

CELLULAR ENGINEERING: COMPUTATIONAL MODELING OF BIOPHYSICAL PROCESSES

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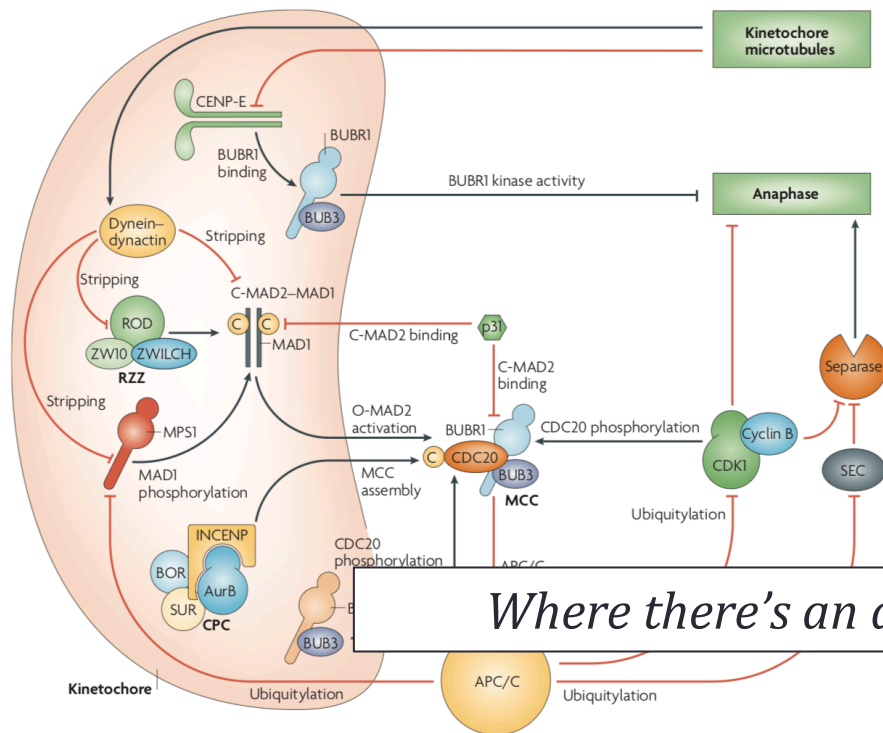
Goals for Module 6:

1. Introduce some of the basic physical and chemical processes that underlie cellular behaviors
2. Give examples of how to approach modeling these intracellular processes
3. Demonstrate how predictive models can be integrated with experiments to gain new insights
4. Inspire you to further explore these concepts and computational modeling of cellular processes!

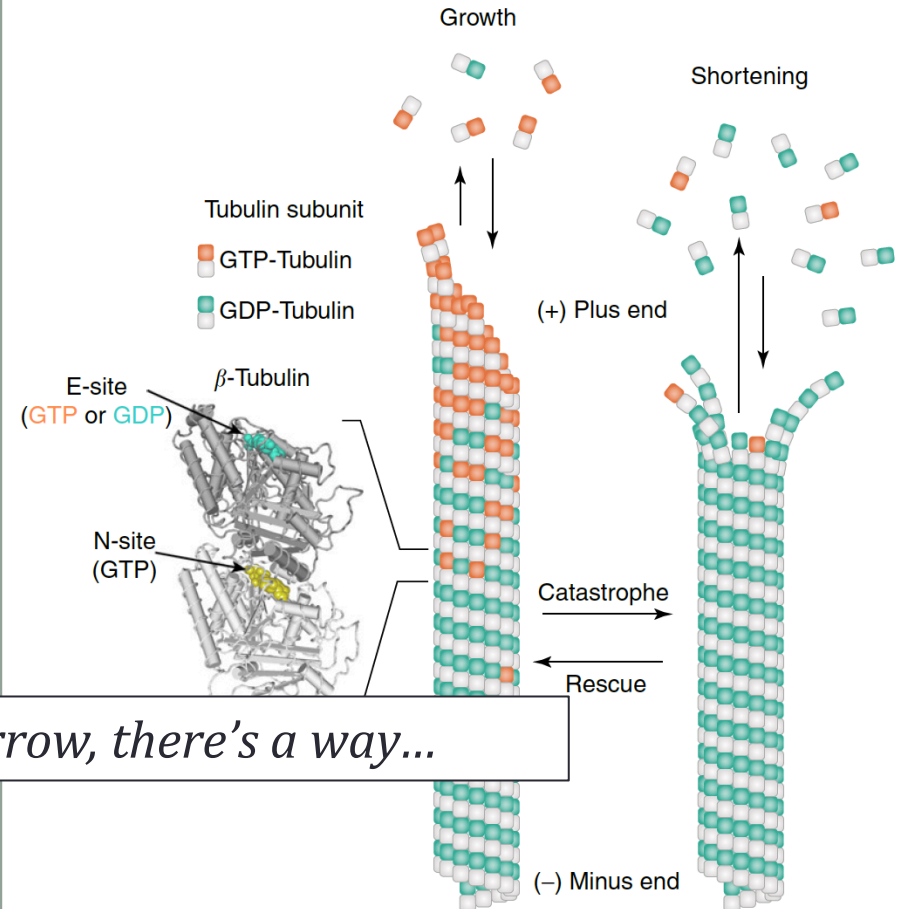
We have entered the post-genomic era, giving us the molecular parts list. We now need to build predictive models for cell behavior, so that we can design more effective therapies.

What can we model?

Spindle assembly checkpoint (SAC) signaling pathway



Biopolymer assembly dynamics



Where there's an arrow, there's a way...

Musacchio and Salmon, *Nat. Rev. Mol. Cell Biol.*, 2007

Castle and Odde, *Ency. of Cell Biol.*, 2016

Models must be based in physical and chemical principles

Essential Cellular Processes

1. Stuff inside cells has to move around...
 - Thermal energy and diffusion

1. Things interact with each other and implement forces...
 - Mechanical forces and energy potentials

2. Interactions produce some signal...
 - Chemical reactions and kinetics

Let's do a quick thought
experiment...

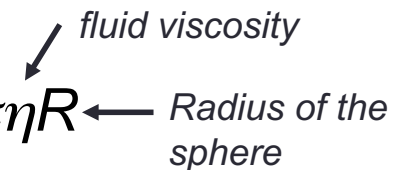
Diffusion

- Proteins and cells are subject to thermal forces, which are the result of collisions with water and other molecules in the surrounding fluid. As a result they are said to have **thermal energy**

Thermal energy \rightarrow in units of $k_B T$,
where k_B is Boltzmann's constant and T is temperature

- Forces due to these collisions are *randomly* directed, and the resulting motion is characterized by frequent changes in direction, called **diffusion**

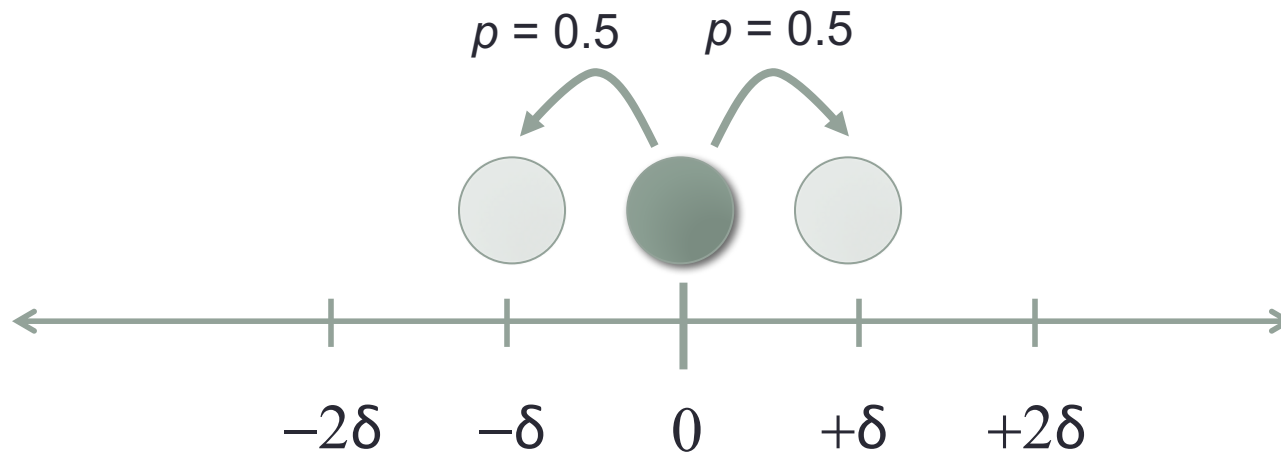
$$D = \frac{k_B T}{\gamma}$$

For a sphere, $\gamma = 6\pi\eta R$
The diagram shows the equation $\gamma = 6\pi\eta R$. An arrow points from the label "fluid viscosity" to the symbol η . Another arrow points from the label "Radius of the sphere" to the symbol R .

here D is the diffusion coefficient and γ is the drag coefficient

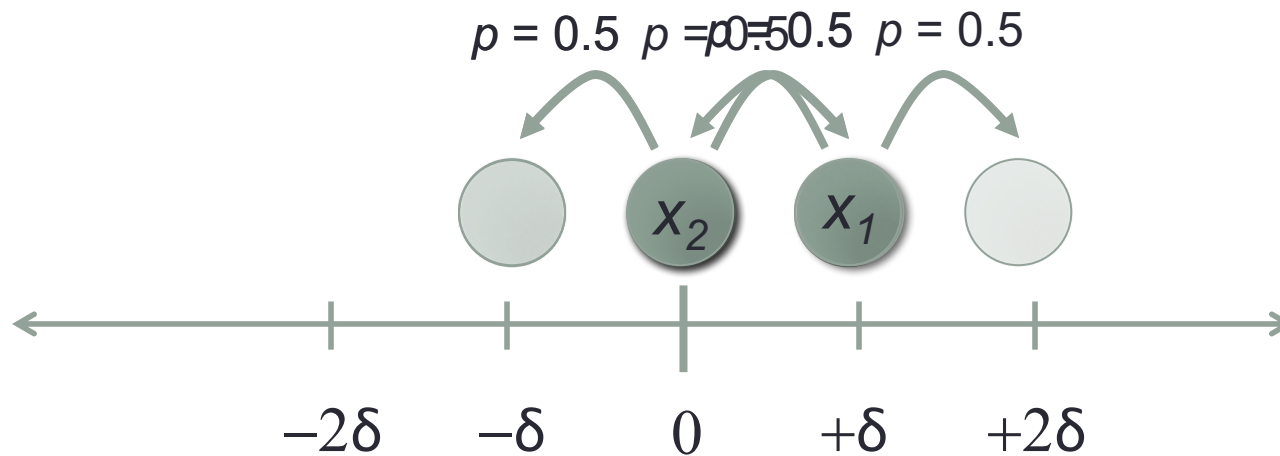
Diffusion as a Random Walk

- Diffusion is a form of random motion that is characterized by frequent, abrupt changes in direction
- Diffusion in the absence of force can be approximated by a **random walk**



1D Random Walk

Diffusion as a Random Walk



$$x_1 = x_0 \pm \delta$$

$$x_2 = x_1 \pm \delta$$

$$\vdots$$

$$x_n = x_{n-1} \pm \delta$$

Let's simulate it...

Diffusion as a Random Walk

How far is the molecule or protein expected to go in time?

Mean-squared displacement (MSD)

$$\langle x_1^2 \rangle = \langle (x_0 \pm \delta)^2 \rangle = \delta^2$$

$$\langle x_2^2 \rangle = \langle (x_1 \pm \delta)^2 \rangle$$

$$= \langle x_1^2 \pm 2x_1\delta + \delta^2 \rangle$$

$$= \langle x_1^2 \rangle + \langle \delta^2 \rangle$$

$$= \delta^2 + \delta^2$$

$$= 2\delta^2$$

\vdots

$$\langle x_n^2 \rangle = n\delta^2$$

If we say

$$t = n\tau$$

then the number of steps in time t is given by

$$n = t / \tau$$

and therefore

$$\langle x^2(t) \rangle = \frac{\delta^2}{\tau} t$$

Diffusion coefficient $\rightarrow D = \frac{\delta^2}{2\tau}$ (from **Fick's Law**)

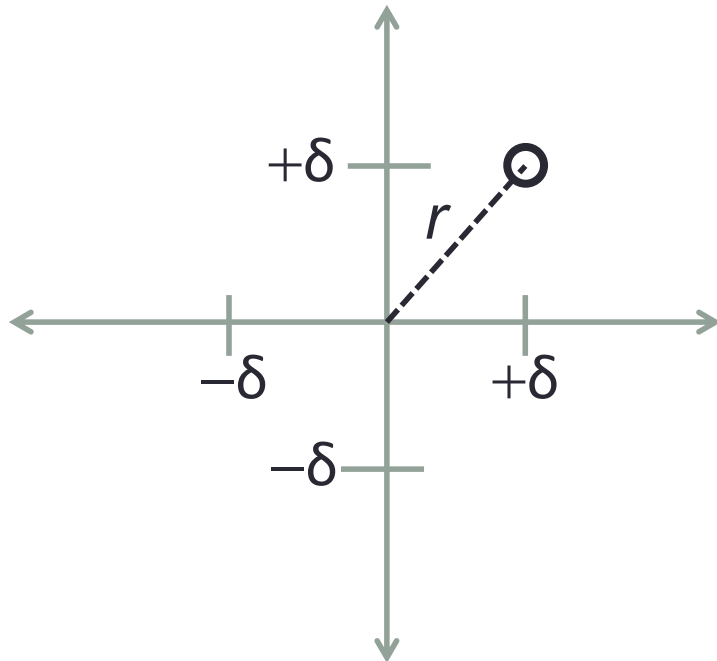
then we have

$$\langle x^2(t) \rangle = 2Dt$$

Diffusion as a Random Walk

$$\langle x^2(t) \rangle = 2Dt$$

What if we expand in to multiple dimensions?



In 2-dimensions

$$r^2 = \delta^2 + \delta^2 = 2\delta^2$$

In 3-dimensions

$$r^2 = \delta^2 + \delta^2 + \delta^2 = 3\delta^2$$

therefore we have that

$$\langle r^2(t) \rangle = 2dDt$$

dimensionality

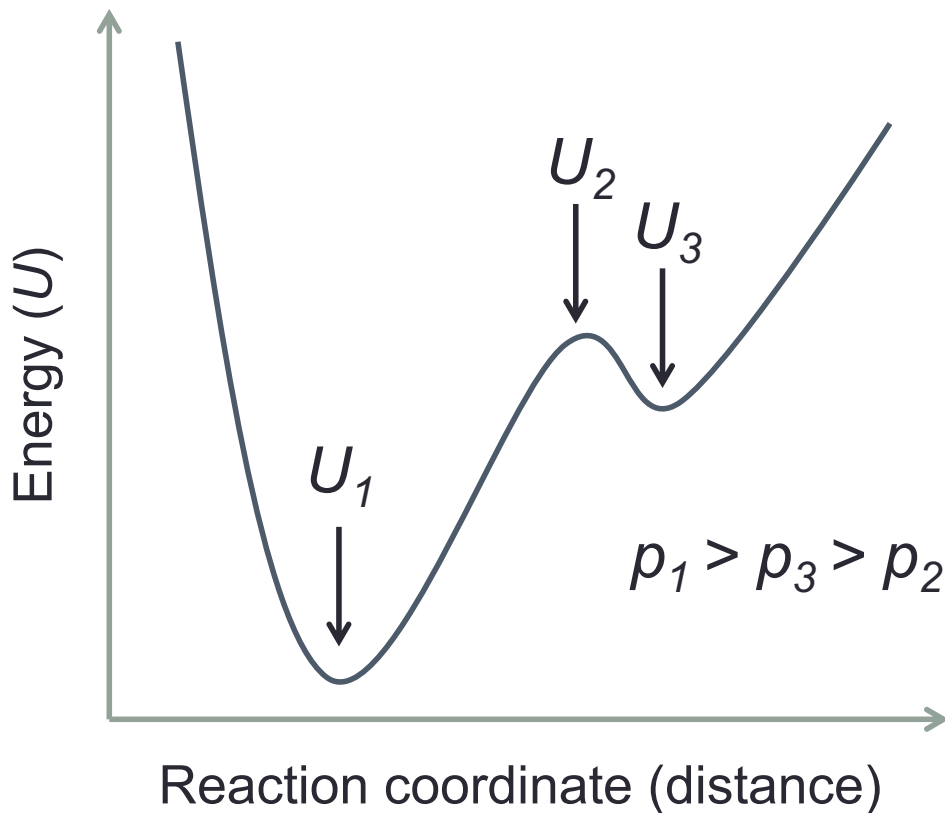
Diffusion in an Energy Potential

- A molecule always tends towards its lowest energy state (whether it is folding conformations or binding interactions)
- The chemical forces that drive biological processes have energies on the order of thermal energy ($k_B T$), meaning diffusive (random) motions are quite large comparatively, causing molecules to not always be at the lowest energy state
- **Boltzmann's law** states that if a particle or system is in thermal equilibrium, then the probability of being in state i that has energy U_i is given by

$$p_i = \frac{1}{Z} \exp\left(\frac{-U_i}{k_B T}\right) \quad \text{where} \quad Z = \sum_i \exp\left(\frac{-U_i}{k_B T}\right) \quad \text{and} \quad \sum_i p_i = 1$$

Diffusion in an Energy Potential

Where would you expect to find more molecules?



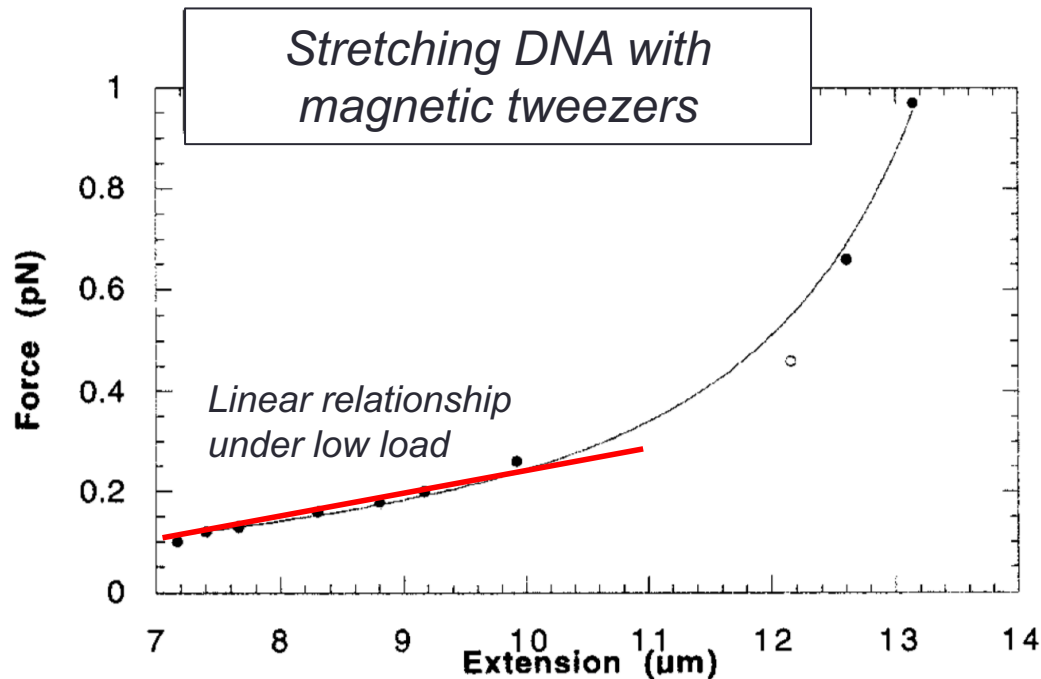
Boltzmann's Law

$$p \propto \exp\left(\frac{-U}{k_B T}\right)$$

$$\frac{p_2}{p_1} = \exp\left(\frac{-(U_2 - U_1)}{k_B T}\right) = \exp\left(\frac{-\Delta U}{k_B T}\right)$$

Macromolecules and Proteins as a Simple Spring

For small extensions, the force-extension relationship of macromolecules and proteins is reasonably approximated by a spring



Haber and Wirtz, *Rev. Sci. Instr.*, 2000

Simple Spring
Hooke's Law

$$U = \frac{1}{2} k x^2$$

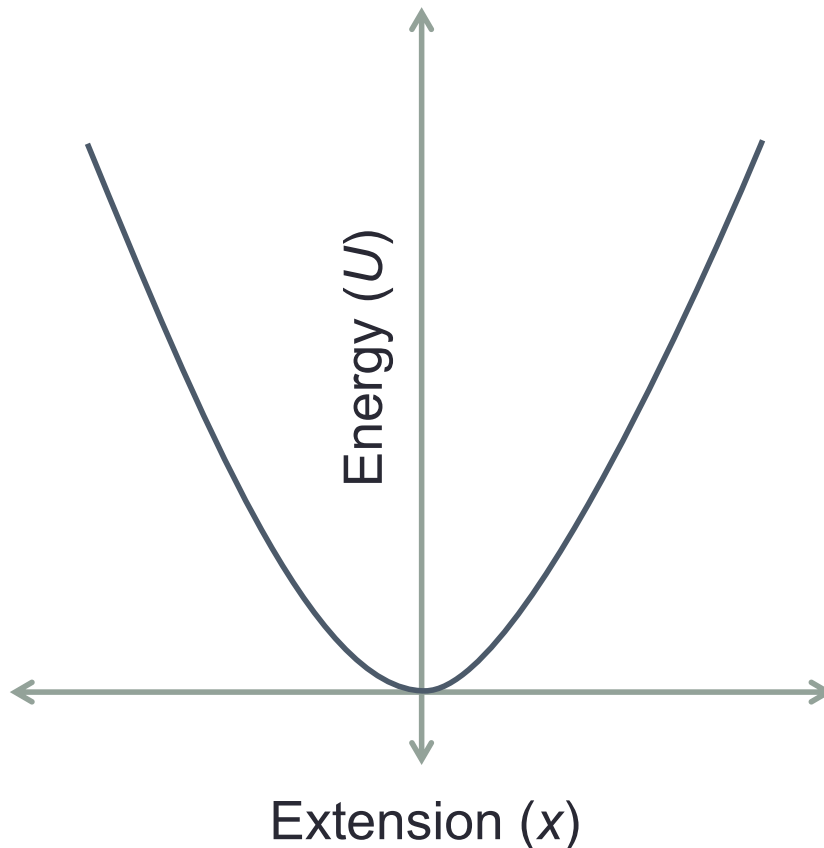
Force \rightarrow $F = -\frac{dU}{dx} = -kx$

extension \rightarrow x

Spring constant \rightarrow k

Macromolecules and Proteins as a Simple Spring

For small extensions, the force-extension relationship of macromolecules and proteins is reasonably approximated by a spring



Simple Spring
Hooke's Law

$$U = \frac{1}{2} k x^2$$

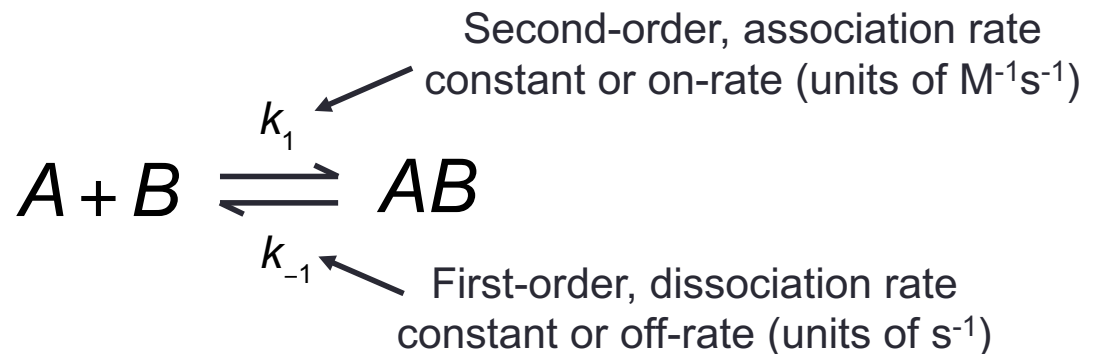
$$\text{Force} \rightarrow F = -\frac{dU}{dx} = -kx$$

extension

Spring constant

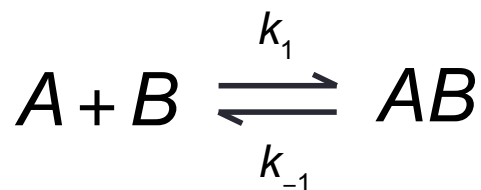
Bimolecular Reactions

- In addition to mechanical and thermal forces, proteins are also subject to chemical forces, which arise from the formation of intermolecular bonds
- A very important chemical reaction in cell biology is the **bimolecular reaction**, in which two molecules come together to react or form a complex. A simple case is



Here A and B reversibly associate to form the complex AB .

Bimolecular Reactions



Dissociation
constant

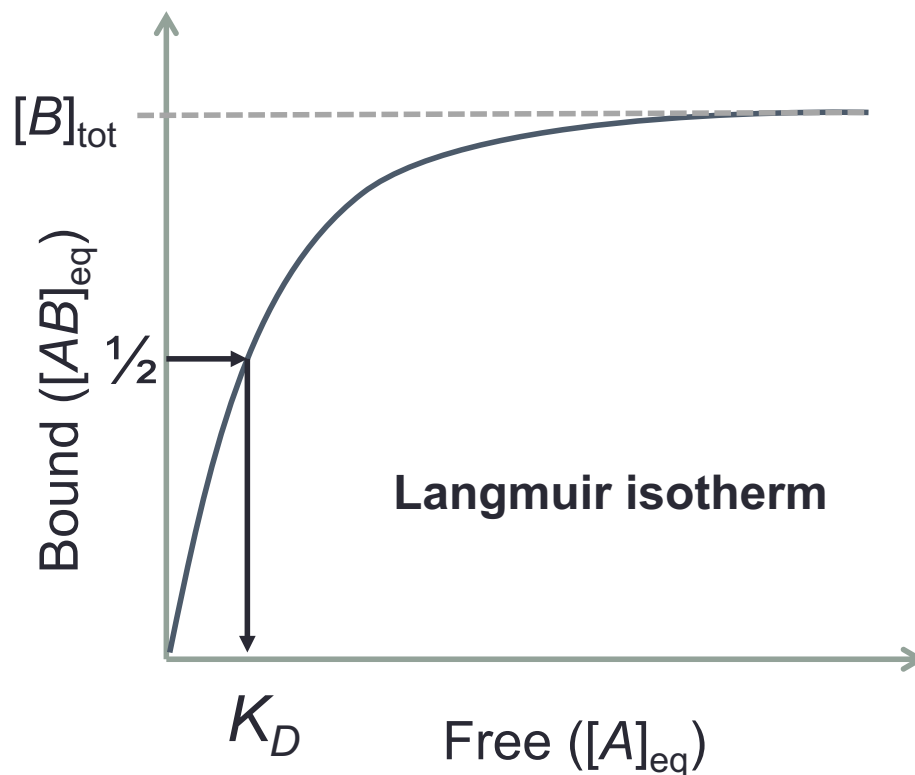
$$\frac{k_{-1}}{k_1} = K_D = \frac{1}{K} = \frac{[A]_{eq} [B]_{eq}}{[AB]_{eq}}$$

Equilibrium
constant

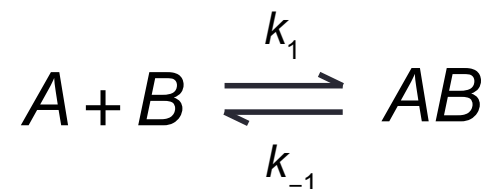
Let's say $[B]_{eq} = [B]_{tot} - [AB]_{eq}$

then $K_D = \frac{([B]_{tot} - [AB]_{eq})[A]_{eq}}{[AB]_{eq}}$

and $[AB]_{eq} = \frac{[B]_{tot} [A]_{eq}}{K_D + [A]_{eq}}$



Reversible Reaction Kinetics

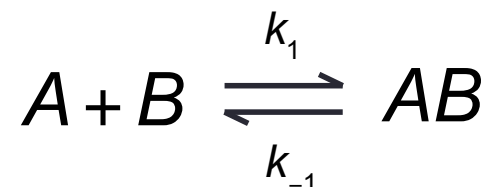


Often we want to know how the concentration of each component changes in time. For species A , it is lost in time due to the forward reaction (binding to B) and created by the reverse reaction (unbinding of AB)

$$\frac{d[A]}{dt} = \overbrace{-k_1[A][B]}^{[A] \text{ lost by the forward reaction}} + \underbrace{k_{-1}[AB]}_{[A] \text{ created by the reverse reaction}}$$

$$\frac{d[A]}{dt} = \frac{d[B]}{dt} = -\frac{d[AB]}{dt}$$

Reversible Reaction Kinetics

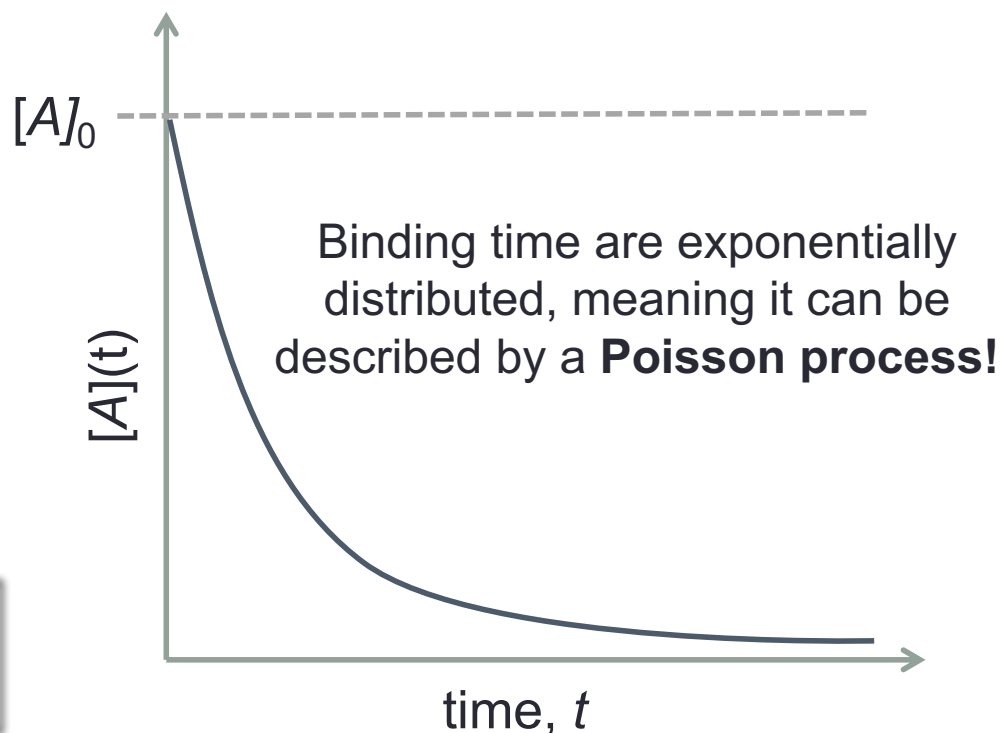


Let's say we add a small pulse of A at the beginning of the reaction, and want to know the timescale of A converting to AB through the forward reaction.

$$\begin{aligned}\frac{d[A]}{dt} &= -k_1[A][B] \\ -\frac{1}{k_1[B]} \int \frac{1}{[A]} d[A] &= \int dt \\ -\frac{1}{k_1[B]} \ln([A]) &= t\end{aligned}$$

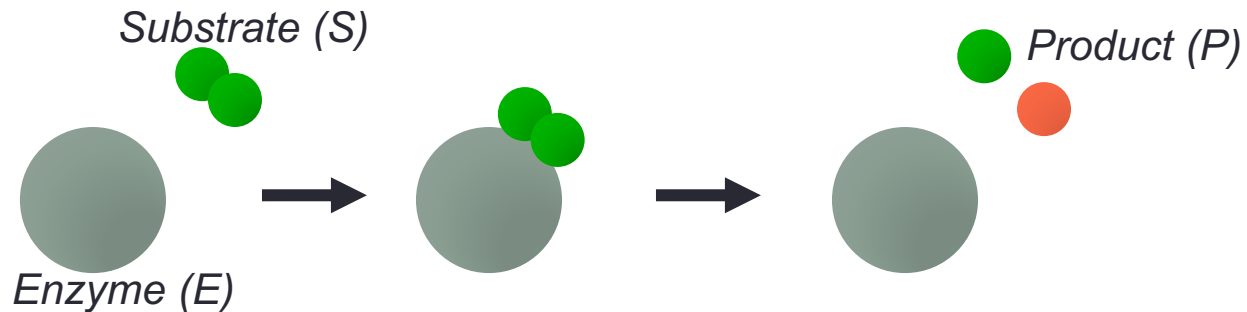
We can solve to get

$$[A](t) = [A]_0 \exp(-k_1[B]t)$$

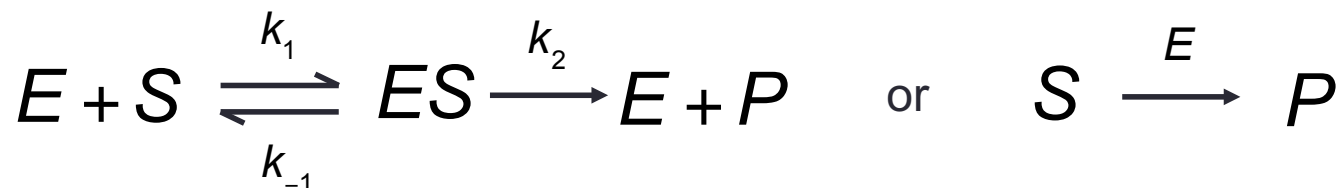


Enzyme Kinetics

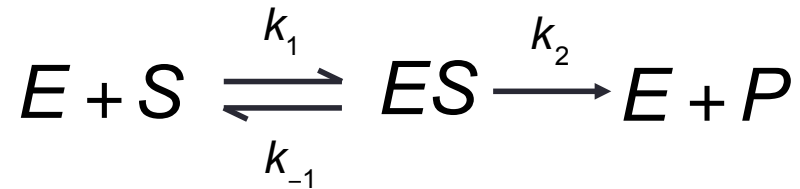
- **Enzymes** act as biological catalysts, increasing the rate of a chemical reaction by lowering the activation energy between states



- An enzymatic reaction can be thought of as special case of the bimolecular reaction. Here we can think of A being the enzyme (E) and B the substrate (S), while AB is the intermediate that breaks down into the enzyme plus the product (P) such that



Enzyme Kinetics



or more simply



$$\frac{d[P]}{dt} = -\frac{d[S]}{dt} = \frac{v_{\max} [S]}{K_M + [S]} \quad \text{where} \quad v_{\max} = k_2 [E]_{\text{tot}}$$

This is known as the **Michaelis-Menten equation**. Here K_M is the Michaelis-Menten constant and k_2 is the maximum catalysis rate per enzyme

Models must be based in physical and chemical principles

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1. Things interact with each other and implement forces...
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For Thursday...

1. Brief introduction to MATLAB and the MATLAB Live environment
 - Make sure you have access to MATLAB ahead of time! An instructional can be found on the Synapse page
2. Examples of how to approach simulating the processes discussed today
3. Introduction to the Module Activity