# 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

$$\underbrace{\frac{\partial n}{\partial t}(t,x)}_{\text{Evol. of number of polymers}} = \underbrace{-B(x)n(t,x)}_{\text{Death}} + \underbrace{\int_{y=x}^{y=\infty} k(y,x)B(y)n(t,y)dy}_{\text{Creation}}$$

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 $Supp\big(k(y,\cdot)\big) \subset [0,y]$ (and $\forall\ \psi\ C^0$, $y \to \int \psi(x)k(y,dx)$ is Lebesgue-measurable)
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- mass conservation $\Longrightarrow \int_0^y xk(y,dx) = y$
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- mass conservation $\implies \int_0^y xk(y,dx) = y$
- If binary fragmentation: $\implies k(y,x) = k(y,y-x)$ (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 $Supp(k_0) \subset [0,1]$.
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 singe cell of size $x_0$.
- cell's growth: deterministic.
- at each time, it has an instantaneous probabillity 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 $B$.

# 3. The probabilistic model
## see Meyn & Tweedie, 1993 and M.H.A. Davis, 1993

Genealogical tree: infinite random marked tree

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

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

$$\boxed{\xi_u = \frac{\xi_{u^-}}{2} \exp\left(\kappa \zeta_{u^-}\right).}$$

# 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 $b_u$.
$X(t) = \big(X_1(t), X_2(t), \dots\big)$ process of the sizes of the population at time $t$, or $A(t) = \big(A_1(t), A_2(t), \dots\big)$ of ages at time $t$.
$X(t)$ has values in the space of finite point measures on $\mathbb{R}_+ \setminus \{0\}$ via

$$\mathcal{M}_{X(t)} = \sum_{i=1}^{\sharp X(t)} \delta_{X_i(t)}, \qquad \mathcal{M}_{A(t)} = \sum_{i=1}^{\sharp A(t)} \delta_{A_i(t)}$$

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

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

Set, for (regular compactly supported) $f$

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

In a weak sense:

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

$$n(t,0) = 2\int_0^\infty B(a)n(t,a)da \quad OR \quad n(t,0) = \int_0^\infty B(a)n(t,a)da$$

So the mean empirical distribution of $A(t)$ satisfies the deterministic renewal equation.

# 3. Size model: growth-fragmentation process or equation

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

Set, for (regular compactly supported) $f$

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

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:

$$\boxed{\partial_t n(t,x) + \partial_x\big(\kappa x\, n(t,x)\big) + B(x)n(t,x) = 4B(2x)n(t,2x).}$$

So the mean empirical distribution of $X(t)$ satisfies the deterministic growth-fragmentation / size-structured / cell division equation (with binary fission and equal mitosis).

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

$$\boxed{\partial_t n(t,x) + \partial_x\big(\kappa x\, n(t,x)\big) + B(x)n(t,x) = 2B(2x)n(t,2x).}$$

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 $a$.

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

$$n(t, a = 0, x) = 8 \int_0^\infty x B(a, 2x) n(t, a, 2x) da$$

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

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# Fourth step: model analysis: long-time behaviour

# The age model

A very pedagogical reference: B. Perthame, *Transport Equations in Biology*, 2007

historically the first structured-population model to be studied (Kermack and Mc Kendrick, 1927 ; Metz and Diekmann, 1981)
$n(t,a)e^{-\lambda t} \to N(a)$, with $\lambda$ and $N$ uniquely determined by

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

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:

$$\frac{\partial}{\partial t} n(t,dx) + \frac{\partial}{\partial x}\big(\tau(x) n(t,dx)\big) =$$

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

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:

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

$$\int_{x=0}^{y} xk(y,dx) = \sum_{j\geq 0} p(j) \int_{0}^{y} jxP^{(j)}(y,dx) = y \sum_{j\geq 0} p(j) = y.$$

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# General form

$$\frac{\partial}{\partial t} n(t,dx) + \frac{\partial}{\partial x}\big(\tau(x) n(t,dx)\big) =$$

$$-B(x)n(t,dx) + \int\limits_{y=x}^{\infty} B(y)n(t,y)k(dy,dx),$$

with

$$\int\limits_0^y x k(y,dx) = y, \qquad \int\limits_0^y k(y,dx) = m > 1.$$

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

$$\frac{\partial}{\partial t} n_1(t,dx) + \frac{\partial}{\partial x}\big(\tau(x) n_1(t,dx)\big) =$$

$$-B(x)n_1(t,dx) + \int\limits_{y=x}^{\infty} B(y)n_1(t,y)k_1(dy,dx).$$

# 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:

$$\frac{d}{dt}\int n(t,x)dx = \int B(x)\Big(\int_0^x k(x,dy) - 1\Big)n(t,x)dx.$$

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$$\frac{d}{dt}\int n(t,x)dx = \int B(x)\Big(\int_0^x k(x,dy) - 1\Big)n(t,x)dx.$$

- More generally: balance between growth & fragmentation

$$\frac{d}{dt}\int_0^\infty x^p n(t,x)dx = \int_0^\infty px^{p-1}\tau(x)n(t,x)dx$$

$$+\int_0^\infty B(x)x^p\Big(1-\int_0^x \frac{y^p}{x^p}k(x,dy)\Big)n(t,x)dx$$

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)

$$n(t,x)e^{-\lambda t} \to N(x) \int n^0(x) dx$$

$(N, \lambda)$ : dominant eigenpair of the semi-group generator $L^* + \mathcal{F}^*$.

For compact strictly positive operators: Krein-Rutman.

# Long-time asymptotics 1: steady growth

Eigenvalue problem and adjoint problem:

$$
\left\{
\begin{array}{l}
\frac{\partial}{\partial x}(\tau(x)N(x)) + \lambda N(x) = -B(x)N(x) + \int_x^\infty B(y)k(x,y)N(y)dy, \\
\tau N(x=0) = 0, \qquad N(x) \geq 0, \qquad \int_0^\infty N(x)dx = 1, \\
-\tau(x)\frac{\partial}{\partial x}(\phi(x)) + \lambda\phi(x) = B(x)(-\phi(x) + \int_0^x k(y,x)\phi(y)dy), \\
\phi(x) \geq 0, \qquad \int_0^\infty \phi(x)N(x)dx = 1.
\end{array}
\right.
\tag{1}
$$

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*

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

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

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

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

Generalizes previous results by Michel, M3AS, 2004.

# Some ideas on the proof

2 opposite dynamics:

- Growth $\Rightarrow$ bigger and bigger $\Rightarrow$ mass goes to infinity ?
- Fragmentation $\Rightarrow$ smaller and smaller $\Rightarrow$ dust formation ?

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Balance: asymptotic steady profile.

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

$$\exists\, C > 0, \gamma \geq 0 \quad s.t. \qquad \int_0^x k(y, dz) \leq \min\Big(m, C\Big(\frac{x}{y}\Big)^{\gamma}\Big)$$

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

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

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Proof:

- regularized equation: Krein-Rutman/Perron-Frobenius
- balance assumptions$\Rightarrow$ 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: (Laurençot, Perthame, 2009) (Balagué, Cañizo, Gabriel, KRM, 2012) (Bernard, Gabriel, 2019) (Càceres, Cañizo, Mischler, JMPA, 2011)

- (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?