Actin' Weird: Why Does the Cell Cortex Contract?

Alex Tam Dietmar Oelz

School of Mathematics and Physics, University of Queensland

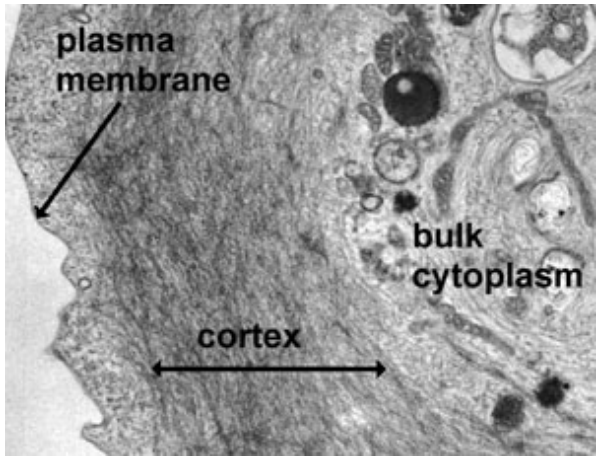
February 3, 2020

THE UNIVERSITY OF QUEENSLAND

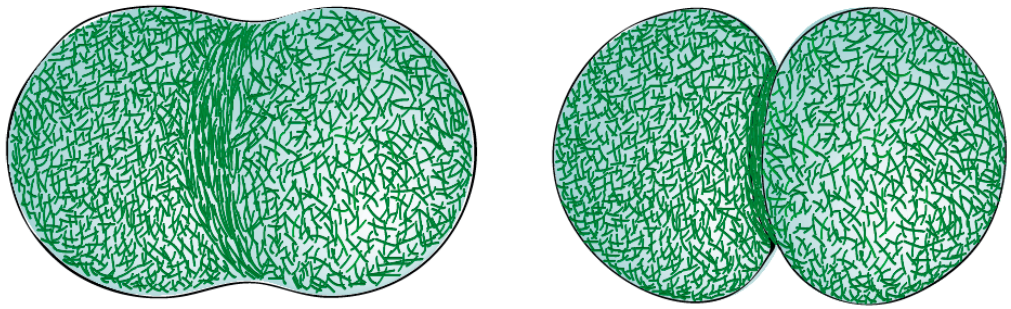
AUSTRALIA

Cell Cortex

- Thin layer of proteins on the inside of the cell membrane

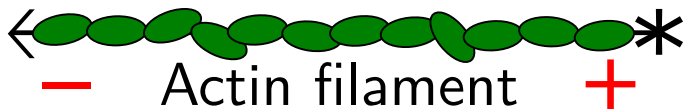


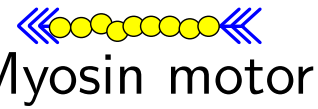
- Cortex deformation controls cell shape, motility, and division
- Movement of **actin** and **myosin** deforms cortex
- Actin and myosin form a contractile ring that divides cells



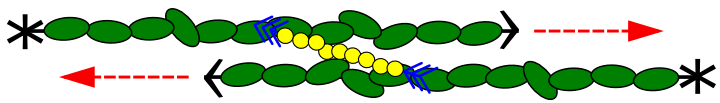
Actomyosin Networks

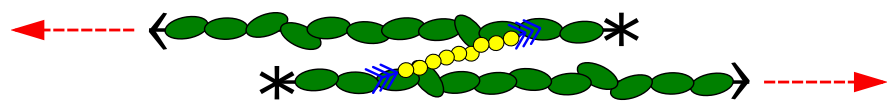
- Actin molecules form polarised filaments
- Myosin molecules form shorter 'motors' that bind to filaments
  - Hydrolyse ATP and move towards actin filament plus ends





- Actin–myosin interactions can generate contraction/expansion

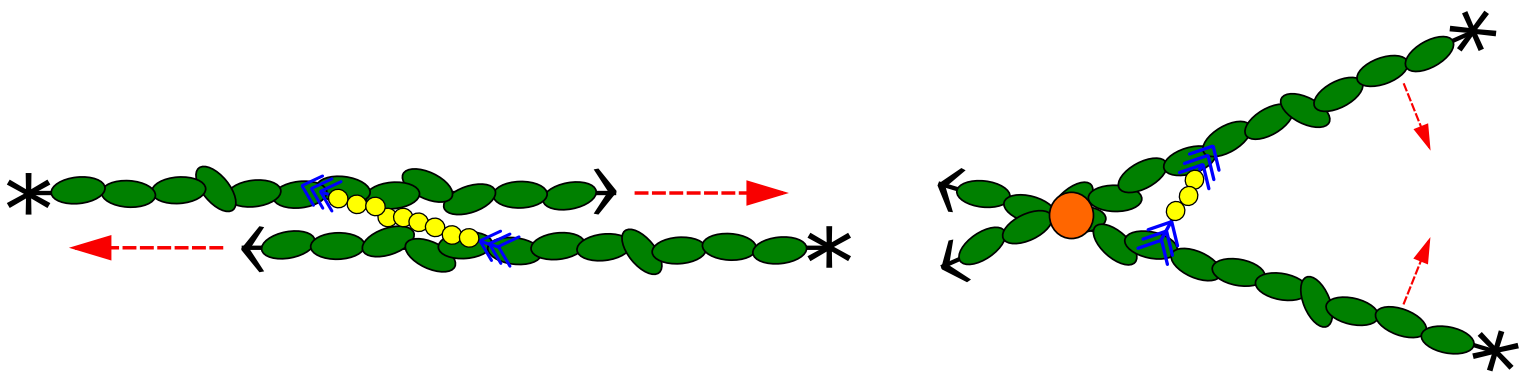




- In random networks (*e.g.* cell cortex), we would expect contraction or expansion with equal probability
- Research question: **Why do random networks contract?**

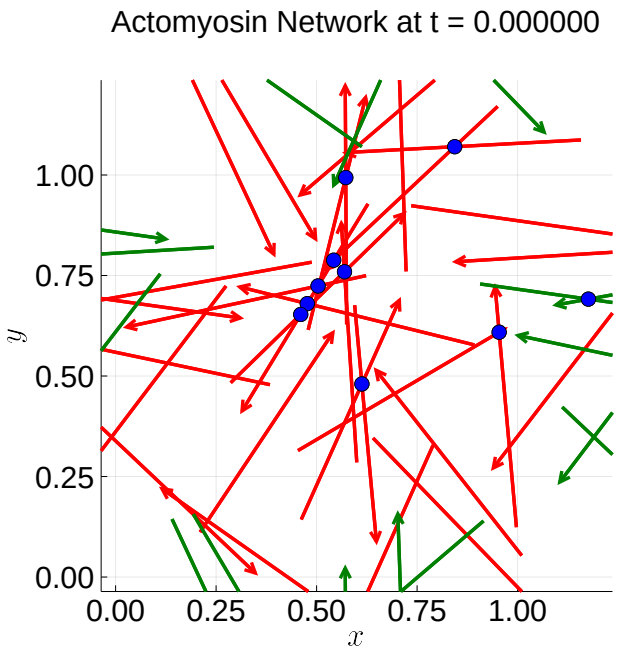
Contraction Mechanisms

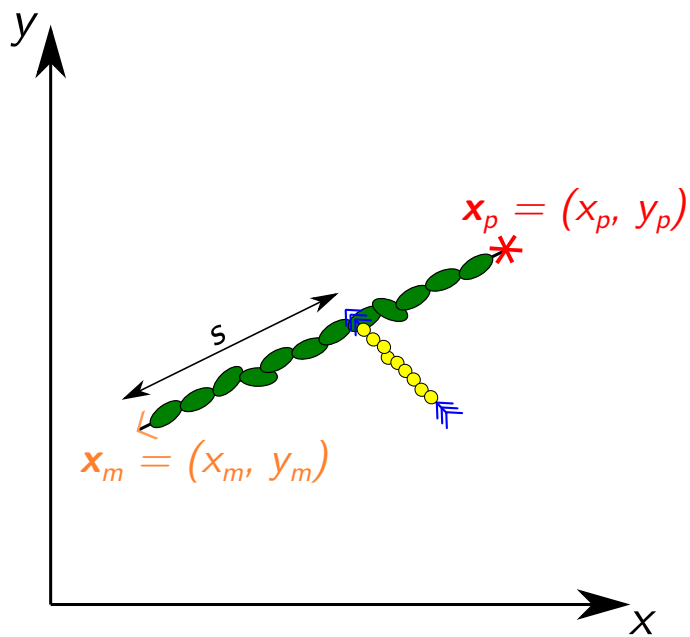
- Many hypothesised symmetry-breaking mechanisms in 2D random networks:
  - Force asymmetry
    - Actin filament buckling
  - Structural asymmetry
    - Actin filament 'treadmilling'
    - Delayed myosin unbinding
    - Network architecture, anchoring
    - **Motor activity and cross-linking**



2D Agent-Based Model

- Model Assumptions:
  - Rigid actin filaments
  - Inertial effects negligible
  - Cross-linkers resist motion (via drag) at filament intersections
- $\boldsymbol{x}_{pi}$, $\boldsymbol{x}_{mi}$: Positions of actin filament plus and minus ends
- $s_{ij} \in [0, 1]$: Relative position of myosin motor





Governing Equations

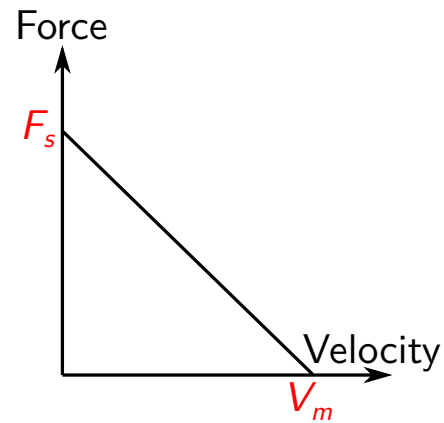
- Write model in terms of network potential energy

$$E_{network} = E_{a,spring} + E_{a,drag} + E_{a,xl} + E_{m,spring} + E_{a,m}$$

- Energy terms depend on parameters and DOF

$$E_{a,spring} = \sum_{i=1}^{N_a} k_a \frac{(L_i - L_a)^2}{2}, \qquad E_{m,spring} = \sum_{j=1}^{N_m} k_m \frac{L_m^2}{2}$$

$$E_{a,drag} = \sum_{i=1}^{N_a} \lambda_a \int_0^1 \frac{\left\| \boldsymbol{P}_i - \boldsymbol{P}_i^k \right\|^2}{2\Delta t} \, \mathrm{d}p$$



$$E_{a,xl} = \sum_{i=1}^{N_a} \sum_{j>i}^{N_a} A_{ij} \lambda_{xl} \frac{\left\| \boldsymbol{R}_{ij} - \boldsymbol{R}_{ij}^k \right\|^2}{2\Delta t}$$

$$E_{a,m} = \sum_{j=1}^{N_m} \sum_{i=1}^{N_a} \vartheta_{ij} \frac{F_s}{V_m} \frac{\left[L_i (s_{ij} - s_{ij}^k) \right]^2}{2\Delta t} - \vartheta_{ij} F_s L_i \left(s_{ij} - s_{ij}^k \right)$$

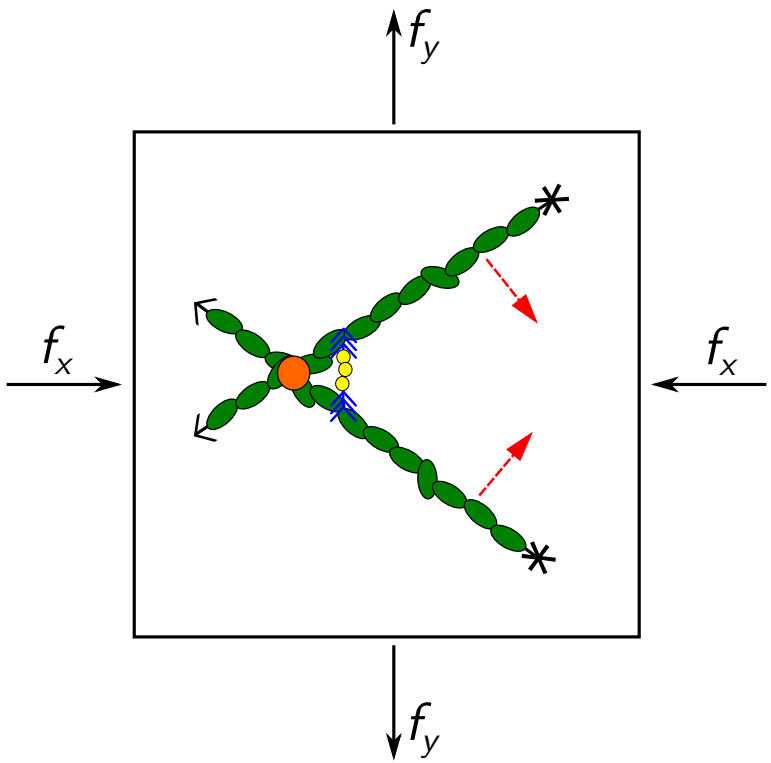
Energy Minimisation Method

- Minimising energy at each time step yields a time-implicit numerical scheme for the DOF
- Equivalent to solving overdamped force-balance equations
- Optimisation performed using the Julia package `Optim.jl`
- Minimiser found using Newton's method with automatic differentiation (`ForwardDiff.jl`)

Contractile Force

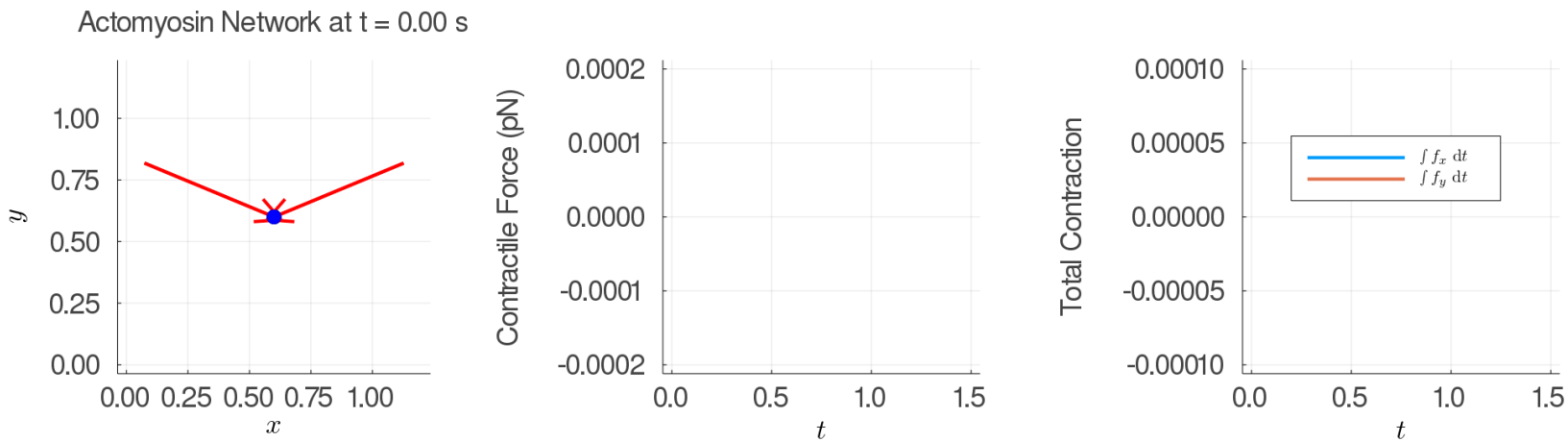
- Net contractile force computed directly in our model
- Network components can deform the underlying cortex
- Solve equations with constraint of constant domain size
- Contractile force components are Lagrange multipliers that enforce this constraint

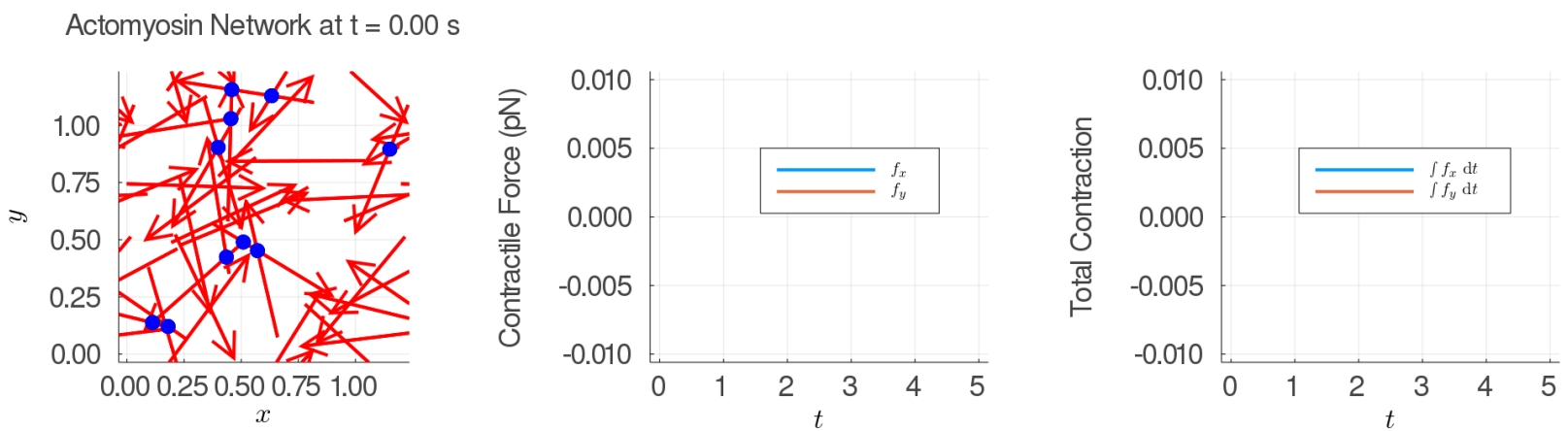
$$E_{total} = E_{network} + f_x(L_x - l_x) + f_y(L_y - l_y)$$



Results: No Cross-Linking

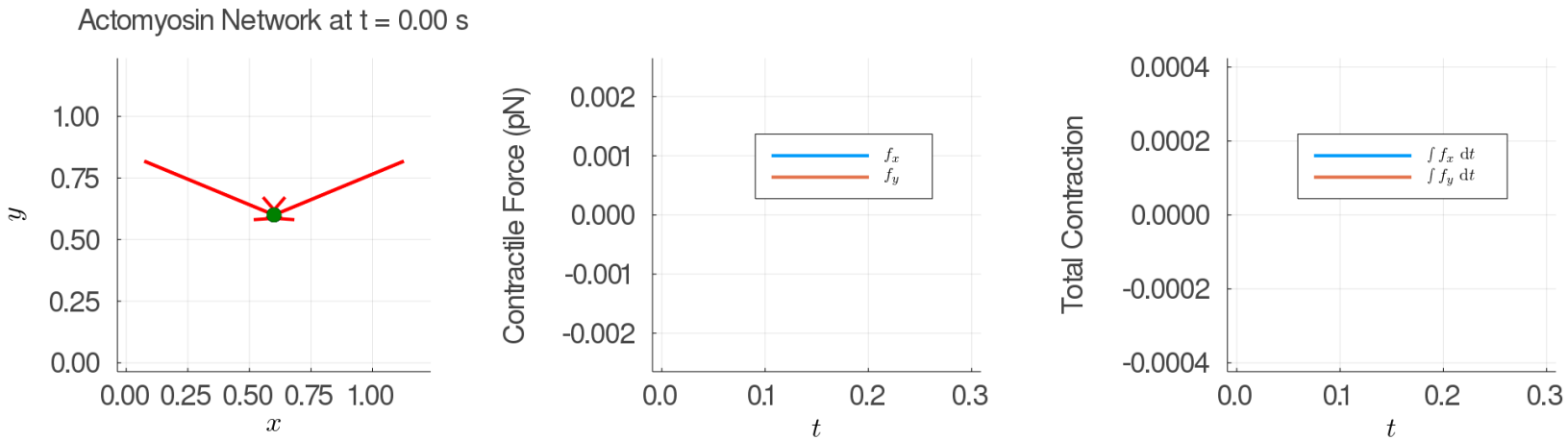
- Parameters: $l_x = l_y = 1.2\,\mu\text{m}$, $L_a = 0.6\,\mu\text{m}$, $k_a = 1\,\text{pN}\,\mu\text{m}^{-1}$, $\lambda_a = 0.001\,\text{pN}\,\mu\text{m}^{-1}\,\text{s}$, $k_m = 1\,\text{pN}\,\mu\text{m}^{-1}$, $F_s = 4.7\,\text{pN}$, $V_m = 0.5\,\mu\text{m}\,\text{s}^{-1}$, $\lambda_{xl} = 0\,\text{pN}\,\mu\text{m}^{-1}\,\text{s}$

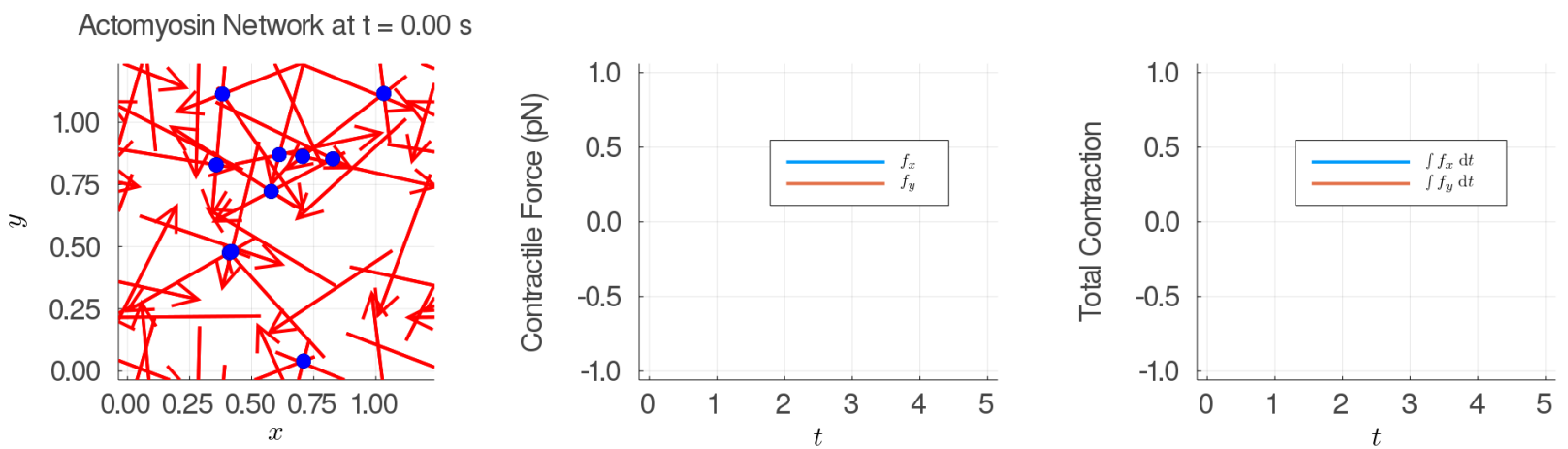




Results: Strong Cross-Linking

- Parameters: $l_x = l_y = 1.2\,\mu\text{m}$, $L_a = 0.6\,\mu\text{m}$, $k_a = 1\,\text{pN}\,\mu\text{m}^{-1}$, $\lambda_a = 0.001\,\text{pN}\,\mu\text{m}^{-1}\,\text{s}$, $k_m = 1\,\text{pN}\,\mu\text{m}^{-1}$, $F_s = 4.7\,\text{pN}$, $V_m = 0.5\,\mu\text{m}\,\text{s}^{-1}$, $\lambda_{xl} = 1\,\text{pN}\,\mu\text{m}^{-1}\,\text{s}$





Summary

- Actin and myosin control cell division and motility
- We developed an agent-based model for 2D random actomyosin networks
- Myosin motors generate contraction with sufficient cross-linking

Future work:

- Alternative contraction mechanisms
- Long-time pattern formation
- Continuum modelling

Acknowledgements:

- Funding: ARC Discovery Project DP180102956

Australian Government
Australian Research Council

@xelamaths

Force-Balance Equations

- Filament and motor positions governed by balance of forces

Forces on the i-th actin filament:

$$\boldsymbol{0} = \underbrace{\lambda_a \int_0^1 \frac{\mathrm{d}}{\mathrm{d}t}\left[\boldsymbol{x}_{mi} + p\left(\boldsymbol{x}_{pi} - \boldsymbol{x}_{mi}\right)\right] \mathrm{d}p}_{\text{Drag friction}} + \underbrace{k_a\left(L_i - L_a\right)\hat{\boldsymbol{e}}_i}_{\text{Spring forces}}$$

$$+ \underbrace{\sum_{j=1}^{N_a} A_{ij}\lambda_{xl}\frac{\mathrm{d}}{\mathrm{d}t}\left(\boldsymbol{R}_i - \boldsymbol{R}_j\right)}_{\text{Cross-linking}} - \underbrace{\sum_{j=1}^{N_m} \vartheta_{ij} F_s\left(1 - \frac{L_i}{V_m}\frac{\mathrm{d}s_{ij}}{\mathrm{d}t}\right)\hat{\boldsymbol{e}}_i}_{\text{Myosin–actin interactions}}$$

Forces on the j-th myosin motor:

$$\boldsymbol{0} = \underbrace{k_m\left(L_j - L_m\right)\hat{\boldsymbol{e}}_j}_{\text{Spring forces}} + \underbrace{\sum_{i=1}^{N_a} \vartheta_{ij} F_s\left(1 - \frac{L_i}{V_m}\frac{\mathrm{d}s_{ij}}{\mathrm{d}t}\right)}_{\text{Myosin–actin interactions}}$$

Muscle Contraction

- In muscles, actin and myosin are arranged for contraction