Growth-fragmentation equations

1 Description of the model

We consider a set of particles that undergo growth and fragmentation. The population is structured by the size x of the particles (x= length, or volume, or mass...), and we use a deterministic and continuous description of the evolution of the population. Hence the framework of PDEs. The growth-fragmentation equation is written

$$\begin{cases} \dfrac{\partial}{\partial t}u(t,x) + \dfrac{\partial}{\partial x}\left(\tau(x)u(t,x)\right) = -B(x)u(t,x) + 2\displaystyle\int_x^\infty B(y)k(x,y)u(t,y)dy, \\ u(0,x) = u_0(x), x \in \mathbb{R}^+ \qquad \tau(0)u(t,0) = 0,\ t > 0. \end{cases} \tag{1}$$

- $u(t,x)$ is the density of particles of size x at time t,
- $\tau(x)$ is the growth rate of particles of size x.
- $B(x)$ is the division rate or fragmentation rate of particles of size x. A straightforward dimensional analysis indicates that the division rate of the equation is a rate per unit of time: $B(x)dt$ is the probability for any cell reaching size x to divide in at most dt.
- $k(x,y)$ is the division kernel or fragmentation kernel. A particle of size y divides into two particles of sizes x and $y-x$ with rate $k(x,y)$. To ensure mass conservation, it is assumed that

  $$\int k(x,y)dx = 1, \qquad \int xk(x,y)dx = \frac{y}{2}, \qquad k(x,y) = k(y-x,y). \tag{2}$$

  A classical additional assumption is the self-similarity of the division kernel, i.e.

  $$k(x,y) = \frac{1}{y}\kappa\left(\frac{x}{y}\right). \tag{3}$$

- The factor 2 is the right-hand-side expresses that the division of one particle leads to the creation of 2 new particles.

The total number of particles increases because of fragmentation

$$\frac{d}{dt}\int_{\mathbb{R}+} u(t,x)dx = \int_{\mathbb{R}+} B(x)u(t,x)dx. \tag{4}$$

The total mass of the system increases because of growth

$$\frac{d}{dt}\int_{\mathbb{R}+} xu(t,x)dx = \int_{\mathbb{R}+} \tau(x)u(t,x)dx. \tag{5}$$

1.1 Exemple of applications

- **Grinding rocks (historical example).** In 1940, A.N. Kolmogorov writes for the first time a *pure* fragmentation equation to describe a population of grinding stones [3]. He assumes that the division rate is constant and equal to $B(x) = 1$, and the model is discrete in time. He proves that for some constants a and b

$$\lim_{t\to\infty} u(t, x\sqrt{t} + at) = \frac{1}{\sqrt{2\pi}b} \exp\left(-\frac{x^2}{2b^2}\right)$$

  The study has been continued by Filippov in 1960 in [2] for monomial division rates $B(x) = \alpha x^\gamma$ and extended to the time continuous models.

- **Polymer chains and droplet breakage.** From the 70's scientist from Chemical and Engineering departments have been using growth-fragmentation. One of the main challenges is to extract information on the parameters (division rate and daughter-drop-distribution (in modern terms: the fragmentation kernel), as a function of drop sizes data, obtained from experiments.

- **Cells**. Cell division can be modelled using mitotic kernels, i.e.

$$\kappa(z) = \delta_{z=1/2}.$$

  The equation writes

$$\begin{cases} \dfrac{\partial}{\partial t} u(t,x) + \dfrac{\partial}{\partial x}(xu(t,x)) = -B(x)u(t,x) + 4B(2x)u(t,2x), \\ u(0,x) = u_0(x). \end{cases} \tag{6}$$

- **Yeasts**. Contrarily to cells, yeast division involves a budding event and is non-symmetrical. It is described using the model

$$\begin{cases} \dfrac{\partial}{\partial t} u(t,x) + \dfrac{\partial}{\partial x}(xu(t,x)) = -B(x)u(t,x) + 2B\left(\dfrac{x}{r}\right) u\left(t, \dfrac{x}{r}\right) + 2B\left(\dfrac{x}{1-r}\right) u\left(t, \dfrac{x}{1-r}\right), \\ u(0,x) = u_0(x), \end{cases} \tag{7}$$

  for some $0 < r < 1$. Bacteria as Eschereschia Coli and Yeasts are living being extensively used in biology to understand genomic effect in a population.

- **Microtubules** Microtubules are dynamic protein polymers that are found in all eukaryotic cells. They are crucial for normal cell development, aiding in many cellular processes, including cell division, cell polarization, and cell motility. Because of their role

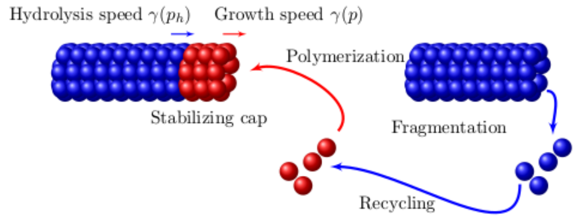

Figure 1: Schematic representation of the polymerization-fragmentation-recycling cycle.

in cell movement and cell division, these polymers are often used as targets for a variety of cancer chemotherapy drugs. Many experimental studies have been completed to understand microtubule dynamics, and how these dynamics are altered by the addition of microtubule targeting drugs.. Microtubuless are composed of α/β-tubulin dimers, and grow through the addition of GTP-bound tubulin (guanosine triphosphate), generally from the plus end of the microtubule, and shrink through dissociation of GDP-bound tubulin (guanosine diphosphate) at this end.

The evolution of the density $u(x, t)$ of microtubules of length $x \geq 0$ at time $t > 0$ is described by the one-dimensional growth-fragmentation equation (1.1)

$$\frac{\partial u(x,t)}{\partial t} + \gamma(p(t))\frac{\partial u(x,t)}{\partial x} = \beta(p(t))\left(-B(x)u(x,t) + \int_x^\infty B(y)k(x,y)u(y,t)dy\right) + N(p(t))\xi(x).$$

Equation (1.1) is coupled with a system of two ODEs, describing the time evolution of the concentrations of GTP-tubulin $p(t)$ and GDP-tubulin $q(t)$, respectively,

$$\frac{dp}{dt}(t) = -\gamma(p(t))\int_0^\infty u(x,t)dx - N(p(t)) + \kappa q(t),$$

$$\frac{dq}{dt}(t) = \beta(p(t))\int_0^\infty u(y,t)\int_0^y (y-x)k(x,y)dxdy - \kappa q(t),$$

endowed with initial conditions $u(x, 0) = 0$, $q(0) = 0$, and $p(0) = p_0 > 0$, and with the boundary condition $u(0, t) = 0$. The challenging questions for such systems is the identification of the asymptotic bahaviour (periodic or not?).

- **Amyloid fibrils, Prions.** The fragmentation of amyloid and prion protein fibrils are associated with their biological response ranging from being inert, functional to toxic, infectious and pathological. The experimental methods to characterize the dynamics of amyloid fibril fragmentation has been evolving from indirect bulk kinetics measurements to direct observations in population level time-dependent nano-imaging experiments. To analyze the division of protein filaments when the experimental information we have is at the level of the population distribution, for instance when the type of data we currently can acquire are time-point samples of fibril length distributions and individual dividing particles cannot yet be isolated and tracked, the pure fragmentation equation reveals to be a powerful mathematical tool.

The next two sections follow the steps of [4, Chapter 4].

2 Well-posedness of the growth-fragmentation equation

Definition 1 (Weak solutions.). *A weak solution* $u \in \mathcal{C}(\mathbb{R}^+, L^1(\mathbb{R}^+))$ *to the fragmentation equation is a function that satisfies for all* $\varphi \in C^1(\mathbb{R}^+)$

$$\frac{d}{dt}\int_{\mathbb{R}^+} u(t,x)\varphi(x)dx = \int_{\mathbb{R}^+} \tau(x)u(t,x)\varphi'(x)dx - \int_{\mathbb{R}^+} B(x)u(t,x)\varphi(x)dx + \int_{\mathbb{R}^+}\int_{\mathbb{R}^+} B(y)k(x,y)u(t,y)\varphi(x)dydx$$

Theorem 2 (Existence, uniqueness and stability). *Assume that* $\tau \in L^\infty(\mathbb{R}^+)$, $B \in L^\infty(\mathbb{R}^+)$ *and that* $k \in \mathcal{M}(\mathbb{R}^+ \times \mathbb{R}^+)$ *satisfies* (2). *Then, for* $(1+x)u^0 \in L^1(\mathbb{R}^+)$, *there exsits a unique weak solution* $u \in \mathcal{C}(\mathbb{R}^+, L^1(\mathbb{R}^+))$*to* (1) *and it satisfies*

$$u_1^0 \le u_2^0 \quad \Rightarrow \quad u_1(t,x) \le u_2(t,x), \quad x \in \mathbb{R}^+, \tag{8}$$

$$\|u(t,.)\|_1 \le e^{\|B\|_\infty t}\|u_0\|_1 \tag{9}$$

Proof. □

Remark 3. • *The contractivity of the map only holds for division rates $B \in L^\infty(\mathbb{R}^+)$. An extension of this theorem for B continous satisfying*

$$B_0 \mathbb{1}_{x>x_0} x^{\gamma_0} \leq B(x) \leq B_1 \max(1, x^{\gamma_1}),$$

can be found in [?] using semi-group theory.

3 Asymptotic behaviour

A remarkable feature of many reproducing populations, observed before crowding or ressource limitation can occur and therefore expected to be captured by the model, is exponential growth coupled to asynchronicity –referred to as asynchronous exponential growth (A.E.G.) [51]. Mathematically, A.E.G. corresponds to the existence of a stationary profile N , independent of the initial state, and positive constants C, such that

$$u(t,x) \equiv Ce^{\lambda t} N(x),$$

where the only memory of the initial state is a weighted average contained in C. The asymptotic exponential growth rate λ is called Malthus parameter.

3.1 Eigenelements

We consider the first eigenelements (λ, N, Φ) associated to the growth-fragmentation equation

$$\begin{cases} (\tau N)'(x) + \lambda N(x) + B(x)N(x) = 2\displaystyle\int_x^\infty B(y)k(x,y)N(y)dy \\ N(x=0) = 0, \qquad N(x) > 0, \qquad \displaystyle\int_{\mathbb{R}^+} N(x)dx = 1. \end{cases} \tag{10}$$

$$\begin{cases} \tau(x)\Phi'(x) - \lambda\Phi(x) - B(x)\Phi(x) = -2\displaystyle\int_0^y B(x)k(x,y)\Phi(x)dx, \\ \Phi(x) > 0, \qquad \displaystyle\int_{\mathbb{R}^+} \Phi(x)N(x)dx = 1. \end{cases} \tag{11}$$

Theorem 4 (Existence of eigenelements)**.** *Assume $B \in L^\infty \cap C^0(\mathbb{R}^+)$ and $\tau \in L^\infty \cap C^0(\mathbb{R}^+)$ such that*

$$0 < b_m \leq B(x) \leq B_M, \qquad x \in \mathbb{R}^+, \tag{12}$$

and take $k \in \mathcal{M}(\mathbb{R}^+ \times \mathbb{R}^+)$ satisfying (2), then there exsits a unique solution $(\lambda, N, \Phi) \in \mathbb{R}^+ \times L^1(\mathbb{R}^+) \times L^\infty(\mathbb{R}^+)$ to (10)(11). Moreover, we have

$$b_m \leq \lambda \leq B_M$$

Proof. The proof consists in applying a version of the Krein-Rutman theorem to a regularized problem, and then pass to the limit. □

Definition 5 (cone)**.** *A subset K of a vector sapce E is called a cone if*

- $0 \in K$
- *for* $\lambda, \mu > 0$, *we have* $(x, y) \in K^2 \Rightarrow \lambda x + \mu y \in K$
- $(x \in K \, and \, (-x) \in K) \Rightarrow (x = 0)$.

We can then define an order thanks to the cone K by

$$(x \geq y) := (x - y \in K), \qquad (x > y) := (x - y \in Int(K)),$$

Theorem 6 (Krein-Rutman theorem)**.** *Let* $(E, \|.\|)$ *be a Banach space and* $A : E \to E$ *a continuous linear compact map, such that* A *is strongly positive on a closed cone* K*, i.e.*

$$A(x) > 0 \text{ for } x \in K \setminus \{0\},$$

then the spectral radius $\rho(A)$ *of* A *is a positive simple eigenvalue of* A *associated to a positive eigenvector* X *(in the sense that* $X \in Int(K)$*. Moreover,* X *is the only nonnegative eigenvector.*

Remark 7. *Krein-Rutman theorem cannot be directly applied to our problem. Due to the transport term* τN*, the natural space of solutions is* $L^1(\mathbb{R}^+)$*, and the interior of the positive functions in* L^1 *is empty. We need to regularize the problem and work with continuous solutions.*

Proof of Theorem 4. □

Assumptions of Theorem 4 are relaxed in [1] where the authors allow more general τ, B (in particular unbounded. To prevent formation of particles of infinite sizes (gelation), they add the condition

$$\lim_{x\to\infty} \frac{xB(x)}{\tau(x)} = +\infty$$

To avoid shattering (zero-size polymers formation) they impose that for some $C, a, \alpha > 0$

$$\frac{\tau}{B} \in L^1(0,a), \quad \frac{x^\alpha}{\tau} \in L^1(0,a), \quad \int_0^x k(z,y)dz \leq \min\{1, C\left(\frac{x}{y}\right)^\alpha\}$$

Some examples, in the case of the uniform fragmentation kernel $\kappa(z) = 1, \ z \in [0,1]$

- $\tau(x) = 1, \ B(x) = x$, then $\lambda = 1, N(x) = 2\left(x + \frac{x^2}{2}\right) exp\left(-x - \frac{x^2}{2}\right), \Phi(x) = \frac{1}{2}(1+x)$,
- $\tau(x) = x, \ B(x) = x$, then $\lambda = 1, N(x) = exp\,(-x)\,, \Phi(x) = x$.

Theorem 8 (The Malthus parameter). *Consider the growth fragmentation equation with the two sets of parameters* $(\tau = \tau_1, B = \tau_1\beta, k)$ *and* $(\tau = \tau_2, B = \tau_2\beta, k)$. *If we assume that*

$$\tau_1(x) \leq \tau_2(x), \qquad x \in \mathbb{R}^+$$

Then the associated Malthus parameters verify

$$\lambda_1 \leq \lambda_2.$$

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3.2 General relative entropy

Theorem 9 (Entropy dissipation). *Assume that* $\tau \in L^\infty(\mathbb{R}^+) \cap C^0(\mathbb{R}^+)$, $B \in L^\infty(\mathbb{R}^+) \cap C^0(\mathbb{R}^+)$ *and that* $k \in \mathcal{M}(\mathbb{R}^+ \times \mathbb{R}^+)$ *satisfies* (2). *Then, for* $(1+x)u^0 \in L^1(\mathbb{R}^+)$, *let us denote by* u, p *two solutions to* (1) *with* $p > 0$ *and* Φ *solution to* (11). *Then, for all convex and continuous function* H, *it holds the entropy dissipation*

$$\frac{d}{dt}\int_{\mathbb{R}^+} H\left(\frac{u(t,x)}{p(t,x)}\right) p(t,x)\Phi(x)dx = -D^H[u|p](t) \leq 0,$$

where the entropy dissipation D^H *is*

$$D^H[u|p](t) := \int_{\mathbb{R}^+}\int_{\mathbb{R}^+} \Phi(x)p(t,y)k(x,y)$$
$$\left[H\left(\frac{n(t,y)}{p(t,y)}\right) - H\left(\frac{n(t,x)}{p(t,x)}\right) - H'\left(\frac{n(t,x)}{p(t,x)}\right)\left[\frac{n(t,y)}{p(t,y)} - \frac{n(t,x)}{p(t,x)}\right]\right] dxdy.$$

Corollary 10 (Conservation law, contraction principle, maximum principle)**.** *Take* $\tau \in L^\infty(\mathbb{R}^+) \cap C^0(\mathbb{R}^+)$*,* $B \in L^\infty(\mathbb{R}^+) \cap C^0(\mathbb{R}^+)$*,* $k \in \mathcal{M}(\mathbb{R}^+ \times \mathbb{R}^+)$ *satisfies* (2)*. Assume* $u_0 \in L^1((1+\Phi(x))dx)$*. Then, there is a unqiue solution* u *to* (1) *in* $\mathcal{C}(\mathbb{R}^+, L^1(\Phi(x)dx)$ *and it satisfies*

$$\int_{\mathbb{R}^+} u(t,x)e^{-\lambda t}\Phi(x)dx = \int_{\mathbb{R}^+} u_0(x)\Phi(x)dx$$
$$\int_{\mathbb{R}^+} |u(t,x)|e^{-\lambda t}\Phi(x)dx = \int_{\mathbb{R}^+} |u_0(x)|\Phi(x)dx$$
$$C^-N(x) \le u_0(x) \le C^+N(x) \quad \Rightarrow \quad C^-N(x) \le u(t,x)e^{-\lambda t} \le C^+N(x)$$

Corollary 11. *Take* $\tau \in L^\infty(\mathbb{R}^+) \cap C^0(\mathbb{R}^+)$*,* $B \in L^\infty(\mathbb{R}^+) \cap C^0(\mathbb{R}^+)$*,* $k \in \mathcal{M}(\mathbb{R}^+ \times \mathbb{R}^+)$ *satisfies* (2)*.Assume* $u_0 \in L^1((1+\Phi(x))dx)$*, and*

$$|u_0(x)| \le C_0 N(x), \quad u_0'(x) \in L^1(\Phi(x)dx).$$

Then, the unqiue solution u *to* (1) *in* $\mathcal{C}(\mathbb{R}^+, L^1(\Phi(x)dx)$ *satisfies*

$$\int_{\mathbb{R}^+} \left|\frac{\partial}{\partial t}\tilde{u}(t,x)\right| \Phi(x)dx \le C(u_0),$$
$$\int_{\mathbb{R}^+} \left|\frac{\partial}{\partial x}\tilde{u}(t,x)\right| \Phi(x)dx \le C(u_0),$$

where $\tilde{u}(t,x) = e^{-\lambda t}u(t,x)$*.*

Theorem 12 (Entropy minimizers)**.** *Take* $\tau \in L^\infty(\mathbb{R}^+) \cap C^0(\mathbb{R}^+)$*,* $B \in L^\infty(\mathbb{R}^+) \cap C^0(\mathbb{R}^+)$*,* $k \in \mathcal{M}(\mathbb{R}^+ \times \mathbb{R}^+)$ *satisfies* (2) *and* $supp(k) = \{(x,y) \in \mathbb{R}^2 | x \le y\}$*. Take* $p > 0, u \in L^1(\mathbb{R}^+)$ *such that*

$$D^H[u|p] = 0.$$

Then, there is $C \in \mathbb{R}$ *such that*

$$u(x) = Cp(x), \quad x \in \mathbb{R}^+.$$

3.3 Asymptotic exponential growth

Theorem 13 (AEG)**.** *Take $\tau \in L^\infty(\mathbb{R}^+) \cap C^0(\mathbb{R}^+)$, $B \in L^\infty(\mathbb{R}^+) \cap C^0(\mathbb{R}^+)$, $k \in \mathcal{M}(\mathbb{R}^+ \times \mathbb{R}^+)$ satisfies* (2) *and $supp(k) = \{(x, y) \in \mathbb{R}^2 | x \leq y\}$. Then, any weak solution u to the growth-fragmentation equation* (1) *satisfies*

$$\|e^{-\lambda t} u(t, .) - CN(.)\|_{L^1(\mathbb{R}^+, \Phi(x)dx)} \underset{t\to\infty}{\to} 0,$$

where

$$C = \int_{\mathbb{R}^+} u_0(x)\Phi(x)dx.$$

Remark 14. • **The mitosis case with linear growth $\tau(x) = x$.** *In the specific case*

$$\tau(x) = x, \qquad \kappa(z) = \delta(z = 1/2),$$

which is the ideal model for cell division, the A.E.G. is not true anymore. Instead, solutions oscillate.

- **Asymptotic behaviour for the pure fragmentation equation.** *Consider the pure fragmentation equation*

$$\begin{cases} \dfrac{\partial}{\partial t} u(t,x) = -B(x)u(t,x) + 2\displaystyle\int_x^\infty B(y)k(x,y)u(t,y)dy, \\ u(0,x) = u_0(x). \end{cases} \tag{13}$$

with the additional assumption $B(x) = \alpha x^\gamma$. The fragmentation equation can be turned into a growth-fragmentation equation with the change of variables $(t = t, y = t^{1/\gamma}x)$.

References

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