Virtual Cell Model

Mohammad Reza Ejtehadi

Sharif University of Technology, 2016

Spring Conference, IPM, June 2018
Soft Condensed matter @ Sharif
Life, Cells and Biological Molecules

• Biological systems are Big and out of equilibrium
• Biological matters are soft
• Life is very complex
Living organisms do not wait until food and energy find them
They need to move for catching the food or escaping dangers.
In Cellular Scale

Neutrophil Chasing Bacteria

bacteria

Taken in 1950s by David Rogers at Vanderbilt University
Biological Matters are Soft

• Life is not possible without movement
• The elasticity is a main feature of biological matter (in many different time and size scales)
• The life machinery is actually embedded in viscous (aquatic) media
• DNA, proteins and membranes are good examples
Dynamics of over twisted DNA loops

Casjens, S. R. Nature Reviews Microbiology. 2011

http://textbookofbacteriology.net/
DNA is injected inside the capsid by applying a force.
A Model 2D Swimmer

For small tumble probability $p \ll 1$ and tumble rate $\eta = \frac{p}{\Delta \theta}$

$$D = \frac{1}{2} \omega \rho^2 \frac{\eta}{(\eta^2 + 1)}$$
ii. Low Reynolds swimmers:

- The equations of motion of the active triangular swimmers in low Reynolds is solvable, here we want to have a active membrane made up of hundreds of these triangular swimmers. To simulate this model, the MPCD part of the software is employed.
Cell responses to deformations

• Much larger time and size scale
Mechanotransduction

[O. Mashinchian, MRE and et al, ACS Applied Materials and Interfaces (2014)]
Proper concentration:

Connectivity network of the chromatin fibers is

- Robust against thermal fluctuations
- But responses to mechanical deformations
- And it is not reversible
How does a cell responses to mechanical deformations?

- Need to have a more detailed model for cell motility
Virtual Cell Model

Shahrzad Zareh, Oveis Sheibani, ...
Components of Virtual Cell

cell membrane

cytoskeleton

nucleus membrane

chromatin fibers

substrate
Membrane: Triangulated model

- Membranes are discretized into the triangular elements (vertices which are inter connected via tethers).
- The potential energy consists of the energy of the tethers (bonding and repulsion), the curvature between neighboring triangular elements and the surface area constraining energy:

\[
U_{\text{bonding}} + U_{\text{repulsion}} + U_{\text{curvature}} + U_{\text{surface area}} \\
= b \sum_{<i',j'>} \frac{\exp\left(\frac{1}{l_{c0} - r_{ij}}\right)}{l_{\text{max}} - r_{ij}} + b \sum_{<i',j'>} \frac{\exp\left(\frac{1}{r_{ij} - l_{c1}}\right)}{r_{ij} - l_{\text{min}}} + \frac{\kappa_{\text{curve}}}{2} \sum_{<i'e,j'>} (1 - \cos \theta_{ij}) + \frac{\kappa_s}{2} (S - S_0)^2
\]

Diffusion of membrane nodes

$$\text{Prob}(\pi_{\text{new}} \to \pi_{\text{old}}) = e^{-\frac{(U_{\text{new}} - U_{\text{old}})}{k_B T}}$$

Cytoskeleton

Polymer network

Three building blocks

Responsible for cell mechanics

Adding chemical processes: complex dynamical system

Boal, David, and David H. Boal. Mechanics of the Cell
Viscoelastic elements:

\[ \dot{\varepsilon} = \frac{T}{\mu} \]

\[ \varepsilon = \frac{T}{E} \]

From 1D to 3D:

• Cytoskeleton is modeled as a 3D viscoelastic network which fills the volume between the nucleus and cell membranes also connected to some of the membrane nodes.

• Collective behavior: rheology

Inside nucleus: Bead-Spring to model Chromatin fibers

\[
U_{\text{bond}} + U_{\text{bending}} + U_{\text{excluded volume}} = \frac{\kappa_{\text{bonding}}}{2} \sum_{i=1}^{N_c} \sum_{j=1}^{N_j-1} (r_{ij}^i - r_0)^2 + \frac{\kappa_{\text{bending}}}{2} \sum_{i=1}^{N_c} \sum_{j=1}^{N_j-2} (\theta_{ij}^i - \theta_0)^2 + \sum_{i<j}^{<i,j>}{\left\{ \left( \frac{\sigma_{\text{ch}}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{\text{ch}}}{r_{ij}} \right)^6 \right\}}
\]

Chromatins inside the nucleus


ECM/Substrate is modeled as a elastic/viscoelastic network with a triangulate top surface that interact with the cell in three ways:

I) Lennard-Jones interaction:

\[
\Phi(h) = 4 \epsilon_{ECM} \left\{ \left( \frac{\sigma}{h} \right)^{10} - \left( \frac{\sigma}{h} \right)^{4} \right\}
\]

if \( D \in ABC^\Delta \)

II) Focal adhesion points:

\[
F_A = -\frac{S_{CD}}{S_{ABC}} F^D,
\]
\[
F_B = -\frac{S_{AD}}{S_{ABC}} F^D,
\]
\[
F_C = -\frac{S_{AB}}{S_{ABC}} F^D.
\]

III) Active speeding:

\[
P_{bond} = e^{-\beta U_{bond}}
\]
\[
P_{unbond} = e^{-\beta U_{unbond}}
\]


Modeling the aquatic media

**MPCD Algorithm**

\[ r_i(t + \Delta t_{CD}) = r_i(t) + \Delta t_{CD} \mathbf{v}_i(t) \]

\[ \mathbf{v}_i^{new} = \mathbf{v}_{cm}(t) + \Omega(\varphi)[\mathbf{v}_i(t) - \mathbf{v}_{cm}(t)] \]

+ Elastic collision with membrane and the other components.

Development of a Virtual Cell Model to Predict Cell Response to Substrate Topography

Tiam Heydari,† Maziar Heidari,‡ Omid Mashinchian,§⊥ Michal Wojcik,∥ Ke Xu,∥∥ Matthew John Dalby,¶ Morteza Mahmoudi,¶¶ and Mohammad Reza Ejtehad†✉
Cell on Grooved substrate
Cell on Grooved substrate

A. Grooved substrate with different depths: 100 nm, 300 nm, 500 nm.
B. Cellular and nuclear deformation with different depths: 0.1 a, 0.5 a, 0.9 a.
C. Graph showing aspect ratio of nucleus for different depths (100 nm, 300 nm, 400 nm).
D. Graph showing aspect ratio of virtual cell nucleus for different depths (0.1a, 0.2a, 0.5a, 0.9a).
E. Graph showing aspect ratio for different angles (-60, 0, 30, 60).
Chromatin interaction network
Cell on soft substrate

top and side views of asymmetric cell on soft substrate with the rigidity of ECM network linkage of 1 k0

top and side views of asymmetric cell on soft substrate with the rigidity of ECM network linkage of 80 k0
Cell on soft substrate
Cell on imprinted substrate
Chromatin condensation

Modeling cell Chemotaxis

- To have very minimal model of the activity of the cytoskeleton at the cell periphery of the migrating cell, the direction of the generated force is considered normal to the periphery of the cell membrane and the distribution of the force is scaled by $|\cos(\alpha)|^{\frac{1}{8}} \text{sign}(\cos(\alpha))$, where $\alpha$ is the angle between the polarity direction and the point on the cell periphery.

Cell motility
Collaborations:

Tiam Heydari
Maziar Heidari
Ali Farnoodi
Shahrzad Zareh
Oveis Sheibani
Mehran Ebrahiminian
Mohammad Yekezareh
Vahid Satarifard
Arman Fathizadeh
Morteza Mahmoudi
Matthew Dalby
Omid Machinchian