Université Paris-Saclay

École doctorale de mathématiques Hadamard (ED 574)
Laboratoire de mathématiques de Versailles (UMR 8100 CNRS-UVSQ)

Mémoire présenté pour l'obtention du

Diplôme d'habilitation à diriger les recherches

Discipline : Mathématiques

par

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Asymptotic analysis of non-local equations arising in biology

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Date de soutenance : le 13 janvier 2021

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À Eleonora,
Marcel et Émil

Remerciements

En premier lieu je tiens à adresser mes remerciements aux membres du jury, devant lequel c'est un honneur de présenter mes travaux. Je suis extrêmement reconnaissant à José Antonio Carrillo, François Golse et Stéphane Mischler d'avoir consacré de leur temps à la relecture de ce mémoire. Ces quelques lignes sont l'occasion d'exprimer ma profonde gratitude à Marie Doumic et Benoît Perthame, qui m'ont ouvert les portes du monde passionnant de la recherche et des mathématiques appliquées à la biologie ; depuis le début j'ai pu compter sur leur soutien. Une partie importante de ce mémoire repose sur des idées d'inspiration probabiliste, et je suis vraiment touché que Sylvie Méléard ait accepté d'être membre du jury. Je suis très heureux que Luc Robbiano soit le représentant de Versailles pour cette soutenance.

L'activité de recherche serait nettement moins passionnante si elle devait s'effectuer seul. Je souhaite ici remercier tous mes collaborateurs : Matthieu Alfaro, Daniel Balagué, Vincent Bansaye, Étienne Bernard, Hugues Berry (que je remercie également chaleureusement pour m'avoir accueilli en post-doc chez Beagle), Emeric Bouin, Vincent Calvez, José Alfredo Cañizo (aussi pour son accueil à Cambridge et à Grenade), Monique Chyba, Bertrand Cloez, Jean-Michel Coron, Marie Doumic, Grégory Dumont, Shawn Garbett, Stéphane Gaubert, Otared Kavian, Thomas Lepoutre, Aline Marguet, Hugo Martin, Léon Matar Tine, Álvaro Mateos González, Vito Quaranta, Human Rezaei, Francesco Salvarani, Peipei Shang (également pour son accueil à Shanghai), Magali Tournus, Darren Tyson, Bruce van Brunt, Glenn Webb et Havva Yoldaş. Et merci encore à Hugo de m'avoir accordé sa confiance pour le co-encadrement de sa thèse.

Merci à mes collègues du Département et du Laboratoire de Mathématiques de Versailles pour l'ambiance conviviale qui y règne au quotidien, et peut-être plus intensément encore lors d'événements comme l'école Cimpa 2016 (merci à Laurent et Zaid), le Canum 2018, les courses Paris-Versailles (avec Catherine, Christophe, Laurent et Pascal), et également Imose grâce à qui j'ai entre autres appris qu'on pouvait nager avec des poneys. Une pensée particulière pour Laure, Liliane et Nadège, pour le couloir de Germain, et pour mes co-bureaux successifs Tahar et Vahagn.

Enfin, et surtout, merci à Eleonora, à Émil et à Marcel, pour tout leur amour.

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Présentation générale

Dans ce mémoire, on s'intéresse aux propriétés asymptotiques d'équations aux dérivées partielles non-locales qui apparaissent dans l'étude du vivant, et plus précisément en biologie cellulaire, en neurosciences, ou en théorie de l'évolution. Les équations considérées sont du type

$$\frac{\partial u_t}{\partial t} + \nabla \cdot (u_t F) + a\, u_t = \int_{\mathbf{X}} u_t(y) k(y, \mathrm{d}x) \mathrm{d}y$$

où l'inconnue u_t dépend de la variable x. Ce "trait" x appartient à un espace d'états $\mathbf{X}$ qui est typiquement un ouvert de $\mathbb{R}^n$, même si cela peut être un espace mesurable plus général dans le cas où le champ de force F est nul. Suivant les modèles considérés, ces équations pourront être de trois types :

- linéaires autonomes quand les coefficients F, a et k ne dépendent que de x. On s'intéresse alors à des problèmes ergodiques de type Krein-Rutman.
- linéaires non-autonomes quand les coefficients dépendent de t et de x. On considérera le cas de coefficients périodiques en temps, qui apparaissent naturellement en biologie ou en écologie, ainsi que le cas où la dépendance en temps est due à un terme de contrôle.
- non-linéaires de type champ-moyen où les coefficients dépendent de l'inconnue u_t à travers des termes moyens $\int_{\mathbf{X}} u_t \psi$, pour certaines fonctions positives ψ.

Le présent manuscrit donne un aperçu des résultats que j'ai obtenus sur ces équations entre 2012 et 2020, avec divers collaborateurs. La question principale qui est abordée est celle du comportement des solutions en temps long. Les différents résultats présentés illustrent la variété de ces comportements : convergence vers une distribution stationnaire, phénomène de concentration ou d'oscillations. Le dernier chapitre est un peu à part puisqu'on y considère des problèmes de passage à la limite de l'échelle mésoscopique vers des descriptions macroscopiques. Détaillons maintenant brièvement les résultats principaux des différents chapitres.

Le premier chapitre est consacré à l'analyse des états stationnaires d'un modèle champ-moyen pour un réseau de neurones "intègre et tire". On montre en particulier un résultat de stabilité globale exponentielle dans le cas de faible connectivité. Ce premier chapitre permet également d'introduire le critère de contraction de Doeblin qui est à la base des méthodes développées au chapitre 2.

Dans le deuxième chapitre, on présente un résultat abstrait qui caractérise de manière quantitative l'ergodicité géométrique des semi-groupes positifs non-conservatifs (Théorème 2.1). On propose également une condition d'irréductibilité faible qui s'avère très utile pour l'application de ce théorème général à des modèles de dynamique des populations (Proposition 2.4). Ces résultats d'inspiration probabiliste s'inscrivent dans la lignée des travaux de Harris [130], Meyn et Tweedie [162] sur les semi-groupes de Markov (*i.e.* conservatifs).

Le chapitre 3 regroupe une série de résultats sur le comportement en temps long de l'équation de croissance-fragmentation, obtenus en utilisant différentes méthodes : l'approche à la Harris développée au chapitre 2, la théorie spectrale des semigroupes fortement continus, ou encore des inégalités d'entropie. Nous avons notamment obtenu avec Hugo Martin, au cours de sa thèse de doctorat que j'ai co-encadrée avec Marie Doumic, un résultat quantitatif de convergence exponentielle dans un cas non-ergodique où le comportement en temps grand est périodique (Théorème 3.13). Ces oscillations sont dues à l'existence d'une famille dénombrable de valeurs propres dominantes, et à notre connaissance c'est la première fois que l'existence d'un trou spectral est prouvée dans une telle situation.

Dans le chapitre 4, on s'intéresse aux phénomènes de concentration dans les modèles de mutation-sélection avec mutations non-locales. On présente en particulier un résultat récent, non encore publié, de convergence vers une mesure singulière pour une version générale du modèle de château de cartes de Kingman (Théorème 4.4). Ces phénomènes de concentration sont particulièrement intéressants, à la fois d'un point de vue biologique puisqu'ils permettent d'interpréter les phénomènes de spéciation en théorie de l'évolution, et d'un point de vue mathématique puisqu'ils fournissent des exemples d'obstruction aux hypothèses du théorème de Harris présenté au chapitre 2.

Dans le cinquième chapitre, on considère un problème de contrôle optimal qui apparaît dans la modélisation de la technique de PMCA (Protein Misfolding Cyclic Amplification), développée pour les maladies à prions. On analyse ce problème sous deux angles différents : la théorie géométrique du contrôle optimal et le principe de programmation dynamique. Bien que le système étudié ne soit pas uniformément contrôlable, on parvient à établir dans la seconde approche un résultat d'ergodicité en horizon infini en tirant parti de la contraction dans la métrique projective de Hilbert (Théorème 5.5).

Le chapitre 6 traite de la modélisation des phénomènes sous-diffusifs par des équations aux dérivées partielles. J'ai commencé à m'intéresser à ce sujet lors de mon post-doctorat à l'Inria de Lyon avec Hugues Berry. La sous-diffusion est en effet un phénomène couramment observé dans le déplacement de molécules à l'intérieur des cellules. Dans ce dernier chapitre, on présente la dérivation de deux équations macroscopiques comme limites d'échelle d'une description mésoscopique de processus sous-diffusifs.

List of publications

[P22] J. A. Cañizo, P. Gabriel, and H. Yoldaş. Spectral gap for the growth-fragmentation equation via Harris's Theorem. Submitted, *arXiv:2004.08343*.

[P21] P. Gabriel and H. Martin. Periodic asymptotic dynamics of the measure solutions to an equal mitosis equation. Submitted, *arXiv:1909.08276*.

[P20] B. Cloez and P. Gabriel. On an irreducibility type condition for the ergodicity of nonconservative semigroups. *C. R. Math. Acad. Sci. Paris*, 358(6):733–742, 2020.

[P19] V. Bansaye, B. Cloez, P. Gabriel, and A. Marguet. A non-conservative Harris ergodic theorem. Submitted, *arXiv:1903.03946*.

[P18] É. Bernard and P. Gabriel. Asynchronous exponential growth of the growth-fragmentation equation with unbounded fragmentation rate. *J. Evol. Equ.*, 20(2):375–401, 2020.

[P17] P. Gabriel and H. Martin. Steady distribution of the incremental model for bacteria proliferation. *Netw. Heterog. Media*, 14(1):149–171, 2019.

[P16] V. Bansaye, B. Cloez, and P. Gabriel. Ergodic behavior of non-conservative semigroups via generalized Doeblin's conditions. *Acta Appl. Math.*, 166:29–72, 2020.

[P15] G. Dumont and P. Gabriel. The mean-field equation of a leaky integrate-and-fire neural network: measure solutions and steady states. *Nonlinearity*, 33:6381–6420, 2020.

[P14] P. Gabriel. Measure solutions to the conservative renewal equation. *ESAIM Proc. Surveys*, 62:68–78, 2018.

[P13] V. Calvez, P. Gabriel, and Á. Mateos González. Limiting Hamilton-Jacobi equation for the large scale asymptotics of a subdiffusion jump-renewal equation. *Asymptot. Anal.*, 115(1-2):63–94, 2019.

[P12] É. Bernard, M. Doumic, and P. Gabriel. Cyclic asymptotic behaviour of a population reproducing by fission into two equal parts. *Kinetic Related Models*, 12(3):551–571, 2019.

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[P9] P. Gabriel. Global stability for the prion equation with general incidence. *Math. Biosc. Eng.*, 12(4):789–801, 2015.

[P8] M. Chyba, J.-M. Coron, P. Gabriel, A. Jacquemard, G. Patterson, G. Picot, and P. Shang. Optimal Geometric Control Applied to the Protein Misfolding Cyclic Amplification Process. *Acta Appl. Math.*, 135(1):145–173, 2015.

[P7] V. Calvez, P. Gabriel, and S. Gaubert. Non-linear eigenvalue problems arising from growth maximization of positive linear dynamical systems. In *53rd IEEE Conference on Decision and Control*, pp.1600-1607, 2014.

[P6] J.-M. Coron, P. Gabriel, and P. Shang. Optimization of an amplification protocol for misfolded proteins by using relaxed control. *J. Math. Biol.*, 70(1-2):289–327, 2015.

[P5] P. Gabriel and F. Salvarani. Exponential relaxation to self-similarity for the superquadratic fragmentation equation. *Appl. Math. Lett.*, 27:74–78, 2014.

[P4] D. Balagué, J. A. Cañizo, and P. Gabriel. Fine asymptotics of profiles and relaxation to equilibrium for growth-fragmentation equations with variable drift rates. *Kinetic Related Models*, 6(2):219–243, 2013.

[P3] V. Calvez and P. Gabriel. Optimal growth for linear processes with affine control. *arXiv:1203.5189 [math.AP]*, 2012.

[P2] S. Prigent, A. Ballesta, F. Charles, N. Lenuzza, P. Gabriel, L. M. Tine, H. Rezaei, and M. Doumic. An efficient kinetic model for amyloid fibrils assemblies and its application to polyglutamine aggregation. *PLoS ONE*, 7(11):e43273, 2012.

[P1] P. Gabriel, S. P. Garbett, V. Quaranta, D. Tyson, and G. F. Webb. The contribution of age structure to cell population responses to targeted therapeutics. *J. Theoret. Biol.*, 311:19–27, 2012.

*** This list does not contain the publications presented in my PhD thesis manuscript.**

Notations

For a set A, we denote by $\mathbf{1}_A$ the indicator function of A.

For any Banach space E, we denote by E' its topological dual and by $\langle\cdot,\cdot\rangle$ the duality bracket.

For any Banach lattice E, we denote by E_+ its positive cone.

For $\mathbf{X}$ a measurable space, we denote by

- $\mathscr{L}^\infty(\mathbf{X})$ the space of bounded measurable functions $\mathbf{X} \to \mathbb{R}$ endowed with the supremum norm

$$\|f\|_\infty = \sup_{x\in\mathbf{X}} |f(x)|,$$

- $\mathscr{M}(\mathbf{X})$ the space of finite signed measures on $\mathbf{X}$ endowed with the total variation norm

$$\|\mu\|_{\mathrm{TV}} = \sup_{\|f\|_\infty \leq 1} \int_{\mathbf{X}} f\,\mathrm{d}\mu,$$

- $\mathscr{P}(\mathbf{X})$ the set of probability measures, *i.e.* positive measures with mass 1.

For $V : \mathbf{X} \to (0,\infty)$ measurable we denote by

- $\mathscr{L}^\infty(V) = \mathscr{L}^\infty(\mathbf{X},V)$ the space of measurable functions $f : \mathbf{X} \to \mathbb{R}$ such that

$$\|f\|_{\mathscr{L}^\infty(V)} = \sup_{x\in\mathbf{X}} \frac{|f(x)|}{V(x)} < +\infty,$$

- $\mathscr{M}_+(V) = \mathscr{M}_+(\mathbf{X},V)$ the set of positive measures that integrate V, namely $\mu \geq 0$ such that

$$\langle\mu,V\rangle = \int_{\mathbf{X}} V\,\mathrm{d}\mu < +\infty,$$

- $\mathscr{M}(V) = \mathscr{M}(\mathbf{X},V)$ the quotient space

$$\mathscr{M}(V) = {}^{\mathscr{M}_+(V)\times\mathscr{M}_+(V)}\!\big/_{\sim}$$

  where $(\mu_1,\mu_2) \sim (\tilde{\mu}_1,\tilde{\mu}_2)$ if $\mu_1 + \tilde{\mu}_2 = \mu_2 + \tilde{\mu}_1$. An element μ of $\mathscr{M}(V)$ acts on $\mathscr{L}^\infty(V)$ through

$$\langle\mu,f\rangle = \langle\mu_1,f\rangle - \langle\mu_2,f\rangle,$$

  where (μ_1,μ_2) is any representative of the equivalence class μ. We endow $\mathscr{M}(V)$ with the weighted total variation norm

$$\|\mu\|_{\mathscr{M}(V)} = \sup_{\|f\|_{\mathscr{L}^\infty(V)} \leq 1} \langle\mu,f\rangle,$$

  which makes it a Banach space.

When $\mathbf{X}$ is a measurable subset of $\mathbb{R}^n$ endowed with the Lebesgue measure, we denote by

- $L^p(\mathbf{X})$ the standard Lebesgue space on $\mathbf{X}$ for any $p \in [1, \infty]$.

For $V : \mathbf{X} \to (0, \infty)$ measurable we denote by

- $L^p(V) = L^p(\mathbf{X}, V(x)\,\mathrm{d}x)$ the weighted Lebesgue space with Lebesgue density V, endowed with the norm

  $$\|f\|_{L^p(V)} = \left(\int_{\mathbf{X}} |f(x)|^p V(x)\,\mathrm{d}x \right)^{\frac{1}{p}}$$

  when $p < \infty$, and

  $$\|f\|_{L^\infty(V)} = \sup_{x \in \mathbf{X}} \mathrm{ess}\, \frac{|f(x)|}{V(x)}.$$

Chapter 1

Doeblin in a neural network model

In this first chapter, we present the results obtained with Grégory DUMONT in [P15] about the mean field equation of an excitatory network of leaky integrate-and-fire (LIF) neurons. More precisely we explain how Doeblin's argument allowed us to get new results about the steady states.

The LIF model is a well-established neuron model within the neuroscience community [137]. It consists in an ordinary differential equation that describes the subthreshold dynamics of a neuron's membrane potential. Whenever the membrane potential reaches the firing threshold, the neuron initiates an action potential and the membrane potential is reset, see [41] for a review and [1, 35] for historical consideration. In its normalized form, the LIF model reads

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}V_t = -V_t + h\displaystyle\sum_{j=1}^{+\infty}\delta_{t=t_j} \\ \text{If} \quad V_t > 1 \quad \text{then} \quad V_t \to V^R. \end{cases} \tag{1.1}$$

Here, $V^R \in (0,1)$ is the reset potential, δ is the Dirac measure, $h \in (0,1)$ is the so-called synaptic strength, and t_j are the arrival times of action potentials that originate from presynaptic cells. The fact that h is positive means that we consider excitatory neurons. This dynamics describes a piecewise deterministic Markov process [75], whose stochastic feature is embedded in the Poisson distribution of time arrivals [195]. It is worth saying that, despite its vast simplifications, the LIF model yields amazingly accurate predictions and is known to reproduce many aspects of actual neural data [114]. In Fig. 1.1, a simulation of the LIF model is presented. It illustrates the different processes involved in the membrane equation such as the voltage jumps at the reception of an action potential, and the reset mechanism at the initiation of an action potential.

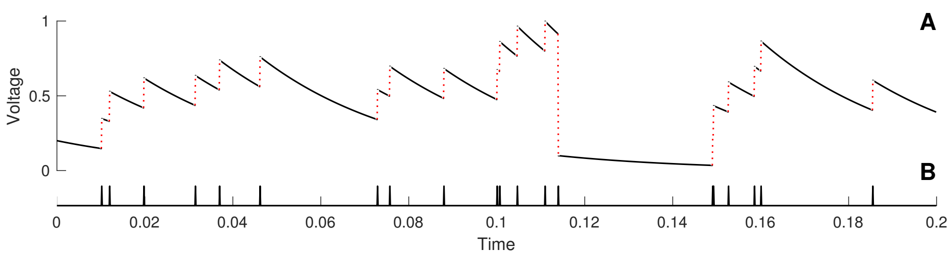


Fig. 1.1 Simulation of the LIF model. A) Time evolution of the membrane potential. B) The panel illustrates the arrival times of impulses, so-called Poisson spike train. The red dots correspond to discontinuities induced by the jump process. The parameters are: $h = 0.2$, $V^R = 0.1$ and Poisson rate 100.

In a network, when a cell fires, the dynamics of each other neuron might be affected by the action potential. This gives rise to an extremely complex dynamics, a population of neurons in the brain being composed of thousands of nervous cells. Mean-field theory is a powerful convenient tool to establish a mathematically tractable characterization of such large neural networks. Because each neuron receives input from many others, a single cell is mostly responsive to the average activity of the population – the mean-field – rather than the specific pattern of individual units. We are interested in the following mean-field approximation of excitatory LIF neural networks, see [175] for details on the formal derivation and [92] for a first mathematical study. Assuming that each neuron receives excitatory synaptic input with average rate $\sigma(t)$ and fires action potentials at rate $r(t)$, we denote the probability density function $p_t(v)$, such that $Np_t(v)dv$ gives the approximate number of neurons with membrane potential in $[v-dv,v)$ at time t for a network made up of N neurons. The dynamics of the density $p_t(v)$ is prescribed by the following nonlinear partial differential equation:

$$\frac{\partial}{\partial t}p_t(v)-\underbrace{\frac{\partial}{\partial v}\big(vp_t(v)\big)}_{\text{Leak}}+\underbrace{\sigma(t)\big(p_t(v)-p_t(v-h)\mathbf{1}_{[h,1)}(v)\big)}_{\text{Jump}}=\underbrace{r(t)\delta_{v=V^R}}_{\text{Reset}},\qquad 0<v<1, \tag{1.2}$$

complemented with a zero flux boundary condition $p_t(1)=0$. The firing activity of the network $r(t)$ is easily extracted from the mean-field equation. The proportion of cells crossing the threshold is given by:

$$r(t)=\sigma(t)\int_{1-h}^{1}p_t(w)\,\mathrm{d}w.$$

This expression guarantees that Equation (1.2) is formally conservative, in the sense that the integral of the solution is preserved along time. This is required since it should describe the evolution of a probability density. To account for the arrival of action potentials coming from an external source, the arrival rate $\sigma(t)$ is given by the sum of an external rate and the firing rate

$$\sigma(t)=\sigma_0+Jr(t),$$

where J is the average number of synaptic connexions. This is justified in the mean-field framework where it is assumed that single cells are only sensitive to the average population activity [175]. Combining the two above relations between $\sigma(t)$ and $r(t)$ we get an explicit formula for the arrival rate

$$\sigma(t)=\frac{\sigma_0}{1-J\int_{1-h}^{1}p_t(w)dw}, \tag{1.3}$$

provided that the denominator is positive. This makes the value $J=1$ appear critical, the arrival rate being in particular always well-defined when $J<1$.

Measure solutions to structured population equations have attracted increasing interest over the past few years [42, 55, 125], to cite but a few. Here we are concerned with measure solutions to Equation (1.2), which offers a very natural framework for at least two reasons. First it allows considering a Dirac mass initial distribution. Such an initial profile corresponds to a fully synchronous state and is thus perfectly relevant in neuroscience. Second it is very well suited for dealing with equations having a singular source term (the reset part in Equation (1.2)). We prove in [P15] the global well-posedness of Equation (1.2) in $\mathscr{P}([0,1])$ when $J<1$, *i.e.* that for any initial probability distribution p_0 there exists a unique family $(p_t)_{t\geq 0}\subset\mathscr{P}([0,1])$ such that the arrival rate σ defined in (1.3) is positive and locally integrable on $[0,\infty)$, the mapping $t\mapsto p_t$ is weak*-continuous on $[0,\infty)$, and for all $f\in C^1([0,1])$ and all $t\geq 0$

$$\langle p_t,f\rangle=\langle p_0,f\rangle+\int_0^t\langle p_s,-vf'+\sigma(s)\mathscr{B}f\rangle\,\mathrm{d}s$$

where

$$\mathscr{B}f(v) = f(v+h)\mathbf{1}_{[0,1-h)}(v) + f(V^R)\mathbf{1}_{[1-h,1]}(v) - f(v).$$

We also prove the existence of steady states when the parameters J or σ_0 are not too large, and the exponential asymptotic stability of the unique steady state in the weakly connected regime.

Theorem 1.1. *Depending on the network connectivity, the following situations occur:*

(i) Under the conditions

$$J > 1 + \left\lfloor \frac{1-V^R}{h} \right\rfloor \qquad \text{and} \qquad \sigma_0 < \frac{1-h}{4J},$$

there exist at least two steady states.

(ii) If the following inequality holds

$$J < 1 + \left\lfloor \frac{1-V^R}{h} \right\rfloor,$$

then there exists at least one steady state.

(iii) In the case when

$$J < (5-2\sqrt{6})\left(\frac{h}{4}\right)^{\sigma_0+1},$$

the steady state $\bar{p}$ is unique and globally exponentially stable. More precisely there exist explicit constants $\omega = \omega_J > 0$ and $\tau = \tau_J > 0$ such that for all p_0 taken from $\mathscr{P}([0,1])$ and all $t \geq 0$

$$\|p_t - \bar{p}\|_{\mathrm{TV}} \leq \mathrm{e}^{-\omega(t-\tau)} \|p_0 - \bar{p}\|_{\mathrm{TV}}.$$

Sketch of the proof. The key step is a careful analysis of the dynamics (1.1) of a single LIF neuron submitted to a Poisson spike train with fixed rate σ. A linear semigroup $(M_t)_{t\geq 0}$ is associated to this stochastic dynamics, given by

$$M_t f(v) = \mathbb{E}\big[f(V_t)\,|\,V_0 = v\big]$$

for f bounded measurable function on $[0,1]$. This semigroup yields the solutions to the following linear PDE

$$\frac{\partial}{\partial t}\varphi_t(v) = -v\frac{\partial}{\partial t}\varphi_t(v) + \sigma\big(\varphi_t(v+h)\mathbf{1}_{[0,1-h)}(v) + \varphi_t(V^R)\mathbf{1}_{[1-h,1]}(v) - \varphi_t(v)\big)$$

which is nothing but the dual equation of (1.2) with constant σ. By duality we can thus define a left action of the semigroup on the space of signed measures by setting

$$\langle \mu M_t, f\rangle = \langle \mu, M_t f\rangle.$$

This left semigroup then yields the measure solutions to Equation (1.2) with constant σ. The study of a single neuron can then be also seen as the dynamics of an unconnected network, *i.e.* with connectivity $J = 0$.

The semigroup $(M_t)_{t\geq 0}$ is positive and conservative, in the sense that it leaves invariant the set of probability measures, and it additionally satisfies the following Doeblin condition:

$$\mu M_\tau \geq c\nu \tag{1.4}$$

for all $\mu \in \mathscr{P}([0,1])$, with

$$\tau = \log\frac{4}{h} > 0, \qquad c = \frac{\sigma}{2}\left(\frac{h}{4}\right)^{\sigma} \in (0,1), \qquad \nu = \frac{2}{h}\mathbf{1}_{[\frac{h}{2},h]} \in \mathscr{P}([0,1]).$$

Consequently it admits a unique invariant measure γ_σ, and it is exponentially ergodic with explicit constants: for all $\mu \in \mathscr{P}([0,1])$ and for all $t \geq 0$

$$\|\mu M_t - \gamma_\sigma\|_{\mathrm{TV}} \leq \mathrm{e}^{-\omega(t-\tau)}\,\|\mu - \gamma_\sigma\|_{\mathrm{TV}}$$

where τ is given above, and

$$\omega = \frac{-\log\left(1-\frac{\sigma}{2}\left(\frac{h}{4}\right)^{\sigma}\right)}{\log\frac{4}{h}}.$$

This result is crucial for studying the nonlinear coupled model, *i.e.* when $J>0$. First, finding a steady state now reduces to find $\sigma>0$ such that

$$\sigma = \frac{\sigma_0}{1-J\gamma_\sigma([1-h,1])}$$

and this allows us to prove points *(i)* and *(ii)* by performing an asymptotic analysis of $\gamma_\sigma([1-h,1])$ when σ goes to zero or infinity.

Next, for the uniqueness and the exponential asymptotic stability of the steady state in the weakly connected regime, we use the following Duhamel formula

$$\langle p_t, f\rangle = \langle p_0, M_t f\rangle + \int_0^t (\sigma(s)-\sigma)\langle p_s, \mathscr{B}M_{t-s}f\rangle \mathrm{d}s$$

which is rigorously proved to be valid. Then combining the exponential ergodicity of $(M_t)_{t\geq 0}$ and Grönwall's lemma yields the result of point *(iii)*. □

Some comments and perspectives. To our knowledge, it is the first time the asynchronous property of the mean-field LIF model is proved mathematically. Before this work, the asynchronicity was studied only on the diffusion approximation of Equation (1.2). This variant takes the form of a nonlinear Fokker-Planck equation, and can be derived formally by making an asymptotic expansion when $h\to 0$ in Equation (1.2), see [174, 175, 193], or directly from the LIF model (1.1) by replacing the jumps by a Gaussian white noise [33, 34]. Using entropy method and Poincaré inequalities, the diffusive model has been studied mathematically by Cáceres, Carrillo, Perthame, Salort, and Smets [45, 56].

The mean-field equation (1.2) as well as its diffusion approximation allow to capture the synchrony property of the neural circuits. The dynamics of a neural network made up of LIF neurons is exposed in Fig. 1.2, for two different coupling parameters. As we can see, for weak coupling, the network displays an asynchronous activity where each neuron fires irregularly (Fig. 1.2 A). In contrast, when the coupling parameter is taken sufficiently large, the network enters into a synchronous state (Fig. 1.2 B). The system seems to have a critical coupling value for which, above this value, the system is driven to a synchronous state, while below this value, it remains asynchronous [170, 171]. At the mean-field level, the asynchronous case corresponds to the existence of a steady state while a synchronous spiking event can be interpreted as the blow-up of the firing activity $r(t)$. Finite time blow-up was first proved to occur for the diffusive equation when $J>1$ and the initial distribution is concentrated enough around $v=1$ in [45]. The proof was then adapted by Dumont and Henry in [93] to prove that the solutions to Equation (1.2) blow-up in finite time for any initial data when

$$J \geq 1 + \frac{1-V^R}{h} \qquad \text{and} \qquad \sigma_0 > \frac{1}{h}.$$

It is worth comparing these conditions to the ones appearing in points *(i)* and *(ii)* of Theorem 1.1, since of course no steady state can exist when blow-up occurs whatever the initial data.

Looking at Fig. 1.2 B, a natural perspective of future work would be to find a rule for restarting the dynamics after blow-up. A good starting point is [79] where such a rule is proposed in the case of non leaky neurons,

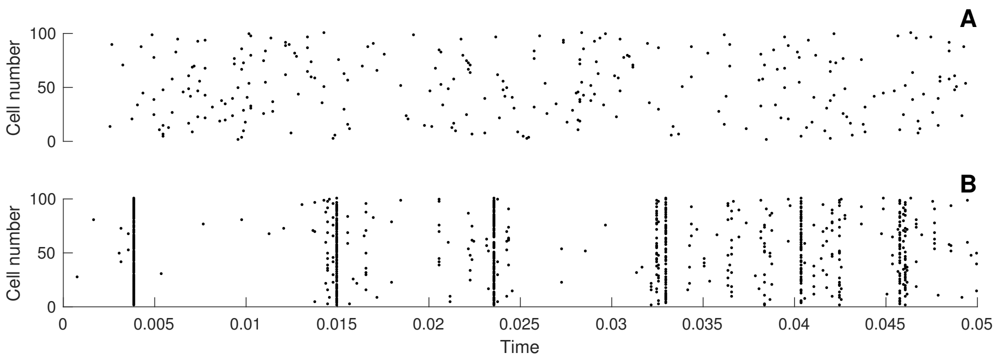


Fig. 1.2 Simulations of the neural network. The network contains $N = 100$ neurons. In each panel is shown the spiking activity of every neuron in a raster plot (dots represent spikes). The parameters are: $h = 0.1$, $V^R = 0.1$ and Poisson rate 200. The average affected cells J is: A) $J = 1$, B) $J = 9$.

i.e. without the drift term in Equation (1.2). Then a interesting but challenging question would concern the existence of solutions with periodic blow-up events.

Chapter 2

A non-conservative Harris theorem

The results presented in this chapter are based on the publications [P14, P16, P19, P20], which are the fruits of a collaboration with Vincent BANSAYE, Bertrand CLOEZ, and Aline MARGUET.

2.1 Introduction

We have introduced in Chapter 1 a semigroup $(M_t)_{t\geq 0}$ associated to a Markov process, and we have seen the crucial role played by the ergodicity of this semigroup in the study of the asynchrony of a neural network. This ergodicity was a consequence of the Doeblin condition satisfied by the semigroup. We recall here this result in a more abstract setting.

Doeblin contraction. Consider a measurable state space $\mathbf{X}$ and a positive semigroup $(M_t)_{t\geq 0}$ of kernel operators on $\mathbf{X}$, namely a semigroup of linear operators M_t which act both on $\mathscr{L}^\infty(\mathbf{X})$ on the right and on $\mathscr{M}(\mathbf{X})$ on the left, are positive in the sense that they leave invariant the positive cones of both spaces, and enjoy the duality relation $\langle \mu M_t, f\rangle = \langle \mu, M_t f\rangle$ for all $\mu \in \mathscr{M}(\mathbf{X})$ and $f \in \mathscr{L}^\infty(\mathbf{X})$. Such a semigroup is said to be *conservative* if its right action is a Markov semigroup, meaning that $M_t\mathbf{1} = \mathbf{1}$ for all $t \geq 0$, or equivalently if its left action is a stochastic semigroup, meaning that it leaves invariant the set $\mathscr{P}(\mathbf{X})$ of probability measures. If $(M_t)_{t\geq 0}$ is conservative and additionally satisfies the so-called Doeblin condition

$$M_\tau f(x) \geq c\langle \nu, f\rangle \tag{2.1}$$

for some $\tau > 0$, $c \in (0,1)$ and $\nu \in \mathscr{P}(\mathbf{X})$, and for all $x \in \mathbf{X}$ and $f \in \mathscr{L}^\infty_+(\mathbf{X})$, then it admits a unique invariant measure $\gamma \in \mathscr{P}(\mathbf{X})$ which is exponentially stable for the total variation distance: for all $t \geq 0$ and all $\mu \in \mathscr{P}(\mathbf{X})$

$$\|\mu M_t - \gamma\|_{\mathrm{TV}} \leq \mathrm{e}^{-\omega(t-\tau)}\, \|\mu - \gamma\|_{\mathrm{TV}}$$

where

$$\omega = \frac{-\log(1-c)}{\tau}.$$

This result originates from the pioneering work of Doeblin [83] and is now standard. We refer for instance to [P14, P15] for a proof, noting that Doeblin's condition (2.1) is equivalent to its dual formulation (1.4) due to the duality between the left and right actions of M_τ. The proof is elementary but crucially uses the conservativeness of the semigroup and Doeblin's inequality, which are quite restrictive conditions.

Harris ergodicity. Doeblin's condition essentially means that there is an area in $\mathbf{X}$, characterized by ν, which can be reached with positive probability c after a fixed time τ, uniformly with respect to the initial position x in $\mathbf{X}$. This typically fails when $\mathbf{X}$ is "unbounded", with the probability usually vanishing when x tends to "infinity". Harris's idea [130] allows relaxing Doeblin's condition by localizing it in some "small" set which is visited infinitely often. By using Lyapunov functions, this idea allows getting a spectral gap in a weighted supremum norm [162, 163], see also [127] for a simplified analytical proof. Consider a conservative semigroup $(M_t)_{t\geq 0}$ which acts on $\mathscr{L}^\infty(V)$ and $\mathscr{M}(V)$ for some $V:\mathbf{X}\to[1,\infty)$ measurable, in such a way that

$$t\mapsto \|M_tV\|_{\mathscr{L}^\infty(V)}=\sup_{x\in\mathbf{X}}\frac{M_tV(x)}{V(x)} \quad \text{is locally bounded on } [0,\infty). \tag{2.2}$$

Assume that there exist $\tau>0$ and a subset $K\subset\mathbf{X}$ such that V is a Lyapunov function for M_τ and K, *i.e.* there exist some constants $\alpha\in(0,1)$ and $\theta>0$ such that

$$M_\tau V\leq \alpha V+\theta\mathbf{1}_K,$$

and K is a small set for M_τ, *i.e.* there exist a constant $c\in(0,1)$ and a probability measure ν supported by K such that for any $f\in\mathscr{L}^\infty_+(V)$

$$M_\tau f\geq c\langle\nu,f\rangle\mathbf{1}_K.$$

Then $(M_t)_{t\geq0}$ admits a unique invariant probability measure γ, which belongs to $\mathscr{M}(V)$, and there exist $C\geq1,\omega>0$ such that for all $\mu\in\mathscr{P}(\mathbf{X})\cap\mathscr{M}(V)$ and all $t\geq0$

$$\|\mu M_t-\gamma\|_{\mathscr{M}(V)}\leq C\mathrm{e}^{-\omega t}\|\mu-\gamma\|_{\mathscr{M}(V)}.$$

This V-uniform ergodicity result provides both quantitative estimates [127] and a necessary and sufficient condition [87, Chapter 15].

Doob h-transform. Conservative semigroups are classically generated by linear partial differential equations that model systems where the total number of particles is preserved along time. It arises when particles move without birth and/or death. When studying biological systems, birth and death processes are often involved, giving rise to non-conservative semigroups. In such situations, the dynamics is not expected to converge to an invariant measure, but rather to enjoy the so-called asynchronous exponential growth property, or asynchronous Malthusian behaviour,

$$\mu M_t\sim\langle\mu,h\rangle\mathrm{e}^{\lambda t}\gamma \qquad \text{as } t\to\infty \tag{2.3}$$

for all measure μ, where $\lambda\in\mathbb{R}$ is the Malthus parameter, h is a positive function, and γ is a positive measure with $\langle\gamma,h\rangle=1$. The triplet (λ,γ,h) consists of the Perron-Frobenius eigenelements of $(M_t)_{t\geq0}$, namely

$$\gamma M_t=\mathrm{e}^{\lambda t}\gamma \qquad \text{and} \qquad M_th=\mathrm{e}^{\lambda t}h$$

for all $t\geq0$. When λ and h are known to exist, the Doob h-transform [85, 172] allows defining a conservative semigroup $(P_t)_{t\geq0}$ by setting

$$P_tf=\frac{M_t(hf)}{\mathrm{e}^{\lambda t}h}. \tag{2.4}$$

Applying Harris's theorem to this conservative semigroup then provides conditions ensuring the existence of the eigenmeasure γ and a quantified exponential rate of convergence in (2.3) for the original semigroup $M_tf=\mathrm{e}^{\lambda t}hP_t(f/h)$. More precisely if (2.2) is verified for some $V\geq h$ and if there exist $\tau>0$ and $K\subset\mathbf{X}$ such that

$$M_\tau V \le \alpha V + \theta \mathbf{1}_K h, \tag{2.5}$$

for some $\alpha \in (0, \mathrm{e}^{\lambda\tau})$ and $\theta > 0$, and

$$M_\tau(fh) \ge c\langle \nu, f\rangle \mathrm{e}^{\lambda\tau}\mathbf{1}_K h \tag{2.6}$$

for any $f \in \mathscr{L}_+^\infty(V/h)$, with $c \in (0,1)$ and $\nu \in \mathscr{P}(\mathbf{X})$ such that $\operatorname{supp}\nu \subset K$, then there exist $\gamma \in \mathscr{M}(V)$ with $\langle\gamma, h\rangle = 1$ and constants $C \ge 1, \omega > 0$ such that for all $\mu \in \mathscr{M}(V)$ and all $t \ge 0$

$$\left\|\mathrm{e}^{-\lambda t}\mu M_t - \langle\mu, h\rangle\gamma\right\|_{\mathscr{M}(V)} \le C\mathrm{e}^{-\omega t}\left\|\mu - \langle\mu, h\rangle\gamma\right\|_{\mathscr{M}(V)}.$$

Embedded non-homogeneous semigroup. Getting the existence of λ and h is generally not trivial. In [P19] we consider the case when the existence of these eigenelements is not known *a priori*. We propose a counterpart of Harris's ergodic theorem in the non-conservative setting by deriving necessary and sufficient conditions for the existence of the triplet (λ, γ, h) and the exponential convergence. We additionally obtain quantitative estimates for the eigenelements and the speed of convergence. Our proof relies on the following non-homogeneous transform:

$$P_{u,s}^{(t)} f = \frac{M_{s-u}(f M_{t-s}\psi)}{M_{t-u}\psi}.$$

For a fixed time t and a positive function ψ, the family $(P_{u,s}^{(t)})_{0\le u\le s\le t}$ is conservative and satisfies the non-homogeneous semigroup property

$$P_{u,v}^{(t)}(P_{v,s}^{(t)} f) = P_{u,s}^{(t)} f.$$

Besides, for $u = 0$ and $s = t$ we have $P_{0,t}^{(t)} f = M_t(f\psi)/M_t\psi$, which reminds (2.4) but is not a semigroup in t unless ψ is an eigenfunction. To mimic the stabilizing property of the eigenfunction h in the h-transform, we assume that ψ satisfies

$$M_\tau \psi \ge \beta\psi$$

for some $\beta > 0$ and $\tau > 0$, similarly as in [70, 71]. This condition is in general much easier to check than the existence of an eigenfunction. We then construct a family of Lyapunov functions $(V_n)_{n\in\mathbb{N}}$ as follows

$$V_n = \left\langle \nu, \frac{M_{n\tau}\psi}{\psi}\right\rangle \frac{V}{M_{n\tau}\psi},$$

where ν is a probability measure. Assuming that V satisfies (2.5) with h replaced by ψ and $\alpha \in (0, \beta)$, these functions allow us to prove that $P^{(t)}$ enjoys some Lyapunov conditions. To prove that small set conditions are also met and invoke the contraction of the conservative framework, we complement the counterpart of (2.6) with a condition which ensures that there is no favored initial position in K in terms of asymptotical growth of mass. Such a mass control condition was first proposed by Champagnat and Villemonais in [62] for the study of the convergence of processes conditioned on non-absorption.

The next section is devoted to the precise statement of the main results obtained in [P19, P20]. Before that, let us mention that our results and method are linked to the study of the geometric ergodicity of Feynman-Kac type semigroups

$$M_t f(x) = \mathbb{E}\left[f(X_t)\mathrm{e}^{\int_0^t F(X_s)\mathrm{d}s} \,|\, X_0 = x\right].$$

The analysis of these non-conservative semigroups has been developed in a general setting in [103, 143, 144] and is motivated by various applications. They appear in particular for the study of branching processes [24, 26, 69, 156] and large deviations [84, 143, 144, 201], as well as metastability [135]. Our approach allows us to relax some assumptions and provide more quantitative results.

2.2 Main results

We consider two measurable functions $V:\mathbf{X}\to(0,\infty)$ and $\psi:\mathbf{X}\to(0,\infty)$, with $V\geq\psi$, and a positive semigroup $(M_t)_{t\geq0}$ of kernel operators on $\mathscr{L}^\infty(V)\times\mathscr{M}(V)$ which verifies (2.2). We state now the key Assumption **A**.

Assumption A. *There exist $\tau>0$, $\beta>\alpha>0$, $\theta>0$, $(c,d)\in(0,1)^2$, $K\subset\mathbf{X}$, and ν a probability measure on $\mathbf{X}$ supported by K, such that $\sup_K V/\psi<\infty$ and*

(A1) $M_\tau V\leq\alpha V+\theta\mathbf{1}_K\psi$,

(A2) $M_\tau\psi\geq\beta\psi$,

(A3) $\displaystyle\inf_{x\in K}\frac{M_\tau(f\psi)(x)}{M_\tau\psi(x)}\geq c\langle\nu,f\rangle$ *for all* $f\in\mathscr{L}^\infty_+(V/\psi)$,

(A4) $\displaystyle\left\langle\nu,\frac{M_{n\tau}\psi}{\psi}\right\rangle\geq d\sup_{x\in K}\frac{M_{n\tau}\psi(x)}{\psi(x)}$ *for all positive integers n.*

Assumption **A** is related to classical assumptions for the ergodicity of non-conservative semigroups [63, 103, 135, 143, 144, 202, 203, P16]. It relaxes such criteria and provides necessary conditions for exponential convergence in weighted total variation distance. More precisely we have the following theorem, which is the main result of [P19] [1].

Theorem 2.1. *(i) Assume that (V,ψ) satisfies Assumption **A**. Then, there exists a unique triplet $(\lambda,\gamma,h)\in\mathbb{R}\times\mathscr{M}_+(V)\times\mathscr{L}^\infty_+(V)$ of eigenelements of $(M_t)_{t\geq0}$ with $\langle\gamma,h\rangle=\|h\|_{\mathscr{L}^\infty(V)}=1$. Moreover, there exist $C\geq1$ and $\omega>0$ such that for all $t\geq0$ and $\mu\in\mathscr{M}(V)$,*

$$\left\|\mathrm{e}^{-\lambda t}\mu M_t-\langle\mu,h\rangle\gamma\right\|_{\mathscr{M}(V)}\leq C\mathrm{e}^{-\omega t}\left\|\mu-\langle\mu,h\rangle\gamma\right\|_{\mathscr{M}(V)}. \tag{2.7}$$

*(ii) Assume that there exist an eigentriplet $(\lambda,\gamma,h)\in\mathbb{R}\times\mathscr{M}_+(V)\times\mathscr{L}^\infty_+(V)$ and constants $C,\omega>0$ such that (2.7) holds. Then, the couple (V,h) satisfies Assumption **A**.*

In case *(i)* we have additionally the estimates $\log(\beta)/\tau\leq\lambda\leq\log(\alpha+\theta)/\tau$ and $\frac{1}{R}(\psi/V)^q\psi\leq h\leq V$ for some $q,R>0$. Besides, all the constants ω, C, q and R are explicit in the proof.

The inequalities in Assumption **A** may seem difficult to check in practice. We now give more tractable sufficient conditions.

Drift conditions on the generator for (A1)-(A2). Assumptions (A1)-(A2) can be checked more easily by using the generator $\mathscr{A}$ of the semigroup $(M_t)_{t\geq0}$, similarly as for the Lyapunov condition in the consevative setting [163]. We give here such sufficient conditions by adopting a weak but practical definition of the generator, which can be seen as a mild formulation of $\mathscr{A}=\partial_t M_{t|_{t=0}}$, similarly as in [126]. For $F,G\in\mathscr{L}^\infty(V)$ we say that

$$\mathscr{A}F=G$$

if for all $x\in\mathbf{X}$ the function $s\mapsto M_sG(x)$ is locally integrable, and for all $t\geq0$

$$M_tF=F+\int_0^t M_sG\,ds.$$

[1] Subsequently, the strict positivity assumption on ψ was relaxed in [64, 65].

In general for $F \in \mathscr{L}^\infty(V)$, there may not exist $G \in \mathscr{L}^\infty(V)$ such that $\mathscr{A}F = G$, meaning that F is not in the domain of $\mathscr{A}$. Therefore we relax the definition by saying that

$$\mathscr{A}F \leq G, \qquad \text{resp.} \quad \mathscr{A}F \geq G,$$

if for all $t \geq 0$

$$M_tF - F \leq \int_0^t M_sG\,ds, \qquad \text{resp.} \quad M_tF - F \geq \int_0^t M_sG\,ds.$$

We can now state the drift conditions on $\mathscr{A}$ guaranteeing the validity of Assumptions (A1)-(A2).

Proposition 2.2. *Let $V, \psi_0 : \mathbf{X} \to (0,\infty)$ such that, for some constants $a < b$ and $\zeta \geq 0$,*

$$\mathscr{A}V \leq aV + \zeta\psi_0 \qquad \text{and} \qquad \mathscr{A}\psi_0 \geq b\psi_0.$$

Then, for any $\tau > 0$, there exists $R > 0$ such that V and $\psi = M_\tau\psi_0$ satisfy (A1)-(A2) with $K = \{V \leq R\psi\}$.

Irreducibility (and aperiodicity) for (A3)-(A4). Irreducibility is known to be a fundamental notion in Perron-Frobenius theory or Krein-Rutman theory, as well as in the study of Markov chains. We propose here irreducibility-type criteria based on coupling arguments that provide tractable sufficient conditions for Assumptions (A3) and (A4). The notion of irreducibility basically refers to the property that all the states are reachable from any initial position. In its classical form, it can be defined as the property that any x in $\mathbf{X}$ is send to any y of $\mathbf{X}$ with positive probability after a certain time τ. This corresponds to the standard definition which proves very useful in the case a finite state space for studying nonnegative matrices. We first give a result which guarantee that such a condition is sufficient for ensuring (A3)-(A4) in the case of a finite set K, provided that the time τ is the same for all the couples (x,y) in K, which ensures an additional property of aperiodicity.

Proposition 2.3. *Let K be a finite subset of $\mathbf{X}$ and assume that there exists $\tau > 0$ such that for any $x, y \in K$,*

$$\delta_x M_\tau(\{y\}) > 0. \tag{2.8}$$

Then (A3)-(A4) are satisfied for any positive function $\psi \in \mathscr{L}^\infty(V)$.

This sufficient condition is relevant for the study of irreducible processes on discrete spaces. As a motivation, let us mention the study of the first moment semigroup of discrete branching or absorbed processes in continuous time and more generally of the exponential of denumerable non-negative matrices, for which irreducibility is generally easy to check.

In the case of a continuous state space, the irreducibility condition (2.8) is not relevant since the probability of reaching a prescribed position at a fixed time is most of the time zero. When dealing with continuous time Markov processes, one can relax this condition by asking any position y to be visited with positive probability during a time interval, whatever the initial position x. Formulating this idea in terms of the semigroup associated to the Markov process is not entirely clear. In [P20] we propose a condition in this vein, which is actually even a bit weaker.

Proposition 2.4. *Assume that $t \mapsto \|\psi/M_t\psi\|_\infty$ is locally bounded. If for some $\tau > 0$ and a family of probability measures $(\sigma_{x,y})_{x,y\in K}$ over $[0,\tau]$ there exists a constant $c > 0$ such that for all $f \in \mathscr{L}^\infty_+(V)$ and all $x, y \in K$*

$$\frac{M_\tau f(x)}{\psi(x)} \geq c \int_0^\tau \frac{M_{\tau-s}f(y)}{\psi(y)}\sigma_{x,y}(\mathrm{d}s), \tag{2.9}$$

then Assumption (A4) is verified for some $d > 0$ and any probability measure ν on K.

When ψ is bounded from above and below by a positive constant on K, (2.9) with $\sigma_{x,y} = \delta_\tau$ reads equivalently $\delta_x M_\tau(\{y\}) \geq c$. Condition (2.9) can thus be seen as a generalisation of Condition (2.8). It is typically satisfied when, starting from x, the position y is visited in the time interval $[0,\tau]$ with positive probability. But more generally Condition (2.9) means that the trajectories issued from x at time 0 cross at time τ the trajectories issued from y at random times $s \in [0,\tau]$ distributed according to $\sigma_{x,y}$, with probability $c\psi(x)/\psi(y)$. Condition (2.9) is stronger than (A4), but when it holds true it appears to be often easier to check than (A4) since it is restricted to a finite time interval.

Contrary to Proposition 2.3, Condition (2.9) does not imply (A3), since it does not prevent from periodicity. A typical example is provided by the semigroup defined on $\mathbf{X} = [0,1]$ by $M_t f(x) = f(x+t-\lfloor x+t \rfloor)$, which satisfies (2.9) but not (A3). A way to prevent such a behaviour is to impose the following additional aperiodicity condition:

$$\sup_{x_1,x_2 \in K} \inf_{y \in K} \int_0^\tau \frac{M_{\tau-s}(\psi \mathbf{1}_K)(y)}{\psi(y)} (\sigma_{x_1,y} \wedge \sigma_{x_2,y})(\mathrm{d}s) > 0. \tag{2.10}$$

It is still not enough for ensuring (A3), but it suffices to guarantee a weaker variant, namely the existence of a constant $c \in (0,1)$ and a family $(\nu_{x_1,x_2})_{x_1,x_2 \in K}$ of probability measures on K such that for all $x_1, x_2 \in K$, $i \in \{1,2\}$, and all $f \in \mathscr{L}^\infty_+(V/\psi)$

$$\frac{M_\tau(f\psi)(x_i)}{M_\tau \psi(x_i)} \geq c \langle \nu_{x_1,x_2}, f \rangle.$$

It turns out that it is actually enough using this relaxed small set condition instead of (A3) in Assumption **A** for proving the point *(i)* of Theorem 2.1.

Proposition 2.5. *Assume that $t \mapsto \|\psi/M_t\psi\|_\infty$ is locally bounded and that there exist $\tau > 0$ and $K \subset \mathbf{X}$ such that $\sup_K V/\psi < \infty$ and*

- *(A1) and (A2) are satisfied for some $\beta > \alpha > 0$ and $\theta > 0$,*
- *(2.9) and (2.10) are satisfied for some $c > 0$ and a family of probability measures $(\sigma_{x,y})_{x,y \in K}$ over $[0,\tau]$.*

Then the conclusion of (i) in Theorem 2.1 holds true.

We end this paragraph with a remark about other standard notions of irreducibility.

Remark 2.6. *A notion of irreducibility which classically arises in probability is the so-called φ-irreducibility, see e.g. [162, 172]. It means that there is a σ-finite measure φ on $\mathbf{X}$ such that for all $\Omega \subset \mathbf{X}$ satisfying $\varphi(\Omega) > 0$ and any initial position $x \in \mathbf{X}$*

$$\delta_x M_\tau(\Omega) > 0$$

for some $\tau > 0$. This can be strengthened by requiring this positivity to hold for all time sufficiently large: A semigroup $(M_t)_{t\geq 0}$ is said to be φ-irreducible and aperiodic if for all $\Omega \subset \mathbf{X}$ satisfying $\varphi(\Omega) > 0$ and any initial position $x \in \mathbf{X}$ there exists $\tau > 0$ such that $\delta_x M_t(\Omega) > 0$ for all $t \geq \tau$.

Irreducibility is also an important concept in Banach lattice theory. A positive semigroup $(M_t)_{t\geq 0}$ on a Banach lattice E is called irreducible if for all $\mu \in E_+$, $f \in E'_+$, $\mu \neq 0$, $f \neq 0$, there exists $\tau > 0$ such that

$$\langle \mu M_\tau, f \rangle > 0.$$

We refer to [8, Definition C-III.3.1] for alternative equivalent definitions. Irreducibility in $E = \mathscr{M}(\mathbf{X})$ implies the original form of irreducibility, namely that for any $x, y \in \mathbf{X}$ there exists $\tau > 0$ such that (2.8) is satisfied, while irreducibility in $E = L^1(\mathbf{X},\varphi)$ is implied by φ-irreducibility for semigroups defined on $\mathscr{M}(\mathbf{X})$ that leave invariant $L^1(\mathbf{X},\varphi)$.

2.3 Comparison with other methods

Theorem 2.1 provides a powerful tool for proving the exponential ergodicity of linear partial differential equations (PDEs). We now briefly compare this approach to two classical other methods: spectral analysis of linear semigroups and entropy inequalities.

Spectral analysis of semigroups. Let E be a Banach lattice and $(M_t)_{t\geq 0}$ a strongly continuous positive semigroup on E: $\mu \in E \mapsto \mu M_t \in E$. By duality we can define the dual semigroup on E': $f \in E' \mapsto M_t f \in E'$. We have the following result, readily deduced from *e.g.* [207, Remark 2.2] or [8, Theorem C-IV.2.1 and Remarks 2.2].

Theorem 2.7 ([207] or [8]). *Assume that $(M_t)_{t\geq 0}$ is irreducible and that there exist $\tau > 0$, $\alpha > \beta > 0$, two operators $S, R \in \mathscr{L}(E)$ with $\|S\| \leq \alpha$ and R compact, and $\psi \in E'$ such that*

$$M_\tau = S + R \qquad \textit{and} \qquad M_\tau \psi \geq \beta \psi. \tag{2.11}$$

Then there exist $(\lambda, \gamma, h) \in \mathbb{R} \times E \times E'$ and $C \geq 1, \omega > 0$ such that for all $\mu \in E$ and all $t \geq 0$

$$\left\| \mu M_t \mathrm{e}^{-\lambda t} - \langle \mu, h \rangle \gamma \right\|_E \leq C \mathrm{e}^{-\omega t} \left\| \mu - \langle \mu, h \rangle \gamma \right\|_E. \tag{2.12}$$

Let us make some comments on this result.

- The proof relies on the notions of *measure of noncompactness* and *essential spectrum*. Assumption (2.11) guarantees that $r_{\mathrm{ess}}(M_\tau) = r_{\mathrm{ess}}(S) \leq r(S) \leq \|S\| \leq \alpha < \beta \leq r(M_\tau)$. This spectral gap property combined with the irreducibility condition yields the result.
- There are links between the essential spectral radius and the existence of a Lyapunov function. More precisely it is proved in [209] that for $\mathbf{X}$ a Polish space and under a local Dunford-Pettis type assumption, if there exist a function $V : \mathbf{X} \to [1, \infty)$, a compact subset K of $\mathbf{X}$, and constants $\alpha, \theta > 0$ such that $M_\tau V \leq \alpha V + \theta \mathbf{1}_K V$, then $r_{\mathrm{ess}}(M_\tau) \leq \alpha$ in the space $\mathscr{L}^\infty(V)$.
- Due to the works of Kato [140] and Pelczyński [176] on strictly singular operators, the compactness condition on R can be replaced by weak compactness when E is a L^1 space.
- When the eigentriplet (λ, γ, h) is known to exist *a priori* and is unique, the irreducibility assumption is not required for getting the exponential convergence, see Remark 2.2 in [207]. Also, we can use $\psi = h$.
- Recently Mischler and Scher [167] revisited the spectral analysis of semigroups without using the notions of measure of non-compactness or essential spectrum. They proposed a more elementary proof, based on a splitting of the generator, of a variant of Theorem 2.11 where the irreducibility condition of the semigroup is replaced by a strong maximum principle on the generator.

Finally, let us list some positive and negative points of this method compared to Harris's theory:

+ The result in Theorem 2.7 applies in general Banach lattices, while Harris's theorem deals with semigroups on the spaces $\mathscr{M}(V)$ and $\mathscr{L}^\infty(V)$.
+ The spectral gap property $r_{\mathrm{ess}}(M_\tau) < r(M_\tau)$ actually provides more informations about the spectrum than only the conclusion of Theorem 2.7.
– The constants C and ω in Theorem 2.7 are not quantified.
– Spectral methods are not applicable to time-inhomogeneous semigroups, contrary to Harris's approach (see Section 2.4).

General Relative Entropy. Entropy methods, reminiscent from Lyapunov functions for (nonlinear) ordinary differential equations, are elegant and powerful tools for analysing stability and convergence issues in the theory of (linear or nonlinear) PDEs. Consider an evolution equation posed on a subset D of vector space E. An entropy (or Lyapunov functional) for this equation is a function $\mathscr{H} : D \to \mathbb{R}$ which decreases along the trajectories: for any solution $(u_t)_{t\geq 0}$ to the evolution equation and for all time $t \geq 0$ the dissipation of entropy is non-negative

$$\mathscr{D}[u_t] = -\frac{\mathrm{d}}{\mathrm{d}t}\mathscr{H}[u_t] \geq 0.$$

Using compactness arguments, this inequality usually allows deriving LaSalle's invariance principle, namely that the set of accumulation points of any trajectory is contained in F, the largest subset of $\{u \in D : \mathscr{D}[u] = 0\}$ which is invariant under the dynamics of the equation. When F is reduced to a single point $\bar{u}$, this point is then the unique equilibrium and it is asymptotically stable. If additionally the entropy is non-negative and is dominated by its dissipation through a Poincaré type inequality, *i.e.* there exists $\omega > 0$ such that for all $u \in D$

$$\mathscr{H}[u] \leq \frac{1}{\omega}\mathscr{D}[u], \tag{2.13}$$

then it decreases exponentially fast along the trajectories to its minimum $0 = \mathscr{H}[\bar{u}]$

$$\mathscr{H}[u_t] \leq \mathscr{H}[u_0]\mathrm{e}^{-\omega t}. \tag{2.14}$$

In the context of linear PDEs, the notion of *General Relative Entropy* (GRE) was introduced in 2005 by Michel, Mischler, and Perthame [164]. It extends to non-conservative equations the notion of relative entropy for conservative parabolic, hyperbolic, or integral equations, by involving a solution to the associated dual equation. Consider such an equation set on a space E of functions defined on a state space $\mathbf{X}$. In the case where particular solutions are provided by a Perron-Frobenius eigenvalue problem, *i.e.* when there exist positive solutions $t \mapsto \mathrm{e}^{\lambda t}\gamma$ and $t \mapsto \mathrm{e}^{\lambda t}h$ to the direct and dual equations respectively, the GRE principle states that for any convex function $H : E \to \mathbb{R}$ the functional

$$\mathscr{H}[u] = \int_{\mathbf{X}} H\Big(\frac{u}{\gamma}\Big)\gamma h$$

is an entropy for the rescaled dynamics $t \mapsto \mathrm{e}^{-\lambda t}u_t$. When the set F is the vector space spanned by γ, LaSalle's invariance principle usually allows deriving the asynchronous exponential growth property. If additionally the function H is non-negative and a Poincaré inequality is available on the level sets of $u \mapsto \langle u, h\rangle$, then the convergence is exponential. Note that an important class of convex functions is provided by the choice $H(u) = |u|^p$ with $p \geq 1$, since in this case $\mathscr{H}[u] = \|u\|_E^p$ with $E = L^p(\gamma^{p-1}h)$.

Let us now list some positive and negative points of this method compared to Harris's theory:

+ If the Poincaré inequality (2.13) is valid for the choice $H(u) = |u|^p$ $(p \geq 1)$, then inequality (2.14) yields coercivity in the space $E = L^p(\gamma^{p-1}h)$, *i.e.* (2.12) holds with the optimal constant $C = 1$.
+ LaSalle's invariance principle allows addressing more general situations than the convergence to a steady state. In Chapter 3, Section 3.3, we give an example of application of GRE in a case where F is an infinite dimensional space, leading to an oscillatory asymptotic behaviour.
- The Perron-Frobenius eigentriplet (λ, γ, h) is required to be known *a priori* for defining the GRE.
- Poincaré inequalities can be hard to obtain in general, especially for non-local equations.

2.4 Time-inhomogeneous semigroups and a few other perspectives

Harris's approach is based on a contraction argument for discrete times, and can thus be applied to time-inhomogeneous semigroups. We call time-inhomogeneous semigroup a two indexed family $(M_{s,t})_{0\leq s\leq t}$ of operators which satisfies the following extension of the semigroup property

$$M_{s,u}M_{u,t} = M_{s,t}$$

for any $t \geq u \geq s \geq 0$. It is naturally associated to PDEs with time-varying coefficients or time-inhomogeneous Markov processes. A particular interesting case is provided by periodic semigroups, *i.e.* time-inhomogeneous semigroups which are T-periodic for some $T > 0$ in the sense that

$$M_{s+T,t+T} = M_{s,t}$$

for all $t \geq s \geq 0$. They typically appear in biological models which take into account the time periodicity of the environment. Harris's method can be easily adapted to the periodic framework to provide some extension of the Floquet theory of periodic matrices [107] to periodic semigroups. We say that $(\lambda_F, \gamma_{s,t}, h_{s,t})_{0\leq s\leq t}$ is a Floquet eigenfamily for the T-periodic semigroup $(M_{s,t})_{0\leq s\leq t}$ if the families $(\gamma_{s,t})_{0\leq s\leq t}$ and $(h_{s,t})_{0\leq s\leq t}$ are T-periodic in the sense that

$$\gamma_{s+T,t+T} = \gamma_{s,t} = \gamma_{s,t+T} \qquad \text{and} \qquad h_{s+T,t+T} = h_{s,t} = h_{s,t+T}$$

for all $t \geq s \geq 0$, and are associated to the Floquet eigenvalue λ_F in the sense that

$$\gamma_{s,s}M_{s,t} = \mathrm{e}^{\lambda_F(t-s)}\gamma_{s,t} \qquad \text{and} \qquad M_{s,t}h_{t,t} = \mathrm{e}^{\lambda_F(t-s)}h_{s,t}$$

for all $t \geq s \geq 0$. The following result is readily deduced from the proofs of Theorem 2.1 above and [P16, Theorem 3.15].

Theorem 2.8. *Let $(M_{s,t})_{0\leq s\leq t}$ be a T-periodic semigroup such that $(s,t) \mapsto \|M_{s,t}V\|_{\mathscr{L}^\infty(V)}$ is locally bounded, and suppose that $M_{0,\tau}$ satisfies Assumption* **A** *for some functions $V \geq \psi > 0$, with $\tau = nT$ for some integer n. Then there exist a unique T-periodic Floquet family $(\lambda_F, \gamma_{s,t}, h_{s,t})_{0\leq s\leq t} \subset \mathbb{R} \times \mathscr{M}(V) \times \mathscr{L}^\infty(V)$ such that $\langle \gamma_{s,s}, h_{s,s}\rangle = \|h_{s,s}\|_{\mathscr{L}^\infty(V)} = 1$ for all $s \geq 0$, and there exist $C \geq 1$, $\omega > 0$ such that for all $t \geq s \geq 0$ and all $\mu \in \mathscr{M}(V)$,*

$$\left\|\mathrm{e}^{-\lambda_F(t-s)}\mu M_{s,t} - \langle \mu, h_{s,s}\rangle\gamma_{s,t}\right\|_{\mathscr{M}(V)} \leq C\mathrm{e}^{-\omega(t-s)}\left\|\mu - \langle \mu, h_{s,s}\rangle\gamma_{s,s}\right\|_{\mathscr{M}(V)}.$$

To conclude this section and this chapter, let us give some chalenging perspectives of future work.

- In [P16], generalized Doeblin's conditions are proposed for deriving the ergodicity of general non-conservative time-inhomogeneous semigroups (not only periodic). It would be interesting to localize these conditions in small sets by means of Lyapunov functions as in the Harris approach. This would provide a powerful tool for tackling various time-inhomogeneous problems, as for instance optimal control problems.
- Assumption (A4) is usually the most delicate condition to verify in Assumption **A**. It can be deduced from Harnack inequalities when available, typically in the case of diffusive processes as in [62, 63, 202], or through other sufficient conditions as the ones proposed in [203] for the study of absorbed Markov processes or Condition (2.9) in Proposition 2.4. While (2.9) is well suited for the case of a one dimensional state space **X**, it is generally too restrictive to be applicable in higher dimensions. It would be valuable to relax this condition for deriving a handy criterion which could be applied to a wide range of semigroups.
- Working with total variation distances is quite demanding. Wasserstein type distances are more flexible and can reveal more suitable in some situations. A result of exponential ergodicity in the flat norm, also

called Fortet-Mourier norm, was recently obtained in [100] by means of spectral analysis of semigroups. In [128] a general form of Harris's theorem is proposed, which extends the classical conservative Harris result to more general distances. Extending this work to non-conservative semigroups might be tricky but could prove very useful for applications.

- Ergodicity with sub-geometric speed of convergence can also be addressed via Harris's theory, see [86, 126]. These results are about conservative semigroups and, again, it would be interesting to extend this approach to the non-conservative setting.

Chapter 3

Growth-fragmentation

We gather in this chapter some results obtained in joint works with Daniel BALAGUÉ, José A. CAÑIZO and Havva YOLDAŞ [P4, P22], Vincent BANSAYE, Bertrand CLOEZ and Aline MARGUET [P16, P19], Étienne BERNARD and Marie DOUMIC [P11, P12, P18], Hugo MARTIN [P21], Francesco SALVARANI [P5], as well as in [P9].

3.1 Introduction and state of the art

We are interested in the following so-called growth-fragmentation equation

$$\frac{\partial}{\partial t}u_t(x)+\frac{\partial}{\partial x}\big(g(x)u_t(x)\big)+B(x)u_t(x)=\int_0^1 B\Big(\frac{x}{z}\Big)u_t\Big(\frac{x}{z}\Big)\frac{\wp(\mathrm{d}z)}{z} \tag{3.1}$$

This non-local evolution PDE appears in the modelling of various physical or biological phenomena [11, 12, 160, 177, 188]. The unknown u_t represents the population density at time t of some "particles" characterized by their "size" $x>0$. Each particle with size x grows with speed $g(x)$ and splits with rate $B(x)$ to produce smaller particles of sizes zx with $0<z<1$ distributed with respect to the fragmentation kernel $\wp$. This kernel is a finite positive measure on the open interval $(0,1)$ with unit first moment

$$\int_0^1 z\,\wp(\mathrm{d}z)=1.$$

This condition guarantees that the total "mass" is preserved at fragmentation events: the sum of the sizes of the fragments is equal to the size of the mother particle.

Equation (3.1) is also the Kolmogorov (forward) equation of the underlying piecewise deterministic Markov process [27, 52, 69, 77, 90, 156]. Let us explain this briefly and informally. Consider the measure-valued branching process $Z=(Z_t)_{t\geq 0}$ defined as the empirical measure

$$Z_t=\sum_{i\in\mathscr{V}_t}\delta_{X_t^i}$$

where $\mathscr{V}_t$ is the set of individuals alive at time t and $\{X_t^i : i\in\mathscr{V}_t\}$ the set of their sizes. For each individual $i\in V_t$ the size X_t^i grows following the deterministic flow $\frac{\mathrm{d}}{\mathrm{d}t}X_t^i=g(X_t^i)$ until a division time T_i which occurs stochastically in a Poisson-like fashion with rate $B(X_t^i)$. Then the individual i dies and gives birth to n new smaller particles $i_1,\cdots,i_n$ with sizes $X_{T_i}^{i_1},\cdots,X_{T_i}^{i_n}$ such that $X_{T_i}^{i_1}+\cdots+X_{T_i}^{i_n}=X_{T_i}^i$. These new particles evolve independently according to the same dynamics. Taking the expectation of the random measures Z_t, we get a family of measures u_t, defined for any Borel set $A \subset (0,\infty)$ by

$$u_t(A) = \mathbb{E}\big[Z_t(A)\big] = \mathbb{E}\big[\#\{i \in \mathscr{V}_t,\ X_t^i \in A\}\big],$$

which is a weak solution to Equation (3.1). Another Kolmogorov equation is classically associated to $(Z_t)_{t\geq 0}$, which is the dual equation of (3.1)

$$\frac{\partial}{\partial t}\varphi_t(x) = g(x)\frac{\partial}{\partial x}\varphi_t(x) - B(x)\varphi_t(x) + B(x)\int_0^1 \varphi_t(zx)\wp(\mathrm{d}z). \tag{3.2}$$

This second equation is sometimes written in its backward version where $\frac{\partial}{\partial t}\varphi_t(x)$ is replaced by $-\frac{\partial}{\partial t}\varphi_t(x)$, and is then usually called Kolmogorov backward equation. For an observation function f, we have that

$$\varphi_t(x) = \mathbb{E}\big[\langle Z_t, f\rangle \,|\, Z_0 = \delta_x\big] = \mathbb{E}\Bigg[\sum_{i\in\mathscr{V}_t} f(X_t^i) \,\Big|\, Z_0 = \delta_x\Bigg]$$

is the solution to (3.2) with initial condition $\varphi_0 = f$.

Before stating our contributions, we make a brief review of the literature about the asynchronous exponential growth property of Equation (3.1). It was first extensively investigated by Diekmann, Heijmans and Thieme in [81] through spectral analysis of semigroups in the case of a bounded state space $\mathbf{X} = [\underline{x}, \overline{x}] \subset (0,\infty)$, see also [121, 131–133]. More recently Banasiak, Pichór and Rudnicki revisited this case by using the notion partially integral semigroups [13, 187]. The first result for the case $\mathbf{X} = (0,\infty)$ was obtained by Perthame and Ryhzik [179] for $g(x) = 1$ and B (almost) constant by means of functional inequalities, see also [146]. Similar results were then derived by [15, 59] via probabilistic coupling arguments. Shortly after [179], Michel, Mischler and Perthame introduced the General Relative Entropy (GRE) principle in [164], which ensures the Malthusian long-time behaviour for general coefficients but without rate of convergence, see also [95]. This method was recently extended to measure solutions by Dębiec, Doumic, Gwiazda and Wiedeman [76]. A Poincaré inequality was proved by Cáceres, Cañizo and Mischler in [44] for the quadratic GRE when $\wp$ is “not singular”, thus guaranteeing an exponential rate of convergence in the corresponding wheighted L^2 norm. This spectral gap result was extended to larger weighted Lebesgue spaces in [43, 44] by using the enlargement result in [123]. Some time later, general results in weighted L^1 spaces were obtained through a new approach of the spectral analysis of semigroups by Mischler and Scher [167]. Let us also mention [211] where Zaidi, van Brunt and Wake derived a point-wise higher-order asymptotic expansion in the case B constant and $\wp = 2\delta_{1/2}$. Finally, a probabilistic analysis through a h-transform and many-to-one formulae was proposed by Cloez [69], and more recently a new probabilistic approach based on a Feynman-Kac formula was developed by Bertoin and Watson [24, 26, 27], see also Cavalli [57, 58].

In the next two sections, we present new results that complement the above mentioned studies. More precisely we are interested in the uniform exponential convergence to the Malthusian behaviour:

$$\big\|\mathrm{e}^{-\lambda t}u_t - \langle u_0, h\rangle\gamma\big\|_E \leq C\mathrm{e}^{-\omega t}\,\|u_0 - \langle u_0, h\rangle\gamma\|_E\,. \tag{3.3}$$

Most of the results in the literature deal with one of the two particular growth rates that are constant and linear rates. The constant rates are relevant for instance in the modelling of fibrils polymerization, while the linear ones are well suited for the exponential growth of cells. For the sake of conciseness and clarity, we restrict the presentation of our results to these two cases. The questions we address are:

- For which spaces E and under which assumptions on the coefficients do we have (3.3)?
- When (3.3) holds true, can we quantify the constants C and ω?
- What are the possible obstructions to (3.3)?

Regarding the two first questions, our main contribution is a quantified proof of the convergence (3.3) in spaces of measures under general assumptions, see Theorems 3.1 and 3.9. Concerning the third question, the most obvious obstruction to (3.3) is the non-existence of the eigenelements in E, as in [25, 88]. We do not consider this case here, but rather focus on situations where the eigenelements exist but the uniform convergence (3.3) fails to be true, see Theorem 3.5 and Theorems 3.12 and 3.13.

In Section 3.4 we show how some results on the long-time behaviour of Equation (3.1) can be used for studying a nonlinear model of prion replication.

Section 3.5 is devoted to the analysis of the long-time behaviour of generalisations of Equation (3.1) where the division rate depends on time in a periodic way.

3.2 Constant growth rate

In this section we are concerned with the case $g(x) = 1$, and Equation (3.1) is then complemented with the zero flux boundary condition $u_t(0) = 0$. It is useful to define, for any $k \in \mathbb{R}$,

$$\wp_k = \int_0^1 z^k \wp(\mathrm{d}z)$$

the k-th moment of $\wp$, which belongs to $(0,+\infty]$. We will also need the following definition

$$k_* = \inf\{k \in \mathbb{R},\ \wp_k < +\infty\}.$$

We have by assumption that $\wp_1 = 1$, so that $k_* \in [-\infty, 1]$. For instance we have $k_* = -\infty$ for $\wp = 2\delta_{1/2}$ and $k_* = -1$ for $\wp \equiv 2$. The function $k \mapsto \wp_k$ is continuous and strictly decreasing on $(k_*, +\infty)$. The zero order moment $\wp_0 > 1$ represents the mean number of fragments. For the sake of clarity we assume that $B : (0,\infty) \to [0,\infty)$ is a continuous function.

Harris's method. We use our result of Theorem 2.1 for the semigroup generated by Equations (3.1) and (3.2), namely $\mu M_t = u_t$ is the solution to Equation (3.1) with initial distribution $u_0 = \mu$ and $M_t f = \varphi_t$ is the solution to Equation (3.2) with initial condition $\varphi_0 = f$. Interestingly enough, the embedded semigroup presented in Chapter 2.1, which is at the core of the proof of Theorem 2.1, can be here expressed in terms of the branching process Z by

$$P^{(t)}_{s_0,s} f(x) = \frac{\mathbb{E}\big[\sum_{i\in\mathscr{V}_t} f(X^i_s)\psi(X^i_t)\,|\,Z_{s_0} = \delta_x\big]}{\mathbb{E}\big[\sum_{i\in\mathscr{V}_t} \psi(X^i_t)\,|\,Z_{s_0} = \delta_x\big]}$$

for $0 \le s_0 \le s \le t$. It is associated to an inhomogeneous Markov process $Y^{(t)}$, *i.e.* $P^{(t)}_{s_0,s} f(x) = \mathbb{E}[f(Y^{(t)}_s)\,|\,Y^{(t)}_{s_0} = x]$, which basically provides the trajectory of the backward lineage of a particle sampled at time t with a bias ψ, see [155, 156] for more details. Before stating the result we give the assumption on $\wp$, which is supposed to satisfy the following lower bound: there exist $z_0 \in (0,1)$, $\varepsilon \in [0, z_0]$ and $c_0 > 0$ such that

$$\wp(\mathrm{d}z) \ge \frac{c_0}{\varepsilon}\mathbf{1}_{(z_0-\varepsilon,z_0)}(z)\mathrm{d}z \quad \text{if } \varepsilon > 0 \qquad \text{or} \qquad \wp \ge c_0\delta_{z_0} \quad \text{if } \varepsilon = 0. \tag{3.4}$$

Theorem 3.1. *Assume that (3.4) is satisfied and that we are in one of the following cases:*

(i) B is continuously differentiable and increasing, $B \not\equiv 0$, and $V(x) = 1 + x^k$ with $k > 1$,

(ii) $B(x) = 0$ in a neighbourhood of the origin, $\lim_{x\to\infty} xB(x) = +\infty$, and $V(x) = 1 + x^k$ with $k > 1$,

(iii) $\lim_{x\to 0} xB(x) = 0$, $\lim_{x\to\infty} xB(x) = +\infty$, $k_* < 0$, and $V(x) = x^\ell + x^k$ with $\ell \in (k_*, 0)$ and $k > 1$.

Then the convergence (3.3) holds true in $E = \mathscr{M}(V)$ with computable constants C and ω.

Main steps of the proof. We apply Theorem 2.1 after having checked Assumption **A**. For verifying (A1) and (A2) we use Proposition 2.2.

(A2) holds with $\psi(x) = 1+x$ and $\beta = 1$,

(A1) is satisfied with $\alpha \in (0,1)$ by the Lyapunov function $V(x) = 1+x^k$, $k > 1$, for some $K = [0,x_1]$, and, when $k_* < 0$, by $V(x) = x^\ell + x^k$, $k > 1$, $\ell \in (k_*,0)$, for some $K = [x_0,x_1]$, $0 < x_0 < x_1 < \infty$.

(A3) is checked through (iterated) Duhamel formula on any bounded interval,

(A4) is proved directly by monotonicity arguments in case (i) in [P19]. In the two other cases it is checked by using Proposition 2.4: on $K = [0,x_1]$ for any $x_1 > 0$ in case (ii), and on $K = [x_0,x_1]$ for any $0 < x_0 < x_1 < \infty$ in case (iii). □

The most general assumption on B is the one in *(iii)*. However, to check Assumption (A4) through Condition (2.9) in that case, we need to work on a set K which is away from the origin. It forces us to strengthen the Lyapunov function by adding x^ℓ with $\ell < 0$, thus shrinking the space $\mathscr{M}(V)$. An alternative for extending the result to $V(x) = 1+x^k$ is to use a h-transform. It requires knowing *a priori* the existence of h and λ, but it has the advantage that there is no need to check (A4). Indeed the approach via h-transform corresponds to choosing $\psi = h$ in Assumption **A**, so that (A2) and (A4) are trivially verified since h is an eigenfunction. In [P22] we prove the existence of h and λ by using the Krein-Rutman theorem, Lyapunov functions, and compactness arguments. It allows us to prove the following result.

Theorem 3.2. *Assume that* (3.4) *is satisfied,* $\lim_{x\to 0} xB(x) = 0$*, and* $\lim_{x\to\infty} xB(x) = +\infty$*. Then the convergence* (3.3) *holds true in* $E = \mathscr{M}(V)$ *for the weight* $V(x) = 1+x^k$ *with* $k > 1$.

The drawback of this h-transform approach is that since the existence of h is obtained in a non constructive way, the constants in the convergence result are not quantifiable (unless h is known explicitly, which occurs when B is affine).

Spectral analysis.

Before being aware of Harris's method, we had used in [P18] the spectral analysis of strongly continuous semigroups to prove the following theorem.

Theorem 3.3. *Assume that B has a connected support and that*

$$B_1(x-x_0)_+^{b_1} \le B(x) \le B_2(1+x)^{b_2}$$

for all $x \ge 0$ *and some* $b_2 \ge b_1 > 0$, $B_2 \ge B_1 > 0$, *and* $x_0 > 0$. *Suppose also that* $\wp$ *is either absolutely continuous with respect to the Lebesgue measure or that* $\operatorname{supp}\wp \subset [\varepsilon, 1-\varepsilon]$ *for some* $\varepsilon > 0$. *Then convergence* (3.3) *holds true in* $E = L^1(V)$ *with* $V(x) = 1+x^k$ *for any* $k > \max(1, k_* + 2b_2 - 2b_1)$.

This anterior result is essentially covered by Theorem 3.2. However the proof is worth of interest since it relies on a moment creation result, given in Lemma 3.4 below, that can be useful by itself.

Idea of the proof. We use the spectral approach of Theorem 2.7. From [91] we know that the Perron eigentriplet (λ,γ,h) exists and is unique. So we do not need to check the irreducibility assumption, and the condition on ψ is satisfied by h. The splitting $M_\tau = S+R$ is obtained through a Duhamel formula, and the (weak) compactness of R is established by using the *strong convex compactness property* [190, 208] (see also [168] for a direct proof in Lebesgue spaces). For applying this property, we need to prove the following regularity result.

Lemma 3.4. *For all* $\ell > k > k_0 > 1$ *there exist two positive constant* $a = a(\ell,k)$ *and* $C = C(\ell,k,k_0)$ *such that for all* $u_0 \in L^1(1+x^k)$ *and all* $t > 0$

$$\|u_t\|_{L^1(1+x^\ell)} \le C t^{-(\ell-k_0)/m_0} e^{at} \|u_0\|_{L^1(1+x^k)}.$$

Interestingly enough, the proof of this lemma relies on the use of Lyapunov functions. □

It is known that when it exists, the function h is dominated by $(1+x)^k$ for any $k>1$. So the results in Theorems 3.1, 3.2, and 3.3 hold in spaces with weights stronger than h. A natural question then is wether or not they can be extended to $L^1(h)$ or $\mathscr{M}(h)$, which are the largest function or measure spaces for which the quantity $\langle u_0,h\rangle$ is well defined. In [44] it is proved by means of GRE inequalities that pointwise convergence holds in $L^1(h)$ under general assumptions on the coefficients, so that

$$\sup_{\|u_0\|=1}\lim_{t\to\infty}\left\|\mathrm{e}^{-\lambda t}u_t-\langle u_0,h\rangle\gamma\right\|_{L^1(h)}=0. \tag{3.5}$$

The stronger convergence that interests us in (3.3) is equivalent to switching the "sup" and the "lim" in (3.5). In [P11] we prove that this uniform convergence does not hold in $L^1(h)$ in general, at least for bounded fragmentation rates. More precisely we prove the following result.

Theorem 3.5. *Assume that* $\lim_{k\to k_*}\wp_k=+\infty$, *$B$ is bounded, with connected support, and* $B(x)=B_\infty>0$ *for all x large enough. Then*

$$\inf_{t\geq 0}\sup_{\|u_0\|=1}\left\|\mathrm{e}^{-\lambda t}u_t-\langle u_0,h\rangle\gamma\right\|_{L^1(h)}\geq 1.$$

Ingredients of the proof. We start with the case $\inf\operatorname{supp}\wp>0$, for which we can prove more, namely that

$$\sup_{\|u_0\|=1}\left\|\mathrm{e}^{-\lambda t}u_t-\langle u_0,h\rangle\gamma\right\|_{L^1(h)}=2 \tag{3.6}$$

for all $t\geq 0$. Then we treat the case $\inf\operatorname{supp}\wp=0$ by using the notion of quasi-compactness, which is an topological invariant. To do so we need precise estimates on the dual eigenfunction h, that are stated in Theorem 3.8 below (case $b_\infty=0$) and are valid under the only assumptions of Theorem 3.5. □

The method for proving (3.6) also allows us to bound the size of the spectral gap in smaller weighted L^1 spaces when $\inf\operatorname{supp}\wp>0$. We illustrate this on the example of constant division rate with equal mitosis kernel.

The case of constant fragmentation rate with equal mitosis. This case, which corresponds to $B(x)=B>0$ and $\wp=2\delta_{1/2}$, is well understood. First we readily check that $\lambda=B$ and $h(x)=1$ are eigenelements. There is also an explicit expression for γ [129]. Sharp rates of convergence for Wasserstein distances are provided by [59] via coupling arguments. For the 1-Wasserstein distance this spectral gap is equal to B, which was already proved by means of functional inequalities in [179]. It allows deriving convergence with the same rate in total variation distance, but with a stronger control on the initial data [15, 179].

A more precise description can be obtained in weighted L^1 spaces, by combining the spectral result in [167, Proposition 4.4] and the point-wise higher-order asymptotic expansion derived in [211]. This expansion is given by a sequence of eigenfunctions $(\gamma_m)_{m\geq 0}$ associated to the explicit eigenvalues

$$\lambda_m=(2^{1-m}-1)B.$$

The eigenfunctions γ_m derived in [199, 200] are given by Dirichlet series that decay rapidly as $x\to\infty$. The Weyl theorem available in [167] then allows us to strengthen this point-wise convergence into a uniform exponential convergence. It provides as a by-product the existence of a sequence $(h_m)_{m\geq 0}$ of eigenfunctions that grow at most polynomially as $x\to+\infty$. Using the result in [P11, Theorem 6.1] we can also bound from above the rate of convergence. Finally we have the following result.

Theorem 3.6. *Let* $a\in(-B,B)$. *For any* $k>\max(1,k_a)$ *where*

$$k_a=\frac{\log(2B)-\log(B+a)}{\log 2},$$

we have $(\gamma_m,h_m)\in L^1(V)\times L^\infty(V)$ *with* $V(x)=1+x^k$*, and for all* $u_0\in L^1(V)$ *and all* $t\geq 0$

$$\Big\|u_t-\sum_{m=0}^{m_a}\langle u_0,h_m\rangle e^{\lambda_m t}\gamma_m\Big\|_{L^1(V)}\leq Ce^{at}\Big\|u_0-\sum_{m=0}^{m_a}\langle u_0,h_m\rangle\gamma_m\Big\|_{L^1(V)} \tag{3.7}$$

where $m_a=\lceil k_a-1\rceil$ *is the integer such that* $\lambda_{m_a+1}\leq a<\lambda_{m_a}$*. On the other hand,* (3.7) *does not hold true for* $k\in[0,\frac{B-a}{2Be\log 2})$.

Entropy method. Let us place ourselves in a situation where the conditions in [91] ensuring the existence of the Perron eigenelements (λ,γ,h) are met, and consider the GRE corresponding to the quadratic convex function $H(u)=(u-1)^2$, namely

$$\mathscr{H}[u]=\int_0^\infty(u-\gamma)^2\frac{h}{\gamma}=\|u-\gamma\|^2_{L^2(h/\gamma)}.$$

This functional is an entropy for the rescaled dynamics $e^{-\lambda t}u_t$. The corresponding dissipation of entropy is given by

$$\mathscr{D}[u]=\int_0^\infty\int_0^1 h(zx)\gamma(x)B(x)\Big(\frac{u(x)}{\gamma(x)}-\frac{u(zx)}{\gamma(zx)}\Big)^2\wp(\mathrm{d}z)\mathrm{d}x.$$

The analysis in [164] guarantees that, if $\langle u_0,h\rangle=1$, then $\mathscr{H}[e^{-\lambda t}u_t]$ decreases to zero under fairly general assumptions on B and $\wp$, but without providing decay rate. An exponential rate of convergence readily follows from the validity of the Poincaré inequality

$$\mathscr{H}[u]\leq\frac{1}{2\omega}\mathscr{D}[u] \tag{3.8}$$

for some $\omega>0$ and all u in the set $\{u\in L^2(\gamma/h),\,\langle u,h\rangle=1\}$, which is invariant under the rescaled dynamics $t\mapsto e^{-\lambda t}u_t$. In the particular case $\wp=2\delta_{1/2}$, the dissipation of entropy is too weak to produce such a Poincaré inequality, since $\mathscr{D}[u]=0$ for any $u=w\gamma$ with w such that $w(2x)=w(x)$. To avoid such an obstruction, the authors of [44] consider fragmentation kernels satisfying

$$\wp(\mathrm{d}z)\geq c_0\,\mathrm{d}z \tag{3.9}$$

for some $c_0>0$ and they prove the validity of (3.8) under some assumptions on B. In [P4] we extend this result to other fragmentation rates B under additional conditions on the fragmentation kernel $\wp$. More precisely we assume that $\wp$ is absolutely continuous with respect to the Lebesgue measure around 0 and 1, and that the corresponding densities verify

$$\wp(z)\to p_0\quad\text{when } z\to 0\qquad\text{and}\qquad\wp(z)=p_1+O((1-z)^\eta)\quad\text{when } z\to 1 \tag{3.10}$$

for some $p_0,p_1,\eta>0$. The function B is supposed to have the following asymptotic behaviours

$$B(x)\sim B_0x^{b_0}\quad\text{as } x\to 0\qquad\text{and}\qquad B(x)=B_\infty x^{b_\infty}+O(x^{b_\infty-\eta})\quad\text{as } x\to+\infty \tag{3.11}$$

for some $B_0,B_\infty,\eta>0$ and $b_0,b_\infty>-1$. Note that these assumptions ensure in particular the existence of (λ,γ,h), see [91]. In addition, we have the following result, mainly taken from [P4].

Theorem 3.7. *Suppose that* (3.9)*,* (3.10)*, and* (3.11) *are satisfied with* $b_0\in(-1,2]$ *and* $b_\infty>-1$*. Then there exists* $\omega>0$ *such that the Poincaré inequality* (3.8) *is valid in* $\{u\in L^2(\gamma/h),\,\langle u,h\rangle=1\}$*. Consequently,* (3.3) *is verified in* $E=L^2(h/\gamma)$ *with this same* ω *and* $C=1$.

The Poincaré inequality is obtained following the proof in [44], which is inspired by a work of Diaconis and Stroock [80]. It requires estimates from above and below on the eigenfunctions. Our main contribution in [P4] is the derivation of such estimates, which drastically refine those of [44]. We gather in the following theorem the estimates that allow to prove Theorem 3.7. They are particular cases of the ones derived in [P4], except the bounds on the dual eigenfunction h in the case $b_\infty = 0$ which are proved in [179] for the equal mitosis case and in [P11] for general fragmentation kernels. The asymptotic behaviour of γ as $x \to +\infty$ involves the function

$$\Lambda(x) = \int_1^x \frac{\lambda + B(y)}{g(y)}\,\mathrm{d}y.$$

Theorem 3.8. *Under Assumptions (3.10) and (3.11), the following estimates hold true, where in each of them C is a positive constant. The dual eigenfunction h satisfies*

$$\frac{1}{C}(1+x)^k \le h(x) \le C(1+x)^k$$

for some $k \in \mathbb{R}$, and the asymptotic behaviour of the eigenfunction γ is given by

$$\gamma(x) \underset{x\to 0}{\sim} Cx \qquad \text{and} \qquad \gamma(x) \underset{x\to\infty}{\sim} C\mathrm{e}^{-\Lambda(x)}x^q$$

where q is a positive number. The values of k and q are explicit and depend on the sign of b_∞. More precisely,

- *if $b_\infty > 0$ then $k = 1$ and $q = p_1$,*
- *if $b_\infty = 0$ and either $B(x) = B_\infty$ for all x large enough or $\wp \equiv 2$, then $k < 1$ is the unique real number such that $\wp_k = 1 + \frac{\lambda}{B_\infty}$, and $q = p_1/\wp_k$,*
- *if $b_\infty < 0$ then $k = b_\infty - 1$ and $q = 0$.*

3.3 Linear growth rate

We now consider the case $g(x) = x$, for which $\lambda = 1$ and $h(x) = x$ are eigenelements. Notice that in this case there is no need of a boundary condition for Equation (3.1) at $x = 0$. As in Section 3.2 we still assume that $B : (0,\infty) \to [0,\infty)$ is a continuous function.

Harris's method. Since h is known explicitly, it is quite appropriate to apply Harris's theorem trough a h-transform. Similarly as in Theorem 3.2 we can prove the following result for the case of linear growth rate.

Theorem 3.9. *Assume that there exist $z_0 \in (0,1)$, $\varepsilon \in (0,z_0]$ and $c_0 > 0$ such that*

$$\wp(\mathrm{d}z) \ge c_0 \mathbf{1}_{(z_0-\varepsilon,z_0)}(z)\mathrm{d}z$$

and that B is a continuous function such that

$$\lim_{x\to 0} B(x) = 0 \qquad \text{and} \qquad \lim_{x\to\infty} B(x) = +\infty.$$

Then the convergence (3.3) holds true in $E = \mathscr{M}(V)$ with $V(x) = x^\ell + x^k$, $k_* < \ell < 1 < k$, and computable constants C and ω.

Entropy and functional inequalities. As for the case of constant growth rate, we can use the quadratic GRE to get (3.3) in the corresponding weighted L^2 space by proving a Poincaré inequality. Since here $h(x) = x$ is known explicitly we only need estimates on the eigenfunction γ. Assuming that (3.10) and (3.11) are satisfied with $b_0, b_\infty > 0$, we have the following estimates from [P4], where in each of them C is a positive constant,

$$\gamma(x) \xrightarrow[x\to 0]{} C \qquad \text{and} \qquad \gamma(x) \underset{x\to\infty}{\sim} C\mathrm{e}^{-\Lambda(x)}x^{p_1}.$$

It allows us to prove the following result in [P4].

Theorem 3.10. *Suppose that* (3.9), (3.10), *and* (3.11) *are satisfied with* $b_0 \in (0,2]$ *and* $b_\infty > 0$. *Then there exists* $\omega > 0$ *such that the Poincaré inequality* (3.8) *is valid in* $\{u \in L^2(\gamma/h),\, \langle u,h\rangle = 1\}$. *Consequently,* (3.3) *is verified in* $E = L^2(h/\gamma)$ *with this same* ω *and* $C = 1$.

As in the case of constant growth rate, this result requires b_0 to be smaller than 2. In [P5] we obtain a spectral gap in $L^2(h)$ for the special case $B(x) = x^b$ with $b \geq 2$ and $\wp \equiv 2$, by means of a functional inequality. More precisely we prove that for any $u_0 \in L^2(h)$ such that $\langle u_0,h\rangle = 0$ we have for all $t \geq 0$

$$\frac{\mathrm{d}}{\mathrm{d}t}\|u_t\|^2_{L^2(h)} = -(b-2)\int_0^\infty x^{b-3}U_t^2(x)\,\mathrm{d}x - \int_0^\infty x^{b+1}u_t^2(x)\,\mathrm{d}x \leq 0$$

where $U_t(x) = \int_0^x yu_t(y)\mathrm{d}y$. This is a spectral gap inequality since it readily implies the following result, recalling that here the Perron eigenvalue is $\lambda = 1$.

Theorem 3.11. *Assume that* $B(x) = x^b$ *with* $b \geq 2$ *and* $\wp \equiv 2$. *Then the convergence* (3.3) *holds true in* $E = L^2(h)$ *with* $C = 1$ *and* $\omega = \frac{1}{2}$.

The equal mitosis case. The assumptions in Theorems 3.9, 3.10 and 3.11 preclude the equal mitosis kernel $\wp = 2\delta_{1/2}$. It is not a technical but a necessary restriction, since asynchronous exponential growth does not occur in this case. It can be easily understood through the branching Markov process Z. If at time $t = 0$ the population is composed of only one individual with deterministic size $x > 0$, then for any positive time t and any $i \in \mathscr{V}_t$ we have that $X_t^i \in \{2^{-m}\mathrm{e}^t x : m \in \mathbb{N}\}$. This observation was made already by Bell and Anderson in [21]. It shows that the solution $u_t = \mathbb{E}[Z_t]$ cannot relax to a steady size distribution and it prevents Equation (3.1) from having the asynchronous exponential growth property. The dynamics does not mix enough the trajectories to generate ergodicity, and the asymptotic behaviour keeps a strong memory of the initial distribution. This situation has been much less studied than the classical ergodic case. In [81, 132] Diekmann, Heijmans and Thieme made the link with the existence of a nontrivial boundary spectrum: all the complex numbers

$$\lambda_n = 1 + \frac{2n\pi}{\log 2}i$$

with n lying in $\mathbb{Z}$, are eigenvalues. As a consequence the Perron eigenvalue $\lambda = \lambda_0 = 1$ is not strictly dominant and it results in persistent oscillations, generated by the boundary eigenfunctions. The convergence to this striking behaviour was first proved by Greiner and Nagel [121] in the space $L^1(\mathbf{X})$ with $\mathbf{X} = [\underline{x},\overline{x}] \subset (0,\infty)$ through spectral analysis of semigroups. More recently it was derived in $L^1((0,\infty),x^{1+r}\mathrm{d}x)$ for monomial division rates $B(x) = x^r$ $(r > 0)$ and smooth initial data by means of Mellin's transform [198].

In [P12, P21] we tackle this problem by using the GRE principle and obtain new and very fine convergence results. Consider again the quadratic functional

$$\mathscr{H}[u] = \int_0^\infty |u-\gamma|^2\frac{h}{\gamma} = \|u-\gamma\|^2_{L^2(h/\gamma)}$$

which is an entropy for the rescaled solutions $t \mapsto \mathrm{e}^{-t}u_t$ with dissipation

$$\mathscr{D}[u] = \int_0^\infty xB(x)\gamma(x)\left|\frac{u(x)}{\gamma(x)} - \frac{u(x/2)}{\gamma(x/2)}\right|^2\mathrm{d}x.$$

As we already noticed in Section 3.2, this dissipation of entropy does not vanish only for $u \in \mathrm{span}\{\gamma\}$ but for any $u = w\gamma$ with $w(2x) = w(x)$. The main difference with the case of constant growth rate is that for $g(x) = x$ the set of such functions u is invariant under Equation (3.1). Let us now relate this to the boundary spectrum. Since the eigenvalues λ_n are associated to eigenfunctions γ_n that yield periodic rescaled solutions, these eigenfunctions necessarily nullify the dissipation of entropy. The direct and dual eigenfunctions associated to λ_n are actually explicitly related to γ and h and given by

$$\gamma_n(x) = x^{-\frac{2in\pi}{\log 2}}\gamma(x) \qquad \text{and} \qquad h_n(x) = x^{\frac{2in\pi}{\log 2}} h(x) = x^{1+\frac{2in\pi}{\log 2}}.$$

The family $(\gamma_n)_{n\in\mathbb{Z}}$ clearly belongs to the null set of the entropy dissipation, but we can also prove that it forms a Hilbert basis of this vector subspace of $L^2(h/\gamma)$. Let us make this more precise. First we clearly assume that γ exists in $L^1(h)$, which is guaranteed from [91] if B has a connected support and verifies $B_1(x-x_0)_+^{b_1} \leq B(x) \leq B_2(x^{b_0} + x^{b_2})$ for some $B_1, B_2, b_0, b_1, b_2, x_0 > 0$. Then we consider the complex Hilbert space $L^2(h/\gamma)$ endowed with the inner product

$$(f,g) = \int_0^\infty f(x)\bar{g}(x)\frac{x\,\mathrm{d}x}{\gamma(x)}.$$

Since $\langle \gamma, h\rangle = 1$ and γ_n, h_n are direct and dual eigenfunctions associated to λ_n with $\lambda_n \neq \lambda_m$ when $n \neq m$, we deduce that

$$(\gamma_n, \gamma_m) = \langle \gamma_n, h_m\rangle = \begin{cases} 1 & \text{if } n = m \\ 0 & \text{if } n \neq m \end{cases},$$

meaning that $(\gamma_n)_{n\in\mathbb{Z}}$ is an orthonormal family of $L^2(h/\gamma)$. By means of Fourier analysis, we prove in [P12] that

$$\overline{\mathrm{span}}(\gamma_n)_{n\in\mathbb{Z}} = \big\{u \in L^2(h/\gamma),\ \mathscr{D}[u] = 0\big\}.$$

This result combined with the GRE inequality allows us to derive the convergence of the rescaled solutions $\mathrm{e}^{-t}u_t$ to their orthogonal projection on the null space of the entropy dissipation.

Theorem 3.12. *For any $u_0 \in L^2(h/\gamma)$ we have*

$$\left\| \mathrm{e}^{-t}u_t - \sum_{n=-\infty}^{+\infty} (u_0, \gamma_n)\mathrm{e}^{\frac{2in\pi}{\log 2}t}\gamma_n \right\|_{L^2(h/\gamma)} \xrightarrow[t\to+\infty]{} 0.$$

As we already noticed, u_t is a Dirac comb for all time $t \geq 0$ when u_0 is a Dirac mass. This observation motivates studying the long time behaviour in a space of measures. The question is then what becomes the convergence in Theorem 3.12 in the absence of Hilbert structure. We answer this question in [P21] by using both the GRE structure of the dual equation (3.2), which is set on a space of functions, and Harris's ergodic theorem. The Fourier type series is replaced by a Fejér type sum and the convergence occurs with an explicit exponential rate. To our knowledge, it is the first time a spectral gap is obtained in such a periodic setting.

Theorem 3.13. *Let $V(x) = x^\ell + x^k$ with $\ell < 1 < k$. There exist computable constants $C \geq 1$ and $\omega > 0$ such that for all $u_0 \in \mathscr{M}(V)$ and all $t \geq 0$*

$$\left\|\mathrm{e}^{-t}u_t - \rho_t\right\|_{\mathscr{M}(V)} \leq C\mathrm{e}^{-\omega t}\left\|u_0 - \rho_0\right\|_{\mathscr{M}(V)}$$

where for all $f \in C_c^1(0,\infty)$

$$\langle \rho_t, f\rangle = \lim_{N\to\infty} \sum_{n=-N}^{N} \Big(1 - \frac{|n|}{N}\Big)\langle u_0, h_n\rangle\langle \gamma_n, f\rangle \mathrm{e}^{\frac{2in\pi}{\log 2}t}.$$

Main steps of the proof. We work on the dual equation (3.2) which, similarly as Equation (3.1), enjoys a GRE structure. The quadratic one reads

$$\mathscr{H}[\varphi] = \int_0^\infty |\varphi - h|^2 \frac{\gamma}{h}.$$

It is an entropy for the rescaled solutions $t \mapsto \mathrm{e}^{-t}\varphi_t$ with dissipation

$$\mathscr{D}[\varphi] = \int_0^\infty xB(x)\gamma(x) \left| \frac{\varphi(x)}{x} - \frac{\varphi(x/2)}{x/2} \right|^2 \mathrm{d}x,$$

which vanishes for the functions φ satisfying $\varphi(2x) = 2\varphi(x)$. We start by proving via Fejér's Theorem that for any $\varphi \in \mathscr{L}^\infty(h) \cap C(0,\infty)$ such that $\varphi(2x) = 2\varphi(x)$, the sequence $(F_N(\varphi))_{N\geq 1}$ defined by

$$F_N(\varphi) = \sum_{n=-N}^{N} \Big(1 - \frac{|n|}{N}\Big) \langle \gamma_n, \varphi \rangle h_n$$

converges to φ in $\mathscr{L}^\infty(h)$. The GRE inequality then allows us to prove that for any $\varphi_0 \in C_c^1(0,\infty)$ and any $t \geq 0$ the sequence

$$F_N(\mathrm{e}^{-t}\varphi_t) = \sum_{n=-N}^{N} \Big(1 - \frac{|n|}{N}\Big) \langle \gamma_n, \varphi_0 \rangle \mathrm{e}^{\frac{2in\pi}{\log 2}t} h_n$$

converges in $\mathscr{L}^\infty(h)$ to a limit $R_t\varphi_0$. This defines a $\log 2$-periodic family of bounded linear operators R_t from $\{\varphi \in \mathscr{L}^\infty(h), \varphi/h \in C_0(0,\infty)\}$ to $\mathscr{L}^\infty(h) \cap C(0,\infty)$. The GRE principle guarantees additionally that for all $\varphi_0 \in \{\varphi \in \mathscr{L}^\infty(h), \varphi/h \in C_0(0,\infty)\}$

$$\mathrm{e}^{-t}\varphi_t - R_t\varphi_0 \xrightarrow[t\to+\infty]{} 0$$

locally uniformly on $(0,\infty)$. In terms of the direct equation, this implies the weak-* convergence

$$\mathrm{e}^{-t}u_t - \rho_t \overset{*}{\rightharpoonup} 0 \tag{3.12}$$

for any $u_0 \in \mathscr{M}(h)$.

The second step consists in strengthening this weak convergence by using Harris's theorem. Let us denote by $(M_t)_{t\geq 0}$ the semigroup generated by Equations (3.1) and (3.2), namely such that $\mu M_t = u_t$ is the solution to Equation (3.1) with initial distribution $u_0 = \mu$ and $M_t f = \varphi_t$ is the solution to Equation (3.2) with initial condition $\varphi_0 = f$. Of course we cannot apply Harris's theorem to $(M_t)_{t\geq 0}$ since we just proved that it is not ergodic. But we can apply it, for any fixed $x \in (0,\infty)$, to the discrete time semigroup $(M_{n\log 2})_{n\in\mathbb{N}}$ on the discrete state space

$$\mathbf{X}_x = \big\{ y \in (0,\infty) : \exists m \in \mathbb{Z}, y = 2^m x \big\}.$$

Indeed the space of measures on $(0,\infty)$ supported by $\mathbf{X}_x$ is invariant under $M_{\log 2}$. Harris's ergodic theorem then allows us to prove that for all $f \in \mathscr{L}^\infty(V)$

$$\left| \mathrm{e}^{-n\log 2} M_{n\log 2} f(x) - R_{n\log 2} f(x) \right| \leq C r^n \, \|f - R_0 f\|_{\mathscr{L}^\infty(V)}$$

for some explicit constants $C \geq 1$ and $r \in (0,1)$ which are independent of x. This independence on x combined with the weak-* converge (3.12) yields the result.

□

Some numerics. The oscillating asymptotic behaviour proved in Theorems 3.12 and 3.13 is very sensitive to the coefficients $g(x) = x$ and $\wp = 2\delta_{1/2}$. If $g(2x) \neq 2g(x)$ for some $x > 0$, then asynchronous exponential growth takes place, see [188, Section 6.3.3]. Similarly, if $\delta_{1/2}$ is approximated by a density probability measure, then the solutions converge to γ, as guaranteed by Theorem 3.9. In terms of numerics, it implies that capturing the persistent oscillations at the discrete level requires an accurate numerical scheme. Otherwise the numerical simulations will result in damped oscillations and convergence to a stationary profile. For the numerical analysis, it is more convenient to consider the function $w_t(x) = xu_t(x)\mathrm{e}^{-t}$, which is solution to the conservative equation

$$\partial_t w_t(x) + \partial_x(xw_t(x)) + B(x)w_t(x) = 2B(2x)w_t(2x).$$

This equation generates a positive semigroup of contractions in $L^1(0,\infty)$, meaning that $\|w_t\|_{L^1} \leq \|w_0\|_{L^1}$ for all $t \geq 0$. For preserving the periodic solutions, the numerical scheme needs to satisfy the two following conditions:

(C1) The discretization of the transport equation $\frac{\partial}{\partial t}w_t + \frac{\partial}{\partial x}(xw_t)$ must be non-diffusive. If we use a standard upwind scheme, we thus need a Courant number equal to 1, meaning that each point of the grid at time t is transported to the next point of the grid at time $t + \Delta t$.

(C2) The discretization of the fragmentation term $2B(2x)w_t(2x) - B(x)w_t(x)$ must ensure that if x is a point of the grid, then so is $x/2$, so that there is no approximation when applying the fragmentation operator.

Condition (C2) leads us to define the following geometric grid, for given $n, N \in \mathbb{N}^*$:

$$\Delta x = 2^{\frac{1}{n}} - 1, \qquad x_k = (1+\Delta x)^{k-N}, \qquad 0 \leq k \leq 2N.$$

Then, for any $k \in \mathbb{N}$, $0 \leq k \leq 2N$, $2x_k = x_{k+n}$ is in the grid. The computational domain is $[x_0, x_{2N}] = \left[2^{-\frac{1}{n}}, 2^{\frac{N}{n}}\right]$. Due to the properties of the eigenvector γ established in [91], we have that $\gamma(x)$ quickly vanishes as $x \to 0$ and $x \to \infty$, so that the truncation results in only a small and quantifiable error.

For ensuring the existence of γ, we typically assume that $B(x)$ tends to infinity as $x \to \infty$ [91]. For such fragmentation rates, satisfying Condition (C1) gives rise to a difficulty. If we use a classical explicit finite difference discretization, then the Courant-Friedrichs-Lewy (CFL) stability condition requires the Courant number to be smaller than $1/\sup_{[x_0,x_{2N}]} B$, due to the term $B(x)w_t(x)$. A solution is then to treat this term implicitly. But if we want to preserve the conservation law $\int w_t = \int w_0$ for all $t \geq 0$ at the discrete level, which is a very important property in a numerical and physical point of view, the term $2B(2x)w_t(2x)$ also has to be handled in an implicit way, making the constraint on the CFL reappear. We overcome this issue by considering the semi-implicit scheme with splitting given by

$$\frac{w_k^{\ell+\frac{1}{2}} - w_k^\ell}{\Delta t} + \frac{x_k w_k^\ell - x_{k-1}w_{k-1}^\ell}{x_k - x_{k-1}} + B_k w_k^{\ell+\frac{1}{2}} = 0, \quad 1 \leq k \leq 2N,$$

$$\frac{w_k^{\ell+1} - w_k^{\ell+\frac{1}{2}}}{\Delta t} = 2B_{k+n}w_{k+n}^{\ell+\frac{1}{2}}, \quad 1 \leq k \leq 2N,$$

where $B_k = B(x_k)$. In the first half-step, the term $B_k w_k^{\ell+\frac{1}{2}}$ is implicit, and in the second half-step the term $2B_{k+n}w_{k+n}^{\ell+\frac{1}{2}}$ is explicit, allowing the CFL condition to not depend on B. But since the two terms do not appear in the same half-step, they are evaluated at the same discrete time $\ell + \frac{1}{2}$, so that the conservativeness property is preserved. More precisely, if we choose the influx boundary condition

$$w_0^\ell = \frac{x_{2N}}{x_0}w_{2N}^\ell + \frac{1}{x_0}\sum_{k=1}^{n}(x_k - x_{k-1})B_k w_k^{\ell+\frac{1}{2}}$$

which means that what comes in the interval $[x_0, x_{2N}]$ equals what goes out, then the numerical scheme is conservative in the sense that for all $\ell \geq 0$

$$\sum_{k=1}^{2N} (x_k - x_{k-1}) w_k^{\ell+1} = \sum_{k=1}^{2N} (x_k - x_{k-1}) w_k^{\ell}. \tag{3.13}$$

Choosing a Courant number equal to 1 in our framework means imposing

$$\Delta t = \frac{\Delta x}{1 + \Delta x}.$$

Indeed under this condition the discretization of the transport term follows the characteristics and sends exactly a point of the grid on the next point of the grid. The first step of the scheme can then be written as

$$w_k^{\ell+\frac{1}{2}} = \frac{1}{1 + \Delta t B_k} \frac{\Delta t}{\Delta x} w_{k-1}^{\ell}$$

which leads to the condensed form of the full scheme

$$w_k^{\ell+1} = \frac{1}{1 + \Delta t B_k} \frac{x_{k-1}}{x_k} w_{k-1}^{\ell} + \frac{2 \Delta t B_{k+n}}{1 + \Delta t B_{k+n}} \frac{\Delta t}{\Delta x} w_{k+n-1}^{\ell}, \quad 1 \leq k \leq 2N, \tag{3.14}$$

and

$$w_0^{\ell} = (1 + \Delta t B_1) \left[\frac{x_{2N}}{x_0} w_{2N}^{\ell} + \sum_{k=1}^{n-1} \frac{x_k}{x_0} \frac{\Delta t B_{k+1}}{1 + \Delta t B_{k+1}} w_k^{\ell} \right]. \tag{3.15}$$

This scheme is clearly positive. Together with the discrete conservation law (3.13) we deduce that it is a contraction for the discrete L^1 norm $\|\cdot\|_1$ defined for a vector $u = (u_k)_{1 \leq k \leq 2N}$ by

$$\|u\|_1 = \sum_{k=1}^{2N} (x_k - x_{k-1}) |u_k| = \frac{\Delta x}{1 + \Delta x} \sum_{k=1}^{2N} x_k |u_k|.$$

This stability property allows us to prove in [P12] that the numerical scheme is convergent for this norm.

Theorem 3.14. *Let u_0 be such that the associated solution $w(t,x)$ belongs to $C_b^2([0,+\infty) \times (0,+\infty))$. Let w_k^ℓ be the numerical solution obtained by the iteration rule (3.14)–(3.15) and with the initial data $w_k^0 = u_0(x_k)$. Then for all $r > 0$ there exists a constant $C_r > 0$ such that for all $T > 0$*

$$\sup_{t_\ell \leq T} \|\mathbf{e}^\ell\|_1 \leq C_r T \left(2^{\frac{N}{n} - \frac{\log n}{\log 2}} + 2^{-r\frac{N}{n}} \right),$$

where $\mathbf{e}$ is the "error" vector defined by $\mathbf{e}_k^\ell = w_k^\ell - w_{t_\ell}(x_k)$.

This is a convergence result since if n and N/n tend to infinity in such a way that $\frac{\log n}{\log 2} - \frac{N}{n} \to +\infty$, then the error tends to zero. For instance if we take $N = \lfloor \frac{\varepsilon}{\log 2} n \log n \rfloor$ with $\varepsilon \in (0,1)$ we get a speed of convergence of order $n^{\varepsilon-1} + n^{-r\varepsilon}$. Choosing $r = \frac{1}{\varepsilon} - 1$ we obtain an order $n^{\varepsilon-1}$ for any $\varepsilon \in (0,1)$, meaning that the scheme is "almost" of order 1 in n.

We illustrate in Figures 3.2 that this numerical scheme indeed capture the periodic oscillations. We choose $B(x) = x^2$ and two different initial distributions (Figure 3.1, Left and Right respectively), one a peak very close to the Dirac delta at $x = 2$ and the other one very smooth.

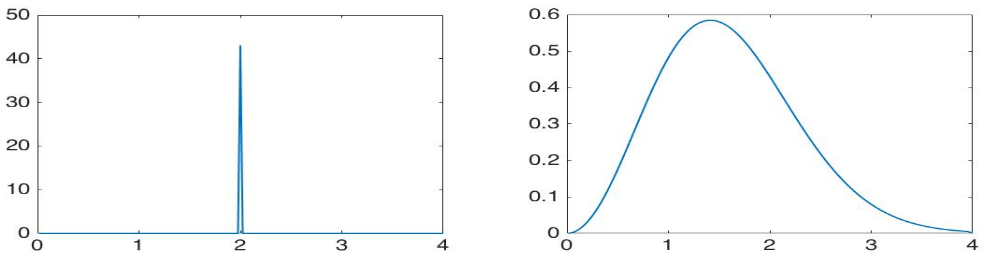


Fig. 3.1 Two different initial conditions. Left: peak in $x=2$. Right: $u_0(x)=x^2\exp(-x^2/2)$.

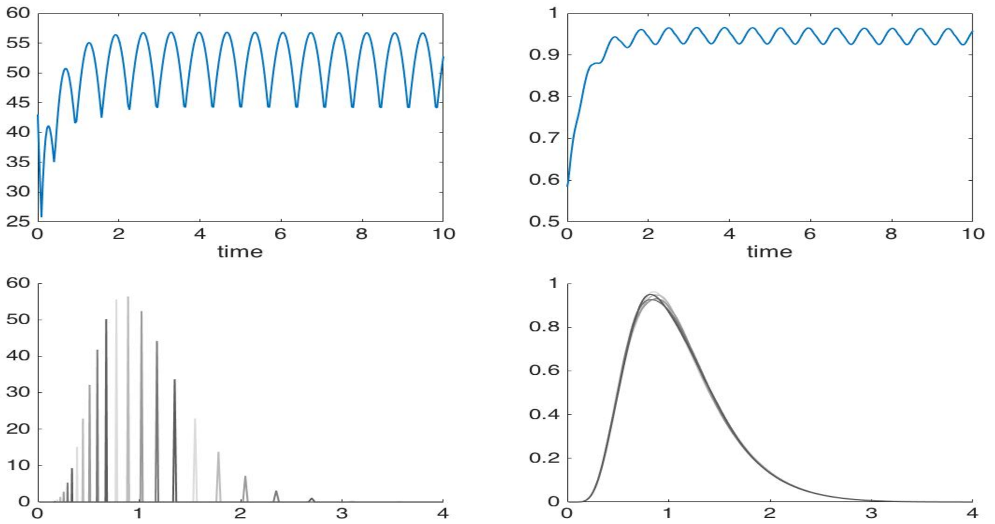


Fig. 3.2 Time evolution of $\max_{x>0} u_t(x)\mathrm{e}^{-t}$ (Top) and size distribution $u_t(x)\mathrm{e}^{-t}$ at five different times (Bottom, each time is in a different grey). Left: for the peak as initial condition. Right: for the smooth initial condition.

3.4 A nonlinear model

In this section we show how the result in Theorem 3.9 can be used to analyse a nonlinear growth-fragmentation equation coming from the modelling of prion protein aggregation.

Prion diseases, also referred to as transmissible spongiform encephalopathies, are infectious and fatal neurodegenerative diseases. They include bovine spongiform encephalopathy in cattle, scrapie in sheep, and Creutzfeld-Jakob disease in human. It is now widely admitted that the agent responsible for these diseases, known as prion, is a protein which has the ability to self-replicate by an autocatalytic process [122, 182]. The infectious prion, called $\mathrm{PrP^{Sc}}$ for Prion Protein Scrapie, is a misfolded form of a normally shaped cellular prion protein, the $\mathrm{PrP^{c}}$. The so-called *nucleated polymerization* was proposed by [139] as a conversion mechanism of $\mathrm{PrP^{c}}$ into $\mathrm{PrP^{Sc}}$. According to this theory the $\mathrm{PrP^{Sc}}$ is in a polymeric form and the polymers can lenghten by attaching $\mathrm{PrP^{c}}$ monomers and transconforming them into $\mathrm{PrP^{Sc}}$. To understand more qualitatively this mechanism, a mathematical model consisting in a infinite number of coupled ordinary differential equations (ODEs) was introduced in [157]. Then a PDE version of this model was proposed in [119], see also [89] for a rigourous derivation. This equation, known as the prion equation, was studied in various works in the last few years [50, 51, 94, 111, 147, 183, 192, 206]. A more general model including general incidence of the total population of polymers on the polymerization process and polymer joining was proposed in [120], see also [148, 149] for recent works on the well-posedness of this model. Here we propose to analyse the prion equation with general incidence, but without polymer joining, which reads

$$\begin{cases} \dot{n}(t) = \mathfrak{a} - \left(\mathfrak{b} + \dfrac{c\langle u_t, g\rangle}{1+\eta\langle u_t, x^p\rangle}\right) n(t), \\ \partial_t u_t(x) = -\dfrac{c\,n(t)}{1+\eta\langle u_t, x^p\rangle}\,\partial_x\big(g(x)u_t(x)\big) - d\,u_t(x) - B(x)u_t(x) + \displaystyle\int_0^1 B\Big(\frac{x}{z}\Big)u_t\Big(\frac{x}{z}\Big)\frac{\wp(\mathrm{d}z)}{z}. \end{cases} \tag{3.16}$$

The unknown $n(t)$ represents the quantity of $\mathrm{PrP^c}$ monomers at time t and $u_t(x)$ the quantity of $\mathrm{PrP^{Sc}}$ polymers of size x. The $\mathrm{PrP^c}$ is produced by the cells with the rate $\mathfrak{a} > 0$ and degraded with the rate $\mathfrak{b} > 0$. The $\mathrm{PrP^{Sc}}$ polymers have a death rate $d > 0$ and they can break into smaller pieces with rate $B(x)$, according to the self-similar fragmentation kernel $\wp$. The "general incidence" corresponds to the term $\frac{c}{1+\eta\langle u_t, x^p\rangle}$ in front of the polymerization rate $g(x)$, with $c > 0$ and $\eta, p \geq 0$. The case $\eta = 0$ corresponds to the mass action law, *i.e.* the original model without general incidence. The more interesting case $\eta > 0$ corresponds to the case when the total population of polymers induces a saturation effect on the polymerization process. In [120] the parameter p is equal to 1, meaning that the saturation is a function of the total number of polymerized proteins. To be more general and to take into account the fact that the polymers are not necessarily linear fibrils but can have more complex 3D structure [157], we consider in our study any parameter $p \geq 0$. In [120], the polymerization rate $g(x)$ is supposed to be independant of x. But some works [111, 191] indicate that the polymerization ability, which relies on the infectivity of a polymer, may depend on its size. For mathematical convenience we assume that this dependence is linear and take

$$g(x) = x.$$

In [120] they restrict their study to linear global fragmentation rates $B(x)$ and to the homogeneous fragmentation kernel $\wp(\mathrm{d}z) = 2\mathrm{d}z$. It allows them to reduce the PDE model to a system of three ODEs. Here we consider more general global fragmentation rates

$$B(x) = Bx^b$$

with $b, B > 0$, and general fragmentation kernels $\wp$ satisfying as in Theorem 3.9

$$\wp(\mathrm{d}z) \geq c_0 \mathbf{1}_{(z_0-\varepsilon, z_0)}(z)\mathrm{d}z$$

for some $z_0 \in (0,1)$ and $\varepsilon \in (0, z_0]$. Our result is about the stability of the equilibria of Equation (3.16). We easily check that $(\bar{n} = \frac{\mathfrak{a}}{\mathfrak{b}}, \bar{u} \equiv 0)$ is an equilibrium, usually called disease free equilibrium (DFE) since there is no polymerized proteins in this situation. A natural question is to know whether there exist endemic equilibria (EE), namely equilibria (n_∞, u_∞) with $n_\infty > 0$, $u_\infty \geq 0$ and $u_\infty \not\equiv 0$. The existence of such an EE, as well as the stability of the DFE, depend on the basic reproduction number $\mathscr{R}_0$ of Equation (3.16) given by

$$\mathscr{R}_0 = \frac{\mathfrak{a}c}{\mathfrak{b}d}.$$

It is worth noticing that this parameter does not depend on the fragmentation coefficients. We prove in [P9] the following theorem about the existence and stability of equilibria.

Theorem 3.15. *If $\mathscr{R}_0 \leq 1$, then the unique equilibrium in $[0,\infty) \times L^1_+(0,\infty)$ is the DFE, and it is globally asymptotically stable.*

If $\mathscr{R}_0 > 1$, then there exists a unique EE which coexists with the DFE. The EE is locally asymptotically stable in $(0,\infty) \times L^1(V)$ for any function $V(x) = x^\ell + x^k$ with $k_* < \ell < 1 < k$. The DFE is unstable in the sense that

$$u_0 \geq 0, u_0 \not\equiv 0 \qquad \Longrightarrow \qquad \liminf_{t\to+\infty} \int_0^\infty x u_t(x)\,\mathrm{d}x > 0.$$

In the case $p \geq 1$ and $\mathfrak{b} \geq d$, the EE is globally asymptotically stable in $[0,\infty) \times \big(L^1_+(V) \setminus \{0\}\big)$.

Idea of the proof. The main idea consists in performing a self-similar transformation on the unknown u_t, as introduced in [112]. Define $w_t(x)$ through

$$w_{\tau(t)}(x) = m^{1/b}(t)u_t\big(m^{1/b}(t)x\big)\mathrm{e}^{d(t-\tau(t))} \tag{3.17}$$

where the functions τ and m satisfy

$$\dot{\tau} = m \qquad \text{and} \qquad \dot{m} = \frac{1}{b}m\Big(\frac{c}{1+\eta\langle u_t, x^p\rangle}n - dm\Big).$$

We choose $\tau(0) = 0$ and $m(0) = 1$, so that $w_0 = u_0$. We can prove that $\dot{\tau}(t) = m(t) > 0$ and $\tau(t) \geq \frac{b}{d}\log(1+\frac{d}{b}t)$, so that $\tau : [0,\infty) \to [0,\infty)$ is an increasing bijection and (3.17) indeed defines uniquely $w_t(x)$ for any $t, x > 0$. Simple calculations enable us to check that w_t is solution to the linear growth-fragmentation equation

$$\frac{\partial}{\partial t}w_t(x) + d\frac{\partial}{\partial x}\big(xw_t(x)\big) + dw_t(x) + B(x)w_t(x) = \int_0^1 B\Big(\frac{x}{z}\Big)w_t\Big(\frac{x}{z}\Big)\frac{\wp(\mathrm{d}z)}{z}$$

and Theorem 3.9 then ensures that

$$\big\|w_t - \langle u_0, h\rangle\gamma\big\|_{L^1(V)} \leq C\mathrm{e}^{-\omega t}\big\|u_0 - \langle u_0, h\rangle\gamma\big\|_{L^1(V)} \tag{3.18}$$

for all $u_0 \in L^1(V)$ and some $C \geq 1$, $\omega > 0$, $\gamma \in L^1_+(V)$ with $h(x) = x$ and $\langle\gamma, h\rangle = 1$. In particular, using (3.17), this implies that $\langle u_t, x^p\rangle \sim \langle u_0, h\rangle\langle\gamma, x^p\rangle m^{p/b}(t)\mathrm{e}^{d(\tau(t)-t)}$ as $t \to +\infty$, and defining $q(t) = \langle u_0, h\rangle\mathrm{e}^{d(\tau(t)-t)}$ we get an "asymptotically closed" system of ODEs:

$$\begin{cases} \dot{n} \underset{t\to\infty}{\sim} \mathfrak{a} - n\Big(\mathfrak{b} + \dfrac{cm^{1/b}q}{1+\eta\langle\gamma, x^p\rangle m^{p/b}q}\Big), \\ \dot{m} \underset{t\to\infty}{\sim} \dfrac{1}{b}m\Big(\dfrac{cn}{1+\eta\langle\gamma, x^p\rangle m^{p/b}q} - dm\Big), \\ \dot{q} = dq(m-1). \end{cases}$$

Since $u_t(x) = \frac{q(t)m^{-1/b}(t)}{\langle u_0, h\rangle}w_{\tau(t)}\big(m^{-1/b}(t)x\big)$, the steady state analysis of this system combined with (3.18) allows us to derive the stability results about Equation (3.16). □

3.5 Time-periodic coefficients

Structured population models with time periodic coefficients naturally appear in biology, and Harris's method is well suited to analyse their long-time behaviour. We present here two examples.

Circadian rhythms. The impact of circadian rhythms on the cell cycle is the basis of the idea of cancer chronotherapy. It can be modelled by the classical renewal equation with time periodic coefficients, as in [66, 67]. When no death rate is considered, this equation reads

$$\begin{cases} \dfrac{\partial}{\partial t}u_t(a) + \dfrac{\partial}{\partial a}u_t(a) + B(t,a)u_t(a) = 0, \\ u_t(0) = 2\displaystyle\int_0^\infty B(t,a)u_t(a)\,da, \end{cases} \tag{3.19}$$

where $a \geq 0$ stands for the age of the cells and $B(t,a)$ is the time periodic division rate. This age-structured model can be seen as a particular case of the growth-fragmentation equation with fragmentation kernel

$\wp = 2\delta_0$. In [P16] we propose generalized Doeblin's conditions that ensure ergodicity of time-inhomogeneous semigroups. In the periodic case, it allows us to give conditions on the division rate B that guarantee the periodic asynchronous exponential growth of the solutions to Equation (3.19).

Theorem 3.16. *Let B be a non-negative bounded function, periodic in the time variable with period $T > 0$, which satisfies additionally one of the two following conditions*

(i) there exist $a_0 \geq 0$ and $\underline{B} > 0$ such that $B(t,a) \geq \underline{B}$ for all $t \geq 0$ and $a \geq a_0$,

(ii) $B(t,a) = B(t)$ is not identically zero.

Then there exist a Floquet eigenvalue $\lambda_F > 0$, a function $h \in \mathscr{L}^\infty([0,\infty))$, a T-periodic family $(\gamma_t)_{t\geq 0} \subset \mathscr{M}([0,\infty))$ and explicit constants $C \geq 1$, $\omega > 0$ such that for all $t \geq 0$ and all $u_0 \in \mathscr{M}([0,\infty))$,

$$\left\| \mathrm{e}^{-\lambda_F t} u_t - \langle u_0, h \rangle \gamma_t \right\|_{\mathrm{TV}} \leq C \mathrm{e}^{-\omega t} \left\| u_0 - \langle u_0, h \rangle \gamma_0 \right\|_{\mathrm{TV}}.$$

Moreover in case (ii) we have $\lambda_F = \dfrac{1}{T}\displaystyle\int_0^T B(s)\,\mathrm{d}s$ and $\omega = 2\lambda_F$.

Let us point out that the exponential rate of convergence $2\lambda_F$ in case (ii) is kind of optimal since when $B(t,a) = B$ is independent of t and a, it is known that the spectral gap is equal to $2B$.

Protein Misfolding Cyclic Amplification. Protein Misfolding Cyclic Amplification (PMCA) is a technique that aims at mimicking and accelerating *in vitro* the polymerization process of misfolded prions, see Chapter 5 for more details. It allows detecting the presence of $\mathrm{PrP^{Sc}}$ in a sample by multiplying their amount, and is used as a test for spongiform encephalopathies. It consists of two phases: first a small amount of $\mathrm{PrP^{Sc}}$ is incubated with an excess of $\mathrm{PrP^{c}}$, so that the conversion takes place; then the growing polymers are broken with ultrasound to increase their number. By repeating the cycle, the normal $\mathrm{PrP^{c}}$ proteins are rapidly converted into $\mathrm{PrP^{Sc}}$. This cyclic alternation of incubation and sonication phases can be modelled via the growth-fragmentation equation by considering time periodic fragmentation rates $B(t,x)$:

$$\frac{\partial}{\partial t} u_t(x) + \frac{\partial}{\partial x} u_t(x) + B(t,x) u_t(x) = \int_0^1 B\Big(t, \frac{x}{z}\Big) u_t\Big(\frac{x}{z}\Big) \frac{\wp(\mathrm{d}z)}{z}.$$

Similarly as for Equation (3.19), periodic asynchronous exponential growth can be derived. More precisely we can apply Theorem 2.8 when the fragmentation rate B is a time periodic function with period T, continuous and non-negative, such that $\lim_{x\to 0} \sup_{t\in[0,T]} xB(t,x) = 0$ and $\lim_{x\to\infty} \inf_{t\in[0,T]} xB(t,x) = +\infty$, and the fragmentation kernel $\wp$ satisfies (3.4).

Chapter 4

Selection-mutation

The results in this chapter are mainly ongoing works, in collaboration with Matthieu ALFARO, Bertrand CLOEZ, and Otared KAVIAN.

4.1 Introduction

We are interested in the following mutation-selection equation

$$\frac{\partial}{\partial t}u_t(x) = \int_{\mathbf{X}} u_t(y)k(y,\mathrm{d}x)\mathrm{d}y + a(x)u_t(x) - \langle u_t, \psi\rangle\, u_t(x). \tag{4.1}$$

This now standard model in evolutionary biology was first proposed by Kimura [141]. It can be derived from stochastic individual based models [60, 61, 108, 205]. The trait space $\mathbf{X}$ is a subset of $\mathbb{R}^n$ and the fitness function a is supposed to be continuous. When $\mathbf{X}$ is unbounded we assume that the fitness is confining, in the sense that

$$\lim_{|x|\to+\infty} a(x) = -\infty.$$

We will consider different mutation kernels k, but it will always be a mapping $x \mapsto k(x,\cdot) \in \mathscr{M}_+(\mathbf{X})$ satisfying

$$\sup_{x\in\mathbf{X}} \int_{\mathbf{X}} k(x,\mathrm{d}y) < +\infty.$$

Depending on modelling considerations, the interaction function ψ can take one of two forms.

Replicator-mutator. The so-called replicator-mutator model corresponds to the function

$$\psi(x) = \int_{\mathbf{X}} k(x,\mathrm{d}y) + a(x). \tag{4.2}$$

It was derived by Kimura in his original paper [141] as a model for quantitative genetics, $u_t(x)$ representing the relative frequency of allele x at time t in a large population. It is thus a conservative equation which prescribes the time evolution of a probability distribution u_t. It is easily seen that the equation is left unchanged by adding a constant to a, so that we can always assume that $\psi \le 0$.

In [141] Kimura considered a quadratic fitness $a(x) = -x^2$ and showed the existence of an explicit Gaussian equilibrium for the diffusion approximation of this equation, namely when the mutation operator is replaced by a Laplace term. The stability of this unique equilibrium was recently proved by Alfaro and Carles [6], see also [7] for more general confining fitnesses. The original model with non-local mutations was extensively studied by Bürger under general assumptions on the coefficients [36, 37, 39, 40]. Let us also mention that the non-confining fitness $a(x) = x$ appears as a model of RNA virus evolution [197] and was investigated by some authors in the last few years [5, 115, 116], see also [38] for a well-posedness result.

Competitive interactions. In evolutionary ecology, a natural process of selection is through the competition for resources [82, 165, 166]. In our setting it corresponds to considering

$$\psi(x) \geq 0 \tag{4.3}$$

in Equation (4.1). The nonlinear term thus has a logistic type effect, ensuring essentially that the mass of the solutions is bounded in time. Contrary to the replicator-mutator model, it is not conservative and can exhibit extinction. Models with such competition-driven selection were extensively studied in the recent years, see [19, 29, 46–49, 68, 113, 153, 154] to cite only a few.

Equation (4.1) is strongly related to the linear equation

$$\frac{\partial}{\partial t} v_t(x) = \int_{\mathbf{X}} v_t(y) k(y, \mathrm{d}x) \mathrm{d}y + a(x) v_t(x). \tag{4.4}$$

For the same inital distribution $u_0 = v_0$ we have

$$v_t(x) = u_t(x) \mathrm{e}^{\int_0^t \langle u_s, \psi \rangle \mathrm{d}s} \qquad \text{and} \qquad u_t(x) = \frac{v_t(x)}{1 + \int_0^t \langle v_s, \psi \rangle \mathrm{d}s}.$$

In the replicator-mutator case (4.2), for any probability measure u_0 we have $\langle v_t, \mathbf{1} \rangle = 1 + \int_0^t \langle v_s, \psi \rangle \mathrm{d}s$. So we get

$$u_t = \frac{v_t}{\langle v_t, \mathbf{1} \rangle}$$

and it emphasizes that u_t is a probability measure for all time. Due to the link between the linear and nonlinear equations, the eigenvalue problem associated to Equation (4.4) which consists in finding (λ, γ, h) with $\gamma \geq 0$, $h \geq 0$ such that

$$\lambda \gamma(\mathrm{d}x) = \int_{\mathbf{X}} k(y, \mathrm{d}x) \gamma(\mathrm{d}y) + a(x) \gamma(\mathrm{d}x) \qquad \text{and} \qquad \lambda h(x) = \int_{\mathbf{X}} h(y) k(x, \mathrm{d}y) + a(x) h(x) \tag{4.5}$$

plays a crucial role in the analysis of Equation (4.1). Note that the spectral properties of Equation (4.4) is an active research topic [22] since it also appears in ecology to model long-range dispersion, leading to nonlocal reaction-diffusion equations, see *e.g.* [23] and the references therein.

4.2 Convolutive mutations

A classical mutation operator is provided by the convolution with a symmetric kernel. Assume that $\mathbf{X} = \mathbb{R}^n$ and

$$k(x, \mathrm{d}y) = J(x - y) \mathrm{d}y$$

with $J \in L^1(\mathbb{R}^n) \cap L^2(\mathbb{R}^n)$ such that $J(-x) = J(x)$, and $J(x) > 0$ for almost every x in a neighbourhood of zero. Note that the symmetry of J implies that the two equations in (4.5) are the same. Let us also suppose that

$$a(x) \leq 0, \qquad a(0) = 0,$$

and that there exist $\varepsilon > 0$ and a Borel set A such that

$$\int_{A_\varepsilon}\int_{A_\varepsilon}\frac{J(x-y)}{a(x)a(y)}\mathrm{d}x\mathrm{d}y > \int_{A_\varepsilon}\frac{1}{-a(x)}\mathrm{d}x \tag{4.6}$$

where $A_\varepsilon = \{a < -\varepsilon\} \cap A$. With Matthieu Alfaro and Otared Kavian, we proved the following result, yet unpublished.

Theorem 4.1. *Under the above assumptions, there exists a unique triplet $(\lambda, \gamma, h = \gamma)$ solution to the eigenproblem (4.5) with $\langle\gamma, h\rangle = 1$. Moreover $\gamma \in E$ for $E = C_0(\mathbb{R}^n)$, $E = L^p(\mathbb{R}^n)$ with $1 \le p < \infty$, or $E = \mathscr{M}(\mathbb{R}^n)$, and there exist constants $C \ge 1$ and $\omega > 0$ such that for any $v_0 \in E$ the solution v_t of Equation (4.4) verifies*

$$\left\|\mathrm{e}^{-\lambda t}v_t - \langle v_0, \gamma\rangle\gamma\right\|_E \le C\mathrm{e}^{-\omega t}\left\|v_0 - \langle v_0, \gamma\rangle\gamma\right\|_E.$$

Idea of the proof. The ground state γ is built as the minimizer of the energy functional

$$\mathscr{E}(u) = -\int (J * u)(x)u(x)\mathrm{d}x - \int a(x)u^2(x)\mathrm{d}x$$

over the set $S = \left\{u \in L^2(1-a) : \langle u, u\rangle = 1\right\}$, and λ is the corresponding minimal energy $\lambda = \inf_{u\in S}\mathscr{E}(u) = \mathscr{E}(\gamma)$. Condition (4.6) ensures that $\lambda < 0$, which is a crucial property for building γ. Then the long time behaviour of v_t is obtained by using the spectral approach of Theorem 2.7. □

This result allows us to analyse the long-time behaviour of the nonlinear equation (4.1).

Corollary 4.2 (replicator-mutator)**.** *Normalizing γ by $\langle\gamma, \mathbf{1}\rangle = 1$, there exists a constant $\omega > 0$ such that, for any $u_0 \in \mathscr{P}(\mathbb{R}^n) \cap E$ there is a constant $C(u_0) > 0$ for which the solution u_t to Equation (4.1)-(4.2) starting from u_0 satisfies*

$$\|u_t - \gamma\|_E \le C(u_0)\mathrm{e}^{-\omega t}.$$

Corollary 4.3 (competition-mutation)**.** *Assume that $\psi \in E'$ if $E = C_0(\mathbb{R}^n)$ or $E = L^p(\mathbb{R}^n)$ with $1 \le p < \infty$, and that $\psi \in \mathscr{L}^\infty(\mathbb{R}^n)$ if $E = \mathscr{M}(\mathbb{R}^n)$. Normalize γ by $\langle\gamma, \psi\rangle = 1$ and consider $u_0 \in E_+ \setminus \{0\}$. Then the solution u_t to Equation (4.1)-(4.3) with initial distribution u_0 verifies as $t \to +\infty$*

- *$u_t \to \lambda\gamma$ exponentially fast if $\lambda > 0$,*
- *$u_t \to 0$ with speed in $O(\frac{1}{t})$ if $\lambda = 0$,*
- *$u_t \to 0$ exponentially fast if $\lambda < 0$.*

Condition (4.6) is milder than

$$\inf_{y\in A}\int_A \frac{J(x-y)}{-a(x)}\mathrm{d}x > 1 \tag{4.7}$$

which appears in [150] and can also be proved to be sufficient from [37], see [40, p.250, *Note added in proof*]. Deriving sharp conditions for the existence of a ground state function is an important issue. Indeed we know from [37] that such a principal eigenfunction does not always exist, see also [72]. In this case the principal eigenvalue may be associated to a singular eigenmeasure [40], see also [73]. This indeed occurs when

$$\operatorname*{sup\,ess}_{x\in\mathbf{X}}\int_{\mathbf{X}}\frac{J(x-y)}{-a(y)}\mathrm{d}y < 1$$

as it is proved in [40]. Filling the gap between this condition and (4.6) is still an open question. However in the simpler case of house-of-cards mutations we have a complete picture of the eigenvalue problem.

4.3 House-of-cards mutations

In [142], Kingman analysed a discrete-time version of Equation (4.1)-(4.2) in the case $\mathbf{X} = [0,1]$, $a(x) = x-1$, and a mutation kernel of the form

$$k(x,\mathrm{d}y) = q(y)\mathrm{d}y.$$

Such a kernel that does not depend on x is now usually referred to as house-of-cards mutations, and the corresponding eigenvalue problem can be fully characterized [40]. For the sake of simplicity, we assume here that the fitness a admits a unique maximum. We are interested in the replicator-mutator equation (4.1)-(4.2), so we can consider without loss of generality that

$$0 \in \mathbf{X}, \qquad a(0) = 0, \qquad \text{and} \qquad x \neq 0 \implies a(x) < 0.$$

We also assume that $\int_{\mathbf{X}} \frac{q(x)}{1-a(x)}\mathrm{d}x < \infty$. The eigenvalue problem (4.5) then depends on the value of $\int \frac{q}{-a}$ compared to 1. More precisely

- if $\displaystyle\int_{\mathbf{X}} \frac{q(x)}{-a(x)}\mathrm{d}x \geq 1$ then $\lambda \geq 0$ is the unique solution to $\displaystyle\int_{\mathbf{X}} \frac{q(x)}{\lambda - a(x)}\mathrm{d}x = 1$ and $\gamma(\mathrm{d}x) = \dfrac{q(x)}{\lambda - a(x)}\mathrm{d}x$,
- if $\rho = \displaystyle\int_{\mathbf{X}} \frac{q(x)}{-a(x)}\mathrm{d}x < 1$ then $\lambda = 0$ and $\gamma(\mathrm{d}x) = (1-\rho)\delta_0 + \dfrac{q(x)}{-a(x)}\mathrm{d}x$.

The case $\rho < 1$ is of particular interest since it indicates a possible concentration phenomenon, which is supported by numerical evidences [29]. However it seems that this striking behaviour was never proved mathematically. With Bertrand Cloez, we proved the convergence of the solutions of the replicator-mutator equation (4.1)-(4.2) toward the singular measure γ. This result is still unpublished.

Theorem 4.4. *If $\rho < 1$, then for any $u_0 \in \mathscr{P}(\mathbf{X})$ the solution u_t to the replicator-mutator equation (4.1)-(4.2) verifies*

$$\frac{1}{t}\int_0^t u_s\,\mathrm{d}s \xrightarrow[t\to+\infty]{} (1-\rho)\delta_0 + \frac{q}{-a}$$

in the weak- topology.*

Concentration phenomena are very relevant in evolutionary biology. It was proved to occur for competitive interactions but only in the pure selection case [2–4, 78, 138, 185] or in the vanishing mutation regime [19, 152, 178, 184]. For the replicator-mutator model, a result similar to ours is proved in [115, 116] for the specific case $a(x) = x$ with $\mathbf{X} = \mathbb{R}$ and purely deleterious convolutive mutations, by means of an explicit formula of the so-called cumulant generating function. To our knowledge Theorem 4.4 is the first concentration result for a generalized version of Kingman's house-of-cards model.

We point out that this concentration is due to a nonlinear effect. When $\rho < 1$ the solutions v_t to the linear equation (4.4) tend to zero in norm as $t \to +\infty$ for any $v_0 \in L^1(\mathbf{X})$. Our result ensures the convergence to γ of the Cesàro mean of the renormalized function $u_t = \frac{v_t}{\langle v_t, \mathbf{1}\rangle}$.

Remark 4.5 (Concentration in a pure mutation model)**.** *Concentration phenomena can actually occur for linear jump models. In the work with Bertrand Cloez, we also considered the conservative scattering equation*

$$\frac{\partial}{\partial t}v_t(x) = \langle v_t, -a\rangle q(x) + a(x)v_t(x),$$

which can be seen as a pure mutation model. We proved that

$$\text{if} \quad \int_{\mathbf{X}} \frac{q(x)}{-a(x)}\mathrm{d}x = +\infty \quad \text{then} \quad v_t \overset{*}{\rightharpoonup} \delta_0 \quad \text{as } t \to +\infty.$$

Note that this contrasts with the smallness condition $\rho < 1$ of the replicator-mutator equation.

4.4 Varying environment

Adaptation to varying environment is an important issue in population dynamics, particularly in the context of climate change. To model this question we consider the one-dimensional trait space $\mathbf{X} = \mathbb{R}$, convolutive mutations $k(x, \mathrm{d}y) = J(x-y)\mathrm{d}y$, an interaction function ψ given either by (4.2) or by the homogeneous competitive case $\psi = 1$, and we make depend the fitness function on time in two ways.

Shifting environment. The simplest way to model climate change is to consider a translation with constant speed $c \in \mathbb{R}$ of the fitness function which becomes $a(x-ct)$. Due to the form of the coefficients we chose, we can perform a change of variable $x \leftarrow x - ct$ to follow the moving environment. We get the equation

$$\frac{\partial}{\partial t}u_t(x) = c\frac{\partial}{\partial x}u_t(x) + \int_{\mathbb{R}} u_t(y)J(x-y)\mathrm{d}y + a(x)u_t(x) - \langle u_t, \psi\rangle\, u_t(x) \tag{4.8}$$

which is as Equation (4.1) with an additional drift term. As for Equation (4.1), the analysis of Equation (4.8) strongly relies on the linear equation

$$\frac{\partial}{\partial t}v_t(x) = c\frac{\partial}{\partial x}v_t(x) + \int_{\mathbb{R}} v_t(y)J(x-y)\mathrm{d}y + a(x)v_t(x). \tag{4.9}$$

The spectral problem associated to this linear equation was investigated recently in [74], motivated by the question of the survival of a population under a climate shift in non-local reaction-diffusion models. A notable difference with the case $c = 0$ is that when $c \neq 0$ the solution γ to the eigenvalue problem cannot be a singular measure, and the existence of a principal eigenfunction holds true under fairly general assumptions on a and J. In [P20] we apply Proposition 2.5 of Chapter 2 to prove the following result.

Theorem 4.6. *Assume that J is such that $J(z) \geq \kappa_0 \mathbf{1}_{(-\varepsilon,+\varepsilon)}(z)$ for some $\kappa_0, \varepsilon > 0$. Then there exist constants $C \geq 1$, $\omega > 0$, and a unique eigentriplet $(\lambda, \gamma, h) \in \mathbb{R} \times L^1(\mathbb{R}) \times C_b^1(\mathbb{R})$ with $\langle \gamma, h\rangle = \|h\|_\infty = 1$ such that for any initial condition $v_0 \in \mathscr{M}(\mathbb{R})$ the corresponding solution v_t of Equation (4.9) verifies*

$$\left\|\mathrm{e}^{-\lambda t}v_t - \langle v_0, h\rangle\gamma\right\|_{\mathscr{M}(\mathbb{R})} \leq C\mathrm{e}^{-\omega t}\left\|v_0 - \langle v_0, h\rangle\gamma\right\|_{\mathscr{M}(\mathbb{R})}.$$

The explicit relation between u_t and v_t presented in the introduction section still holds with the drift term, namely for Equations (4.8) and (4.9). We thus deduce from Theorem 4.6 that for the replicator-mutator model, the population follows the moving environment by aligning to the profile $\gamma(x-ct)$. For the competitive case with $\psi = 1$, we deduce similarly as in Corollary 4.3 that the survival of the population relies on the sign of the eigenvalue λ. Since $a(x)$ tends to $-\infty$ when x goes to $-\infty$, we can show that λ is negative for c positive large enough. If $\lambda > 0$ when $c = 0$, it is thus expected that there exists a threshold for c below which the population survives and above which it does not manage to adapt and gets extinct.

Oscillating and shifting environment. In order to take into account some periodicity induced for instance by seasonal fluctuations, we can consider a fitness function $a(t, x-ct)$ with periodicity in the first variable that encodes the oscillatory behaviour of the environment [54, 104, 105, 151]. The survival of the population subjected to this fitness landscape for the competitive selection-mutation model with $\psi = 1$ and diffusive mutations is investigated in [54, 104] for the case $c = 0$ and in [105] for the case $c \neq 0$. Applying Theorem 2.8 it would be possible to extend some of these results to non-local mutations.

4.5 Some perspectives

The results presented in this chapter are the fruit of recently initiated works, and their extensions are natural perspective for future investigations:

- A still open problem is to find a condition on the coefficients that characterizes the existence of a ground state function, similarly as for the house-of-cards case but for general mutation kernels. There are two natural first questions in this direction. We have proved in Theorem 4.1 that (4.6) is a sufficient condition for convolutive kernels. Is it also a necessary condition? In [40] and [150], condition (4.7) is proved to be sufficient for general mutation kernels. Can we also extend the milder condition (4.6) to non-convolutive cases?
- When the ground state is a singular measure, the question of its attractiveness is a challenging open problem in general. In Theorem 4.4 we have treated the case of house-of-cards mutations. In [115, 116] a very specific fitness function is considered and concentration is obtained for convolutive mutations. The first step toward the general case would be adressing the case of convolutive mutations with more general fitness functions. Another interesting improvement of Theorem 4.4 would be to remove the Cesàro mean in the convergence result.
- As mentioned in the previous section, an interesting extension of the method we used in [P20] would be to consider oscillating environments.

Chapter 5

An optimal control problem

The results presented in this chapter are issued from works in collaboration with Vincent CALVEZ and Stéphane GAUBERT [P3, P7] and others together with Monique CHYBA, Jean-Michel CORON and Peipei SHANG which lead to the publications [P6, P8, P10].

5.1 Modelling and statement of the problem

The optimal control problem we consider in this chapter is motivated by the modelling of an amplification technique which aims at *in vitro* multiplying misfolded proteins involved in Transmissible Spongiform Encephalopathies (TSEs). Note that in Chapter 3 an *in vivo* model for these diseases is investigated in Section 3.4 and the amplification method is evoked in Section 3.5.

Prions and PMCA. Unlike the other infectious diseases which are caused by viruses, bacteria, parasites or fungi, the pathogenic agent of TSEs has no nucleic acid (DNA or RNA), which makes it very resistant. According to the widely admitted "protein-only hypothesis" proposed by the mathematician Griffith [122] and then supported by the experimental works of Prusiner's group [182], the pathogenic agent is a misfolded protein. This *proteinaceous infectious particle* was named prion by Prusiner.

Based on the protein-only hypothesis, Protein Misfolding Cyclic Amplification (PMCA) was developed by Soto and colleagues [189] to mimic *in vitro*, in an accelerated way, the prion conversion process that takes place *in vivo*. The success of this technique is a strong support to the prion hypothesis. The method relies on the nucleated polymerization model proposed by Lansbury [139] as conversion mechanism of normal proteins into misfolded ones, see Figure 5.1. PMCA starts with a few polymers of abnormally-shaped proteins added to an excess of normal monomeric prion proteins, and alternates incubation and sonication phases. During the incubation phases, the sample is left at rest in order to allow the conversion of normal proteins into misfolded ones by templating process. The sonication aims at periodically breaking the growing chains into smaller polymers with ultrasounds in order to rapidly increase the number of templating interfaces.

PMCA is extensively used for fundamental molecular-level investigations on prions. Another important application of PMCA is the diagnosis of TSEs, which is an important public health issue. Even for advanced states of the disease, the pathogenic prion agent is mainly concentrated in brain tissues and central nervous system, and the other body tissues or fluids contain very few. This little amount is both enough for possibly transmitting the disease and too small for directly detecting its presence in blood or urine samples for instance. By amplifying the minute amount of pathogenic prion agent present in a sample, PMCA allows making them detectable. In France, the national medicines safety agency actually requires using PMCA for verifying that some medicines derived from human tissues are innocuous.

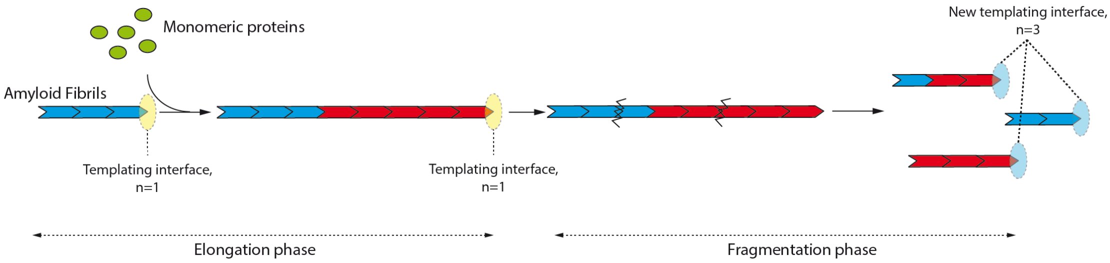


Fig. 5.1 The nucleated polymerization model is based on the templating phenomenon, where the amyloid assembly which constitutes the template induces a structural change in the monomeric substrate. The templating process leads to an increase in the size of amyloid fibrils but keeps the number of templating interfaces constant. This phase corresponds to the elongation phase. The fragmentation phase leads to the generation of de novo templating interfaces.

Mathematical model and Mayer problem. Since the contributions of Griffith, prion's history is strongly linked to mathematical modelling. However PMCA seems not having been investigated through equations. We propose here a mathematical model which leads to an interesting optimal control problem.

The growth-fragmentation equation investigated in Chapter 3 is widely used as a basis for models of nucleated polymerization, see Section 3.4. Here we start from a discrete approximation of this equation, in the spirit of Masel's model [157], and introduce a control parameter representing the sonication intensity. More precisely we consider the following controlled system

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} + r(\alpha(t))(g_i x_i - g_{i-1}x_{i-1}) = \alpha(t)\bigg(\sum_{j=i+1}^{n} B_j \kappa_{ij} x_j - B_i x_i\bigg). \tag{5.1}$$

In this model $x_i(t)$ is the quantity of polymers of size $i \in \{1,\cdots,n\}$ at time $t \geq 0$. The coefficients g_i and B_i represent respectively the elongation and fragmentation rates of polymers of size i, and we assume that $B_1 = g_n = 0$ while B_i and g_{i-1} are strictly positive for $i \in \{2,\cdots,n\}$. The coefficient $\kappa_{ij} \geq 0$ provides the mean number of i-size fragments resulting from the fragmentation of a polymer of size $j > i$, and we thus impose the mass conservation condition

$$\sum_{i=1}^{j-1} i\kappa_{ij} = j$$

for all $j > 1$. The fragmentation is modulated by a multiplicative factor $\alpha(t) \in [\alpha_{\min},\alpha_{\max}]$ which stands for the sonication intensity, $\alpha_{\min} = 1$ corresponding to the absence of sonication (*i.e.* the incubation phases) and $\alpha_{\max} > 1$ representing the maximal power of the sonicator. We also take into account the possible influence of the sonication on the elongation process through the positive term $r(\alpha(t))$ where the function r is typically decreasing for reflecting a negative effect of the ultrasounds on the conversion and attachment of monomers. Since the monomers are supposed to be in excess in PMCA, we do not consider their amount as being a limiting quantity for the elongation and it thus does not appear in the model.

Optimizing the efficiency of PMCA means maximizing the quantity of polymerized proteins at a given time $T > 0$. In our model, it corresponds to the quantity

$$\sum_{i=1}^{n} i x_i(T).$$

Finding the control $\alpha : [0,T] \to [\alpha_{\min},\alpha_{\max}]$ which maximizes this terminal gain is known as Mayer problem in optimal control theory.

In the next section, we investigate this Mayer problem and in particular the properties of singular arcs by using tools of geometric control. In Section 5.3 we consider the infinite horizon limit problem when $T \to +\infty$ and prove an ergodicity result. Finally, in the last section, we give some insights about the possible extension of the ergodicity property to the continuous version of Equation (5.1).

5.2 Finite horizon

System (5.1) can be written as bi-input control system

$$\dot{x}(t) = \big(\alpha(t)F + \beta(t)G\big)x(t)$$

where $\beta(t) = r(\alpha(t))$, and F, G represent respectively the fragmentation and growth matrices:

$$F = \begin{bmatrix} 0 & & (\kappa_{ij}B_j)_{i<j} \\ & -B_2 & \\ & & \ddots & \\ 0 & & & -B_n \end{bmatrix}, \qquad G = \begin{bmatrix} -g_1 & & & & 0 \\ g_1 & -g_2 & & & \\ & \ddots & \ddots & & \\ 0 & & g_{n-2} & -g_{n-1} & \\ & & & g_{n-1} & 0 \end{bmatrix}.$$

We assume that $r : [\alpha_{\min}, \alpha_{\max}] \to (0, \infty)$ is a decreasing convex function. The pair $(\alpha(t), \beta(t))$ belongs by definition to the graph of the function r, which is not convex except in the particular case of an affine function r. This lack of convexity prevents guaranteeing the existence of an optimal control. It is then standard to relax the problem by assuming that $(\alpha(t), \beta(t))$ belongs to the convex hull of the graph of r. For this relaxed control problem the optimal control exists, and we prove in [P6] that it belongs to the line that links $(\alpha_{\min}, r(\alpha_{\min}))$ to $(\alpha_{\max}, r(\alpha_{\max}))$ in the $\alpha\beta$-plane. Therefore, there is no loss of generality to consider $r(\alpha) = \theta\alpha + 1$ for some $\theta \le 0$. We obtain an affine control system and, denoting $F_\theta = F + \theta G$, the Mayer problem reads

$$\dot{x}(t) = Gx(t) + \alpha(t)F_\theta x(t), \tag{5.2}$$

$$\max_{\alpha:[0,T]\to[\alpha_{\min},\alpha_{\max}]} \psi x(T), \tag{5.3}$$

where $x(0) > 0$ is given and $\psi = (1 \cdots n)$.

Maximum principle. The Pontryagin Maximum Principle [181] gives necessary conditions for a solution of a control problem to be optimal. Let $\alpha^*(\cdot)$ be an optimal control for Mayer problem (5.2)-(5.3) and $x^*(\cdot)$ be the corresponding trajectory, and let $p^* : [0, T] \to \mathbb{R}^n$ be the row vector solution to the costate equation

$$\dot{p}^*(t) = -p^*(t)\big(G + \alpha^*(t)F_\theta\big) \tag{5.4}$$

with the transversality terminal condition

$$p^*(T) = \psi. \tag{5.5}$$

Introducing the Hamiltonian function

$$H(x, p, \alpha) = p(G + \alpha F_\theta)x,$$

Pontryagin's maximum principle states that (x^*, p^*, α^*) must maximize the Hamiltonian H in the sense that

$$H(x^*(t), p^*(t), \alpha^*(t)) = \max_{\alpha\in[\alpha_{\min},\alpha_{\max}]} H(x^*(t), p^*(t), \alpha) \tag{5.6}$$

holds for almost every time $t \in [0,T]$. In addition, the mapping $t \mapsto H(x^*(t), p^*(t), \alpha^*(t))$ is constant. A triplet $(x(\cdot), p(\cdot), \alpha(\cdot))$ solution of (5.2), (5.4) and (5.6) is called an *extremal* of the problem.

Let us introduce the function

$$\Phi(t) = \frac{\partial H}{\partial \alpha}(x^*(t), p^*(t), \alpha^*(t)) = p^*(t) F_\theta x^*(t).$$

The maximization condition (5.6) implies the following. If $\alpha^*(\cdot)$ is an optimal control, we have

$$\alpha^*(t) \begin{cases} = \alpha_{\min} & \text{if } \Phi(t) < 0, \\ = \alpha_{\max} & \text{if } \Phi(t) > 0, \\ \in [\alpha_{\min}, \alpha_{\max}] & \text{if } \Phi(t) = 0. \end{cases}$$

The function Φ is called the switching function and an isolated zero t of the switching function is called a switching time. If $\Phi(t) = 0$ on a nonempty time interval, a further analysis must be performed to deduce the value of $\alpha^*(t)$, see below. A bang extremal defined on (t_1, t_2), $t_2 > t_1$, corresponds to a constant maximum or minimum control, *i.e.* the sign of the switching function is constant over the entire interval (either strictly positive or strictly negative). An extremal is said to be singular on (t_1, t_2), $t_2 > t_1$, if Φ identically zero on that interval. The maximum principle implies that an optimal solution $x^*(\cdot)$ is the projection of a concatenation of bang and singular extremals. For instance, since $\psi F = 0$, $\psi G \geq 0$, $\psi G \not\equiv 0$, and $x^*(t) > 0$ for all time $t \geq 0$, the tranversality condition (5.5) implies that the optimal strategy must finish by a bang arc $\alpha_{\min}$ when $\theta < 0$. In the case of PMCA, the alternation of incubation and sonication phases corresponds to a bang-bang strategy. However it is well known that singular arcs play a major role in optimal synthesis [28]. We will show that singular controls can indeed provide a better performance.

To compute singular controls we proceed as follows. Along a singular arc, we have $\Phi(t) = 0$ on a nonzero time interval (t_1, t_2), namely

$$p(t) F_\theta x(t) = \Phi(t) = 0. \tag{5.7}$$

Differentiating this equation we obtain

$$p(t)[G, F_\theta] x(t) = \dot{\Phi}(t) = 0, \tag{5.8}$$

where $[G,F] = GF - FG$. Differentiating (5.8) with respect to time, we get

$$p(t)[[G,F_\theta],G]x(t) + \alpha(t) p(t)[[G,F_\theta],F_\theta]x(t) = \ddot{\Phi}(t) = 0 \tag{5.9}$$

almost everywhere on (t_1, t_2). Outside the surface $\{(x,p);\ p[[G,F_\theta],F_\theta]x = 0\}$, the singular control is said to be of order one and is given by

$$\alpha_{sing}(t) = -\frac{p(t)[[G,F_\theta],G]x(t)}{p(t)[[G,F_\theta],F_\theta]x(t)}. \tag{5.10}$$

The generalized Legendre-Clebsch condition is a second order necessary condition for optimality in the Mayer problem [145]. In its general form it reads $\frac{\partial}{\partial \alpha} \frac{\mathrm{d}^2}{\mathrm{d}t^2} \frac{\partial H}{\partial \alpha} \leq 0$ and it is satisfied for our problem if

$$p(t)[[G,F_\theta],F_\theta]x(t) \leq 0 \tag{5.11}$$

along the singular arc.

Perron extremals. A particular feature of system (5.2) is that it is linear in x. Moreover, for any $\alpha \in (0, \frac{1}{-\theta})$, the matrix $G + \alpha F_\theta$ is irreducible and has non-negative off-diagonal entries. Such matrices are sometimes referred to as irreducible Metzler matrices, and the Perron-Frobenius theorem ensures that they admit a unique eigenvalue associated to positive eigenvectors. In addition this Perron eigenvalue is real, simple, and dominant. For our problem, it implies that for any constant control $\alpha \in [\alpha_{\min}, \alpha_{\max}]$ there exist a particular solution to (5.2) and (5.4) of the form

$$x_\alpha(t) = \mathrm{e}^{\lambda t}\gamma \qquad \text{and} \qquad p_\alpha(t) = \mathrm{e}^{-\lambda t}h$$

where $\lambda = \lambda(\alpha)$ is the Perron eigenvalue of the matrix $G + \alpha(F + \theta G)$ and the column and row vectors $\gamma > 0$ and $h > 0$ are right and left corresponding eigenvectors:

$$(G + \alpha F_\theta)\gamma = \lambda\gamma \qquad \text{and} \qquad h(G + \alpha F_\theta) = \lambda h.$$

Normalizing h or γ so that $h\gamma = 1$, we have $\lambda(\alpha) = h(G + \alpha F_\theta)\gamma$ which gives by differentiation

$$\lambda'(\alpha) = hF_\theta\gamma.$$

Since $\Phi(t) = p(t)F_\theta x(t)$, the above expression makes appear the correlation between the critical points of the function $\lambda(\cdot)$ and the extremals of the Mayer problem. More precisely, a Perron solution $(x_\alpha(\cdot), p_\alpha(\cdot), \alpha)$ is an extremal if and only if the constant control α maximizes the eigenvalue λ over the interval $[\alpha_{\min}, \alpha_{\max}]$, *i.e.* $\alpha = \bar{\alpha}$ with

$$\lambda(\bar{\alpha}) = \max_{\alpha_{\min} \le \alpha \le \alpha_{\max}} \lambda(\alpha).$$

If $\bar{\alpha} = \alpha_{\min}$ or $\bar{\alpha} = \alpha_{\max}$ we obtain a bang extremal, and if $\alpha_{\min} < \bar{\alpha} < \alpha_{\max}$ a singular extremal. The singular case is both more interesting mathematically and more relevant biologically since it indicates that a trade-off has to be found between elongation and fragmentation. The following result provides sufficient conditions for the existence of a singular Perron extremal.

Proposition 5.1. *If $\theta < 0$, then $\lambda(\alpha) > 0$ for all $\alpha \in (0, \frac{1}{-\theta})$ and*

$$\lim_{\alpha \to 0} \lambda(\alpha) = \lim_{\alpha \to \frac{1}{-\theta}} \lambda(\alpha) = 0.$$

If $\theta = 0$ and $g_2 > 2g_1$, then $\lambda(\alpha) > 0$ for all $\alpha > 0$ and

$$\lim_{\alpha \to 0} \lambda(\alpha) = \lim_{\alpha \to +\infty} \lambda(\alpha) = 0.$$

In the sequel we focus on the case $\bar{\alpha} \in (\alpha_{\min}, \alpha_{\max})$ and we denote by $(\bar{x}(\cdot), \bar{p}(\cdot), \bar{\alpha})$ the corresponding Perron singular extremal. By construction, this extremal maximizes the Lyapunov exponent $\lambda(\alpha)$ among all the constant controls and it can thus be expected that it is involved in the optimal control strategy $\alpha^*(\cdot)$. To test further this intuition, we compare $\lambda(\bar{\alpha})$ to the Lyapunov exponents provided by periodic controls. For $\alpha(\cdot)$ a τ-periodic function, there exist a periodic eigenfunction $\gamma_\alpha(\cdot)$ associated to a Floquet eigenvalue $\lambda_F(\alpha)$ such that

$$\dot{\gamma}_\alpha(t) + \lambda_F(\alpha)\gamma_\alpha(t) = (G + \alpha(t)F_\theta)\gamma_\alpha(t).$$

We consider small periodic perturbations of the best constant control, $\alpha(t) = \bar{\alpha} + \varepsilon\zeta(t)$, where ζ is τ-periodic. We assume that the matrix $G + \bar{\alpha}F_\theta$ is diagonalizable and we denote by $(\gamma_1, \cdots, \gamma_n)$ and $(h_1, \cdots, h_n)$ the right and left eigenvector bases associated to the eigenvalues $(\lambda_1, \cdots, \lambda_n)$ with $\lambda_1 = \lambda$, $\gamma_1 = \gamma$, $h_1 = h$, and $h_i\gamma_i = 1$. We can compute the two first directional derivatives of λ_F in terms of these eigenelements, which allows us to derive a second order necessary condition for $\bar{\alpha}$ to be a local maximum of λ_F over the set of periodic controls. We use the notation

$$\langle\alpha\rangle = \frac{1}{\tau}\int_0^\tau \alpha(t)\mathrm{d}t.$$

Proposition 5.2. *We have*

$$\left.\frac{\mathrm{d}\lambda_F(\bar\alpha+\varepsilon\zeta)}{\mathrm{d}\varepsilon}\right|_{\varepsilon=0}=\langle\zeta\rangle\lambda'(\bar\alpha)=0 \tag{5.12}$$

and

$$\left.\frac{\mathrm{d}^2\lambda_F(\bar\alpha+\varepsilon\zeta)}{\mathrm{d}\varepsilon^2}\right|_{\varepsilon=0}=2\sum_{i=2}^{n}\langle|\zeta_i|^2\rangle\frac{(h_1F_\theta\gamma_i)(h_iF_\theta\gamma_1)}{\lambda_1-\lambda_i}, \tag{5.13}$$

where $\zeta_i(t)$ is the unique τ-periodic solution of the relaxation equation $\dfrac{\dot\zeta_i(t)}{\lambda_1-\lambda_i}+\zeta_i(t)=\zeta(t)$.

Equation (5.12) ensures that the constant control $\bar\alpha$ is also a critical point in the class of periodic controls. Taking $\gamma\equiv 1$ in (5.13), we get the second derivative of the Perron eigenvalue at $\bar\alpha$,

$$\lambda''(\bar\alpha)=2\sum_{i=2}^{n}\frac{(h_1F_\theta\gamma_i)(h_iF_\theta\gamma_1)}{\lambda_1-\lambda_i}, \tag{5.14}$$

which is nonpositive since $\bar\alpha$ is a maximum point. The question then is wether (5.13) can be positive while (5.14) is nonpositive. This is clearly not possible in dimension $n=2$ because the sum in (5.13) is reduced to a single term which is nonpositive as (5.14).

By considering periodic perturbations of the form $\zeta(t)=\cos(\omega t)$ we get the formula

$$\left.\frac{\mathrm{d}^2\lambda_F(\bar\alpha+\varepsilon\zeta)}{\mathrm{d}\varepsilon^2}\right|_{\varepsilon=0}=2\sum_{i=2}^{n}\frac{\lambda_1-\lambda_i}{|\lambda_1-\lambda_i|^2+\omega^2}(h_1F_\theta\gamma_i)(h_iF_\theta\gamma_1).$$

An asymptotic expansion as $\omega\to+\infty$ yields the following corollary.

Corollary 5.3. *If $G+\bar\alpha F_\theta$ is diagonalizable, then*

$$\sum_{i=2}^{n}(\lambda_1-\lambda_i)(h_1F_\theta\gamma_i)(h_iF_\theta\gamma_1)\le 0 \tag{5.15}$$

is a necessary condition for $\bar\alpha$ to be a local maximum of λ_F over the set of periodic controls.

Condition (5.15) is actually the generalized Legendre-Clebsch condition (5.11) for the Perron singular extremal $(\bar x(\cdot),\bar p(\cdot),\bar\alpha)$. Indeed, we have the identities

$$\bar p(t)[[G,F_\theta],F_\theta]\bar x(t)=2hF_\theta(\lambda-G-\bar\alpha F_\theta)F_\theta\gamma=2\sum_{i=2}^{n}(\lambda_1-\lambda_i)(h_1F_\theta\gamma_i)(h_iF_\theta\gamma_1).$$

The 2D case. We consider here the case $n=2$. We thus have $g_2=0$ and, in view of Proposition 5.1, we suppose that $\theta<0$ in order to guarantee the existence of a Perron singular extremal. As noticed above, for $n=2$, such an extremal necessarily satisfies the generalized Legendre-Clebsch condition. Theorem 5.4 below, obtained in [P6] and illustated by Figure 5.2, actually shows that the Perron singular extremal essentially provides the solution to the Mayer problem. The optimal control $\alpha^*(\cdot)$ consists mainly in the singular control $\bar\alpha$, except in the regions close to the endpoints of $[0,T]$. For small time, the optimal control depends on the initial data $x(0)$ and it aims at reaching as fast as possible the singular arc. Then the control remains constant equal to $\bar\alpha$ as long as possible. At the end of the experiment, the control is $\alpha_{\min}$ due to the transversality condition induced by the objective function. Such a strategy is said to exhibit the so-called turnpike property [196, 212]. The "turnpike" is the singular trajectory $\bar x(\cdot)$.

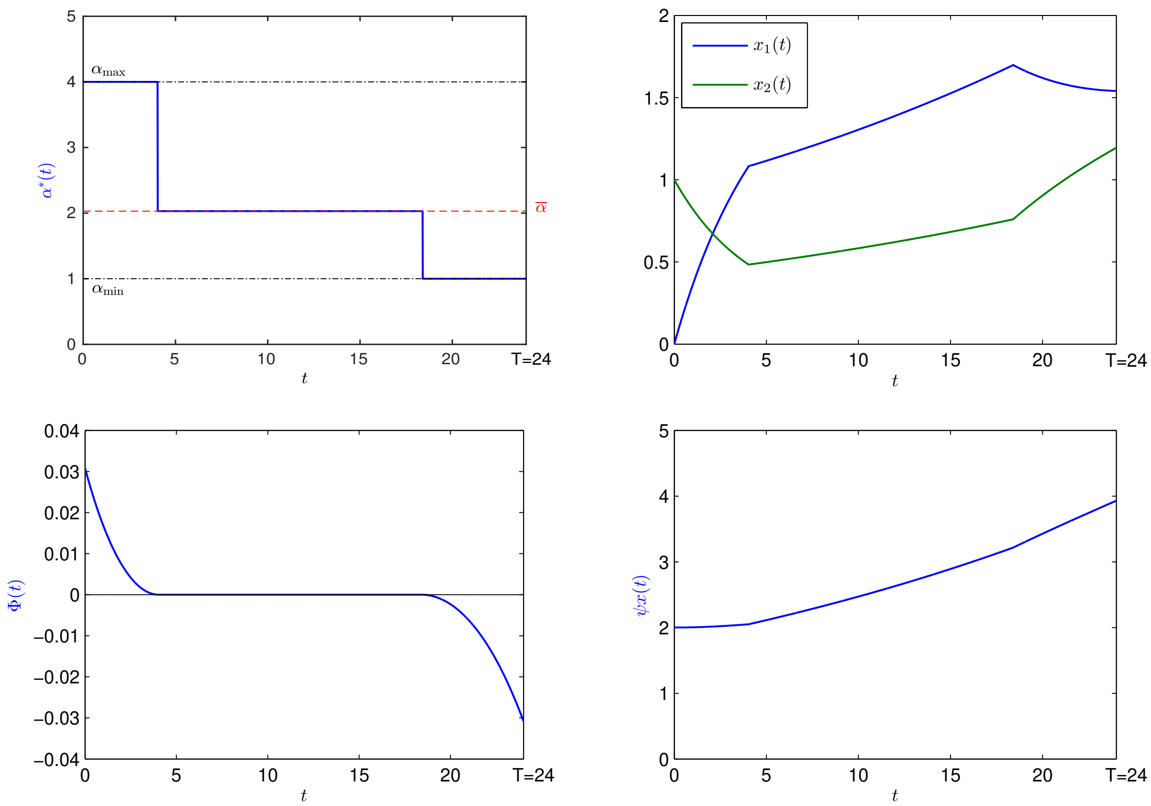


Fig. 5.2 Top left: the optimal control $\alpha^*(t)$ for $T = 24$, $n = 2$, $\theta = -0.2$, $g_1 = 0.1$, $B_2 = 0.05$ and the initial data $x_1(0) = 0$, $x_2(0) = 1$. Top right: the corresponding trajectories $x_1(t)$ and $x_2(t)$. Bottom left: the switching function $\Phi(t)$. Bottom right: the evolution of the objective $\psi x(t) = x_1(t) + 2x_2(t)$.

Theorem 5.4. *Let $x(0)$ be a nonnegative and nonzero vector. There exist a time $T_0 = T_0(x(0))$, a time $T_\psi > 0$ independent of $x(0)$, and a time $T_c > T_0 + T_\psi$ such that for any $T > T_c$, the optimal control is given by*

$$\alpha^*(t) = \begin{cases} \left.\begin{array}{ll} \alpha_{\min} & \text{if } \frac{x_1(0)}{x_1(0)+x_2(0)} > \frac{\gamma_1}{\gamma_1+\gamma_2} \\ \alpha_{\max} & \text{if } \frac{x_1(0)}{x_1(0)+x_2(0)} < \frac{\gamma_1}{\gamma_1+\gamma_2} \end{array}\right\} & \text{for } t \in [0, T_0], \\ \bar{\alpha} & \text{for } t \in (T_0, T - T_\psi], \\ \alpha_{\min} & \text{for } t \in (T - T_\psi, T]. \end{cases} \tag{5.16}$$

Moreover, on the time interval $[T_0, T - T_\psi]$, the optimal trajectory $(x^*(\cdot), p^*(\cdot), \alpha^*(\cdot))$ is aligned to the Perron singular extremal $(\bar{x}(\cdot), \bar{p}(\cdot), \bar{\alpha})$.

Main steps of the proof. In [P6], this result is split into three theorems:

- First, by using (5.7), (5.8), (5.9) and (5.10), we prove that the Perron extremal $(\bar{x}(\cdot), \bar{p}(\cdot), \bar{\alpha})$ is the unique singular extremal of our problem, up to normalization;
- Then we prove that for a suitable definition of the times T_0 and T_ψ, the control defined in (5.16) satisfies the maximization condition (5.6);
- Finally, through a careful analysis of the switching function Φ, we prove that for T large enough the optimal control is necessarily given by (5.16).

□

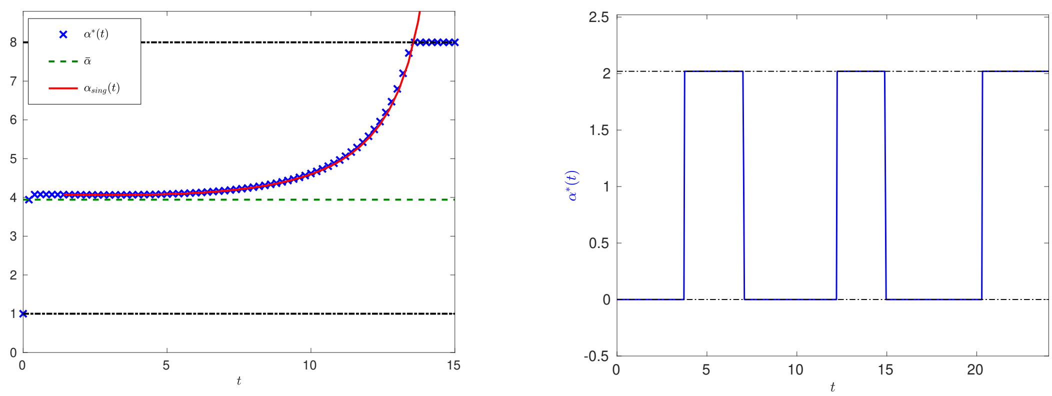
The 3D case. We have seen that in the two-dimensional case, the only singular control is $\bar{\alpha}$ and that it constitutes the best strategy. In dimension $n \geq 3$, the singular flow is more complex. In dimension three, the costate vector p can be eliminated from (5.10) and the singular control is determined as a feedback from the state only. Introducing the determinants

$$D_1(x) = \det\big(F_\theta x, [G,F_\theta]x, [[G,F_\theta],G]x\big), \qquad D_2(x) = \det\big(F_\theta x, [G,F_\theta]x, [[G,F_\theta],F_\theta]x\big),$$

the relations (5.7)-(5.8)-(5.9) ensure that singular trajectories of order one are solutions of $\dot{x}(t) = X_s(x(t))$ where X_s is given by

$$X_s(x) = Gx - \frac{D_1(x)}{D_2(x)} F_\theta x \tag{5.17}$$

with the feedback control $\alpha_{sing} = -\frac{D_1(x)}{D_2(x)}$. In Figure 5.3a, we illustrate numerically that in dimension three the optimal control is again essentially singular but that contrary to the two-dimensional case the singular arc is not provided by $\bar{\alpha}$. However, backward in time, α_{sing} seems to converge to $\bar{\alpha}$. This suggests that, similarly as for the two-dimensional case, the optimal gain $\psi x^*(T)$ behaves like $\mathrm{e}^{\lambda(\bar{\alpha})T}$ when T becomes large.



(a) Growth-fragmentation with $\alpha_{\min} = 1$, $\alpha_{\max} = 8$, $g_1 = 0.01$, $g_2 = 10$, $B_2 = 0.1$, $B_3 = 0.9$, $\kappa_{13} = \kappa_{23} = 1$, $\theta = 0$, and $x(0) = (3\ 4\ 4)^\top$. Blue crosses represent the numerical optimal control $\alpha^*(t)$ obtained through a relaxation method; the green dashed line is the Perron singular control $\bar{\alpha}$; the red curve is the singular control $\alpha_{sing}(t)$ computed by solving (5.17) numerically, starting from the optimal trajectory x^* at time $t = 1.5$.

(b) The bang-bang numerical optimal control $\alpha^*(t)$ for matrices F and G (not of the fragmentation and growth type) that fail to meet the generalized Legendre-Clebsch condition (5.11).

Fig. 5.3 Two three-dimensional optimal control examples.

In the example of Figure 5.3a, the generalized Legendre-Clebsch condition (5.11) is verified and the optimal control is bang-singular-bang. We did not find any growth and fragmentation matrices F and G that defeat the generalized Legendre-Clebsch condition. However, by looking in another subclass of Metzler matrix pairs, we managed to find three-dimensional examples of matrices F and G that do not satisfy (5.11), see [P7]. In such cases the Perron singular control $\bar{\alpha}$ does not maximize the Lyapunov exponent among periodic controls, and the optimal control seems to follow a bang-bang strategy, see Figure 5.3b for a numerical evidence.

Hamilton-Jacobi-Bellman equation. Another approach of optimal control problems is to focus on the optimal gain rather than on the optimal trajectories. Let us define the cone $K = \{x \in \mathbb{R}^n,\ x \geq 0\}$, which is invariant under the dynamics (5.2), and the value function $v : [0,+\infty) \times K \to [0,+\infty)$ by

$$v(T,x) = \sup_{\alpha:[0,T]\to[\alpha_{\min},\alpha_{\max}]} \big\{ \psi x(T) \ : \ x(0) = x,\ \dot{x}(t) = Gx(t) + \alpha(t)F_\theta x(t) \big\}.$$

This function is a viscosity solution of the Hamilton-Jacobi-Bellman equation

$$-\partial_t v(t,x) + \max_{a\in[\alpha_{\min},\alpha_{\max}]} \langle (G + aF_\theta)x, D_x v(t,x)\rangle = 0$$

with initial condition $v(0,x) = \psi x$. The so-called dynamic programming method actually allows designing the optimal control α^* as a feedback control once this Hamilton-Jacobi-Bellman equation is solved [96, 106].

Since our problem is linear in x, the value function v is homogeneous of degree one in space and accordingly there exists a function w defined on the simplex $S = \{x \in K : \langle x, \mathbf{1}\rangle = 1\}$ such that for all $x \in K$ and $t \geq 0$

$$v(t,x) = \langle x, \mathbf{1}\rangle w\Big(t, \frac{x}{\langle x, \mathbf{1}\rangle}\Big).$$

This new function is defined on a compact and lower dimensional space. It satisfies the Hamilton-Jacobi equation

$$-\partial_t w(t,y) + \max_{a\in[\alpha_{\min},\alpha_{\max}]} \big(L(y,a)w(t,y) + \langle b(y,a), D_y w(t,y)\rangle \big) = 0$$

where the Lagrangian L and the vector field b are given by

$$L(y,a) = \langle (G + aF_\theta)y, \mathbf{1}\rangle, \qquad b(y,a) = (G + aF_\theta)y - L(y,a)y.$$

Note that each vector field $b(\cdot,a)$ is tangent to the simplex S. It gives indeed the projected dynamics on the simplex: if $x(\cdot)$ is solution to (5.2) then $y(\cdot) = \frac{x(\cdot)}{\langle x(\cdot),\mathbf{1}\rangle}$ is solution to the non-linear ODE

$$\dot{y}(t) = b(y(t), \alpha(t)).$$

We can derive a maximization problem on the simplex by performing the logarithmic transformation

$$u(t,y) = \log w(t,y).$$

The function u satisfies the Hamilton-Jacobi-Bellman equation

$$-\partial_t u(t,y) + \max_{a\in[\alpha_{\min},\alpha_{\max}]} \big(L(y,a) + \langle b(y,a), D_y u(t,y)\rangle \big) = 0$$

and is solution to the maximization problem with running reward

$$u(t,y) = \sup_{\alpha:[0,t]\to[\alpha_{\min},\alpha_{\max}]} \Big\{ \int_0^t L(y(s),\alpha(s))\mathrm{d}s + \log(\psi y(t)) \ : \ y(0) = y,\ \dot{y}(s) = b(y(s),\alpha(s)) \Big\}.$$

5.3 Infinite horizon

In this section, we investigate the long time behaviour of the value function of Mayer problems slightly more general than (5.2)-(5.3). Let $\mathfrak{A}$ be a compact set of irreducible Metzler matrices. For $t > 0$, $x \in K$ and $A : [0,t] \to \mathfrak{A}$, we consider the following linear system controlled by A:

$$\begin{cases} \dot{x}_A(s) = A(s)x_A(s), \quad 0 < s < t, \\ x_A(0) = x. \end{cases} \tag{5.18}$$

The Lyapunov exponent $\lambda(\mathfrak{A})$ is defined as the maximal possible growth rate realized by the trajectories of (5.18) when $x \in K_0 = K \setminus \{0\}$,

$$\lim_{t\to+\infty} \frac{1}{t}\left(\sup_{A:[0,t]\to\mathfrak{A}} \log v_0(x_A(t)) \right) = \lambda(\mathfrak{A}), \tag{5.19}$$

where $v_0 : K_0 \to (0,\infty)$ is any continuous function homogeneous of degree one. The fact that the limit (5.19) exists and does not depend on the initial condition x is a corollary of the following theorem, obtained in [P7].

Theorem 5.5. *For any compact set of irreducible Metzler matrices $\mathfrak{A}$, there exist a real $\lambda(\mathfrak{A})$ and a function $\bar{v} : K \to [0,+\infty)$, homogeneous of degree one, positive on K_0, Lipschitz continuous, such that for all $t \geq 0$ and all $x \in K$*

$$e^{\lambda(\mathfrak{A})t}\bar{v}(x) = \sup_{A:[0,t]\to\mathfrak{A}} \bar{v}(x_A(t)). \tag{5.20}$$

The Lyapunov exponent $\lambda(\mathfrak{A})$ is also called the joint spectral radius of $\mathfrak{A}$, after Rota and Strang [186], and the potential $\bar{v}$ shares features with so-called Barabanov norms [14]. Identity (5.20) means that the potential $\bar{v}$ is such that the optimal trajectories with respect to $\bar{v}$ grow exactly exponentially, with rate $\lambda(\mathfrak{A})$. It can be seen as an extension of the Perron-Frobenius theorem which ensures that, in the case where $\mathfrak{A} = \{A\}$ is a made of a single matrix, the potential is given by $\bar{v}(x) = \langle x, h\rangle$ where h is the left eigenvector of A associated to the Perron eigenvalue $\lambda(A) = \lambda(\mathfrak{A})$. This is perhaps even clearer on the infinitesimal version of (5.20),

$$\lambda(\mathfrak{A})\bar{v}(x) = \max_{A\in\mathfrak{A}} \langle Ax, D_x\bar{v}(x)\rangle,$$

which is a stationary Hamilton-Jacobi-Bellman equation in the viscosity sense [16].

Sketch of the proof. Due to the presumed homogeneity of $\bar{v}$ and the exponential growth in time in (5.20), we perform the transformation

$$\mathring{u}(x) = \log\bar{v}(x) - \log\langle x, \mathbf{1}\rangle.$$

The function $\mathring{u}$ is zero-homogeneous and thus naturally defined on the projective space $PK_0 = K_0/\sim$, where $\sim$ is the equivalence relation induced by the colinearity of vectors. In terms of this new function, (5.20) becomes

$$\lambda(\mathfrak{A})t + \mathring{u}(x) = \sup_{A:[0,t]\to\mathfrak{A}} \left\{ \int_0^t L(x_A(s), A(s))\mathrm{d}s + \mathring{u}(x_A(t)) \right\}, \tag{5.21}$$

where the Lagrangian (or running reward) L is given by $L(x,A) = \frac{\langle Ax, \mathbf{1}\rangle}{\langle x, \mathbf{1}\rangle}$. The problem is thus to find a real $\lambda(\mathfrak{A})$ and a zero-homogeneous function $\mathring{u}$ such that (5.21) is satisfied, or equivalently such that $\mathring{u}$ is a viscosity solution of the ergodic Hamilton-Jacobi equation

$$-\lambda(\mathfrak{A}) + H(x, D_x\mathring{u}(x)) = 0, \tag{5.22}$$

where the Hamiltonian is defined as $H(x,p) = \max_{A\in\mathfrak{A}}(L(x,A) + \langle Ax, p\rangle/\langle x, \mathbf{1}\rangle)$.

The key point is to notice that, due to Birkhoff's theorem, each flow associated to a given control $A : [0,t] \to \mathfrak{A}$ is a contraction for the Hilbert projective metric defined on the projective space PK_0 by

$$d(x,y) = \max_{1\leq i\leq n}\left(\log\frac{x_i}{y_i}\right) - \min_{1\leq j\leq n}\left(\log\frac{x_j}{y_j}\right).$$

More precisely, we can prove that for any $\tau > 0$ there exists $\omega > 0$ such that for any $A = [0,\infty) \to \mathfrak{A}$, any $x, y \in PK_0$ and all $t \geq 0$

$$d(x_A(t), y_A(t)) \leq e^{-\omega(t-\tau)} d(x,y). \tag{5.23}$$

Furthermore, by exploiting the Finsler structure of the projective space PK_0 endowed with Hilbert's metric [173], we can establish that the Lagrangian L is Lipschitz continuous from (PK_0, d) to $(\mathbb{R}, |\cdot|)$. More precisely, the Lipschitz constant is bounded from above by

$$\operatorname{Lip} L(\cdot, A) \leq \sup_{x \in PK_0} \inf_{a \in \mathbb{R}} \left(\frac{\langle |A - a\,\mathrm{Id}|x, \mathbf{1}\rangle}{\langle x, \mathbf{1}\rangle} \right).$$

Then, for any discount rate $\varepsilon > 0$, we consider the infinite-horizon counterpart of (5.21) defined as

$$u_\varepsilon(x) = \sup_{A:(0,\infty)\to\mathfrak{A}} \left\{ \int_0^\infty \mathrm{e}^{-\varepsilon t} L(x_A(t), A(t))\mathrm{d}t \right\}.$$

It is a viscosity solution of the stationary Hamilton-Jacobi equation

$$-\varepsilon u_\varepsilon(x) + H(x, D_x u_\varepsilon(x)) = 0. \tag{5.24}$$

Clearly, $\varepsilon u_\varepsilon$ is uniformly bounded by $\|L\|_\infty$. Besides, the exponential contraction of trajectories yields an *a priori* Lipschitz estimate, uniformly with respect to ε. Let us fix x and y in PK_0. For any $\eta > 0$, there exists a η-close-to-optimal control function $A : [0,\infty) \to \mathfrak{A}$ associated to the initial condition x, namely such that

$$u_\varepsilon(x) \leq \eta + \int_0^\infty \mathrm{e}^{-\varepsilon t} L(x_A(t), A(t))\mathrm{d}t.$$

Choosing the same control for the initial point y we get

$$\begin{aligned}
u_\varepsilon(x) - u_\varepsilon(y) &\leq \eta + \int_0^\infty \mathrm{e}^{-\varepsilon t}(L(x_A(t), A(t)) - L(y_A(t), A(t))\mathrm{d}t \\
&\leq \eta + (\sup_{A\in\mathfrak{A}} \operatorname{Lip} L(\cdot, A)) \int_0^\infty \mathrm{e}^{-\varepsilon t} d(x_A(t), y_A(t))\mathrm{d}t \\
&\leq \eta + (\sup_{A\in\mathfrak{A}} \operatorname{Lip} L(\cdot, A))\mathrm{e}^{\omega\tau} \int_0^\infty \mathrm{e}^{-(\varepsilon+\omega)t} d(x,y)\mathrm{d}t \\
&\leq \eta + (\sup_{A\in\mathfrak{A}} \operatorname{Lip} L(\cdot, A)) \frac{\mathrm{e}^{\omega\tau}}{\varepsilon+\omega} d(x,y).
\end{aligned}$$

As x, y, and η are arbitrary we deduce

$$\operatorname{Lip} u_\varepsilon \leq \frac{\mathrm{e}^{\omega\tau}}{\omega} \operatorname{Lip} L.$$

Hence, up to extraction, $\varepsilon u_\varepsilon$ converges locally uniformly towards a constant $\lambda(\mathfrak{A})$. In addition, we can extract a subsequence $(u_{\varepsilon'})$ which converges towards some Lipschitz function $\mathring{u}$, up to the substraction of a (possibly large) constant, say $\min u_{\varepsilon'}$. It can be proven that $\mathring{u}$ is globally Lipschitz on PK_0, up to the boundary. Passing to the limit in (5.24) in the viscosity sense, the limit function $\mathring{u}$ is a viscosity solution ot the ergodic equation (5.22), and the proof is complete. □

Lack of controllability/coercivity and the ergodic set. Contrary to our approach which is based on the long time contraction of the trajectories, classical arguments for proving ergodicity results such as Theorem 5.5 rather rely on short time dynamics of the system. This is the case for instance of the ergodicity result in Capuzzo-Dolcetta and Lions [53, Theorem X.2], and of the weak KAM Theorem of Fathi [101]. In the former the authors assume a uniform controllability condition which basically states that the vector field of the controlled system allows going in all directions with speed uniformly bounded from below. The latter relies on a regularizing property of the Lax-Oleinik semi-group which holds true for Tonelli Lagrangians. Both cases imply that the Hamiltonian is coercive, *i.e.* $\lim_{|p|\to\infty} H(x,p) = +\infty$, a property which is not satisfied in our case.

One noticeable exception can be found in [16, Section VII.1.2], where the controllability condition is replaced by a dissipativity condition which is somehow similar to our uniform contraction estimate (5.23).

Uniform controllability is far from being satisfied in our case, where some strict subsets of PK_0 are positively invariant by all the flows. In a couple of papers [9, 10], Arisawa made clear the equivalence between ergodicity, in the sense of (5.19), and the existence of a so-called ergodic set when controllability is lacking. The ergodic set satisfies the following properties: it is non empty, closed and positively invariant by the flows; it is attractant; it is controllable.

In [P3], we characterized the ergodic set in the case of the growth-fragmentation problem (5.2)-(5.3) in dimension $n = 3$, with $\theta = 0$. Actually we used this characterization to prove the ergodicity property (5.19) in this specific case, before being aware by S. Gaubert that ideas and techniques from max-plus linear algebra could allow to dramatically improve the result by proving Theorem 5.5. The ergodic set of the three-dimensional growth-fragmentation problem is the area enclosed between the projective trajectory issued from the Perron projective eigenline of the matrix $G + \alpha_{\min} F$ with constant control $\alpha_{\max}$, and the trajectory starting from the Perron projective eigenline of $G + \alpha_{\max} F$ with constant control $\alpha_{\min}$, see Figure 5.4.

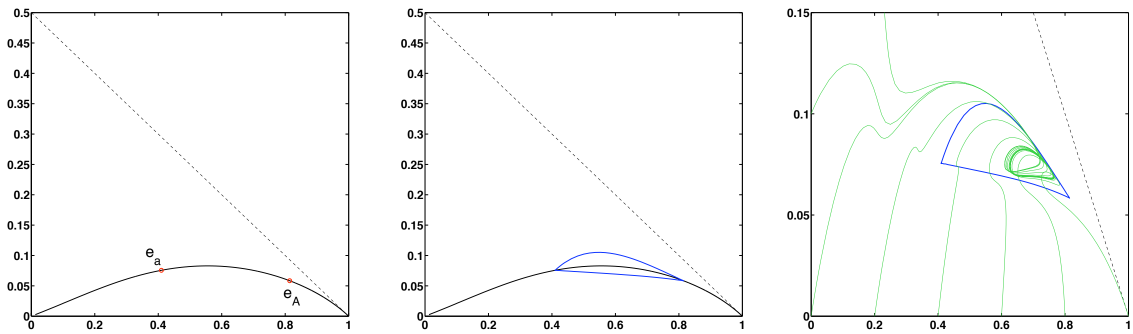


Fig. 5.4 The three-dimensional growth-fragmentaion process with typical parameters. The projective space PK_0 is identified with the two-dimensional simplex $\{x \in K : \langle x, \mathbf{1} \rangle = 1\}$. The dashed line represents the boundary $x_3 = 0$. Left: the two red dots are the projective eigenlines for $\alpha = \alpha_{\min}$ and $\alpha = \alpha_{\max}$, and the black curve represents the set of all the eigenlines for α browsing $(0, \infty)$. Middle: the blue curves delimit the ergodic set. Right: illustration of the attraciveness and stability of the ergodic set through the plot of several periodic trajectories. Parameters are $g_1 = 2\text{E}-2$, $g_2 = 1$, $B_3 = 2B_2 = 8\text{E}-2$, $\kappa_{13} = \kappa_{23} = 1$, and $\alpha_{\min} = 2$, $\alpha_{\max} = 8$.

About the optimality of the maximal Perron eigenvalue. In Theorem 5.4, we fully characterized the optimal trajectories of the two-dimensional growth-fragmentation problem. Since these trajectories consist essentially in Perron extremals, we get as a by-product that for $\mathfrak{A} = \{G + \alpha F_\theta,\ \alpha_{\min} \leq \alpha \leq \alpha_{\max}\}$ the Lyapunov exponent is given by the best Perron eigenvalue of $\mathfrak{A}$, namely

$$\lambda(\mathfrak{A}) = \max_{A \in \mathfrak{A}} \lambda(A). \tag{5.25}$$

By taking advantage of the Pontryagin maximum principle, we can actually prove that (5.25) holds true for any set $\mathfrak{A}$ of two-dimensional irreducible Metzler matrices [P7]. It is in this same paper [P7] that we proposed the three-dimensional counter-example presented in Figure 5.3b, for which some periodic controls provide a better Floquet eigenvalue than the best Perron's. This example shows that the strict inequality $\lambda(\mathfrak{A}) > \max_{A \in \mathfrak{A}} \lambda(A)$ can occur in dimension $n \geq 3$.

Meanwhile, we realized that the optimality of constant controls in dimension $n = 2$ was already proven by a different approach in [124]. Also, a three-dimensional counter-example was described in [99], thus answering a question raised in [124]. These two works deal with more general linear inclusion systems, without the monotonicity property.

In Figures 5.5 and 5.6 we illustrate two kinds of behaviours for optimal trajectories in dimension three: the convergence to the best Perron eigenline when (5.25) holds true, Figure 5.5, and the convergence to a limit cycle when it does not, Figure 5.6. Proving that only these two types of behaviour can take place in dimension three is still an open question.

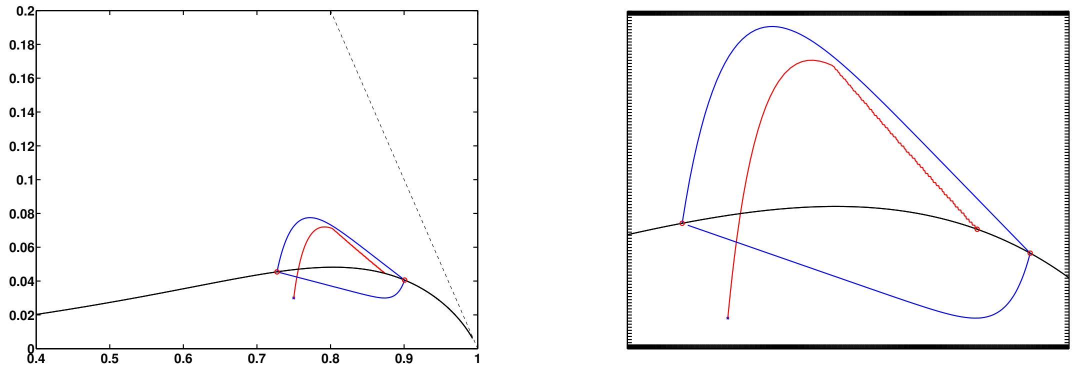


Fig. 5.5 Illustration of convergence of optimal trajectories towards the optimal Perron eigenline for the three-dimensional growth-fragmentation process with the same parameters as in Figure 5.4. We have plotted the curve of Perron eigenvectors (black line), the boundary of the ergodic set (blue line), and an arbitrary optimal trajectory (red line). The optimal trajectory enters the ergodic set and then converges towards a limit cycle. Right picture is a zoom of the left one. The numerical grid is plotted on the axes: the space step is $\Delta x = 5\text{E}{-4}$ to fall much below the width of the ergodic set.

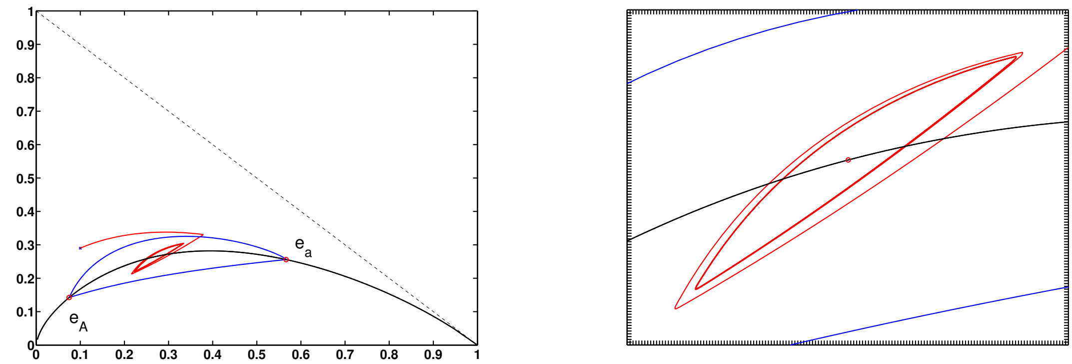


Fig. 5.6 Illustration of the optimal limit cycle for the same example as in Figure 5.3b. We have plotted the curve of Perron eigenvectors (black line), the boundary of the ergodic set (blue line), and an arbitrary optimal trajectory (red line). The optimal trajectory enters the ergodic set and then converges towards a limit cycle. Right picture is a zoom of the left one. The numerical grid is plotted on the axes: the space step is $\Delta x = 1\text{E}{-3}$ to fall much below the width of the limit cycle.

5.4 Infinite dimension in infinite horizon (perspectives)

A challenging problem is the extension of Theorem 5.5 to the continuous version of Equation (5.1), namely the controlled growth-fragmentation equation

$$\frac{\partial}{\partial t}u_t(x)+r(\alpha(t))\frac{\partial}{\partial x}\big(g(x)u_t(x)\big)=\alpha(t)\bigg(\int_0^1 B\Big(\frac{x}{z}\Big)u_t\Big(\frac{x}{z}\Big)\frac{\wp(\mathrm{d}z)}{z}-B(x)u_t(x)\bigg), \tag{5.26}$$

or more generally to infinite dimensional systems enjoying some positivity properties. To our knowledge, such infinite-dimensional ergodicity results do not exist in the literature, and the methods classically used to prove the existence of Barabanov norms seem not being easily extendable to the infinite-dimensional setting. By contrast, our approach based on the exponential contraction of the flows could be applicable. However, Birkhoff's theorem requires a very strong positivity property to derive (5.23), which fails in general for infinite-dimensional systems and in particular for Equation (5.26).

The option we are considering to work around this problem is the method presented in Chapter 2, by replacing Hilbert's projective metric by a weighted total variation projective distance of the type

$$d(\mu_1,\mu_2)=\left\|\frac{\mu_1}{\langle\mu_1,\psi\rangle}-\frac{\mu_2}{\langle\mu_2,\psi\rangle}\right\|_{\mathscr{M}(V)}$$

on the positive cone $\mathscr{M}_+(V)$, for some suitable positive functions ψ and V. In [P16] we proposed sufficient generalized Doeblin's conditions for time-inhomogeneous semigroups to be contractions with respect to this metric. Unfortunately these conditions are to restrictive to be satisfied by the semigroup generated by Equation (5.26). We shall follow Harris's approach to relax these conditions by using Lyapunov functions, similarly as in [P19], in order to derive general conditions on time-inhomogeneous semigroups to be contractions for the above weighted total variation projective distance.

Chapter 6

Subdiffusion

I started studying subdiffusion during my post-doc with Hugues BERRY at Inria Lyon in 2011-2012, with the aim to better understand and model the motion of molecules in living cells. We have continued since then, with the help of Emeric BOUIN, Vincent CALVEZ, Thomas LEPOUTRE and Álvaro MATEOS GONZÁLEZ. Section 6.2 presents a yet unpublished result, and Section 6.3 the main result of [P13].

6.1 The continuous time random walk model

Continuous time random walks (CTRW) were introduced by Montroll and Weiss as a generalisation of random walks [169], where the residence time between jumps is a random variable. They are widely used to model anomalous diffusive behaviour when the mean squared displacement does not grow linearly with time, unlike Brownian motion, see [161]. Anomalous diffusion is observed in the intra-cellular motion of molecules which usually present a sub-diffusive behaviour (namely a sub-linear growth of the mean squared displacement) due to molecular crowding and trapping, see the review article [134].

CTRW are characterized by two probability distributions: one for the waiting times between two consecutive jumps, and one for the direction and length of the jumps. In particular, the residence time between jumps does not necessarily follow an exponential law. This flexibility allows modelling sub-diffusive motion by considering that the longer a particle is trapped at some position, the less likely it jumps. In the context of cell biology, such a phenomenon is rather natural due to chemical bonding of molecules in the cell. Sub-diffusion arises in CTRW when the mean residence time is infinite, namely when

$$\int_0^\infty t\,\Phi(t)\mathrm{d}t = \infty$$

where Φ is the probability distribution of waiting times. CTRW are Markovian processes only when Φ is an exponential law, and thus not in the sub-diffusive cases. A classical trick for recovering the Markov property is to increase the dimension of the state space by adding a new independent variable. We associate to the random walker an "age" $a \geq 0$ which represents the time elapsed since its previous jump. For the sake of simplicity, we consider CTRW in one dimension of space. If we denote by $u(t,x,a)$ the probability distribution for a particle to be at time $t \geq 0$ at position $x \in \mathbb{R}$ since a time $a \geq 0$, then its evolution is prescribed by the following jump-renewal equation, initially proposed by [204],

$$\begin{cases} \dfrac{\partial}{\partial t}u(t,x,a) + \dfrac{\partial}{\partial a}u(t,x,a) + B(a)u(t,x,a) = 0, \\ u(t,x,0) = \displaystyle\int_0^\infty B(a)\int_{\mathbb{R}} J(x-y)u(t,y,a)\,\mathrm{d}y\,\mathrm{d}a, \end{cases} \tag{6.1}$$

where J is the probability distribution of jumps and B is the escape rate, so that $\Phi(t)$ is given by

$$\Phi(t) = B(t)\mathrm{e}^{\int_0^t B(a)\mathrm{d}a}.$$

The function Φ is usually supposed to behave as $t \to +\infty$ like

$$\Phi(t) \sim \Phi_\infty t^{-1-\alpha}, \quad 0 < \alpha < 1, \tag{6.2}$$

which leads, when the variance of J is finite, to a mean squared displacement that behaves as t^α for large times [161]. We will therefore consider escape rates B such that (6.2) is satisfied and, to simplify, that J is a Gaussian distribution with zero mean and variance σ^2.

6.2 The subdiffusion limit

In order to highlight the α-power long time behaviour of the mean squared displacement when Φ verifies (6.2), we accelerate time and rescale space in an accurate manner by considering, for a small parameter $\varepsilon > 0$,

$$u_\varepsilon(t,x,a) = \frac{1}{\varepsilon}u\Big(\frac{t}{\varepsilon^{2/\alpha}}, \frac{x}{\varepsilon}, a\Big).$$

By using Laplace and Fourier transform, it is shown formally in [159, 210] that the limit $p(t,x)$ of the marginal $p_\varepsilon(t,x) = \int_0^\infty u_\varepsilon(t,x,a)\mathrm{d}a$ when $\varepsilon \to 0$ satisfies the time-fractional diffusion equation

$$^C\!D_t^\alpha p(t,x) = \frac{\sigma^2}{2\tau^\alpha}\Delta_x p(t,x) \tag{6.3}$$

where $^C\!D_t^\alpha$ is the Caputo fractional derivative of order α defined by

$$^C\!D_t^\alpha f(t) = \frac{1}{\Gamma(1-\alpha)}\int_0^t \frac{f'(s)}{(t-s)^\alpha}\mathrm{d}s$$

and τ is a characteristic time given by $\tau^\alpha = \Phi_\infty \int_0^\infty \frac{1-\mathrm{e}^{-s}}{s^{1+\alpha}}\mathrm{d}s$. Classical fractional calculus allows us to deduce from (6.3) that the mean squared displacement grows as t^α through the formula

$$\int_{\mathbb{R}} x^2 p(t,x)\,\mathrm{d}x = \int_{\mathbb{R}} x^2 p(0,x)\,\mathrm{d}x + \frac{\sigma^2}{\Gamma(1+\alpha)\tau^\alpha}t^\alpha.$$

Our aim is to give a rigorous convergence result of p_ε to a solution of (6.3).

In the set of functions Φ that verify (6.2), a special place is occupied by the function

$$\Phi(t) = -\frac{\mathrm{d}}{\mathrm{d}t}E_\alpha(-t^\alpha)$$

where E_α is the Mittag-Leffler function with parameter α, see [117, 118]. Indeed it is a generalization of the exponential law for the Caputo derivative, in the sense that the function $\Psi(t) = \int_t^\infty \Phi(s)\mathrm{d}s = E_\alpha(-t^\alpha)$ verifies

$$^C\!D_t^\alpha \Psi(t) = -\Psi(t).$$

With Hugues Berry and Thomas Lepoutre, we proved a convergence result to an integrated version of Equation (6.3) in the Mittag-Leffler case, namely starting from u solution to (6.1) with escape rate

$$B(a) = -\frac{\mathrm{d}}{\mathrm{d}a}\log E_\alpha(-a^\alpha). \tag{6.4}$$

Theorem 6.1. *Assume that B is given by (6.4). Then under suitable conditions on the initial distribution $u_\varepsilon(0,x,a)$, when ε goes to 0, after extraction, the limit p of p_ε in $C([0,T],\mathscr{M}(\mathbb{R}))$ where $\mathscr{M}(\mathbb{R})$ is endowed with the weak-* topology satisfies: for all $\varphi \in C_c^2(\mathbb{R})$ and all $t \in [0,T]$*

$$\int_{\mathbb{R}} \varphi(x)p(t,x)\,\mathrm{d}x = \int_{\mathbb{R}} \varphi(x)p(0,x)\,\mathrm{d}x + \frac{\sigma^2}{2\tau^\alpha\Gamma(\alpha)}\int_0^t \frac{1}{(t-s)^{1-\alpha}}\int_{\mathbb{R}} \varphi''(x)p(s,x)\,\mathrm{d}x\mathrm{d}s.$$

6.3 A Hamilton-Jacobi limit

In [P13] we consider the hyperbolic regime instead of the subdiffusive regime of Section 6.2, and we perform a so-called Hopf-Cole transformation:

$$u_\varepsilon(t,x,a) = u\Big(\frac{t}{\varepsilon},\frac{x}{\varepsilon},a\Big) = \exp\Big(-\frac{\phi_\varepsilon(t,x,a)}{\varepsilon}\Big).$$

This enables us to accurately measure the behaviour of small, exponential tails of the probability density function u, reminiscent of large deviation principle theory. This approach was used in [30] for analysing a linear kinetic model.

We assume that the escape rate and the associated waiting time distribution are given by

$$B(a) = \frac{\alpha}{1+a}, \qquad \Phi(a) = \frac{\alpha}{(1+a)^{1+\alpha}}.$$

Contrary to [30], the local Maxwellian of our problem, *i.e.* the stationary solution of the first equation in (6.1), given by

$$\Psi(a) = \mathrm{e}^{-\int_0^a B(a')\mathrm{d}a'} = \frac{1}{(1+a)^\alpha},$$

is not integrable. To bypass this issue, we consider the boundary condition function

$$\psi_\varepsilon(t,x) = \phi_\varepsilon(t,x,0)$$

and we prove that its limit as $\varepsilon \to 0$ satisfies a Hamilton-Jacobi equation. Still, the non-integrability of the stationary distribution Ψ yields the main difficulties in the proof.

Theorem 6.2. *Under suitable hypotheses on the initial condition $\phi_\varepsilon(0,x,a)$, the family $(\psi_\varepsilon)_{\varepsilon>0}$ converges locally uniformly on $[0,+\infty)\times\mathbb{R}$ to the unique viscosity solution ψ of the limiting Hamilton-Jacobi equation*

$$1 = \int_0^\infty \Phi(a)\mathrm{e}^{a\partial_t\psi(t,x)}\mathrm{d}a\int_{\mathbb{R}} J(z)\mathrm{e}^{z\partial_x\psi(t,x)}\mathrm{d}z. \tag{6.5}$$

Observe that Equation (6.5) is equivalent to

$$\frac{\partial}{\partial t}\psi(t,x) + H(D_x\psi(t,x)) = 0 \tag{6.6}$$

with H given by

$$H(p) = \hat{\Phi}^{-1}\left(\frac{1}{\int_{\mathbb{R}} J(z)\mathrm{e}^{zp}\mathrm{d}z}\right)$$

where $\hat{\Phi}^{-1}$ is the inverse function of the Laplace transform of Φ. We also prove in [P13] that the Hamiltonian H is a smooth convex function, not strictly uniformly convex, which exhibits quadratic growth at infinity, and that when $p \to 0$

$$H(p) \sim \Big(\frac{\sigma^2}{2\Gamma(1-\alpha)}\Big)^{1/\alpha}|p|^{2/\alpha}. \tag{6.7}$$

6.4 Conclusion and some perspectives

We derived two different limiting equations of the jump-renewal equation (6.1). The subdiffusive limit (6.3) is linear but non-local in time, which is the trace of the non-Markovian property of the underlying CTRW. On the contrary the Hamilton-Jacobi limit (6.6) is nonlinear but local in time. The latter approach seems better-suited for analysing front propagation when subdiffusion is coupled to nonlinear reaction terms, similarly as in [102] where speeds of propagation are formally computed through Hopf-Cole transformation. The Hamilton-Jacobi method was successfully used for studying front propagation in reaction-diffusion equations [17, 18, 20, 32, 98, 109, 110, 194], as well as for non-local jump models [31, 158, 180]. With Emeric Bouin, we have started investigating the case of reaction-subdiffusion equations.

Another Hamilton-Jacobi equation can be derived from Equation (6.1) by performing subdiffusive and hyperbolic scaling simultaneously. Defining

$$\phi_\varepsilon(t,x,a) = -\varepsilon \log u\Big(\frac{t}{\varepsilon^{2/\alpha+1}}, \frac{x}{\varepsilon^2}, a\Big),$$

the limit ψ of $\psi_\varepsilon(t,x) = \phi_\varepsilon(t,x,0)$ when $\varepsilon \to 0$ formally satisfies

$$\frac{\partial}{\partial t}\psi(t,x) + \Big(\frac{\sigma^2}{2\tau^\alpha}\Big)^{1/\alpha} \big|D_x \psi(t,x)\big|^{2/\alpha} = 0. \tag{6.8}$$

We essentially recover Equation (6.6) where the Hamiltonian H is replaced by its equivalent at the origin (6.7). Equation (6.8) is a well known Hamilton-Jacobi equation [136], which is the classical eikonal equation in the diffusive case $\alpha = 1$ [97]. Proving rigorously the convergence to Equation (6.8) would require handling two scalings at the same time, which is a substantial additional difficulty.

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