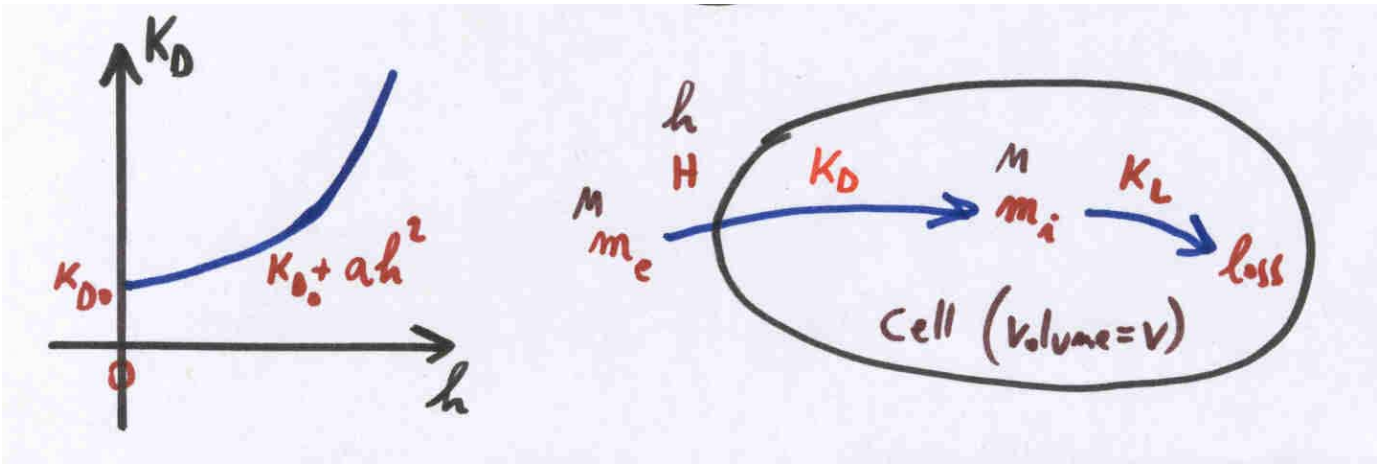
- What happens if B concentration y(t) is no longer constant? (that is, $y \neq y_0$).
- For instance, assume that B is made inside the cell at a rate $dy/dt = \alpha - \beta z$ if $z \geq 0$ (a biochemical feedback!)

Another example



- A Hormone H controls the diffusion of molecules M into a cell. Extra-cellular hormone concentration is h [ng/ml].
- Extra-cellular M concentration is m_e and intracellular concentration is m_i (all in [ng/ml])

Example requirements (cont'd)



- Molecules M are wasted (inside the cell) at a loss rate constant of K_L .
- Let the diffusion rate constant be $K_D=K_{D0}+ah^2$
- Write the model. Is it linear? [Answer: Yes, as m_e and h are external inputs]