Northeastern University

How to move faster together than alone?

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NYU

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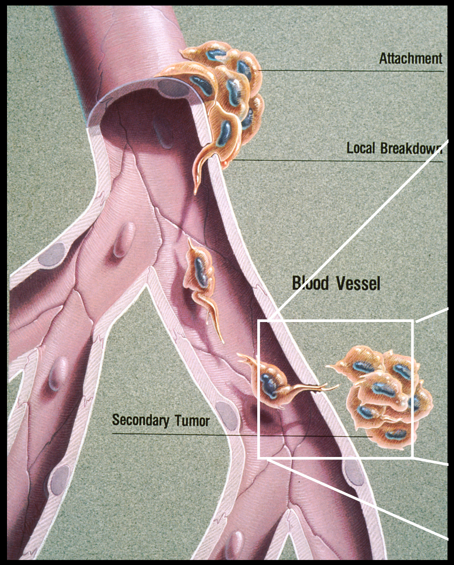
University of Bergen

Copos Lab

Our focus: The living cell as a moving evolving material

White blood cells in wound healing

Metastatic cancer



What are we motivated by?
Immune system response, cancer metastasis, embryogenesis

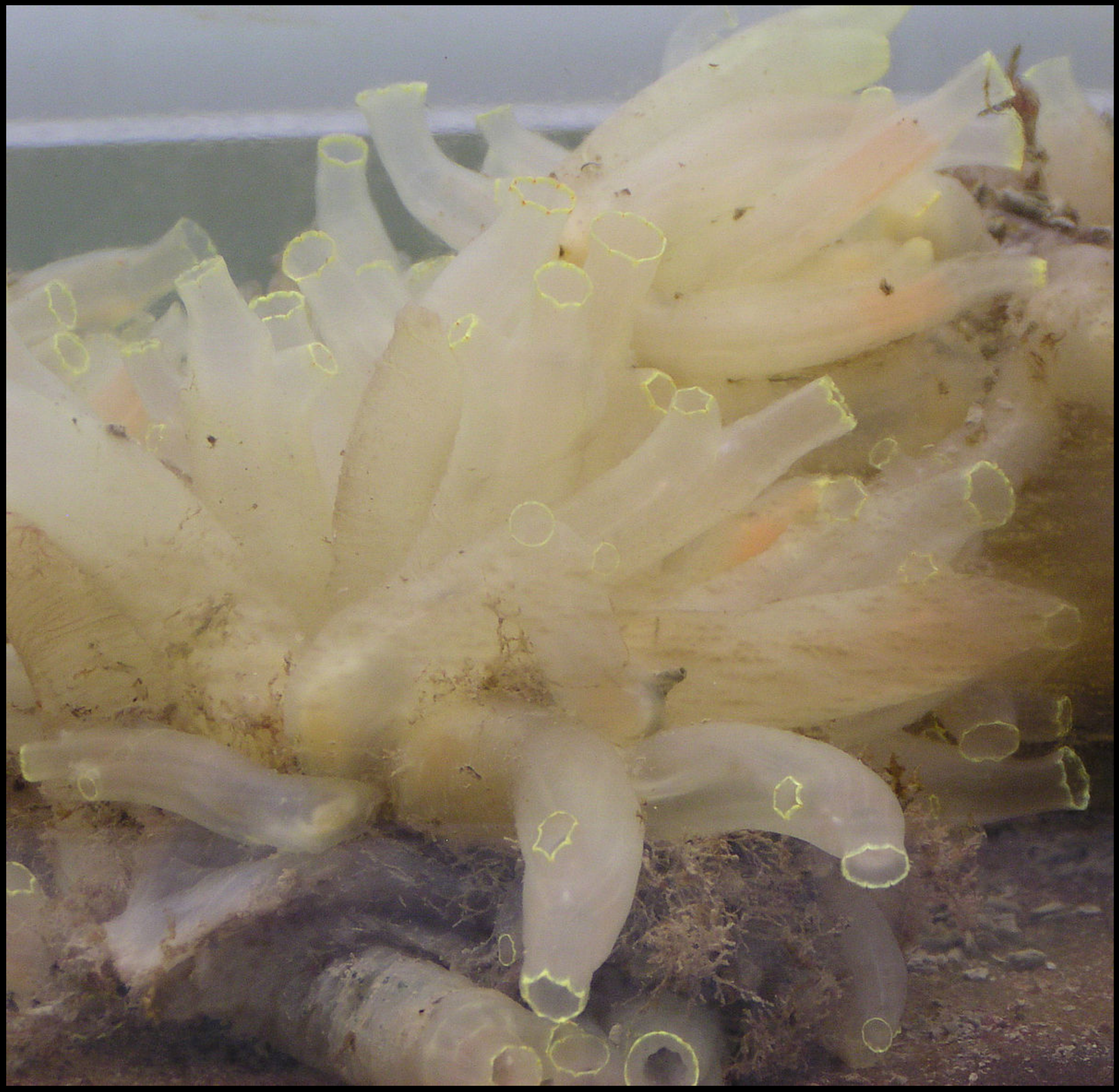
What drives us scientifically?
Governing laws at small scales
Time and spatial dependence
Plasticity/deformability
Higher order structures

Copos Lab

Ciona intestinalis

- Invertebrate chordate model organism in developmental biology and genomics.
- Closest invertebrate relatives of vertebrates.
- Very small genome size, less than 1/20 of the human genome.

Experimental collaborators: *Lionel Christiaen (Univ of Bergen), Yelena Bernadskaya (NYU)*



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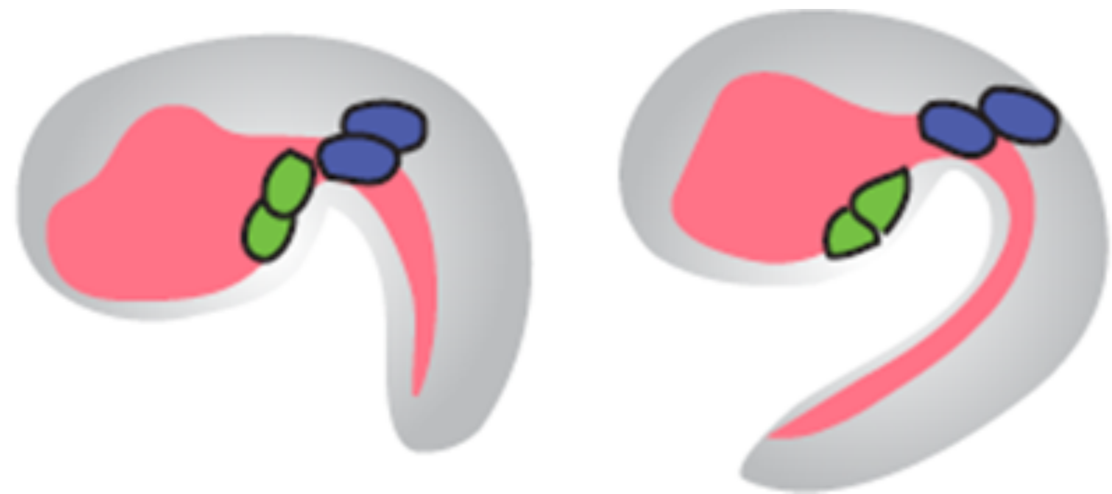
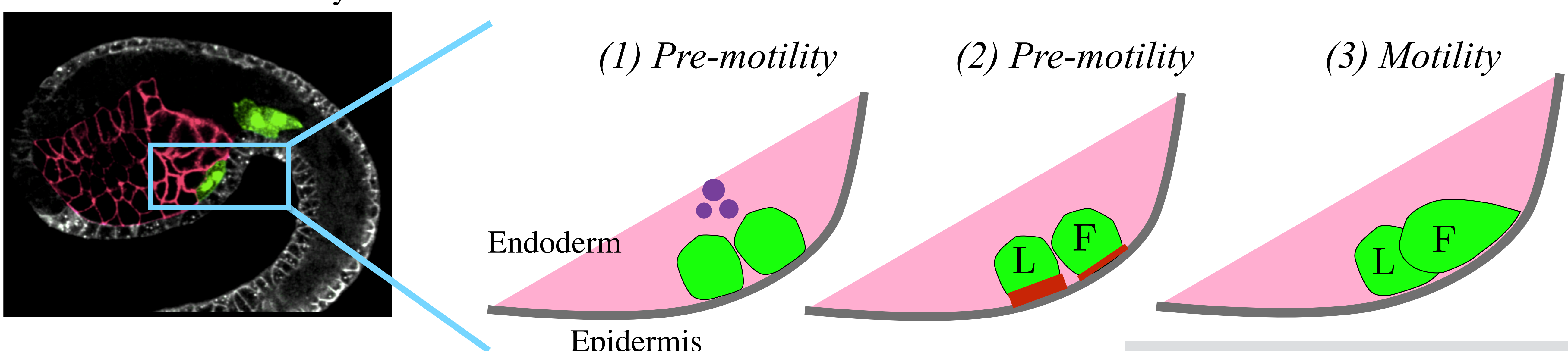
Migration of the trunk ventral cell (TVC) pair: one of the simplest cases of collective cell migration

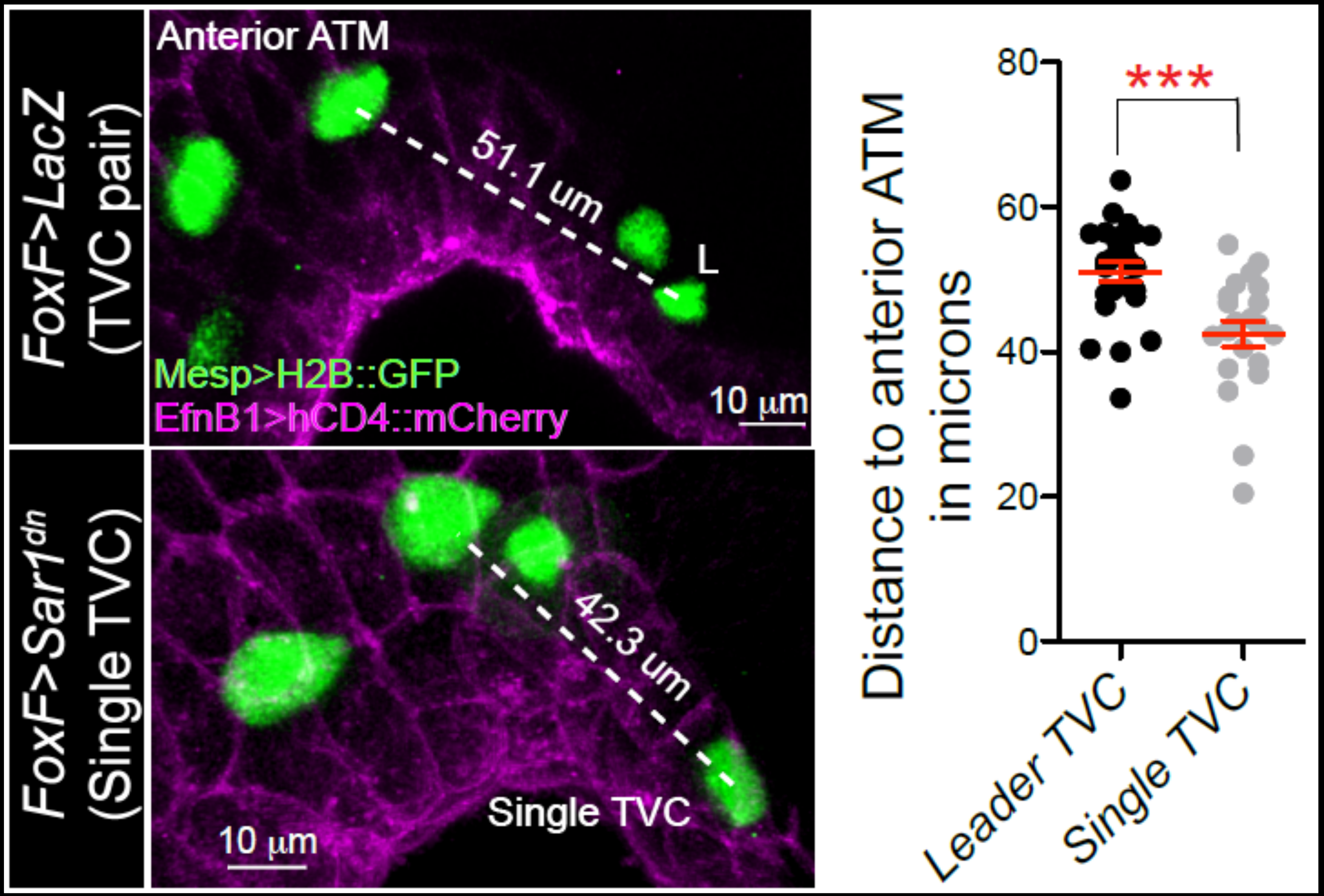


Ciona intestinalis embryo



Cells take on roles of
LEADER & FOLLOWER

Speed of one vs two cells (experiments):



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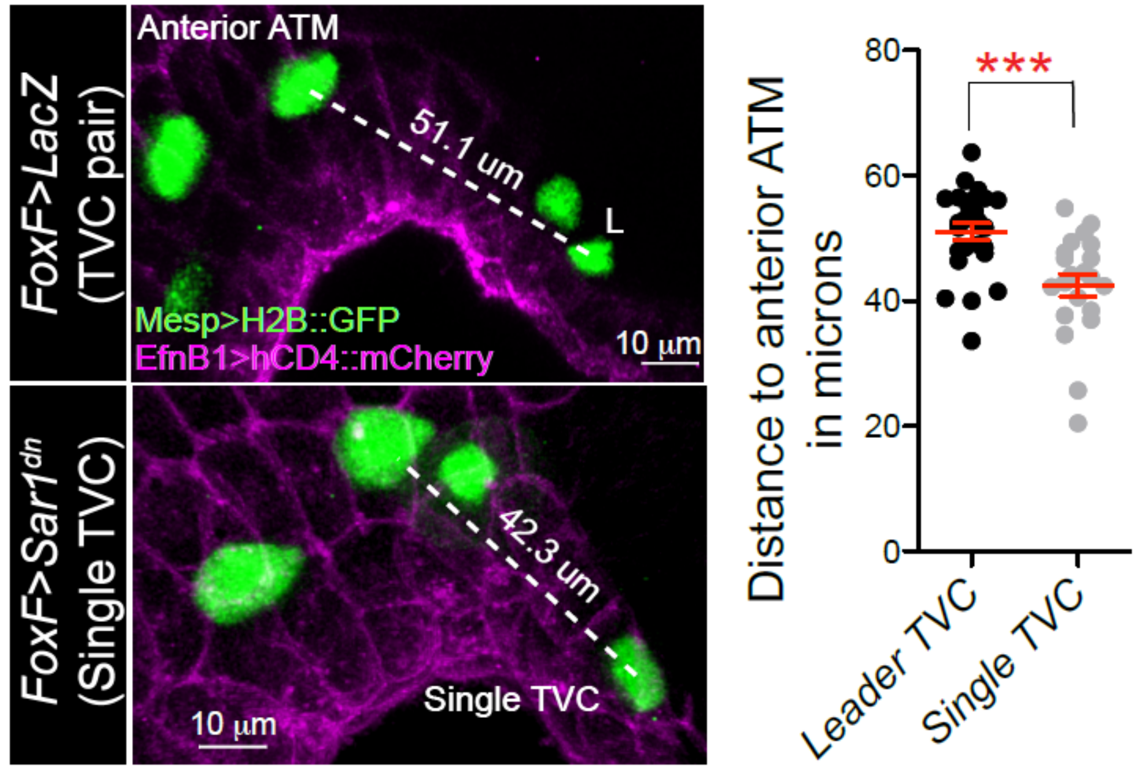
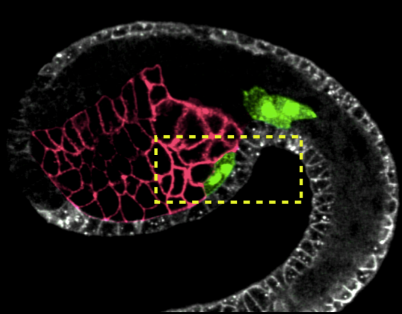




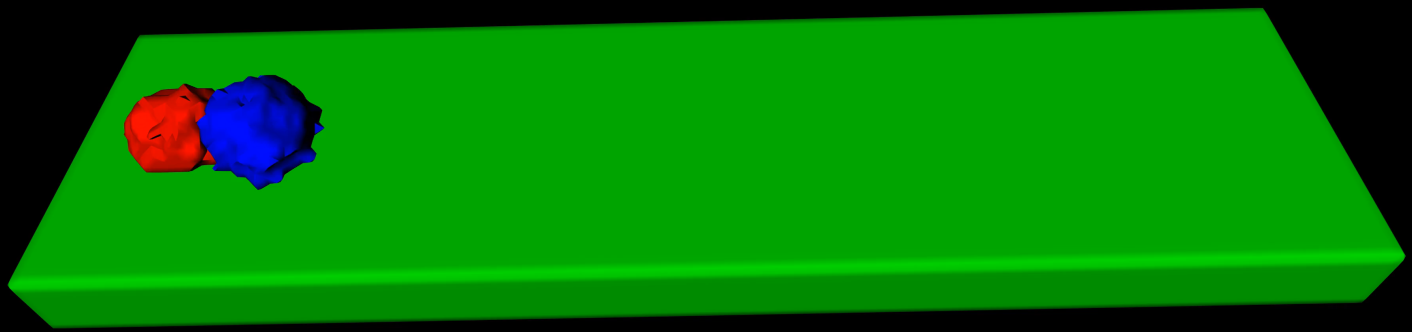
Moving as a pair is "better" than alone

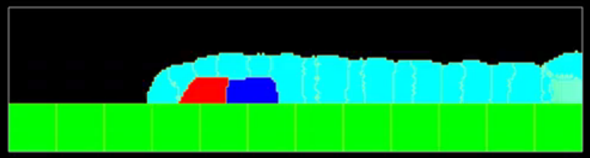
Hypothesis #1: There is a *mechanical* advantage to move as a two-cell system

Hypothesis #2: It is easier to *initiate* locomotion as a pair.

On the mechanical advantage of a pair:

Mechanical (Cellular Potts) model





Y. Bernadskaya, H. Yue, C. Copos, L. Christiaen, A. Mogilner. eLife (2021)

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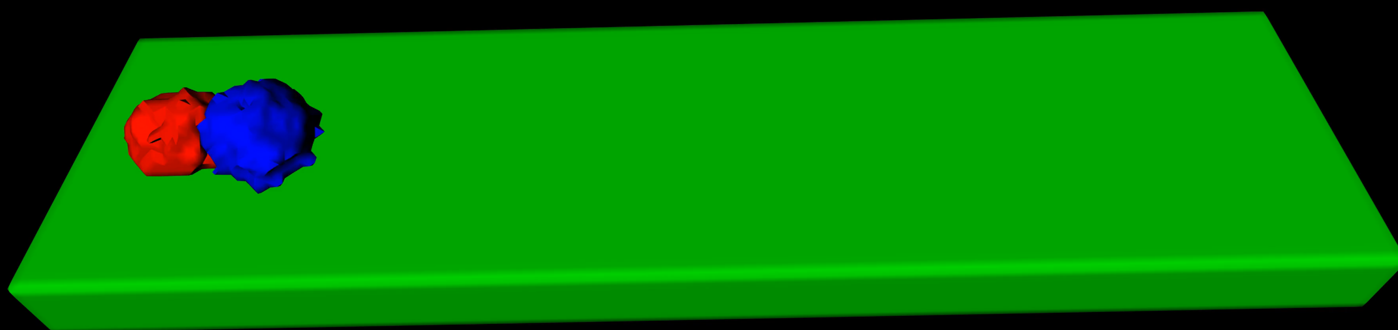
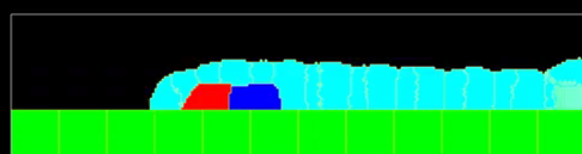
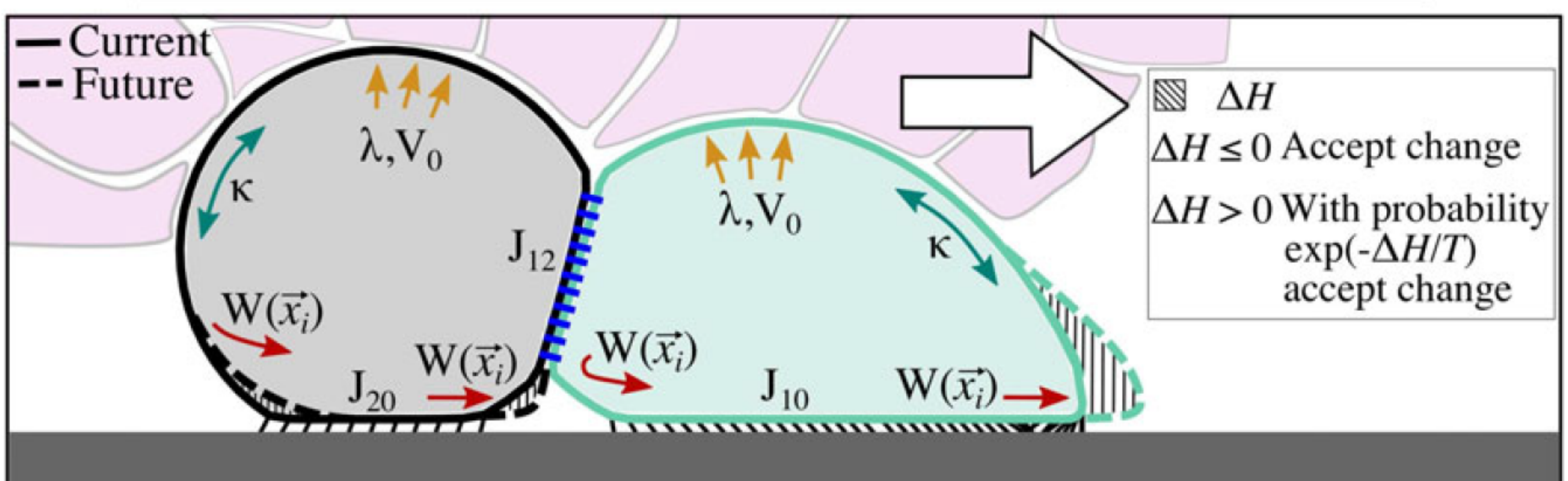




Y. Bernadskaya, H. Yue, C. Copos, L. Christiaen, A. Mogilner. eLife (2021)

$$H = \kappa(a_1{}^2+a_2{}^2) + \lambda\left((v_1-v_0)^2+(v_2-v_0)^2\right) + J_{12}a_{12} + J_{10}a_{10} + J_{20}a_{20} + W(\vec{x}_i)$$



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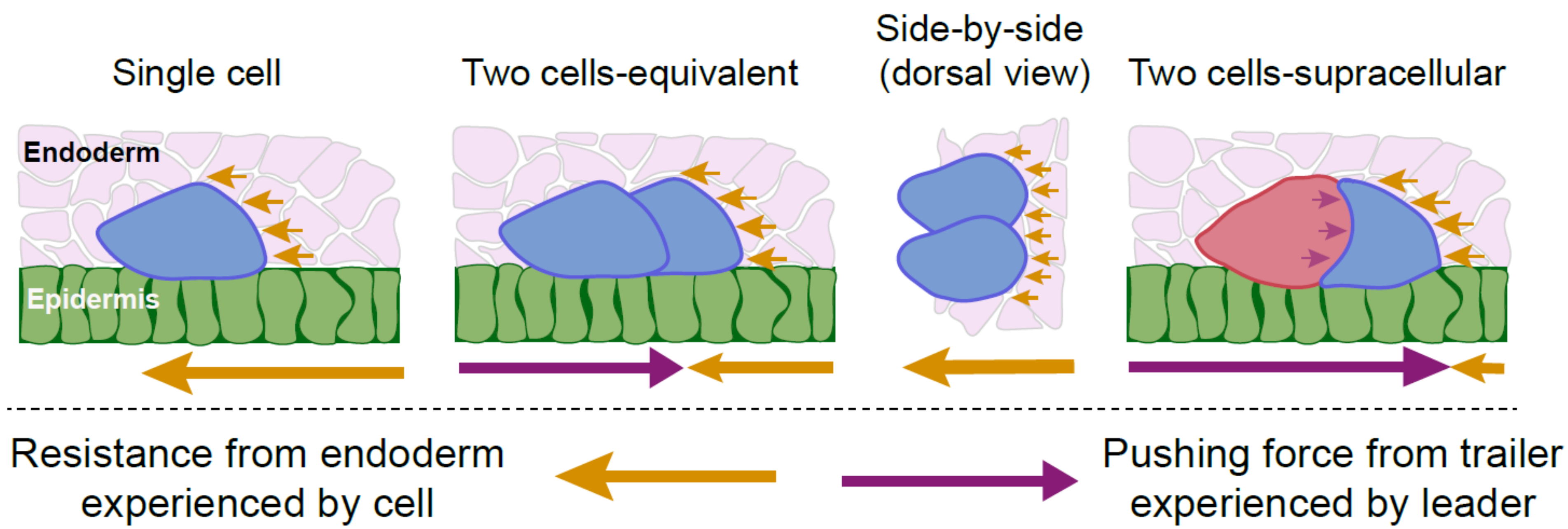
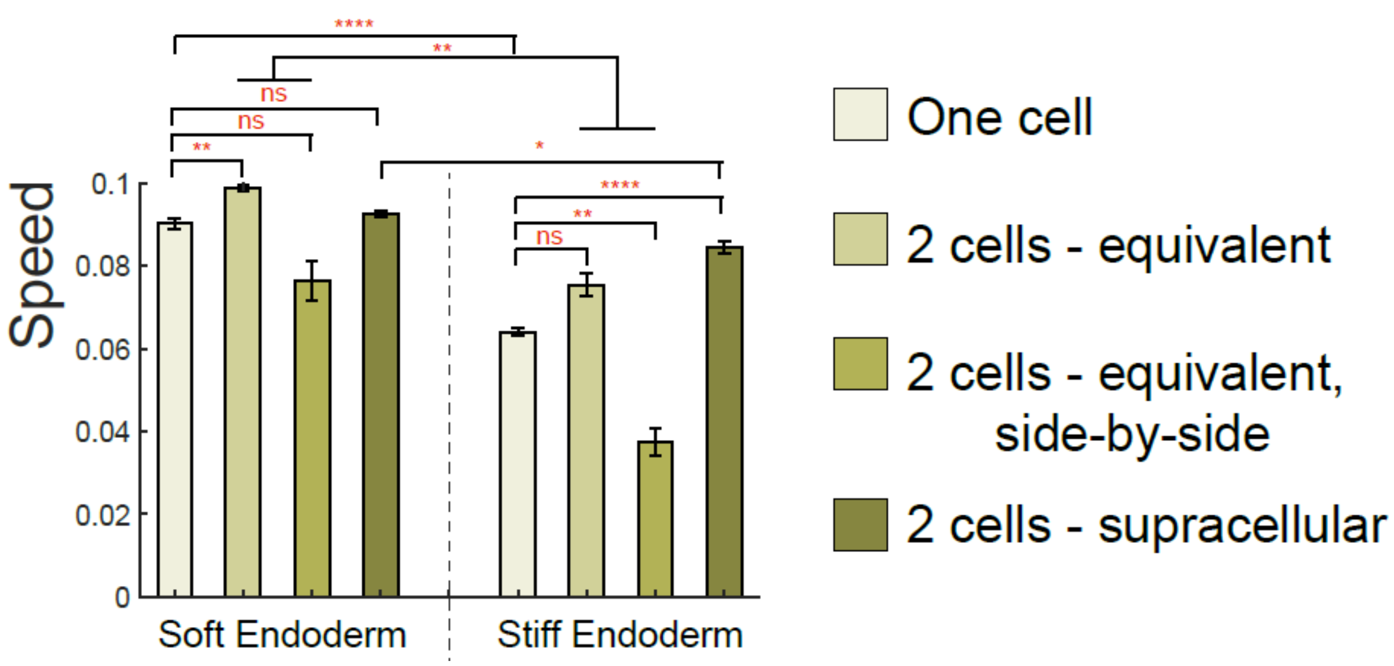


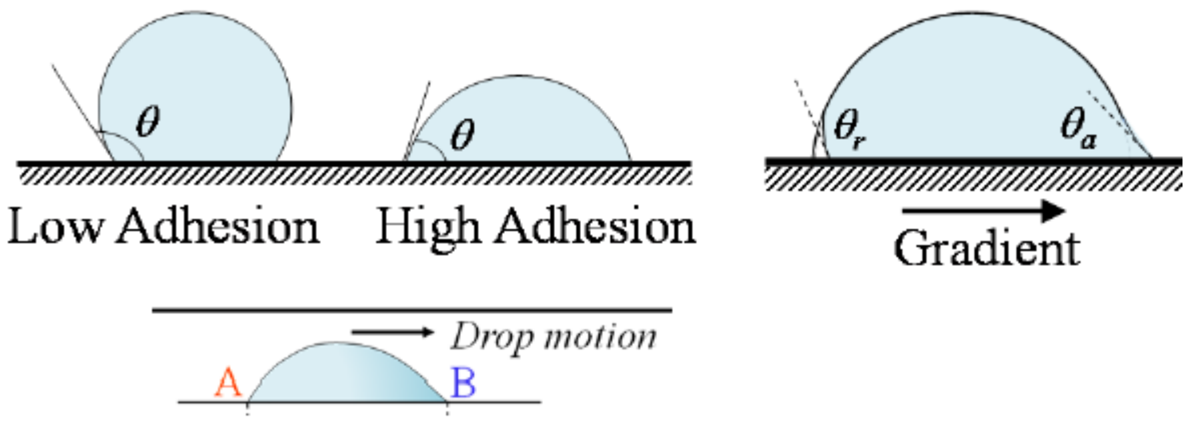


On the mechanical advantage of a pair:

Active Drop model

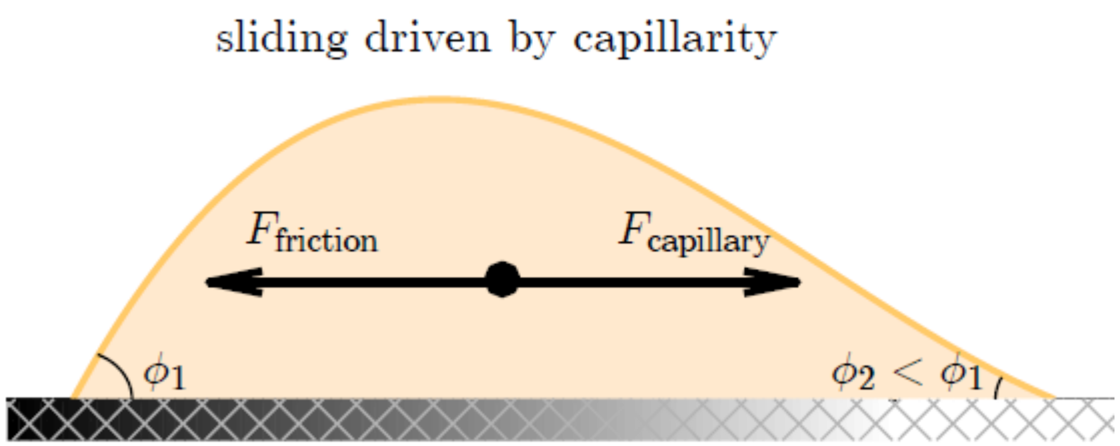
Generation of Motion of Drops with Interfacial Contact

Manoj K. Chaudhury,[*,†] Aditi Chakrabarti,[†] and Susan Daniel[‡]



How many ways a cell can move: the modes of self-propulsion of an active drop

Aurore Loisy, [*a] Jens Eggers [a] and Tanniemola B. Liverpool [*a]



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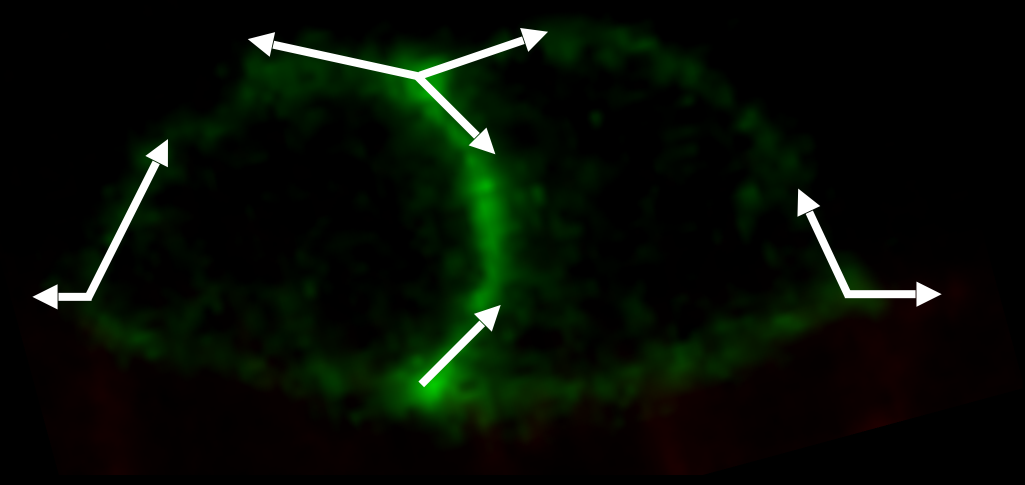
Active Drop model



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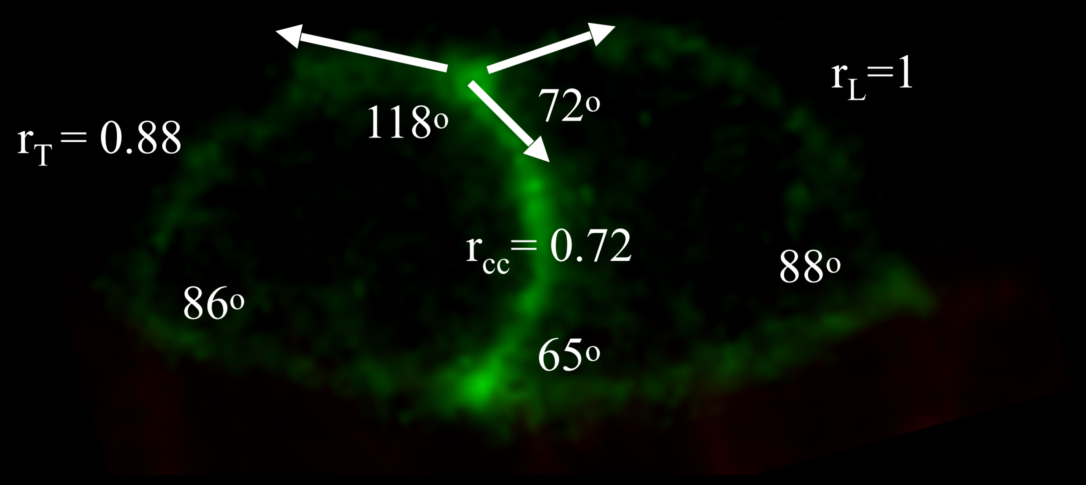

Morphological Measurements to Forces to Velocities

On the mechanical advantage of a pair:

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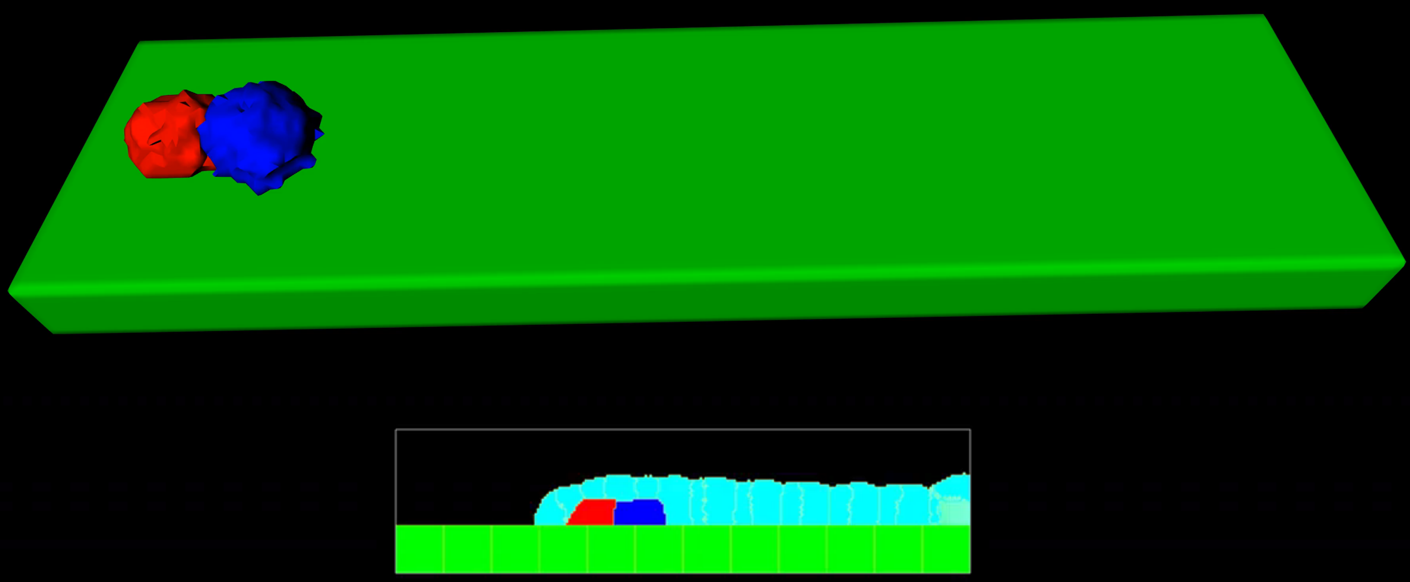

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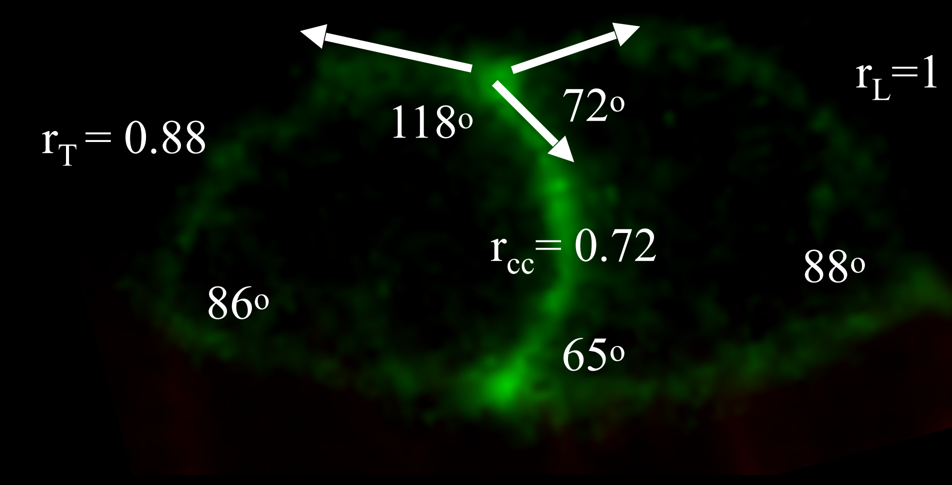

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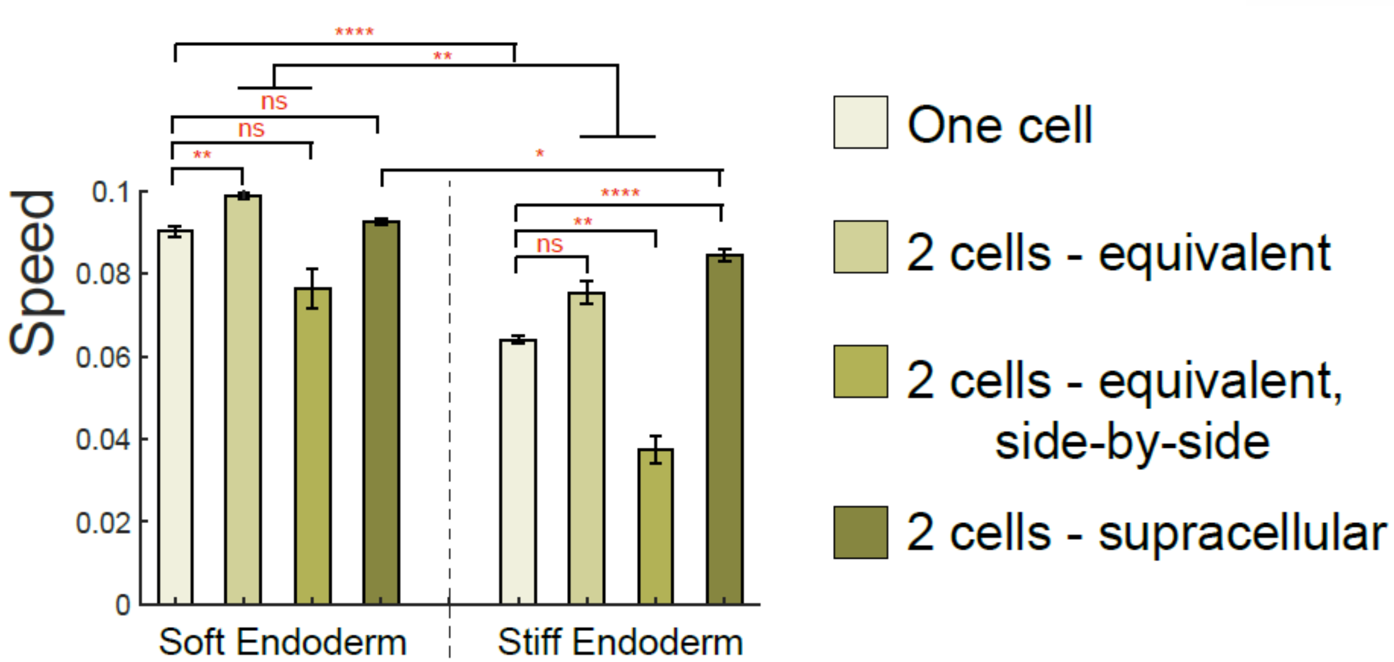

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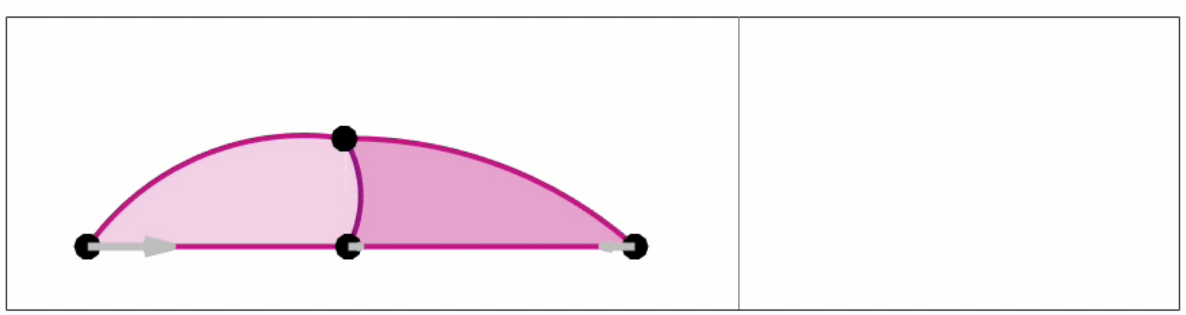

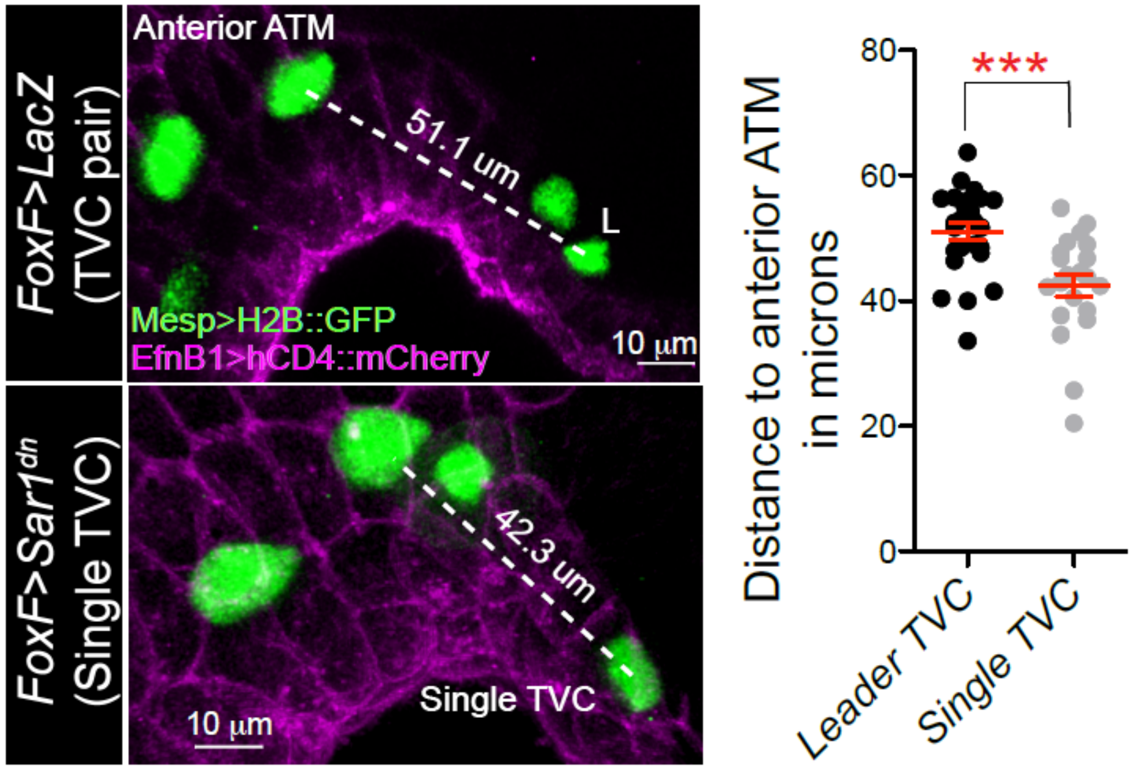

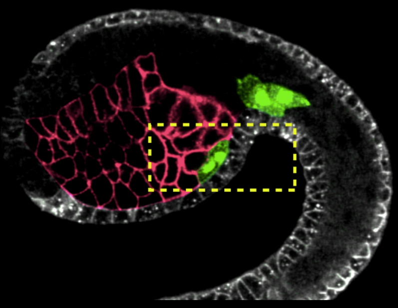

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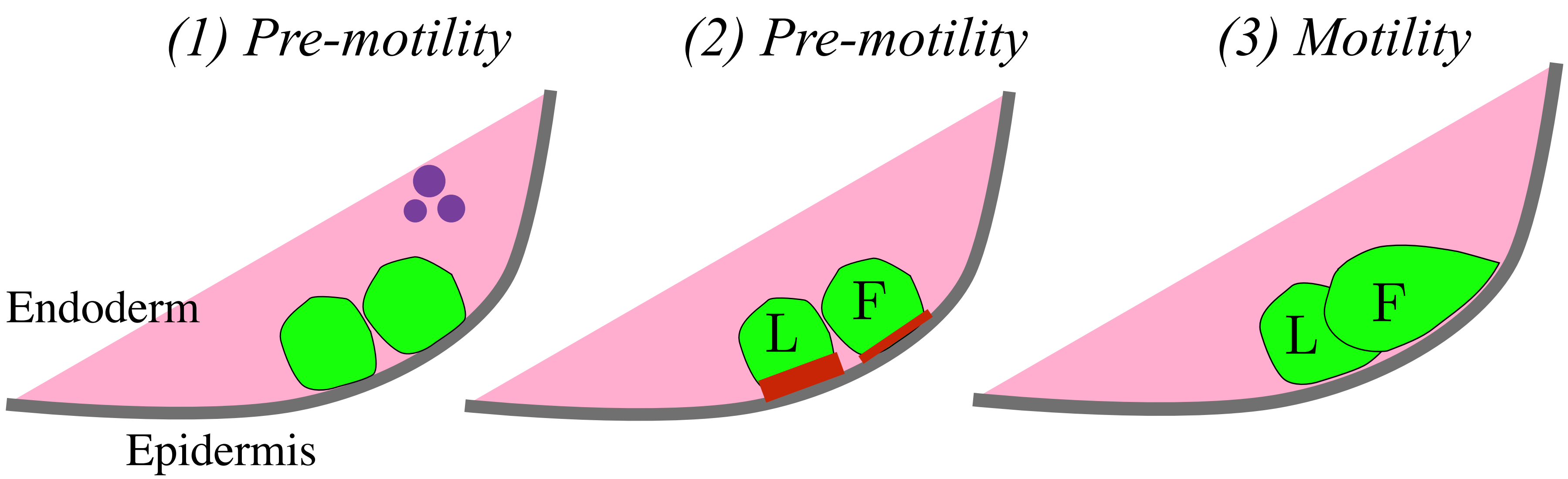
On the biochemical advantage of a pair



- Literature search revealed a lot of polymerization / symmetry breaking theoretical models focus on specific pathways with nonlinearities (accessory proteins)
- **<u>Wanted</u>**: general framework (mechanics & signaling are integrated)
- **<u>Is it easier to polarize in a pair? Role of cell-cell junction proteins?</u>**

Copos Lab

Big step back:

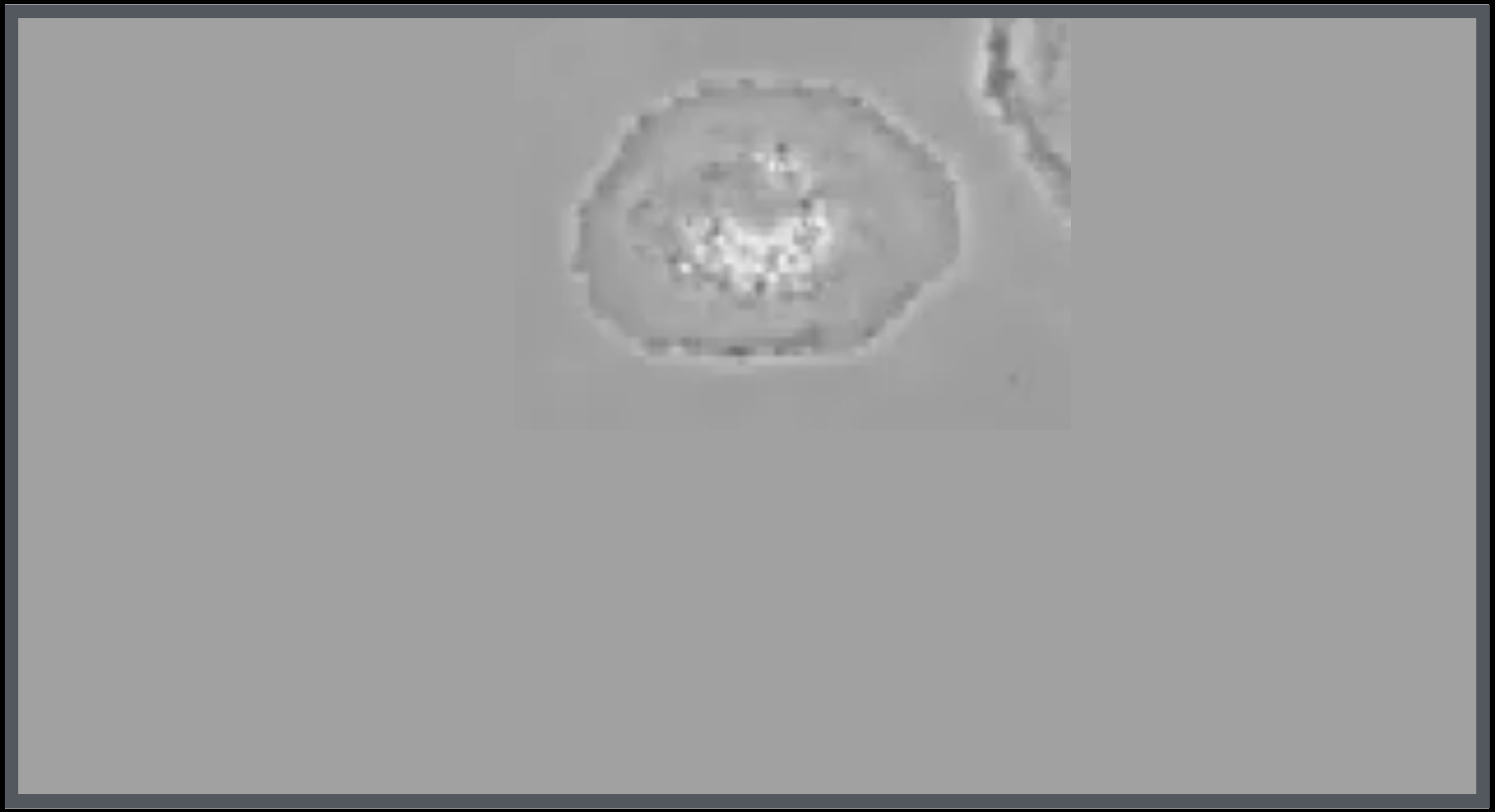
Construct general framework for symmetry breaking in a SINGLE cell

For any interested students: the big question remains to be answered…

Emergent organization inside cells

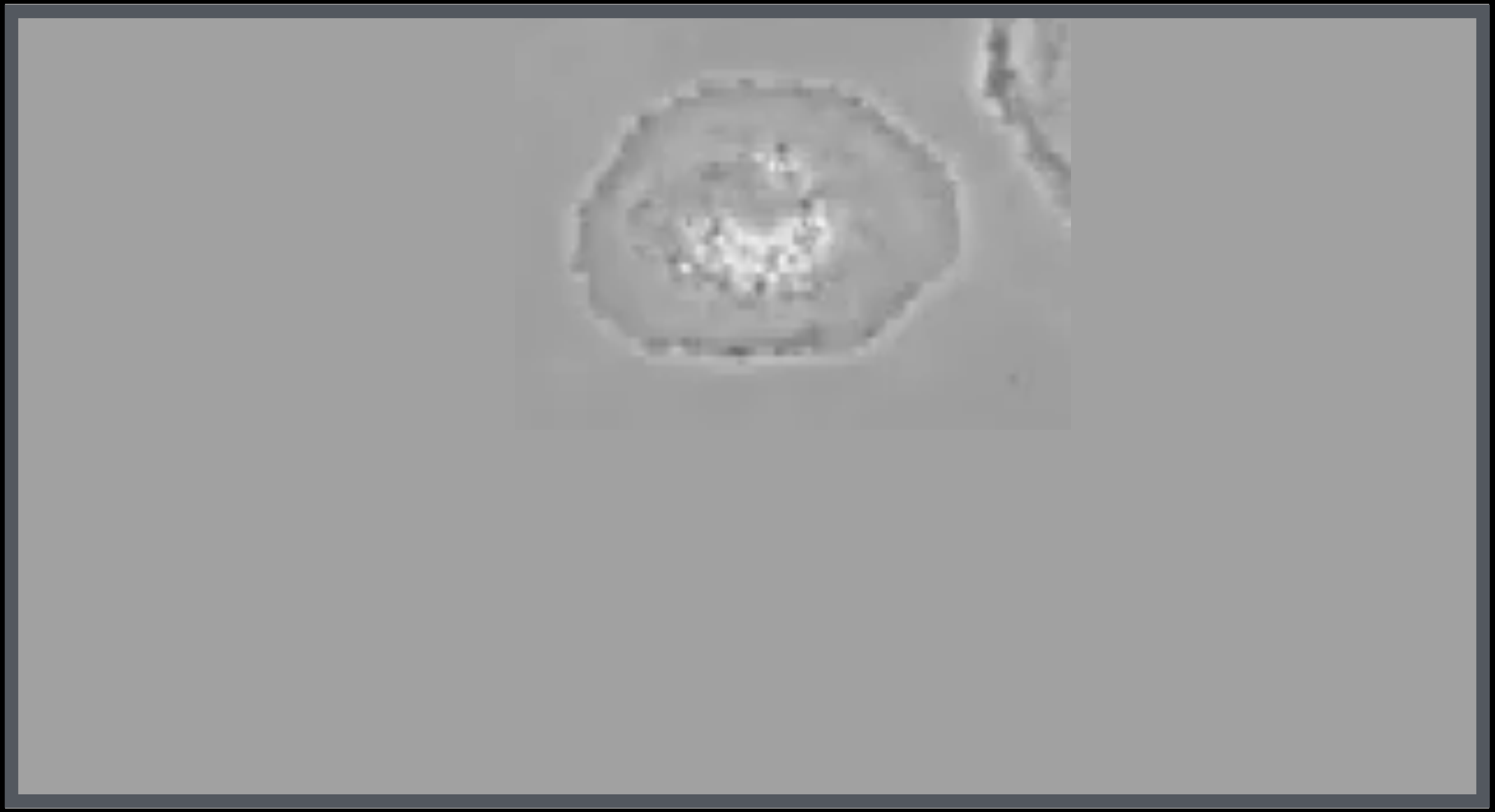
to initiate locomotion

Breaking symmetry to initiate locomotion



Yam…Theriot 2007

Breaking symmetry to initiate locomotion

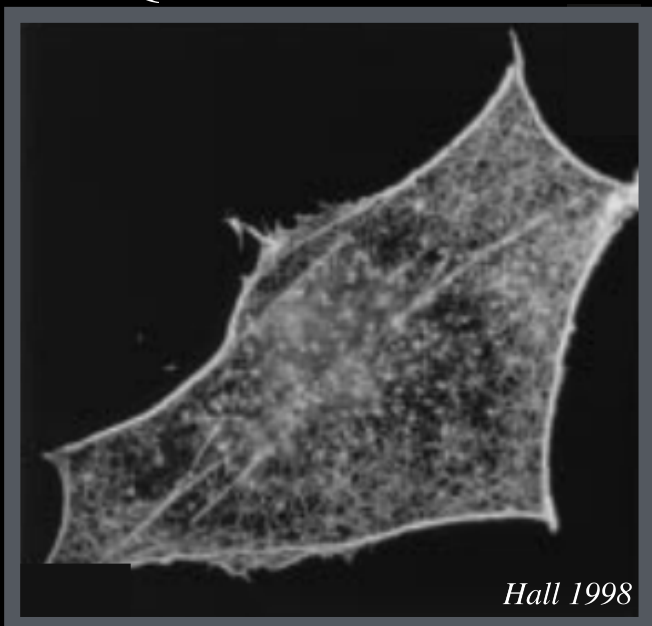


Yam…Theriot 2007

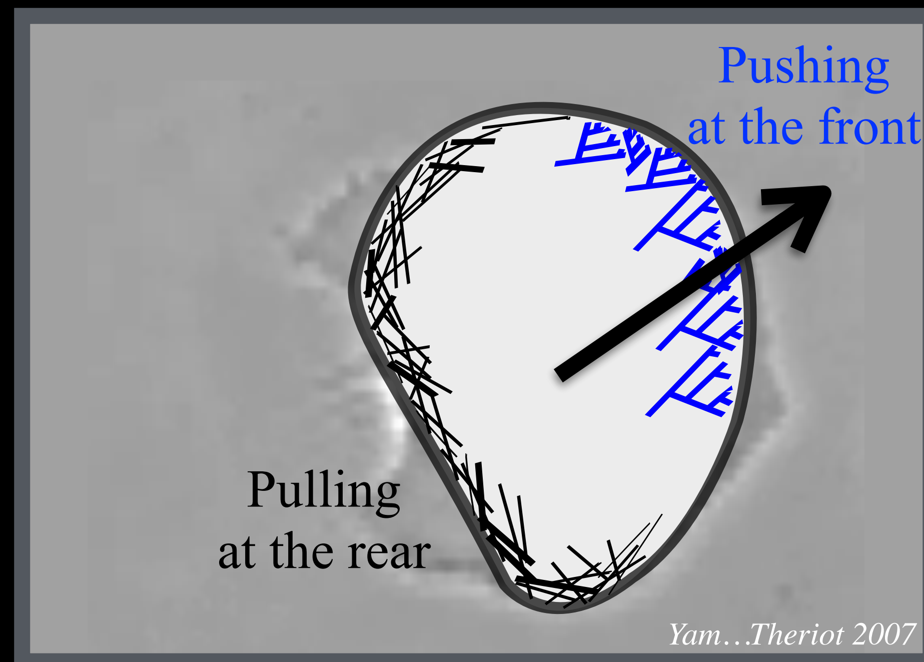
- <u>Breaking symmetry = Form a cell “front” and “rear” = Cell ‘polarization’</u>

Breaking symmetry to initiate locomotion

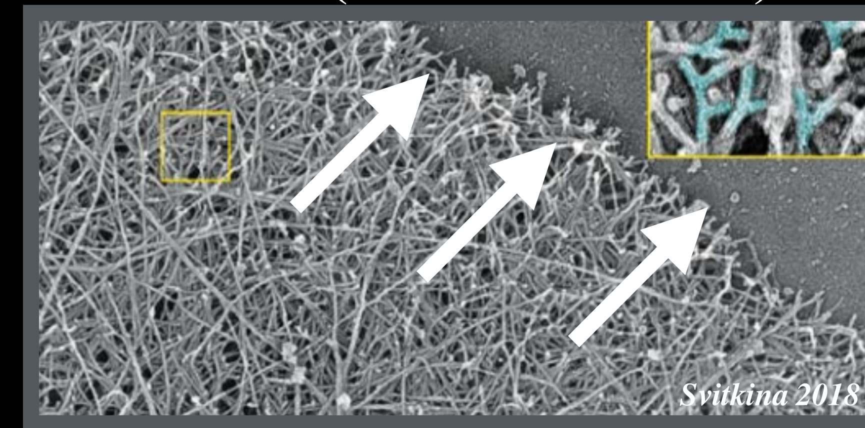
Quiescent cell



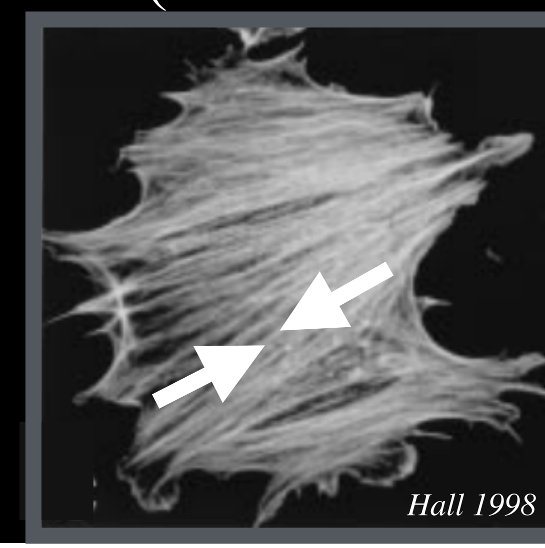
Motile cell



Front (branched actin)



Rear (contractile actin)

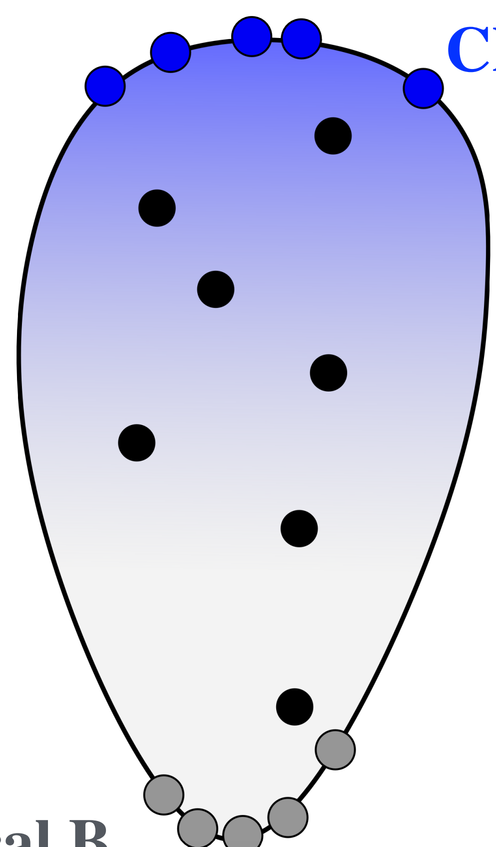


- <u>Breaking symmetry = Form a cell “front” and “rear” = Cell ‘polarization’</u>
- This process happens prior to movement

What triggers symmetry breaking
(i.e. formation of front and rear)?

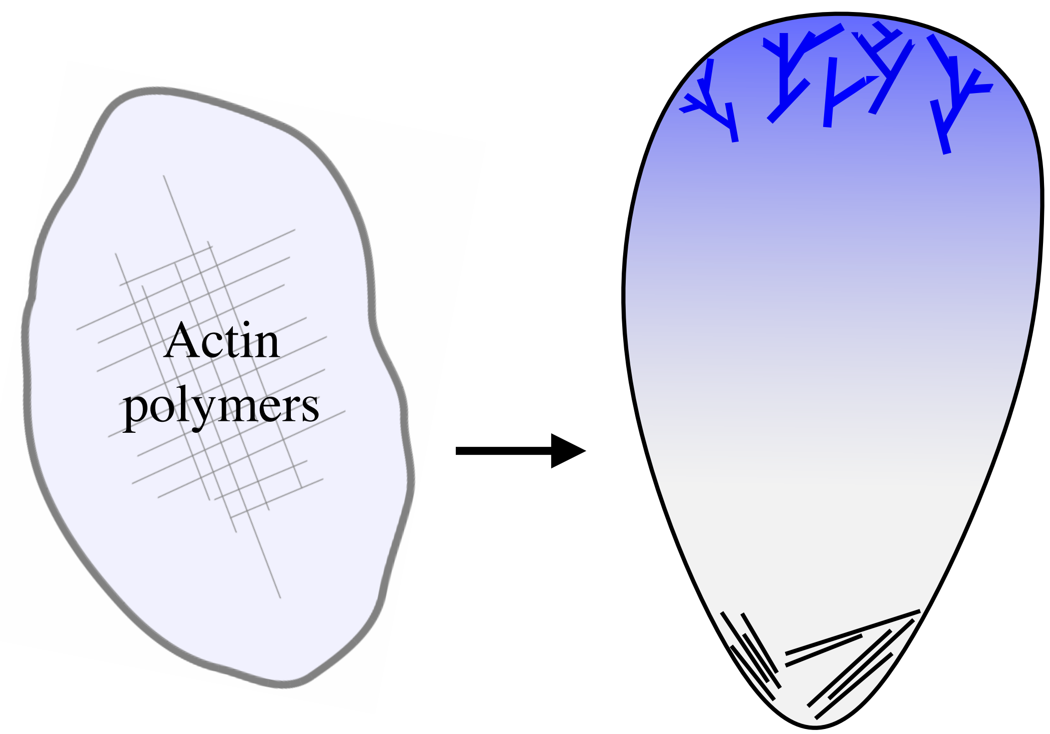
What triggers symmetry breaking?

(1) **Biochemical** signaling



Spatial segregation of chemicals through kinetics

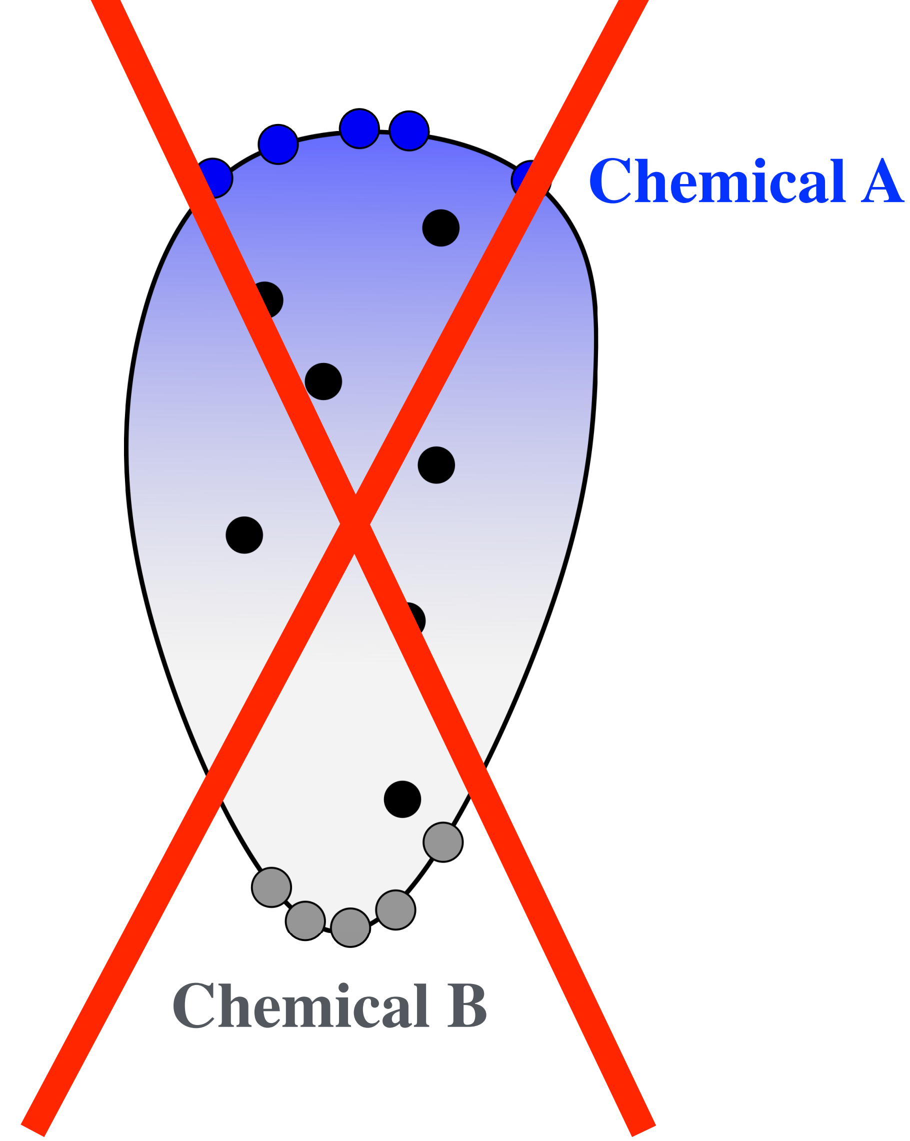
(2) Polymer **mechanics**



Rearrangement of cytoskeleton

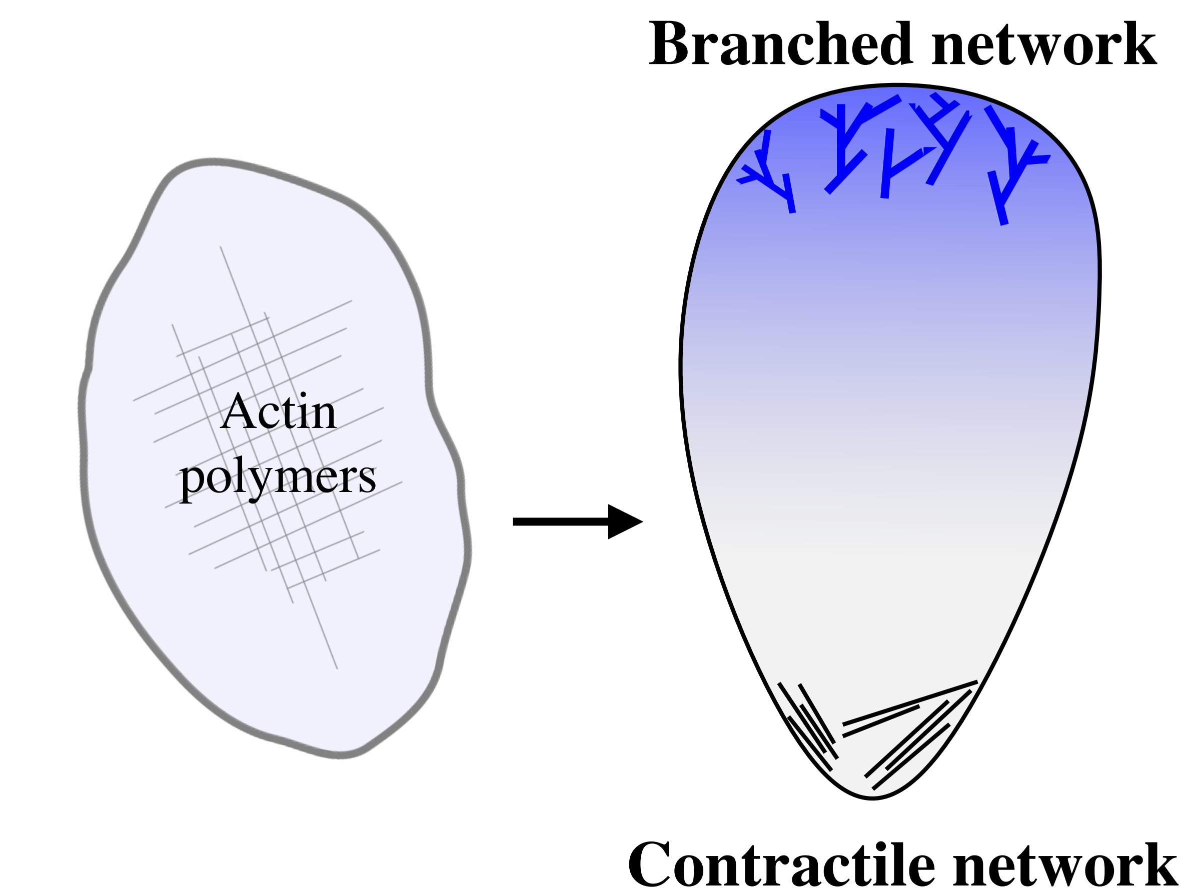
In reality, both are necessary

~~(1) Biochemical signaling~~



Spatial segregation of chemicals through kinetics

(2) Polymer mechanics

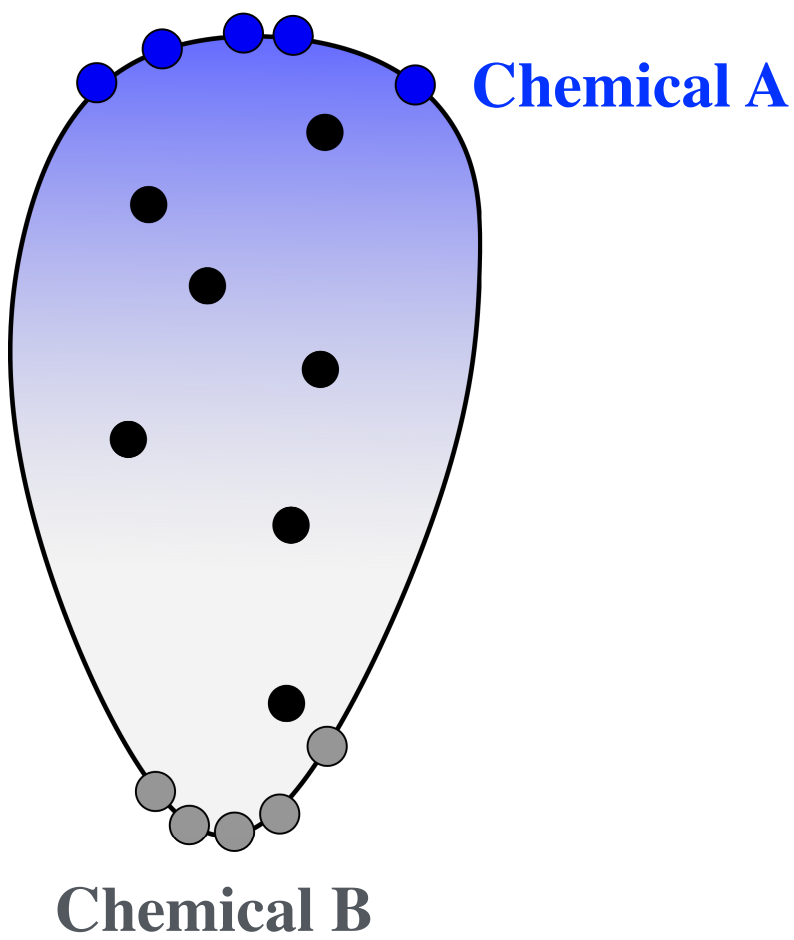


Rearrangement of cytoskeleton

In neutrophils, **inhibition of signaling chemicals (Rac)**: no front edge formation *(Schwarz 2004)*

In reality, both are necessary

(1) Biochemical signaling



Spatial segregation of chemicals through kinetics

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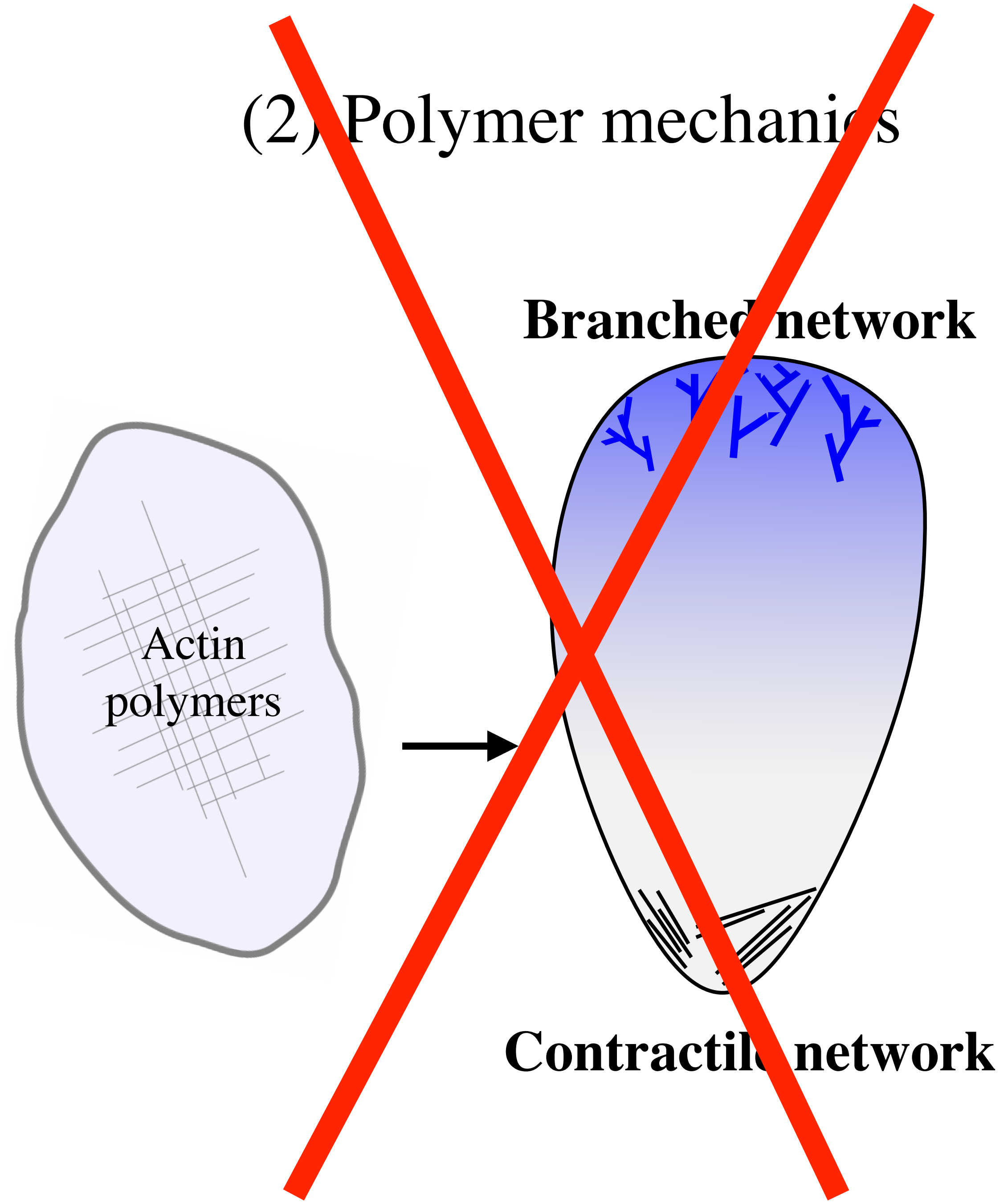
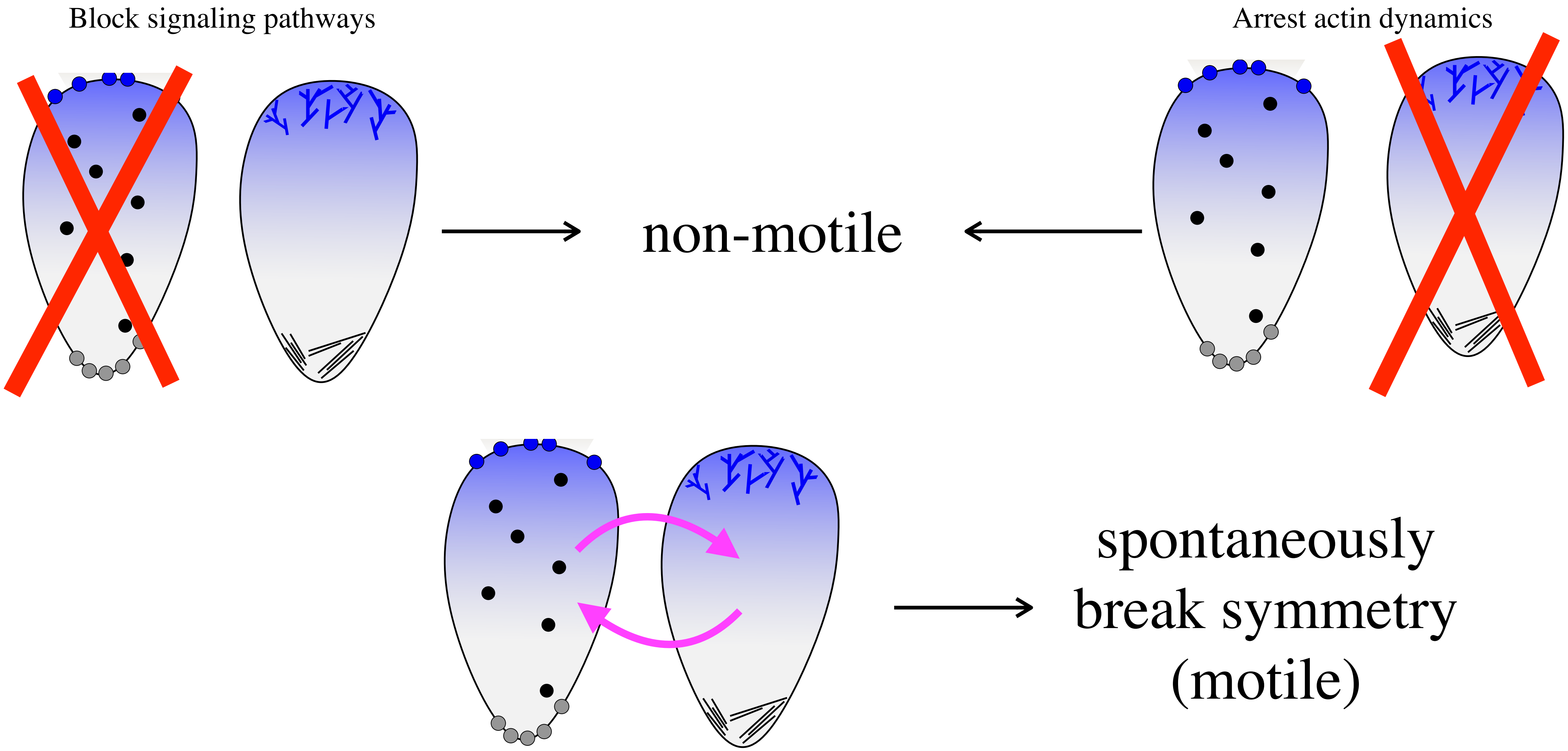


Rearrangement of cytoskeleton

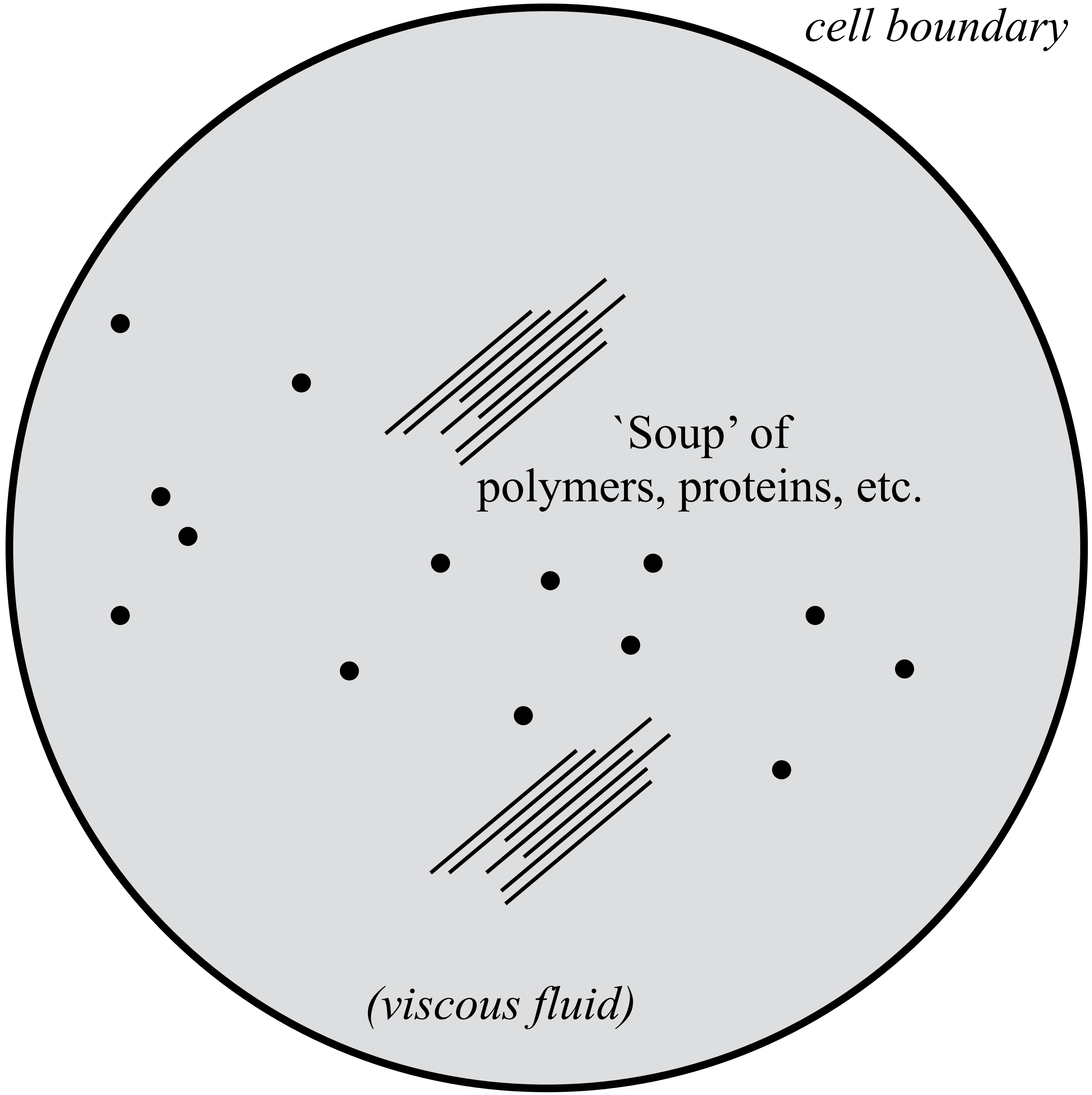
In neutrophils, **arresting the actin polymer dynamics**: desensitization to new incoming signals *(Dandekar et al. 2013)*

Hypothesis: Not only both (mechanics and biochemical pathways) are at play. Their **coupling/reinforcement** leads to a polarized cell state.

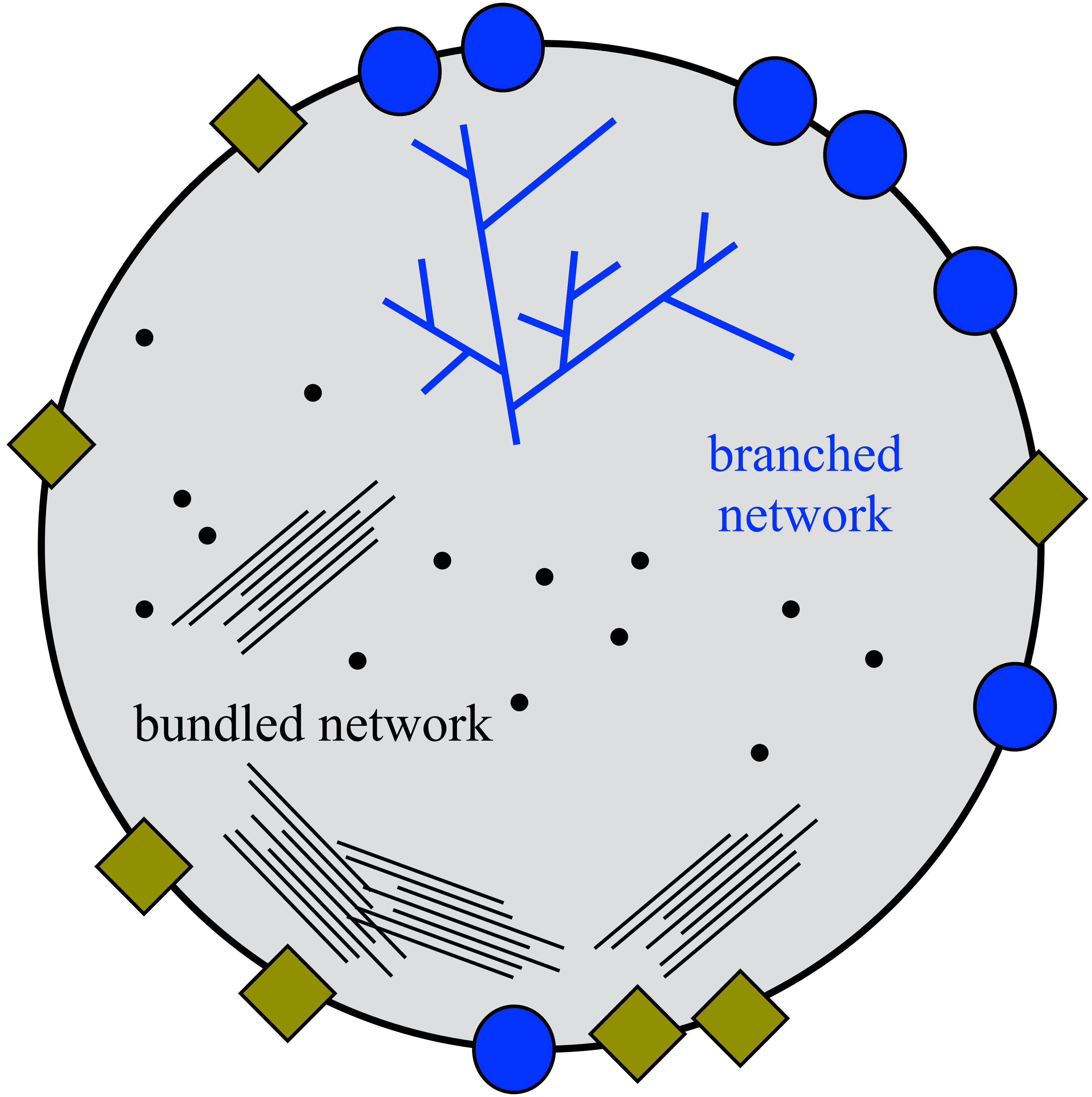
What are the necessary and sufficient conditions?



The `spherical' ~~cow~~ cell



The model overview



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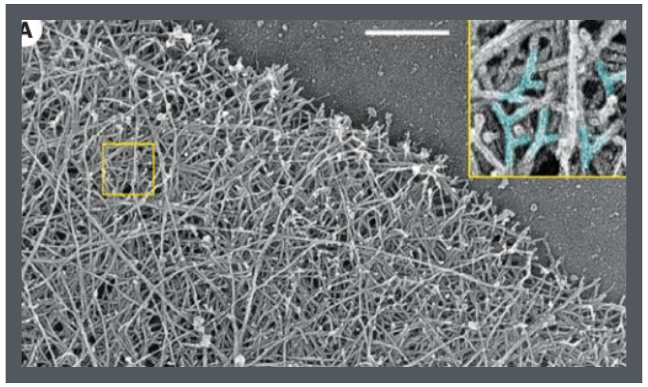
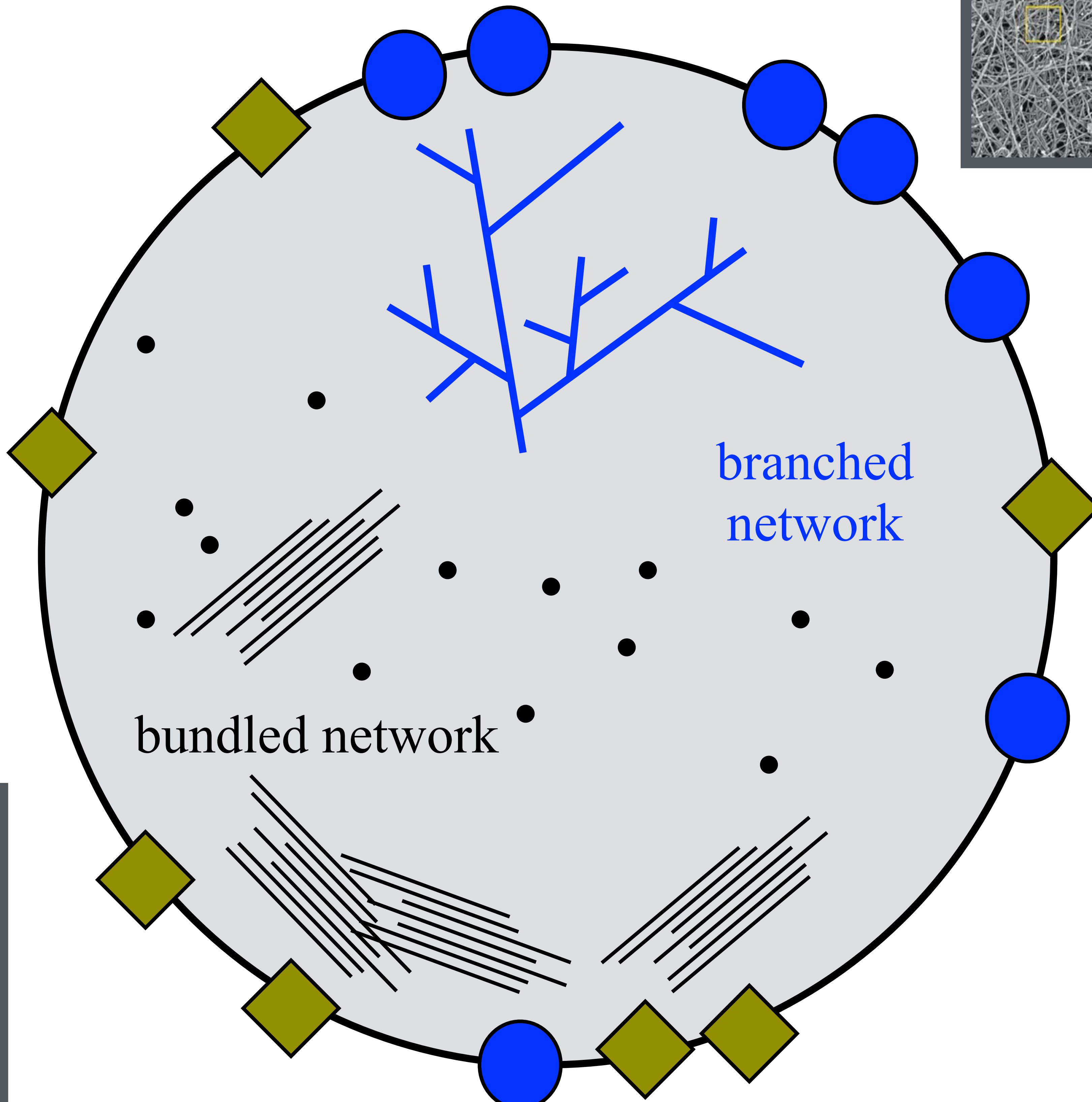
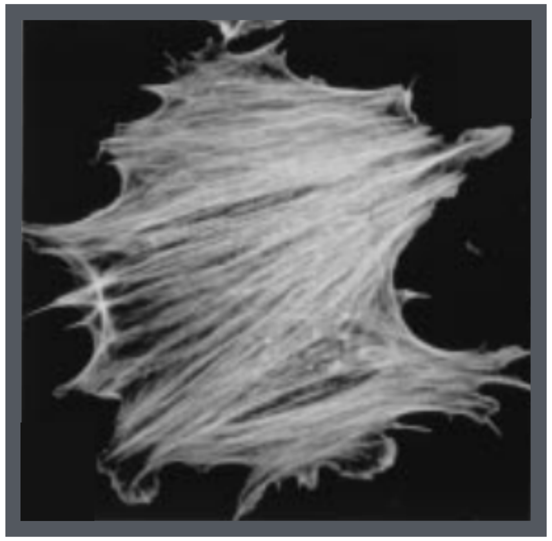


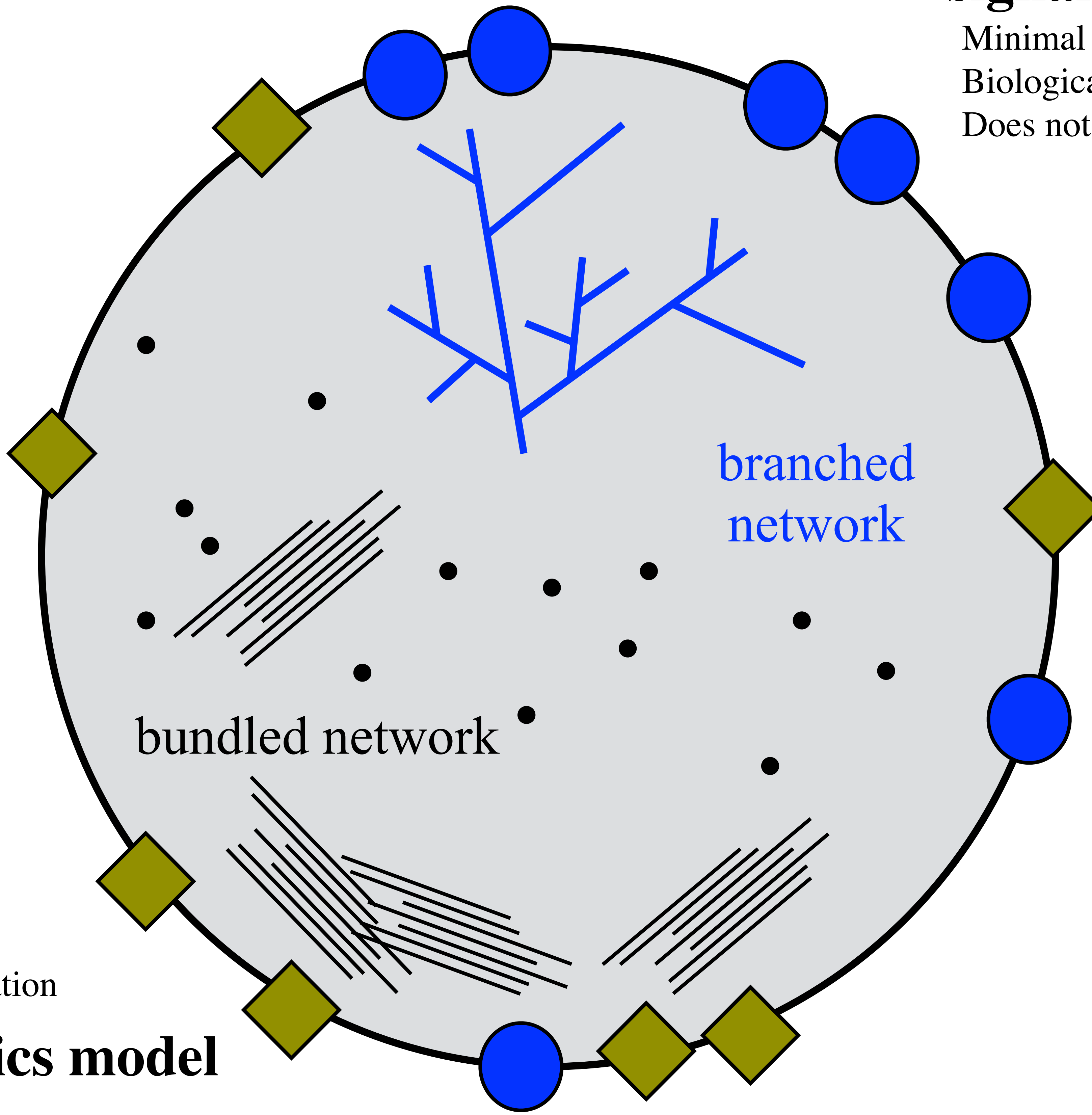




The model overview

1. Biochemical signaling model

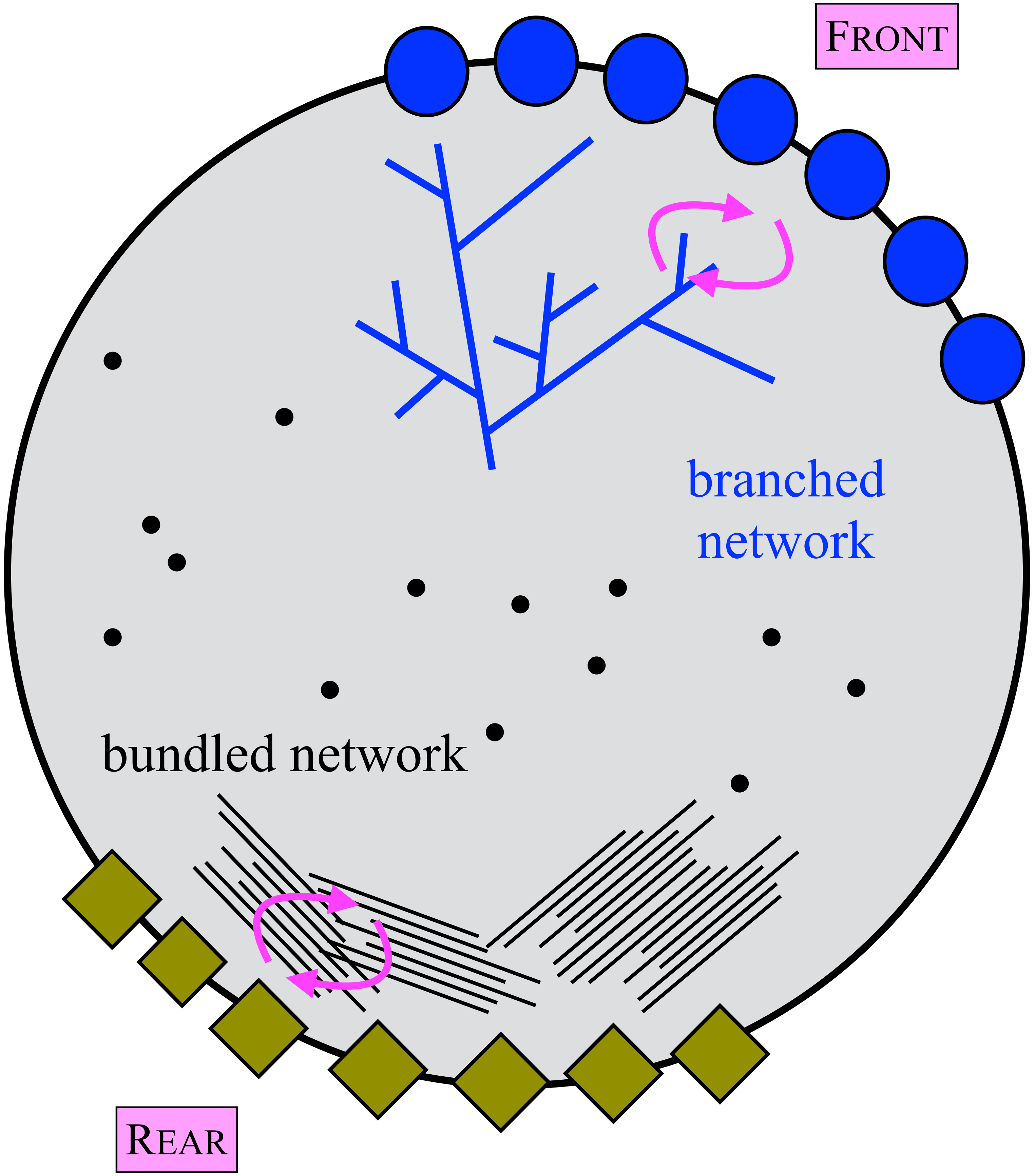
Minimal
Biologically inspired
Does not produce polarization on its own



Minimal model
Does not produce polarization

2. Actin dynamics model

The model overview



Coupling?

3 out of 4 directions are well-established biologically.

Will result in spontaneous symmetry breaking.

1. Biochemical module

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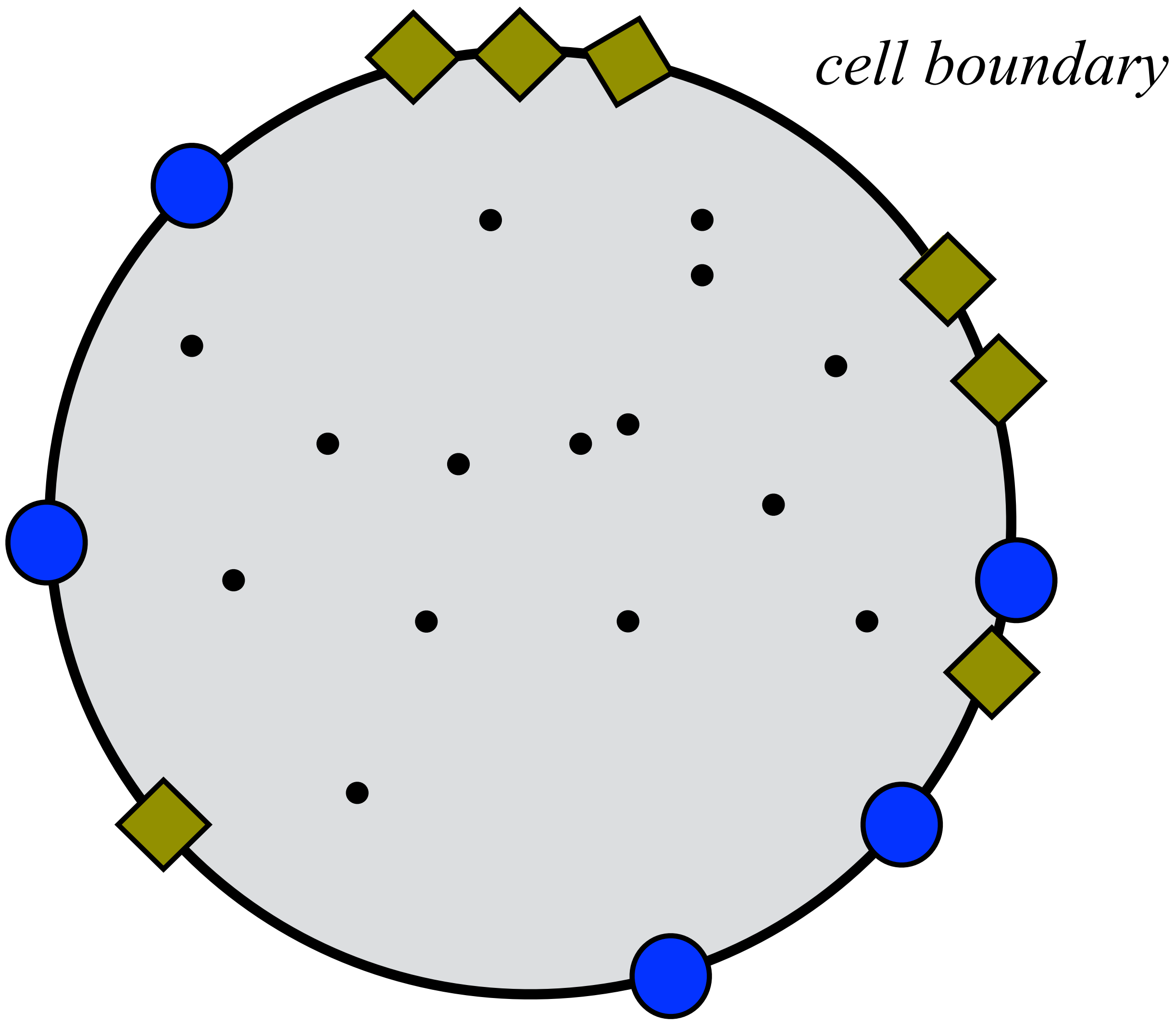


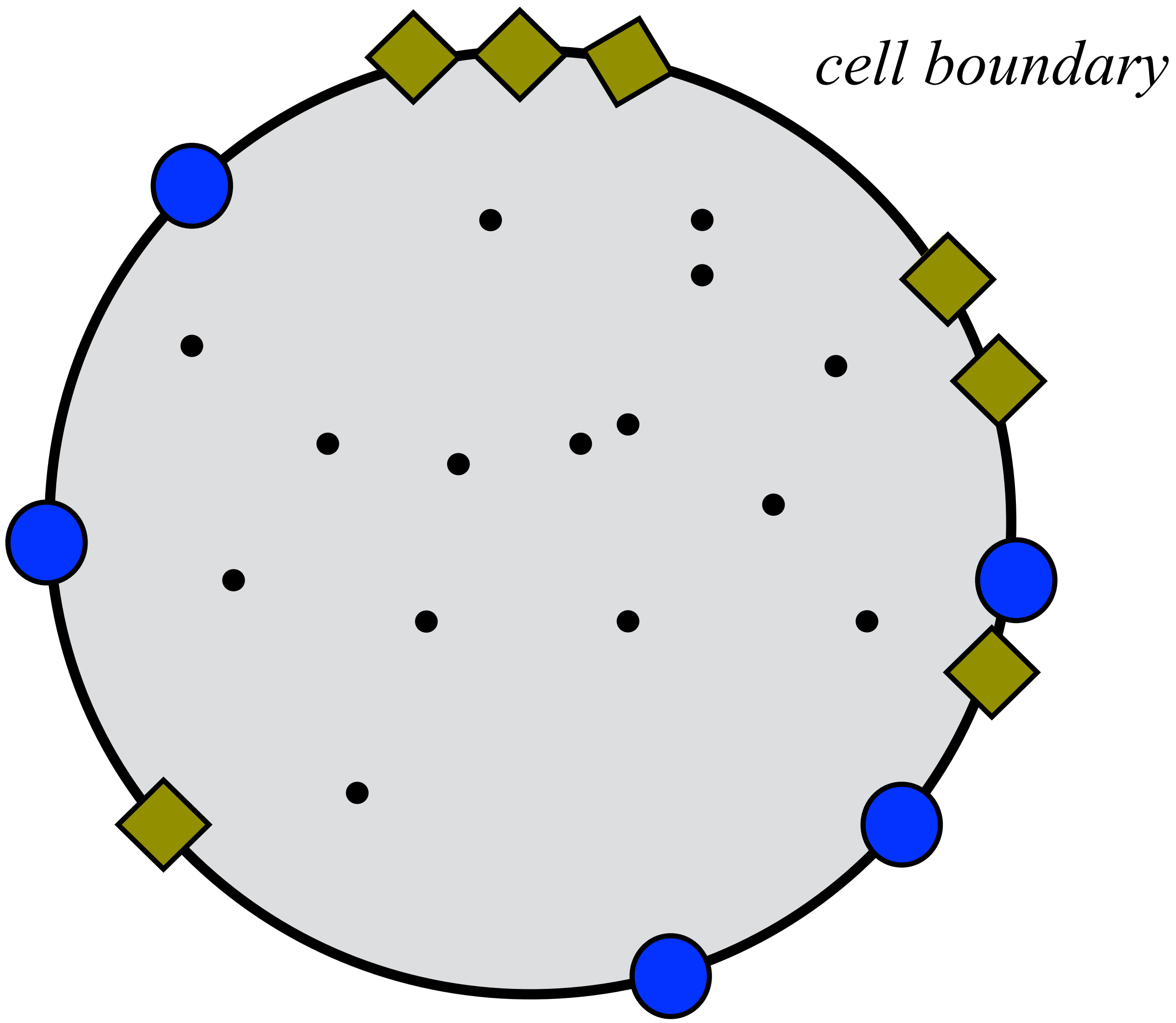
<u>What we know biologically:</u>

1. *Rac/Rho signaling pathway* is a generic mechanism for breaking symmetry

2. **Actors**: **Rac (Front)** and **Rho (Rear)** with well-characterized dynamics (i.e. rates)

3. **Dynamics**: Exist in two states: (1) boundary-bound (active)
(2) cytosol (inactive)

1. Biochemical module



1. Spontaneous association to the boundary (k_{on})

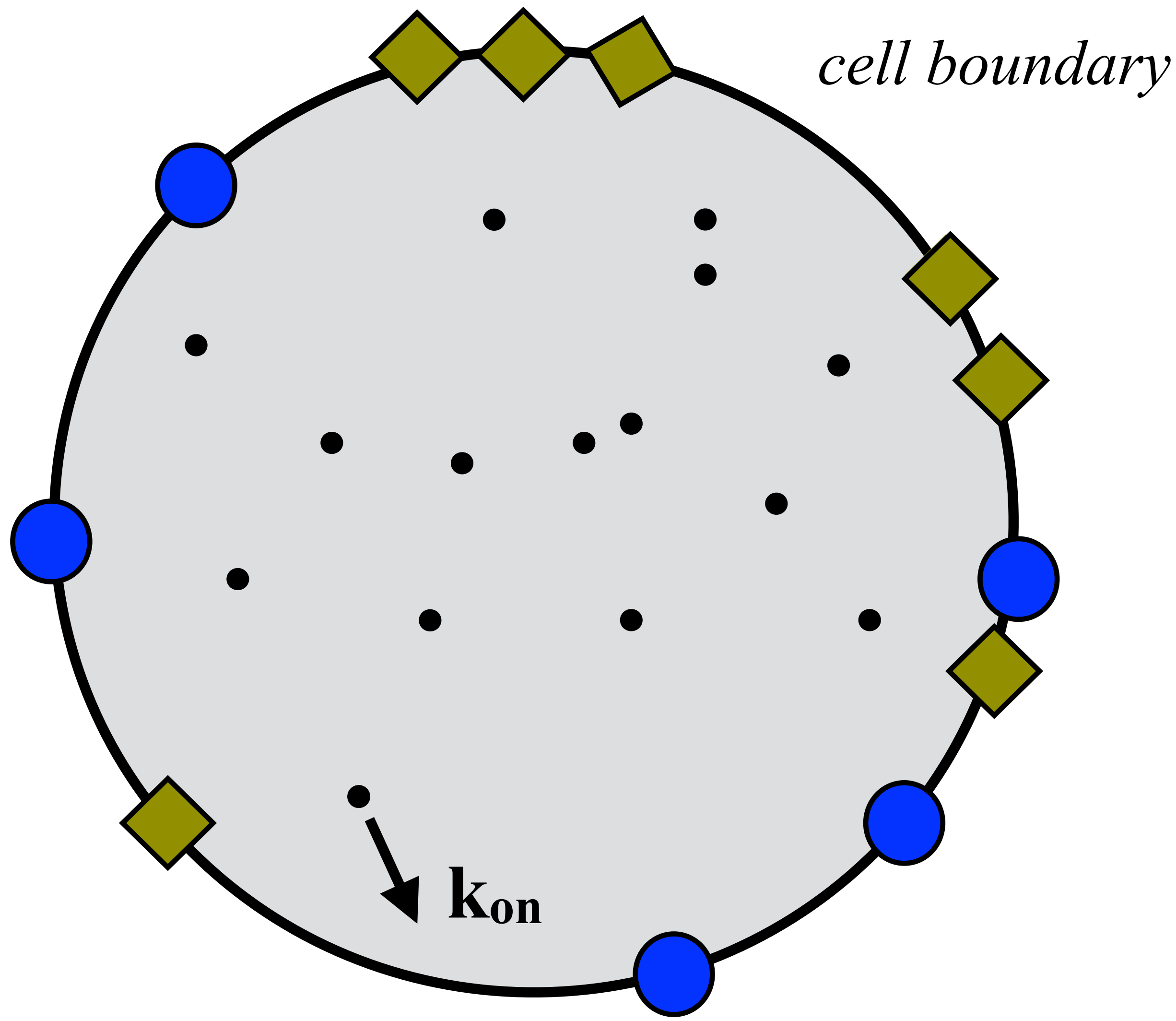
2. Spontaneous disassociation from the boundary (k_{off})

3. Enhanced boundary association through activators (k_{fb})

4. Brownian motion (diffusion) on the boundary (D)

Kinetic rates and diffusion have been measured experimentally.

1. Biochemical module



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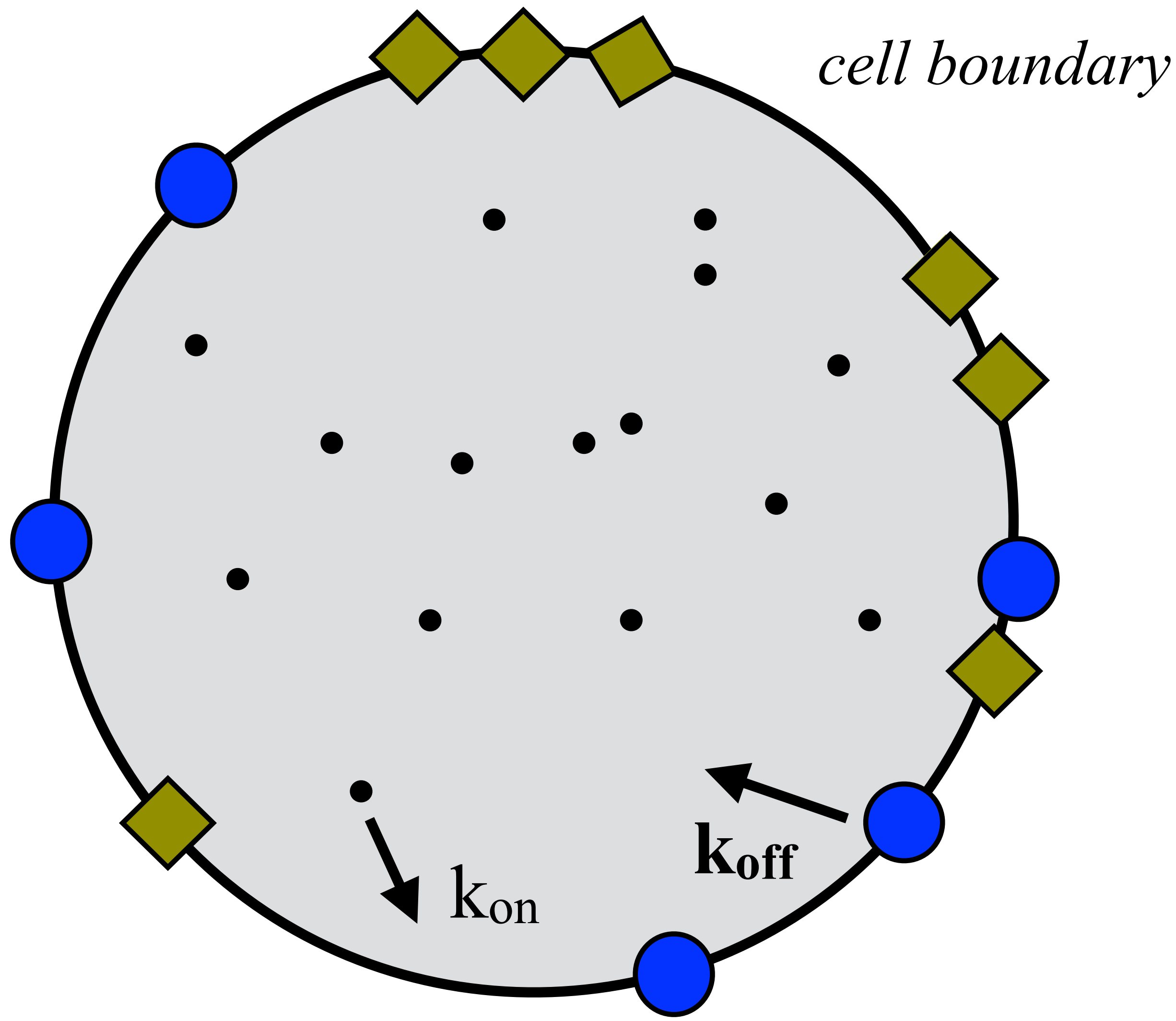

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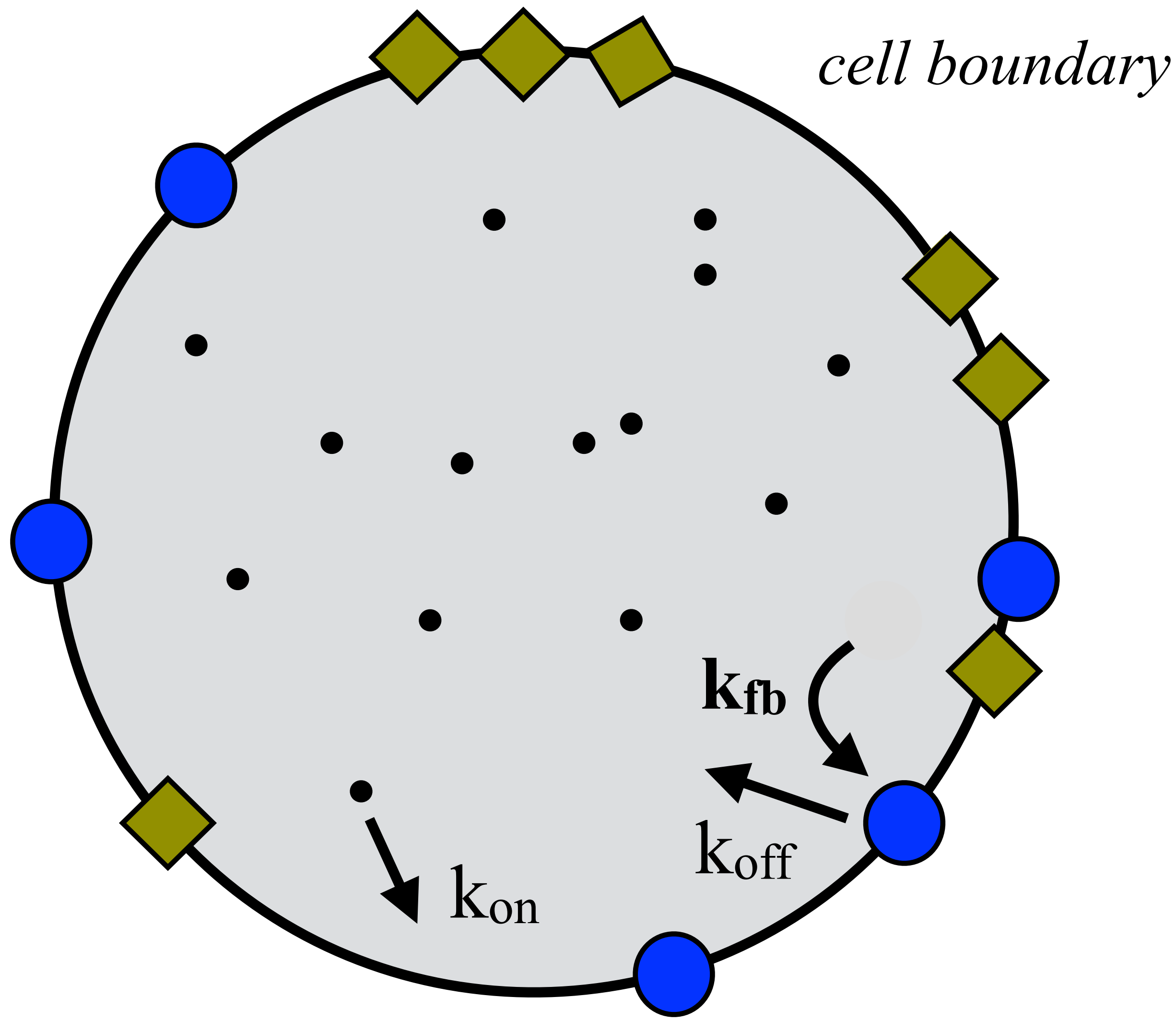

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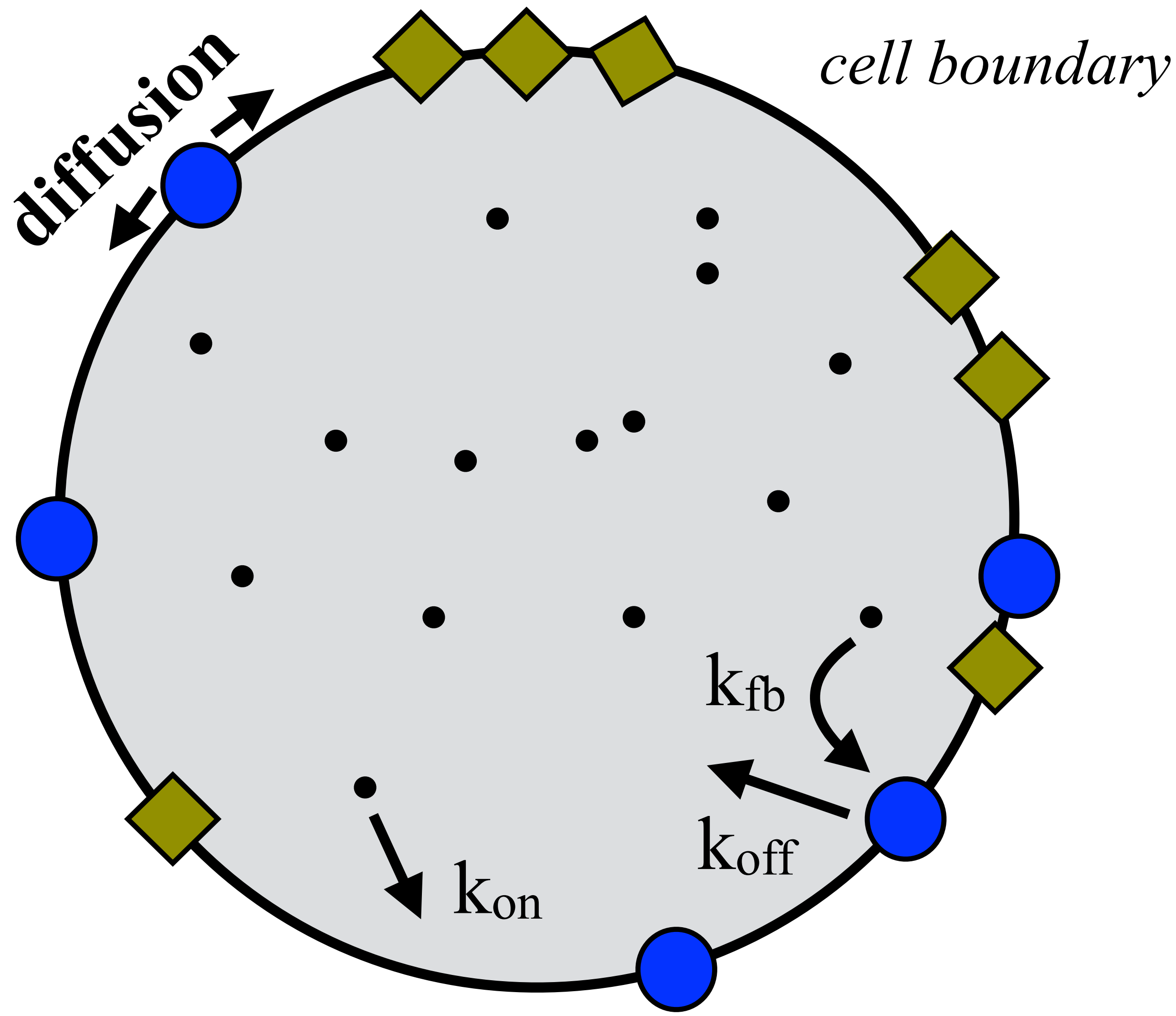

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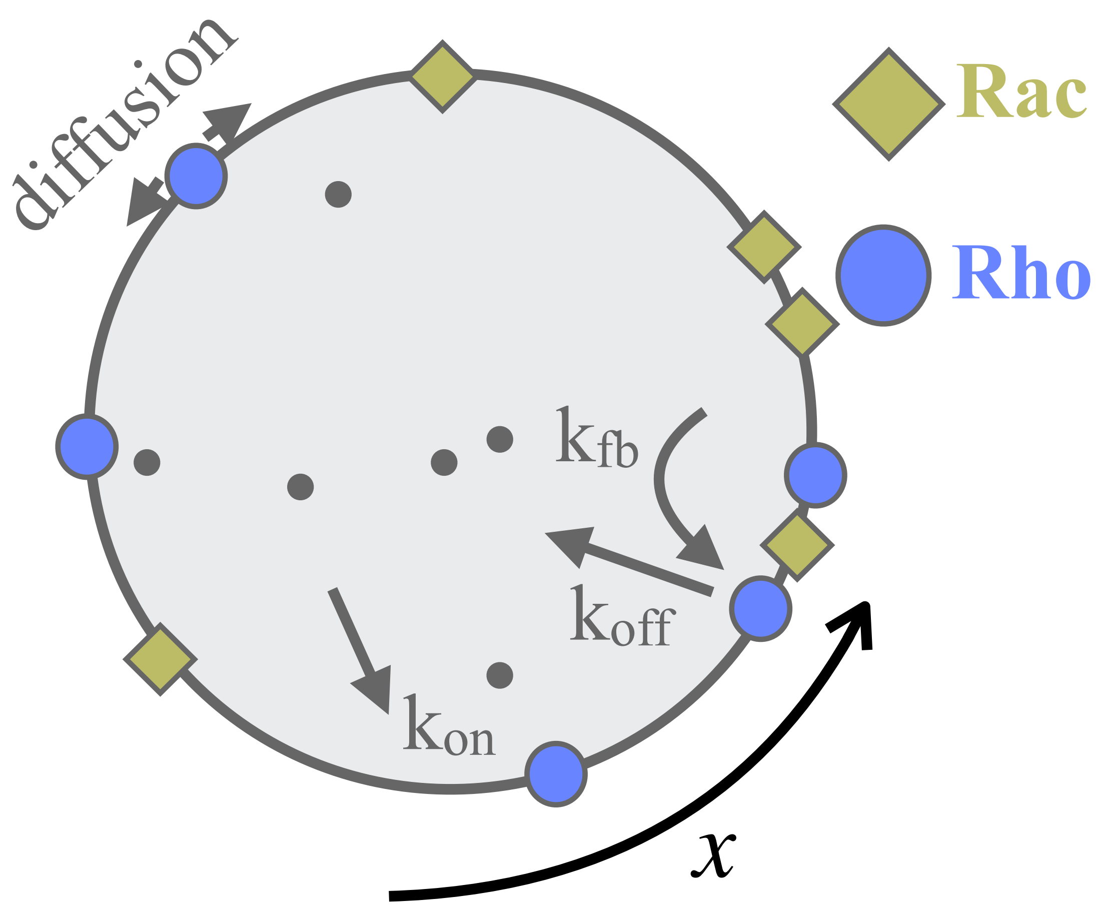
Kinetic rates and diffusion have been measured experimentally.

1. Biochemical module - Equations



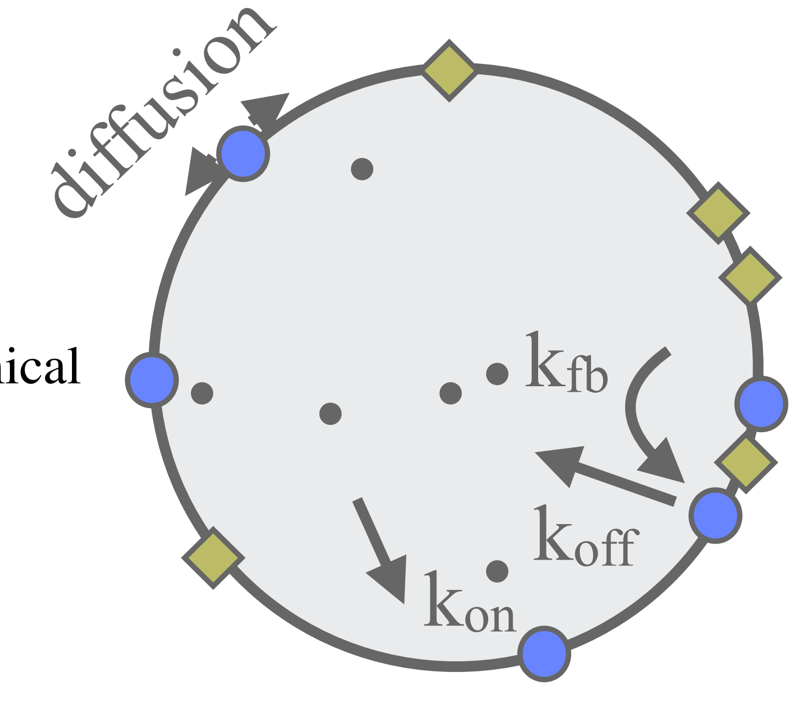
Assumptions

(1) Interior particles are well-mixed and homogeneous

(2) Dynamics of **only** boundary-bound (active) particles (# and locations)

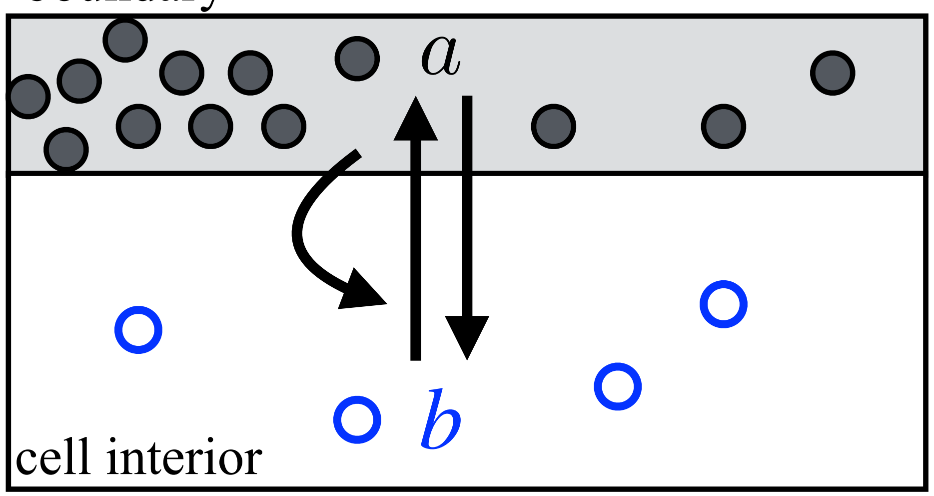
(3) Solved on a circle (thin boundary)

1. Biochemical module - Equations



Deterministic / Continuum (averaged) / PDE system

Mori, Jilkine, Edelstein-Keshet (2008): Reaction-diffusion system for one chemical



Concentration of **active** chemical

Concentration of **inactive** chemical

$$\frac{\partial a}{\partial t} = D_a \frac{\partial^2 a}{\partial x^2} + f(a,b)$$

$$\frac{\partial b}{\partial t} = D_b \frac{\partial^2 b}{\partial x^2} - f(a,b)$$

$$f(a,b) = k_0 b + \frac{\gamma a^2}{K^2 + a^2} b - \delta a$$

Conservation of mass

Nonlinear term

What about other models for the biochemical system?

Mori et al. 2008 model:

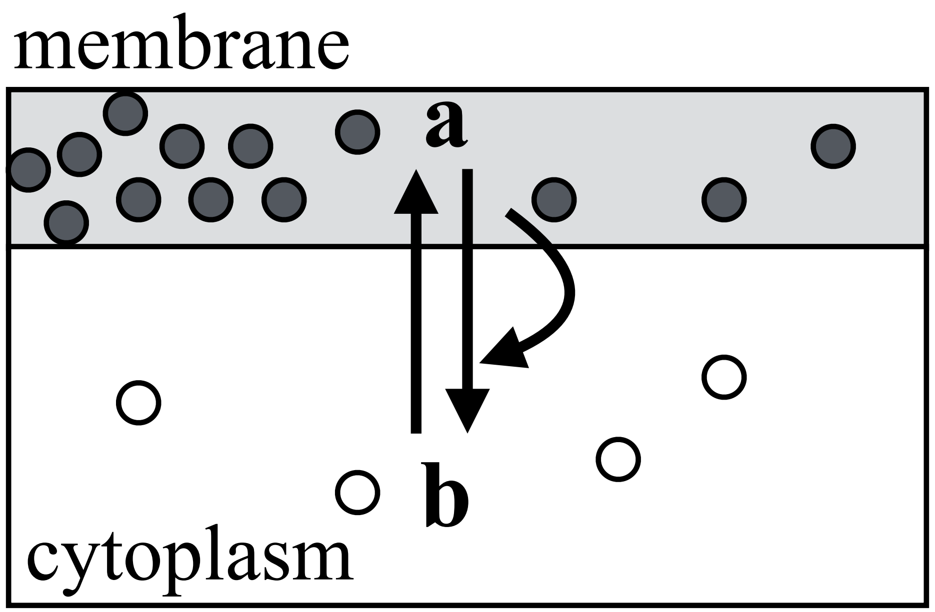
One polarity molecule in 2 states:
a (active, membrane-bound, slow)
b (inactive, cytoplasm, fast)

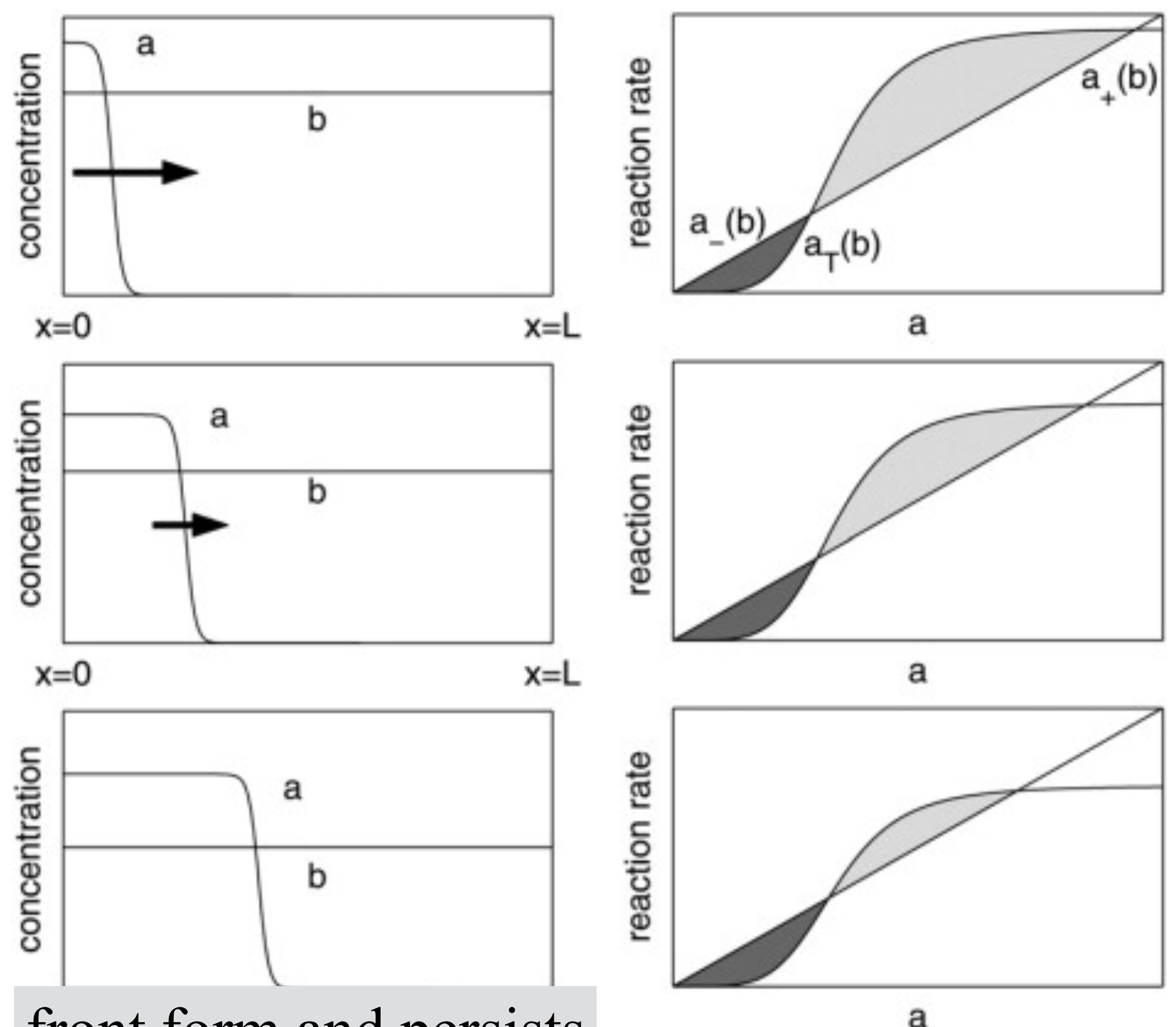
$$\left.\begin{aligned}\frac{\partial a}{\partial t} &= D_a \frac{\partial^2 a}{\partial x^2} + f(a,b) \\ \frac{\partial b}{\partial t} &= D_b \frac{\partial^2 b}{\partial x^2} - f(a,b)\end{aligned}\right\}$$

traveling wave solutions

$$f(a,b) = \left(k_0 + \frac{\gamma a^2}{K^2 + a^2}\right) b - \delta a$$

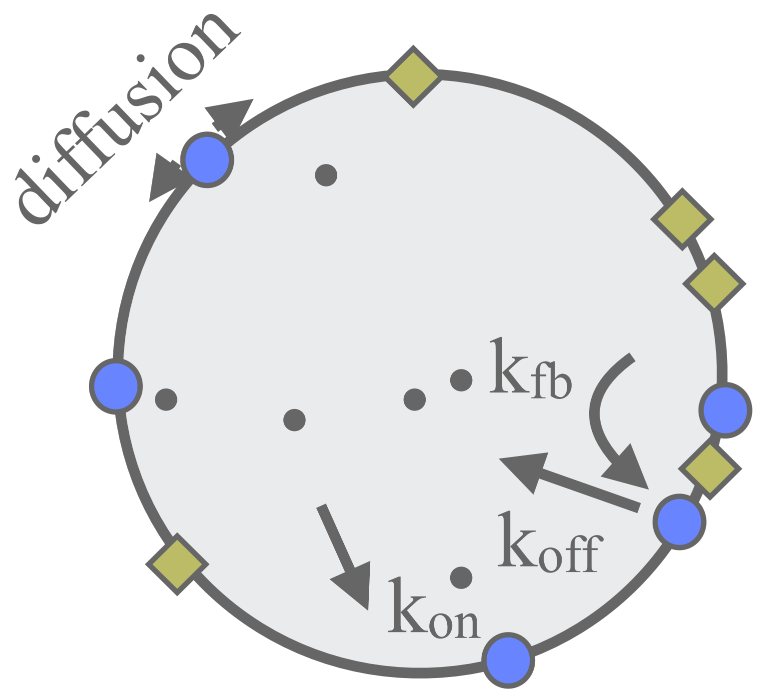
No flux boundary conditions.





front form and persists

1. Biochemical module - Equations

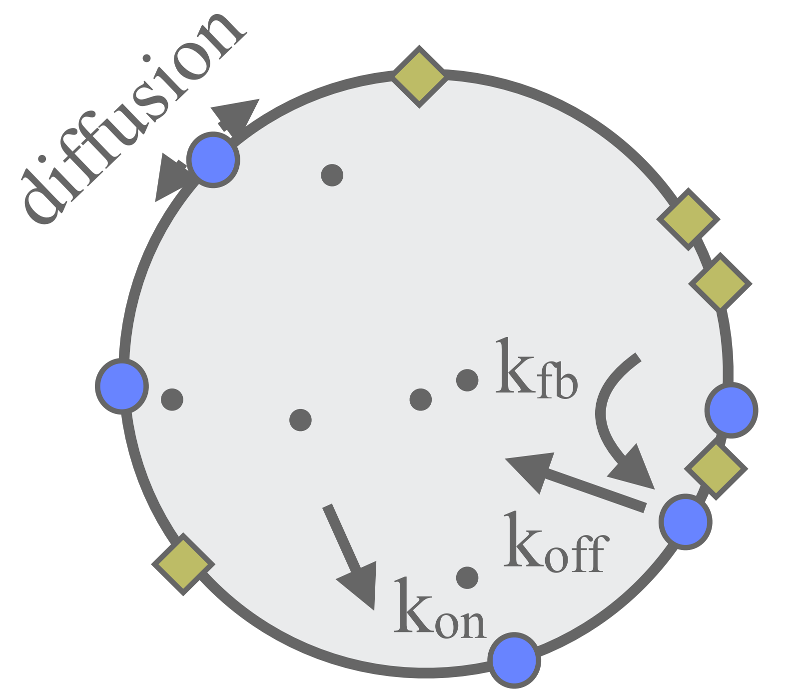


Our model is stochastic

Few molecules O(100)

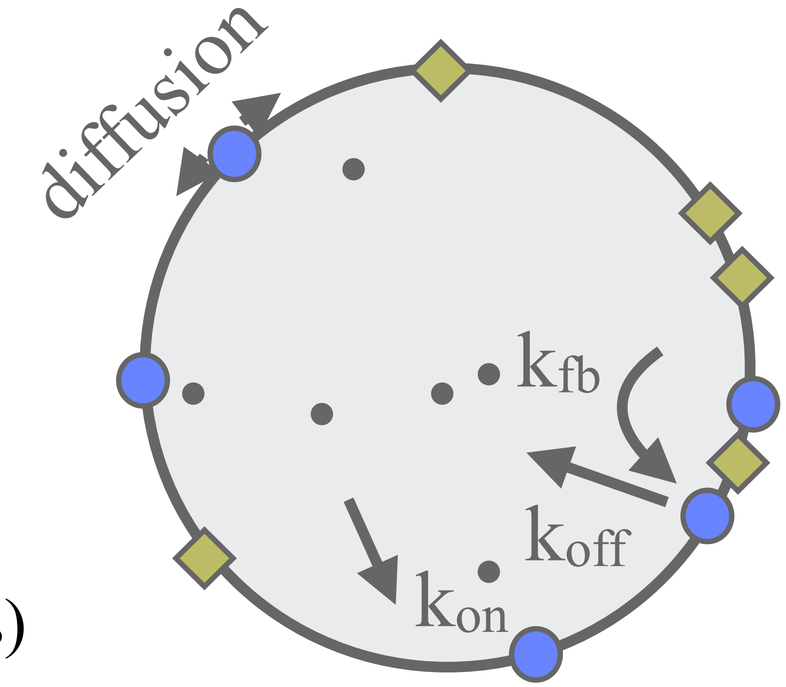
Track chemicals with experimentally measured interaction rules

1. Biochemical module - Equations



Track number of particles and their location.

1. Biochemical module - Equations



Track number of particles and their location.

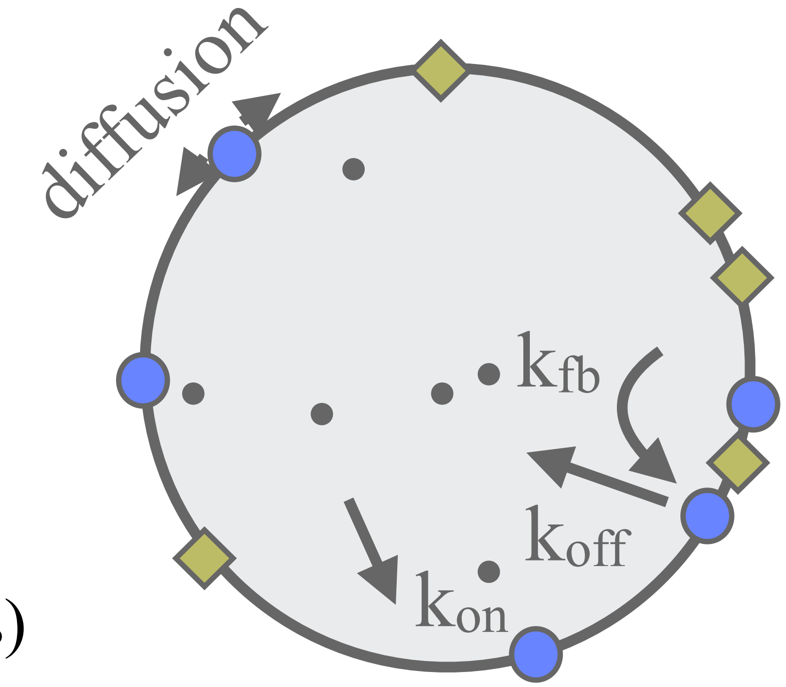
(1) Number of active particles at a given time:

- Modeled by a continuous time Markov chain process (+/- 1 jumps)
- Time between events: independent, RV exponentially distributed with rate:

rate: $$\lambda(n) = \underbrace{k_{\text{off}}\, n}_{\text{unbinding}} + \underbrace{\left(k_{\text{on}} + k_{\text{fb}}\frac{n}{N}\right)(N-n)}_{\text{binding}}$$

$n(t)$	Number of membrane-bound / active molecules
N	Total number of molecules

1. Biochemical module - Equations



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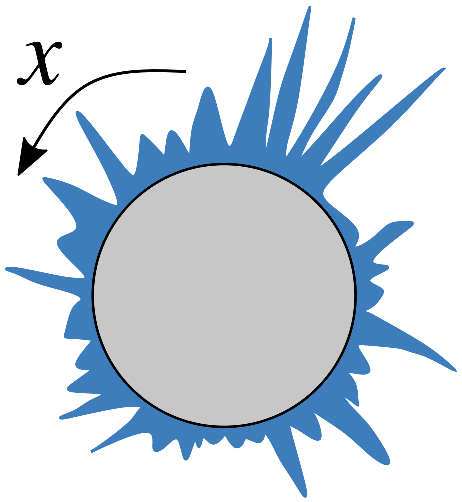
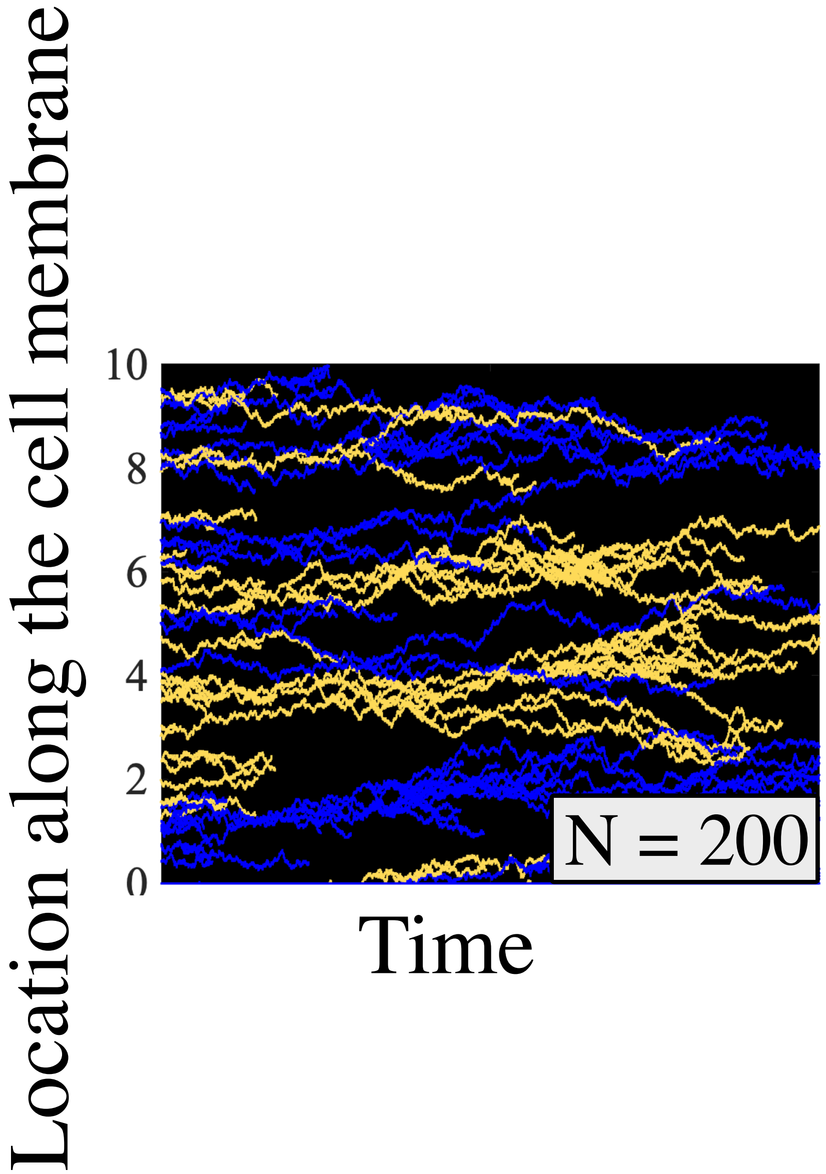
(2) Location of active particles:

- Between Markov events: Random diffusion on circle
- Within a Markov event: Location depends on type of event
  - (a) Association: random location
  - (b) Association via recruitment: random BUT from already bound particles
  - (c) Disassociation: random bound particle

Numerical simulations: (1) Spatial Gillespie algorithm (2) Brownian motion between events.

1. Biochemical module

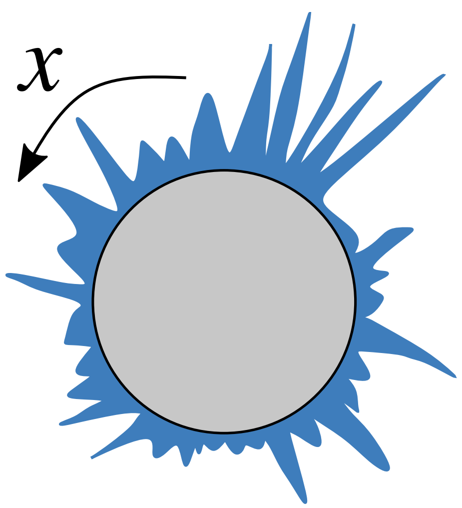




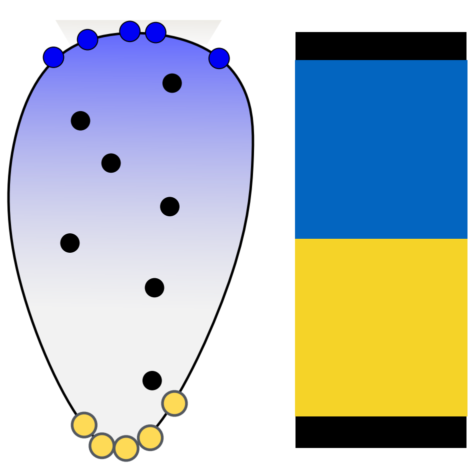
Rho

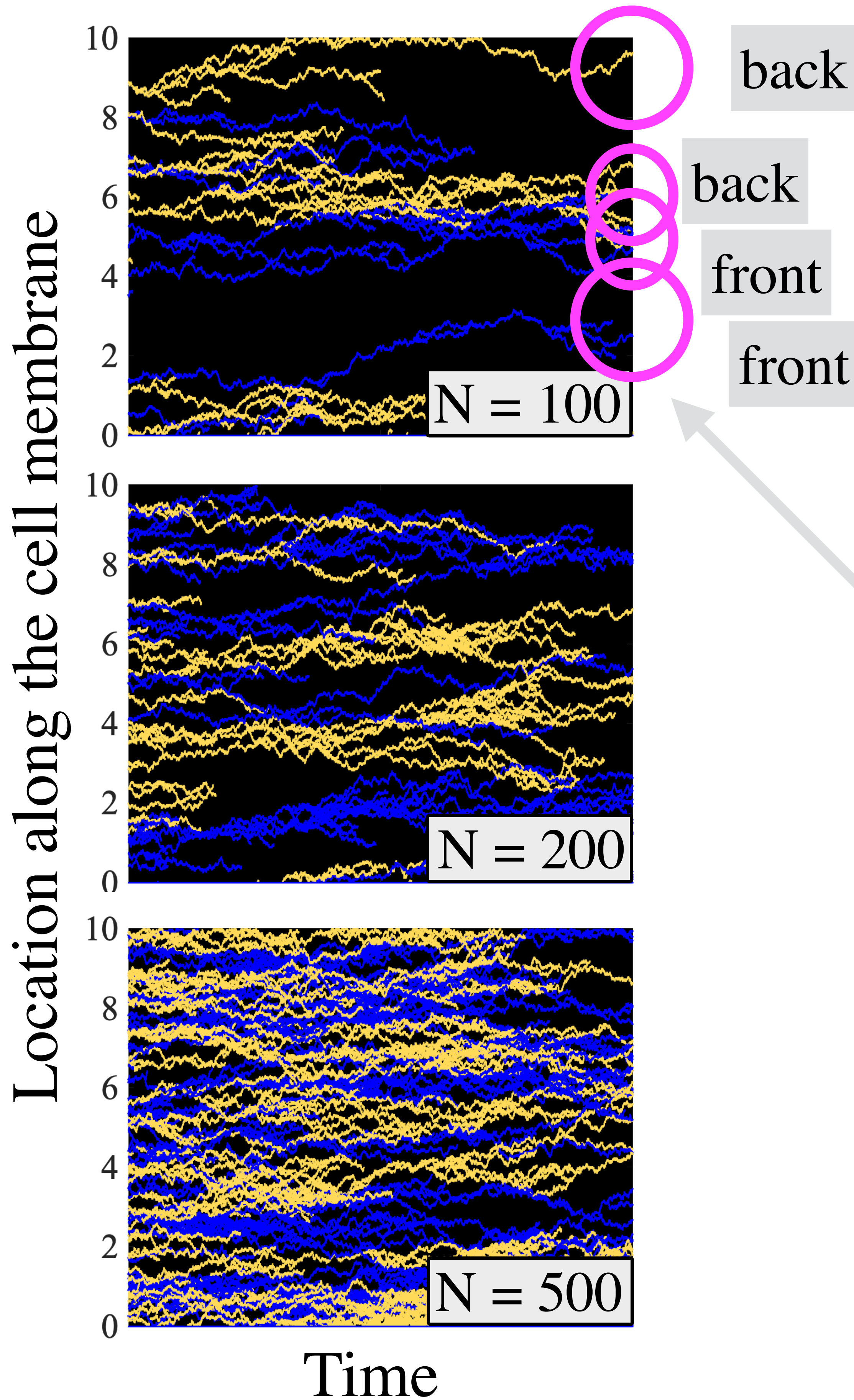
Rac

1. Biochemical module



The desired result:





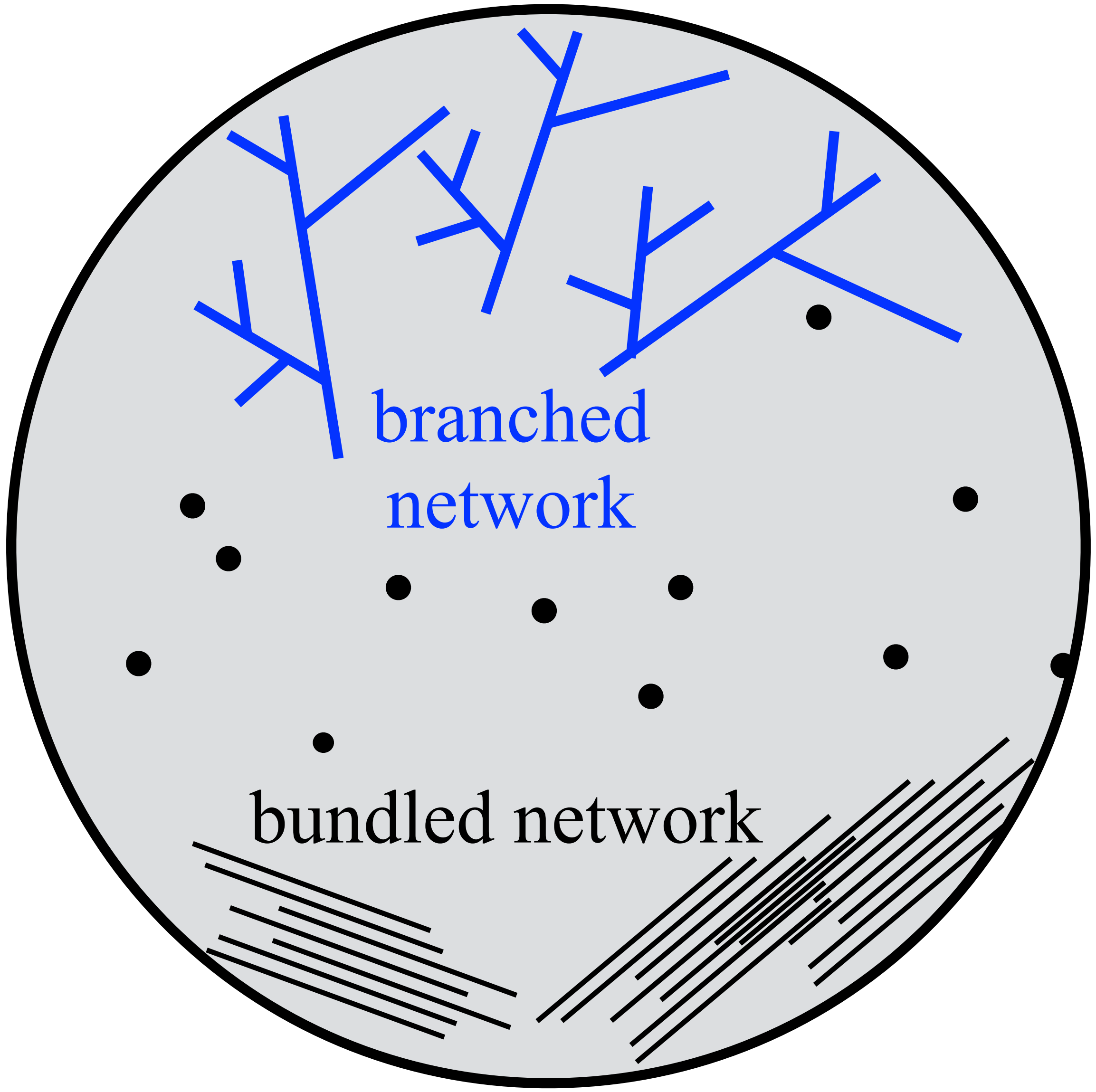
Multiple zones of activity emerge

Rho

Rac

2. Actin module

2. Actin module - Assumptions



What we know biologically:

1. **Actors**: Free actin monomers, **branched actin**, and **bundled actin**
2. **Dynamics**: Two major actin networks assembled & maintained while competing for a limited resource

2. Actin module - Equations

$$\frac{\partial A(x,t)}{\partial t} = A - A^2 - m_0 AB + D\frac{\partial^2 A}{\partial x^2}$$

$$\frac{\partial B(x,t)}{\partial t} = B - B^2 - m_0 AB + D\frac{\partial^2 B}{\partial x^2}$$

$A(x,t)$	Branched actin concentration
$B(x,t)$	Bundled actin concentration

Equations: Lotka-Volterra with diffusion

- Limited resource: free actin monomers
- Continuum/deterministic: Larger number in concentration

2. Actin module - Equations

$$\frac{\partial A(x,t)}{\partial t} = \boxed{A - A^2} - m_0 AB + D\frac{\partial^2 A}{\partial x^2}$$

$$\frac{\partial B(x,t)}{\partial t} = \boxed{B - B^2} - m_0 AB + D\frac{\partial^2 B}{\partial x^2}$$

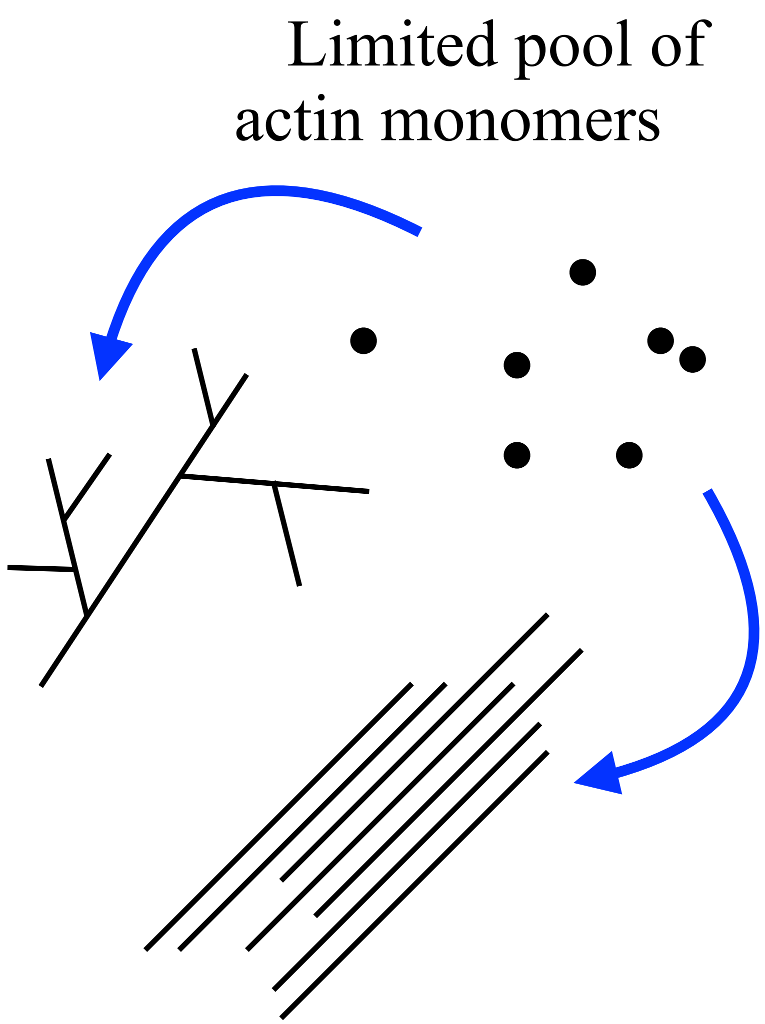
Saturated growth term but limited at high density

2. Actin module - Equations

$$\frac{\partial A(x,t)}{\partial t} = A - A^2 \boxed{- m_0 AB} + D\frac{\partial^2 A}{\partial x^2}$$

$$\frac{\partial B(x,t)}{\partial t} = B - B^2 \boxed{- m_0 AB} + D\frac{\partial^2 B}{\partial x^2}$$

Mechanics of competition

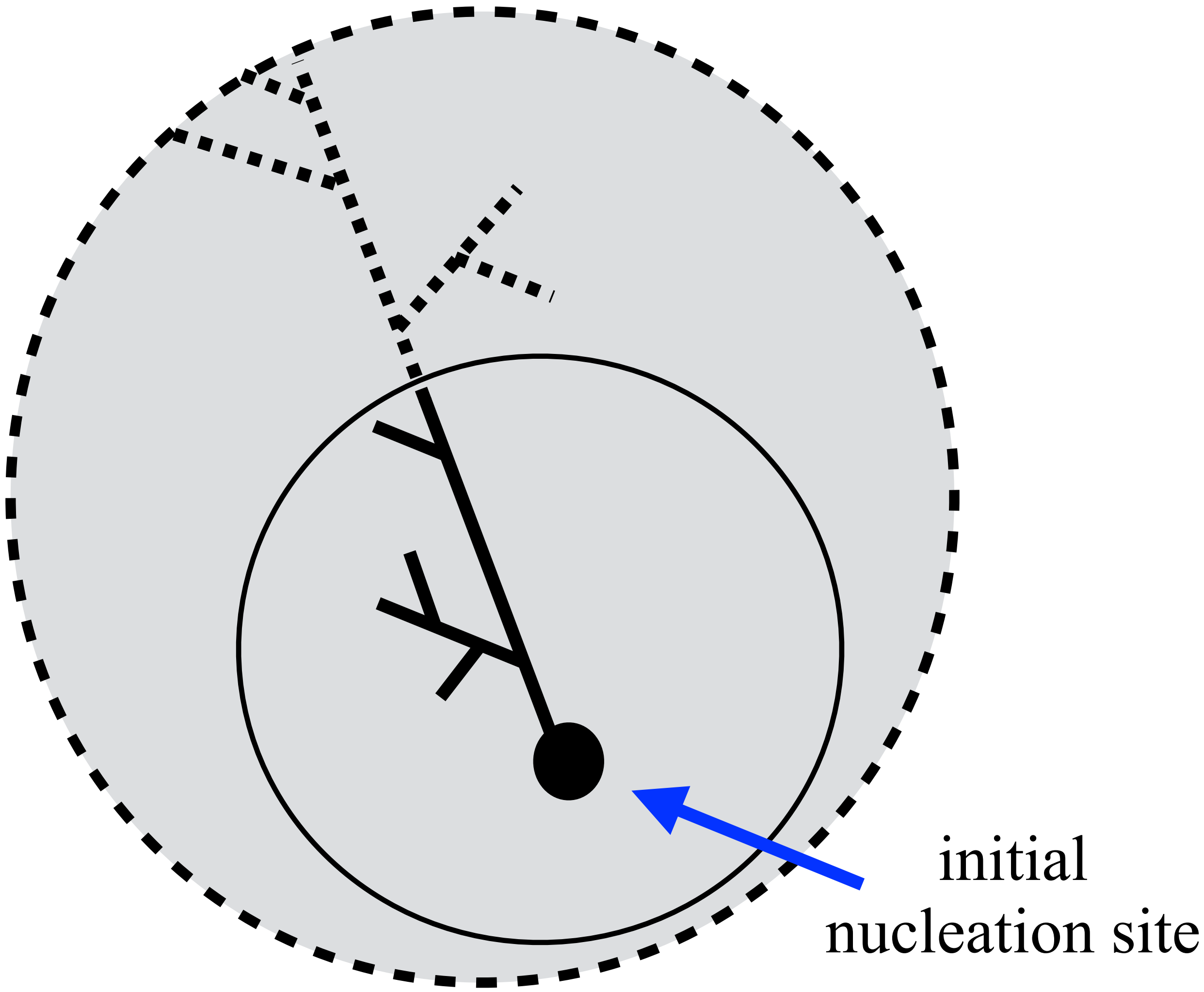


2. Actin module - Equations

$$\frac{\partial A(x,t)}{\partial t} = A - A^2 - m_0 AB + \boxed{D\frac{\partial^2 A}{\partial x^2}}$$

$$\frac{\partial B(x,t)}{\partial t} = B - B^2 - m_0 AB + \boxed{D\frac{\partial^2 B}{\partial x^2}}$$

Diffusion



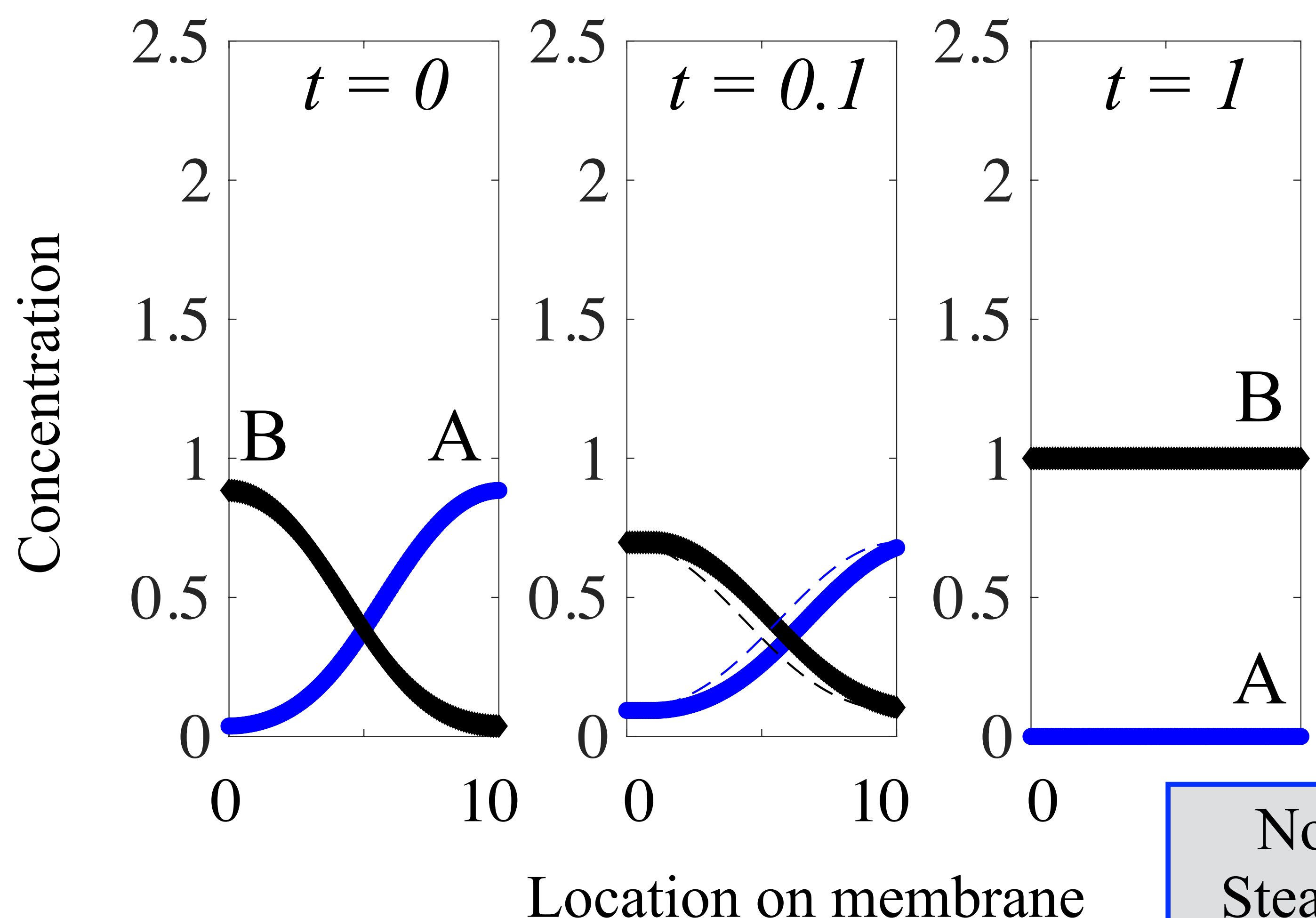
\+ sliding/shuffling of actin filaments due to molecular motors

2. Actin module - Solutions

Equations: Competition of two species for a limited resource with diffusion

- Limited resource: free actin monomers
- Continuum/deterministic: Larger number in concentration

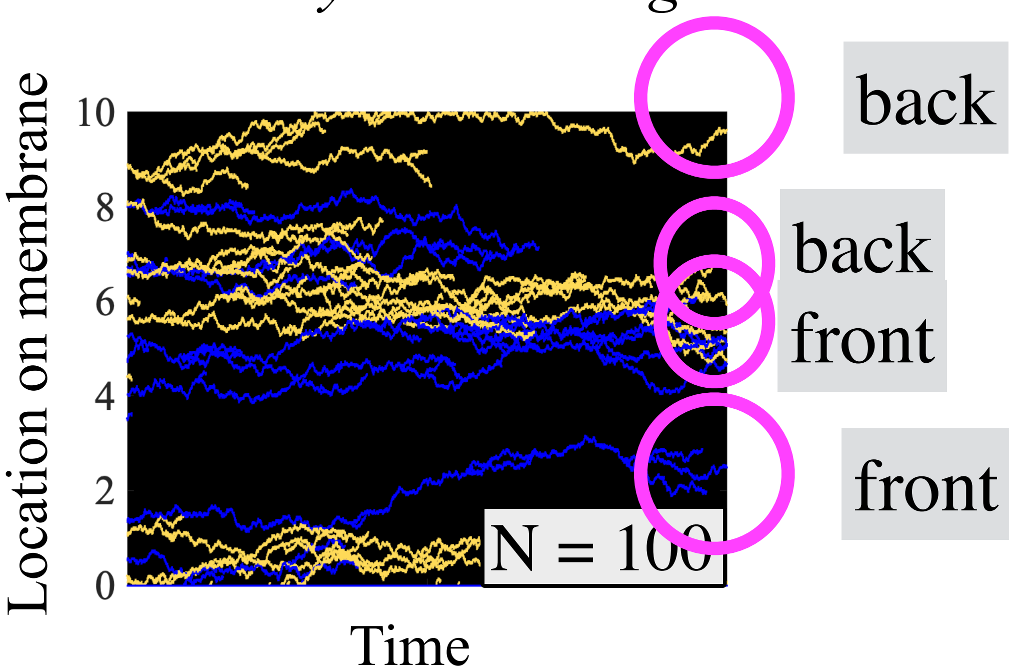
Computational simulation:



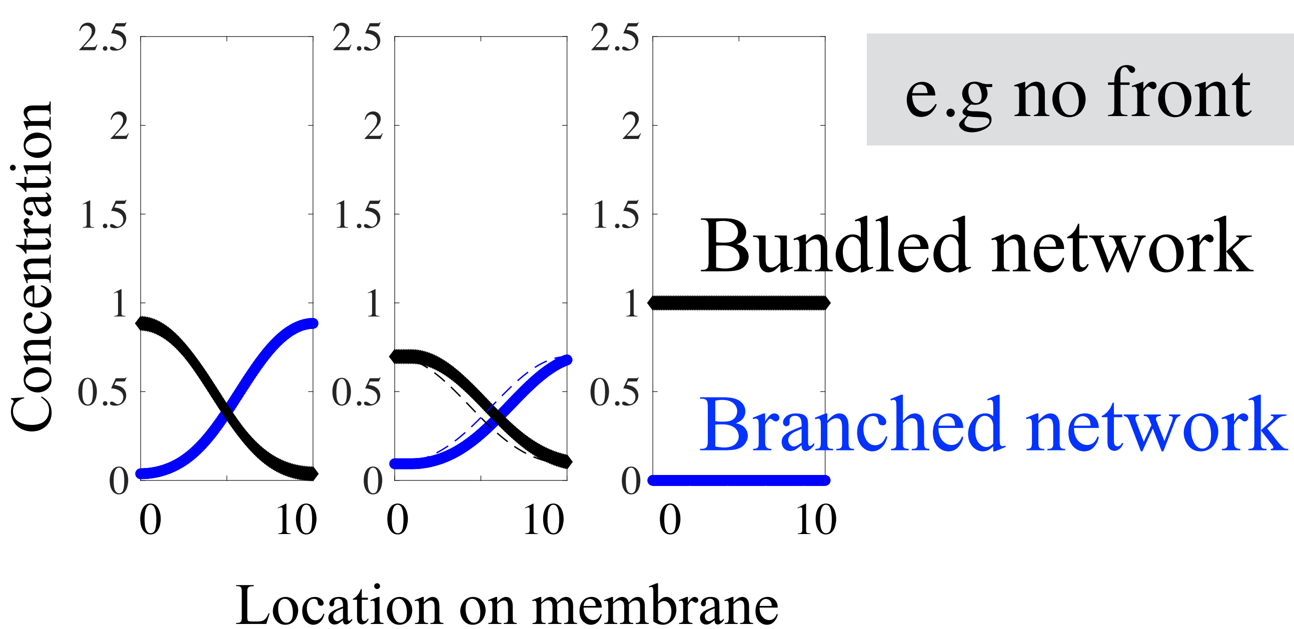
No stable polarized solutions
Steady state depends on relative concentrations

Is it possible for two minimal, non-polarizing models to work together to break cell symmetry and achieve polar distributions?

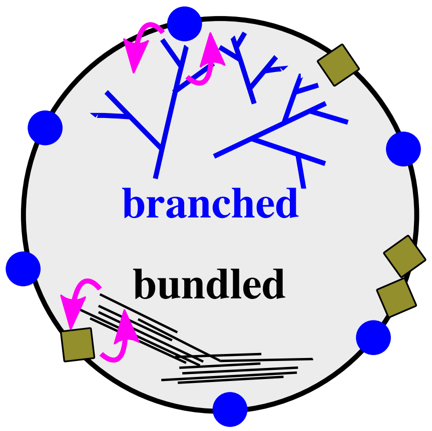
A number of Rac and Rho activity zones emerge

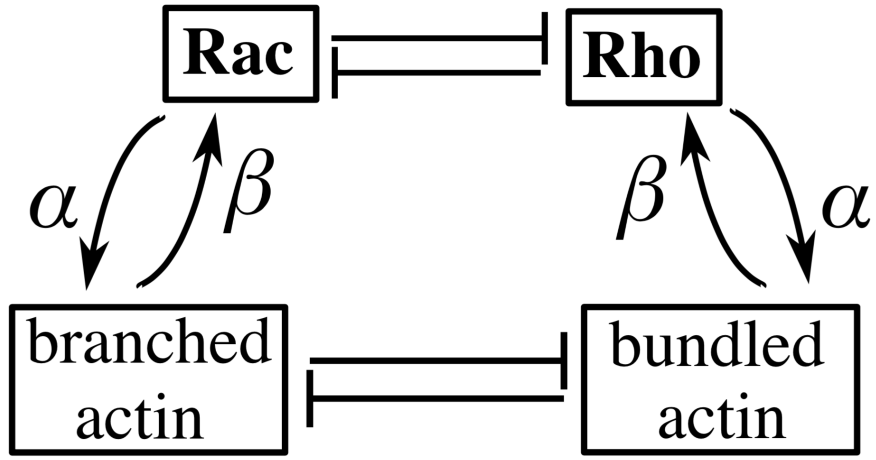


Depending on initial conditions, either one of the two actin networks can persist while the other becomes extinct



Couple the signaling module to the cytoskeleton module





local, linear coupling

At any given time, reaction rates depend on local actin concentrations:

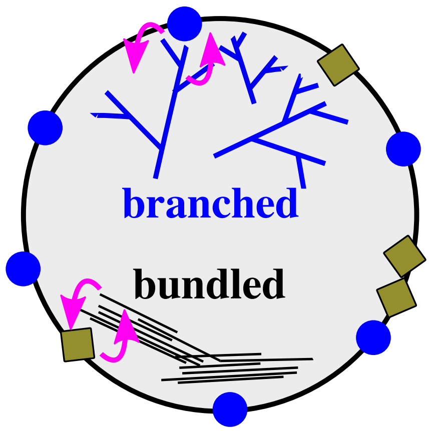
Rac/Rho dynamics

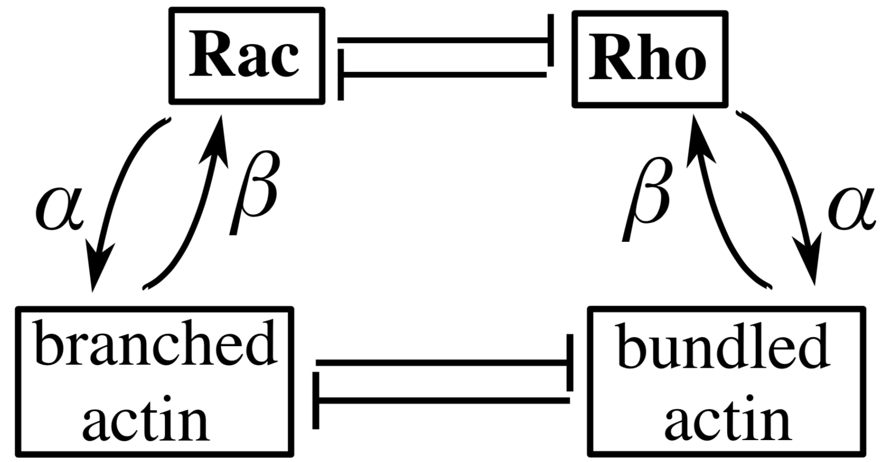
$$\begin{cases} k_{\text{on,fb}} = k_{\text{on,fb}} \left(1 + \beta C(x,t)\right) \\ k_{\text{off}} = k_{\text{off}} \end{cases}$$

$C(s,t) = A(s,t)$ or $B(s,t)$

Kinetic rates are spatially-dependent

Couple the signaling module to the cytoskeleton module





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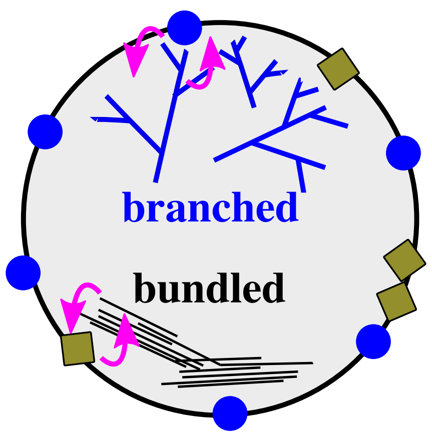
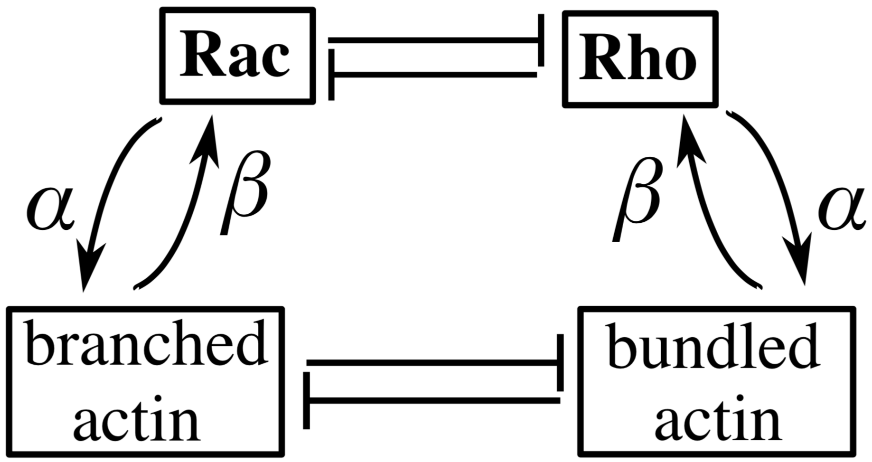
$C(x,t)$: $A(x,t)$ or $B(x,t)$

Cytoskeleton dynamics

$$\begin{cases} \dfrac{\partial A(x,t)}{\partial t} = A(1 + \alpha n^{\text{Rac}}(x,t)) - A^2 - m_0 AB + D\dfrac{\partial^2 A}{\partial x^2} \\ \dfrac{\partial B(x,t)}{\partial t} = B(1 + \alpha n^{\text{Rho}}(x,t)) - B^2 - m_0 AB + D\dfrac{\partial^2 B}{\partial x^2} \end{cases}$$

Couple the signaling module to the cytoskeleton module





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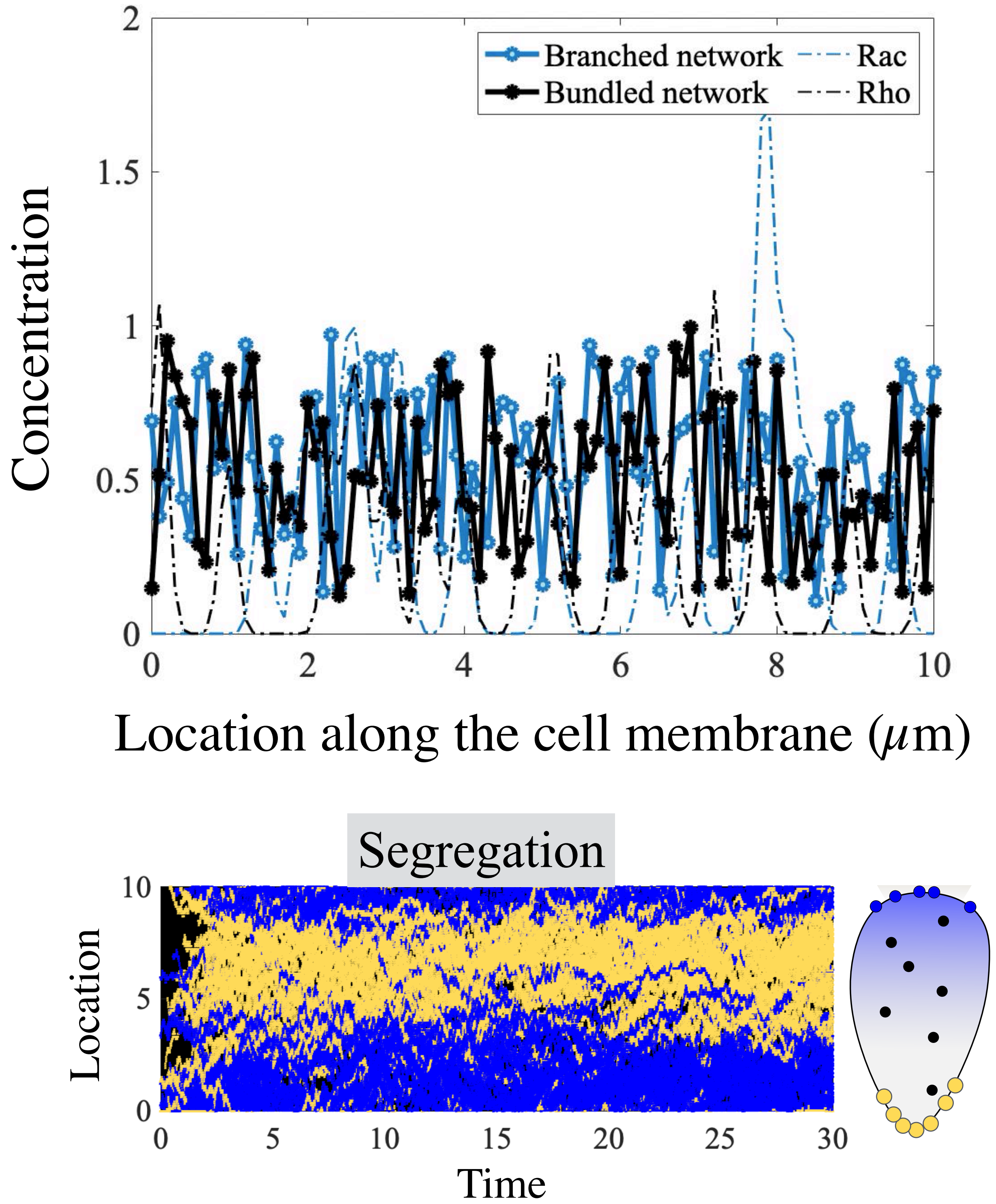
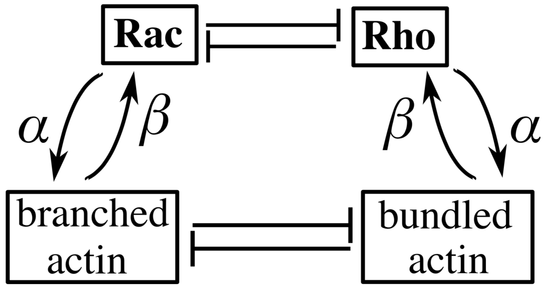
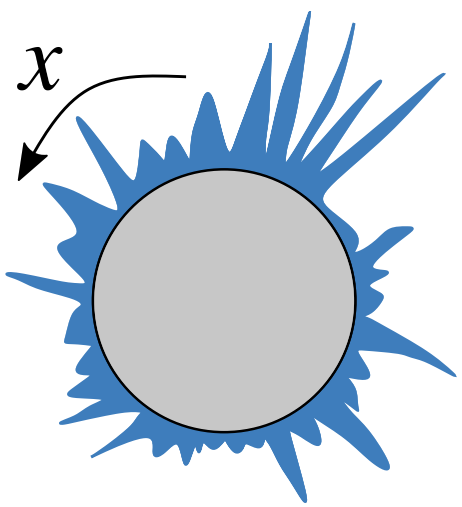
A **strongly** coupled system yields spontaneous symmetry breaking
α, β large

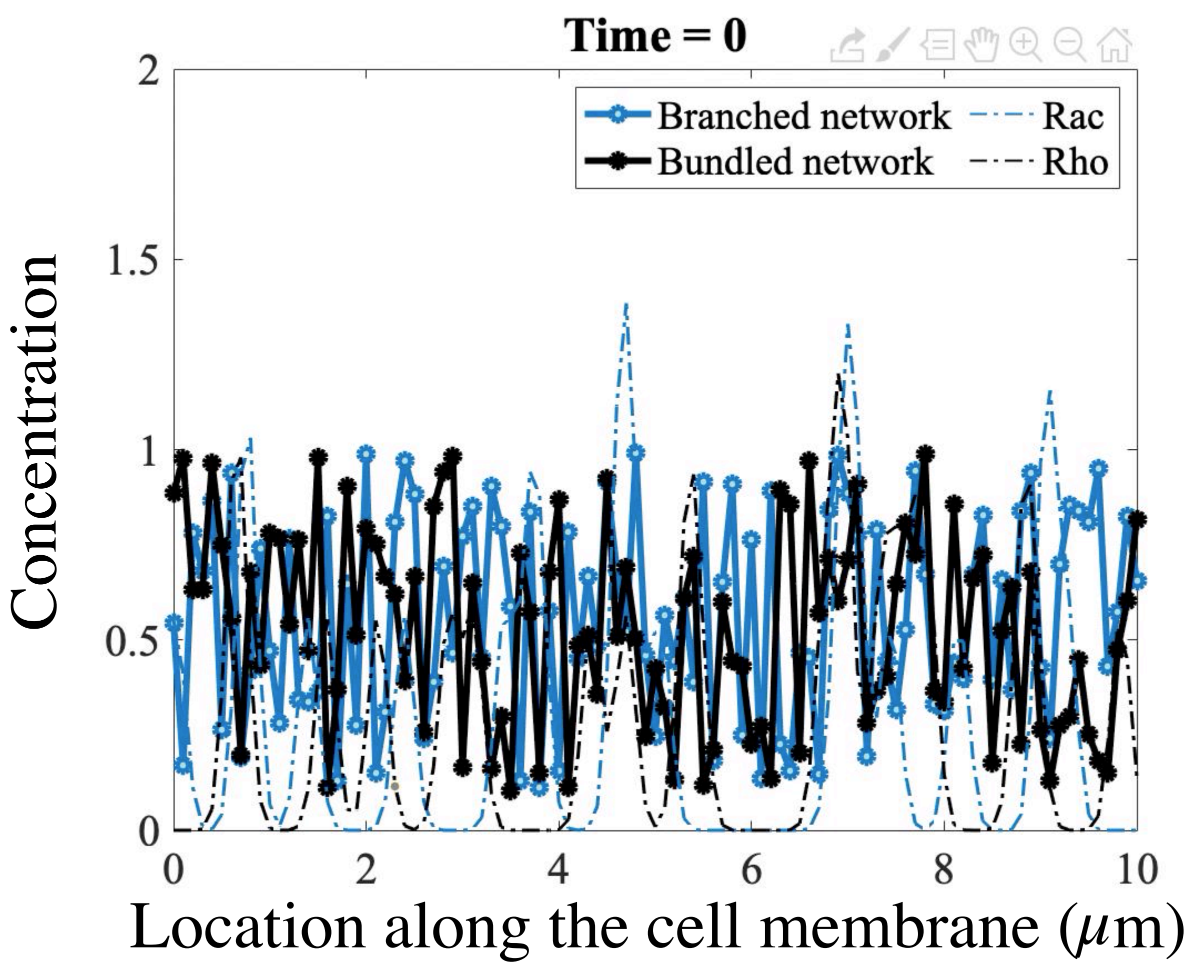




A **weakly** coupled system

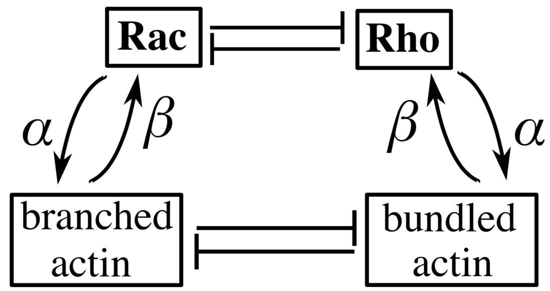
α, β small





Dotted lines (chemicals)

Solid lines (networks)



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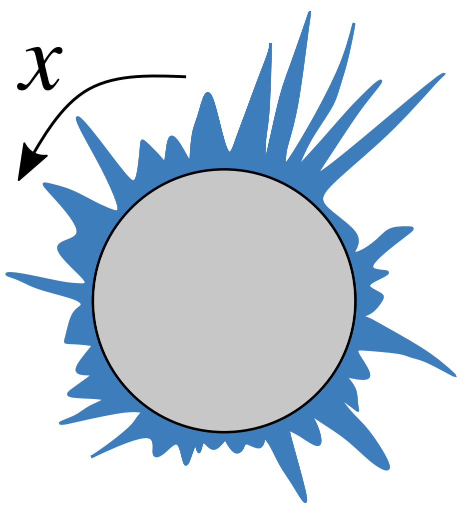
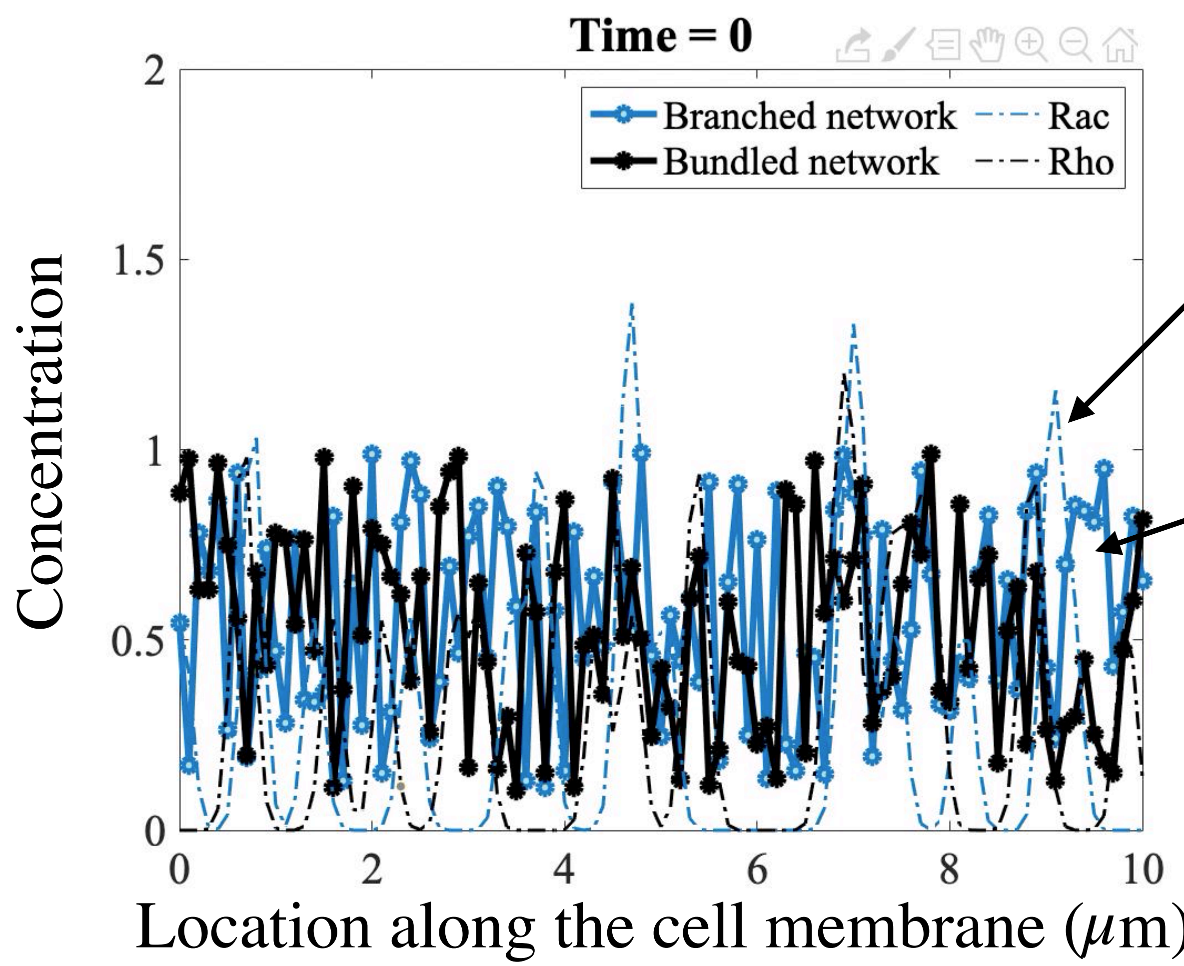
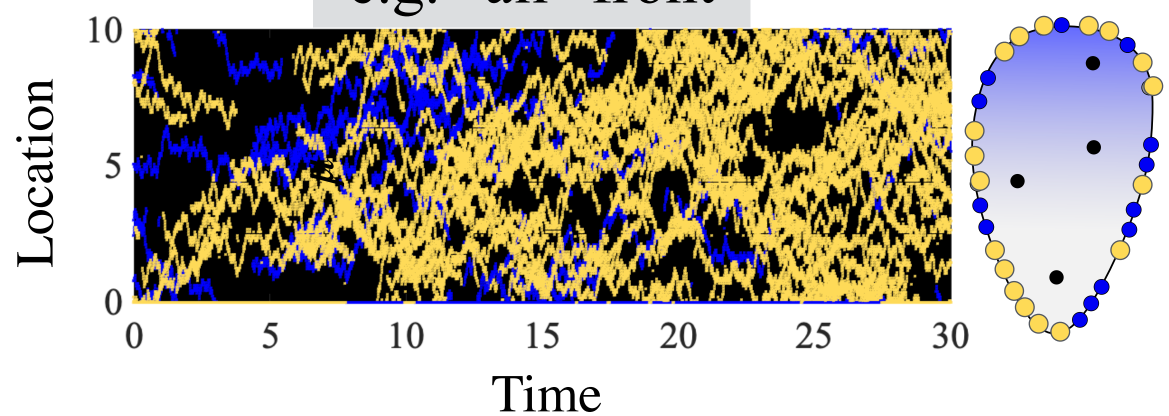




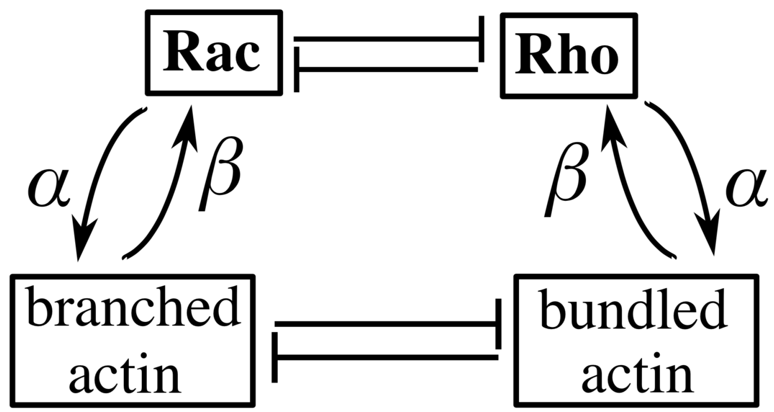
Dotted lines (chemicals)

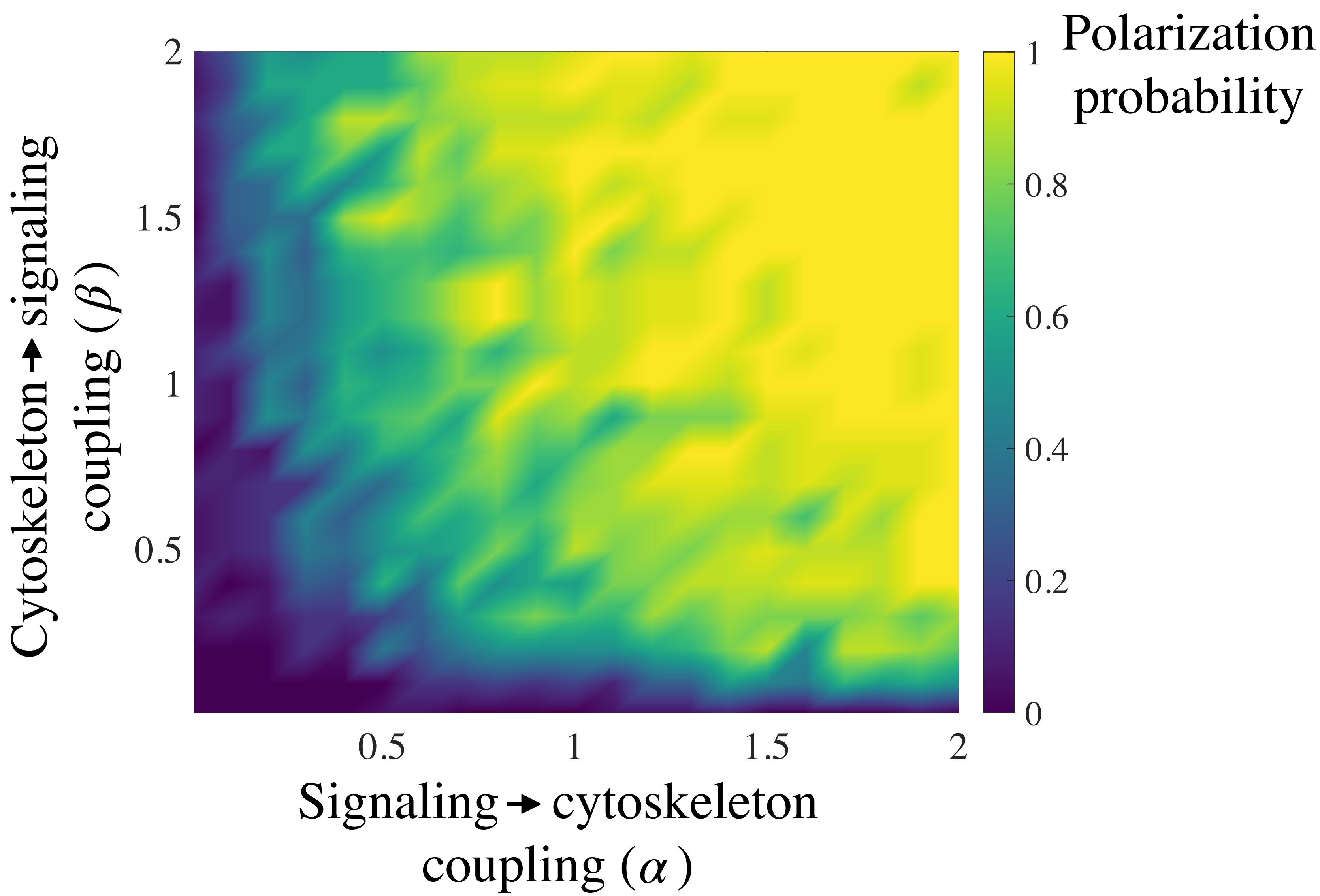
Solid lines (actin networks)

e.g. “all" front



Self-polarization requires mutual reinforcement/coupling

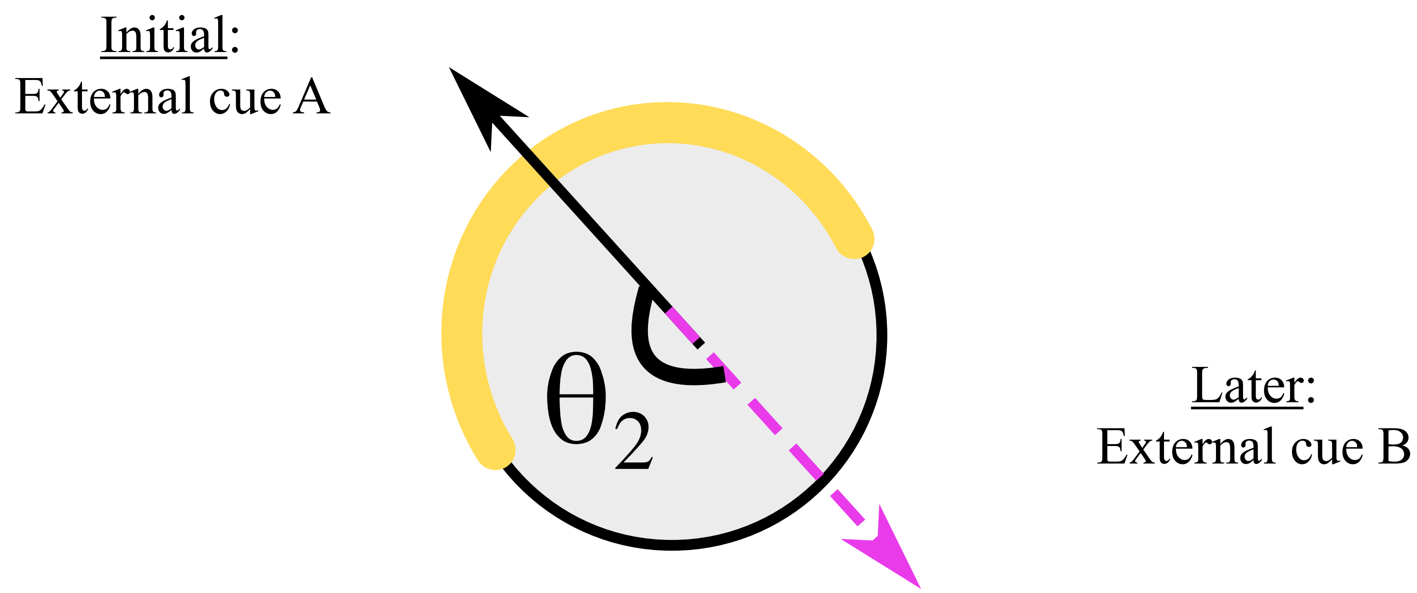


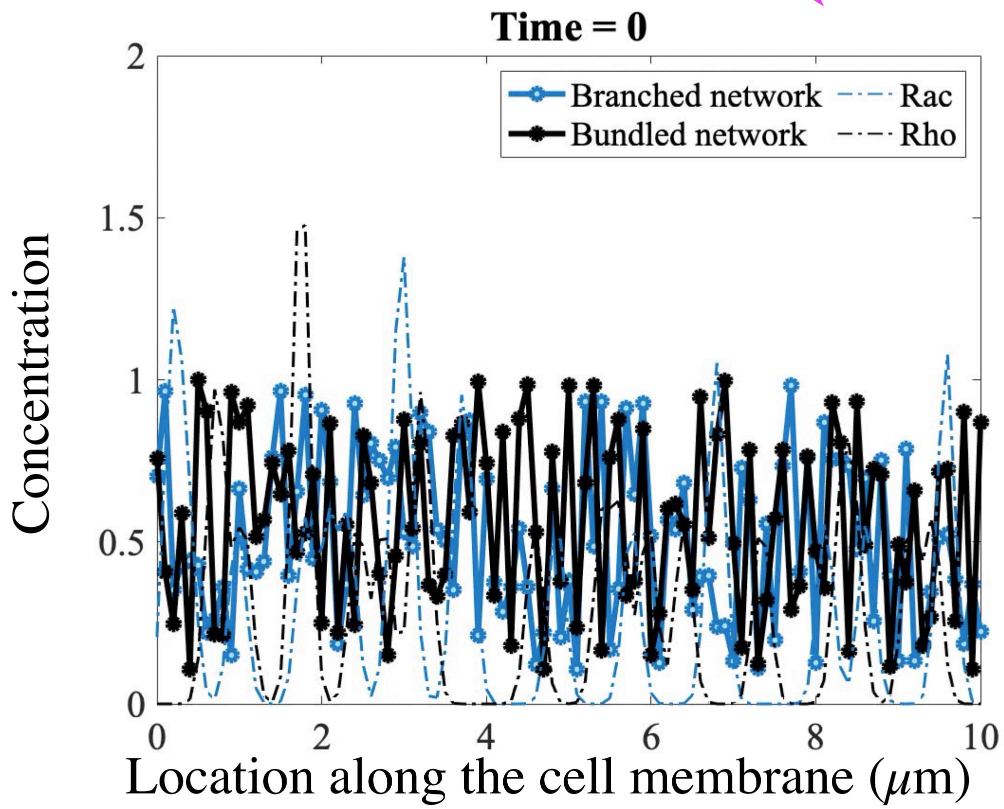


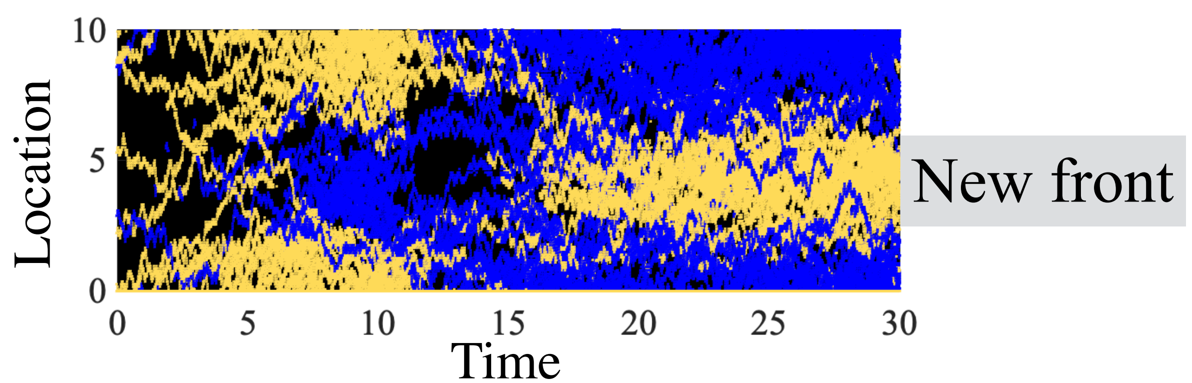
Can the model capture re-orientation?

Motivation: Cells frequently change direction of locomotion in the presence of external cues.

Can the model capture re-orientation?







What mechanism is responsible for the formation of cell "front" and "rear"?

1. Biochemical Signaling Pathways

Meinhardt and Gierer 1974
Levchenko and Iglesias 2002
Mori, Jilkine, Edelstein-Keshet 2008
Maree, Jilkine, Dawes, Grieneisen, Edelstein-Keshet, and Dawes 2007
Altschuler, Angenent, Wang, Wu 2008
Pablo, Ramirez, Elston 2018
and many more

2. Polymer Network Rearrangement

Lomakin, Lee, Han, Bui, Davidson, Mogilner, Danuser 2015

A minimal mechano-chemical model captures spontaneous symmetry breaking

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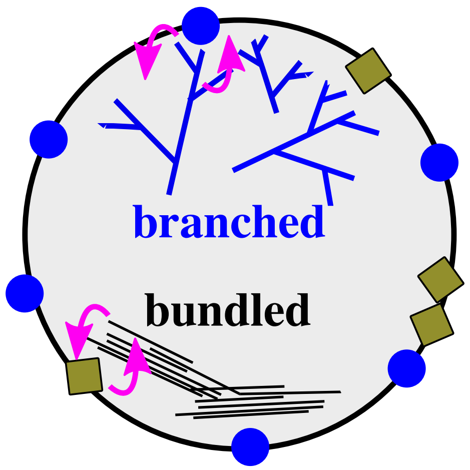

- **Minimally nonlinear**
- **Introduced feedback/coupling (local, linear)**
  - <u>Biologically "speculated" (3 out of 4 directions are established)</u>
  - **Novel testable component**: Positive feedback loop between Rho and formation of actomyosin bundles

A minimal mechano-chemical model captures spontaneous symmetry breaking

WHAT MECHANISM IS RESPONSIBLE FOR THE FORMATION OF CELL "FRONT" AND "REAR"?

1. BIOCHEMICAL SIGNALING PATHWAYS

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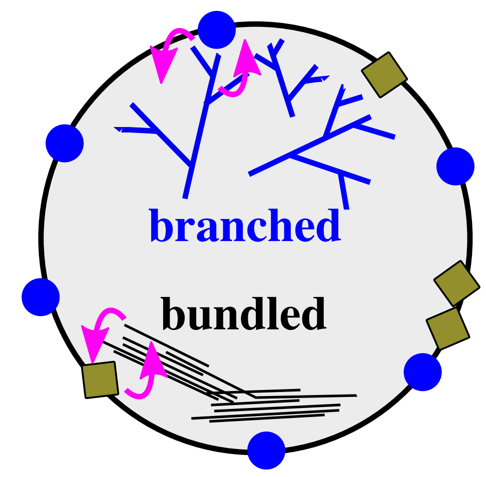
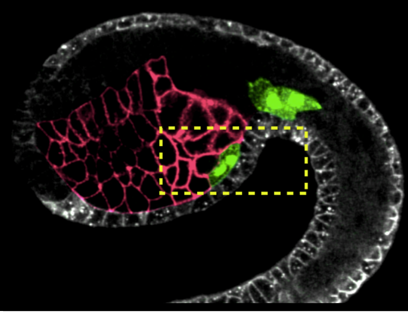
2. CELL CYTOSKELETON REARRANGEMENT

Lomakin, Lee, Han, Bui, Davidson, Mogilner, Danuser 2015



- **Mathematical challenges**
  - Coupling stochastic-deterministic systems
  - Time to establish cell polarity?
    Continuum description? Not feasible
    Peak detection? Statistical learning approach
  - 3D (Multiple zones? Any additional complexity?)
  - Resolved across multiple cells



Moving as a pair is “better” than alone

Hypothesis #1: There is a **mechanical advantage** to move as a two-cell system

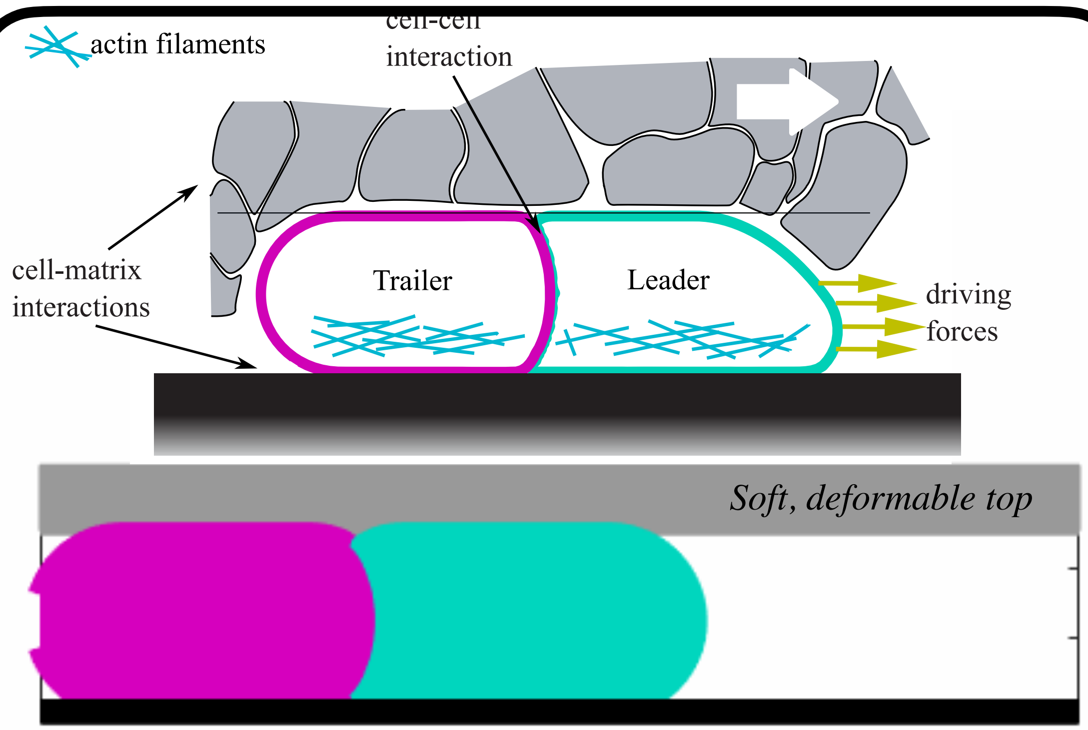
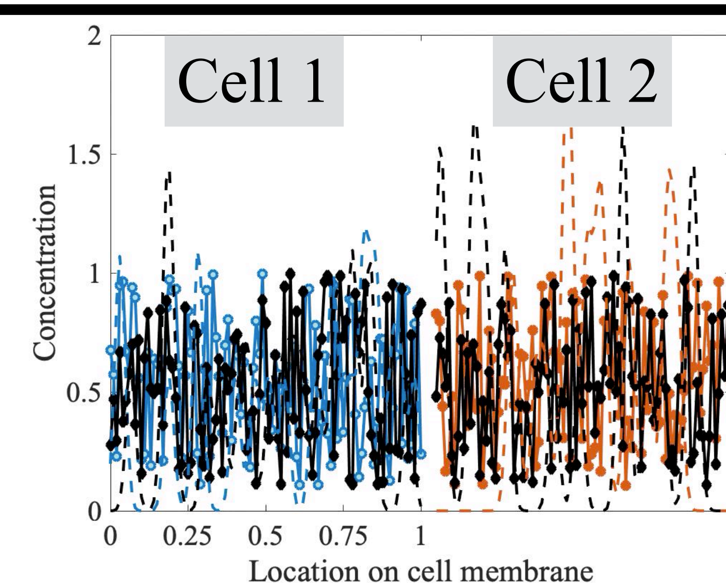


Image analysis (morphometrics)
Mechanical models (force balance)
Traction forces

Hypothesis #2: It is easier to **initiate** locomotion as a pair



Hybrid stochastic-deterministic model
Modeling of cell-cell junction behavior
Peak detection algorithms
Eventually, coupled to moving domains

Thank You For Listening!

More info:

- Y. Bernadskaya, H. Yue, **C. Copos**, L. Christiaen, A. Mogilner. (2021) S*upracellular organization confers directionality and mechanical potency to migrating pairs of cardiopharyngeal progenitor cells*. Accepted at eLife.

- T. Vignaud, **C. Copos**, Q. Tseng, L. Blanchoin, A. Mogilner, M. Thery, L. Kurzawa. (2020) *Stress fibers are embedded in a contractile cytoplasmic meshwork*. Nature Materials, Vol. 20, 410-420.

- Y.-H. Sun, H. Yue, **C. Copos**, Y. Sun, K. Zhu, B. Reid, B.W. Draper, M. Zhao, A. Mogilner. (2020) *PI3K inhibition reverses migratory direction of single cells but not cell groups in electric fields*. In review at Biophysical Journal.

- **C. Copos**, A. Mogilner. (2020) *A hybrid stochastic-deterministic mechanochemical model of cell polarization*.Molecular Biology of the Cell, Vol. 31, 1637-1649.

- **C. Copos**, B. Bannish, K. Glasior, R. Pinals, M. Rostami, A. Dawes. (2020) *Connecting actin polymer dynamics across multiple scales*. R.Segal at al. (eds), Using Mathematics to Understand Biological Complexity, Series 22, Springer.

- **C. Copos**, R.D. Guy. (2018) *A porous viscoelastic model for the cell cytoskeleton*. ANZIAM Journal, Vol. 59, 472-498.

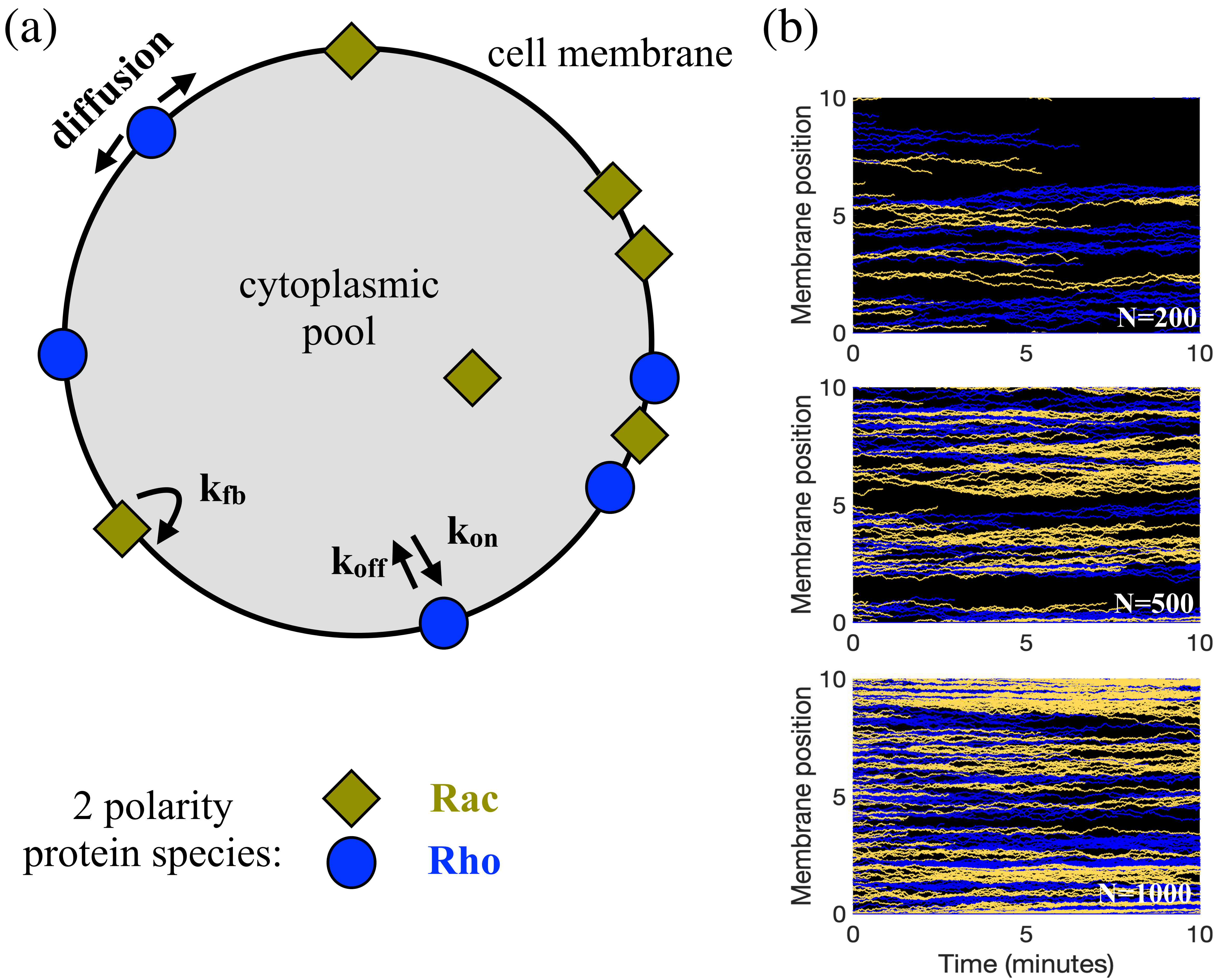
- **C. Copos**, S. Walcott, J.C. del Alamo, E. Bastounis, A. Mogilner, R.D. Guy. (2017) *Mechanosensitive adhesion explain stepping motility in amoeboid cells*. Biophysical Journal, Vol. 112, 2672-2682.

- W. Strychalski, **C. Copos**, O.L. Lewis, R.D. Guy. (2015) *A poroelastic immersed boundary method with applications to cell biology*. Journal of Computational Physics, Vol. 282, 77-97.

- C. Bodea, **C. Copos**, M.F. Der, D. O'Neal, J.A. Davis. (2011) *Shared autocorrelation property of sequences*. IEEE: Transactions on Information Theory, Vol. 57, 3805-3809.

Copos Lab

Figure 2


(a)
diffusion
cell membrane
cytoplasmic
pool
kfb
koff
kon
2 polarity
protein species:
Rac
Rho
(b)
10
5
0
Membrane position
N=200
N=500
N=1000
Time (minutes)

Wave pinning model - why this reaction term

$$\frac{\partial a}{\partial t} = D_a \frac{\partial^2 a}{\partial x^2} + f(a,b)$$

$$\frac{\partial b}{\partial t} = D_b \frac{\partial^2 b}{\partial x^2} - f(a,b)$$

$$f(a,b) = \left(k_0 + \frac{\gamma a^2}{K^2 + a^2}\right) b - \delta a$$

$$\mathrm{a} \underset{k_{ba}}{\overset{k_{ab}}{\rightleftharpoons}} \mathrm{b}$$

$$\frac{da}{dt} = \text{Rate of activation} - \text{Rate of inactivation}$$

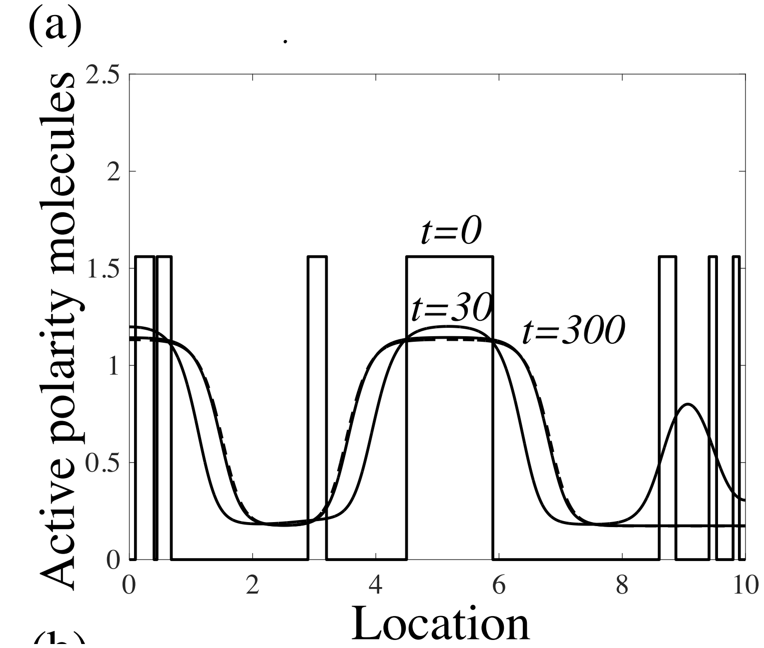
$$= k_{ba} b - k_{ab} a = f(a,b)$$

Bistability requires either rate to be nonlinear. Here, authors assume cooperative positive feedback:

$$k_{ba} = k_0 + \frac{\gamma a^2}{K^2 + a^2}, k_{ab} = \delta$$

Lower diffusion scenario

(A) Wave pinning with D = 0.01 um²/sec



(B) Our hybrid model with D = 0.01 um²/sec