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Multilevel mathematical models for cell migration in dense fibrous environments

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Take-home message and plan

- Stay away from the carpenter syndrome

"To a man with a hammer, everything looks like a nail"

- Look at the biomedical problem with no mathematical bias

Plan of the talk

- Take a phenomenon (migration in fibrous environments)
- Present several modelling frameworks to study the problem

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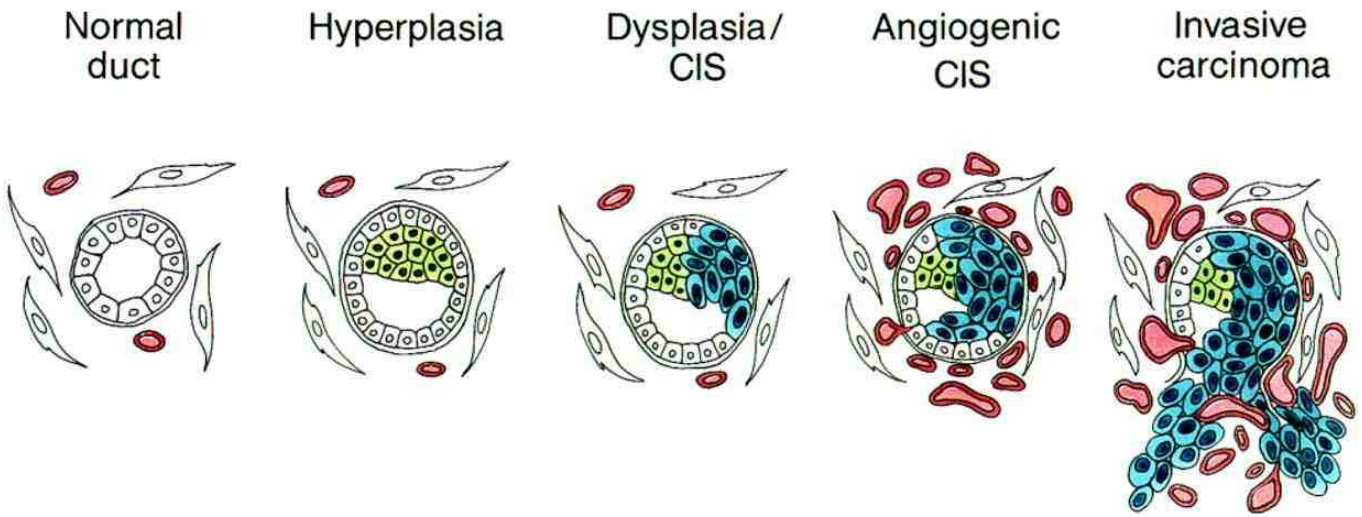
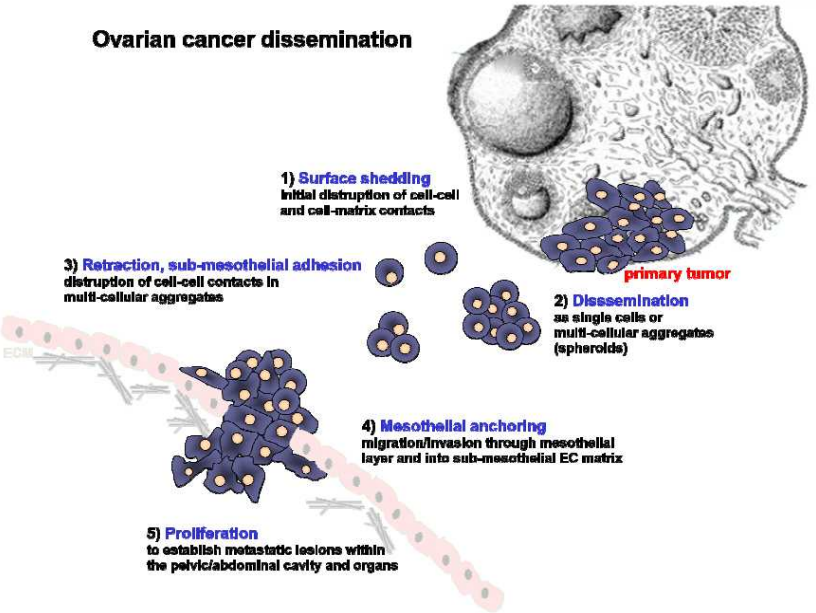
Tumour compartimentalization and invasion

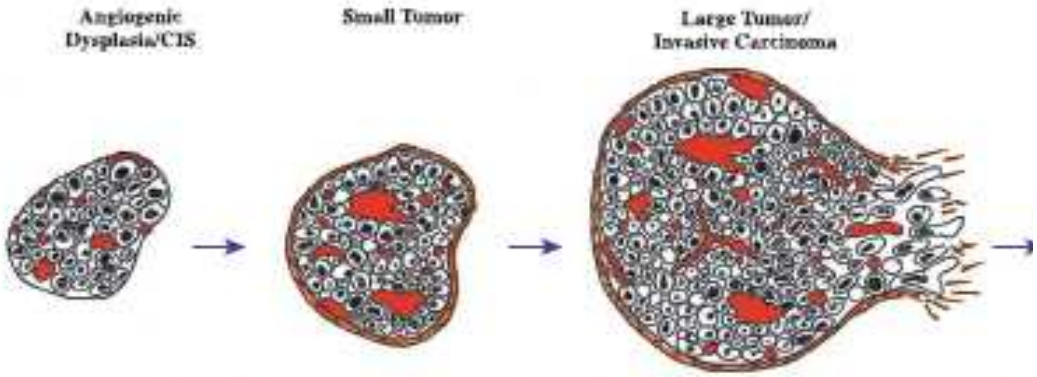


Breast

Ovary



Pancreas



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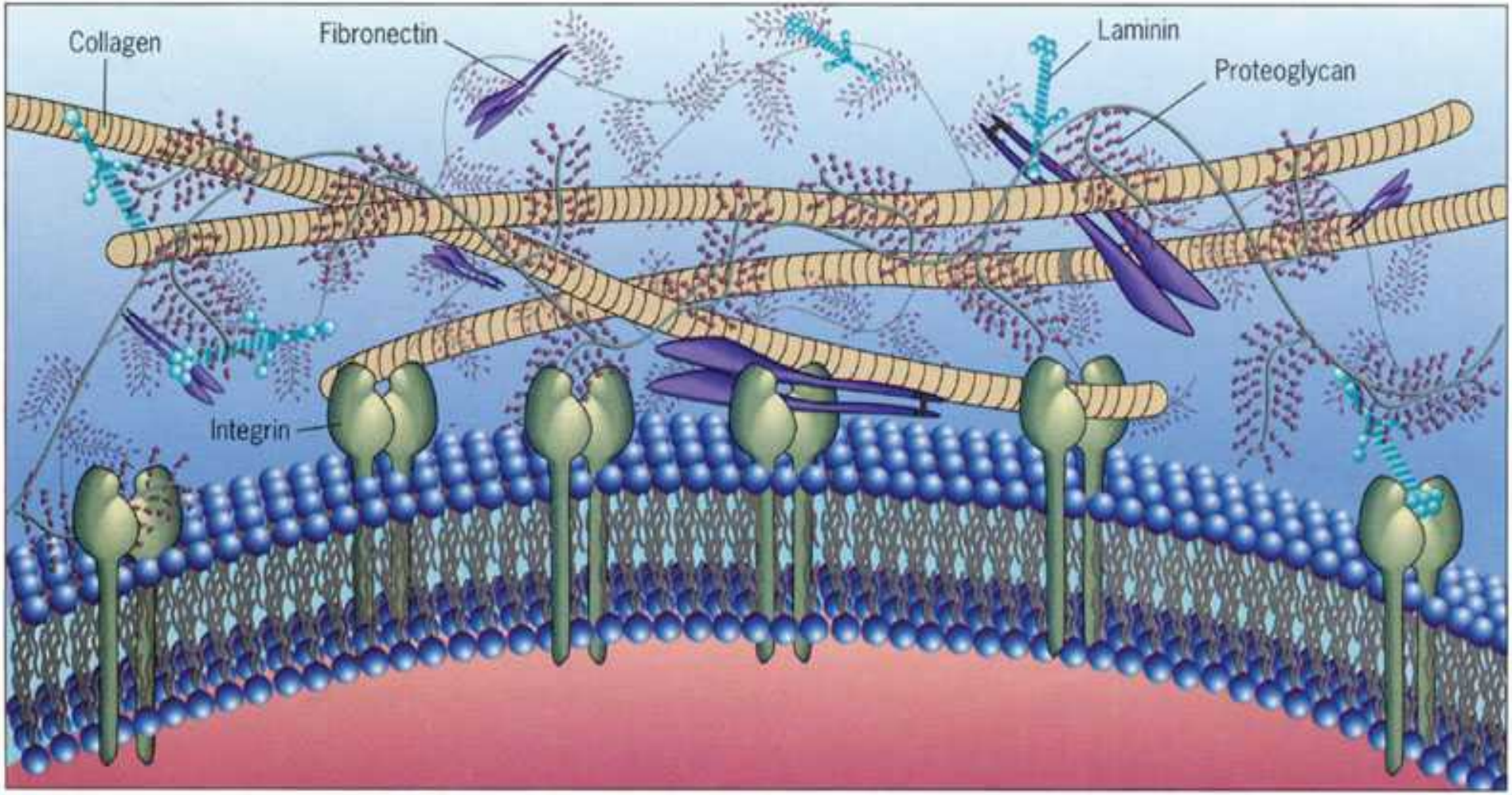
Extra-cellular matrix



video video

jcb.rupress.org/cgi/content/full/jcb.200209006/DC1

Extra-cellular matrix

Heart

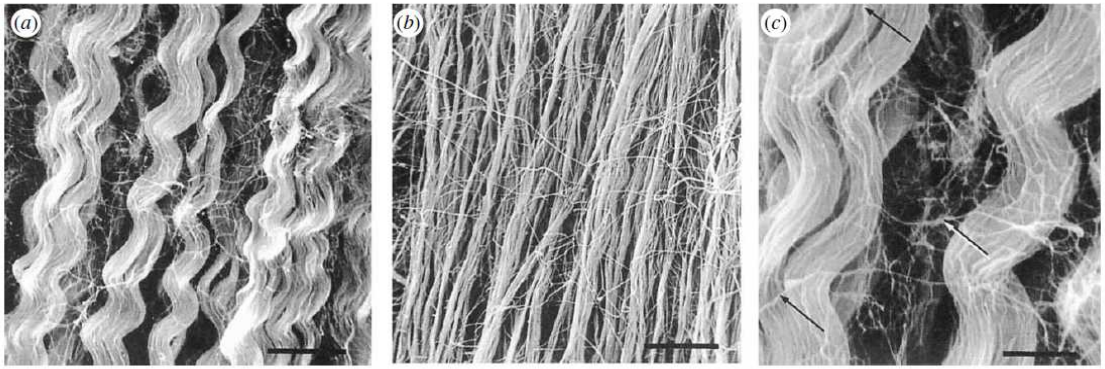
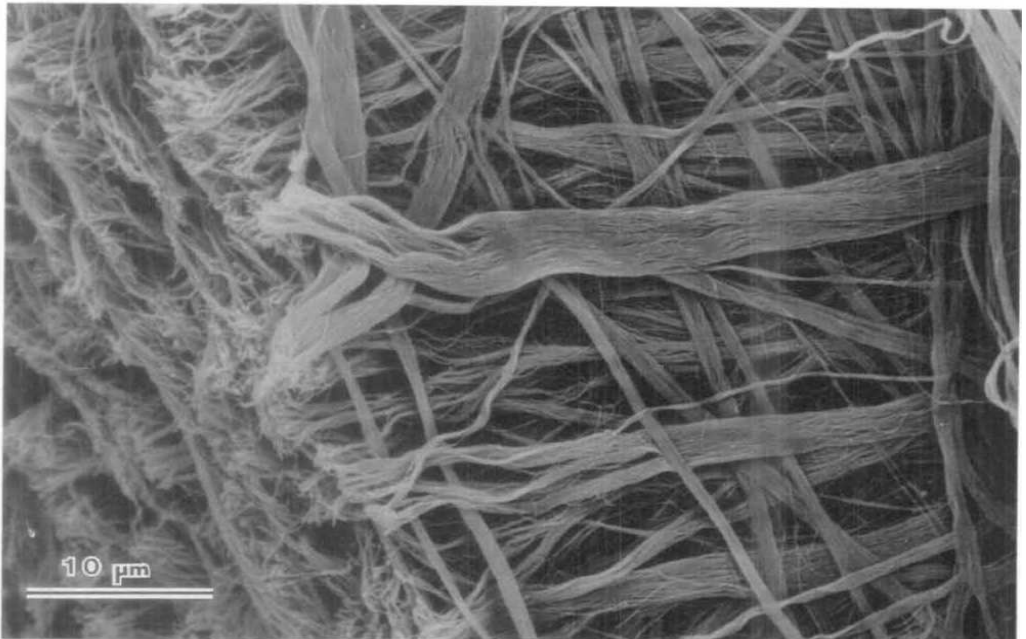
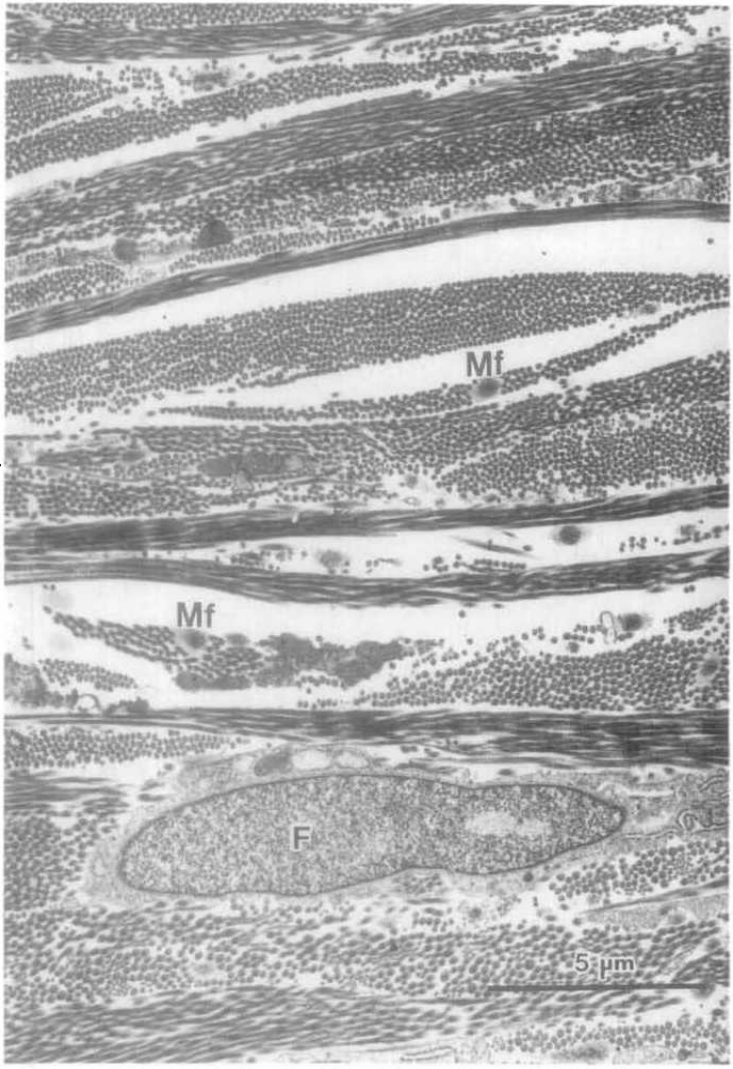


Figure 11. Electron micrograph of the arrangement of collagenous fibrils of the lamina radialis of an aortic valve leaflet at different magnifications. Arrows indicate non-directional fibrils surrounding helical arranged collagenous fibrils. (*a*,*b*) Scale bars, 8 µm and (*c*) 3 µm (adapted from Fastenrath 1995, p. 43).



Sclera



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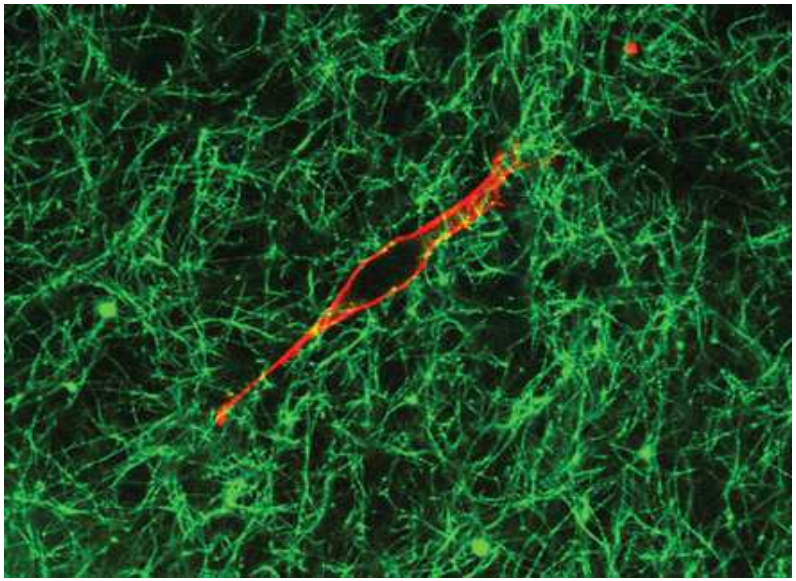
Cell motion in dense ECM

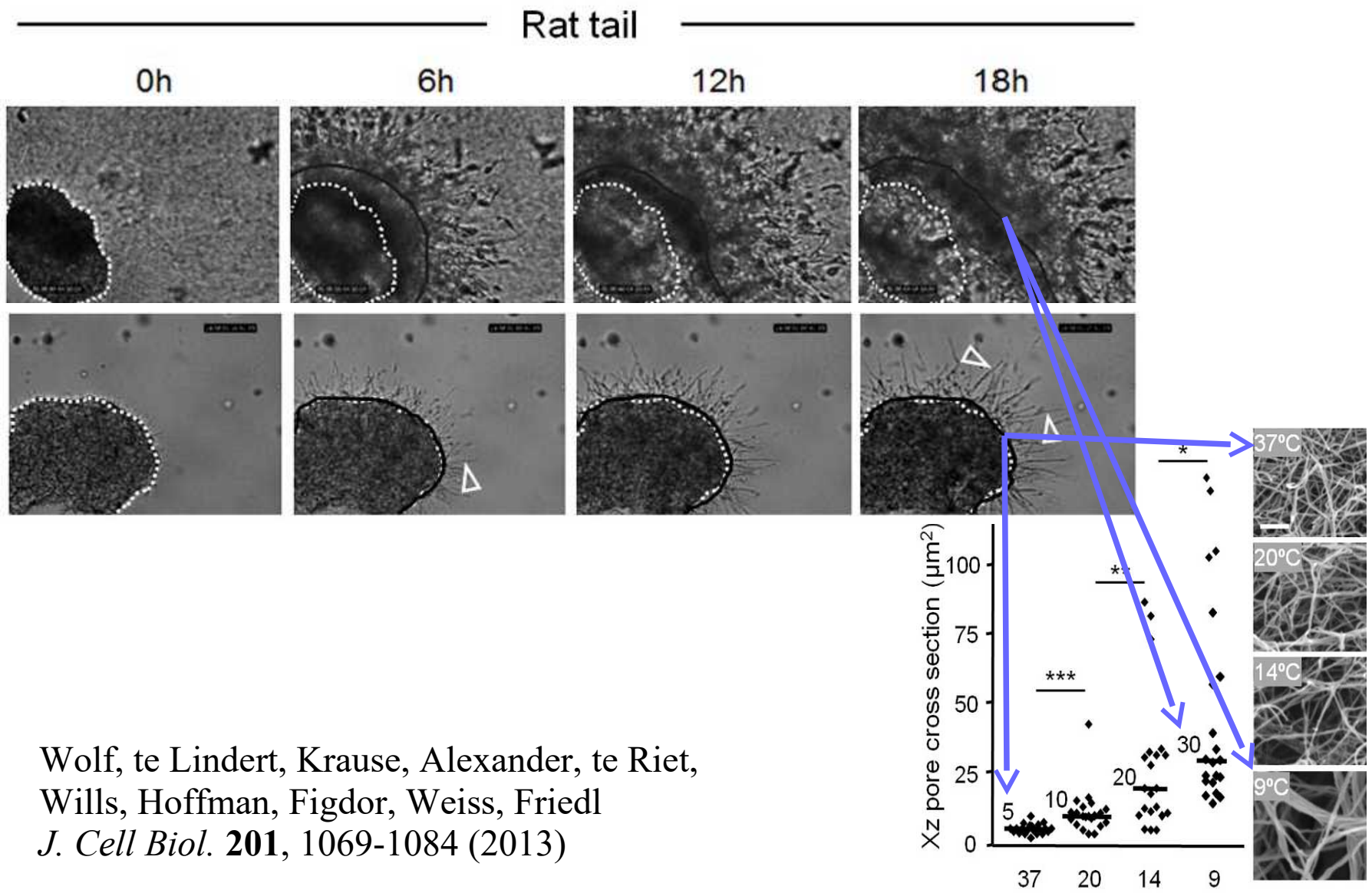


HT1080 migration in rat tail collagen (1.7 mg/ml) in presence of MMP inhibitor

Neutrophil migration in rat tail collagen (1.7 mg/ml) in presence of IL-8

(P. Friedl, K. Wolf)

Cell motion in dense ECM



Wolf, te Lindert, Krause, Alexander, te Riet, Wills, Hoffman, Figdor, Weiss, Friedl
J. Cell Biol. **201**, 1069-1084 (2013)

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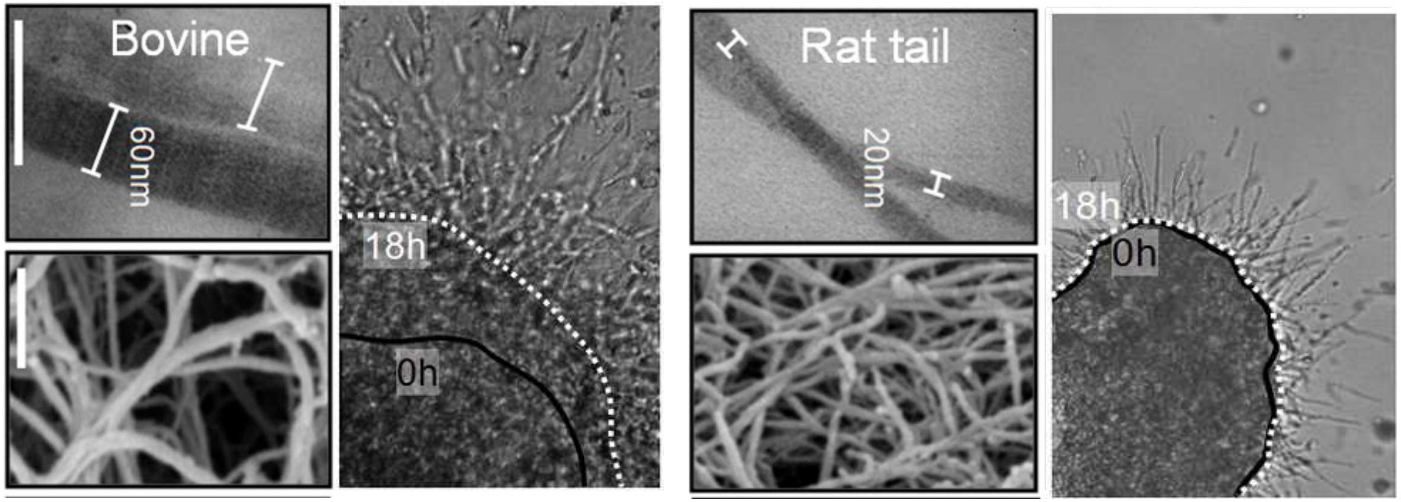
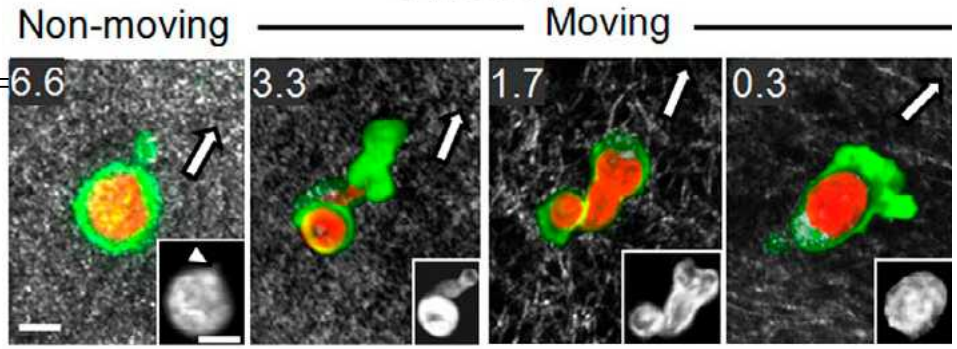
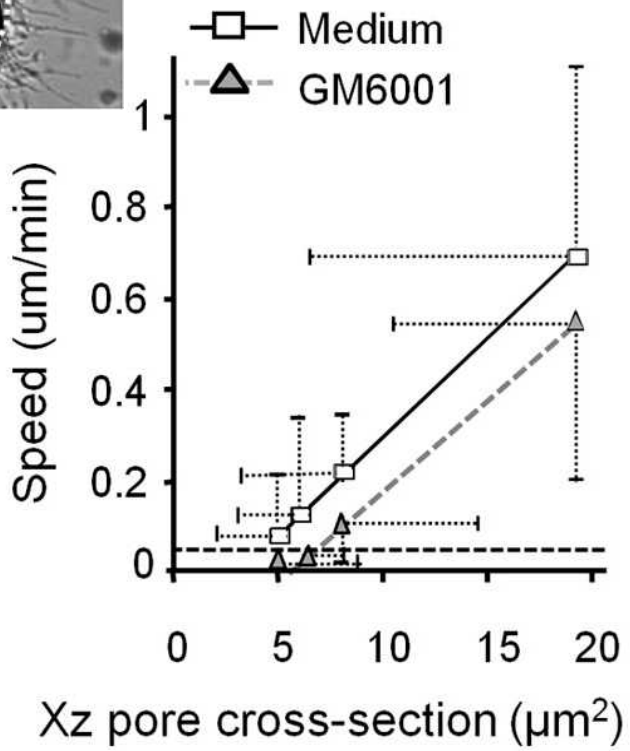
Cell motion in dense ECM



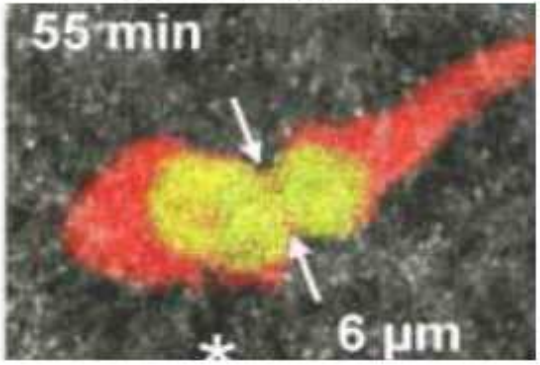
Collagen concentration =



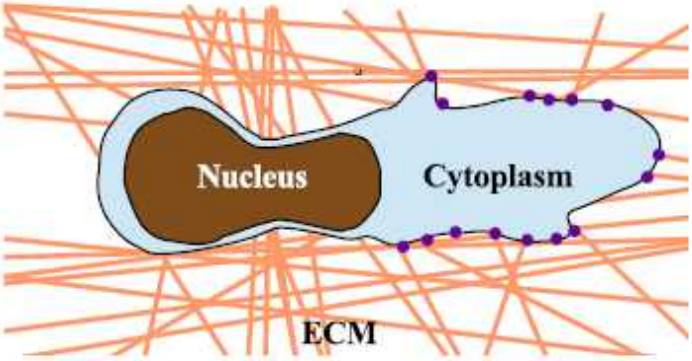


Taking into account of the nucleus

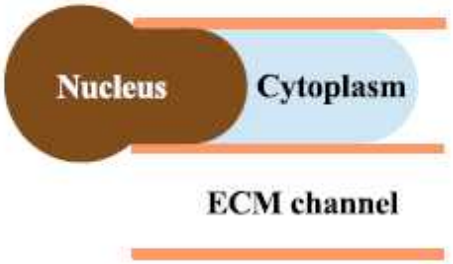
BIOLOGICAL EXPERIMENT



BIOLOGICAL REPRESENTATION



MATHEMATICAL REPRESENTATION



Work done by traction > Energy required to squeeze the nucleus

C. Giverso & L.P., *Biomech. Model. Mechanobiol.* **13**, 481-502 (2014)
C. Giverso, A. Arduino & L.P., *Bull. Math. Biol.* (2018)

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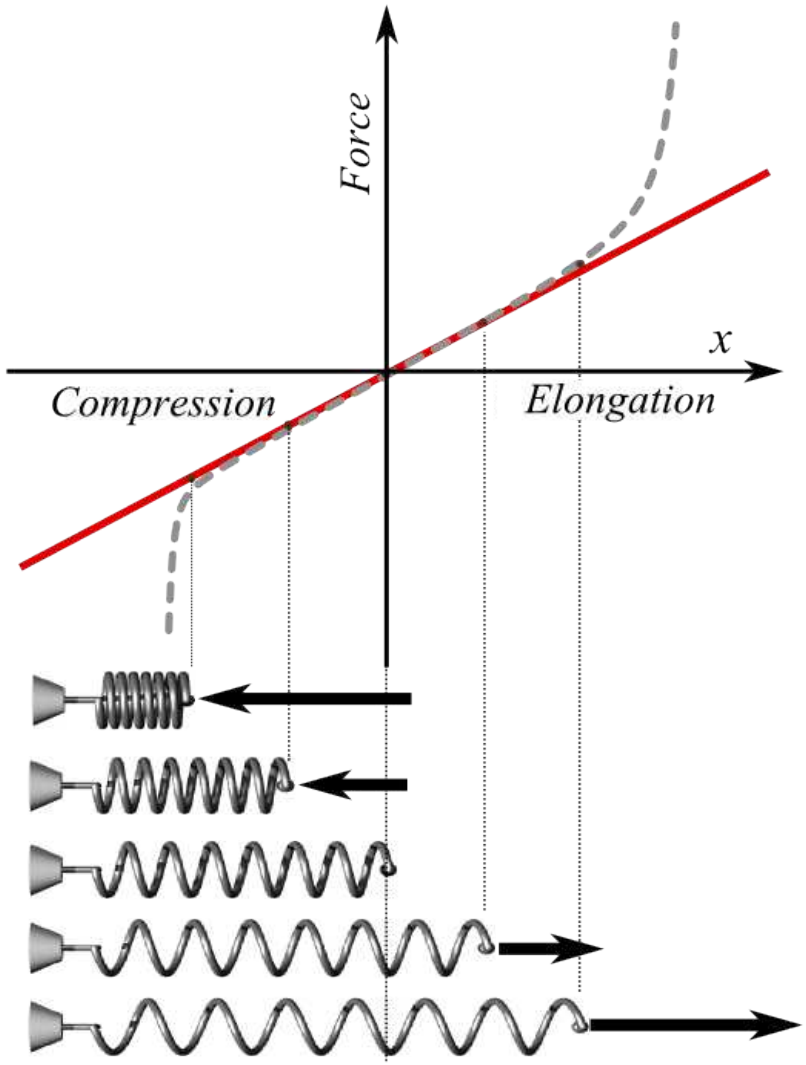
Taking into account of the nucleus



The force field is conservative

⇕

The work is independent on the path

⇕

There exists a potential energy

$$U(\mathbf{x})$$

related to the elastic force **f** by

$$\mathbf{f} = -\nabla U$$

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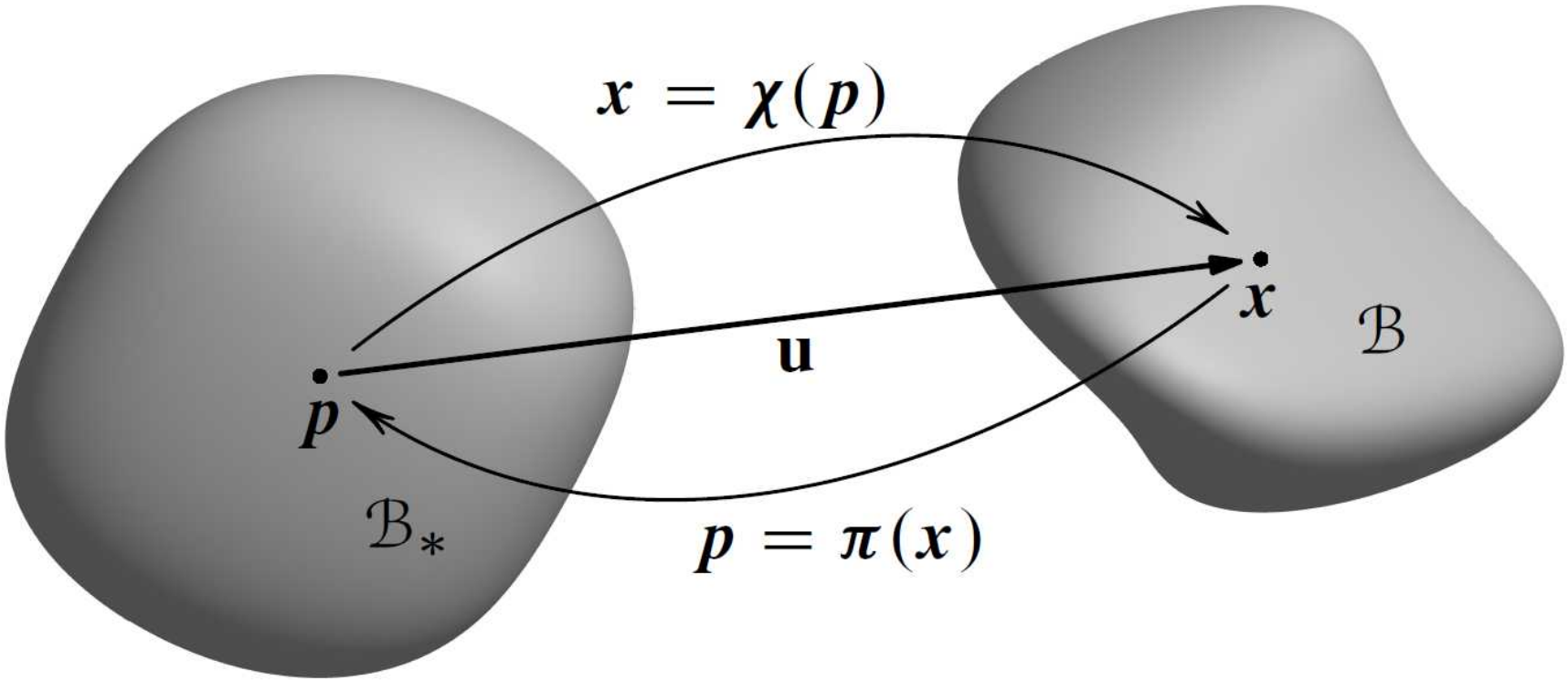
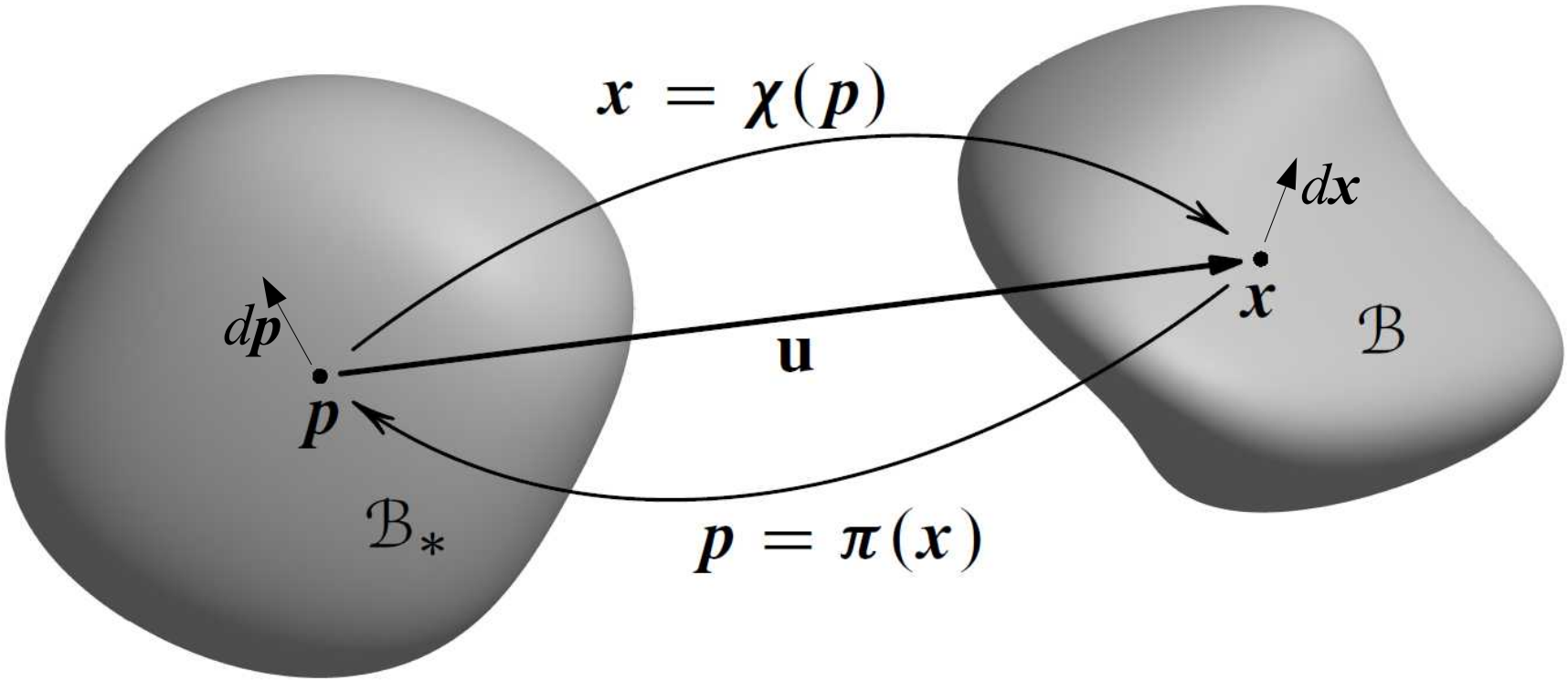
Continuum mechanics in a nutshell



Continuum mechanics in a nutshell

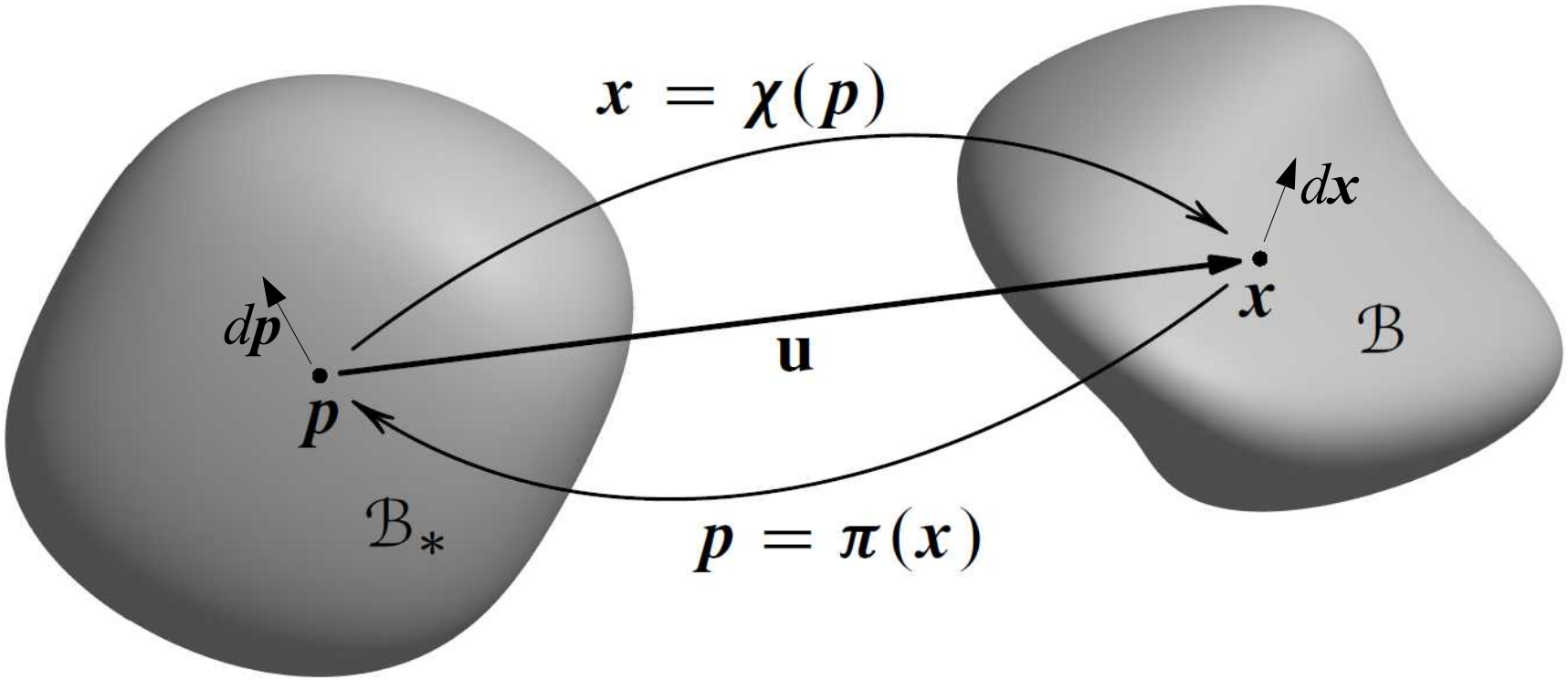


$$dx = \mathbf{F}\, dp$$

$$F_{iK} = \frac{\partial \chi_i}{\partial X_K}$$

Deformation gradient

Continuum mechanics in a nutshell



$$dx = \mathbf{F}\, dp$$

Cauchy-Green deformation tensor

$$|d\mathbf{X}|^2 = d\mathbf{x} \cdot \mathbf{B}^{-1} d\mathbf{x} \qquad \mathbf{B} = \mathbf{F}\mathbf{F}^T$$

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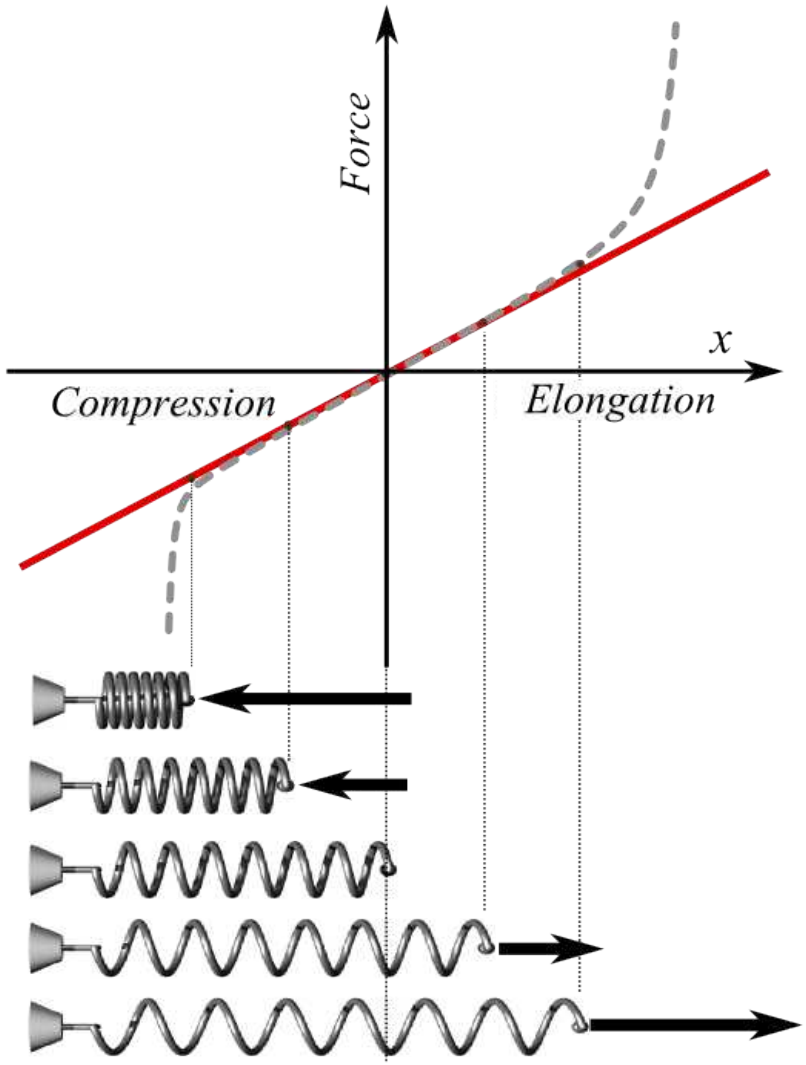
Taking into account of the nucleus



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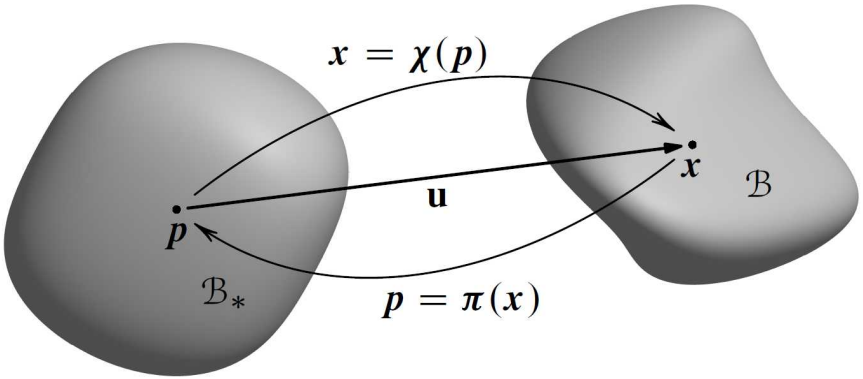


The force field is conservative

The work is independent on the path

There exists a potential energy

$$W(\mathbf{F}) = \rho_* \sigma(\mathbf{F})$$

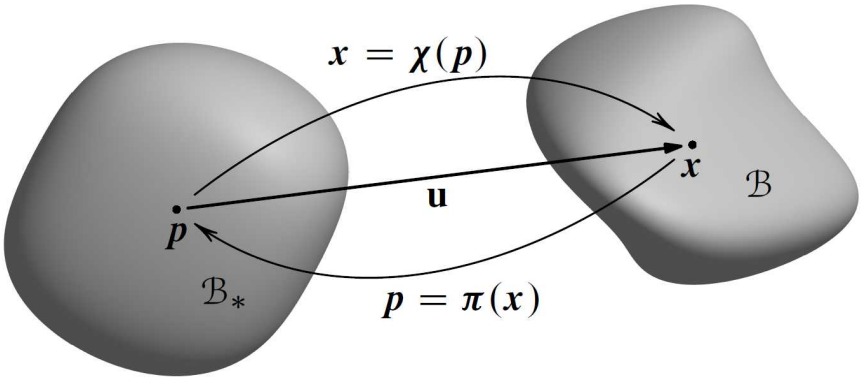
related to the Piola stress tensor **S** by

$$\mathbf{S} = \frac{\partial W}{\partial \mathbf{F}}$$

and related to the Cauchy stress tensor **T** by

$$\mathbf{T}(\mathbf{F}) = \rho \frac{\partial \sigma}{\partial \mathbf{F}} \mathbf{F}^T$$

Continuum mechanics in a nutshell



The force field is conservative

⇕

The work is independent on the path

⇕

There exists a potential energy

$$W(\mathbf{F}) = \rho_* \sigma(\mathbf{F})$$

Frame indifference + isotropy ⇒ $\sigma = \bar{\sigma}(\mathrm{I}_\mathbf{B}, \mathrm{II}_\mathbf{B}, \mathrm{III}_\mathbf{B})$

e.g., neo-Hookean material $W(\mathrm{I}_\mathbf{B}) = \dfrac{\mu}{2}(\mathrm{I}_B - 3)$

Gent material $W(\mathrm{I}_\mathbf{B}) = -\dfrac{\mu}{2} K \ln\left(1 - \dfrac{\mathrm{I}_B - 3}{K}\right)$

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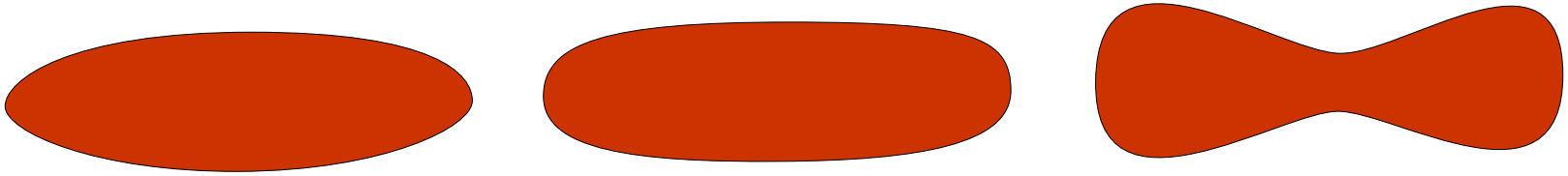
Computing the energy required

Work done by traction > Energy required to squeeze the nucleus

- Given the deformation **F**



- Given the constitutive equation *W*

- Compute **B** and then, for instance, $W(\mathrm{I_B}) = \frac{\mu}{2}(\mathrm{I}_B - 3)$

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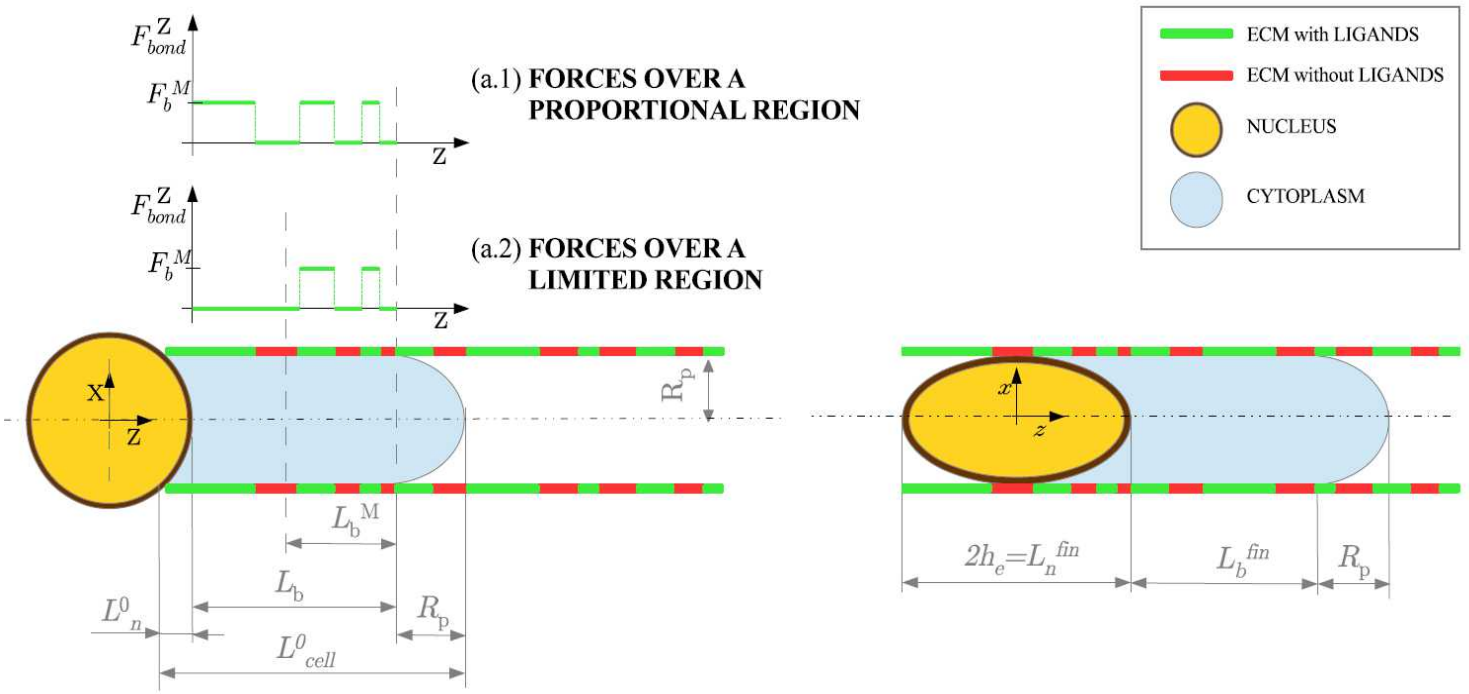
Computing the work done by traction

Work done by traction > Energy required to squeeze the nucleus



$$\mathbf{F}_{adhesion} = \int_S \rho_b(\mathbf{X})\alpha_{ECM}(\mathbf{X})\mathbf{F}_{bond}(\mathbf{X})dS$$

$$\mathcal{W}_{adhesion} = F^Z_{adhesion}\Delta L$$

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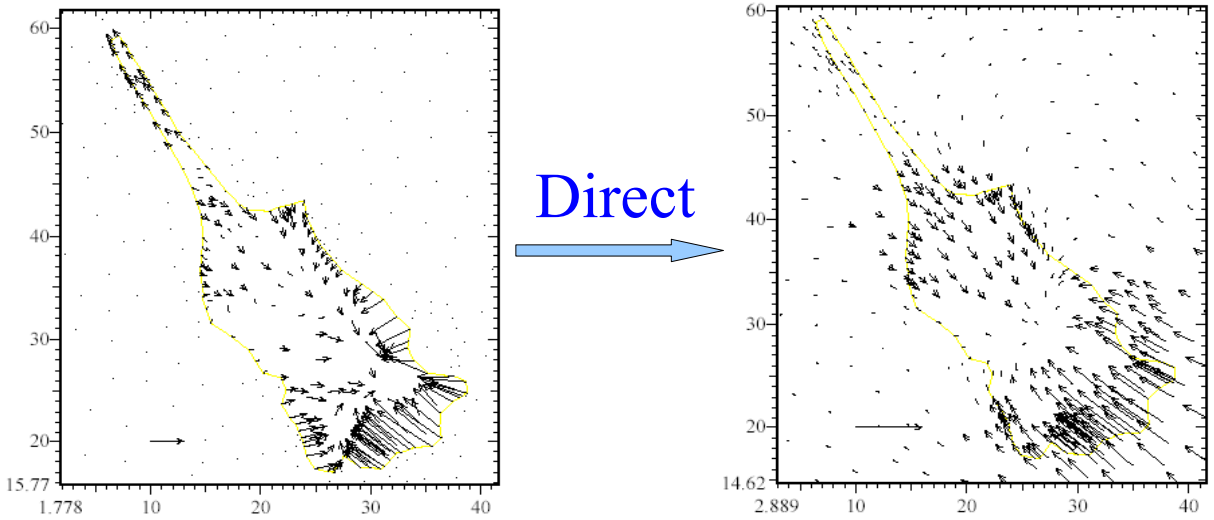
Cell traction

The classical (direct) problem in elasticity:

Given the stress **f**, find the deformation **u** of the substratum such that

$$\left.\begin{aligned} A\mathbf{u} &= \mathbf{f}, \qquad \mathbf{u}|_{\partial\Omega} = 0, \\ A\mathbf{u} &= -\mu\Delta\mathbf{u} - (\mu+\lambda)\nabla(\nabla\cdot\mathbf{u}) \end{aligned}\right\} \mathcal{S}: \mathbf{f} \rightarrow \mathbf{u}$$



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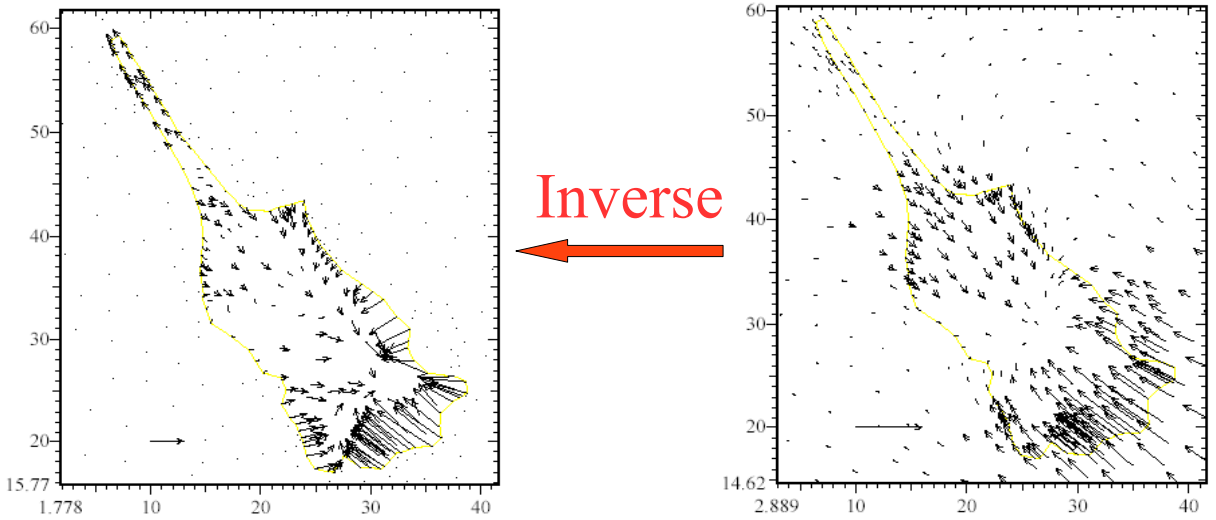
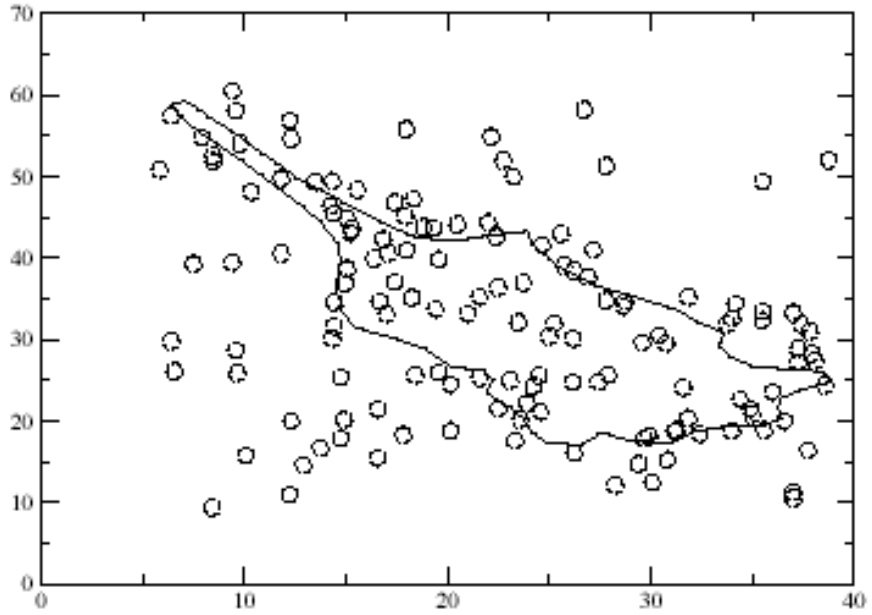


Cell traction

deformation

Ω is the whole domain,
Ω_0 is the subdomain where $\mathbf{u}$ is measured,
Ω_c is the area covered by the cell.



(A. Cavalcanti)

Where are the forces exerted in Ω_c?

What is their magnitude?

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

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The inverse problem

Set of forces acting on Ω_c with null resultant and momentum

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

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

Take the smallest force possible

Compute the deformation for a given virtual force

Measured deformation

Evaluate the computed deformation in the measurement points

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The inverse problem

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

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

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.

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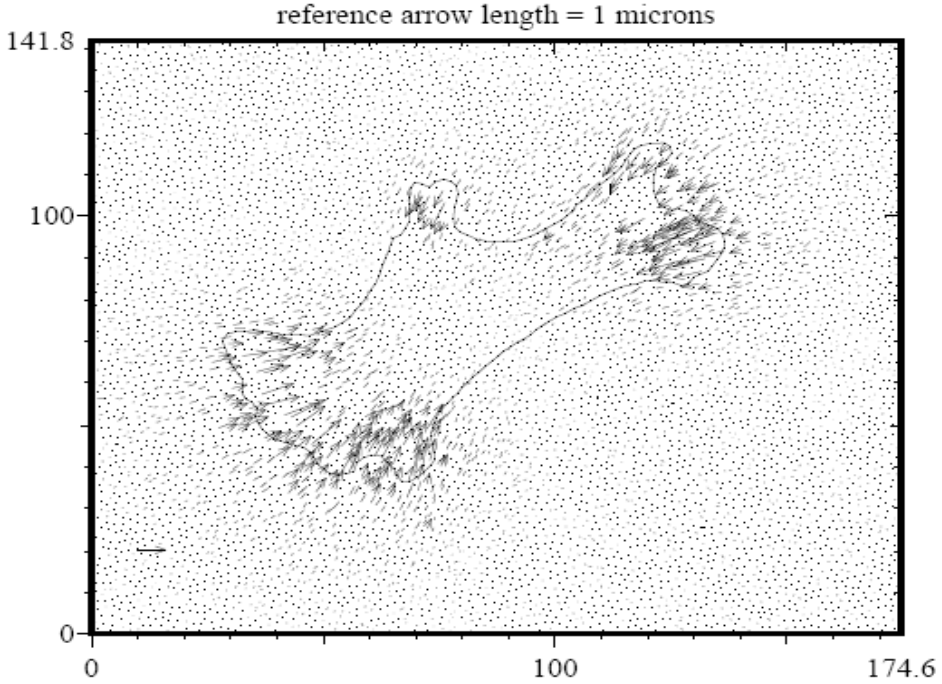
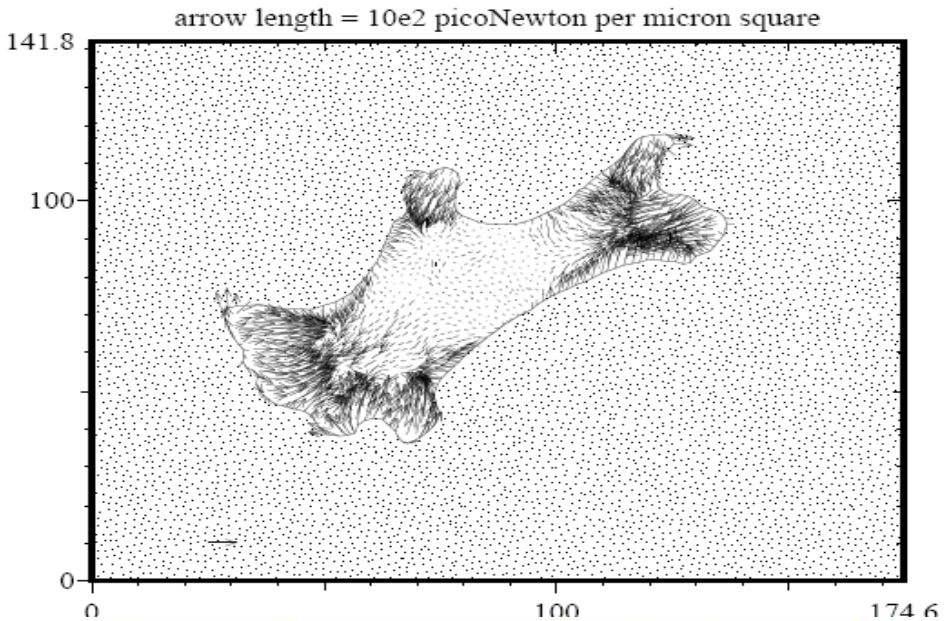
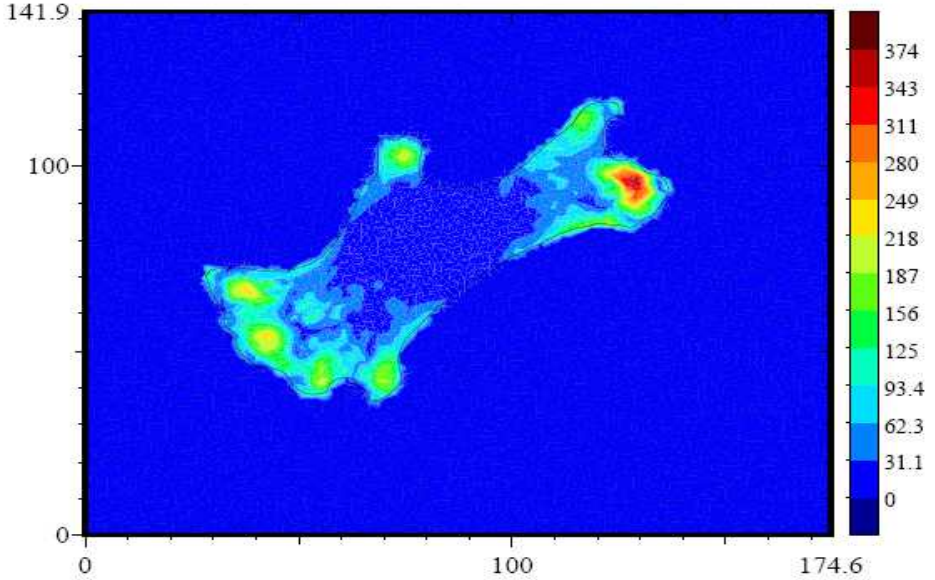
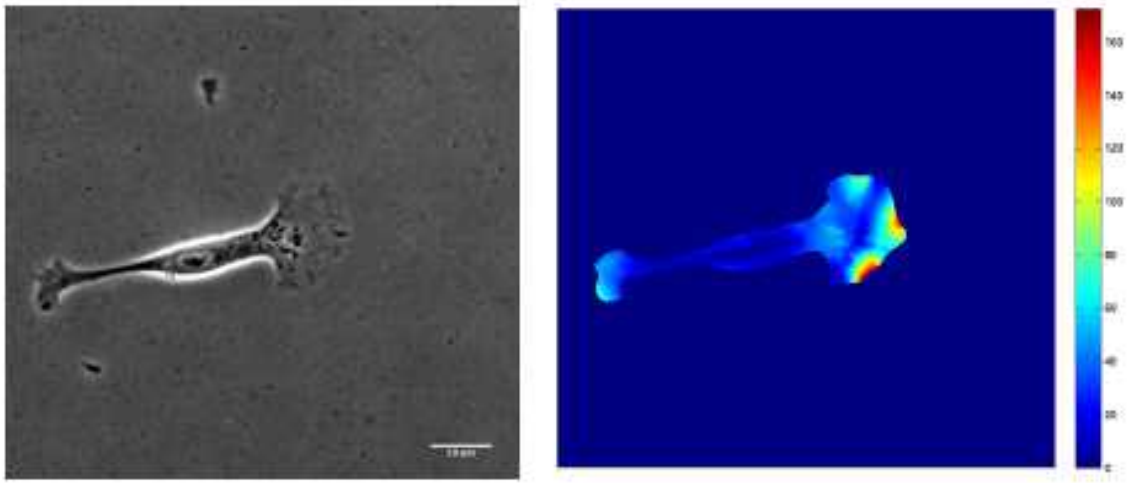
Traction force microscopy







Cell traction



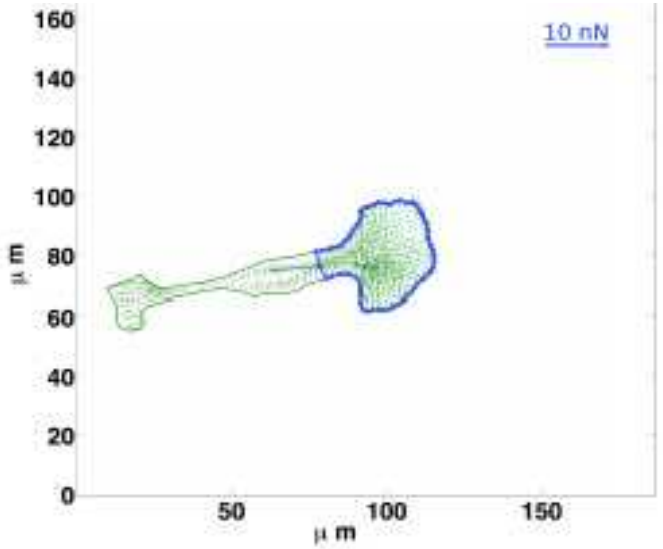
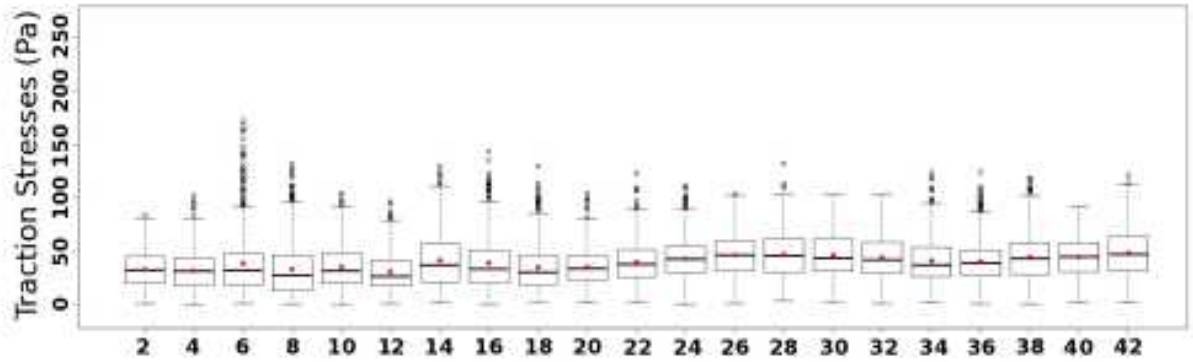
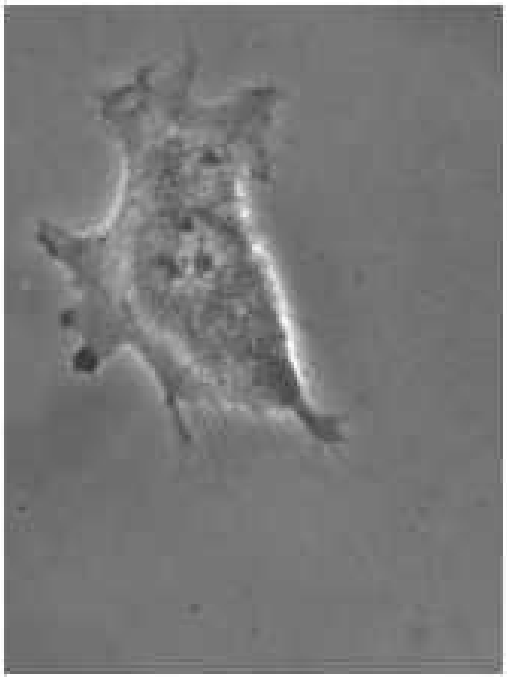


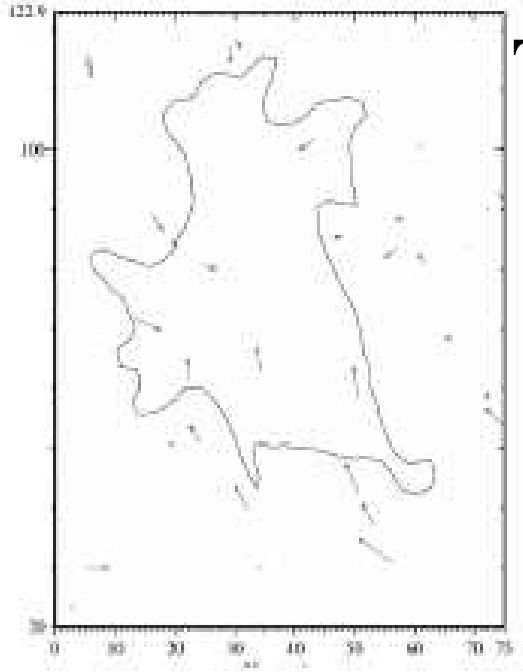
Figure 1: Phase–contrast image of a T24 cancer cell (at time $t = 6$ min from Fig. 2) and corresponding traction field of a T24 cell represented as a color map. The color scale for stresses reads in Pascal (Pa).

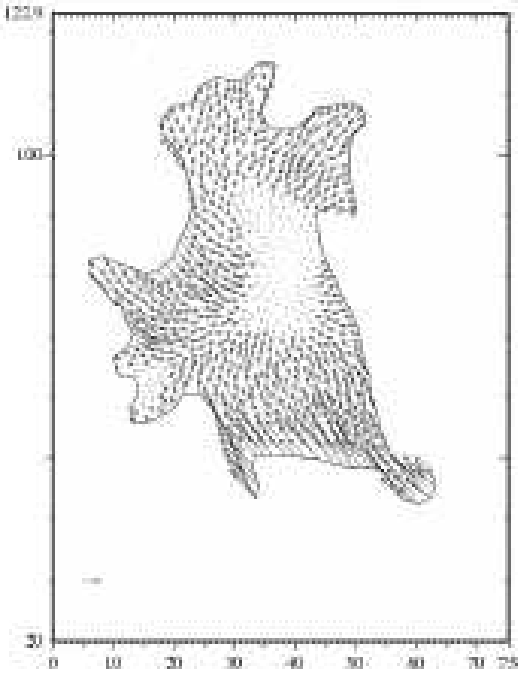


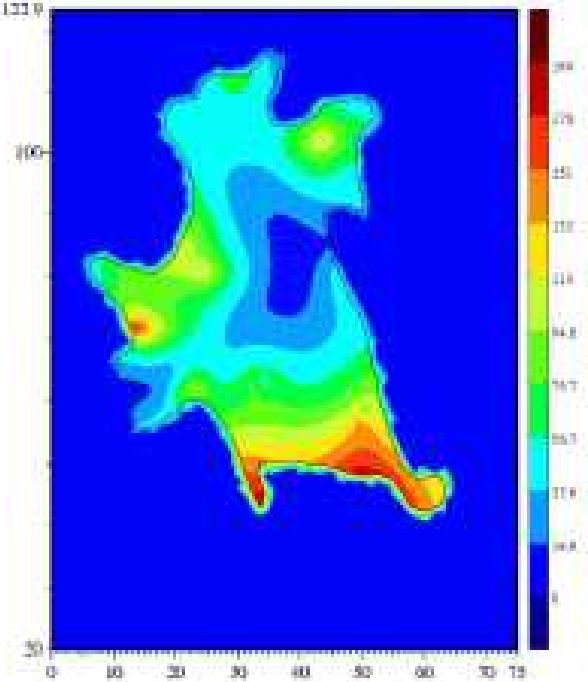
V. Peschetola et al.
Comp. Methods Biomech. Biomed. Engng. **14**, 159-160 (2011).

Traction on a stiff gel





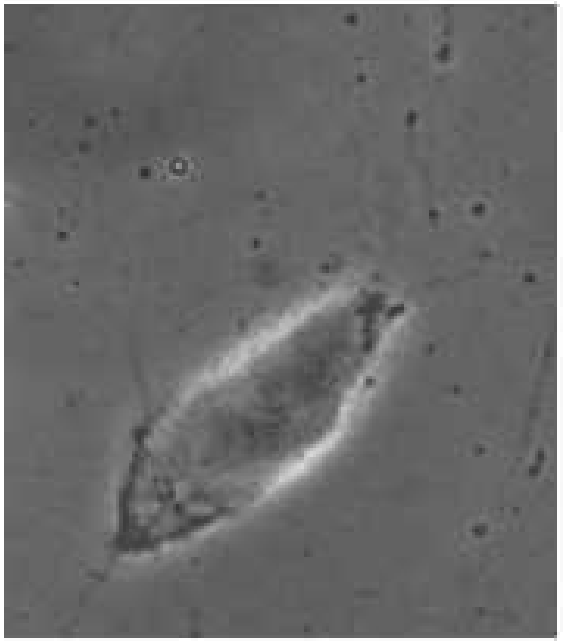


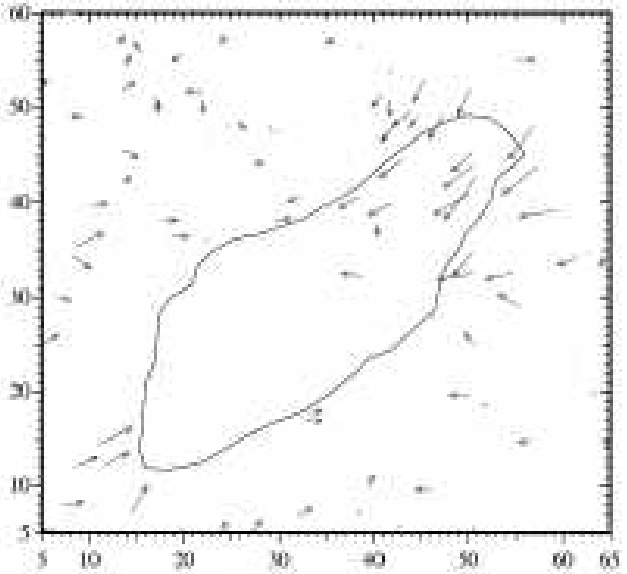


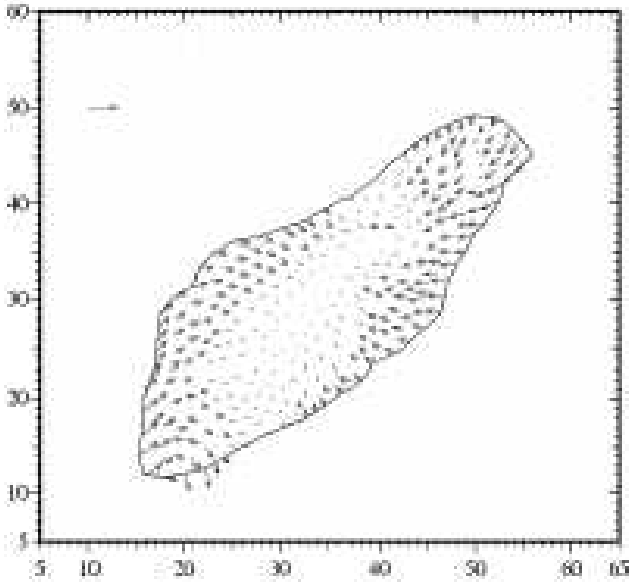
Ambrosi, Peschetola,Verdier
SIAM J. Appl. Math, (2006)

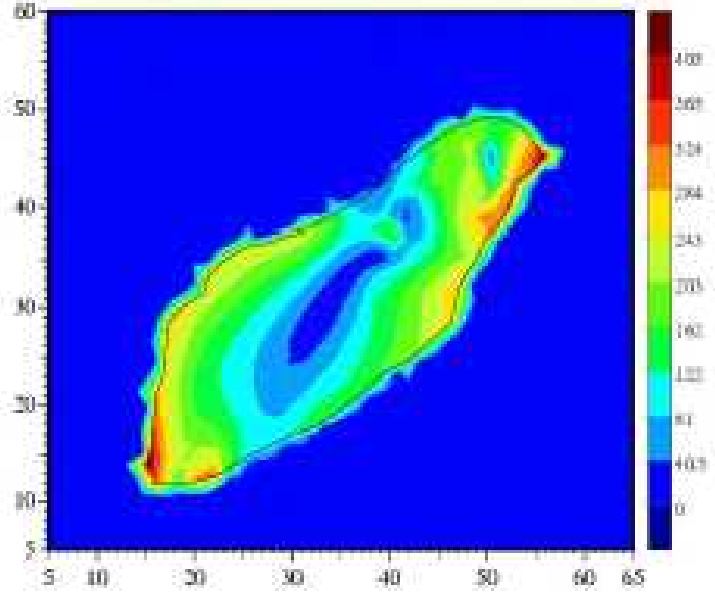
T24 cancer cells

Traction on softer gel









T24 cancer cells

Conclusions

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

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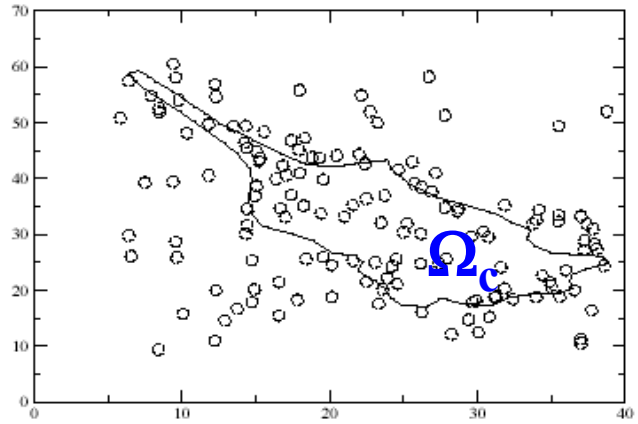
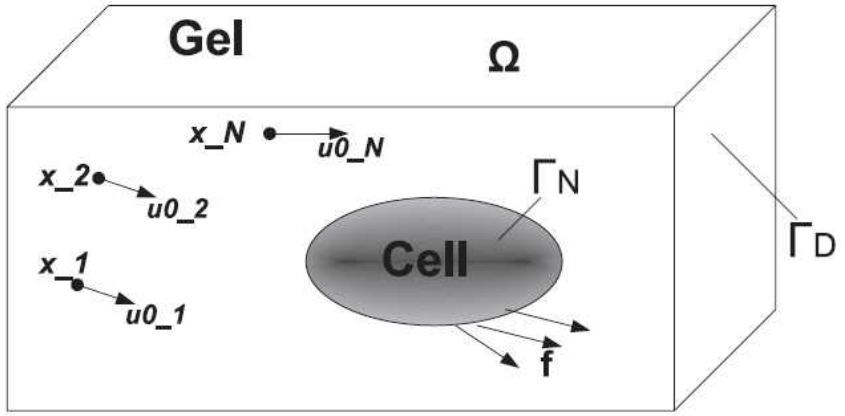
Traction in 3D





2D Differences 3D

- Measurements everywhere (even below the cell or "inside" the cell domain Ω_c)
- Forces below the cell or "inside" the cell domain Ω_c)

- Measurements outside the cell
- Forces exerted on the cell boundary

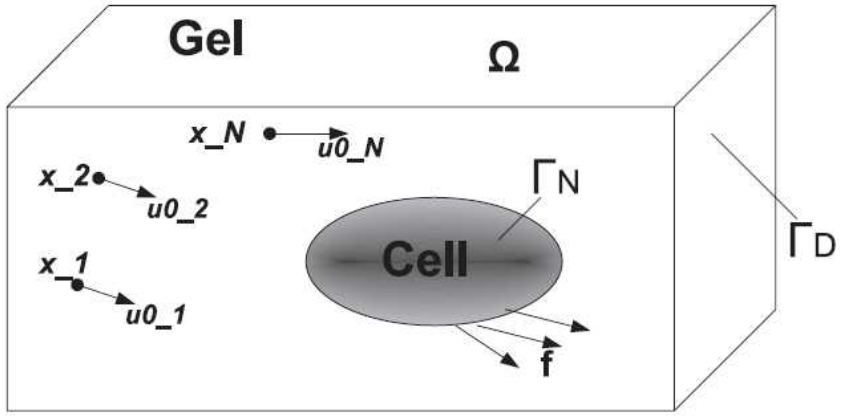
$$\mathcal{S}: \mathbf{f} \longrightarrow \mathbf{u} \Longleftrightarrow \begin{cases} -\nabla \cdot \mathbb{C}[\nabla \mathbf{u}] = 0, & \text{in } \Omega, \\ \mathbb{C}[\nabla \mathbf{u}]\mathbf{n} = \mathbf{f}, & \text{on } \Gamma_N, \\ \mathbf{u} = 0, & \text{on } \Gamma_D. \end{cases}$$

POLITECNICO DI TORINO

Traction in 3D

Penalty function for the minimization problem

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



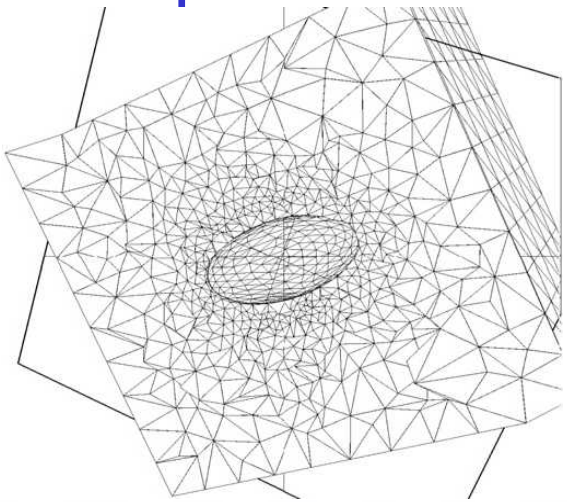
G. Vitale, D. Ambrosi, L.P.,
J. Math. Anal. Appl. **395**, 788-801 (2012)
Inverse Problems **28**, 095013 (2012)

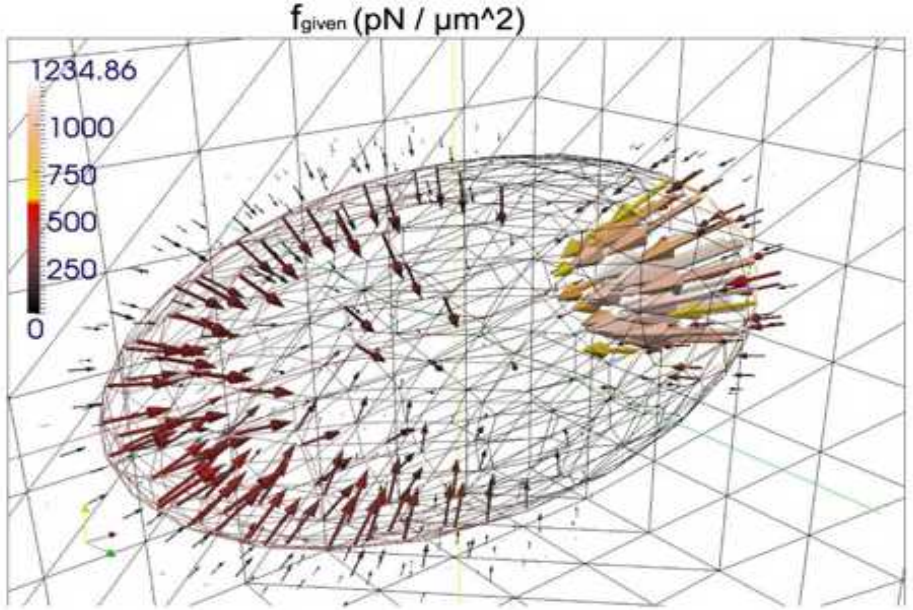
Self-adjoint problem

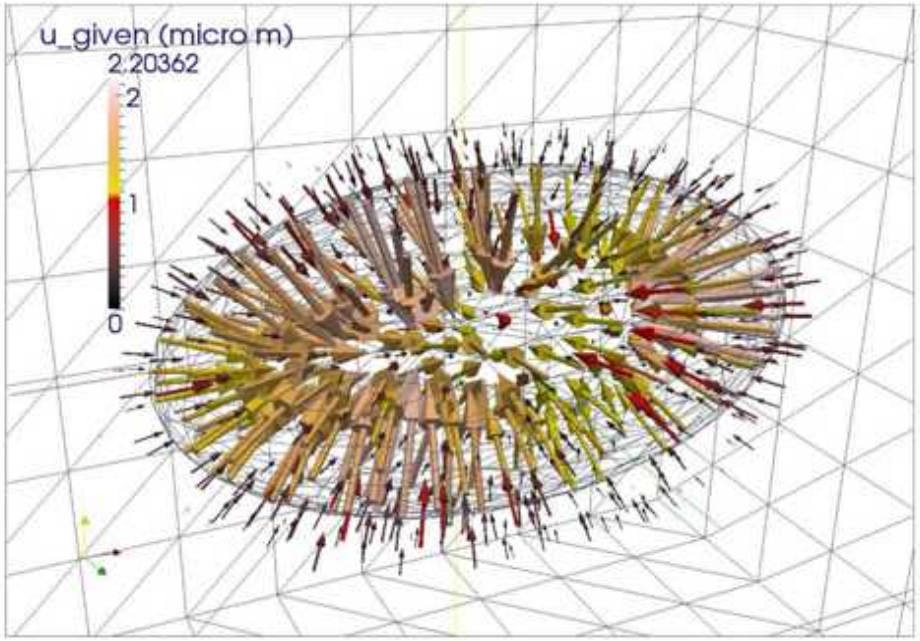
$$\begin{cases} \displaystyle\int_\Omega (\mu\nabla\mathbf{u}\cdot\nabla\mathbf{v} + \lambda(\nabla\cdot\mathbf{u})(\nabla\cdot\mathbf{v})) + \frac{1}{\varepsilon}\left(\int_{\Gamma_N}\mathbf{p}\cdot\mathbf{v} - \frac{1}{|\Gamma_N|}\int_{\Gamma_N}\mathbf{p}\cdot\int_{\Gamma_N}\mathbf{v}\right) = 0, \\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

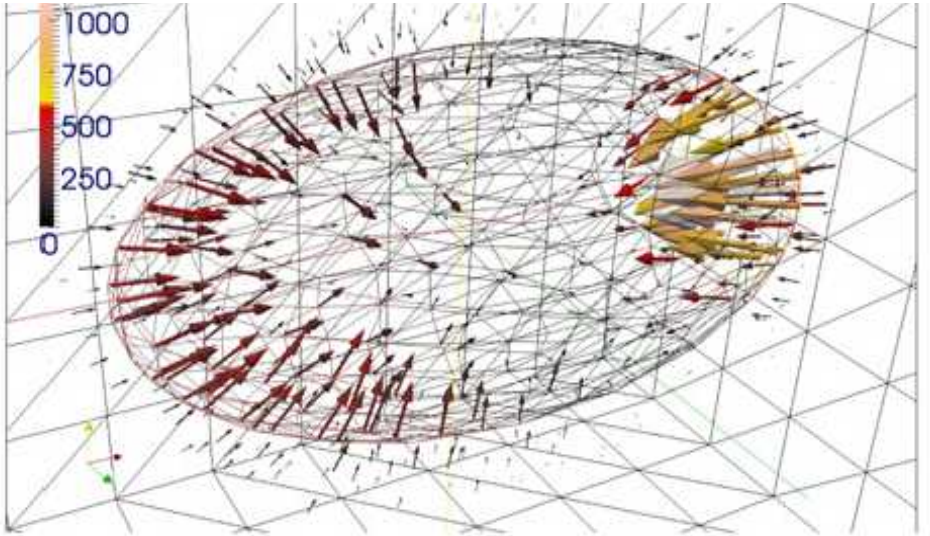
POLITECNICO DI TORINO

Traction in 3D







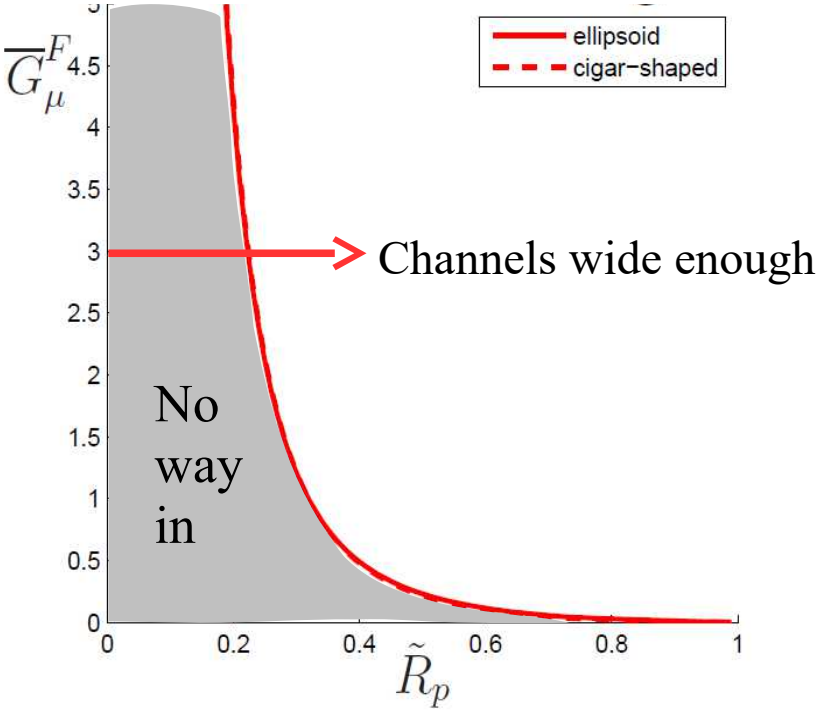


POLITECNICO DI TORINO

Criterium for invasion

Work done by traction > Energy required to squeeze the nucleus

Elastic nucleus	Ellipsoid	$G_\mu^F \geq \frac{2}{3} \frac{2\tilde{R}_p^2 + \frac{1}{\tilde{R}_p^4} - 3}{\tilde{R}_p \tilde{L}_b^{(*)} \Delta \tilde{L}_{ellips}}$
	Cigar	$G_\mu^F \geq \frac{2}{3} \frac{\mathcal{I}(\tilde{R}_p)}{\tilde{R}_p \tilde{L}_b^{(*)} \Delta \tilde{L}_{cigar}}$



Traction

$$G_\mu^F = \frac{\rho_b \alpha_{ECM} F_b^M}{\mu}$$

Nucleus stiffness

$$\tilde{R}_p = R_p / R_n$$

Criterium for invasion

Work done by traction > Energy required to squeeze the nucleus

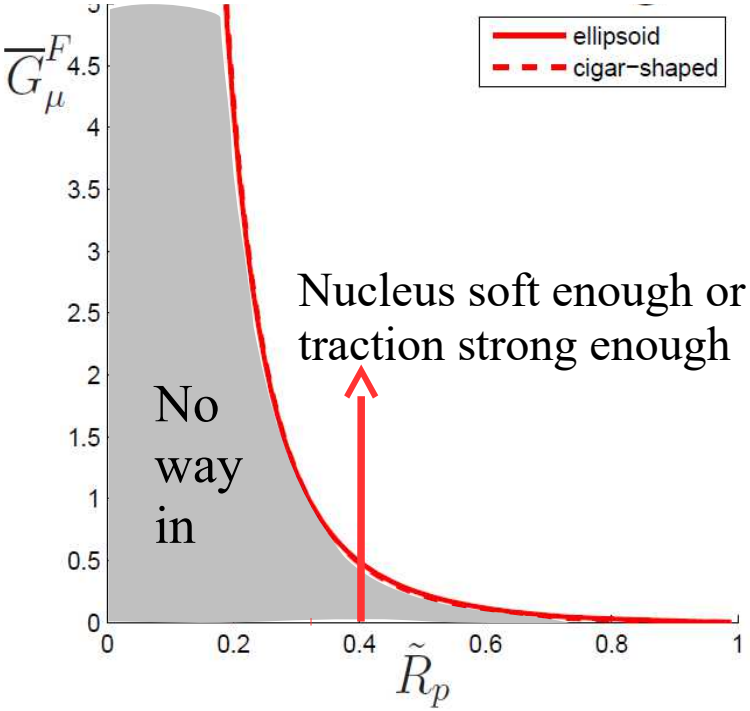
Elastic nucleus	Ellipsoid	$G_\mu^F \geq \frac{2}{3} \frac{2\tilde{R}_p^2 + \frac{1}{\tilde{R}_p^4} - 3}{\tilde{R}_p \tilde{L}_b^{(*)} \Delta \tilde{L}_{ellips}}$
	Cigar	$G_\mu^F \geq \frac{2}{3} \frac{\mathcal{I}(\tilde{R}_p)}{\tilde{R}_p \tilde{L}_b^{(*)} \Delta \tilde{L}_{cigar}}$

$$G_\mu^F = \frac{\rho_b \alpha_{ECM} F_b^M}{\mu}$$

Traction

Nucleus stiffness

$$\tilde{R}_p = R_p / R_n$$

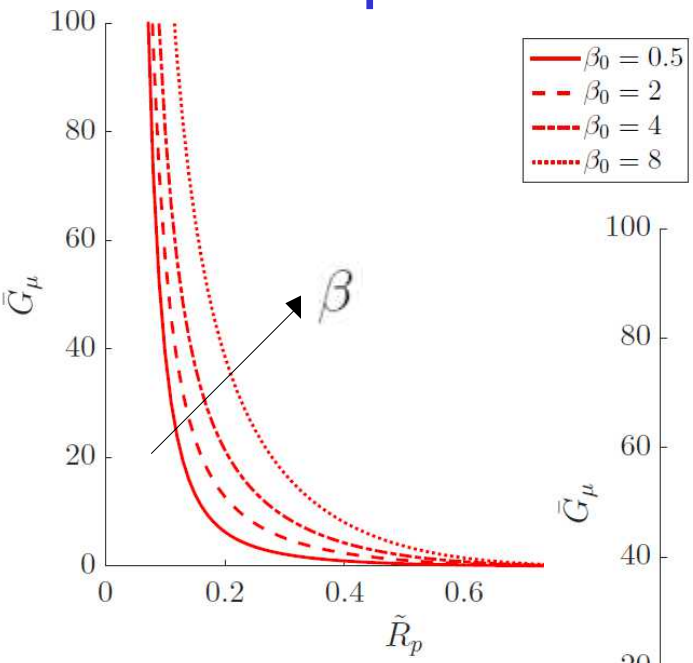


C. Rolli, *PlosOne* **5**, e8726 (2010)

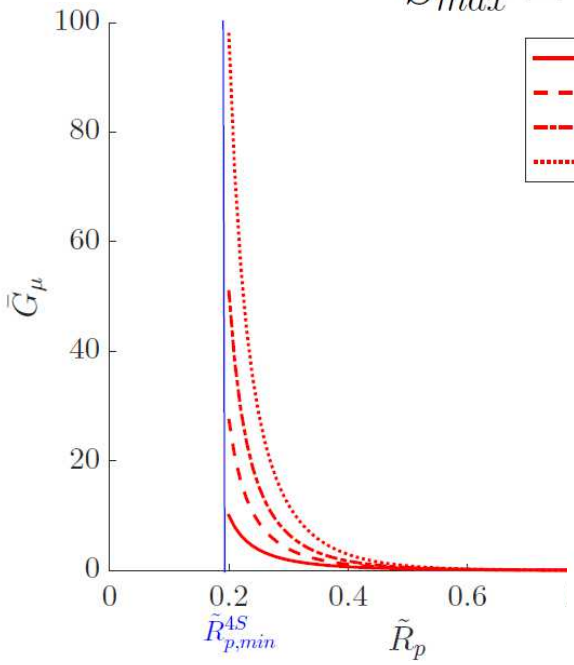
POLITECNICO DI TORINO

Effect of nucleus envelope stretchability

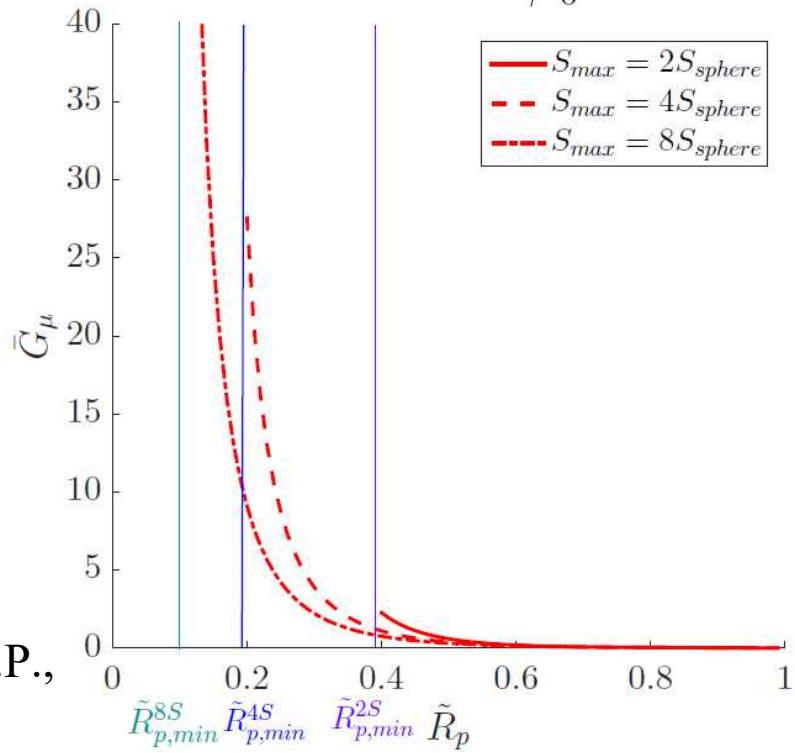
$$\lambda(\Delta S) = \lambda_0 \left(\frac{\Delta S}{S_{max} - S} \right)$$



$$S_{max} = 4S_{sphere}$$



$$\beta_0 = 2$$



$$\tilde{R}_p = R_p / R_n$$

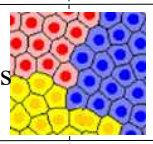
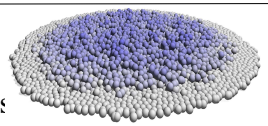
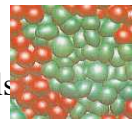
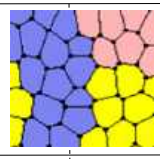
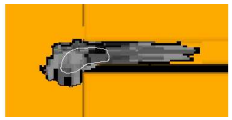
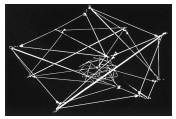
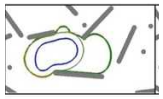
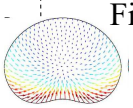
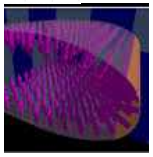
$$\beta := \frac{\lambda R_n}{\mu}$$

Membrane

Nucleus

C. Giverso, A. Arduino & L.P., *Bull. Math. Biol.* (2017)

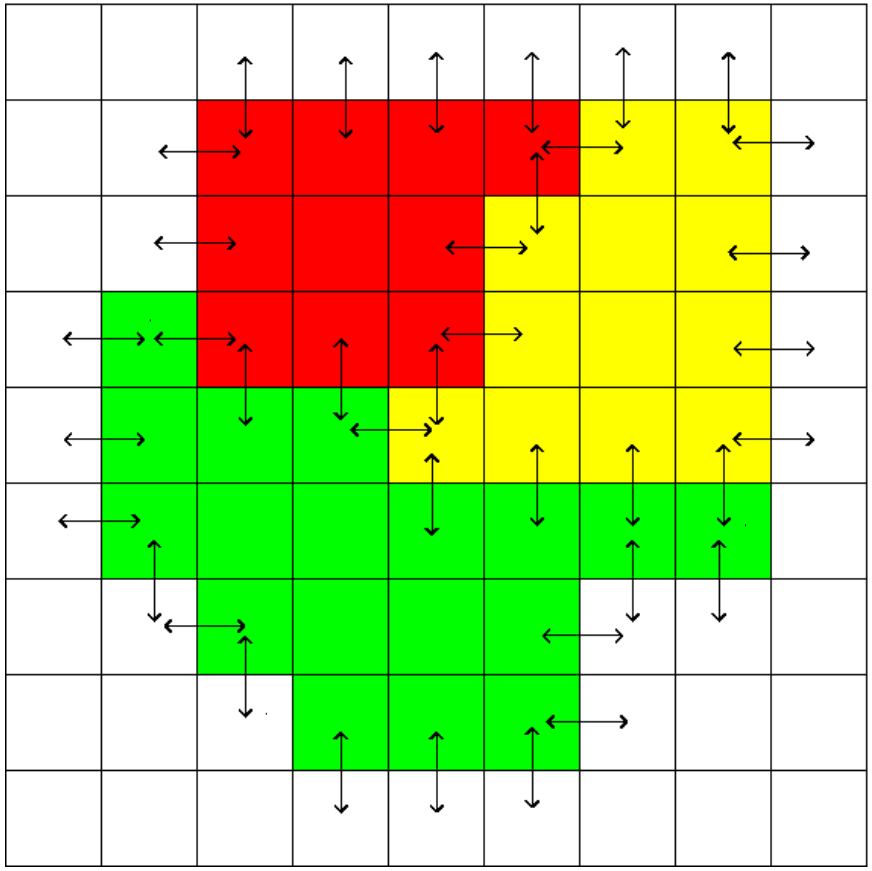
Number of degrees of freedom

	Models based on a regular grid		Grid-free models	
	Rule based	**Energy based**	**Force based**	**Energy based**
Cell center	Lattice-gas cellular automata 		Cell center Voronoi models 	Self-propelled Voronoi models
Cell center and radius			Individual cell-based models 	
Cell center and dimensions of ellipsoidal shape			Ellipsoidal cell-based models 	
Vertices of polygonal cells			Force based vertex models 	Energy based vertex models
Many points per cell body		Cellular Potts models 	Tensegrity models   Sub-cellular element models 	
Continuous membrane and cytoplasm			Finite element methods  Boundary element methods	
Kinetic model for cytoplasm			Filament based model of the lamellipodium 	

POLITECNICO DI TORINO

The cellular Potts model

A cell is represented by several nodes



- Based on a generalized energy H

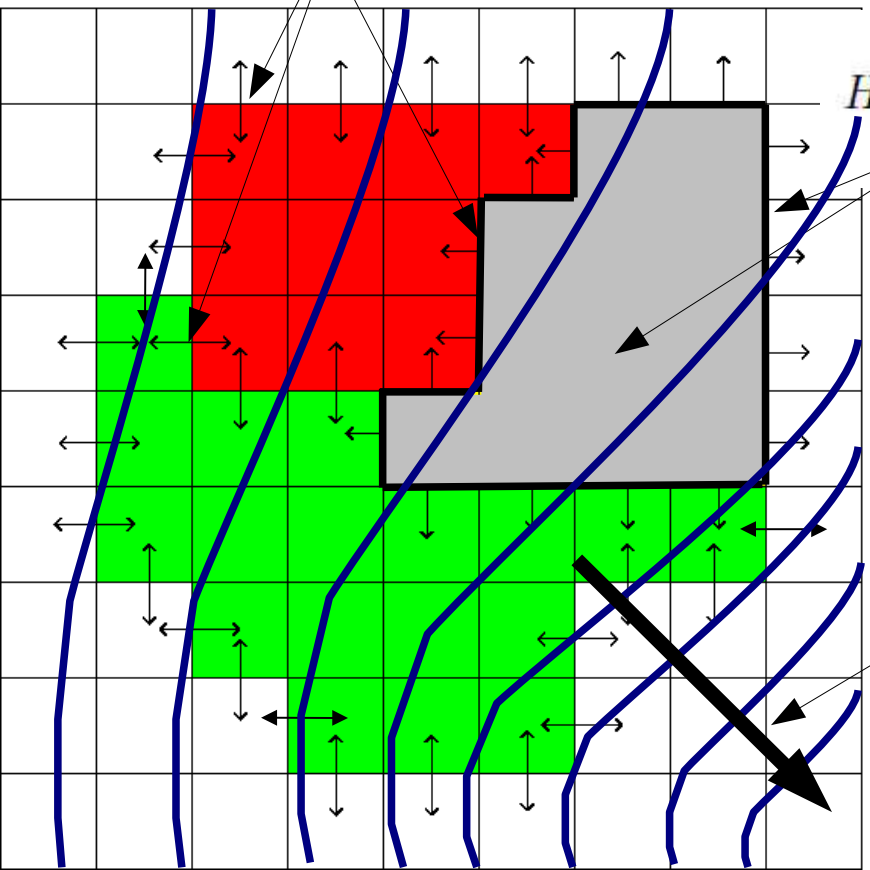
- Evolution stochastically tries to minimize the system energy

POLITECNICO DI TORINO

The cellular Potts model

$$H(t) = H_{adhesion}(t) + H_{attribute}(t) + H_{force}(t).$$

$$H_{adhesion}(t) = \sum_{\mathbf{x},\mathbf{x}' \in \Omega} J_{\tau(\sigma(\mathbf{x})),\tau(\sigma(\mathbf{x}'))}(t)[1 - \delta_{\sigma(\mathbf{x}),\sigma(\mathbf{x}')}(t)],$$



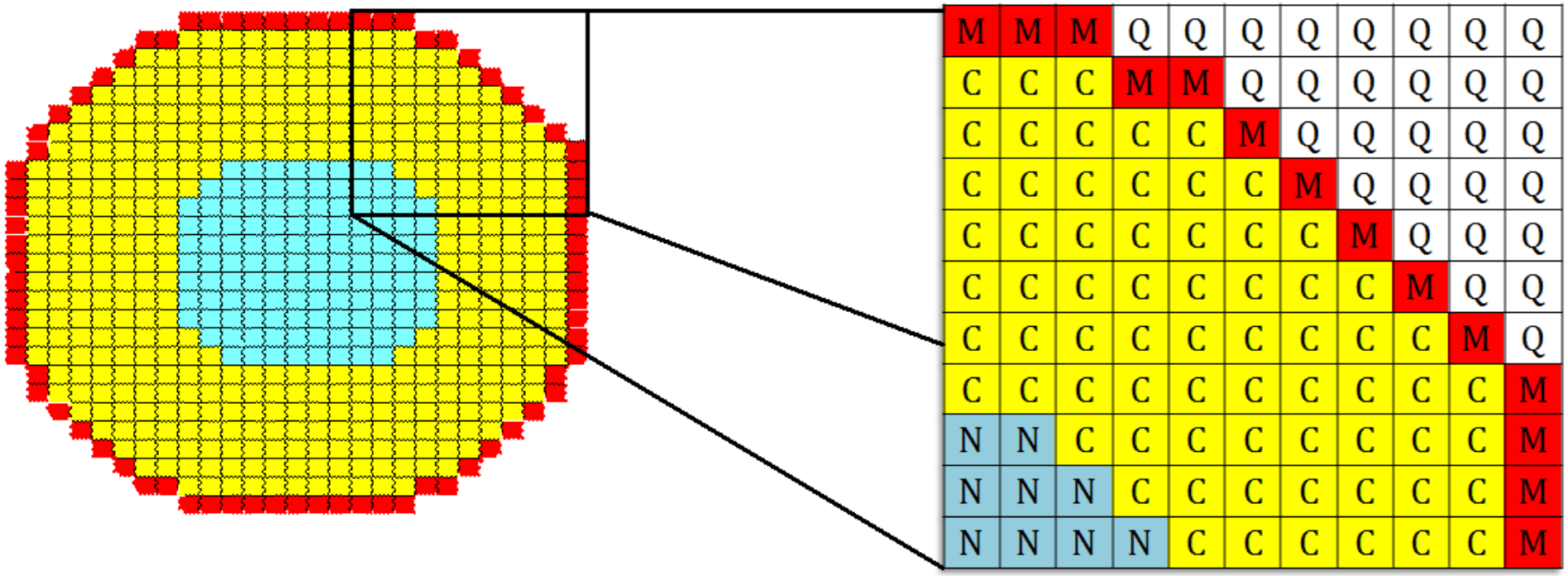
$$H_{attribute}(t) = \sum_{\eta,\sigma,i-attribute} \lambda^i_{\eta,\sigma}(t) \left| \frac{a^i_{\eta,\sigma}(t) - A^i_{\eta,\sigma}(t)}{a^i_{\eta,\sigma}(t)} \right|^p.$$

$$H^{chemical}_{force}(t) = -\sum_{\sigma} \sum_{\mathbf{x} \in \sigma} \mu_\sigma(t) c(\mathbf{x}, t),$$

POLITECNICO DI TORINO

Generalized cellular Potts model

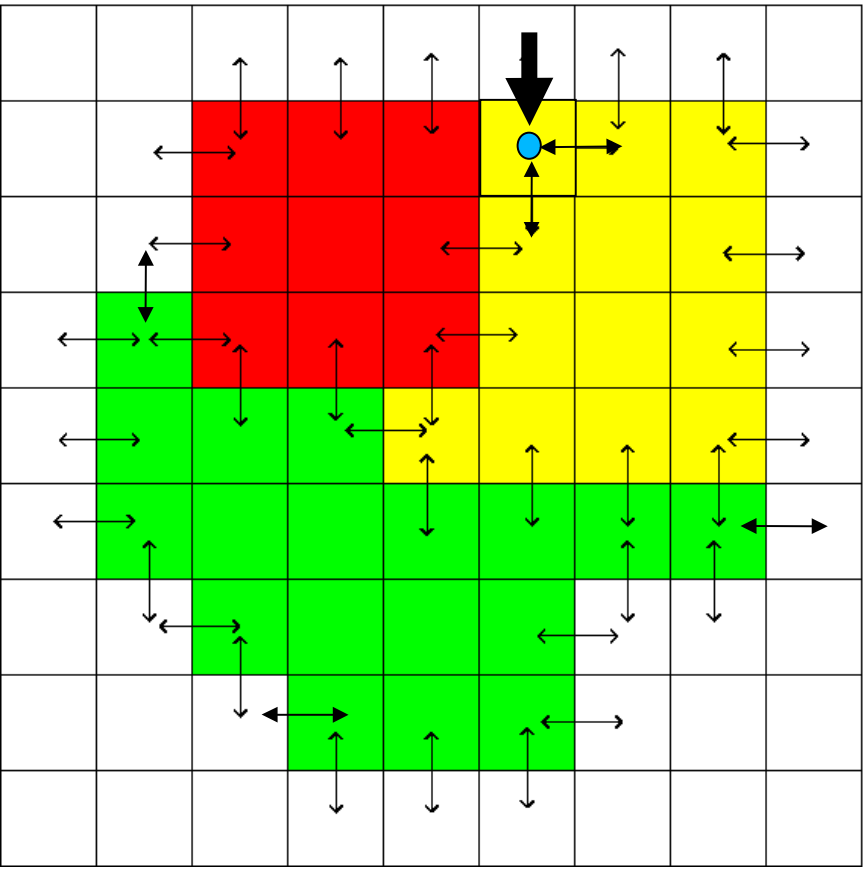
Taking into account of sub-cellular elements (e.g., nucleus)



M. Scianna & L.P.,
J. Theor. Biol. **317**, 394-406 (2013).

POLITECNICO DI TORINO

The cellular Potts model



Choose a node at random

Choose a neighbour at random

Choose an action

Compute the change in energy ΔH

ΔH < 0 ?

ΔH > 0 ?

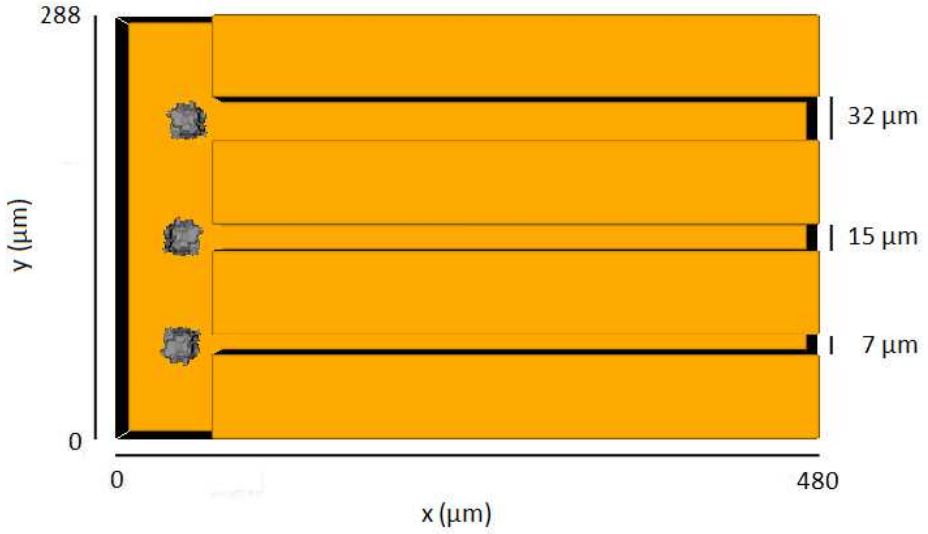
Accept the action (always)

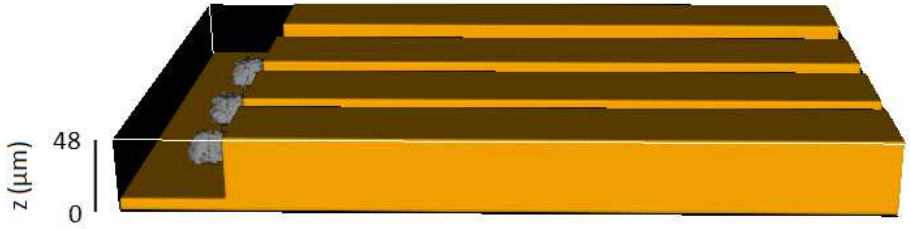
Accept the action with probability decreasing exponentially with ΔH

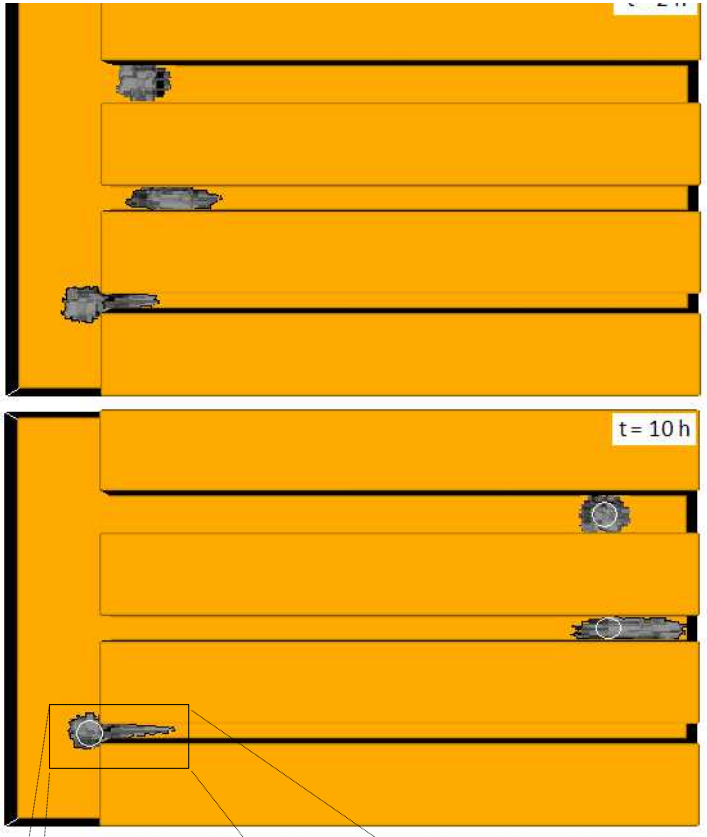
Repeat till all nodes are chosen

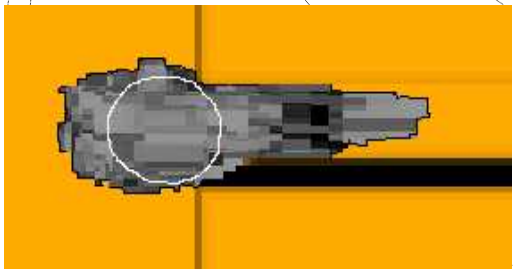
increase time

Cells with stiff nuclei in microchannel







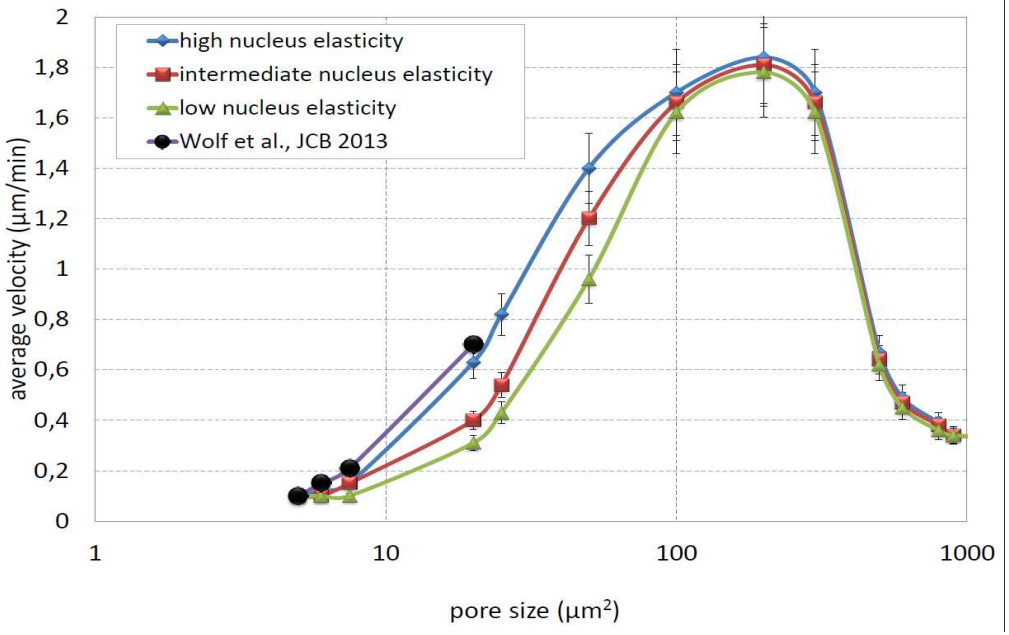


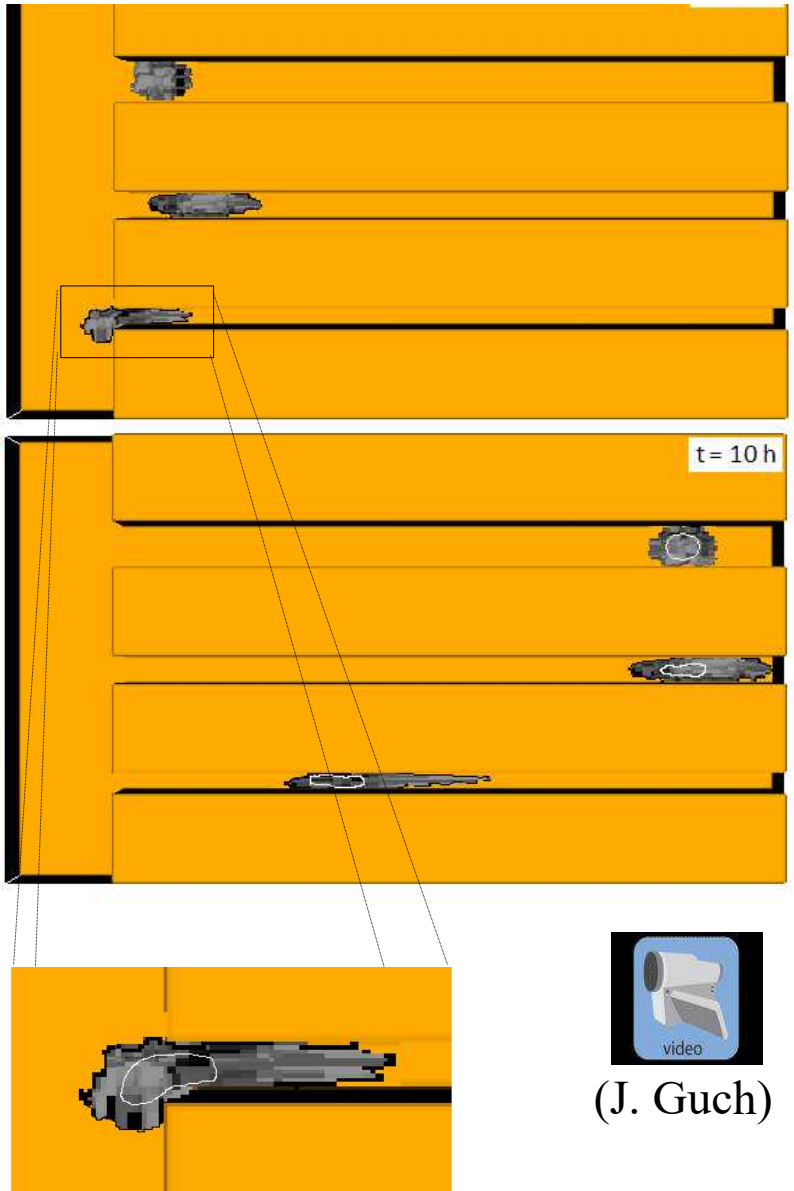
(J. Guch)

bottom channel size < nucleus diameter < middle channel size < cell diameter < top channel size

M. Scianna, L.P., *J. Theor. Biol.* **317**, 394-406 (2013)

Cells with deformable nuclei in microchannel



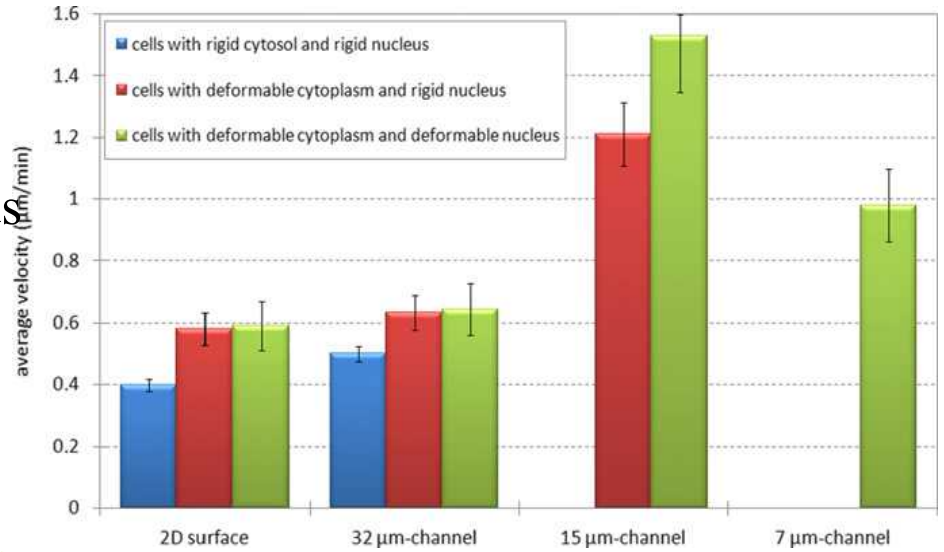


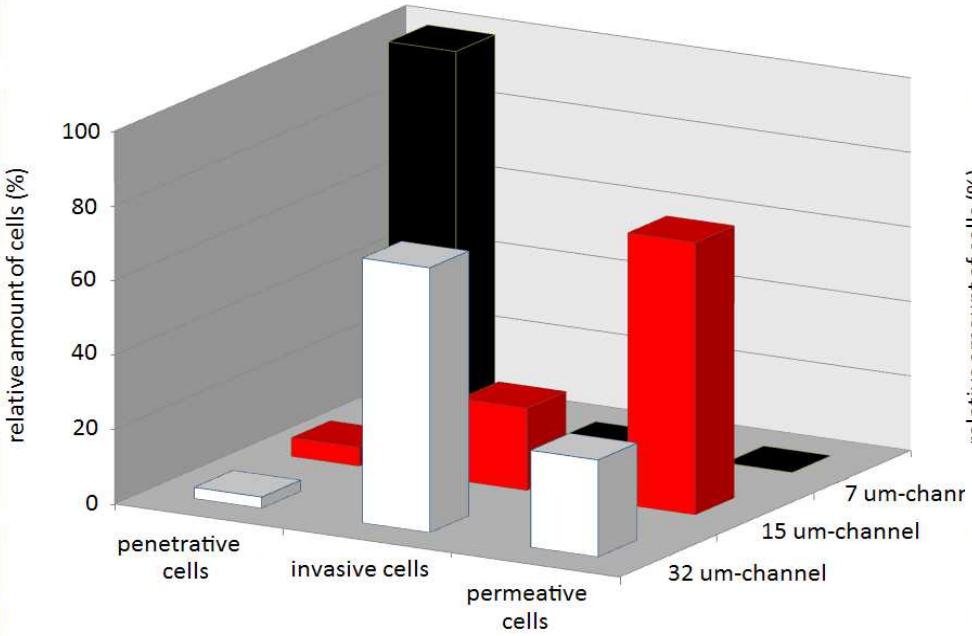
(J. Guch)

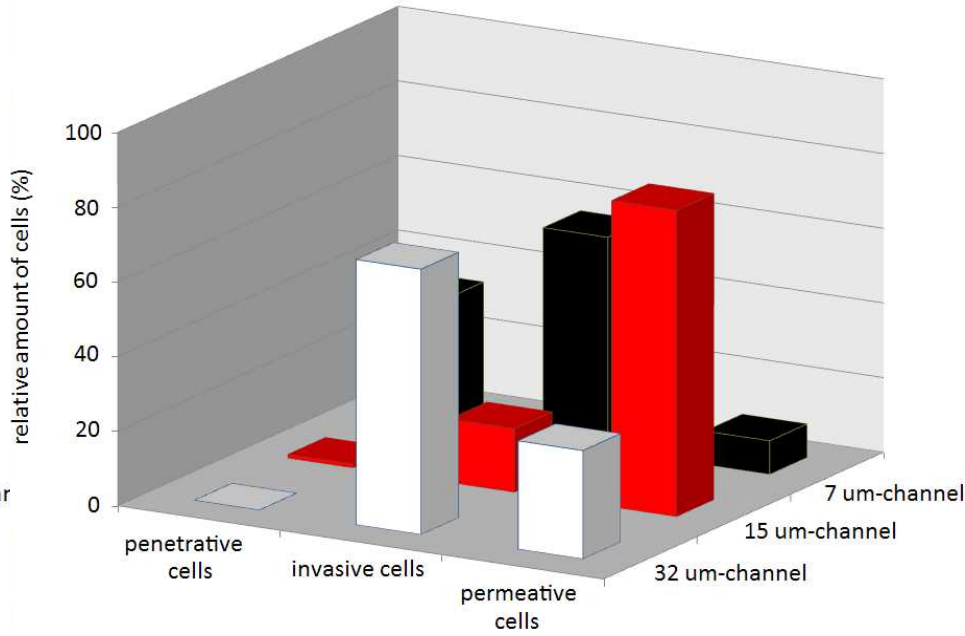
Influence of nucleus rigidity

C. Rolli, *PlosOne* **5**, e8726 (2010)

- Penetrative = Stay out with the nucleus (not with the cytoplasm)
- Invasive = Enter but do not reach the other side
- Permeative = Enter and reach the other side

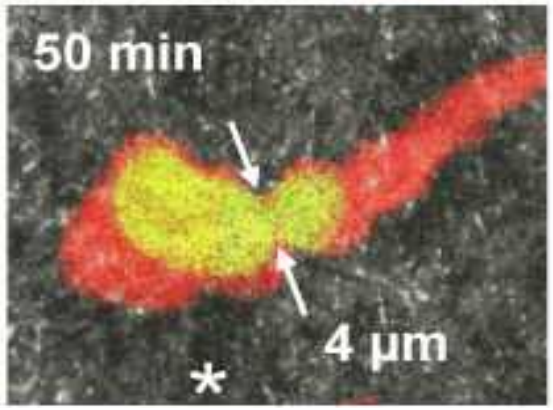


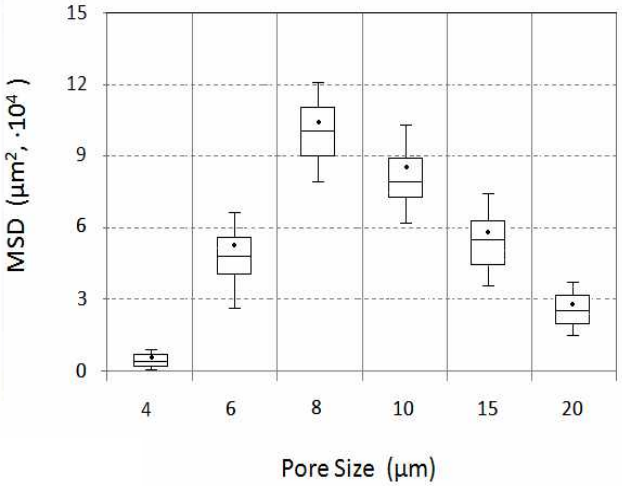


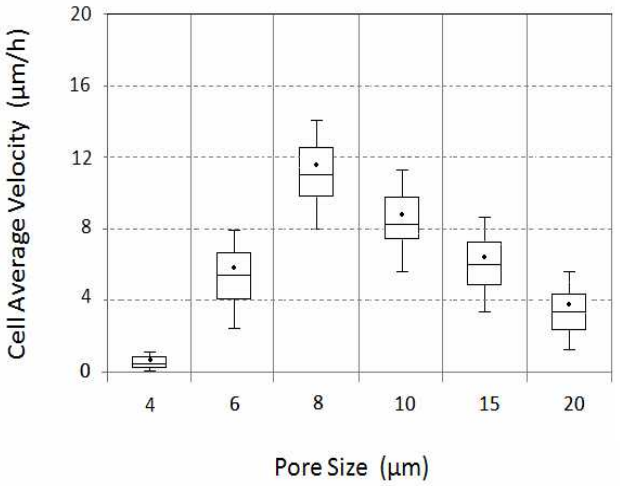


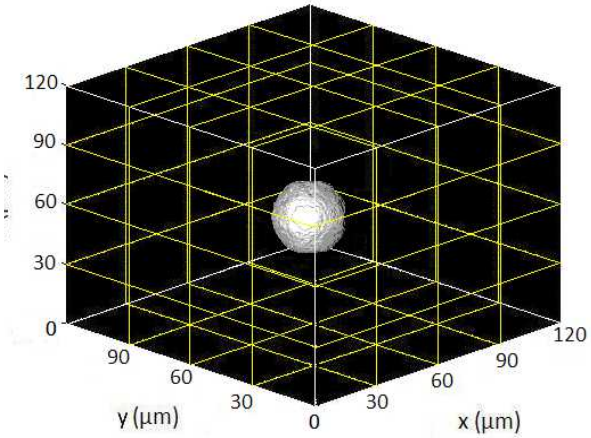
POLITECNICO DI TORINO

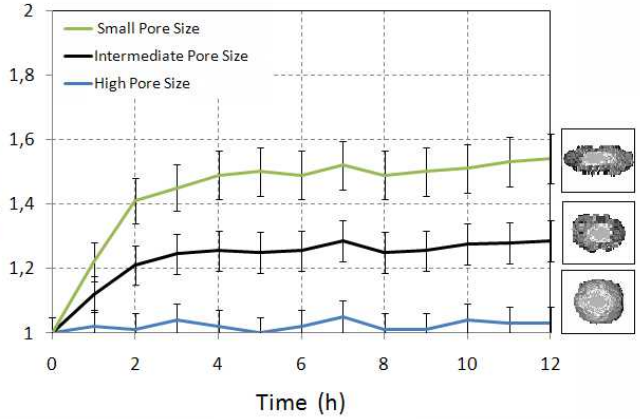
Effect of pore size in ECM

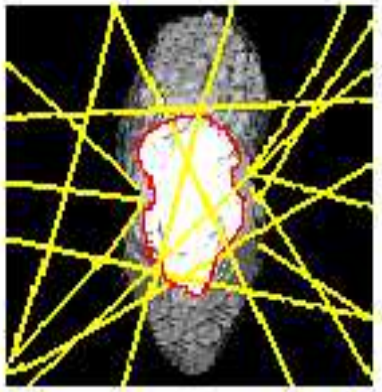










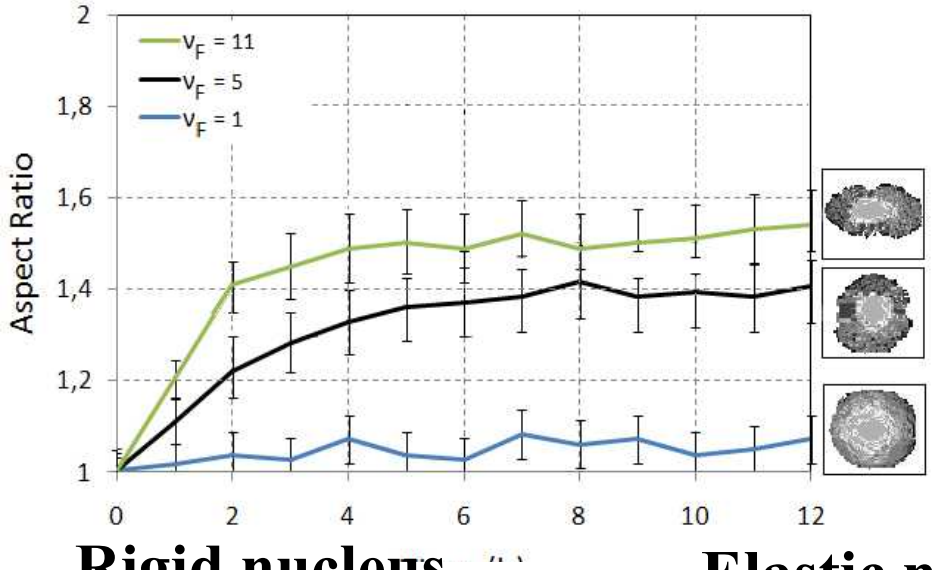


M. Scianna, L.P., & K. Wolf, *Biosci. Engng.* **10**, 235-261 (2013)

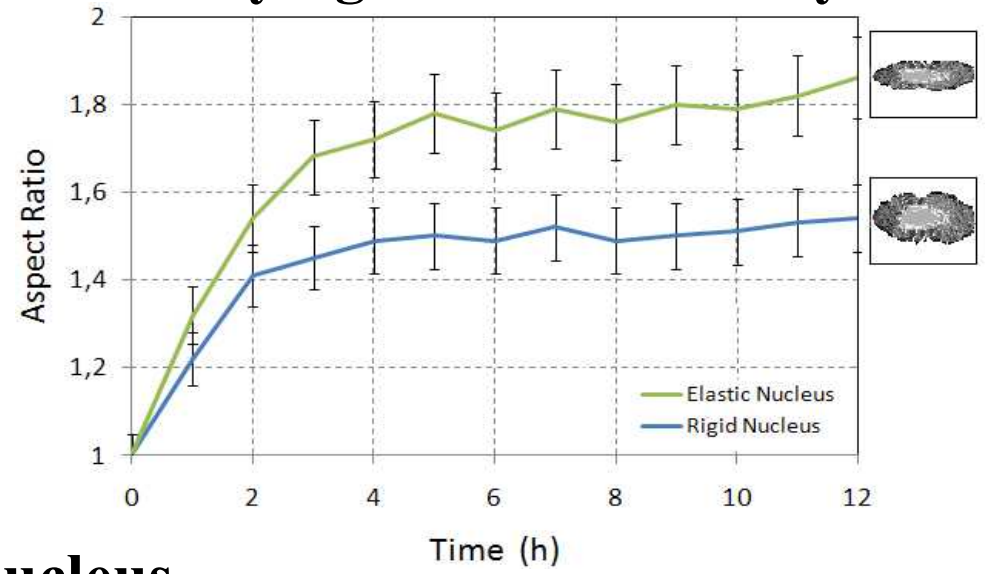
POLITECNICO DI TORINO

Effect of deformability

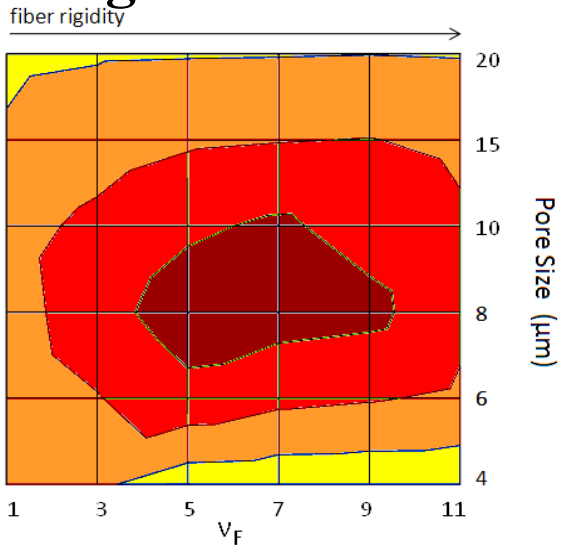
Varying fiber elasticity



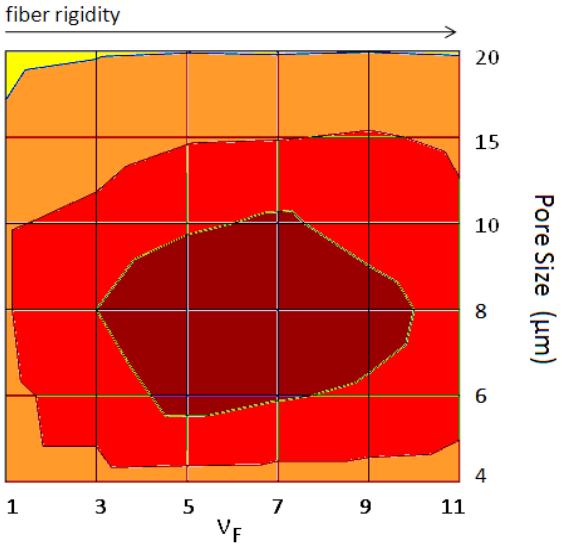
Varying nucleus elasticity



Rigid nucleus

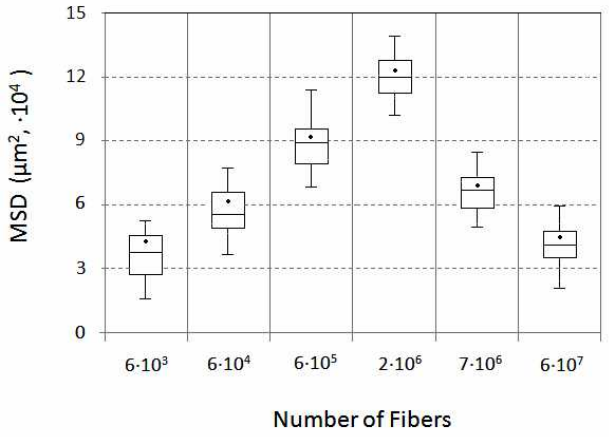


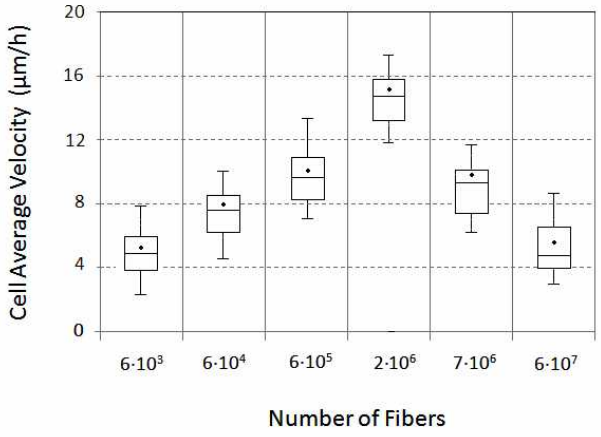
Elastic nucleus

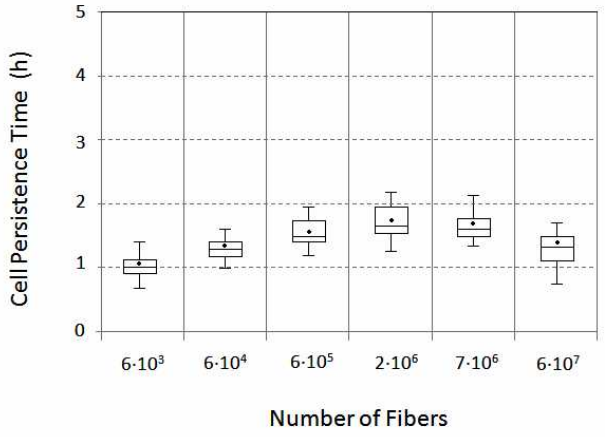


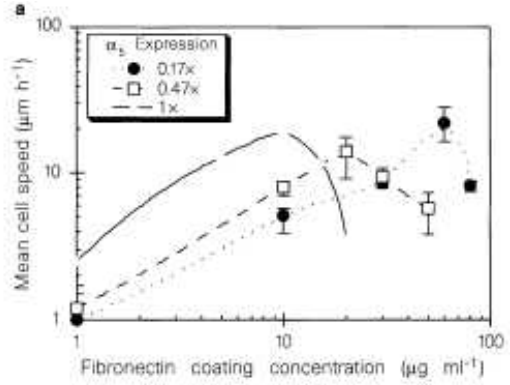
POLITECNICO DI TORINO

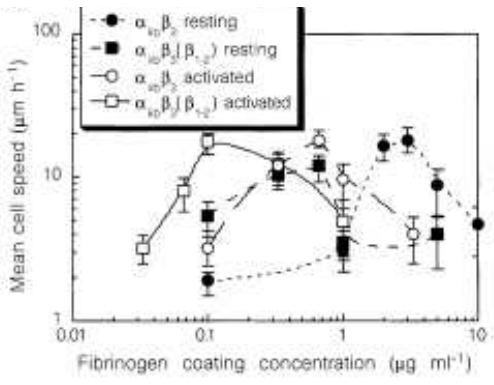
Effect of adhesion in 2D

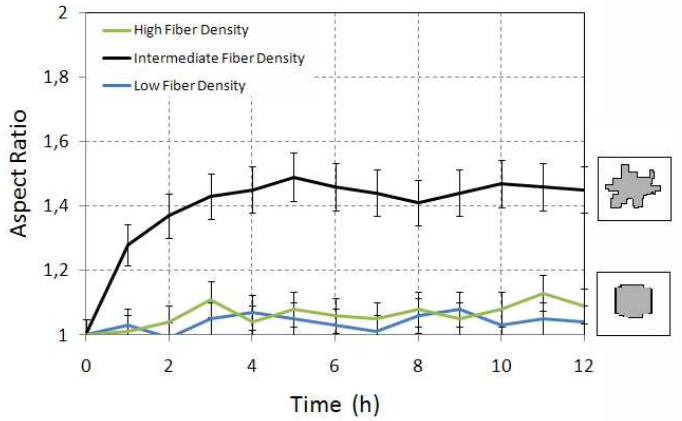








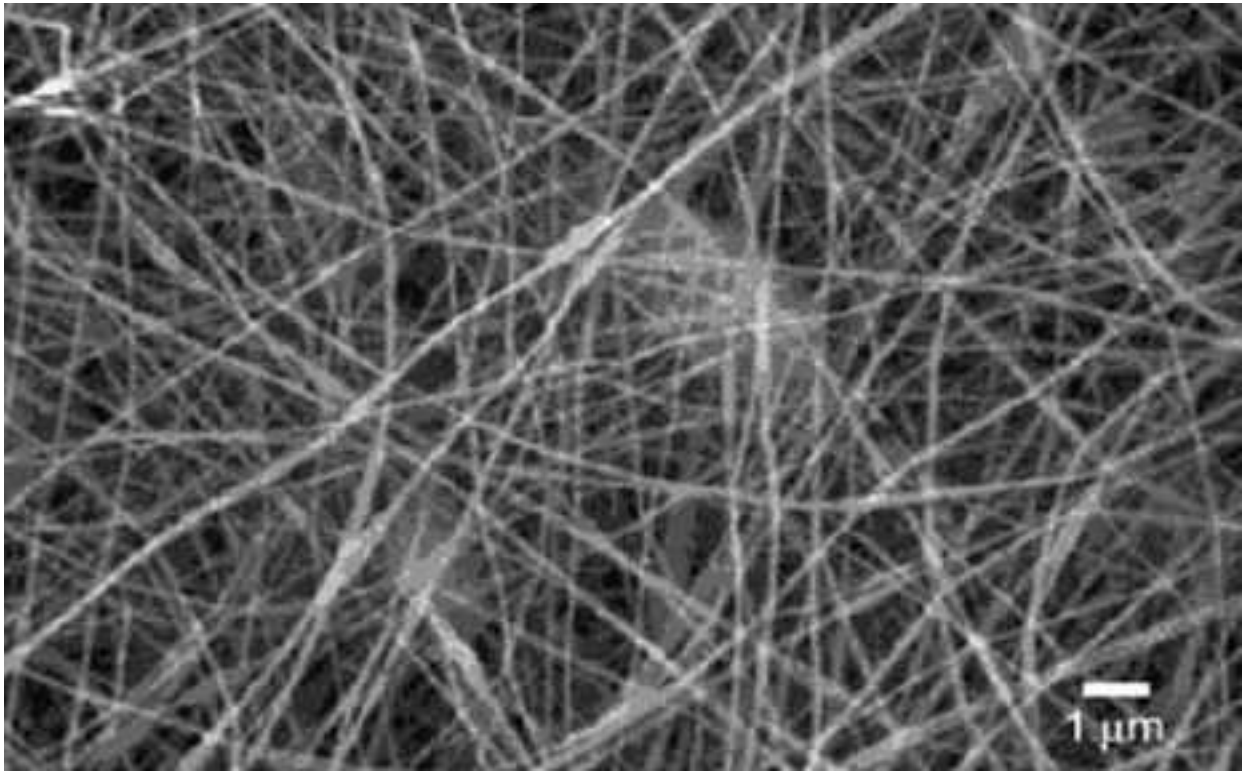


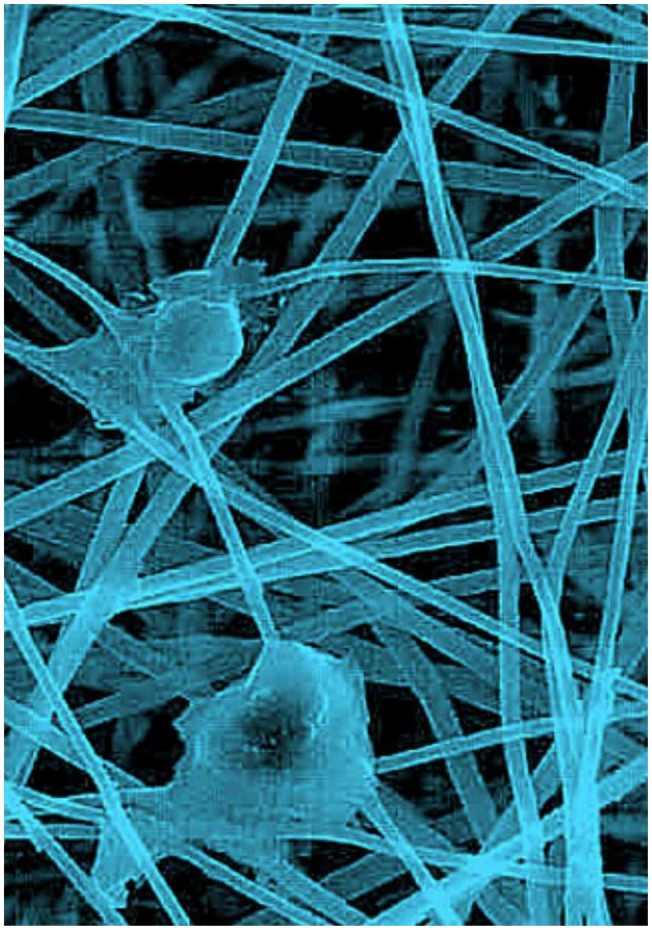


Palecek et al., *Nature* **385**, 537-540 (1997)

POLITECNICO DI TORINO

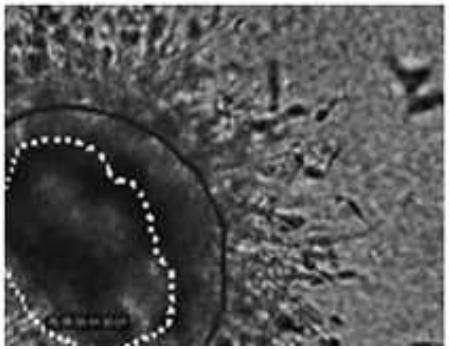
Optimising motion in artificial ECM

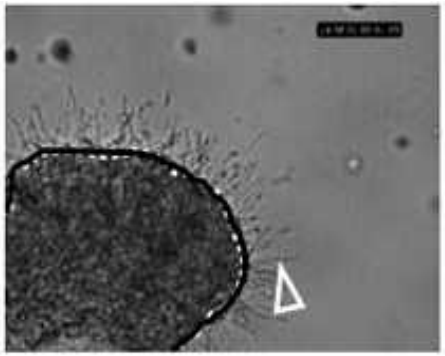


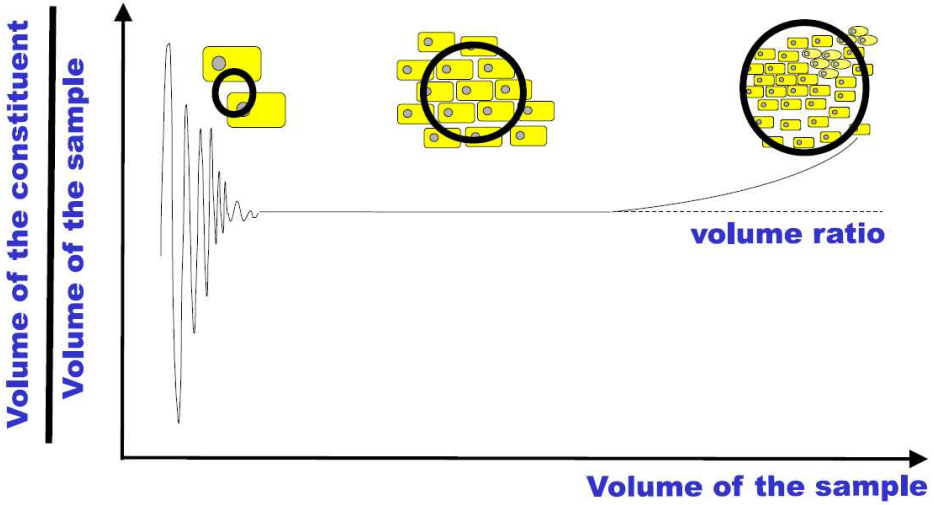


POLITECNICO DI TORINO

Upscaling the information

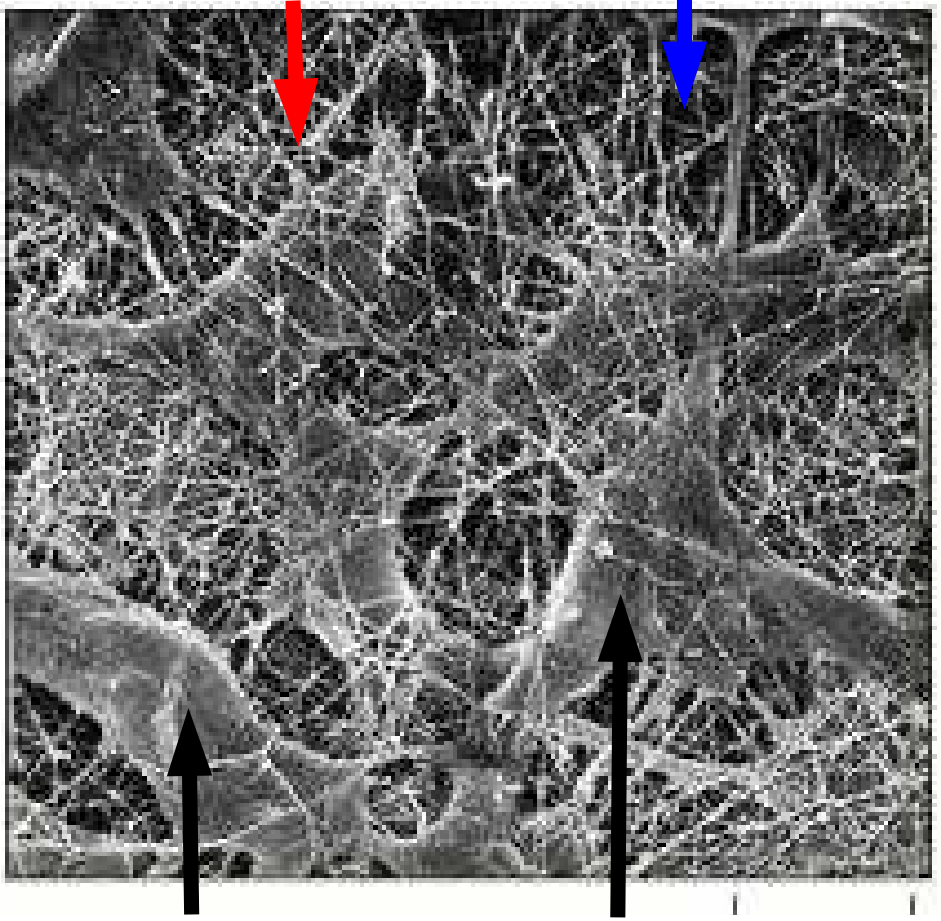






deformable and degradable ECM

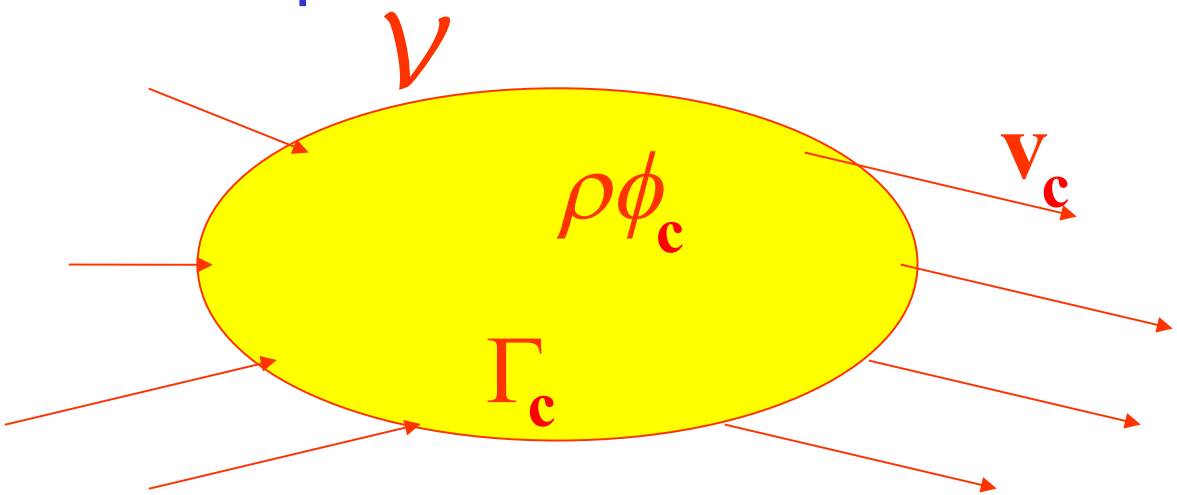
extracellular liquid



host cells and tumour cells

POLITECNICO DI TORINO

Mass balance equations



$$\overbrace{\frac{d}{dt}\int_{\mathcal{V}} \rho\phi_c \, dV}^{\text{Cell mass}} = -\overbrace{\int_{\partial\mathcal{V}} \rho\phi_c \mathbf{v}_c \cdot \mathbf{n} \, d\Sigma}^{\text{Outflux}} + \overbrace{\int_{\mathcal{V}} \rho\Gamma_c \, dV}^{\text{Growth/death}}$$

$$\frac{\partial}{\partial t}(\ \phi_c) + \nabla \cdot (\ \phi_c \mathbf{v}_c) = \ \Gamma_c \quad \Longrightarrow \quad \frac{\partial \phi_{c_i}}{\partial t} + \nabla \cdot (\phi_{c_i} \mathbf{v}_{c_i}) = \Gamma_{c_i}$$

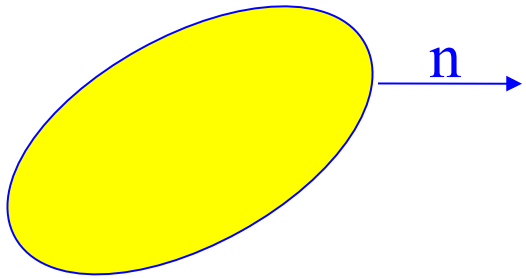
POLITECNICO DI TORINO

Only tumour cells in 3D

1. Constant density $\cancel{\frac{\partial \bar{\varphi}}{\partial t}} + \nabla \cdot (\bar{\varphi}\mathbf{v}) = \Gamma \quad \Rightarrow \quad \nabla \cdot \mathbf{v} = \frac{\Gamma}{\bar{\varphi}}$

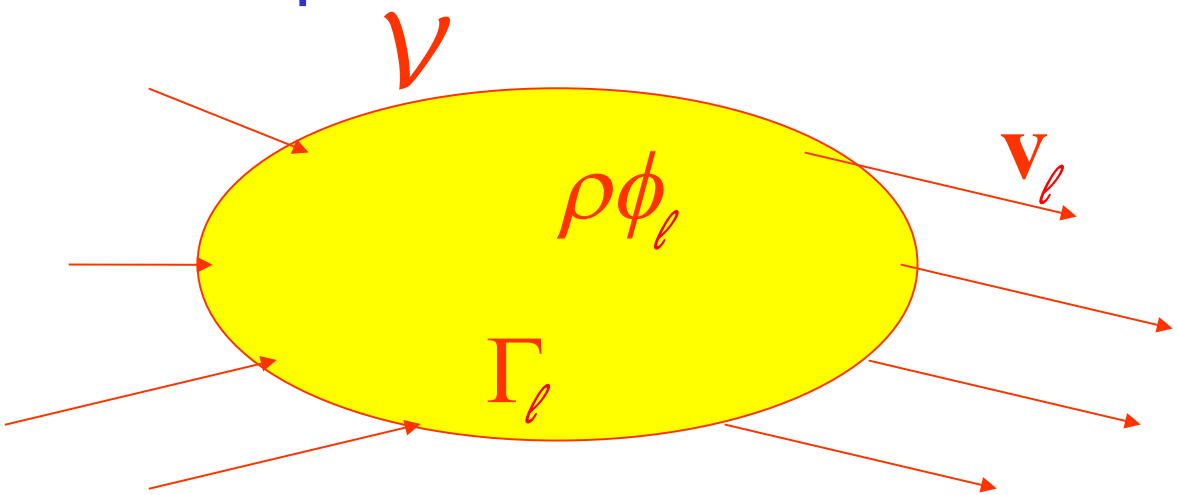
2. Potential flow assumption $\mathbf{v} = \nabla \Psi$

$$\begin{cases} \nabla^2 \Psi = \dfrac{\Gamma}{\bar{\varphi}} \\ \mathbf{n} \cdot \frac{d\mathbf{x}_\Gamma}{dt} = \mathbf{n} \cdot \nabla \Psi \\ \Psi = 0\,, \quad \text{on free part of the boundary} \\ \mathbf{n} \cdot \nabla \Psi = 0\,, \quad \text{on obstacles} \end{cases}$$



POLITECNICO DI TORINO

Tumours as multiphase systems



Extracellular liquid

$$\frac{\partial \phi_\ell}{\partial t} + \nabla \cdot (\phi_\ell \mathbf{v}_\ell) = \Gamma_\ell$$

ECM components

$$\frac{\partial \phi_m}{\partial t} + \nabla \cdot (\phi_m \mathbf{v}_m) = \Gamma_m \quad \Longrightarrow \quad \frac{\partial \phi_{m_j}}{\partial t} + \nabla \cdot (\phi_{m_j} \mathbf{v}_m) = \Gamma_{m_j}$$

POLITECNICO DI TORINO

Tumours as multiphase systems

$$\frac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha \mathbf{v}_\alpha) = \Gamma_\alpha$$

saturation $\sum_\alpha \phi_\alpha = 1$

closed mixture assumption

$$\nabla \cdot \sum_{\alpha=c,m,\ell,v} (\phi_\alpha \mathbf{v}_\alpha) = \sum_{\alpha=c,m,\ell,v} \Gamma_\alpha = \mathbf{0}$$

Constrained mixture assumption

$$\mathbf{v}_\alpha = \mathbf{v} \quad \forall \alpha$$

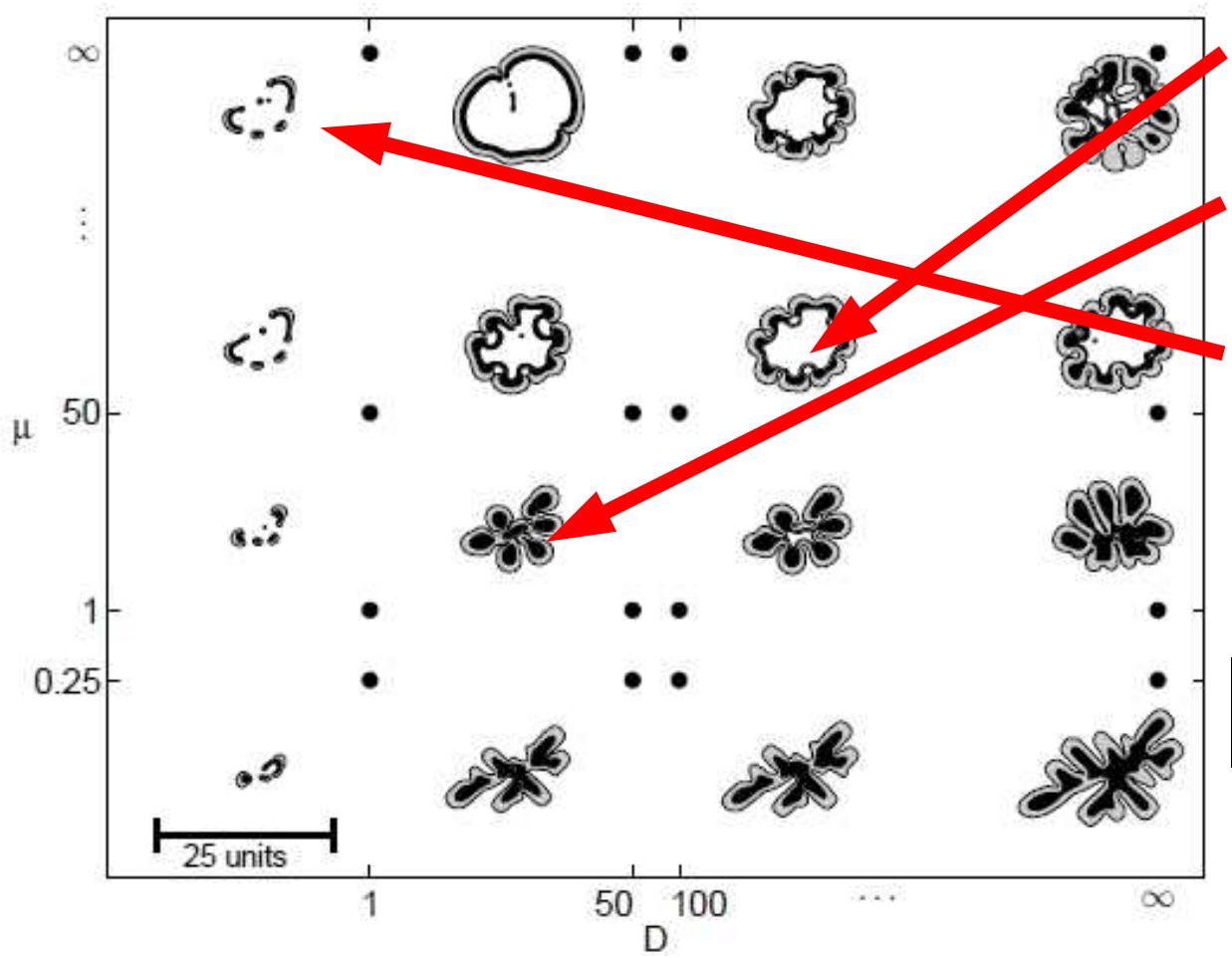
$$\nabla \cdot \mathbf{v} = \sum_{\alpha=c,m,\ell,v} \Gamma_\alpha = \mathbf{0}$$

Potential flow assumption

$$\mathbf{v} = \nabla \Psi$$

Only tumour cells in 3D

Macklin & Lowengrub JTB (2008)



Compact

Fingering

Fragmenting

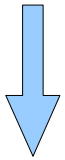
Original movies at biomathematics.shis.uth.tmc.edu/Multimedia.php

POLITECNICO DI TORINO

Momentum balance equations

$$\frac{d}{dt}\int_{\mathrm{V}} \rho\phi_c \mathbf{v}_c \, dV = -\int_{\partial\mathrm{V}} \rho\phi_c \mathbf{v}_c (\mathbf{v}_c \cdot \mathbf{n}) \, d\Sigma + \int_{\partial\mathrm{V}} \widetilde{\mathbf{T}}_c^T \mathbf{n} \, d\Sigma$$

$$+ \int_{\mathrm{V}} \widetilde{\mathbf{m}}_c \, dV + \int_{\mathrm{V}} \rho\Gamma_c \mathbf{v}_c \, dV + \int_{\mathrm{V}} \rho\phi_c \mathbf{b}_c \, dV \, ,$$



$$\rho\phi_c \left(\frac{\partial \mathbf{v}_c}{\partial t} + \mathbf{v}_c \cdot \nabla \mathbf{v}_c \right) = \nabla \cdot \widetilde{\mathbf{T}}_c + \rho\phi_c \mathbf{b}_c + \widetilde{\mathbf{m}}_c$$

$$\rho\phi_\ell \left(\frac{\partial \mathbf{v}_\ell}{\partial t} + \mathbf{v}_\ell \cdot \nabla \mathbf{v}_\ell \right) = \nabla \cdot \widetilde{\mathbf{T}}_\ell + \rho\phi_\ell \mathbf{b}_\ell + \widetilde{\mathbf{m}}_\ell$$

$$\rho\phi_m \left(\frac{\partial \mathbf{v}_m}{\partial t} + \mathbf{v}_m \cdot \nabla \mathbf{v}_m \right) = \nabla \cdot \widetilde{\mathbf{T}}_m + \rho\phi_m \mathbf{b}_m + \widetilde{\mathbf{m}}_m$$

POLITECNICO DI TORINO

Momentum balance equations

$$\frac{d}{dt}\int_{\mathrm{V}} \rho\phi_c \mathbf{v}_c \, dV = -\int_{\partial \mathrm{V}} \rho\phi_c \mathbf{v}_c (\mathbf{v}_c \cdot \mathbf{n}) \, d\Sigma + \int_{\partial \mathrm{V}} \widetilde{\mathbf{T}}_c^T \mathbf{n} \, d\Sigma$$

$$+ \int_{\mathrm{V}} \widetilde{\mathbf{m}}_c \, dV + \int_{\mathrm{V}} \rho\Gamma_c \mathbf{v}_c \, dV + \int_{\mathrm{V}} \rho\phi_c \mathbf{b}_c \, dV \,,$$

$$\rho\phi_c \left(\frac{\partial \mathbf{v}_c}{\partial t} + \mathbf{v}_c \cdot \nabla \mathbf{v}_c \right) = \nabla \cdot \widetilde{\mathbf{T}}_c + \rho\phi_c \mathbf{b}_c + \widetilde{\mathbf{m}}_c$$

$$\begin{cases} \dfrac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha \mathbf{v}_\alpha) = \Gamma_\alpha \,, \\ \nabla \cdot \widetilde{\mathbf{T}}_\alpha + \widetilde{\mathbf{m}}_\alpha = \mathbf{0} \,, \end{cases}$$

POLITECNICO DI TORINO

Darcy's law

$-\phi_\ell \nabla P$ $\qquad$ $-\phi_\ell^2 \mathbf{K}^{-1} \mathbf{v}_\ell$

$$\rho\phi_\ell \left(\frac{\partial \mathbf{v}_\ell}{\partial t} + \mathbf{v}_\ell \cdot \nabla \mathbf{v}_\ell \right) = \nabla \cdot \widetilde{\mathbf{T}}_\ell + \rho\phi_\ell \mathbf{b}_\ell + \widetilde{\mathbf{m}}_\ell$$

$$\mathbf{v}_\ell = -\frac{\mathbf{K}}{\mu\phi_\ell} \nabla P$$

Darcy's law

POLITECNICO DI TORINO

Brinkman equation

$$-\phi_\ell \nabla P + \mu \nabla^2 \mathbf{v} \qquad -\phi_\ell^2 \mathbf{K}^{-1} \mathbf{v}_\ell$$

$$\rho\phi_\ell \left(\frac{\partial \mathbf{v}_\ell}{\partial t} + \mathbf{v}_\ell \cdot \nabla \mathbf{v}_\ell \right) = \nabla \cdot \widetilde{\mathbf{T}}_\ell + \rho\phi_\ell \mathbf{b}_\ell + \widetilde{\mathbf{m}}_\ell$$

Brinkman equation

POLITECNICO DI TORINO

Unsaturated cells in ECM

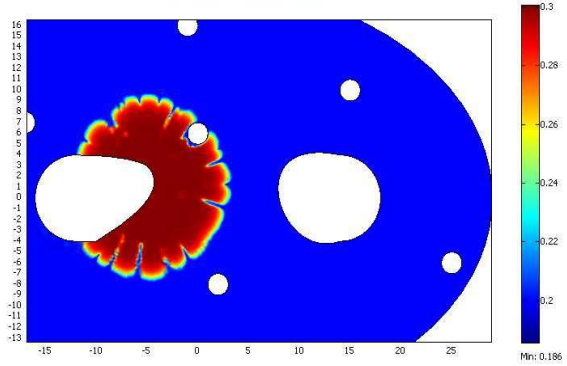
$$\nabla \cdot \mathbf{T}_c + \mathbf{m}_{cm} + \rho \phi_c \mathbf{b}_c = \mathbf{0}$$

$-\Sigma\ (\phi_c)\mathbf{I}$ $\quad -\mathbf{K}^{-1}\mathbf{v}_c$ $\quad \chi \nabla C$

$$\mathbf{v}_c = \mathbf{K}\left(-\nabla \Sigma(\phi_c) + \chi \nabla C\right)$$

$$\frac{\partial \phi_c}{\partial t} + \nabla \cdot (\phi_c \mathbf{v}_c) = \Gamma_c$$

$$\frac{\partial \phi_c}{\partial t} + \nabla \cdot (\chi \phi_c \mathbf{K} \nabla C) = \nabla \cdot (\phi_c \mathbf{K} \nabla \Sigma_c) + \Gamma_c$$



degenerate parabolic eq. Generalized Keller-Segel eq.

POLITECNICO DI TORINO

Saturated biphasic mixture

$$\frac{\partial \varphi_1}{\partial t} + \nabla \cdot (\varphi_1 \mathbf{v}_1) = \Gamma_1$$

$$\frac{\partial \varphi_2}{\partial t} + \nabla \cdot (\varphi_2 \mathbf{v}_2) = \Gamma_2$$

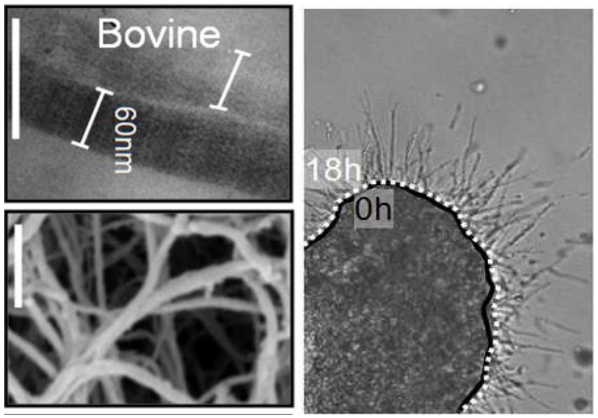
$$\nabla \cdot \mathbf{T} - \mathbf{M}\mathbf{v} = \mathbf{0}$$

$$\varphi_1 + \varphi_2 = \text{const}$$

$$\mathbf{T} = \lambda \mathbf{I} + \ldots.$$

$$\mathbf{v} = \mathbf{M}^{-1} \nabla \lambda$$

Back to the continuous model



$$\frac{\partial \phi_c}{\partial t} + \nabla \cdot (\phi_c \mathbf{v}_c) = \Gamma_c \,,$$

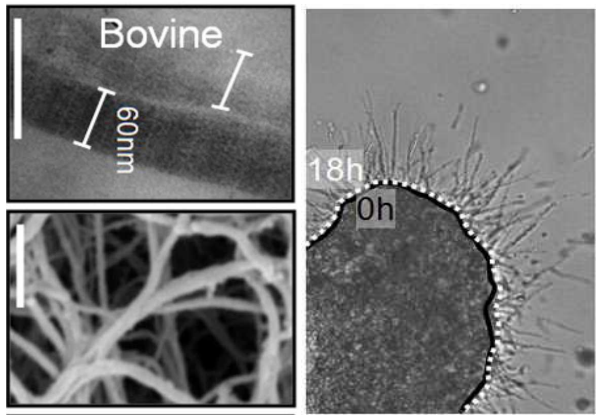
$$\nabla \cdot \mathbf{T}_c + \mathbf{m}_{cm} = \mathbf{0}$$

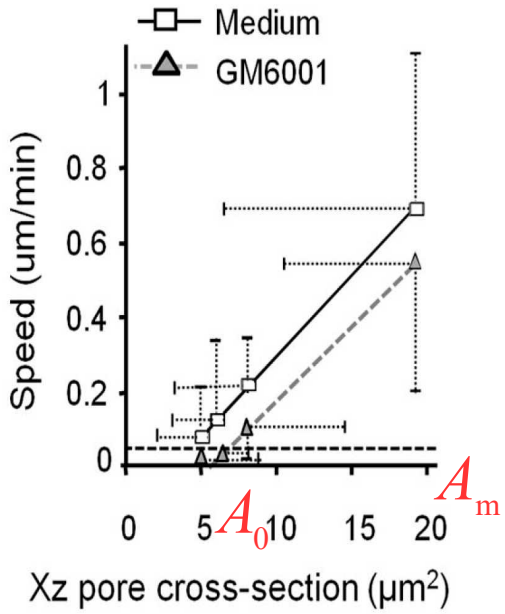
$$\mathbf{v}_c = -\mathbf{K} \nabla \cdot \mathbf{T}_c$$

Motility tensor

POLITECNICO DI TORINO

Back to the continuous model





Implications for interaction force $\mathbf{m}_{cm}$ and motility K?

$$\frac{\partial \phi_c}{\partial t} + \nabla \cdot (\phi_c \mathbf{v}_c) = \Gamma_c \,,$$

$$\nabla \cdot \mathbf{T}_c + \mathbf{m}_{cm} = \mathbf{0}$$

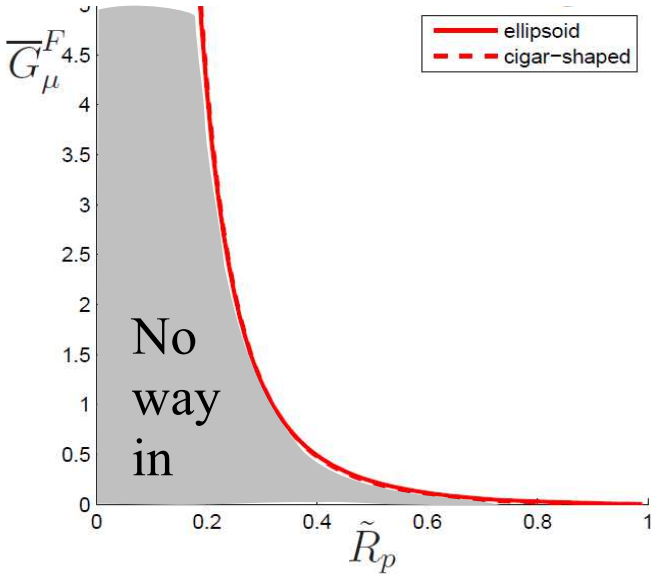
$$\mathbf{v}_c = \alpha \frac{[A_m(\phi_m) - A_0]_+}{\left(1 + \frac{A_m(\phi_m) - A_0}{A_1}\right)^n} \nabla \cdot \mathbf{T}_c$$

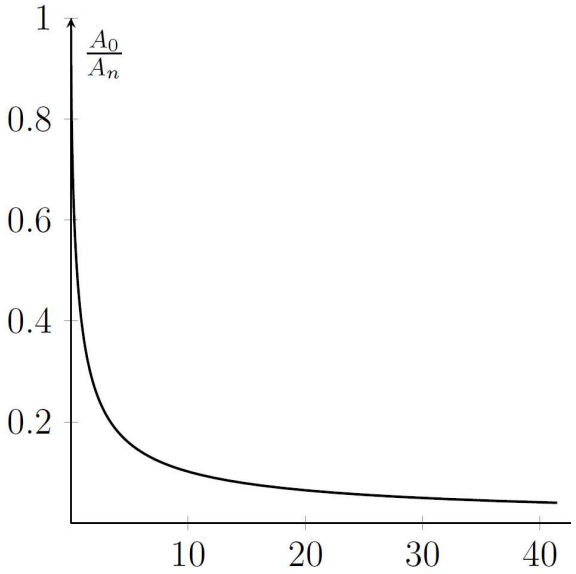
A_0 depends on:

- **Pore vs. nucleus size**
- **Nucleus elasticit**
- **Cell adhesion**
- **Active traction**
- **Action of MMP**

Back to the continuous model

$$G_\mu^F = \frac{\rho_b \alpha_{ECM} F_b^M}{\mu}$$





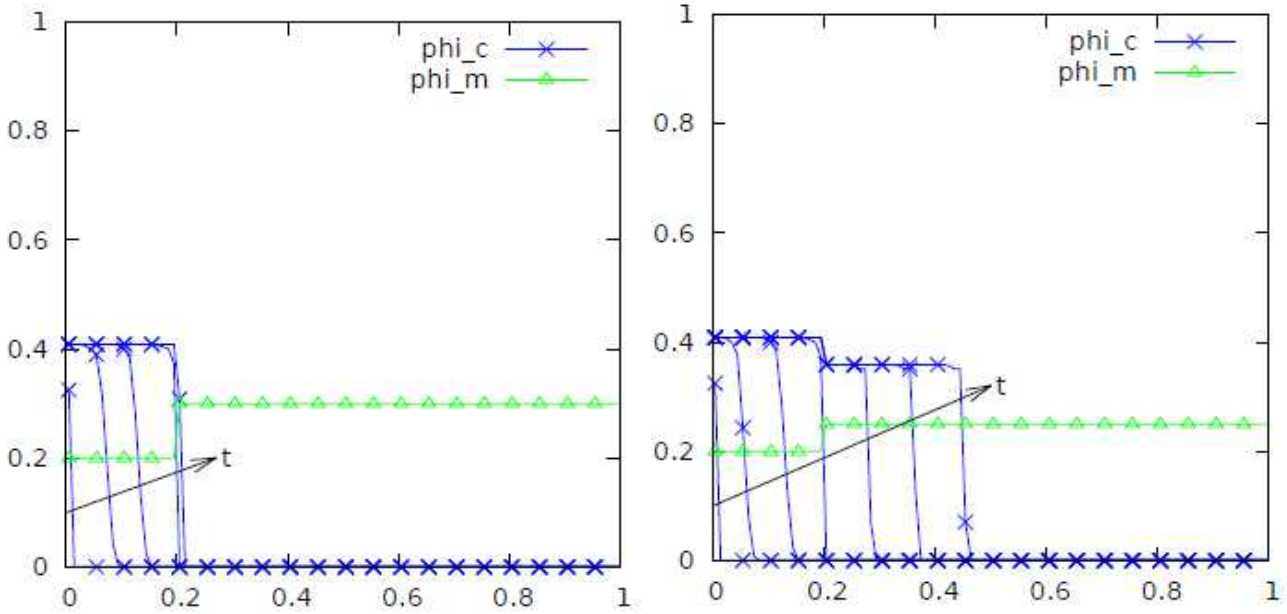
$$G = \frac{1}{3\mu}|\mathrm{tr}\mathbf{T}_c|$$

POLITECNICO DI TORINO

One population

$$\frac{\partial \phi_c}{\partial t} + \nabla \cdot (\phi_c \mathbf{v}_c) = \Gamma_c; \longleftarrow \left[\gamma_c^i \mathcal{H}_\varepsilon(\psi_0^i - \psi) - \delta_c^i\right] \phi_c^i$$

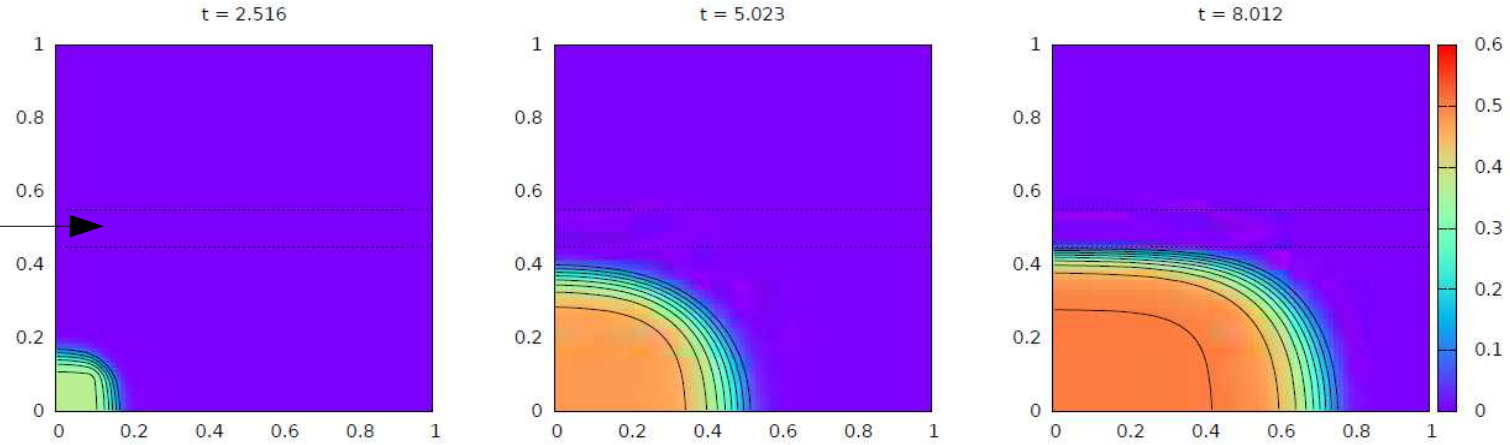
$$\mathbf{v}_c = \alpha \frac{[A_m(\phi_m) - A_0]_+}{\left(1 + \frac{A_m(\phi_m) - A_0}{A_1}\right)^n} \nabla \cdot \mathbf{T}_c$$



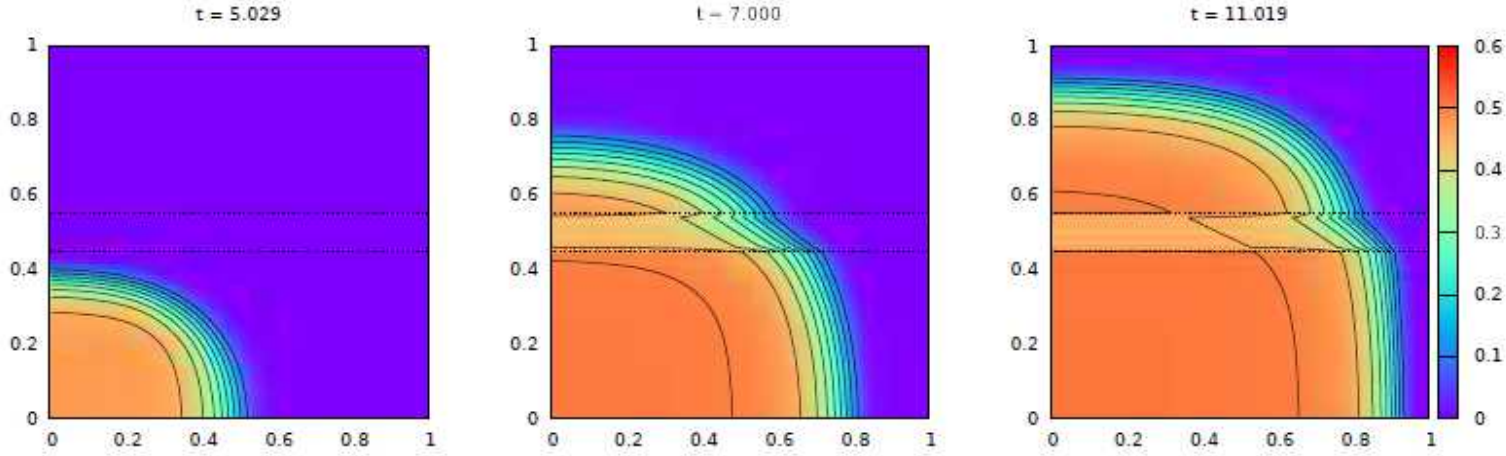
POLITECNICO DI TORINO

Growth below a thick region of ECM

$\phi_m^+ = 0.3$



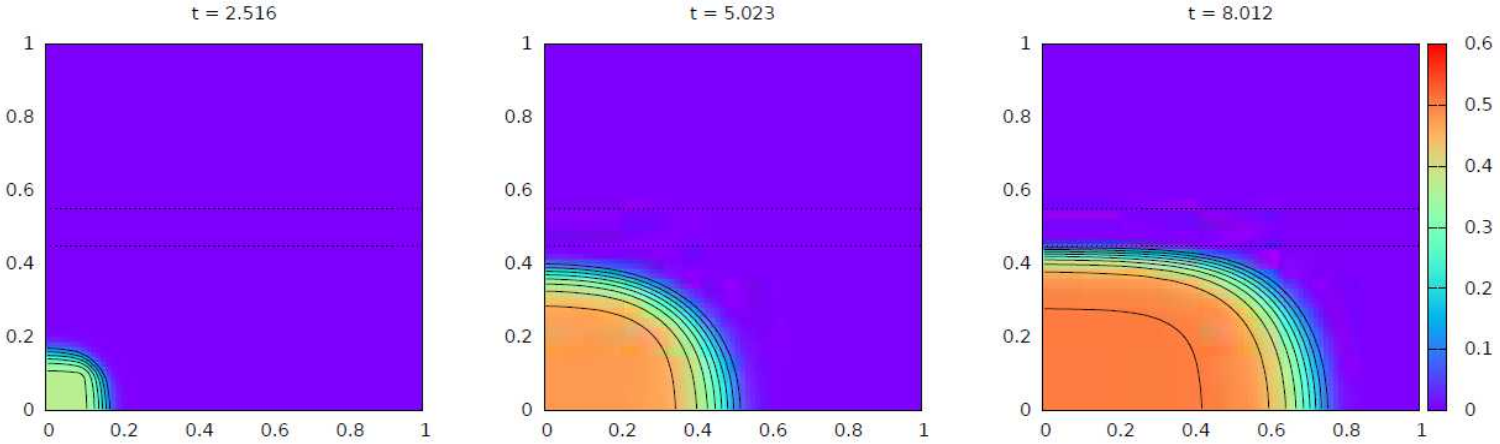
$\phi_m^+ = 0.25$



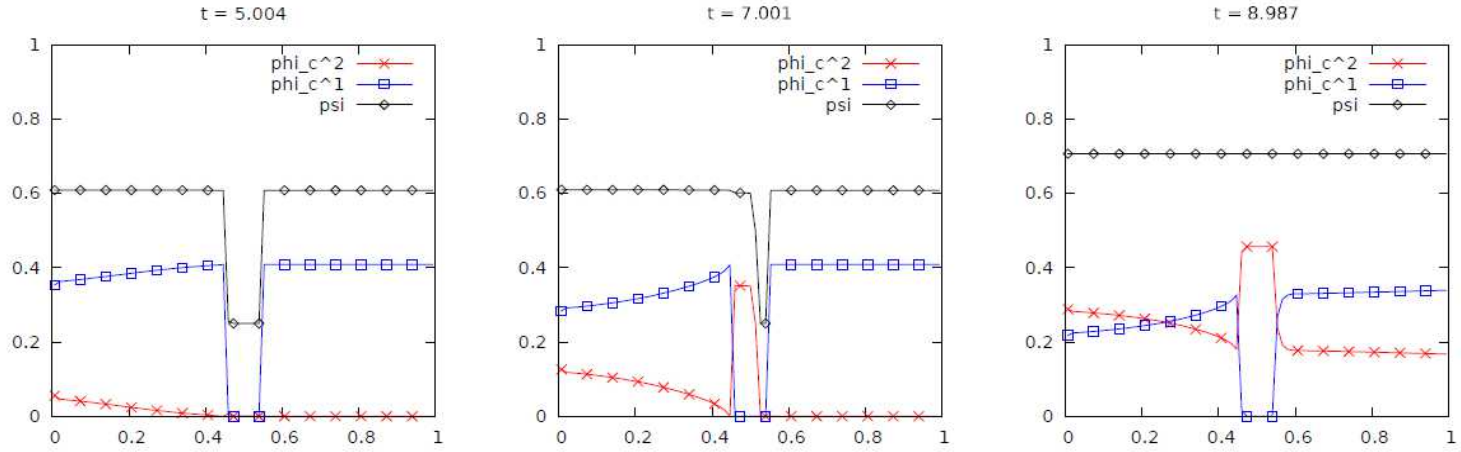
POLITECNICO DI TORINO

Effect of nucleus deformability

Stiffer nucleus



Softer nucleus

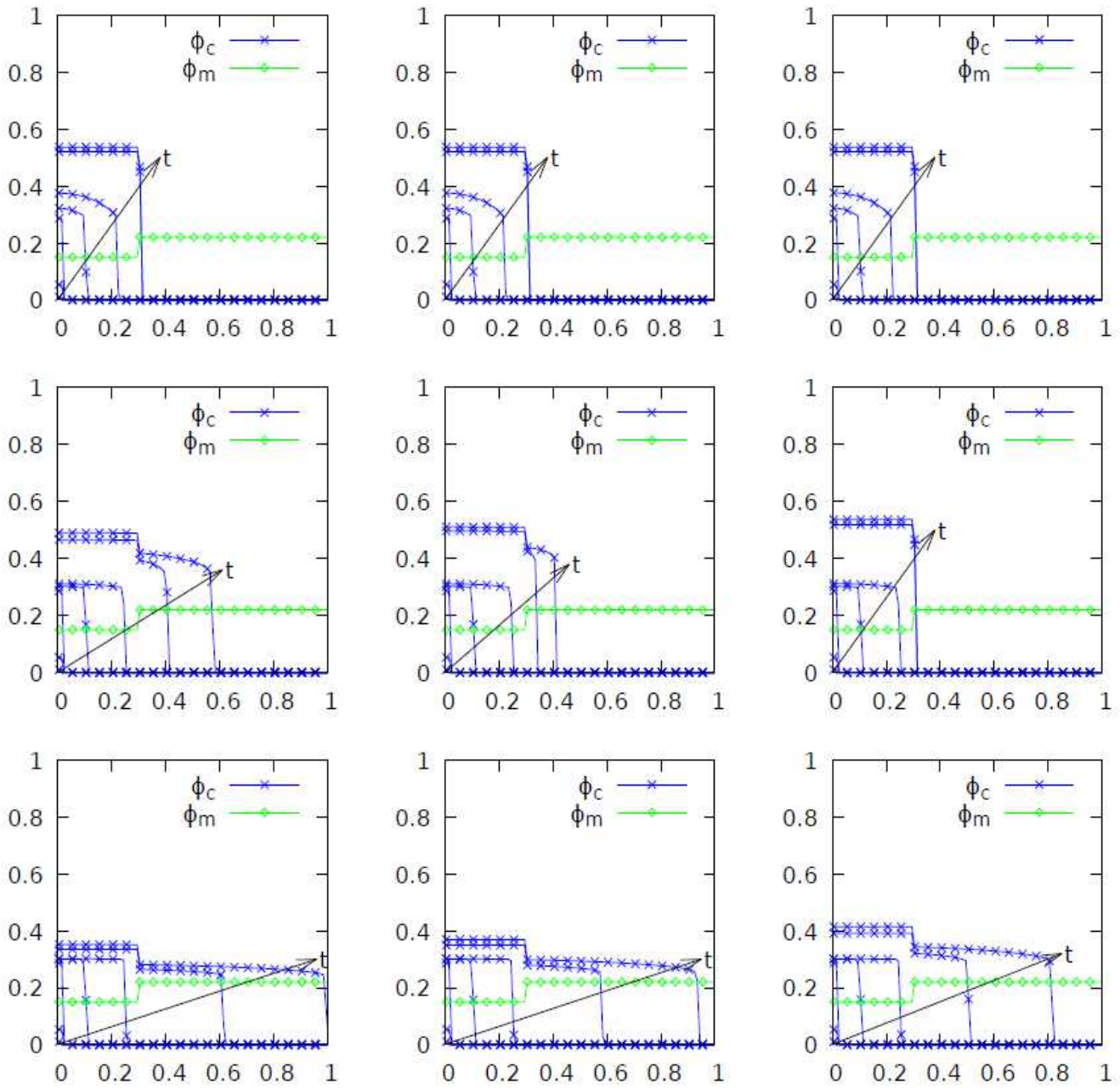


Nuclear membrane stiffness

Bulk stiffness

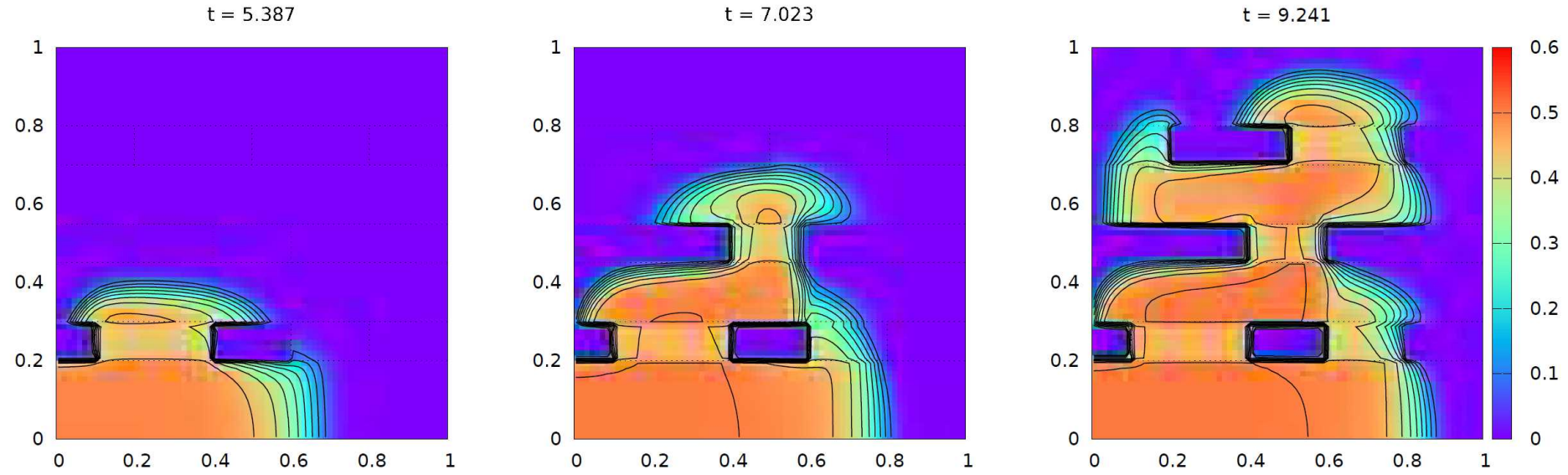
$\beta_0 = 0.5$ $\beta_0 = 2$ $\beta_0 = 8$

$$\beta := \frac{\lambda R_n}{\mu}$$



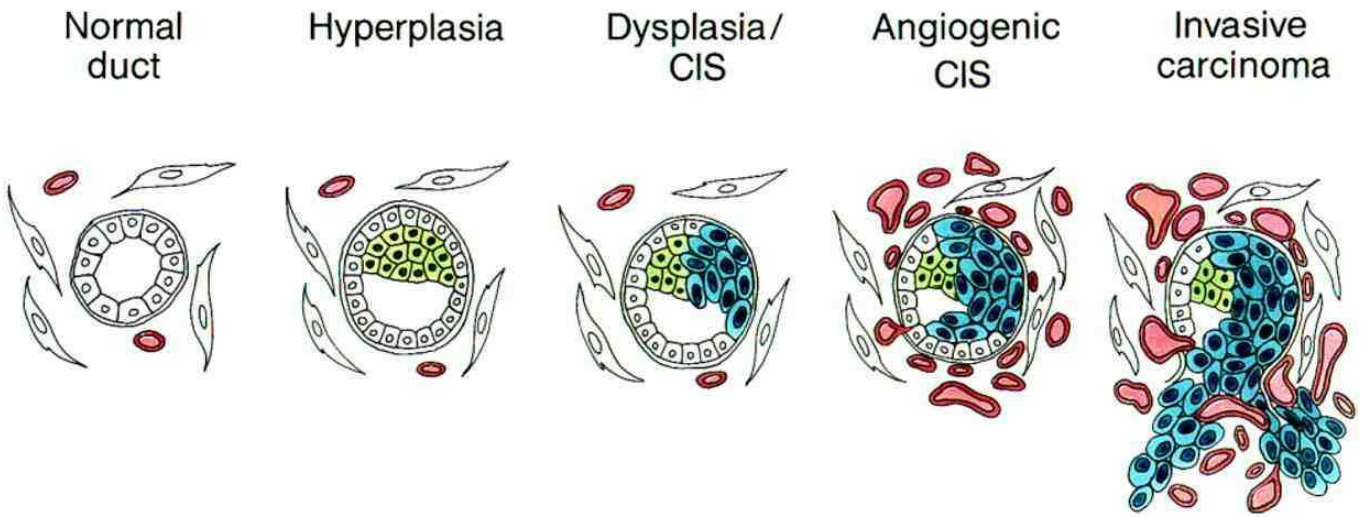
POLITECNICO DI TORINO

Heterogeneus ECM



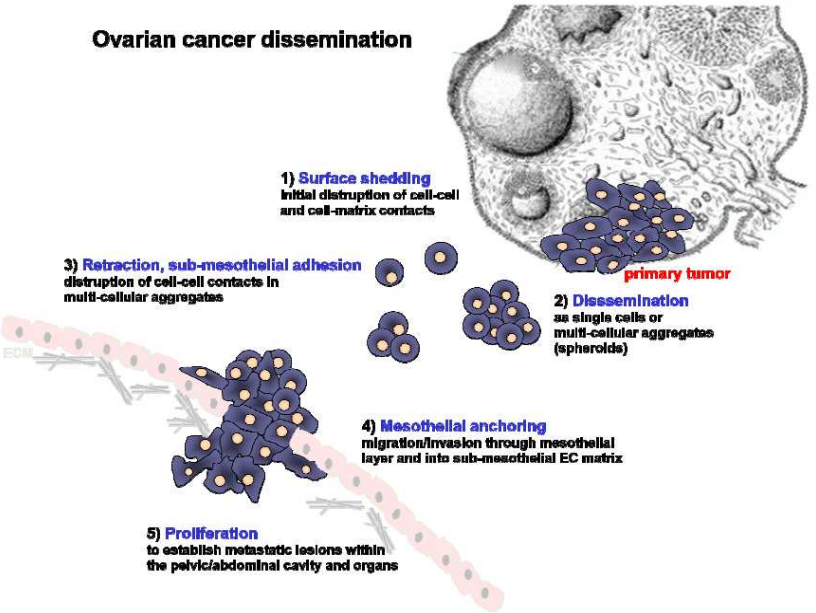
POLITECNICO DI TORINO

Tumour compartimentalization and invasion

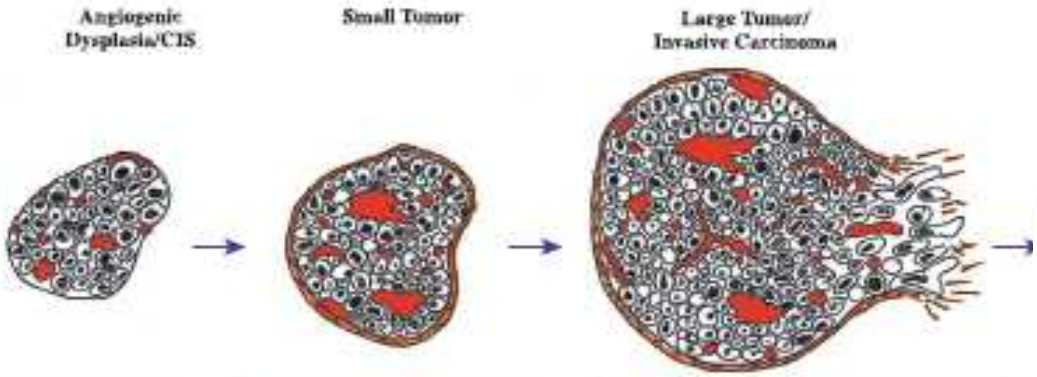


Breast

Ovary



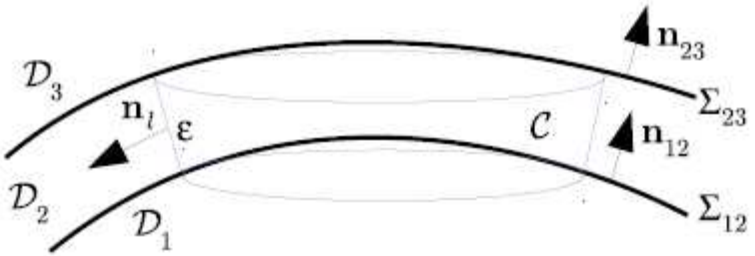
Pancreas



POLITECNICO DI TORINO

Membrane problem

$$
\begin{cases}
\dfrac{\partial n_i}{\partial t} = \nabla \cdot (\mu_i n_i \nabla p) + \Gamma_i & \text{in } \mathcal{D}_i, \quad i = 1,2,3, \\
\mu_1 n_1 \mathbf{n}_{12} \cdot \nabla p(n_1) = \mu_2 n_2 \mathbf{n}_{12} \cdot \nabla p(n_2) & \text{on } \Sigma_{12}, \\
\mu_2 n_2 \mathbf{n}_{23} \cdot \nabla p(n_2) = \mu_3 n_3 \mathbf{n}_{23} \cdot \nabla p(n_3) & \text{on } \Sigma_{23}, \\
p(n_1) = p(n_2) & \text{on } \Sigma_{12}, \\
p(n_2) = p(n_3) & \text{on } \Sigma_{23},
\end{cases}
$$



$\varepsilon \to 0$

$$
\tilde{\mu}_2 [\![\Pi]\!] = \mu_1 n_1 \nabla p \cdot \mathbf{n} = \mu_3 n_3 \nabla p \cdot \mathbf{n}, \qquad \textit{where } \tilde{\mu}_2 = \lim_{\epsilon \to 0} \frac{\mu_2}{\epsilon}
$$

$$
\Pi'(n) := n\, p'(n),
$$

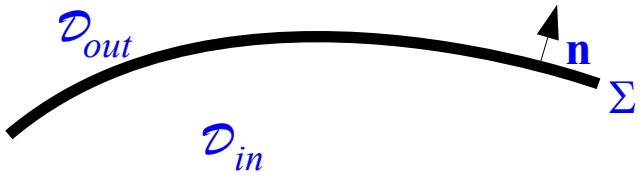
Generalization to more cell populations

$$
[\Pi(n_2)] = \sum_{\alpha=1}^{N} \frac{\mu_1^\alpha}{\tilde{\mu}_2^\alpha} n_1^\alpha \nabla p(n_2) \cdot \mathbf{n} = \sum_{\alpha=1}^{N} \frac{\mu_3^\alpha}{\tilde{\mu}_2^\alpha} n_3^\alpha \nabla p(n_3) \cdot \mathbf{n}, \qquad \text{on } \Sigma,
$$

POLITECNICO DI TORINO

Membrane problem

$$\begin{cases} \dfrac{\partial n}{\partial t} = \nabla \cdot (\mu n \nabla p(n)) + \Gamma, \\ [\![\mu n \mathbf{n} \cdot \nabla p(n)]\!] = 0, \qquad \text{on } \Sigma, \\ \tilde{\mu}[\![\Pi]\!] = \mu n \mathbf{n} \cdot \nabla p(n), \qquad \text{on } \Sigma, \end{cases}$$



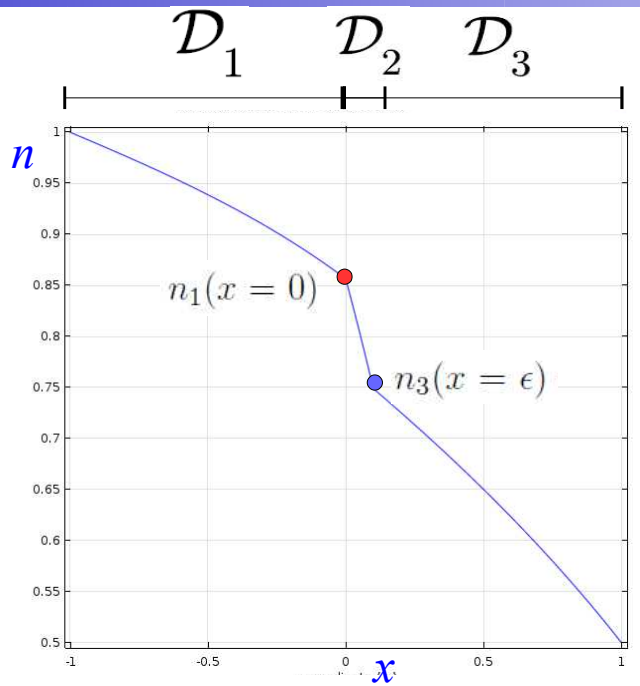
where

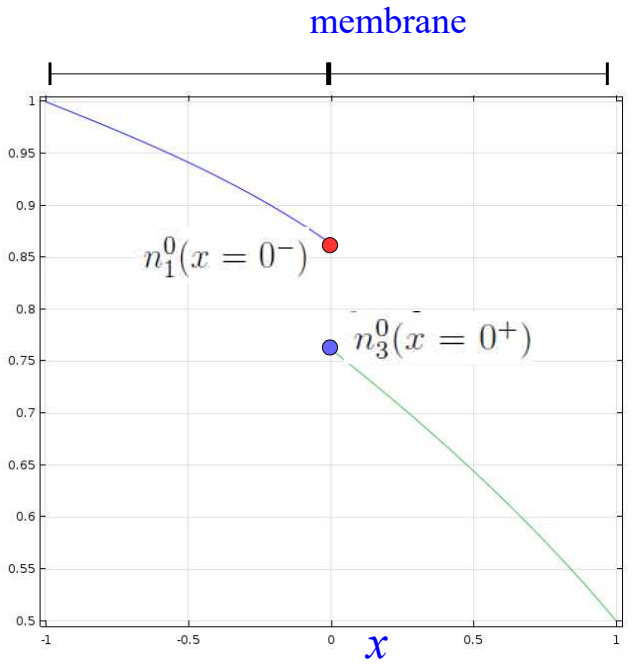
$$\Pi'(n) := n\, p'(n),$$

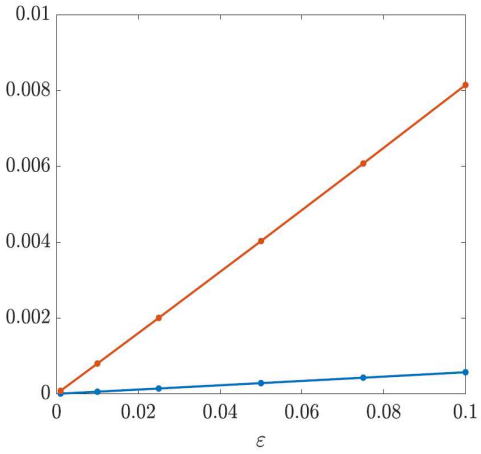
$$\text{if } \; p(n) = P \ln \frac{n}{n_0} \longrightarrow \tilde{\mu}[\![n]\!] = \mu \mathbf{n} \cdot \nabla n \longrightarrow$$

Kadem-Katchalsky interface condition

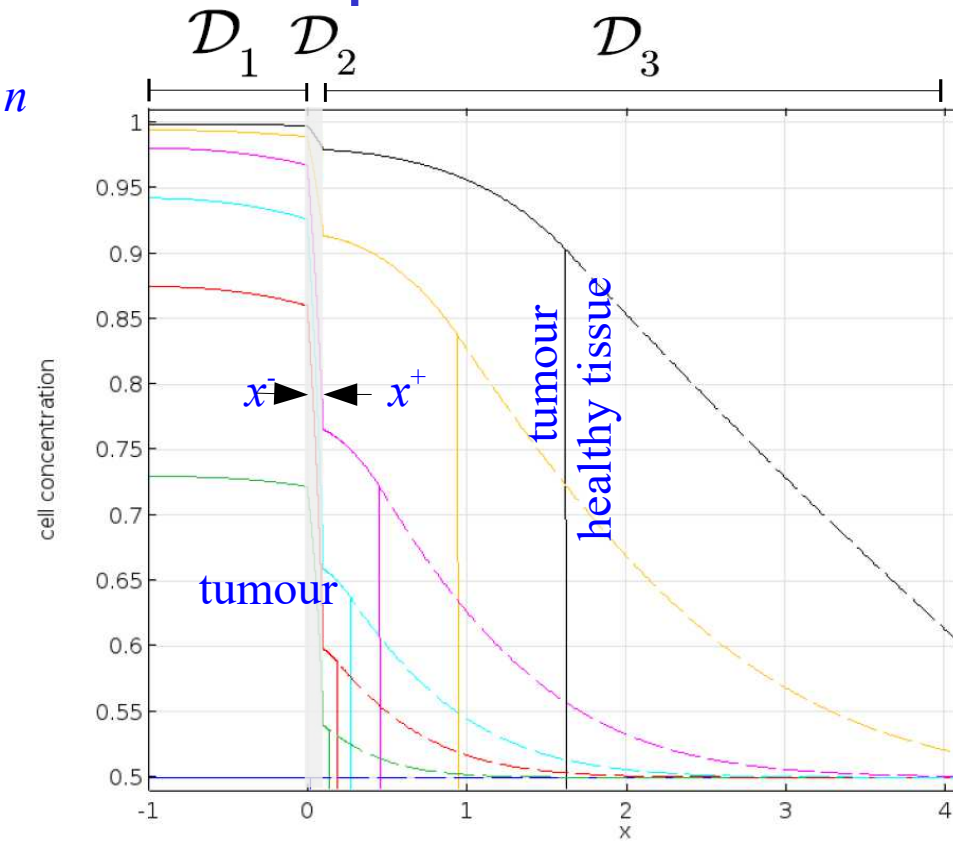
Stationary 1D problem



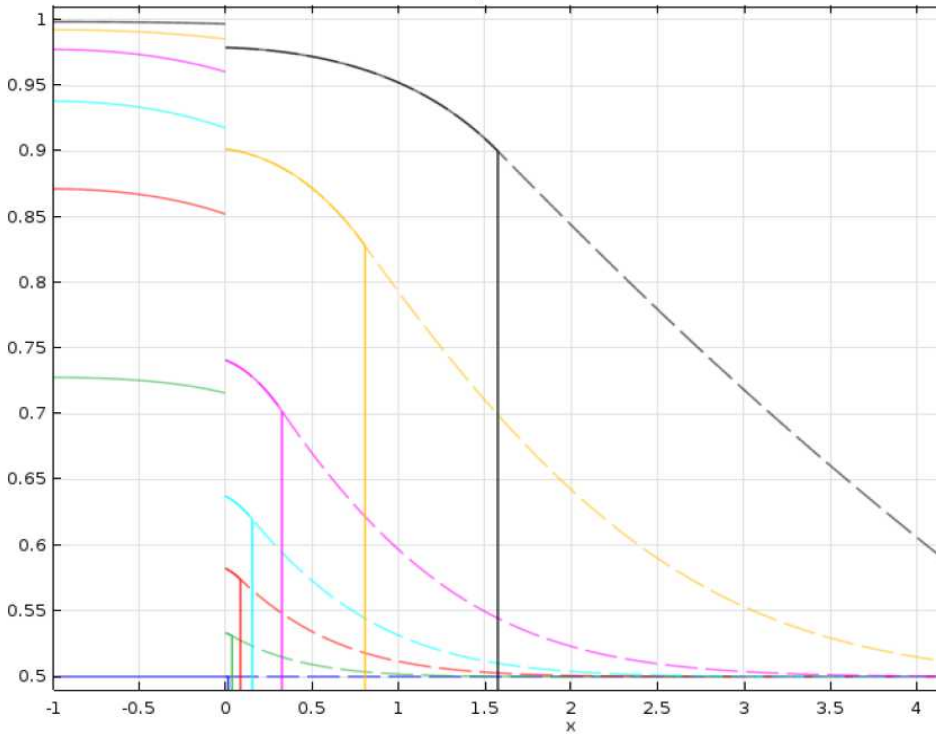




Unsteady 1D problem

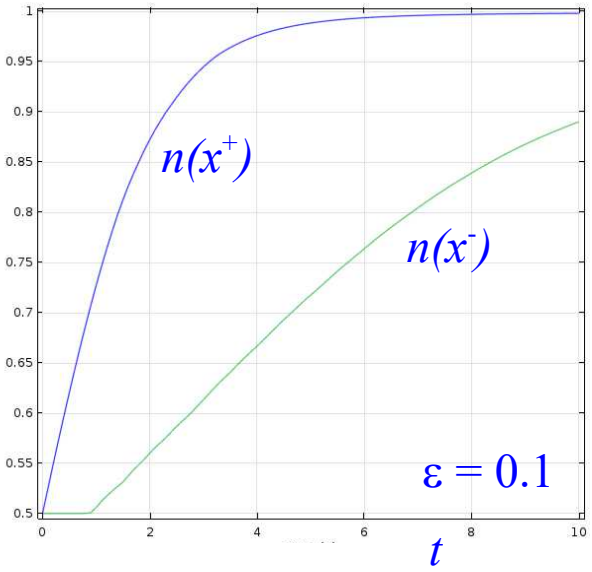


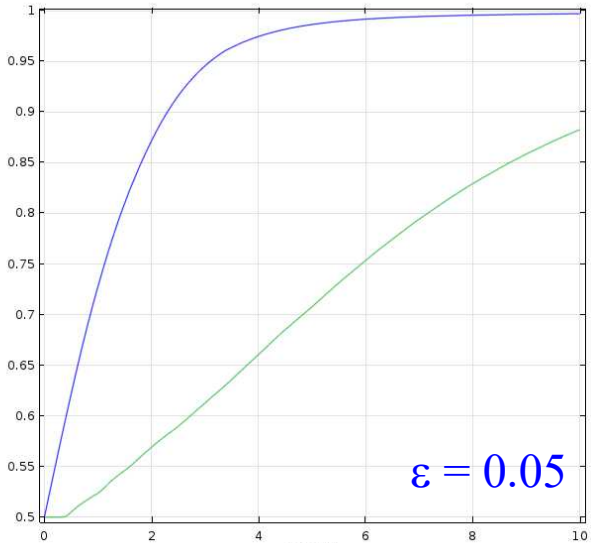
ε = 0.1

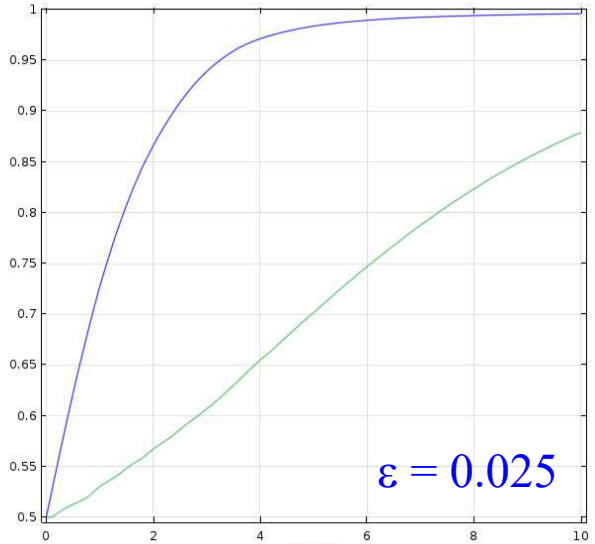


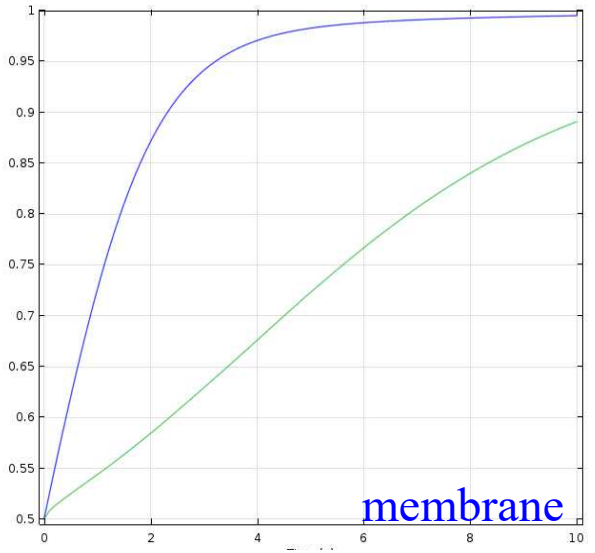
membrane

Unsteady 1D problem









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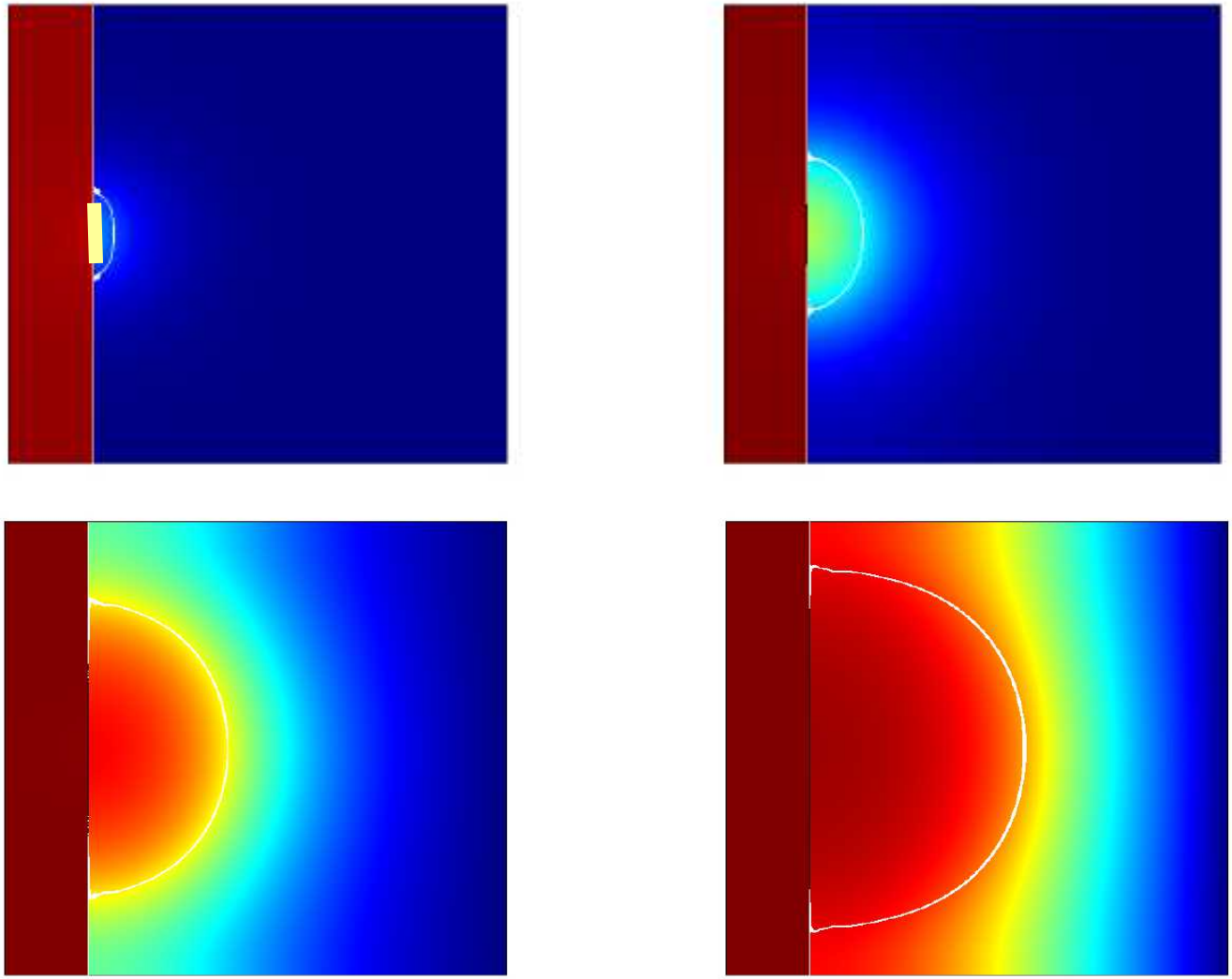
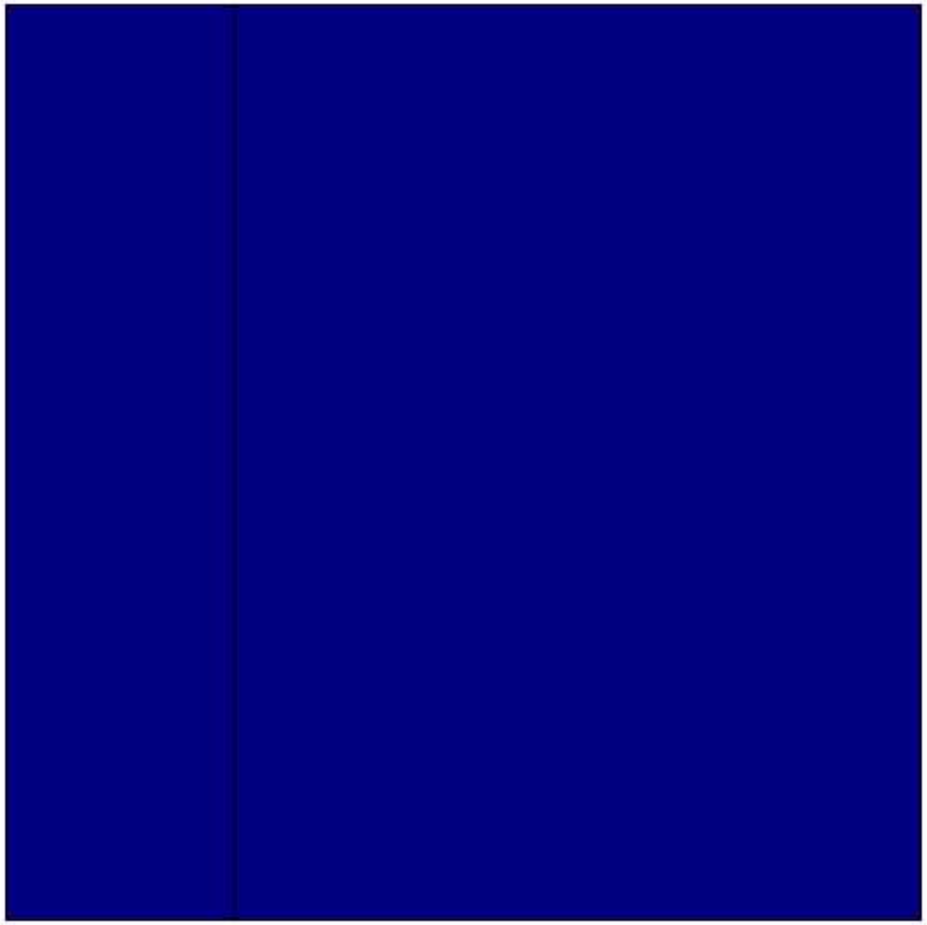
Unsteady 2D problem



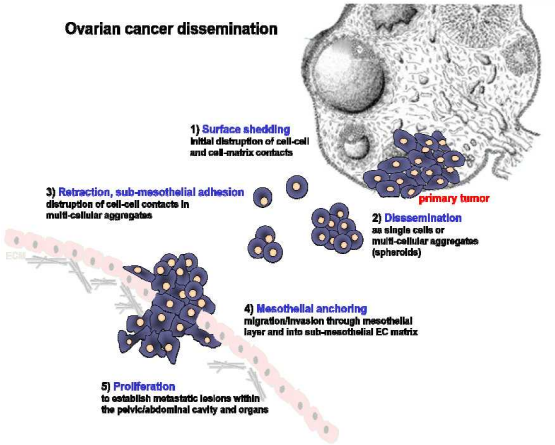
POLITECNICO
DI TORINO

Multiscale features



POLITECNICO DI TORINO

Invasion of ovary cancer cells

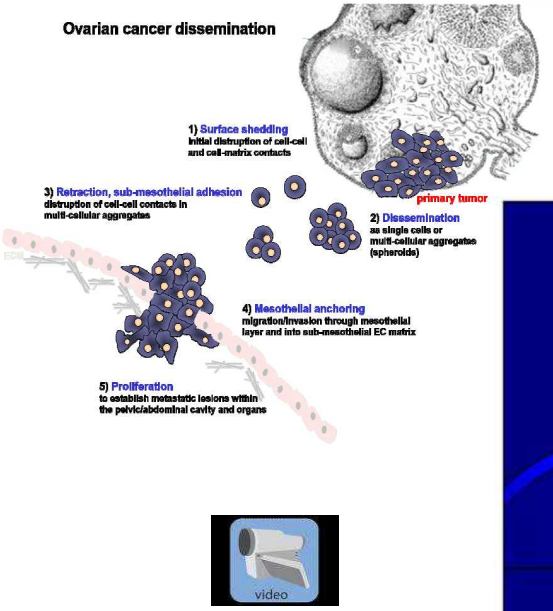


Adding tumour produced metallo-proteinases

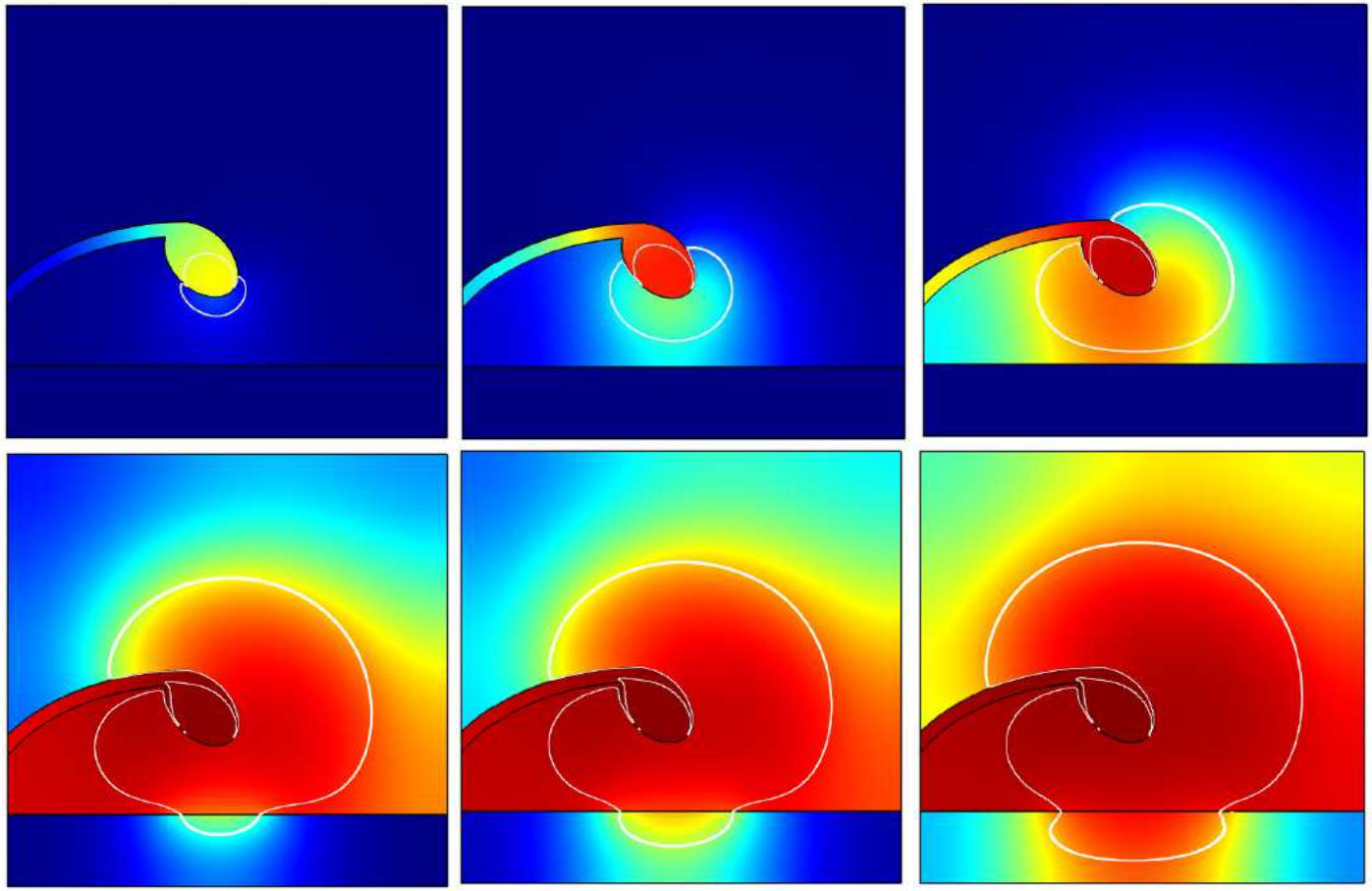
$$\frac{dA}{dt} = \alpha\left(A_1 - A\right) + \beta c_{MMP}$$

$$\tilde{\mu} = \bar{\mu}\ \frac{[A - A_0]_+}{1 + (A - A_0)}$$

Invasion of ovary cancer cells

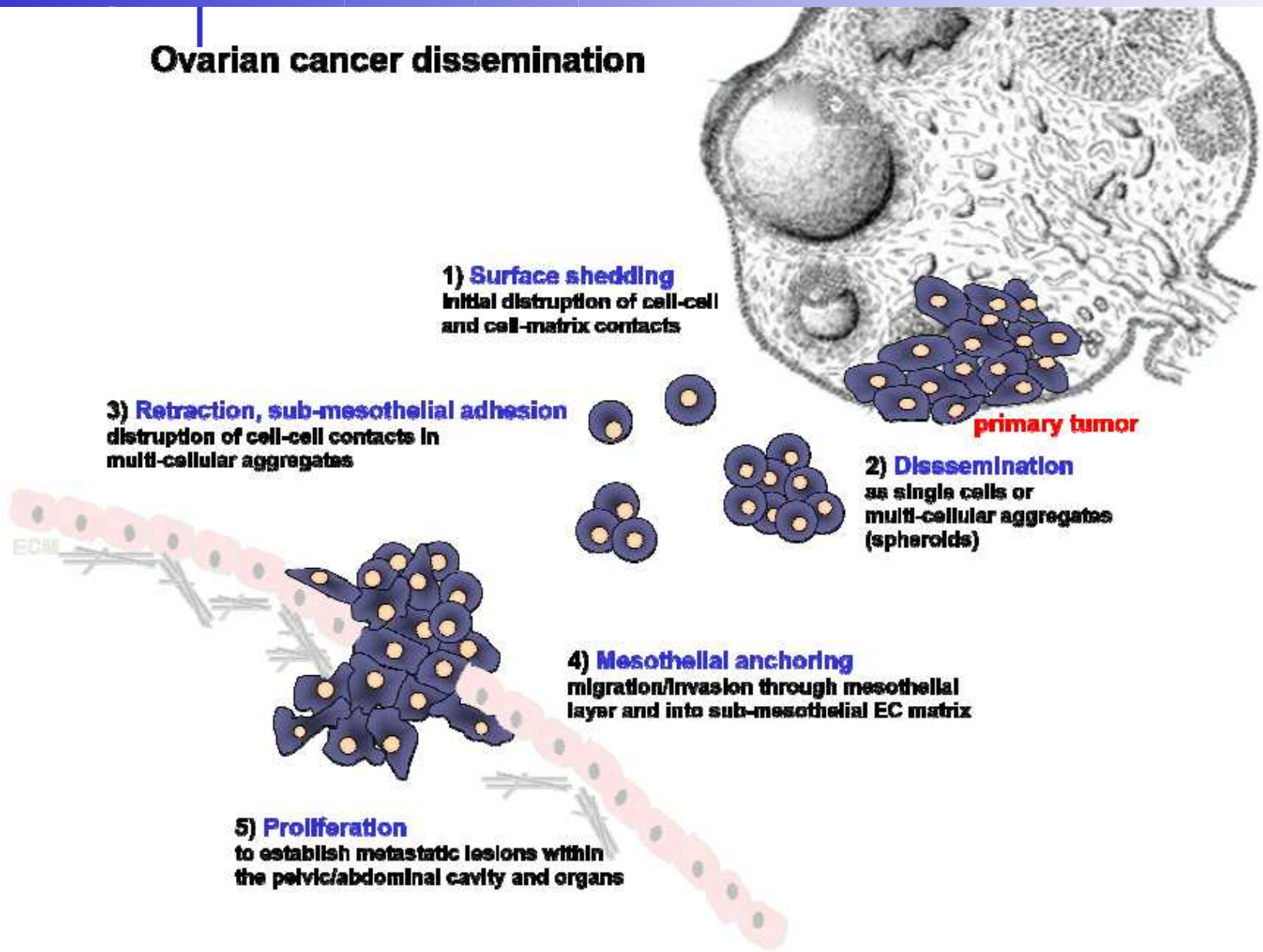


Adding tumour produced metallo-proteinases

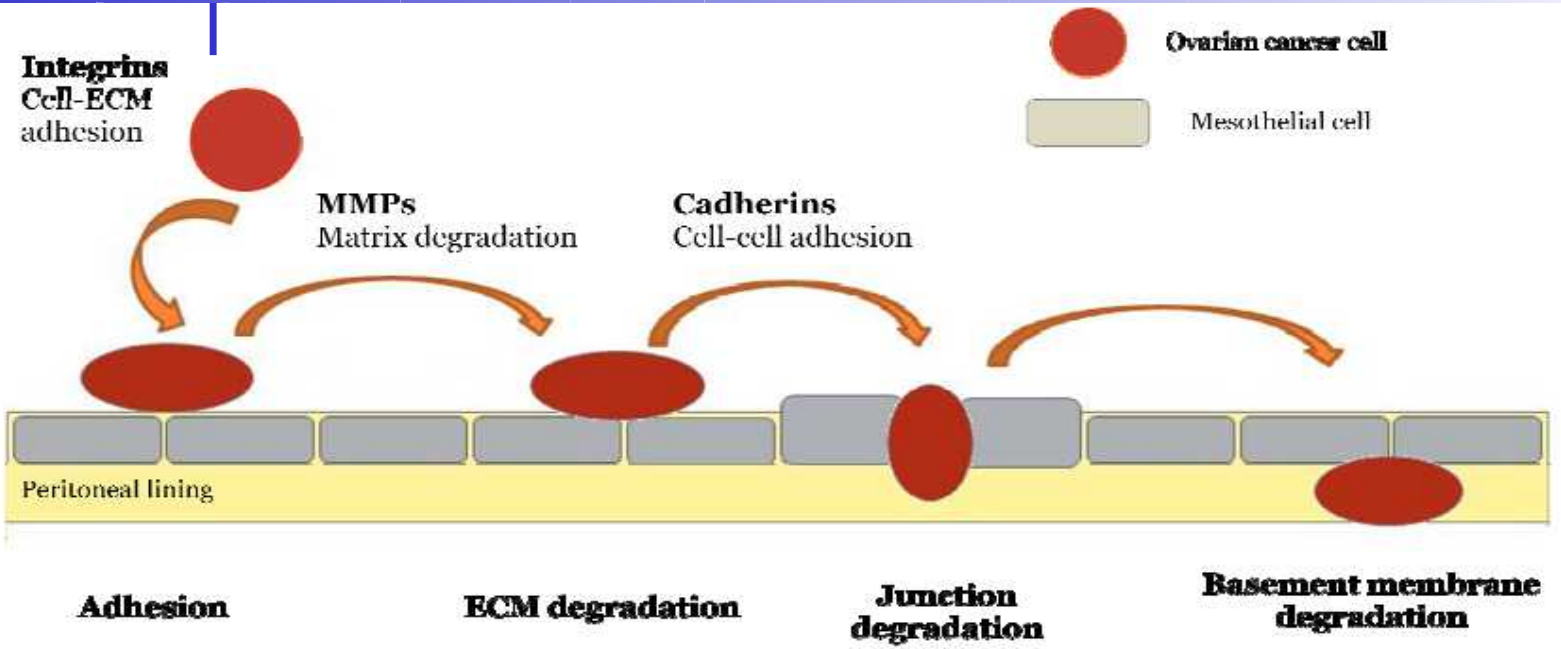


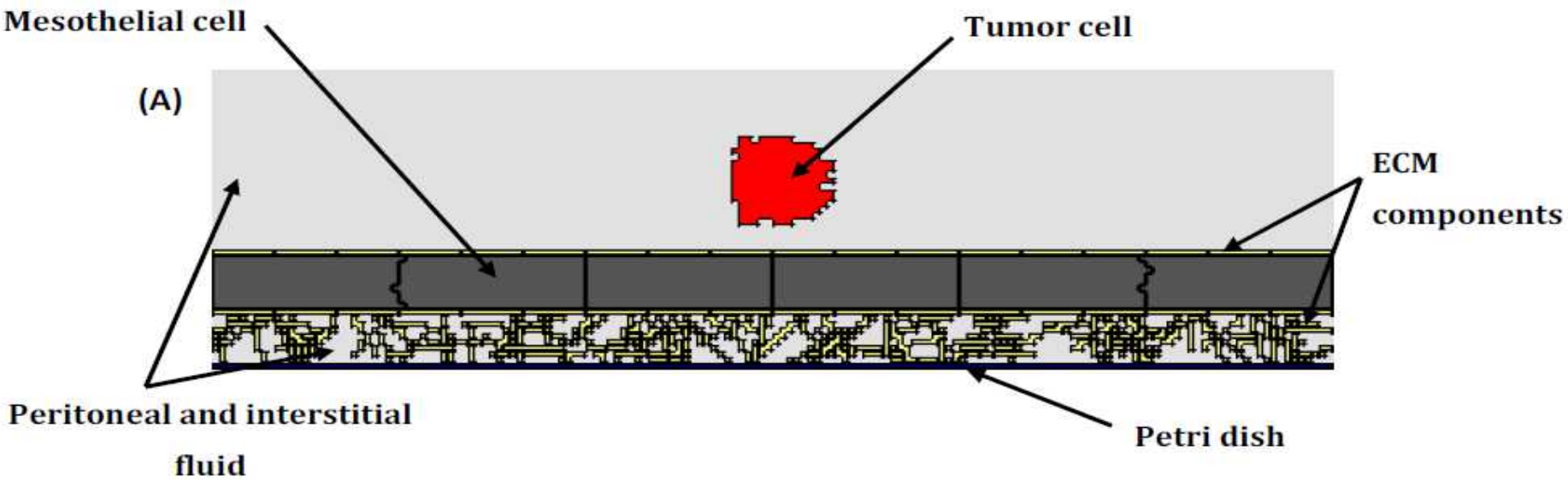
POLITECNICO DI TORINO

Invasion of ovary cancer cells

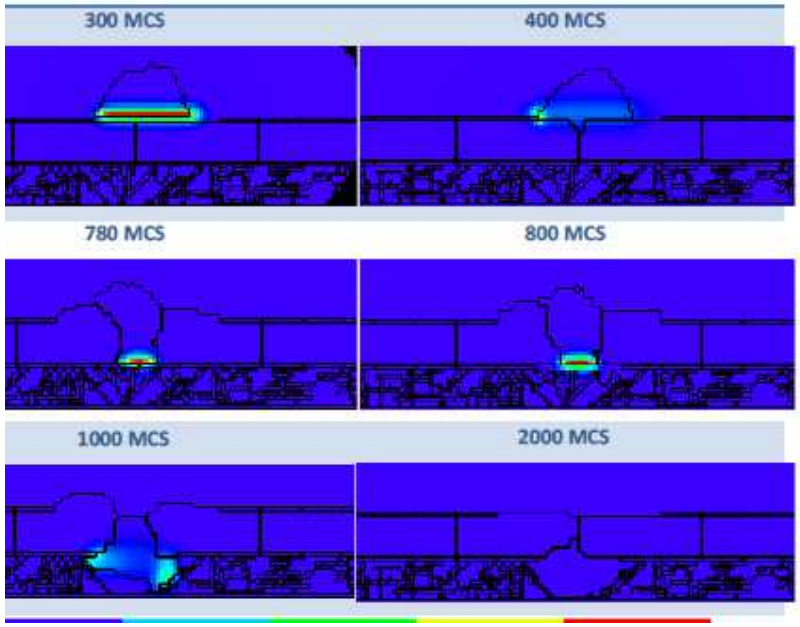


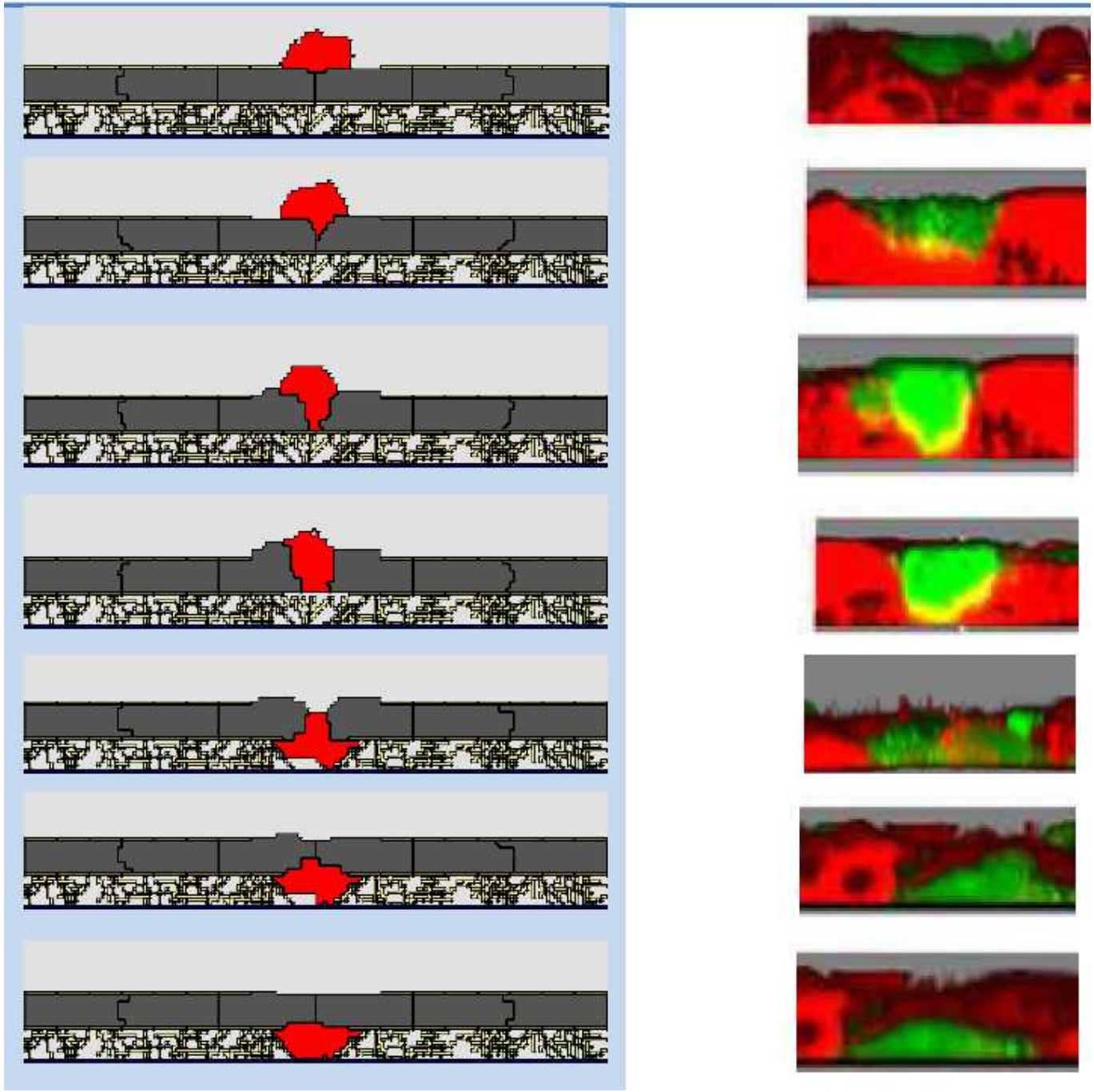
Invasion of ovary cancer cells






0 MCS
200 MCS
400 MCS
600 MCS
700 MCS
750 MCS
800 MCS
1000 MCS
1200 MCS
1400 MCS
1600 MCS
1800 MCS
2000 MCS
5000 MCS


300 MCS
400 MCS
780 MCS
800 MCS
1000 MCS
2000 MCS



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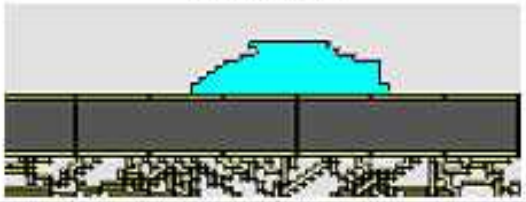
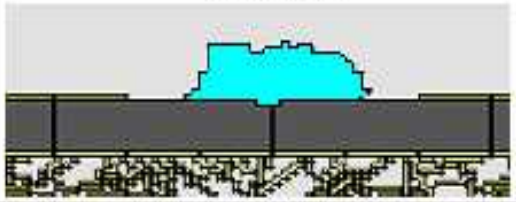
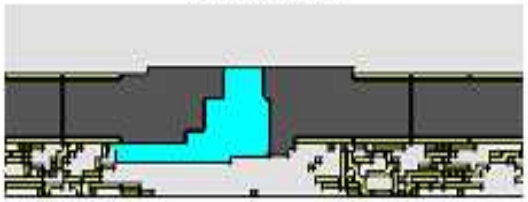
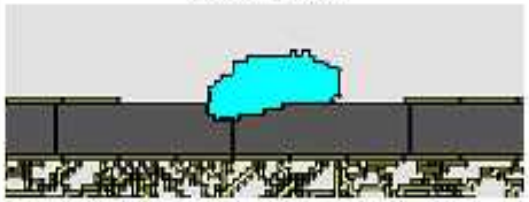
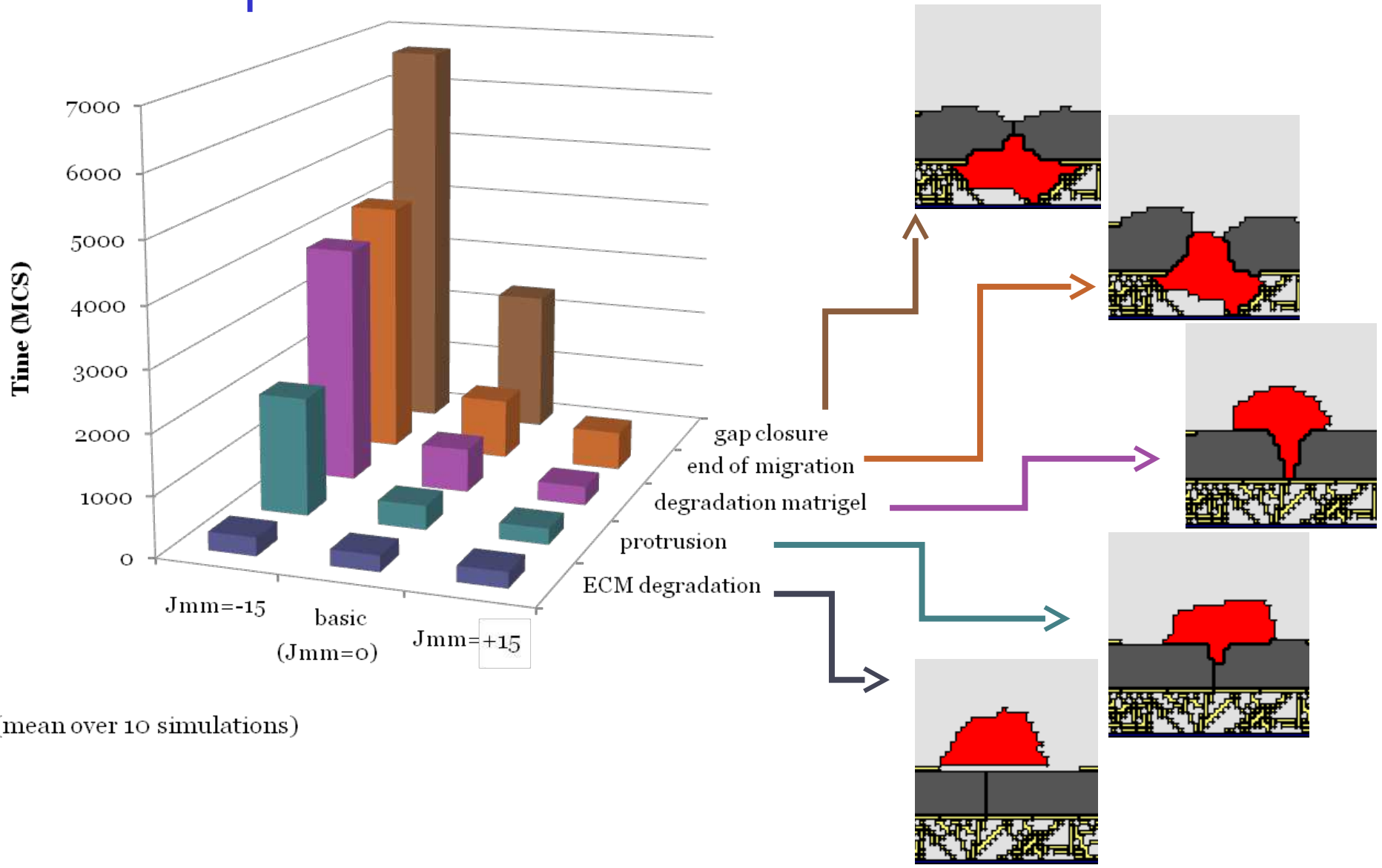
Invasion of ovary cancer cells

Parameter	Low	High
ϑ_{MMP}	5000 MCS 	180 MCS 
$J_{m,m}$	5000 MCS 	400 MCS 
$J_{c,m}$	5000 MCS 	5000 MCS 

POLITECNICO DI TORINO

Invasion of ovary cancer cells

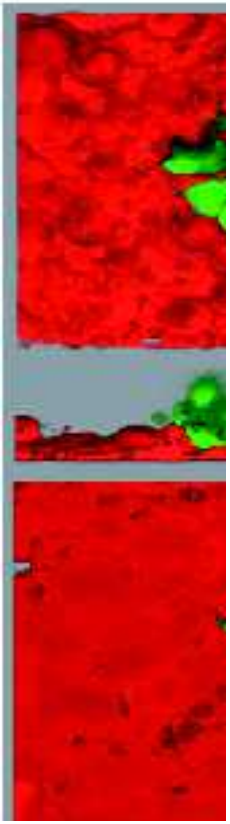


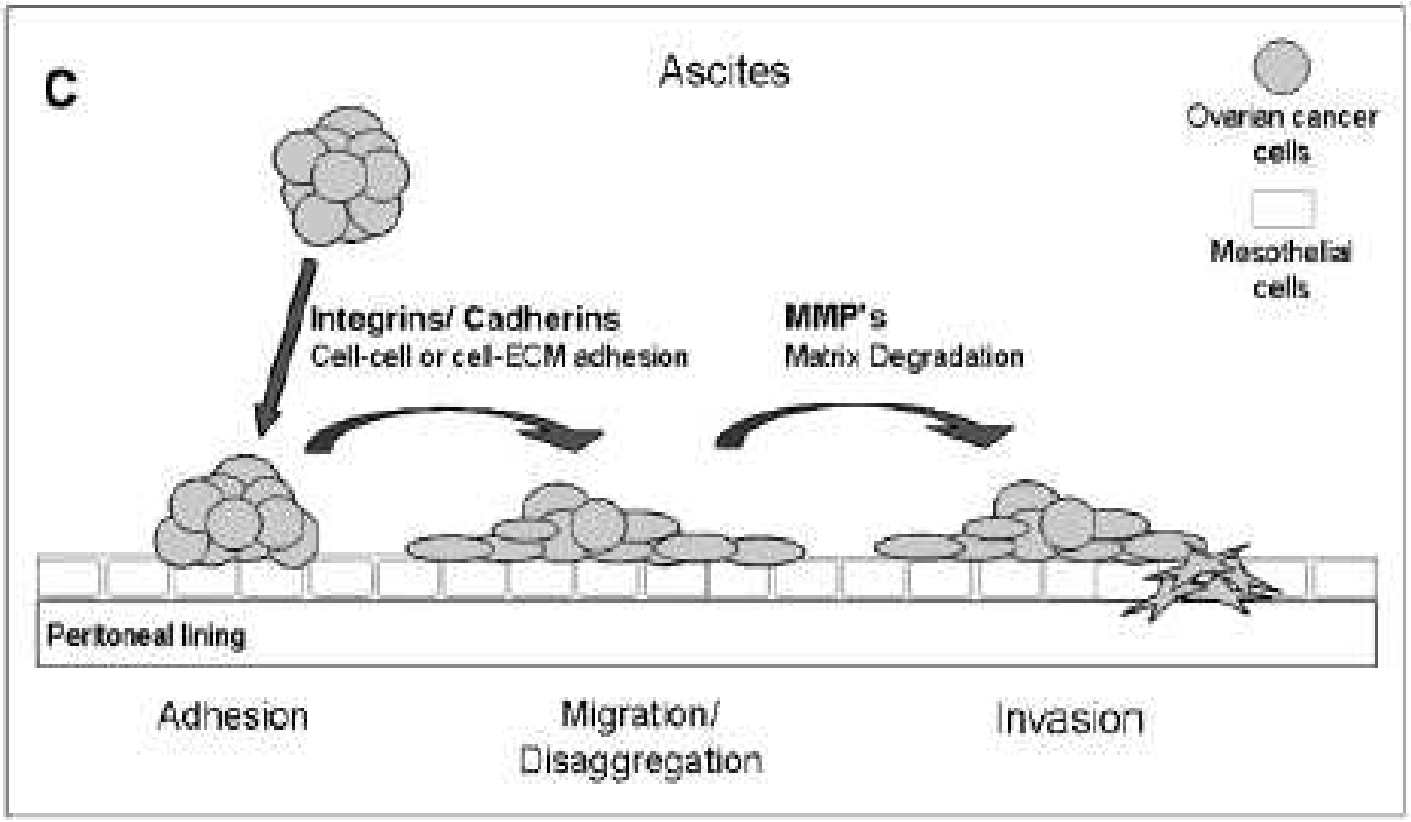
(mean over 10 simulations)

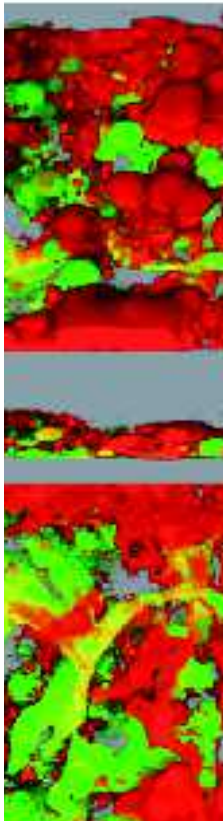
POLITECNICO DI TORINO

Invasion of multicellular spheroids

Top view



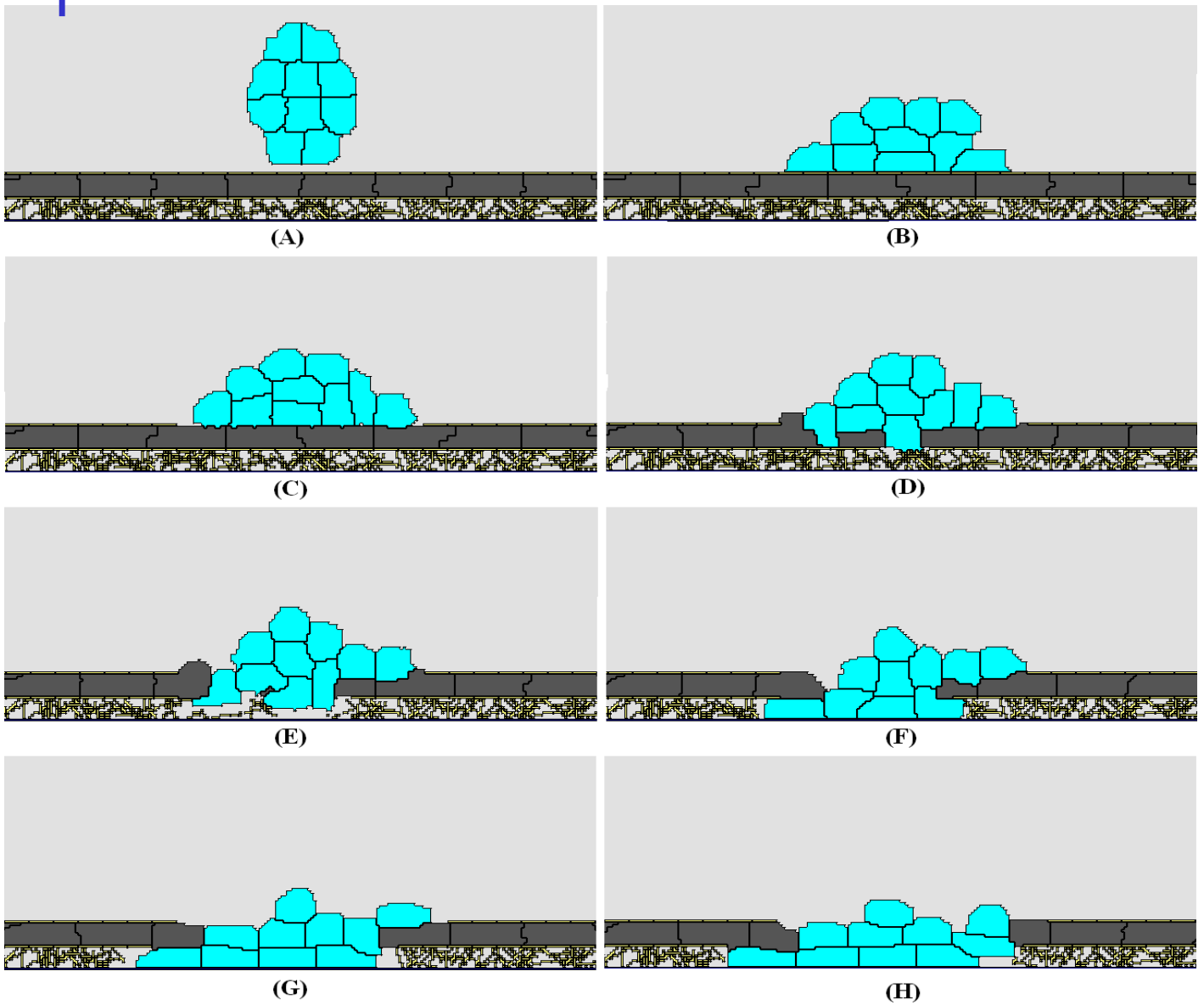




Bottom view

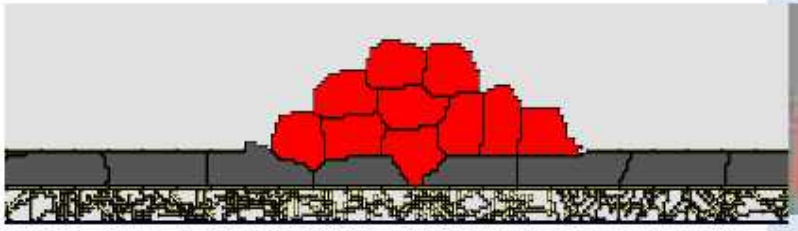
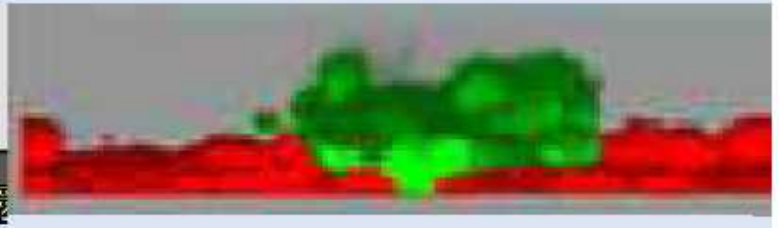
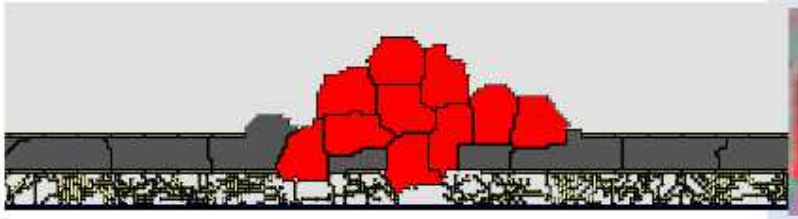
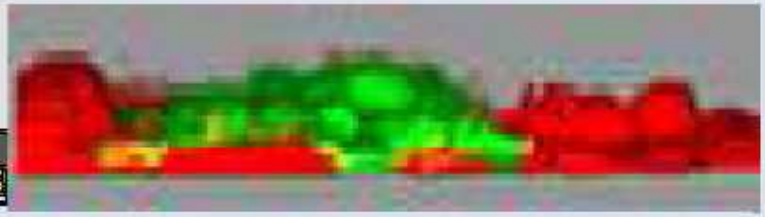
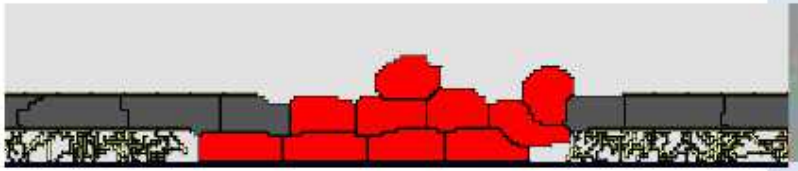
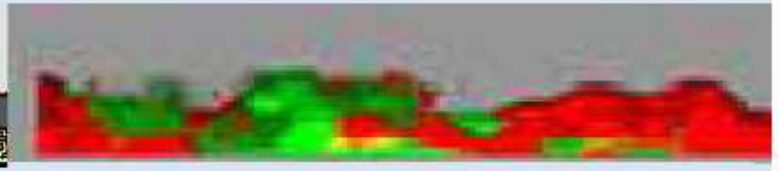
POLITECNICO DI TORINO

Invasion of multicellular spheroids



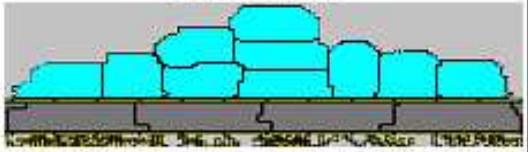
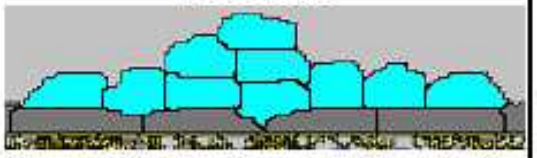
POLITECNICO DI TORINO

Invasion of multicellular spheroids

Simulations	Biological assays
	
	
	

POLITECNICO DI TORINO

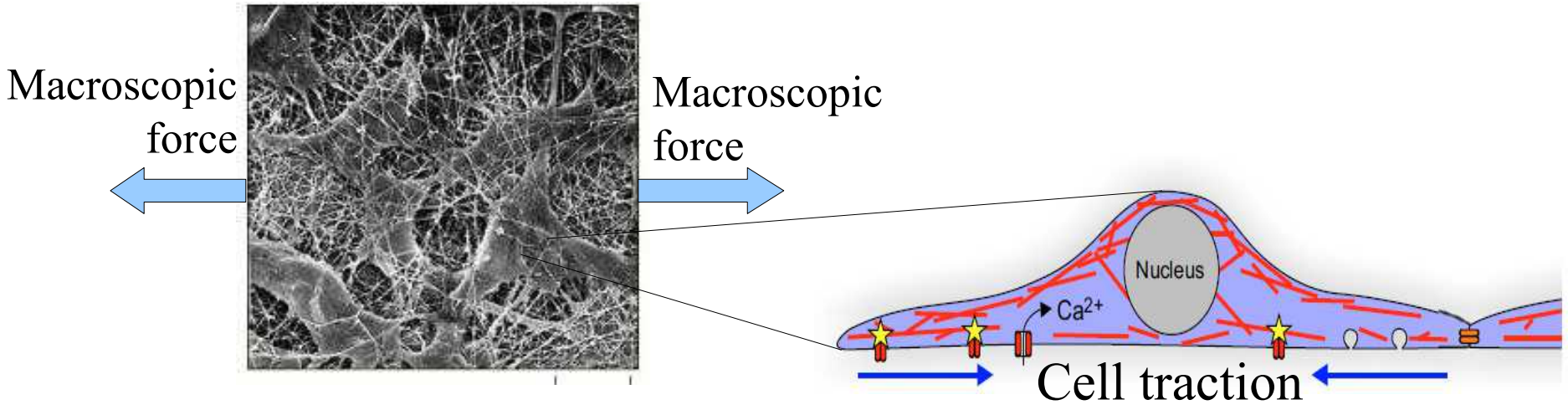
Invasion of multicellular spheroids

Parameter	Low	High
ϑ_{MMP}	12000 MCS 	2000 MCS 
$J_{c,c}$	7800 MCS 	7800 MCS 
$J_{c,e}$	8000 MCS  12000 MCS 	8000 MCS  12000 MCS 

Mechanosensing & mechanotransduction

Mechanosensing = How cells sense mechanical forces

Mechano-transduction = How cells respond to mechanical signals, either directly or via the activation of signalling pathways



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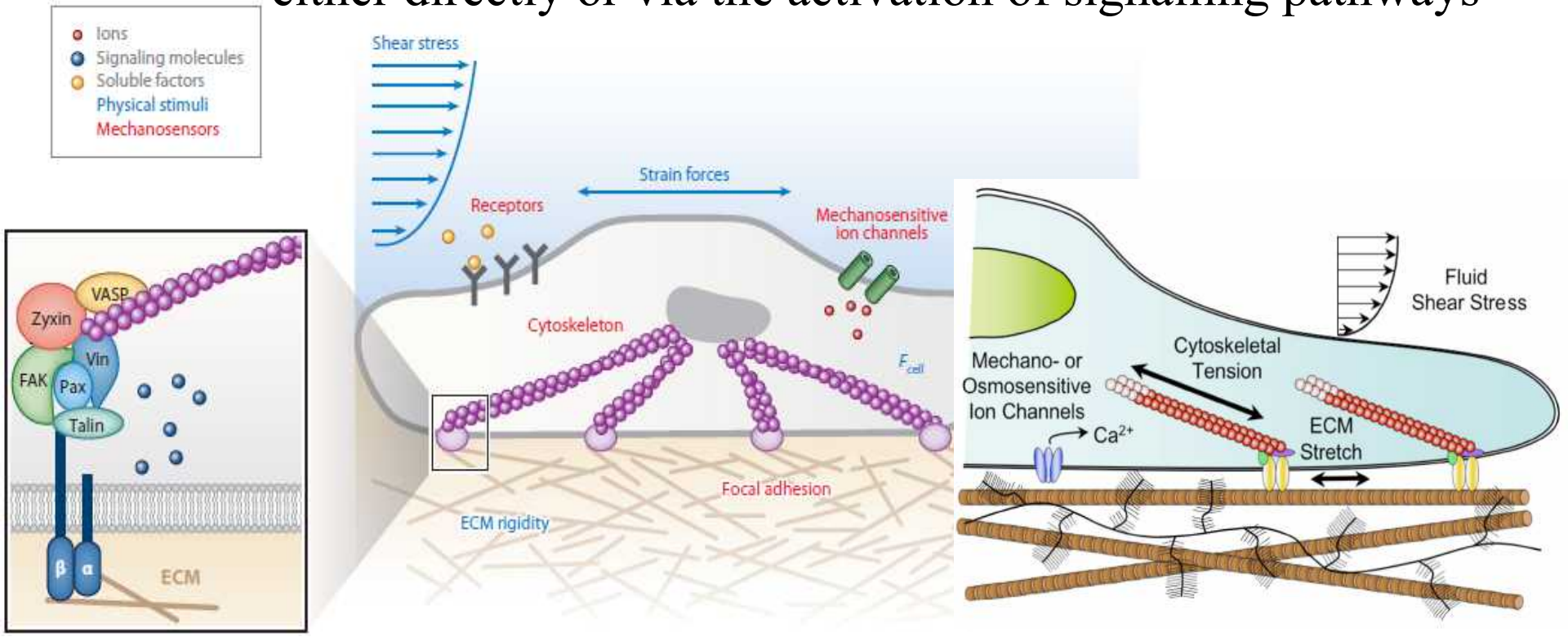
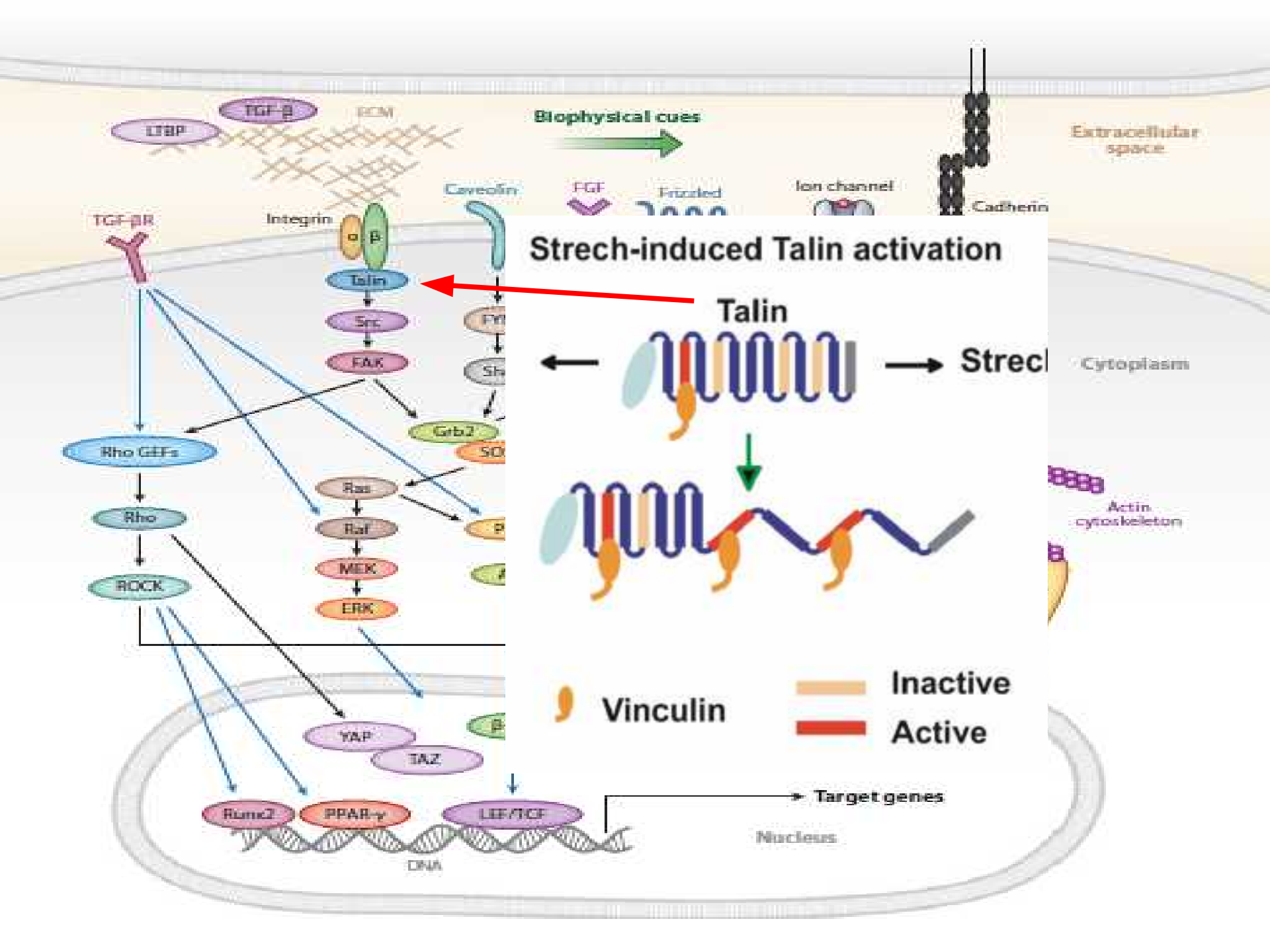


Sun, Chen, Fu, Forcing stem cells to behave: A biophysical perspective of the cellular microenvironment *Ann. Rev. Biophys.* **41**, 519-542 (2012)

Guilak, … & Chen, Control of stem cells by physical interaction with the ECM, *Cell Stem Cell* **5**, 17-26 (2009)


Biophysical cues
Extracellular space
Cytoplasm
Actin cytoskeleton
Nucleus
DNA
TGF-β
LTBP
ECM
TGF-βR
Integrin
α
β
Caveolin
FGF
Frizzled
Ion channel
Cadherin
Talin
Src
FAK
Grb2
Rho GEFs
Rho
ROCK
Ras
Raf
MEK
ERK
YAP
TAZ
Runx2
PPAR-γ
LEF/TCF
Target genes
Strech-induced Talin activation
Talin
Strecl
Vinculin
Inactive
Active

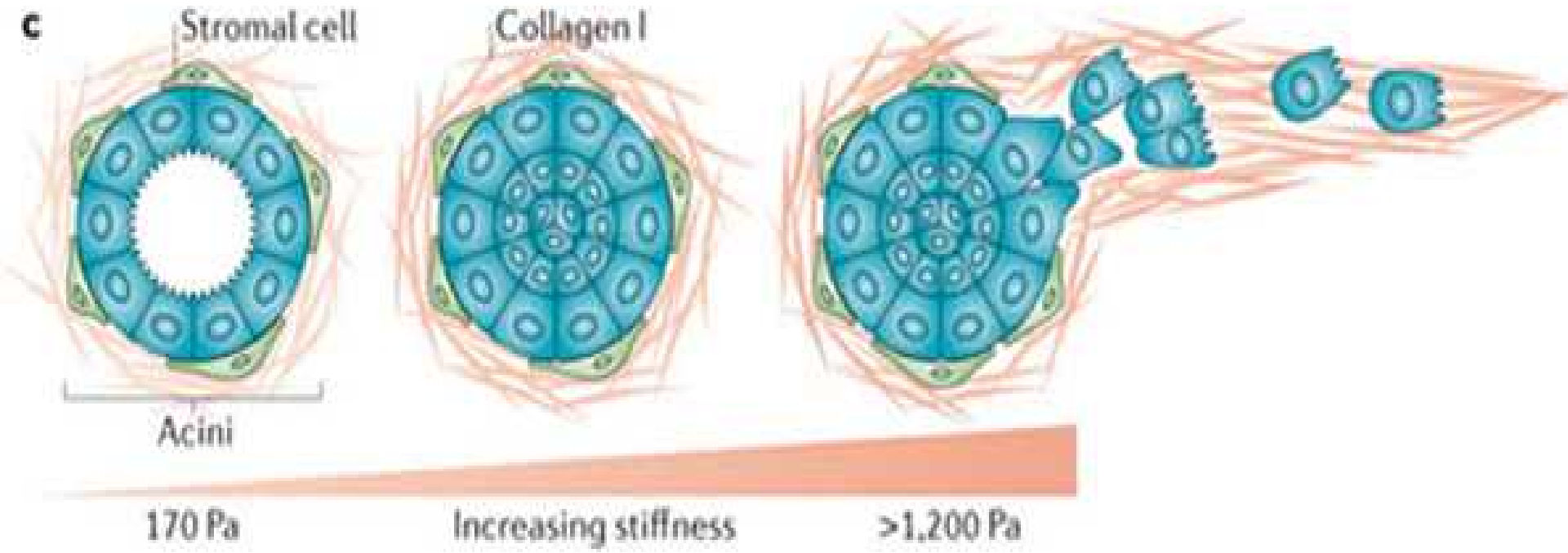
POLITECNICO DI TORINO

Tumour-stroma interaction

Relations between ECM stiffness and cell tensile stress influences

- Proliferation
- Apoptosis
- Migration

Kass, Erler, Dembo & Weaver, Mammary epithelial cell Influence of ECM composition and organization during development and tumorigenesis
Int J Biochem Cell Biol **39**, 1987-94 (2007)



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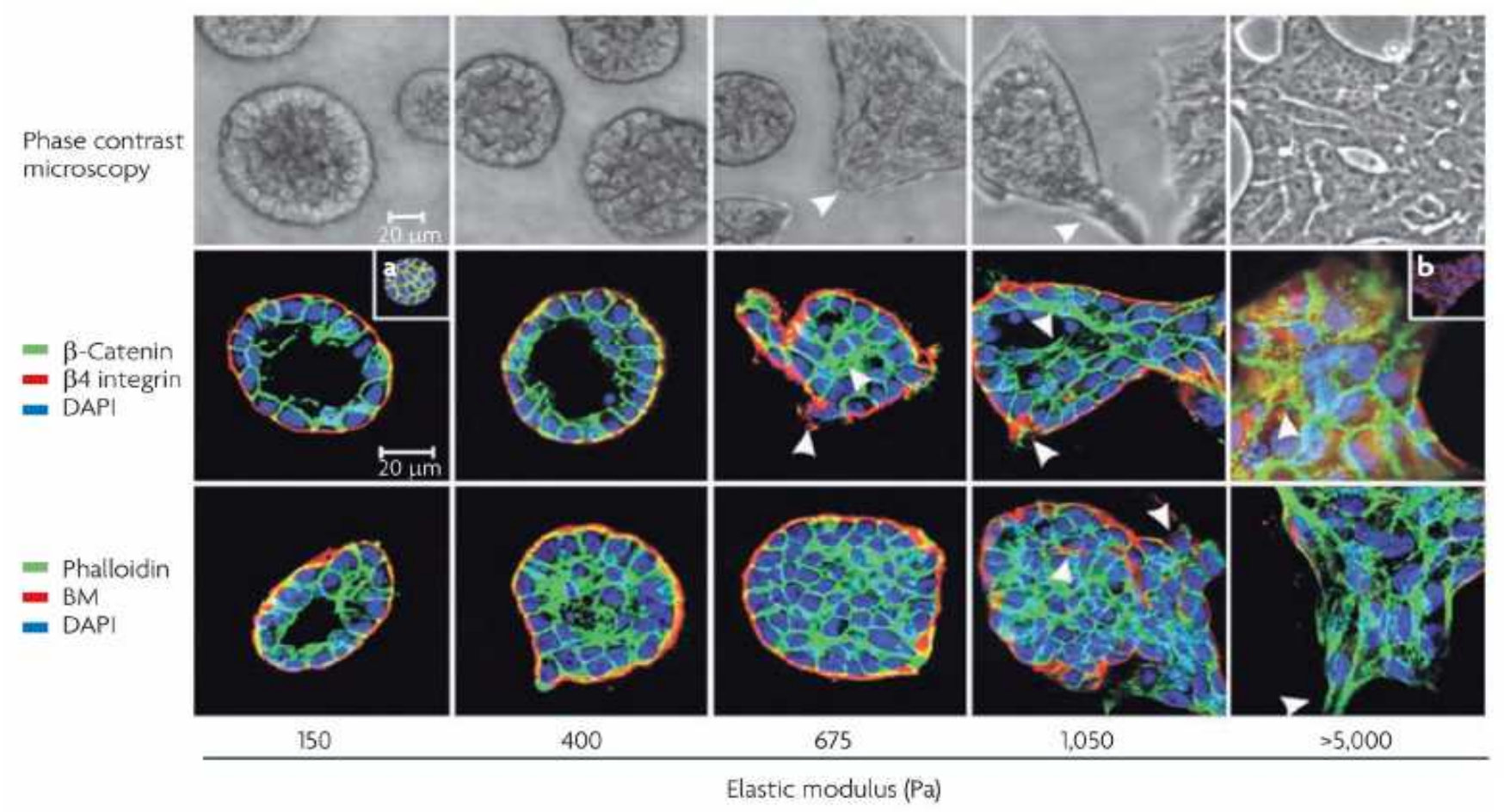
Tumour-stroma interaction



Butcher, Alliston & Weaver,
A tense situation: forcing tumour progression
Nat Rev Cancer **9**, 108-122 (2009)

Diseases of mechanotransduction

Cardiology	Angina (vasospasm)
	Atherosclerosis
	Atrial fibrillation
	Heart failure
	Hypertension
	Intimal hyperplasia
	Valve disease
Dermatology	Scleroderma
Gastroenterology	Achalasia
	Irritable bowel syndrome
	Volvulus
Nephrology	Diabetic nephropathy
	Glomerulosclerosis
Neurology	Cerebral edema
	Facial tics
	Hydrocephalus
	Migraine
	Stroke
	Stuttering
	Dementhia

Abnormal conversion of mechanical stress into intracellular gradients of electrical activity

Stretch activated signalling cascades due to stents and grafts

Abnormal ECM accumulation

Stretching of mesangial cells through ECM and integrins due to glomerular hypertension

Vasculature feels and adapt to shear and pressure

Ingber, Mechanobiology and diseases of mechanotransduction
Annals Medicine **35**, 1-14 (2009)

POLITECNICO DI TORINO

Diseases of mechanotransduction

Oncology	Cancer
	Metastasis
Opthalmology	Glaucoma
Orthopedics	Ankylosing spondylitis
	Carpal tunnel syndrome
	Chronic back pain
	Dupytren's contracture
	Osteoporosis
	Osteoarthritis
	Rheumatoid arthritis
Pediatrics	Collagenopathies
	Congenital deafness
	Mucopolysaccharidoses
	Musculodystrophies
	Osteochondroplasias
	Polycystic kidney disease
	Pulmonary hypertension of newborn
Pulmonary medicine	ARDS
	Asthma
	Emphysema
	Pulmonary fibrosis
	Pulmonary hypertension
	Ventilator injury
Reproductive medicine	Pre-eclampsia
	Sexual dysfunction (male & female)
Urology	Urinary frequency/incontinence

Loss of contact inhibition
Matrix Metallo Proteinases
Excessive production of ECM

Insufficient mechanosensing

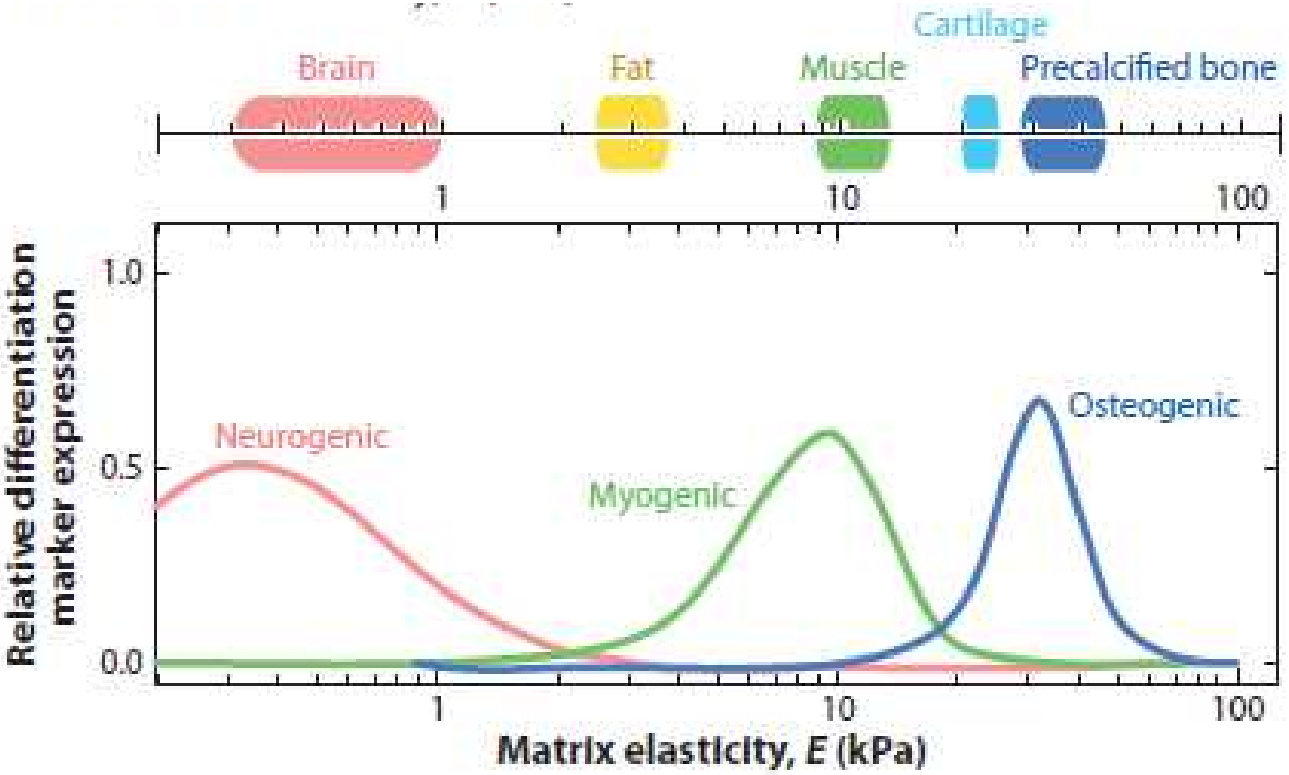
Enhanced ECM breakdown

Excessive ECM

Cell hypercontractility

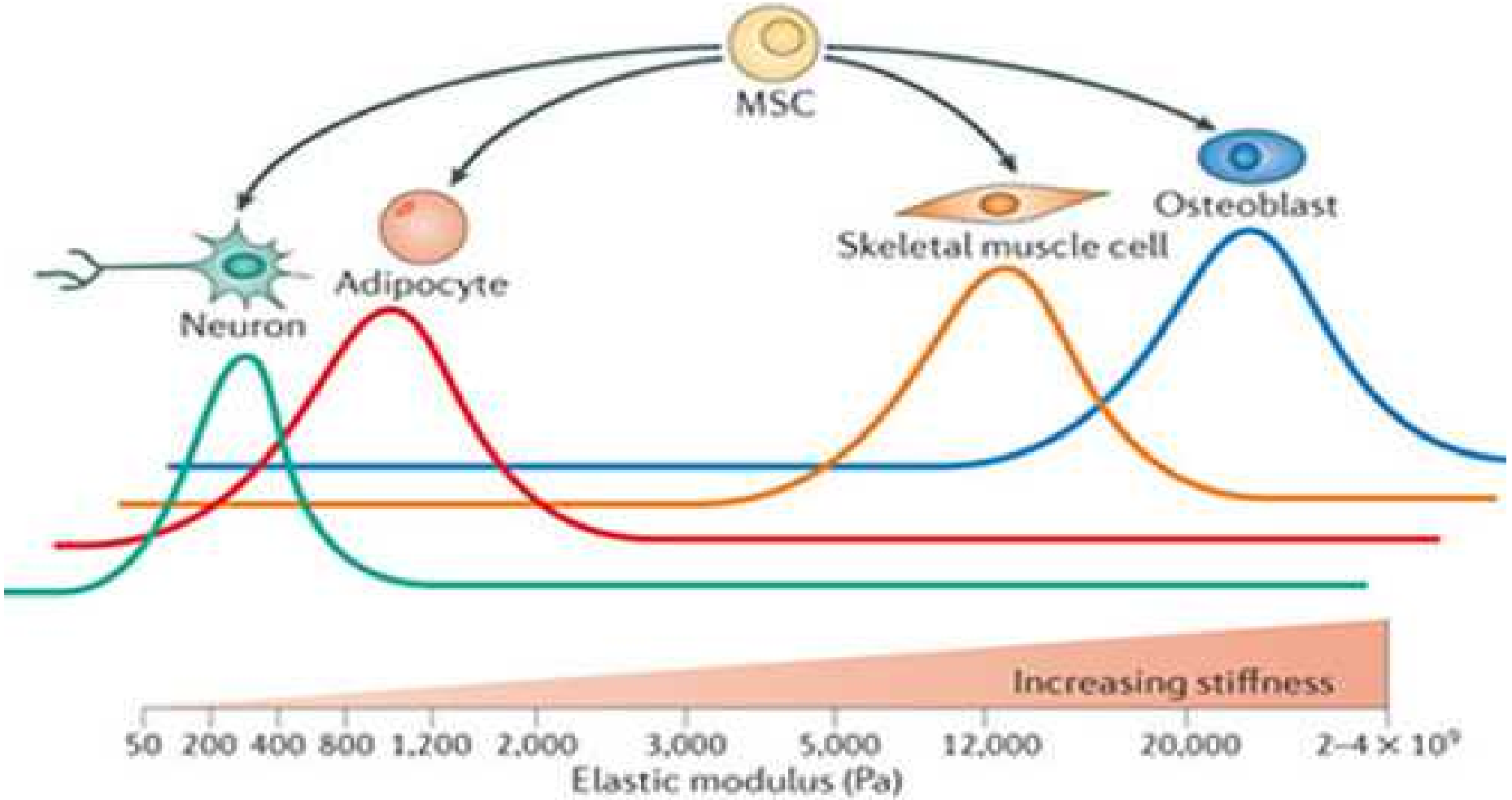
POLITECNICO
DI TORINO

Mechano-reciprocity



POLITECNICO DI TORINO

Mechano-reciprocity



Mechano-reciprocity

- It mantains tensional homeostasis in the tissue
- It is necessary for development and tissue-specific differentiation
- Its loss promotes disease progression, including liver fibrosis, atherosclerosis and cancer

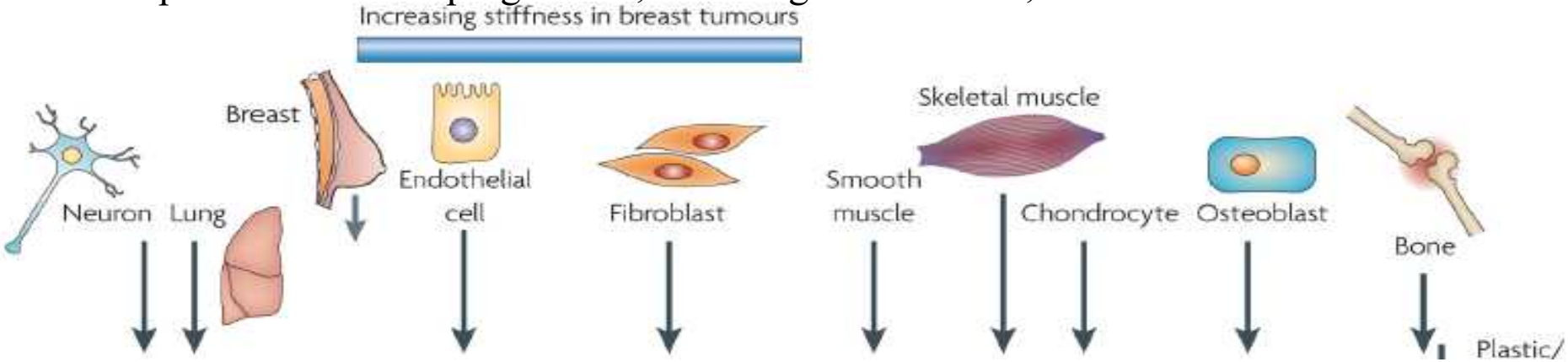


Figure 1. Cells are tuned to the materials properties of their matrix

All cells, including those in traditionally mechanically static tissues, such as the breast or the brain, are exposed to isometric force or tension that is generated locally at the nanoscale level by cell–cell or cell–extracellular matrix interactions and that influences cell function through actomyosin contractility and actin dynamics. Moreover, each cell type is specifically tuned to the specific tissue in which it resides. The brain, for instance, is infinitely softer than bone tissue. Consequently, neural cell growth, survival and differentiation are favoured by a highly compliant matrix. By contrast, osteoblast differentiation and survival occurs optimally on stiffer extracellular matrices with material properties more similar to newly formed bone. Normal mammary epithelial cell growth, survival, differentiation and morphogenesis are optimally supported by interaction with a soft matrix. Following transformation, however, breast tissue becomes progressively stiffer and tumour cells become significantly more contractile and hyper-responsive to matrix compliance cues. Normalizing the tensional homeostasis of tumour cells, however, can revert them towards a non-malignant phenotype[6],

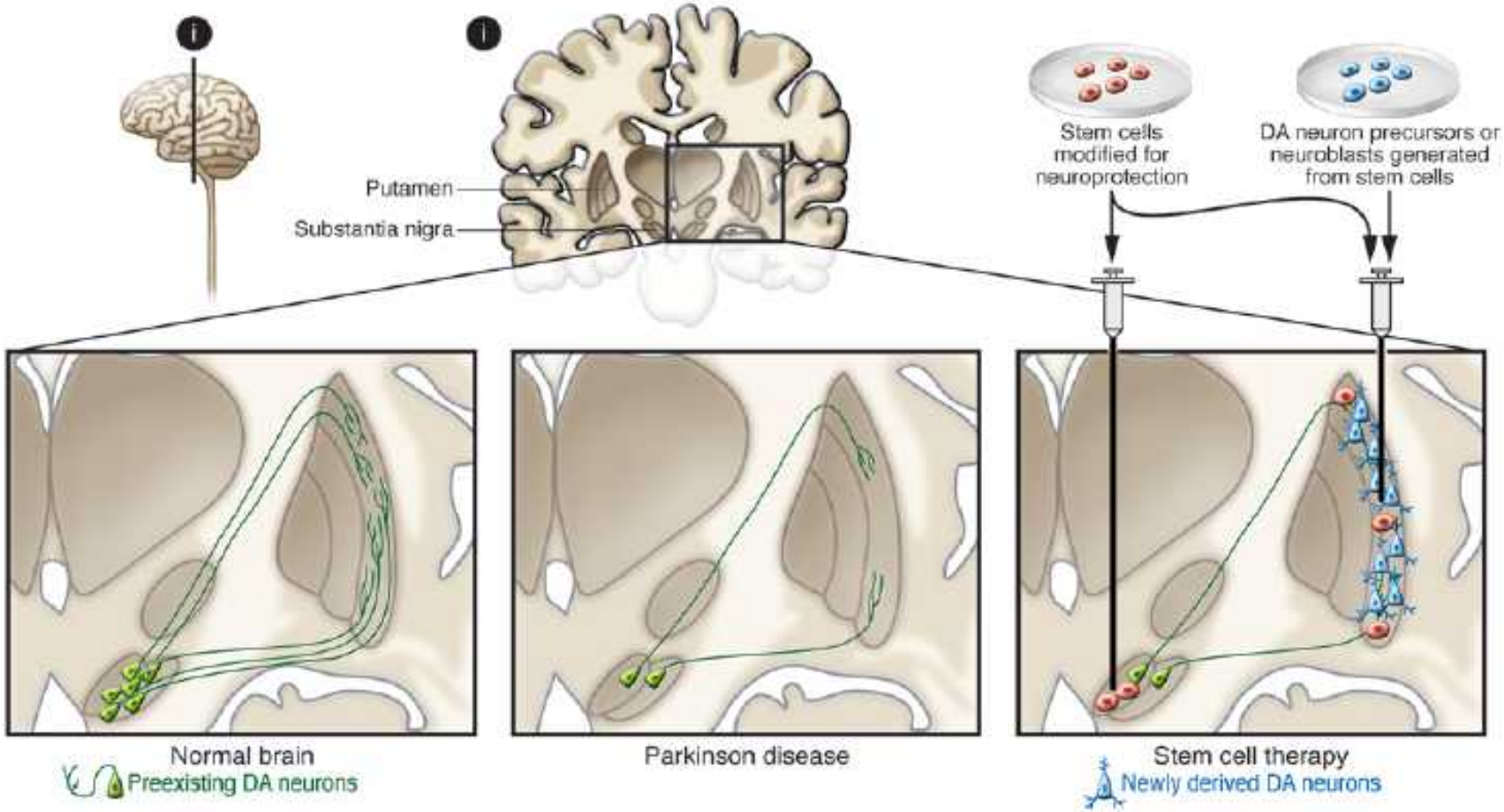


Figure 1

Stem cell–based therapies for PD. PD leads to the progressive death of DA neurons in the substantia nigra and decreased DA innervation of the striatum, primarily the putamen. Stem cell–based approaches could be used to provide therapeutic benefits in two ways: first, by implanting stem cells modified to release growth factors, which would protect existing neurons and/or neurons derived from other stem cell treatments; and second, by transplanting stem cell–derived DA neuron precursors/neuroblasts into the putamen, where they would generate new neurons to ameliorate disease-induced motor impairments.

Lindvall, Kokaia, Stem cells in human neurodegenerative disorders: Time for clinical translation? *J. Clinical Inv* **120**, 29-40 (2010)

Progress stem cells for the treatment of neurological disorders, *Nature **441*** 1094-1096 (2006)

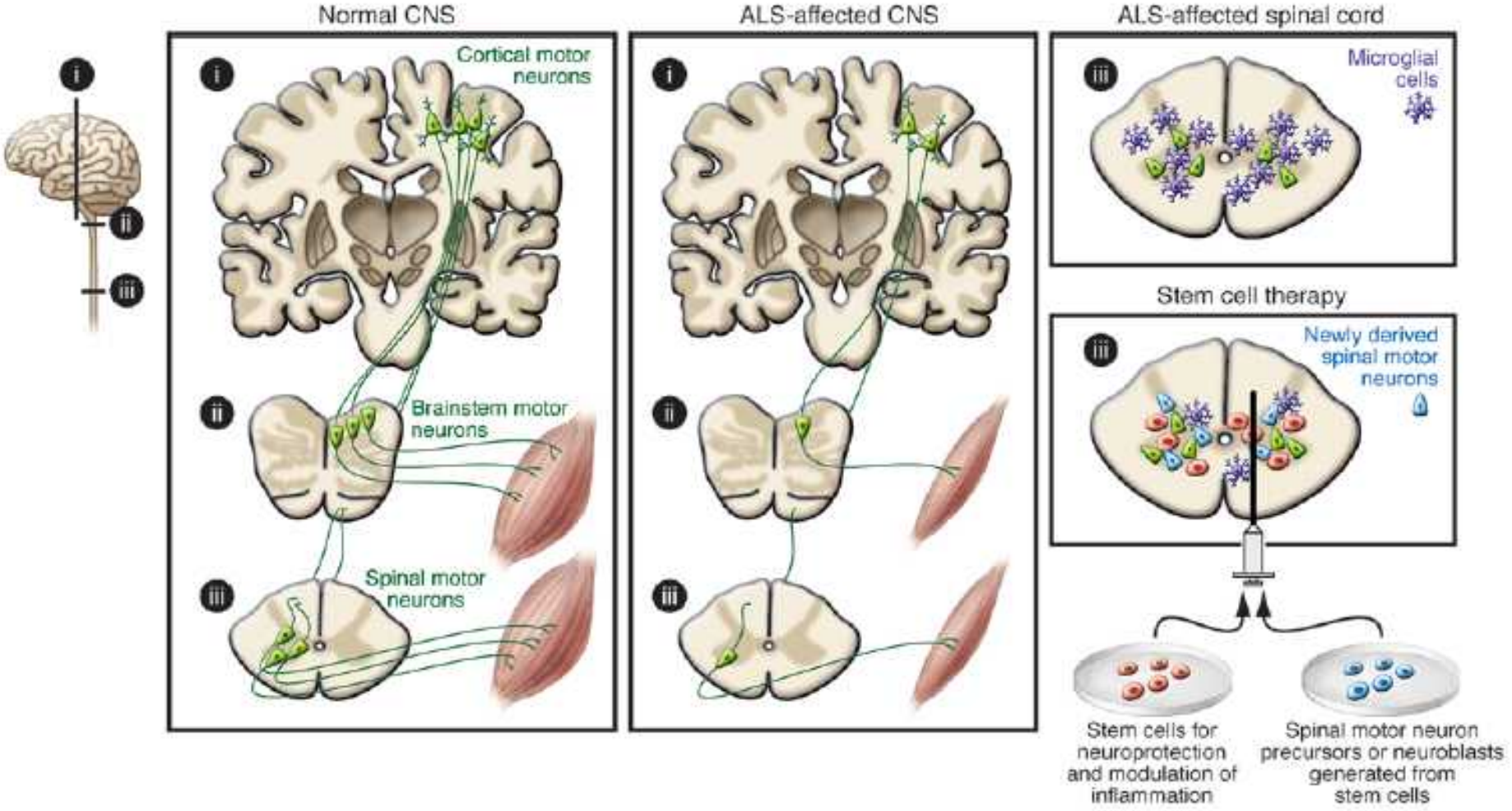


Figure 2
Stem cell–based therapies for ALS. ALS leads to degeneration of motor neurons in the cerebral cortex, brainstem, and spinal cord. Stem cell–based therapy could be used to induce neuroprotection or dampen detrimental inflammation by implanting stem cells releasing growth factors. Alternatively, stem cell–derived spinal motor neuron precursors/neuroblasts could be transplanted into damaged areas to replace damaged or dead neurons.

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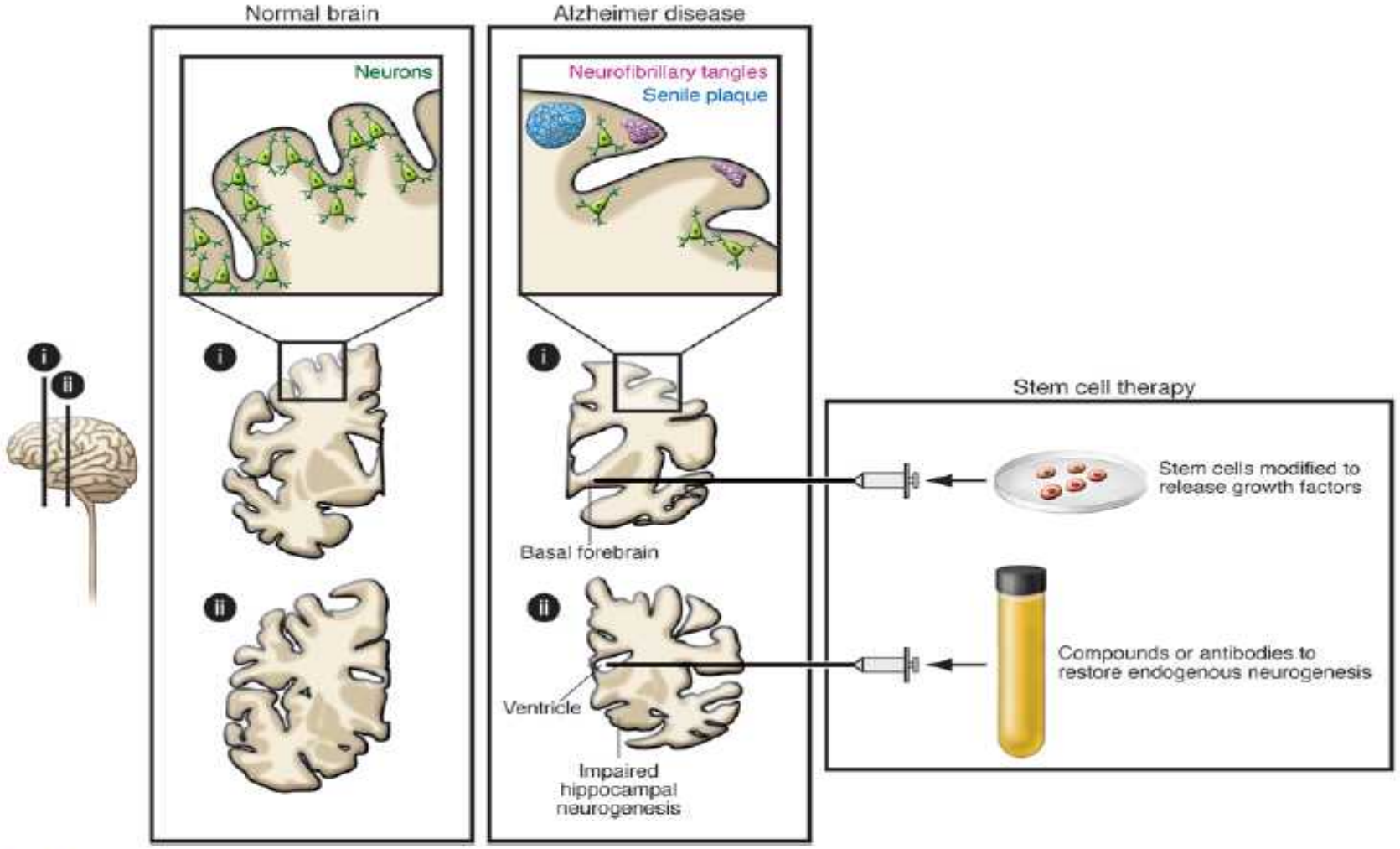

Figure 3
Stem cell–based therapies for AD. AD leads to neuronal loss in the basal forebrain cholinergic system, amygdala, hippocampus, and cortical areas of the brain; formation of neurofibrillary tangles; and β-amyloid protein accumulation in senile plaques. Stem cell–based therapy could be used to prevent progression of the disease by transplanting stem cells modified to release growth factors. Alternatively, compounds and/or antibodies could be infused to restore impaired hippocampal neurogenesis.

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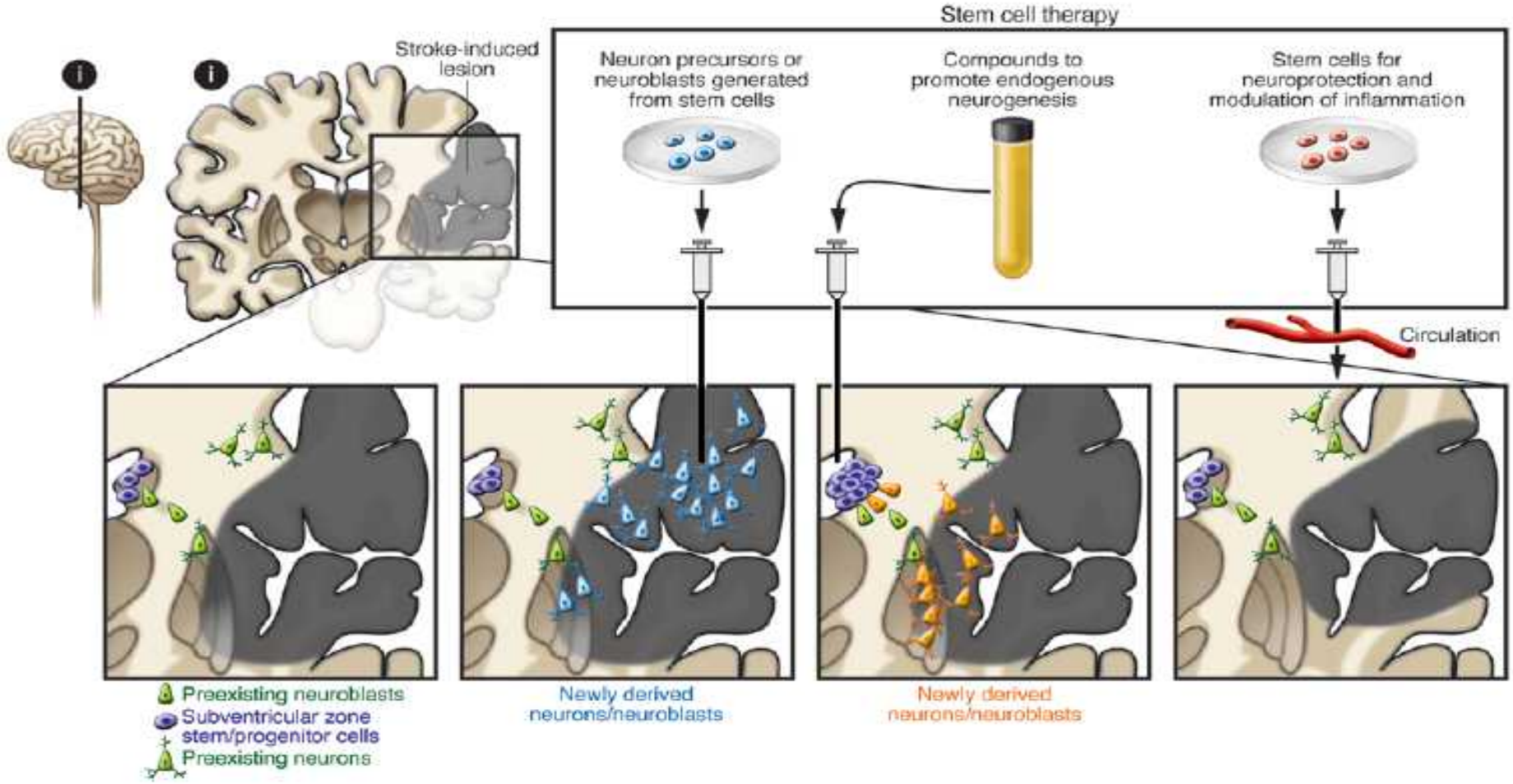

Figure 4
Stem cell–based therapies for stroke. Ischemic stroke leads to the death of multiple neuronal types and astrocytes, oligodendrocytes, and endothelial cells in the cortex and subcortical regions. Stem cell–based therapy could be used to restore damaged neural circuitry by transplanting stem cell–derived neuron precursors/neuroblasts. Also, compounds could be infused that would promote neurogenesis from endogenous SVZ stem/progenitor cells, or stem cells could be injected systemically for neuroprotection and modulation of inflammation.

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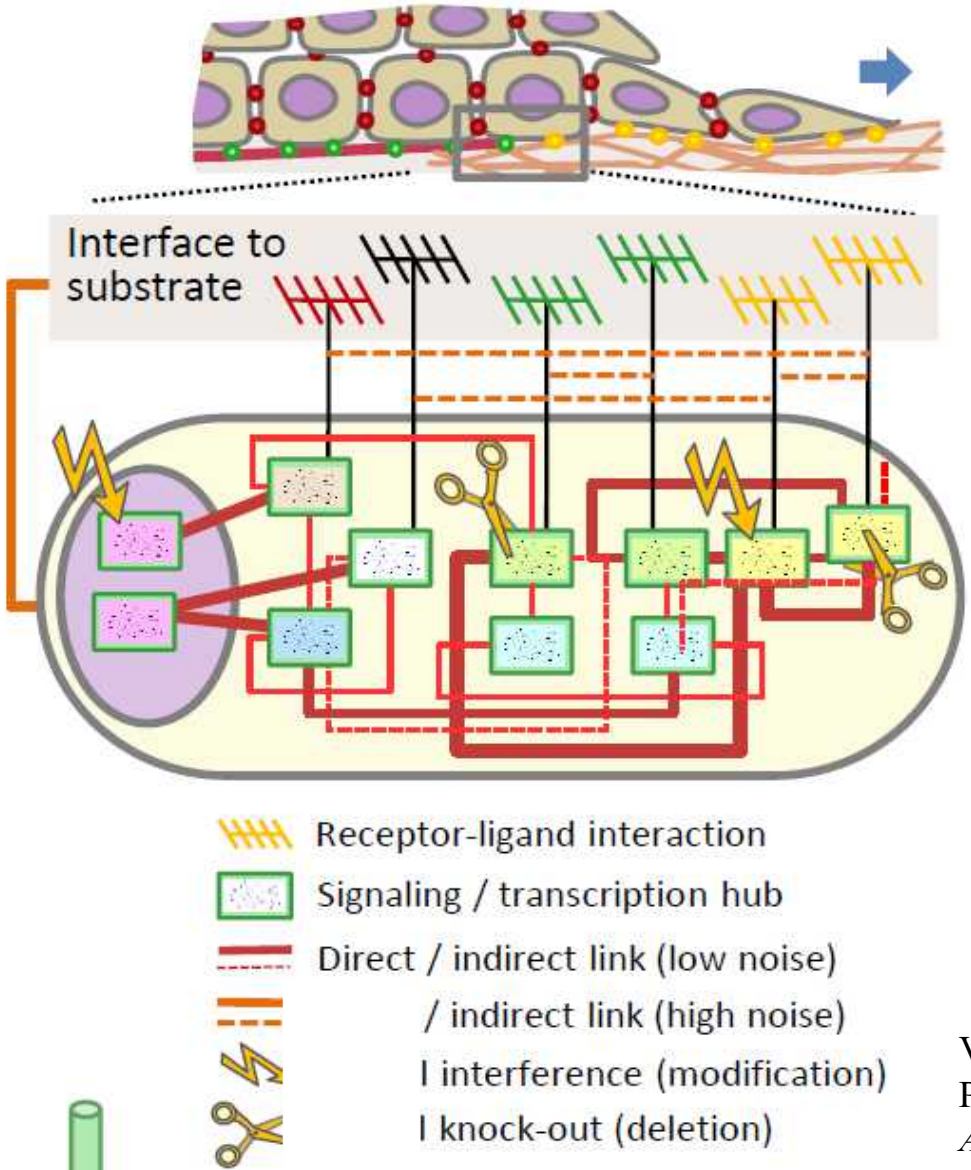
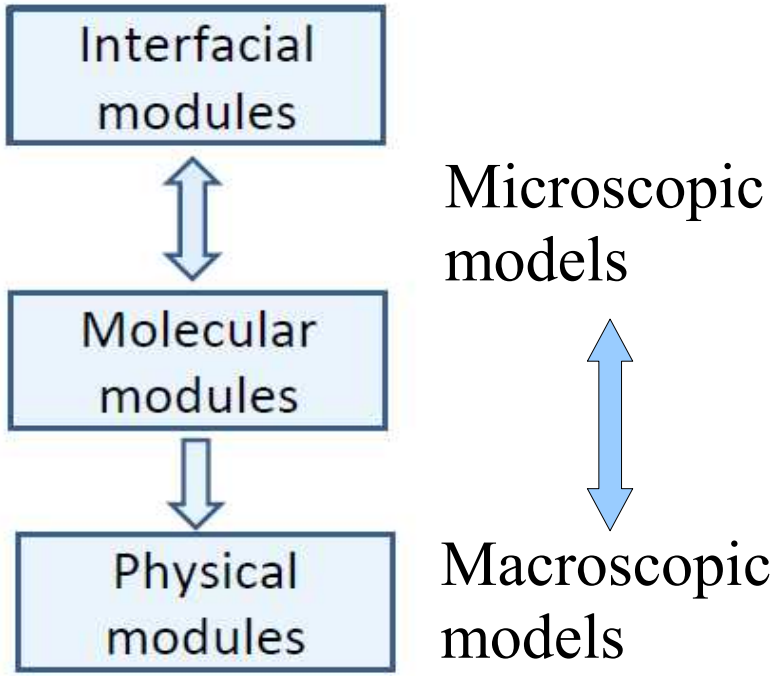
Multiscale features





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