Estimating the division rate and kernel for a model describing the amyloid fragmentation

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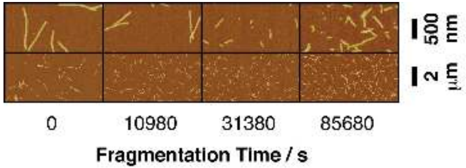
Goal

Understand the dynamical behaviour of a system of fibrils undergoing a mechanichal fragmentation.

Context : Diseases involving Amyloid fibrils (Prion, Alzeihmer).

Tools : Deterministic models of the fragmentation mechanism.

Data : Experiment performed at the University of Kent, UK, by the team of Prof Xue.



1. Introduction: The fragmentation equation
2. Fragmentation of fibrils: A new experiment
3. Uniqueness and Reconstruction formula for the inverse problem
4. Numerical simulations and application to real data

Deterministic equation describing the evolution of a population of particles with characteristic size $x \rightsquigarrow$ Size-structured PDE.

Unknown: f(t,x) = Density of particles of size x at time t.

$$\underbrace{\frac{\partial f}{\partial t}(t,x)}_{\text{Evolution of the number of particles}} = \underbrace{-B(x)f(t,x)}_{\text{Death}} + \underbrace{\int_{y=x}^{y=\infty} k(x,y)B(y)f(t,y)dy}_{\text{Creation}}$$

Parameters:

- $B(x)$ = Fragmentation rate of particles of size x.
  Classical assumption : $B(x) = \alpha x^{\gamma}$, $\gamma > 0$, $\alpha > 0$,
- $k(x,y)$ = Fragmentation kernel.
  Classical assumptions : $k(x,y) = \frac{1}{y} k_0\left(\frac{x}{y}\right)$, where k_0 is a measure on $[0,1]$,

$$supp\,(k_0) \subset [0,1], \quad \int_0^1 dk_0(z) = 2, \quad \int_0^1 z dk_0(z) = 1.$$

Related size-structured PDE

- **Pure Fragmentation.** Particles can only break up.
  Example: Amyloid fibrils

$$\frac{\partial f}{\partial t}(t,x) = -B(x)f(t,x) + \int_{y=x}^{y=\infty} k(x,y)B(y)f(t,y)dy$$

- **Transport-Fragmentation.** Particles can break up and grow.
  Example: Cells, microtubules

$$\frac{\partial f}{\partial t}(t,x)+\frac{\partial}{\partial x}\left(g(x)f(t,x)\right) = -B(x)f(t,x) + \int_{y=x}^{y=\infty} k(x,y)B(y)f(t,y)dy$$

- **Coagulation-Fragmentation.** Particles can break up or merge.
  Example: Dispersion of dust, smoke, or pollutants.

$$\frac{\partial f}{\partial t}(t,x) = -B(x)f(t,x) + \int_{y=x}^{y=\infty} k(x,y)B(y)f(t,y)dy$$
$$-f(t,x)\int_0^{+\infty} k_c(x,y)f(y)dy + \int_{y=0}^{y=x} k_c(y,x-y)f(t,y)f(t,x-y)dy$$

The fragmentation equation :

$$\begin{cases} \dfrac{\partial f}{\partial t}(t,x) = -B(x)f(t,x) + \displaystyle\int_{y=x}^{y=\infty} \frac{B(y)}{y} k_0\left(\frac{x}{y}\right) f(t,y)dy, \\ \quad f(x,0) = f_0(x). \end{cases} \tag{1}$$

Under the assumptions on the fragmentation rate ($B(x) = x^{\gamma}$) and on the scaling of the kernel, **the fragmentation equation has a global solution** (Smith, Thieme, Escobedo, Michel, Perthame, Mishler, ...) which lies in $\mathcal{C}([0,T); L^1(\mathbb{R}^+, xdx)) \cap L^1(0,T; L^1(\mathbb{R}^+, x^{\gamma+1}dx)$.

Conservation properties :

$$\frac{d}{dt}\int_0^{+\infty} f(t,x)dx = \int_0^{+\infty} B(x)f(t,x)dx \qquad \text{Number of clusters increases}$$

$$\frac{d}{dt}\int_0^{+\infty} xf(t,x)dx = 0 \qquad \text{Mass conservation}$$

A Non-preserving mass solution (Stewart)

Uniqueness is true only in $\mathcal{C}([0,T);L^1(\mathbb{R}^+,xdx))\cap L^1(0,T;L^1(\mathbb{R}^+,x^{\gamma+1}dx)$. The fact that the solution is in $L^1(0,T;L^1(\mathbb{R}^+,xB(x)dx)$ is crucial.

For

$$B(x)=\frac{x}{2}(1+x)^{-r},\ r\in(0,1),\ k_0=2\mathbb{1}_{[0,1]},$$

and for the initial condition $f_0\in L^1(\mathbb{R}^+,xdx)\setminus L^1(\mathbb{R}^+,xB(x)dx)$ defined as

$$f_0(x)=\exp\left(-\int_0^x\frac{3-ru(1+u)^{-1}}{2\lambda(1+u)^r+u}du\right),$$

there is a solution

$$f(t,x)=\exp(\lambda t)f_0(x)$$

belonging to $\mathcal{C}([0,T);L^1(\mathbb{R}^+,(1+x)dx))$ and for which the total mass of the system increases exponentially fast.

Theorem (Michel-Perthame-Escobedo-Mishler-Ricard – 2005)

Under reasonable technical assumptions, for large time, the profile f tends to distribute according to the self-similar profile g In other words, $f(t,x)$ satisfies

$$f(t,x) \to t^{\frac{2}{\gamma}} g\left(xt^{\frac{1}{\gamma}}\right), \qquad L^1(x\,dx)$$

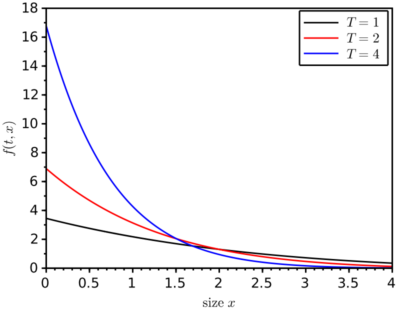
where the self-similar profile g is the unique solution of

$$z\frac{dg}{dz}(z) + (2+\alpha\gamma z^\gamma)g(z) = \alpha\gamma \int_{u=z}^{u=\infty} \frac{1}{u} k_0\left(\frac{z}{u}\right) u^\gamma g(u)\,du, \qquad \int_0^\infty zg(z)dz = \rho.$$

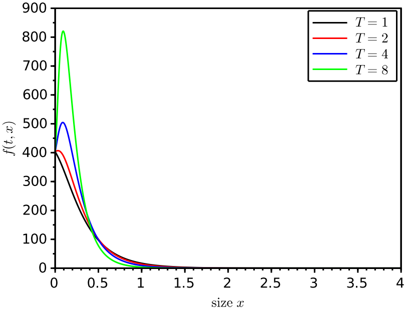
- No admissible stationary state. Change of coordinates.
- In the new coordinates, the fragmentation equation rewrites as a transport/fragmentation equation.
- The moments of f for large t are then related to the moments of g via the following formula

$$\int_0^\infty y^s g(y)dy \quad \sim \quad t^{(s-1)/\gamma} \int_0^\infty y^s f(t,y)dy, \qquad s \in [0,\infty),\ t \text{ large}.$$

Two examples.



$k_0(x) = 2\mathbb{1}_{[0,1]}(x)$



$k_0(x) = 2\delta_{x=1/2}(x) + \epsilon\mathbb{1}_{[0,1]}$

Remark

Mitosis is not included in the model. We exclude $k_0(x) = 2\delta_{x=1/2}(x)$.

Inverse Problem (IP): Given a (noisy) measurement of $g(x)$ solution in $L^1((1 + x^{\gamma+1})dx)$ of the stationary equation, is it possible to estimate the functional parameters of the evolution equation, namely the triplet $(\alpha, \gamma, k_0) \in (0, +\infty) \times (0, +\infty) \times \mathcal{M}^+(0, 1)$?

- Class of **biological nanomaterial** with tensile strength compared to that of steel: mechanical stability toward breakage is not well characterized,

- The breakage of amyloid polymers into small more infective particles is a **key in the spread** of phenotypes, and it has been shown recently that the **smaller particles** generated by fibrils fragmentation are **more cytotoxic**.

A new approach: To understand the fragmentation of Amyloid fibrils, MEASURE the time-evolution of the SIZE DISTRIBUTION

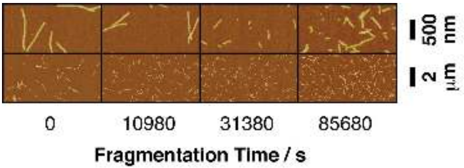
- **Proteins under study**: β2-Amyloid, Lysozyme, a-Synuclein, $\beta-$Lactoglobuline.
- Step 1. Prepare a pure sample of proteins.
- Step 2. **Recreating the experimental conditions of mechanical fragmentation.** The suspension is continuously agitated during two weeks by a magnetic agitator.

  From time to time, a small sample is taken out from the aliquot and saved.

- Step 3. A picture of each set taken out from the sample is done.

  Tool: **Atomic Force Microscopy (AFM)**.

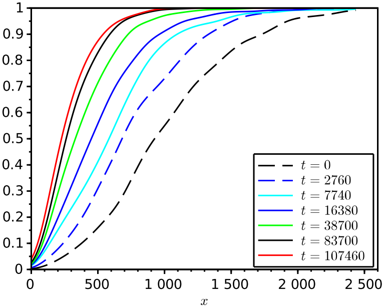
  $\rightsquigarrow$ Fibrils can be identified visually.

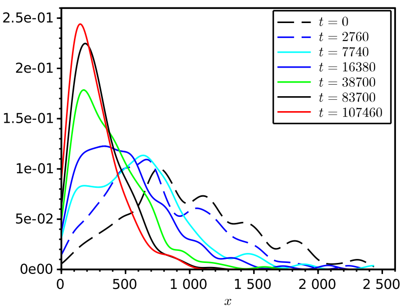


- Step 4. **Determine** the localization and a **measure of the size of each fibril of the picture.**
  Large fibrils are harder to detect than small fibrils:
  $\boxed{a}$ Fibrils touching the border.
  $\boxed{b}$ Fibrils which are crossing each other in a complicated way so that it is tricky to determine which is which.
  $\rightsquigarrow$ **It seems then that the number of large fibrils is underestimated.**

- Step 5. Estimate of how much we lose and **modify the frequencies** by allocating a higher weight to the large sized fibrils. Very unusual technique since most experimentalists use directly the frequencies they measure as final data.

- We access **normalized cumulative distribution** function h of the length distribution of each fibril sample.





What is done by the Experimentalists (Pr Xue team)

Question : Determine $\gamma \in \mathbb{R}, \alpha \in \mathbb{R}$ and $k_0 \in \mathbb{R}^{N \times N}$.

- **Regularization of the data**. Approximate the data by polynomial functions.
- Make an **hypothesis on the fragmentation kernel** k_0: Parametrization.
$\rightsquigarrow$ The problem becomes : Determine $\gamma, \alpha, k1, k2, k3, k4 \in \mathbb{R}^6$
- Solve the direct problem for the comprehensive set of admissible parameters $\gamma, \alpha, k1, k2, k3, k4 \in \mathbb{R}^6$.
- Determine which set of parameters gives rise to the dynamical behaviour observed experimentally. **Total linear least square analysis** (Minimization Problem).

Definition

Let μ be a measure over $\mathbb{R}$. We denote by $M[\mu]$ the Mellin transform of μ, defined by the integral

$$M[\mu](s) = \int_{x=0}^{x=+\infty} x^{s-1}\, d\mu(x),$$

for those values of s for which the integral exists.

Properties.

1. **Riemann-Lebesgue theorem.**
If $f \in L^1_{\text{loc}}(\mathbb{R})$, then $F(u+iv) \underset{v\to\pm\infty}{\rightarrow} 0$.
2. If $M[\mu](a)$ exists for some real number a,b then $M[\mu]$ is **holomorphic** in the open bande $\{s \in \mathbb{C} | a < Res < b\}$.

3. The **inverse-Mellin** transform is defined by

$$f(x) := \frac{1}{2i\pi} \int_{q^*-i\infty}^{q^*+i\infty} F(q^* + it) x^{-q^*} x^{-it}\, dt.$$

- $\exists \varepsilon > 0, \quad 0 < \eta_1 < \eta_2 < 1$ such that $\quad k_0(z) \geq \varepsilon, \quad z \in [\eta_1, \eta_2],$
- There exists $\varepsilon > 0$ such that k_0 is a bounded continuous function on $[1-\varepsilon, 1]$ and on $[0, \varepsilon]$.
- There exists $s_- < 2$ such that $K_0(s) \neq 1$ for all $s \in \mathbb{C}$ such that $\Re e(s) \in (s_-, 2)$.
- There exists $h_0 \in L^1(0,1) \setminus \{0\}$, $n \geq 0$, $a_j \in (0,1)$ and $C_j \geq 0$, for $j = 1 \ldots n$, such that

$$k_0(x) = h_0(x) + \sum_{j=1}^{n} C_j \delta_{a_j}(x),$$

  where the a_j are such that there exists $m_j \in \mathbb{Q}^n$ and θ such that $a_j = \theta^{m_j}$, $j = 1 \ldots n$.

The stationary fragmentation equation in Mellin-coordinates: used to recover parameters

Define $G(s) := M[g](s)$, $K_0(s) := M[k_0](s)$ $\quad (K_0(2) = 1)$.

Turn an integro-differential equation into a functional equation

$$\boxed{(2-s)G(s) + \alpha\gamma G(s+\gamma) = \alpha\gamma K_0(s) G(s+\gamma), \qquad s \in D_1.} \tag{2}$$

- **Determine γ.**

- **Determine α.** Plug $s = 2$.

$$\alpha = \frac{G(1)}{\gamma G(1+\gamma)}.$$

- **Determine K_0. ($\rightsquigarrow k_0$)**

$$K_0(s) = 1 + \frac{G(s)(2-s)}{\alpha\gamma G(s+\gamma)}, \qquad s \in D_1.$$

The Mellin transform of g

Proposition

Suppose that a function g, satisfying

$$x^k g \in W^{1,1}(0,\infty)\ \forall k \geq 0,\ \ x^k g \in L^\infty(0,\infty),\ \forall k \geq 1;\ g \in W^{1,\infty}_{loc}(0,\infty)$$

is a solution of the stationary fragmentation equation in the sense of distributions on $(0,\infty)$, for some kernel $k_0 \in \mathcal{M}^+(0,1)$. Then, its Mellin transform:

$$G(s) = \int_0^\infty x^{s-1} g(x)dx$$

is well defined for all $s \in \mathbb{C}$ such that $\Re e(s) \geq 1$, it is analytic in the domain

$$D_1 = \{s \in \mathbb{C}; \Re e(s) > 2\ \}$$

and it satisfies:

$$(2-s)G(s) = \alpha\gamma(K_0(s)-1)G(s+\gamma) \quad in\ \ D_1.$$

Theorem (Doumic,Escobedo, T.)

For all $g \in L^1(\mathbb{R}^+)$ such that for all $k \geq 0$, $\int_0^\infty y^k g(y)dy < \infty$, there exists at most one triplet $(\gamma, \alpha, k_0) \in \mathbb{R}^+ \times \mathbb{R}^+ \times \mathcal{M}(0,1)$ such that g is the solution of the stationary equation in the sense of distributions.

Proof of the uniqueness for (γ, α) :

Proof 1. Relies on the estimates obtained by Balague, Canizo, Gabriel: There exists a constant $C > 0$ and a power $p \geq 0$ such that

$$g(x) \underset{x \to \infty}{\sim} C x^p e^{-\frac{\alpha}{\gamma} x^\gamma} \to \quad \log\left(\frac{1}{g}\right) \underset{x \to \infty}{\sim} \frac{\alpha}{\gamma} x^\gamma,$$

Proof 2. Relies on estimates we obtain for $G(s)$ when $\mathrm{Re}(s)$ is large.

$$G(s+\gamma) = \Phi(s) G(s), \qquad \Phi(s) = \frac{2-s}{\alpha\gamma(K_0(s)-1)}.$$

Both proofs relie strongly on computations on the moments of g, and their behaviour when the power of the moment tends to infinity.

Proposition (Necessary condition for γ)

Suppose that $g \in L^1_{loc}(\mathbb{R}^+)$ such that $\int_{\mathbb{R}^+} x^k g(x)dx < +\infty,\ k \geq 1$, and g solves the stationary fragmentation equation for some parameters $\gamma > 0$, $\alpha > 0$ and some non negative measure k_0, compactly supported in $[0,1]$. Let G be the Mellin transform of g. Then, given any constant $R > 0$:

$$\lim_{s\to\infty,\, s\in\mathbb{R}^+} \frac{s\,G(s)}{G(s+R)} = \begin{cases} 0, & \forall R > \gamma \\ \alpha\gamma, & \text{if } R = \gamma \\ \infty, & \forall R \in (0,\gamma) \end{cases}$$

Idea of the proof: Equation satisfied by G is close, for s large, to equation

$$AG(s+\gamma) = sG(s), \qquad s \in \mathbb{R}, \qquad G(2) = \rho.$$

It has a unique analytical solution $\Gamma_{A,\gamma}(s) = K\left(\frac{\gamma}{A}\right)^{\frac{s}{\gamma}}\Gamma\left(\frac{s}{\gamma}\right)$,

$$\Gamma_{A,\gamma}(s) \sim K\sqrt{\frac{2\pi\gamma}{s}}\left(\frac{\gamma}{A}\right)^{\frac{s}{\gamma}}\left(\frac{s}{e\gamma}\right)^{\frac{s}{\gamma}}\left(1 + \mathop{\mathcal{O}}_{s\to\infty}\left(\frac{1}{s}\right)\right) = K\sqrt{2\pi\gamma}\, s^{-\frac{1}{2}}\, e^{\frac{s}{\gamma}(\log s - 1 - \log A)}$$

Since $G(s+\gamma)$ is strictly positive for $s \in (-\gamma, +\infty)$ we deduce that for $s \in [1, \infty)$ we can define $K_0(s)$ by

$$K_0(s) := 1 + \frac{G(s)(2-s)}{\alpha\gamma G(s+\gamma)}, \qquad 1 \leq s < +\infty.$$

$$K_0(s) := \int_0^1 x^{s-1} k_0(x)dx = \int_0^\infty e^{-sy}\mathcal{K}(y)dy = \hat{\mathcal{K}}(s)$$

The Mellin transform K_0 can be interpreted as a Laplace transform $\hat{K}$ of the function $\mathcal{K}(y) := k_0(e^{-y})$ with $y \in (0, +\infty)$, (if k_0 is diffuse) or of the pushforward $T\#k_0$ of k_0 by a function T .

Using the uniqueness property of the Laplace transform for measures , we conclude that this defines uniquely $\mathcal{K}$ and thus k_0.

We have a constructive way to determine γ and α, but not k_0.

Idea : Define its Mellin transform using the fomula

$$K_0^{\mathrm{est}} := 1 + \frac{(2-s)G(s)}{\alpha\gamma G(s+\gamma)}, \qquad \Re(s) \geq 2 \tag{3}$$

To define k_0 from this formula, 2 points need to be solved:

- be allowed to divide by $G(s+\gamma)$, *i.e.* prove that G does not cancel at least on a vertical strip of the complex plane,
- be allowed to define the inverse Mellin transform of K_0^{est}, and prove that this corresponds to the original k_0.

Theorem

Suppose that $g \in \cap_{k=1}^{\infty} L^1(x^k dx) \cap L^1_{loc}(0,\infty)$ is the unique solution of the stationary equation for some given parameters α and γ and where k_0 is a non negative measure, compactly supported in $[0,1]$. Let $G(s)$ be the Mellin transform of the function g . Then, there exists $s_0 > 0$ such that

$$(i) \quad |G(s)| \neq 0, \ \ \forall s \in \mathbb{C}; \ \Re e(s) \in [s_0, s_0+\gamma],$$

$$(ii) \quad K_0(s) = 1 + \frac{(2-s)G(s)}{\alpha\gamma G(s+\gamma)}, \ \ \textit{for } \Re e(s) = s_0$$

$$(iii) \quad k_0(x) = \frac{1}{2i\pi} \int\limits_{\Re e(s)=s_0} x^{-s} \left(1 + \frac{(2-s)G(s)}{\alpha\gamma G(s+\gamma)}\right) ds.$$

Remark: In the point (*iii*) of this Theorem, the formula of the inverse Mellin transform has to be taken in a generalized sense, since under our assumptions we only have K_0 bounded.

Direct problem. Goal : check that G does not cancel.

Based on the Wiener-Hopf method, we can exhibit an explicit solution to the functional equation

$$\boxed{G(s+\gamma) = \Phi(s)G(s), \qquad \Phi(s) = \frac{2-s}{\alpha\gamma(K_0(s)-1)},\ G(2) = \rho.} \qquad (4)$$

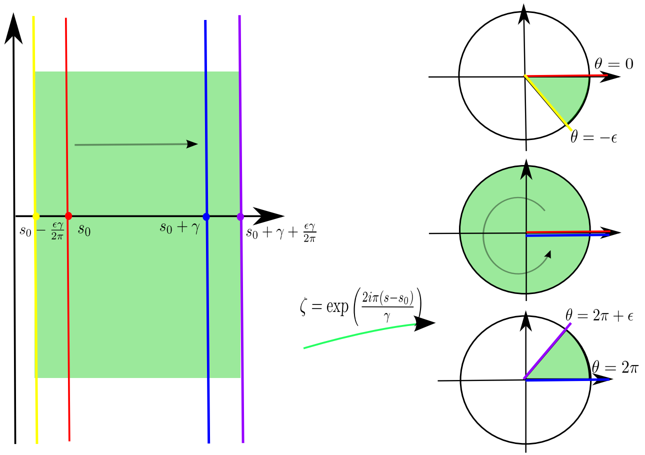
Useful to

- check that the Mellin transform G of the function g never cancels,
- provide estimates on the inverse problem and derive a stability result.

Not useful to

- invert the problem, and to get the parameters from the solution.

$\boxed{1.}$ Transform the strip $\{z \in \mathbb{C} \mid s_0 - \varepsilon\frac{\gamma}{2\pi} < Im(z) < s_0 + \gamma + \varepsilon\frac{\gamma}{2\pi}\}$ into $D(\varepsilon)$



We denote by $\quad F(\zeta) = G(s), \qquad \tilde{\varphi}(\zeta) = \Phi(s), \qquad \zeta \in \mathbb{C} \setminus \mathbb{R}^+,$

$\boxed{2.}$ **Change of variable** to obtain a "typical" Carleman equation (additive),

$$P(x - i0) = \log(\varphi(x)) + P(x + i0), \qquad x \in \mathbb{R}^+.$$

we look for a solution of the shape

$$F(\zeta) = \exp(P(\zeta)), \qquad \zeta \in \mathbb{C} \setminus \mathbb{R}^+.$$

$\boxed{3.}$ **A candidate.** The function P is analytic in $\mathbb{C} \setminus \mathbb{R}^+$ and its jump through the half-line $\mathbb{R}^+$ is determined by the Carleman equation. A candidate for the function P is the function

$$P(\zeta) = -\frac{1}{2i\pi} \int_0^{+\infty} \log(\varphi(w)) \Big\{ \frac{1}{w - \zeta} - \frac{1}{w+1} \Big\} \, dw, \qquad \zeta \in \mathbb{C} \setminus \mathbb{R}^+.$$

(Plemelj -Sokhostky formula)

$\boxed{4.}$ **Back to F and G**

$$\overline{F}(\zeta) = \exp\Big(- \frac{1}{2i\pi} \int_0^{+\infty} \log(\varphi(w)) \Big\{ \frac{1}{w - \zeta} - \frac{1}{w+1} \Big\} \, dw \Big) \rightsquigarrow \overline{G}. \qquad (5)$$

$\boxed{5.}$ **Check** that $\overline{G} \equiv G$.

Both functions $\overline{G}$ and $G =$ the Mellin transform of g are analytic and satisfy the functional equation, but nothing guarantees that $G = \overline{G}$.
Indeed, for $\Phi(s) = s$ and $\gamma = 1$, the functions

$$s \mapsto \frac{1}{2}\Gamma(s) \quad \text{and} \quad s \mapsto \frac{1}{2}\Gamma(s)\Big[1 + \sin(2\pi s)\Big]$$

are two distinct solutions. The first one never cancels whereas the second one does.

$\rightsquigarrow$ We first prove that the inverse Mellin transform of $\widetilde{G}$, that we denote $\tilde{g}$, is a function, with suitable integrability properties on $(0, \infty)$.
We then use a uniqueness result for the solutions of the stationary fragmentation equation.

Lemma

The function $P(\zeta)$ defined for all $\zeta \in D(0)$ by

$$P(\zeta) = -\frac{1}{2i\pi} \int_0^{+\infty} \log(\varphi(w)) \Big\{ \frac{1}{w-\zeta} - \frac{1}{w+1} \Big\} \, dw$$

and can analytically be extended on the whole Riemann surface S, its unique analytic continuation satisfying the equation

$$P(x - i0) = \log(\varphi(x)) + P(x + i0), \qquad x \in \mathbb{R}^+.$$

Moreover, the analytical continuation of P (which we will denote by P as well) on S has a simple expression

$$P(\zeta) = P(\tilde{\zeta}) + \frac{k}{2} \log(\varphi(|\zeta|)), \qquad \arg(\zeta) \in (2k\pi, 2(k+1)\pi), \ k \in \mathbb{Z},$$

where $\tilde{\zeta} \in D(0), \ |\zeta| = |\tilde{\zeta}|, \ \arg(\tilde{\zeta}) \equiv \arg(\zeta) \mod (2\pi)$.

We deduce that the function

$$F(\zeta) = \exp\left(P(\zeta)\right)$$

given by

$$F(\zeta) = \exp\Big(-\frac{1}{2i\pi}\int_0^{+\infty} \log(\varphi(w))\Big\{\frac{1}{w-\zeta} - \frac{1}{w+1}\Big\}\,dw\Big), \qquad \zeta \in D(0),$$

can be analytically continued in S, from where we get (undo change of variable):
For any $s_0 > 2$ and $\varepsilon > 0$ such that $s_0 - \frac{\gamma\varepsilon}{\pi} > 2$, define the complex valued function $\tilde{G}$ for $\Re e(s) \in (s_0, s_0+\gamma)$

$$\widetilde{G}(s) = \exp\left(-\frac{1}{\gamma}\int_{\Re e(\sigma)=s_0} \log\left(\Phi(\sigma)\right)\left\{\frac{1}{1-e^{2i\pi\frac{s-\sigma}{\gamma}}} - \frac{1}{2+e^{2i\pi\frac{s_0-\sigma}{\gamma}}}\right\} d\sigma\right),$$

For $s_0 - \frac{\varepsilon\gamma}{2\pi} > 2$, both functions $\widetilde{G}$ and G are analytic on $\Big\{s \in \mathbb{C}; \quad \Re e(s) \in (s_0 - \frac{\varepsilon\gamma}{2\pi}, s_0 + \frac{(2\pi+\varepsilon)\gamma}{2\pi})\Big\}$ and satisfy the functional equation, (but nothing guarantees yet that $G = \tilde{G}$).

Theorem

Let g be the solution to the stationary equation (1), and $\widetilde{G}$ the function we just defined for $s_0 > 2+\gamma$. Then

$$g(x) = \frac{1}{2i\pi}\int_{\Re e(s)=u} \widetilde{G}(s)x^{-s}ds,\ \forall u > s_0.$$

Lemma

The inverse Mellin transform of $\widetilde{G}$ defined in a generalized sense as

$$\widetilde{g}(x) = \frac{1}{2i\pi}\int_{\Re e(s)=u} \widetilde{G}(s)x^{-s}ds$$

for $u \in \left(s_0 - \frac{\varepsilon\gamma}{2\pi}, s_0 + \frac{(2\pi+\varepsilon)\gamma}{2\pi}\right)$, satisfies $g \in L^1((x+x^{\gamma+1}))$.

Lemma

The function $\tilde{g}$ defined above satisfies the stationary fragmentation equation.

1. The integral is convergent

- Since $\widetilde{G}$ is analytic, for all $x > 0$ and $u \in (s_0 - \frac{\varepsilon\gamma}{2\pi}, s_0 + \gamma + \frac{\varepsilon\gamma}{2\pi})$ fixed, the function $|\widetilde{G}(u+iv)x^{-u-iv}|$ is locally integrable with respect to v.
- We prove that for s_0 large enough, and $\zeta \in \mathbb{C} \setminus \mathbb{R}^+$:

$$\log(\widetilde{\varphi}(\zeta)) = \log|\log|\zeta|| + \mathcal{O}(1), \quad \text{for} \quad |\zeta| \to 0^+ \text{ or } |\zeta| \to \infty.$$

and that as $|\zeta| \to \infty$ or $|\zeta| \to 0$.

$$-\Im m(I(\tilde{\zeta})) = -\Im m(\int_0^\infty \log|\log w| \left(\frac{1}{w-\tilde{\zeta}} - \frac{1}{w+2}\right) dw = -\log|\log(|\zeta|)| \, (\pi - \theta) + \mathcal{O}(1).$$

We have then, as $|\zeta| \to \infty$ or $|\zeta| \to 0$:

$$\begin{aligned}
|F(\zeta)| &= \left| \exp\left(-\frac{1}{2i\pi} I(\tilde{\zeta}) + \frac{k}{2} \log\left(\varphi(|\zeta|)\right) + \mathcal{O}(1) \right\} \right) \Big| \\
&= \exp\left(-\frac{1}{2\pi} \Im m(I(\zeta)) + \frac{k}{2} \Re e\left(\log(\varphi(|\zeta|))\right) + \mathcal{O}(1) \right). \\
&= \exp\left(-\log|\log|\zeta|| \frac{\pi - \theta - 2k\pi}{2\pi} + \mathcal{O}(1) \right)
\end{aligned}$$

We deduce that for ζ such that $\theta \in (0, \pi)$ and $k \leq 0$,

$$|F(\zeta)| = o(1), \text{ as } |\zeta| \to 0 \text{ and } |\zeta| \to \infty.$$

Thus, for all $u \in (s_0 - \frac{\varepsilon\gamma}{2\pi}, s_0 + \frac{\gamma}{2})$ fixed: $|\widetilde{G}(s)| = o(1)$, as $|\Im m(s)| \to \infty$, $\Re e(s) = u$.

2. $\tilde{g}$ can be defined.
The function $\widetilde{G}$ is analytic in the strip $\Re e(s) \in (s_0 - \frac{\varepsilon\gamma}{2\pi}, s_0 + \frac{(2\pi+\varepsilon)\gamma}{2\pi})$ and bounded as $|s| \to \infty$ for $\Re e(s) \in (s_0 - \frac{\varepsilon\gamma}{2\pi}, s_0 + \frac{\gamma}{2})$. Its inverse Mellin transform $\widetilde{g}$ is then uniquely defined as a distribution on $(0, \infty)$ where u may take any value in the interval $(s_0 - \frac{\varepsilon\gamma}{2\pi}, s_0 + \frac{\gamma}{2})$

3. The regularity of $\tilde{g}$.

- **The choice of u.** Let us assume $u < s_0$. Then, there is $b > 1$ such that

$$|F(\zeta)| \le Ce^{-\frac{b\pi}{2\pi}\log(\log|\zeta|)}, \ |\zeta| \to 0, \ |\zeta| \to \infty, \quad |\widetilde{G}(u+iv)| \le C|v|^{-\frac{b}{2}}, \ |v| \to \infty,$$

This shows that for any $u < s_0$ the function $\widetilde{G}_u(v) : v \to \widetilde{G}(u+iv)$ is such that $\widetilde{G}_u \in L^2(\mathbb{R})$. It follows that its Fourier transform also belongs to $L^2(\mathbb{R})$: Using the change of variables $z = \log x$,

$$\begin{aligned}\int_{-\infty}^{\infty}\left|\int_{-\infty}^{\infty}\widetilde{G}(u+iv)e^{-ivz}dv\right|^2 dz &= \int_{-\infty}^{\infty}\left|\int_{-\infty}^{\infty}\widetilde{G}(u+iv)e^{-iv\log x}dv\right|^2 \frac{dx}{x}\\ &= \int_{-\infty}^{\infty}\left|\int_{-\infty}^{\infty}\widetilde{G}(u+iv)x^{-\frac{1}{2}-iv}dv\right|^2 dx.\end{aligned}$$

Then, since

$$\widetilde{g}(x) = \frac{1}{2\pi}\int_{v=-\infty}^{v=\infty}\widetilde{G}(u+iv)x^{-(u+iv)}dv = ix^{-u}\int_{-\infty}^{\infty}\widetilde{G}(u+iv)x^{-iv}dv,$$

$$|\tilde{g}(x)| = x^{-u+\frac{1}{2}}\left|\int_{-\infty}^{\infty}\widetilde{G}(u+iv)x^{-\frac{1}{2}-iv}dv\right|.$$

Hence $\tilde{g}(x)x^{u-\frac{1}{2}} \in L^2_x$ as soon as $u < s_0$.

• **The choice of ε.**
Asymptotic behavior of $\tilde{g}$ around $x = +\infty$.

$$\int_1^\infty x^{1+\gamma}|\tilde{g}(x)|dx = \int_1^\infty x^{1+\gamma-u+\frac{1}{2}} \left|\int_{-\infty}^\infty \widetilde{G}(u+iv)x^{-\frac{1}{2}-iv}dv\right| dx$$
$$\leq \left(\int_1^\infty \left|\int_{-\infty}^\infty \widetilde{G}(u+iv)x^{-\frac{1}{2}-iv}dv\right|^2 dx\right)^{1/2} \left(\int_1^\infty x^{2(1+\gamma-u)+1}dx\right)^{1/2},$$

the last integral in the right hand side being convergent whenever $2+\gamma < u$ i.e. whenever we choose s_0 such that

$$2+\gamma < u < s_0.$$

Asymptotic behavior of $\tilde{g}$ around $x = 0$.
Same king of computaion leads to the condition $u < 2$, then we need to choose $u \in (s_-, 2)$.
To be allowed to take $u \in (s_-, 2)$ with $2+\gamma < s_0$, we need to impose that ε satisfies

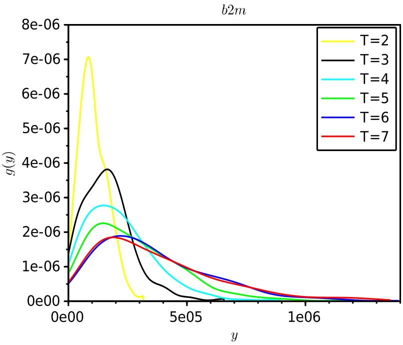
$$2 > u > s_0 - \frac{\varepsilon\gamma}{2\pi} > 2+\gamma - \frac{\varepsilon\gamma}{2\pi}, \qquad \text{i.e.} \qquad \varepsilon > 2\pi.$$

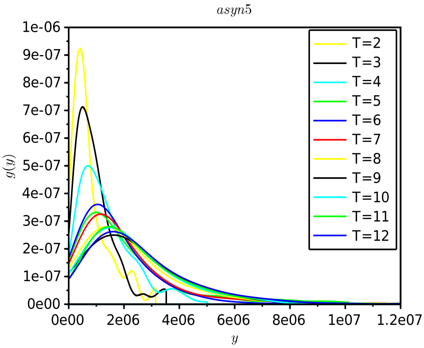
Conclusion of the theoretical part

- We provided a first theoretical ground to the question of estimating the function parameters of a pure fragmentation equation from its solution.
- We proved two main results: 1.uniqueness for the fragmentation rate and kernel, and 2. a reconstruction formula for the fragmentation kernel based on the Mellin transform of the equation.
- The most delicate point lies in the proof of the reconstruction formula. This requires to prove that the Mellin transform of the asymptotic profile does not vanish on a vertical strip of the complex plane
- **Future work:** Stability of the reconstruction formula needs to be studied in an adapted space, and this inverse problem appears as severely ill-posed, as most problems of deconvolution type.

1. Introduction: The fragmentation equation
2. Fragmentation of fibrils: A new experiment
3. Uniqueness and Reconstruction formula for the inverse problem
4. Numerical simulations and application to real data

After a sufficiently long time, a proper rescaling of the distribution of fibrils gives rise to a steady profile, shrinking in size as a power of the time.
We use this steady behaviour to estimate the three parameters γ, α and k_0 characterising the breakage.





Determination of γ

The Mellin transform of f (or the moment of order s)

$$M(t,s) = M[f(t,.)](s+1) = \int_0^\infty x^s f(t,x)dx.$$

Assuming that the distribution f has reached equilibrium for a given time t, i.e.

$$f(t,x) = t^{2/\gamma} g(t^{1/\gamma} x)$$

for a some g and γ, Then, there exists a constant C_s such that

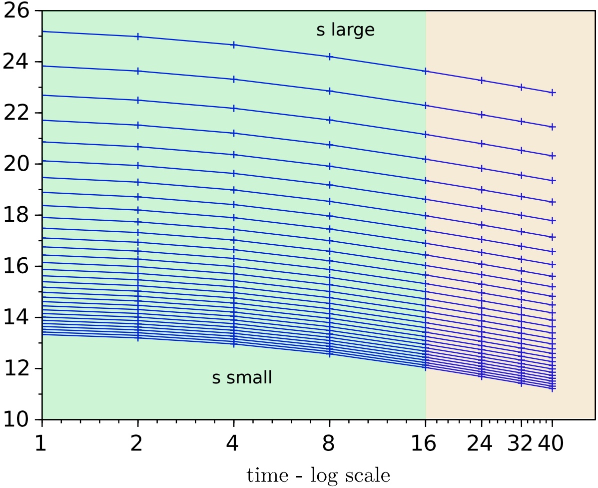
$$\log\left(M(t,s)\right) = -\frac{s}{\gamma}\log(t) + \log(C_s),$$

which means that log(M(t,s)) is expected to be linearly decreasing with respect to log(t) with a slope $-s/\gamma$. Two consequences:

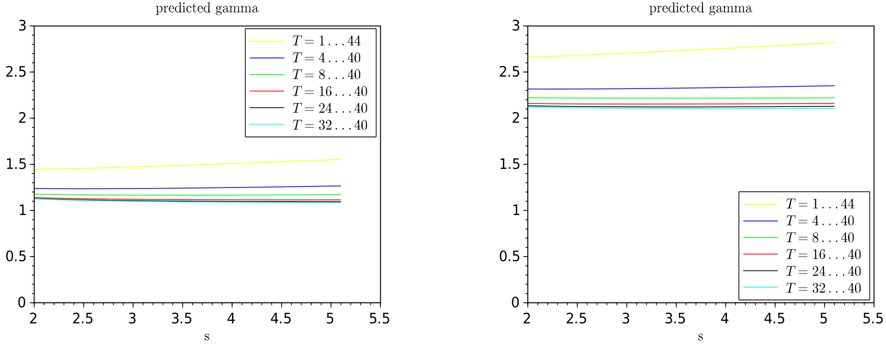
• a test for the model – does such a tendency appear in the experiments?

• in the case of a positive answer to this model test, the parameter may be calculated by estimating the slope in time of M(t,s) in a log-log scale.

Plots of the function $\log(M(s,t)$ as a function of $\log(t)$ for $s \in [1,6]$, for simulated data ($\gamma = \alpha = 1$, uniform kernel).

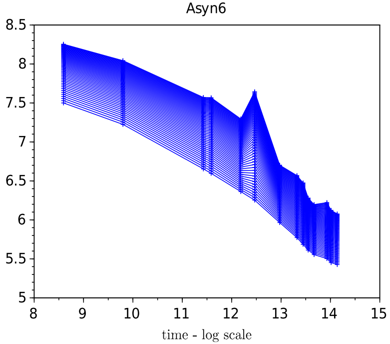


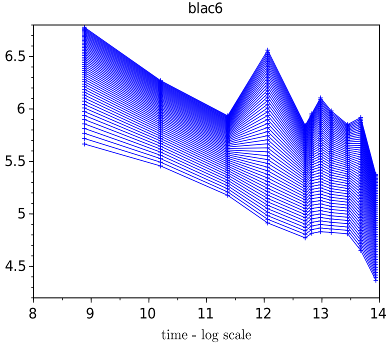
Determination of γ: Simulated data (gaussian kernel).



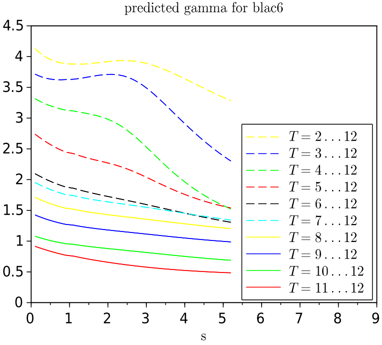
$\gamma = 1$ $\qquad\qquad$ $\gamma = 2$

Plots of the function $\log(M(s,t))$ as a function of $\log(t)$ for $s \in [1,6]$.

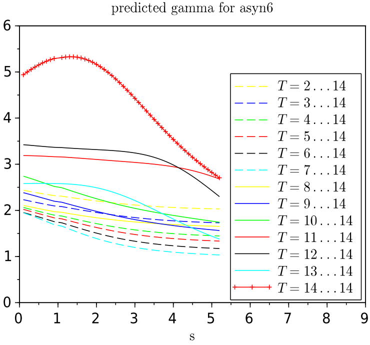




Data are noisy: Should we take into account all the data points to predicts γ?



β-lactamase



α-synuclein

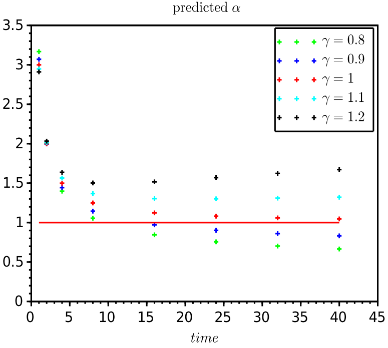
Need to set up a protocol to determine which data points we take intoo account:

- Early data points not relevant: equilibrium may not be reached
- Very late data points not relevant?
- Late data points more relevant since the protein sample is larger?

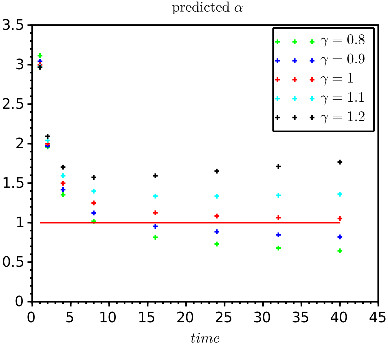
The value for α is directly obtained as a function of γ and G (which depends on γ) by using $K_0(1) = 2$

$$\alpha_{est} = \frac{G(1)}{\gamma_{est}\, G(1+\gamma_{est})}.$$

.

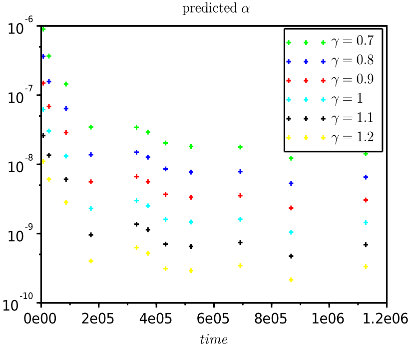


Uniform kernel

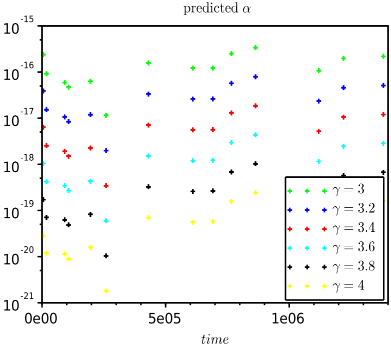


Gaussian kernel

Determination of α: Real data



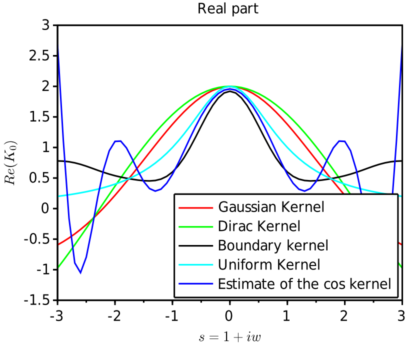
β-lactamase



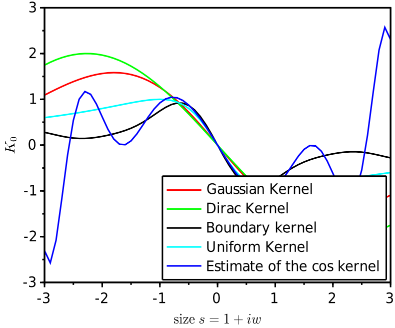
α-synuclein

- The value of α is very sensitive to the value of γ ($B(x) = \alpha x^{\gamma}$)
- Not a problem since the value of α does not impact the value of k_0

$$K_0^{est}(s) = 1 + \frac{(2-s)G(s)}{\alpha_{est}\gamma_{est}G(s+\gamma_{est})}, \quad Re(s) > 2, \quad k_0^{est}(x) = \frac{1}{2\pi}\int_{u-i\infty}^{u+i\infty} K_0^{est}(s)x^{-s}ds.$$



Real part

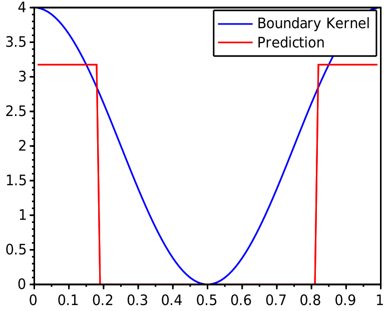


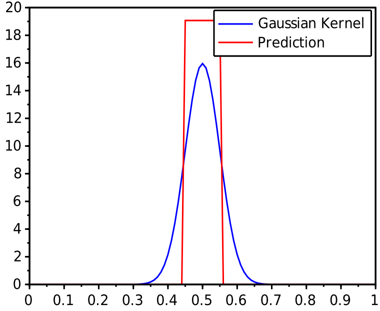
Imaginary part

$\rightsquigarrow$ Complicated to estimate k_0 using the Mellin inverse formula.

Questions of interest Does k_0 charge the boundaries, or the center of the fibrils? If the center is more likely to break apart, what is the spread of the gaussian?

What we do Assume $k_0^{a,b,\eta}(x) = a\mathbf{1}_{[\eta,1-\eta]} + b\mathbf{1}_{([0,\eta]\cup[1-\eta,\eta])}$, and find a, b and η such that $\|K_0^{est} - K_0^{a,b,\eta}\|_{L^2(1+i[-1,1])}$ is minimal.





Result for real data: For all the proteins tested, $k_0 = \delta_{1/2}$.

We assume that an estimation γ_ε and α_ε of the parameters γ and α were obtained with an error of the order of ε.

We denote by $k_{0,\varepsilon}$ the estimation for k_0 we obtain from a perturbation of the profile g_ε and the parameters γ_ε and α_ε, i.e. such that

$$K_{0,\varepsilon}(s) = 1 + \frac{G_\varepsilon(s)(2-s)}{\alpha\gamma G_\varepsilon(s+\gamma)}, \qquad s \in \mathbb{C}, \qquad k_{0,\varepsilon}(x) = M_{app}^{-1}[K_{0,\varepsilon}].$$

Question: Can we estimate $\|k_{0,\varepsilon} - k_0\|$?