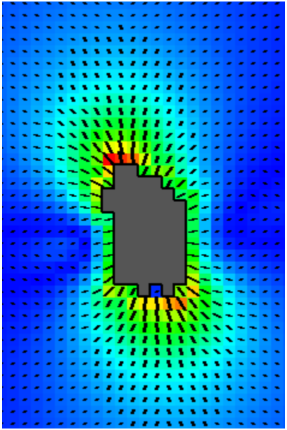
Cell traction forces serve as an amplifier for mechanical cues



Speaker: Lisanne Rens (Life Sciences Group, Centrum Wiskunde & Informatica)
Roeland Merks (CWI, Mathematical Institute Leiden)

Cells respond to mechanical cues in the extracellular matrix

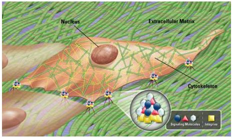


Figure: Copied from *http://www.osteopata.it*

ECM supports tissue

cells adhere to ECM

ECM guide cell migration

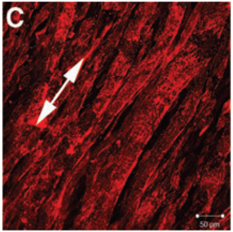


Figure: [van der Schaft et al., 2011]

cells:

migrate to stiffer areas

spread more on stiff substrates

more stable focal adhesions on stiff substrates

elongate along stretch orientation

cells deform the ECM

Cells apply a traction force to the ECM $\rightarrow$ local ECM deformations

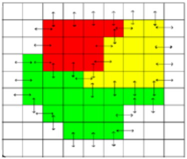
Figure: Copied from [Califano and Reinhart-King, 2010]

Q: How do traction forces affect response to mechanical cue in the ECM?

A: try to find out by mathematical modeling

Cellular Potts Model

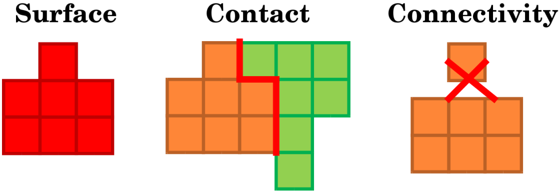
Cells are modelled as a collection of lattice sites
[Glazier and Graner, 1993]



Monte Carlo Step:

- Move: extension/retraction of one lattice site
- Accept or decline move

System behavior based on balance of forces



Accept move with Boltzmann probability

Traction forces and mechanotaxis

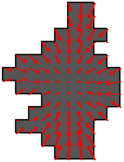
Cell traction forces : cell nodes pull on cell nodes

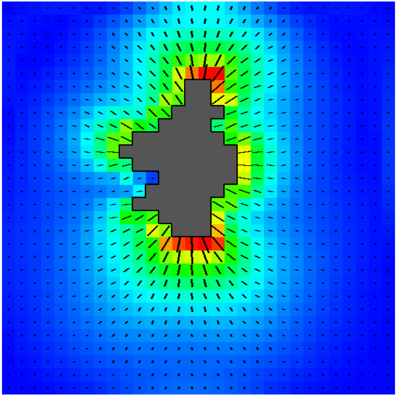
$F_i = \mu \sum_j d_{ij}$ [Lemmon and Romer, 2010]

Substrate Linear elastic, isotropic, infinitesimal strain

$Ku = f$, $\epsilon = (\epsilon_{xx}, \epsilon_{yy}, 2\epsilon_{xy}) = (\frac{\partial u_x}{\partial x}, \frac{\partial u_y}{\partial y}, \frac{\partial u_x}{\partial x} + \frac{\partial u_y}{\partial y})$

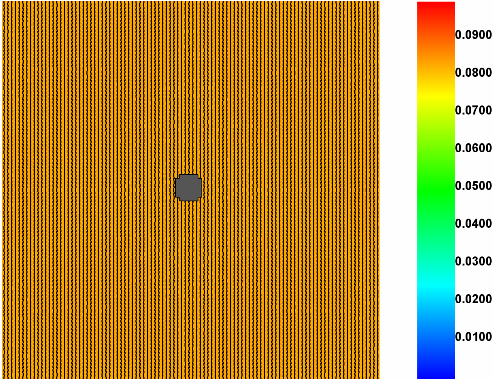
Mechanotaxis Cells prefer to adhere to higher strained areas and in the strain orientation.





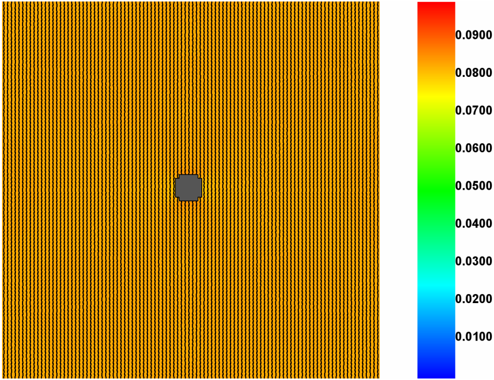
Static stretch

single cell
no cellular traction forces

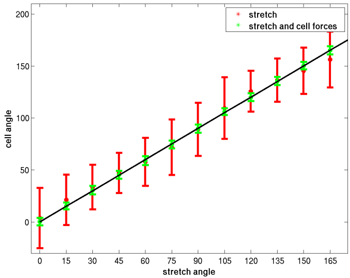


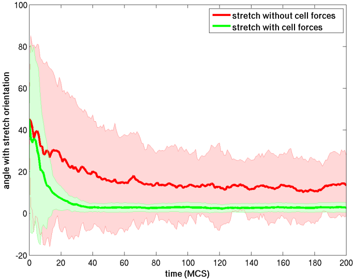
Static stretch

single cell
cellular traction forces



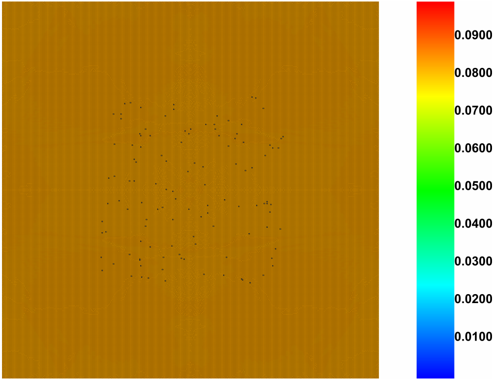
Cell forces amplify and speed up single cell response to static stretch





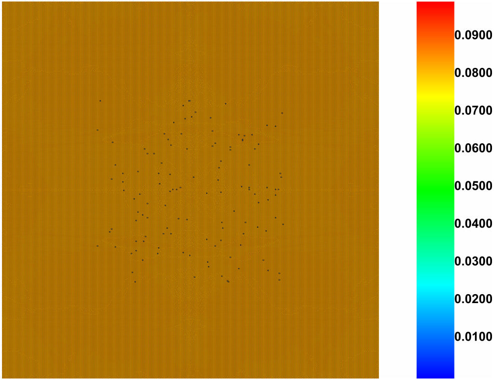
Static stretch

group of cells
no cellular traction forces



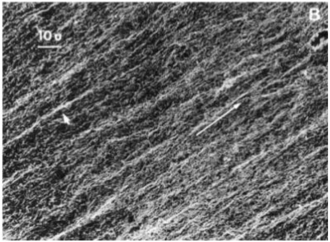
Static stretch

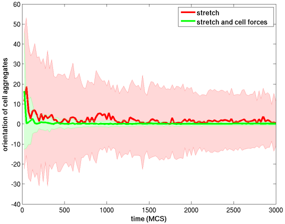
group of cells
cellular traction forces

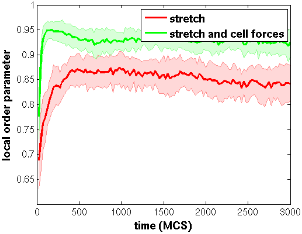


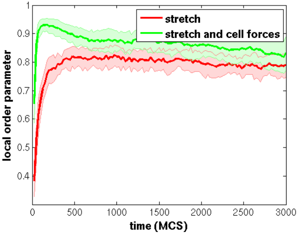
Cell forces induce self organization

[Eastwood et al., 1998]



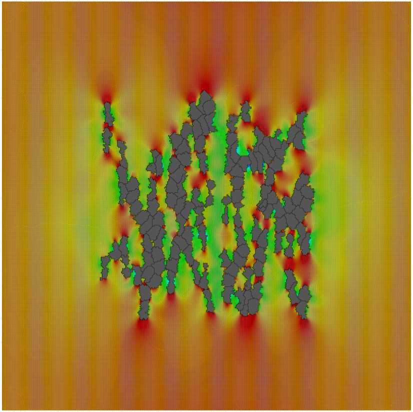






Conclusion

Cell traction forces can amplify response to mechanical cues and promote self-organization



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Hamiltonian

$$H = \sum_{(\vec{x},\vec{x}')} J(\tau(\sigma_{\vec{x}}), \tau(\sigma_{\vec{x}'}))(1-\delta(\sigma_{\vec{x}}, \sigma_{\vec{x}'})) + \lambda_A \sum_{\sigma} (a(\sigma) - A)^2 \quad (1)$$

$$P(\Delta H) = \begin{cases} 1 & \text{if } \Delta H < 0 \\ e^{-\frac{\Delta H}{T}} & \text{if } \Delta H \geq 0. \end{cases} \quad (2)$$

Mechanotaxis

To incorporate cell response to strains in the substrate, another term is added to the Hamiltonian:

$$\Delta H_{\mathrm{mech}} = -g(\vec{x}, \vec{x}')\lambda_{\mathrm{mech}} \left[f(E(\epsilon_1))(\vec{v_1} \cdot \vec{v_m})^2 + f(E(\epsilon_2))(\vec{v_2} \cdot \vec{v_m})^2 \right]$$

g : ± 1 extensions/retractions

λ_{dur} : durotaxis parameter

$\vec{v}_1, \vec{v}_2, \epsilon_1, \epsilon_2$: principal directions and strains

$\vec{v}_m$: copy direction

$E(\epsilon)$: $E_0(1 + \frac{\epsilon}{\epsilon_{\mathrm{st}}})$ modelling strain-stiffening

$f(E)$: sigmoid function "A certain level of stiffness is needed to cause a cell to spread, and there is a maximum of response"

Order parameter

Orientational order parameter

- $\vec{v}(\sigma(\vec{x}))$ direction of long axis of cell at $\vec{x}$.
- $\vec{n}$ local director, the weighted local average of cell orientations, within a radius r around $\vec{x}$, such that $\vec{n}(\vec{x}, r) = \langle \vec{v}(\sigma(\vec{y})) \rangle_{\{\vec{y} \in \mathbb{Z} : |\vec{x} - \vec{y}| < r\}}$.
- $\theta(\vec{x}, r)$ angle between $\vec{v}(\sigma(\vec{x}))$ and $\vec{n}$
- S order parameter, defined as $S(r) = \left\langle \frac{3 \cos^2 \theta(\vec{X}(\sigma), r) - 1}{2} \right\rangle_{\sigma}$ where $\vec{X}(\sigma)$ is the center of mass of cell σ.