Modelling Preliminaries

Physical principles
- conservation statements
- physics and Newton's laws

Appropriate regimes and "reality checks"
- densities, concentrations ≥ 0
- units of terms in eqn should match

Chemical rate equations
- first order (linear decay)
- mass action (interactions)
- Michaelis - Menten kinetics
- Sigmoidal kinetics and cooperativity

Mechanics of springs
- forces and potentials
- 2nd order ODE's (dynamics)
- large drag in the cellular realm

Mechanochemical effects
- forces affecting binding / unbinding
- molecular motors
- force - velocity relation.

Chemical conservation in well mixed system

$c(t)$ = concentration at time t

$$\frac{dc}{dt} = \text{rate of production} - \text{rate of decay}$$

(1) Simplest assumptions: - decay modeled as first-order kinetics

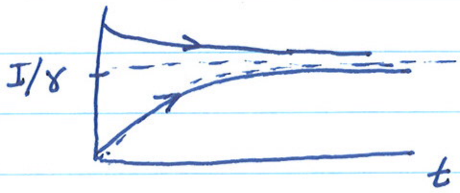
$\sim \gamma c \qquad \gamma \geq 0$

- production at some constant rate $I \geq 0$

$$\Rightarrow \boxed{\frac{dc}{dt} = I - \gamma c}$$

Advantages: from any initial $c(0)$ value, we have
$c(t) \to I/\gamma$ = constant steady state level

Typical solution curves



(2) Two state system with interconversion:

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \qquad k_{-1}, k_1 \text{ rate coefficients}$$

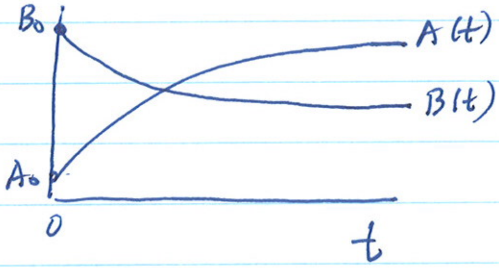
This chemical scheme corresponds to the ODEs

$$\begin{cases} \dfrac{dA}{dt} = -k_1 A + k_{-1} B \\ \dfrac{dB}{dt} = -k_{-1} B + k_1 A \end{cases}$$

To have same units on each term, assuming A, B concentrations
then k_1, k_{-1} have units $(\text{time})^{-1}$

The above interconversion automatically implies that the total $(A+B)$ is conserved since $\frac{dA}{dt} + \frac{dB}{dt} = 0$

$$\Rightarrow \quad A(t) + B(t) = M = \text{constant}$$



(3) Interactions and Law of Mass Action. (<u>LMA</u>)

For reactions in which two (or more) reactants must combine to form product (i.e. requiring "molecular collisions") we use an approximation that holds for "ideal gas"

$$A + B \underset{k_-}{\overset{k_+}{\rightleftharpoons}} P$$

<u>LMA</u>: Rate of reaction $A+B$ assumed to be $k_+ A \cdot B$

$$\Rightarrow \quad \frac{dA}{dt} = -k_+ AB + k_- P$$

$$\frac{dB}{dt} = -k_+ A \cdot B + k_- P$$

$$\frac{dP}{dt} = k_+ AB - k_- P$$

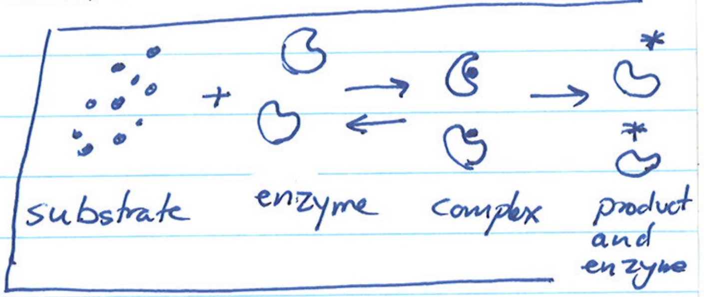
Conservation: above $\Rightarrow$ $\frac{dA}{dt} + \frac{dB}{dt} + 2\frac{dP}{dt} = 0$

$$A + B + 2P = \text{constant}$$

units: A, B, P : concentration
k_- : $(\text{time})^{-1}$
k_+ : $(\text{time})^{-1} (\text{concentr.})^{-1}$

Common Models for biochemical reactions

Enzyme-mediated (Michaelis-Menten) kinetics



Most biochemical reactions are mediated by a (limited supply of) enzymes, each catalyzing a conversion of substrate molecules to product molecules. Forming a complex is part of this process.

chemical scheme:

$$\underset{(\text{substr.})}{S} + \underset{(\text{enzyme})}{E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{(\text{complex})}{C} \xrightarrow{k_2} \underset{(\text{enzyme})}{E} + \underset{(\text{product})}{P}$$

Assumptions:

- The enzyme is not "used up". Conservation $\Rightarrow$ $E + C = \text{constant} = E_0$
- There is large excess of substrate ($S(0)$ is large)
- The complex is formed rapidly and "equilibrates" fast, so that $dC/dt \approx 0$ ($\leftarrow$ "Quasi steady state")

$\Rightarrow$ Set of ODES for S, P can be approximated by

$$\boxed{\frac{dP}{dt} = \frac{V_{max}\, S}{k_m + S}} \approx -\frac{dS}{dt}$$

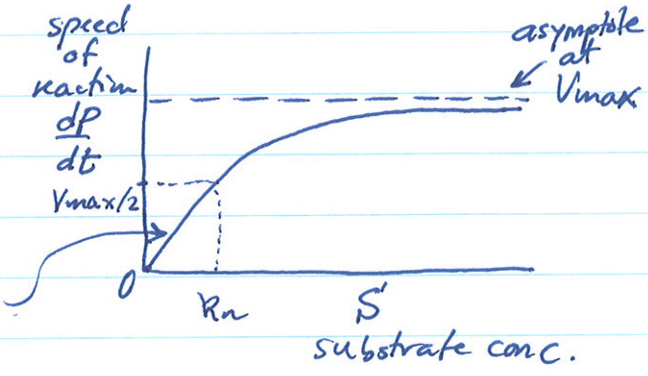
this is also called the "Reaction Speed"

where

$$\begin{cases} V_{max} = k_2 E_0 \\ k_m = \dfrac{k_{-1} + k_2}{k_1} \end{cases}$$

The above Michaelis-Menten kinetics holds after a short transient period of duration $\lambda \approx k_1 (S_0 + k_m)$

Michaelis - Menten, con'td



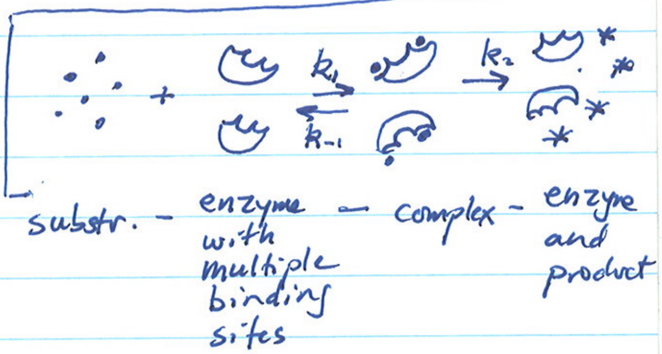
for low conc. of substrate, shape is roughly linear with slope $\frac{V_{max}}{K_m}$

Saturation is due to the limited amt. of enzyme available to catalyze the reaction.

For large S, the reaction speed is $\approx V_{max}$

Cooperativity and Hill functions

Enzymes with multiple binding sites or undergoing dimerization can exhibit sigmoidal kinetics.



Approximation:

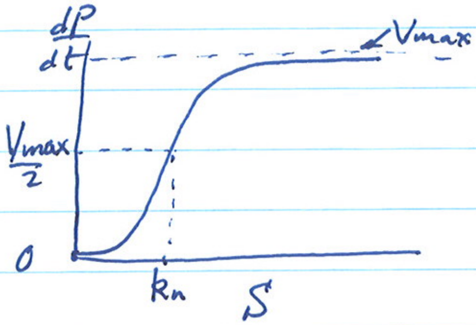
$$2S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} E + 2P$$

complex of enzyme with 2 substrate molecules

(Note: usually one substrate attaches first, accelerating the binding of the second. Here this is simplified.)

By analogy with Michaelis-Menten kinetics (with S replaced by S^2 by mass action approx) we get

$$\frac{dP}{dt} = \frac{V_{max}\, S^2}{k_n^2 + S^2}$$



More generally, we often use a Hill Function to describe sigmoidal kinetics (without detailed derivations)

$$f(S) = \frac{V_{max}\, S^n}{k_n^n + S^n}$$

$n = 2, 3, \ldots$ Hill coefficient

as n increases, so does the steepness of the transition.

Competitive Inhibition

(Rubinow, S.I. (1975)
Intro to Math Bio
Wiley NY).
p 56 - 58

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \xrightarrow{k_2} P_1 + E$$

$$I + E \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \xrightarrow{k_4} P_2 + E$$

S is the natural substrate of enzyme E, I an inhibitor that competes with S for binding to E

By writing down ODES for the above reaction scheme and assuming

$\frac{e_0}{s_0} \ll 1$ (excess of substrate concentration)

$\frac{k_1}{k_3} \approx 1$ (inhibitor and substrate on-rates comparable)

$\frac{s_0}{i_0} \sim 1$ (similar quantities of substrate and inhibitor)

Also taking QSS $\frac{dc_1}{dt} \approx 0$ $\frac{dc_2}{dt} \approx 0$ (complexes form fast)

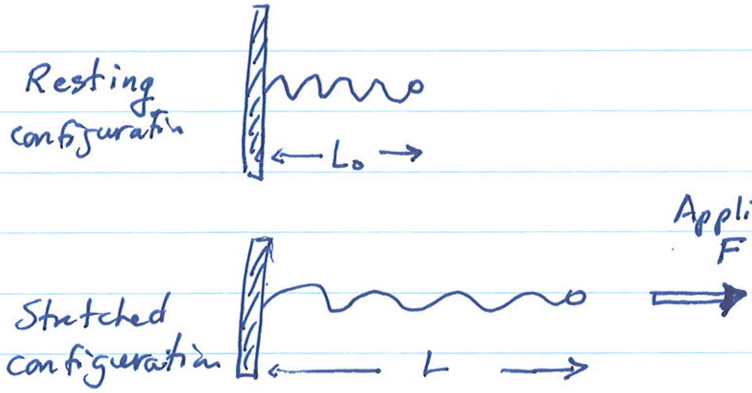
Can eliminate c_1, c_2 from ODES and (eventually) arrive at:

$$V_0 \approx \text{Reaction Rate} \approx V_s \frac{s}{\left[s + K_m^s\left(1 + \frac{i}{K_m^i}\right)\right]} = -\frac{ds}{dt}$$

where $K_m^s = \frac{k_{-1} + k_2}{k_1}$, $K_m^i = \frac{k_{-3} + k_4}{k_3}$, $V_s = k_2 E_0$

Remark: Competitive inhibitor effectively raises the critical conc K_m^s of the substrate.

Mechanics of springs



Rest length: $L_0 \geq 0$, constant

Applied force causes a displacement, e.g. stretch

Stretched length $L = L_0 + x$

"Linear spring": spring force is proportional to the displacement

The spring force is: $F_{spr} = - K x$

$\uparrow$ direction opposite to displacement

K = "spring constant" (units: Force/distance

e.g. picoNewton / micro-meter

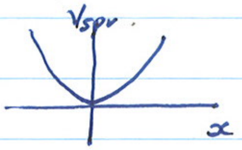
(pN / μm)

(this linearity assumption usually applies to small displacements)

This force can be expressed as the -ve gradient of a spring "potential function,"

$$F_{spr} = - \frac{\partial}{\partial x} V_{spr}. \qquad \text{where } V_{spr} = \frac{K}{2} x^2$$

V_{spr} has units of energy (and represents the energy stored in the stretched spring, i.e. its ability to do work.)



We can also think of V_{spr} as the energy required to deform an elastic material (spring).

Newton's Laws and spring dynamics

Conservation of momentum: Suppose the applied force is suddenly released, so system responds to new balance of forces

$$\frac{d}{dt}(mv) = F_{spring} + F_{friction}$$

rate of change of momentum

where m = mass of particle (assumed constant)
V = velocity = dL/dt = dx/dt

$F_{friction}$ = drag force or frictional force $\approx -\gamma v$
(linear approx)
γ = frictional (or drag) coefficient

$$\Rightarrow \quad m\frac{d^2x}{dt^2} = -Kx - \gamma\frac{dx}{dt}$$

$$\Rightarrow \quad \boxed{m\frac{d^2x}{dt^2} + \gamma\frac{dx}{dt} + Kx = 0}$$

General eqn for spring-mass system with linear spring and constant mass

To characterize full dynamics $x(t)$, need two initial conditions, e.g. $x(0) = x_0$, $v(0) \equiv x'(0) = v_0$

Cell scale springs : have tiny masses, huge drag coefficients so the inertial term, $m\frac{d^2x}{dt^2} \approx 0$

$$\Rightarrow \quad \gamma v \simeq F_{spring} = -Kx$$

(or, restated, the spring is in "overdamped" regime)

Review : dynamics of spring-mass systems

Solns of 2nd order ODE $m\frac{d^2x}{dt^2} + \gamma\frac{dx}{dt} + Kx = 0$

(linear, constant coeffs) $x(t) = Ce^{rt}$

⇒ characteristic eqn:

$$mr^2 + \gamma r + K = 0$$

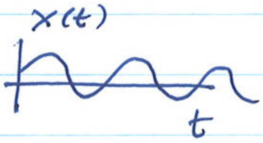
⇒ eigenvalues

$$r_{1,2} = \frac{-\gamma \pm \sqrt{\gamma^2 - 4mK}}{2m}$$

Cases: $\gamma = 0$ (no damping) $r = \pm\sqrt{\frac{K}{m}}\, i \equiv \pm \omega i$

solns

$$x(t) = C_1 e^{i\omega t} + C_2 e^{-i\omega t}$$
$$= A\sin(\omega t) + B\cos(\omega t)$$

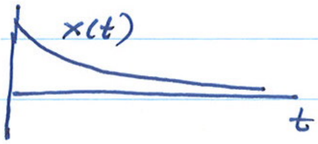


$\gamma^2 > 4mK$ (large damping)

$$x(t) = Ae^{r_1 t} + Be^{r_2 t}$$

⇒ decay

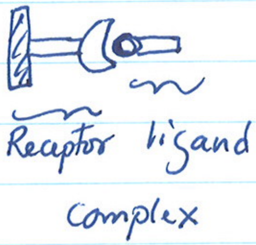
$r_1, r_2 < 0$

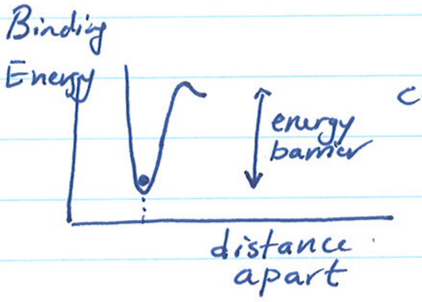


A, B (or C_1, C_2) found using the initial conditions.

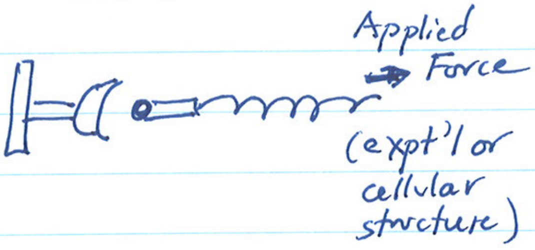
External forces cause increased rate of bond dissociation.

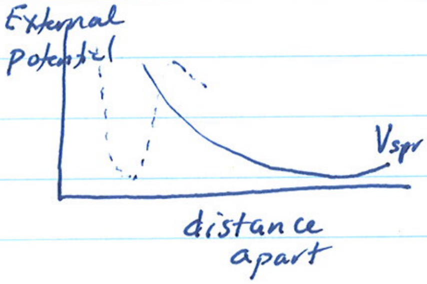
Forces can affect the rate of unbinding of a molecular complex (G.I Bell 1978, Science 200:618)



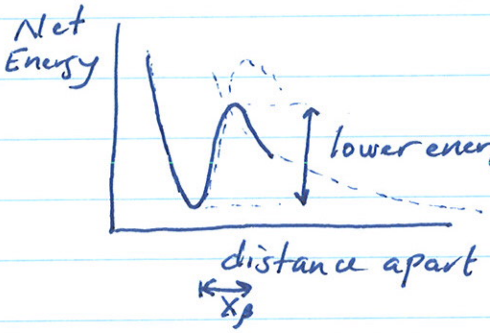


chemical energy "landscape" determines bond kinetics for receptor-ligand pair.





potential due to external applied force



The applied force (and its associated "spring"-potential) lowers the chemical energy barrier, making unbinding more likely.

Bond survival decreases exponentially with the pulling force f

$$t_{off}(f) \approx t^{\circ}_{off}\, e^{-f/f_\beta} \qquad \text{where } f_\beta = \frac{k_B T}{x_\beta}$$

x_β = typical distance needed for unbinding

where $k_B T$ = unit of thermal energy $\simeq 4.1$ pN/nm

Boltzman's const.

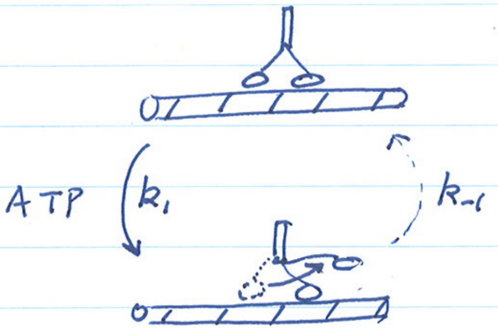
temperature (°K)

Unbinding rate increases exponentially

$$k_{off}(f) = k^{\circ}_{off}\, e^{+f/f_\beta}$$

Molecular Motors - 'machines' that can perform work, usually by "burning" chemical energy in the form of ATP. There are two distinct types: (Figs from Karsenti et al (2006))

Powerstroke

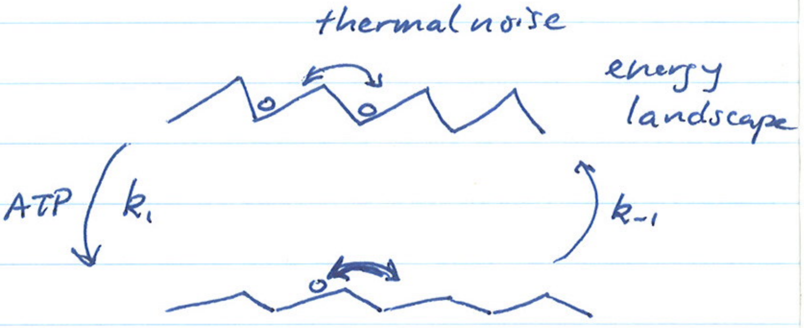


In this version, ATP hydrolysis changes the configuration of some part of the motor, doing work to move it or unbind some part of it

$$\text{Force} \approx \frac{\text{Energy}}{\text{stepsize}} \approx \frac{E_{ATP}}{\Delta X}$$

$$\approx \frac{80\,pN \cdot nm}{8\,nm} \sim 10pN$$

Ratchet



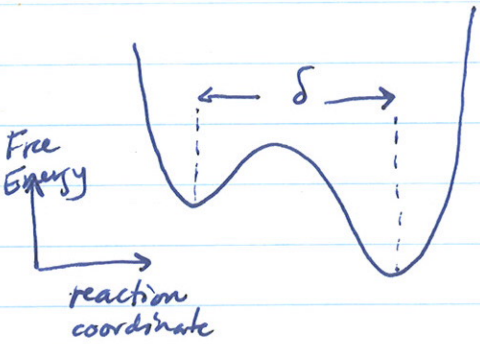
In this version, ATP hydrolysis changes the chemical "landscape" (i.e. chem. potential), making it easier for thermal noise to 'bump' the motor past some energy barrier.

$$\text{Force} \approx \frac{\text{Energy}}{\text{stepsize}} \approx \frac{k_B T}{\Delta x} \approx \frac{4pN \cdot nm}{8nm}$$

$$\approx 0.5pN$$

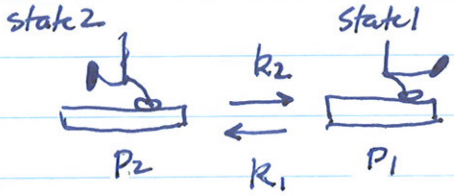
Mechanochemical cycle of 2-step motor

(minimodel by Alex Mogilner)



Consider a motor with two states. Suppose the transition 2 → 1 is a "power stroke", where motor does work against a load force f.
Let $p_1(t), p_2(t)$ be probabilities of states 1, 2.

powerstroke ⇒ $k_2 = k_2^\circ e^{-f\delta/k_B \cdot T}$ $\qquad k_1 = $ constant



$$p_1 + p_2 = 1 \qquad \text{(only 2 states)}$$

$k_1 \approx 100 \text{ sec}^{-1}$

$k_2 \approx 10^4 \text{ sec}^{-1}$

$\delta \approx 8 \text{ nm}$

$$\begin{cases} \dfrac{dp_1}{dt} = -k_1 p_1 + k_2 p_2 \\[2ex] \dfrac{dp_2}{dt} = k_1 p_1 - k_2 p_2 \end{cases}$$

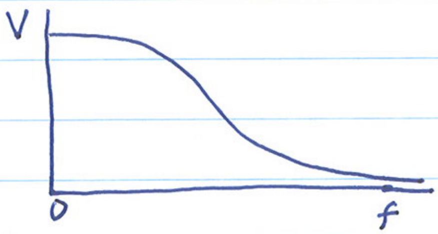
Equilibria: $\quad k_1 p_1 = k_2 p_2 \qquad p_1 = \dfrac{k_2}{k_1} p_2 \quad \Rightarrow \quad p_2\left(1 + \dfrac{k_2}{k_1}\right) = 1$

$$p_2 = \frac{k_1}{k_1 + k_2}$$

Velocity: $\quad V = \delta k_2 p_2 = \dfrac{\delta k_1 k_2}{k_1 + k_2} = \dfrac{\delta k_1 k_2^\circ}{k_1 e^{f\delta/k_B T} + k_2^\circ}$

⇒

"Force-velocity relationship":



Linear approximation

$$V = V_0 (1 - f/f_s)$$