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**

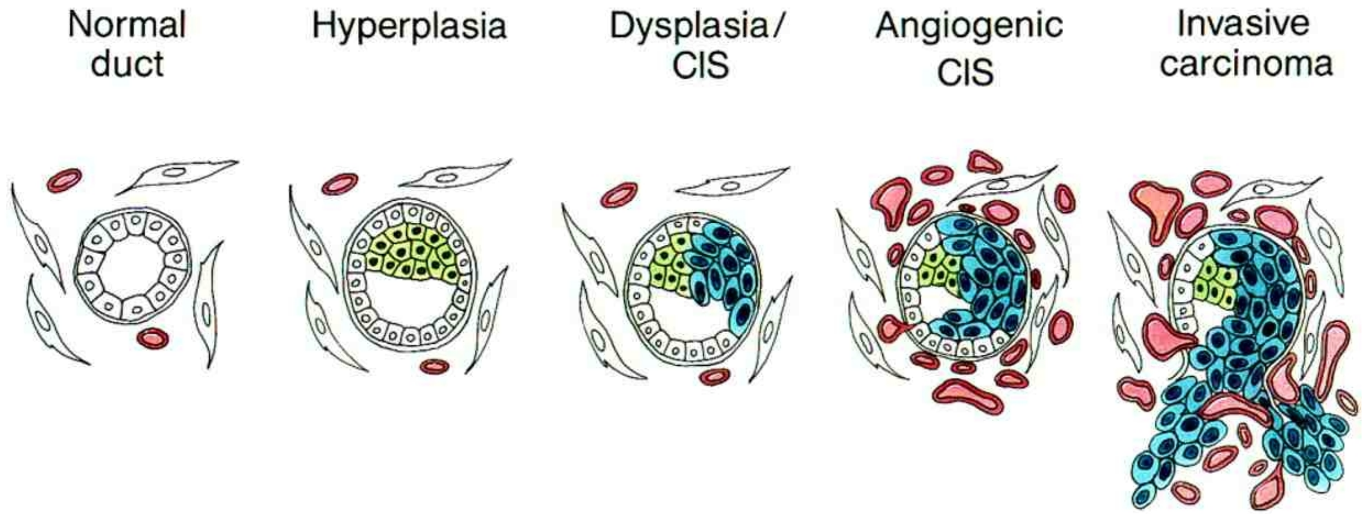
"To a man with a hammer, everything looks like a nail"

- **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**

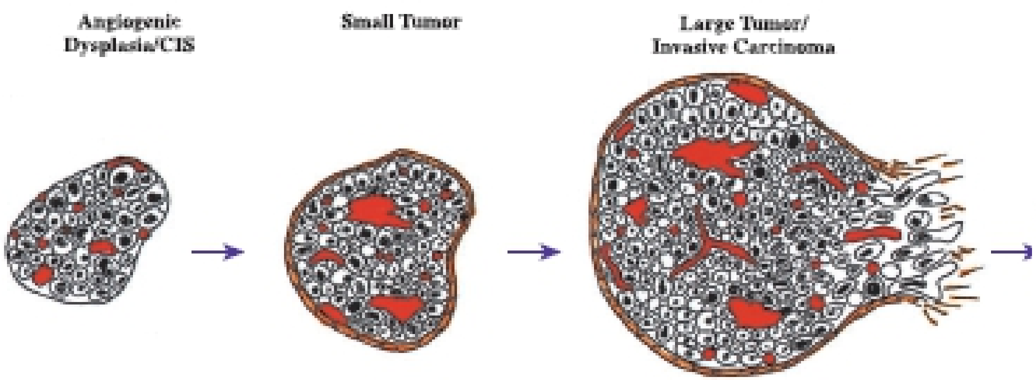
Tumour compartimentalization and invasion

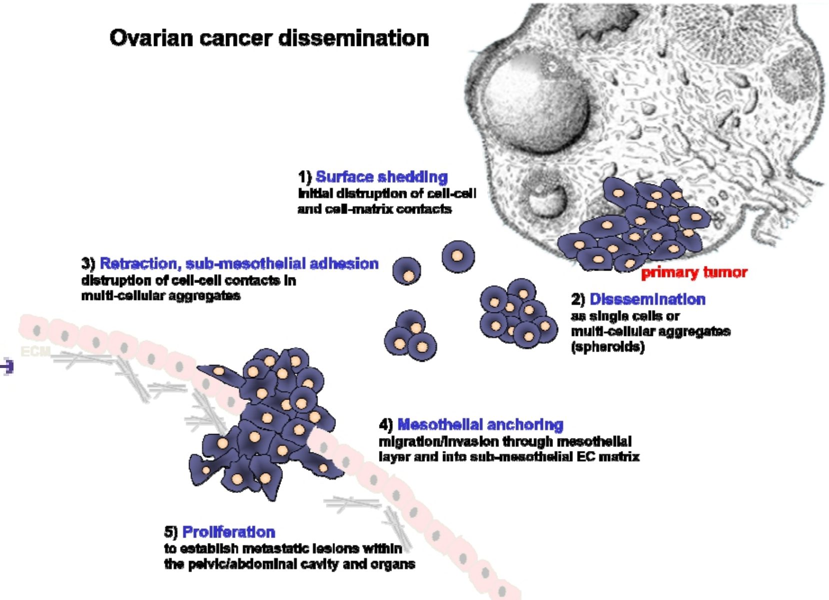


Breast

Ovary

Pancreas





Cell motion

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Life at Low Reynolds Number

E.M. Purcell
Lyman Laboratory, Harvard University, Cambridge, Mass 02138
June 1976

American Journal of Physics vol 45, pages 3-11, 1977.

Editor's note: This is a reprint of a (slightly edited) paper of the same title that appeared in the book Physics and Our World: A Symposium in Honor of Victor F. Weiskopf, published by the American Journal of Physics (1976). The personal tone of the original talk has been preserved in the paper, which was itself a slightly edited transcript of a tape. The figures reproduce transparencies used in the talk. The demonstration involved a tall rectangular transparent vessel of corn syrup, projected by an overhead projector turned on its side. Some essential hand waving could not be reproduced.

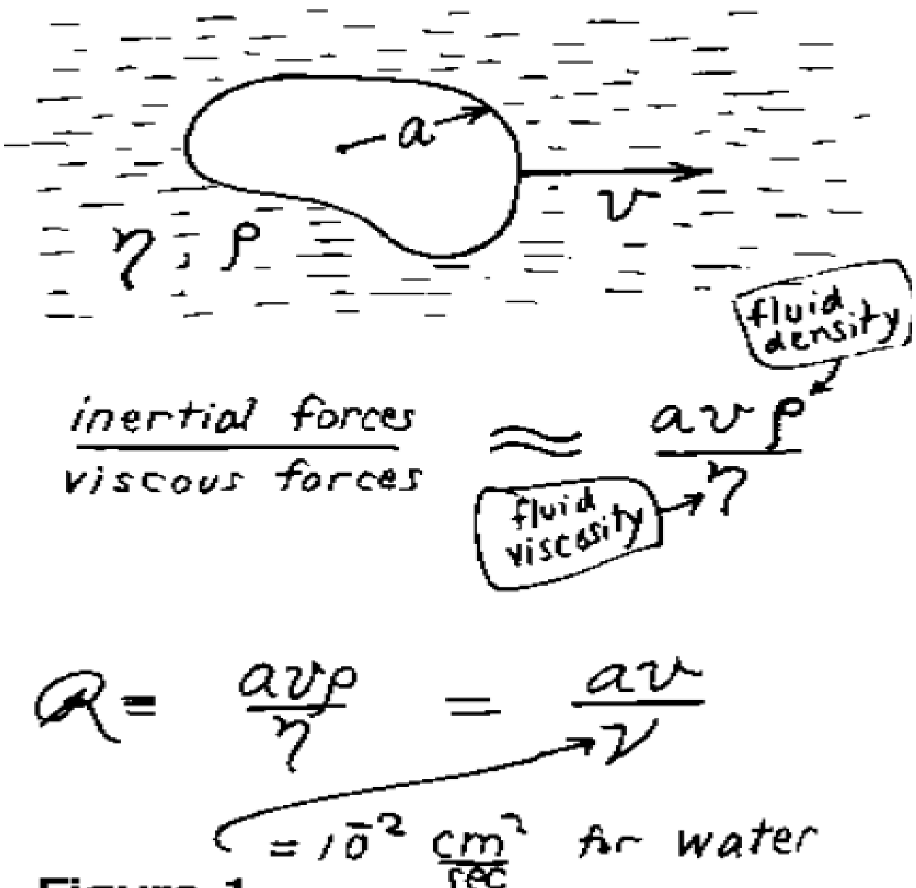

Figure 1

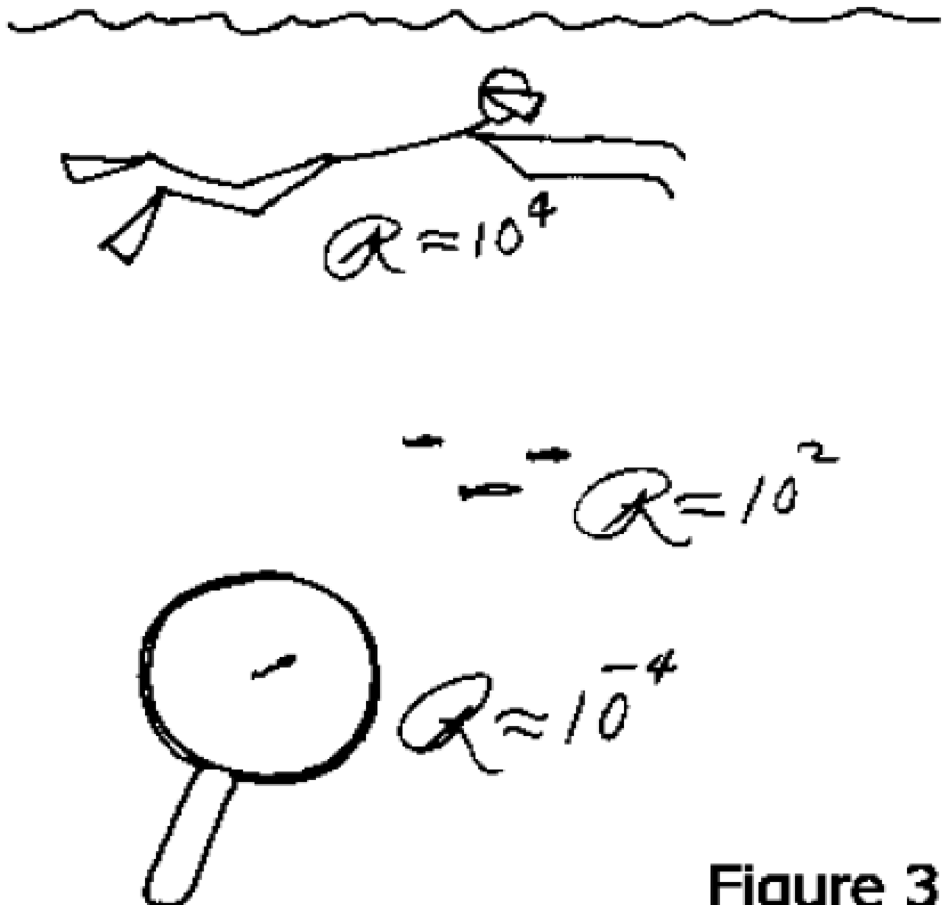

Figure 3

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Life at Low Reynolds Number

E.M. Purcell
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$$\mathrm{Re} = \frac{VL\rho}{\eta}$$

Velocity (typical order of magnitude) V

Diameter (typical size) L

Mass density of the fluid ρ

Viscosity of the fluid η

For water at room temperature $\rho/\eta = 10^{6}\,(m^{2}s^{-1})^{-1}$.

Orders of magnitude for swimmers:

Men, dolphins, sharks:	$L=1m$, $V=1\text{-}10\ ms^{-1}$	$Re=10^{6}\text{-}10^{7}$
Bacteria:	$L=1x10^{-6}m$, $V=1\text{-}10x10^{-6}\ ms^{-1}$	$Re=10^{-6}\text{-}10^{-5}$

$$Re = \frac{VL}{\nu}$$

Kinematic viscosity

Water = 10^{-6} m^2/s

Nutella = 0.1 m^2/s

	Length	Speed	Reynolds
Men	1.6-1.8 m	1 m/s	10^{6}-10^{7}
Fish	0.1-1 m	0.01-10 m/s	10^{2}-10^{7}
Micro-organisms	0.1-1 mm	1 mm/s	1
Sperm cell	10 μm	1-4 mm/min	10^{-3}-10^{-4}
Bacteria	1 μm	10 μm/s	10^{-5}-10^{-6}

Given $F = 6\pi\rho\nu LV$ ⇒ In a new fluid $V_{visc} = \frac{\nu_{water} V_{water}}{\nu_{visc}}$

$$Re_{visc} = \frac{\nu^2_{visc}}{\nu^2_{water}} Re_{water}$$

⇒ Swimming in Nutella corresponds to $Re_{visc} = 10^{-4}$

Navier - Stokes :

$$-\nabla p + \eta \nabla^2 \vec{v} = \cancel{\rho \frac{\partial \vec{v}}{\partial t}} + \cancel{\rho (\vec{v} \cdot \nabla) \vec{v}}$$

If $\mathcal{R} \ll 1$:

Time doesn't matter. The pattern of motion is the same, whether slow or fast, whether forward or backward in time.

The Scallop Theorem

Figure 6

Scallop theorem

www.youtube.com/watch?v=51-6QCJTAjU

in a flow regime obeying **Stokes equations**, whatever forward motion will be produced by closing the valves, it will be exactly canceled by a backward motion upon reopening them

Micro-motility as a struggle against the scallop theorem

High Reynolds: www.youtube.com/watch?v=4h079P7qRSw

Low Reynolds: www.youtube.com/watch?v=2kkfHj3LHeE

Low Reynolds (spiral): www.youtube.com/watch?v=s_5ygWhcxKk

Life at Low Reynolds Number

E.M. Purcell
Lyman Laboratory, Harvard University, Cambridge, Mass 02138

June 1976

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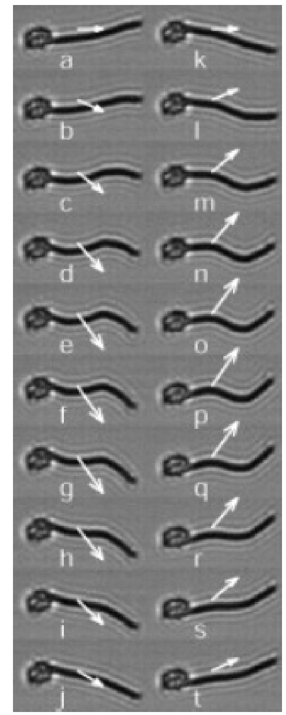
(eukariotic flagella, cilia)

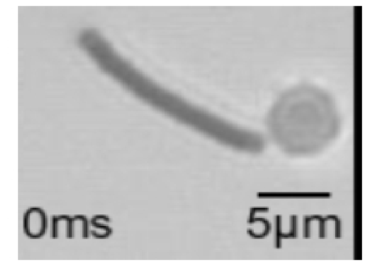
(bending of 9+2 μ-tubule bundles)

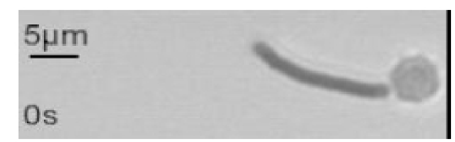
(bacterial flagella)

(20 nm rotary motor)

www.rowland.harvard.edu/labs/bacteria/movies/





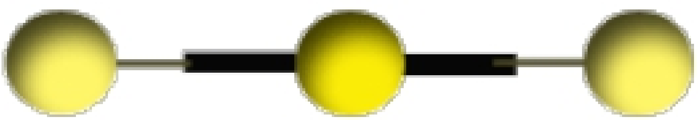


red blood cell + flexible magnetic filament

J. Bibette, H. Stone et al.: Nature (2005)

Nematode: https://www.youtube.com/watch?v=hHSbdbQHk9M

Types of motions



3-sphere swimmer

www.youtube.com/watch?v=B7F7CvHrEHs

Najafi, Golestanian, *Phys. Rev. E* **69,** 062901 (2004)

Race

www.youtube.com/watch?v=aN6I9mJVuas

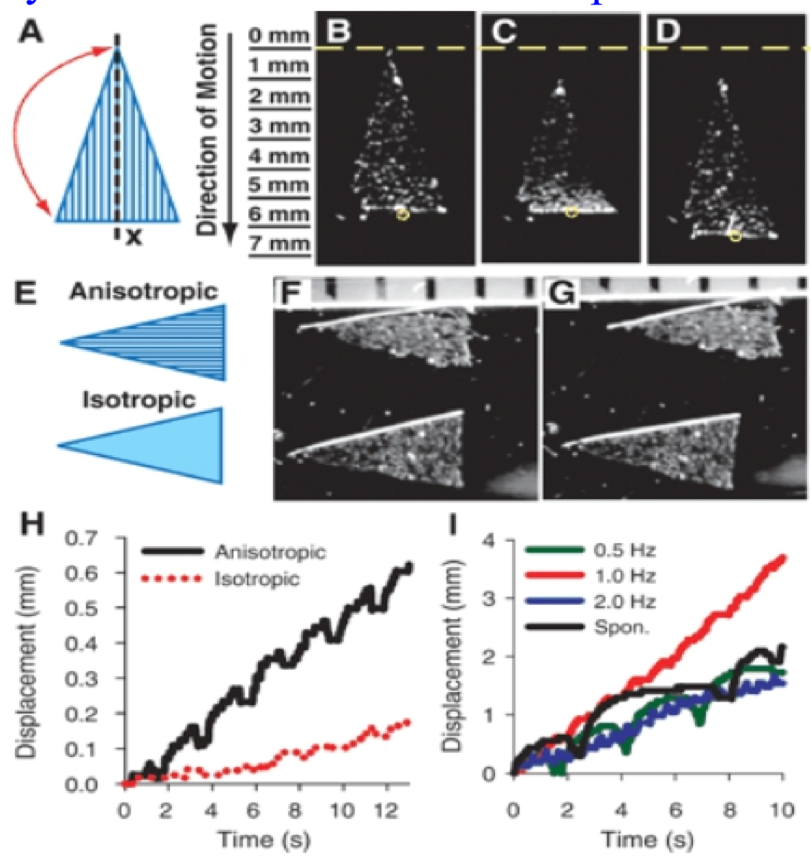
Final aim

www.youtube.com/watch?v=VRMEtCCDR_E

Moving films

www.youtube.com/watch?v=qcebMTFmzUY

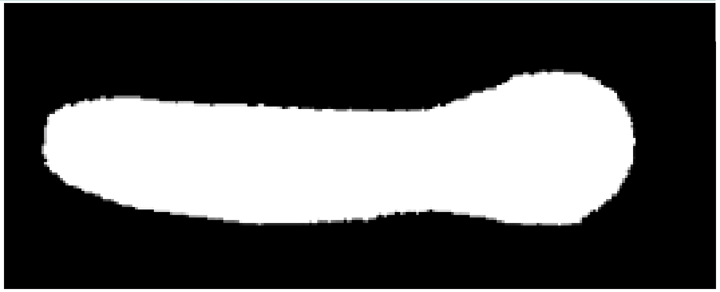
www.youtube.com/watch?v=v0vMp0T6kvI

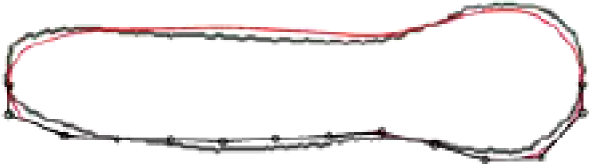


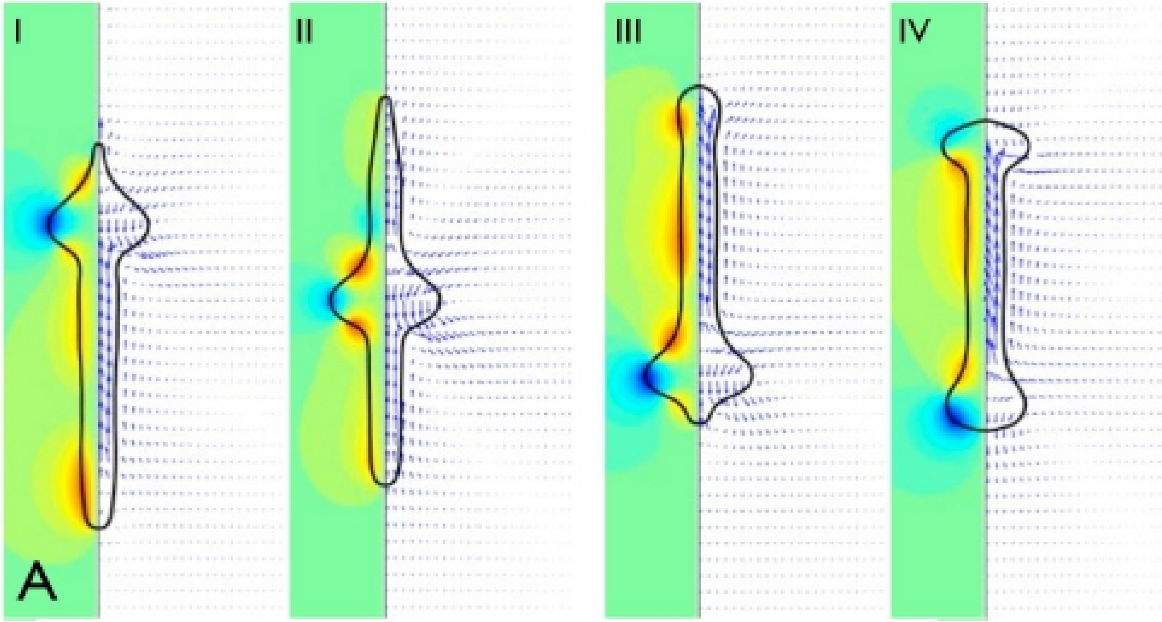
polymer film + muscle cells

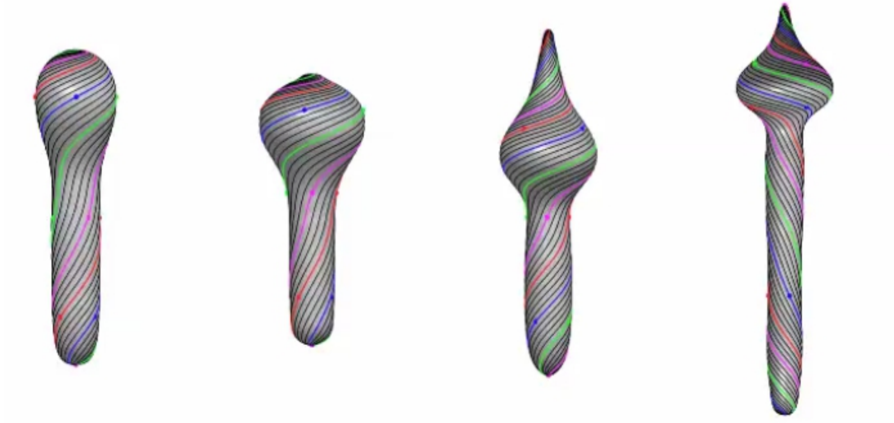
G. Whitesides et al., Science (2007)

Euglenoid motion





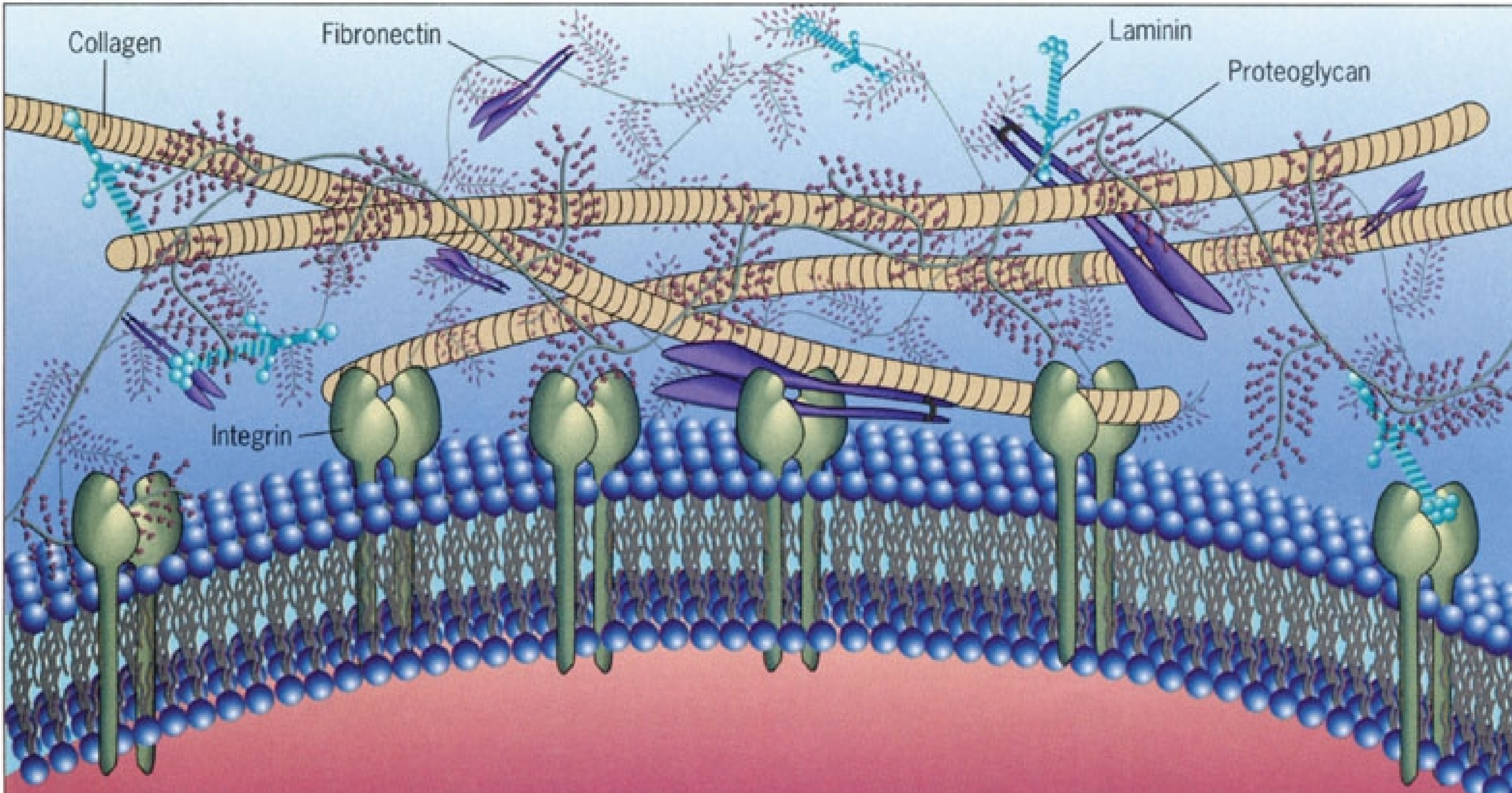




www.youtube.com/watch?v=91yFpzzz4O8

Arroyo, Milan, Heltai, De Simone,
PNAS **109**, 1784-1789 (2012)

Extra-cellular matrix



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

Extra-cellular matrix

Heart

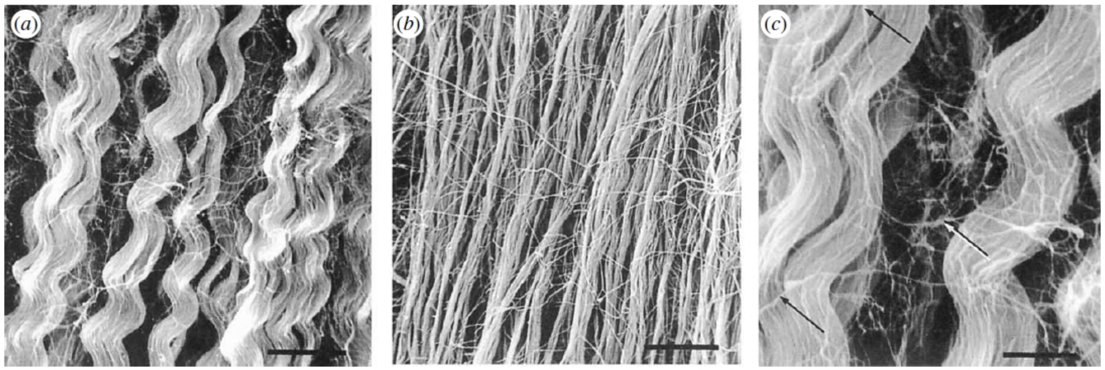
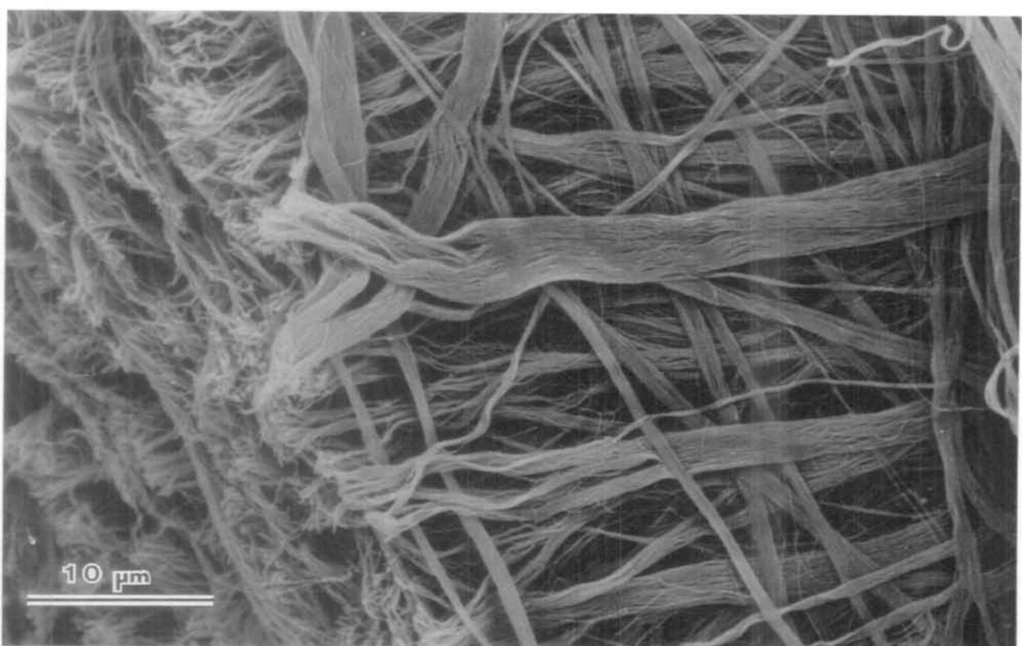
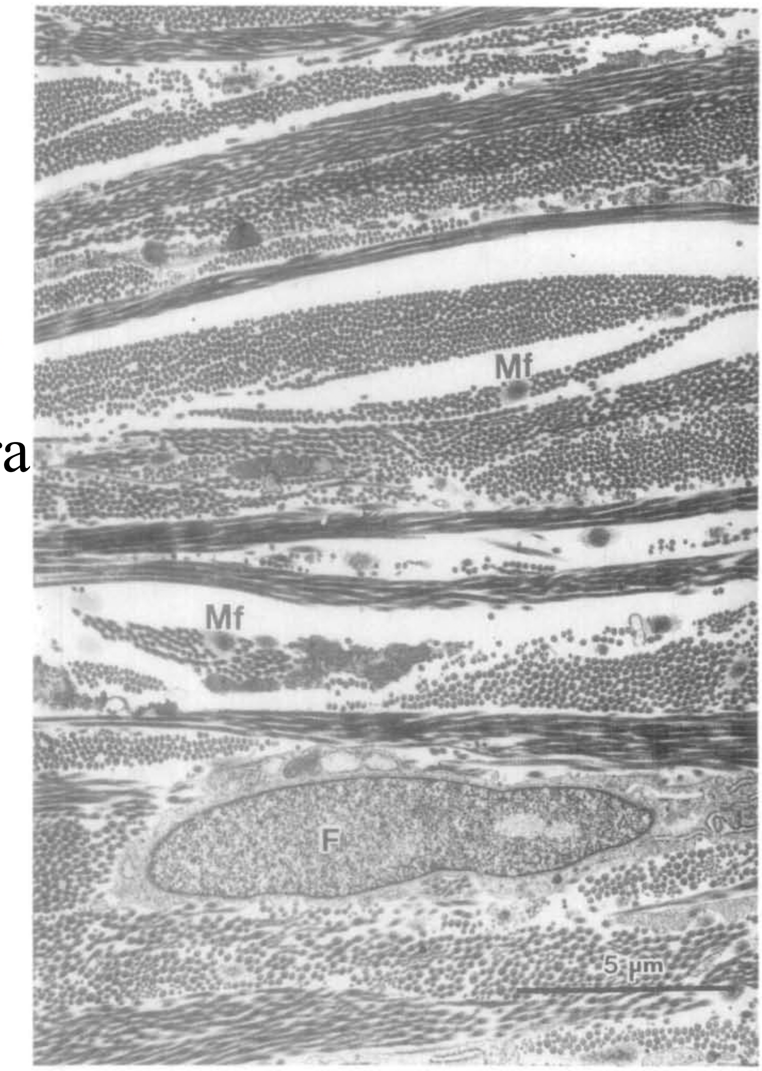


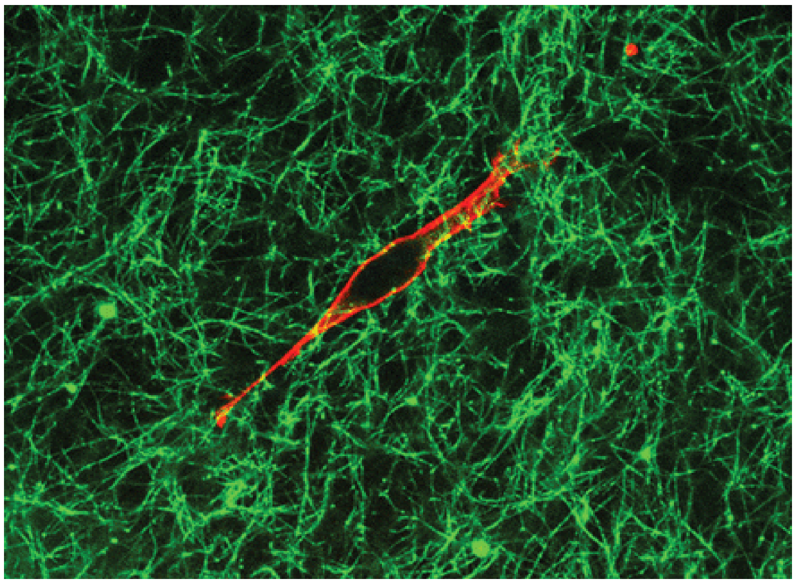
Figure 11. Electron micrograph of the arrangement of collagenous fibrils of the lamina radialis of an aortic valve leaflet at different magnifications. Arrows indicate non-directional fibrils surrounding helical arranged collagenous fibrils. (*a*,*b*) Scale bars, 8 μm and (*c*) 3 μm (adapted from Fastenrath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



Sclera



Cell motion in dense ECM

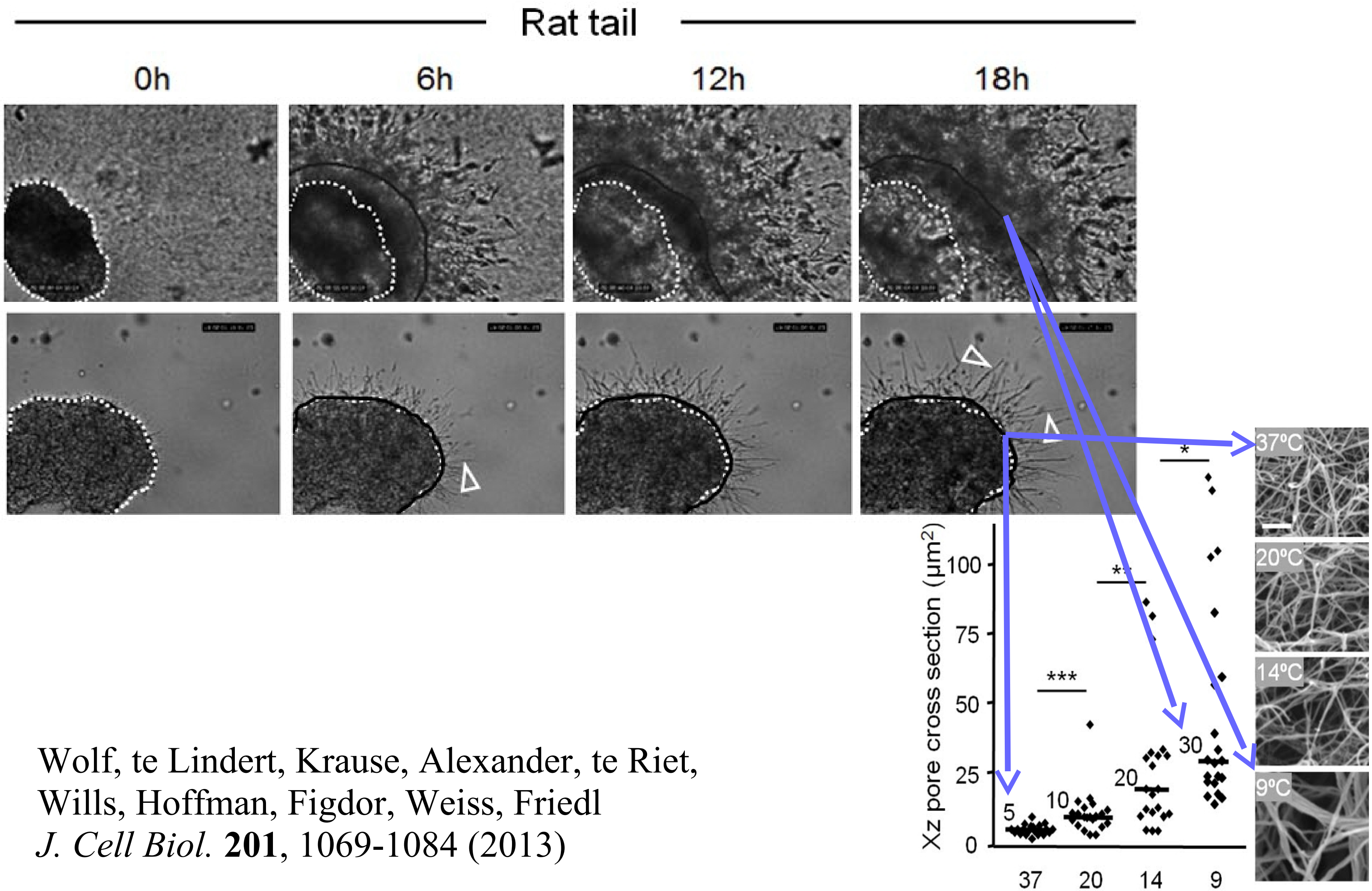


(P. Friedl, K. Wolf)

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

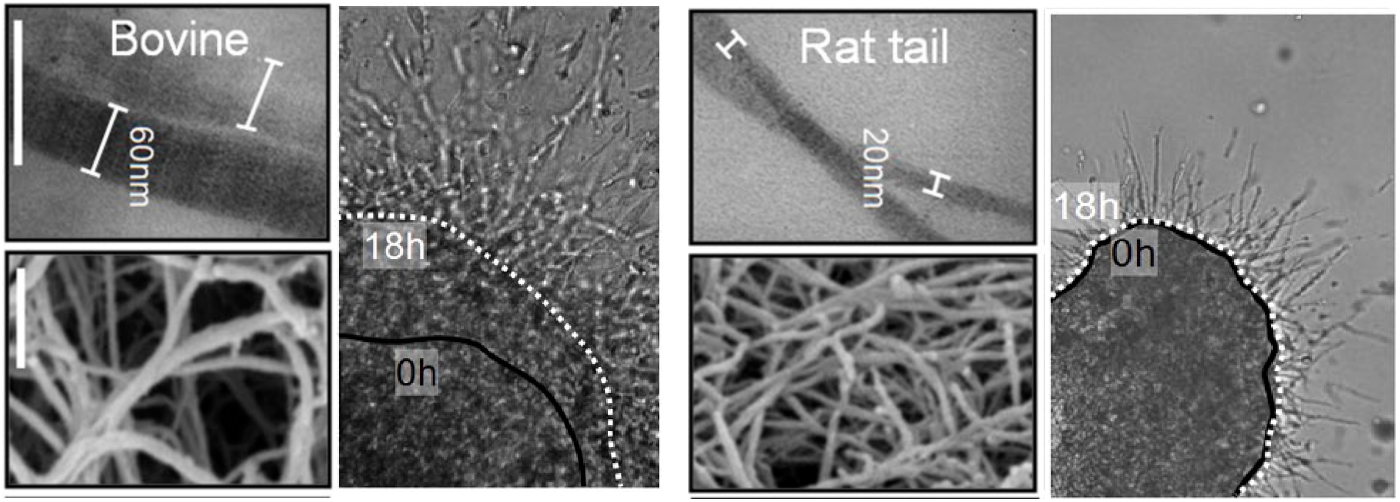
Neutrophil migration in rat tail collagen (1.7 mg/ml) in presence of IL-8

Cell motion in dense ECM

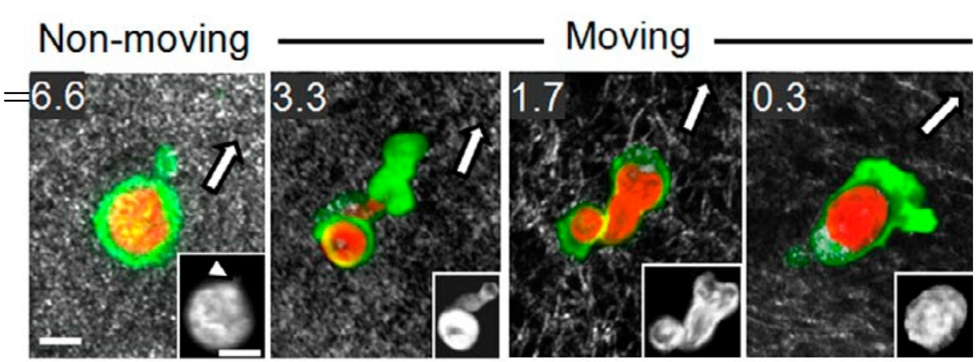


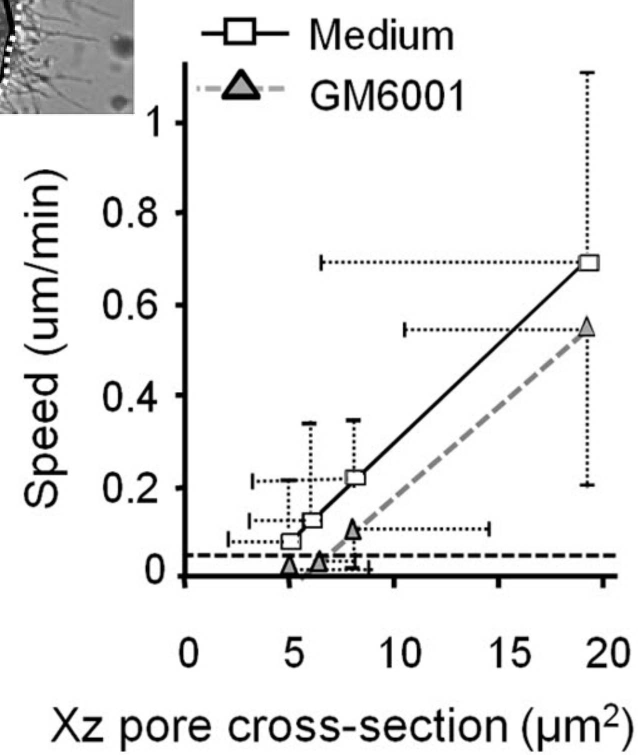
Wolf, te Lindert, Krause, Alexander, te Riet, Wills, Hoffman, Figdor, Weiss, Friedl
J. Cell Biol. **201**, 1069-1084 (2013)

Cell motion in dense ECM



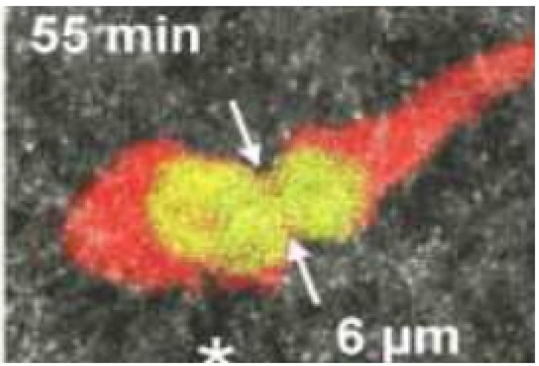
Collagen concentration =



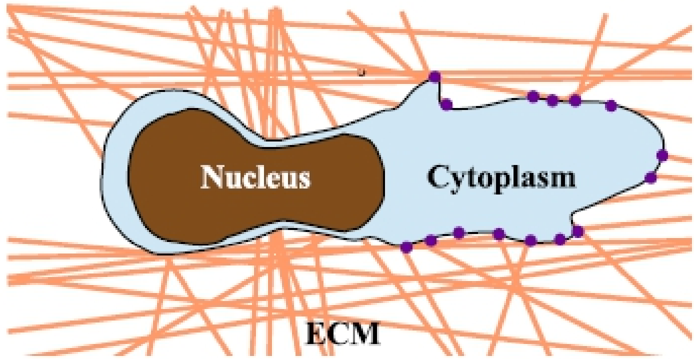


Taking into account of the nucleus

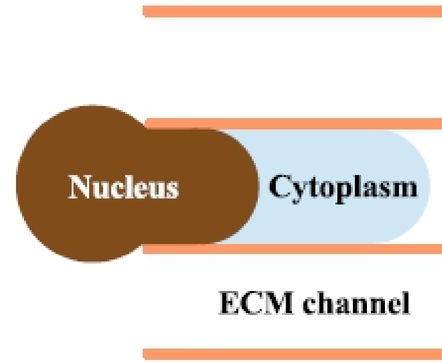
BIOLOGICAL
EXPERIMENT



BIOLOGICAL
REPRESENTATION



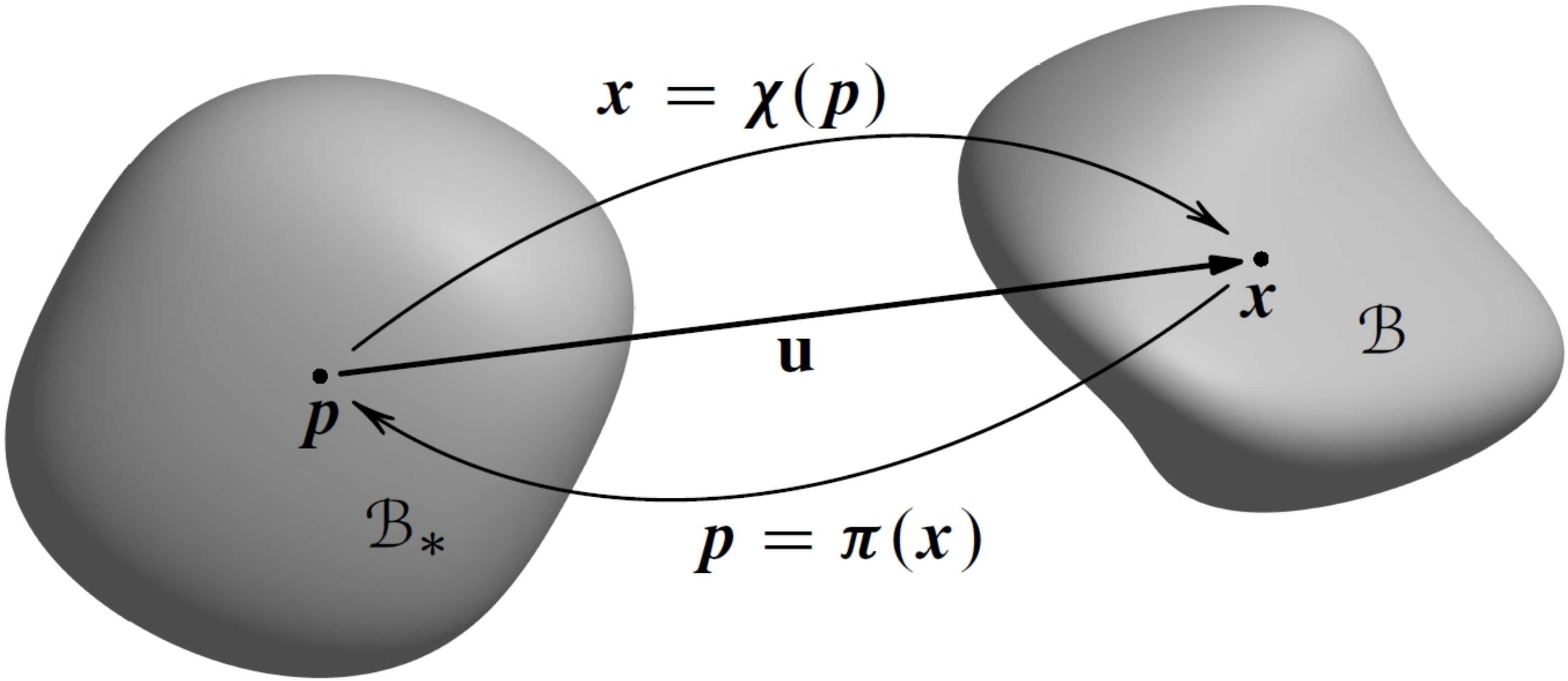
MATHEMATICAL
REPRESENTATION



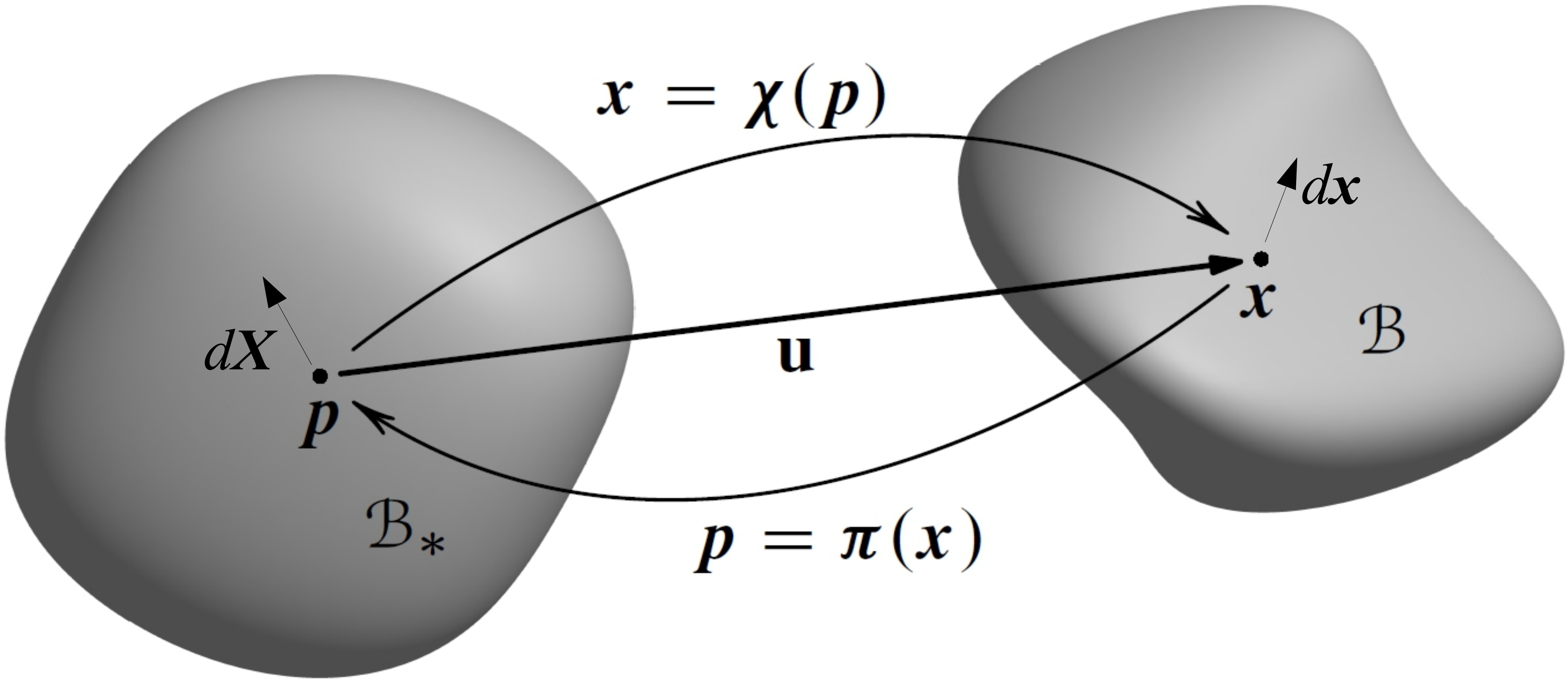
Work done by traction > Energy required to squeeze the nucleus

C. Giverso & L.P., *Biomech. Model. Mechanobiol.* **13**, 481-502 (2014)
C. Giverso, A. Arduino & L.P., *Bull. Math. Biol.* **80**, 1017-1045 (2018)

Continuum mechanics in a nutshell



Continuum mechanics in a nutshell

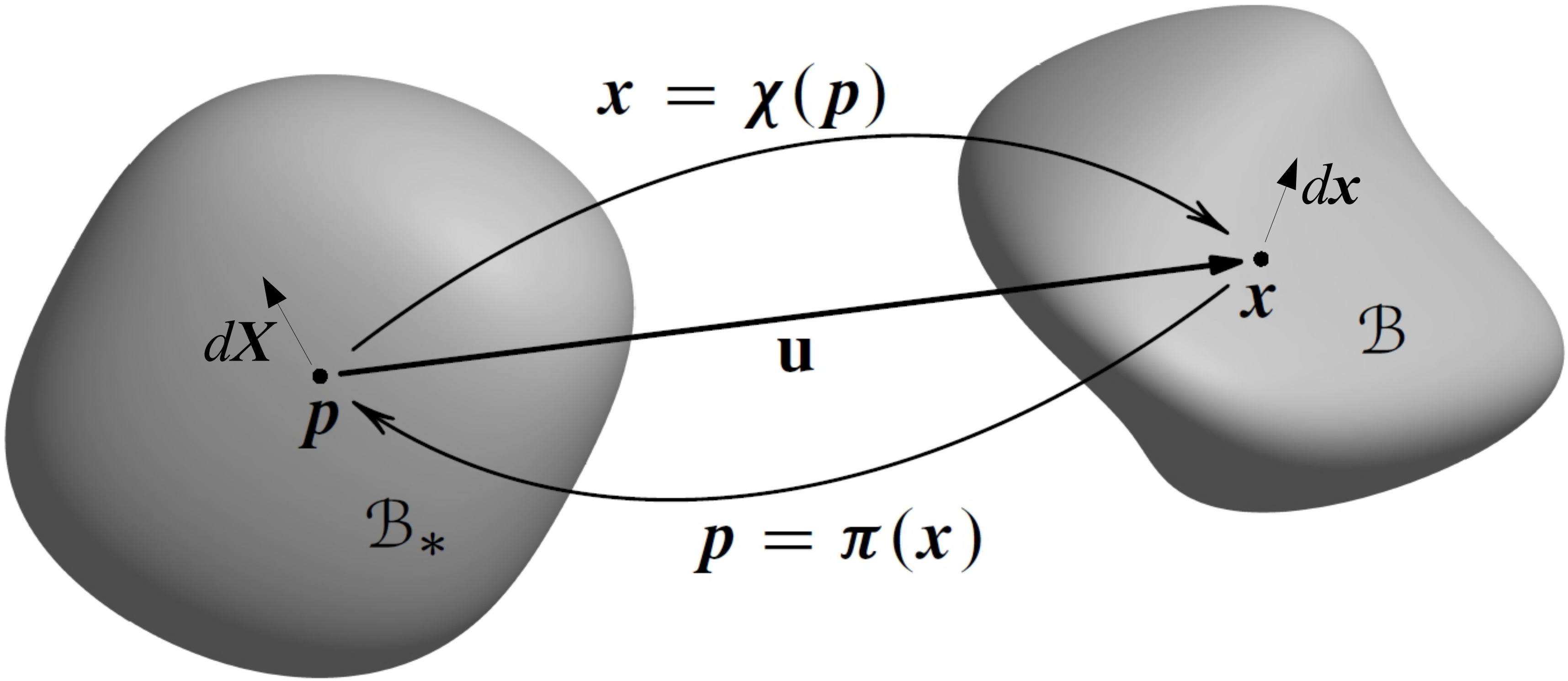


$$d\boldsymbol{x} = \mathbf{F}\, d\boldsymbol{X}$$

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

Deformation gradient

Continuum mechanics in a nutshell



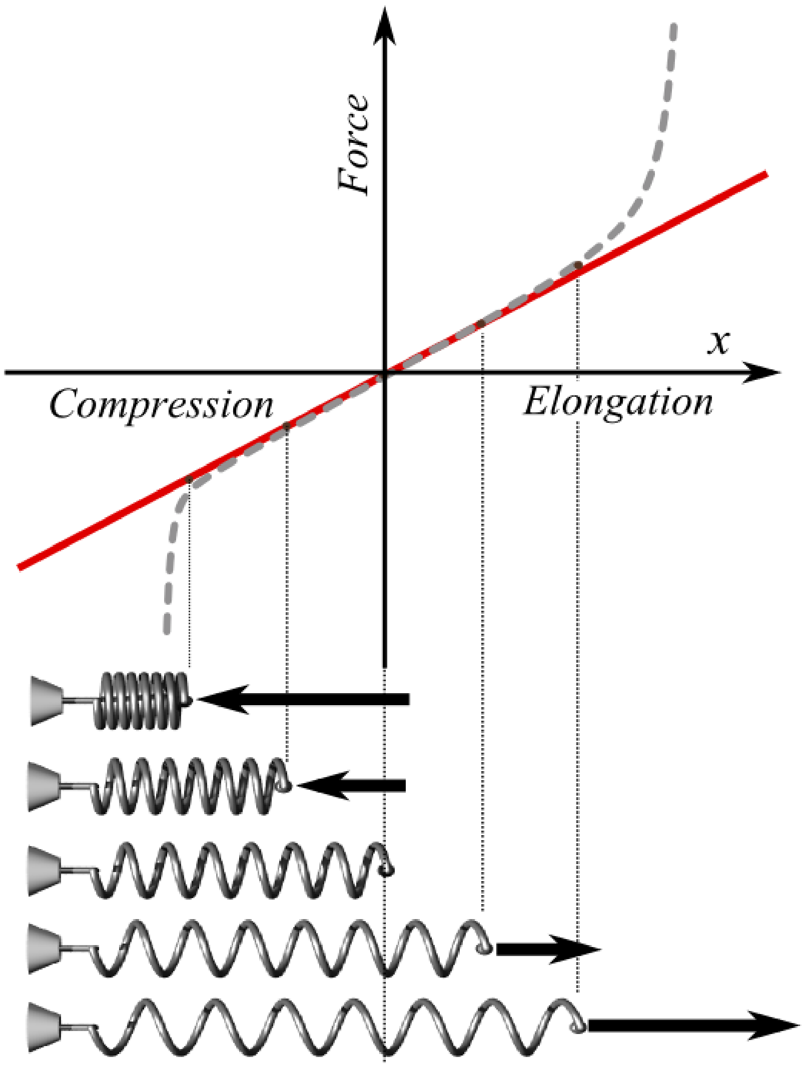
$$d\boldsymbol{x} = \mathbf{F}\, d\boldsymbol{X}$$

Cauchy-Green deformation tensor

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

$$\mathbf{B} = \mathbf{F}\mathbf{F}^T$$

Continuum mechanics in a nutshell



The force field is conservative

⇕

The work is independent on the path

⇕

There exists a potential energy

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

related to the elastic force **f** by

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

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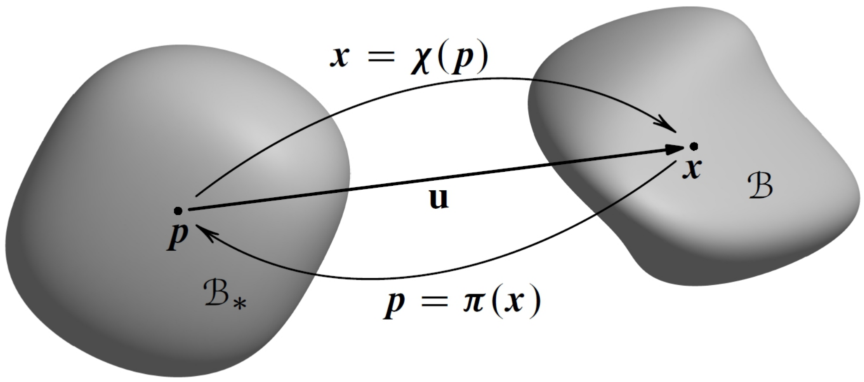
Continuum mechanics in a nutshell



The force field is conservative

⇕

The work is independent on the path

⇕

There exists a potential energy

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

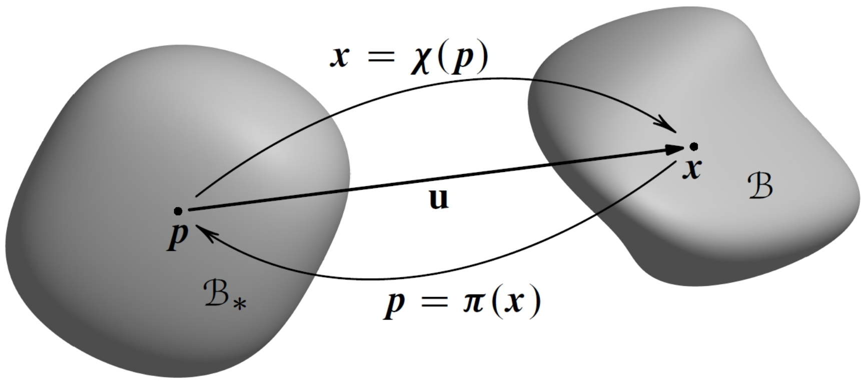
related to the Piola stress tensor **S** by

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

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

$$W(\mathrm{I}_{\mathbf{B}}) = \frac{\mu}{2}(\mathrm{I}_B - 3)$$

$$\mathbf{T} = -p\mathbf{I} + \mu\mathbf{B}$$

Continuum mechanics in a nutshell

neo-Hookean material

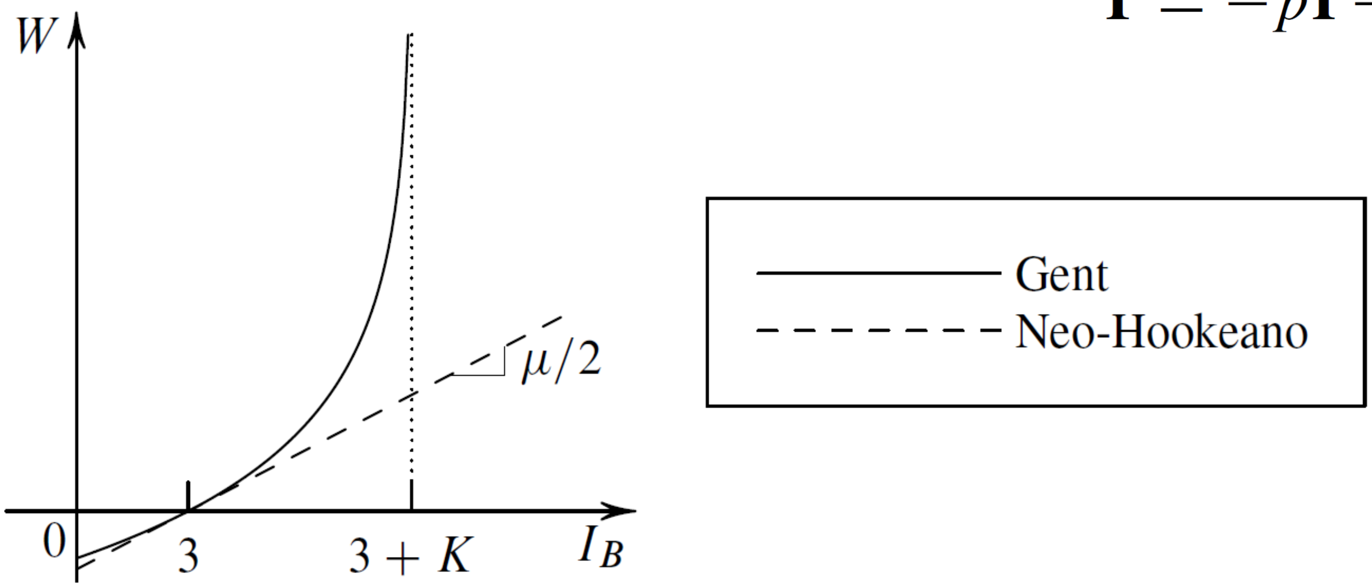
$$W(\mathrm{I_B}) = \frac{\mu}{2}(\mathrm{I}_B - 3)$$

$$\mathbf{T} = -p\mathbf{I} + \mu\mathbf{B}$$

Gent material

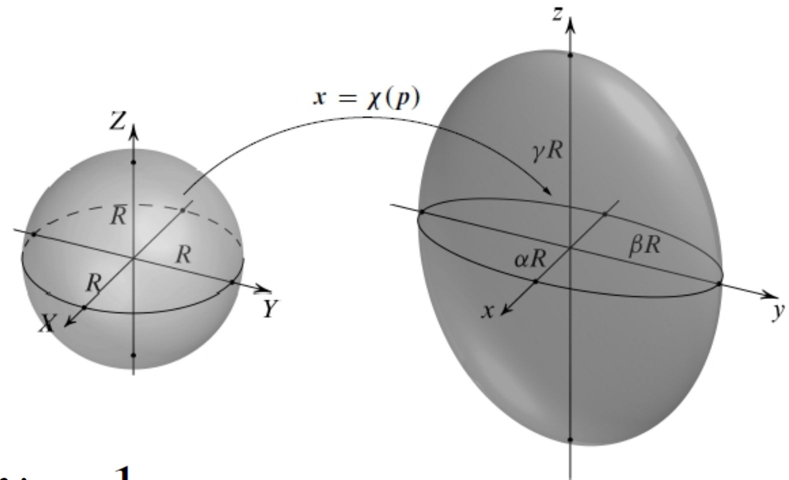
$$W(\mathrm{I_B}) = -\frac{\mu}{2}K\,\ln\left(1 - \frac{\mathrm{I}_B - 3}{K}\right)$$

$$\mathbf{T} = -p\mathbf{I} + \frac{\mu}{1 - \dfrac{\mathrm{I}_B - 3}{K}}\mathbf{B}$$



Pure extension

$$\begin{cases} x = \alpha X \\ y = \beta Y \\ z = \gamma Z \end{cases} \qquad \mathbf{F} = \begin{bmatrix} \alpha & 0 & 0 \\ 0 & \beta & 0 \\ 0 & 0 & \gamma \end{bmatrix}$$



Incompressibility → $J = \det \mathbf{F} = \alpha\beta\gamma = 1$

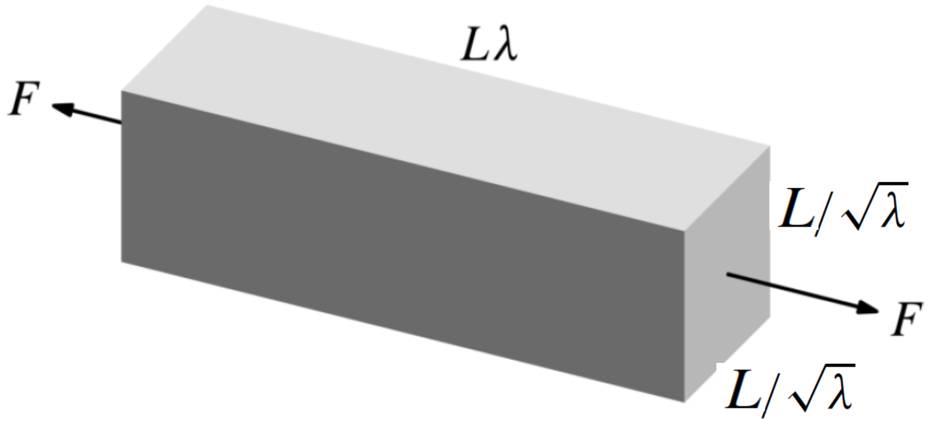
$$\mathbf{B} = \mathbf{F}\mathbf{F}^T = \begin{bmatrix} \alpha^2 & 0 & 0 \\ 0 & \beta^2 & 0 \\ 0 & 0 & \gamma^2 \end{bmatrix}$$

$$\mathbf{T} = -p\mathbf{I} + h_1\mathbf{B} + h_{-1}\mathbf{B}^{-1}$$

$$h_{\pm 1} = h_{\pm 1}(\mathrm{I}_B, \mathrm{I}_{B^{-1}})$$

neo-Hookean material $h_1 = \mu \quad h_{-1} = 0$

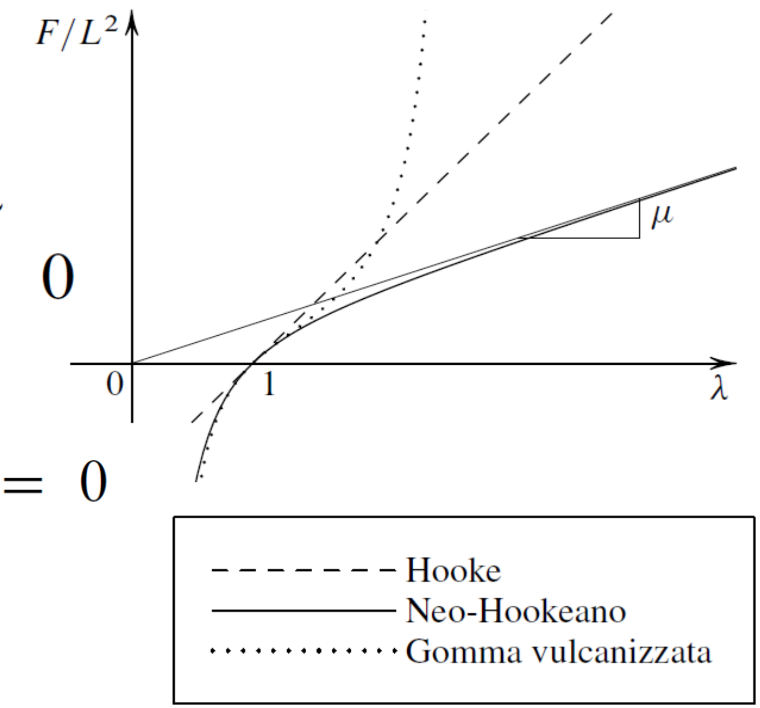
Uniaxial extension



$$\mathbf{F} = \begin{bmatrix} \lambda & 0 & 0 \\ 0 & 1/\sqrt{\lambda} & 0 \\ 0 & 0 & 1/\sqrt{\lambda} \end{bmatrix}$$

$$\mathbf{T} = -p\mathbf{I} + h_1\mathbf{B} + h_{-1}\mathbf{B}^{-1}$$

$$\begin{cases} T_{11} = -p + h_1\lambda^2 + h_{-1}\lambda^{-2} = \dfrac{F}{L^2}\lambda \\ T_{22} = T_{33} = -p + h_1/\lambda + h_{-1}\lambda = 0 \end{cases}$$



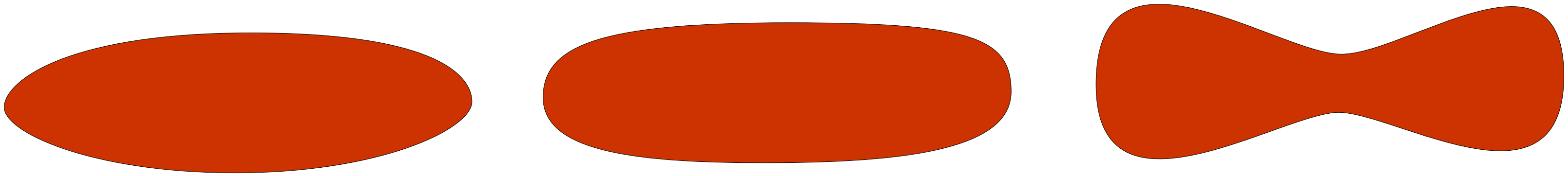
neo-Hookean material $h_1 = \mu \quad h_{-1} = 0$

$$\frac{F}{L^2} = \mu\left(\lambda - \frac{1}{\lambda^2}\right)$$

Computing the energy required

Work done by traction > Energy required to squeeze the nucleus

- Given the deformation **F**

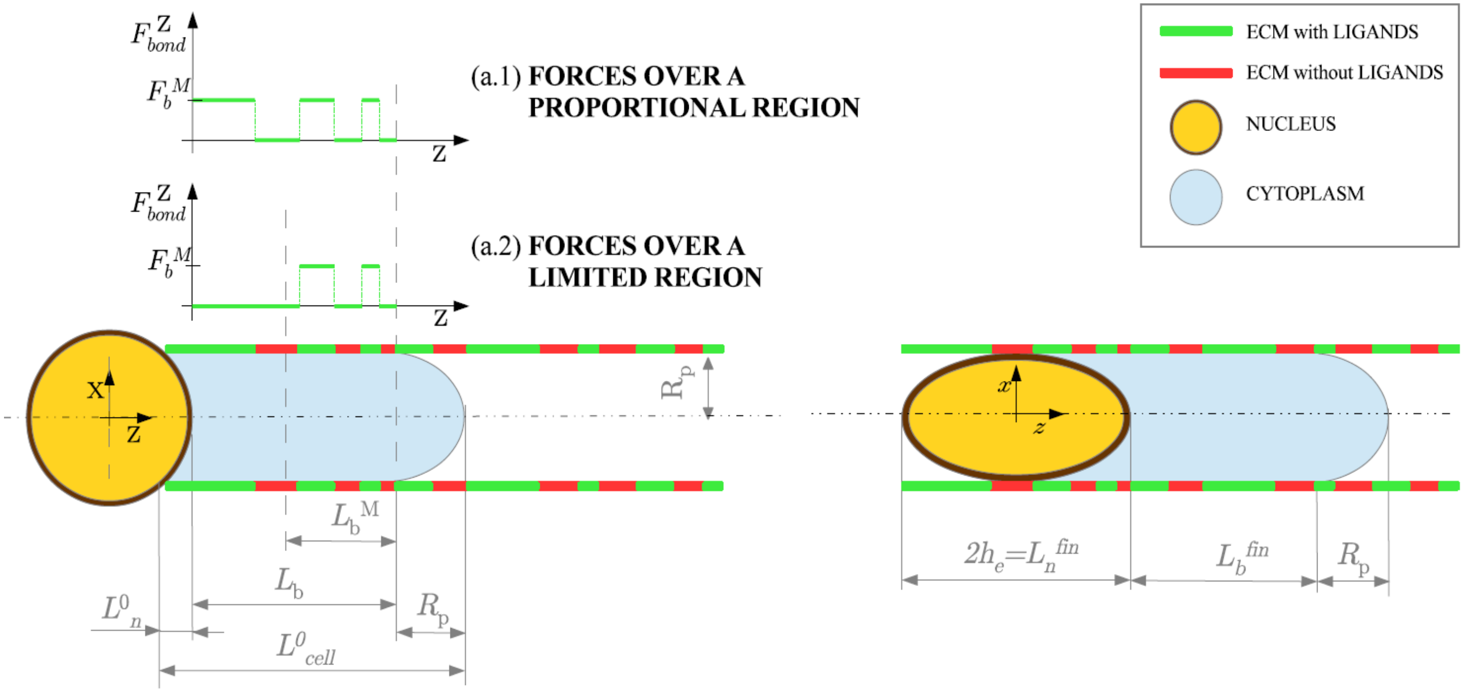


- Given the constitutive equation *W*

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

Computing the work done by traction

Work done by traction > Energy required to squeeze the nucleus



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

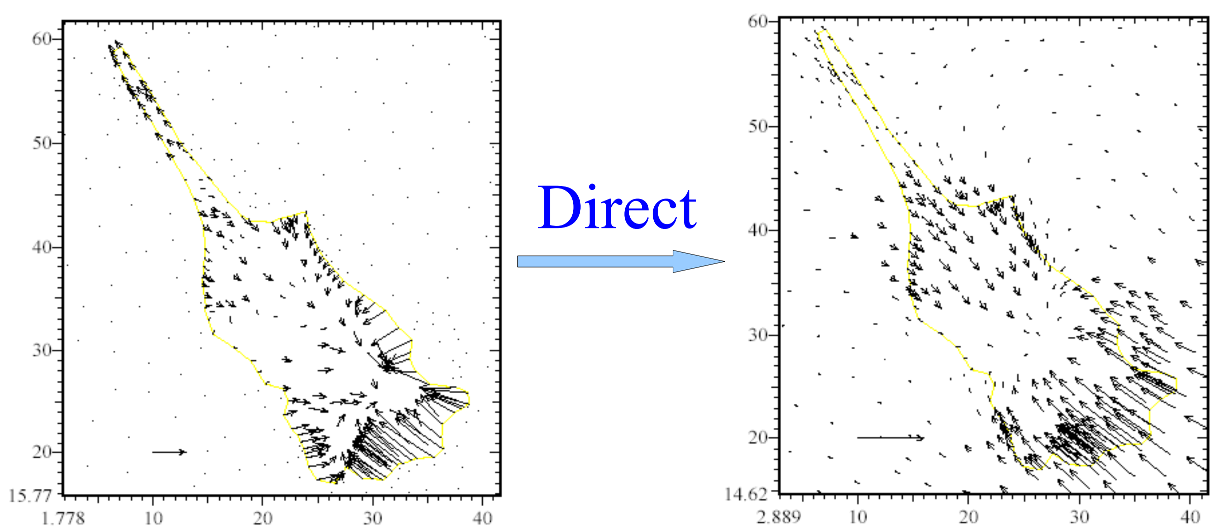
$$\mathcal{W}_{adhesion} = F^Z_{adhesion}\Delta L$$

Cell traction

The classical (direct) problem in elasticity:

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

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

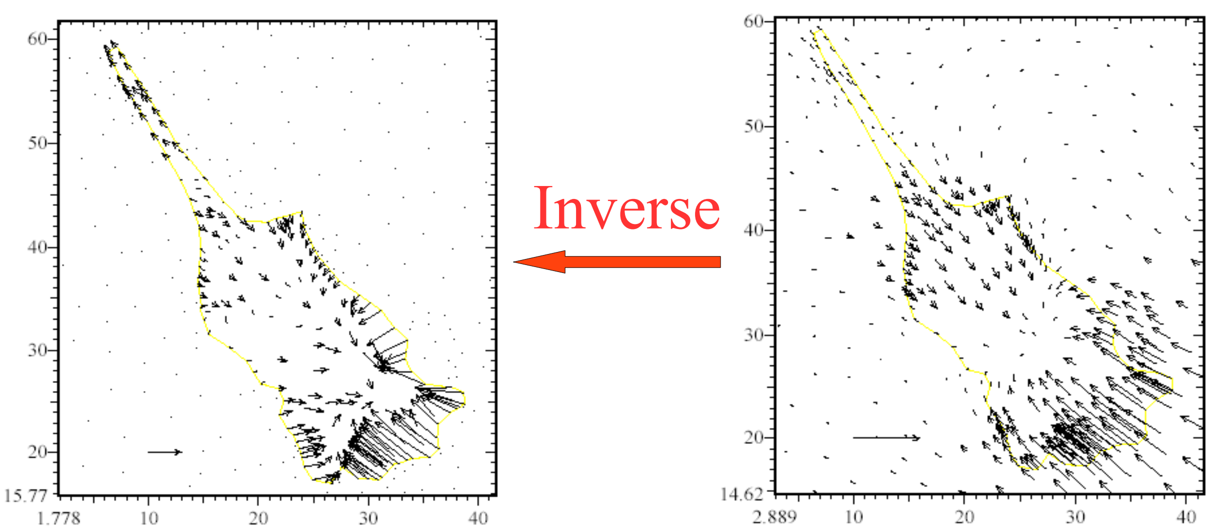


Cell traction

The classical (direct) problem in elasticity:

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

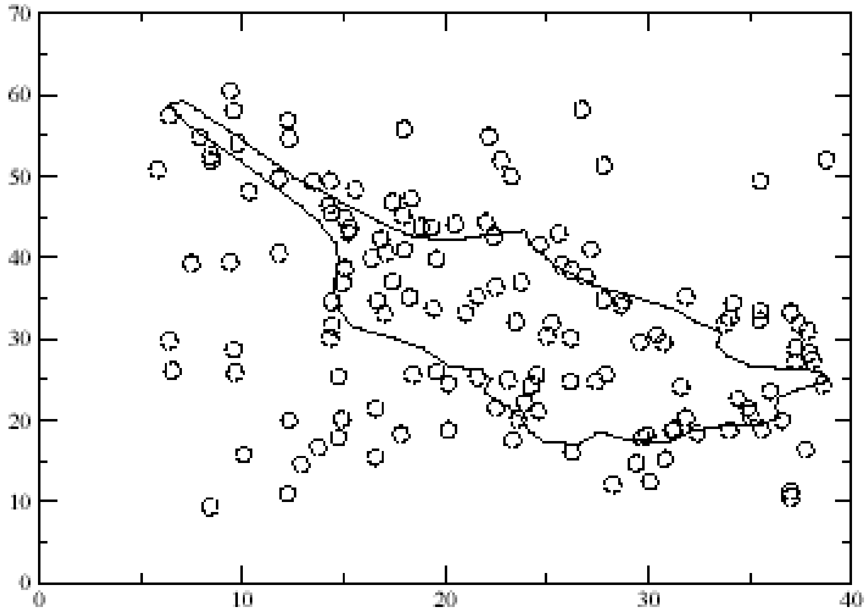
$$\left.\begin{aligned} &A\mathbf{u} = \mathbf{f}, \qquad \mathbf{u}|_{\partial\Omega} = 0, \\ &A\mathbf{u} = -\mu\Delta\mathbf{u} - (\mu+\lambda)\nabla(\nabla\cdot\mathbf{u}) \end{aligned}\right\} \quad \mathcal{S}^{-1}: \mathbf{u} \to \mathbf{f}$$

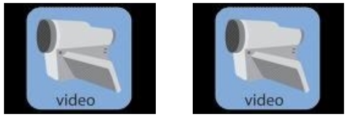


Cell traction

deformation

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





(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 $\mathcal{J} : \mathsf{F} \rightarrow \mathbb{R}^+$ *is defined as:*

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

Take the smallest force possible

Compute the deformation for a given virtual force

Measured deformation

Evaluate the computed deformation in the measurement points

The inverse problem

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

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

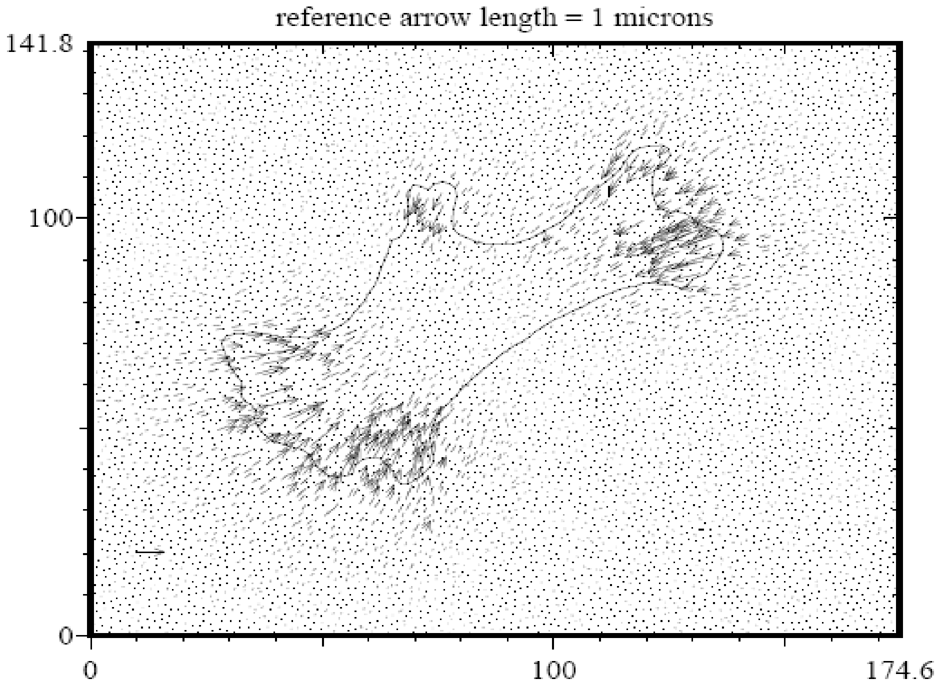
Two coupled sets of elliptic partial differential equations to be solved in Ω,

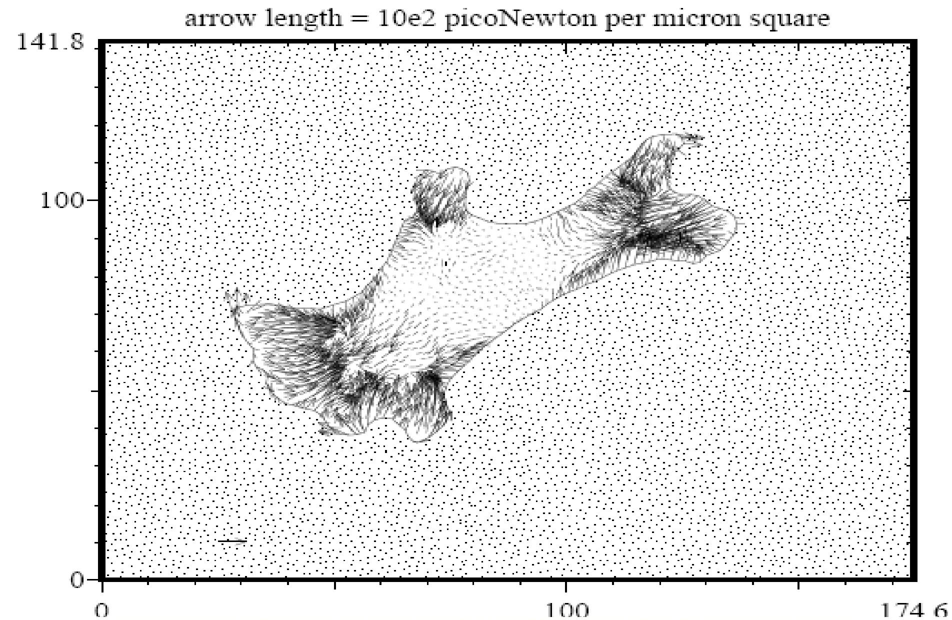
$$-\hat{\mu}\Delta\mathbf{u} - (\hat{\mu} + \hat{\lambda})\nabla(\nabla \cdot \mathbf{u}) = -\frac{\chi_c}{\varepsilon}\mathbf{p}, \qquad \mathbf{u}|_{\partial\Omega} = 0,$$

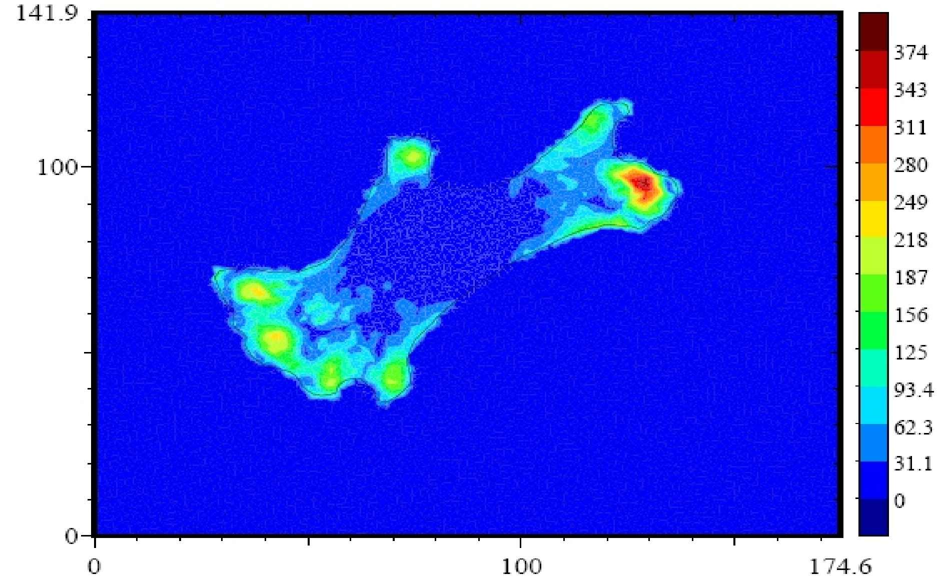
$$-\hat{\mu}\Delta\mathbf{p} - (\hat{\mu} + \hat{\lambda})\nabla(\nabla \cdot \mathbf{p}) = \chi_o\mathbf{u} - \mathbf{u}_0, \qquad \mathbf{p}|_{\partial\Omega} = 0.$$

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

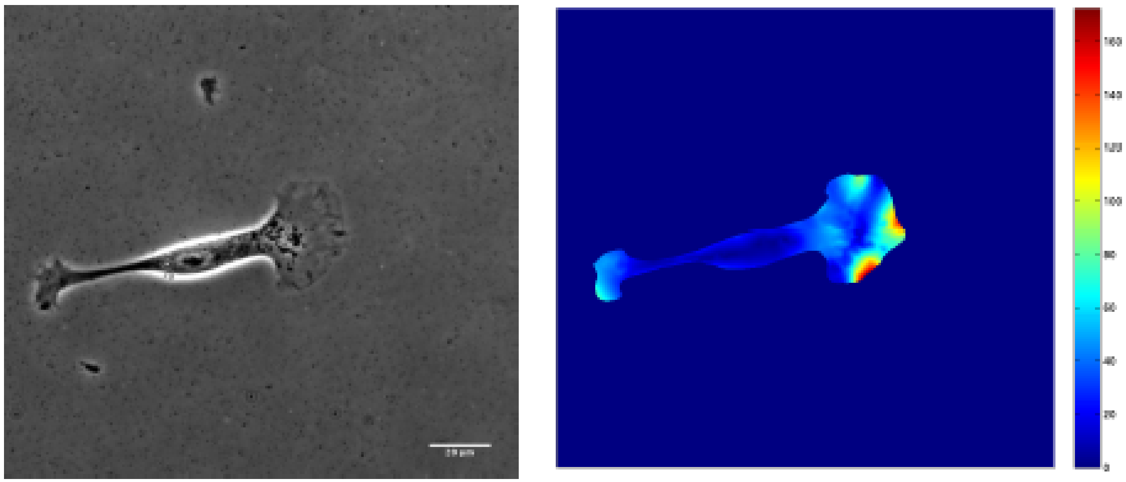
Traction force microscopy







Cell traction



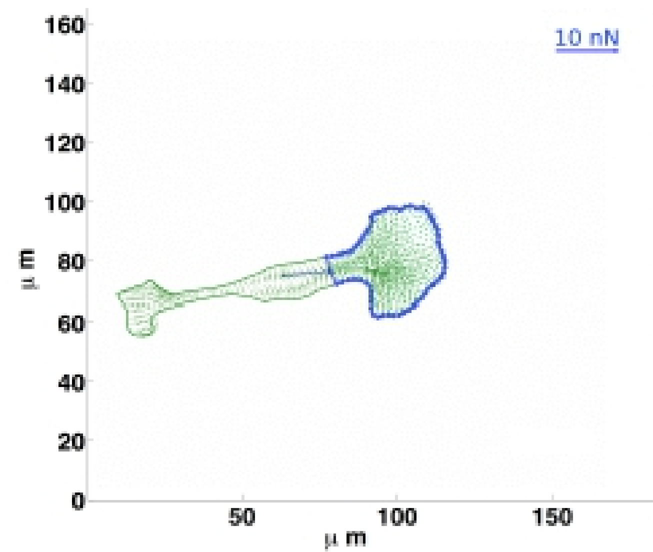
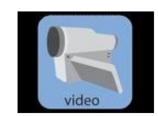
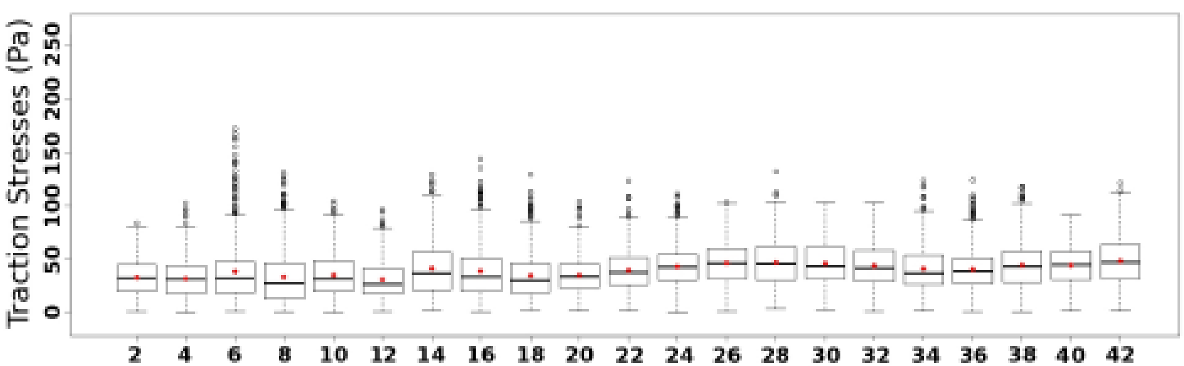


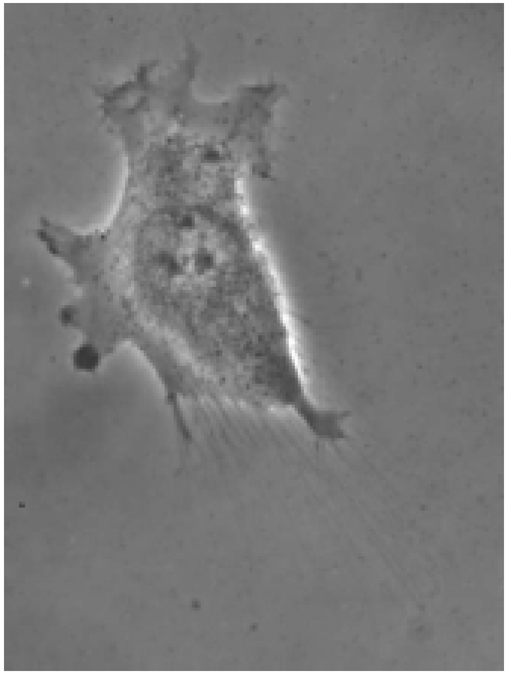
Figure 1: Phase–contrast image of a T24 cancer cell (at time $t = 6$ min from Fig. 2) and corresponding traction field of a T24 cell represented as a color map. The color scale for stresses reads in Pascal (Pa).

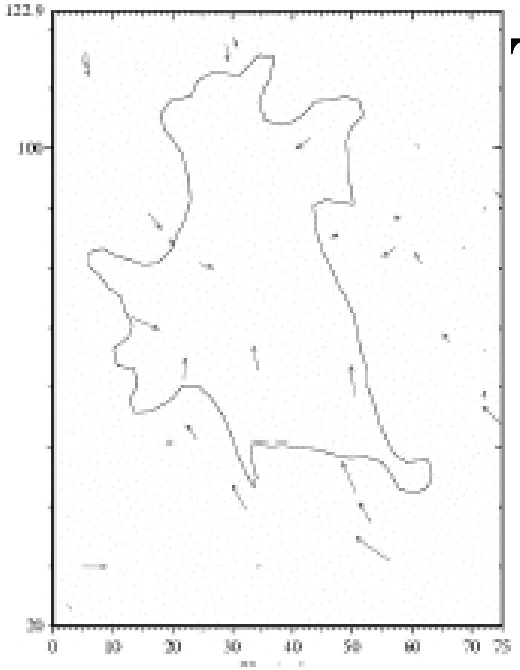




V. Peschetola et al.
Comp. Methods Biomech. Biomed. Engng. **14**, 159-160 (2011).

Traction on a stiff gel

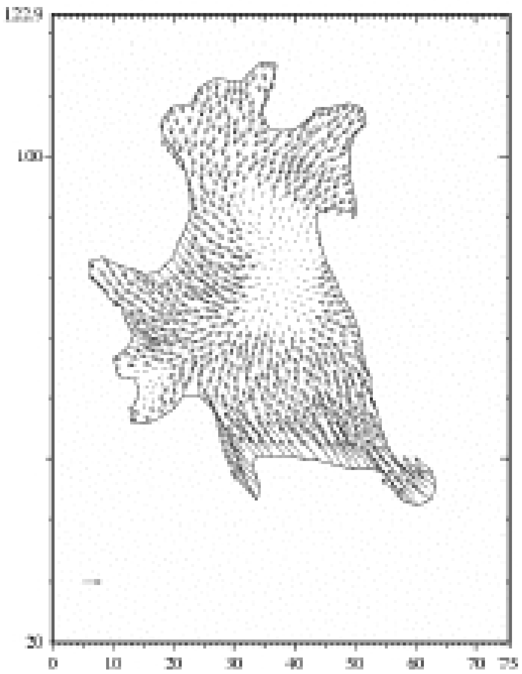


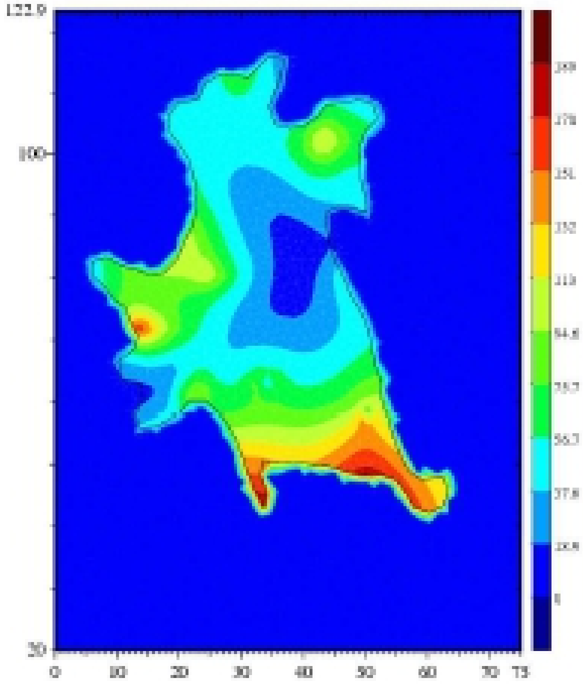


Ambrosi, Peschetola,Verdier
SIAM J. Appl. Math, (2006)

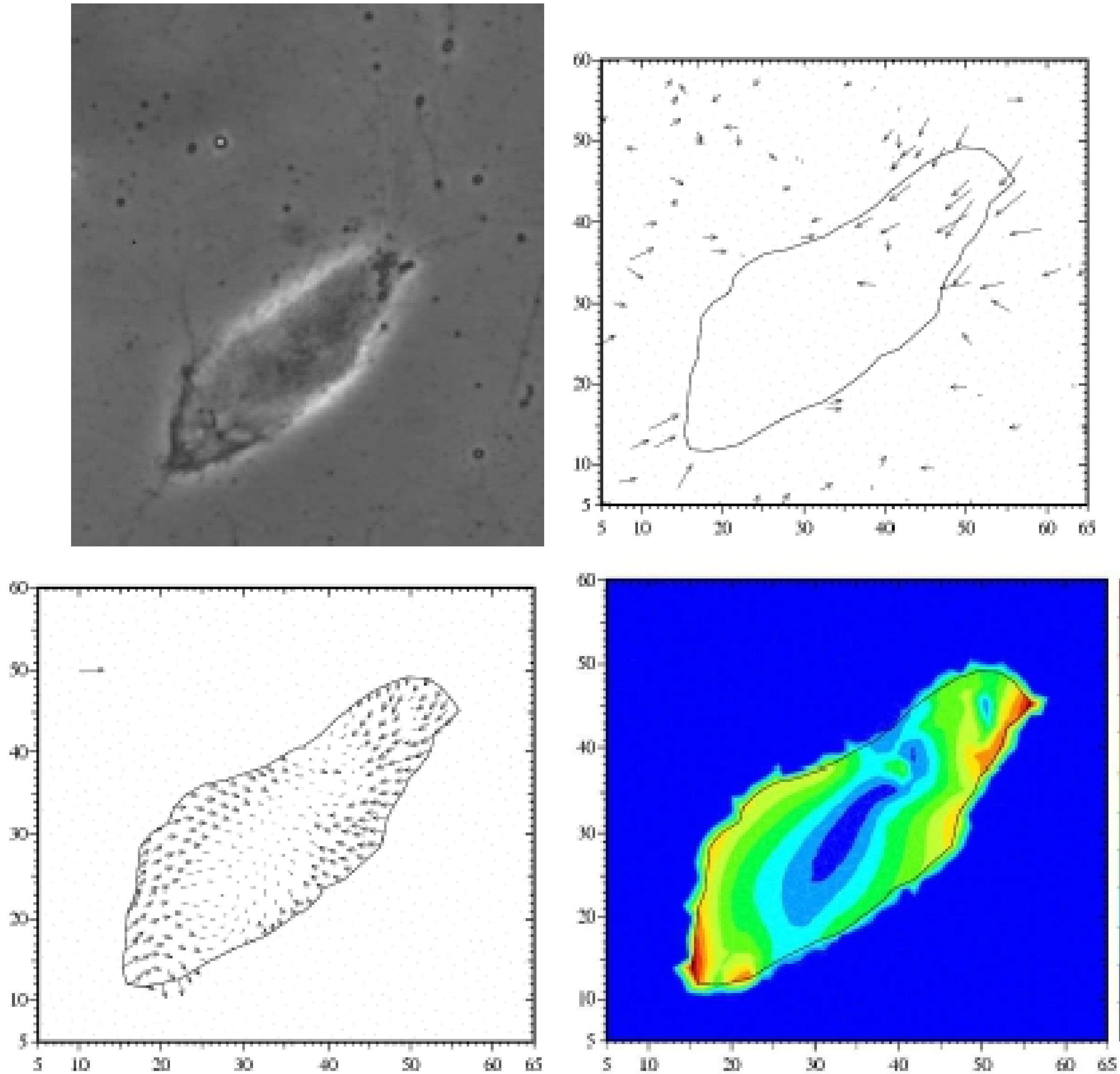
T24 cancer cells

video





Traction on softer gel

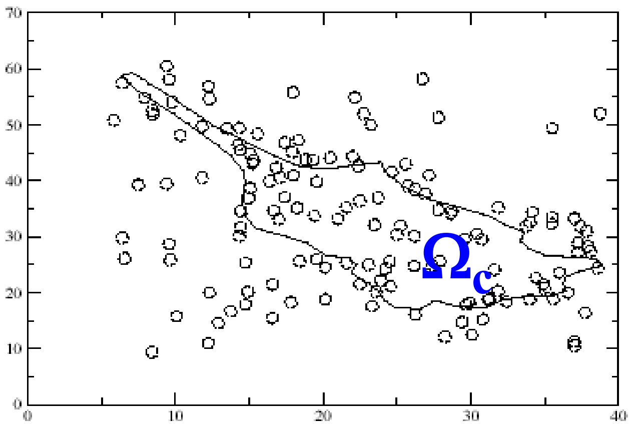


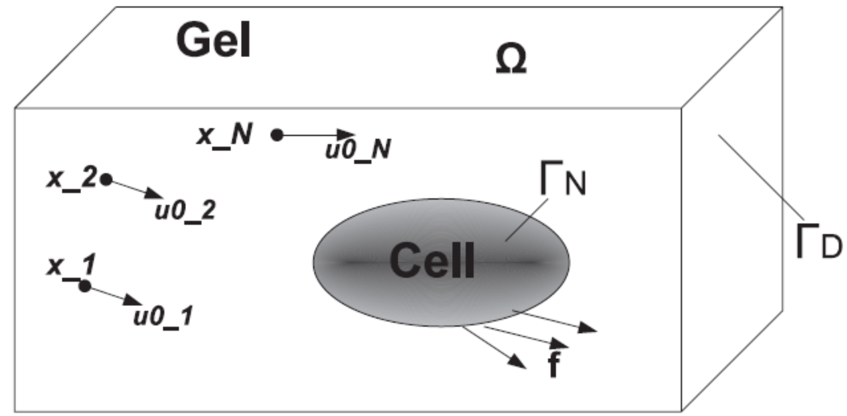
T24 cancer cells

Conclusions

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

Traction in 3D





Differences

2D

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

3D

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

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

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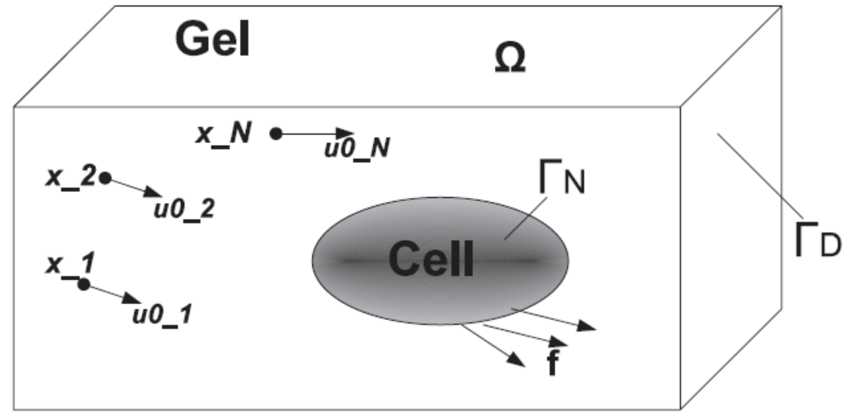
Traction in 3D



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

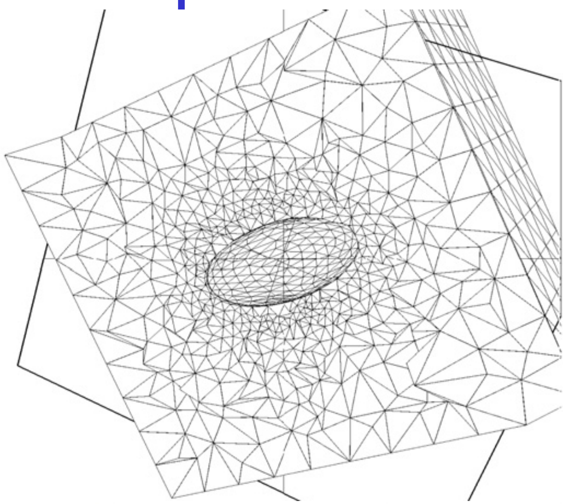
Penalty function for the minimization problem

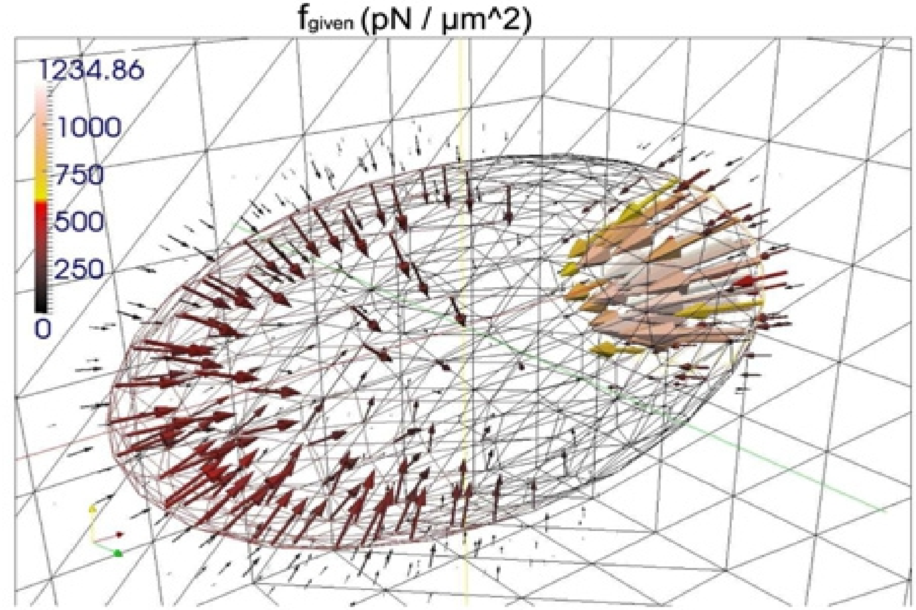
$$\mathcal{J}(\mathbf{f}) = \frac{1}{2}\|\mathcal{O}\mathcal{S}\mathbf{f} - u_0\|^2 + \frac{\varepsilon}{2}\|\mathbf{f}\|^2$$

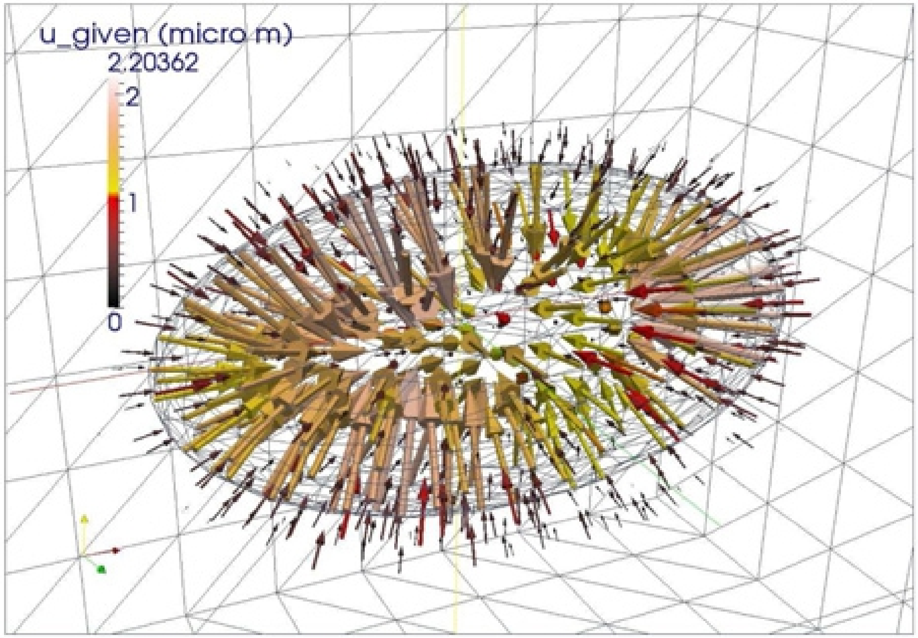
Self-adjoint problem

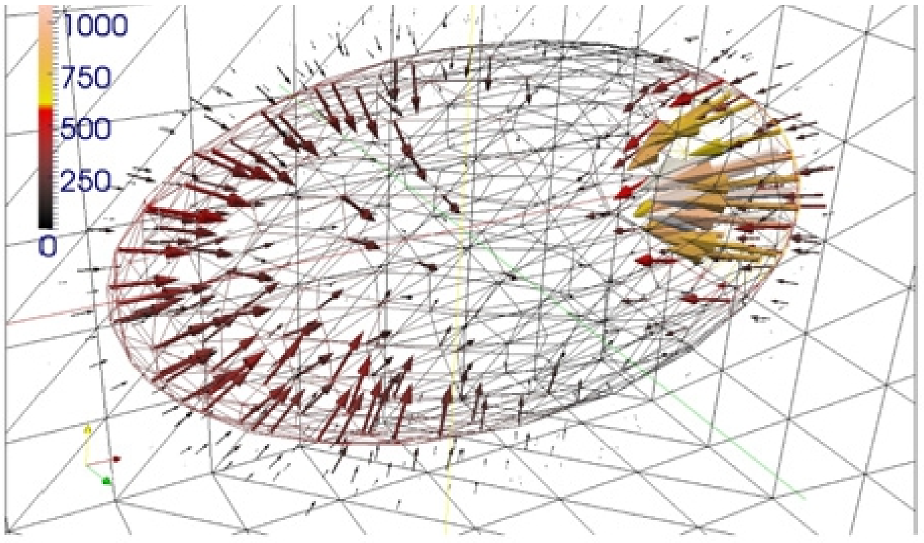
$$\begin{cases} \displaystyle\int_\Omega (\mu \nabla \mathbf{u} \cdot \nabla \mathbf{v} + \lambda (\nabla \cdot \mathbf{u})(\nabla \cdot \mathbf{v})) + \frac{1}{\varepsilon}\left(\int_{\Gamma_N} \mathbf{p} \cdot \mathbf{v} - \frac{1}{|\Gamma_N|}\int_{\Gamma_N} \mathbf{p} \cdot \int_{\Gamma_N} \mathbf{v}\right)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

Traction in 3D





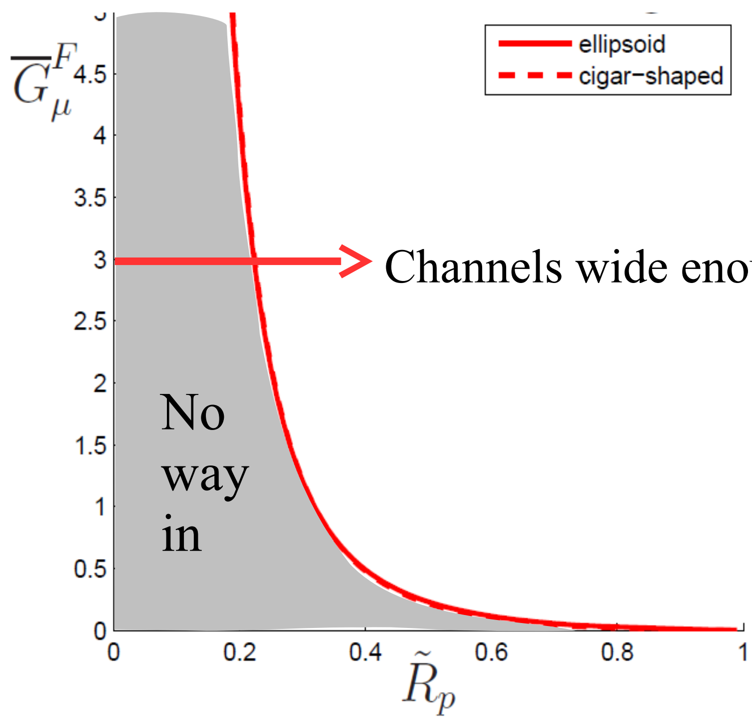




Criterium for invasion

Work done by traction > Energy required to squeeze the nucleus

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



Traction

$$G^F_\mu = \frac{\rho_b \alpha_{ECM} F_b^M}{\mu}$$

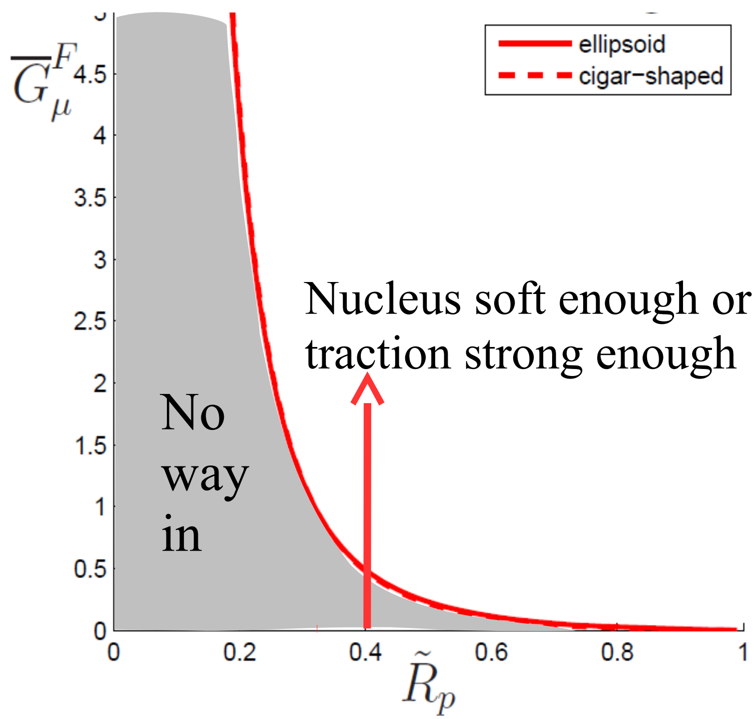
Nucleus stiffness

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

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	$G_\mu^F \geq \frac{2}{3} \frac{\mathcal{I}(\tilde{R}_p)}{\tilde{R}_p \tilde{L}_b^{(*)} \Delta \tilde{L}_{cigar}}$



Traction

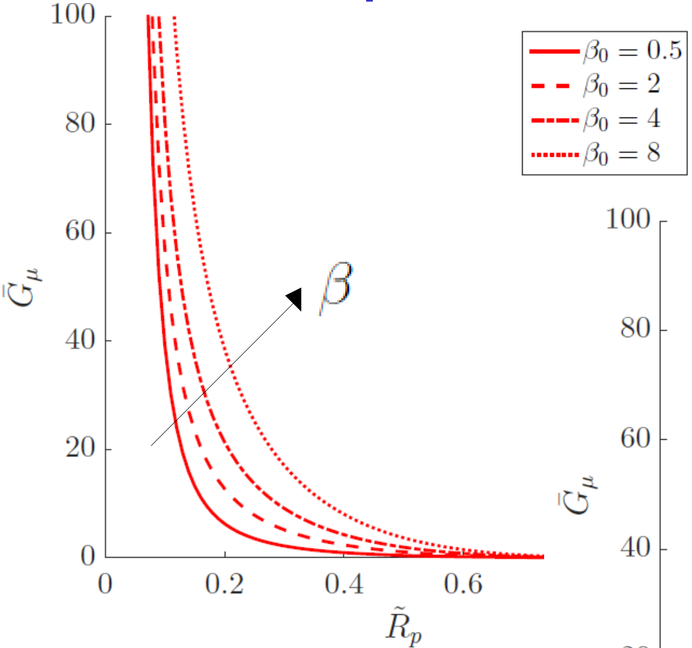
$$G_\mu^F = \frac{\rho_b \alpha_{ECM} F_b^M}{\mu}$$

Nucleus stiffness

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

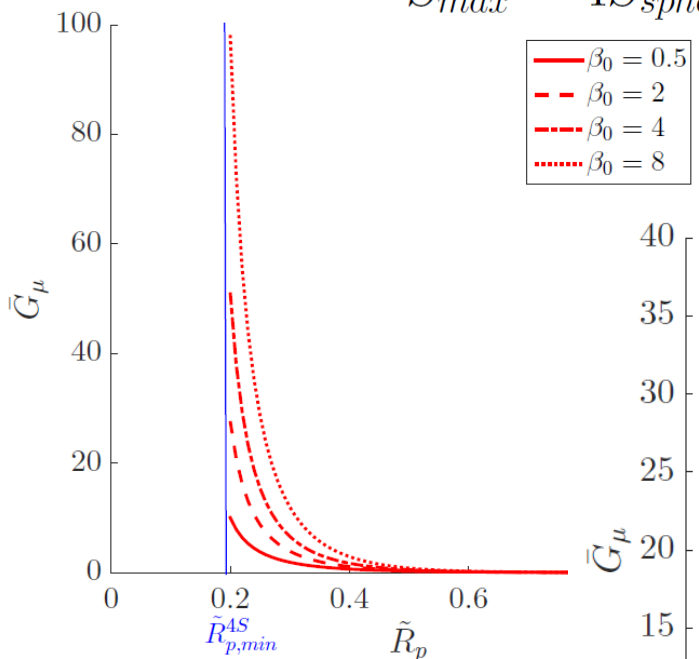
C. Rolli, *PlosOne* **5**, e8726 (2010)

Effect of nucleus envelope stretchability

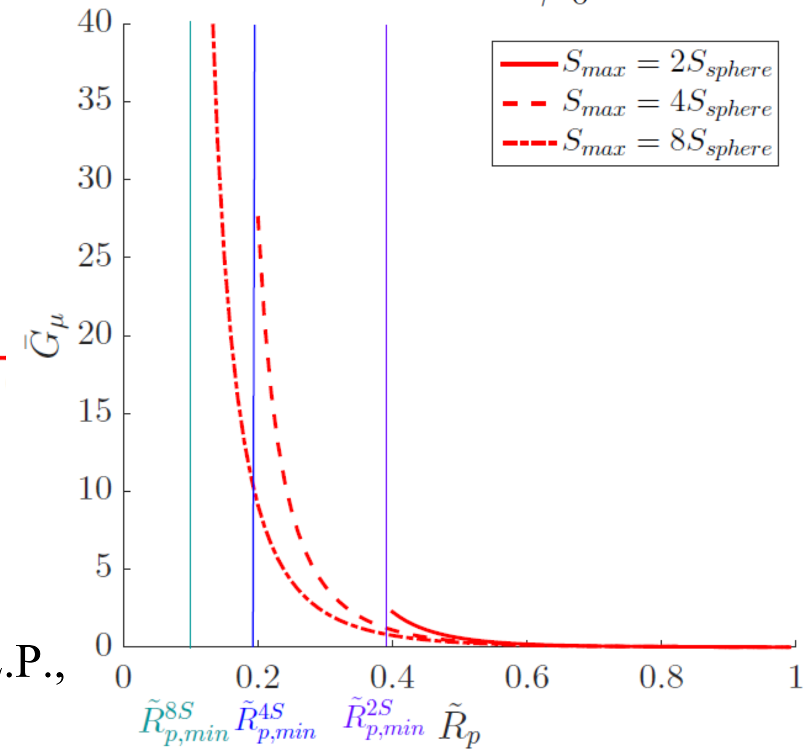


$$\lambda(\Delta S) = \lambda_0 \left(\frac{\Delta S}{S_{max} - S} \right)$$

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



$$\beta_0 = 2$$



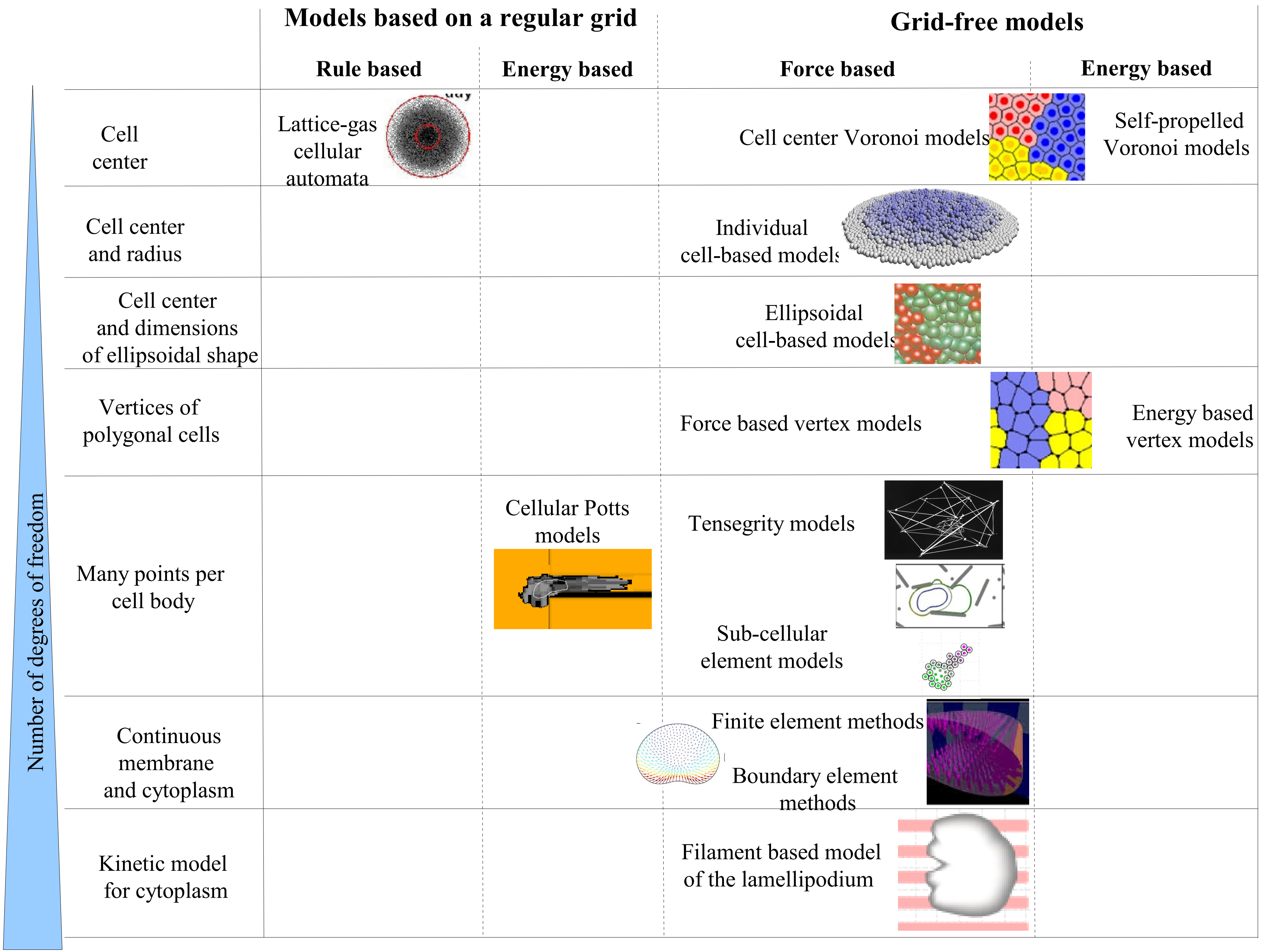
$$\tilde{R}_p = R_p / R_n$$

Membrane

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

Nucleus

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


Models based on a regular grid
Grid-free models
Rule based
Energy based
Force based
Energy based
Number of degrees of freedom
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

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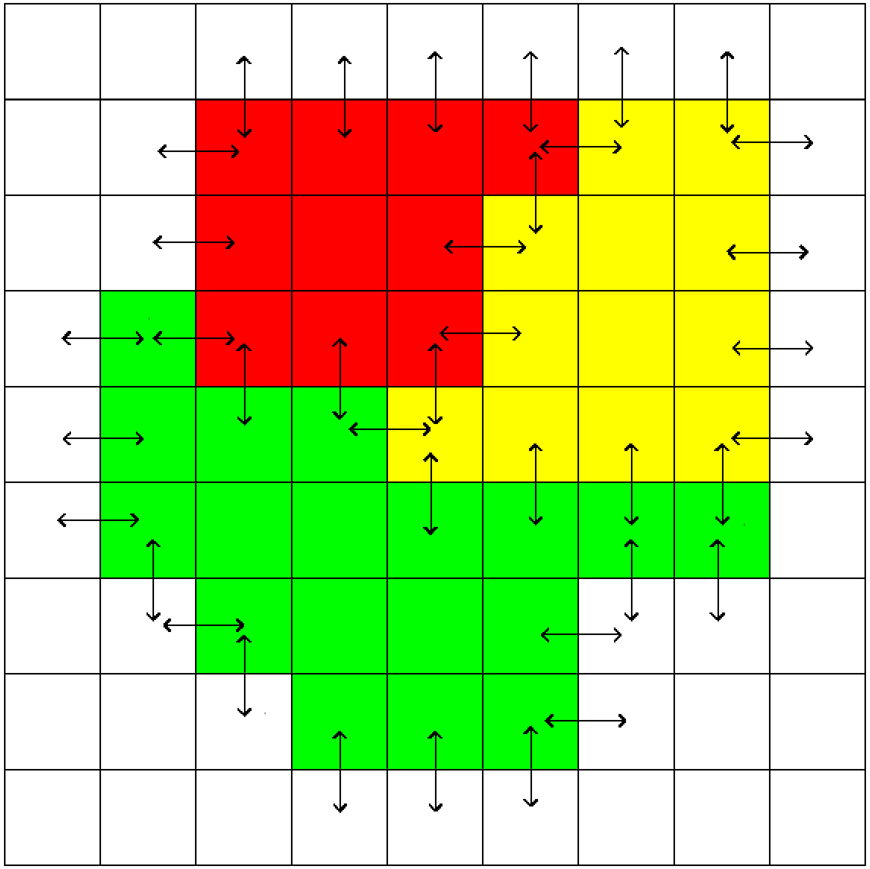
The cellular Potts model

A cell is represented by several nodes



- Based on a generalized energy H
- Evolution stochastically tries to minimize the system energy

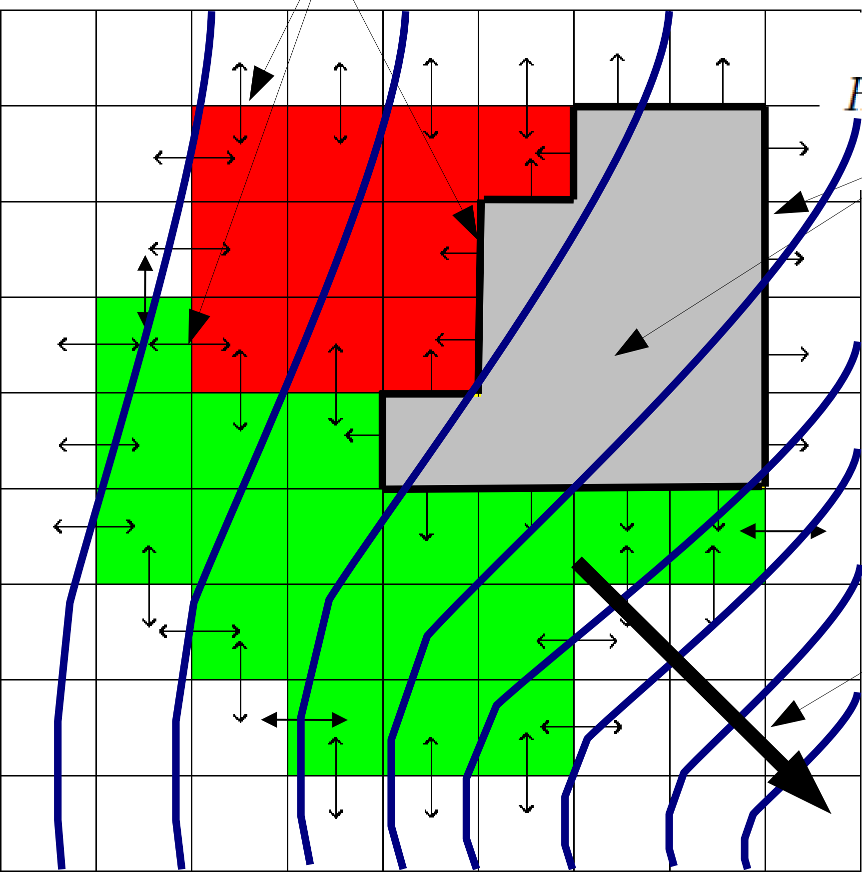
The cellular Potts model

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

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

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

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



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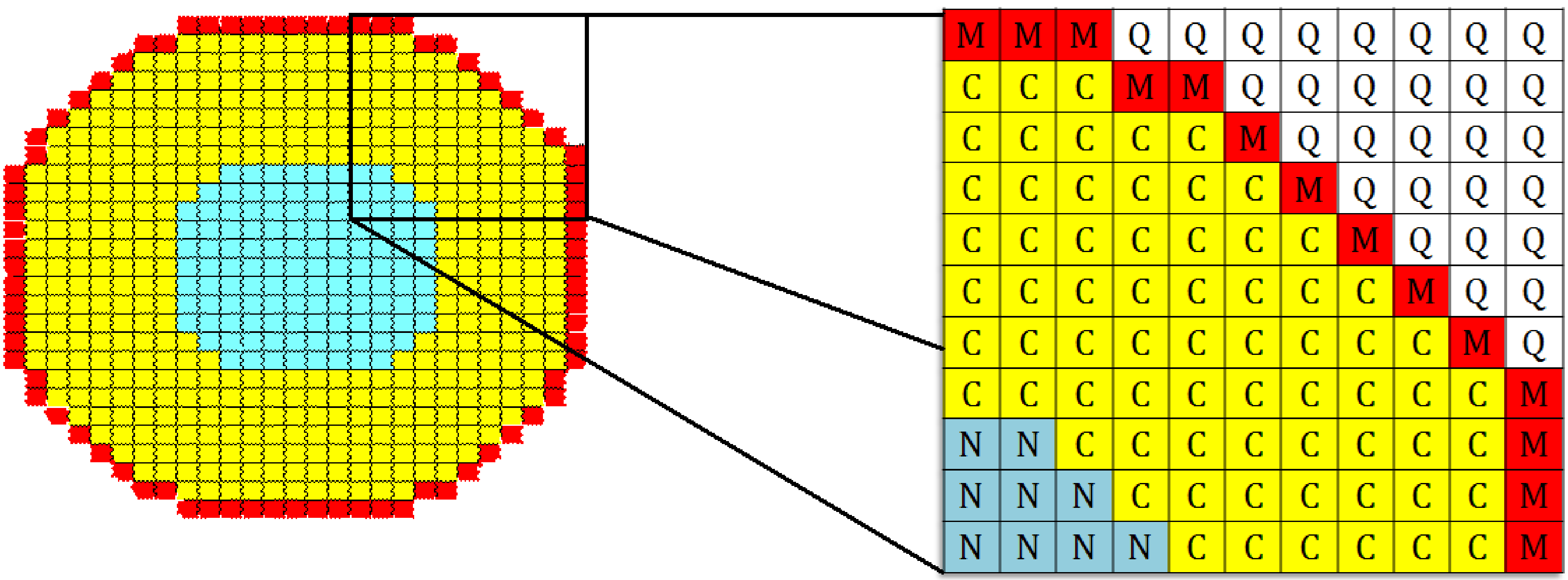
DI TORINO

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).

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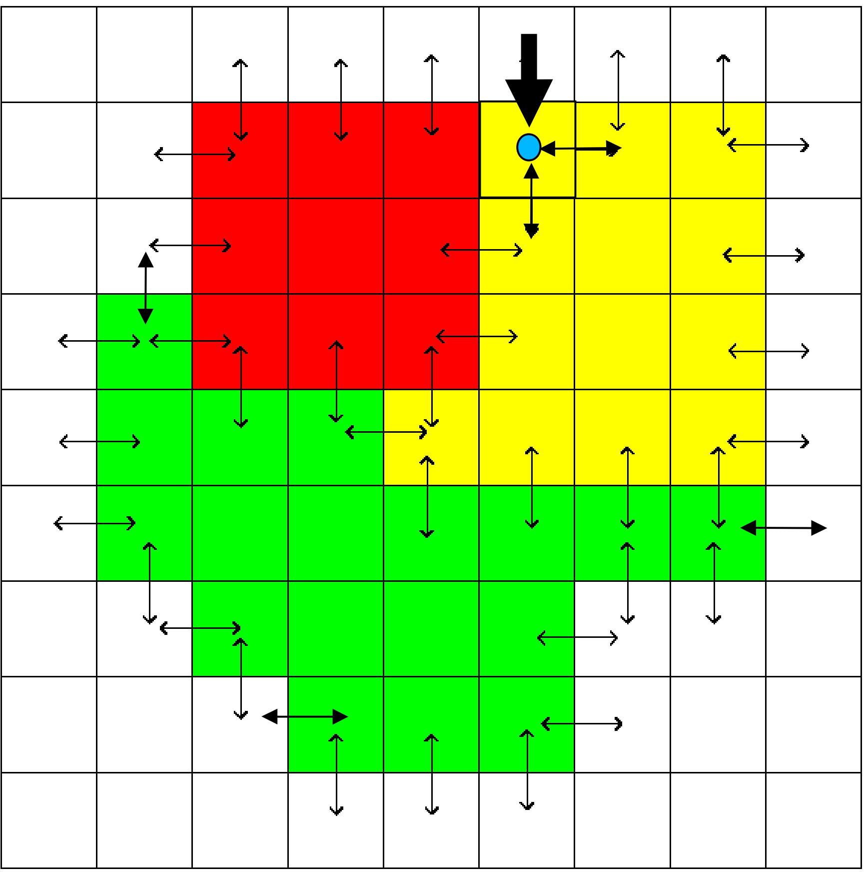
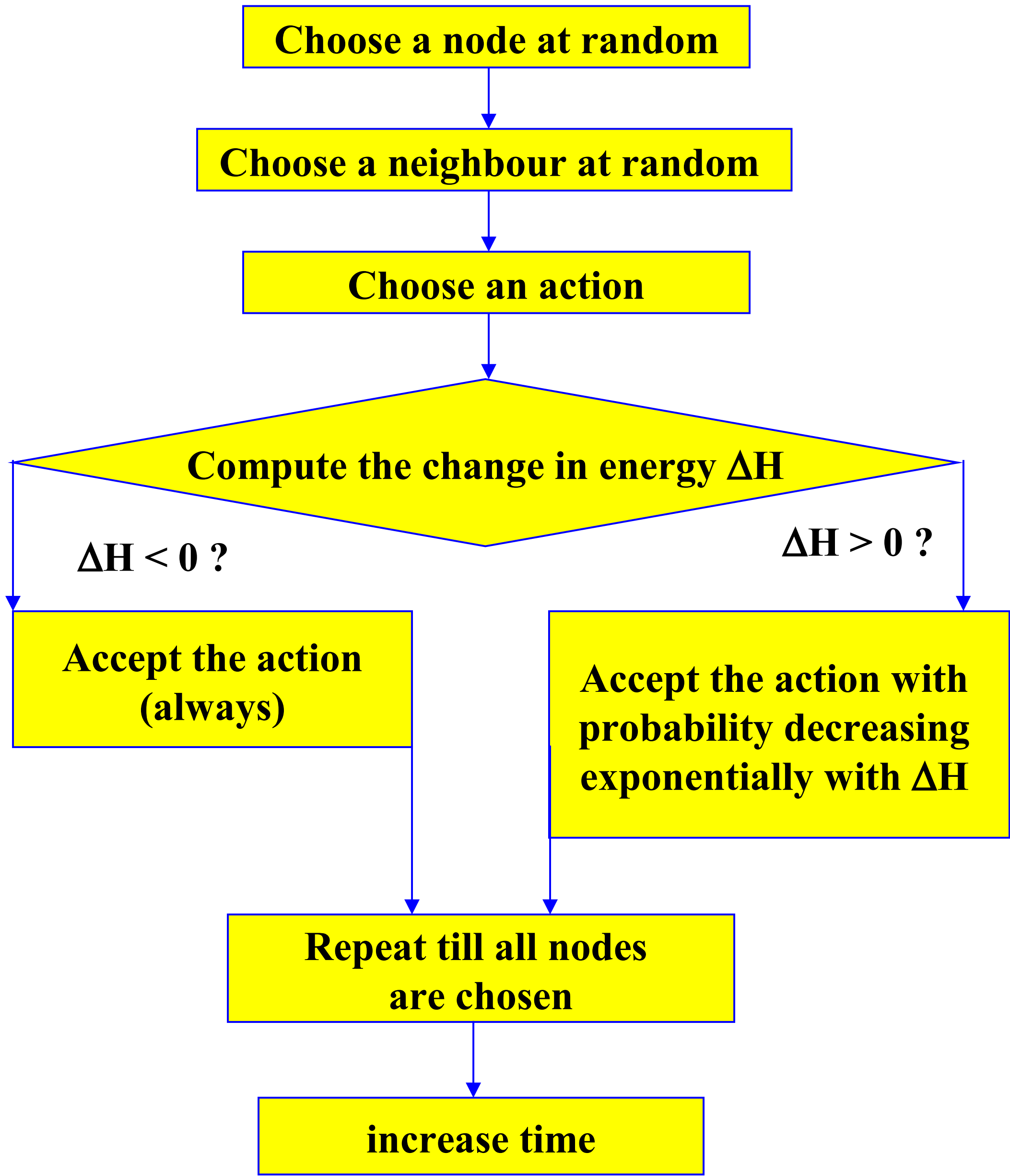
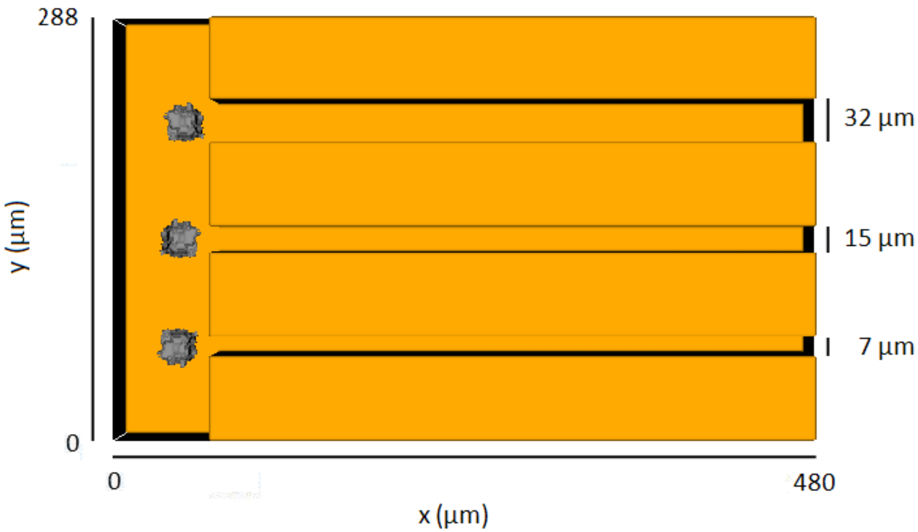
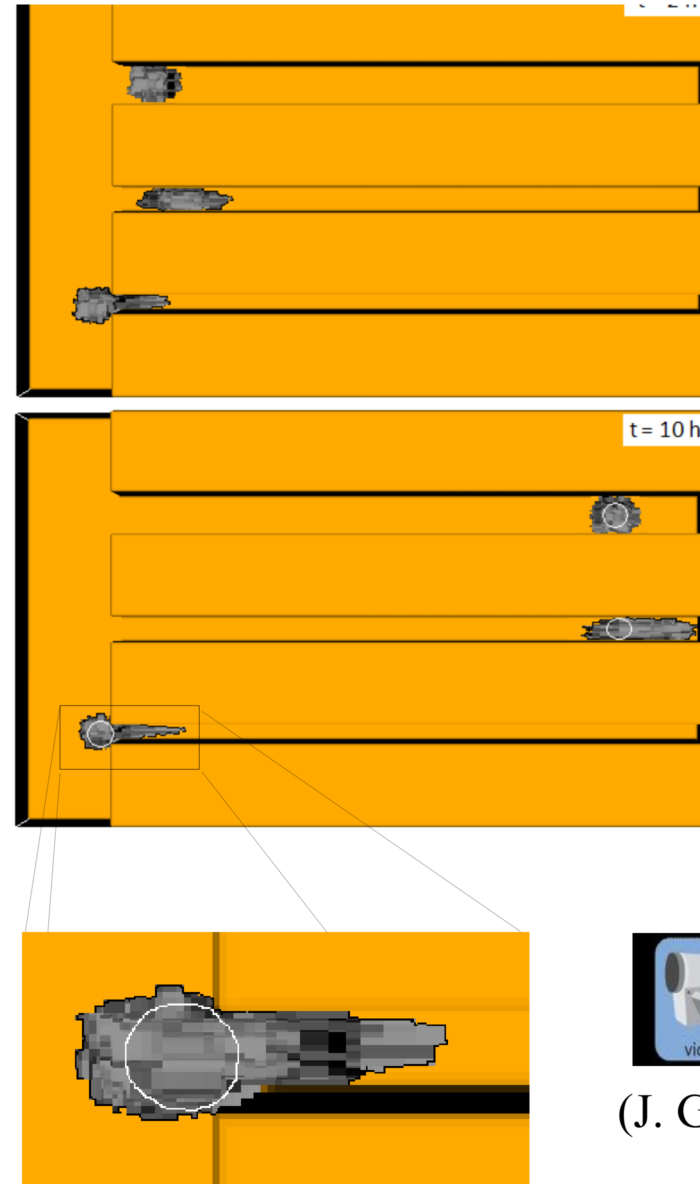
The cellular Potts model





Cells with stiff nuclei in microchannel



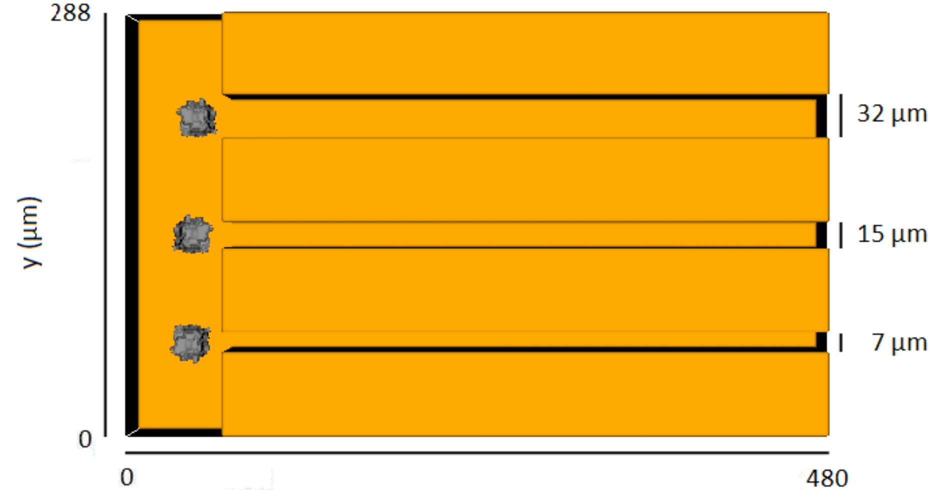


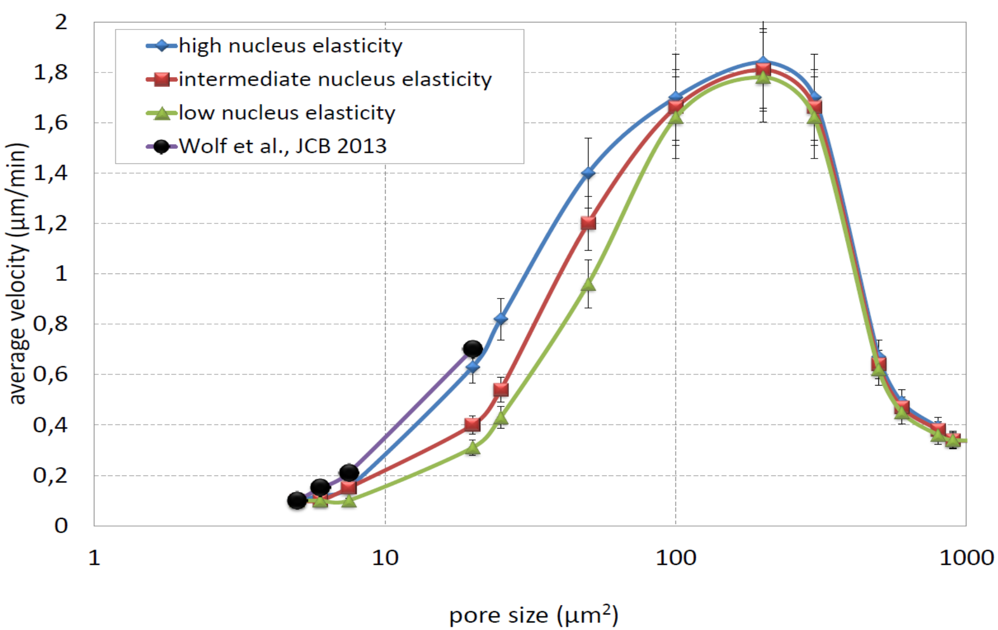
(J. Guch)

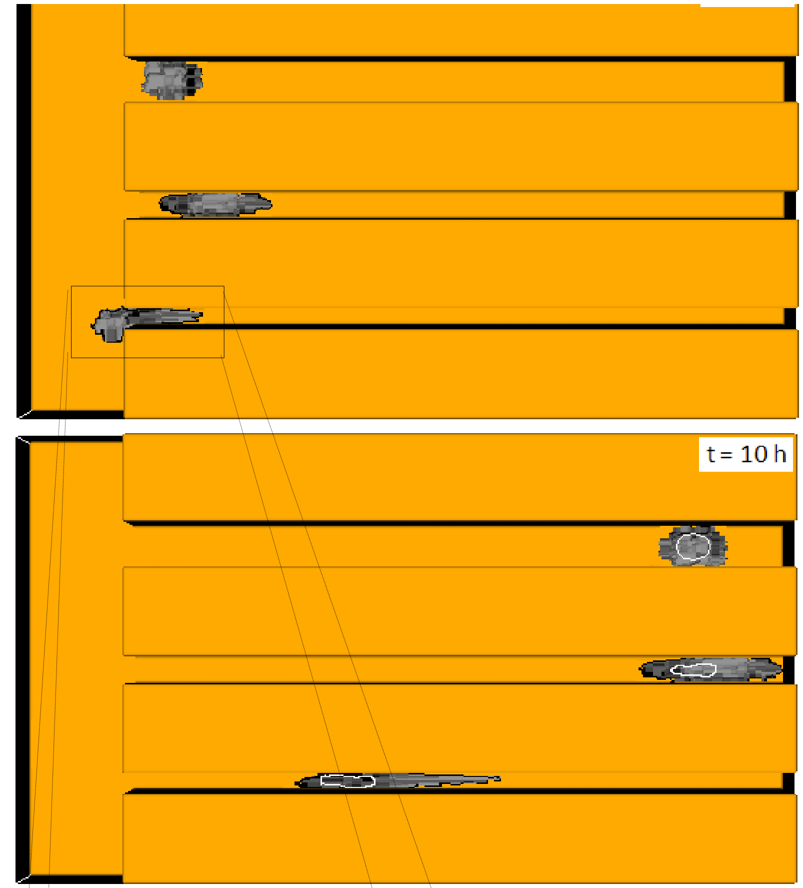
bottom channel size	< nucleus diameter <	middle channel size	< cell diameter <	top channel size

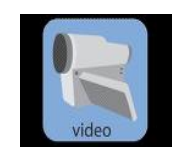
M. Scianna, L.P., *J. Theor. Biol.* **317**, 394-406 (2013)

Cells with deformable nuclei in microchannel







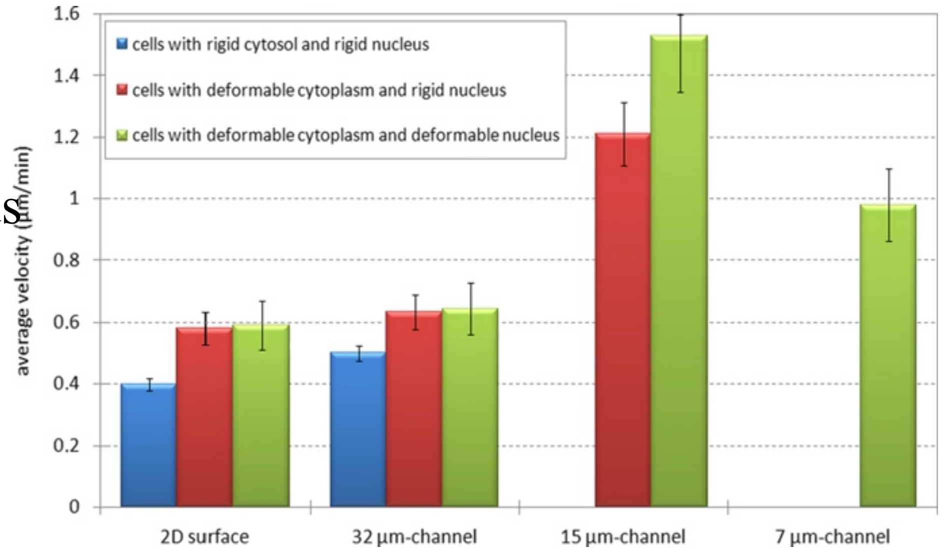


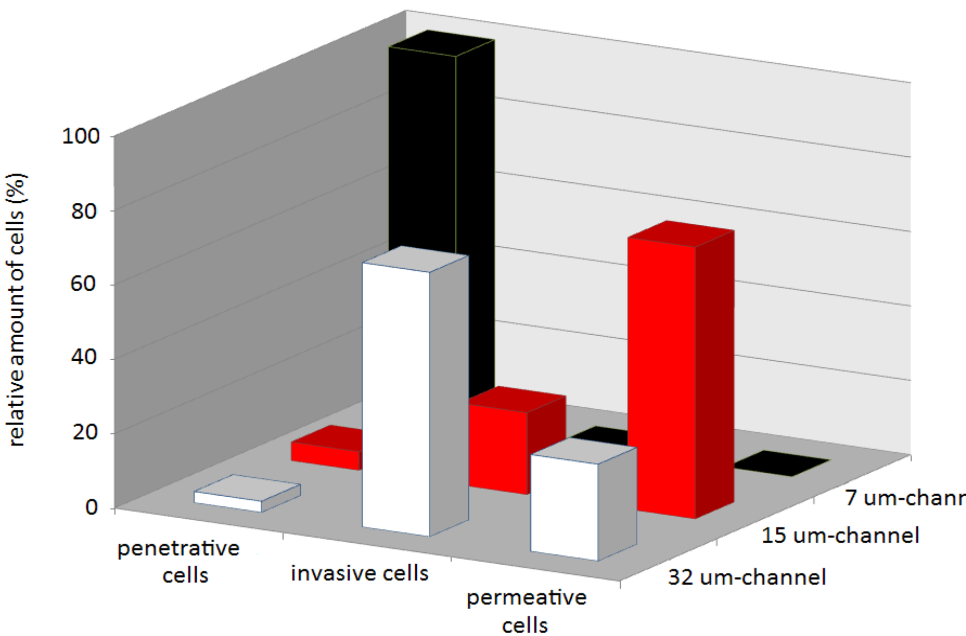
(J. Guch)

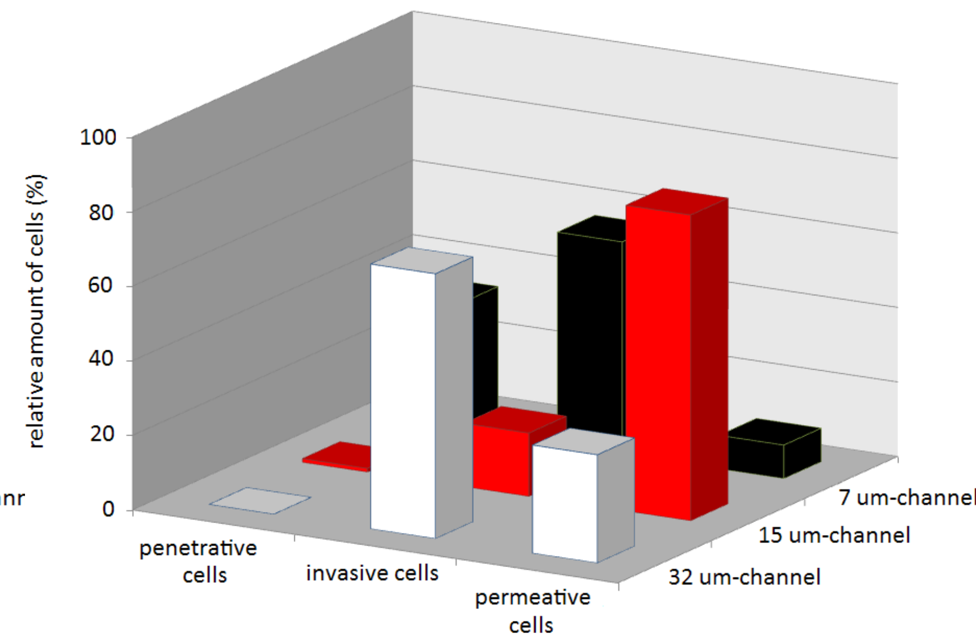
Influence of nucleus rigidity

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

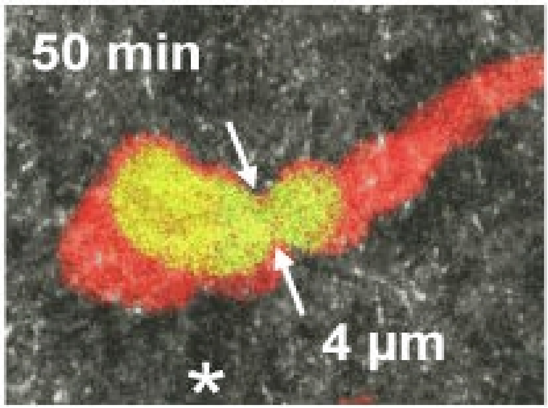
- Penetrative = Stay out with the nucleus (not with the cytoplasm)
- Invasive = Enter but do not reach the other side
- Permeative = Enter and reach the other side

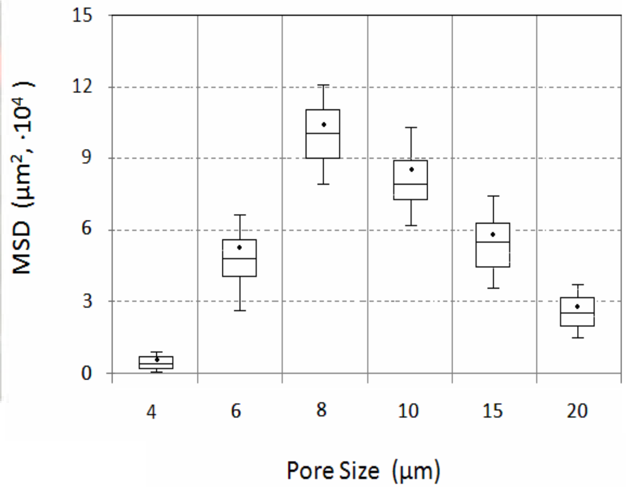


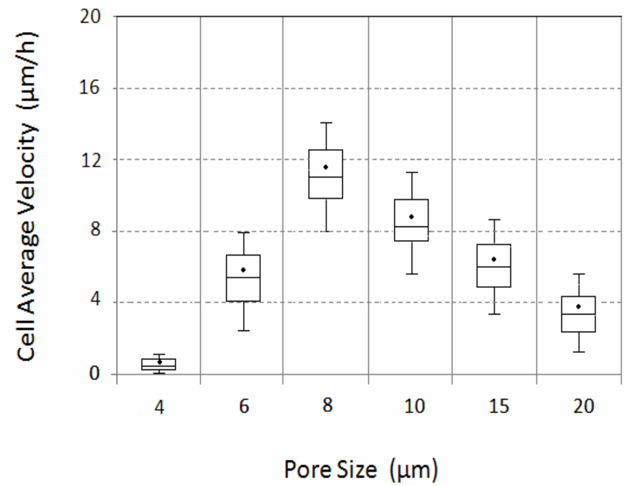


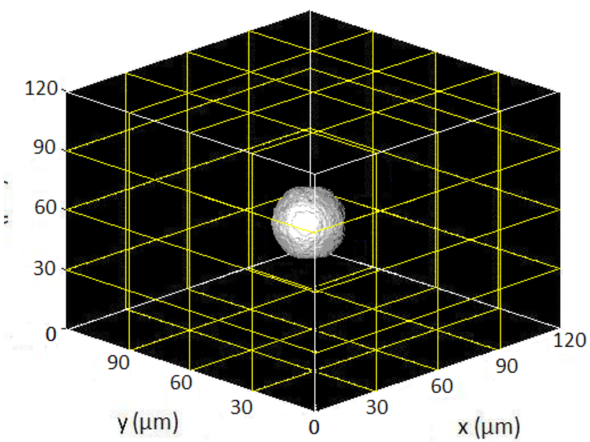


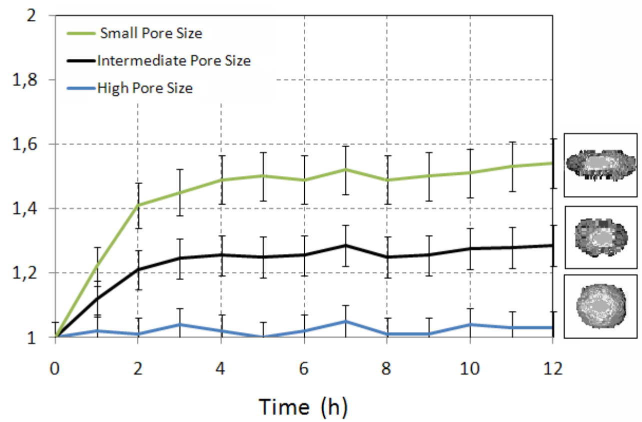
Effect of pore size in ECM

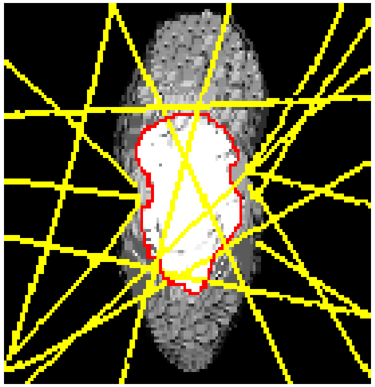










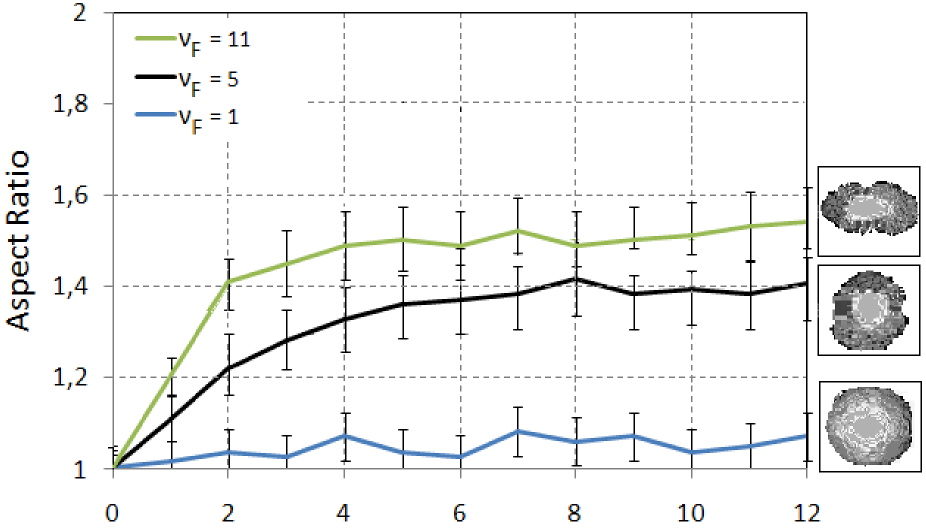


M. Scianna, L.P., & K. Wolf, *Biosci. Engng.* **10**, 235-261 (2013)

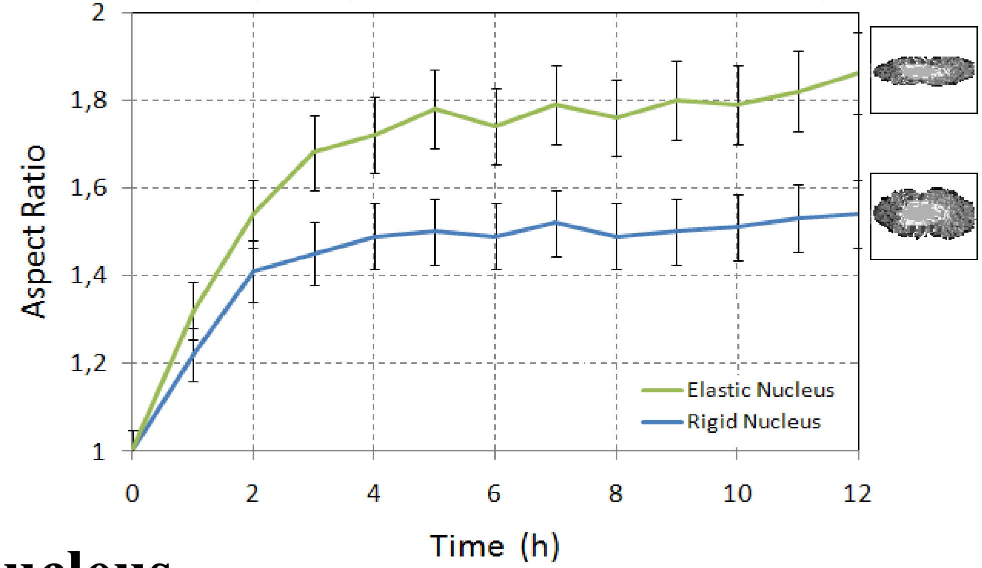
POLITECNICO DI TORINO

Effect of deformability

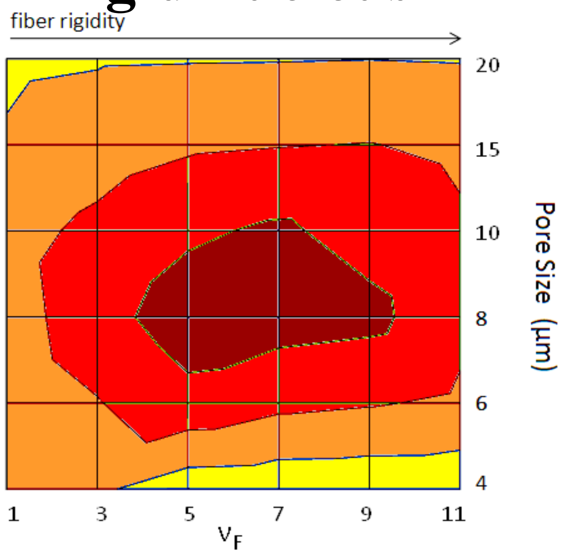
Varying fiber elasticity



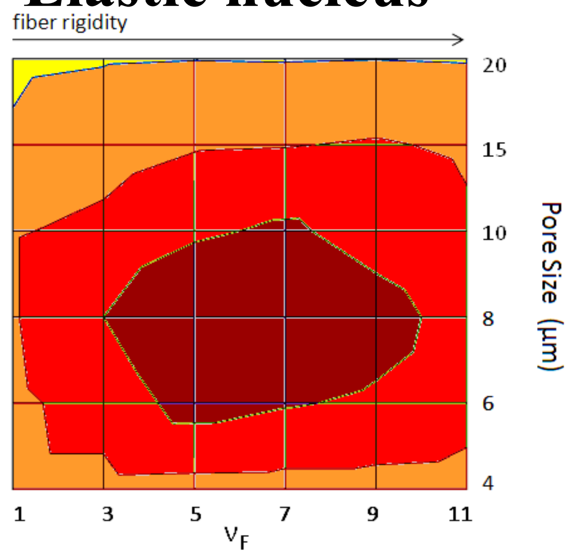
Varying nucleus elasticity



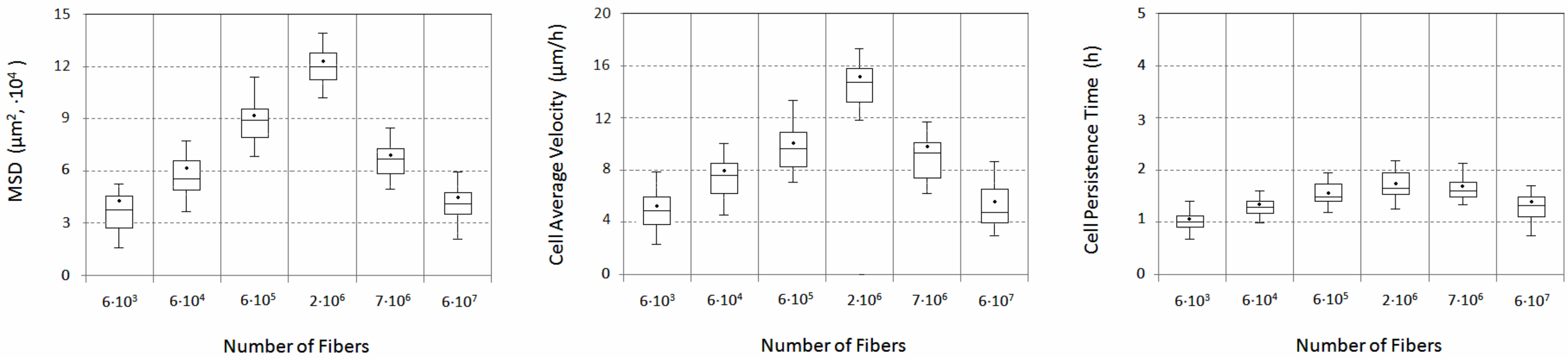
Rigid nucleus

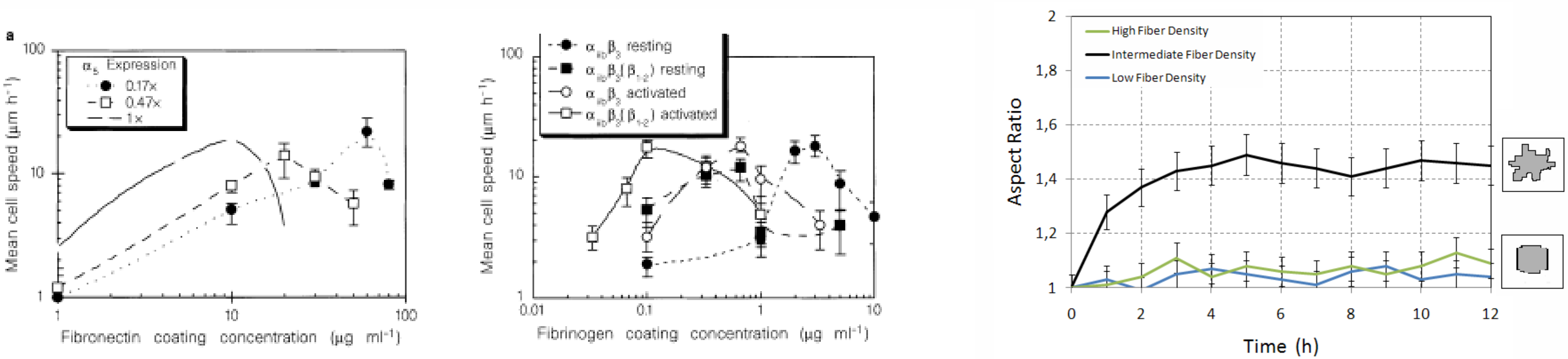


Elastic nucleus



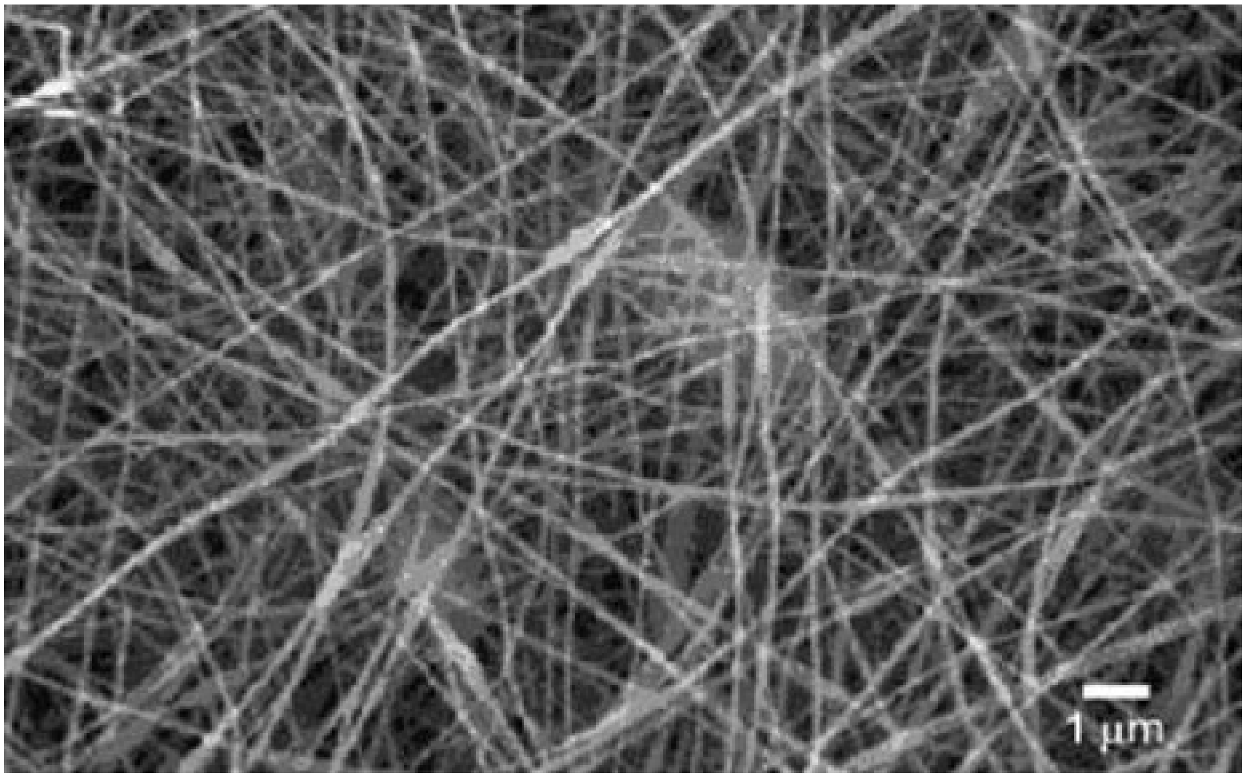
Effect of adhesion in 2D

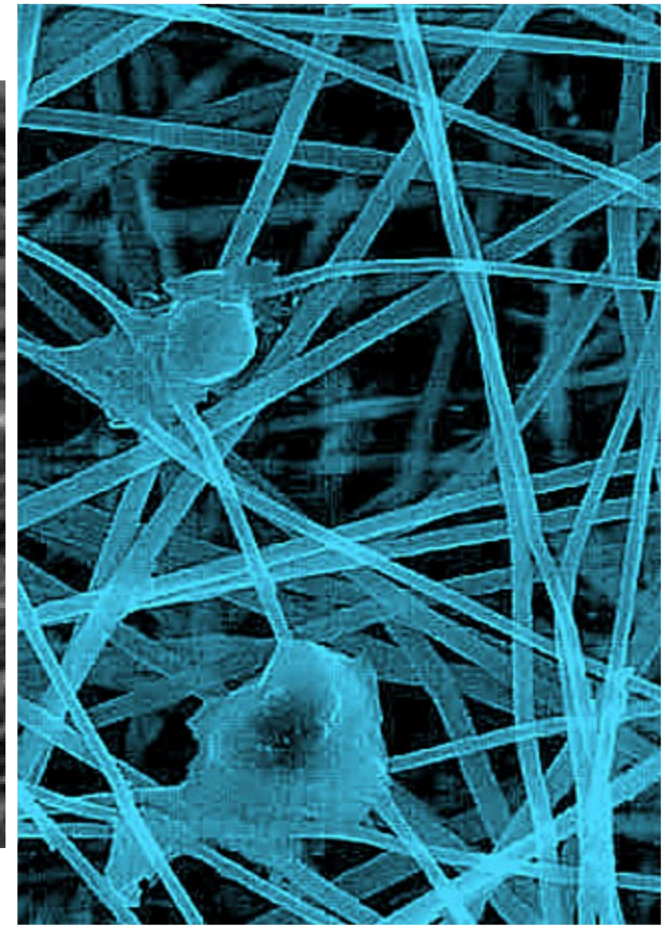




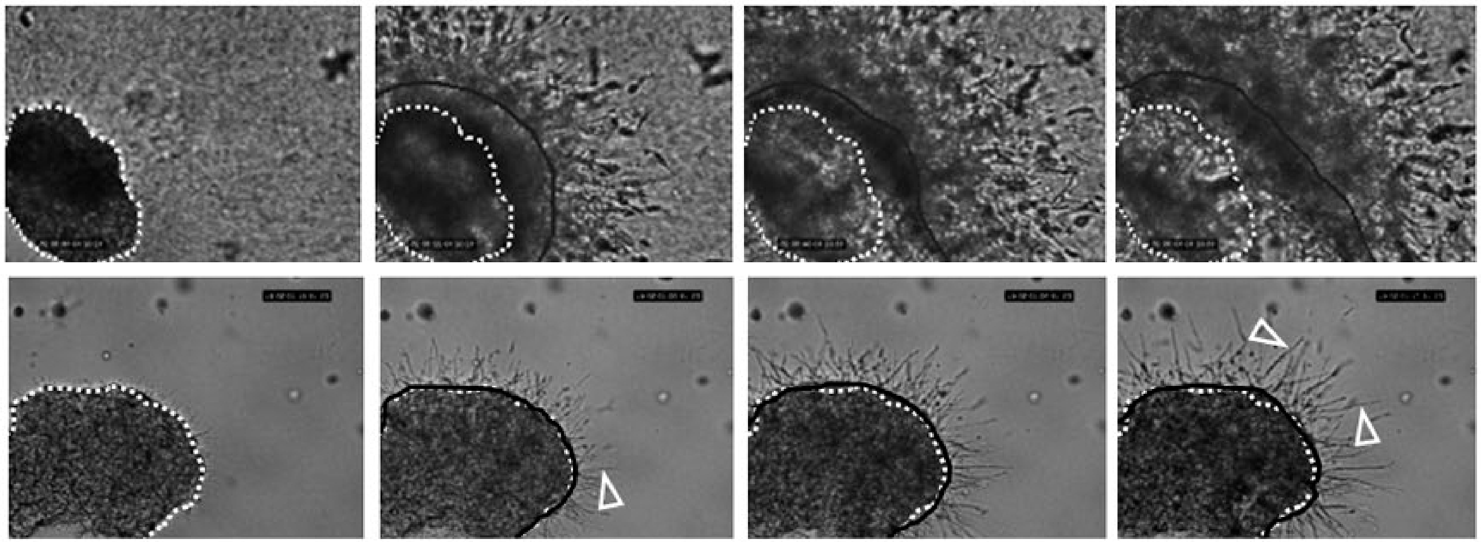
Palecek et al., *Nature* **385**, 537-540 (1997)

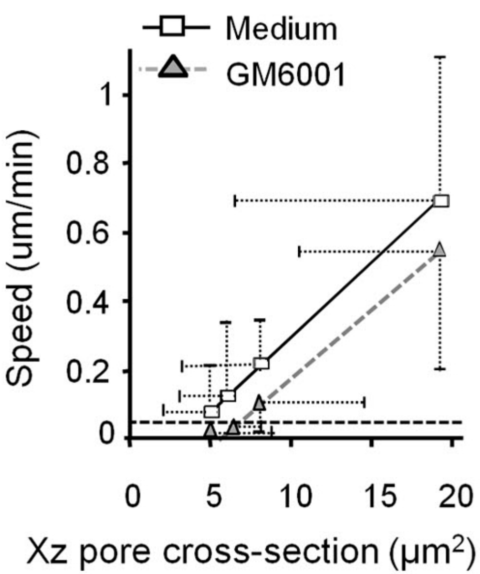
Optimising motion in artificial ECM

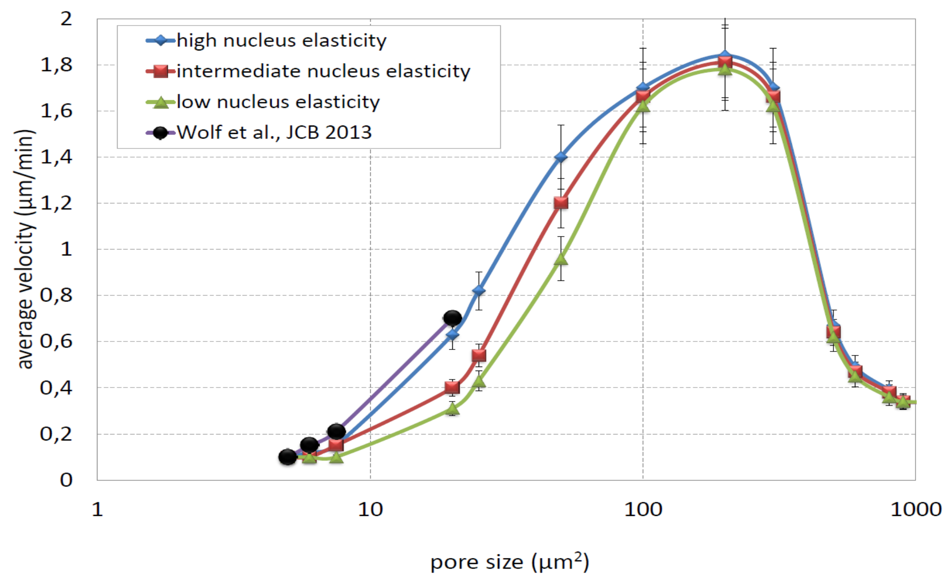




Cell invasion in dense ECM







POLITECNICO DI TORINO

Criterium for invasion

Work done by traction > Energy required to squeeze the nucleus

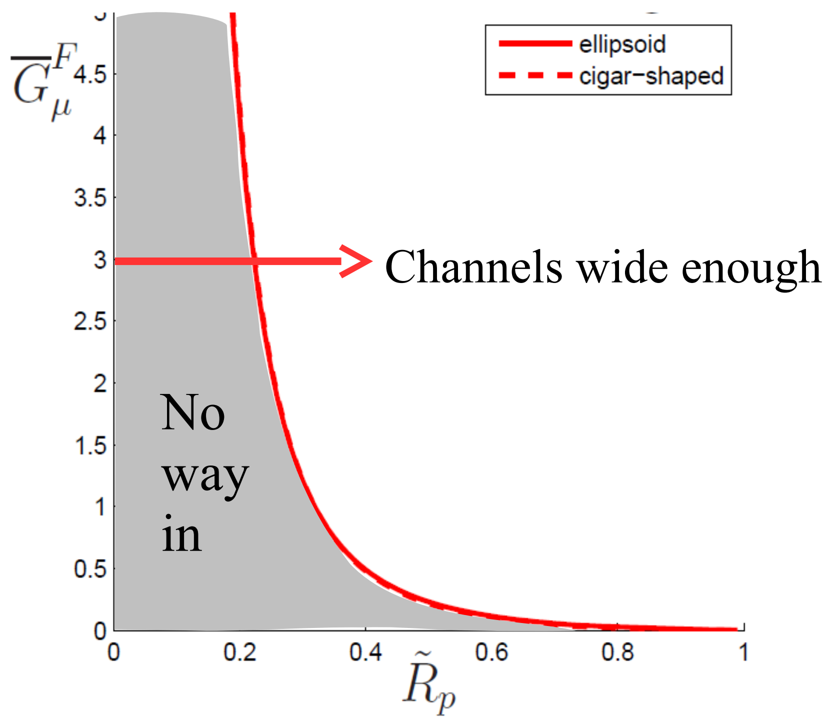
Elastic nucleus	Ellipsoid	$G^F_\mu \geq \frac{2}{3}\frac{2\tilde{R}_p^2 + \frac{1}{\tilde{R}_p^4} - 3}{\tilde{R}_p \tilde{L}_b^{(*)} \Delta\tilde{L}_{ellips}}$
	Cigar	$G^F_\mu \geq \frac{2}{3}\frac{\mathcal{I}(\tilde{R}_p)}{\tilde{R}_p \tilde{L}_b^{(*)} \Delta\tilde{L}_{cigar}}$

Traction

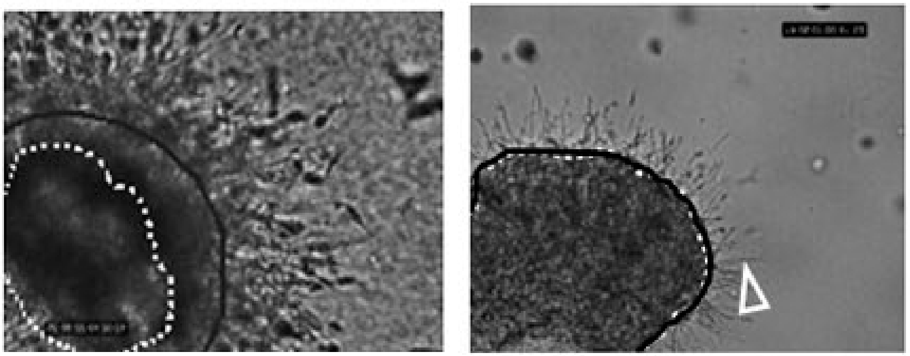
$$G^F_\mu = \frac{\rho_b \alpha_{ECM} F_b^M}{\mu}$$

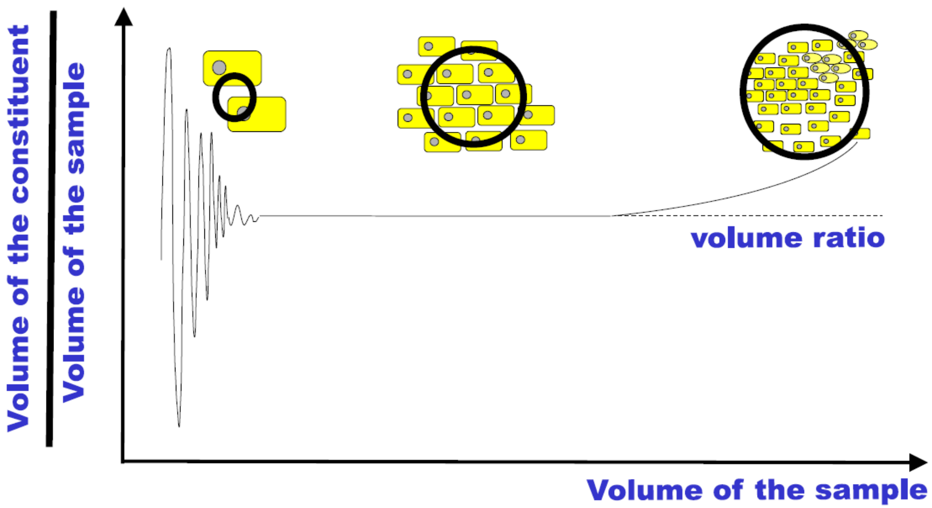
Nucleus stiffness

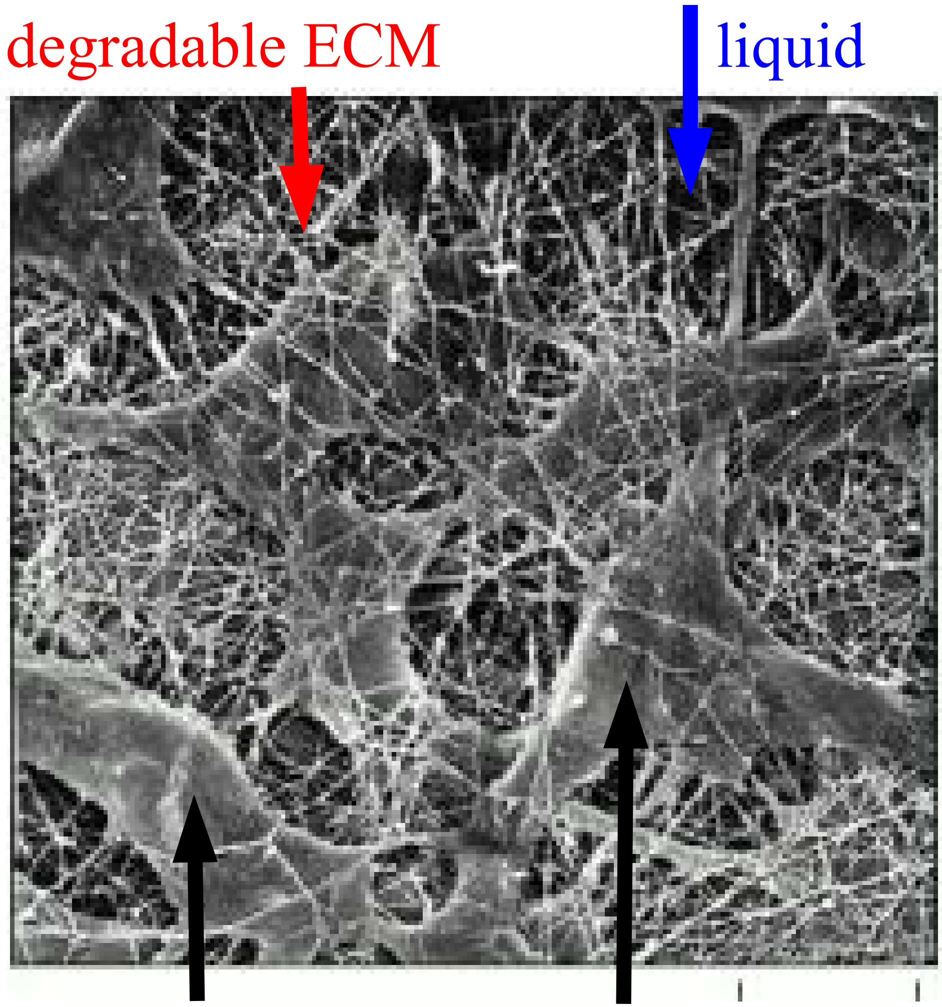
$$\tilde{R}_p = R_p / R_n$$



Upscaling the information

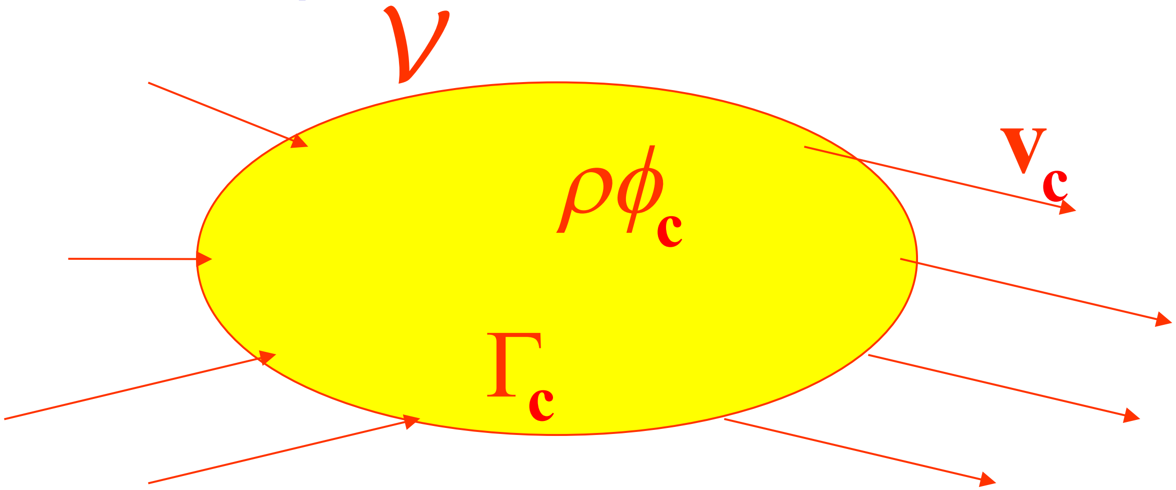






POLITECNICO DI TORINO

Mass balance equations



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

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

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

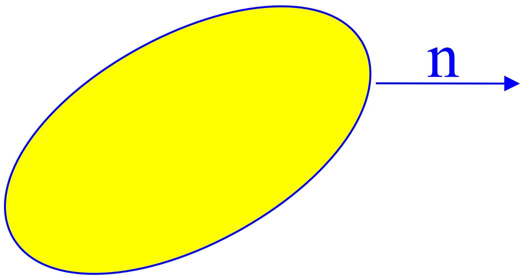
POLITECNICO DI TORINO

Only tumour cells in 3D

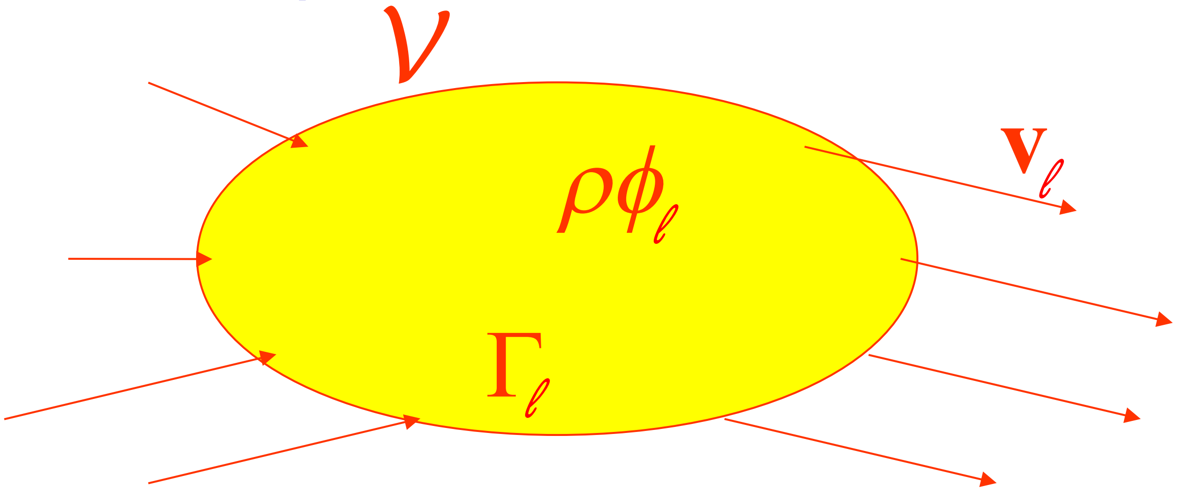
1. Constant density $\frac{\partial \bar{\varphi}}{\partial t} + \nabla \cdot (\bar{\varphi} \mathbf{v}) = \Gamma \quad \Rightarrow \quad \nabla \cdot \mathbf{v} = \frac{\Gamma}{\bar{\varphi}}$

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

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



Tumours as multiphase systems



Extracellular liquid

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

ECM components

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

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

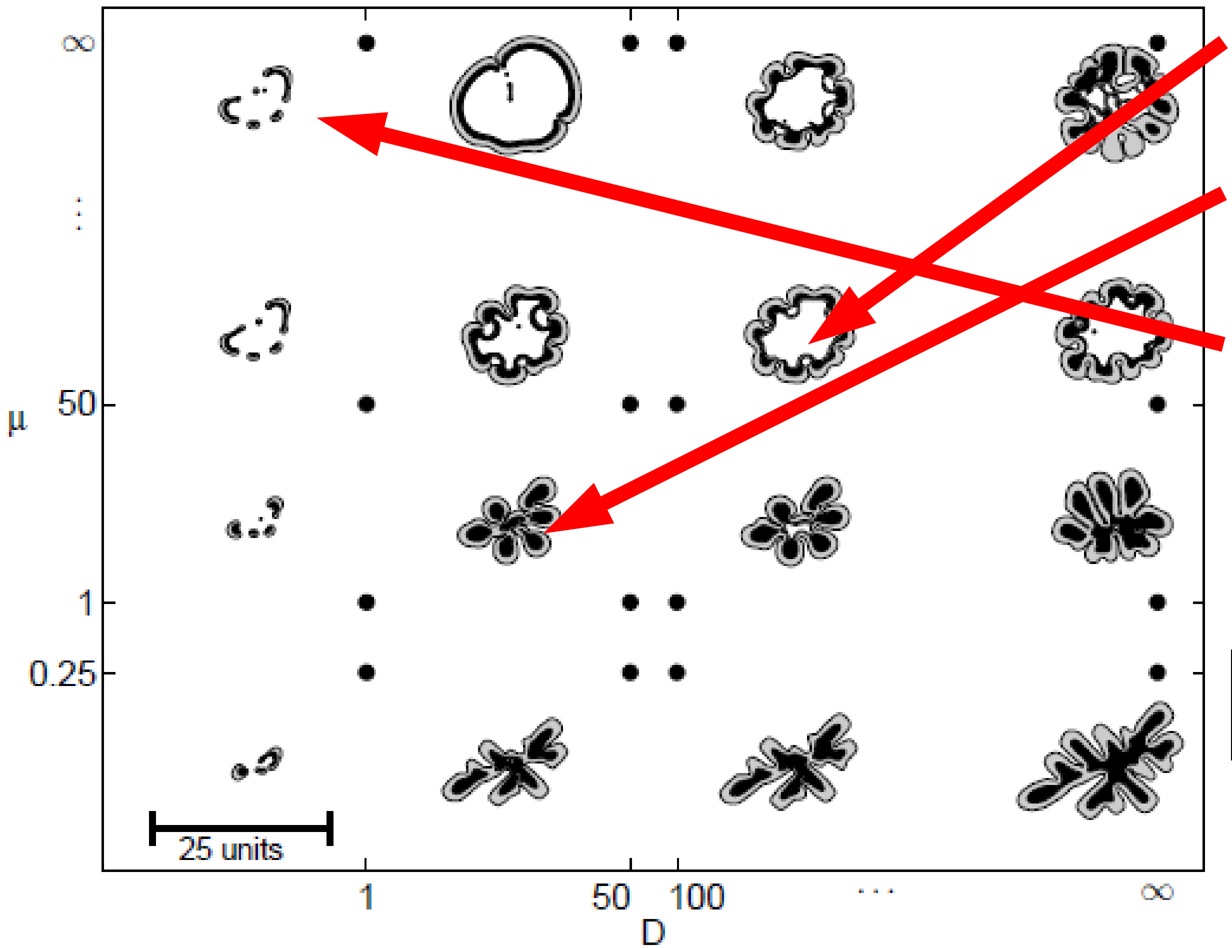
$$\nabla \cdot \mathbf{v} = \sum_{\alpha=c,m,\ell,v} \Gamma_\alpha = \mathbf{0}$$

Potential flow assumption

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

Only tumour cells in 3D

Macklin & Lowengrub JTB (2008)



Cell motility

Nutrient diffusion

Compact

Fingering

Fragmenting

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

Momentum balance equations

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

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

↓

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

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

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

Momentum balance equations

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

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

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

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

Darcy's law

Interstitial (fluid) pressure

Permeability tensor

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

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

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

Darcy's law

POLITECNICO DI TORINO

Brinkman equation

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

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

Brinkman equation

Unsaturated cells in ECM

Cellular (solid) stress

$$-\Sigma_c(\phi_c)\mathbf{I}$$

Chemotaxis

$$\chi \nabla C$$

Motility tensor

$$-\mathbf{K}^{-1}\mathbf{v}_c$$

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

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

Unsaturated cells in ECM

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

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

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

Degenerate parabolic equation

Generalized Keller-Segel equation

Saturated biphasic mixture

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

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

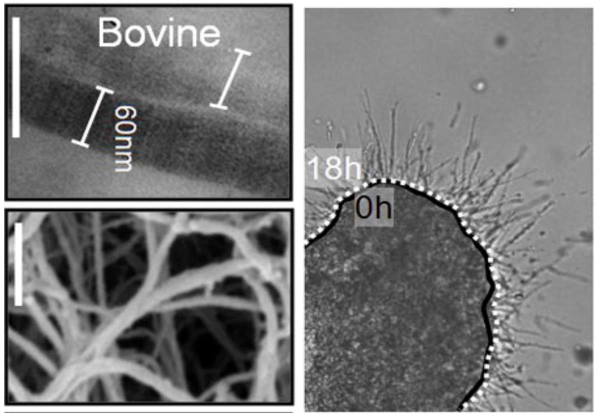
$$\nabla \cdot \mathbf{T} - \mathbf{M}\mathbf{v} = \mathbf{0}$$

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

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

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

Back to the continuous model



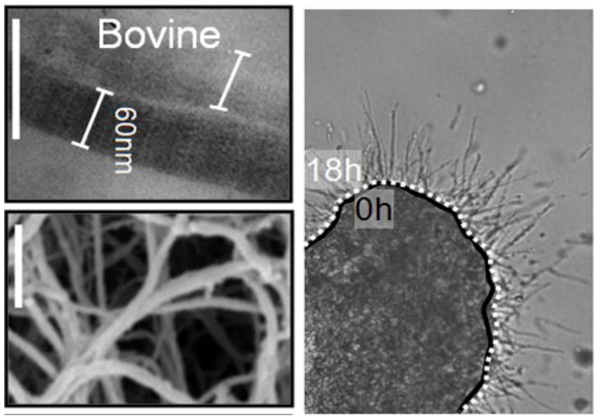
$$\frac{\partial \phi_c}{\partial t} + \nabla \cdot (\phi_c \mathbf{v}_c) = \Gamma_c \,,$$

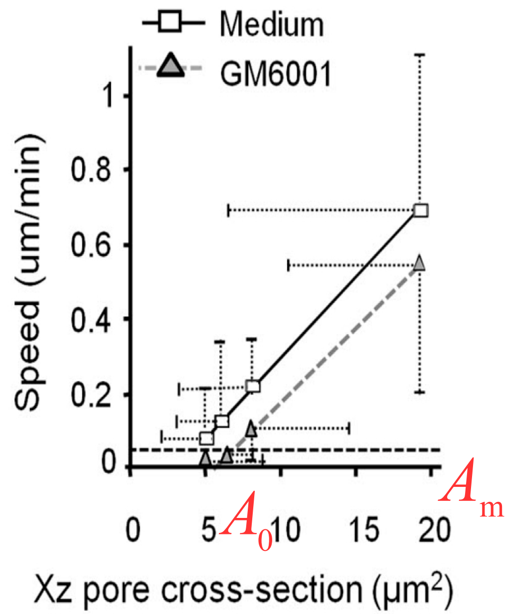
$$\nabla \cdot \mathbf{T}_c + \mathbf{m}_{cm} = \mathbf{0}$$

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

Motility tensor

Back to the continuous model





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

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

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

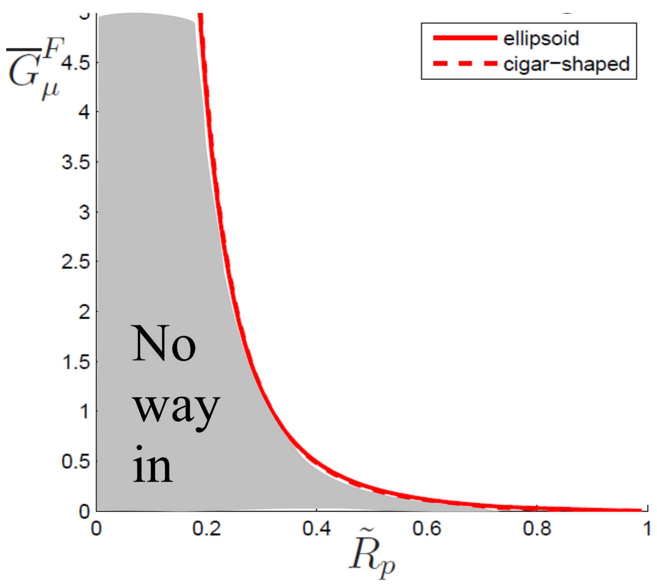
$$\mathbf{v}_c = \alpha \frac{[A_m(\phi_m) - A_0]_+}{\left(1 + \frac{A_m(\phi_m) - A_0}{A_1}\right)^n} \nabla \cdot \mathbf{T}_c$$

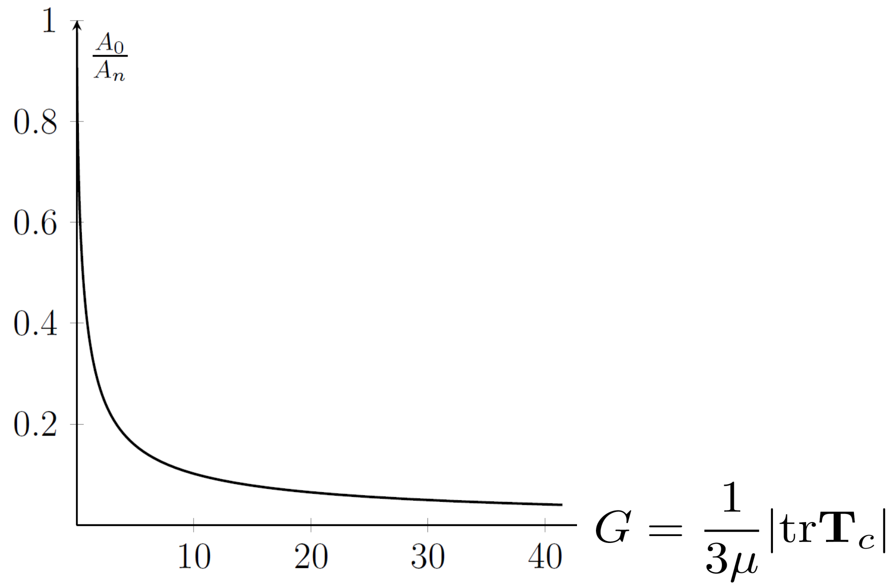
A_0 depends on:

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

Back to the continuous model

$$G^F_\mu = \frac{\rho_b \alpha_{ECM} F^M_b}{\mu}$$





POLITECNICO DI TORINO

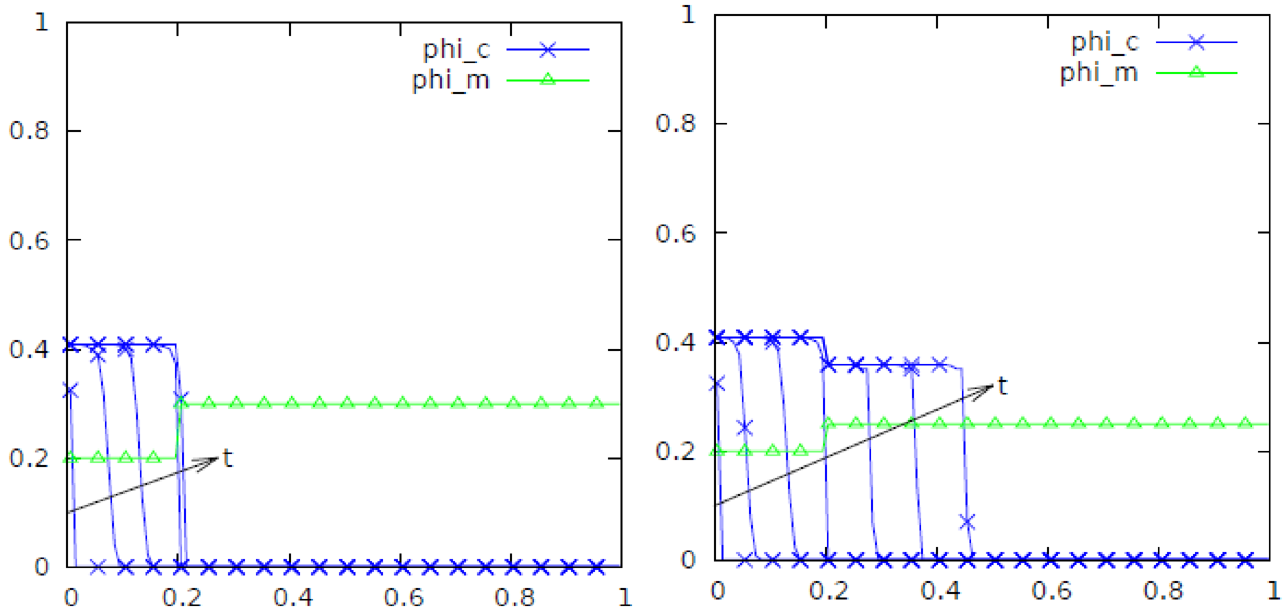
One population

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

$$[\gamma_c H_\epsilon(\bar{\phi} - \phi_c) - \delta]\phi_c$$

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

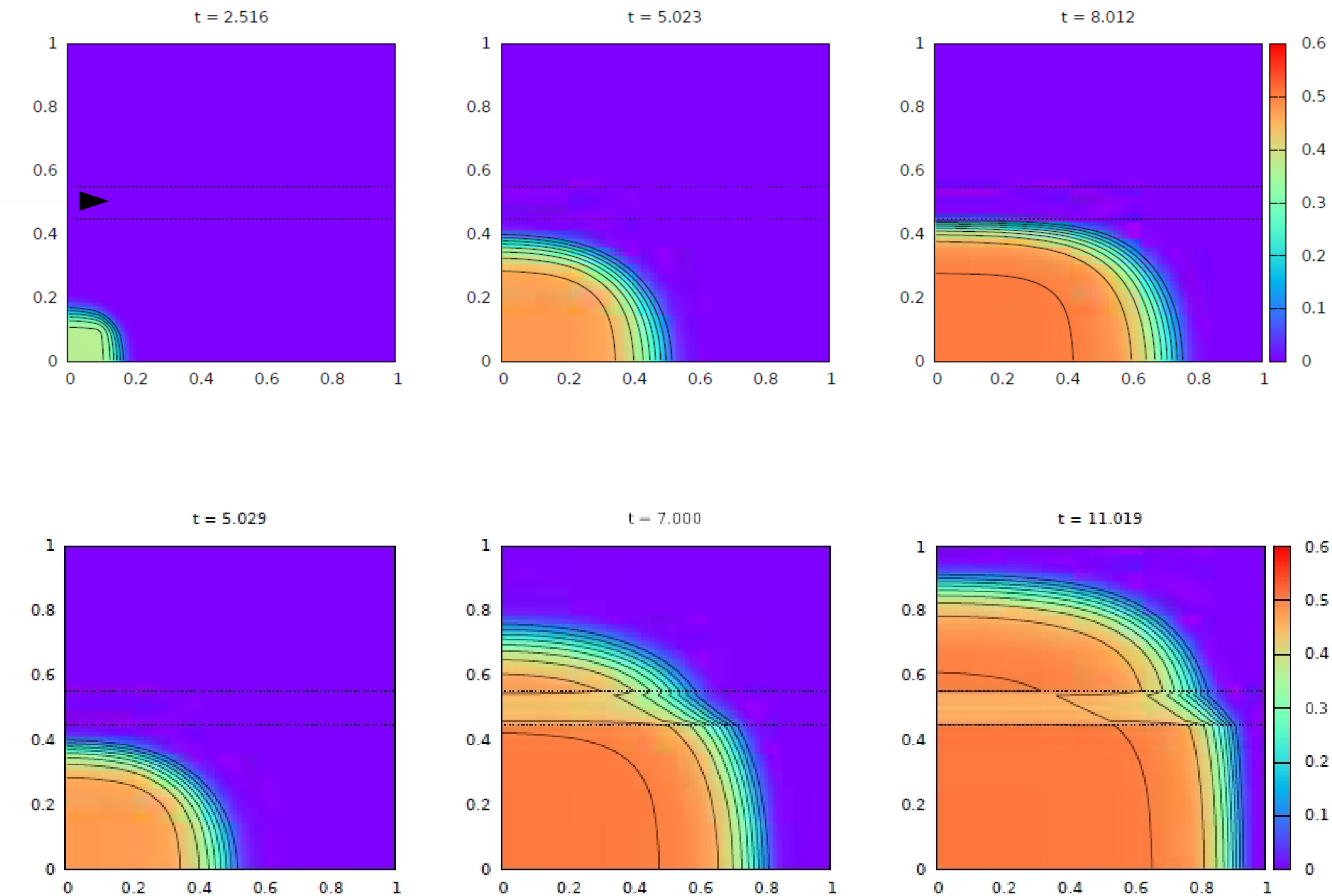
$$-\Sigma_c(\phi_c)\mathbf{I}$$



Growth below a thick region of ECM

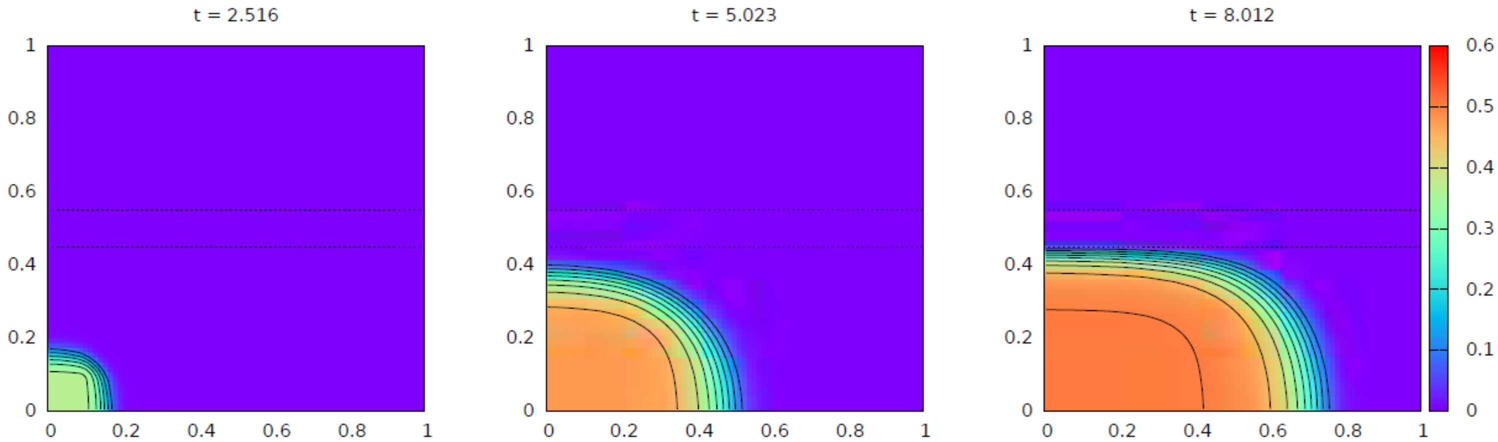
$$\phi_m^+ = 0.3$$

$$\phi_m^+ = 0.25$$

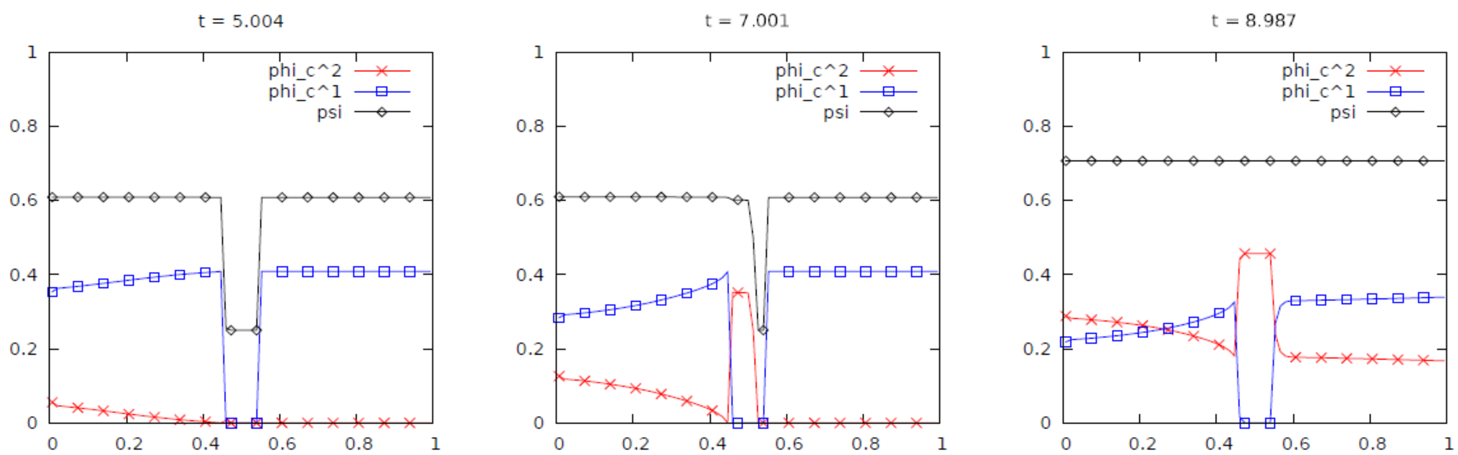


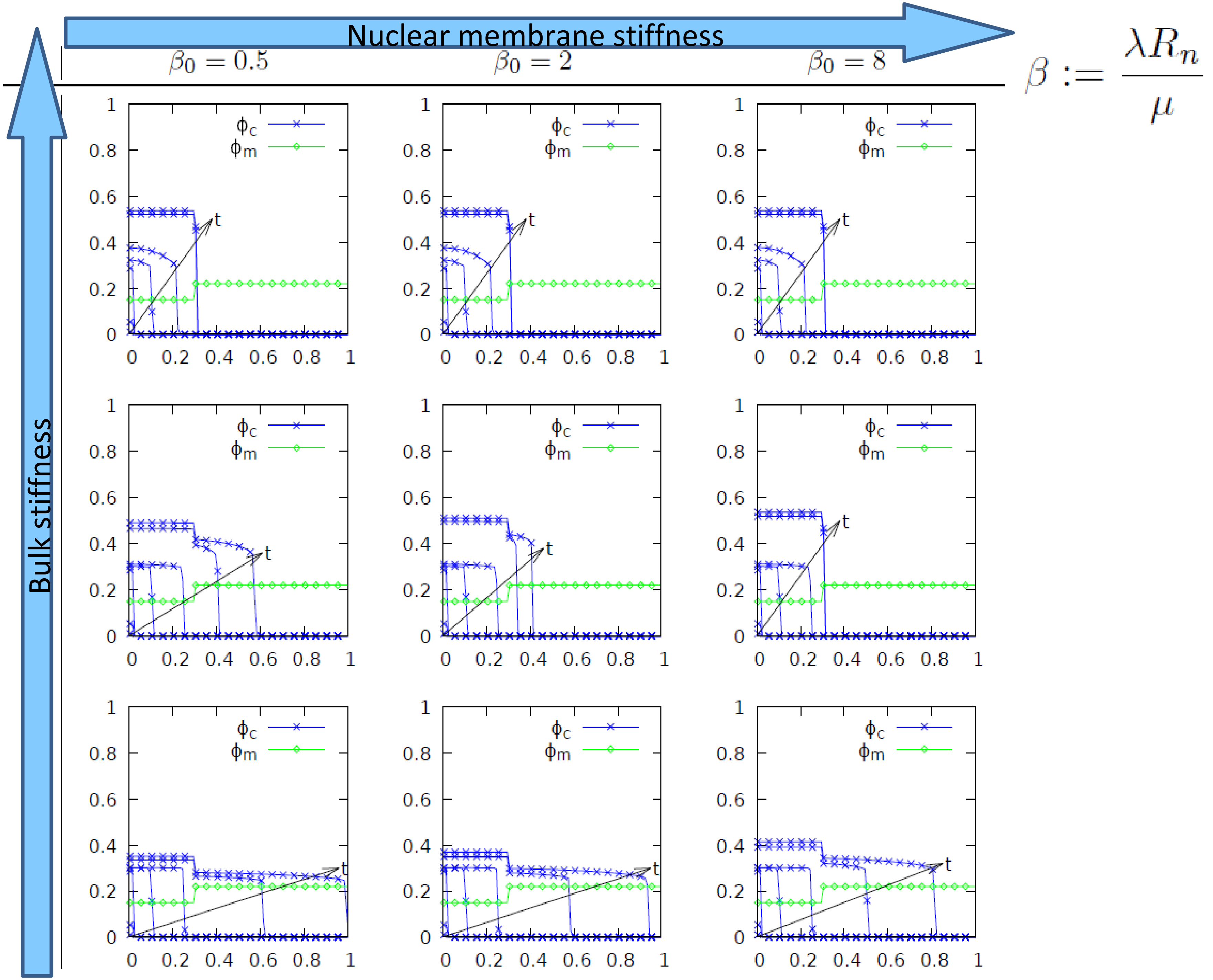
Effect of nucleus deformability

Stiffer nucleus



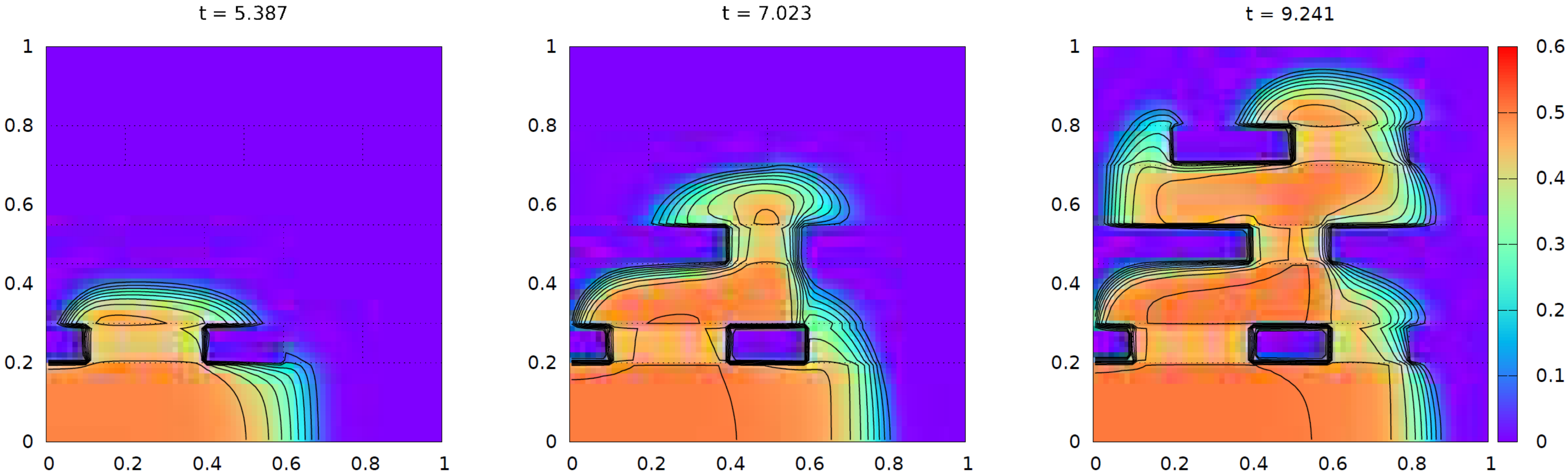
Softer nucleus



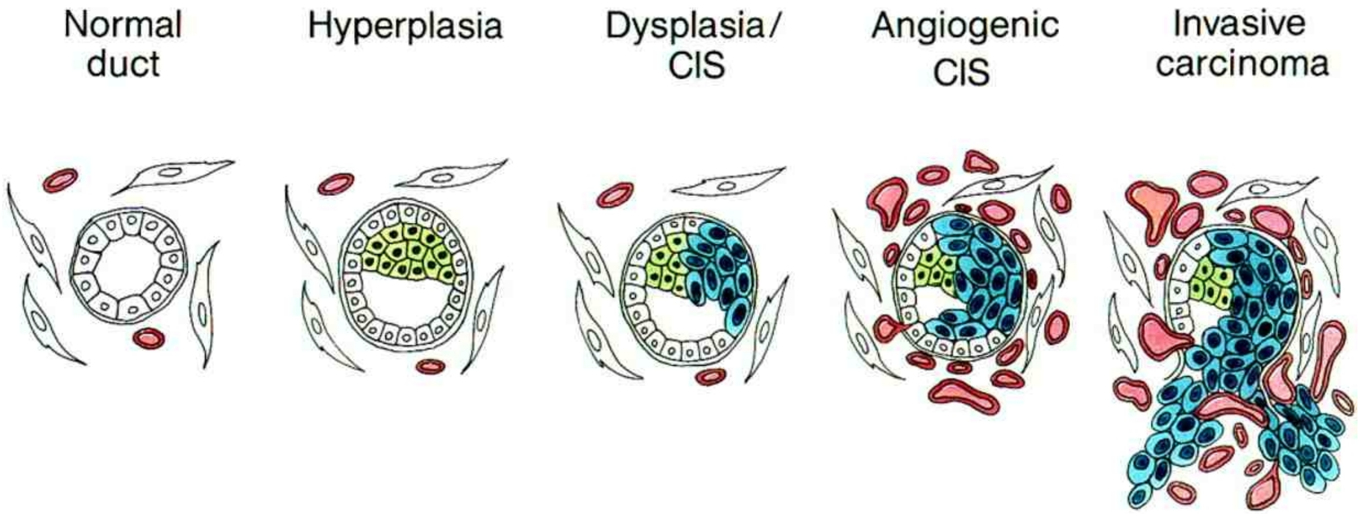


Nuclear membrane stiffness
Bulk stiffness
$\beta_0 = 0.5$
$\beta_0 = 2$
$\beta_0 = 8$
$\beta := \frac{\lambda R_n}{\mu}$
ϕ_c
ϕ_m
t

Heterogeneus ECM



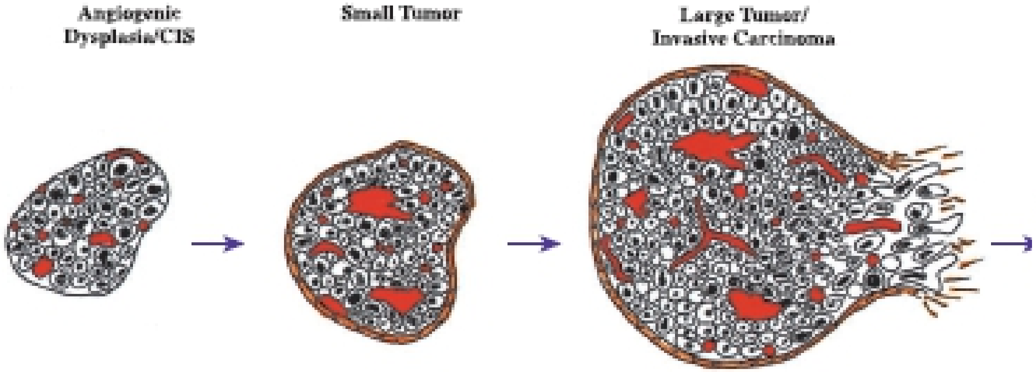
Tumour compartimentalization and invasion

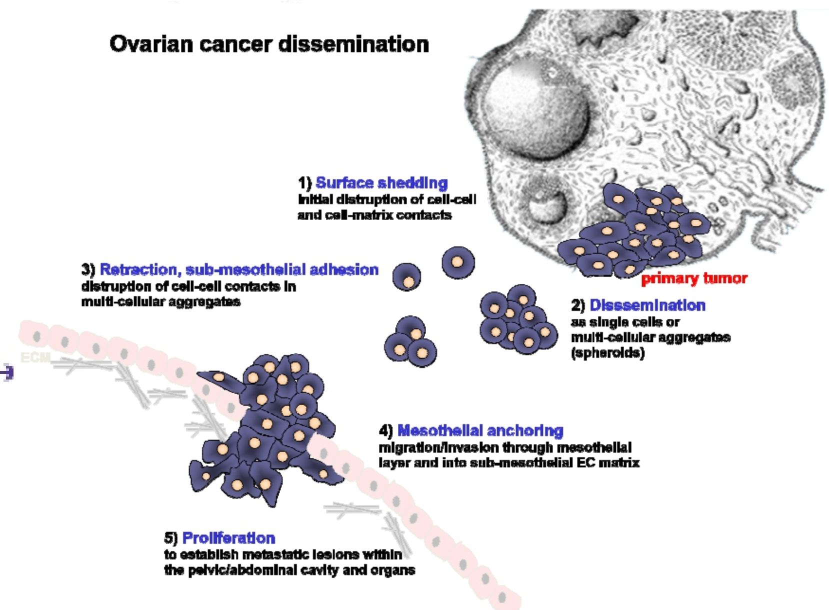


Breast

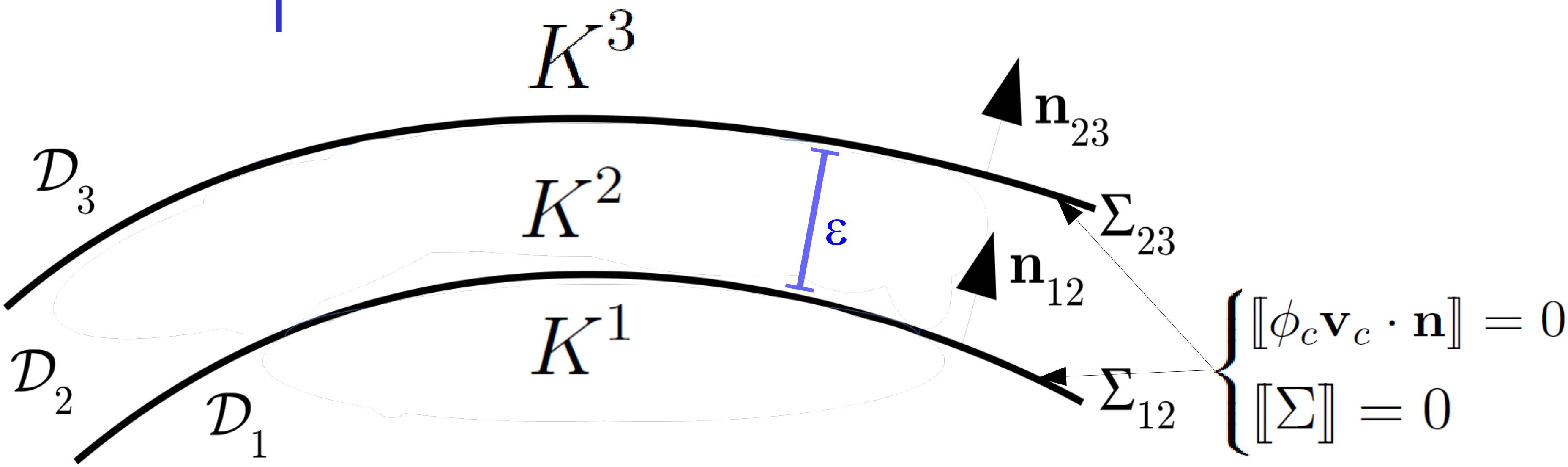
Ovary

Pancreas





Membrane problem

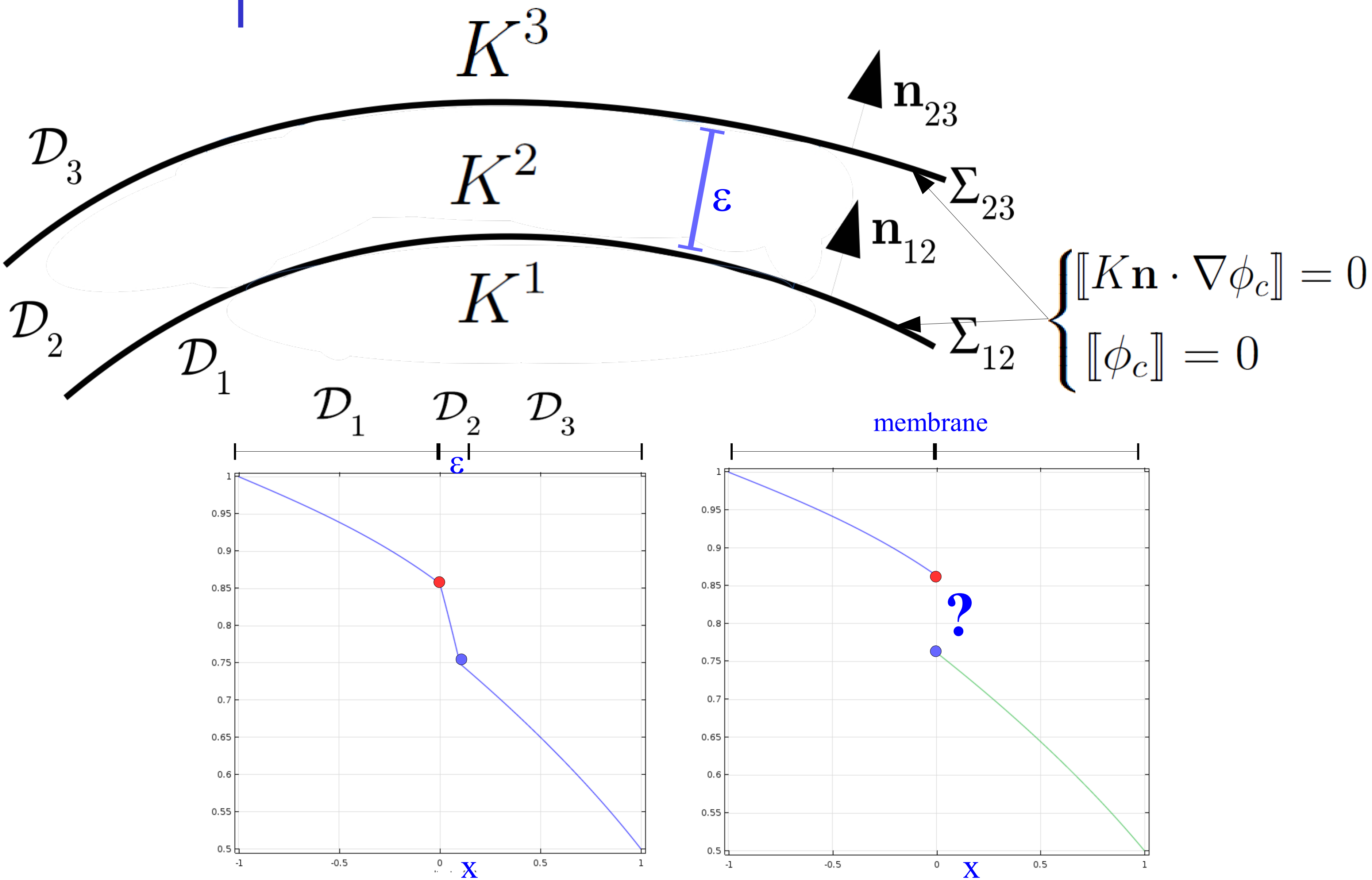


$$\frac{\partial \phi_c^i}{\partial t} + \nabla \cdot \left(\phi_c^i \mathbf{v}_c^i\right) = \Gamma_c^i$$

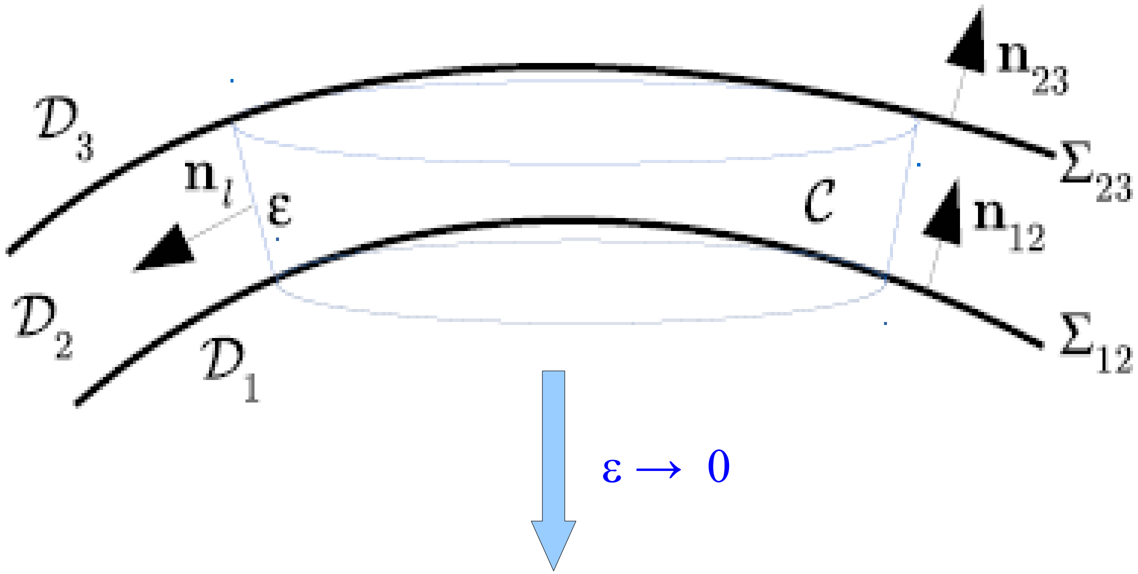
$$\mathbf{v}_c^i = -K^i \nabla \Sigma(\phi_c^i) = -K^i \Sigma'(\phi_c^i) \nabla \phi_c^i$$

$$\frac{\partial \phi_c^i}{\partial t} = \nabla \cdot \left[K^i \phi_c^i \nabla \Sigma(\phi_c^i)\right] + \Gamma_c^i$$

Membrane problem



Membrane problem



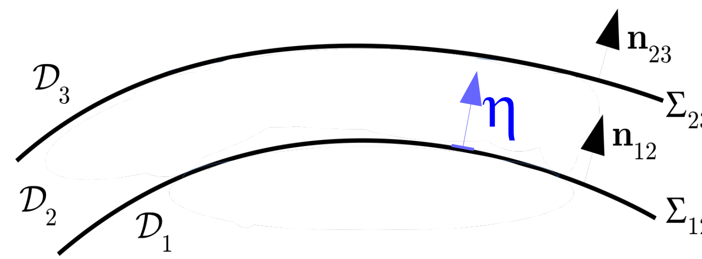
$$\tilde{K}_2[\![\Pi]\!] = K^1\phi_c^1\mathbf{n}\cdot\nabla\Sigma(\phi_c^1) = K^3\phi_c^3\mathbf{n}\cdot\nabla\Sigma(\phi_c^3)$$

where $\Pi'(\phi_c) = \phi_c\Sigma'(\phi_c)$

$$\tilde{K}_2 = \lim_{\varepsilon\to 0}\frac{K^2}{\varepsilon}$$

Membrane problem

$$\frac{\partial \phi_c^i}{\partial t} = \nabla \cdot \left[K^i \phi_c^i \nabla \Sigma(\phi_c^i) \right] + \Gamma_c^i$$



- Scale perpendicular coordinate (η) with ε

- Expand $\phi_c^2 \approx \phi_0^2 + \varepsilon \phi_1^2$

- Leading order $\frac{\partial}{\partial \eta} \left[\tilde{K}_2 \phi_0^2 \frac{\partial \Sigma(\phi_0^2)}{\partial \eta} \right] = 0$

$$\tilde{K}_2 \phi_0^2 \frac{\partial \Sigma(\phi_0^2)}{\partial \eta} = \text{const}$$

$[\![\phi_c \mathbf{v}_c \cdot \mathbf{n}]\!] = 0$

At the interfaces

$$K^1 \phi_0^1 \mathbf{n}_{12} \cdot \nabla \Sigma(\phi_0^1)$$

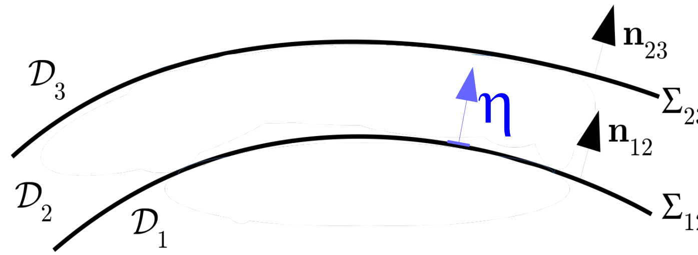
$$\|$$

$$K^3 \phi_0^3 \mathbf{n}_{23} \cdot \nabla \Sigma(\phi_0^3)$$

$$\tilde{K}_2 = \lim_{\varepsilon \to 0} \frac{K^2}{\varepsilon}$$

Membrane problem

$$\frac{\partial \phi_c^i}{\partial t} = \nabla \cdot \left[K^i \phi_c^i \nabla \Sigma(\phi_c^i) \right] + \Gamma_c^i$$



At the interface

$$K^1 \phi_0^1 \Sigma'(\phi_0^1) \phi_0^1 \mathbf{n} \cdot \nabla \phi_0^1$$

$$\parallel$$

$$K^3 \phi_0^3 \Sigma'(\phi_0^3) \phi_0^1 \mathbf{n} \cdot \nabla \phi_0^3$$

$$\int_0^1 \tilde{K}_2 \phi_0^2 \frac{\partial \Sigma(\phi_0^2)}{\partial \eta} = \text{const}$$

$$\parallel$$

$$\int_0^1 \tilde{K}_2 \frac{\partial \Pi}{\partial \eta} \, d\eta = \tilde{K}_2 [\![\Pi]\!]$$

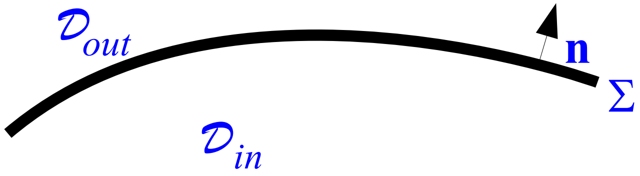
Defining

$$\Pi'(\phi_c) = \phi_c \Sigma'(\phi_c)$$

POLITECNICO DI TORINO

Membrane problem

$$
\begin{cases}
\dfrac{\partial \phi_c}{\partial t} = \nabla \cdot [K \Sigma'(\phi_c) \phi_c \nabla \phi_c] + \Gamma_c \\[2ex]
[\![K \phi_c \mathbf{n} \cdot \nabla \Sigma(\phi_c)]\!] = 0 \qquad \text{on } \Sigma, \\[2ex]
\tilde{K} [\![\Pi]\!] = K \phi_c \mathbf{n} \cdot \nabla \Sigma(\phi_c) \qquad \text{on } \Sigma,
\end{cases}
$$



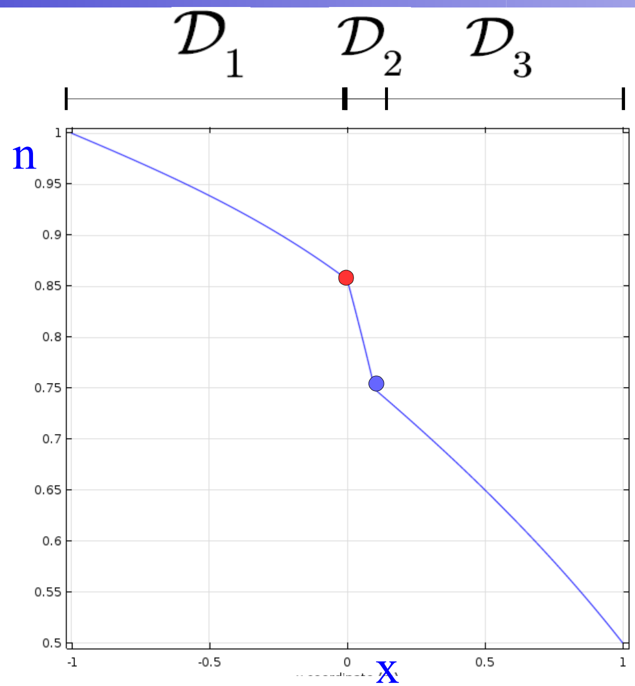
where $\Pi'(\phi_c) = \phi_c \Sigma'(\phi_c)$

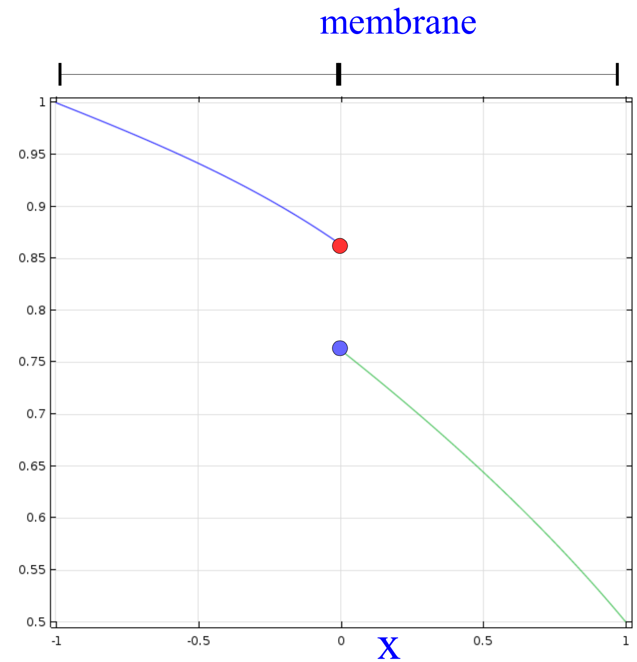
---

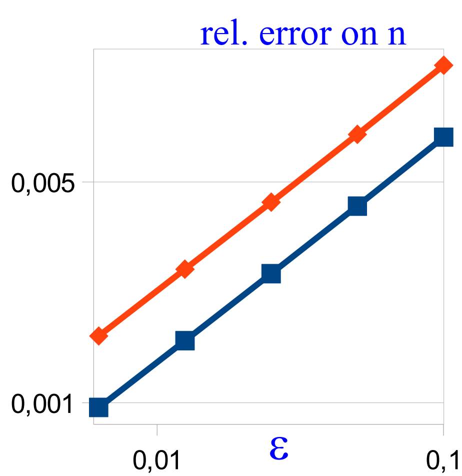
if $\Sigma(\phi_c) = \Phi \ln \dfrac{\phi_c}{\phi_0}$ → $\phi_c \Sigma'(\phi_c) = \Phi$ → $\Pi = \Phi \phi_c$

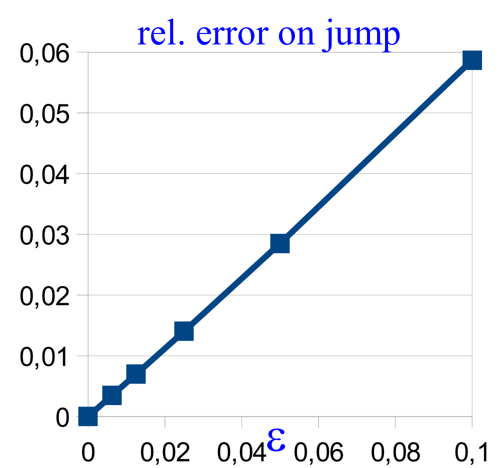
→ $\tilde{K} [\![\phi_c]\!] = K \mathbf{n} \cdot \nabla \phi_c$ Kadem-Katchalsky interface condition

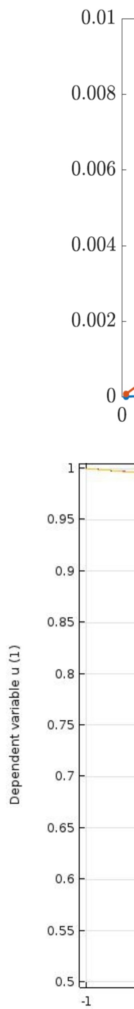
Stationary 1D problem



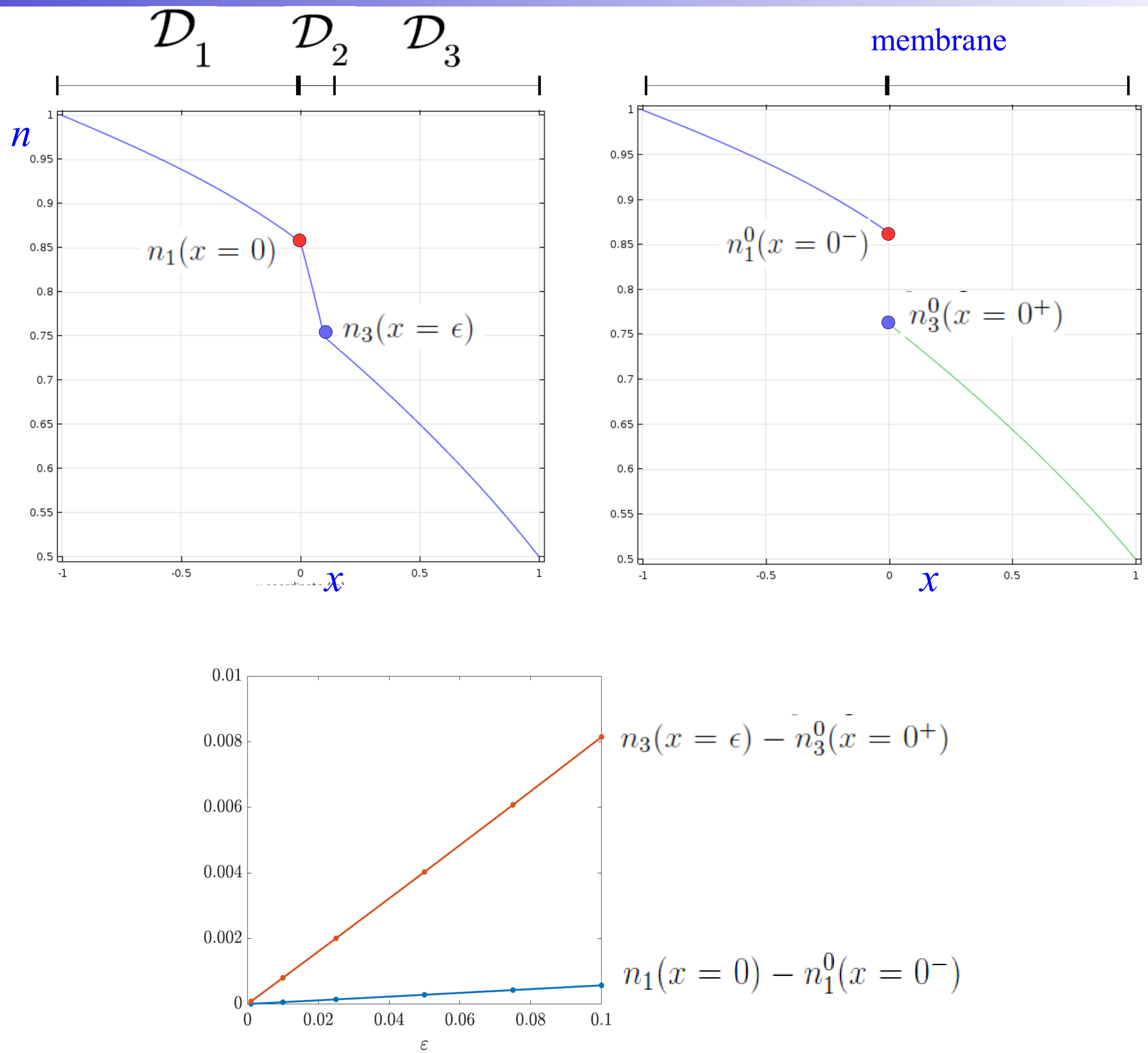




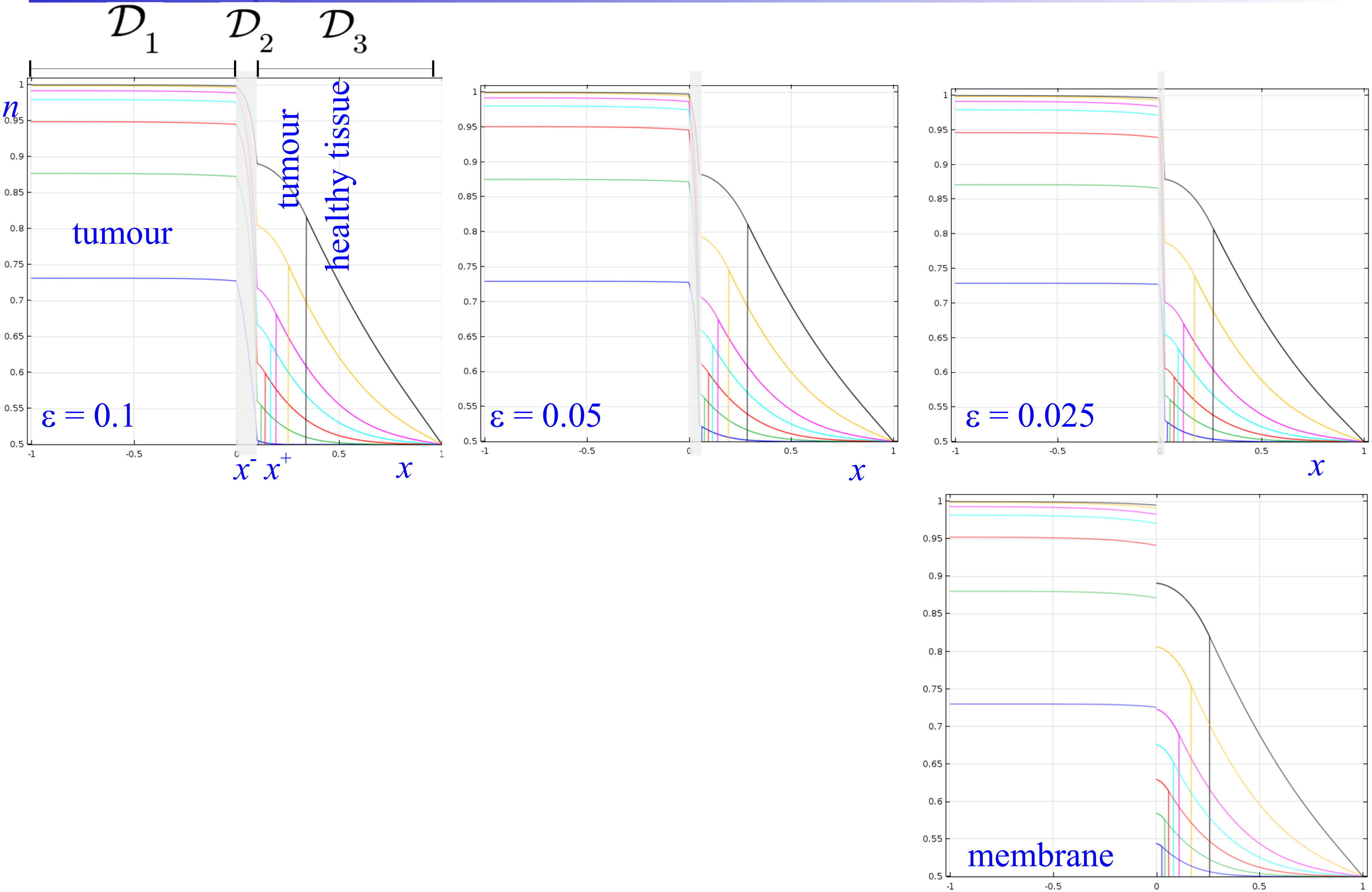




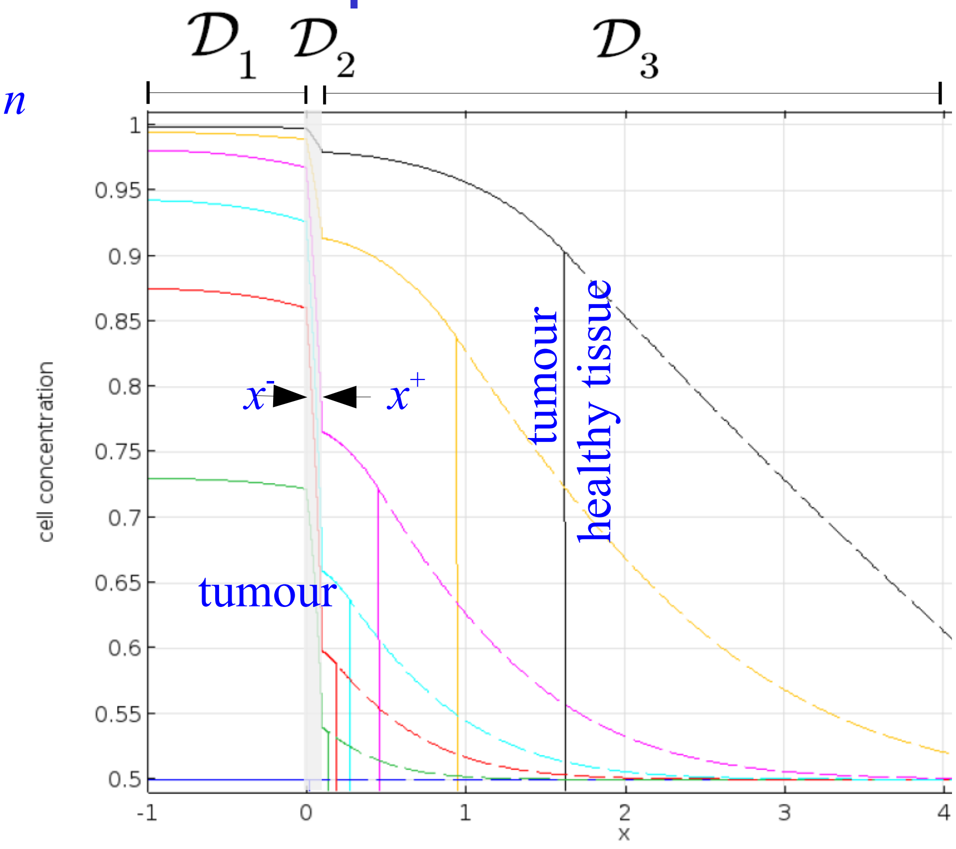
Stationary 1D problem



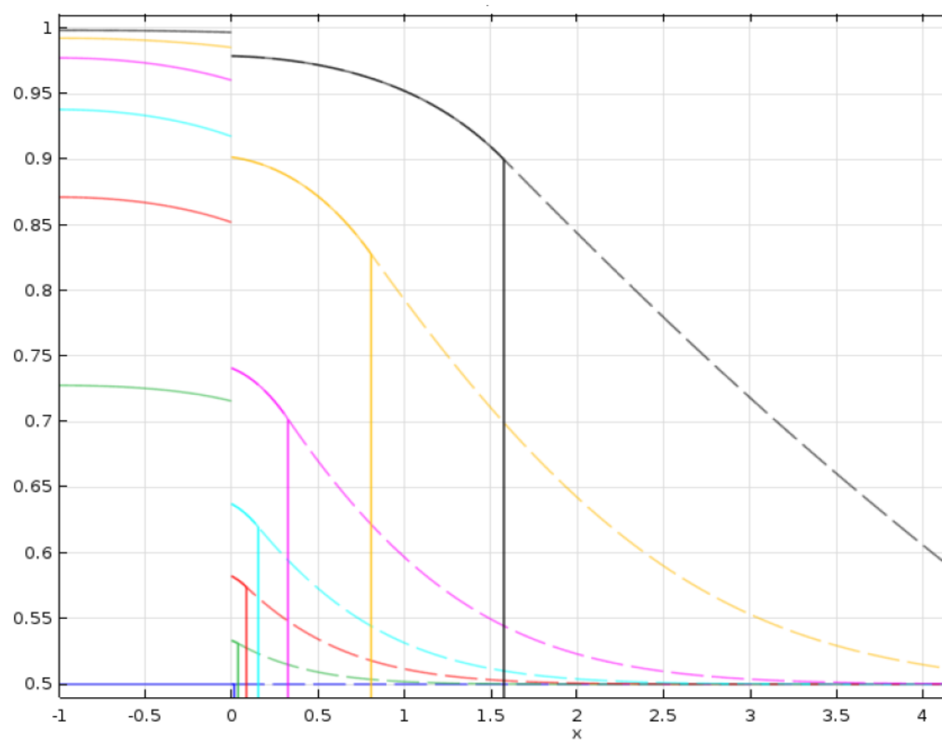
Unsteady 1D problem



Unsteady 1D problem

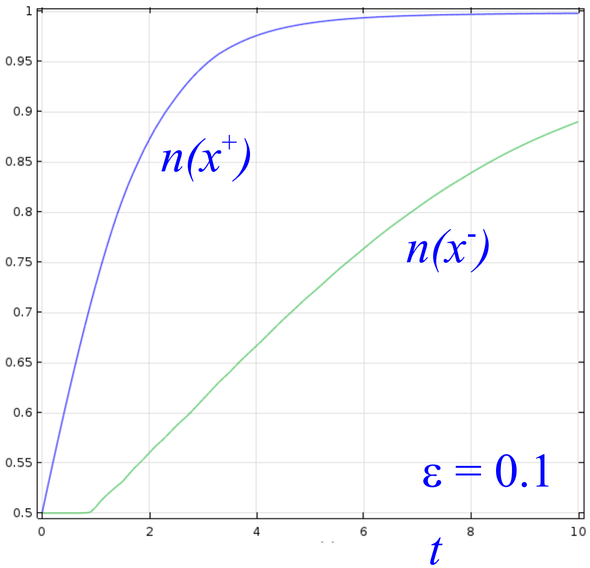


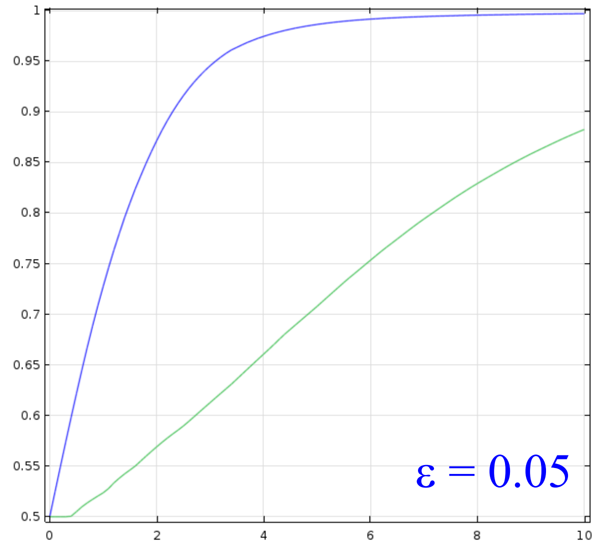
ε = 0.1

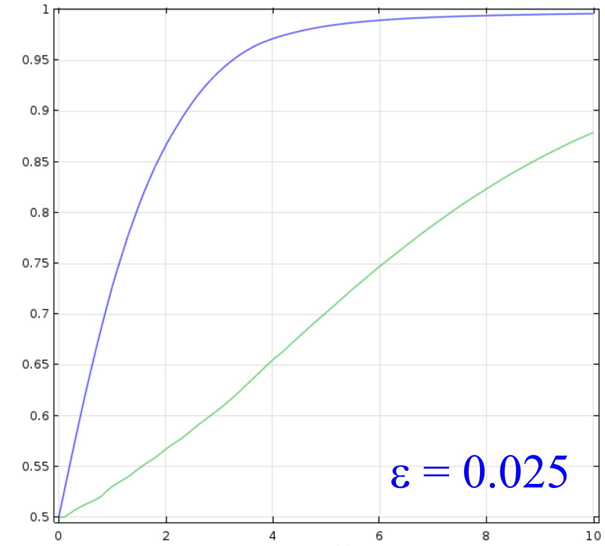


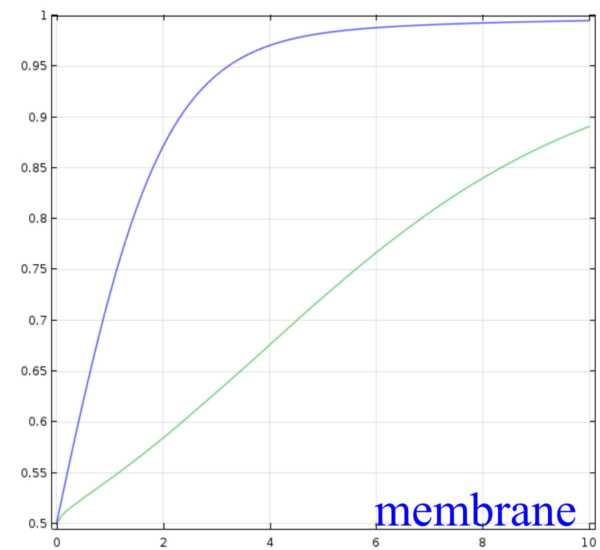
membrane

Unsteady 1D problem

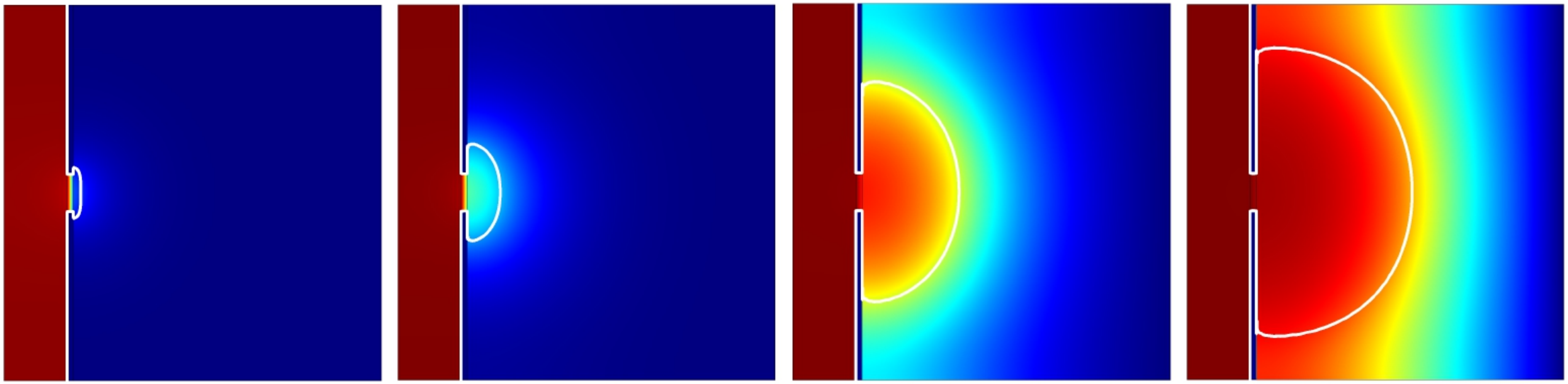




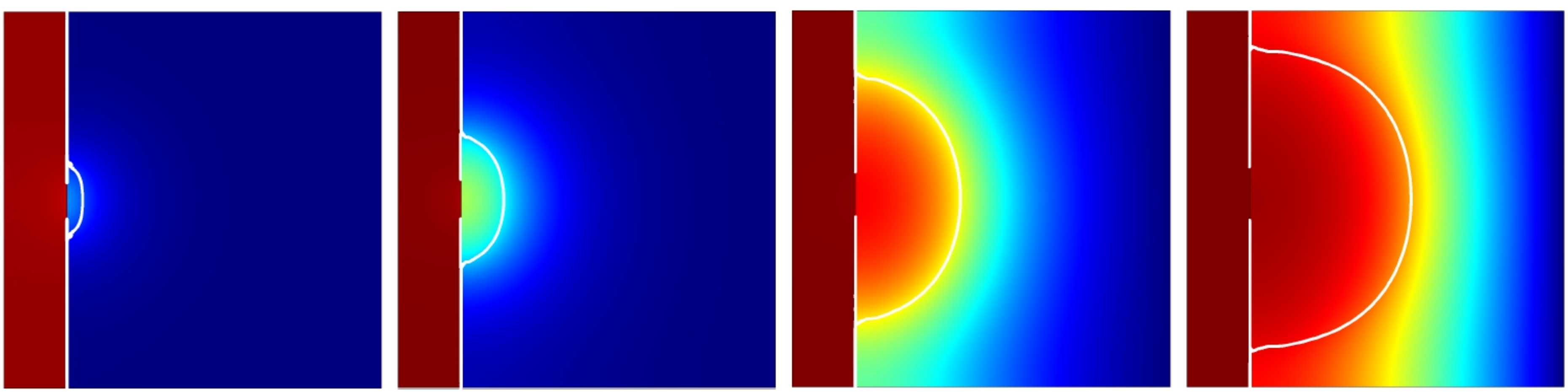




Invasion from a duct

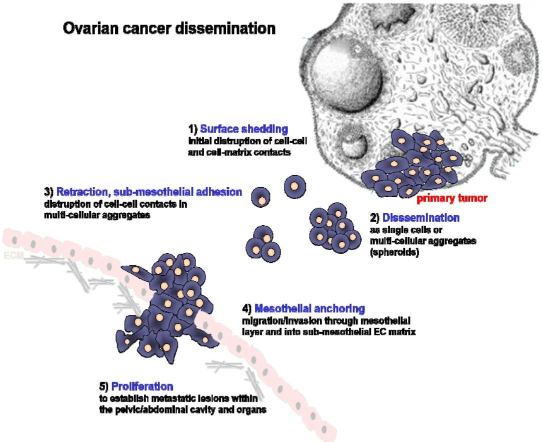


(a) $t = 5$ (b) $t = 10$ (c) $t = 20$ (d) $t = 30$



(e) $t = 5$ (f) $t = 10$ (g) $t = 20$ (h) $t = 30$

Invasion of ovary cancer cells

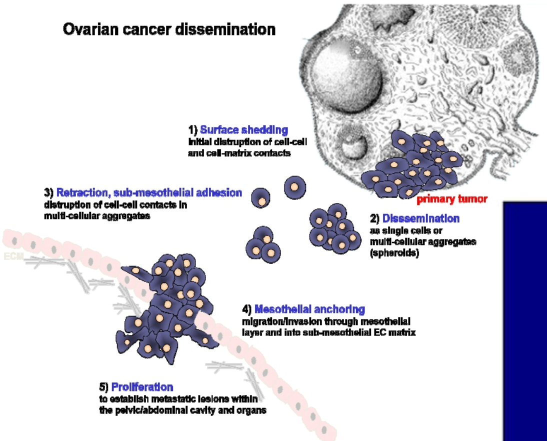


Adding tumour produced metallo-proteinases

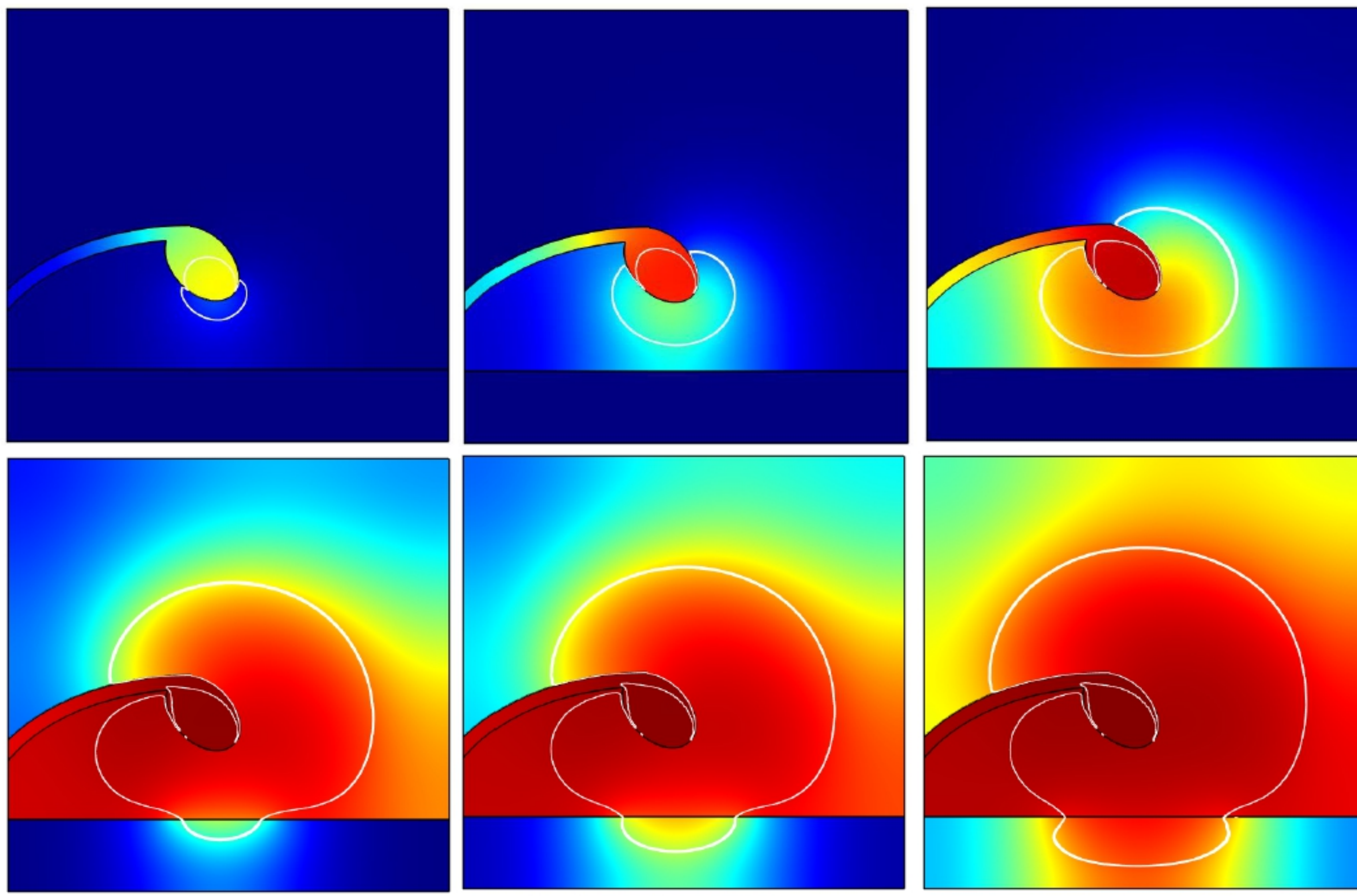
$$\frac{dA}{dt} = \alpha\left(A_1 - A\right) + \beta c_{MMP}$$

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

Invasion of ovary cancer cells



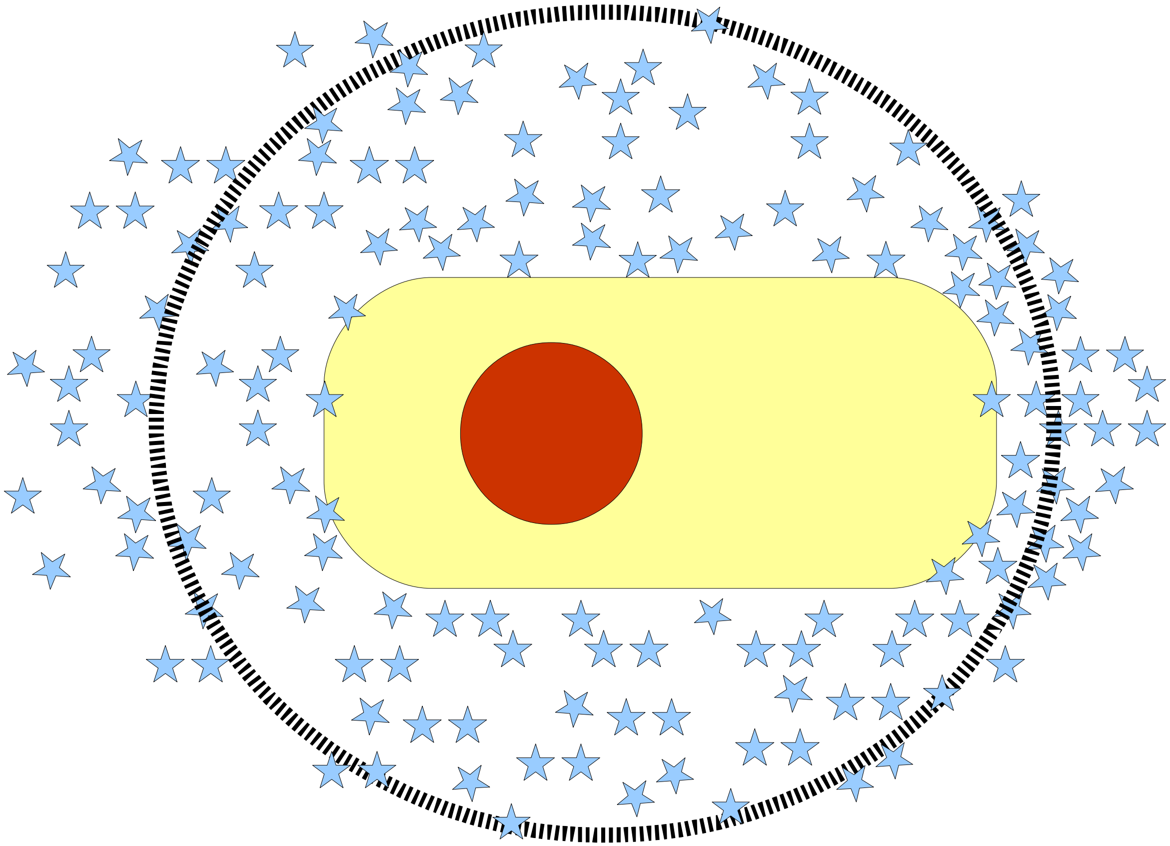
Adding tumour produced metallo-proteinases



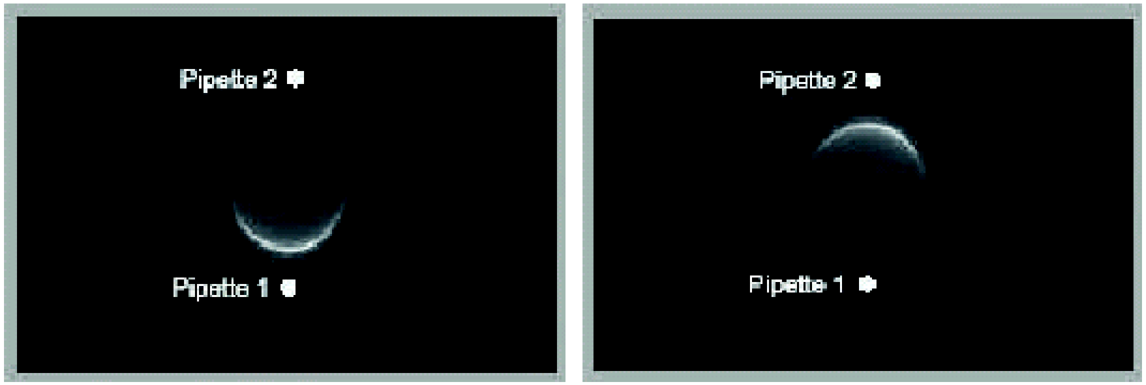
POLITECNICO DI TORINO

Kinetic Model with Nonlocal Sensing

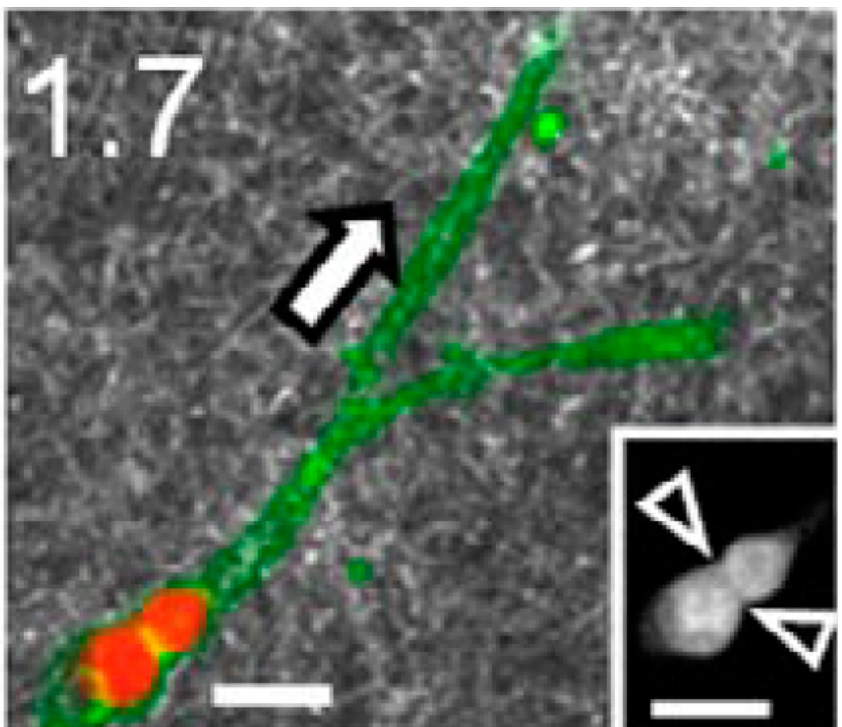
Scouting, polarization and motion



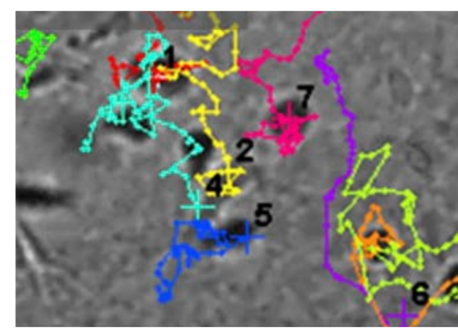
Scouting, polarization and motion



Devreotes,
Janetopoulos



Wolf
Friedl



Distribution function

$$p = p(t, \mathbf{x}, \mathbf{v}_p) \qquad \mathbf{v}_p = (\hat{\mathbf{v}}, v) \in V_p = \mathbb{S}^{d-1} \times [0, U]$$

$$\rho(t, \mathbf{x}) = \int_{V_p} p(t, \mathbf{x}, \mathbf{v}_p)\, d\mathbf{v}_p$$

$$\mathbf{U}(t, \mathbf{x}) = \frac{1}{\rho(t, \mathbf{x})} \int_{V_p} p(t, \mathbf{x}, \mathbf{v}_p)\, \mathbf{v}\, d\mathbf{v}_p$$

Transport equation

$$p = p(t, \mathbf{x}, \mathbf{v}_p) \qquad \mathbf{v}_p = (\hat{\mathbf{v}}, v) \in V_p = \mathbb{S}^{d-1} \times [0, U]$$

$$\frac{\partial p}{\partial t}(t, \mathbf{x}, \mathbf{v}_p) + \mathbf{v} \cdot \nabla p(t, \mathbf{x}, \mathbf{v}_p) = \mathcal{J}[p](t, \mathbf{x}, \mathbf{v}_p)$$

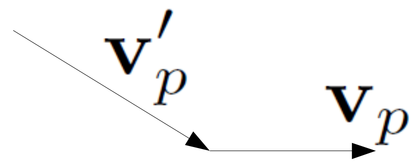
$$\mathcal{J}[p](\mathbf{x}, \mathbf{v}_p) = \mathcal{G}[p](\mathbf{x}, \mathbf{v}_p) - \mathcal{L}[p](\mathbf{x}, \mathbf{v}_p)$$

Turning operator

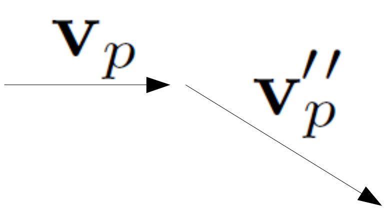
$$\mathcal{J}[p](\mathbf{x},\mathbf{v}_p) = \mathcal{G}[p](\mathbf{x},\mathbf{v}_p) - \mathcal{L}[p](\mathbf{x},\mathbf{v}_p)$$

Turning rate | Turning frequency

$$\mathcal{G}[p](\mathbf{x},\mathbf{v}_p) = \int_{V_p} \mu(\mathbf{x},\mathbf{v}'_p)T[\mathcal{S},\mathcal{S}'](\mathbf{x},\mathbf{v}_p|\mathbf{v}'_p)p(t,\mathbf{x},\mathbf{v}'_p)\,d\mathbf{v}'_p$$



$$\mathcal{L}[p](\mathbf{x},\mathbf{v}_p) = \int_{V_p} \mu(\mathbf{x},\mathbf{v}_p)T[\mathcal{S},\mathcal{S}'](\mathbf{x},\mathbf{v}''_p|\mathbf{v}_p)p(t,\mathbf{x},\mathbf{v}_p)\,d\mathbf{v}''_p$$



Turning operator

T is a transition probability $$\int_{V_p} T[\mathcal{S},\mathcal{S}'](\mathbf{x},\mathbf{v}_p''|\mathbf{v}_p)d\mathbf{v}_p'' = 1$$

$$\mathcal{L}[p](\mathbf{x},\mathbf{v}_p) = \int_{V_p} \mu(\mathbf{x},\mathbf{v}_p)T[\mathcal{S},\mathcal{S}'](\mathbf{x},\mathbf{v}_p''|\mathbf{v}_p)p(t,\mathbf{x},\mathbf{v}_p)\,d\mathbf{v}_p''$$

$$\mathcal{L}[p](\mathbf{x},\mathbf{v}_p) = \mu(\mathbf{x},\mathbf{v}_p)p(t,\mathbf{x},\mathbf{v}_p)$$

Mass conservation

T is a transition probability

$$\int_{V_p} T[\mathcal{S},\mathcal{S}'](\mathbf{x},\mathbf{v}_p''|\mathbf{v}_p)d\mathbf{v}_p''=1$$

$$\mathcal{L}[p](\mathbf{x},\mathbf{v}_p)= \mu(\mathbf{x},\mathbf{v}_p)p(t,\mathbf{x},\mathbf{v}_p)$$

Ensuring mass conservation

Integrate over the velocity space

$$\frac{\partial p}{\partial t}(t,\mathbf{x},\mathbf{v}_p)+\mathbf{v}\cdot\nabla p(t,\mathbf{x},\mathbf{v}_p)=\mathcal{J}[p](t,\mathbf{x},\mathbf{v}_p)$$

POLITECNICO DI TORINO

Turning operator

T is independent from the pre-tumbling velocity

$$T = T[\mathcal{S}, \mathcal{S}'](\mathbf{x}, \mathbf{v}_p)$$

$$\mathcal{G}[p](\mathbf{x}, \mathbf{v}_p) = \int_{V_p} \mu(\mathbf{x}, \mathbf{v}'_p) T[\mathcal{S}, \mathcal{S}'](\mathbf{x}, \mathbf{v}_p | \mathbf{v}'_p) p(t, \mathbf{x}, \mathbf{v}'_p) \, d\mathbf{v}'_p$$

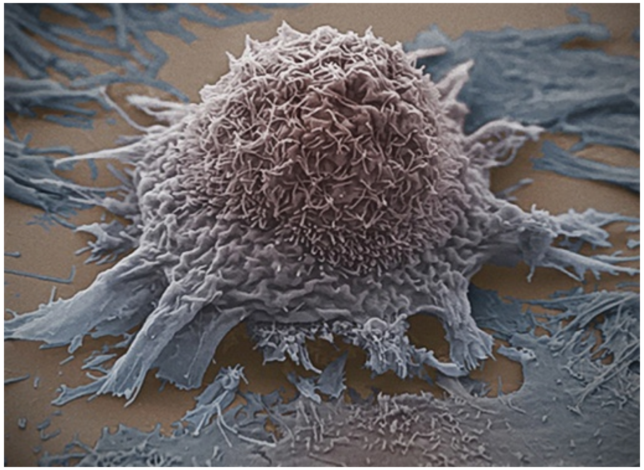
$$\mathcal{J}[p](\mathbf{x}, \mathbf{v}_p) = \int_{V_p} \mu(\mathbf{x}, \mathbf{v}'_p) p(t, \mathbf{x}, \mathbf{v}'_p) \, d\mathbf{v}'_p \, T[\mathcal{S}, \mathcal{S}'](\mathbf{x}, \mathbf{v}_p) - \mu(\mathbf{x}, \mathbf{v}_p) p(t, \mathbf{x}, \mathbf{v}_p)$$

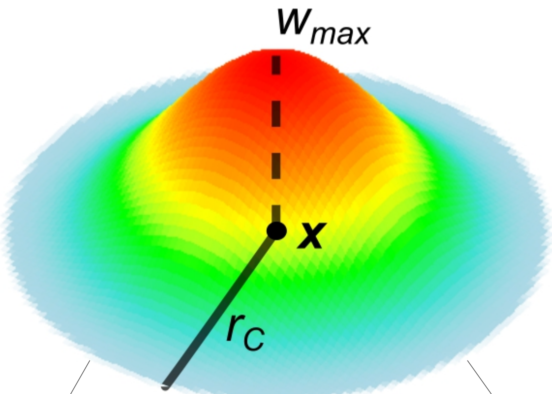
μ is independent from the pre-tumbling velocity

$$\mathcal{J}[p](t, \mathbf{x}, \mathbf{v}_p) = \mu(\mathbf{x}) \left(\rho(t, \mathbf{x}) T[\mathcal{S}, \mathcal{S}'](\mathbf{x}, \mathbf{v}_p) - p(t, \mathbf{x}, \mathbf{v}_p) \right)$$

Nonlocal structure

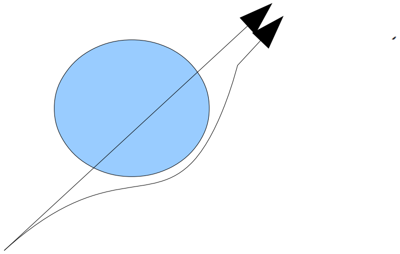
$$\mathcal{J}[p](t,\mathbf{x},\mathbf{v}_p) = \mu(\mathbf{x})\Big(\rho(t,\mathbf{x})T[\mathcal{S},\mathcal{S}'](\mathbf{x},\mathbf{v}_p) - p(t,\mathbf{x},\mathbf{v}_p)\Big)$$



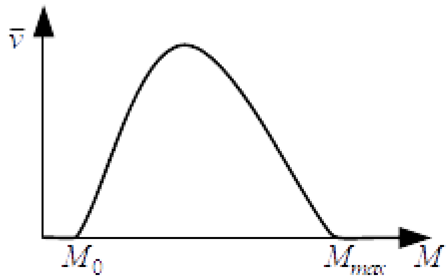


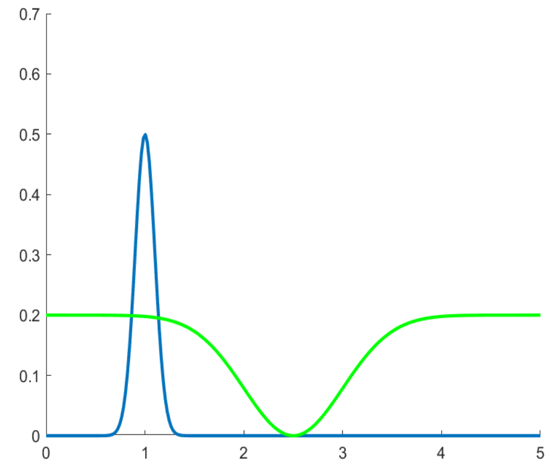
$$T[\mathcal{S},\mathcal{S}'](\mathbf{x},\mathbf{v}_p) = c(\mathbf{x})\int_{\mathbb{R}_+}\gamma_S(\lambda)\mathcal{T}_\lambda^{\hat{\mathbf{v}}}[\mathcal{S}](\mathbf{x})d\lambda \int_{\mathbb{R}_+}\gamma_{S'}(\lambda')\psi(\mathbf{x},v|\mathcal{S}'(\mathbf{x}+\lambda'\hat{\mathbf{v}}))\,d\lambda'$$

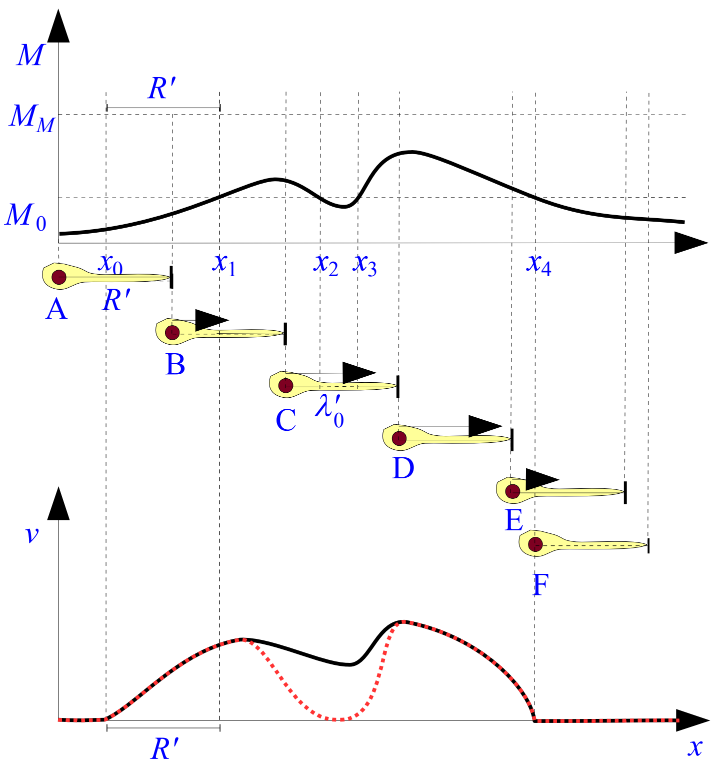
$$b\big(\mathcal{S}(\mathbf{x}+\lambda\hat{\mathbf{v}})\big)$$

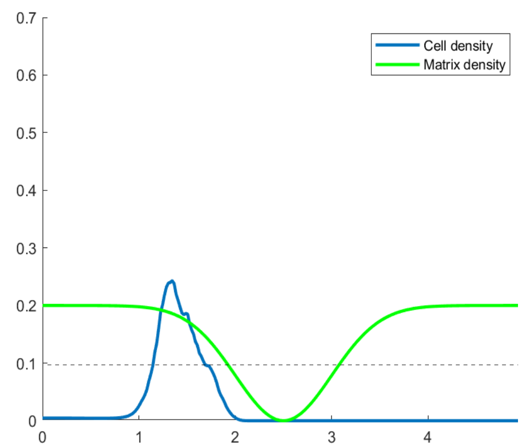


Poor ECM

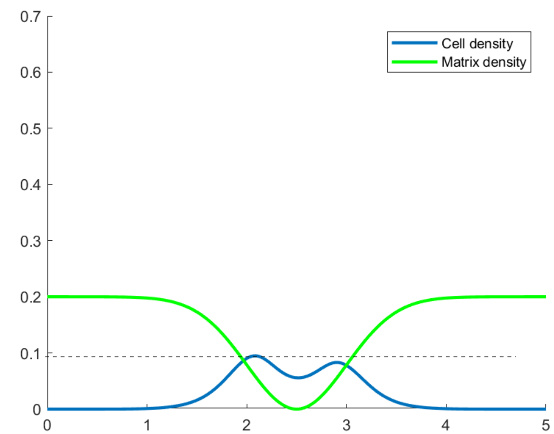






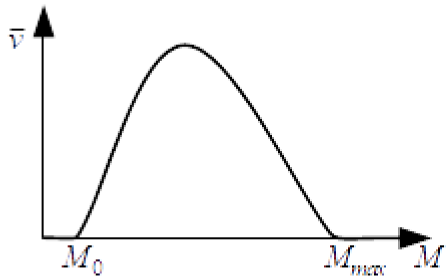


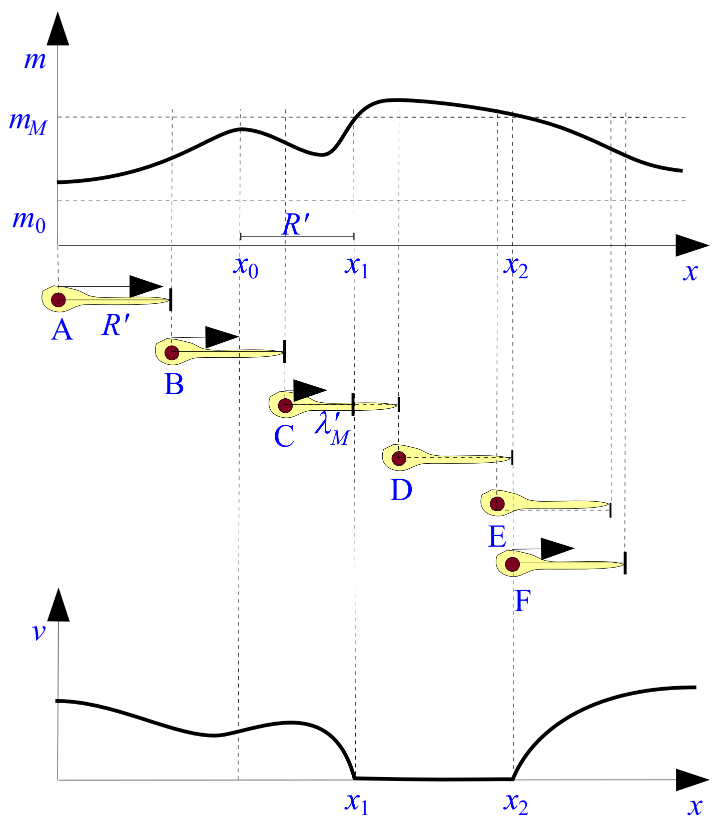
$R_M^{max} = 0.2$

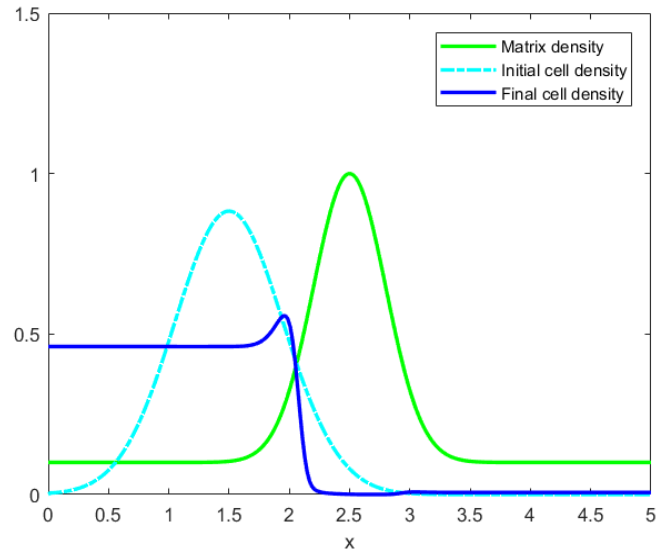


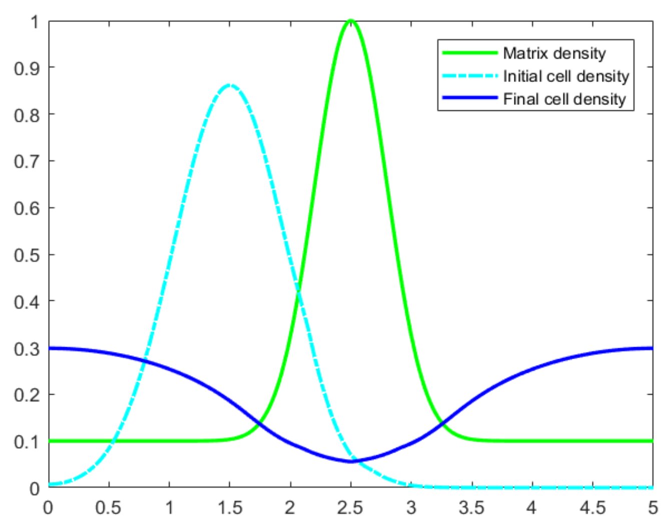
$R_M^{max} = 2$

ECM barrier

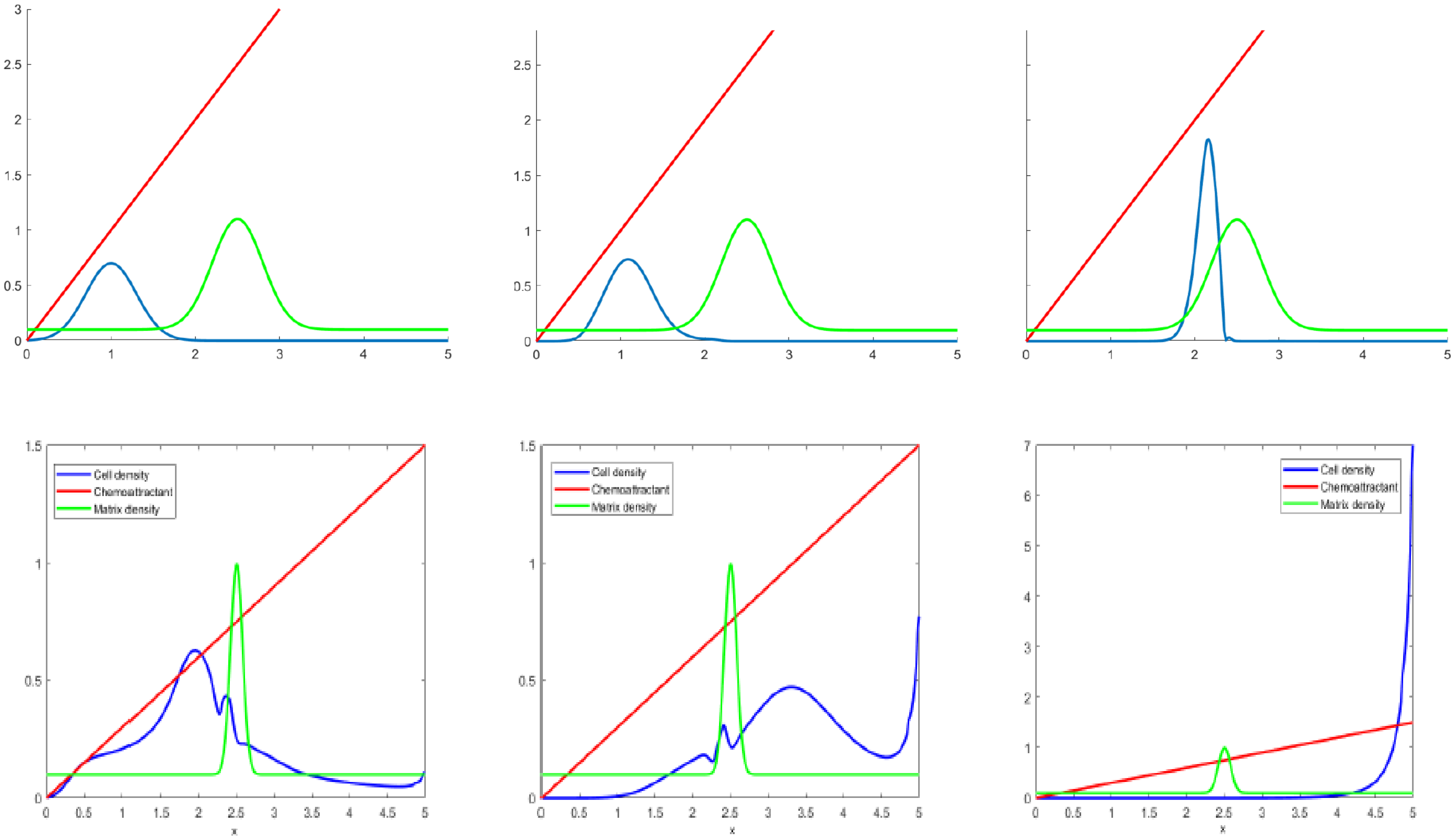

$\bar{v}$
M_0
M_{max}
M


m
m_M
m_0
R'
x_0
x_1
x_2
x
A
R'
B
C
λ'_M
D
E
F
v
x_1
x_2
x

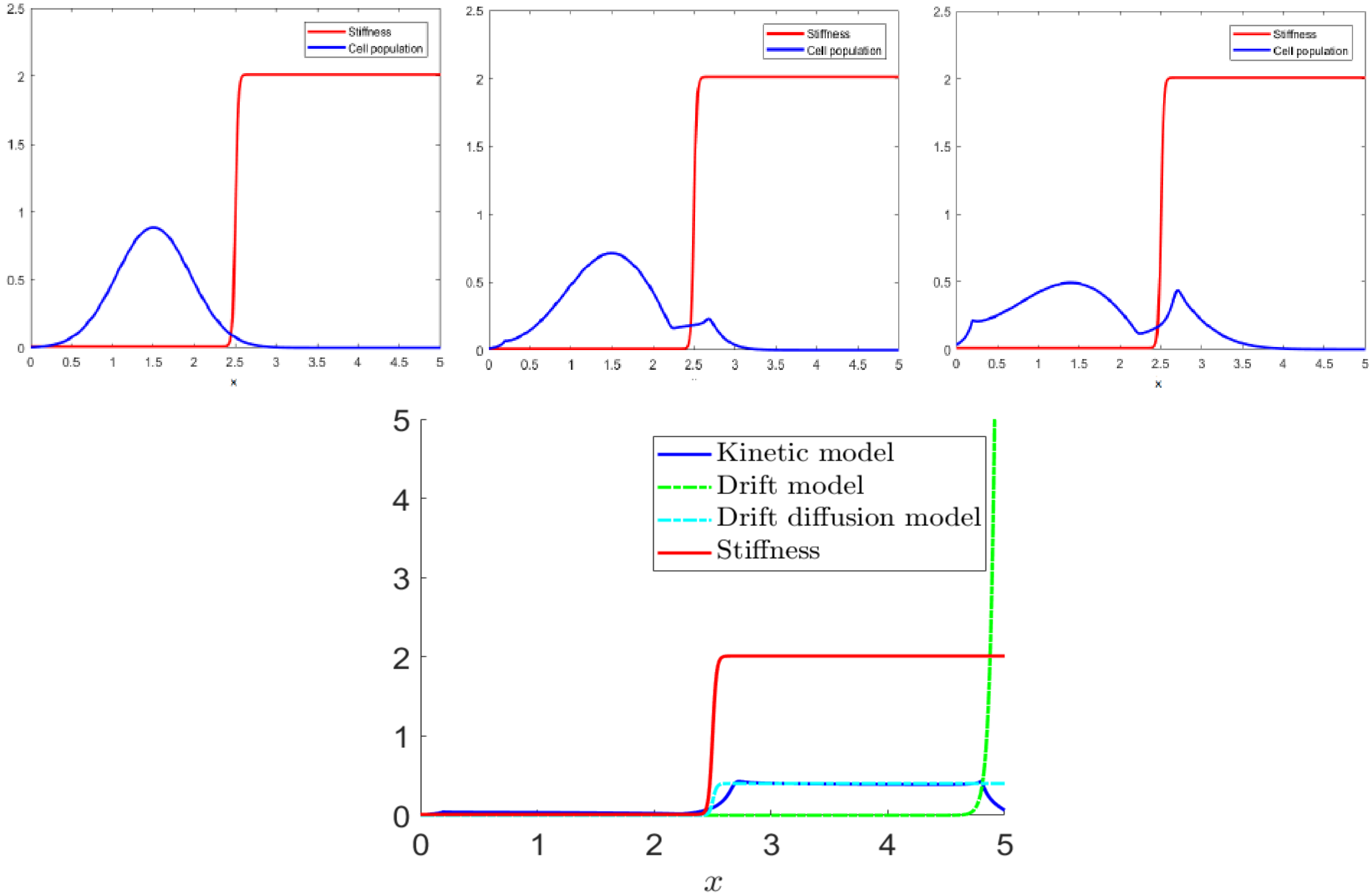

Matrix density
Initial cell density
Final cell density
x


Matrix density
Initial cell density
Final cell density
x

ECM barrier with chemotaxis

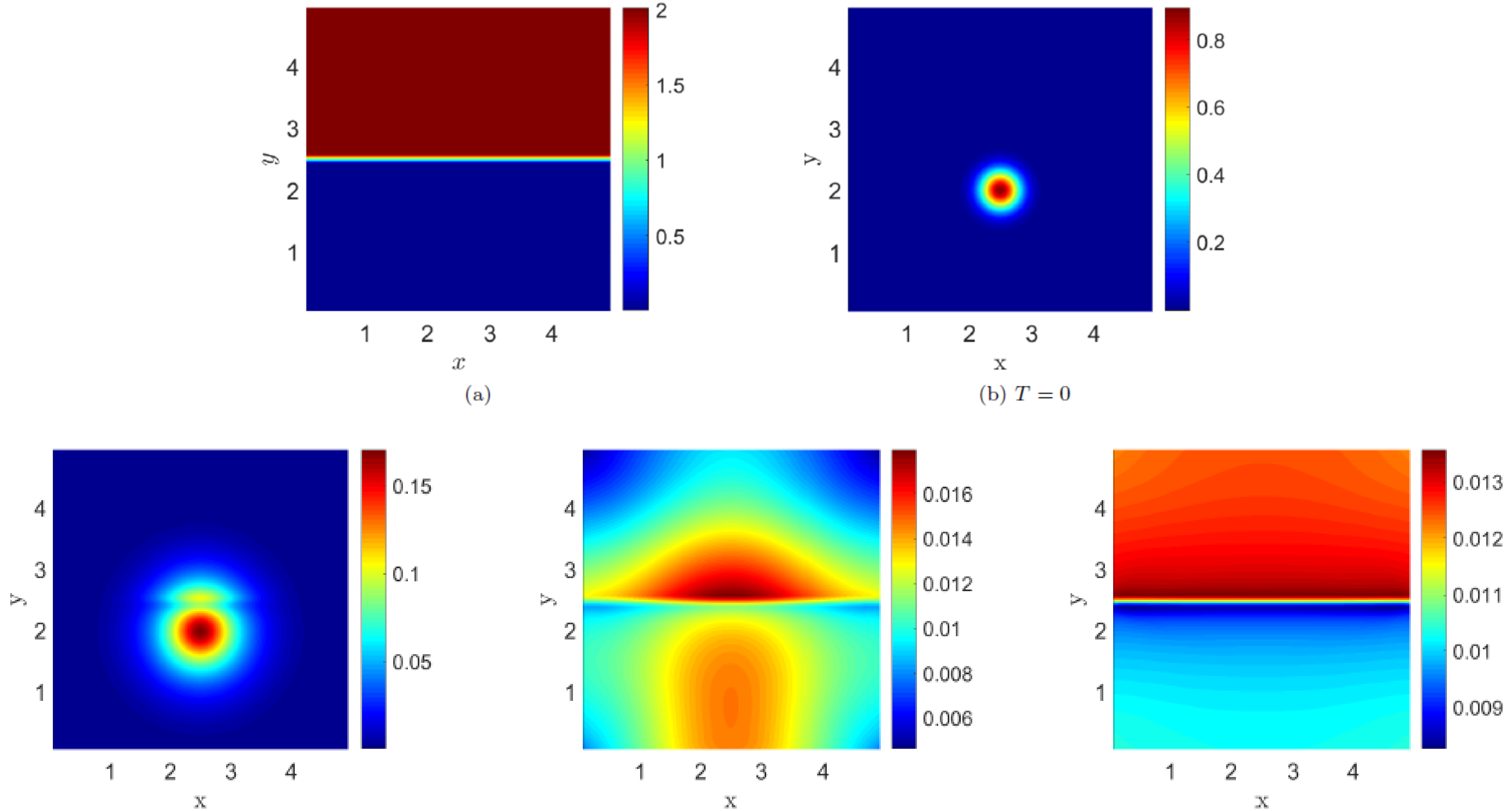


Durotaxis



Stiffness
Cell population
Kinetic model
Drift model
Drift diffusion model
Stiffness
x

Durotaxis



(a)

(b) $T = 0$

(c) $t = 0.6$

(d) $t = 6$

(e) $t = 22$