A model for cell migration involving microtubules

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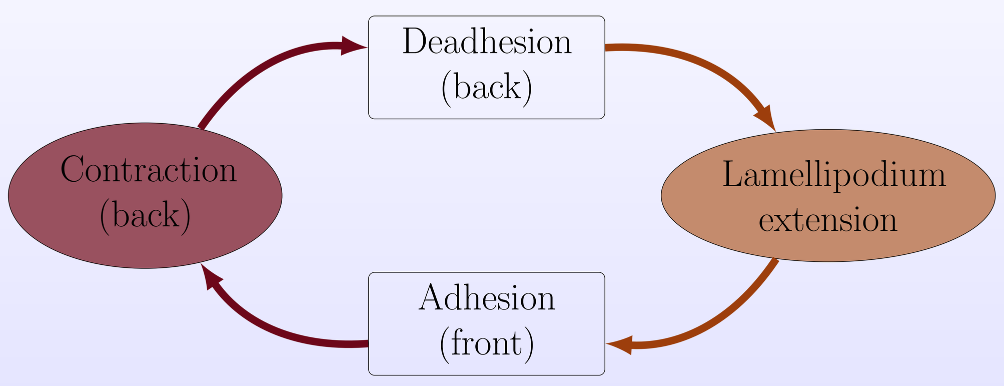
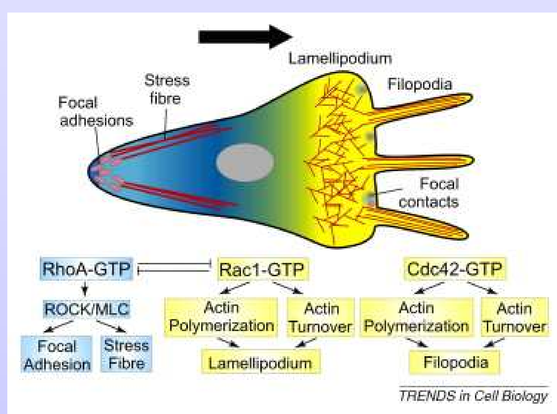
Biological Context

Cell migration is a complex biological process involving a succession of different events :



Many proteins and components of the cell are involved in cell migration. We focus on three important actors that act directly on cell motility :

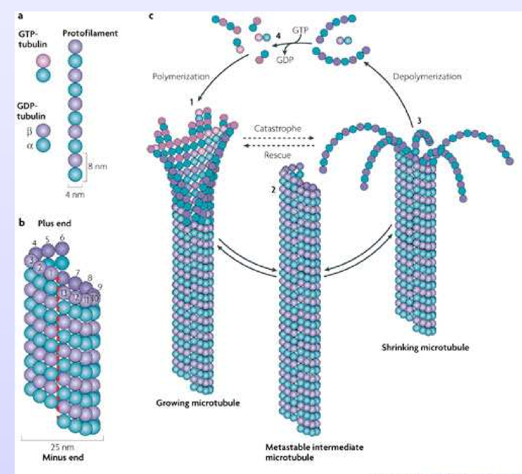
- Actin. Part of cytoskeleton, Creation of lamellipodium, Contraction.
- Rac. Encourage lamellipodium extension.
- Rho. Promote contraction.



Among those actors, Rac and Rho can be active or inactive inside the cytoplasm. Their activity depends strongly on microtubules.

Microtubules Dynamics

Microtubules (MT) are part of the cytoskeleton, constituted of long tubes polymers of tubulin.



MT have a highly dynamic behavior called dynamic instability. Their plus ends alternate between phases :

→ polymerization

→ depolymerization

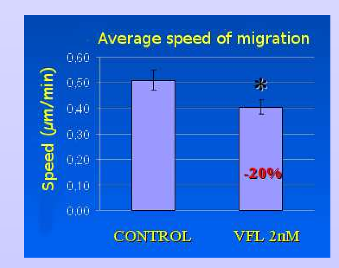
Role of Microtubules

Cell Division :
Microtubules play a crucial role in mitosis. The mitotic spindle, that segregate the chromosomes during mitosis is mainly composed of microtubules.

Transport :
Motor protein, like dynein or kinesin can attach to microtubules. They are involved in vesicules and organelles transportation throughout the cytoplasm.

Cell Migration :
Microtubules have an effect on proteins that regulate migration. Their dynamic activity regulate the activation or inactivation of Rac and Rho proteins. The polymerization of the microtubule activates Rac and the depolymerization activates Rho.

It has been shown that microtubules can be a target for anticancer therapies. In particular during angiogenesis and metastatic process, even at low doses.



One protein Model

Variables :
u-velocity ; p-pressure ; Rac-concentration of active Rac ; $\overline{\text{Rac}}$-concentration of inactive Rac

Mechanical Model :

$$\begin{aligned} -\mu\Delta u + \nabla p &= F_{el} + F_{net}, \quad x \in \mathbb{R}^2 \\ \nabla . u &= 0 \end{aligned}$$

Biochemical Model :

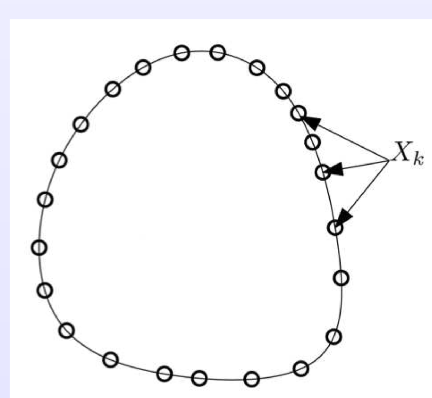
$$\begin{aligned} \frac{\partial \text{Rac}}{\partial t} + u.\nabla \text{Rac} - D_{\text{Rac}}\Delta \text{Rac} &= g(\text{Rac})\overline{\text{Rac}} - \delta \text{Rac}, \quad x \in \Omega(t), t > 0 \\ \frac{\partial \overline{\text{Rac}}}{\partial t} + u.\nabla \overline{\text{Rac}} - D_{\overline{\text{Rac}}}\Delta \overline{\text{Rac}} &= -g(\text{Rac})\overline{\text{Rac}} + \delta \text{Rac} \end{aligned}$$

$$\boxed{g(\text{Rac}) = \tau_{\overline{\text{Rac}}\to\text{Rac}} + \frac{\gamma \text{Rac}^2}{K^2 + \text{Rac}^2}}$$

Interface Representation :

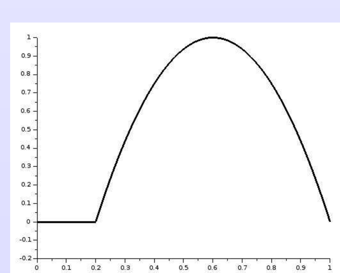
We use a Lagrangian Marker Points(LMP) method, based on a parametrization of the interface.

$$\frac{\partial X}{\partial t}(s,t) = u(X(s,t),t)$$



Forces : F_{el}, elastic force ; F_{net}, protrusion force

$$\begin{aligned} F_{el} &= \frac{\partial}{\partial s}\left[T_0\left(\left|\frac{\partial X}{\partial s}\right| - 1\right)\frac{\partial X}{\partial s}\right] \\ F_{net} &= h(\text{Rac})\left(\frac{\partial X}{\partial s}\right)^{\perp} \end{aligned}$$



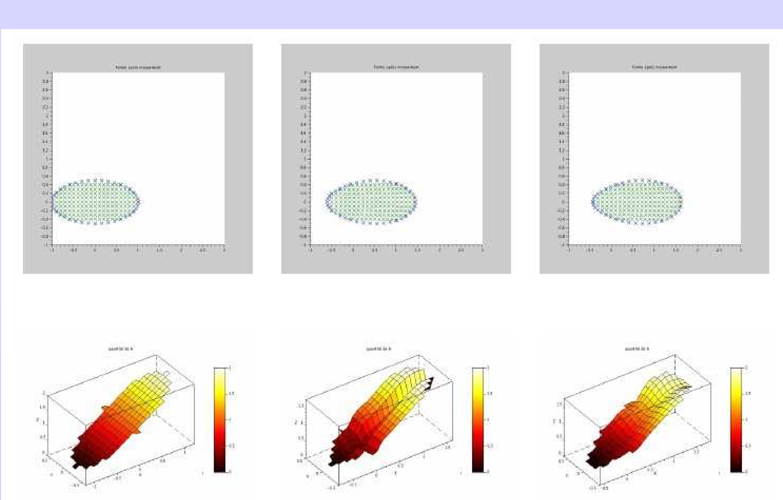
Function h

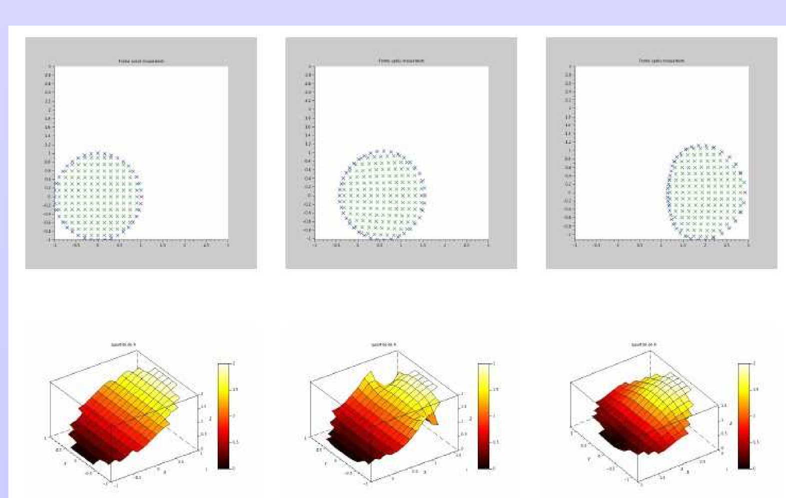
Numerical Results :

Difficulties :

- The cell is a moving domain
- Interpolation Lagrangian-Eulerian
- Limitation on the deformation of the membrane

Methods : Stokeslet - Finite Volume - Euler Scheme





Two Protein Model with MT regulation

Variables :
u-velocity ; p-pressure ; Rac-concentration of active Rac ; $\overline{\text{Rac}}$-concentration of inactive Rac ; Rho-concentration of active Rho ; $\overline{\text{Rho}}$-concentration of inactive Rho ; MT_i-plus end of MT number i ; L_i-length of MT number i ; Tub-concentration of Tubulin

Mechanical Model :

$$\begin{aligned} -\mu\Delta u + \nabla p &= F_{el} + F_{net}, \quad x \in \mathbb{R}^2 \\ \nabla . u &= 0 \end{aligned}$$

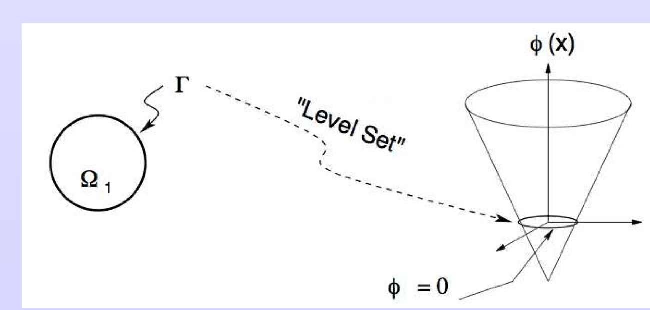
Biochemical Model :

$$\begin{aligned}
&\frac{\partial \text{Rac}}{\partial t} + u.\nabla \text{Rac} - D_{\text{Rac}}\Delta \text{Rac} = \sum_i \left[g(\text{Rac})k_0(x)\overline{\text{Rac}} - \tau_{\text{Rac}\to\overline{\text{Rac}}}(1-k_0(x))\text{RhoRac}\right] \mathbb{1}_{B(\text{MT}_i, d_{MT})} \\
&\frac{\partial \overline{\text{Rac}}}{\partial t} + u.\nabla \overline{\text{Rac}} - D_{\overline{\text{Rac}}}\Delta \overline{\text{Rac}} = -\sum_i \left[g(\text{Rac})k_0(x)\overline{\text{Rac}} - \tau_{\text{Rac}\to\overline{\text{Rac}}}(1-k_0(x))\text{RhoRac}\right] \mathbb{1}_{B(\text{MT}_i, d_{MT})} \\
&\frac{\partial \text{Rho}}{\partial t} + u.\nabla \text{Rho} - D_{\text{Rho}}\Delta \text{Rho} = \sum_i \left[g(\text{Rho})(1-k_0(x))\overline{\text{Rho}} - \tau_{\text{Rho}\to\overline{\text{Rho}}}k_0(x)\text{RhoRac}\right] \mathbb{1}_{B(\text{MT}_i, d_{MT})} \\
&\frac{\partial \overline{\text{Rho}}}{\partial t} + u.\nabla \overline{\text{Rho}} - D_{\overline{\text{Rho}}}\Delta \overline{\text{Rho}} = -\sum_i \left[g(\text{Rho})(1-k_0(x))\overline{\text{Rho}} - \tau_{\text{Rho}\to\overline{\text{Rho}}}k_0(x)\text{RhoRac}\right] \mathbb{1}_{B(\text{MT}_i, d_{MT})} \\
&\frac{\partial \text{Tub}}{\partial t} + u.\nabla \text{Tub} - D_{\text{Tub}}\Delta \text{Tub} = -\sum_i d\frac{\partial L_i}{\partial t}\delta_0(x - \text{MT}_i) \\
&\frac{\partial L_i}{\partial t} = \alpha(\text{Tub} - c_c) \\
&\frac{\partial \text{MT}_i}{\partial t} = \alpha(\text{Tub} - c_c)\left(\frac{\eta\nabla\text{Tub} \pm u}{\|\eta\nabla\text{Tub} \pm u\| + \varepsilon}\right) + u
\end{aligned}$$

Interface Representation :

We use a Level-Set method, based on an implicit representation of the interface as the zero level curve of a function ϕ called the Level-Set function, in order to avoid problem of interpolation between Lagrangian and Eulerian coordinates.

$$\frac{\partial \phi}{\partial t} + u.\nabla\phi = 0$$



Forces : F_{el}, elastic force ; F_{net}, protrusion and contraction force

$$\begin{aligned} F_{el} &= -\lambda\, \nabla . \left(\frac{|\nabla\phi| - 1}{|\nabla\phi|}(\nabla\phi \otimes \nabla\phi)\frac{1}{\varepsilon}\zeta(\frac{\phi}{\varepsilon})\right) \\ F_{net} &= h(\text{Rac})\frac{\nabla\phi}{|\nabla\phi|} - h(\text{Rho})\frac{\nabla\phi}{|\nabla\phi|} \end{aligned}$$

Numerical Tools : Finite Volume on locally refined meshes (DDFV) - WENO

Perspectives : Development of numerical tools - Comparison with experiments

References

[Mai08] E. Maitre. *Equations de transport, Level Set et mécanique eulérienne. Application au couplage fluide-structure.* Habilitation à diriger des recherches, Université de Grenoble, November 2008.

[PHM+12] A. Pagano, S. Honoré, R. Mohan, R. Berges, A. Akhmanova, and D. Braguer. Epothilone B inhibits migration of glioblastoma cells by inducing microtubule catastrophes and affecting EB1 accumulation at microtubule plus ends. *Biochemical Pharmacology*, pages 432–433, May 2012.

[VFEK11] B. Vanderlei, J.J. Feng, and L. Edelstein-Keshet. A computational model of cell polarization and motility coupling mechanics and biochemistry. *Multiscale Model Simul.*, pages 1420–1443, October 2011.