Session 18

COMPUTATIONAL CONTINUUM MODELS
Models for Cell Mechanics

Computational approaches for cell mechanics

- Bridging the length scales

Continuum approaches

- Adherent cells
  - Elastic continua
    - Linear model (ELM)
    - Nonlinear model (ENL)
  - Viscoelastic continua
    - Maxwell model (VMM)
    - Generalized Maxwell model (VGM)
    - Power-law structural dampening model (VPL)
- Suspended cells
  - Liquid drop models
  - Biological continua models
    - Poroelastic model (BPE)
    - Poro-viscoelastic model (BPV)
  - Active continua
    - Bio-chemo-mechanical model (ABM)
    - Active poroelastic gels (APG)

- Multiscale models
  - Other models
    - Percolation models
    - Foam models
    - Tensegrity models (elastic and viscoelastic)
    - Cable network models
  - Monte-Carlo (MC) models
    - Stochastic motor-filament models
    - MC network models
  - Molecular dynamics (MD)
    - MD networks models
    - Mean field MD models

- Microscale approaches
Continuum Elastic Models

- A cell can be treated as a continuous material if the length scale of interest is larger than its microstructure.
- Rule of thumb – one or two orders of magnitude.
Constitutive Law

- A model’s prediction is only as good as its constitutive equations
  - Stress-strain relationship (Hooke’s Law)
    \[ \sigma = E\varepsilon \]
    \[ \sigma_{ij} = C_{ijkl}\varepsilon_{kl} \]
  - Predicts what are the strains \( \varepsilon \), but tells us nothing about microstructure!
- Coarse-graining approach – lower resolution of averaged properties
Goals of Modeling

- Deduction of cells mechanical properties
  - Know stress and strain of a cell, what is constitutive relationship?
    - MTC – magnetic force, bead displacement
    - Micropipette aspiration – vacuum pressure, aspiration length
    - AFM - cantilever force, indentation depth
Goals of Modeling

- Distinguish active from passive response
  - Active responses
    - Remodeling
    - Contraction
    - General mechanotransduction
  - Passive responses
    - Deformation
Finite element methods (FEM)

- Predicts the displacement, strain, and stress fields induced in a model
- Provide
  - Initial geometry
  - Material properties
  - Boundary conditions
- Solves equations that are not doable with analytical approaches
  - Discretize model into computational elements interconnected by nodes
  - Formulate “stiffness matrix” to find displacements

(Images courtesy of Sangyoon Han)
AFM Example

- Osteoblast stimulated with AFM tip showed calcium spikes
- Linear elastic isotropic material
  - $E = 10$ kPa
  - $\nu = 0.2-0.5$
- Geometric model
  - Symmetry
  - Length 15 μm
  - Thickness $t = 0.25 - 5$ μm
- Mesh
  - 8-node elements with dense meshing
- Boundary conditions
  - Fixed displacements
    - $u_z = 0$ on bottom
    - $u_x = 0$ on $yz$-surface
    - $u_y = 0$ on $xz$-surface
  - Loads
    - 1 nN load at $(o,o,t)$

Radial and Tangential Strain

- Radial strains largest on cell surface
- Tangential strain largest at indentation area
Vertical Strain and Deformation

- Vertical strain largest directly under indentation

- Deformation amplified 15x for visualization
Poisson’s Ratio

- Poisson effect is marginal
  - Radial strain (Err) varied 30%
  - Tangential strain (Ett) was drastic
  - Vertical strain (Ezz) varied 12%

Cell Height

- Cell thickness is significant
  - Cells < 2 μm had higher strains
  - Cells > 2 μm were similar

Active Continuum Models

- Incorporates activation of contractility and reorganization of cytoskeleton
Simple Activation Scheme

- Assume contractility is calcium dependent
  - Actin polymerization faster than depolymerization
  - Myosin assembly by Ca\(^{2+}\)/calmodulin/MLCK activation
  - Calcium concentration:

\[
C = \begin{cases} 
0 & t < t_i \\
\exp \left( \frac{(t_i - t)}{\theta} \right) & t \geq t_i
\end{cases}
\]

- \(t_i\) is time at instance of activation
- \(\theta\) is decay time constant for intracellular Ca\(^{2+}\) pumps
Filament Assembly

- Degree of assembly $\eta$ of filaments into the contractile apparatus structure

$$\frac{d\eta}{dt} = (1-\eta) C \frac{k_f}{\theta} - \eta \left(1 - \frac{\sigma}{\sigma_0}\right) \frac{k_b}{\theta}$$

$$0 \leq \eta \leq 1$$

- First term is assembly reaction
  - Negatively on assembly state $\eta$ due to fewer free monomers
  - Positively on Ca$^{2+}$ concentration $C$ that drives polymerization
  - Positively on forward rate constant $k_f$

- Second term is disassembly reaction
  - Positively on assembly state $\eta$
  - Negatively on ratio of tension to isometric tension $\sigma/\sigma_0$ that holds filaments together
  - Positively on backward rate constant $k_b$
Muscle cannot change its length instantly due to actin-myosin dynamics

Partly explained by inertia of weight

Main cause is isotonic contraction produces less force than isometric, which is zero velocity and $T = T_0$.

Hill’s Equation

$$(v + b)(T + a) = b(T_0 + a)$$

$$v_{\text{max}} = bT_0 / a$$
Active strain rate is related to the stress by simplification of Hill’s equation

\[
\frac{\sigma}{\eta \sigma_{max}} = \begin{cases} 
0 & \frac{\varepsilon}{\varepsilon_0} < -\frac{\eta}{k_v} \\
1 + \frac{k_v}{\eta} \frac{\varepsilon}{\varepsilon_0} & -\frac{\eta}{k_v} \leq \frac{\varepsilon}{\varepsilon_0} \leq 0 \\
1 & \frac{\varepsilon}{\varepsilon_0} > 0 
\end{cases}
\]

Relative Stress (\(\sigma / \sigma_{max}\))

Relative Strain Rate ((d\(\varepsilon\)/dt) / (d\(\varepsilon_0\)/dt))
Linear Elastic Constitutive Relationship

- **Active Behavior:** Strain rate and Average stress as vector & tensor

\[ \varepsilon = \varepsilon_{11} \cos^2 \phi + \varepsilon_{22} \sin^2 \phi + \varepsilon_{12} \sin 2\phi \]

\[ S_{ij} = \frac{1}{\pi} \int_{-\pi/2}^{\pi/2} \begin{bmatrix} \sigma(\phi) \cos^2 \phi & \frac{\sigma(\phi)}{2} \sin 2\phi \\ \frac{\sigma(\phi)}{2} \sin 2\phi & \sigma(\phi) \sin^2 \phi \end{bmatrix} \]

- **Passive Behavior:** Linear Isotropic Elastic Material

\[ \sigma_{ij} = S_{ij} + \frac{E v}{(1-2v)(1+v)} \varepsilon_{kk} \delta_{ij} + \frac{E}{1-\nu} \varepsilon_{ij} \]
Principal Stress and Stress Fiber Activation Coincide Spatially and Temporally
Stiffness affects Contraction Development

- Increases in stiffness $k$ yields increased transient and steady state force response.
Multiple Activations

- One activations with slow decay
- Two activations with medium decay
- Four activations with fast decay
- Shows multiple activations more effective than single
Stress Fiber Activation

(a) Two activations versus (b) one activation at early and late times (t/θ)
External Force Response

- Stress fiber activated locally in response to constant external force
- (a) Early and (b) late time points shown
Cells exposed to unidirectional, cyclic stretch observed to realign CSK in opposite direction.