Modeling self-organization and collective migration of biological cells

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January 30, 2023

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Outline:

I. Background and motivation:
   - What are neural crest cells (NCCs)?
   - Two curious emergent behaviors in clusters: how?
   - Existing "rule-based" phenomenological models

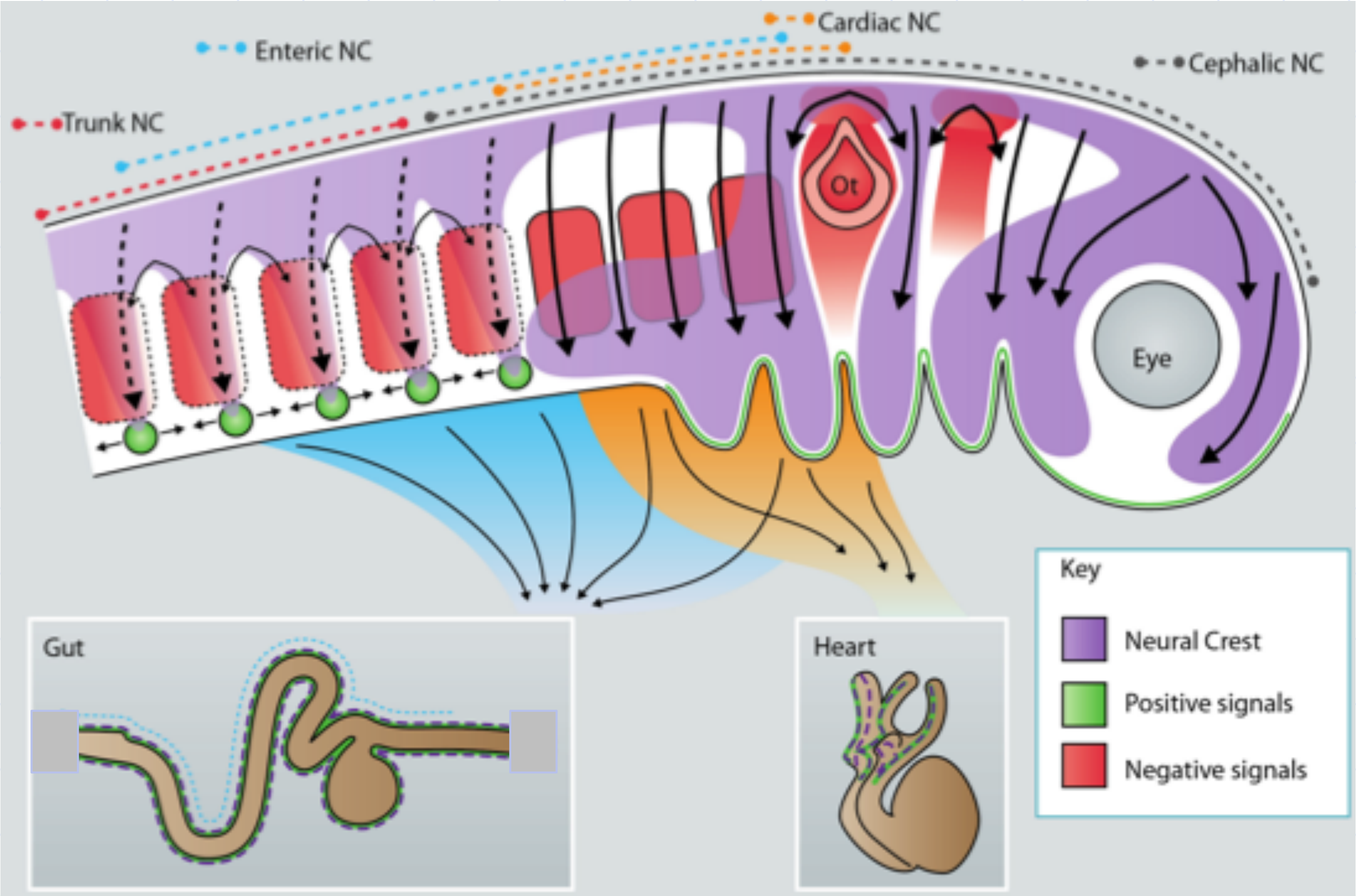
II. A biomechanical model based on GTPase biochemistry

III. Main result: "persistence of polarity" (PoP) is the key

IV. Comparison with experiments

I. Background and motivation

- What are neural crest cells?

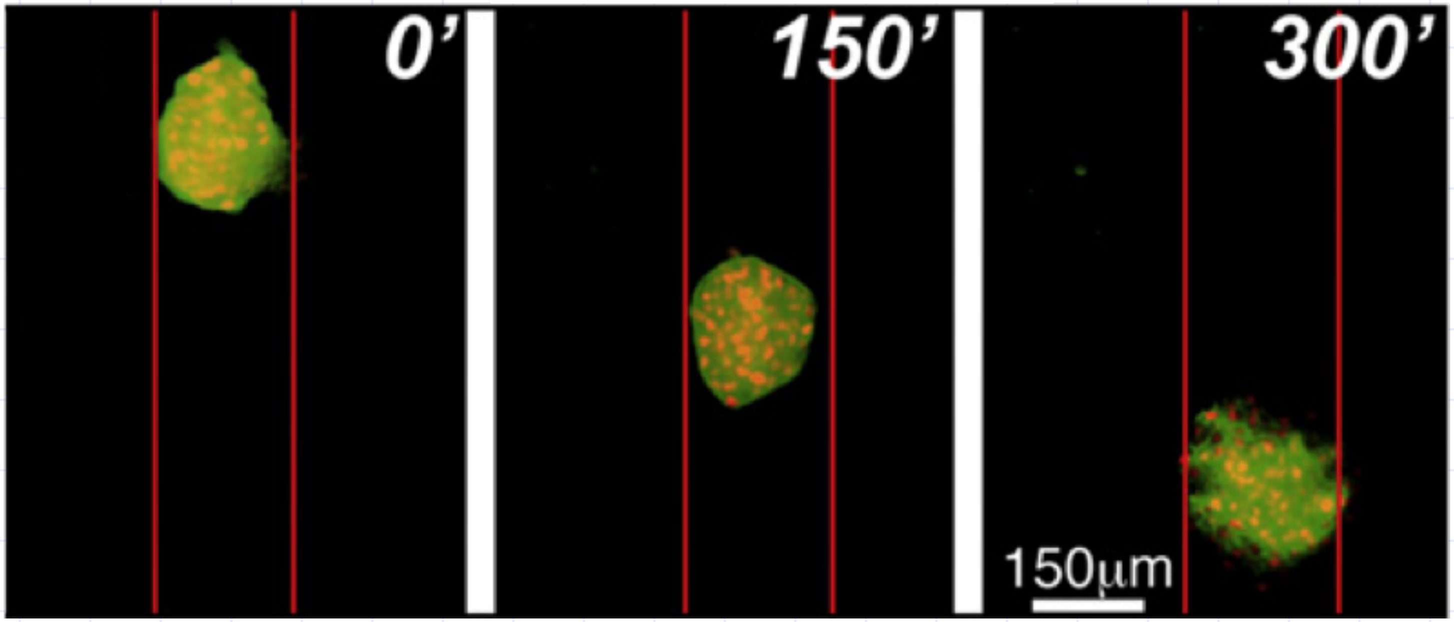


Mayor and Theveneau (2013). Development. 140, 2247-51.

Curious behavior no. 1:

Spontaneous collective migration

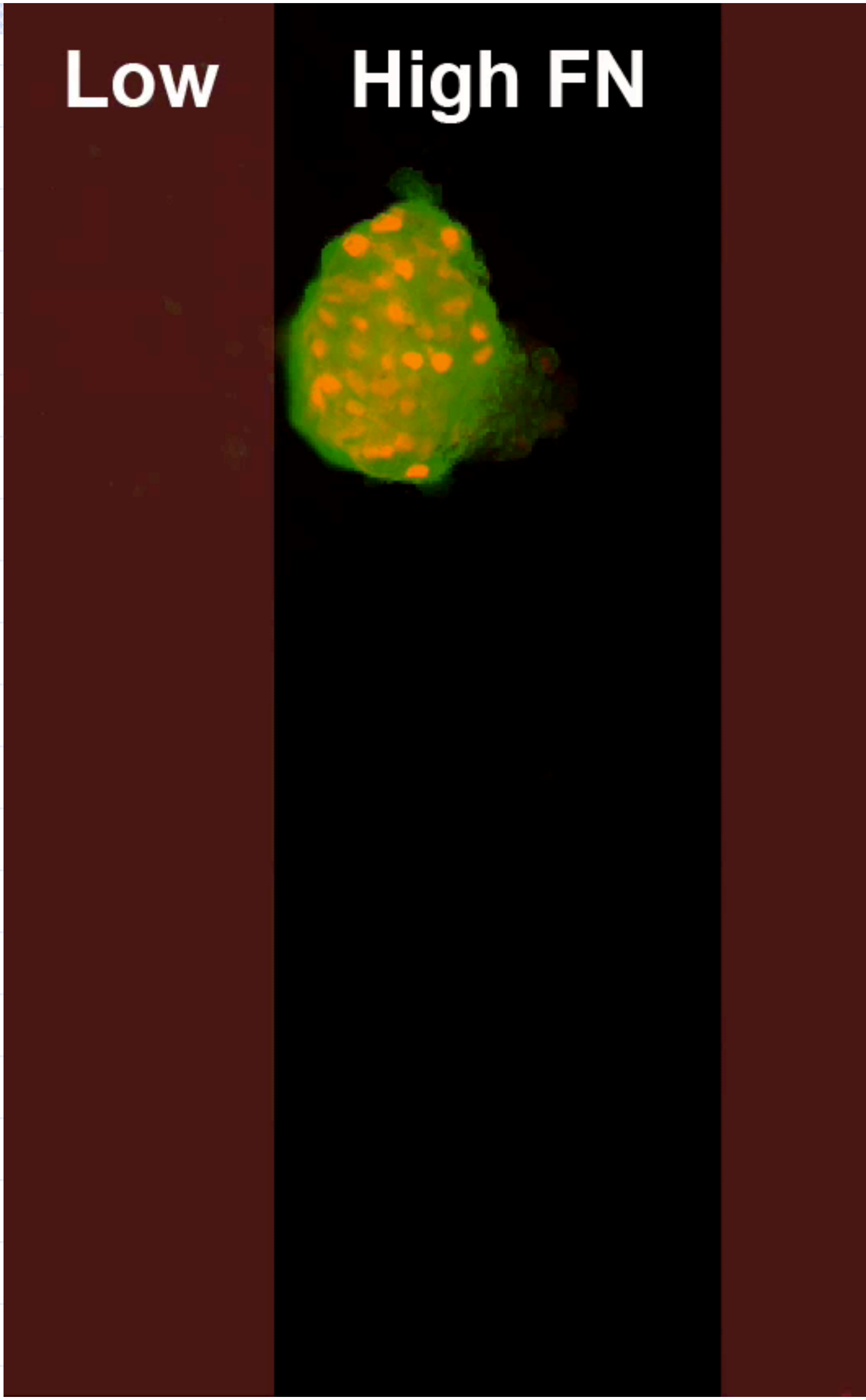
Time (minutes)



Carmona-Fontaine et al. (2011). Dev. Cell 21, 1026-37.

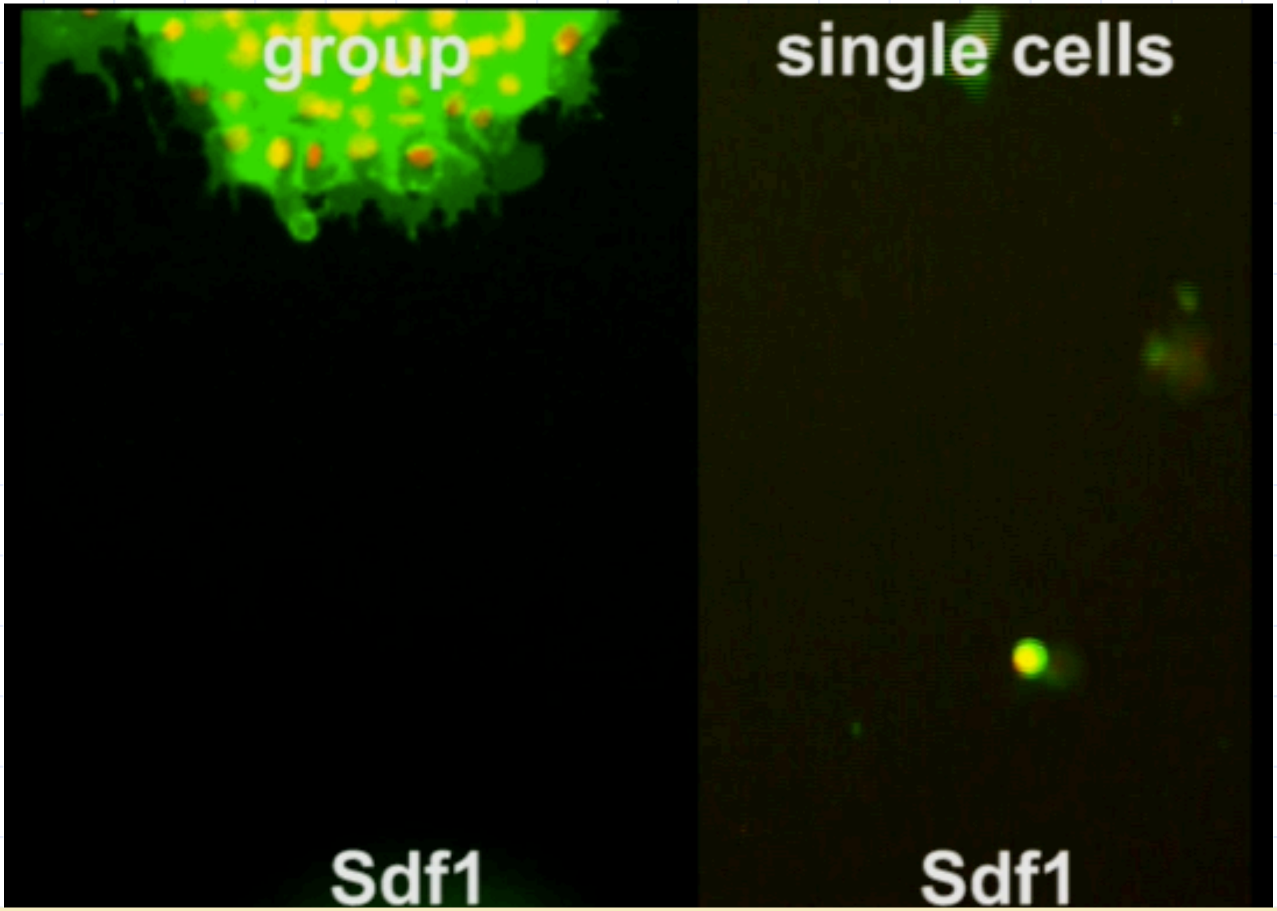
Spontaneous collective migration

Carmona-Fontaine et al. (2011) Dev. Cell 21, 1026-37.



Curious behavior no. 2:

Group advantage in chemotaxis



- Cluster chemotaxes toward Sdf1
- Single cell wanders around (Theveneau et al. 2010)

Emergent property in clusters

Other in vitro/in vivo evidence:

- Clusters of bovine capillary endothelial cells in confined geometry (Huang et al., Cytoskeleton 2005)
- Madin-Darby canine kidney (MDCK) cells in confined geometry (Vedula et al., PNAS 2012)
- Frog: migration depends on confinement to “channels” (Szabó et al. J. Cell Biol. 2016)
- Zebrafish: successful migration without filapodia-mediated chemotaxis (Boer et al., PLoS Gen. 2015)
- Chick: spontaneous migration in opposite directions (Burns et al., Development 2002)
- Lymphocytes: collective chemotaxis (Malet-Engra et al. Curr. Biol. 2015)

✦ How? Propose hypotheses and test them with computations

✦ My narrative: follow story 1 (spontaneous migration); then return to story 2 (chemotaxis) at the end

Spontaneous collective migration: How?

Prevailing model due to Mayor et al:

Result of two competing/cooperating mechanisms:

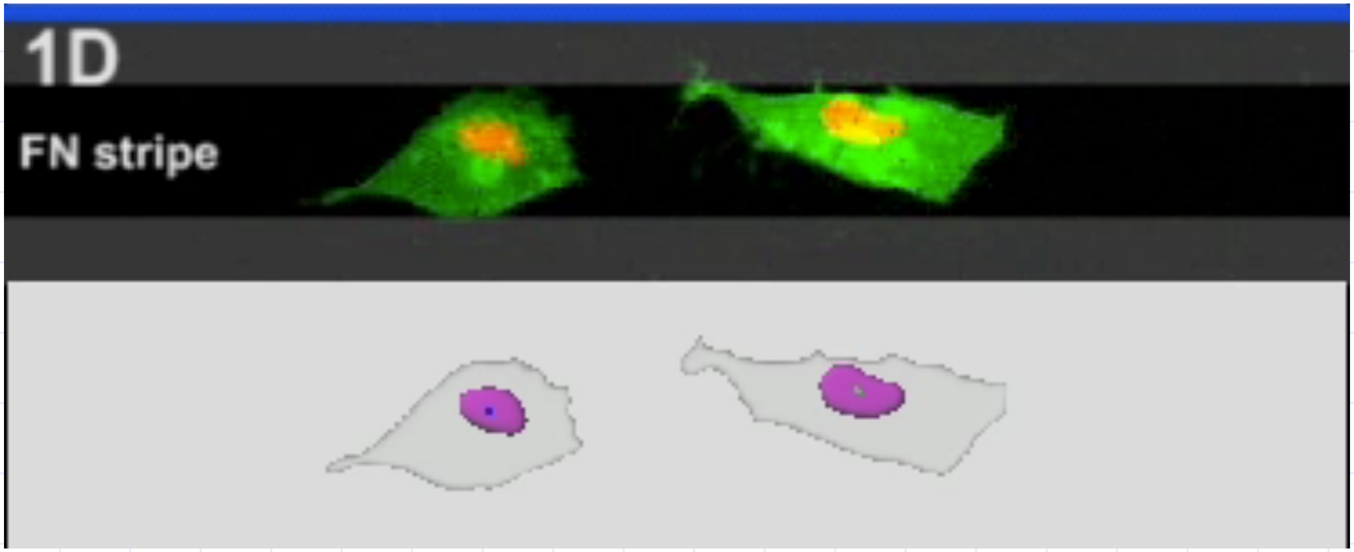
(1) Contact inhibition of locomotion (CIL)

(2) Co-attraction (CoA)

Theveneau & Mayor (2012): Dev. Biol., 366, 34-54.
Woods et al. (2014): PLoS ONE 9(9): e104969.
Szabó et al. (2016): J. Cell Biol. 213: 543-555.

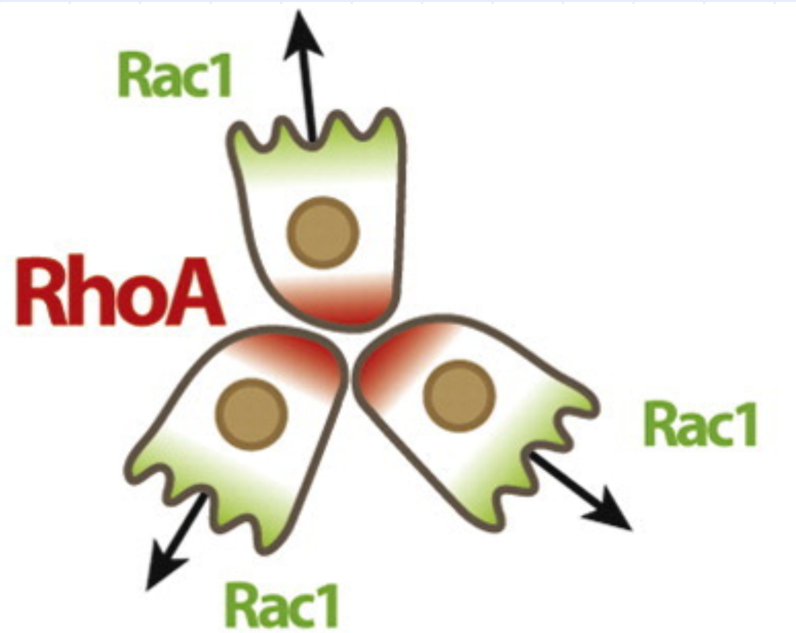
Contact inhibition of locomotion (CIL)

- Observation: cells retract and separate after collision in 1D channel



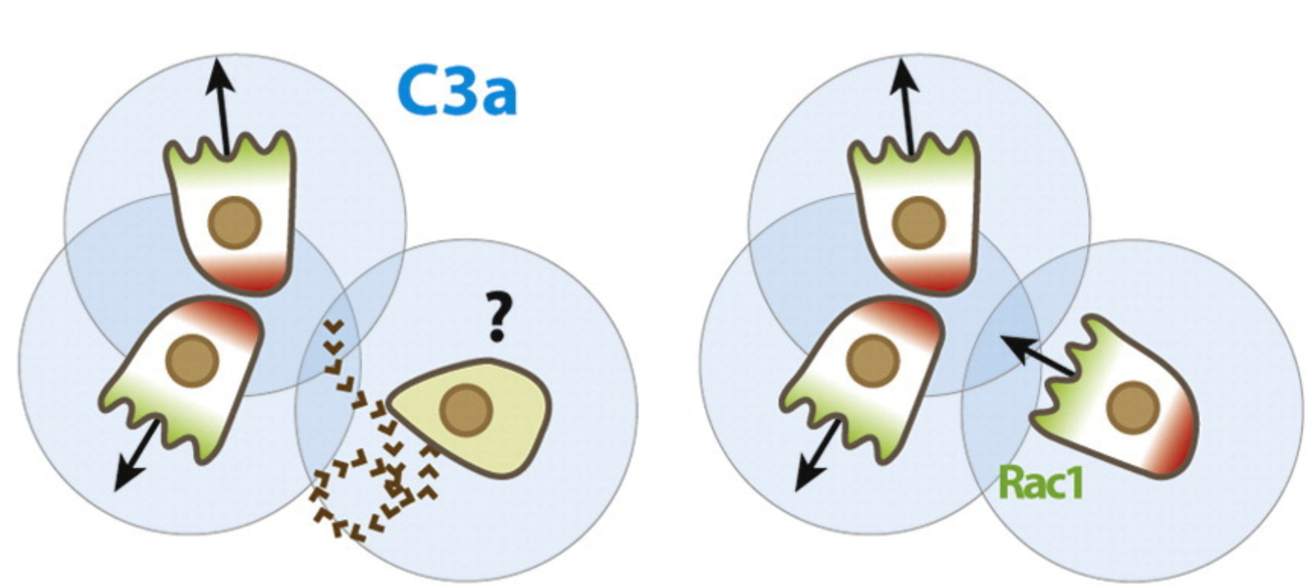
Scarpa et al. Biol. Open (2013), 2, 901-906.

Contact inhibition of locomotion (CIL)



- Mechanical contact triggers Rac-Rho dynamics
- Amounts to a dispersal effect

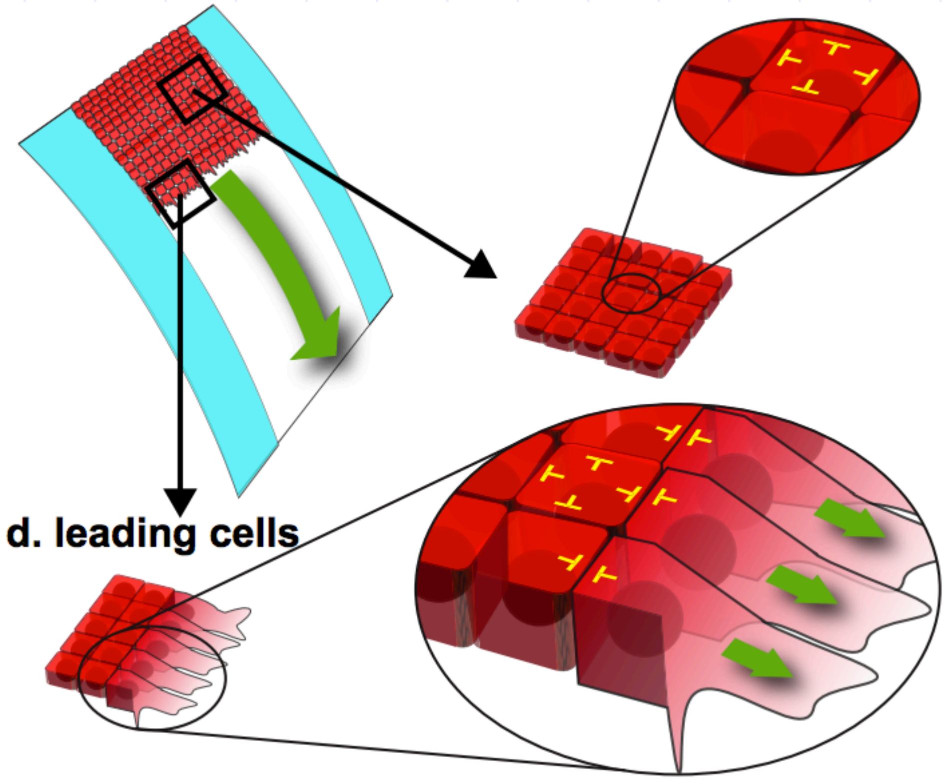
Co-attraction (CoA)



- NC cells release ligand C3a; express receptor C3aR
- C3a + C3aR binding leads to Rac activation
- Amounts to an aggregating effect

Carmona-Fontaine et al. (2011). Dev. Cell 21, 1026-37.

CIL + CoA ➔ Spontaneous collective migration?



- CIL + CoA ➔ clustering + "interior inhibition"
- Cells can only protrude "forward" or "outward"
- [But symmetry breaking?]()

Two model implementations so far

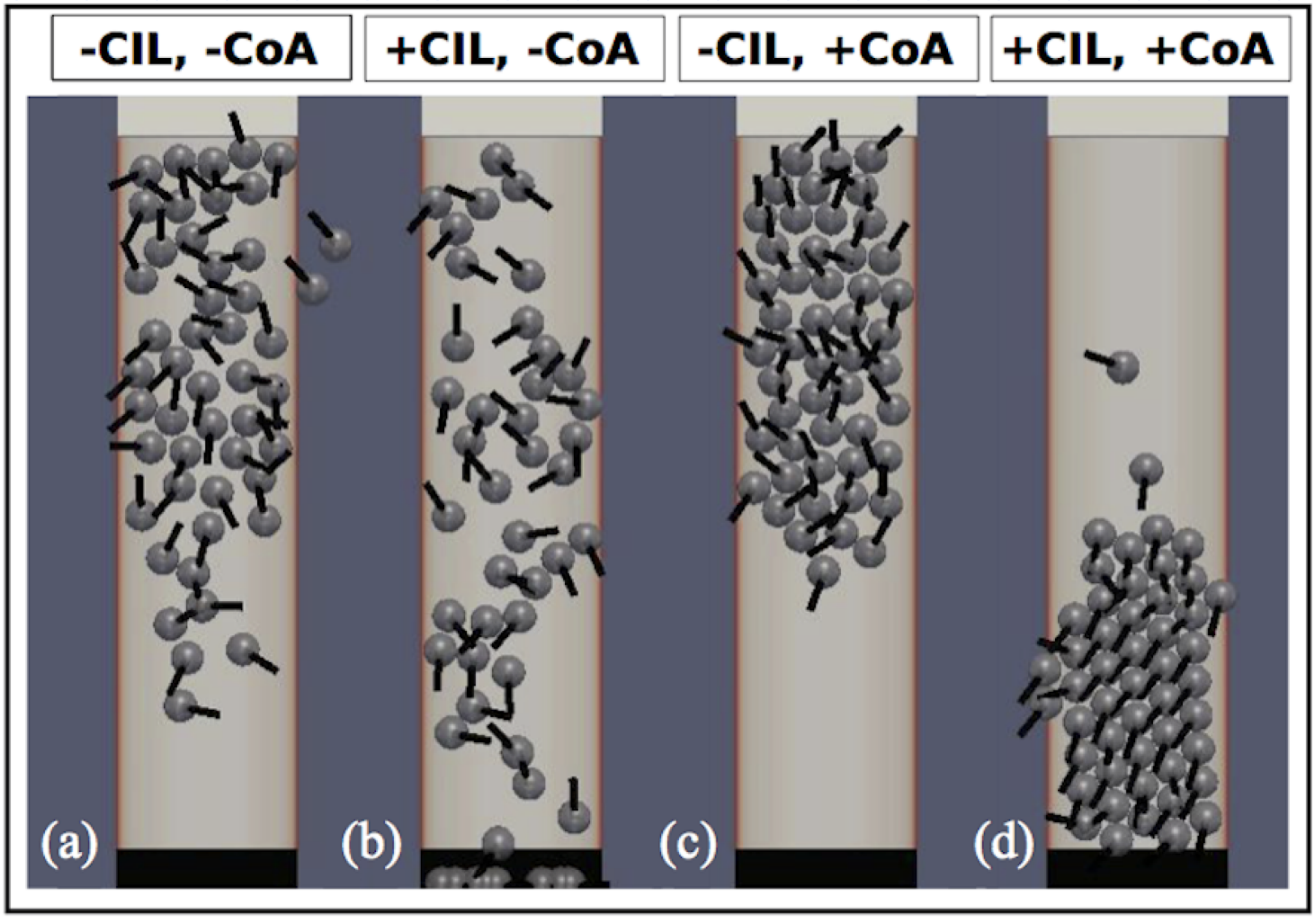
- Woods et al., PLoS ONE (2014) 9(9): e104969.
- Ballistic particle motion subject to force rules:

$$m\ddot{\bar{u}}_i = \bar{F}_i^T$$

$$\bar{F}_i^T = Q\big(a_i(t)\bar{F}_i^a + \omega_i(t)\bar{F}_i^\omega + m_i(t)\bar{F}_i^p\big) + \sum_{k \in C_i}\left(\bar{F}_{ik}^C + \bar{F}_{ik}^{Cd} + \bar{F}_{ik}^{RCIL}\right)$$

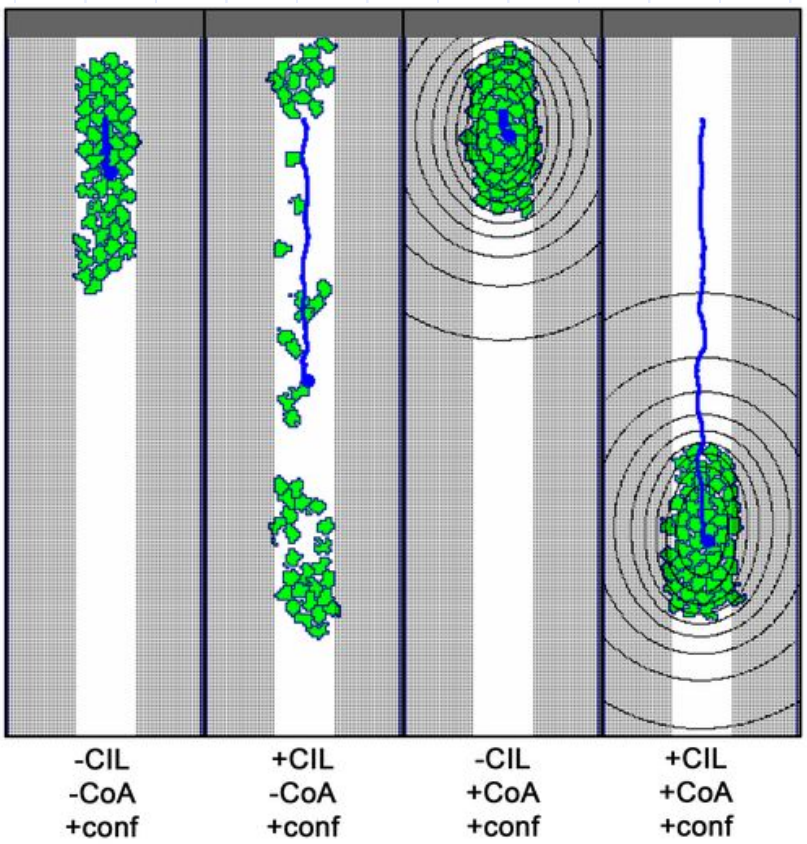
Model implementation 1:

- Woods et al., PLoS ONE (2014) 9(9): e104969.



Model implementation 2:

- Szabó et al., J. Cell Biol. (2016) 213: 543-555.
- Cellular Potts model, with "cell polarity vector" modulated according to CIL and COA



CIL+CoA enough for Spont. Mig.?

We built our own model with CIL and CoA:

- Failed to produce spontaneous collective migration
- The centroid meanders

In these two models:

- Woods et al.: ballistic motion relies on inertia
- Szabó et al.: relies on rules that preserve polarity
- Require additional rules

Our hypotheses:

- CIL + CoA: not sufficient for spontaneous migration
- Some sort of “persistence of polarity” (PoP) is a necessary ingredient
- Biological origin of PoP: suggestions from literature:
  - Noise/random walk: new Rac1 hotspots → repolarization
  - Rac1 suppression → increased single cell persistence

Pankov et al. (2005) J. Cell Biol. 170:793–802.
Bass et al. (2007) J. Cell Biol. 177:527–538.
Matthews et al. (2008) Development 135:1771–1780.

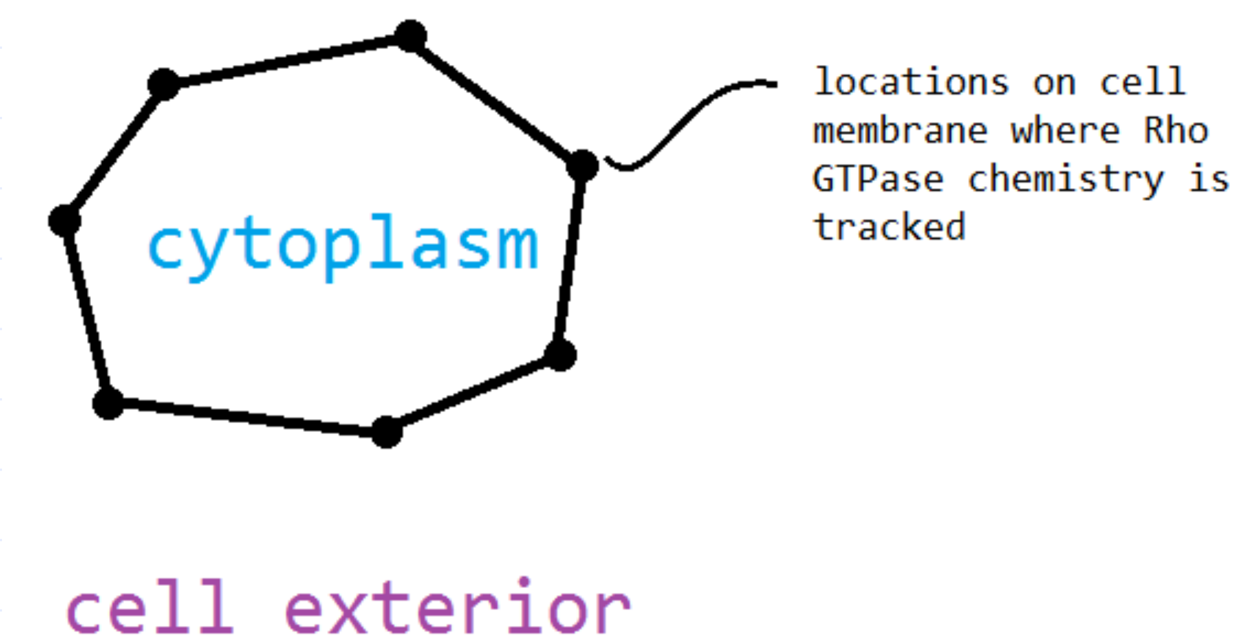
- Our claim: CIL + CoA → Rac1 suppresion → PoP

II. A chemo-mechanical model

- A biochemistry-based model as alternative to phenomenological "rule-based models"
  - ✓ Kinetic model: how GTPases produce polarization
  - ✓ Mechanical model: how cells deform and move
- Coupling the two to produce:
  - ✓ Contact inhibition of locomotion (CIL)
  - ✓ Co-attraction (CoA)
  - ✓ Persistence of polarity (PoP)
  - ✓ Spontaneous collective migration (SCM)

Kinetic model: GTPase biochemistry

- Planar 2D representation
- Rac: active (R^a), inactive (R^i) forms on the membrane; and cytosolic form (R^c) in the cytoplasm
- Similarly for Rho: ρ^a, ρ^i and ρ^c



Reaction-diffusion + conservation

$$\frac{\mathrm{d}R_i^a}{\mathrm{d}t} = K^+R_i^i - K^-R_i^a + D\left(\frac{R_{i+1}^a - R_i^a}{|\mathbf{r}_{i+1}-\mathbf{r}_i|^2} + \frac{R_{i-1}^a - R_i^a}{|\mathbf{r}_{i-1}-\mathbf{r}_i|^2}\right),$$

$$\frac{\mathrm{d}R_i^i}{\mathrm{d}t} = -K^+R_i^i + K^-R_i^a + D\left(\frac{R_{i+1}^i - R_i^i}{|\mathbf{r}_{i+1}-\mathbf{r}_i|^2} + \frac{R_{i-1}^i - R_i^i}{|\mathbf{r}_{i-1}-\mathbf{r}_i|^2}\right) + \frac{M^+R^c}{N} - M^-R_i^i,$$

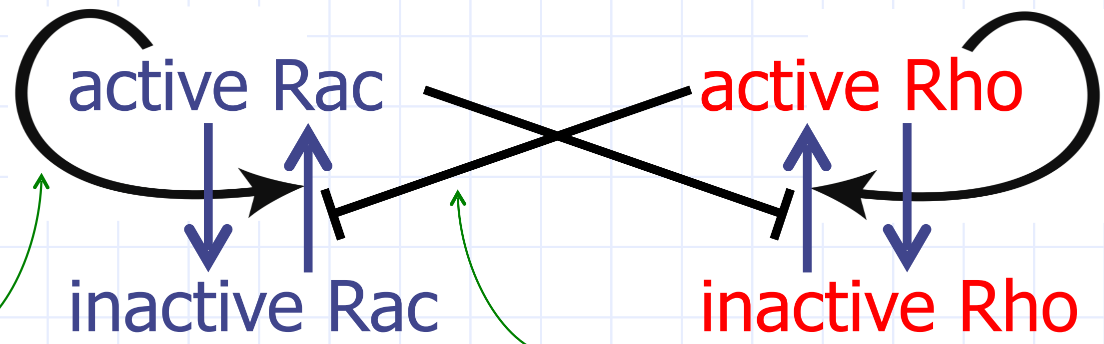
$$\frac{\mathrm{d}R^c}{\mathrm{d}t} = \sum_{i=1}^{N}\left(-\frac{M^+R^c}{N} + M^-R_i^i\right),$$

$$\sum_{i=1}^{N}(R_i^a + R_i^i) + R^c = \text{Constant}.$$

Similar equations for Rho species ρ^a, ρ^i and ρ^c.

Rac-Rho dynamics: root of polarity

Holmes & Edelstein-Keshet, Phys. Biol. 13 (2016) 046001



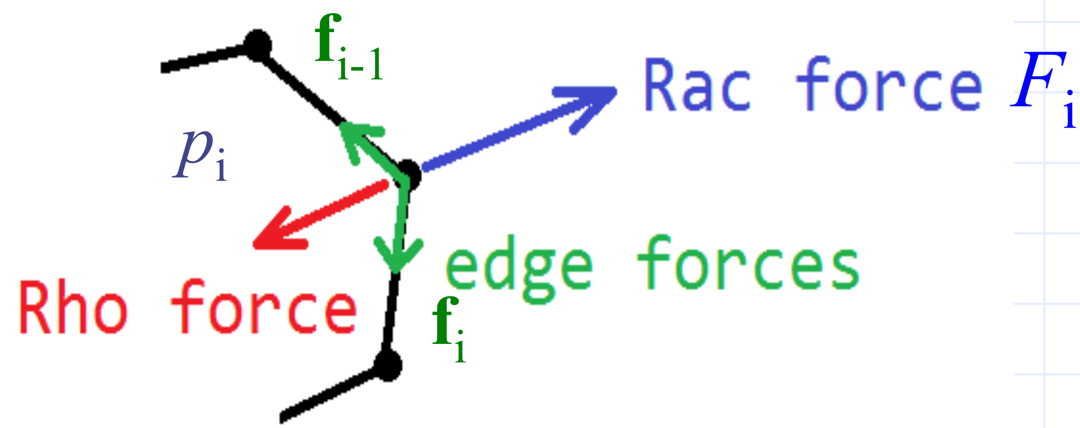
$$K^+(i,t) = K_b^+ + K_A^+ \frac{(R_i^a/L_i(t))^n}{C_R + (R_i^a/L_i(t))^n}$$

$$\frac{(\rho_i^a/L_i(t))^n}{\ldots + (\rho_i^a/L_i(t))^n}$$

CIL and CoA: also coded through the rate coefficients

Mechanical model: nodal motion

$$\eta \frac{d\mathbf{r}_i}{dt} = \mathbf{f}_{i-1} + \mathbf{f}_i + (p_i + F_i)\mathbf{n}_i$$



- Protrusion/contraction forces: depends on Rac/Rho polarity
- Mechanical feedback: membrane tension inhibits local Rac

III. Model predictions

a) Single-cell: polarization, motility, “run-and-tumble”

b) Pairwise interaction: contact inhibition (CIL)

c) Clustering: role of co-attraction (CoA)

d) Symmetry breaking: persistence of polarity (PoP)

Curious behavior no. 1 explained ......

e) Spontaneous collective migration: cluster size effect

Curious behavior no. 2 explained ......

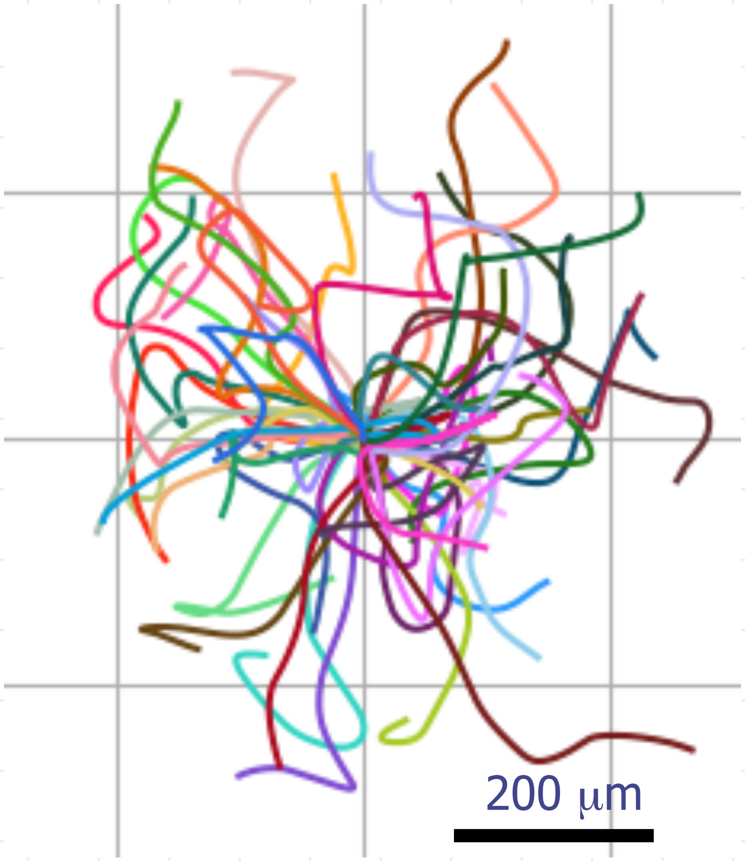
f) Chemotaxis: group advantage in shallow gradient

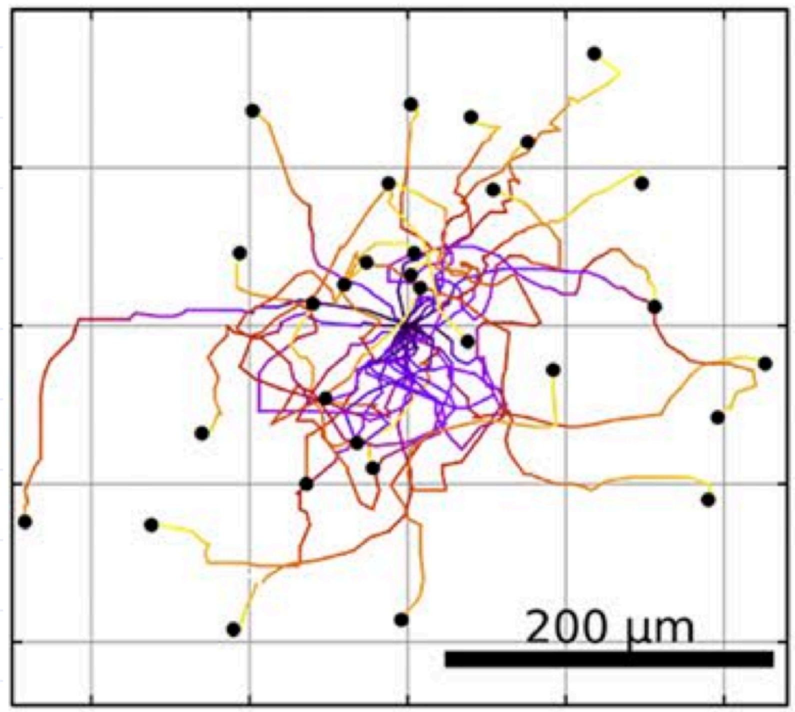
(a) Single cell: polarization & motility

- Cell polarity: Rac-Rho dynamics (Edelstein-Keshet, Cell Syst. 2016)
- Randomization of polarity through Rac modulation
- Reproduces “run-and-tumble” of NCC cells (Theveneau et al. Dev. Cell 2010)

T = 0 min

Multiple runs: persistent ratio

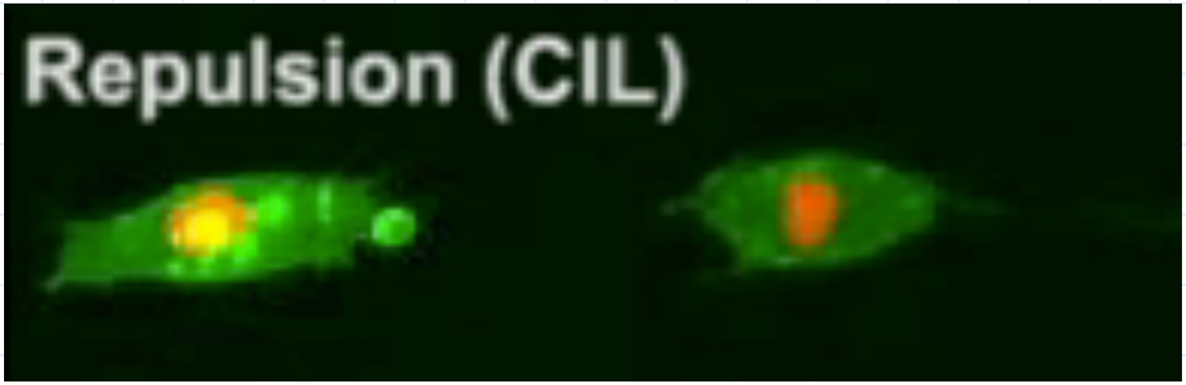




Our model (4 hrs): persistence = 0.564

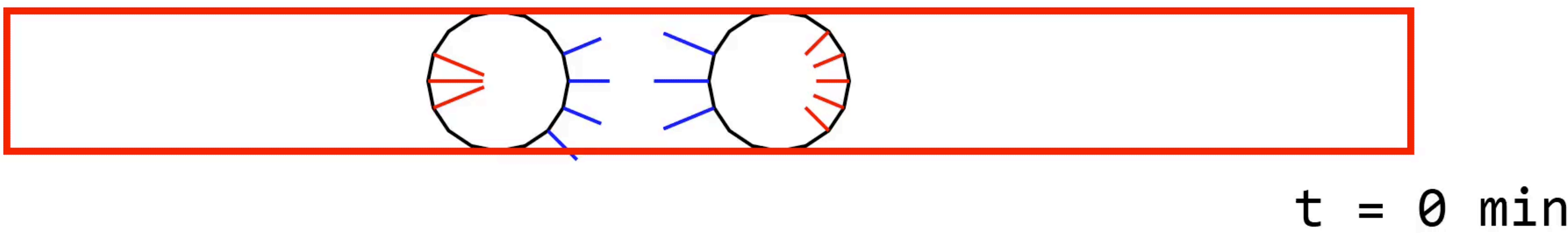
Szabó et al. (2016): 4 hrs; persistence = 0.5 (in vivo), 0.6 (in vitro; above)

(b) CIL: contact inhibition of locomotion



- Motivated by in vitro experiments of Scarpa et al. (2013).

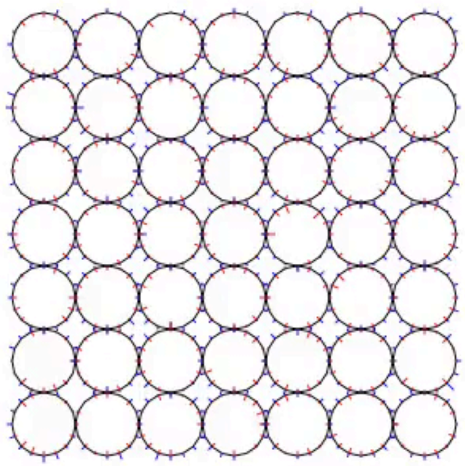
CIL: model prediction



- Model prediction of two-cell encounter in channel
- Realization of CIL in model: upregulating Rho; down Rac

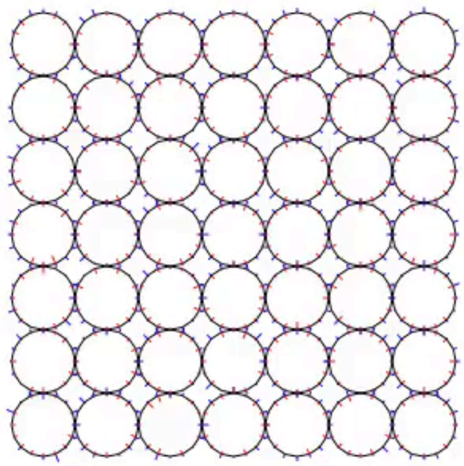
(c) CoA: maintains cell clusters

Without CoA



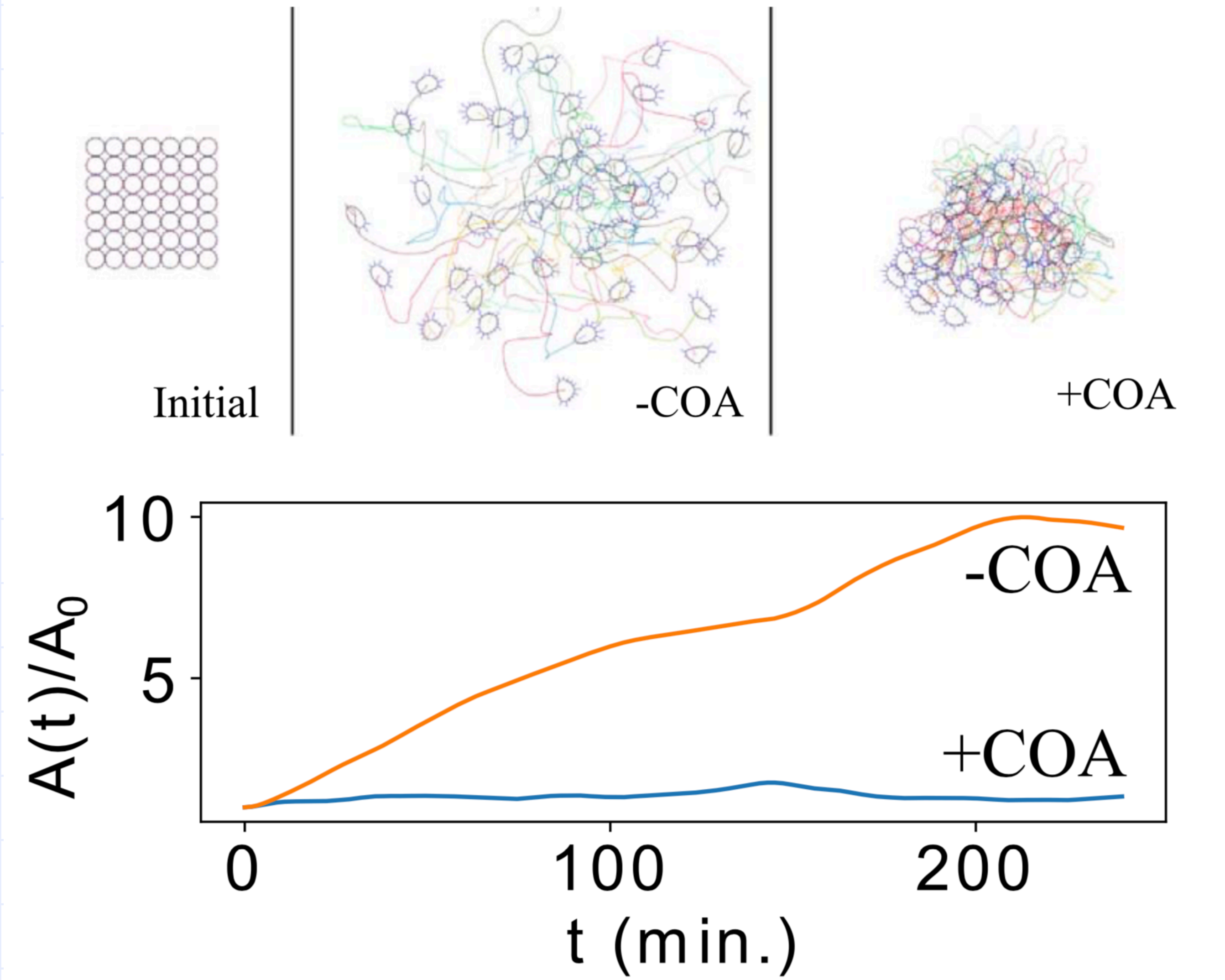
(c) CoA: maintains cell clusters

With CoA

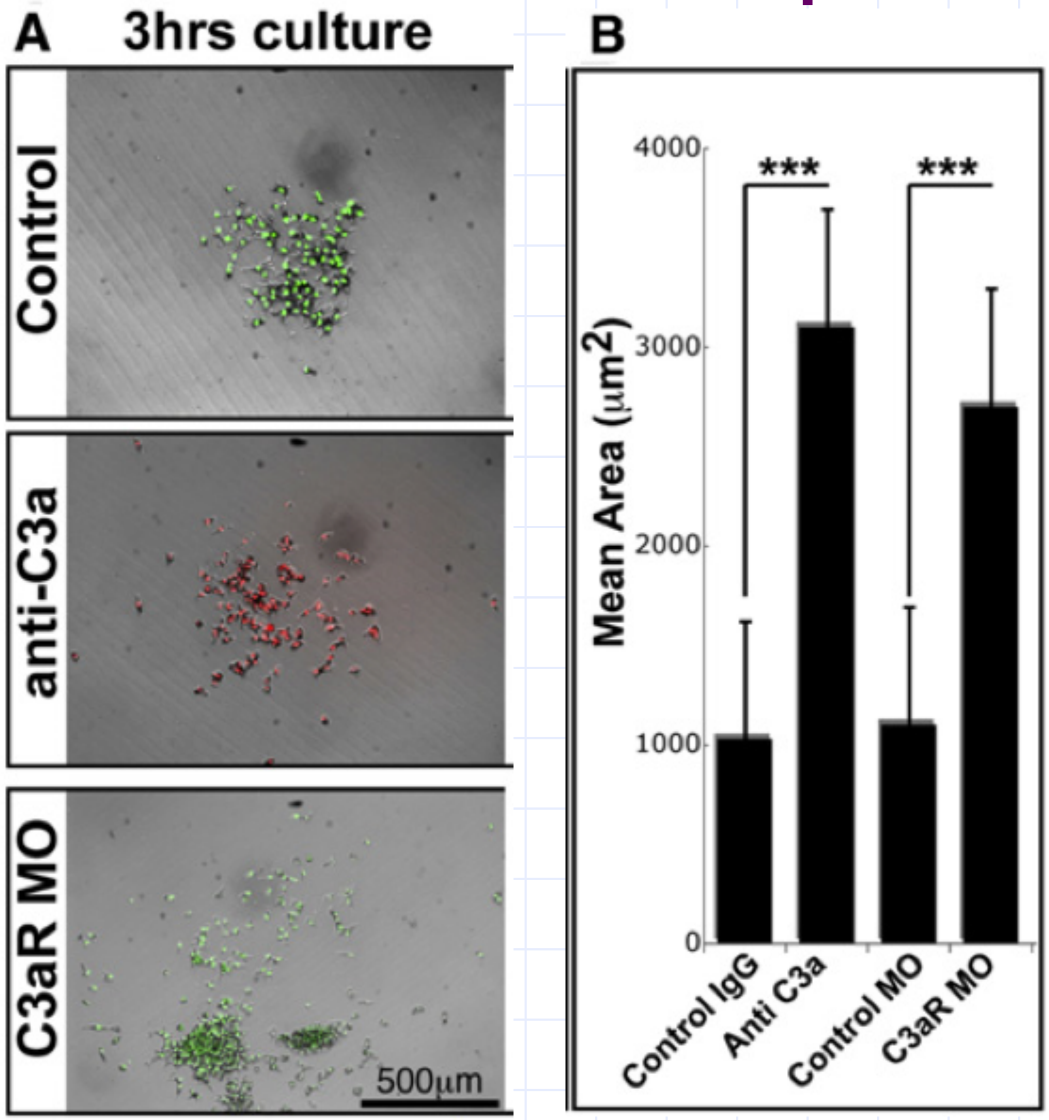


- Each cell boundary node carries C3a field
- CoA: upregulating Rac rate due to neighbor's C3a

(c) CoA: maintains cell clusters

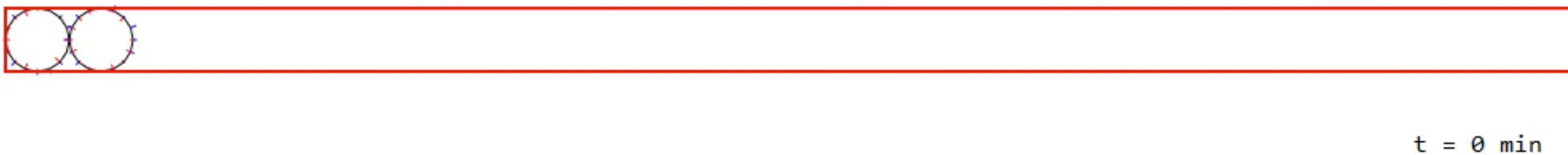


CoA: Comparison with experiment



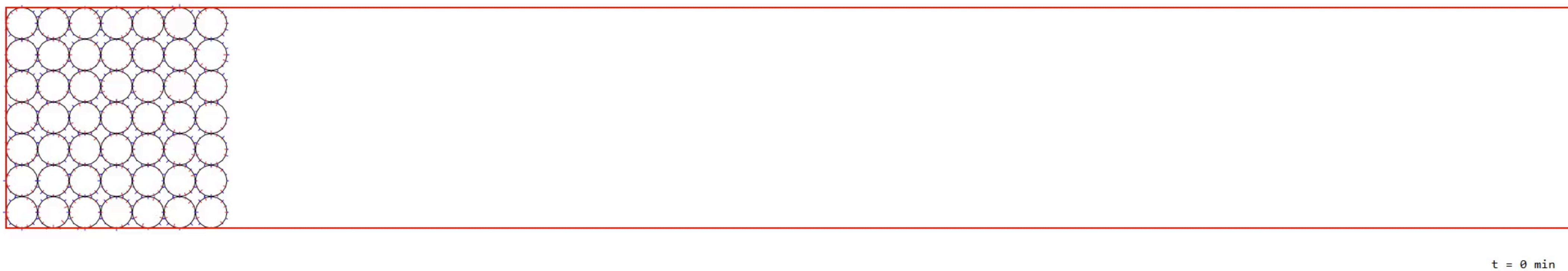
- Carmona-Fontaine et al., Dev. Cell 21, 1026–1037 (2011)

(d) Persistence of Polarity (PoP)



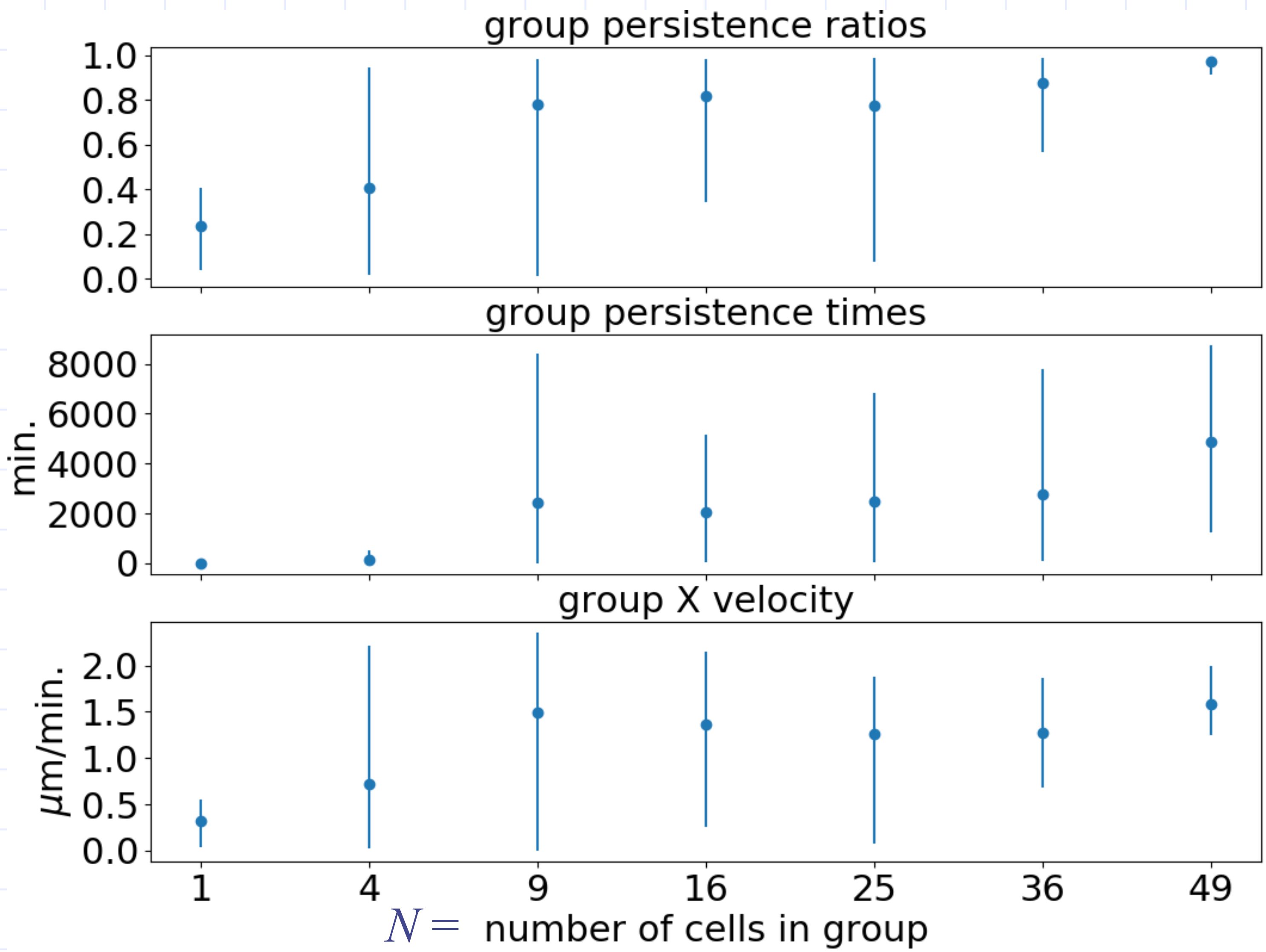
- CIL + CoA: ensures continual interaction
- Suppresses new Rac1 hotspots, produces PoP
- Perpetuates initial asymmetry due to left wall

(e) Spontaneous collective migration



- Spontaneous collective migration of 49 cells

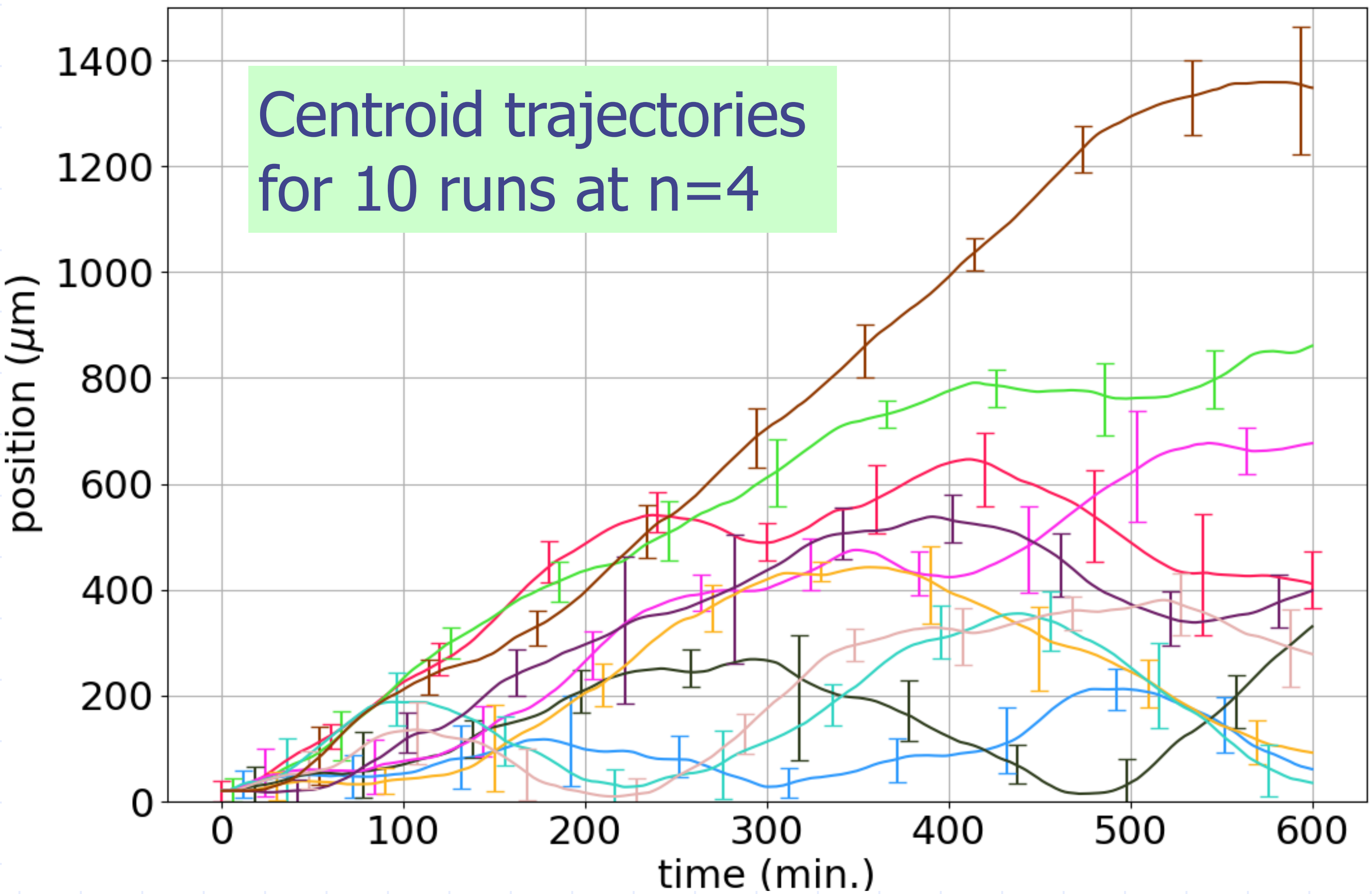
Cluster size effect:



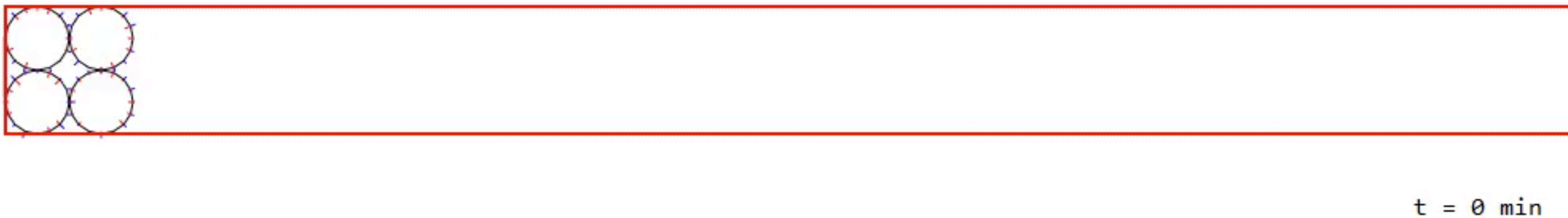
Cluster size effect:

- Collective migration: stronger for larger clusters
- Size effect tends to saturate for large N
- Why?
- Fallibility of persistence of polarity (PoP)

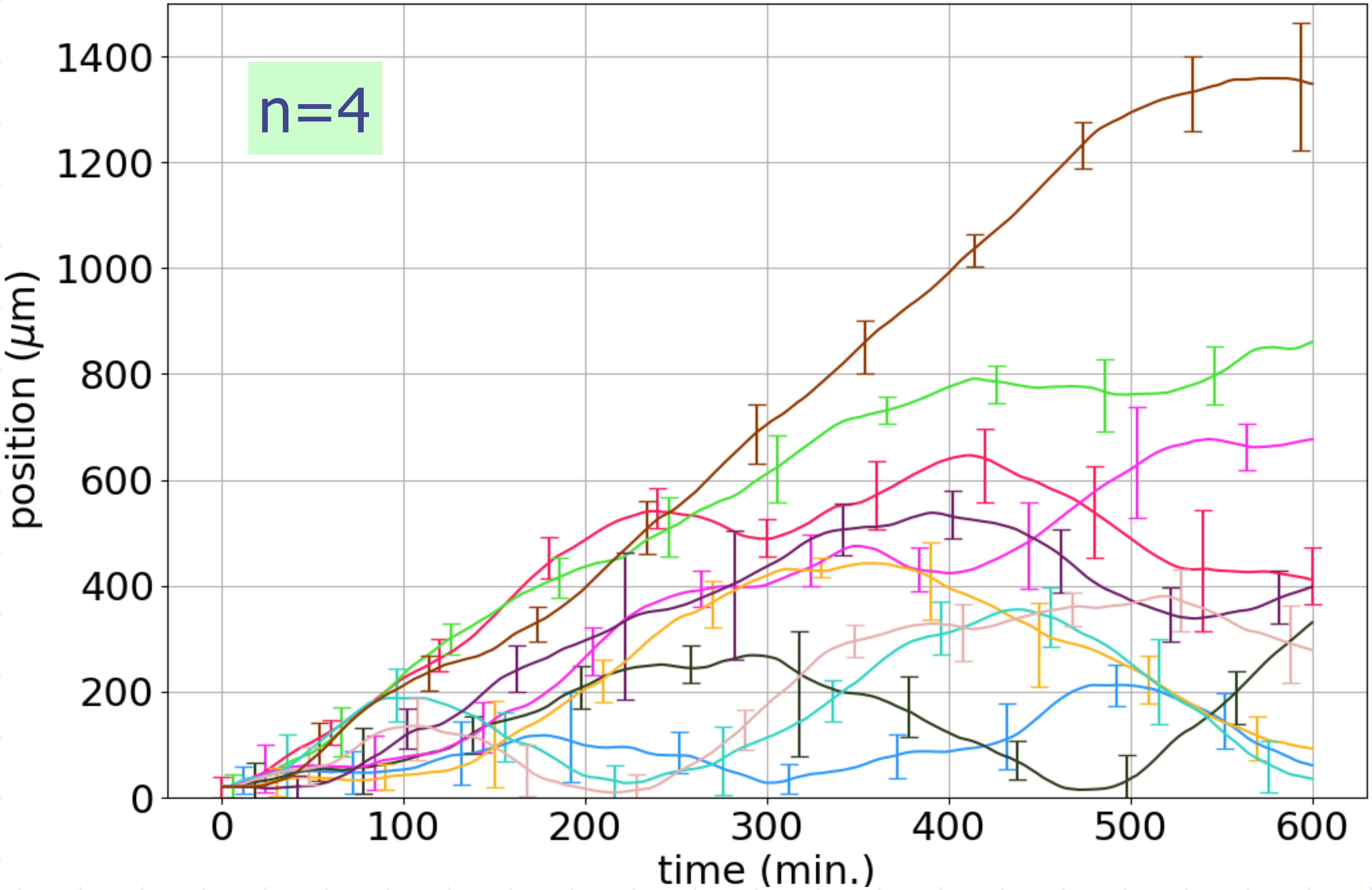
PoP: not foolproof but stochastic



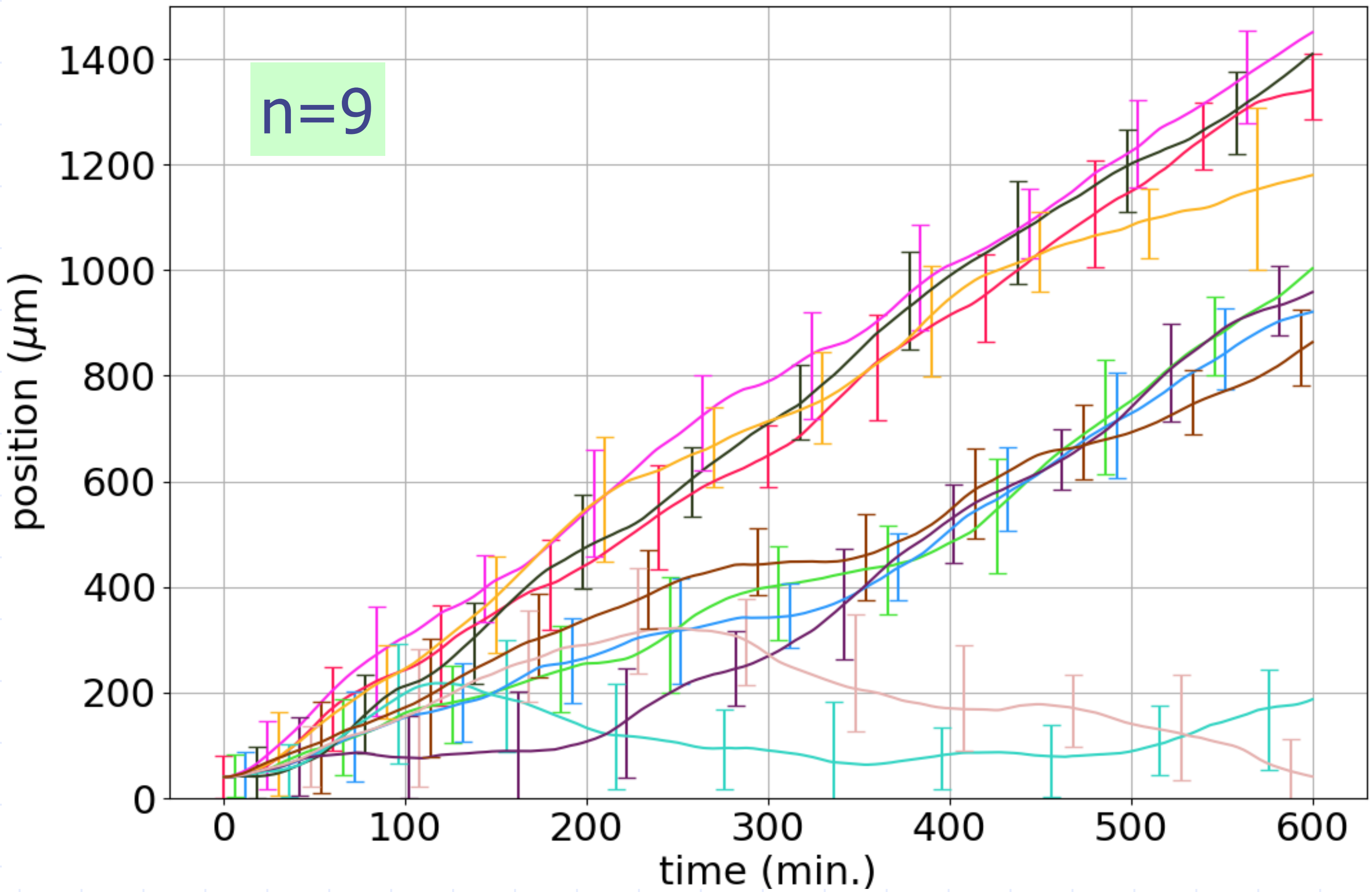
Example of PoP failure for 4 cells



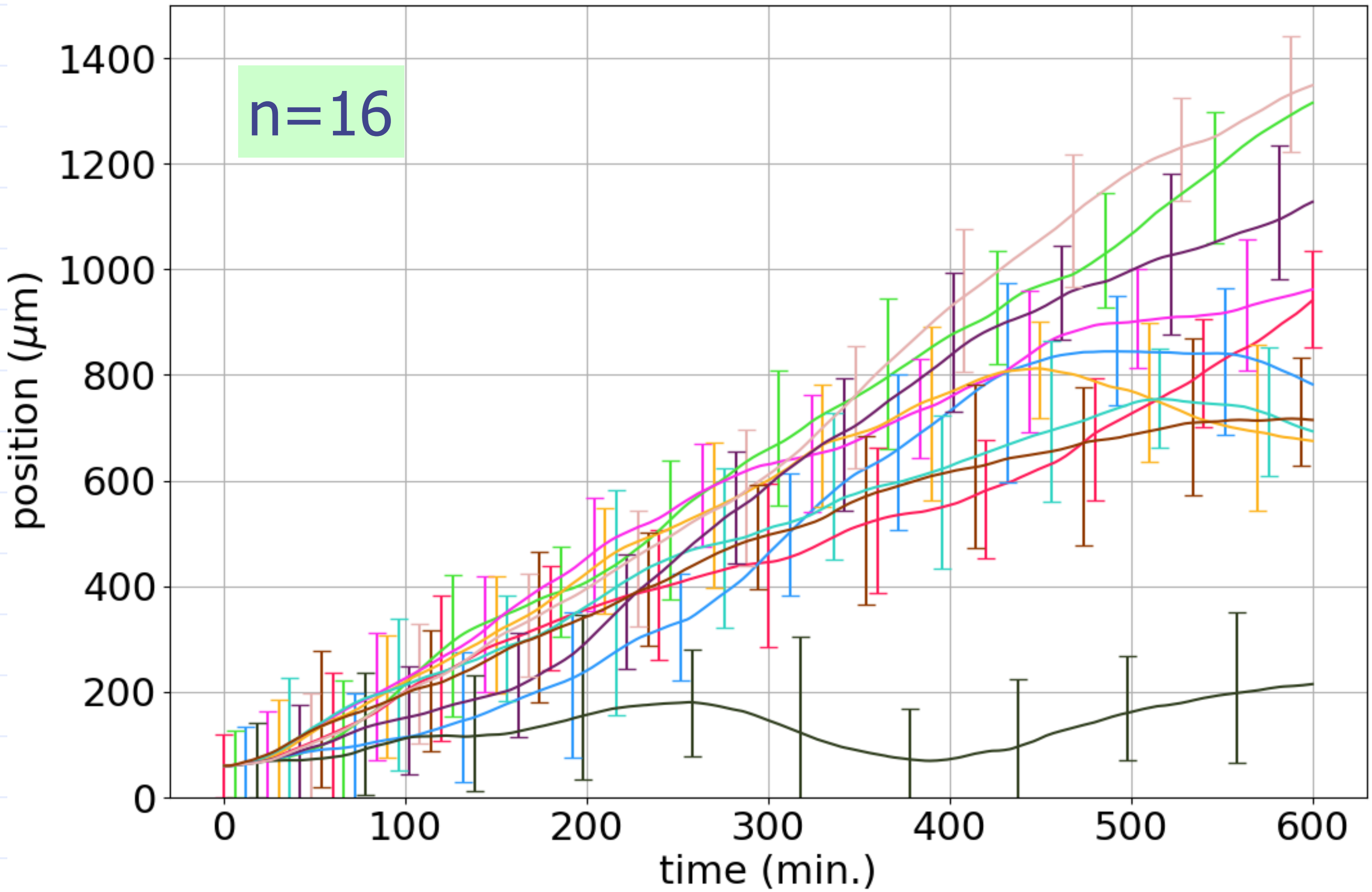
Robustness increases with n



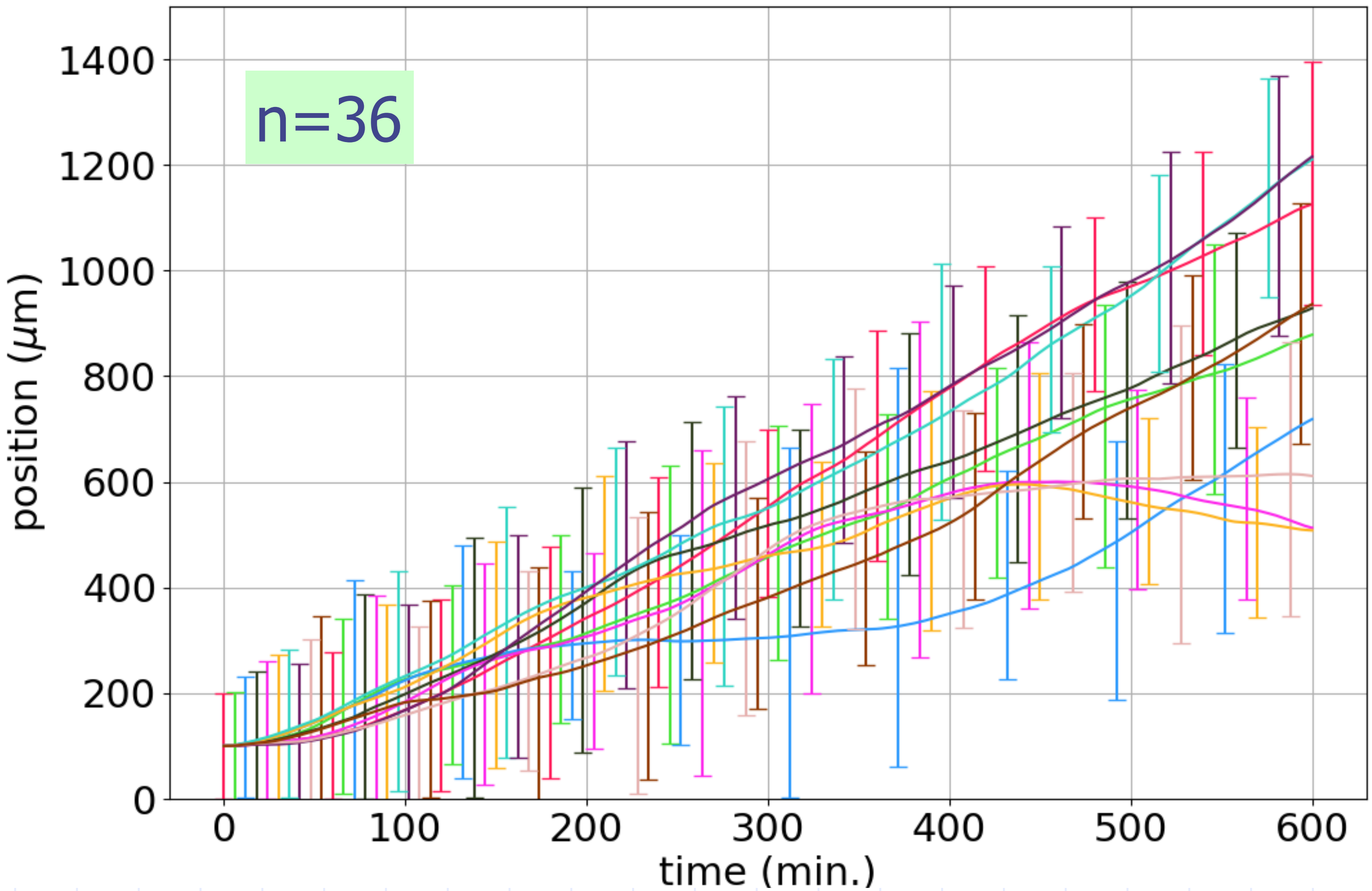
Robustness increases with n



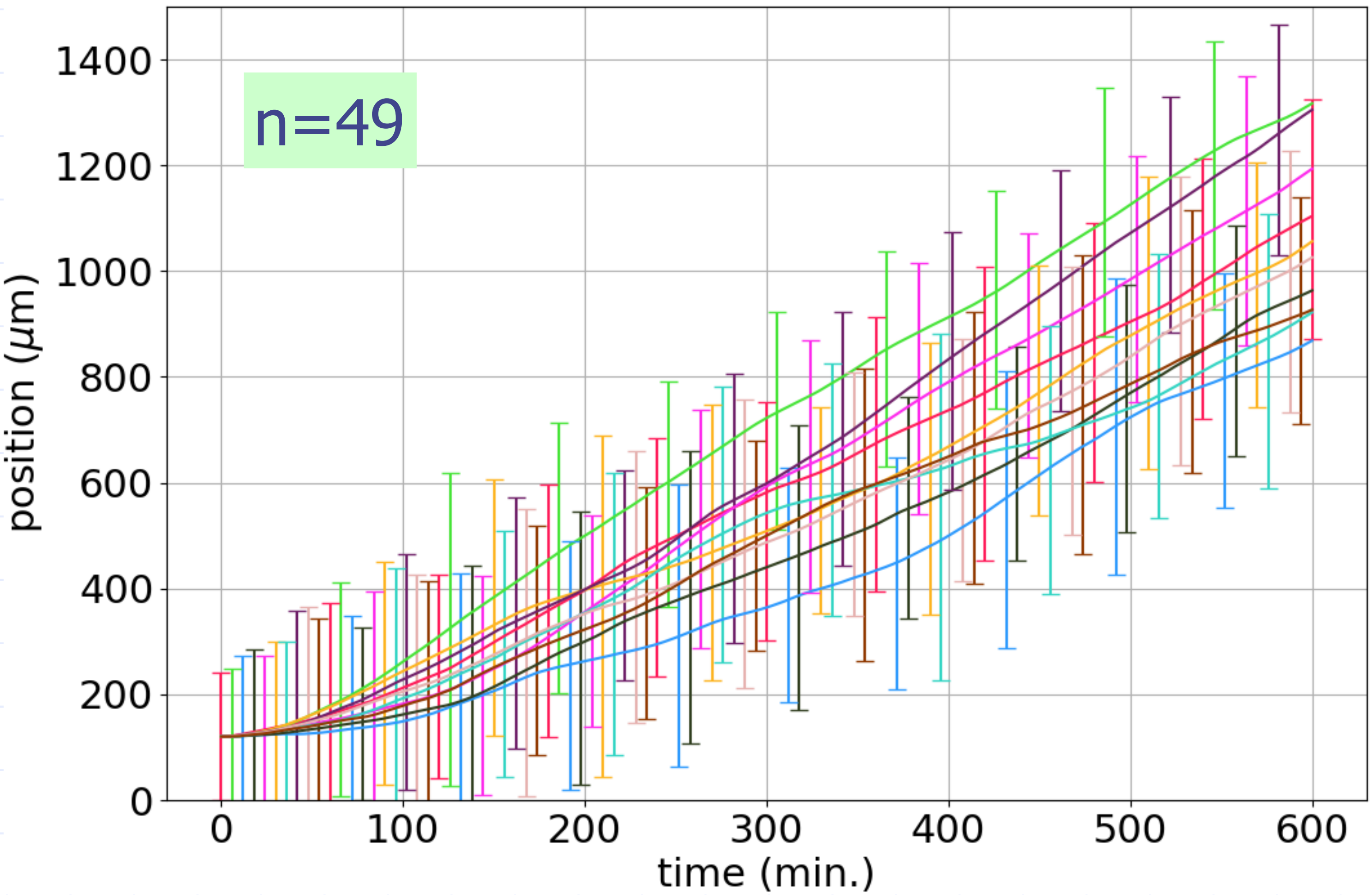
Robustness increases with n



Robustness increases with n



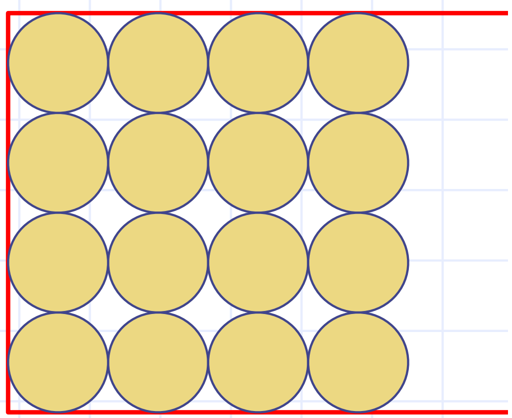
Robustness increases with n



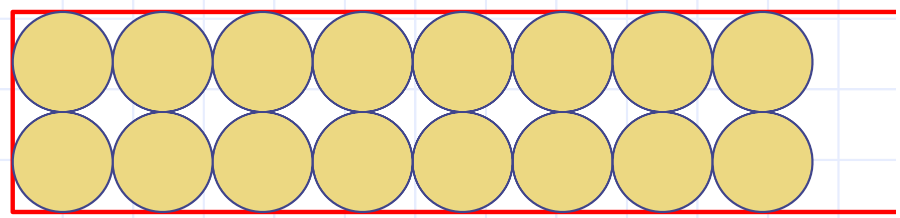
Confinement effect

Fix N, vary corridor height w or confinement ......

Take $N = 16$, for example:

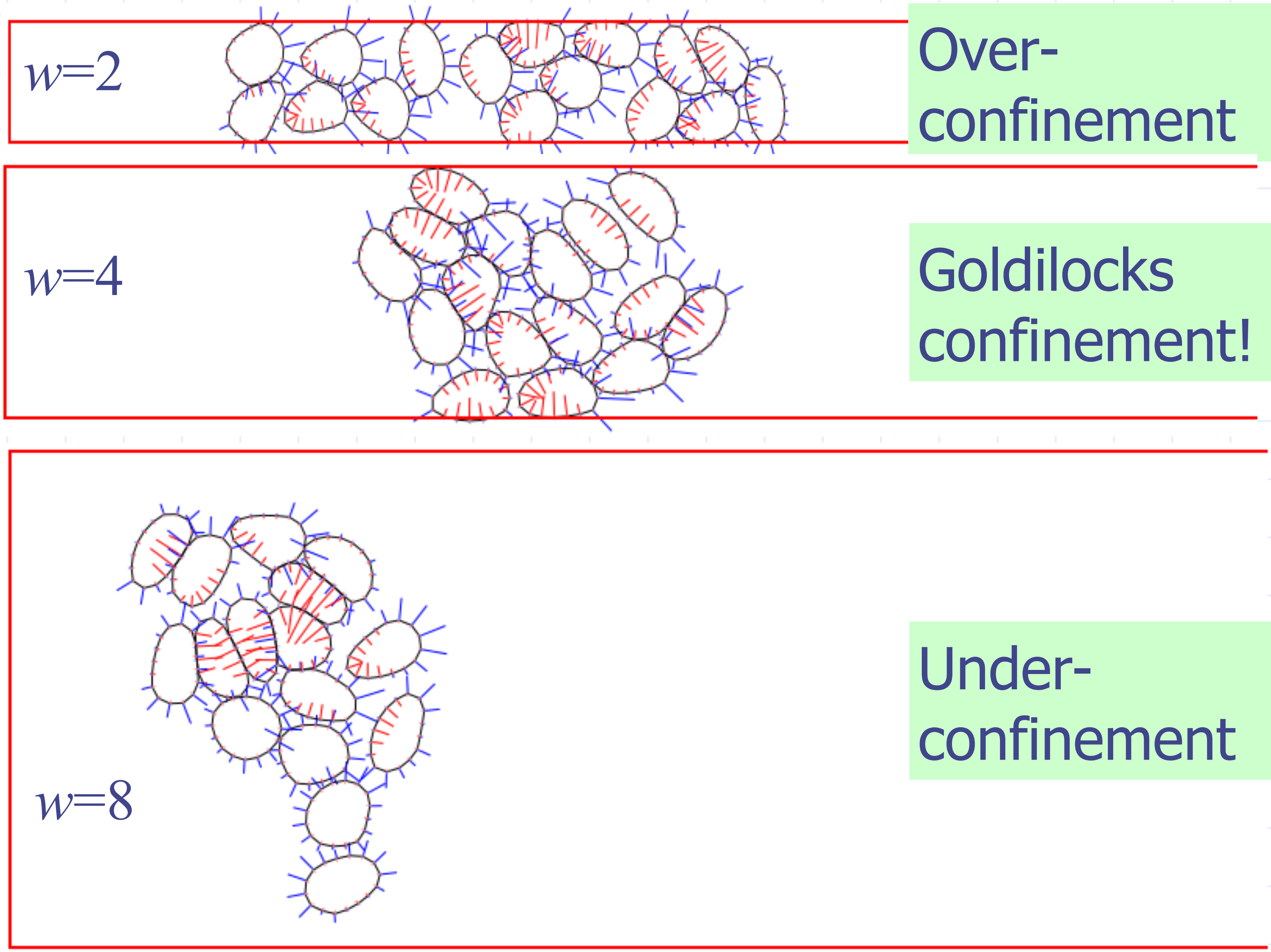


w=4



w=2

Why optimal confinement $w=N^{1/2}$?



Over-confinement

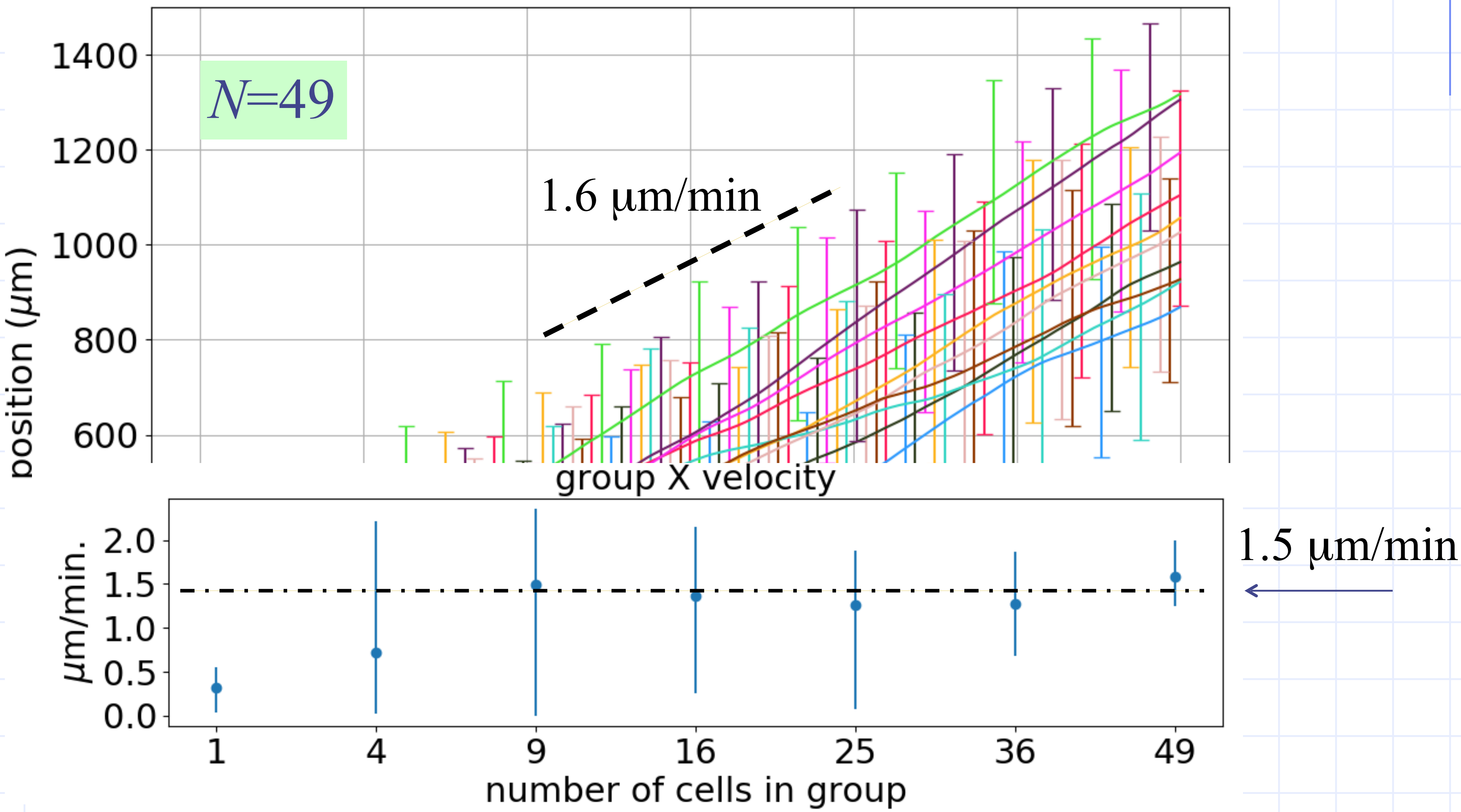
Goldilocks confinement!

Under-confinement

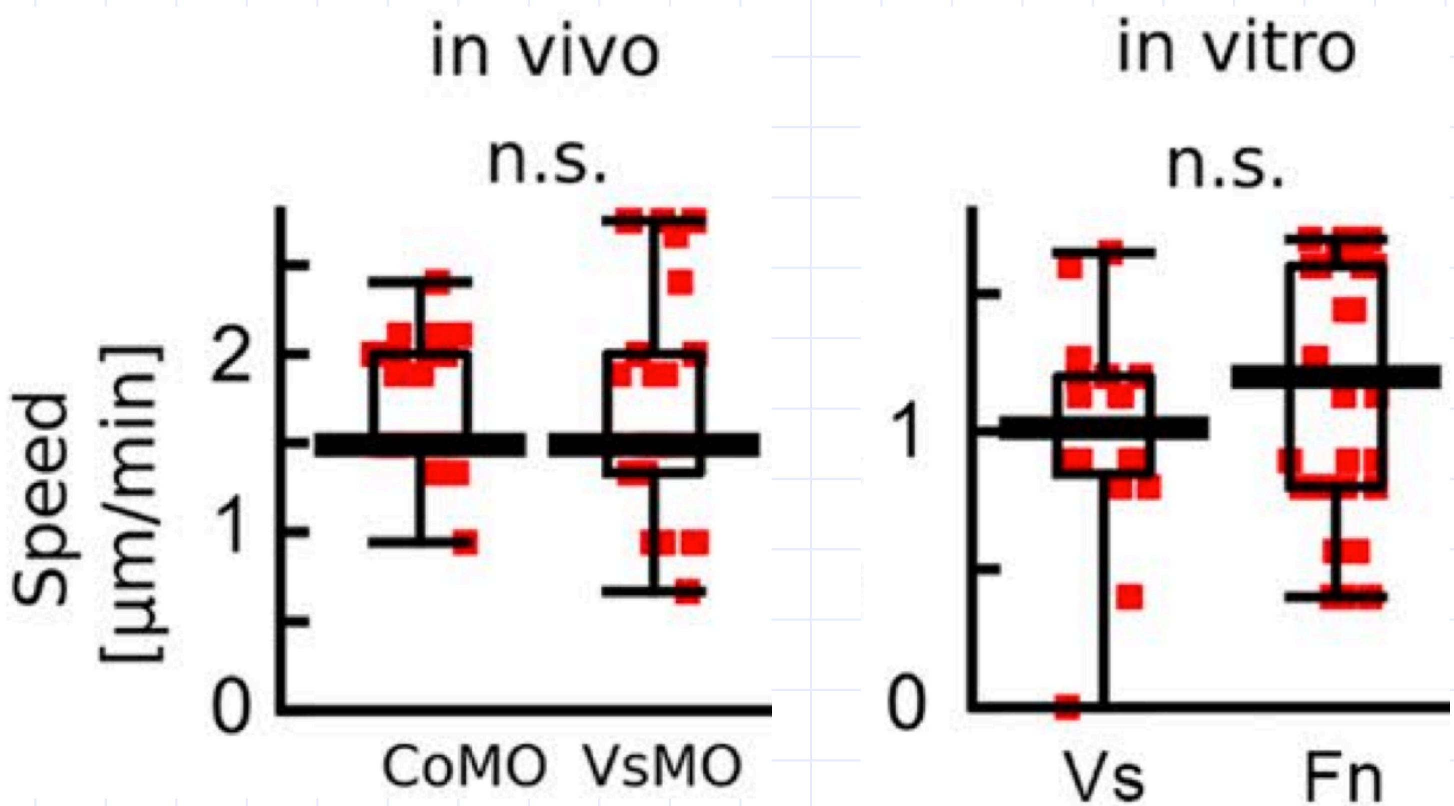
IV. Comparison with experiments

- Qualitatively: spontaneous collective migration
- Quantitatively: comparing 3 numerical indices
  a) Speed of collective migration
  b) Persistence ratio
  c) Optimal confinement

(a) Speed of collective migration

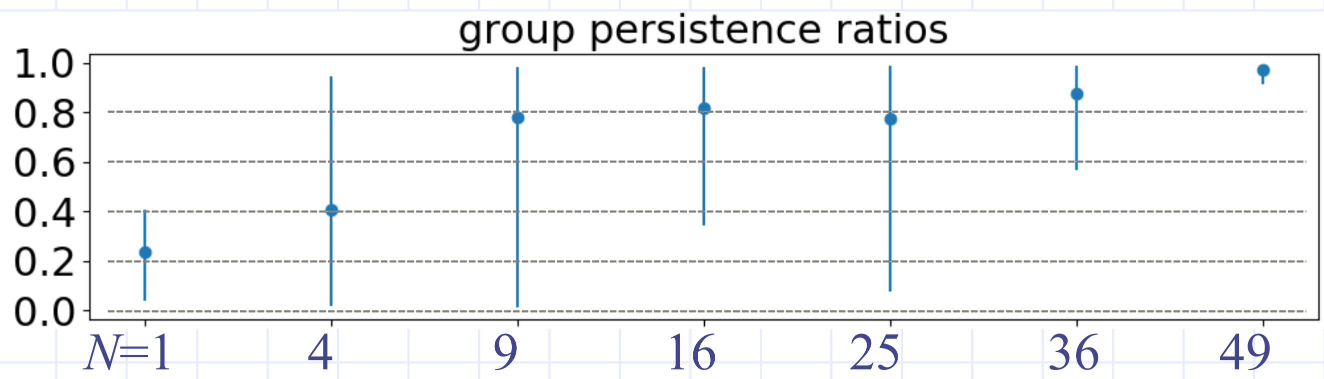


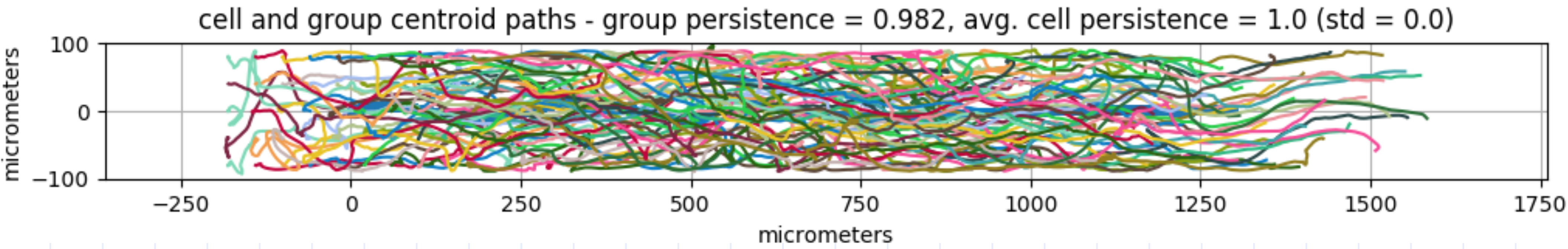
Agreement with experimental data



Captures cluster speed after matching single cell speed of 3 micron/min during "run" phase.

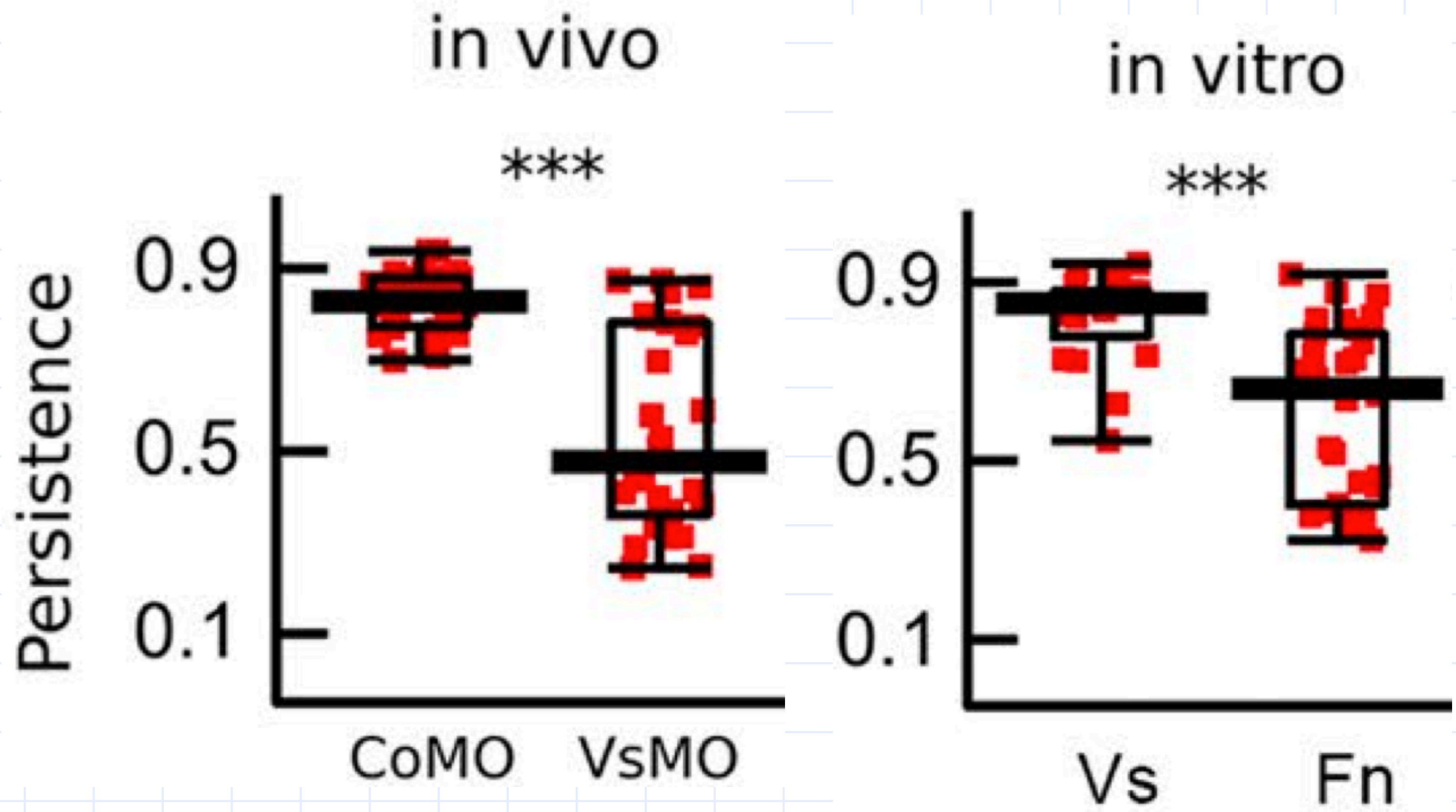
(b) Persistence ratio



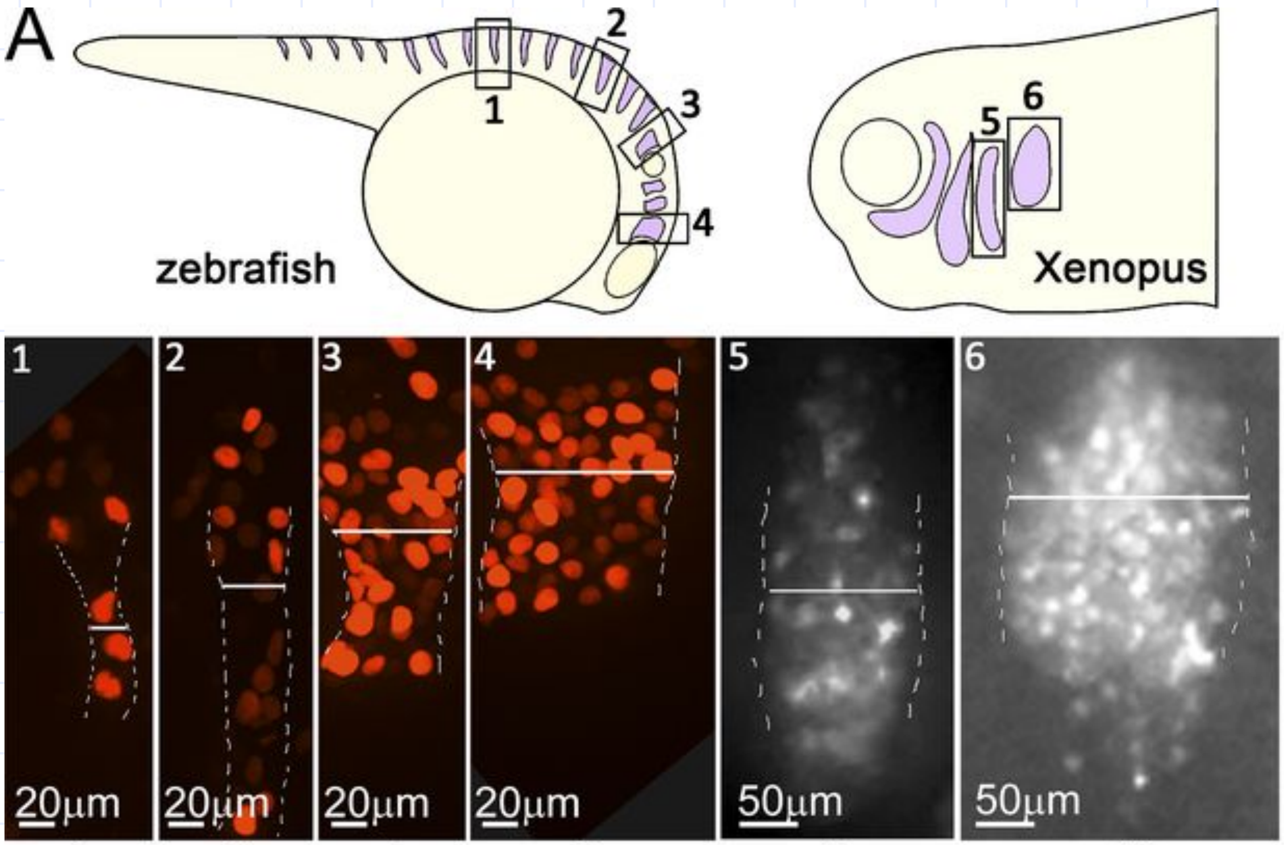


Highly persistent trajectories; almost ballistic for larger clusters

Persistence ratio: in vivo/in vitro



(c) Optimal confinement in vivo

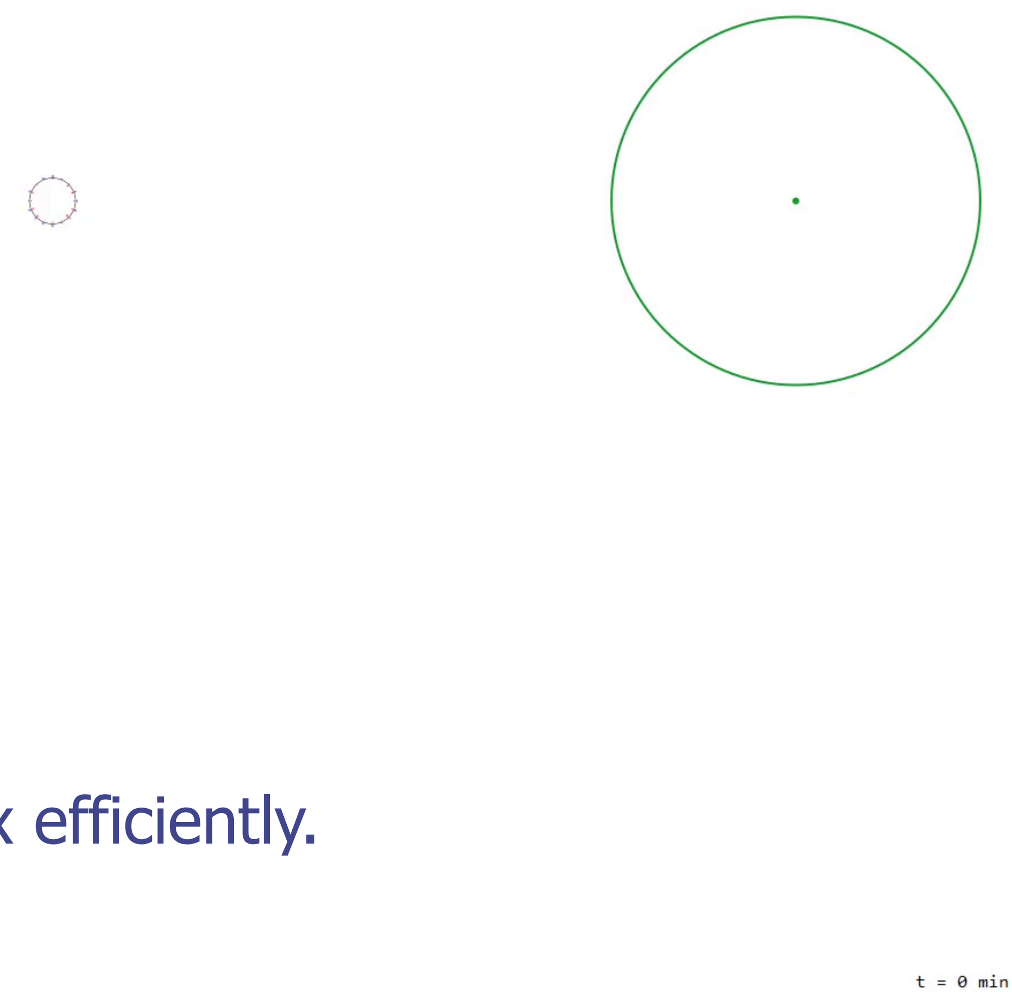


w	1	3	5	6	8	10
N	6 (3)	20 (4)	48 (8)	51 (9)	75 (11)	>100

Our model prediction: optimal $w = N^{1/2}$

Chemotaxis in a weak gradient

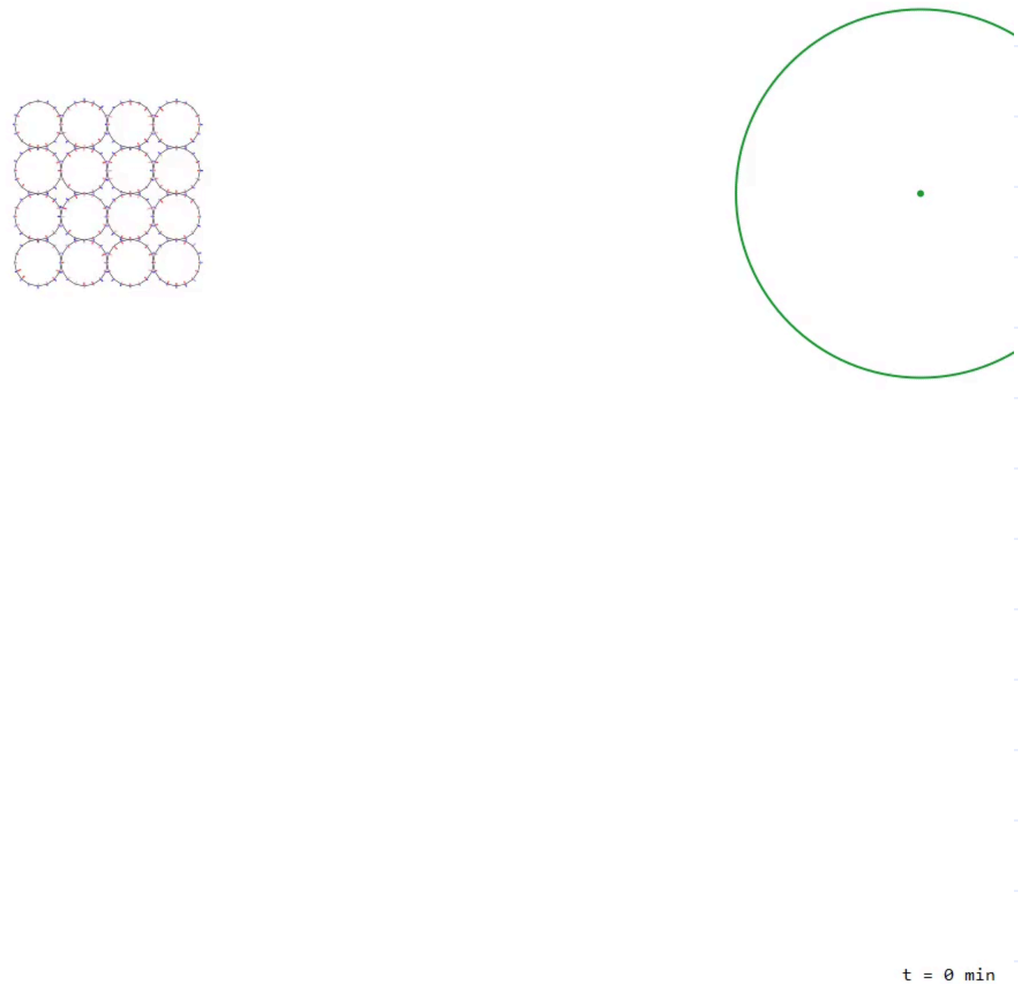
- This was our "curious behavior no. 2"
- Let's look at a single cell first as a baseline ……



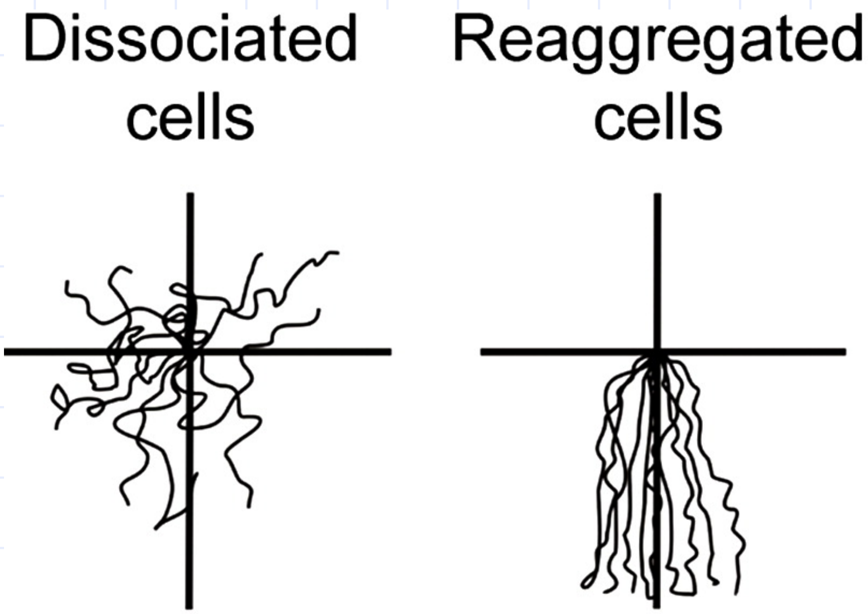
- Failed to chemotax efficiently.

Group advantage in chemotaxis

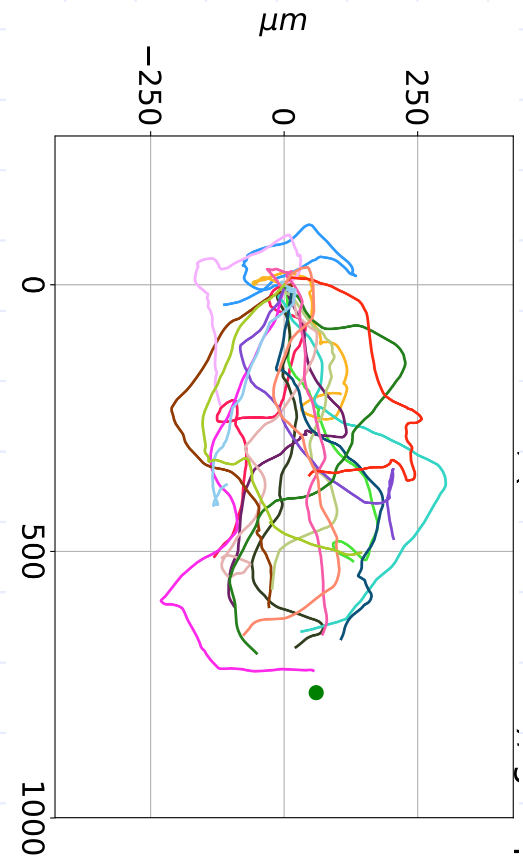
- Successful collective chemotaxis:



Comparison: single and cluster trajectories

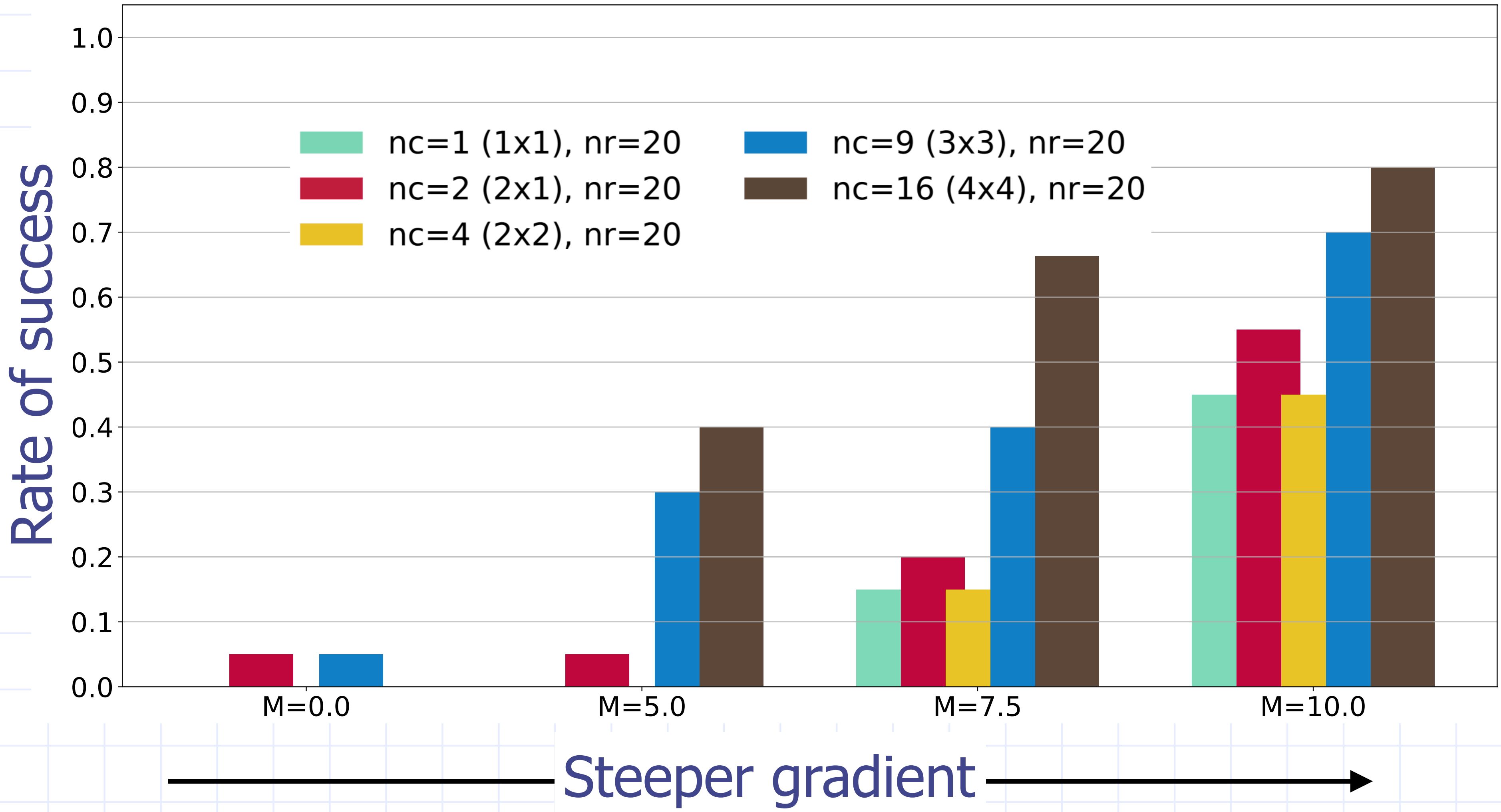


Theveneau et al. (2010)

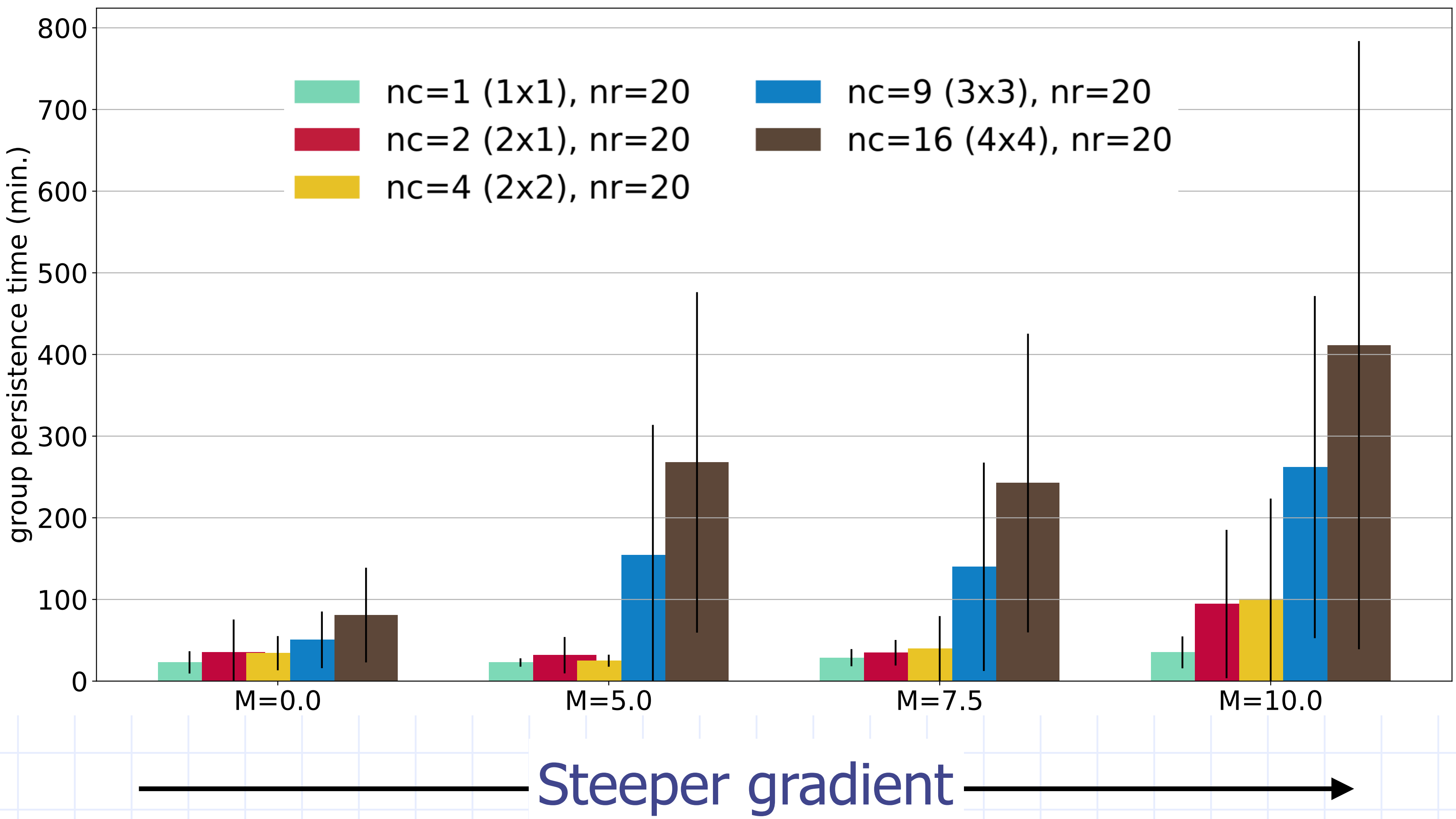


Model prediction

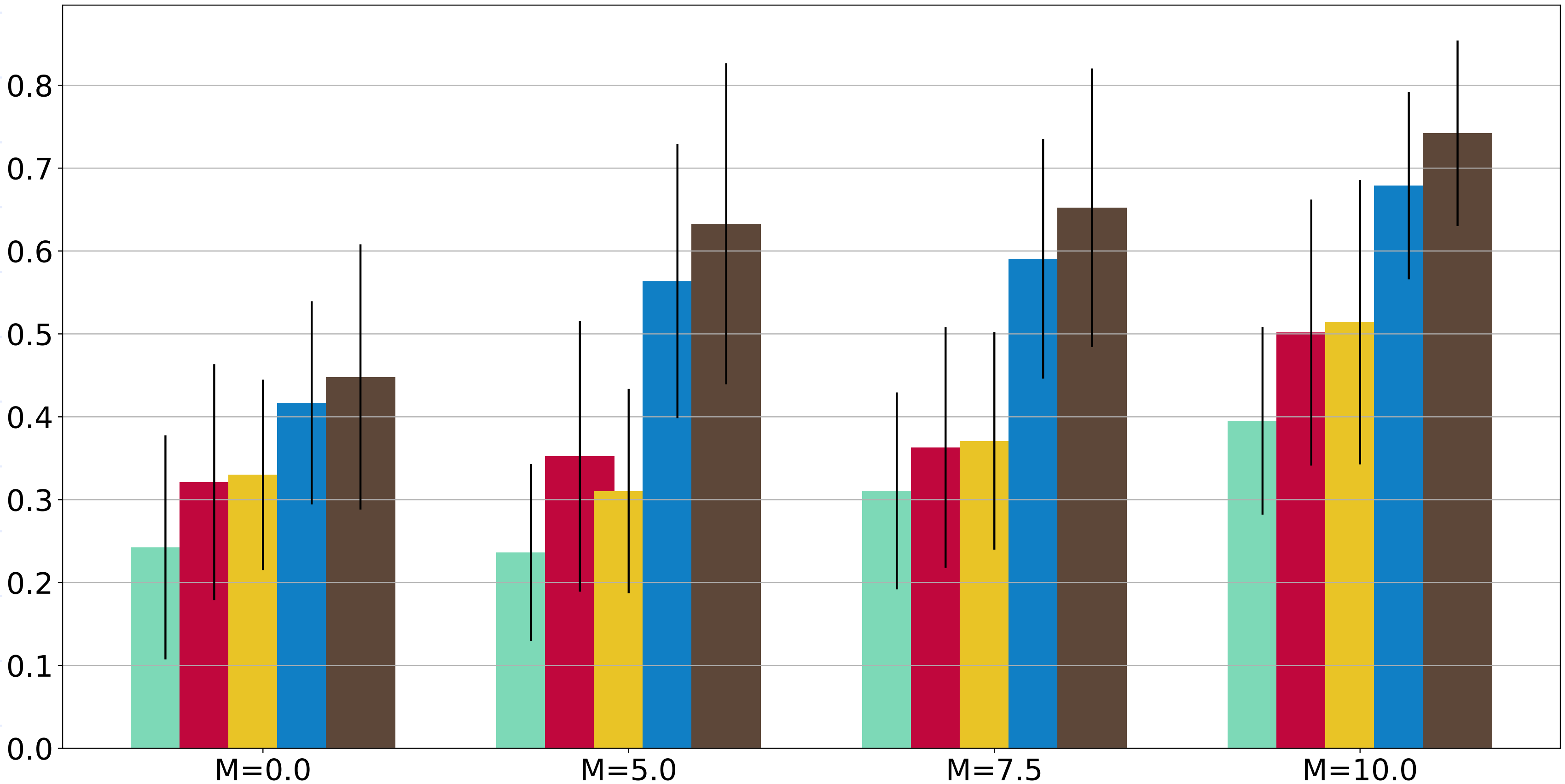
Group advantage: Success rate



Cluster centroid persistence time



Chemotaxis index (CI):



Steeper gradient

Summary

- Advocating modeling on a deeper level than rule-based paradigm
- Integrating GTPase biochemistry with mechanics of cell motility
- Emergent behavior from known biology: CIL + CoA → PoP

Explains two emergent behaviors:

- Spontaneous migration in the absence of chemoattractant:
  - ➡ PoP sensitizes cell cluster to initial bias in confined channel
- Collective chemotaxis: group advantage in sensing weak gradient:
  - ➡ PoP sensitizes cluster to weak gradient

Acknowledgment

NSERC CRSNG

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Acknowledgment for discussions:

Paul Kulesa, Phillip Maini, Roberto Mayor, Luigi Preziosi

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