CWI

Universiteit Leiden

Multiscale modeling of mechanical cell-cell signaling during embryonic development

Roeland Merks

Centrum Wiskunde & Informatica (CWI), Amsterdam
Mathematical Institute, Leiden University

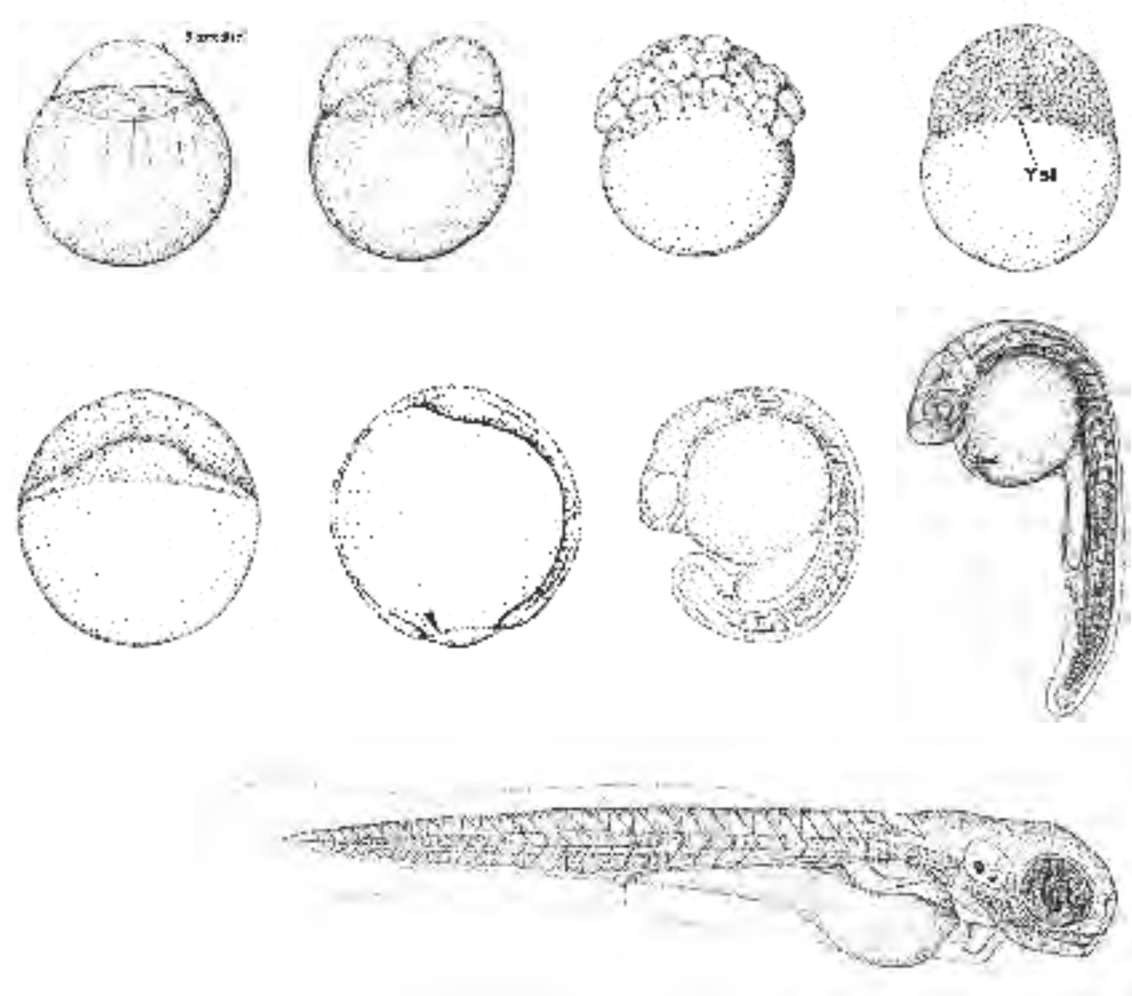
@roeland_merks, merks@cwi.nl
http://biomodel.project.cwi.nl

CWI Scientific Meeting
29 September 2017

Morphogenesis

How is the **linear** information in the DNA translated into the **three-dimensional** shape of organisms?

DNA



Morphogenesis

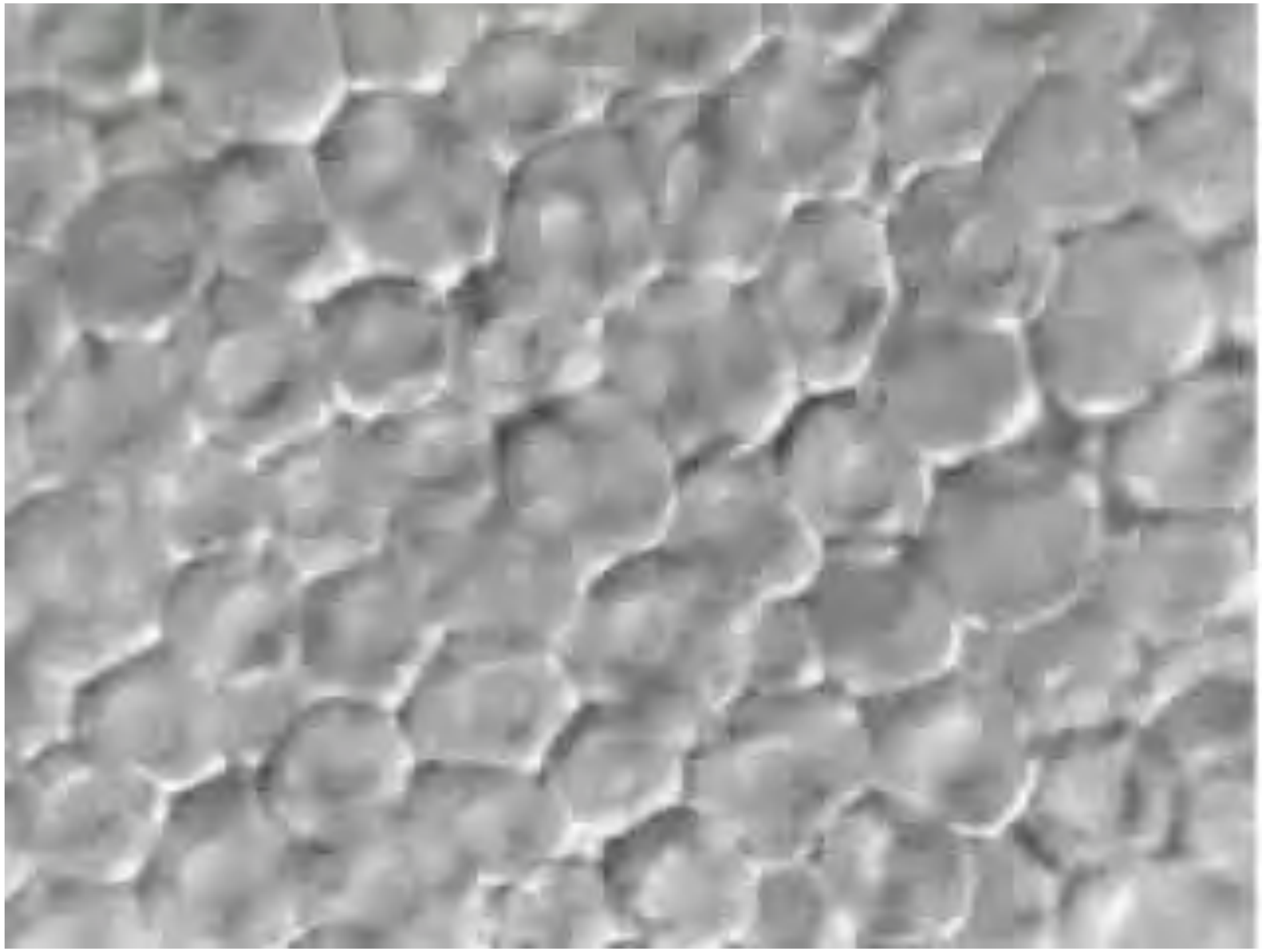
Adult

Animals are ‘swarms’ of cells

- Predict ‘swarm’ properties from cell-cell interactions
- Observe local cell-cell interactions responsible for it

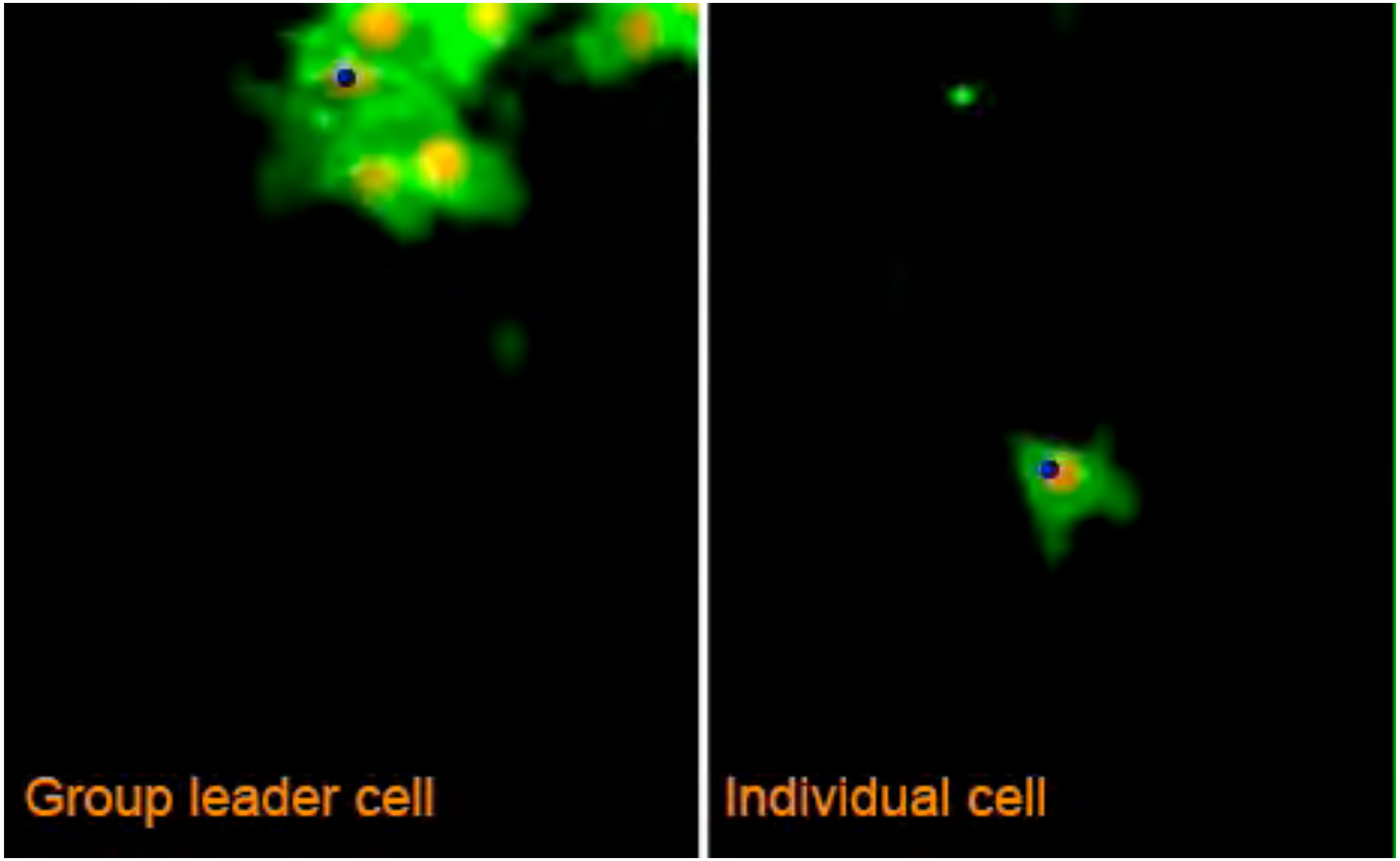
Cells look as if they act independently...

P.Z. Myers, University of Minnesota
(source: YouTube)



Zebrafish blastoderm (embryonic tissue)

... but of course cells respond to one another



Contact-inhibition of frog neural crest cells
Carmona-Fontaine *et al.* Nature 2008 (Mayer/Stern group)

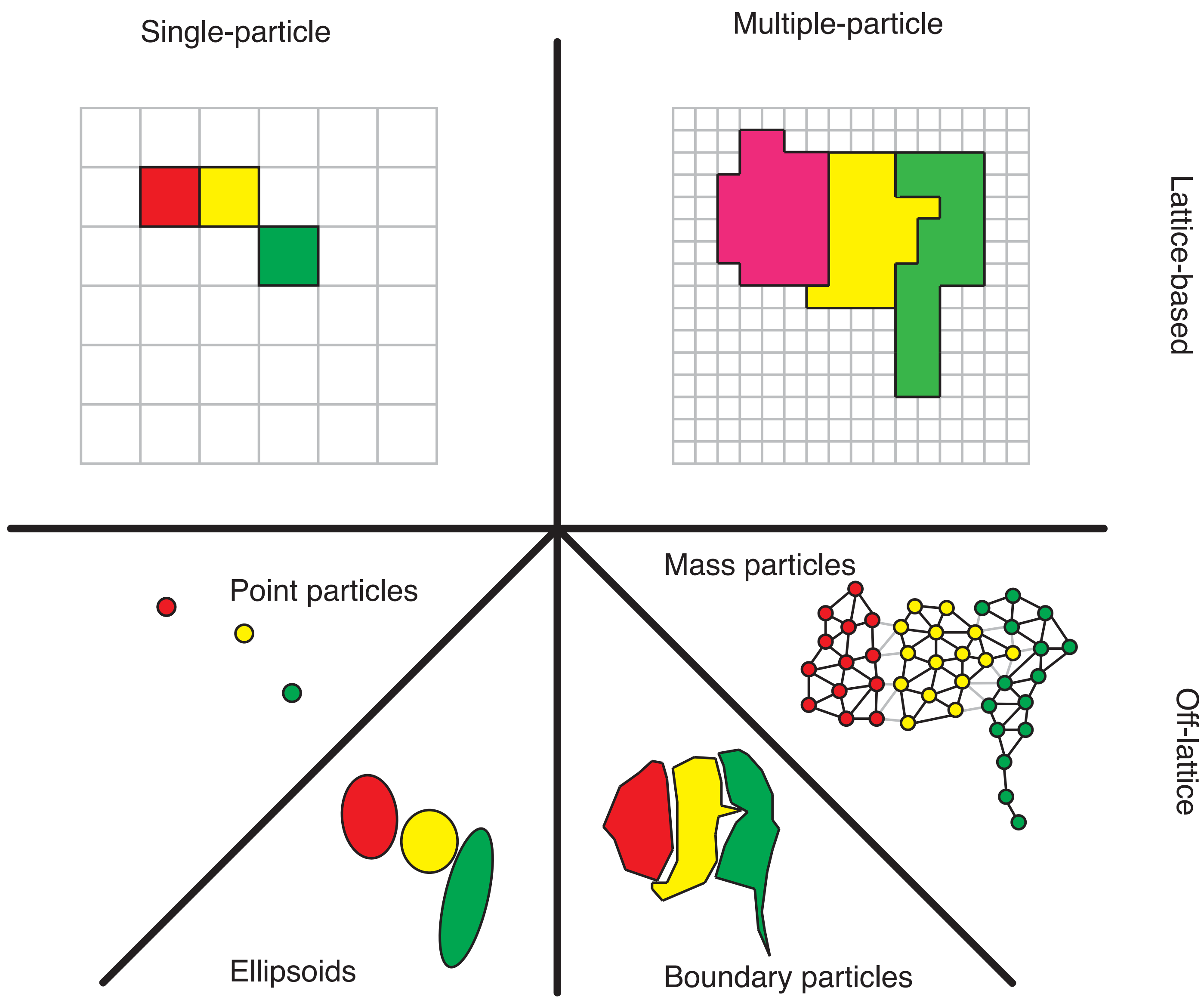
Cell based models

(Merks and Glazier, *Phys. A* 2005)

- **Input:** cell behavior
- **Output:** development of multicellular structure
  - Growth and form of tissues and organs

- **Aim** of cell-based modeling is to understand:
  - How cells ‘build’ animals
  - How tissue structure feeds back onto cell behavior
  - How a genetic mutation can lead to phenotypic changes

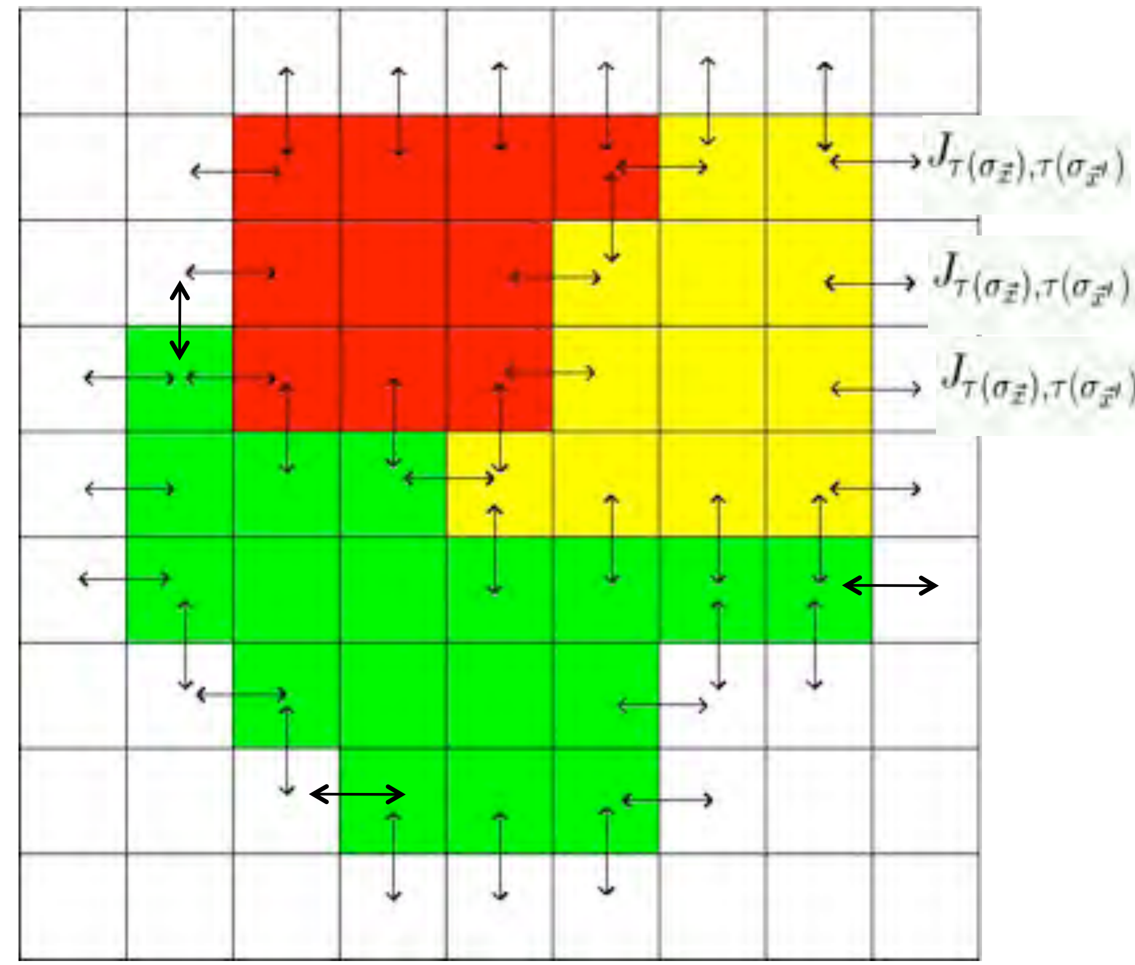
Simulation methods

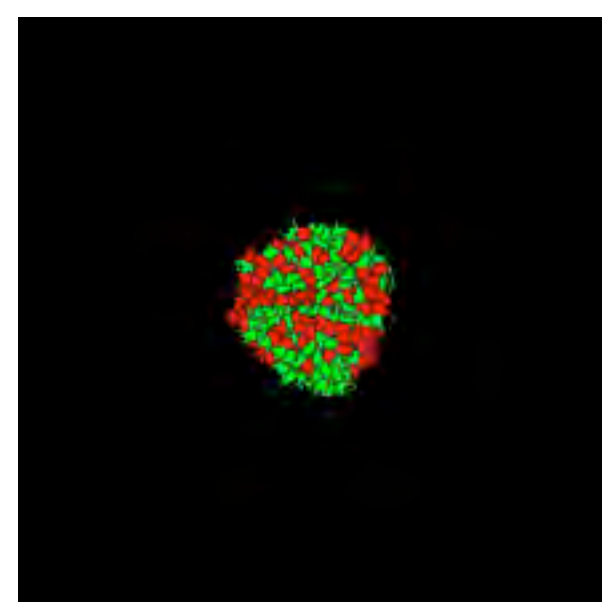


- Membrane movement and cell shape are often key
  - So: **multiparticle methods**

Cellular Potts Model (Graner & Glazier, 1992)

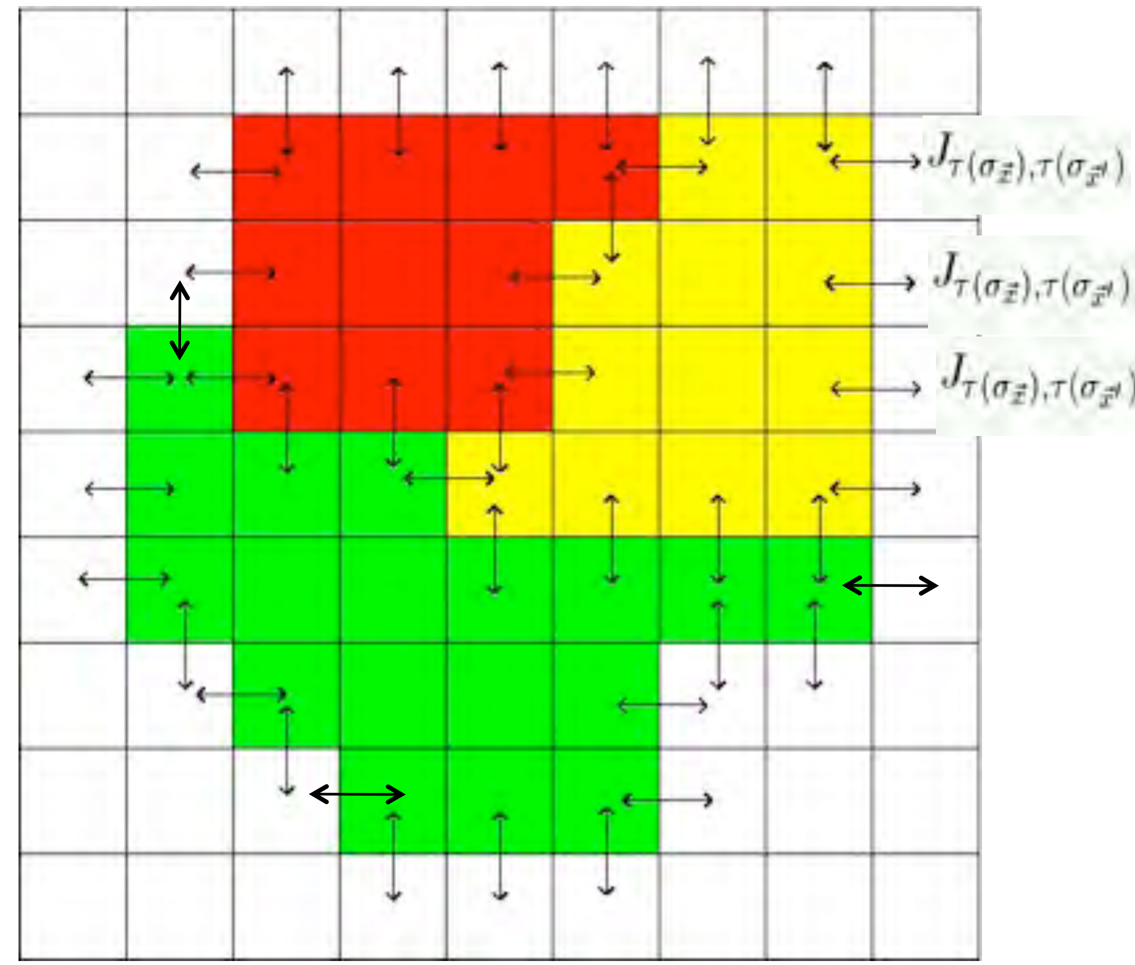
- Describes **random** cell motility
- Cells live on a grid
- One cell covers multiple grid points
- Cell interact with **fields** describing distribution of signaling molecules, strains in ECM, and so forth
- Cells move due to balance between
- Active and reactive cellular forces:
  - **Active:** e.g., random extension/ retraction of pseudopods, chemotaxis
  - **Reactive:** e.g, drag forces, adhesion to cells and matrix, strains in matrix

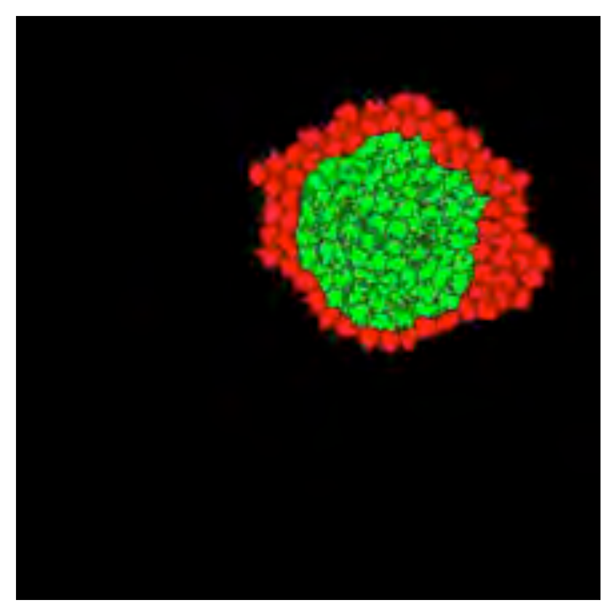




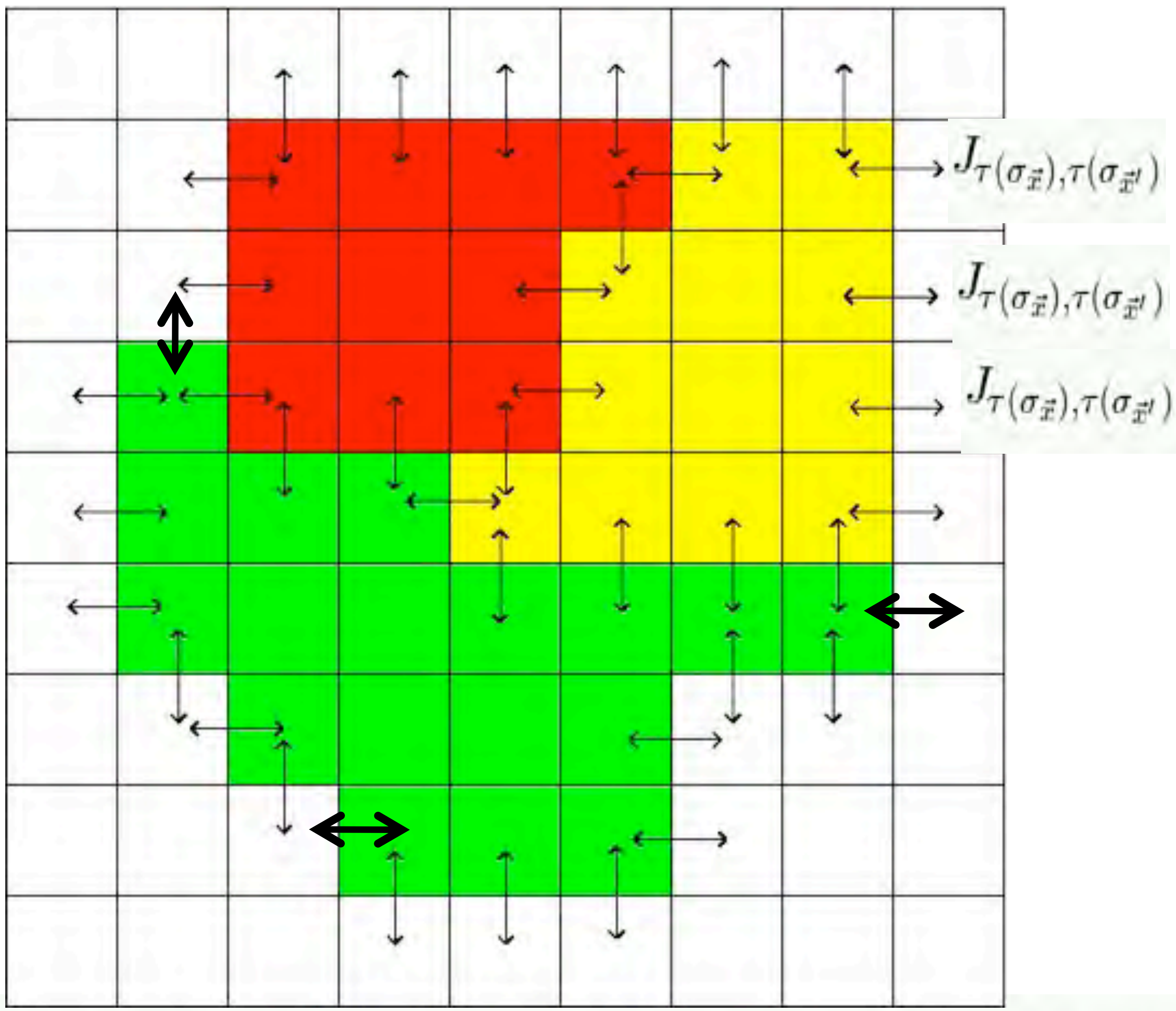
Cellular Potts Model (Graner & Glazier, 1992)

- Describes **random** cell motility
- Cells live on a grid
- One cell covers multiple grid points
- Cell interact with **fields** describing distribution of signaling molecules, strains in ECM, and so forth
- Cells move due to balance between
- Active and reactive cellular forces:
  - **Active:** e.g., random extension/ retraction of pseudopods, chemotaxis
  - **Reactive:** e.g, drag forces, adhesion to cells and matrix, strains in matrix





Cellular Potts Model (CPM)

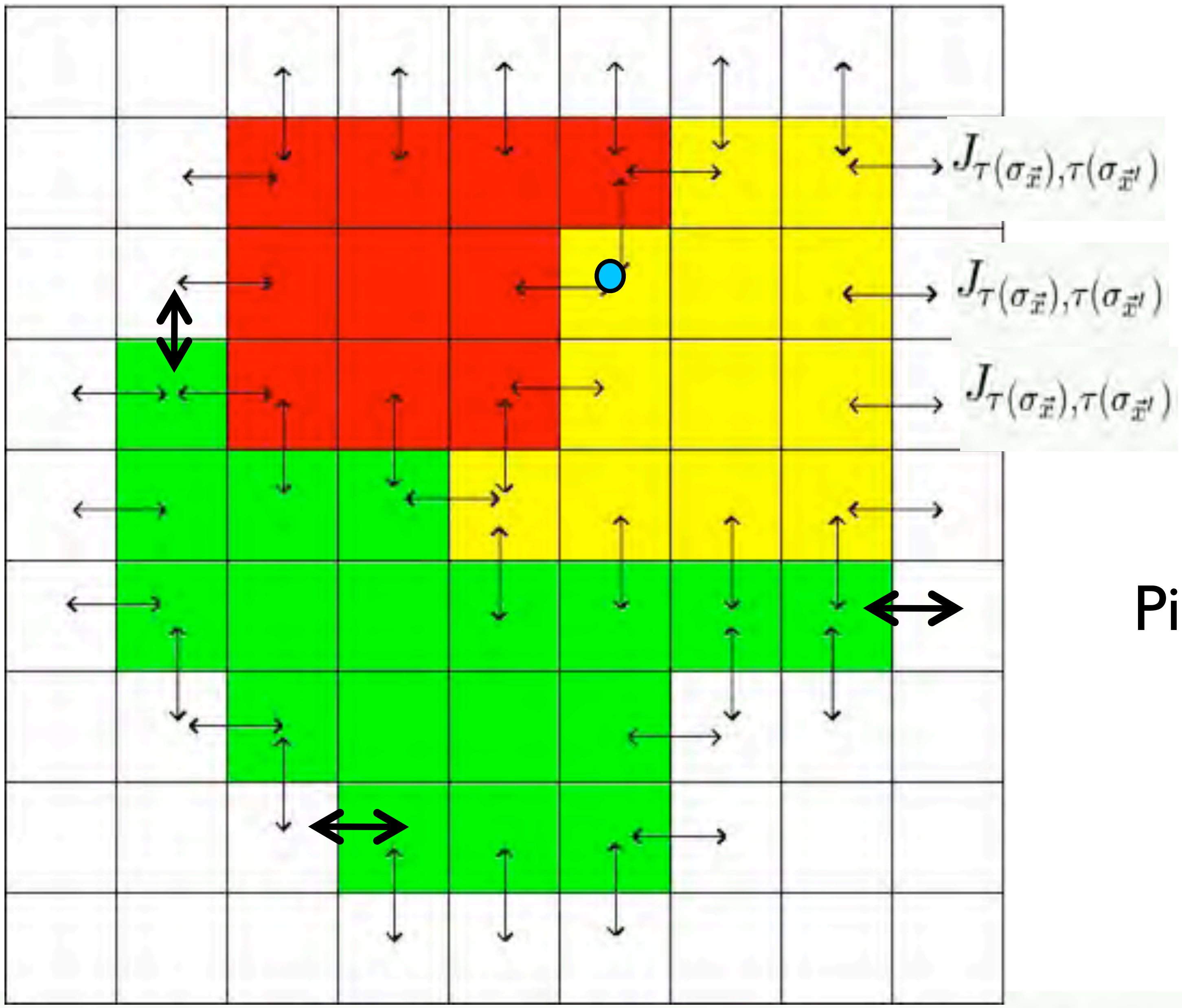


$$H = \sum_{\vec{x},\vec{x}'} J_{\tau(\sigma_{\vec{x}}),\tau(\sigma_{\vec{x}'})}(1 - \delta_{\sigma_{\vec{x}},\sigma_{\vec{x}'}}) + \lambda \sum_{\sigma} (a_\sigma - A_\sigma)^2$$

Cell adhesion

Volume conservation

Cellular Potts Model (CPM)

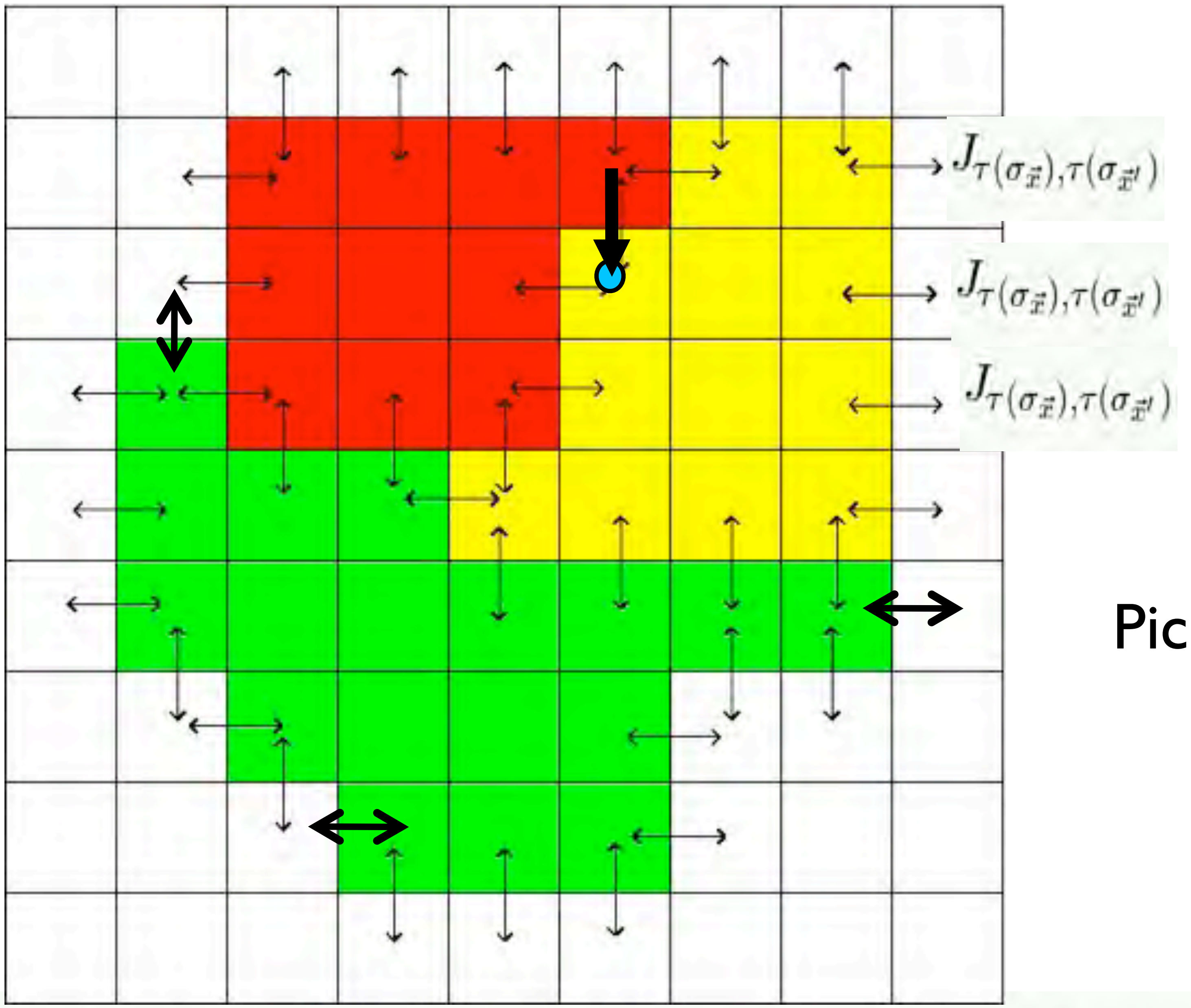


Pick random site

$$H = \sum_{\vec{x},\vec{x}'} J_{\tau(\sigma_{\vec{x}}),\tau(\sigma_{\vec{x}'})}(1 - \delta_{\sigma_{\vec{x}},\sigma_{\vec{x}'}}) + \lambda \sum_{\sigma} (a_\sigma - A_\sigma)^2$$

Cell adhesion | Volume conservation

Cellular Potts Model (CPM)



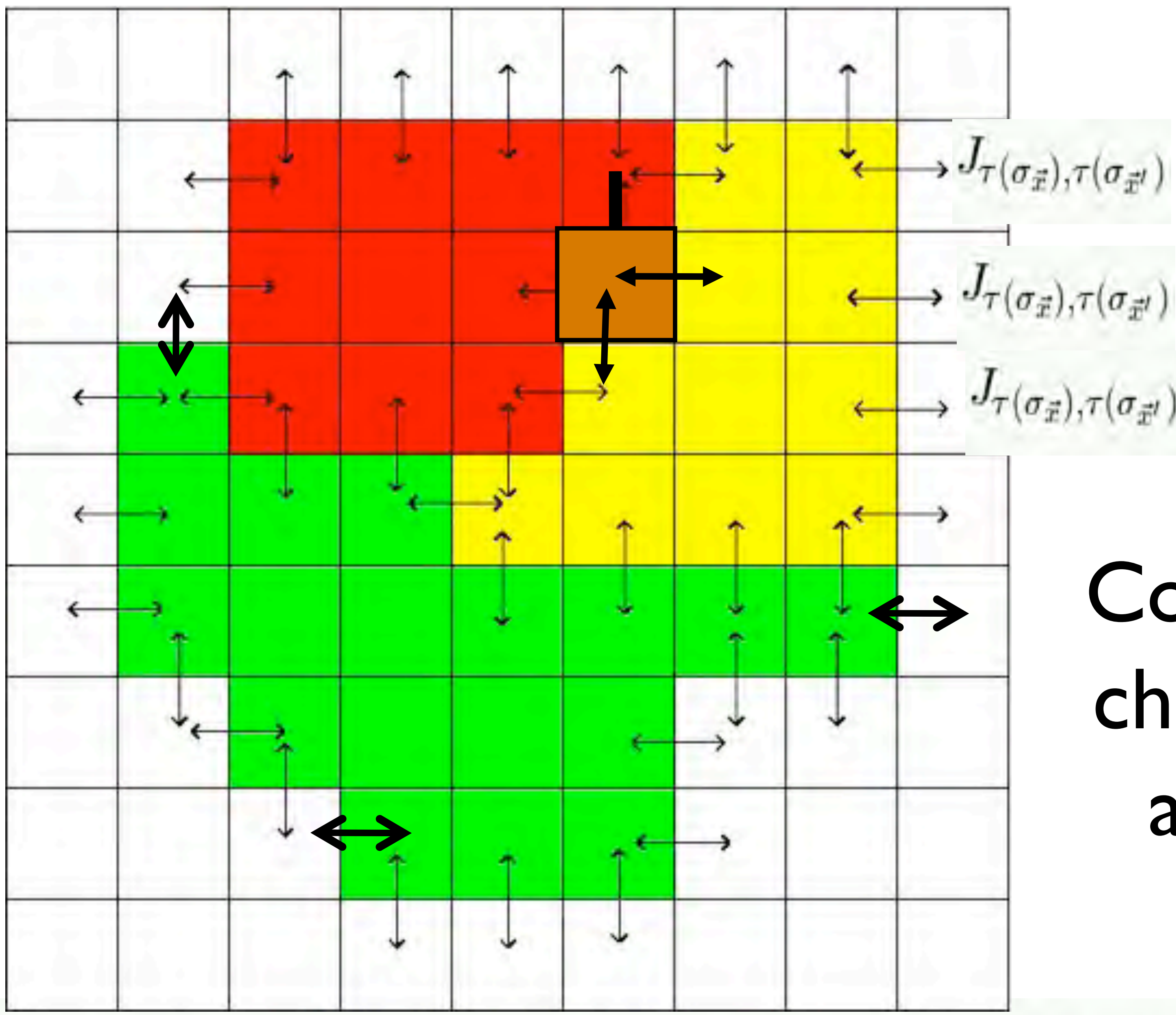
Pick random neighbor

$$H = \sum_{\vec{x},\vec{x}'} J_{\tau(\sigma_{\vec{x}}),\tau(\sigma_{\vec{x}'})}(1 - \delta_{\sigma_{\vec{x}},\sigma_{\vec{x}'}}) + \lambda \sum_{\sigma}(a_\sigma - A_\sigma)^2$$

Cell adhesion

Volume conservation

Cellular Potts Model (CPM)



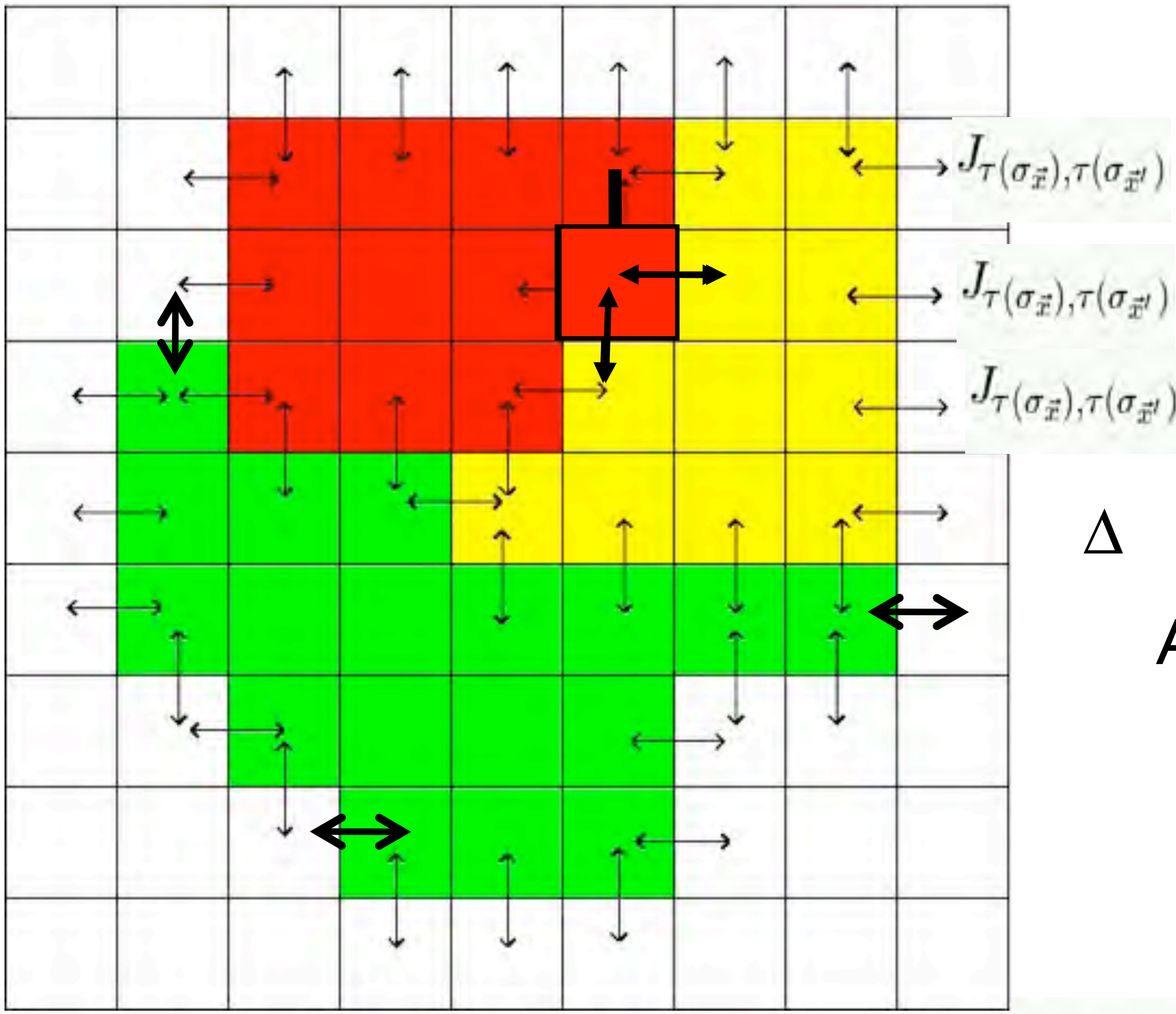
Consider energy change ΔH if we accepted this copying

$$H = \sum_{\vec{x},\vec{x}'} J_{\tau(\sigma_{\vec{x}}),\tau(\sigma_{\vec{x}'})}(1-\delta_{\sigma_{\vec{x}},\sigma_{\vec{x}'}}) + \lambda \sum_{\sigma}(a_\sigma - A_\sigma)^2$$

Cell adhesion

Volume conservation

Cellular Potts Model (CPM)



Δ H < 0 ?

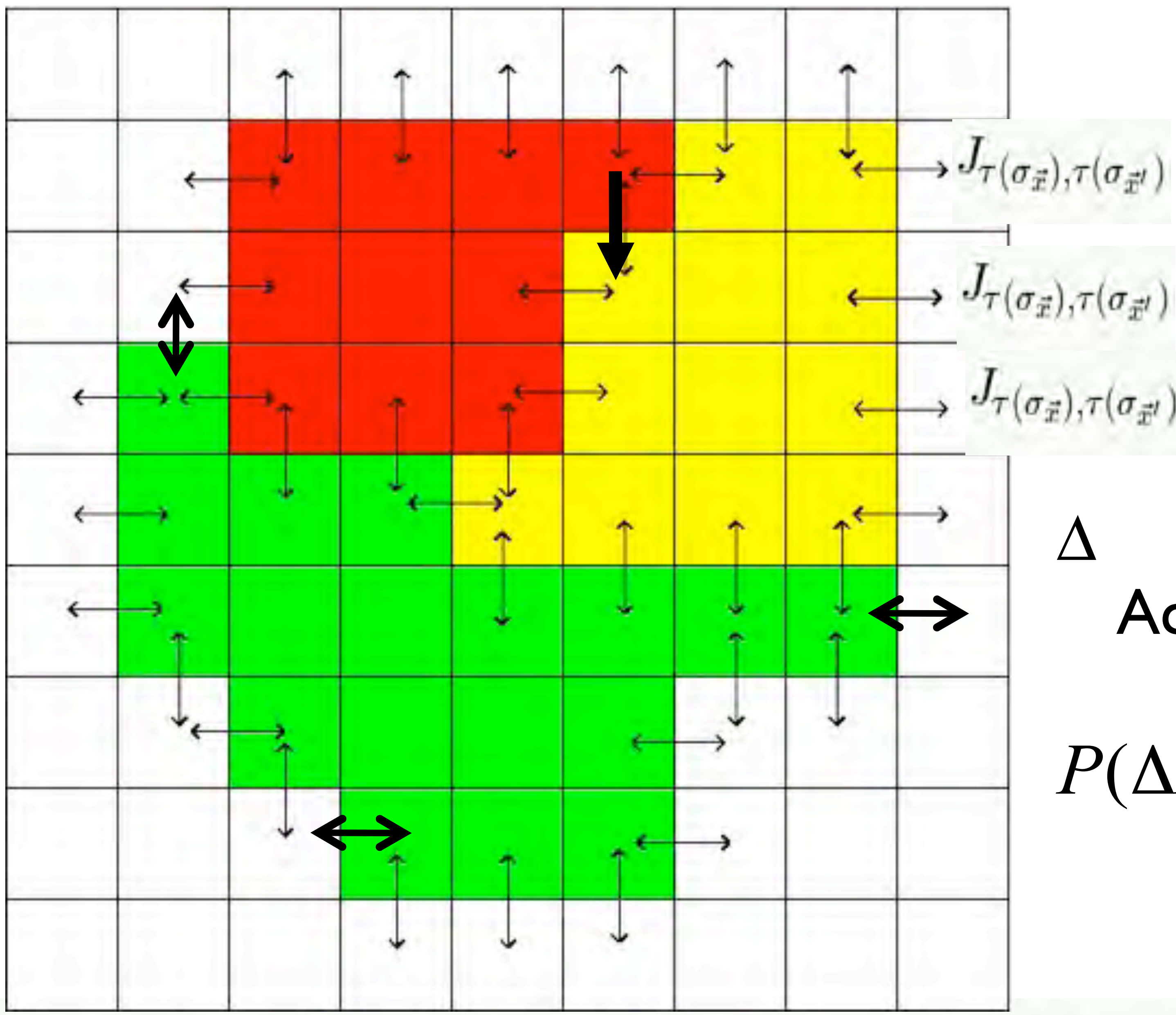
Accept always

$$H = \sum_{\vec{x},\vec{x}'} J_{\tau(\sigma_{\vec{x}}),\tau(\sigma_{\vec{x}'})}(1-\delta_{\sigma_{\vec{x}},\sigma_{\vec{x}'}}) + \lambda \sum_{\sigma}(a_\sigma - A_\sigma)^2$$

Cell adhesion

Volume conservation

Cellular Potts Model (CPM)



Δ H > 0 ?

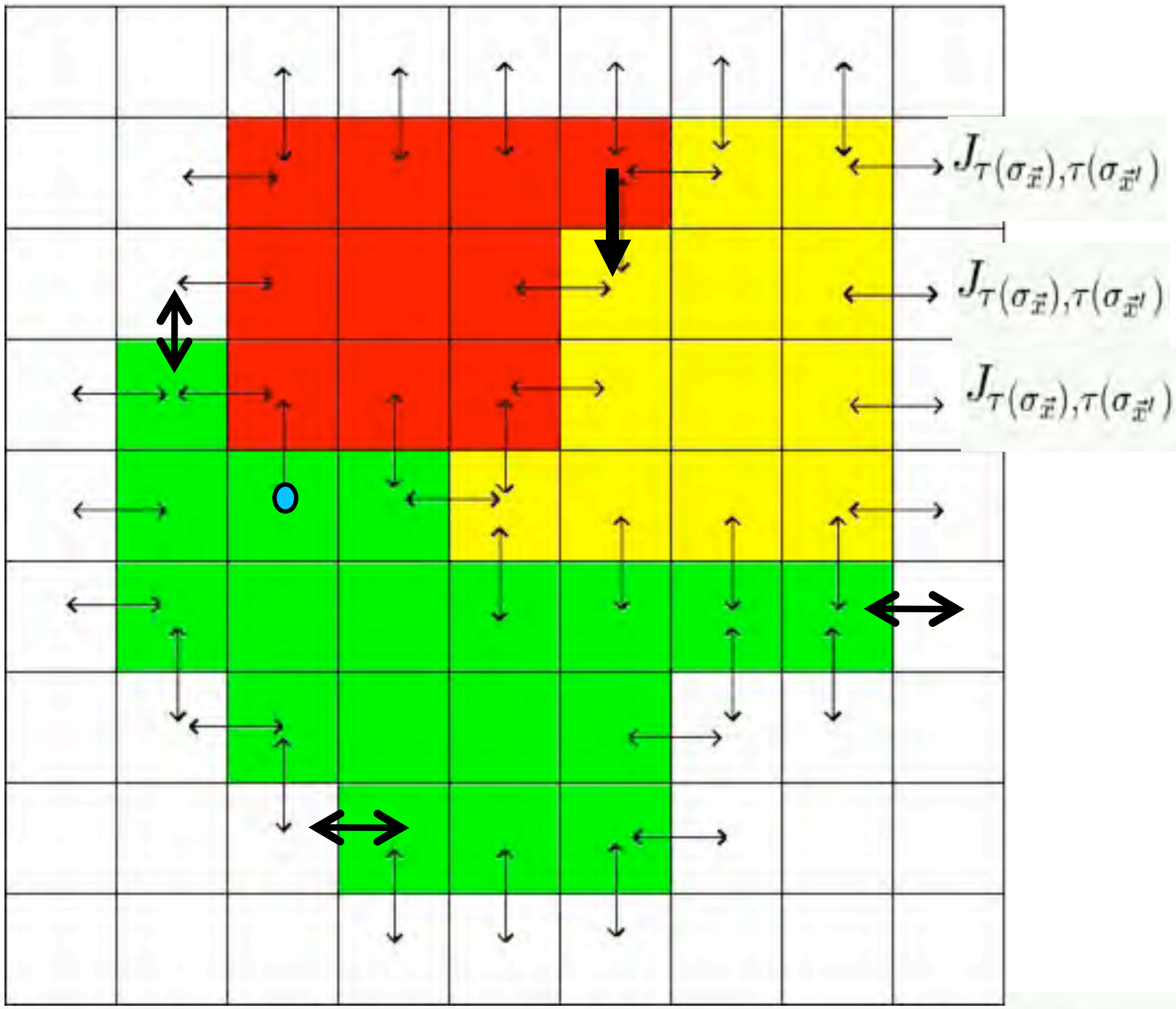
Accept with

$$P(\Delta H) = e^{\frac{-\Delta H + H_0}{T}}$$

$$H = \sum_{\vec{x},\vec{x}'} J_{\tau(\sigma_{\vec{x}}),\tau(\sigma_{\vec{x}'})}(1 - \delta_{\sigma_{\vec{x}},\sigma_{\vec{x}'}}) + \lambda \sum_{\sigma} (a_\sigma - A_\sigma)^2$$

Cell adhesion — Volume conservation

Cellular Potts Model (CPM)



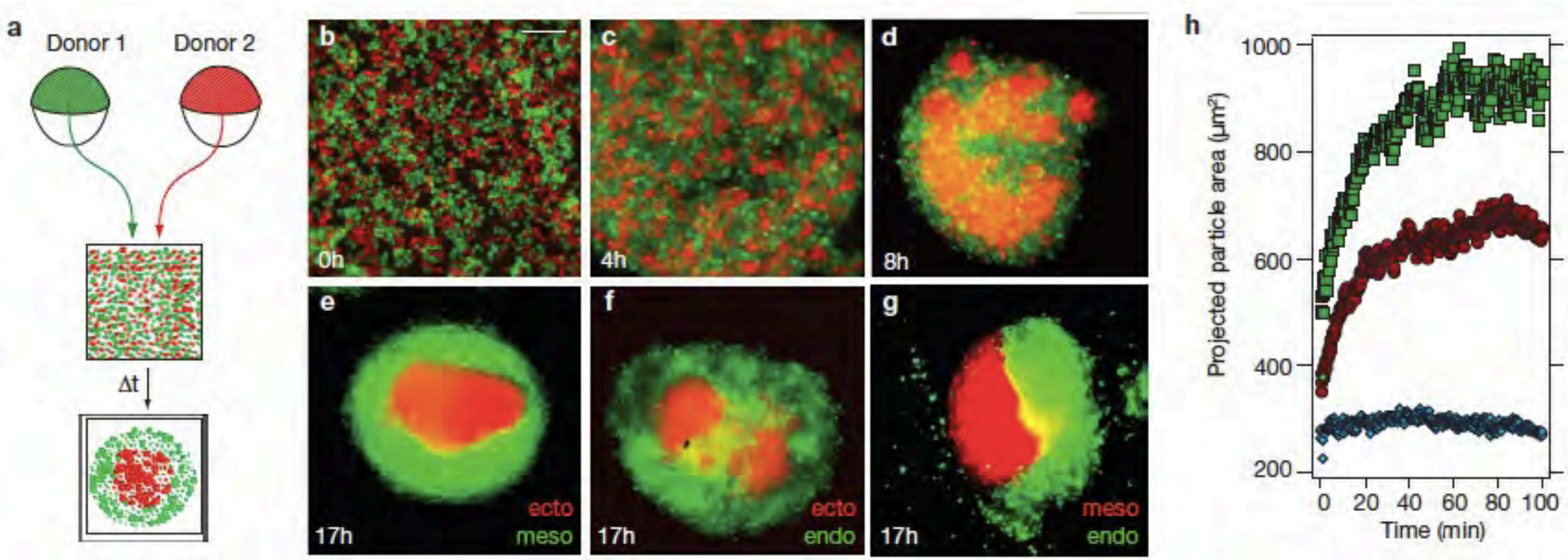
Repeat

$$H = \sum_{\vec{x},\vec{x}'} J_{\tau(\sigma_{\vec{x}}),\tau(\sigma_{\vec{x}'})}(1 - \delta_{\sigma_{\vec{x}},\sigma_{\vec{x}'}}) + \lambda \sum_{\sigma}(a_\sigma - A_\sigma)^2$$

Cell adhesion

Volume conservation

Typical problem: Differential-adhesion-driven cell sorting

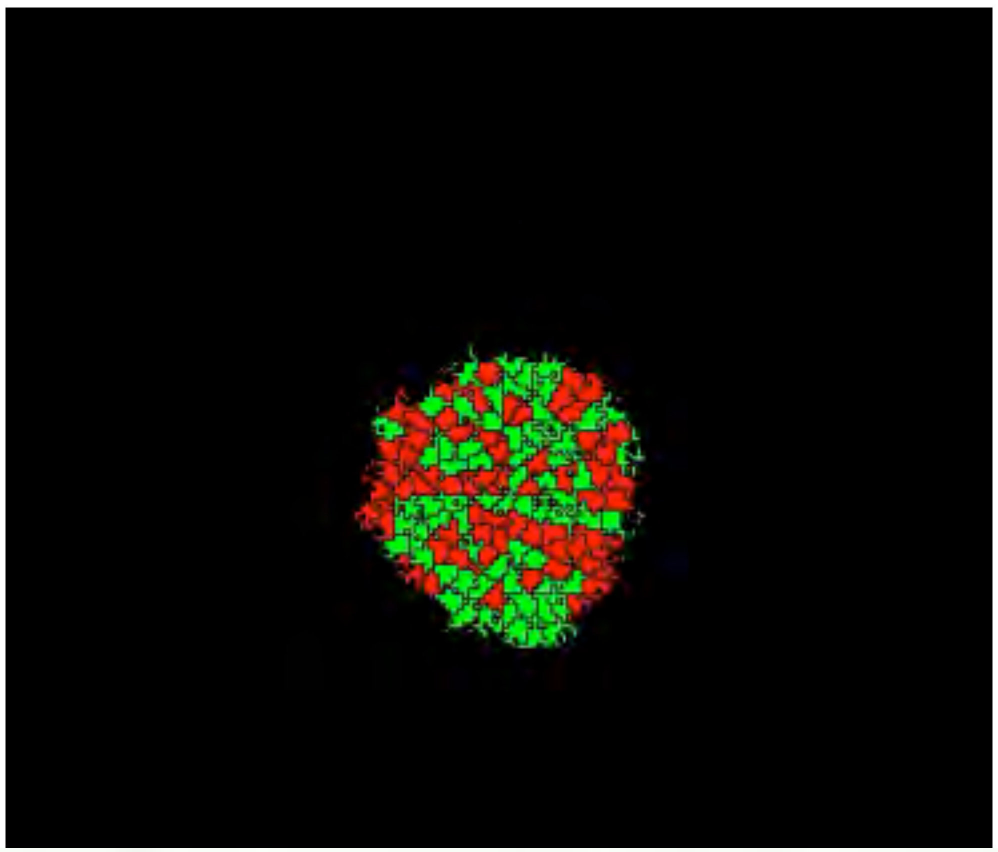


Data: Krieg et al. Nature Cell Biology, 2008

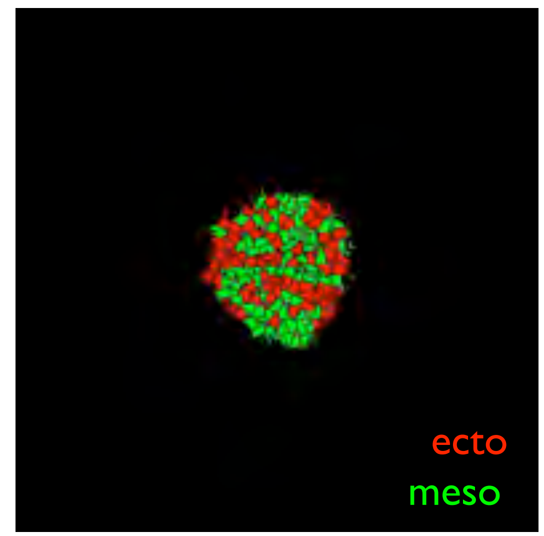
Simulation result

$$J_{\text{red,green}} = J_{\text{red,red}}$$

Model simulation



Speed up (10 x)



$$H = \sum_{\vec{x},\vec{x}'} J_{\tau(\sigma_{\vec{x}}),\tau(\sigma_{\vec{x}'})}(1-\delta_{\sigma_{\vec{x}},\sigma_{\vec{x}'}}) + \lambda \sum_{\sigma}(a_\sigma - A_\sigma)^2$$

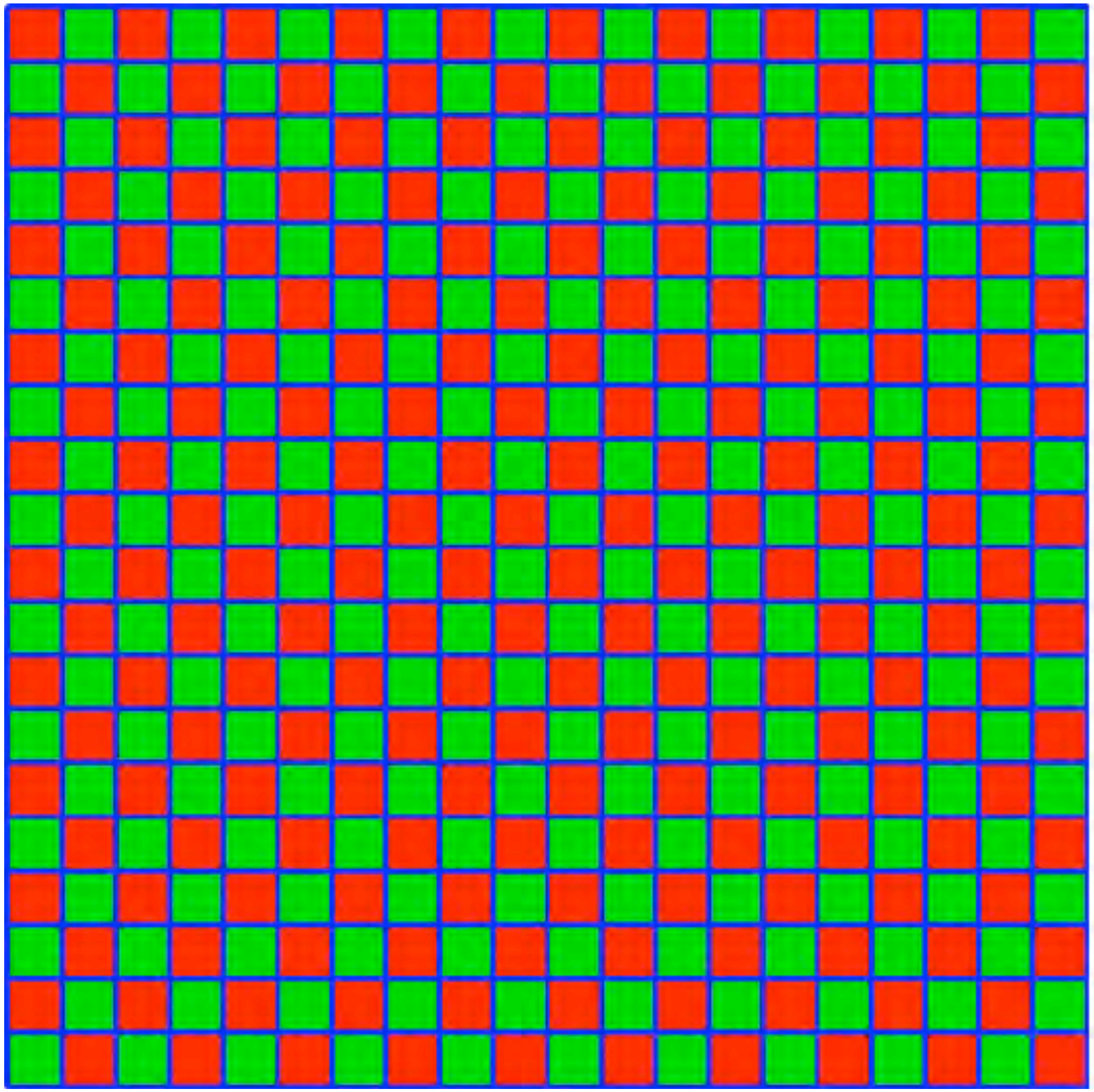
Cell adhesion

Volume conservation

CWI

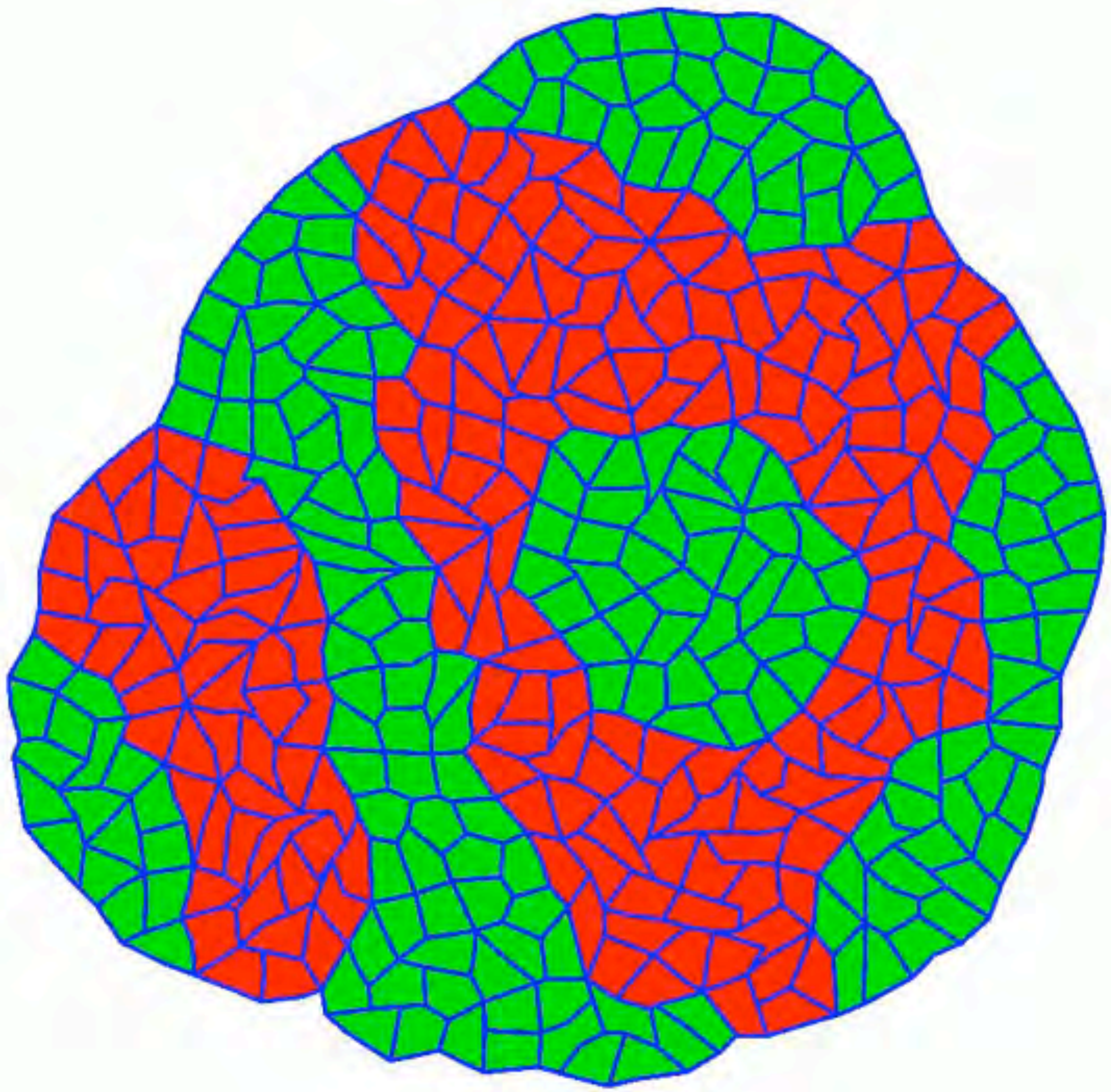
Universiteit Leiden

Alternative representation: Boundary-element model



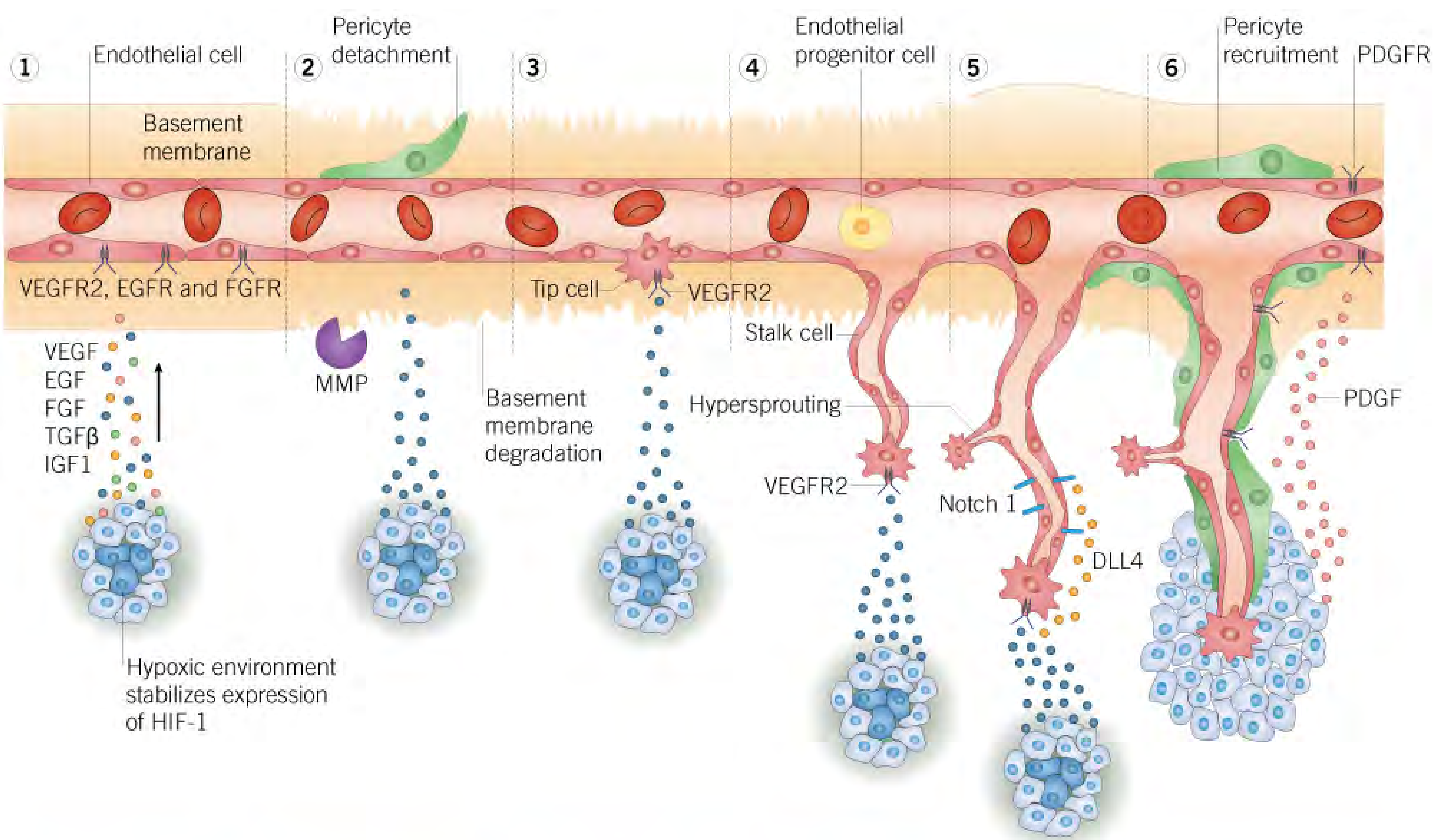
Harold Wolff

Alternative representation: Boundary-element model



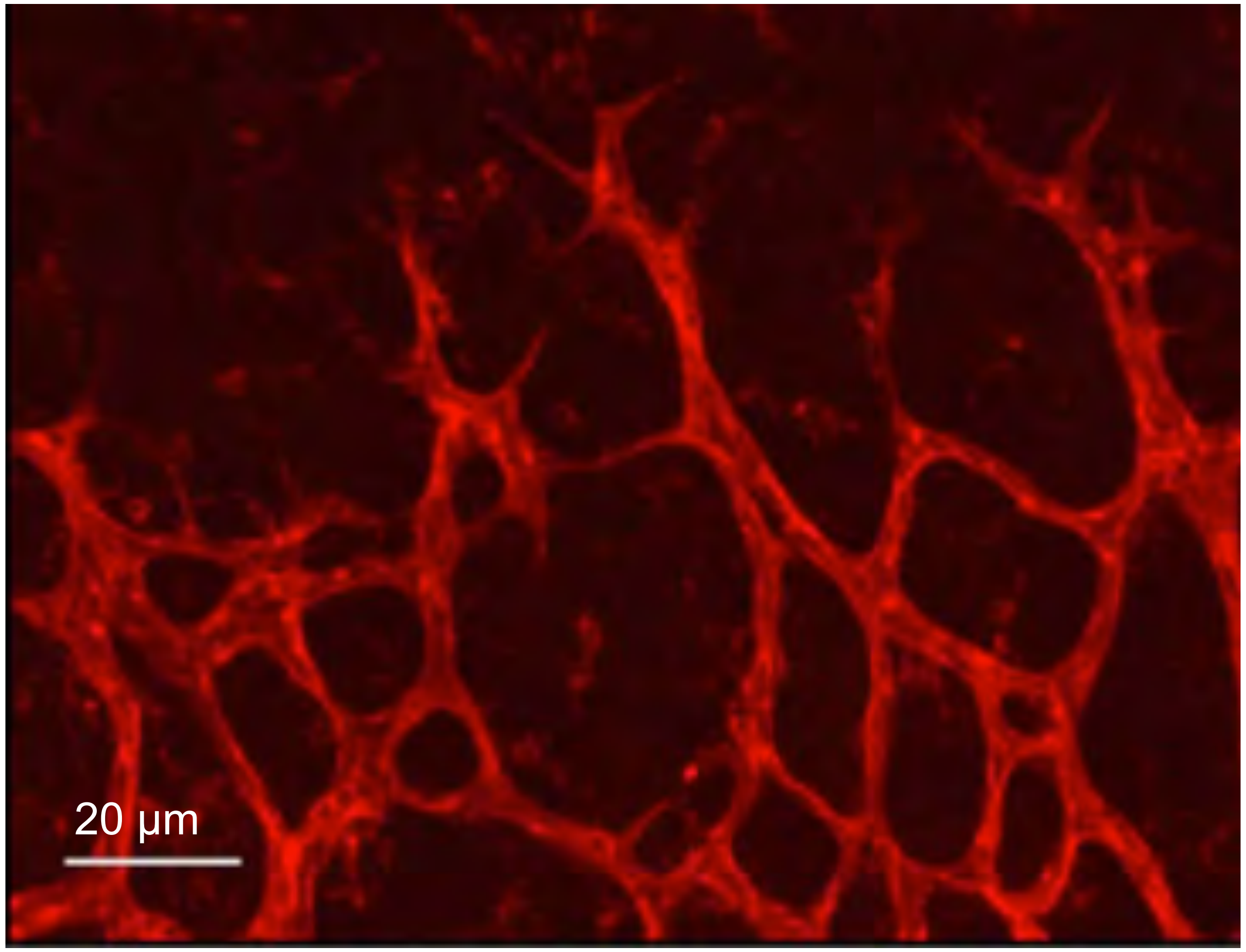
Harold Wolff

Favourite problem: Angiogenesis
Growth of new blood vessels, e.g., in cancer



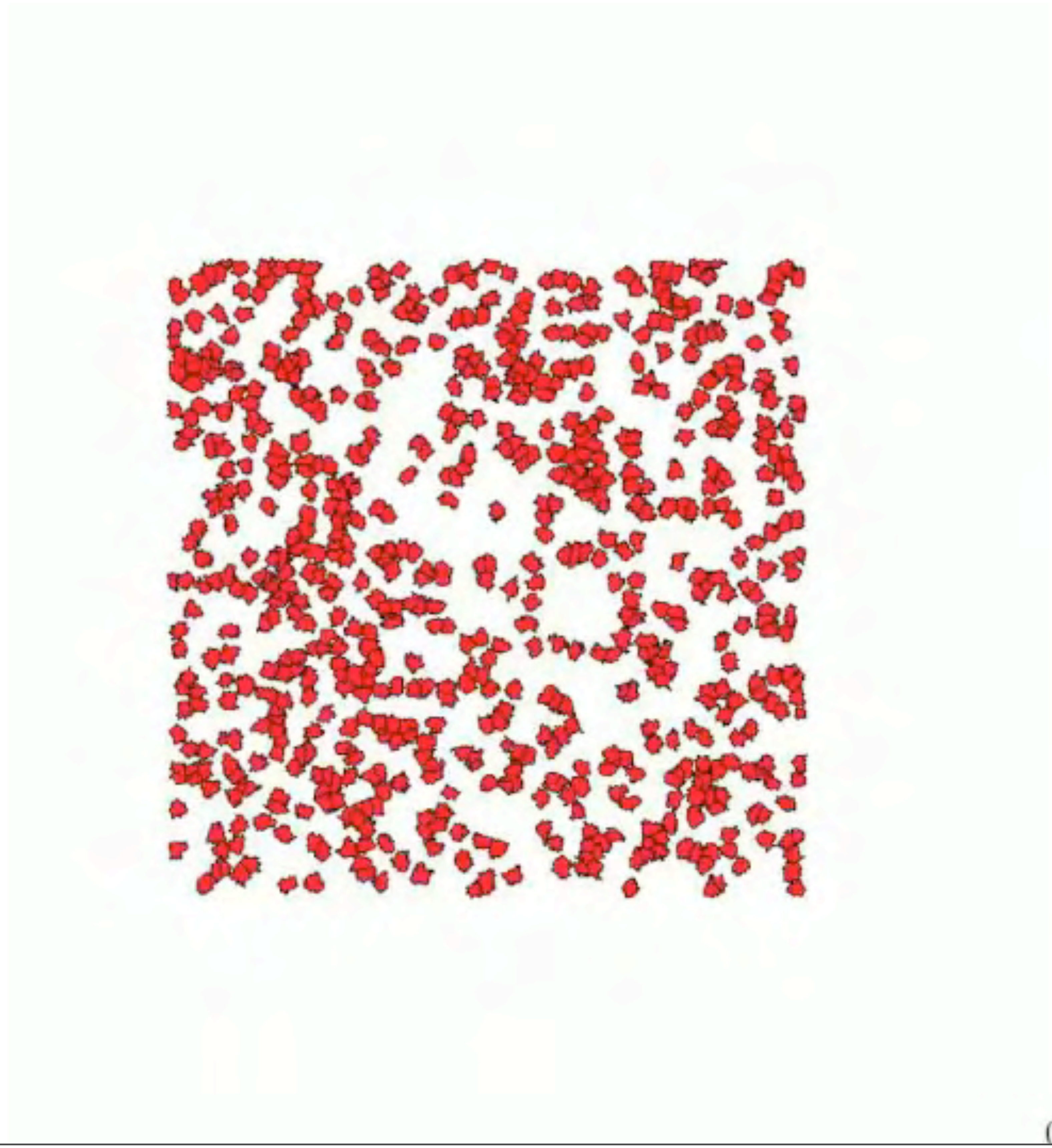
Modified from tocris.com: *Angiogenesis, Cancer Research Product Guide* Edition 3, 2015

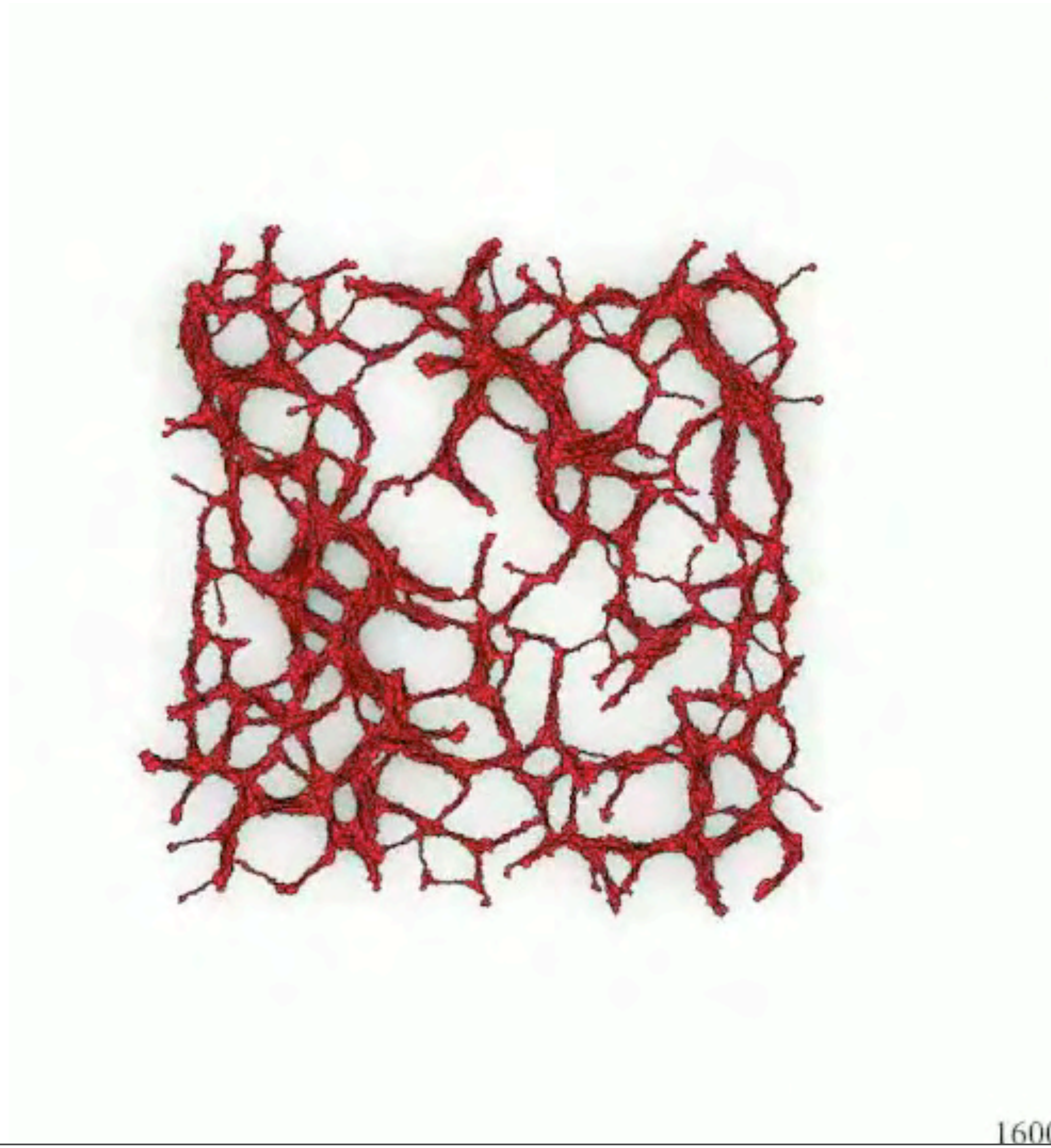
Angiogenesis:
collective cell behavior
How do cells (ECs) form vascular networks?



Mouse retinal vascular network. From: Cruys et al. *Nature Communications* 2016

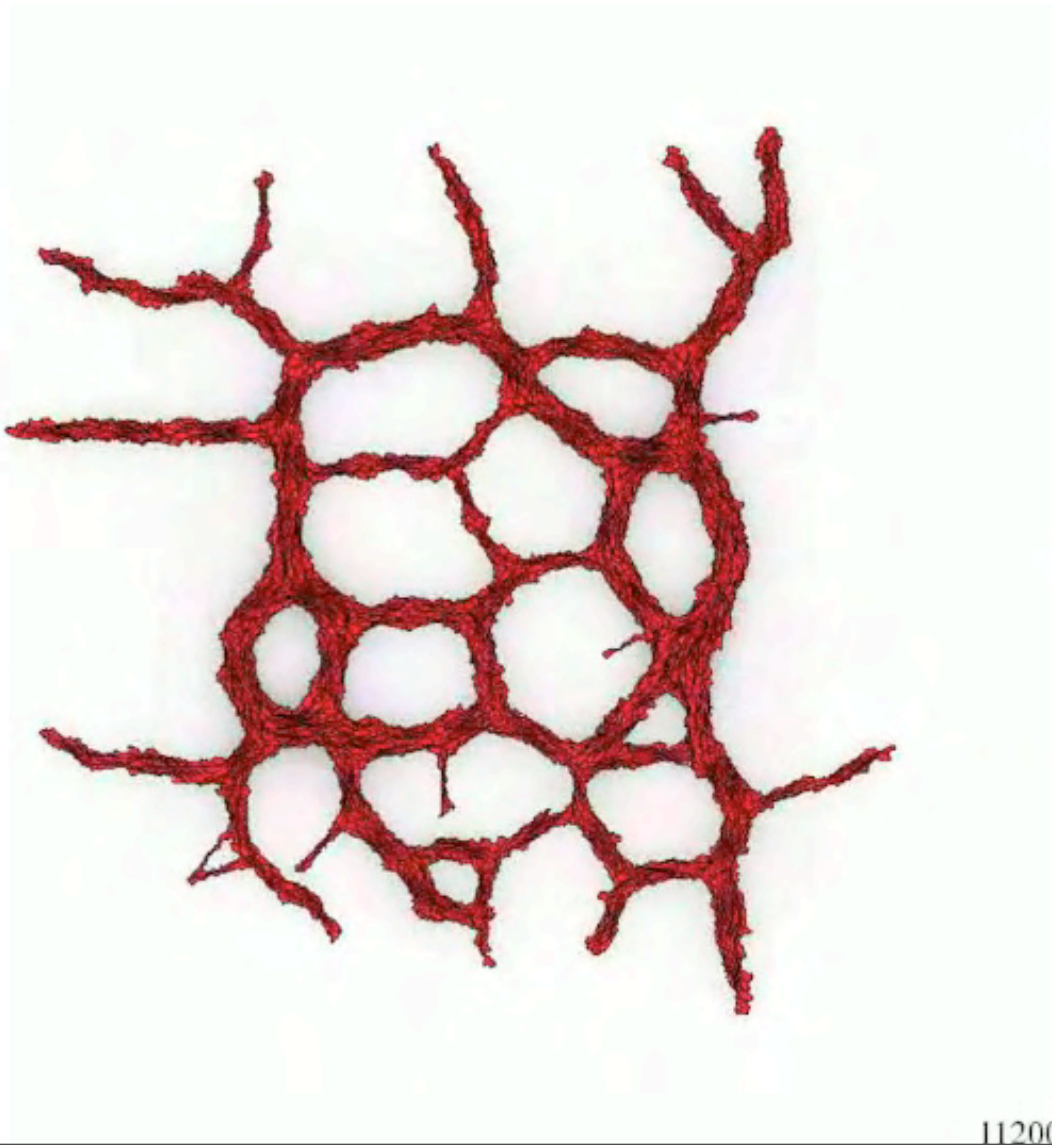
Universiteit Leiden

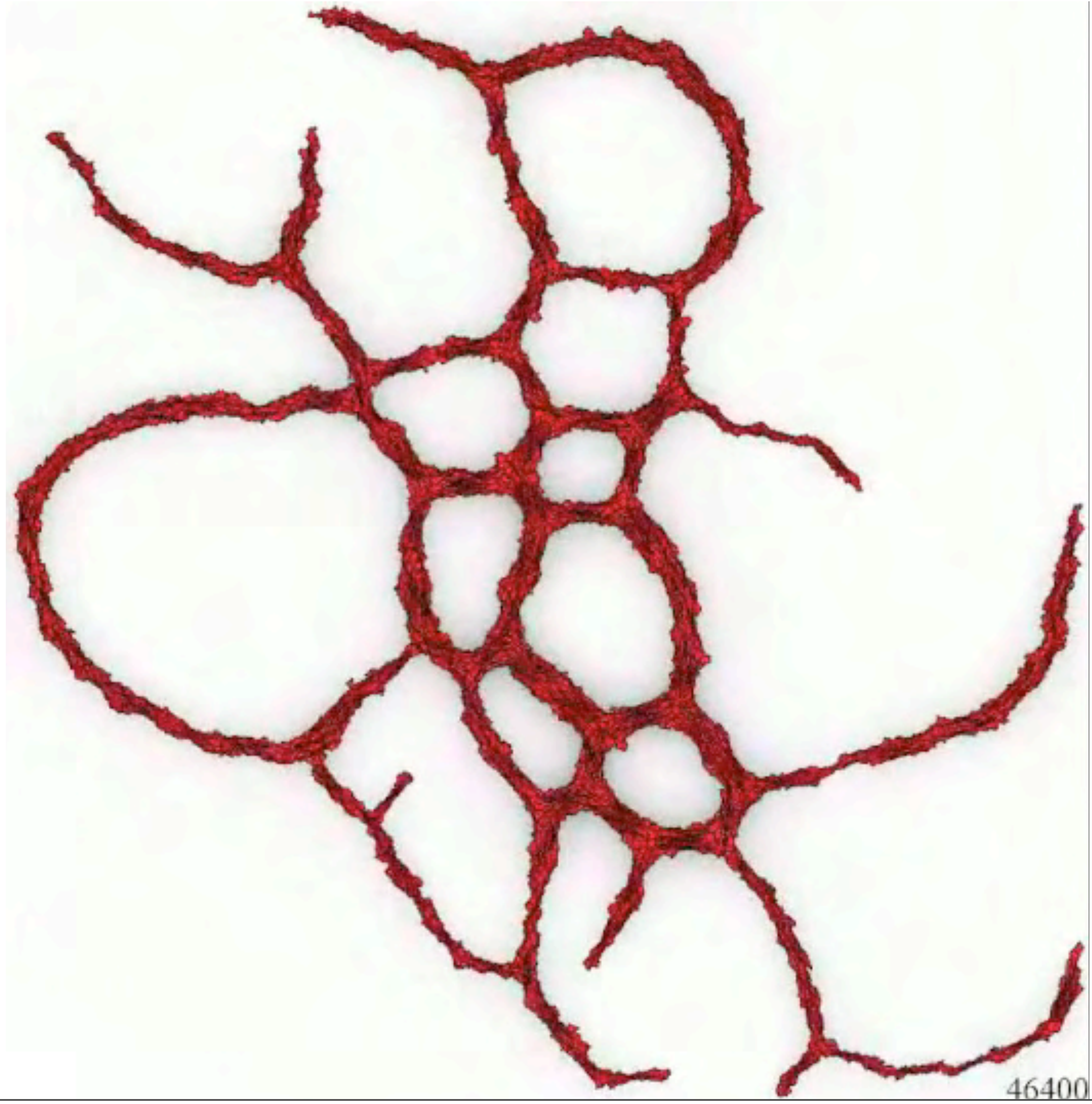



1600

CWI

Universiteit Leiden




46400

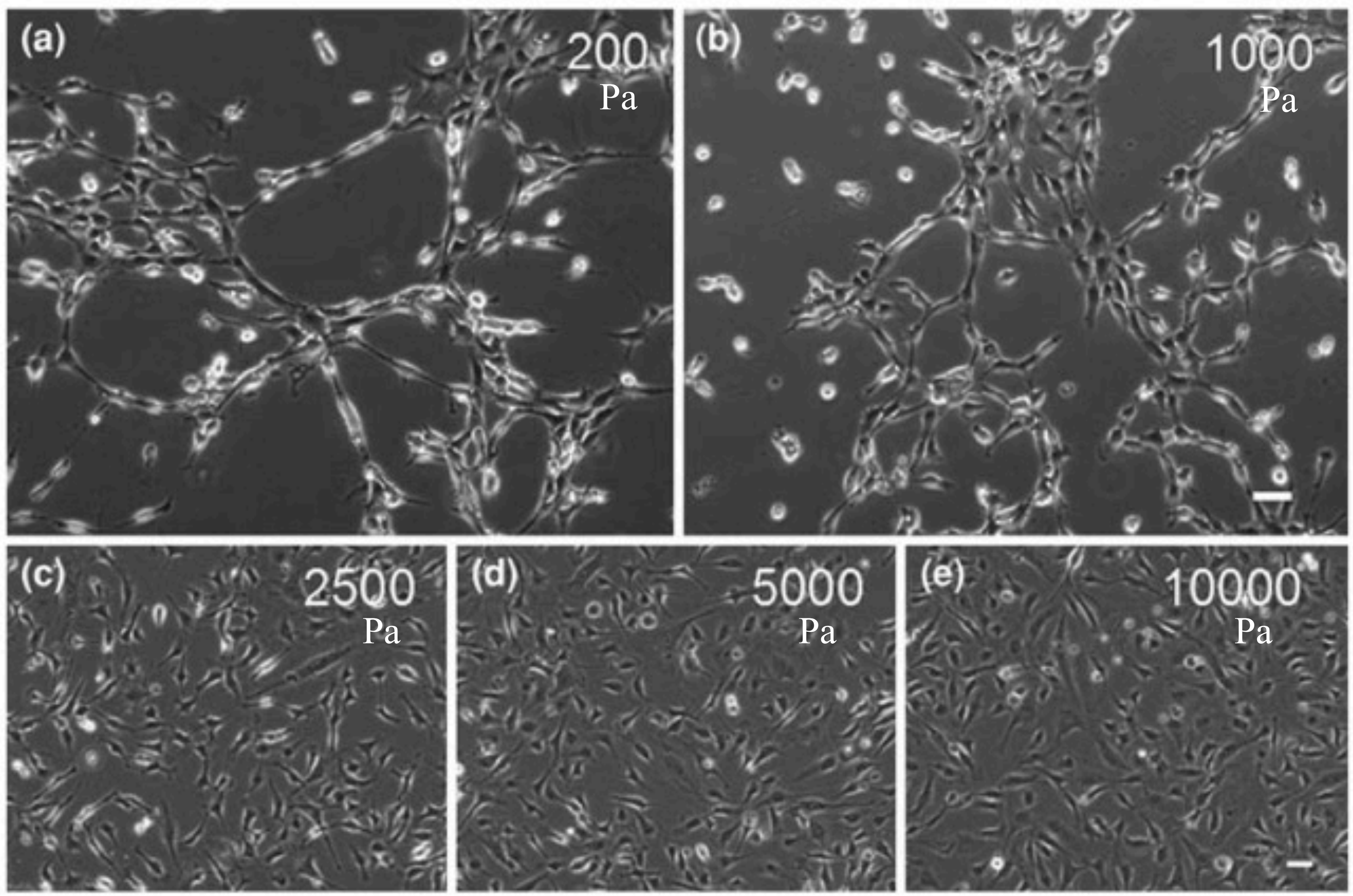
CWI

Universiteit Leiden

But: substrate stiffness steers cells

Bovine aortic endothelial cells on
poly-acrylamide substrate (non-fibrous)

Soft matrix

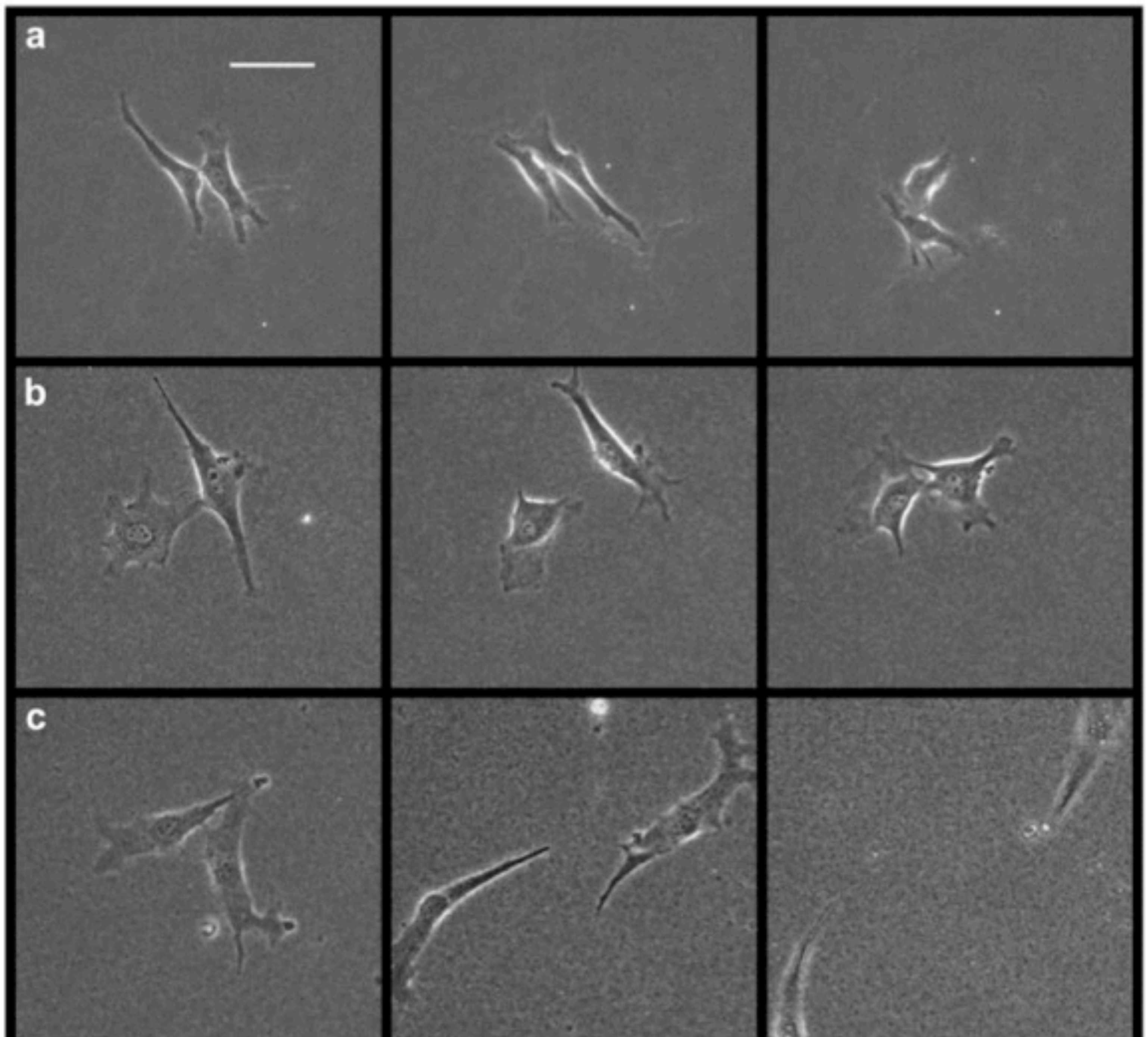


Stiff matrix

Califano and Reinhart-King, 2008

And.. cells can communicate mechanically

(Reinhart-King et al. 2008)



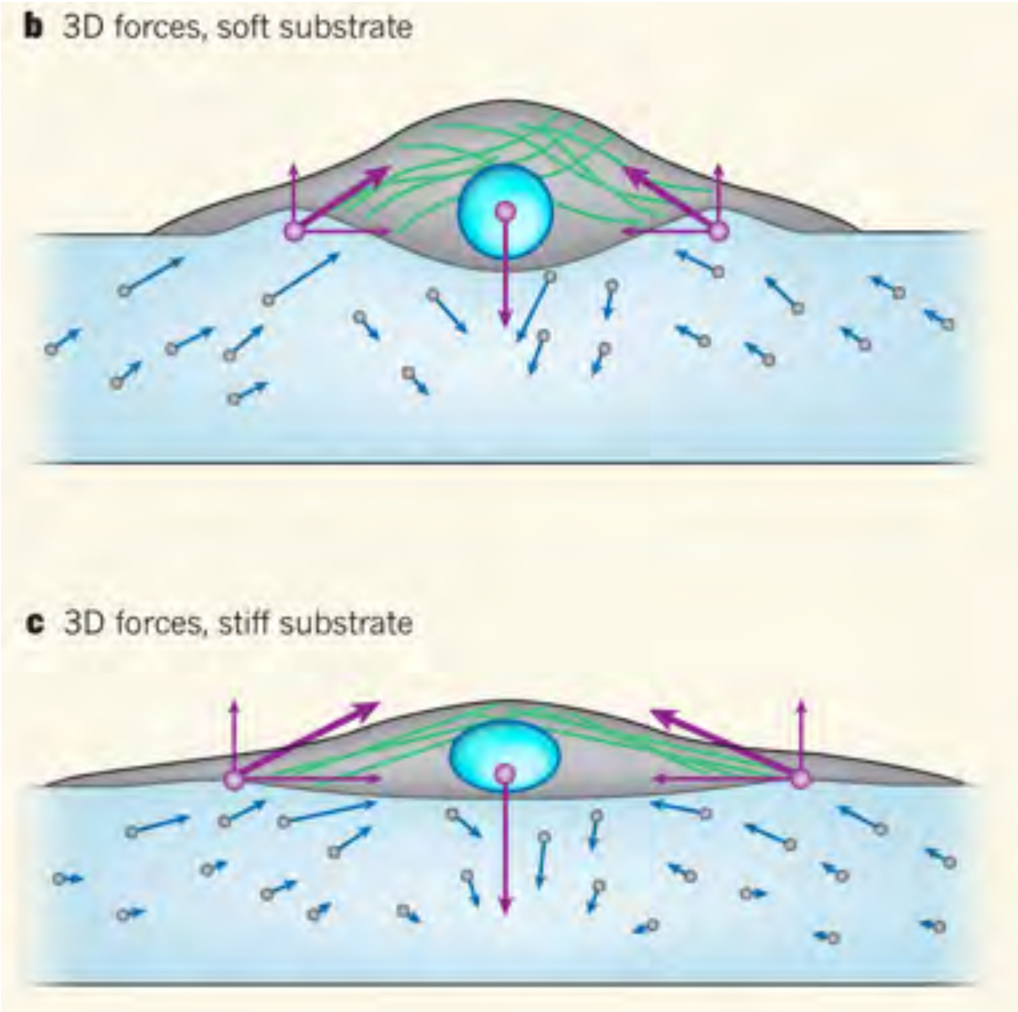
Soft matrix (500 Pa)
Cells touch and remain in contact

Stiffer matrix (5.5 kPa)
Cells touch, loose contact, touch again

Stiff matrix (33 kPa)
Cells touch and walk away

Hypothesis: 'active cell sensing'

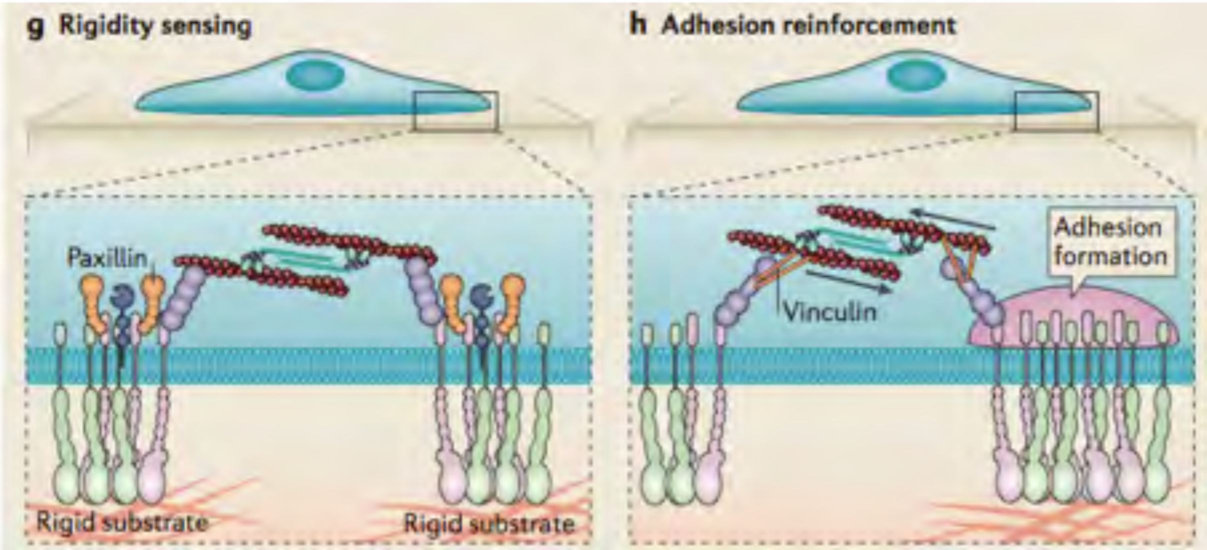
- (1) Cells pull on matrix



Hersen & Ladoux, Nature (2011)

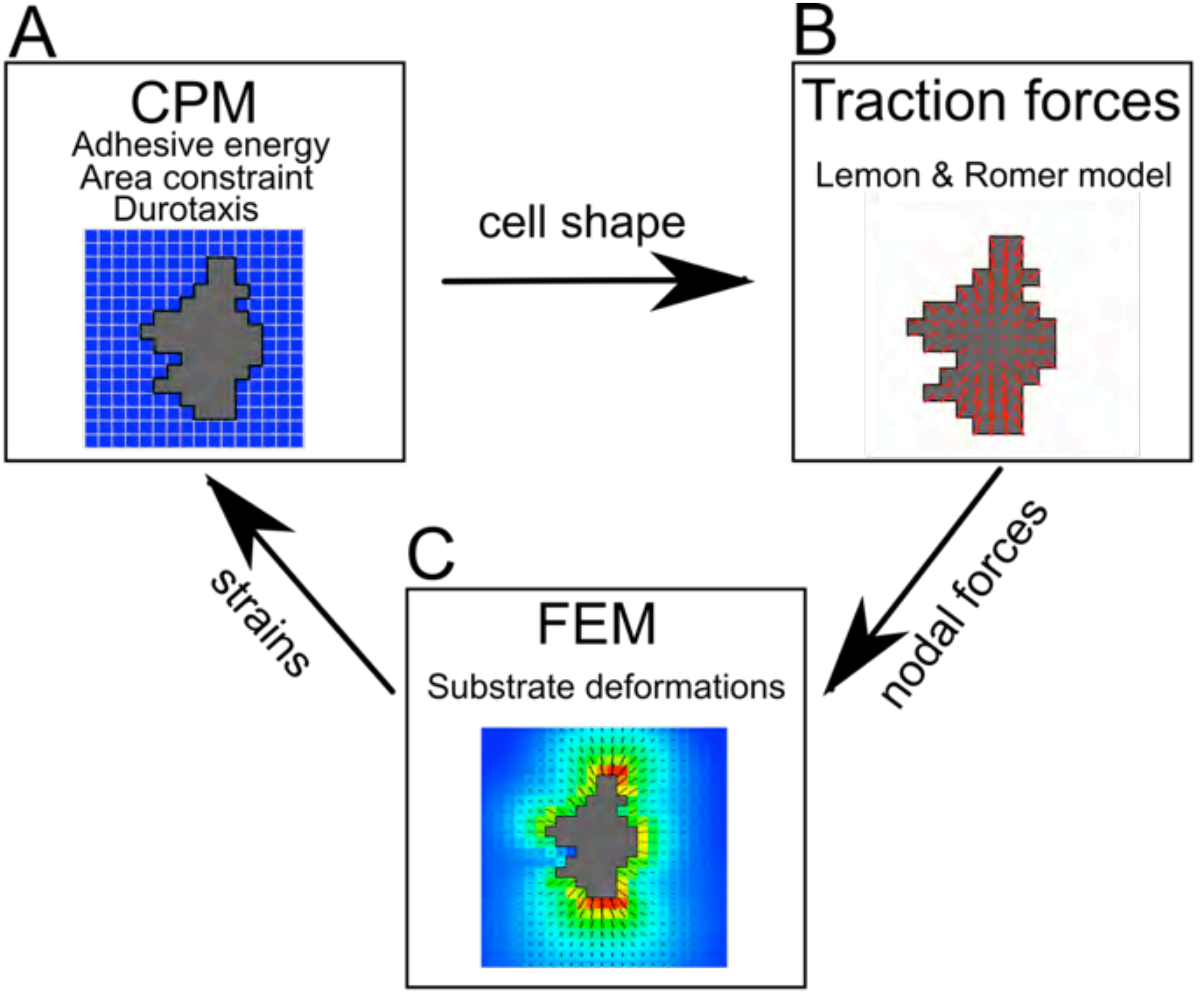
- (2) matrix strain-stiffens

- (3) Increased tension stabilizes focal adhesions
on strained matrixes



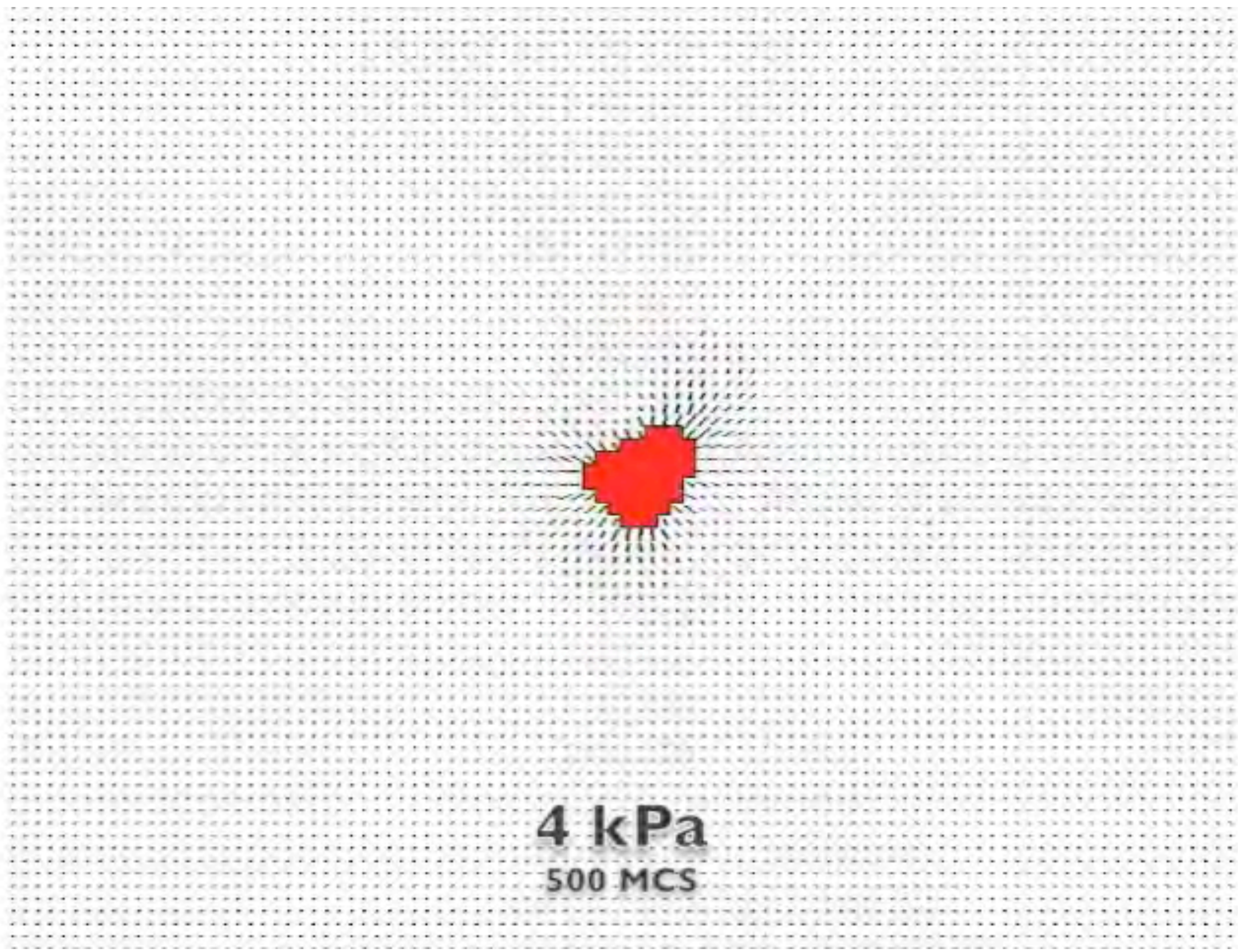
Iskratsch et al. Nat. Rev. Mol. Cell. Biol. (2014)

Mechanical cell-substrate feedback



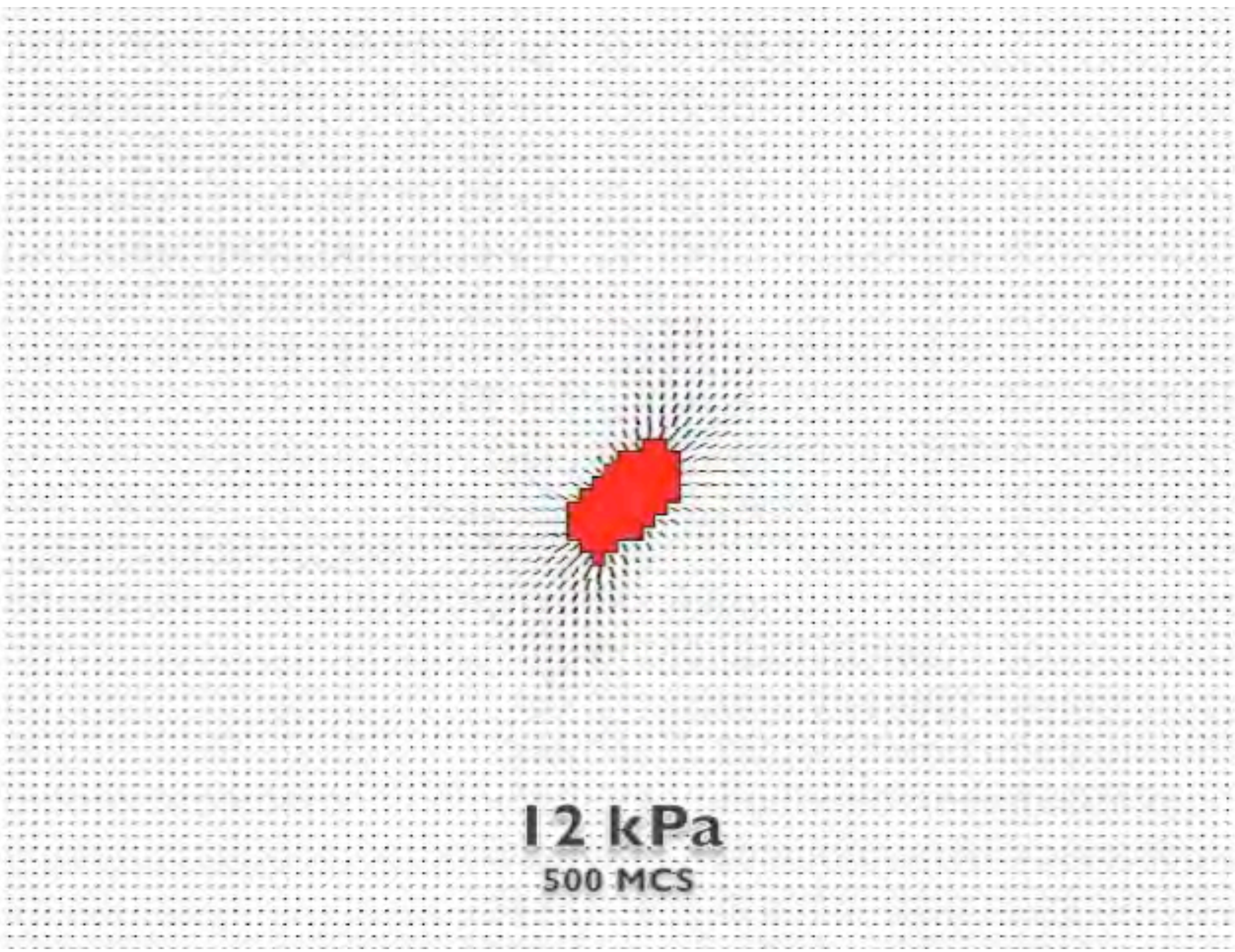
Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

Feedback between cell traction and strain response



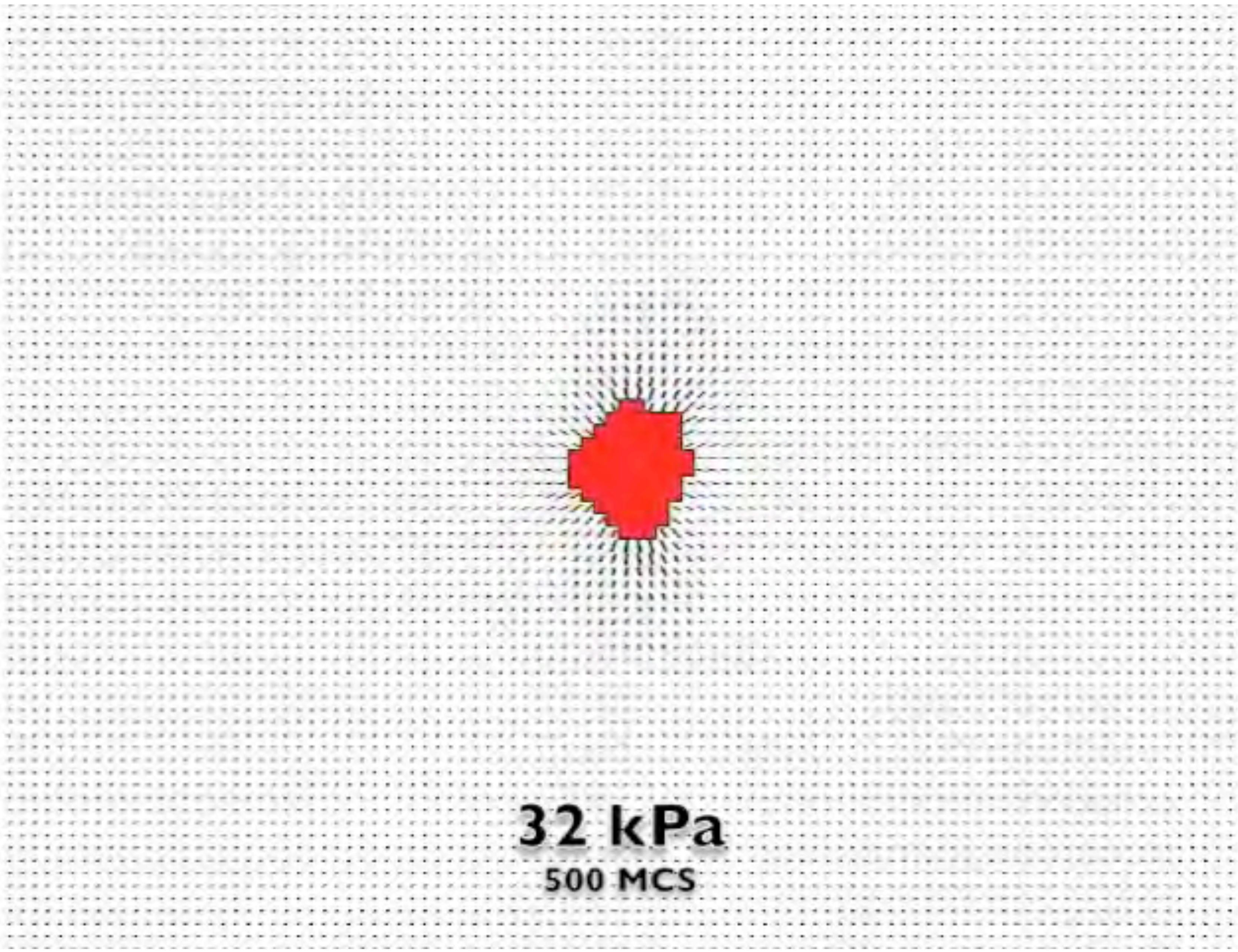
Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

Feedback between cell traction and strain response



Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

Feedback between cell traction and strain response

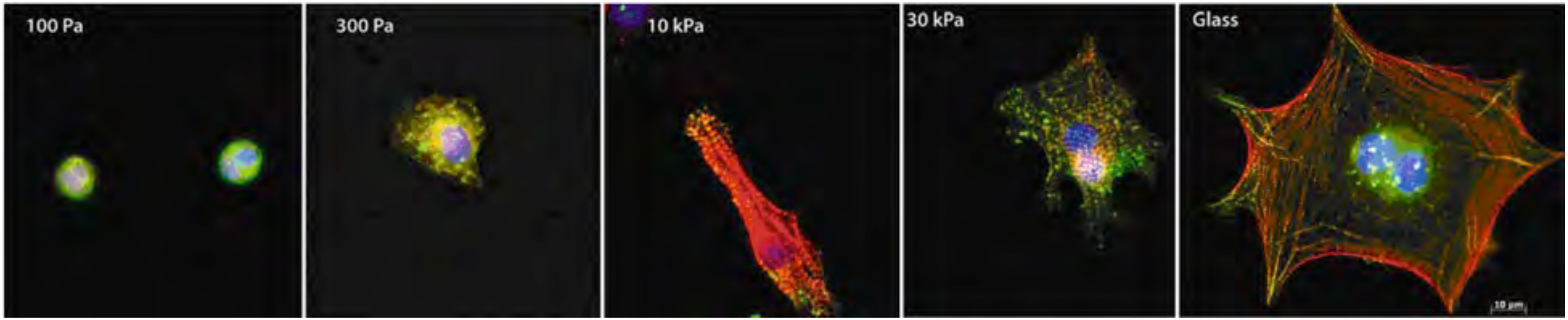


Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

Behavior of single cells

Feedback between cell-induced strain and cell responses

Cardiomyocytes (it works about the same for ECs...):



Winer et al. , in: Wagoner et al. (eds.), 2011

SOFT SUBSTRATE

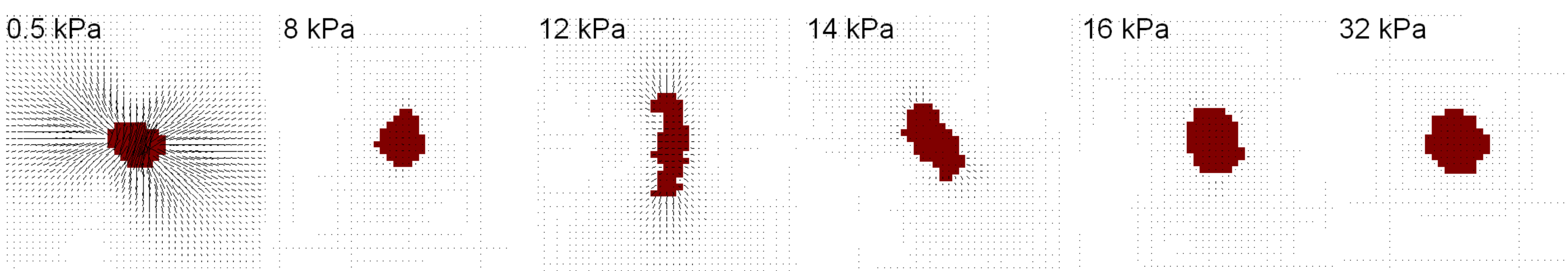
- stretch all around
- contraction

INTERMEDIATE SUBS.

- stretch along long axis
- elongation

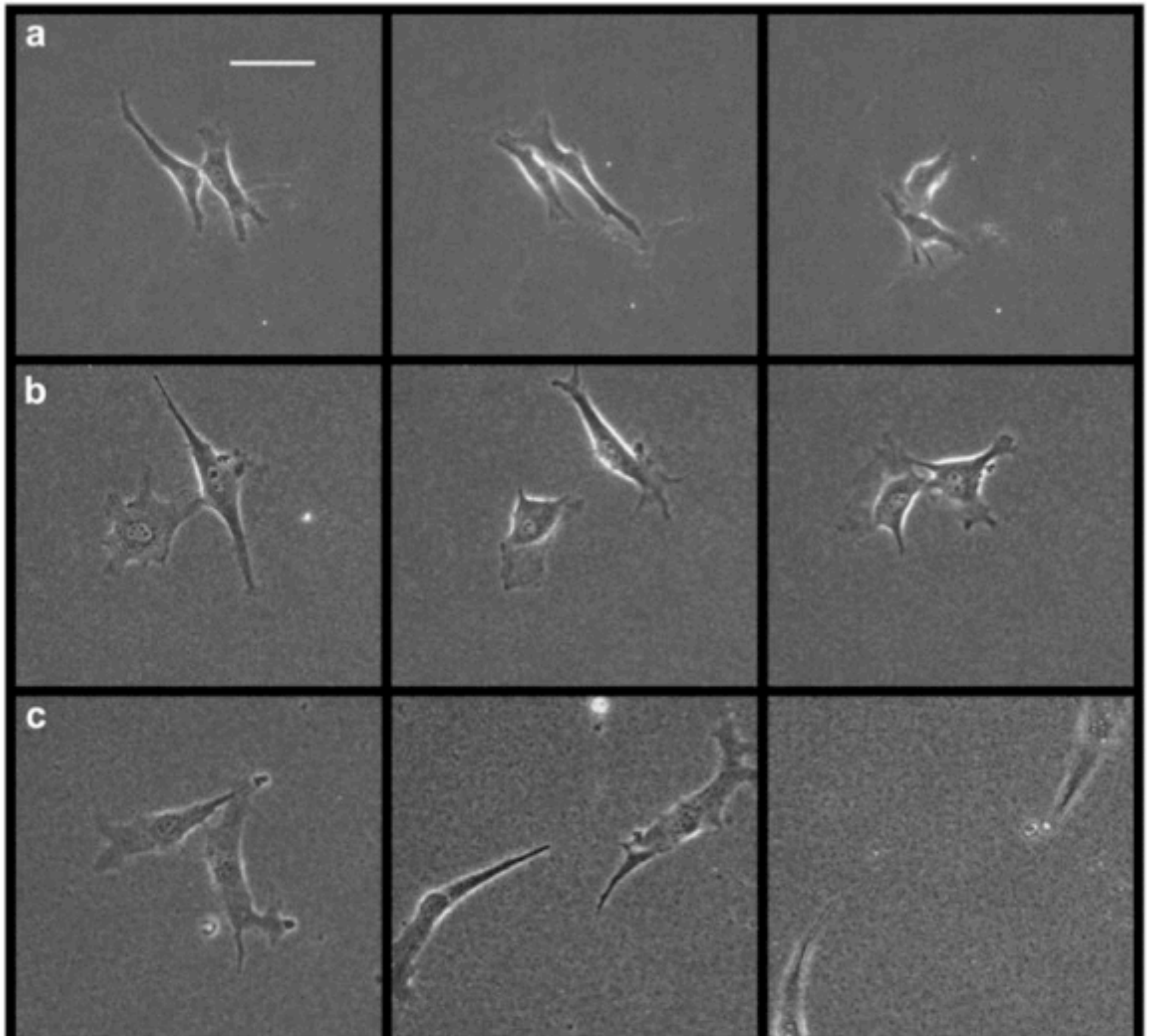
STIFF SUBSTRATE

- little stretch
- spreading



Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

Cell-cell interactions
(Reinhart-King et al. 2008)

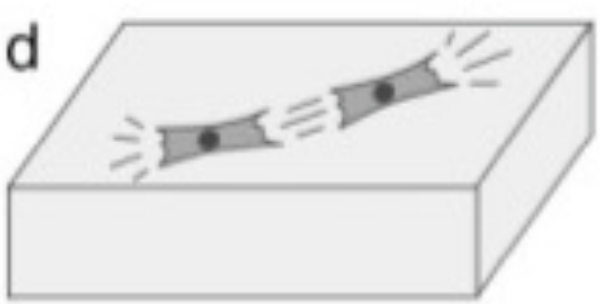


Soft matrix (500 Pa)
Cells touch and remain in contact

Stiffer matrix (5.5 kPa)
Cells touch, loose contact, touch again

Stiff matrix (33 kPa)
Cells touch and walk away

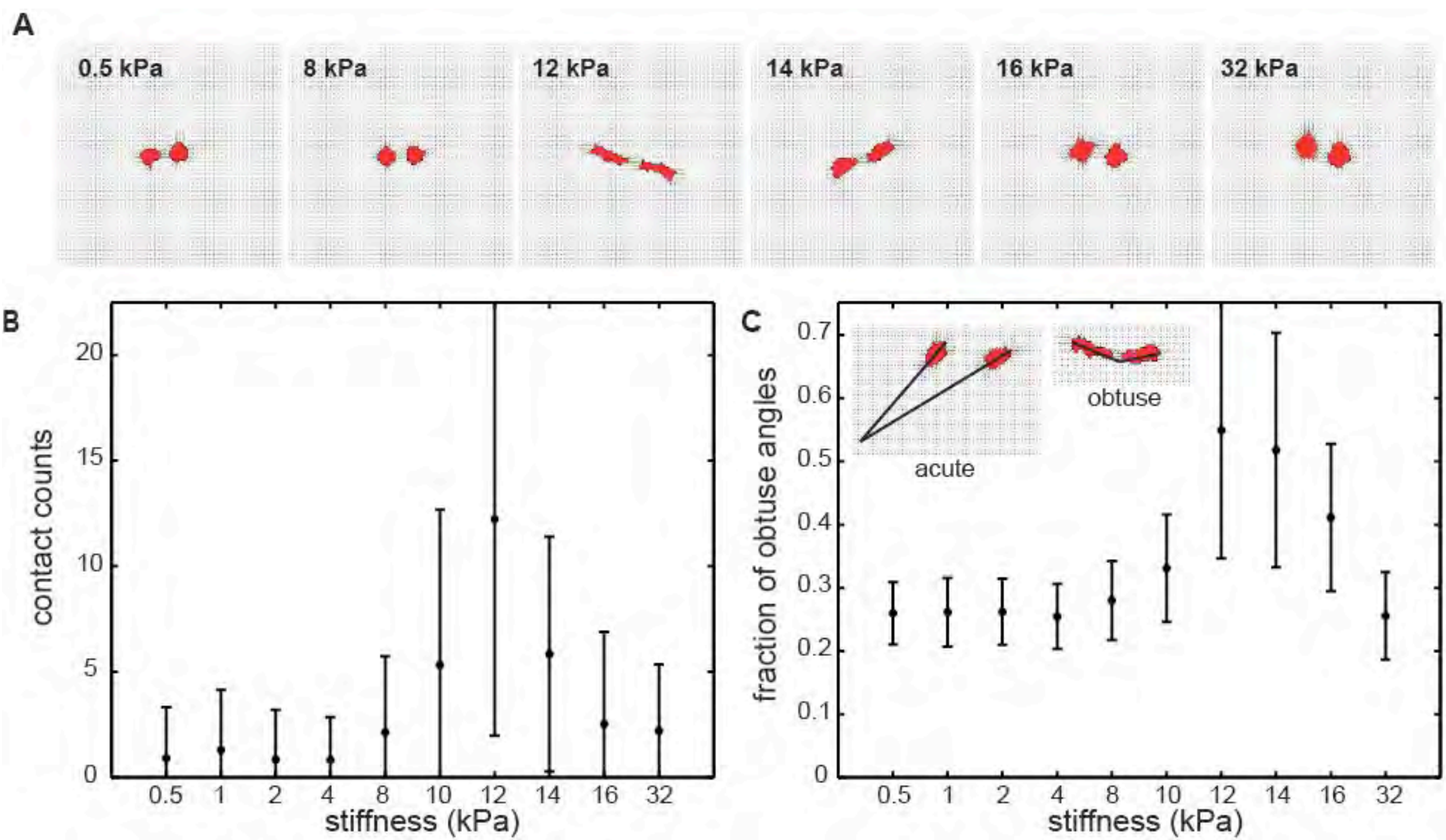
Mechanical cell-cell communication



cf. Bischofs and Schwarz
PNAS 2003

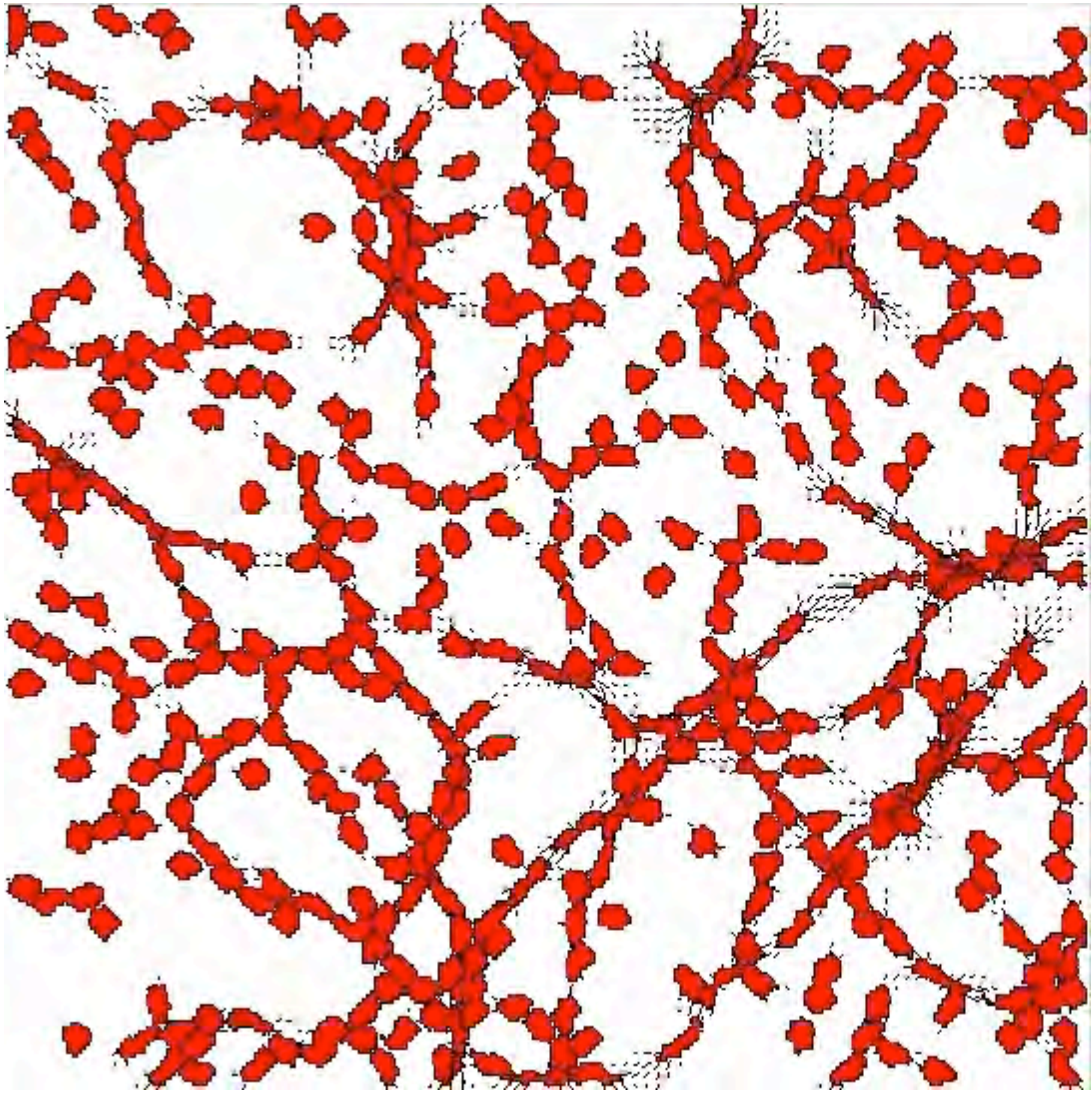
Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

Mechanical cell-cell communication



Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

Resulting collective behavior



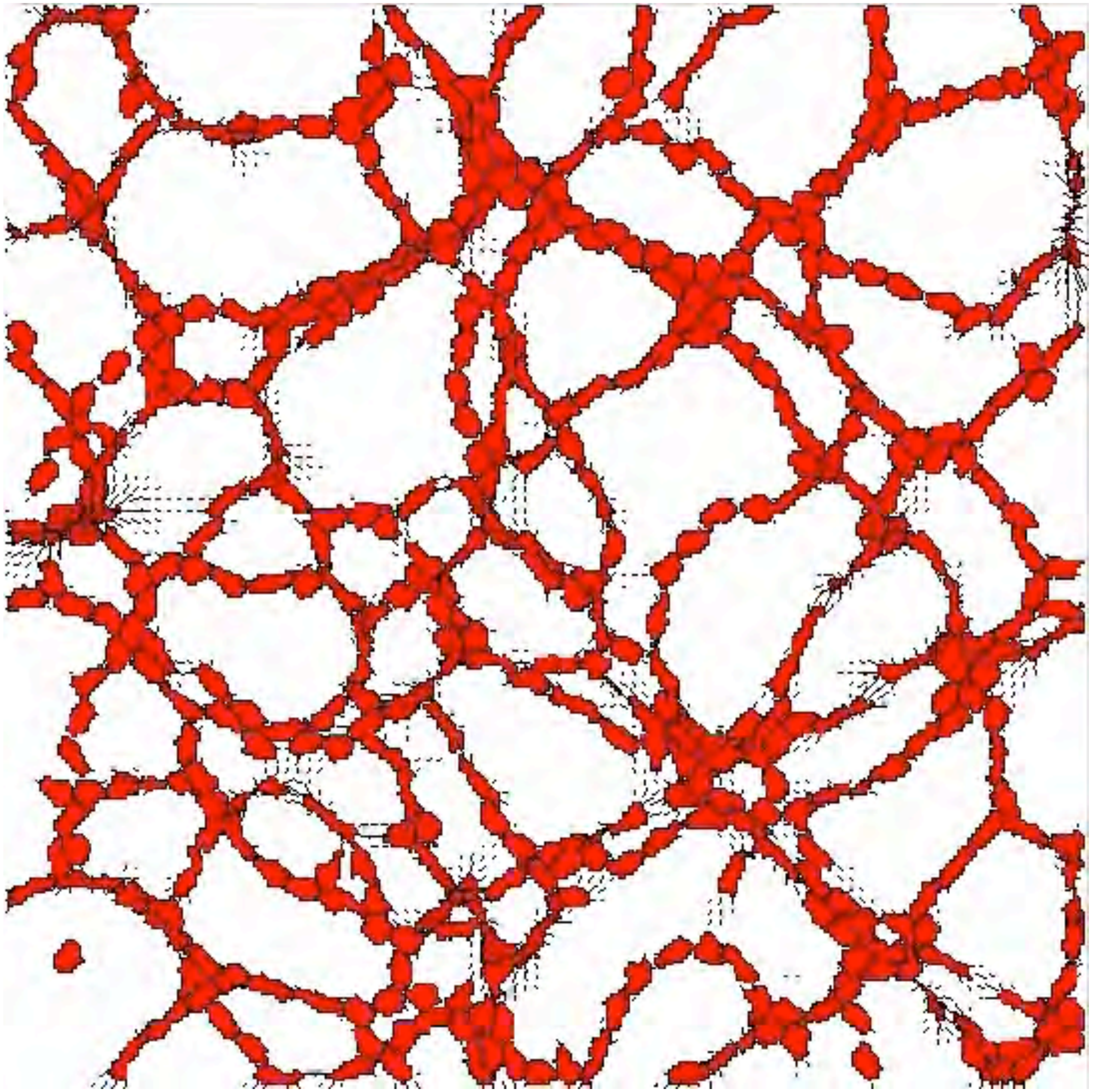
10 kPa

Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

CWI

Universiteit Leiden

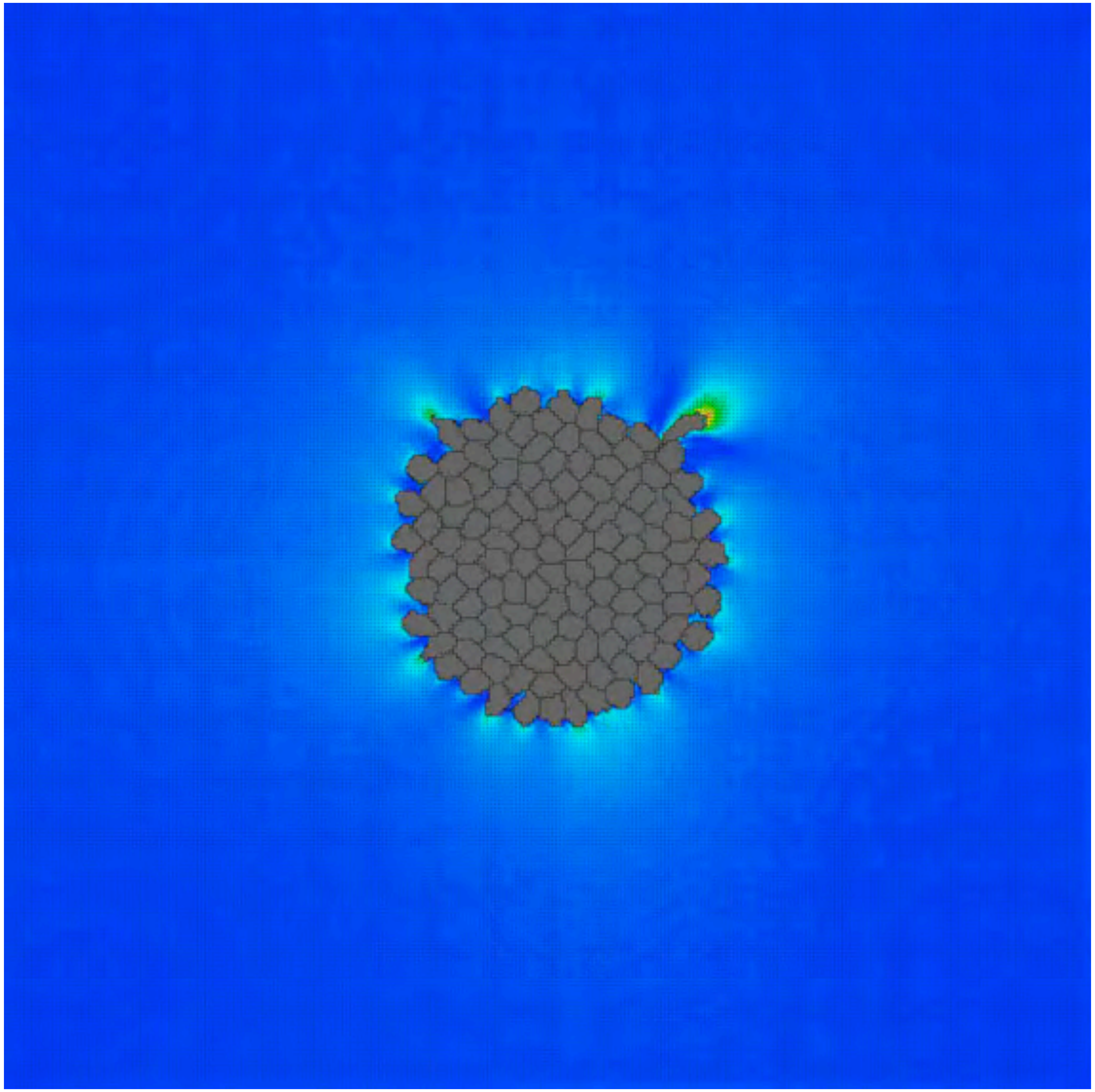
Resulting collective behavior



10 kPa

Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

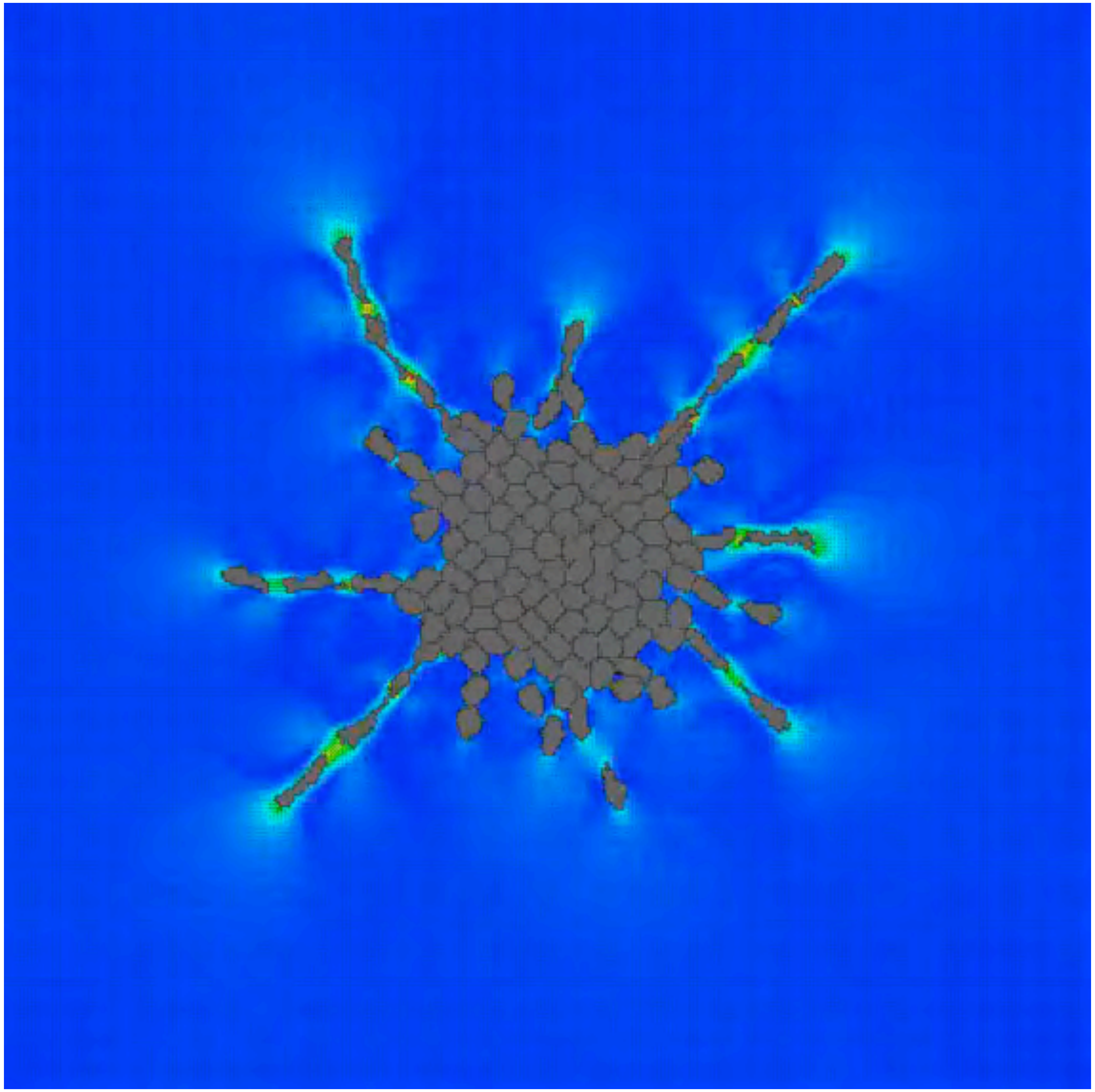
Sprouting



10 kPa

Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

Sprouting

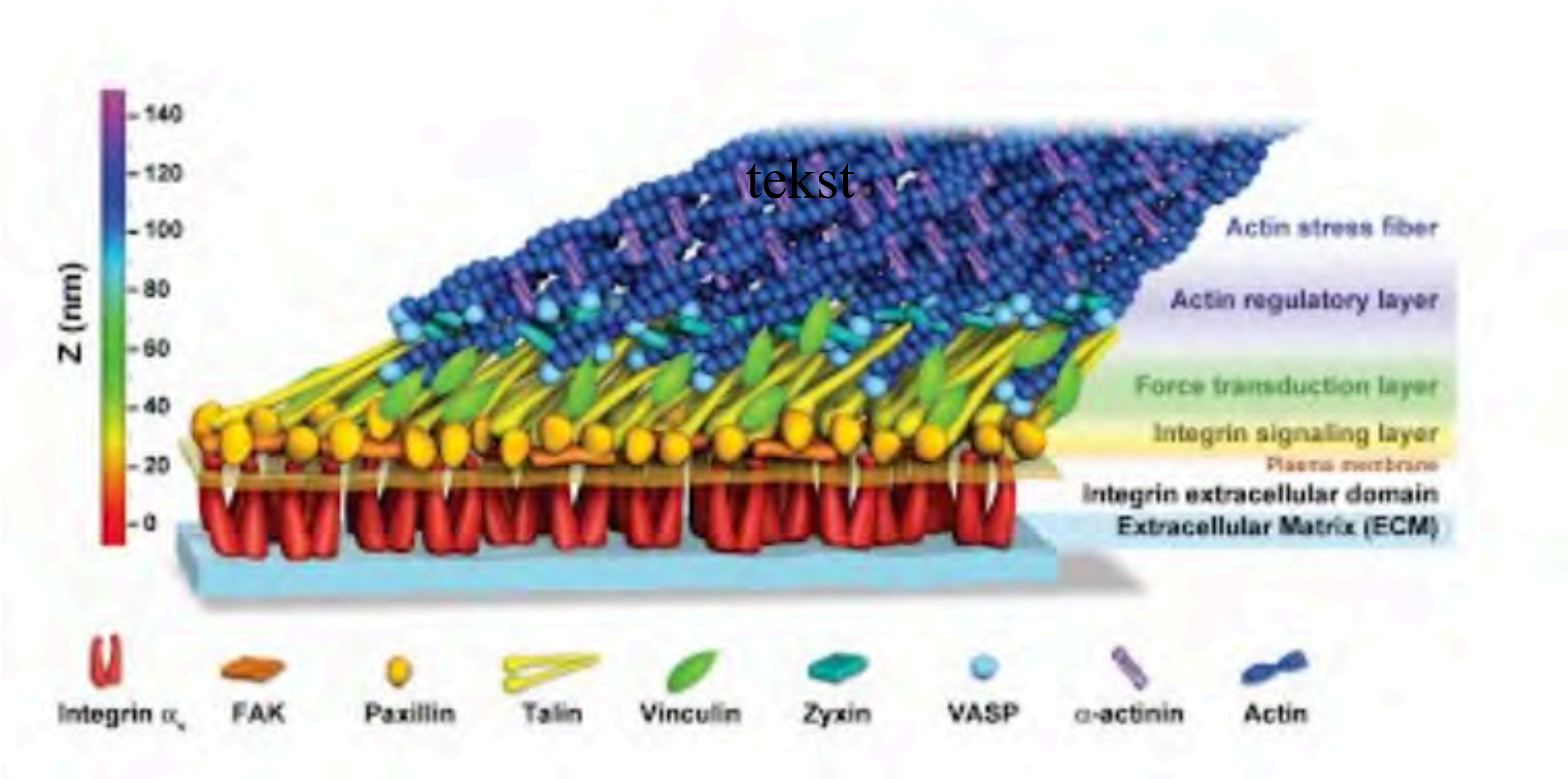


10 kPa

Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

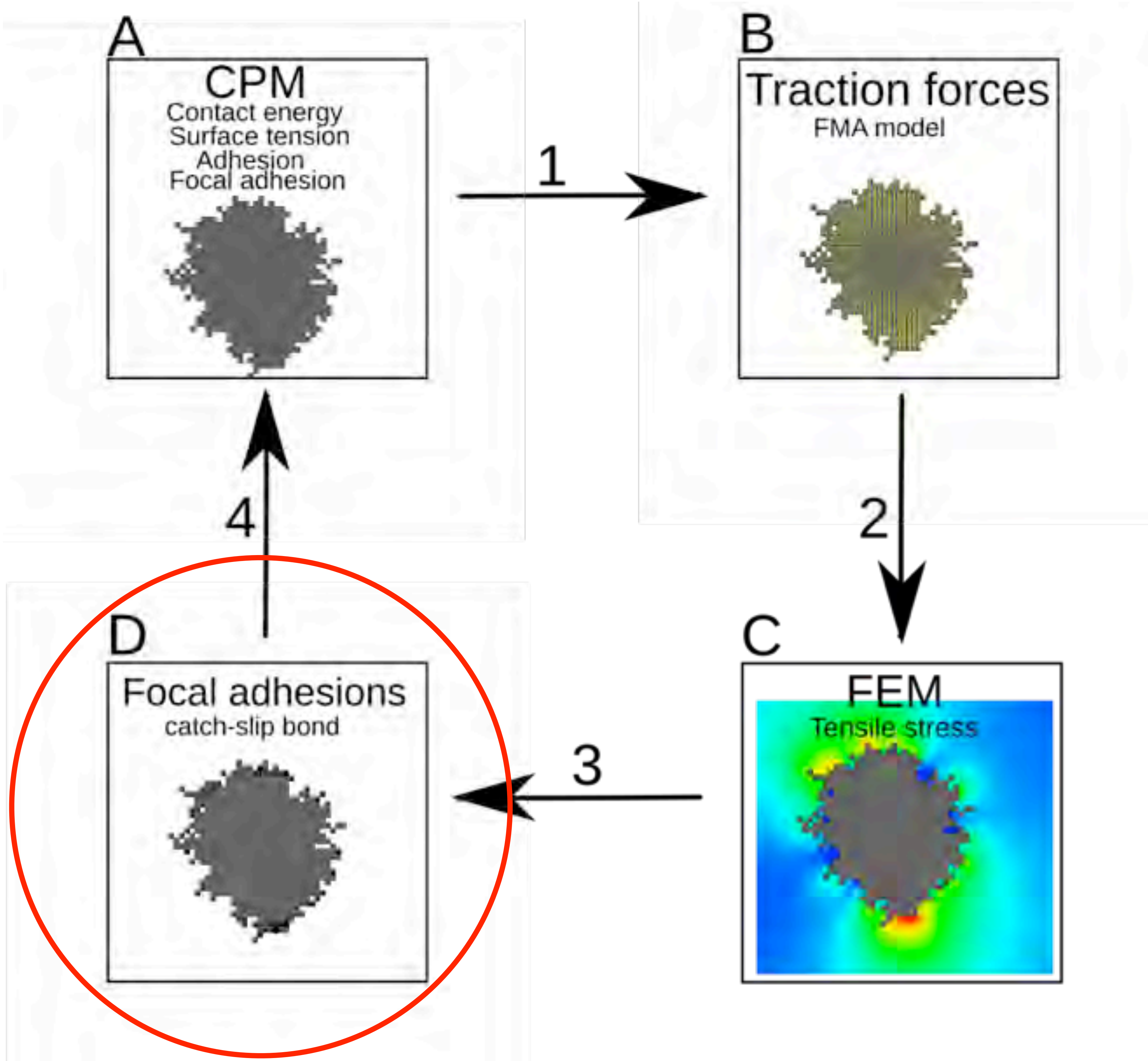
Next step: subcellular regulation of cell ECM interactions

- Focal adhesions: mechano-sensitive cell 'feet'



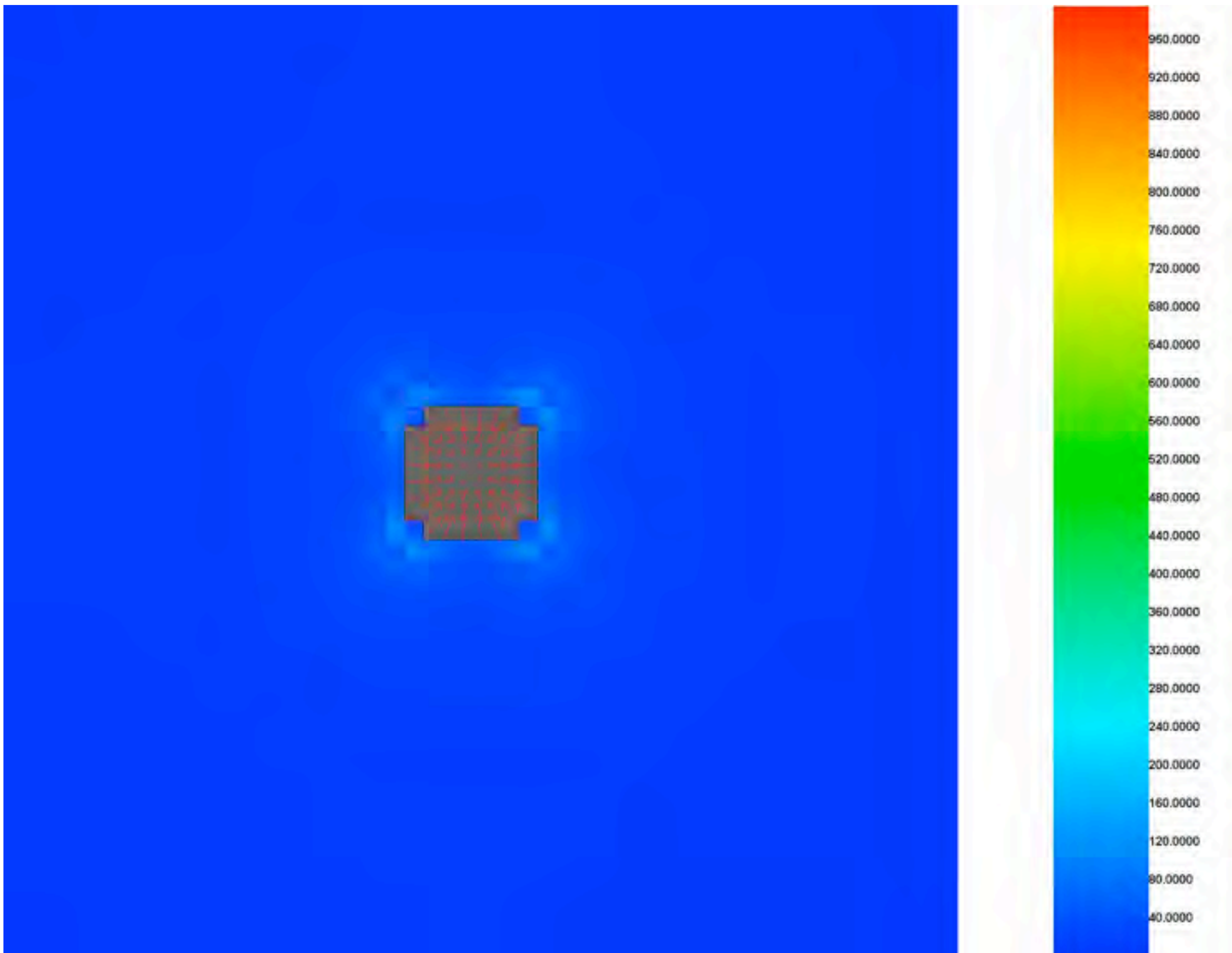
Kanchanawong et al., *Nature* 2010

Introduce explicit models of FAs



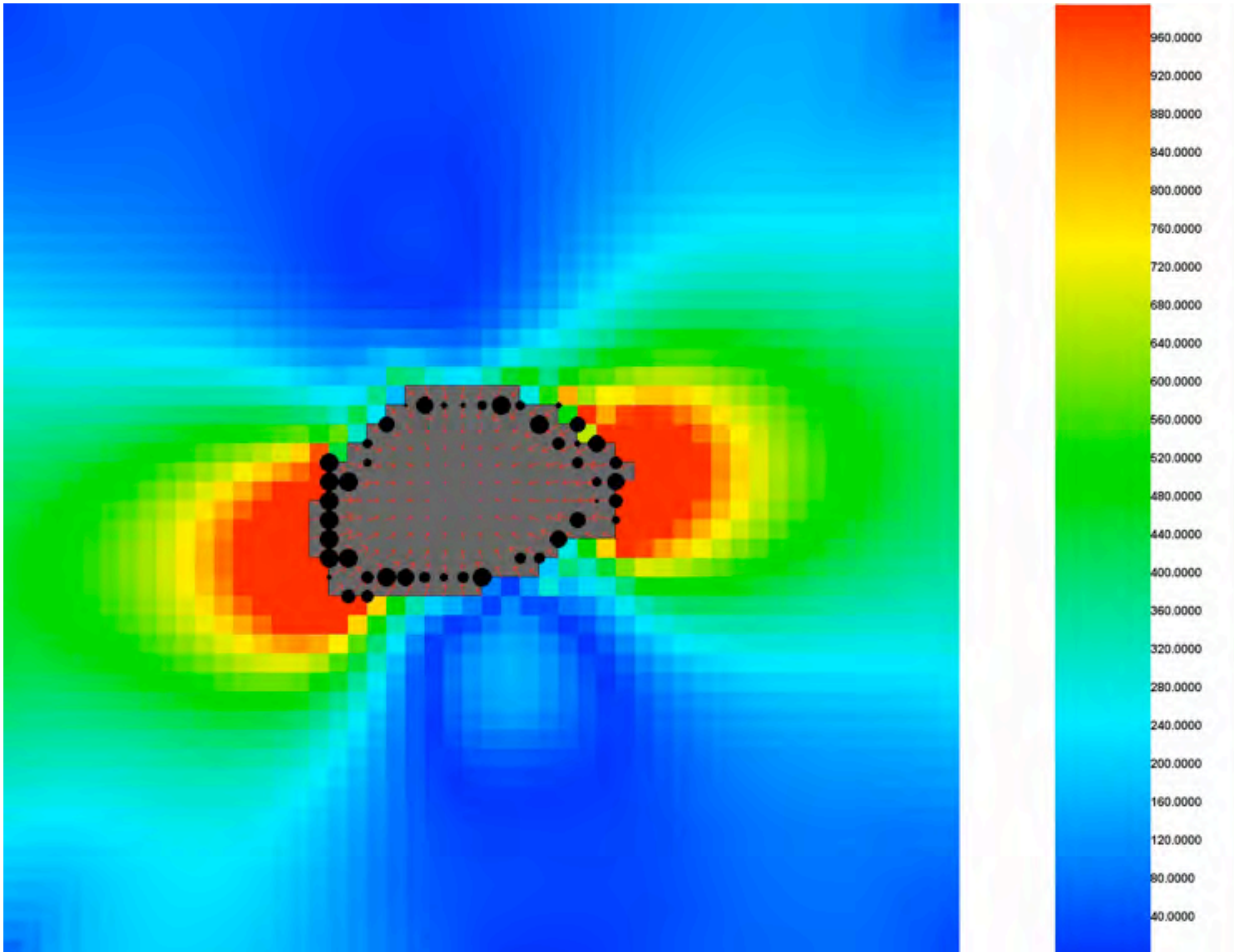
Lisanne Rens

Focal adhesion kinetics



Lisanne Rens

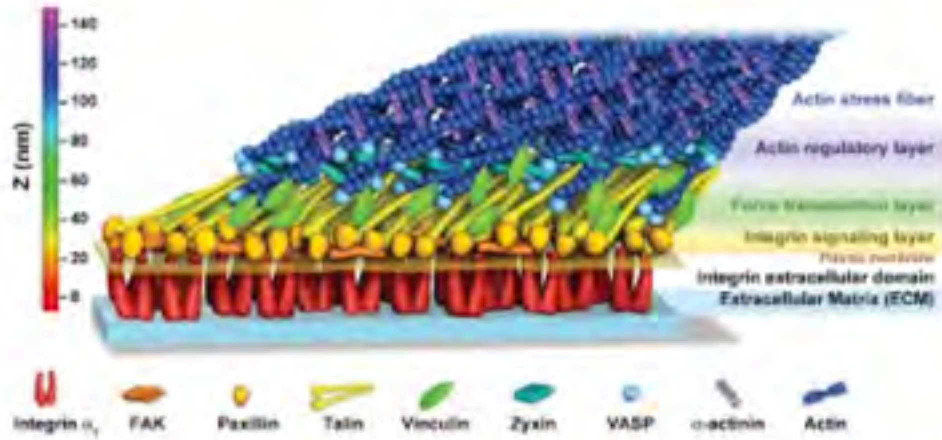
Focal adhesion kinetics



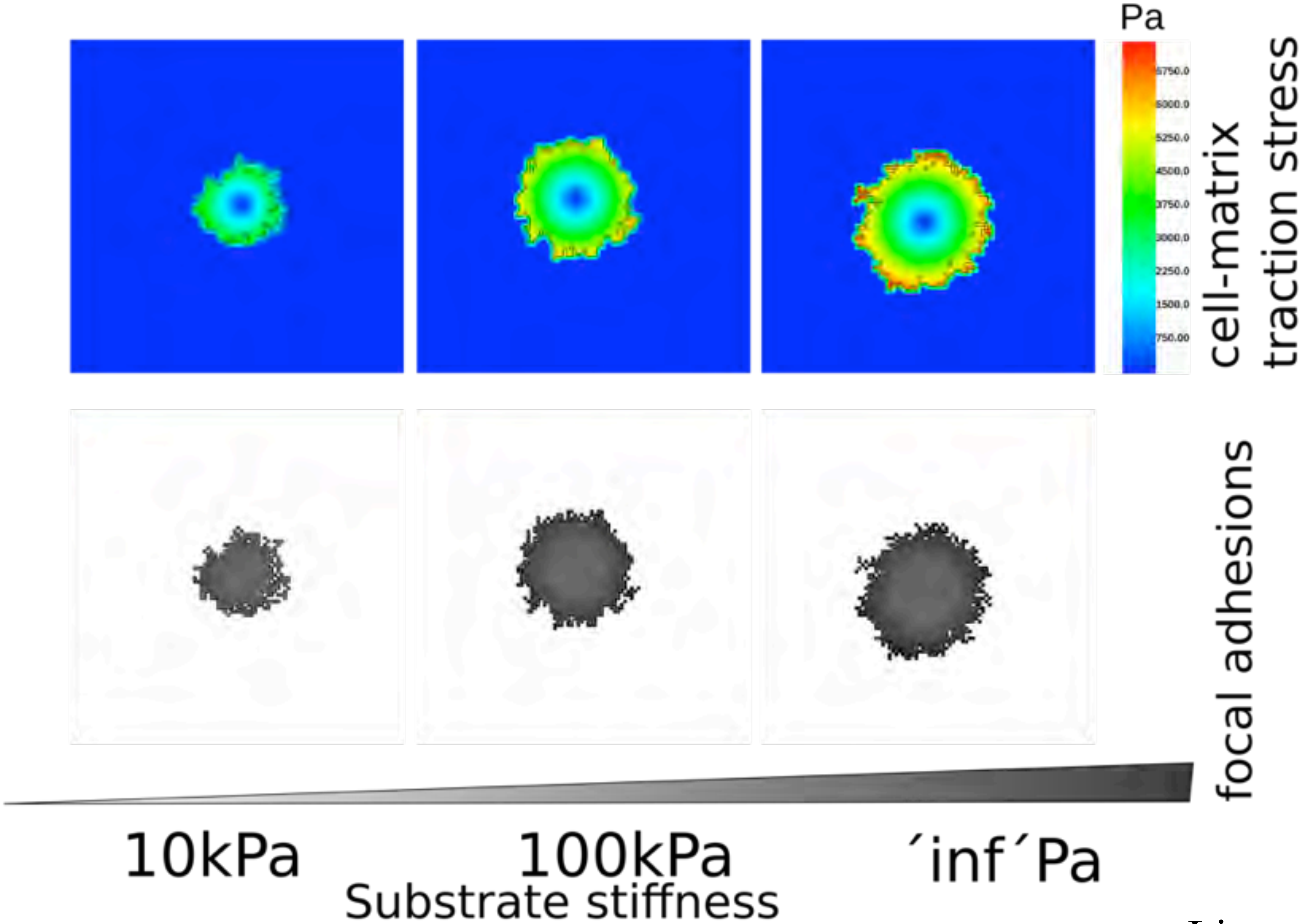
Lisanne Rens

Kinetic descriptions of focal adhesions

- Focal adhesions (FAs) assemble and disassemble continuously
- Tension reduces disassembly rate
  - Forces makes FAs larger and stronger
- I.e. force strenghtens connection of cells to ECM
- One ODE per focal adhesion



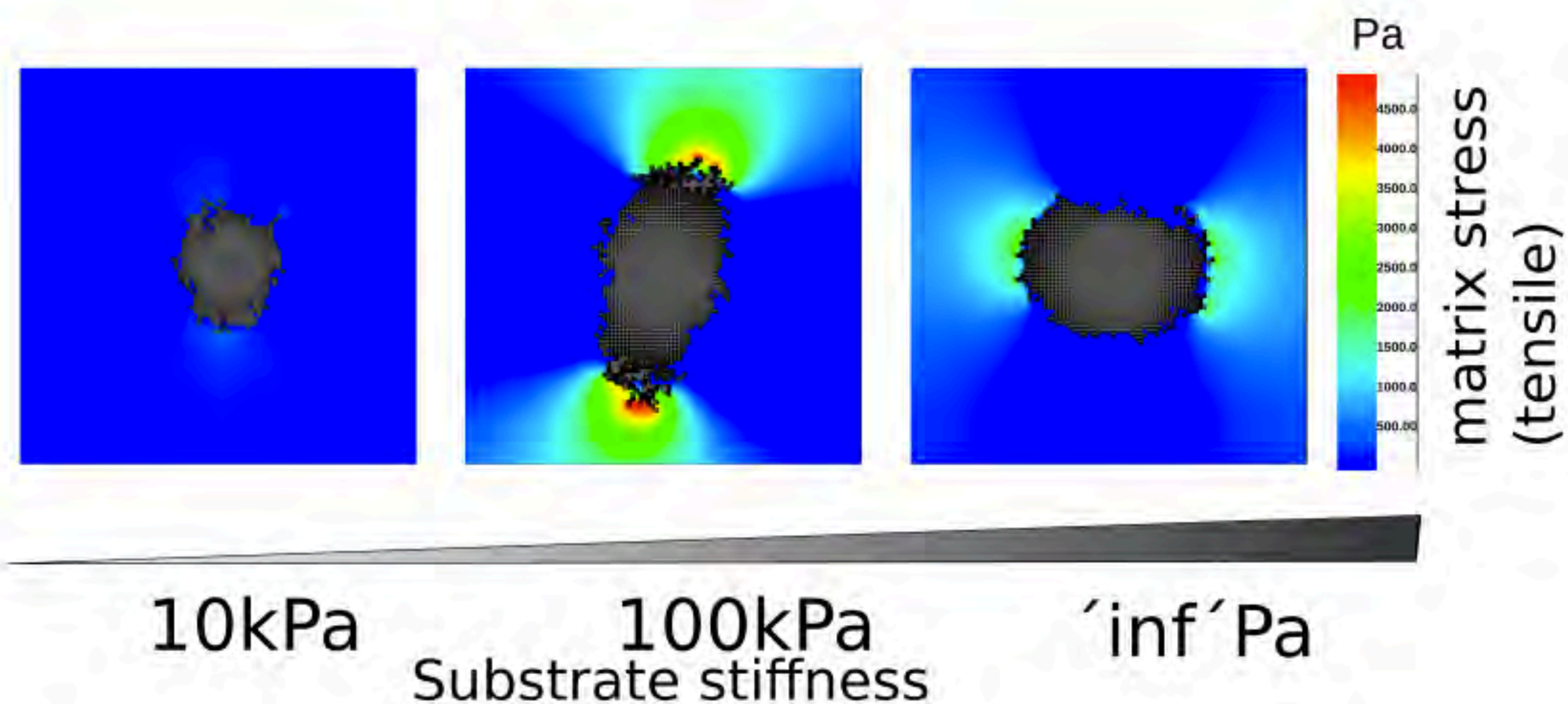
Substrate stiffness determines cell shape



Lisanne Rens

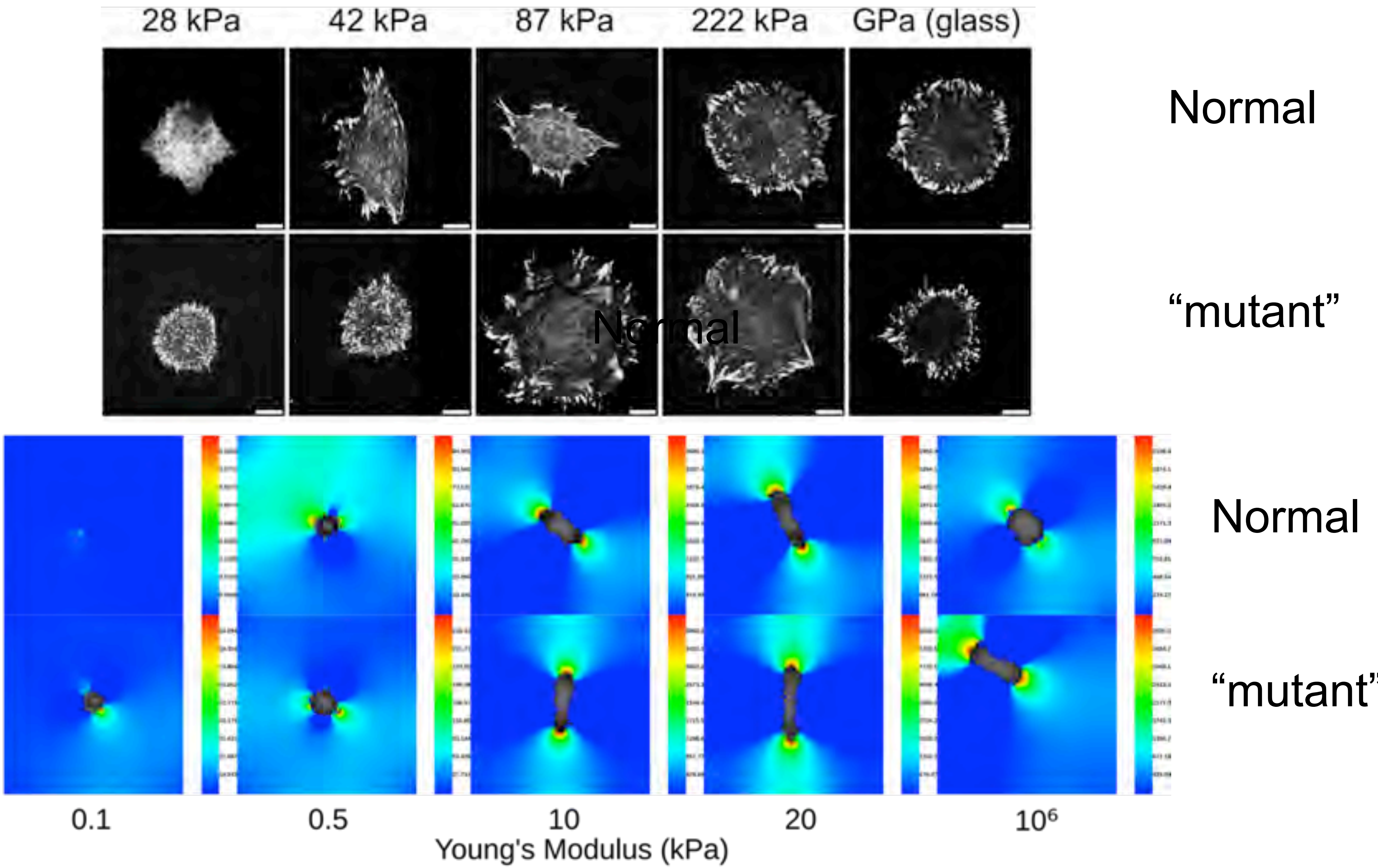
Missing component: stress-induced recruitment of **vinculin**

- Planar stress recruits vinculin
- Vinculin strengthens focal adhesions



Lisanne Rens

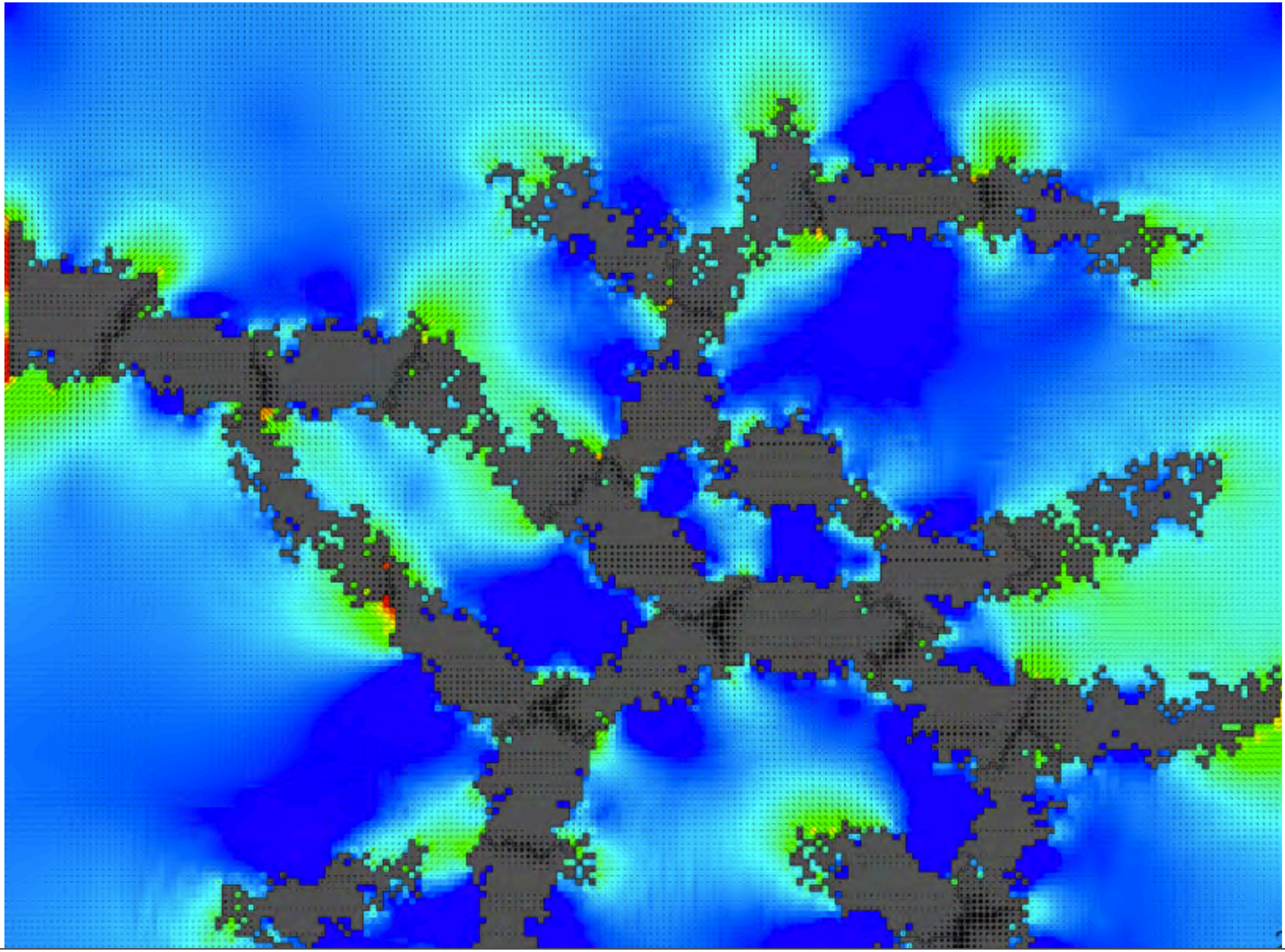
Models help to explain how mutations affect the cell and tissue



"Mutant" (p130Cas-/-) speeds up FA assembly/disassembly

Lisanne Rens

Work in progress:
Multicellular behaviour with full FAs



Conclusions

- Multiscale models help explain how cells build multicellular structures
- Hybrid cellular Potts and finite-element models:
  - mechanical cell-cell communication
- Relevant subcellular detail (focal adhesions):
  - follow relation between “mutation” and morphology
- Study of scale interactions
  - macroscopic scale (tissue) affects behaviour of microscopic scale (molecules and cells)

Acknowledgments

CWI

Lisanne Rens
Hannan Tahir

MI - U Leiden

Claudiu Antonovici
Koen Schakenraad
Leonie van Steijn
Esmée Vendel

Alumni:

Sonja Boas
Josephine Daub
René van Oers
Dimitrios Palachanis
Margriet Palm
András Szabó

Collaborators for this talk:

Cornell University

Danielle LaValley
Cynthia Reinhart-King

AMC Amsterdam

Theo Smit
Manuel Schmitz
Ben Nelemans

Leiden University

Sander Hille (mathematics)
Remko Offringa (biology)

Funding: NWO Netherlands Organisation for Scientific Research