DISMA Dipartimento di Scienze Matematiche G. L. Lagrange

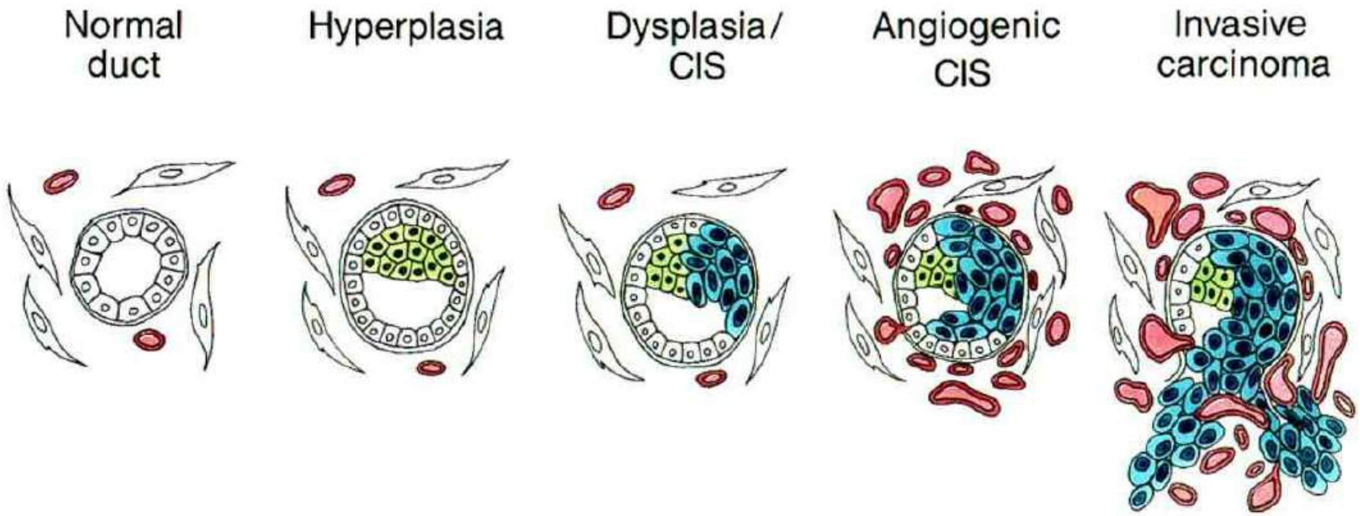
ECCELLENZA 2018 · 2022

Modelling Physical Limits of Migration

Luigi Preziosi

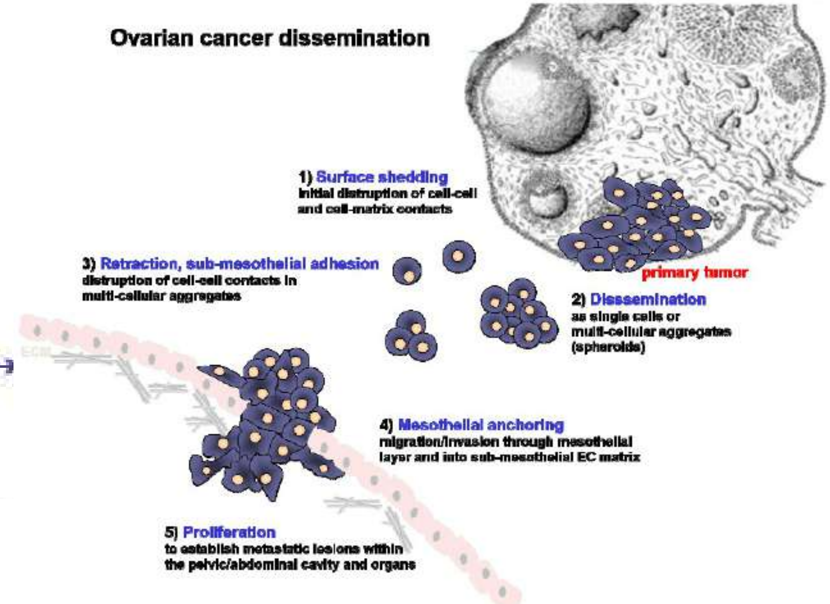
POLITECNICO DI TORINO

Compartimentalization or invasion

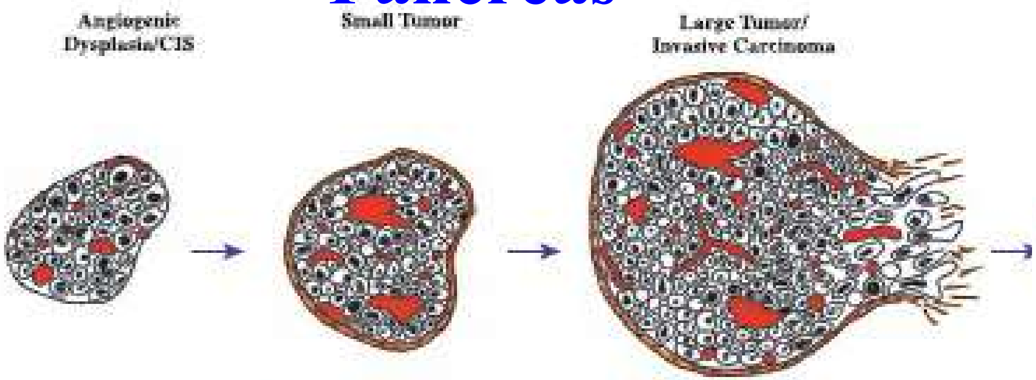


Breast

Ovary



Pancreas

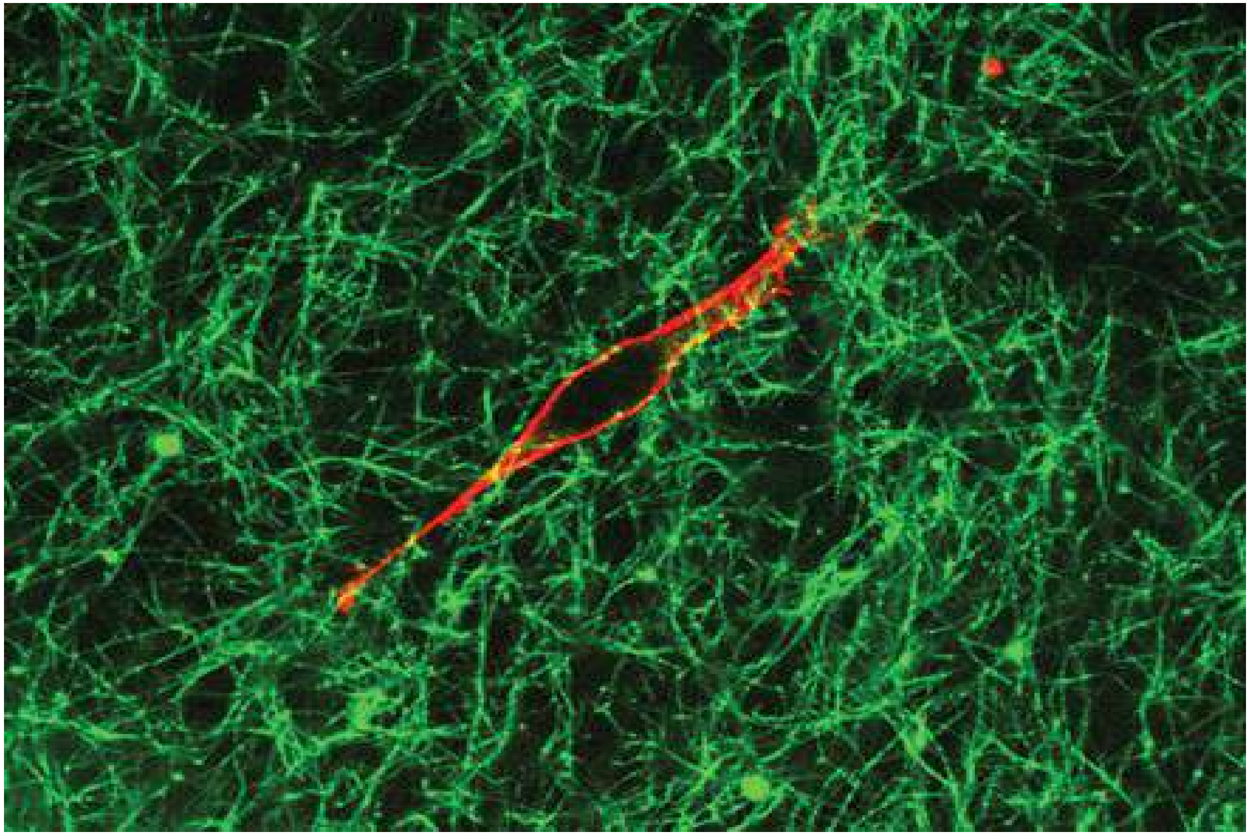


Compartimentalization or invasion

The carpenter syndrome

To a carpenter with a hammer
the entire world is a nail

Physical limit of migration



(P. Friedl, K. Wolf)

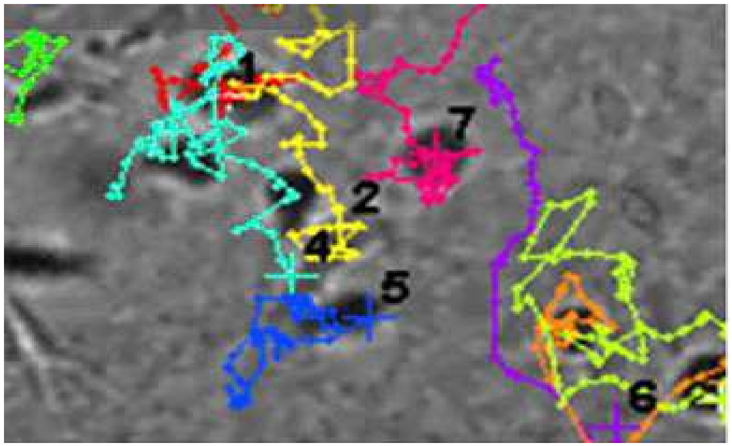
video

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

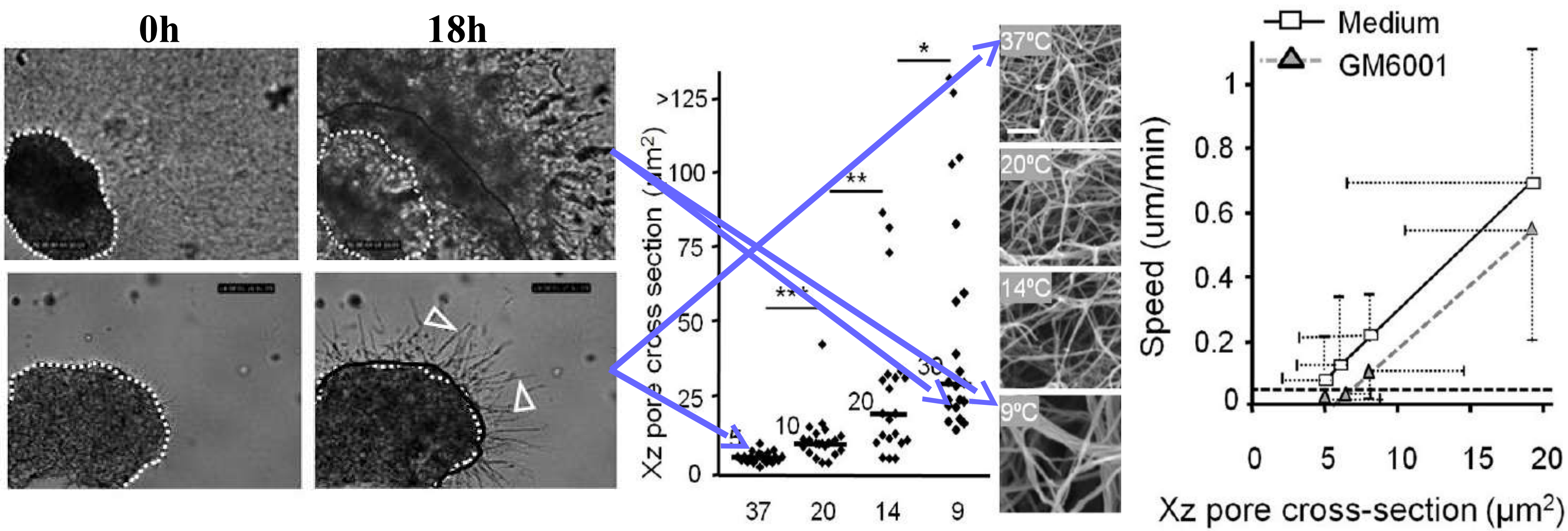
video

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

Physical limit of migration

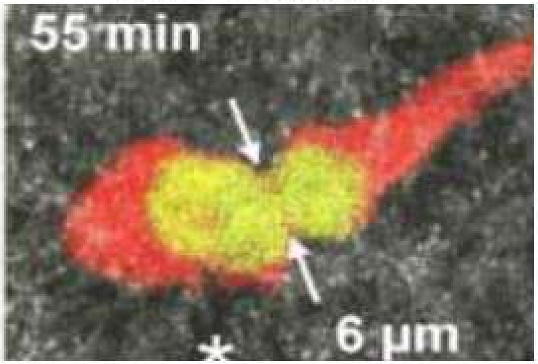


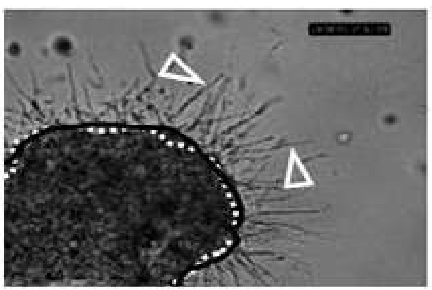
Wolf, te Lindert, Krause, Alexander, te Riet, Wills, Hoffman, Figdor, Weiss, Friedl
J. Cell Biol. **201**, 1069-1084 (2013)

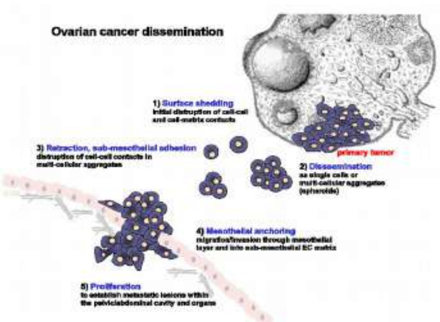


POLITECNICO DI TORINO

Plan of the talk

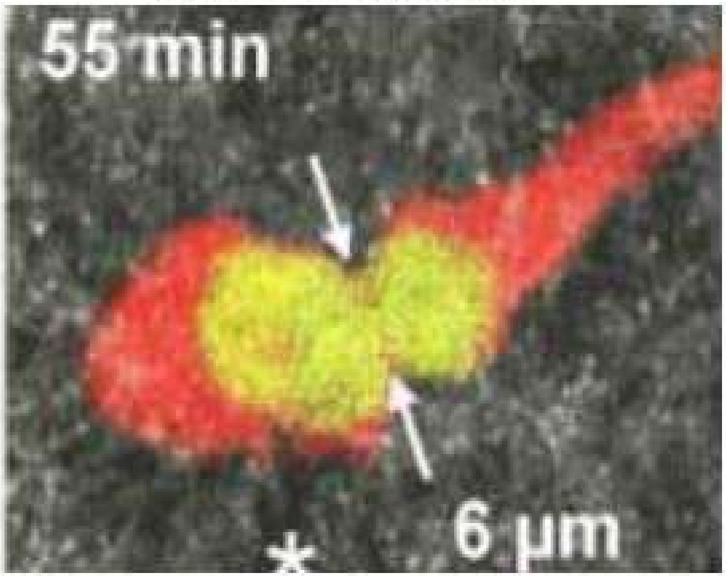


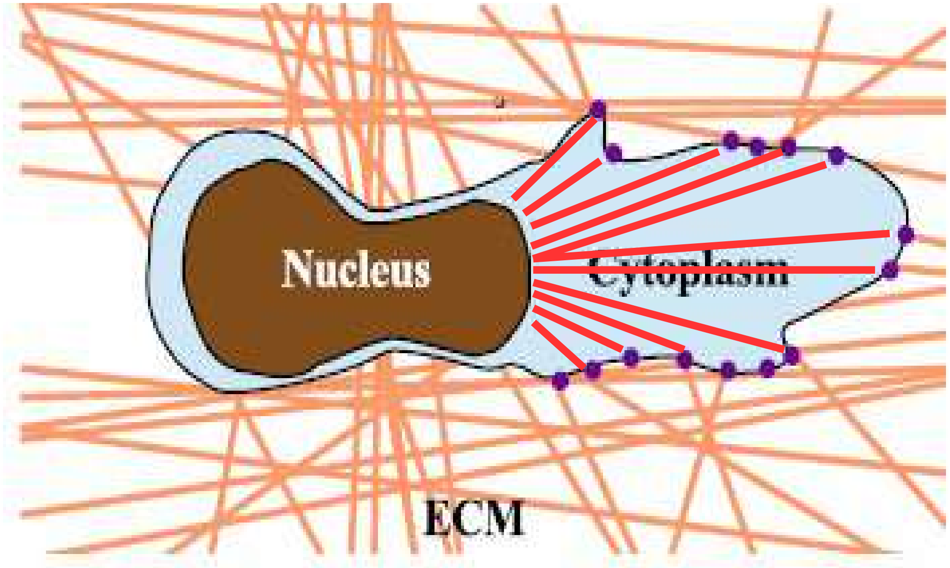




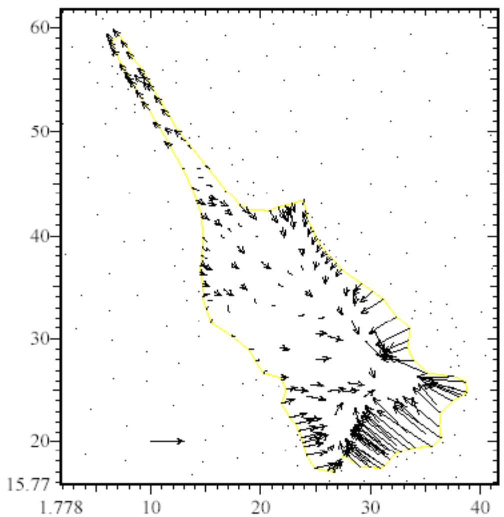
- Cell mechanics
- Individual cell-based model
- Multiphase model
- Asymptotic limit for interface condition

Cell pulling and nucleus squeezing

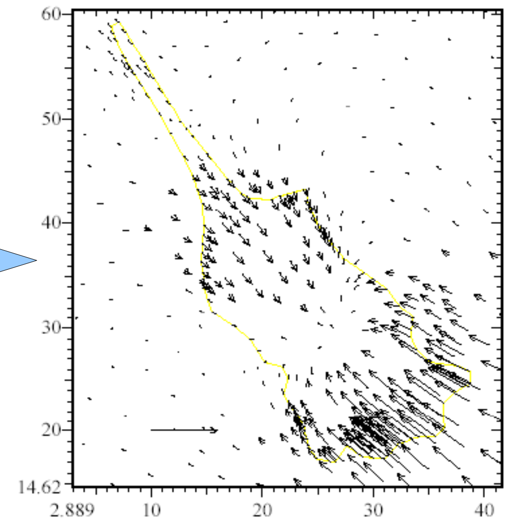




Traction force microscopy



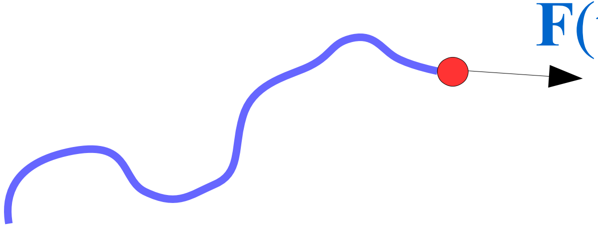
Direct problem



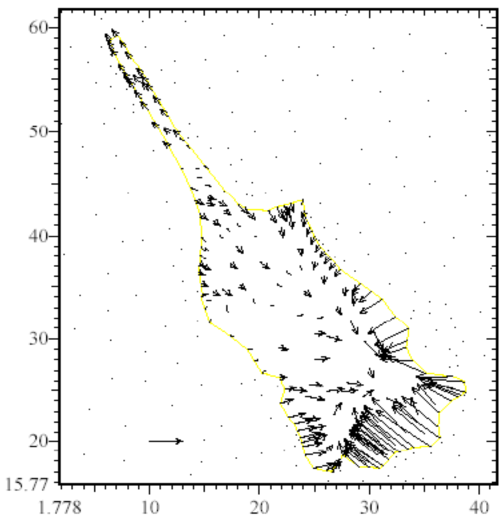
Cell traction determines ECM deformation

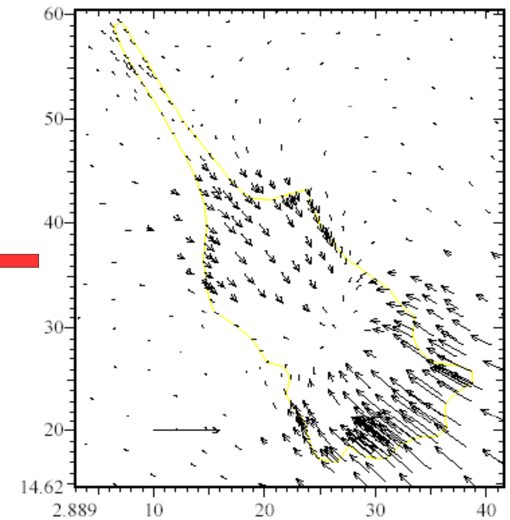
Given the force, determine the motion

$$\mathbf{F}(t) \xrightarrow{m\mathbf{a} = \mathbf{F}} \mathbf{x}(t)$$



Traction force microscopy



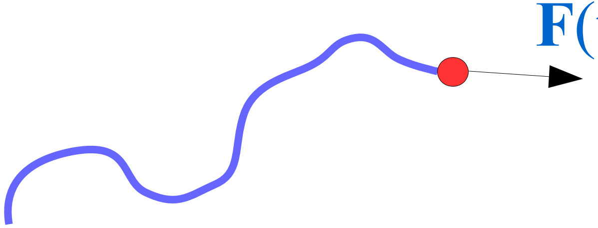


Deformation is determined by cell traction

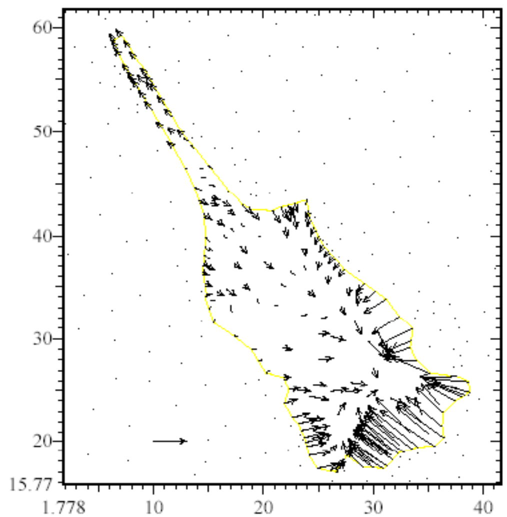
Given the motion determine the force

$$\mathbf{m}\mathbf{a} = \mathbf{F}$$

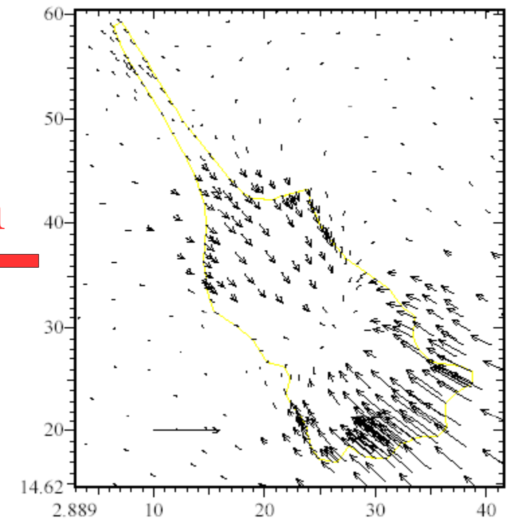
$\mathbf{F}(t) \longleftarrow \mathbf{x}(t)$



Traction force microscopy

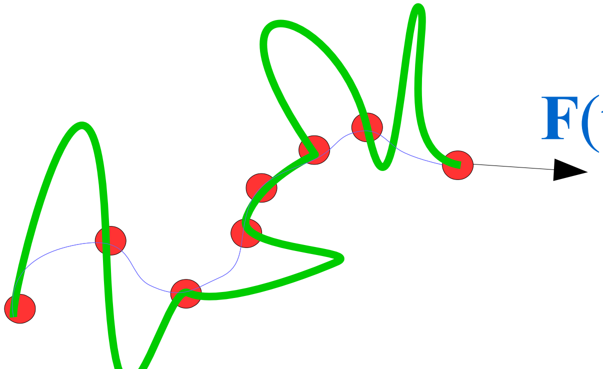


Inverse problem



Deformation is determined by cell traction

Given some information on the motion, determine the most plausible force



$m\mathbf{a} = \mathbf{F}$

$\mathbf{F}(t)$ ← $\mathbf{x}(t_i)$

Traction force microscopy

Given the deformations $\mathbf{u}_{0i}$ in $\mathbf{x}_i$

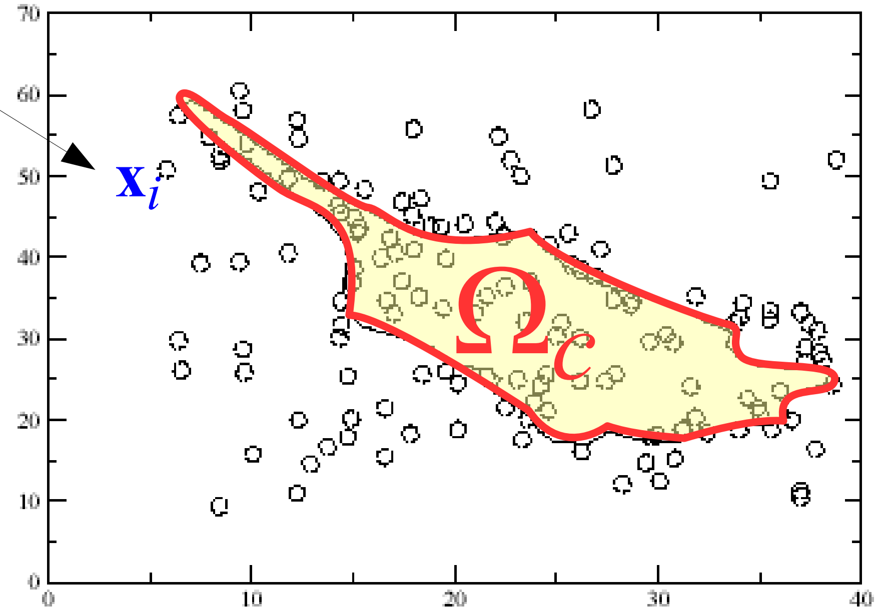
For any admissible force $\mathbf{F}$ exerted in Ω_c

Compute $\mathbf{u}(\mathbf{x})$ such that

$\mathcal{F}(\mathbf{u}) = \mathbf{F}$

Compute the difference between $\mathbf{u}(\mathbf{x}_i)$ and $\mathbf{u}_{0i}$

Among all admissible $\mathbf{F}$ choose the most "economical"



$$\mathcal{J}(\mathbf{F}) = \sum_i \left| \left[\mathcal{F}^{-1}(\mathbf{F})\right](\mathbf{x}_i) - \mathbf{u}_{0i} \right|^2 + \varepsilon \|\mathbf{F}\|^2$$

Traction force microscopy

Linear elasticity operators

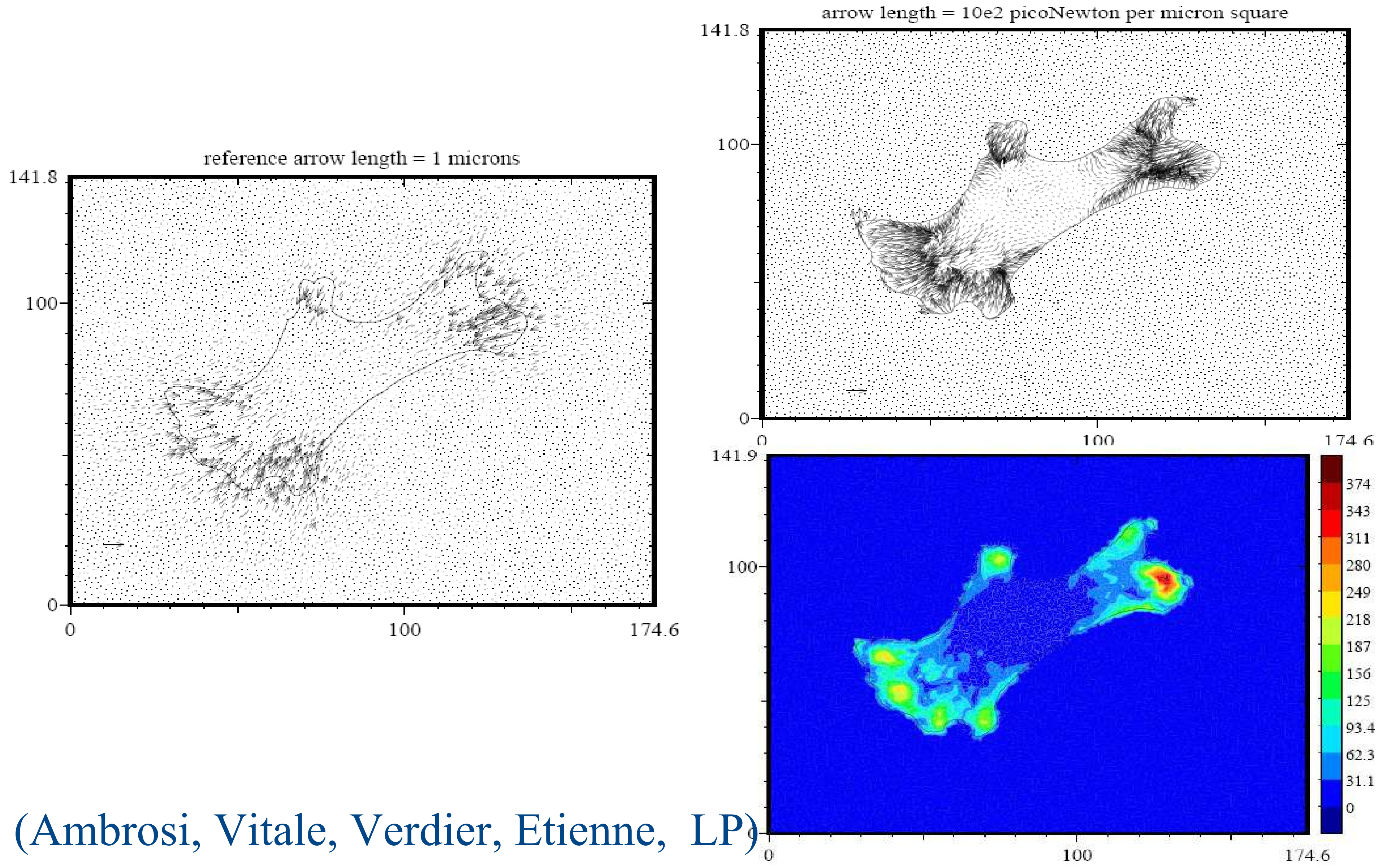
Indicator function of Ω_c

$$\boxed{\begin{aligned} -\hat{\mu}\Delta\mathbf{u} - (\hat{\mu}+\hat{\lambda})\nabla(\nabla\cdot\mathbf{u}) \\ -\hat{\mu}\Delta\mathbf{p} - (\hat{\mu}+\hat{\lambda})\nabla(\nabla\cdot\mathbf{p}) \end{aligned}}\begin{aligned} &= -\frac{\chi_c}{\varepsilon}\mathbf{p}, \qquad \mathbf{u}|_{\partial\Omega} = 0, \\ &= \chi_o\mathbf{u} - \mathbf{u}_0, \qquad \mathbf{p}|_{\partial\Omega} = 0. \end{aligned}$$

Indicator function of Ω_0

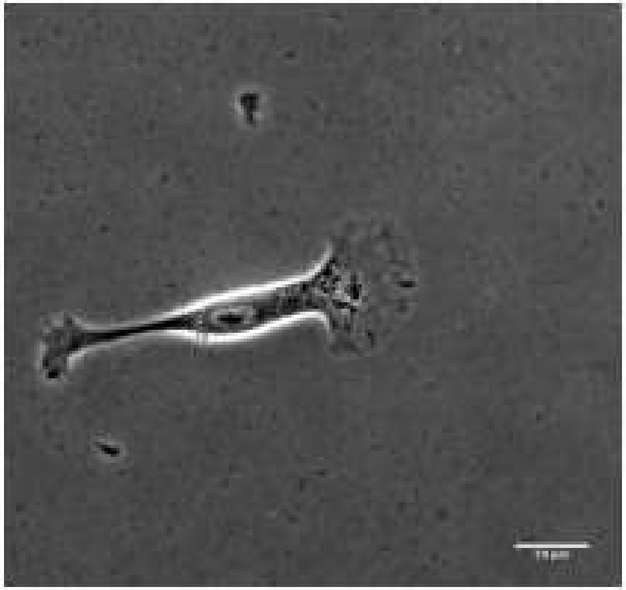
Self-adjoint problem

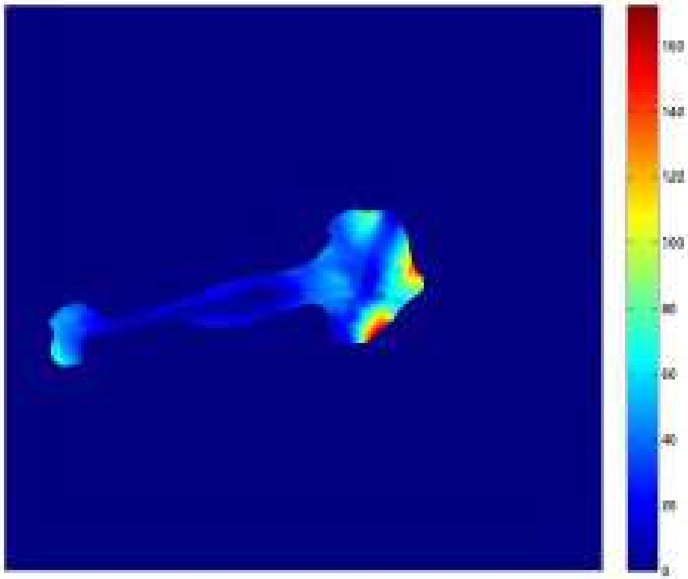
Traction force microscopy

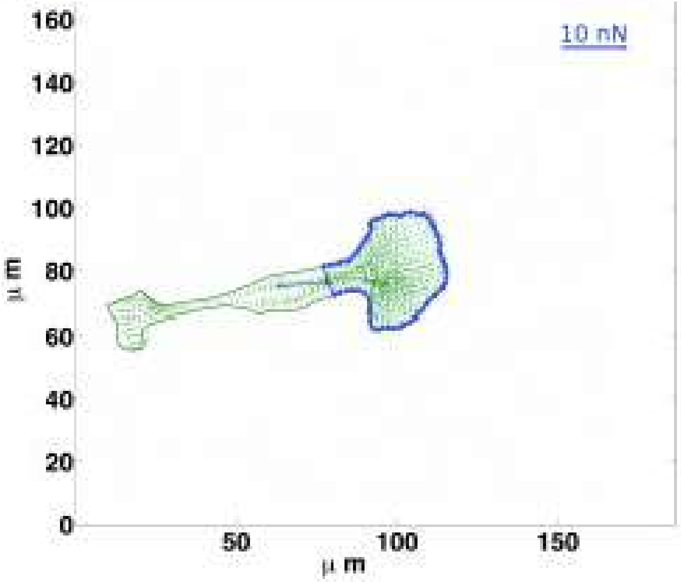


(Ambrosi, Vitale, Verdier, Etienne, LP)

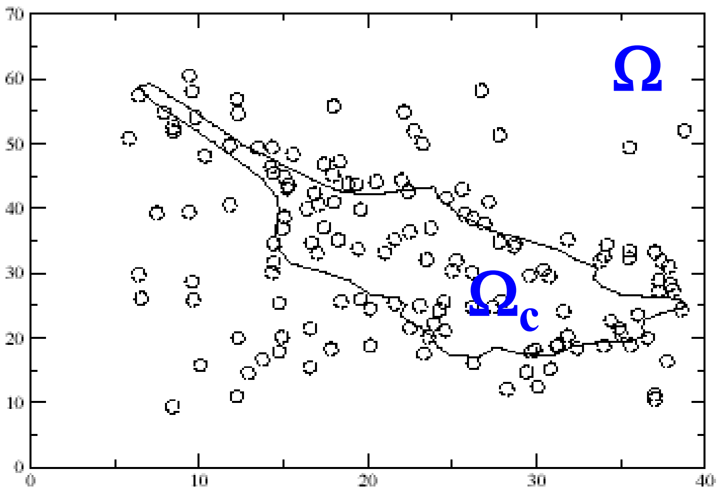
Traction force microscopy





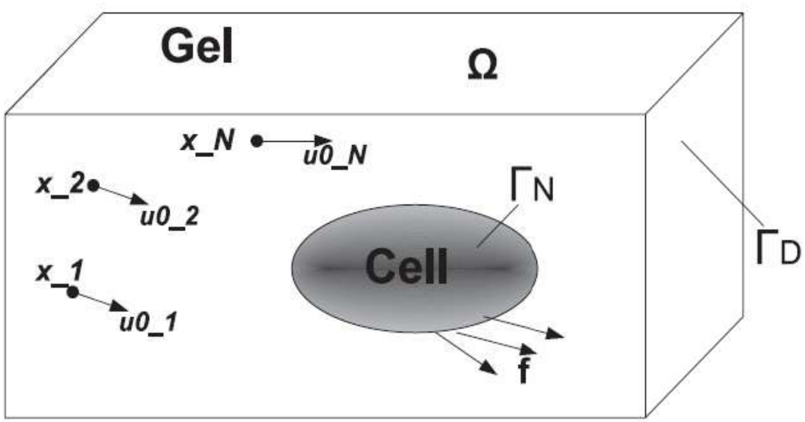


Traction force microscopy in 3D



2D

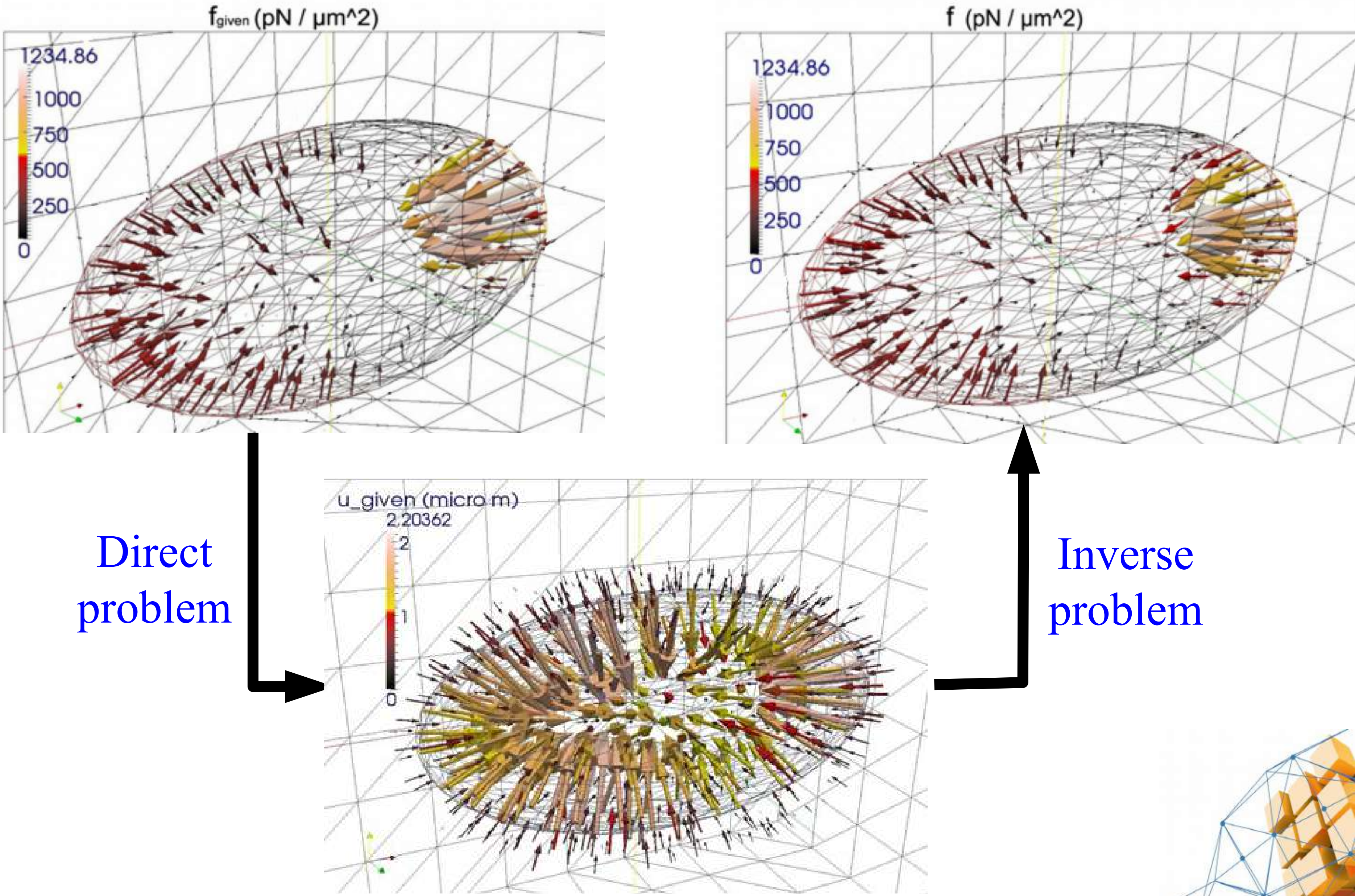
- Measures in Ω (also below the cell)
- Forces in Ω_c (only under the cell)



3D

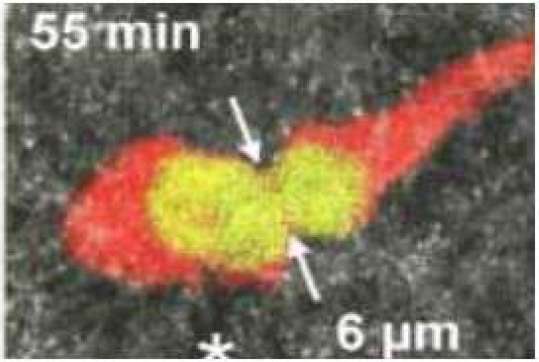
- Measures only outside Ω_c
- Forces on Γ_N (the cell membrane)

Traction force microscopy in 3D

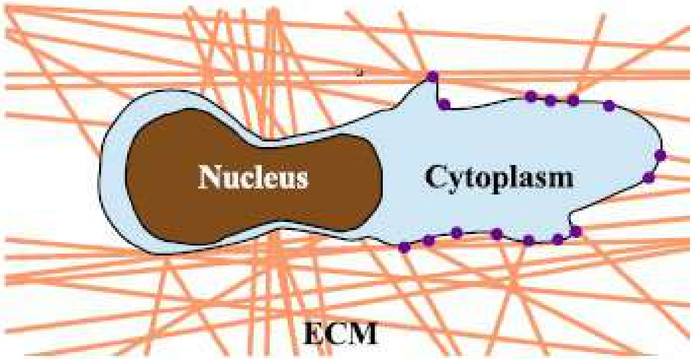


Nucleus squeezing

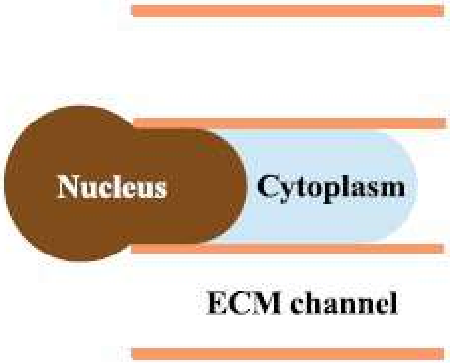
BIOLOGICAL EXPERIMENT



BIOLOGICAL REPRESENTATION



MATHEMATICAL REPRESENTATION



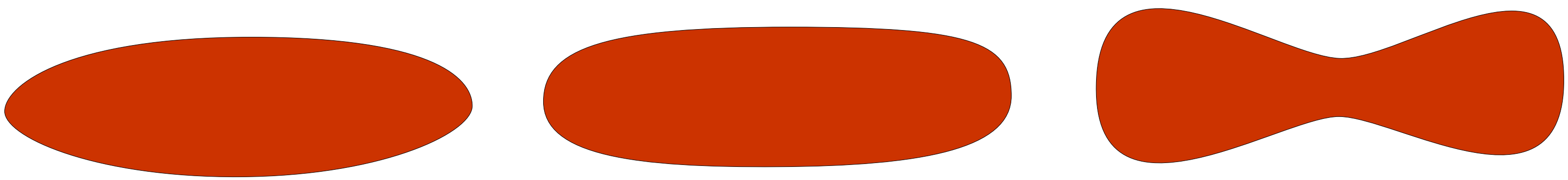
Work done by traction > Energy required to squeeze the nucleus

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

Energy to squeeze

Work done by traction > Energy required to squeeze the nucleus

- Given the deformation gradient **F**



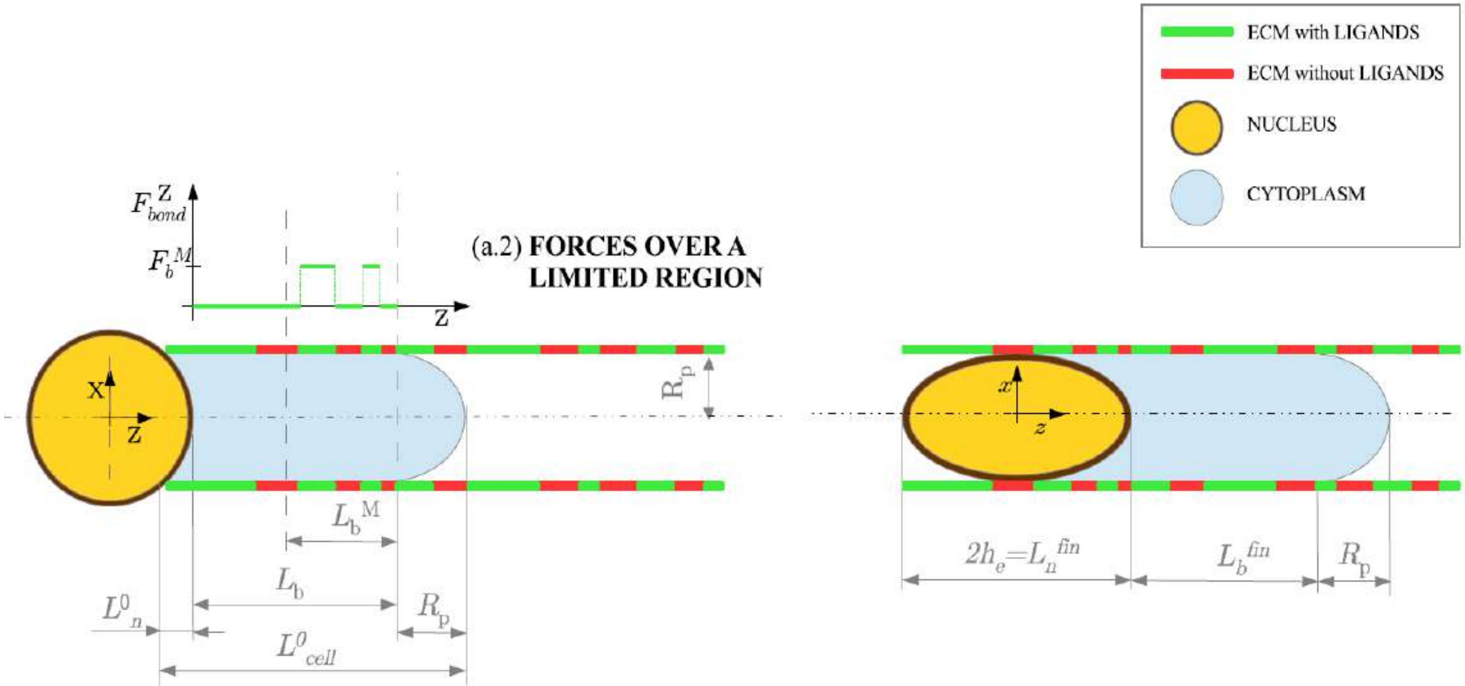
- Given the constitutive equation of the material

- Compute $\mathbf{B} = \mathbf{F}\,\mathbf{F}^T$

- Compute the elastic energy, e.g. $W(\mathrm{I}_{\mathbf{B}}) = \frac{\mu}{2}(\mathrm{I}_B - 3)$

Work of traction forces

Work done by traction > Energy required to squeeze the nucleus



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

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

Invasion criterium

Work done by traction > Energy required to squeeze the nucleus

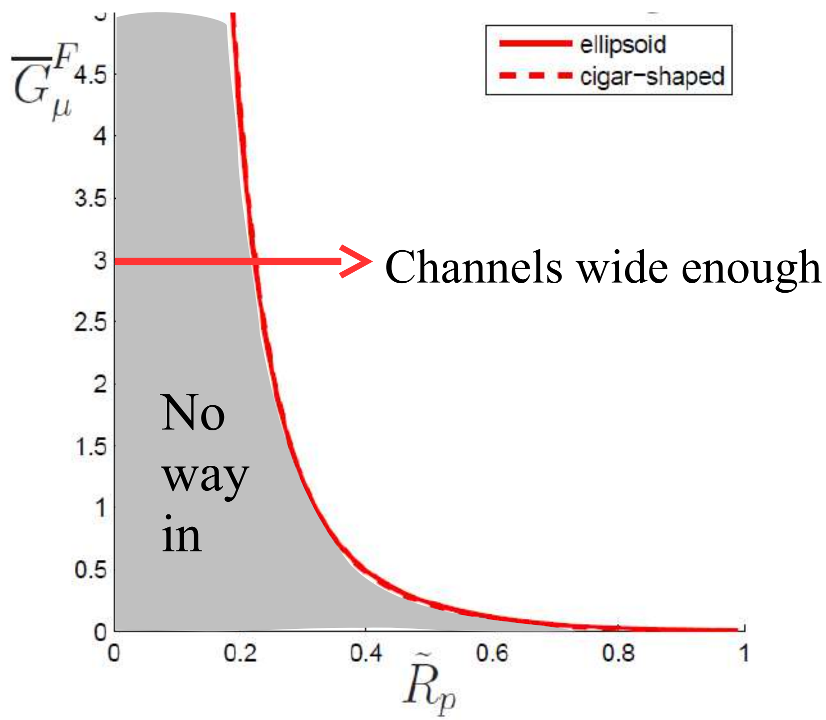
Elastic	Ellipsoid	$G_\mu^F \geq \frac{2}{3} \frac{2\tilde{R}_p^2 + \frac{1}{\tilde{R}_p^4} - 3}{\tilde{R}_p \tilde{L}_b^{(*)} \Delta \tilde{L}_{ellips}}$
nucleus	Cigar	$G_\mu^F \geq \frac{2}{3} \frac{\mathcal{I}(\tilde{R}_p)}{\tilde{R}_p \tilde{L}_b^{(*)} \Delta \tilde{L}_{cigar}}$

Traction

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

Nucleus stiffness

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



Invasion criterium

Work done by traction > Energy required to squeeze the nucleus

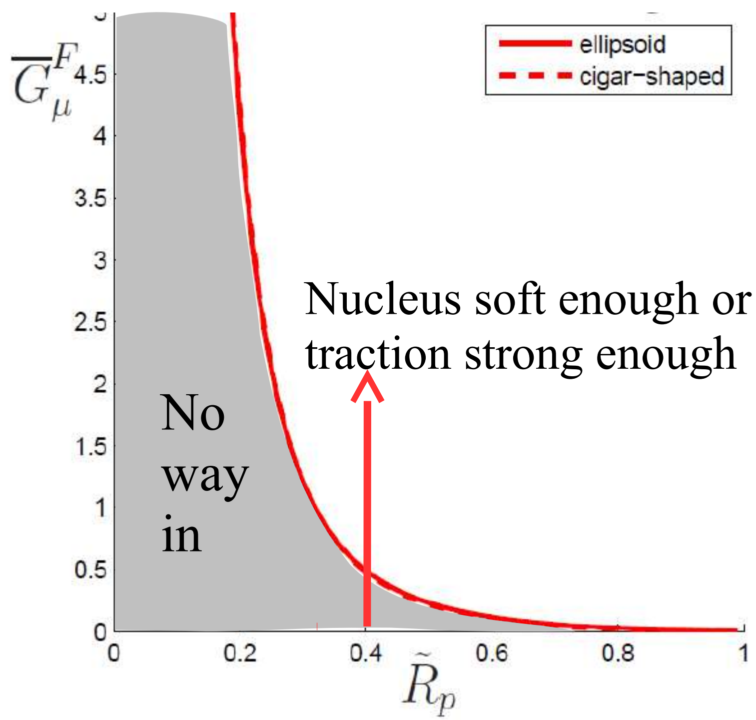
Elastic nucleus	Ellipsoid	$G_\mu^F \geq \frac{2}{3} \frac{2\tilde{R}_p^2 + \frac{1}{\tilde{R}_p^4} - 3}{\tilde{R}_p \tilde{L}_b^{(*)} \Delta\tilde{L}_{ellips}}$
	Cigar	$G_\mu^F \geq \frac{2}{3} \frac{\mathcal{I}(\tilde{R}_p)}{\tilde{R}_p \tilde{L}_b^{(*)} \Delta\tilde{L}_{cigar}}$

Traction

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

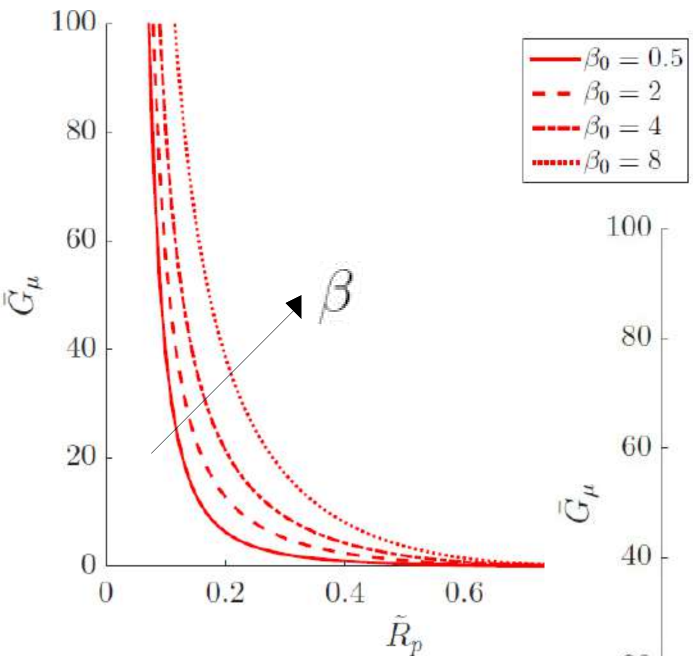
Nucleus stiffness

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

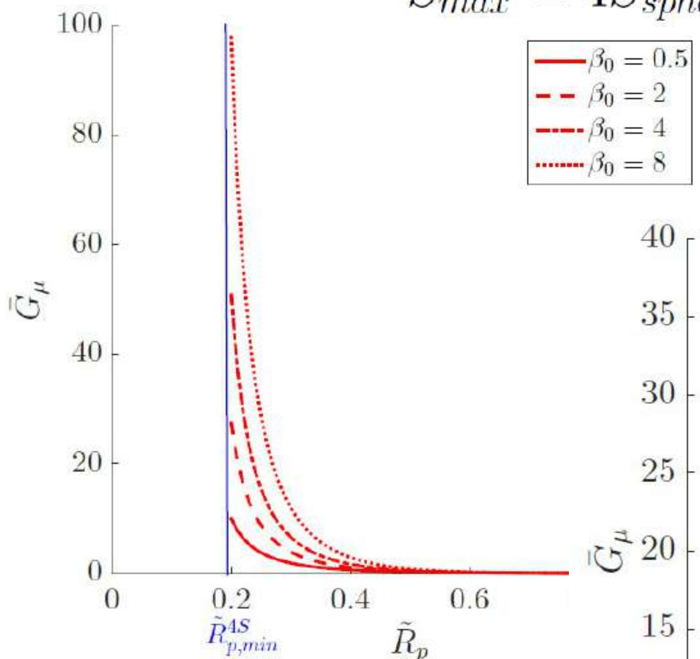


Effect of nuclear membrane

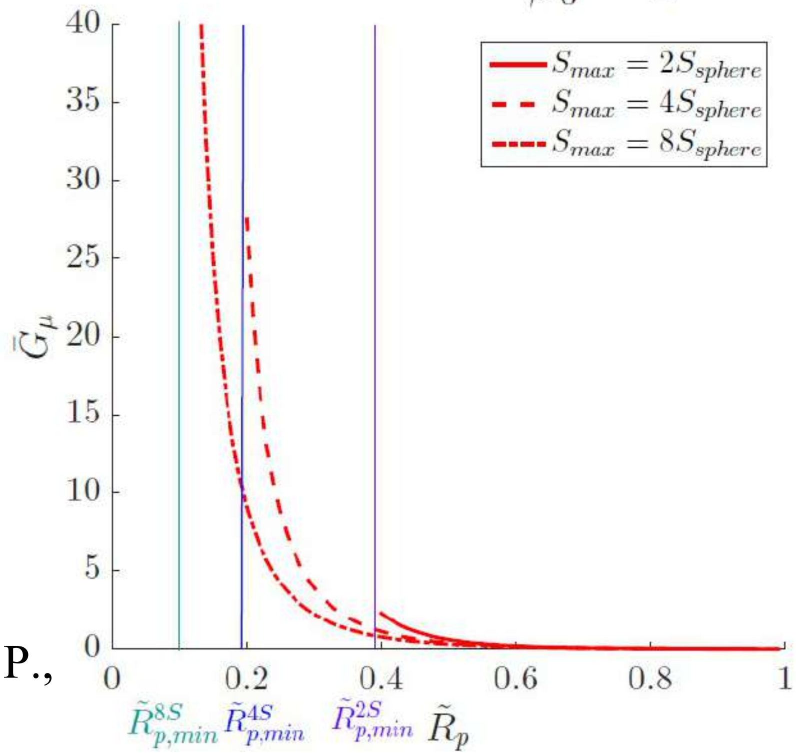
$$\lambda(\Delta S) = \lambda_0 \left(\frac{\Delta S}{S_{max} - S} \right)$$



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



$$\beta_0 = 2$$



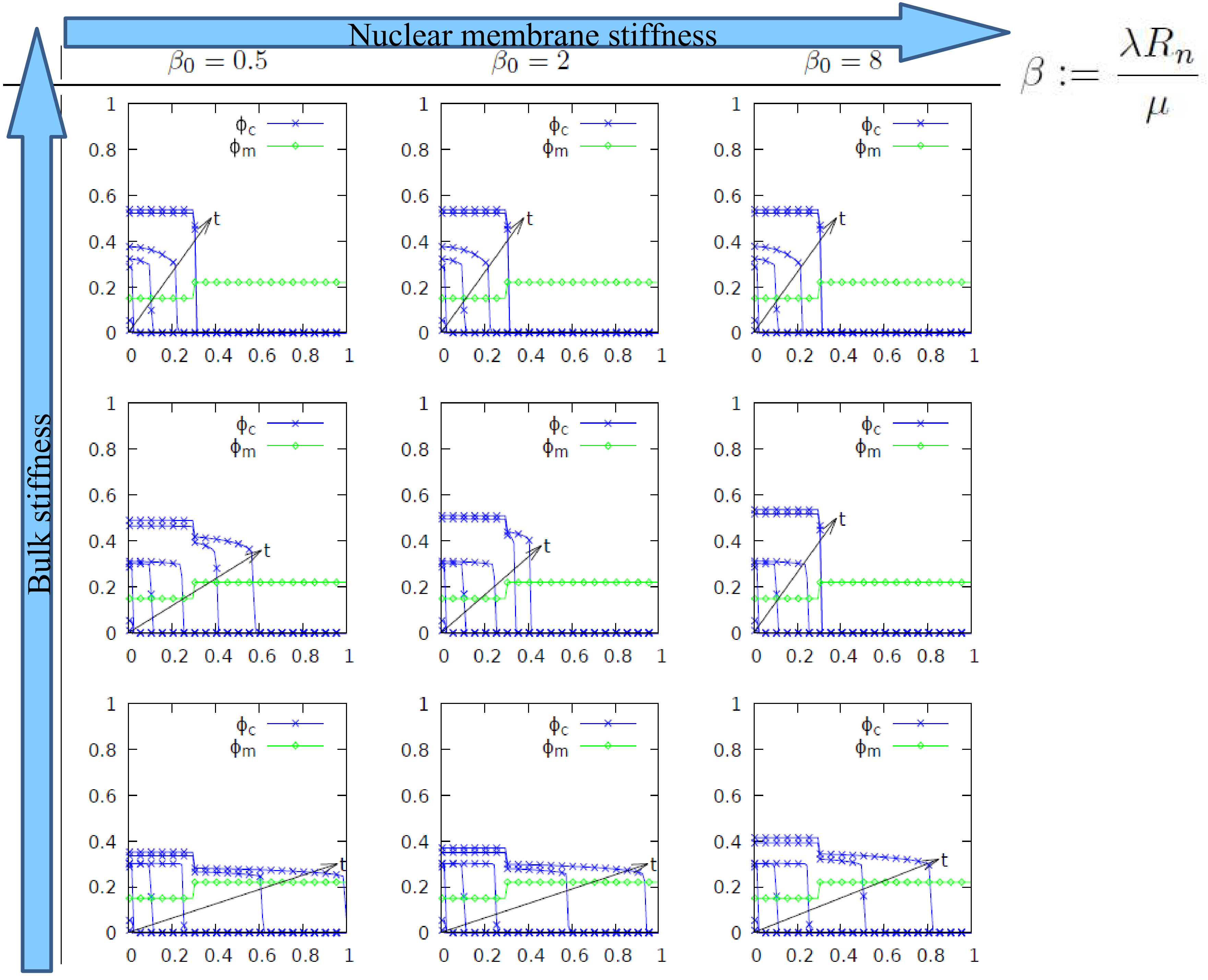
$$\tilde{R}_p = R_p / R_n$$

Membrane

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

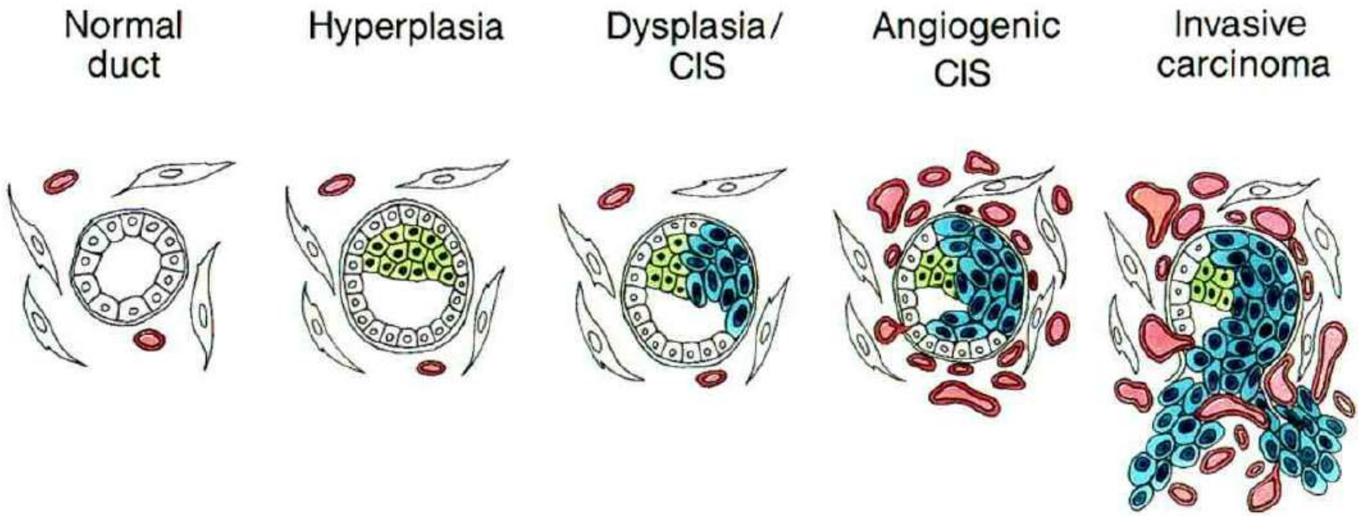
Nucleus

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



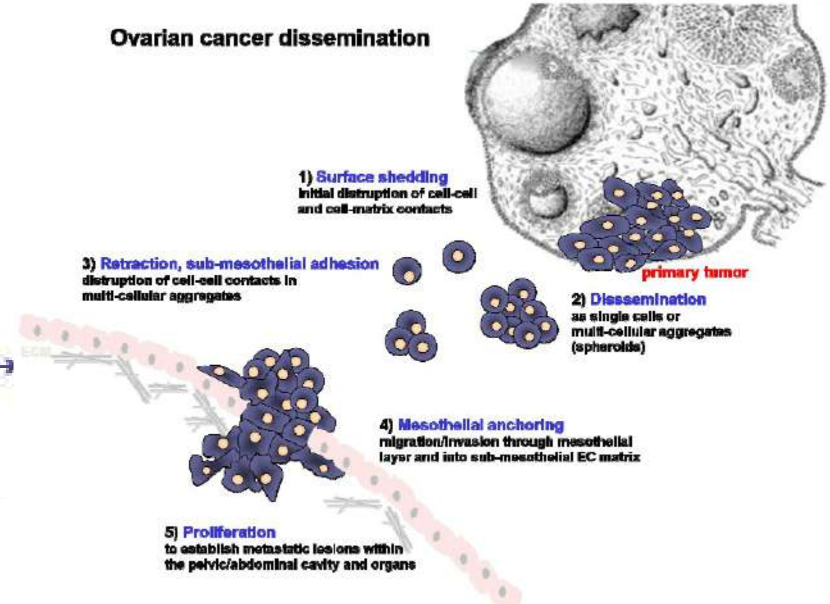
Nuclear membrane stiffness
Bulk stiffness
$\beta_0 = 0.5$
$\beta_0 = 2$
$\beta_0 = 8$
$\beta := \frac{\lambda R_n}{\mu}$
ϕ_c
ϕ_m
t

Compartimentalization or invasion

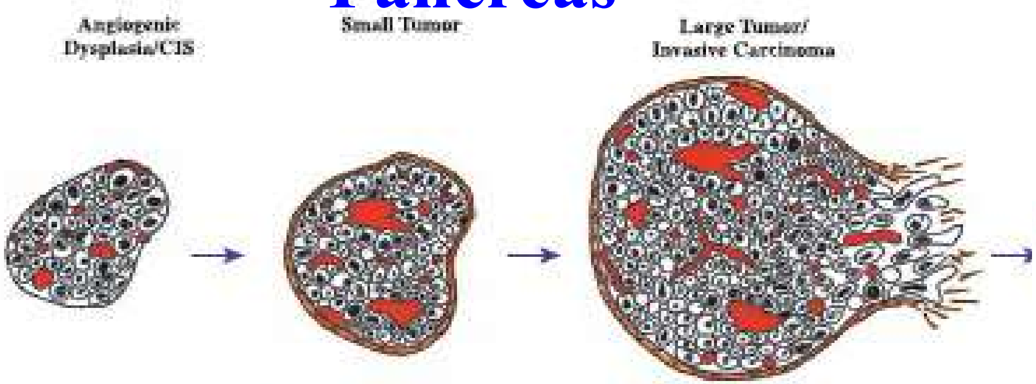


Breast

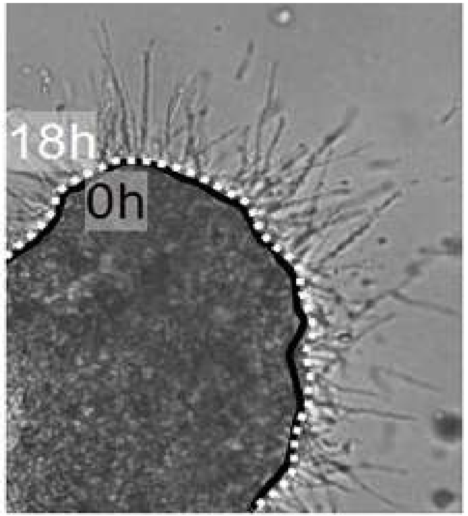
Ovary



Pancreas



Transfer to continuous models



$$\begin{cases} \dfrac{\partial \phi_c}{\partial t} + \nabla \cdot (\phi_c \mathbf{v}_c) = \Gamma_c \\[2ex] \nabla \cdot \mathbb{T}_c + \mathbf{m}_{cm} = \mathbf{0} \end{cases}$$

Growth

Stress

$$-\Sigma(\phi_c)\mathbb{I}$$

Cellular (solid) pressure

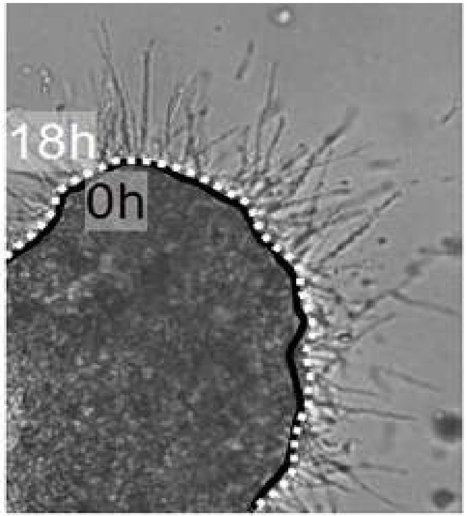
Interaction force

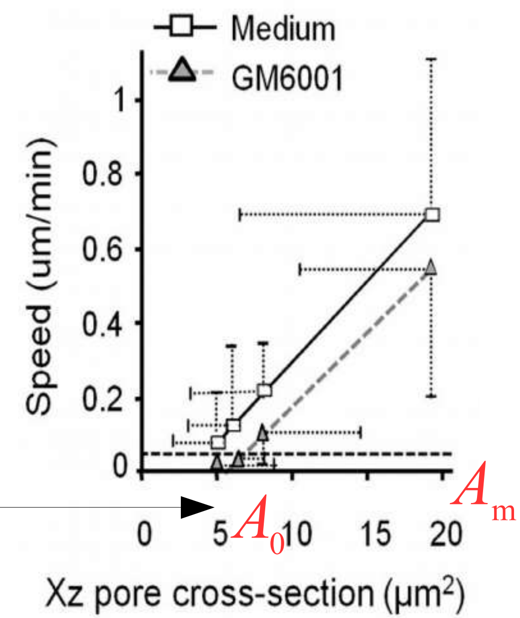
$$-\mathbb{M}_c^{-1}(\mathbf{v}_c - \cancel{\mathbf{v}_m})$$

Motility tensor

$$\mathbf{v}_c = -\mathbb{M}_c \nabla \Sigma$$

Transfer to continuous models





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

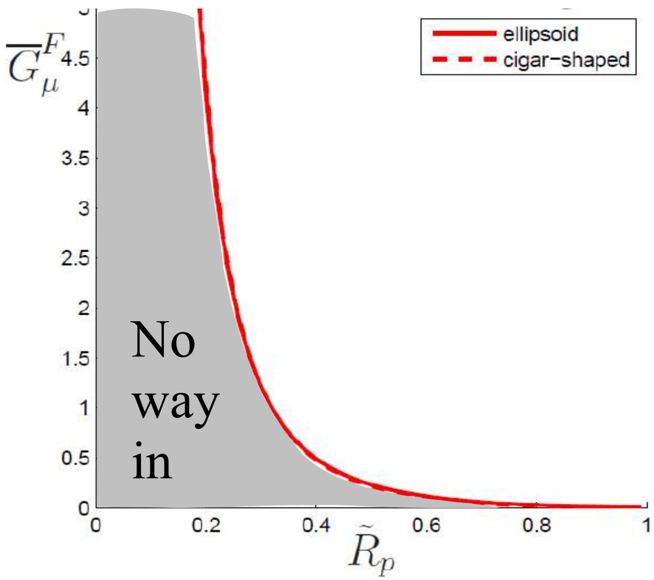
A_0 depends on:

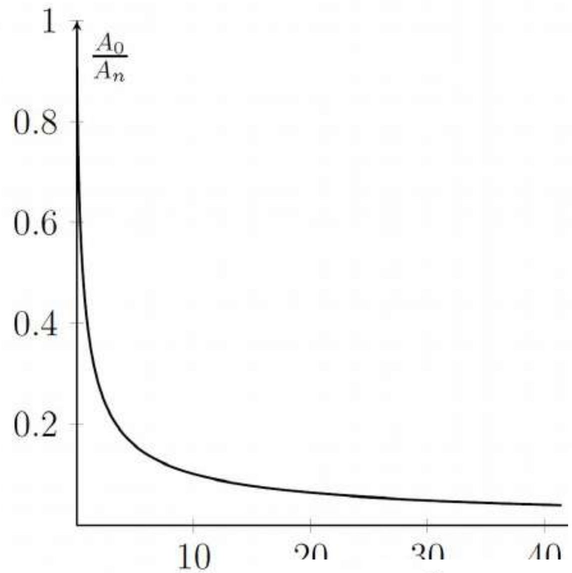
- **Pore vs. nucleus size**
- **Nucleus elasticity**
- **Cell adhesion**
- **Active traction**

$$\mathbb{M}_c \quad \alpha \frac{[A_m(\phi_m) - A_0]_+}{\left(1 + \frac{A_m(\phi_m) - A_0}{A_1}\right)^n} \mathbb{I}$$

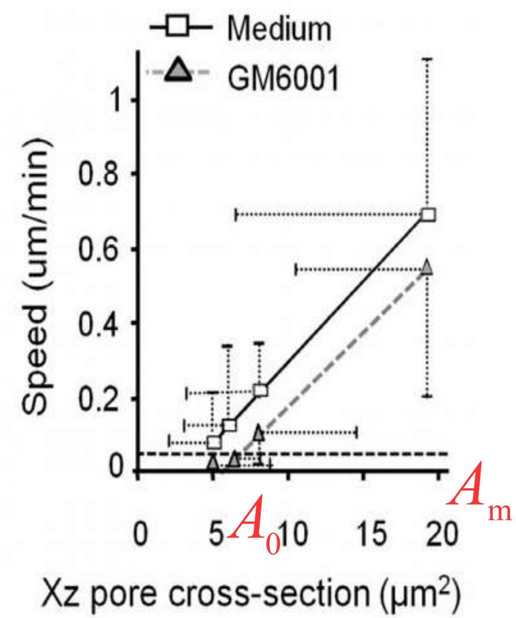
Use in a continuous models

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





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



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

A_0 depends on:

- **Pore vs. nucleus size**
- **Nucleus elasticity**
- **Cell adhesion**
- **Active traction**

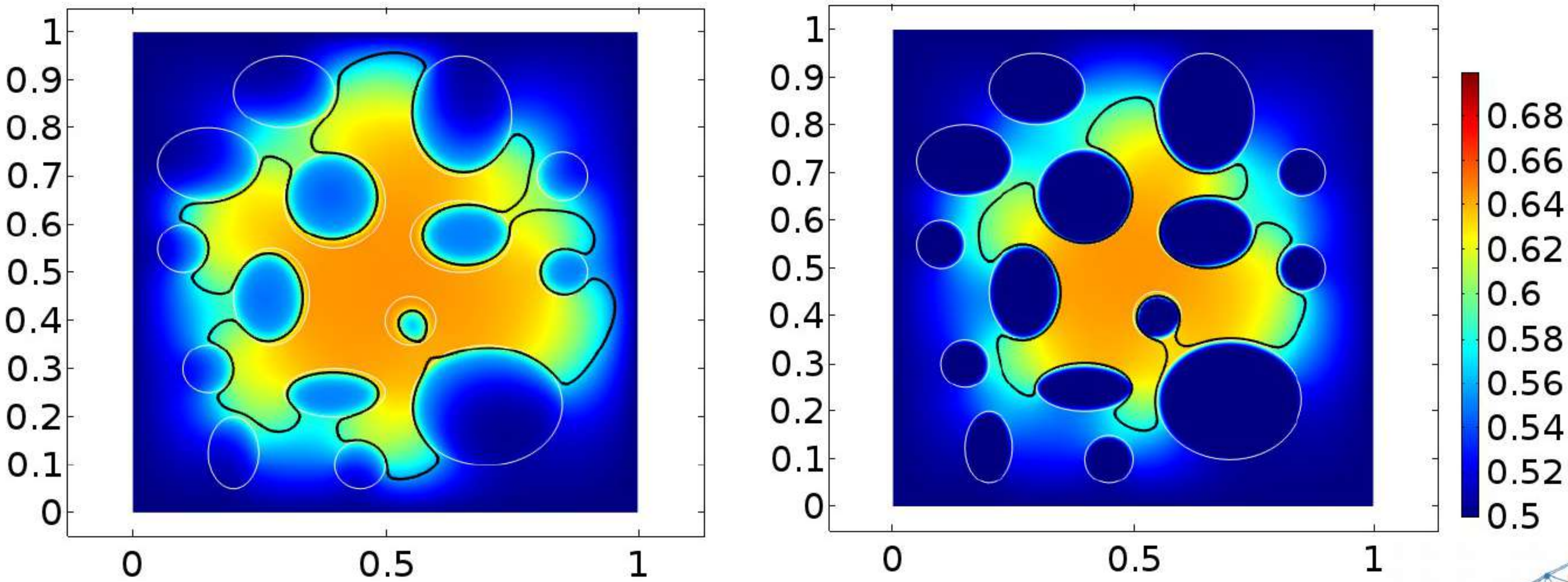
$$\frac{\partial \phi_c}{\partial t} = \nabla \cdot (\phi_c \mathbb{M}_c \nabla \Sigma) + G_c$$

$$\mathbb{M}_c = \alpha \frac{[A_m(\phi_m) - A_0]_+}{\left(1 + \frac{A_m(\phi_m) - A_0}{A_1}\right)^n}$$

Growth in heterogeneous environments

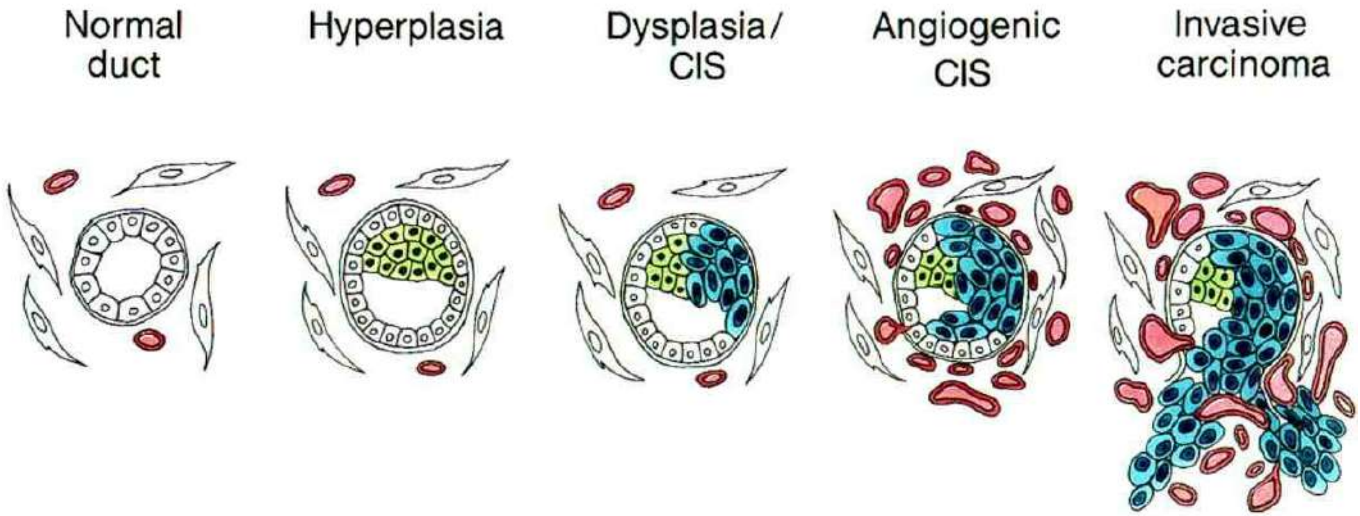
$$\begin{cases} \dfrac{\partial \phi_{c_i}}{\partial t} + \nabla \cdot (\phi_{c_i} \mathbf{v}_{c_i}) = \Gamma_{c_i} \\ \mathbf{v}_{c_i} = \alpha \dfrac{[A_m(\phi_m) - A_0^i]_+}{\left(1 + \frac{A_m(\phi_m) - A_0^i}{A_1}\right)^n} \nabla \cdot \mathbf{T}_c \end{cases}$$

$$\left[\gamma_c^i \mathcal{H}_\varepsilon(\psi_0^i - \psi) - \delta_c^i\right] \phi_c^i$$

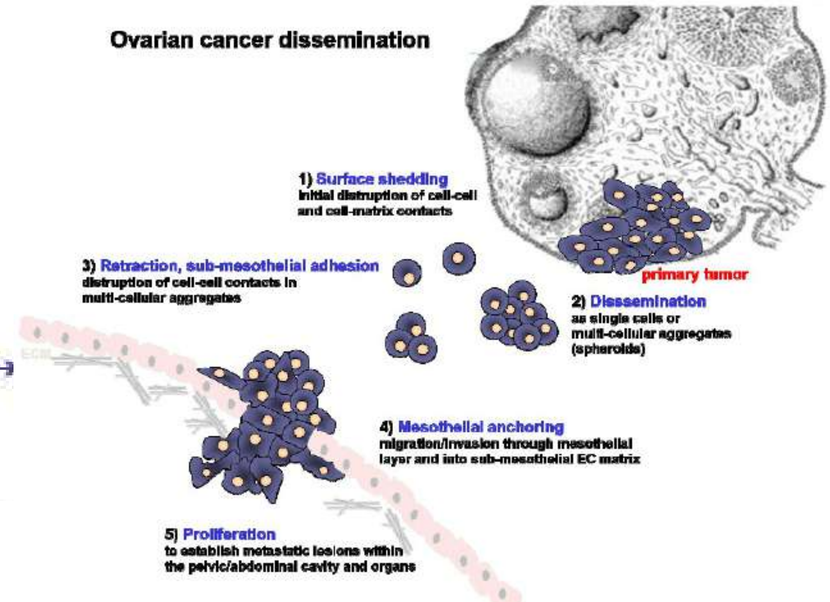


Compartimentalization or invasion

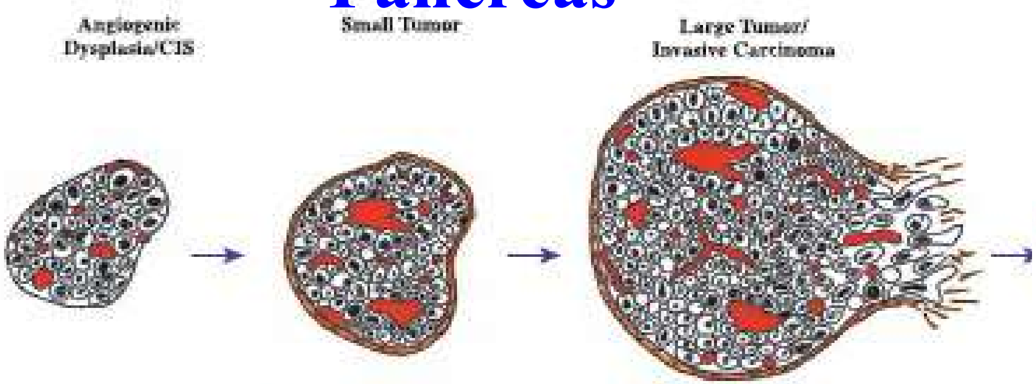
Breast



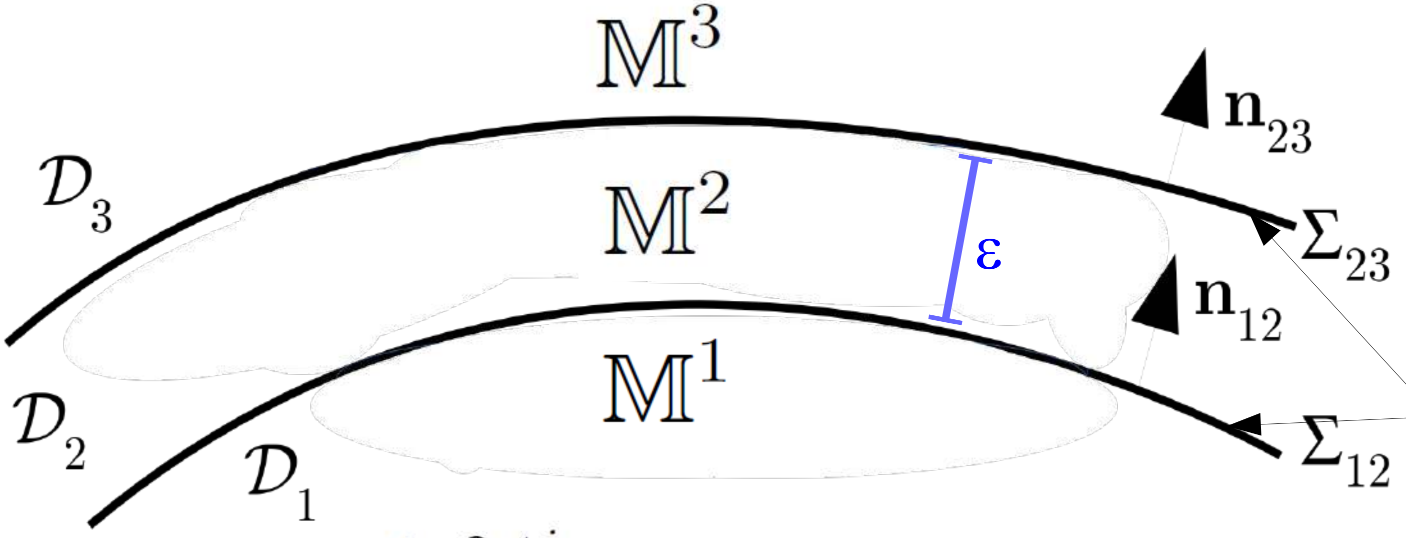
Ovary



Pancreas



Basal membranes



$$\begin{cases} [\![\phi_c \mathbf{v}_c \cdot \mathbf{n}]\!] = 0 \\ [\![\Sigma]\!] = 0 \end{cases}$$

$$\begin{cases} \dfrac{\partial \phi_c^i}{\partial t} + \nabla \cdot (\phi_c^i \mathbf{v}_c^i) = \Gamma_c^i \\ \mathbf{v}_c^i = -\mathbb{M}^i \nabla \Sigma(\phi_c^i) \end{cases}$$

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

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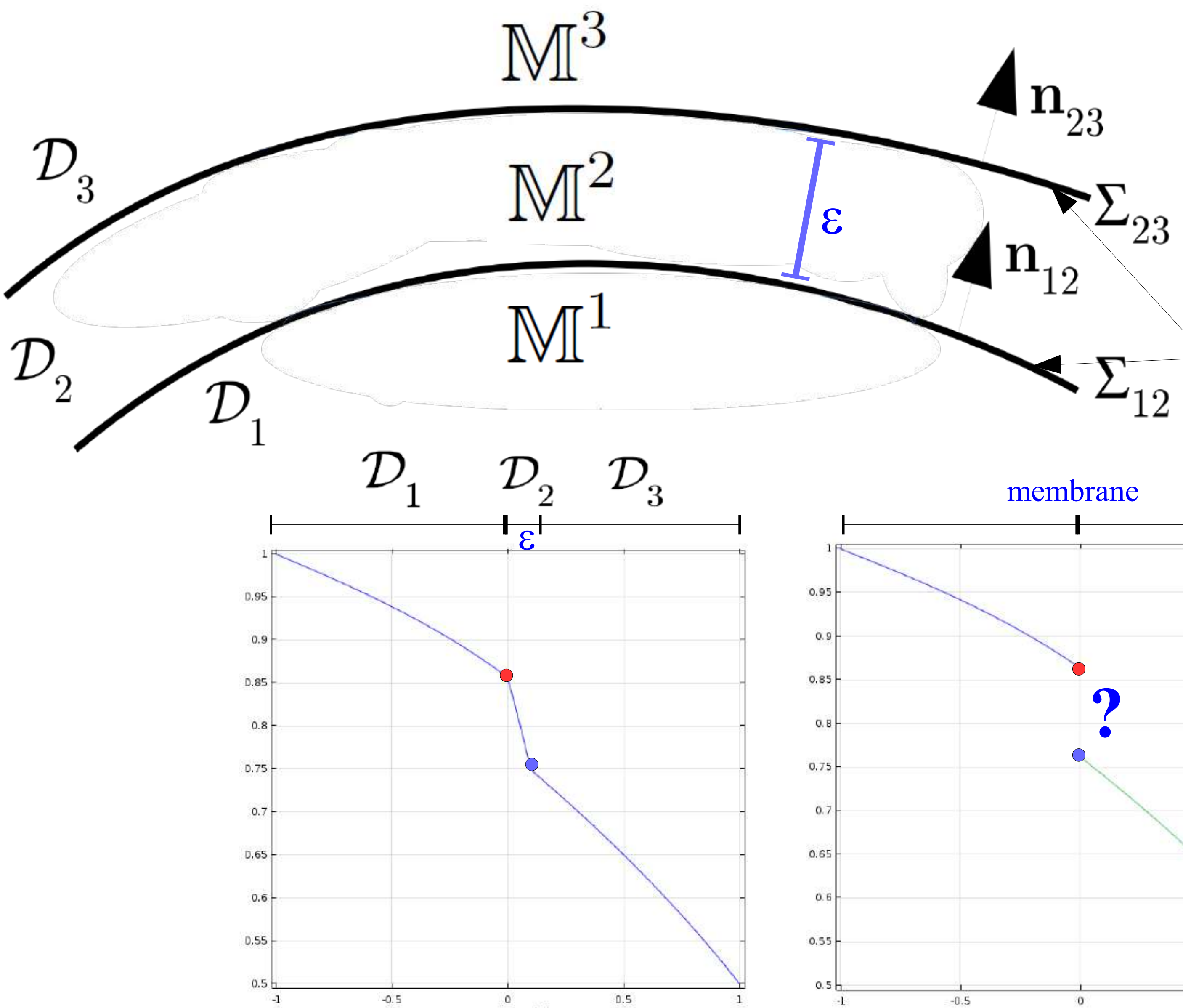
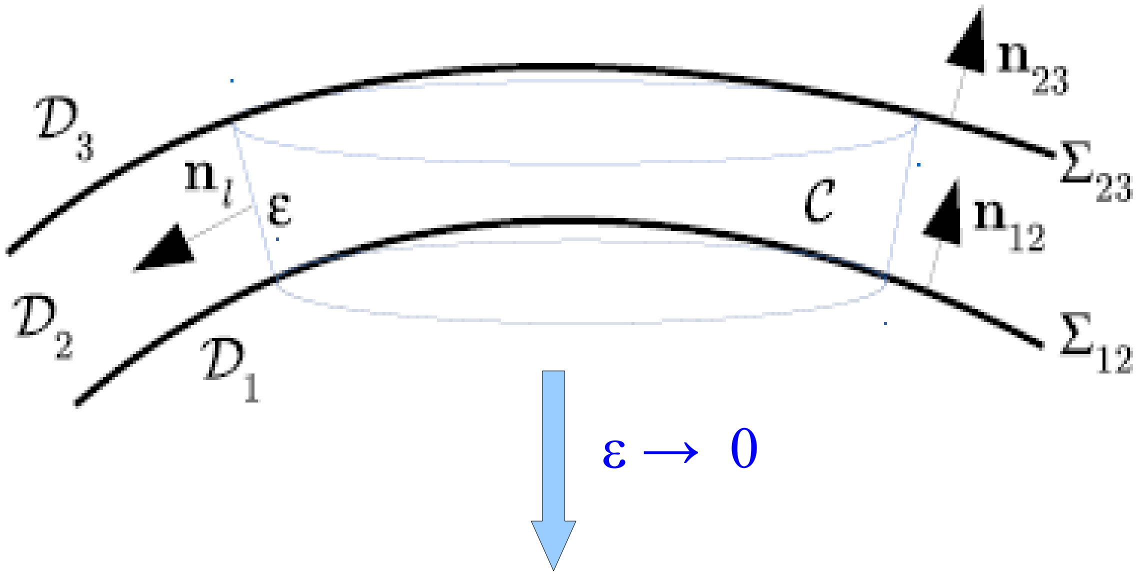
Basal membranes



$$\begin{cases} [\![\mathbb{M}\nabla\phi_c \cdot \mathbf{n}]\!] = 0 \\ [\![\phi_c]\!] = 0 \end{cases}$$

Basal membranes

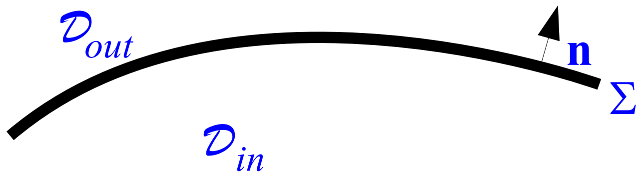


$$\phi_c^1 M^1 \nabla\Sigma(\phi_c^1)\cdot\mathbf{n} = \phi_c^3 M^3 \nabla\Sigma(\phi_c^3)\cdot\mathbf{n} = M_\sigma [\![\Pi]\!]$$

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

$$M_\sigma = \lim_{\varepsilon\to 0}\frac{M^2}{\varepsilon}$$

Interface problem



$$\begin{cases} \dfrac{\partial \phi_c}{\partial t} = \nabla \cdot [\phi_c M_{cm} \nabla \Sigma(\phi_c)] + \Gamma_c \\ [\![\phi_c M_{cm} \nabla \Sigma(\phi_c) \cdot \mathbf{n}]\!] = 0 \qquad \text{on } \Sigma \\ M_\sigma [\![\Pi]\!] = \phi_c M_{cm} \nabla \Sigma(\phi_c) \cdot \mathbf{n} \qquad \text{on } \Sigma \end{cases}$$

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

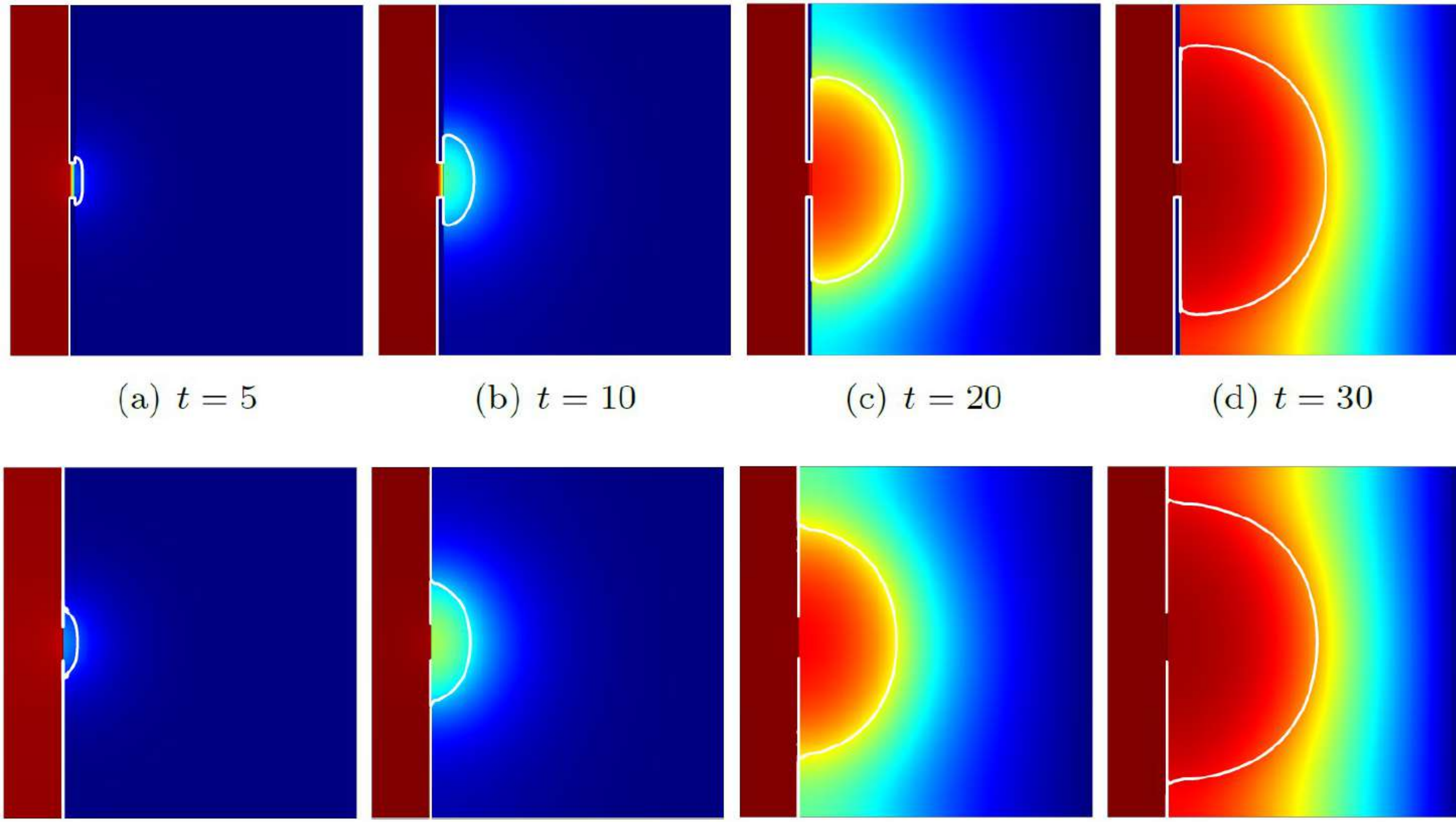
---

if $\Sigma(\phi_c) = A \ln \dfrac{\phi_c}{\phi_0} \longrightarrow \phi_c \Sigma'(\phi_c) = A \longrightarrow \Pi = A\, \phi_c$

$$\longrightarrow M_\sigma [\![\phi_c]\!] = M_{cm} \nabla \phi_c \cdot \mathbf{n}$$

Kedem-Katchalsky interface condition

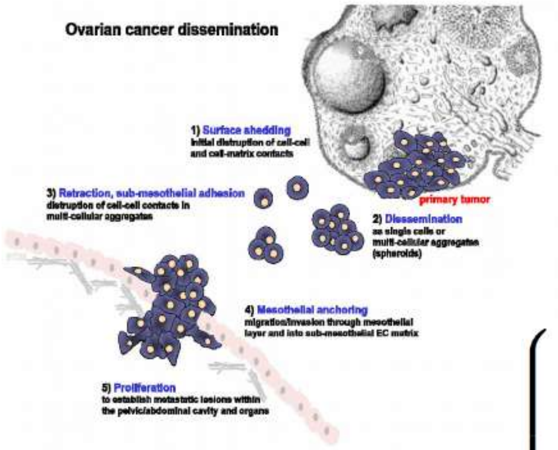
Invasion through a duct wall



(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



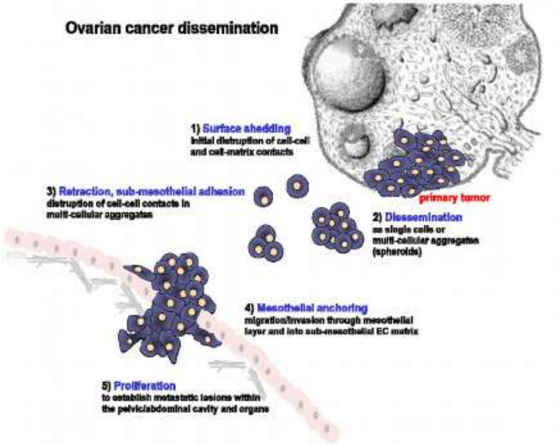
Adding tumour produced metallo-proteinases

$$
\begin{cases}
\dfrac{\partial c_i}{\partial t} = \gamma_c \, \rho_i H(\varphi) + D_c \, \Delta c_i & \text{in } \mathcal{D}_i, \quad i = 1,2,3, \\[2ex]
D_c \nabla c_i \cdot \mathbf{n}_{ij} = D_c \nabla c_j \cdot \mathbf{n}_{ij} & \text{on } \Sigma_{ij}, \quad i = 1,2, \quad j = i+1, \\[2ex]
c_i = c_j & \text{on } \Sigma_{ij}, \quad i = 1,2, \quad j = i+1.
\end{cases}
$$

$$
\mu_{23}[\hat{c}](t,\mathbf{x}) := \bar{\mu}_{23} \frac{(\hat{c}(t,\mathbf{x}) - 1)_+}{K_c + (\hat{c}(t,\mathbf{x}) - 1)},
$$

$$
\hat{c}(t,\mathbf{x}) = \frac{\beta}{\alpha(A_0 - A_1)} \, c(t,\mathbf{x})
$$

Invasion of ovary cancer cells

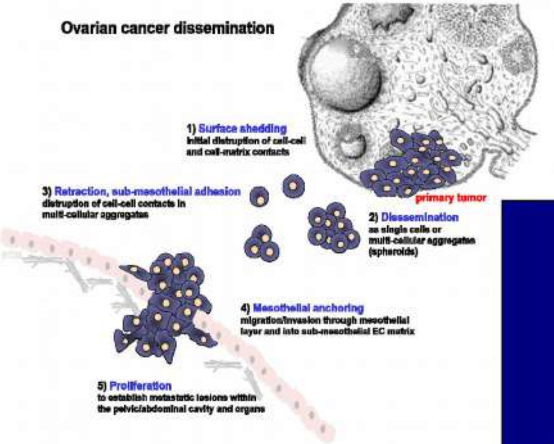


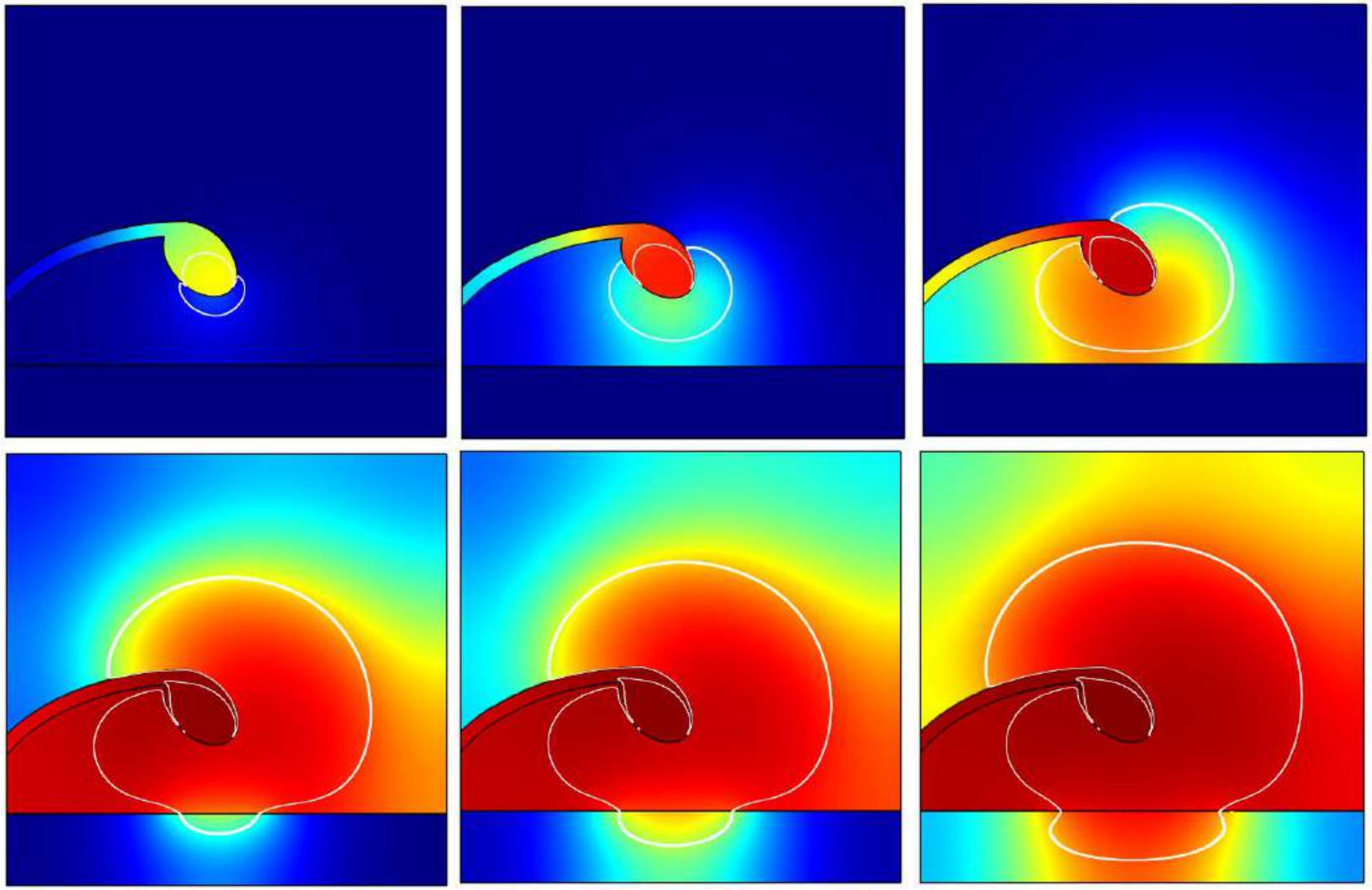
Adding tumour produced metallo-proteinases

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

$$M_\sigma = \bar{M}_\sigma \frac{[A - A_0]_+}{1 + (A - A_0)}$$

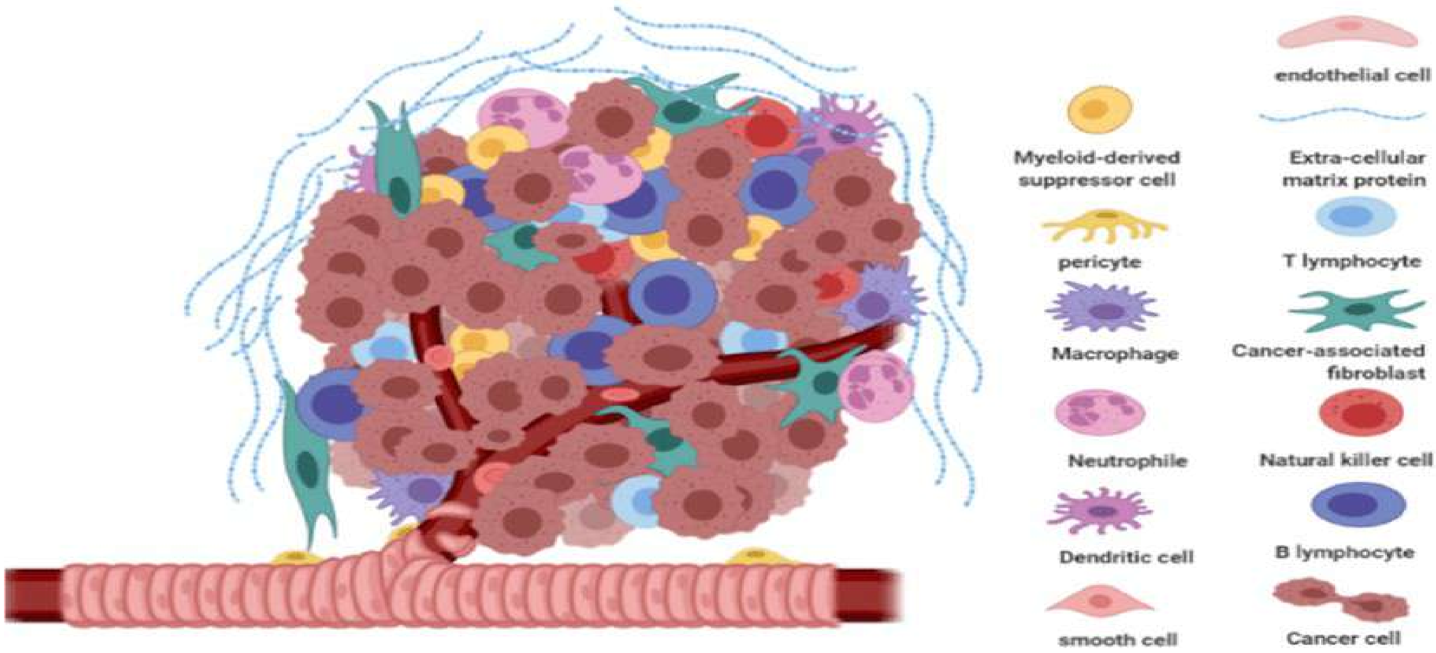
Invasion of ovary cancer cells





More populations

$$\begin{cases} \dfrac{\partial \phi_{c_i}}{\partial t} + \nabla \cdot (\phi_{c_i} \mathbf{v}_{c_i}) = \Gamma_{c_i} \\ \mathbf{v}_{c_i} = -\mathbb{M}_{c_i m} \nabla \Sigma \quad \text{with } \Sigma = \Sigma(\phi_{c_i}, \Phi_c) \qquad \Phi_c = \sum_i \phi_{c_i} \end{cases}$$



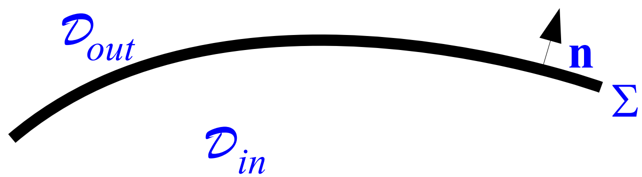
More populations

$$\begin{cases} \dfrac{\partial \phi_{c_i}}{\partial t} + \nabla \cdot (\phi_{c_i} \mathbf{v}_{c_i}) = \Gamma_{c_i} \\ \mathbf{v}_{c_i} = -\mathbb{M}_{c_i m} \nabla \Sigma \quad \text{with } \Sigma = \Sigma(\cancel{\phi_{c_i}}, \Phi_c) \qquad \Phi_c = \sum_i \phi_{c_i} \end{cases}$$

All velocities are "proportional"

If $\mathbb{M}_{c_i m} = \mathbb{M}_{cm}$ and $\Sigma = \Sigma(\Phi_c)$ $\longrightarrow$ $\mathbf{v}_{c_i} = \mathbf{v}_c$

Two populations



If $M_\sigma^1, M_\sigma^2 \neq 0$

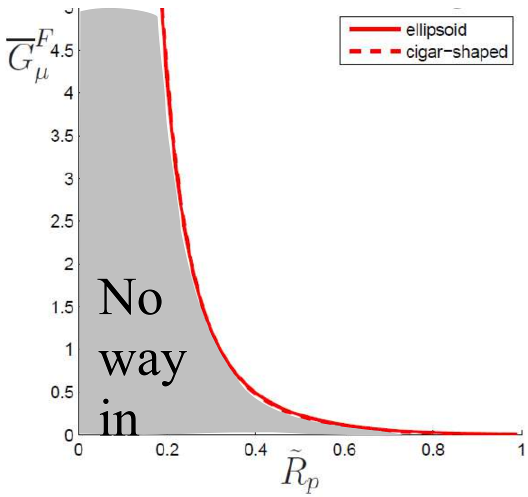
$$
\begin{cases}
\dfrac{\partial \phi_c^n}{\partial t} = \nabla \cdot [\phi_c^n M_{cm}^n \nabla \Sigma(\Phi_c)] + \Gamma_c^n \\[2ex]
[\![\phi_c^n M_{cm}^n \nabla \Sigma(\Phi_c) \cdot \mathbf{n}]\!] = 0 \qquad \text{on } \Sigma \\[2ex]
[\![\Pi]\!] = \left(\phi_c^1 \dfrac{M_{cm}^1}{M_\sigma^1} + \phi_c^2 \dfrac{M_{cm}^2}{M_\sigma^2} \right) \nabla \Sigma(\Phi_c) \cdot \mathbf{n} \qquad \text{on } \Sigma
\end{cases}
$$

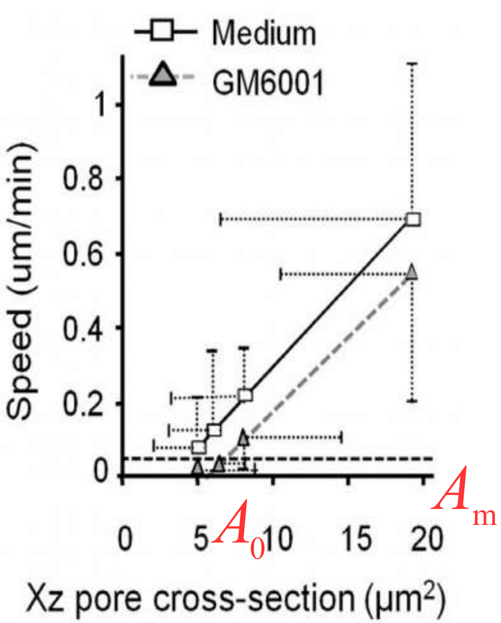
where $\Pi'(\Phi_c) = \Phi_c \Sigma'(\Phi_c)$

C. Giverso, T. Lorenzi, L.P., Appl. Math. Letters **125**, 107708 (2022)

Summary

Work done by traction > Energy required to squeeze the nucleus

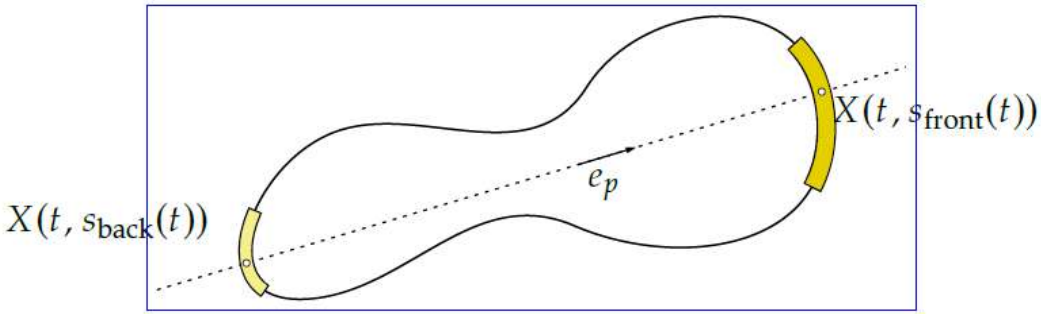


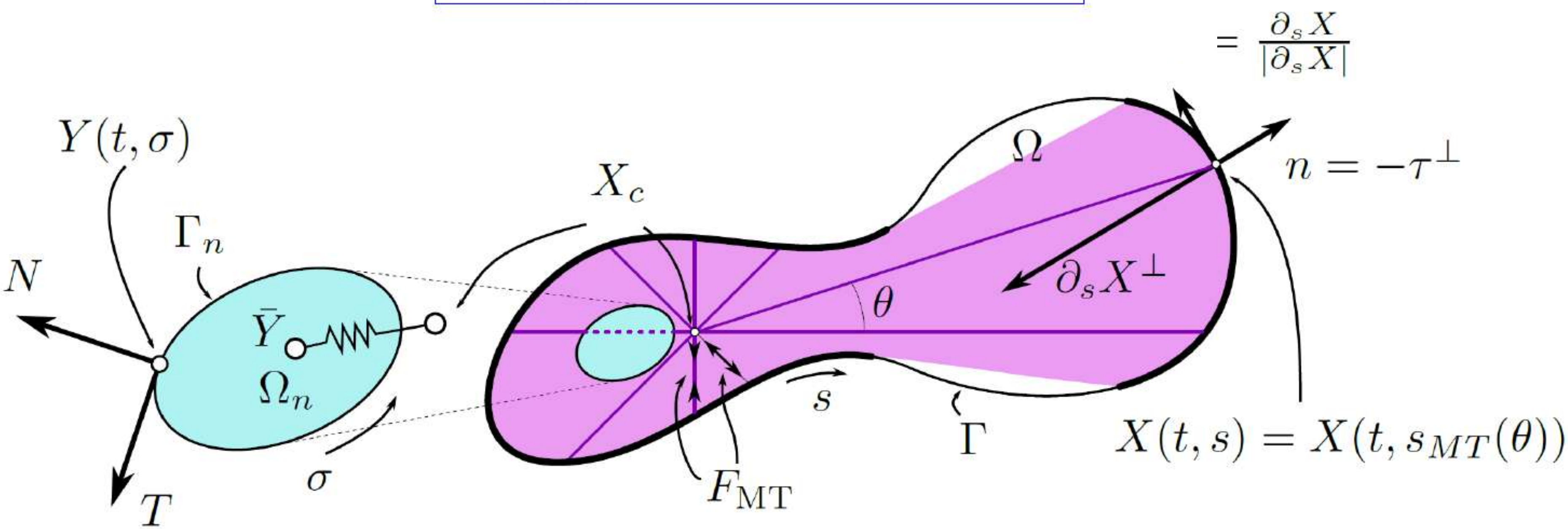


$$
\begin{cases}
\dfrac{\partial \phi_c}{\partial t} = \nabla \cdot [\phi_c M_{cm} \nabla \Sigma(\phi_c)] + \Gamma_c \\
[\![\phi_c M_{cm} \nabla \Sigma(\phi_c) \cdot \mathbf{n}]\!] = 0 \qquad \text{on } \Sigma \\
M_\sigma [\![\Pi]\!] = \phi_c M_{cm} \nabla \Sigma(\phi_c) \cdot \mathbf{n} \qquad \text{on } \Sigma
\end{cases}
$$

$$
\alpha \frac{[A_m(\phi_m) - A_0]_+}{\left(1 + \frac{A_m(\phi_m) - A_0}{A_1}\right)^n}
$$

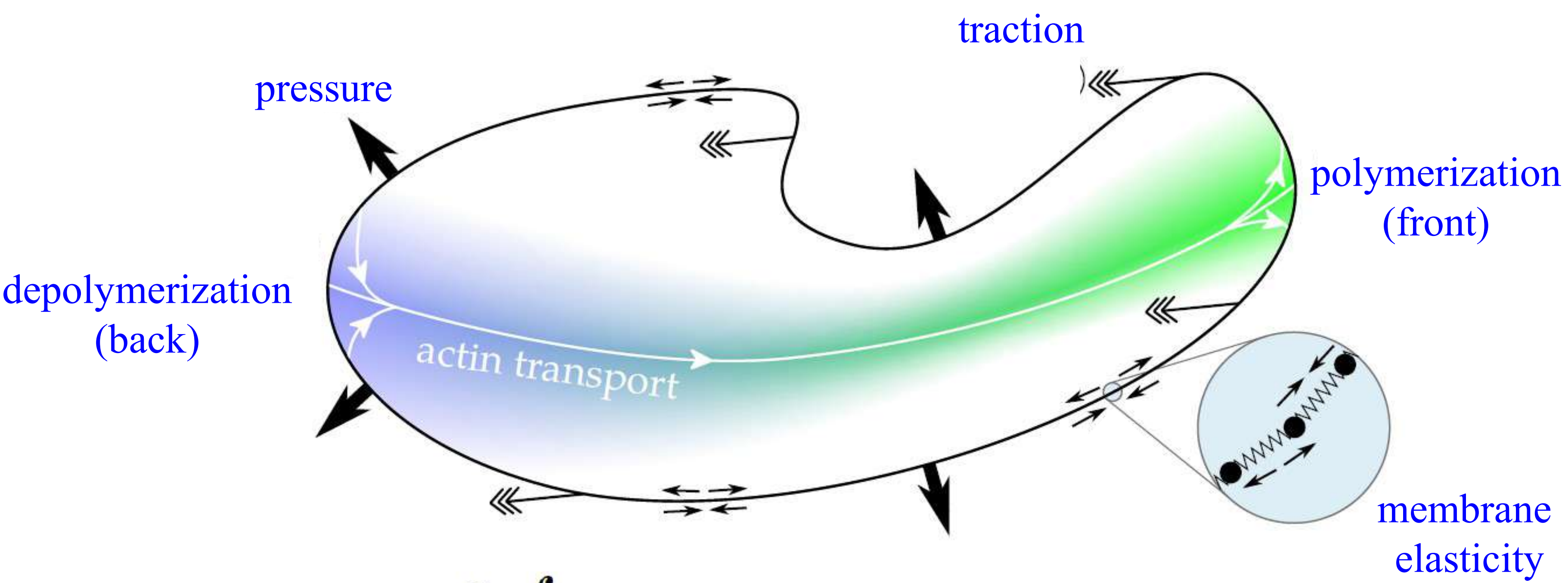
Single cell model





C. Giverso, G. Jankoviak, L. P., C. Schmeiser, BMB (2023)

Single cell model: cytosol

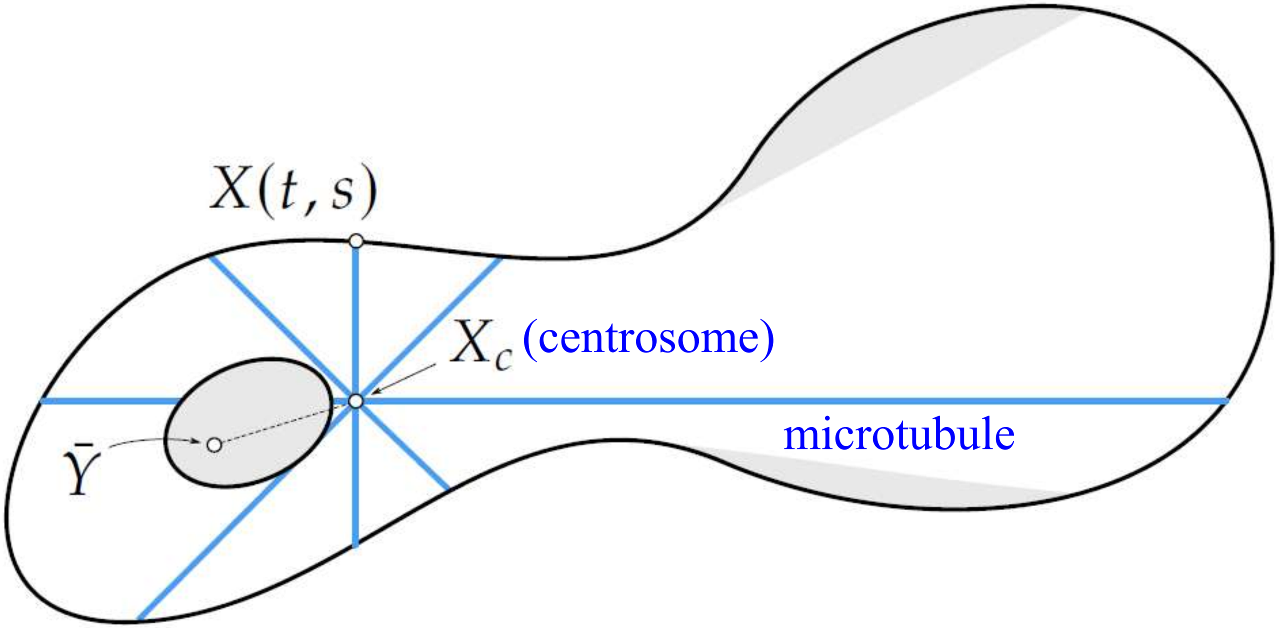


$$E_{\mathrm{p}}(X) = -p\,|\Omega(t)| = \frac{p}{2}\int_{\mathbb{T}^1} X\cdot\partial_s X^{\perp}\,ds$$ Cell pressure

$$E_{\mathrm{el}}(X) = \frac{1}{2}\int_{\mathbb{T}^1} (|\partial_s X| - 1)_+^2\,ds$$ Membrane elasticity

$$E_{\mathrm{obst},\delta}(X) = \int_{\mathbb{T}^1} W_\delta(X)ds$$ Cell-wall interactions

Single cell model: the nucleus



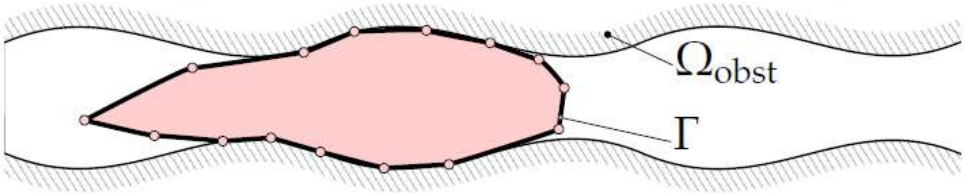
Bending stiffness

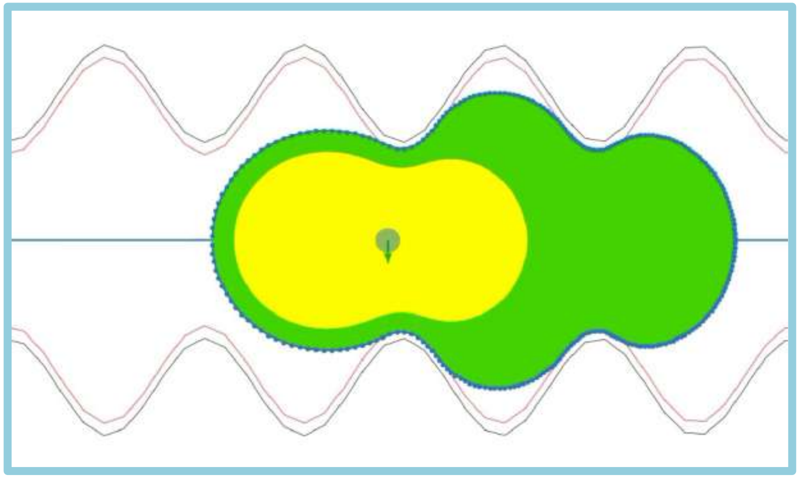
Pressure

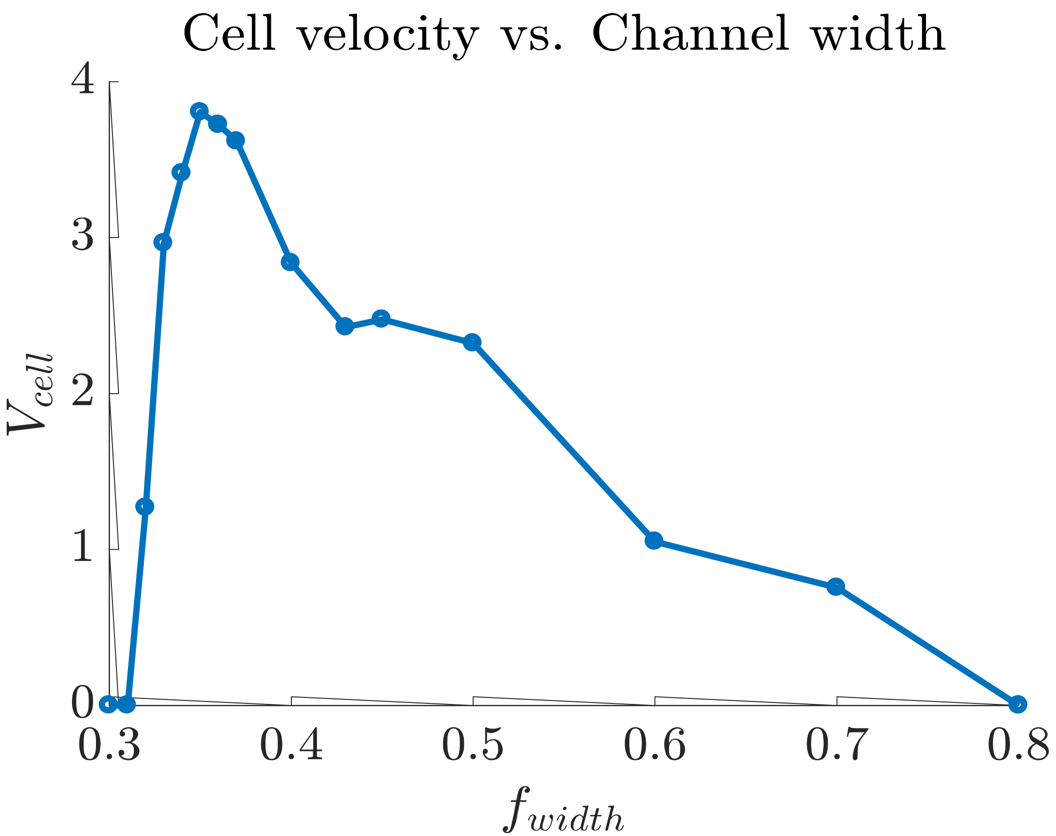
$$E_n = \frac{k_b}{2}\int_{\Gamma_n} \kappa^2 \,\mathrm{d}\ell + \int_{\Gamma_n} W_n(Y(\ell))\,\mathrm{d}\ell + \Delta p_n \int_{\Omega_n} \mathrm{d}A$$

The potential W_n encodes elasticity and the interactions with cortex and centrosome.

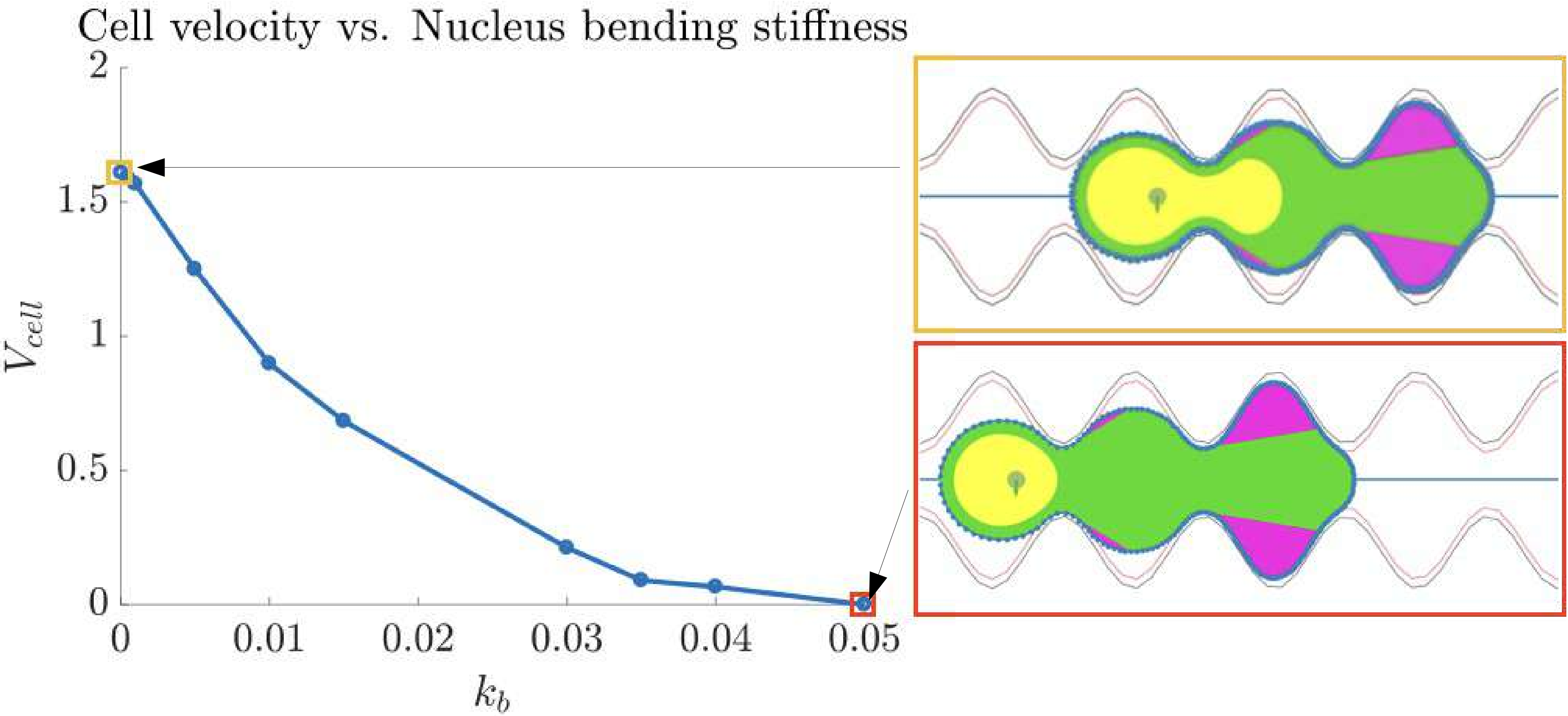
Simulations



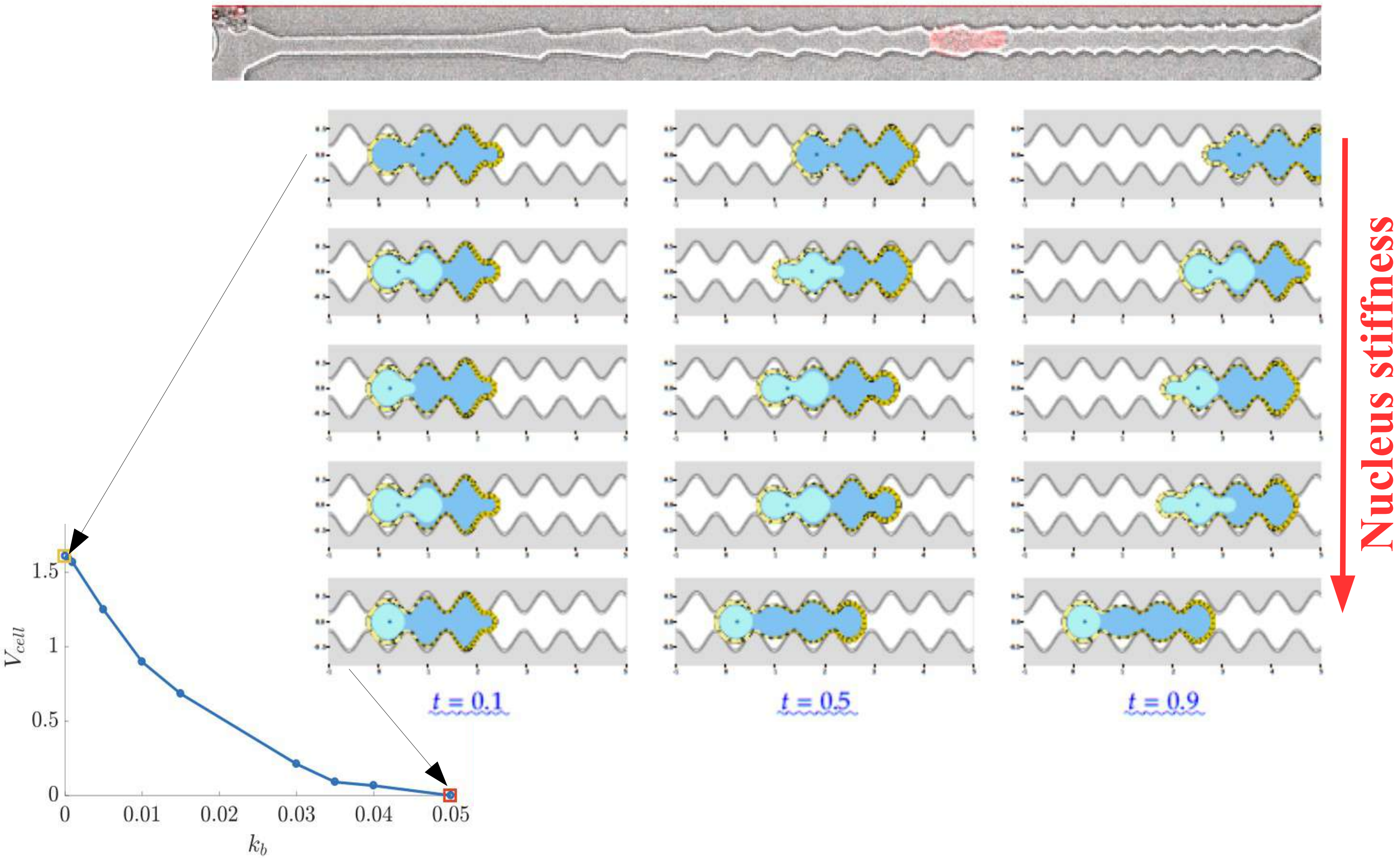




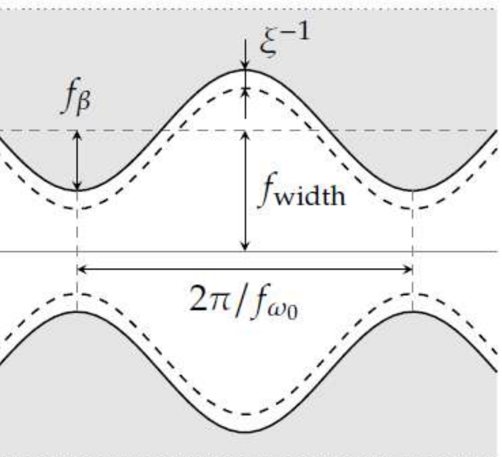
Simulations

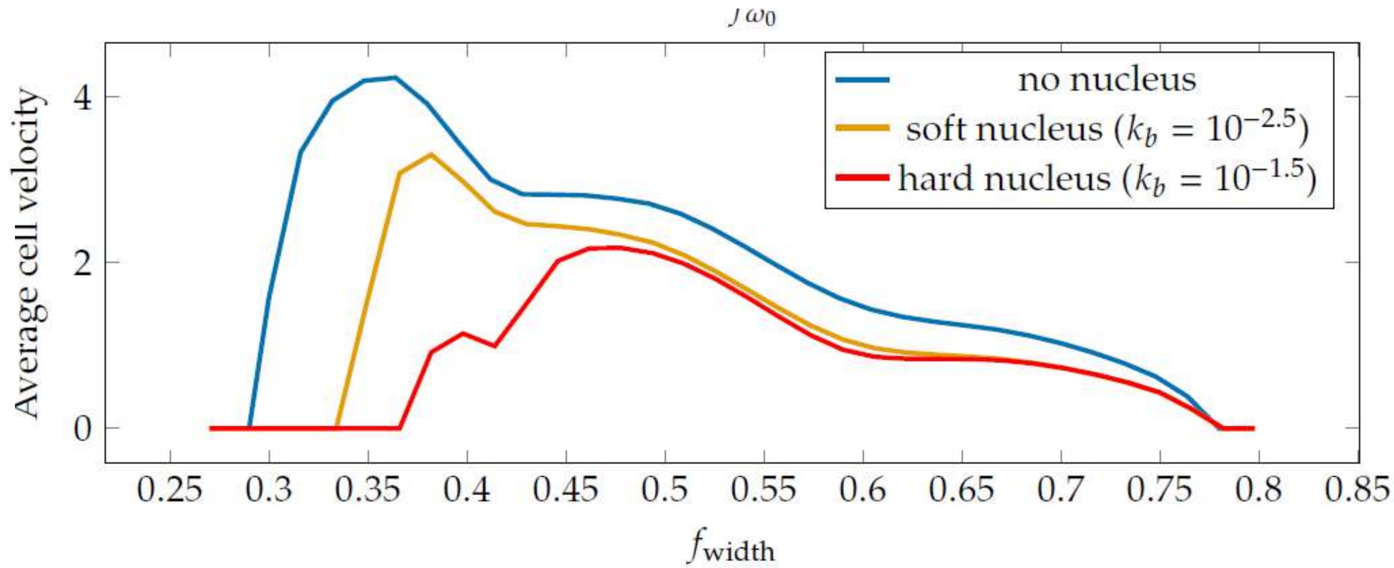


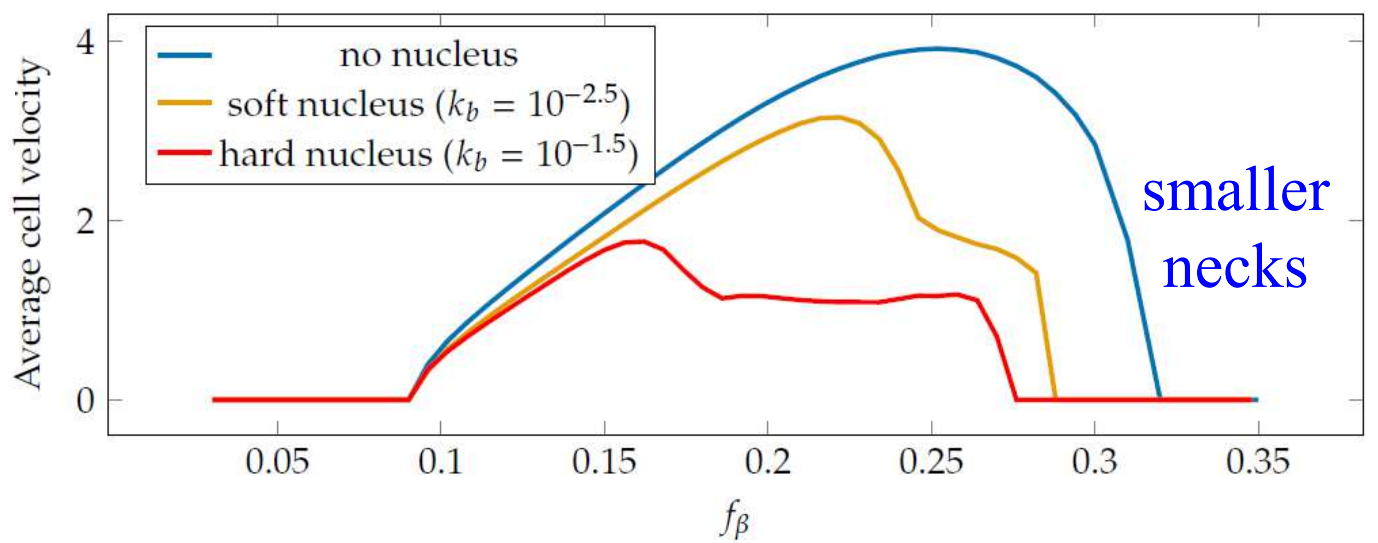
Simulations



Simulations

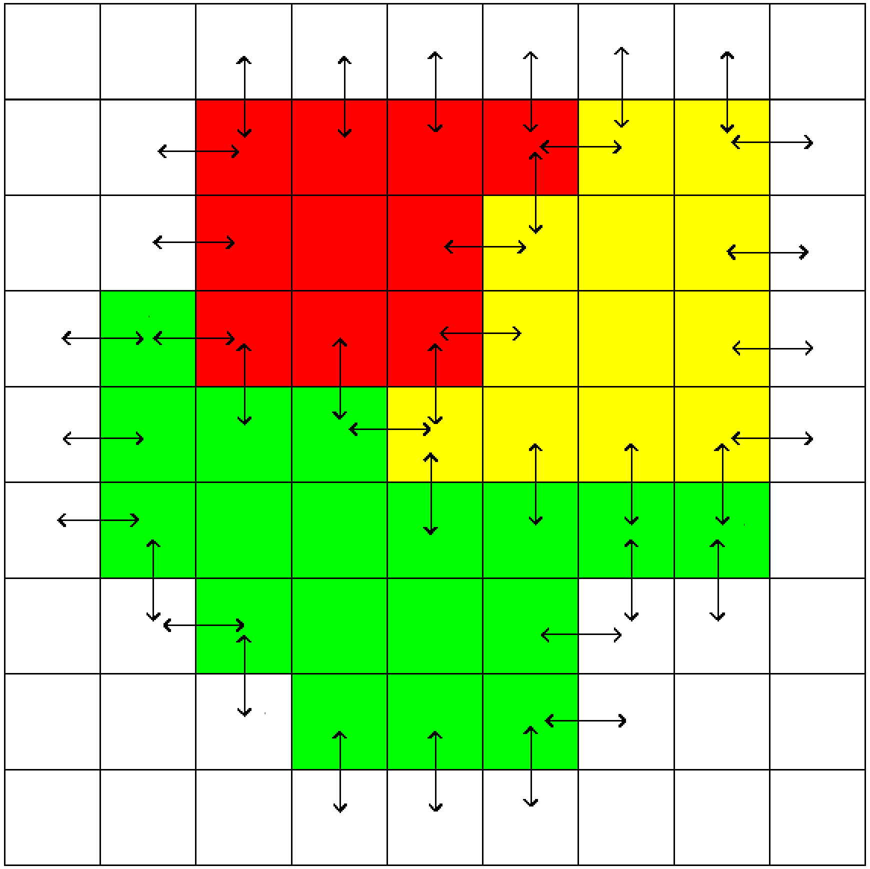






The cellular Potts model

A cell is represented by several nodes



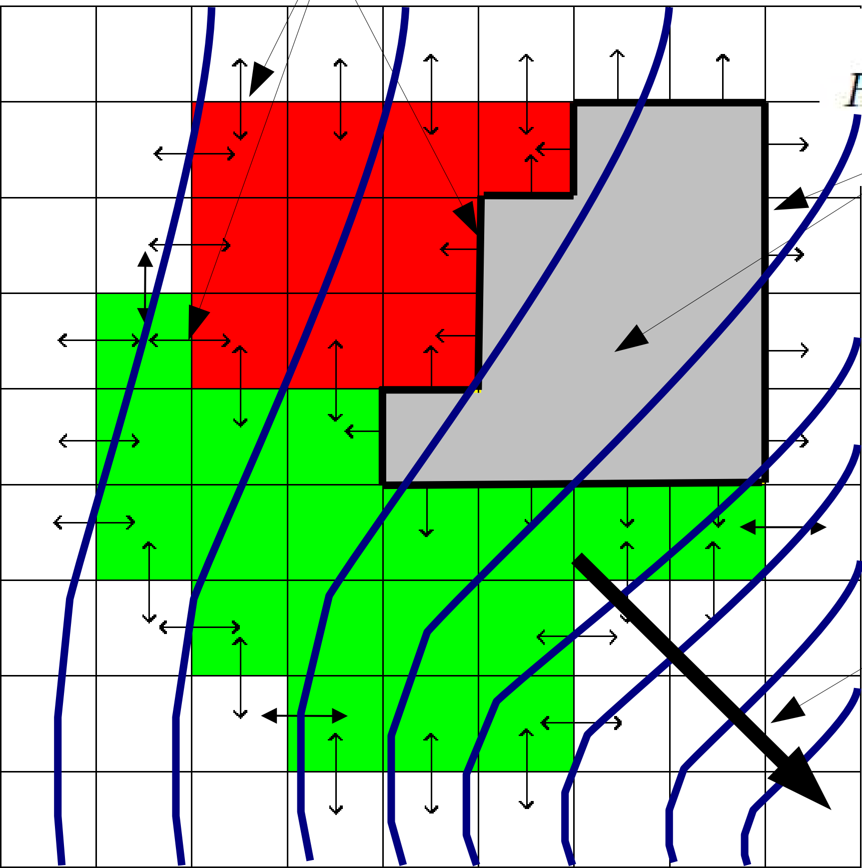
- Based on a generalized energy H

- Evolution stochastically tries to minimize the system energy

The cellular Potts model

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

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

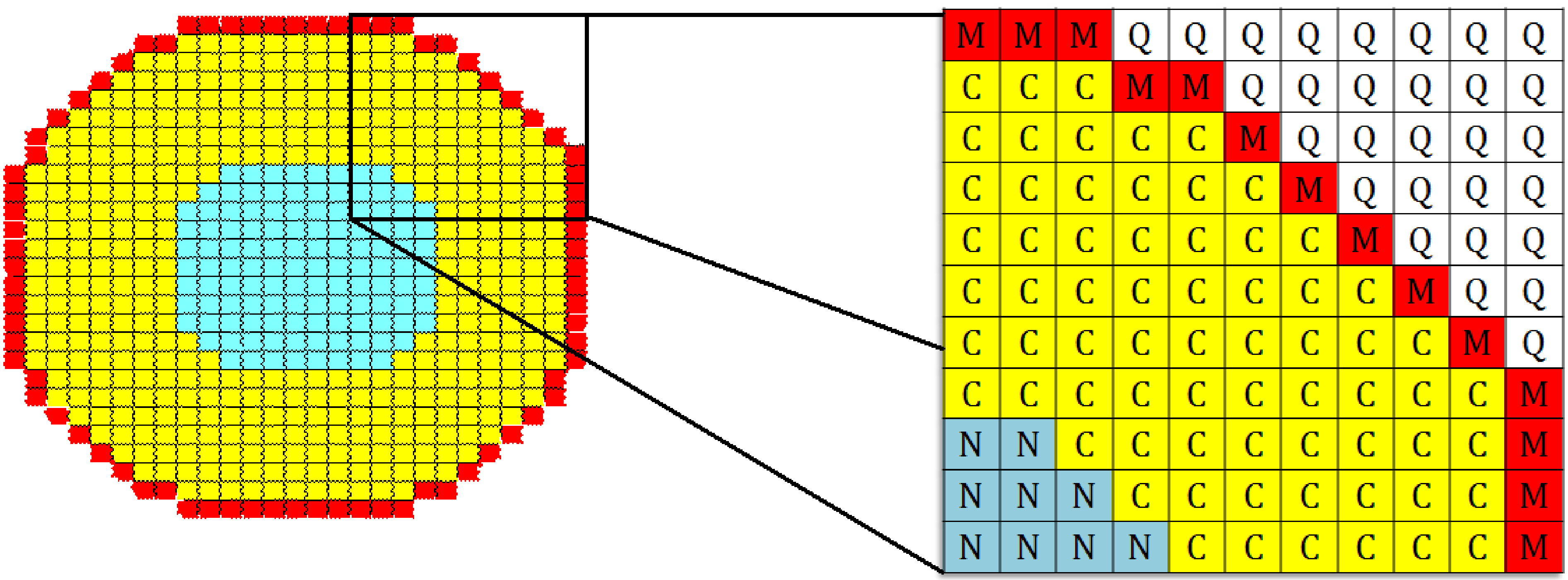


$$H_{attribute}(t) = \sum_{\eta,\sigma,i-attribute} \lambda^i_{\eta,\sigma}(t)\left|\frac{a^i_{\eta,\sigma}(t)-A^i_{\eta,\sigma}(t)}{a^i_{\eta,\sigma}(t)}\right|^p.$$

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

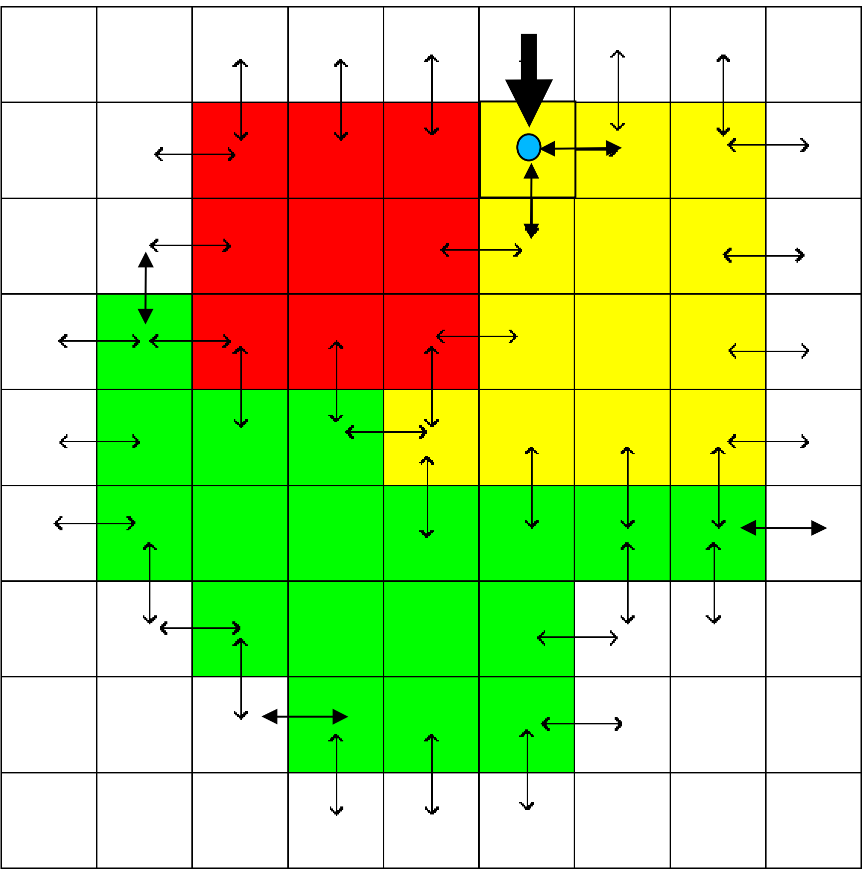
Generalized cellular Potts model

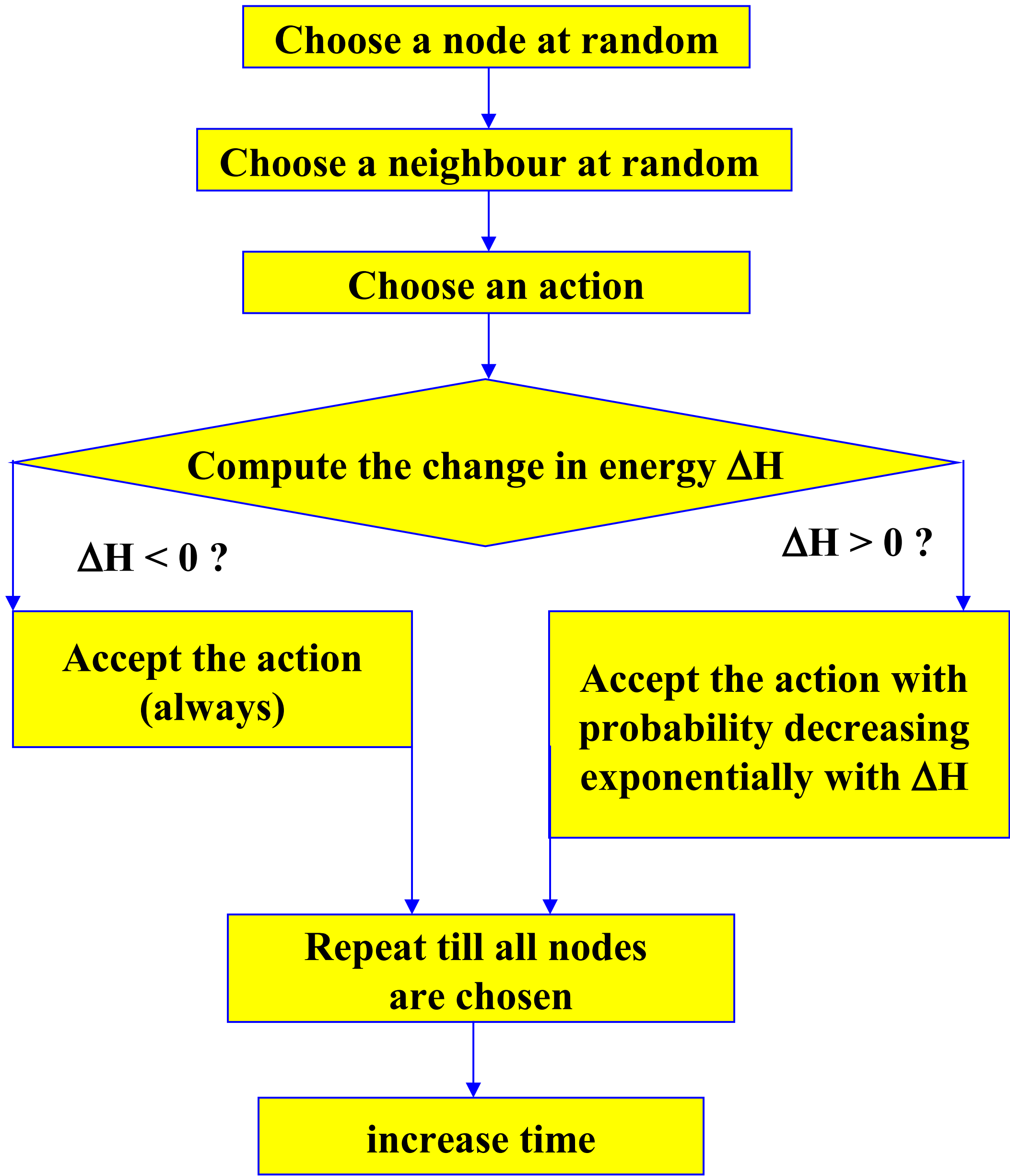
Taking into account of sub-cellular elements (e.g., nucleus)



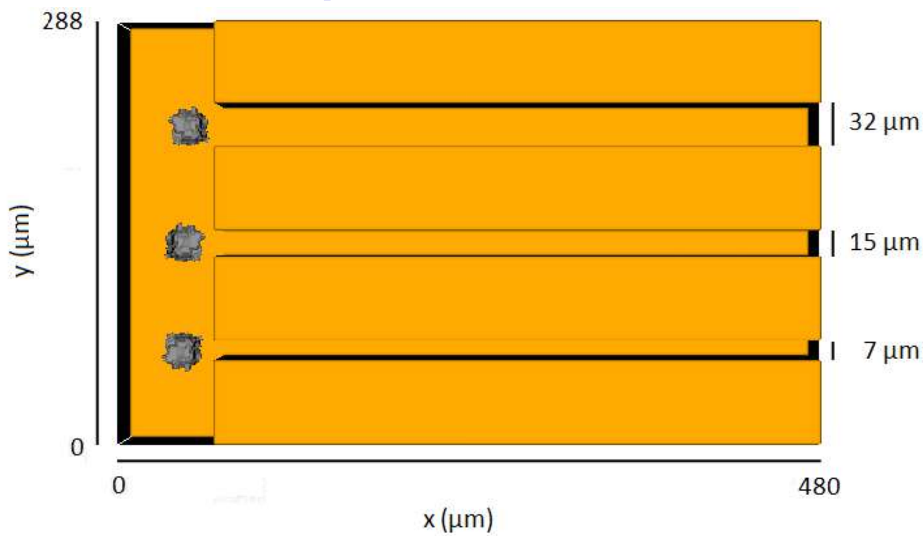
M. Scianna & L.P.,
J. Theor. Biol. **317**, 394-406 (2013).

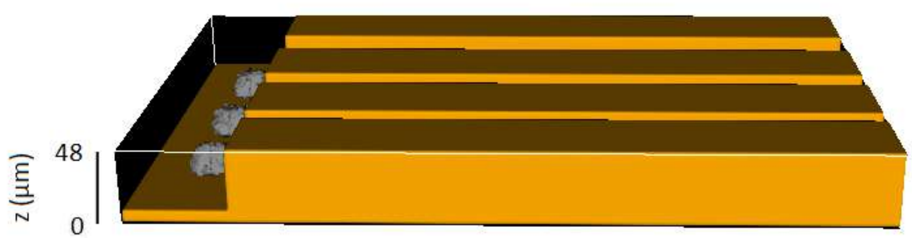
The cellular Potts model

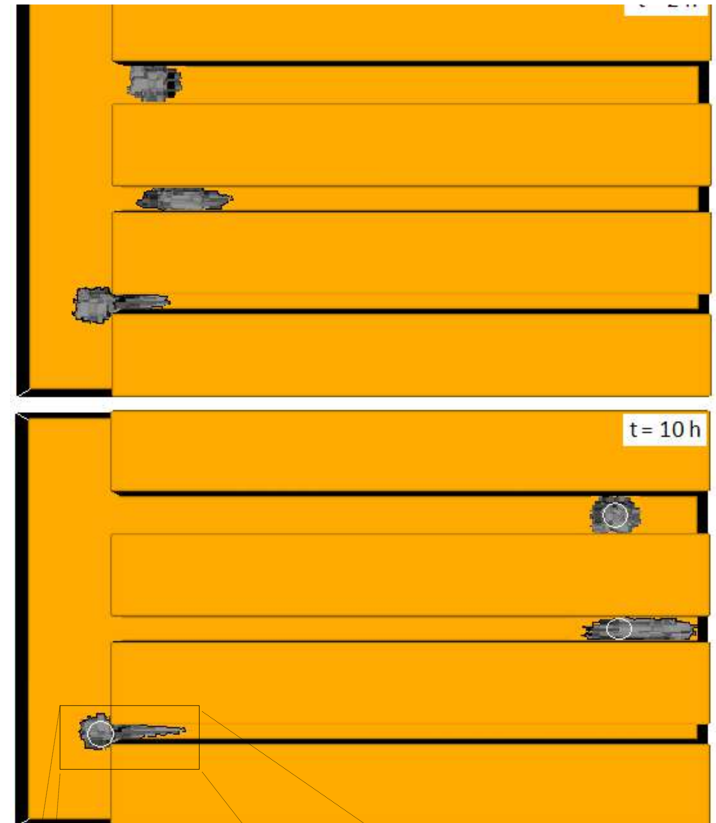


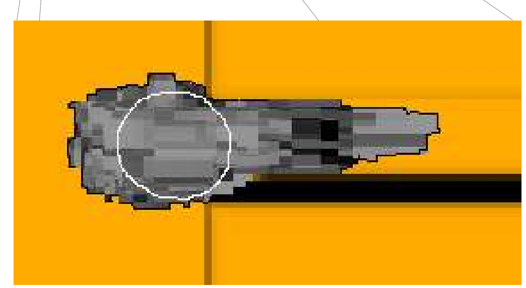


Cells with stiff nuclei in microchannel







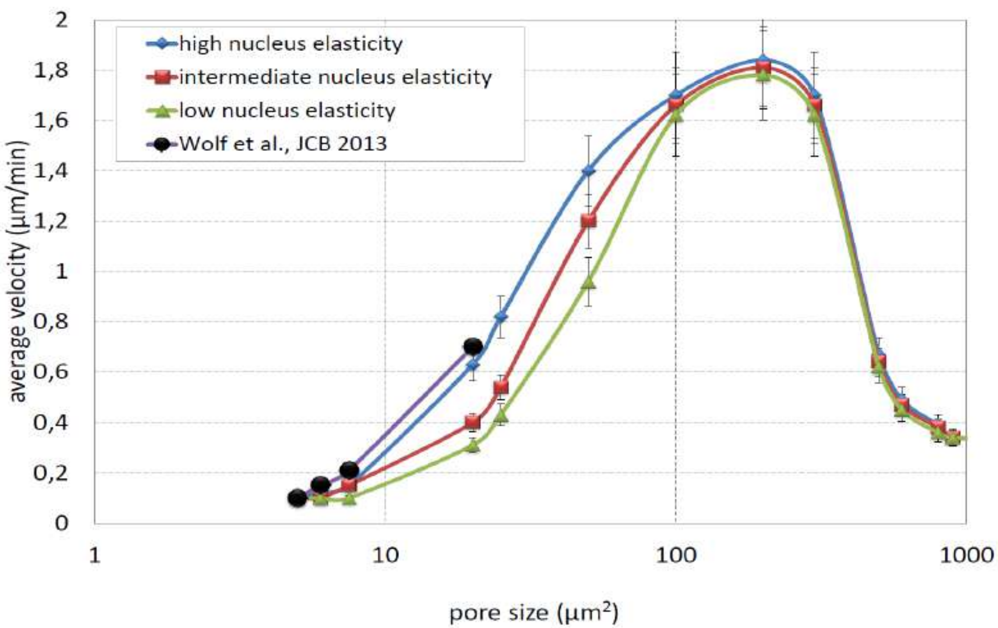


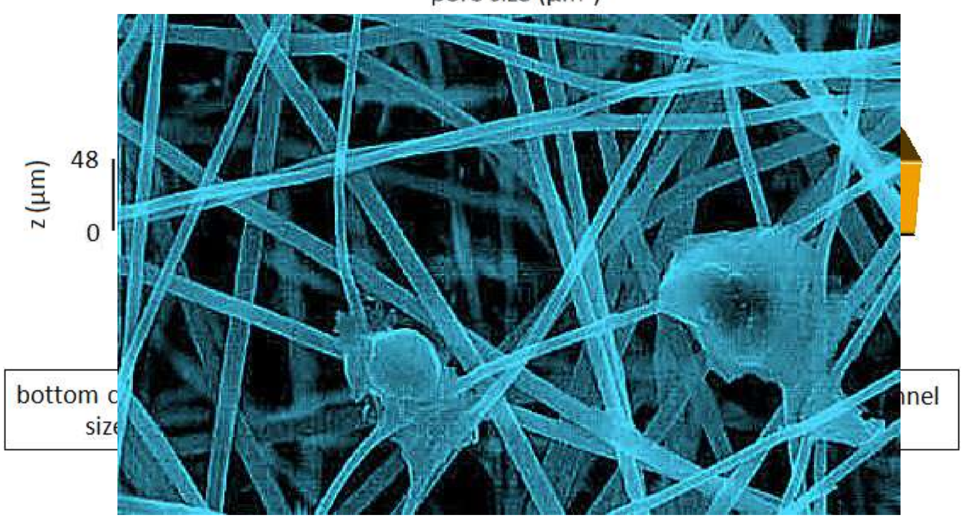
bottom channel size	< nucleus diameter <	middle channel size	< cell diameter <	top channel size

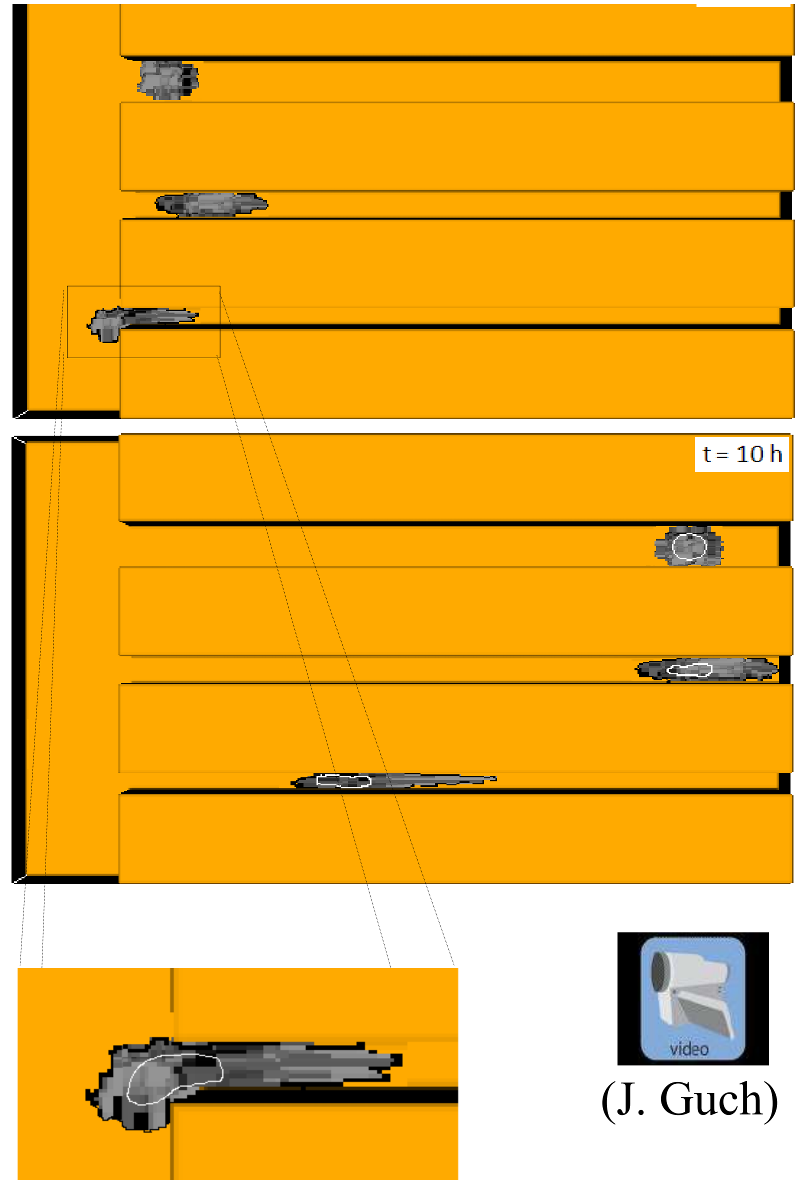
M. Scianna, L.P., *J. Theor. Biol.* **317**, 394-406 (2013)

(J. Guch)

Cells with deformable nuclei in microchannel

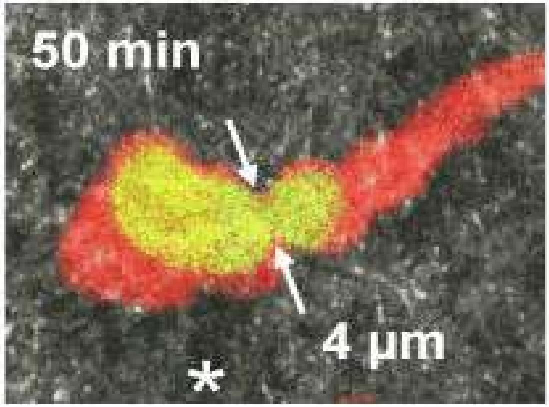


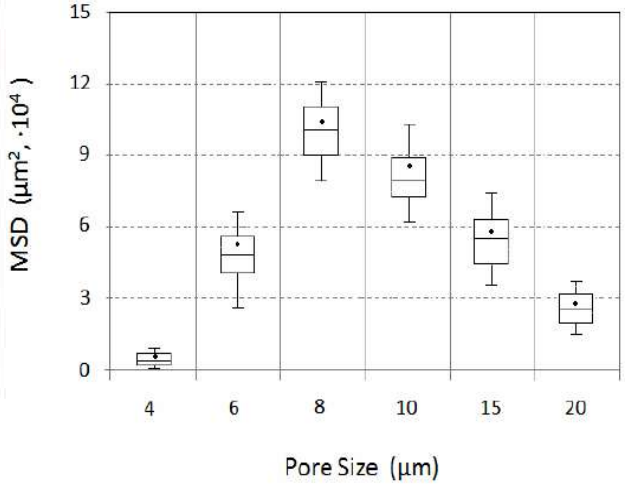


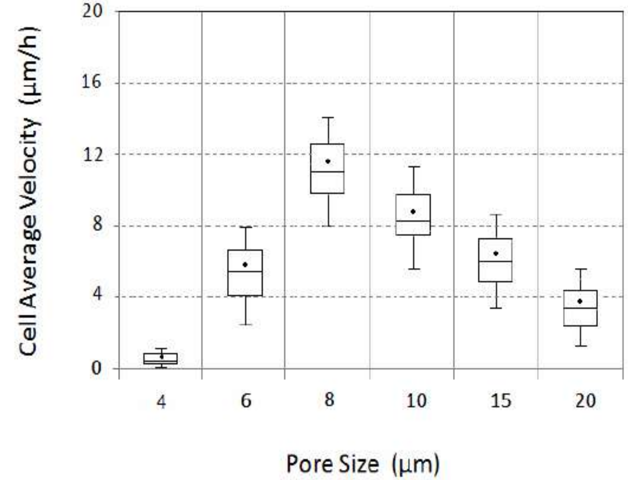


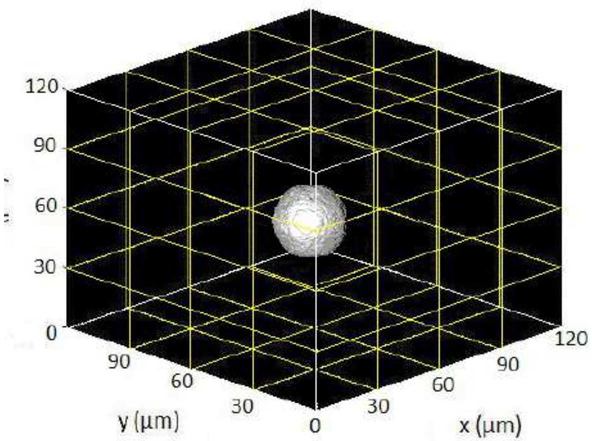
(J. Guch)

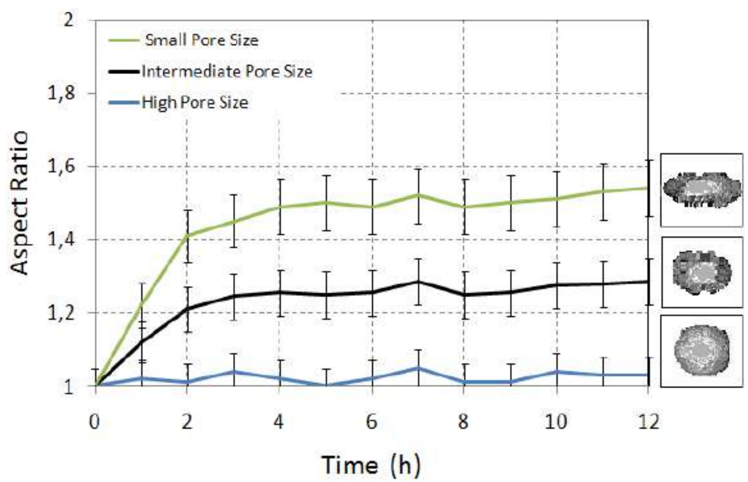
Effect of pore size in ECM

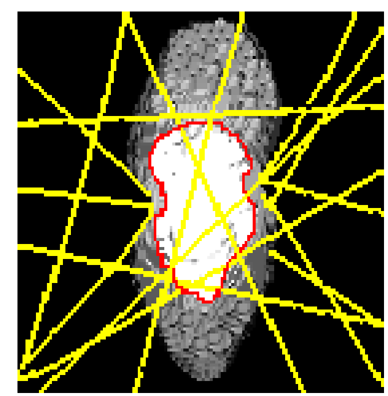






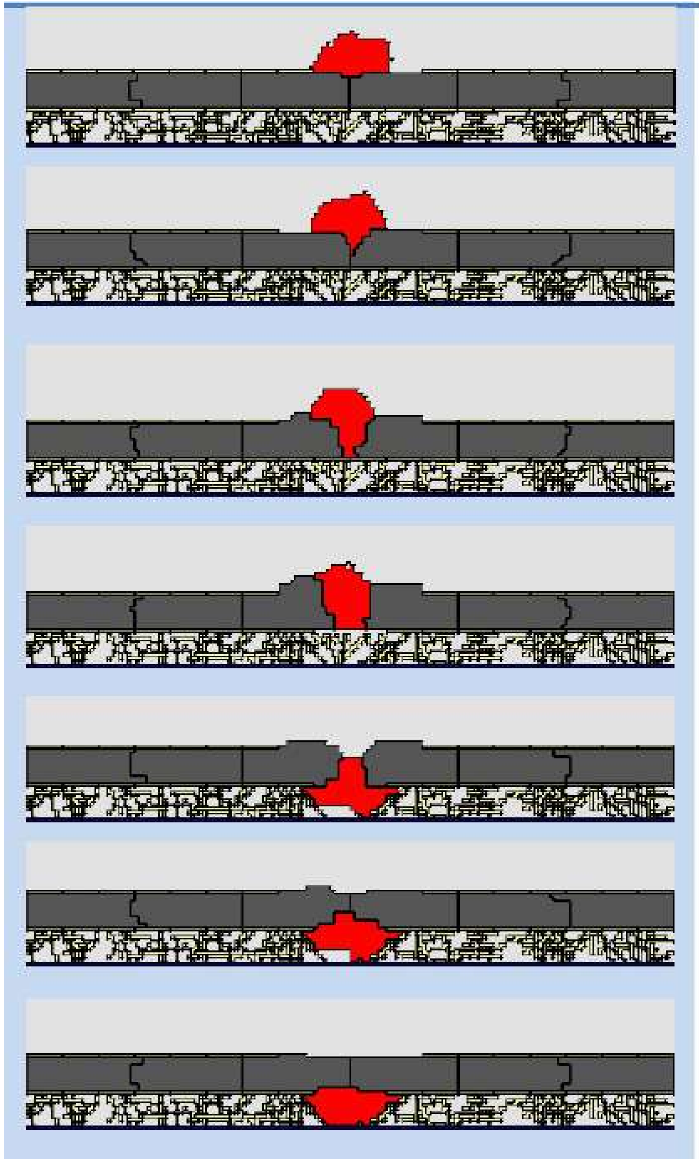


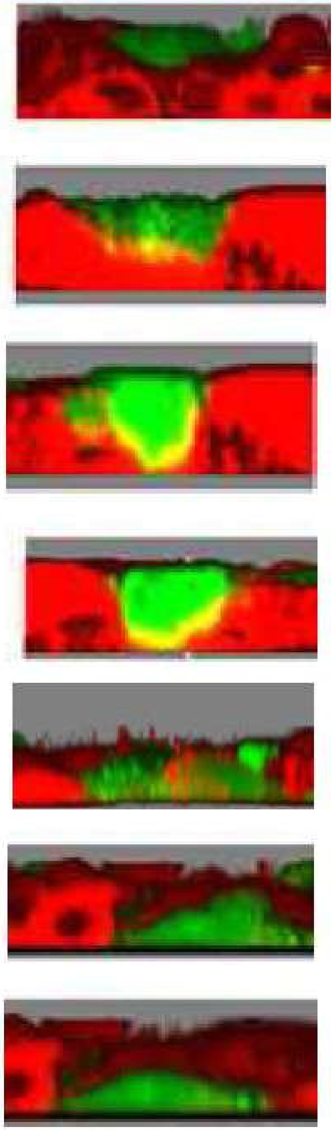




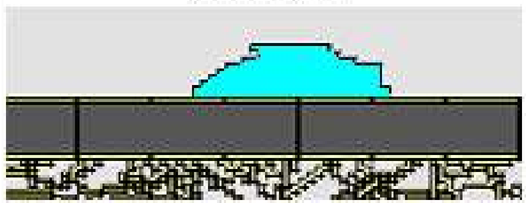
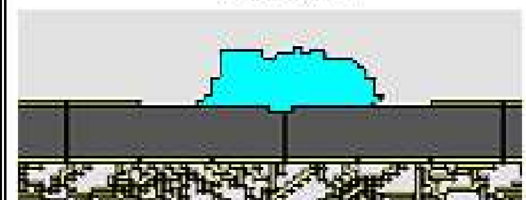
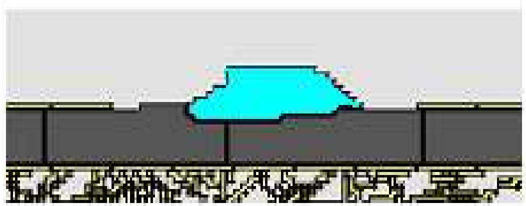
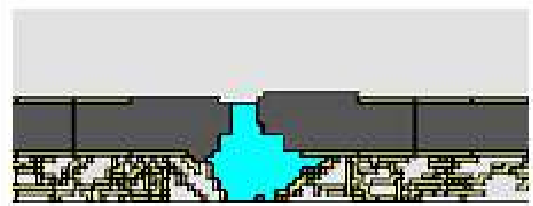
M. Scianna, L.P., & K. Wolf, *Biosci. Engng.* **10**, 235-261 (2013)

Invasion of single ovary cancer cell

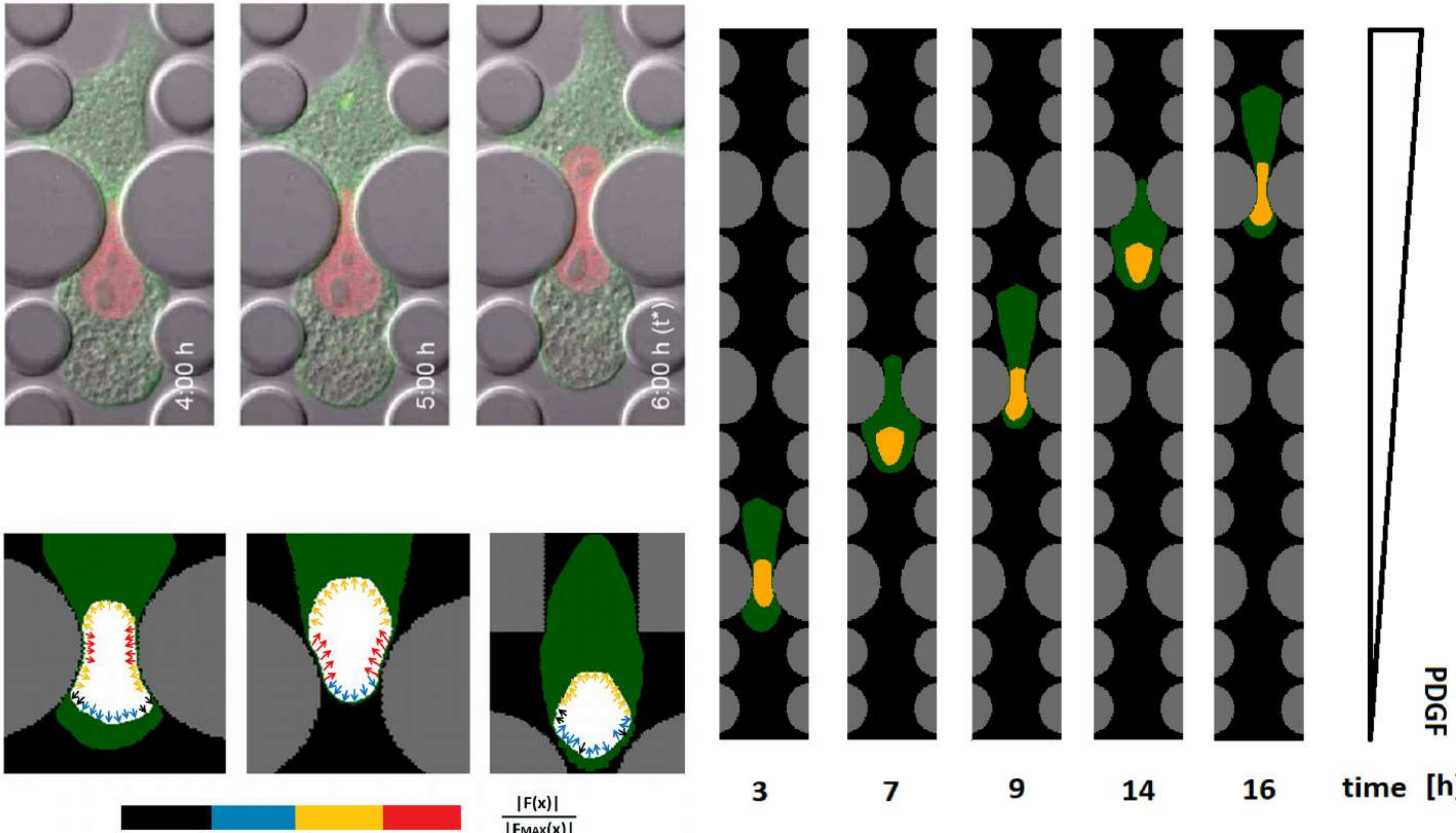




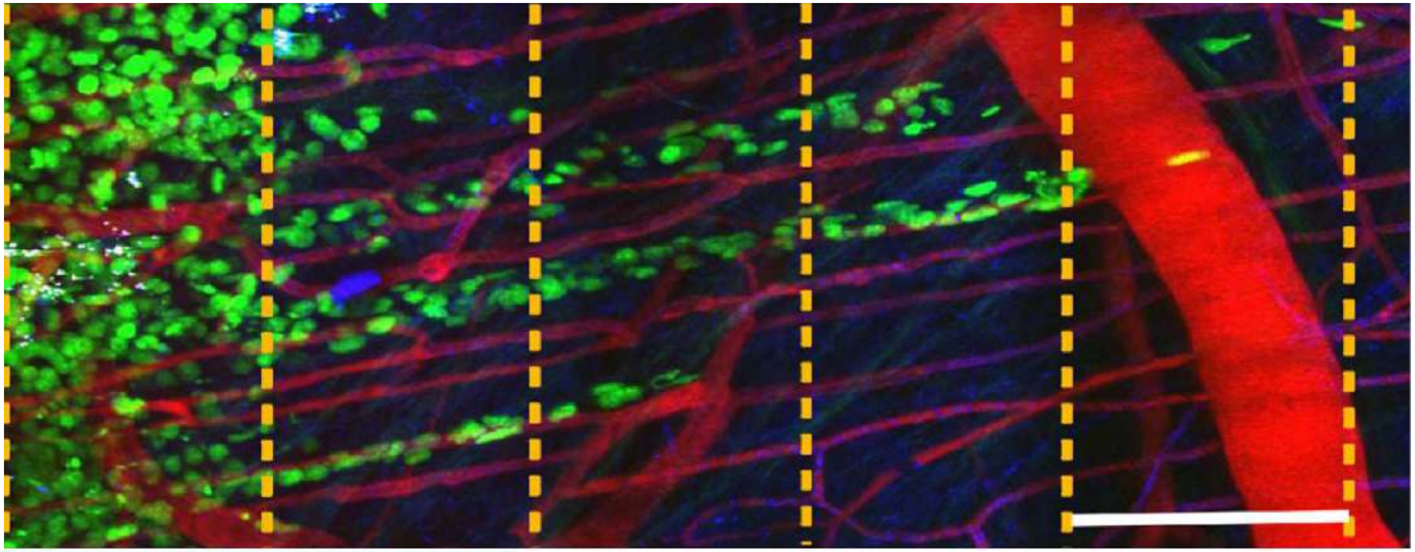
Invasion of single ovary cancer cell

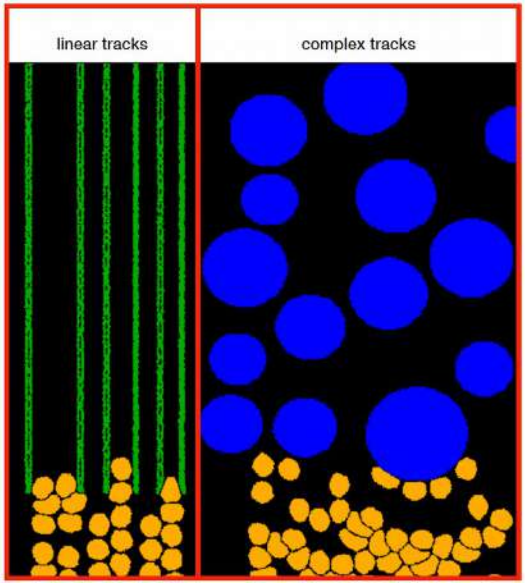
Parameter	Low	High
ϑ_{MMP}	5000 MCS 	180 MCS 
$J_{m,m}$	5000 MCS 	400 MCS 
$J_{c,m}$	5000 MCS 	5000 MCS 

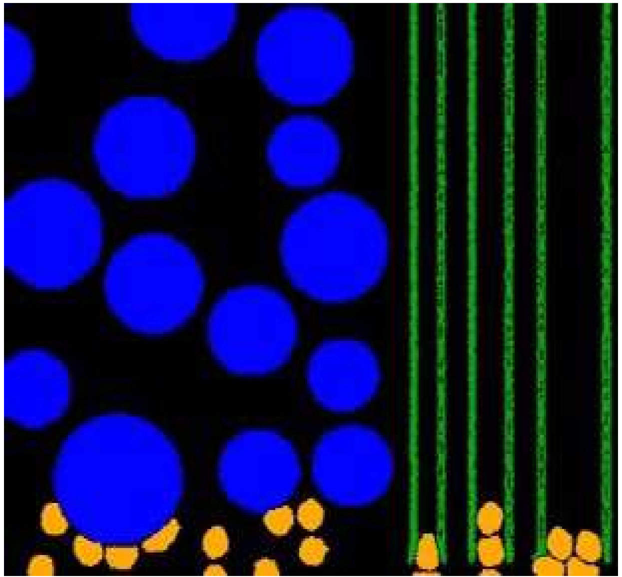
Micropillar arrays



Cell invasion in tissue



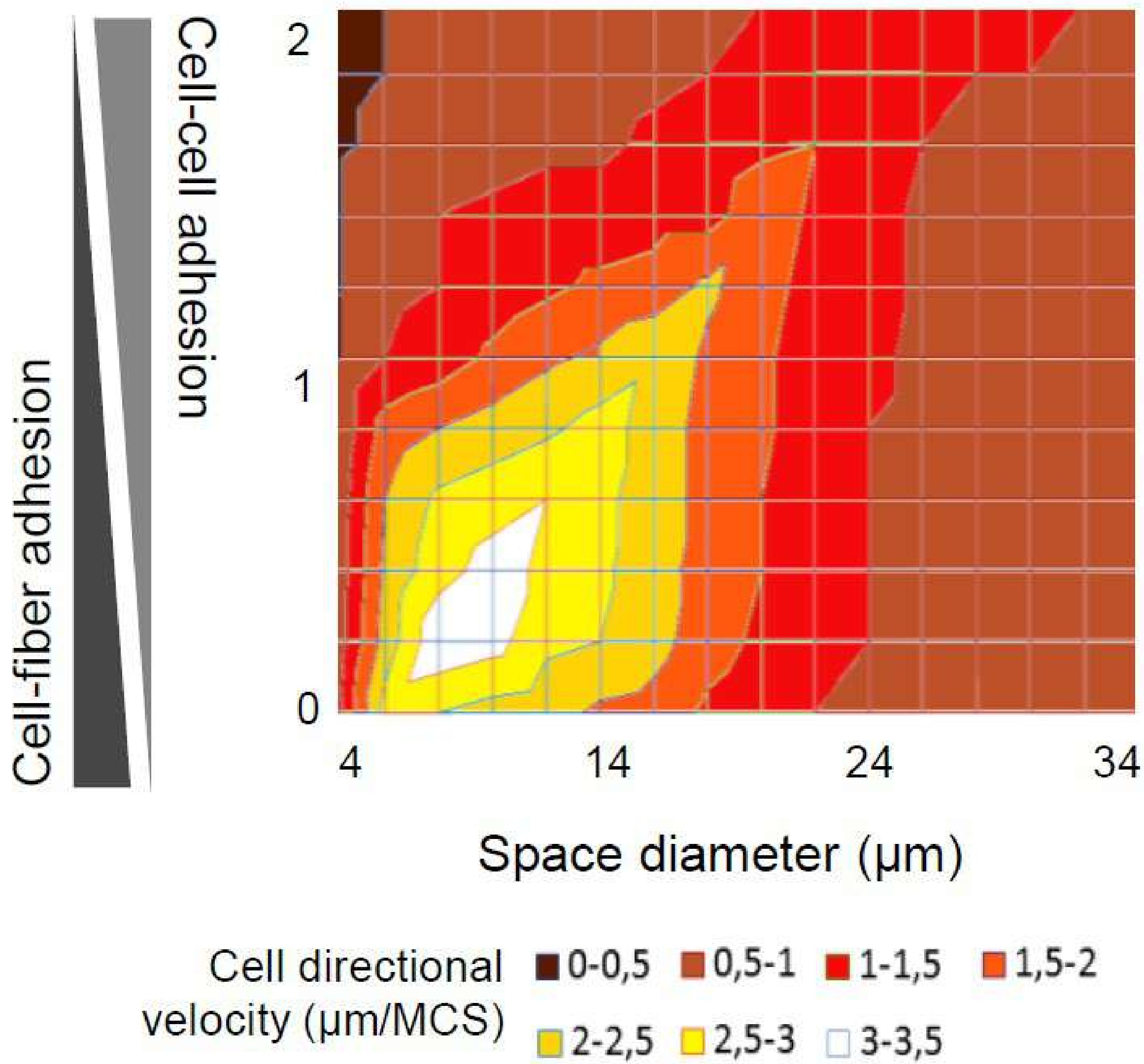




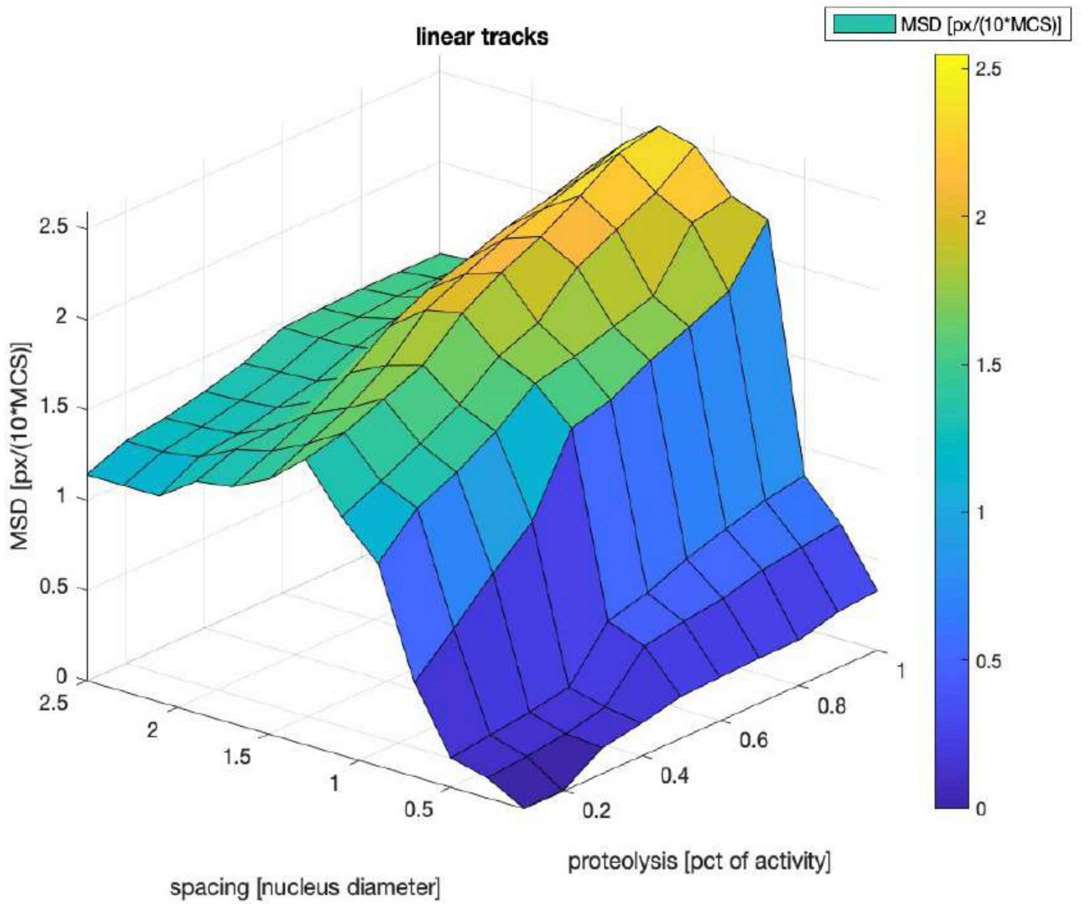
fibre_def_2 (1).mp4

adipociti_2 (1).mp4

Cell invasion in tissue



Cell invasion in tissue



Drawbacks:

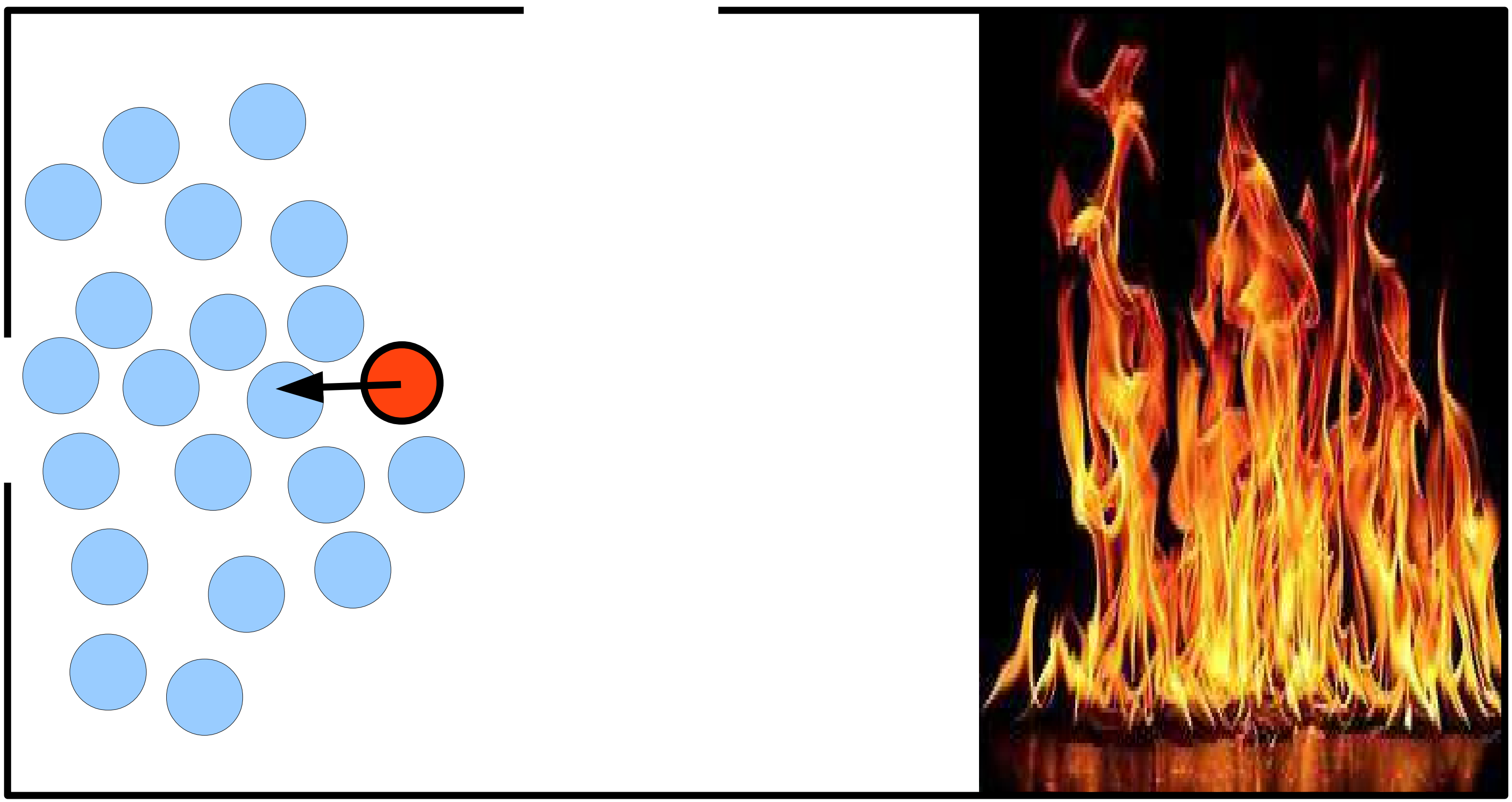
- Limited number of cells
- Simulation-based statistics

Advantages:

- Easier to insert sub-cellular mechanisms
- Looks closer to reality
- Intrinsic nonlocality

Non local sensing and motion

- Sense nonlocally the environment
- Choose where to go
- Move (or try to move)



Nonlocal sensing and motion

- Sense nonlocally the environment
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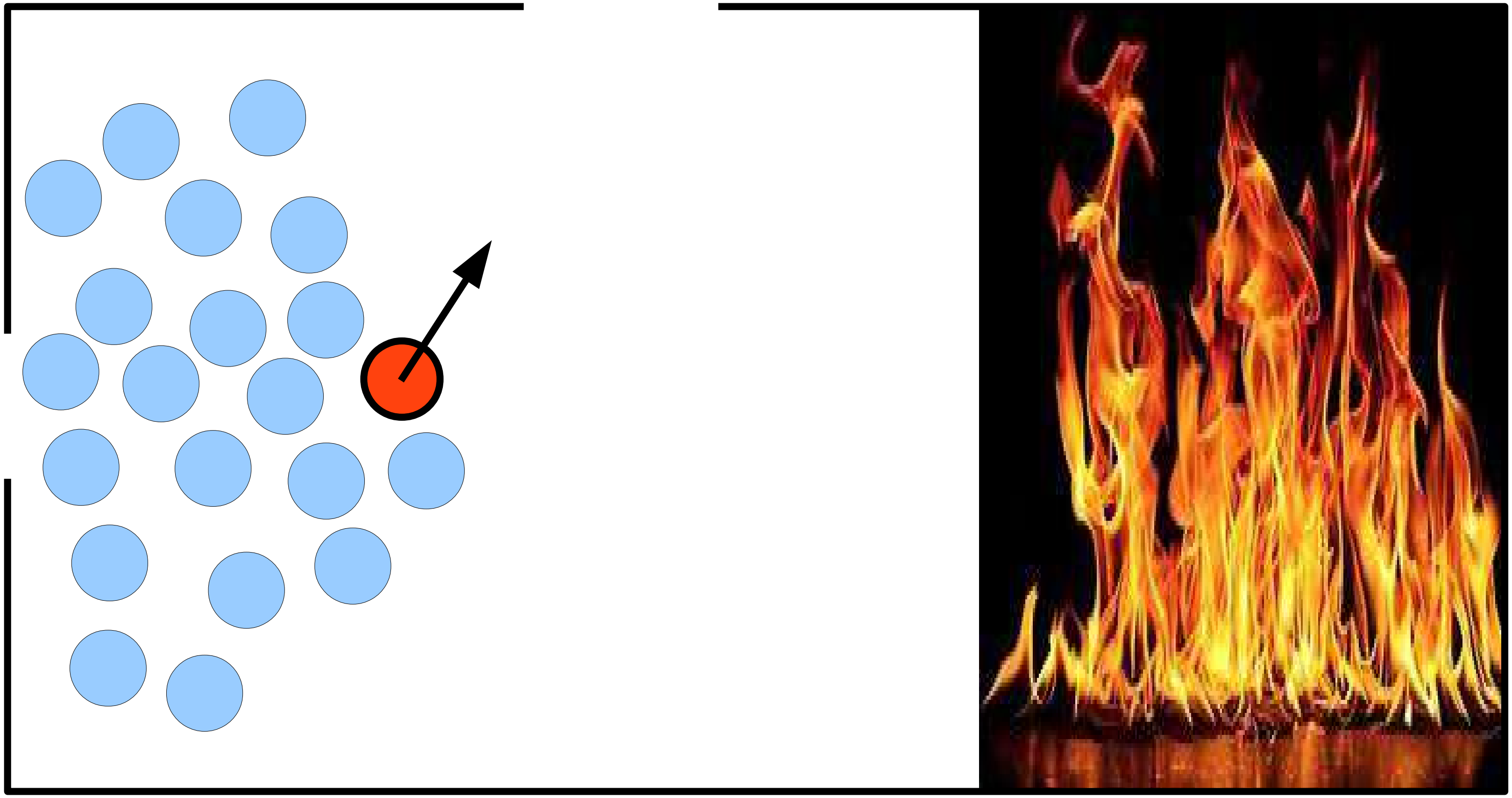
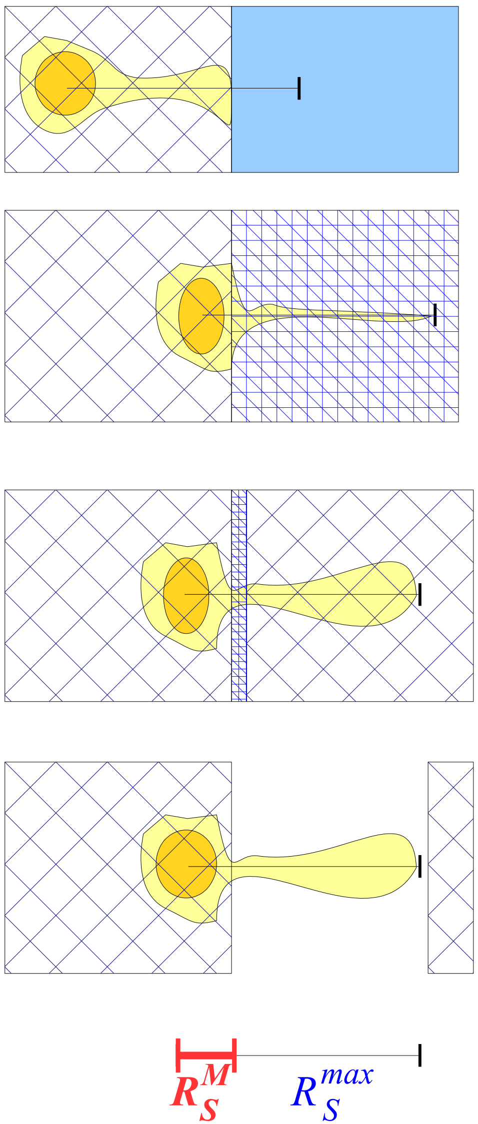


Physical limits of migration

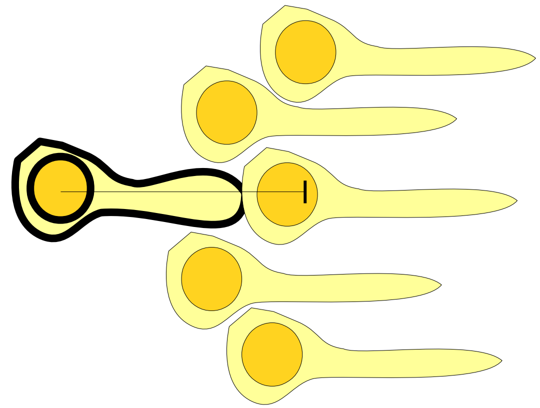


barriers

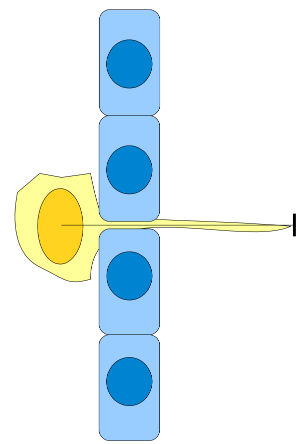
dense
ECM

basal
membranes

lack of
adhesion
sites



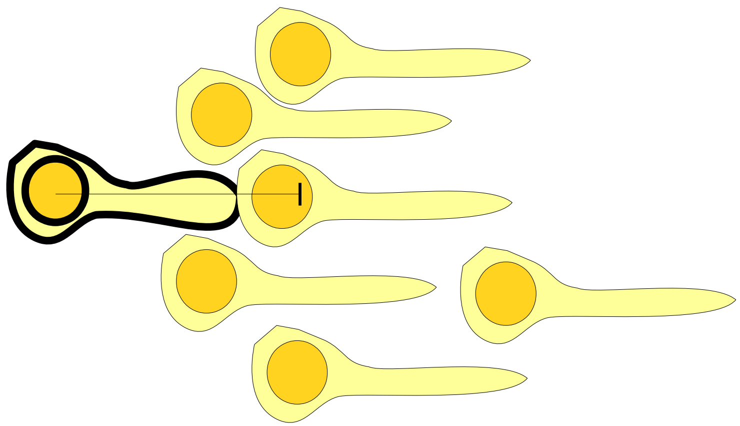
volume
filling

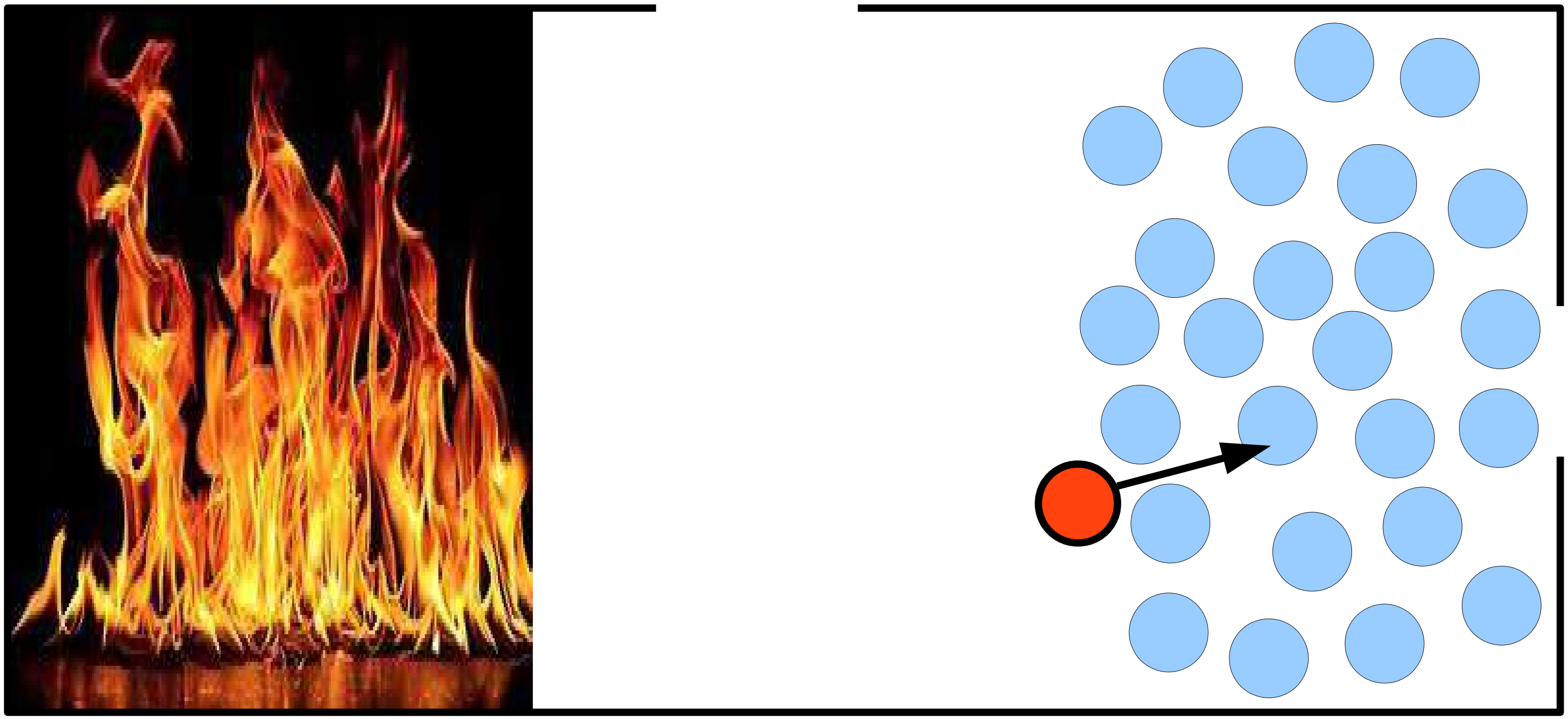


cell layers
epithelial sheets
endothelial walls
capillaries
lymphatics

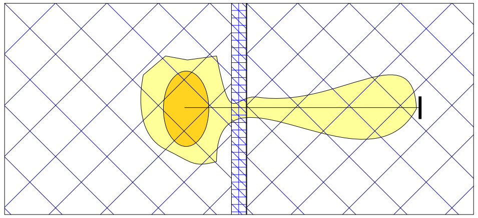
Physical limits of migration

volume
filling

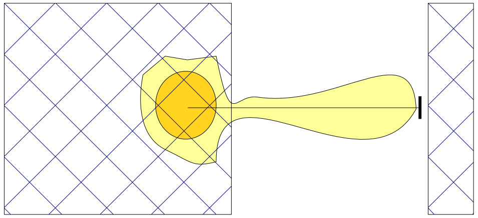




Physical limits of migration



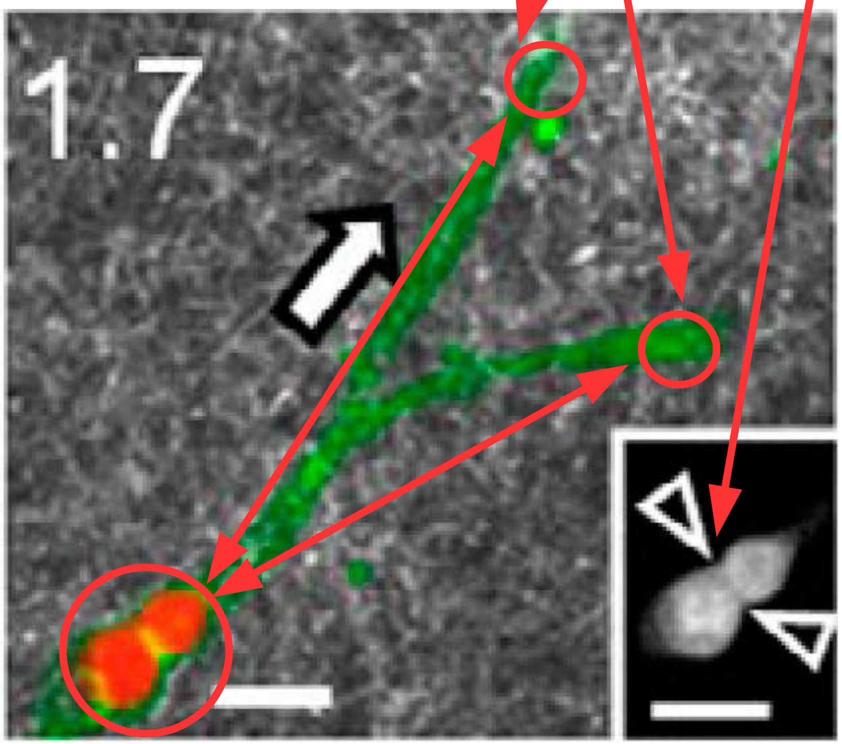
- basal membranes
- cell layers
- intra/extra-vasation



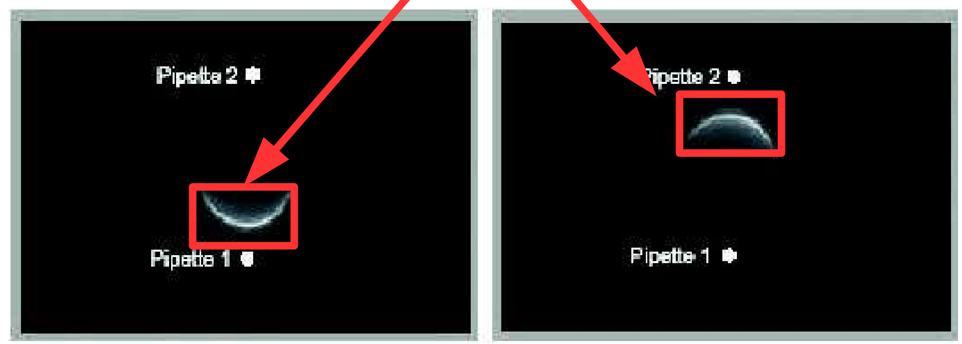
lack of adhesion sites

Sensing, polarization and motion

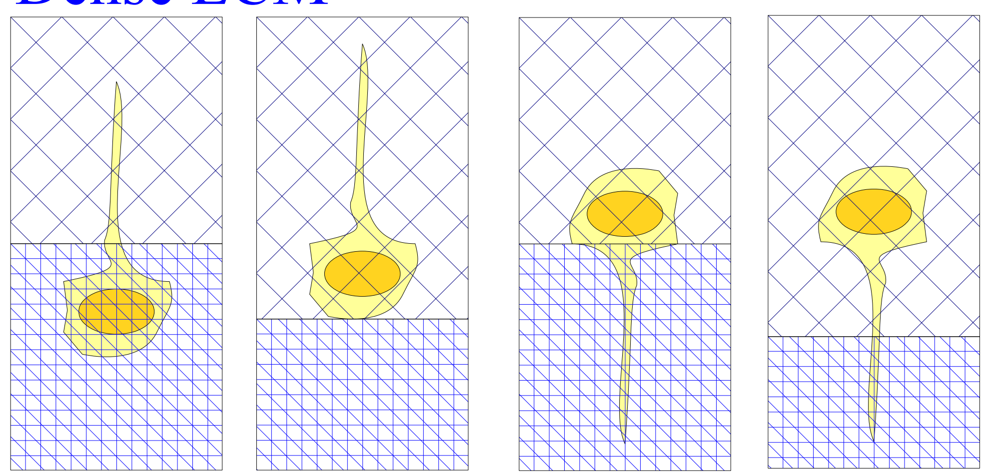
- Non local sensing
- Different cues for polarization and speed
- Physical limits of migration



Wolf, Friedl



Dense ECM



Non local models

- Othmer & Hillen (2002)
- Hillen, Painter & Schmeiser (2006)
- Armstrong, Painter & Sherratt (2007, 2010)
- ….

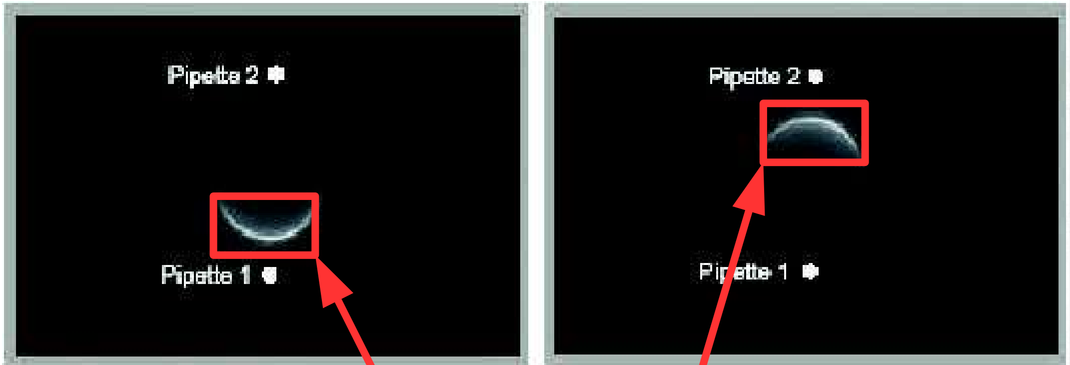
$$\overset{\ominus}{\nabla}_\rho\, v(x,t) = \frac{n}{\omega\rho} \int_{S^{n-1}} \sigma v(x+\rho\sigma, t)\, d\sigma,$$

$$\overset{\circ}{\nabla}_\rho\, v(x,t) = \frac{1}{2\rho}\left(v(x+\rho,t) - v(x-\rho,t)\right)$$

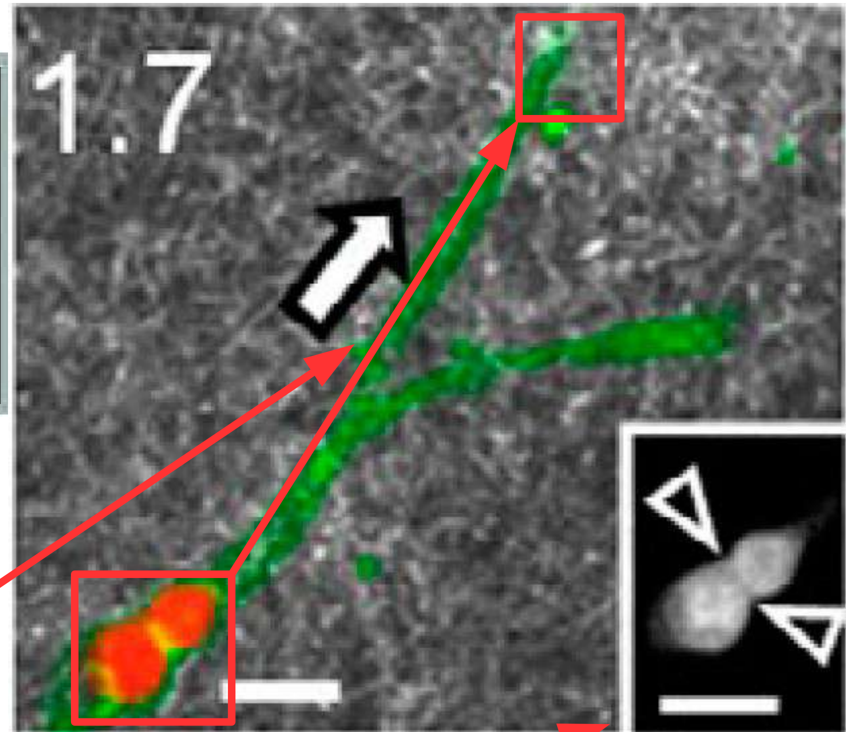
Kinetic model taking into account of

- Different cues for polarization and speed
- Non local sensing
- Physical limits of migration

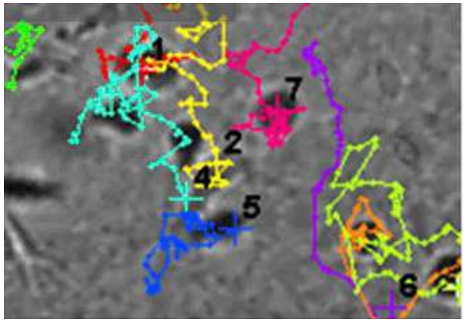
Sensing, polarization and motion



Devreotes, Janetopoulos



Wolf, Friedl

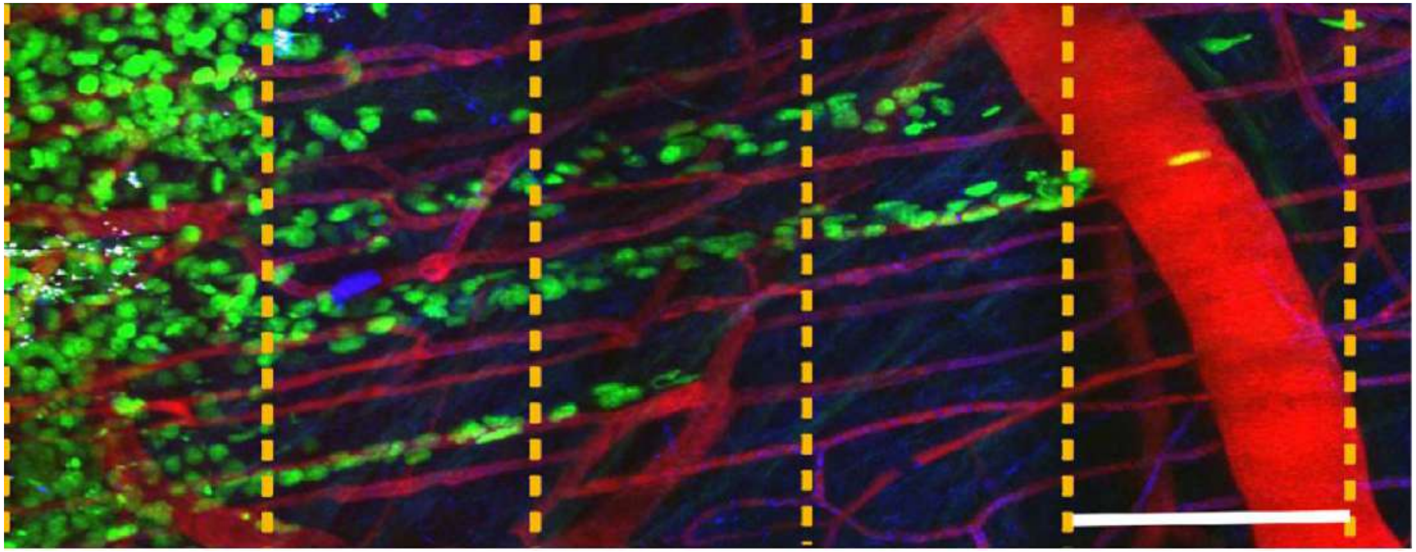


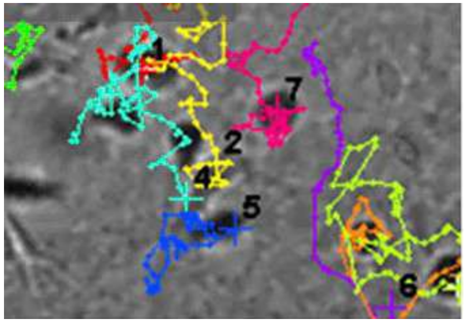
Summary

Kinetic model taking into account of

- Different cues for polarization and speed
- Non local sensing
- Physical limits of migration

Aims and summary





(P. Friedl, K. Wolf)

Distribution function

Distribution density for the cell population

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

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

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

Velocity jump process

Distribution density for the cell population

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

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

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

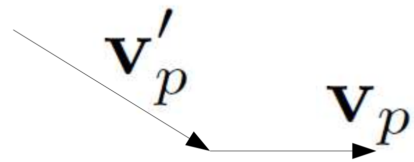
Velocity jump process

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

Turning rate

Turning frequency

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

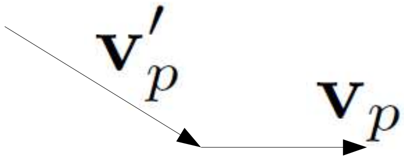


Velocity jump process

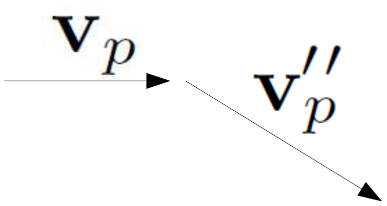
$$\mathcal{J}[p](\mathbf{x},\mathbf{v}_p)=\mathcal{G}[p](\mathbf{x},\mathbf{v}_p)-\mathcal{L}[p](\mathbf{x},\mathbf{v}_p)$$

Turning rate   Turning frequency

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



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



Velocity jump process

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

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

Velocity jump process

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

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

$$\begin{aligned}\frac{\partial p}{\partial t}(t,\mathbf{x},\mathbf{v}_p) + \mathbf{v}\cdot\nabla p(t,\mathbf{x},\mathbf{v}_p) &\\ = \int_{V_p} \mu(\mathbf{x},\mathbf{v}_p')T[\mathcal{S},\mathcal{S}'](\mathbf{x},\mathbf{v}_p|\mathbf{v}_p')p(t,\mathbf{x},\mathbf{v}_p')\,d\mathbf{v}_p' &\\ - \mu(\mathbf{x},\mathbf{v}_p)p(t,\mathbf{x},\mathbf{v}_p)&\end{aligned}$$

Mass conservation

Integrate over the velocity space

$$\int_{V_p} \frac{\partial p}{\partial t}(t, \mathbf{x}, \mathbf{v}_p) + \mathbf{v} \cdot \nabla p(t, \mathbf{x}, \mathbf{v}_p) \; d\mathbf{v}_p$$

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

$$- \mu(\mathbf{x}, \mathbf{v}_p) p(t, \mathbf{x}, \mathbf{v}_p) \; d\mathbf{v}_p$$

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Mass conservation

Integrate over the velocity space

$$\int_{V_p} \frac{\partial p}{\partial t}(t, \mathbf{x}, \mathbf{v}_p) + \mathbf{v} \cdot \nabla p(t, \mathbf{x}, \mathbf{v}_p) \; d\mathbf{v}_p$$

$$= \int_{V_p} \mu(\mathbf{x}, \mathbf{v}'_p) \qquad p(t, \mathbf{x}, \mathbf{v}'_p) \, d\mathbf{v}'_p$$

$$- \int_{V_p} \mu(\mathbf{x}, \mathbf{v}_p) p(t, \mathbf{x}, \mathbf{v}_p) \; d\mathbf{v}_p$$

Turning kernel

μ and T independent from the pre-tumbling velocity

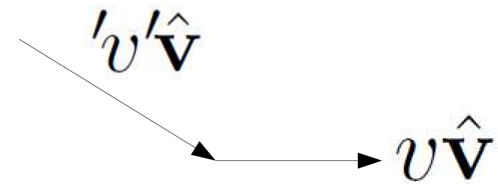
$$\frac{\partial p}{\partial t}(t,\mathbf{x},\mathbf{v}_p) + \mathbf{v}\cdot\nabla p(t,\mathbf{x},\mathbf{v}_p) = \int_{V_p} \mu(\mathbf{x},\cancel{\mathbf{v}'_p})T[\mathcal{S},\mathcal{S}'](\mathbf{x},\mathbf{v}_p|\cancel{\mathbf{v}'_p})p(t,\mathbf{x},\mathbf{v}'_p)\,d\mathbf{v}'_p - \mu(\mathbf{x},\cancel{\mathbf{v}_p})p(t,\mathbf{x},\mathbf{v}_p)$$

$$\Longrightarrow \quad \mathcal{J}[p](t,\mathbf{x},v,\hat{\mathbf{v}}) = \mu(\mathbf{x})\Big(\rho(t,\mathbf{x})T(\mathbf{x},v,\hat{\mathbf{v}}) - p(t,\mathbf{x},v,\hat{\mathbf{v}})\Big)$$

Transport equation

$$p(t, \mathbf{x}, v, \hat{\mathbf{v}}) \qquad \text{s.t.} \qquad \rho(t, \mathbf{x}) = \int_{V_p} p(t, \mathbf{x}, v, \hat{\mathbf{v}})\, dv\, d\hat{\mathbf{v}}$$

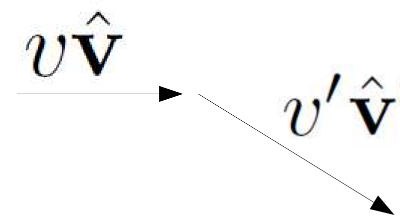
$$\frac{\partial p}{\partial t}(t, \mathbf{x}, v, \hat{\mathbf{v}}) + v\hat{\mathbf{v}} \cdot \nabla p(t, \mathbf{x}, v, \hat{\mathbf{v}}) = \mathcal{J}[p](t, \mathbf{x}, v, \hat{\mathbf{v}})$$



Turning rate

Turning frequency

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



Turning kernel

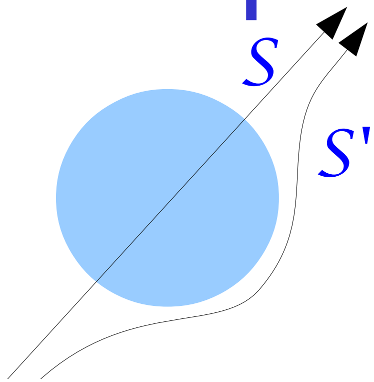
$$\frac{\partial p}{\partial t}(t,\mathbf{x},v,\hat{\mathbf{v}}) + v\hat{\mathbf{v}}\cdot\nabla p(t,\mathbf{x},v,\hat{\mathbf{v}}) = \mathcal{J}[p](t,\mathbf{x},v,\hat{\mathbf{v}})$$

μ and T independent from the pre-tumbling velocity

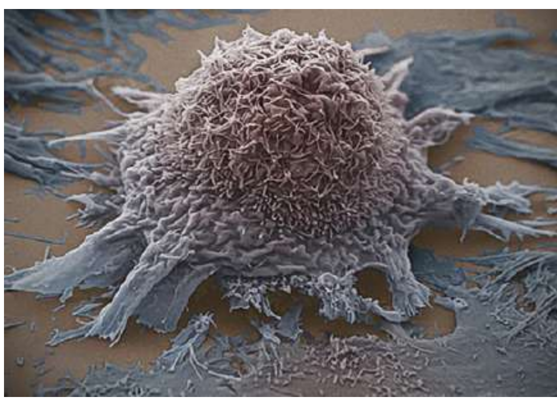
$$\mathcal{J}[p](t,\mathbf{x},v,\hat{\mathbf{v}}) = \int_{V_p} \mu(\mathbf{x},\cancel{'v,'\hat{\mathbf{v}}})T(\mathbf{x},v,\hat{\mathbf{v}}|\cancel{'v,'\hat{\mathbf{v}}})p(t,\mathbf{x},'v,'\hat{\mathbf{v}})\,d'v\,d'\hat{\mathbf{v}}$$
$$-\,\mu(\mathbf{x},\cancel{v,\hat{\mathbf{v}}})p(t,\mathbf{x},v,\hat{\mathbf{v}})$$

$$\Rightarrow\quad \mathcal{J}[p](t,\mathbf{x},v,\hat{\mathbf{v}}) = \mu(\mathbf{x})\Big(\rho(t,\mathbf{x})T(\mathbf{x},v,\hat{\mathbf{v}}) - p(t,\mathbf{x},v,\hat{\mathbf{v}})\Big)$$

Nonlocal structure of the turning kernel



$$T[\mathcal{S},\mathcal{S}'] = c(\mathbf{x}) \int_{\mathbb{R}_+} \overbrace{\gamma_{\mathcal{S}}(\lambda)\; b(\mathcal{S}(\mathbf{x}+\lambda\hat{\mathbf{v}}))\, d\lambda}^{\text{Given } \hat{\mathbf{v}} \text{ measures } S \text{ along } \hat{\mathbf{v}} \text{ weighting the info}} \int_{\mathbb{R}_+} \overbrace{\gamma_{\mathcal{S}'}(\lambda')\psi(\mathbf{x}, v|\mathcal{S}'(\mathbf{x}+\lambda'\hat{\mathbf{v}}))\, d\lambda'}^{\text{Given } \hat{\mathbf{v}} \text{ measures } S' \text{ along } \hat{\mathbf{v}} \text{ evaluating possible speeds weighting the info}}$$



Compact support

Distribution function with

mean $= \bar{U}(\mathbf{x}|\mathcal{S}'(\mathbf{x}+\lambda'\hat{\mathbf{v}}))$

variance $= D(\mathbf{x}|\mathcal{S}'(\mathbf{x}+\lambda'\hat{\mathbf{v}}))$

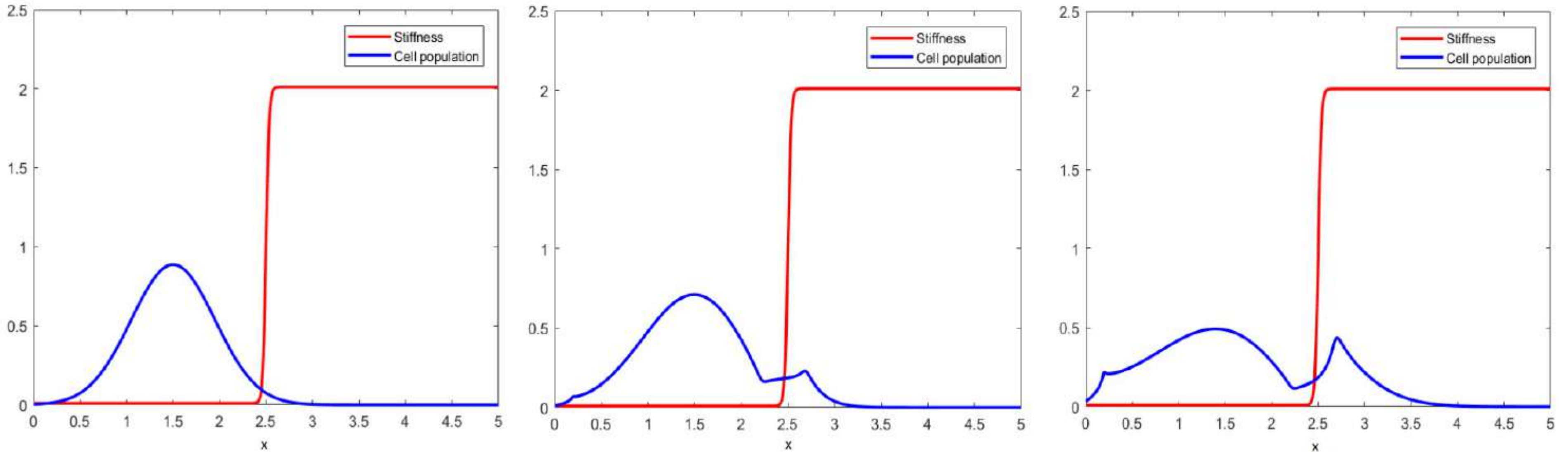
Directional bias (only)

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

$$T[\mathcal{S}](\mathbf{x},\mathbf{v}_p) = \frac{\displaystyle\int_{\mathbb{R}_+} \gamma_{\mathcal{S}}(\lambda)\mathcal{T}_\lambda^{\hat{\mathbf{v}}}[\mathcal{S}](\mathbf{x})\,d\lambda}{\displaystyle\int_{\mathbb{S}^{d-1}}\int_{\mathbb{R}_+} \gamma_{\mathcal{S}}(\lambda)\mathcal{T}_\lambda^{\hat{\mathbf{v}}}[\mathcal{S}](\mathbf{x})d\lambda\,d\hat{\mathbf{v}}}\,\psi(\mathbf{x},v)$$

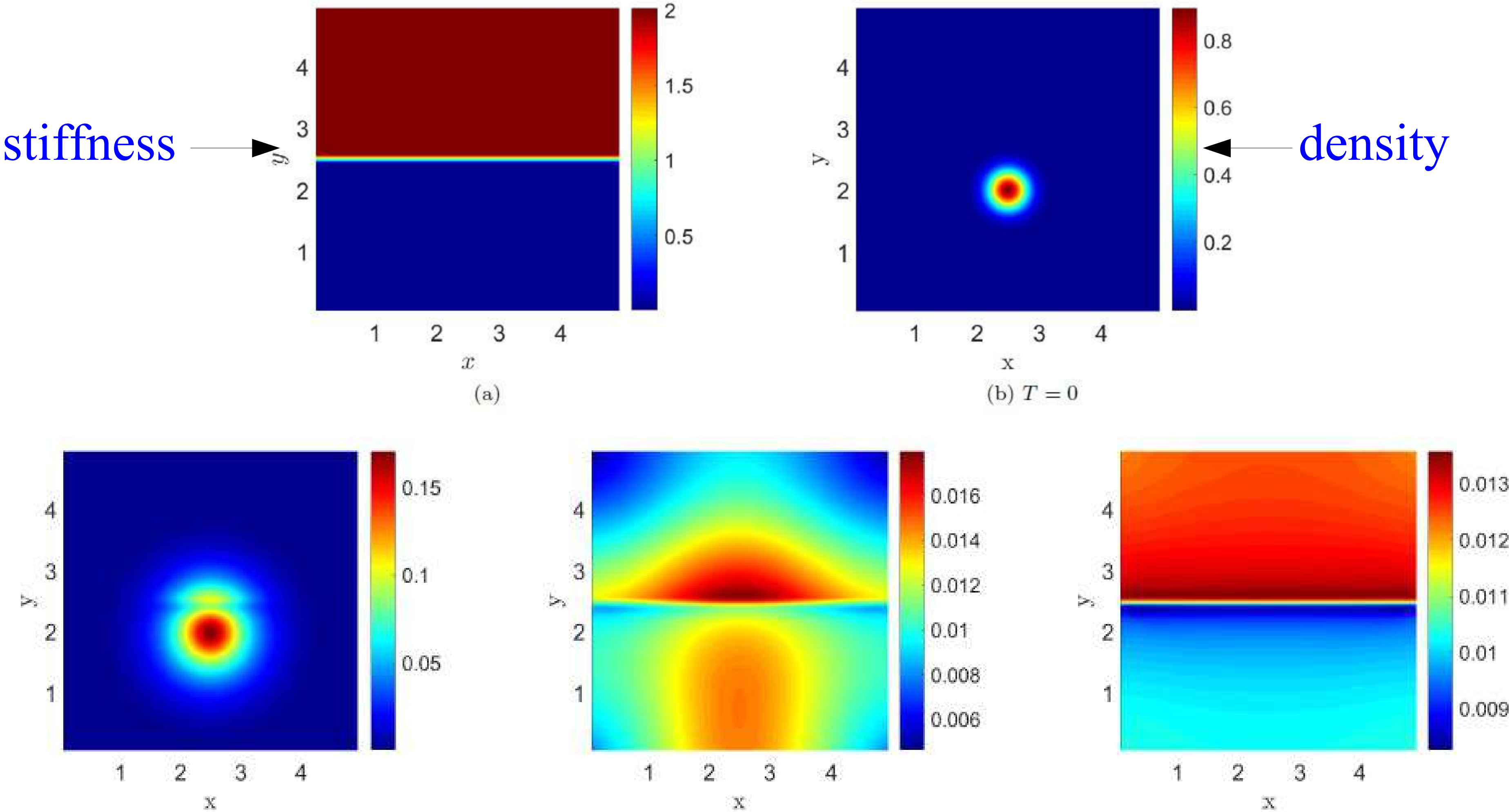
Durotaxis

$$\gamma_S = \delta(\lambda - R_S)$$



Durotaxis

$$\gamma_S = \delta(\lambda - R_S) \qquad R_{\mathcal{S}} = 0.02$$

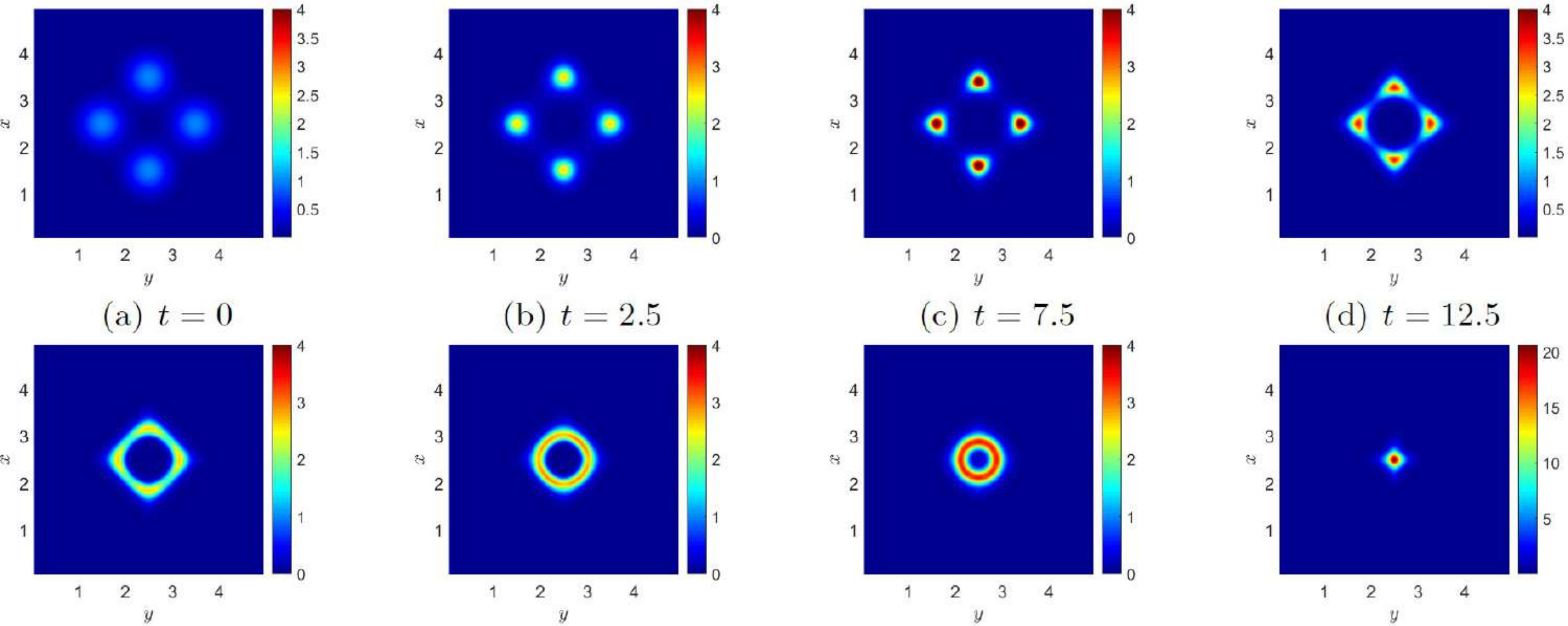


(a) (b) $T = 0$

(c) $t = 0.6$ (d) $t = 6$ (e) $t = 22$

Cell-cell adhesion

$$\frac{\partial p}{\partial t}(t,\mathbf{x},v,\hat{\mathbf{v}}) + v\hat{\mathbf{v}}\cdot\nabla p(t,\mathbf{x},v,\hat{\mathbf{v}}) = \mu\left[c(t,\mathbf{x})\rho(t,\mathbf{x})\int_{\mathbb{R}_+}\gamma_R(\lambda)b\left(\rho(t,\mathbf{x}+\lambda\hat{\mathbf{v}})\right)\,d\lambda\,\psi(v) - p(t,\mathbf{x},v,\hat{\mathbf{v}})\right]$$



(a) $t=0$ (b) $t=2.5$ (c) $t=7.5$ (d) $t=12.5$

(e) $t=15$ (f) $t=17.5$ (g) $t=20$ (h) $t=50$

$$\gamma_\rho = \delta(\lambda - R_\rho) \qquad R_\rho = 0.25$$

Macroscopic limits

Discriminating factor $\mathbf{U}^0_{\mathcal{S},\mathcal{S}'} = \int_{V_p} T[\mathcal{S},\mathcal{S}']_0 \mathbf{v}\, d\mathbf{v}_p \stackrel{?}{=} \mathbf{0}$

Yes → parabolic $\frac{\partial \rho}{\partial \tau} + \nabla \cdot \left(\rho \mathbf{U}^1_{\mathcal{S},\mathcal{S}'}\right) = \nabla \cdot \left(\frac{1}{\mu} \nabla \cdot \left(\mathbb{D}^0_{\mathcal{S},\mathcal{S}'} \rho\right)\right)$

No → hyperbolic $\frac{\partial \rho}{\partial \tau} + \nabla \cdot \left(\rho \mathbf{U}^0_{\mathcal{S},\mathcal{S}'}\right) = 0$

$$\mathbf{U}^i_{\mathcal{S},\mathcal{S}'} = \int_{V_p} T[\mathcal{S},\mathcal{S}']_i \mathbf{v}\, d\mathbf{v}_p$$

$$\mathbb{D}^i_{\mathcal{S},\mathcal{S}'} = \int_{V_p} T[\mathcal{S},\mathcal{S}']_i (\mathbf{v} - \mathbf{U}^i_{\mathcal{S},\mathcal{S}'}) \otimes (\mathbf{v} - \mathbf{U}^i_{\mathcal{S},\mathcal{S}'})\, d\mathbf{v}_p$$

Macroscopic limit

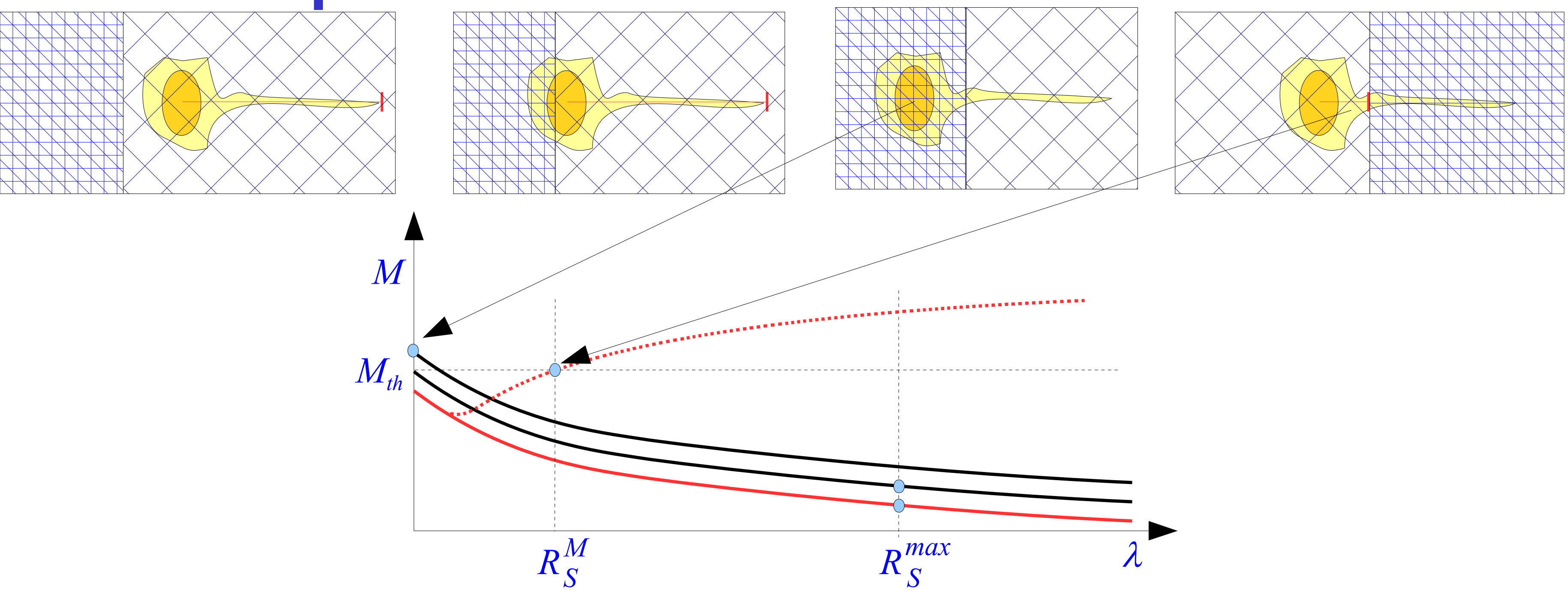
$$\frac{\partial \rho}{\partial \tau} + \nabla \cdot \left(\rho \mathbf{U}_{\mathcal{S}}^{0}\right) = 0$$

For instance, if there is only a signal *S* affecting the orientation (no *S'*)

$$\mathcal{J}[p](t,\mathbf{x},\mathbf{v}_p) = \mu(\mathbf{x}) \left(\rho(t,\mathbf{x})\psi(\mathbf{x},v)c(\mathbf{x}) \int_{\mathbb{R}_+} b(\mathcal{S}(\mathbf{x}+\lambda\hat{\mathbf{v}}))\gamma_S(\lambda)\,d\lambda - p(t,\mathbf{x},\mathbf{v}_p) \right)$$

$$\mathbf{U}_{\mathcal{S}}^{0}(\boldsymbol{\xi}) = \bar{U}(\boldsymbol{\xi}) \frac{\displaystyle\int_{\mathbb{S}^{d-1}} \left(\int_{\mathbb{R}+} b(\mathcal{S}(\boldsymbol{\xi}+\lambda\hat{\mathbf{v}}))\gamma_S(\lambda)\,d\lambda \right) \hat{\mathbf{v}}\,d\hat{\mathbf{v}}}{\displaystyle\int_{\mathbb{S}^{d-1}} \left(\int_{\mathbb{R}+} b(\mathcal{S}(\boldsymbol{\xi}+\lambda\hat{\mathbf{v}}))\gamma_S(\lambda)\,d\lambda \right) d\hat{\mathbf{v}}}$$

Physical limits of migration



limits
their ranges

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

Random polarization + volume filling

Random polarization

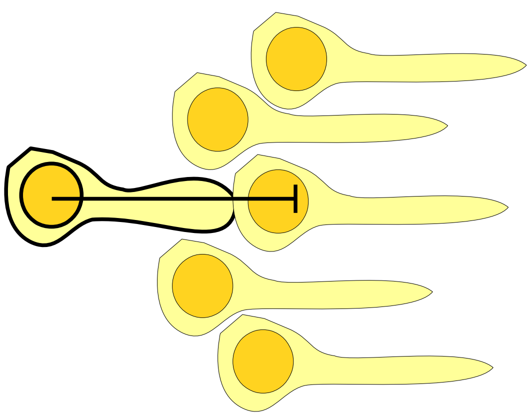
$$T[\mathcal{S},\mathcal{S}'](\mathbf{x},\mathbf{v}_p) = c(\mathbf{x}) \int_{\mathbb{R}_+} \gamma_{\mathcal{S}}(\lambda) \cancel{\mathcal{T}_\lambda^{\hat{\mathbf{v}}}[\mathcal{S}]}(\mathbf{x}) d\lambda \int_{\mathbb{R}_+} \gamma_{\mathcal{S}'}(\lambda')\psi(\mathbf{x}, v|\mathcal{S}'(\mathbf{x}+\lambda'\hat{\mathbf{v}}))\,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

Volume filling

$$\inf\left\{\lambda' \in [0,\, R_\rho^{max}] \,\middle|\, \rho(t,\mathbf{x}+\lambda'\hat{\mathbf{v}}) > \rho_{th}\right\}$$

$$T[\rho](t,\mathbf{x},v,\hat{\mathbf{v}}) = \frac{1}{\int_{\mathbb{S}^{d-1}} \Gamma_0'(t,\mathbf{x},\hat{\mathbf{v}})\, d\hat{\mathbf{v}}} \int_0^{R_\rho(t,\mathbf{x},\hat{\mathbf{v}})} \gamma_\rho(\lambda')\psi(\mathbf{x}, v|\rho(t,\mathbf{x}+\lambda'\hat{\mathbf{v}}))\, d\lambda'$$

$$\bar{v}(t,\mathbf{x}|\rho(t,\mathbf{x}+\lambda'\hat{\mathbf{v}})) = \bar{v}_M \left(1 - \frac{\rho(t,\mathbf{x}+\lambda'\hat{\mathbf{v}})}{\rho_{th}}\right)_+$$



Nonlocality and radius limitation
tend to prevent overcrowding

Random polarization + volume filling

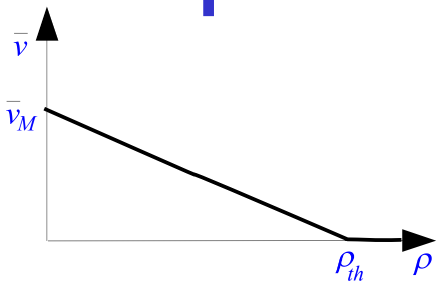
$$T[\rho](t,\mathbf{x},v,\hat{\mathbf{v}}) = \frac{1}{\displaystyle\int_{\mathbb{S}^{d-1}} \Gamma_0'(t,\mathbf{x},\hat{\mathbf{v}})\, d\hat{\mathbf{v}}} \int_0^{R_\rho(t,\mathbf{x},\hat{\mathbf{v}})} \gamma_\rho(\lambda')\psi(\mathbf{x},v|\rho(t,\mathbf{x}+\lambda'\hat{\mathbf{v}}))\, d\lambda'$$

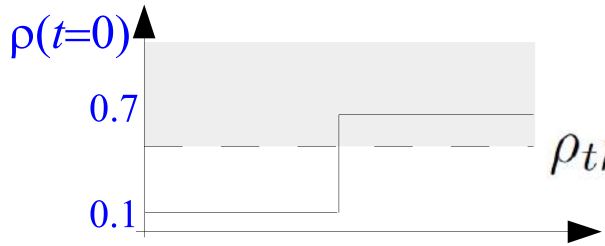
$$\bar{v}(t,\mathbf{x}|\rho(t,\mathbf{x}+\lambda'\hat{\mathbf{v}})) = \bar{v}_M \left(1 - \frac{\rho(t,\mathbf{x}+\lambda'\hat{\mathbf{v}})}{\rho_{th}}\right)_+$$

Hyperbolic scaling

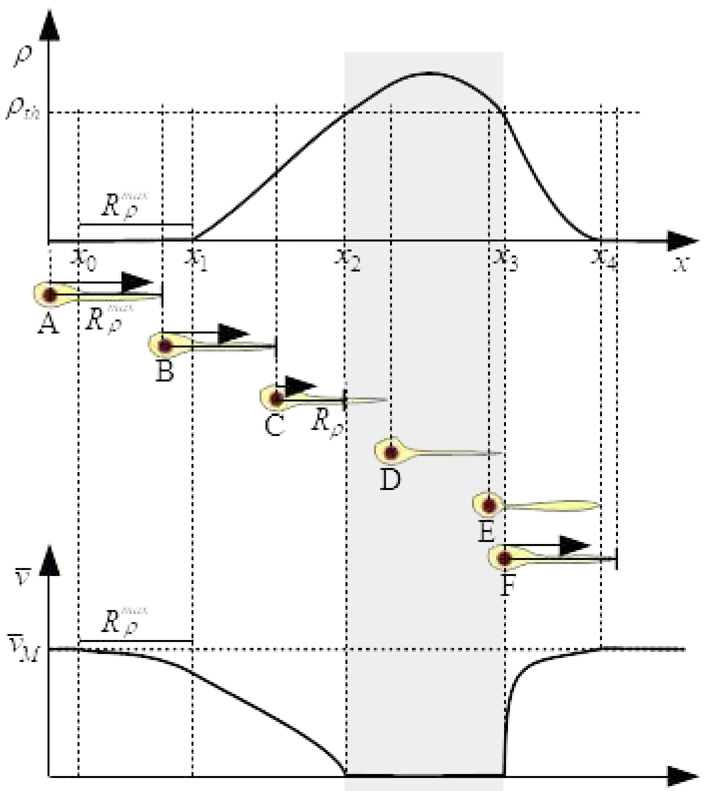
$$\frac{\partial\rho}{\partial\tau} + \nabla\cdot\left\{\rho\bar{v}_M \frac{1}{\displaystyle\int_{\mathbb{S}^{d-1}} \Gamma_0' d\hat{\mathbf{v}}}\left[\int_{\mathbb{S}^{d-1}} \Gamma_0'\hat{\mathbf{v}}\, d\hat{\mathbf{v}} - \frac{1}{\rho_{th}}\int_{\mathbb{S}^{d-1}}\left(\int_0^{R_\rho(\hat{\mathbf{v}})} \rho(\mathbf{x}+\lambda'\hat{\mathbf{v}})\gamma_\rho(\lambda')\, d\lambda'\right)\hat{\mathbf{v}}\, d\hat{\mathbf{v}}\right]_+\right\} = 0$$

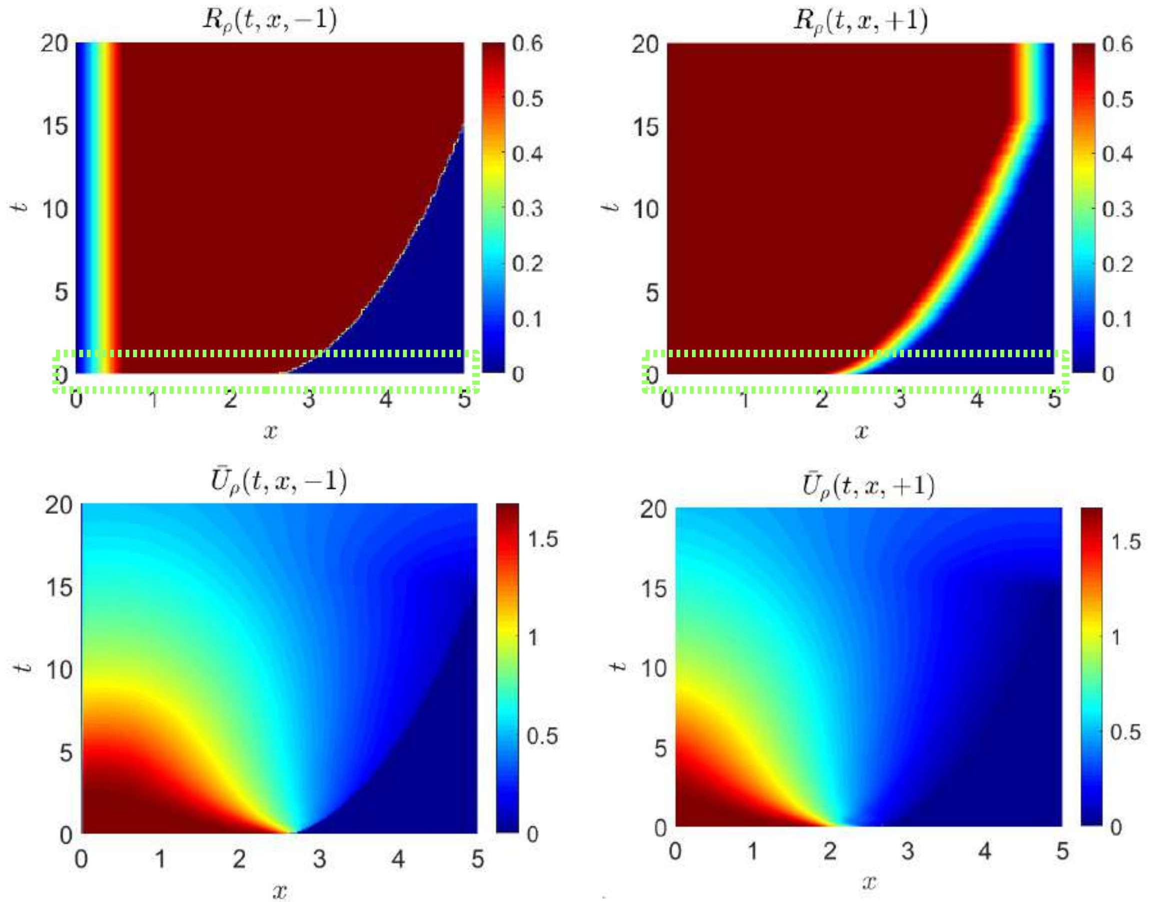
Volume filling as a Physical Limit of Migration





$\rho_{th} = 0.5 \qquad \gamma_\rho = H$

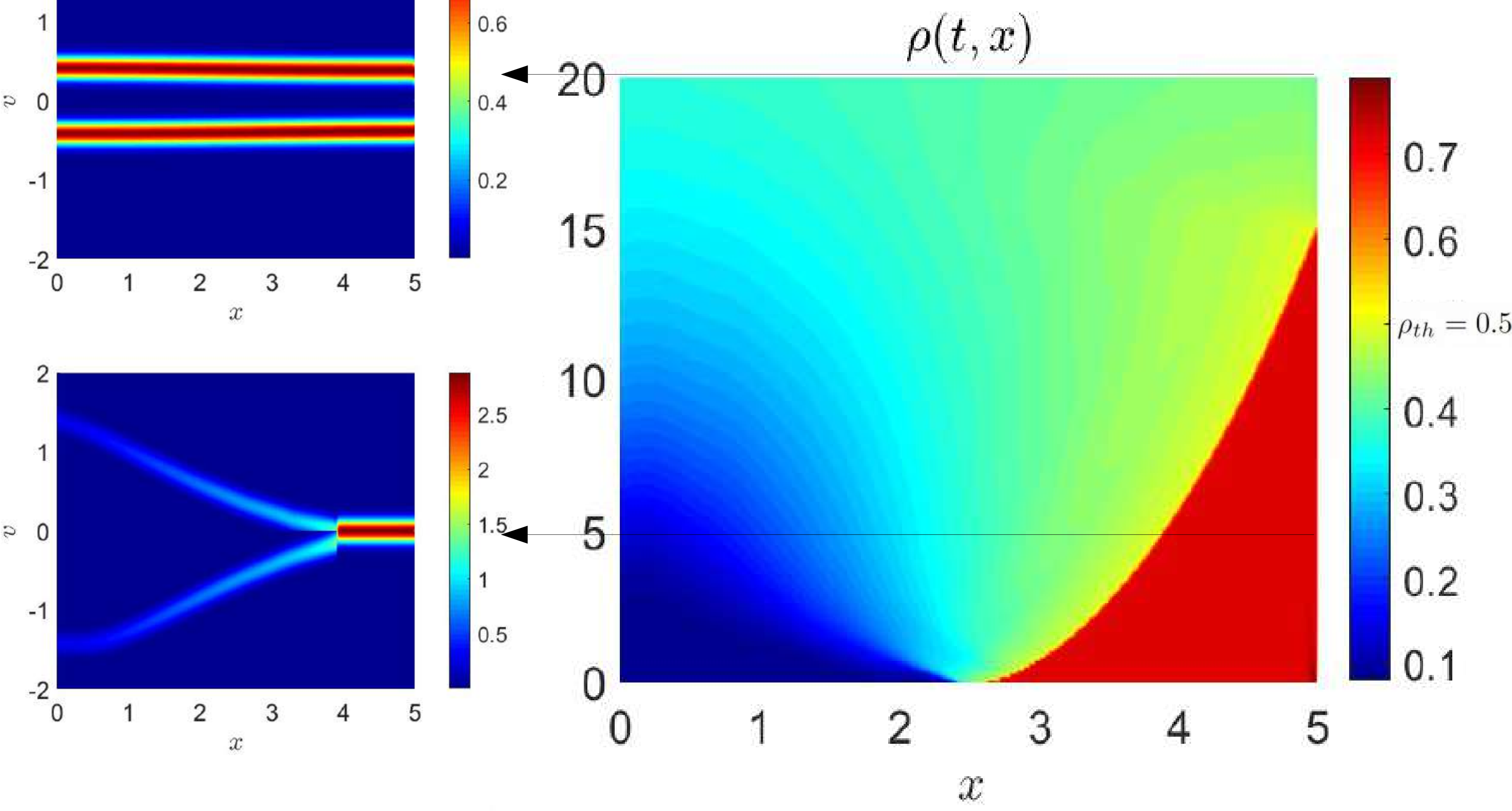




Volume filling as a Physical Limit of Migration

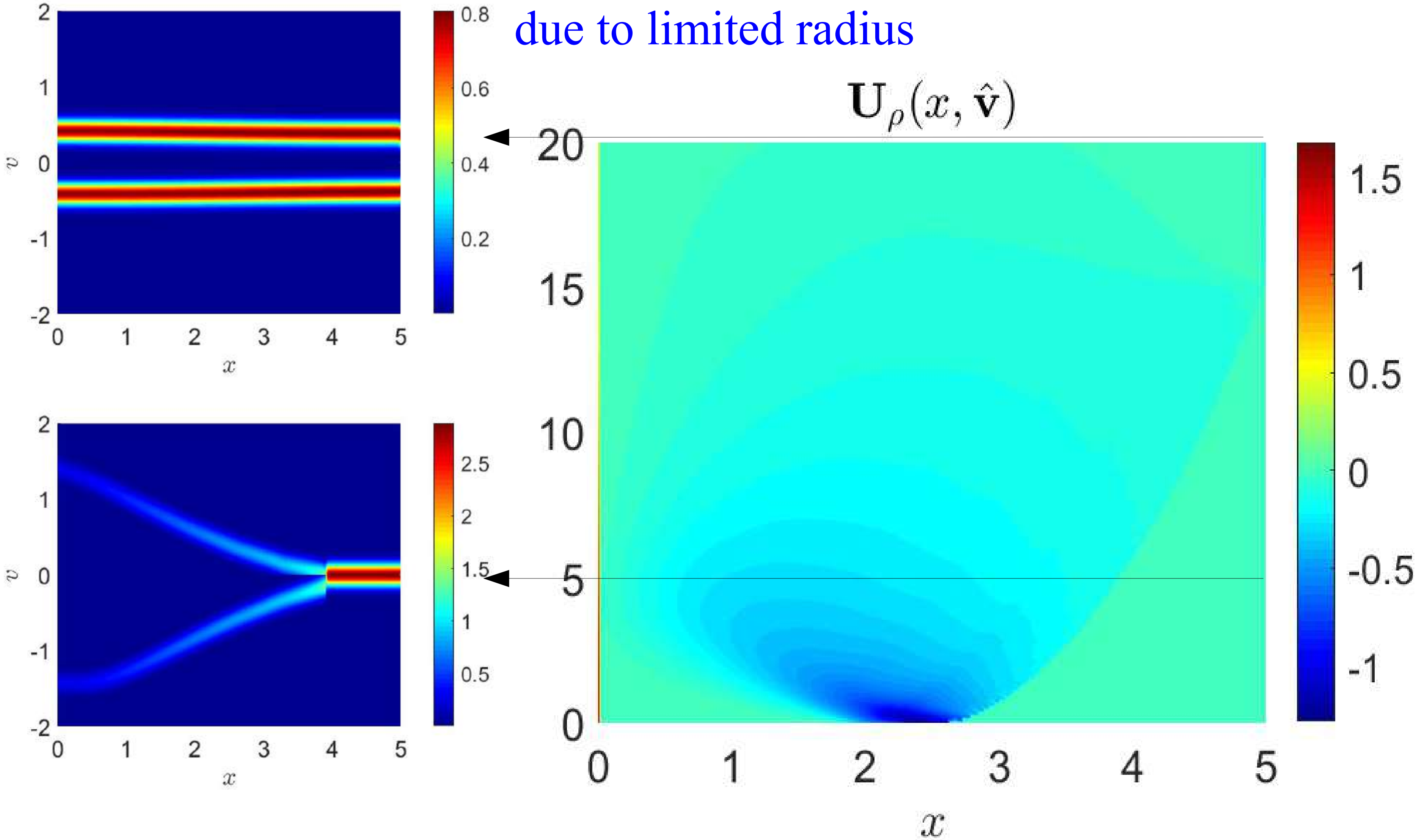
No motion in the overcrowded region due to limited radius

Nonlocality drives dispersal from the interface

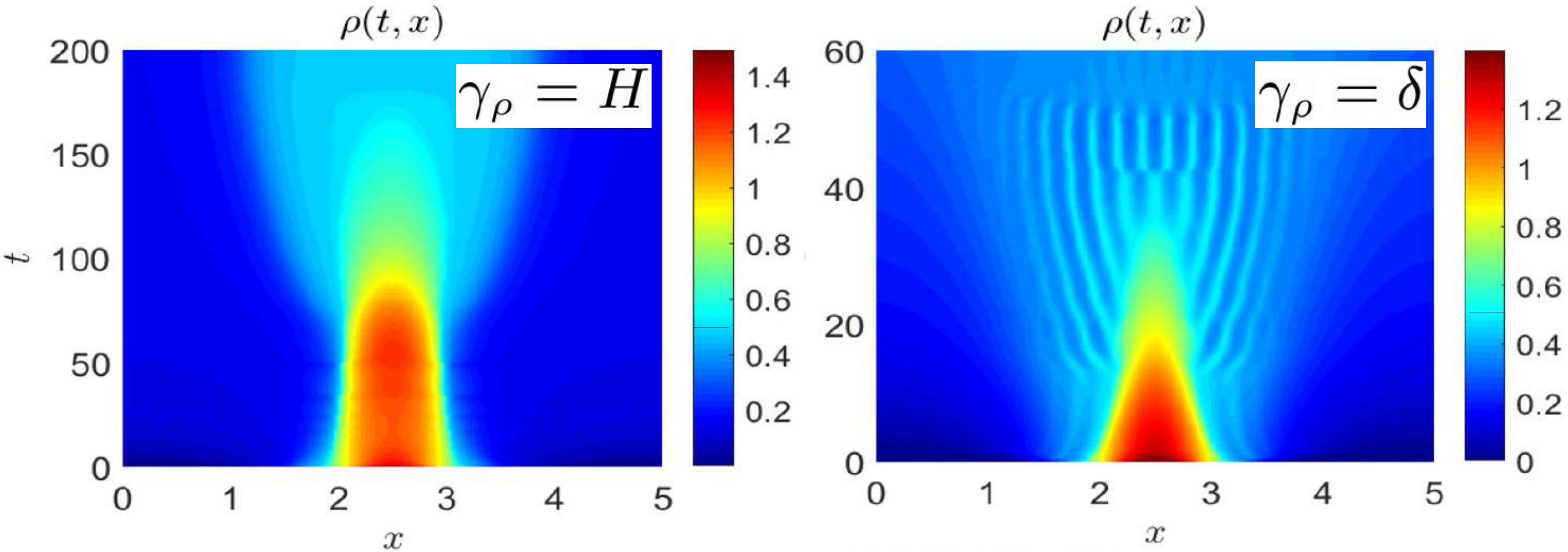


Volume filling as a Physical Limit of Migration

Cell do not move in the overcrowded region due to limited radius



Volume filling



$$R_\rho^{max} = 0.2 \quad \rho_{th} = 0.5.$$

Stability

$$\frac{\partial p}{\partial t}(t,\mathbf{x},v,\hat{\mathbf{v}}) + v\hat{\mathbf{v}}\cdot\nabla p(t,\mathbf{x},v,\hat{\mathbf{v}}) = \frac{1}{\mathscr{V}}\left[\frac{\rho(t,\mathbf{x})}{\Gamma|\mathbb{S}^{d-1}|}\int_{\mathbb{R}_+}\gamma(\lambda)\psi(v|\rho(t,\mathbf{x}+\lambda\hat{\mathbf{v}}))\,\mathrm{d}\lambda - p(t,\mathbf{x},v,\hat{\mathbf{v}})\right]$$

Homogeneous equilibrium: $p_\infty = \dfrac{1}{|\mathbb{S}^{d-1}|}\psi(v|1)$

Perturbation equation

$$\frac{\partial p}{\partial t}(t,\mathbf{x},v,\hat{\mathbf{v}}) + v\hat{\mathbf{v}}\cdot\nabla p(t,\mathbf{x},v,\hat{\mathbf{v}}) =$$

$$\frac{1}{\mathscr{V}}\left[\frac{\rho(t,\mathbf{x})}{|\mathbb{S}^{d-1}|}\psi(v|1) + \frac{1}{\Gamma|\mathbb{S}^{d-1}|}\int_{\mathbb{R}_+}\gamma(\lambda)\rho(t,\mathbf{x}+\lambda\hat{\mathbf{v}})\,\mathrm{d}\lambda\,\frac{\partial\psi}{\partial\rho}(v|1) - p(t,\mathbf{x},v,\hat{\mathbf{v}})\right]$$

POLITECNICO DI TORINO

Stability

$$p(t, \mathbf{x}, v, \hat{\mathbf{v}}) = g(v, \hat{\mathbf{v}}) e^{i\mathbf{k}\cdot\mathbf{x} + \sigma t} \qquad \rho_g = \int_{\mathbb{S}^{d-1}} \int_0^U g(v, \hat{\mathbf{v}}) \, dv \, d\hat{\mathbf{v}}$$

$$\left(\sigma + i\mathbf{k}\cdot\hat{\mathbf{v}} v + \frac{1}{\mathscr{V}}\right) g = \frac{1}{\mathscr{V}|\mathbb{S}^{d-1}|} \left[\psi(v|1) + \hat{\gamma}(\mathbf{k}\cdot\hat{\mathbf{v}}) \frac{\partial\psi}{\partial\rho}(v|1)\right] \rho_g$$

$$\boxed{\mathscr{V} = \frac{\bar{v}(\rho_\infty)}{R\mu}} \qquad \hat{\gamma}(\mathbf{k}\cdot\hat{\mathbf{v}}) = \frac{1}{\Gamma} \int_{\mathbb{R}_+} \gamma(\lambda) e^{i\mathbf{k}\cdot\hat{\mathbf{v}}\lambda} \, d\lambda$$

$$\begin{cases} \displaystyle\int_{\mathbb{S}^{d-1}} \int_0^U \frac{\left[\psi(v|1) + \frac{\partial\psi}{\partial\rho}(v|1)\hat{\gamma}_c(\mathbf{k}\cdot\hat{\mathbf{v}})\right]\left(\sigma_r + \frac{1}{\mathscr{V}}\right) + \frac{\partial\psi}{\partial\rho}(v|1)\hat{\gamma}_s(\mathbf{k}\cdot\hat{\mathbf{v}})(\sigma_i + \mathbf{k}\cdot\hat{\mathbf{v}}v)}{\left(\sigma_r + \frac{1}{\mathscr{V}}\right)^2 + (\sigma_i + \mathbf{k}\cdot\hat{\mathbf{v}}v)^2} \, dv \, d\hat{\mathbf{v}} = |\mathbb{S}^{d-1}|\mathscr{V} \\ \displaystyle\int_{\mathbb{S}^{d-1}} \int_0^U \frac{\left[\psi(v|1) + \frac{\partial\psi}{\partial\rho}(v|1)\hat{\gamma}_c(\mathbf{k}\cdot\hat{\mathbf{v}})\right](\sigma_i + \mathbf{k}\cdot\hat{\mathbf{v}}v) - \frac{\partial\psi}{\partial\rho}(v|1)\hat{\gamma}_s(\mathbf{k}\cdot\hat{\mathbf{v}})\mathbf{k}\cdot\hat{\mathbf{v}}v\left(\sigma + \frac{1}{\mathscr{V}}\right)}{\left(\sigma_r + \frac{1}{\mathscr{V}}\right)^2 + (\sigma_i + \mathbf{k}\cdot\hat{\mathbf{v}}v)^2} \, dv \, d\hat{\mathbf{v}} = 0, \end{cases}$$

$$\hat{\gamma}_c(\mathbf{k}\cdot\hat{\mathbf{v}}) = \frac{1}{\Gamma}\int_{\mathbb{R}_+} \gamma(\lambda)\cos(\lambda\mathbf{k}\cdot\hat{\mathbf{v}}) \, d\lambda\,, \quad \text{and} \quad \hat{\gamma}_s(\mathbf{k}\cdot\hat{\mathbf{v}}) = \frac{1}{\Gamma}\int_{\mathbb{R}_+} \gamma(\lambda)\sin(\lambda\mathbf{k}\cdot\hat{\mathbf{v}}) \, d\lambda$$

POLITECNICO DI TORINO

Stability

$$p(t,\mathbf{x},v,\hat{\mathbf{v}}) = g(v,\hat{\mathbf{v}})e^{i\mathbf{k}\cdot\mathbf{x}+\sigma t} \qquad \rho_g = \int_{\mathbb{S}^{d-1}}\int_0^U g(v,\hat{\mathbf{v}})\,\mathrm{d}v\,\mathrm{d}\hat{\mathbf{v}}$$

$$\left(\sigma + i\mathbf{k}\cdot\hat{\mathbf{v}}v + \frac{1}{\mathscr{V}}\right) g = \frac{1}{\mathscr{V}|\mathbb{S}^{d-1}|}\left[\psi(v|1) + \hat{\gamma}(\mathbf{k}\cdot\hat{\mathbf{v}})\frac{\partial\psi}{\partial\rho}(v|1)\right]\rho_g$$

$$\boxed{\mathscr{V} = \frac{\bar{v}(\rho_\infty)}{R\mu}} \qquad \frac{1}{\Gamma}\int_{\mathbb{R}_+}\gamma(\lambda)e^{i\mathbf{k}\cdot\hat{\mathbf{v}}\lambda}\,\mathrm{d}\lambda$$

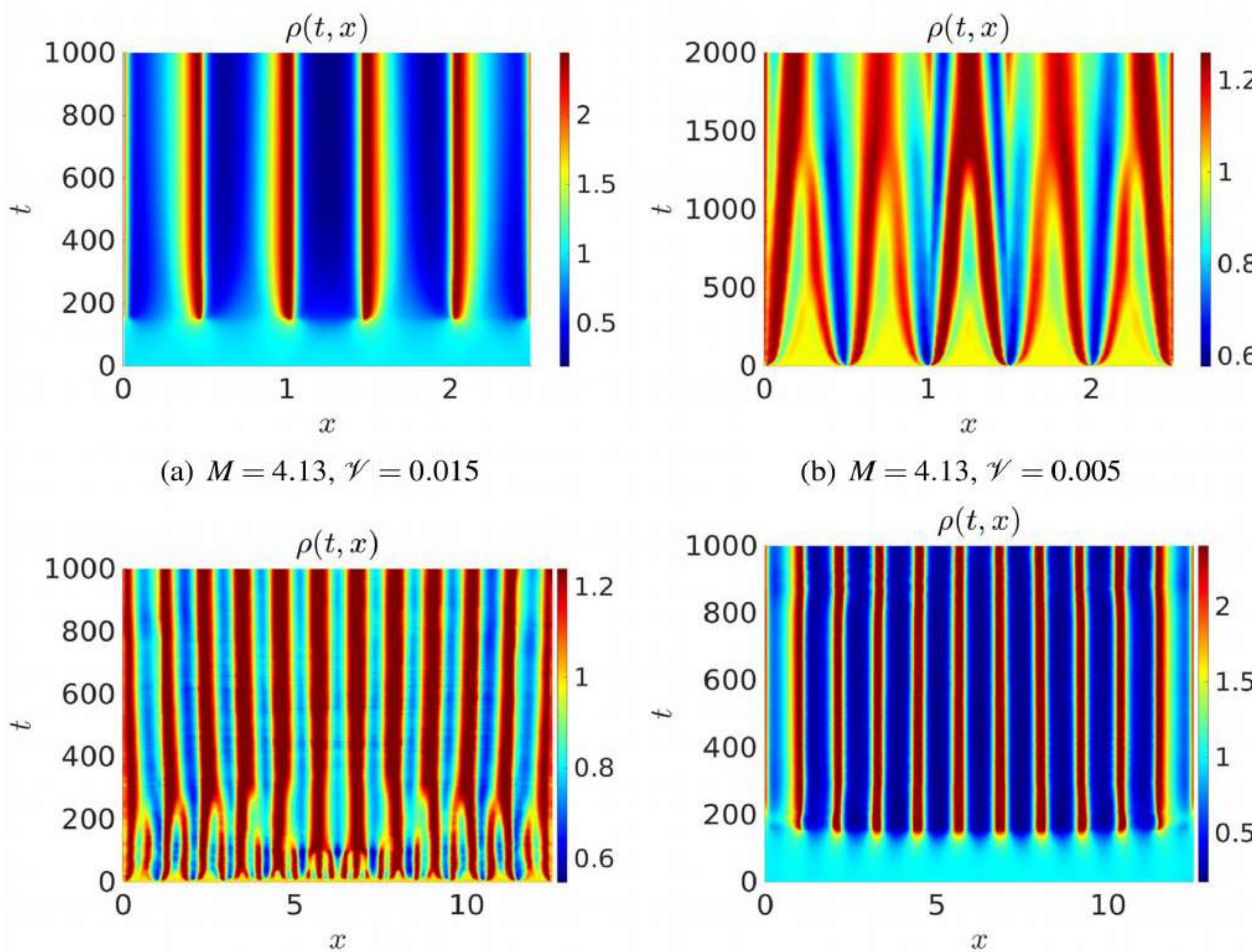
In 1D

$$\begin{cases} \left[\psi(v|1) + \dfrac{\partial\psi}{\partial\rho}(v|1)\hat{\gamma}_c(k)\right]\sigma_i = 0 \\[2ex] 1 = \dfrac{1}{\mathscr{V}}\displaystyle\int_0^U \dfrac{\left(\psi(v|1) + \dfrac{\partial\psi}{\partial\rho}(v|1)\hat{\gamma}_c(k)\right)\left(\sigma + \dfrac{1}{\mathscr{V}}\right) + \dfrac{\partial\psi}{\partial\rho}(v|1)\hat{\gamma}_s(k)kv}{\left(\sigma + \dfrac{1}{\mathscr{V}}\right)^2 + k^2v^2}\,\mathrm{d}v \end{cases}$$

$$\hat{\gamma}_c(\mathbf{k}\cdot\hat{\mathbf{v}}) = \frac{1}{\Gamma}\int_{\mathbb{R}_+}\gamma(\lambda)\cos(\lambda\mathbf{k}\cdot\hat{\mathbf{v}})\,\mathrm{d}\lambda\,, \quad \text{and} \quad \hat{\gamma}_s(\mathbf{k}\cdot\hat{\mathbf{v}}) = \frac{1}{\Gamma}\int_{\mathbb{R}_+}\gamma(\lambda)\sin(\lambda\mathbf{k}\cdot\hat{\mathbf{v}})\,\mathrm{d}\lambda$$

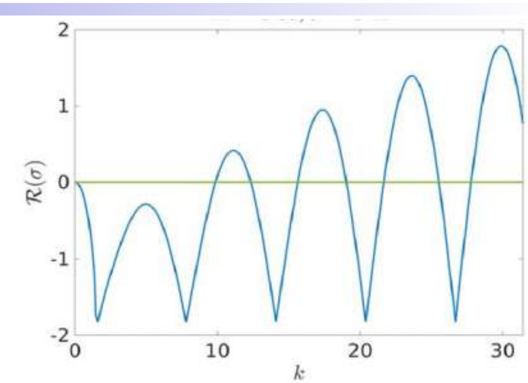
Stability: Dirac sensing

Always unstable to short waves



(a) $M = 4.13$, $\mathscr{V} = 0.015$ (b) $M = 4.13$, $\mathscr{V} = 0.005$

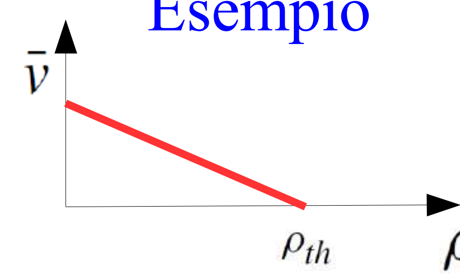
(c) $M = 0.68$, $\mathscr{V} = 0.02$ (d) $M = 0.68$, $\mathscr{V} = 0.008$



$$\mathcal{V} = \frac{\bar{v}(\rho_\infty)}{R\mu}$$

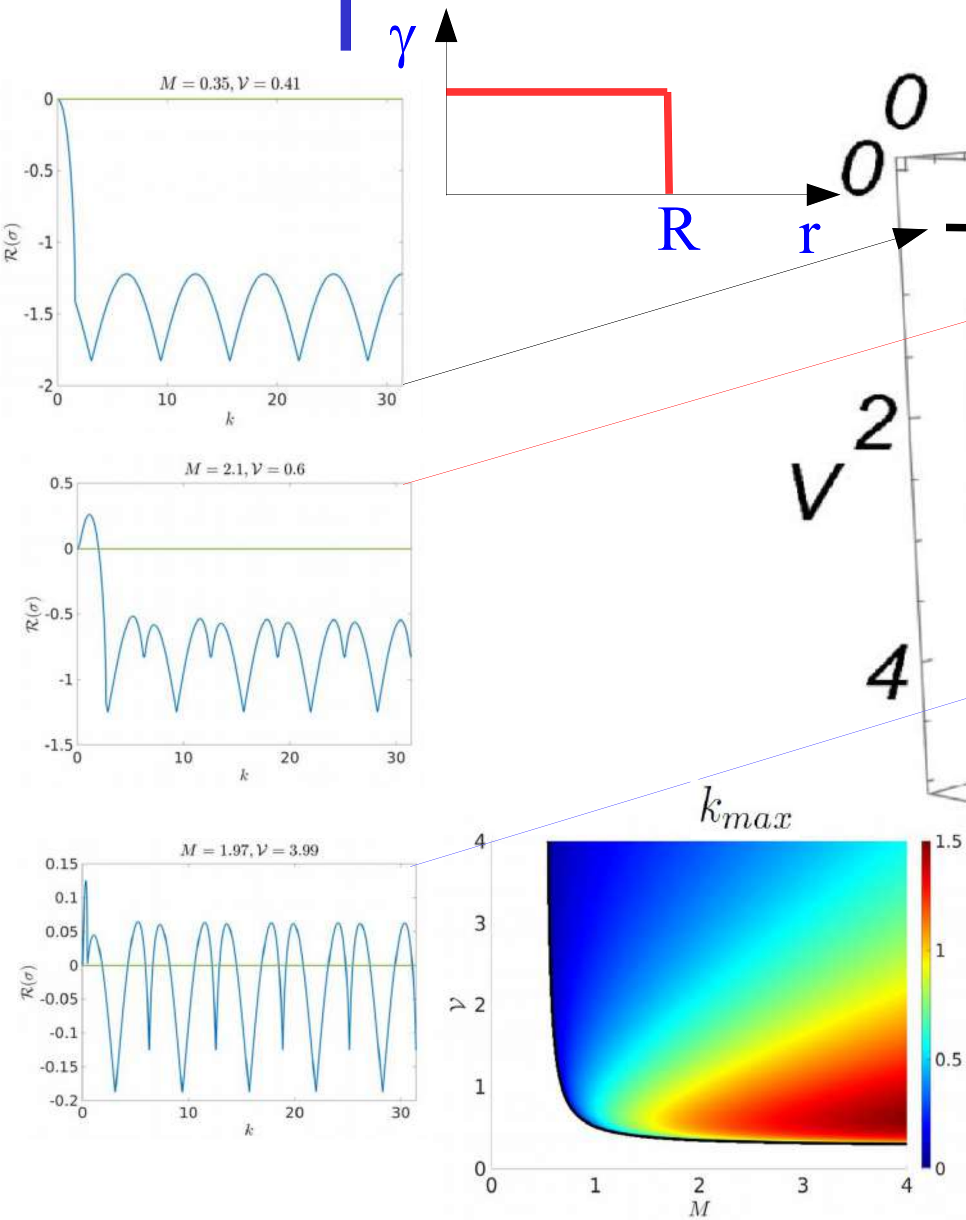
$$M = -\frac{\bar{v}'(\rho_\infty)}{\bar{v}(\rho_\infty)}R$$

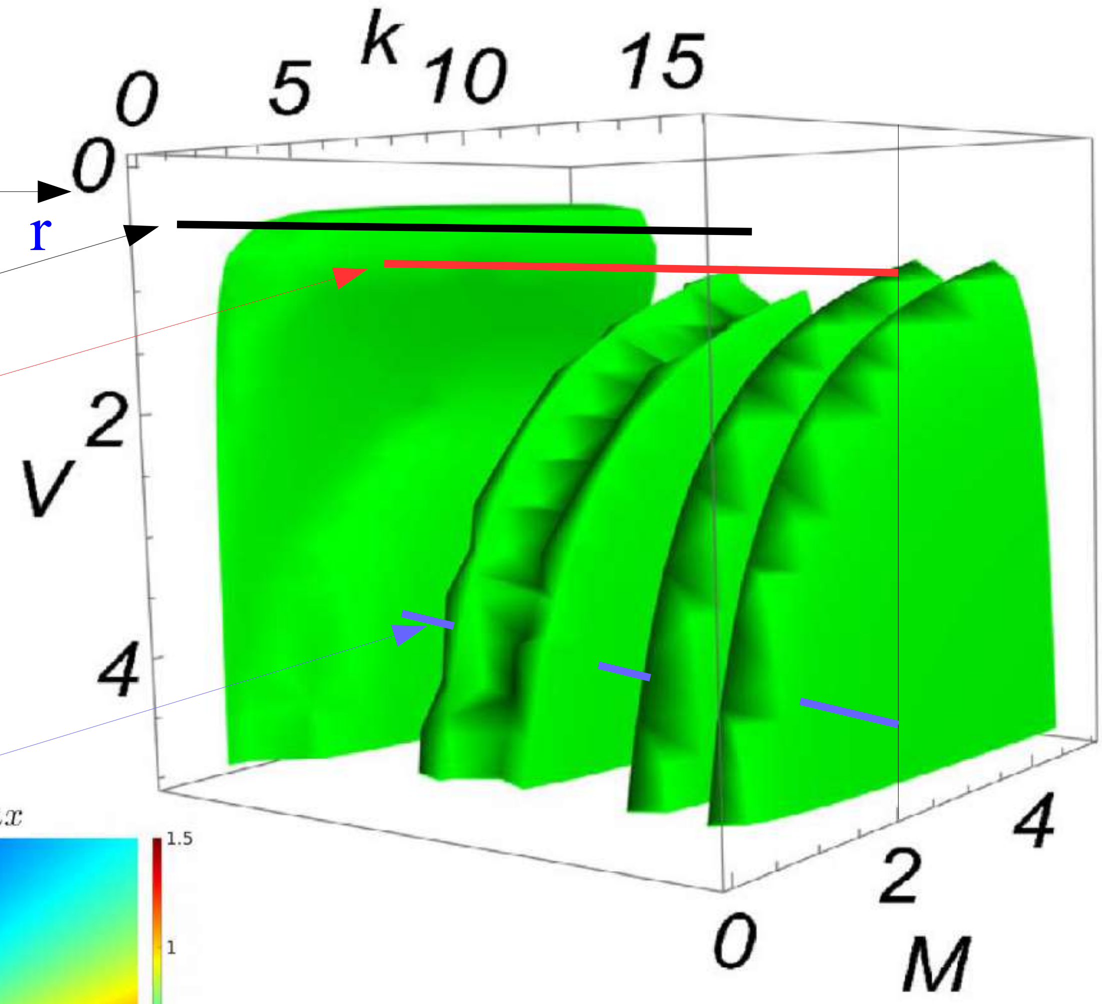
Esempio



$$M = \frac{\rho_\infty}{\rho_{th} - \rho_\infty}$$

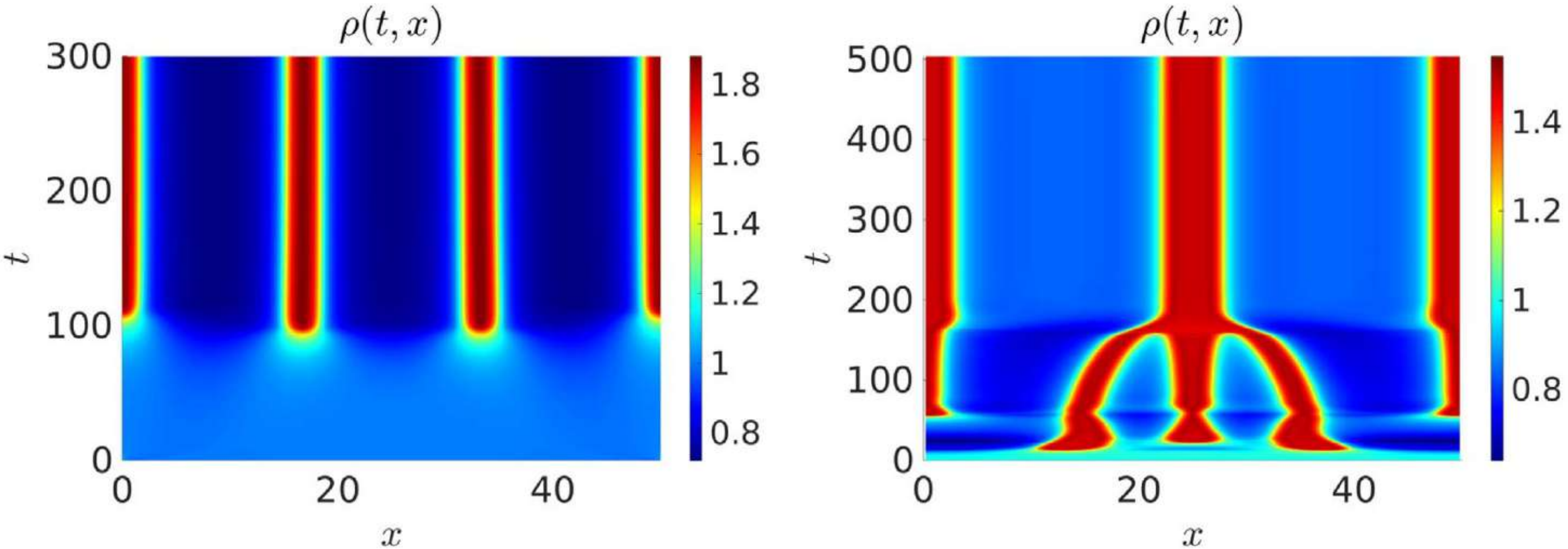
Stability:Uniform sensing





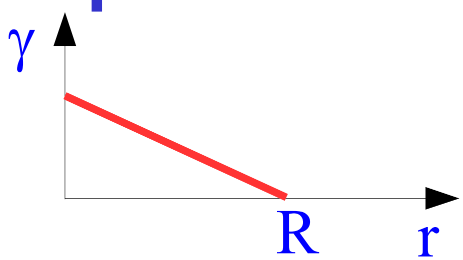
$$\mathcal{V} = \frac{\bar{v}(\rho_\infty)}{R\mu} \qquad M = -\frac{\bar{v}'(\rho_\infty)}{\bar{v}(\rho_\infty)}R$$

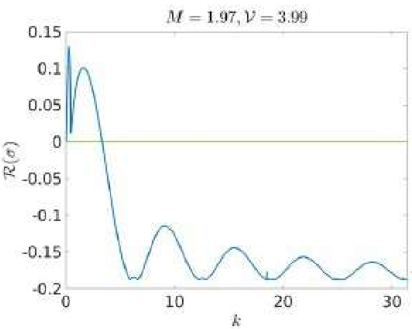
Stability:Uniform sensing

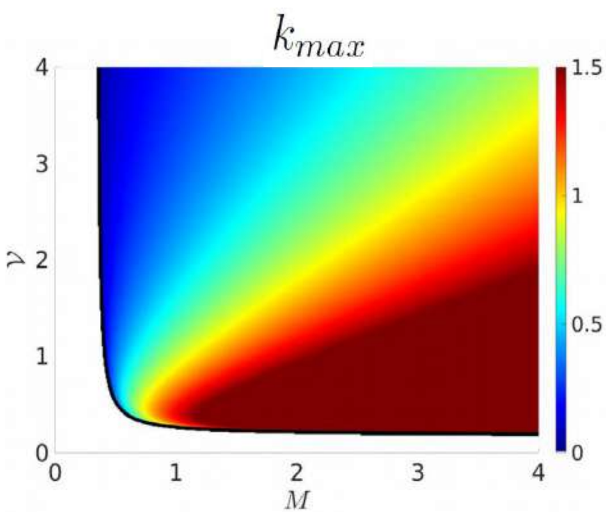


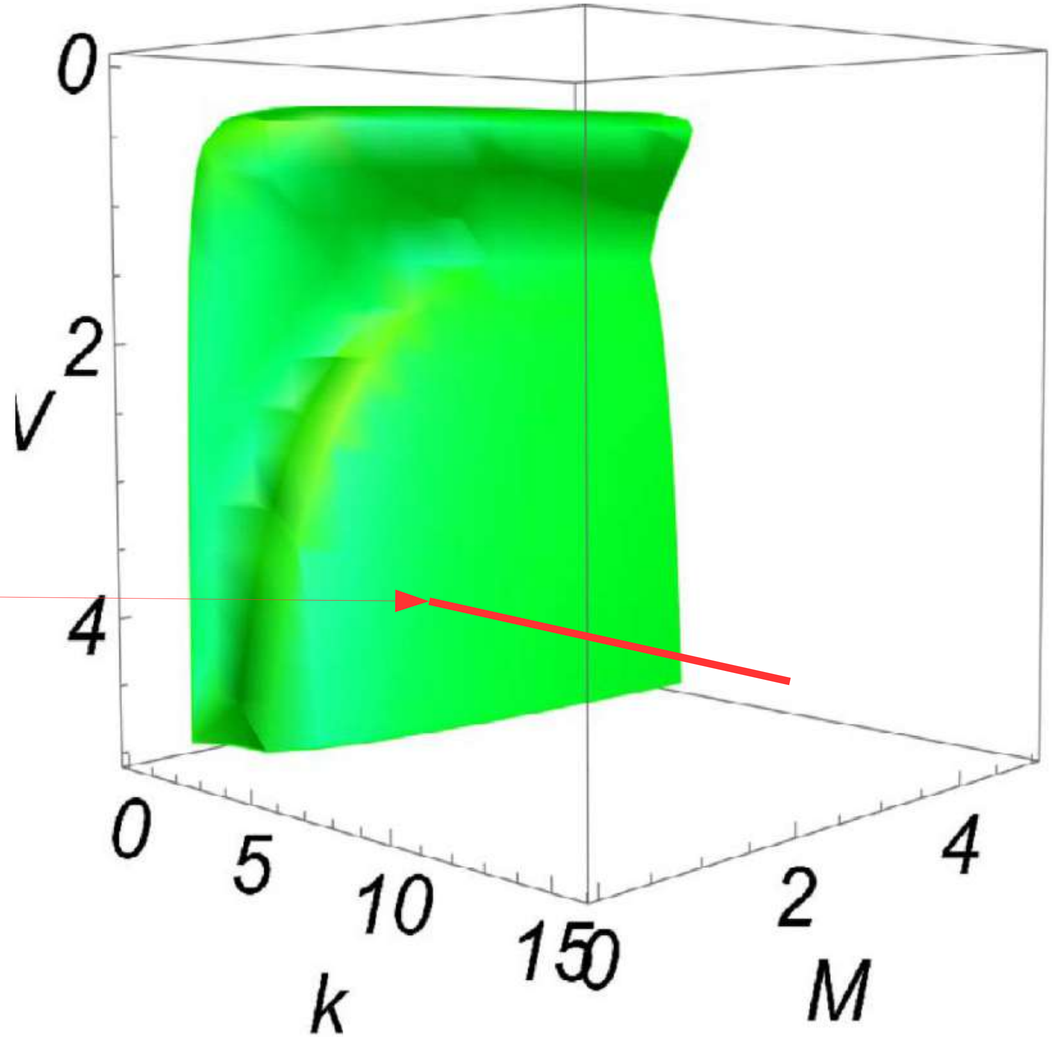
(a) $M = 1.01, \mathscr{V} = 1.65, k_{max} = 0.35, \Lambda = 17.95$ (b) $M = 1.97, \mathscr{V} = 3.99, k_{max} = 0.28, \Lambda = 22.42$

Stability: Decreasing sensing



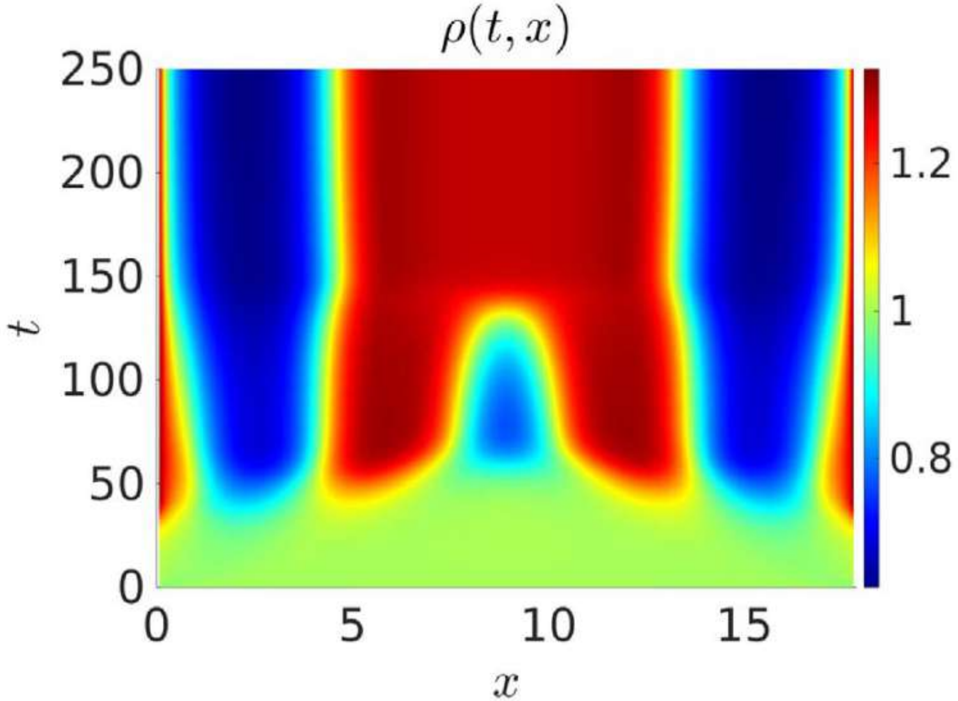






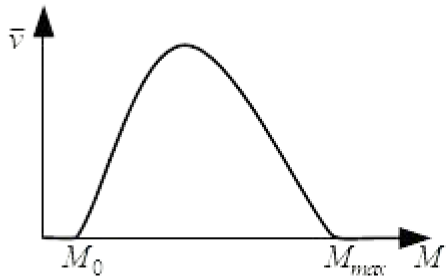
$$\mathcal{V} = \frac{\bar{v}(\rho_\infty)}{R\mu} \qquad M = -V'(1)$$

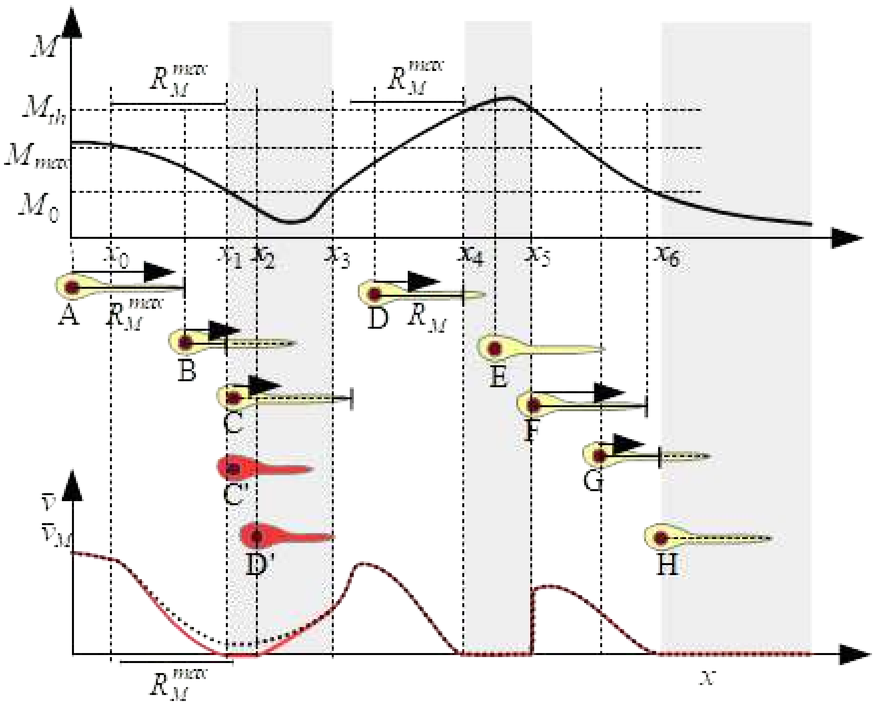
Stability: Decreasing sensing



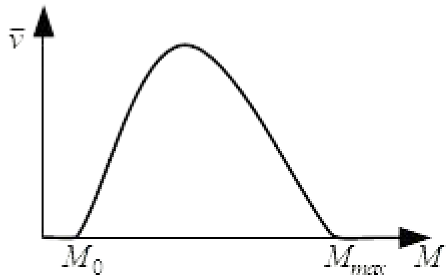
(c) $M = 2.1$, $\mathscr{V} = 0.6$, $k_{max} = 1$, $\Lambda = 6.3$

ECM as a Physical Limit of Migration

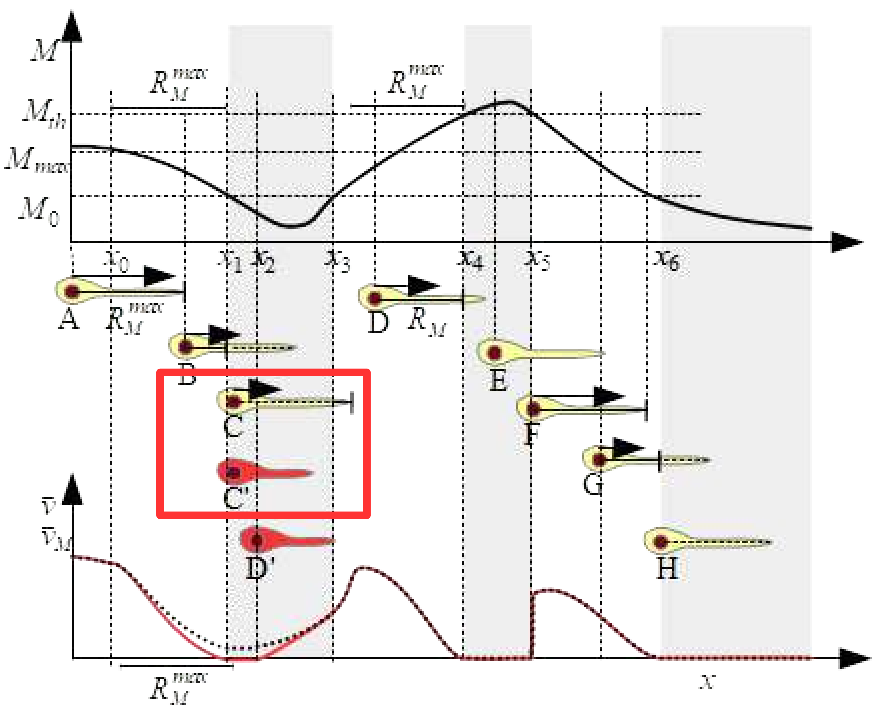




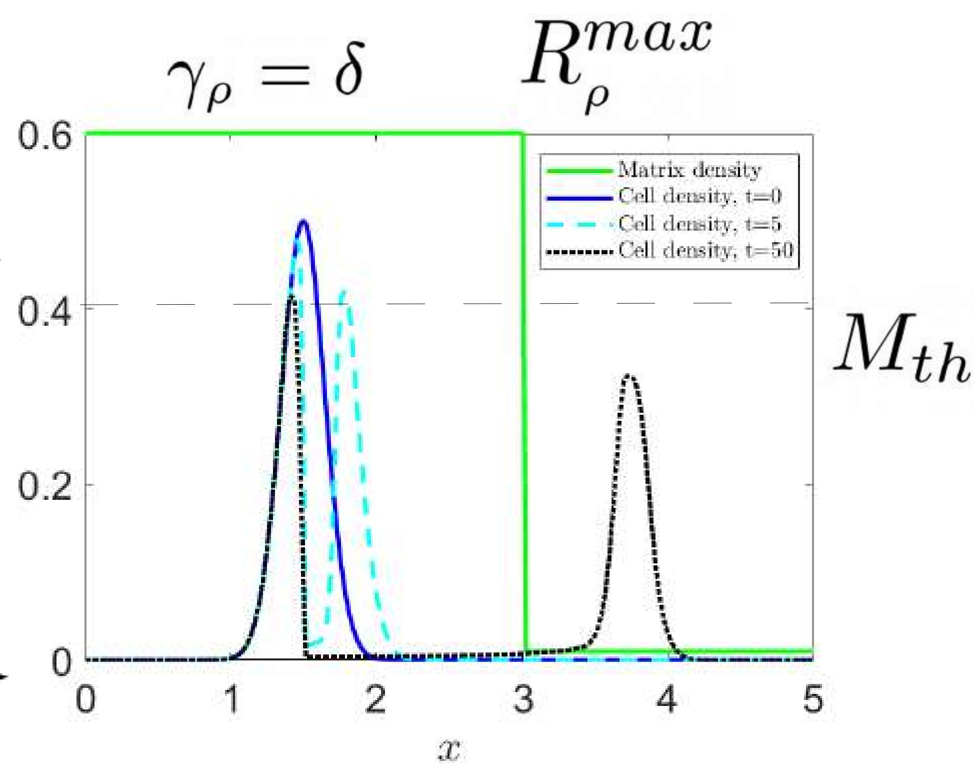
ECM barrier



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

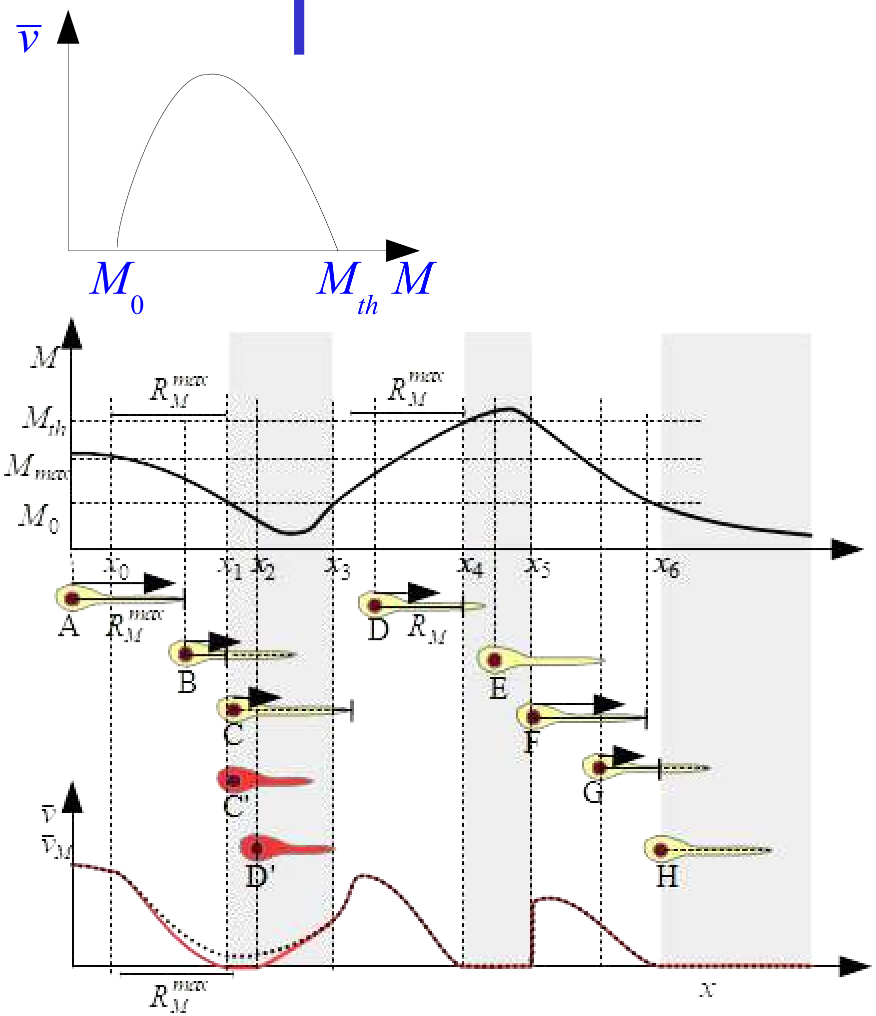


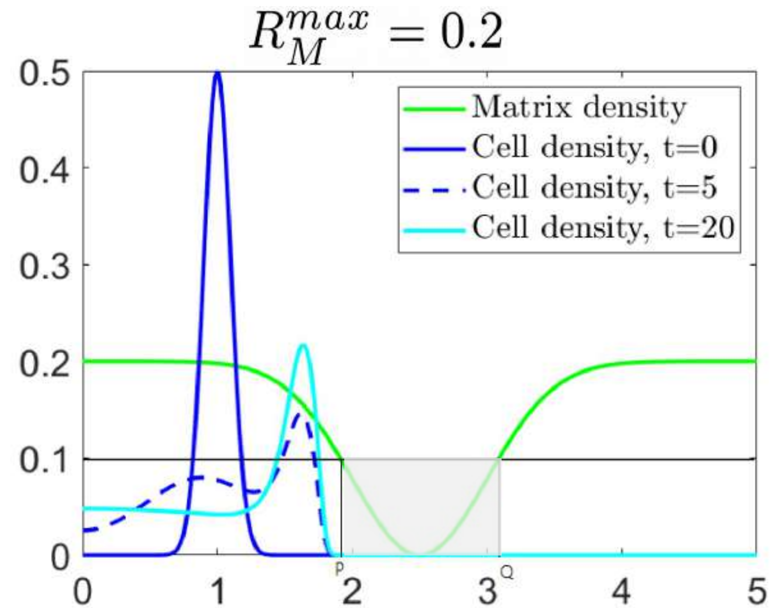
M
M_{th}
M_{max}
M_0
R_M^{max}
x_0
x_1
x_2
x_3
x_4
x_5
x_6
A
B
C
C'
D
D'
E
F
G
H
R_M
$\bar{v}$
$\bar{v}_M$
x

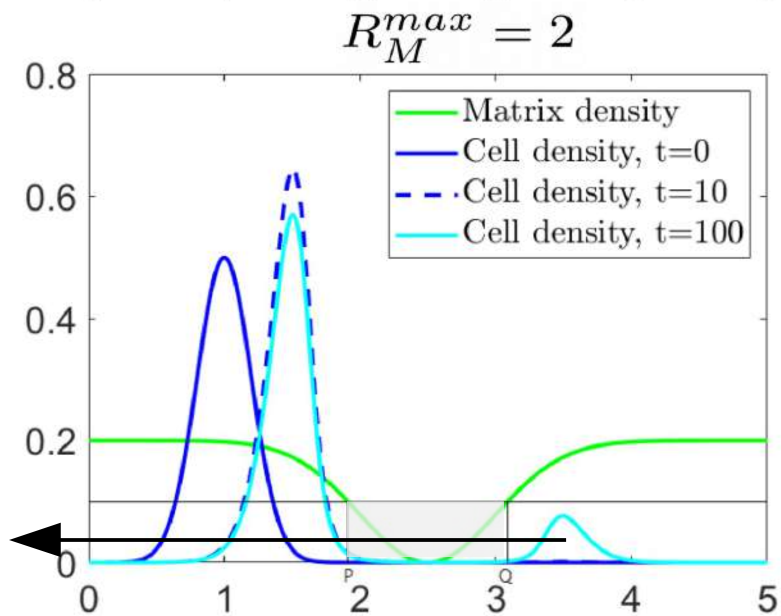


$\gamma_\rho = \delta$
R_ρ^{max}
M_{th}
Matrix density
Cell density, t=0
Cell density, t=5
Cell density, t=50
0.6
0.4
0.2
0
0
1
2
3
4
5
x

Lack of adhesion sites



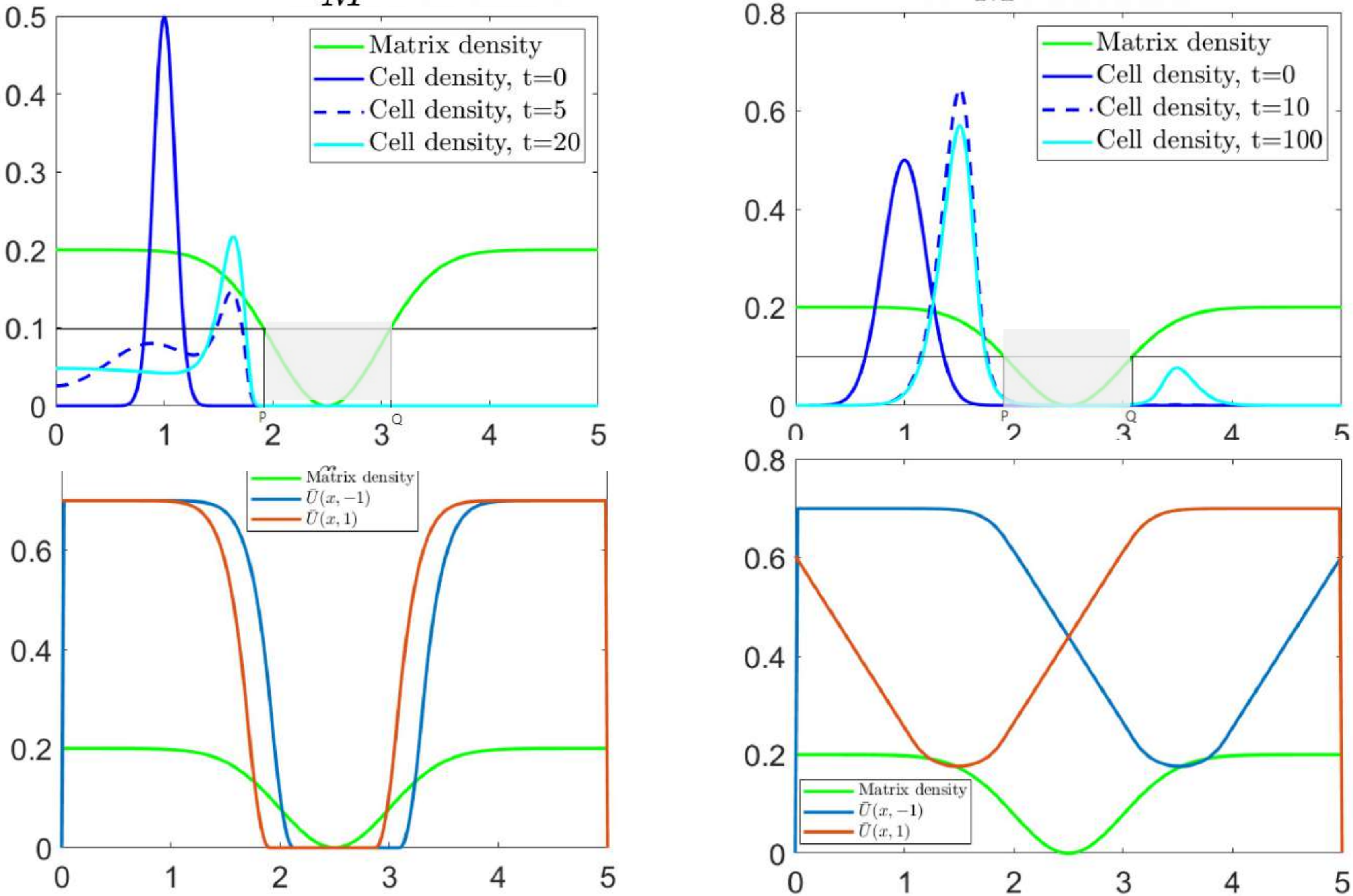




Nonlocality allows jumping beyond the pit

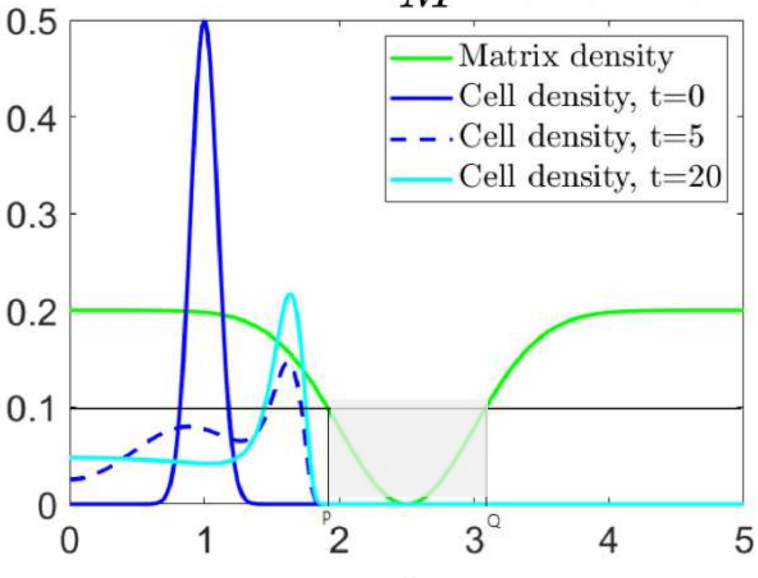
Poor ECM

$R_M^{max} = 0.2$ $\qquad$ $R_M^{max} = 2$

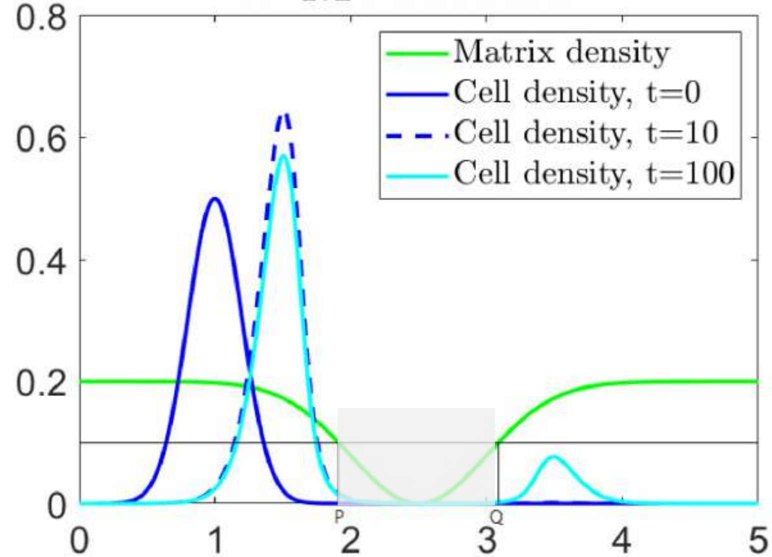


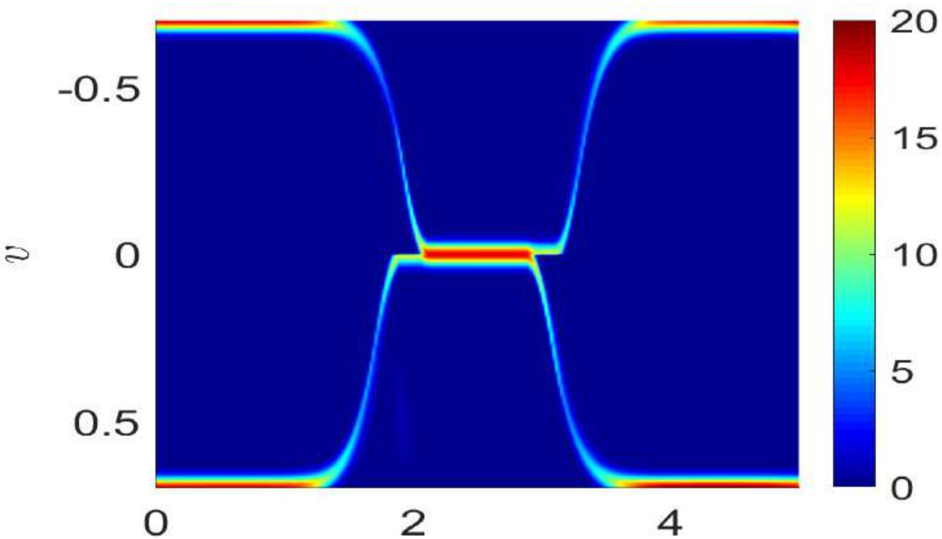
Poor ECM

$R_M^{max} = 0.2$



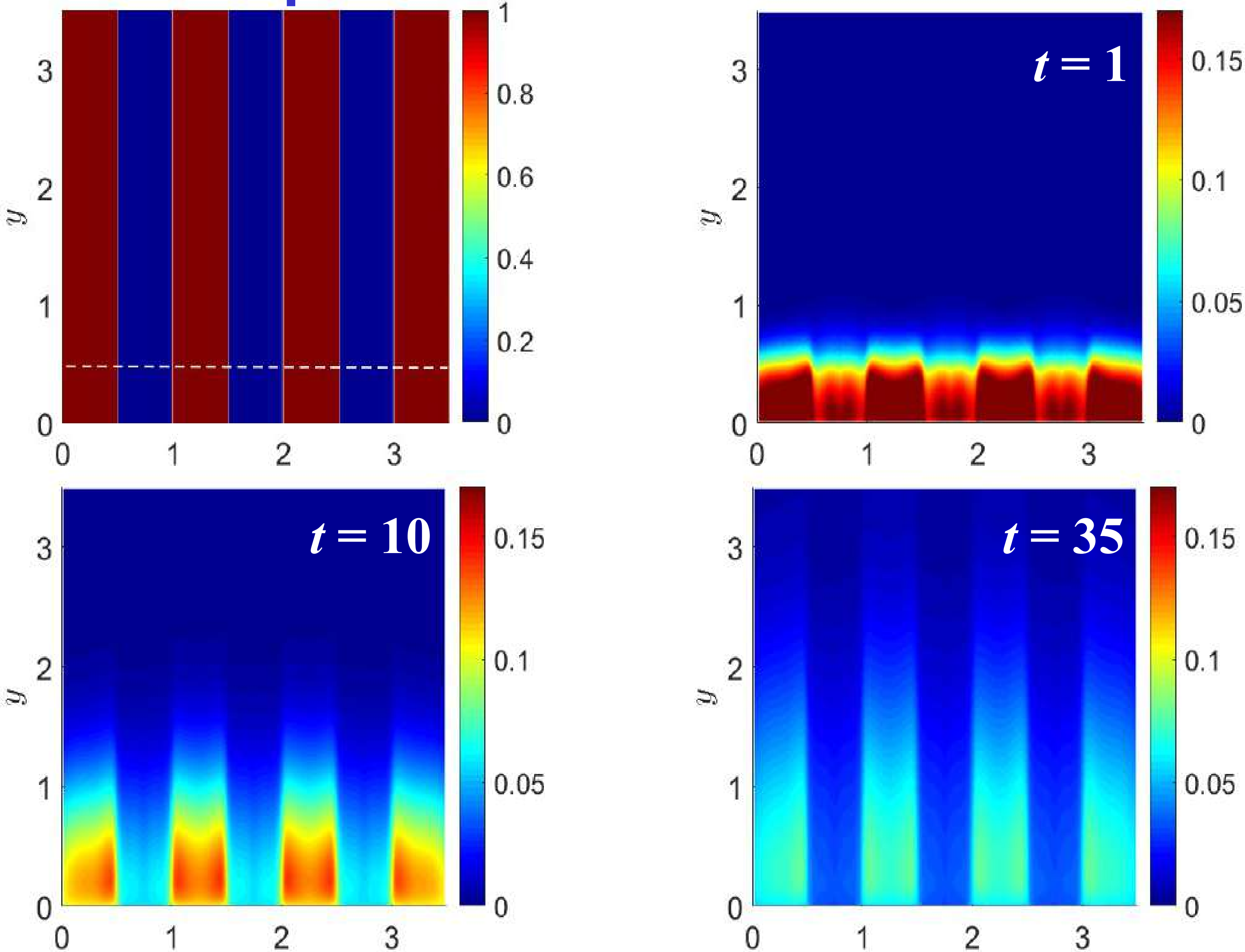
$R_M^{max} = 2$

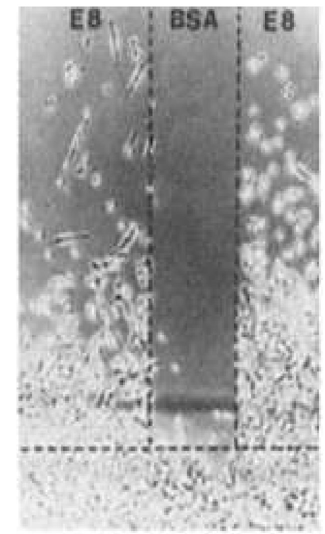




Nonlocality allows jumping beyond the pit

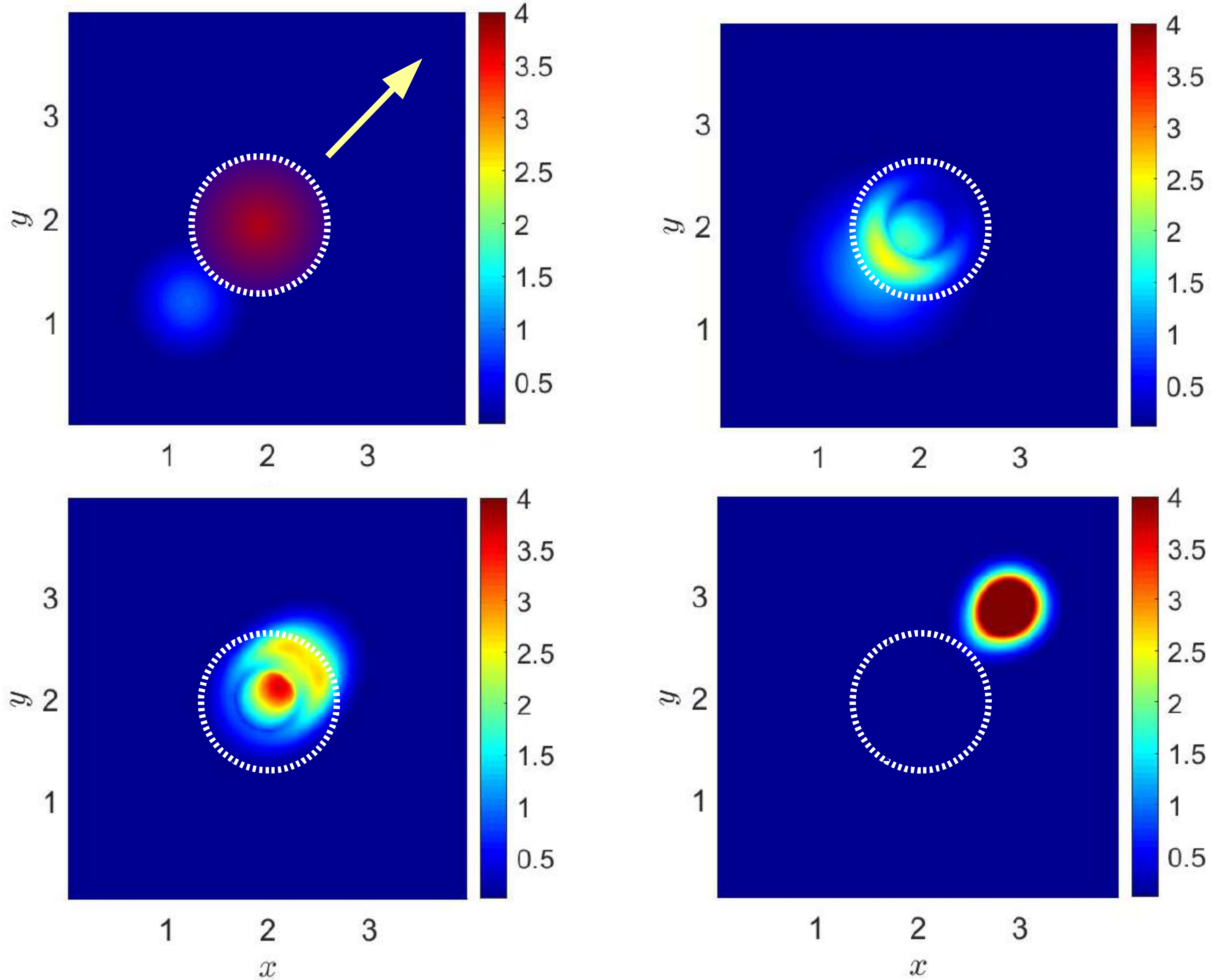
Stripes





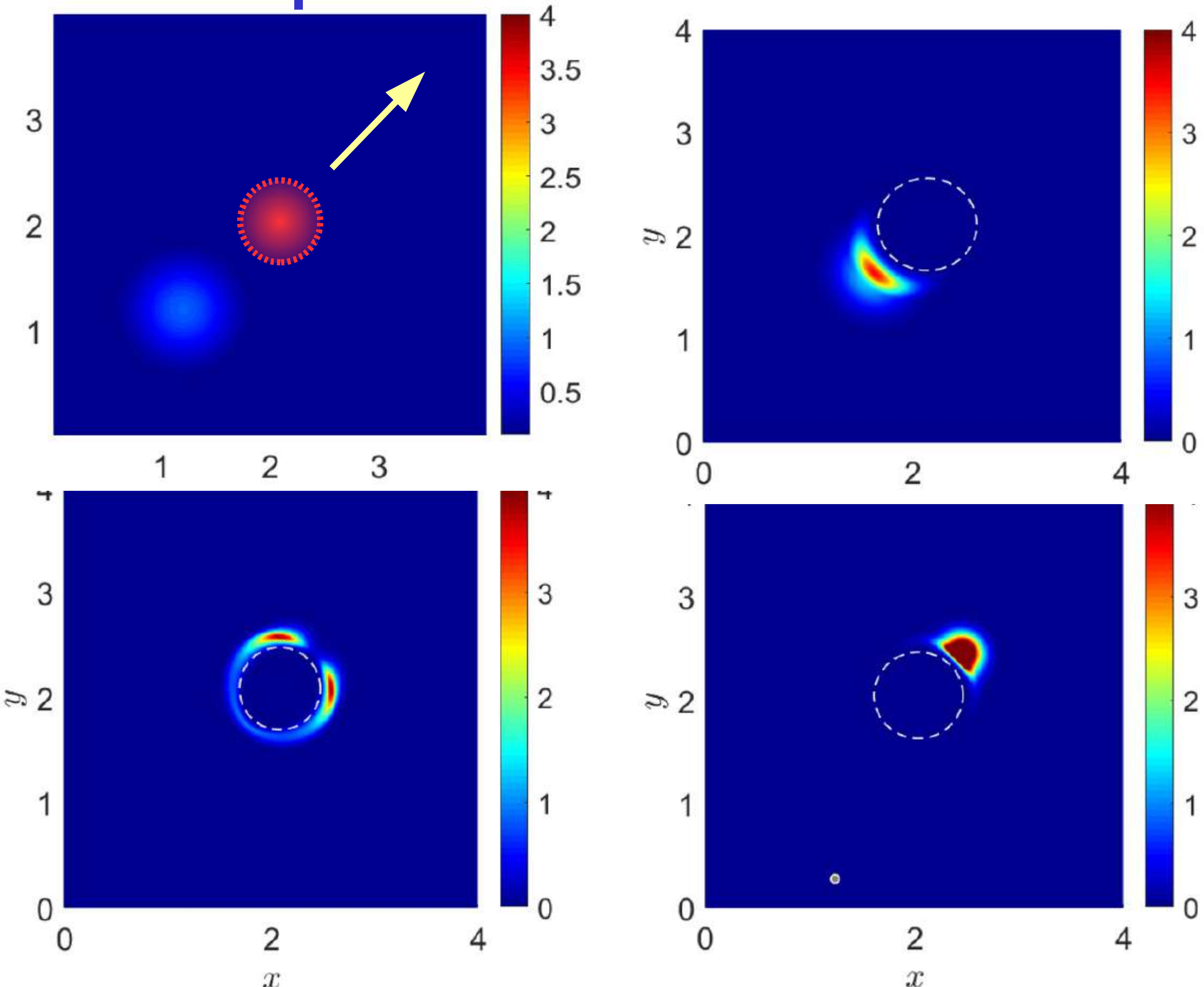
Nonlocality allows jumping on the stripes

Double bias: Effect of independent cues



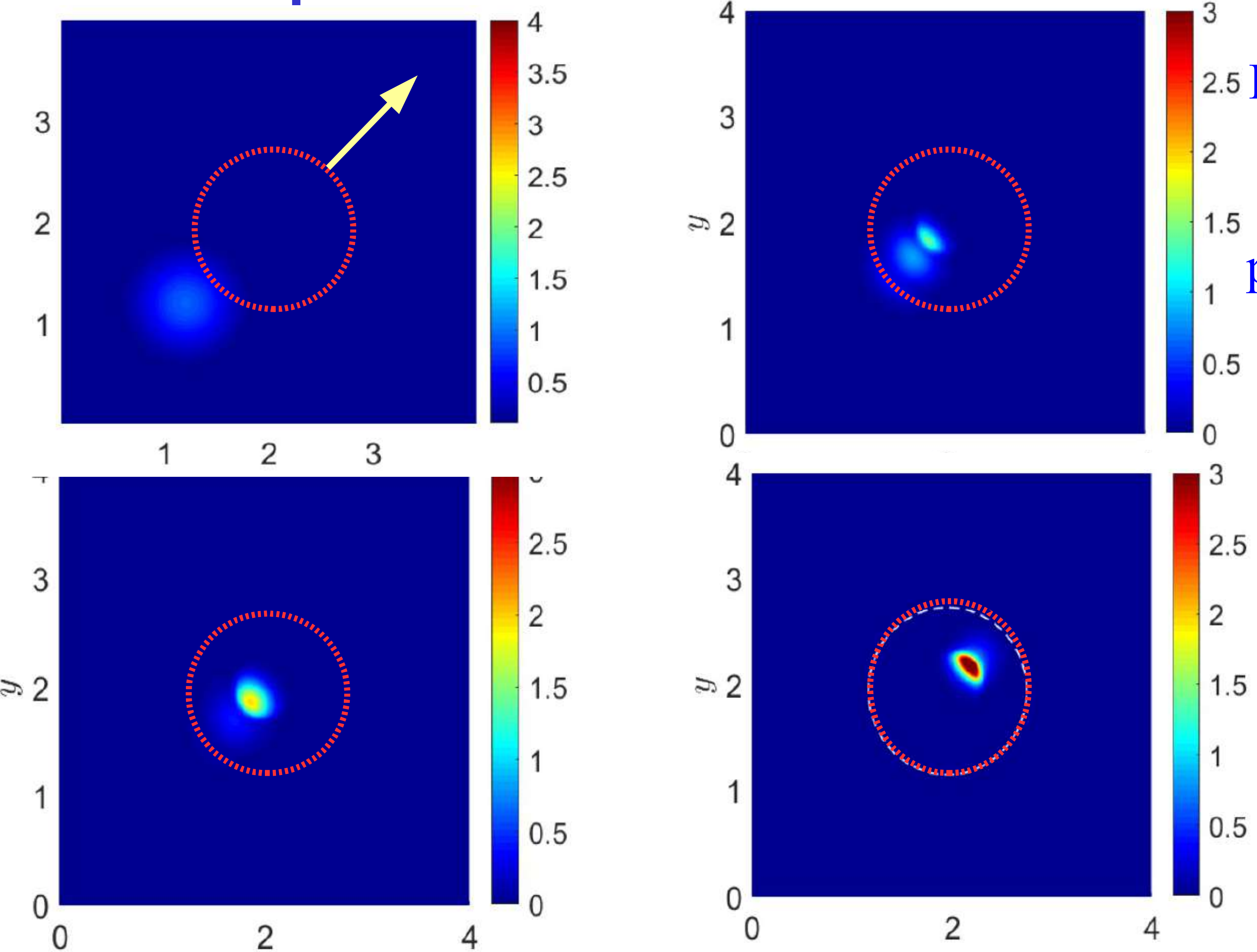
Denser ECM
in circle
(but still OK)

Double bias: Effect of independent cues



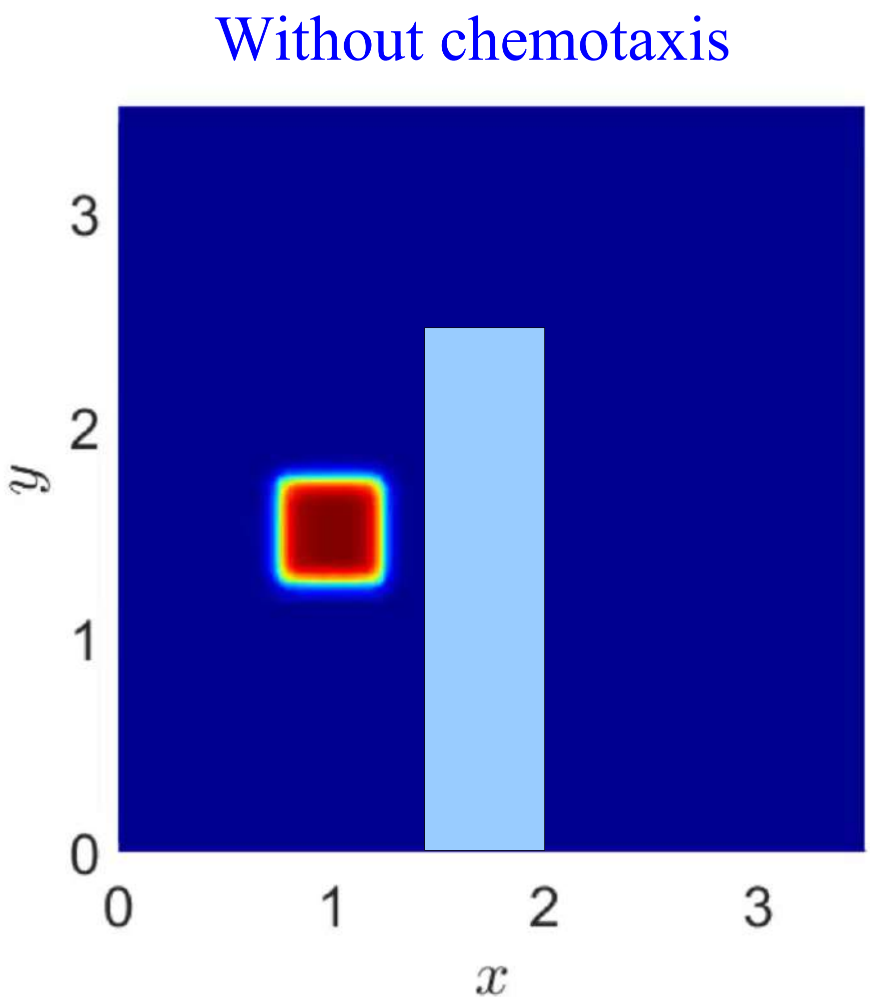
Denser ECM
in circle
(Too dense)

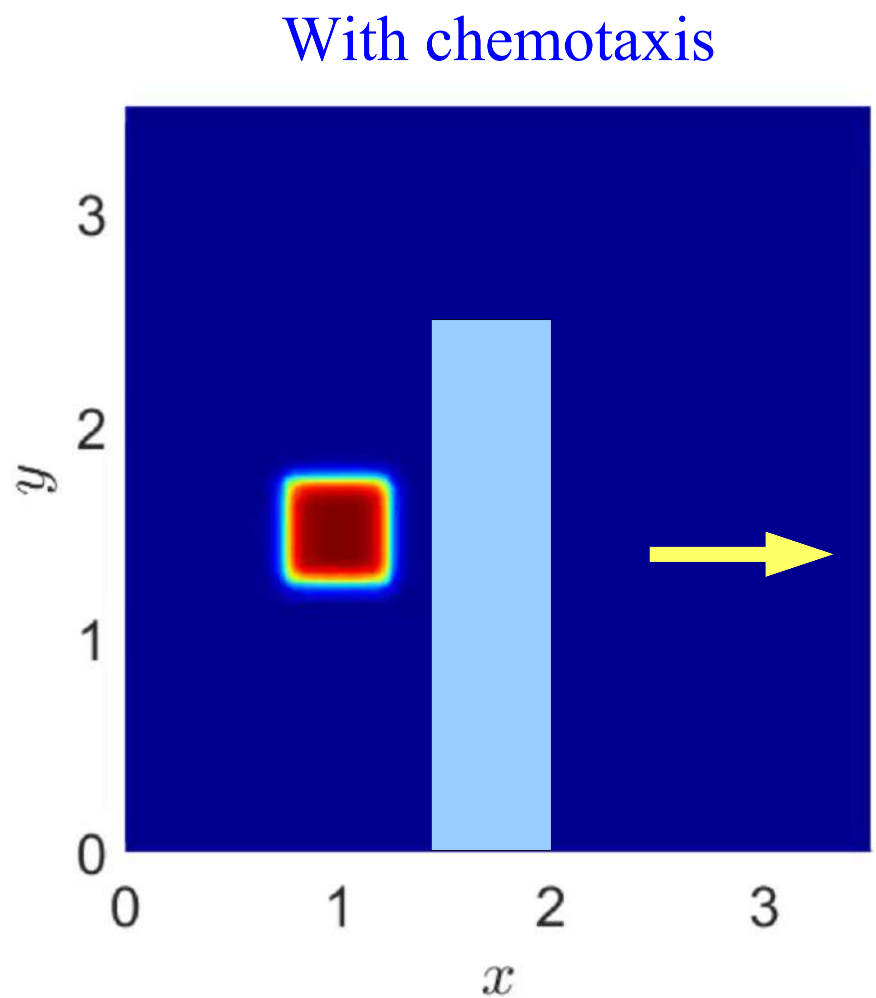
Double bias: Effect of independent cues



Poor ECM outside circle prohibitive

Double bias: Physical limits of migration





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Thanks for your attention!