

MB&B 302: Principles of Biophysics

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Module I: Physical Principles and Biological Macromolecules

Lecture 1: Principles of Classical and Statistical Physics

Reminders of Physical Principles

1. Force is transmitted through direct contact or a field.

	Force	Expression	Magnitude (pN)
	Elastic	$-kx$	1 – 100
	Viscous	$-\gamma v$	1 – 1000
Thermal (Collisional)		$m \frac{dv}{dt}$	100 – 1000
	Gravitational	mg	$< 10^{-9}$
	“Centrifugal”	$m\omega^2 r$	$< 10^{-3}$
	Magnetic	$qv \times B$	$<< 10^{-6}$
	Electrostatic	zE	1 – 1000

Note: $\gamma = 6\pi\eta r$ is the drag coefficient.

2. Reynold’s number (R_e) characterizes the relative importance of friction and inertia.

$$R_e = \frac{\text{Inertia "Force"}}{\text{Viscous Force}} = \frac{(\text{velocity})(\text{particle size})(\text{fluid density})}{\text{fluid viscosity}} = \frac{vL\rho}{\eta}$$

The inertial term scales with mass, and the viscous term scales with the drag coefficient and velocity. R_e tells you what opposes acceleration. Small R_e (e.g., most biological bodies) means drag dominates and systems are overdamped. Large R_e (e.g., ocean liner) means mass dominates.

Ideal Gas Law ($PV = nRT = k_B T$)

1. Both PV and $k_B T$ are expressions of energy (units in Joules).
2. The energy of each molecule is $\frac{3}{2}k_B T$.
Multiply by 3 to account for x , y , and z axes. Divide by 2 because pressure measurements double-count the energy from a particle’s change in momentum $\Delta p = 2mv_x$.
3. Law of Equipartition: The mean energy associated with each degree of freedom is $\frac{1}{2}k_B T$. There are up to 3 dfs associated with translation and 3 dfs associated with rotation.
4. Background thermal energy is $k_B T = \frac{RT}{N_A} \approx 0.6$ kcal/mol
 - a. 1 $k_B T \Rightarrow$ transient conformational changes.
 - b. 1 ATP = 20 $k_B T \Rightarrow$ stable conformational changes.
 - c. 1 Glucose = 36 ATP = 720 $k_B T \Rightarrow$ support multiple enzymatic processes.

Lecture 2: Diffusion, Random Walks, and Brownian Motion

Outline

1. Background thermal noise provides kinetic energy to particles around and overcome activation barriers. In biological systems, this value is $k_B T$, which constitutes the minimum stable energy for resisting thermal motion (increases binding affinity by 3x).
2. Collisions with other molecules results in random Brownian motion.
3. The random walks of diffusing particles yield net displacement without a net change in mean position.

RMS Velocity

Set kinetic energy equal to thermal energy and solve:

$$E_k = \frac{1}{2} m (v^2)_{avg} = \frac{3}{2} k_B T$$
$$v_{rms} = \sqrt{\frac{3k_B T}{m}} = \sqrt{\frac{3RT}{N_A m}} = \sqrt{\frac{3RT}{M}}$$

- For a lysozyme (M.W. = 14 kg/mol), $v_{rms} = 23$ m/s = 50 mph.
- For an H_2O molecule (M.W. = 0.018 kg/mol), $v_{rms} = 640$ m/s = 1400 mph.
- These are instantaneous (pre-collision) velocities.

Collisions with Aqueous Environments

1. Compute the density of water from 55 M.

$$\frac{55 N_A}{1000 \text{ cm}^3} = \frac{55 (6.022 \times 10^{23}) \text{ molecules}}{10^{24} \text{ nm}^3} = 33.1 \frac{\text{molecules}}{\text{nm}^3}$$

- The average volume occupied per H_2O is $1/33.1 = 0.03 \text{ nm}^3$.
 - The mean distance between the centers of water molecules is $\sqrt[3]{0.03} = 0.32 \text{ nm}$.
2. Nanosecond timescale simulations are achieved with MD.

1D Random Walks: Theory

1. We can model the random walk as a Markov chain with states $\{-3\delta, -2\delta, -\delta, 0, +\delta, +2\delta, +3\delta\}$ with transition probabilities $P(\text{left}) = P(\text{right}) = 0.5$.
2. In other words, $X_n = X_{n-1} + \delta I_\delta$, where I_δ is a random variable indicating right movement (1) or left movement (-1). $P(I_\delta = 1) = P(I_\delta = -1) = 0.5$, and $E[I_\delta] = 0$.
3. Result 1: Mean displacement $E[X_n] = 0$.
Proof:

$$E[X_n] = E[X_{n-1}] + \delta E[I_\delta] \tag{1}$$

$$= E[X_{n-1}] + 0 \tag{2}$$

$$= E[X_0] \text{ (by recursion)} \tag{3}$$

$$= 0 \text{ (starting position = 0)} \tag{4}$$

4. Result 2: Mean square displacement (or MSD) $E[X_n^2] \propto n$.
Proof:

$$E[X_n^2] = E[(X_{n-1} + \delta I_\delta)^2] \quad (5)$$

$$= E[X_{n-1}^2 + 2X_{n-1}\delta I_\delta + \delta^2] \quad (6)$$

$$= E[X_{n-1}^2] + 2X_{n-1}\delta E[I_\delta] + E[\delta^2] \quad (7)$$

$$= E[X_{n-1}^2] + \delta^2 \text{ (middle term = 0)} \quad (8)$$

$$= n\delta^2 \text{ (by recursion)} \quad (9)$$

Let τ indicate the time per step ($t = n\tau$). From this, we can compute:

$$E[X_t^2] = t \left(\frac{\delta^2}{\tau} \right) \quad (10)$$

$$E[X_t^2] \propto t \quad (11)$$

$$RMS(X_t) \propto \sqrt{t} \quad (12)$$

1D Random Walks: Application to Diffusion

1. Diffusion vs. Active Transport In diffusion:
 - RMS displacement is proportional to $\sqrt{\text{time}}$.
 - MSD is proportional to time.

In active transport:

- Velocity is constant.
- RMS displacement is proportional to time.
- MSD is proportional to time².

2. Diffusion coefficient (D)

Defining $D = \frac{\delta^2}{2\tau}$ allows us to simplify:

- $E[X_t^2] = 2Dt$
- $RMS(X_t) = \sqrt{2Dt}$

We can use this to compute how fast a molecule diffuses down a line.

3. Diffusion by Increased Variance

Because variance is defined as the centered second moment, we should expect it to vary exactly like the mean squared displacements.

Proof:

$$Var[X_t] = E[X_t^2] - E[X_t]^2 \quad (13)$$

$$= t \left(\frac{\delta^2}{\tau} \right) - 0 \quad (14)$$

$$\propto t \quad (15)$$

The variance of particle displacements increases linearly with time. This means that any initial distribution of particle positions will spread out over time.

Random Walks in N dimensions

If the particle moves independently in n dimensions, we have:

$$d_n^2 = X_1^2 + X_2^2 + \dots + X_n^2 \quad (16)$$

$$E[d_n^2] = E[X_1^2 + X_2^2 + \dots + X_n^2] \quad (17)$$

$$= E\left[\sum_{i=1}^n X_i^2\right] \quad (18)$$

$$= \sum_{i=1}^n 2Dt \quad (19)$$

$$= 2nDt \quad (20)$$

$$(21)$$

- $RMS(d_1) = \sqrt{2Dt}$
- $RMS(d_2) = \sqrt{4Dt}$
- $RMS(d_3) = \sqrt{6Dt}$
- \dots
- $RMS(d_n) = \sqrt{2nDt}$

First passage time: the time it takes to diffuse over a given distance (solve for t in the above equations).

Diffusion Constant Revisited

The Einstein relation (for spherical particle):

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

For translational diffusion:

- $\gamma = 6\pi\eta r$
- D is inversely proportional to size/radius

For rotational diffusion:

- $\gamma_\theta = 8\pi\eta r^3$
- D is inversely proportional to size/radius CUBED

Time Dependence of Diffusion and Active Transport

- It takes 100x longer to diffuse 10x as far.
- Large cells adapted in two ways:
 - Active transport: skip diffusion altogether
 - Confinement (vesicles and organelles): constrains diffusive motion to “corrals”
- Active transport creates a quadratic relationship between time and MSD (as opposed to linear in diffusion).
- Confinement radius is approximately equal to the average RMS displacement, and can therefore be computed as $\sqrt{\text{MSD plateau value}}$.

Lecture 3: Chemical Equilibria, Binding, and Kinetics

Background

Ligand binding to macromolecules can be modeled as a reversible bimolecular reaction.



Equilibrium constant:

$$K_a = \frac{[ML]}{[M][L]} \rightarrow K_d = \frac{[M][L]}{[ML]}$$

Equilibrium is when the chemical potentials are equal. Chemical potential:

$$\mu_i = \frac{\partial G}{\partial N_i}$$

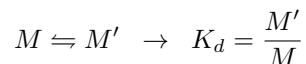
At constant temperature and pressure, chemical potential is equivalent to the molar free energy.

$$G_{eq} = G_{M',eq} - G_{M,eq} = 0$$

Conformational Changes

Structural state: time-averaged mean of conformational states about a stable energy minimum.

Conformation changes can be modeled as a reversible unimolecular reaction.



Boltzmann's Law

Boltzmann's Law defines the probability of occupying any state (i) with energy U_i .

$$p_i = \frac{1}{Z} \exp \left[\frac{-U_i}{k_B T} \right]$$

Z is a normalizing constant called the “partition function,” i.e., the sum of all probability mass contributions.

$$Z = \sum_i \exp \left[\frac{-U_i}{k_B T} \right]$$

Applying Boltzmann's Law

The probability of populating the less favorable energy state $U_2 > U_1$ can be predicted from ΔU :

$$\frac{p_2}{p_1} = \frac{[M']}{[M]} = K_a = \exp \left[\frac{-\Delta U}{k_B T} \right] = \exp \left[\frac{-\Delta G^0}{k_B T} \right]$$

Smaller ΔU (rotational < vibrational < electronic) leads to larger fractions occupying the higher state (between 0-50%).

Adding energy (e.g., work) can shift the equilibrium distribution of states:

$$K_{eq} = \exp \left[\frac{-\Delta G^0 + F \Delta x}{k_B T} \right]$$

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