Modeling and mathematical analysis of some biological systems

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Resume

- Phd thesis University Bordeaux I, December 2001
  - ”Discrete kinetic approximation for initial boundary conservation laws”
  - advisors : Denise Aregba, Bernard Hanouzet, Roberto Natalini
- Post-docs :
  - 2002-2004, Alio Quarteroni’s Scientific computing and modelling chair , Geometrical multi-scale modelling of blood flow
  - 2004-2005, Laboratoire Jean Kuntzmann (LJK), Grenoble, *mycordium contraction*
- CR1 CNRS :
  - September 2005,
  - Section 41 (Math at the interface with biology), Commission interdisciplinaire (CID) 51
  - 2005-2008 LJK
- International mobility :
  - 2008-2010
  - Wolfgang Pauli Institute, Vienna, Austria.
- Université Paris 13 :

Outline

Sommatic hypermutation and LLC

Blood flows

Kidney's nephron

Cell motility and adhesion mechanisms

Neutrophils' in arteries

Sommatic Hypermutation and Chronic Lymphocytic Leukemia

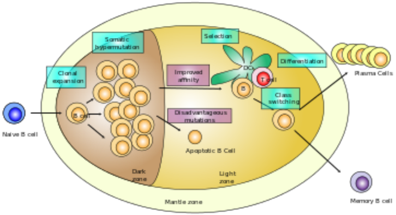
Academic context

Labex inflamex : `http://inflamex.fr`

- 10 bio-labs on various aspects of inflammatory deseases.
- Collaboration with Nadine Varin-Blank's Inserm team UMR-U978 *Adaptateurs de Signalisation en Hématologie*
- topic : Chronic Lymphocytic Leukemia (LLC),
- Irène Balelli's Phd Thesis :
  - title :*Mathematical foundations of antibody affinity maturation*
  - PhD defense november 30th 2016
  - co-advisors :
    - Hatem Zaag (DR CNRS),
    - Gilles Wainrib (UP13/ENS Ulm), Owkin

Scientific content

- CLL :
  - adaptative immune system :
    - antigens identified presented by dendritic cells
    - immune system trains antibody response : B-cells in Germinal Centers (GC)
    - antibodies target foreign agents as non-self
    - macrophages and other immunity's actors destroy marked entities
  - CLL's symptoms :
    - single B-cell clone proliferates
    - poor anti-body response
    - immunodeficiency
  - origin : poorly understood & multi-factorial



Math modelling I

- A non-linear reaction-diffusion system
  - space $x \in \Omega \subset \mathbb{R}$= B cell's traits
  - mutation : diffusion
  - antigene's threshold

$$\begin{cases} \partial_t n(t,x) = (Q(\varrho(t)) - d - s(x))n(t,x) + \operatorname{div}(\mu \nabla n(t,x)), \\ \mu \partial_{\mathbf{n}} n(t,\cdot) = 0, \\ n(0,x) = n_0(x) \end{cases}$$

where

$$\varrho(t) = \int_0^t \int_\Omega s(x) n(z,x) dx dz$$

and Q step function.

VM and G. Wainrib,
Mathematical modeling of lymphocytes selection in the germinal center,
Journal of Mathematical Biology, 2017

Math modelling II

- DNA = amino acid chains
- identifying affinity = gene sequence of BCR coding
- Simplification : binary chains

Thus

- mutation rule = specific random walk on the hypercube $\{0,1\}^N$ for N large
- division & selection : Galton Watson multi-types

Irene Balelli, VM, Gilles Wainrib,
Random walks on binary strings applied to the somatic hypermutation of B-cells.
Math. Biosci, 2018.

Irene Balelli, VM, Gilles Wainrib,
Multi-type Galton-Watson processes with affinity-dependent selection applied to antibody affinity maturation.
Bull. Math. Biol.Journal, 2019.

Blood flows

Blood flows I

- Blood flow network :
  - model reduction :
    - FSI 3D
    - 2D axi-symmetric
    - 1D hyperbolic (Saint-Venant type)
    - 0D electric-hydraulic analogy (ODE's)
  - $\exists$ 0D-1D coupling (fixed point ODE's + hyperbolic non-linear system)
  - 0D - 1D consistency (Lax Theorem)

M. Ferandez, and VM, and A. Quarteroni,
Analysis of a geometrical multiscale blood flow model based on the coupling of ODEs and hyperbolic PDEs.
SIAM Multiscale Model. Simul., 2005.

VM, and A. Quarteroni,
Analysis of lumped parameter models for blood flow simulations and their relation with 1D models.
M2AN, Math. Model. Numer. Anal. 2004.

Blood flows II

Stents

- Industrial partner `Cardiatis` designing stents
- 2006
- 25 K€
- Modelling and math analysis of blood flow in a stented artery/bifurcation
- Roughness and periodic homogenization

D. Bresch and VM,
High order multi-scale wall-laws, part I : the periodic case
Quat. Appl. Math. 2010)

E. Bonnetier and D. Bresch and V. Milisic,
A priori convergence estimates for a rough Poisson-Dirichlet problem with natural vertical boundary conditions
Advances in mathematical fluid mechanics, 2010).

V. Milisic,
Very weak estimates for a rough Poisson-Dirichlet problem with natural vertical boundary conditions
Methods and Applications of Analysis 2009.

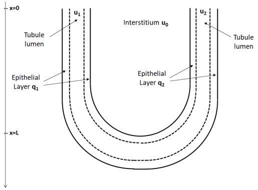
V. Milisic and U. Razafison
Weighted Lp-theory for Poisson, biharmonic and Stokes problems on periodic unbounded strips of $\mathbb{R}^n$,
Annali dell'Universita' di Ferrara, 2015,

Kidney's nephron

Nephron

Henle's loop

- Kidney filtrates blood
- Urine's sodium concentration regulated by nephrons
- Toy model with epithelium



$$\begin{cases} a_1\partial_t u_1^\varepsilon + \alpha\partial_x u_1^\varepsilon = \frac{1}{\varepsilon}(q_1^\varepsilon - u_1^\varepsilon) \\ a_2\partial_t u_2^\varepsilon - \alpha\partial_x u_2^\varepsilon = \frac{1}{\varepsilon}(q_2^\varepsilon - u_2^\varepsilon) \\ a_3\partial_t q_1^\varepsilon = \frac{1}{\varepsilon}(u_1^\varepsilon - q_1^\varepsilon) + K_1(u_0^\varepsilon - q_1^\varepsilon) \\ a_4\partial_t q_2^\varepsilon = \frac{1}{\varepsilon}(u_2^\varepsilon - q_2^\varepsilon) + K_2(u_0^\varepsilon - q_2^\varepsilon) - G(q_2^\varepsilon) \\ a_0\partial_t u_0^\varepsilon = K_1(q_1^\varepsilon - u_0^\varepsilon) + K_2(q_2^\varepsilon - u_0^\varepsilon) + G(q_2^\varepsilon) \end{cases}$$

IC + $u_1(t,0) = u_b$,
+ reflection boundary conditions $x = L$, $u_2(t,L) = u_1(t,L)$.

Results

- Marta Marulli's PhD thesis, defended in 2020, co-tutelle with Bologna University
- Co-advising with
  - B. Franchi (Bologna Univ.),
  - N. Vauchelet (Univ. P13),
- Asymptotics when :
  - time : $t \to \infty$
  - resistivity : $\varepsilon \to 0$.

M. Marulli and V. M. and N. Vauchelet,
On the role of the epithelium in a model of sodium exchange in renal tubules
Mathematical Biosciences, 2020.

M. Marulli, and V. M., and N. Vauchelet,
Reduction of a model for sodium exchanges in kidney nephron
Networks and Heterogeneous Media, in revision, 2021.

Adhesion

Cell motility

academic context

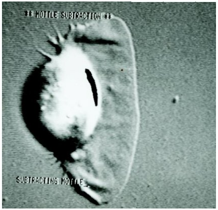
- Collaboration with
  - Dietmar Oelz, assistant professor, School of Mathematics and Physics University of Queensland
  - Christian Schmeiser, Professor at Faculty of Mathematics of the University of Vienna
- Co-advisor of Samar Allouch's PhD thesis,
  - FSMP's Cofund grant,
  - start 2019,
  - main advisor : N. Vauchelet.

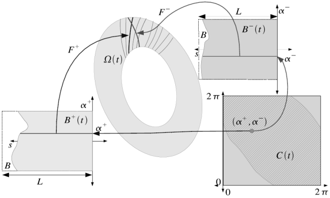
Starting paper(s)

Dietmar Oelz and Christian Schmeiser
How do cells move ? Mathematical modeling of cytoskeleton dynamics and cell migration. 2010, Cell mechanics.

Assumptions

1. 2D phenomenon
2. lamellipodium lies between 2 closed curves
3. 2 families of inextensible filaments orientated $F^{\pm}(s, \alpha)$
   - clockwise +
   - anti-clockwise -
4. barbed ends touch leading edge





Derivation of a PDE model

Lagrangian motion of filaments driven by

$$\underbrace{\kappa^B \partial_s^2(\eta^\pm \partial_s^2 F^\pm)}_{\text{bending}} - \underbrace{\partial_s(\eta^\pm \lambda^\pm \partial_s F^\pm)}_{\text{unextensibility constraint}} + \eta^\pm \underbrace{\mu^A D_t^\pm F^\pm}_{\text{adhesion}}$$

$$\underbrace{\pm\partial_s\left(\eta^+\eta^-\mu_\pm^T(\varphi-\varphi_0)\partial_s F^{\pm,\perp}\right)}_{\text{twisting}} \pm\eta^+\eta^- \underbrace{\mu_\pm^S\left(D_t^+F^+ - D_t^-F^-\right)}_{\text{stretching}} = 0$$

Notation

α:: filament index

s:: position on a given filament

$F^\pm(t,\alpha,s) \in \mathbb{R}^2$::parametrizations of right and left moving filaments

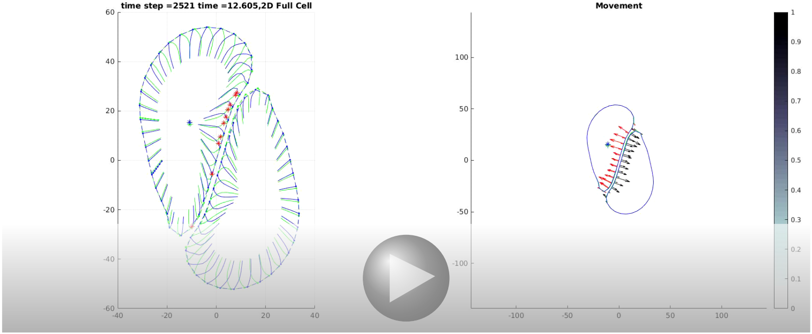
$\eta^\pm(t,\alpha,s) \in \mathbb{R}_+$:: length "distribution"

$v^\pm(t,\alpha) \in \mathbb{R}$:: polymerization rates

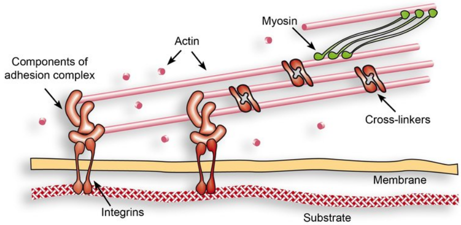
$D_t^\pm = \partial_t - v^\pm \partial_s$ and $\left|\partial_s F^\pm\right| \equiv 1$

Numerical illustration

Contact and adhesion (D. Peurichard)



Adhesion : at the microscopic scale



Adhesion plays twofold role :

- cell / substrate
- filament / filament

based on binding of proteins on adhesion sites

Microscopic adhesion modelling

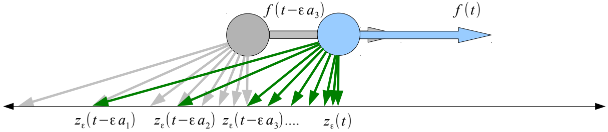
A minimal model

- the unknown is $z(t) \in \mathbb{R}$, position of a single adhesion point
- at time t_0 : adhesion
- for $t > t_0$ account for this adhesion :

$$z(t) = \underset{w \in \mathbb{R}}{\operatorname{argmin}} \frac{k_s}{2}(w - z(t_0))^2 - f(t)w$$

- then generalize to a distribution of past positions

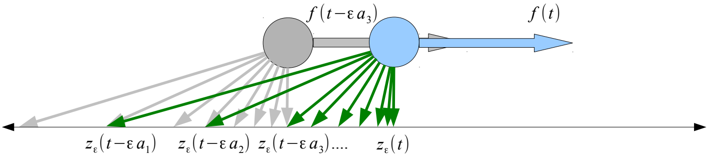
$$z(n\Delta t) = \underset{w \in \mathbb{R}}{\operatorname{argmin}} \frac{\Delta a}{2} \sum_{i \in I} k_s (w - z(n\Delta t - i\Delta a))^2 R_i - f(n\Delta t)w$$



Adhesion modelling

- in the continuous setting this reads :

$$z_\varepsilon(t) := \underset{w\in\mathbb{R}}{\operatorname{argmin}} \left\{ \frac{1}{2\varepsilon} \int_{\mathbb{R}_+} |w - z_\varepsilon(t-\varepsilon a)|^2 \rho_\varepsilon(a,t)da - f(t)w \right\}$$



- $a \geq 0$ age of the linkage
- ε represents
  - characteristic age of linkages
  - the inverse of stiffness

A simplest mathematical model

Euler-Lagrange equation associated to the energy

$$\begin{cases} \int_0^\infty \left\{ \frac{z_\varepsilon(t) - z_\varepsilon(t - \varepsilon a)}{\varepsilon} \right\} \rho_\varepsilon(a,t)\, da = f(t)\,, & t \geq 0\,, \\ z_\varepsilon(t) = z_p(t)\,, & t < 0\,, \end{cases}$$

where ρ_ε, density of linkages, solves

$$\begin{cases} \varepsilon \partial_t \rho_\varepsilon + \partial_a \rho_\varepsilon + \zeta_\varepsilon(a,t) \rho_\varepsilon = 0\,, & t > 0\,,\ a > 0\,, \\ \rho_\varepsilon(a = 0, t) = \beta_\varepsilon(t) \left(1 - \int_0^\infty \rho_\varepsilon(\tilde{a}, t)\, d\tilde{a} \right)\,, & t > 0\,, \\ \rho_\varepsilon(a, t = 0) = \rho_{I,\varepsilon}(a)\,, & a \geq 0\,, \end{cases}$$

with the kinetic rate functions

- $\beta_\varepsilon = \beta_\varepsilon(t) \in \mathbb{R}_+$ growth factor
- $\zeta_\varepsilon = \zeta_\varepsilon(a,t) \in \mathbb{R}_+$ death rate

Formal limit when $\varepsilon \to 0$

The formal limit is given by

$$\begin{cases} \mu_{1,0}\,\partial_t z_0 = f \quad \text{with} \quad \mu_{1,0}(t) := \int_0^\infty a\rho_0(a,t)\,da\ , \quad t > 0\ , \\ z_0(t=0) = z_I := z_p(0)\ , \end{cases}$$

where the limit distribution ρ_0 is the solution of

$$\begin{cases} \partial_a \rho_0 + \zeta_0(a,t)\rho_0 = 0\ , & t > 0\ , \quad a > 0\ , \\ \rho_0(t, a=0) = \beta_0(t)\left(1 - \int_0^\infty \rho_0(\tilde{a},t)\,d\tilde{a}\right)\ , & t > 0\ . \end{cases}$$

First convergence results

Formal limit proved when $\varepsilon \to 0$:

V. Milišić and D. Oelz.
On the asymptotic regime of a model for friction mediated by transient elastic linkages.
J. Math. Pures Appl. (9), 96(5):484–501, 2011.

V. Milišić and D. Oelz.
On a structured model for the load dependent reaction kinetics of transient elastic linkages.
SIAM J. Math. Anal., 47(3):2104–2121, 2015.

JMPA 2011

Main ingredients first paper :

- Liapunov functional specific to the saturation case :
  $\hat{\rho}_\varepsilon := \rho_\varepsilon - \rho_0$

$$\mathcal{H}(t) := \int_{\mathbb{R}_+} |\hat{\rho}_\varepsilon(a,t)|\, da + \left| \int_{\mathbb{R}_+} \hat{\rho}_\varepsilon(a,t) da \right|$$

  and the estimates :

$$\mathcal{H}(t) \leq \mathcal{H}(0) \exp(-\zeta_{\min} t/\varepsilon) + o_\varepsilon(1)$$

- Comparison principle specific to Volterra equations with non-positive kernels : $\hat{z} := z_\varepsilon - z_0$

$$|\hat{z}(t)| \leq U_\varepsilon(t) \lesssim \varepsilon(1+T)$$

SIAM J. Math. Anal. 2015

Recall that z_ε satisfies :

$$\int_{\mathbb{R}_+} \left(\frac{z_\varepsilon(t) - z_\varepsilon(t-\varepsilon a)}{\varepsilon} \right) \rho_\varepsilon(a,t) da = f(t)$$

The elongation variable : set

$$u_\varepsilon(a,t) := \begin{cases} \frac{z_\varepsilon(t) - z_\varepsilon(t-\varepsilon a)}{\varepsilon} & \text{if } t \geq \varepsilon a \\ \frac{z_\varepsilon(t) - z_p(t-\varepsilon a)}{\varepsilon} & \text{if } t < \varepsilon a \end{cases}$$

it satisfies :

$$\int_{\mathbb{R}_+} u_\varepsilon(a,t) \rho_\varepsilon(a,t) da = f(t), \text{ and } (\varepsilon \partial_t + \partial_a) u_\varepsilon = \partial_t z_\varepsilon$$

then

$$\varepsilon \frac{\mathrm{d}}{\mathrm{d}t} \int_{\mathbb{R}_+} \rho_\varepsilon u_\varepsilon da = - \int_{\mathbb{R}_+} \zeta_\varepsilon \rho_\varepsilon u_\varepsilon da + \left(\int_{\mathbb{R}_+} \rho_\varepsilon(a,t) da \right) \partial_t z_\varepsilon$$

SIAM J. Math. Anal. 2015

Recall that z_ε satisfies :

$$\int_{\mathbb{R}_+} \left(\frac{z_\varepsilon(t) - z_\varepsilon(t - \varepsilon a)}{\varepsilon} \right) \rho_\varepsilon(a,t) da = f(t)$$

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$$\int_{\mathbb{R}_+} u_\varepsilon(a,t) \rho_\varepsilon(a,t) da = f(t), \text{ and } \left(\varepsilon \partial_t + \partial_a \right) u_\varepsilon = \partial_t z_\varepsilon$$

then

$$\varepsilon \frac{\mathrm{d}}{\mathrm{d}t} f = - \int_{\mathbb{R}_+} \zeta_\varepsilon \rho_\varepsilon u_\varepsilon da + \left(\int_{\mathbb{R}_+} \rho_\varepsilon(a,t) da \right) \partial_t z_\varepsilon$$

SIAM J. Math. Anal. 2015

Recall that z_ε satisfies :

$$\int_{\mathbb{R}_+} \left(\frac{z_\varepsilon(t) - z_\varepsilon(t - \varepsilon a)}{\varepsilon} \right) \rho_\varepsilon(a,t) da = f(t)$$

The elongation variable : set

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it satisfies :

$$\int_{\mathbb{R}_+} u_\varepsilon(a,t)\rho_\varepsilon(a,t) da = f(t), \text{ and } (\varepsilon \partial_t + \partial_a) u_\varepsilon = \partial_t z_\varepsilon$$

then

$$(\varepsilon \partial_t + \partial_a) u_\varepsilon = \partial_t z_\varepsilon = \frac{1}{\int_{\mathbb{R}_+} \rho_\varepsilon(\tilde{a},t) d\tilde{a}} \left\{ \varepsilon \partial_t f + \int_{\mathbb{R}_+} (\zeta_\varepsilon u_\varepsilon \rho_\varepsilon)(\tilde{a},t) d\tilde{a} \right\}$$

New coupled system

The density of linkages :

$$\begin{cases} \varepsilon\partial_t\rho_\varepsilon + \partial_a\rho_\varepsilon + \zeta_\varepsilon(a,t)\rho_\varepsilon = 0\,, & t>0\,,\ a>0\,, \\ \rho_\varepsilon(a=0,t) = \beta_\varepsilon(t)\left(1 - \int_0^\infty \rho_\varepsilon(\tilde{a},t)\,d\tilde{a}\right)\,, & t>0\,, \\ \rho_\varepsilon(a,t=0) = \rho_{I,\varepsilon}(a)\,, & a\geq 0\,, \end{cases}$$

and the elongation

$$\begin{cases} (\varepsilon\partial_t + \partial_a)\,u_\varepsilon = \frac{1}{\int_{\mathbb{R}_+}\rho_\varepsilon(\tilde{a},t)d\tilde{a}}\left\{\varepsilon\partial_t f + \int_{\mathbb{R}_+}(\zeta_\varepsilon u_\varepsilon\rho_\varepsilon)(\tilde{a},t)d\tilde{a}\right\} \\ u_\varepsilon(0,t) = 0 \\ u_\varepsilon(a,0) = u_{I,\varepsilon}(a) := \frac{z_\varepsilon(0) - z_p(-\varepsilon a)}{\varepsilon} \end{cases}$$

(Weak) convergence(s)

Stability property :

$$\int_{\mathbb{R}_+} |u_\varepsilon(a,t)|\, \rho_\varepsilon(a,t) da \leq \int_{\mathbb{R}_+} |u_\varepsilon(a)|\, \rho_{I,\varepsilon}(a) da + \int_0^t |\partial_t f|\, ds$$

Duhamel's principle then implies :

$$\left| \frac{u_\varepsilon(a,t)}{(1+a)} \right| \leq C_1 + \sup_{\tilde{a} \in \mathbb{R}_+} \left| \frac{u_{I,\varepsilon}(\tilde{a})}{(1+\tilde{a})} \right| \leq C_1 + \|z_p\|_{\mathrm{Lip}(\mathbb{R}_-)}$$

Weak-* convergence

$$u_\varepsilon \overset{*}{\rightharpoonup} u_0 \text{ in } L^\infty(\mathbb{R}_+ \times (0,T), (1+a)^{-1})$$

and then

$$\boxed{z_\varepsilon \to z_0 \text{ strongly in } C([0,T])}$$

Full coupling linkages/elongation

[VM D. Oelz, CMS 2016]

The density of linkages :

$$\begin{cases} \varepsilon \partial_t \rho_\varepsilon + \partial_a \rho_\varepsilon + \zeta(u_\varepsilon)\rho_\varepsilon = 0\,, & t > 0\,,\ a > 0\,, \\ \rho_\varepsilon(a=0,t) = \beta_\varepsilon(t)\left(1 - \int_0^\infty \rho_\varepsilon(\tilde a, t)\, d\tilde a\right)\,, & t > 0\,, \\ \rho_\varepsilon(a, t=0) = \rho_{I,\varepsilon}(a)\,, & a \geq 0\,, \end{cases}$$

and the elongation

$$\begin{cases} (\varepsilon \partial_t + \partial_a)\, u_\varepsilon = \dfrac{1}{\int_{\mathbb{R}_+} \rho_\varepsilon(\tilde a, t) d\tilde a} \left\{ \varepsilon \partial_t f + \int_{\mathbb{R}_+} (\zeta(u_\varepsilon) u_\varepsilon \rho_\varepsilon)(\tilde a, t) d\tilde a \right\} \\ u_\varepsilon(0,t) = 0 \\ u_\varepsilon(a,0) = u_{I,\varepsilon}(a) := \dfrac{z_\varepsilon(0) - z_p(-\varepsilon a)}{\varepsilon} \end{cases}$$

with for instance :

$$\zeta(u) = 1 + |u|$$

ζ is <u>unbounded</u> from above and the problem is fully coupled!

A blow up result

Theorem (VM, D.Oelz, CMS (2016))

i) $\zeta \in \mathrm{Lip}(\mathbb{R})$ and admits a lower convex envelop ζ_c s.t. $\zeta_c'(0) > 0$,
ii) let $f \in \mathrm{Lip}(\mathbb{R}_+)$ s.t. $\partial_t f(t) > 0$ for a.e. $t \in (0,T)$,
iii) f and β are s.t. $\beta_{\max} < \zeta_c'(0) f_{\min}$,
iv) $u_{I,\varepsilon}(a) \geq 0$ for a.e. $a \in \mathbb{R}_+$,

then if the solution $(\rho_\varepsilon, u_\varepsilon)$ exists until a finite time T_0, this time cannot be greater than

$$t_0 := \frac{\varepsilon}{\beta_{\min} + \zeta_c(0)} \ln\left(1 + \frac{\mu_{0,\varepsilon}(0)(\beta_{\min} + \zeta_c(0))}{\zeta_c'(0) f_{\min} - \beta_{\max}}\right)$$

for which $\mu_{0,\varepsilon}(T_0) \leq 0$. Moreover, on $(0,t_0) \times \mathbb{R}_+$,

$$u_\varepsilon(t,a) \geq \varepsilon \gamma_6 \ln\left(1 + \frac{\min(t,\varepsilon a)}{(t_0 - t)}\right),$$

where $\gamma_6 := t_0 \inf_{t\in(0,t_0)} \partial_t f / \mu_{0,\varepsilon}(0)$.

Introduction of the space variable

A minimal problem

So far a single adhesion point... Now what if z_ε and ρ_ε depend upon a reference space configuration ?

$$
\begin{cases}
\varepsilon \partial_t \rho_\varepsilon + \partial_a \rho_\varepsilon + \zeta_\varepsilon \, \rho_\varepsilon = 0 \, , & \mathbf{x} \in \Omega, \ a > 0 \, , \ t > 0, \\
\rho_\varepsilon(\mathbf{x}, a = 0, t) = \beta_\varepsilon(\mathbf{x}, t) \left(1 - \mu_{0,\varepsilon}(t, \mathbf{x})\right) \, , & \mathbf{x} \in \Omega, \ a = 0, \ t > 0, \\
\rho_\varepsilon(\mathbf{x}, a, t = 0) = \rho_{I,\varepsilon}(\mathbf{x}, a) \, , & \mathbf{x} \in \Omega, a > 0, t = 0,
\end{cases}
$$

and

$$
\begin{cases}
\dfrac{1}{\varepsilon} \displaystyle\int_0^\infty \left(z_\varepsilon(\mathbf{x}, t) - z_\varepsilon(\mathbf{x}, t - \varepsilon a)\right) \rho_\varepsilon(\mathbf{x}, t, a) \, da = \Delta_{\mathbf{x}} z_\varepsilon + f(t) \, , & t \geq 0, \ \mathbf{x} \in \Omega \, , \\
z_\varepsilon(\mathbf{x}, t) = 0, & t \in \mathbb{R}_+ \, , \ \mathbf{x} \in \partial\Omega, \\
z_\varepsilon(\mathbf{x}, t) = z_p(\mathbf{x}, t) \, , & t < 0 \, , \ \mathbf{x} \in \Omega,
\end{cases}
$$

V. Milisic and D. Oelz
Space dependent adhesion forces mediated by transient elastic linkages : new convergence and global existence results
Journal Differential Equations, 2018

Adhesive harmonic map

(VM, Journal Functional Analysis 2020)

The vector position in $\mathbb{R}^m$ of the moving binding site, $\mathbf{z}_\varepsilon(x,t)$, minimizes at each time $t \geq 0$ an energy functional :

$$\mathbf{z}_\varepsilon(x,t) = \operatorname*{argmin}_{w \in \mathcal{A}} \mathcal{E}_t(w),$$

where the minimization is held on the set

$$\mathcal{A} := \left\{ \boldsymbol{w} \in \mathbf{H}^1((0,1))\,;\, |\boldsymbol{w}(x)|^2 = 1,\ \text{a.e. } x \in (0,1) \right\}$$

The energy is defined for every $w \in \mathcal{A}$ as

$$\mathcal{E}_t(\boldsymbol{w}(\cdot)) = \frac{1}{2\varepsilon} \int_\Omega \int_{\mathbb{R}_+} \frac{|\boldsymbol{w}(x) - \mathbf{z}_\varepsilon(x, t - \varepsilon a)|^2}{\varepsilon} \rho_\varepsilon(x,t,a)\,da\,dx, + \frac{1}{2} \int_\Omega |\boldsymbol{w}'|^2 dx$$

Past positions are given by the function $\mathbf{z}_\varepsilon(x,t) = \mathbf{z}_p(x,t)$ for $t < 0$.

Adhesive gradient flow

In our case : minimisation principle involves the whole history

$$\mathbf{z}^n := \operatorname*{argmin}_{\boldsymbol{w}\in\mathcal{A}} \mathcal{E}_n(\boldsymbol{w})$$

$$\mathcal{E}_n(\boldsymbol{w}) := \frac{1}{2}\int_\Omega |\boldsymbol{w}'|^2 dx + \frac{\Delta a}{4\varepsilon}\left\{\int_\Omega (\boldsymbol{w}-\mathbf{z}^{n-1})^2 r^n_{\varepsilon,0} dx \right.$$
$$\left. + \sum_{j=1}^{\infty}\int_\Omega \left((\boldsymbol{w}-\mathbf{z}^{n-j})^2 + (\boldsymbol{w}-\mathbf{z}^{n-j-1})^2\right) r^n_{\varepsilon,j} dx \right\}$$

where

$$r^{n+1}_{\varepsilon,i}(x) := r^n_{\varepsilon,i-1}(x) / \left(1 + \frac{\Delta t}{\varepsilon}\zeta^{n+1}_{\varepsilon,i}(x)\right), \quad i \in \mathbb{N}, \quad n \in \mathbb{N},$$

and when $i = 0$ the non-local boundary value is implicitly treated

$$r^{n+1}_{\varepsilon,b} := \beta^{n+1}_\varepsilon (1 - \mu^{n+1}_\varepsilon), \quad \mu^{n+1}_\varepsilon := \sum_{i=0}^{\infty} r^{n+1}_{\varepsilon,i}\Delta a.$$

Conclusion : no compactness in time given by minimization principle

Conclusion

- Adhesive gradient flow scheme : provides
  - Existence and uniqueness for a fixed ε of $\mathbf{z}_\varepsilon$ solving Euler-Lagrange equations :

$$\int_{\mathbb{R}_+} \left(\frac{\mathbf{z}_\varepsilon(t) - \mathbf{z}_\varepsilon(t - \varepsilon a)}{\varepsilon} \right) \rho_\varepsilon(a,t)da - \mathbf{z}_\varepsilon'' + \lambda_\varepsilon \mathbf{z}_\varepsilon = 0, \quad |\mathbf{z}_\varepsilon'| = 1$$

    where λ_ε is the Lagrange multiplier associated to the constraint.
- Discrete stability estimates uniform wrt ε extend to $\mathbf{z}_\varepsilon$.
- One can pass to the limit wrt ε using the same arguments : $\mathbf{z}_\varepsilon \to \mathbf{z}_0$ when $\varepsilon \to 0$, $\mathbf{z}_0$ solves

$$\left(\int_{\mathbb{R}_+} a\rho_0(x,a,t)da \right) \partial_t \mathbf{z}_0 - \mathbf{z}_0'' + \lambda_0 \mathbf{z}_0 = 0, \quad |\mathbf{z}_0'| = 1$$

  Problems with initial layers :

V.M..
Initial layer analysis for a linkage density in cell adhesion mechanisms.
ESAIM: ProcS, 62:108–122, 2018.

Ultimate goal

ε goes to 0

A single *real* filament adhering, where $\mathbf{z}_\varepsilon \in \mathbb{R}^2$ minimizes

$$\mathcal{E}_t(\boldsymbol{w}) := \frac{1}{2}\int_\Omega \left\{ |\boldsymbol{w}''(x)|^2 + \int_{\mathbb{R}_+} \frac{|\boldsymbol{w}(x) - \mathbf{z}_\varepsilon(x, t - \varepsilon a)|^2}{\varepsilon} \rho_\varepsilon(x,t,a) da \right\} dx \ ,$$

under the inextensibility constraint $|\boldsymbol{w}'| = 1$.
We would like to show that $\mathbf{z}_\varepsilon \to \mathbf{z}_0$ and $\mathbf{z}_0$ solves

$$\left(\int_{\mathbb{R}_+} a\rho_0(x,a,t) da \right) \partial_t \mathbf{z}_0 + \mathbf{z}_0'''' - (\lambda_0 \mathbf{z}_0')' = 0,$$

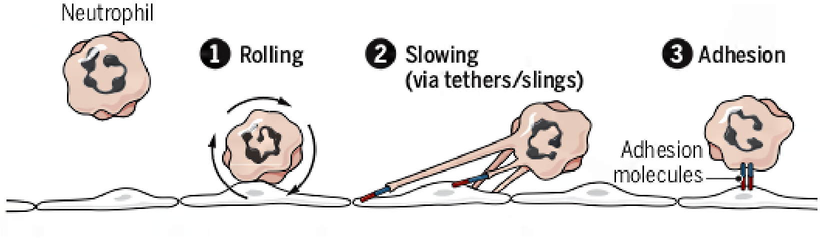
where $\lambda_0(x,t)$ is the Lagrange multiplier associated to the constraint $|\mathbf{z}_0'| = 1$.

- Still an open question because :
  - impossible stability properties of the Lagrange multiplier wrt ε. Numerical simulations suggest that

    $$\|\lambda_\varepsilon\|_{L^\infty_t L^1_x} \sim 1/\sqrt{\varepsilon}$$

  - thus lack of compactness due to the Lagrange multiplier

Neutrophils' rolling and adhesion in arteries



Neutrophil's rolling

$z(t)$ is the cell's center's position at time t.

$$\underbrace{\nu(\partial_t z(t) - v(t))}_{\text{drift}} = \underbrace{-\int_0^t \psi'(z(t) - z(s))\varrho(t-s)ds}_{\text{active forcing}}$$

- v blood flow velocity
- if no adhesion : friction driven motion $\partial_t z = v$
- adhesion forces compensate velocity $\implies$ cell slows down
- ψ related to elastic energy of the filaments
  - $\psi(u) := |u|$ constant force
  - $\psi(u) := u^2/2$ linear elasticity
  - $\psi(u) := (u^2\chi_{|u|<\overline{u}}(u) + \overline{u}^2\chi_{|u|\geq\overline{u}}(u))/2$ rupture of filaments

Grec, Maury, Meunier & Navoret,
A 1D model of leukocyte adhesion coupling bond dynamics with blood velocity
Journal of Theoretical Biology, 452 (2018)

A general frame

At the cell scale : z_ε position of the cell's center

$$\begin{cases} \partial_t z + \int_{\mathbb{R}_+} \psi'\left(\frac{z(t) - z(t-\varepsilon a)}{\varepsilon}\right) \varrho(a,t)da = v(t), & \text{a.e. } t \in (0,T] \\ z(t) = z_p(t), & t \in \mathbb{R}_- \end{cases}$$

where

- the kernel ϱ is time dependent : $\varrho \in C([0,T]; L^1(\mathbb{R}_+, (1+a)))$,
- $z_p \in \text{Lip}(\mathbb{R}_-)$, nota bene :

$$\int_{\mathbb{R}_+} \psi'\left(\frac{z(t) - z(t-\varepsilon a)}{\varepsilon}\right) \varrho(a,t)da =$$

$$\int_0^{\frac{t}{\varepsilon}} \psi'\left(\frac{z(t) - z(t-\varepsilon a)}{\varepsilon}\right) \varrho(a,t)da + \int_{\frac{t}{\varepsilon}}^{\infty} \psi'\left(\frac{z(t) - z_p(t-\varepsilon a)}{\varepsilon}\right) \varrho(a,t)da$$

- $v \in C^1(\mathbb{R}_+)$,

Results

VM, C. Schmeiser, 2020, submitted

- ψ convex and $C^{1,1}(\mathbb{R})$
  - Convergence when $\varepsilon \to 0$
- ψ convex and Lipschitz
  - Existence for a fixed ε of an integro-differential inclusion with memory
- ψ convex and $C^{1,1}(\mathbb{R} \setminus U)$,
  $U := \{u_i \in \mathbb{R}, i \in \{1, \dots, N\}\}$, $N \in \mathbb{N}$.
  - Convergence when $\varepsilon \to 0$
- New scaling

$$z_\varepsilon(t) = \varepsilon z\left(\frac{t}{\varepsilon}\right)$$

shows that :

  - if $t \to \infty \sim \tilde{t}/\ \varepsilon \to \infty$ with $\varepsilon \to 0$ and $\tilde{t} \in (0, 1)$
  - the scaling holds if z grows large as $t \to \infty$.

$$\boxed{\lim_{t\to\infty} z(t) \sim \lim_{\varepsilon\to 0} z_\varepsilon}$$

Conclusions & Perspectives

Analysis of adhesion mechanisms well understood :

- pointwise adhesion
  - linear
  - non-linear

  cases
- introducing the space variable
  - linear elliptic (2nd and 4th order) operators coupled with adhesions
  - non-linear constrained problems :
    - 1D-2nd order : yes
    - 1D-4th order : not yet

Rolling neutrophils :

- $\psi \in C^{1,1}(\mathbb{R})$, convex : ok
- $\psi \in C^{1,1}(\mathbb{R} \setminus U)$, and convex : ok
- $\psi \in \mathrm{Lip}(\mathbb{R})$ and convex : no
- $\psi \in C^{1,1}(\mathbb{R} \setminus U)$, and convex on $\mathbb{R} \setminus U$: in preparation