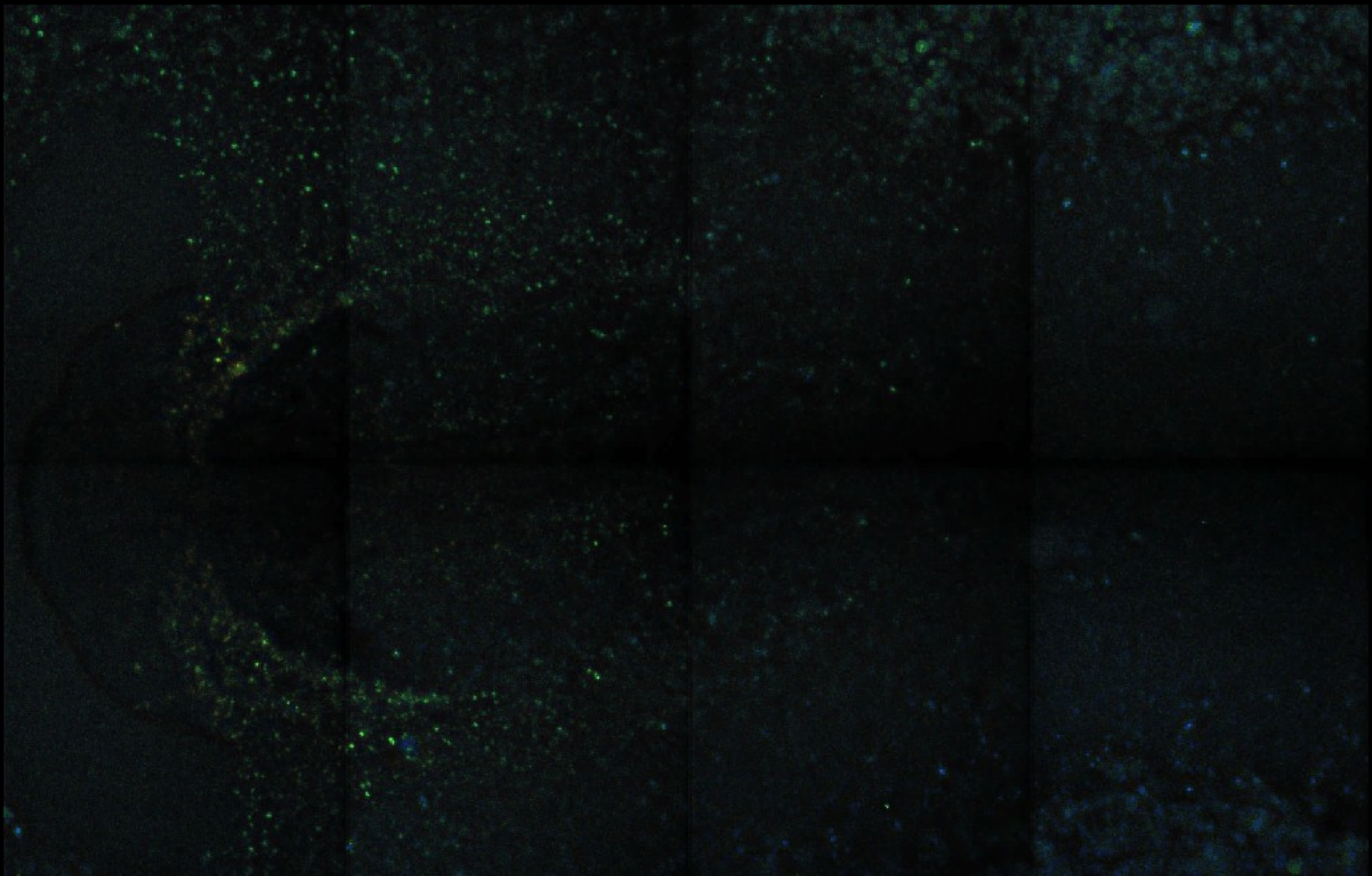
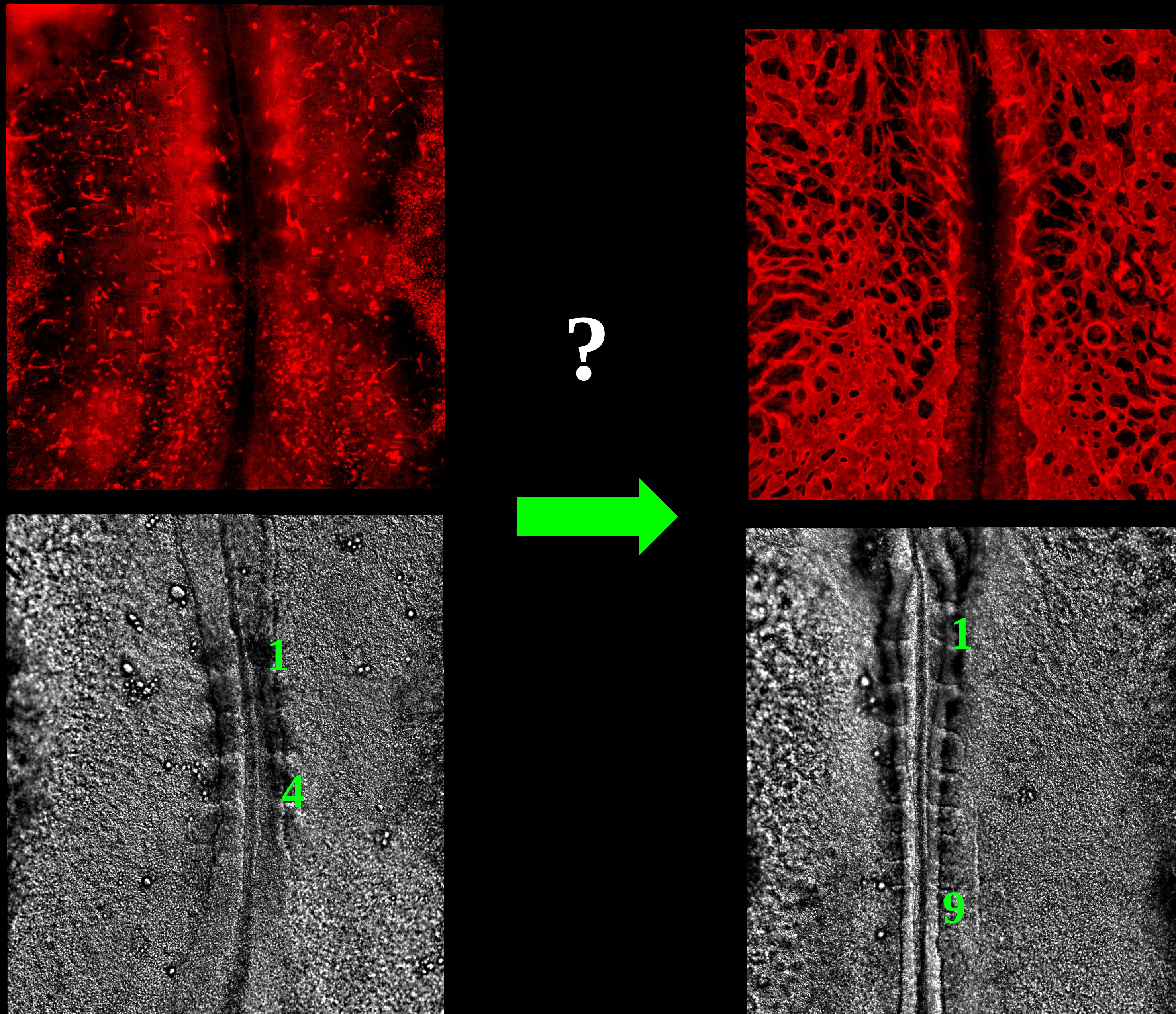
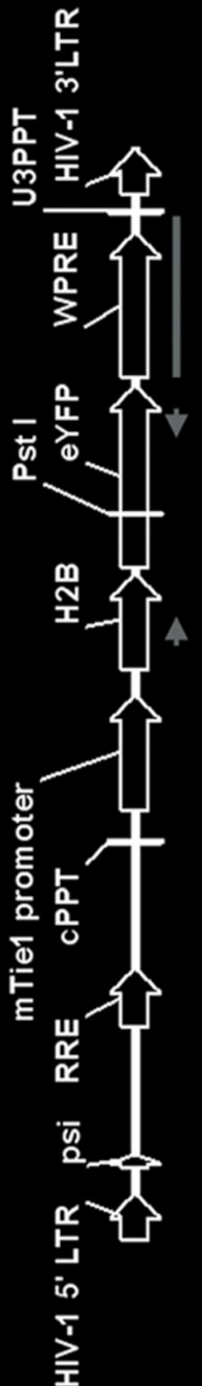
Biophysical aspects of vascular assembly.

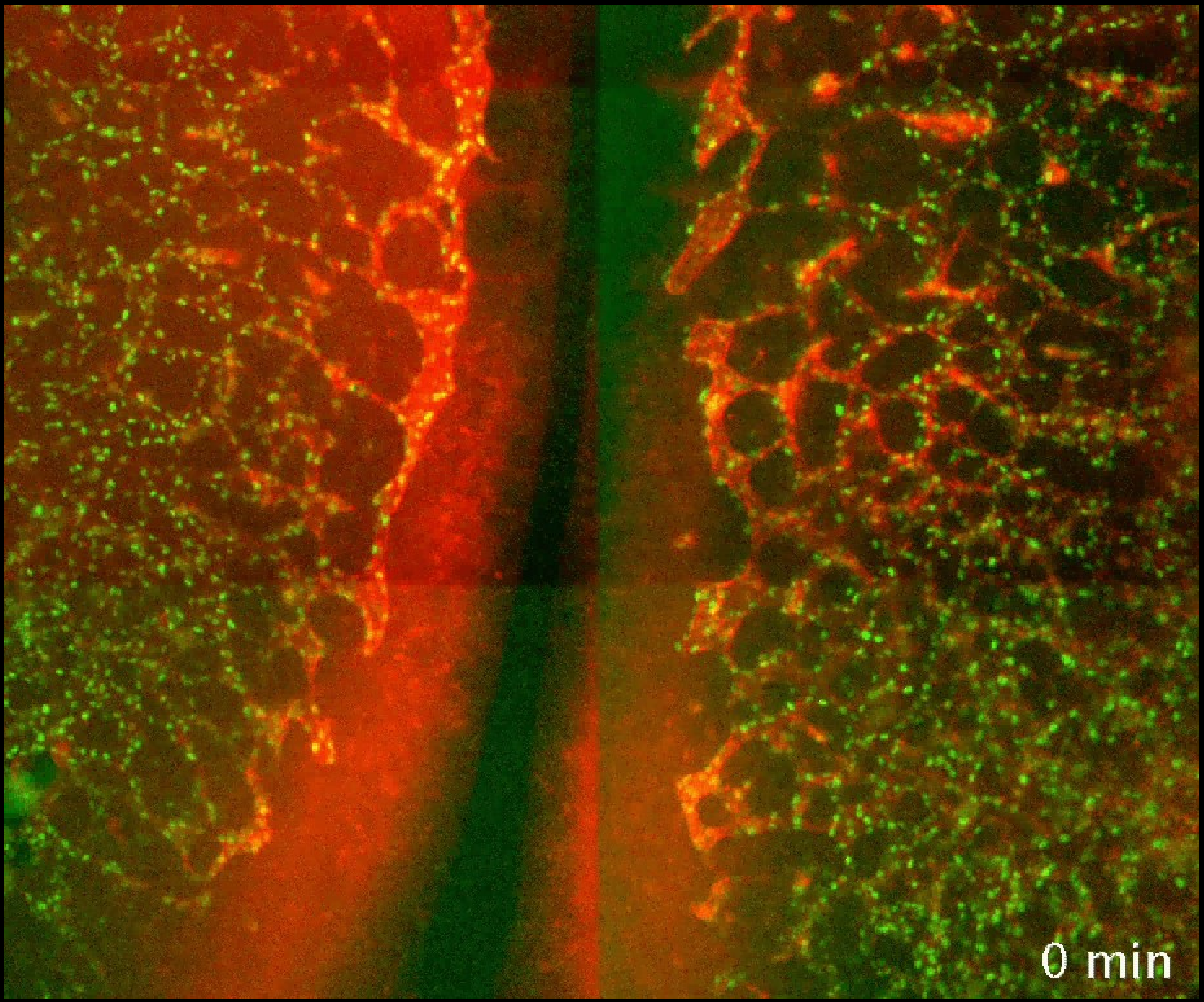


Vasculogenesis: emergence of the vascular plexus



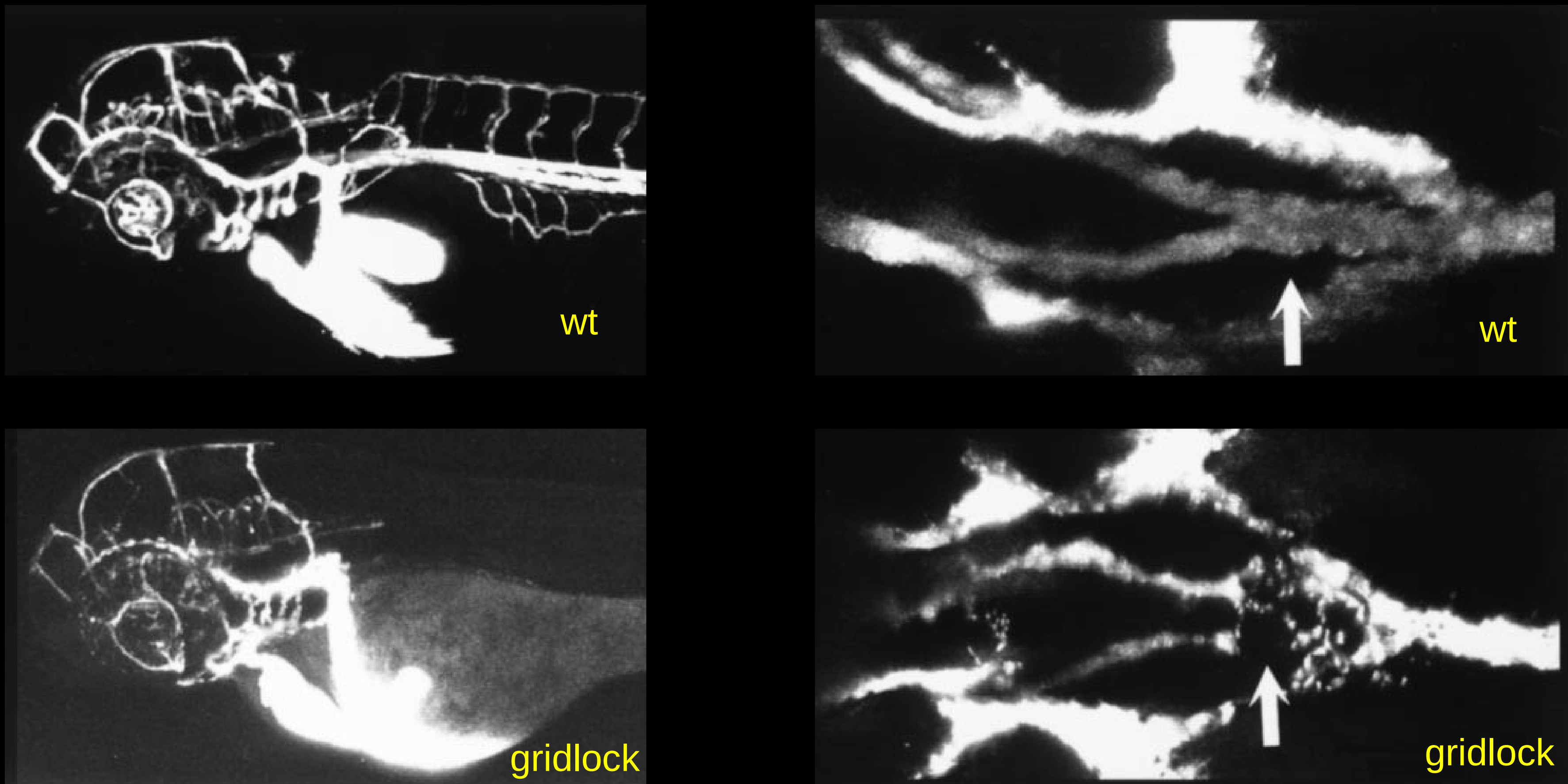
TIE1:H2B-YFP Transgenic Quail Embryos





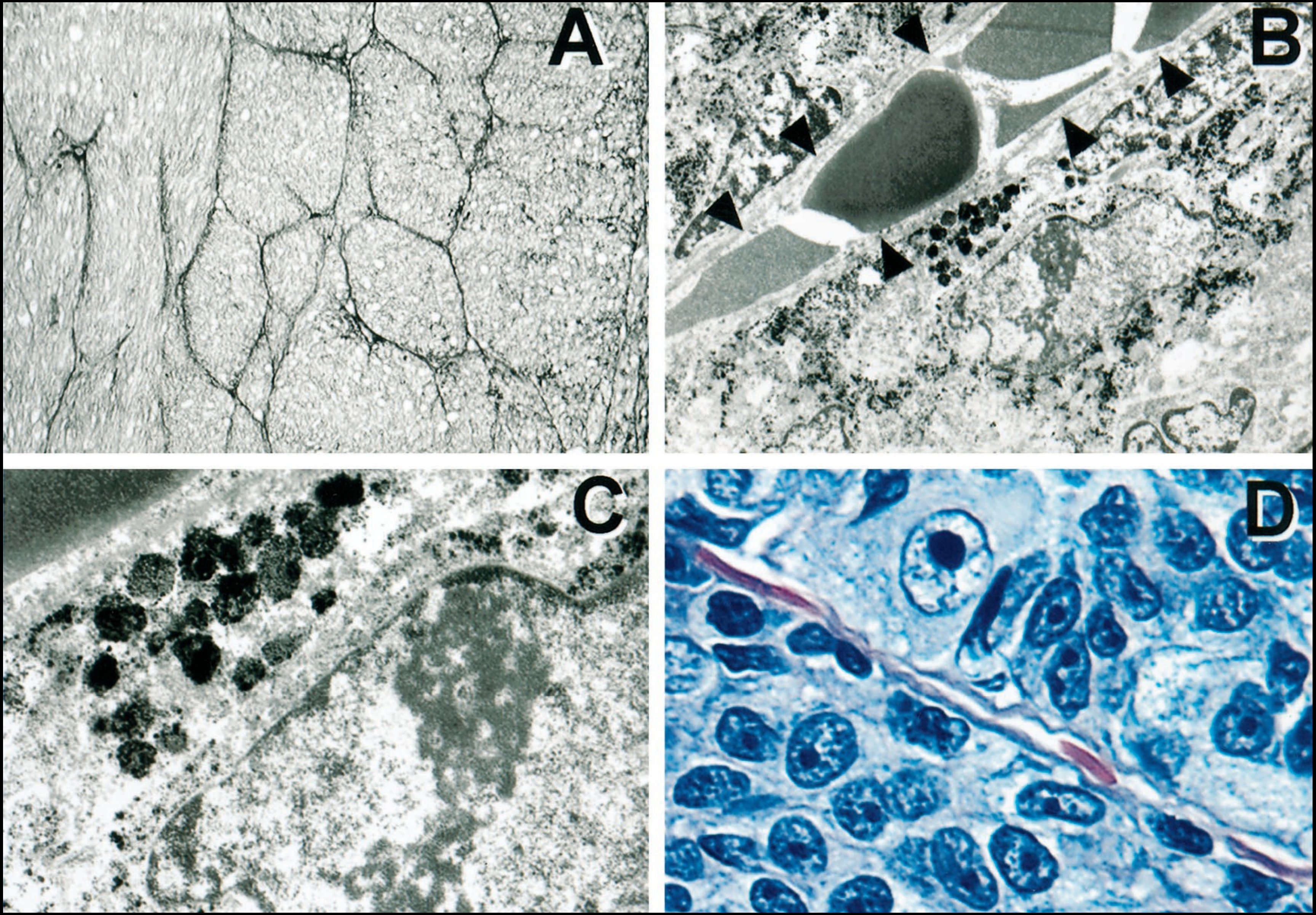
Sato et al, PLOS ONE 2010

Genetic hard-wiring in Zebrafish



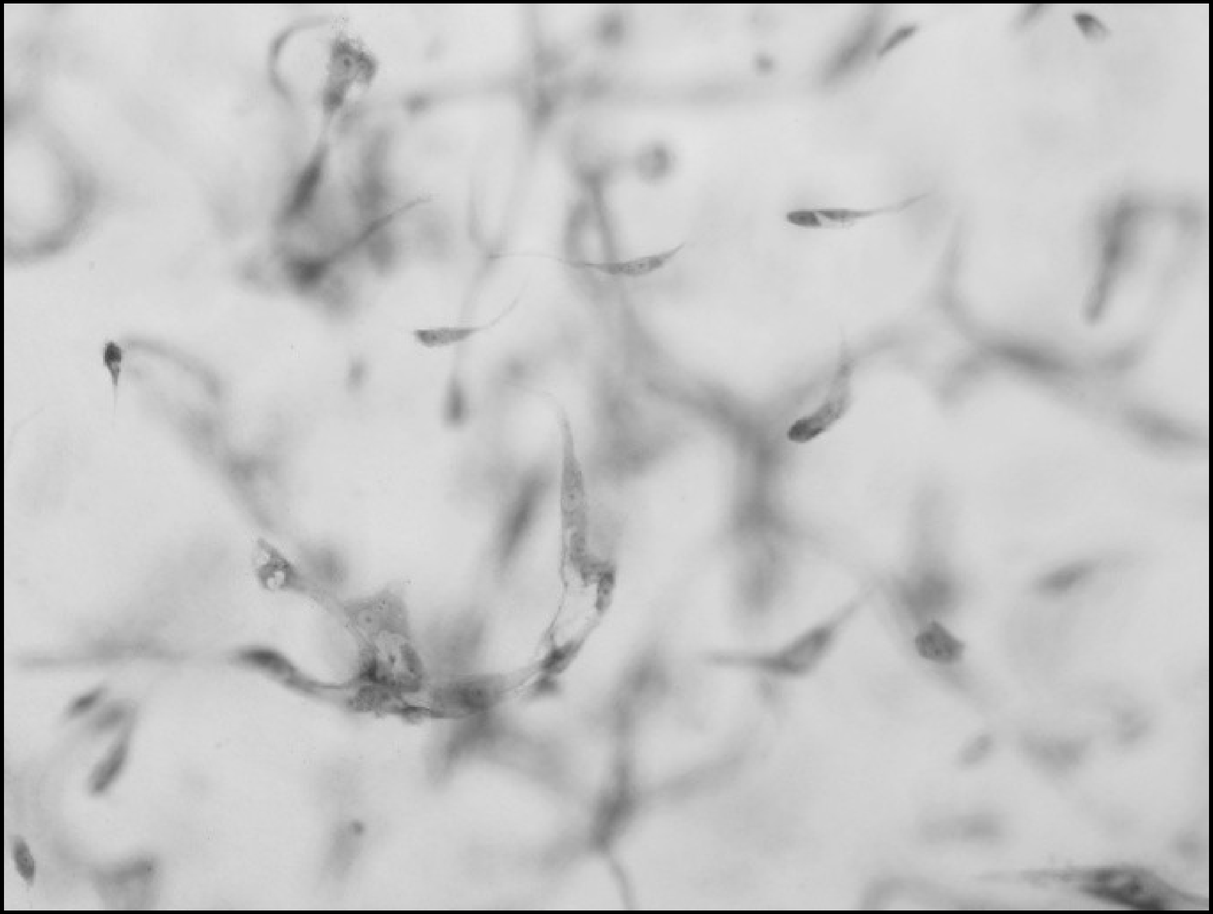
Weinstein, 1999

VASCULOGENIC MIMICRY AND TUMOUR-CELL PLASTICITY



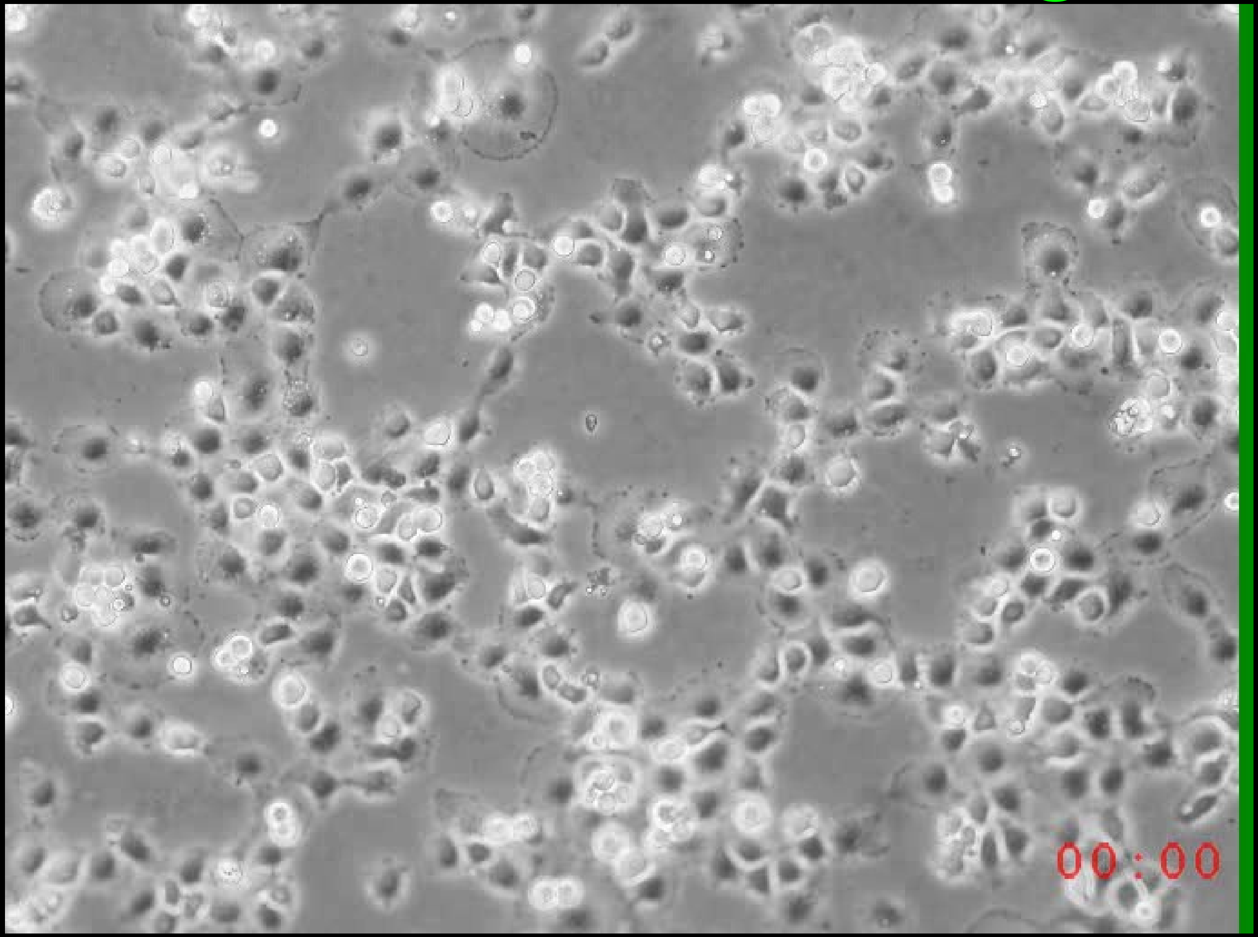
Mary J. C.Hendrix, Nat Rev Cancer ‘03

HUVECs in collagen I gel

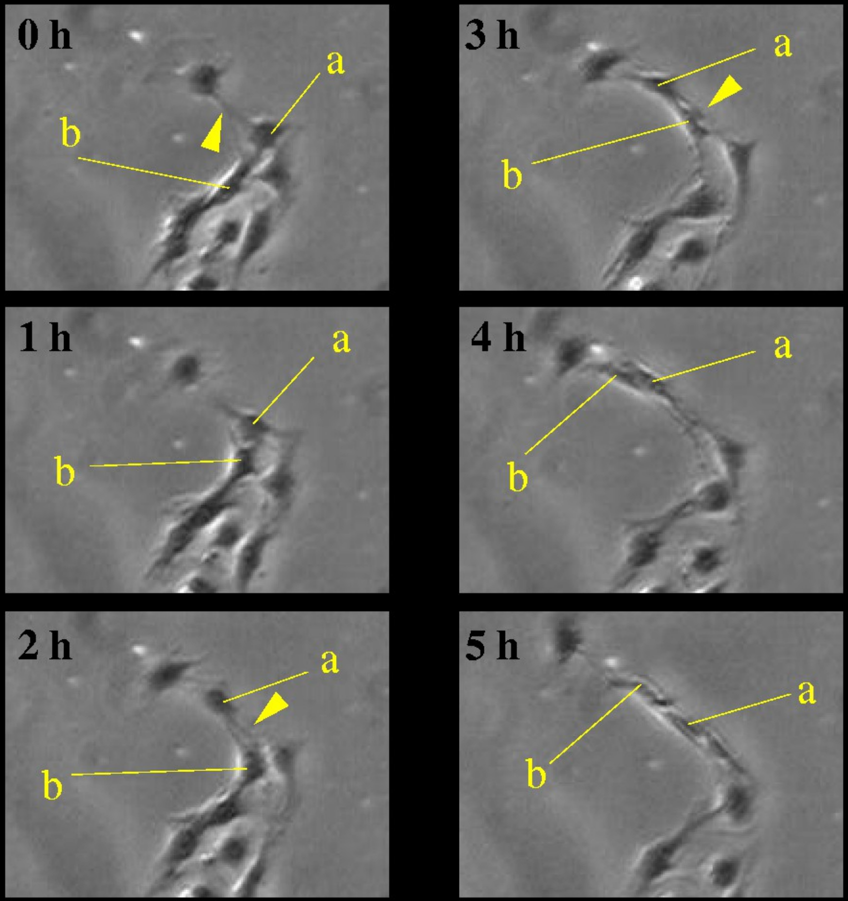


The patterning is an emergent (self-organized) process

HUVECs on Matrigel



Multicellular sprouts of C6 cells

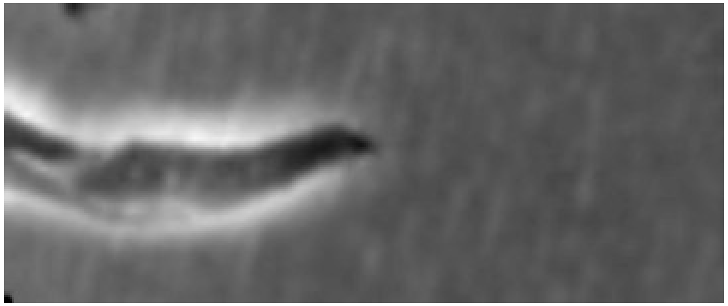


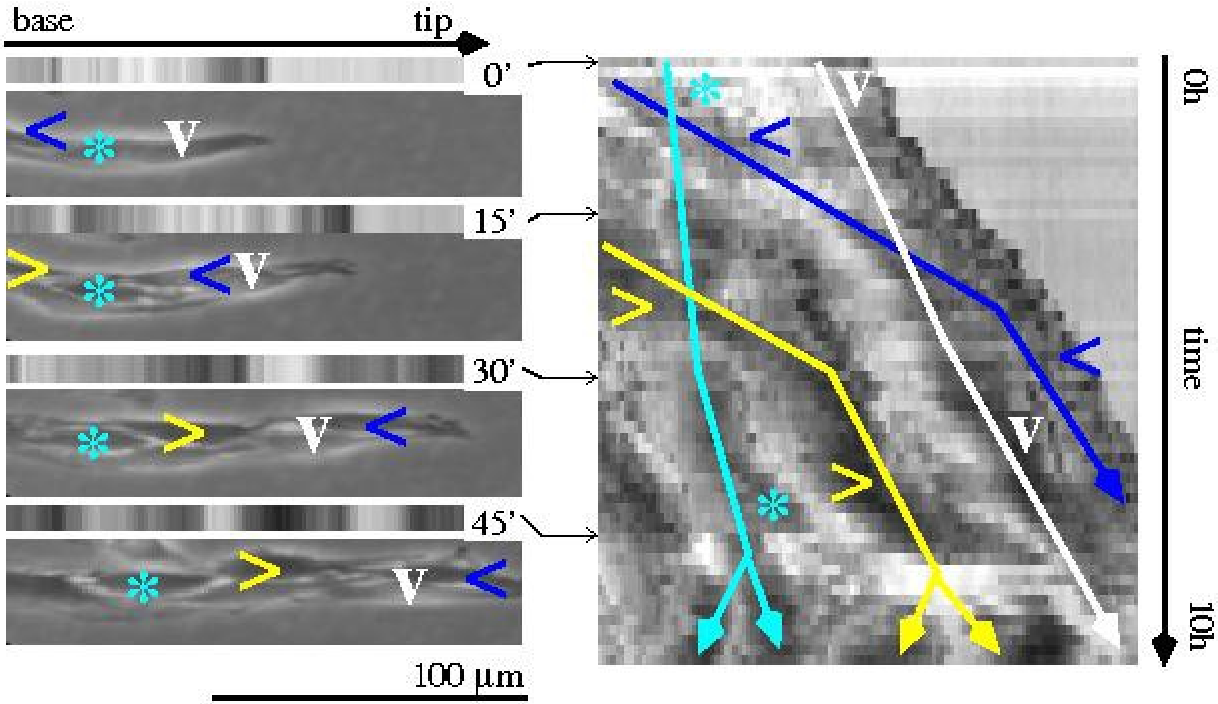
1. rigid substrate
2. Convection in medium

Szabo et al., PRL 2007

C6 cell culture

sprout formation

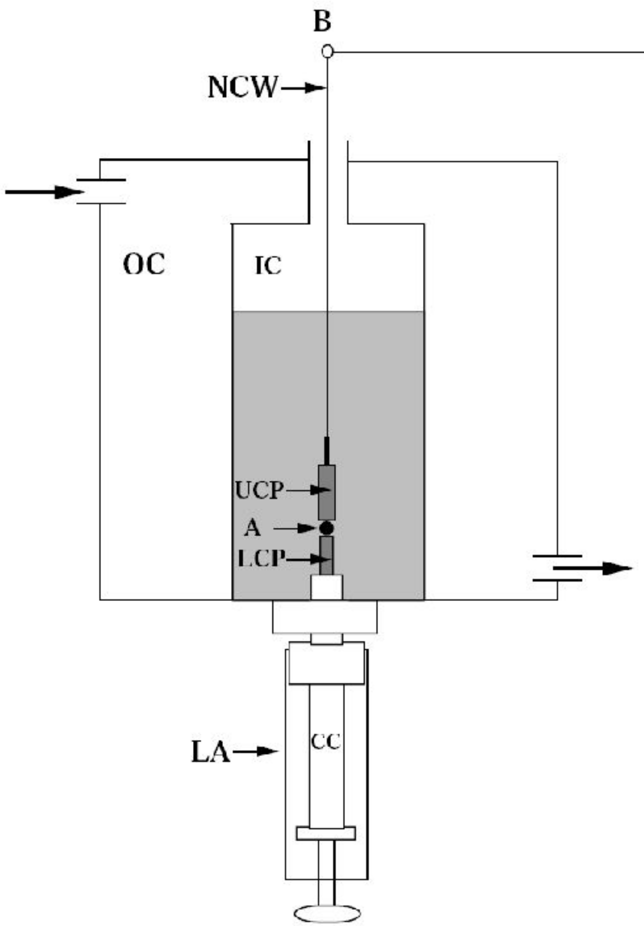


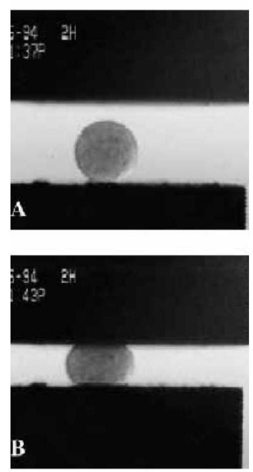


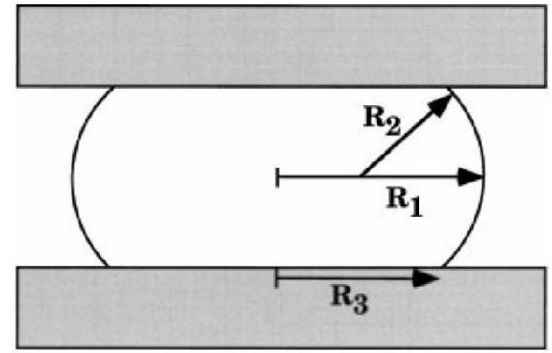
Biophysical Journal Volume 74 May 1998 2227–2234 2227

Viscoelastic Properties of Living Embryonic Tissues: a Quantitative Study

Gabor Forgacs,* Ramsey A. Foty,# Yinon Shafrir,§ and Malcolm S. Steinberg#







$$\frac{F_{eq}}{\pi R_3^2} = \sigma\left(\frac{1}{R_1} + \frac{1}{R_2}\right).$$

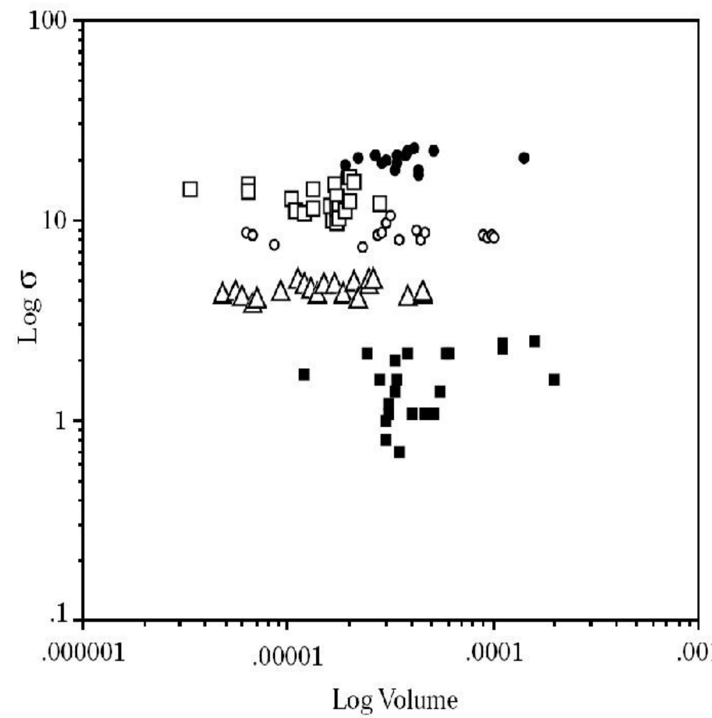
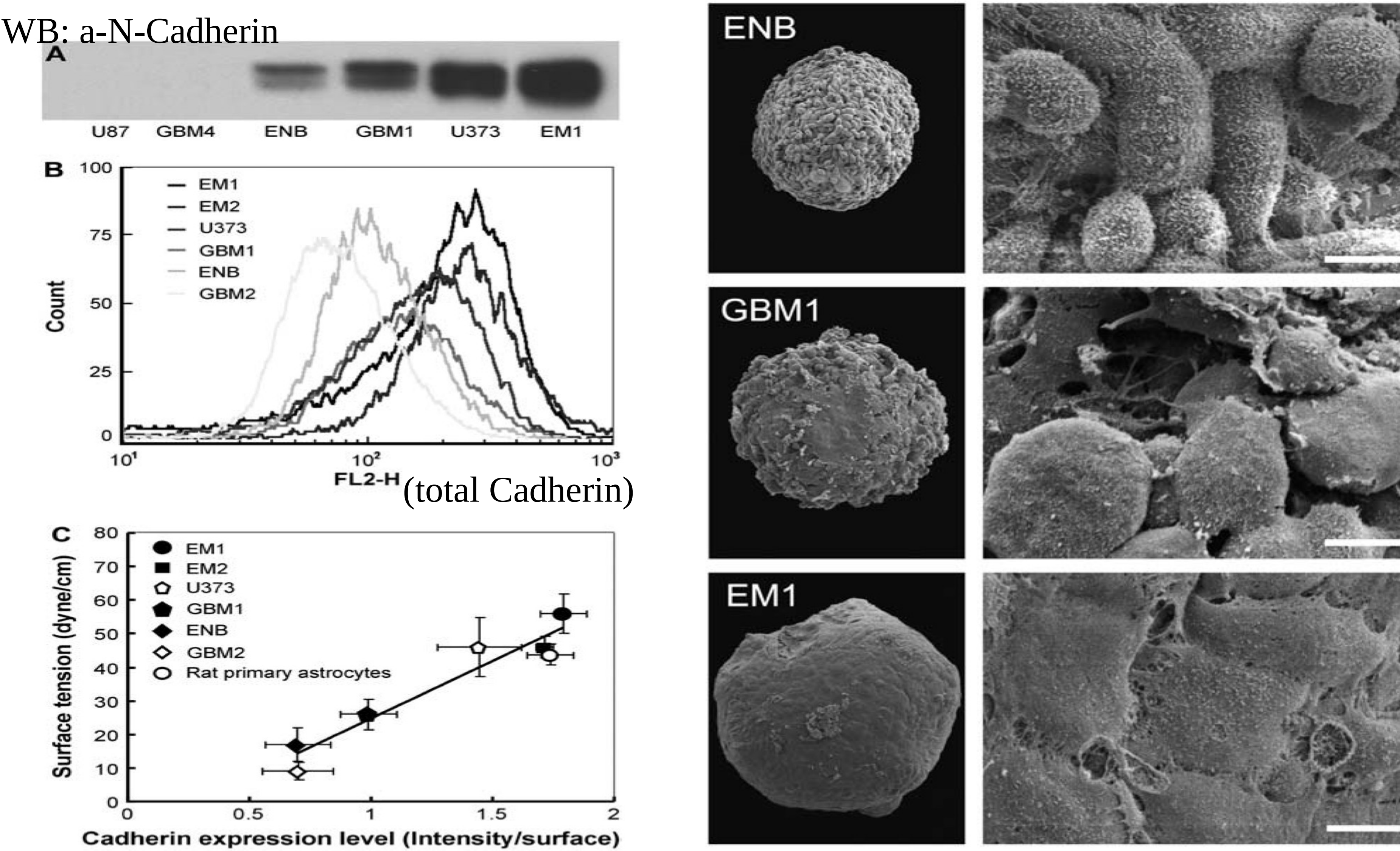


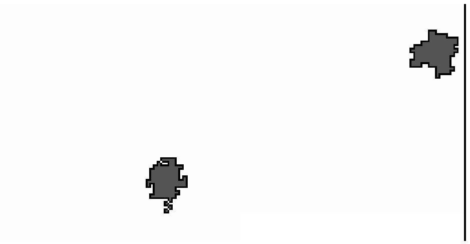
Fig. 7. Aggregate surface tensions are independent of their volume (● limb bud, □ pigmented retina, ○ heart, △ liver, ■ neural retina.).

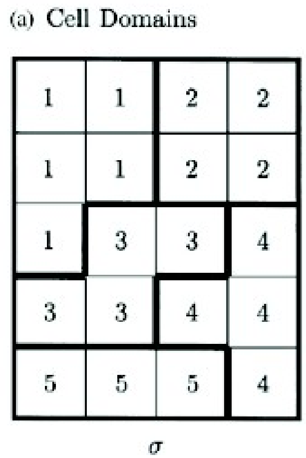
2708 Biophysical Journal Volume 91 October 2006 2708–2716

The Interplay of Cell-Cell and Cell-Matrix Interactions in the Invasive Properties of Brain Tumors

Balázs Hegedüs,*† Françoise Marga,* Károly Jakab,* Kathy L. Sharpe-Timms,‡ and Gabor Forgacs*§

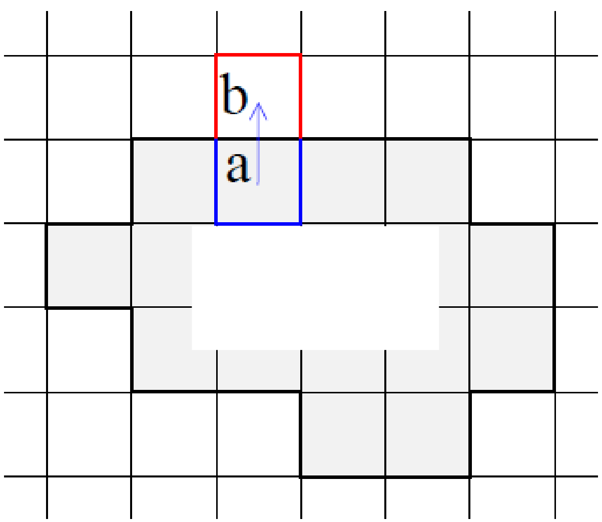




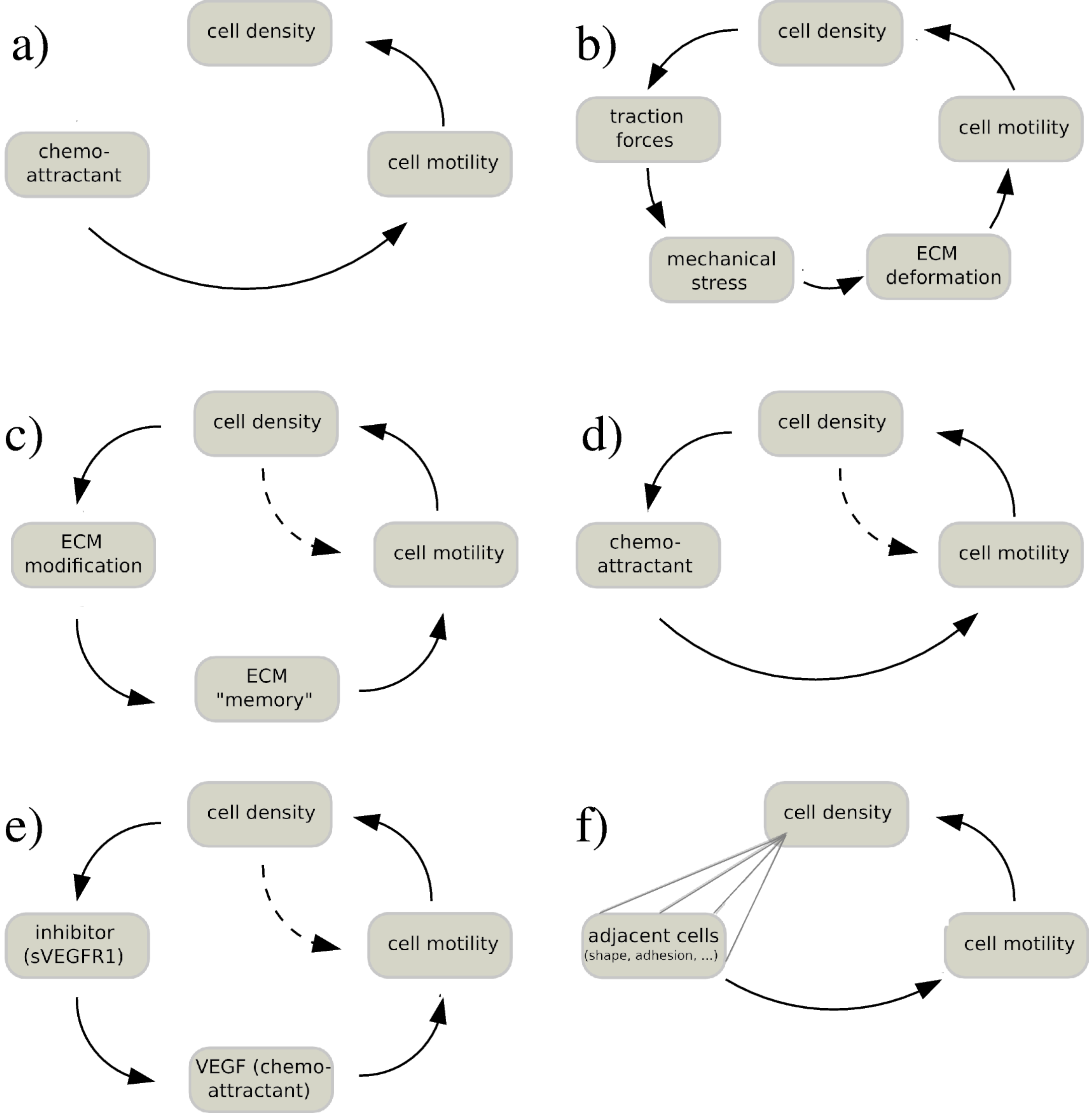


$$u = \sum_{<\mathbf{x},\mathbf{x}'>} J_{\sigma(\mathbf{x}),\sigma(\mathbf{x}')} + \lambda \sum_{i=1}^{N} \delta A_i^2$$

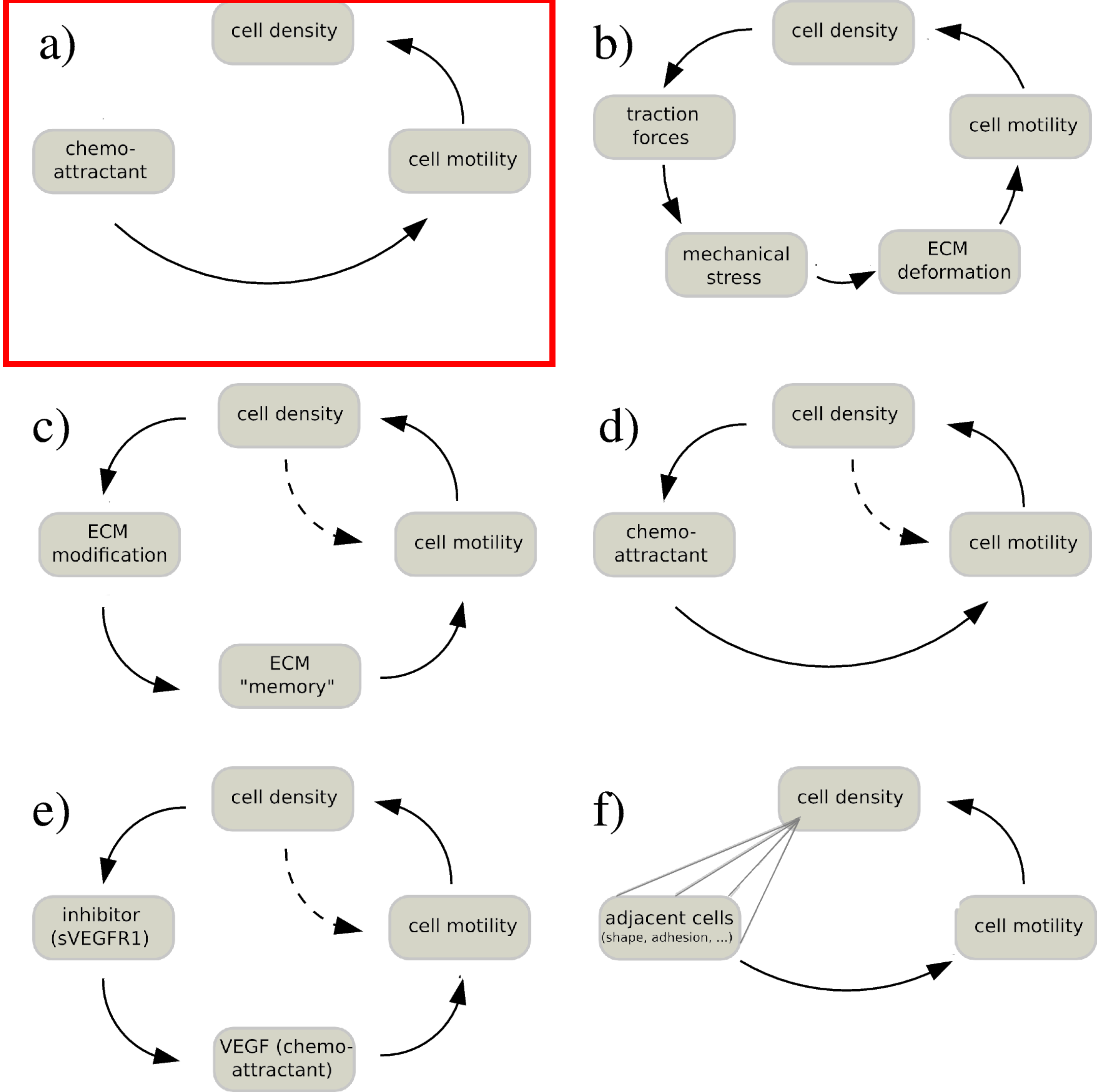
$$J_{i,j} = \begin{cases} 0, & \text{for } i = j \\ \alpha, & \text{for } ij > 0 \text{ and } i \neq j \text{ (cell-cell boundary)} \\ \beta, & \text{for } ij = 0 \text{ and } i \neq j \text{ (free cell boundary).} \end{cases}$$



$$\ln p(\mathbf{a} \to \mathbf{b}) = \min[0, -\Delta u(\mathbf{a} \to \mathbf{b})$$



a)
cell density
chemo-
attractant
cell motility
b)
cell density
traction
forces
cell motility
mechanical
stress
ECM
deformation
c)
cell density
ECM
modification
cell motility
ECM
"memory"
d)
cell density
chemo-
attractant
cell motility
e)
cell density
inhibitor
(sVEGFR1)
cell motility
VEGF (chemo-
attractant)
f)
cell density
adjacent cells
(shape, adhesion, ...)
cell motility


a)
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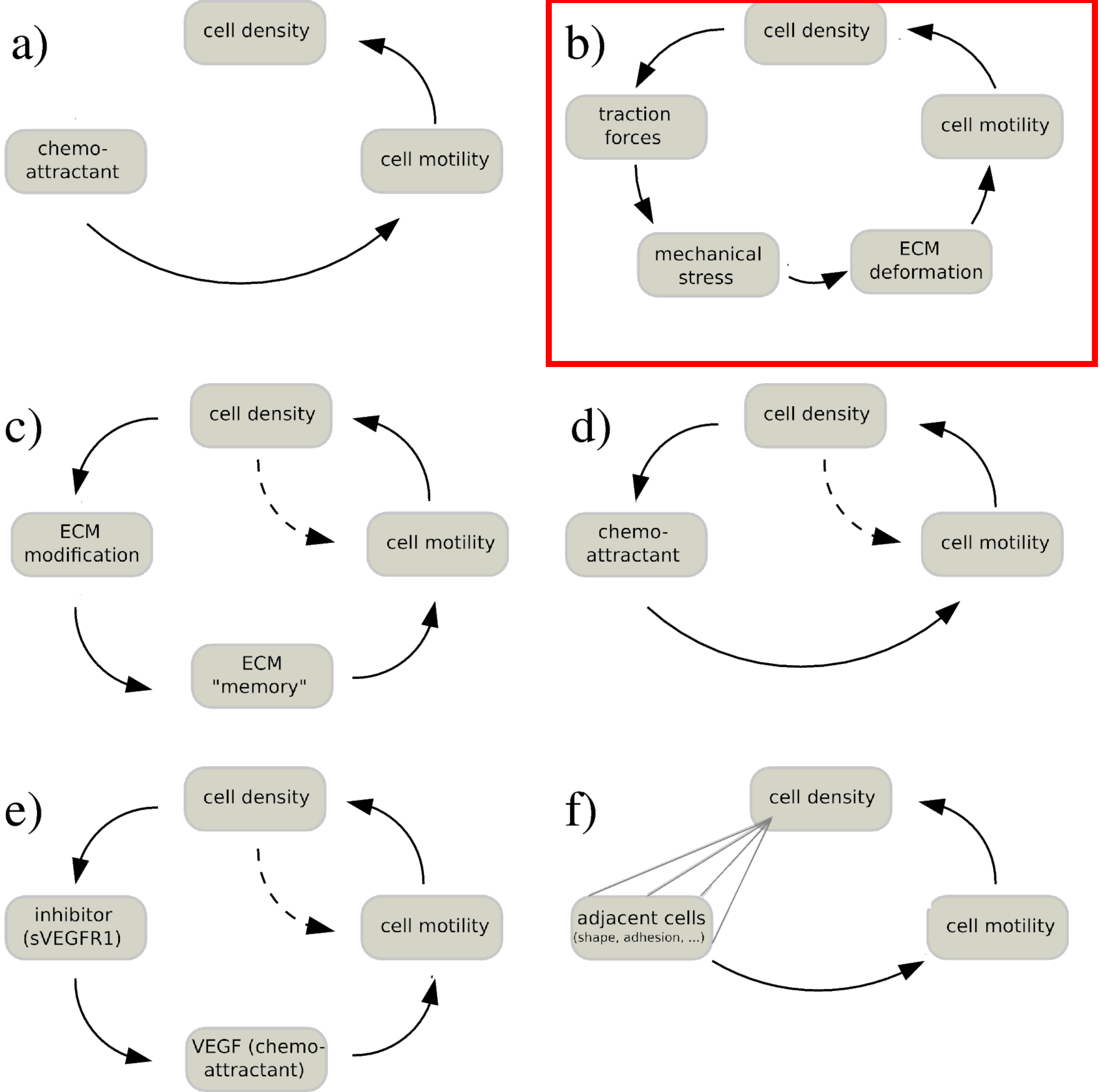
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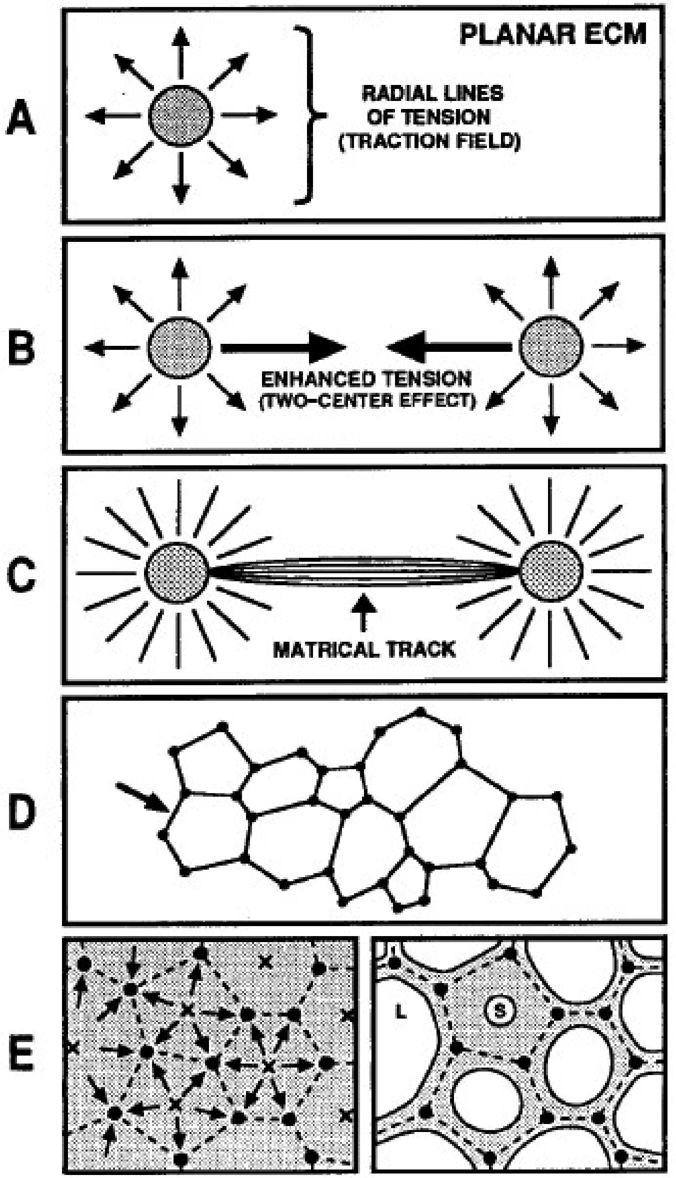
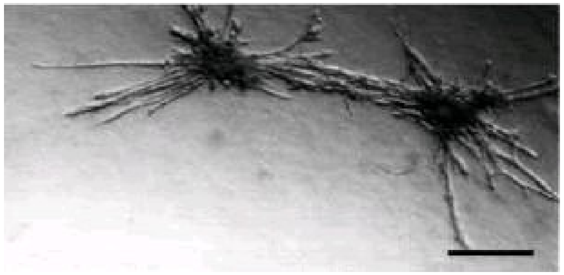
(shape, adhesion, ...)
cell motility

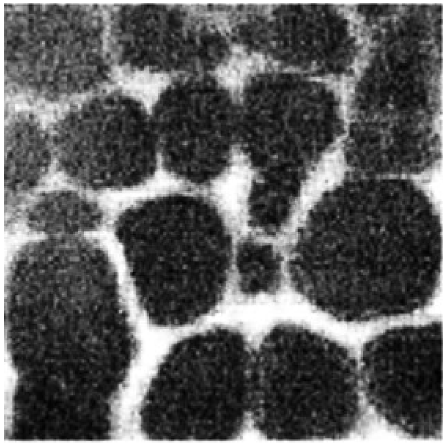
Correlation between ECM structure & cell motion



Vernon et al., 1995



A.K. Harris et al. ’80
Sawhney JCB ’02



Murray, Vernon, Manoussaki, ‘90

Correlation between cell motion and ECM patterns.

Mechanical patterning (Murray et al '80):

$$\partial_t n = -\nabla \cdot J_{\mathrm{cell}}$$

$$\partial_t \rho = -\nabla \cdot J_{\mathrm{ECM}}$$

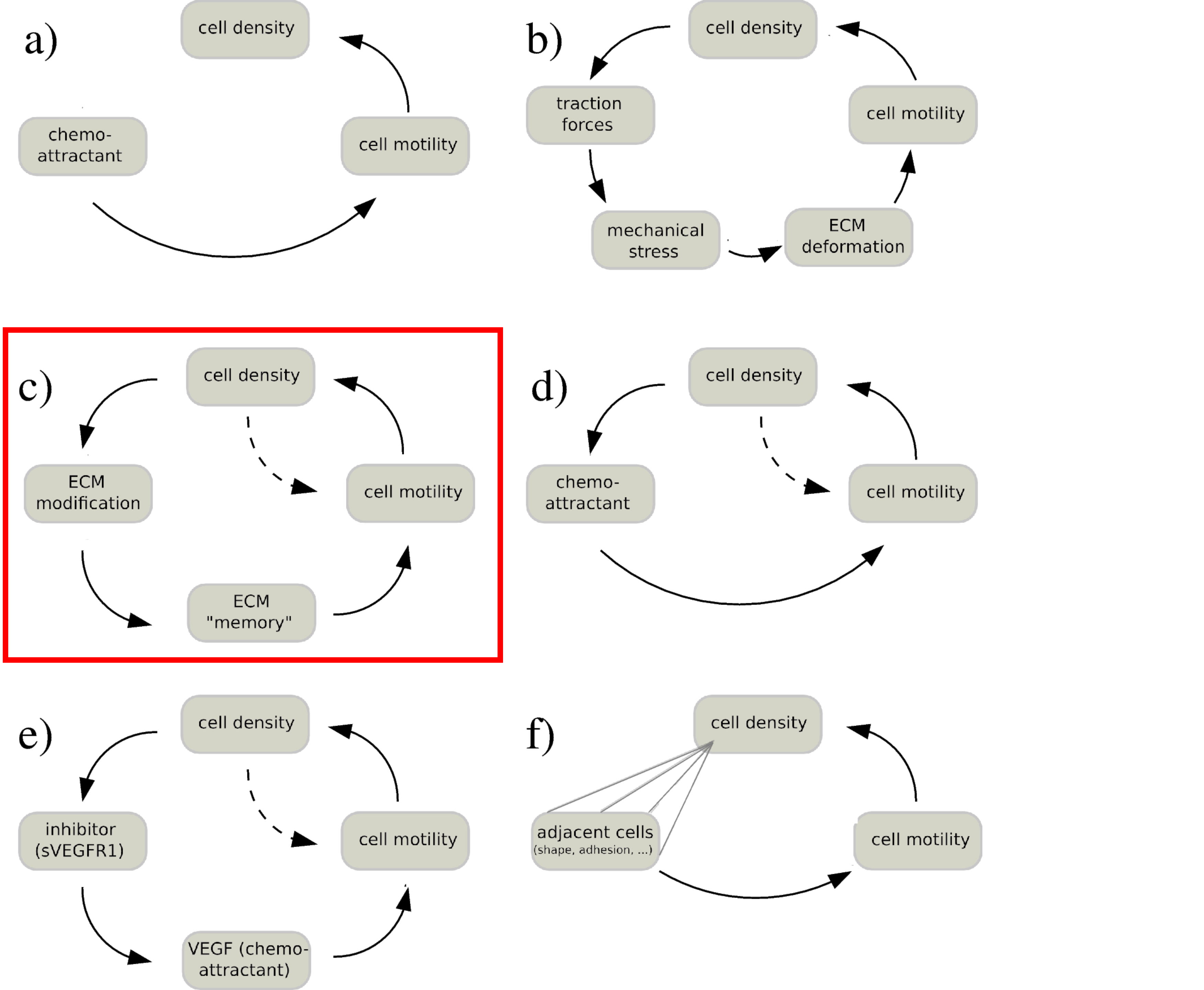
$$J_{\mathrm{ECM}} = \rho v$$

$$J_{\mathrm{cell}} = n v - D(\varepsilon)\nabla n$$

$$\nabla \cdot (\sigma_{\mathrm{ECM}} + \sigma_{\mathrm{cells}}) = F_{\mathrm{ext}}$$

$$\sigma_{\mathrm{ECM}} = \mu_1 \partial_t \varepsilon + \mu_2 (\mathrm{Tr}\partial_t \varepsilon) I + \frac{E}{1+\nu}\left[\varepsilon + \frac{\nu}{1-2\nu}(\mathrm{Tr}\varepsilon) I\right]$$

$$\varepsilon = \frac{\partial_x u + (\partial_x u)^T}{2}$$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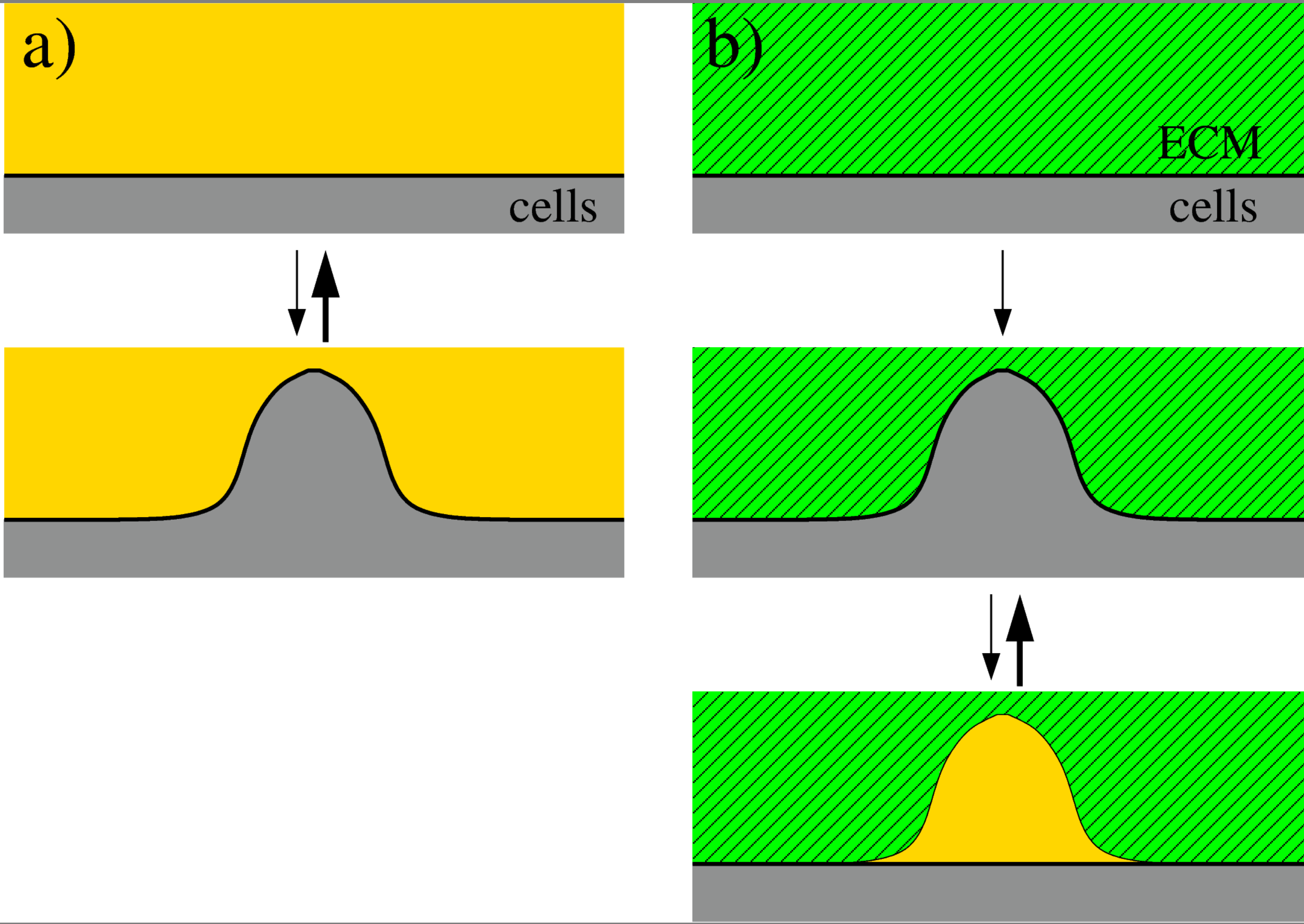
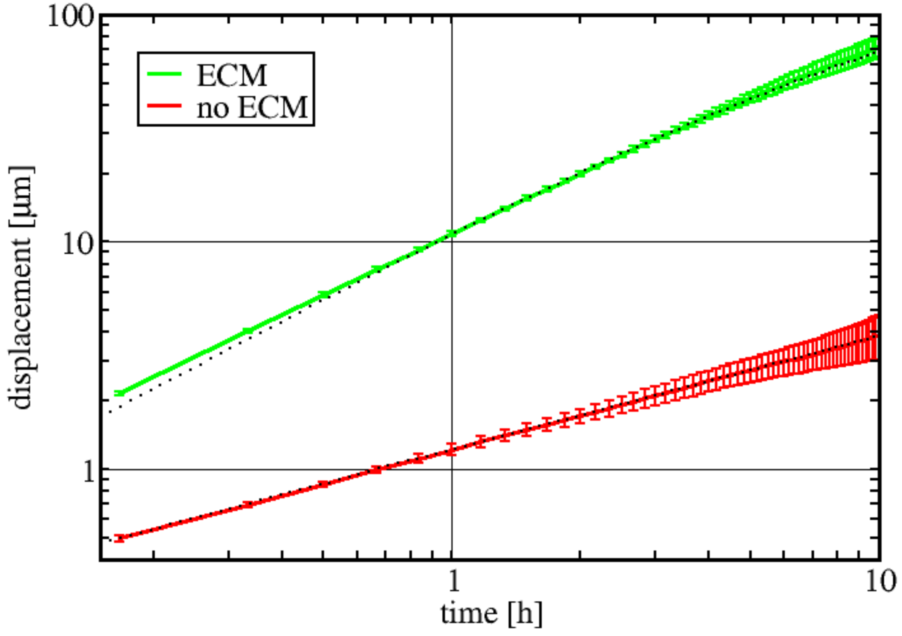
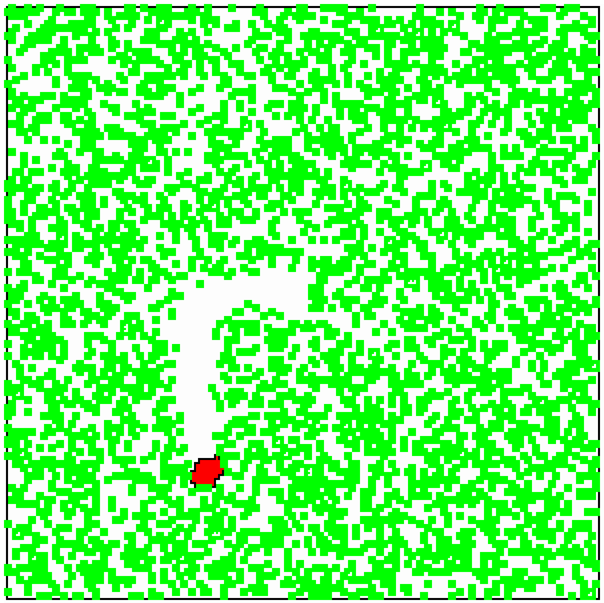
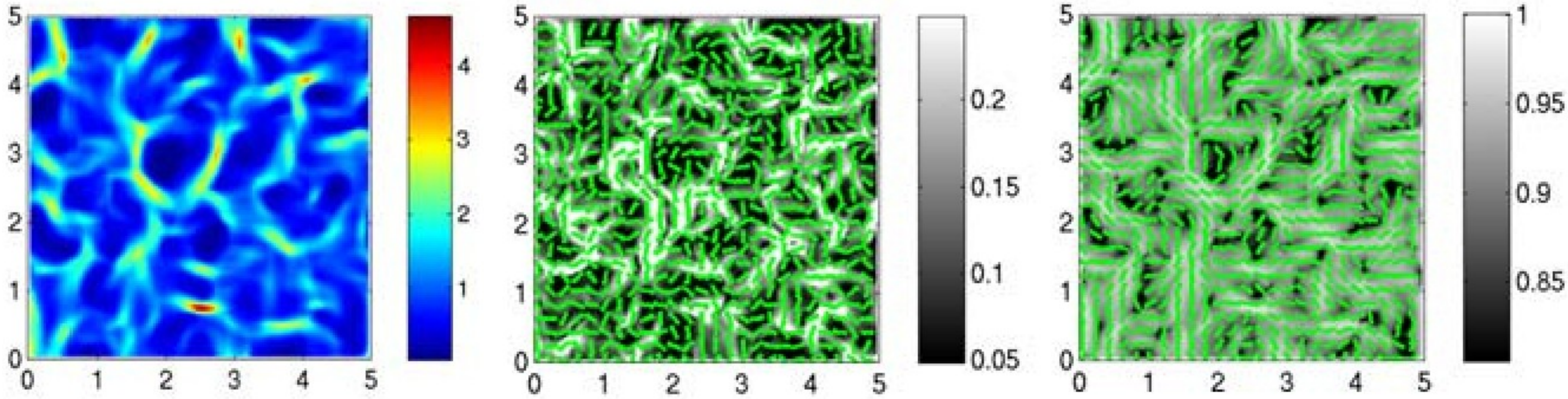
(shape, adhesion, ...)
cell motility


a)
cells
b)
ECM
cells

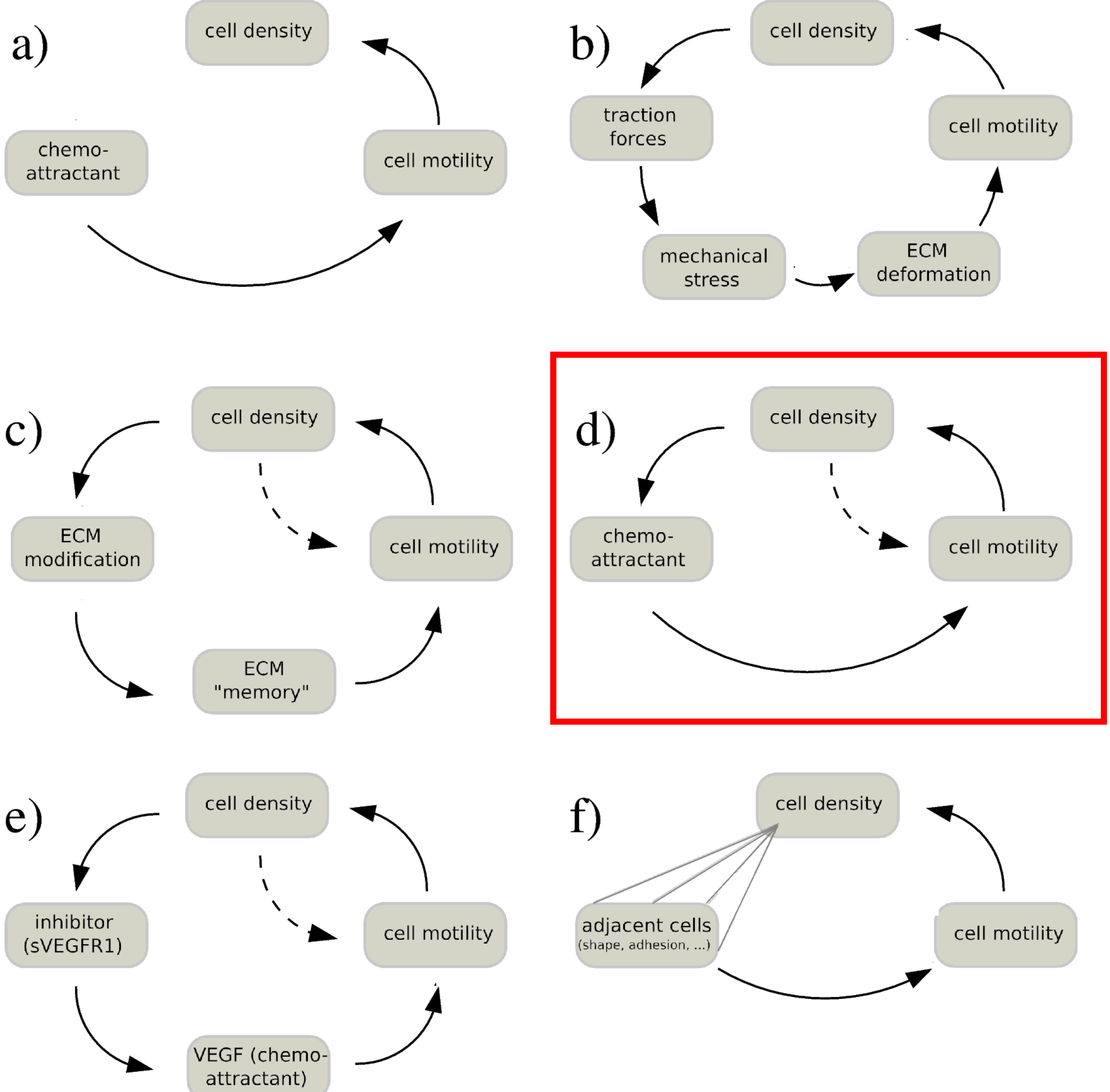




Szabo et al 2012



Painter 2009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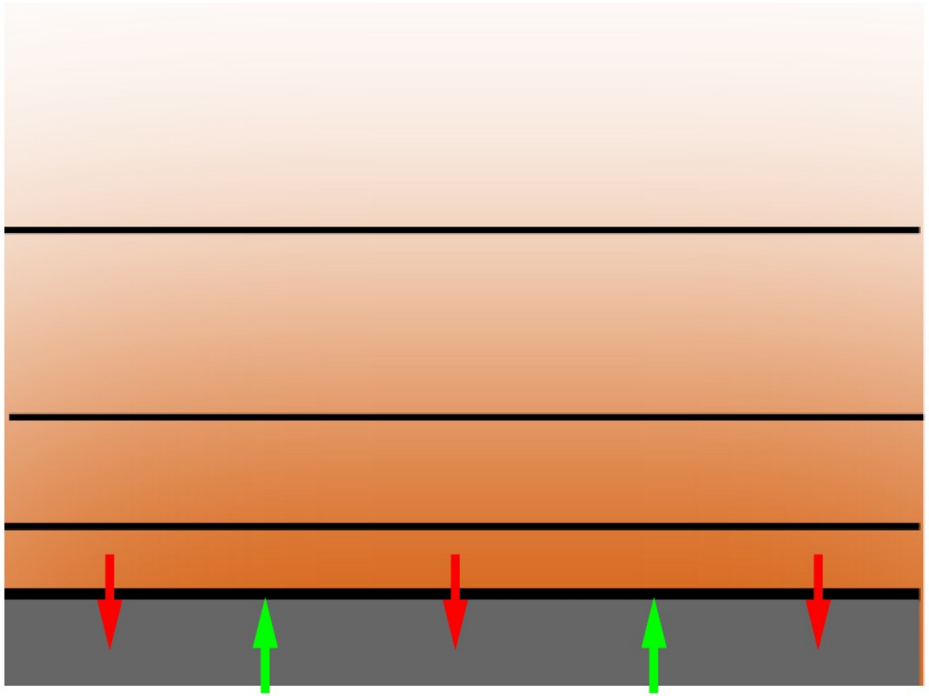
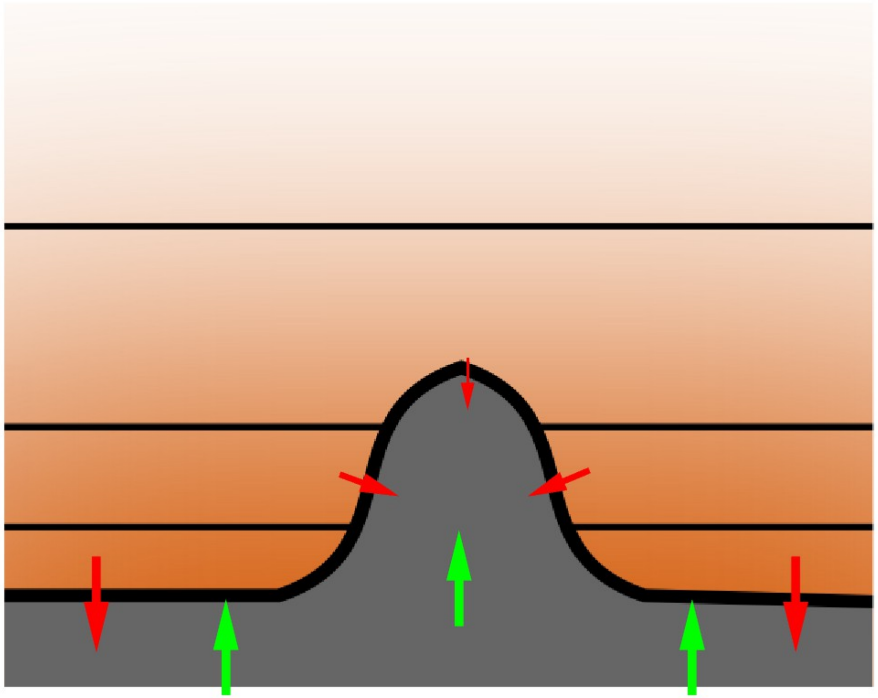
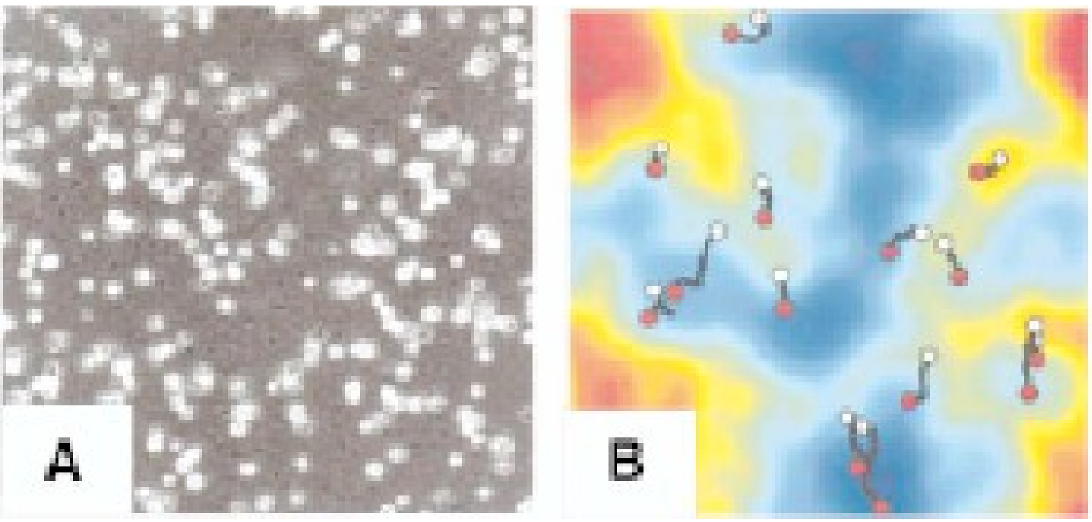
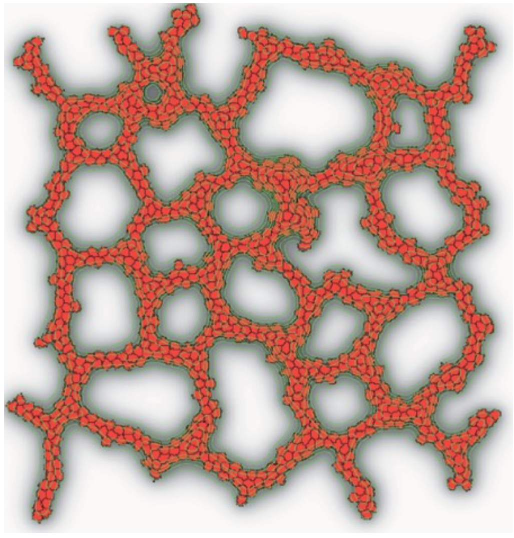


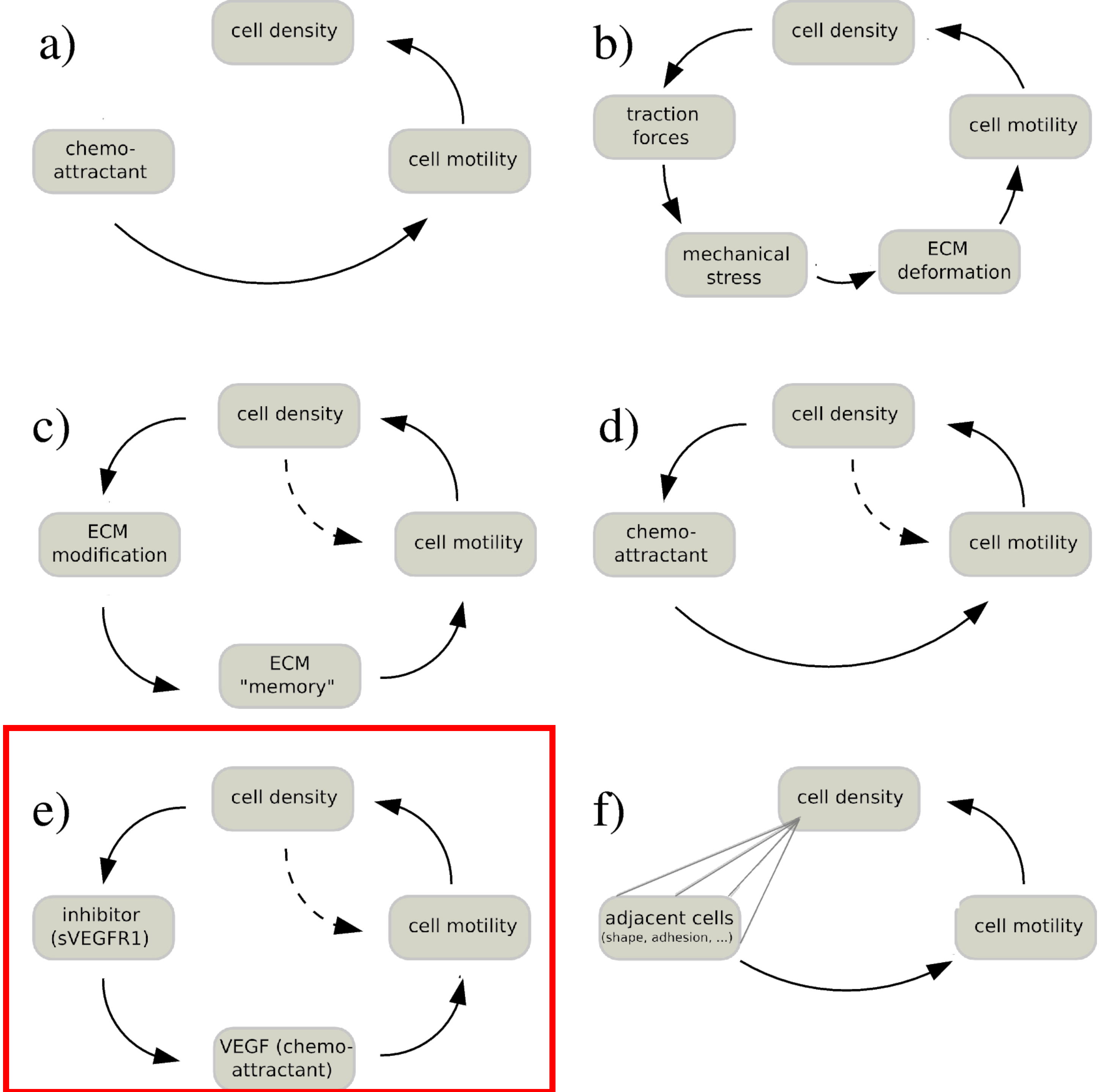






Gamba et al., 2003

Merks et al., 2008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adjacent cells
(shape, adhesion, ...)
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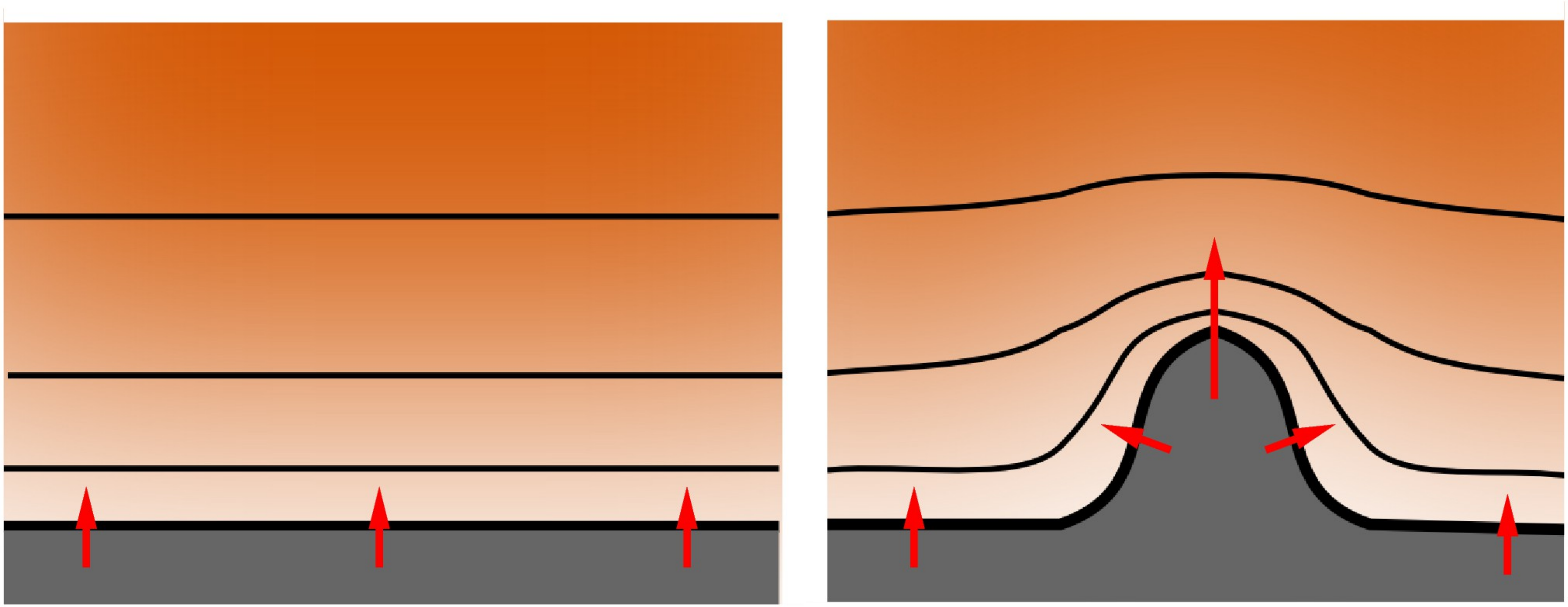
Mullins – Sekerka instability for tip splitting growth



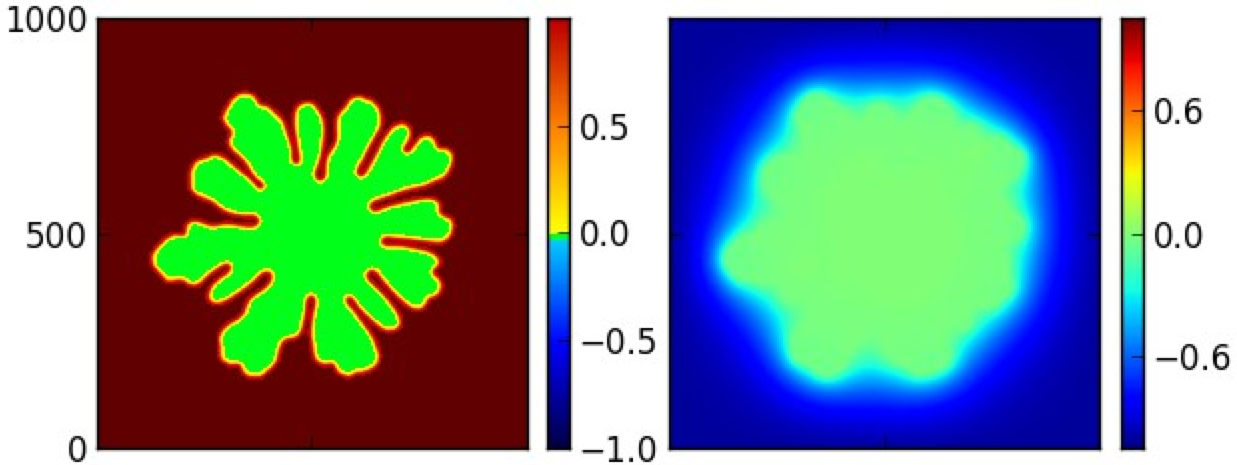
$$\partial_t c = D\nabla^2 c$$

$$v_n \sim n\nabla c$$

Phase field model for crystal growth:

$$\frac{\partial \phi}{\partial t} = \frac{\phi(1-\phi)}{5 * 10^{-4}}[\phi - \frac{1}{2} + 28.875 u \phi(1-\phi)] + \frac{\nabla^2 \phi}{20}$$

$$\frac{\partial u}{\partial t} = \nabla^2 u - \frac{30}{0.55}\phi^2(1-\phi)^2\frac{\partial \phi}{\partial t}$$



Phase field model for crystal growth: $$\frac{\partial \phi}{\partial t} = \frac{\phi(1-\phi)}{5*10^{-4}}[\phi - \frac{1}{2} + 28.875u\phi(1-\phi)] + \frac{\nabla^2 \phi}{20}$$

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Phase field model for vascular growth:

$$\frac{\partial \phi}{\partial t} = \alpha\phi(1-\phi)\left(\phi - \frac{1}{2} + \mu\Big([V] - [V]_{crit}\Big)\phi(1-\phi)\right) + D_\phi \nabla^2 \phi$$

$$[R^*] + [V] = [V]_0$$

$$\begin{aligned}\partial_t[V] = -\partial_t[R^*] &= -k_{on}[V][R] + k_{off}[R^*] + \tau_{R^*}[R^*] \\ \partial_t[R] &= -k_{on}[V][R] + k_{off}[R^*] - \tau_R[R] + \alpha_R\phi + D_R\nabla^2[R]\end{aligned}$$

Phase field model for crystal growth: $$\frac{\partial \phi}{\partial t} = \frac{\phi(1-\phi)}{5 * 10^{-4}}[\phi - \frac{1}{2} + 28.875u\phi(1-\phi)] + \frac{\nabla^2 \phi}{20}$$

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Phase field model for vascular growth:

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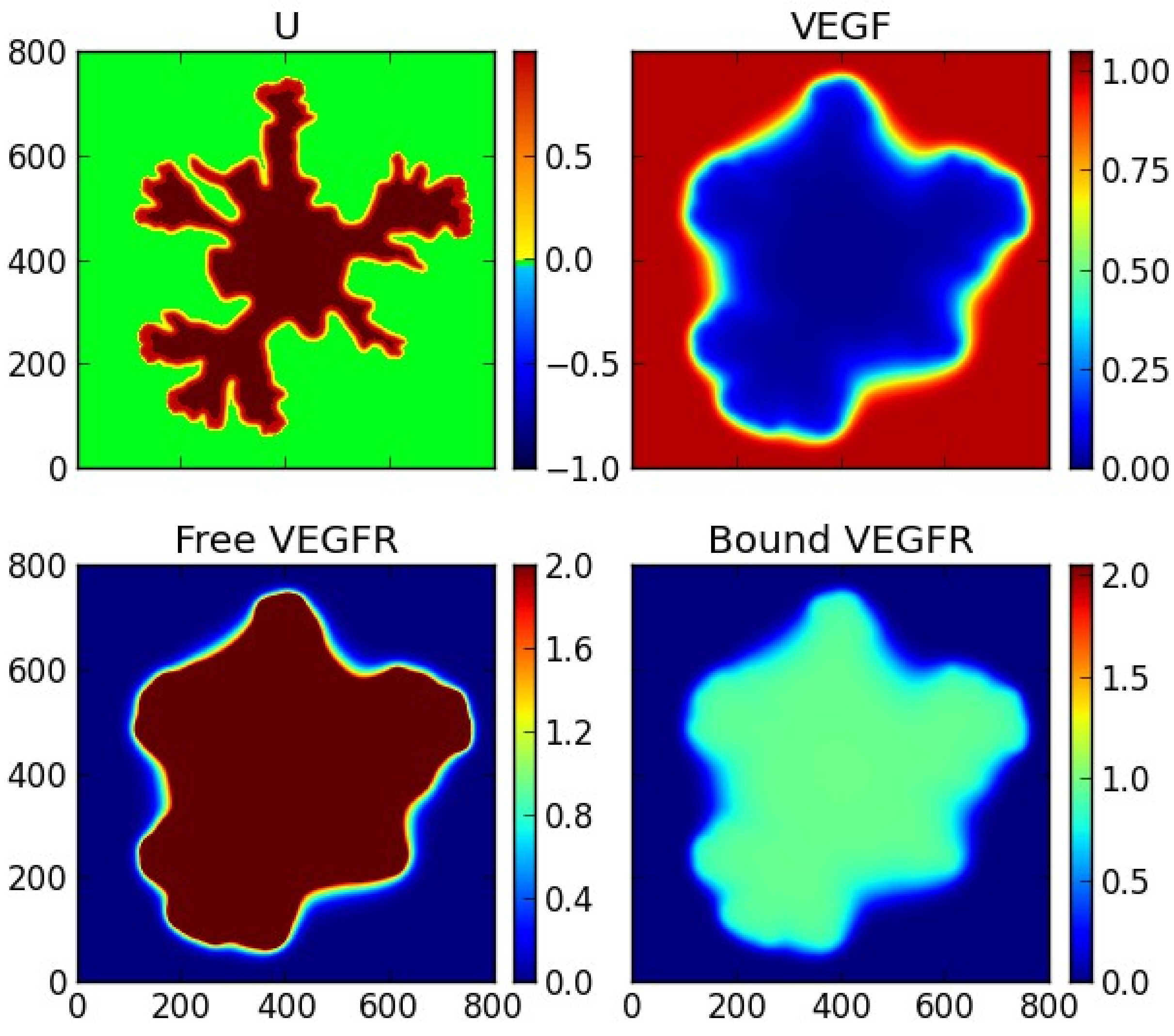
Equilibrium:

$$K = \frac{k_{on}}{k_{off}} \qquad k_{on}[R][V] = k_{off}[R^*] \qquad [R^*] = \frac{K[R]V_0}{1 + K[R]}$$

$$\partial_t[R^*] = -\partial_t[V] = \frac{KV_0}{(1+K[R])^2}\partial_t[R]$$

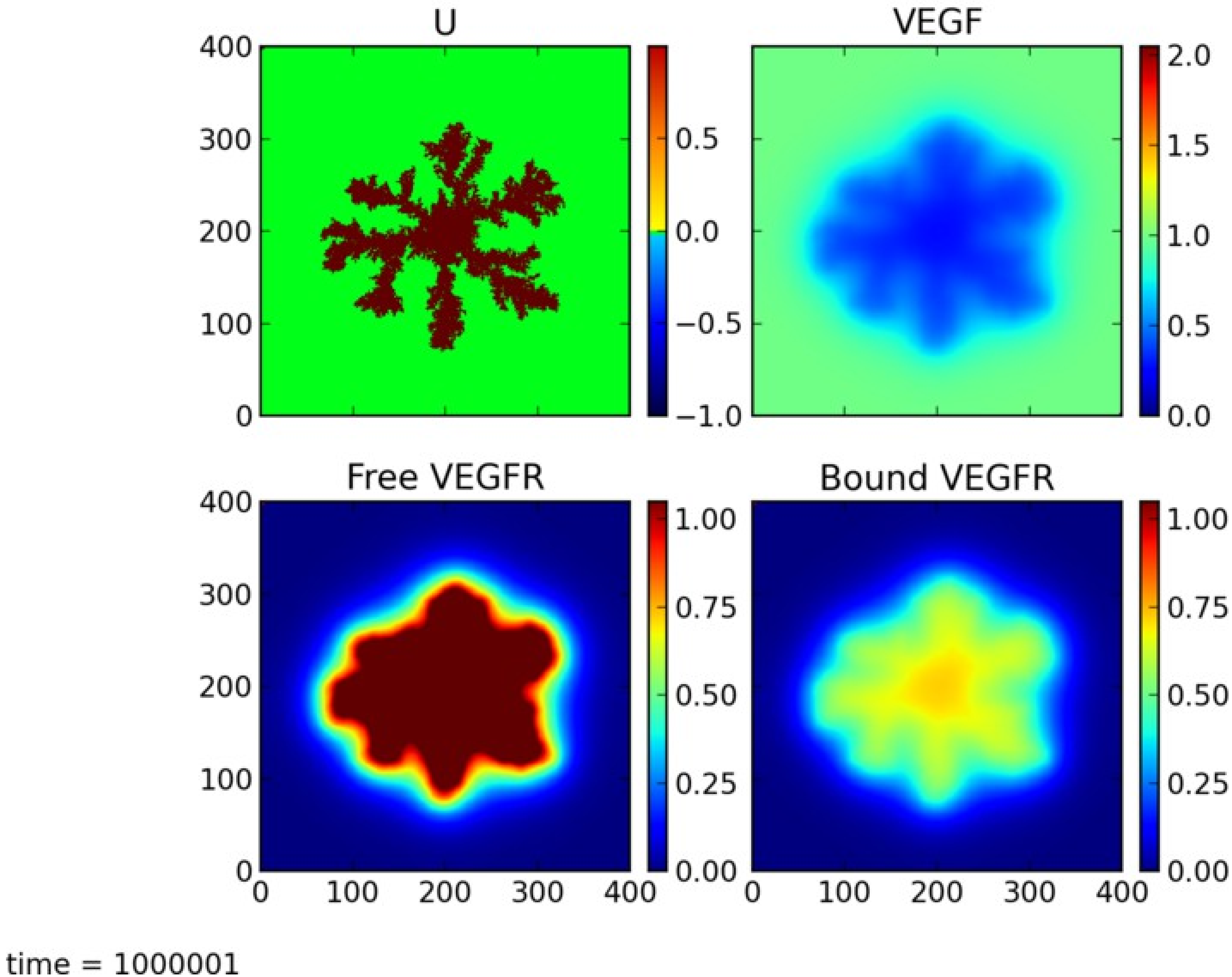
$$\partial_t[R] = \frac{D_R\nabla^2[R] + \alpha_R\phi - \tau_R[R] - \tau_{R^*}[R^*]}{1 + \frac{KV_0}{(1+K[R])^2}}$$

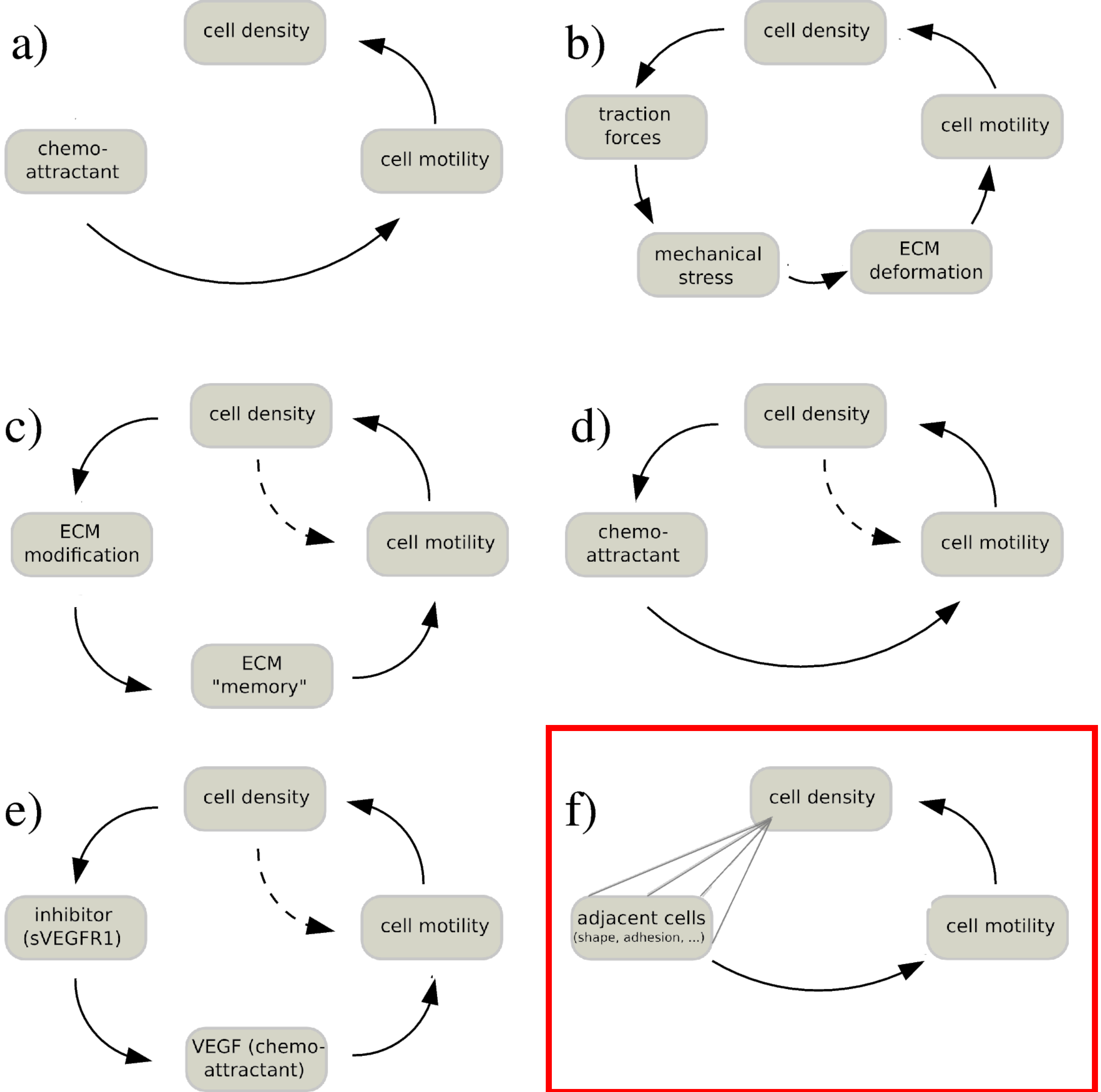
Phase field model for vascular growth:



time = 80001

Discrete (lattice) model for vascular growth:




a)
cell density
chemo-attractant
cell motility
b)
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inhibitor (sVEGFR1)
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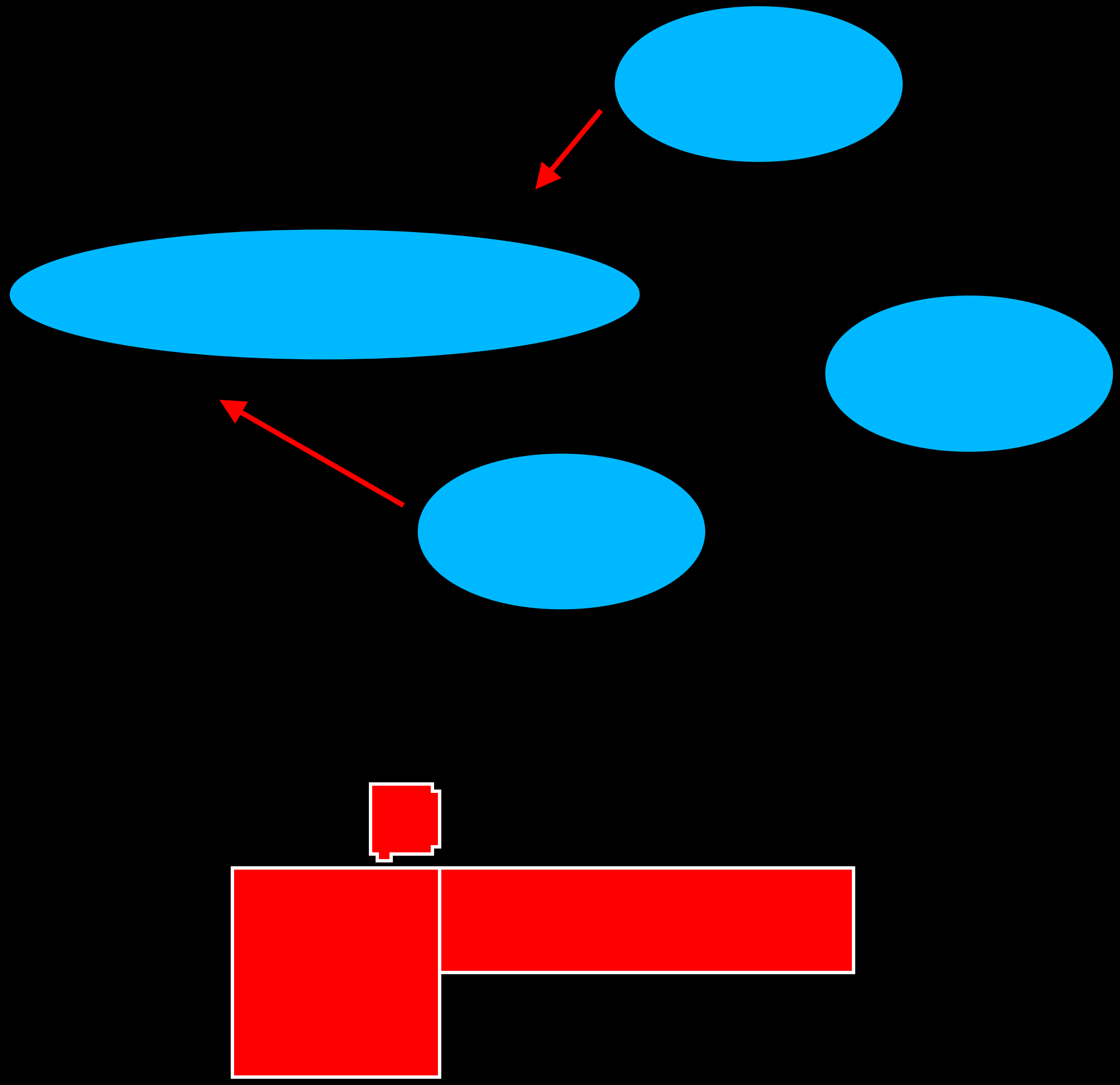
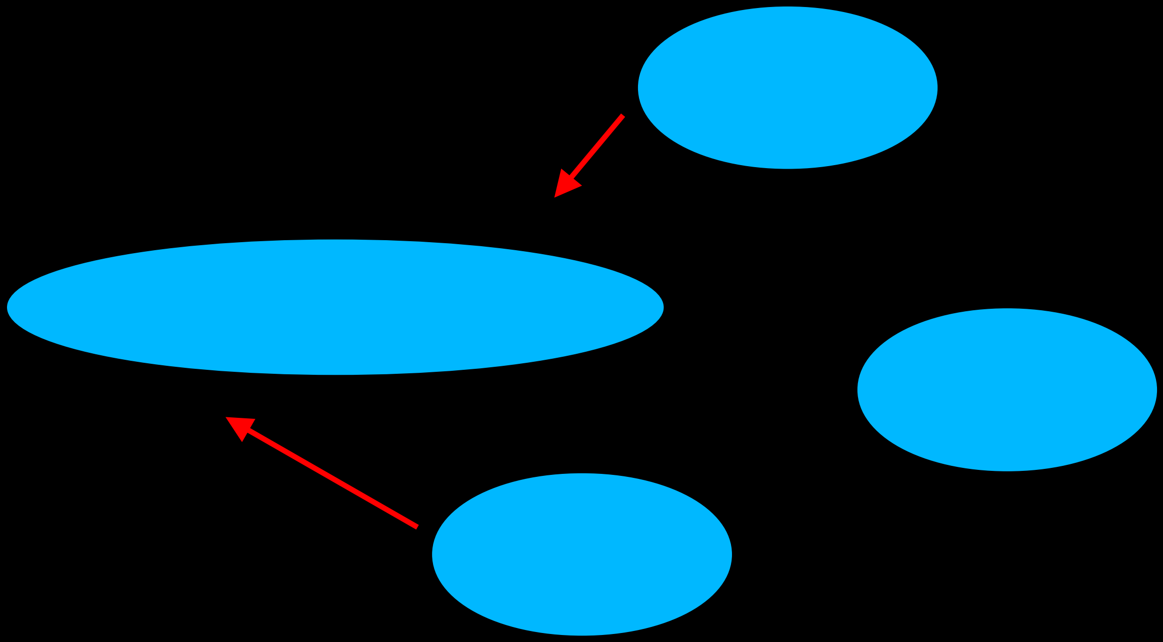
adjacent cells
(shape, adhesion, ...)
cell motility

Hypothesis: preferential migration towards elongated cells



Hypothesis: preferential migration towards elongated cells



…may involve mechanosensing altered micromechanical properties of the cytoskeleton.

In cultures of C6 and 3T3 cells

-AFM measurements yield different stiffness:

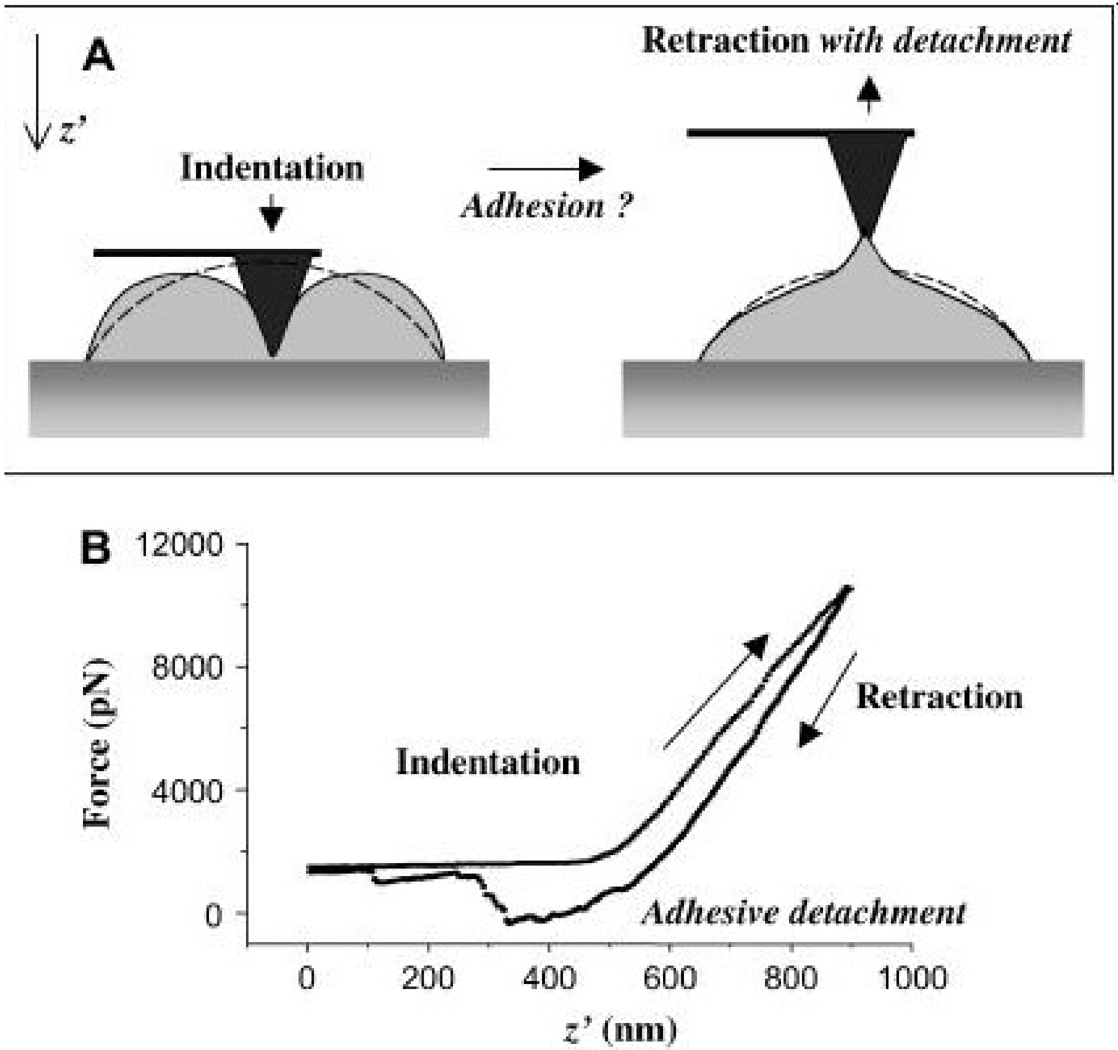
10kPa (elongated) vs 50 kPa (flat)

-Patterning (but not cell motility or adhesion) can be blocked with

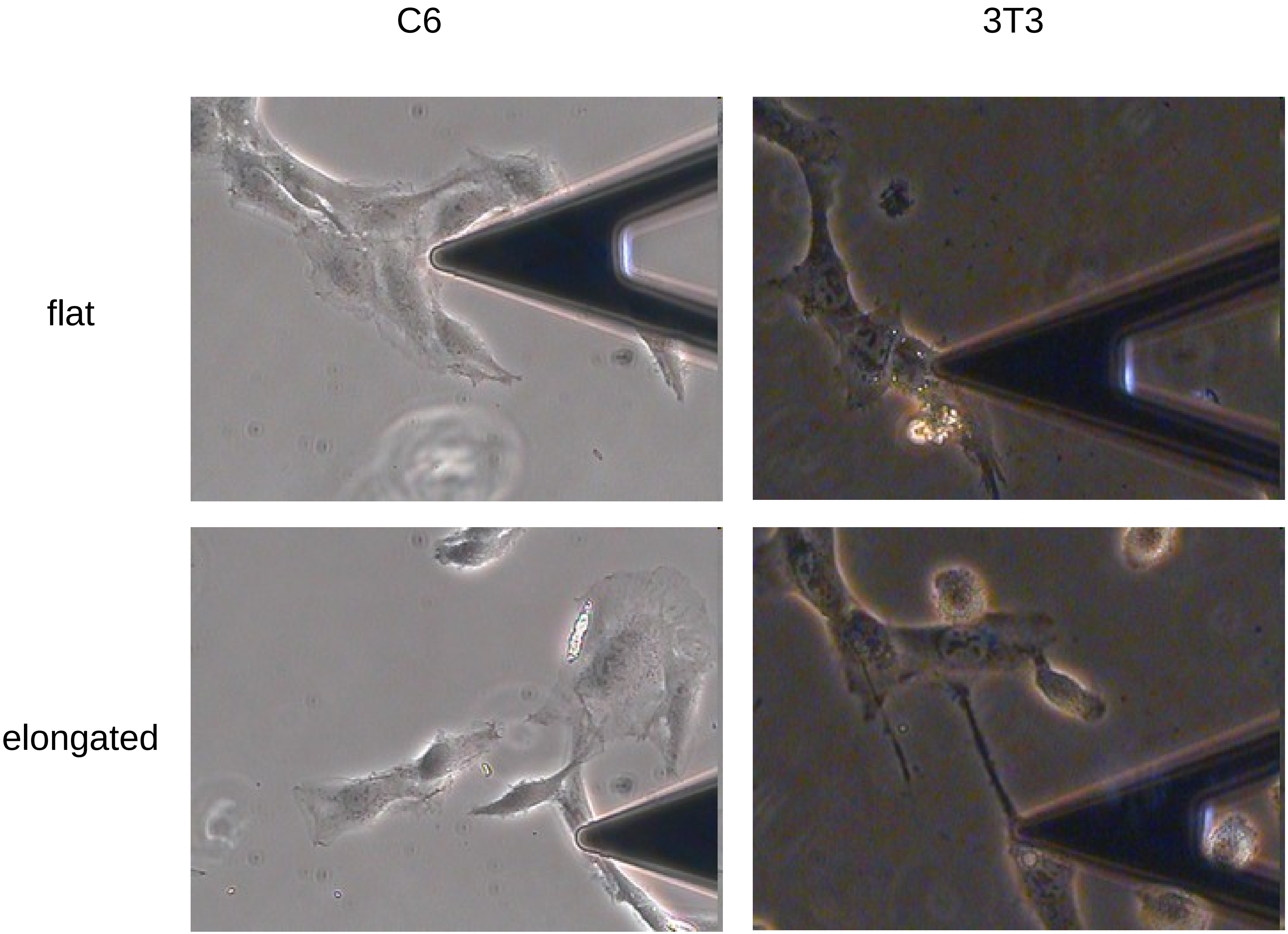
20uM blebbistatin

Differences in cell-mechanical properties between flat and elongated cells

AFM-approach:



after Sen et al., Biophys J. 2005

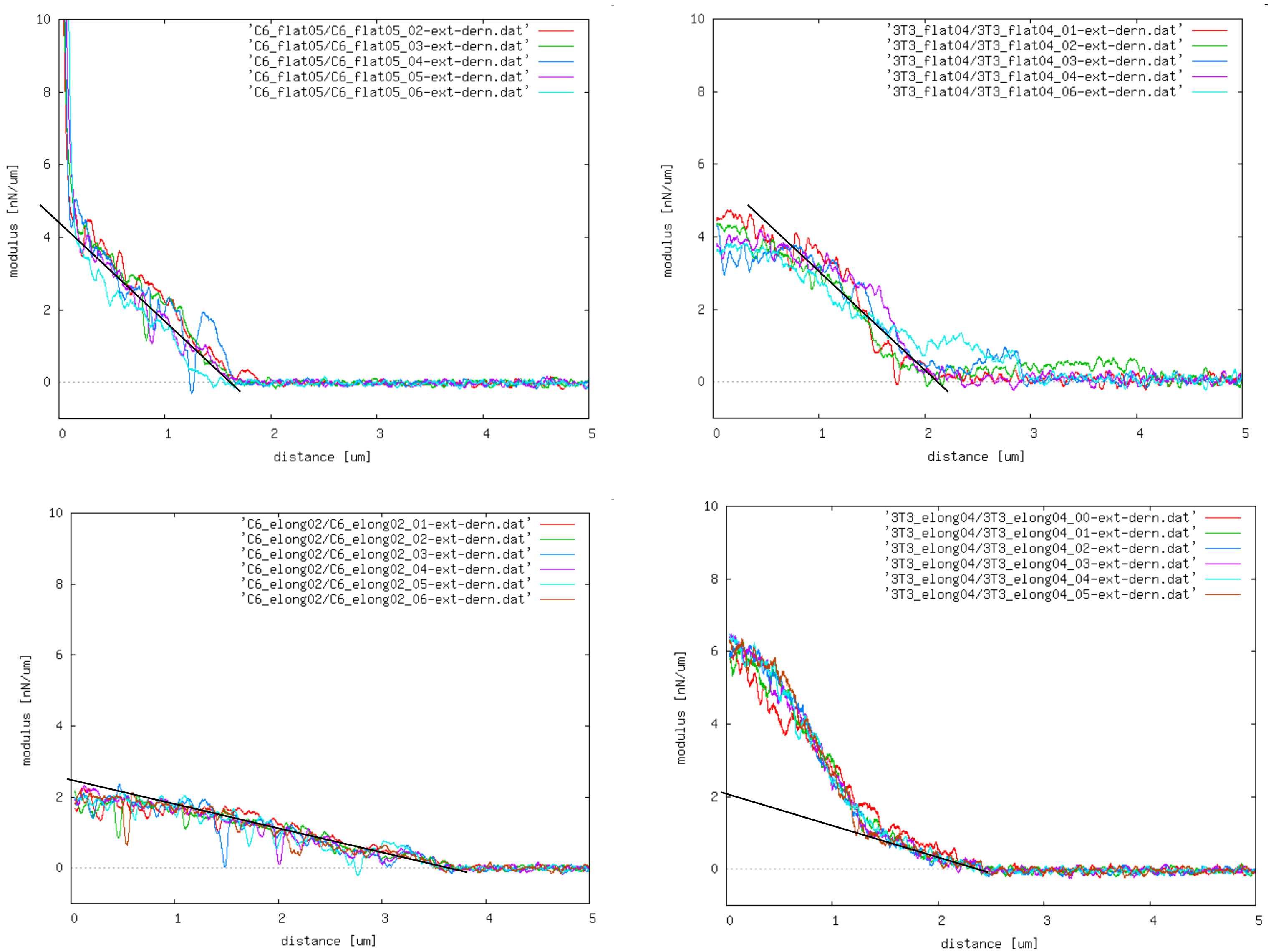

C6
3T3
flat
elongated

C6

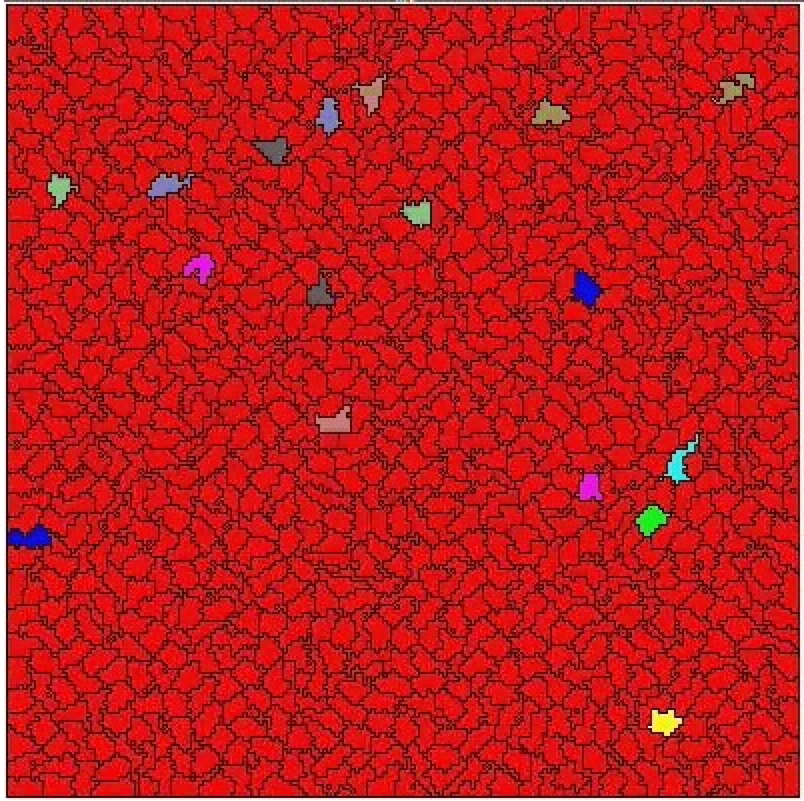
3T3

flat
~50kPa

elongated
~10kPa



“self-propelled” Potts model:

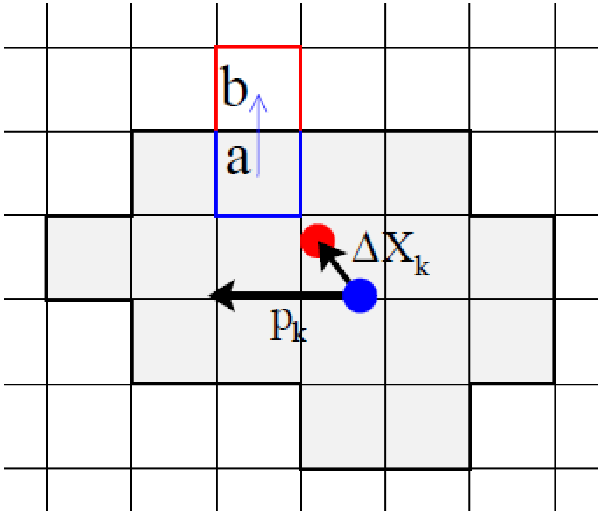


Penalties - for cell boundaries
- for deviations in domain areas

$$u = \sum_{<\mathbf{x},\mathbf{x}'>} J_{\sigma(\mathbf{x}),\sigma(\mathbf{x}')} + \lambda \sum_{i=1}^{N} \delta A_i^2$$

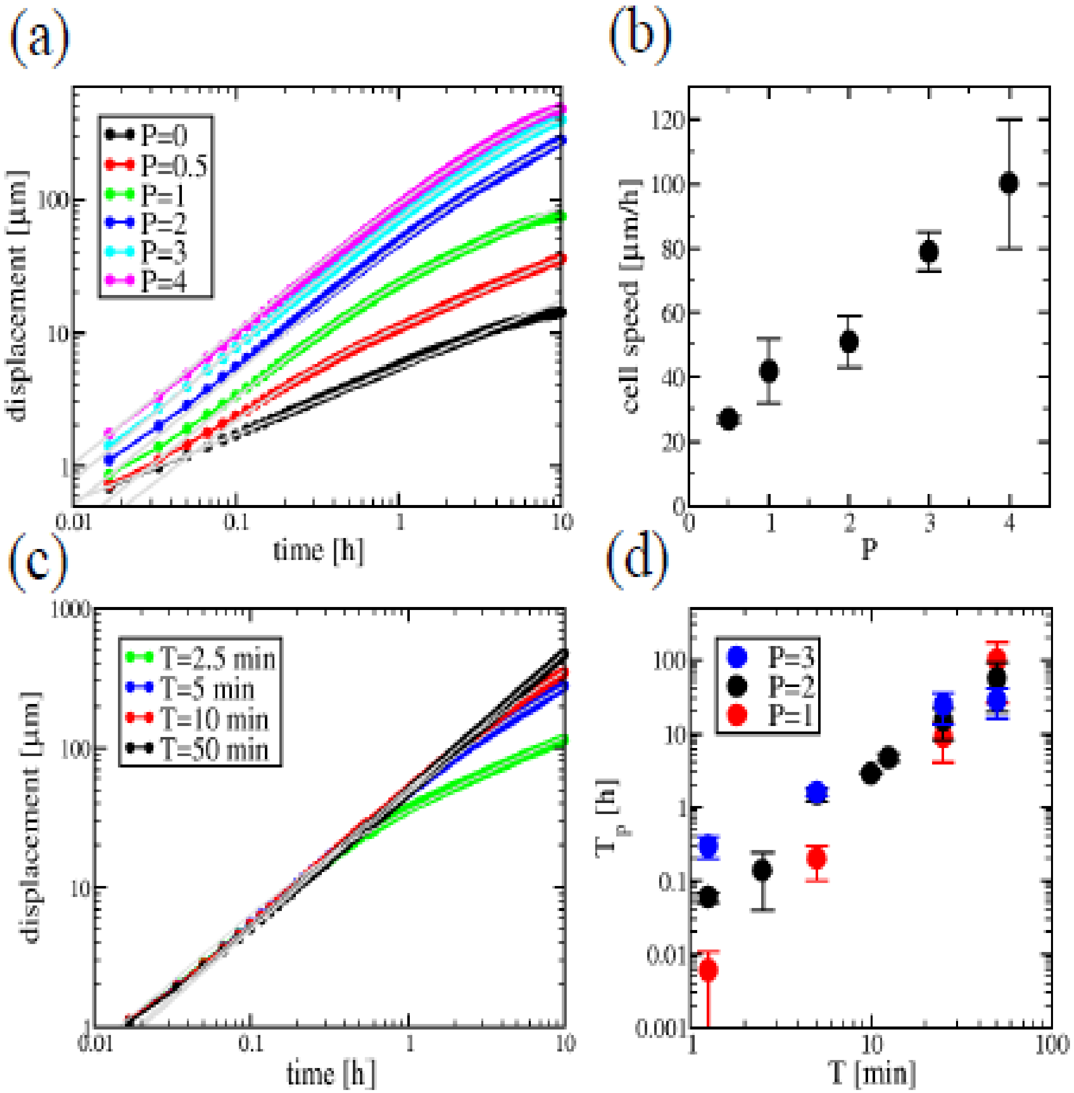
$$\ln p(\mathrm{a} \to \mathrm{b}) = \min[0, -\Delta u(\mathrm{a} \to \mathrm{b}) + w(\mathrm{a} \to \mathrm{b})]$$

$$w(\mathrm{a} \to \mathrm{b}) = P \sum_{k=\sigma(a),\sigma(b)} \frac{\Delta \mathbf{X}_k(\mathrm{a} \to \mathrm{b})\mathbf{p}_k}{|\mathbf{p}_k|}.$$



… and a positive feedback between polarity and movement (actin polymerization). At each MCS:

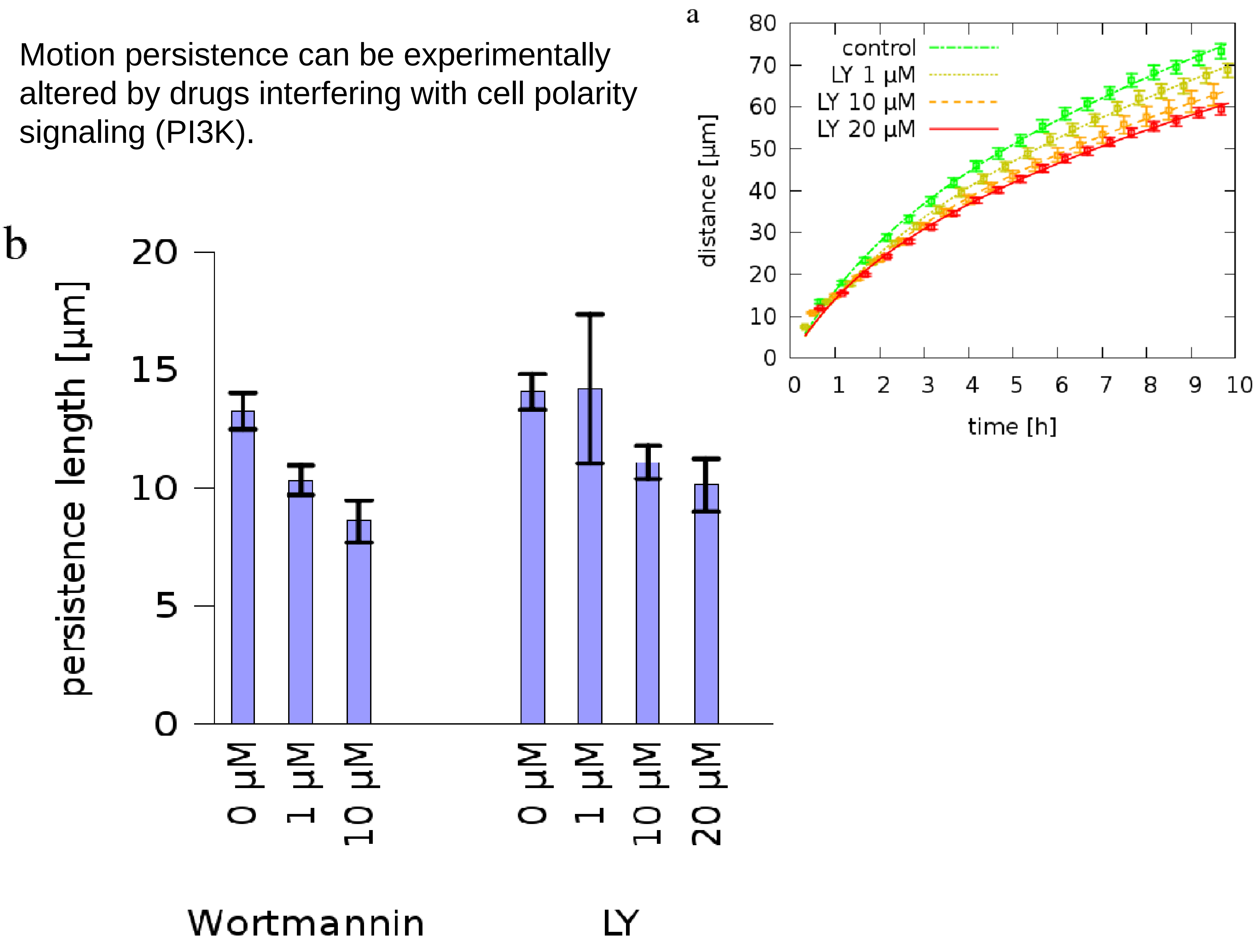
$$\Delta \mathbf{p}_k = -r\mathbf{p}_k + \Delta \mathbf{X}_k$$



$$w(\mathrm{a} \to \mathrm{b}) = P \sum_{k=\sigma(a),\sigma(b)} \frac{\Delta \mathbf{X}_k(\mathrm{a} \to \mathrm{b})\mathbf{p}_k}{|\mathbf{p}_k|}.$$

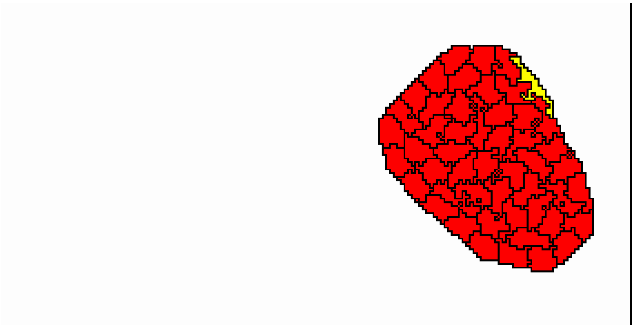
$$\Delta \mathbf{p}_k = -r\mathbf{p}_k + \Delta \mathbf{X}_k$$

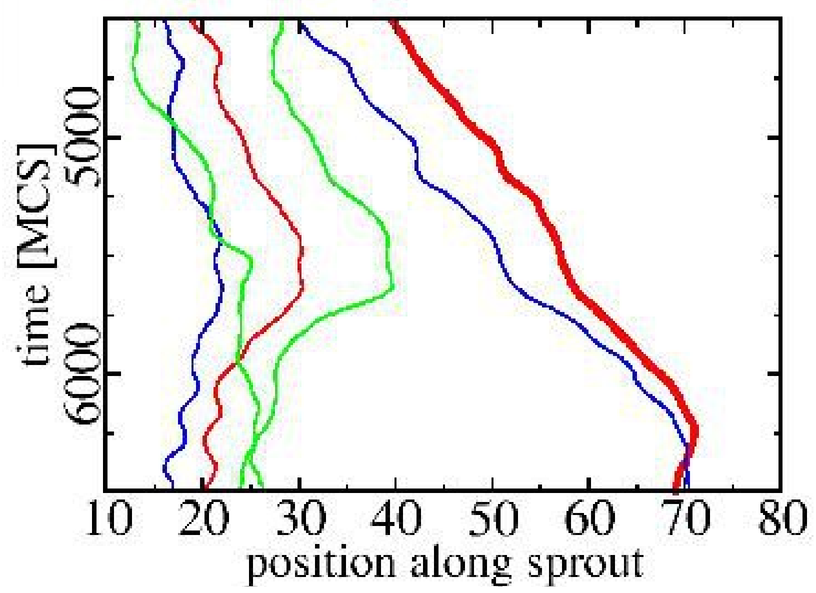
Motion persistence can be experimentally altered by drugs interfering with cell polarity signaling (PI3K).



A leader cell and…

cell-cell adhesion only -- as usually treated in differential adhesion and cell sorting settings.

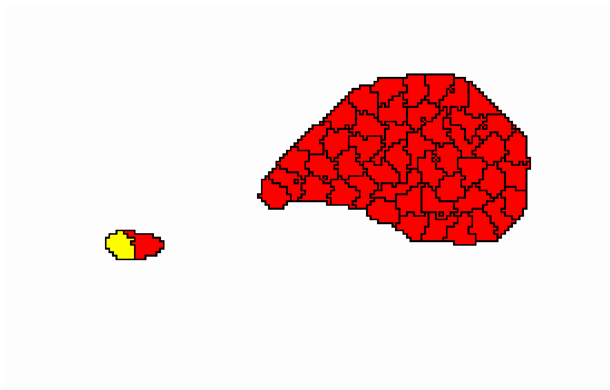


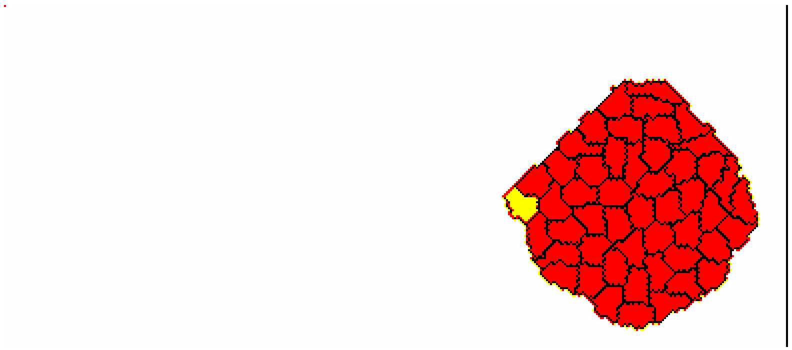


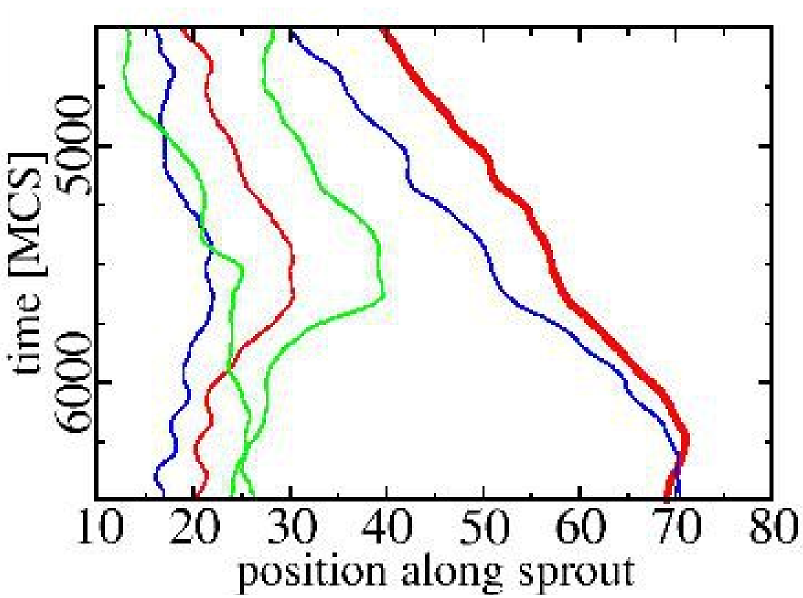
A leader cell and…

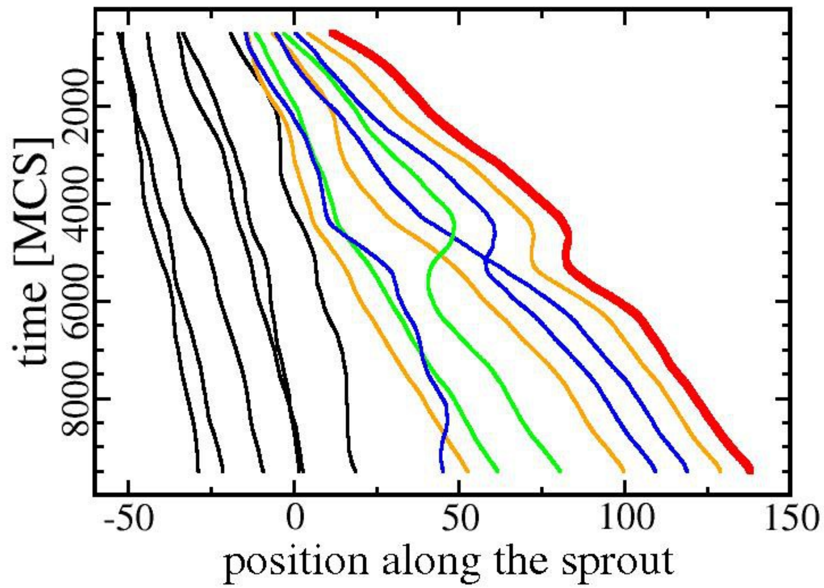
cell-cell adhesion only

preferential adhesion to elongated cells

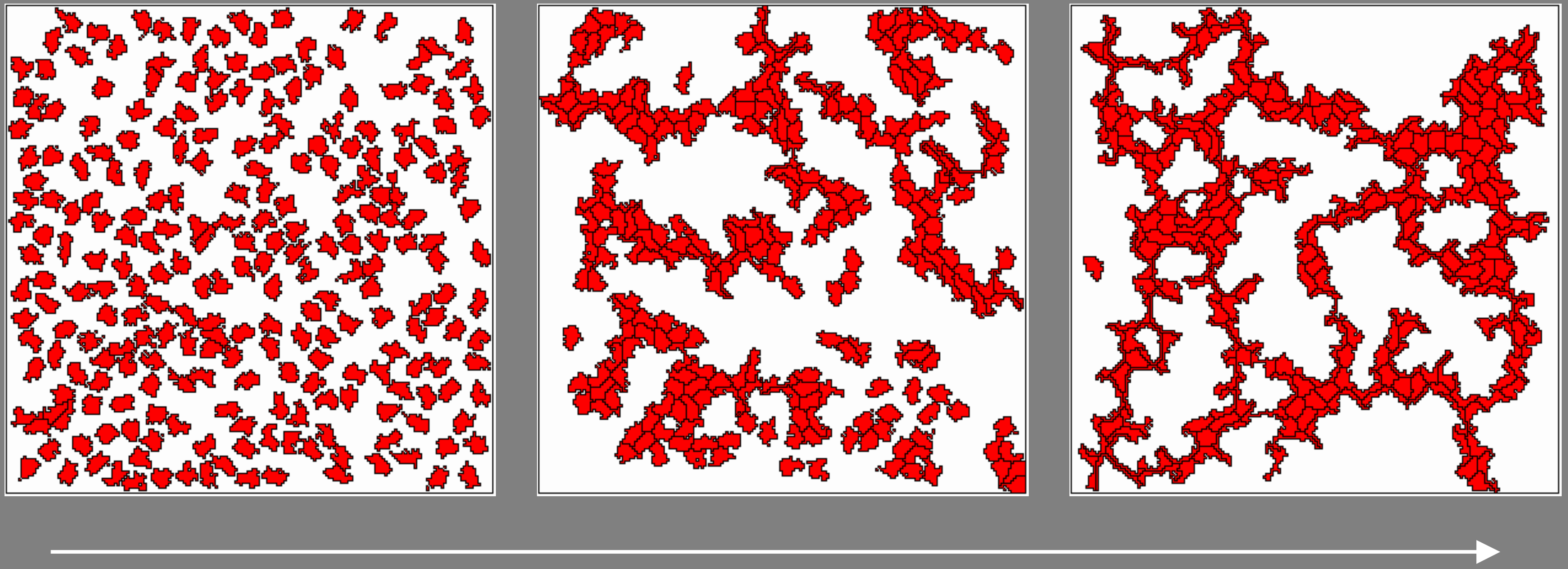








The cellular Potts model (CPM)



Increasing strength of preferential attraction to elongated cells

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- Szabó András (ELTE -> UCL)
- Varga Kata (ELTE -> UCL)
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