Biomolecules as polymers

– at least two of the primary classes of biomolecules are polymers (proteins and DNA/RNA, often saccharides as well)

– physicists have developed a rich set of theories for polymers

– How can we use them to gain new biological understanding?

DNA packing into bacteria
Do atoms always matter?

For understanding the function of an enzyme, we need an atomic-detailed structural description.

The bacterial cell wall on the other hand is often best described from a statistical (average) point of view.
Random walks

A simple model of a polymer is a random walk in space.

Fixed segments of equal length are connected at hinges, can go in any direction.

Length of each segment is defined as the Kuhn length ($a$).

DNA as a random walk.
Measurable properties

What do we want to measure for our random walks?

“random” implies only average properties are useful, e.g., $\langle R \rangle$, $\langle R^2 \rangle$, $p(R,N)$

Apply the tools of statistical mechanics to calculate overall length (macrostate) from its underlying microstates counting # states ($W$) for each $n_r$ or $n_l$
**Probability distributions**

*Binomial distribution*

\[ P(n_r; N) = \frac{N!}{n_r!(N - n_r)!} \left( \frac{1}{2} \right)^N \]

*Gaussian distribution*

\[ p(R; N) = \frac{2}{\sqrt{2\pi N}} e^{-R^2 / 2Na^2} \]

What is \( P(R; N) \)?
Probability distributions

\[ p(R; N) = \frac{2}{\sqrt{2\pi N}} e^{-R^2 / 2Na^2} \]

Normalization (\( \int_{-\infty}^{\infty} p(R; N)dR = 1 \)) implies that

\[ P(R; N) = \frac{1}{\sqrt{2\pi Na^2}} e^{-R^2 / 2Na^2} \]

and in 3D:

\[ P(\mathbf{R}; N) = \left( \frac{3}{2\pi Na^2} \right)^{3/2} e^{-3R^2 / 2Na^2} \]

Distribution is \textbf{Gaussian} with mean \( <R> = 0 \) and variance \( <R^2> = Na^2 \)
Central limit theorem

For a set of $N$ random variables $\{x_n\}$ with finite mean and variance (e.g., the individual segments of a polymer), the sum $X = x_1 + x_2 + \ldots + x_N$ (e.g., the end-to-end distance) will tend towards a Gaussian distribution regardless of the distribution of $x_n$

$$P(R; N) = \frac{1}{\sqrt{2\pi N a^2}} e^{-R^2/2N a^2}$$

sum of $n$ dice throws
Persistence length

Persistence length ($L_p$) is defined microscopically by the correlation between the directions of successive segments of our chain:

$$\langle \vec{t}(s) \cdot \vec{t}(u) \rangle = e^{-|s-u|/L_p}$$

$$\vec{R} = \int_0^L ds \ \vec{t}(s)$$

$$\langle \vec{R}^2 \rangle = \left\langle \int_0^L ds \ \vec{t}(s) \cdot \int_0^L du \ \vec{t}(u) \right\rangle$$

$$= 2 \int_0^L ds \int_s^L du \ e^{-(u-s)/L_p} \approx 2LL_p = Na^2 = aL$$

Therefore $L_p = a/2$ (the Kuhn length)

The random walk model we just developed is also known as the **Freely Jointed Chain** model.
Persistence length

\[
\langle R_G^2 \rangle = \frac{1}{N} \sum_{i=1}^{N} \langle (\vec{R}_i - \vec{R}_{CM})^2 \rangle
\]

Radius of gyration (\(R_G\)): average distance between links and center-of-mass

\[
\vec{R}_{CM} = \frac{1}{N} \sum_{i=1}^{N} \vec{R}_i \quad \Rightarrow \quad \sqrt{\langle R_G^2 \rangle} = \sqrt{\frac{LL_p}{3}}
\]

\(E. coli\) genome is \(\sim 4.6\times10^6\) base pairs

\[
\sqrt{\langle R_G^2 \rangle} \approx 5 \mu m
\]

About 2\(x\) as big as seen in the picture, but it has some constraints (e.g., circular)

Clearly strong forces are necessary to pack it in the cell!
Recall that our free energy $G = U - TS + PV$ (Gibbs)

A change in energy (e.g., from applied tension) generates a restoring force, $F_{\text{restore}} = -\frac{\partial G}{\partial L}$

$U, T, P$ are constant for freely-jointed chain, making

$$F = -T\left(\frac{\partial S}{\partial L}\right)$$

Even though the chain does not store internal energy, it still can exert a force as an entropic spring
Improvements to the FJC model

FJC model (fixed segments)

Worm-like chain (elastic, with an energetic bending cost)

modified WLC, now with a stretching cost as well


“Molecular origin of the hierarchical elasticity of titin: simulation, experiment and theory.”
Worm-like chain (WLC) model

Our polymer is now characterized by a unit tangent vector $t(s)$, where $s$ is the position along the chain.

How much energy does it cost to bend the chain?

$$E_{\text{bend}} = \frac{EIL}{2R^2}$$

Figure 10.5 Physical Biology of the Cell, 2ed. (© Garland Science 2013)
Persistence length

The WLC model represents a balance between internal energy (from the resistance to bending) and entropy.

How does $L_p$ vary with temperature?

Another way of defining persistence length ($L_p$):

$$\langle \cos \theta(s) \rangle = e^{-s/L_p}$$

$L_p$ increases with increasing Young's modulus (stiffer)

$L_p$ decreases with increasing temperature (more flexible)

$$L_p = EI/kT$$
Force-extension relationship for WLC

\[ E_{\text{bend}} = \frac{EI}{2} \int_0^L \frac{ds}{R(s)^2} = \frac{kTLp}{2} \int_0^L \left| \frac{dt}{ds} \right|^2 ds \]

The partition function is summed over all possible curves (a path integral):

\[ Z = \int D\mathbf{t}(s) e^{-E_{\text{bend}}/kT} = \int D\mathbf{t}(s) \exp\left(-\frac{Lp}{2} \int_0^L \left| \frac{dt}{ds} \right|^2 ds\right) \]

Applying a force adds a term to the energy:

\[ E_{\text{app}} = -Fz = -F \int_0^L t_z ds \]

\[ \langle z \rangle = \frac{1}{Z(F)} \int D\mathbf{t}(s) z [e^{-(E_{\text{bend}} + E_{\text{app}}(F))/kT}] \]

\[ = kT \frac{d\ln Z(F)}{dF} \]
A closed form solution for \( <z> \) does not exist

\[
\frac{FL_p}{kT} \approx \frac{z}{L} + \frac{1}{4(1 - z/L)^2} - \frac{1}{4}
\]
Force spectroscopy

DNA

RNA

protein

different force profiles are like molecular signatures
Single-molecule techniques

AFM

optical tweezers

magnetic tweezers

pipette-based

Figure 8.21 Physical Biology of the Cell, 2ed. (© Garland Science 2013)
Atomic-force microscopy

unfolding of titin kinase + Ig domains

fits from WLC model

Atomic-force microscopy

20ns SMD Simulation of fibrinogen, 1.06 million atoms


A Blood Clot
Red blood cells within a network of fibrin fibers, composed of polymerized fibrinogen molecules.

High-speed AFM show agreement with (relatively) slow simulations
optical tweezers

unfocused laser

- Gradient induces lateral force

focused laser

- Gradient induces axial force

PBoC 4.3.1