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Computational Biomechanics notes

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COMPUTATIONAL BIOMECHANICS

08/17/2006

Bruce Tidor

Molecular modeling and simulations
Study of structure-function relationships

Contrast engineering- or physics-based models △ and informatics-based ones ○:

○ observational, statistical, correlational models are popular & performant in biology but they don't provide you with explanations

△ designs based on physical principles can still create new objects, understood and mechanistic.

- why use modeling ?

structure-function relationships ? : we need chemistry models to describe molecules
electrons would be the right level, along with nuclei ; but too detailed !
for small molecules : structure → function, for macromolecules : s. → ? → f.
one amino acid = one degree of freedom in proteins
what set of rules ? what parameters ?

important intermediates (energetics / dynamics / ...)

- levels of representations : electrons, atoms, residues, solvent (explicitly or mean)
  ↳ all-atom models or polar-atom ones (drop H)

Linus Pauling solved the X-ray crystal structures of all 20 a.a. ⇒ C-C bonds
bond length, hydrogen bonds, α helices & β-sheets

- potential energy function (for any conformation = as a function of position)

$$U(\vec{r}) = U_{covalent} + U_{non-covalent} = U_{bond} + U_{bond\ angle} + U_{improper\ dihedral} + U_{torsion} + U_{VdW} + U_{electrostatic}$$

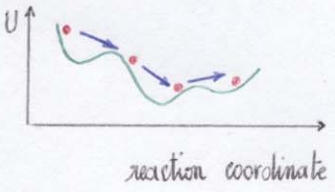
$(\propto N)$ $(\propto N^2)$

force constants embedded in each term come from experiments combined with quantum mechanics.
for the solvent : microscopic (explicit) & Coulomb's law, or macroscopic treatment
(where mean-field dielectric constants & Poisson-Boltzmann equation matter),
(and for which continuum electrostatics approximation has been developed).
faster calculations : cut-off radii beyond which $U_{non-covalent}$ negligible, pair-wise ...
sampling the potential energy surface :

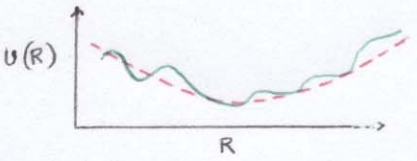
- energy minimization (downhill search)
- normal mode analysis (characteristic motions / distort
- molecular dynamics (movie of motion at given T)

Computational biomechanics - 2.

- energy minimization : iterative downhill search along the gradient, but local minima
  mutant structure prediction via minimization : "minimom perturbation approach"



- normal mode analysis : characteristic motions and their relative ease
  mathematical approximation series of independent harmonic oscillators
  local expansion of potential surface as paraboloid



$$U(R) = U(R_0) + \nabla U (R - R_0) + \frac{1}{2} \frac{\partial^2 U}{\partial R^2} (R - R_0)^2 + \dots$$

0

shallowest dimensions = normal modes
easy motions dominate dynamic behavior

- molecular dynamics, whose simulations approach ensemble statistics
  stimulated annealing
  thermodynamics properties are retrieved because MD ↔ Monte Carlo sampling of ensemble

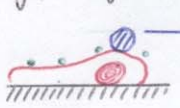
Case studies : cell and molecule modeling

Mohammad Reza Kaazempur Mofrad

- Cells respond to mechanical stimuli : shear stress
  cyclic strain, osmotic pressure, (and in vitro 3D compression, bead pulling)
  mechanotransduction hypothesis : changes in conformation (force-induced) are responsible

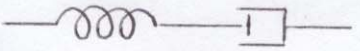
- models of the cell
  - continuum models describe the cytoskeleton by homogeneous elastic (or visco- or poro- elastic)
  - porous gels
  - soft glassy materials
  - tensegrity network incorporating discrete structural elements that bear { compression / tension
- continuum models : stress / strain patterns correlations with biology ?

magnetocytometry :



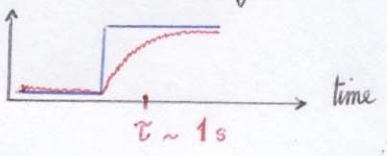
pull on magnetic 4.5 μm bead
watch small polystyrene beads on cell surface

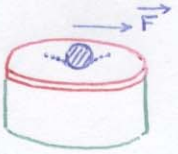
approximate cell as Maxwell fluid



membrane + cytoskeleton

(Hélène Karcher)

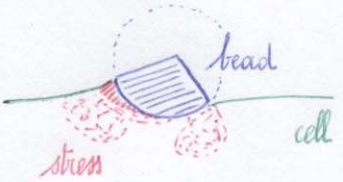




stresses and displacements are localized

asymmetric

membrane stretch > 1.04 behind the bead



opening of ion channels ?

displacements of focal adhesions : localized force transmission (Pete Mack)

nucleus : inner & outer nuclear membranes + nuclear lamina (lamins)

model : nucleoplasm = Maxwell, envelop = elastic

compare wild-type vs. lamin-deficient cells (model)

force-indentation curves (AFM) to extract lamina properties

1000 kPa vs. 10-100 kPa ⇒ softening

comparison of AFM vs. micropipet aspiration results.

- molecular modeling of paxillin / FAT (domain of FAK) interactions in focal adhesions

FAT as a mechanosensor : structure shows two binding sites for paxillin

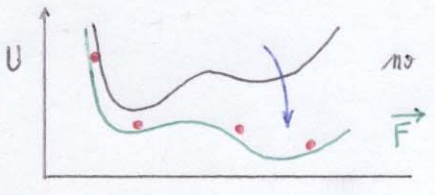
is the integrity of FAT helical bundle critical to paxillin binding ?

hyp : force-induced conformational changes in proteins play a key role in controlling signalling pathways, for instance by affecting intracellular binding affinities

molecular dynamics simulation :

SMD : steered molecular dynamics : tilted energy landscape if $\vec{F}$

more conformations accessible



if $\vec{F}$, hydrophobic groove opens up

75 pN, 7 ns

end-to-end distance of FAT (↗ = unfolding) without or with paxillin

FAT unfolds differently (higher $\vec{F}$ needed) in the presence of paxillin

- molecular modeling of α-actinin (dimer that crosslinks actin)
  how flexible is α-actinin's rod domain ? loops are as stiff as whole protein, the helices are less stiff than these bridging loops !

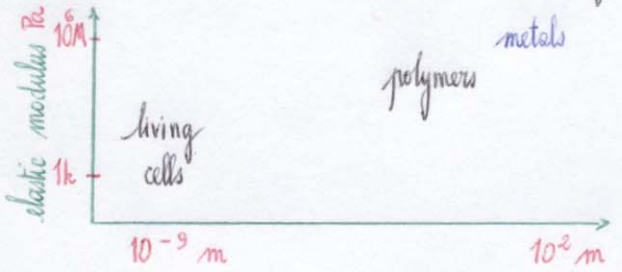
- molecular modeling of filamin (crosslinks actin in orthogonal directions)
  ~ 100 pN to fully unfold filamin
  linker regions appear softer

Conclusion: stress-induced changes in conformations of cytoskeletal proteins can elicit biological response
molecular dynamics = useful tool

Continuum modeling of human red blood cells

Ming Dao

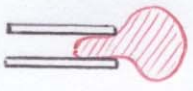
- not limited by size and time scales
  blood flow in microcirculation is influenced by the deformability of RBC ⇒ single cell study

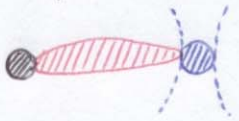


. "dynamic" system ⇒ challenging
. state-of-the-art pN-nm instruments

mechanical properties related to	disease states :	spectrin (mutation in ankyrin) spherocytosis
of single cells	of organisms	. sickle-cell (mutation in haemoglobin)

- techniques : micropipette aspiration and optical tweezers



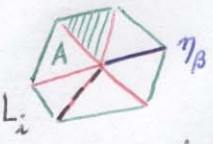


up to > 200pN, whole cell, finite deformation formulation

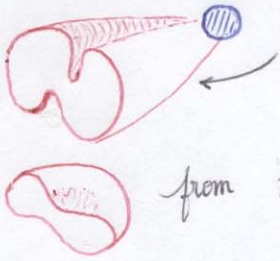
- healthy RBCs
  simple cell : anuclear, solution of haemoglobin in membrane envelop.
  in-plane shear modulus μ + bending stiffness κ
  the spectrin network is triangular (tropomysin, actin, ankyrin, band 3 = partners)

spectrin model $V_{total} = \sum_{L_i} V_{WLC} + \sum \frac{C}{A\alpha} + \sum \kappa (1 - \eta_\beta \cdot \eta_\gamma)$

molecules — worm-like chain — membrane — bending stiffness



finite element modeling depends on contact area (with beads)



- maximum principal strain matches experiments
- axial diameter & transverse diameter reproduced
- shear modulus $\simeq 8\ \mu N/m$

from RBC in resting state

- cytosol added for correct mechanics
- biconcave model ≠ spherical model

- spherocytosis & spleen function

erythrocyte deformation : RBCs become small & spherical ; abnormal osmotic fragility
loss of membrane surface area

in spleen, 10% open circulation ⟹ quality control of RBCs performed by the spleen
splenic sinus & inter-endothelial slits : diseased cells cannot deform!

membrane loss from spectrin deficiency
spectrin misattachment, misbudding?