



New York University
A private university in the public service

ourant Institute and Department of Biology

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Continuous modeling in cell biology

Porquerolles, October 2016

To students and postdocs:

We will use matlab for projects. If you never used it before, attached is a very cryptic intro; practice a little before the workshop, but we'll help you at the workshop. We'll be learning how to use scaling, and also Partial Differential Equations. It'll help if you read the attached file 'Logan' before the workshop, but not to worry if it'll be too hard, we'll explain everything. Below are the slides for the lectures.

We will go over case studies based on these research papers and analyze models and experiments there:

Reverse engineering of force integration during mitosis in the Drosophila embryo.
Wollman R, Civelekoglu-Scholey G, Scholey JM, Mogilner A.
Mol Syst Biol. 2008;4:195.

Doncic A, Ben-Jacob E, Barkai N.
Evaluating putative mechanisms of the mitotic spindle checkpoint.
Proc Natl Acad Sci U S A. 2005 May 3;102(18):6332-7.

Balance between cell-substrate adhesion and myosin contraction determines the frequency of motility initiation in fish keratocytes.
Barnhart E, Lee KC, Allen GM, Theriot JA, Mogilner A.
Proc Natl Acad Sci U S A. 2015 Apr 21;112(16):5045-50.

Yeast kinesin-8 depolymerizes microtubules in a length-dependent manner.
Varga V, Helenius J, Tanaka K, Hyman AA, Tanaka TU, Howard J.
Nat Cell Biol. 2006 Sep;8(9):957-62.

Devore, J.J., G.W. Conrad, and R. Rappaport. 1989. A model for astral stimulation of cytokinesis in animal cells.
The Journal of cell biology. 109:2225-2232.

Odell, G.M., and V.E. Foe. 2008. An agent-based model contrasts opposite effects of dynamic and stable microtubules on cleavage furrow positioning. *J. Cell Biol.* 183:471-483.

We will use ideas from 3 reviews about modeling in cell biology:

Cell polarity: quantitative modeling as a tool in cell biology.
Mogilner A, Allard J, Wollman R.
Science. 2012 Apr 13;336(6078):175-9.

Quantitative modeling in cell biology: what is it good for?
Mogilner A, Wollman R, Marshall WF.
Dev Cell. 2006 Sep;11(3):279-87.

Plus, attached manuscript on modeling cleavage furrow positioning

Modeling process:

Think about the data; is there a question that could benefit from modeling?

Formulate hypotheses

Decide on the modeling method and analytics/code/software

Equations, variables, parameters, algorithms

'Qualitative' analysis, scaling, non-dimensionalization

Numerical solutions, simulations

Thinking about the results and modifying the model

Writing a paper

A Simple Mathematical Model Can Be Used as a Quantitative Hypothesis to Be Tested in Future Experiments or Can Simply Be Thought Provoking

A Model Can Be a Tool for Data Interpretation

Models as Tools for Data Integration and Understanding

Increasingly Complex Generations of Models Can Be Used to Understand Cellular Networks as Systems

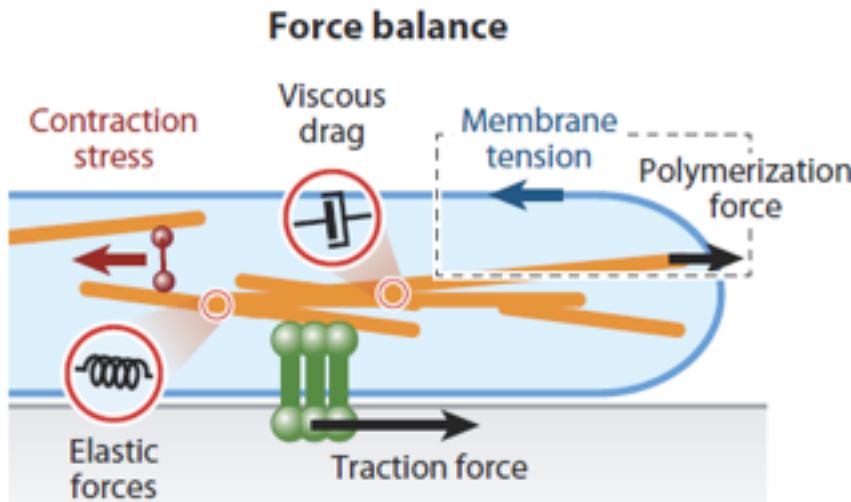
Computer Experiments Can Confirm the Plausibility of a Qualitative Model or Explore a Complex Phenomenon When There Is Little Intuition about It

Model can falsify a hypothesis

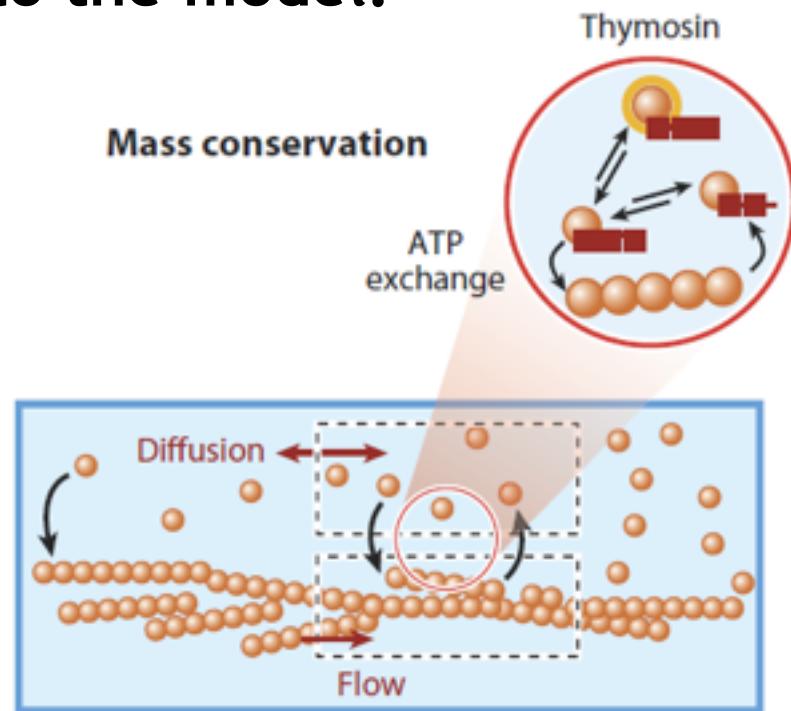
Model can show which pathways and feedbacks are essential and which are not

What goes into the model:

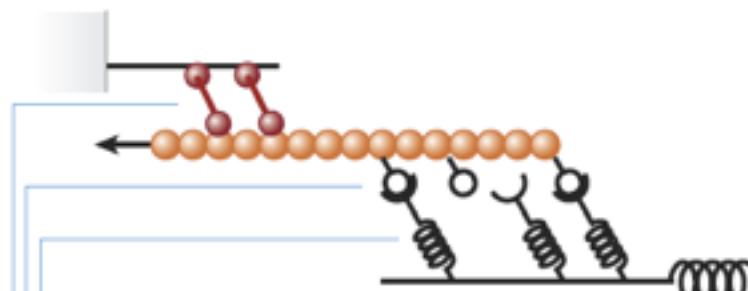
Physical principles



Mass conservation



Actin slip clutch



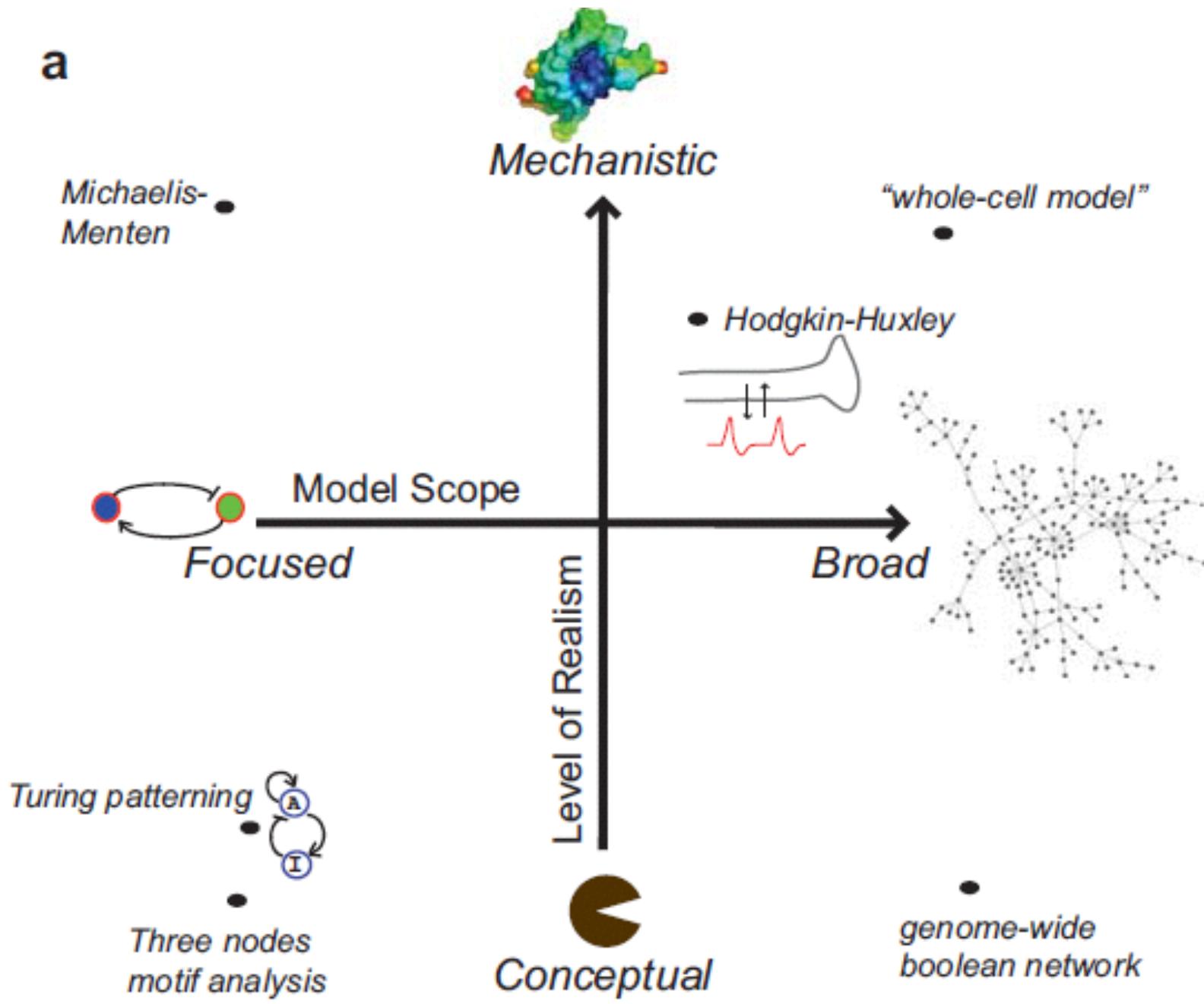
Model assumptions:

- Adhesions obey Hooke's Law
- Adhesions obey Bell's Law
- Myosin force-velocity curve is linear

$$F = k \cdot \delta x$$

$$k_{\text{off}} = k_{\text{off}}^0 \exp\left(\frac{F}{F_b}\right)$$

$$F = F_{\text{stall}} \left(1 - \frac{v}{v_0}\right)$$

a

1. List variables, parameters and their dimensions.

2. Decide what are the characteristic scales for all variables.

Scaling means guessing what are the natural dimensional values of the variables that would be observed

(not unique choice). It means finding ‘special’ values that have biological meaning.



Time scale

$\sim 10^{10}$ sec



Time scale

~ 1 sec

Reasons:

- a) For computer
- b) Insight
- c) To scan parameter space

One of the ideas how to do it: simplicity.
Look for parameters with needed dimensions
and make them scales.

3. Non-dimensionalization Substitute new variables into eqs and initial/boundary conditions

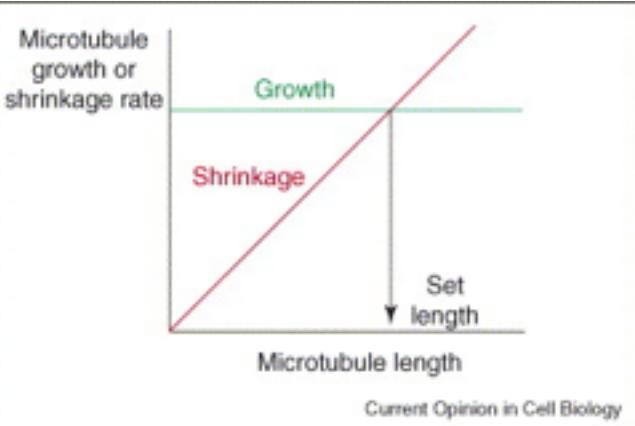
4. Think about the meaning of non-dimensional parameters.

5. Solve, often using perturbation theory or numerical analysis.

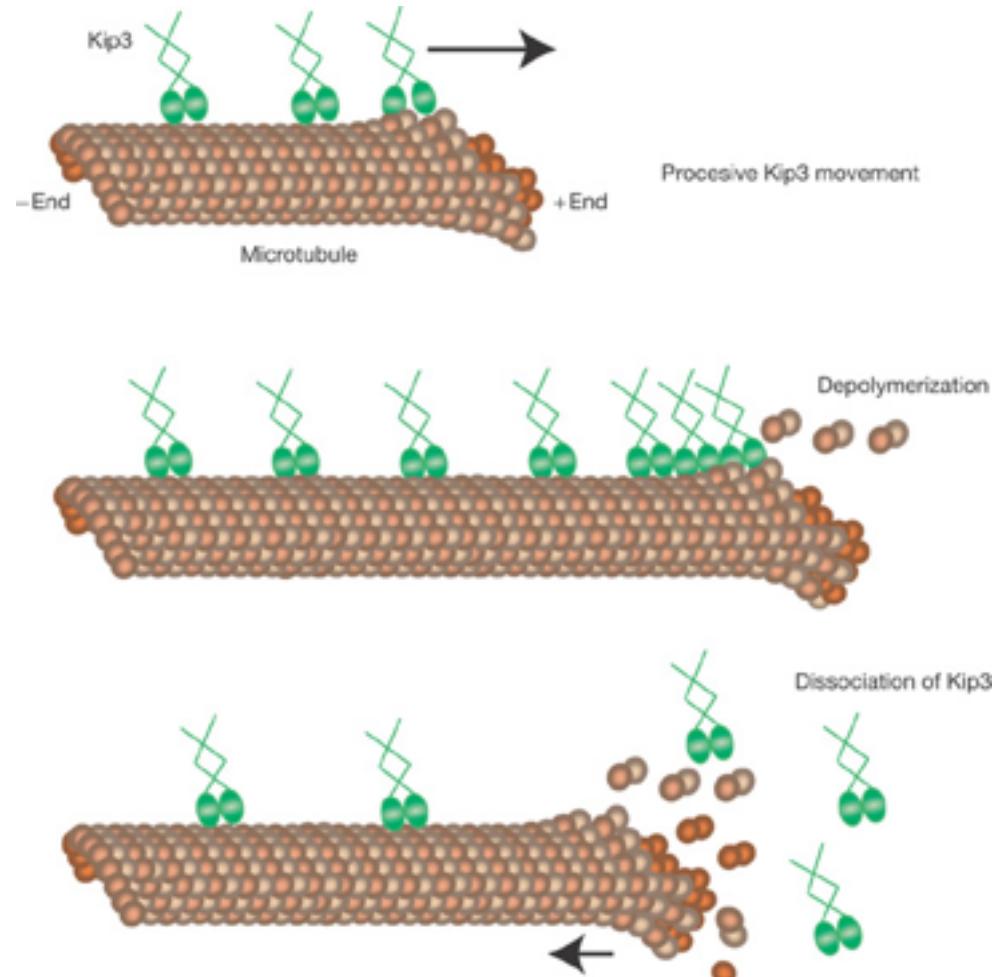
6. Go back to dimensional variables and thinking about biological meaning.

How is polymer length regulated in cells? One of the ways is to use a persistent molecular motor that gets on a MT from the cytoplasm and travels to the MT plus end. At the MT tip, the motor accelerates shrinkage (disassembly). The result is:
the longer the MT is, the more motors accumulate at the tip,
 the faster the shrinkage is.

Why?

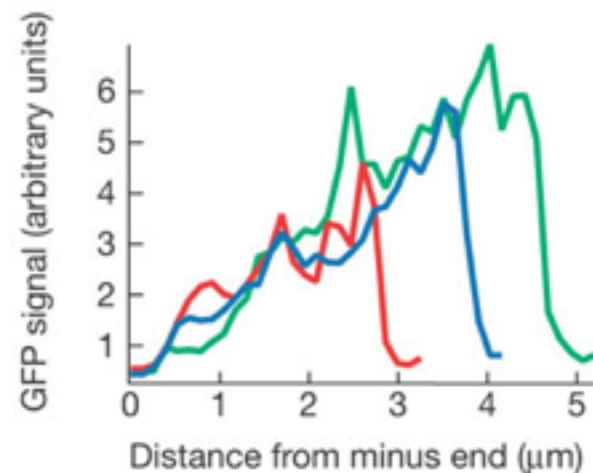
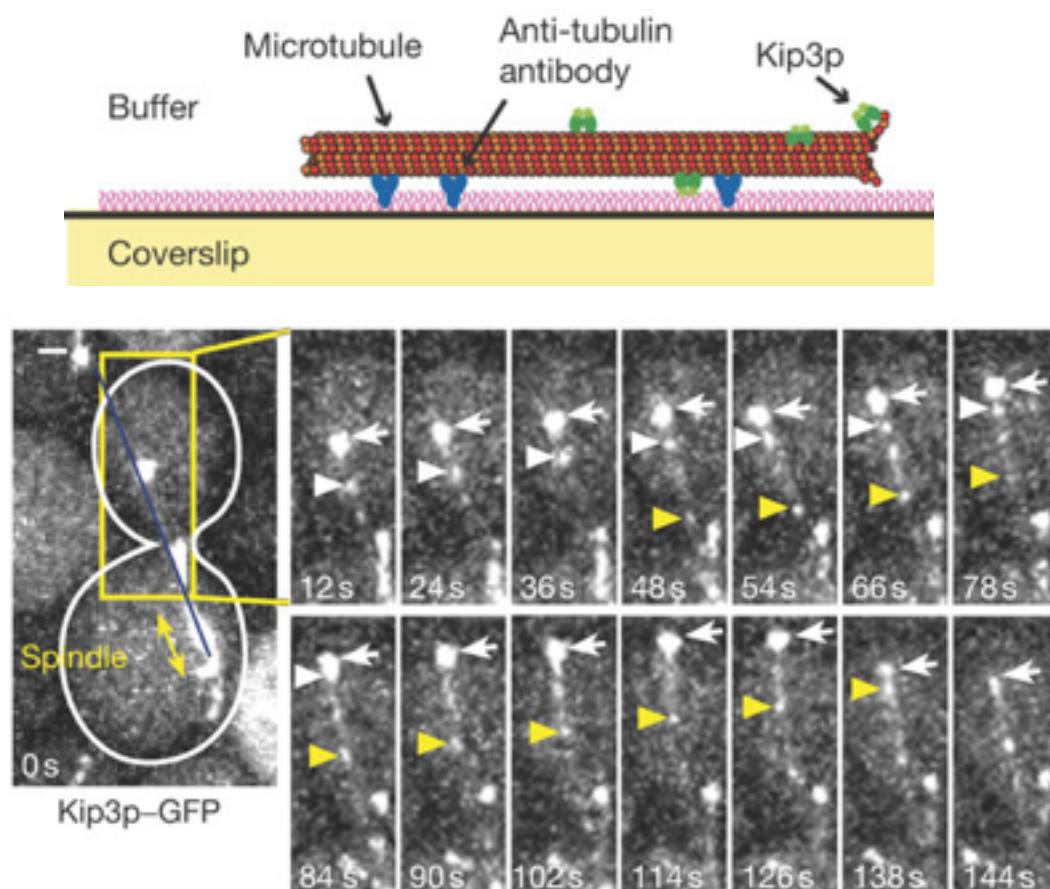


$$\frac{dL}{dt} = g - sL \rightarrow L = \frac{g}{s} (1 - e^{-st})$$

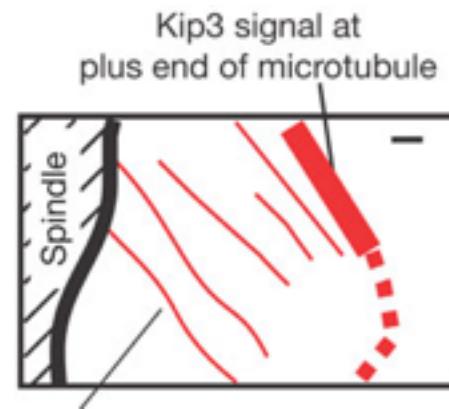
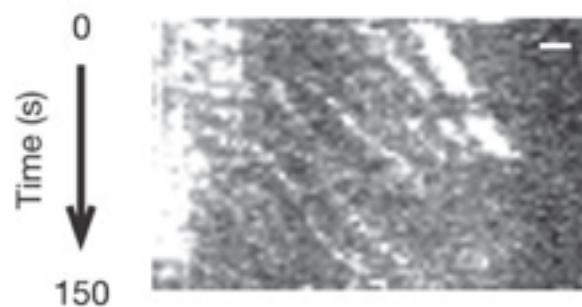


Varga V, Helenius J, Tanaka K, Hyman AA, Tanaka TU, Howard J.
 Yeast kinesin-8 depolymerizes microtubules in a length-dependent manner.
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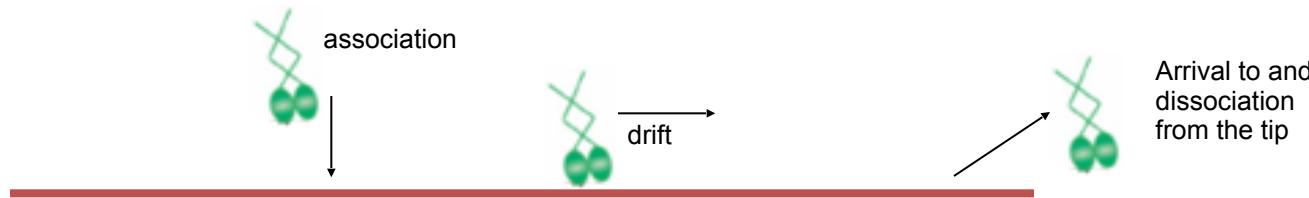
Experiment and observations of Varga et al:



Kip3 kymograph



What processes could contribute to motor distribution along the MT length?



$$\frac{\partial C}{\partial t} = -V \frac{\partial C}{\partial x}$$

- drift equation

$$\frac{dC}{dt} = S$$

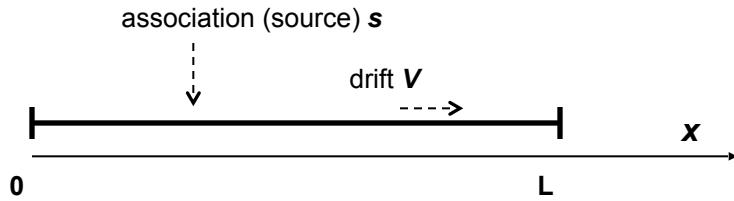
- association equation

Minus corresponds to the right direction.

Solution to $\frac{dC}{dt} = S$ is $C = St$

Solution to $\frac{\partial C}{\partial t} = -V \frac{\partial C}{\partial x}$ is $C = C_{init} (x - Vt)$

Reaction-drift model:



C, X – variables
 V, S, L – parameters

$$\frac{\partial C}{\partial T} = -V \frac{\partial C}{\partial X} + S$$

Concentration, # / μm Speed, $\mu\text{m} / \text{s}$
 Time, s Distance, μm Source, # / $\mu\text{m} \cdot \text{s}$

Steady: $V \frac{dC}{dX} = S$

L – scale of length
 $S \cdot (L/V)$ – scale of concentration

$$x = X/L$$

$$c = CV/(S \cdot L)$$

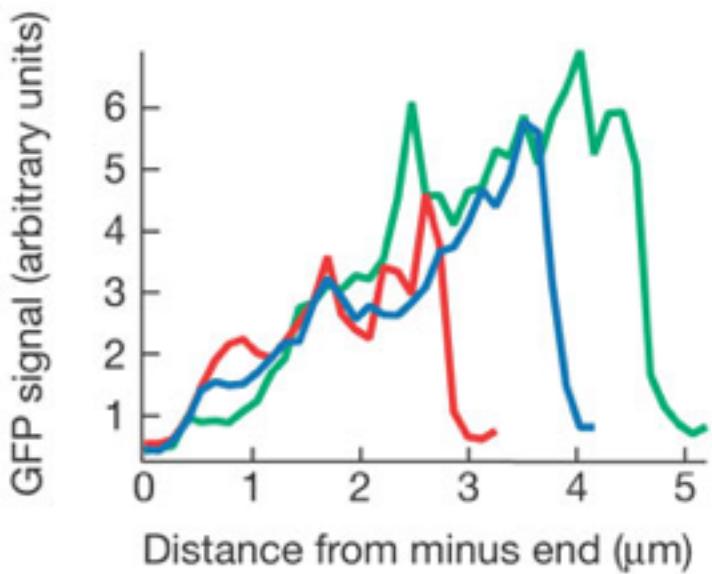
$$\frac{dc}{dx} = 1, 0 \leq x \leq 1 \quad \text{- no parameters!}$$

In our case, $c(0)=0$
 (motors leave the minus end
 to the right immediately)

What is the boundary condition?
 We need just one. For the drift equation,
 the rule is – it has to be at the boundary
from which the flux goes

$$\frac{dc}{dx} = 1, 0 \leq x \leq 1, c(0) = 0$$

$$\frac{dc}{dx} = 1, 0 \leq x \leq 1, c(0) = 0$$



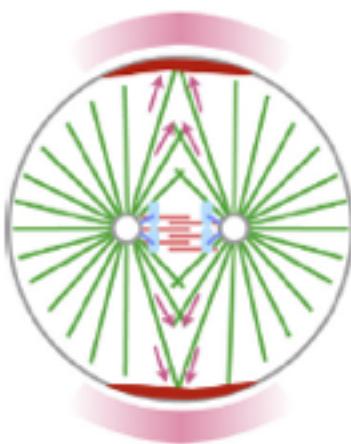
$$c = A + x \rightarrow c = x \rightarrow C = \frac{S}{V} X$$

Slope independent of L , and
so concentration at the tip $\sim L$

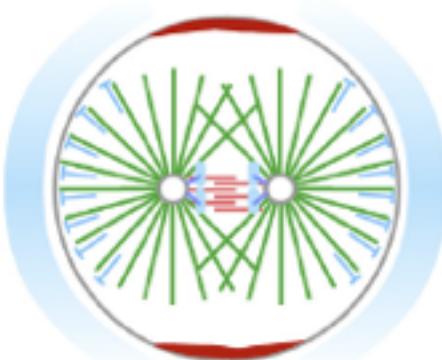


Fragment of Diego Riviera's mural 'Man at Crossroads'

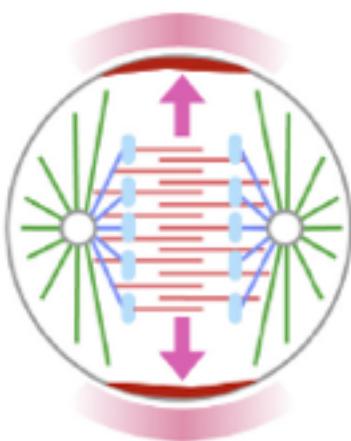
Astral stimulation



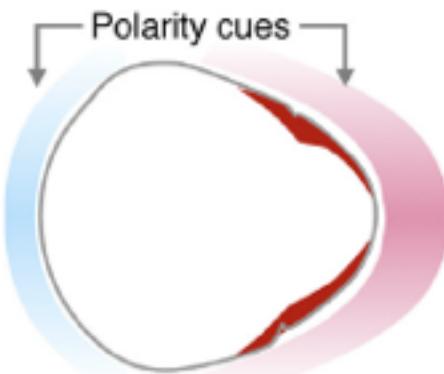
Polar relaxation



Central spindle



MA-independent



astral microtubule

kinetochore microtubule

central spindle microtubule
(spindle midzone microtubule)

← stimulatory signal

↑ inhibitory signal

centrosome

chromosome

assembly of actomyosin network
(contractile ring)

net effect of the

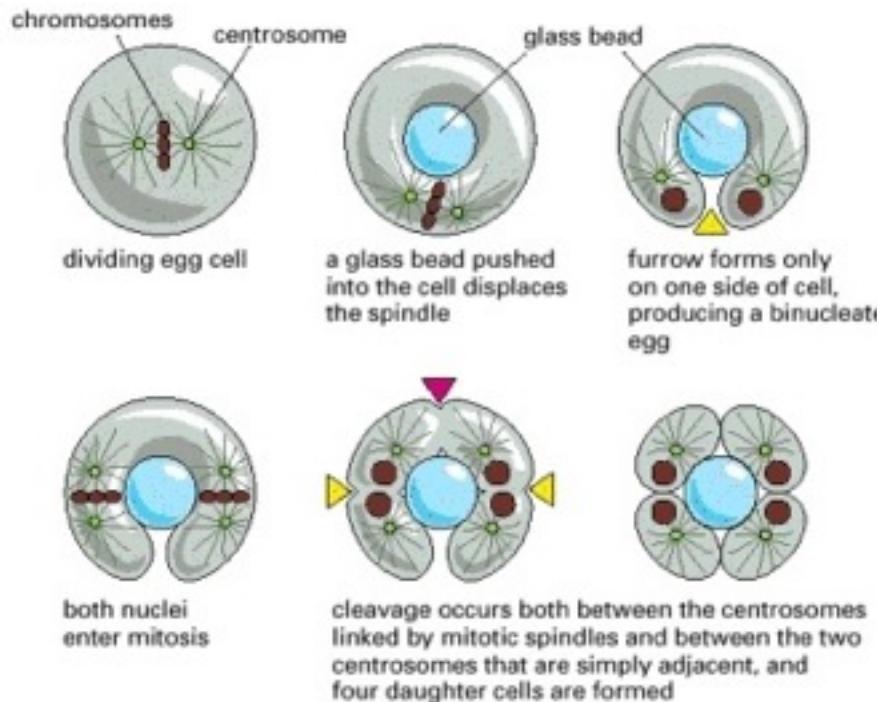
signals at the cortex



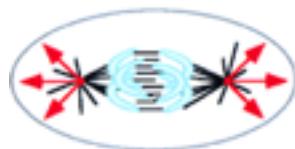
Ray Rappaport (1922 - 2010)

"When I began working on cytokinesis, I thought I was tinkering with a beautifully made Swiss watch, but what I was really working on was an old Maine fishing boat engine: overbuilt, inefficient, never-failed and repaired by simple measures."

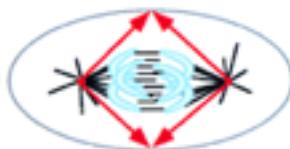
Classic experiment by Raymond Rappaport in sand dollar eggs
Rappaport R (1961) J Exp Zool 148:81-89.



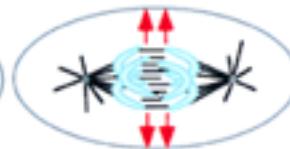
a.



b.



c.



On the mechanisms of cytokinesis in animal cells.

White JG, Borisy GG.

J Theor Biol. 1983 Mar 21;101(2):289-316.

Devore, J.J., G.W. Conrad, and R. Rappaport. 1989.

A model for astral stimulation of cytokinesis in animal cells.

J Cell Biol. 109:2225-2232.

Harris, A.K., and S.L. Gewalt. 1989.

Simulation testing of mechanisms for inducing
the formation of the contractile ring in cytokinesis.

J. Cell Biol. 109:2215-2223.

Canman, J.C., L.A. Cameron, P.S. Maddox, A. Straight, J.S. Tirnauer,

T.J. Mitchison, G. Fang, T.M. Kapoor, and E.D. Salmon. 2003.

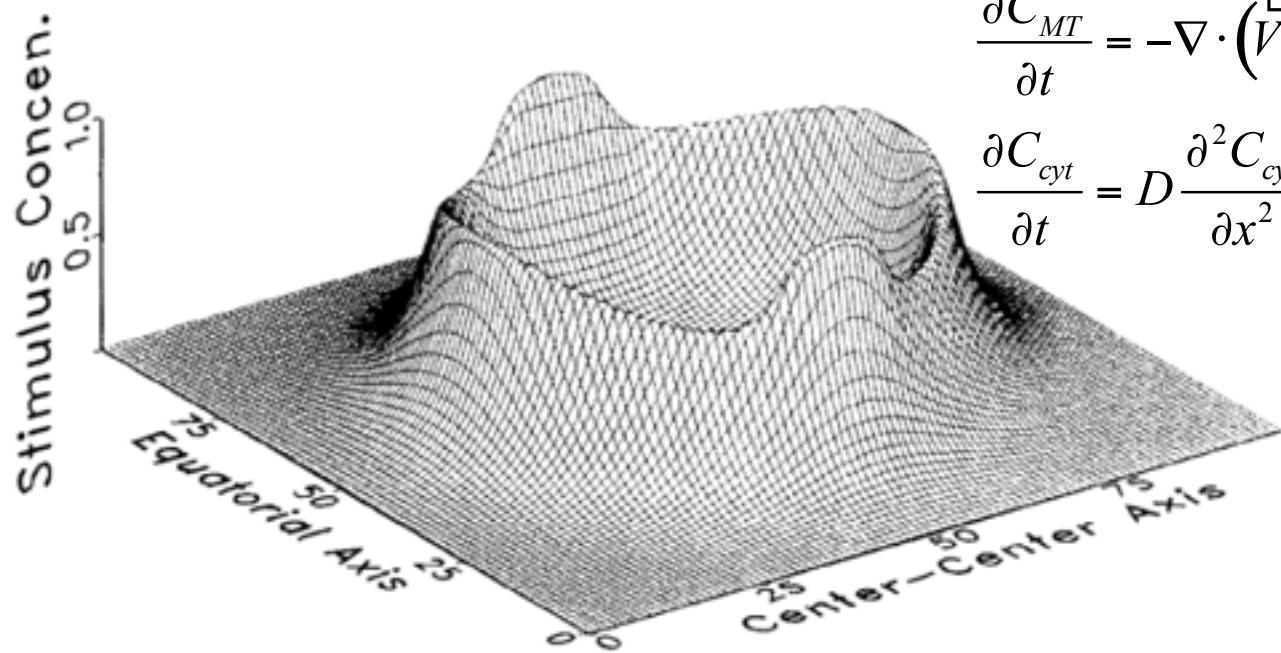
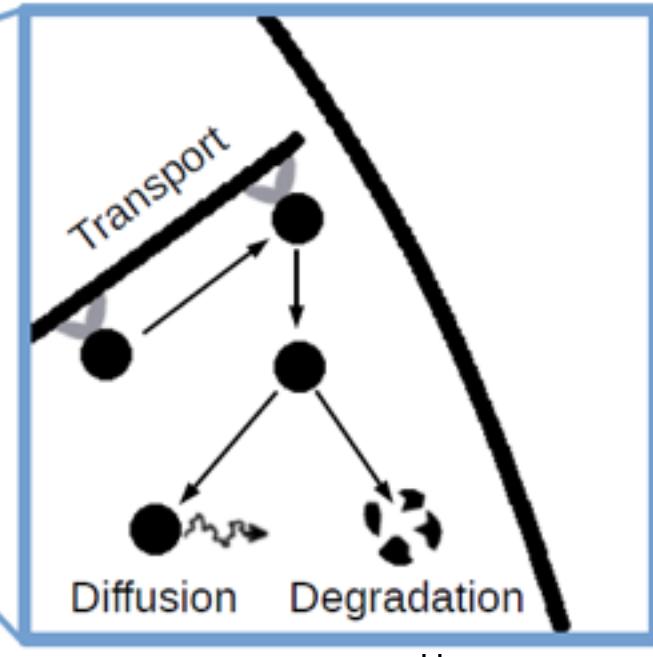
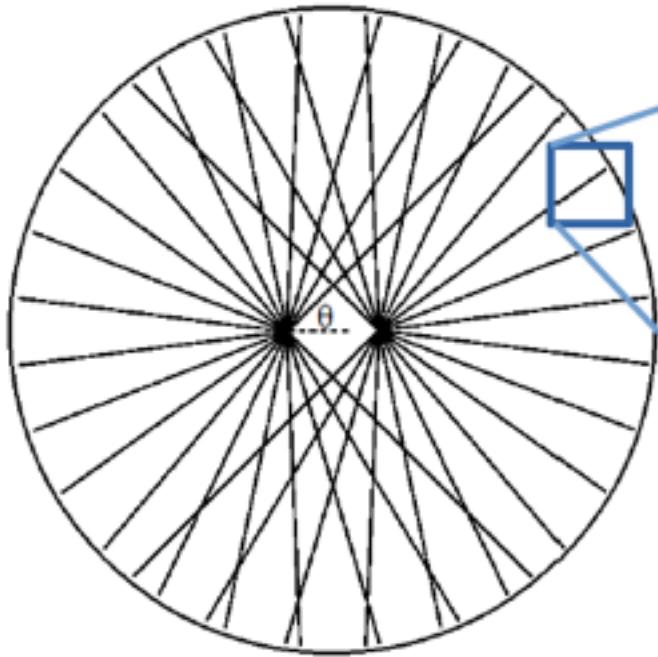
Determining the position of the cell division plane.

Nature. 424:1074-1078.

Odell, G.M., and V.E. Foe. 2008.

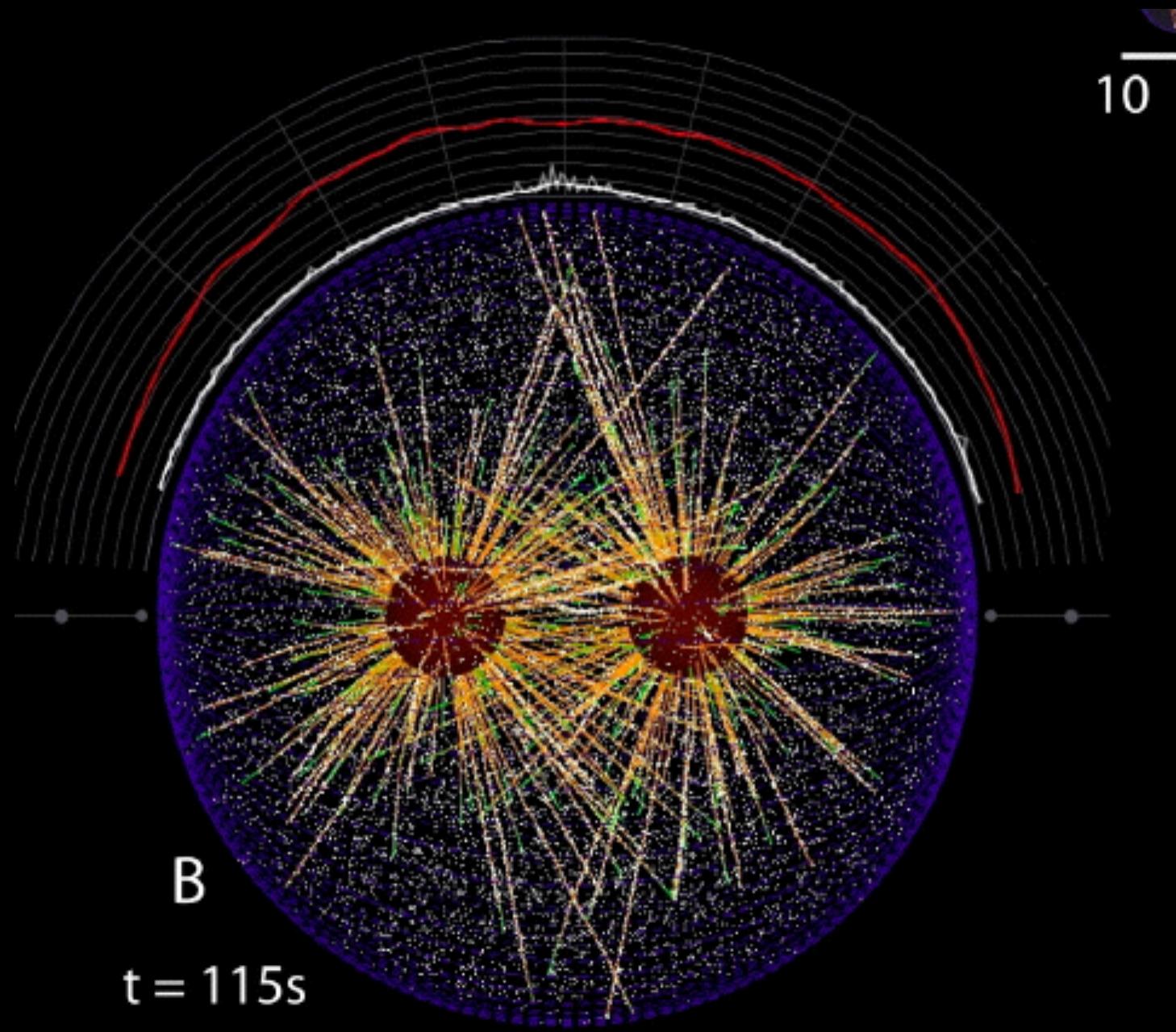
An agent-based model contrasts opposite effects of
dynamic and stable microtubules on cleavage furrow positioning.

J. Cell Biol. 183:471-483.



$$\frac{\partial C_{MT}}{\partial t} = -\nabla \cdot (VC_{MT}) + S(x) - k(x)C_{MT}$$

$$\frac{\partial C_{cyt}}{\partial t} = D \frac{\partial^2 C_{cyt}}{\partial x^2} + k(x)C_{MT} - \gamma C_{MT}$$



AB models - *in silico* reconstitutions of biological systems - produce a life-like simulation of the cellular subsystem. The AB model allows computer experiments with *in silico* system, with an exquisite control of all parameters and easiness of simulating biochemically or genetically perturbed system.

As biological systems do actually consist of a large number of agents, whose simple interaction rules produce mind-bogglingly complex behavior, AB philosophy is very close to biology, and so often fewer approximations have to be made to build an AB model.

Often, an AB model is much simpler than a DE model, especially in cases where complex geometries, a high number of dimensions (including, besides spatial dimensions, distributions in angle and size), heterogeneity and anisotropy, and a great number of types of agents are involved.

AB models capture stochastic effects more naturally than stochastic DE models. When a biological system consists of few discrete objects, the continuous approximation required for a DE models is not faithful.

Computer-savvy and quantitative-minded biologists can do AB modeling without the need to study mathematics.

The main problem with AB models is that it is often much harder than with DE models to get a qualitative insight: *in silico* systems tend to become too complex; in a way, we get interesting results but can only guess how the assumptions lead to those results.

Fewer methods and software exist for AB models.

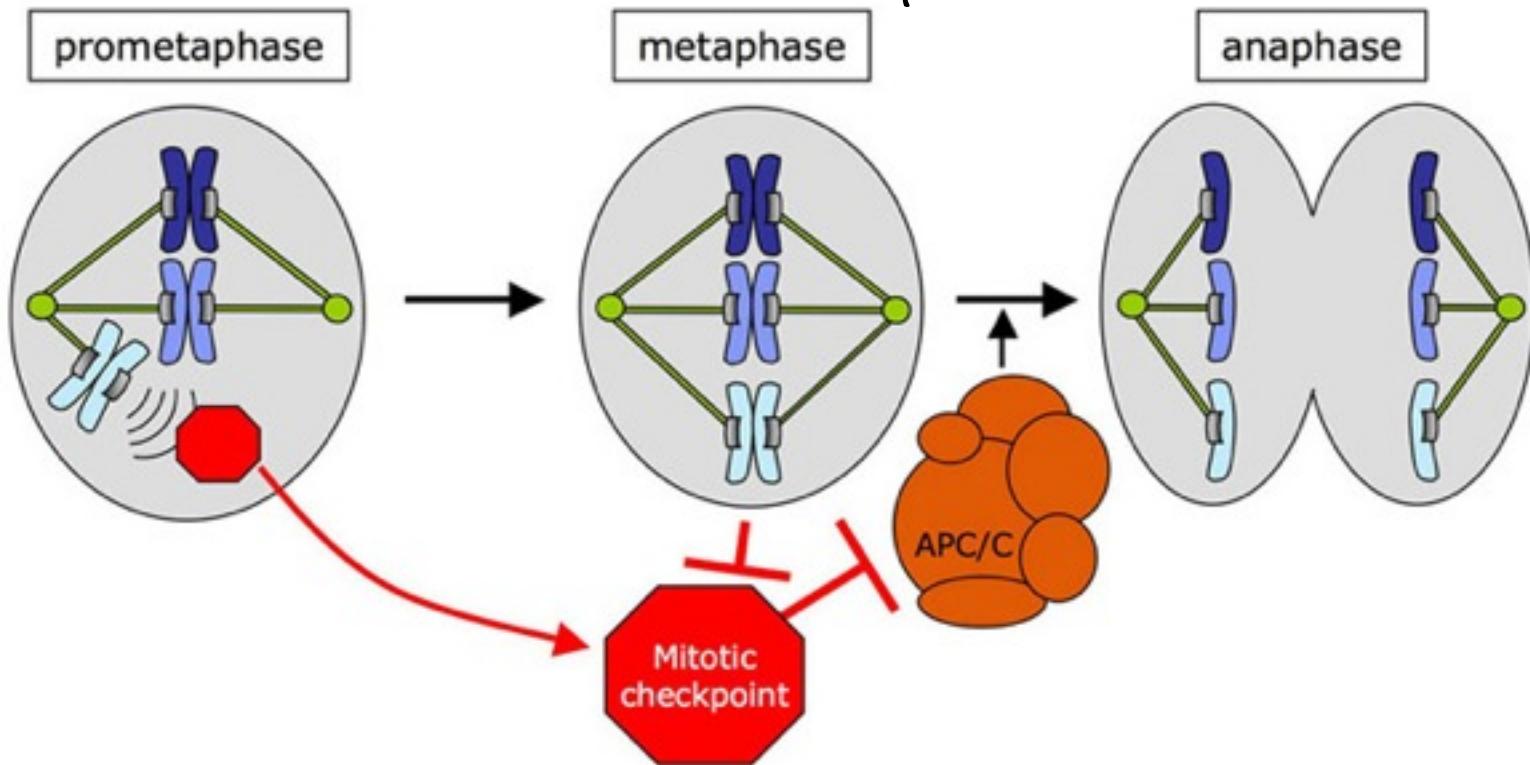
There are some artifacts inherent to some types of AB models, for example, there are artificial oscillatory solutions in Boolean models and difference equations that do not correspond to reality.

There are no analytical solutions to AB models, no benchmark cases.

Usually, multiple simulations and vast and nontrivial statistics are necessary to extract meaningful insight from an AB model.

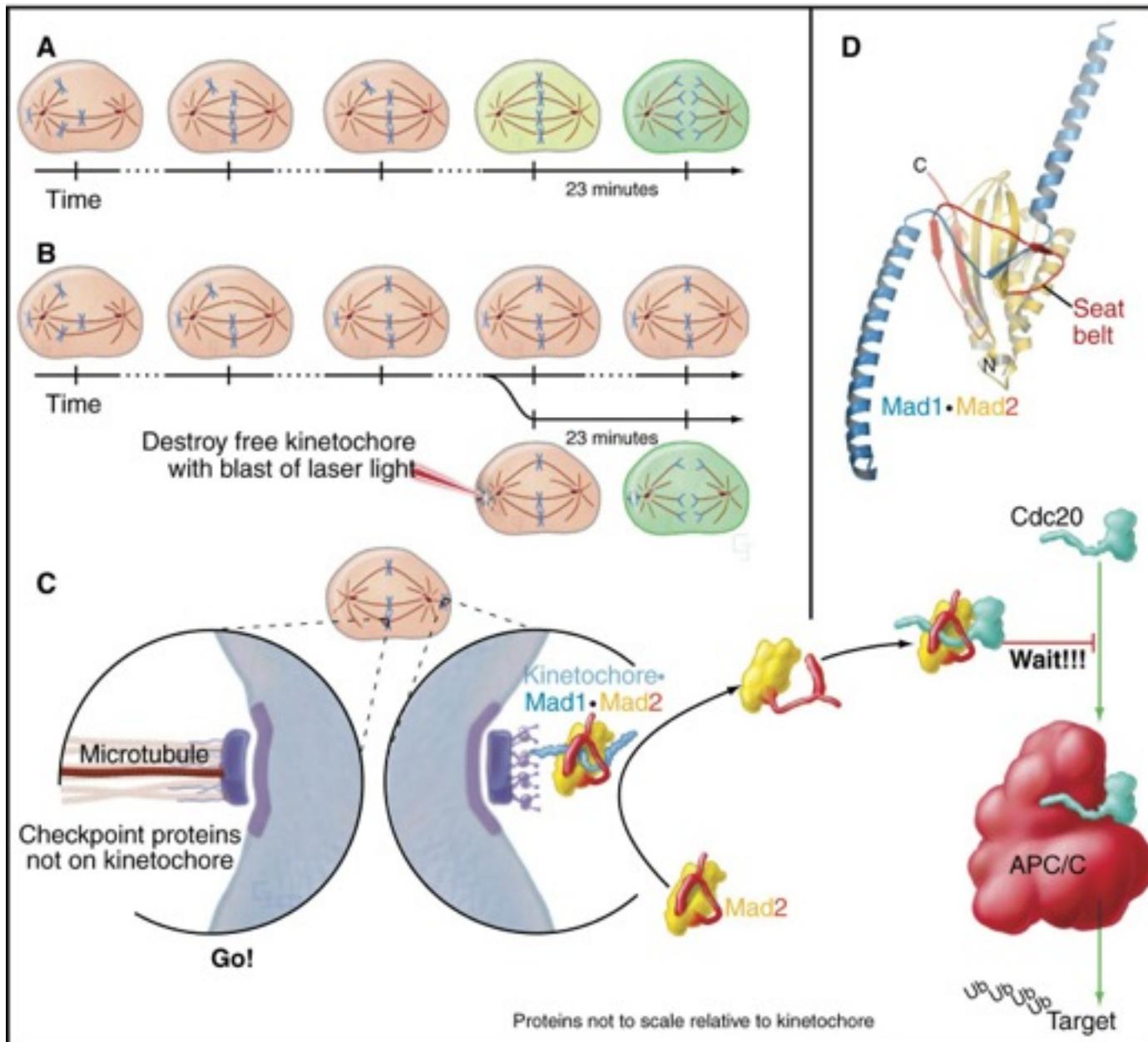
It is usually hard to explore parameter space with AB models.

Mitotic checkpoint

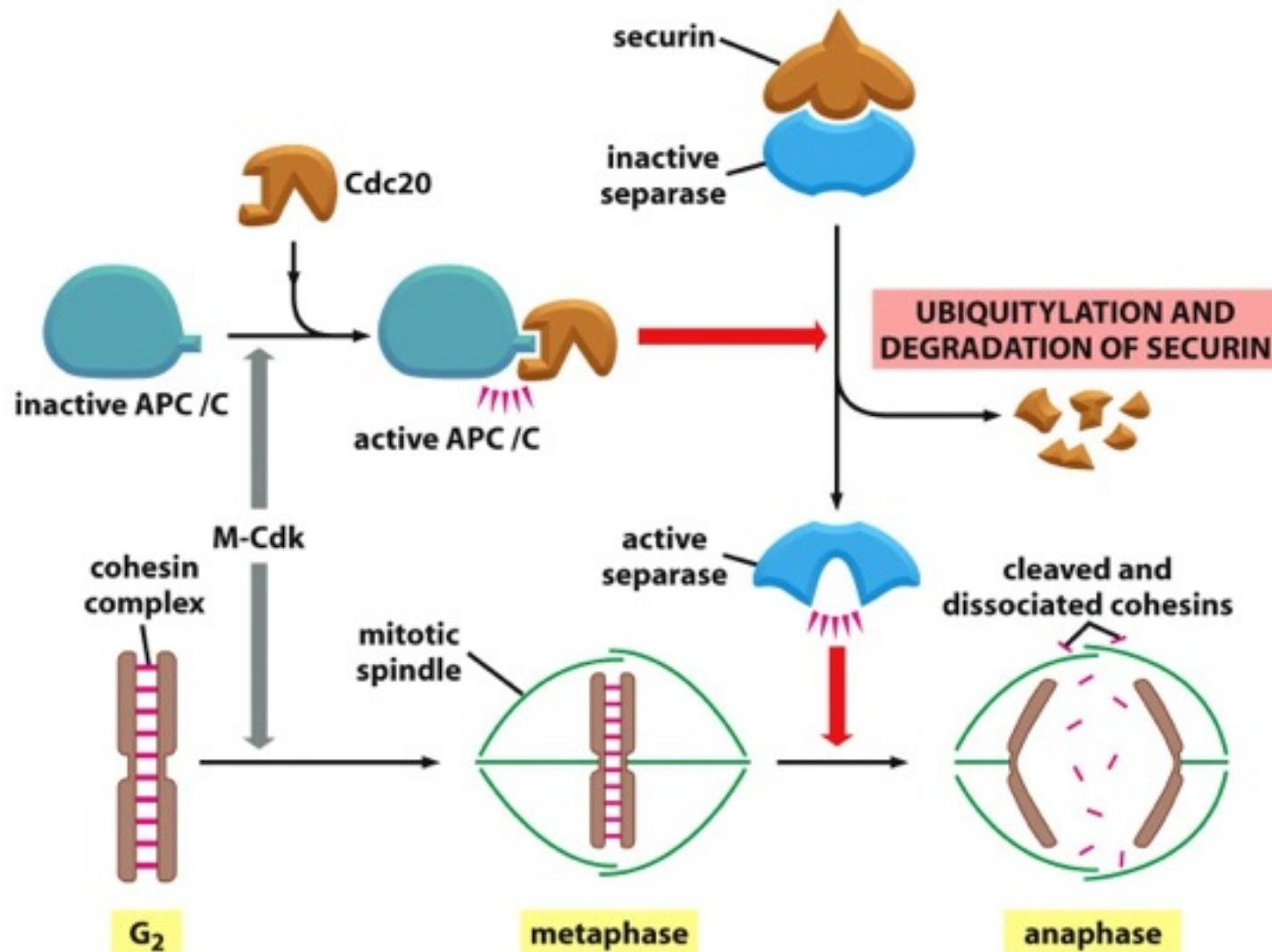


Checkpoint mechanisms like those just described tend to act through negative intracellular signals that arrest the cell cycle, rather than through the removal of positive signals that normally stimulate cell-cycle progression. Consider, for example, the [checkpoint](#) that monitors the attachment of chromosomes to the [mitotic spindle](#). If a cell proceeds into [anaphase](#) and starts to segregate its chromosomes into separate daughter cells before all chromosomes are appropriately attached, one daughter receives an incomplete [chromosome](#) set, while the other daughter receives a surplus. The cell therefore needs to be able to detect the attachment of the last unattached chromosome to the microtubules of the spindle. In a cell with many chromosomes, if each chromosome sends a positive signal to the [cell-cycle control system](#) once it is attached, the attachment of the last chromosome will be hard to detect, as it will be signaled by only a small fractional change in the total intensity of the “go” signal. On the other hand, if each unattached chromosome sends a negative signal to inhibit progress through the cell cycle, the attachment of the last chromosome will be easily detected because it will cause a change from some “stop” signal to none.

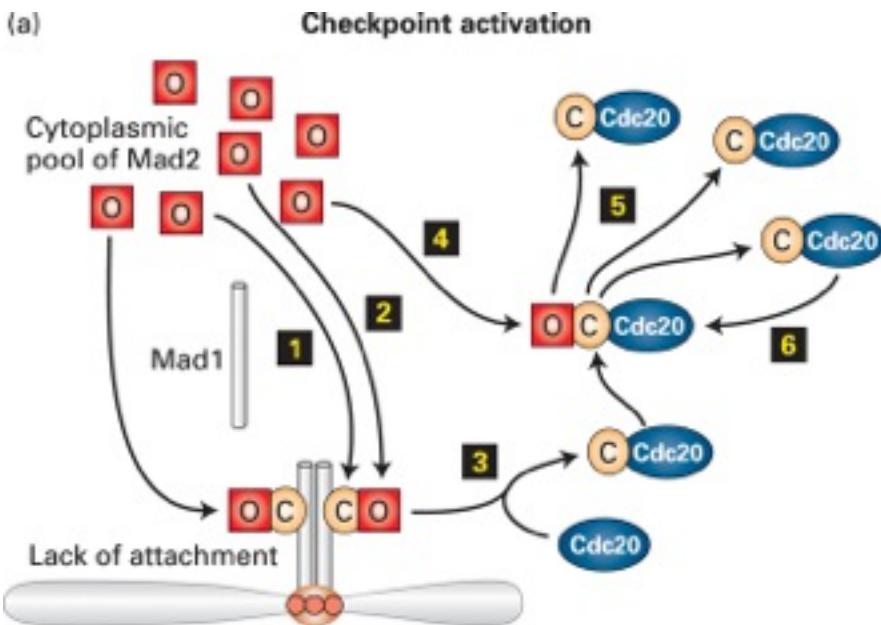
The spindle checkpoint



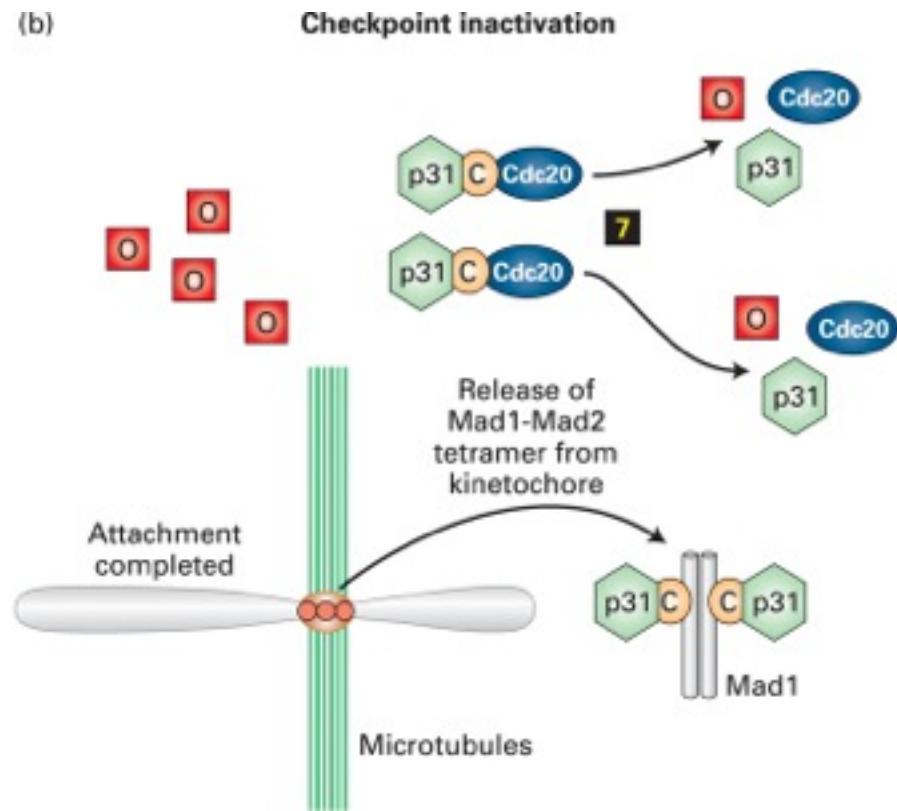
The APC/C triggers sister-chromatid separation and the completion of mitosis



(a)



(b)

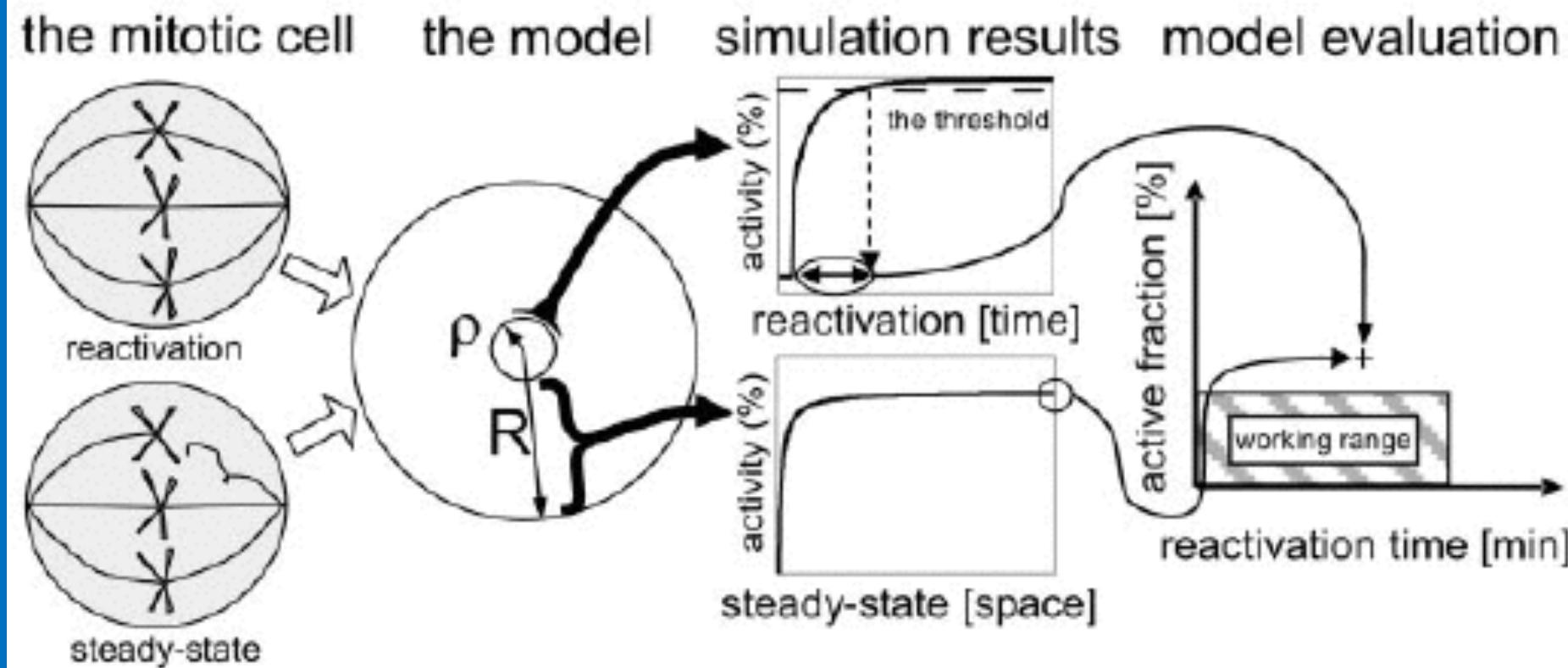


- Mad2 in open conformation
- C Mad2 in closed conformation

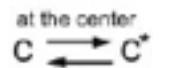
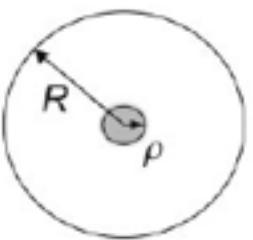
Mitotic checkpoint.

The following two papers examined two central requirements:

- (i) capacity of single kinetochore to maintain tight inhibition of the APC–Cdc20 complex throughout the nucleus,
- (ii) the rapid removal of this inhibition once the final kinetochore is attached



Yeast cell: mitosis
in the nucleus

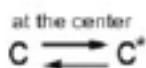
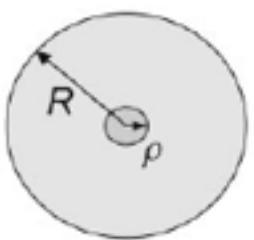


colored area is where the inhibition takes place (all models)

Direct Inhibition

$$\frac{\partial c}{\partial t} = D_c \Delta c + \alpha c - \gamma c e^*$$

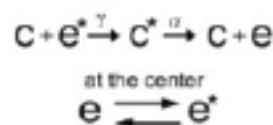
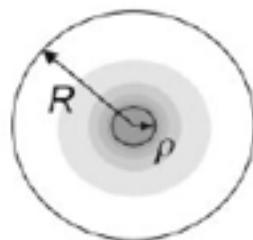
$$\frac{\partial c^*}{\partial t} = D_c \Delta c^* - \alpha c$$



Self-Propagating Inhibition

$$\frac{\partial c}{\partial t} = D_c \Delta c + \alpha c - \kappa c c^*$$

$$\frac{\partial c^*}{\partial t} = D_c \Delta c^* - \alpha c + \kappa c c^*$$



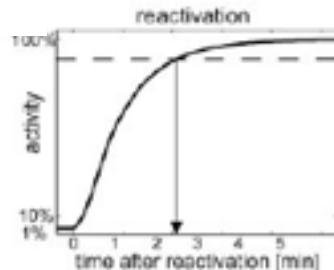
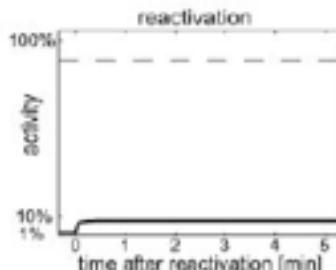
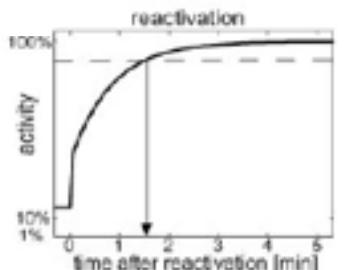
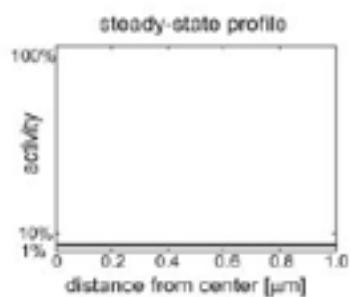
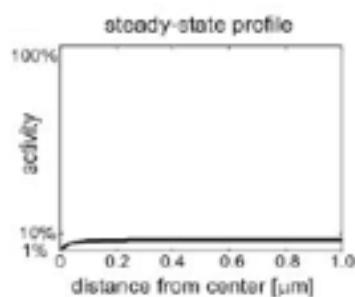
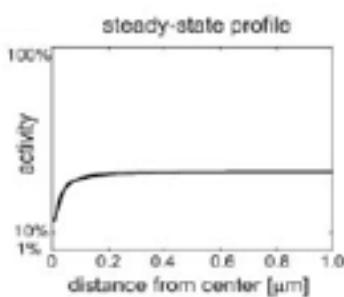
Emitted Inhibition

$$\frac{\partial c}{\partial t} = D_c \Delta c + \alpha c - \gamma c e^*$$

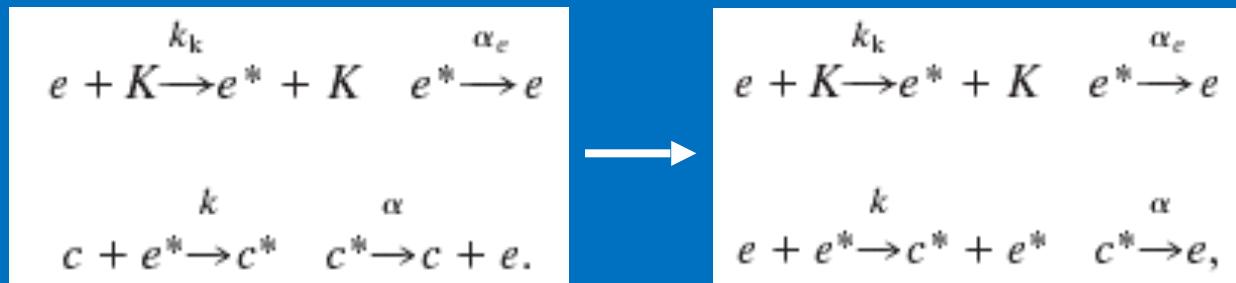
$$\frac{\partial c^*}{\partial t} = D_c \Delta c^* - \alpha c + \gamma c e^*$$

$$\frac{\partial e}{\partial t} = D_e \Delta e + \alpha c^* + \lambda e^*$$

$$\frac{\partial e^*}{\partial t} = D_e \Delta e^* - \lambda e^* - \gamma c e^*$$

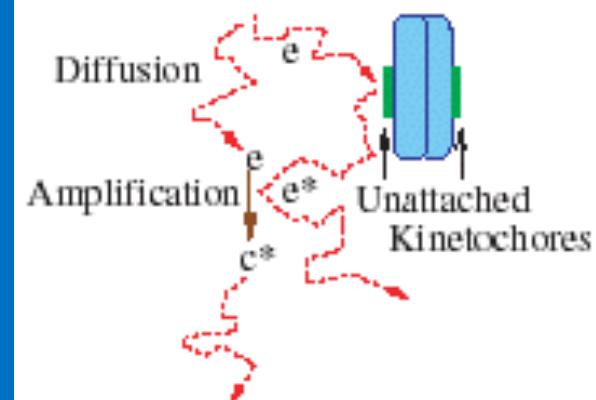


nonautocatalytic amplification

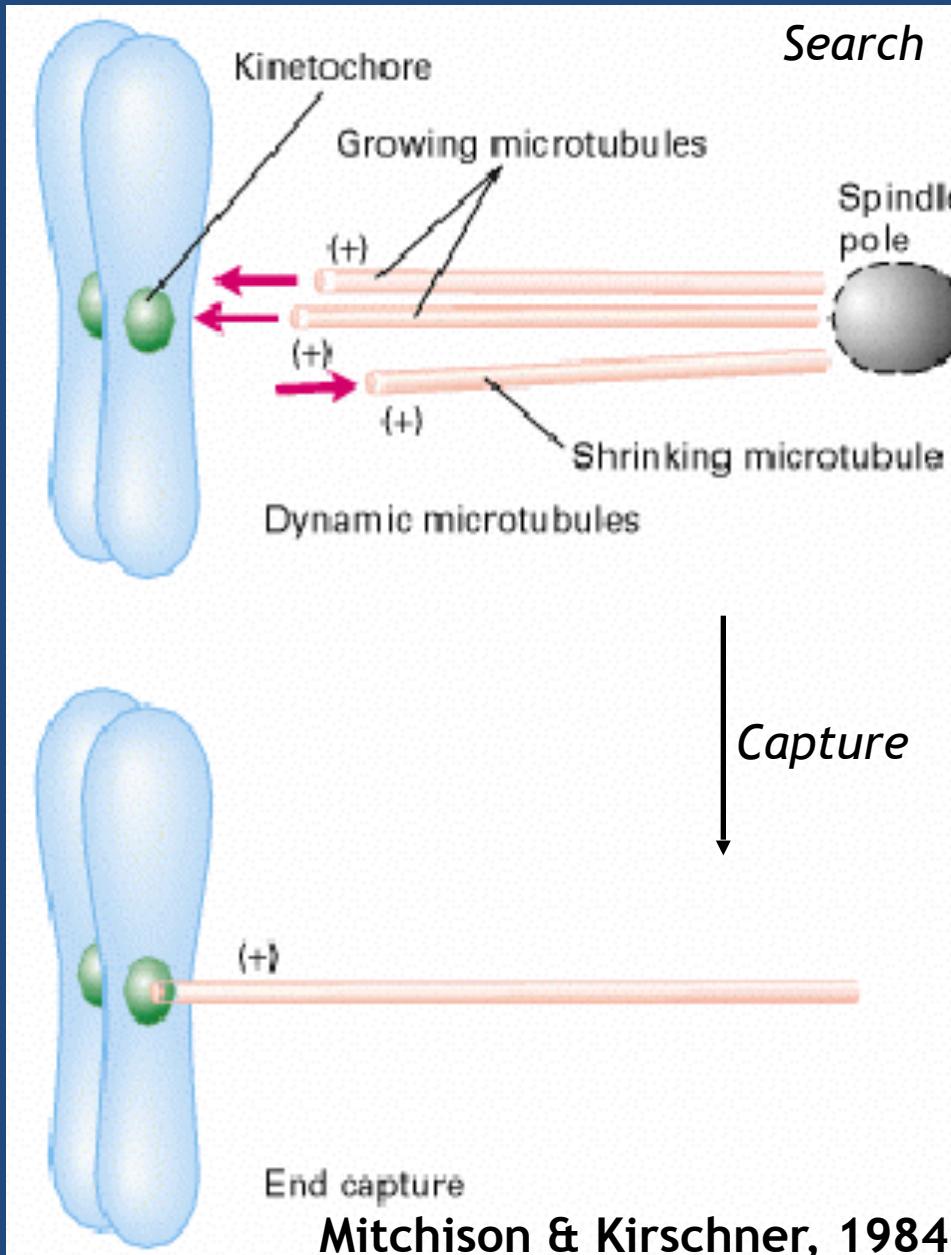


Doncic's scheme does not catalytically amplify the inhibitory signal. One e^* molecule can interact with only one c molecule. In Sear's scheme, a single e^* molecule can convert many molecules into the inhibiting form, thereby producing amplification.

Anaphase inhibited by sequestration of cell cycle regulators

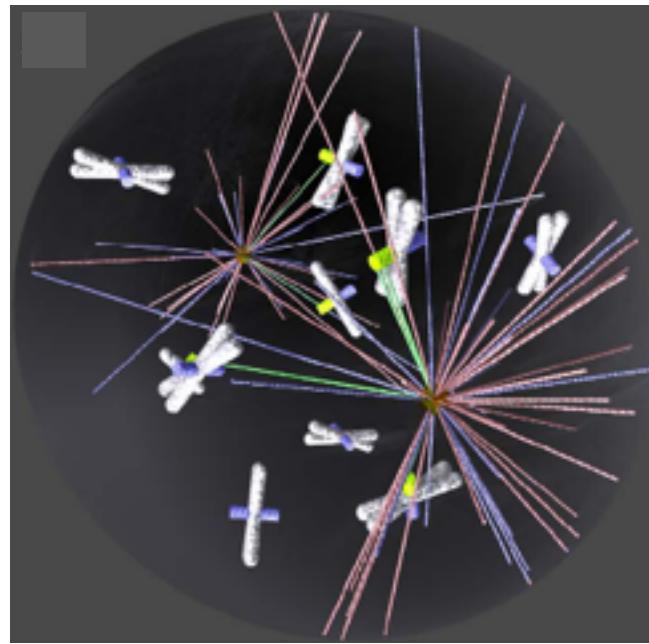
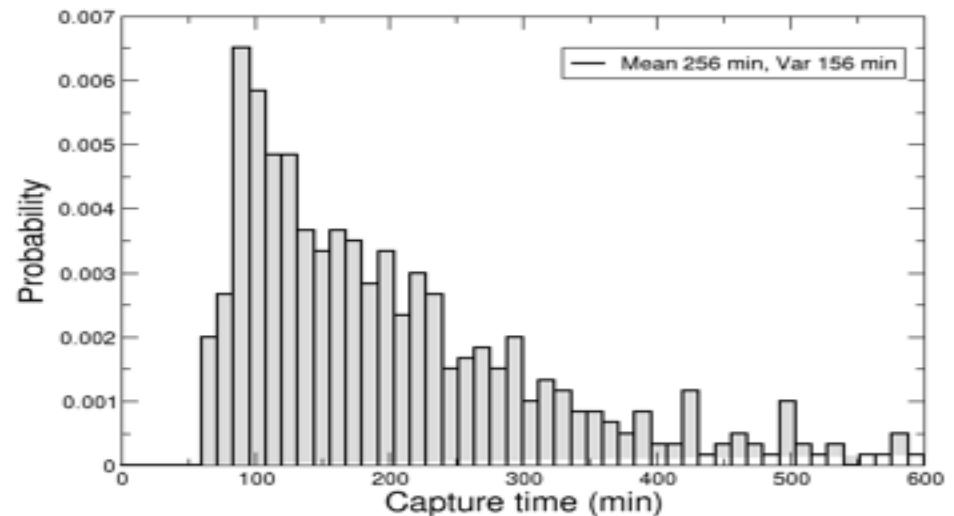
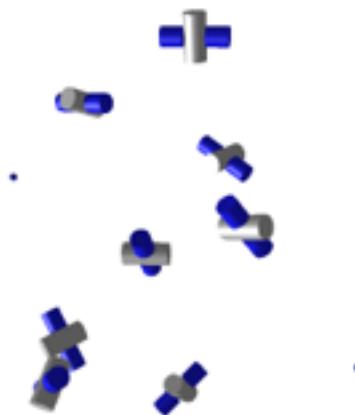


Microtubule dynamic instability and search and capture hypothesis

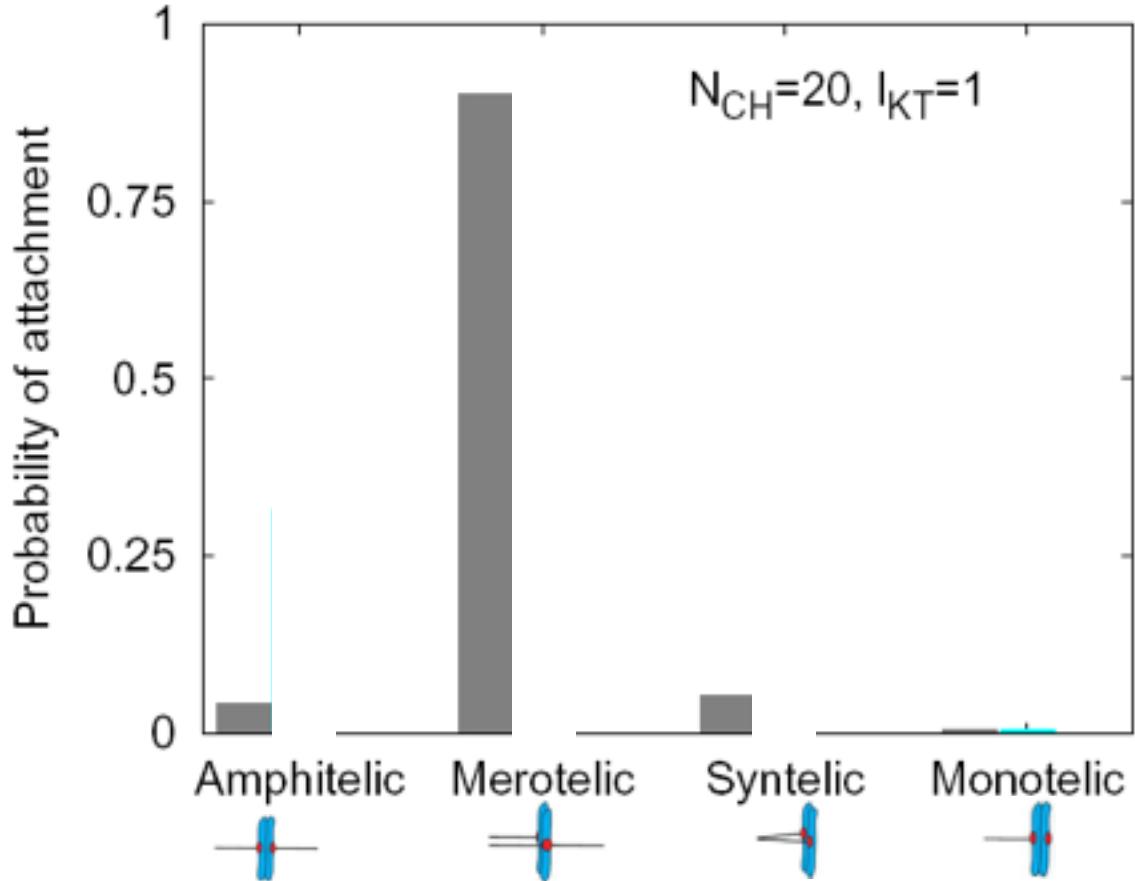
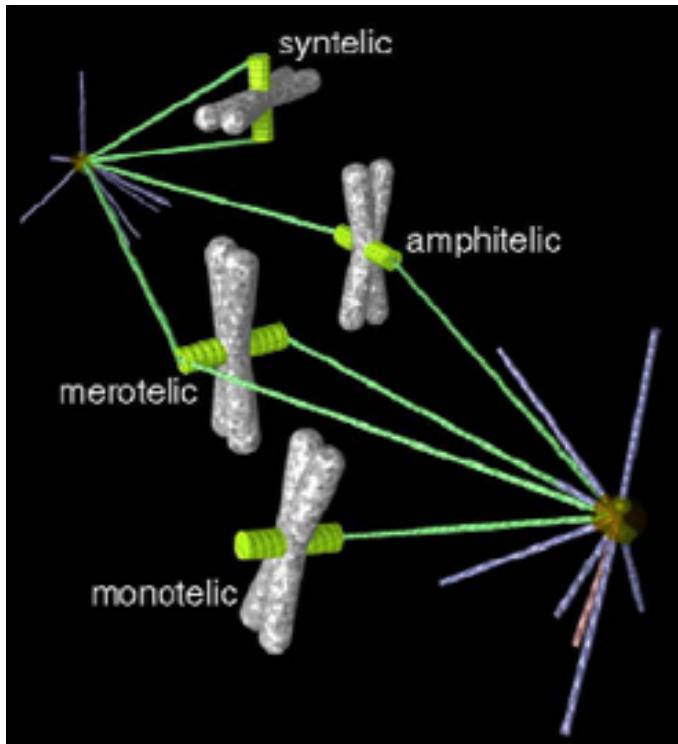


However, for many MTs and KTs, random 'Search and Capture' is not fast enough

Wollman et al. Current Biology 15: 828-832 (2005)
Paul et al, PNAS, 106: 15708-1513 (2009)

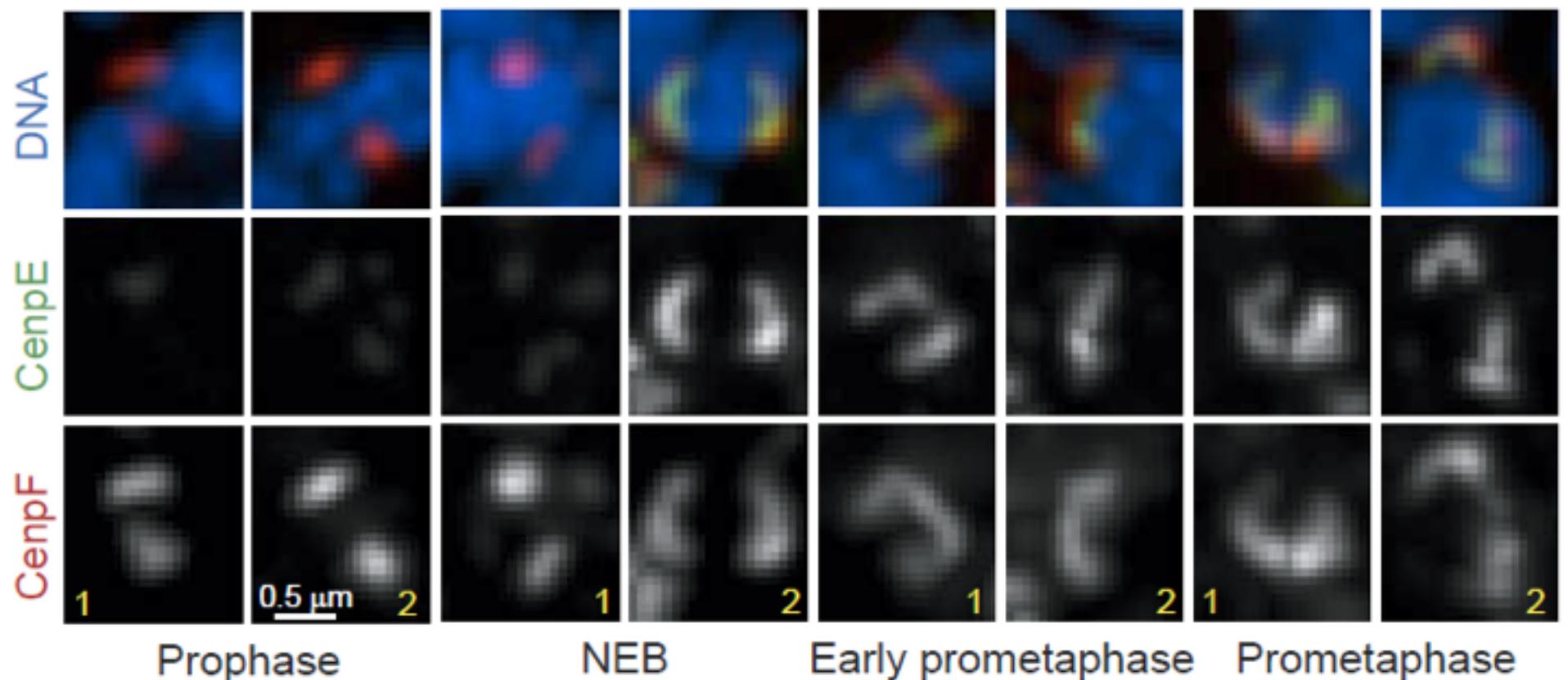
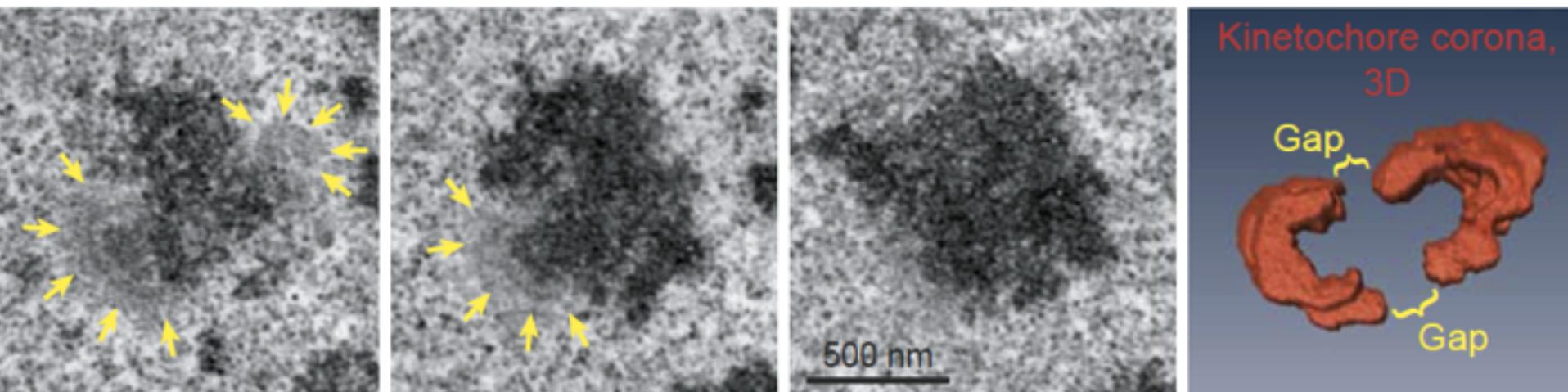


Problem of accuracy

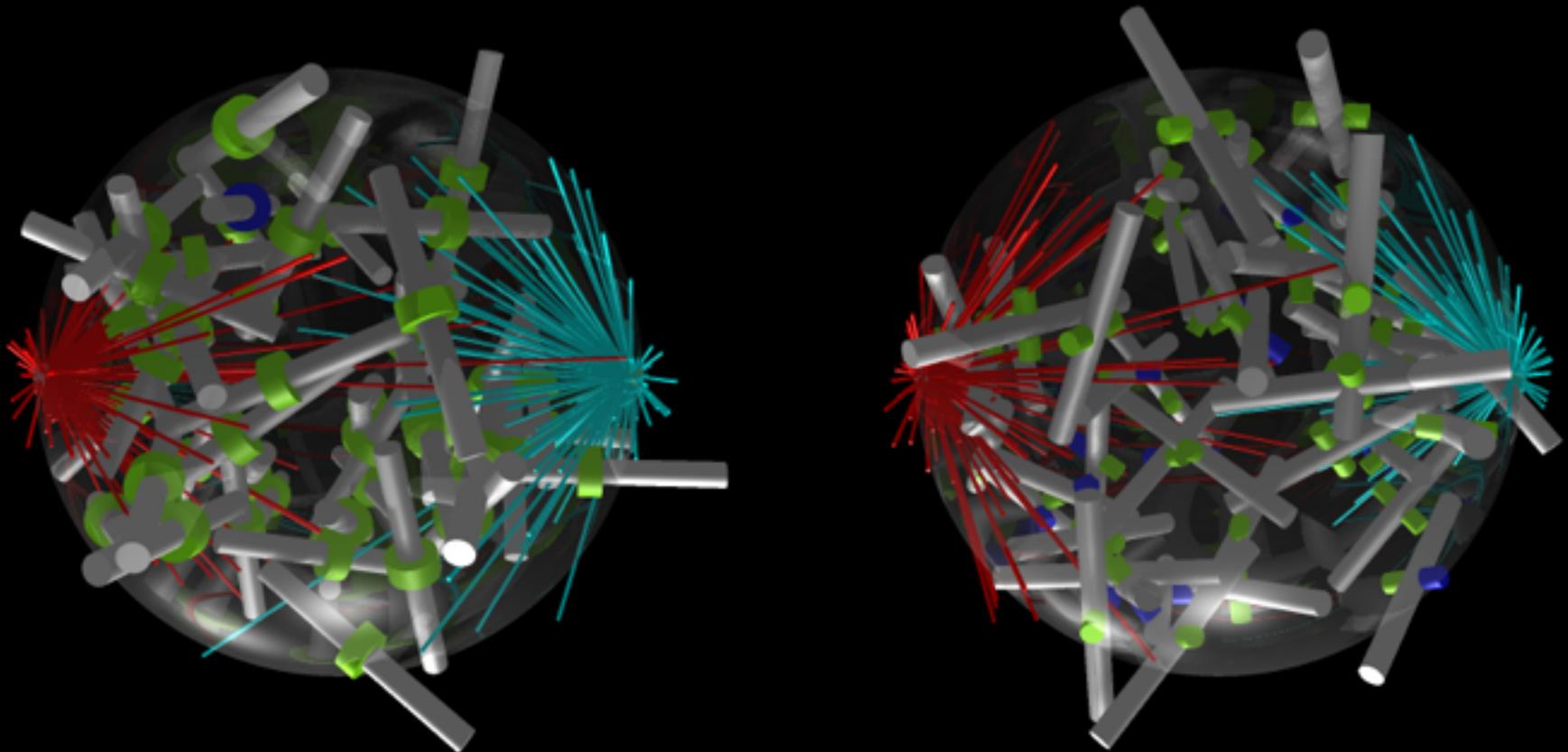


Model simulation shows shocking number of errors:

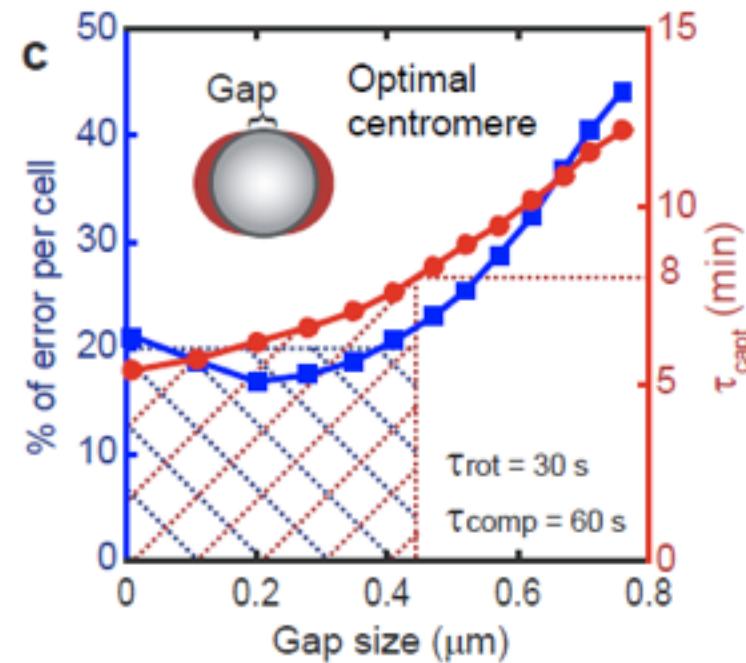
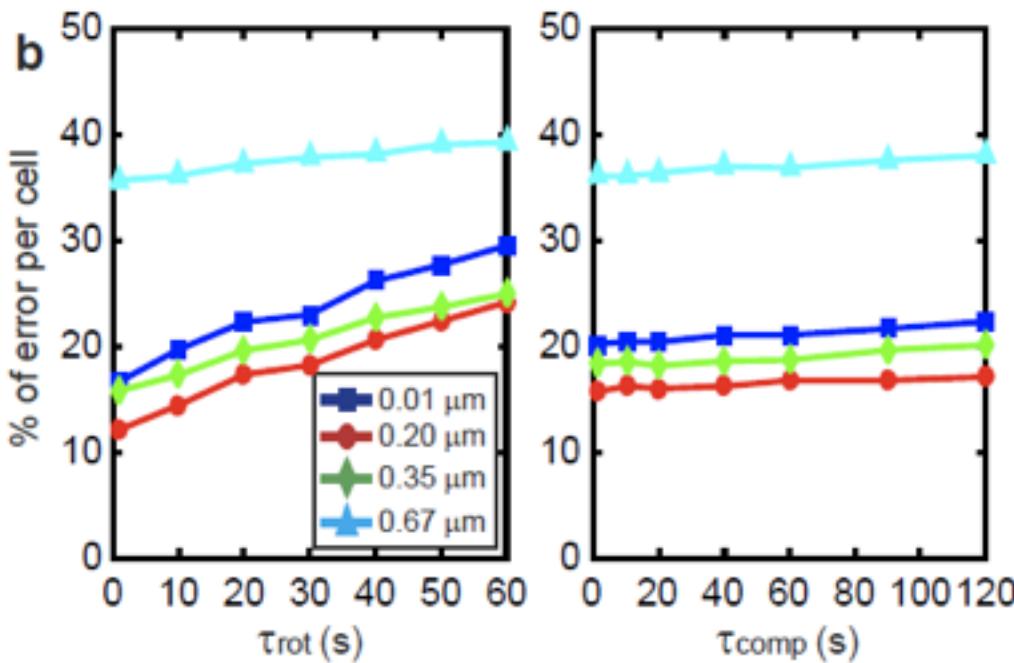
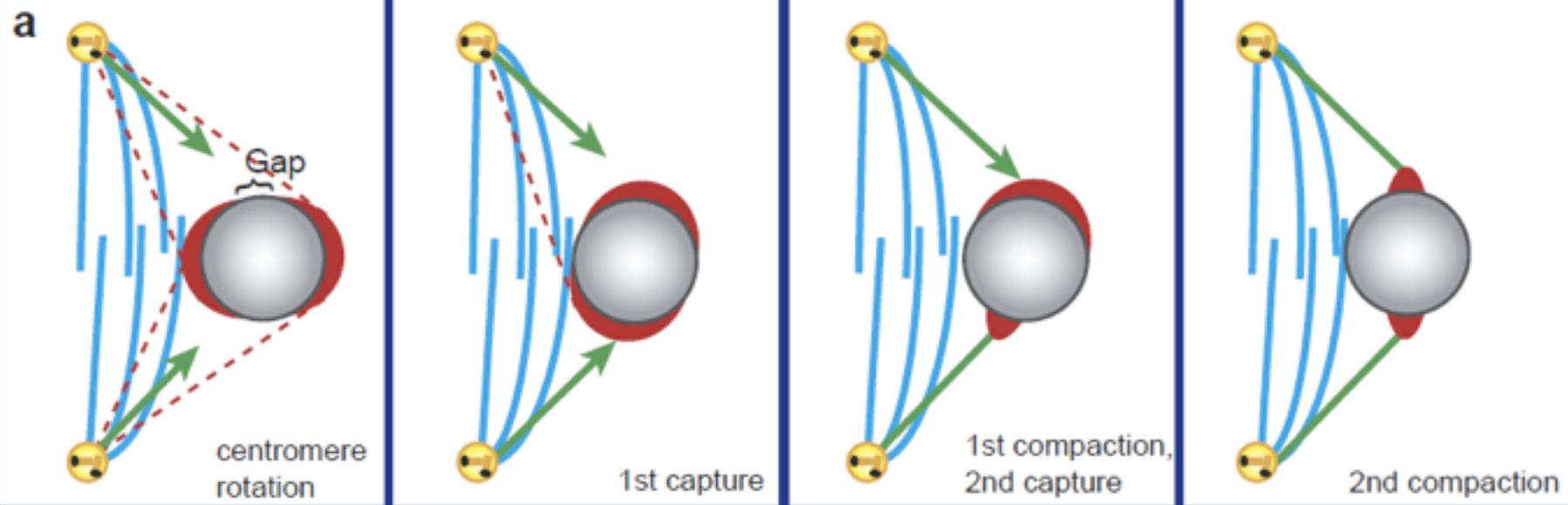
too many syntelic attachments in the beginning; they turn into the merotelic ones later



We can simulate the search-and-capture process
with different geometries

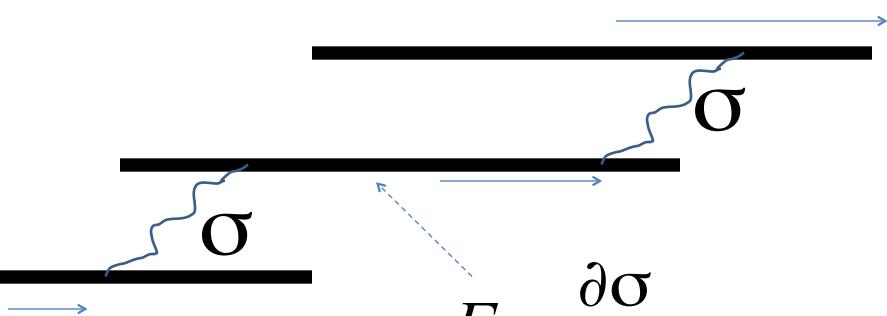


Rotation coordinated with MT-KT lateral attachment achieves both





$$l = U\tau, F = \frac{k\tau}{\zeta} U$$



$$F = \frac{\partial \sigma}{\partial x}$$

$$\begin{matrix} F_{adh} \\ \text{external} \end{matrix} + \begin{matrix} F_{visc} \\ \text{internal} \end{matrix} + \begin{matrix} F_{myo} \\ \text{internal} \end{matrix} = 0$$

$$F_{adh} = -\zeta U$$

$$\sigma_{visc} = \mu' \Delta U = \mu \frac{\partial U}{\partial x}$$

$$F_{visc} = \frac{\partial \sigma_{visc}}{\partial x} = \mu \frac{\partial^2 U}{\partial x^2}$$

$$\sigma_{myo} = kM$$

$$F_{myo} = \frac{\partial \sigma_{myo}}{\partial x} = k \frac{\partial M}{\partial x}$$

$$\mu \frac{\partial^2 U}{\partial x^2} + k \frac{\partial M}{\partial x} - \zeta U = 0$$

$$\frac{\partial U}{\partial T} = \frac{1}{\varepsilon} \left[\mu \frac{\partial^2 U}{\partial X^2} + k \frac{\partial M}{\partial X} - \xi U \right]$$

viscous stress
in actin network
myosin con-
tractile stress
adhesion
viscous drag

$$\frac{\partial M}{\partial T} = D \frac{\partial^2 M}{\partial X^2} - \frac{\partial}{\partial X} (UM)$$

myosin diffusion
myosin drift with actin flow

1/eps term is there because velocity is supposed to adjust to a steady state very fast

$$\frac{\partial U}{\partial T} = \frac{1}{\varepsilon} \left[\mu \frac{\partial^2 U}{\partial X^2} + k \frac{\partial M}{\partial X} - \xi U \right]$$

viscous stress in actin network myosin contractile stress adhesion viscous drag

$$\frac{\partial M}{\partial T} = D \frac{\partial^2 M}{\partial X^2} - \frac{\partial}{\partial X} (UM)$$

myosin diffusion myosin drift with actin flow

$1/\zeta$ - time scale

$L = \sqrt{A}$ - spatial scale (A is target area of the cell, so L is cell size)

\bar{M} - myosin density scale (average myosin density which is conserved)

ζL - scale of velocity

$$\varepsilon \frac{\partial u}{\partial t} = \gamma \frac{\partial^2 u}{\partial x^2} + \beta \frac{\partial m}{\partial x} - \mu$$

viscous stress
in actin network myosin con-
tractile stress adhesion
viscous drag

$$\frac{\partial m}{\partial t} = \alpha \frac{\partial^2 m}{\partial x^2} - \frac{\partial}{\partial x}(um)$$

myosin diffusion myosin drift with actin flow

$$\gamma = \frac{\mu}{\zeta L^2}, \alpha = \frac{D}{\zeta L^2}, \beta = \frac{k\bar{M}}{\zeta^2 L^2}$$

Let us try simplest boundary conditions on $[-1, 1]$: $u(-1)=u(1)=0$. (For m , always no flux b.c.)

For now, the cell is not moving.)

$$u = 0$$

- Steady state. Stable?

$$m = 1$$

Linear stability analysis

$$u = 0 + u$$

$$m = 1 + p$$

$$\varepsilon \frac{\partial u}{\partial t} = \gamma \frac{\partial^2 u}{\partial x^2} + \beta \frac{\partial p}{\partial x} - u$$

$$\frac{\partial p}{\partial t} = \alpha \frac{\partial^2 p}{\partial x^2} - \frac{\partial}{\partial x} (u(1+p))$$

$$\varepsilon\,\frac{\partial u}{\partial t}=\gamma\,\frac{\partial^2 u}{\partial x^2}+\beta\,\frac{\partial p}{\partial x}-u$$

$$\frac{\partial p}{\partial t}=\alpha\,\frac{\partial^2 p}{\partial x^2}-\frac{\partial u}{\partial x}$$

$$u=u_0e^{\lambda t}e^{iqx}$$

$$p=p_0e^{\lambda t}e^{iqx}$$

$$\varepsilon \lambda u_0=-\gamma\,q^2u_0+\beta\,iqp_0-u_0$$

$$\lambda\,p_0=-\alpha\,q^2\,p_0-iq u_0$$

The first mode to break stability corresponds to $q = \pi/2$, so the criterion for instability is:

$$(\beta - \alpha)q^2 - \alpha\gamma q^4 > 0$$

$$\beta > \alpha \left(1 + (\pi/2)^2 \gamma \right)$$

$$k\bar{M} > D\xi \left(1 + \left(\frac{\pi}{2} \right)^2 \frac{\mu}{\xi L^2} \right) \quad \frac{k\bar{M}}{D} > \xi + \left(\frac{\pi}{2L} \right)^2 \mu$$

Two interesting limiting cases: 1) if zeta is big enough, then mu has to be very small, and

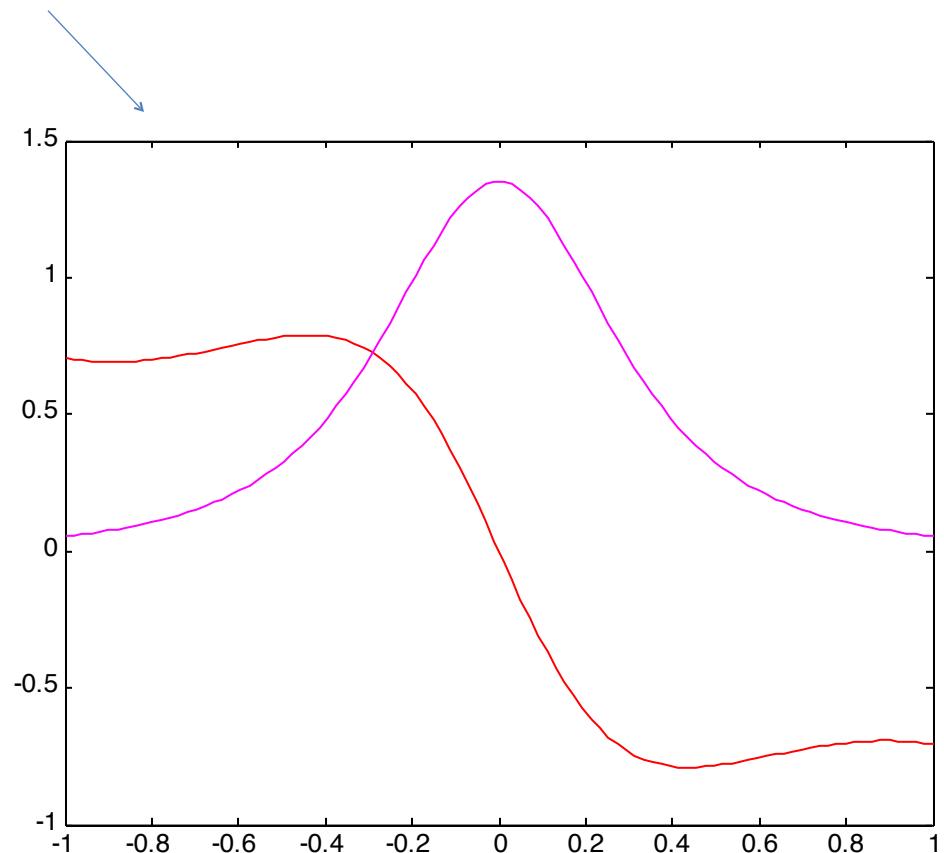
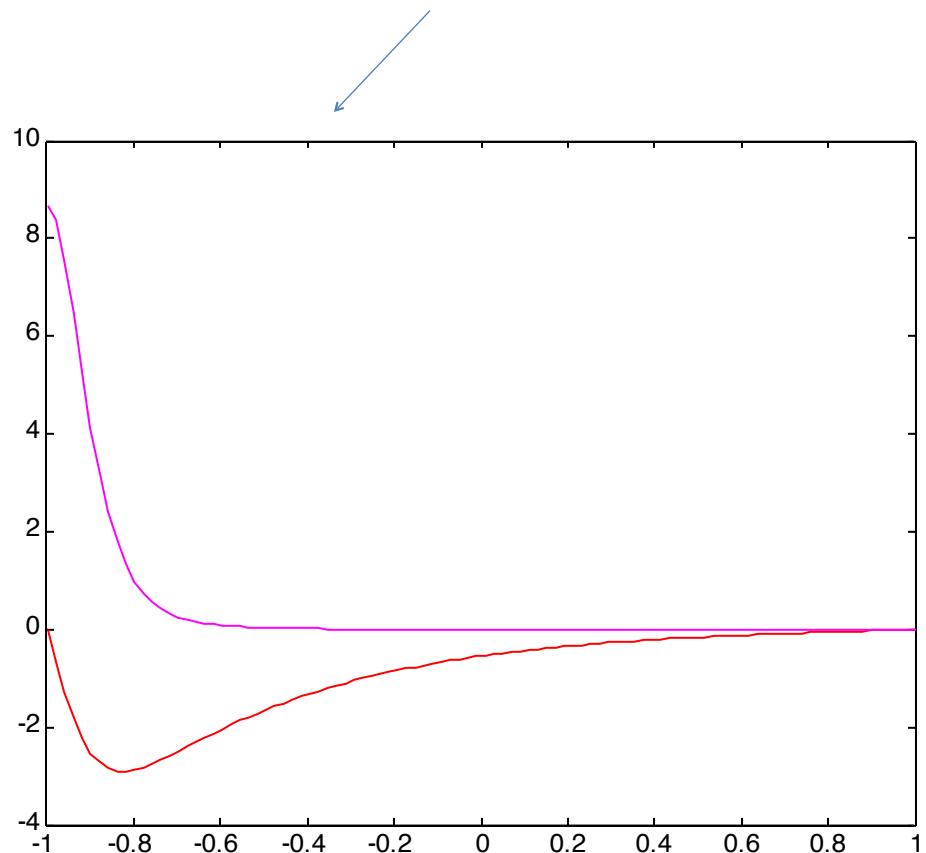
$$k\bar{M} > D\xi$$

2) if D is very small and zeta is moderate, as is usually the case, then the 2nd term in the bracket is much greater than 1, and

$$k\bar{M}L^2 > \pi^2 D \mu / 4$$

I solved the system numerically in 1D, and found that numerics completely confirms the linear stability analysis. Also, note the following interesting dependence on $b.c$.

B.C. for velocity: 1) $U = 0$ at the boundary 2) no flux at the boundary



Why the difference?

<http://www.youtube.com/watch?v=JnIULOjUhSQ>

Neutrophil fans' comments:

hehe, funny.. GO WHITE CELL!

god dam the white blood cell dont give up easy

lol get the wee buggers

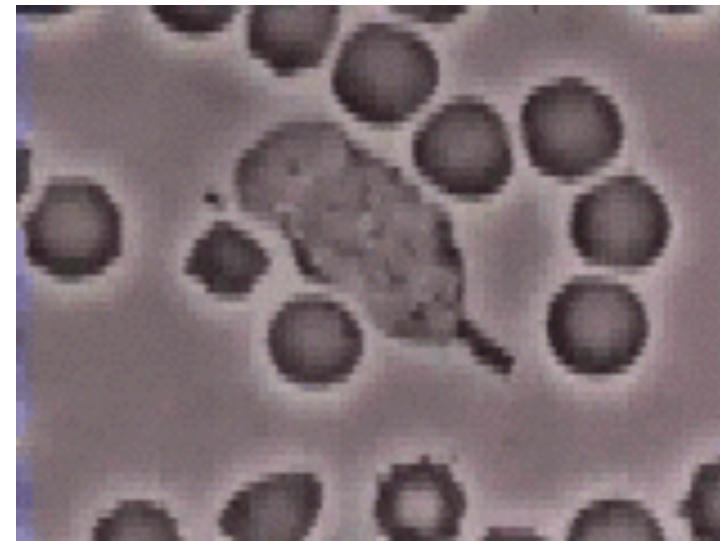
thats right bitch thats our immune system

haha..haha...get em.get em!

IMMUNE SYSTEM FOR THE WIN BITCH!!!

and dont you ever come in my body BITCH!!!!

YEAH YOU BETTER RUN YOU LITTLE BITCH



Bacteria fans' comments:

noooooooooo poor bacteria

Serious thoughtful scientific comments:

If two white cells are near one bacteria, do they fight over each other to eat that bacteria?

there are 7000 to 25000 of these white blood cells blob monsters in each drop of my blood.... I am invincible!

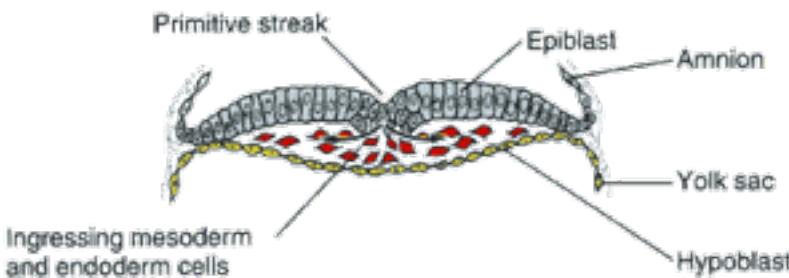
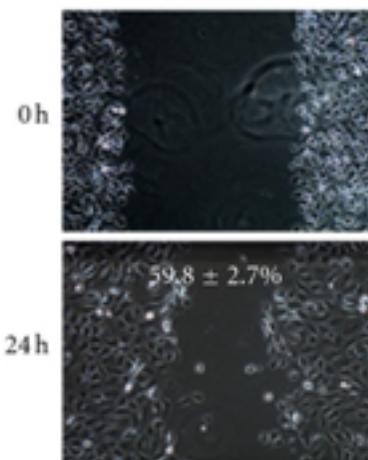
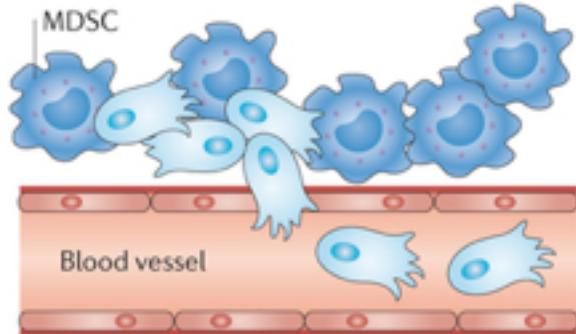
wow is this real!!! or is it made on a computer?

Deep social dialogue with an insight on hygiene:

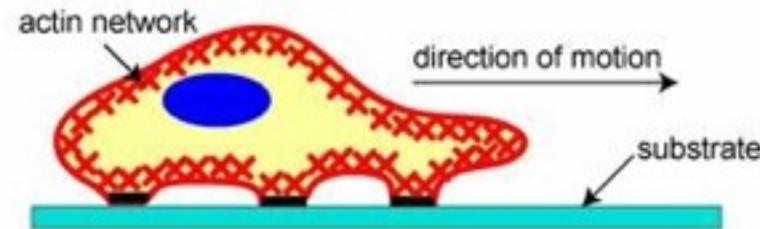
As a liberal I am offended by this video. The bacteria is obviously the minority and on top of that it's black. Then the big powerful WHITE blood cell comes along and strikes at the poor bacteria. Unable to defend itself the bacteria succumbs to whitey. We need to make a change. Wake up America! You say there is nothing 'you' can do, well that just isn't true. Simply stop washing your hands and taking showers regularly, then these poor bacteria may have a fighting chance.

The bacteria is YELLOW, not black, dumbass!

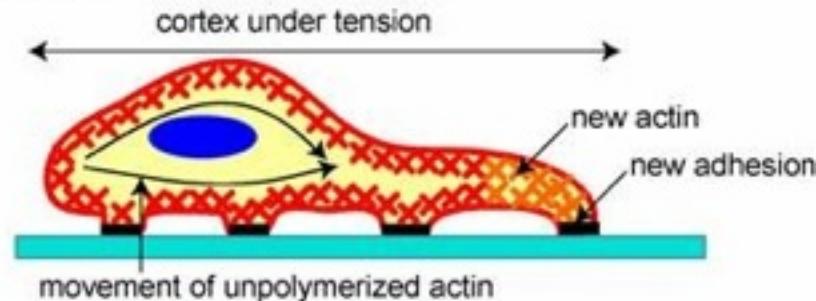
Invasion and intravasation



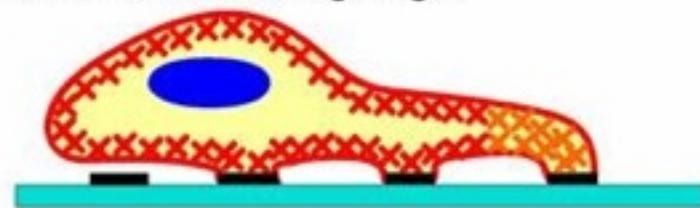
1) Protrusion of the Leading Edge



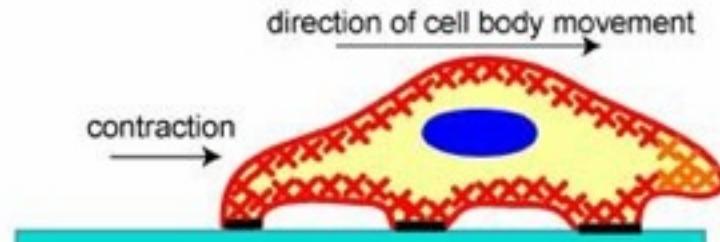
2) Adhesion at the Leading Edge



Deadhesion at the Trailing Edge



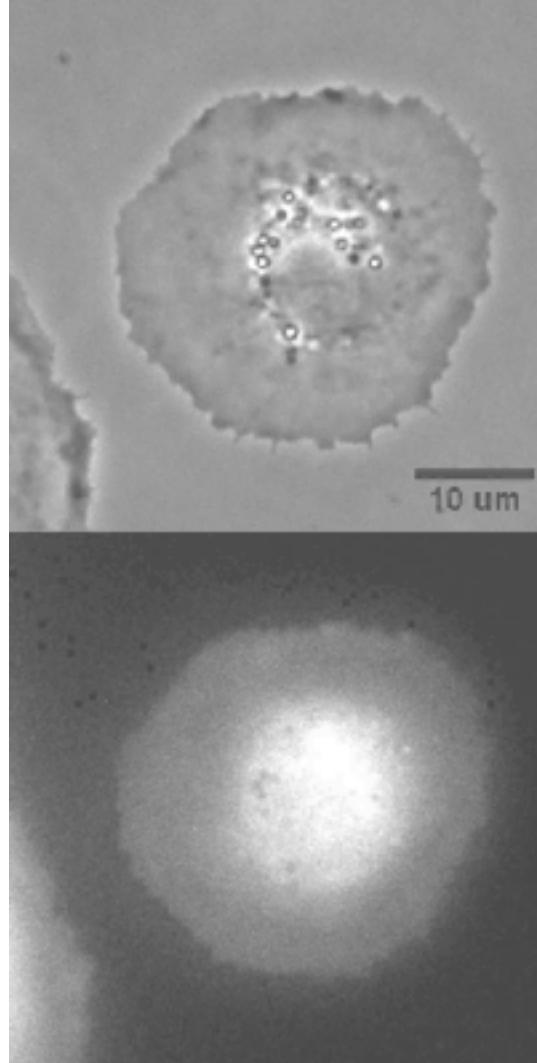
3) Movement of the Cell Body



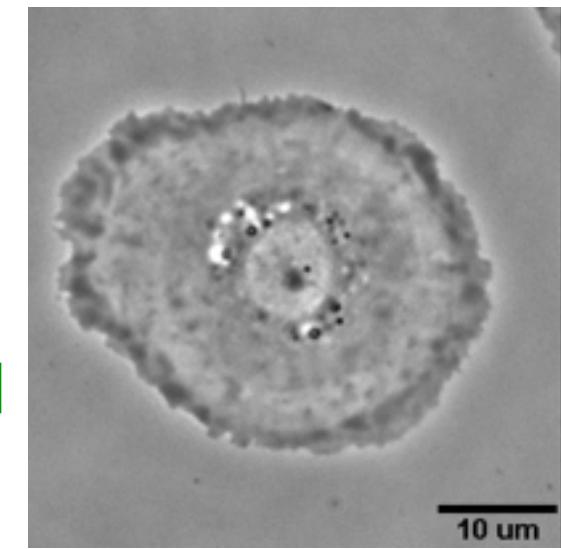
Polarization (symmetry breaking) and motility initiation

Movie: Yam, Theriot et al

Motile cells-
fan-shaped lamellipodium
with cell body at the back



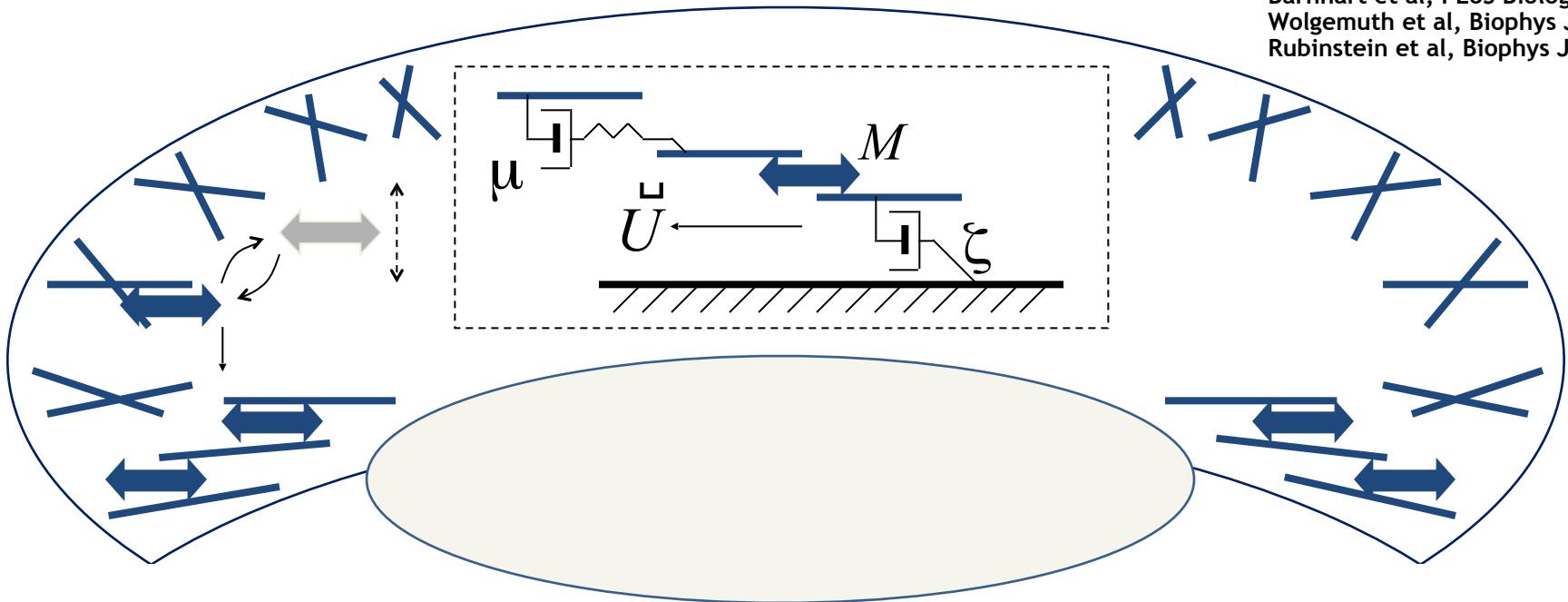
Stationary cells-
circular lamellipodium with
cell body at the center



Spontaneous
transition

Mechanical model of contractile viscous actin gel

Barnhart et al, PNAS (2015)
 Barnhart et al, PLoS Biology (2011)
 Wolgemuth et al, Biophys J (2011)
 Rubinstein et al, Biophys J (2009)



$$\mu \nabla^2 U + k \nabla M = \zeta U$$

viscous stress in actin network myosin contractile stress adhesion viscous drag

$$T = \zeta U$$

traction stress

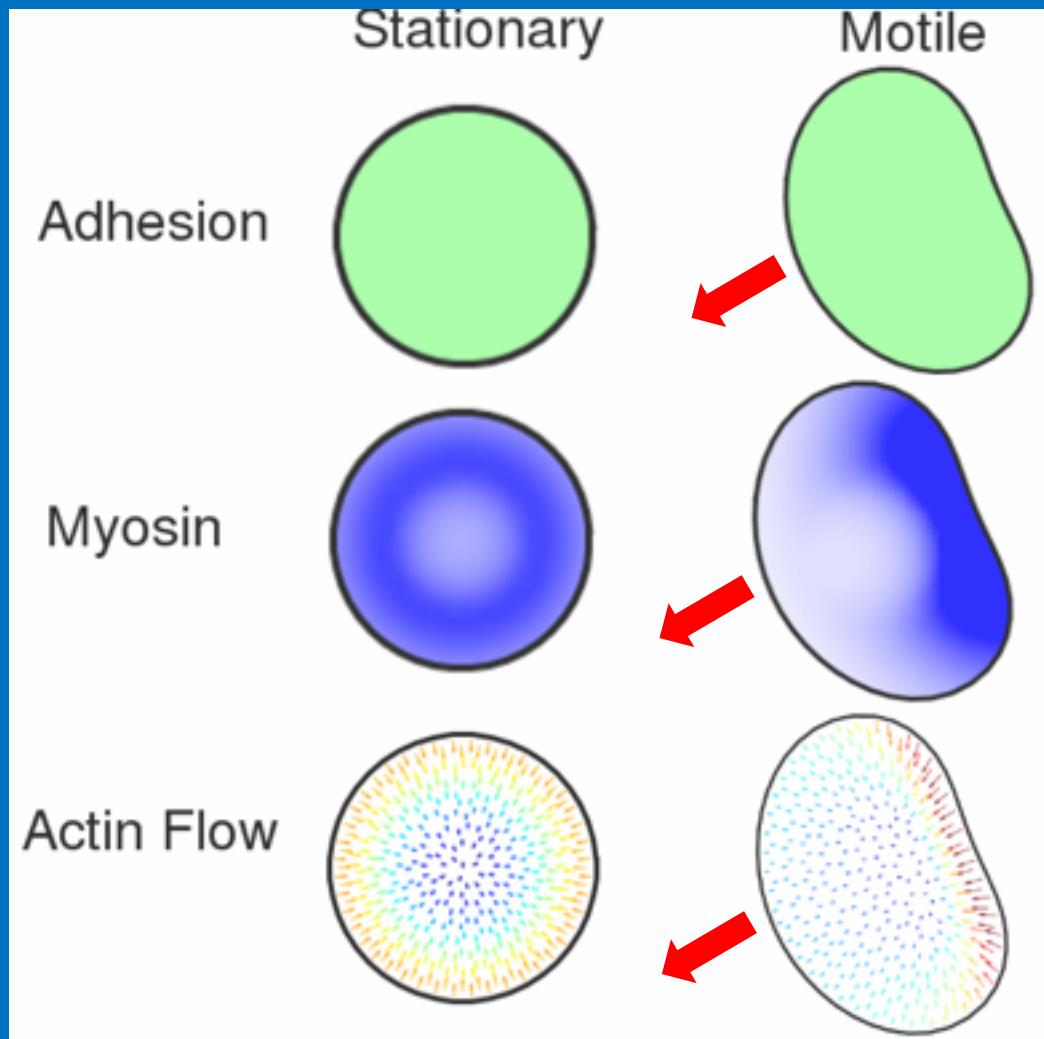
$$\frac{\partial M}{\partial t} = D \nabla^2 M - \nabla \cdot (U M)$$

myosin diffusion myosin drift with actin flow

actin flow
 myosin

The model predicts the myosin and flow distributions

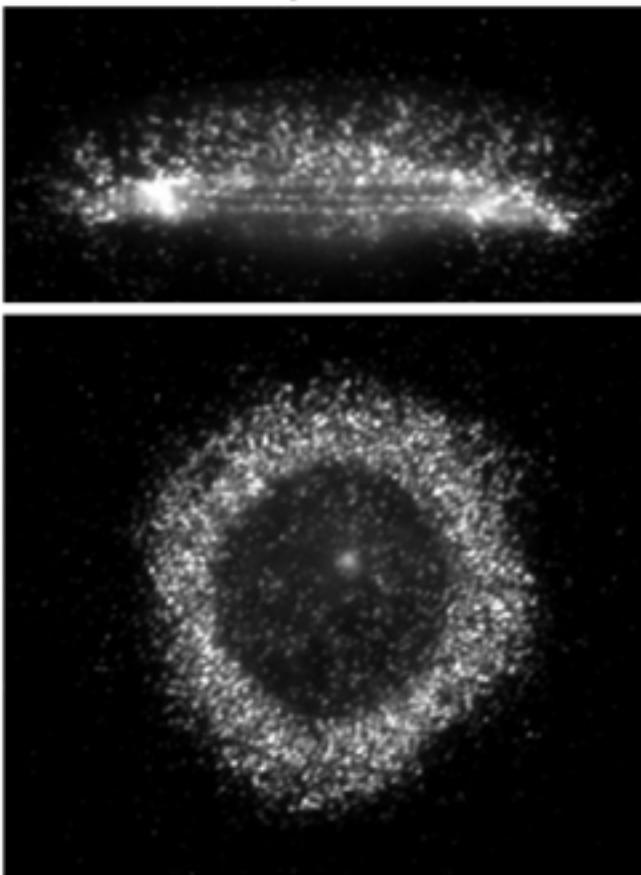
Barnhart et al, PNAS (2015)



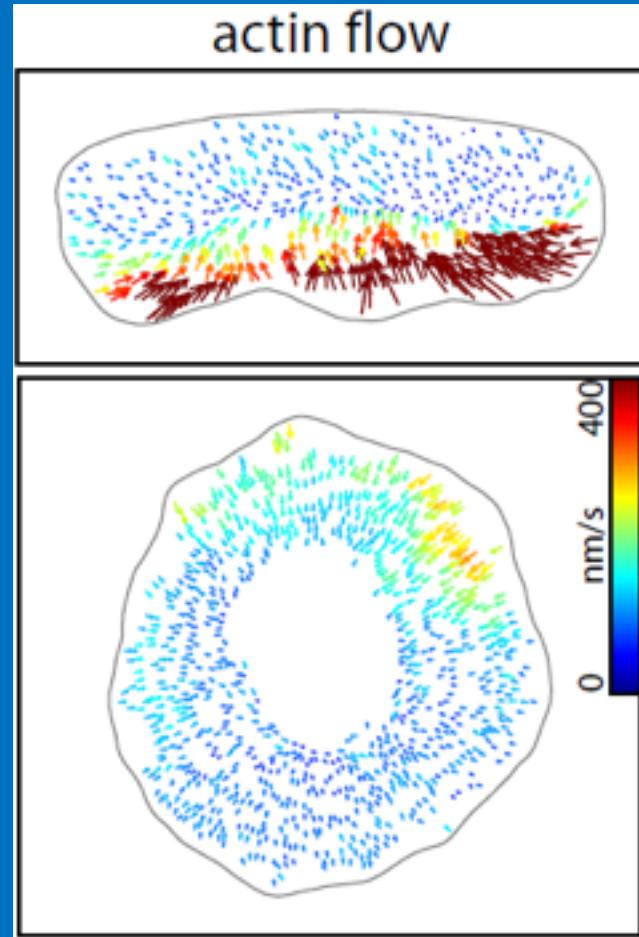
Distributions of flow and myosin in motile and stationary cells

Barnhart et al, PNAS (2015)

myosin

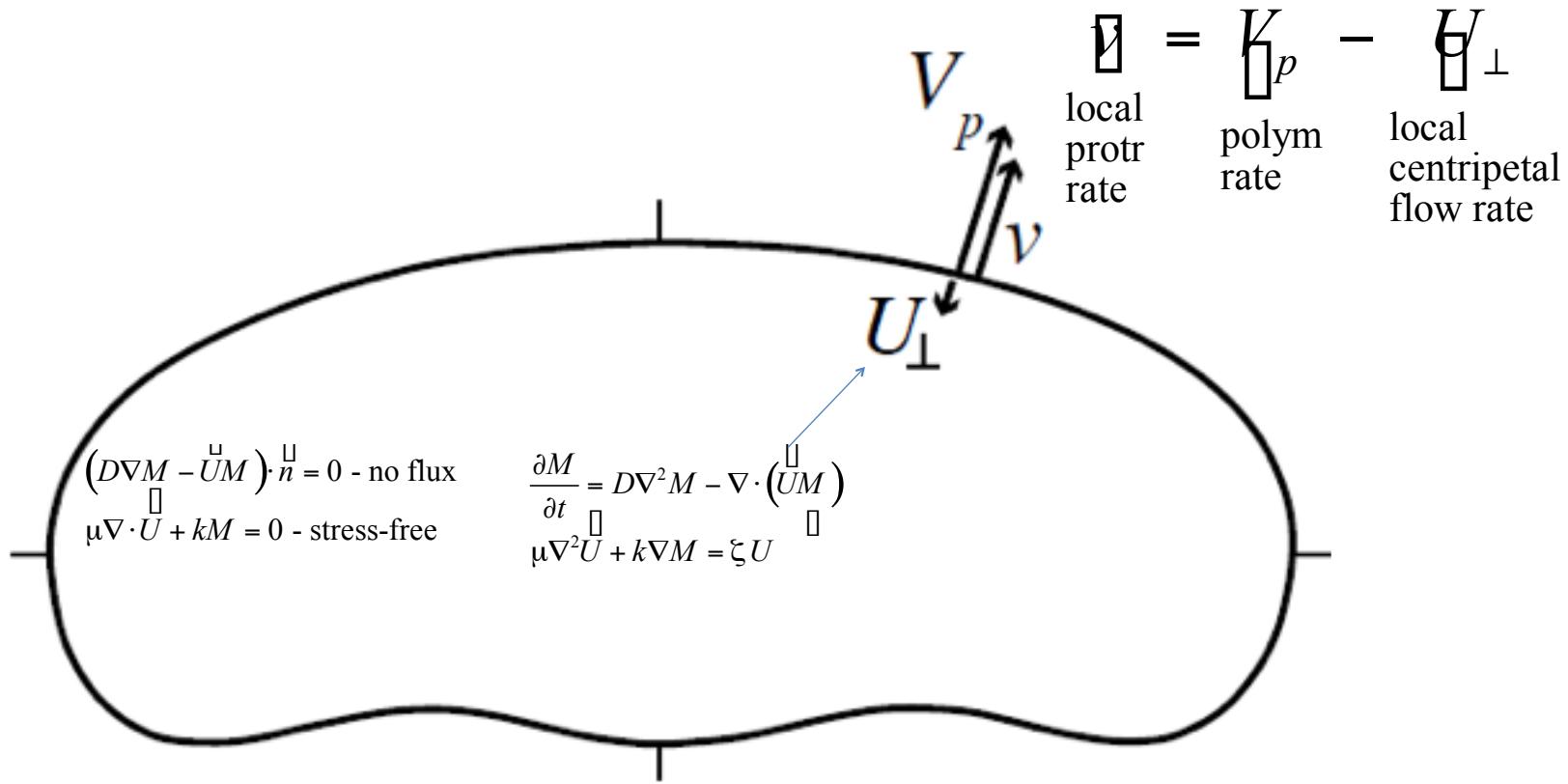


actin flow



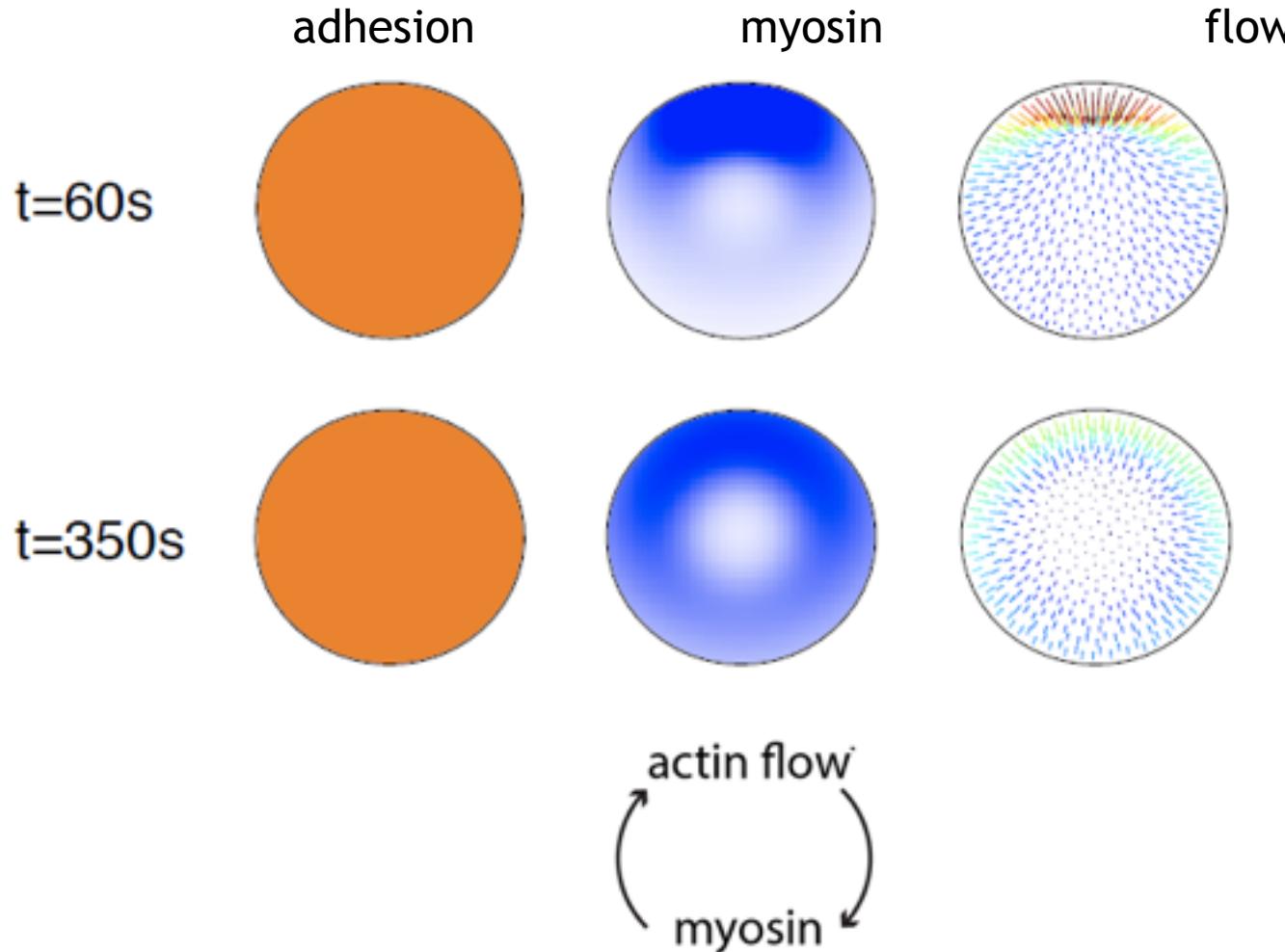
Free-boundary simulations

Barnhart et al, PNAS (2015)



The model suggests that <actin flow – myosin>
feedback alone is sufficient for polarization in principle
but alone is not enough

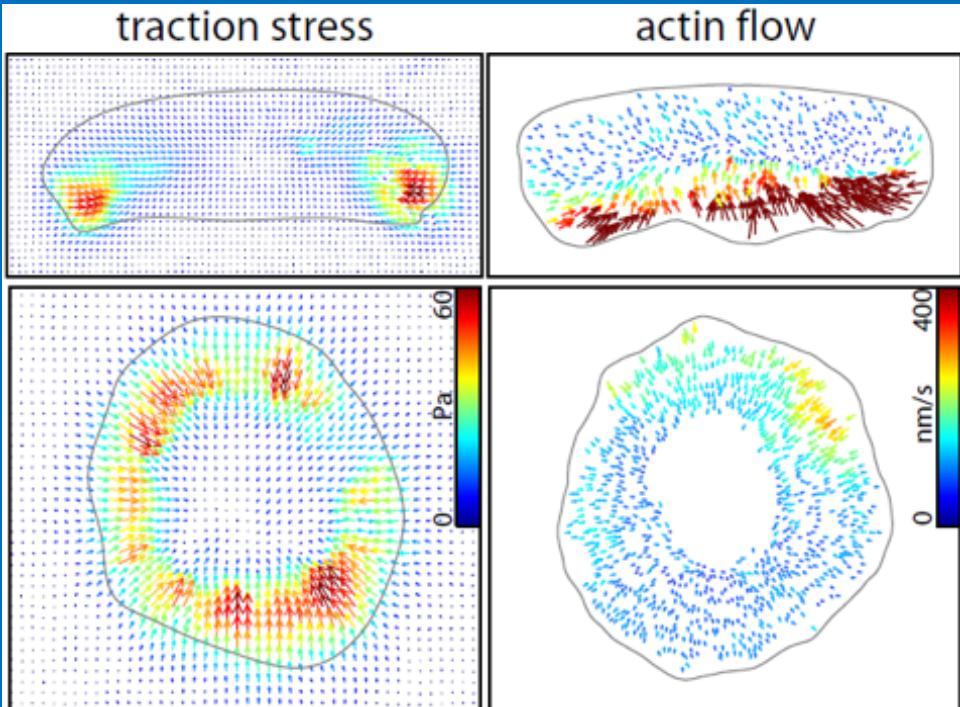
Barnhart et al, PNAS (2015)



Adhesion is stronger in stationary cells and is not uniform across the cell

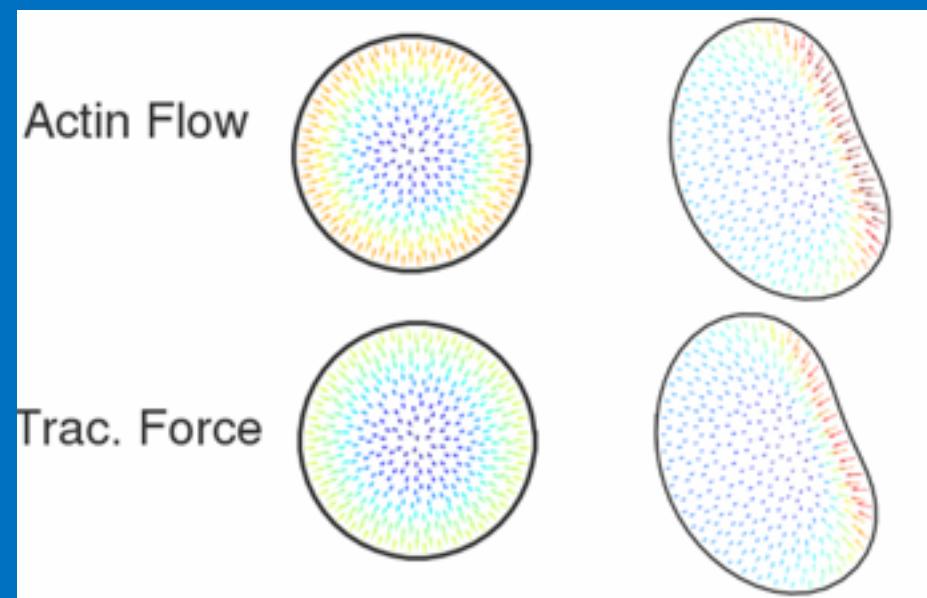
Barnhart et al, PNAS (2015)

Low traction --- Fast flow



$$\overline{T} = \zeta \times \overline{U}$$

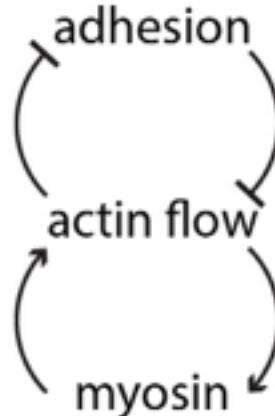
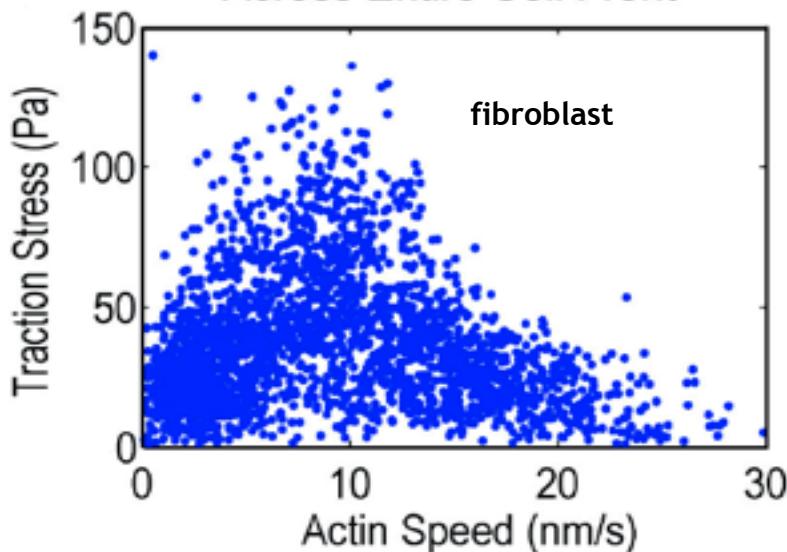
traction adhesion flow



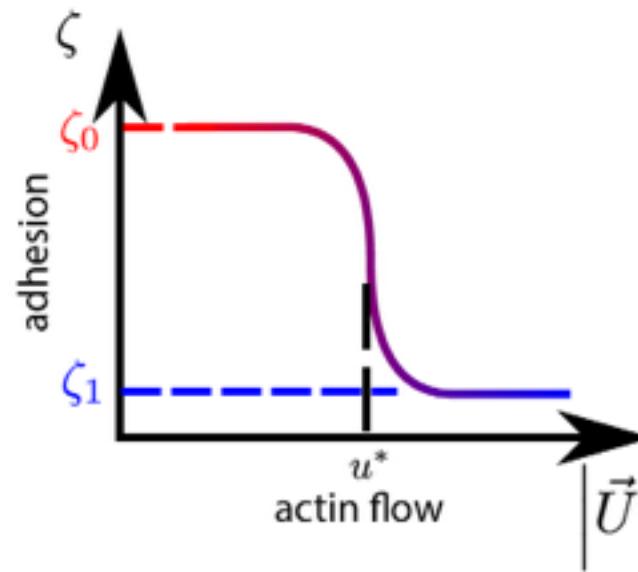
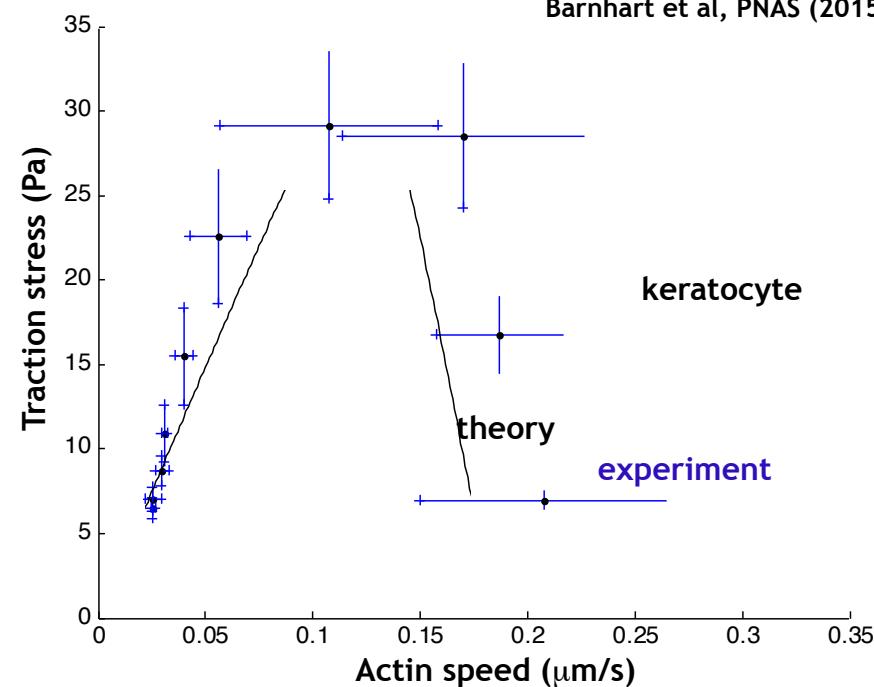
Hypothesis: negative feedback between actin flow and adhesion

Gardel, Waterman-Storer et al

Across Entire Cell Front

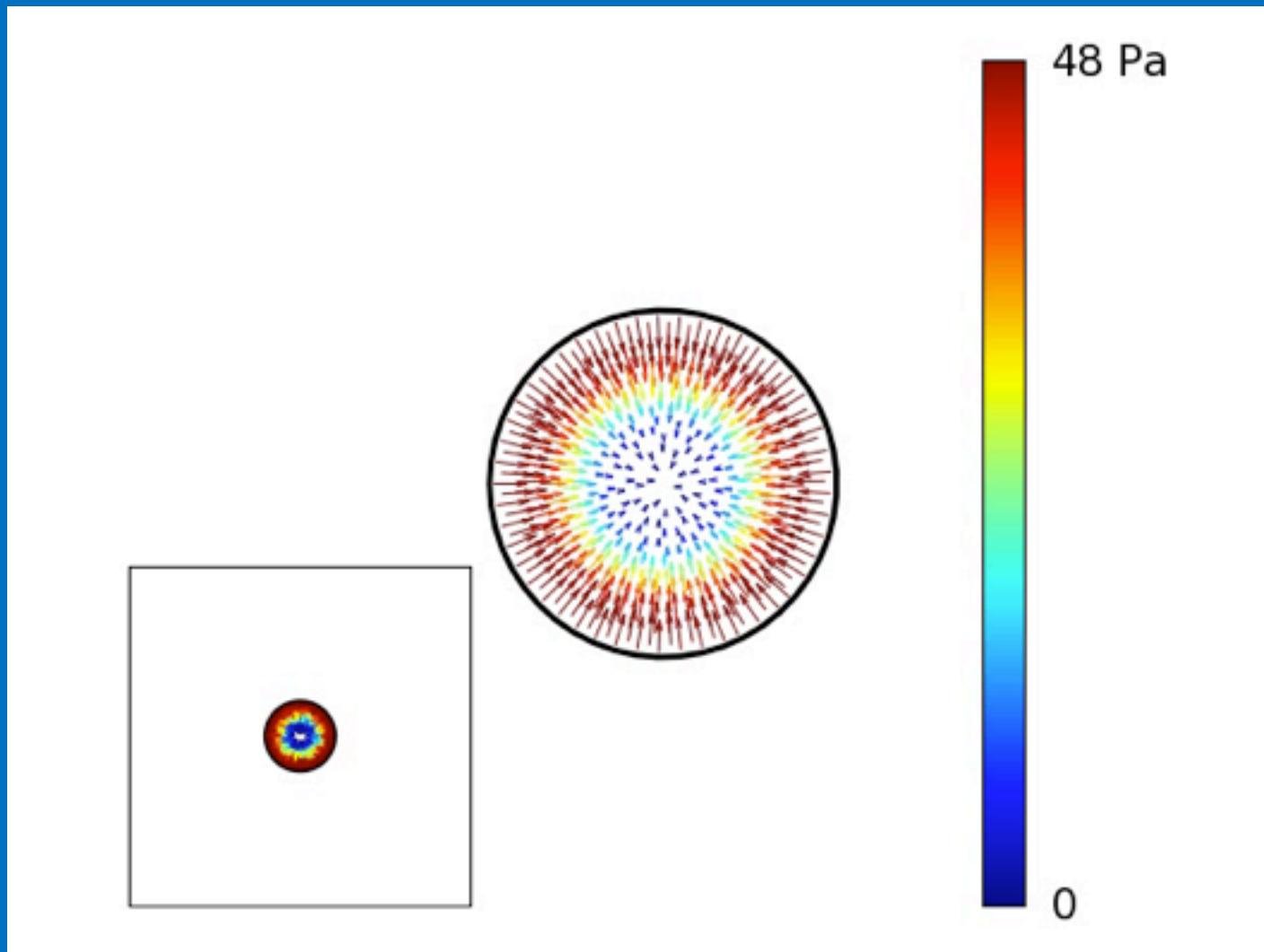


Barnhart et al, PNAS (2015)

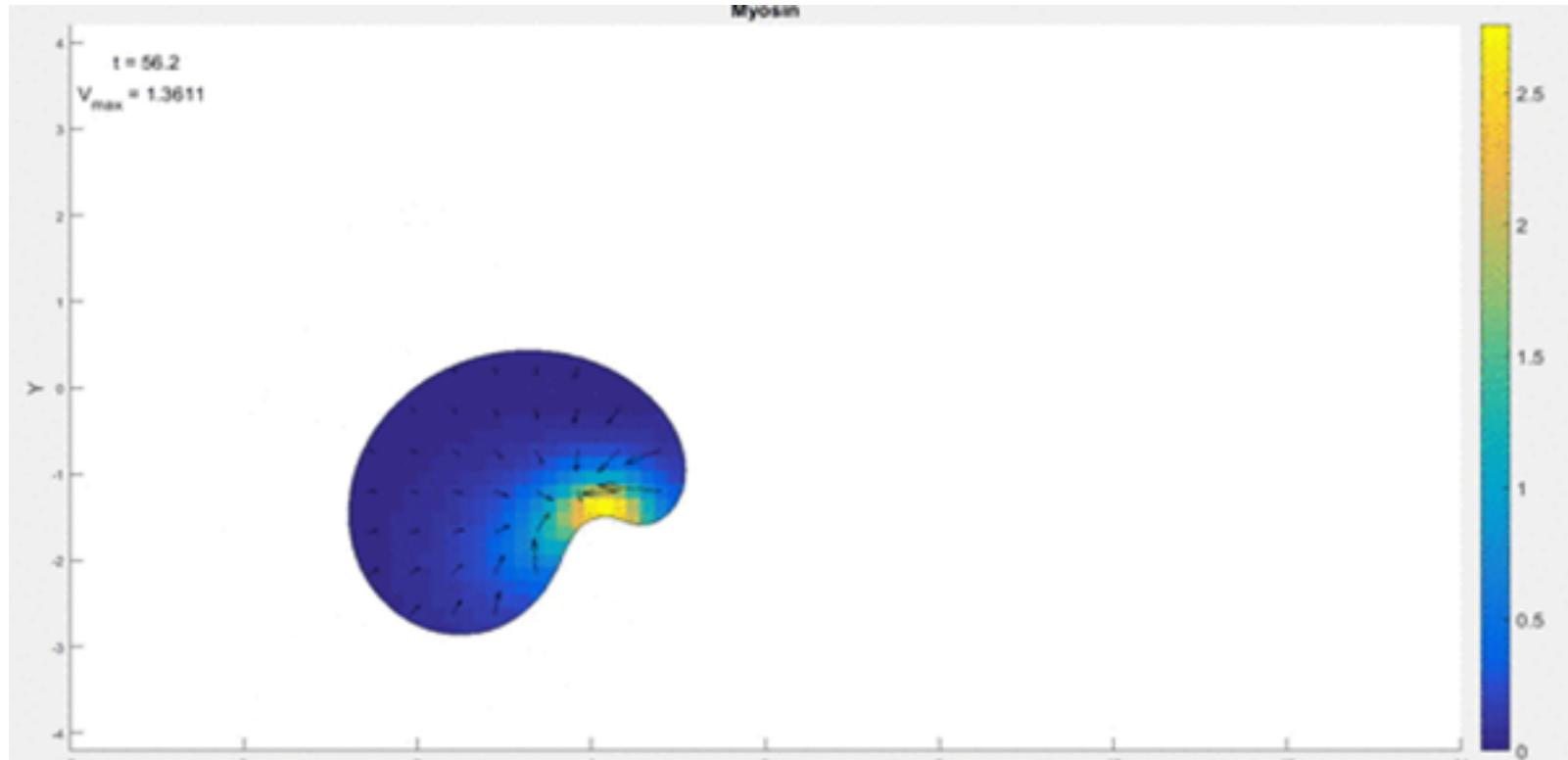


Free boundary simulation

Barnhart et al, PNAS (2015)

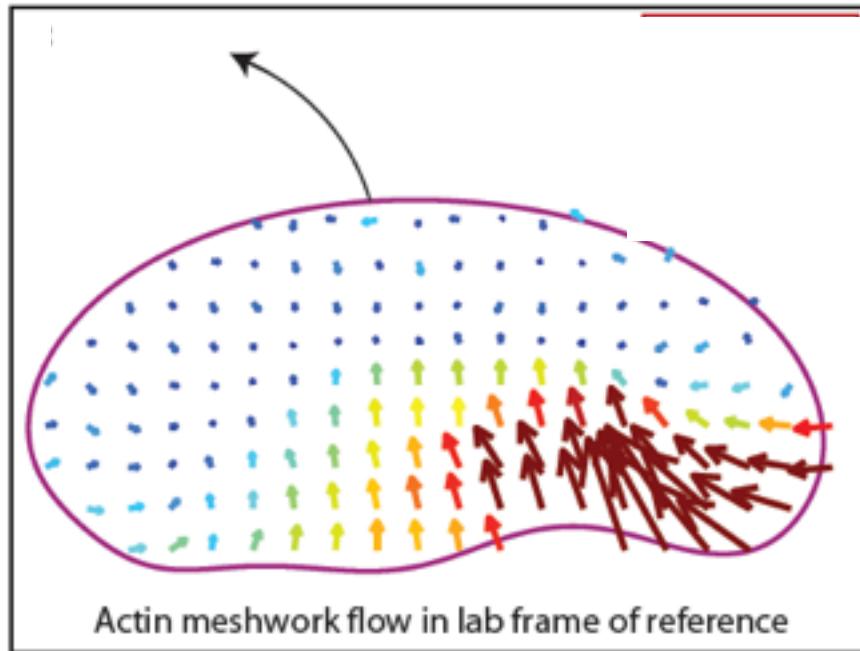
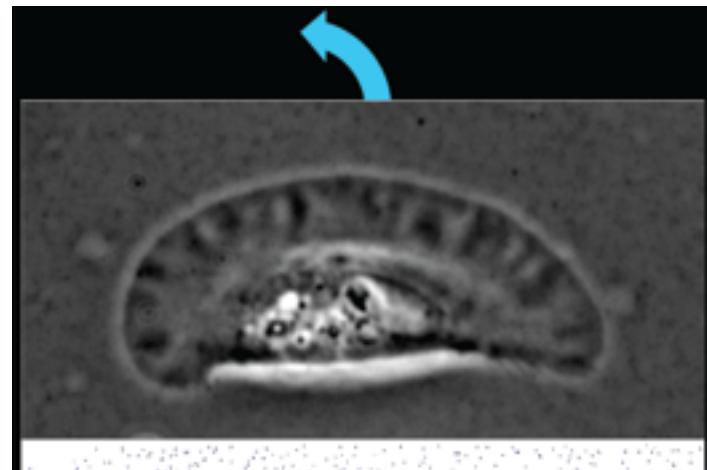
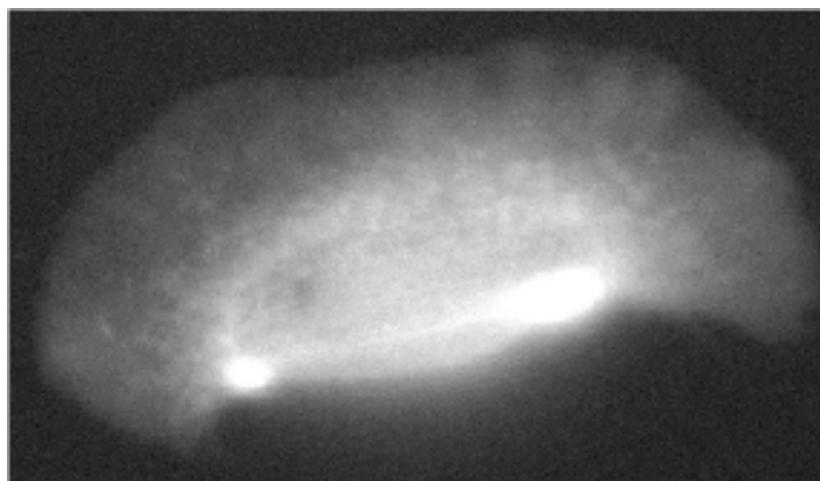


Rotation in the free boundary model



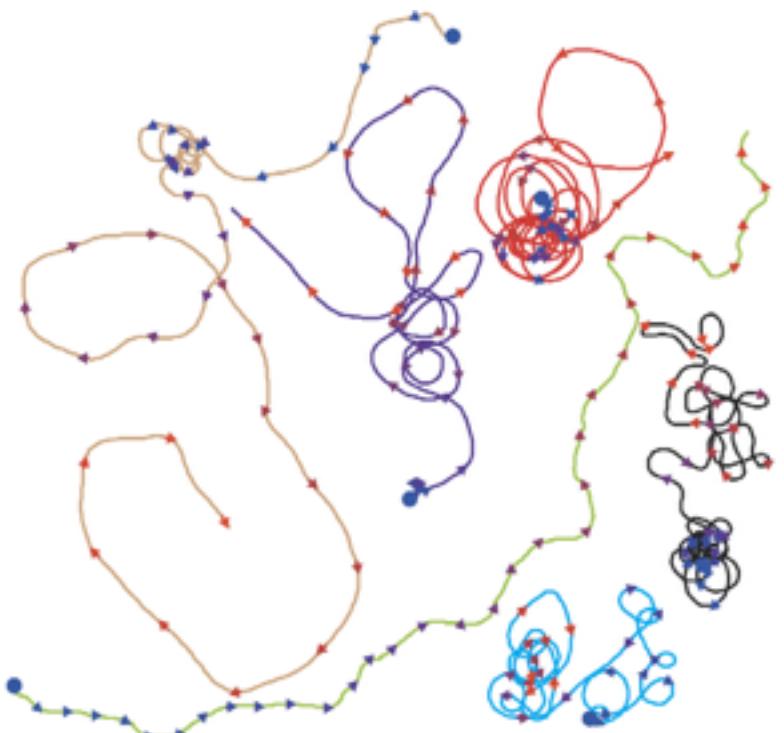
Key asymmetries in internal organization:

Allen et al, Submitted

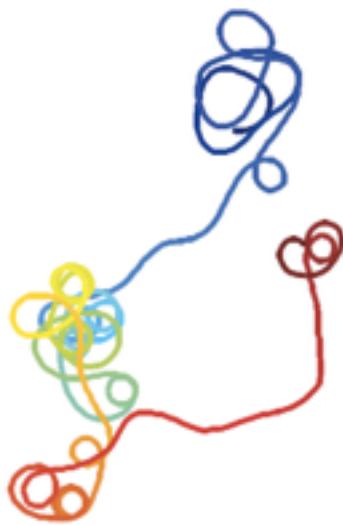


Myosin density and actin flow
are higher at the fast side,
but
traction forces are
higher at the slower side

Erin Barnhart



Experimental trajectories



Theoretical prediction