

Multiscale Developments of Cellular Potts Model

Marco Scianna

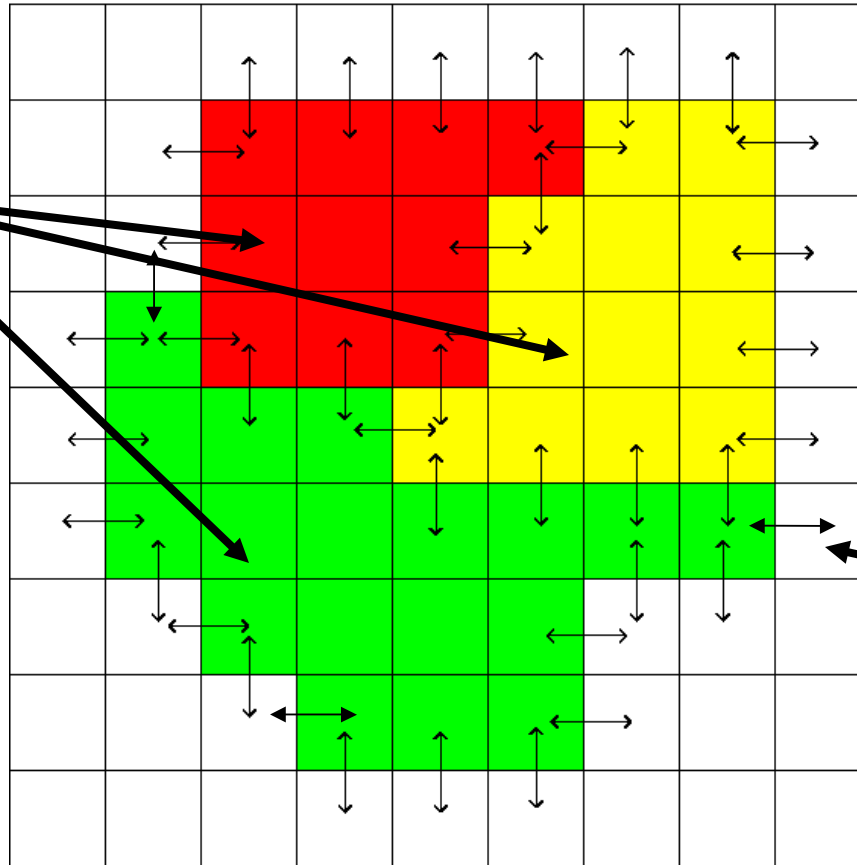
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calvino.polito.it/~preziosi



Classical Cellular Potts Model

A cell is represented by several nodes



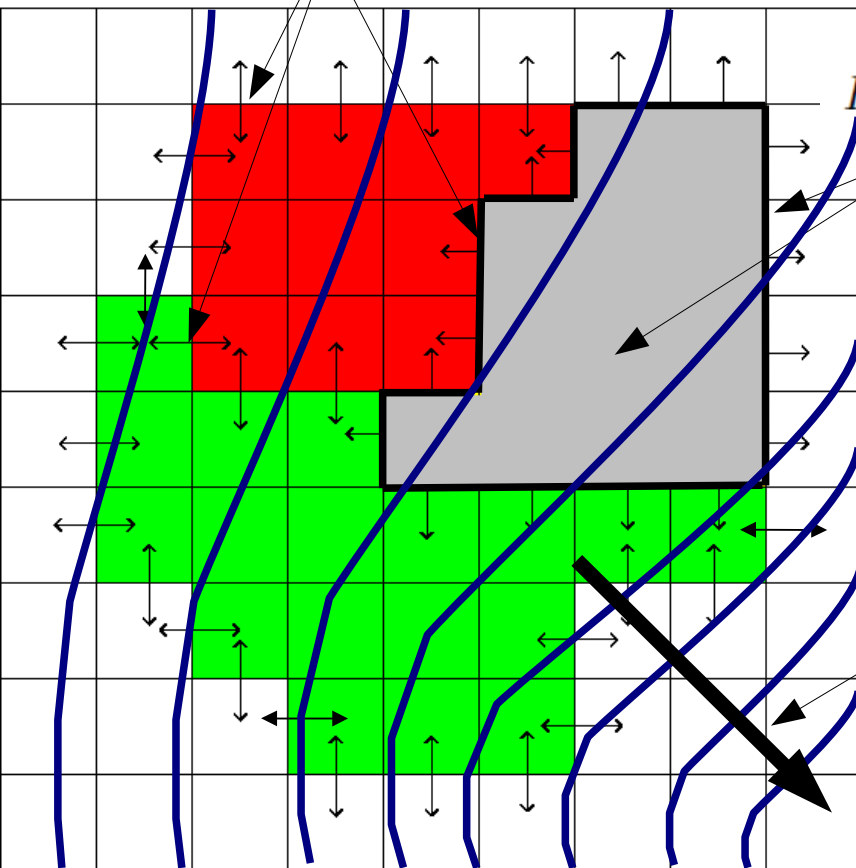
0-nodes represent the outer environment, or the extracellular matrix

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

Cellular Potts Model

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

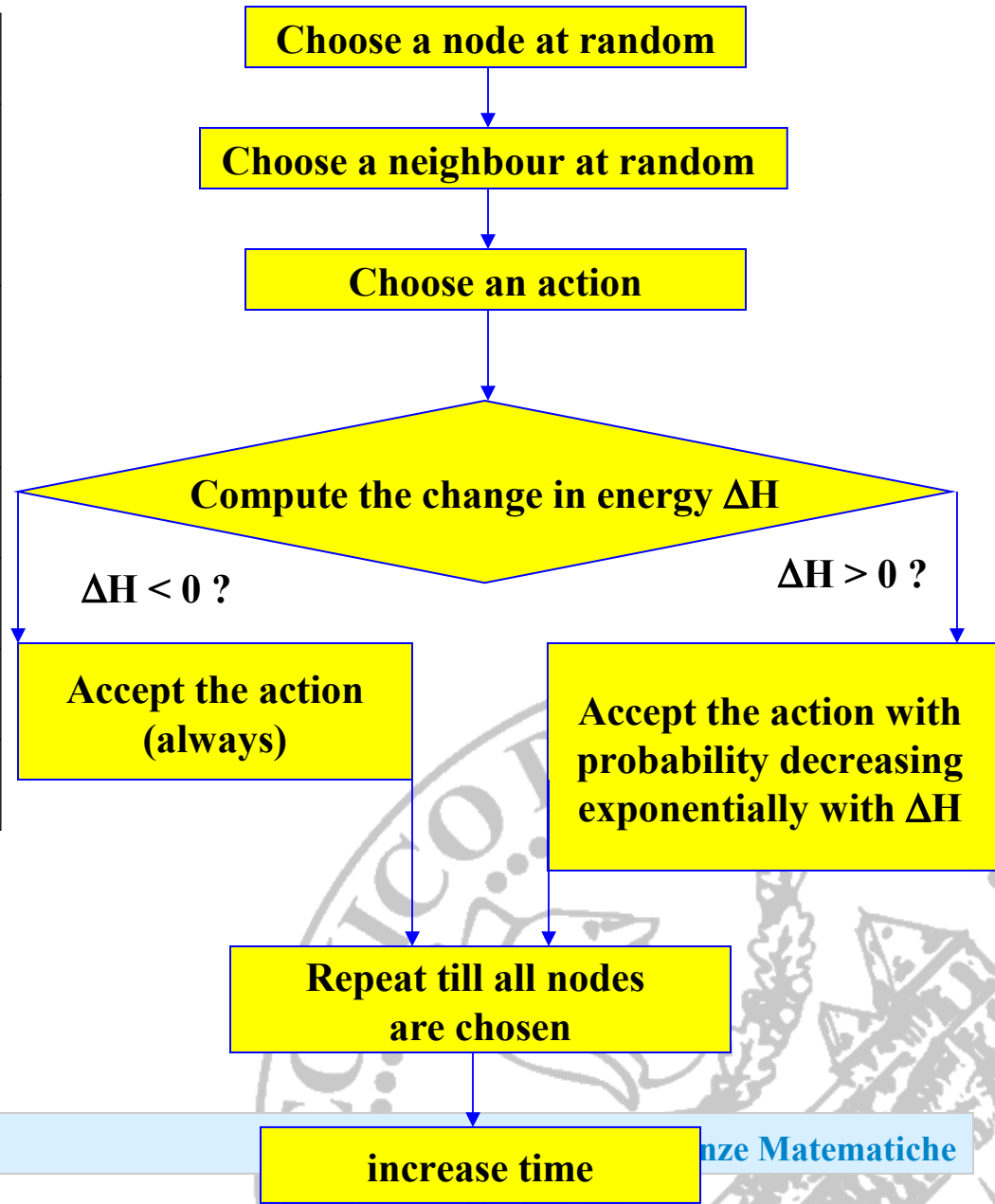
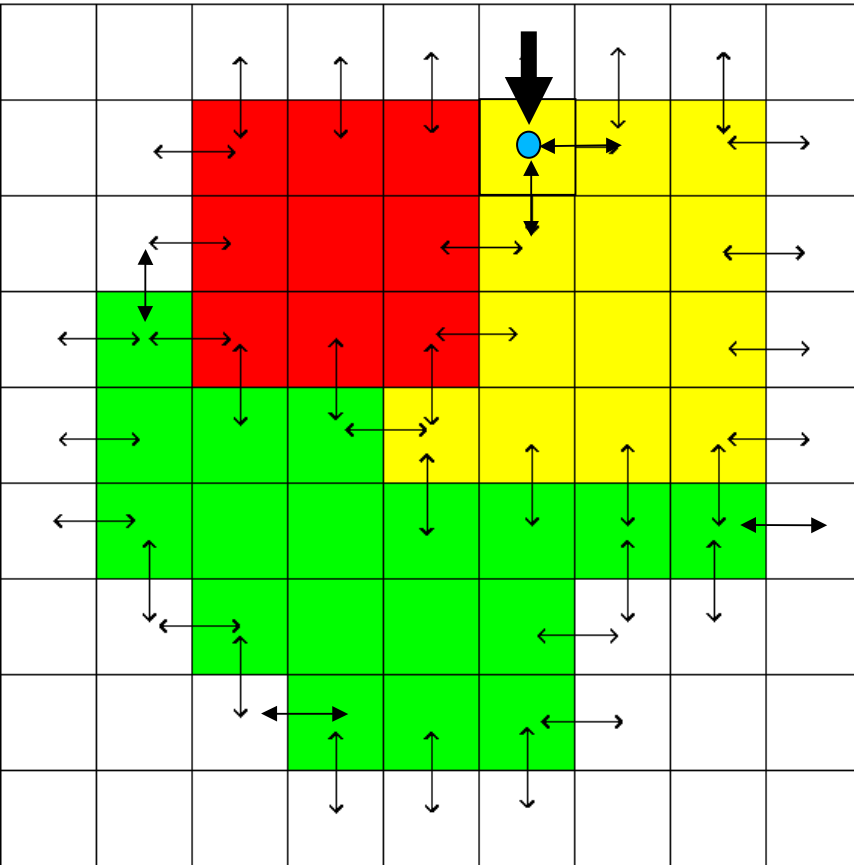
$$H_{adhesion}(t) = \sum_{\mathbf{x}, \mathbf{x}' \in \Omega} J_{\tau(\sigma(\mathbf{x})), \tau(\sigma(\mathbf{x}'))}(t) [1 - \delta_{\sigma(\mathbf{x}), \sigma(\mathbf{x}')} (t)],$$



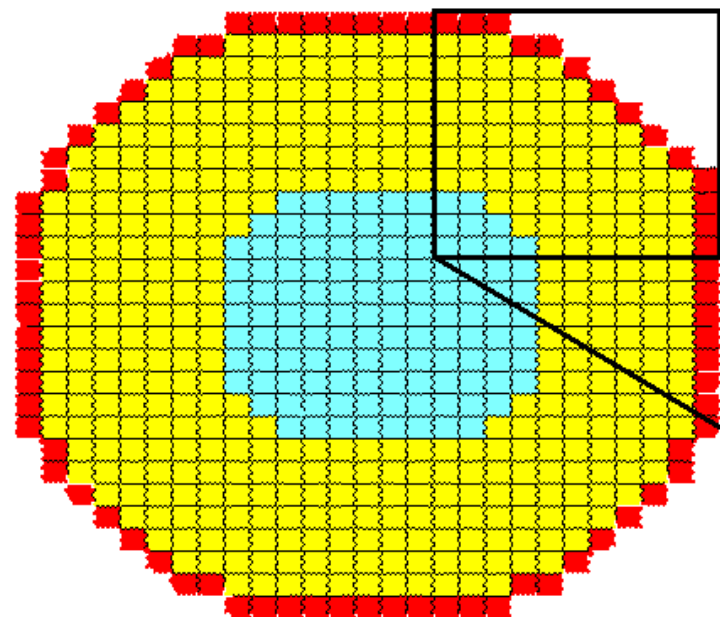
$$H_{attribute}(t) = \sum_{\eta, \sigma, i\text{-attribute}} \lambda_{\eta, \sigma}^i(t) \left| \frac{a_{\eta, \sigma}^i(t) - A_{\eta, \sigma}^i(t)}{a_{\eta, \sigma}^i(t)} \right|^p.$$

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

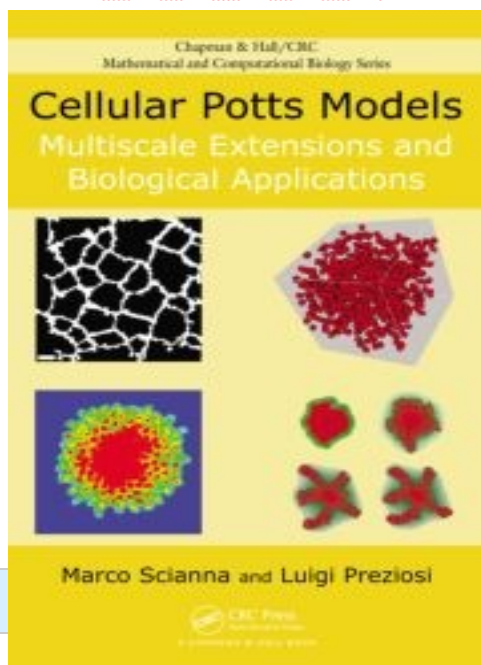
Classical Cellular Potts Model



Sub-Cellular Components in CPM

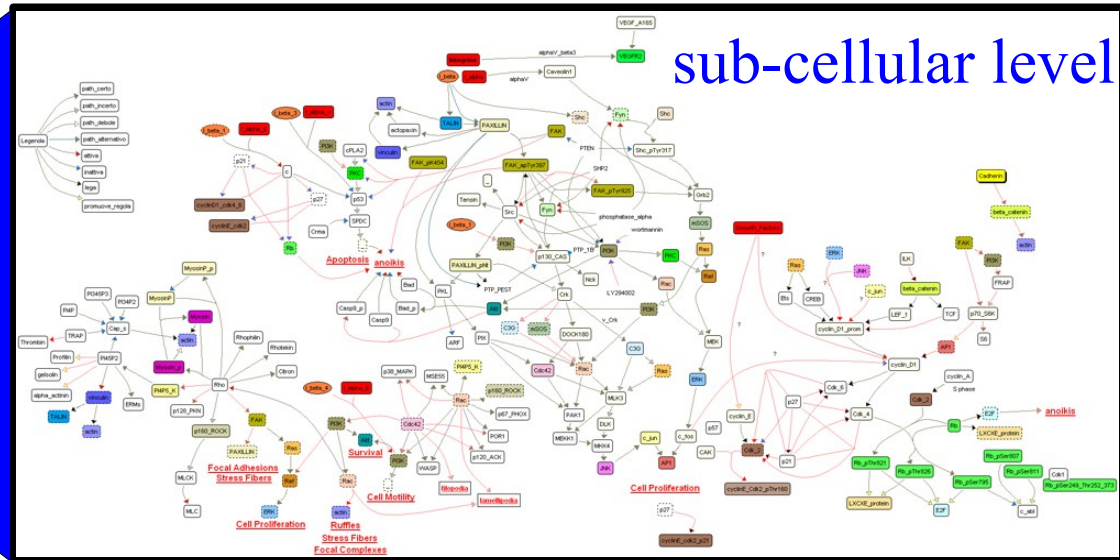
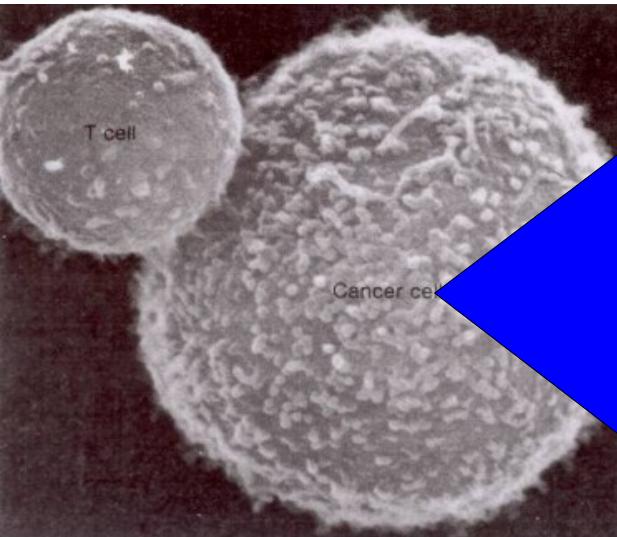


M	M	M	Q	Q	Q	Q	Q	Q	Q	Q
C	C	C	M	M	Q	Q	Q	Q	Q	Q
C	C	C	C	C	M	Q	Q	Q	Q	Q
C	C	C	C	C	C	M	Q	Q	Q	Q
C	C	C	C	C	C	C	M	Q	Q	Q
C	C	C	C	C	C	C	C	M	Q	Q
C	C	C	C	C	C	C	C	C	M	Q
C	C	C	C	C	C	C	C	C	C	M
N	N	C	C	C	C	C	C	C	C	M
N	N	N	C	C	C	C	C	C	C	M
N	N	N	N	C	C	C	C	C	C	M



M. Scianna & L.P.,
Multiscale Model. Simul.
10, 342-382 (2012)

Protein Networks and Nested Approach



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

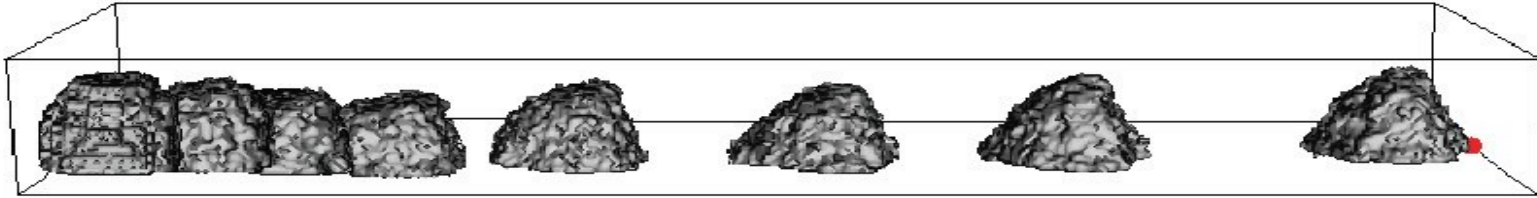
$$H_{adhesion}(t) = \sum_{\mathbf{x}, \mathbf{x}' \in \Omega} J_{\tau(\sigma(\mathbf{x})), \tau(\sigma(\mathbf{x}'))}(t) [1 - \delta_{\sigma(\mathbf{x}), \sigma(\mathbf{x}')} (t)],$$

$$H_{attribute}(t) = \sum_{\eta, \sigma, i\text{-attribute}} \lambda_{\eta, \sigma}^i(t) \left| \frac{a_{\eta, \sigma}^i(t) - A_{\eta, \sigma}^i(t)}{a_{\eta, \sigma}^i(t)} \right|^p.$$

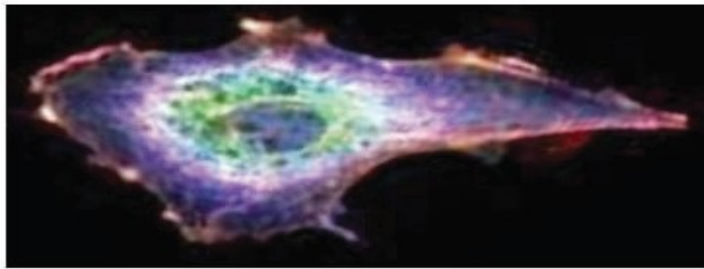
$$H_{force}^{chemical}(t) = - \sum_{\sigma} \sum_{\mathbf{x} \in \sigma} \mu_{\sigma}(t) \phi(\mathbf{x}, t),$$

$$P(\sigma(\mathbf{x}_{source}) \rightarrow \sigma(\mathbf{x}_{target}))(t) = \tanh(\varepsilon T_{\Sigma_{\sigma(\mathbf{x}_{source})}}(t)) \min\{1, e^{-\Delta H|_{\sigma(\mathbf{x}_{source}) \rightarrow \sigma(\mathbf{x}_{target})}} / T_{\Sigma_{\sigma(\mathbf{x}_{source})}}(t)\}$$

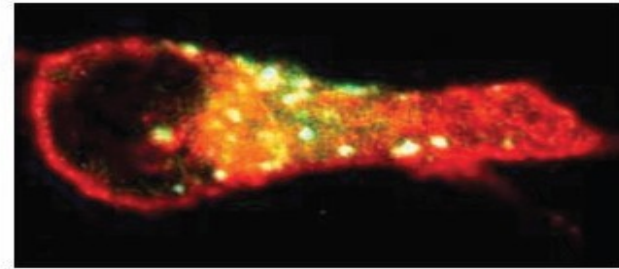
Moving cell morphology with CPM



Classical CPM



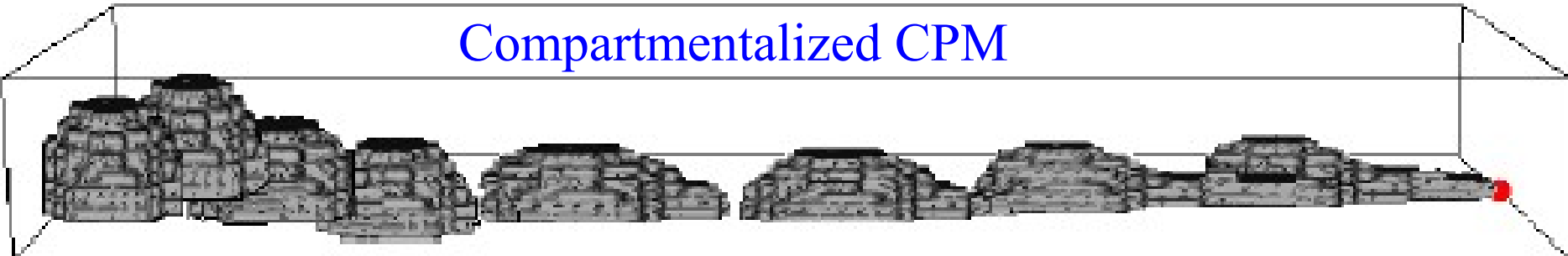
5 μm



----- direction of movement ----->

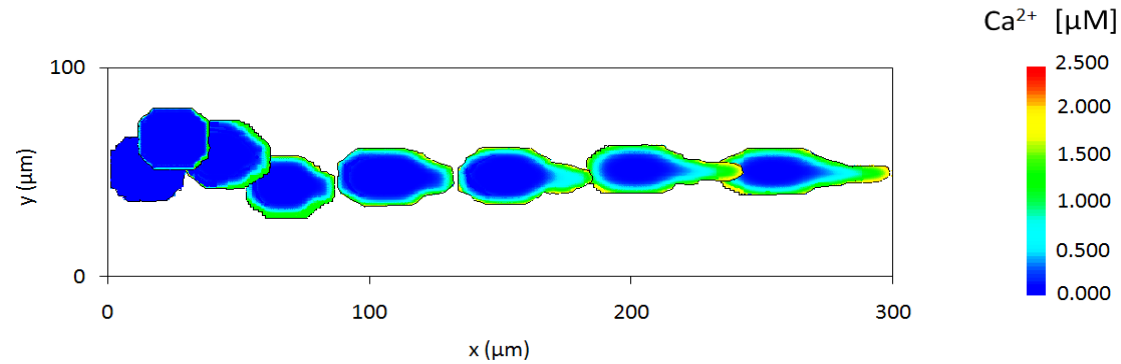
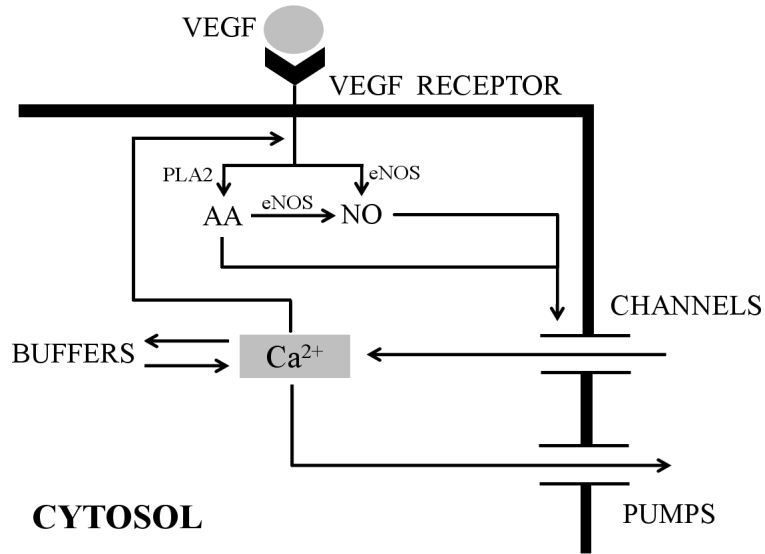


Compartmentalized CPM

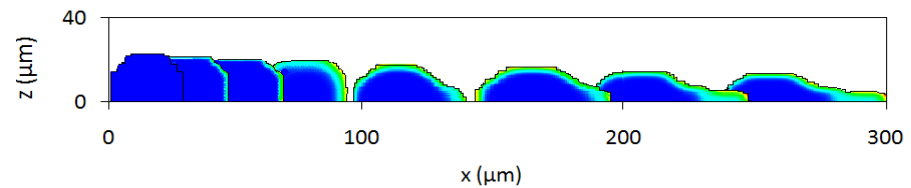


Moving cell morphology with CPM

EXTRACELLULAR ENVIRONMENT



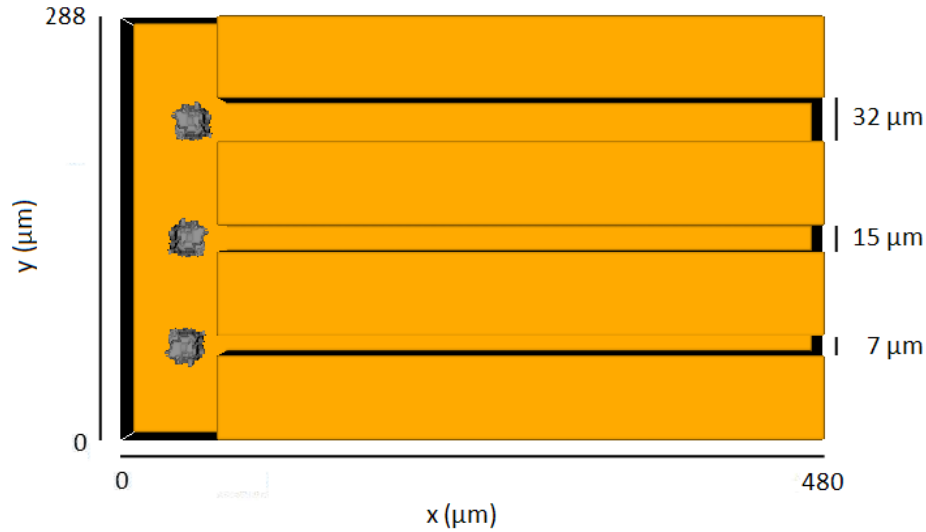
(A)



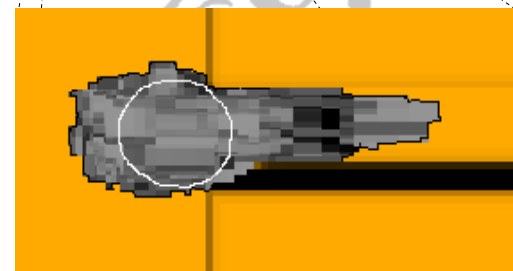
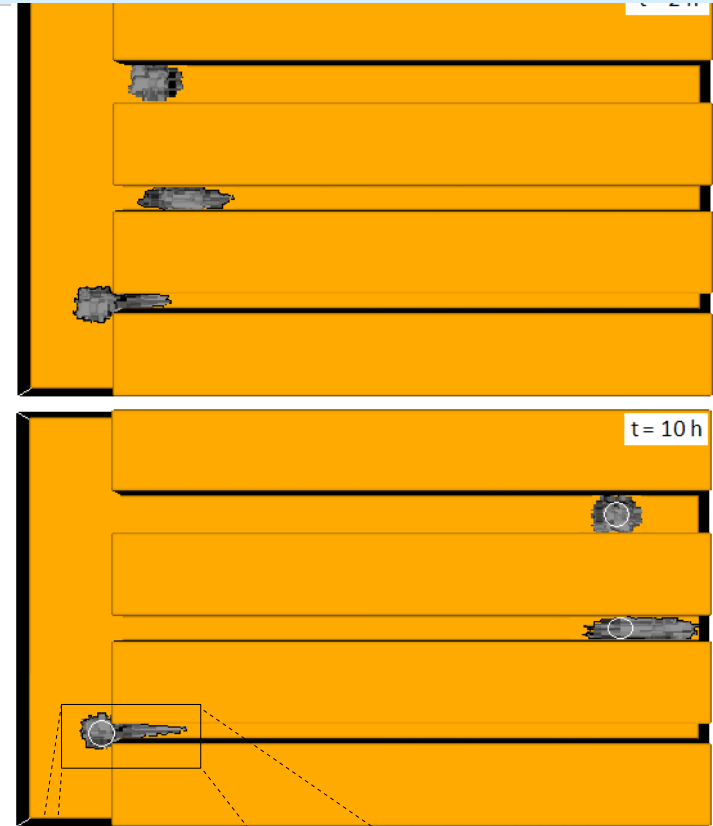
(B)



Rigid nucleus in microchannels



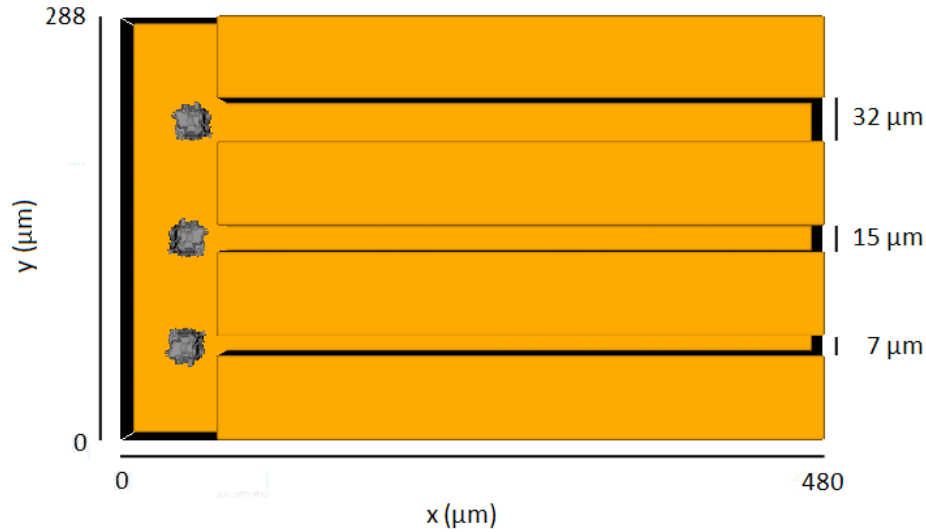
bottom channel size < nucleus diameter < middle channel size < cell diameter < top channel size



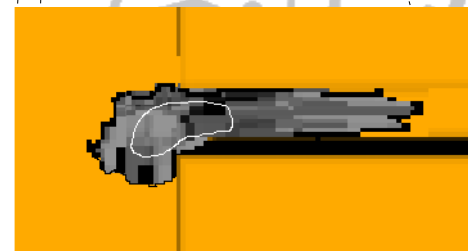
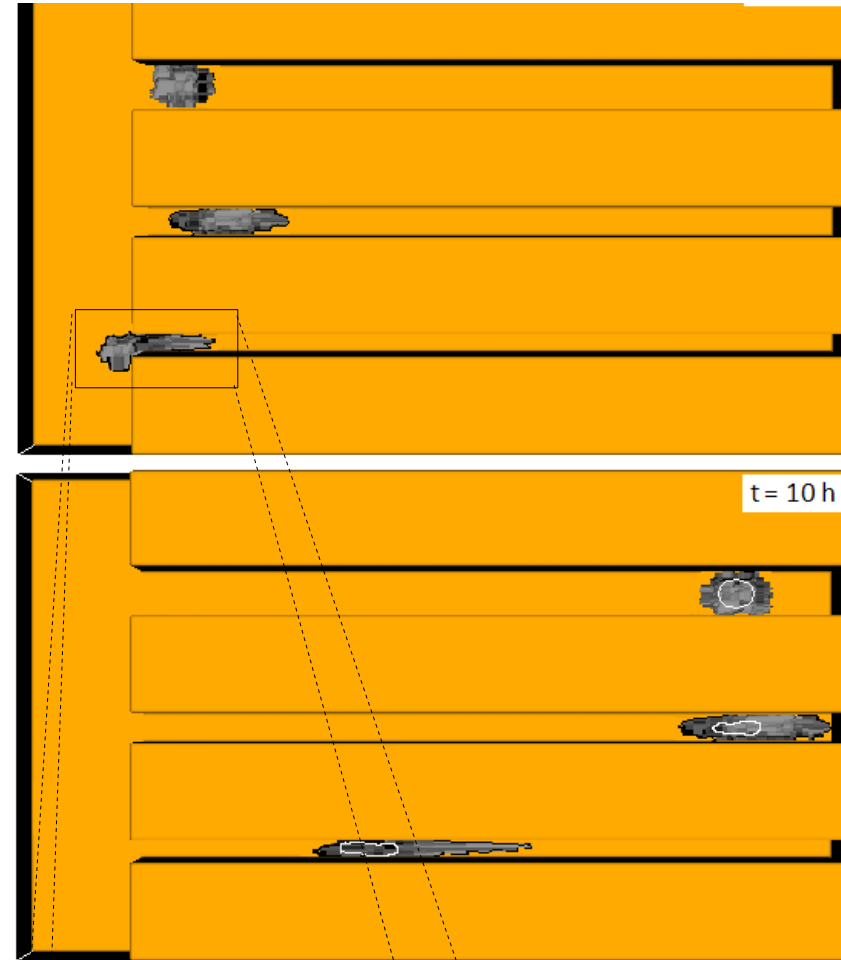
(J. Guch)

Rolli et al. PlosOne, 5, e8726 (2010)

Deformable nucleus in microchannels



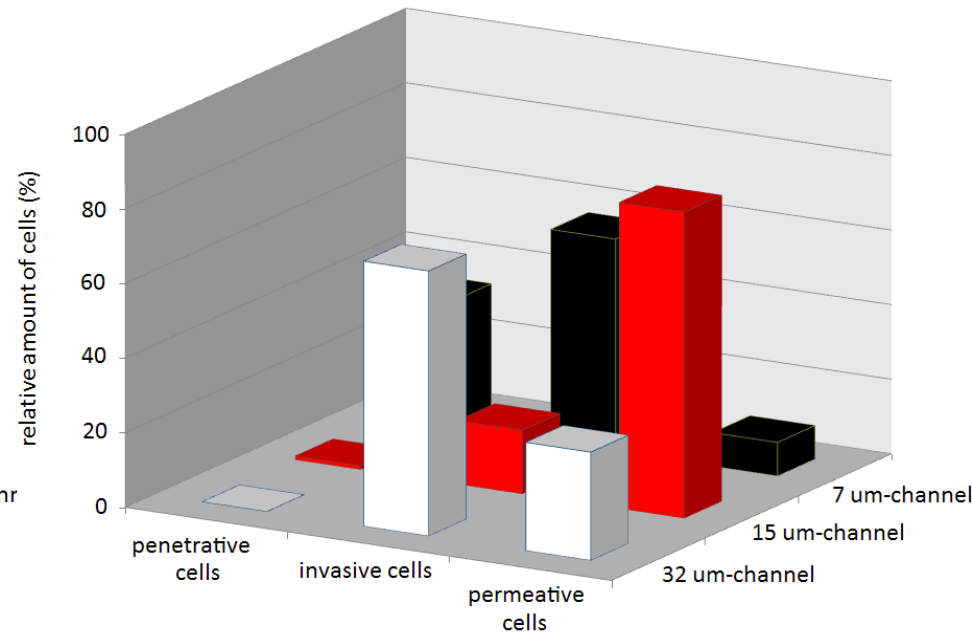
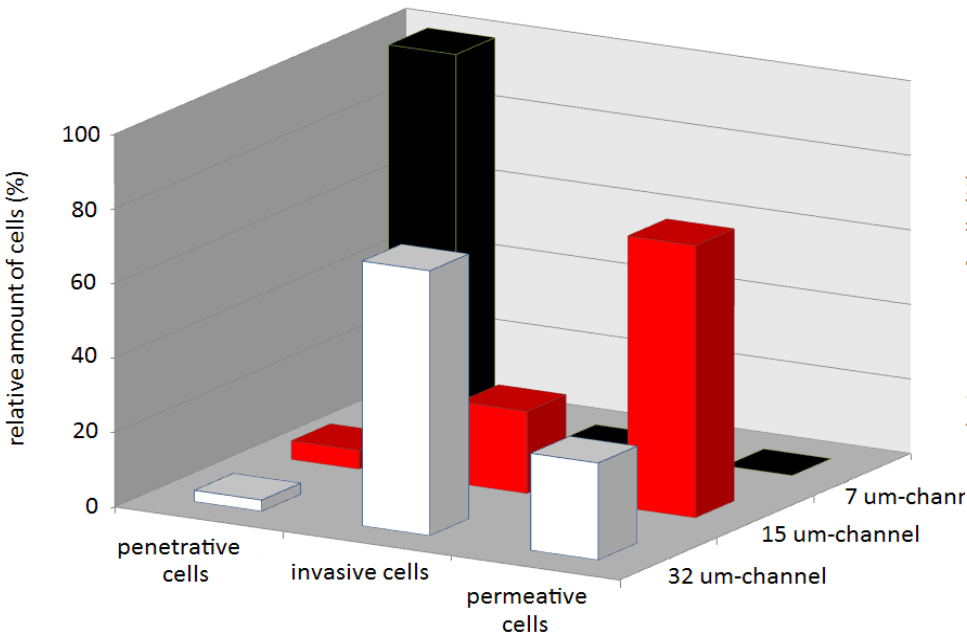
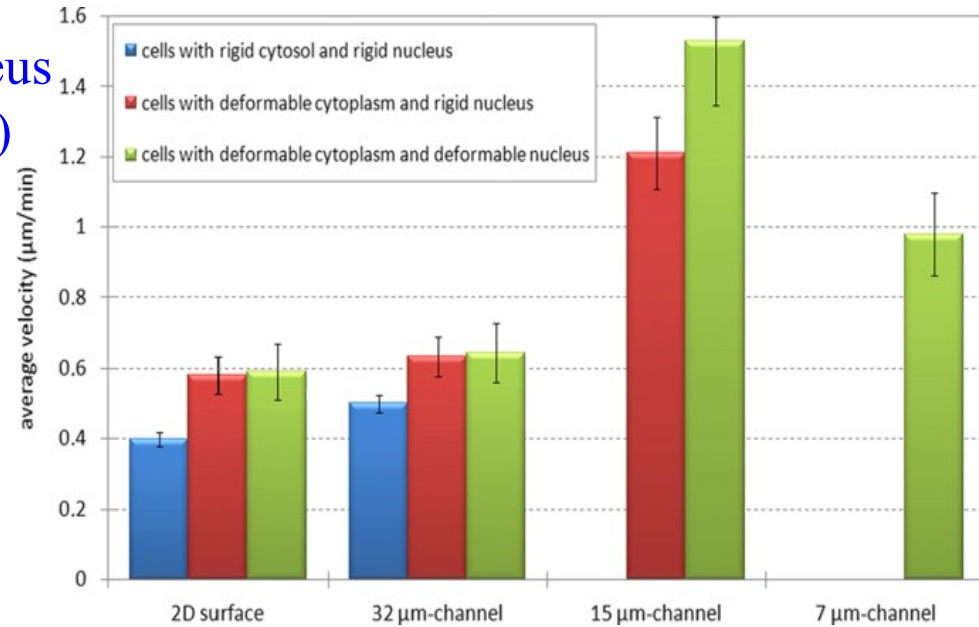
bottom channel size < nucleus diameter < middle channel size < cell diameter < top channel size



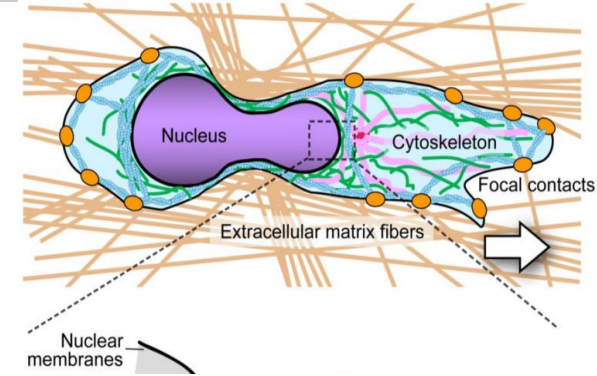
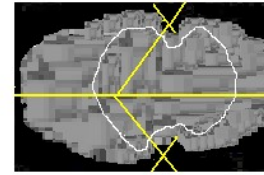
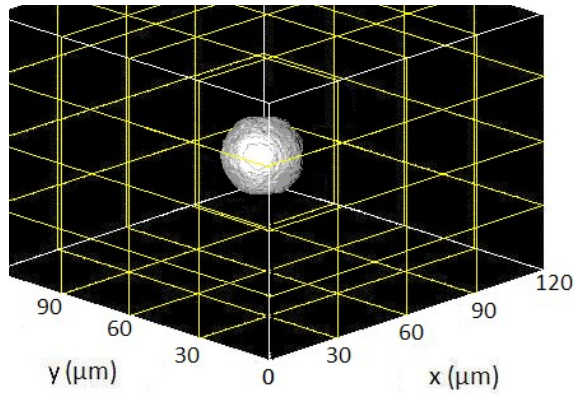
(J. Guch)

Influence of nucleus rigidity

- 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

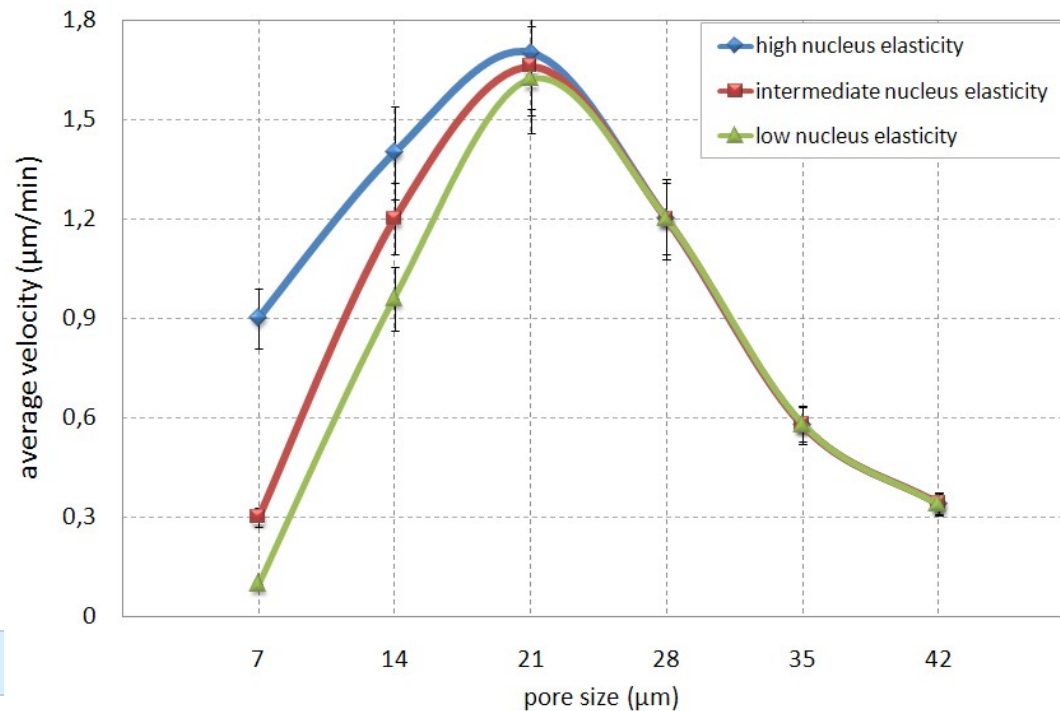


Influence of nucleus rigidity



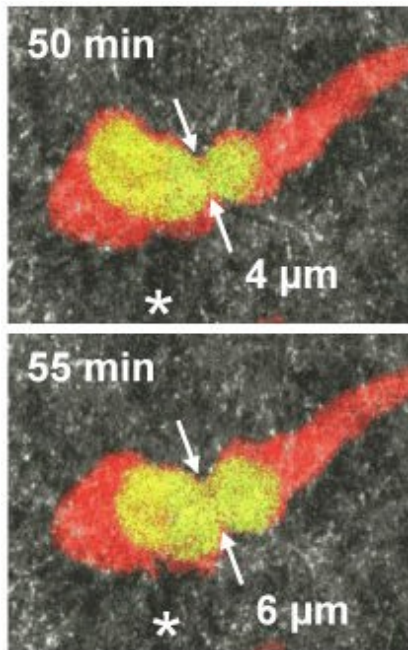
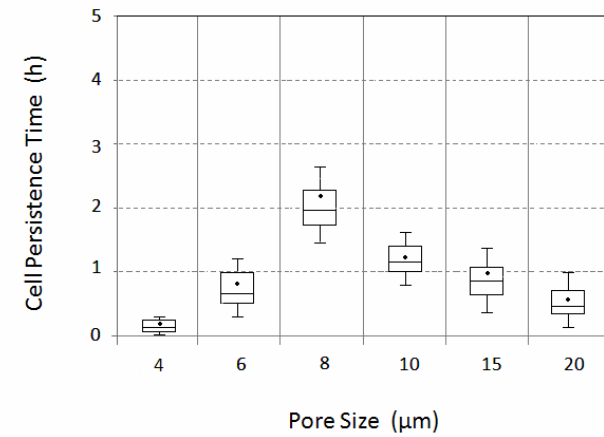
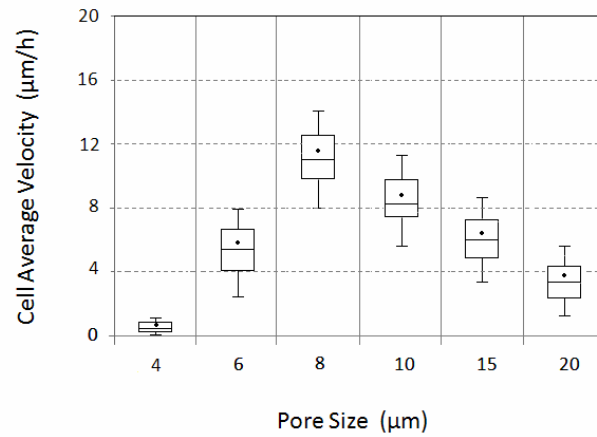
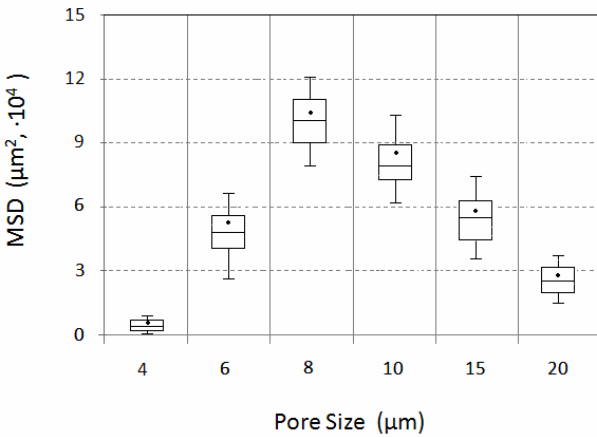
(A)

(B)

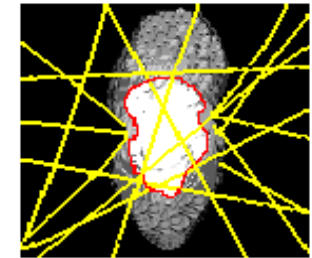
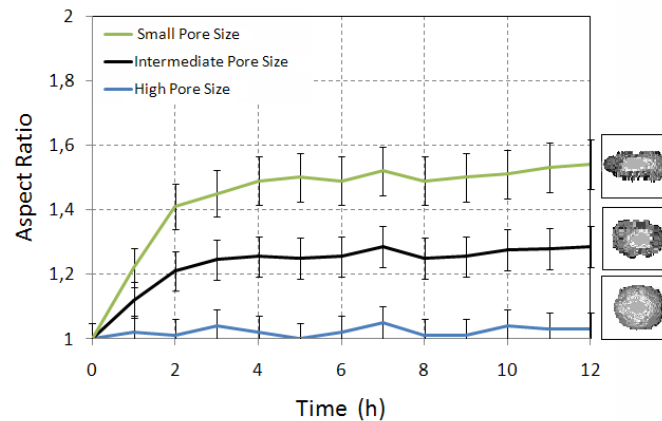


Effect of pore size

pore size

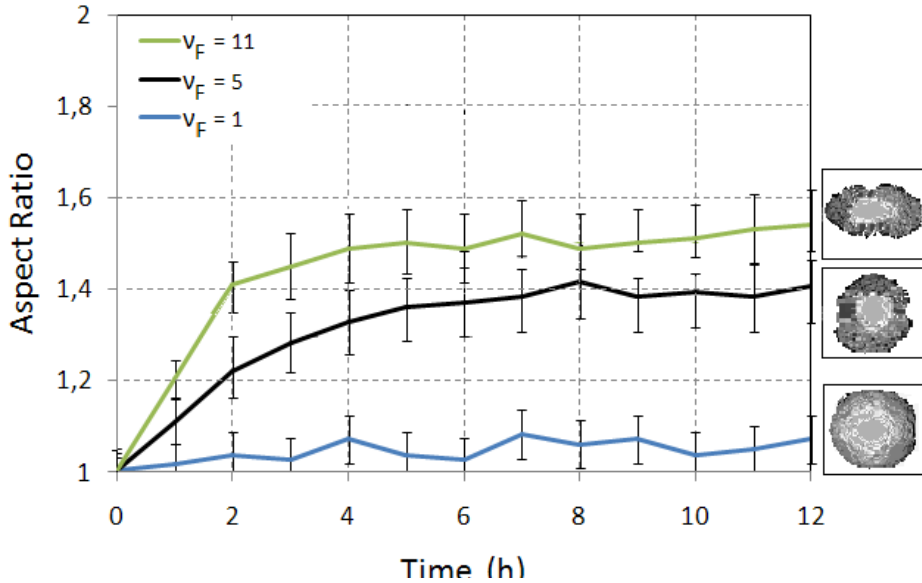


(A)

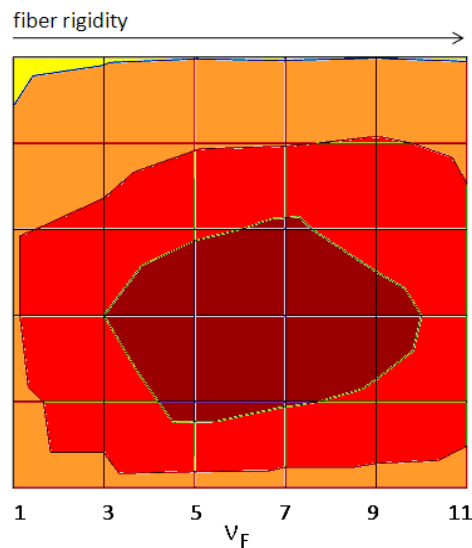
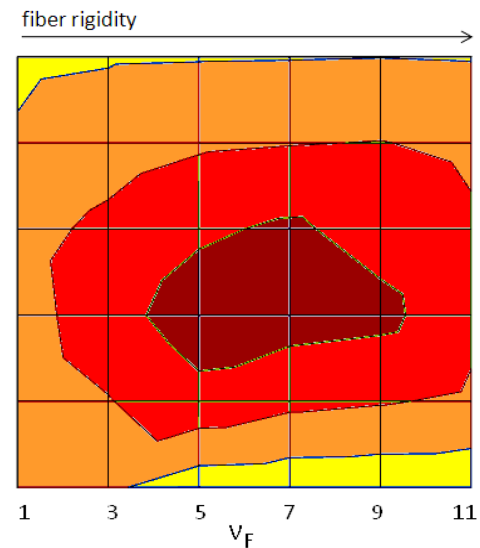
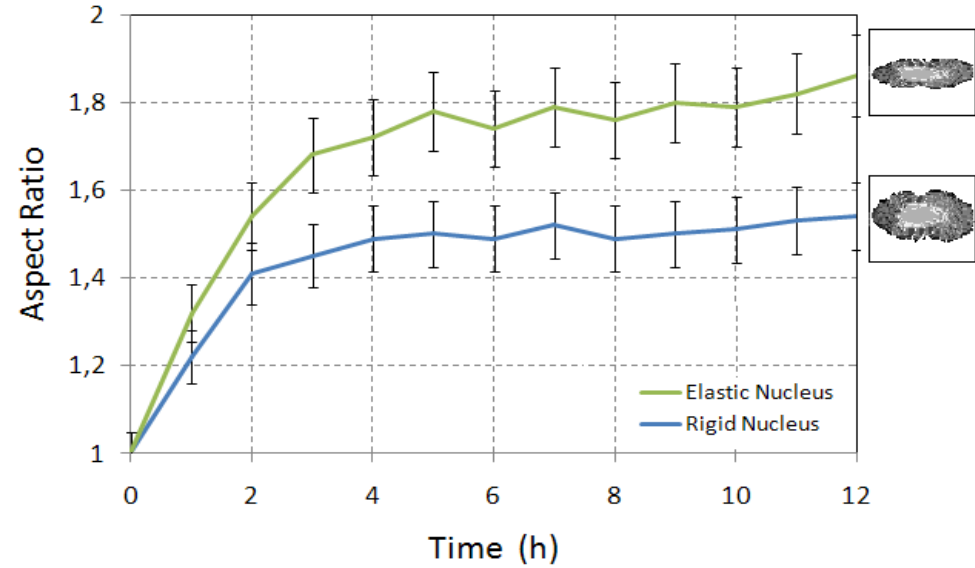


Effect of deformability

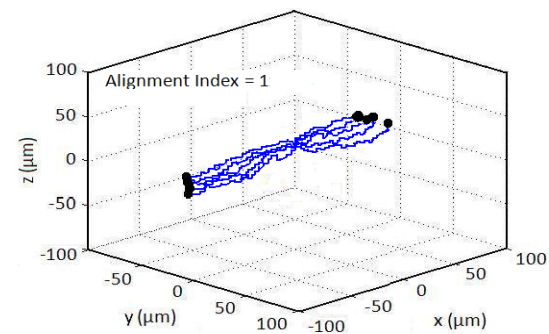
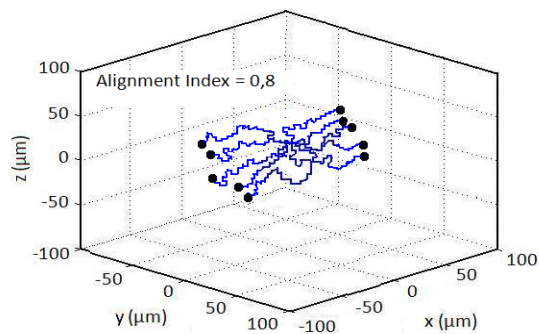
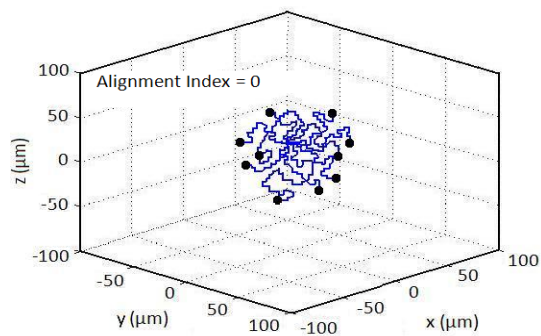
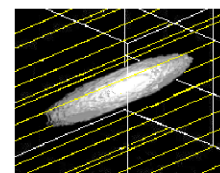
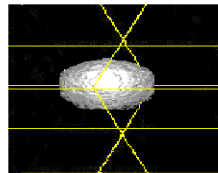
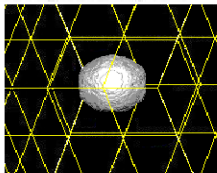
Varying fiber elasticity



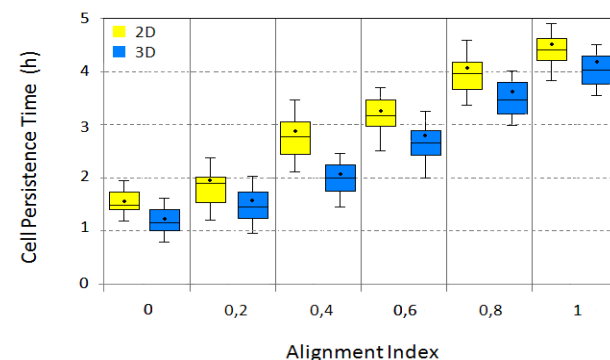
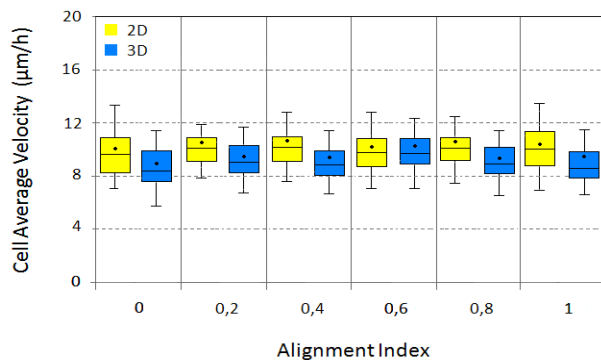
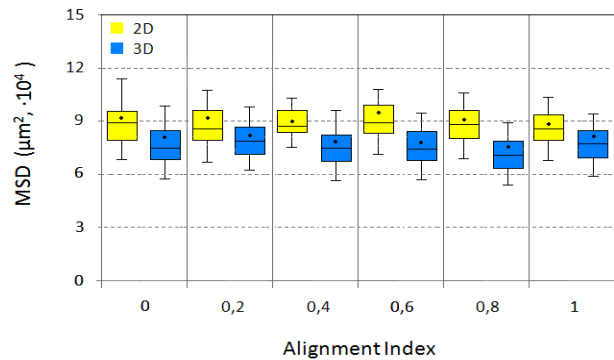
Varying nucleus elasticity



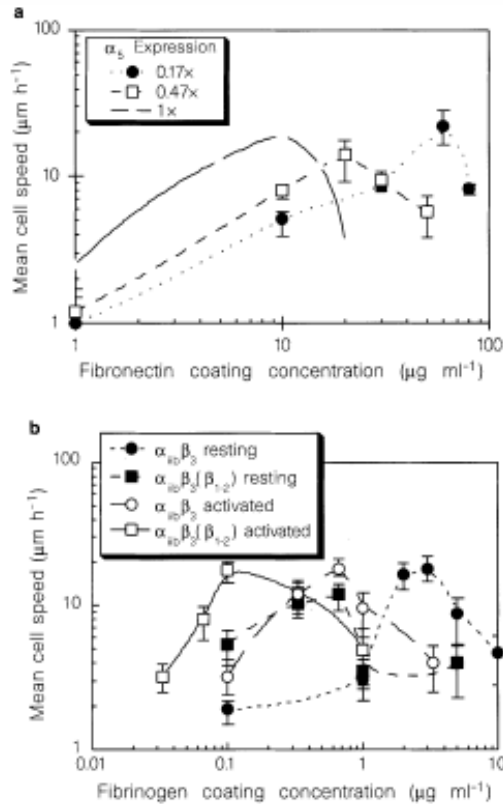
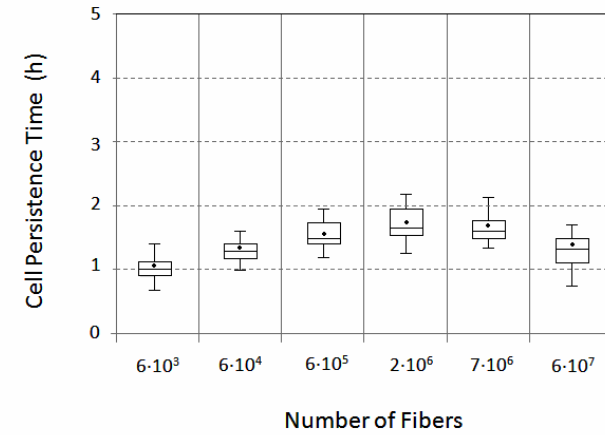
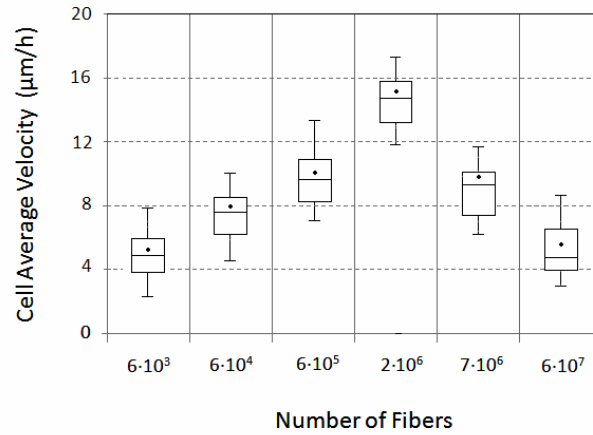
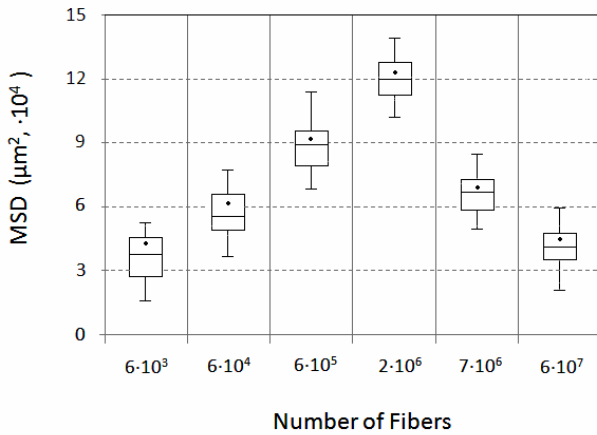
Single cell invasion in anisotropic ECM



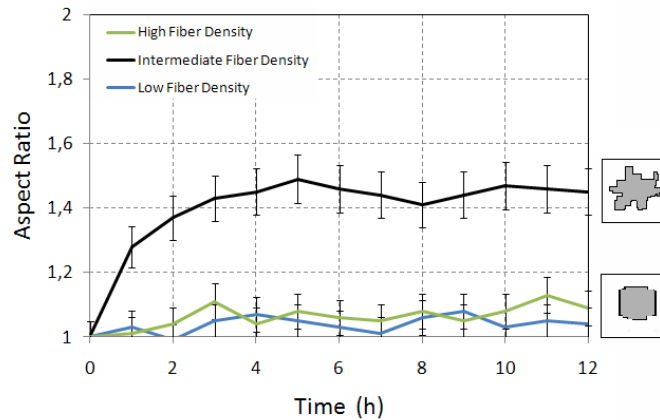
(B)



Effect of adhesion in 2D



(A)



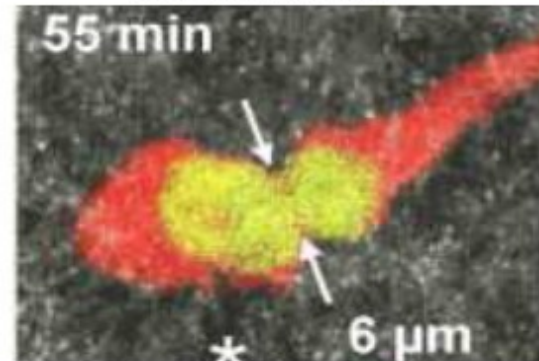
(B)

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

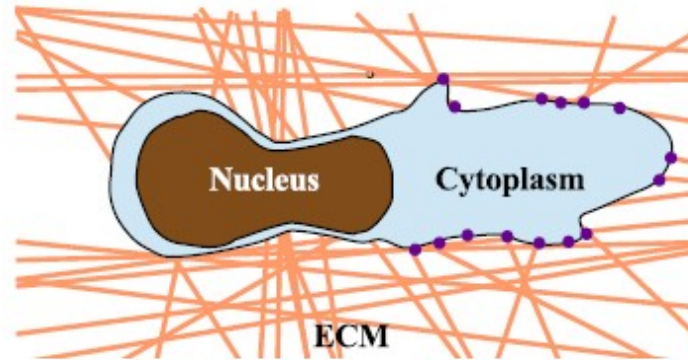
Continuous Criterium for Invasion

Giverso & L.P., Biomech. Model. Mechanobiol.

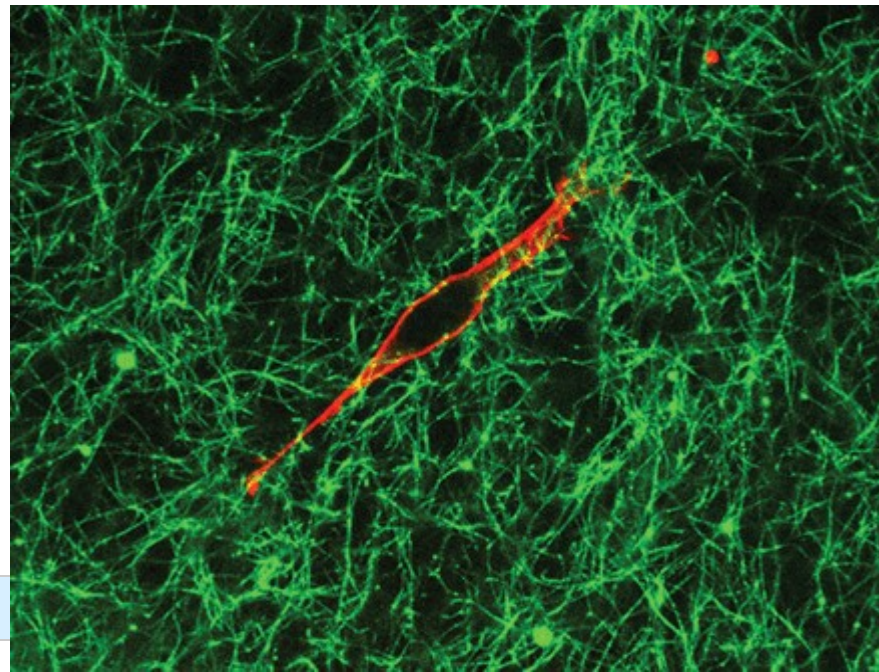
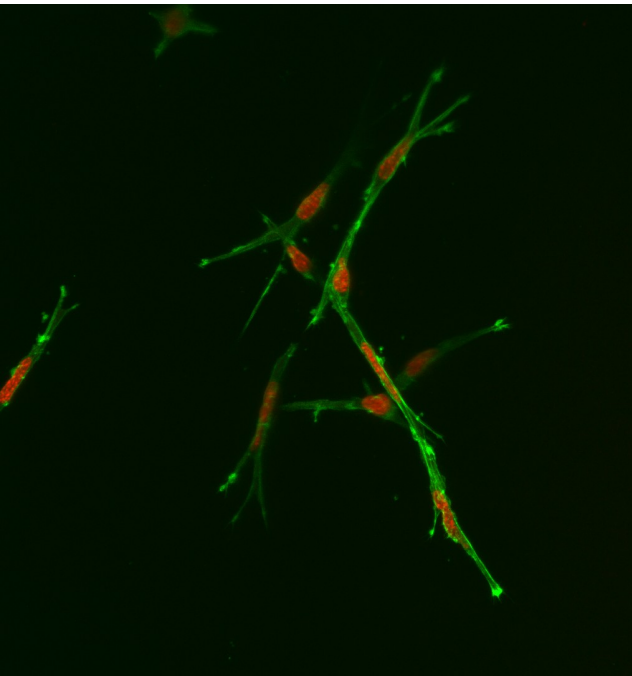
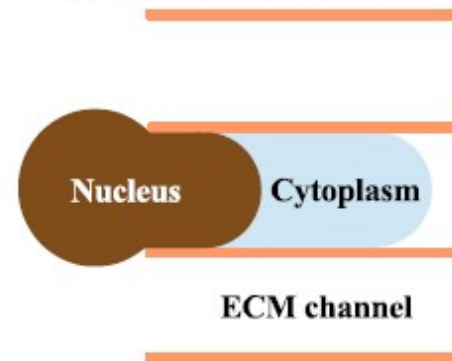
BIOLOGICAL
EXPERIMENT



BIOLOGICAL
REPRESENTATION

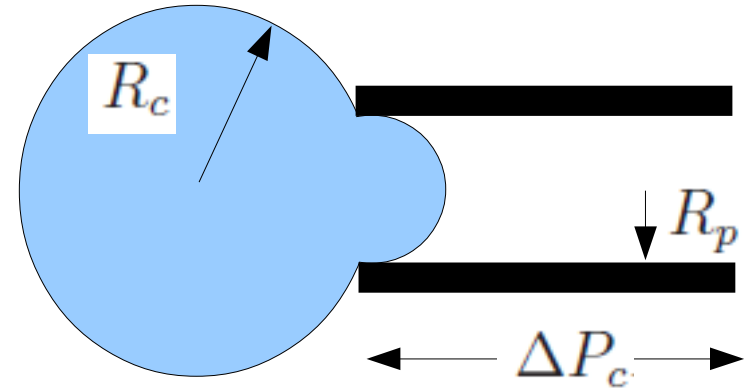


MATHEMATICAL
REPRESENTATION



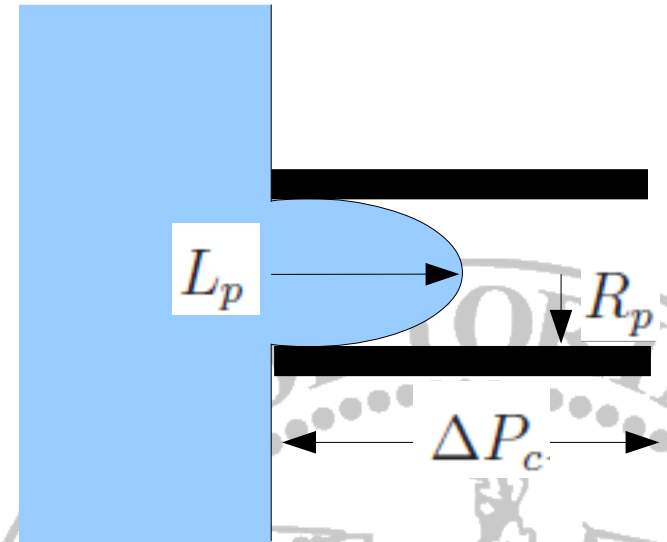
Continuous Criterion for Invasion

Evans:
$$\frac{\Delta P_c R_p}{T_c} = 2 \left(1 - \frac{R_p}{R_c} \right)$$



Chien:
$$\frac{\Delta P R_p}{\gamma} = 2.45 \frac{L_p}{R_p} \quad \left(\frac{L_p}{R_p} > 1 \right)$$

Shear elastic modulus of the membrane



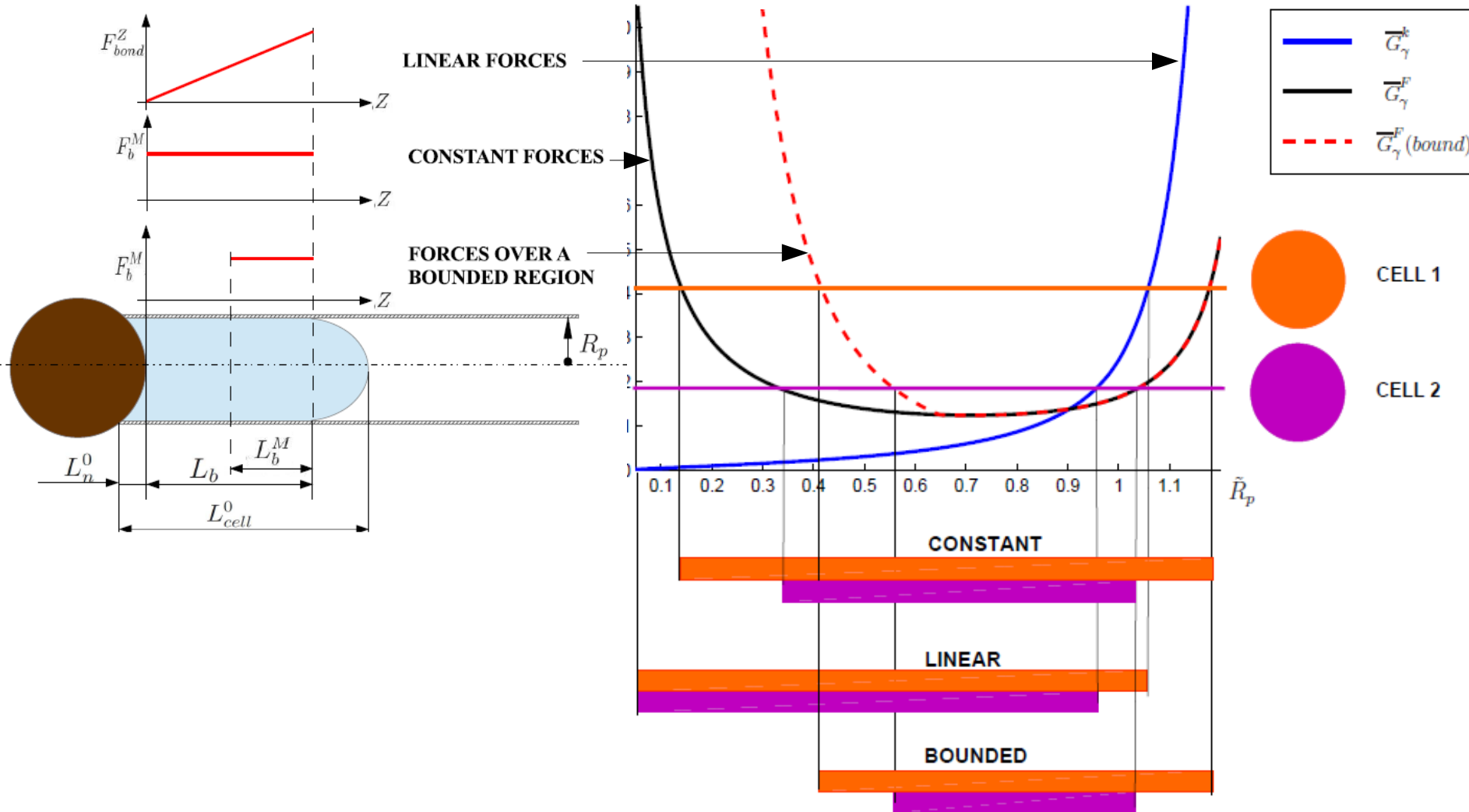
Brugués et al., *PNAS*, **107**, 15415-15420 (2010)

Chien's model

$$\pi R_p^2 \Delta P \approx F_{adhesion}^Z$$

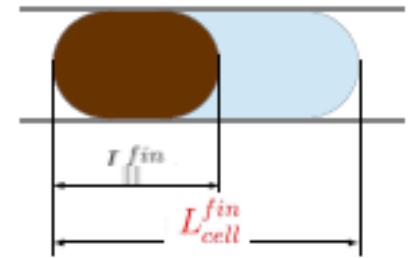
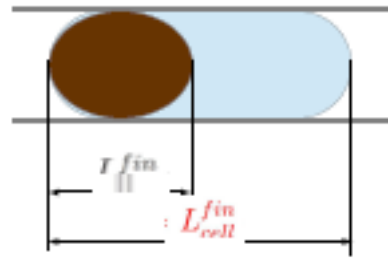
$$G_\gamma^F = \frac{\rho_b \alpha_{ECM} F_b^M R_n}{\gamma}$$

$$G_\gamma^k = \frac{\rho_b \alpha_{ECM} k_b R_n^2}{\gamma}$$



Elastic membrane

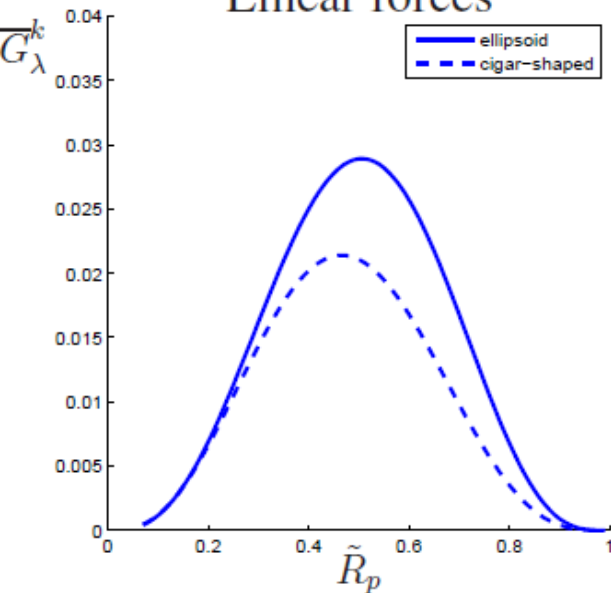
$$W_{tot}^S = \lambda(\Delta S)^2$$



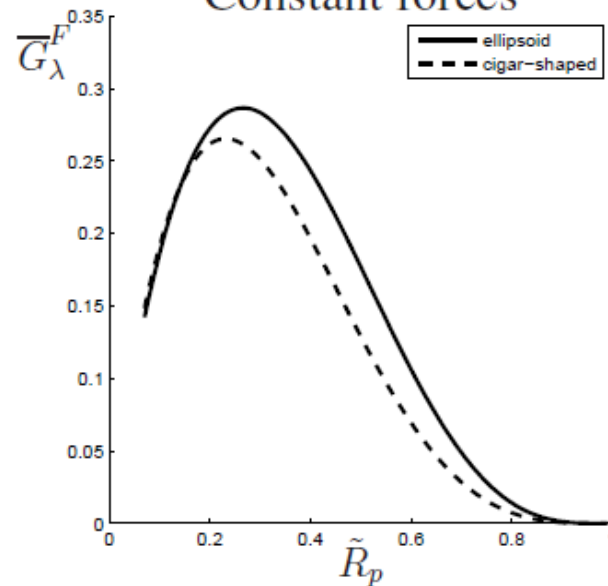
$$G_{\lambda}^k = \frac{\rho_b \alpha_{ECM} k_b}{\lambda}$$

$$G_{\lambda}^F = \frac{\rho_b \alpha_{ECM} F_b^M / R_n}{\lambda}$$

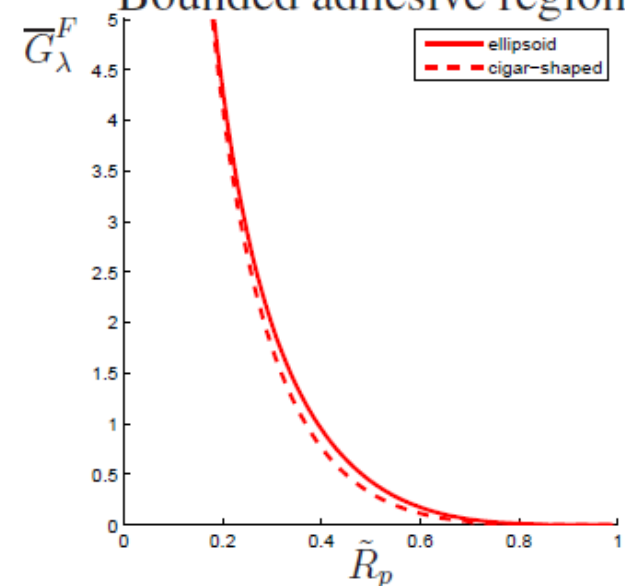
Linear forces



Constant forces

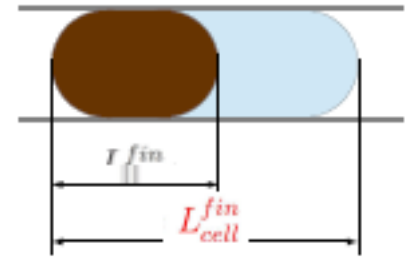
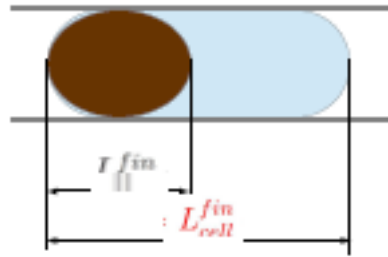


Bounded adhesive region



Elastic solid

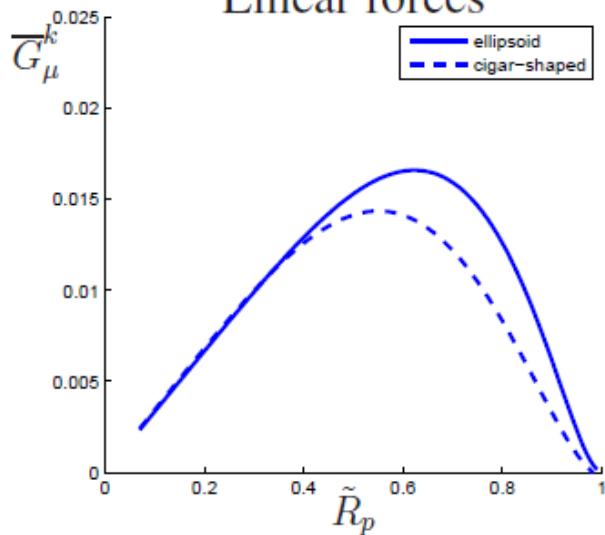
$$W^V = \frac{\mu}{2} [\text{tr}(\bar{\mathbb{C}}) - 3]$$



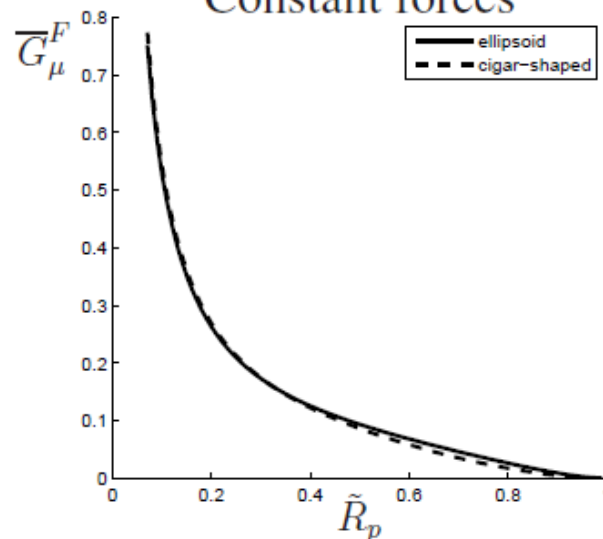
$$G_{\mu}^k = \frac{\rho_b \alpha_{ECM} k_b R_n}{\mu}$$

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

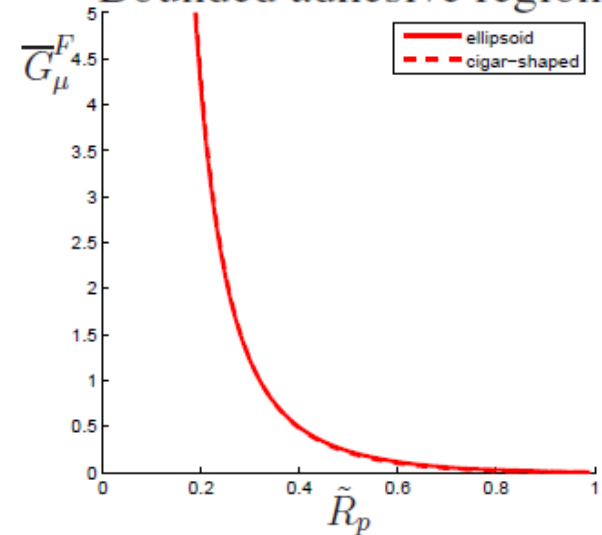
Linear forces



Constant forces



Bounded adhesive region



Elastic solid

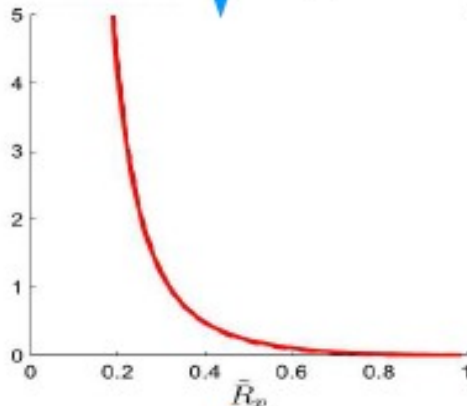
Ellipsoidal or Cigar

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

$$\bar{G}_{\mu}^F = \frac{2}{3} \frac{\left[2\tilde{R}_p^2 + \frac{1}{\tilde{R}_p^4} - 3 \right]}{\tilde{R}_p \tilde{L}_b^{(*)} \Delta \tilde{L}_{ellips}}$$

CELL MECHANICAL AND ACTIVE PROPERTIES

G_{μ}^F

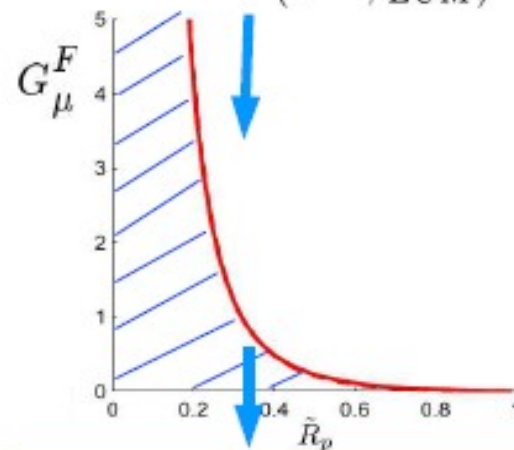


R_p

MICROCHANNEL AND SCAFFOLD DESIGN

CELLS' MIGRATORY CAPABILITY

$$v_c = -\frac{k}{\nu(1 - \phi_{ECM})} \nabla P$$

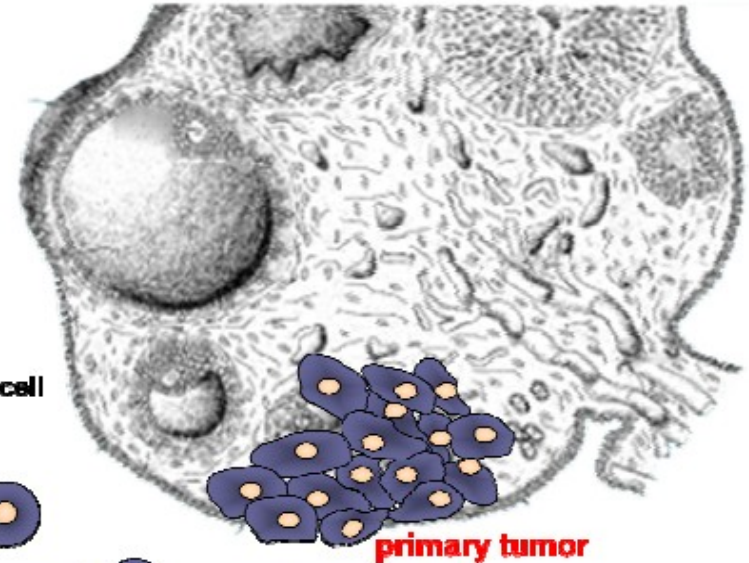


NULL PERMEABILITY REGION $k = 0$



Invasion of Ovary Cancer Cells

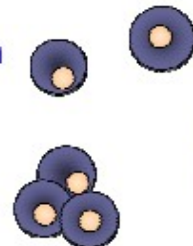
Ovarian cancer dissemination



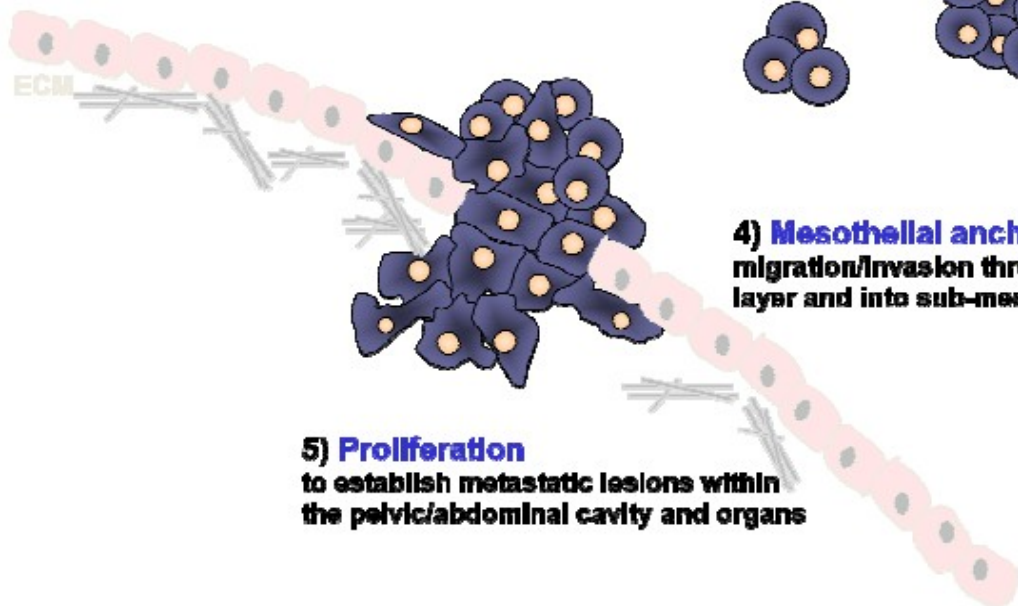
1) Surface shedding
Initial disruption of cell-cell
and cell-matrix contacts



3) Retraction, sub-mesothelial adhesion
disruption of cell-cell contacts in
multi-cellular aggregates



2) Dissemination
as single cells or
multi-cellular aggregates
(spheroids)



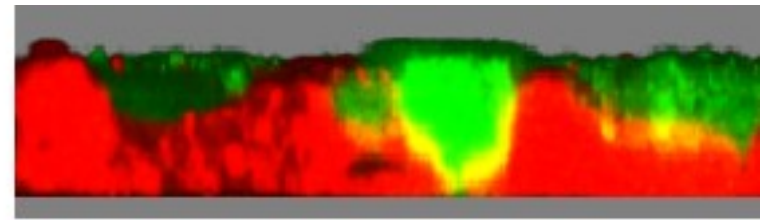
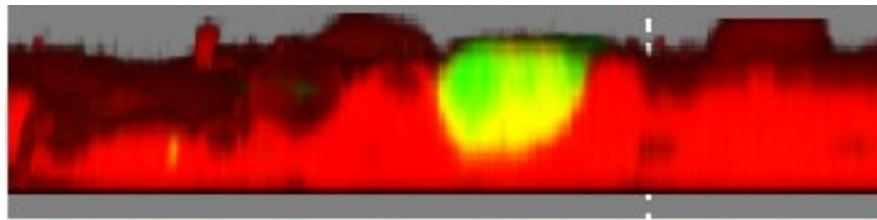
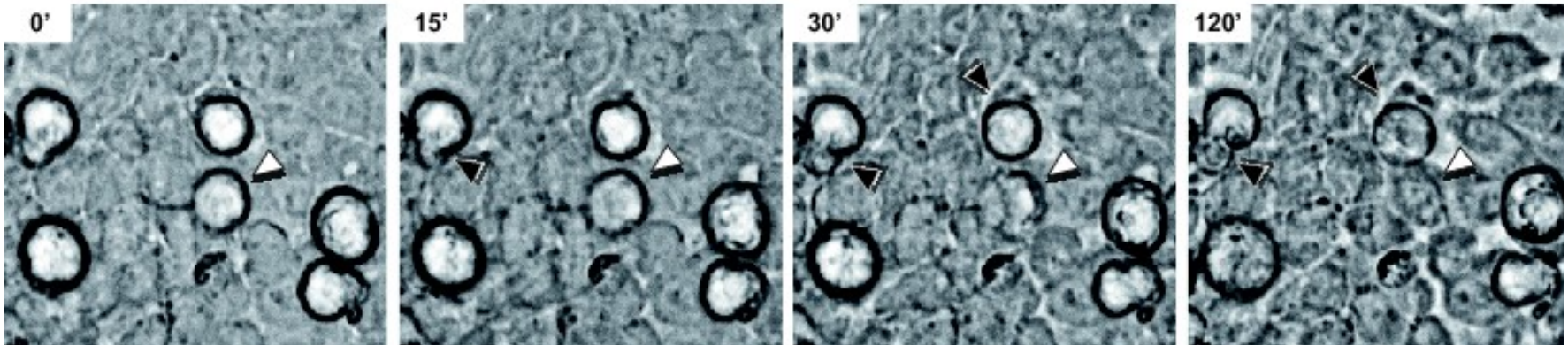
4) Mesothelial anchoring
migration/invasion through mesothelial
layer and into sub-mesothelial EC matrix

5) Proliferation
to establish metastatic lesions within
the pelvic/abdominal cavity and organs



Invasion of Ovary Cancer Cells

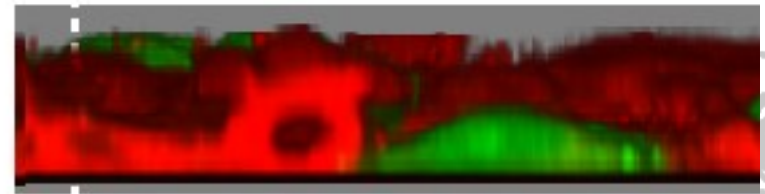
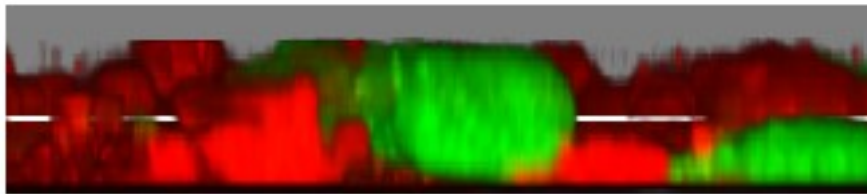
Top view



(A)

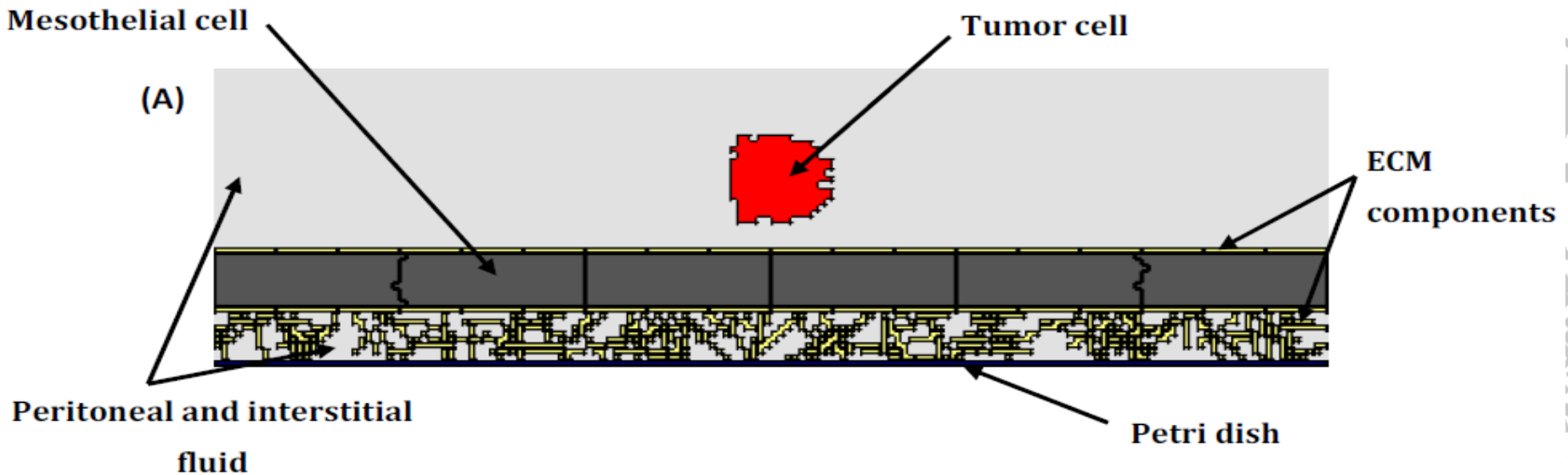
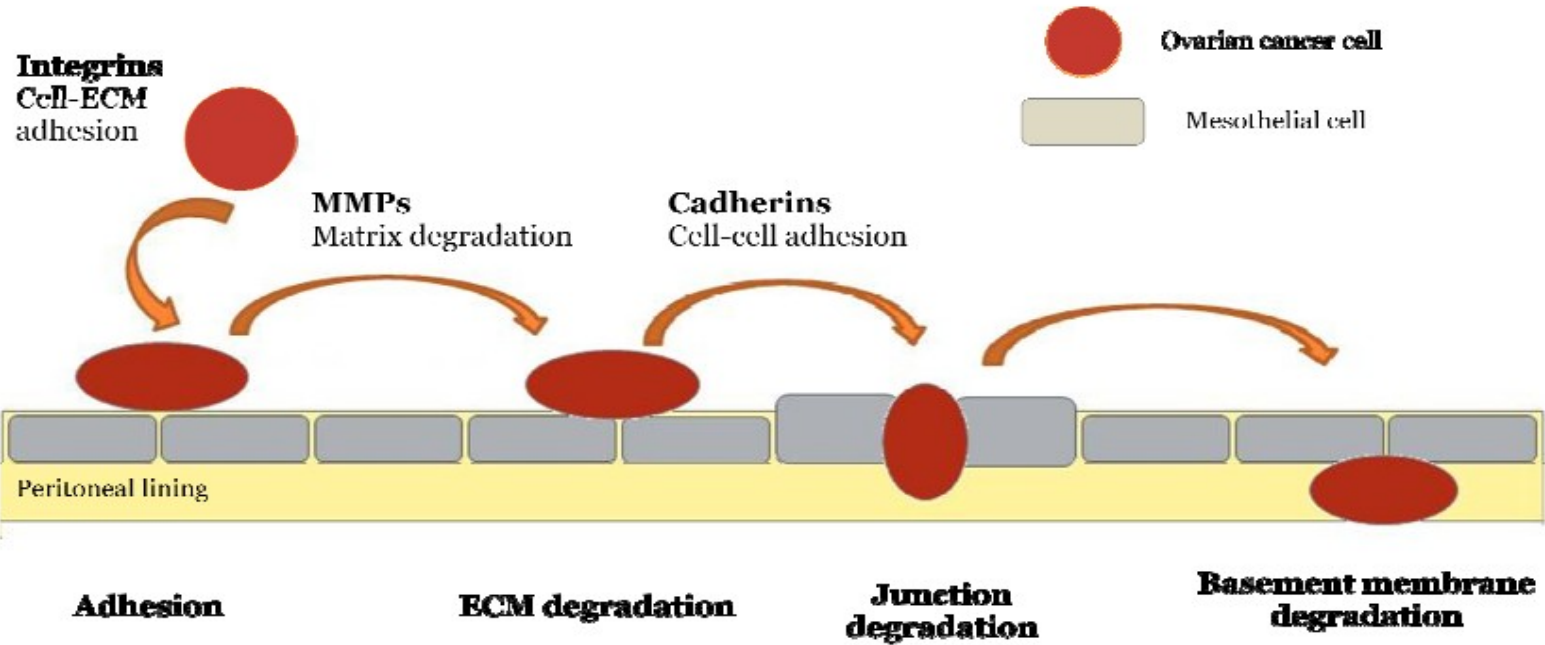
Side view

(B)

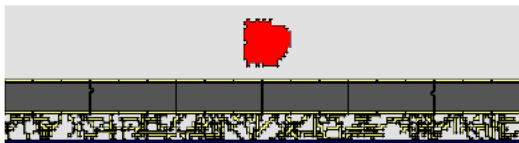


C. Giverso, M. Scianna, L.P., N. Lo Buono & A. Funaro
Math. Model. Nat. Phenom. **5**, 203-223 (2010)

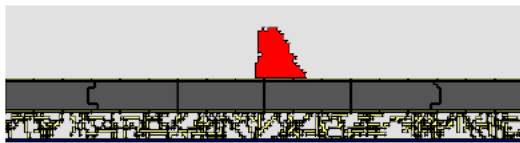
Invasion of Ovary Cancer Cells



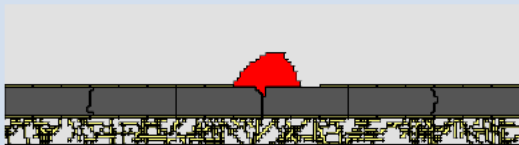
0 MCS



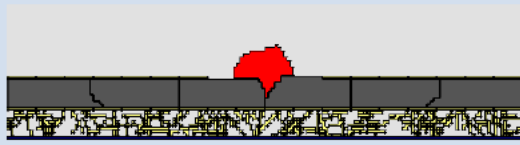
200 MCS



400 MCS



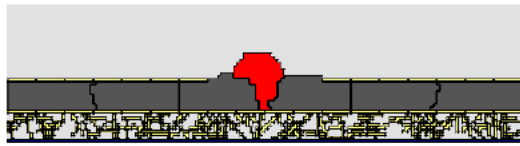
600 MCS



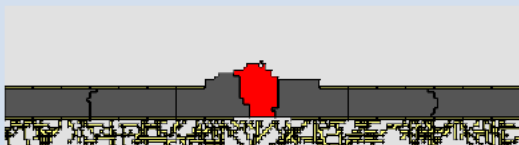
700 MCS



750 MCS



800 MCS



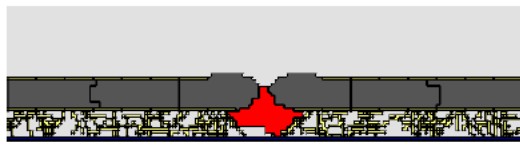
1000 MCS



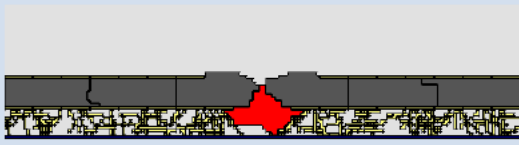
1200 MCS



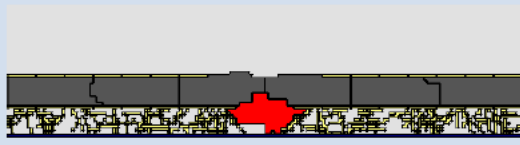
1400 MCS



1600 MCS



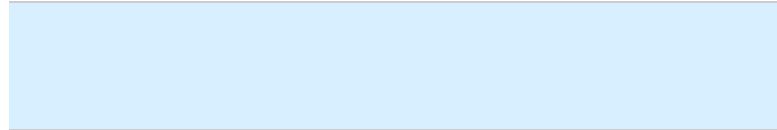
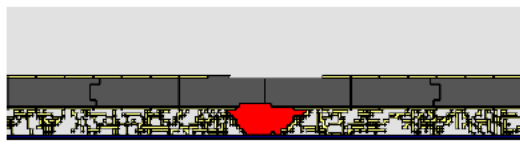
1800 MCS



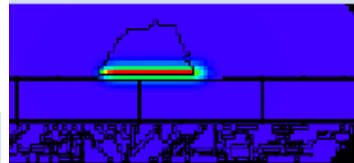
2000 MCS



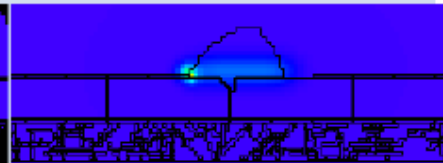
5000 MCS



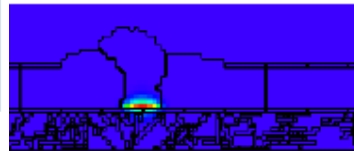
300 MCS



400 MCS



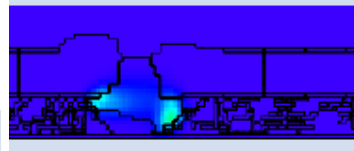
780 MCS



800 MCS

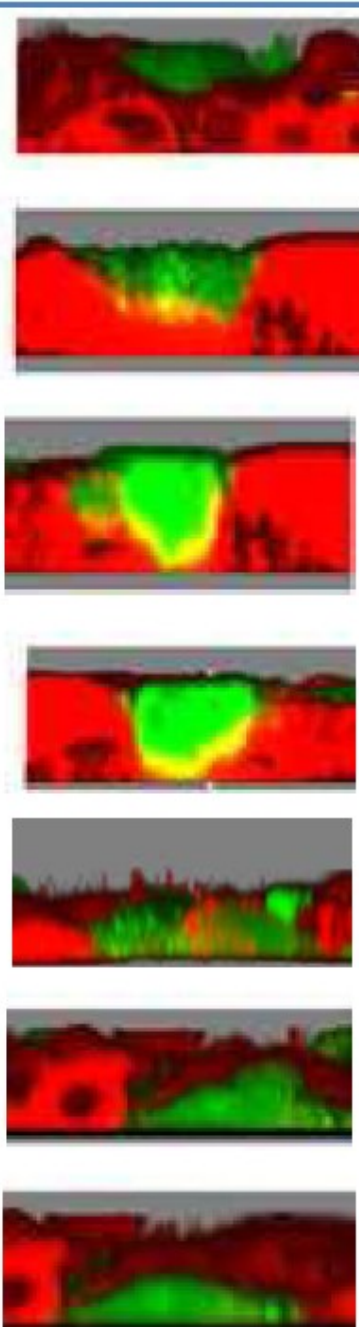
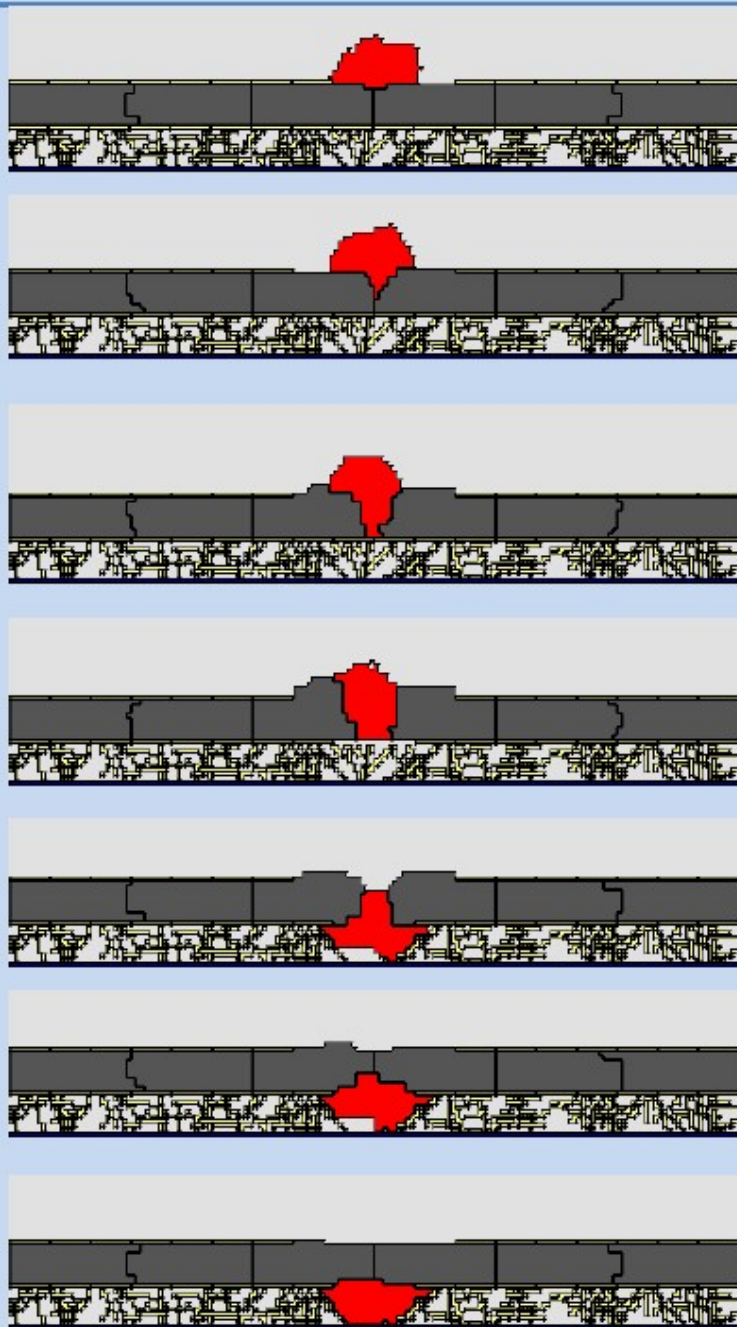


1000 MCS

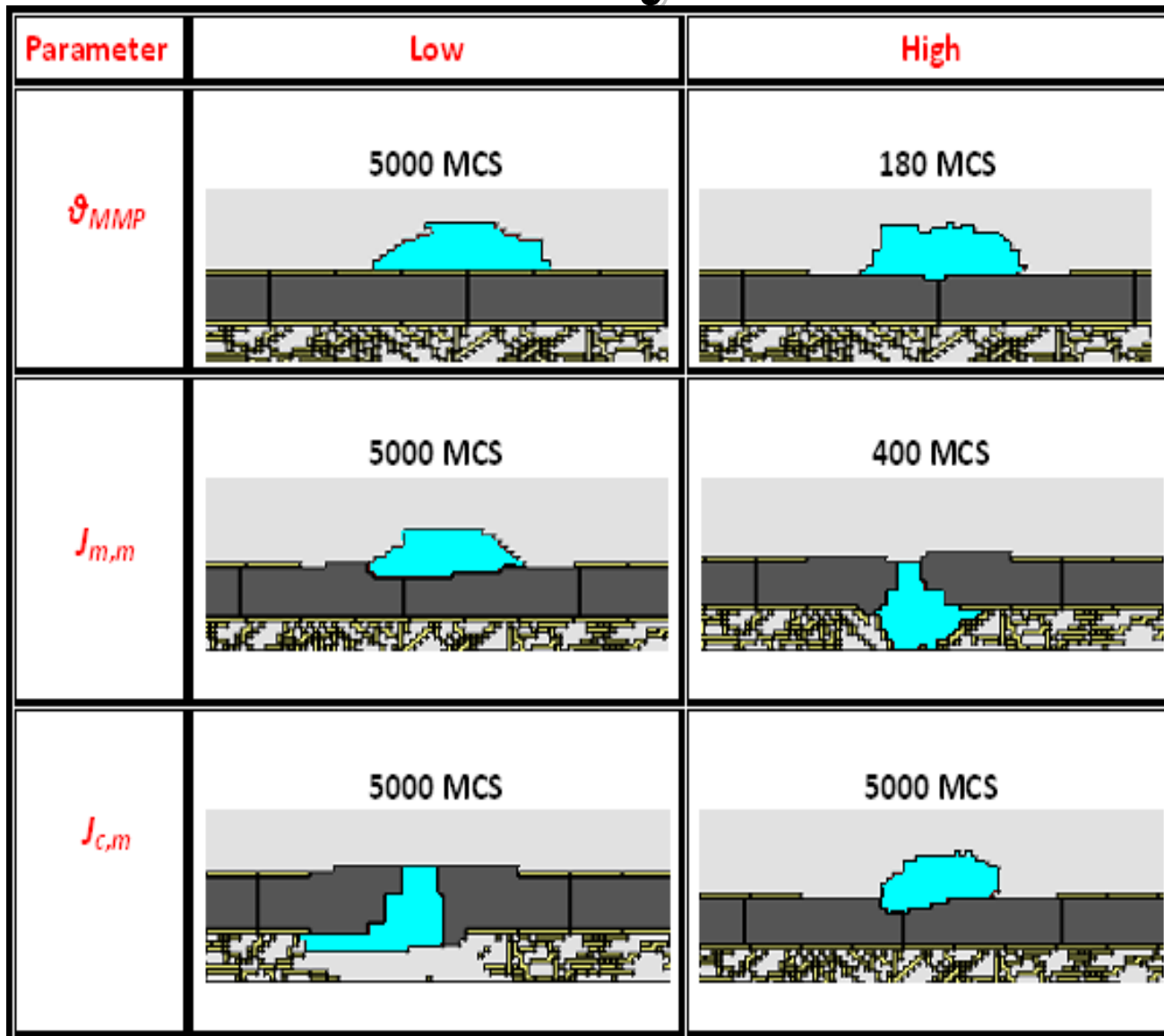


2000 MCS

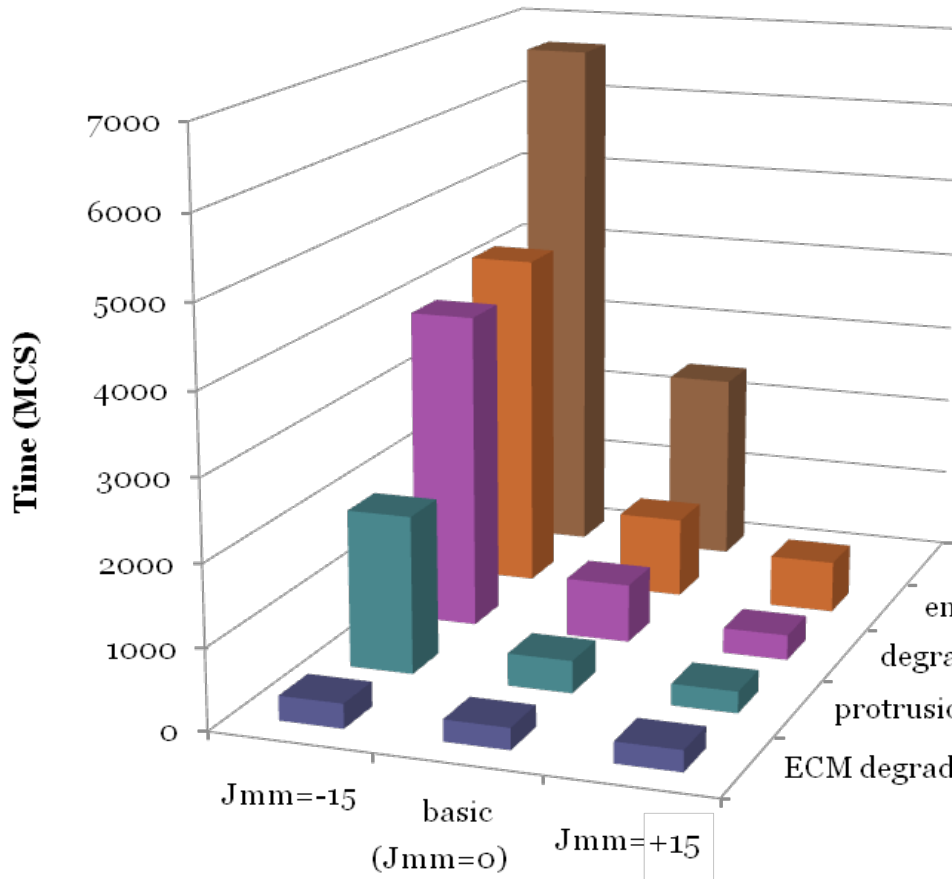




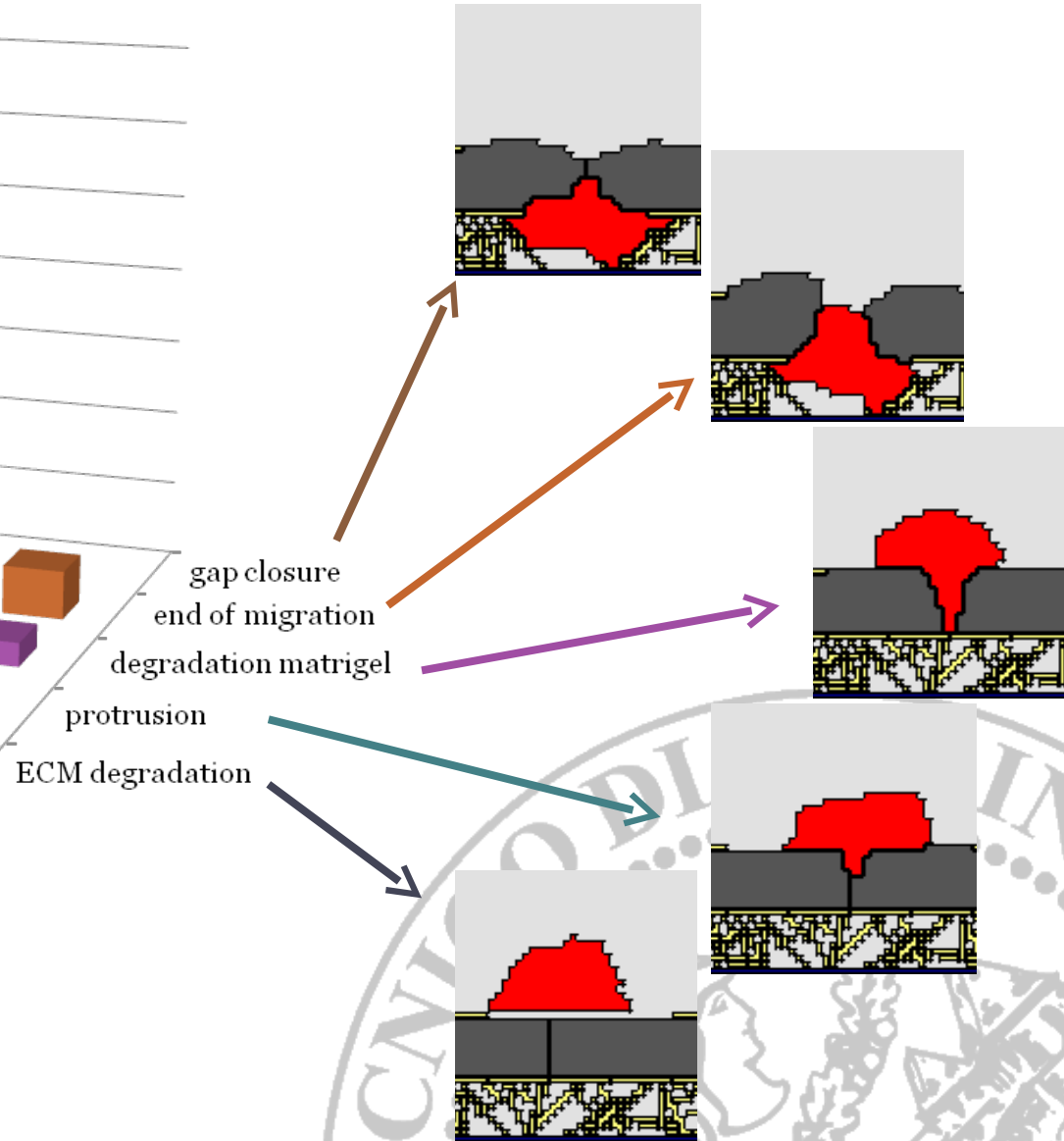
Invasion of Ovary Cancer Cells



Invasion of Ovary Cancer Cells

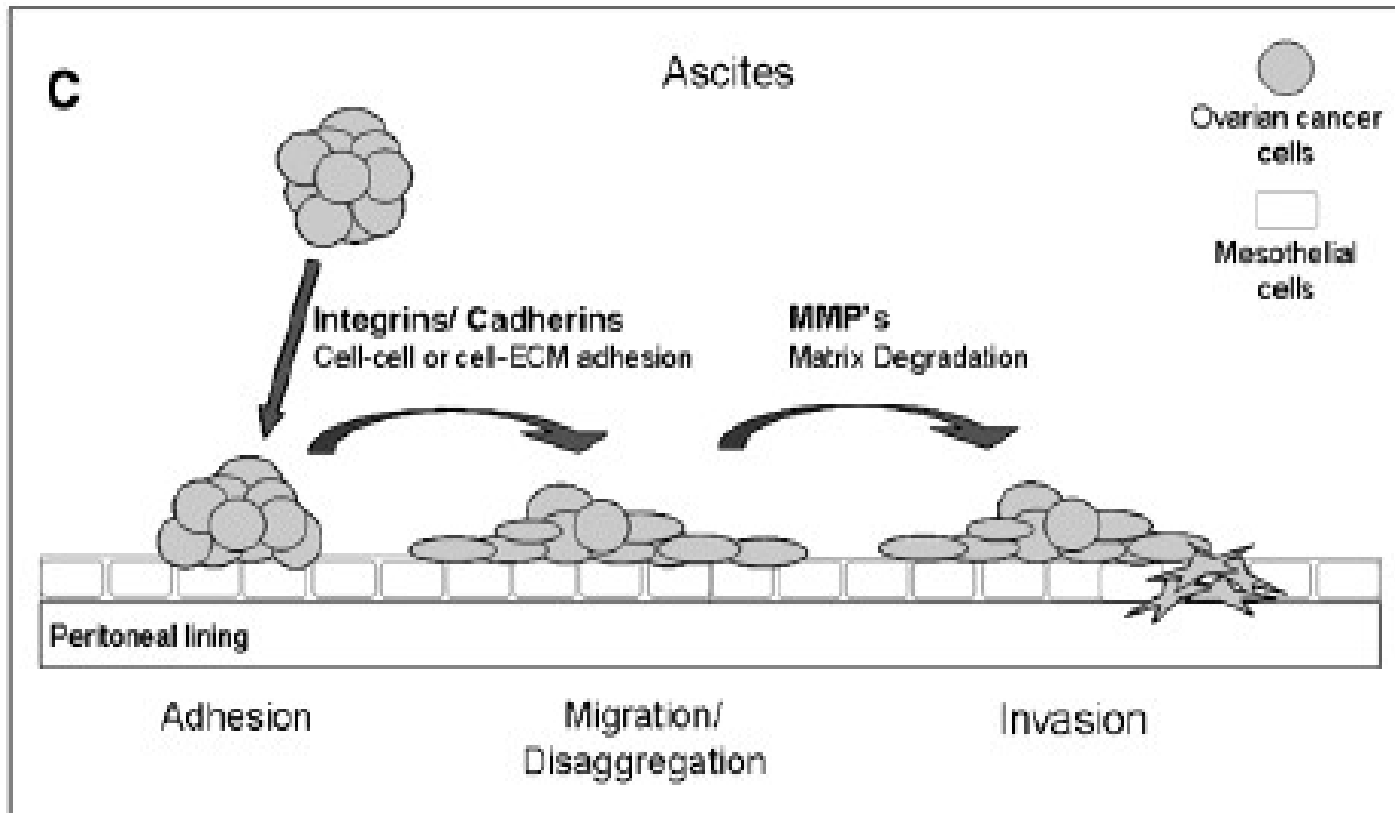


(mean over 10 simulations)



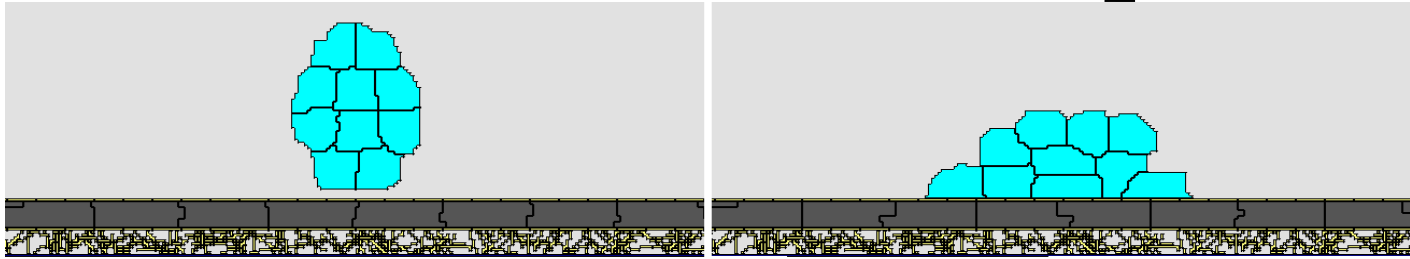
Invasion of Ovary Cancer Cells

Top view



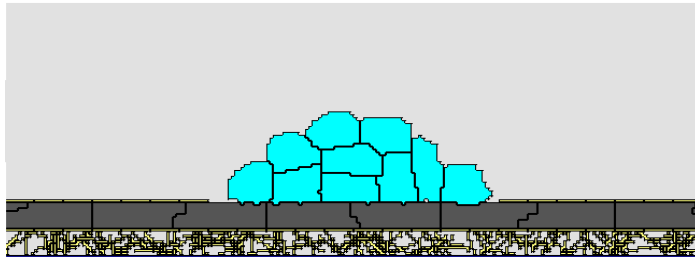
Bottom view

Invasion of Multicellular Spheroids

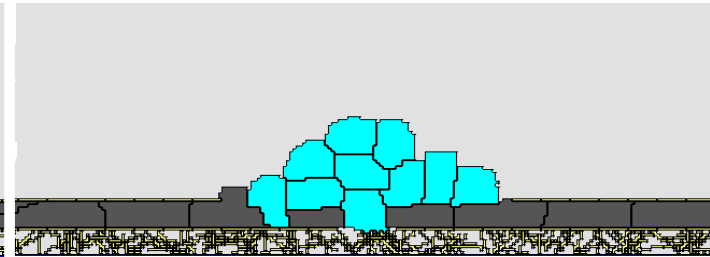


(A)

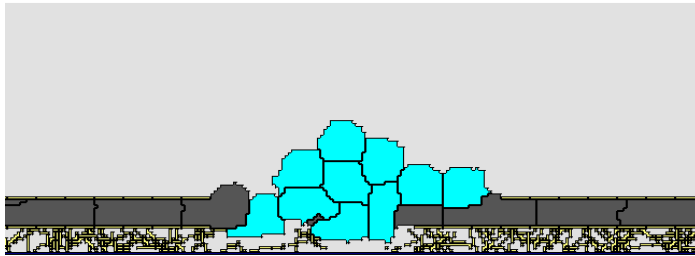
(B)



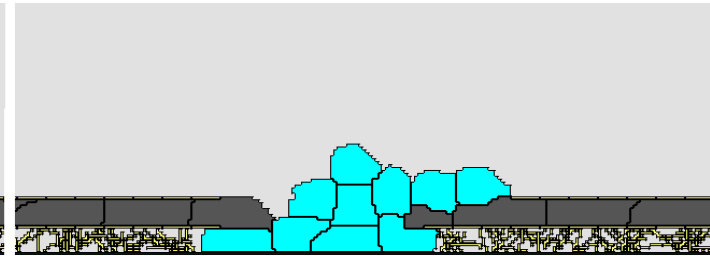
(C)



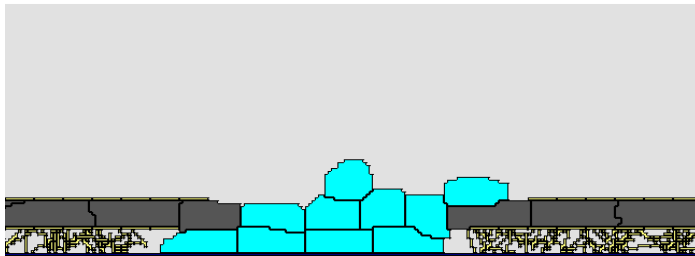
(D)



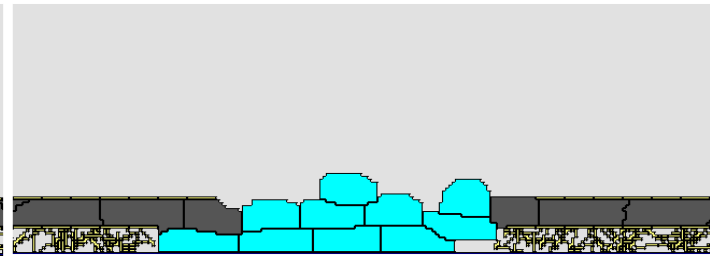
(E)



(F)



(G)

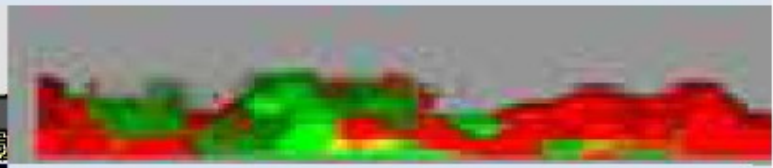
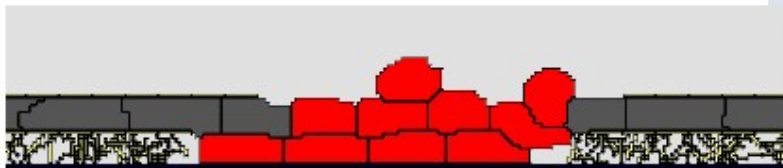
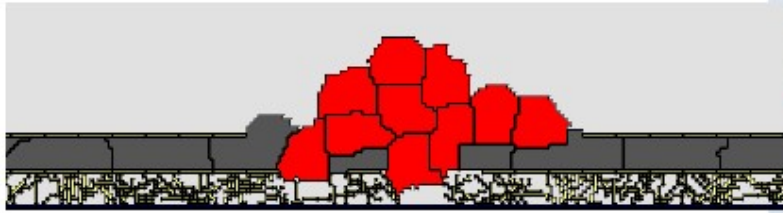
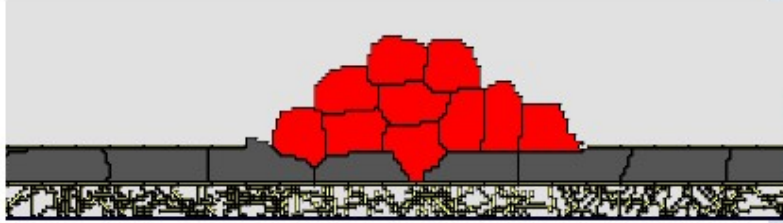


(H)

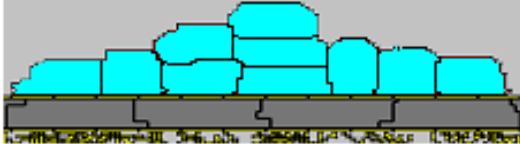

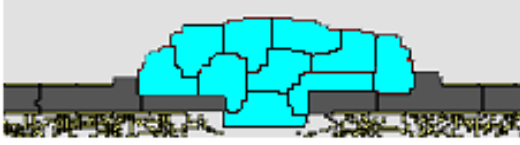

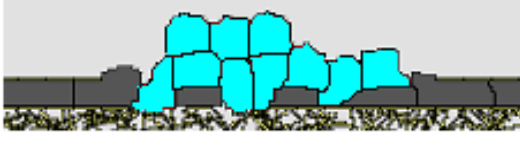

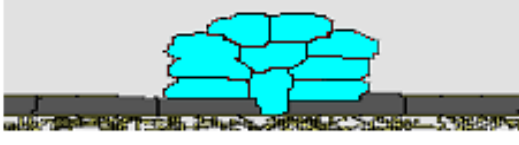

Invasion of Multicellular Spheroids

Simulations

Biological assays

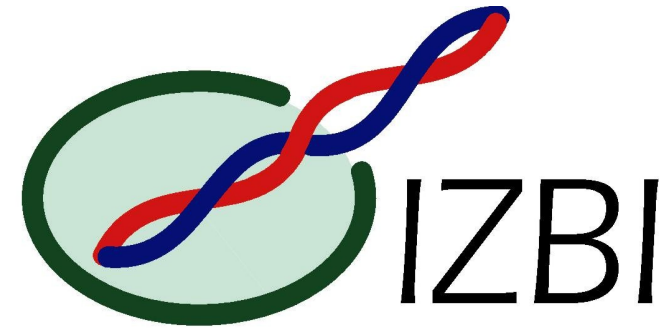


Invasion of Ovary Cancer Cells

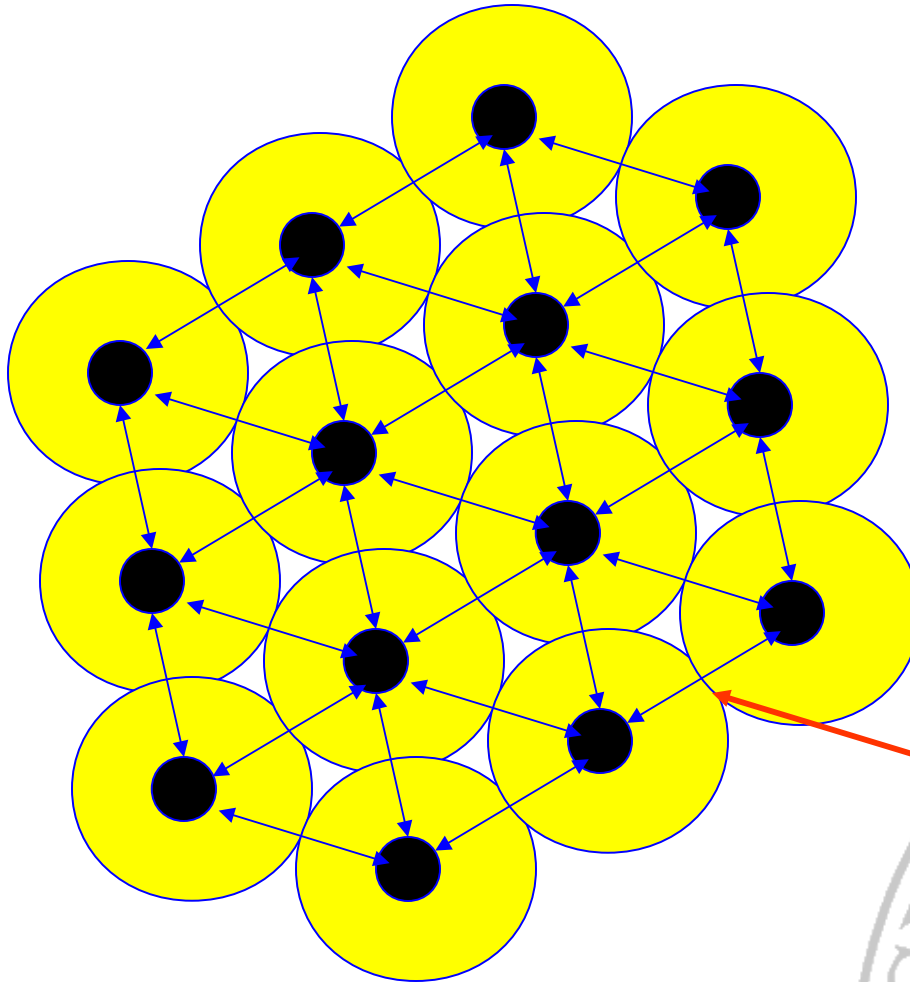
Parameter	Low	High
\mathcal{G}_{MMP}	<p>12000 MCS</p> 	<p>2000 MCS</p> 
$J_{c,c}$	<p>7800 MCS</p> 	<p>7800 MCS</p> 
$J_{c,e}$	<p>8000 MCS</p>  <p>12000 MCS</p> 	<p>8000 MCS</p>  <p>12000 MCS</p> 

Individual based models

J. Galle & D. Drasdo



Interdisciplinary Centre for Bioinformatics



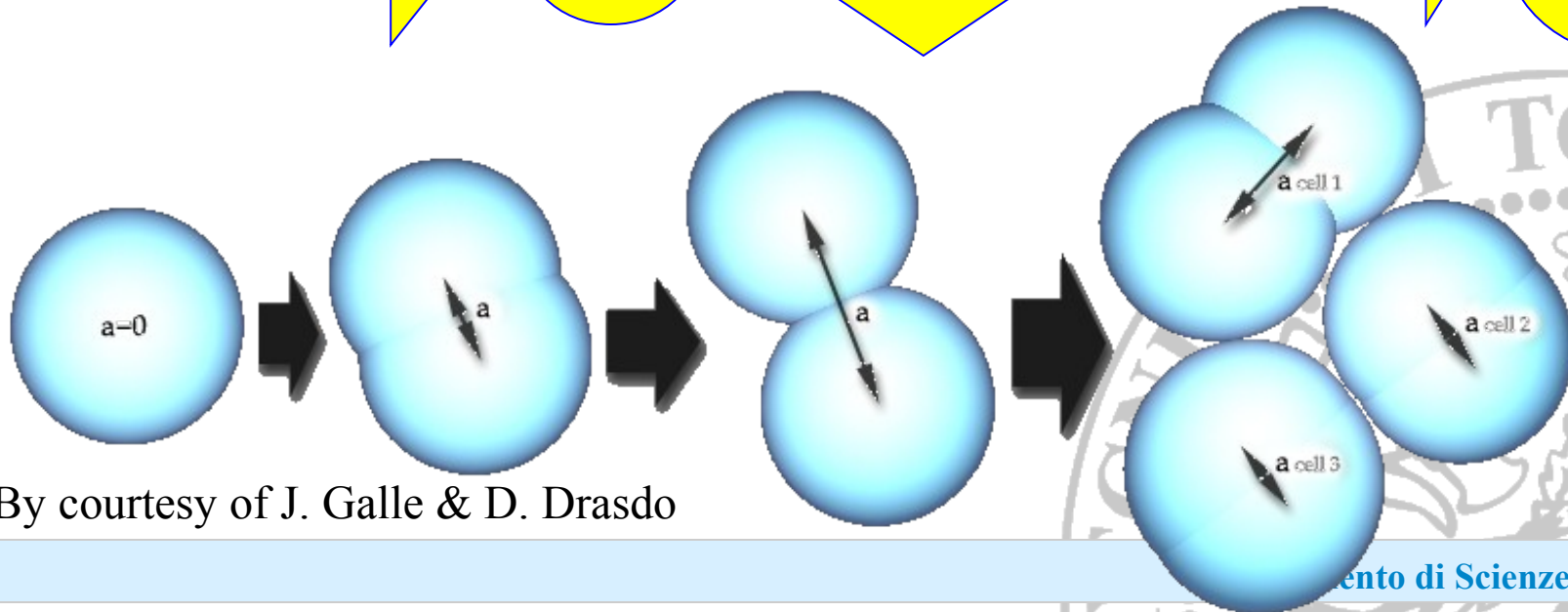
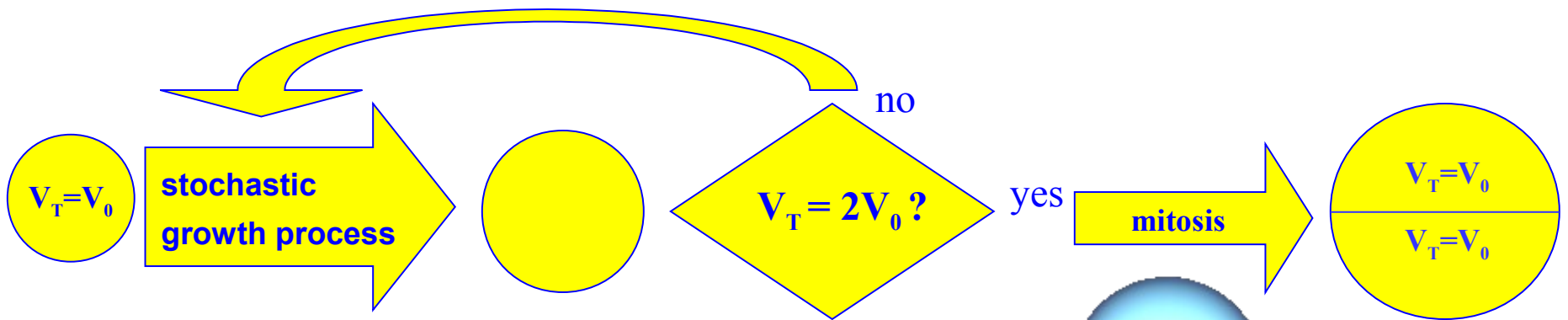
cell-cell and
cell-substratum
interaction

Cell cycle model

2-phase cell cycle

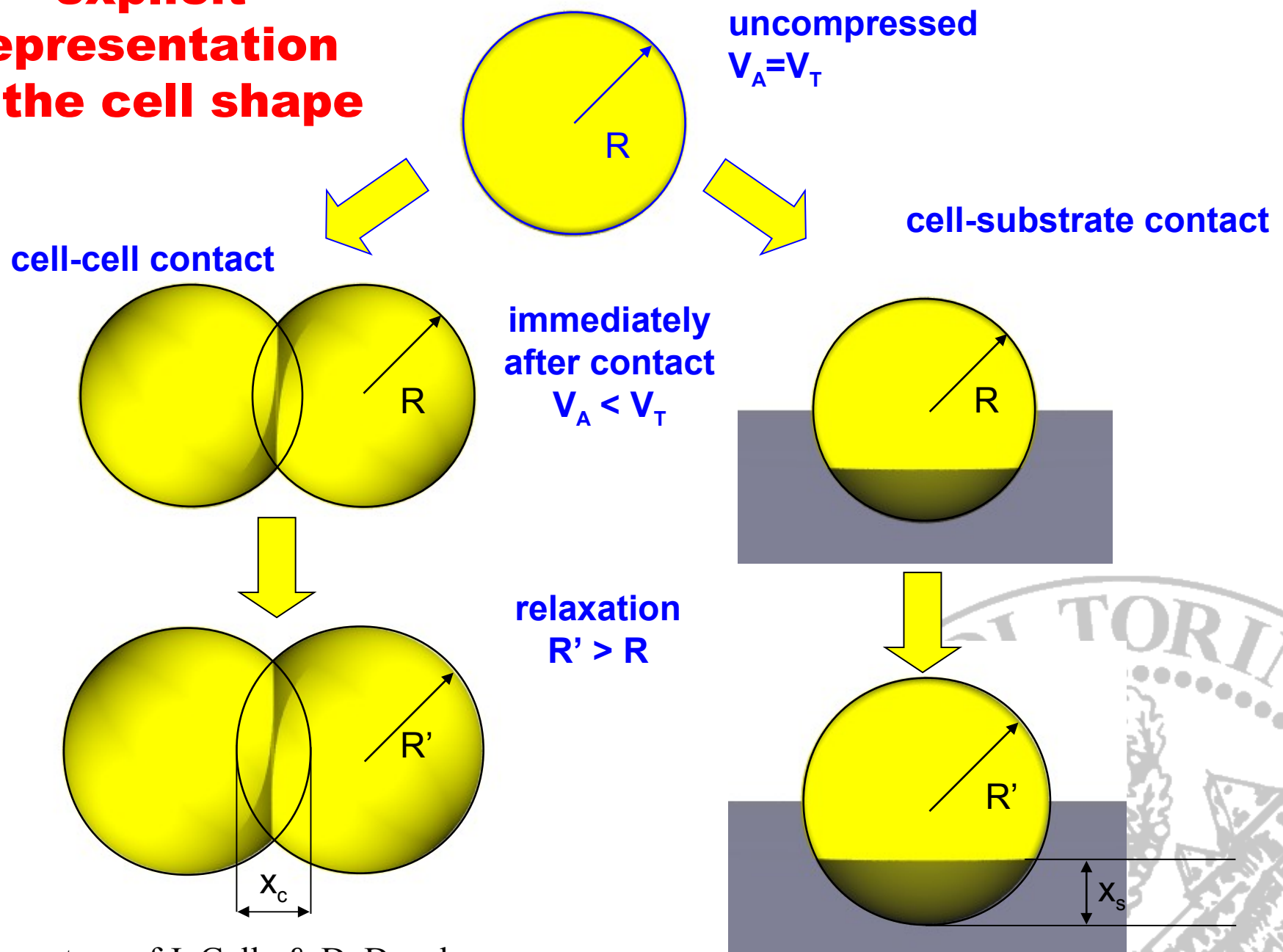
interphase cell doubles its target volume

mitotic phase cell divides into 2 daughter cells of equal target volume



By courtesy of J. Galle & D. Drasdo

**explicit
representation
of the cell shape**

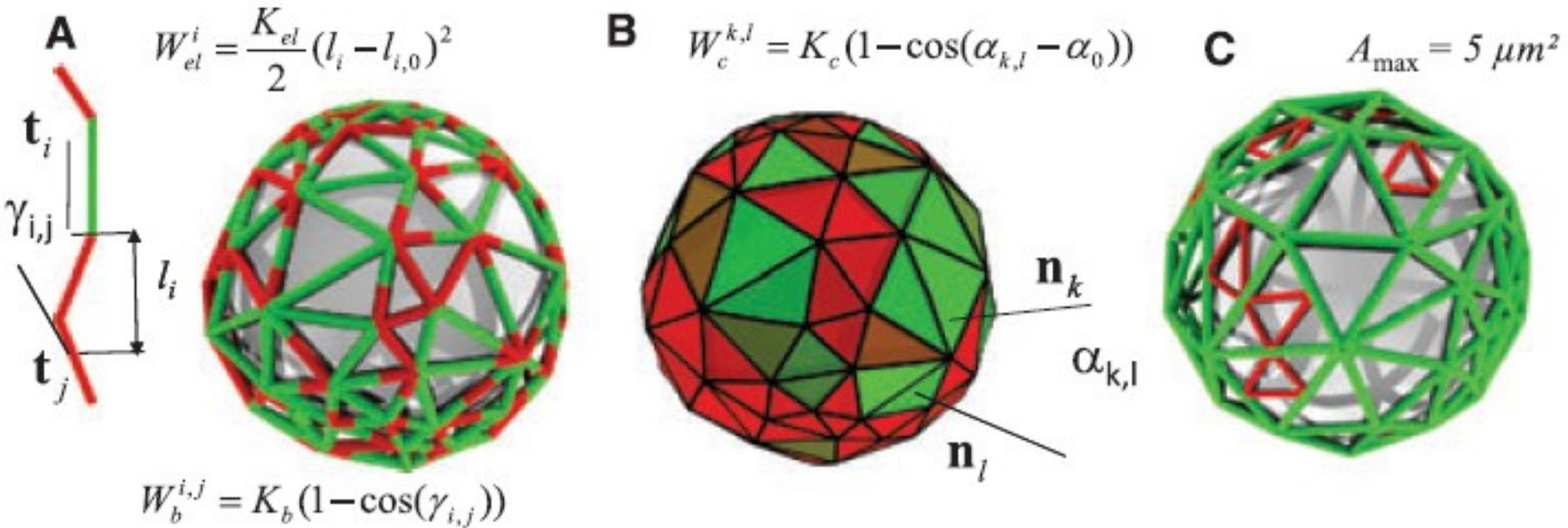


By courtesy of J. Galle & D. Drasdo

IBM interacting with a membrane

Buske et al., *FEBS J.* 279, 3475-3487 (2012)

Model of a re-organisable and flexible basal membrane (BM)



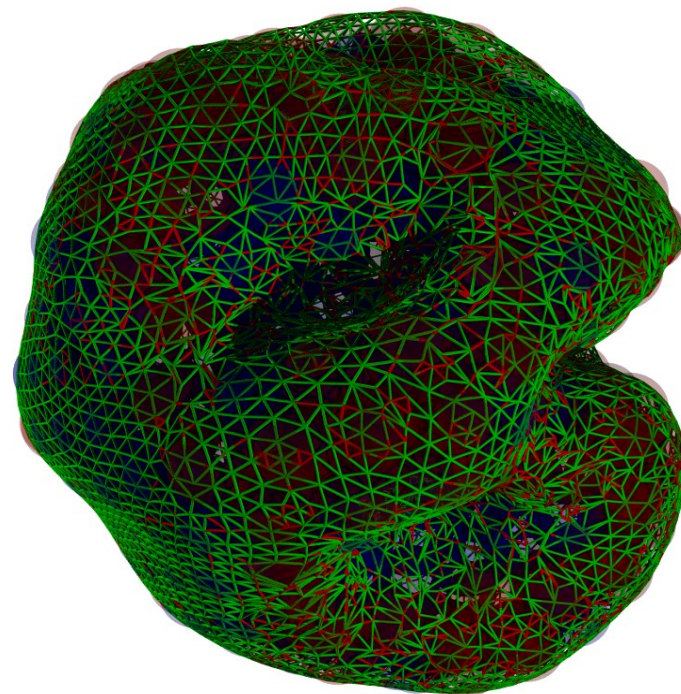
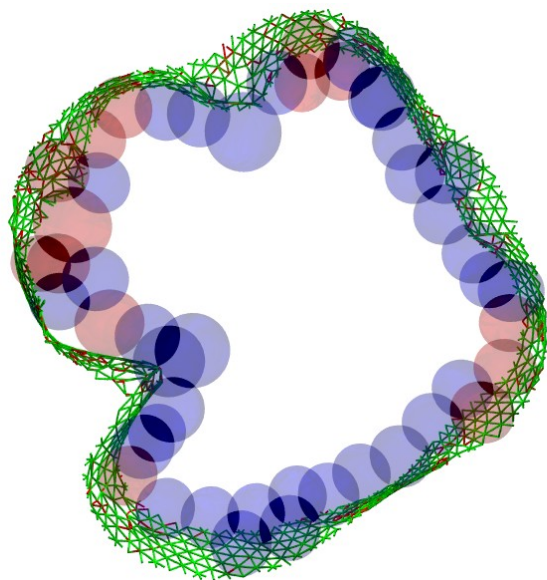
- Basal membrane consists of semiflexible elastic polymers
- Polymers are organized in triangles

- New triangles are added if a triangle area is too large
- Surface curvature potential controls shape

IBM interacting with a membrane

Buske et al., *FEBS J.* **279**, 3475-3487 (2012)

- Cells adhere to the basal membrane
- Cells modify its properties of the membrane



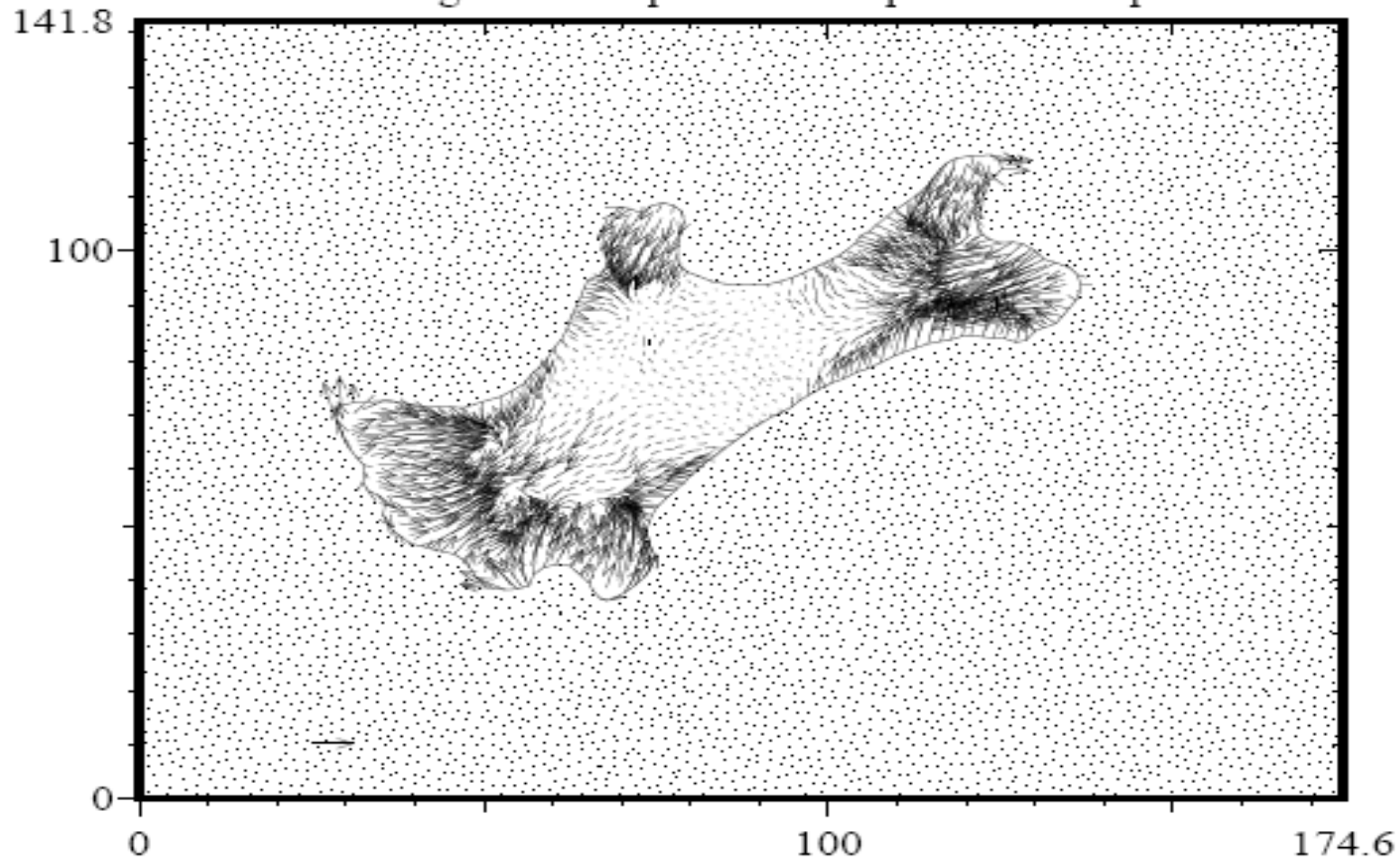
Original at:

<http://onlinelibrary.wiley.com/doi/10.1111/j.1742-4658.2012.08646.x/supinfo>

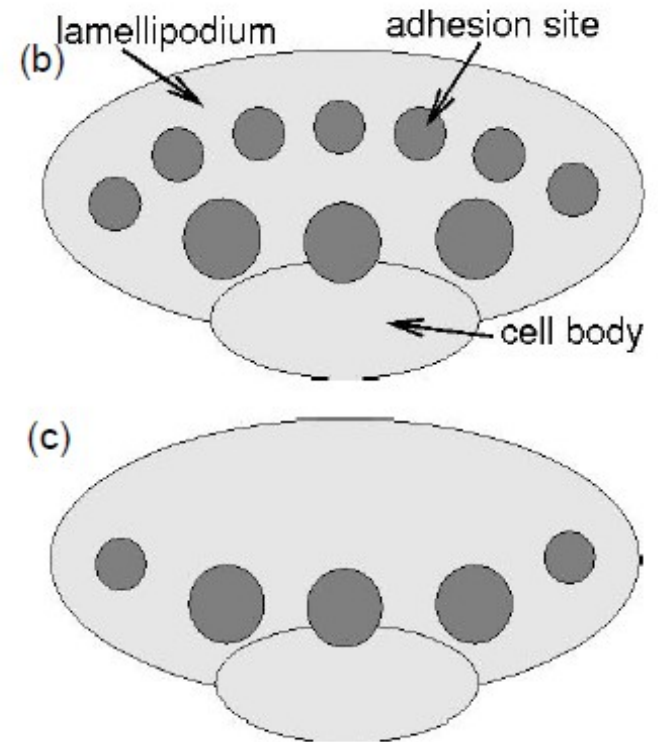
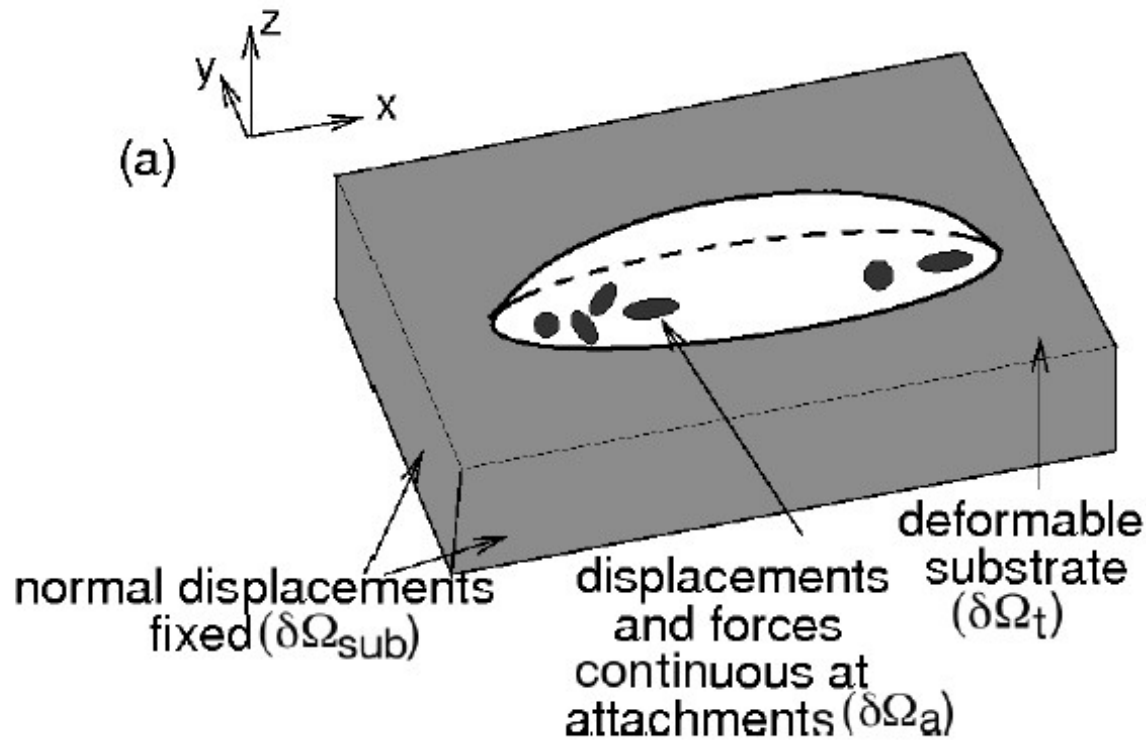
What's missing? Active behaviours

Force

arrow length = $10e2$ picoNewton per micron square



What's missing? Active behaviours

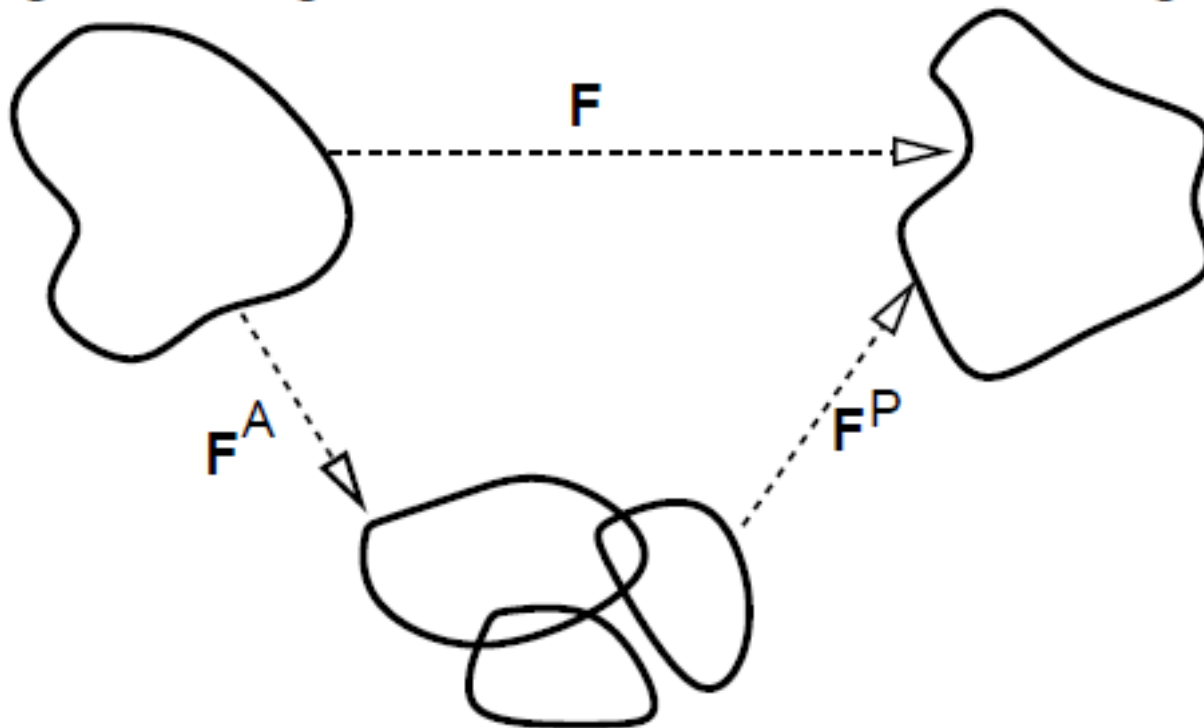


What's missing? Active behaviours

$$\mathbf{F} = \mathbf{F}^P \mathbf{F}^A$$

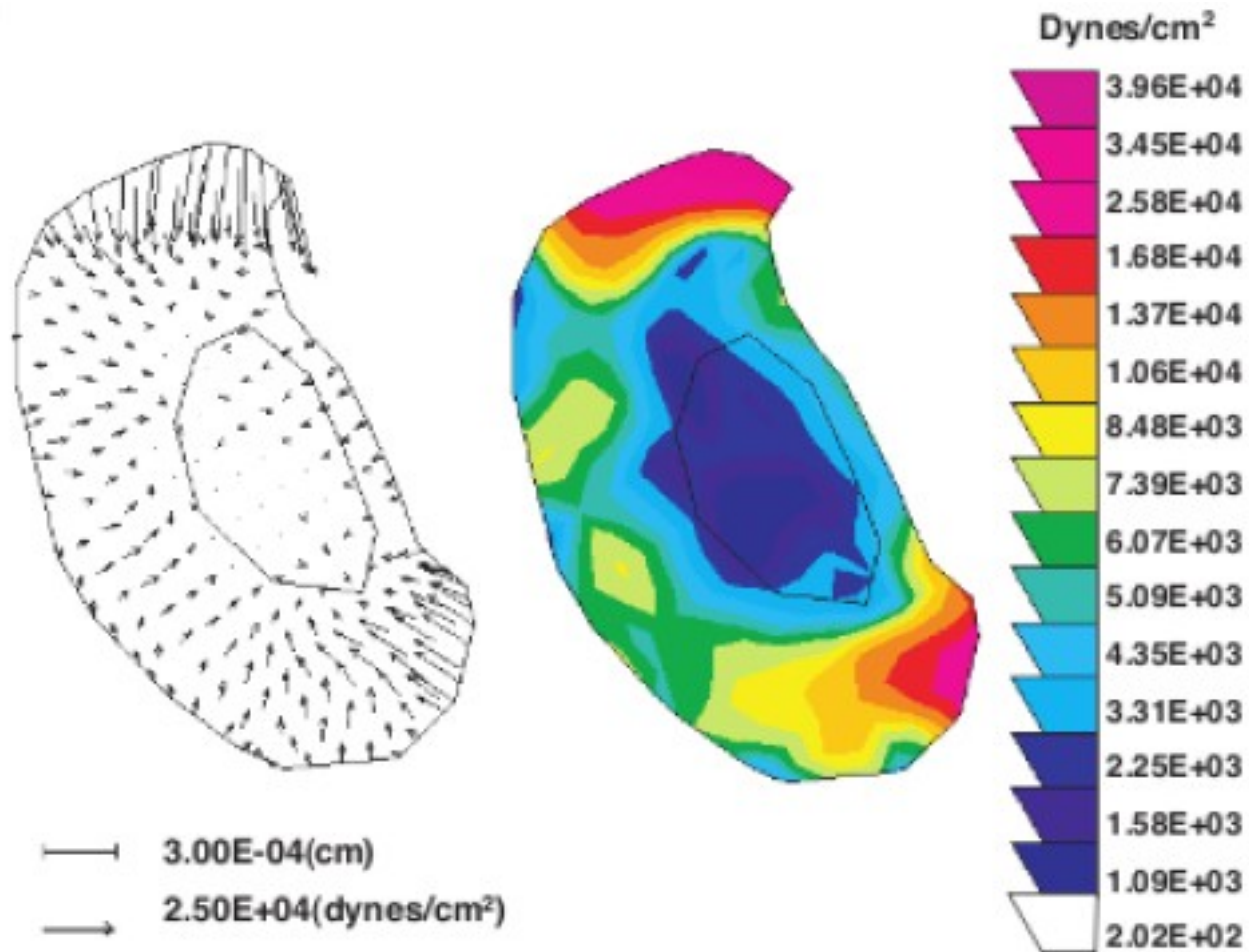
Original configuration

Current configuration

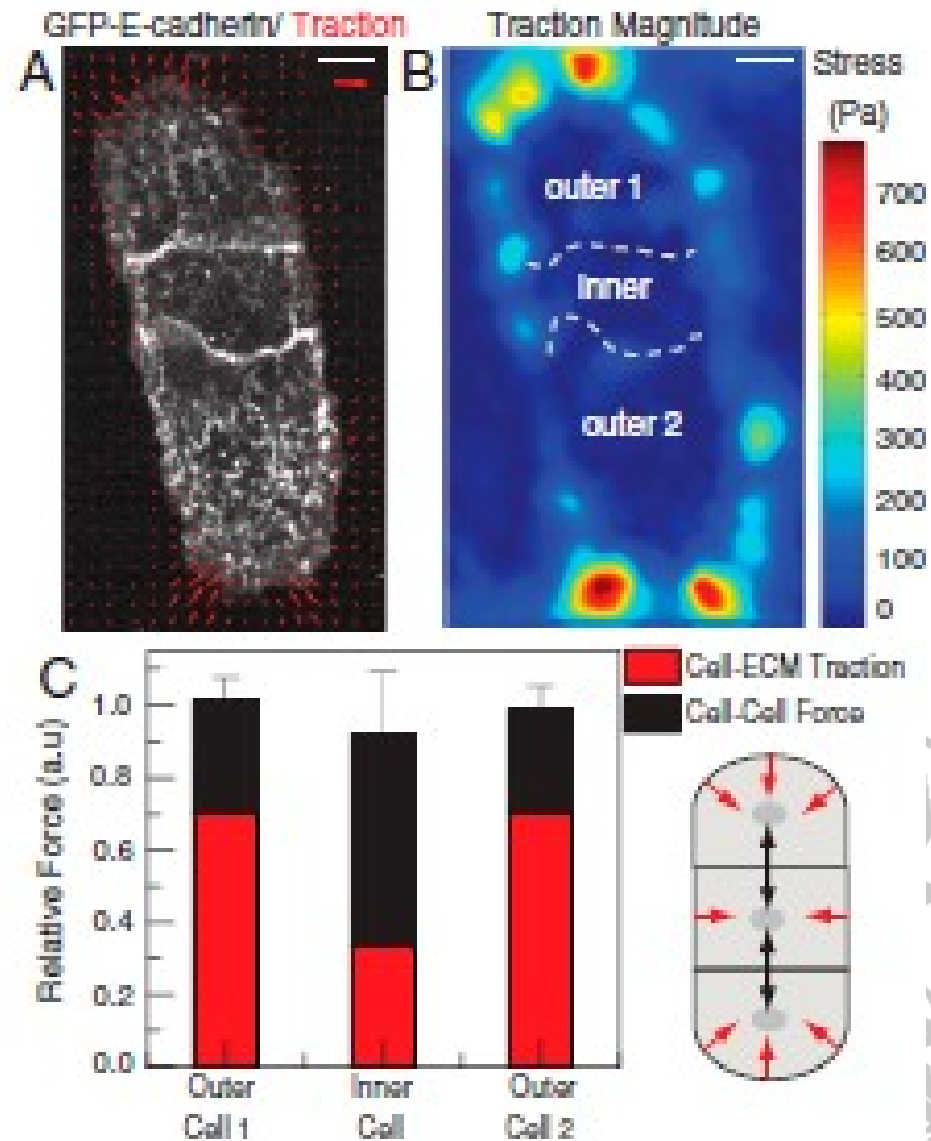
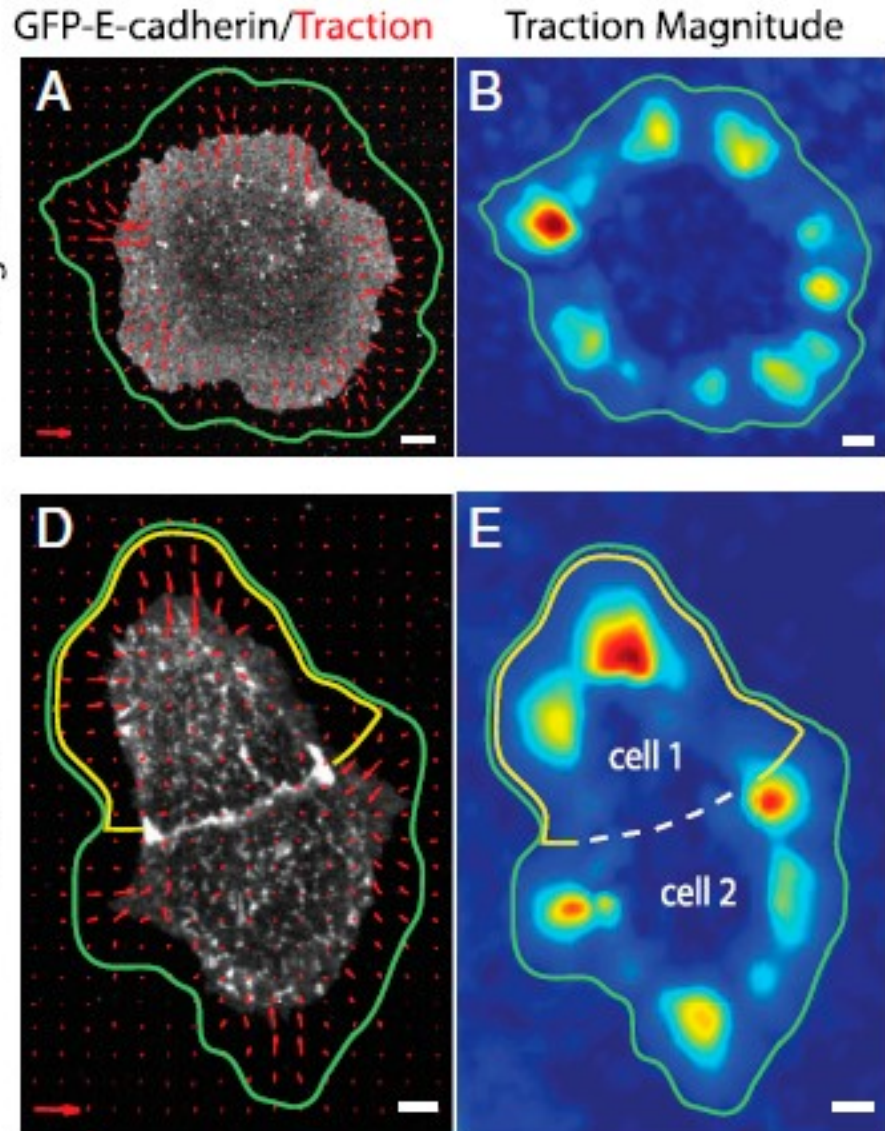


Intermediate stress-free configuration

What's missing? Active behaviours



What's missing? Active behaviours



A. Chauviere

C. Verdier

S. Astanin



D. Ambrosi

A. Tosin

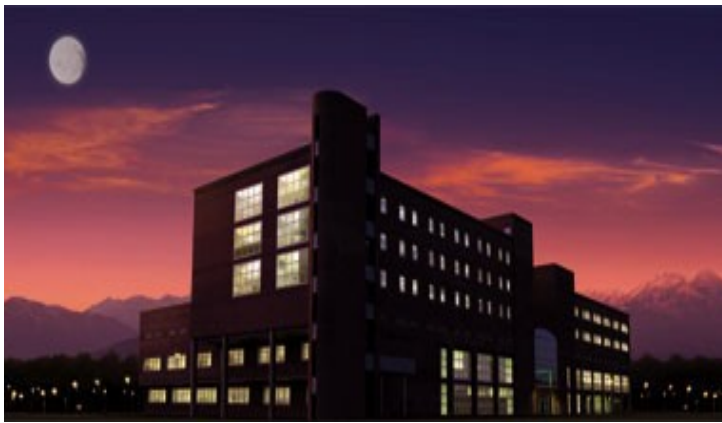
G. Vitale

V. Peschetola

C. Giverso

M. Scianna





Istituto per la Ricerca e la Cura del Cancro
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