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Cell-based modeling of tissue-level responses to mechanical strain

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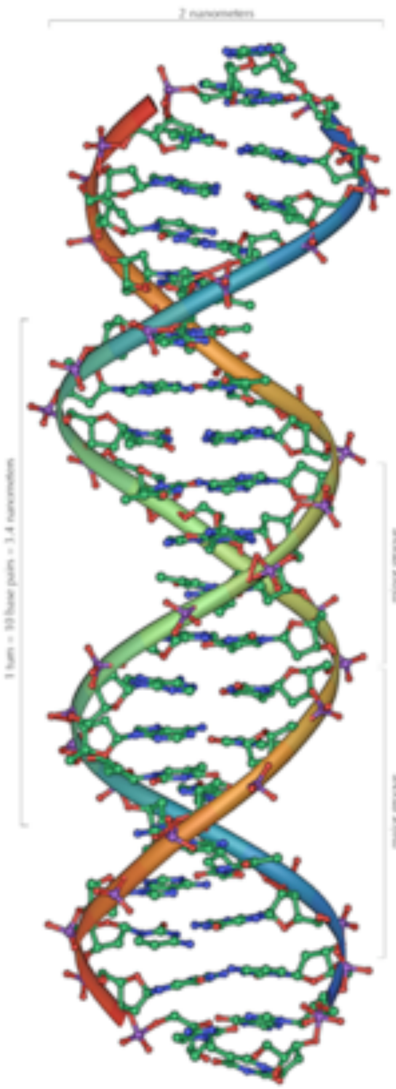
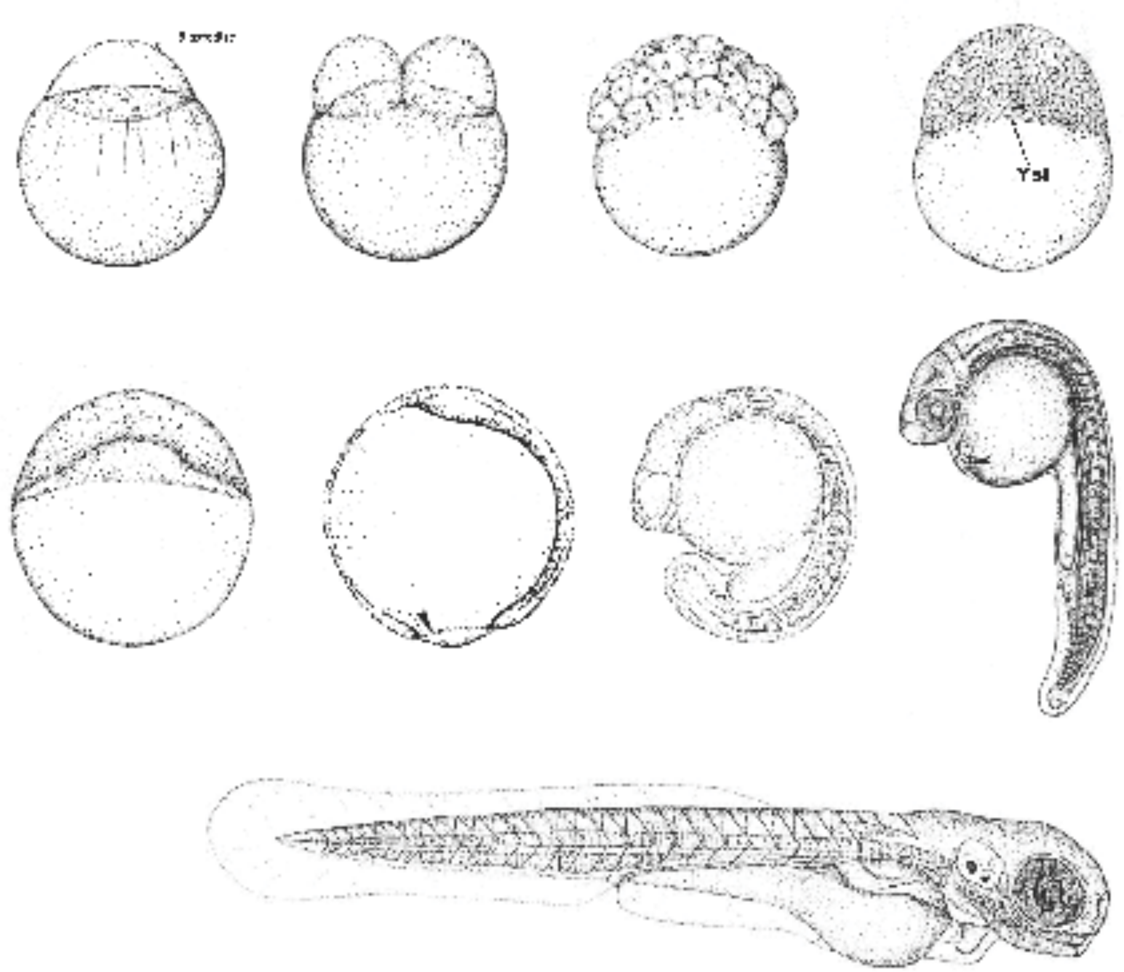
Eighth Workshop
Dynamical Systems Applied to Biology and Natural Sciences
Évora, Portugal, February 1st 2017

Morphogenesis

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



DNA



Morphogenesis

Adult

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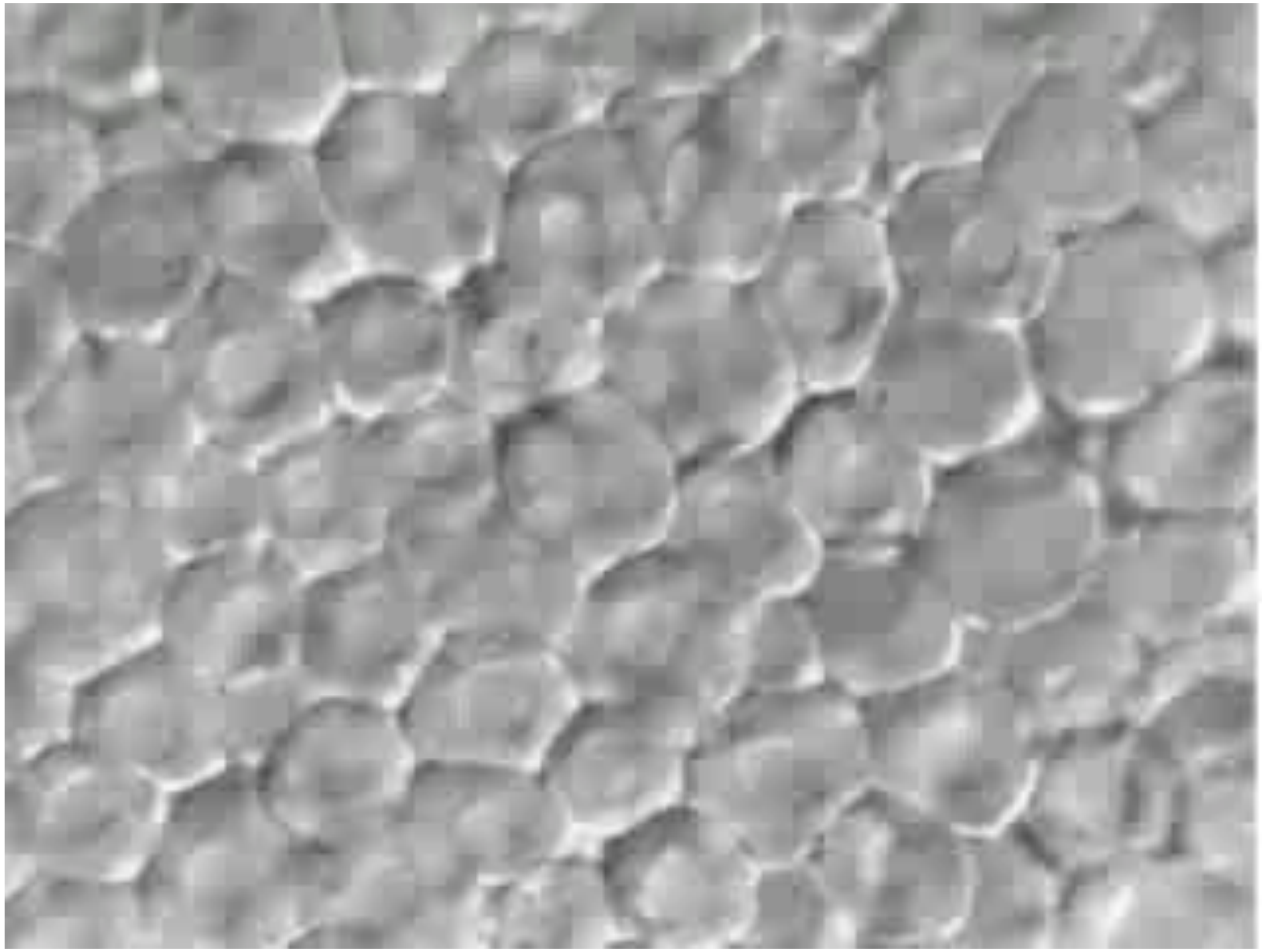
Animals are ‘swarms’ of cells

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

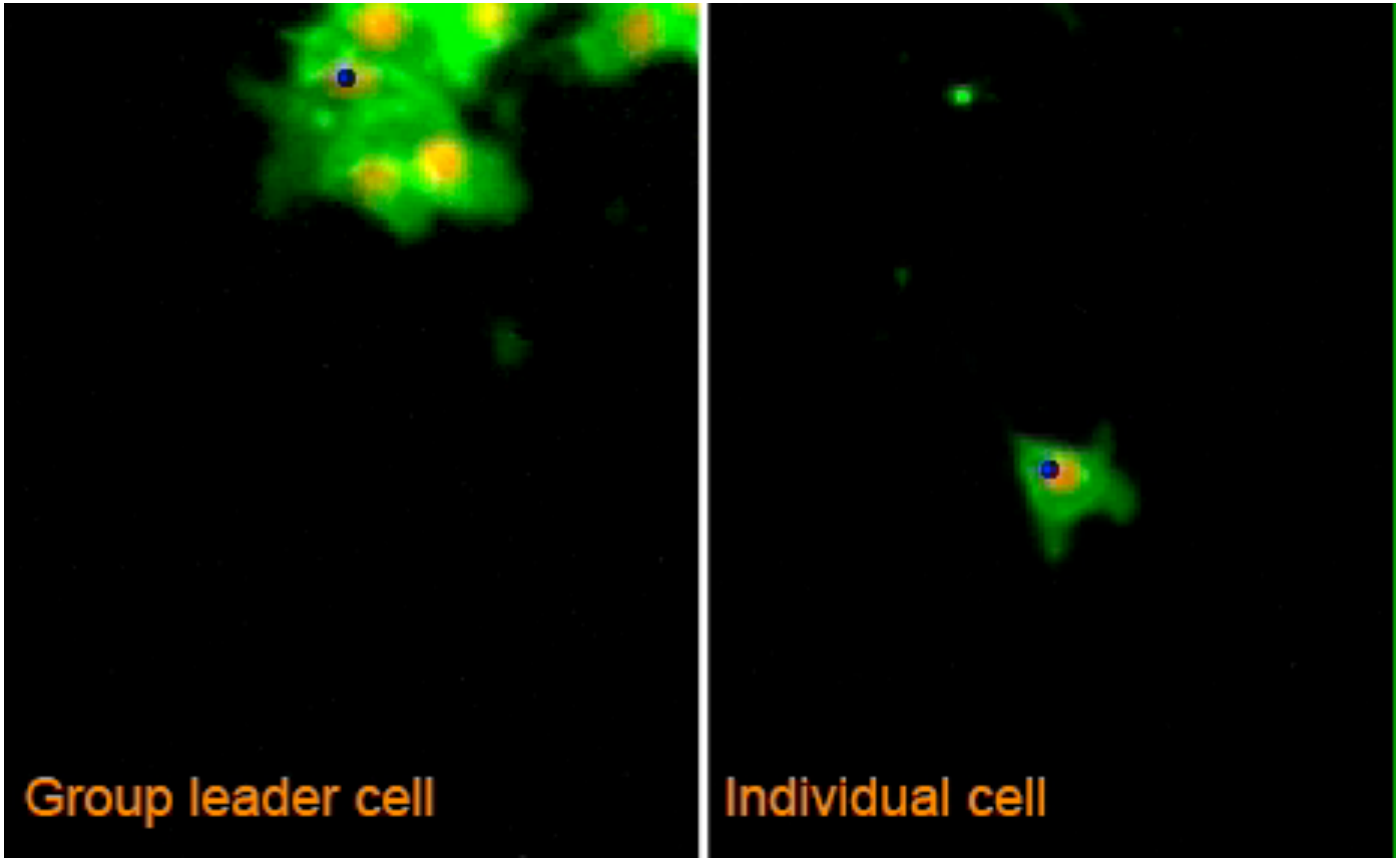
Cells look as if they act independently...

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)

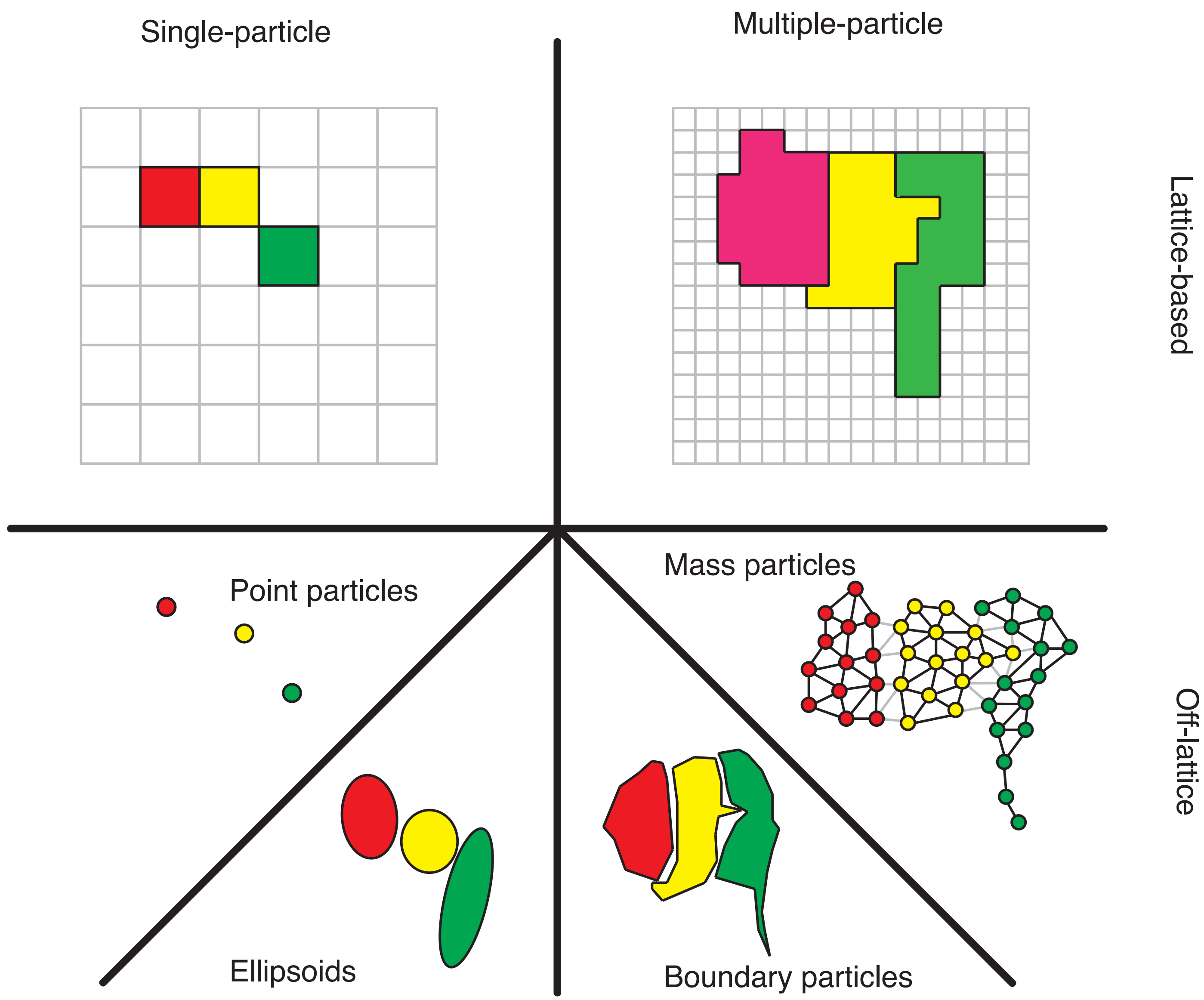
Cell based models

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

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

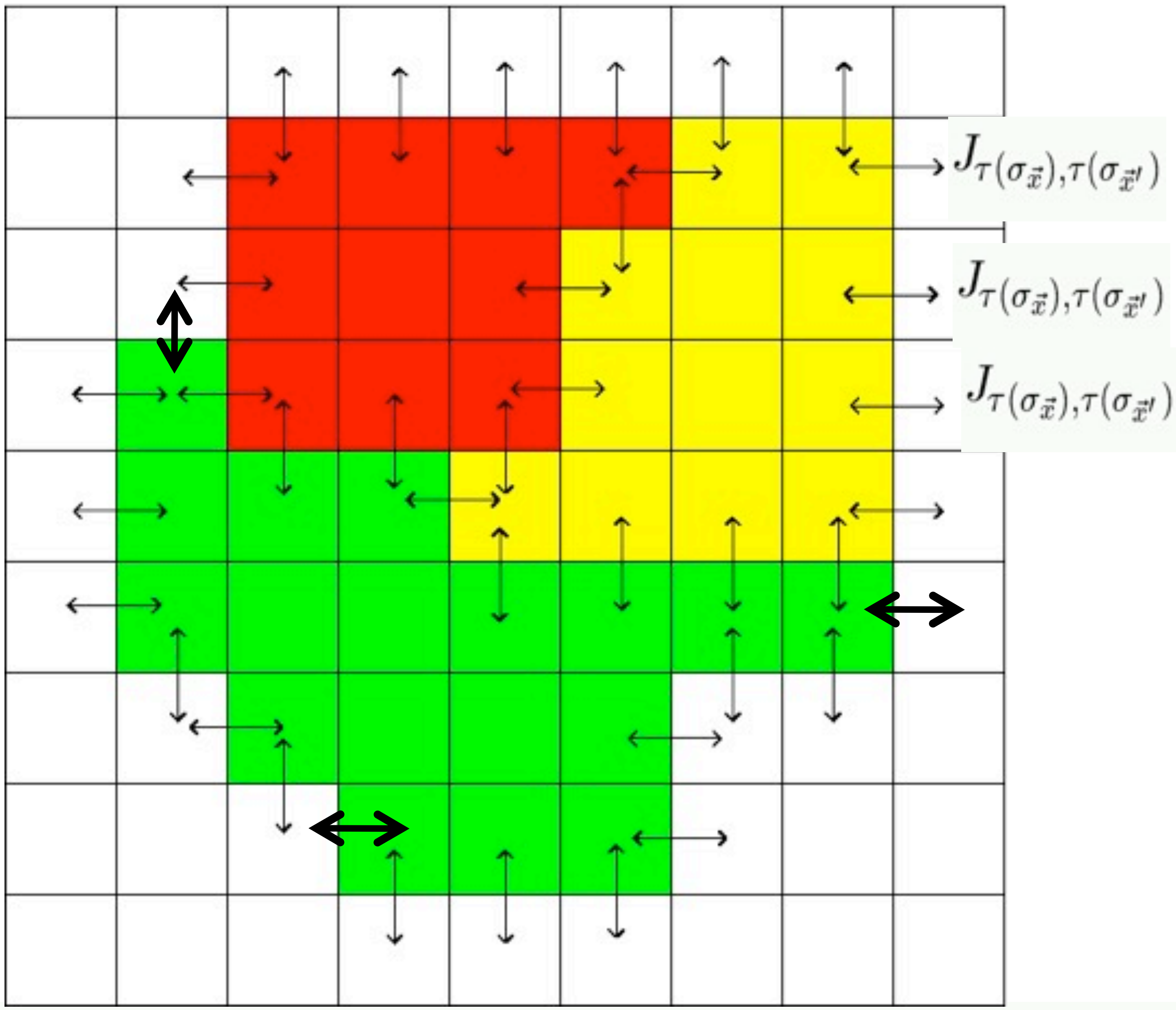
- **Aim** of cell-based modeling is to understand:
  - How cells 'build' animals
  - How tissue structure feeds back onto cell behavior
  - How a genetic mutation can lead to phenotypic changes

Simulation methods



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

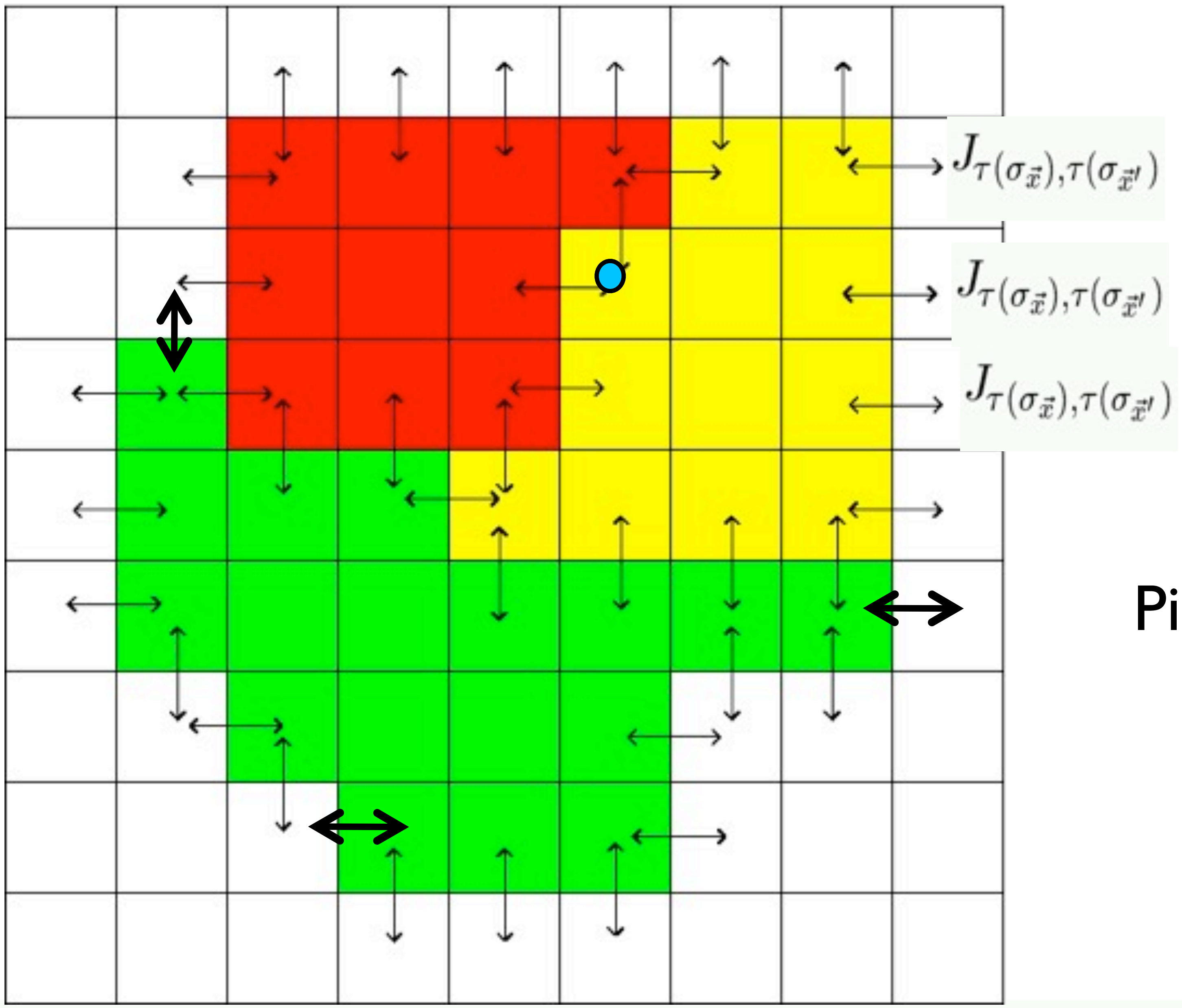
Cellular Potts Model (CPM)



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

Cell adhesion — Volume conservation

Cellular Potts Model (CPM)



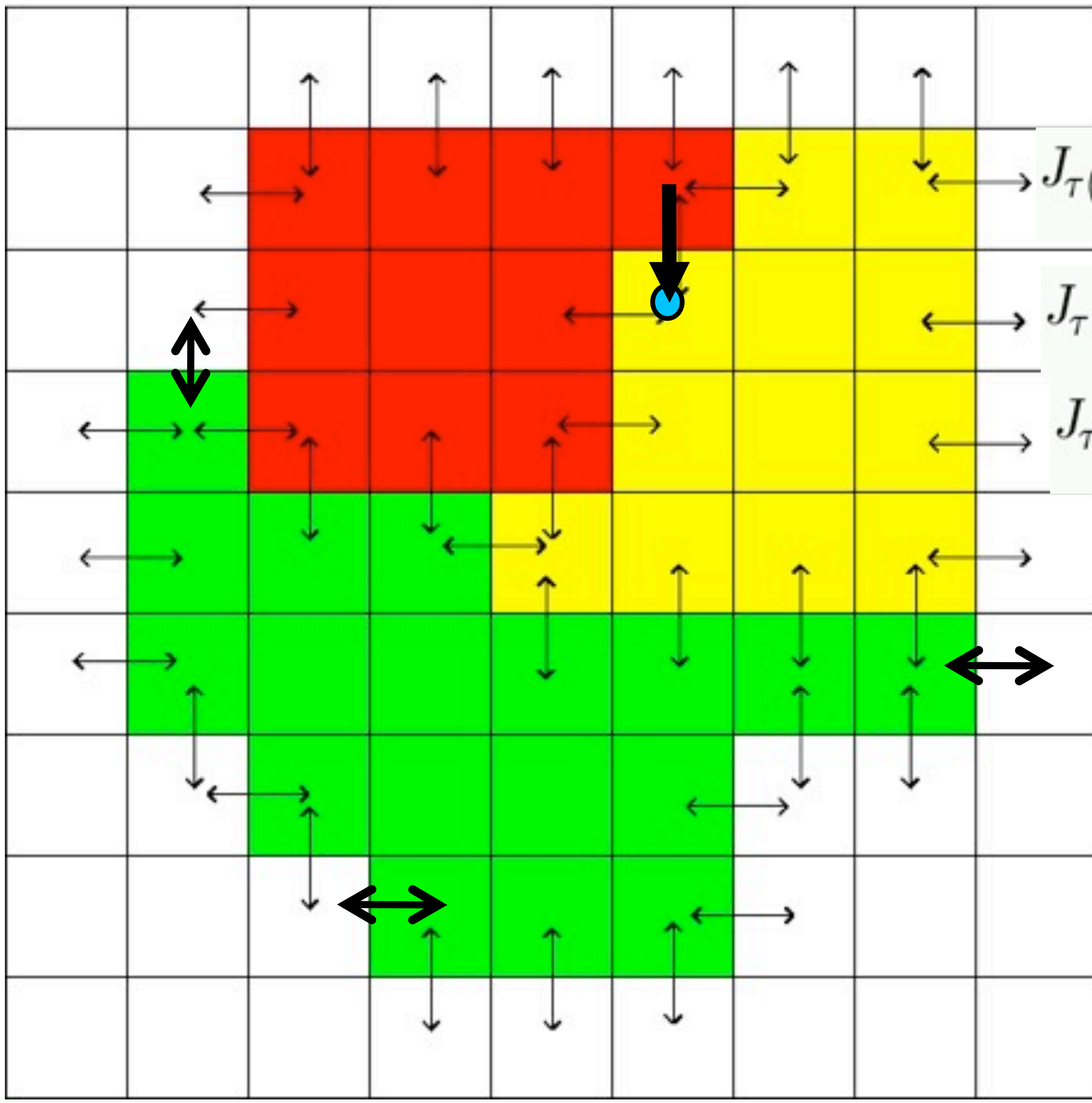
Pick random site

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

Cell adhesion

Volume conservation

Cellular Potts Model (CPM)



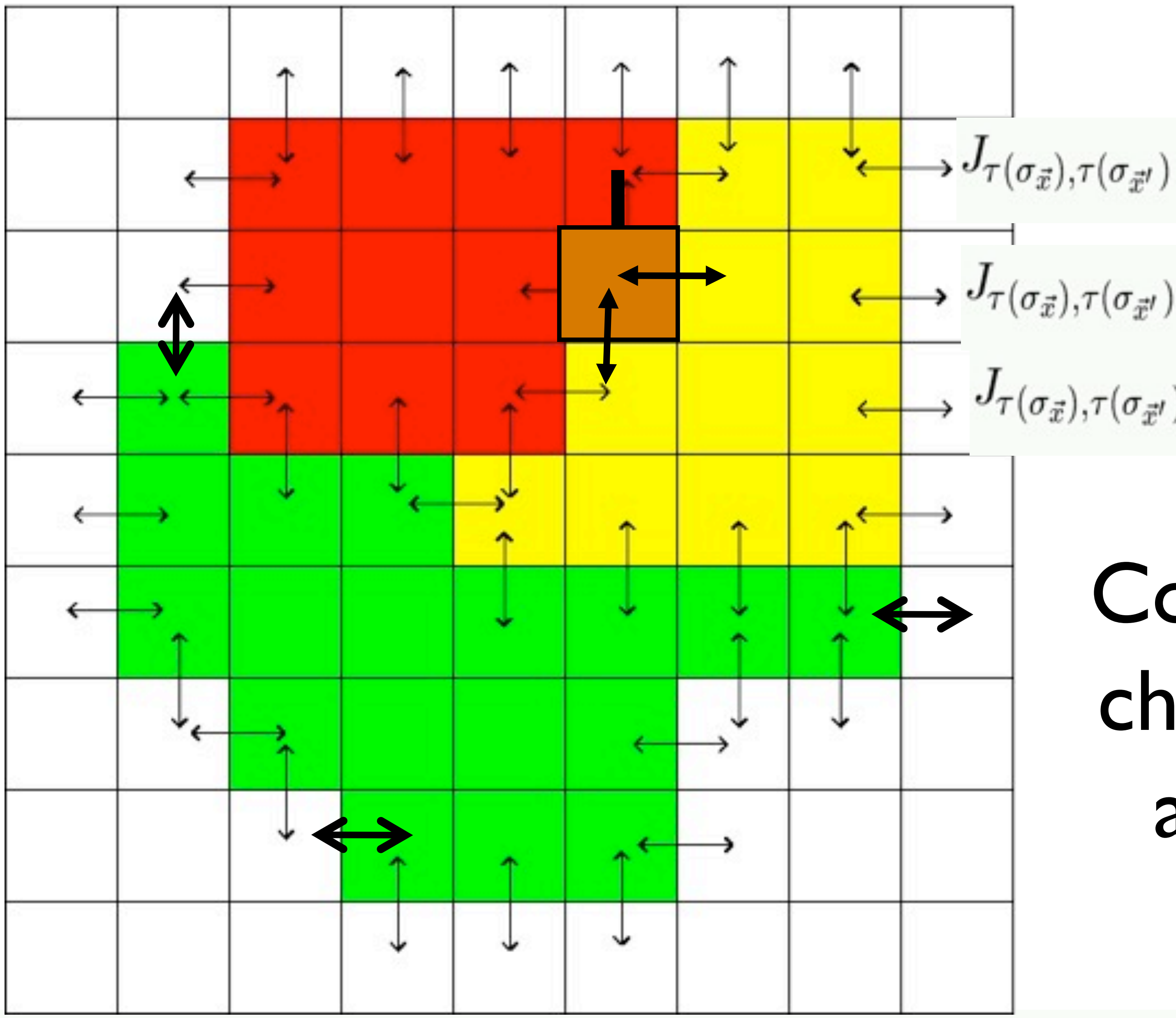
Pick random neighbor

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

Cell adhesion

Volume conservation

Cellular Potts Model (CPM)

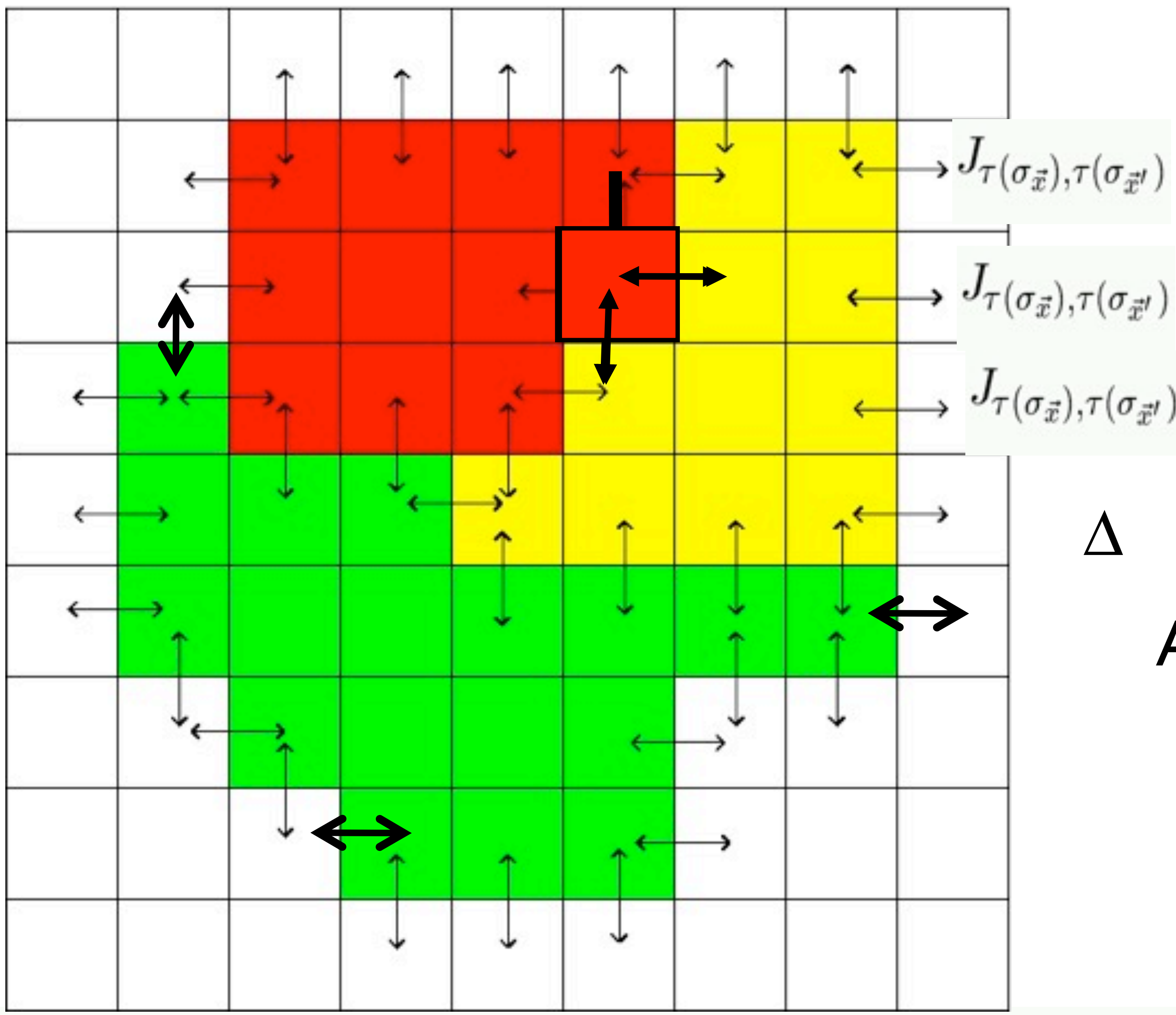


Consider energy change ΔH if we accepted this copying

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

Cell adhesion — Volume conservation

Cellular Potts Model (CPM)



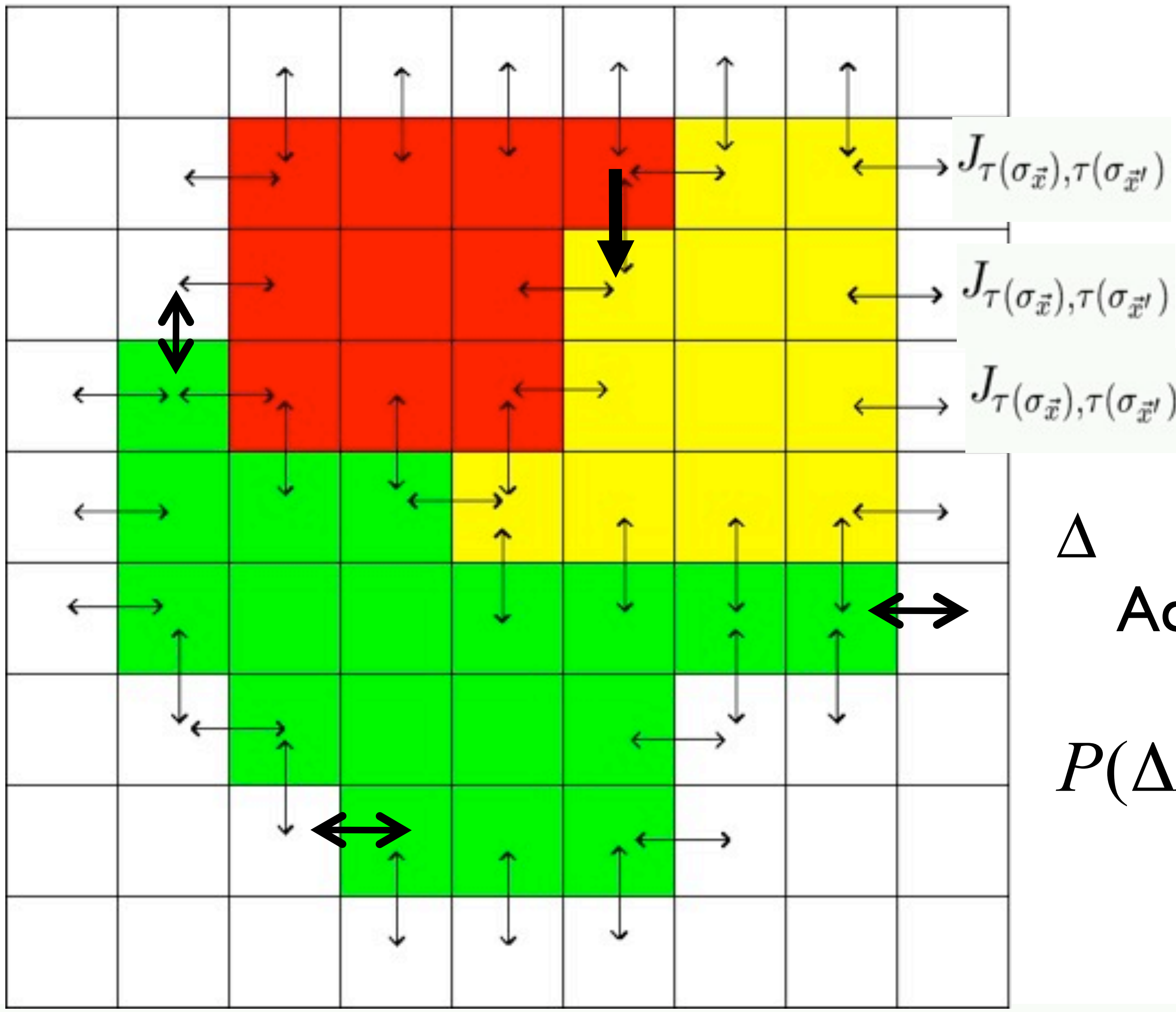
Δ H < 0 ?

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)



$\Delta H > 0$?

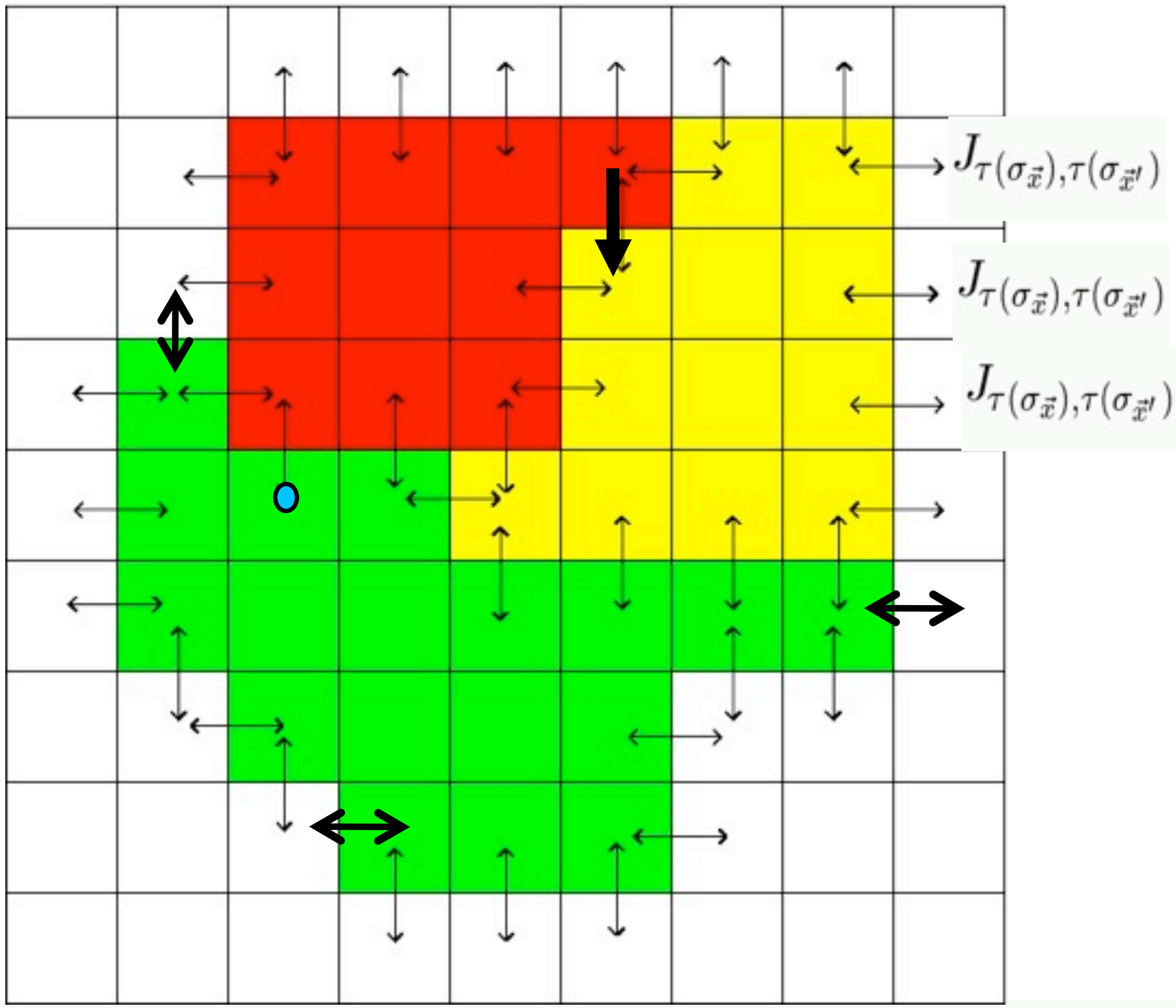
Accept with

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

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

Cell adhesion — Volume conservation

Cellular Potts Model (CPM)



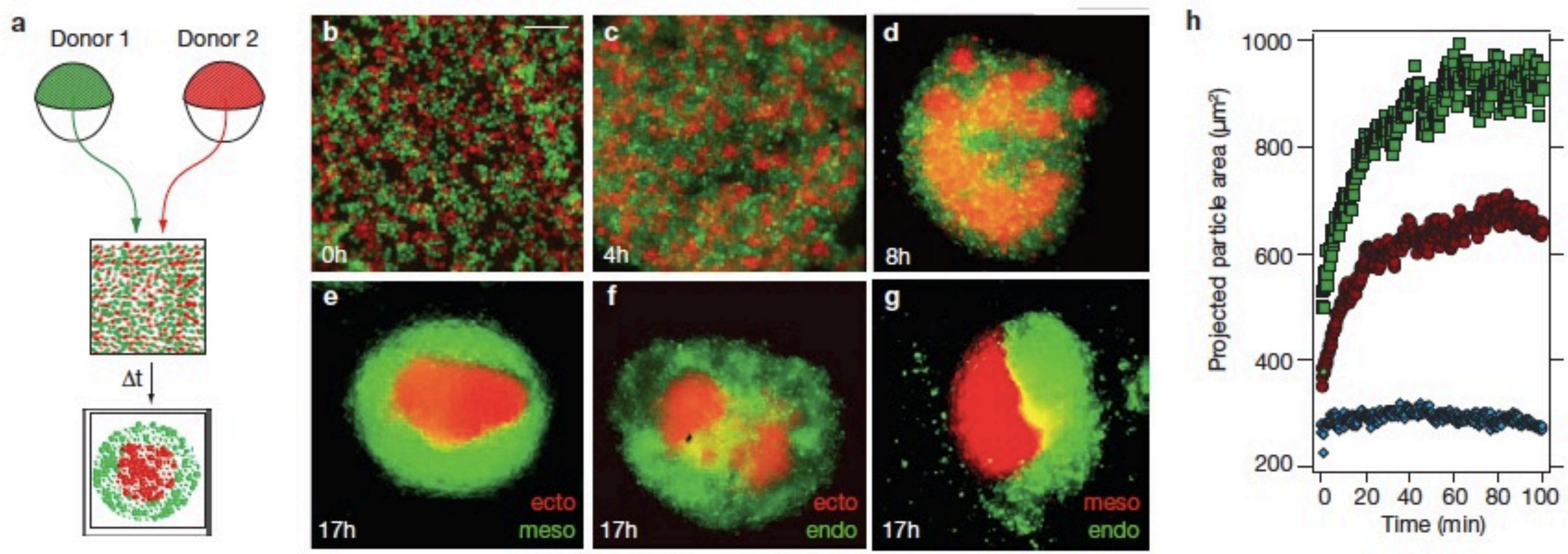
Repeat

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

Cell adhesion

Volume conservation

Typical problem: Differential-adhesion-driven cell sorting



Data: Krieg et al. Nature Cell Biology, 2008

Simulation result

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

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

Modelsimulatie

10x versneld

ecto

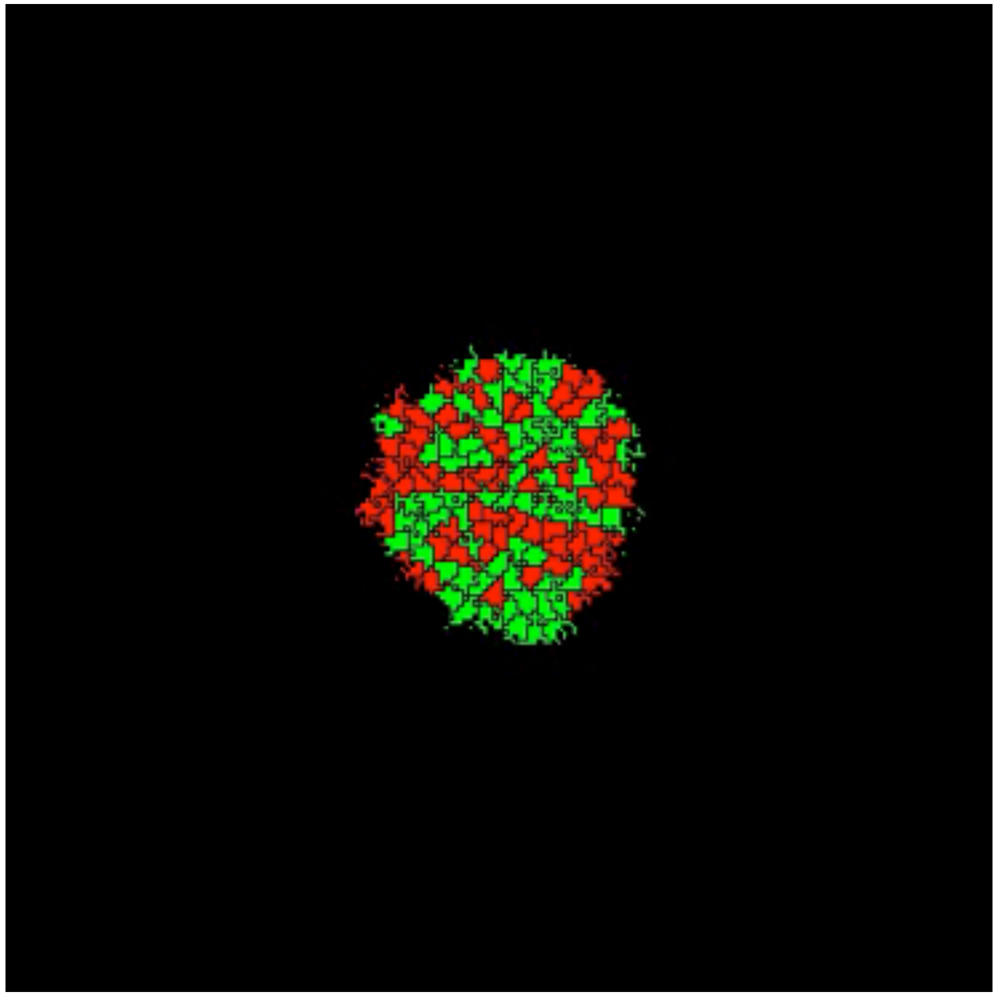
meso

Simulation result

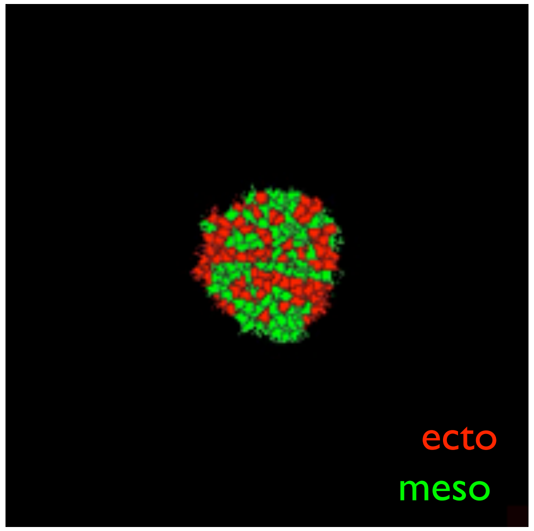
$$J_{\text{green,green}} < J_{\text{red,red}}$$

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

Modelsimulatie



10x versneld

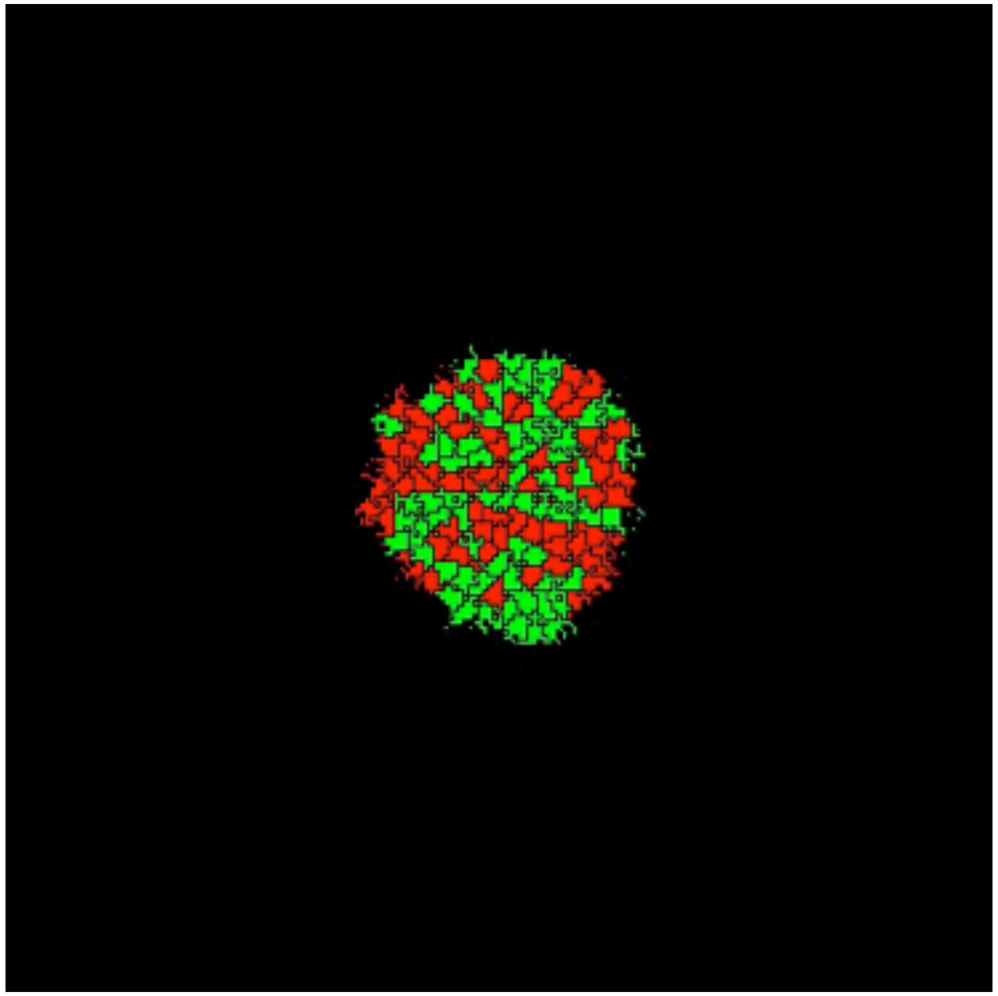


Simulation result

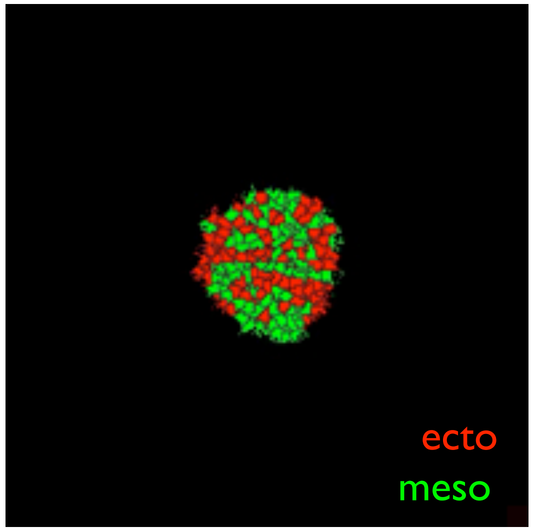
$$J_{\text{green,green}} < J_{\text{red,red}}$$

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

Modelsimulatie



10x versneld



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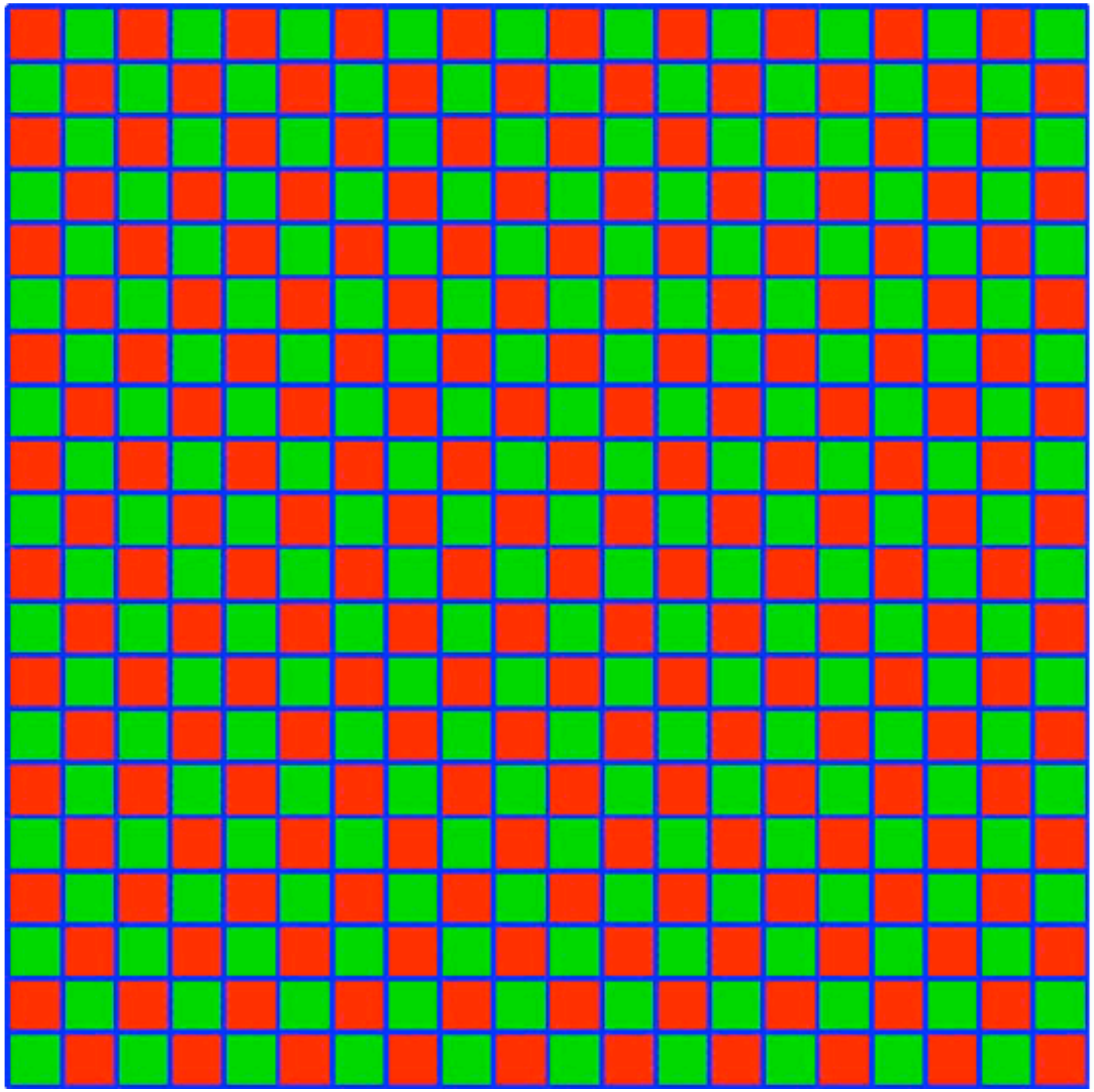
Alternative representation: Boundary-element model



Harold Wolff

Coordination of tissue growth during morphogenesis

- If one tissue grows in the embryo:
  - adjacent tissues need to follow
  - internal structure of tissues needs to adapt to strain
- Examples:
  - Relative growth of bones and muscles
    - Muscle fibers must be oriented parallel or at a specific angle to the long axis of the muscle
  - Connective tissues and skin
  - Orientation of segments along the extending body axis

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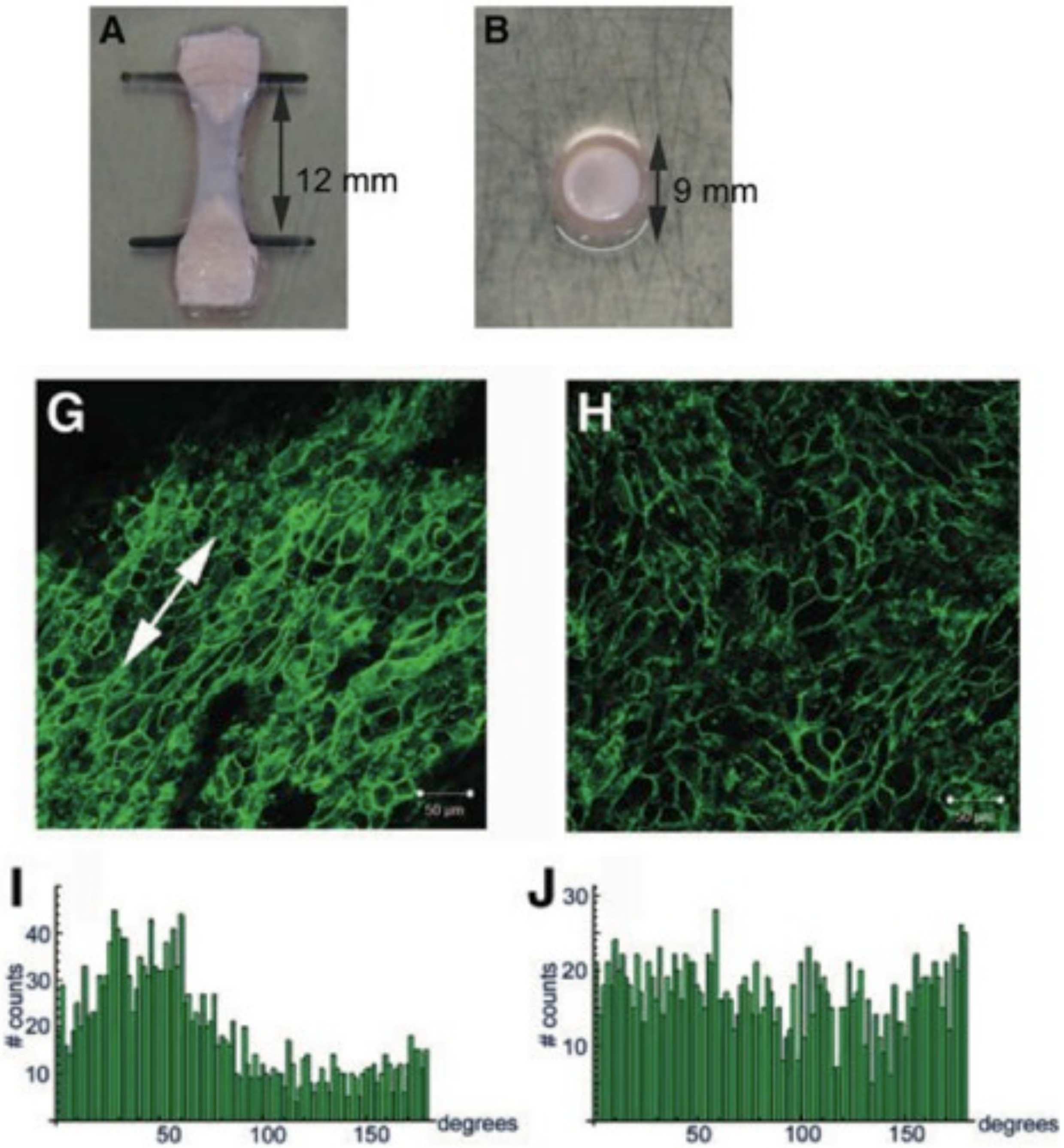
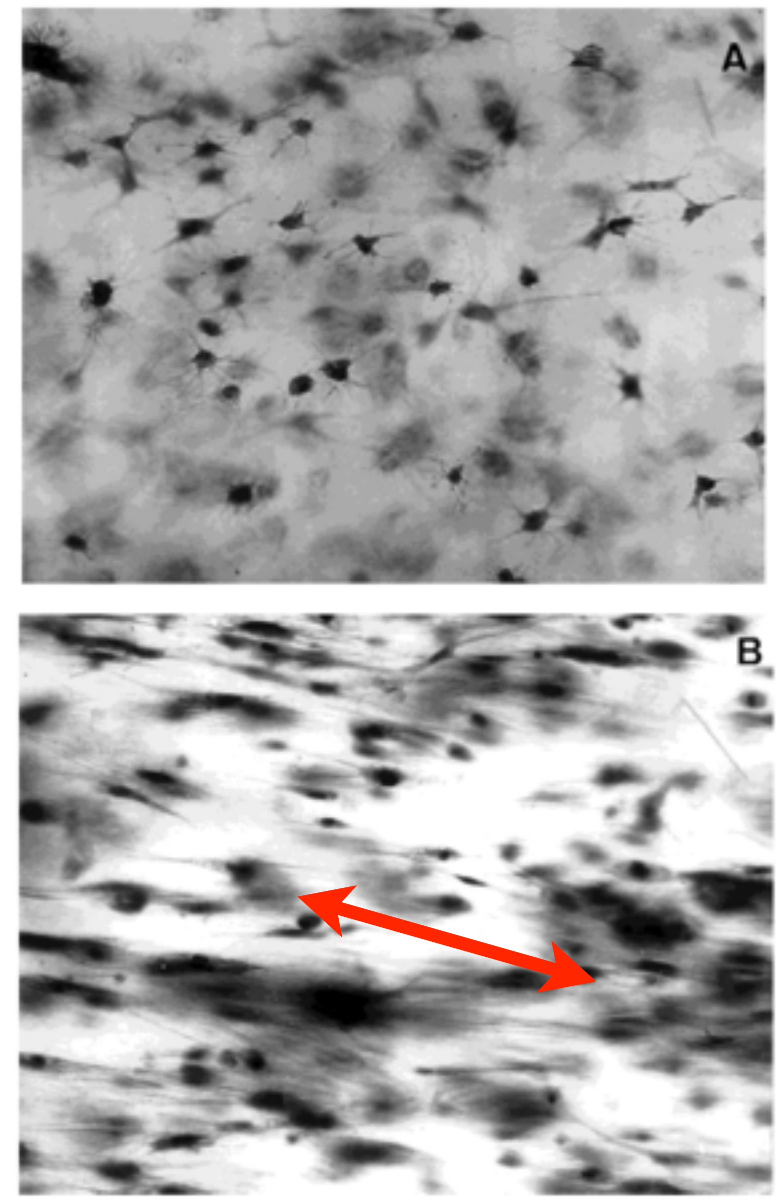
In vitro model: Cells align to static strain in **fibrous** substrates

Endothelial cells on collagen (BAEC)



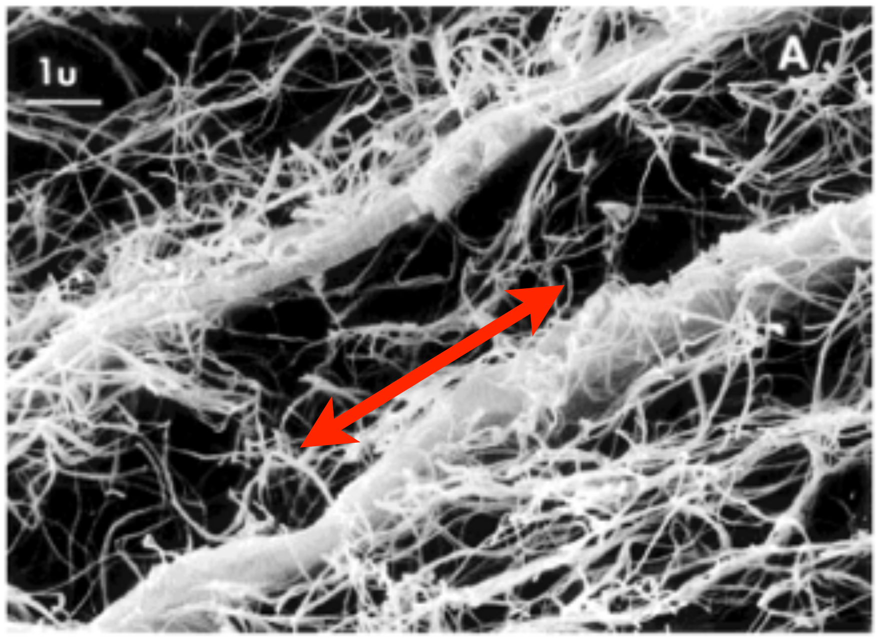
Van der Schaft et al. Tiss Eng A, 2011

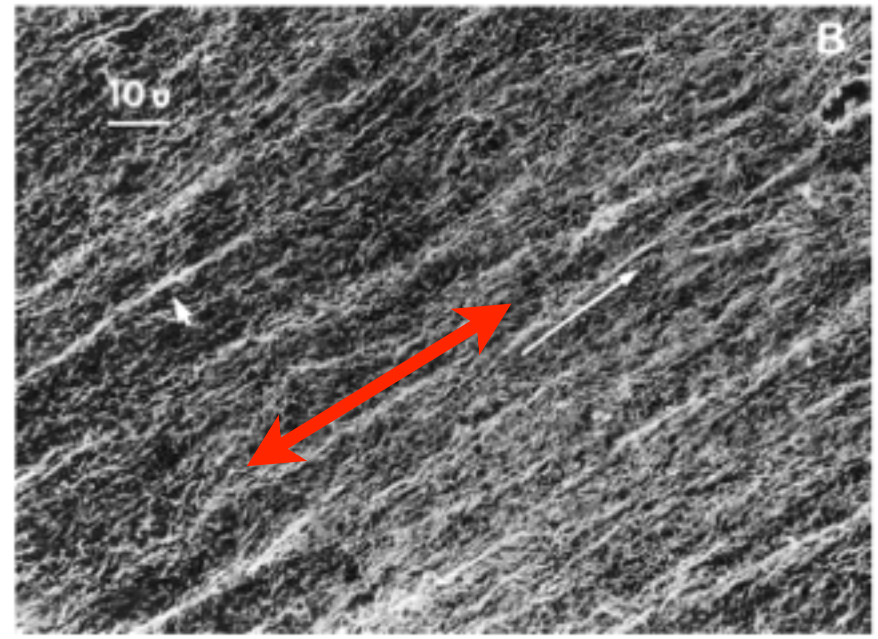
Fibroblasts on collagen



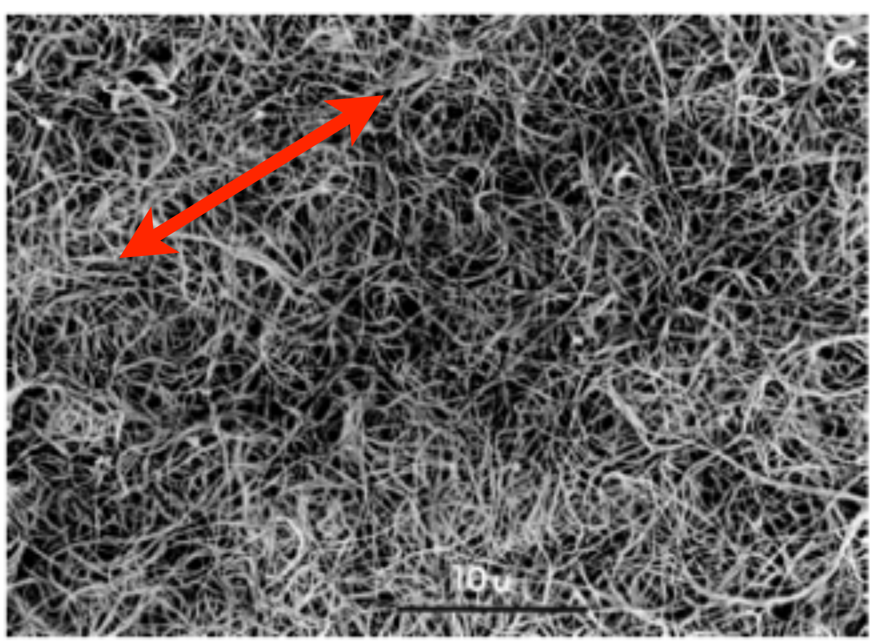
Eastwood et al. 1998

Fibroblasts align to stretch, but collagen fibers do not





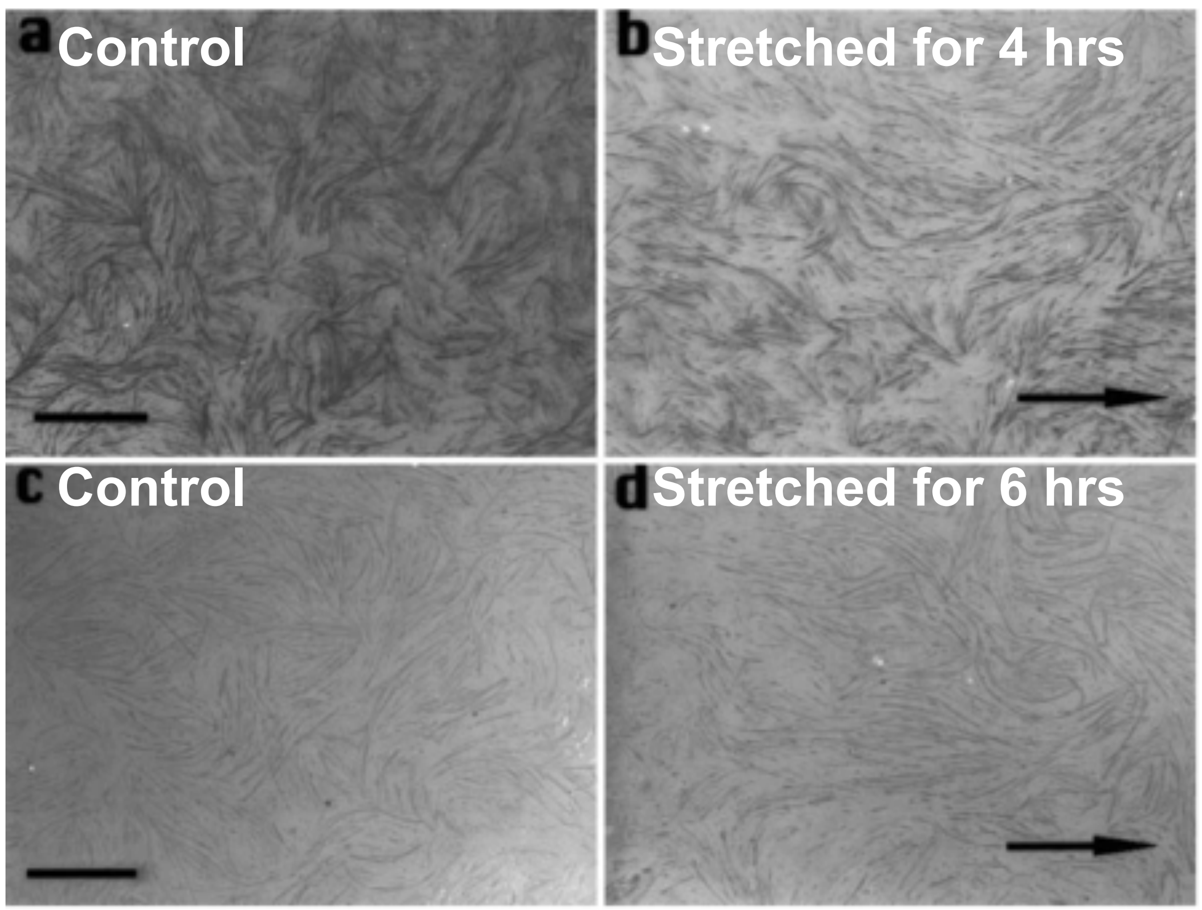
Cell-free matrix stretched overnight



Eastwood et al.
Cell Motil. Cytoskel. 1998

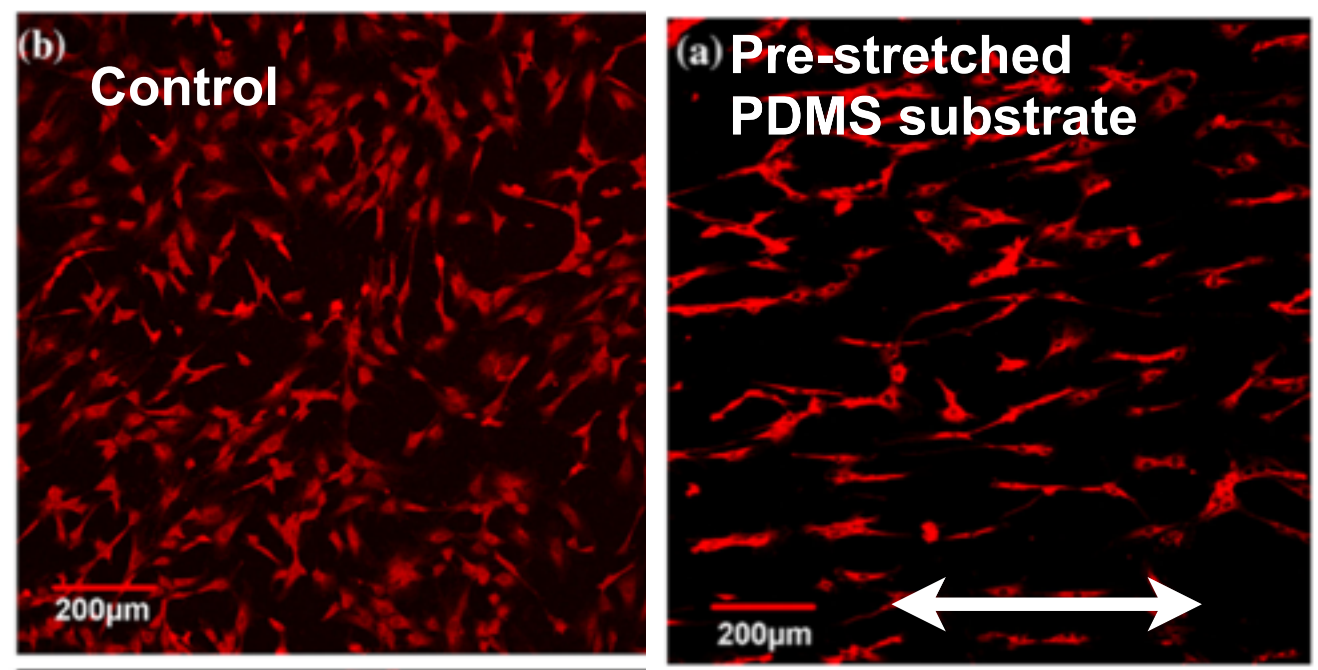
Cells also align to static stretch on **non-fibrous** substrates

Muscle fibers (mouse - Matrigel)



Collinsworth et al. Cell Tiss. Res. 2000

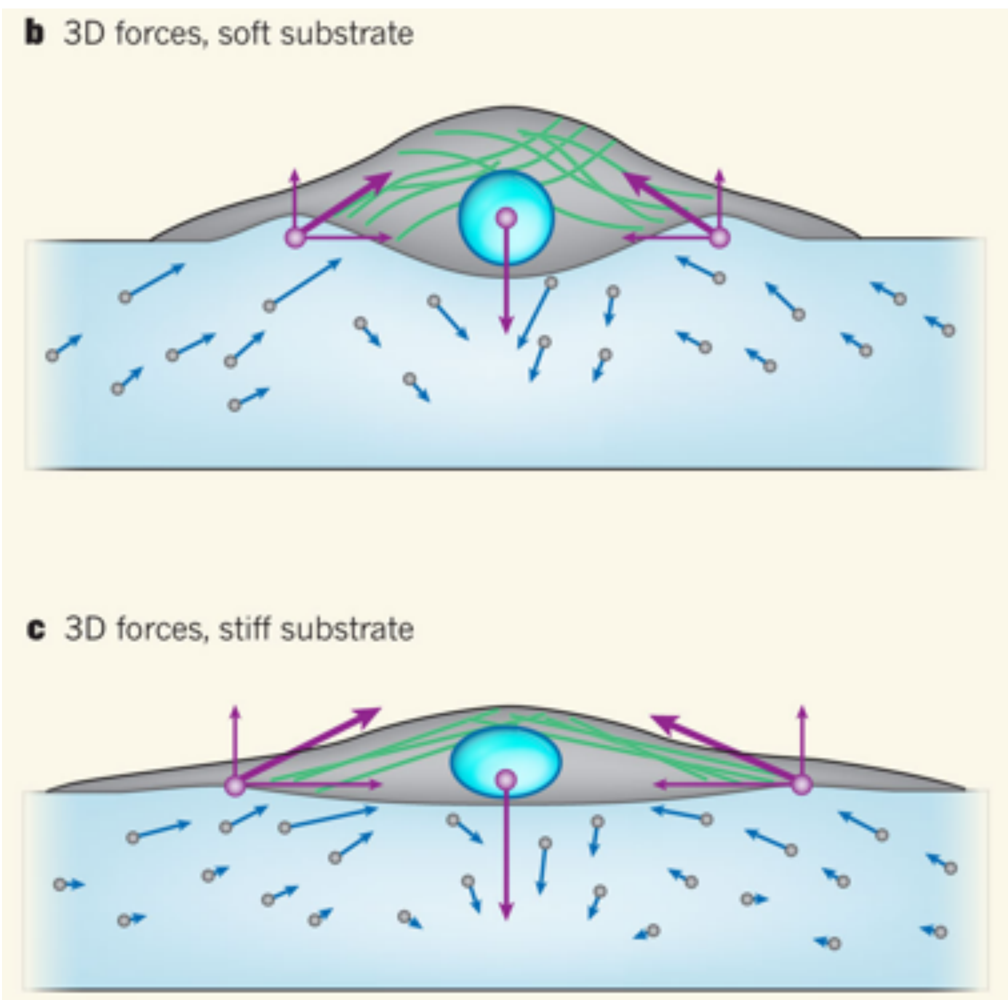
Mesenchymal stem cells (rat - PDMS)



Liu et al. Cell Mol Bioeng 2014

Hypothesis: 'active cell sensing'

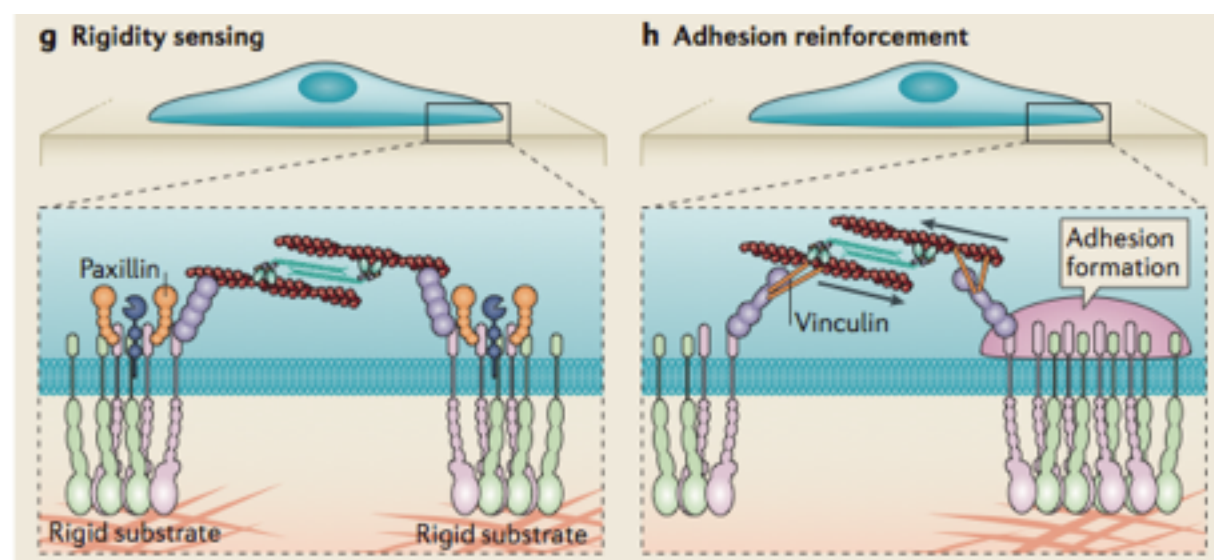
- (1) Cells pull on matrix



Hersen & Ladoux, Nature (2011)

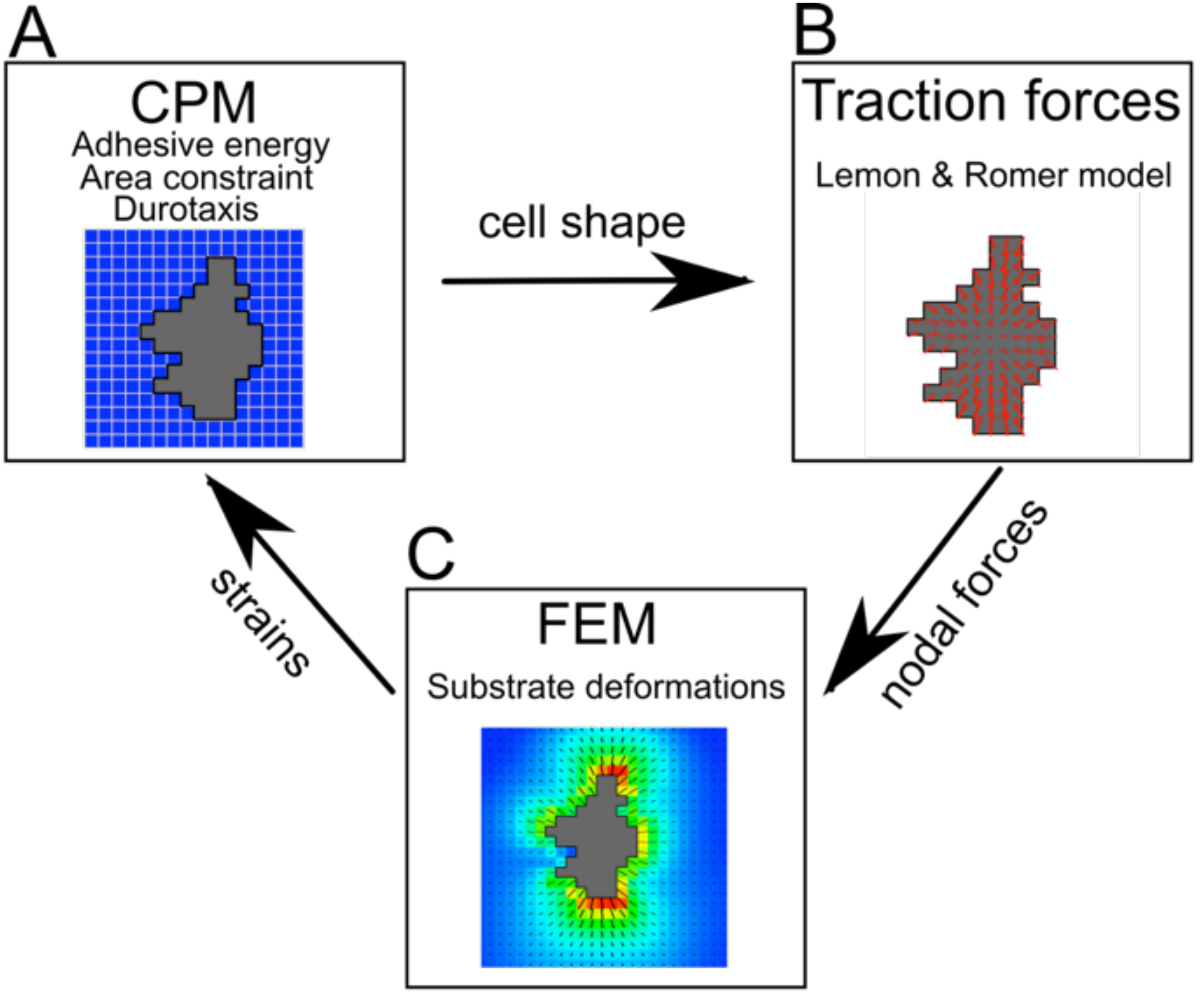
- (2) matrix strain-stiffens

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



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

Mechanical cell-matrix feedback



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

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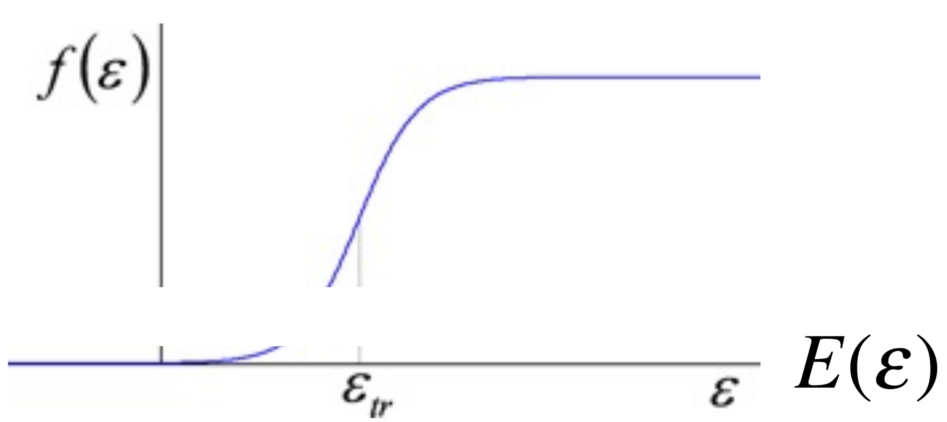
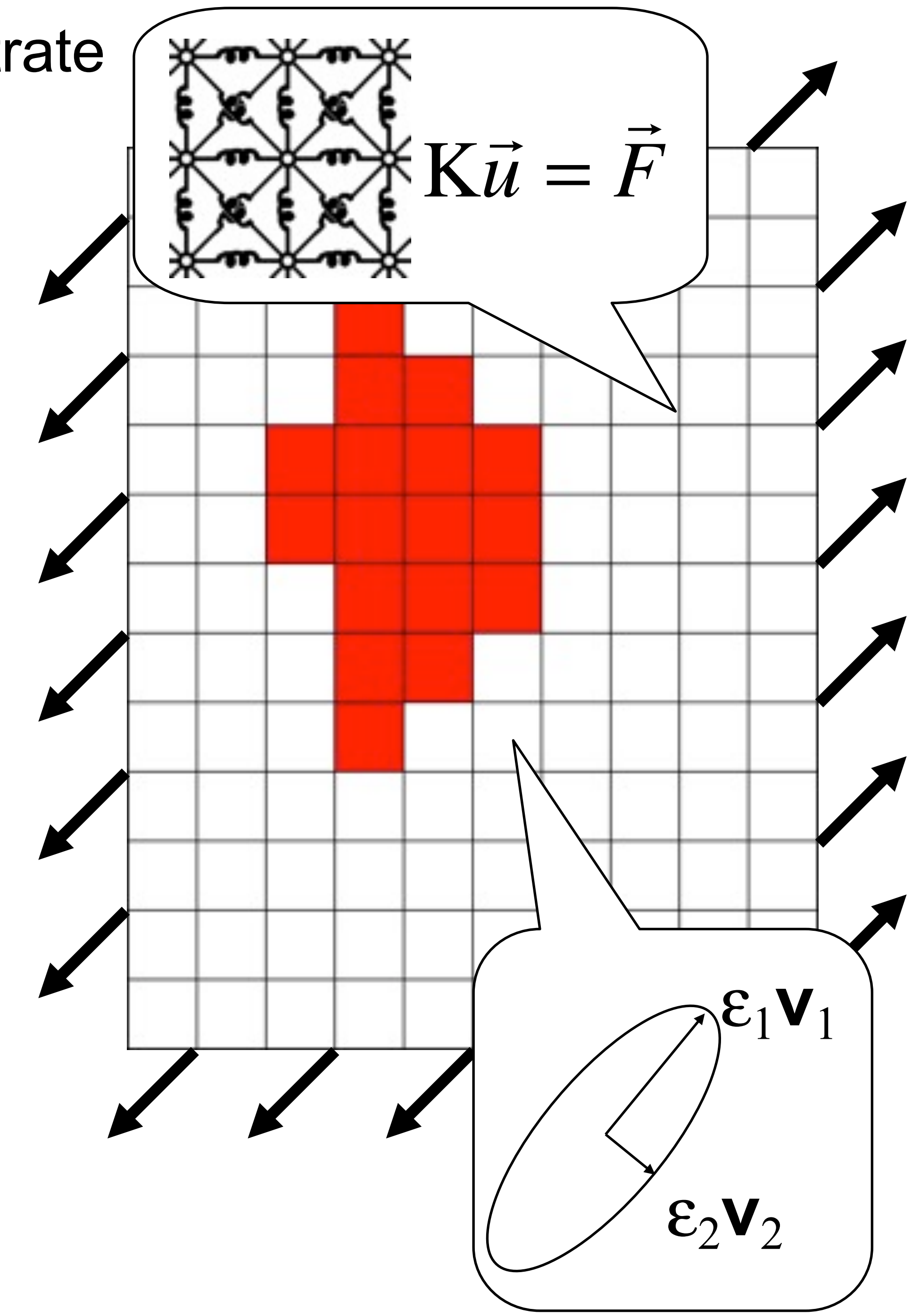
Modeling cell response to stretch using Cellular Potts Model

- ECM: Finite-element model (FE) of compliant substrate
  - Linear elastic assumptions
- FE-calculations yield local principal strains
  - (magnitudes ε_1 and ε_2, along $\vec{v}_1$ and $\vec{v}_2$)
- Approximate strain stiffening:
  - Perceived ECM stiffness: $E(\varepsilon_1)$
- Mimic focal adhesion maturation under strain:

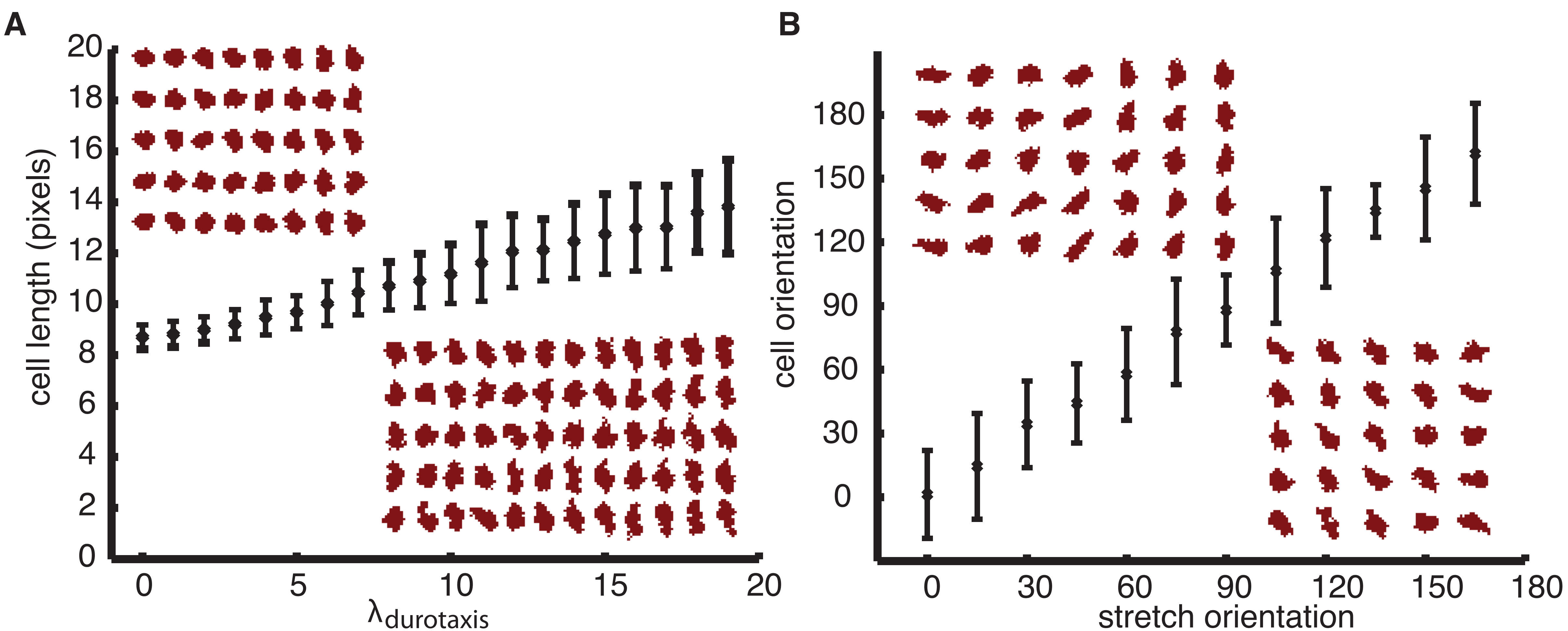
$$\Delta H_{\text{mech}} = -g(\vec{x},\vec{x}')\lambda_{\text{durotaxis}}(f(E(\varepsilon_1))(\vec{v}_1.\vec{v}_m)^2 + f(E(\varepsilon_2))(\vec{v}_2.\vec{v}_m)^2)$$





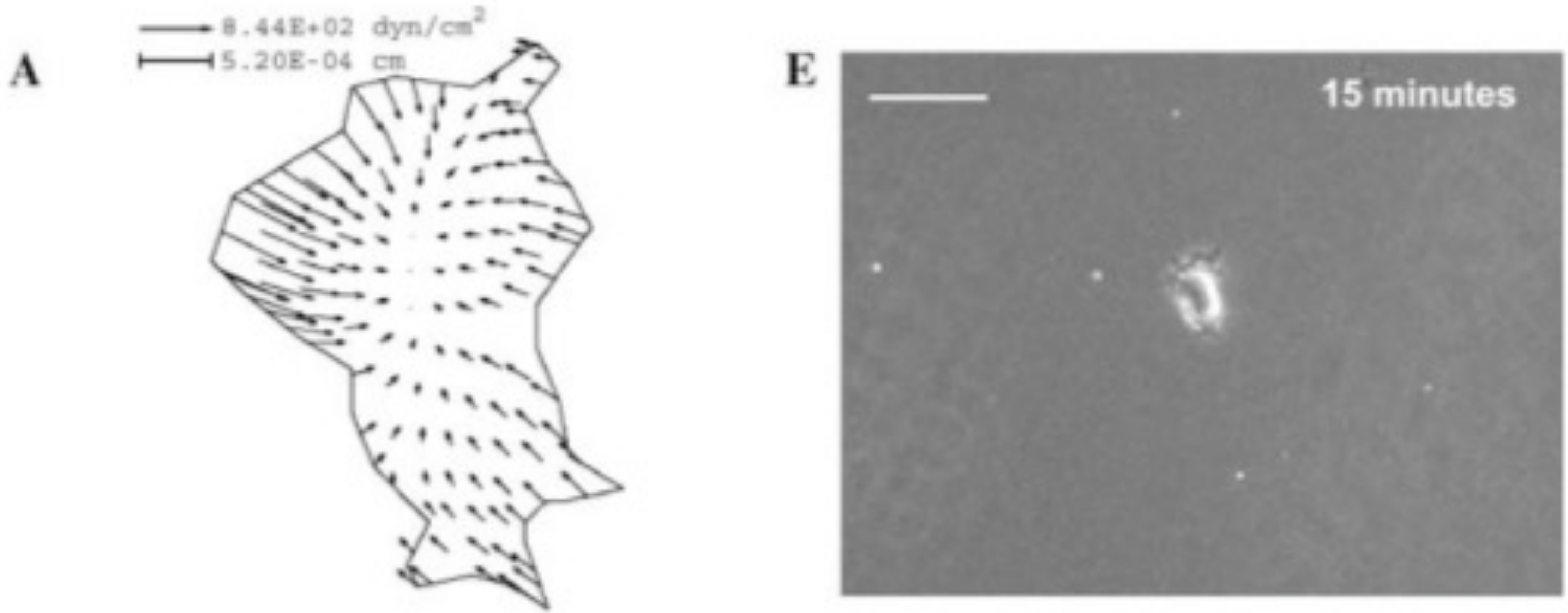
Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

Response of single cells to external, static strain



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

Cells pull on substrate

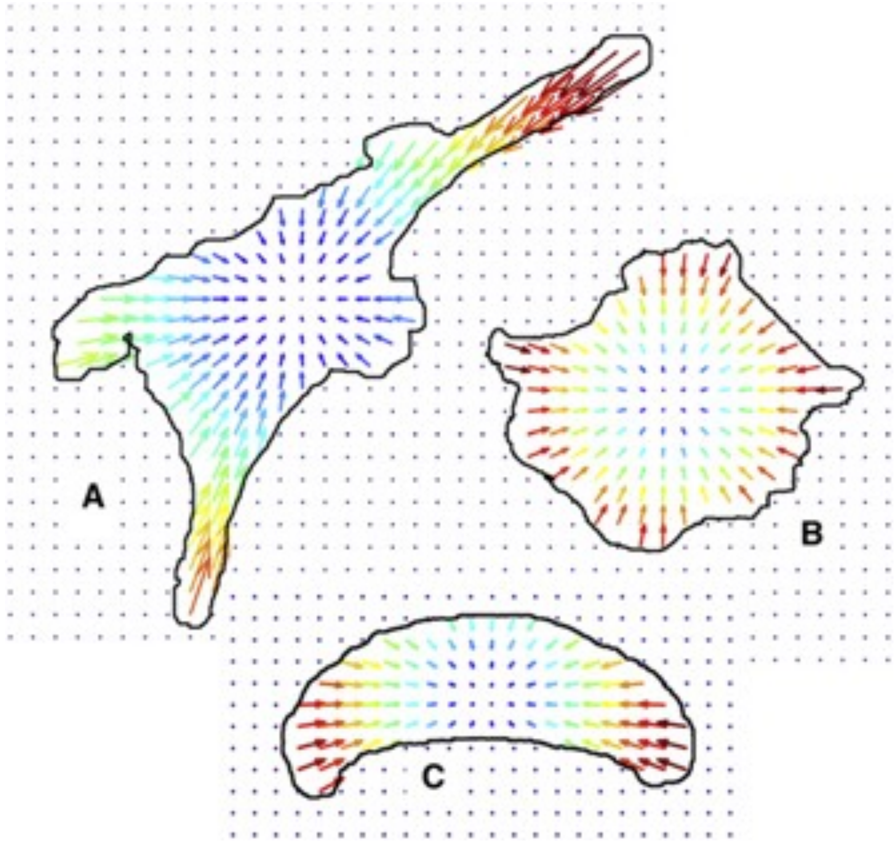


Reinhart-King et al. Biophys. J. 2005

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

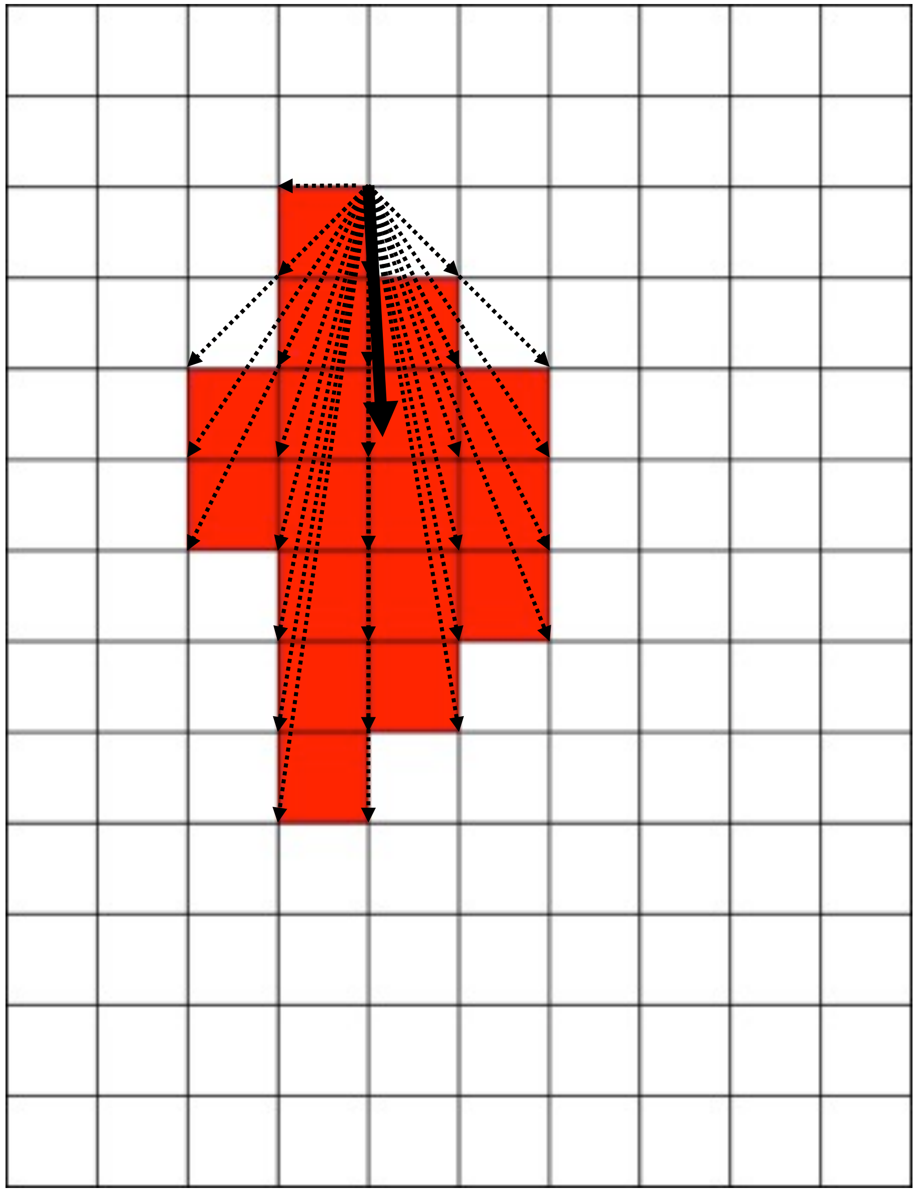
Cells pull on substrate

- Lemmon & Romer (*Biophys. J.* 2010):
  - Cells "acts as single cohesive unit"
  - Force between any two points in cell proportional to distance between them
  - Zero traction in cell centroid



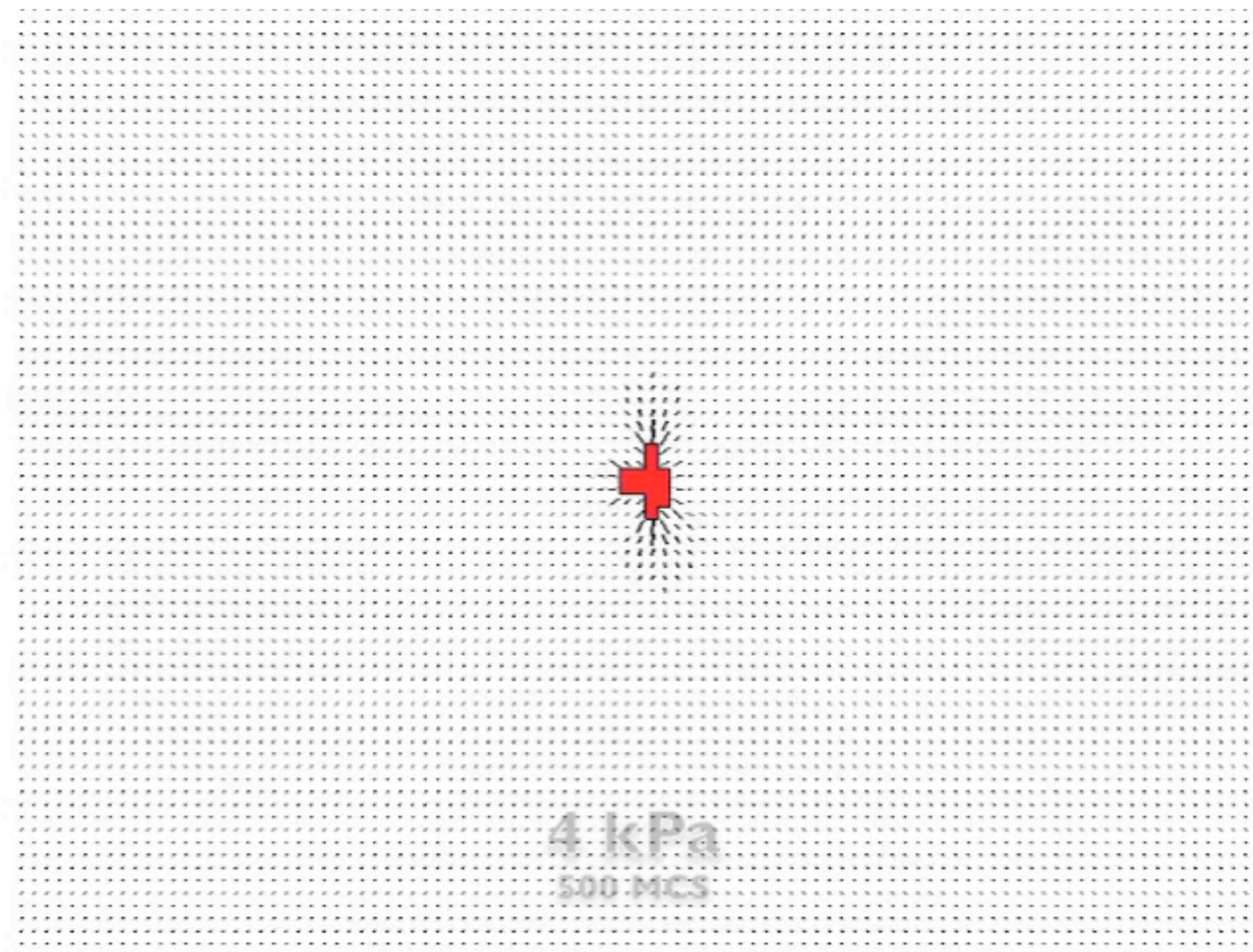
$$\mathbf{F}_i = \mu \sum_j \mathbf{d}_{i,j}$$

Implementation in CPM:



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

Feedback between cell traction and strain response

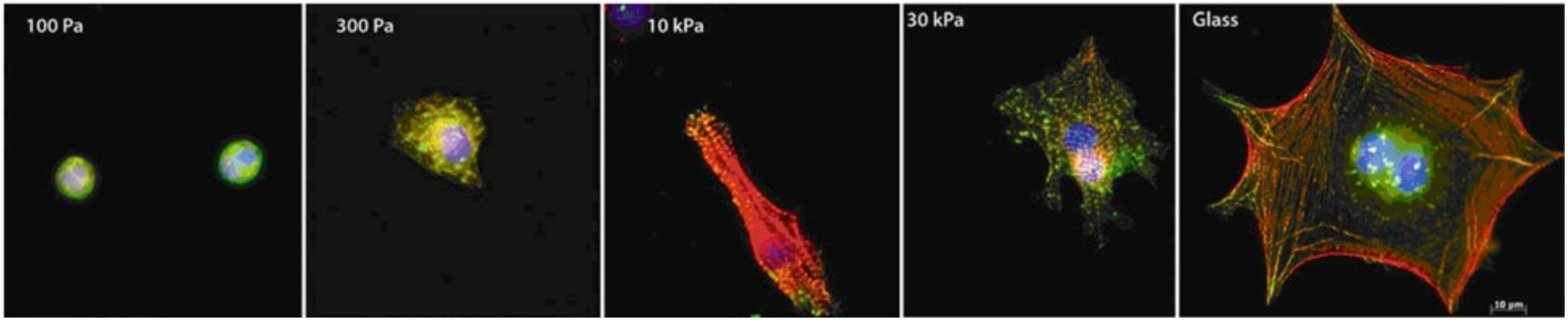


Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

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

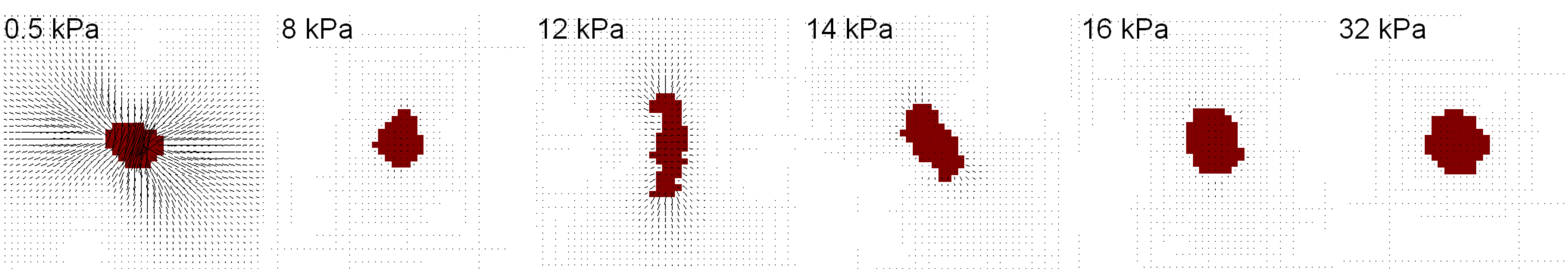
- stretch all around
- contraction

INTERMEDIATE SUBS.

- stretch along long axis
- elongation

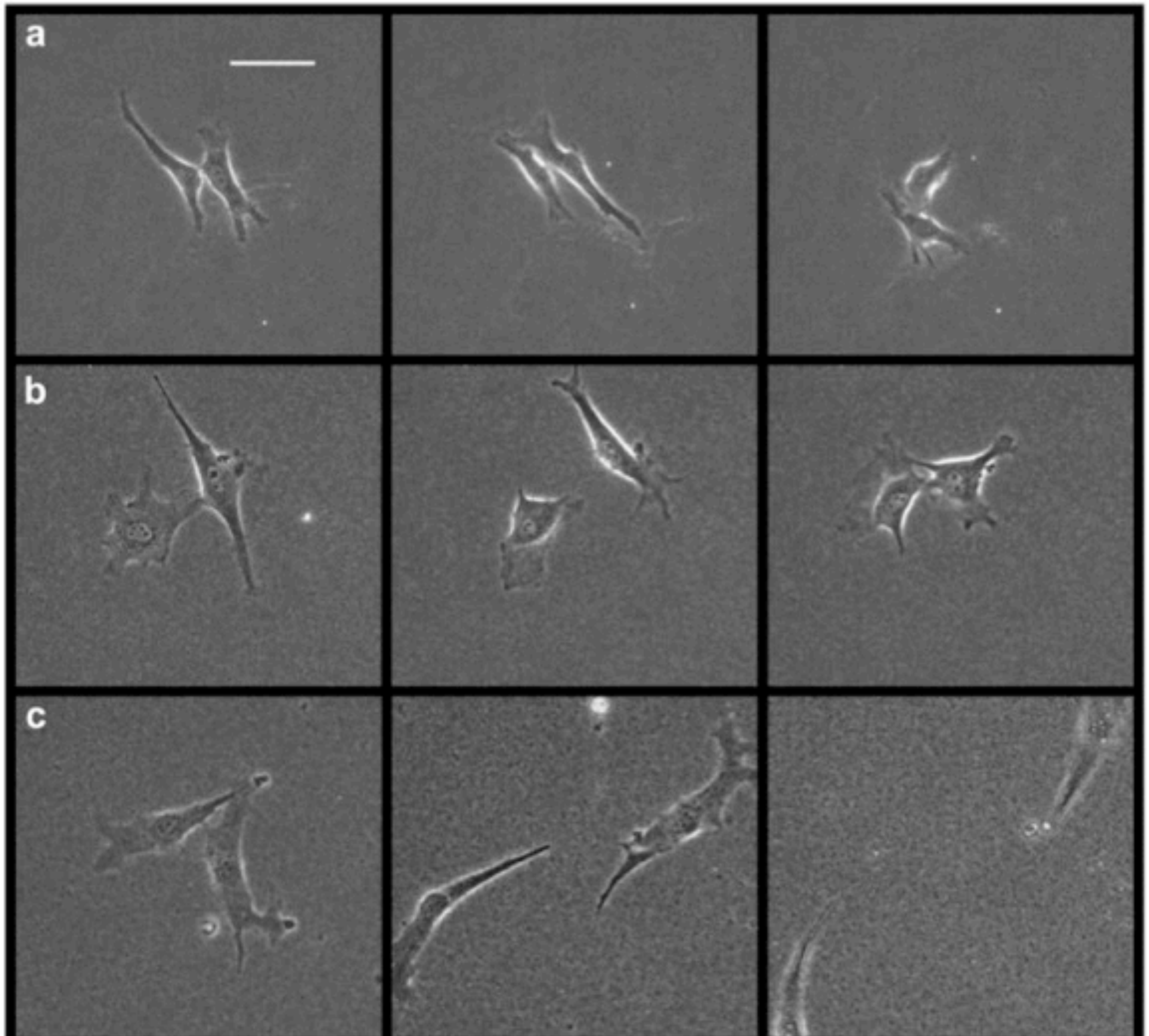
STIFF SUBSTRATE

- 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

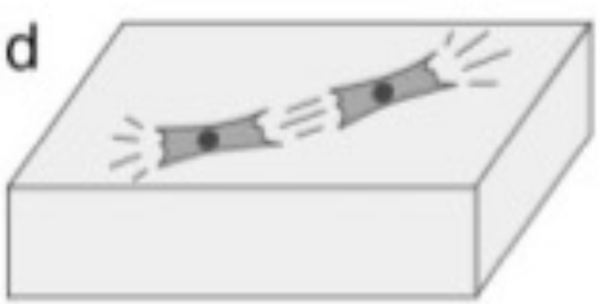
Stiff matrix (33 kPa)
Cells touch and walk away

Mechanical cell-cell communication

Video S2 - cell pairs

Van Oers, Rens, LaValley, Reinhart-King, and Merks

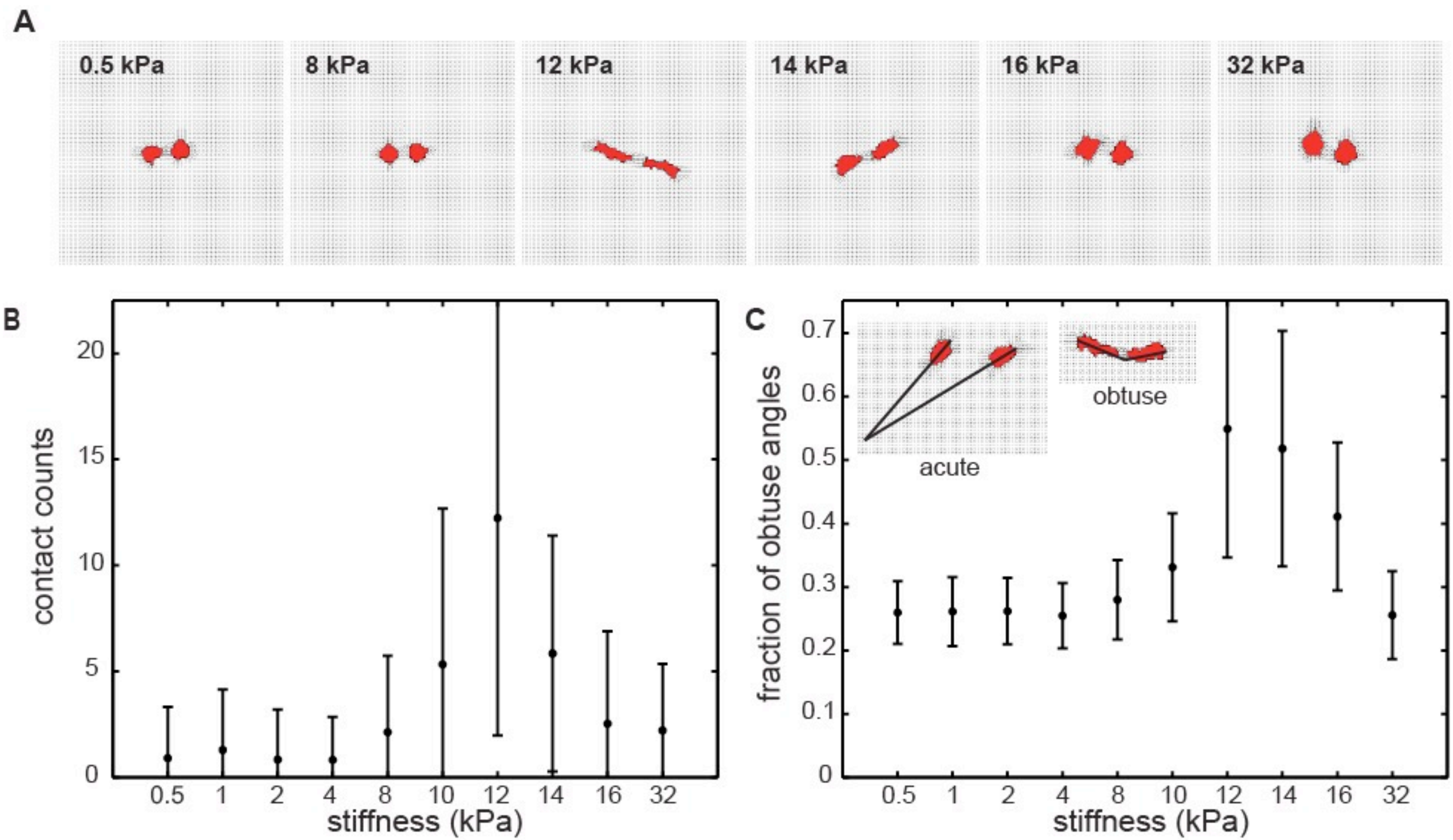
PLoS Comp Biol 2014



cf. Bischofs and Schwarz
PNAS 2003

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

Mechanical cell-cell communication

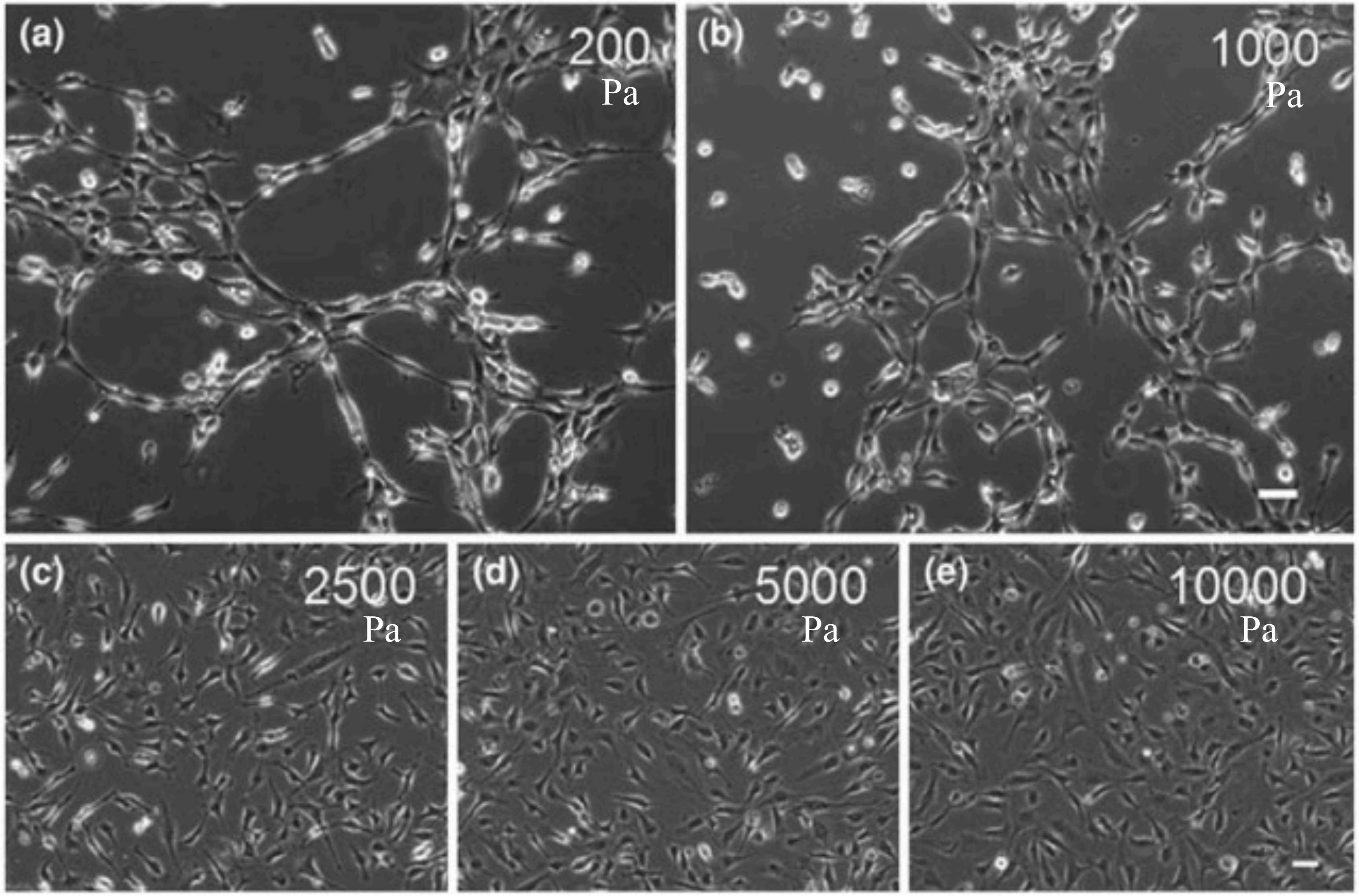


Van Oers, Rens, et al. *PLoS Comp Biol.* 2014

Collective cell behavior on unstretched matrix

Example: bovine aortic endothelial cells on poly-acrylamide substrate (non-fibrous)

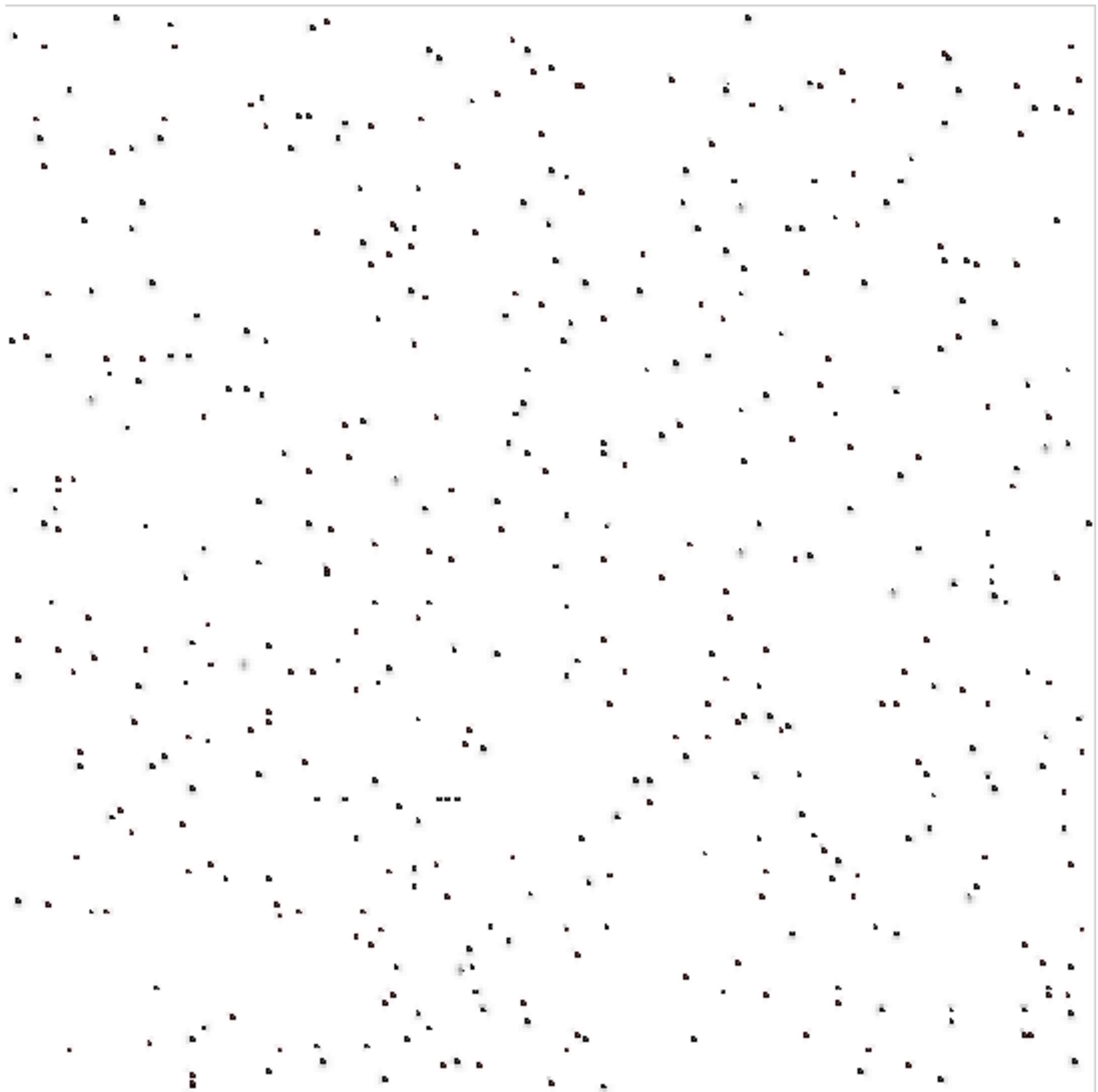
Soft matrix



Stiff matrix

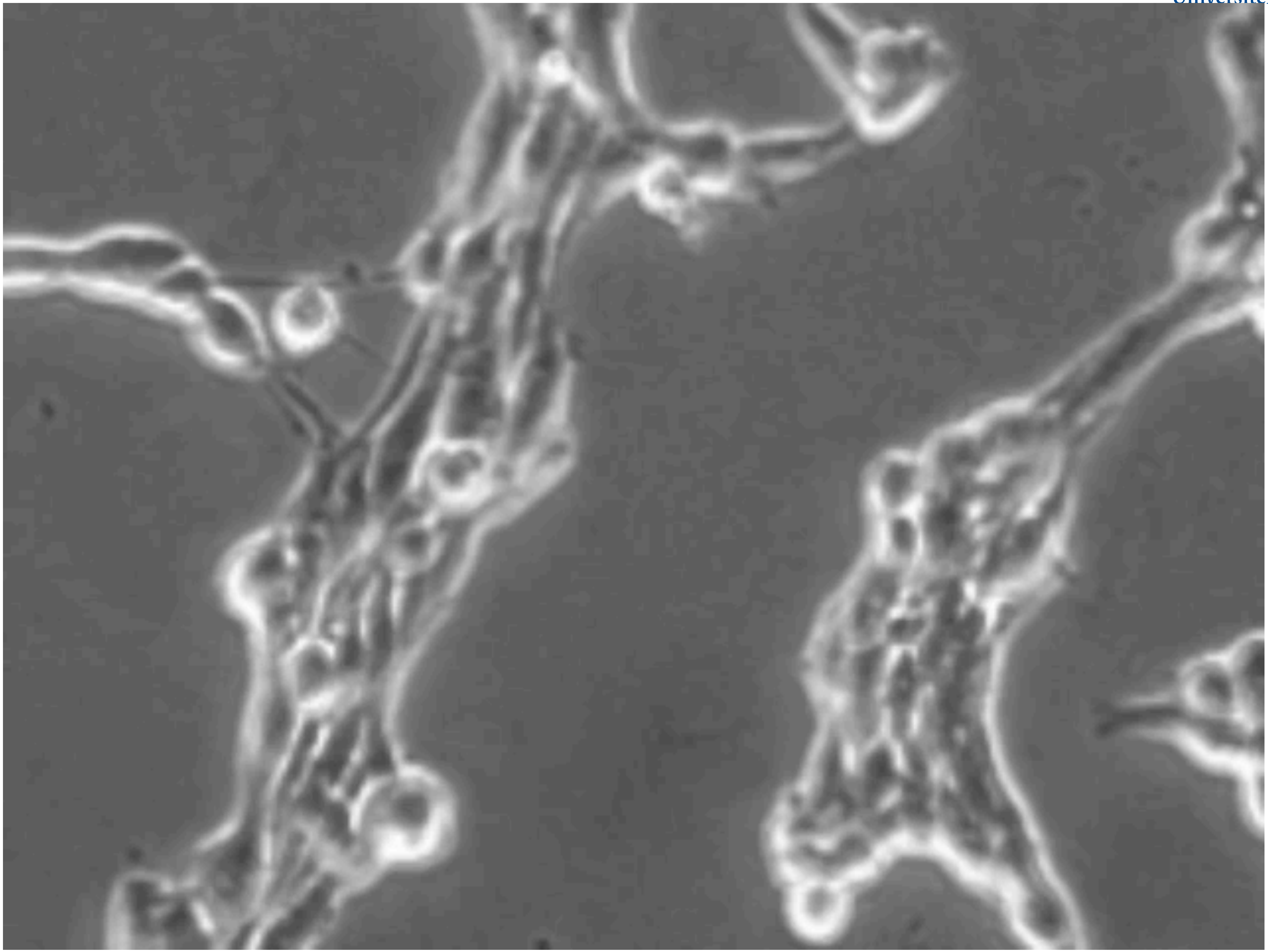
Califano and Reinhart-King, 2008

Resulting collective behavior

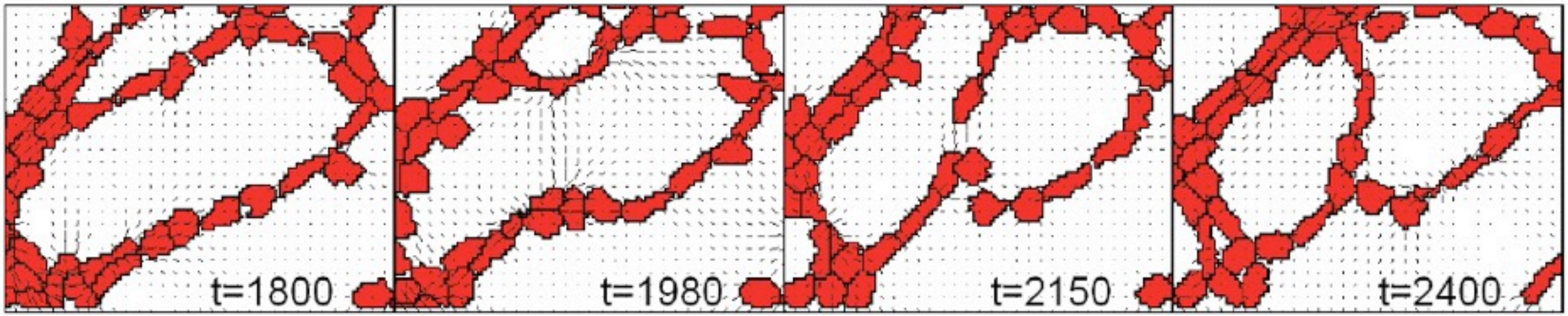


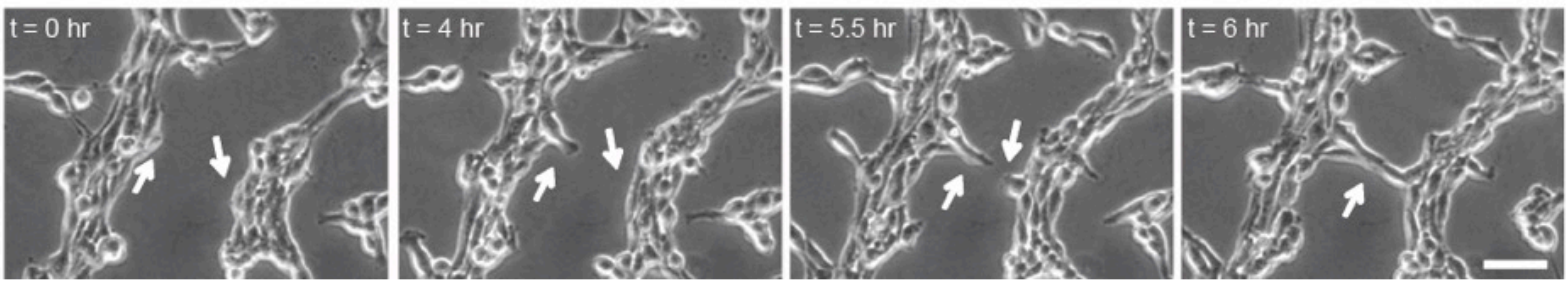
10 kPa

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



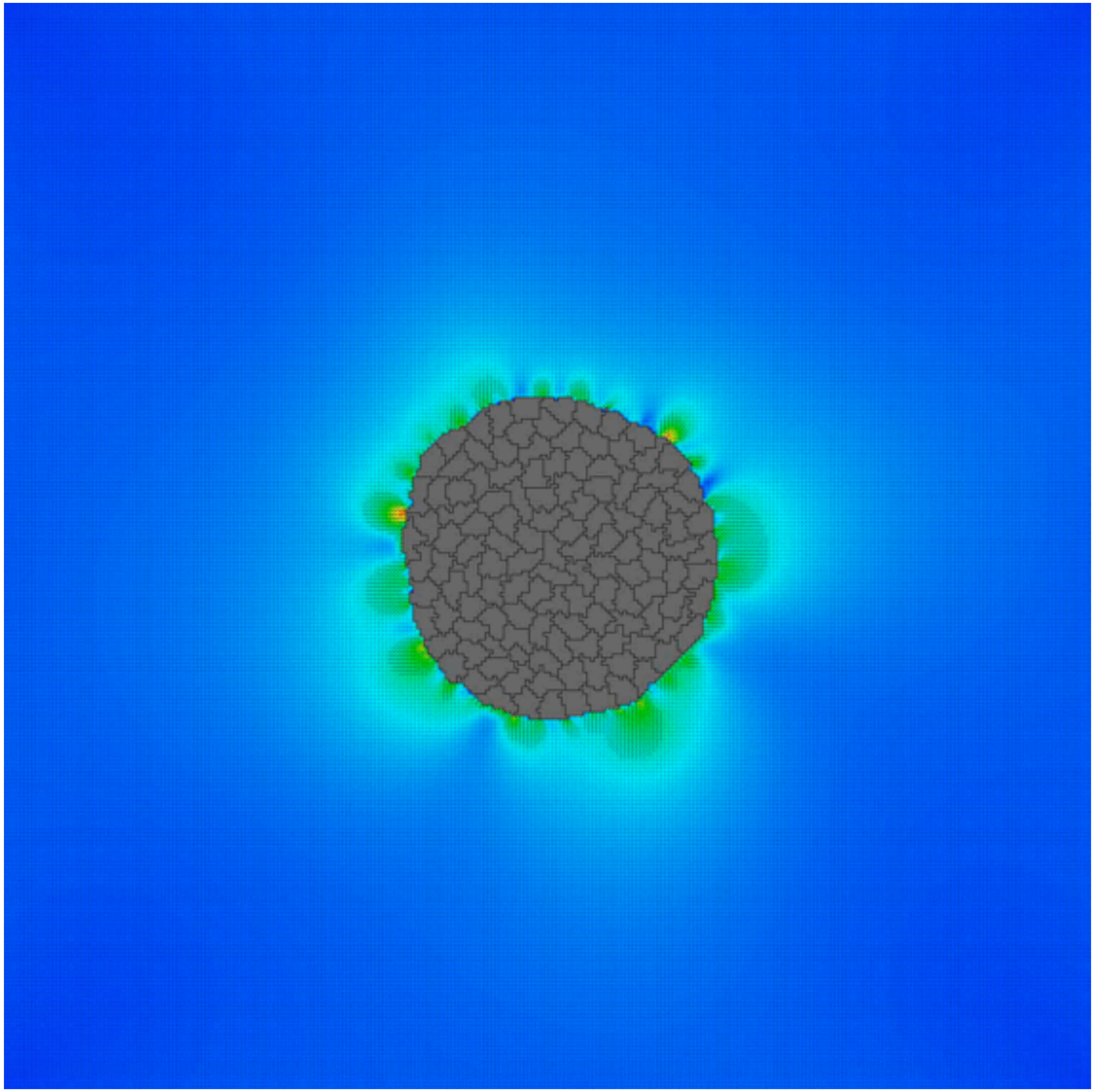
Bridging events





Danielle LaValley and
Cynthia Reinhart-King

Sprouting

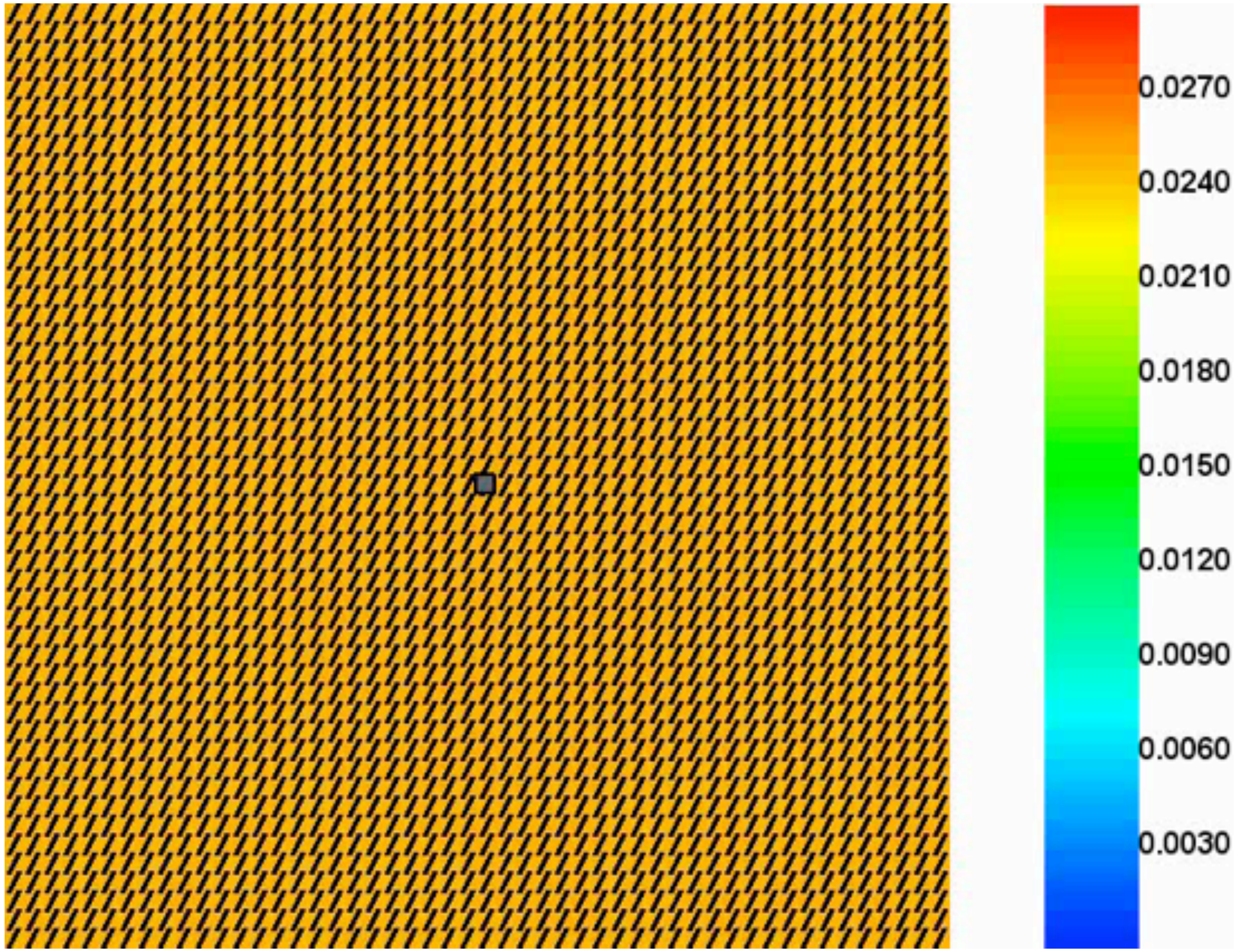


10 kPa

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

Cell contractility ("active sensing") amplifies sensitivity to matrix strain

- Only external strain - 30 degrees, 0.025
- Cells do not exert forces on matrix



Rens & Merks
Biophys. J. 2017
arXiv:1605.03987

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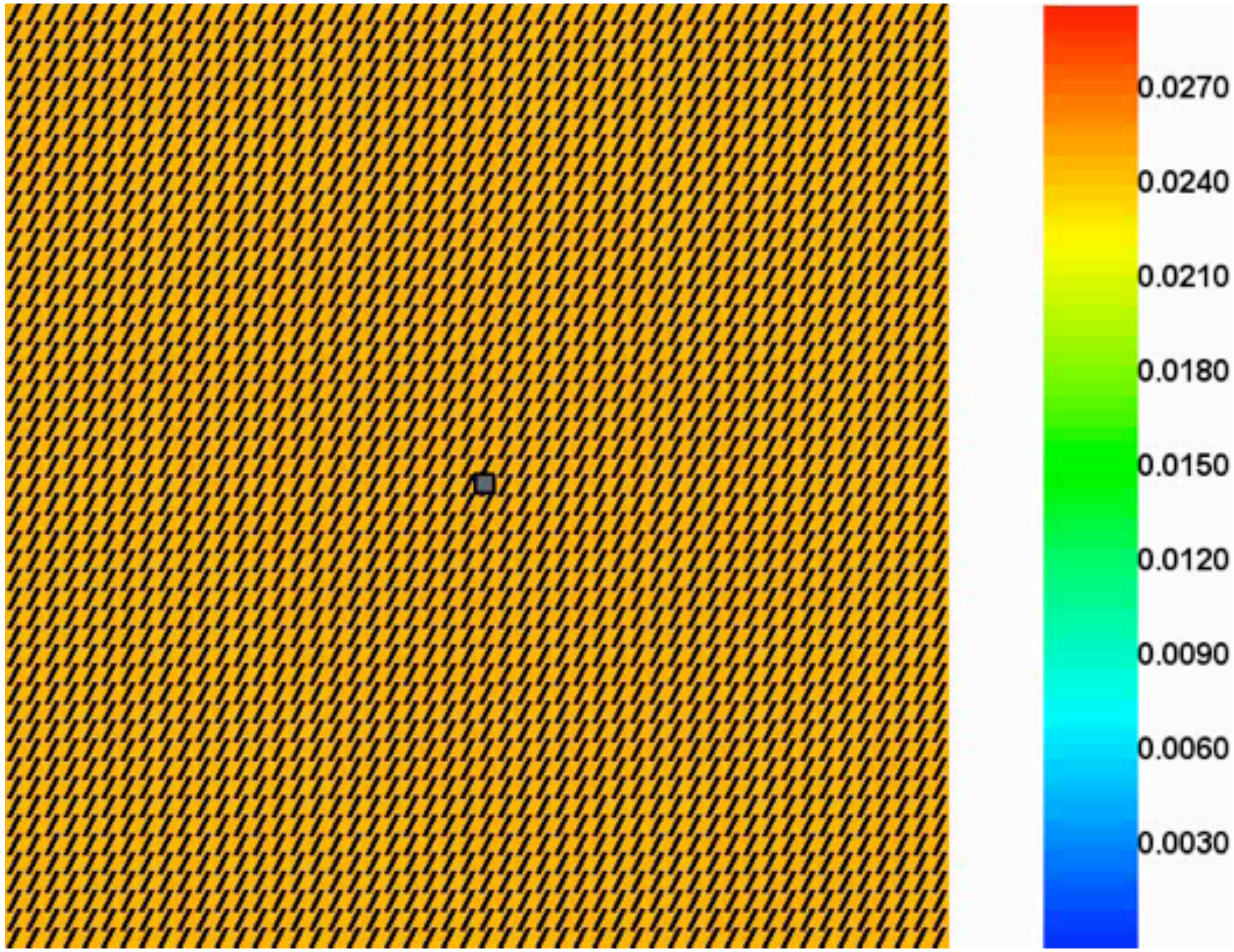
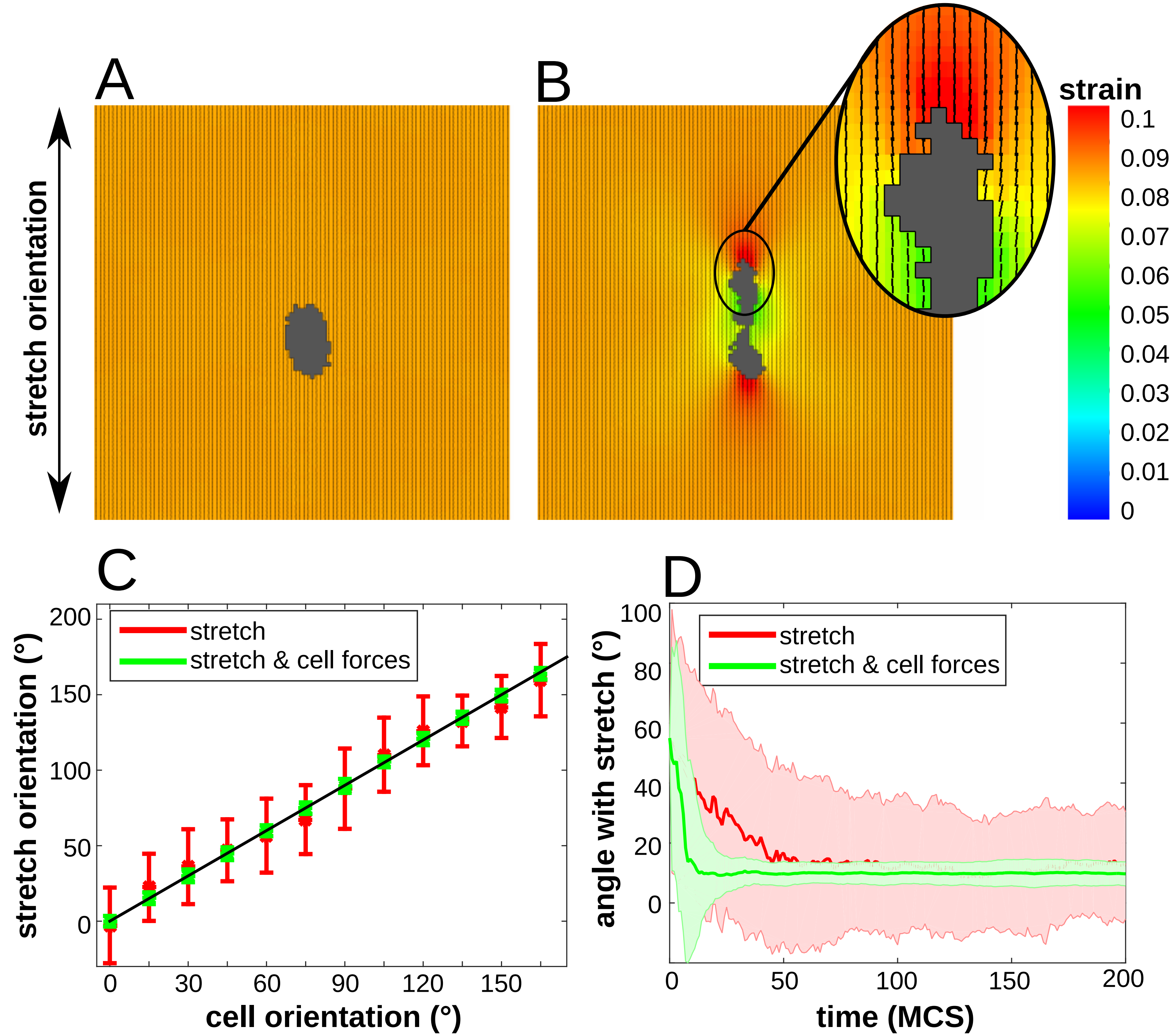
Cell contractility ("active sensing") amplifies sensitivity to matrix strain

- External strain - 0.025, 30 degrees
- Cells **do** exert forces on matrix



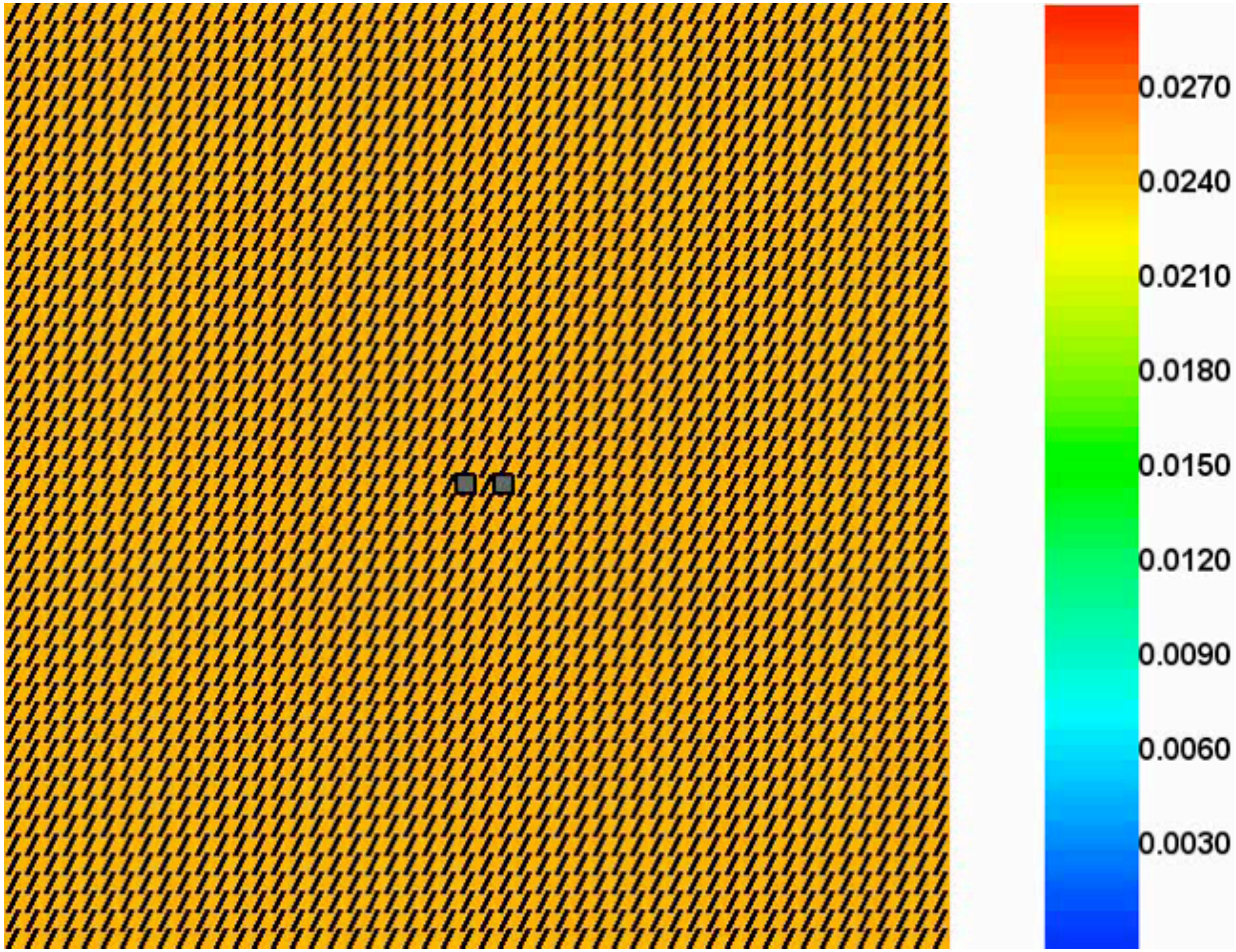
Rens & Merks, Biophys. J. 2017, arXiv:1605.03987

Contractility increases precision and speed of cell orientation



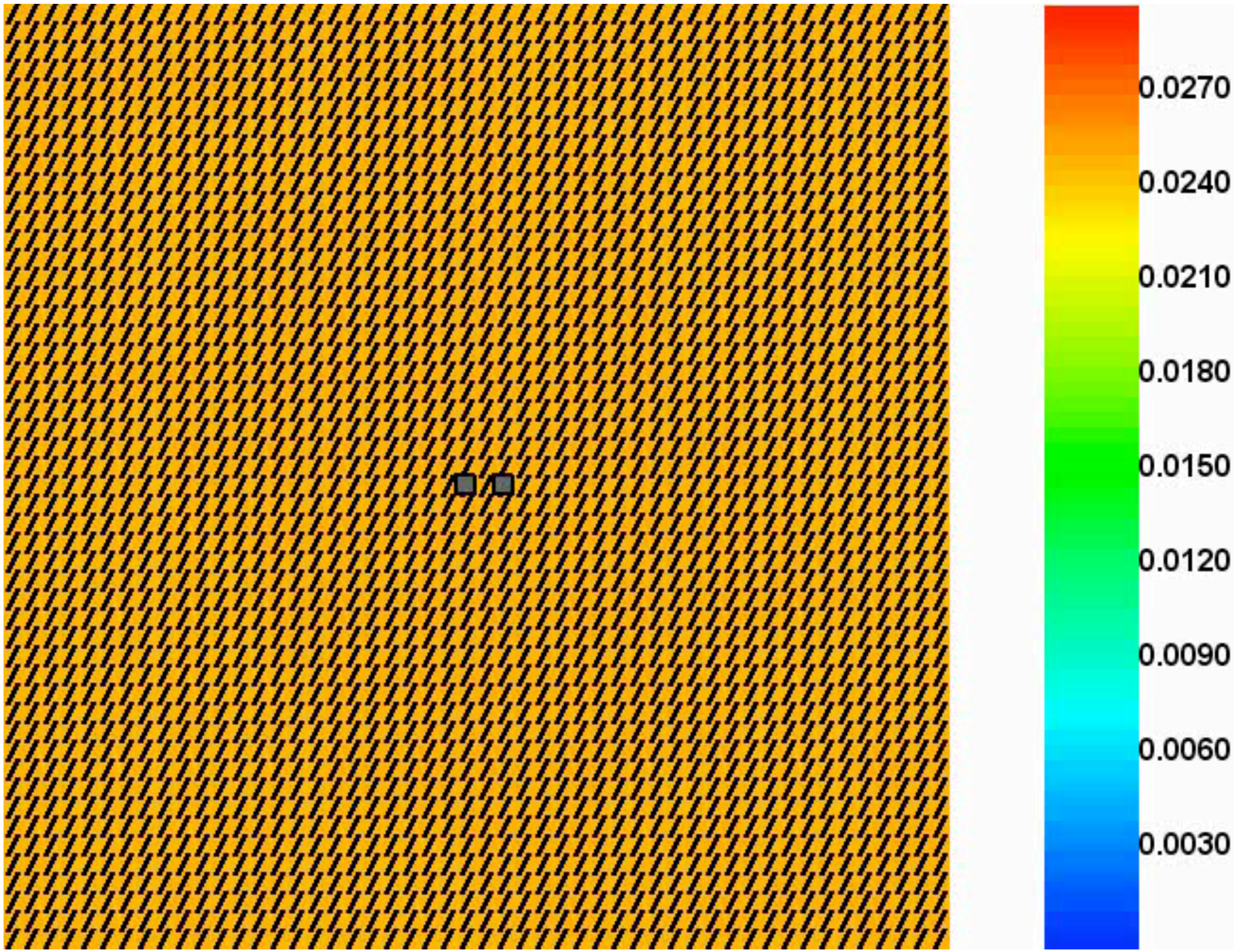
Rens & Merks, Biophys. J. 2017, arXiv:1605.03987

Two cells, no cellular traction



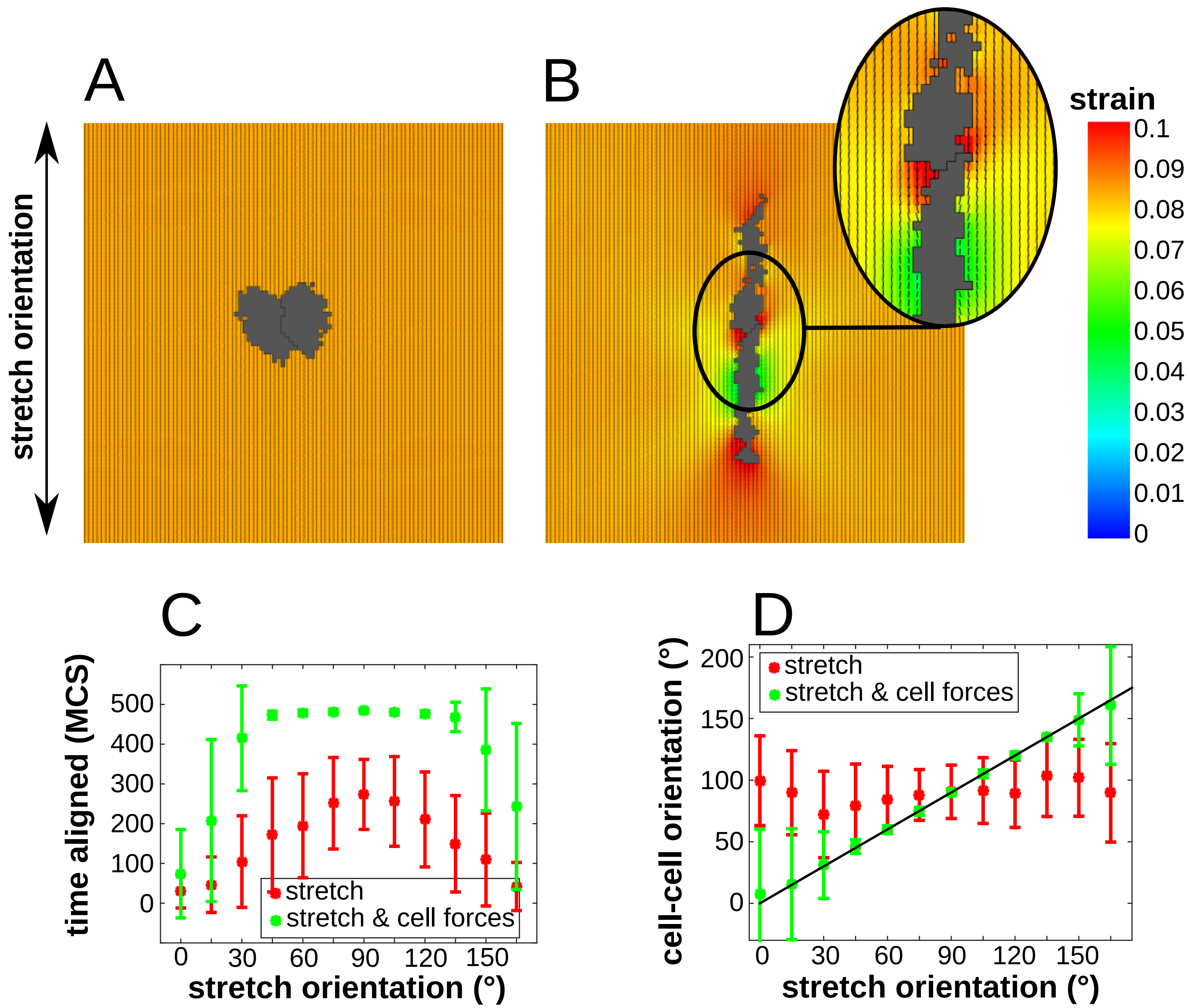
Rens & Merks, Biophys. J. 2017, arXiv:1605.03987

Two cells, cellular traction



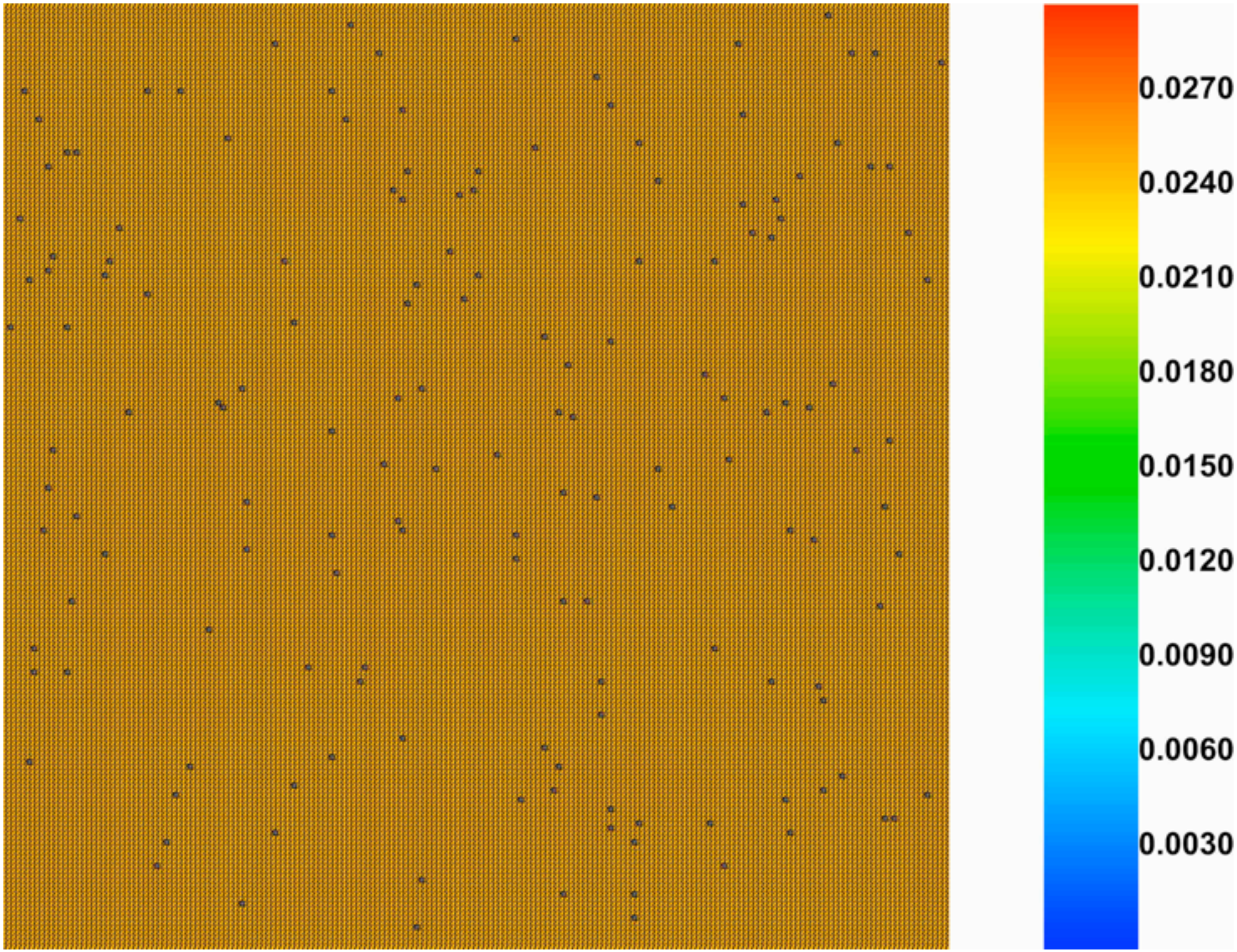
Rens & Merks, Biophys. J. 2017, arXiv:1605.03987

Contractility enhances speed and precision of cell-cell alignment



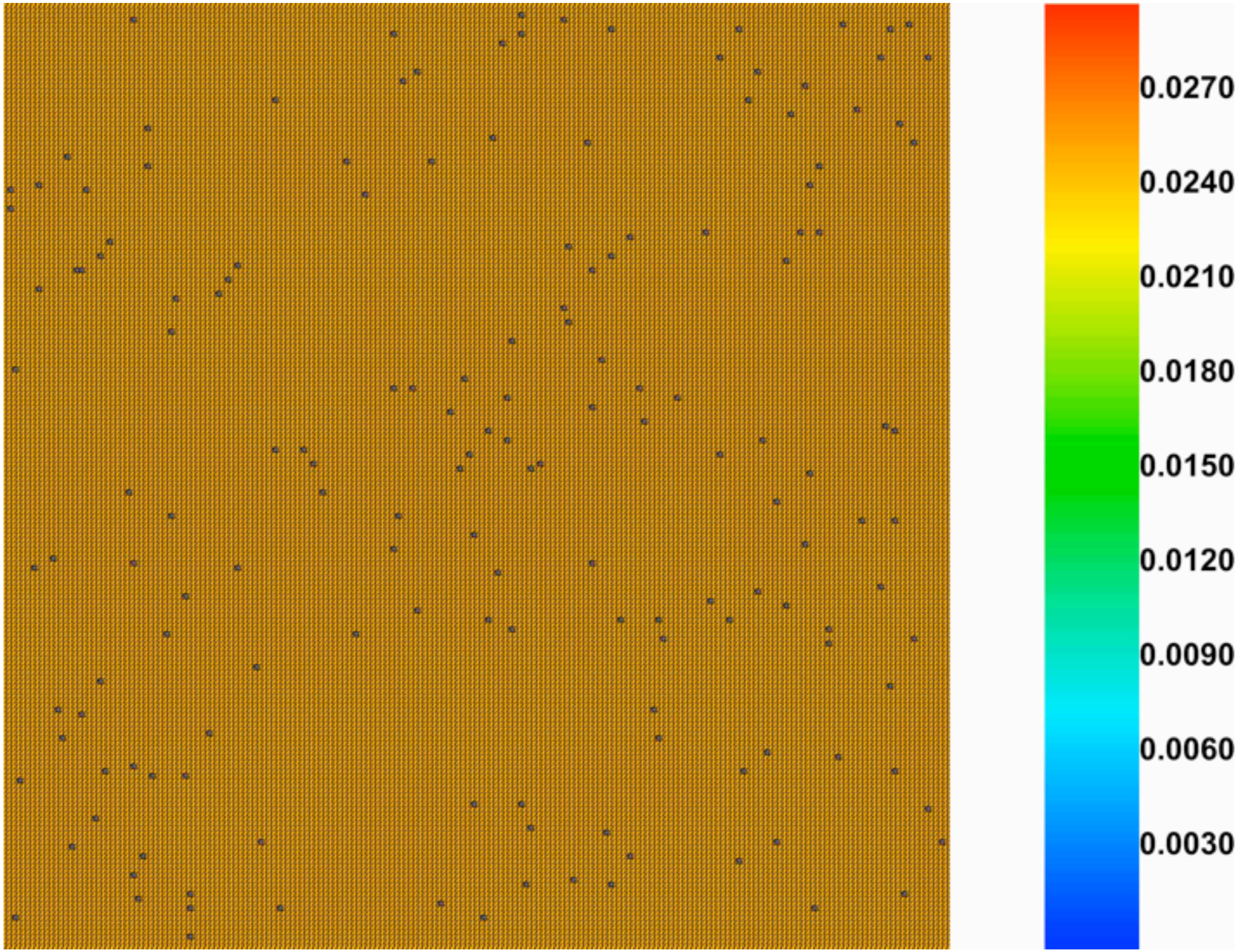
Rens & Merks, Biophys. J. 2017, arXiv:1605.03987

Cells align along stretch orientation...



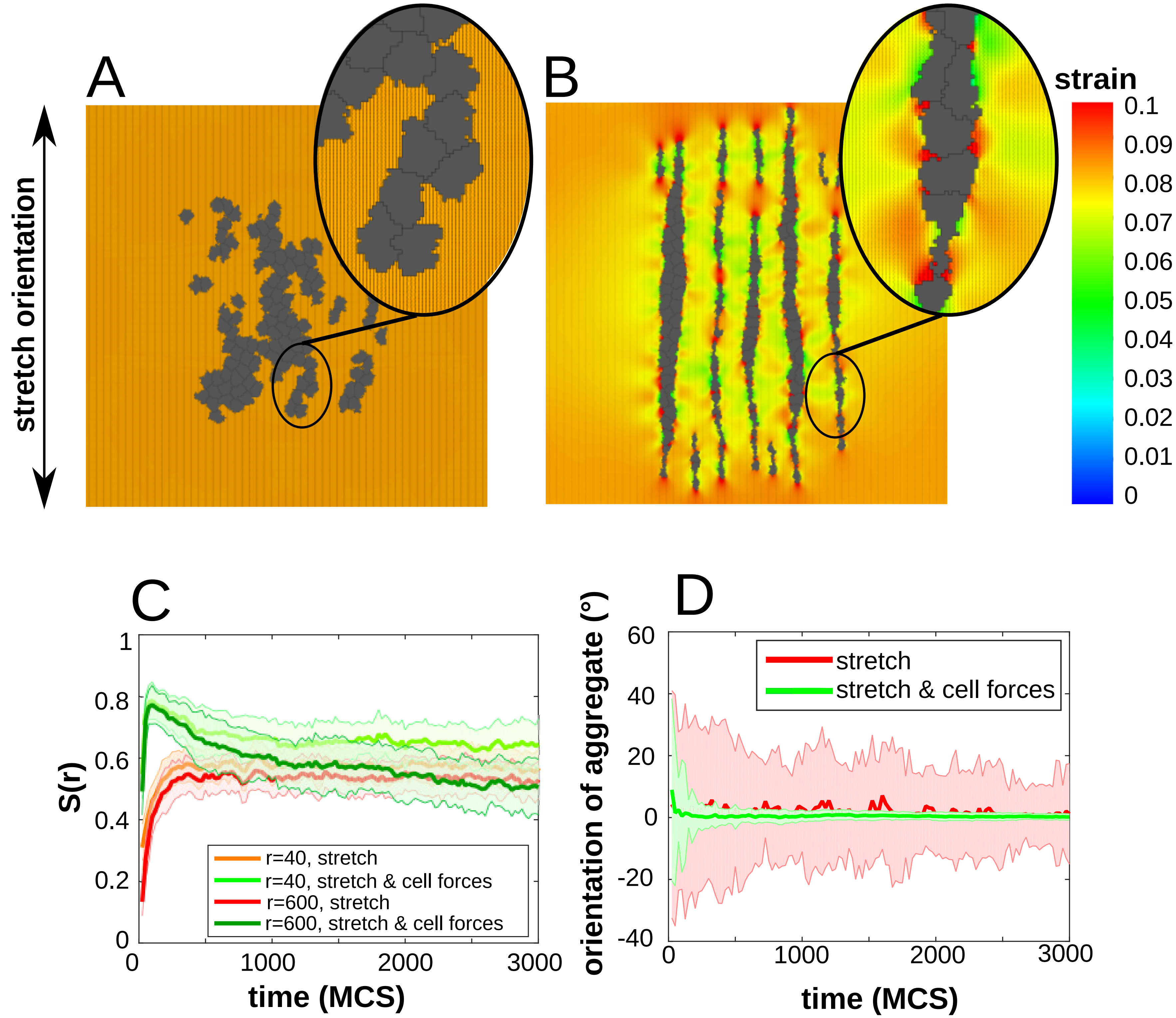
Rens & Merks, Biophys. J. 2017, arXiv:1605.03987

... but only if cells exert forces on matrix



Rens & Merks, Biophys. J. 2017, arXiv:1605.03987

Active cell sensing accelerates response to strain



Rens & Merks, Biophys. J. 2017, arXiv:1605.03987

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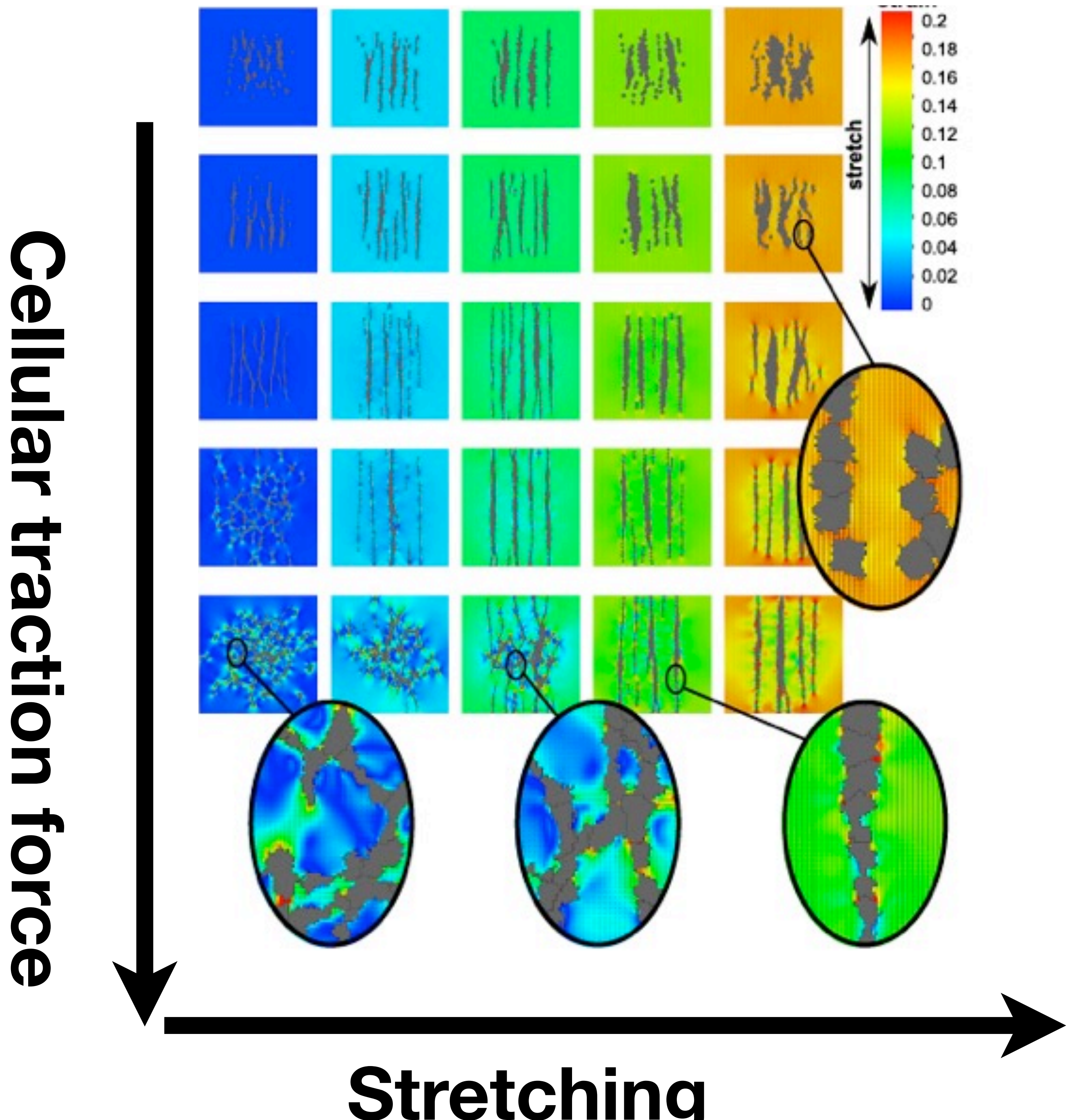
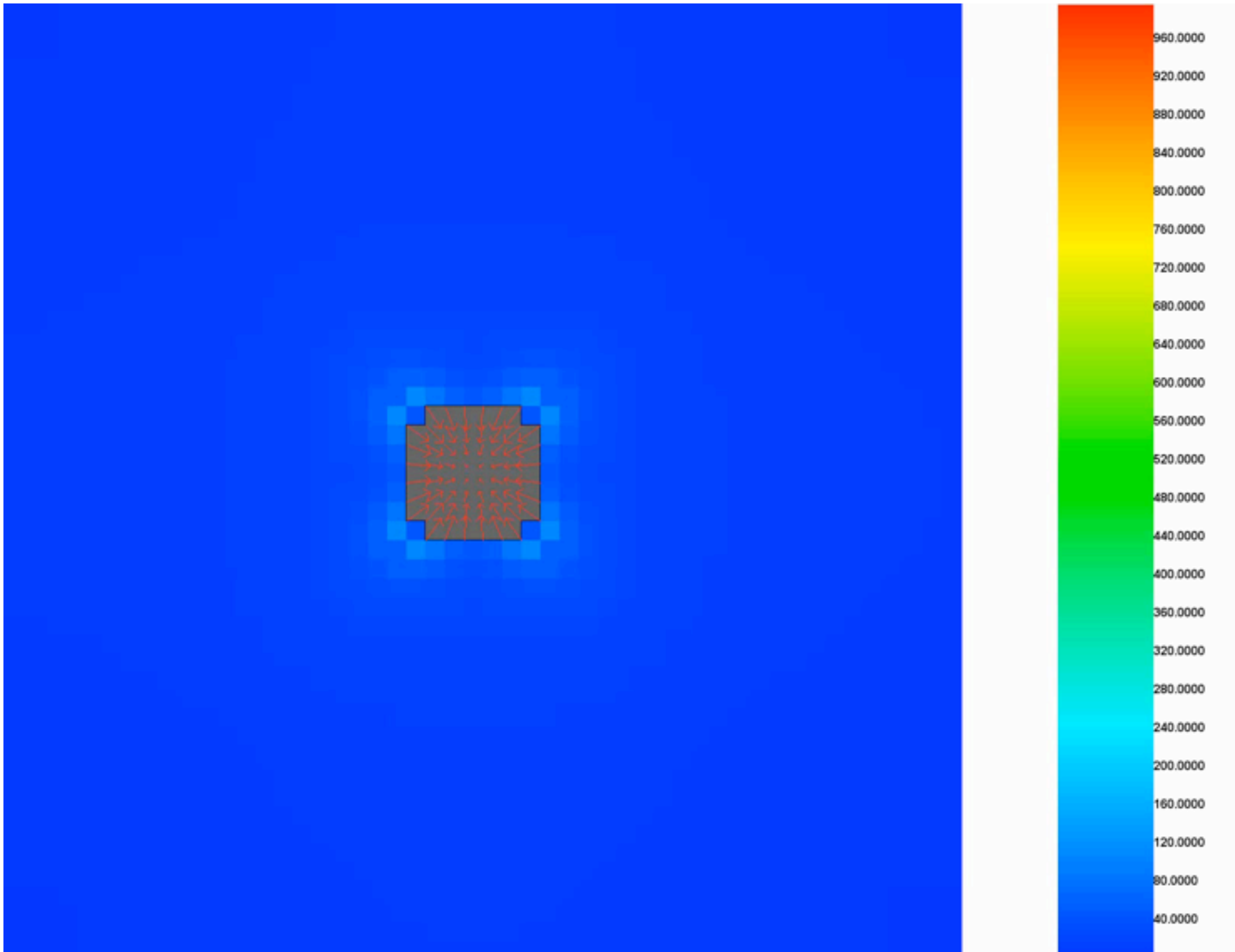
Balance between cell contractility and stretch determines patterning



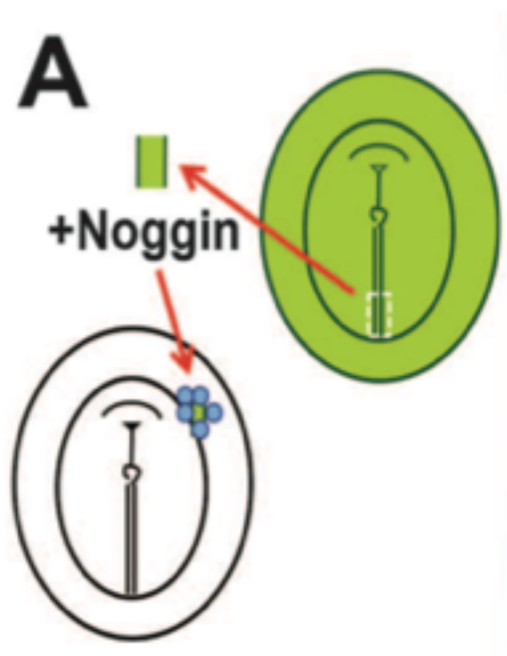
Next step:
Focal adhesion kinetics

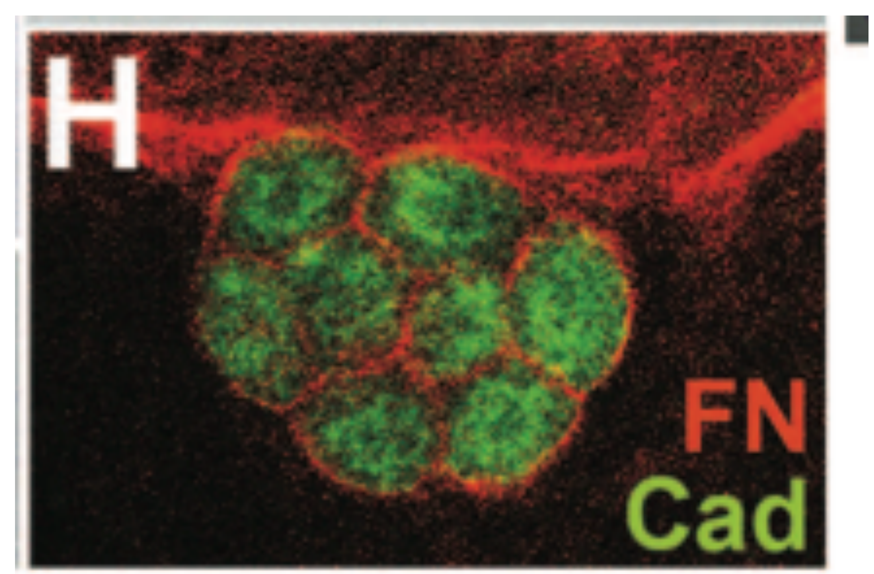


Lisanne Rens

Mechanical strain during somitogenesis

- "Somites without a clock" (Dias et al. *Science* 2014)
  - Ectopic somites form from dorsalized, ventral primitive streak tissue





  - Ectopic somites not polarized, no cyclic gene expression
- **Can extension of body axis put somites in a row?**

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Acknowledgments

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Lisanne Rens
Hannan Tahir

MI - U Leiden

Claudiu Antonovici
Koen Schakenraad
Leonie van Steijn
Esmée Vendel

Alumni:

Sonja Boas
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René van Oers
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Sander Hille (mathematics)
Remko Offringa (biology)

Funding: NWO Netherlands Organisation for Scientific Research