Modeling the Distribution and Dynamics of Actin Cables

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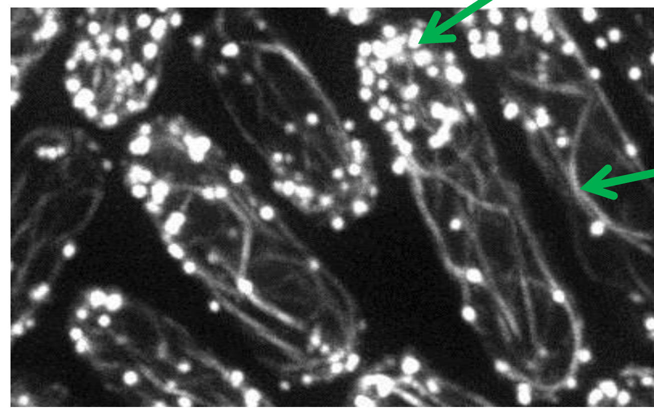
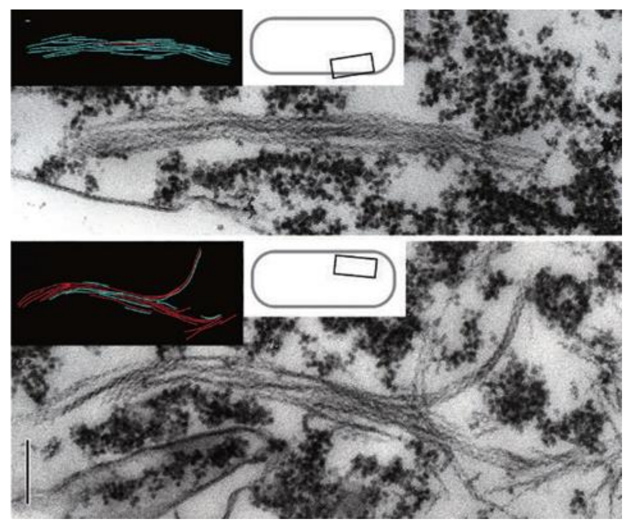
Fission Yeast

- Fission yeast: model organism in cell biology.
- Shape: tube-like shape.
- Amenable to genetic modifications and microscopic imaging.
- Actin patches: meshwork of branched actin filaments.
- Actin cables: bundles of actin filaments; guide the transport of organelles.



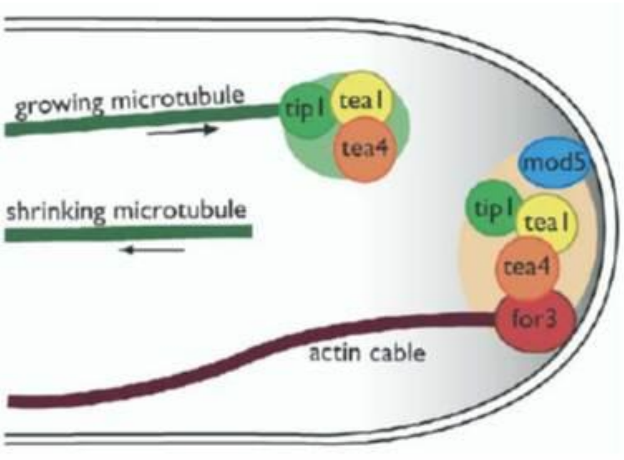
Actin patches and cables.
(JQ Wu, OSU)



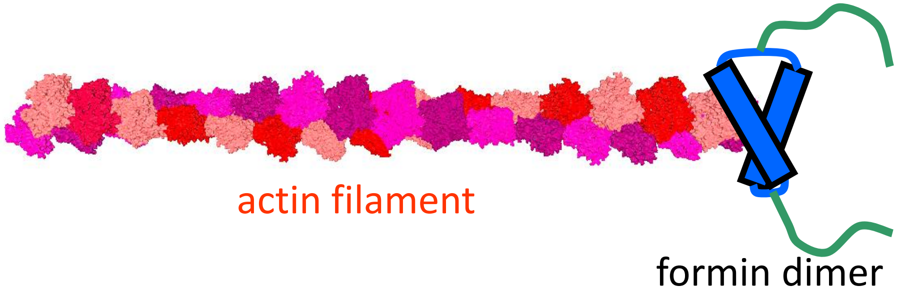
(T. Kamasaki et al., Nature Cell Biol. (2005).)

Actin Cable Regulatory Proteins

- Formin: For3p nucleates and elongates actin filaments.
- Cross-linkers: cross-linkers (likely fimbrin Sac6p in budding yeast) bundle actin filaments.



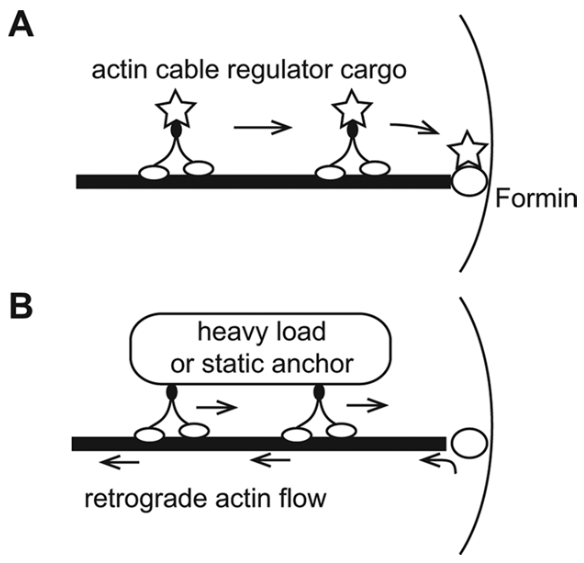
Nucleation mechanism of actin cables.
(S. Martin and F. Chang, Dev. Cell (2005)).



Actin Cable Regulatory Proteins

- Cofilin, Aip1, Coronin: sever actin filaments.

- Tropomyosin: inhibits severing.
- Myosin V: transports cargo to cell tips or attaches to static anchor.

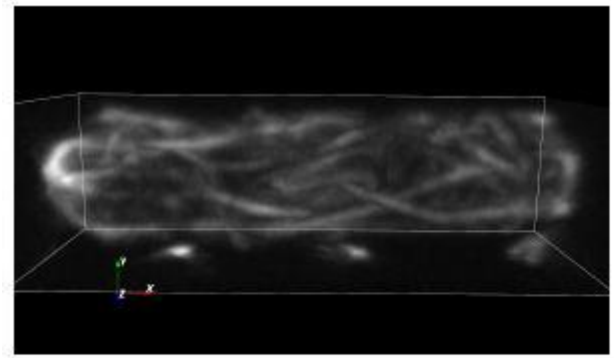


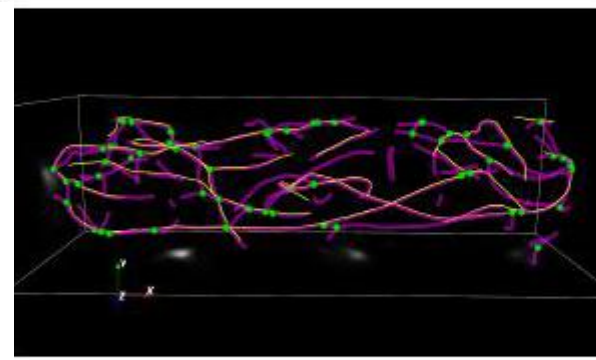
Myosin V carries cargo or anchors on organelle.
(Presti, F Chang and S Martin, MBoC (2012)).

Compare simulations to cell images to understand how molecular interactions → large scale morphology

1. Can model that includes polymerization, severing, cross-linking explain important features of actin cables?

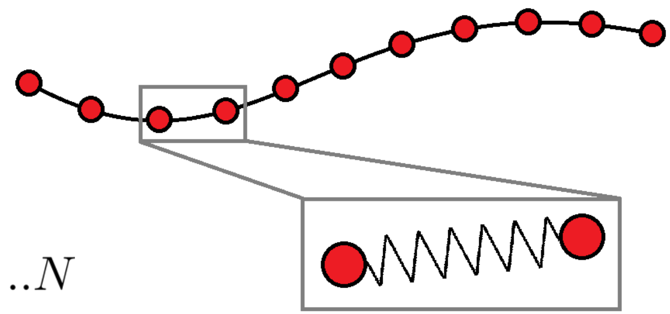
2. Effect of cross-linking strength?





Confocal microscopy images of actin cables and profiles generated using SOAX.
(images: Wu Lab.)
(Software: Xu, Vavylonis, Huang, submitted).

Model of Single Actin Filament



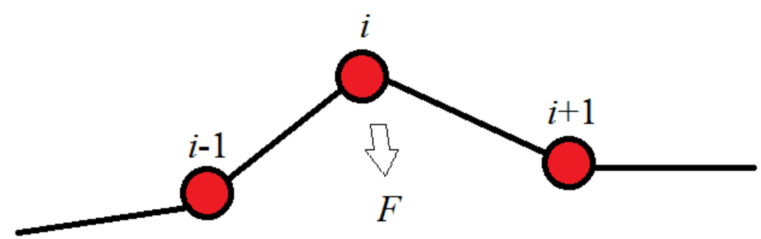
- Bead-spring model.
- Langevin equation of motion:

$$\vec{F}_i^{spring} + \vec{F}_i^{bend} + \vec{F}_i^{thermal} = \zeta_b \frac{d\vec{r}_i}{dt}, \quad i = 1, 2, ..N$$

- Spring force:

$$\vec{F}_i^{spring} = -\frac{\partial E^{spring}}{\partial \vec{r}_i} = -\frac{k}{2} \sum_{j=1}^{N-1} \frac{\partial(|\vec{r}_{j+1} - \vec{r}_j| - l_0)^2}{\partial \vec{r}_i}$$

- Bending force:



$$\vec{F}_i^{bend} = -\frac{\partial E^{bend}}{\partial \vec{r}_i} = -\frac{\kappa}{l_0} \sum_{j=2}^{N-1} \frac{\partial(\vec{t}_j \cdot \vec{t}_{j-1})}{\partial \vec{r}_i}$$

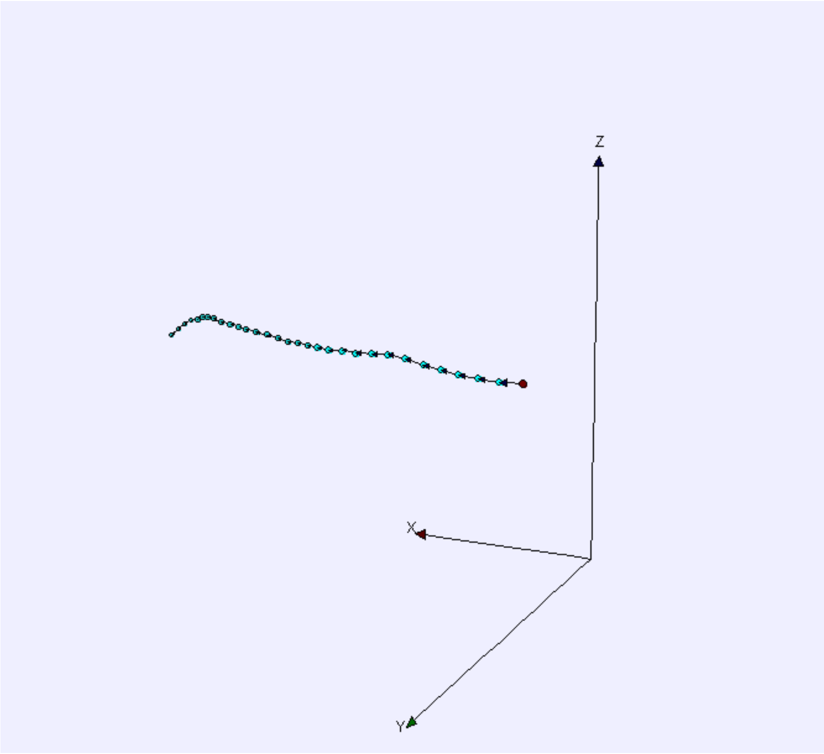
- Thermal force

$$\langle \vec{F}_i^{thermal} \vec{F}_i^{thermal^T} \rangle_{\alpha,\beta} = \frac{2k_B T \zeta_b}{\Delta t} \hat{I}_{\alpha,\beta},$$

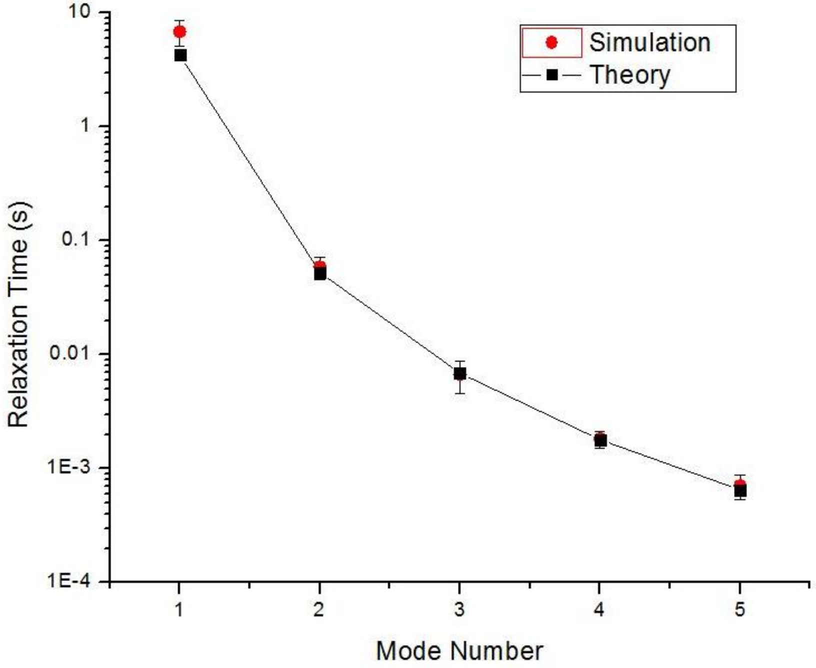
(Laporte et al. MBoC (2012);
Ndlec et al. Nature (1997);
Kim et al. PLoS Comput. Biol. (2009);
Pasquali et al. Phys. Rev. E (2001))

Simulation of Single Actin Filament

- Simulated single actin filament. (l_0=0.1μm≈37 subunits; L=3 μm; l_p=10 μm;)
- Tested tangent correlation function, relaxation dynamics and elastic energy.

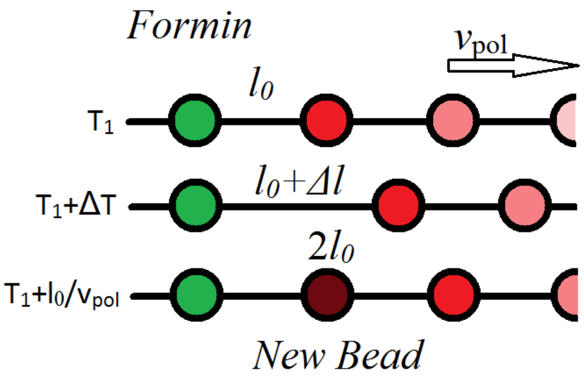


Relaxation Dynamics Test



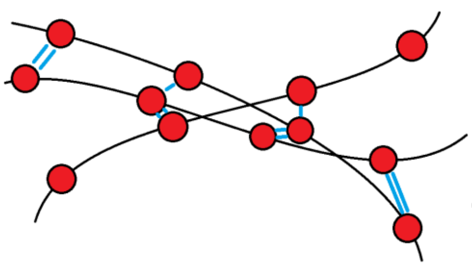
Model of Actin Cables in Fission Yeast

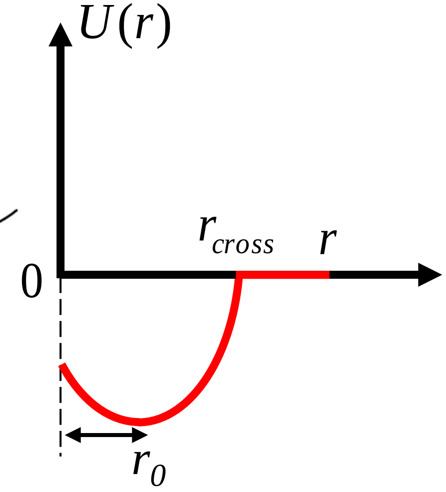
Formin nucleation. Simulated as elongation of the first segment of the semi-flexible polymer chain.



Cross-linking. Simulated as attraction between beads that come close to one another.

$$\vec{F}_i^{crslnk} = -\frac{k_{crslnk}}{2}\sum_j \frac{\partial(|\vec{r}_i - \vec{r}_j| - r_0)^2}{\partial \vec{r}_i}$$

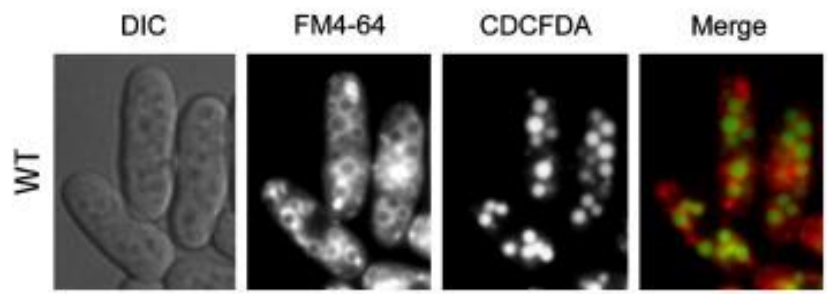




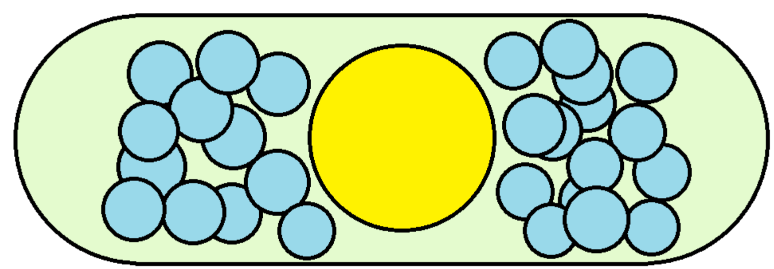
Model of Actin Cables in Fission Yeast

Severing. Simulated as by randomly removing filament segments or whole filaments.

Excluded volume. Simulated as immobile spheres randomly distributed inside the cell.



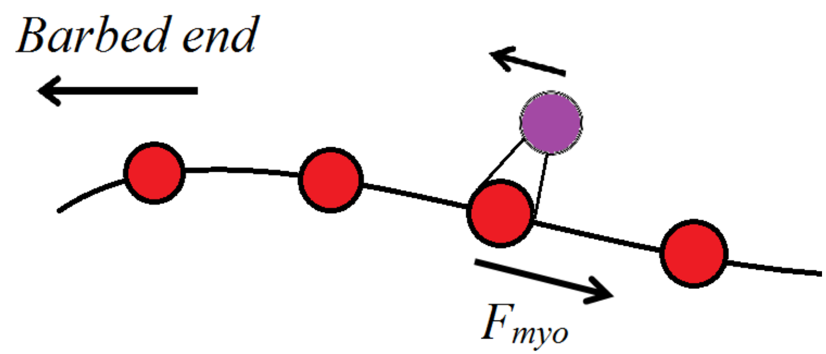
Röthlisberger et al. Fungal Genetics and Biology (2009)



Model of Actin Cables in Fission Yeast

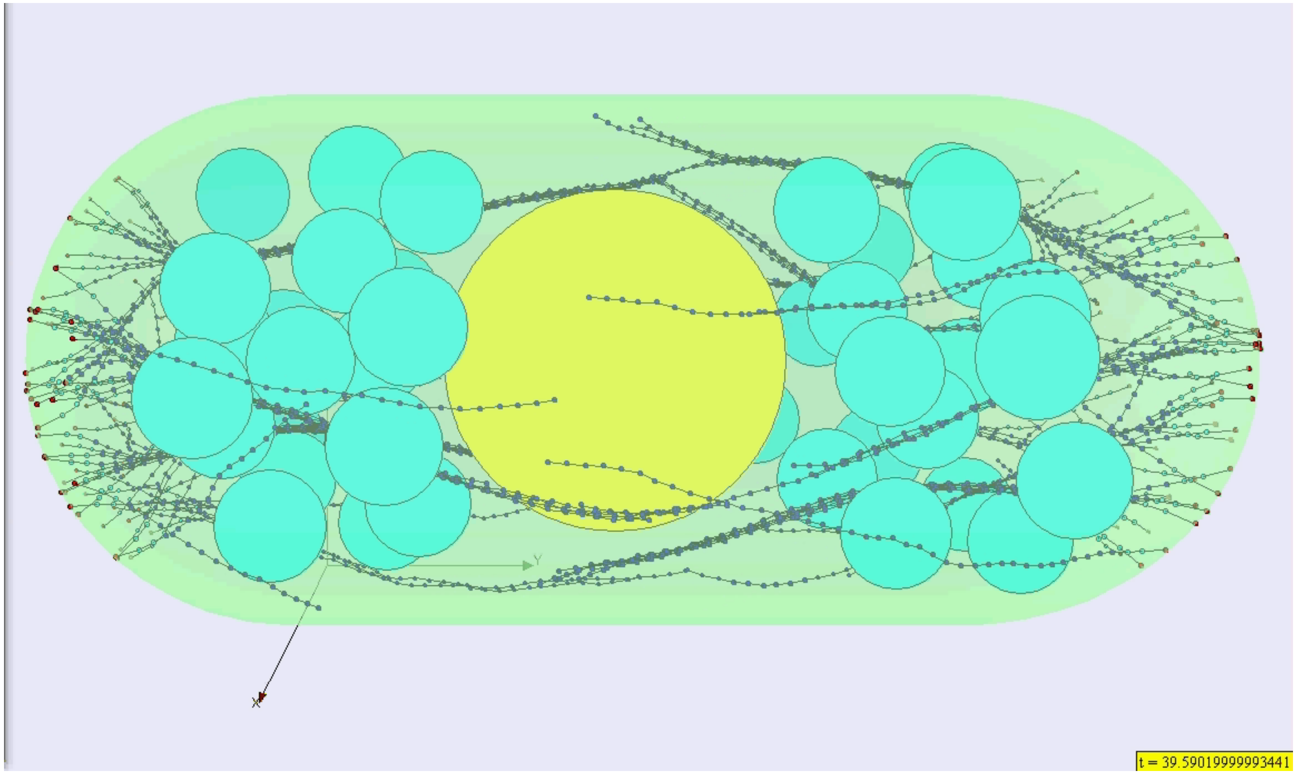
Myosin walking. Simulated as a transient constant force in the tangential direction. (Used 0.1pN for F_{myosin} in simulations.)

$$\vec{F}_i^{myosin} = -F_{myosin} \cdot \vec{t}_{i-1}$$



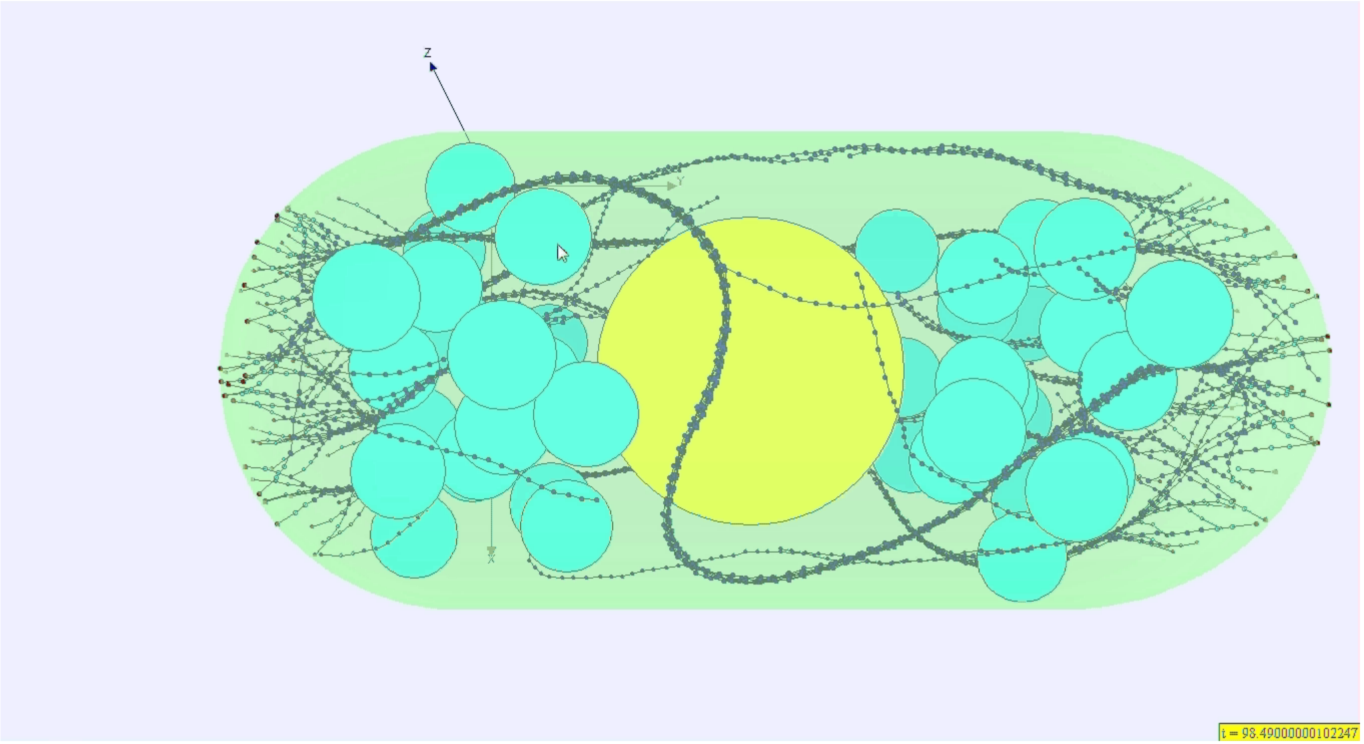
Simulation of Actin Cables in Fission Yeast

- Movie: Simulation of actin cables (Yeast length: 8 µm; Diameter: 3.6 µm; Characteristic severing length: 3 µm; Polymerization rate: 0.1 µm; Formin #: 160; k_{cross}=2 pN/µm.)

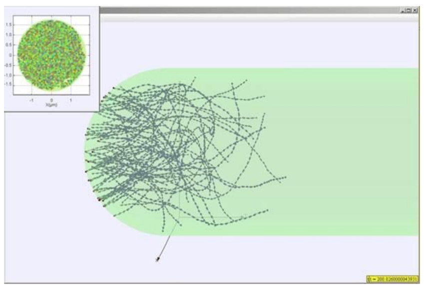


Simulation of Actin Cables in Fission Yeast

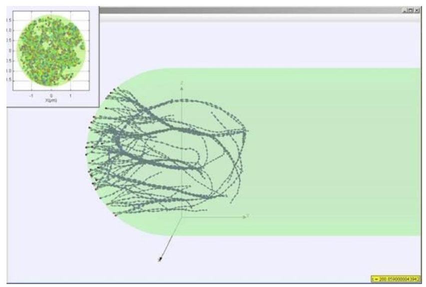
- Movie: 3D structure demonstration at 98s



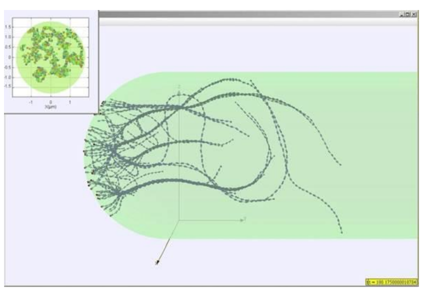
Simulations as function of cross-linking strength



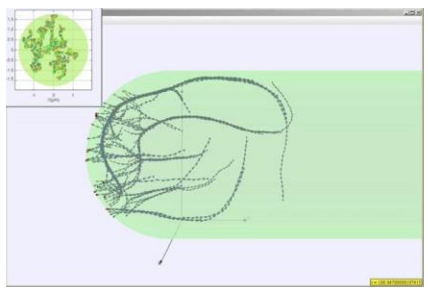
$r_{cross}/l_0 = 0.6$



$r_{cross}/l_0 = 1$

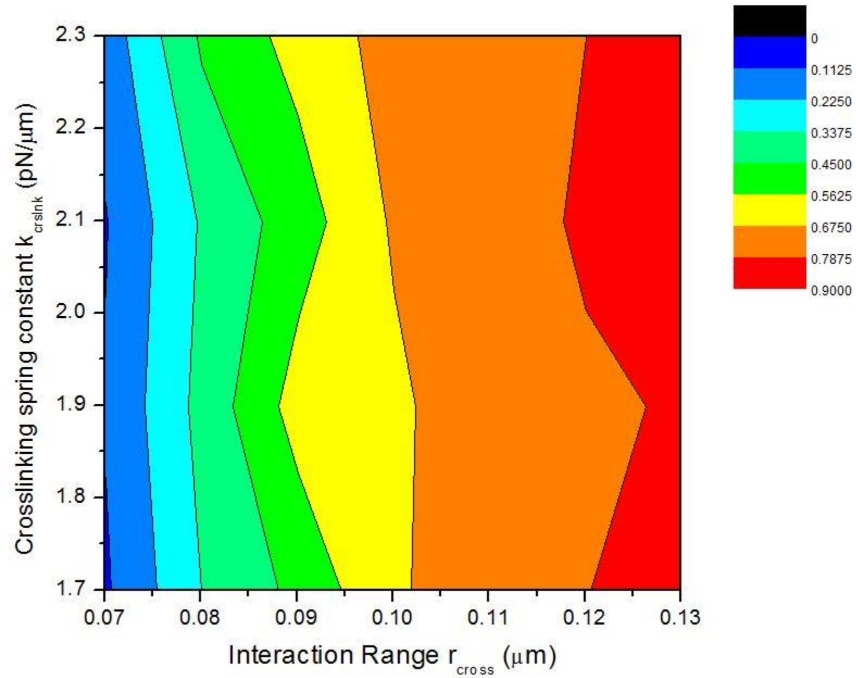


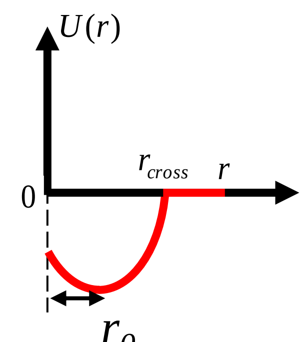
$r_{cross}/l_0 = 1.2$



$r_{cross}/l_0 = 1.4$

Probability filament belongs to cable

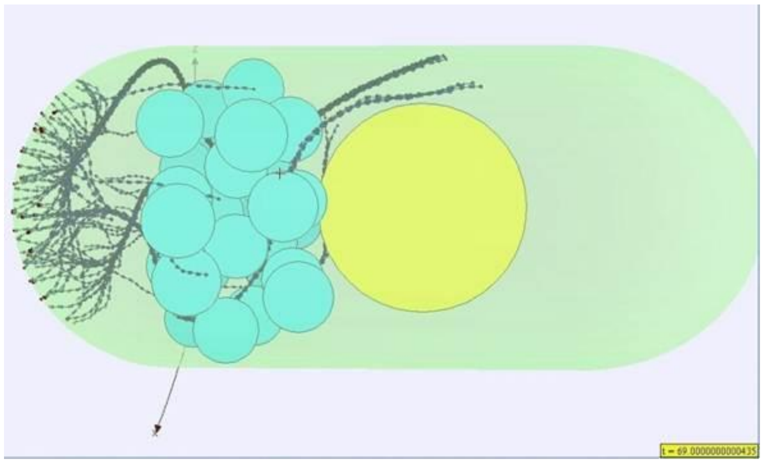




- Cross-linking bundles actin filament into cables.
- Higher cross-linking: thicker and fewer cable formations.

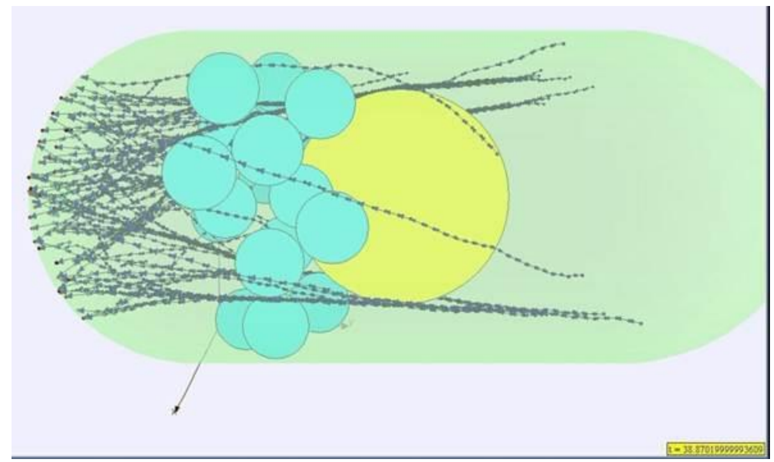
Simulations with pulling force show role of Myosin V in stretching actin cables

Without myosin pulling.



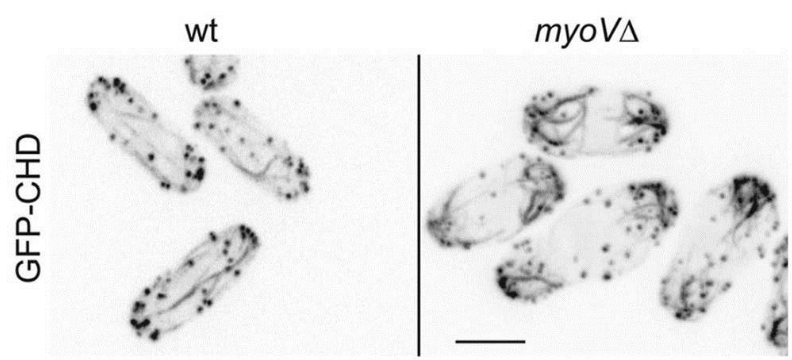
In simulations with vacuoles, actin cables were tangled up.

With myosin pulling (F_{myo}= 0.1 pN; Myosin concentration per filament: 2/μm).



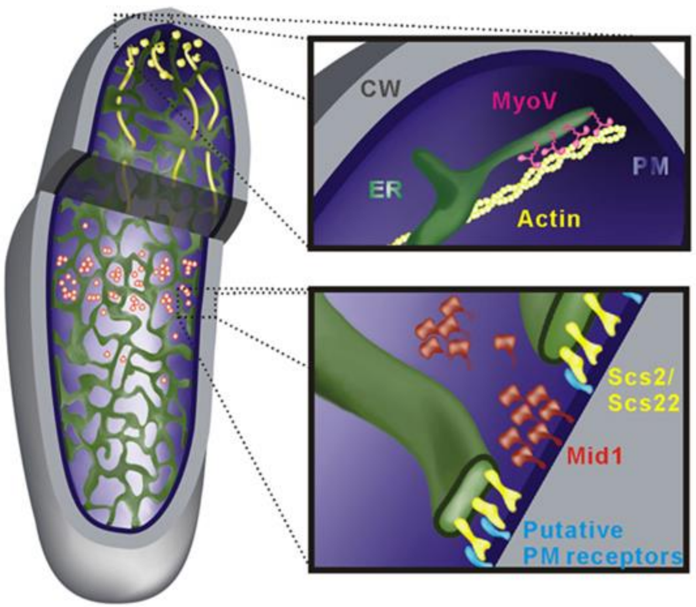
After applying myosin force, cables no longer have straightening defects.

Consistent with experiments of MyoVΔ cells that exhibit straightening cable defects.
(L. Lo Presti, F. Chang and S. Martin, MBoC (2012)).

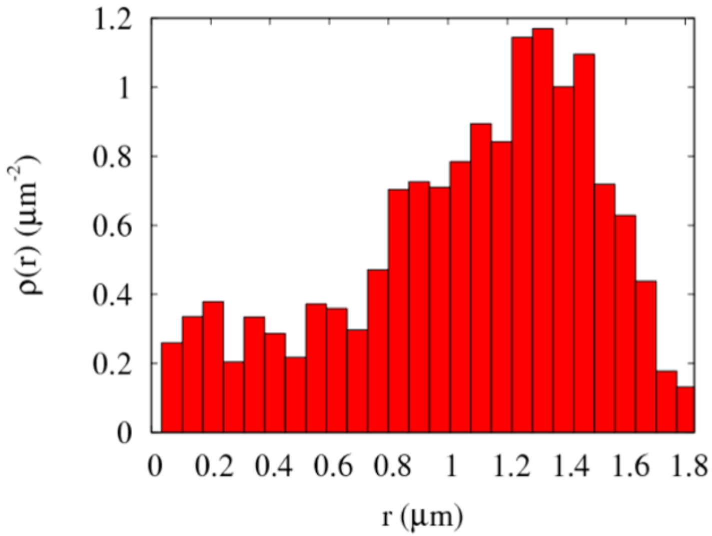


Exploring how ER attachment to plasma membrane contributes to actin cable positioning

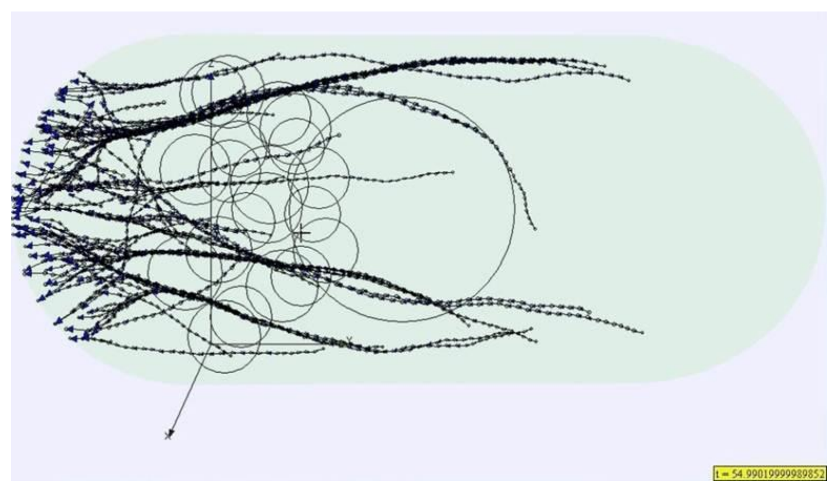
- Adding a radial pulling force to the myosin-bound beads towards the cell periphery influences the distribution of actin cables.



D Zhang et al. Curr. Biol. (2012)



Radial cable distribution.
(E. Yusuf, I-J. Lee, J-Q. Wu, D. Vavylonis).



Conclusion

- Simulated 3D distribution and dynamics of actin cables in fission yeast.
- Model included formin polymerization, cross-linking, turnover, myosin V pulling.
- Cross-linking (possibly via fimbrin) generates bundles of actin filaments that resemble actin cables even when filament polymerization occurs randomly along cell tip.
- Longer persistence length leads to straighter and less tangled cables.
- Simulated myosin V walking stiffens the actin cables and prevents cables from tangling, in agreement with prior experiments.
- Radial pulling, simulating ER attachment influences the radial distribution of actin cables.

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