Mathematical Cell Biology Graduate Summer Course
University of British Columbia, May 1-31, 2012

Leah Edelstein-Keshet

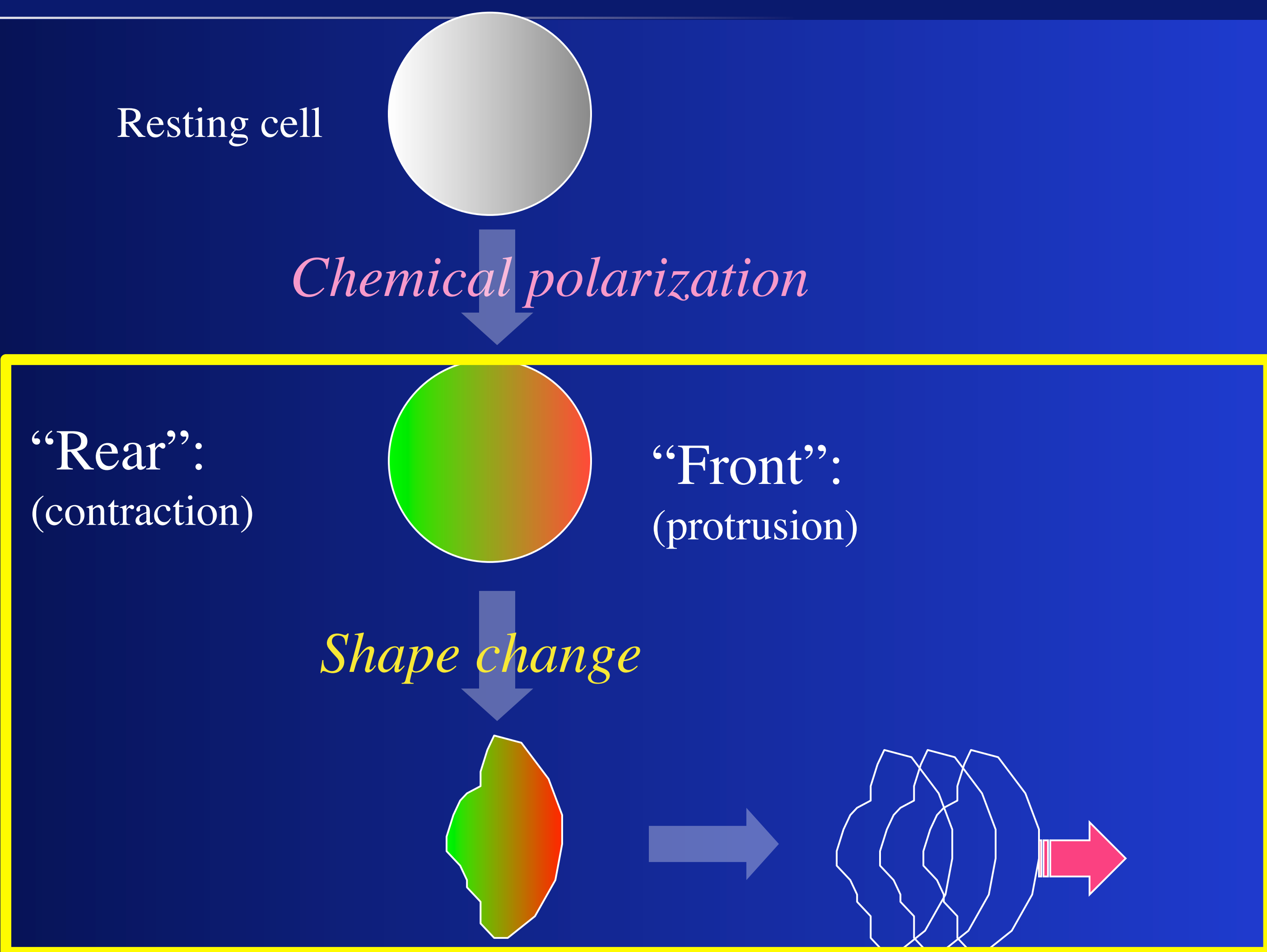
Part 2: Simulating cell motility using CPM

mprime

PIMS

www.math.ubc.ca/~keshet/MCB2012/

Shape change and motility



What are the overarching questions?

- How is the shape and motility of the cell regulated?
- What governs cell morphology, and why does it differ over different cell types?
- How do cells polarize, change shape, and initiate motility?
- How do they maintain their directionality?
- How can they respond to new signals?
- How do they avoid getting stuck?

Types of models

- Fluid-based
- Mechanical (springs, dashpots, elastic sheets)
- Chemical (reactions in deforming domain)
- Other (agent-based, filament based, etc)

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CPM: Stan Marée

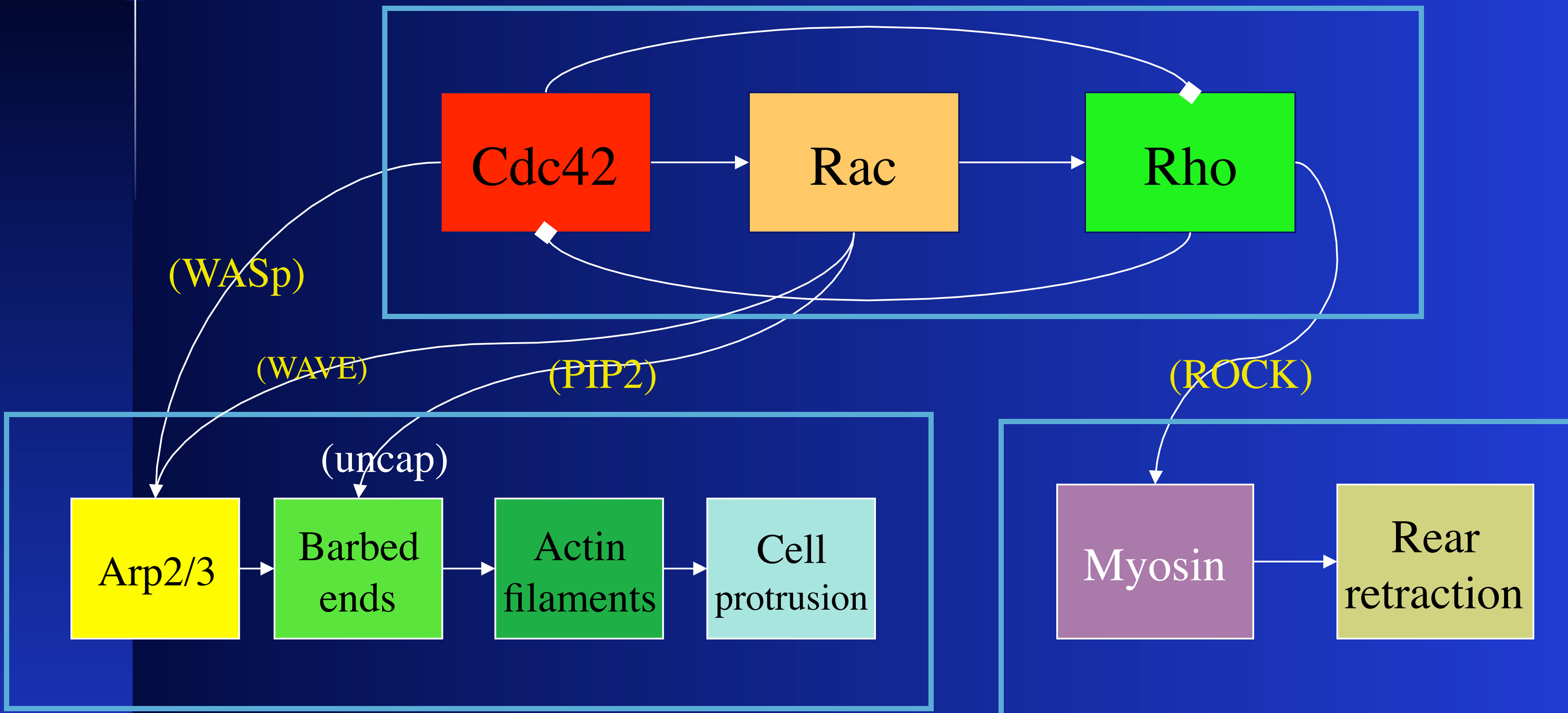
AFM Maree

V Grieneisen

Marée AFM, Jilkine A, Dawes AT, Greineisen VA, LEK (2006) Bull Math Biol, 68(5):1169-1211.

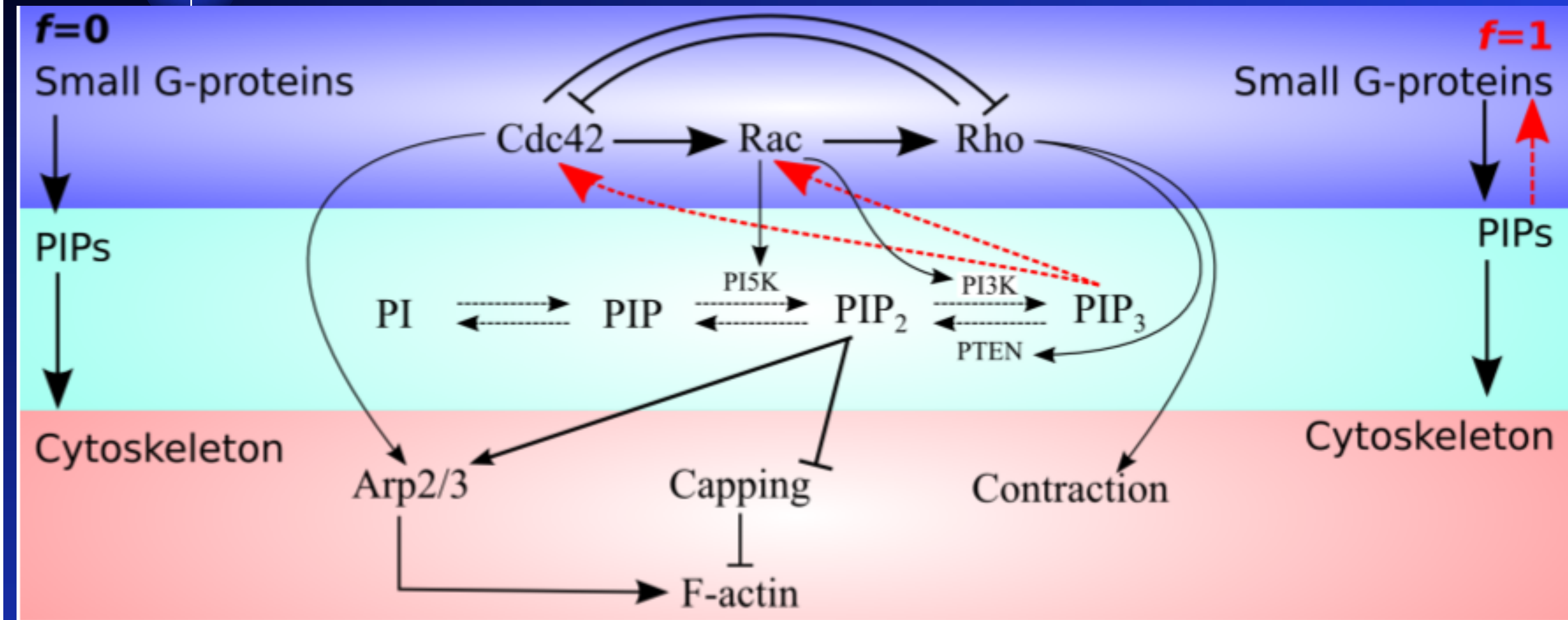
Mare ´e AFM, Grieneisen VA, Edelstein-Keshet L (2012) How Cells Integrate Complex Stimuli: The Effect of Feedback from Phosphoinositides and Cell Shape on Cell Polarization and Motility. PLoS Comput Biol 8(3): e1002402. doi:10.1371/journal.pcbi.1002402

Signaling "layers"



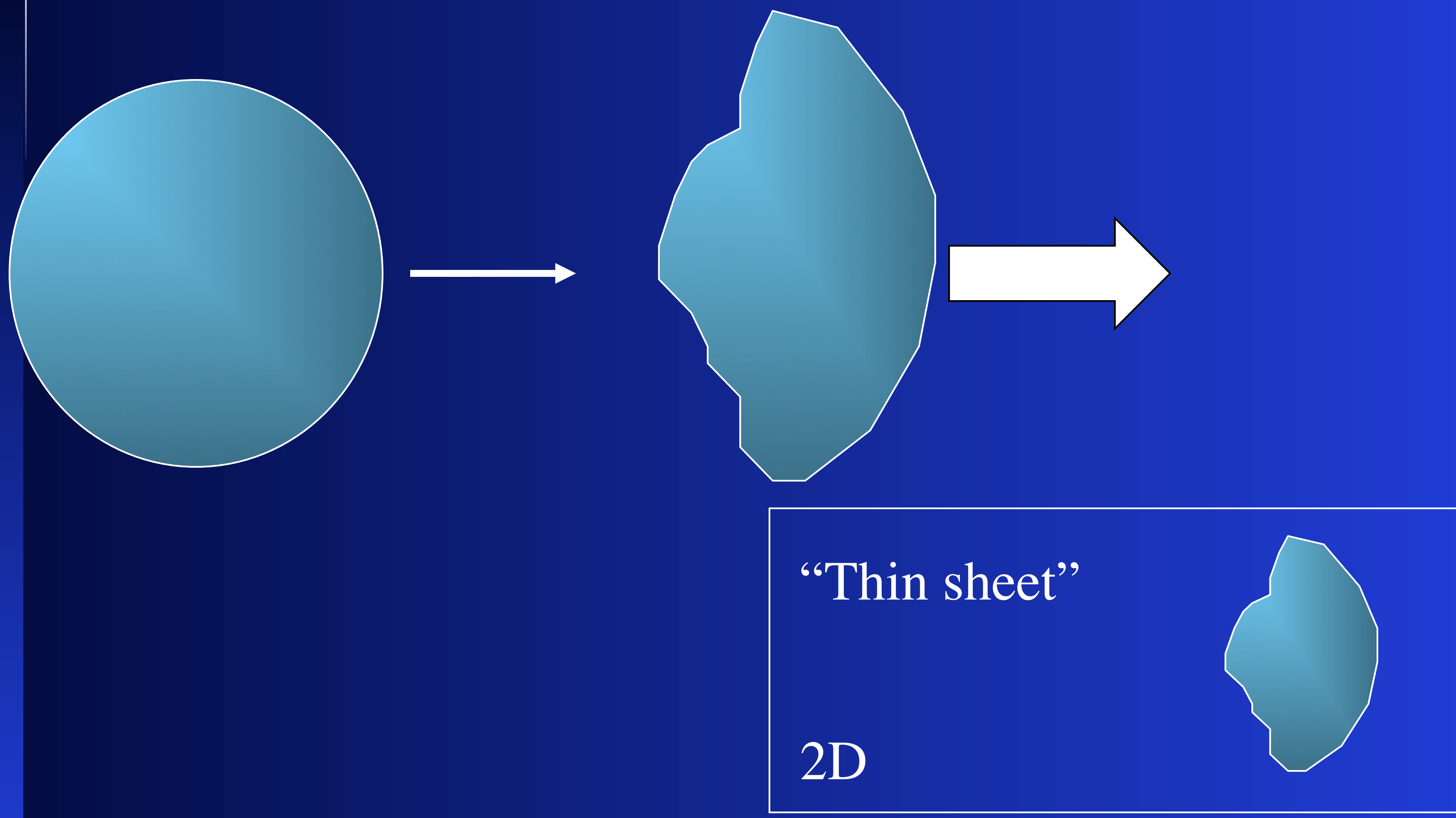
Represent reaction-diffusion and actin growth/nucleation in a 2D simulation of a "motile cell"

More recently:

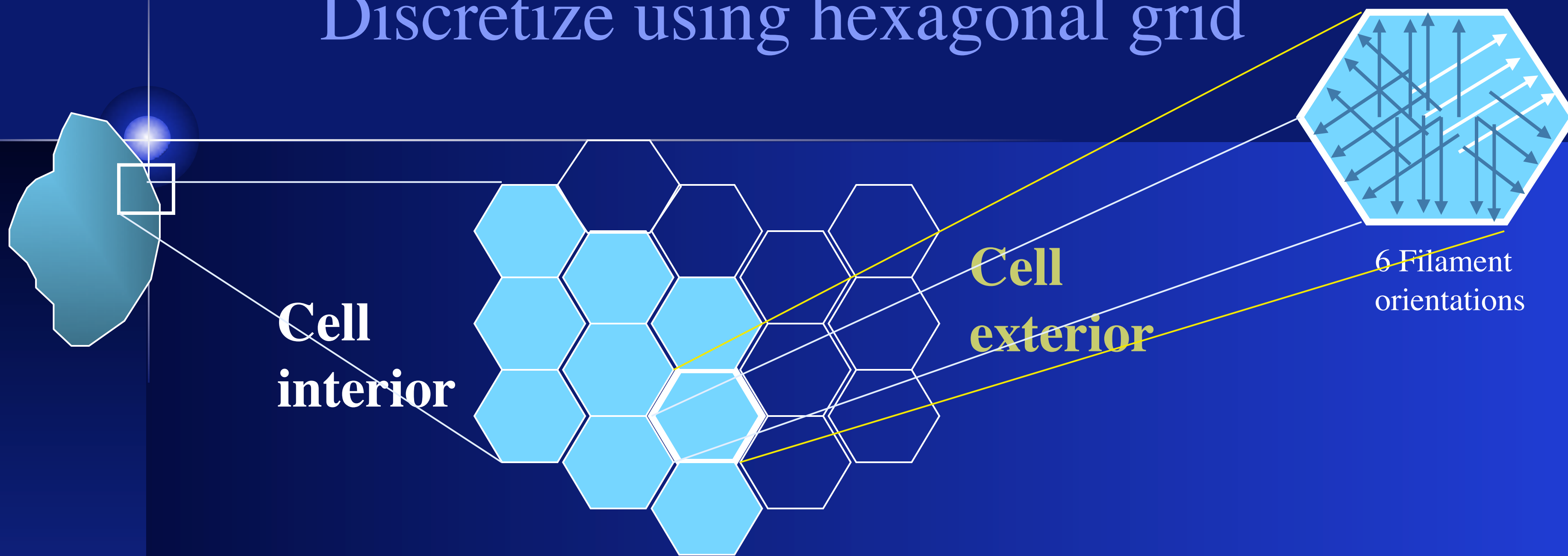


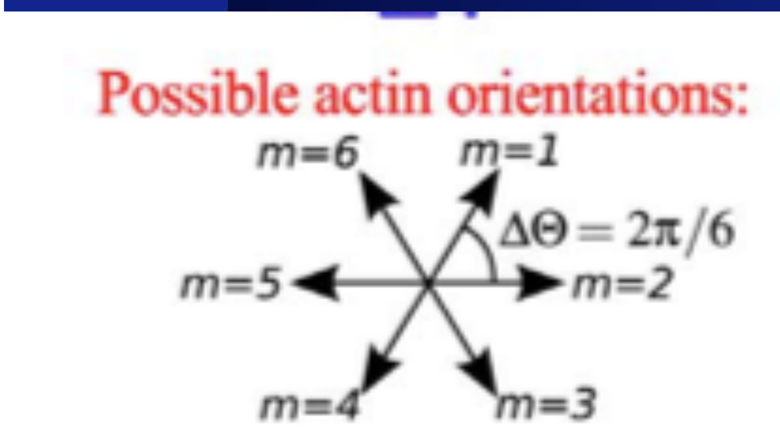
Mare ´e AFM, Grieneisen VA, Edelstein-Keshet L (2012).
PLoS Comput Biol 8(3): e1002402. doi:10.1371/journal.pcbi.1002402

2D cell motility using Potts model formalism



Discretize using hexagonal grid





- compute actin density at 6 orientations
- allow for branching by Arp2/3

Hamiltonian based computation:

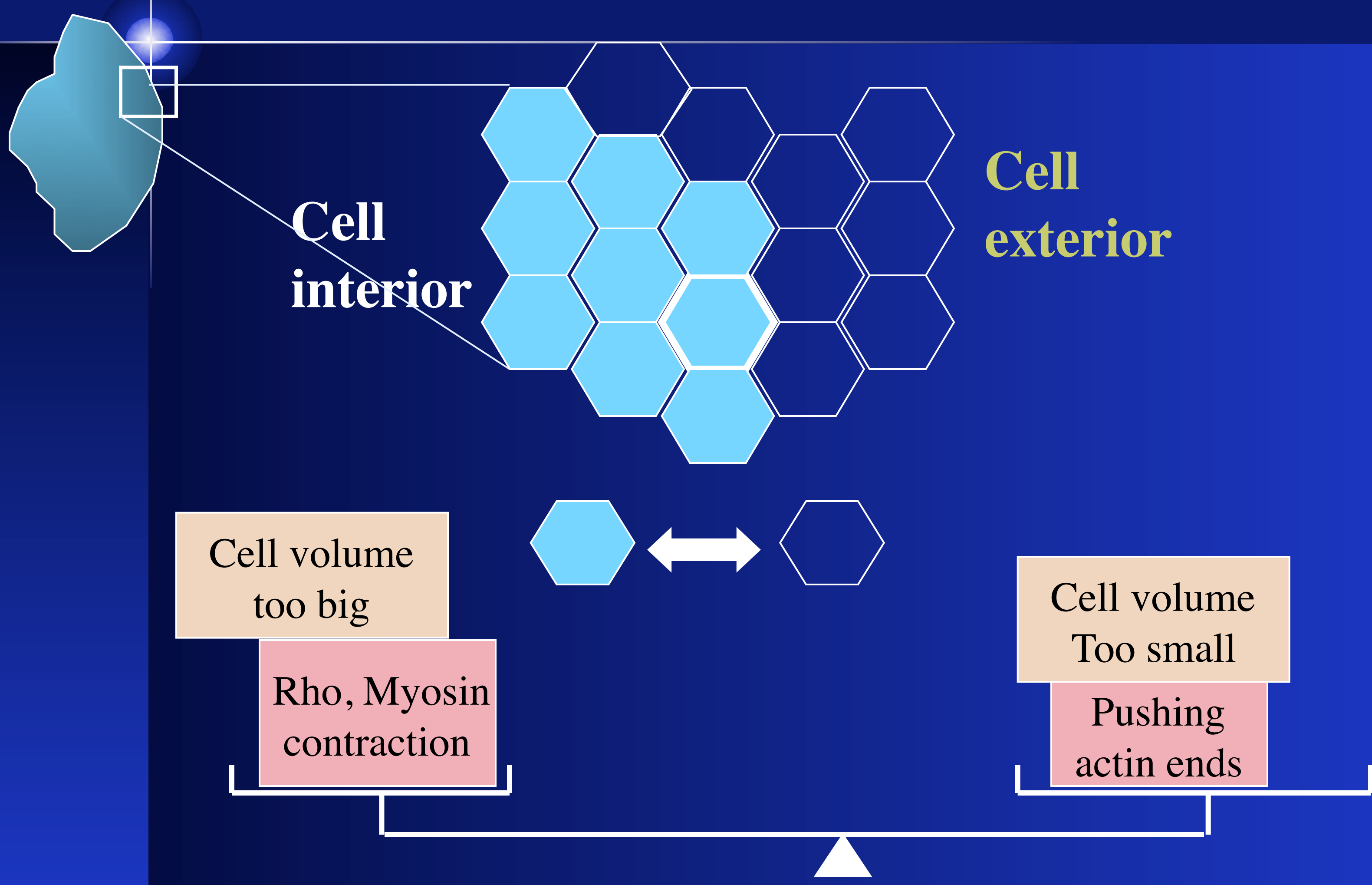
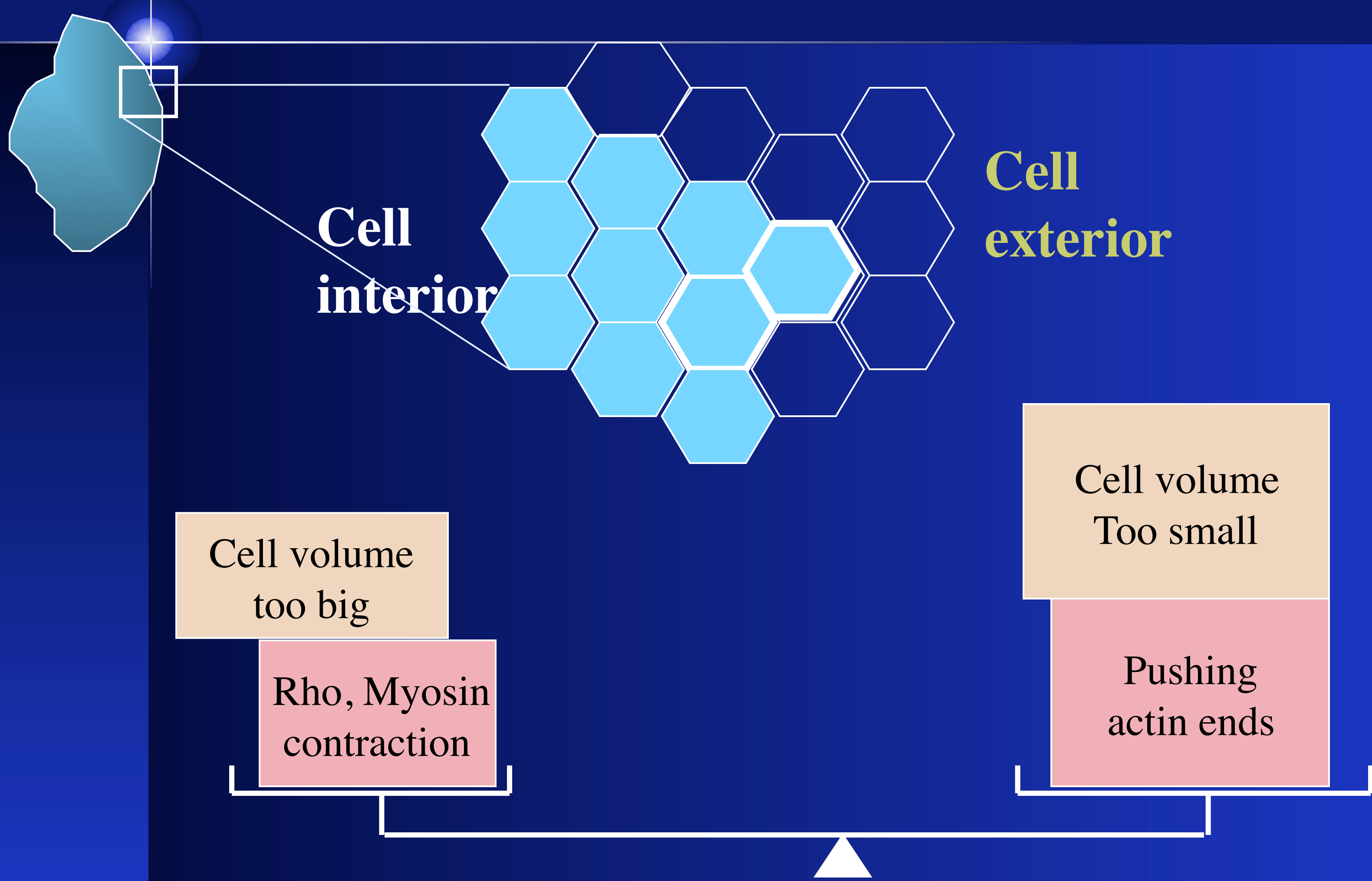


Fig: revised & adapted from: Segel, Lee A. (2001) PNAS

Protrusion


Cell interior
Cell exterior
Cell volume too big
Rho, Myosin contraction
Cell volume Too small
Pushing actin ends

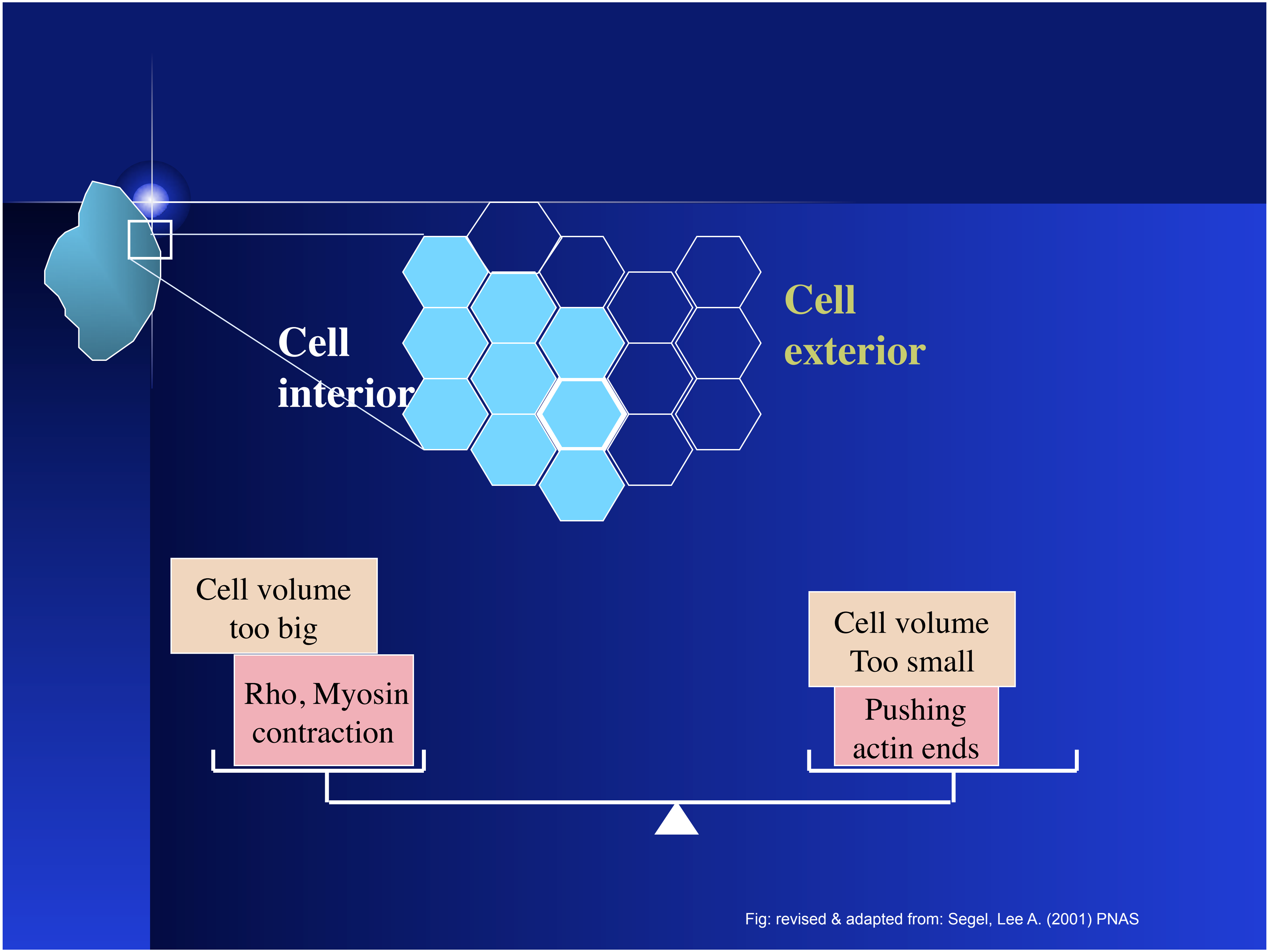
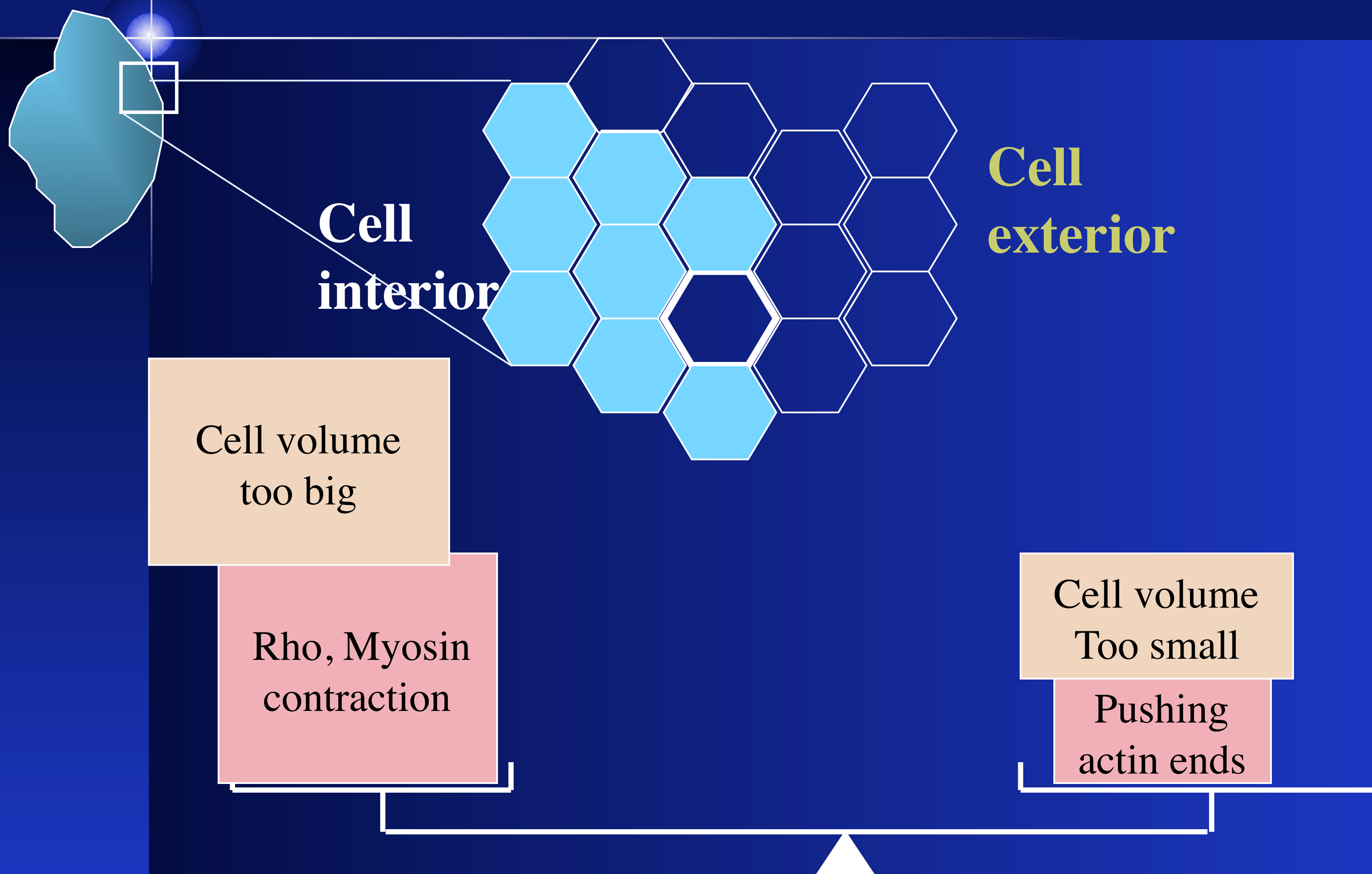


Fig: revised & adapted from: Segel, Lee A. (2001) PNAS

Retraction


Cell
interior
Cell
exterior
Cell volume
too big
Rho, Myosin
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Too small
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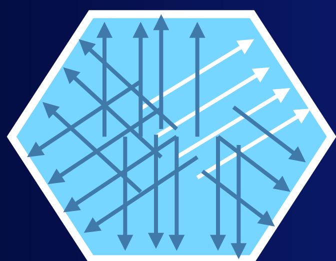
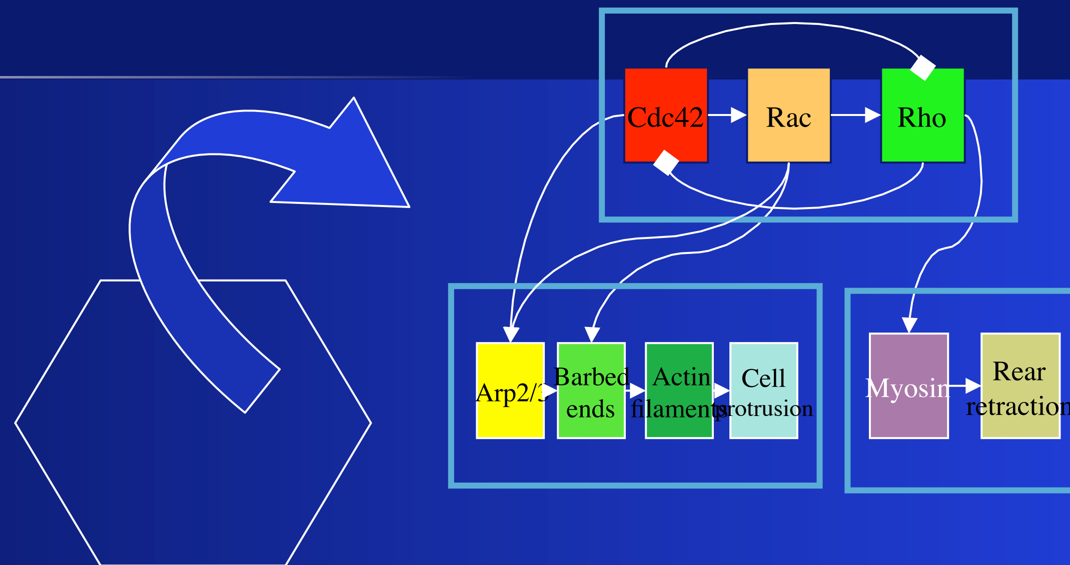
actin ends

Each hexagonal site contains:





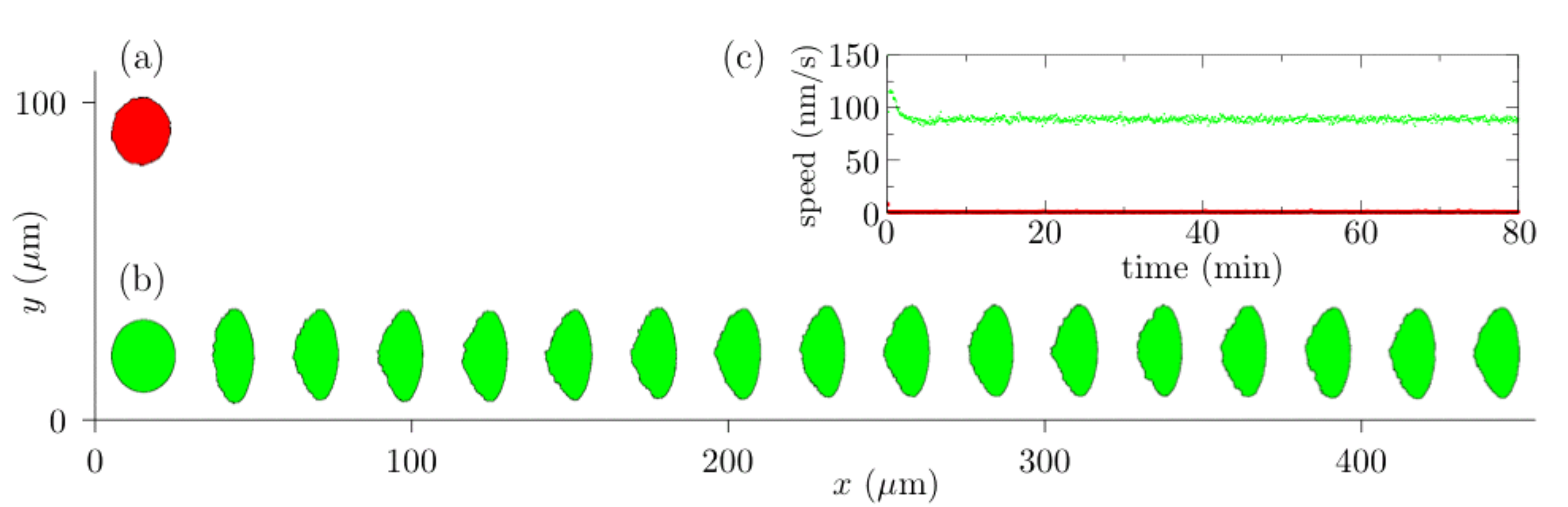
6 Filament orientations

6 barbed end orientations

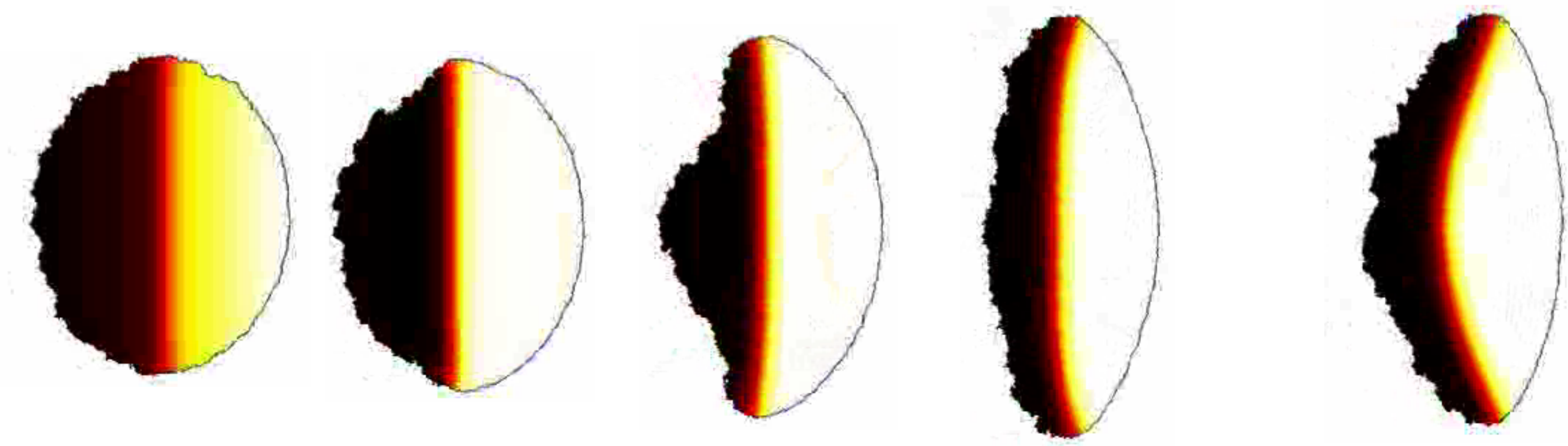
Cdc42 (active, inactive)
Rac (active, inactive)
Rho (active, inactive)
Arp2/3

PIP, PIP2, PIP3

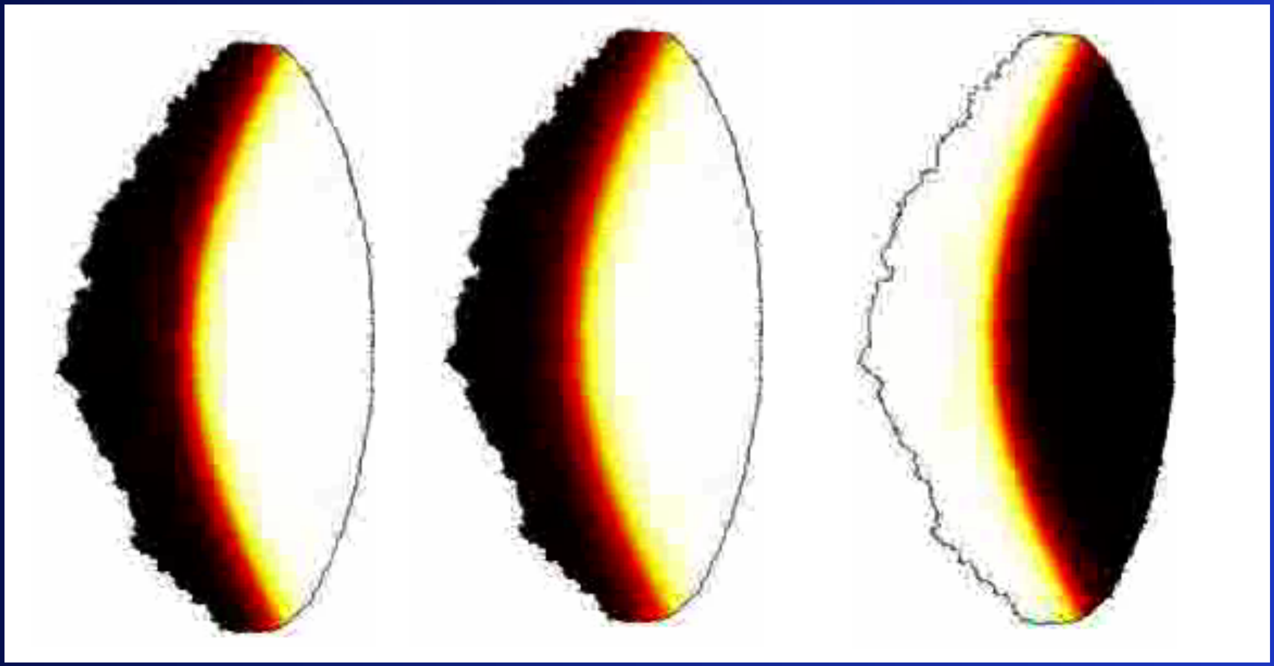
Resting vs stimulated cell



Cdc42 distribution



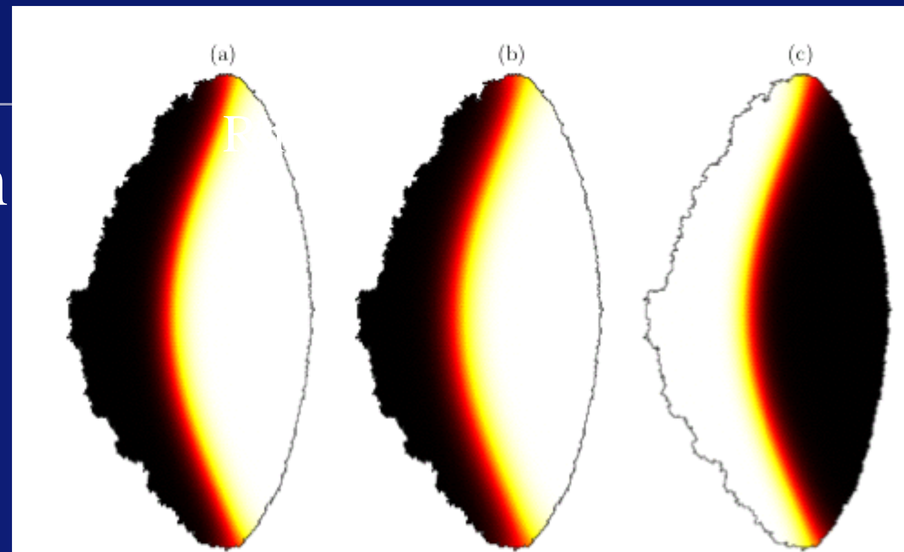
Cdc42, Rac, Rho



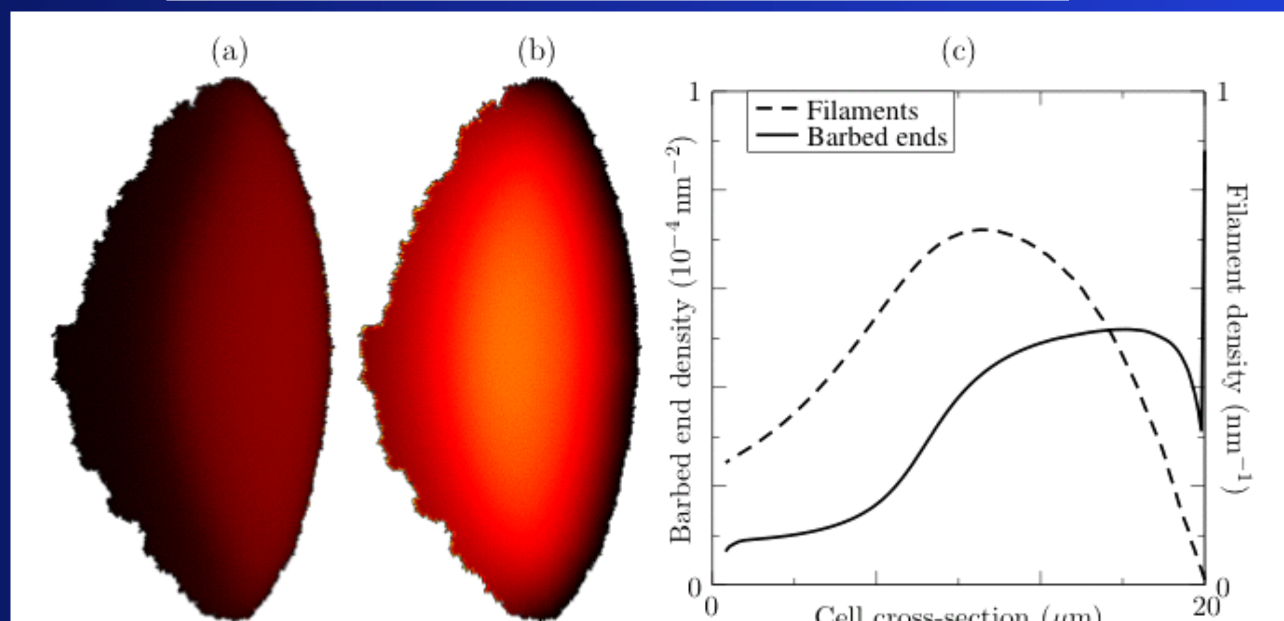
Distribution of internal biochemistry

high

low

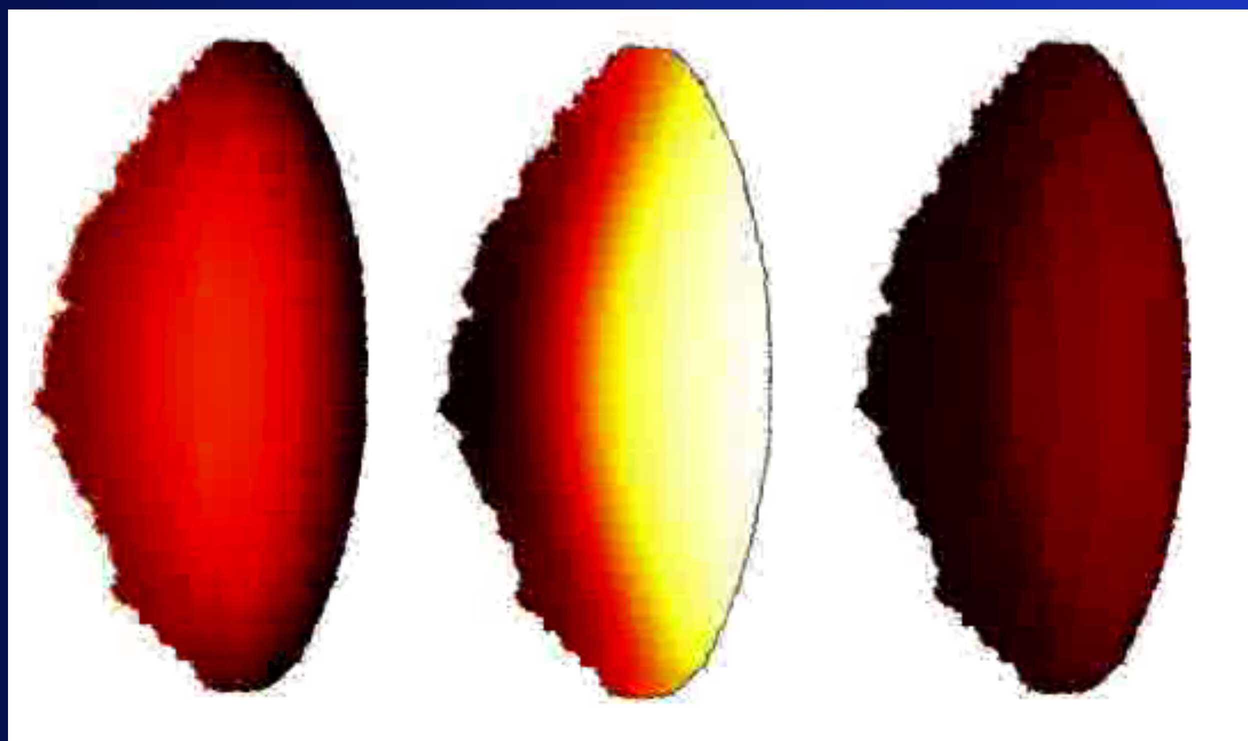


And actin:



Barbed end and filament density

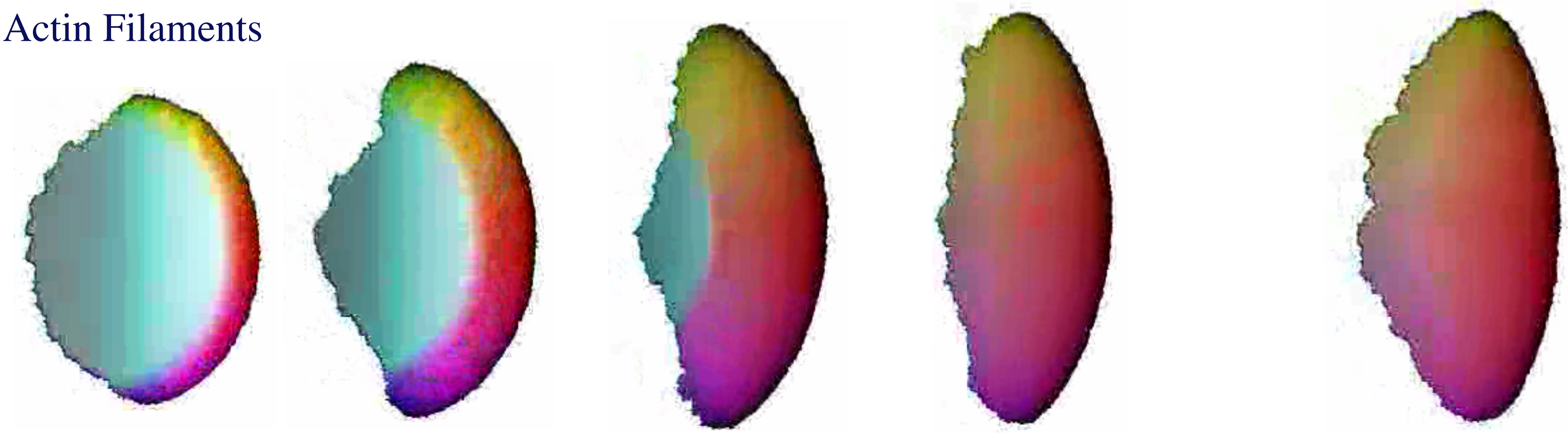
Filaments, Arp2/3, Tips

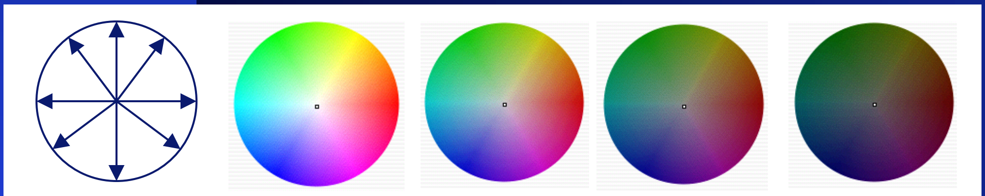


Low High

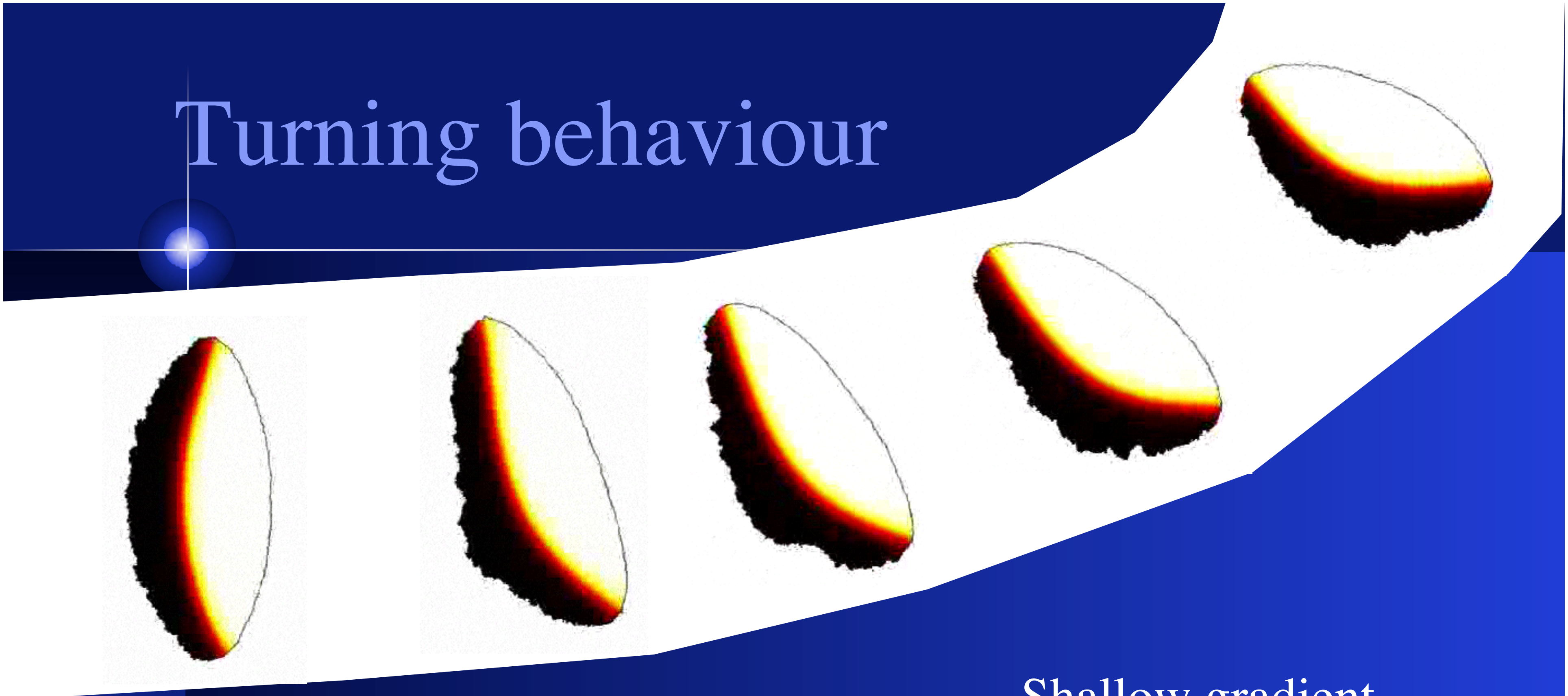
Cytoskeleton

Actin Filaments

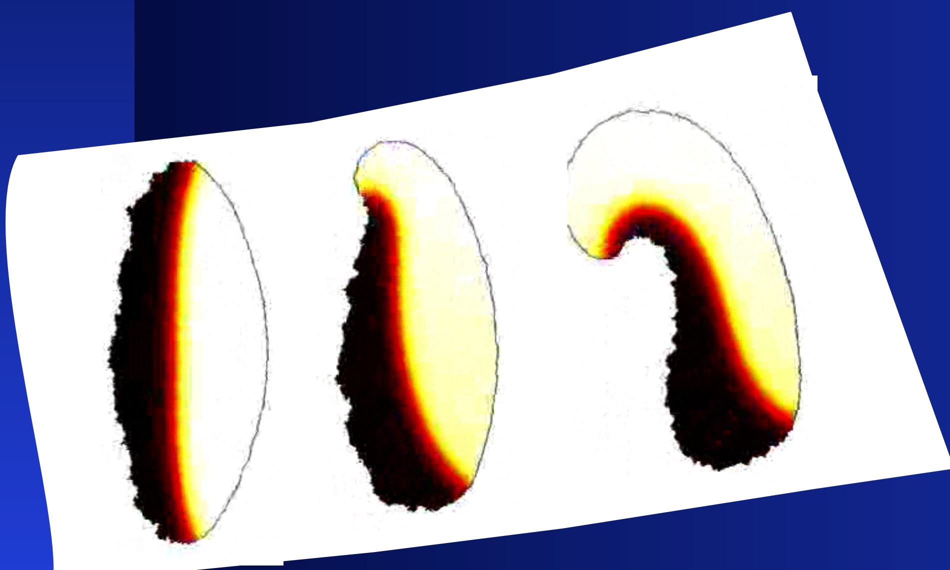




Turning behaviour



Shallow gradient

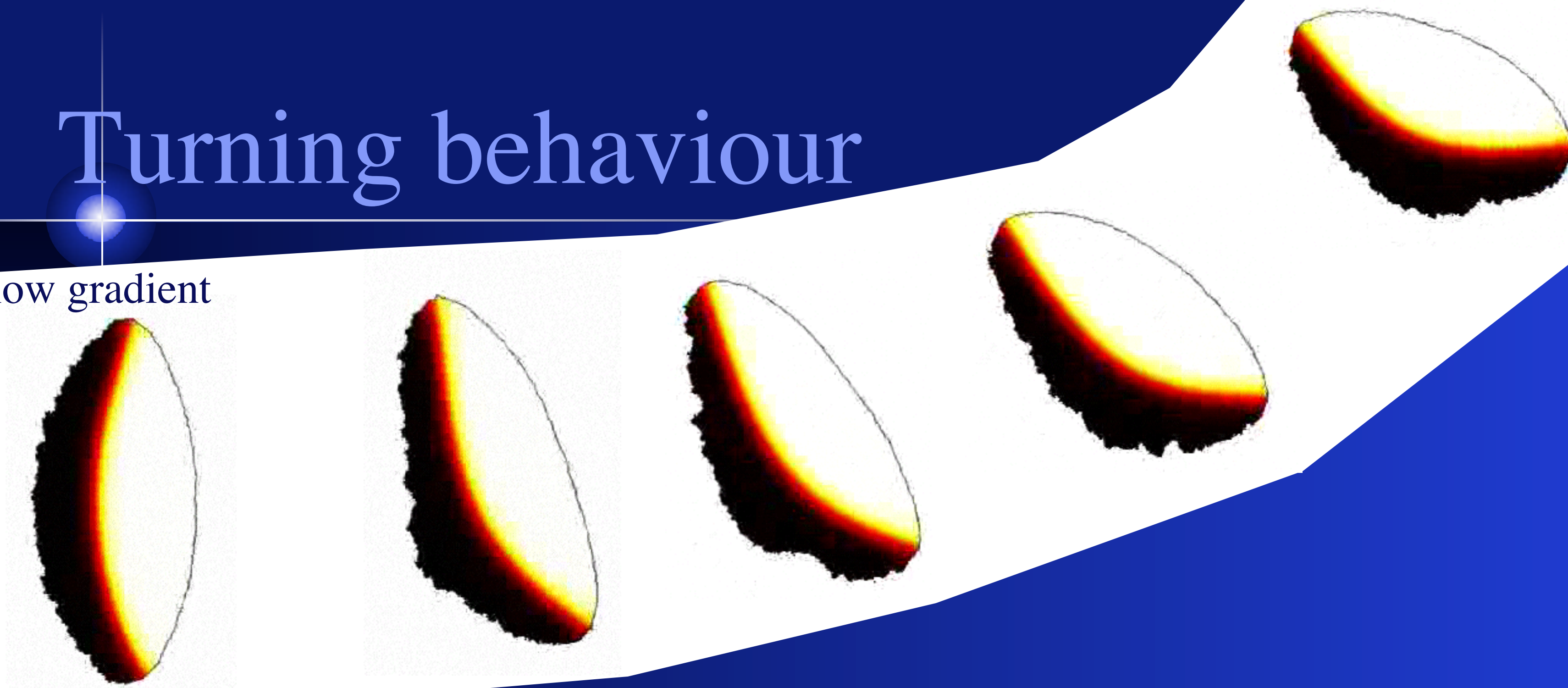


Steep gradient

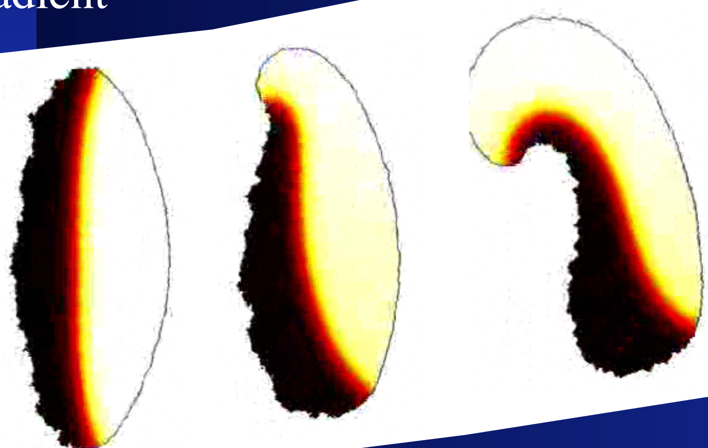
http://theory.bio.uu.nl/stan/keratocyte/

Turning behaviour

Shallow gradient



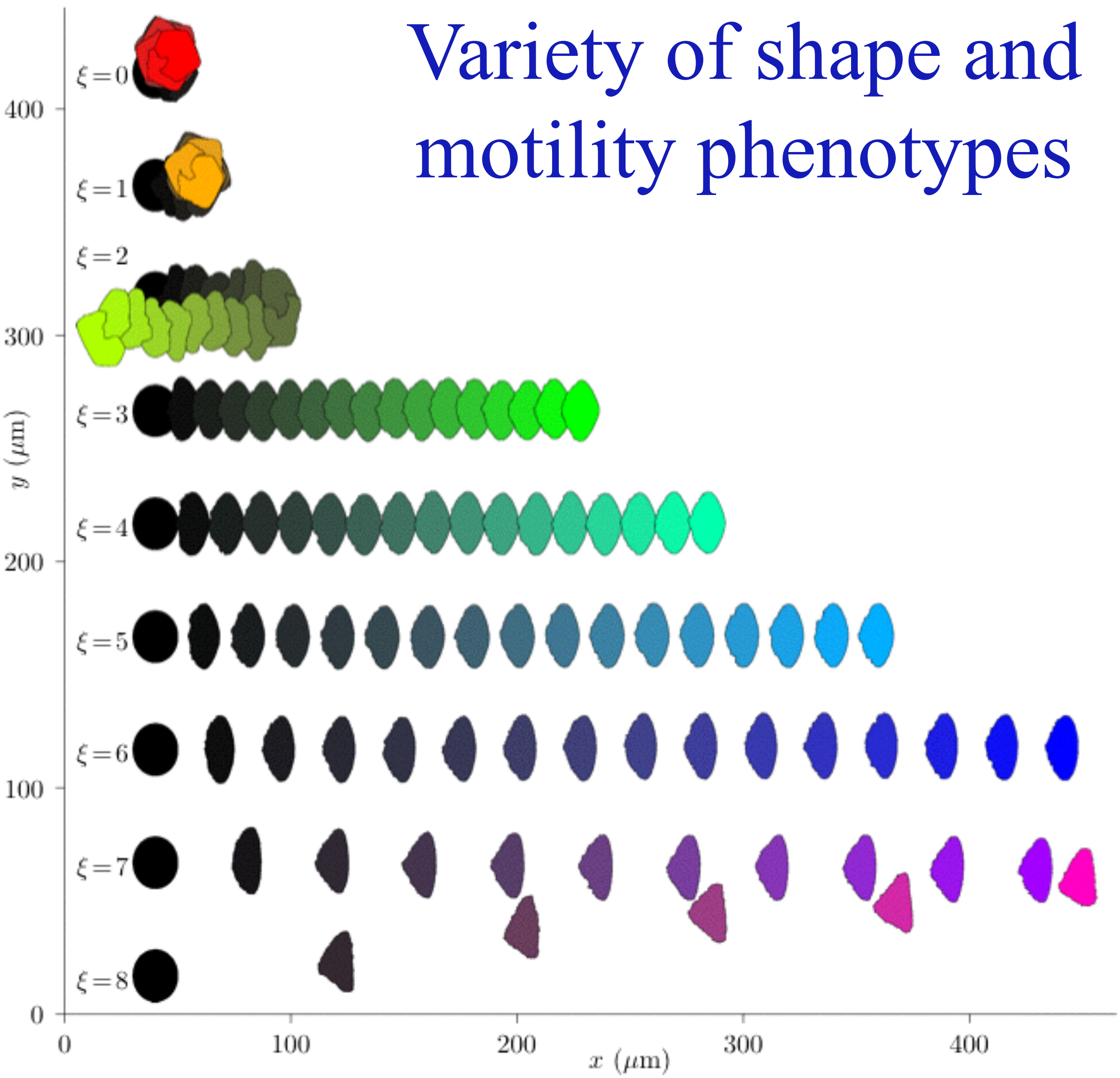
Steep gradient



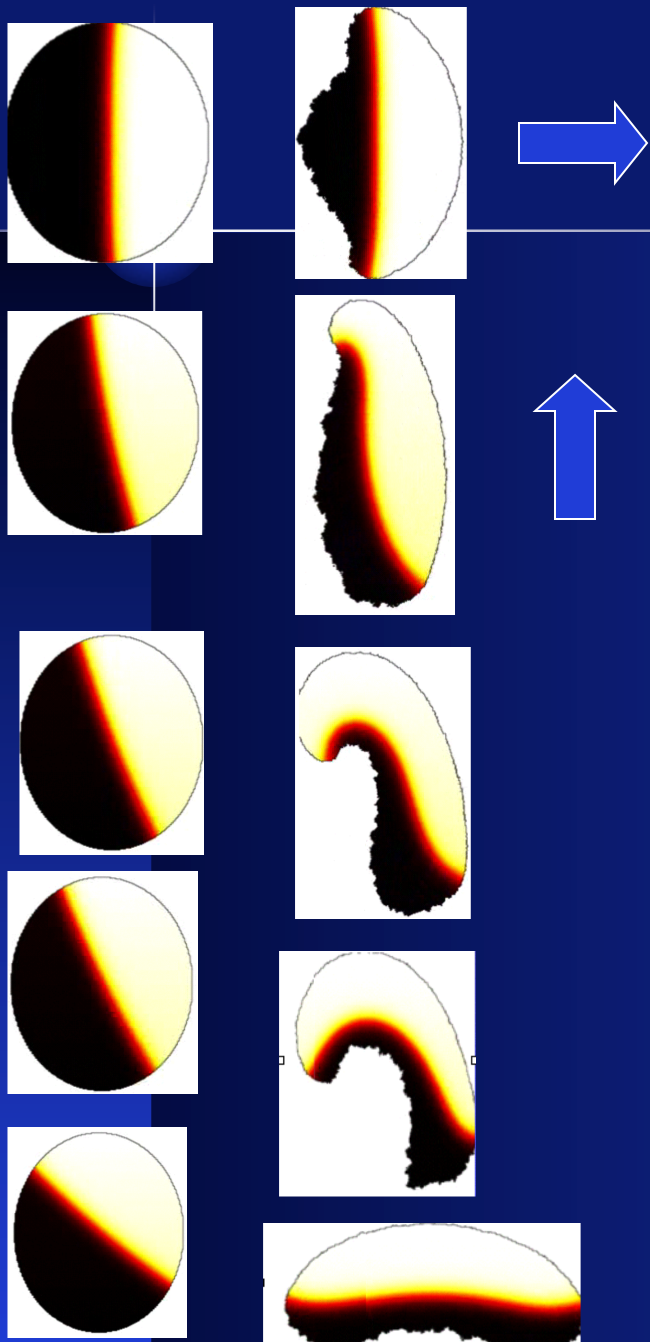
http://theory.bio.uu.nl/stan/keratocyte/

Rho induced contractility

Variety of shape and motility phenotypes

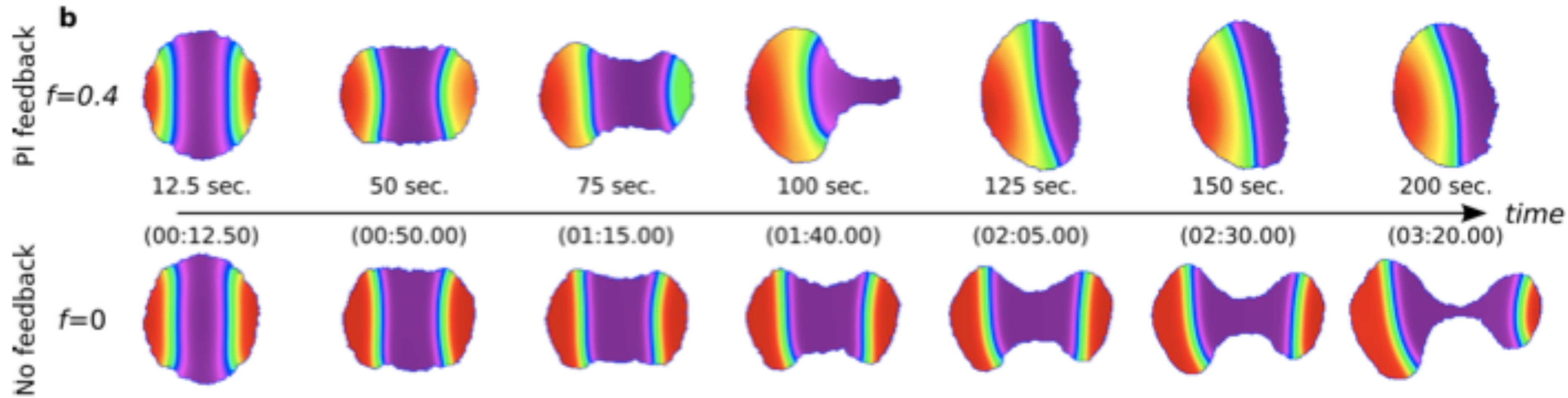


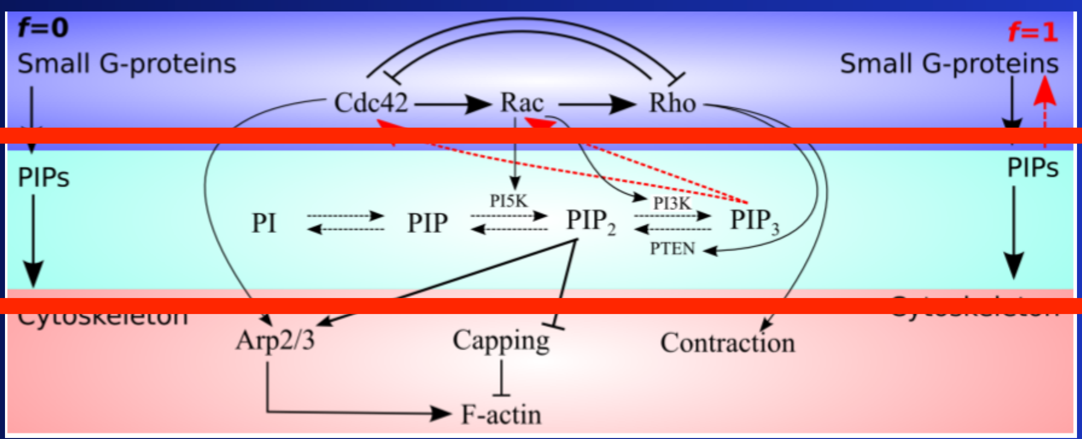
Effect of shape

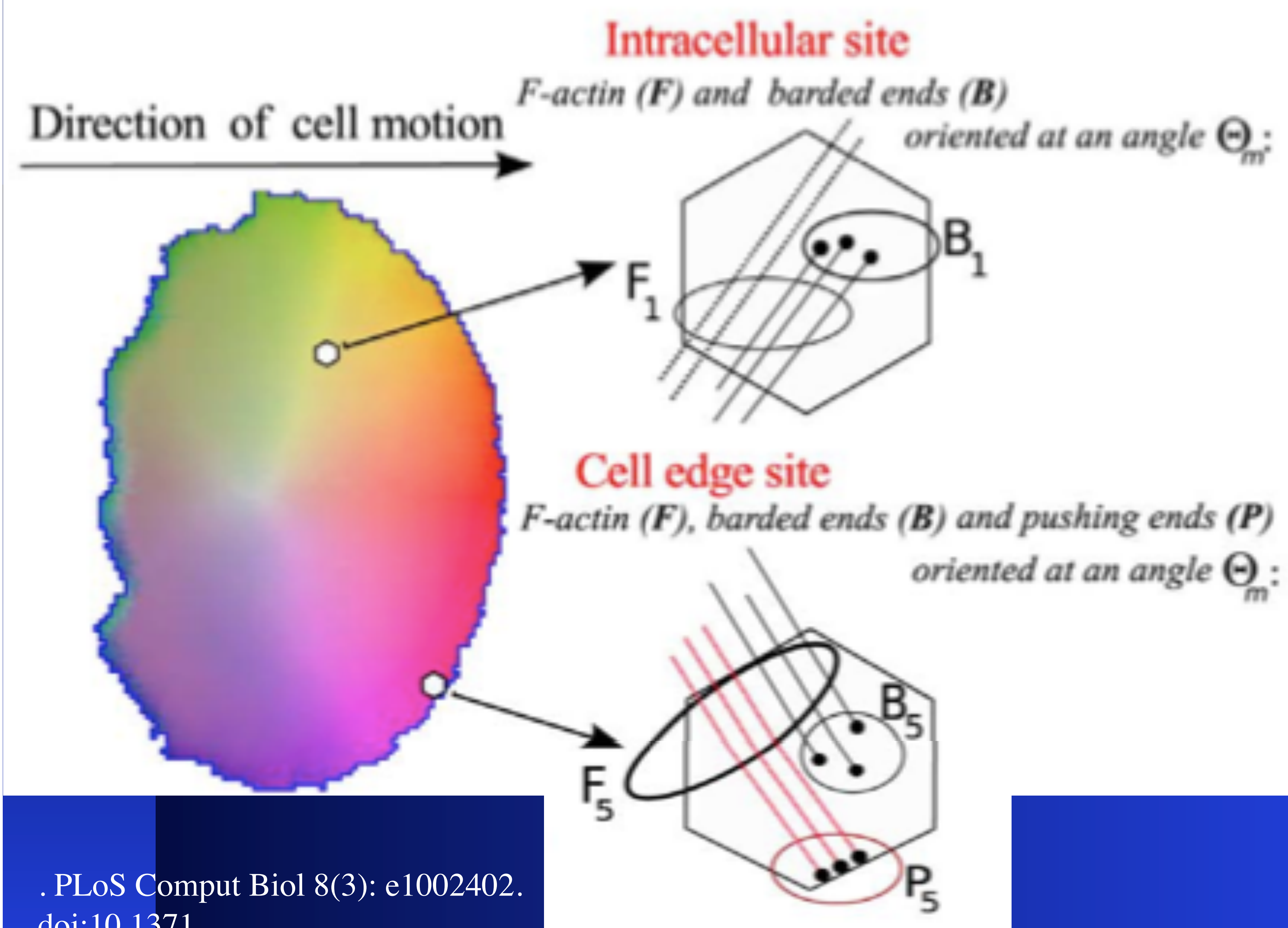


- cell can repolarize whether or not its shape is allowed to evolve
- when shape is dynamic, reaction to new stimuli is much more rapid

What the lipids do: fine tuning

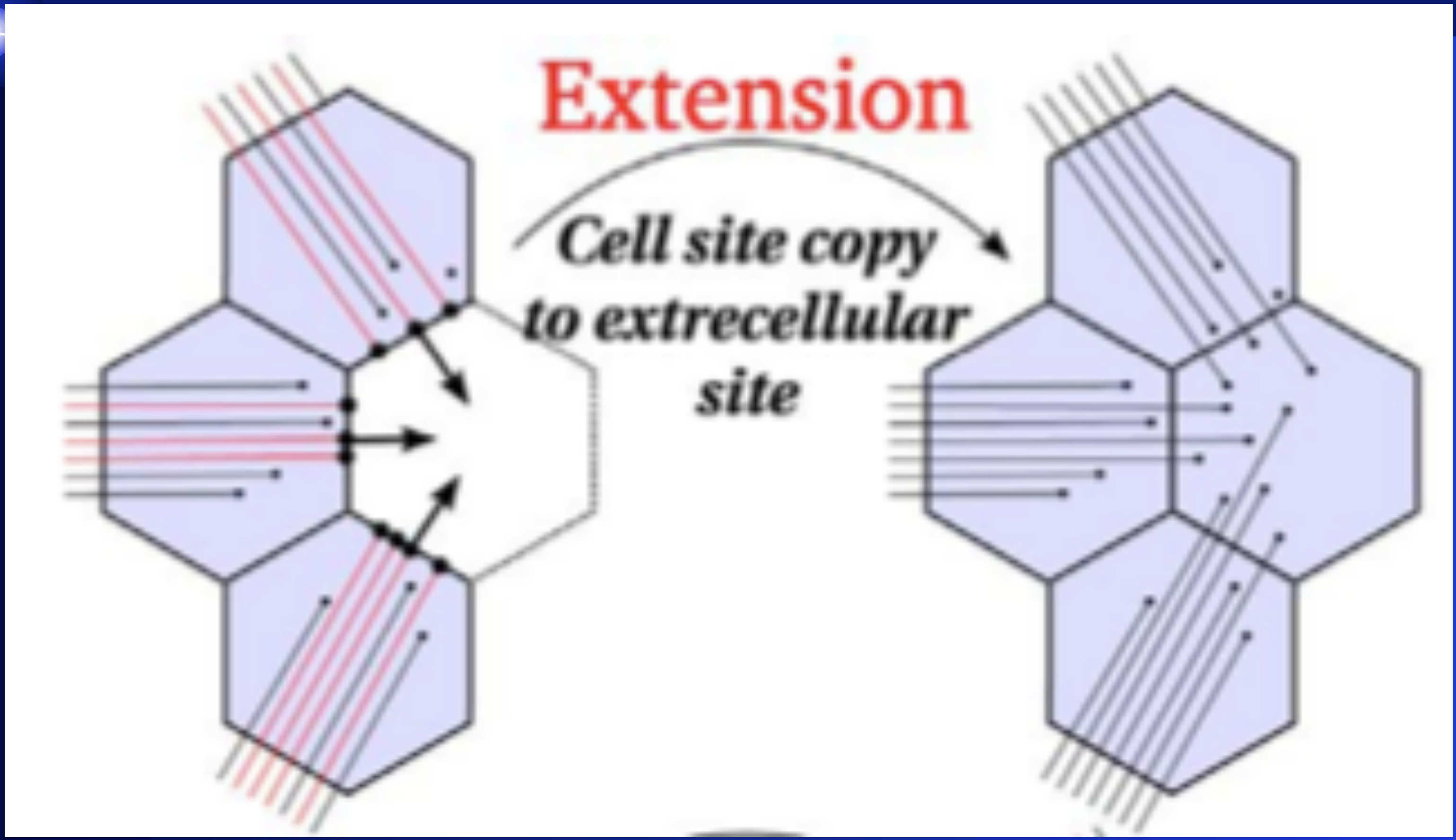






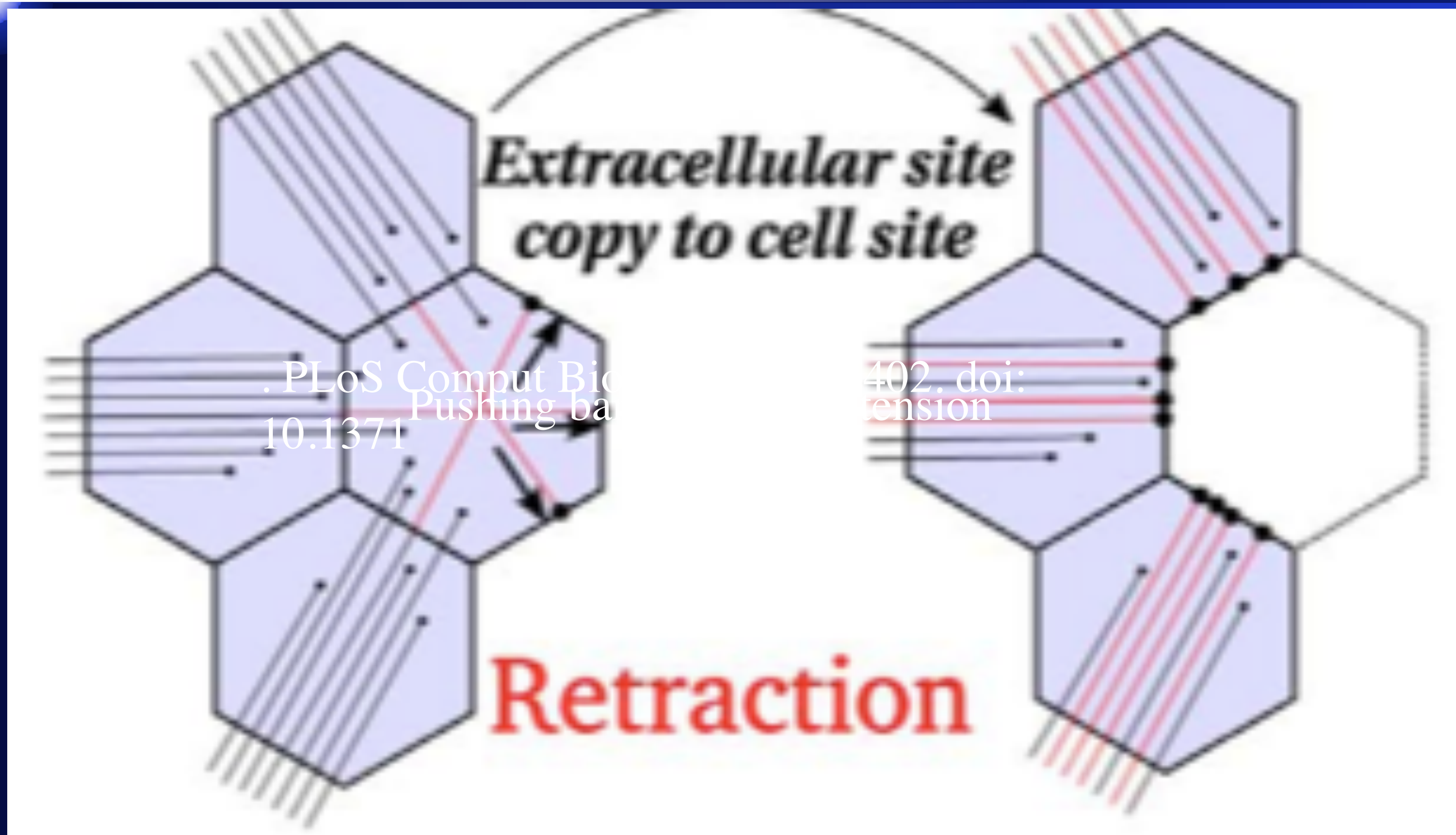
. PLoS Comput Biol 8(3): e1002402.
doi:10.1371

Pushing barbed ends: extension



Mare ´e AFM, Grieneisen VA, Edelstein-Keshet L (2012) How Cells Integrate Complex Stimuli: The Effect of Feedback from Phosphoinositides and Cell Shape on Cell Polarization and Motility. PLoS Comput Biol 8(3): e1002402. doi:10.1371/journal.pcbi.1002402

Pushing barbed ends: retraction



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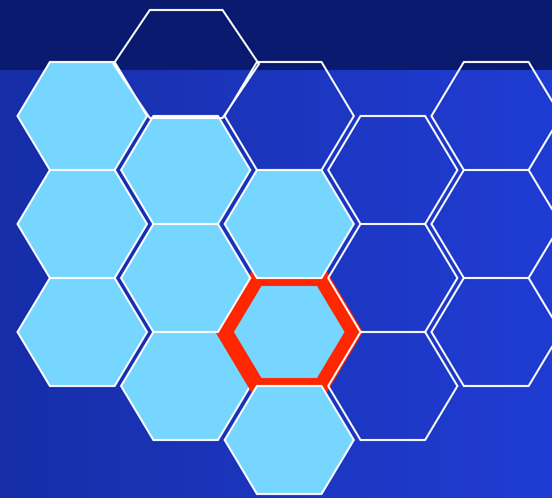
From Jun Allard's Lecture 5: (Simulating membrane mechanics)

Metropolis-Hastings simulation

1. Choose node at random
2. Propose to move node by a random distance
3. Compute new E{zi,j}
4. If $\Delta E < 0$, keep move

   If $\Delta E > 0 \quad P(\text{keep}) = e^{-\Delta E / k_B T}$

CPM Metropolis:



1. Choose edge site at random
2. Propose to extend or retract
3. Compute new H
4. If $\Delta H < -H_b$ keep this move
5. If $\Delta H \geq -H_b$ accept move with probability

$$\exp\left(-\frac{\Delta H + H_b}{T}\right)$$

6. Iterate over each lattice site randomly

Hamiltonian and Energy minimization

- Energy of cell interface
- of area expansion
- of perimeter change

$$H = \sum J_{CM} + \lambda_a (a - \mathcal{A})^2 + \lambda_p (p - \mathcal{P})^2,$$

Effective forces

- Effect of pushing barbed ends
- of myosin contraction

$$\Delta H' = \Delta H - \sum_m P_{\theta_m} + \xi(\rho - \rho_{th}) \text{when the cell extends,}$$

$$\Delta H' = \Delta H + \sum_m P_{\theta_m} - \xi(\rho - \rho_{th}) \text{when the cell retracts.}$$

CPM parameters

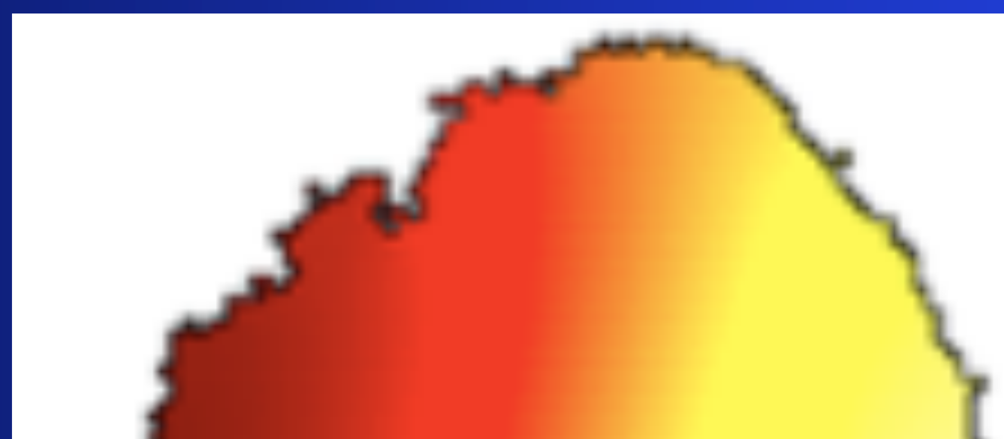
Parameter	Meaning	Values	Units
Δx	grid step size	100	nm
Δt	Monte Carlo time step (MCS)	0.1	s
T	simulation "temperature"	0.008	nm^{-1}
H_b	membrane yield	0.046	nm^{-1}
J_{CM}	coupling energy per boundary site	7.5×10^{-4}	nm^{-1}
λ	inelasticity constant	10^{-9}	nm^{-3}
$\mathcal{A}$	target area of the cell	3×10^{8}	nm^{2}
ρ_{th}	Rho threshold for contraction	1.25	M
ξ	effect of Rho on contraction	0.06	$M\,nm^{-1}$
w	renormalised membrane resistance	0.05	nm^{-1}

“Temperature”

- This parameter governs the fluctuation intensity

$$\exp\left(-\frac{\Delta H + H_b}{T}\right)$$

- Note edge of “cell” thereby fluctuates:



Relationship between v and b: edge protrusion and barbed end density

- Consider case of no capping, no branching
- Suppose fraction (1-*f*) barbed ends pushing, and fraction *f* are not.
- Probability to extend and to retract:

$$P_{\text{extend}} = \exp\left(\frac{-H_b - (1-f)b}{T}\right)$$

$$P_{\text{retract}} = \exp\left(\frac{-H_b + (1-f)b}{T}\right)$$

Protrusion speed

- Effective speed of protrusion:

$$v = \frac{\Delta x}{\Delta t}\left(P_{\mathrm{extend}} - P_{\mathrm{retract}}\right)$$

Mean velocity related to fraction *f*:

- Mean velocity = $v = f\, v_0$
- $$= \frac{fb \times v_0 + (1 - f)b \times 0}{b}$$
- $f = v / v_0$

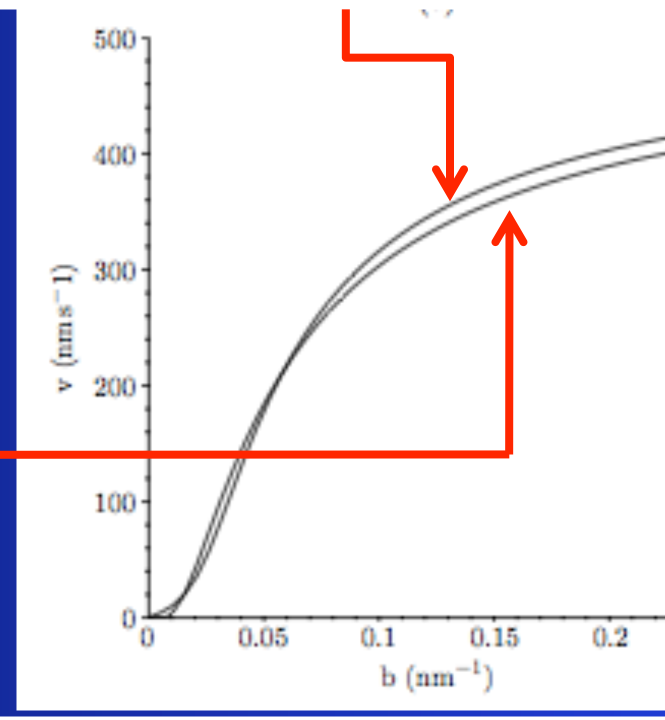
CPM Parameters T and H_b "tuned" to known relationship of v to b

- CPM formula:

$$v = \frac{\Delta x}{\Delta t} \exp(-H_b/T)\left(\exp\left(\frac{(1-v/v_0)b}{T}\right) - \exp\left(\frac{-(1-v/v_0)b}{T}\right)\right).$$

- "known" relationship

$$v = v_0 \exp(-w/b),$$



CPM Pluses

- Reasonably "easy" fast computations allow for more detailed biochemistry
- Captures fluctuations well
- Can be tuned to behave like thermal-ratchet based protrusion
- Easily extended to multiple interacting cells

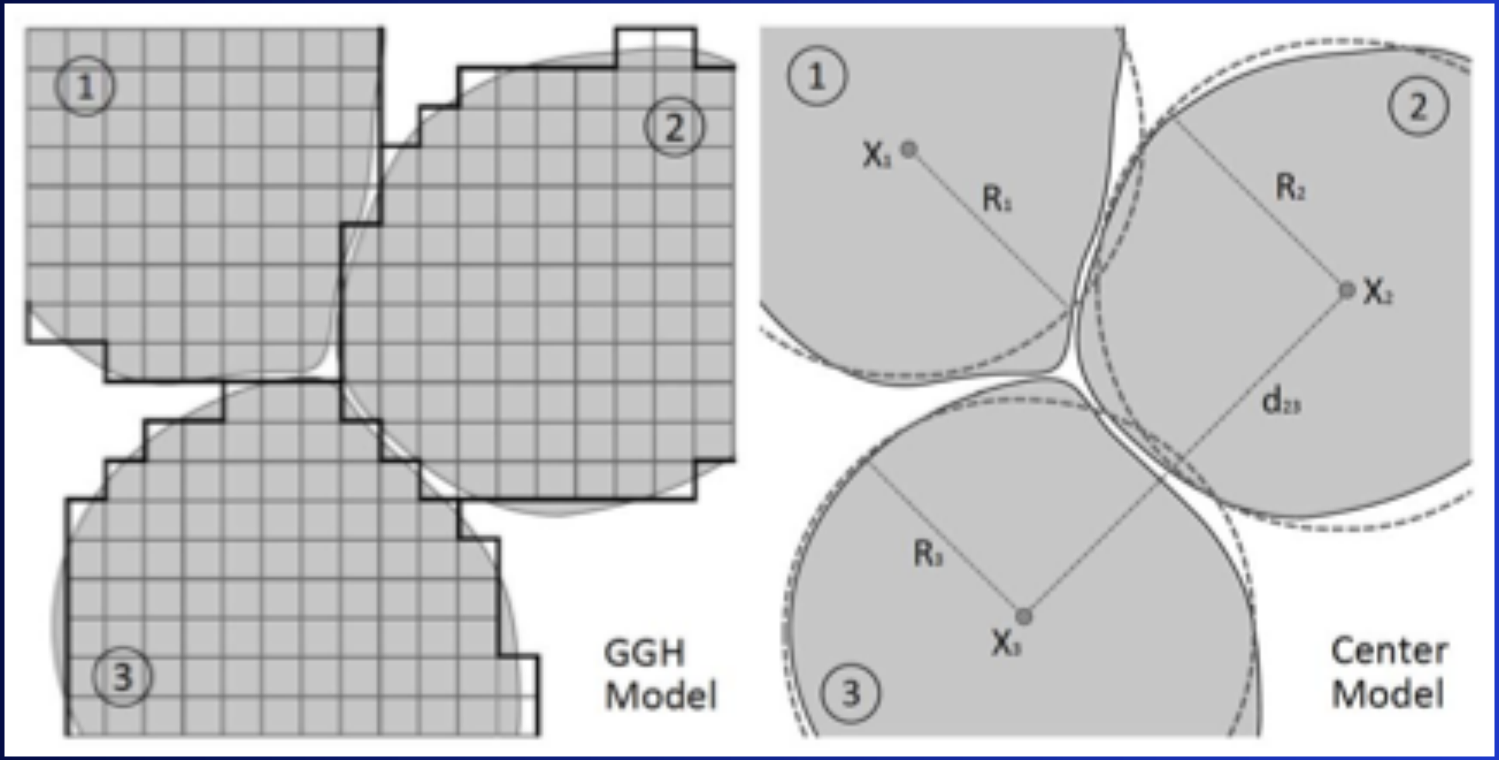
CPM minuses

- Mechanical forces not explicitly described
- Interpretation of CPM parameters less direct
- No representation of fluid properties of cell interior, exterior
- Controversy of application of Metropolis algorithm to non-equilibrium situations.

Comparative study

- CPM

Mechanical cells



Andasari V, Roper RT, Swat MH, Chaplain MAJ (2012) Integrating Intracellular Dynamics Using CompuCell3D and Bionetsolver: Applications to Multiscale Modelling of Cancer Cell Growth and Invasion. PLoS ONE 7(3): e33726. doi:10.1371/journal.pone.0033726