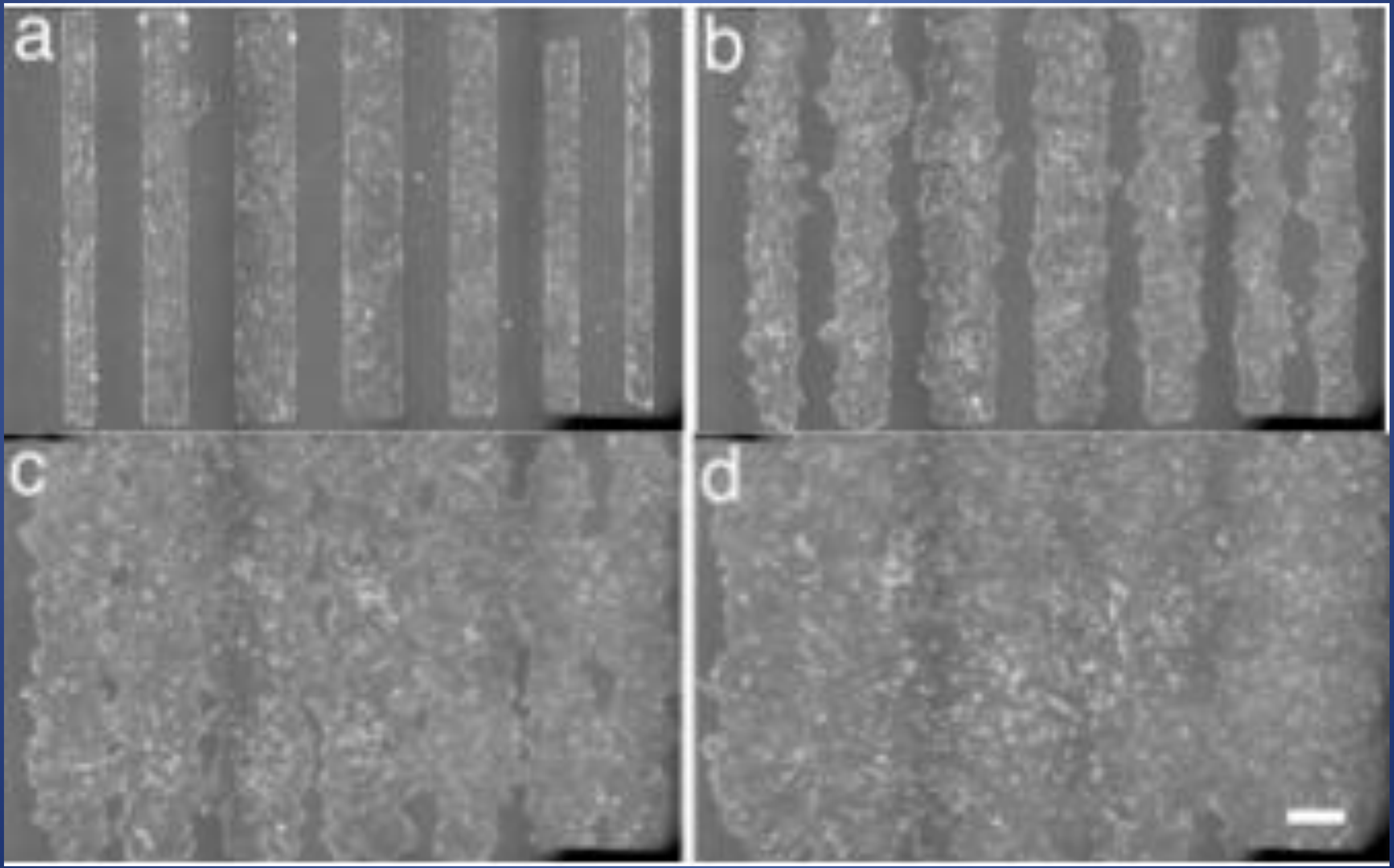
Swirls, fingers and directed bulk motility in spreading epithelial sheets

Markus Basan, Jens Elgeti, Edouard Hannezo, Wouter-Jan Rappel, and Herbert Levine

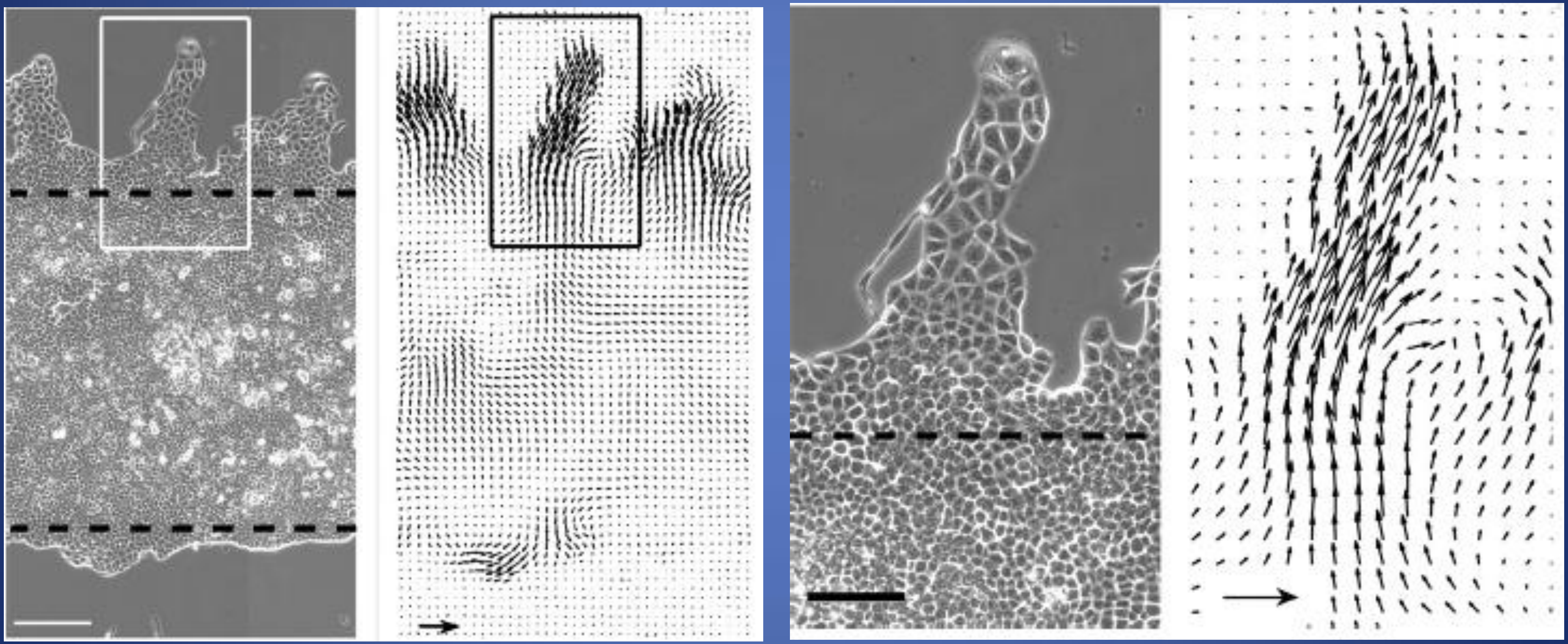
Spreading mono-layers of epithelial cells are a model for epithelization



Poujade et al. (2007). Proc. Natl. Acad. Sci. USA **104**, 15988–15993.

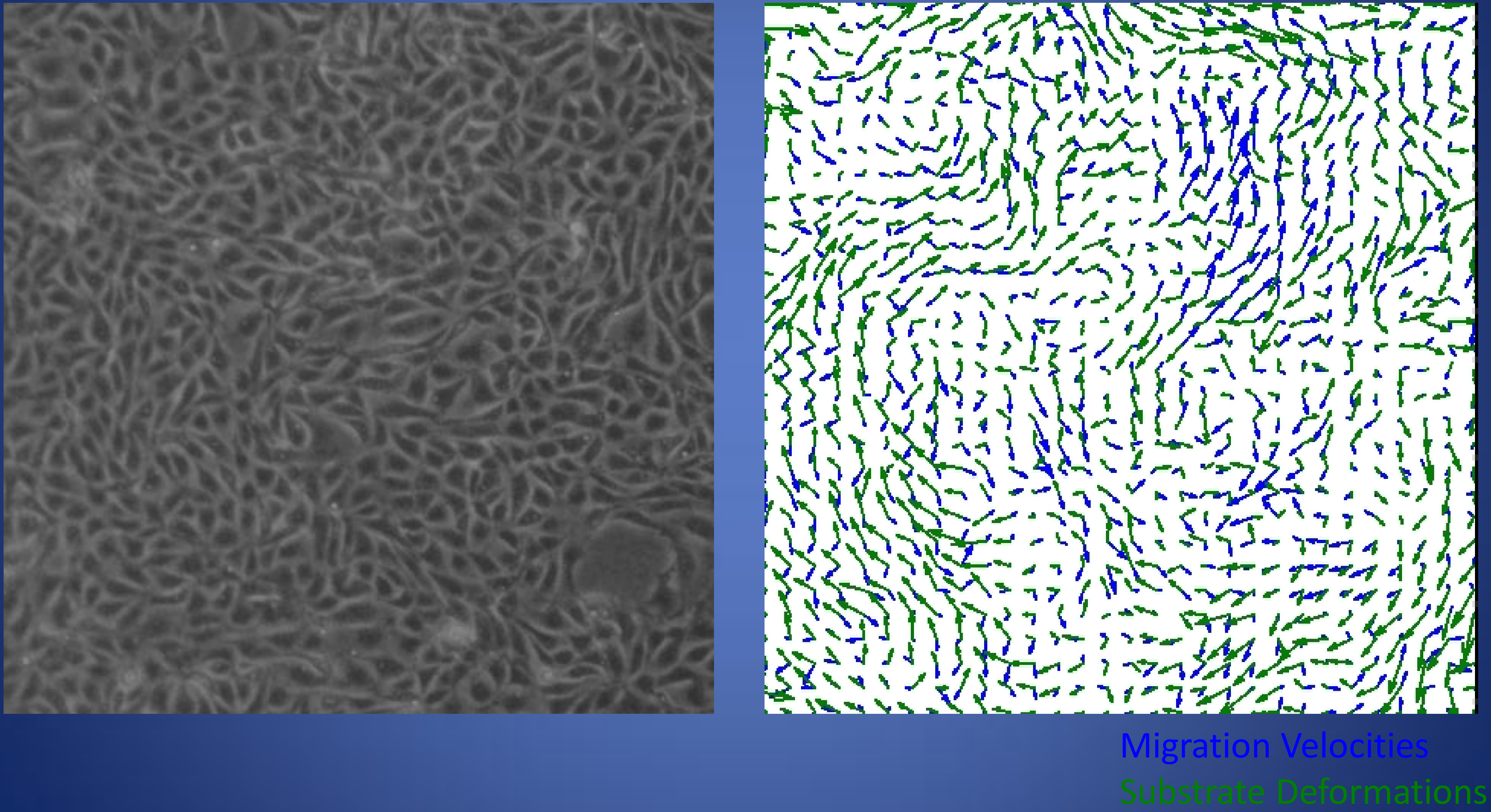
Bar: 400 micron.

Finger-like protrusions arise at the tissue front.



Petitjean et al. (2010). Biophysical Journal **98**, 1790–1800.

Large-scale swirls occur in the tissue bulk.



Angelini et al. (2010). PRL **104**, 168104–168108.

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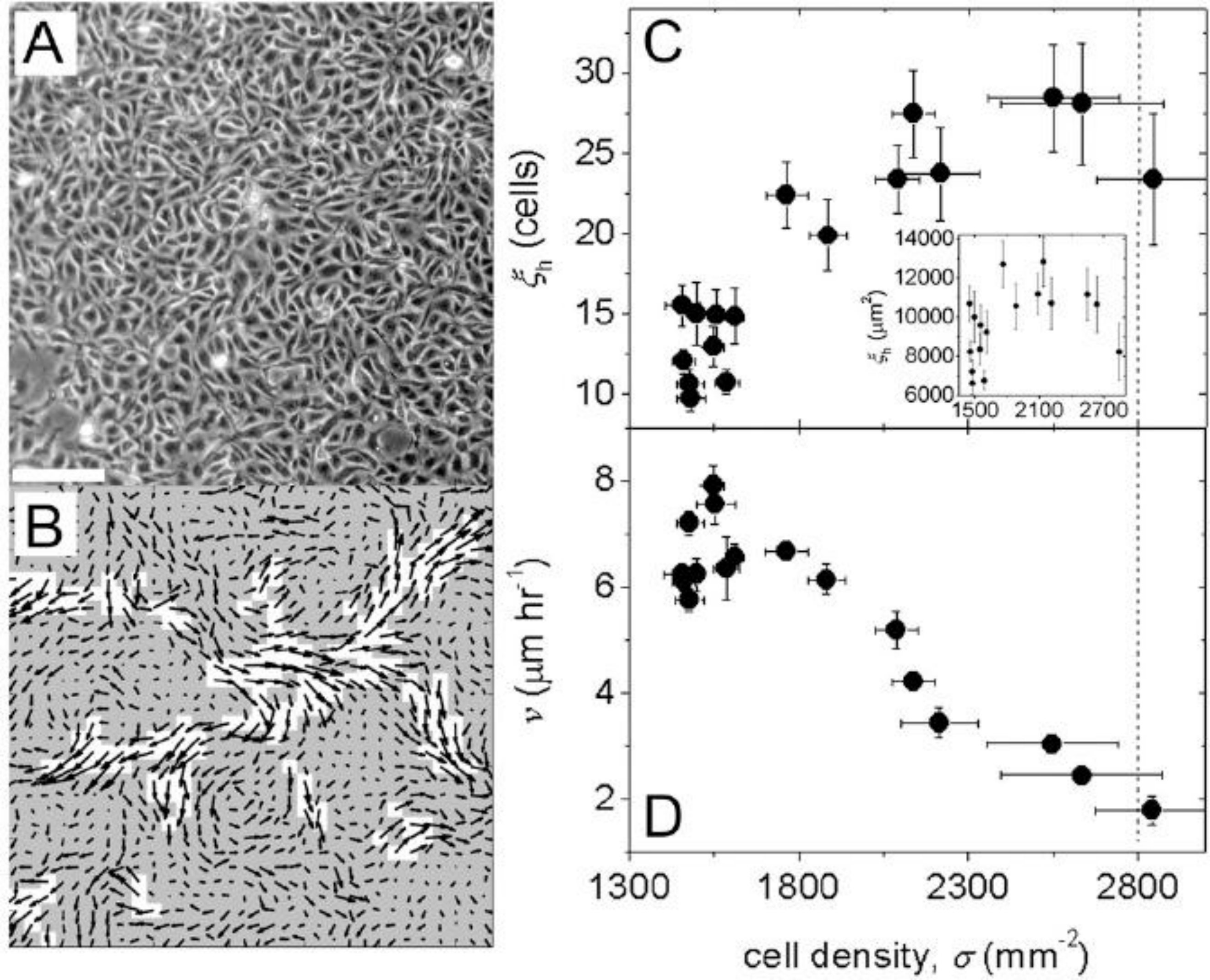
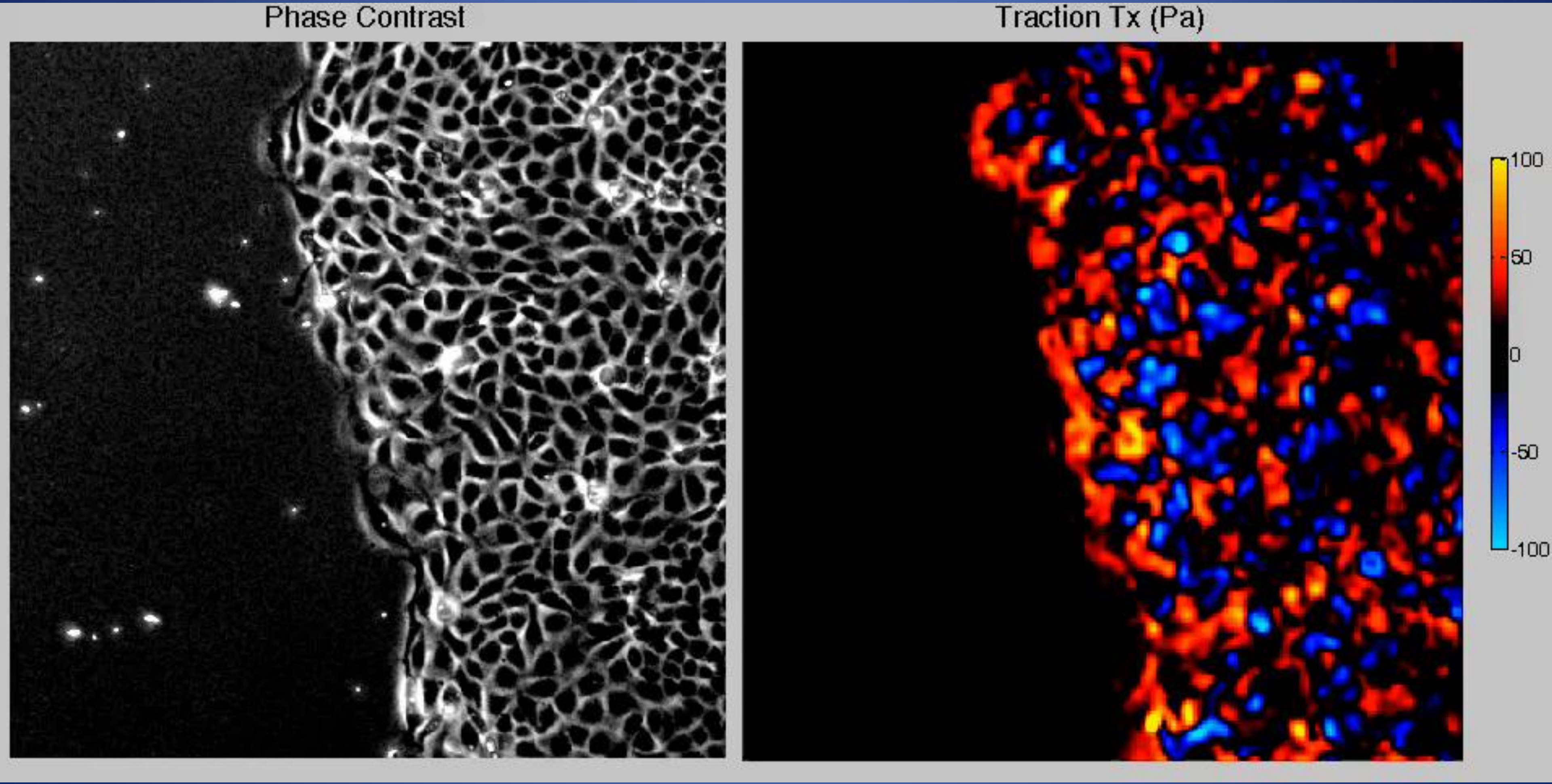


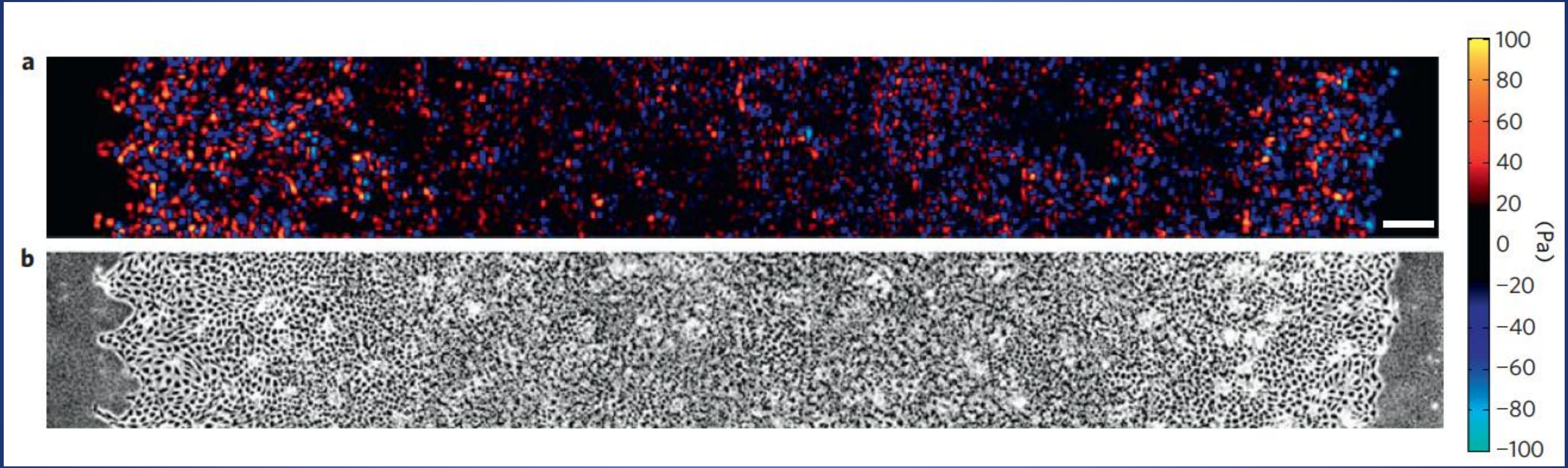
Angelini et al. (2011). PNAS **108**, 4714–4719.

Motility forces can be measured using traction force microscopy.



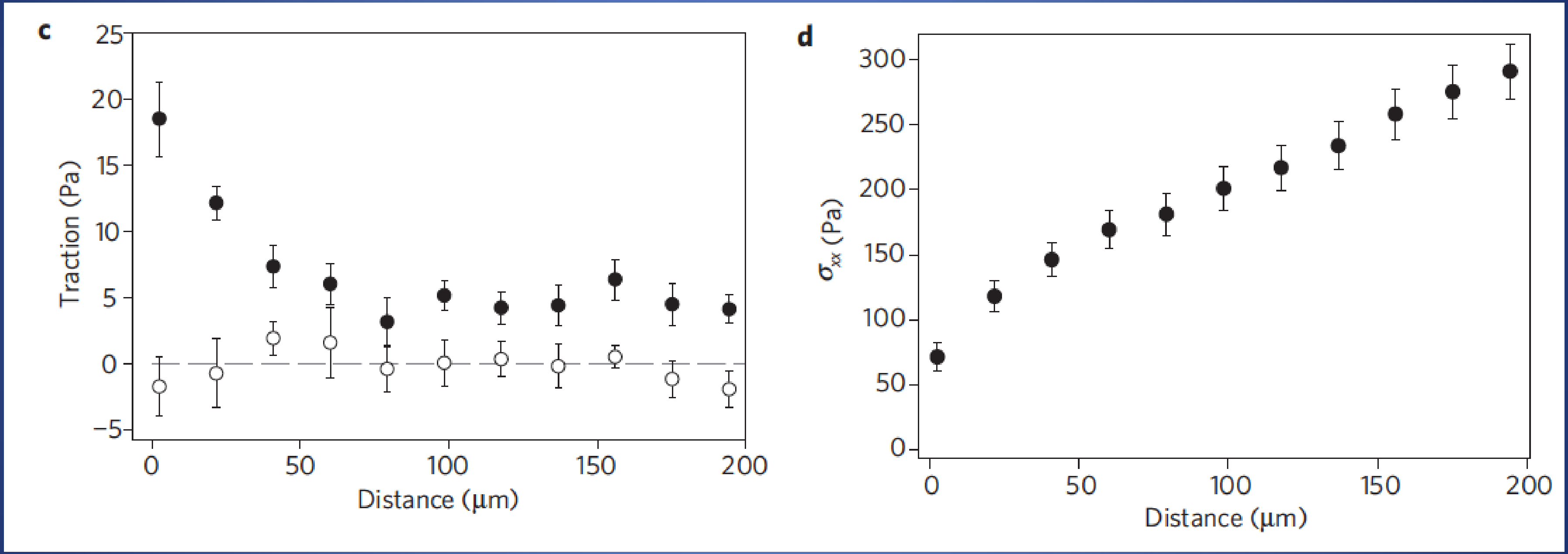
Trepat et al. (2009). Nature Physics **5**, 426-430.

Cells in the bulk of the tissue exert motility forces with cryptic lamellipodia.



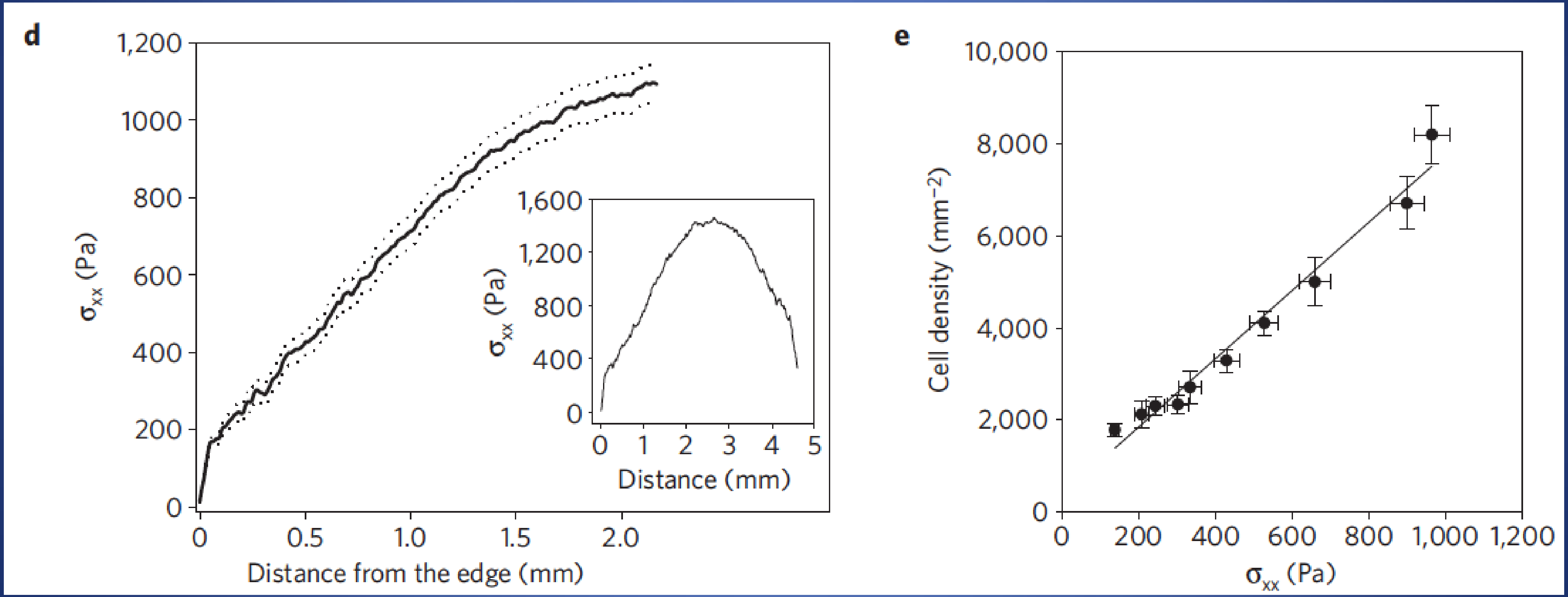
Trepat et al. (2009). Nature Physics **5**, 426-430.

Traction forces deep in the bulk of the tissue are biased in the direction of the front.



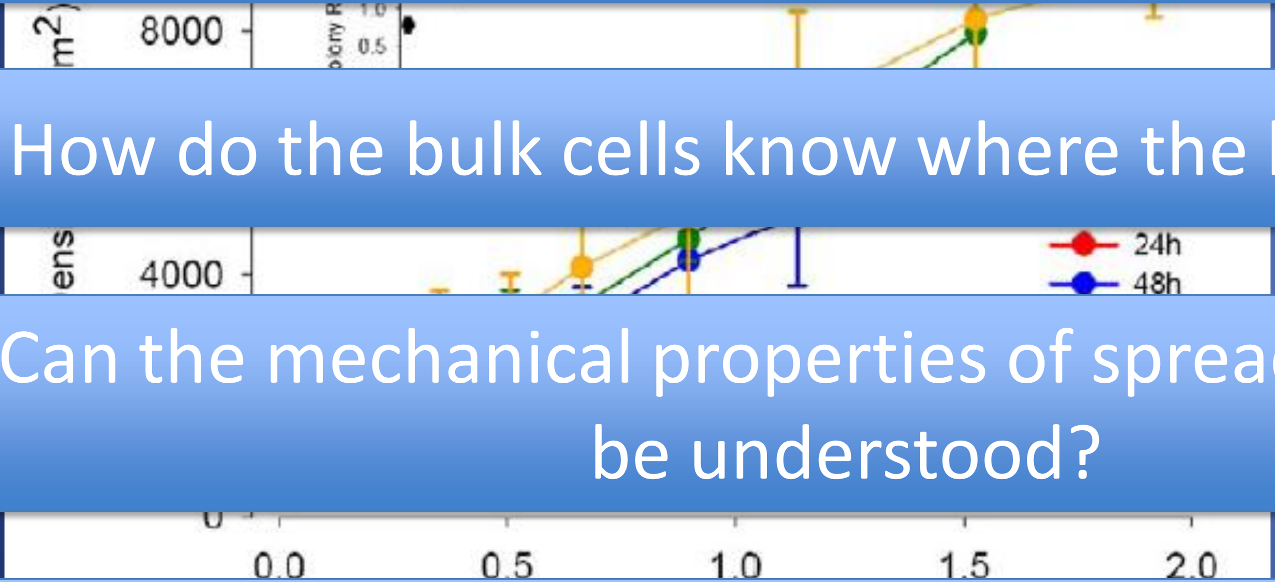
Trepat et al. (2009). Nature Physics **5**, 426-430.

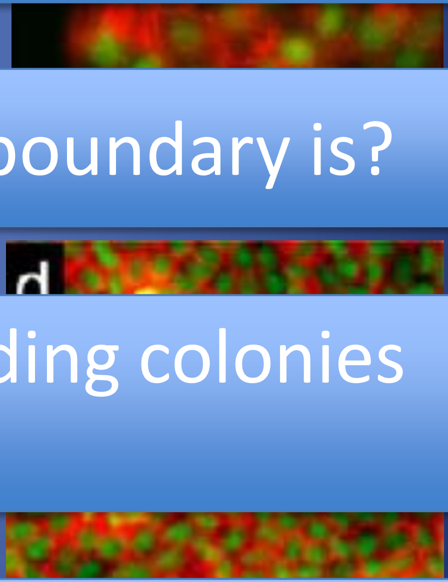
Bulk traction forces are the main contributor to overall tension in the sheet.



Trepat et al. (2009). Nature Physics **5**, 426-430.

Cell density is larger in the sheet and increases everywhere within the colony.





Could there be a common mechanism behind fingering, swirls and motility coordination?

How do the bulk cells know where the boundary is?

Can the mechanical properties of spreading colonies be understood?

Can the advantage of a coordination of motility forces be quantified?

0.

Possible mechanisms for coordinated motility:

A) Biochemical signaling

B) Interaction with neighboring cells

- Local alignment of polarization via elastic interactions *(Gov, N. (2009). HFSP J* ***3****, 223–227.)*
- Reorientation by torque from a spatially non-uniform tissue flow *(Lee, P. et al. (2011). PLoS Comp. Biol.* ***7,*** e1002007.*)*
- Orientation along the principal axis of the stress tensor *(Tambe et al. (2011). Nature Materials* ***10****, 469-475.)*
- Orientation along the gradient of pressure *(devil's advocate Jens)*

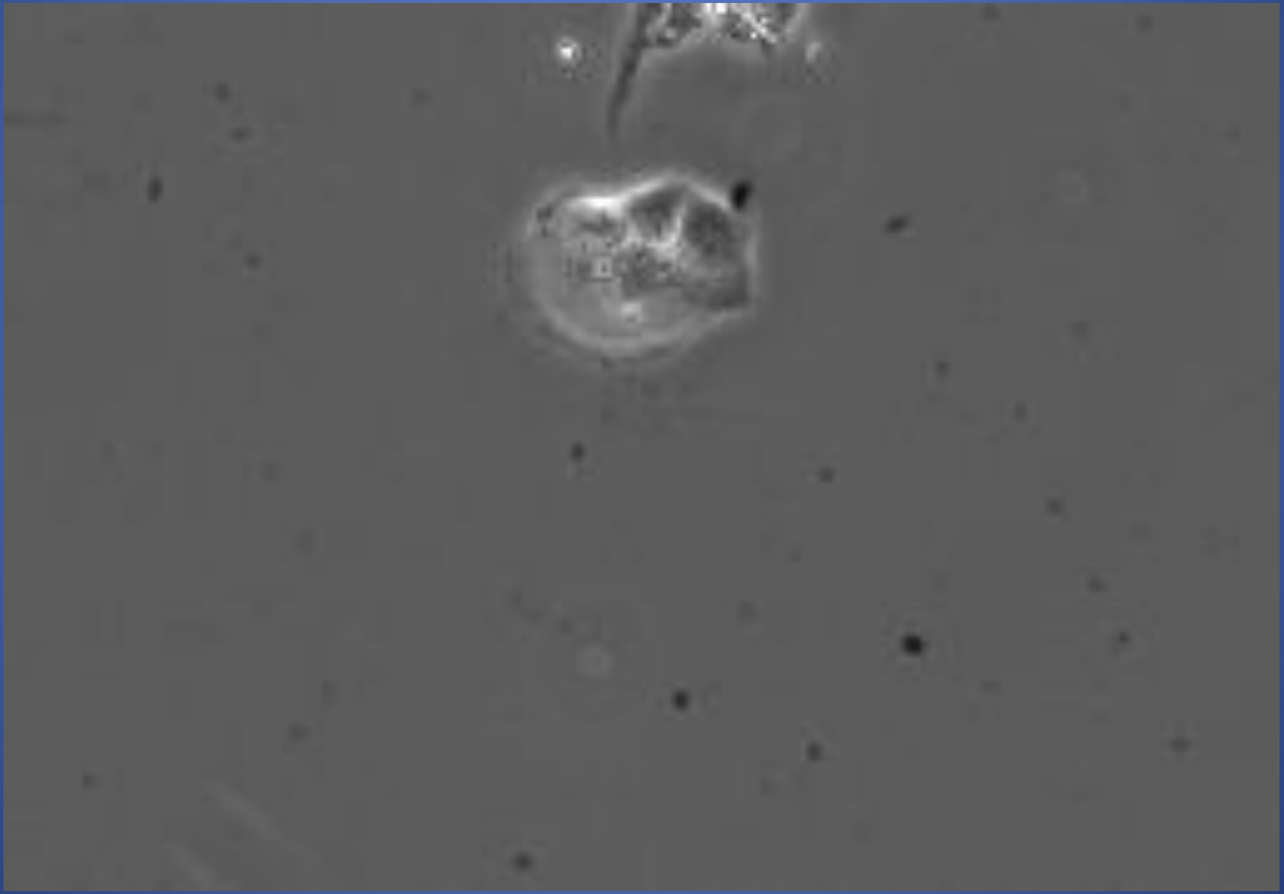
C) Interaction with the substrate

- Motility forces have the tendency to align with the cell velocity. *(Toner et al. (1998). Phys. Rev. E* ***58****, 4828.)*

Lamellipodia tend to align with cell velocity and are unstable otherwise?

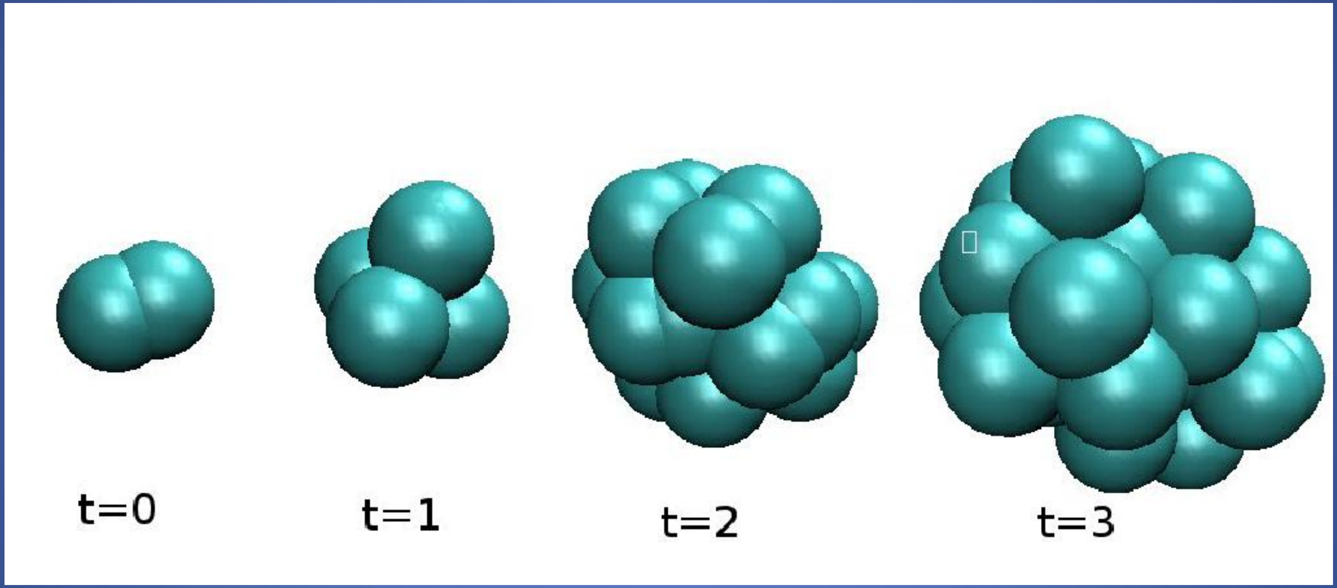
Lo et al. (2000). Biophys. J. **79**, 144-152.

Leader cells can be separated from the finger via laser ablation.



Reffay et al. (2011). Biophysical Journal **100**, 2566-2575.

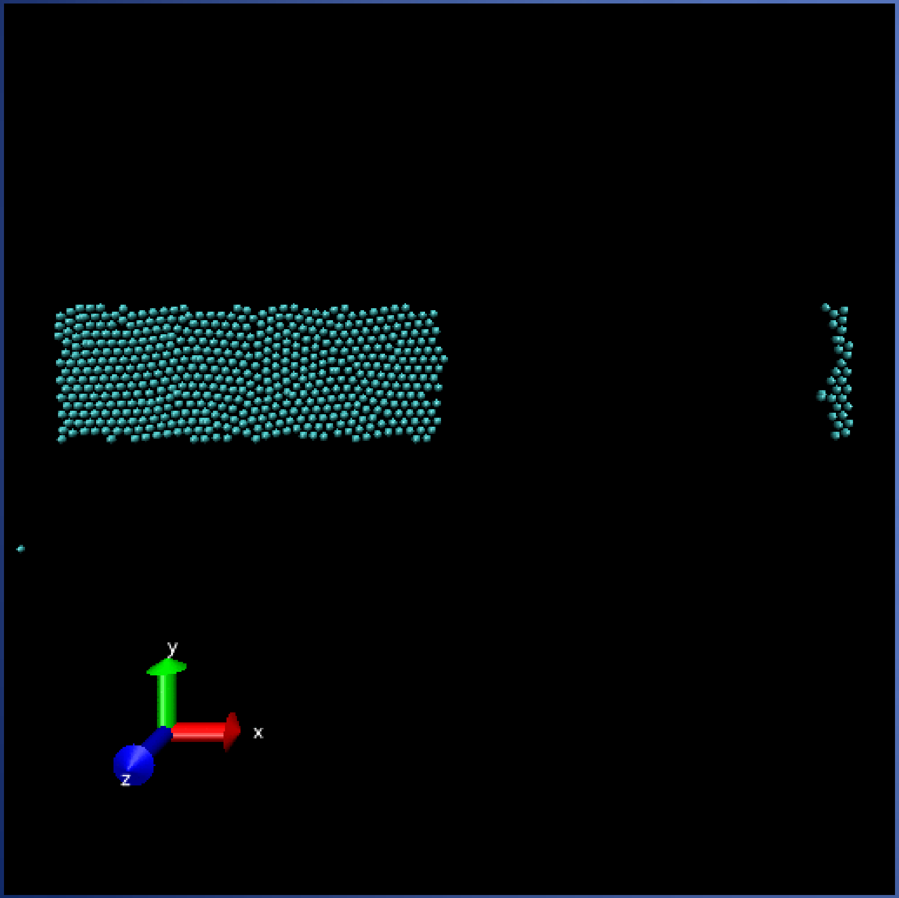
2D Particle-Based Tissue Simulation



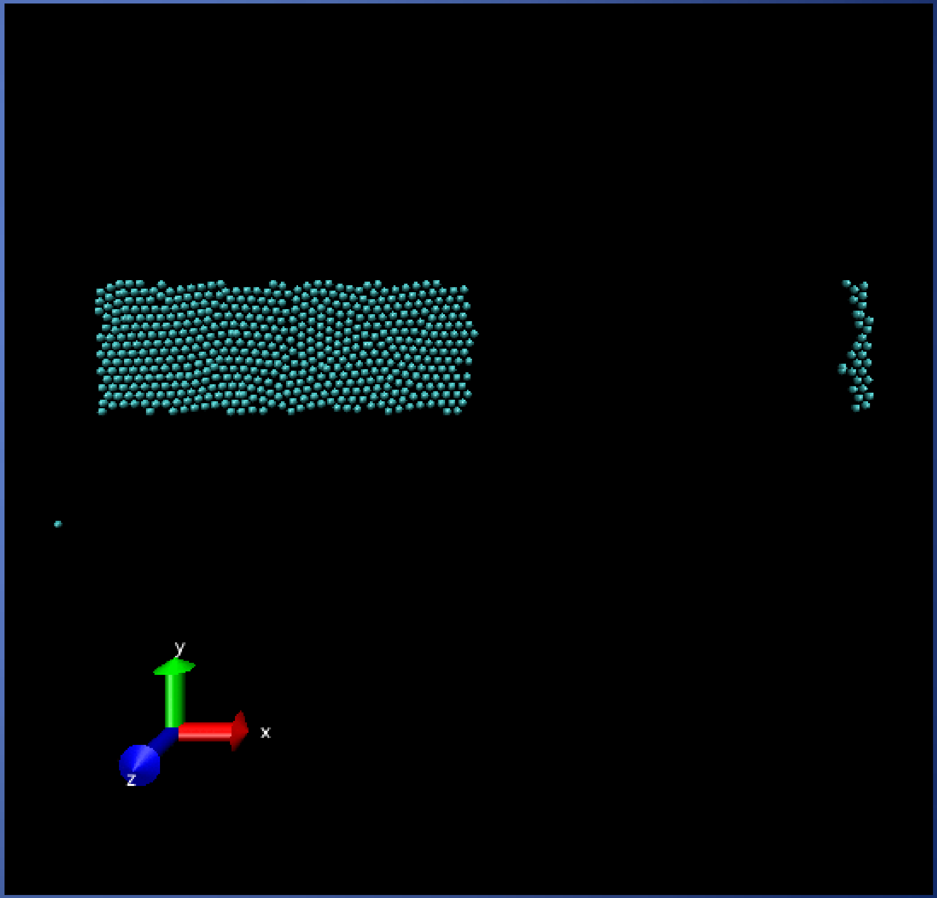
Basan et al. (2011). Physical Biology **8**, 026014.

Velocity-motility coupling can help close wounds more effectively.

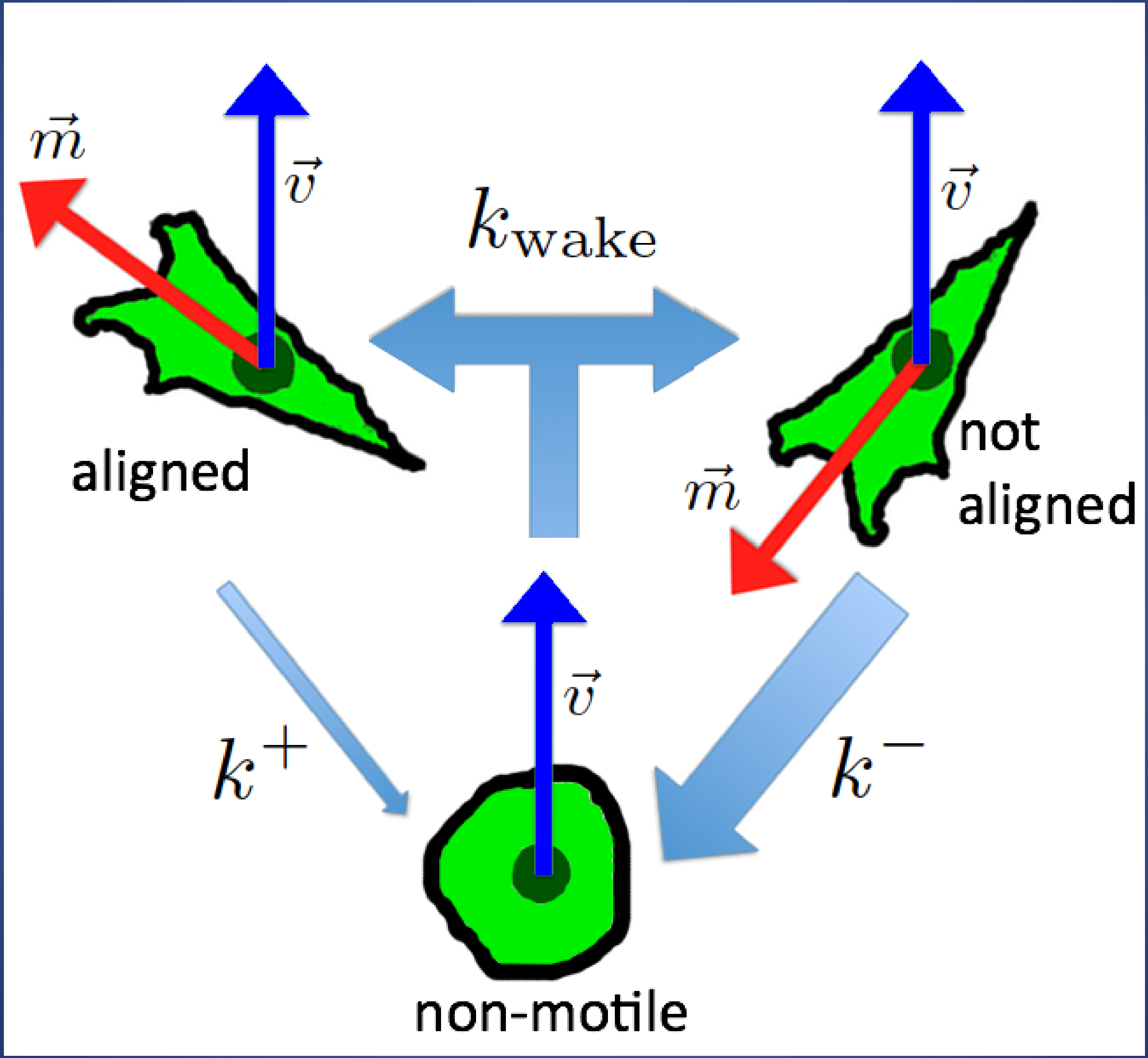
Random motility force:



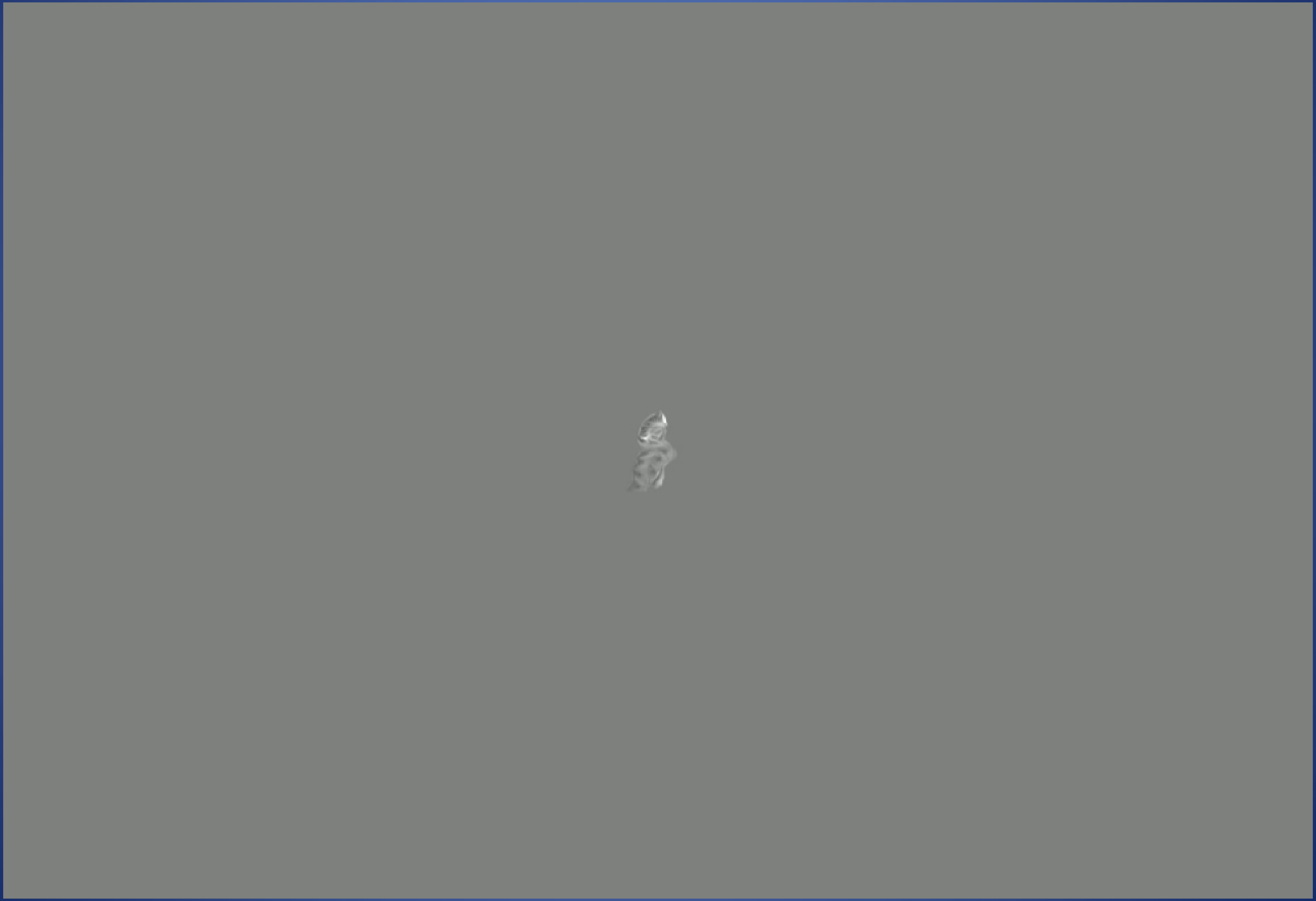
Coupled motility force:



Motility Model

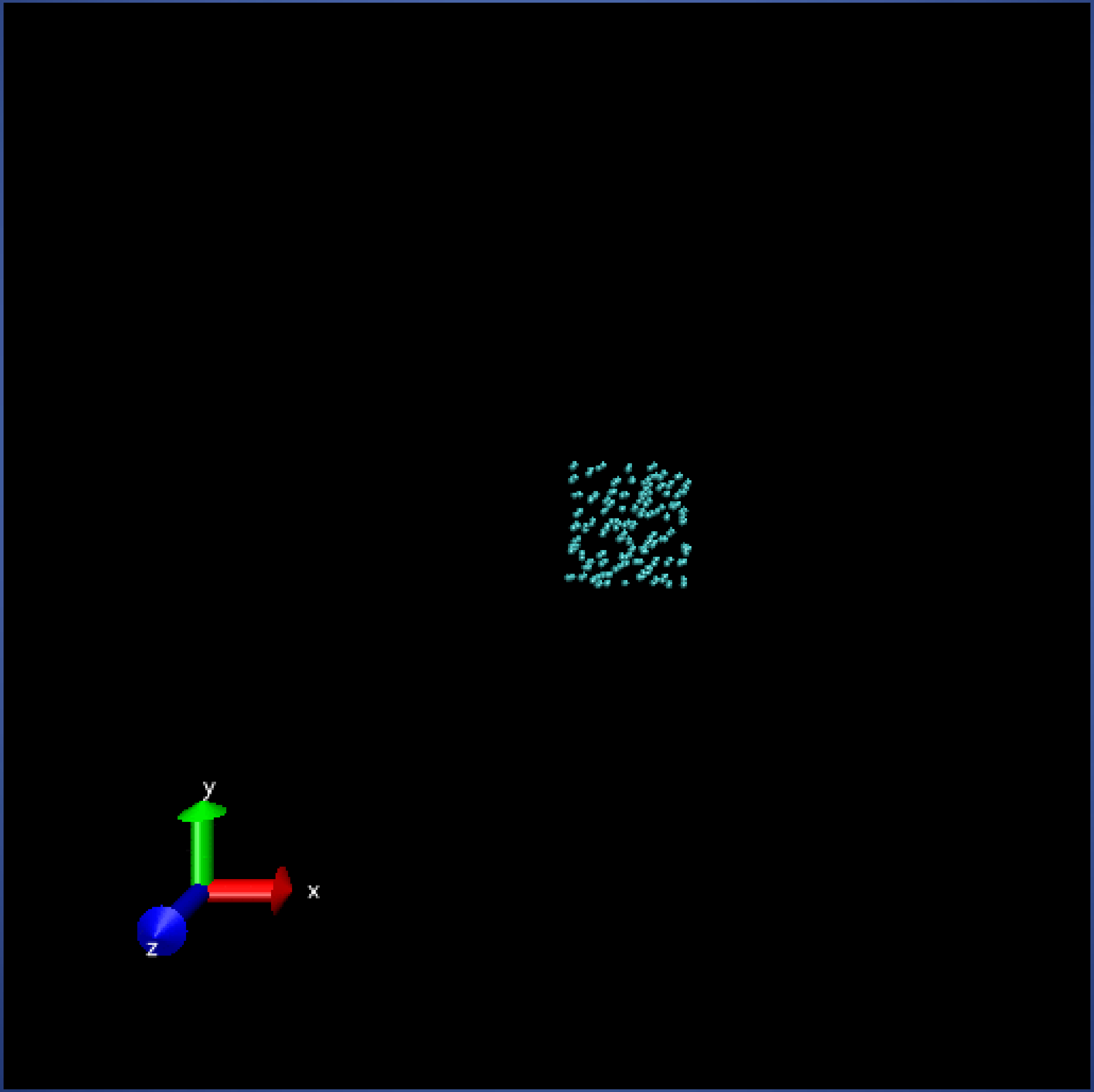


Growing Colony

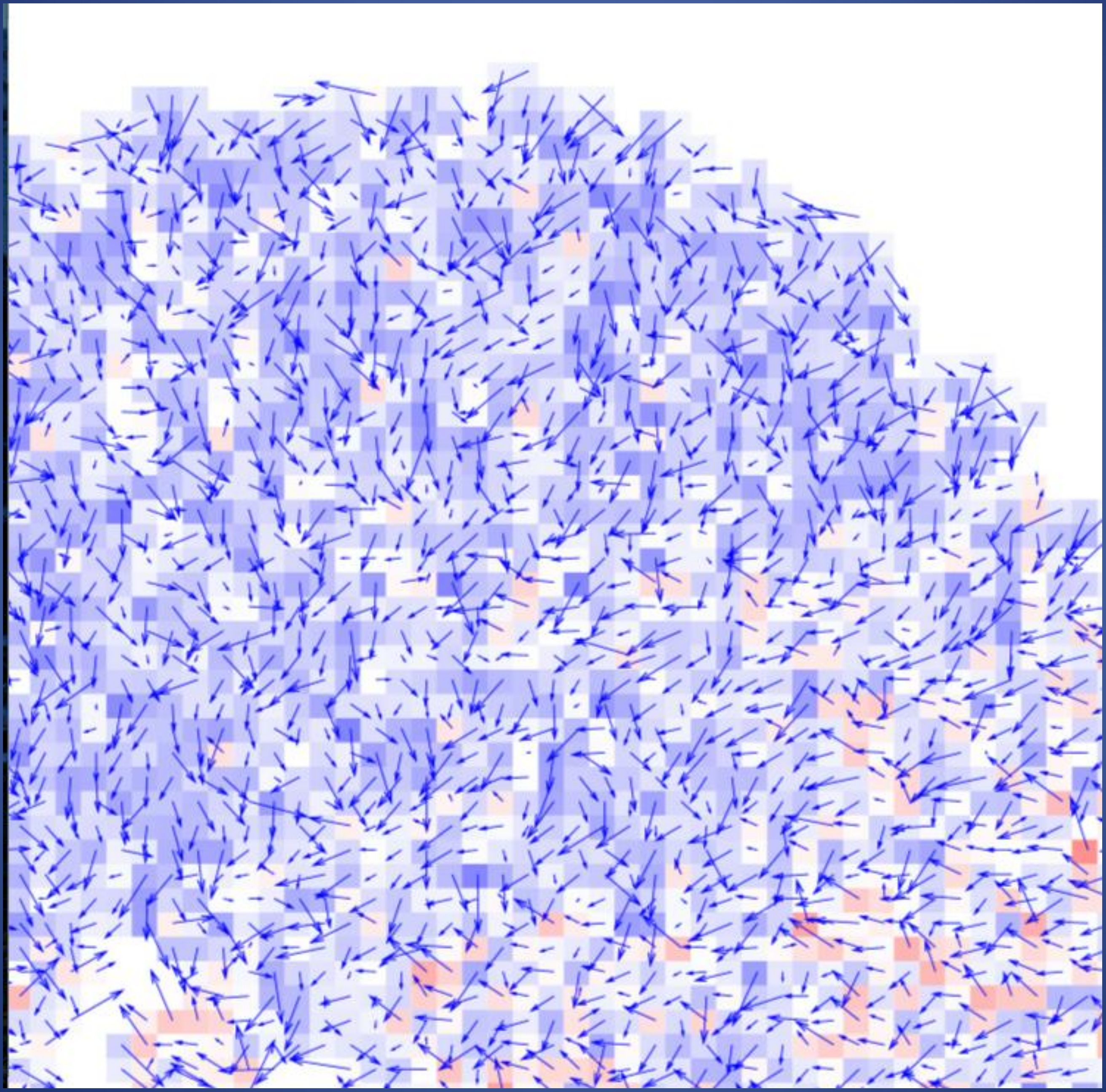


Puliafitoet al. (2012). Proc. Natl. Acad. Sci. USA **109**, 739-744.

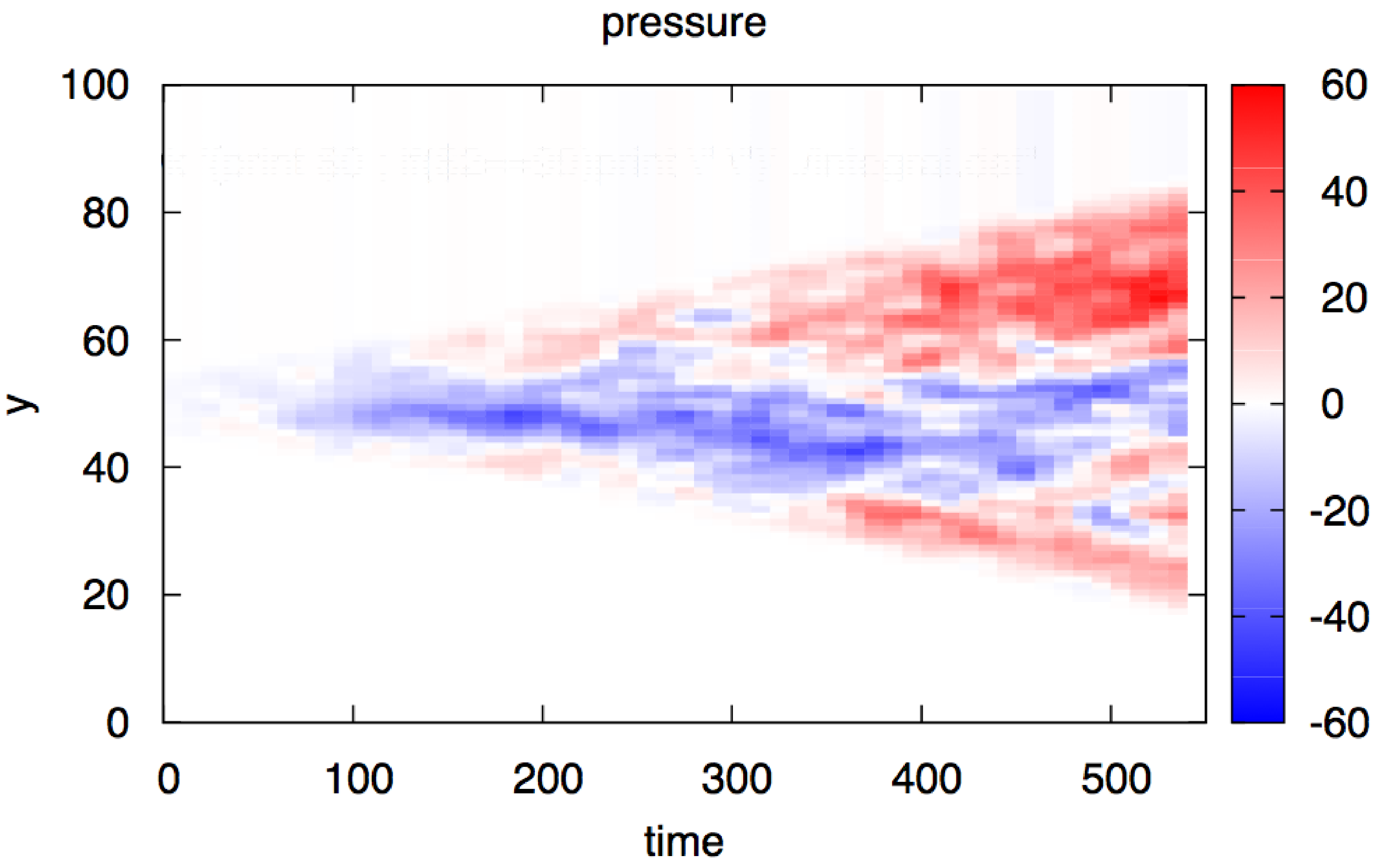
Colony Spreading on a Substrate (from 200 to 45 000 cells)



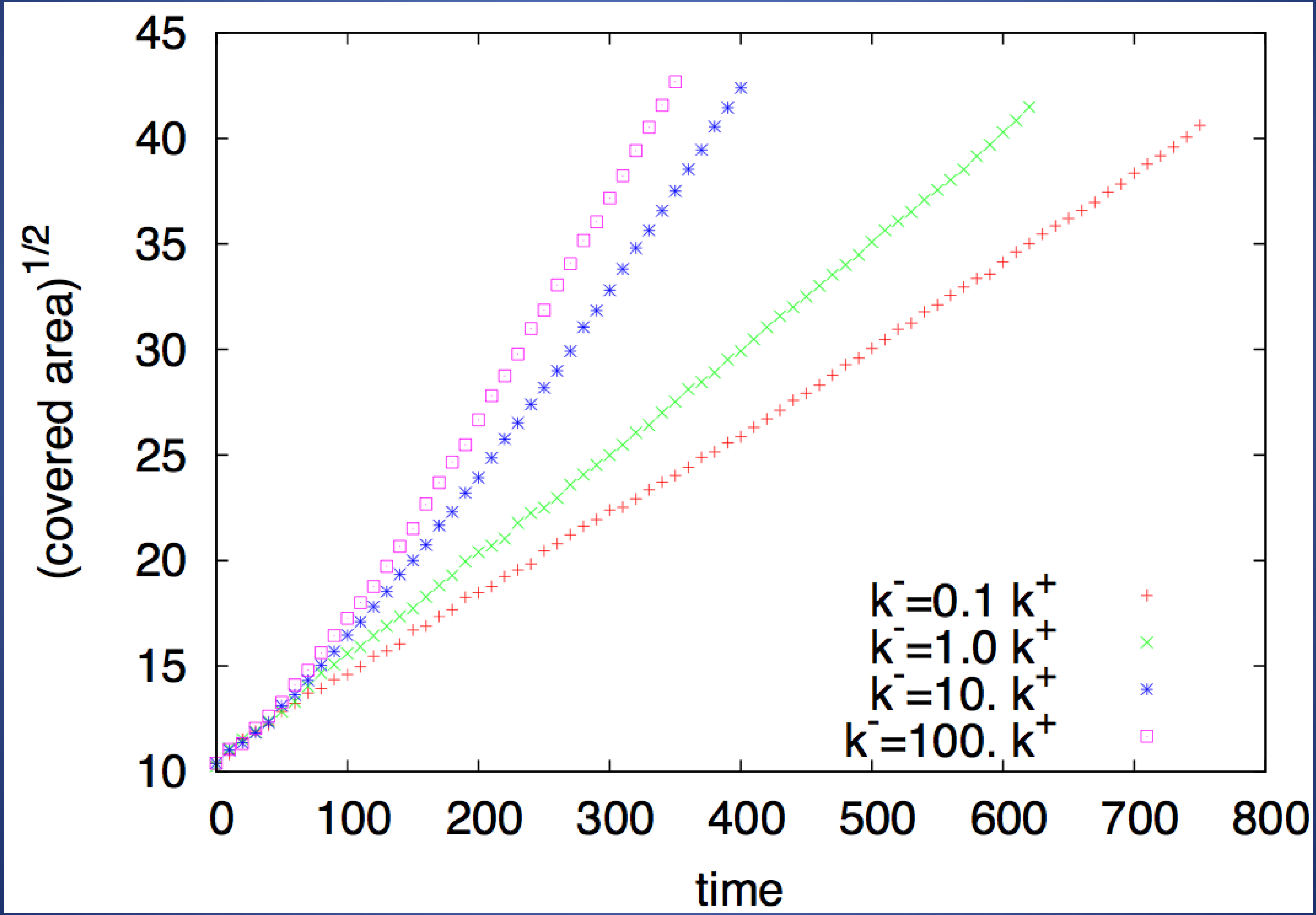
Traction Force Map Within the Colony



Velocity-motility coupling can produce tension within the spreading colony.



Velocity-motility coupling enhances the spreading velocity of colonies.



Velocity-motility coupling enhances the spreading velocity of colonies.

$$\nabla \cdot \vec{v} = -\kappa(p - p_0)$$

$$\vec{\nabla} p = -\xi \vec{v}$$

$$v_{\mathrm{pres}} \sim \sqrt{p_0 k_{\mathrm{div}} / \xi}$$

$$\xi = 1\ (\mathrm{Pa\ hr})/\mu\mathrm{m}^2$$

$$p_0 = 100\ \mathrm{Pa}$$

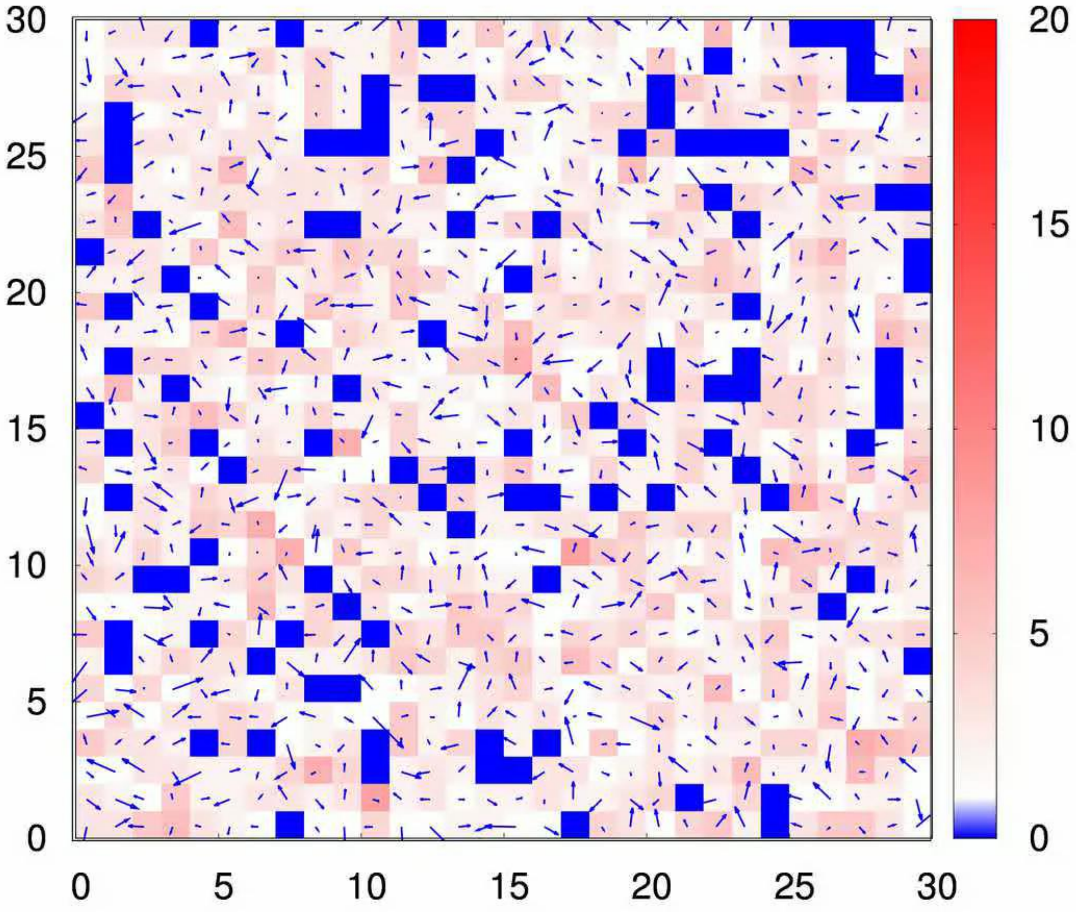
$$k_{\mathrm{div}} = 1/24\ \mathrm{hr}^{-1}$$

$$v_{\mathrm{pres}} \sim 2\mu\mathrm{m/hr}$$

$$v_{\mathrm{mot}} \sim 10\mu\mathrm{m/hr}$$

Trepat et al. (2009). Nature Physics **5**, 426-430.

Velocity-motility coupling gives rise to spontaneous swirls in the tissue.



Finger-like protrusions can occur along the edge.

Velocity-motility coupling gives rise to undulations of the tissue interface.

Continuity Equation:

$$\nabla \cdot \vec{v} = 0$$

Force Balance:

$$\eta(\nabla^2 \vec{v} + \vec{\nabla}(\vec{\nabla} \cdot \vec{v})) - \vec{\nabla} p = -m\vec{v} + \xi_3 v^2 \vec{v}$$

We assume a semi-infinite tissue, homogeneous in y-direction:

Unperturbed Solution:

$$v_x^0 = 0, p_x^0 = 0$$

Velocity-motility coupling gives rise to undulations of the tissue interface.

Perturbation of the Interface:

$$\delta h = h_0 \exp(\omega t + iqy)$$

Boundary Conditions:

$$\sigma_{xx}|_{x=0} = -\gamma q^2 \delta h \qquad \sigma_{xy}|_{x=0} = 0$$

$$\omega \delta h = \delta v_x|_{x=0}$$

Dispersion Relation:

$$\omega = -\frac{\gamma q^3}{2\eta q^2 - m}$$

Instability between

$$q_0 = 0$$

and

$$q_1 = \sqrt{m/(2\eta)}$$

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Parameter Estimates:

$$m \sim \xi \sim 1 \text{ Pa hr}/\mu\text{m}^2$$

Trepat et al. (2009). Nature Physics **5**, 426-430.

$$\eta \sim 10^4 \text{ Pa s}$$

Forgacs et al. (1998). Biophysical Journal **74**, 2227-2234.

We expect an instability over a wide range of wavelengths:

$$q_1 \sim 10^6 \text{m}^{-1}$$

Important questions beyond the scope of our model

- Is there experimental evidence for the proposed mechanism (alignment of motility forces with cell velocity)?

- What is the role of leader cells for fingers at the tissue edge (contact inhibition)?

- What is the relative importance of tissue tension and cell-cell contact for cell proliferation and changes in active motility (contact inhibition)?

- What is the influence of initial conditions on spreading behavior?