Mathematical Modelling of the protein fragmentation experiment

Noise model:

At time $t$, we measure $x_1, \cdots x_n$ an i.i.d. sample of density $n(t, x)$

Model for $n(t, x)$: the fragmentation equation

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

Evol. of number of polymers

Death

Creation

Measurement: at different times $t_i$, a (noisy) $n(t_i, x)$ provided by samples $x_1(t_i), \cdots x_n(t_i)(t_i)$

Unknowns: the non-parametric functions $B(x)$ (fragmentation rate) and $k(y, x)$ (fragmentation kernel)
The pure fragmentation equation: basic properties

"Fragmentation conserves the mass": \( \forall B(\cdot)n(t, \cdot) \in L^1(xdx) : \)

\[
\int_0^\infty xB(x)n(t, x)dx = \int_0^\infty \int_x^\infty xk(y, x)B(y)n(t, y)dydx
\]

The fragmentation kernel \( k(y, x) \) must satisfy

- \( y \to k(y, \cdot) \) nonnegative measure with \( \text{Supp}(k(y, \cdot)) \subset [0, y] \) (and \( \forall \psi \in C^0, y \to \int \psi(x)k(y, dx) \) is Lebesgue-measurable)

- mass conservation
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► mass conservation \( \implies \int_0^y xk(y, dx) = y \)

► If binary fragmentation:
The pure fragmentation equation: basic properties

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The fragmentation kernel \( k(y, x) \) must satisfy

\[ y \rightarrow k(y, \cdot) \text{ nonnegative measure with } \text{Supp}(k(y, \cdot)) \subset [0, y] \]

(and \( \forall \psi C^0, y \rightarrow \int \psi(x)k(y, dx) \) is Lebesgue-measurable)

\[ \text{mass conservation } \implies \int_0^y xk(y, dx) = y \]

\[ \text{If binary fragmentation: } \implies k(y, x) = k(y, y-x) \text{ (may be relaxed); with the mass conservation it implies } \int_0^y k(y, dx) = 2 \]

Self-similar fragmentation: \( k(y, x) := \frac{2}{y}k_0(\frac{x}{y}), \) with \( \text{Supp}(k_0) \subset [0, 1] . \)

2 main examples: uniform \( k_0(z) \equiv 2, \) equal mitosis \( k_0(z) = 2\delta_{z=\frac{1}{2}}. \)
Models: Branching processes modeling
see Meyn & Tweedie, 1993 and M.H.A. Davis, 1993

Piecewise Deterministic Markov Processes (PDMP):

- start: a single cell of size $x_0$.
- cell’s growth: deterministic.
- at each time, it has an instantaneous probability rate $B$ to divide (jump); $B$ depends on size $x$ or age $a$ of the cell.
- At division, two offspring of age 0 and initial size $x_1/2$, where $x_1$ is the size of the mother at division.
- The two offspring start independent growth (Markov property) according to the (deterministic) rate $\kappa$ and divide according to the (probabilistic) rate $B$. 
Genealogical tree: infinite random marked tree

\[ \mathcal{U} = \bigcup_{n=0}^{\infty} \{0, 1\}^n \text{ with } \{0, 1\}^0 := \emptyset. \]

To each node \( u \in \mathcal{U} \), we associate a cell with size at birth \( \xi_u \) and lifetime \( \zeta_u \).

If \( u^- \) denotes the parent of \( u \) then

\[ \xi_u = \frac{\xi_{u^-}}{2} \exp \left( \kappa \zeta_{u^-} \right). \]
3. Models: From probability back to PDE...

Equivalent view: Piecewise Deterministic Markov Process (PDMP): To each cell labeled by $u \in \mathcal{U}$, we associate a birth time $b_u$. $X(t) = (X_1(t), X_2(t), \ldots)$ process of the sizes of the population at time $t$, or $A(t) = (A_1(t), A_2(t), \ldots)$ of ages at time $t$. $X(t)$ has values in the space of finite point measures on $\mathbb{R}_+ \setminus \{0\}$ via

$$M_{X(t)} = \sum_{i=1}^{\#X(t)} \delta_{X_i(t)}, \quad M_{A(t)} = \sum_{i=1}^{\#A(t)} \delta_{A_i(t)}$$

Branch tree case: always 1 and only 1 Dirac mass $\delta_{X_i(t)}$, with $i =$ number of divisions till time $t$. 
3. Age model: renewal process and renewal equation

\[ P(\zeta_u \geq a) = e^{-\int_0^a B(s)ds} \]

Set, for (regular compactly supported) \( f \)

\[ \langle n(t, \cdot), f \rangle := \mathbb{E} \left[ \sum_{i=1}^{\infty} f(A_i(t)) \right]. \]

In a weak sense:

\[ \partial_t n(t, a) + \partial_a n(t, a) = -B(a)n(t, a), \]

\[ n(t, 0) = 2 \int_0^{\infty} B(a)n(t, a)da \quad \text{OR} \quad n(t, 0) = \int_0^{\infty} B(a)n(t, a)da \]

So the mean empirical distribution of \( A(t) \) satisfies the deterministic renewal equation.
3. Size model: growth-fragmentation process or equation

\[ \mathbb{P}(\zeta_u \geq a | \xi_u = x) = e^{-\int_0^a B(x e^{\kappa s}) ds} \]

Set, for (regular compactly supported) \( f \)

\[ \langle n(t, \cdot), f \rangle := \mathbb{E} \left[ \sum_{i=1}^{\infty} f(X_i(t)) \right] \]

Proof: tagged fragment approach (Bertoin, Haas, ...), many-to-one formula (Bansaye et al, 2009, Cloez, 2011, Bertoin & Watson, 2019...)

We have (in a weak sense) IF we keep the 2 daughters at each generation:

\[ \partial_t n(t, x) + \partial_x(\kappa x n(t, x)) + B(x) n(t, x) = 4B(2x) n(t, 2x) \]

So the mean empirical distribution of \( X(t) \) satisfies the deterministic growth-fragmentation / size-structured / cell division equation (with binary fission and equal mitosis).
3. Size model: growth-fragmentation process or equation

\[ \mathbb{P}(\zeta_u \geq a | \xi_u = x) = e^{-\int_0^a B(xe^{\kappa s})ds} \]

Set, for (regular compactly supported) \( f \)

\[ \langle n(t, \cdot), f \rangle := \mathbb{E} \left[ \sum_{i=1}^{\infty} f(X_i(t)) \right]. \]

Proof: tagged fragment approach (Bertoin, Haas, ...), many-to-one formula (Bansaye et al, 2009, Cloez, 2011, Bertoin & Watson, 2019...)

We have (in a weak sense) IF we keep 1 daughter at each generation:

\[ \partial_t n(t, x) + \partial_x (\kappa x \ n(t, x)) + B(x)n(t, x) = 2B(2x)n(t, 2x). \]

So the mean empirical distribution of \( X(t) \) satisfies a deterministic conservative growth-fragmentation equation (also encountered e.g. for TCP/IP protocol)
3. Age and Size model: PDE

\( n(t, a, x) \) density of cells of size \( x \) and age \( a \).

PDE obtained from the PDMP (as previously) or by a mass balance:

\[
\frac{\partial}{\partial t} n + \frac{\partial}{\partial a} n + \frac{\partial}{\partial x} (\kappa x n) = -B(a, x) n(t, a, x),
\]

\[
n(t, a = 0, x) = 4 \int_0^\infty B(a, 2x) n(t, a, 2x) da
\]

with \( n(0, a, x) = n^{(0)}(a, x), \ x \geq 0. \)

IF \( B = B(x) \) : back to growth-fragmentation equation

IF \( B = B(a) \) : back to renewal equation

IF we keep only 1 daughter at each generation: the boundary condition becomes:

\[
n(t, a = 0, x) = 2 \int_0^\infty B(a, 2x) n(t, a, 2x) da
\]
3. A Specific Age and Size model: the ”adder model”

\(n(t, a, x)\) density of cells of size \(x\) and increment \(a\).

Definition of an increment: difference between size and size at birth.

\[P(\zeta u \geq a) = e^{-a \int B(s) \, ds},\]
\[\frac{d}{dt}n = \kappa x \frac{\partial}{\partial t} n + \frac{\partial}{\partial a} \left( \kappa x n \right) + \frac{\partial}{\partial x} \left( \kappa x n \right) = -\kappa x B(a) n(t, a, x),\]
\[n(t, a = 0, x) = \int_0^\infty B(a) n(t, a, 2x) \, da\]

If we keep only 1 daughter at each generation: the boundary condition becomes:

\[n(t, a = 0, x) = \int_0^\infty B(a) n(t, a, 2x) \, da\]
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\( n(t, a, x) \) density of cells of size \( x \) and increment \( a \).
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PDE obtained from the PDMP (as previously): same as the age process:

\[
P(\zeta_u \geq a) = e^{-\int_0^a B(s) \, ds},
\]

IF we keep only 1 daughter at each generation: the boundary condition becomes:

\[
n(t, a = 0, x) = \int_0^\infty x B(a) \, \int_0^a B(s) \, ds,\]

3. A Specific Age and Size model: the ”adder model”

\( n(t, a, x) \) density of cells of size \( x \) and \textit{increment} \( a \).

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PDE obtained \textit{from the PDMP (as previously)}: same as the age process:

\[
\mathbb{P}(\zeta_u \geq a) = e^{-\int_{0}^{a} B(s) \, ds}, \quad \frac{da}{dt} = \kappa x
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3. A Specific Age and Size model: the "adder model"

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\[
\mathbb{P}(\zeta_u \geq a) = e^{-\int_0^a B(s)ds}, \quad \frac{da}{dt} = \kappa x
\]

\[
\frac{\partial}{\partial t} n + \frac{\partial}{\partial a} (\kappa x n) + \frac{\partial}{\partial x} (\kappa x n) = -\kappa x B(a)n(t, a, x),
\]

\[
n(t, a = 0, x) = 8 \int_0^{\infty} x B(a, 2x)n(t, a, 2x)da
\]

IF we keep only 1 daughter at each generation: the boundary condition becomes:

\[
n(t, a = 0, x) = 4 \int_0^{\infty} x B(a)n(t, a, 2x)da
\]
Fourth step: model analysis: long-time behaviour
The age model


historically the first structured-population model to be studied (Kermack and Mc Kendrick, 1927 ; Metz and Diekmann, 1981)

\[ n(t, a)e^{-\lambda t} \rightarrow N(a), \text{ with } \lambda \text{ and } N \text{ uniquely determined by} \]

\[
\frac{\partial}{\partial a} N + \lambda N = -B(a)N, \quad N(0) = 2 \int_0^\infty B(a)N(a)da.
\]

Explicit solution: \( N(a) = N(0)e^{-\lambda a - \int_0^a B(s)ds} \),

\( \lambda \) uniquely determined by the boundary condition:

either \( \lambda = 0 \) (1 branch case) or

\[
2 \int_0^\infty B(a)e^{-\lambda a - \int_0^s B(s)ds} da = 1
\]
The fragmentation and growth-fragmentation equations

General form

From a probability viewpoint:

\[ \frac{\partial}{\partial t} n(t, dx) + \frac{\partial}{\partial x} (\tau(x)n(t, dx)) = \]

\[ -B(x)n(t, dx) + \sum_{j \geq 0} jp(j) \int_{y=x}^{\infty} B(y)n(t, y)P^{(j)}(dy, dx), \]

in a weak sense (for measure solutions: see e.g. (Canizo, Carrillo, Cuadrado, 2013); (MD, Gwiazda, Wiedemann, 2018))

\(P^{(j)}(x, dy)\): probability of an individual of size \(x\) to split in \(j\) parts, one of them of size \(y\). In a more compact way:

\[ k(y, dx) := \sum_{j \geq 0} jp(j)P^{(j)}(y, dx), \quad \text{with} \]

\[ \int_x^y xk(y, dx) = \sum_{j \geq 0} p(j) \int_0^y jxP^{(j)}(y, dx) = y \sum_{j \geq 0} p(j) = y. \]
The fragmentation and growth-fragmentation equations

General form

\[
\frac{\partial}{\partial t} n(t, dx) + \frac{\partial}{\partial x} \left( \tau(x)n(t, dx) \right) = -B(x)n(t, dx) + \int\limits_{y=x}^{\infty} B(y)n(t, y)k(dy, dx),
\]

with

\[
\int\limits_{0}^{y} xk(y, dx) = y, \quad \int\limits_{0}^{y} k(y, dx) = m > 1.
\]

"One branch" process: \( k_1(y, dx) := \frac{1}{m} \sum_{j \geq 0} jp(j)P^{(j)}(y, dx) \) with \( m = \sum_{j \geq 0} jp(j) : \)

\[
\frac{\partial}{\partial t} n_1(t, dx) + \frac{\partial}{\partial x} \left( \tau(x)n_1(t, dx) \right) = -B(x)n_1(t, dx) + \int\limits_{y=x}^{\infty} B(y)n_1(t, y)k_1(dy, dx).
\]
The growth-fragmentation equation

Two fundamental relations
(and more generally: moments equations)

- First moment: mass balance only evolves by growth
  \[
  \frac{d}{dt} \int xn(t, x)dx = \int \tau(x)n(t, x)dx.
  \]

- Zeroth moment: number of individuals only evolves by fragmentation:
  \[
  \frac{d}{dt} \int n(t, x)dx = \int B(x) \left( \int_0^x k(x, dy) - 1 \right) n(t, x)dx.
  \]
The growth-fragmentation equation

Two fundamental relations
(and more generally: moments equations)

- First moment: mass balance only evolves by growth
  \[
  \frac{d}{dt} \int x n(t, x) \, dx = \int \tau(x) n(t, x) \, dx.
  \]

- Zeroth moment: number of individuals only evolves by fragmentation:
  \[
  \frac{d}{dt} \int n(t, x) \, dx = \int B(x) \left( \int_0^x k(x, dy) - 1 \right) n(t, x) \, dx.
  \]

- More generally: balance between growth & fragmentation
  \[
  \frac{d}{dt} \int_0^\infty x^p n(t, x) \, dx = \int_0^\infty px^{p-1} \tau(x) n(t, x) \, dx
  \]
  \[
  + \int_0^\infty B(x)x^p \left( 1 - \int_0^x \frac{y^p}{x^p} k(x, dy) \right) n(t, x) \, dx
  \]
Asymptotic behaviour 1: balance assumption on $\tau(x)$ and $B(x)$: \[ \Rightarrow \] convergence to a steady profile $+$ exponential growth starts in the 1980s (Diekmann, Heijmans, Thieme and Gyllenberg & Webb)

\[ n(t, x)e^{-\lambda t} \rightarrow N(x) \int n^0(x)dx \]

$(N, \lambda)$ : dominant eigenpair of the semi-group generator $L^* + F^*$. For compact strictly positive operators: Krein-Rutman.
Long-time asymptotics 1: steady growth

Eigenvalue problem and adjoint problem:

\[
\begin{cases} 
\frac{\partial}{\partial x} (\tau(x)N(x)) + \lambda N(x) = -B(x)N(x) + \int_x^\infty B(y)k(x, y)N(y)dy, \\
\tau N(x = 0) = 0, \quad N(x) \geq 0, \quad \int_0^\infty N(x)dx = 1, \\
-\tau(x)\frac{\partial}{\partial x} (\phi(x)) + \lambda \phi(x) = B(x)(-\phi(x) + \int_0^x k(y, x)\phi(y)dy), \\
\phi(x) \geq 0, \quad \int_0^\infty \phi(x)N(x)dx = 1.
\end{cases}
\]

(1)

If \( \tau(x) = x^\nu, \ B(x) = x^\gamma \): if \( 1 + \gamma - \nu > 0 \) (Michel, M3AS, 2004)

which optimal assumptions on \((\tau, k, B)\) ?
1. Long-time asymptotics

Theorem (MD, P. Gabriel, 2010)

Under balance assumptions on $\tau$, $B$ and $k$, there exists a unique triplet $(\lambda, N, \phi)$ with $\lambda > 0$, solution of the eigenproblem (3) and

$$x^\alpha \tau N \in L^p(\mathbb{R}^+), \quad \forall \alpha \geq -\gamma, \quad \forall p \in [1, \infty], \quad x^\alpha \tau N \in W^{1,1}(\mathbb{R}^+),$$

$$\exists p > 0 \text{ s.t. } \frac{\phi}{1 + x^p} \in L^\infty(\mathbb{R}^+), \quad \tau \frac{\partial}{\partial x} \phi \in L^\infty_{loc}(\mathbb{R}^+).$$

(proof by ”General Relative Entropy”: Michel, Mischler, Perthame, 2004)

$$\int_{\mathbb{R}^+} |n(t, x)e^{-\lambda t} - \langle n^{(0)}, \phi \rangle N(x)|\phi(x)dx \to 0 \text{ as } t \to \infty$$

Some ideas on the proof

2 opposite dynamics:

▶ Growth ⇒ bigger and bigger ⇒ mass goes to infinity ?
▶ Fragmentation ⇒ smaller and smaller ⇒ dust formation ?
Some ideas on the proof

2 opposite dynamics:

- Growth ⇒ bigger and bigger ⇒ mass goes to infinity ?
- Fragmentation ⇒ smaller and smaller ⇒ dust formation ?

Balance: asymptotic steady profile.

- Enough growth at zero: $\frac{B(x)}{\tau(x)} \in L^1_0$
- Avoid *shattering* (0-size polymers)

\[ \exists C > 0, \gamma \geq 0 \ s.t. \quad \int_0^x k(y, \, dz) \leq \min(m, C \left(\frac{x}{y}\right)\gamma) \]

and $\frac{x^\gamma}{\tau(x)} \in L^1_0$

- Enough fragmentation at infinity: $\frac{xB(x)}{\tau(x)} \to x \to \infty \infty$

Proof:

- Regularized equation: Krein-Rutman/Perron-Frobenius
- Balance assumptions ⇒ compactness through successive moments estimates
- Uniqueness and convergence by entropy method
Some ideas on the proof

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and $\frac{x^\gamma}{\tau(x)} \in L^1_0$

▶ Enough fragmentation at infinity: $\frac{x B(x)}{\tau(x)} \to_{x \to \infty} \infty$

Proof:

▶ regularized equation: Krein-Rutman/Perron-Frobenius
▶ balance assumptions ⇒ compactness through successive moments estimates
▶ uniqueness and convergence by entropy method
Long-time asymptotics 1
Further comments on the "steady growth regime"

- Under extra assumptions, exponential convergence in some sense:

- (Mischler, Scher, 2015): spectral gap for a large class for a more restrictive norm $L^1_{\psi} \subsetneq L^1_{\phi}$
  Based on semi-group spectral analysis & a generalization of Krein-Rutman theorem
  Proof of no spectral gap in $L^1_{\phi}$
  (Bernard & Gabriel, 2017 & 2019)

- Age-Size Model: (MD, MMNP, 2007); Increment model: (Gabriel & Martin, NHM, 2019)

Other types of behaviours?