Microtubules, Migration... and Maths!

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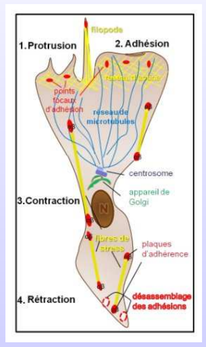
Biological Observations

Microtubules and Migration :

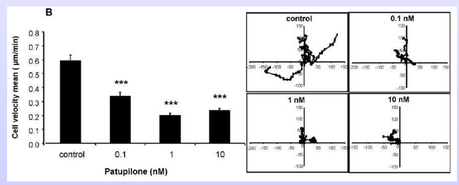
Cell migration is a complex biological process involving a lot of differents proteins like :

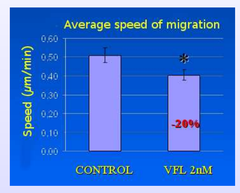
- Actin. Part of cytoskeleton, Creation of lamellipodium, Contraction.
- Rac. Promote lamellipodium extension.
- Rho. Promote contraction.
- ...

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. Beside their anti-mitotic properties, MT-targeting agents exert, even at low doses anti-migratory and anti-angiogenic activities.



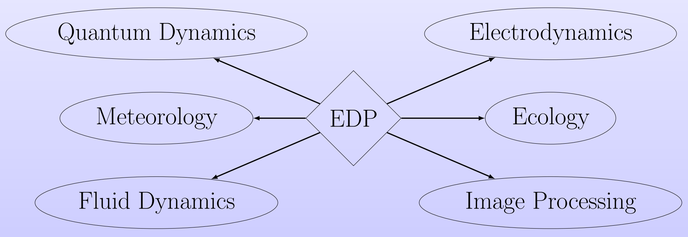


Anti-migratory effects of vinflunine on endothelial cells were associated with the alteration of MT stabilization at the cell cortex and a decrease of EB1 comet length at MT plus ends. The inhibition of cell migration by MTAs has also been described to be associated with suppression in MT dynamic instability.

Linking Maths and Biology

What kind of Models ?

PDE : Deterministic models used to describe systems that evolve in time and/or space. Like concentration of proteins, displacement of a rigid body, fluid flow,...



What about Calibration ?

Measurable : Some parameters of the mathematical model are measurable and can be set using litterature or experiences. Ex : viscosity, diffusion coefficient, size of the cells,...

Computation : Some parameters are not measurable but are related to measurable quantities and can be then computed. Ex : polymerization speed, critical concentration, ...

Confrontation with data : The other parameters must be ajusted by several tests and the confrontation with experimental data. Ex : concentration of proteins, activation rate,...

What kind of results ?

Qualitative : Is the model able to reproduce realistic behaviors?

Quantitative : Can we quantify the differences between experience and simulation?

Predictive : Can we use the model to predict the results of an experiment?

In our case ?

Goals :

- Reproduce qualitatively the migratory behavior of endothelial cells.
- Understand the influence of MTAs on migration (velocity, trajectories, area visited by the cell,...)

Modelisation Process

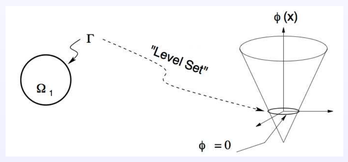
Which Proteins ?

Rac and Rho : Seen here as markers of the activity of the actin. Promotes respectvively protrusion and contraction.

Tubuline and MT : MT are responsible for the activation of Rac and Rho.

How to track the cell ?

Level-Set Method : The membrane of the cell is the zero level set of a function ϕ. Inside the cell $\phi < 0$, outside of the cell $\phi > 0$.



How to move the membrane ?

Immersed Boundary Method : The membrane is replaced by forces acting on the extracellular matrix.

Mechanical Model :

Variables : u-velocity ; p-pressure

Stokes Equations : Fluids Mechanics equations valid at low Reynolds number that compute the velocity of the cell.

Transport Equations : Move the cell with the velocity given by Stokes equations.

Biochemical Model :

Variables : 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 ;

- Rac, Rho, Tub : Reaction-Diffusion equations describe the evolution of the concentrations of proteins.

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

transport (the cell move!) — diffusion — activation-inactivation

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

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

activation — inhibition — localisation of MT

- MT :

$$\frac{\partial \text{MT}_{i\pm}}{\partial t} = H(\phi) \gamma_{pol} (\text{Tub} - c_c) \left(\frac{\eta \nabla \text{Tub} \pm \nabla \text{Rac}}{\| \eta \nabla \text{Tub} \pm \text{Rac} \| + \varepsilon} \right) + u$$

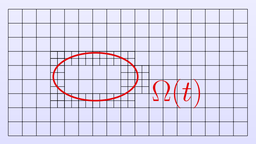
impermeability of the membrane — polymerization speed — direction of polymerization

Numerical Tools

Numerical Method :

DDFV : Numerical method used to solve PDE. Fully implemanted by our team in Fortran 90.

Discretization : Locally refined meshes around the membrane of the cell.



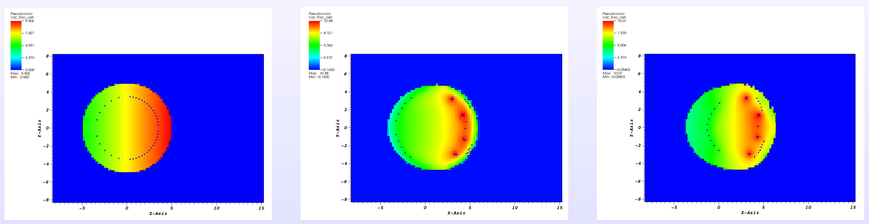
Development of Methods :

Transport Equations : We develop a DDFV approach for WENO scheme which is an high order method commonly used in transport problems.

Reaction-Diffusion Equations : We justify a splitting method for reaction-diffusion-advection equations allowing to treat separetly transport and diffusion.

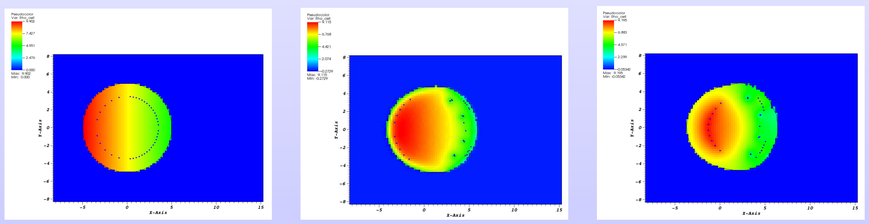
Some Results

Rac ad MT : Cell polarisation is preserved over time. The cell shape is realistic.



On Video :

Rho ad MT : Cell polarisation is also preserved over time.



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