

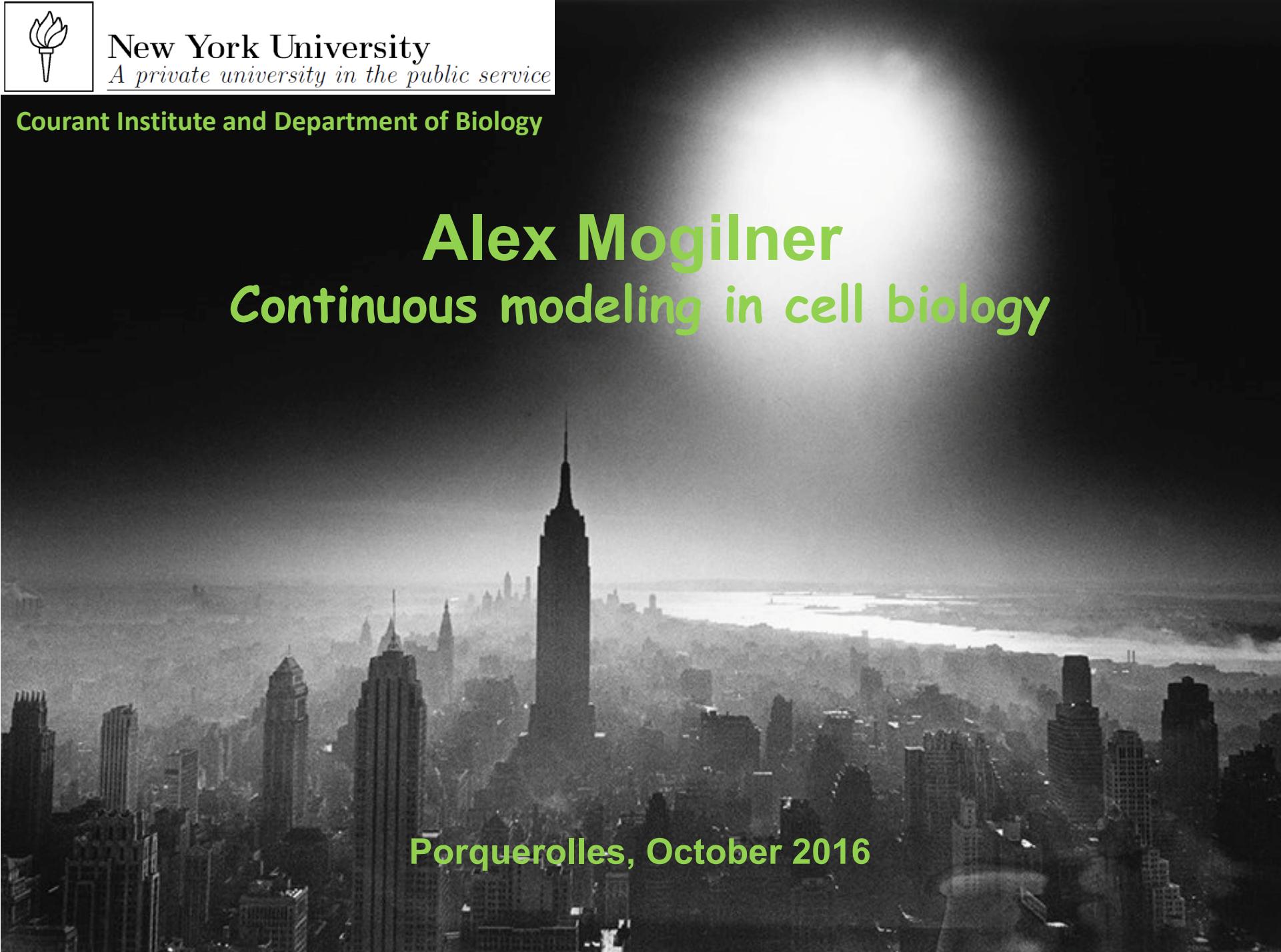


New York University
A private university in the public service

Courant 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

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

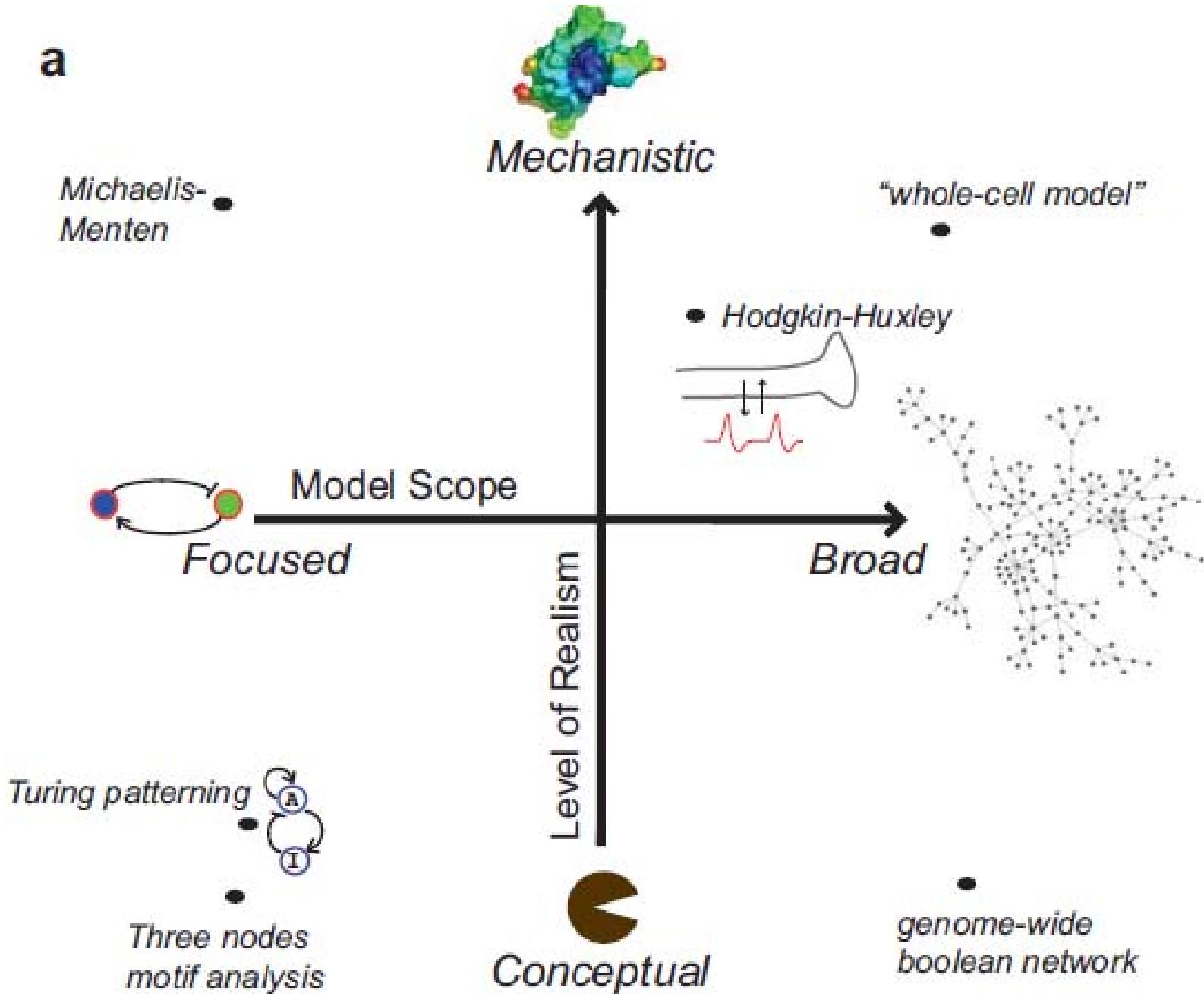
Increasingly Complex Generations of Models Can Be Used to Understand Cellular Networks as Systems

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

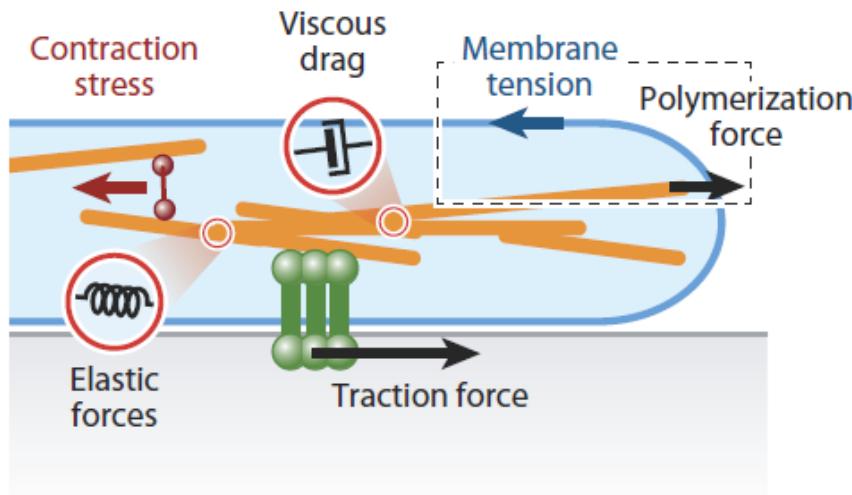
a



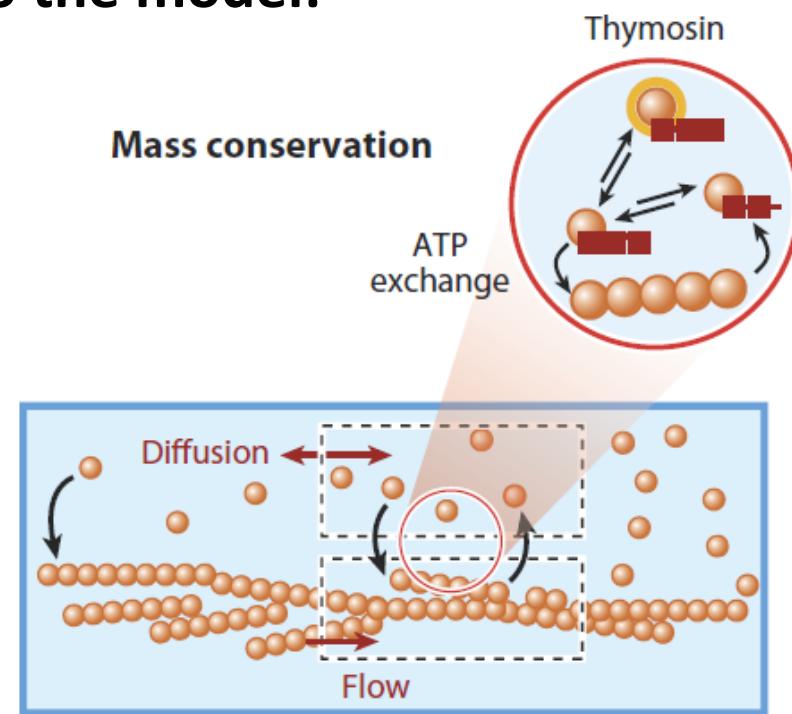
What goes into the model:

Physical principles

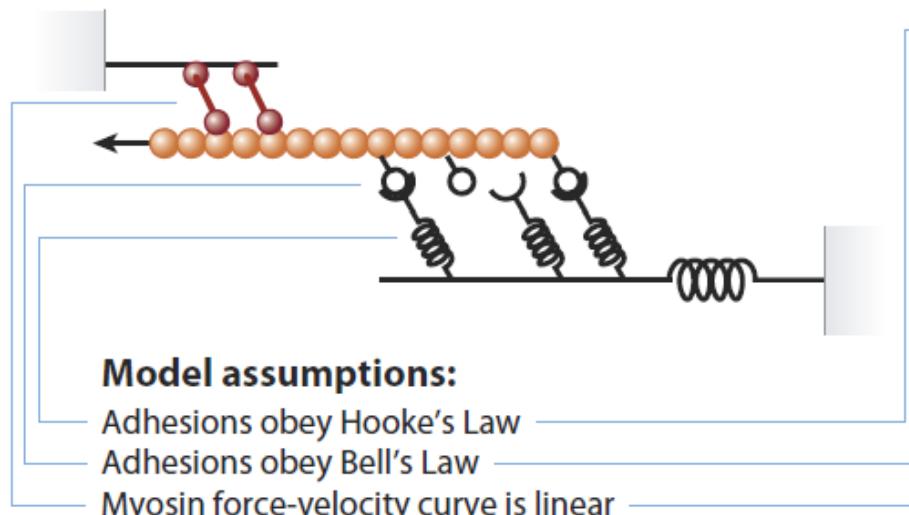
Force balance



Mass conservation



Actin slip clutch



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

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

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

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:

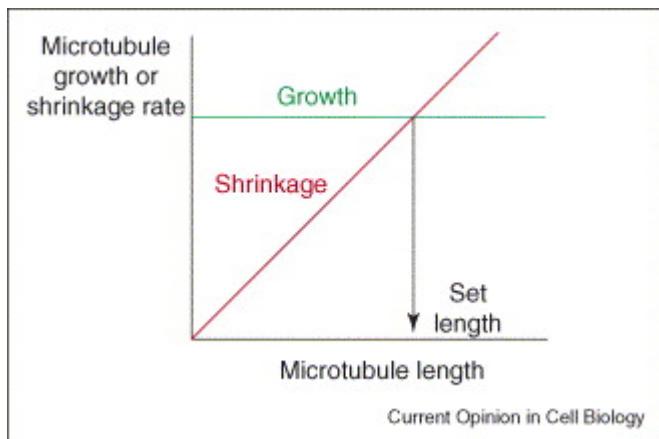
- a) For computer
- b) Insight
- c) To scan parameter space

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

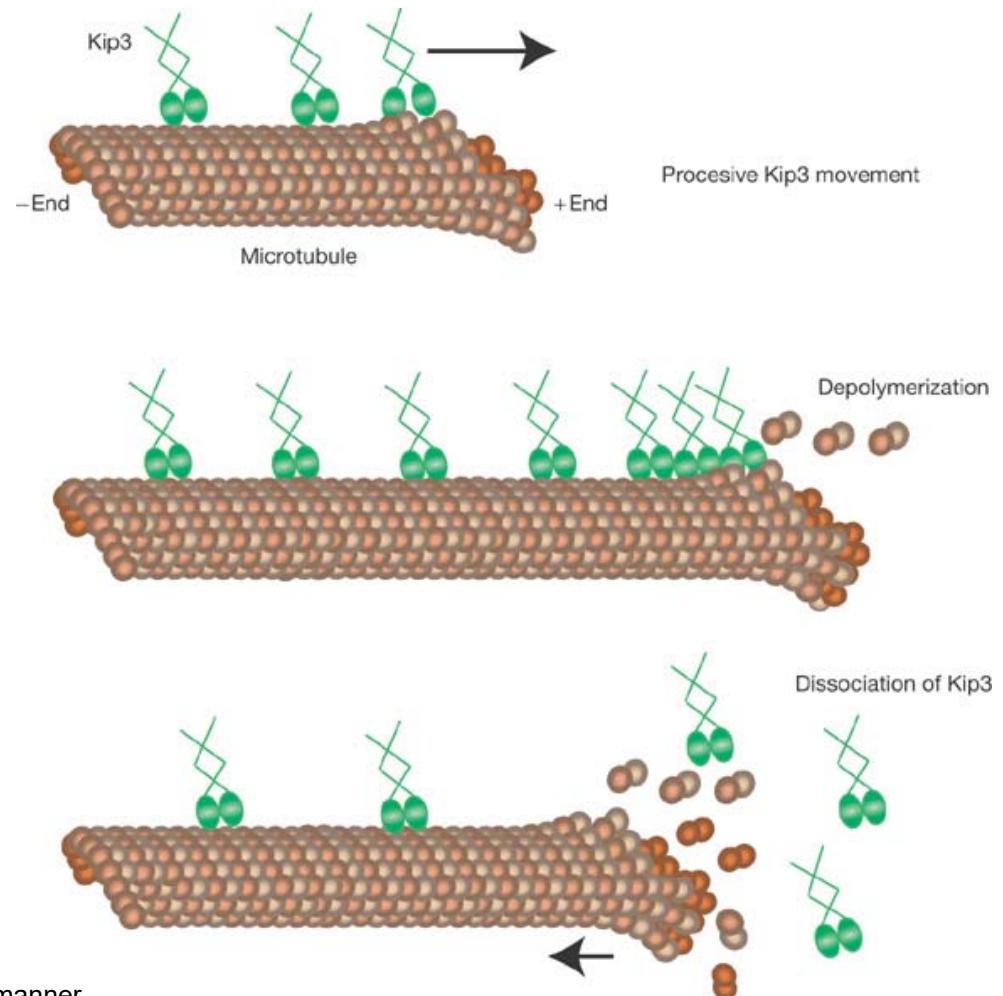
-
3. Non-dimensionalization. Substitute new variables into eqs and initial/boundary conditions.
 4. Think about the meaning of non-dimensional parameters.
 5. Solve, often using perturbation theory or numerical analysis.
 6. Go back to dimensional variables and thinking about biological meaning.

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?

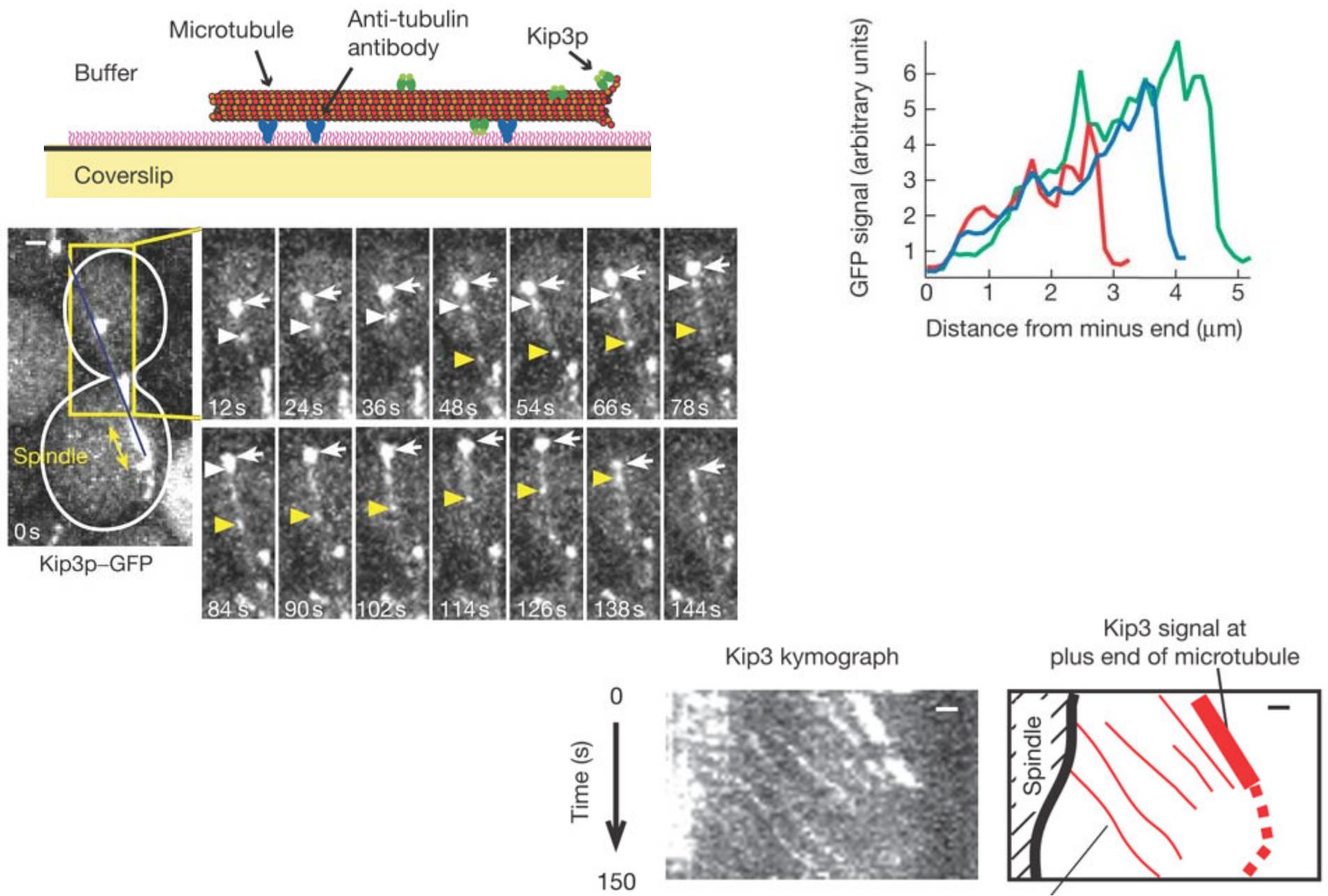


$$\frac{dL}{dt} = g - sL \rightarrow L = \frac{g}{s} (1 - e^{-st})$$

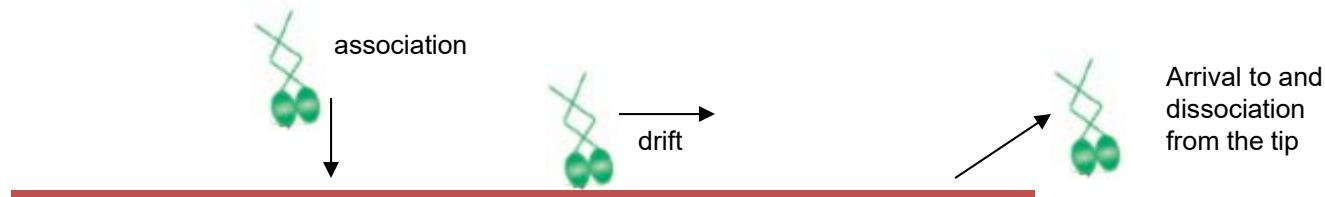


Varga V, Helenius J, Tanaka K, Hyman AA, Tanaka TU, Howard J.
 Yeast kinesin-8 depolymerizes microtubules in a length-dependent manner.
 Nat Cell Biol. 2006 Sep;8(9):957-62.

Experiment and observations of Varga et al:



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



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

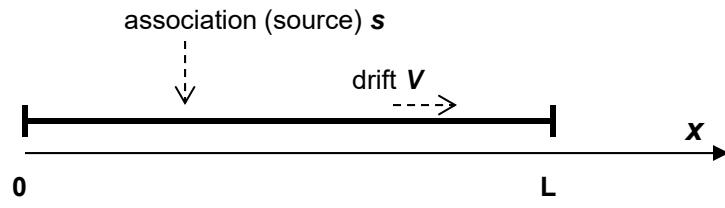
$$\frac{dC}{dt} = S$$
 - association equation

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

L – scale of length

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

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

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

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

$$x = X/L$$

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

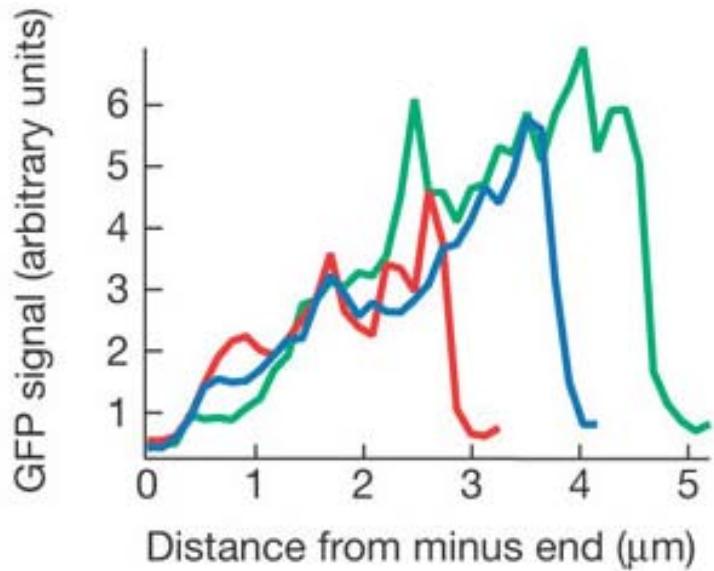
$$\frac{dc}{dx} = 1, 0 \leq x \leq 1 \quad \text{- no parameters!}$$

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

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

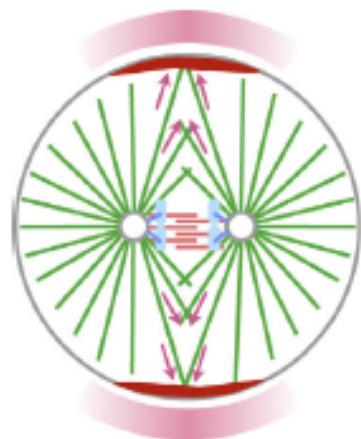
$$\frac{dc}{dx} = 1, 0 \leq x \leq 1, c(0) = 0$$



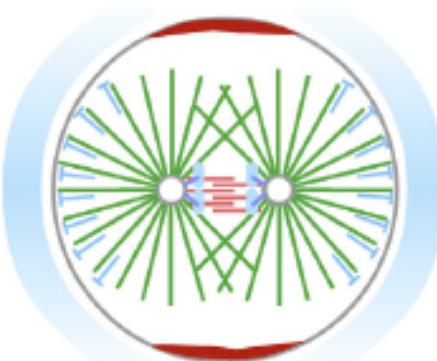
$$c = A + x \rightarrow c = x \rightarrow C = \frac{S}{V} X$$

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

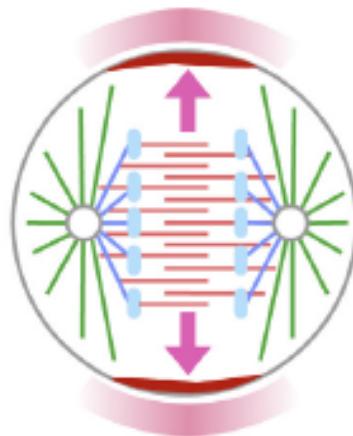
Astral stimulation



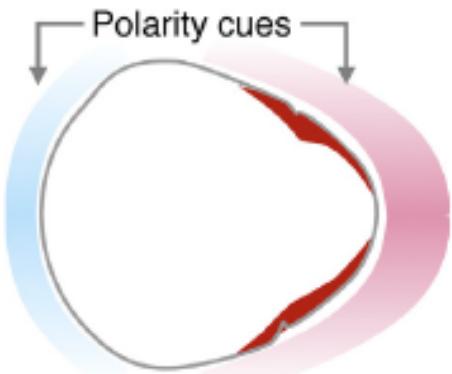
Polar relaxation



Central spindle



MA-independent



astral microtubule

kinetochore microtubule

central spindle microtubule
(spindle midzone microtubule)

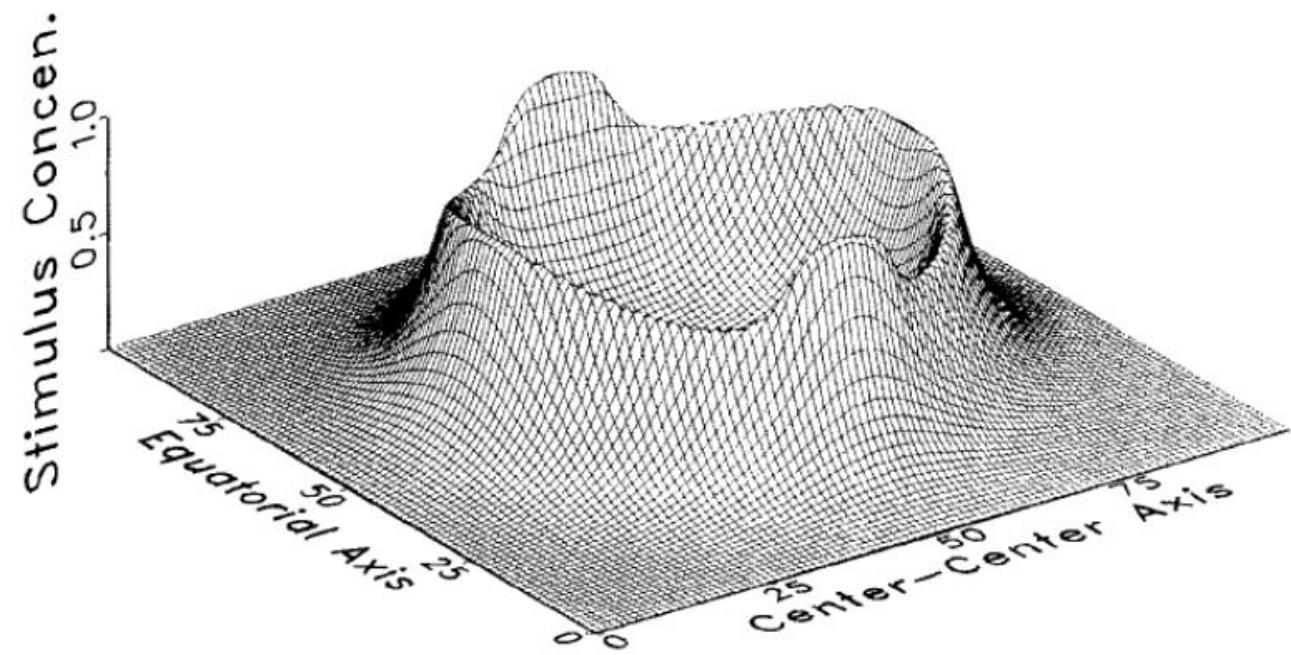
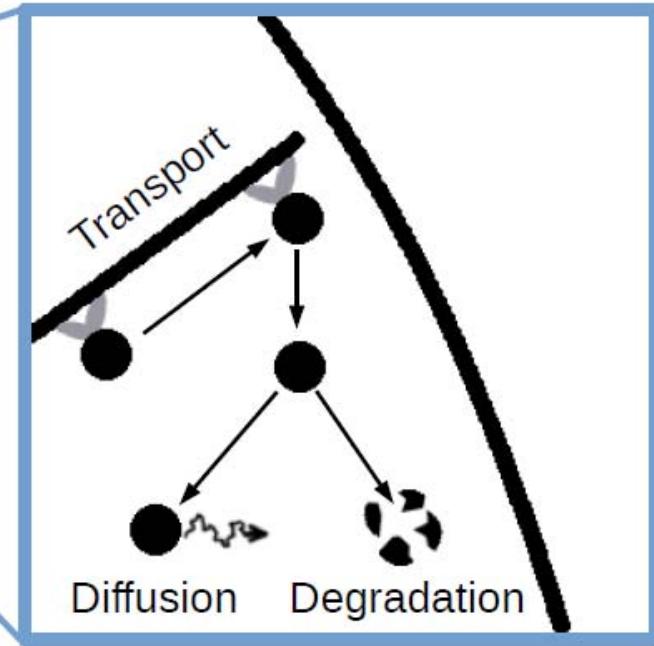
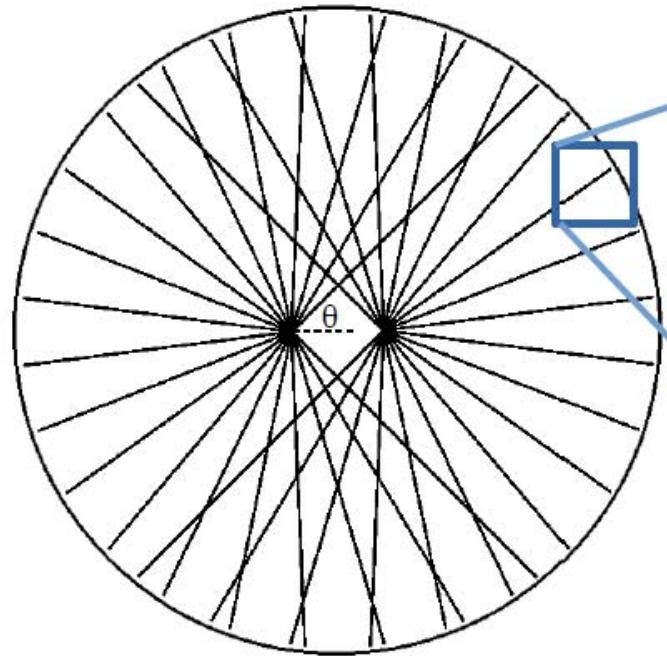
← stimulatory signal
↑ inhibitory signal

centrosome

chromosome

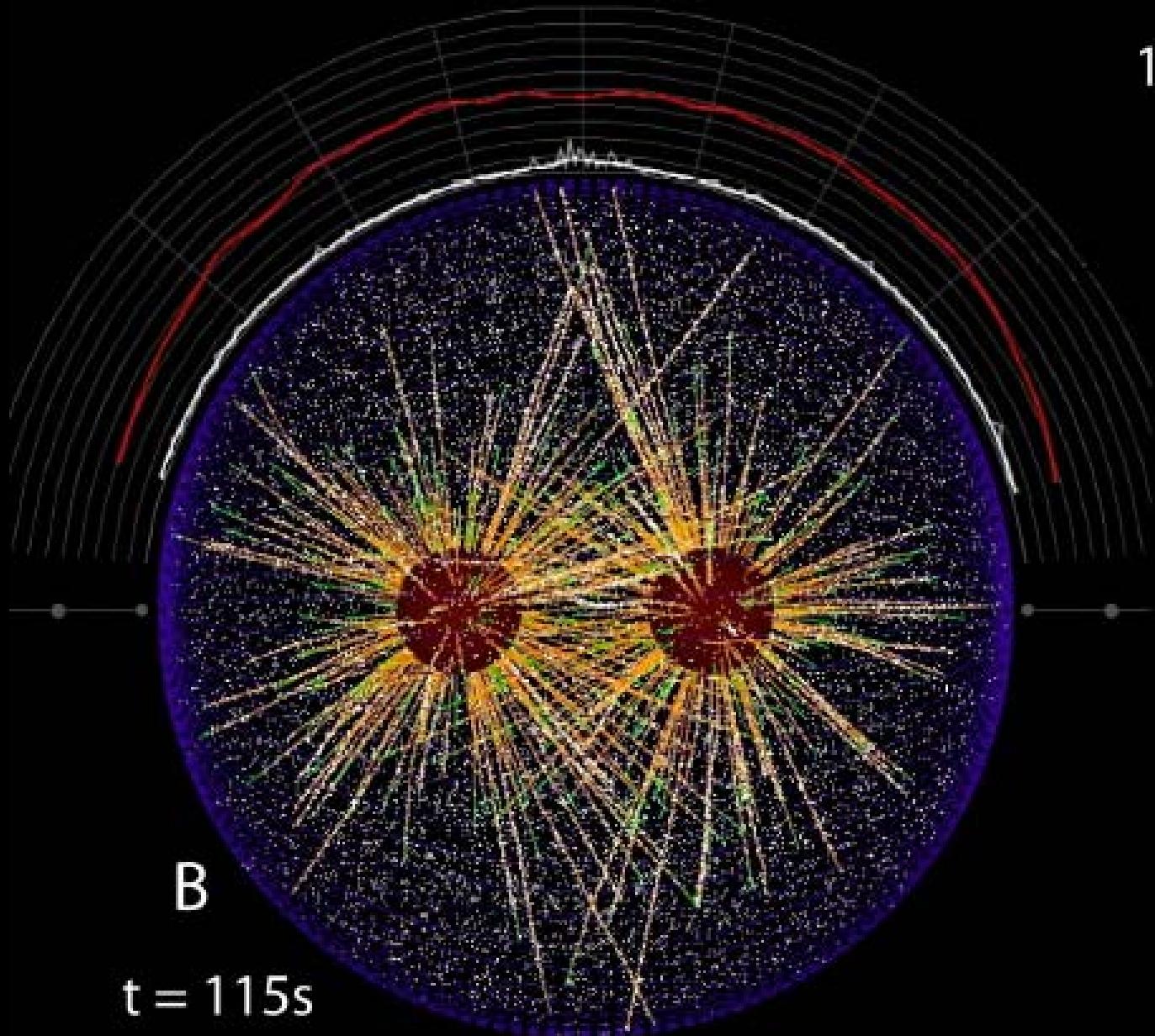
assembly of actomyosin network
(contractile ring)

net effect of the
signals at the cortex



10

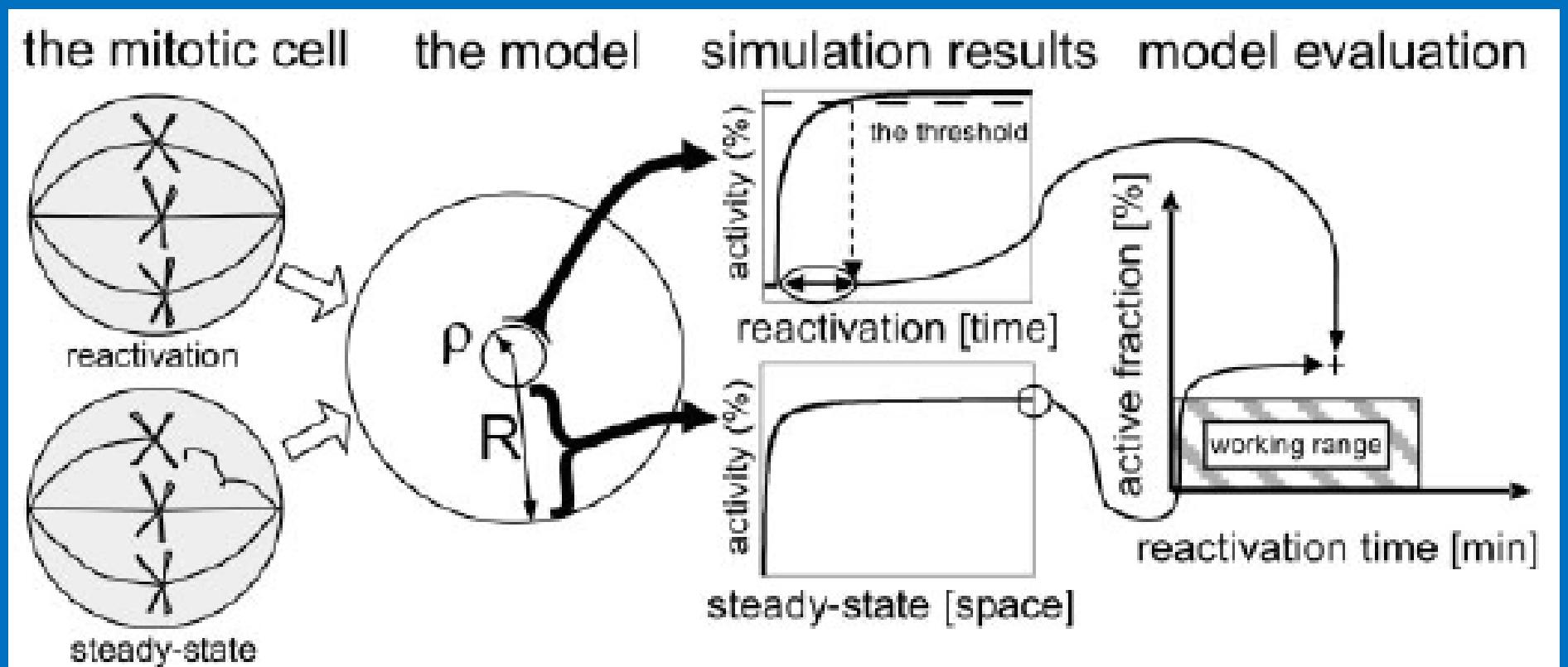
B
 $t = 115s$



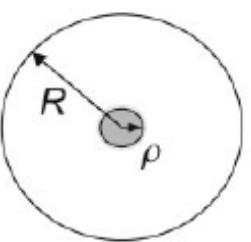
So far, we did not discuss where the reactions take place; how the molecules go where they are needed.

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
without assuming the exact form of reactions (this is what physics is good for)



Yeast cell: mitosis
in the nucleus

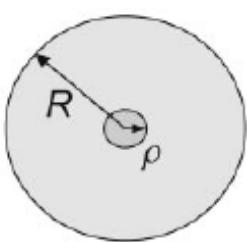


at the center
 $C \xrightleftharpoons[\alpha]{\gamma} C^*$
 colored area is where
 the inhibition takes
 place (all models)

Direct Inhibition

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

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

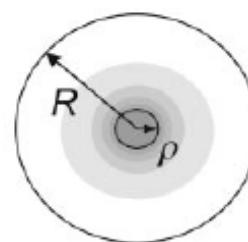


at the center
 $C \xrightleftharpoons[\alpha]{\gamma} C^*$
 $C + C^* \xrightarrow{\kappa} 2C$

Self-Propagating Inhibition

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

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



$c + e^* \xrightarrow{\gamma} C^* \xrightleftharpoons[\alpha]{\gamma} c + e$
 at the center
 $e \xrightleftharpoons[\lambda]{\gamma} e^*$

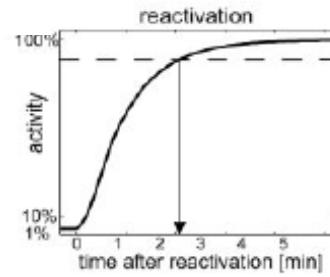
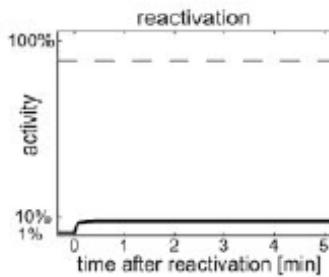
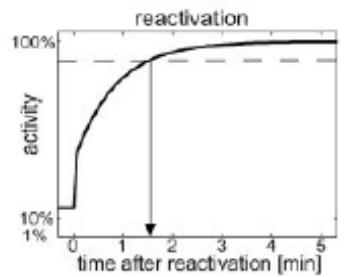
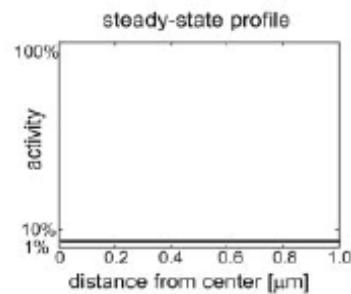
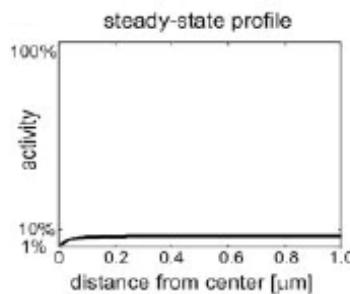
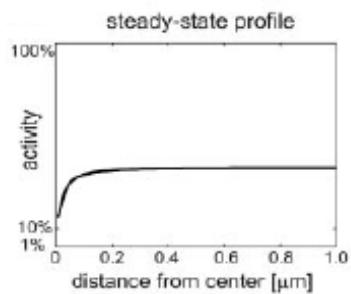
Emitted Inhibition

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

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

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

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



$$\frac{\partial C^*}{\partial T} = \tilde{D} \frac{\partial^2 C^*}{\partial X^2} - \alpha C^*$$

$$0 \leq X \leq L$$

$$X = Lx, T = t / \alpha, C^* = \bar{C}c^*$$

$$\frac{\partial c^*}{\partial t} = D \frac{\partial^2 c^*}{\partial x^2} - c^*, D = \frac{\tilde{D}}{L^2 \alpha}, 0 \leq x \leq 1$$

Boundary conditions: no flux at the right; activated concentration is zero at the left; activated ‘flux in’ is equal to inactivated ‘flux out’ at the left.

$$\tilde{D} \sim 1 \mu m^2 / s$$

$D > 10$ for effective inactivation

$$\alpha < \frac{\tilde{D}}{10L^2} \sim 0.1s, L \sim 1 \mu m, T \sim \frac{1}{\alpha} > 10s$$

Where are 100's of sec in the paper coming from?

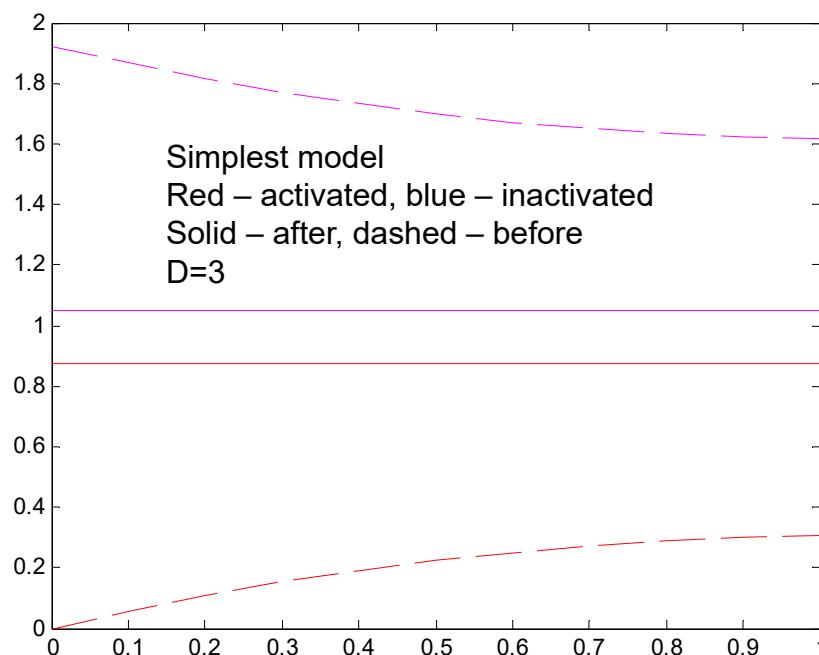
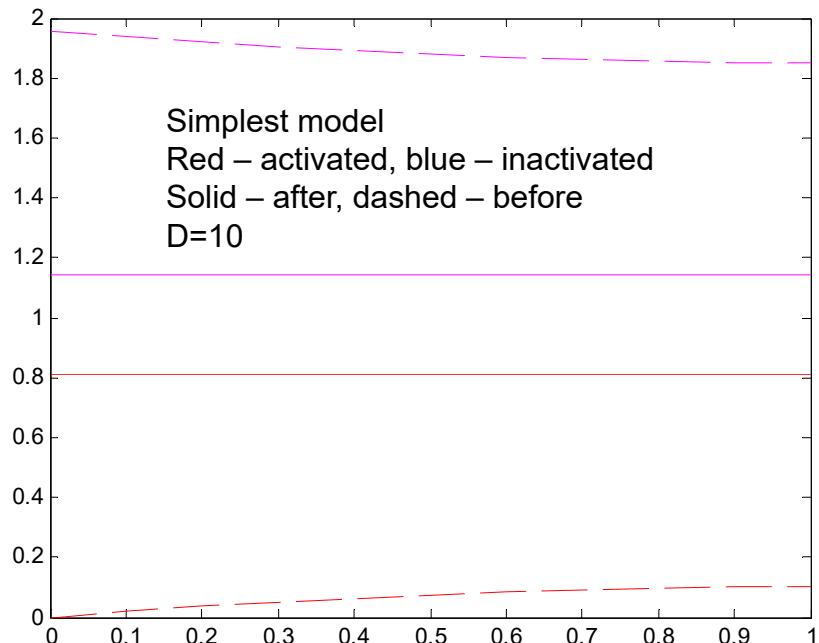
```
% ca - active; ci - inhibited
a = 0; b = 1; t0 = 0; t1 = 6; k = 0.1; h = 0.0005;
D = 10; D = D*h/k^2; N = (b-a)/k; M = (t1-t0)/h;
ca = ones(M+1,N+1); ci = ones(M+1,N+1); % Init Cond
%-----MainLoop-----
for i = (1:M/2)
    ca(i+1,2:N) = ca(i,2:N) + h*ci(i,2:N) + ...
        D*(ca(i,1:N-1) + ca(i,3:N+1) - 2*ca(i,2:N));
    ci(i+1,2:N) = ci(i,2:N) - h*ci(i,2:N) + ...
        D*(ci(i,1:N-1) + ci(i,3:N+1) - 2*ci(i,2:N));

    ca(i+1,1) = 0;
    ci(i+1,1) = ci(i,1) + D*ca(i,2) + D*(ci(i,2) - ci(i,1));

    ca(i+1,N+1) = ca(i,N+1) + h*ci(i,N+1) + D*(ca(i,N) - ca(i,N+1));
    ci(i+1,N+1) = ci(i,N+1) - h*ci(i,N+1) + D*(ci(i,N) - ci(i,N+1));
end
for i = (M/2+1:M)
    ca(i+1,2:N) = ca(i,2:N) + h*ci(i,2:N) + ...
        D*(ca(i,1:N-1) + ca(i,3:N+1) - 2*ca(i,2:N));
    ci(i+1,2:N) = ci(i,2:N) - h*ci(i,2:N) + ...
        D*(ci(i,1:N-1) + ci(i,3:N+1) - 2*ci(i,2:N));

    ca(i+1,1) = ca(i,1) + h*ci(i,1) + D*(ca(i,2) - ca(i,1));
    ci(i+1,1) = ci(i,1) - h*ci(i,1) + D*(ci(i,2) - ci(i,1));

    ca(i+1,N+1) = ca(i,N+1) + h*ci(i,N+1) + D*(ca(i,N) - ca(i,N+1));
    ci(i+1,N+1) = ci(i,N+1) - h*ci(i,N+1) + D*(ci(i,N) - ci(i,N+1));
end
%-----GraphicOutput-----
plot((0:N)/N,ca(M/2,:), 'r--', (0:N)/N,ci(M/2,:),'m--',...
    (0:N)/N,ca(M/2+1000,:), 'r', (0:N)/N,ci(M/2+1000),'m')
```



$$\frac{\partial c^*}{\partial t} = D \frac{\partial^2 c^*}{\partial x^2} - c^* + rcc^*$$

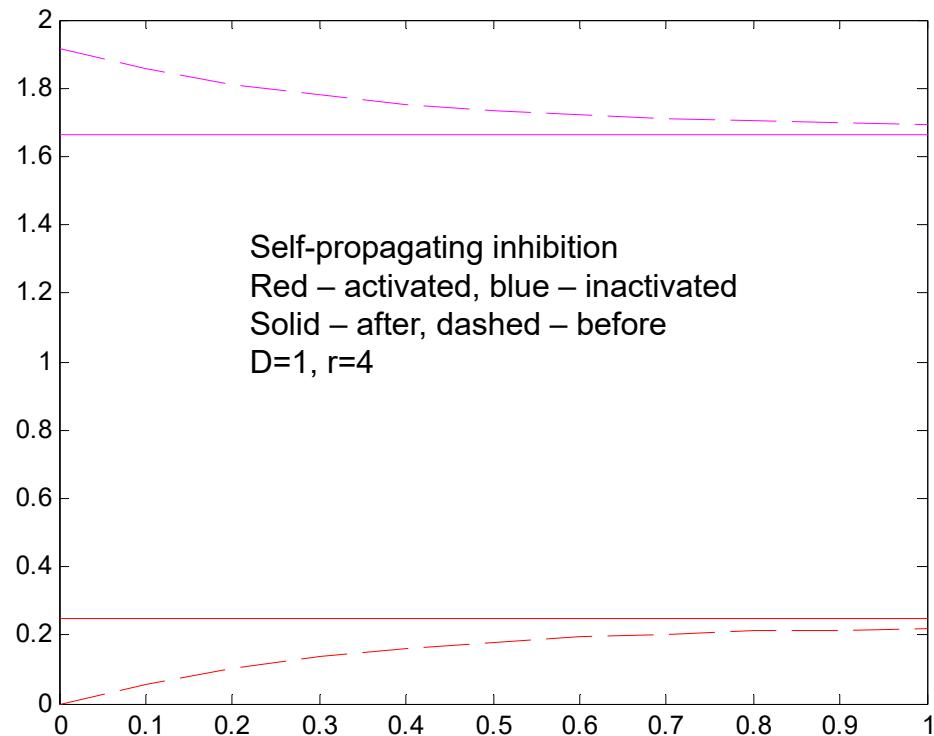
$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} + c^* - rcc^*$$

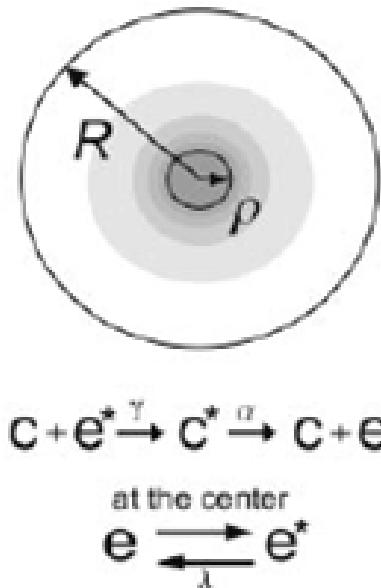
$D \sim 1, r \gg 1$: decent spatial inhibition;
alpha does not have to be small
anymore, so switch can be fast.
But: ‘Auto-lock’ in an inhibited state;
do not need KT anymore:

$$c^* - rcc^* = c^*(1 - rc) = 0, c + c^* = 1$$

$$1) c^* = 0, c = 1$$

$$2) c = \frac{1}{r}, c^* = 1 - \frac{1}{r}$$





Emitted inhibition:

$$\begin{array}{ll}
 \alpha c^* - \gamma c e^* = 0 & c^* = 0 \\
 \alpha c^* + \lambda e^* = 0 & c = 1 \\
 \lambda e^* - \gamma c e^* = 0 & e^* = 0 \\
 c + c^* = 1 & e = 1 \\
 e + e^* + c^* = 1 &
 \end{array}$$



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

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

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

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

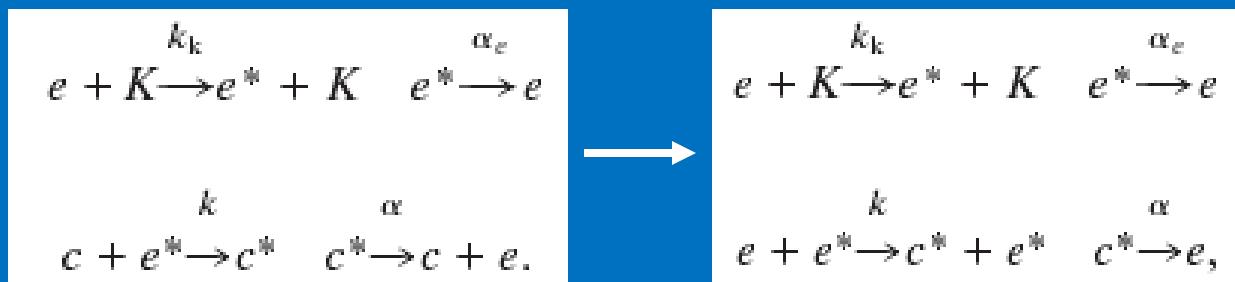
Inhibition range: $\sqrt{D/\lambda}$ or $\sqrt{D/\alpha}$

Switching time: $1/\lambda$ or $1/\alpha$

So, benefit is not obvious... just twice better?

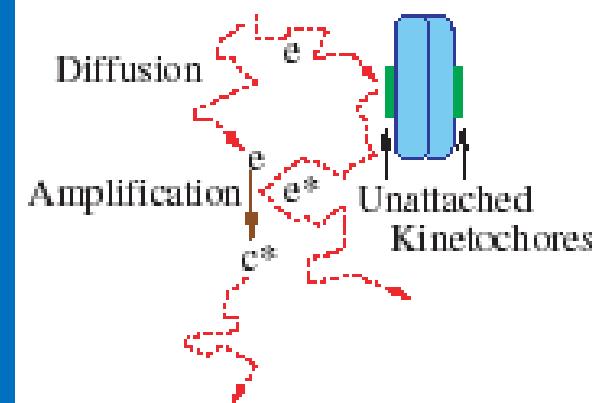
Small yeast; big animal cells

nonautocatalytic amplification



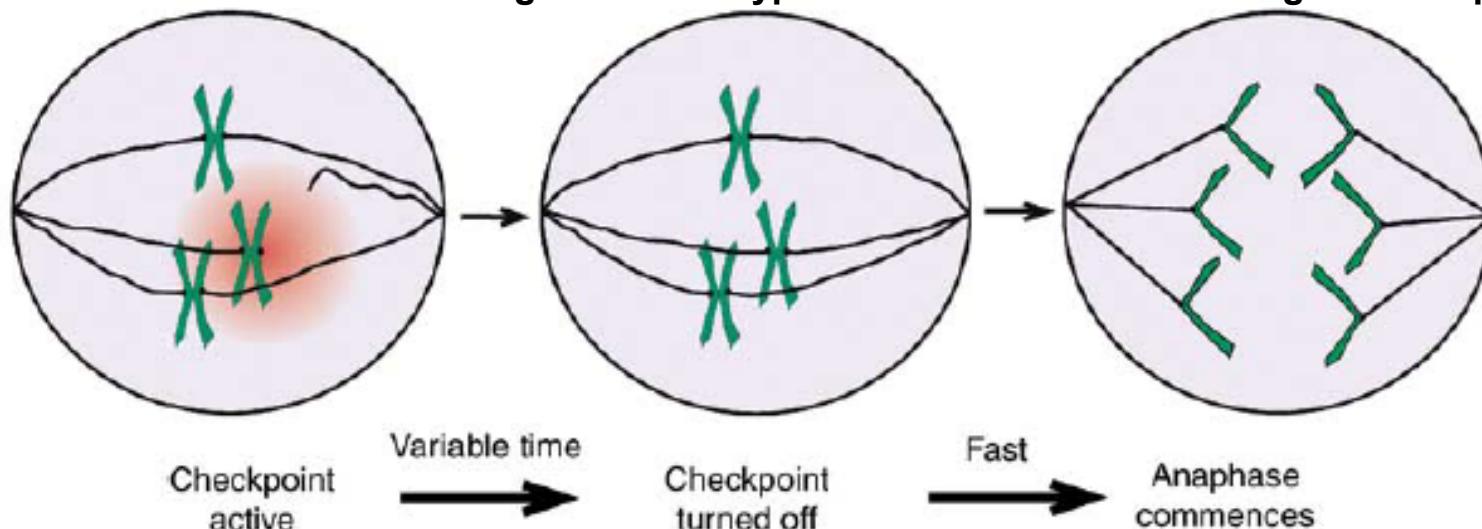
Doncic's scheme does not catalytically amplify the inhibitory signal. One e^* molecule can interact with only one c molecule. In Sear's scheme, a single e^* molecule can convert many molecules into the inhibiting form, thereby producing amplification.

Anaphase inhibited by sequestration of cell cycle regulators

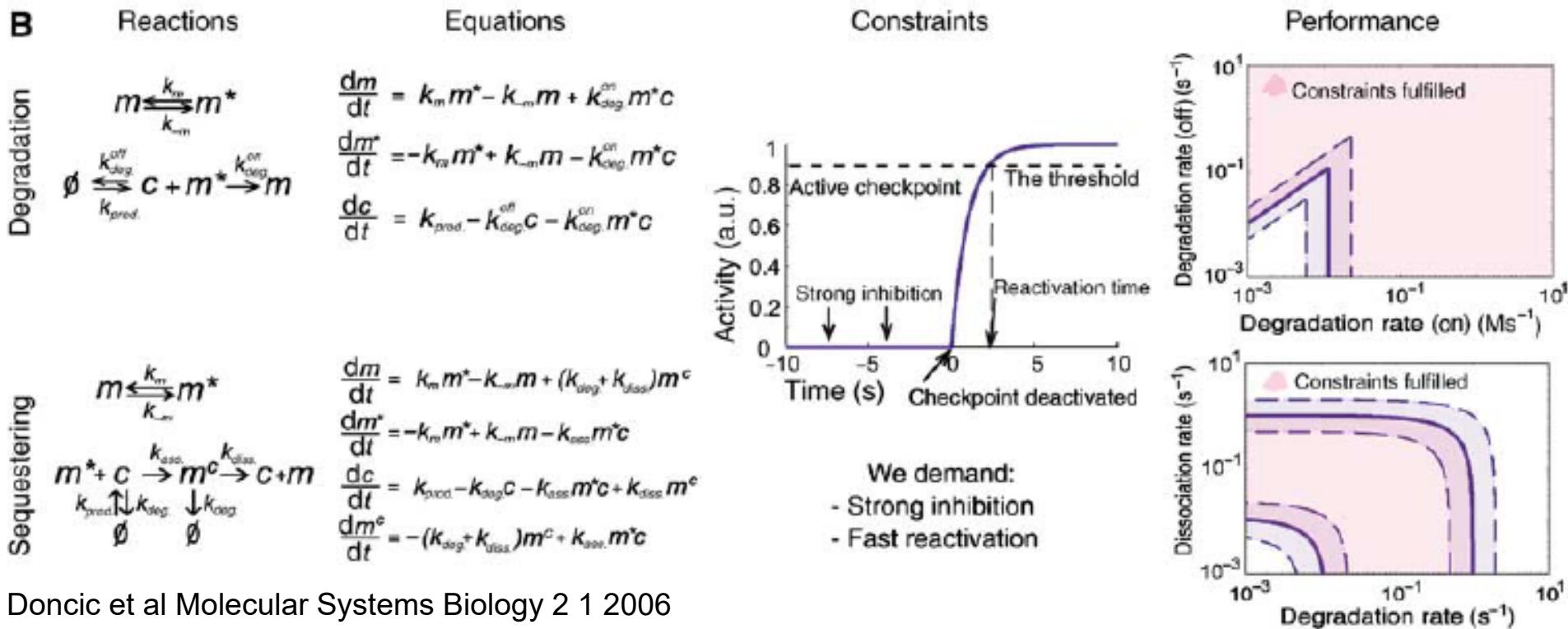


A

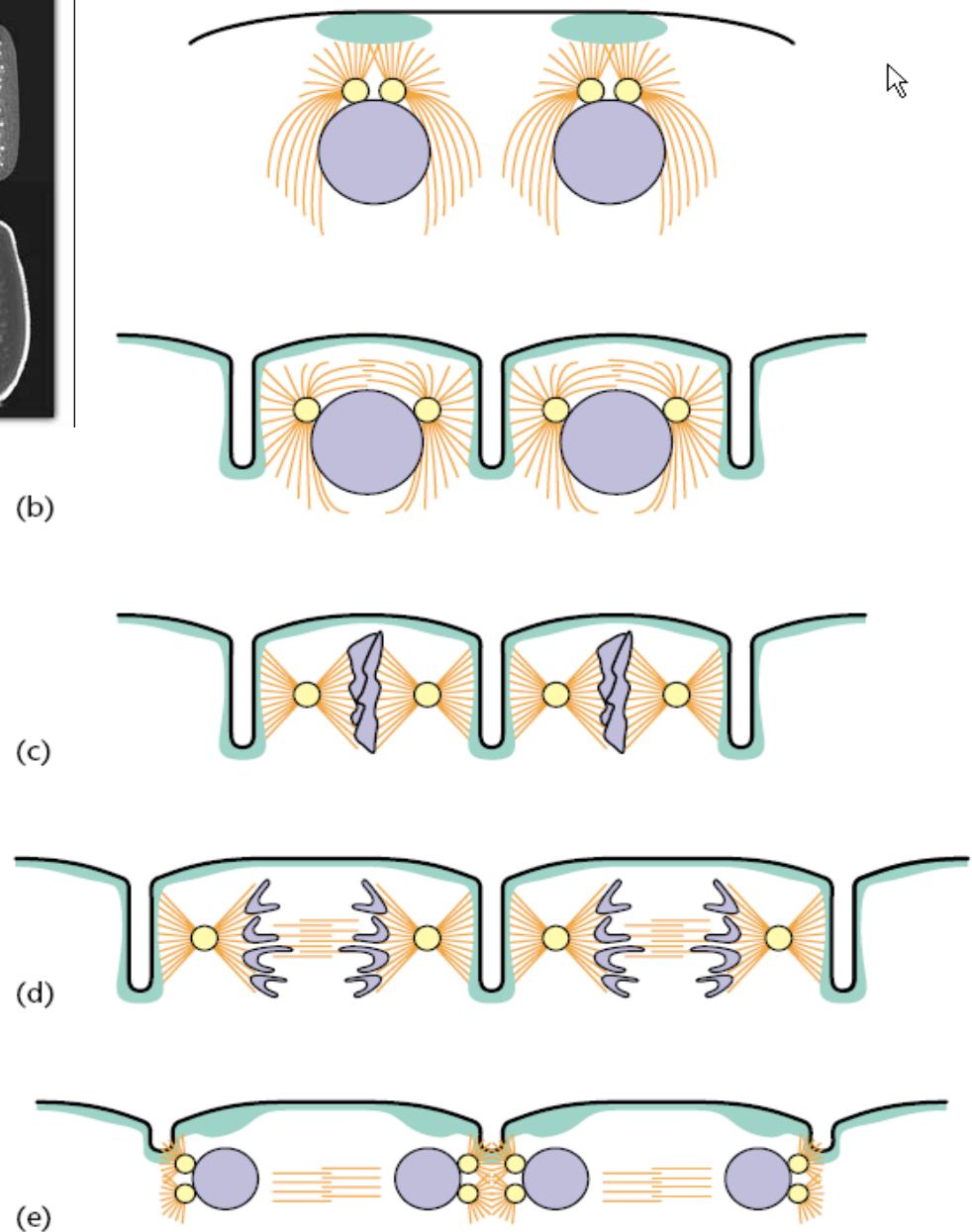
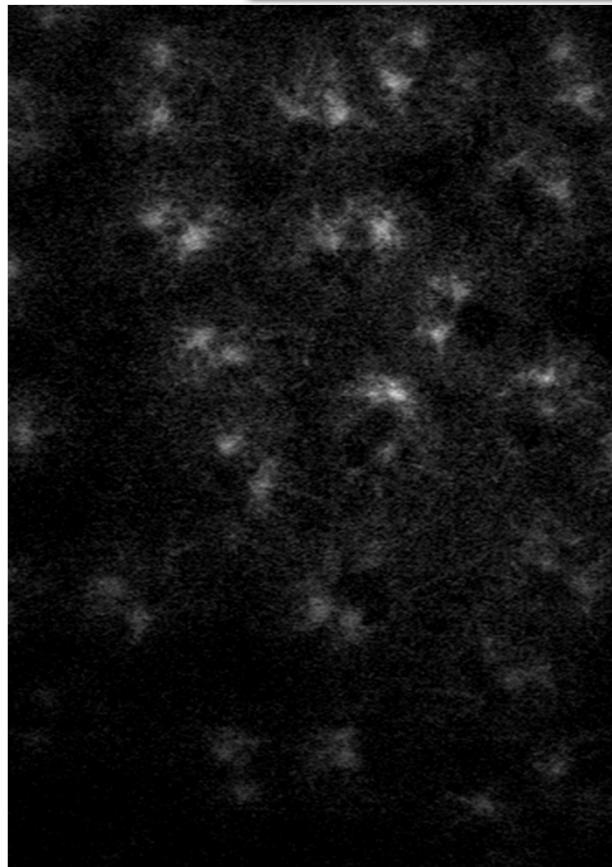
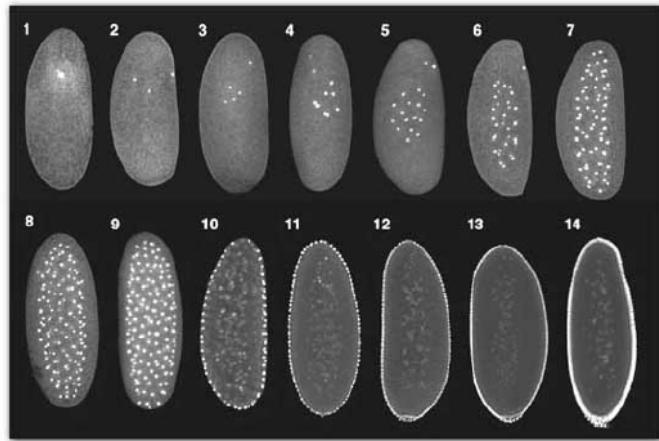
A schematic view Can we figure out the type of certain reaction from a general requirement?



B



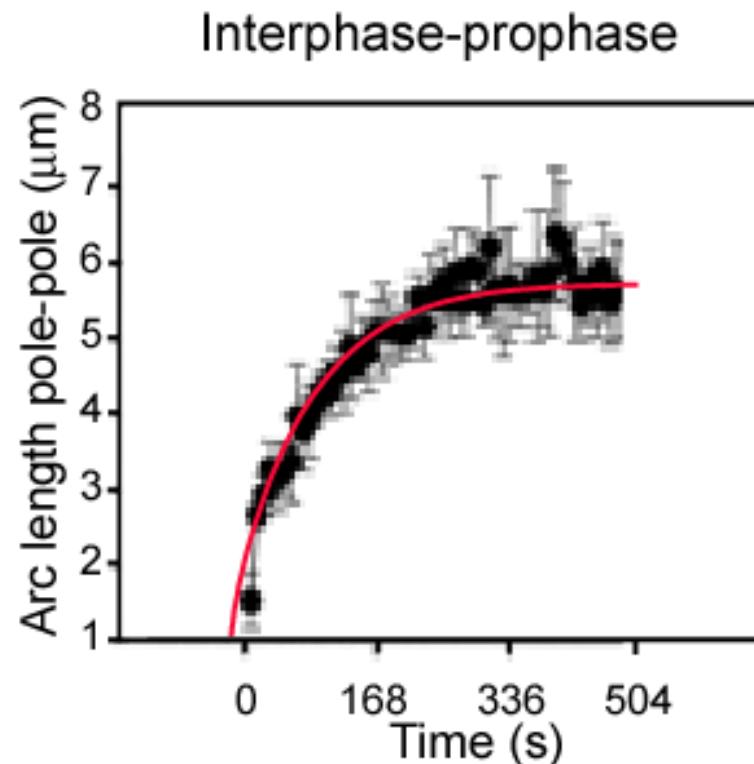
Mitosis (segregation of chromosomes before cell division) in Drosophila Embryo



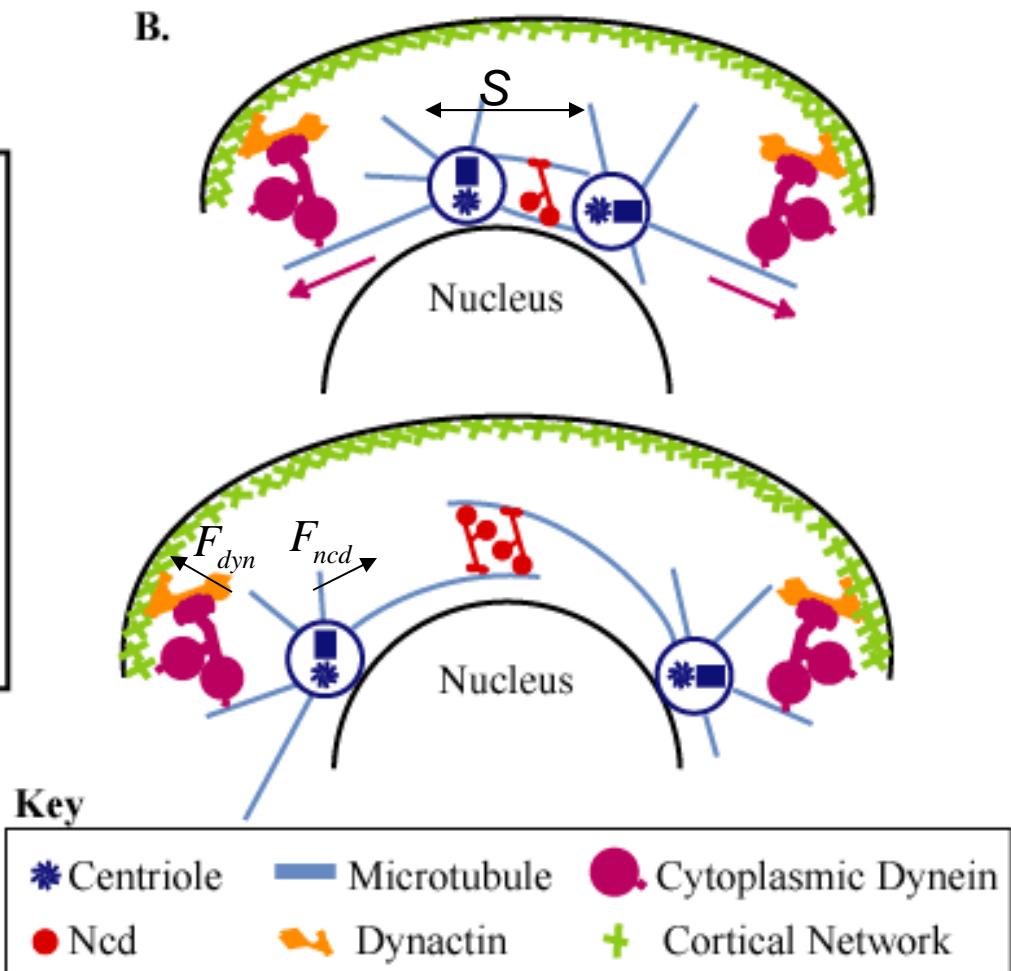
Tram et al., Encyclopedia of Life Sciences, 2002

Balance of dynein (outward) and ncd (inward) forces explains pole separation and transient steady state in interphase - prophase

A.



B.



$$\frac{dS}{dt} = \frac{2}{\mu} (F_{dyn} - F_{ncd} \times S)$$

Cytrynbaum et al., 2003, 2005

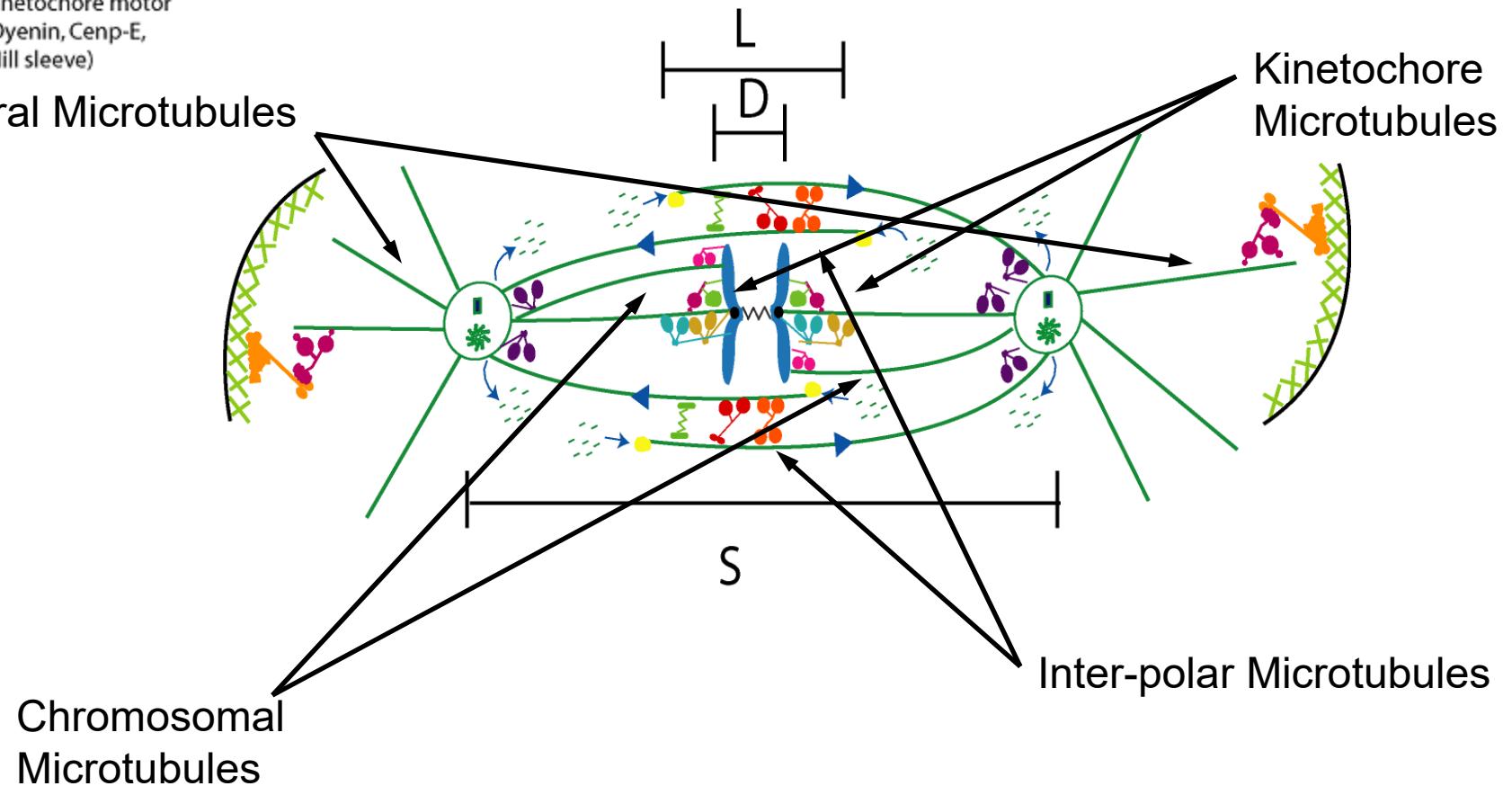
- Chromokinesins (Klp3A, Klp38B, Nod)
- Dynein
- Kinetocore MT polymerization regulators (Clasp,...)
- Ncd
- KLP61F
- Kinetochore MTs depolymerization regulators (Klp67A, Klp59C,...)
- Klp10A

- Kinetochore motor (Dynein, Cenp-E, Hill sleeve)

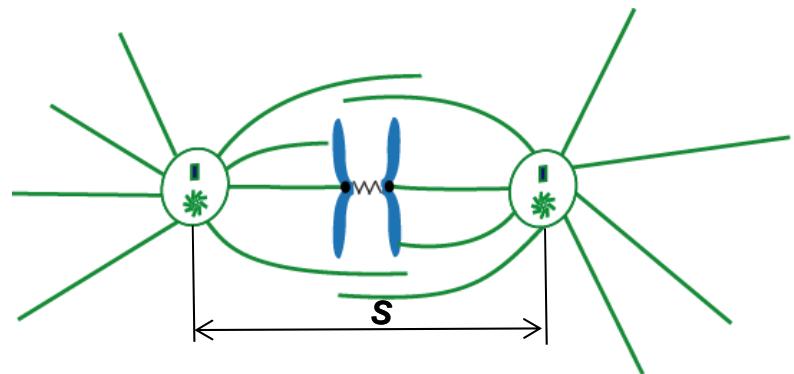
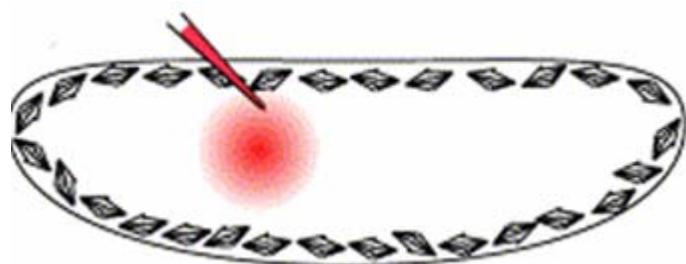
Astral Microtubules

- Microtubule
- +TIPs proteins
- MT bundling/cross linking: Klp3A, Pavarotti, Feo, Ncd?, Klp61F?....
- Dynactin
- Centriole
- Cortical Network
- Kinetochore
- Chromosome Arm

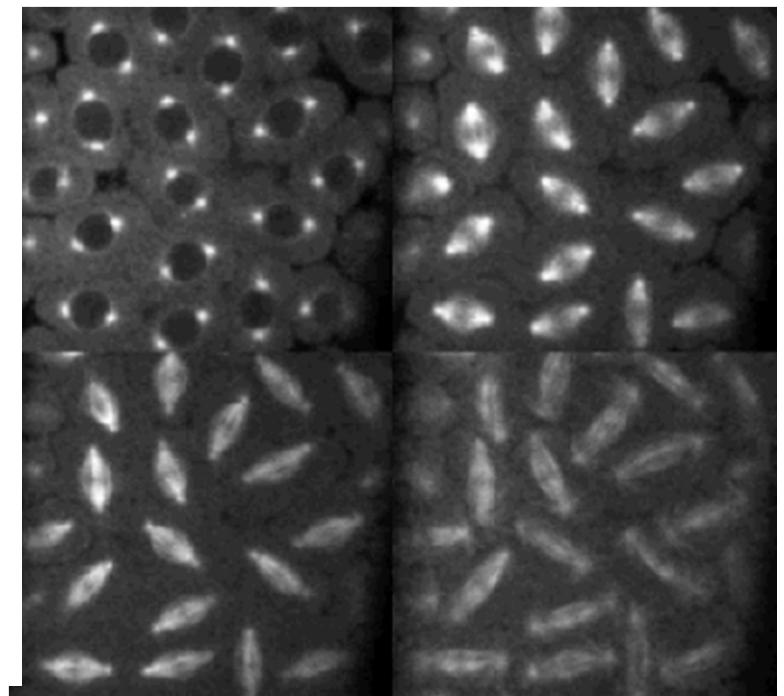
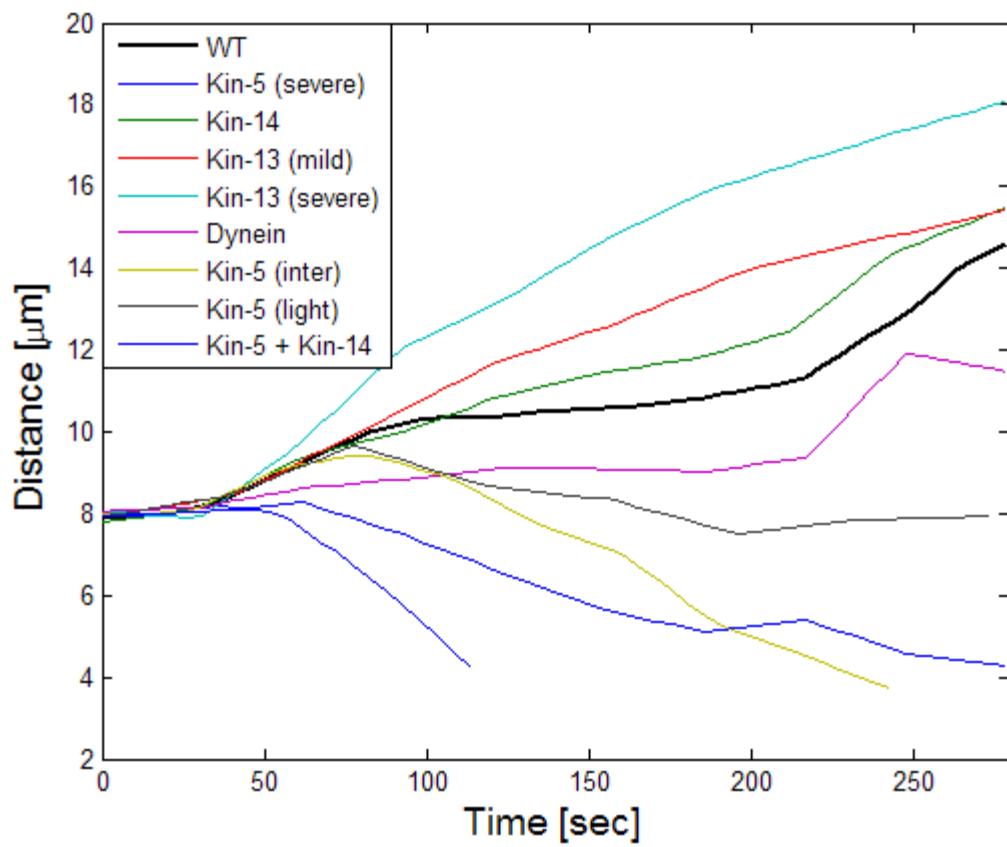
After prophase the dance is very complex



Quantitative measure of mitotic progression



Pole – Pole distance s over time



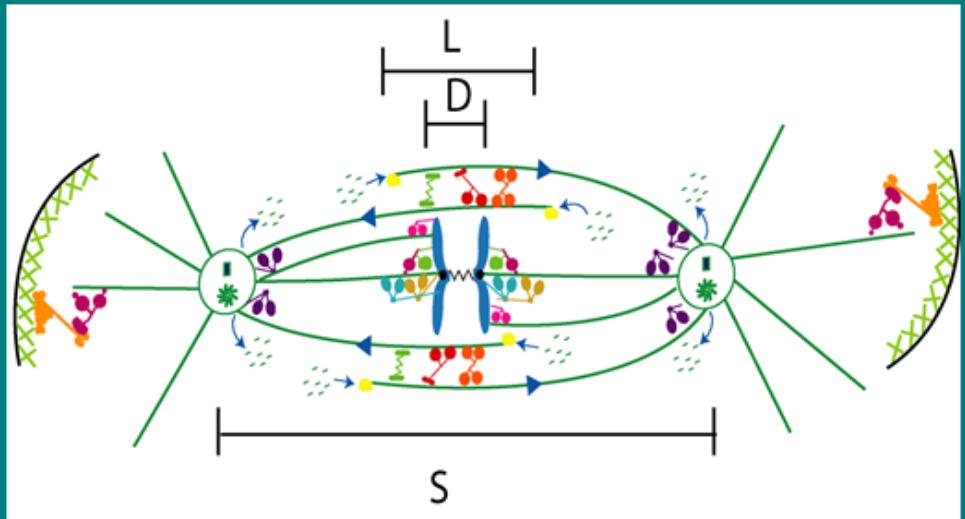
Forces on the spindle and dynamic equations

$$\frac{dS}{dt} = \frac{2(F_{ip} + F_{chrk} + F_{aster} - F_{kt})}{\mu_{pole}}$$

$$\frac{dD}{dt} = \frac{2(F_{kt} - F_{chrk} - F_{cohesion})}{\mu_{chr}}$$

$$\frac{dL}{dt} = 2V_{ploy}^{ip} - 2((1 - P_{dep})V_{pole} + P_{dep}V_{MT}^{ip})$$

$$V_{pole} = \frac{1}{2} \frac{dS}{dt} \quad V_{chr} = \frac{1}{2} \frac{dD}{dt}$$



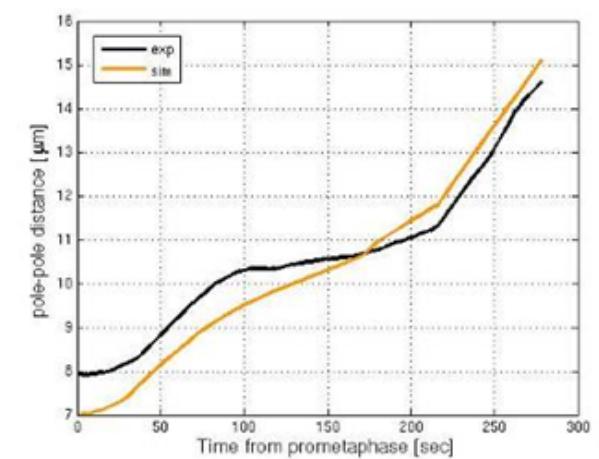
Numerical solution of the model equations (stiff ODE solver)

Solve for single microtubule ($v \rightarrow f$)

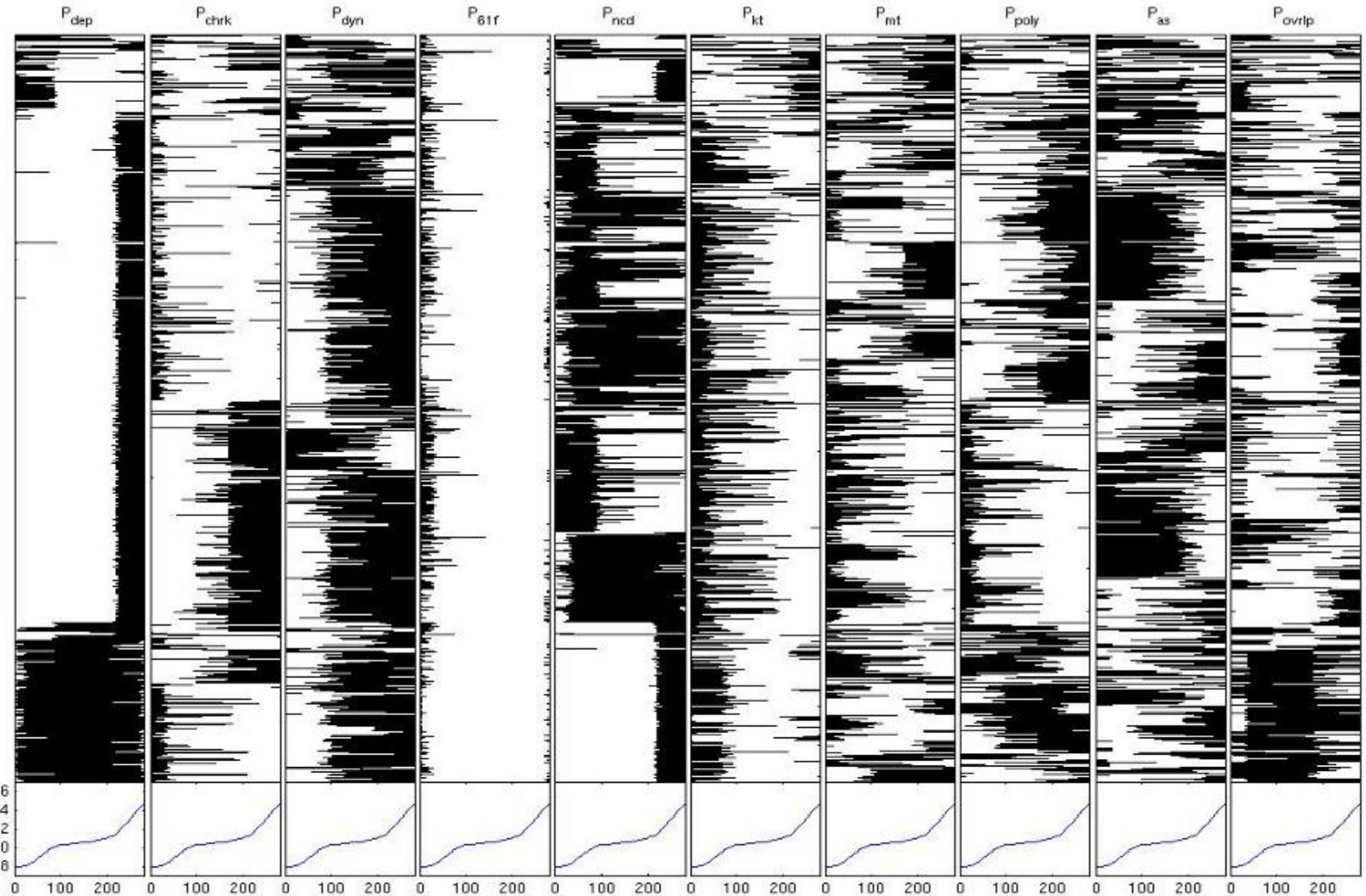
Score

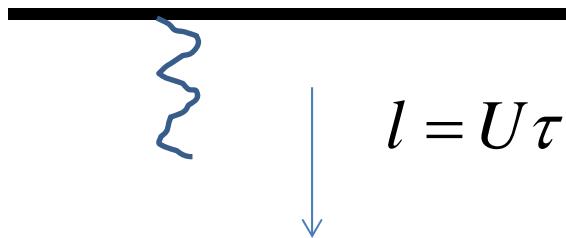
Integrate for microtubule population ($f \rightarrow F$)

Integrate for entire spindle ($F \rightarrow v$)

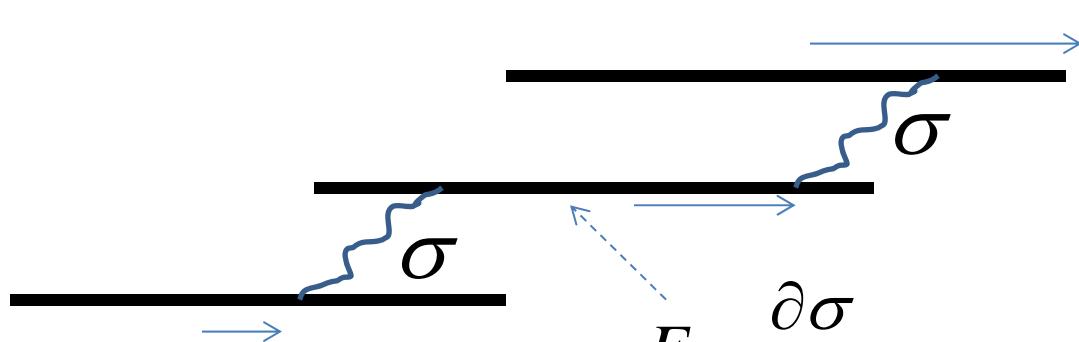
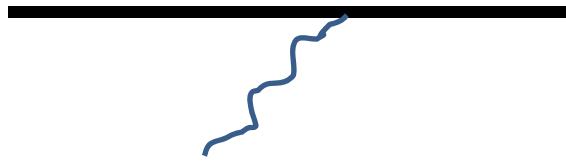


Bewildering variety of the ‘perfect’ models: switches





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



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

$$\underbrace{F_{adh}}_{\text{external}} + \underbrace{F_{visc} + F_{myo}}_{\text{internal}} = 0$$

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

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

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

$$\sigma_{myo} = kM$$

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

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

$$\frac{\partial U}{\partial T} = \frac{1}{\varepsilon} \left[\underbrace{\mu \frac{\partial^2 U}{\partial X^2}}_{\text{viscous stress in actin network}} + \underbrace{k \frac{\partial M}{\partial X}}_{\text{myosin contractile stress}} - \underbrace{\zeta U}_{\substack{\text{adhesion} \\ \text{viscous drag}}} \right]$$

$$\frac{\partial M}{\partial T} = \underbrace{D \frac{\partial^2 M}{\partial X^2}}_{\text{myosin diffusion}} - \underbrace{\frac{\partial}{\partial X} (UM)}_{\text{myosin drift with actin flow}}$$

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

$$\frac{\partial U}{\partial T} = \frac{1}{\varepsilon} \left[\underbrace{\mu \frac{\partial^2 U}{\partial X^2}}_{\text{viscous stress in actin network}} + \underbrace{k \frac{\partial M}{\partial X}}_{\text{myosin contractile stress}} - \underbrace{\zeta U}_{\substack{\text{adhesion} \\ \text{viscous drag}}} \right]$$

$$\frac{\partial M}{\partial T} = \underbrace{D \frac{\partial^2 M}{\partial X^2}}_{\text{myosin diffusion}} - \underbrace{\frac{\partial}{\partial X}(UM)}_{\text{myosin drift with actin flow}}$$

$1/\zeta$ - 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

$$\varepsilon \frac{\partial u}{\partial t} = \underbrace{\gamma \frac{\partial^2 u}{\partial x^2}}_{\text{viscous stress in actin network}} + \underbrace{\beta \frac{\partial m}{\partial x}}_{\text{myosin contractile stress}} - \underbrace{u}_{\substack{\text{adhesion} \\ \text{viscous drag}}}$$

$$\frac{\partial m}{\partial t} = \underbrace{\alpha \frac{\partial^2 m}{\partial x^2}}_{\text{myosin diffusion}} - \underbrace{\frac{\partial}{\partial x}(um)}_{\text{myosin drift with actin flow}}$$

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

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

$$u = 0 + u$$

$$m = 1 + p$$

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

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

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

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

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

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

$$\varepsilon \lambda u_0=-\gamma q^2u_0+\beta iq p_0-u_0$$

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

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

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

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

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

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

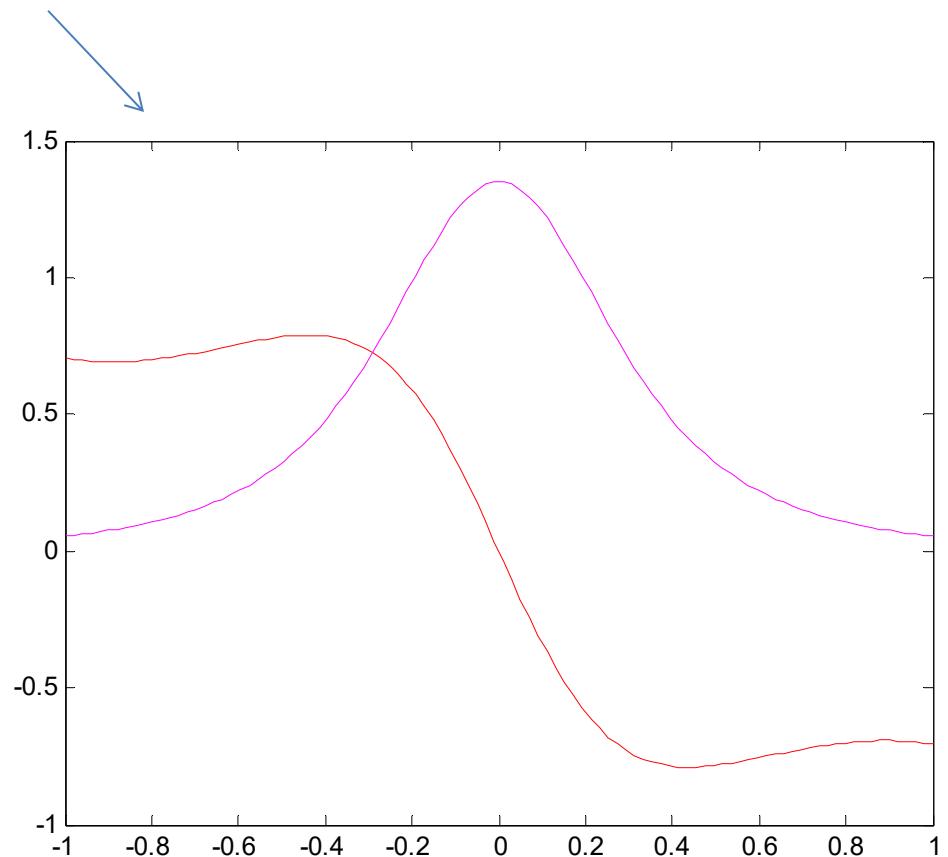
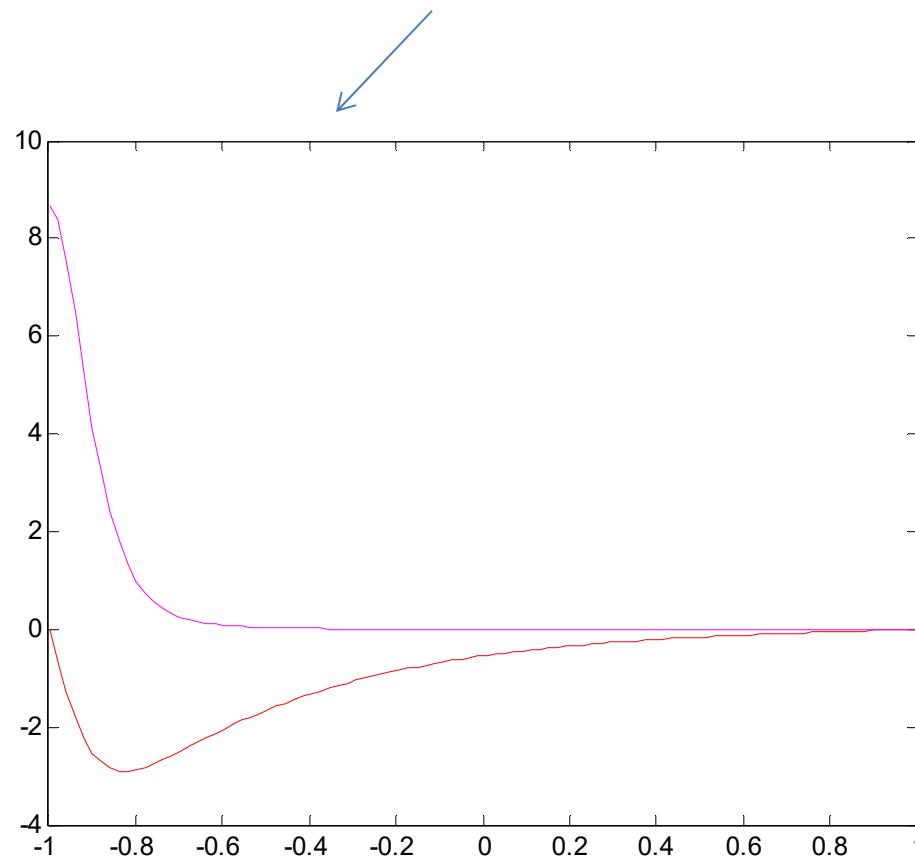
$$k\bar{M} > D\zeta$$

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

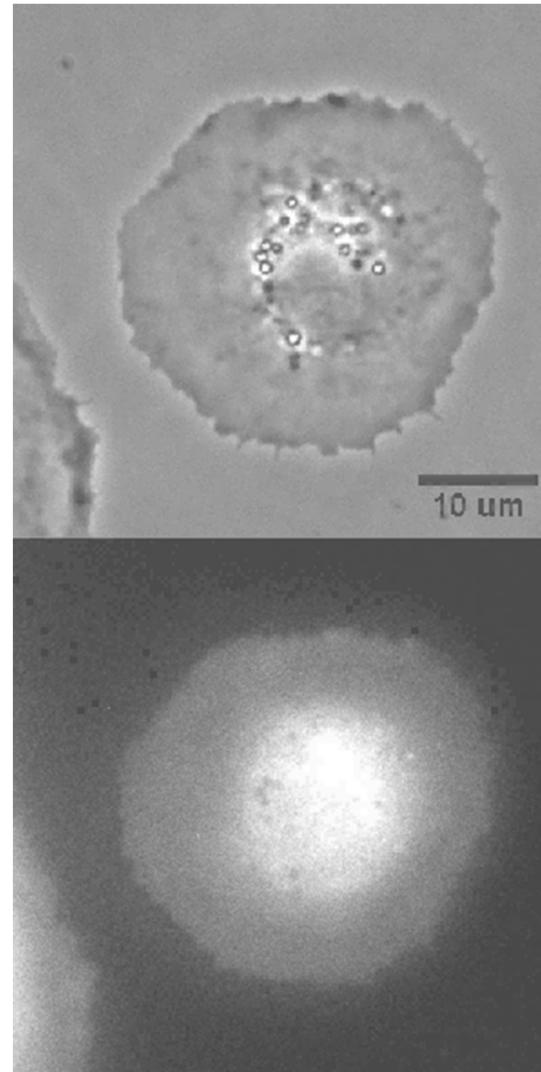


Why the difference?

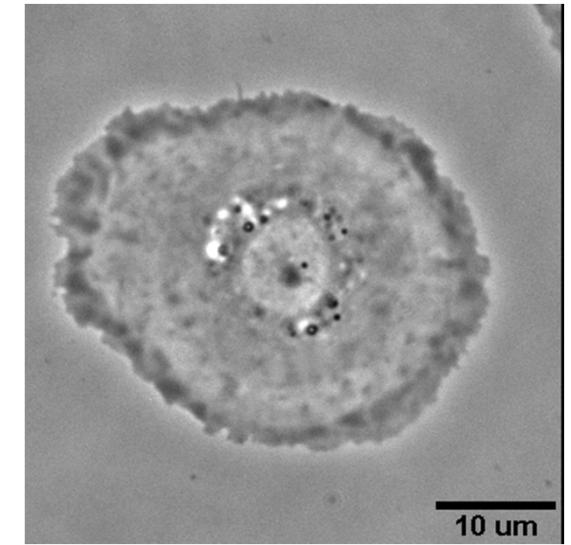
Polarization (symmetry breaking) and motility initiation

Movie: Yam, Theriot et al

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



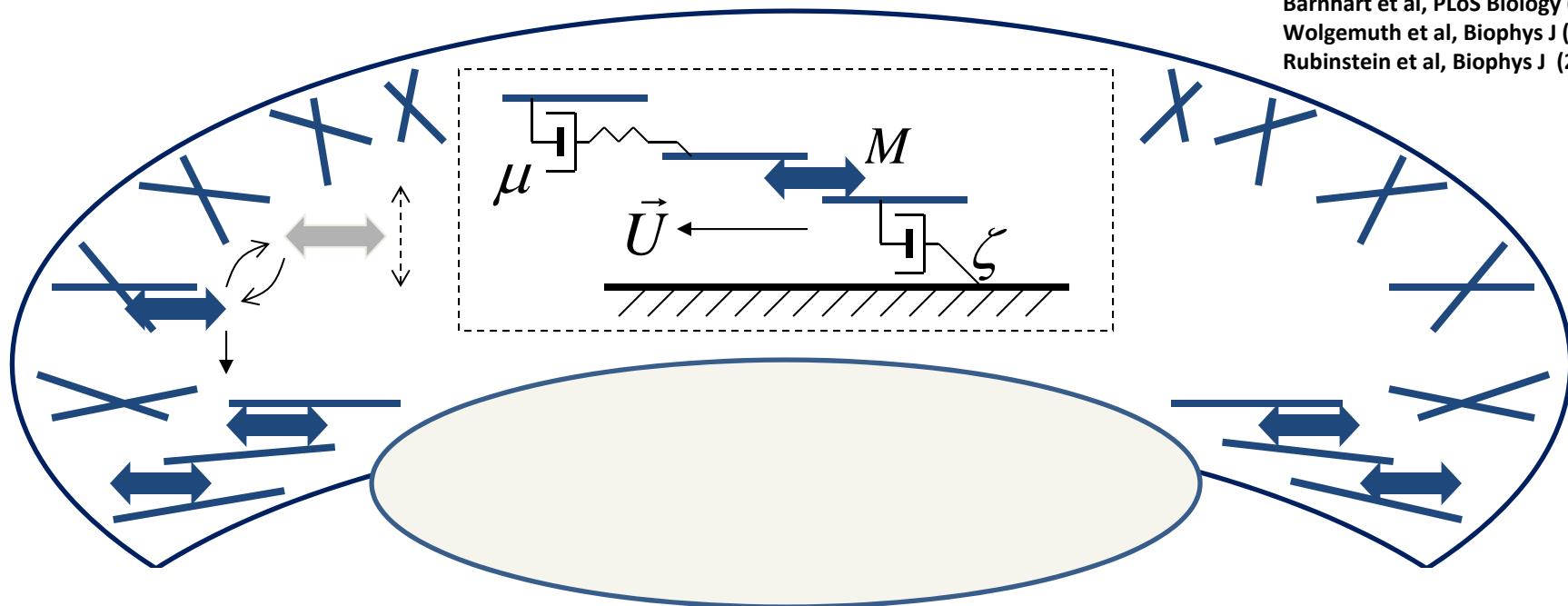
Stationary cells-
circular lamellipodium with
cell body at the center



Spontaneous
transition

Mechanical model of contractile viscous actin gel

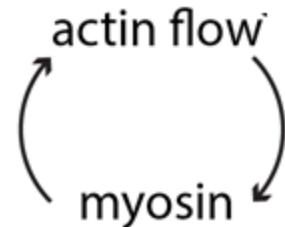
Barnhart et al, PNAS (2015)
 Barnhart et al, PLoS Biology (2011)
 Wolgemuth et al, Biophys J (2011)
 Rubinstein et al, Biophys J (2009)



$$\underbrace{\mu \nabla^2 \vec{U}}_{\text{viscous stress in actin network}} + \underbrace{k \nabla M}_{\text{myosin contractile stress}} = \underbrace{\zeta \vec{U}}_{\text{adhesion viscous drag}}$$

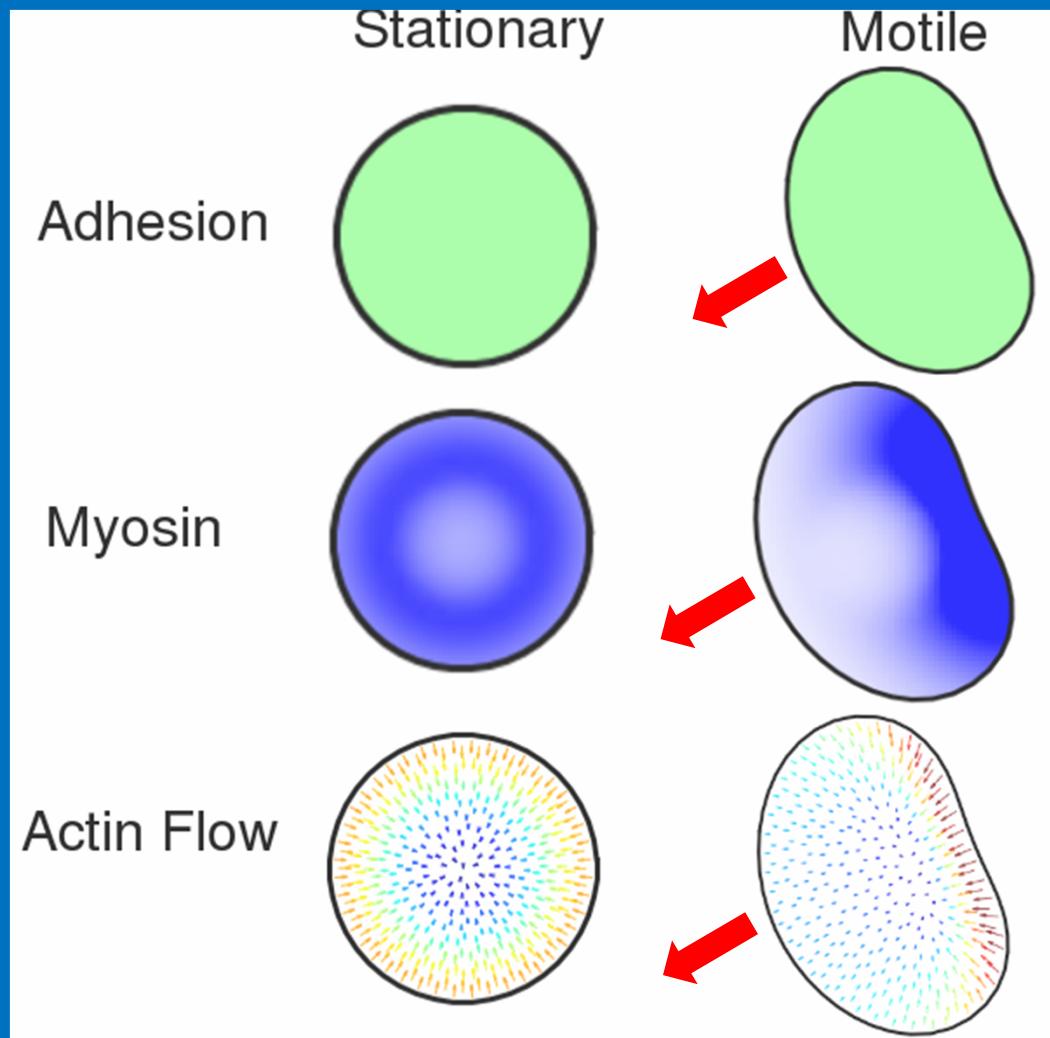
$$T = \underbrace{\zeta \vec{U}}_{\text{traction stress}}$$

$$\frac{\partial M}{\partial t} = \underbrace{D \nabla^2 M}_{\text{myosin diffusion}} - \underbrace{\nabla \cdot (\vec{U} M)}_{\text{myosin drift with actin flow}}$$



The model predicts the myosin and flow distributions

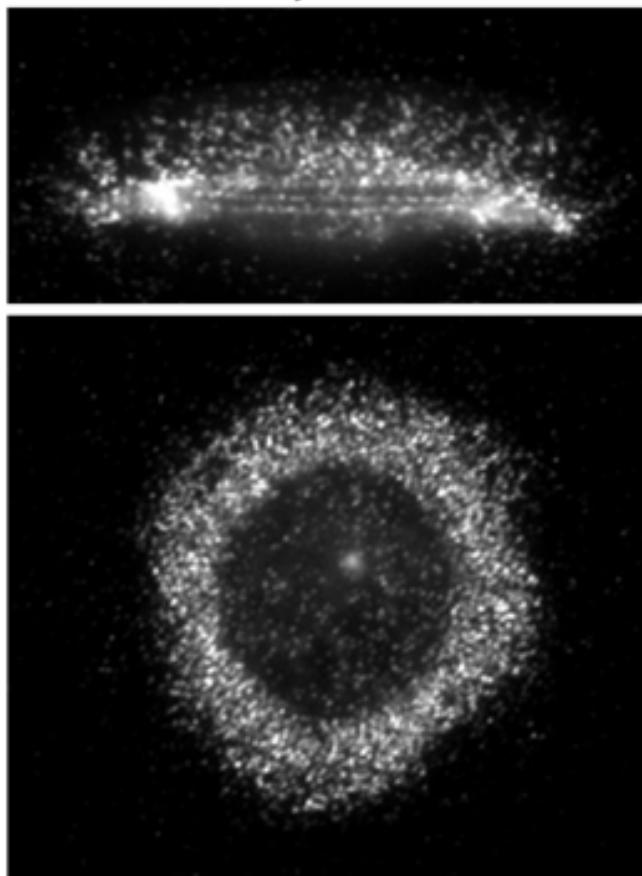
Barnhart et al, PNAS (2015)



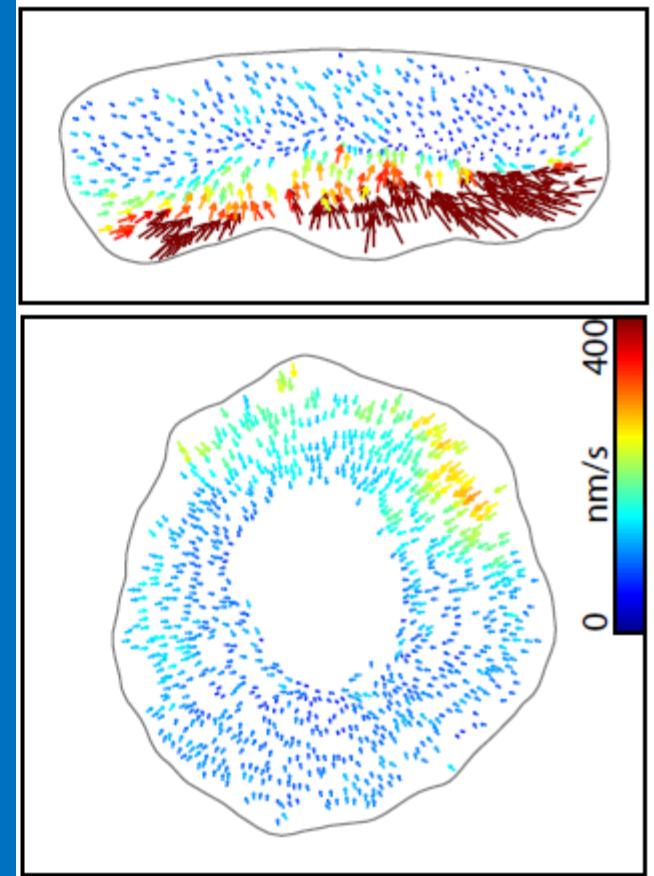
Distributions of flow and myosin in motile and stationary cells

Barnhart et al, PNAS (2015)

myosin

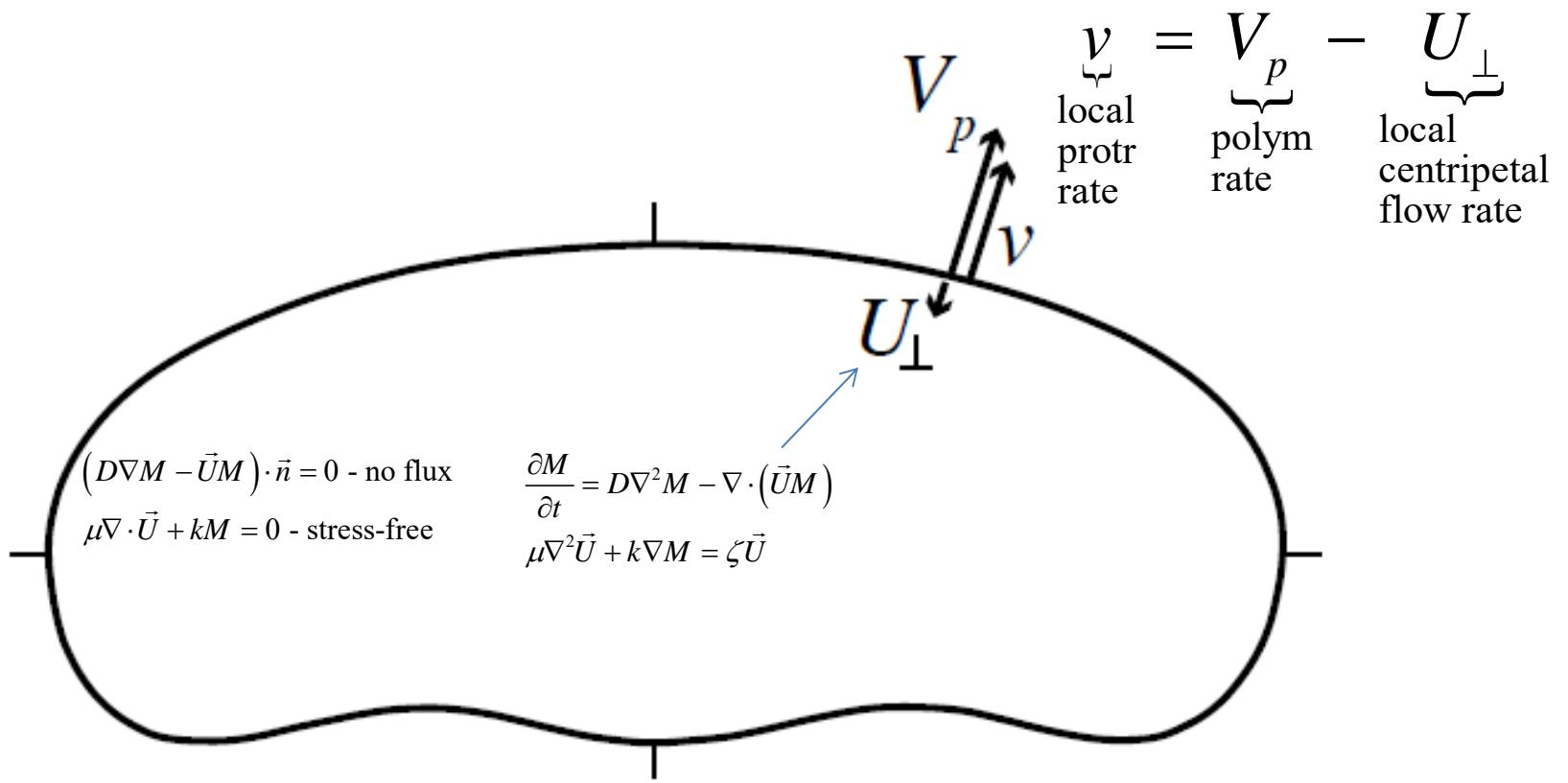


actin flow



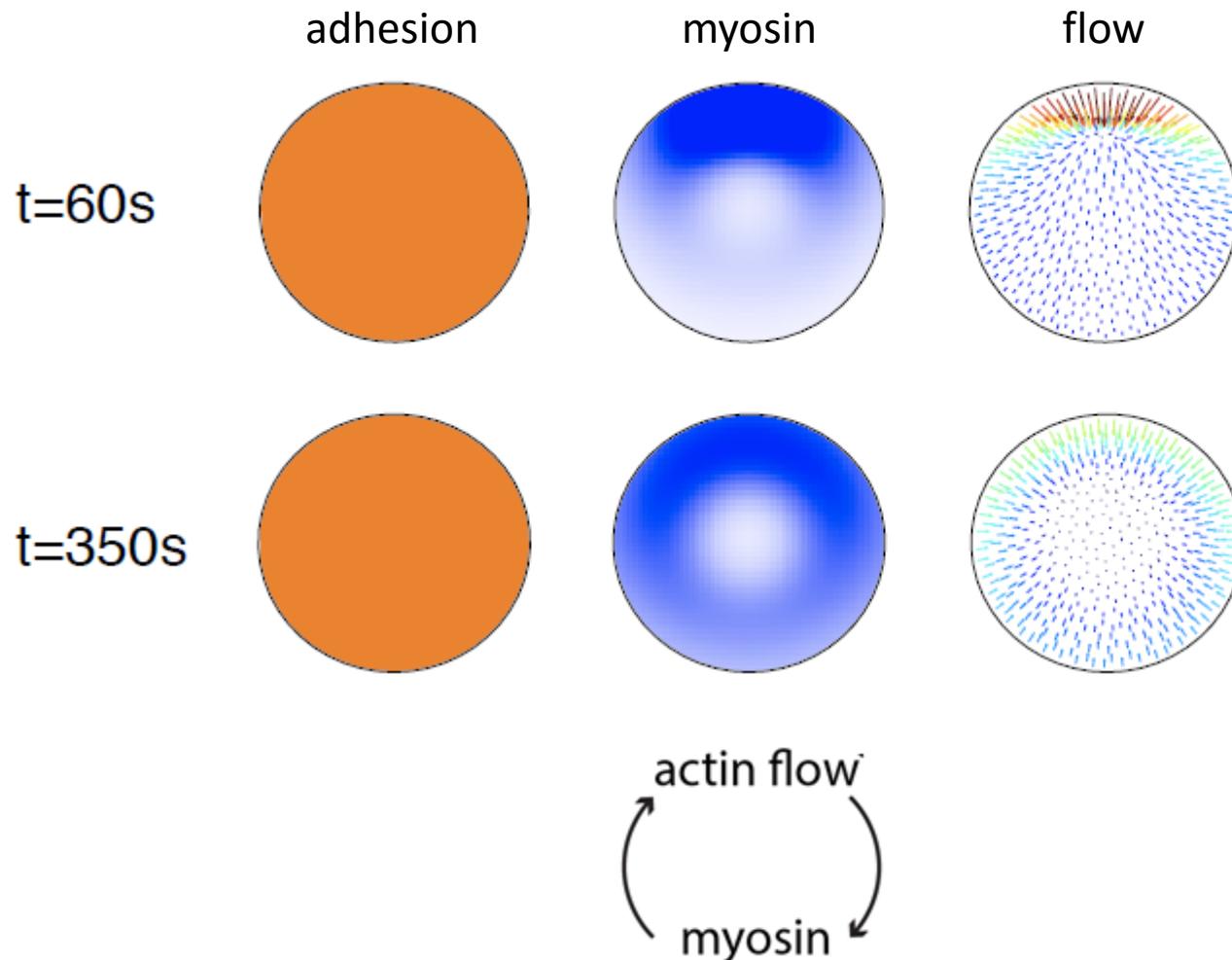
Free-boundary simulations

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

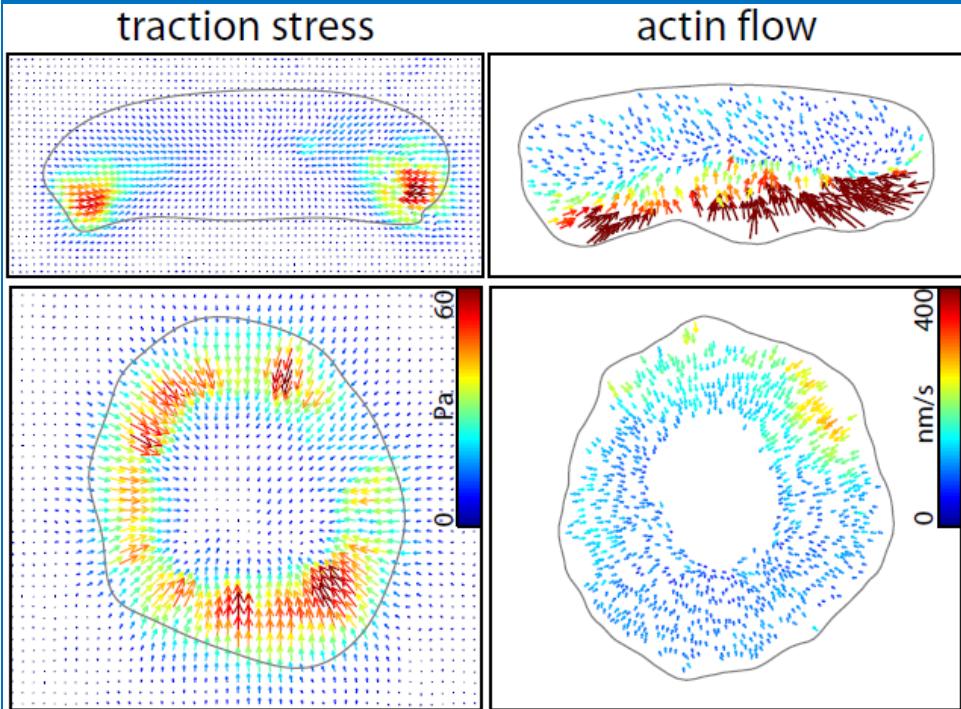
Barnhart et al, PNAS (2015)



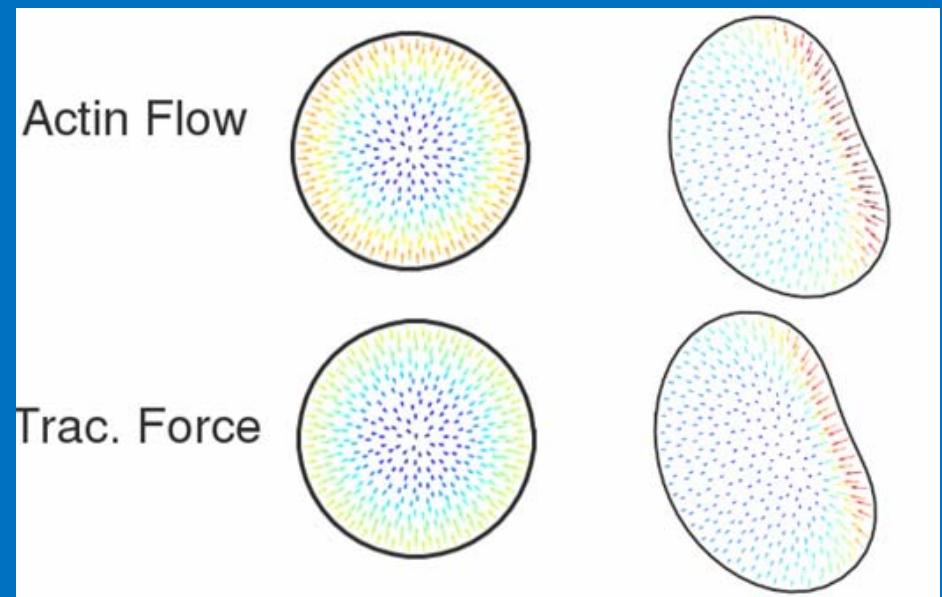
Adhesion is stronger in stationary cells
and is not uniform across the cell

Barnhart et al, PNAS (2015)

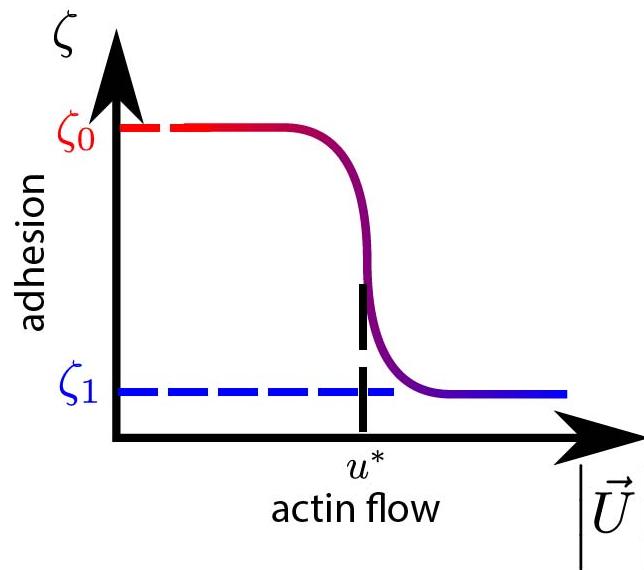
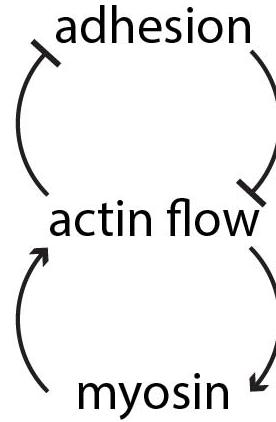
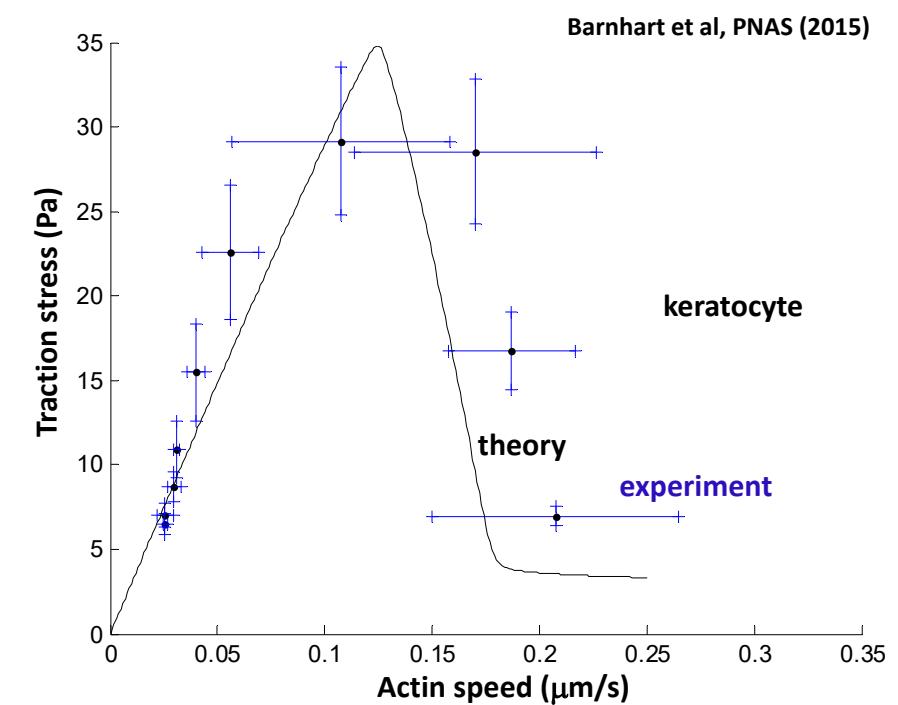
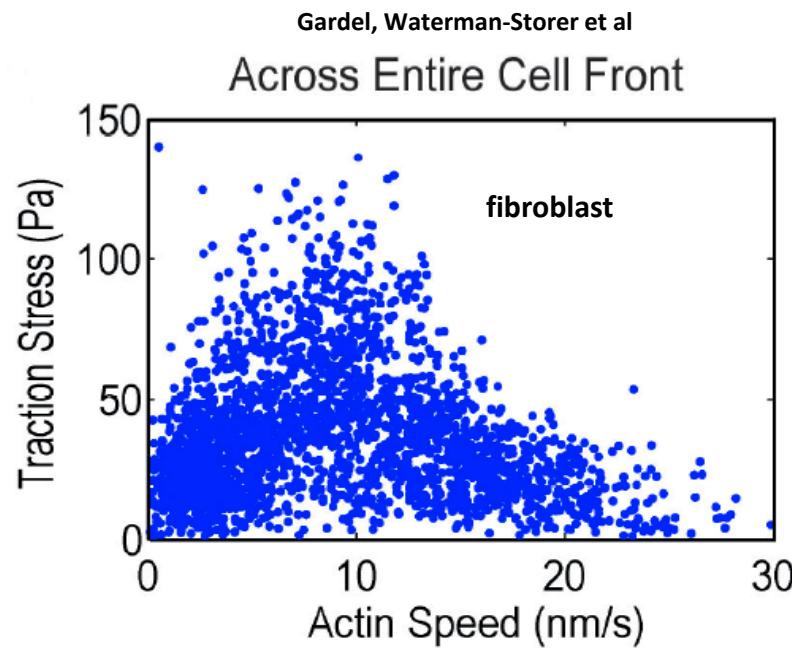
Low traction --- Fast flow



$$T_{\text{traction}} = \zeta_{\text{adhesion}} \times U_{\text{flow}}$$

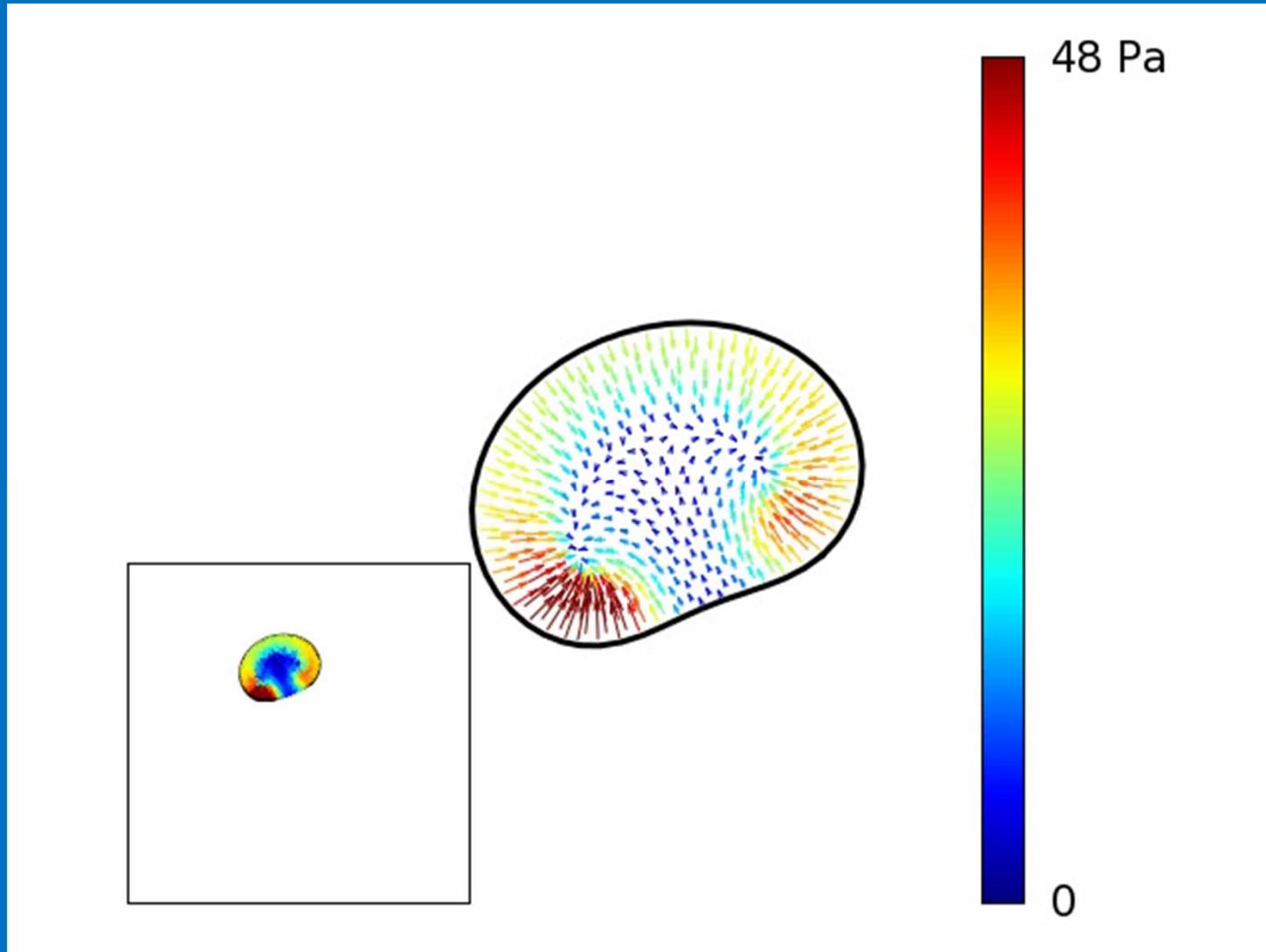


Hypothesis: negative feedback between actin flow and adhesion



Free boundary simulation

Barnhart et al, PNAS (2015)



Motility initiation by transient local adhesion weakening

Barnhart et al, PNAS (2015)

