On the asymptotic regime of a model framework for friction mediated by transient elastic linkages.

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   - Adhesion phenomena
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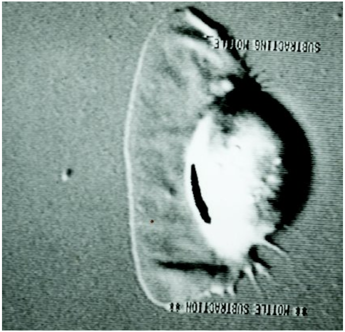
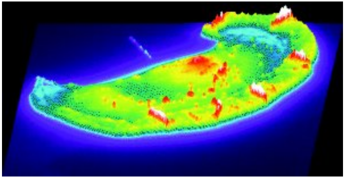
Introduction

Context of this work: Cell motility



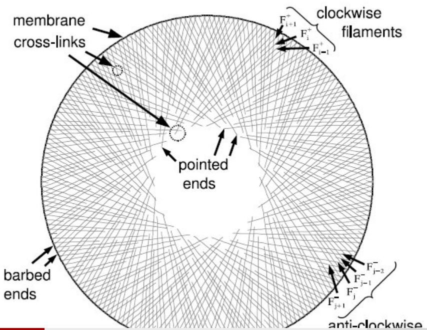


- Lamelopodium:
  cytoskeletal protein actin projection on the mobile edge of the cell.
- Lamellipodia are found in very mobile cells , example:
  - the keratinocytes of fish and frogs
- propulsion velocity : 10-20μm/minute

Modelling of cell motilty

Assumptions [D. Ölz, C. Schmeiser, *Cell mechanics* 2009]

1. 2D phenomenon
2. lamellipodium lies between 2 closed curves
3. 2 families of inextensible filaments orientated
   - clockwise
   - anti-clockwise
4. barbed ends touch leading edge



Discrete case

- $n^{\pm}$ clockwise filaments indexed i and j
- arclength parametrisation

$$\{F_i^+(t,s) : -L_i^+(t) \leq s \leq 0\} \in \mathbb{R}^2 \quad \{F_j^-(t,s) : -L_j^-(t) \leq s \leq 0\} \in \mathbb{R}^2$$

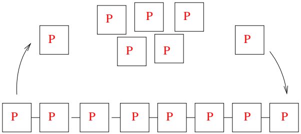
- inextensible

$$|\partial_s F_i^+| \equiv |\partial_s F_i^+| \equiv 1 \quad \forall (i,j) \in \{\, 0, n^+\} \times \{\, 0, n^-\}$$

- Crosslinks : proteic connection between clockwise and anti-clockwise filaments
  - spontaneous creation at crossings of filaments
  - spontaneous rupture
  - stochastic proces
  - unique: any pair of filaments cross at most once any time.

Treadmilling & cross-links

- Polymerisation at barbed end: constant polymerisation speed $\nu_0^\pm$



- Lagrange variable along the filaments

$$\sigma^+ = s + t\nu_0^+, \quad \sigma^- = s + t\nu_0^-$$

- Crossing between filaments at time t

$$\overline{\mathcal{C}}(t) := \{(i,j) : \exists s_{i,j}^\pm(t) \;\text{ s.t. }\; F_i^+(t, s_{i,j}^+(t)) = F_j^-(t, s_{i,j}^-(t))\}$$

- But the crosslinks remain after filament crossings: a age of the crosslink

$$s_{a,i,j}^+ = s_{i,j}^+(t-a) - \nu^+ a, \quad s_{a,i,j}^- = s_{i,j}^-(t-a) - \nu^- a,$$

Modelling issues

bending

- Elastic forces related to bending

$$U^{+,i}_{\mathrm{bend}}(t) = \frac{\kappa^B}{2} \int_{(-L,0)} | \partial_s^2 F_j^+ |^2 ds$$

- Add boundary conditions for ex. a rubber linking the barbed ends

$$U_{\mathrm{membrane}} = \sum_{i=1}^{n^+-2} (|F_{i+1}^+(t,0) - F_i^+(t,0)| - l_0)_+^2 + \sum_{j=1}^{n^- -2} (|F_{j+1}^-(t,0) - F_j^-(t,0)| - l_0)_+^2$$

- Add a constraint

$$F_i^+(t,0) = F_j^-(t,0) \quad \forall\, i = j, \quad (i,j) \in \{0, \ldots, \min(n^-, n^+)\}^2$$

Modelling issues

stretching and twisting

- Elastic forces related to
  - stretching
$$S_{i,j} := F_i^+(t, s_{a,i,j}^+(t)) - F_j^-(t, s_{a,i,j}^-(t))$$
  - twisting
$$T_{i,j}(t,a) := \varphi_{i,j}(t,a) - \varphi_0,$$
$$\varphi_{i,j}(t,a) := \arccos\left(\partial_s F_i^+(t, s_{a,i,j}^+(t)) \cdot \partial_s F_j^-(t, s_{a,i,j}^-(t))\right)$$
- Probability distribution of crosslinks $r_{i,j}(a,t)$
$$\begin{cases} \partial_t r_{i,j} + \partial_a r_{i,j} = -\zeta\ (S_{i,j}, T_{i,j})\, r_{i,j} & \forall (a,t) \in (\mathbb{R}_+)^2 \\ r_{i,j}(0,t) = \beta(T_{i,j})\,(1 - r_{i,j}(a,t)da) & a = 0,\ t > 0 \end{cases}$$
- stretching and twisting
$$U_{\mathrm{str+tw}}^{i,j} = \int_{\mathbb{R}_+} \left(\frac{\kappa^S}{2} |S_{i,j}|^2 + \frac{\kappa^T}{2} |T_{i,j}|^2 \right) r_{i,j}(a,t)da$$

Integrins: adhesion on the substrate

- *Integrins*: Transmembrane proteins connecting the cytoskeleton to the ECM (extracelular matrix).

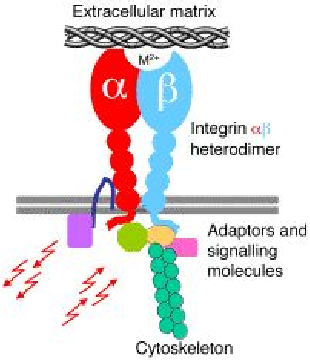


Figure: Picture from the website of Dan Baeckström, Göteborg.

Integrins: adhesion on the substrate

- Dynamic making and breaking of integrins
- Overall effect: friction (force transmission)

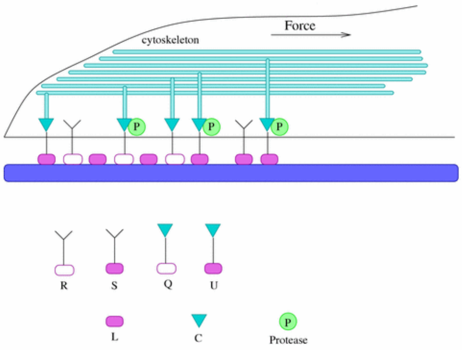


Figure: Picture from http://www.cellml.org

Adhesion

- Adhesion forces depending on stretching of adhesions

$$S_{\mathrm{adh}}^{+,i} = F_i^+(t,s) - F_i^+(t-a, s+\nu^+ a)$$

- Density of adhesions $\rho_i^+(a,t,s)$ and ρ_i^- to the extracellular matrix

$$\begin{cases} \partial_t \rho_i^+ + \partial_a \rho_i^+ - \nu^+ \partial_s \rho_i^+ = -\zeta_{\mathrm{adh}}\left(S_{\mathrm{adh}}^+\right)\rho_i^+ & \text{in } \mathbb{R}_+ \times \mathbb{R}_+ \times]-L;0[\\ \rho_i^+(0,t,s) = \beta_{\mathrm{adh}}\left(\rho_{\mathrm{adh}}^{\max} - \int_{\mathbb{R}_+} \rho_i^+ da\right) & \text{in } \{0\} \times \mathbb{R}_+ \times]-L;0[\\ \rho_i^+(a,t,0) = 0 & \text{in } \mathbb{R}_+ \times \mathbb{R}_+ \times \{0\} \end{cases}$$

- energy associated

$$U_{\mathrm{adh}}^{+,i}(G^+) := \frac{\kappa^A}{2} \int_{(-L,0)} \int_{\mathbb{R}_+} |G^+ - F_i^+(t-a, s+\nu^+ a)|^2 \rho_i^+(a,t,s) da ds$$

Finaly

The deformation of filaments minimizes at each time t the total energy

$$\mathbf{F}^{\pm} = \underset{\left\{ \begin{array}{c} |\partial_s G_i^+| = |\partial_s G_j^-| = 1 \\ \text{a.e. } s \in]-L;0[\end{array} \right\}}{\text{argmax}} (U_{\text{bend}} + U_{\text{membrane}} + U_{\text{str+tw}} + U_{\text{adh}})(\mathbf{G}^{\pm})$$

Possible rescaling w.r.t characteristic values of

$$L, \quad \nu, \quad a$$

leading to the main scaling assumption

$$\varepsilon := \frac{\overline{a}\ \nu_0}{L} << 1$$

Rescaled formulation

Rescaled energies

$$U_{\mathrm{str}}(\mathbf{G}^{\pm}) = \sum_i \int_{\mathbb{R}_+} \left(\frac{\kappa^S}{2\varepsilon} |S^{\varepsilon}_{i,j}|^2 \right) r^{\varepsilon}_{i,j}(a,t) da$$

$$U_{\mathrm{tw}}(\mathbf{G}^{\pm}) = \sum_i \int_{\mathbb{R}_+} \left(\frac{\kappa^T}{2} |T^{\varepsilon}_{i,j}|^2 \right) r^{\varepsilon}_{i,j}(a,t) da$$

$$U_{\mathrm{adh}}(\mathbf{G}^{\pm}) = \sum_i \int_{\mathbb{R}_+ \times (0,1)} \left(\frac{\kappa^A}{2\varepsilon} |G^{\varepsilon}_i - F^{+,*}_i|^2 \right) r^{+,\varepsilon}_i(a,t) da\, ds$$

where

$$\begin{cases} S^{\varepsilon}_{i,j} := G^+_i(t, s^+_i(t-\varepsilon a) + \varepsilon a \nu^+) - G^-_j(t, s^-_j(t-\varepsilon a) + \varepsilon a \nu^-) \\ T^{\varepsilon}_{i,j} := \varphi_{i,j}(t, \varepsilon\, a) - \varphi_0 \\ F^{+,*}_i := F^+_i(t-\varepsilon a, s + \varepsilon a \nu^+) \\ F^{-,*}_j := F^-_j(t-\varepsilon a, s + \varepsilon a \nu^-) \end{cases}$$

Rescaled formulation

Rescaled density of cros-links and adhesions

- Probability distribution of crosslinks $r_{i,j}(a,t)$

$$\begin{cases} \varepsilon \partial_t r^\varepsilon_{i,j} + \partial_a r^\varepsilon_{i,j} = -\zeta \ \left(S^\varepsilon_{i,j}, T^\varepsilon_{i,j} \right) r^\varepsilon_{i,j} & \forall (a,t) \in (\mathbb{R}_+)^2 \\ r_{i,j}(0,t) = \beta(T^\varepsilon_{i,j}) \left(1 - r_{i,j}(a,t) da\right) & a = 0,\ t > 0 \end{cases}$$

- Density of adhesions $\rho^+_i(a,t,s)$

$$\begin{cases} \varepsilon \partial_t \rho^{+,\varepsilon}_i + \partial_a \rho^{+,\varepsilon}_i - \nu^+ \partial_s \rho^{+,\varepsilon}_i = -\zeta_{\mathrm{adh}} \left(S^{+,\varepsilon}_{\mathrm{adh}} \right) \rho^{+,\varepsilon}_i & \text{in } \mathbb{R}_+ \times \mathbb{R}_+ \times]-1;0[\\ \rho^{+,\varepsilon}_i(0,t,s) = \beta_{\mathrm{adh}} \left(1 - \int_{\mathbb{R}_+} \rho^{+,\varepsilon}_i da \right) & \text{in } \{0\} \times \mathbb{R}_+ \times]-L;0[\\ \rho^{+,\varepsilon}_i \mathrm{adh}(a,t,0) = 0 & \text{in } \mathbb{R}_+ \times \mathbb{R}_+ \times \{0\} \end{cases}$$

Main objective of this work

Rigorous derivation of the limit model when ε goes to 0

Simplified problem:

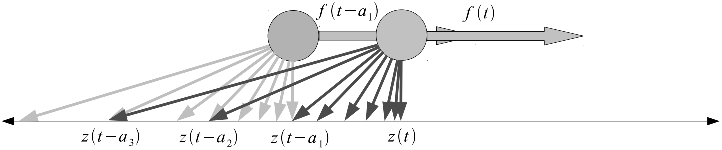
from a treadmilling network of beams

reduce to a single adhesion point

Adhesion vs. exterior force

- $z(t) \in \mathbb{R}$ represents the time dependent position of a linkage binding site.
- no treadmilling
- Force balance between exteriour force $f(t) \in \mathbb{R}$ and adhesions.

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



Mathematical model

$$\begin{cases} \dfrac{1}{\varepsilon}\displaystyle\int_0^\infty (z_\varepsilon(t) - z_\varepsilon(t-\varepsilon a))\,\rho_\varepsilon(a,t)\,da = f(t)\,, & t \geq 0\,,\\ z_\varepsilon(t) = z_p(t)\,, & t < 0\,,\end{cases}$$

where

- $\rho_\varepsilon = \rho_\varepsilon(a,t)$ density of existing linkages to the substrate
- $a \geq 0$ age of the linkage
- $\varepsilon \sim \bar{a}/L > 0$ speed of linkage turnover.

ρ_ε solves a specific renewal model

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

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

Cross-linker proteins and integrins: experimental data

List of parameter rate constants.

Parameter	Value	Reference
v_0 …polymerisation rate	$8\mu m/\min$	
β …rate of cross-link (filamin) attachment	$1.3\sec^{-1}$	c.p. Goldmann, Isenberg 1993 assuming $1\mu M$ of filamin
ζ …rate of cross-link (filamin) detachment	$0.6\sec^{-1}$	Goldmann, Isenberg 1993.
$\overline{\rho}^{adh}_{max}$ ...max. density of integrins on a filament	$0.491-0.685\mu m^{-1}$	
β^{adh} … rate of integrin attachment	$0.03\sec^{-1}$	
ζ^{adh} … rate of integrin detachment	$0.012\times\exp\left(\frac{S}{0.04\mu m}\right)\sec^{-1}$	Li e.a. 2003

D. Oelz, C. Schmeiser, and V. Small.
Modelling of the actin-cytoskeleton in symmetric lamellipodial fragments.
Cell Adhesion and Migration, 2:117–126, 2008.

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

$$\begin{cases} \partial_a \rho_0 + \zeta_0(a,t)\rho_0 = 0\,, & t > 0\,, \quad a > 0\,, \\ \rho_0(t, a=0) = \beta_0(t)\left(1 - \int_0^\infty \rho_0(\tilde{a}, t)\, d\tilde{a}\right)\,, & t > 0\,. \end{cases} \tag{1.1}$$

D. Oelz and C. Schmeiser.
How do cells move? mathematical modelling of cytoskeleton dynamics and cell migration.
In A. Chauviere, L. Preziosi, and C. Verdier, editors, *Cell mechanics: from single scale-based models to multiscale modelling*. 2009.

Viscosity constant

ρ_0 solves an ODE, thus

$$\rho_0(a,t) = \frac{1}{\frac{1}{\beta_0(t)} + \int_0^\infty \exp\left(-\int_0^a \zeta_0(t,\tilde{a})\,d\tilde{a}\right) da} \exp\left(-\int_0^a \zeta_0(t,\tilde{a})\,d\tilde{a}\right)$$

Thus as

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

gives an explicit friction formula.
In the special case $\zeta_0 = \zeta_0(t)$,

$$\mu_{1,0}(t) = \frac{1}{\zeta_0(t)(1+\zeta_0(t)/\beta(t))}\,. \tag{1.2}$$

Assumptions

1. $\beta_\varepsilon \in \mathrm{Lip}_t$, $\zeta_\varepsilon \in \mathrm{Lip}_t([0,T]; L^\infty_a(\mathbb{R}_+))$ with uniform upper and lower bounds

$$0 < \zeta_{\min} \leq \zeta_\varepsilon(a,t) \leq \zeta_{\max} \quad \text{and} \quad 0 < \beta_{\min} \leq \beta_\varepsilon(t) \leq \beta_{\max}\ .$$

2. There is $a_0 > 0$ such that $\zeta_\varepsilon(a,t) \nearrow$ on $[a_0, \infty)$.

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3. Limit functions $\beta_0 \in \mathrm{Lip}_t$ and $\zeta_0 \in \mathrm{Lip}_t(L^\infty_a)$ it holds that

$$\zeta_\varepsilon \to \zeta_0 \quad \text{in} \quad L^\infty_t L^\infty_a \quad \text{and} \quad \beta_\varepsilon \to \beta_0 \quad \text{in} \quad L^\infty_t \quad \text{as} \quad \varepsilon \to 0 \,.$$

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4. It holds that $\rho_{I,\varepsilon} \in L^\infty_a(\mathbb{R}_+)$ with $\rho_{I,\varepsilon}(a) \geq 0$ a.e. in $\mathbb{R}_+$ and

$$0 < \int_{\mathbb{R}_+} \rho_{I,\varepsilon}(a) da \leq 1 \quad \text{and} \quad \int_{\mathbb{R}_+} a^p \rho_{I,\varepsilon}(a) \, da \leq c_p \, , \quad \text{for } p = 1, 2 \, .$$

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4. It holds that $\rho_{I,\varepsilon} \in L^\infty_a(\mathbb{R}_+)$ with $\rho_{I,\varepsilon}(a) \geq 0$ a.e. in $\mathbb{R}_+$ and

$$0 < \int_{\mathbb{R}_+} \rho_{I,\varepsilon}(a) da \leq 1 \quad \text{and} \quad \int_{\mathbb{R}_+} a^p \rho_{I,\varepsilon}(a)\, da \leq c_p \ , \quad \text{for } p = 1,2 \ .$$

5. $f \in \mathrm{Lip}([0,T])$, $z_p \in \mathrm{Lip}((-\infty,0])$.

Bond renewal equation

Bond renewal equation ($\varepsilon > 0$ fixed)

$$\begin{cases} \varepsilon \partial_t \rho_\varepsilon + \partial_a \rho_\varepsilon + \zeta_\varepsilon(a,t)\rho_\varepsilon = 0\,, & t > 0\,,\ a > 0\,, \\ \rho_\varepsilon(a=0,t) = \beta_\varepsilon(t)\left(1 - \int_0^\infty \rho_\varepsilon(\tilde{a},t)\,d\tilde{a}\right)\,, & t > 0\,, \\ \rho_\varepsilon(a,t=0) = \rho_{I,\varepsilon}(a)\,, & a \geq 0\,, \end{cases} \tag{2.1}$$

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Theorem

* *$\forall \varepsilon > 0$, $\exists\,!\ \rho_\varepsilon \in C^0(\mathbb{R}_+; L^1(\mathbb{R}_+)) \cap L^\infty(\mathbb{R}^2_+)$ solution of the problem*
* *$\rho_\varepsilon(a,t) \geq 0$ a.e. in $\mathbb{R}^2_+$.*
* *Moreover setting: $\mu_\varepsilon(t) := \int_{\mathbb{R}_+} \rho_\varepsilon(a,t)da$, it holds that*

$$\mu_{\min} \leq \mu_\varepsilon(t) \leq 1, \quad \forall t \in \mathbb{R}_+$$

where $\mu_{\min} := \min\left(\mu_\varepsilon(0), \frac{\beta_{\min}}{\beta_{\min} + \zeta_{\max}}\right)$.

* *Higher moments bounded above & below*

Time asymptotics of the “Classical” renewal equation

B. Perthame.
Transport equations in biology.

$$\begin{cases} \partial_t n + \partial_a n = 0\,, \quad (a,t) \in (\mathbb{R})^2 \\ n(a=0,t) = + \int_0^\infty B(\tilde{a}) n(\tilde{a},t)\, d\tilde{a}\,, \quad t > 0 \\ n(a,t=0) = n_I(a)\,, \quad a \geq 0\,. \end{cases}$$

Tools available:

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Tools available:

- Eigenproblem *a la* Perron-Frobenius $\exists!(\lambda > 0, \phi, N)$ s.t.

$$\begin{cases} \partial_a N + \lambda_0 N = 0, & a \geq 0 \\ N(0) = \int_{\mathbb{R}_+} B(a) N(a) da, & a = 0, \\ N(a) \geq 0, \int_{\mathbb{R}_+} N(a) = 1 \end{cases} \qquad \begin{cases} -\partial_a \phi + \lambda_0 \phi = \phi(0) B(a) \\ \int_{\mathbb{R}_+} N \phi \, da = 1 \end{cases}$$

Time asymptotics of the "Classical" renewal equation

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Tools available:

- Eigenproblem *a la* Perron-Frobenius
- Long time asymptotic: using the Generalized Entropy Method

$$\int_{\mathbb{R}_+} |\tilde{n}(a,t) - m^0 N| \phi(a) da \to 0, \text{ when } t \to \infty$$

where $m_0 = \int_{\mathbb{R}_+} n_I(a)\phi(a)da$.

Homogeneous equation

Considering the homogeneous version of that model

$$\begin{cases} \varepsilon \partial_t \hat{\rho}_\varepsilon + \partial_a \hat{\rho}_\varepsilon + \zeta_\varepsilon(a,t)\hat{\rho}_\varepsilon = 0 \\ \hat{\rho}_\varepsilon(a=0,t) = -\beta_\varepsilon(t) \int_0^\infty \hat{\rho}_\varepsilon(\tilde{a},t)\, d\tilde{a} \\ \hat{\rho}_\varepsilon(a,0) = \hat{\rho}_{\varepsilon,I}(a), \quad a \geq 0, t = 0 \end{cases}$$

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$$\frac{d}{dt} \int |\hat{\rho}_\varepsilon| = \frac{1}{\varepsilon} \left(\beta_\varepsilon \left| \int_0^\infty \hat{\rho}_\varepsilon \right| - \int_0^\infty \zeta_\varepsilon \, |\hat{\rho}_\varepsilon| \right)$$

$$\frac{d}{dt} \left| \int \hat{\rho}_\varepsilon \right| = \frac{1}{\varepsilon} \left(-\beta_\varepsilon \left| \int_0^\infty \hat{\rho}_\varepsilon \right| - \operatorname{sign} \left(\int_0^\infty \hat{\rho}_\varepsilon \right) \int_0^\infty \zeta_\varepsilon \hat{\rho}_\varepsilon \right)$$

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$$\begin{cases} \varepsilon \partial_t \hat{\rho}_\varepsilon + \partial_a \hat{\rho}_\varepsilon + \zeta_\varepsilon(a,t)\hat{\rho}_\varepsilon = 0 \\ \hat{\rho}_\varepsilon(a=0,t) = -\beta_\varepsilon(t) \int_0^\infty \hat{\rho}_\varepsilon(\tilde{a},t)\, d\tilde{a} \\ \hat{\rho}_\varepsilon(a,0) = \hat{\rho}_{\varepsilon,I}(a), \quad a \geq 0, t = 0 \end{cases}$$

$$\frac{d}{dt}\int |\hat{\rho}_\varepsilon| = \frac{1}{\varepsilon}\left(\beta_\varepsilon \left|\int_0^\infty \hat{\rho}_\varepsilon\right| - \int_0^\infty \zeta_\varepsilon |\hat{\rho}_\varepsilon|\right)$$
$$\frac{d}{dt}\left|\int \hat{\rho}_\varepsilon\right| = \frac{1}{\varepsilon}\left(-\beta_\varepsilon \left|\int_0^\infty \hat{\rho}_\varepsilon\right| - \operatorname{sign}\left(\int_0^\infty \hat{\rho}_\varepsilon\right)\int_0^\infty \zeta_\varepsilon \hat{\rho}_\varepsilon\right)$$

Define:

$$\mathcal{H}[\bar{\rho}_\varepsilon] := \left|\int \bar{\rho}_\varepsilon(a,t)\, da\right| + \int |\bar{\rho}_\varepsilon(a,t)|\, da \,,$$

Liapunov functional

$$\frac{d}{dt}\mathcal{H}[\hat{\rho}_\varepsilon] = \frac{1}{\varepsilon}\left(- \int_0^\infty \zeta_\varepsilon |\hat{\rho}_\varepsilon| - \mathrm{sign}\left(\int_0^\infty \hat{\rho}_\varepsilon \right) \int_0^\infty \zeta_\varepsilon \hat{\rho}_\varepsilon \right)$$

Liapunov functional

$$\begin{aligned}\frac{d}{dt}\mathcal{H}[\hat{\rho}_\varepsilon] &= \frac{1}{\varepsilon}\left(-\int_0^\infty \zeta_\varepsilon |\hat{\rho}_\varepsilon| - \operatorname{sign}\left(\int_0^\infty \hat{\rho}_\varepsilon\right)\int_0^\infty \zeta_\varepsilon \hat{\rho}_\varepsilon\right) \\ &= -\frac{1}{\varepsilon}\int_0^\infty \zeta_\varepsilon \underbrace{\left(|\hat{\rho}_\varepsilon| + \operatorname{sign}\left(\int_0^\infty \hat{\rho}_\varepsilon\right)\hat{\rho}_\varepsilon\right)}_{=:A\geq 0}\end{aligned}$$

Liapunov functional

$$\begin{aligned}
\frac{d}{dt}\mathcal{H}[\hat\rho_\varepsilon] &= \frac{1}{\varepsilon}\left(-\int_0^\infty \zeta_\varepsilon|\hat\rho_\varepsilon| - \text{sign}\left(\int_0^\infty \hat\rho_\varepsilon\right)\int_0^\infty \zeta_\varepsilon\hat\rho_\varepsilon\right) \\
&= -\frac{1}{\varepsilon}\int_0^\infty \zeta_\varepsilon \underbrace{\left(|\hat\rho_\varepsilon| + \text{sign}\left(\int_0^\infty \hat\rho_\varepsilon\right)\hat\rho_\varepsilon\right)}_{=:A\geq 0} \\
&\leq -\frac{1}{\varepsilon}\zeta_{\min}\int_0^\infty \left(|\hat\rho_\varepsilon| + \text{sign}\left(\int_0^\infty \hat\rho_\varepsilon\right)\hat\rho_\varepsilon\right)
\end{aligned}$$

Liapunov functional

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&= -\frac{1}{\varepsilon}\int_0^\infty \zeta_\varepsilon \underbrace{\left(|\hat{\rho}_\varepsilon| + \text{sign}\left(\int_0^\infty \hat{\rho}_\varepsilon\right)\hat{\rho}_\varepsilon\right)}_{=:A\geq 0} \\
&\leq -\frac{1}{\varepsilon}\zeta_{\min}\int_0^\infty \left(|\hat{\rho}_\varepsilon| + \text{sign}\left(\int_0^\infty \hat{\rho}_\varepsilon\right)\hat{\rho}_\varepsilon\right) \\
&= -\frac{1}{\varepsilon}\zeta_{\min}\left(\int|\hat{\rho}_\varepsilon| + \left|\int\hat{\rho}_\varepsilon\right|\right)
\end{aligned}$$

Liapunov functional

$$
\begin{aligned}
\frac{d}{dt}\mathcal{H}[\hat{\rho}_\varepsilon] &= \frac{1}{\varepsilon}\left(-\int_0^\infty \zeta_\varepsilon|\hat{\rho}_\varepsilon| - \mathsf{sign}\left(\int_0^\infty \hat{\rho}_\varepsilon\right)\int_0^\infty \zeta_\varepsilon\hat{\rho}_\varepsilon\right)\\
&= -\frac{1}{\varepsilon}\int_0^\infty \zeta_\varepsilon \underbrace{\left(|\hat{\rho}_\varepsilon| + \mathsf{sign}\left(\int_0^\infty \hat{\rho}_\varepsilon\right)\hat{\rho}_\varepsilon\right)}_{=:A\geq 0}\\
&\leq -\frac{1}{\varepsilon}\zeta_{\min}\int_0^\infty \left(|\hat{\rho}_\varepsilon| + \mathsf{sign}\left(\int_0^\infty \hat{\rho}_\varepsilon\right)\hat{\rho}_\varepsilon\right)\\
&= -\frac{1}{\varepsilon}\zeta_{\min}\left(\int|\hat{\rho}_\varepsilon| + \left|\int\hat{\rho}_\varepsilon\right|\right)\\
\frac{d}{dt}\mathcal{H}[\bar{\rho}_\varepsilon] &\leq -\frac{1}{\varepsilon}\zeta_{\min}\,\mathcal{H}[\bar{\rho}_\varepsilon]\,.
\end{aligned}
$$

Convergence as $\varepsilon \to 0$, I

Formal limit solution: Given $\zeta_0(t,a)$, $\beta_0(t)$ and $\rho_{0,I}$, let ρ_0 be a solution of

$$\begin{cases} \partial_a \rho_0 + \zeta_0(t,a)\rho_0 = 0 \,, & \\ \rho_0(a=0) = \beta_0(t)\left(1 - \int_0^\infty \rho_0(\tilde{a})\, d\tilde{a}\right) & t > 0\,,\ a \geq 0 \\ \rho_0(a,0) = \rho_{0,I}(a), \quad a \geq 0, t = 0 \,, & \end{cases} \tag{2.2}$$

Convergence as $\varepsilon \to 0$, I

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then $\hat{\rho}_\varepsilon := \rho_\varepsilon - \rho_0$ satisfies

$$\begin{cases} \varepsilon \partial_t \hat{\rho}_\varepsilon + \partial_a \hat{\rho}_\varepsilon + \zeta_\varepsilon(a,t)\hat{\rho}_\varepsilon = \mathcal{R}_\varepsilon \\ \hat{\rho}_\varepsilon(a=0,t) = -\beta_\varepsilon(t) \int_0^\infty \hat{\rho}_\varepsilon(\tilde{a},t)\, d\tilde{a} + M_\varepsilon \\ \hat{\rho}_\varepsilon(a,0) = \hat{\rho}_{\varepsilon,I}(a), \quad a \geq 0, t = 0 \end{cases}$$

with $\mathcal{R}_\varepsilon := -\varepsilon \partial_t \rho_0 - \rho_0(\zeta_\varepsilon - \zeta_0)$ and $M_\varepsilon := (\beta_\varepsilon - \beta_0)\left(1 - \int \rho_0\, da\right)$.

Convergence as $\varepsilon \to 0$, II

$$\frac{d}{dt}\mathcal{H}[\hat{\rho}_\varepsilon] \leq -\frac{\zeta_{\min}}{\varepsilon}\mathcal{H}[\hat{\rho}_\varepsilon] + \frac{2}{\varepsilon}\left(\int_{\mathbb{R}_+} |\mathcal{R}_\varepsilon| \, da + |M_\varepsilon|\right) .$$

where

$$\begin{cases} \hat{\rho}_\varepsilon(a,t) = \rho_\varepsilon(a,t) - \rho_0(a,t) \\ R_\varepsilon(a,t) = -\varepsilon \partial_t \rho_0(a,t) - (\zeta_\varepsilon - \zeta_0)(a,t)\rho_0(a,t) \\ M_\varepsilon(t) = (\beta_\varepsilon - \beta_0)\left(1 - \int_0^\infty \rho_0 \, da\right) \end{cases}$$

Convergence as $\varepsilon \to 0$, II

$$\frac{d}{dt}\mathcal{H}[\hat{\rho}_\varepsilon] \leq -\frac{\zeta_{\min}}{\varepsilon}\mathcal{H}[\hat{\rho}_\varepsilon] + \frac{2}{\varepsilon}\left(\int_{\mathbb{R}_+} |\mathcal{R}_\varepsilon| \, da + |M_\varepsilon|\right) .$$

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$$\begin{cases} \hat{\rho}_\varepsilon(a,t) = \rho_\varepsilon(a,t) - \rho_0(a,t) \\ R_\varepsilon(a,t) = -\varepsilon\partial_t\rho_0(a,t) - (\zeta_\varepsilon - \zeta_0)(a,t)\rho_0(a,t) \\ M_\varepsilon(t) = (\beta_\varepsilon - \beta_0)\left(1 - \int_0^\infty \rho_0 \, da\right) \end{cases}$$

Theorem

$\rho_\varepsilon \to \rho_0$ *in* $C^0(]0,T]; L^1(\mathbb{R}_+))$ *i.e.*

$$\|(\rho_\varepsilon - \rho_0)(\cdot,t)\|_{L^1_a(\mathbb{R}_+)} \leq e^{-\frac{\zeta_{\min} t}{\varepsilon}}\mathcal{H}[\rho_{\varepsilon,I} - \rho_{0,I}] + cT\left\| \|\mathcal{R}_\varepsilon(\cdot,t)\|_{L^1_a} + |M_\varepsilon| \right\|_{L^\infty_t}$$

$$\leq c_1 e^{-\frac{\zeta_{\min} t}{\varepsilon}} + \varepsilon c_2 T$$

Integral equation for z

Integral equation for z

$$\begin{cases} \dfrac{1}{\varepsilon} \displaystyle\int_0^\infty (z_\varepsilon(t) - z_\varepsilon(t - \varepsilon a))\, \rho_\varepsilon(a,t)\, da = f(t)\ , & t \geq 0\ , \\ z_\varepsilon(t) = z_p(t)\ , & t < 0\ , \end{cases}$$

- $z_\varepsilon \in \mathbb{R}$ the time dependent position of a linkage binding site
- $f(t) \in \mathrm{Lip}(\mathbb{R}_+, \mathbb{R})$ given exterior force
- $\rho_\varepsilon = \rho_\varepsilon(a,t)$ density of existing linkages to the substrate with respect to the age $a \geq 0$

Formal limit equation

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

Existence and uniquenes ε fixed

G. Gripenberg, S.-O. Londen, and O. Staffans.
Volterra integral and functional equations,
Cambridge University Press, 1990.

Theorem

- $\rho_\varepsilon \in C^0(\mathbb{R}_+; L^1(\mathbb{R}_+)) \cap L^\infty(\mathbb{R}^2_+)$ *be given,*
- *assumptions on the data* f, z_p *hold,*

then

$$\forall \varepsilon > 0, \quad \exists! z_\varepsilon \in C^0(\mathbb{R}_+) \quad \textit{solving the integral pbm}$$

Convergence as $\varepsilon \to 0$

Consider $\tilde{z} := z_\varepsilon - z_0$ and $\tilde{\rho}_\varepsilon := \rho_\varepsilon / \mu_{0,\varepsilon}$, it solves

$$\int_0^\infty \left(\tilde{z}_\varepsilon(t) - \tilde{z}_\varepsilon(t - \varepsilon a)\right) \tilde{\rho}_\varepsilon \, da = \varepsilon \frac{f}{\mu_{0,\varepsilon}} - \int_0^\infty \left(z_0(t) - z_0(t - \varepsilon a)\right) \tilde{\rho}_\varepsilon \, da =$$

$$= \varepsilon \frac{f}{\mu_{0,\varepsilon}} - \int_0^{t/\varepsilon} \int_{t-\varepsilon a}^{t} \partial_t z_0(s) ds \tilde{\rho}_\varepsilon(a,t) da - \int_{t/\varepsilon}^{\infty} (z_0(t) - z_0(t - \varepsilon a)) \tilde{\rho}_\varepsilon(a,t) \, d$$

$$= \varepsilon \frac{f}{\mu_{0,\varepsilon}} - \int_0^{t/\varepsilon} \int_{t-\varepsilon a}^{t} \frac{f}{\mu_{1,0}}(s) ds \, \tilde{\rho}_\varepsilon(a,t) da - \int_{t/\varepsilon}^{\infty} \int_0^{t} \frac{f}{\mu_{1,0}} ds \tilde{\rho}_\varepsilon(a,t) \, da$$

$$=: \varepsilon h_\varepsilon(t)$$

Proposition

If $f \in \mathrm{Lip}(\mathbb{R}_+)$,

$$h_\varepsilon(t) \leq C_1 \exp\left(-\frac{\zeta_{\min} t}{\varepsilon}\right) + \varepsilon \, C_2.$$

Comparison principle

G. Gripenberg, S.-O. Londen, and O. Staffans.
Volterra integral and functional equations,
Cambridge University Press, 1990.

Proposition

If one has

$$z(t) = (k * z)(t) + g(t), \quad (k * z)(t) = \int_0^t k(\tilde{a}, t) z(\tilde{a}) d\tilde{a}, \quad a.e. t \in J$$

$$\|k\|_{B^\infty(J)} := sup_{t \in J} \int_J k(a,t) da < 1, \quad J \text{ compact and } k > 0$$

then $\exists r$ *s.t.* $z := g + r * g$ *and*

$$\left. \begin{array}{l} x(t) \leq (k * x)(t) + g(t) \\ y(t) = (k * y)(t) + g(t), \end{array} \right\} \Longrightarrow x(t) \leq y(t) \quad a.e.\ t \in J$$

- Our problem fits the frame
  Set $k(\tilde{a}, t) := \frac{1}{\mu_\varepsilon(t)} \frac{1}{\varepsilon} \rho_\varepsilon(\frac{t-\tilde{a}}{\varepsilon}, t)$ our problem reads

$$\tilde{z}_\varepsilon(t) = \int_0^t \tilde{z}_\varepsilon(\tilde{a}) k(\tilde{a}, t) \, d\tilde{a} + \tilde{h}_\varepsilon \ ,$$

with $\tilde{h}_\varepsilon(t) := \varepsilon h_\varepsilon(t) + \int_{-\infty}^0 \tilde{z}_\varepsilon(\tilde{a}) k(\tilde{a}, t) \, d\tilde{a}$ for all $t \geq 0$.

- Our problem fits the frame
  Set $k(\tilde{a},t) := \frac{1}{\mu_\varepsilon(t)}\frac{1}{\varepsilon}\rho_\varepsilon(\frac{t-\tilde{a}}{\varepsilon},t)$ our problem reads

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  with $\tilde{h}_\varepsilon(t) := \varepsilon h_\varepsilon(t) + \int_{-\infty}^0 \tilde{z}_\varepsilon(\tilde{a})k(\tilde{a},t)\,d\tilde{a}$ for all $t \geq 0$.
- It holds that

$$|\tilde{z}_\varepsilon(t)| \leq \int_0^t |\tilde{z}_\varepsilon(\tilde{a})|k(\tilde{a},t)\,d\tilde{a} + |\tilde{h}_\varepsilon|$$

  Let $u(t)$ satisfy

$$u(t) = \int_0^t u(\tilde{a})k(\tilde{a},t)\,d\tilde{a} + |\tilde{h}_\varepsilon|$$

  Hence it holds that $0 \leq |\tilde{z}_\varepsilon(t)| \leq u(t)$.

- Same comparison argument

$$(U-u)(t) - \int_0^t k(\tilde{a},t)(U-u)(\tilde{a})d\tilde{a} \geq 0, \quad \text{a.e. } t \in J$$

implies

$$U(t) > u(t), \quad \text{a.e. } t \in J$$

Is there such a U ?

Consider $$U = \begin{cases} \varepsilon C + \frac{1}{\mu_{1,\min}} \int_0^t \|h\|_{L^\infty(\tilde{t},T)} \, d\tilde{t} & t > 0 \\ \varepsilon C + \frac{1}{\mu_{1,\min}} \|h\|_{L^\infty(0,T)} \, t & t \leq 0 \end{cases}$$

for a constant $C > 0$:

$$U(t) - \int_0^t U(\tilde{a}) k(\tilde{a}, t) \, d\tilde{a} =$$

$$= \int_{-\infty}^t (U(t) - U(\tilde{a})) \; k(\tilde{a}, t) \, d\tilde{a} + \int_{-\infty}^0 U(\tilde{a}) \; k(\tilde{a}, t) \, d\tilde{a} =$$

$$= \int_0^\infty \varepsilon a \left(\frac{1}{\varepsilon a} \int_{t-\varepsilon a}^t \frac{\|h\|_{L^\infty(\bar{a},T)}}{\mu_{1,\min}} \, d\bar{a} \right) \frac{\rho_\varepsilon(a,t)}{\mu_\varepsilon(t)} \, da + \int_{-\infty}^0 \left(\varepsilon C + \frac{1}{\mu_{1,\min}} \|h\|_{L^\infty(0,T)} \, \tilde{a} \right) k(\tilde{a}, t) \, d\tilde{a}$$

$$\geq \varepsilon \frac{1}{\mu_\varepsilon(t)} h_\varepsilon(t) + \int_{-\infty}^0 \tilde{z}_\varepsilon(\tilde{a}) k(\tilde{a}, t) \, d\tilde{a} = |\tilde{h}_\varepsilon|$$

by choosing

$$C \geq \left(\frac{\|h\|_{L^\infty(0,T)}}{\mu_{1,\min}} + L \right) \frac{\int_0^\infty a \; \rho_\varepsilon(\frac{t}{\varepsilon} + a, t) \, da}{\int_0^\infty \; \rho_\varepsilon(\frac{t}{\varepsilon} + a, t) \, da} \, .$$

Hence as $\|h\|_{L^\infty(\tilde{t},T)} \leq ke^{-t/\varepsilon}$

$$0 \leq |\tilde{z}_\varepsilon| \leq u \leq U(t) = \varepsilon C + \frac{1}{\mu_{1,\min}} \int_0^t \|h\|_{L^\infty(\tilde{t},T)} \, d\tilde{t} \to 0 \quad \text{as} \quad \varepsilon \to 0$$

Thus $z_\varepsilon \to z_0$ in $L^\infty((0,T))$.

Theorem

Let (z_0, ρ_0) the formal limit, $\forall T > 0$ it holds that

$$\|z_\varepsilon - z_0\|_{C^0([0,T])} + \|\rho_\varepsilon - \rho_0\|_{C^0(]0,T];L^1(\mathbb{R}_+))} \to 0 \,,$$

as $\varepsilon \to 0$.

A simple example

Set

$$\zeta_\varepsilon = \zeta_0 = \zeta = C^{st}, \quad \beta_\varepsilon = \beta_0 = \beta = C^{st}, \text{ and } \rho_{I,\varepsilon} = \rho_0 = \frac{\beta\zeta}{\beta+\zeta} e^{-\zeta a},$$

then z is explicit as well

$$\begin{cases} z_\varepsilon(t) = \displaystyle\int_0^t \frac{f}{\mu_{1,0}} ds + \frac{\varepsilon f(t)}{\mu_{0,0}} + \int_{\mathbb{R}_+} z_p(-\varepsilon a) \zeta \exp\left(-\zeta a\right) da, & t > 0, \\ \qquad = z_p(0) + \displaystyle\int_0^t \frac{f}{\mu_{1,0}} ds + \frac{\varepsilon f(t)}{\mu_{0,0}} - \int_{-\infty}^0 z_p'(s) \exp\left(\frac{\zeta s}{\varepsilon}\right) ds, & \\ z_\varepsilon(t) = z_p(t), & t < 0. \end{cases}$$

Conclusion & Perspectives

- Lipshitz data (f, z_p) everything works, what a proof for $f \in L^1(\mathbb{R}_+)$?
- Stronger coupling

$$\zeta_\varepsilon := \zeta_\varepsilon(|z(t) - z(t - \varepsilon a)|), \quad \beta_\varepsilon := \beta_\varepsilon(z(t))$$

- Full model $z(s,t) \in \mathbb{R}^2$ is a deformation of the reference variable s at time t

$$z(t,s) := \operatorname{argmin}_{|\partial_s w(t,s)|=1} \left\{ \int_0^L |\partial_{s^2}^2 w|^2 ds \right.$$
$$\left. + \int_0^L \int_{\mathbb{R}_+} |w(t,s) - z(t - \varepsilon a, s + \nu_0 a)|^2 \rho_\varepsilon(a,t,s)\, da\, ds \right\}$$

- Numerics