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Molecular Biomechanics notes

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INTRO:

MOLECULAR BIOMECHANICS - DR. GANG BAO (GEORGIA TECH & EMORY COLLEGE)

MECHANICAL FORCES IN BIOLOGY:

- CELL MIGRATION
- CELL DIVISION (ALIGNMENT AND SEPARATION OF CHROMOSOMES)
- SHEAR FLOW IN ENDOTHELIAL CELLS

WHY MOLECULAR BIOMECHANICS?

- MECHANICAL FORCES CAN AFFECT MOST CELLULAR PROCESSES
- LITTLE IS KNOWN ABOUT HOW CELLS SENSE FORCE
- CRITICAL NEED TO UNDERSTAND MOLECULAR BASIS OF MECHANOTRANSDUCTION

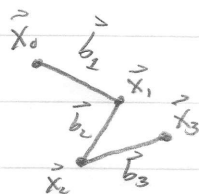
HOW DO CELLS SENSE FORCE?

- ION CHANNELS
 - TENSEGRITY
 - PROTEIN DEFORMATION
- ← POSSIBLE ANSWERS

I

MECHANICS OF POLYMER CHAINS - DR. JULI

FREELY JOINTED CHAIN (FJC)



$$\{\vec{x}_i\}, \quad i=0 \dots N$$

$$\vec{b}_i = \vec{x}_i - \vec{x}_{i-1}, \quad |\vec{b}_i| = b_i = b \text{ (Kuhn Length)}$$

PROBABILITY DISTRIBUTION OF \vec{b}_i :

$$dP = \underbrace{\rho(\vec{b}_i)}_{\substack{\text{SOLID} \\ \text{ANGLE}}} d^3 \vec{b}_i = \delta(b_i - b) db_i \cdot \frac{d\Omega_i}{4\pi}$$

$$\langle \vec{b}_i \rangle = 0, \quad \text{Var}[\vec{b}_i] \equiv \langle |\vec{b}_i|^2 \rangle = b^2$$

END-TO-END DISTANCE = \vec{D}

$$\vec{D} \equiv \vec{b}_1 + \vec{b}_2 + \dots + \vec{b}_N$$

$$\langle \vec{D} \rangle = 0$$

$$\langle \vec{D} \cdot \vec{D} \rangle = \langle b_1^2 \rangle + \langle b_2^2 \rangle + \dots + \langle b_N^2 \rangle = Nb^2$$

$$\langle D_x D_x \rangle = \langle D_y D_y \rangle = \langle D_z D_z \rangle = \frac{Nb^2}{3}$$

$$dP = \rho(\vec{D}) d^3 \vec{D} = \left(\frac{1}{\sqrt{2\pi Nb^2/3}} \right)^3 \exp \left[-\frac{|\vec{D}|^2}{2(Nb^2/3)} \right]$$

↓ RADIUS OF GYRATION

$$R_g \sim (\langle \vec{D} \cdot \vec{D} \rangle)^{1/2} = N^{1/2} b$$

$$L = Nb \gg R_g$$

EXTERNAL FORCE

$$G = F - \vec{f} \cdot \vec{D}, \quad F = -k_B T \ln Z$$

$$Z = \int d^3 b_1 d^3 b_2 \dots d^3 b_N \cdot \exp(-\beta \sum_i h(\vec{b}_i))$$

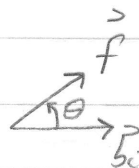
$h(\vec{b}_i) \equiv \delta(|\vec{b}_i| - b)$

$$G = -k_B T \ln \underbrace{(Z e^{\beta \vec{f} \cdot \vec{D}})}_{z'}$$

$$h'(\vec{b}_i) \equiv \delta(|\vec{b}_i| - b) - \vec{f} \cdot \vec{b}_i$$

Let

$$z_i \equiv \int d^3 b_i e^{-\beta h'(\vec{b}_i)}$$



$$= \int dR_i e^{-\beta \vec{f} \cdot \vec{b}}$$

$$\vec{f} \cdot \vec{b}_i = f b \cos \theta$$

$$z_i = \int_{-1}^1 2\pi d \cos\theta_i e^{\beta f b \cos\theta_i}$$

$$= \frac{4\pi \sinh(\beta f b)}{\beta f b}$$

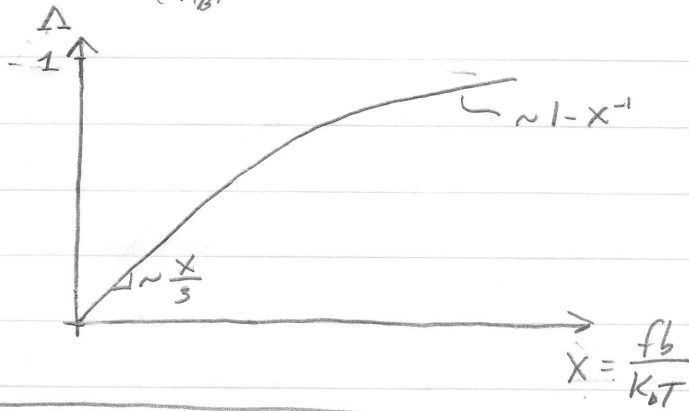
$$\beta \equiv \frac{1}{k_B T}$$

$$\langle \cos\theta_i \rangle = \frac{\int d\Omega_i e^{\beta f b \cos\theta_i} \cos\theta_i}{\int d\Omega_i e^{\beta f b \cos\theta_i} = z_i} = \frac{\frac{\partial z_i}{\partial(\beta f b)}}{\partial(\beta f b)} = \frac{\partial \ln z_i}{\partial(\beta f b)}$$

$$\frac{\partial \ln z_i}{\partial(\beta f b)} = \frac{\cosh(\beta f b)}{\sinh(\beta f b)} - \frac{1}{\beta f b} = \underbrace{\Delta(\beta f b)}_{\text{LANGEVIN EQUATION}}$$

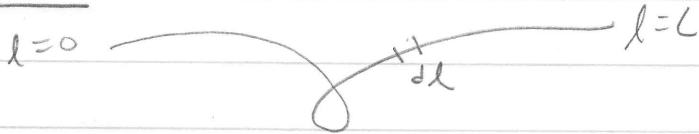
$$X = \langle \vec{D} \cdot \hat{f} \rangle = \langle \sum b_i \cdot \hat{f} \rangle = \langle \sum b \cos\theta_i \rangle = \overline{N} b \Delta(\beta f b)$$

$$\frac{X}{L} = \Delta\left(\frac{fb}{k_B T}\right)$$



$$f < \frac{k_B T}{b}, \quad f \rightarrow \frac{3k_B T}{b} \frac{X}{L}$$

WLC



BENDING ENERGY PENALTY:

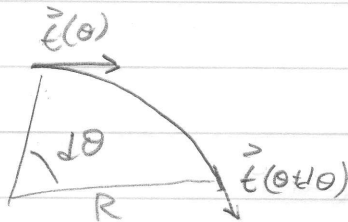
$$E[\vec{x}(l)] = \int_0^L dl \left(\frac{K C^2}{2} \right)$$

C = CURVATURE = $\frac{1}{R} \equiv \left| \frac{d^2 \vec{x}}{dl^2} \right| = \left| \frac{d\vec{t}}{dl} \right|$

\vec{t} = TANGENT VECTOR
 $\vec{t} = \frac{d\vec{x}}{dl}$

$K = \frac{Y \pi^2 r^4}{4}$

BENDING MODULUS



$$\left| \frac{d\vec{t}}{dl} \right| = \frac{1}{R}$$

$$R \left| \frac{d\vec{t}}{dl} \right| = \left[\vec{t}(0+d\theta) - \vec{t}(0) \right] R = d\theta R = dl$$

$$E = \int_0^L dl \frac{K}{2} \frac{d\vec{t}}{dl} \cdot \frac{d\vec{t}}{dl} = \int_0^L \frac{K d\vec{t} \cdot d\vec{t}}{2 dl}$$

AFTER SOME MANIPULATIONS AND APPROXIMATIONS

$$\langle |\vec{t}(l) - \vec{t}(0)|^2 \rangle \approx \frac{2l}{\beta K} \quad \text{IF } l \text{ IS SMALL}$$

$$\langle \vec{t}(l) \cdot \vec{t}(0) \rangle \approx 1 - \frac{l}{\beta K} \approx \exp\left(-\frac{l}{\beta K}\right)$$

DEFINE PERSISTENCE LENGTH $p = \beta K = \frac{K}{k_B T}$

$$\langle \vec{t}(l) \cdot \vec{t}(0) \rangle \approx \exp\left(-\frac{l}{p}\right)$$

$R > \frac{k}{k_{BT}} = p$, you can afford to make a loop of $R > p$

INTERPOLATION FORM:

$$\frac{fR}{k_{BT}} = \frac{x}{L} - \frac{1}{4} + \frac{1}{4(1-\frac{x}{L})^2}$$

FOR FJC \Rightarrow $b = 2p$

FJC & WLC MATCH AT LOW FORCE REGIME BUT DEVIATE AT INTERMEDIATE FORCES (WLC IS A BETTER APPROXIMATION)

II

DNA AND PROTEIN MECHANICS - DR. GANG BAO

DNA \Rightarrow CONSTANTLY BENDING, STRETCHING, TWISTING

FOR dsDNA, $p \approx 50 \text{ nm}$

ssDNA, $p \approx 1 \text{ nm}$

$$k = p k_{BT} \\ 4.3 \text{ pN} \cdot \text{nm} @ 37^\circ \text{C}$$

AT $\sim 12 \text{ pN}$ dsDNA STARTS A TRANSITION FROM B-DNA TO Z-DNA

AT $\sim 65 \text{ pN}$ IT REACHES A PLATEAU OF CONTINUOUS EXTENSION

AT A CONSTANT FORCE

ALSO, OTHER STUDIES HAVE EXPLORED TWISTING DYNAMICS OF DNA.

BUT DIFFICULT TO STUDY HOW IN VIVO, FORCES ARE

TRANSMITTED TO DNA. ALSO, HOW DOES DNA DEFORMATION

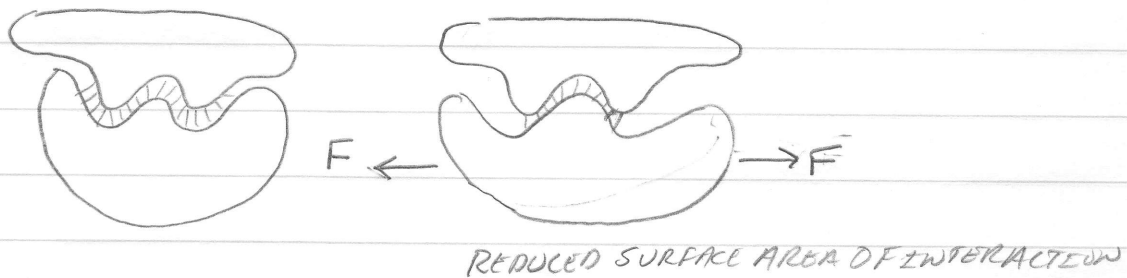
AFFECT GENE REGULATION? NOT KNOWN

PROTEINS \Rightarrow DIFFERENT FOLDING GEOMETRIES

PROTEIN DEFORMATION MODES

- ① DOMAIN MOTION $\sim 1-10 \text{ pN}$
- ② DOMAIN UNFOLDING $\sim 100 \text{ pN}$
- ③ DENATURING/MELTING $\sim 200 \text{ pN}$

PROTEIN CONFORMATION CAN CHANGE LIGAND BINDING



RESEARCH LOOKING AT HINGE ELASTICITY

→ COMPUTATIONAL & EXPERIMENTAL

FEATURES OF PROTEIN MISFOLDING INDUCED DISEASES

→ IT CAN BECOME TOXIC OR LOSE NORMAL BIOLOGICAL FUNCTION

→ CAN PROMOTE PROTEIN OLIGOMERIZATION OR AGGREGATION

EXAMPLES: ALZHEIMER'S, PARKINSON'S, DIABETES TYPE 2

• FORCE INDUCED CONFORMATIONAL CHANGES CAN LEAD TO MISFOLDING

MECHANICS OF ENDOCYTOSIS

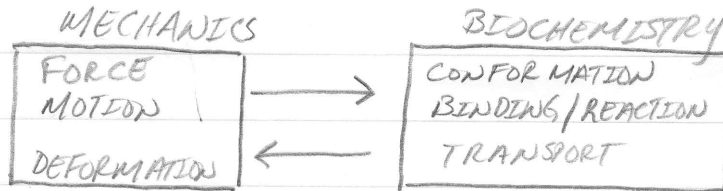
• IMPORTANT TO UNDERSTAND VIRAL INFECTION

- SEE SLIDES FOR FORMULATION -

CHALLENGES IN MOLECULAR BIOMECHANICS

- SMALL SIZE, SMALL FORCE
- LACK OF THEORETICAL BASES FOR PROTEIN FOLDING/UNFOLDING
- INTEGRATE MECHANICS, THERMODYNAMICS, STATISTICAL MECHANICS WITH BIOLOGY
- SIMULATIONS ARE TIME CONSUMING AND UNRELIABLE
- LACK OF STRUCTURAL INFORMATION / IMAGING

MECHANOCHEMICAL COUPLING



$$G = U - \sum Fx - TS$$

Labels for the equation:

- G: GIBBS
- U: INTERNAL
- $\sum Fx$: GENERAL DEFORMATION
- T: TEMPERATURE
- S: ENTROPY

 An arrow labeled 'GENERAL FORCE' points to the $\sum Fx$ term.

III

MOLECULAR MOTORS AND PROTEIN NANOMACHINES - DR. GANG BAO

- MECHANOENZYMES (MYOSIN, KINESIN)
- PROCESSIVE NUCLEIC ACID ENZYMES
- ATPases
- BACTERIAL MOTORS
- POLYMERIZATION
- OTHERS



MYOSIN HAS A LEVER ARM
 ↳ 2-6 pN OF FORCE

THERE ARE SEVERAL SINGLE MOLECULE ASSAYS TO STUDY MOTOR PROTEINS

MECHANICAL CYCLE \longleftrightarrow BIOCHEMICAL CYCLE
(MOTION/FORCE) (ATP \rightarrow ADP + P_i)

KINESIN \Rightarrow TRANSPORT ALONG AXONS

\hookrightarrow ATP DRIVEN

\hookrightarrow NO LEVER ARM

\hookrightarrow 8nm STEP SIZE

\hookrightarrow \sim 80% EFFICIENCY

RNA POLYMERASE \rightarrow \sim 25pN OF FORCE

ATP SYNTHASE (F₁-F₀ ATPase) \Rightarrow SOURCE OF ATP

\hookrightarrow CLOSE TO 100% EFFICIENCY

\hookrightarrow REVERSIBLE

HOW TO DRIVE NANODEVICES?

- USE MOLECULAR MOTORS!

- VERY EFFICIENT, NO NEED FOR BATTERIES