GENERAL SESSION #   J FERRER

GEM4 - AUGUST 2006   8/16/06

INTRO: <u>MOLECULAR BIOMECHANICS</u> - 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 MECHANOTRANDUCTION

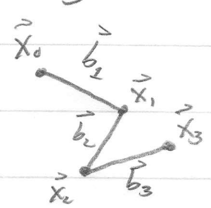
HOW DO CELLS SENSE FORCE?

→ ION CHANNELS
→ TENSEGRITY
→ PROTEIN DEFORMATION

} POSSIBLE ANSWERS

I <u>MECHANICS OF POLYMER CHAINS</u> - DR JU LI

FREELY JOINTED CHAIN (FJC)



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

$\vec{b}_i = \vec{x}_i - \vec{x}_{i-1}$, $|\vec{b}_i| = b_i = b$ (KUHN LENGHT)

PROBABILITY DISTRIBUTION OF $\vec{b}_i$:

$$dP = \rho(\vec{b}_i)\underbrace{d^3\vec{b}_i}_{\vec{b}_i^{\,2}\, db_i\, d\underbrace{\Omega_i}_{\text{SOLID ANGLE}}} = \delta(b_i - b)\, db_i \cdot \frac{d\Omega_i}{4\pi}$$

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

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

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

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

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

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

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

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

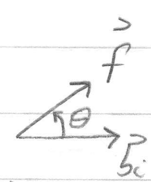
$$G = F - \vec{f}\cdot\vec{D} \quad , \quad F = -K_B T \ln Z$$

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

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

$$G = -K_B T \ln \underbrace{\left(Z e^{\beta \vec{f}\cdot\vec{D}}\right)}_{\equiv Z'} \qquad h'(\vec{b}_i) \equiv \delta(|\vec{b}_i| - b) - \vec{f}\cdot\vec{b}_i$$

LET



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

$$= \int d\Omega_i\, e^{-\beta \vec{f}\cdot\vec{b}}$$

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

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

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

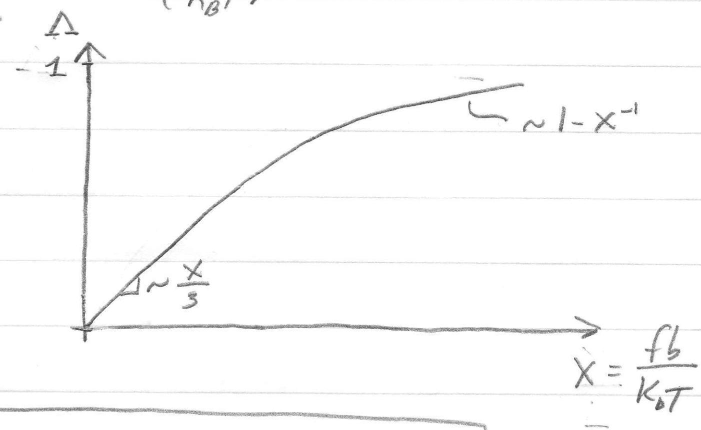
$$= 4\pi \frac{\sinh(\beta f b)}{\beta f b}$$

$$\langle \cos\theta_i \rangle = \frac{\overset{\frac{\partial Z_i}{\partial(\beta f b)}}{\int d\Omega_i \, e^{\beta f b \cos\theta_i} \cos\theta_i}}{\underbrace{\int d\Omega_i \, e^{\beta f b \cos\theta_i}}_{= Z_i}} = \frac{\partial \ln Z_i}{\partial(\beta f b)}$$

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

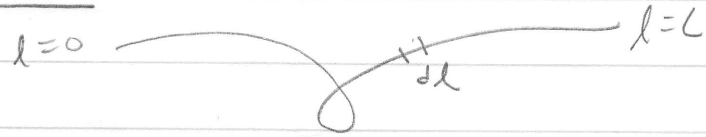
$$X = \langle \vec{b} \cdot \hat{f} \rangle = \langle \sum b_i \cdot \hat{f} \rangle = \langle \sum b \cos\theta_i \rangle = \overbrace{Nb}^{L} \Lambda(\beta f b)$$

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



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

WLC



BENDING ENERGY PENALTY:

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

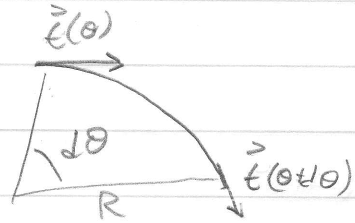
$$C = \text{CURVATURE} = \frac{1}{R} \equiv \left|\frac{d^2\vec{x}}{dl^2}\right| = \left|\frac{d\vec{t}}{dl}\right|$$

$\vec{t}$ = TANGENT VECTOR

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

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

BENDING MODULUS



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

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

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

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:

$$\frac{fp}{K_Bt} = \frac{X}{L} - \frac{1}{4} + \frac{1}{4(1-\frac{X}{L})^2}$$

FOR FJC $\Rightarrow$ $\boxed{b = 2p}$

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

II <u>DNA AND PROTEIN MECHANICS</u> - DR. GANG BAO

<u>DNA</u> $\Rightarrow$ CONSTANTLY BENDING, STETCHING, TWISTING

FOR dsDNA , $p \approx 50nm$
ssDNA, $p \approx 1nm$ $\Big\}$ $K = p\underbrace{K_BT}_{4.3pN \cdot nm\ @\ 37°C}$

AT ~12pN dsDNA STARTS A TRANSITION FROM B-DNA TO Z-DNA
AT ~65pN 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? <u>NOT KNOWN</u>

<u>PROTEINS</u> $\Rightarrow$ DIFFERENT FOLDING GEOMETRIES

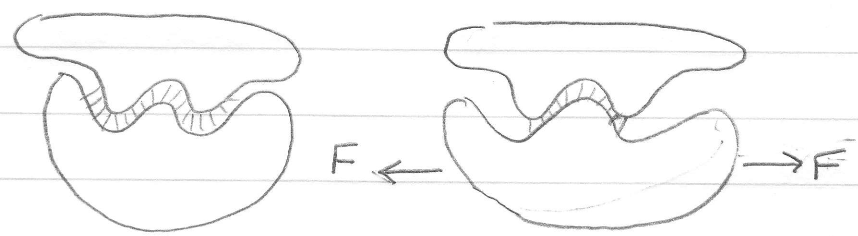
PROTEIN DEFORMATION MODES

① DOMAIN MOTION ~1-10pN

② DOMAIN UNFOLDING ~100pN

③ DENATURING/MELTING ~200pN

PROTEIN CONFORMATION CAN CHANGE LIGAND BINDING



REDUCED SURFACE AREA OF INTERACTION

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

<u>EXMPLES</u>: ALZHEIMER'S, PARKINSON'S, DIABETES TYPE 2

· FORCE INDUCED CONFORMATIONAL CHANGE 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 FOLDIN/UNFOLDING
- INTEGRATE MECHANICS, THERMODYNAMICS, STATISTICAL MECHANICS WITH BIOLOGY
- SIMULATIONS ARE TIME CONSUMING AND UNRELIABLE
- LACK OF STRUCTURAL INFORMATION / IMAGING

MECHANOCHEMICA COUPLING

MECHANICS		BIOCHEMISTRY
FORCE MOTION DEFORMATION	→ ←	CONFORMATION BINDING/REACTION TRANSPORT

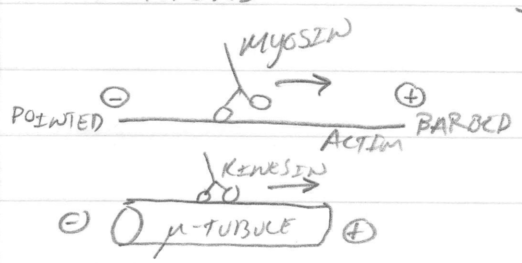
GENERAL FORCE
TEMPERATURE

$$G = U - \sum F\ell - TS$$

GIBBS, INTERNAL, GENERAL DEFORMATION, ENTROPY

III MOLECULAR MOTORS AND PROTEIN NANOMACHINES — DR. GANG BAO

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



MUSCLE CONTRACTION (ATP DRIVEN)

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 $\longrightarrow$ ADP + P_i)

KINESIN $\Rightarrow$ TRANSPORT ALONG AXONS
↳ ATP DRIVEN
↳ NO LEVER ARM
↳ 8nm STEP SIZE
↳ ~80% EFFECIENCY

RNA POLYMERASE $\rightarrow$ ~25pN OF FORCE

ATP SYNTHASE (F_1-F_0 ATPase) $\Rightarrow$ SOURCE OF ATP
↳ CLOSE TO 100% EFFICIENCY
↳ REVERSIBLE

HOW TO DRIVE NANODEVICES?
- USE MOLECULAR MOTORS!
- VERY EFFICIENT, NO NEED FOR BATTERIES