A MODEL FOR CELL MIGRATION INVOLVING MICROTUBULES

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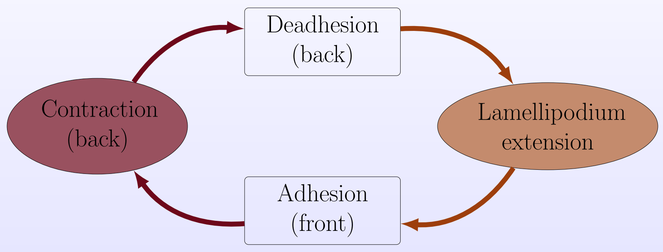
Biological Context

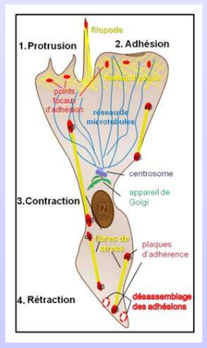
Cell migration is a complex biological process involving a succession of different events :



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

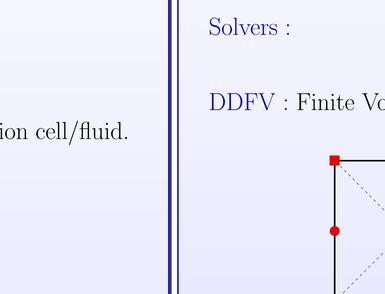
- Actin. Part of cytoskeleton, Creation of lamellipodium, Contraction.
- Rac. Encourage lamellipodium extension.
- Rho. Promote contraction.

Among those actors, Rac and Rho can be active or inactive inside the cytoplasm. Their activity depends strongly on microtubules. They both regulate the action of the actine.



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

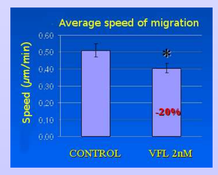
Role of Microtubules

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. Moreover, there is an inhibition between Rac and 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.



Two Proteins 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 ;
Tub-concentration of Tubulin ;
MT_i-plus end of MT number i ; L_i-length of MT number i ;

Note : Rac and Rho can be seen as markers of the activity of actine.

Mechanical Model :

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

Immersed Boundary Method (IBM) to model the interaction cell/fluid. The low Reynolds Number leads to Stokes equation.

Biochemical Model :

$$\frac{\partial \text{Rac}}{\partial t} + u.\nabla\text{Rac} - D_{\text{Rac}}\Delta\text{Rac} = G_{\text{Rac}}$$
$$\frac{\partial \overline{\text{Rac}}}{\partial t} + u.\nabla\overline{\text{Rac}} - D_{\overline{\text{Rac}}}\Delta\overline{\text{Rac}} = -G_{\text{Rac}}$$
$$\frac{\partial \text{Rho}}{\partial t} + u.\nabla\text{Rho} - D_{\text{Rho}}\Delta\text{Rho} = G_{\text{Rho}}$$
$$\frac{\partial \overline{\text{Rho}}}{\partial t} + u.\nabla\overline{\text{Rho}} - D_{\overline{\text{Rho}}}\Delta\overline{\text{Rho}} = -G_{\text{Rho}}$$

$$\frac{\partial \text{Tub}}{\partial t} + u.\nabla\text{Tub} - D_{\text{Tub}}\Delta\text{Tub} = -\sum_i d\frac{\partial L_i}{\partial t}\delta_0(x - \text{MT}_i)$$
$$\frac{\partial L_i}{\partial t} = \alpha(\text{Tub} - c_c)$$
$$\frac{\partial \text{MT}_{i\pm}}{\partial t} = \alpha(\text{Tub} - c_c)\left(\frac{\eta\nabla\text{Tub} \pm u}{\|\eta\nabla\text{Tub} \pm u\| + \varepsilon}\right) + u$$

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

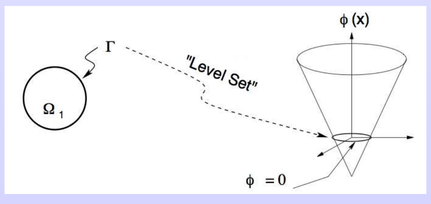
$$G_{\text{Rac}} = \sum_i \left[g(\text{Rac})k_0(x)\overline{\text{Rac}} - \tau_{\text{Rac}\to\overline{\text{Rac}}}(1 - k_0(x))\text{RhoRac} \right] \mathbb{1}_{B(\text{MT}_i, d_{MT})}$$

activation — inhibition — localisation of MT

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.

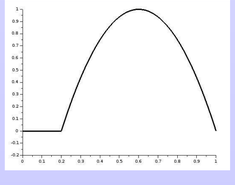
$$\frac{\partial \phi}{\partial t} + u.\nabla\phi = 0$$



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

F_{el} comes from an energy. $|\nabla\phi|$ is the local stretch.

$$\mathcal{E}_{el}(\phi) = \int_{\{\phi=0\}} E_{el}(|\nabla\phi|)\frac{1}{|\nabla\phi|}d\sigma$$
$$F_{net} = h_{\text{Rac}}(\text{Rac})\frac{\nabla\phi}{|\nabla\phi|} - h_{\text{Rho}}(\text{Rho})\frac{\nabla\phi}{|\nabla\phi|}$$



Profil of function h

References

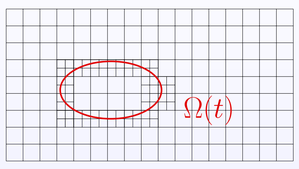
[Kre10] S. Krell. *Schémas Volumes Finis en mécanique des fluides complexes.* PhD thesis, Aix-Marseille Université, September 2010.

Numerical Resolution

Meshes :

Goal : Work with an initial coarse mesh that can be dynamically reffined.

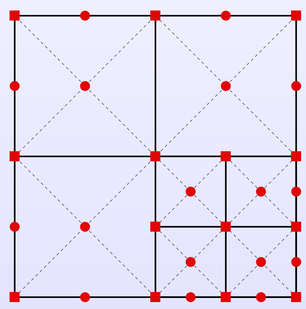
→ Choice of an adapted method of discretisation : DDFV



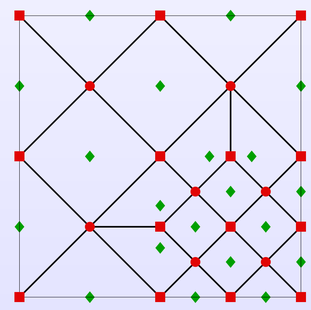
Solvers :

1. Stokes 2. Transport 3. Reaction-Diffusion

DDFV : Finite Volume method



Initial Mesh



Diamonds Cell Structure

✓ Stokes : Based on [Kre10]

u is located on centers and vertices. p is located on diamonds.

✓ Reaction-Diffusion : Difficulty : Moving domain

Lagrangian change of variables in order to reduce the problem to a fix domain.

$$\begin{cases} \frac{\partial \Phi}{\partial s}(s;t,x) = u(s,\Phi(s;t,x)) \\ \Phi(t;t,x) = x \end{cases}$$

We set $X = \Phi(0;t,x)$: $\quad \frac{\partial \widehat{\text{Rac}}}{\partial t} - D_{\text{Rac}}\nabla.\left((\nabla\Phi)(\nabla\Phi)^T\widehat{\text{Rac}}\right) = \tilde{g}(\widehat{\text{Rac}}, \widehat{\overline{\text{Rac}}}), \quad X \in \Omega(0)$

⇒ **Anisotropic Diffusion on a fix domain**, that can be handled by DDFV.

We solve this anisoptropic diffusion to obtain $\widehat{\text{Rac}}$. To come back to Rac, we have to solve a transport equation on a domain Ω such as $\forall t, \Omega(t) \subset \Omega$.

$$\frac{\partial \widehat{\text{Rac}}}{\partial t} + u.\nabla\widehat{\text{Rac}} = 0$$

Transport : (In Progress)

→ RK in time and WENO scheme in space, for DDFV structure : $\quad \frac{\partial}{\partial t}\int_K \phi + \int_{\partial K} \phi u.\vec{n} = 0$

Back to Biology

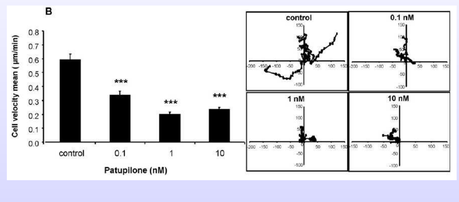
Step 1 :

To validate the qualitative behavior of the model for cell like endothelial cells.

Step 2 :

To understand the influence of types and doses of MTAs on migration in terms of :

• velocity • trajectories • area visited by the cell



MTA → MT → Rac, Rho → Migration