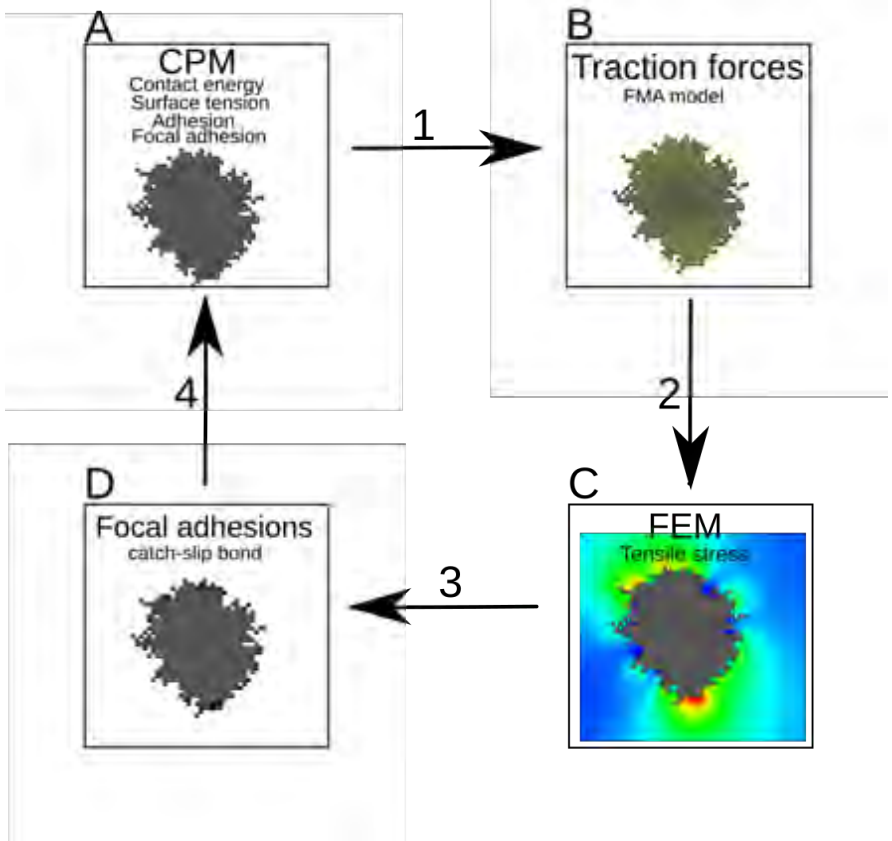
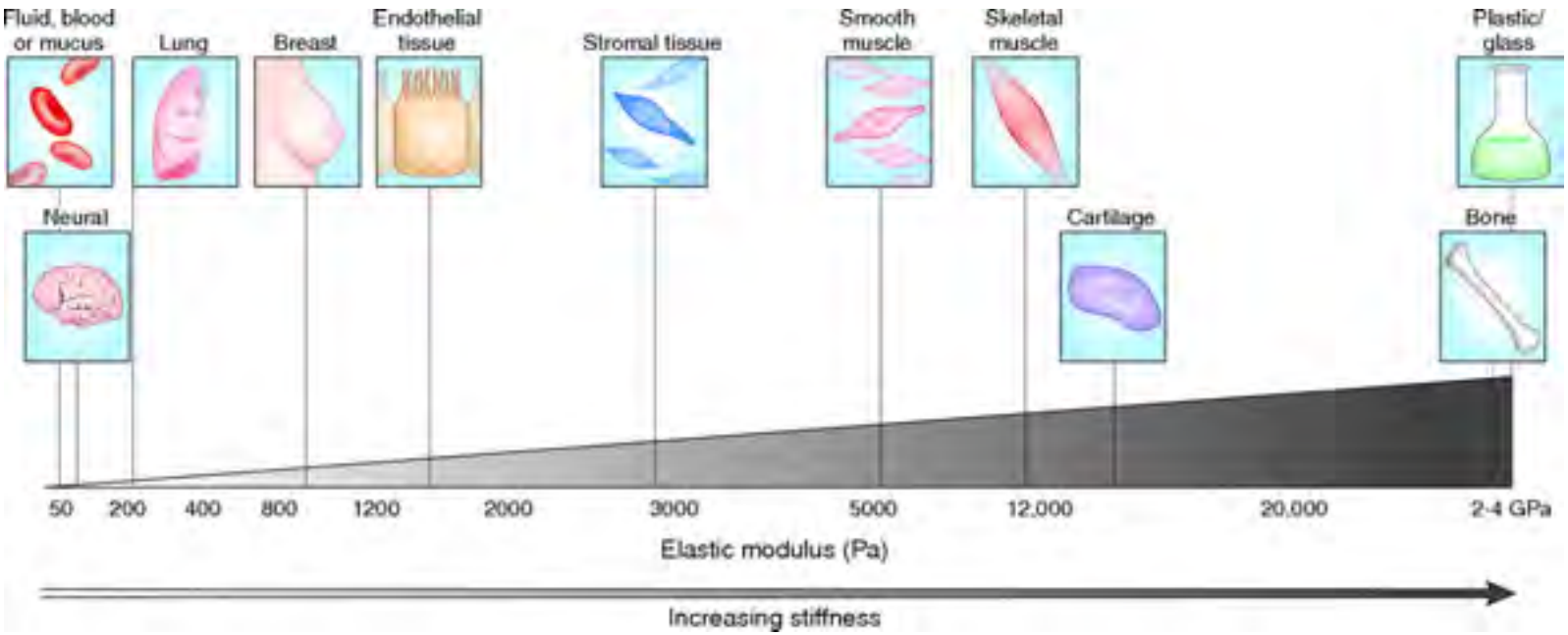
Catch bond model of focal adhesions explains cell response to matrix stiffness



Elisabeth (Lisanne) **Rens**, Roeland Merks
Centrum Wiskunde & Informatica, Amsterdam
Leiden University

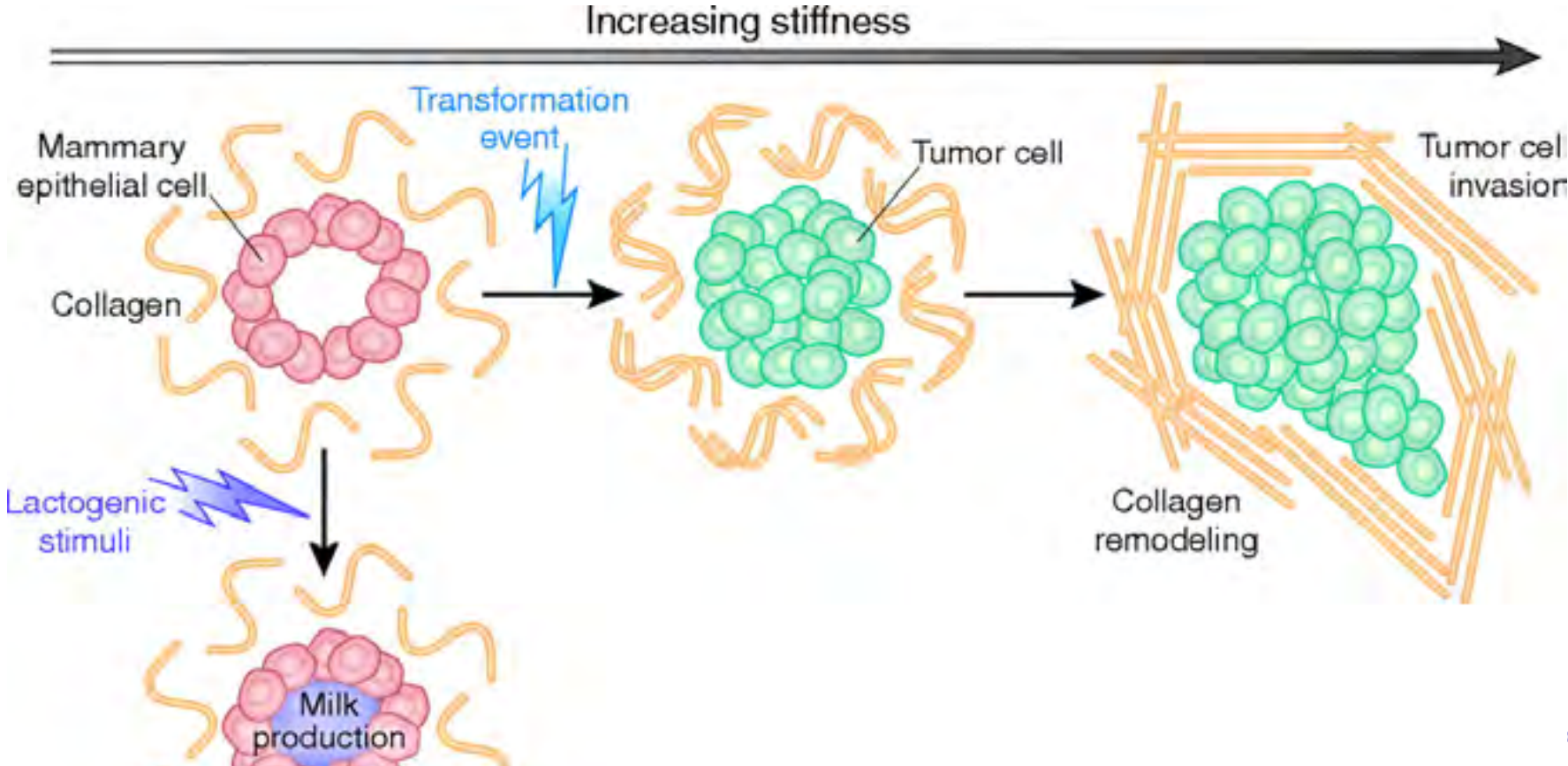
Tissue stiffness

Cox2011



Tissue stiffness can change

- embryonic development
- tissue remodeling
- fibrotic diseases
- tumours
- aging



Tissue stiffness affects morphogenesis

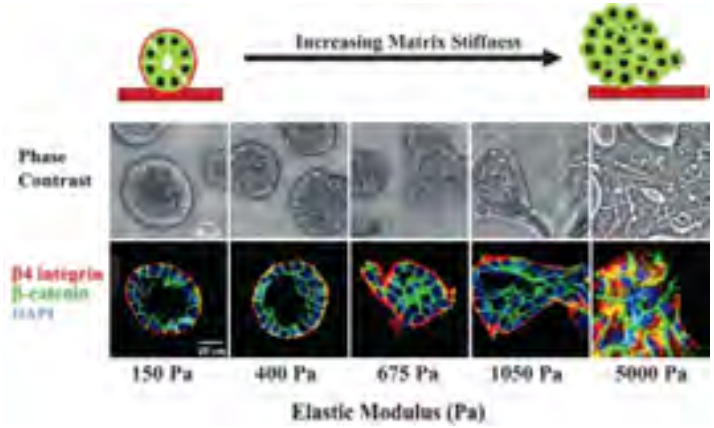


Figure: Mammary epithelial cells (Paszek2011)

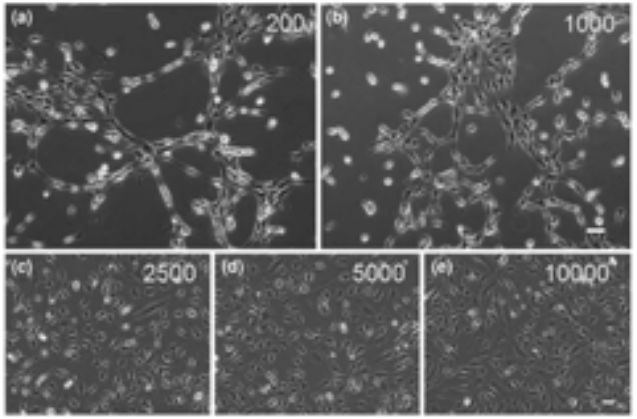


Figure: Vasculogenesis (Califano2008)

Tissue stiffness affects cell behavior

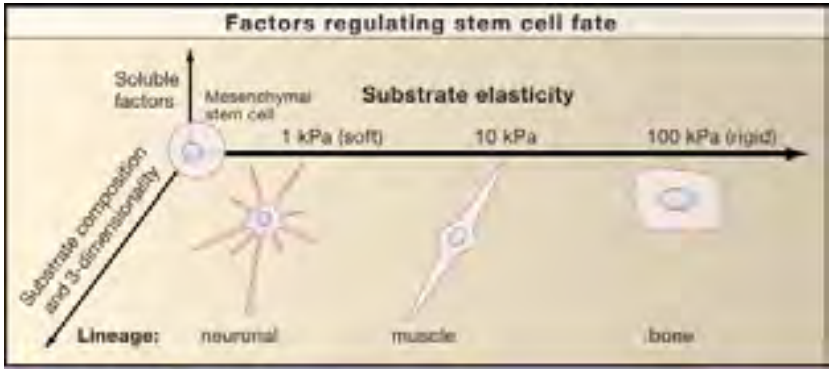


Figure: (Even-Ram2006)

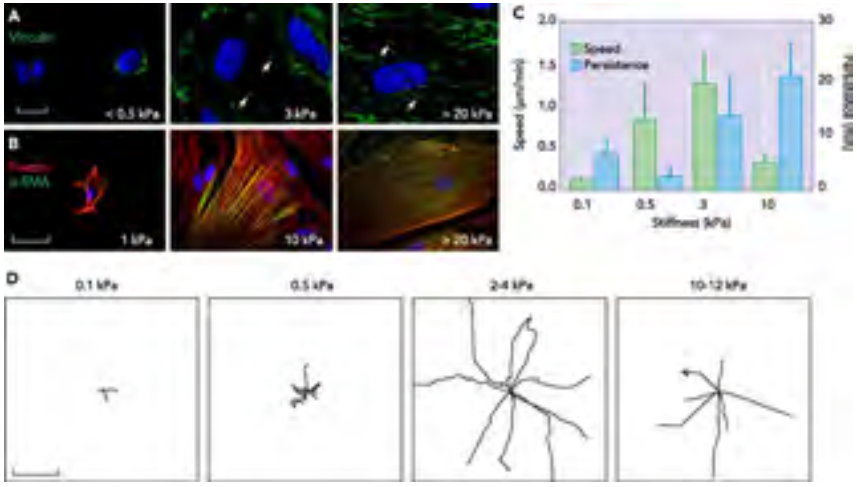
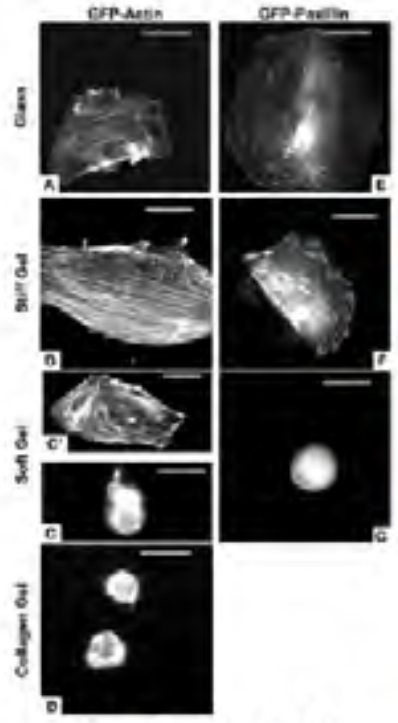
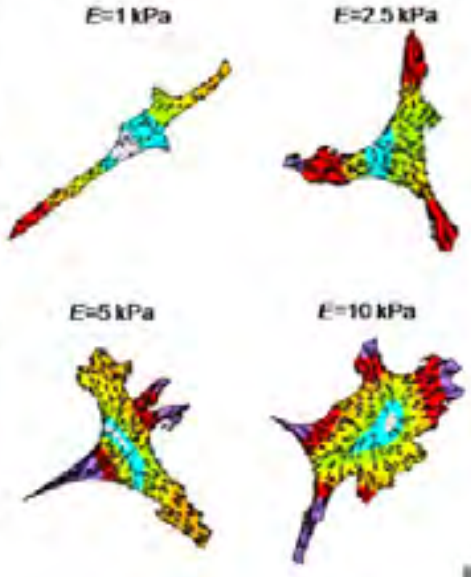


Figure: (Tschumperlin2013)

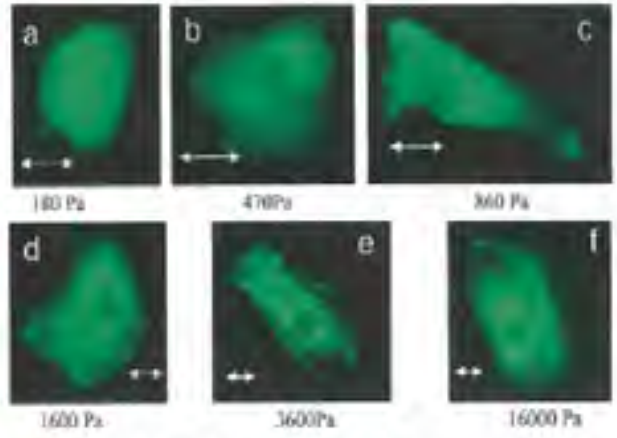
Tissue stiffness affects cell spreading



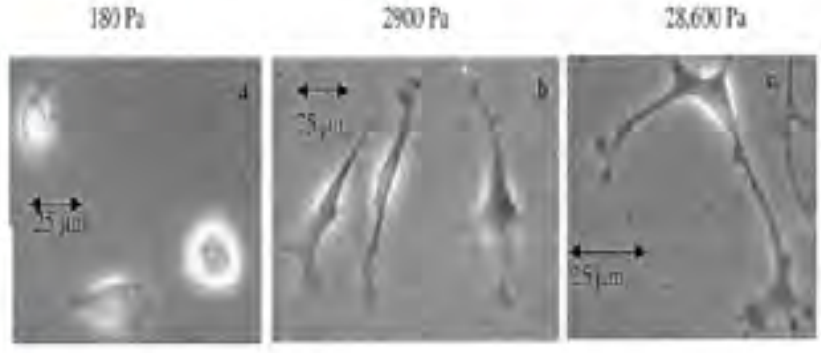
SMC, Engler2004



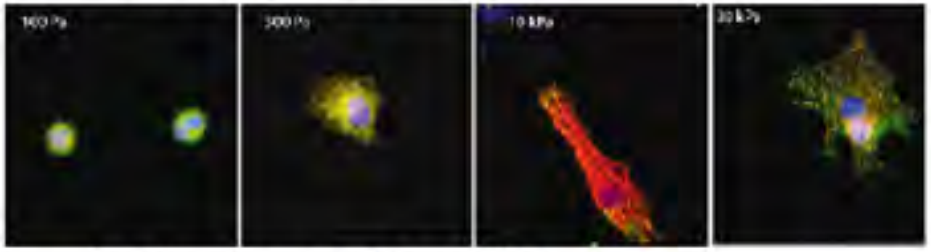
EC, Reinhart-King2010



Fibroblasts, Yeung2005



EC, Yeung2005



Cardiomyocytes, Winer2011

Aim of our research

Explain the molecular mechanism behind cell spreading on substrates of different stiffness

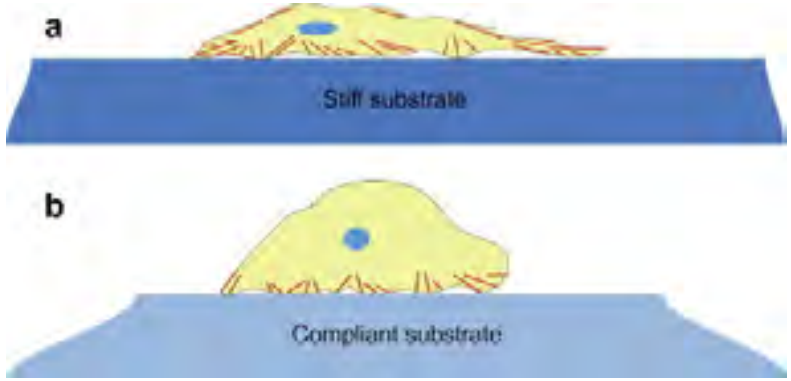


Figure: (Walters2014)

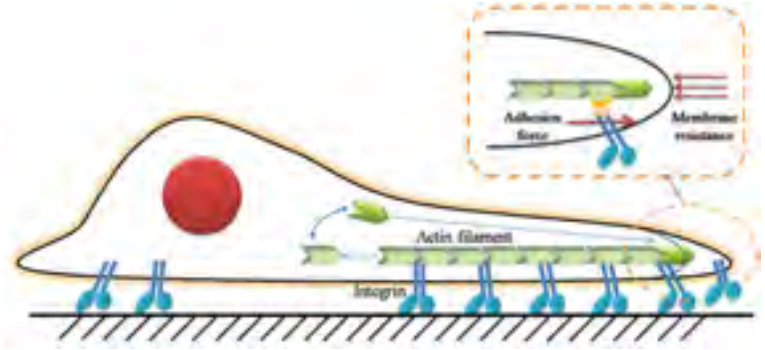
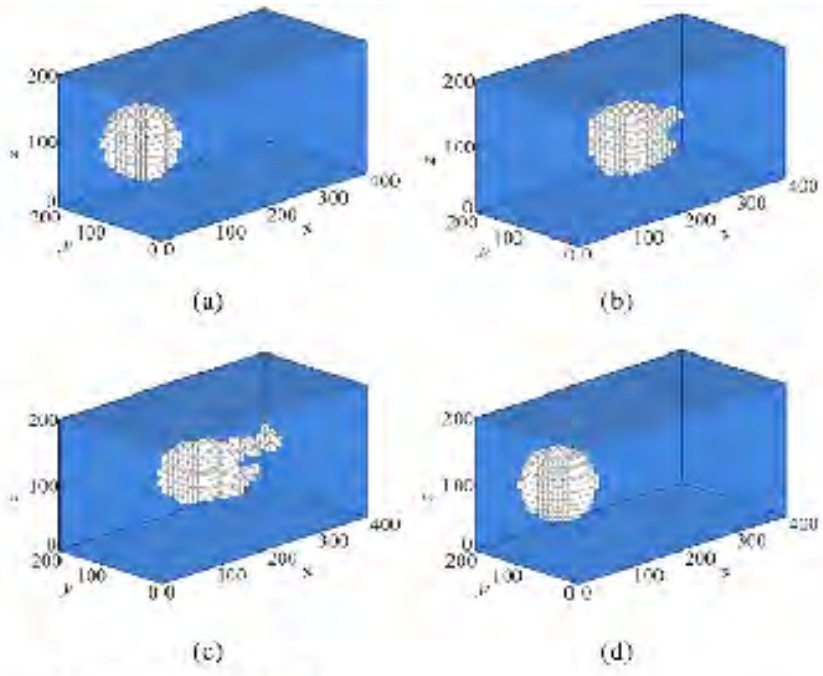
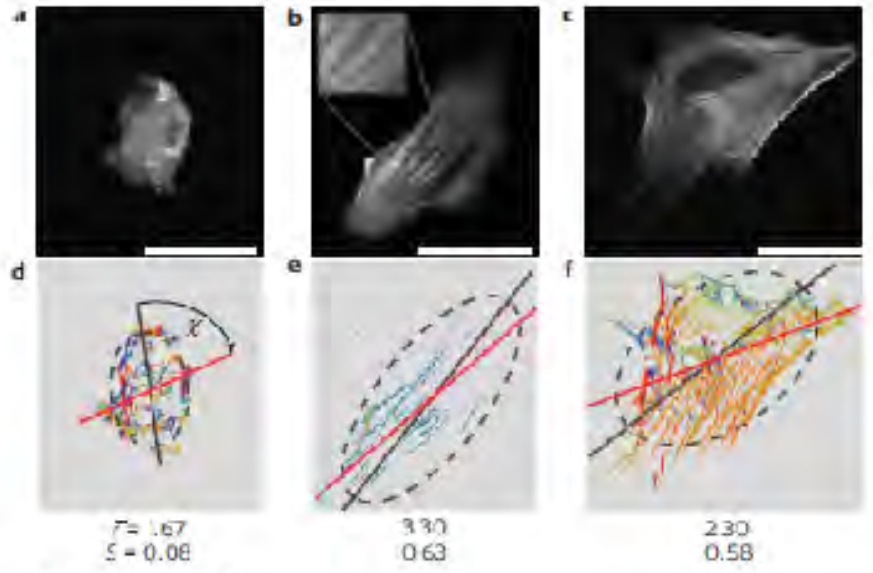


Figure: (Li2014)

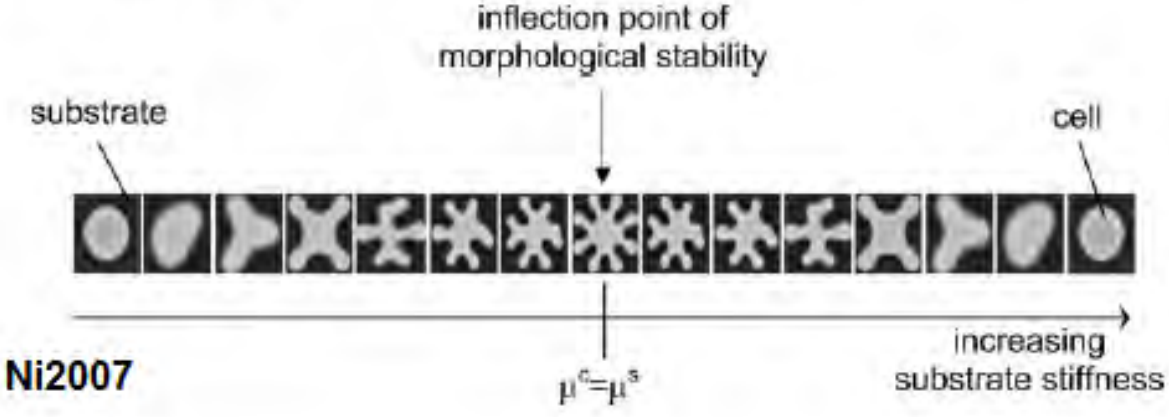
Mathematical models



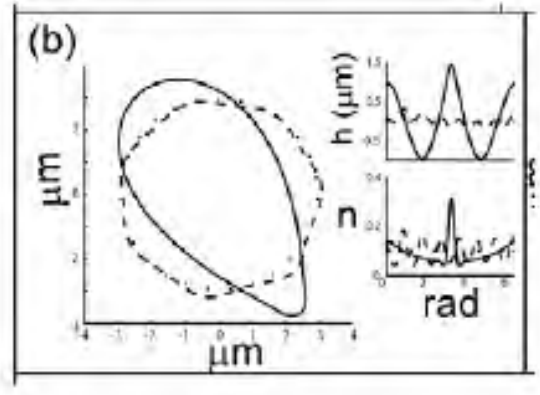
Doweidar2014



Zemel2010

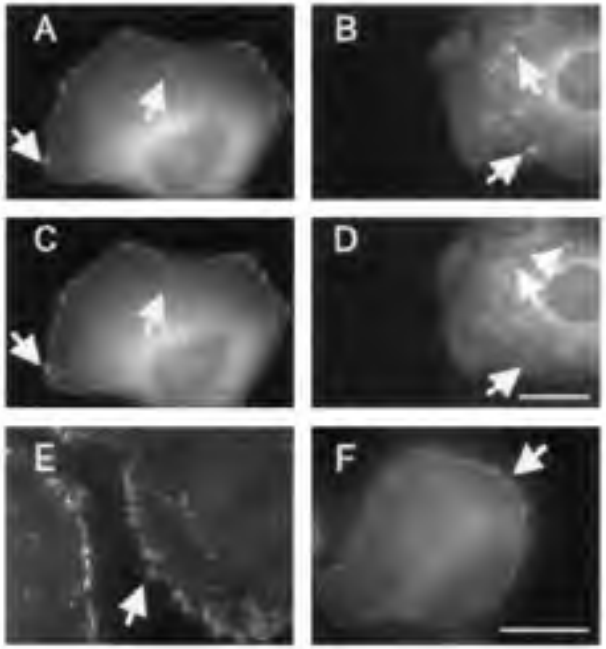


Ni2007

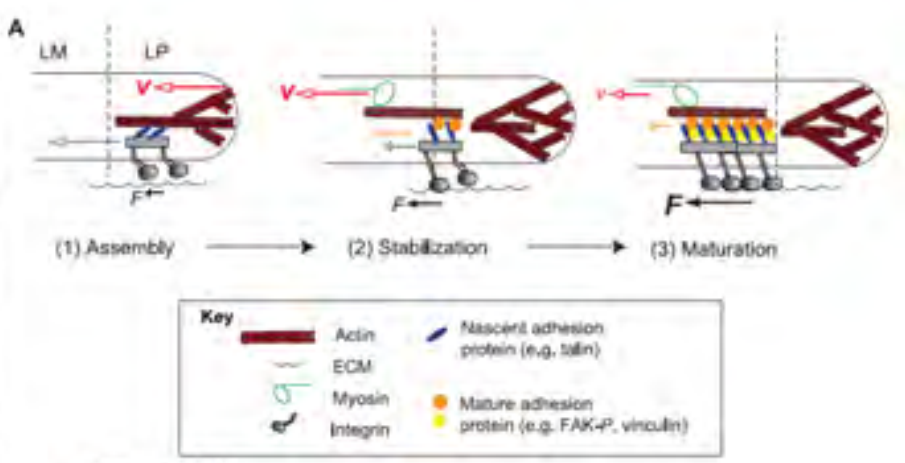


Kabaso2011

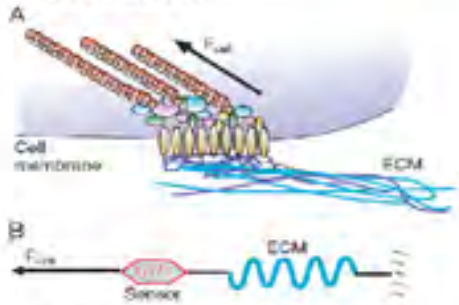
Focal adhesion as mechanosensors



Pelham1997



Schwarz2012



Chen2008

Integrin bonds in focal adhesions act as catch bonds

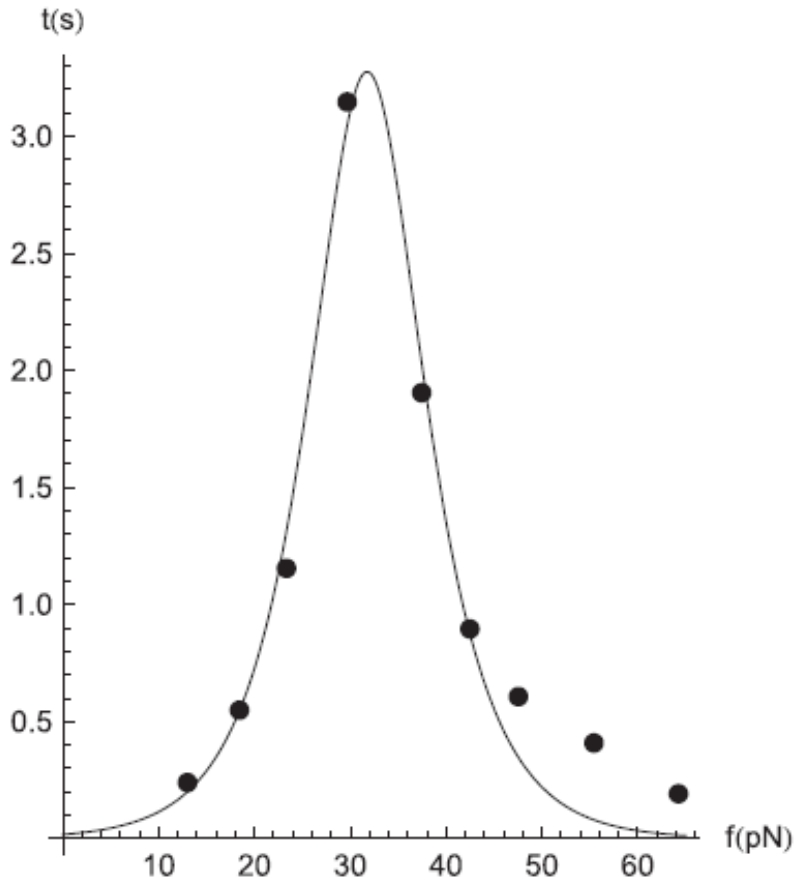


Figure: (Novikova2013)

Catch bond mechanism? (Thomas2008)

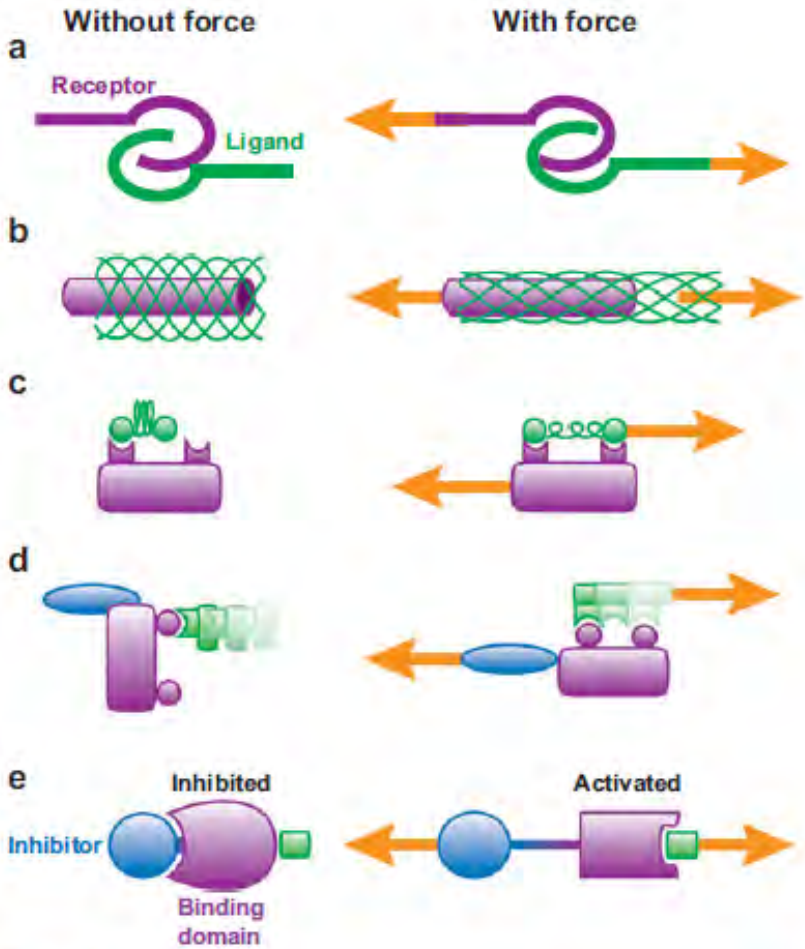
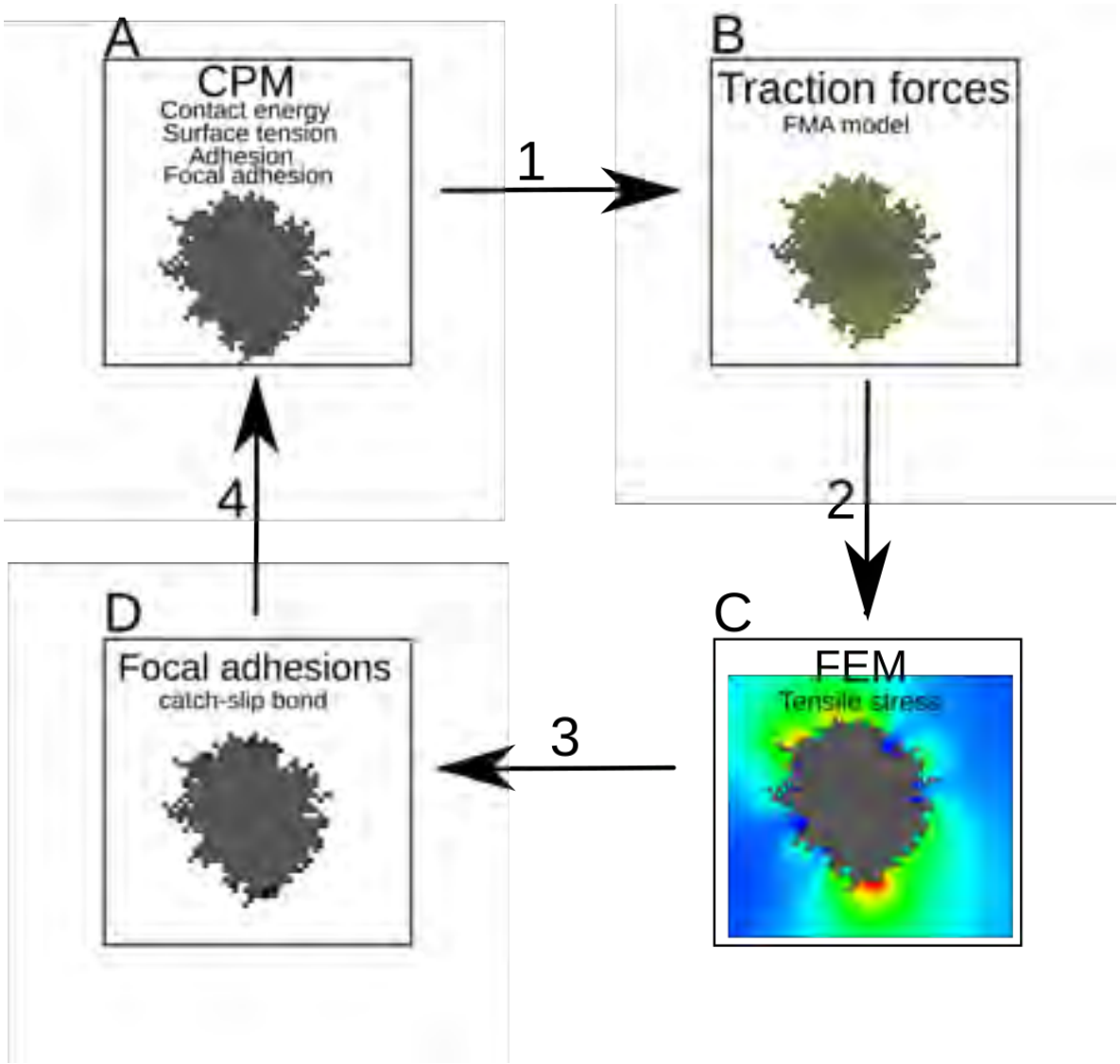


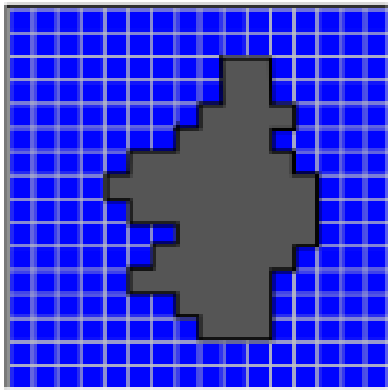
Figure 2

Conceptual models for catch bonds. (*a*) The harpoon or hook model assumes that the ligand must be brought toward the receptor to unbind. Like a children's finger trap (*b*), the deformation model (*c*) assumes that the ligand can deform to make a better fit with the binding partner. (*d*) The sliding-rebinding model assumes that force changes the orientation of the ligand to change the unbinding pathway and allow new contacts to form. (*e*) The allosteric model assumes that the bond undergoes a discrete conformational change to a stronger-binding state, for example, by pulling away an allosteric inhibitor. The binding domain is drawn rounded in the inactive state and rectangular with a pocket in the active state.

Our methodology



Cellular Potts Model



Energy functional:

$$H = \lambda A^2 + \sum_{\text{neighbours}(\vec{x},\vec{x\prime})} J(s(\vec{x}), s(\vec{x\prime})) - \lambda_C \frac{A}{k_1 + A} \qquad (1)$$

Motility:

$$P(\Delta H) = \begin{cases} 1 & \text{if } \Delta H < 0 \\ e^{(-\Delta H + \Delta H_{\mathrm{N}})/T} & \text{if } \Delta H \geq 0. \end{cases} \qquad (2)$$

FA model (catch-slip bond cluster)

Based on Novikova2013

$$\frac{dN_e}{dt}(t) = gN_a(t) - d(\phi_e(t))N_e(t) \tag{3}$$

with g the growth rate and N_a the available bonds in the whole cell. The decay of the focal adhesions $d(\epsilon_e)$ is assumed to depend on the tension ϕ_e on the focal adhesion N_e. The degradation rate is given by

$$d(\phi_e(t)) = \exp\left(\frac{\phi_e(t)}{N_e(t)} - \phi_s\right) + \exp -\left(\frac{\phi_e(t)}{N_e(t)} - \phi_c\right) \tag{4}$$

where ϕ_e is the tension shared by the bound bonds and ϕ_s and ϕ_c describe the slip and catch bond regime, respectively.

Steady state ODE

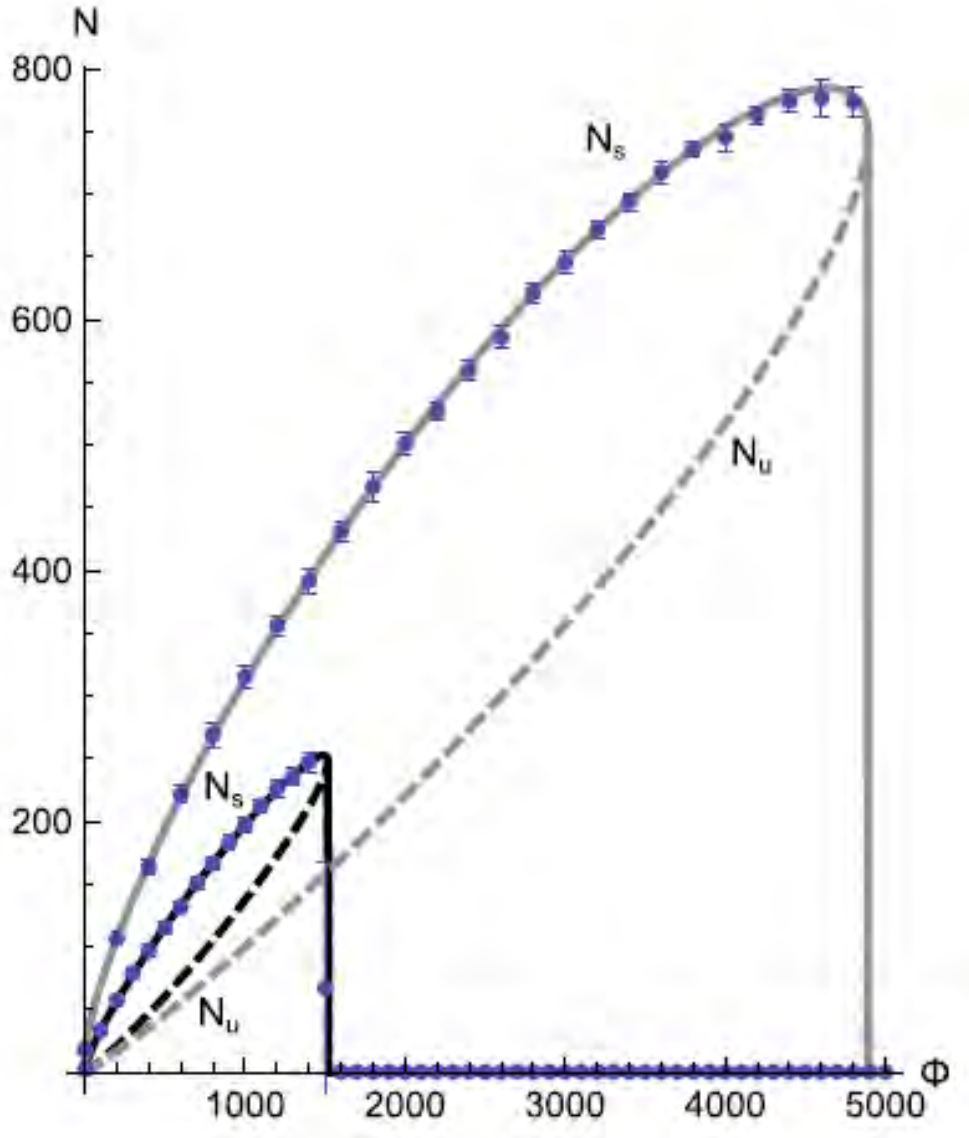


Figure: (Novikova2013)

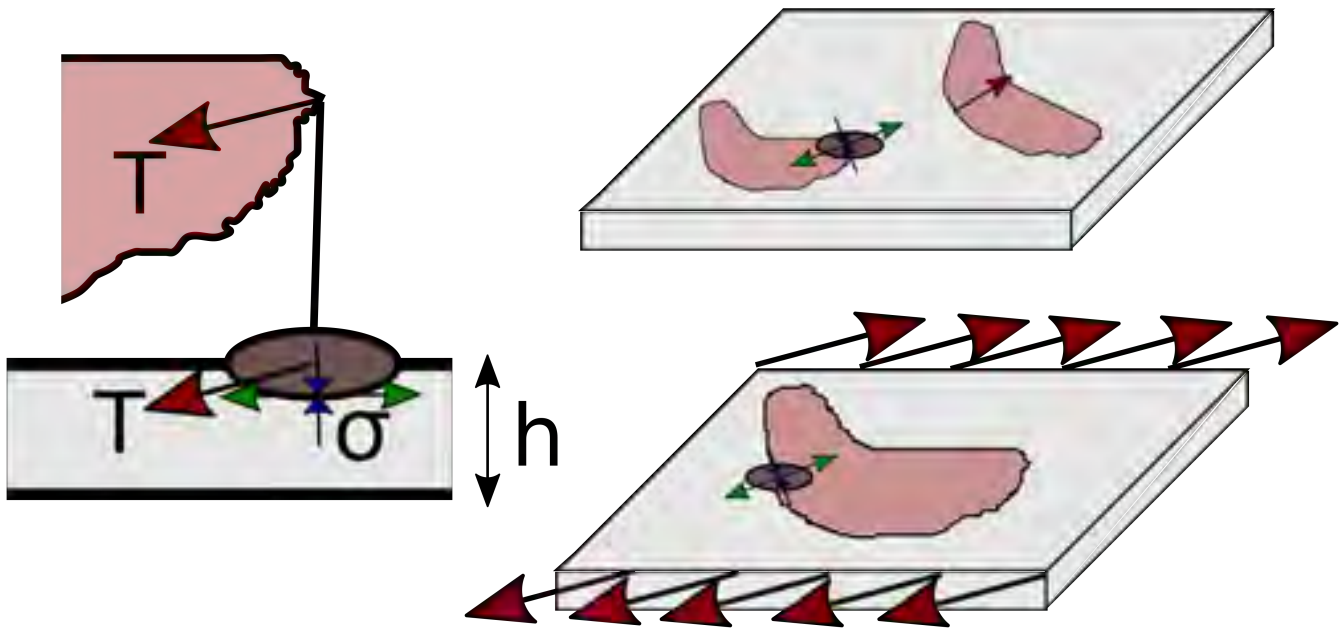
Tension ϕ_e on FA?

Assume plane stress, then equilibrium equation is given by:

$$h(\partial_x \sigma_{xx} + \partial_y \sigma_{xy}) = T_x \quad (5)$$

$$h(\partial_y \sigma_{yy} + \partial_x \sigma_{xy}) = T_y \quad (6)$$

where T is cell-matrix traction and σ is internal matrix stresses

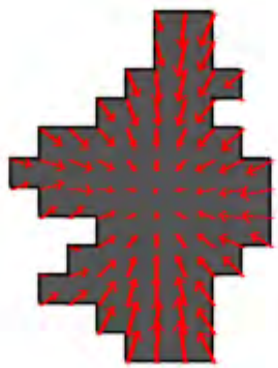


Cellular traction forces

First-moment-of-area (FMA) model, Lemmon2010.

$$\vec{F}_i = \mu \sum_j \vec{d}_{i,j}, \tag{7}$$

divide μ with area of cell A so that force increases roughly linear with cell area, as experimentally observed



Conformational change due to matrix stress strengthens actin binding

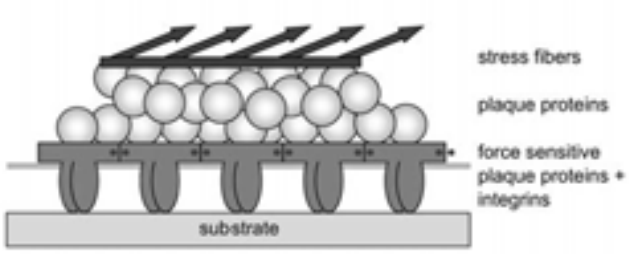


Figure:Besser2006.

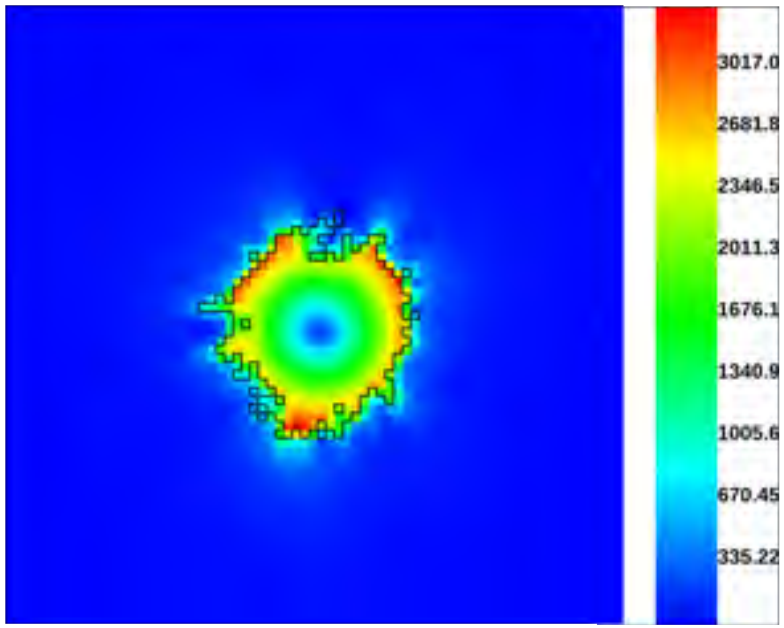
Yield energy:

$$\Delta H_{\mathrm{N}} = \lambda_{\mathrm{N}} N(\vec{x}')(1 + p\frac{h(\sigma)}{\sigma_0 + h(\sigma)}) \text{ if retraction} \tag{8}$$

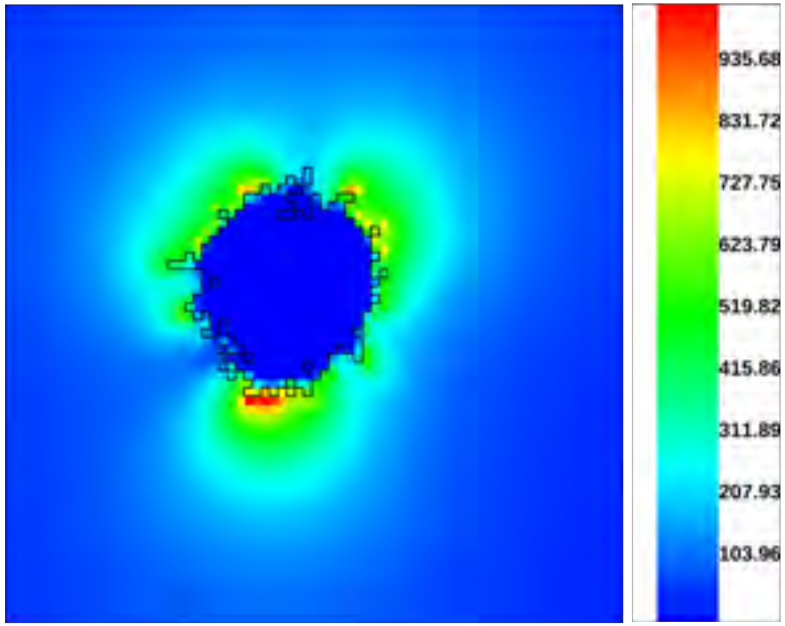
With $h(\sigma) = \frac{1}{2}(\sigma_{xx} + \sigma_{yy})$ the hydrostatic stress of the stress tensor (Stolarska2007).
Motility:

$$P(\Delta H) = \begin{cases} 1 & \text{if } \Delta H + \Delta H_{\mathrm{N}} < 0 \\ e^{(-\Delta H + \Delta H_{\mathrm{N}})/T} & \text{if } \Delta H + \Delta H_{\mathrm{N}} \geq 0. \end{cases} \tag{9}$$

Tension on FA



cell-matrix traction stress



internal matrix stresses (tensile)

Tension ϕ_e on FA in equilibrium! (t=∞)

Since we do not want to do a dynamic FEM (very costly and need additional assumptions) we adopt a model from Schwarz2006 that

describes how fast a cell can build up force depending on matrix stiffness

Tension build up due to matrix stiffness

(Schwarz2006)

$$F(t) = F_s(1 - e^{-t/t_k}) \tag{10}$$

where $t_k = \frac{F_s}{v_0 K}$ with K the matrix stiffness and v_0, speed myosin motors and stall force F_s.

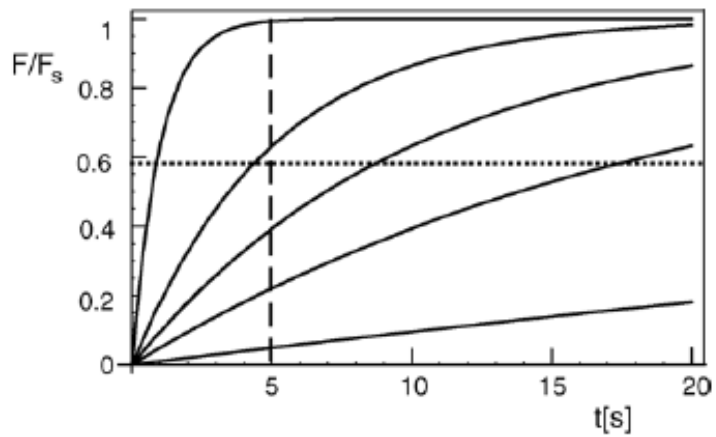
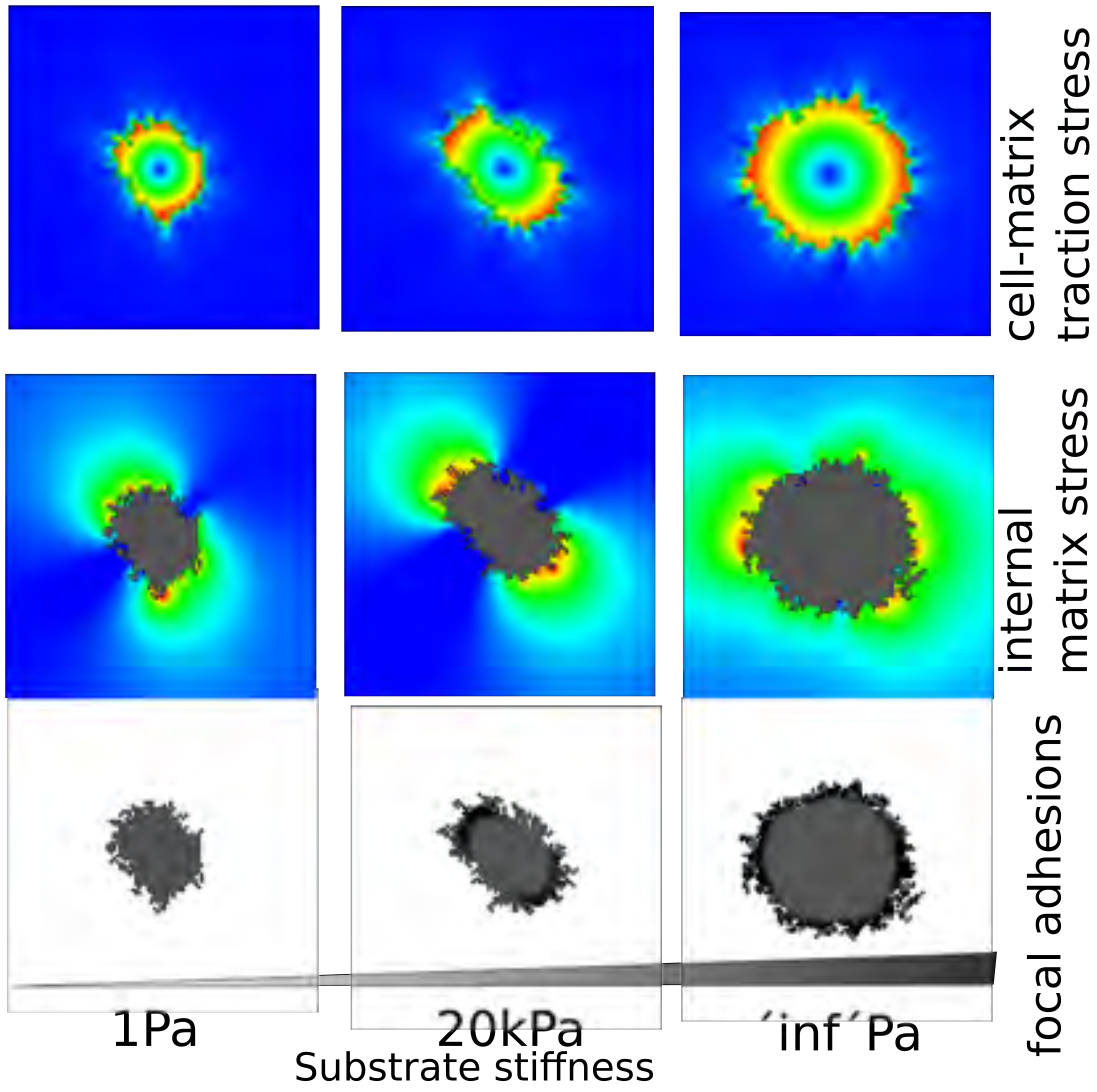


Figure: (Schwarz2006)

Cell shape depends on matrix stiffness



Future work

- Cell-cell communication
- Collective cell behavior
- Cell response to (cyclic) loading of the matrix
- Durotaxis (stiffness gradient)