Modelling cell motion:
From microscopic to macroscopic scale

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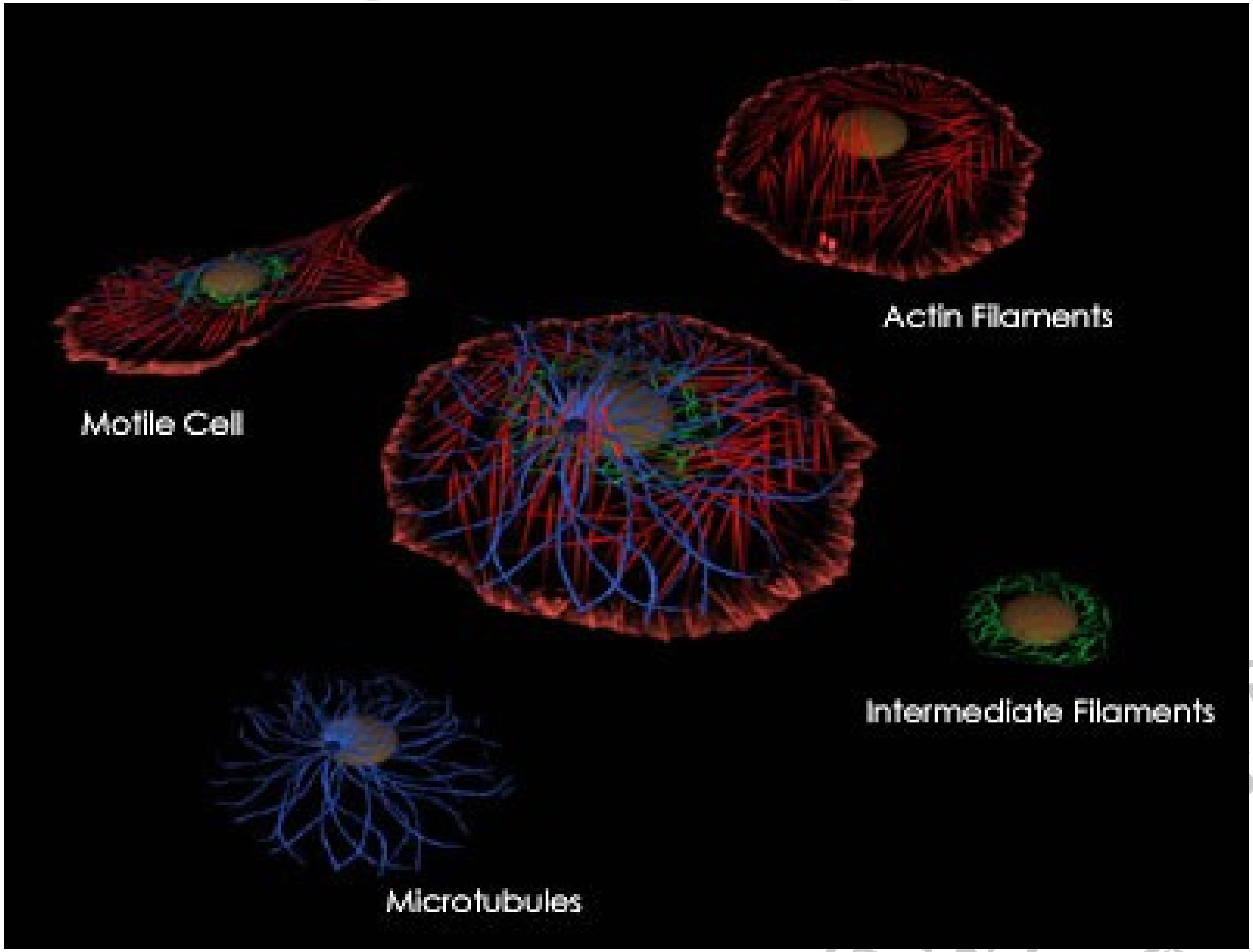
Modelling cell-ECM interaction:
An opportunity to present different modelling frameworks

1. Biological mechanisms underlying cell motion
2. Cell motion in fiber networks: a kinetic model
3. Cell-matrix interactions in multiphase models
4. Nested models
5. Cell migration by cellular Potts models
6. Modelling cell motion in microchannels
7. Modelling intravasation processes
8. Cell-ECM interaction with Individual Cell-based Models (IBMs)

CIMAB
CENTRO INTERUNIVERSITARIO PER LA MATEMATICA APPLICATA A BIOLOGIA MEDICINA ED AMBIENTE

...ECNICO DI TORIN...

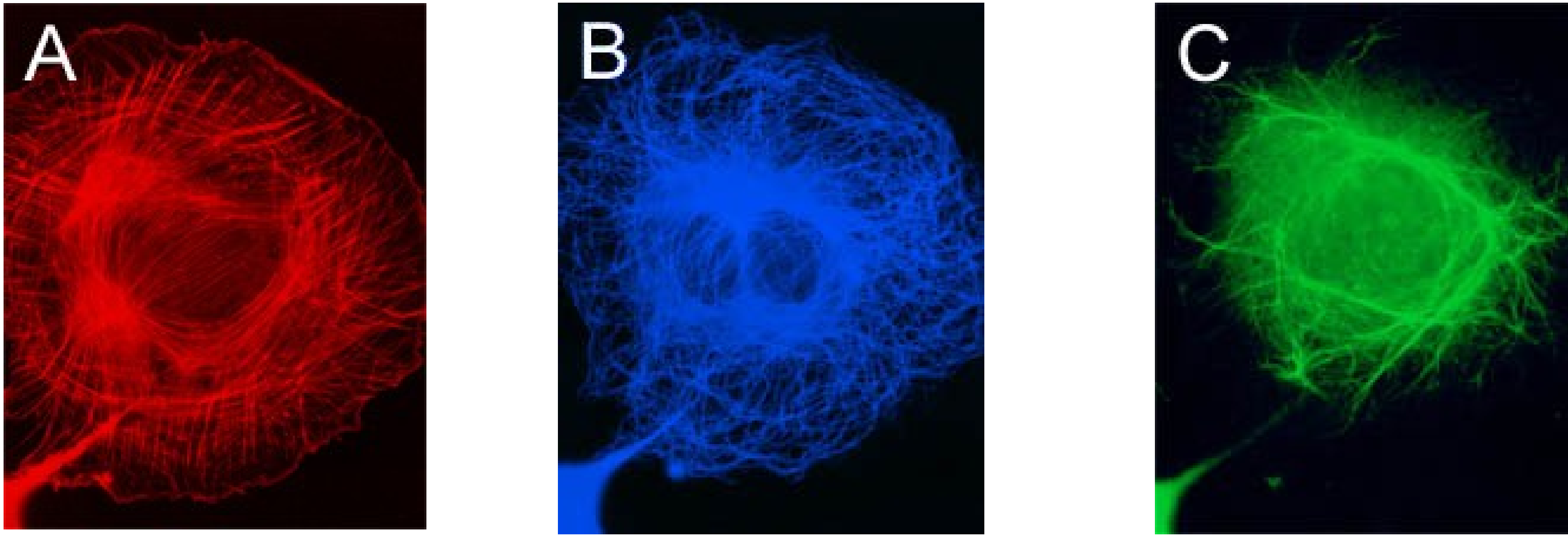
Biological background



(V. Small)

Original at: cellix.imba.oeaw.ac.at

Cell Motion

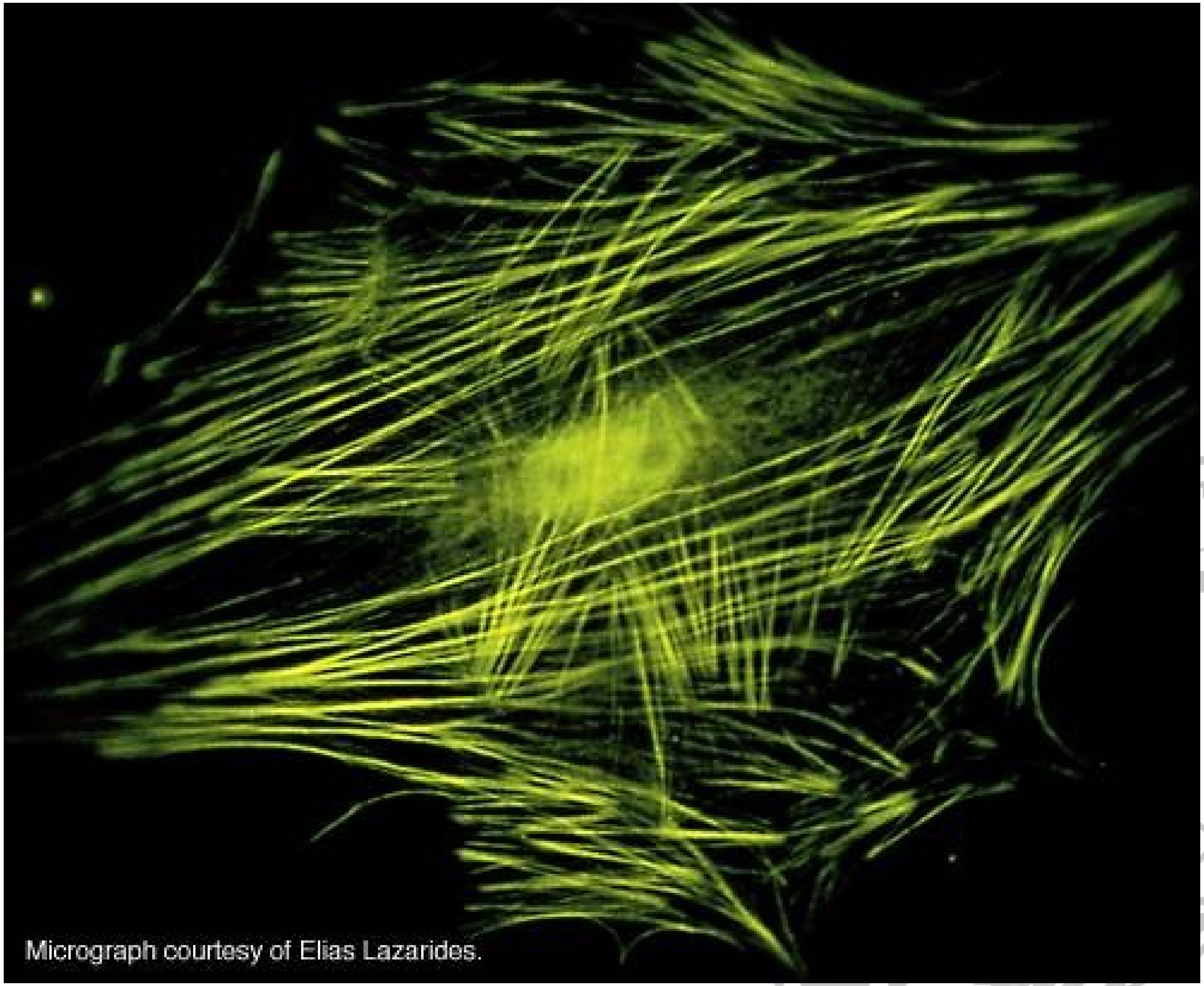


A, the actin cytoskeleton, labelled with fluorescent phalloidin;
B, the microtubule cytoskeleton labelled with an antibody to tubulin;
C, the intermediate filament cytoskeleton labelled with antibodies to the intermediate filament protein, vimentin.

Original at: cellix.imba.oeaw.ac.at

The cytoskeleton

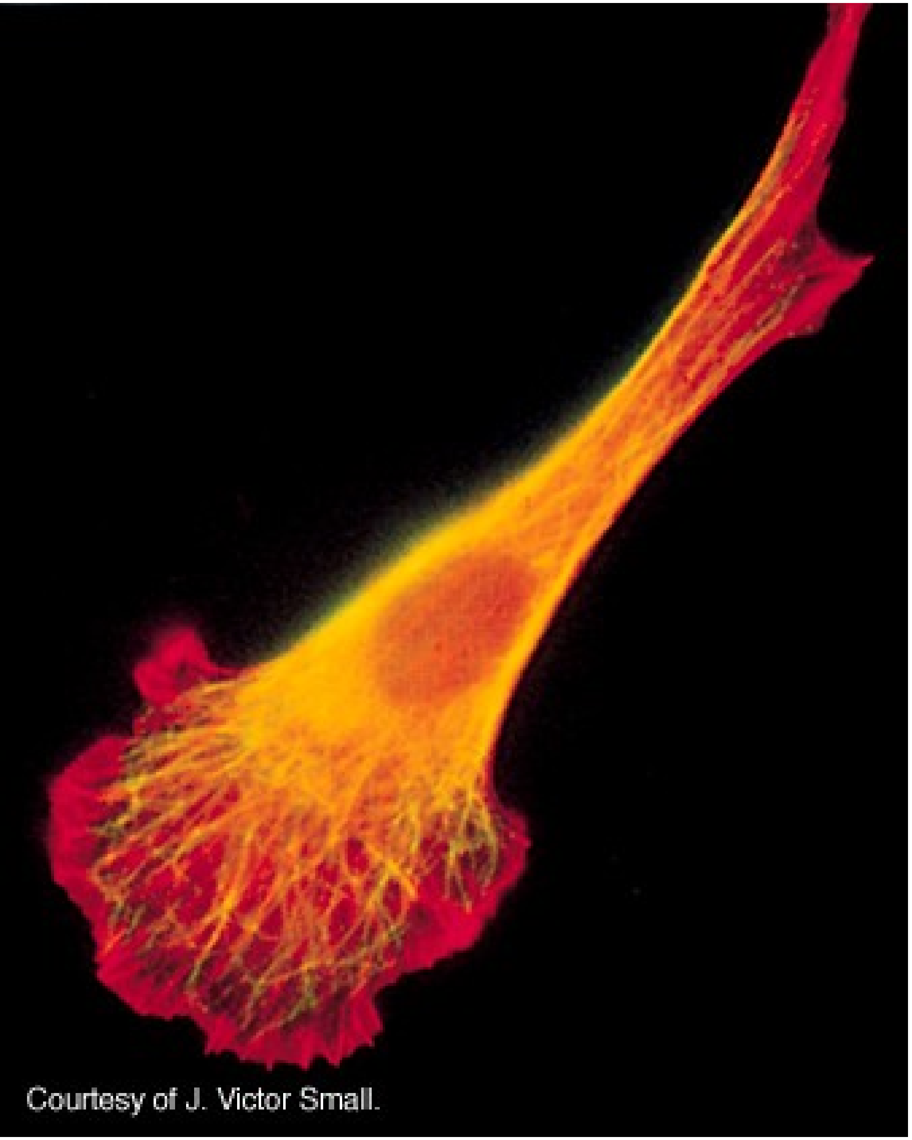
- The cytoskeleton is an intricate network of protein filaments that extends throughout the cytoplasm.



The cytoskeleton

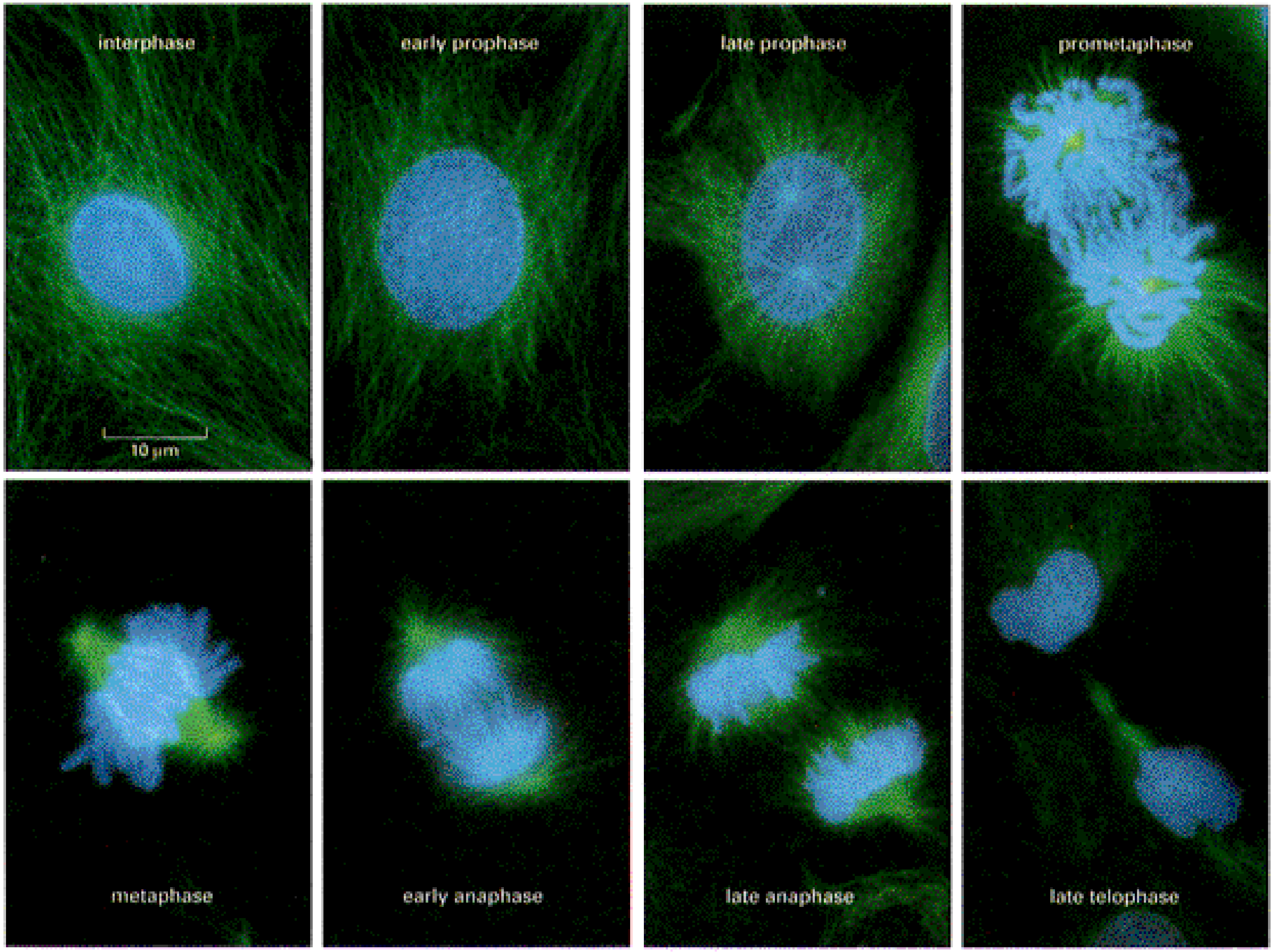
- The cytoskeleton is an intricate network of protein filaments that extends throughout the cytoplasm.

Functions of the cytoskeleton



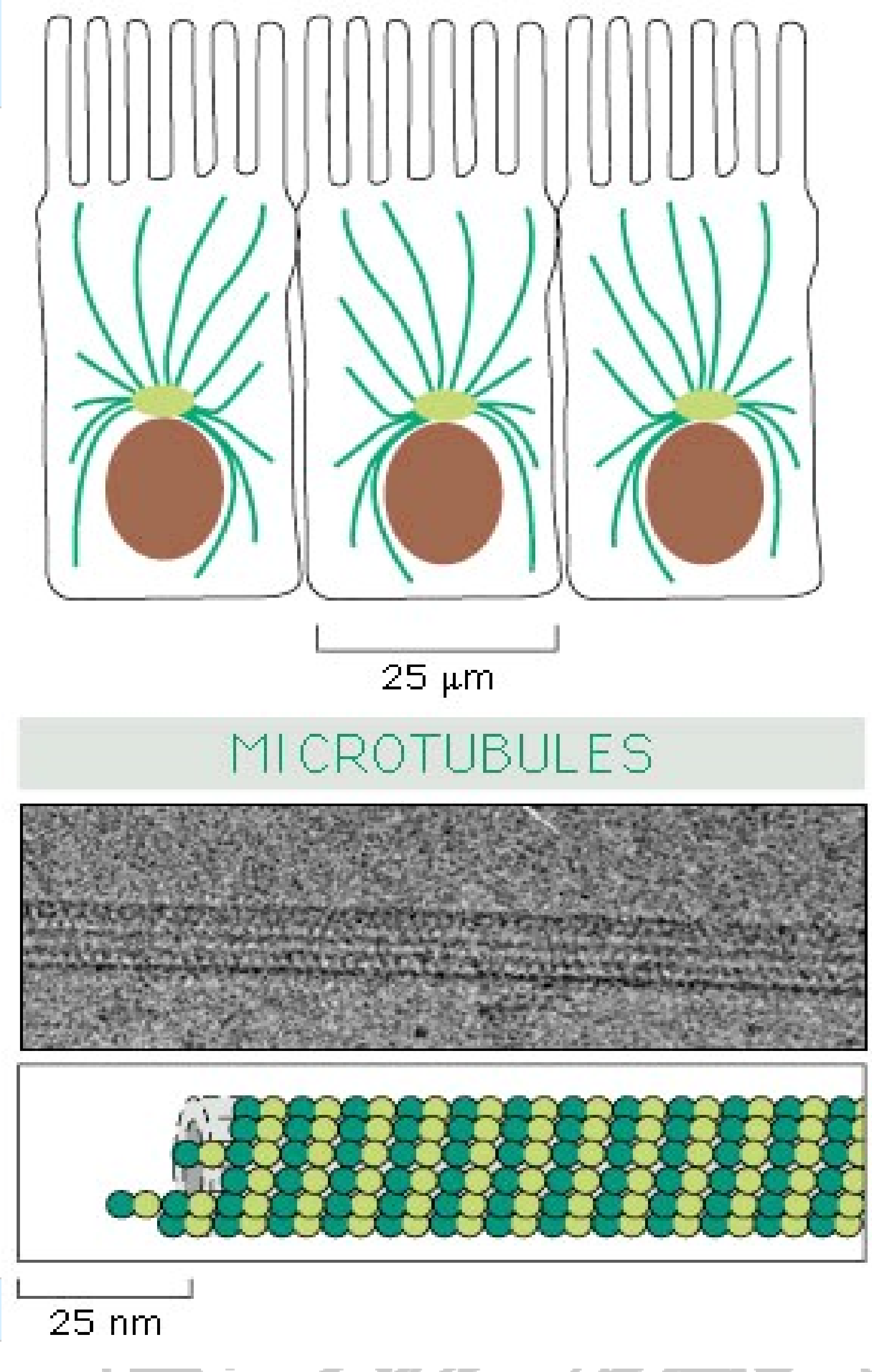
- Structural support for the cytoplasm
- Causes changes in cell shape
- Facilitates cell division
- Causes cell movements
- Causes muscle contraction
- Controls location of organelles
- Provides transport between organelles

Motion or Mitosis



Microtubules

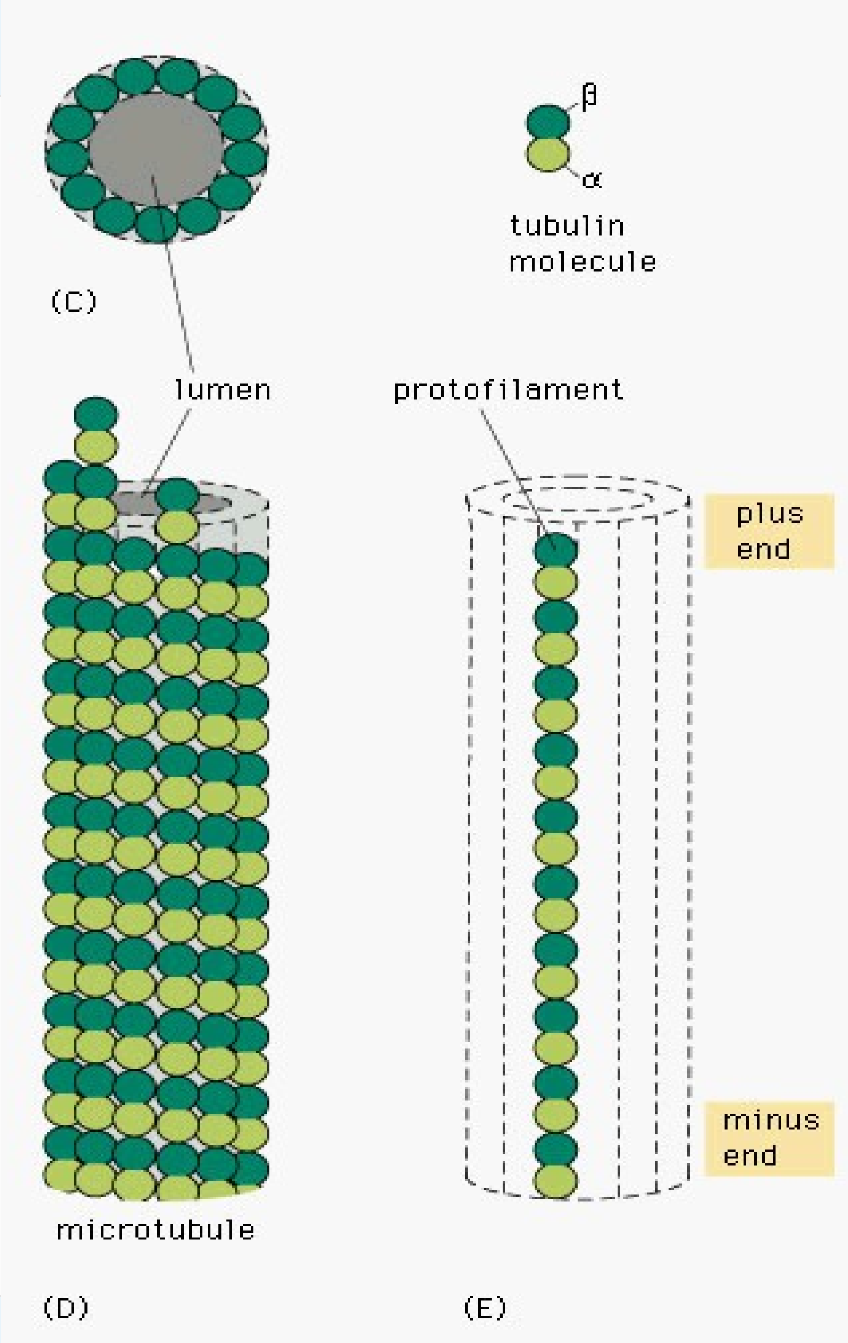
- long hollow cylinders made of a protein named tubulin.



Microtubules

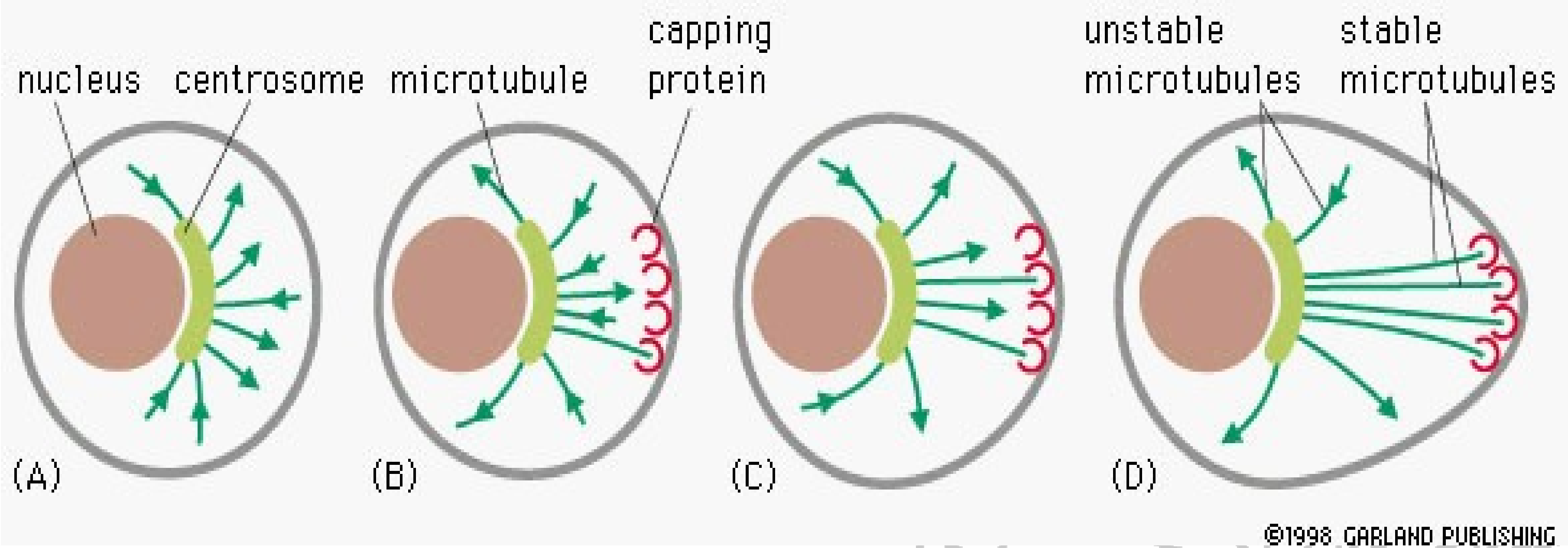
- They are built from subunits of α– and β–tubulin.
- They are maintained by a balance of assembly and disassembly.
- GTP (favors polymerization) or GDP

www.youtube.com/watch?v=PvDlilBgoSs

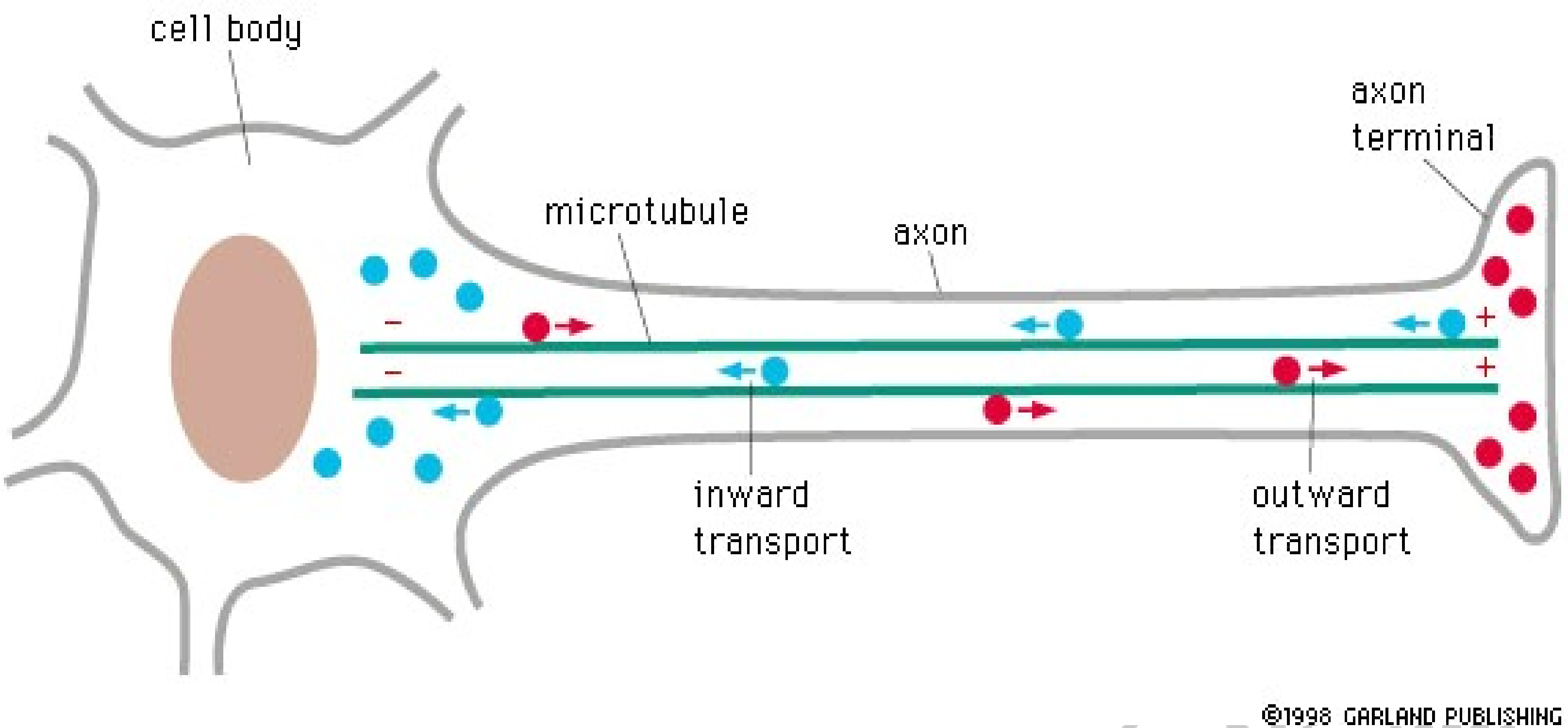


Capping proteins

- Capping proteins bind to the ends of microtubules and provide stabilization by protection from depolymerization

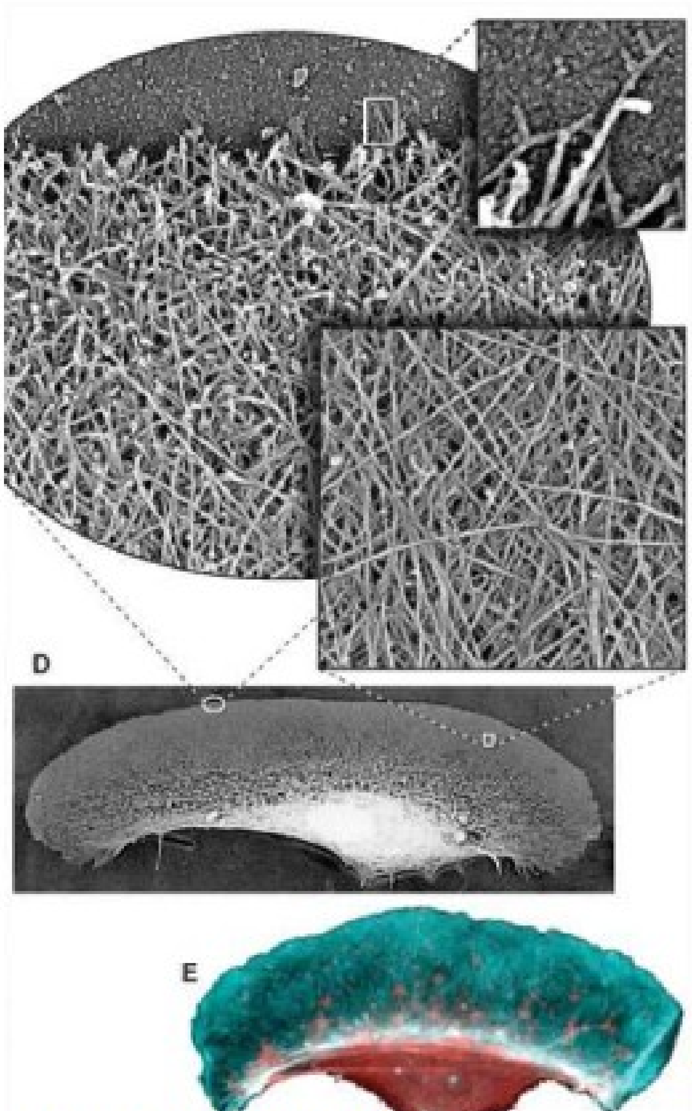


Microtubules provide tracks for transport

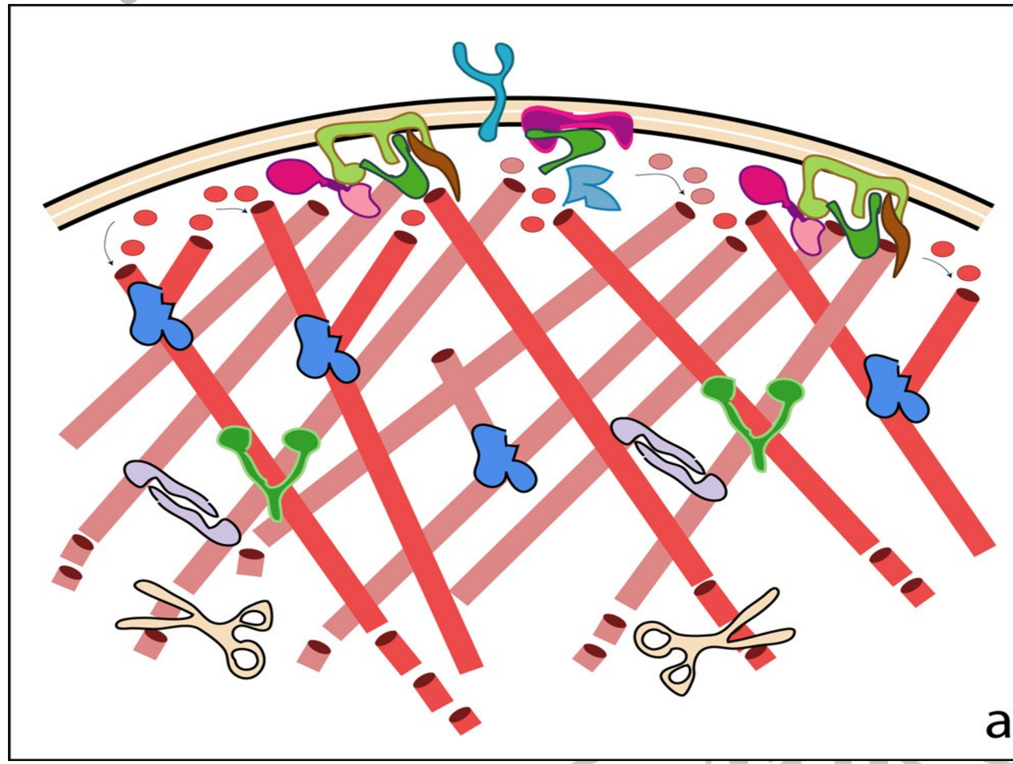


Microtubules are conveyer belts inside the cells. They move vesicles, granules, organelles like mitochondria, and chromosomes.

The actin cytoskeleton



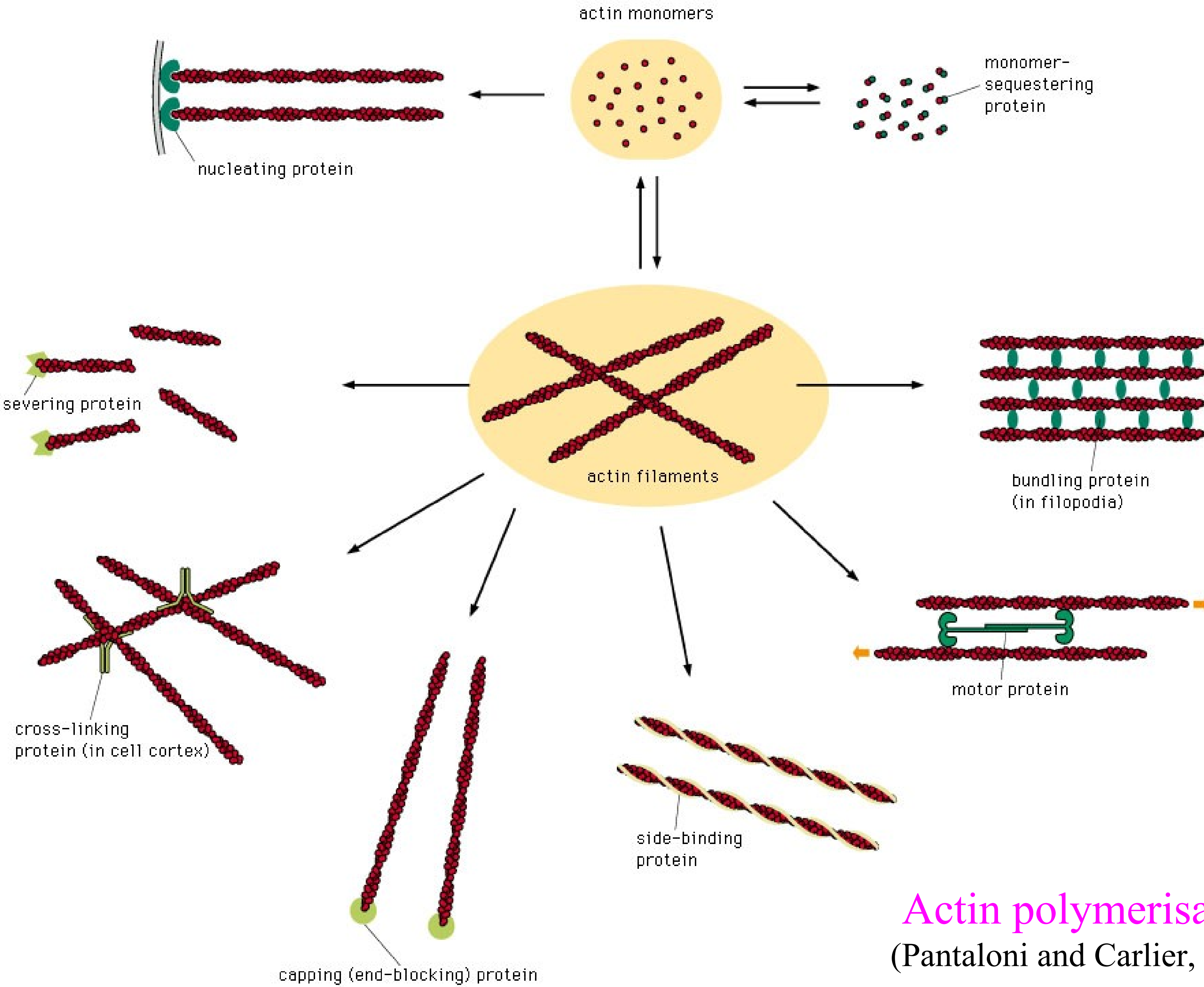
Pollard & Earnshaw, 2002



www.youtube.com/watch?v=saYK4Xseg2g

- **Keratocyte**
- **Keratocyte fragment**

Alexander Verkhovsky

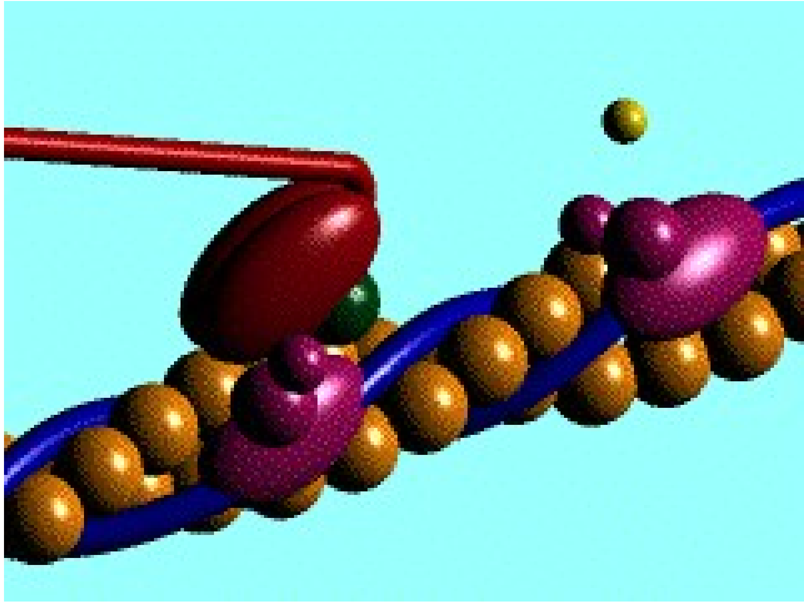


Actin polymerisation

(Pantaloni and Carlier, 2002)

Actin filaments

- Actin filaments are concentrated beneath the plasma membrane (cell cortex) and give the cell mechanical strength.
- Assembly of actin filaments can determine cell shape and cause cell movement.
- Association of actin filaments with myosin can form contractile structures.

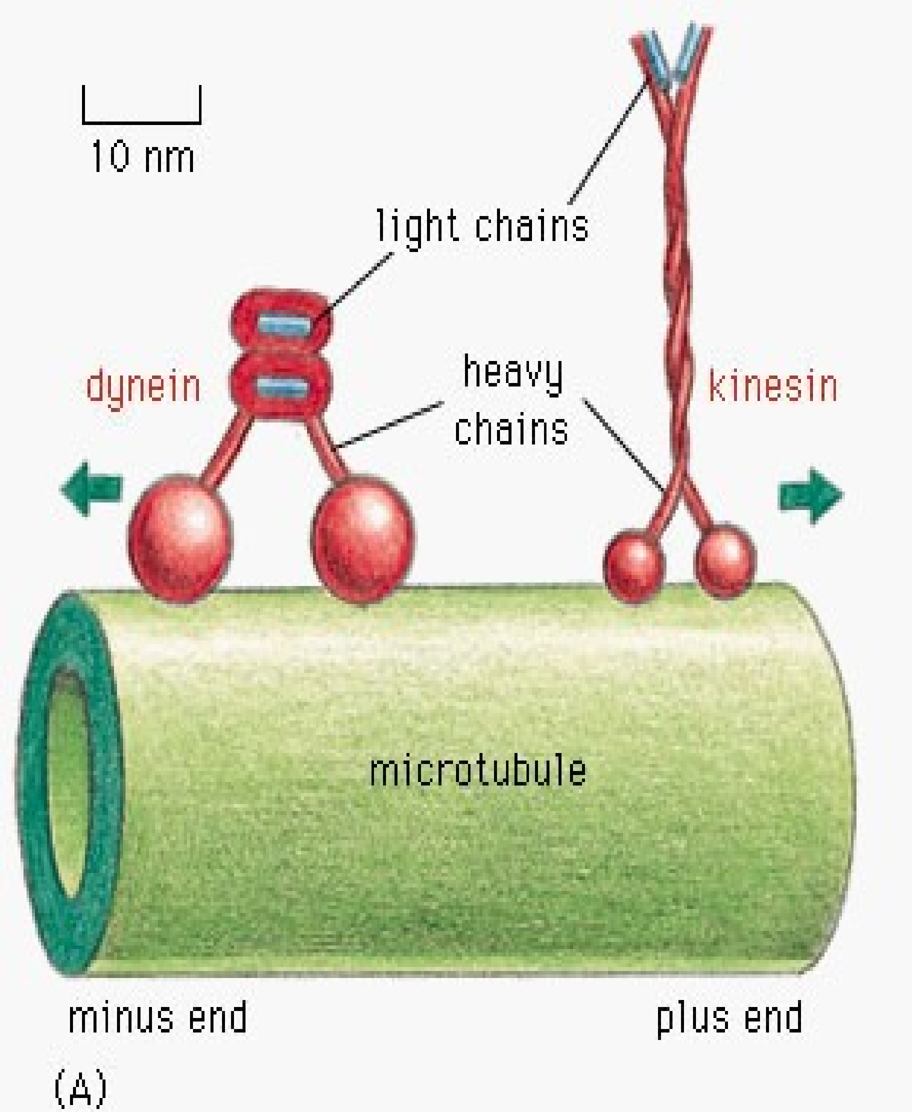


www.sci.sdsu.edu/movies/actin_myosin_gif.html

Motor proteins

- Motor proteins bind to actin filaments and microtubules and move by cycles of conformational changes using energy from ATP.

- One end of the protein can bind to specific cellular components.



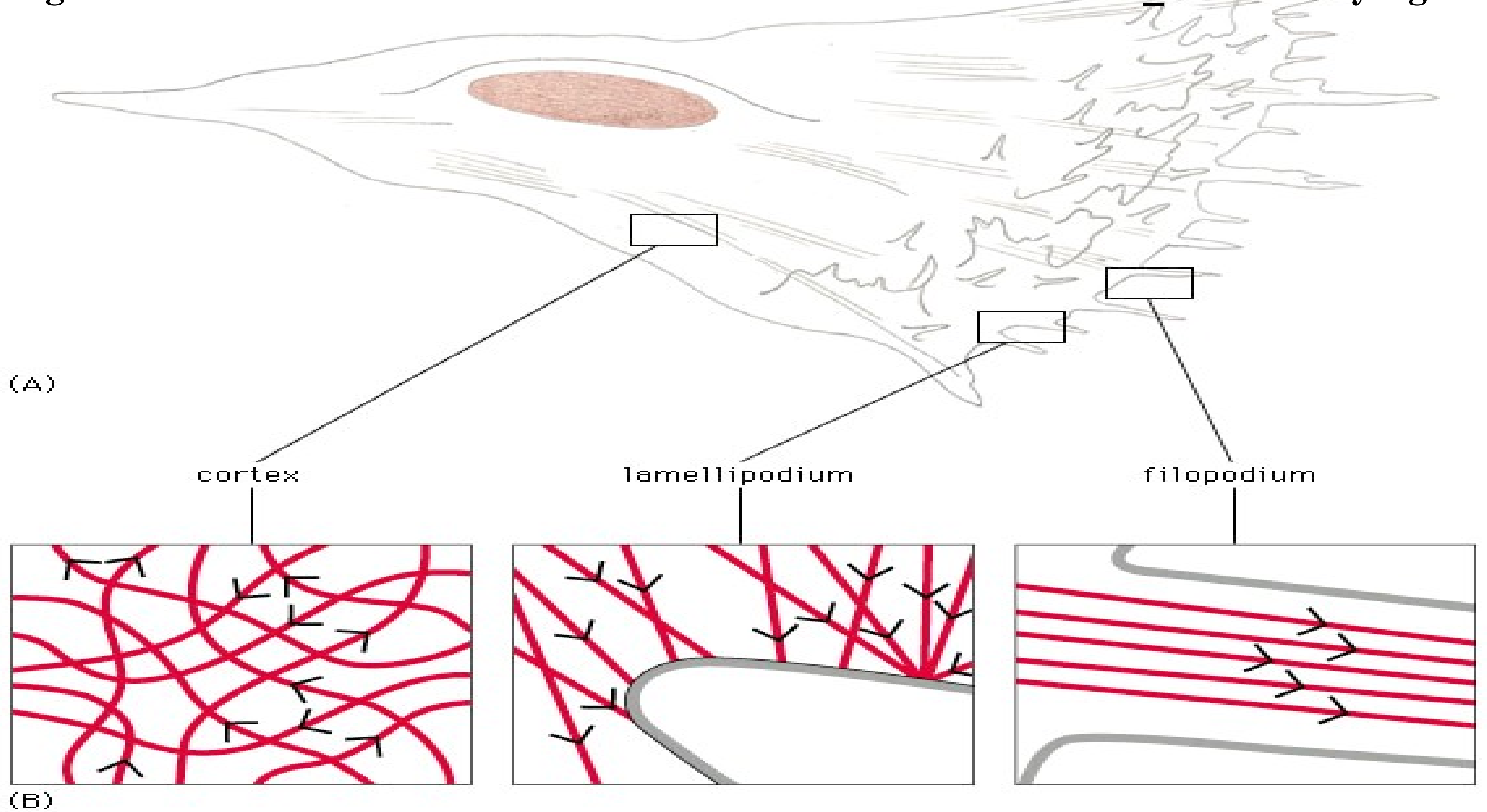
myosin

Original at: www.youtube.com/watch?v=vJ9ffKeUCvE&hl=it

Cell crawling

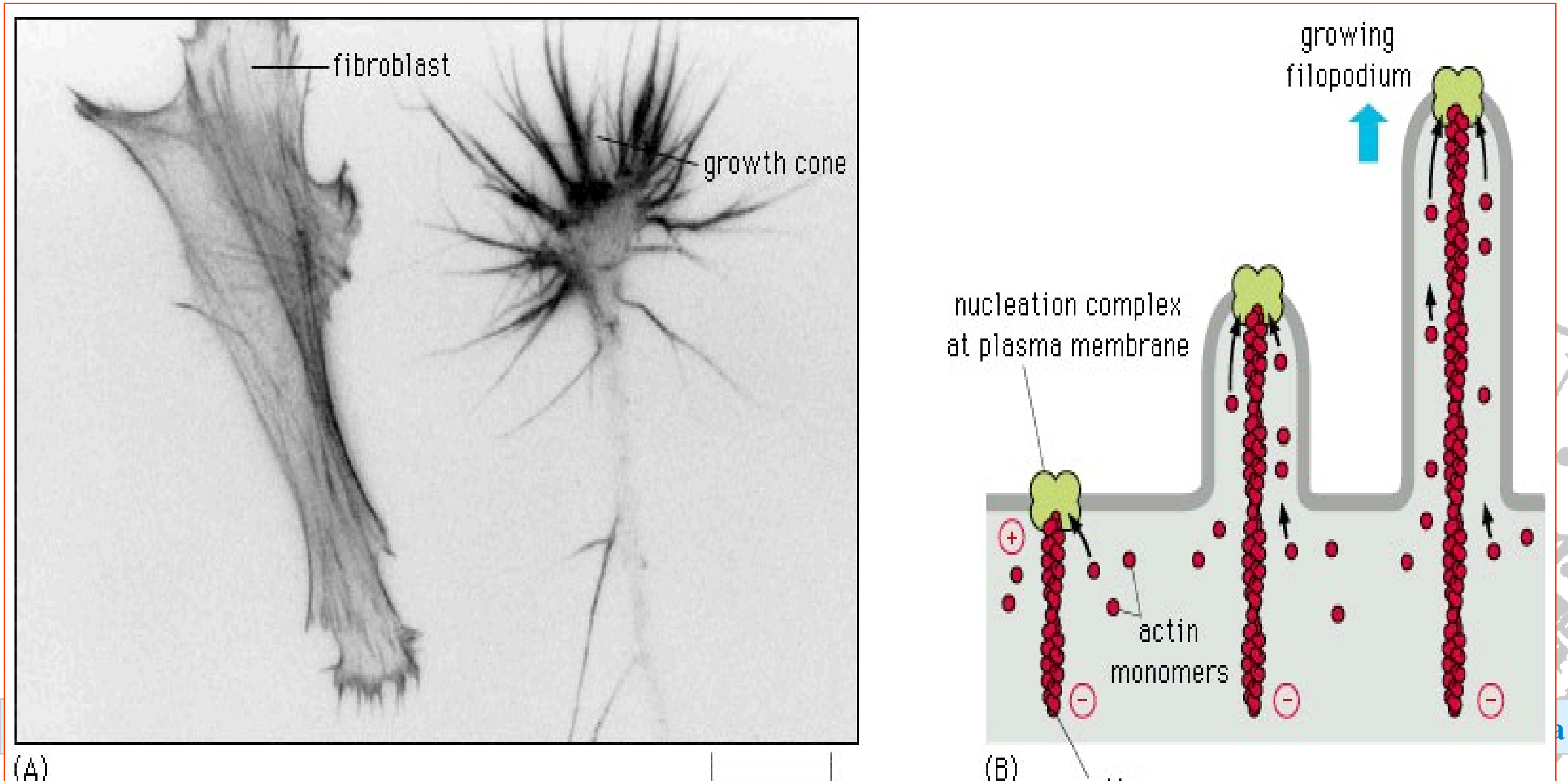
- Motion of a melanoma cell
- Motion of a fibroblast

Original at: cellix.imba.oeaw.ac.at/fileadmin/conferences/Videotour_CellMotility/fig3.mov

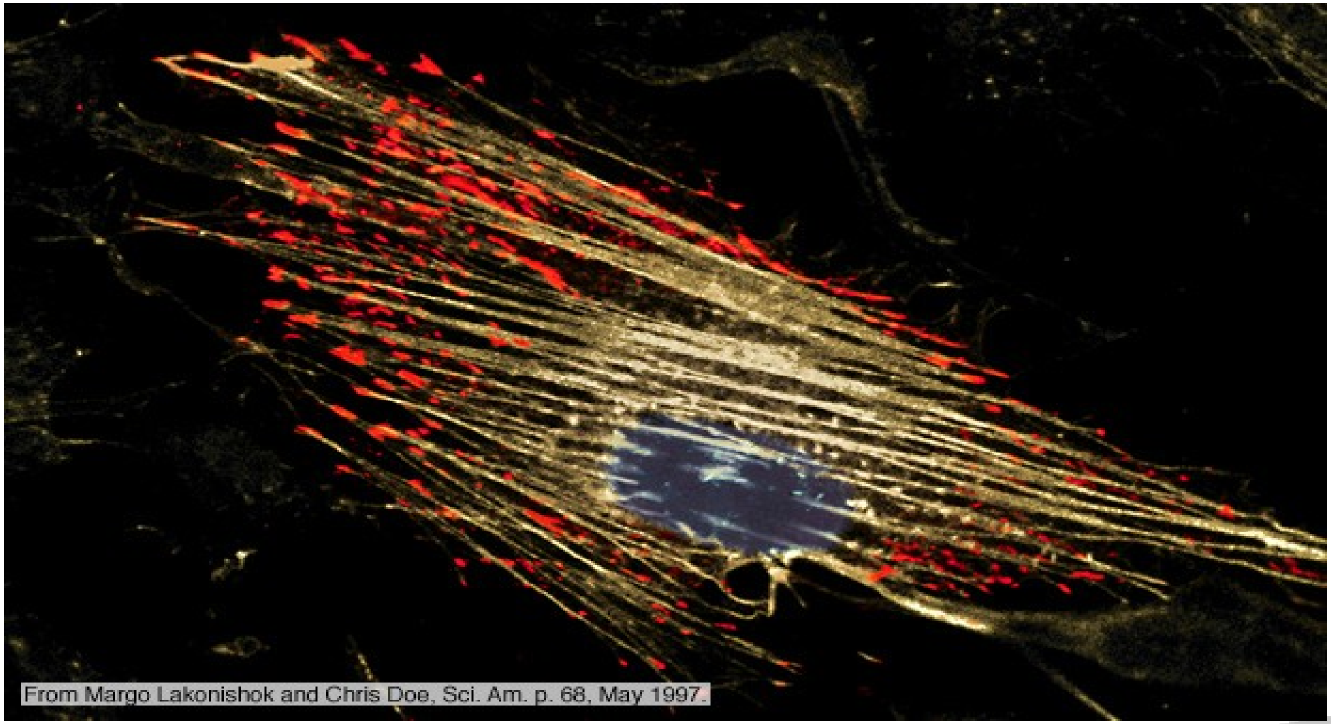


Growth of filopodia

• Treadmilling
•Actin depolimerisation
(cellix.imba.oeaw.ac.at/fileadmin/conferences/Videotour_CellMotility/fig9.mov fig10.mov and fig51.mov)

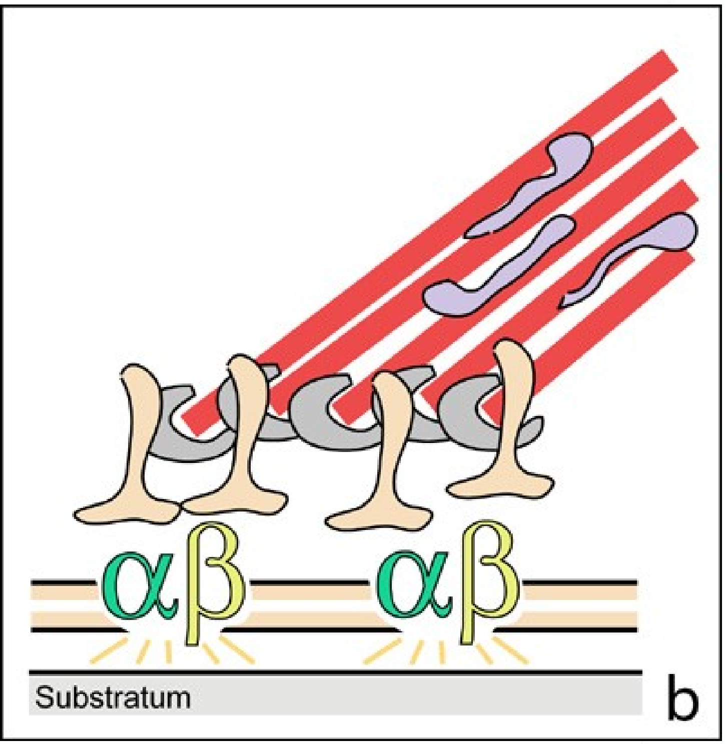


Focal contacts

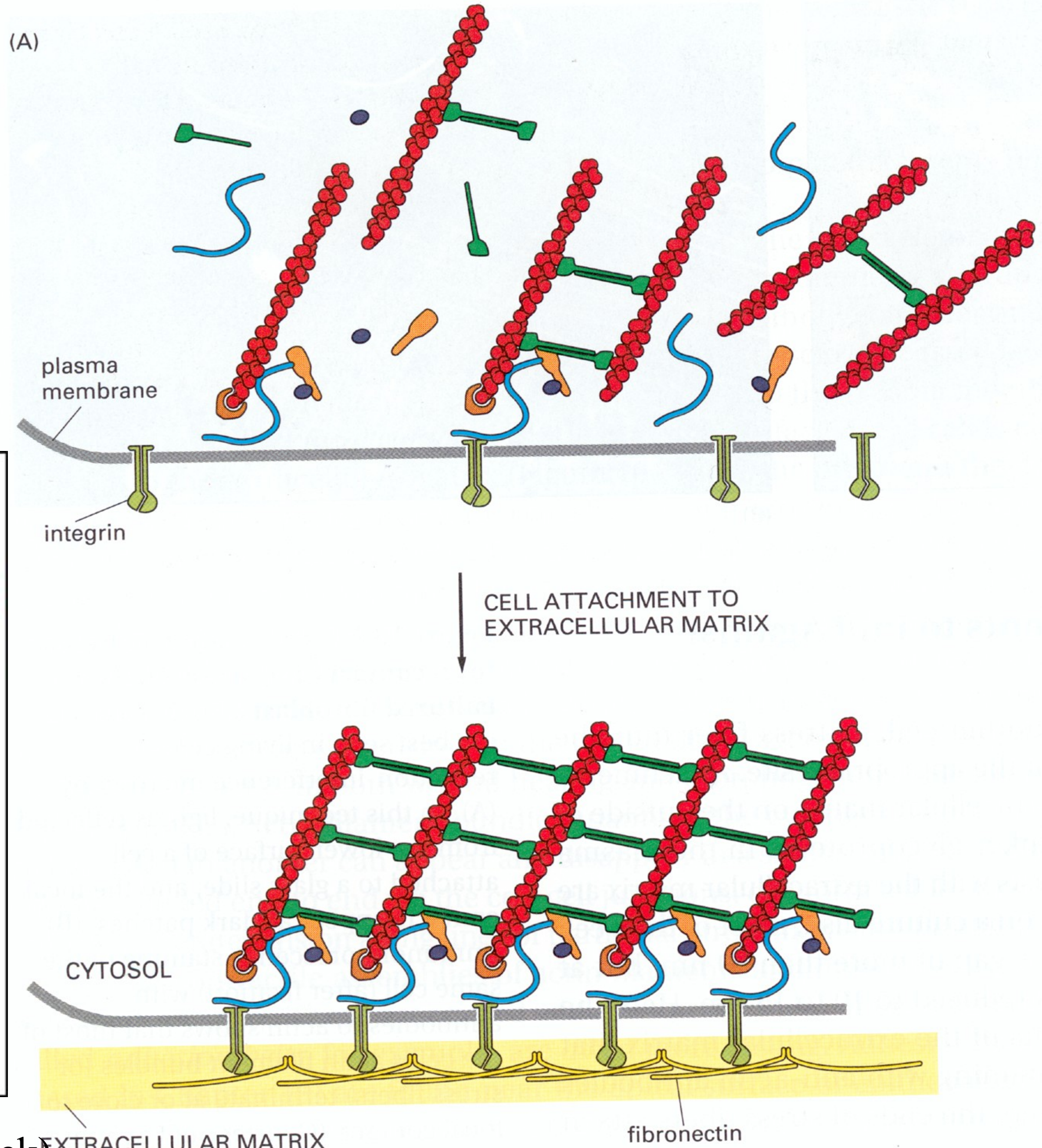


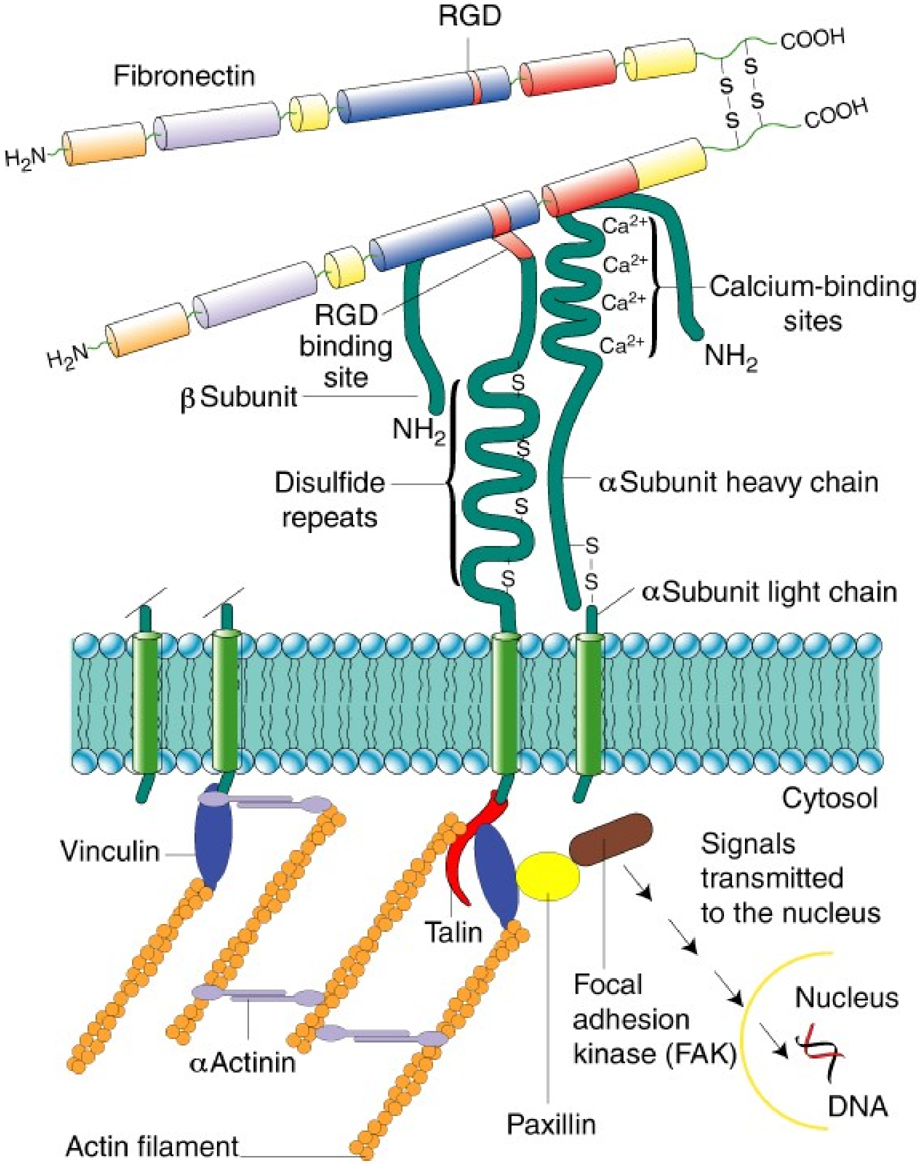
- Focal contacts and microtubulin
- Animation focal contact and cytoskeleton
- Making a focal contact

(cellix.imba.oeaw.ac.at/fileadmin/conferences/Videotour_CellMotility/fig40.mov fig26.mov fig15.mov)

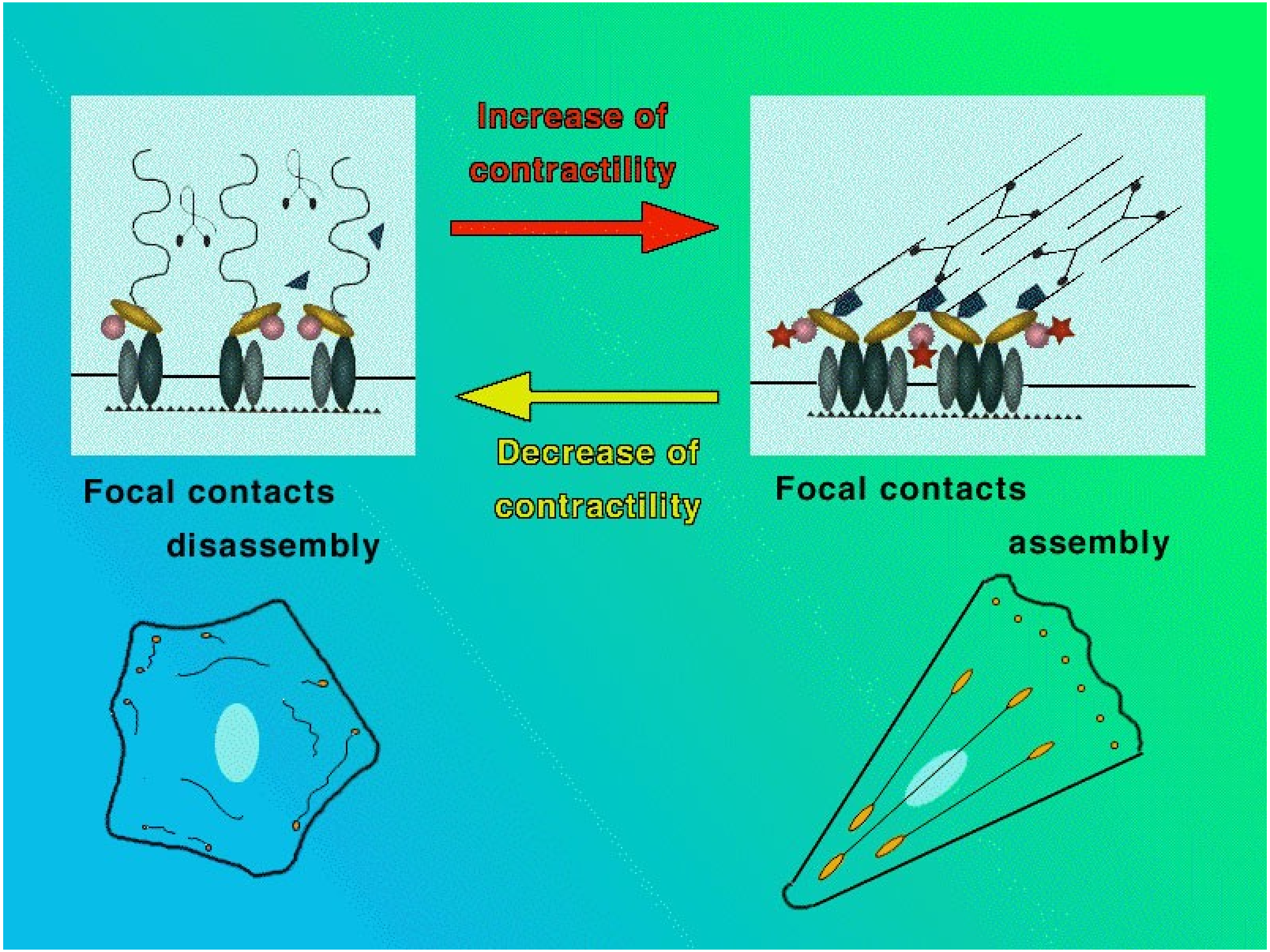


(Burridge and Chrzanowska-Wodnick)

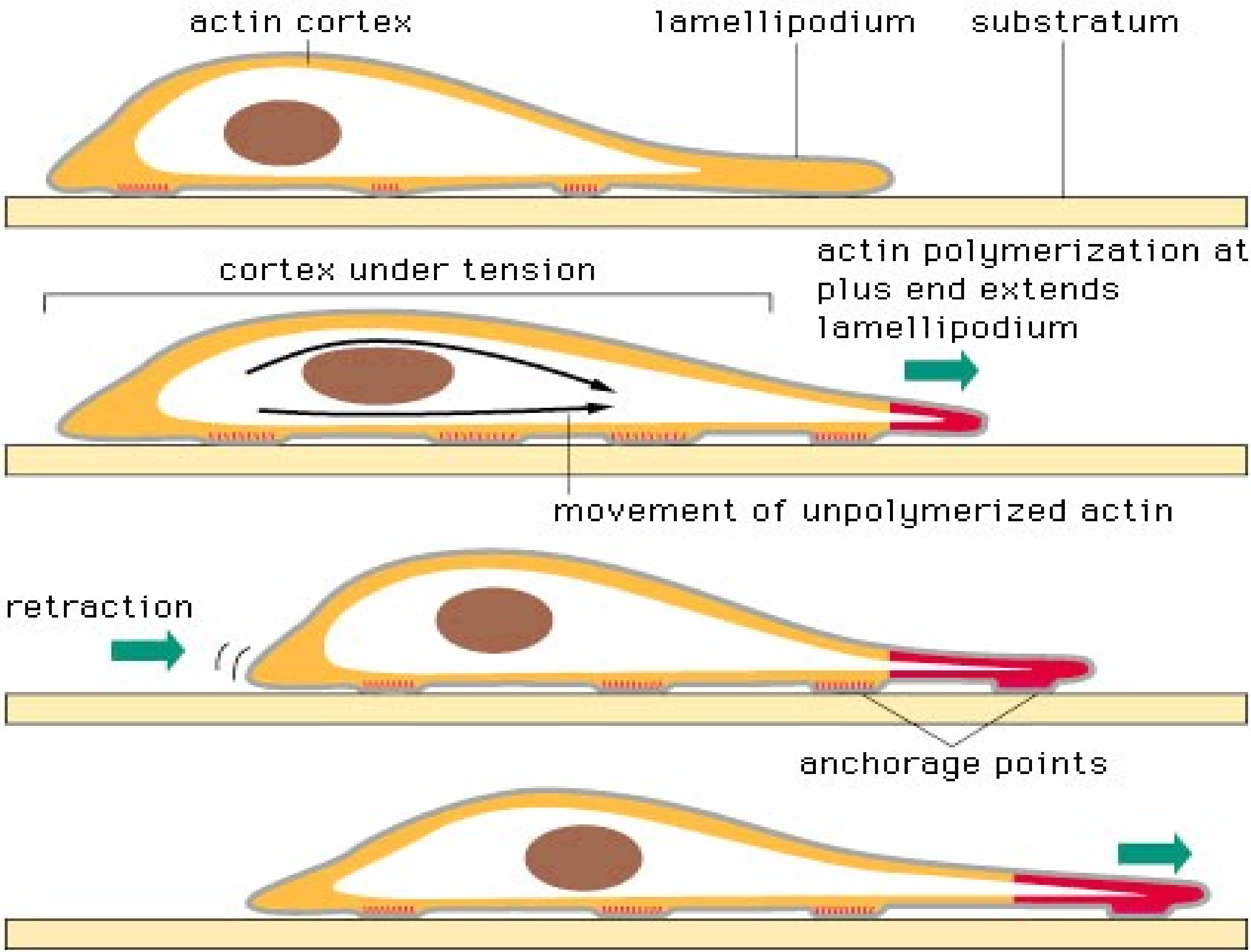




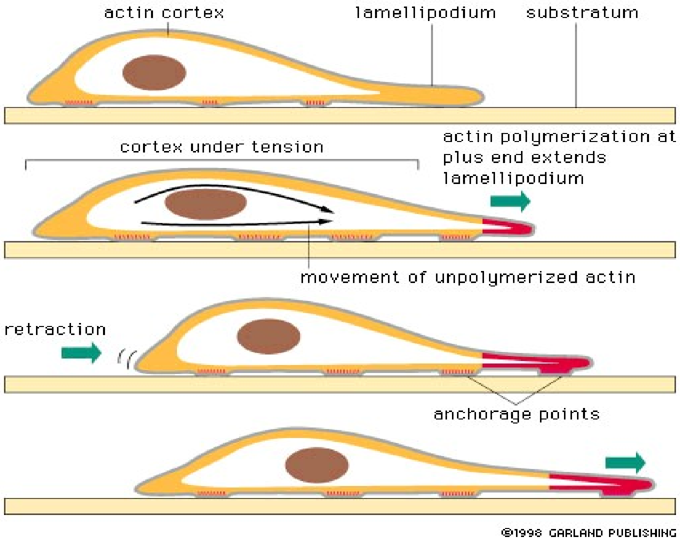
RGD
Fibronectin
COOH
S
S
S
S
COOH
H_2N
H_2N
Ca^{2+}
Ca^{2+}
Ca^{2+}
Ca^{2+}
Calcium-binding sites
RGD binding site
NH_2
β Subunit
NH_2
S
S
S
S
Disulfide repeats
α Subunit heavy chain
S
S
α Subunit light chain
Cytosol
Vinculin
Signals transmitted to the nucleus
Talin
Focal adhesion kinase (FAK)
Nucleus
α Actinin
DNA
Paxillin
Actin filament



(Burridge et al. Trends Cell Biol. 7, 342-347, 1997)


actin cortex
lamellipodium
substratum
cortex under tension
actin polymerization at plus end extends lamellipodium
movement of unpolymerized actin
retraction
anchorage points

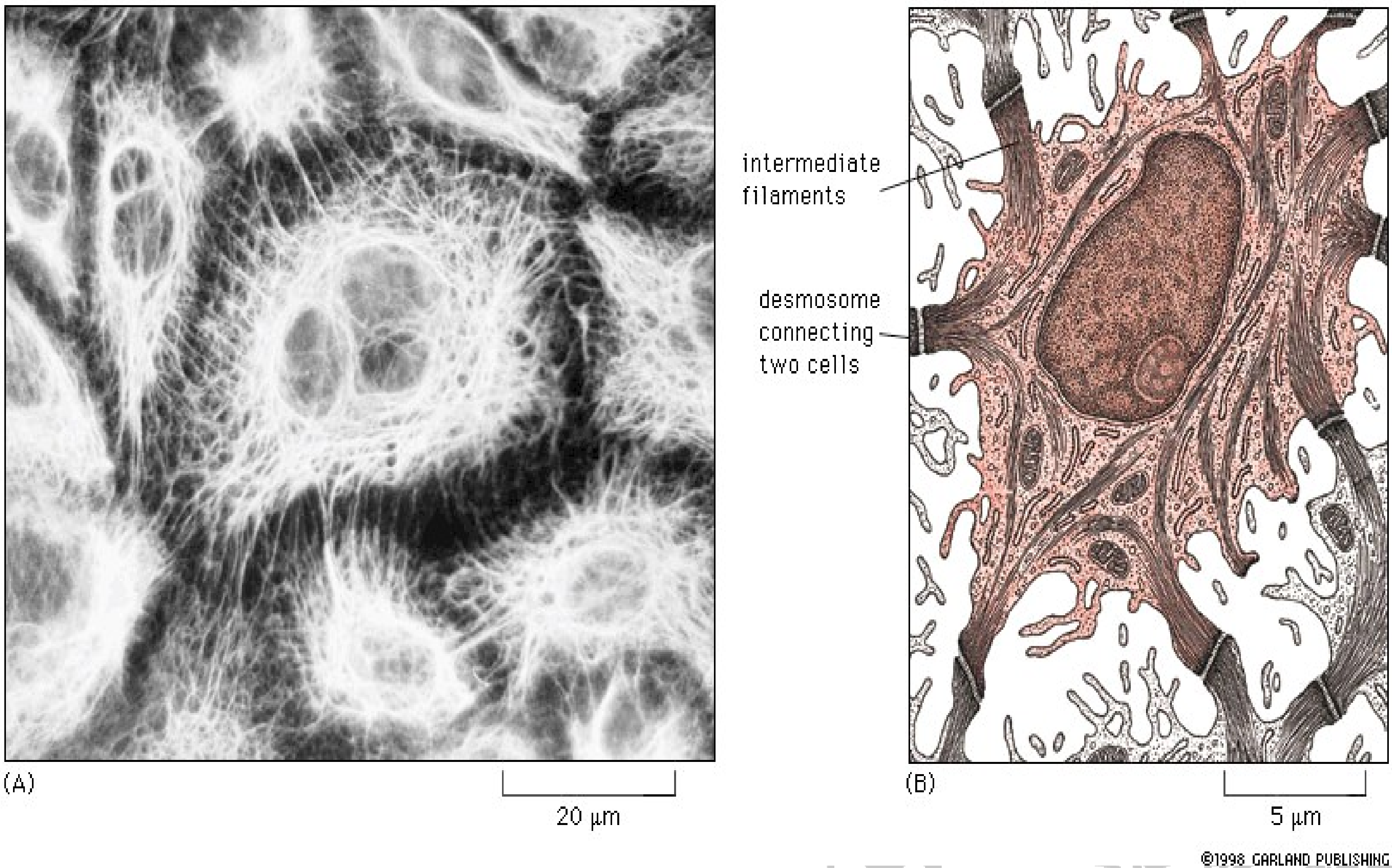
Focal Adhesion



Integrins anchor the outside cell surface to the extra cellular matrix by binding to proteins like fibronectin and collagen.

Fibronectin----> “molecular flypaper”

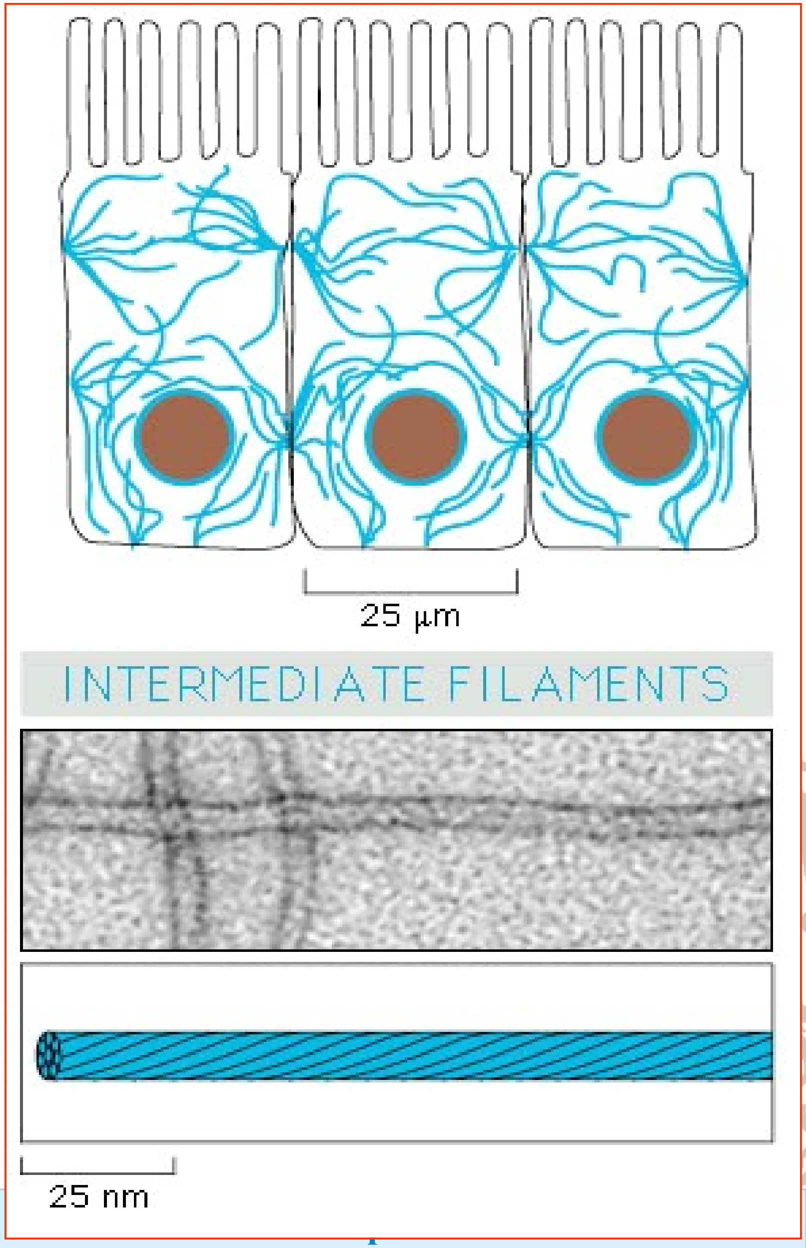
Intermediate Filaments



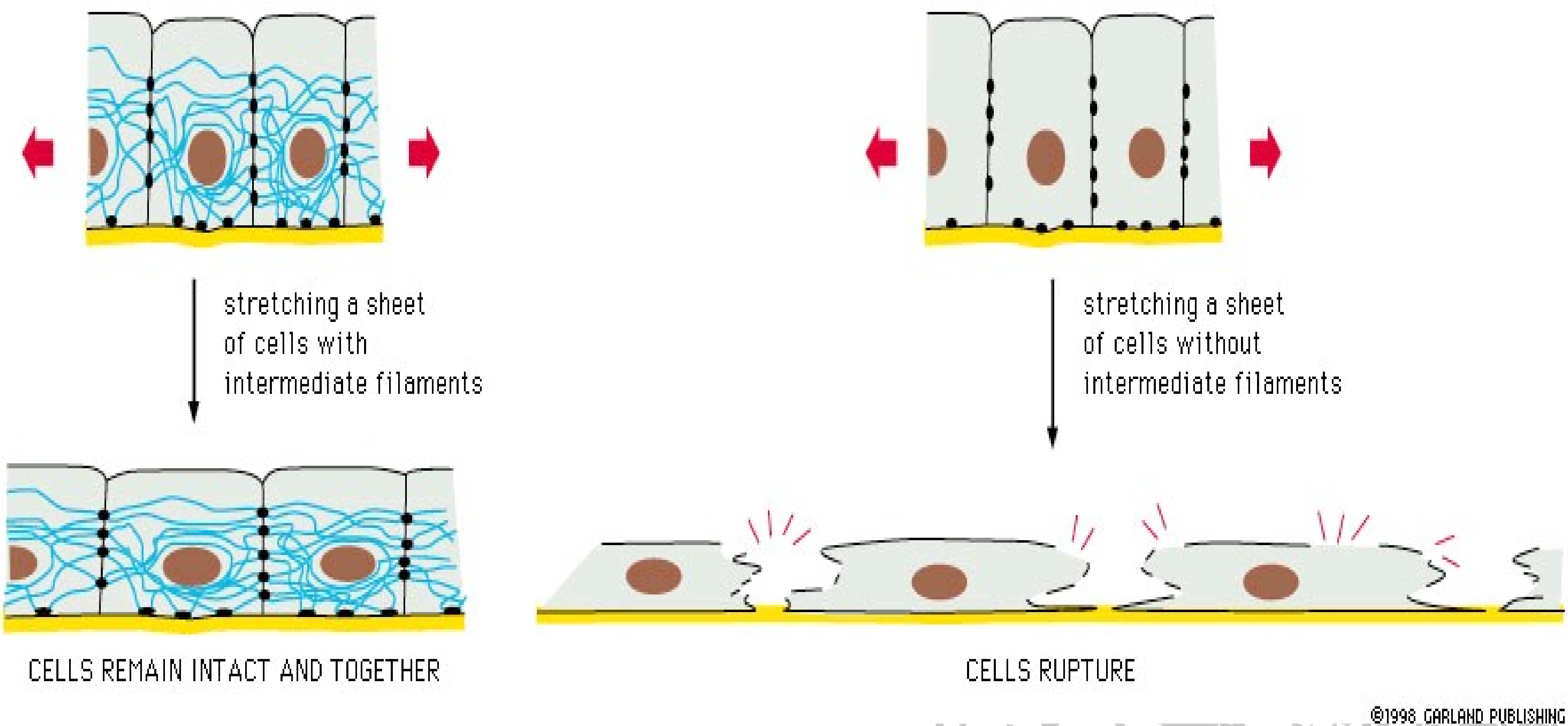
Intermediate Filaments

- They enable cells to withstand mechanical stress when cells are stretched.

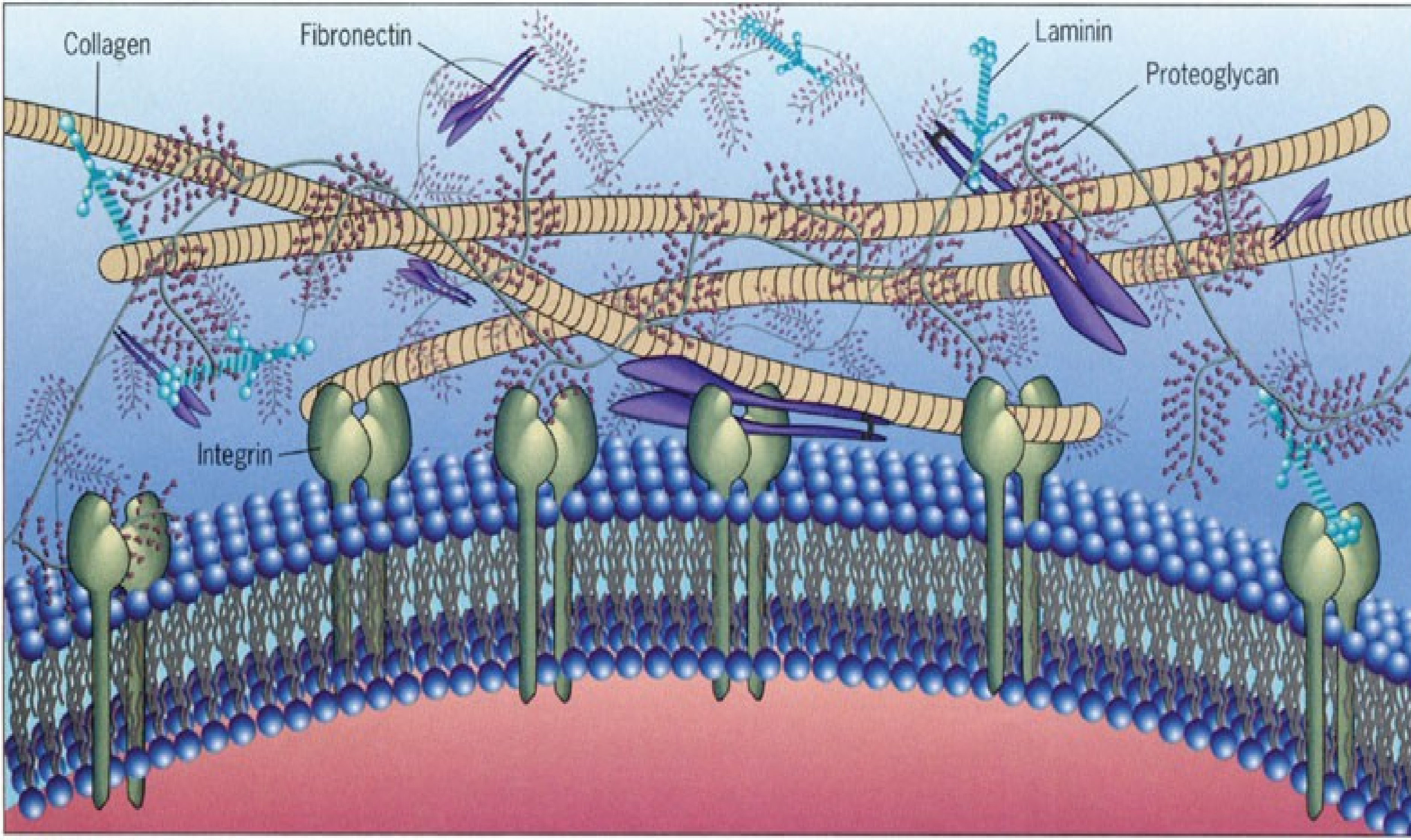
- They can span the entire cytoplasm and are anchored to the plasma membrane.



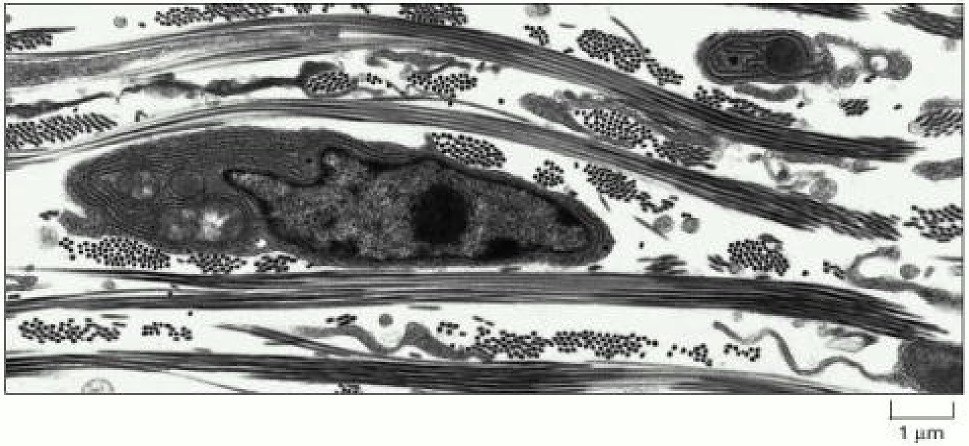
Intermediate Filaments Strengthen Cells

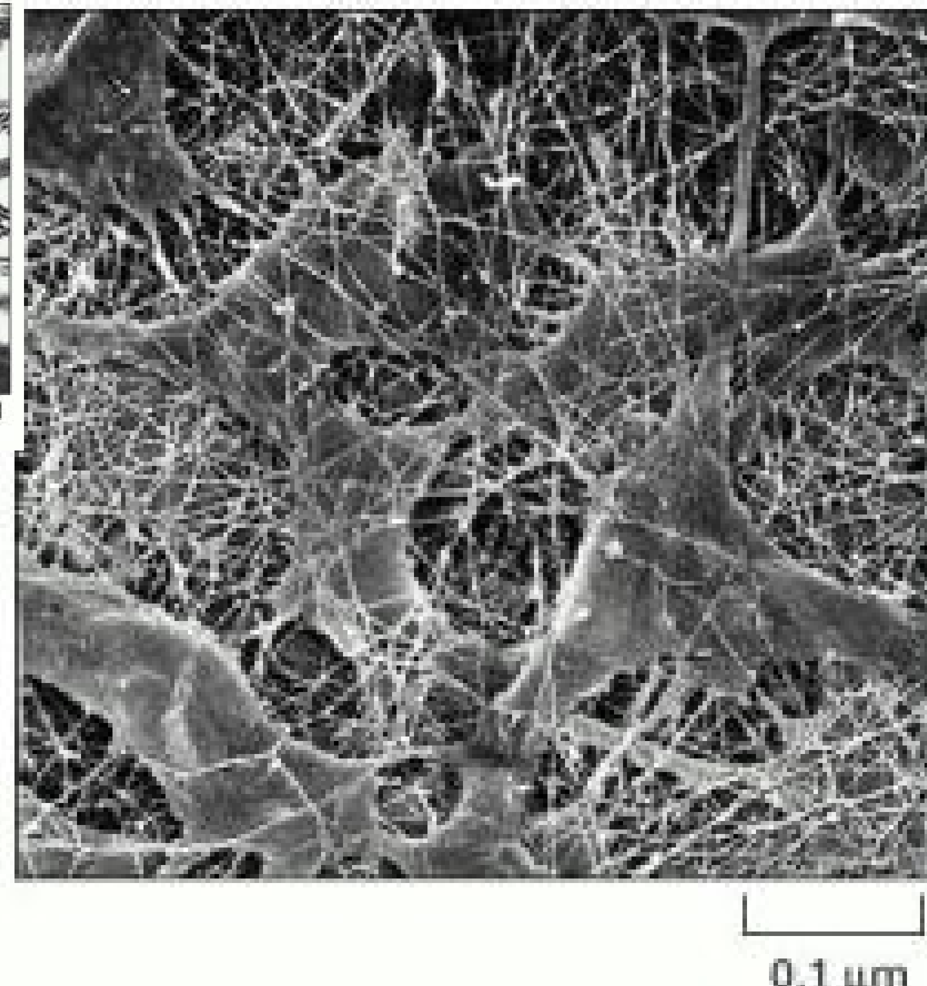


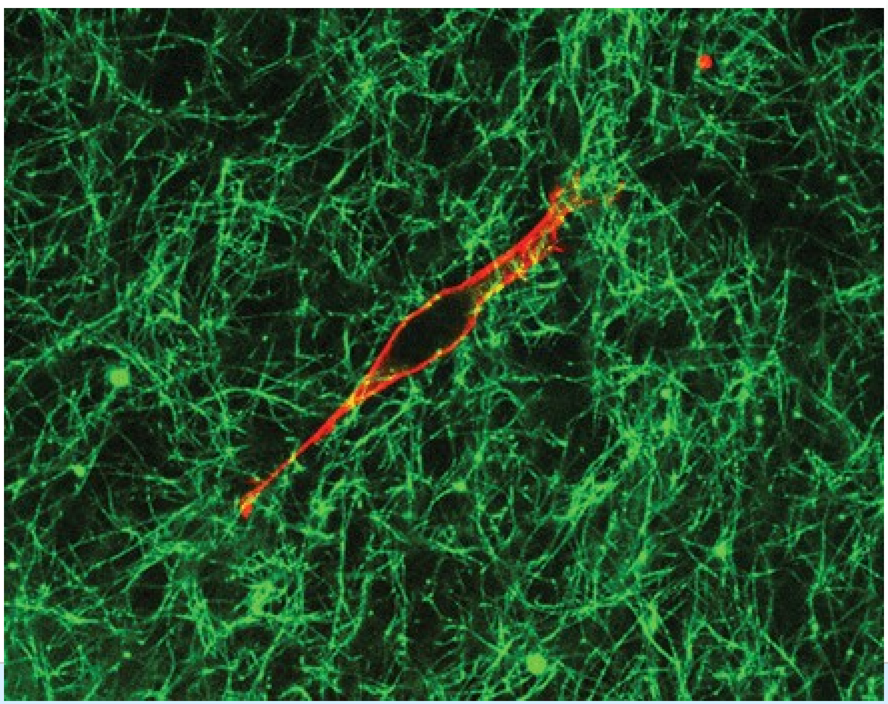
Extra-cellular Matrix



Extra-cellular Matrix

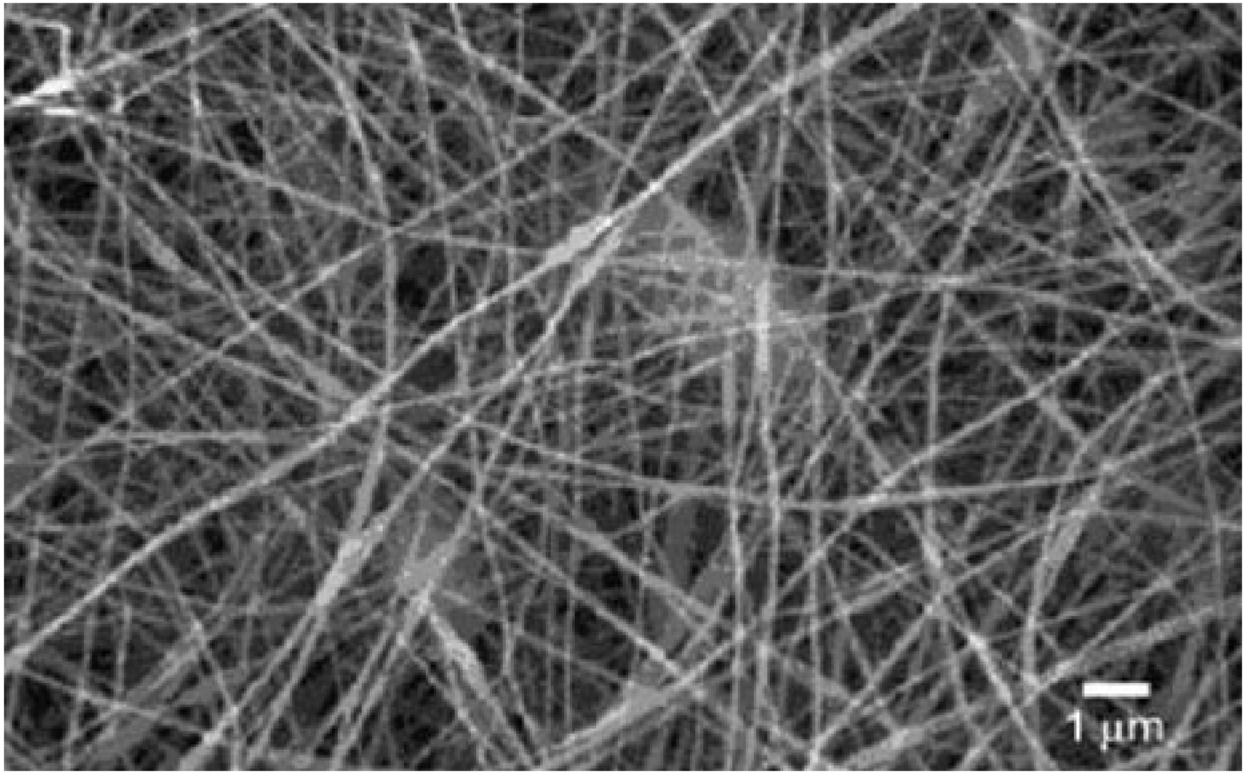


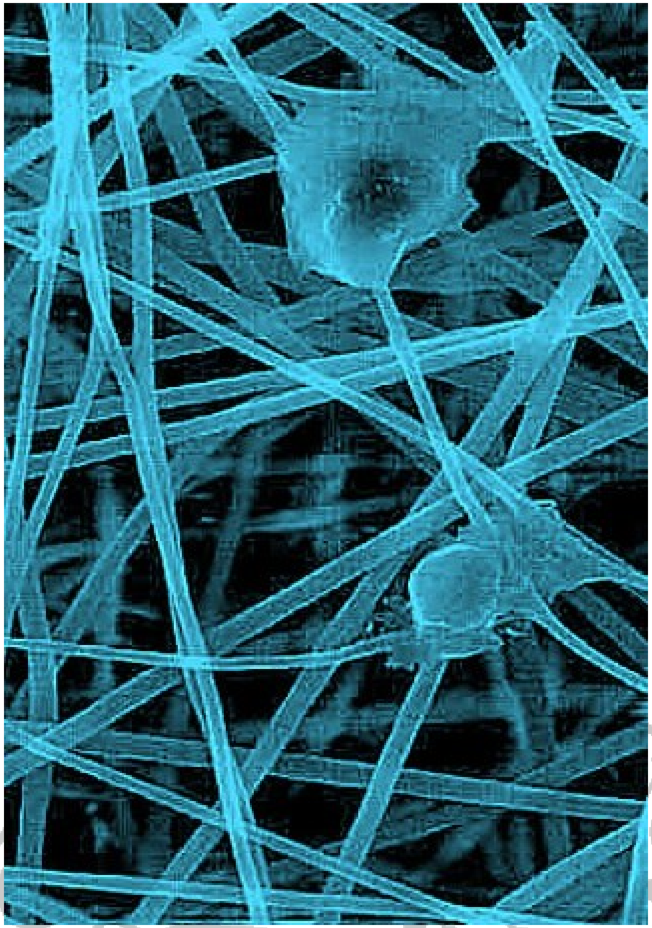




(P. Friedl)

Artificial ECM





Taxis

- **Taxis = motion toward regions with a higher …....**

- **Chemotaxis = …. concentration of a chemical factor**

  - Neutrophil
  (from www.freesciencelectures.com/video/neutrophil-chemotaxis/
  (from www.biochemweb.org/neutrophil.shtml)
  - Dictyostelium moving toward a source of cAMP.
  (recording time ~ 20 min)
  (from www-biology.ucsd.edu/~firtel/video/)

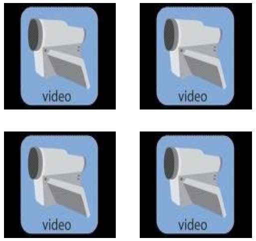
- **Haptotaxis = …. concentration of cellular adhesion sites or substrate-bound chemoattractants**

Taxis

- **Taxis = motion toward regions with a higher …….**

- **Durotaxis = …. rigidity of substratum**

  Fibroblasts Migration
  (from users.ece.cmu.edu/~yuliwang/Videos/Migration/Durotaxis.html)
  - away from soft substrates (recording time, 138 min)
  - toward stiff substrates (recording time, 240 min)
  - toward stretching forces (recording time, 109 min)
  - away from compressing forces



- **Phototaxis = …. stronger light**

  Tetrahymena pyriformis
  (from www.youtube.com/watch?v=q_O7HTeLz0c)

- **Cromotaxis**

Chemotaxis and Cell Motion

EXTERNAL SIGNAL

shallow spatial gradients of extracellular chemotactic factor (~5%)

chemotactic factor binds to receptors

receptor activation mirrors shallow chemotactic gradient

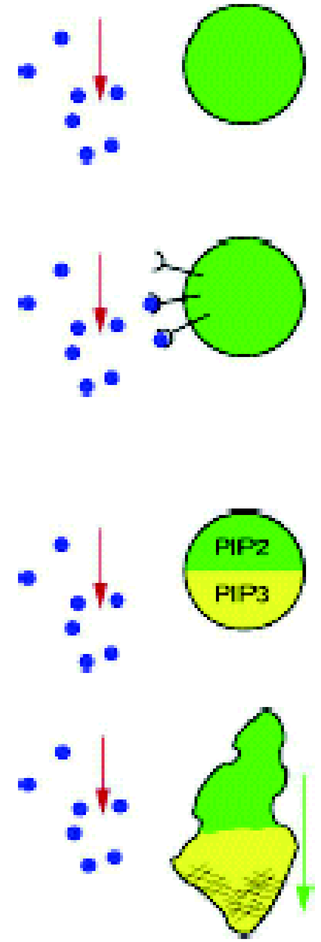
DIRECTIONAL SENSING

?

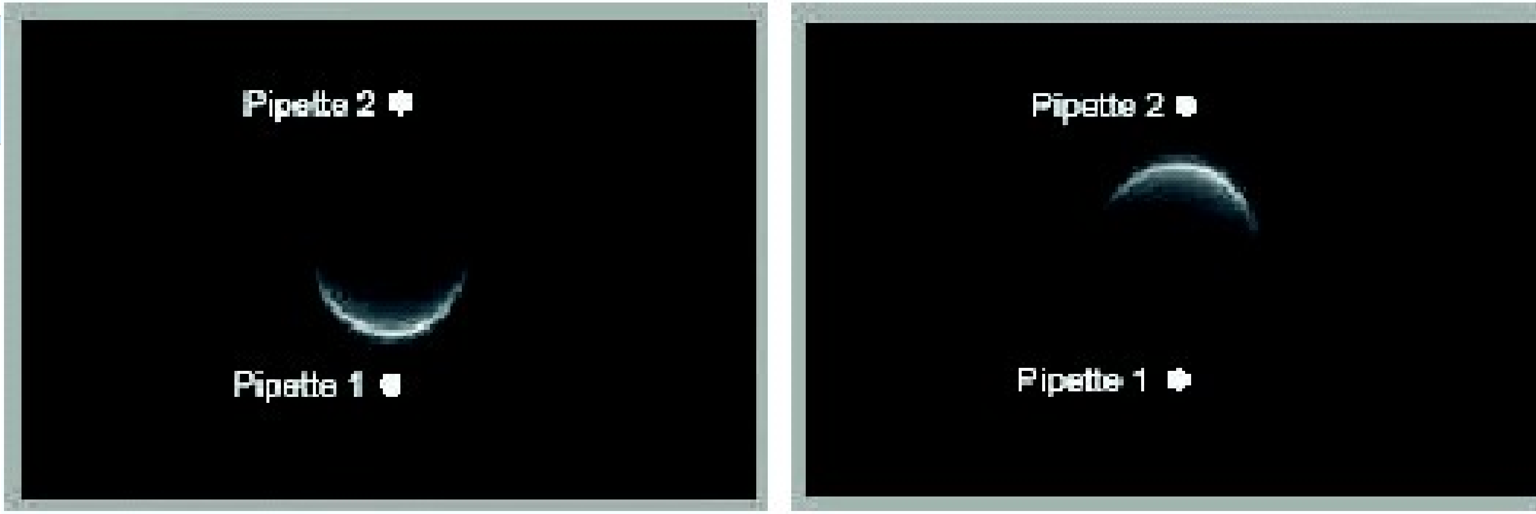
an "all or nothing" response is somehow generated

CELL POLARIZATION, DIRECTED MOTION

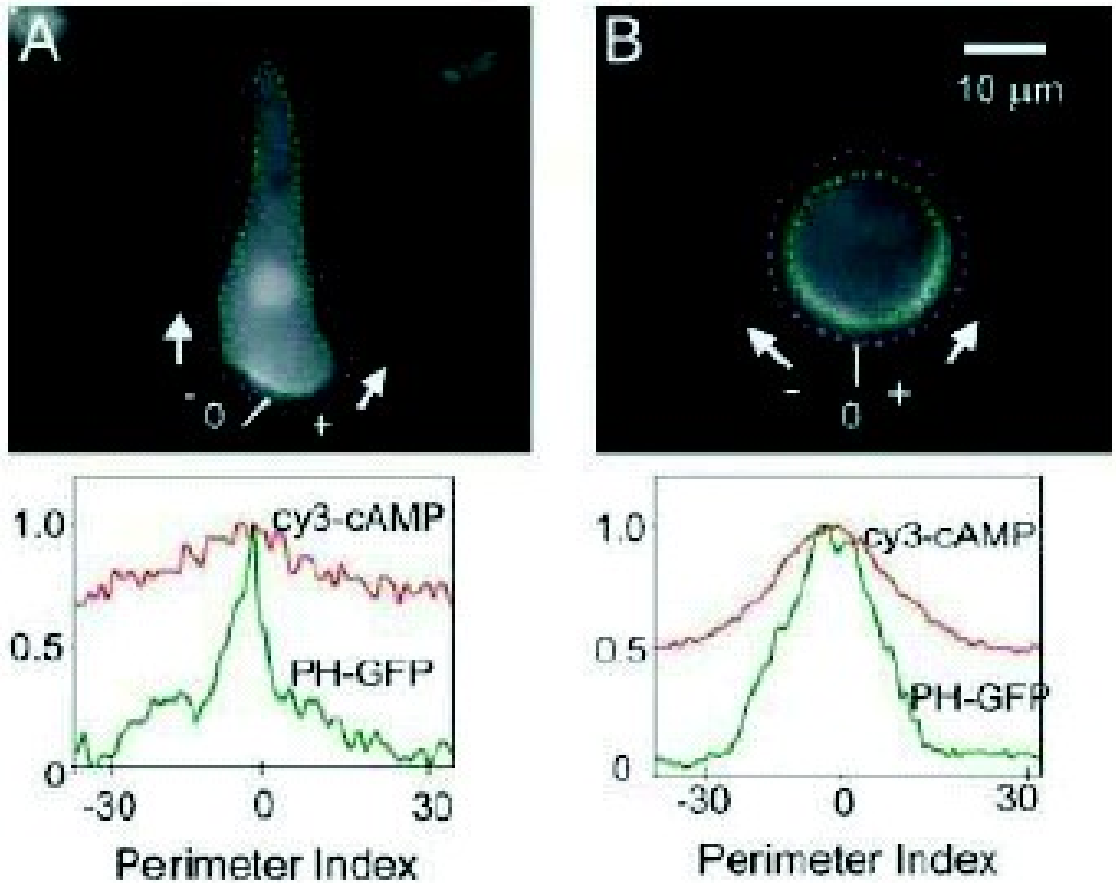
localized PIP3 patches induce actin polimerization



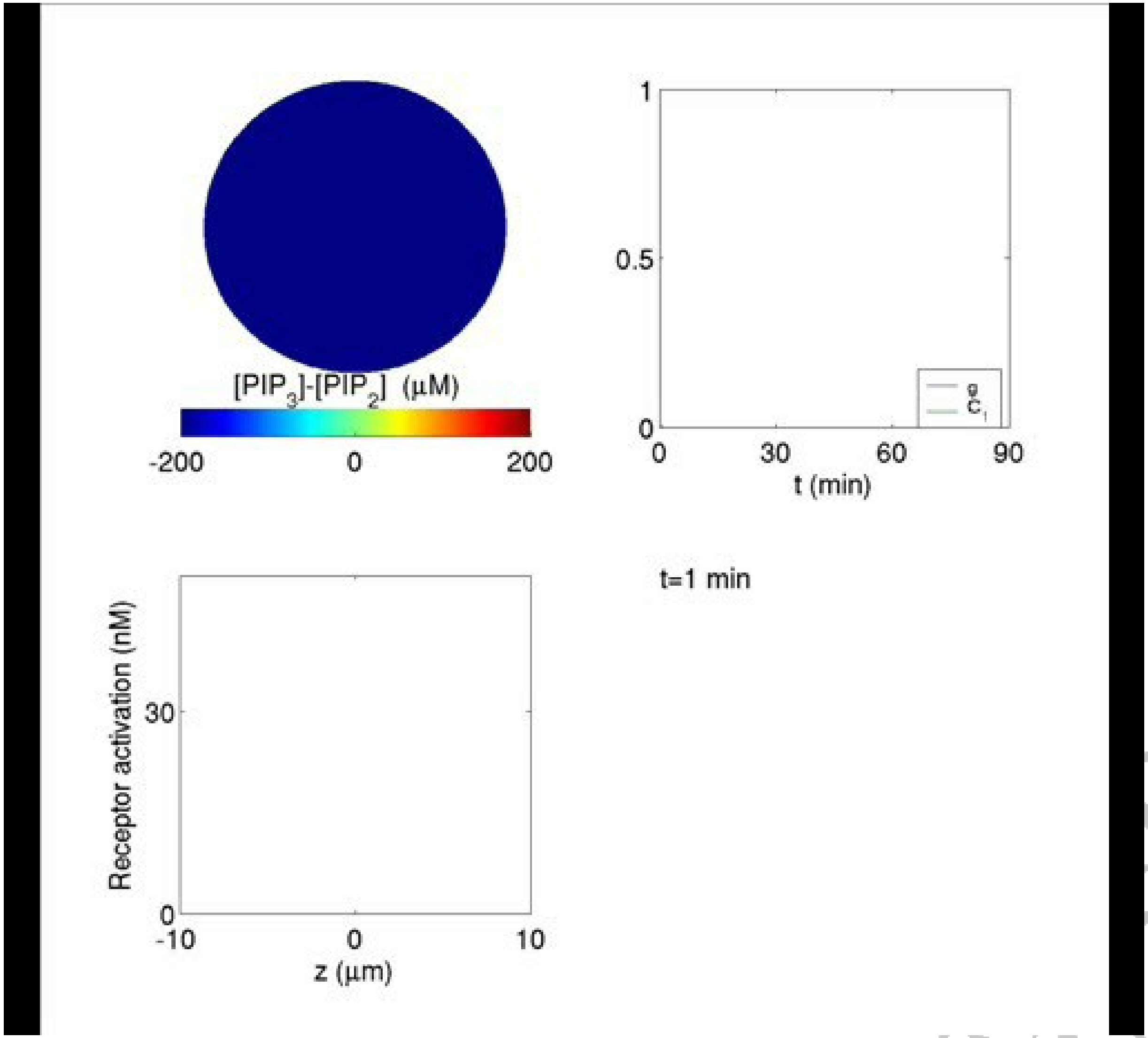
Devreotes, Janetopoulos



Janetopoulo, Ma, Devreotes , Iglesias



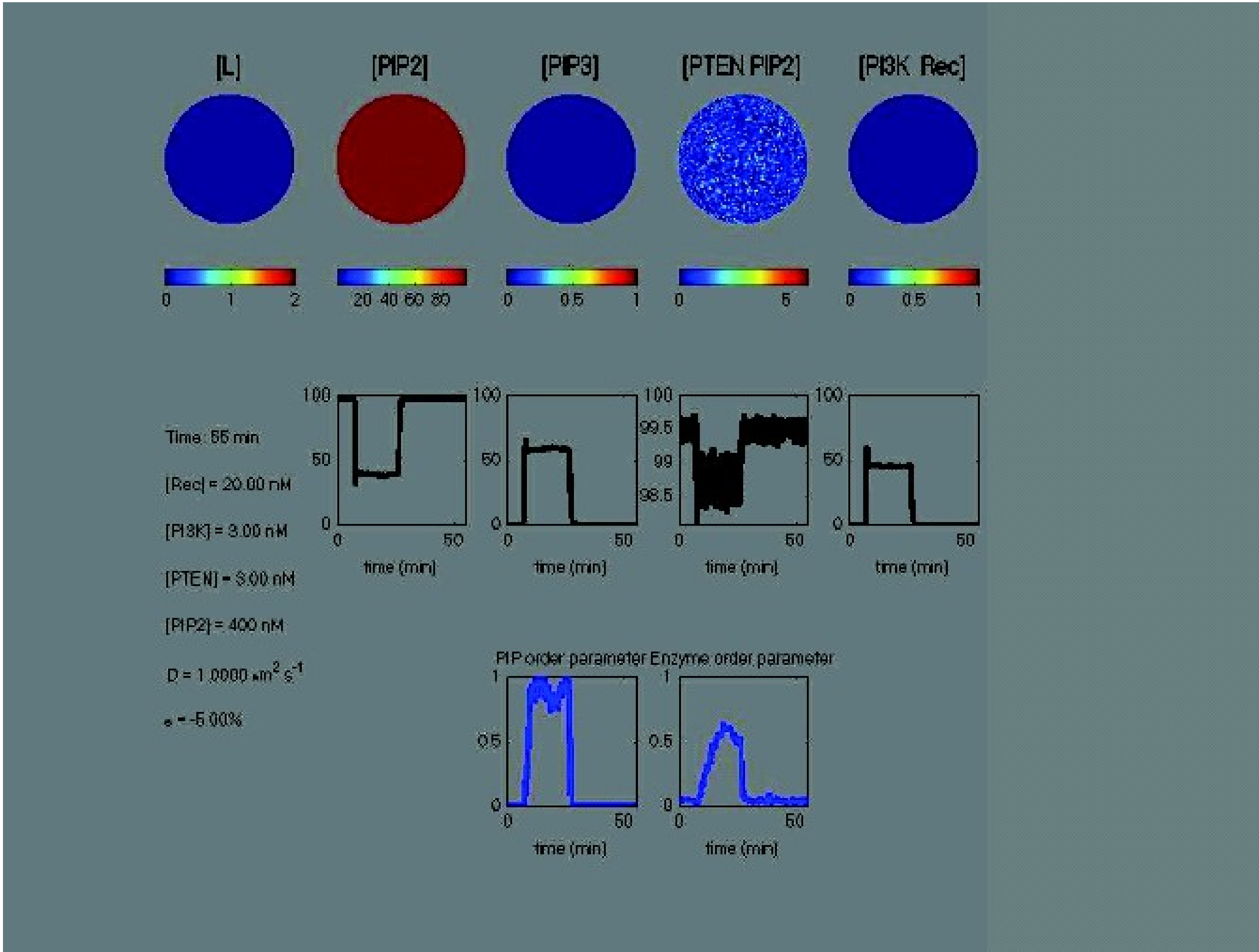
Polarization induced by phase transition



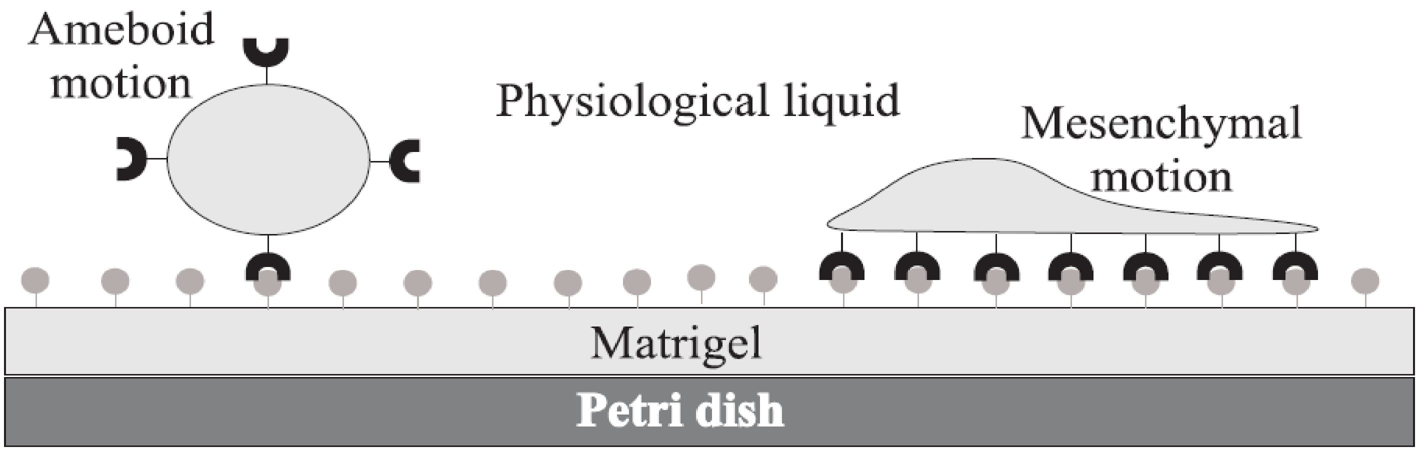
Gamba, Di Talia De Candia, PNAS (2005)

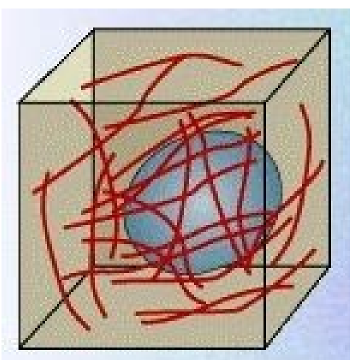
Original at www.pnas.org/content/102/47/16927/suppl/DC1#M1

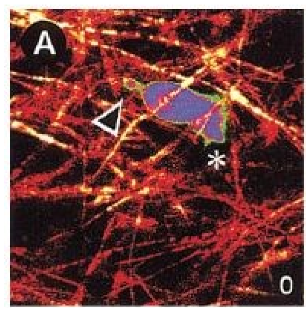
5% anisotropy in the chemotactic signal

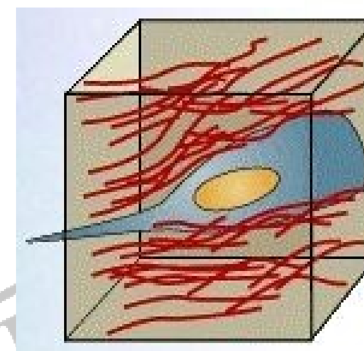


Types of motions





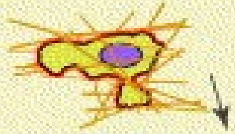
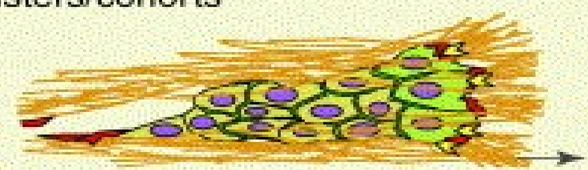
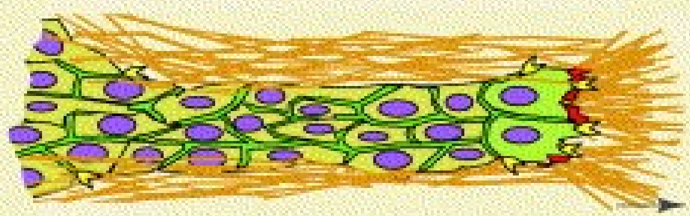




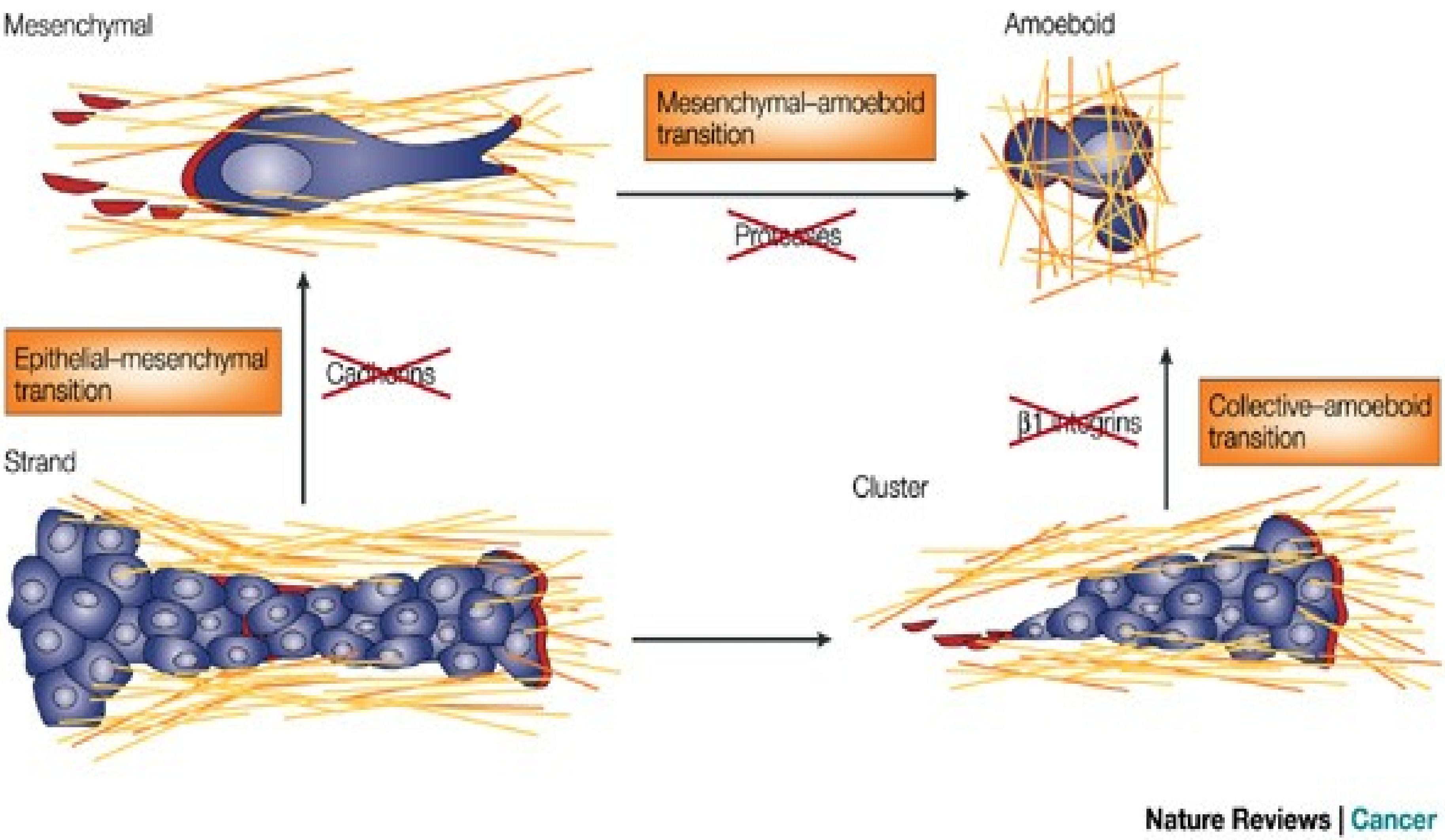
- high deformation of cells
- weak adherence to the surrounding tissue
- no degradation of the ECM
- high migration speed

- strong adherence
- ECM degradation by enzymes (MMP)
- fibers deformation and/or rupture
- low migration speed

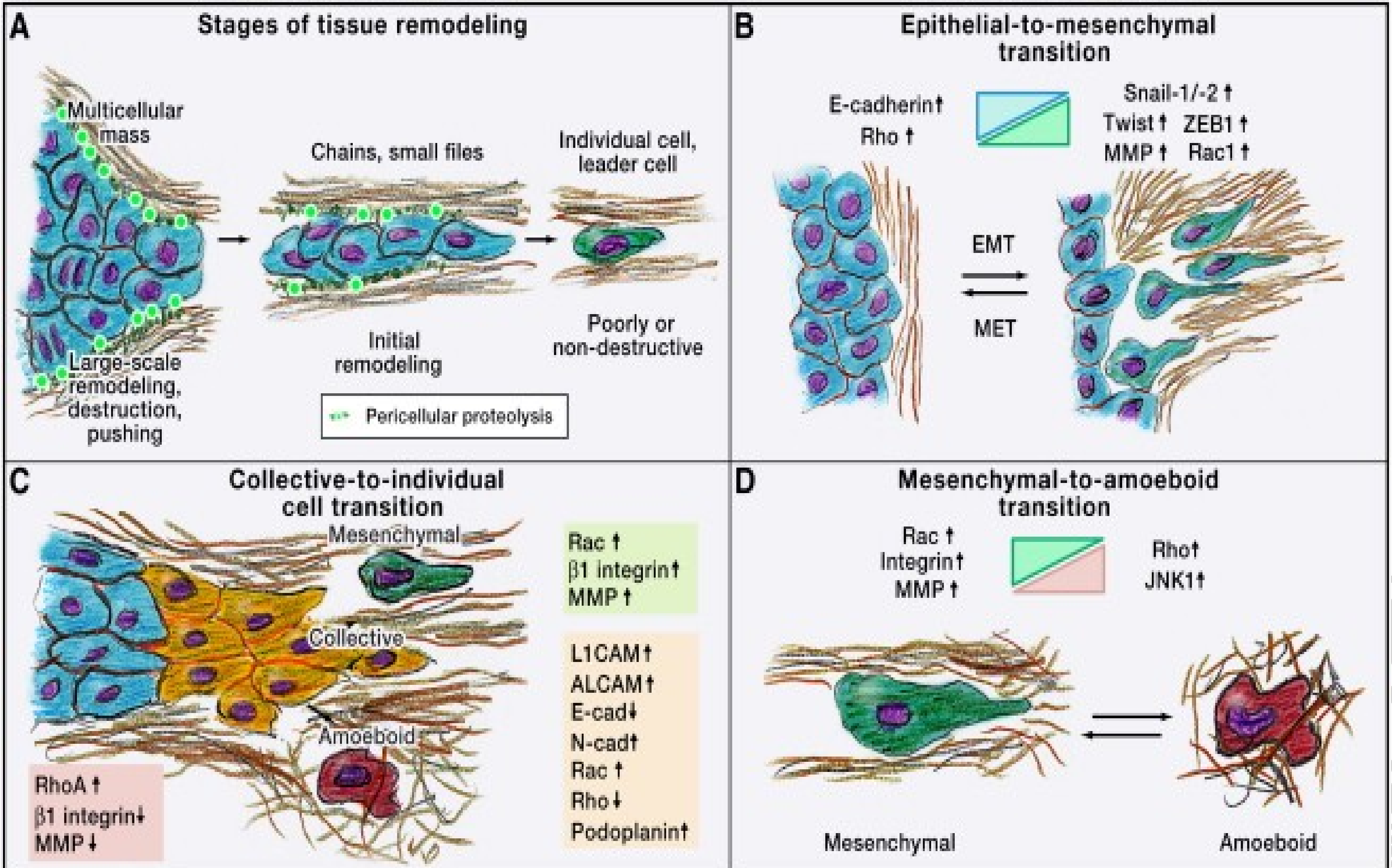
Types of motions

	Integrins	Proteases	Cadherins
(a) Amoeboid 	–/+	–/+	–
(b) Mesenchymal (single cells) 	+	+	–
(c) Mesenchymal (chains) 	+	+	–/+
(d) Clusters/cohorts 	+ +	+ +	+ +
(e) Multicellular sheets/strands 	+ +	+ +	+ +

Types of motions



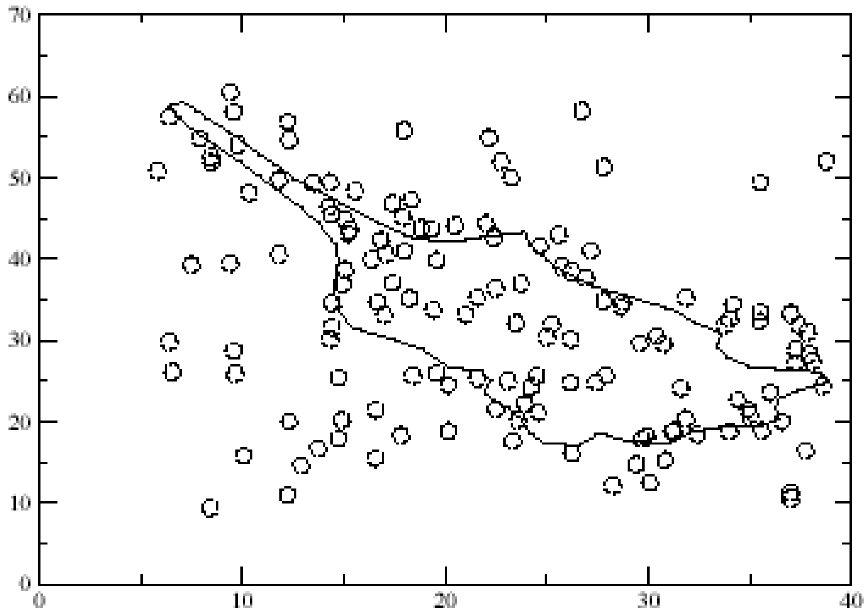
Types of motions



Understanding cell traction

deformation

Ω is the whole domain,
Ω_0 is the subdomain where u is measured,
Ω_c is the area covered by the cell.



D. Ambrosi
J.Math.Biol 58, 163 (2009)

(A. Cavalcanti)

Where in Ω_c the force is exerted?

Direct and Inverse Problem

The penalty functional $\mathcal{J} : \mathsf{F} \to \mathbb{R}^+$ *is defined as:*

$$\mathcal{J}(\mathrm{g}) = \frac{1}{2}\|\mathcal{O}\mathcal{S}\mathrm{g} - u_0\|_{\mathsf{X}}^2 + \frac{\varepsilon}{2}\|\mathrm{g}\|_{\mathsf{F}}^2.$$

Two coupled sets of elliptic partial differential equations to be solved in Ω,

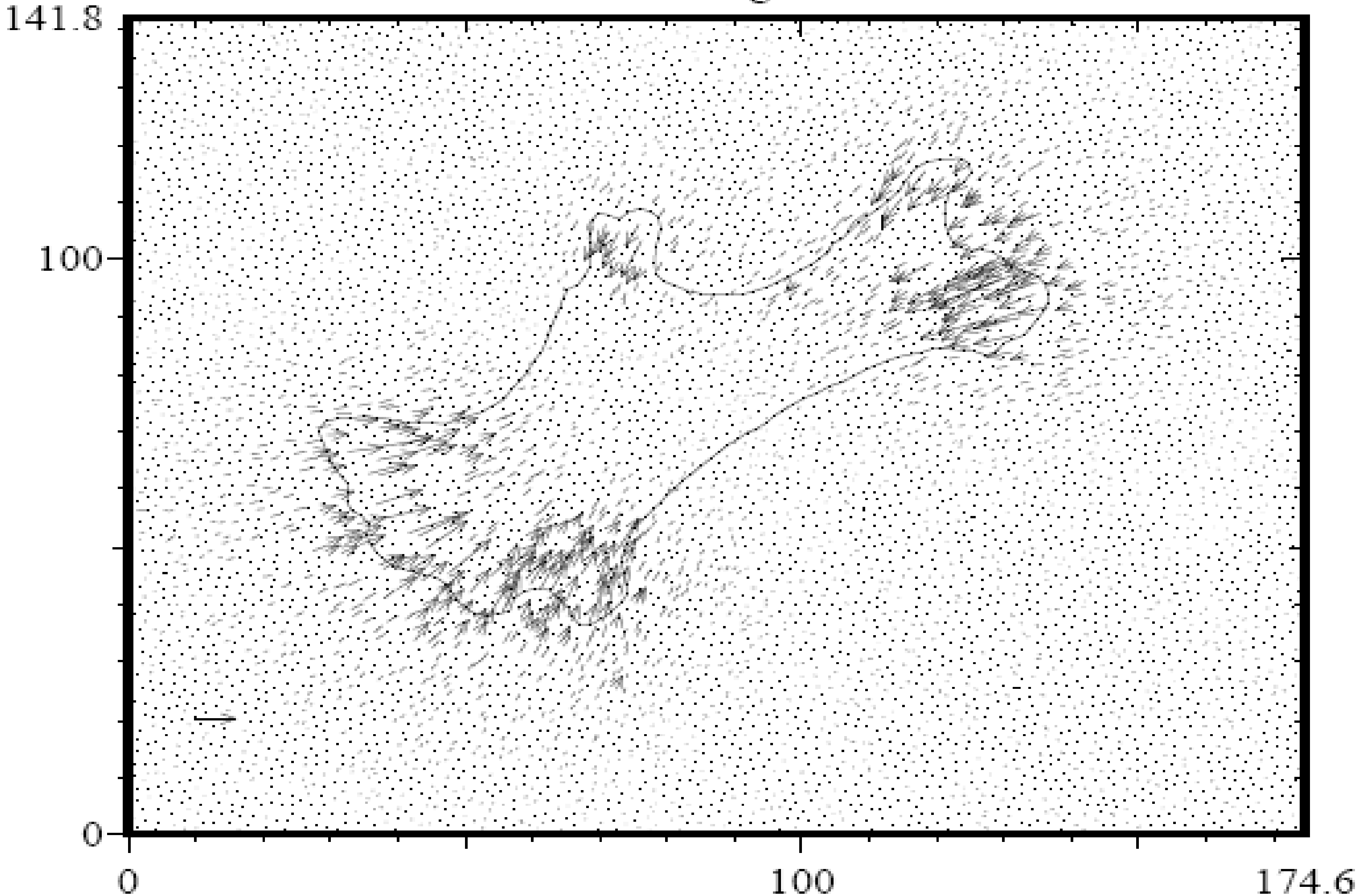
$$-\hat{\mu}\Delta\mathbf{u} - (\hat{\mu} + \hat{\lambda})\nabla(\nabla\cdot\mathbf{u}) = -\frac{\chi_c}{\varepsilon}\mathbf{p}, \qquad \mathbf{u}|_{\partial\Omega} = 0,$$

$$-\hat{\mu}\Delta\mathbf{p} - (\hat{\mu} + \hat{\lambda})\nabla(\nabla\cdot\mathbf{p}) = \chi_o\mathbf{u} - \mathbf{u}_0, \qquad \mathbf{p}|_{\partial\Omega} = 0.$$

where χ_c and χ_0 are the characteristic functions related to Ω_c and Ω_0, respectively.

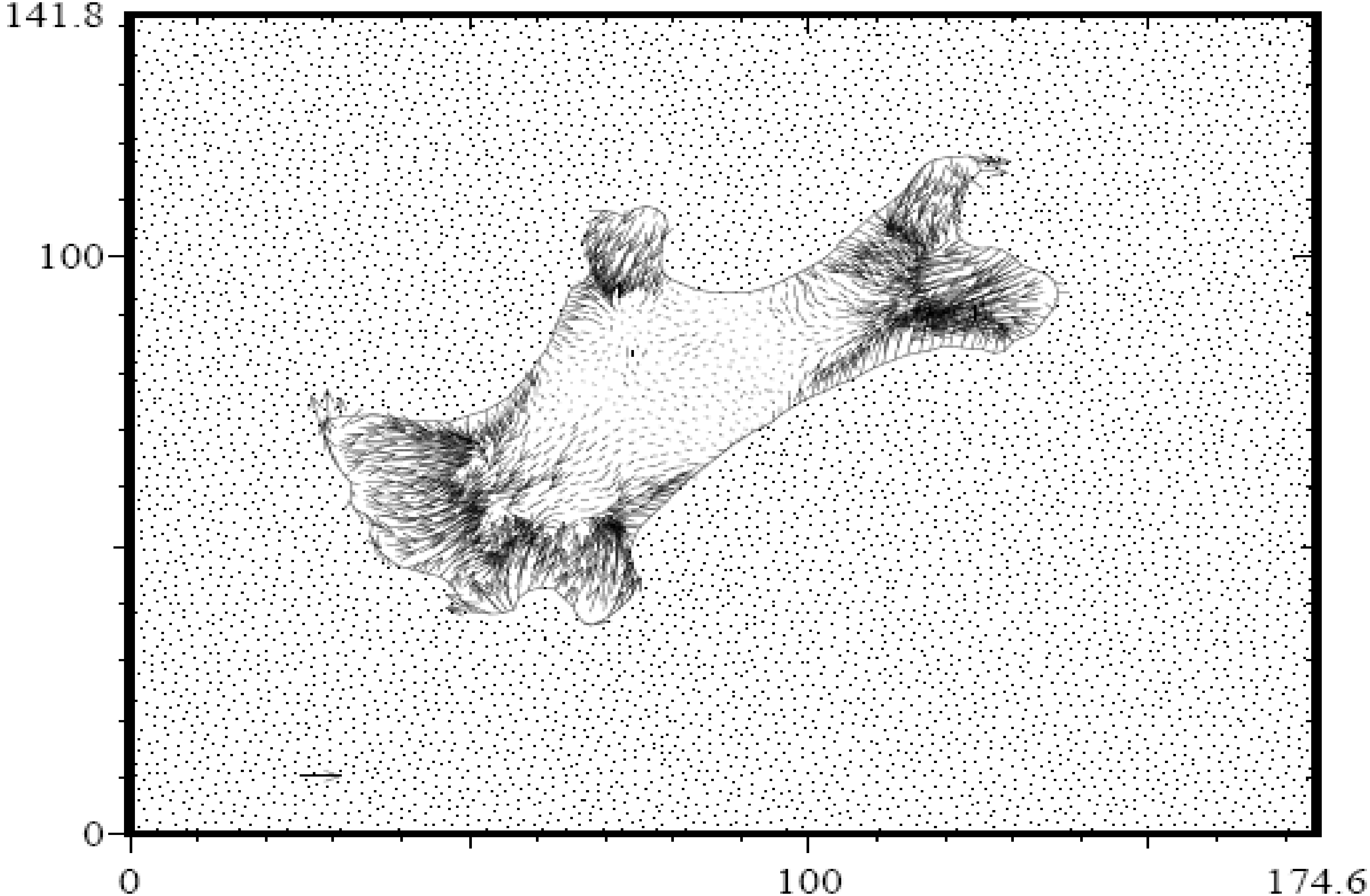
Measured displacement (microns)

reference arrow length = 1 microns

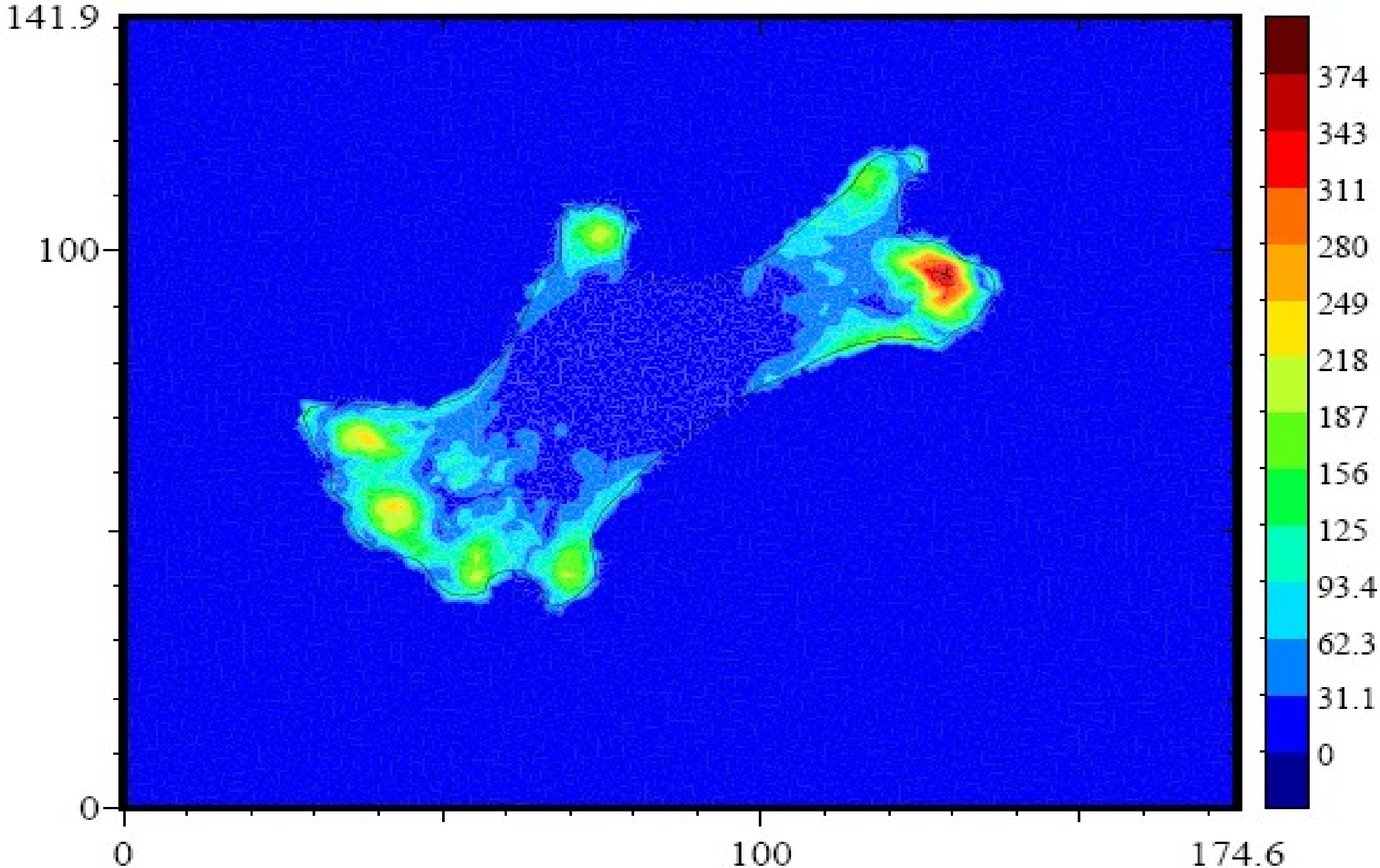


Force

arrow length = 10e2 picoNewton per micron square

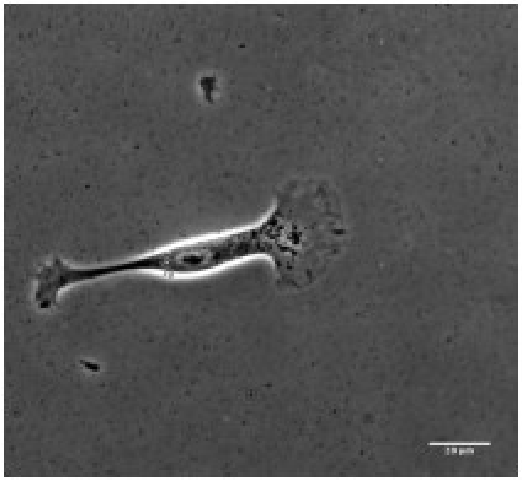


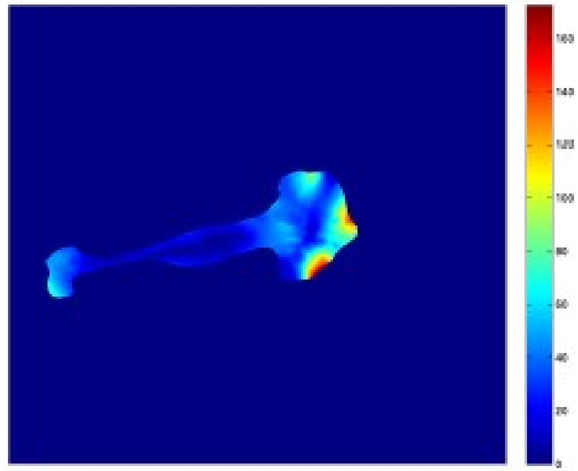
Force−magnitude



Cell Traction

V. Peschetola, V. Laurent, A. Duperray, L. Preziosi, D. Ambrosi, C. Verdier, Comp. Methods Biomech. Biomed. Engng. **14**, 159-160 (2011).





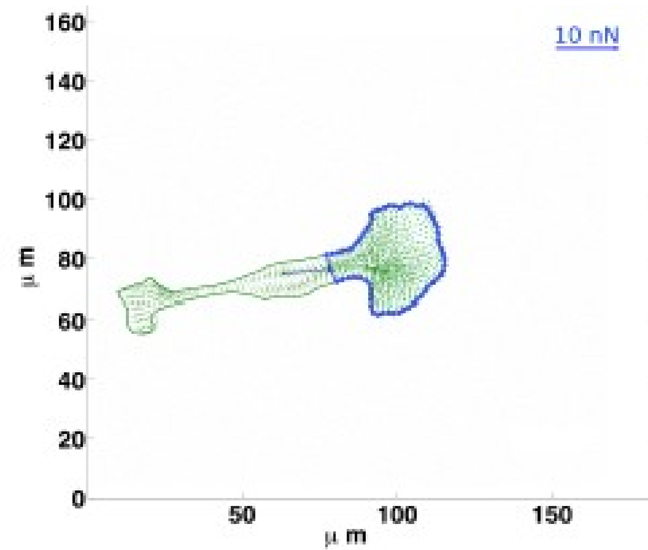
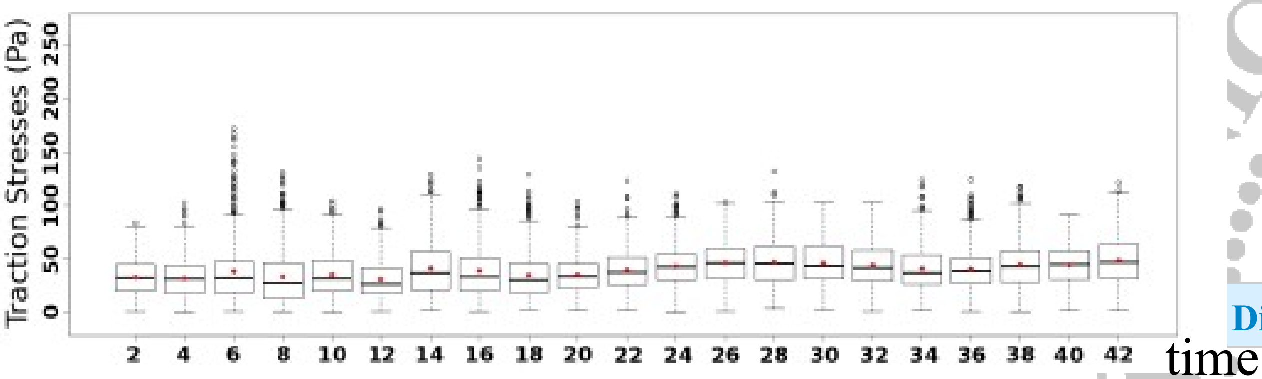
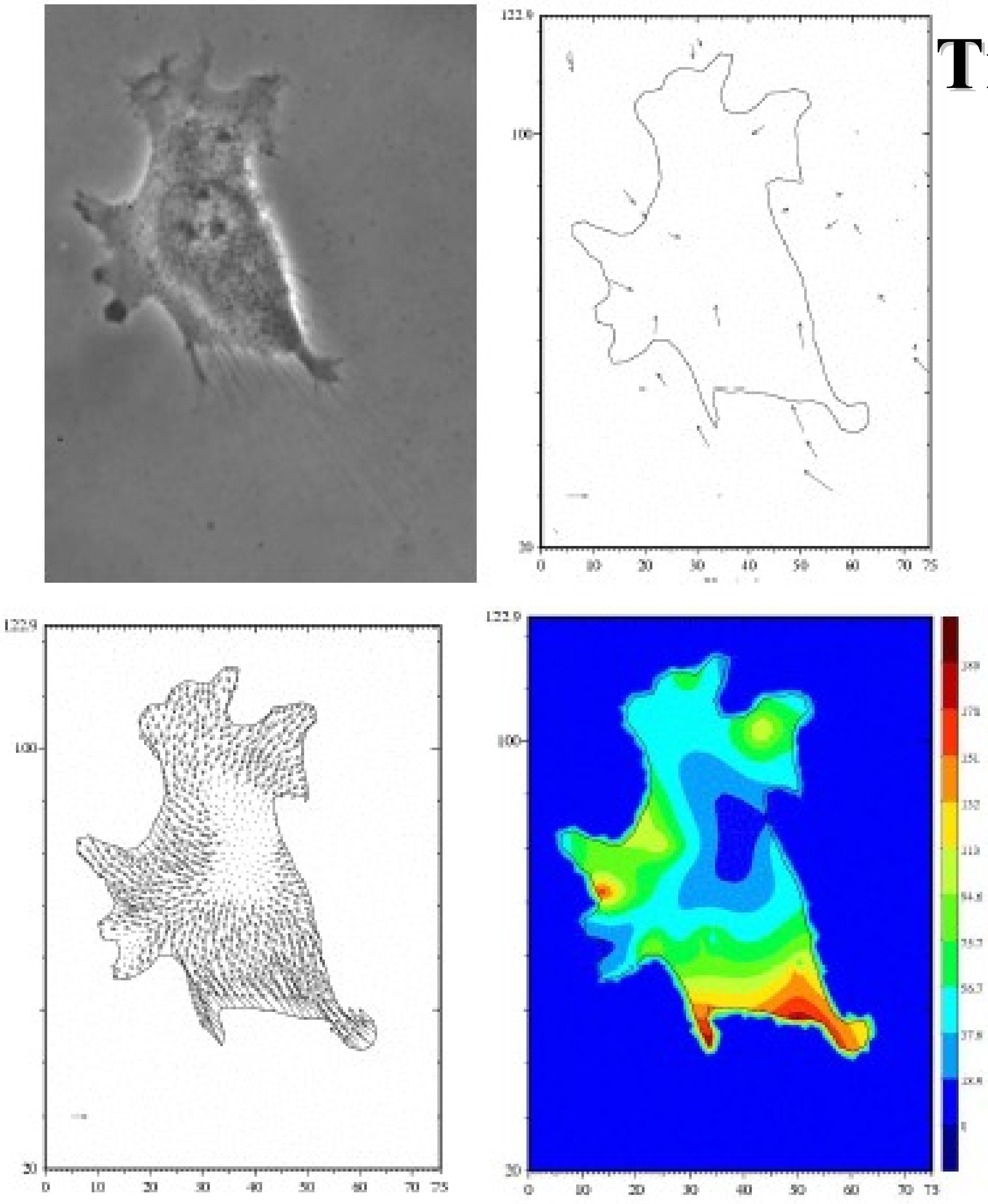


Figure 1: Phase–contrast image of a T24 cancer cell (at time $t = 6$ min from Fig. 2) and corresponding traction field of a T24 cell represented as a color map. The color scale for stresses reads in Pascal (Pa).



Dipartimento di Scienze Matematiche

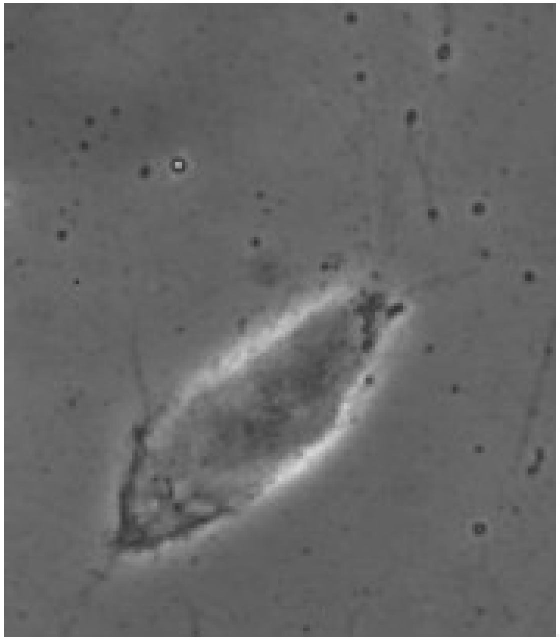
Traction on a stiff gel

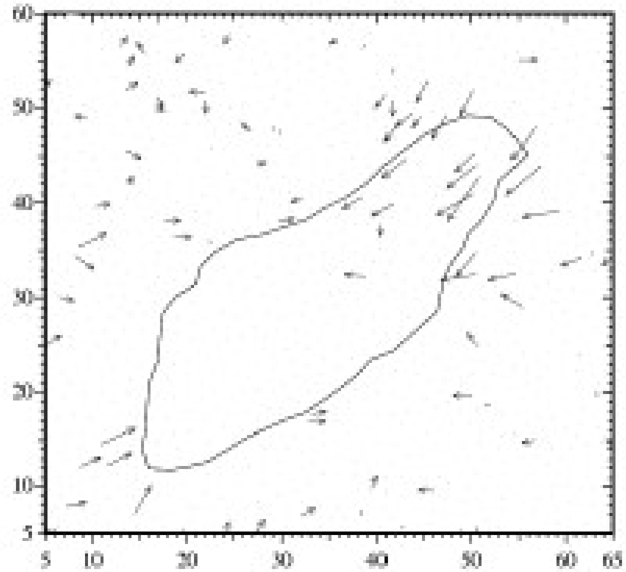


Ambrosi, Peschetola,Verdier
SIAM J. Appl. Math, (2006)

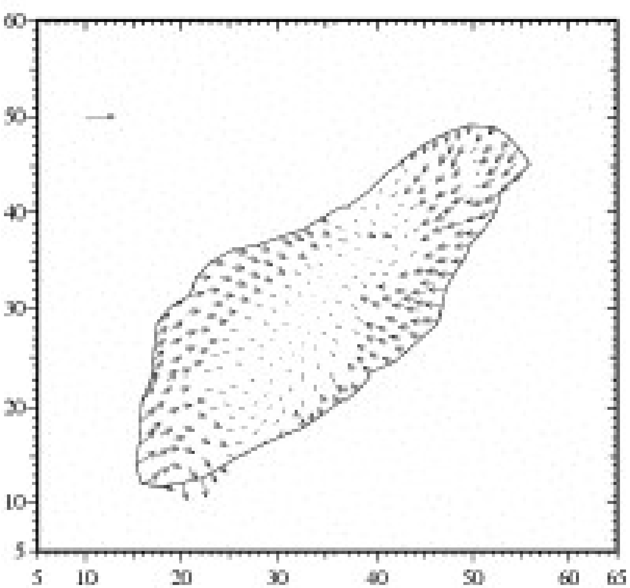
T24 cancer cells

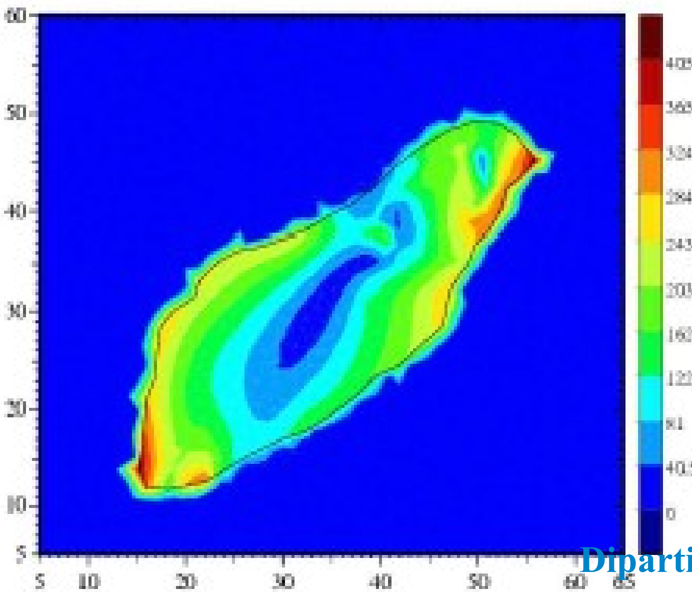
Traction on softer gel





T24 cancer cells





Conclusions

- **minor traction ability than fibroblasts**
- **larger forces on stiffer gels**

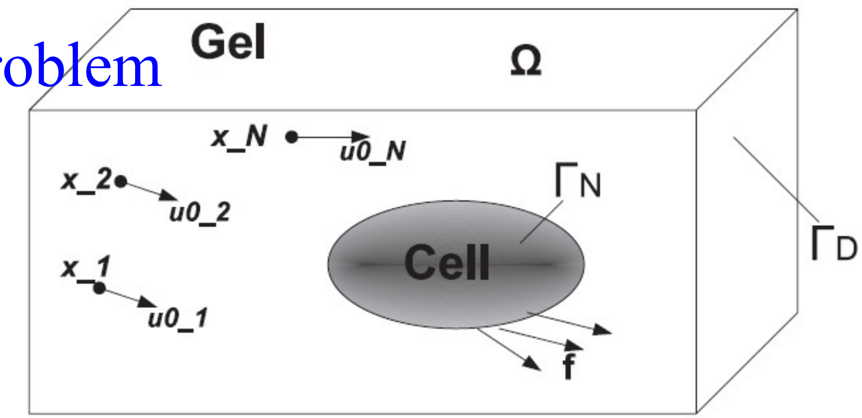
Traction in 3D

$$\mathcal{S}: \mathbf{f} \longrightarrow \mathbf{u} \begin{cases} -\nabla \cdot \mathbb{C}[\nabla \mathbf{u}] = 0, & \text{in } \Omega, \\ \mathbb{C}[\nabla \mathbf{u}]\mathbf{n} = \mathbf{f}, & \text{on } \Gamma_N, \\ \mathbf{u} = 0, & \text{on } \Gamma_D. \end{cases}$$

G. Vitale, D. Ambrosi, L.P.,
J. Math. Anal. Appl. **395**, 788-801 (2012).
Inverse Problems **28**, 095013 (2012)

Penalty function for the minimization problem

$$\mathcal{J}(\mathbf{f}) = \frac{1}{2}\|\mathcal{O}\mathcal{S}\mathbf{f} - u_0\|^2 + \frac{\varepsilon}{2}\|\mathbf{f}\|^2$$



Self-adjoint problem

$$\begin{cases} \displaystyle\int_\Omega (\mu \nabla \mathbf{u} \cdot \nabla \mathbf{v} + \lambda (\nabla \cdot \mathbf{u})(\nabla \cdot \mathbf{v})) + \frac{1}{\varepsilon}\left(\int_{\Gamma_N} \mathbf{p} \cdot \mathbf{v} - \frac{1}{|\Gamma_N|}\int_{\Gamma_N} \mathbf{p} \cdot \int_{\Gamma_N} \mathbf{v}\right) = 0, \\ \displaystyle\int_\Omega (\mu \nabla \mathbf{p} \cdot \nabla \mathbf{q} + \lambda (\nabla \cdot \mathbf{p})(\nabla \cdot \mathbf{q})) + \sum_{j=1}^{N} \delta_{\mathbf{x}_j} \mathbf{u} \cdot \delta_{\mathbf{x}_j} \mathbf{q} = \sum_{j=1}^{N} u_{0_j} \cdot \delta_{\mathbf{x}_j} \mathbf{q}, \end{cases}$$

Traction in 3D