

COMPUTATIONAL BIOMECHANICS



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Bruce Lidor

Molecular modeling and simulationsStudy of structure-function relationships

Contrast engineering- or physics-based models^Δ and informatics-based ones[◦]:

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

- 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)

$$U(\vec{r}) = U_{\text{covalent}} + U_{\text{non-covalent}} = U_{\text{bond}} + U_{\text{bond angle}} + U_{\text{improper}} + U_{\text{torsion}} \\ (\propto N) \quad (\propto N^2) \quad + U_{\text{vdW}} + U_{\text{electrostatic}} \quad \text{dihedral}$$

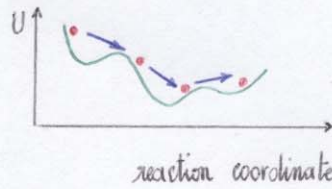
force constants embedded in each term come from experiments combined with quantum mechanics.
for the solvent: microscopic (explicit) & Coulomb's law, or macroscopic treatment (where mean-field dielectric constants & Poisson-Boltzmann equation matter), (and for which continuum electrostatics approximation has been developed).

faster calculations: cut-off radii beyond which $U_{\text{non-covalent}}$ negligible, pair-wise ...
sampling the potential energy surface:

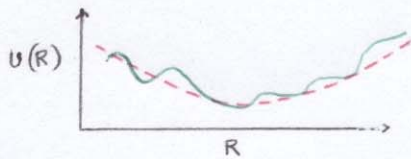
- energy minimization (downhill search)
- normal mode analysis (characteristic motions/distort)
- molecular dynamics (movie of motion at given T)

Computational Biomechanics - 2.

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



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

shallowest dimensions = normal modes
easy motions dominate dynamic behavior

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

Case studies: cell and molecule modeling

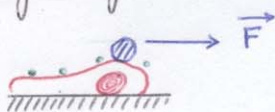
Mohammad Reza
Khaazempour Mofrad

- 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 $\left. \begin{array}{l} \text{compression} \\ \text{tension} \end{array} \right\}$
- continuum models: stress/strain patterns correlations with biology?

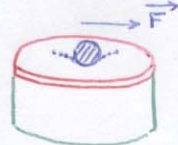
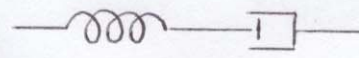
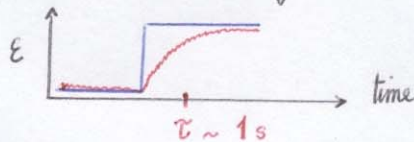
magnetocytometry:



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

approximate cell as Maxwell fluid
membrane + cytoskeleton

(Helène Karcher)

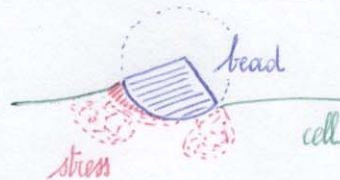


stresses and displacements are localized
asymmetric

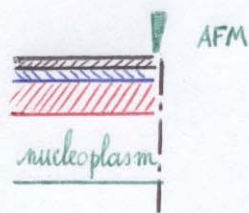
membrane stretch > 1.04 behind the bead

opening of ion channels?

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



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



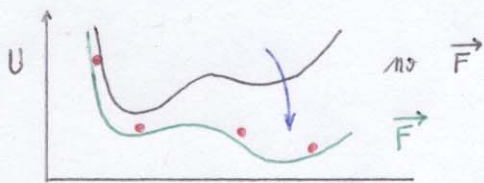
model: nucleoplasm = Maxwell, envelop = elastic
compare wild-type vs. lamin-deficient cells (model)
force-indentation curves (AFM) to extract lamina properties
1000 kPa vs. 10-100 kPa ⇒ softening

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

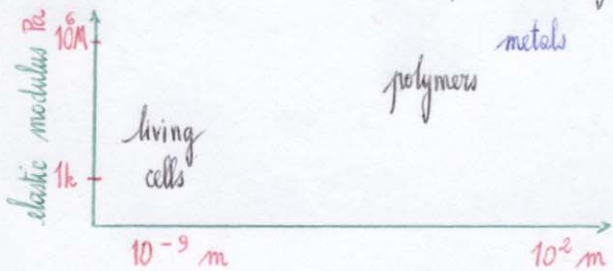


Conclusion: stress-induced changes in conformations of cytoskeletal proteins can elicit biological response
 molecular dynamics = useful tool

Continuum modeling of human red blood cells

Ming Dao

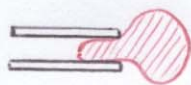
- not limited by size and time scales
 blood flow in microcirculation is influenced by the deformability of RBC \Rightarrow single cell stud



• "dynamic" system \Rightarrow challenging
 • state-of-the-art pN-nm instruments

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

- techniques: micropipette aspiration and optical tweezers



up to > 200 pN, 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 (tropomyosin, actin, ankyrin, band 3 = partners)

Computational Biomechanics - 5.

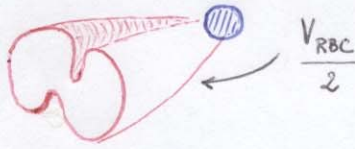
spectrin model

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

molecules
membrane
bending stiffness



finite element modeling depends on contact area (with beads)



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



from RBC in resting state

- cytosol added for correct mechanics
- biconcave model \neq spherical model

- spherocytosis & spleen function

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

in spleen, 10% open circulation \rightarrow 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?