Modelling cells as contractile matter

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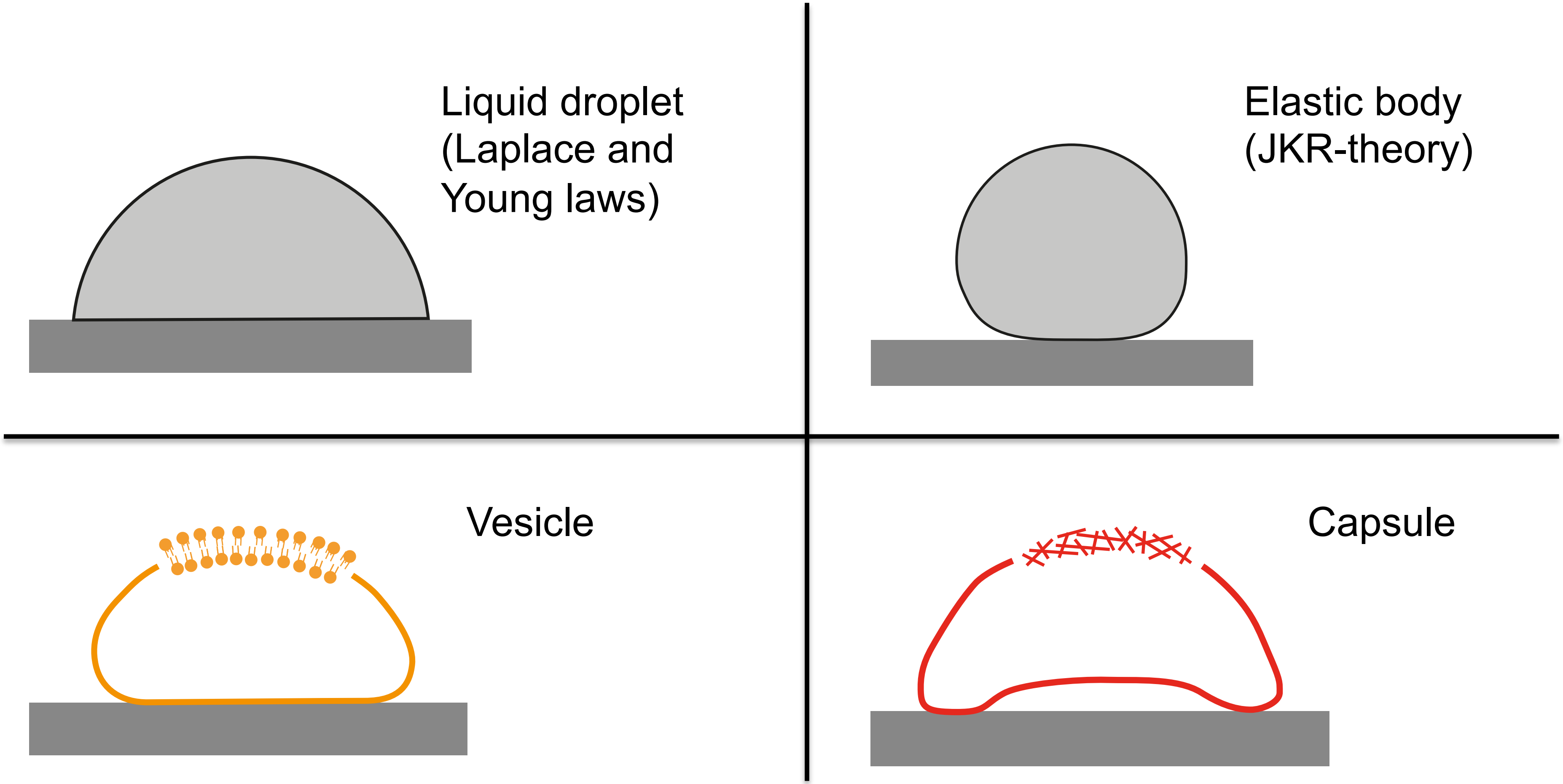
Introduction

Soft matter models for cell adhesion



Liquid droplet
(Laplace and
Young laws)

Elastic body
(JKR-theory)

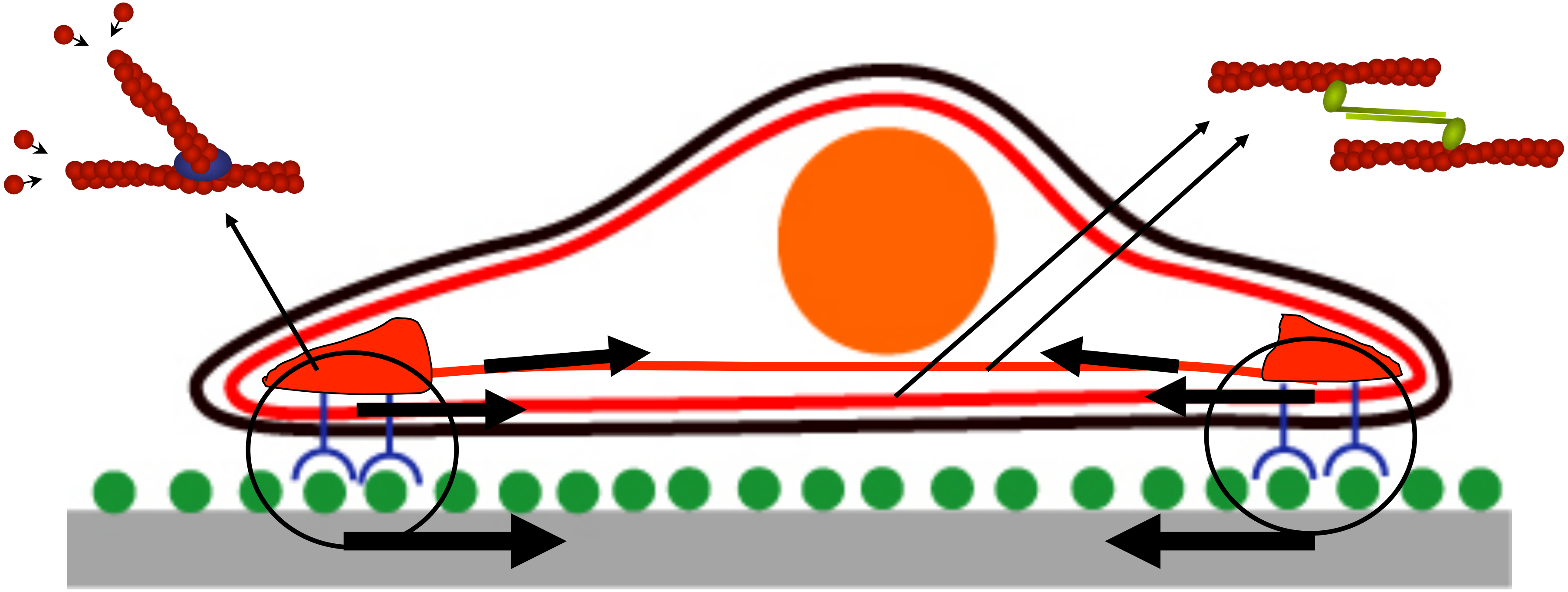
Vesicle

Capsule

Cell adhesion is different because it is characterized by large contact area, tangential traction forces and localized adhesions

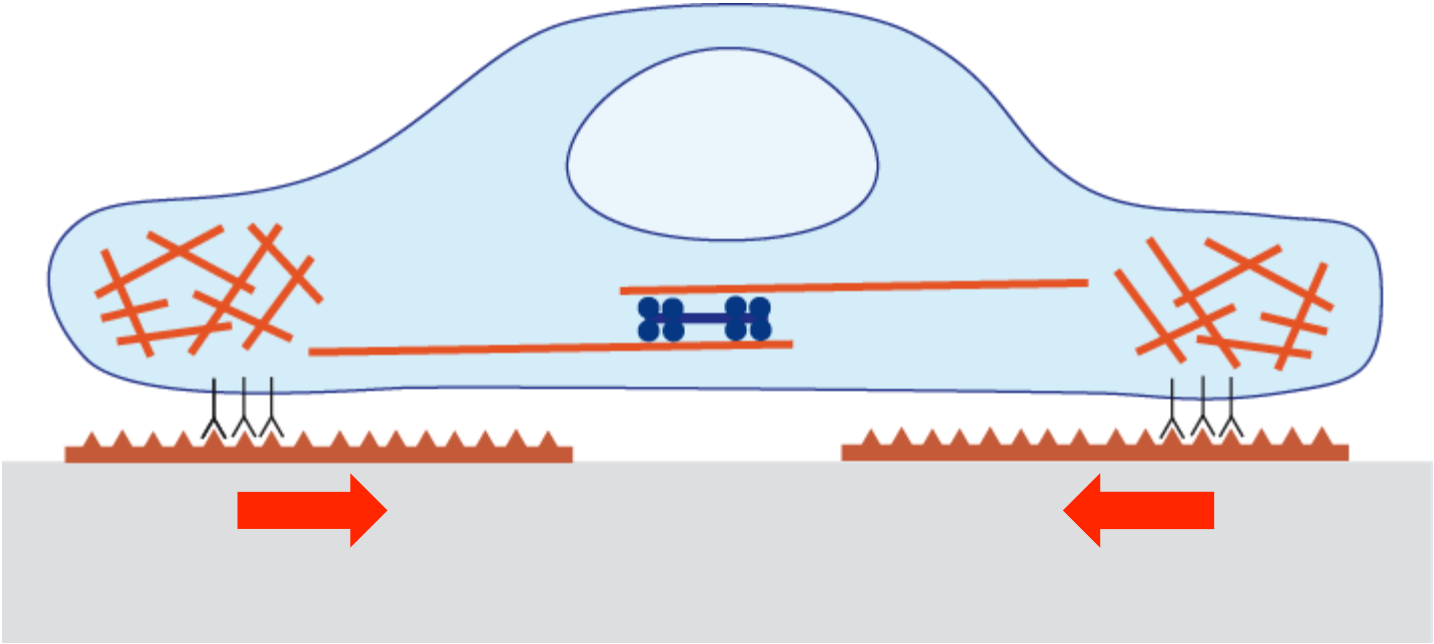
[Schwarz and Safran RMP 2013]

Active processes during cell adhesion



- actin polymerization pushes out **lamellipodia**
- contractile forces generated in **stress fibers** and **actin networks**
- force is transmitted to substrate through **focal adhesions**

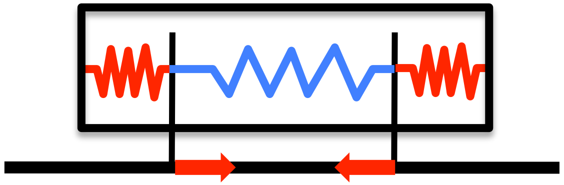
Overall force balance in the cell



Network polymerization: compressed spring

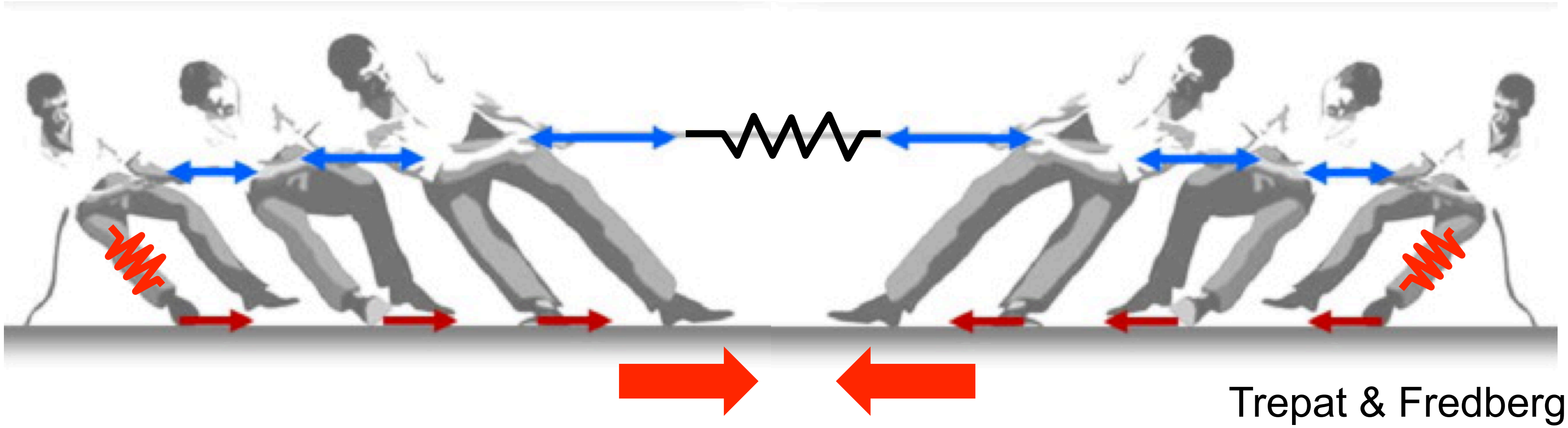
Motor contraction: tensed spring

Whole system: contraction force dipole



[Schwarz and Safran RMP 2013]

Both contraction and polymerization contribute to traction force



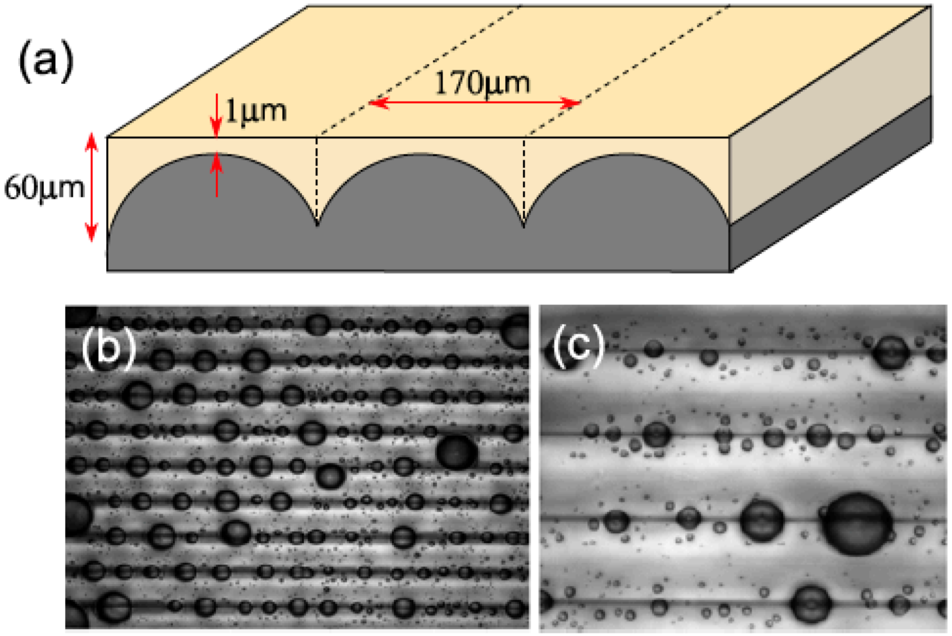
Trepat & Fredberg

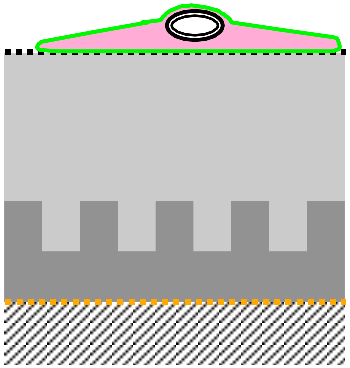
Motor contraction: tensed spring

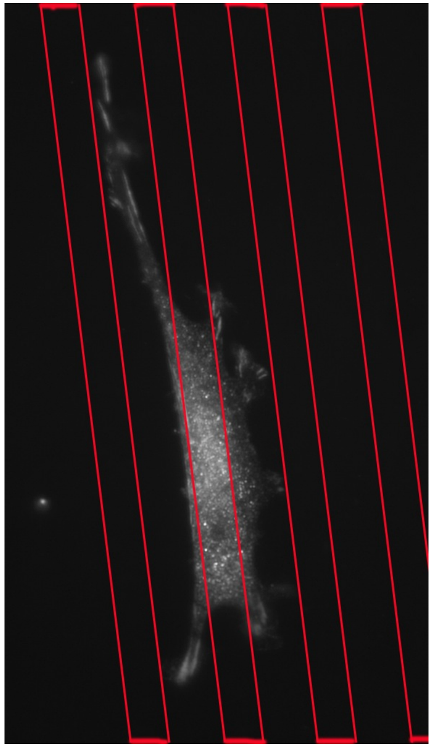
Network polymerization: compressed spring

Whole system: contraction force dipole

Durotaxis of droplets versus cells







Droplets move to the positions of minimal effective stiffness

Cells move to positions of maximal effective stiffness (durotaxis)

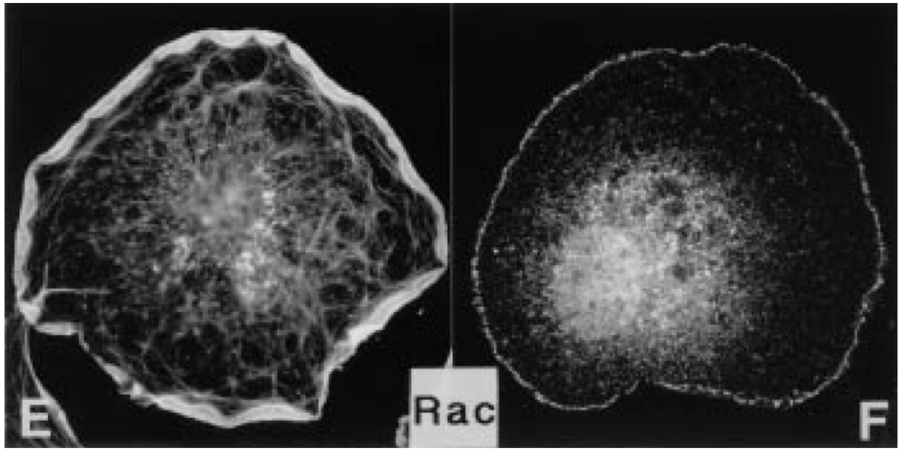
[Style et al. PNAS 2013]

[Mathis Riehle]

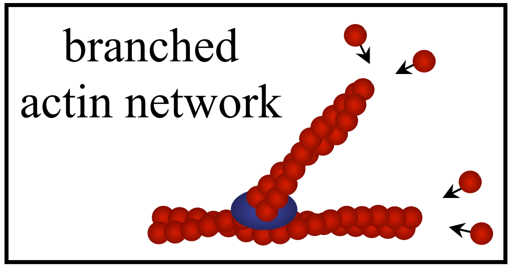
Regulation of the actin cytoskeleton through small Rho-GTPases

Ridely and Hall and coworkers Cell 1992

Rac: spreading and migration

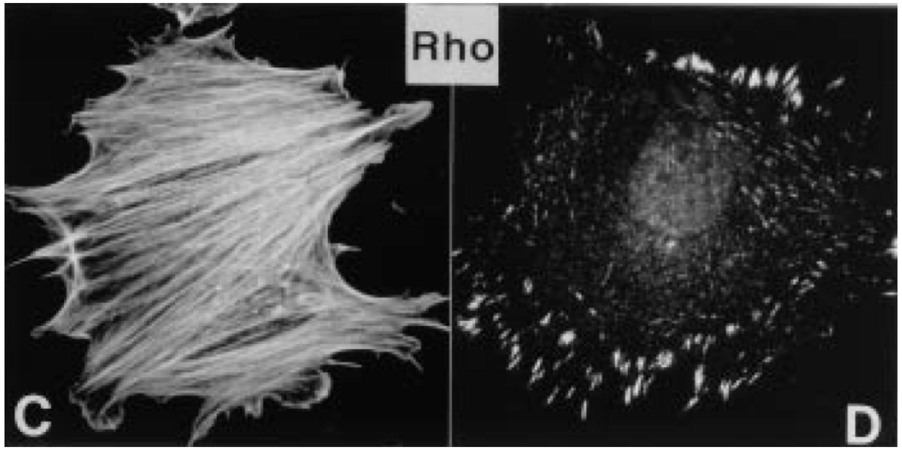


lamellipodia and focal complexes

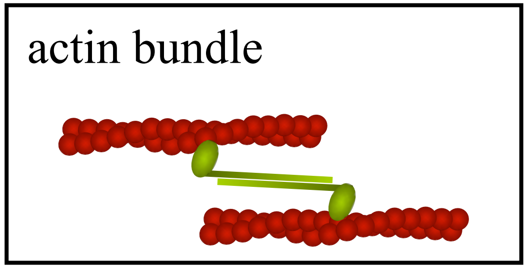


Arp2/3

Rho: mature adhesion

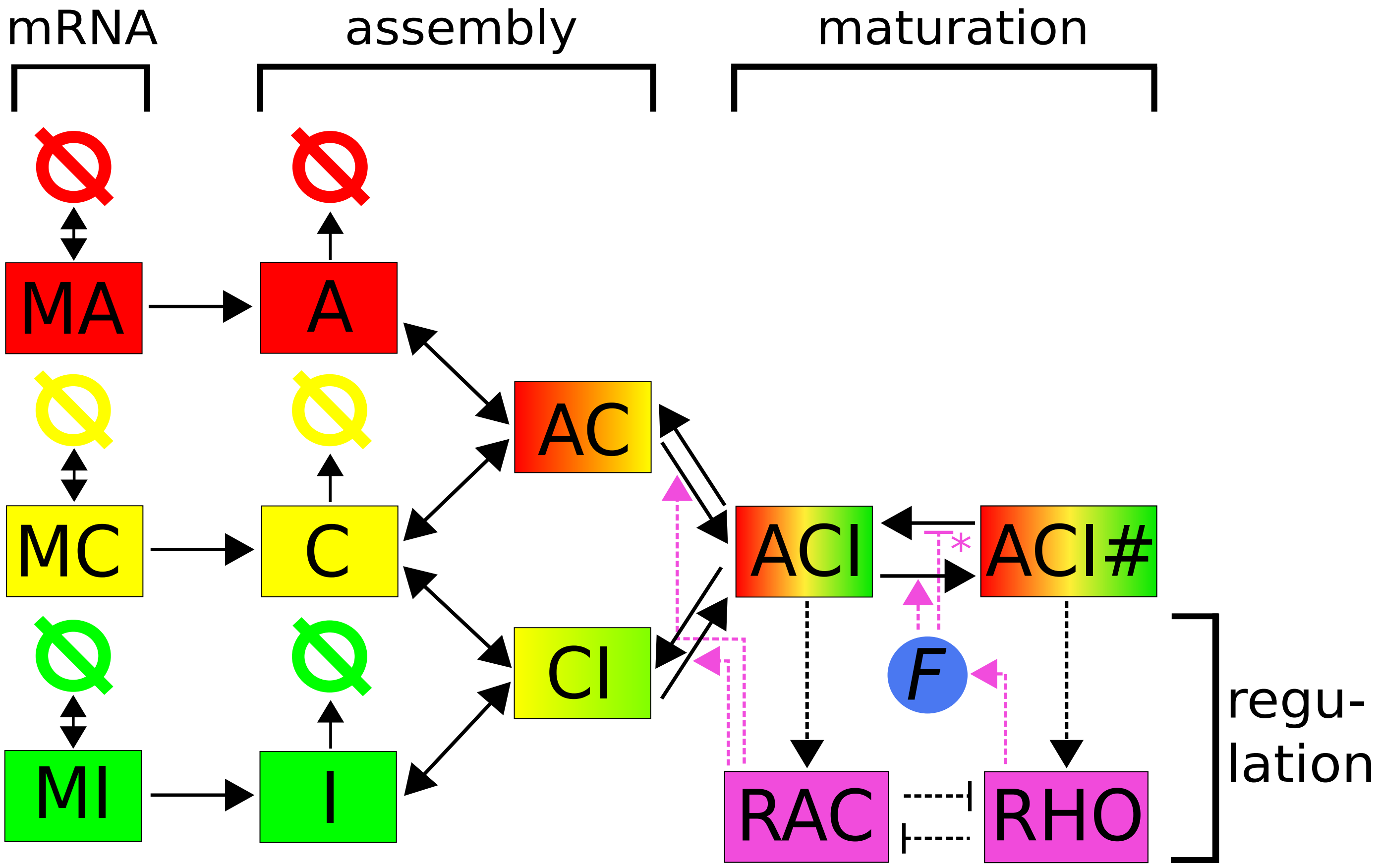


stress fibers and focal adhesions



myosin II

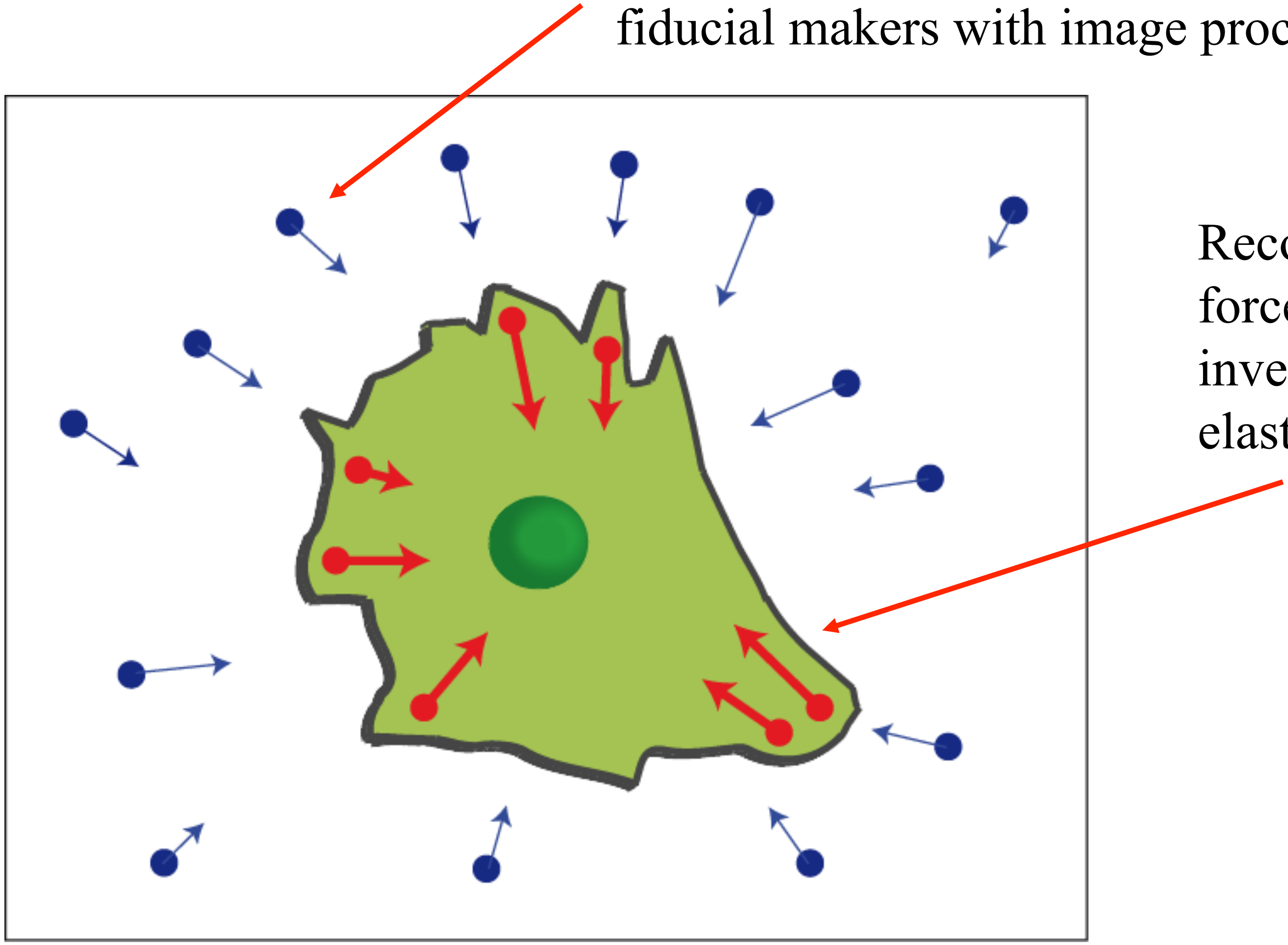
Kinetic model for focal adhesions



[Hoffmann and Schwarz, BMC Systems Biology 2013]

Traction force microscopy

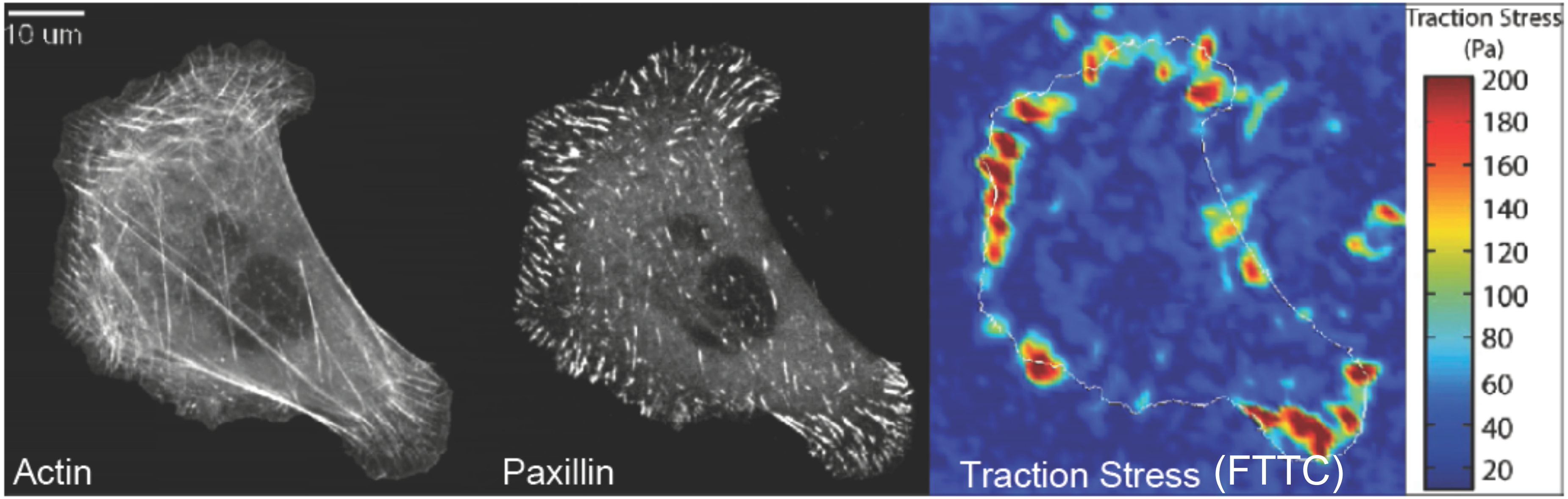
Traction force microscopy on soft elastic substrates



Pick up deformations by extracting movement of fiducial makers with image processing

Reconstruct cellular forces by solving the inverse problem of elasticity theory

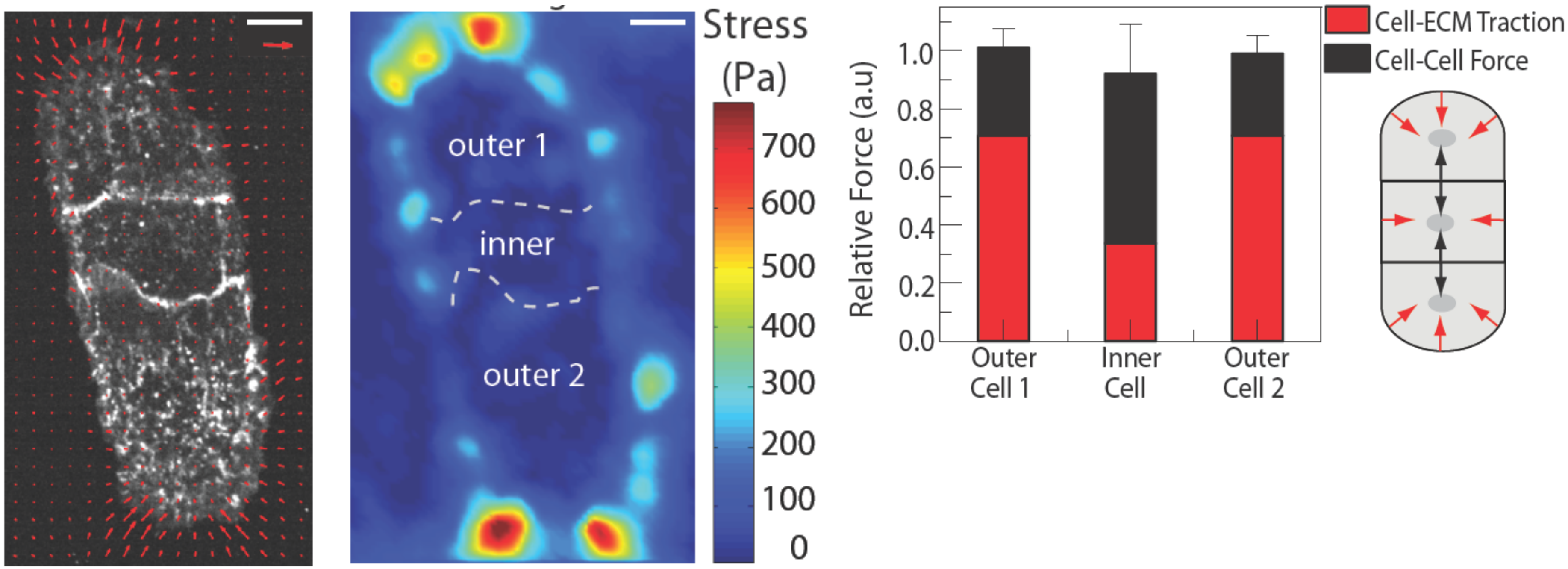
Traction map single U2OS cell



Traction forces correlate strongly with the organization of the actin cytoskeleton and the adhesion structure

[Sabass et al. BPJ 2008, Stricker et al. JPCM 2010, Schwarz and Gardel JCS 2012]

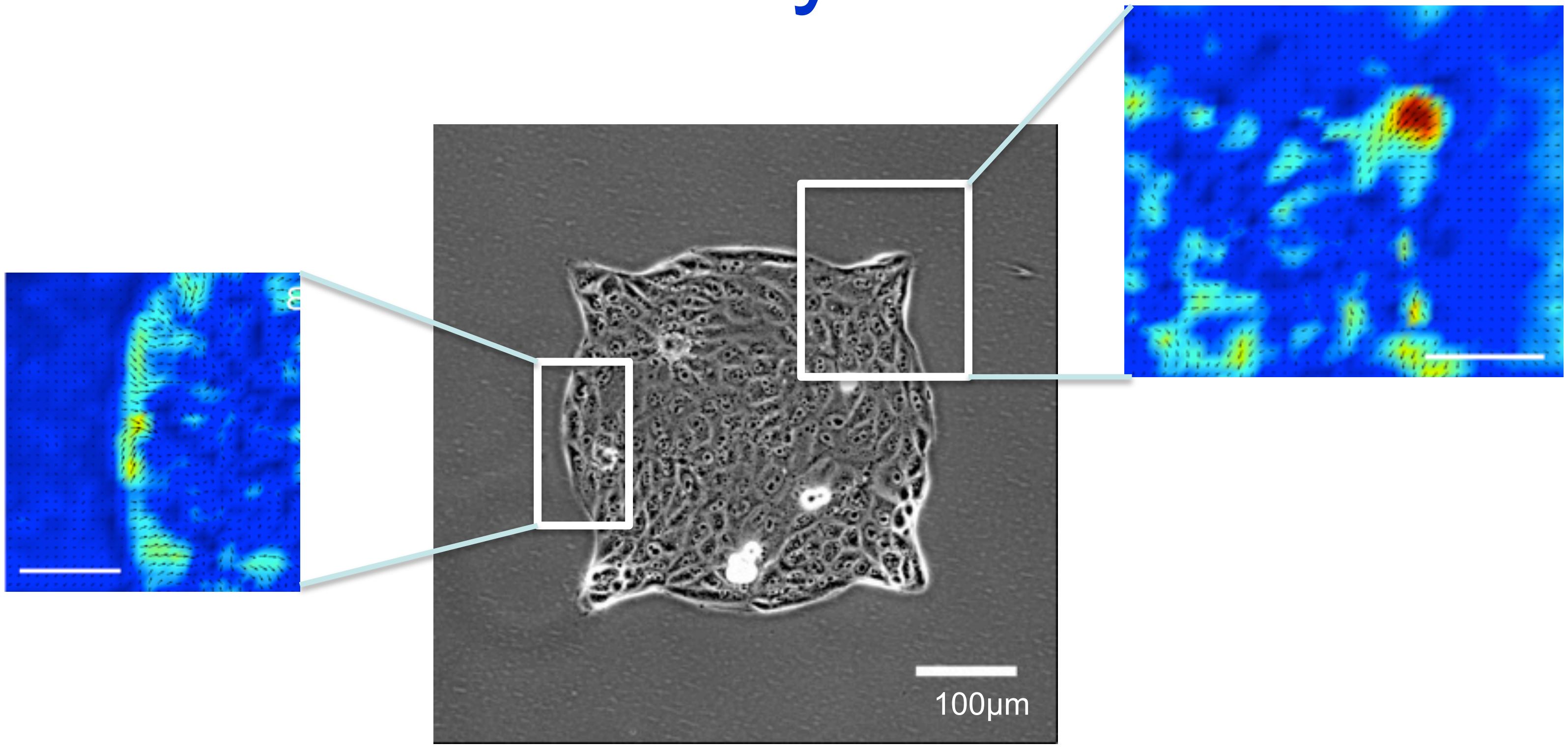
Traction force imbalance method



Cell-cell forces can be calculated from force balance.

[Maruthamuthu et al., PNAS 2011]

Traction forces of patterned cell monolayers



Geometry determines stress distribution
Leader cells emerge from traction hotspots

[Rausch et al., Biointerphases 2014]

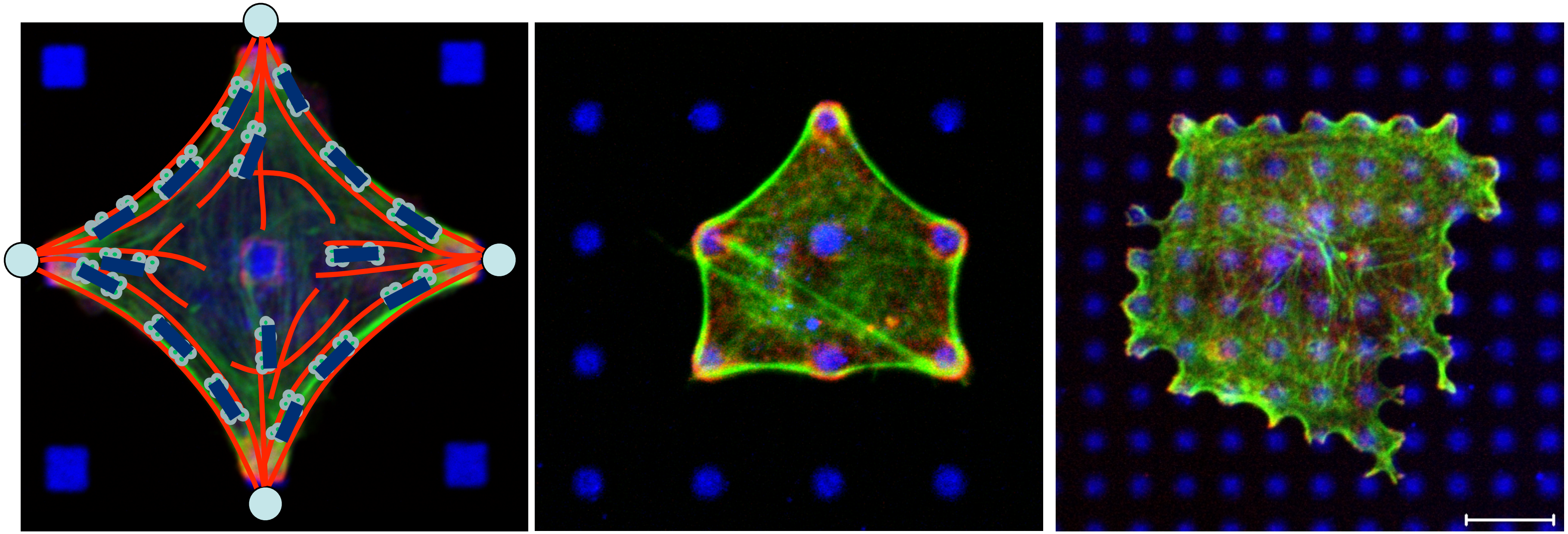
Modelling cell shape and forces

Different modelling approaches to contractile matter

- Mechanical (polymer) networks
- Active cable networks
- Contour models
- Active gels
- Active elasticity
- Cellular Potts Model
- Phase field or level set models

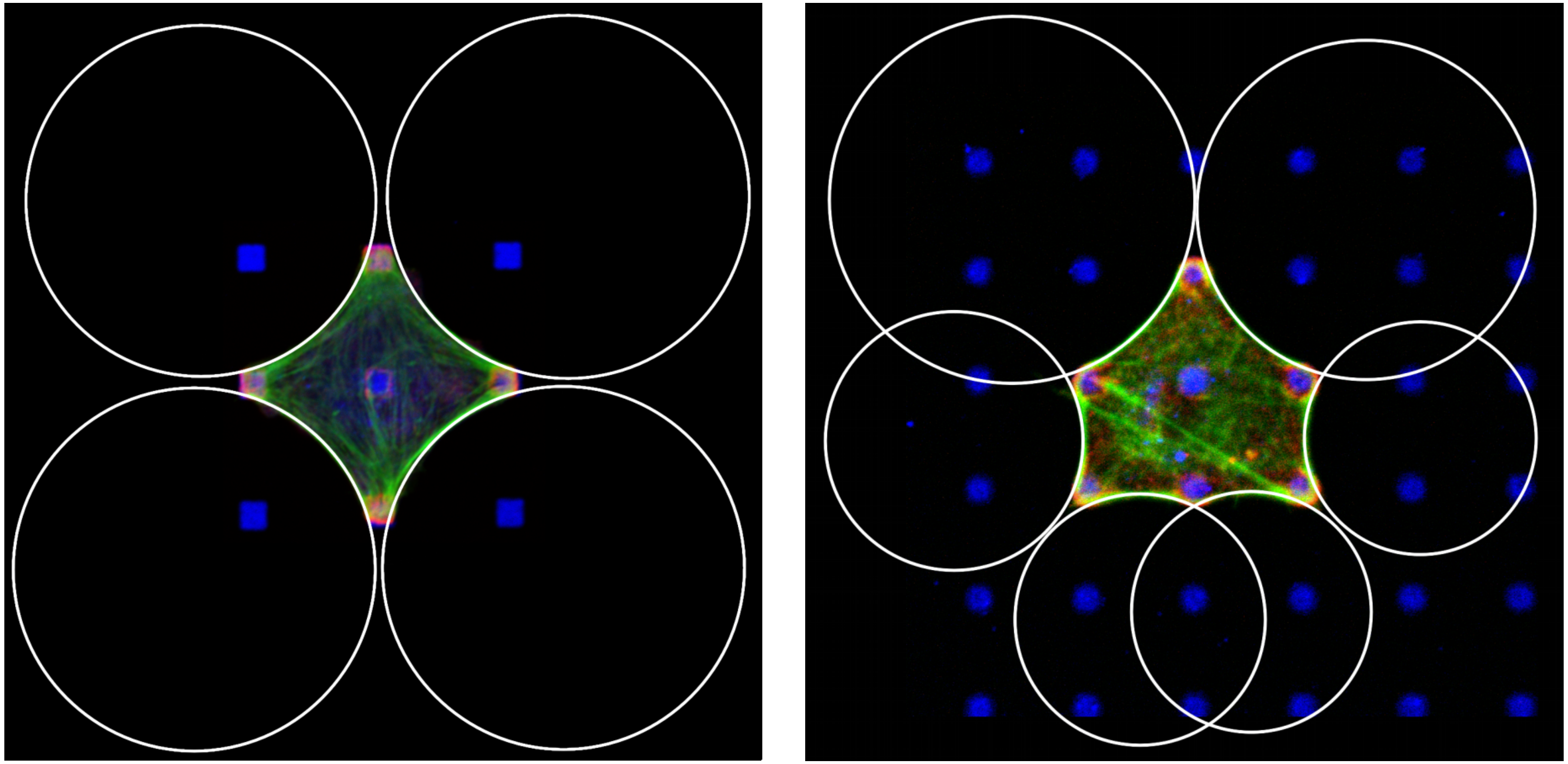
Active cable networks

Cell shape on micropatterns



[Lehnert et al. JCS 2003]

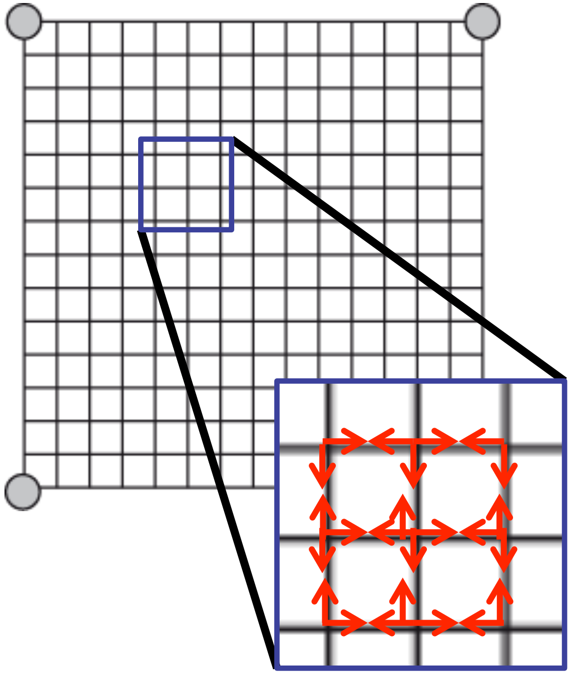
Quantitative analysis of cell shape

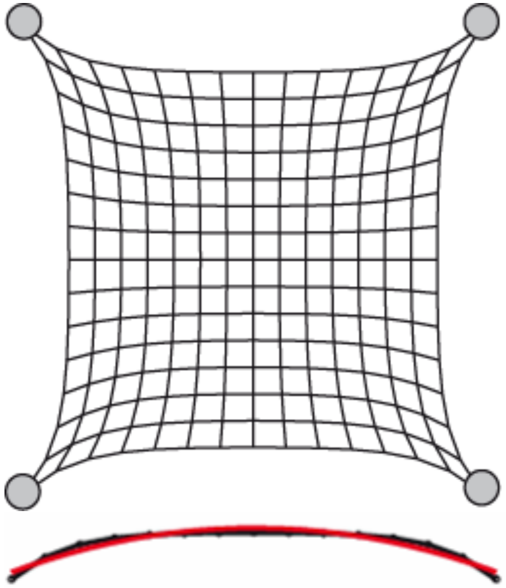


Cell shape on spatially constrained ligand patches resembles a sequence of circular arcs.

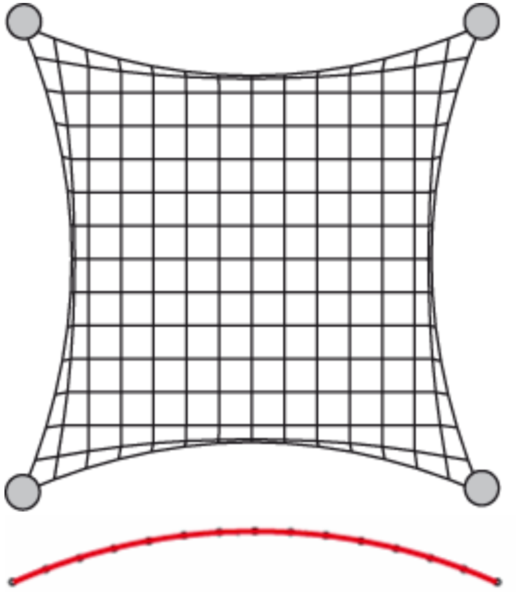
[Bischofs et al. BPJ 2008]

Actively contracting cable networks





Hookean network:
contour is flat

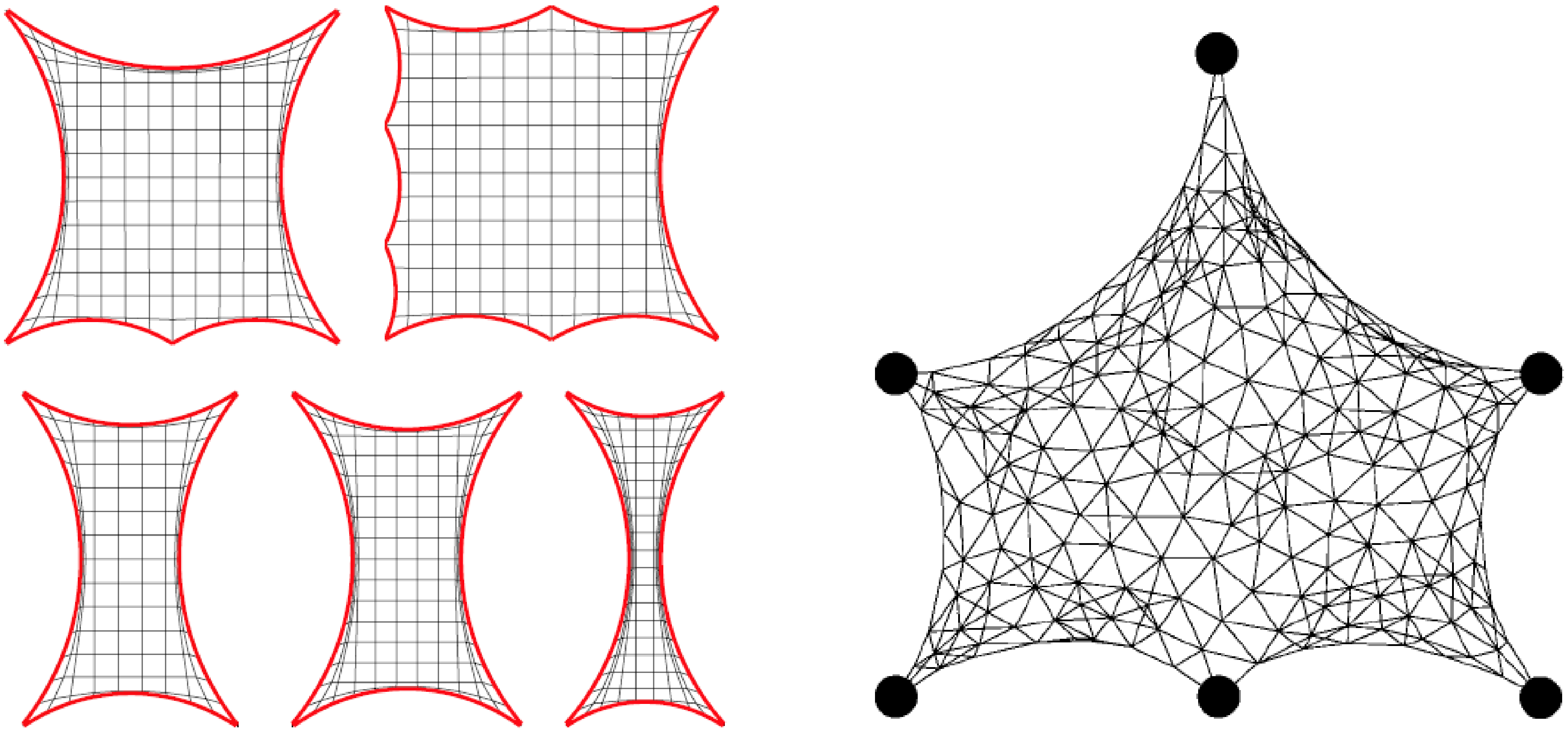


Cable network:
contour is circular

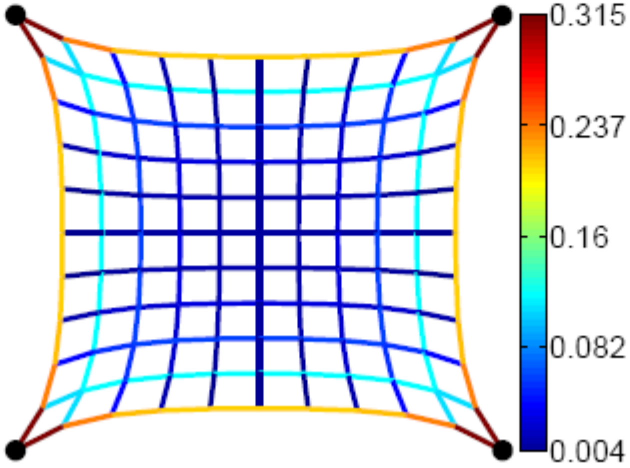
Actively contracting cable networks result in circular arc morphology

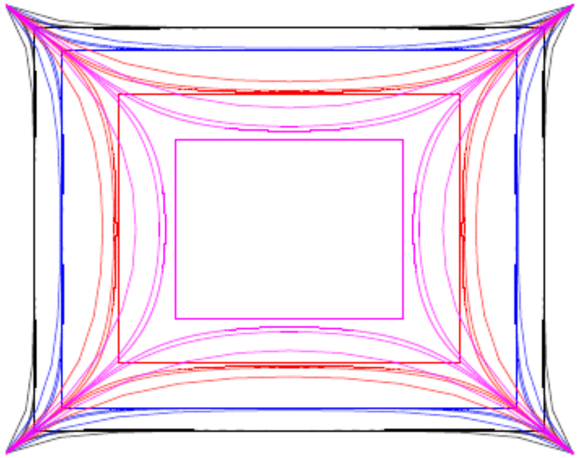
[Bischofs et al. BPJ 2008, Guthardt Torres et al. PRE 2012]

Robustness of arc feature in regard to adhesion geometry and network topology

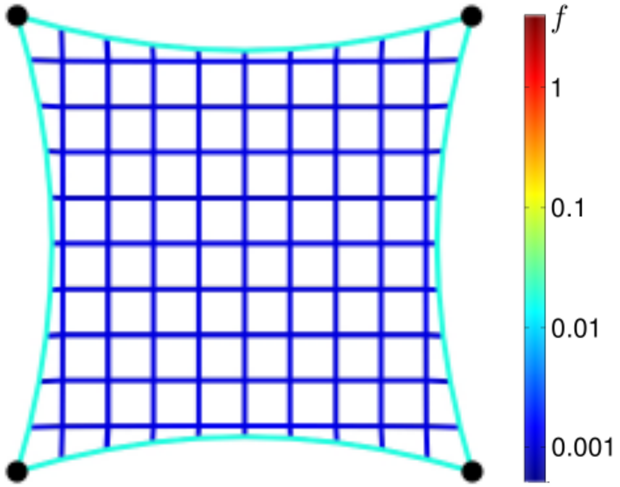


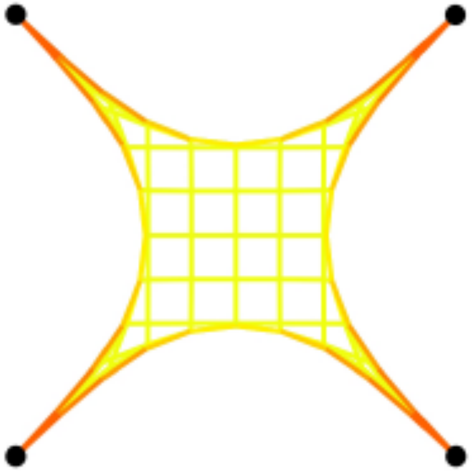
Spring versus cable networks





Flat contour results from reference shape.





Active cable networks do not have a reference state.

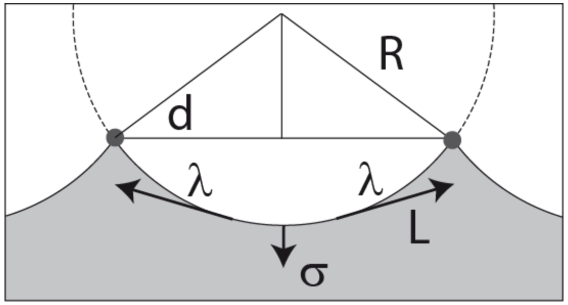
[Guthardt Torres et al. PRE 2012]

Contour model

Tension-elasticity model

Line tension results from elastic deformation:

$$\lambda = \mathrm{EA}\frac{L - L_0}{L_0}, \quad L_0 = \alpha d$$



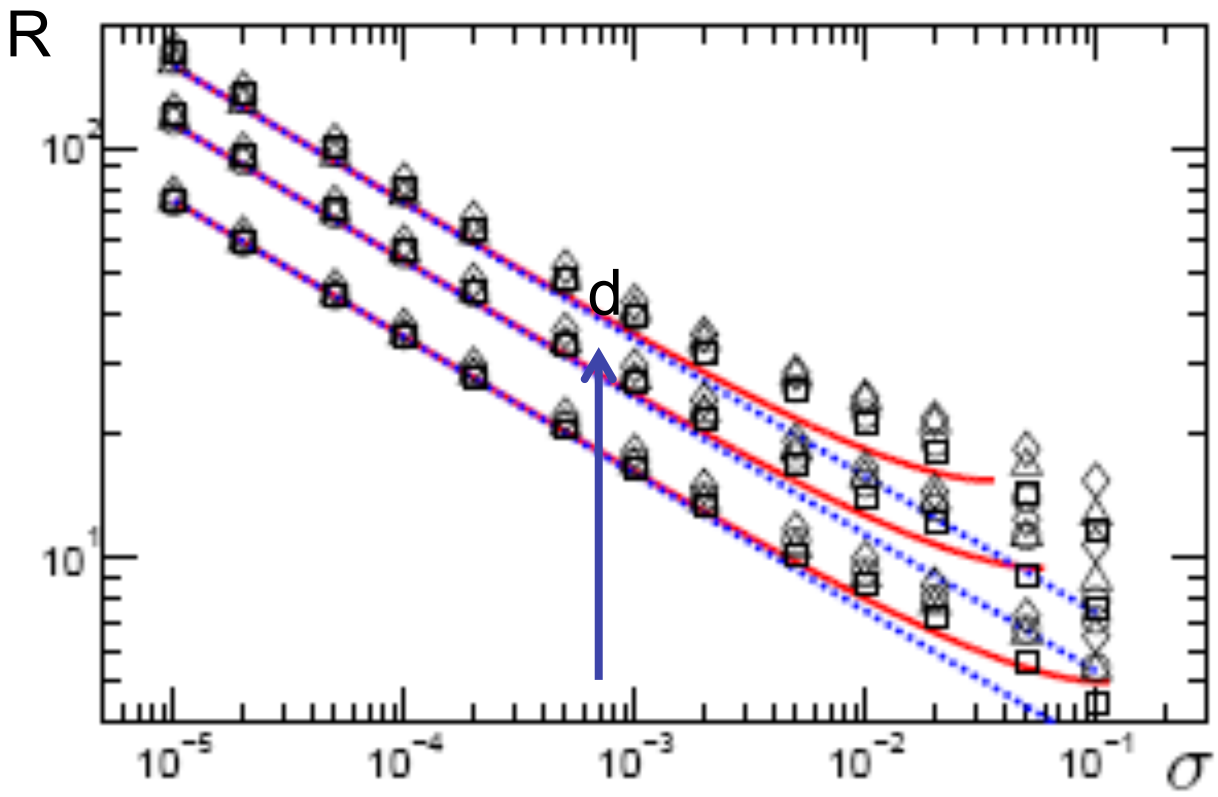
geometry: $$R = \frac{d}{2\sin\left(\frac{L}{2R}\right)}$$

$$\boxed{\Rightarrow R = \frac{EA}{\sigma}\left(\frac{2R}{\alpha d}\arcsin\left(\frac{d}{2R}\right) - 1\right)}$$

self-consistent equation for R(d,σ)

[Bischofs et al. BPJ 2008, PRL 2009]

Modified Laplace law



Theoretical prediction by TEM-model:

$$R = 24^{-1/3} d^{2/3} \sigma^{-1/3}$$

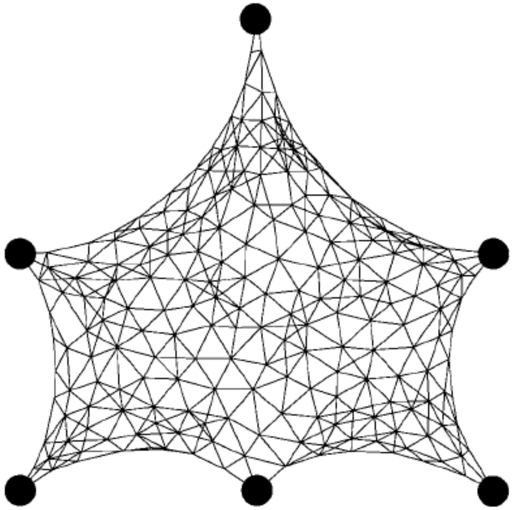
Good agreement between computer simulations, TEM-model and exps.

symbols – network simulations | solid – TEM numerical | dotted – TEM analytical

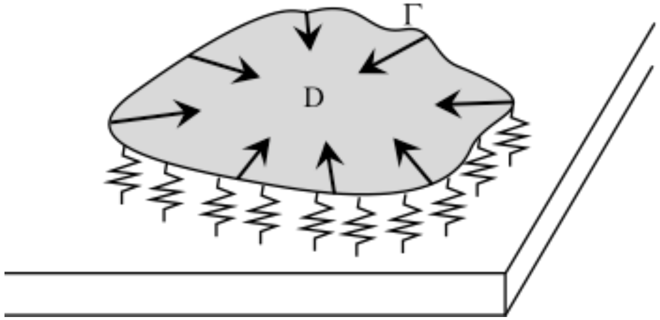
[Guthardt Torres et al. PRE 2012]

Active elasticity

Coupling cellular contractility to cell area



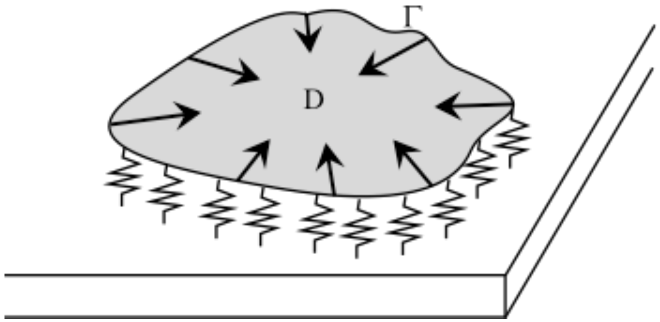
Until now: coupling to point-like adhesions



Now: coupling to adhesion area

A minimal model has to start from continuum mechanics

Simple model: contracting film on elastic foundation



Linear elasticity theory (plane stress):

$$\nabla \cdot \mathbf{F} - T = 0$$

$$\mathbf{F} = \underbrace{\frac{E_C h}{1+\nu}\left(\epsilon_{ij} + \frac{\nu}{1-\nu}\epsilon_{ij}\delta_{ij}\right)}_{\text{Elastic stress}} - \underbrace{\frac{1}{2(1-\nu)}P(x,y)\delta_{ij}}_{\text{Active cell contraction}}$$

Simplest assumption for traction force: T=ku

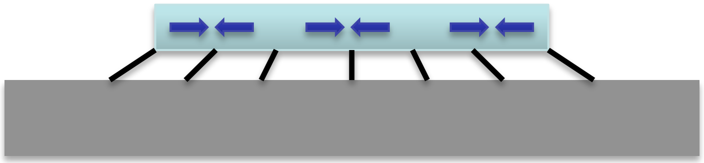
Plus appropriate zero-stress boundary conditions.

Note contraction analogy to thermal heating/cooling. Model can be implemented with FEM.

[Edwards and Schwarz PRL 2011]

[Banjeree and Marchetti: EPL 2011, PRL 2012]

One-dimensional case (contracting stripe)



force balance: F internal stress, u deformation

$$F(x)-F(x+dx)-ku(x+dx/2)=0 \Rightarrow \frac{dF}{dx} = ku$$

constitutive relation (E 1d modulus, P active stress):

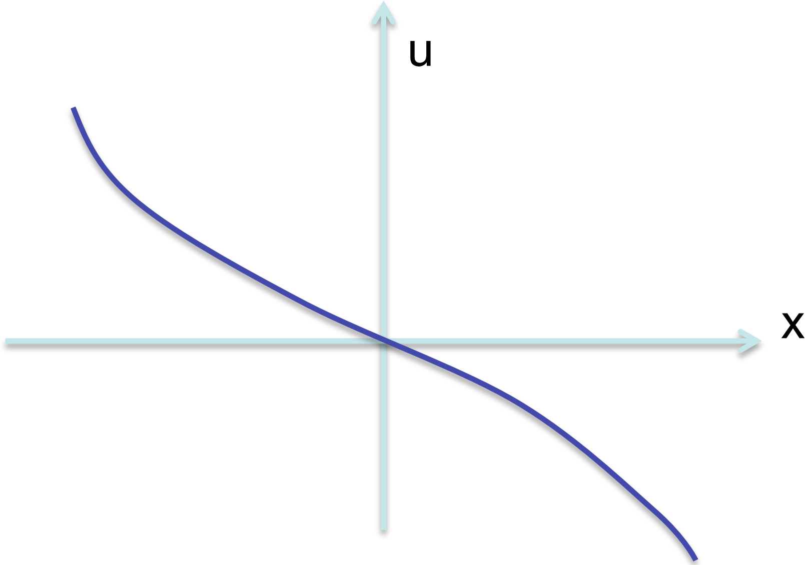
$$F = E(\frac{du}{dx} + P)$$

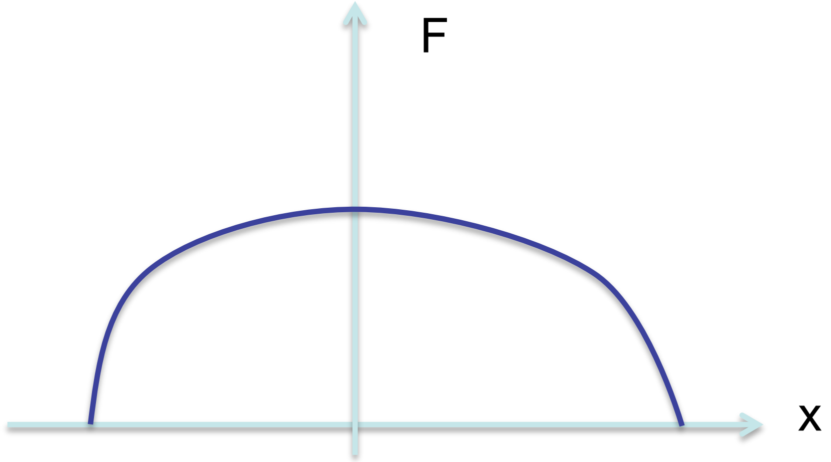
P=const $\Rightarrow \frac{d^2u}{dx^2} - \frac{1}{l^2}u = 0$

$l = \sqrt{E/k}$ localization length

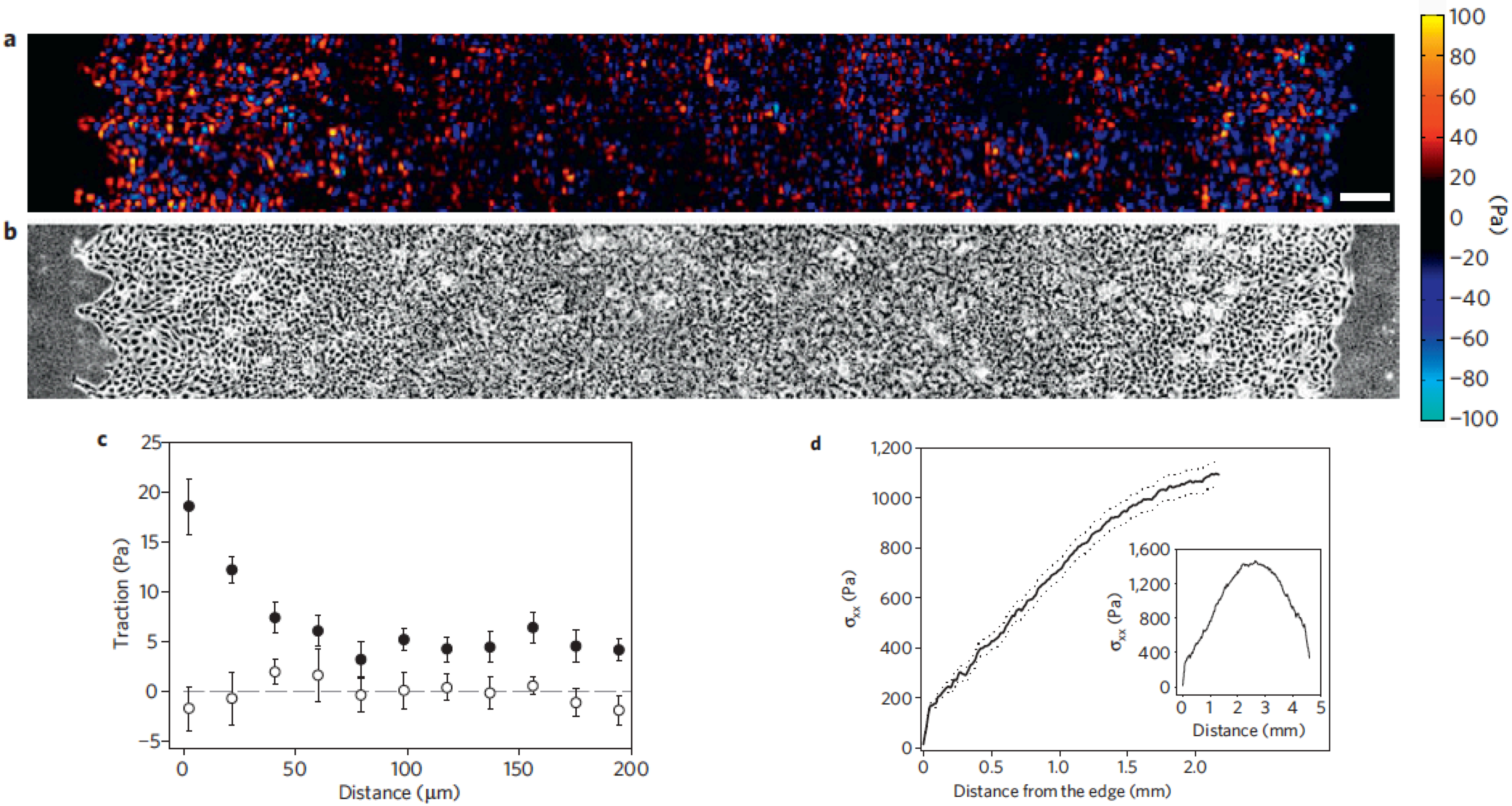
zero stress boundary: $F(\pm l_0) = 0 \Rightarrow \frac{u}{l_0} = -P\frac{\sinh(\gamma x/l_0)}{\gamma\cosh(\gamma)}$

$\gamma = l_0/l$
localization
parameter





Traction and stress for cell monolayer

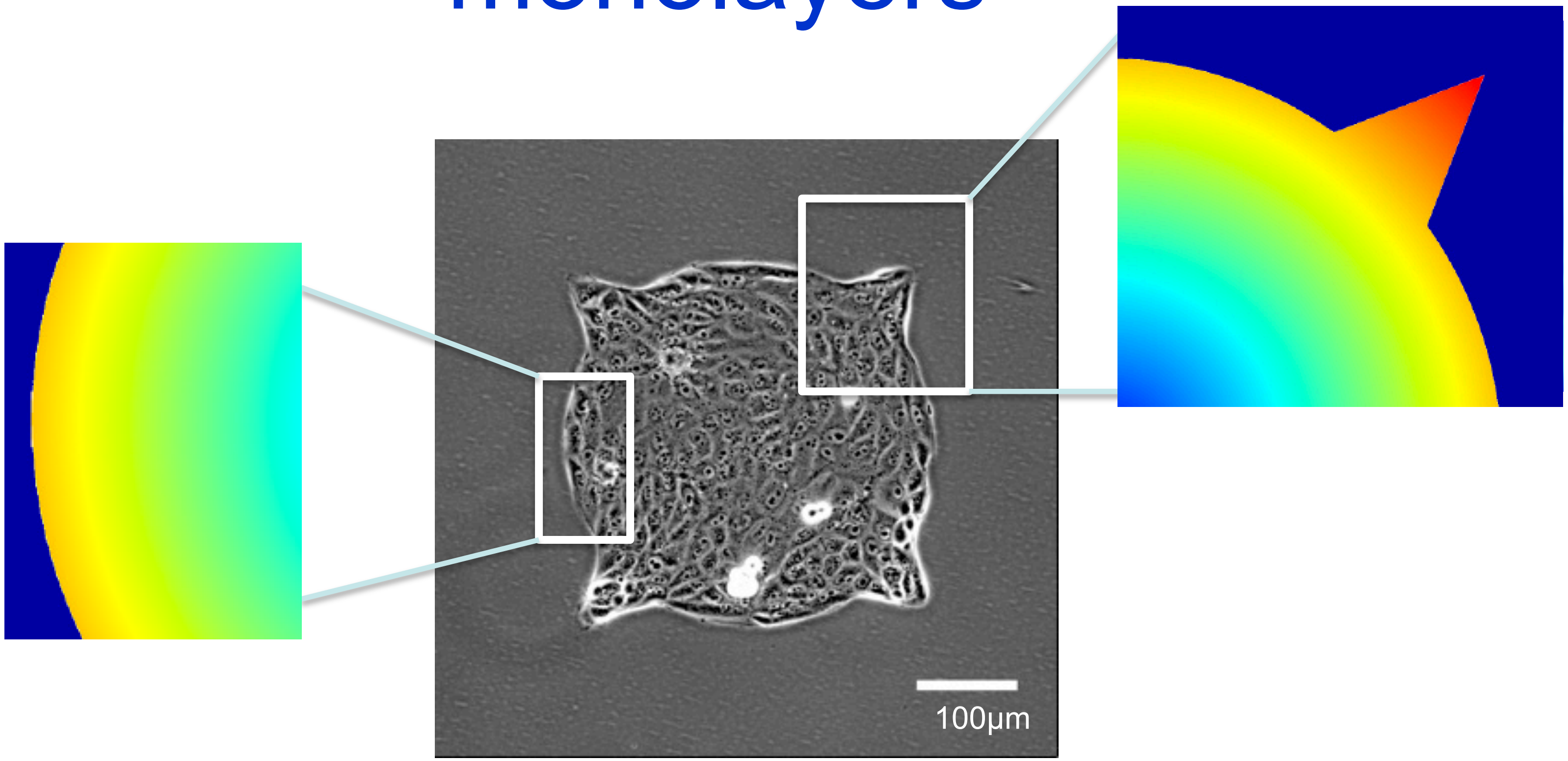


Traction is strongest
at the rim

Intralayer stress
peaks at the middle

[Trepat et al. Nature Physics 2009]

Traction forces of patterned cell monolayers

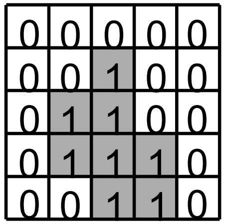


Geometry determines stress distribution as predicted by active elasticity

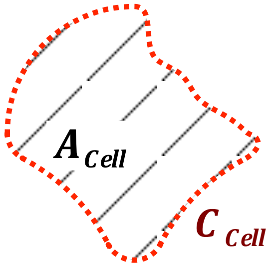
[Rausch et al., Biointerphases 2014]

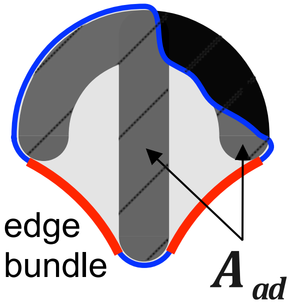
Cellular Potts Model

Cellular Potts Model



0	0	0	0	0
0	0	1	0	0
0	1	1	0	0
0	1	1	1	0
0	0	1	1	0





$$E = \sigma A_{Cell} + J C_{Cell} + \sum_{\text{bundel } i} \frac{EA}{2L_{0,i}}(L_i - L_{0,i})^2 - \frac{W}{A_{ref} + A_{Ad}} A_{Ad}$$

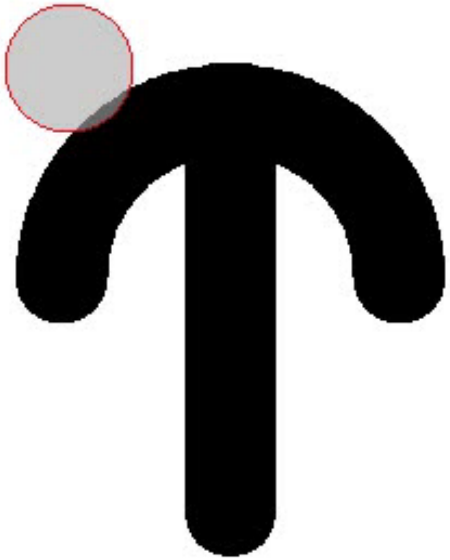
surface tension

simple line tension

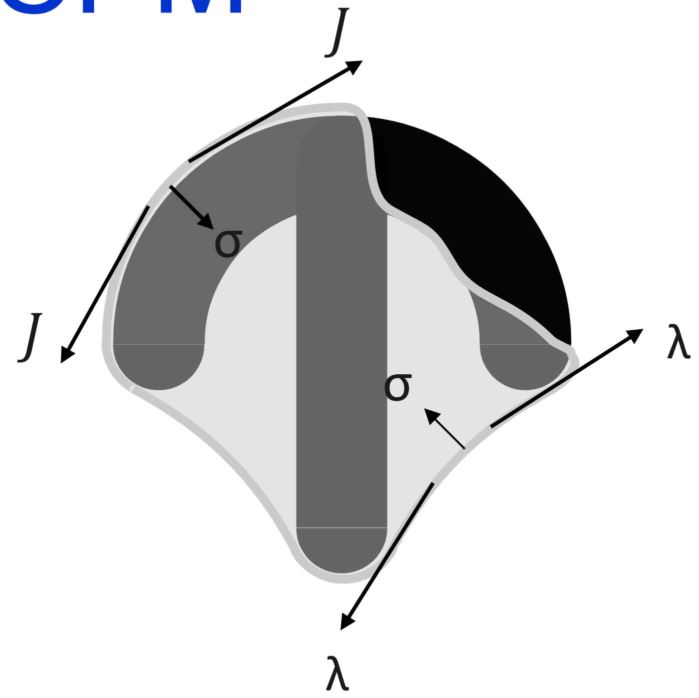
elastic line tension

adhesive energy

- Cell is represented by an ensemble of spins on a lattice
- Metropolis dynamics
- Combines elements of contour model and active elasticity continuum model



Traction forces from CPM



- Contractile forces are balanced by adhesive substrate
- At adhesive boundaries

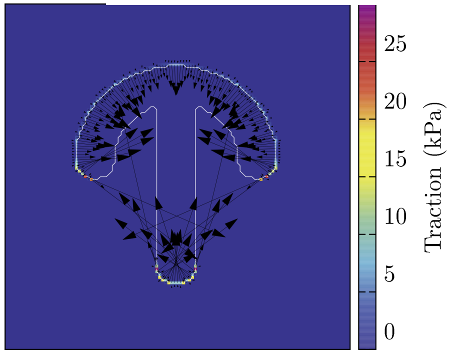
$$\vec{f} = [\sigma + J\ \kappa]\vec{n}$$

$\vec{n}$ normal
κ curvature

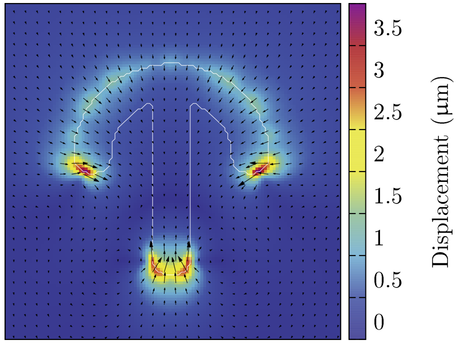
- At endpoints of edge bundles

$$\vec{F}_{arc} = \lambda_e \vec{t},$$

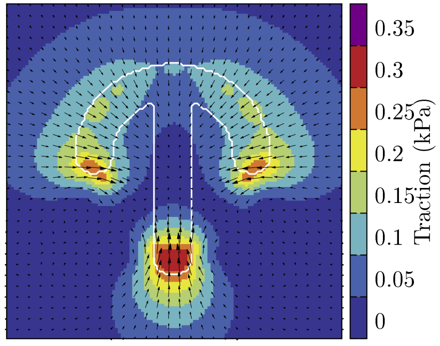
$\vec{t}$ tangent



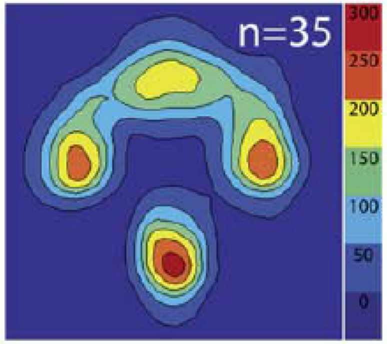
Boundary Forces



Displacements



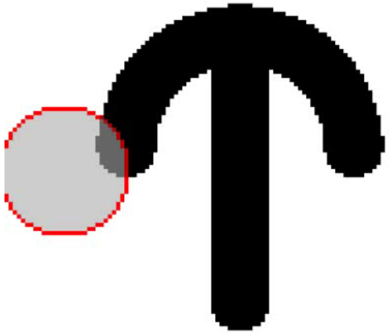
Reconstructed forces

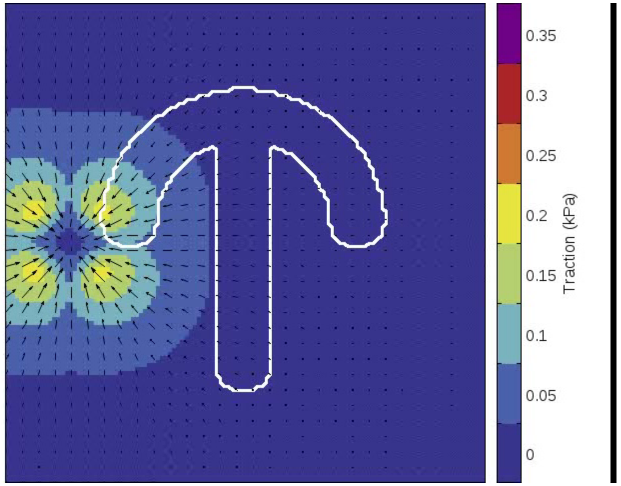


Experiments (Tseng Lab Chip 2011)

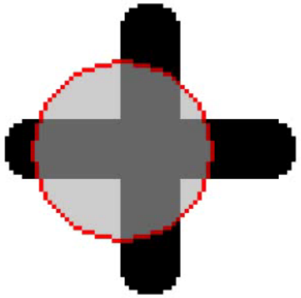
Dynamic traction on patterns

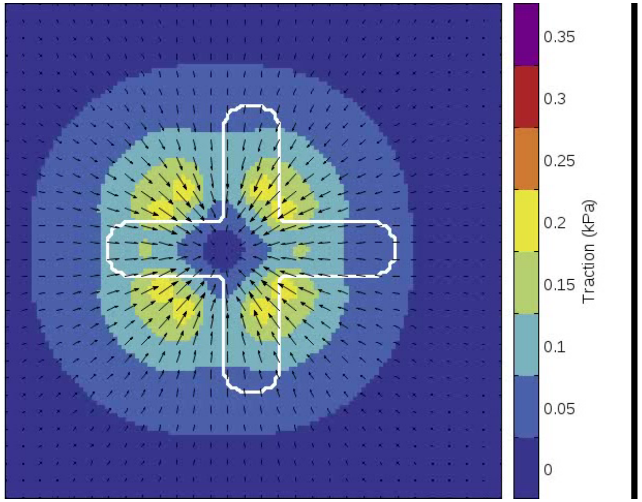
crossbow





cross





Conclusions

Active cable networks	Circular arc morphology, modified Laplace law, represents polymer nature of cytoskeleton and constant pull by motors
Contour model	Represents bulk and contour tensions, easy to use, appropriate for strong contraction and point-like adhesions
Active elasticity	Continuum model, appropriate for coupling to adhesion area, can be implemented with FEM
Cellular Potts model	Dynamical, can be adapted to include elements of all the above models, includes the cell protrusion missing from the other models

Acknowledgments

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- **Sebastian Rausch, Jerome Soine, Heike Böhm, Joachim Spatz** (cell monolayers)
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- **Ilka Bischofs-Pfeifer, Philip Guthardt Torres** (active cable networks, contour models)
- **Carina Edwards-Dunlop** (active elasticity)
- **Philipp Albert** (cellular Potts model)

Funding

BioQuant
MODEL base of LIFE

EXZELLENZCLUSTER
CellNetworks

Bundesministerium
für Bildung
und Forschung

mehtrics

SEVENTH FRAMEWORK
PROGRAMME

www.thphys.uni-heidelberg.de/~biophys/