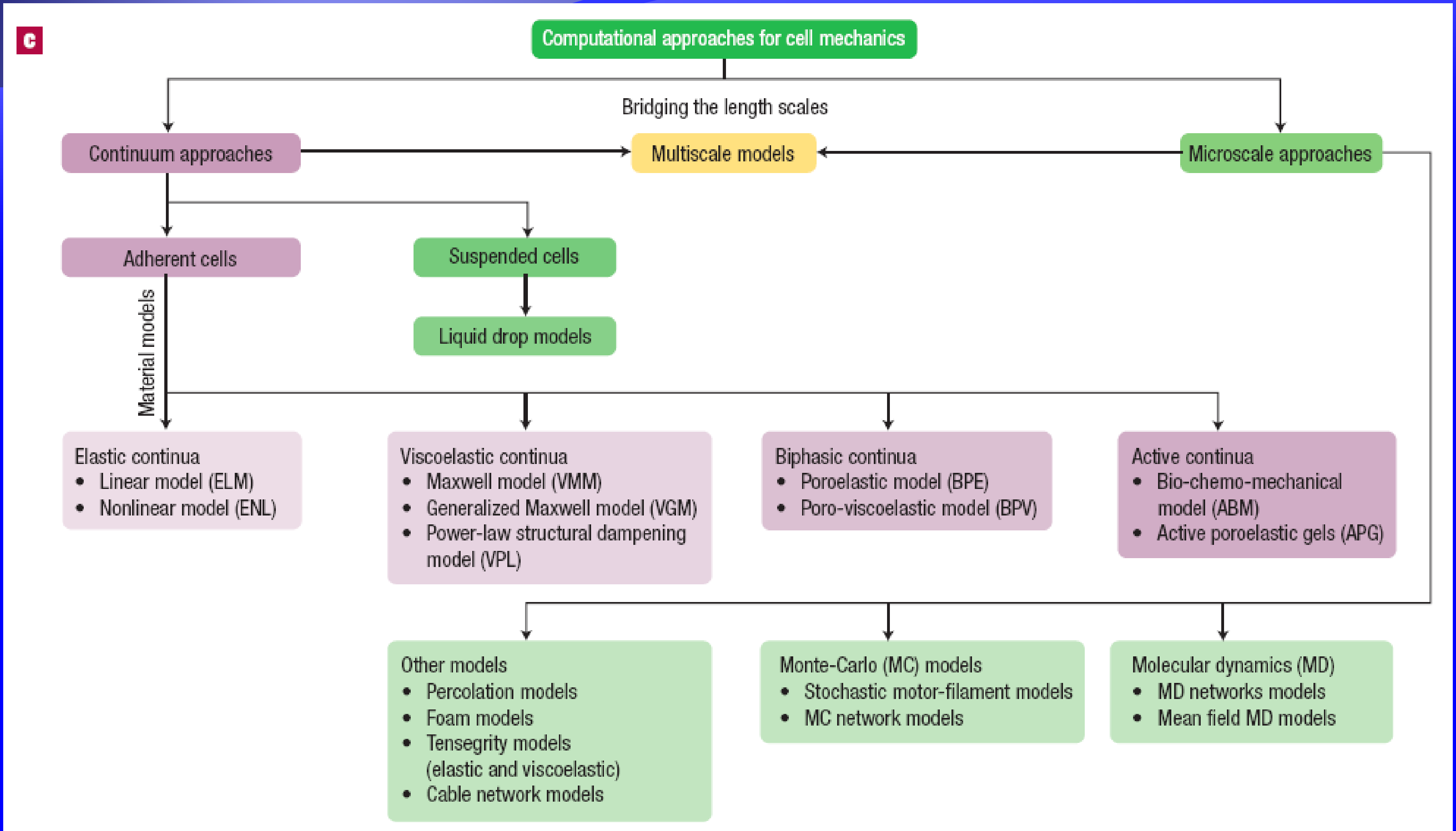
Session 18

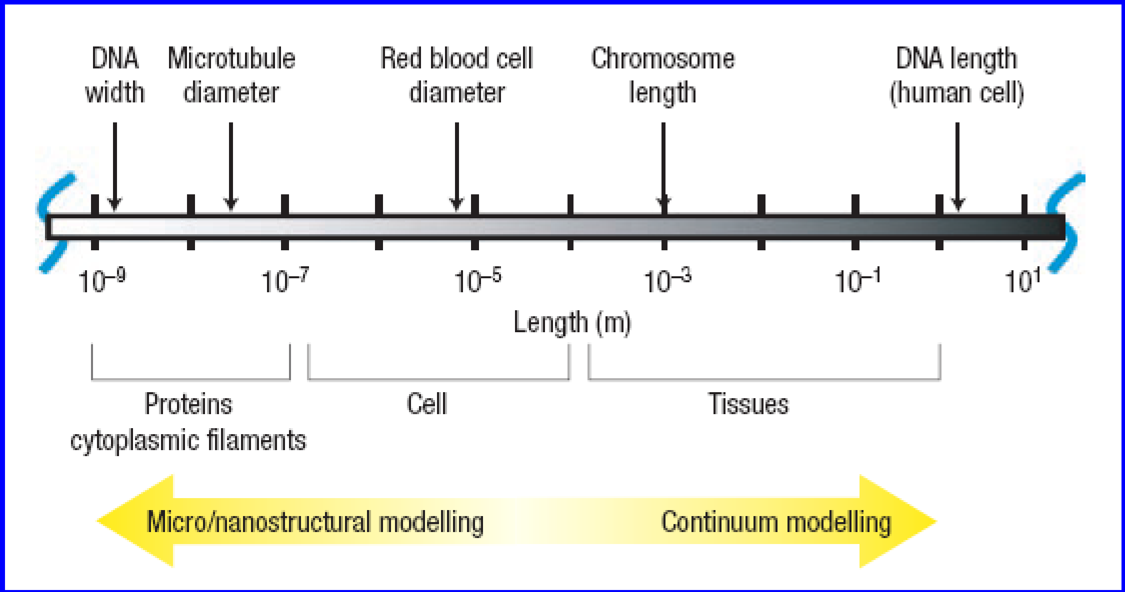
COMPUTATIONAL CONTINUUM MODELS

Models for Cell Mechanics



Continuum Elastic Models

- A cell can be treated as a continuous material if 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 ε, but tells us nothing about microstructure!
- Coarse-graining approach – lower resolution of averaged properties

Goals of Modeling

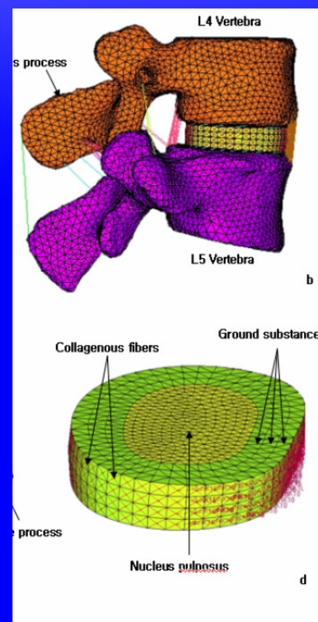
- Deduction of cells mechanical properties
  - Know stress and strain of a cell, what is constitutive relationship?
    - MTC – magnetic force, bead displacement
    - Micropipette aspiration – vacuum pressure, aspiration length
    - AFM - cantilever force, indentation depth

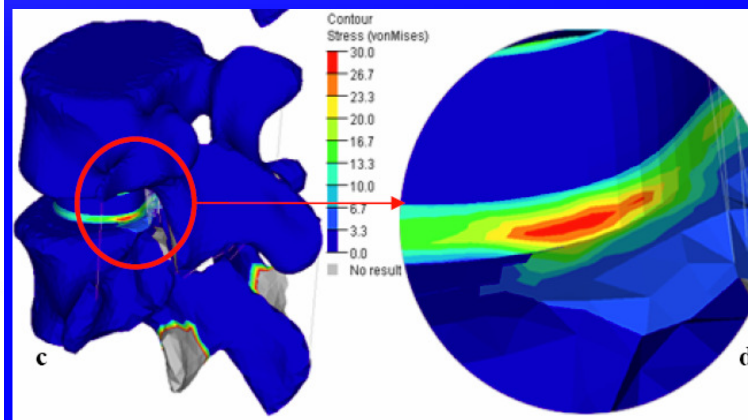
Goals of Modeling

- 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



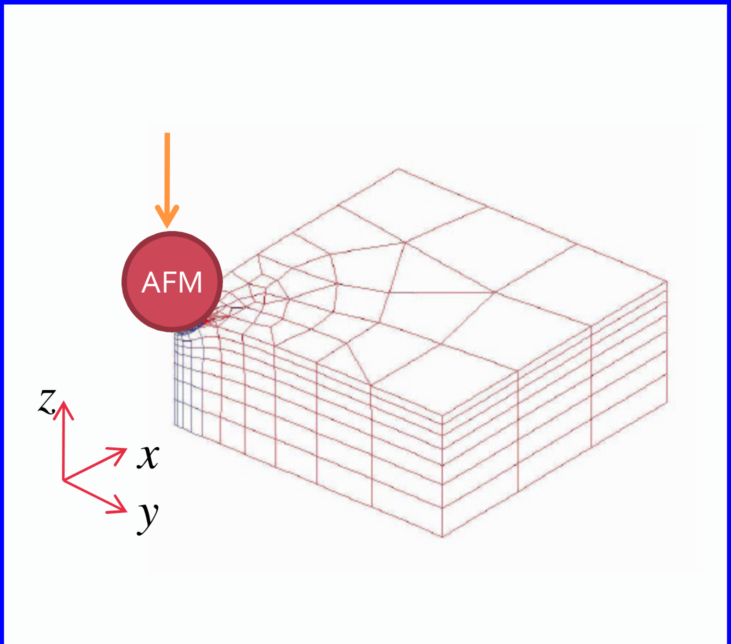


(Courtesy of Sangyoon Han)

  - Discretize model into computational elements interconnected by nodes
  - Formulate “stiffness matrix” to find displacements

AFM Example

- Osteoblast stimulated with AFM tip showed calcium spikes
- Linear elastic isotropic material
  - E = 10 kPa
  - ν = 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 (0,0,t)



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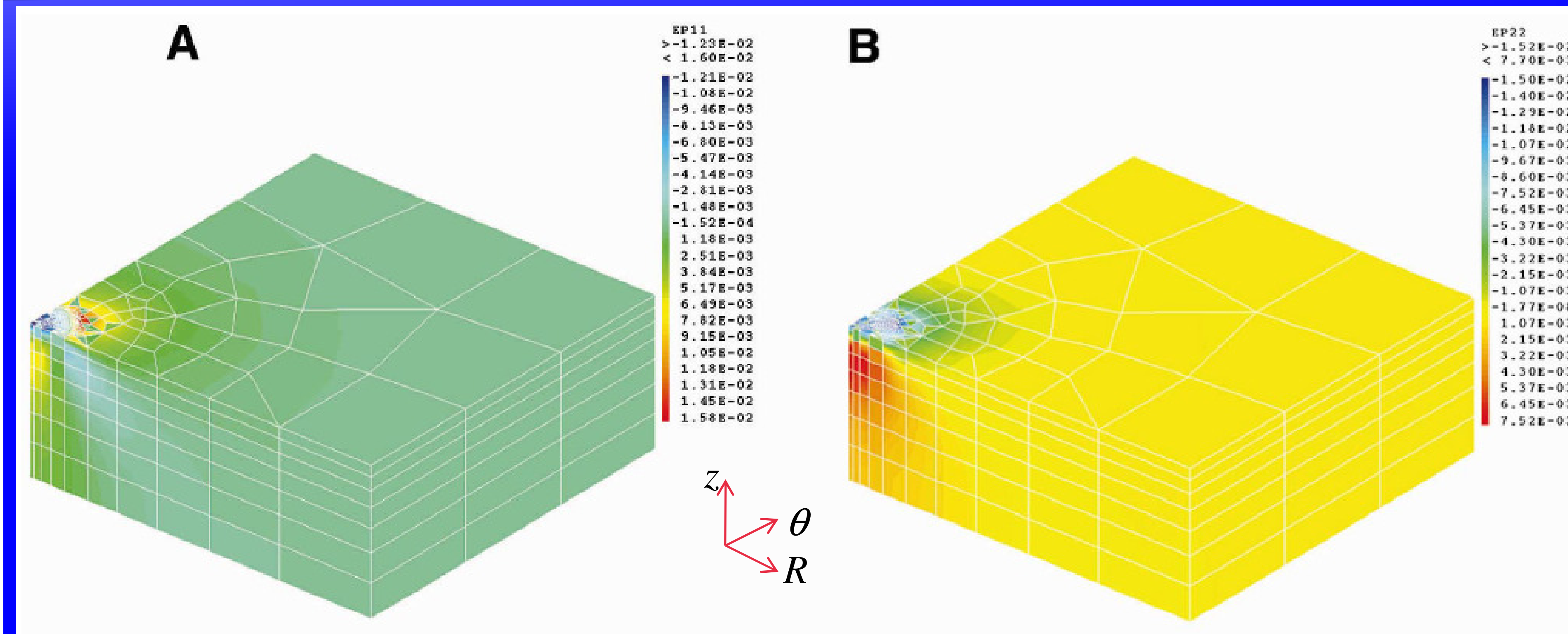
Radial and Tangential Strain

- Radial strains largest on cell surface



- Tangential strain largest at indentation area

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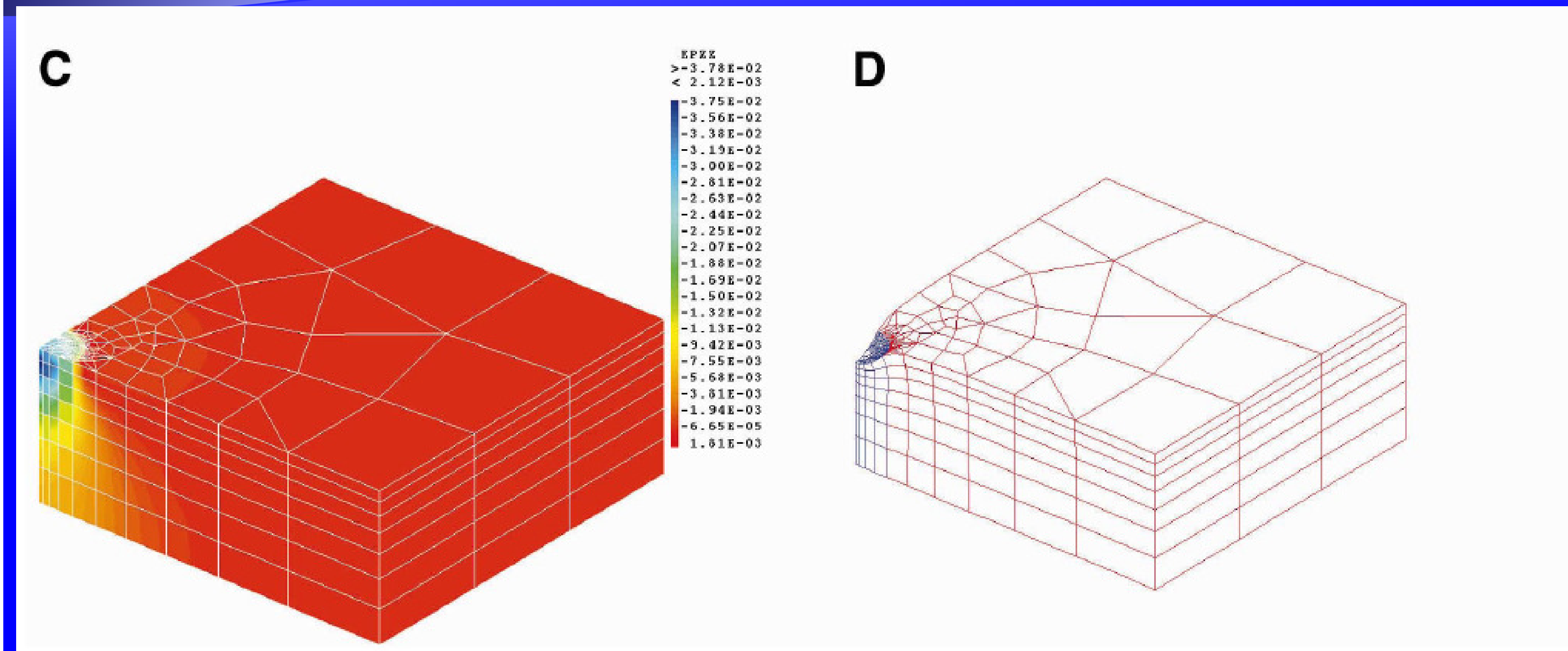
Vertical Strain and Deformation

- Vertical strain largest directly under indentation

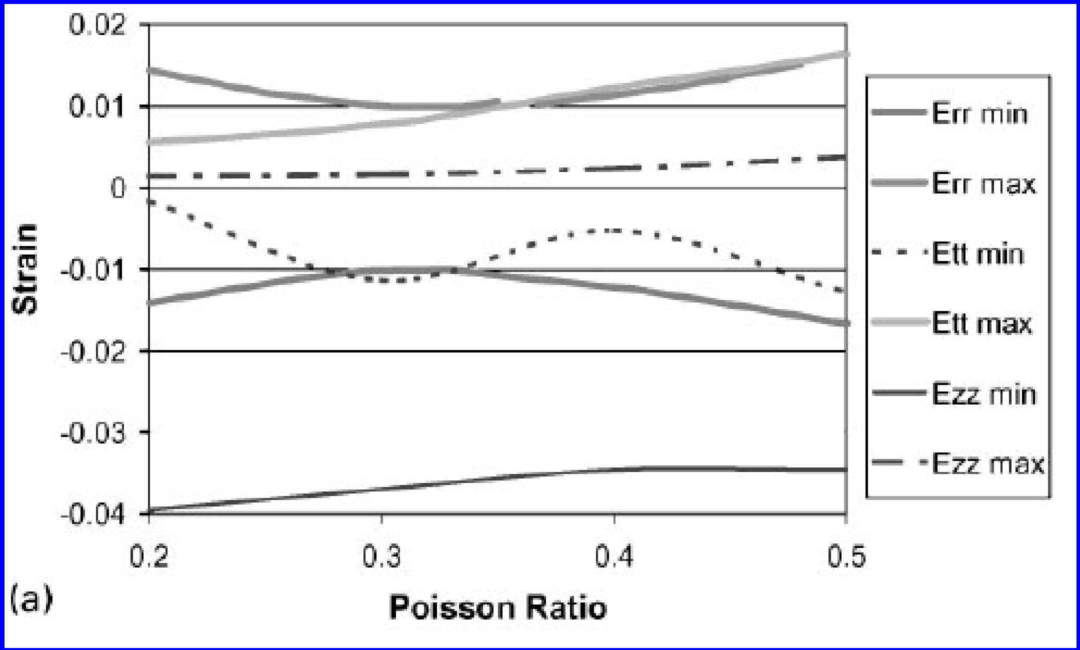


- Deformation amplified 15x for visualization

G.T. Charras, P.P. Lehenkari, M.A. Horton (2001) *Ultramicroscopy*, 86:85-95

Poisson's Ratio

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



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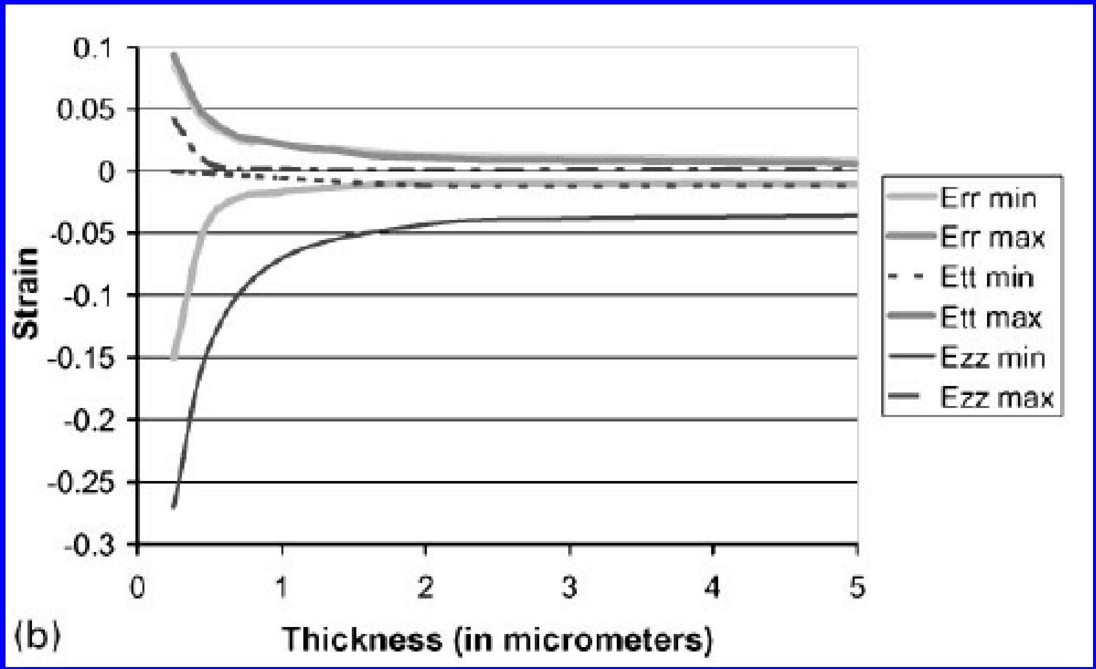
Cell Height

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



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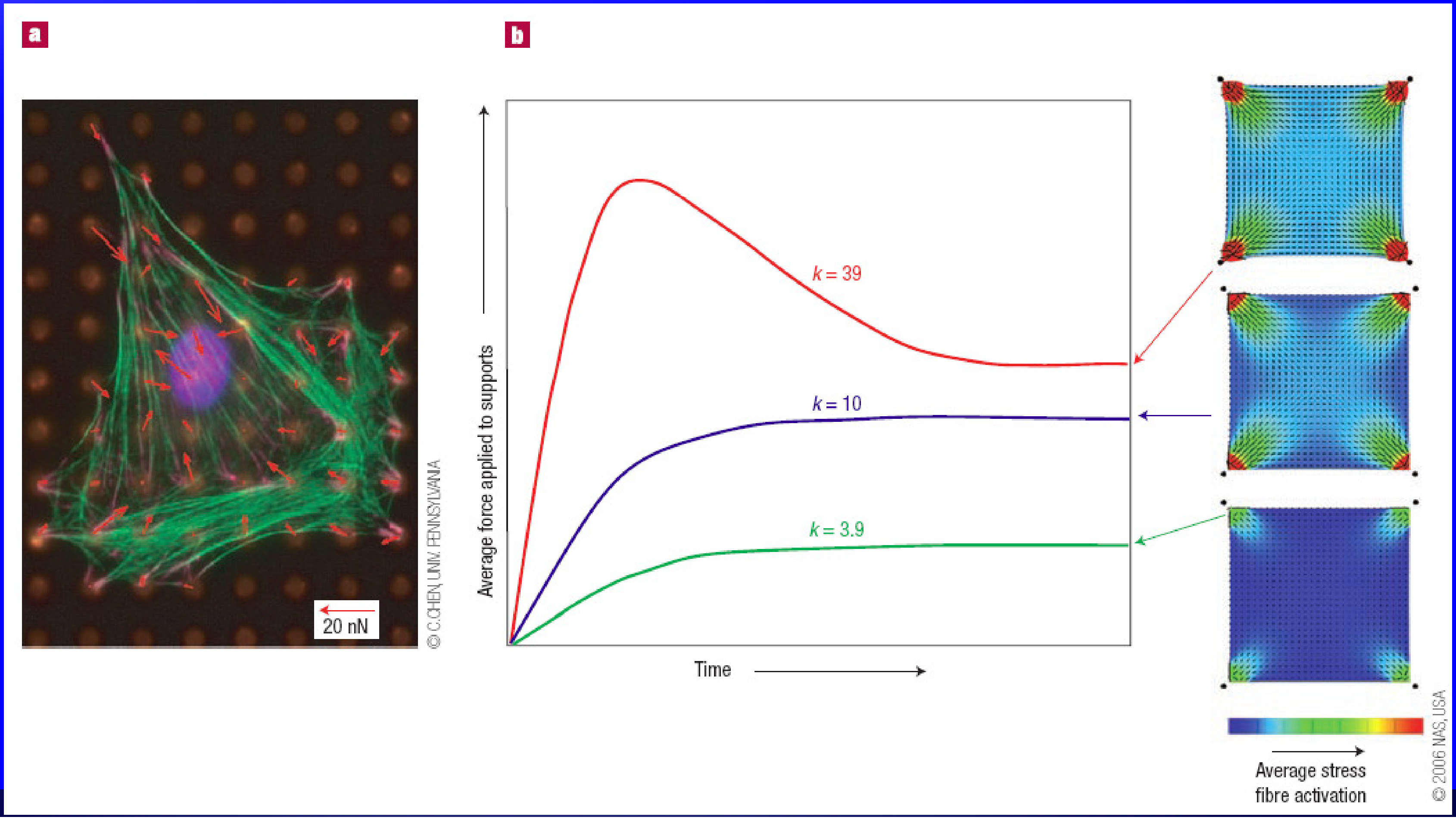
Active Continuum Models

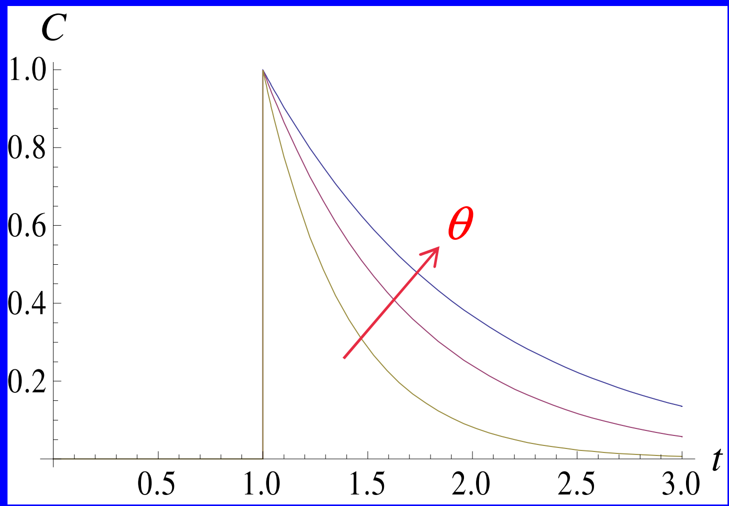
- Incorporates activation of contractility and reorganization of cytoskeleton



Simple Activation Scheme

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

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



  - t_i is time at instance of activation
  - θ is decay time constant for intracellular Ca^{2+} pumps

Filament Assembly

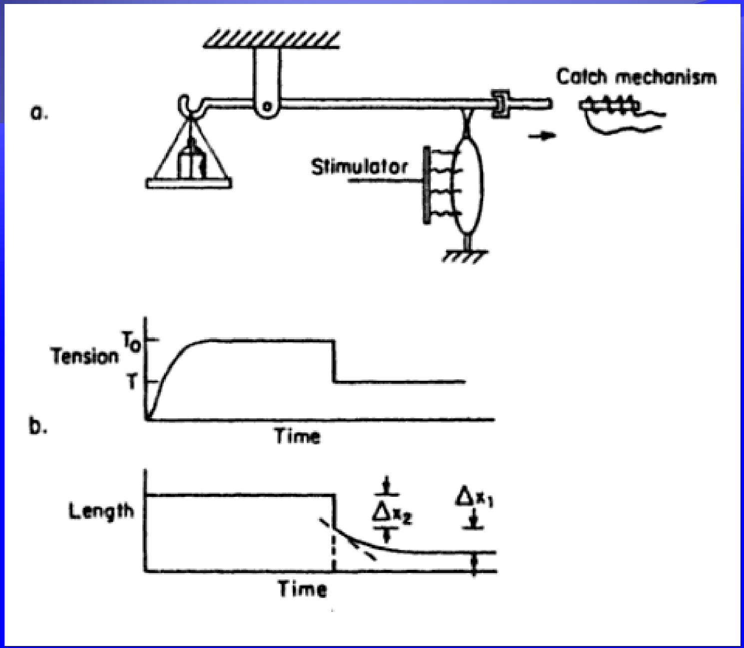
- Degree of assembly η of filaments into the contractile apparatus structure

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

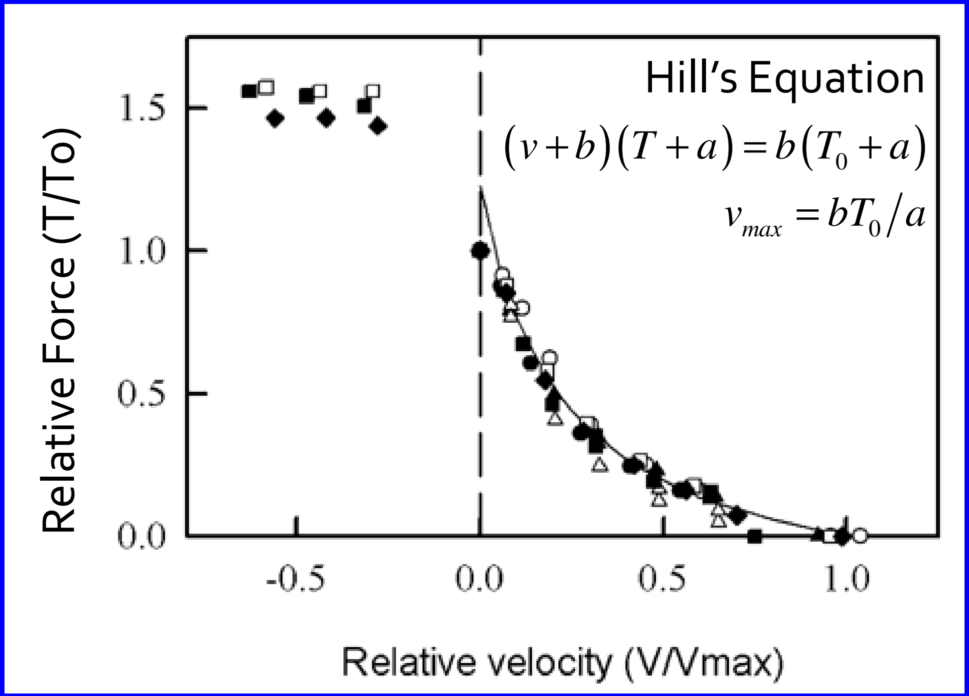
$$0 \le \eta \le 1$$

- First term is assembly reaction
  - Negatively on assembly state η due to fewer free monomers
  - Positively on Ca² concentration C that drives polymerization
  - Positively on forward rate constant k_f
- Second term is disassembly reaction
  - Positively on assembly state η
  - Negatively on ratio of tension to isometric tension σ/σ_0 that holds filaments together
  - Positively on backward rate constant k_b

Force-Velocity Dynamics



- Muscle cannot change its length instantly due to actin-myosin dynamics

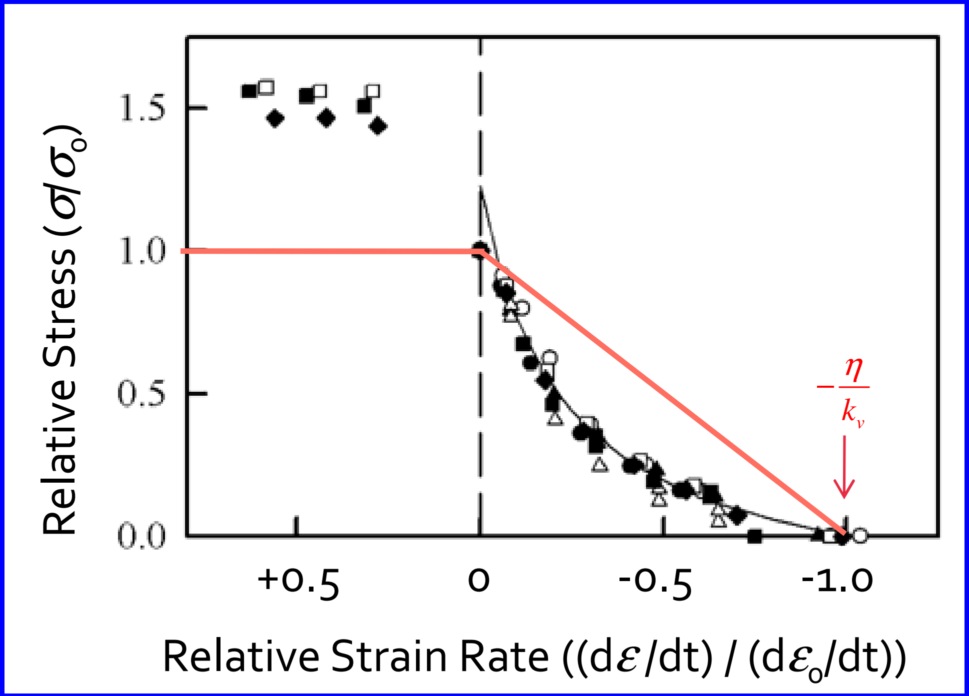


- Partly explained by inertia of weight
- Main cause is isotonic contraction produces less force than isometric, which is zero velocity and $T = T_o$.

Stress-Strain Rate Relationship

- Active strain rate is related to the stress by simplification of Hill's equation

$$\frac{\sigma}{\eta\sigma_{max}} = \begin{cases} 0 & \frac{\dot{\varepsilon}}{\dot{\varepsilon}_0} < -\frac{\eta}{k_v} \\ 1 + \frac{k_v}{\eta}\frac{\dot{\varepsilon}}{\dot{\varepsilon}_0} & -\frac{\eta}{k_v} \le \frac{\dot{\varepsilon}}{\dot{\varepsilon}_0} \le 0 \\ 1 & \frac{\dot{\varepsilon}}{\dot{\varepsilon}_0} > 0 \end{cases}$$



Linear Elastic Constitutive Relationship

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

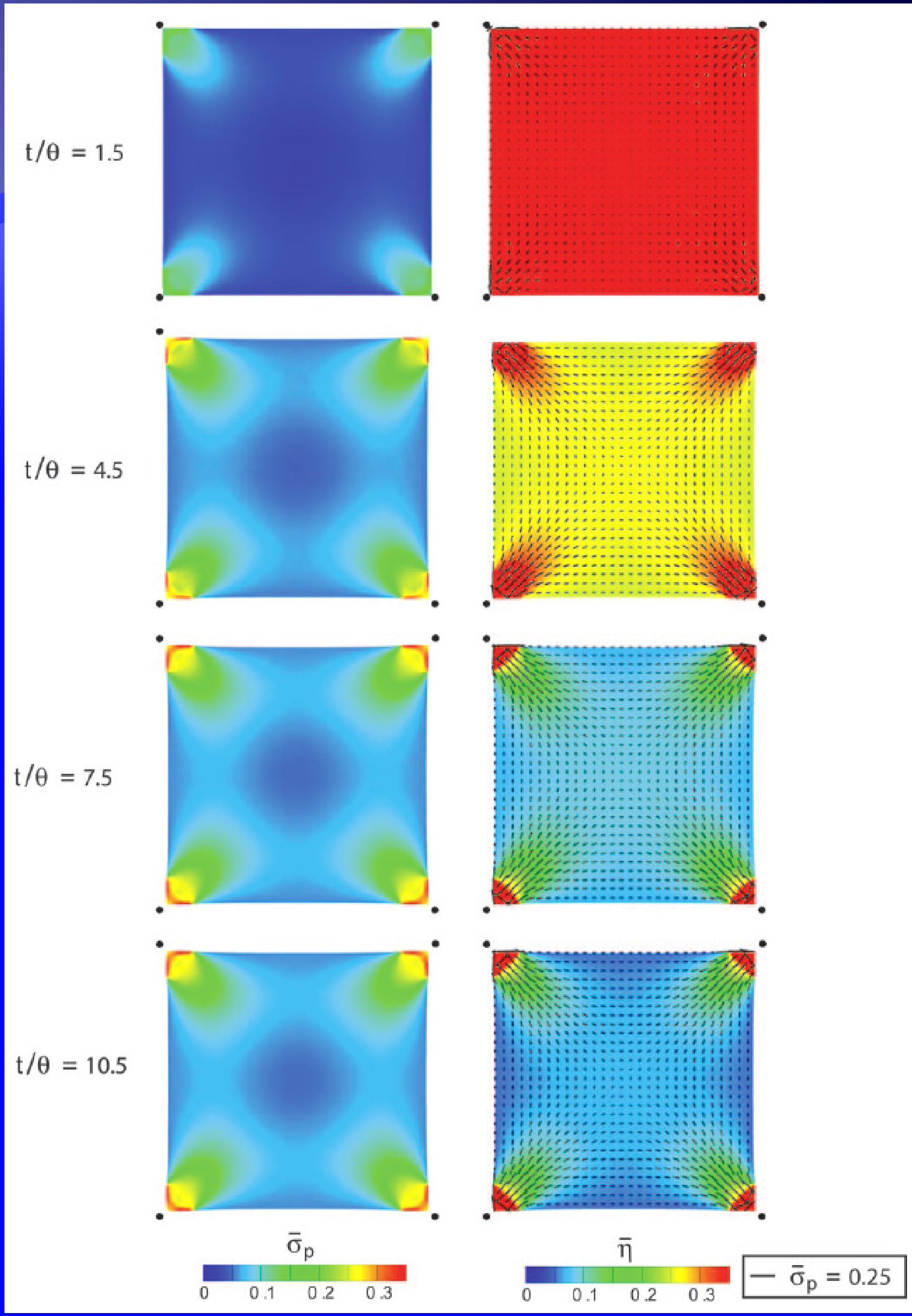
$$\dot{\varepsilon} \equiv \dot{\varepsilon}_{11}\cos^2\phi + \dot{\varepsilon}_{22}\sin^2\phi + \dot{\varepsilon}_{12}\sin 2\phi$$

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

- Passive Behavior: Linear Isotropic Elastic Material

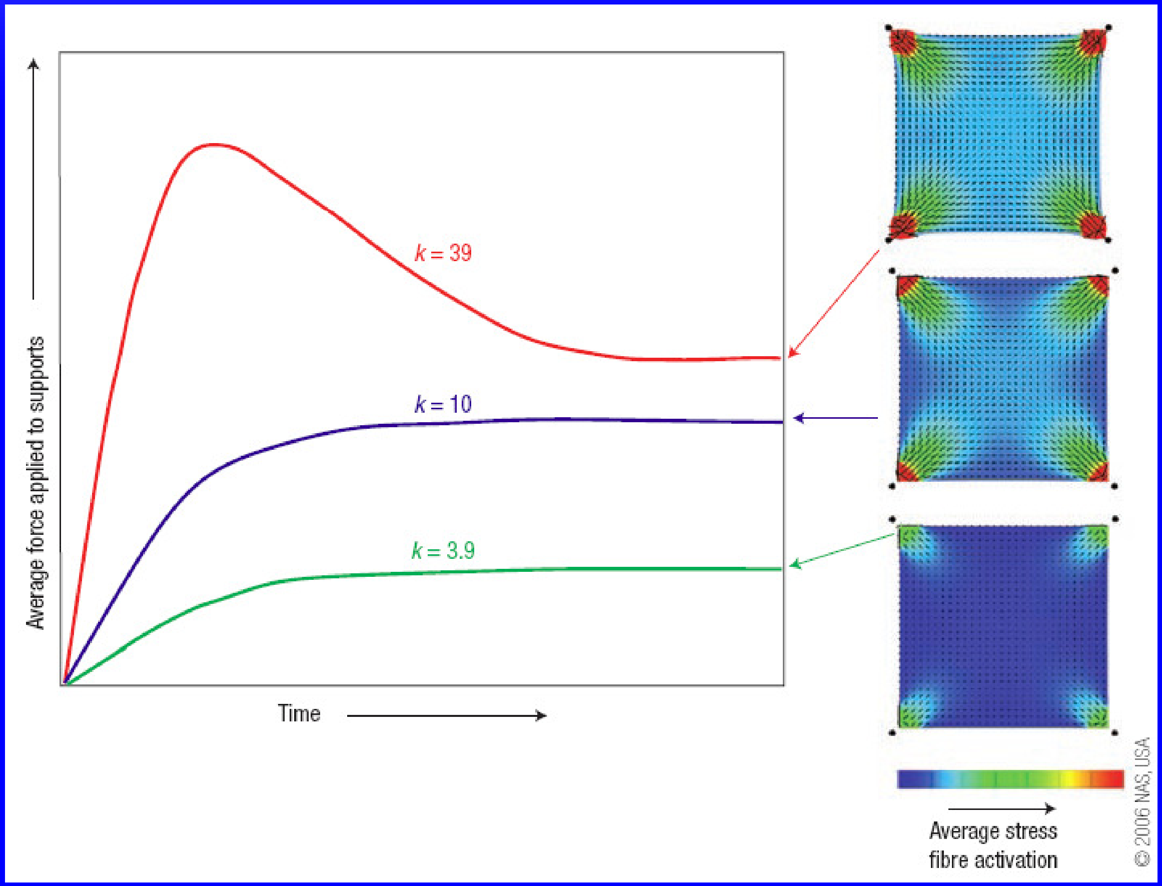
$$\sigma_{ij} = S_{ij} + \frac{E\nu}{(1-2\nu)(1+\nu)}\varepsilon_{kk}\delta_{ij} + \frac{E}{(1-\nu)}\varepsilon_{ij}$$

Principal Stress and Stress Fiber Activation Coincide Spatially and Temporally



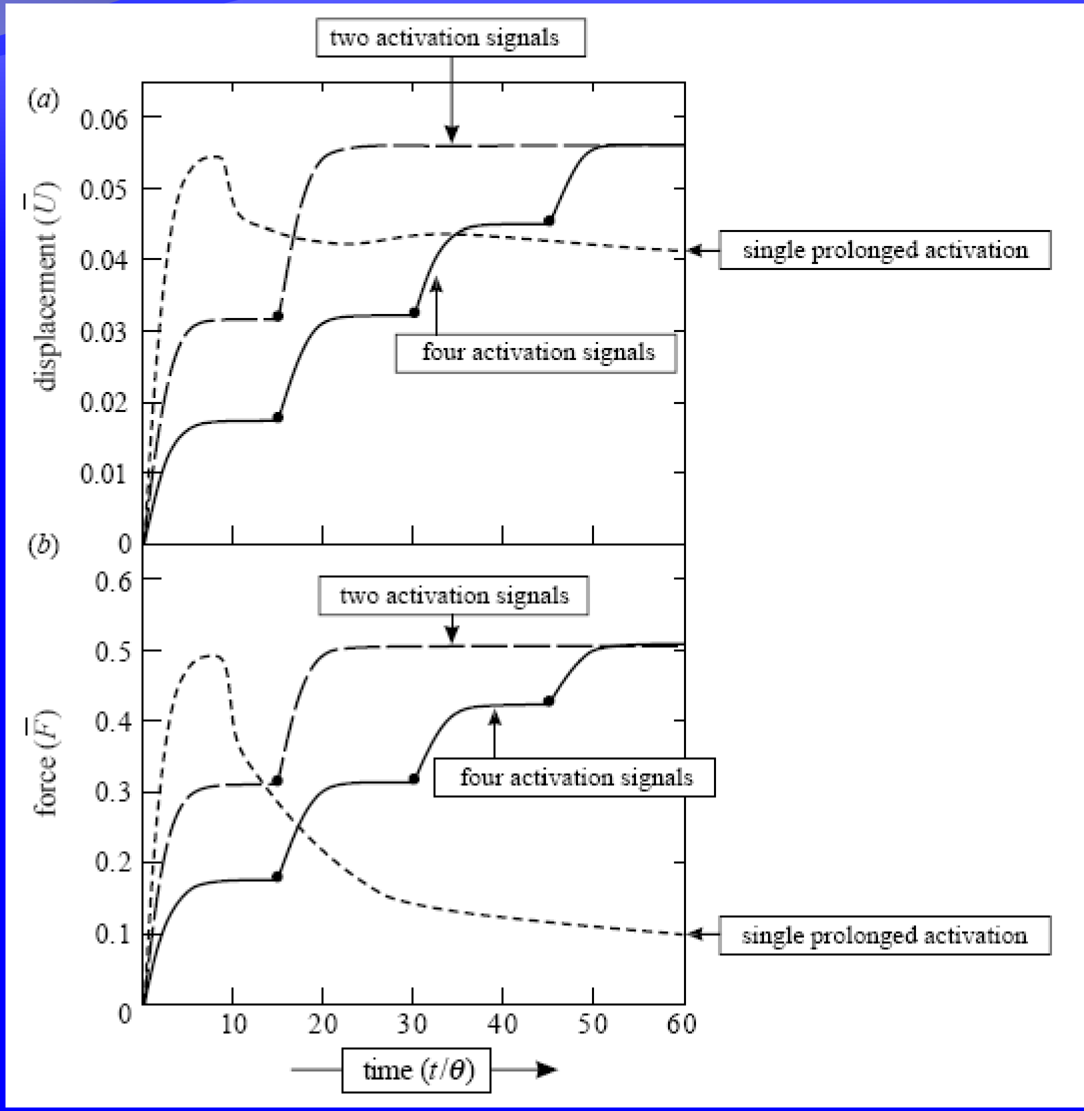
Stiffness affects Contraction Development

- Increases in stiffness k yields increased transient and steady state force response



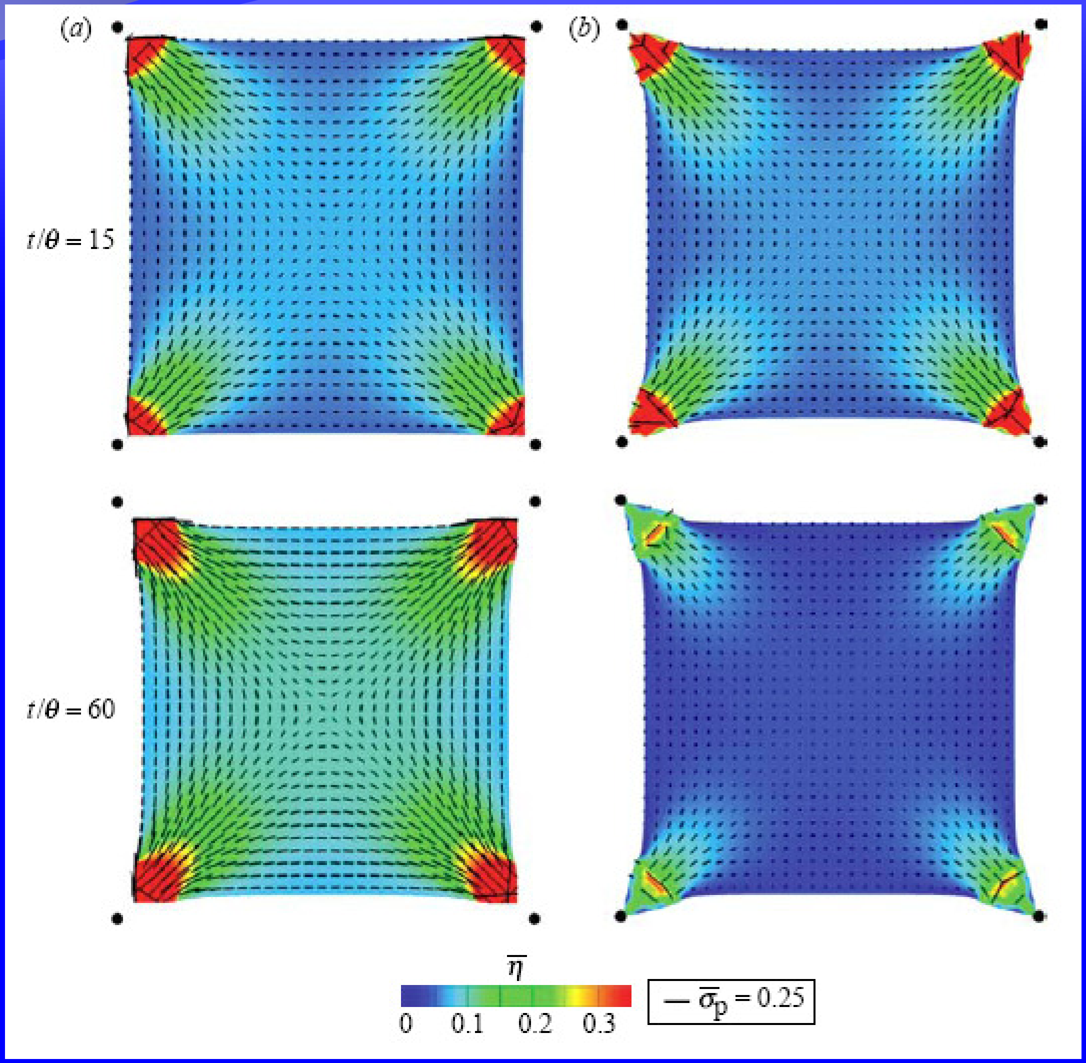
Multiple Activations

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



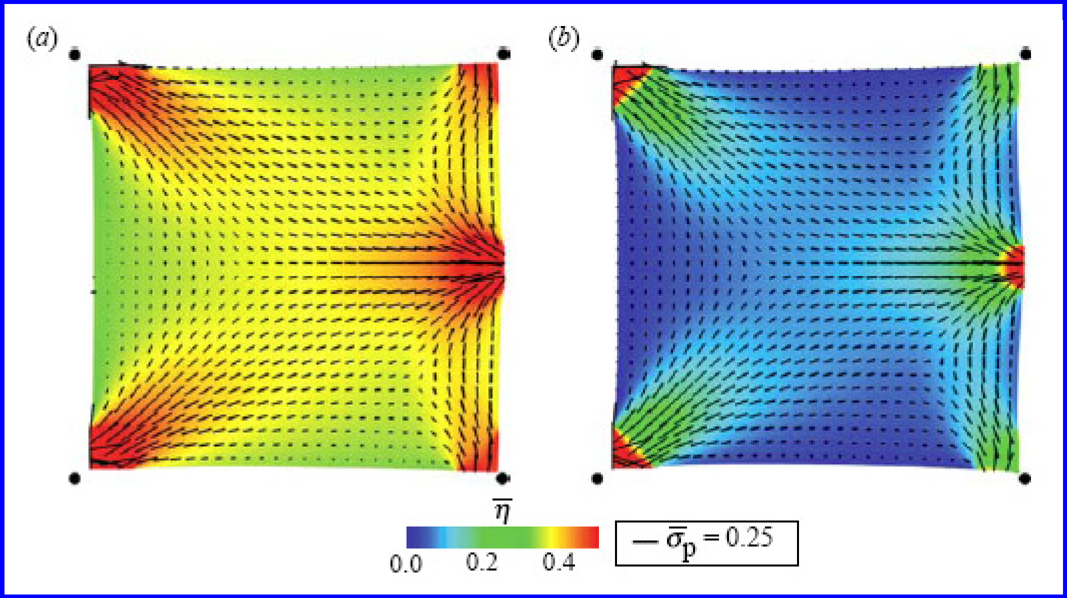
Stress Fiber Activation

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



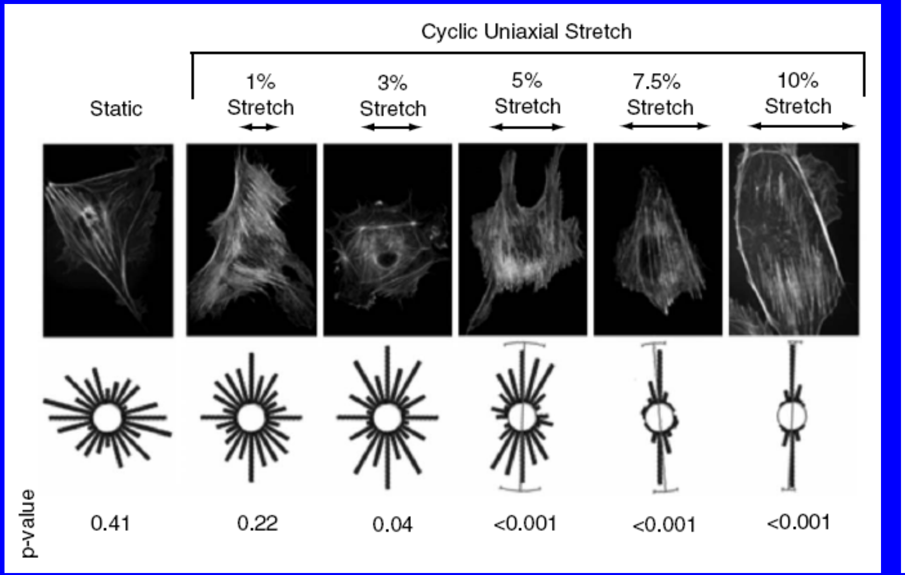
External Force Response

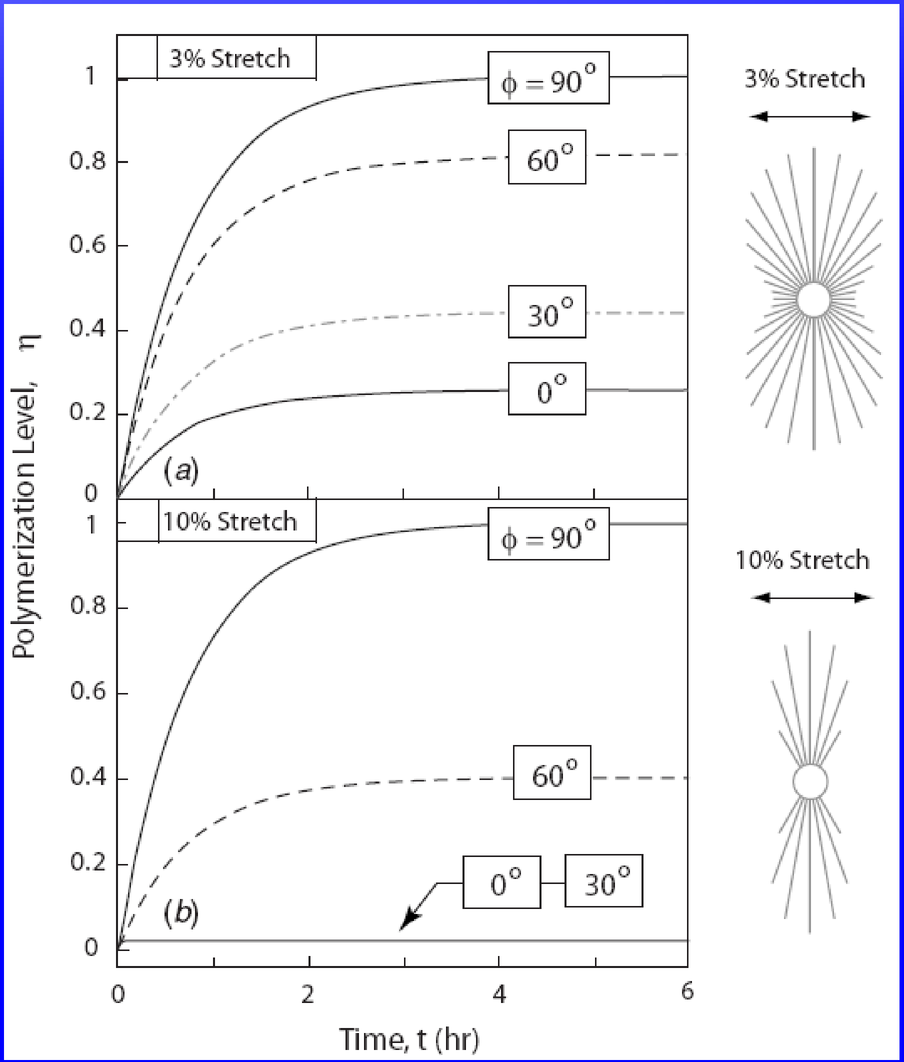
- Stress fiber activated locally in response to constant external force
- (a) Early and (b) late time points shown



Stretch Response

- Cells exposed to unidirectional, cyclic stretch observed to realign CSK in opposite direction





Wei, Z., Deshpande, V.S., McMeeking, R.M., Evans, A.G., (2008) *J Biomech Engr*, 130:031009