Bend, and Snap! How Flexible Actin Filaments Enable Cell Division

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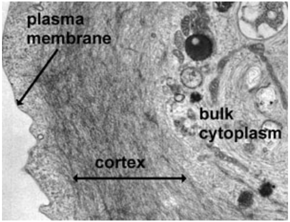
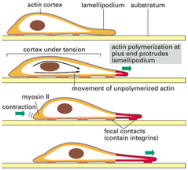
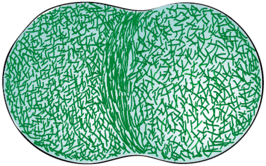
Motivation: Cell Cortex

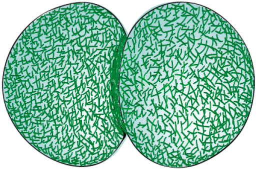
- Thin layer of proteins and fluid beneath the cell membrane



- Cortex deformation controls cell motility and division
- Movement of **actin** and **myosin** deforms the cortex

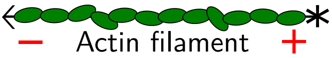


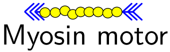


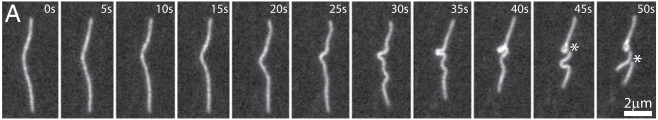


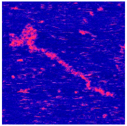
Actin and Myosin

- **Actin** molecules form polarised filaments ($\sim 1\,\mu m$)
- **Myosin** forms molecular motors that bind to filaments
  - Hydrolyse ATP and move towards actin filament plus ends

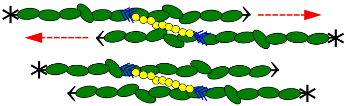


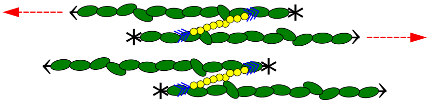






- Actin–myosin interactions can generate contraction/expansion

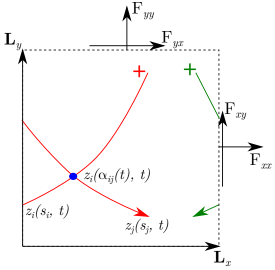


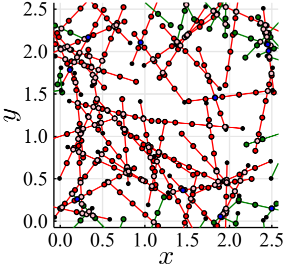


- In the cortex, filaments have random positions and orientations
- Research question: **Why do disordered networks contract?**

2D Agent-Based Model

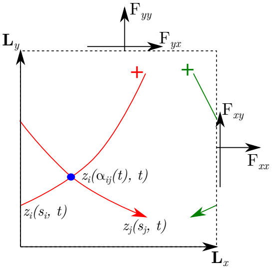
- Simulate evolution of network model DOF:
  - Filament positions: $z_i(s, t) = (x_i, y_i)$, represented as chains of springs connected by nodes
  - Motor relative positions: $m_{ik}(t) \in [0, L_i]$, represented as springs with equilibrium length zero
- Motors attach at random intersections, detach at force-dependent rate
- Protein friction acts at filament intersections without a motor
  - Point-wise drag that restricts relative filament motion

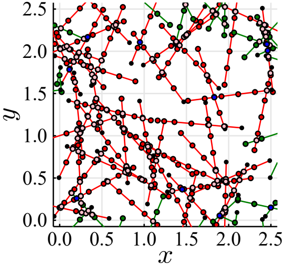




Energy Method

- Minimiser of energy functional solves force-balance equations
- Time-discrete functional contains each mechanical feature as a potential 'energy':
    - Filament stretching
    - Filament bending
    - Filament drag
    - Protein friction
    - Motor stretching
    - Motor movement
- Parameters provide measure of resistance to each force





Energy Method

$$E_{network} = \sum_{\substack{filaments\ i,j \\ motors\ k}} E_{a,bend} + E_{a,spring} + E_{a,drag} + E_{a,pf} + E_{m,spring} + E_{m,a}$$

$$E_{a,spring} = \int_0^{L_i} \frac{\tilde{k}_a}{2} \left(|z_i'| - 1 \right)^2 \, ds,$$

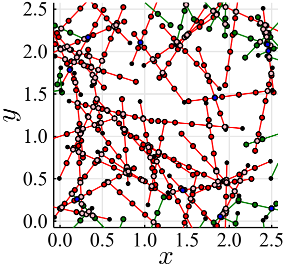
$$E_{a,bend} = \int_0^{L_i} \frac{\kappa_a}{2} \left| z_i'' \right|^2 \, ds$$

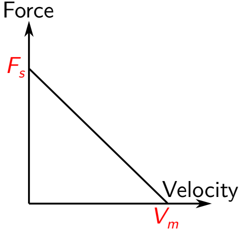
$$E_{a,drag} = \int_0^{L_i} \frac{\lambda_a}{2\Delta t} \left| z_i - \boldsymbol{F} z_i^{\text{old}} \right|^2 \, ds$$

$$E_{a,pf} = \frac{\lambda_{pf}}{2\Delta t} \left| z_i(\alpha_{ij}) - z_j(\alpha_{ji}) \right|^2$$

$$E_{m,spring} = \frac{k_m}{2} \left| z_i(m_{ik}) - z_j(m_{jk}) \right|^2$$

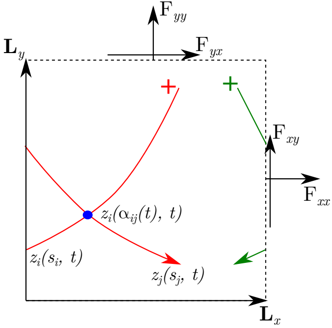
$$E_{m,a} = \frac{F_s}{V_m} \frac{\left(m_{ik} - m_{ik}^n \right)^2}{2\Delta t} - F_s m_{ik}$$





Forces and Stress

- Introduce forces acting on domain boundary
- Lagrange multipliers that constrain domain size and shape



$$E_{total} = E_{network} + \boldsymbol{F}_x \cdot \boldsymbol{L}_x + \boldsymbol{F}_y \cdot \boldsymbol{L}_y$$

- Method enables calculation of:
  - Force components

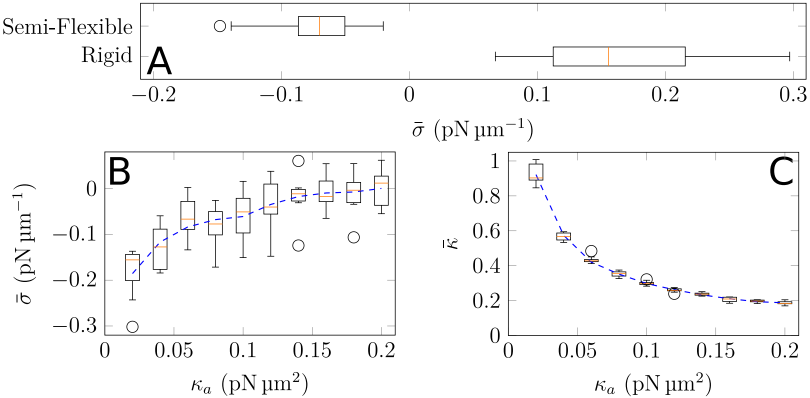
$$F_{xx} = -\frac{\partial E_{network}}{\partial L_{xx}}, \quad F_{yy} = -\frac{\partial E_{network}}{\partial L_{yy}}, \quad \text{etc.}$$

  - Stress ($\sigma < 0$: contraction, $\sigma > 0$: expansion)

$$\boldsymbol{\sigma} = \begin{bmatrix} F_{xx}/L_{yy} & F_{xy}/L_{yy} \\ F_{yx}/L_{xx} & F_{yy}/L_{xx} \end{bmatrix}, \quad \sigma = \frac{1}{2}\left(\frac{F_{xx}}{L_{yy}} + \frac{F_{yy}}{L_{xx}}\right)$$

Results: Actin Bending Facilitates Contraction

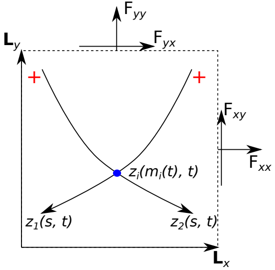
- Semi-flexible networks contract in repeated (25) simulations[1]

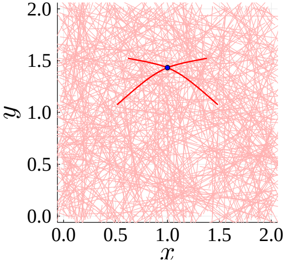


[1] A. K. Y. Tam, A. Mogilner, and D. B. Oelz, "Protein friction and filament bending facilitate contraction of disordered actomyosin networks", Biophysical Journal 120, 11247 (2021).

Two-Filament System

- Follow-up question: **Is bending-induced contraction a network-scale effect, or can two filaments explain it?**





- Assumptions:
  - Filaments and motors are inextensible
  - No protein friction
  - Dense background network provides drag
  - Vertical symmetry
  - Fast-moving motor: $V_m^* \to \infty$
  - Small bending: $\kappa^* = 1/\varepsilon$, $\varepsilon \ll 1$

Simplified PDE Model for Two Filaments

- Taking $\Delta t \to 0$ yields the PDEs

$$\frac{\partial z}{\partial t} + \frac{1}{\varepsilon} z'''' - \left(\lambda z'\right)' + \mu \begin{pmatrix} 1 \\ 0 \end{pmatrix} \delta(s - m)$$

$$0 = 1 - \mu \begin{pmatrix} 1 \\ 0 \end{pmatrix} \cdot z'(m(t), t)$$

- Expand variables: $z = z_0 + \varepsilon z_1 + \mathcal{O}(\varepsilon^2)$, $m = m_0 + \varepsilon m_1 + \mathcal{O}(\varepsilon^2)$, $\sigma = \sigma_0 + \varepsilon \sigma_1 + \mathcal{O}(\varepsilon^2)$, etc.

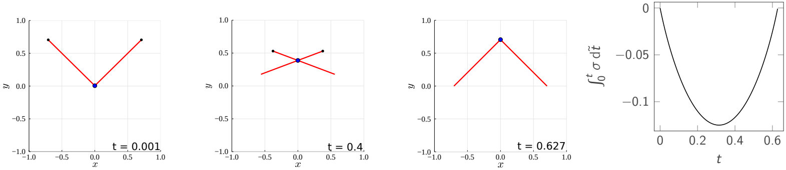
$$\sigma = 2 \int_0^1 \frac{\partial z}{\partial t} \cdot z \, \mathrm{d}s = -2 \int_0^1 \frac{1}{\varepsilon} \left(z''\right)^2 + \lambda \, \mathrm{d}s$$

$$\int_0^T \sigma \, \mathrm{d}t = J(T) - J(0), \quad J(t) = \int_0^1 \left|z(s, t)\right|^2 \, \mathrm{d}s$$

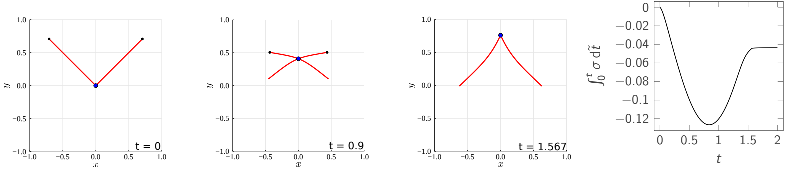
- Leading-order solution is for rigid filaments
- First-order corrections describe effect of bending

Geometric Asymmetry Facilitates Contraction

- Rigid filaments have polarity-reversal symmetry and generate zero net stress



- Flexible filaments break this symmetry, facilitating contraction[2]



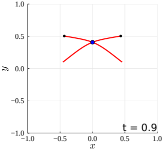
[2] A. K. Y. Tam, A. Mogilner, and D. B. Oelz, "F-Actin Bending Facilitates Net Actomyosin Contraction By Inhibiting Expansion With Plus-End-Located Myosin Motors", BioRxiv (2021).

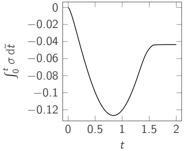
Summary

- We simulated actomyosin networks and a two-filament-motor system to understand how actin bending produces contraction

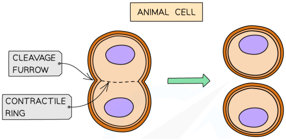
Summary

- We simulated actomyosin networks and a two-filament-motor system to understand how actin bending produces contraction
- **“Legally Blonde theory of actomyosin contraction”**: If you want ~~an 83% rate of return on dinner invitations~~ to understand how actin filaments facilitate cell division, just remember...
  - Bend...





  - And snap!



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