Modeling Cdc42 Oscillations and Polarity Transition in Fission Yeast

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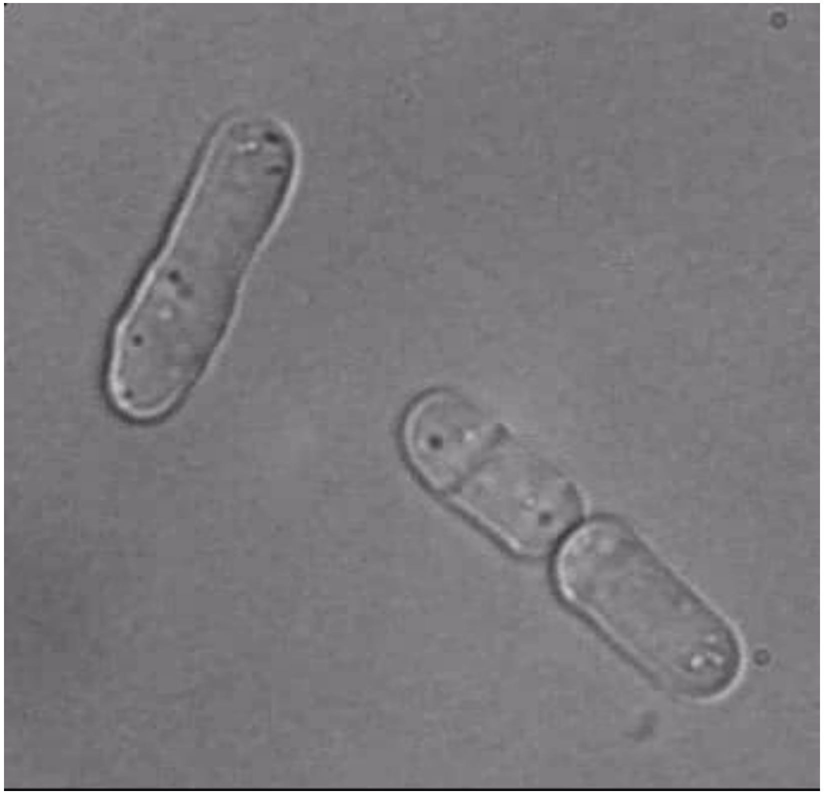
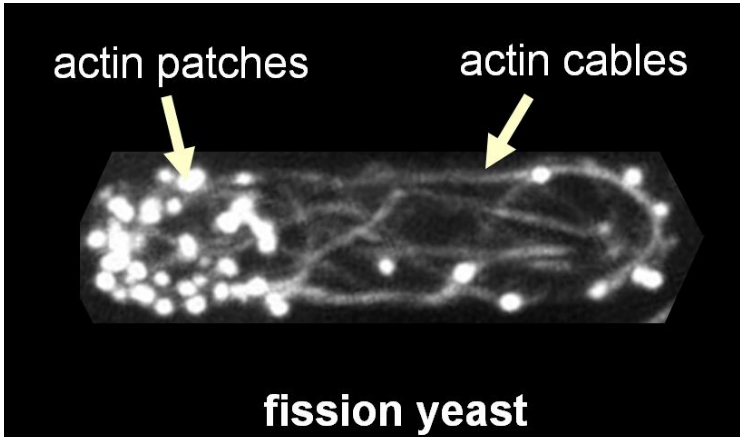
Mathematical Biology of the Cell: Cytoskeleton and Motility
Banff, Aug 3, 2011

Fission yeast cell growth and cytoskeleton

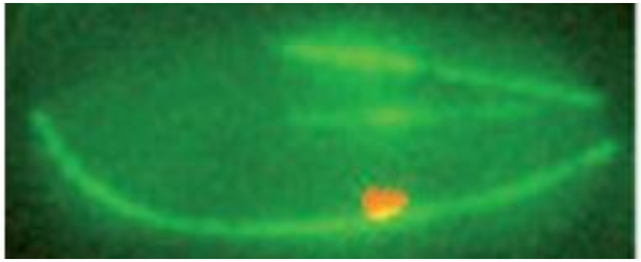
Growth occurs from the tips





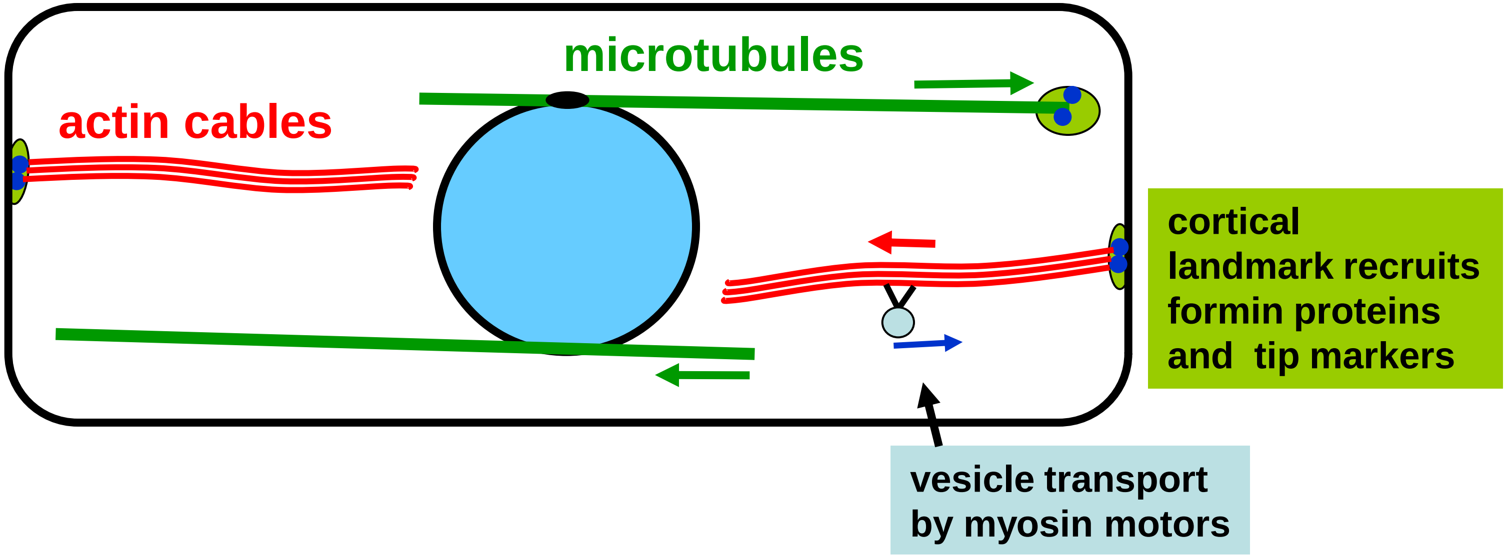
CHD-GFP (Wu)

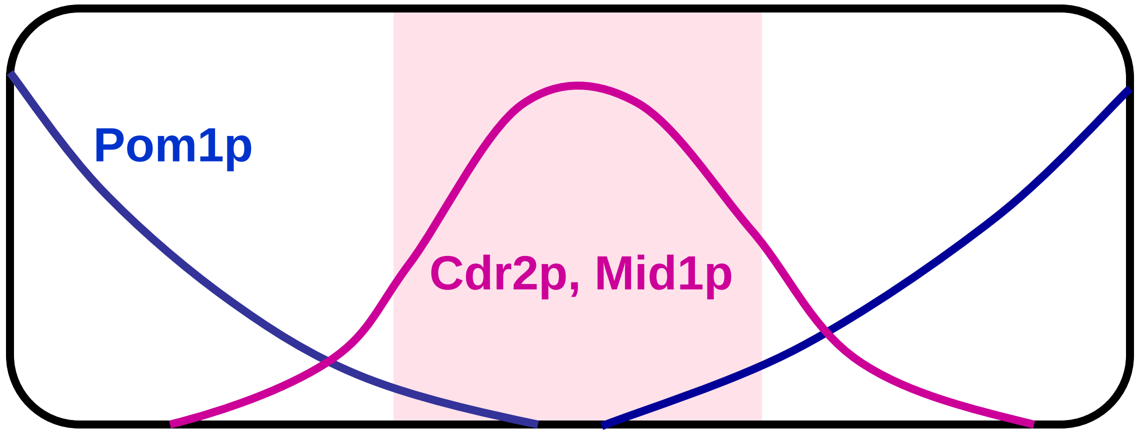
Microtubules



(Carazo-Salazs and Nurse)

Maintenance of cell polarity in fission yeast

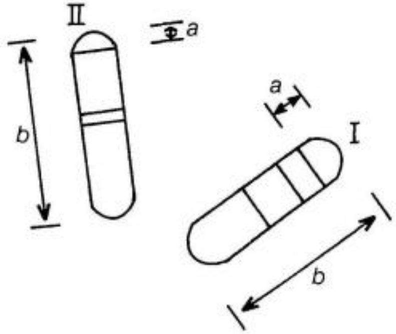




Padte et al. Curr. Biol 2006
Celton-Morizur et al. J. Cell Sci. 2006
Wu et al Dev Cell 2003

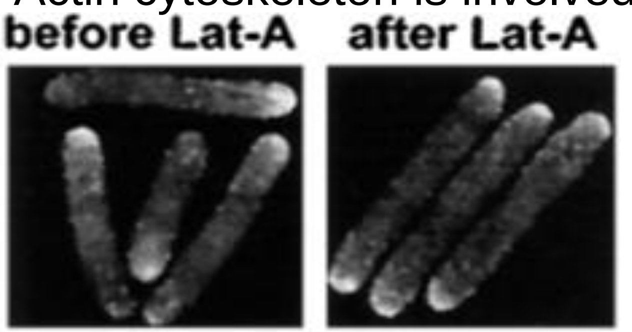
S. G. Martin and M. Berthelot-Grosjean, Nature **459**, 852 (2009).
J. B. Moseley, A. Mayeux, A. Paoletti, and P. Nurse, Nature **459**, 857 (2009).

Polarized Growth Transition



J. Mitchison and P. Nurse
Journal of Cell Science (1985)

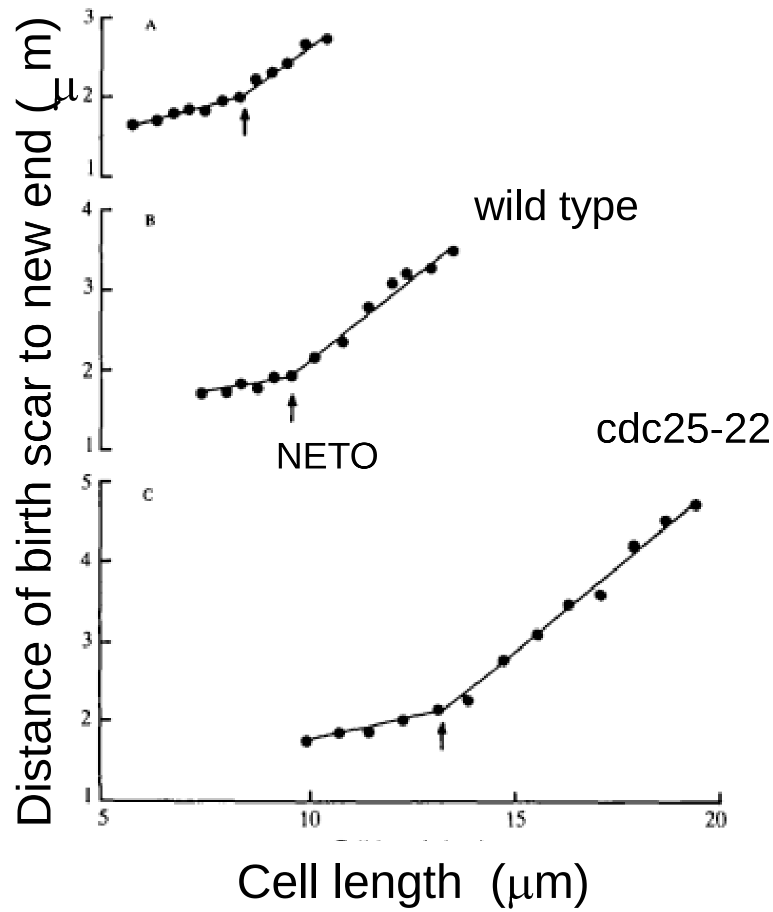
Actin cytoskeleton is involved



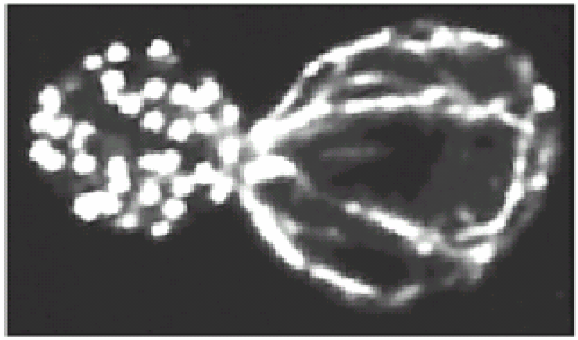
actin

cdc10 mutants

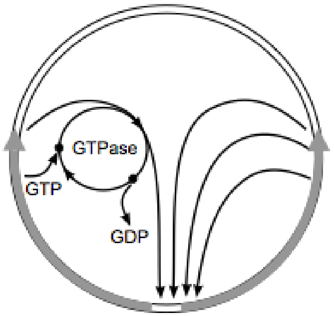
Rupes, I., Z. Jia, and P.G. Young, Mol. Biol. Cell, 1999. **10**: p. 1495-510.

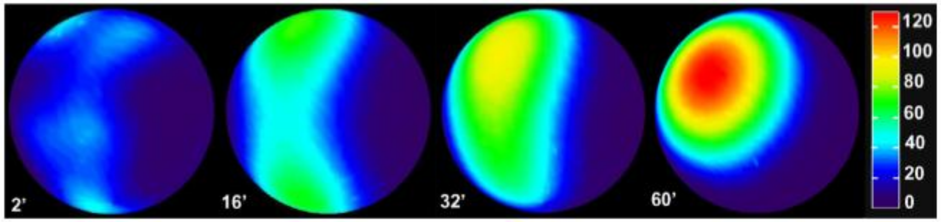


Budding Yeast: Winner-Take-All Mechanism

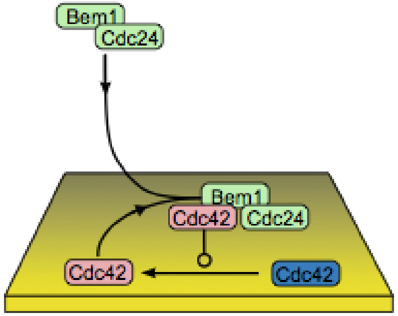


Self-recruitment of Cdc42 helps the cell select a single site for growth

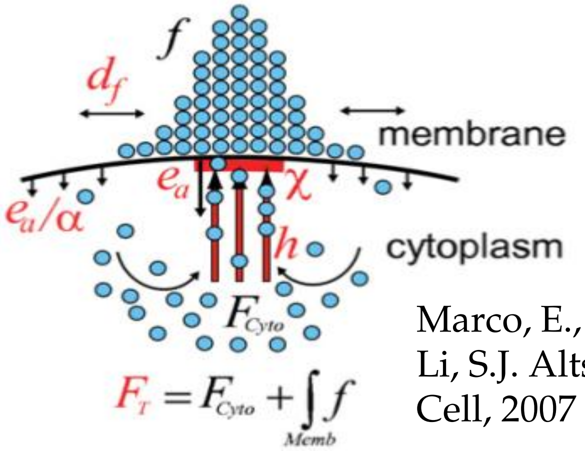




Goryachev and Pokhilko, *FEBS Letters*, 2008.



Actin positive feedback

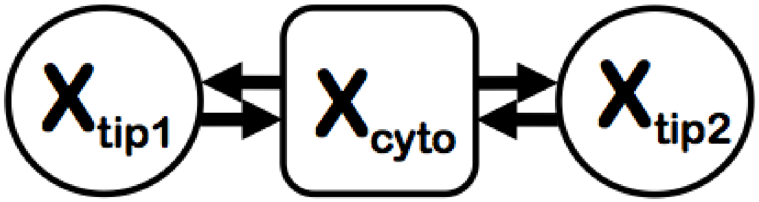


Marco, E., R. Wedlich-Soldner, R. Li, S.J. Altschuler, and L.F. Wu, Cell, 2007

Actin-dependent negative feedback has also been suggested

Ozbudak, Becskei, van Oudenaarden, *Dev Cell (20 05).*

A Simple, Symmetric Model Requires Nonlinearity



(total concentration remains constant)

$$\frac{dX_{tip1}}{dt} = \frac{\lambda^+}{V} X_{cyto} - k^- X_{tip1}$$

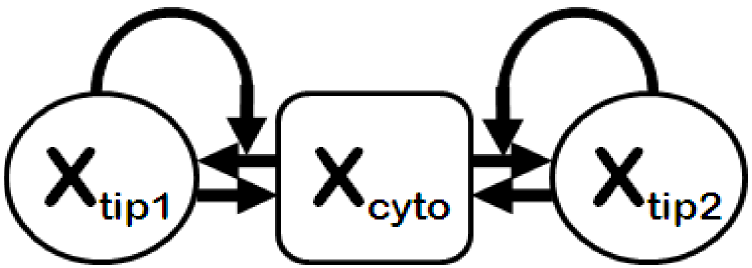
$$\frac{dX_{tip2}}{dt} = \frac{\lambda^+}{V} X_{cyto} - k^- X_{tip2}$$

$$X_{cyto} + X_{tip1} + X_{tip2} = X_{total} = \varrho V$$

Linear model: always symmetric steady state!

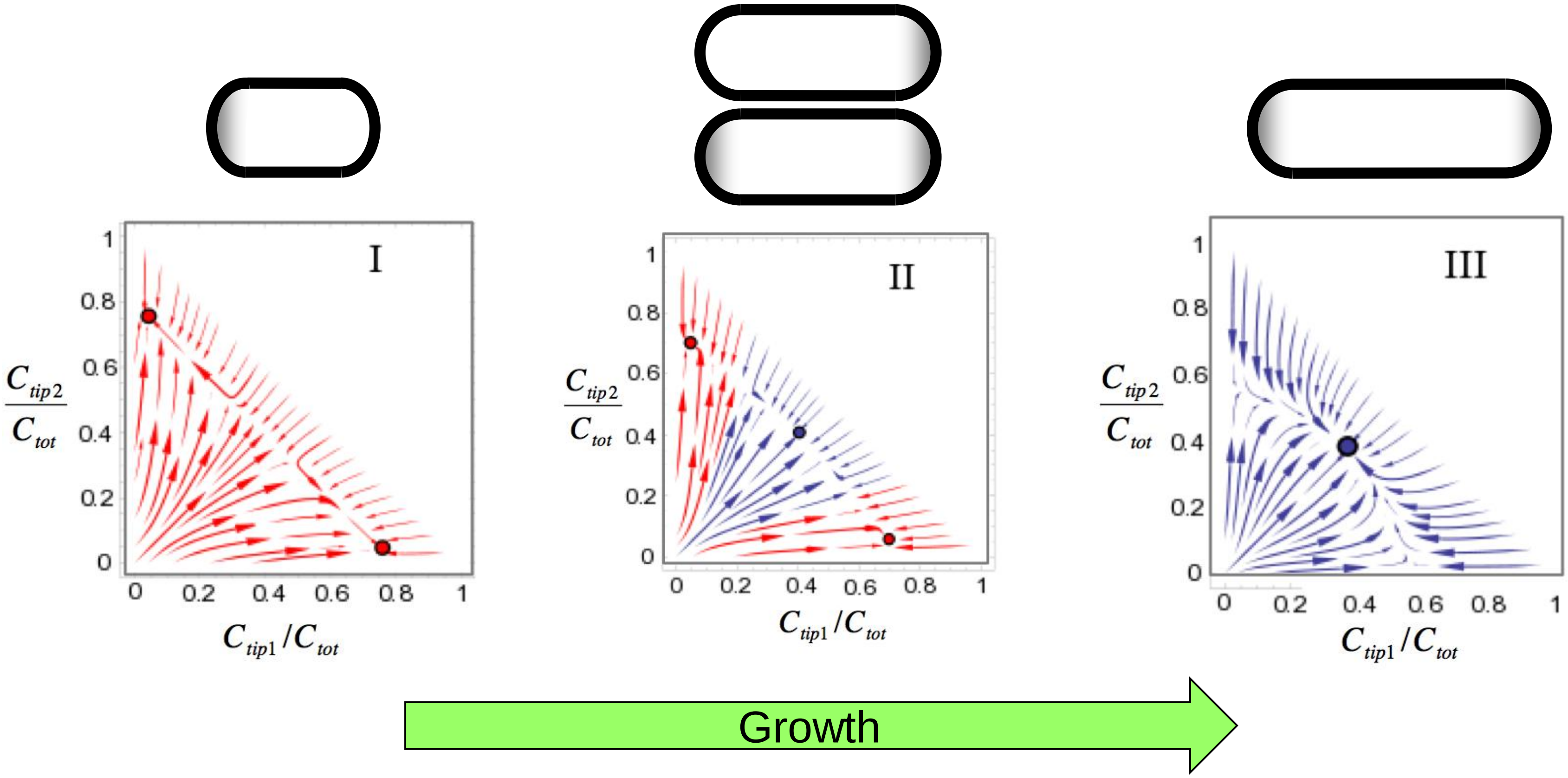
$$\lambda^+(X_{tip}) = \lambda_0^+ + \lambda_2^+ X_{tip}^2 \exp\left(-\frac{\mathrm{X_{tip}}}{\mathrm{X_{sat}}}\right)$$

Autocatalytic association, saturated



Elongation Recovers Symmetry

- Assume: total amount increases with length
- Short cells: broken symmetry.
- As the dominant tip saturates, the second has a chance to accumulate *X*



A coexistence region in a symmetric system was also proposed by Csikasz-Nagy, *et al*. *Yeast,* 2008 in the context of actin.

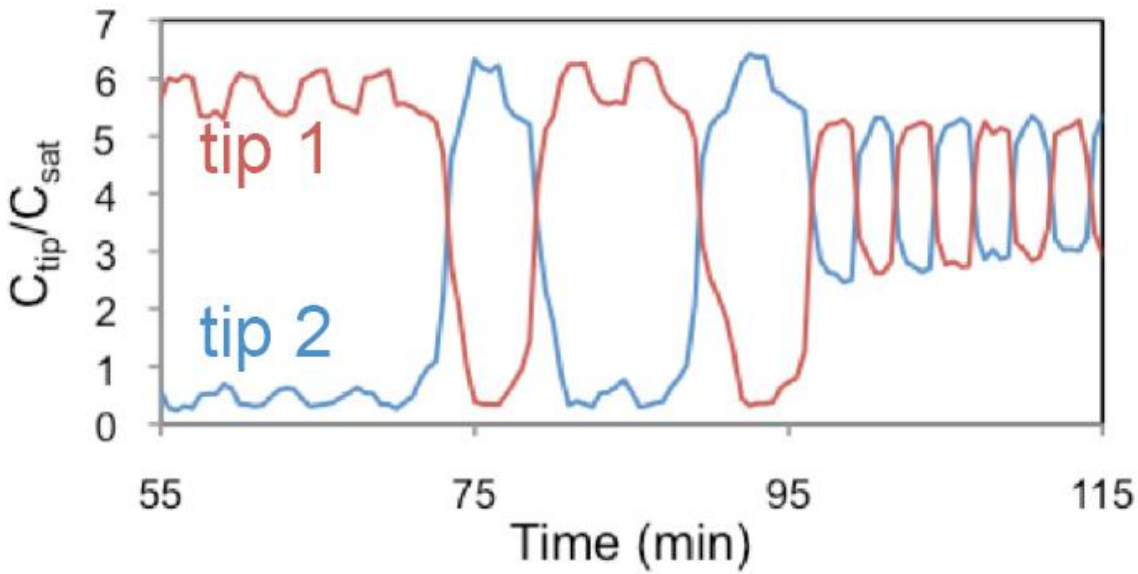
Addition of delayed inhibition and noise to autocatalytic model reproduces experimental time courses

$$\frac{dX_{tip1}}{dt} = \frac{\lambda^+}{V} X_{cyto} - k^- X_{tip1}$$

$$k^- = k_0^- \left[(1 - \frac{\varepsilon}{2}) + \varepsilon \frac{X_{tip1}(t-\tau)^h}{X_{tip1}(t)^h + X_{tip1}(t-\tau)^h} \right]$$

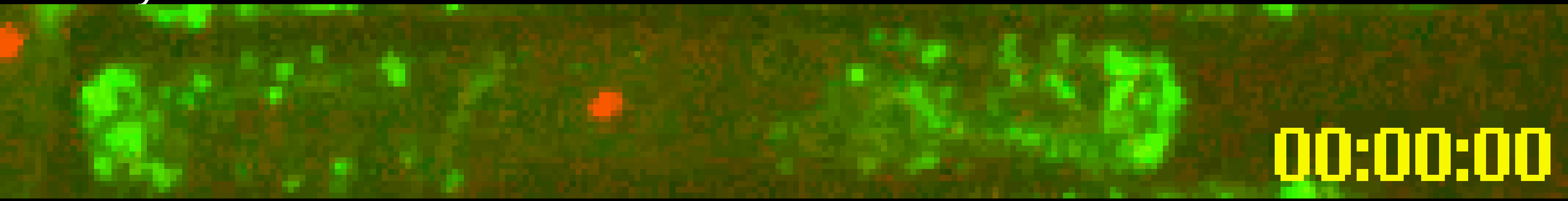
delayed dissociation rate

could be actin-dependent



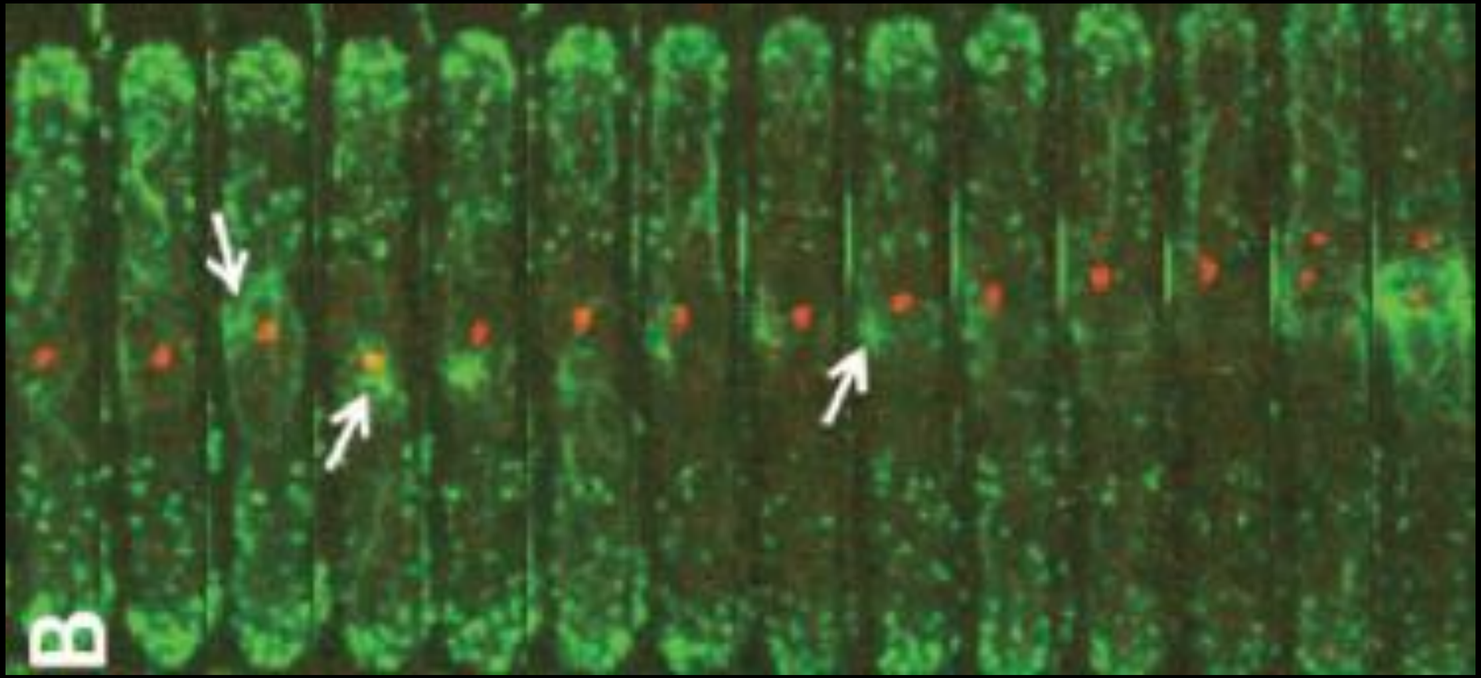
Actin Cytoskeleton in Cell Division

fission yeast cdc25-22 cell



CHD-GFP
binds to sides of
actin filaments

spindle poles
Spb1



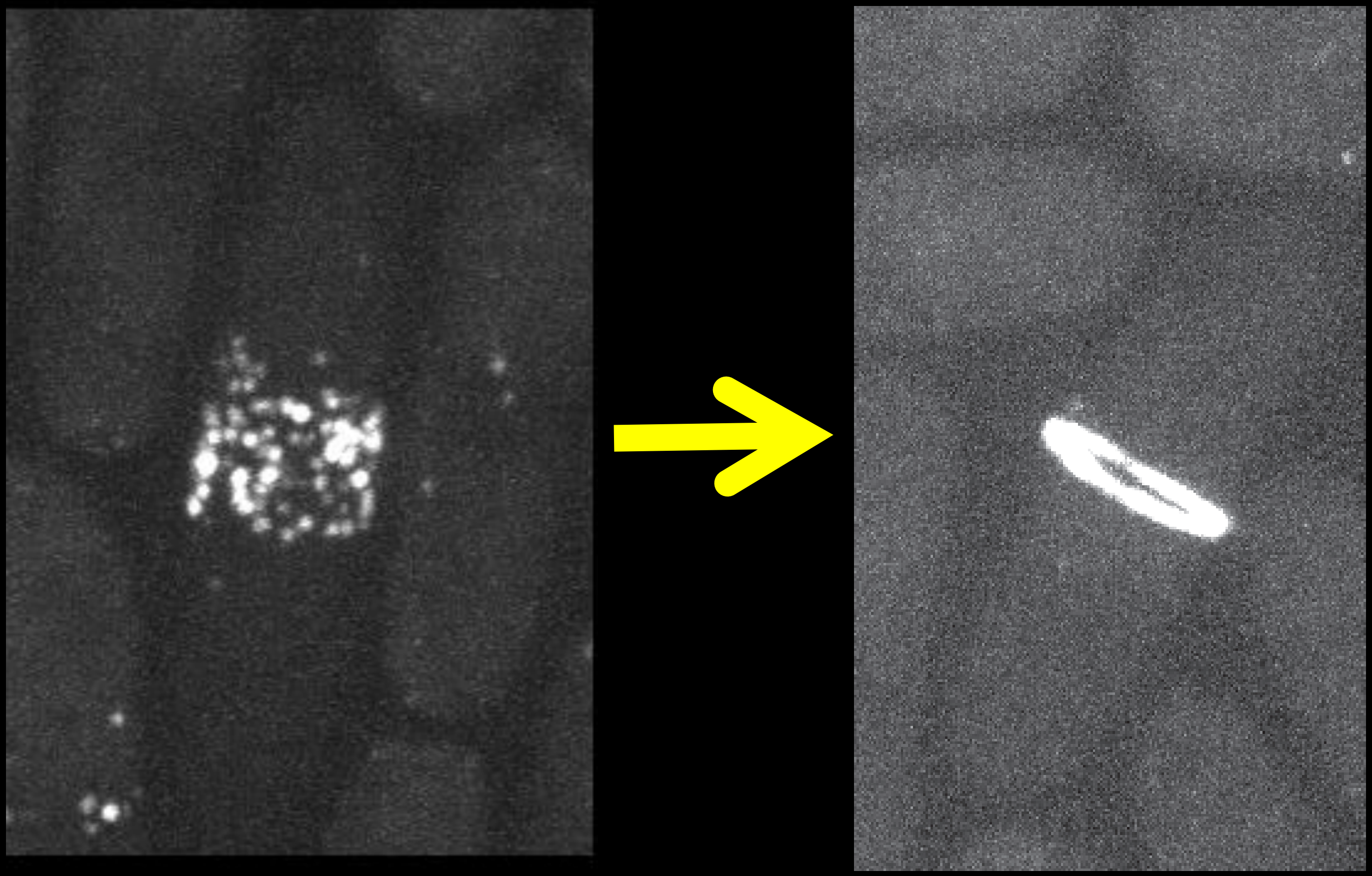
Jian-Qiu Wu (Pollard lab, Yale Univ 2007)
Vavylonis, Wu, et al. *Science* 2008

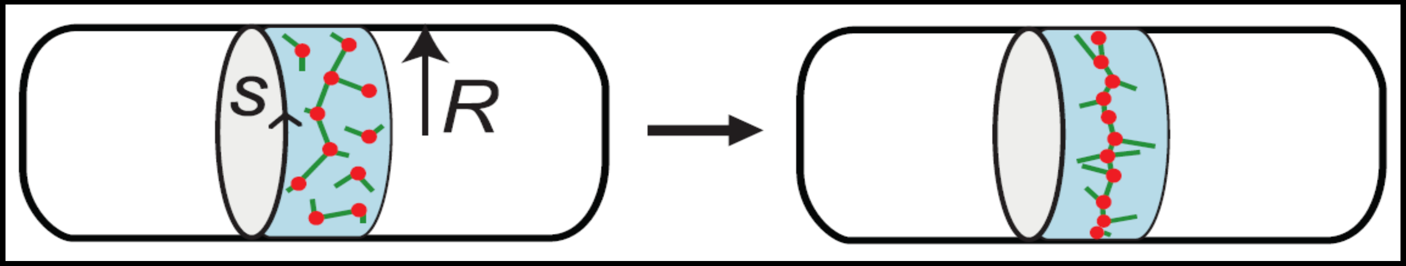
Contractile ring assembly from ~ 65 myosin II nodes in ~ 10 min

Vavylonis, Wu, Hao, O'Shaughnessy, Pollard, *Science* 2008

Rlc1p-3GFP

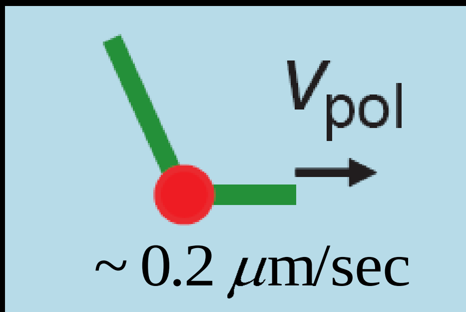
spinning disk confocal microscopy

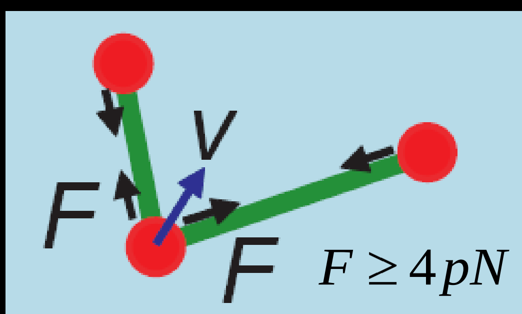




Search, capture, pull and release model

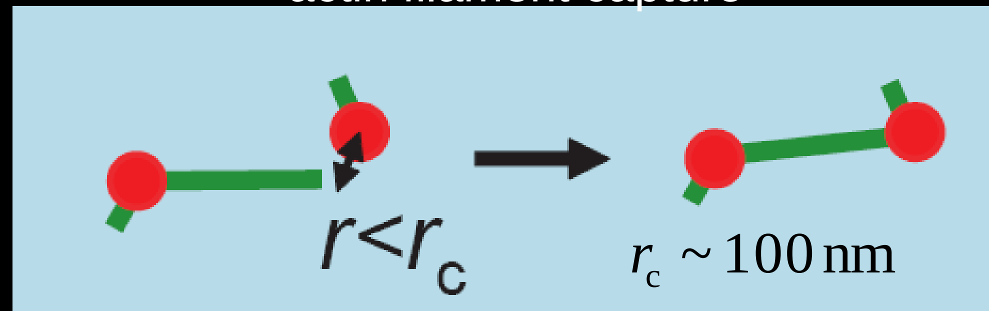
actin filament polymerization





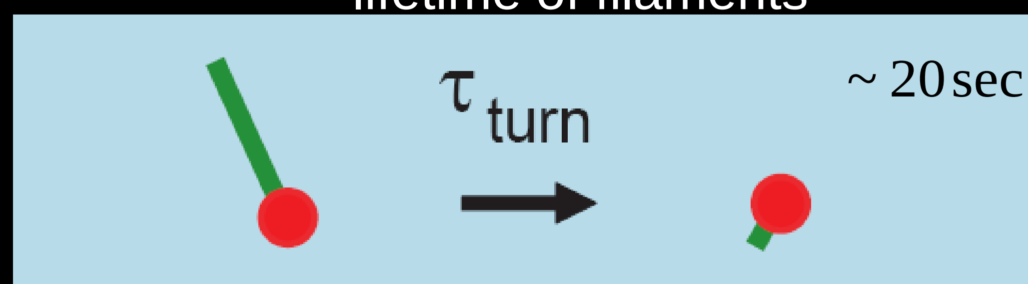
traction on filaments between nodes

actin filament capture



lifetime of connections

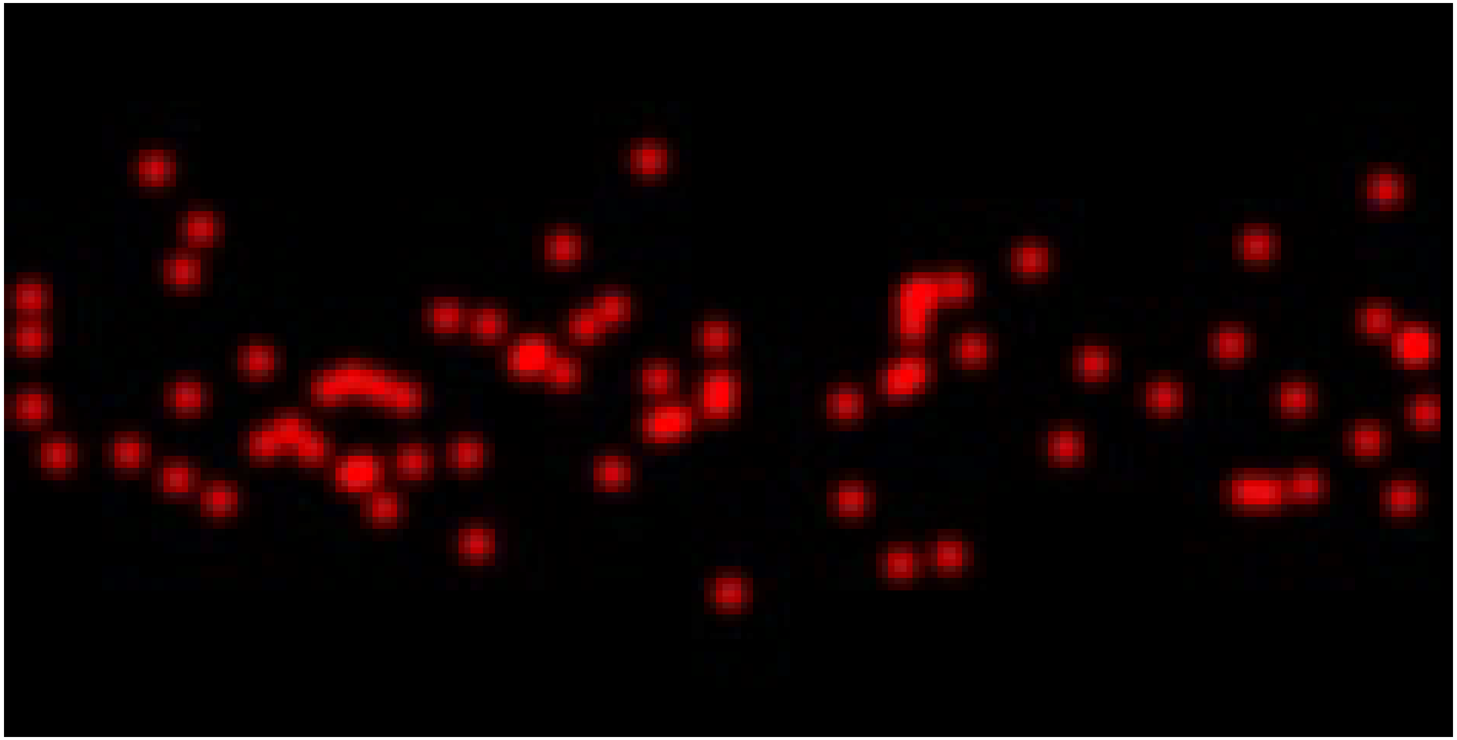
lifetime of filaments



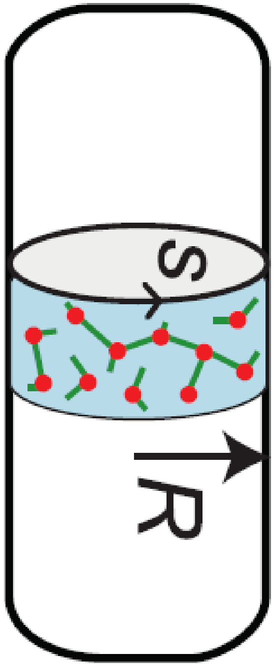
Simulations with search, capture, pull and release

red: nodes
green: actin

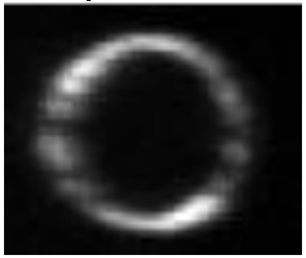
Simulated radial projection



0 — 30x time lapse, 20min — $2\pi R$

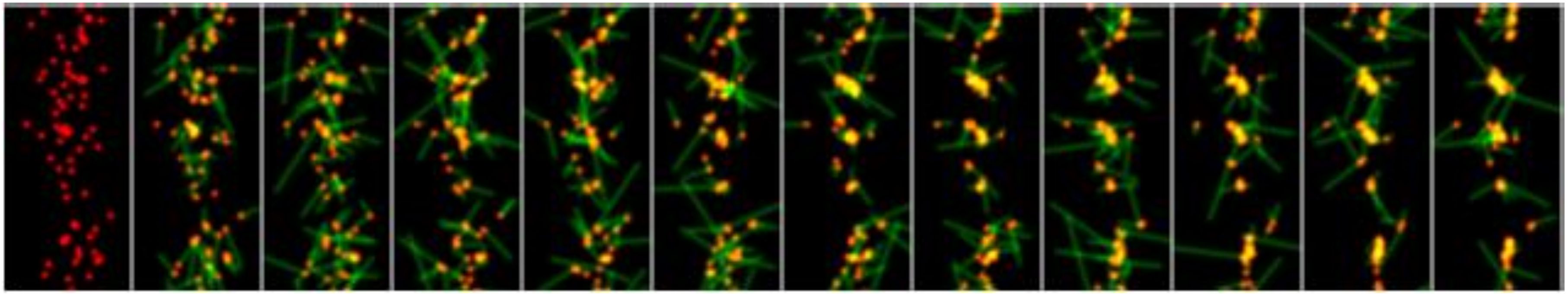


experiment:



- ***model reproduces many observed features***

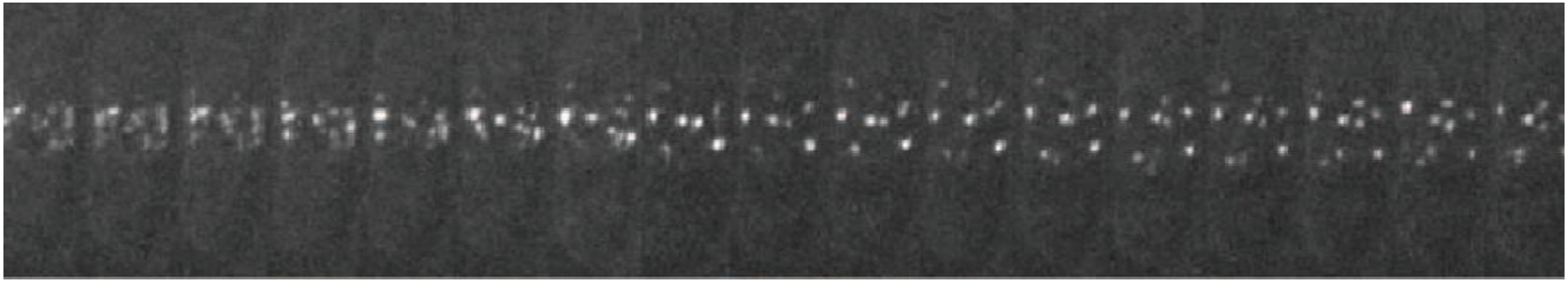
Node clump formation



$v_{pol} = 0.04\ \mu\text{m/sec}$

Rlc1p-GFP

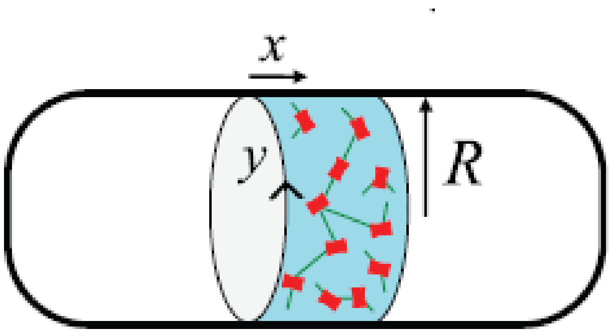
cdc12-112

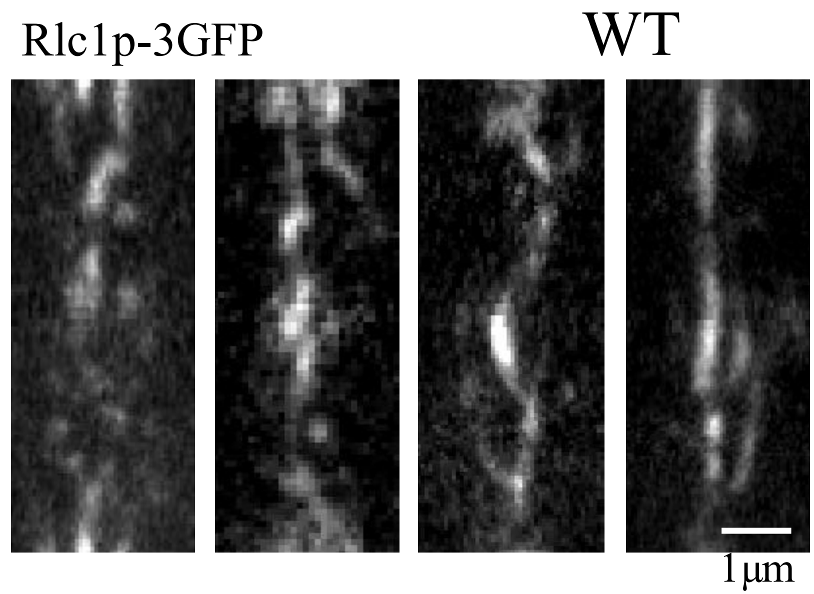


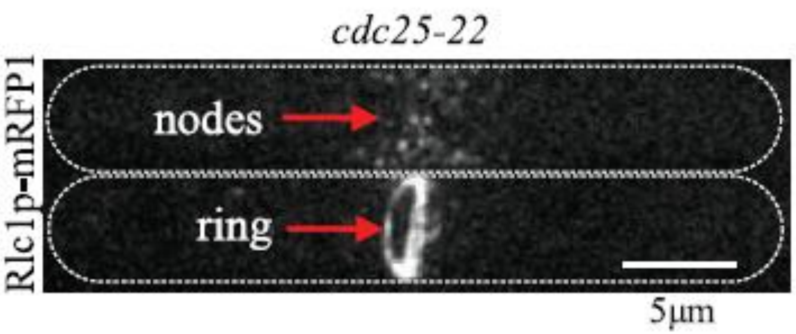
Hachet and Simanis, *Genes and Development*, 2008

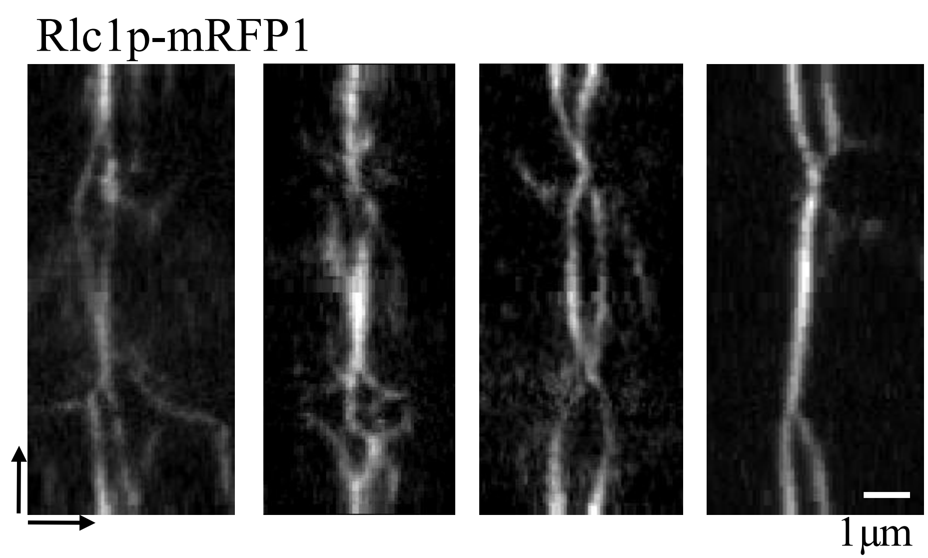
Vavylonis, Wu, Hao, O'Shaughnessy, Pollard, *Science* 2008
Ojkic, Vavylonis Phys. Rev. Lett. 2010

Bundled structures appear near the end of ring assembly



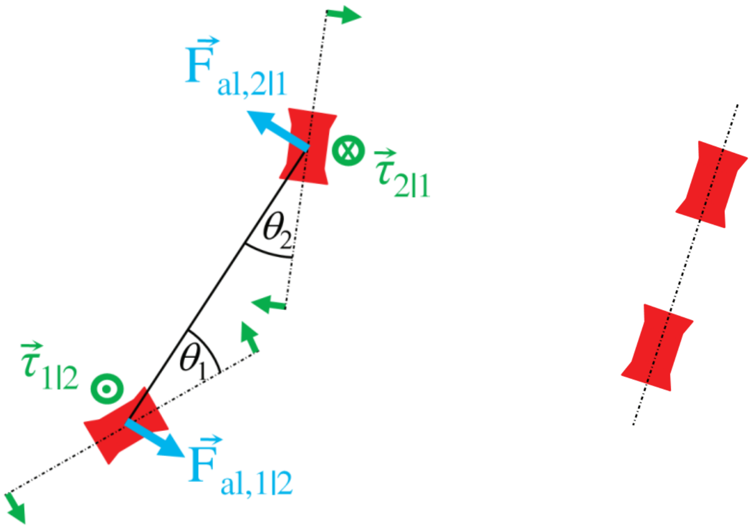


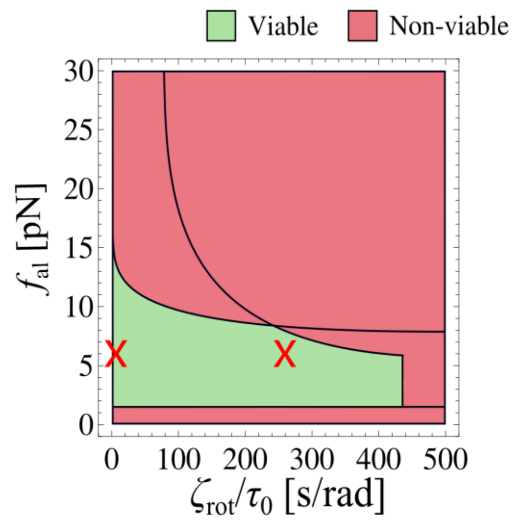




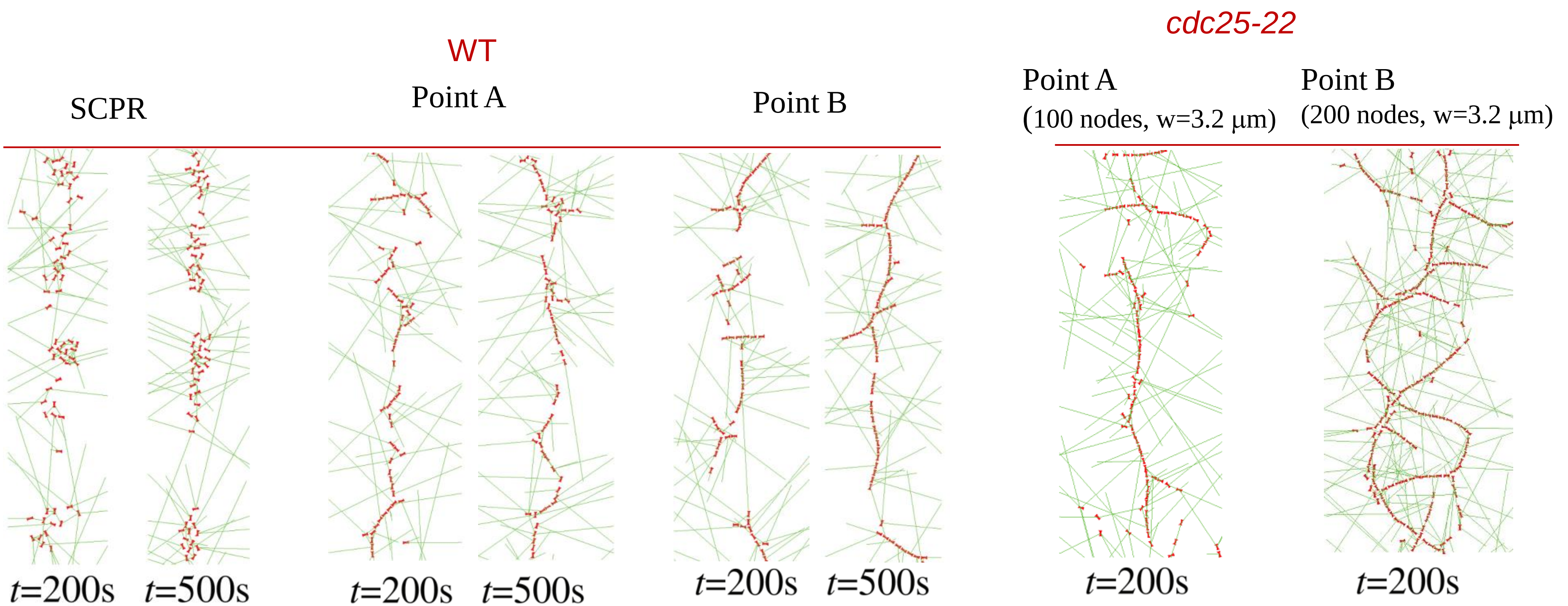
Ojkic, Wu, Vavylonis J. Phys. Cond Matt (2011)

SCPR + LOCAL NODE ALIGNMENT

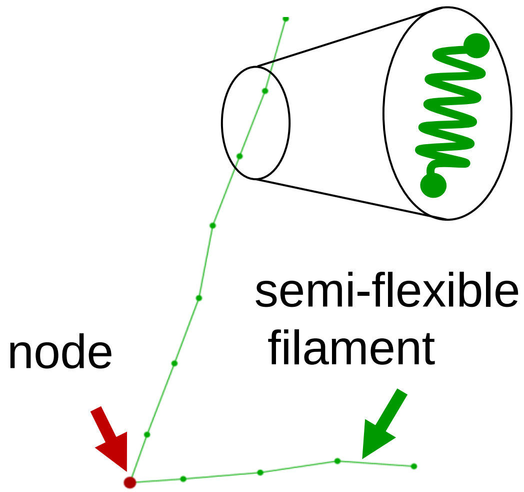




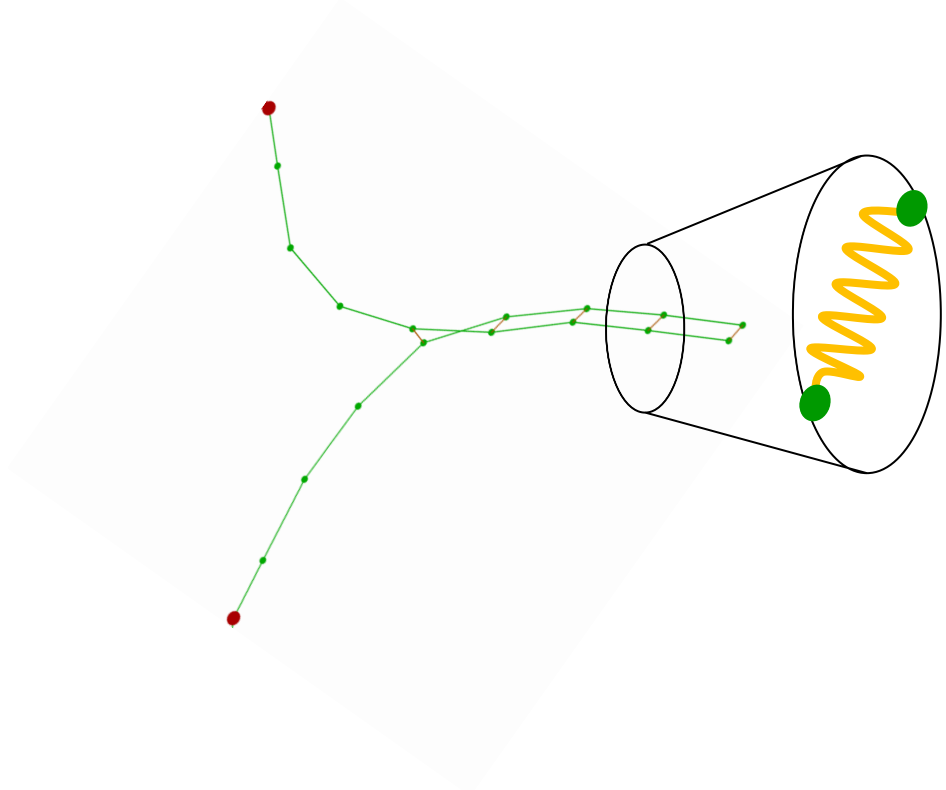
Ojkic, Wu, Vavylonis J. Phys. Cond Matt (2011)



Simulations of search, capture, pull and release model with semi-flexible filaments and cross-linking



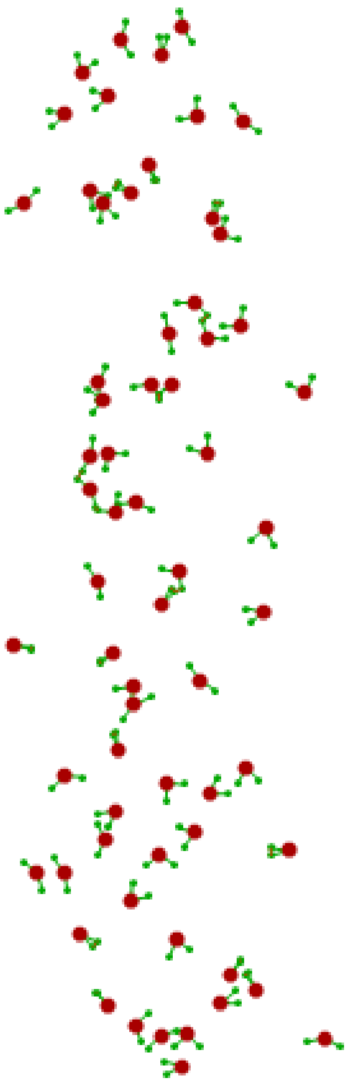
Actin cross-linking by α-actinin is modeled as a spring connection when filaments come close to one another

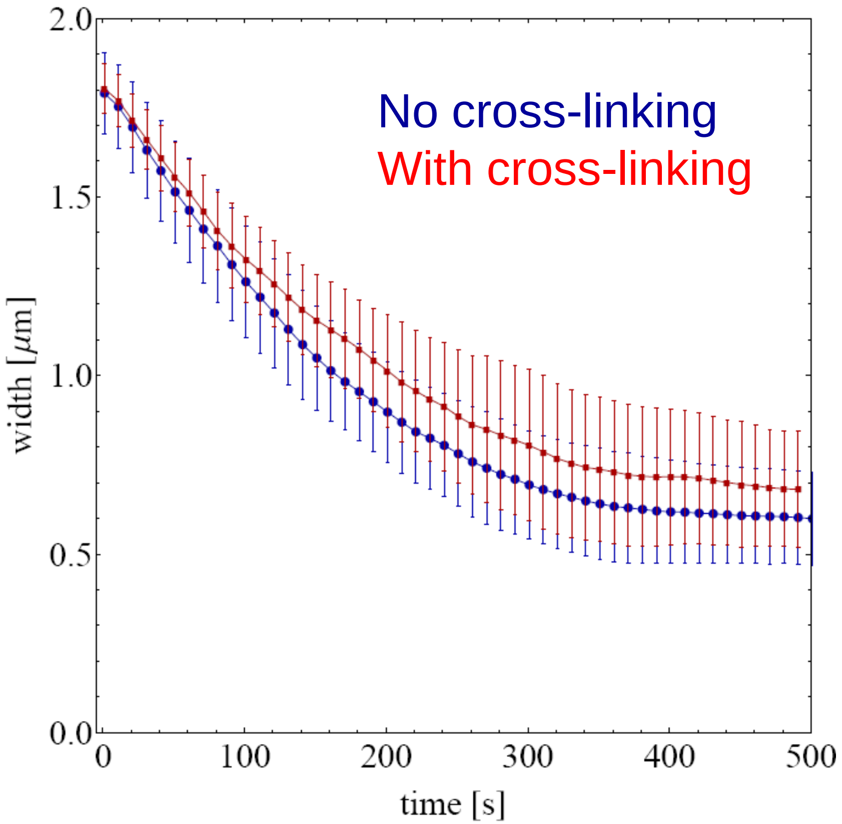


•Actin filaments modeled as beads connected with springs
• Langevin dynamics (2D)

$$\zeta_i \frac{d\vec{R}_i}{dt} = \vec{F}_i^{thermal} + \vec{F}_i^{spring} + \vec{F}_i^{bending}$$

Preliminary results: weak influence of filament cross-linking on broad band condensation time





Nikola Ojkic

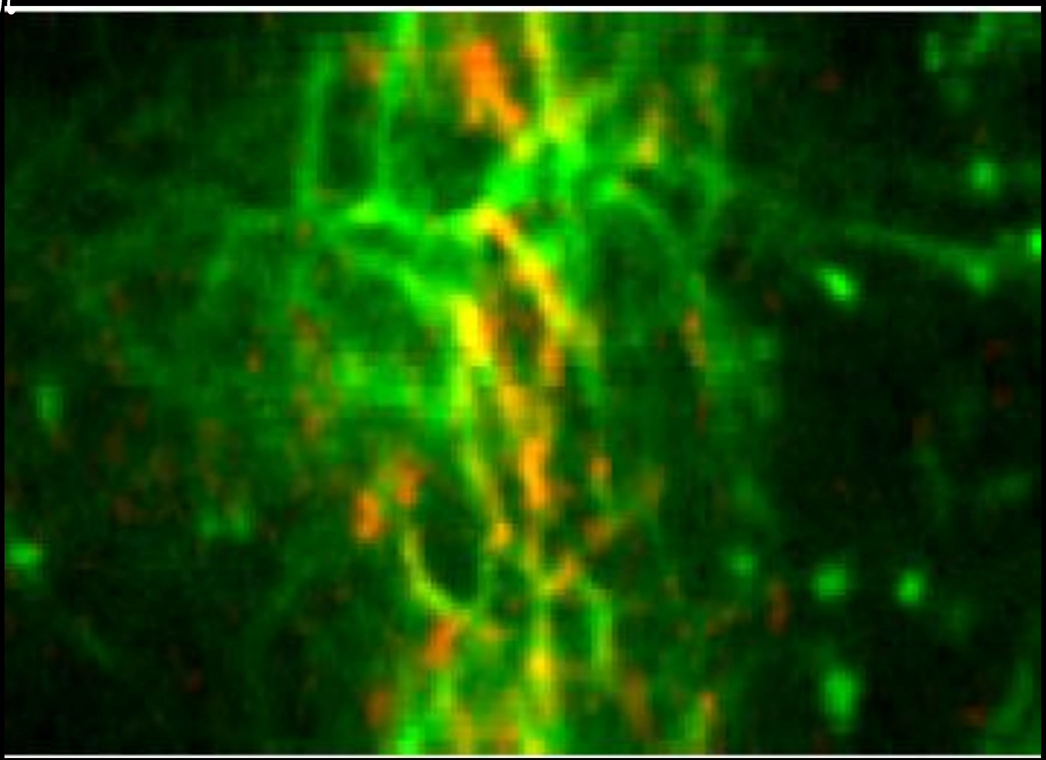
Model captures morphology of dynamic actin meshwork

radial projection *cdc25-22* cells

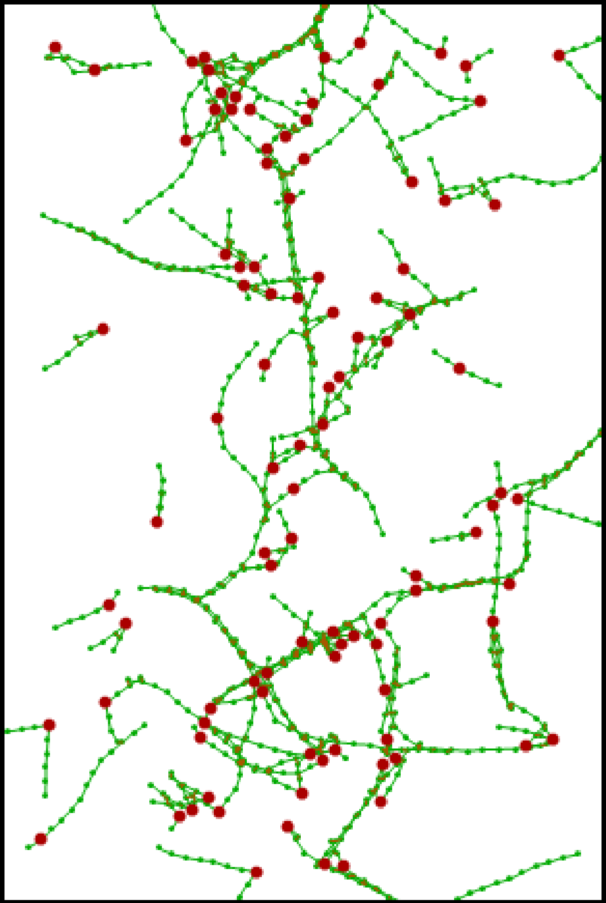
2 πR

arc length *s*

0



simulation



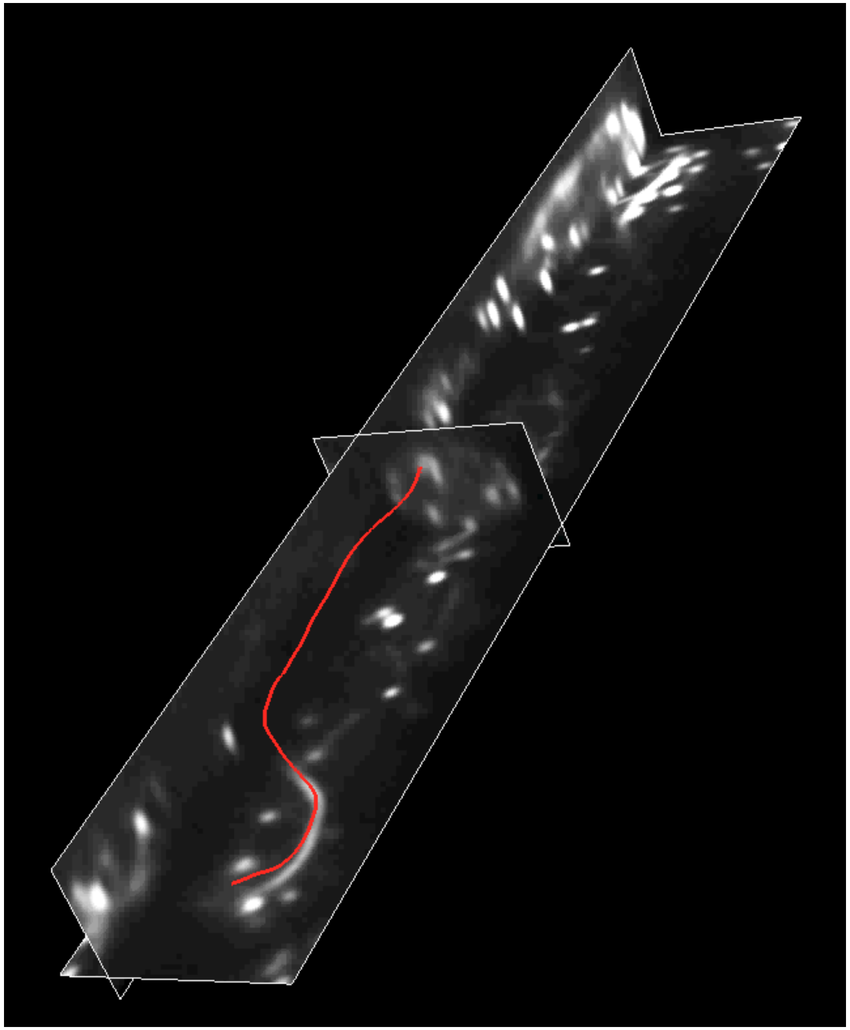
red: nodes (Rlc1-RFP1)

green: actin filaments (GFP-CHD)

data: Wu

Filament segmentation and tracking

CHD-GFP



ImageJ plugin available at http://athena.physics.lehigh.edu/jfilament

Smith, Li, Shen, Huang, Yusuf, Vavylonis, *Cytoskeleton* 2010

Acknowledgments

Cdc42 oscillations: Tyler Drake

Ring assembly: Nikola Ojkic

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