Université de Paris VI Pierre et Marie Curie

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Analyse et modélisation de phénomènes de croissance et mouvement issus de la biologie.

THÈSE

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Mis en page avec la classe thloria.

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Introduction

Introduction et présentation des travaux

Nous présentons dans ce document les résultats obtenus au cours de cette de thèse sous la direction de Jean Clairambault, Stéphane Gaubert et Benoît Perthame. Le travail suivant se décompose selon deux axes mathématiques autour des équations aux dérivées partielles d'évolution :

- l'étude de modèles de dynamique de population structurées concernant la division cellulaire et la polymérisation (prion) dont fait l'objet de la première partie du manuscrit.
- l'étude de modèles de mouvements d'espèces où chacune se déplace plus en présence de l'autre (comportement représenté par un terme de diffusion croisée) à laquelle est consacrée la seconde partie.

Il est motivé par trois thèmes issus des sciences du vivant :

- l'étude du cycle de division cellulaire entraîné de manière périodique par l'horloge circadienne et la chronothérapie,
- la justification théorique d'un modèle continu pour la dynamique du prion, basée sur un modèle discret,
- l'apparition ou non de ségrégation entre deux espèces qui ont tendance à quitter les zones où l'autre est nombreuse mais restent confinées dans un espace clos où elles doivent se répartir.

L'importance de la périodicité : incidence et traitement du cancer

Dans le cadre que nous considérons, la période typique est la journée afin d'examiner les effets des rythmes circadiens. Par circadien, on entend les rythmes ayant une période de 24h. De tels rythmes s'observent jusque dans la brique de base des êtres vivants : la cellule. Le cycle cellulaire semble ainsi faire partie des mécanismes présentant une périodicité autour de 24h (il a été montré que des déterminants du cycle cellulaire ont de tels rythmes [16]). L'origine de notre intérêt pour des modèles soumis à un environnement périodique en temps est la cancérologie. La compréhension de tels phénomènes est en effet un enjeu de taille en oncologie. D'une part la perturbation des rythmes circadiens est reconnue comme un facteur aggravant de certains cancers (ceci est vérifiée de façon statistique sur les personnes travaillant à horaires décalés, comme les veilleurs de nuits, les infirmières, qui se révèlent des populations à risque plus élevé ([33, 53]) et de façon expérimentale chez des animaux de laboratoire [46, 45]). D'autre part, on peut tirer avantage des rythmes différents entre les cellules saines et tumorales pour optimiser les traitements du cancer. On parle de chronothérapie. L'idée consiste pour simplifier à donner le bon médicament à la bonne heure. Un des avantages recherché est de minimiser les dommages sur les cellules saines, en administrant le médicament au moment où elle affecte le moins ces dernières. On peut ainsi espérer à effets constants sur les cellules tumorales, faire le moins de dégâts possibles sur le patient. Rappelons en effet que les traitements anticancéreux sont des traitements lourds pour le patient.

En cancérologie, il existe également des modèles proposant non pas de profiter de la plus grande sensibilité des cellules saines aux rythmes circadiens mais des périodes intrinsèques différentes entre cellules saines et tumorales (on parle de résonance [37, 1, 109]). On trouve aussi de la périodicité à d'autres échelles de temps(l'année et les saisons pour les modèles en agriculture, le mois pour les rythmes hormonaux ...). De façon générale, les oscillations intervenant dans le domaine de la biologie sont très étudiées (voir par exemple [49, 47] pour un panorama).

Croissance et valeurs propres.

Dans les deux premiers chapitres de cette thèse nous nous intéressons à des modèles linéaires de type renouvellement qui ont un principe de positivité. En bons modèles linéaires, ils ont tendance à croître (ou décroître, même si c'est la croissance qui nous intéresse davantage) de façon exponentielle. Intervient alors un paramètre λ qui caractérise cette croissance (en $e^{\lambda t}$ donc). La question que nous traitons est celle de l'influence de la périodicité sur ce paramètre (propriétés qualitatives, comparaison avec un milieu moyenné).

La réplication du prion : du discret au continu.

Le prion a fait son entrée dans le vocabulaire commun lors de la crise de l'encéphalopathie spongiforme bovine (plus connue sous le nom de « maladie de la vache folle »). Les maladies à prion sont caractérisées par l'accumulation d'une protéine (PrP ou **Pr**ion **P**rotein) sous une forme anormalement repliée (PrPres pour **rés**istant ou PrPsc pour **sc**rapie, la tremblante du mouton). Elles ne font notamment pas intervenir l'ADN. Les liens entre l'étude du prion et les mathématiques sont assez étroits, presque originels, puisque dès 1967, le mathématicien J.S. Griffith propose dans [51] l'hypothèse (admise dans cette thèse) d'un mécanisme purement protéique (Prion=**Pr**oteinaceous **i**nfectious **o**nly), hypothèse confortée par les travaux expérimentaux de Prusiner [96] en 1982. Dans le mécanisme que nous étudions, l'agent infectieux est un oligomère capable de polymériser les monomères (pour simplifier, la présence de polymères de protéines mal repliées PrP^{res} aurait tendance à « contaminer » les protéines normales PrP, qui viendraient se rattacher aux polymères de protéines mal repliées PrP^{res} présents). Notons que si cette hypothèse convainc encore aujourd'hui, elle n'en demeure pas moins une hypothèse et les difficultés expérimentales empêchent l'étude *in vivo* du mécanisme de réplication du prion. C'est d'ailleurs d'une certaine façon cette difficulté, ainsi que la longueur des temps d'incubation (dans le cas de l'épidémie de Kuru en Papouasie Nouvelle Guinée, on a observé jusqu'à quarante années d'incubation) qui rendent encore plus nécessaire une approche théorique. Le travail effectué dans le chapitre 3 vise à justifier l'introduction des EDP dans la modélisation de la réplication du prion comme approximation d'un modèle la décrivant par un système infini d'équations différentielles.

Ségrégation et mouvement.

Dans la seconde partie de cette thèse, nous nous intéressons à des équations modélisant le comportement d'espèces qui se déplacent de façon aléatoire (modélisé donc en EDP par de la diffusion) et ont tendance à augmenter leur mouvement en présence de l'autre espèce (diffusion croisée). La question que nous nous posons peut s'écrire ainsi : cet effet conduit-il à la ségrégation des espèces ou à un mélange homogène ? Dans le cas d'un comportement ségrégatif, il se crée des zones où l'une ou l'autre domine. C'est un cas de « pattern formation » à la Turing.

1 Dynamiques de populations

1.1 Les populations structurées

La dynamique de population la plus élémentaire consiste à estimer une population totale P^n et à voir par quel facteur a_n, elle se multiplie à chaque instant (la population évolue donc en $P^{n+1} = a_n P^n$). L'une des idées de base de la dynamique de populations structurées est de dire que cela est insuffisant (on peut imaginer qu'à population totale P^n fixée, une population ne contenant que des nouveau-nés ne se reproduit pas de la même façon qu'une population d'adultes). Pour remédier à ce problème, on introduit une variable qui serait la caractéristique essentielle d'un individu. Citons quelques exemples :

- le plus classique est l'âge ou la maturité d'un individu : si on considère les naissances et les morts, il semble naturel de considérer que les jeunes enfants se reproduisent moins que les adultes et que les gens ont plus de chances mourir s'ils ont 100 ans que s'ils en on 40. On utilise également beaucoup l'âge en épidémiologie, il mesure alors l'avancement de l'infection. Un individu qui vient d'être infecté peut par exemple être contagieux sans que la maladie augmente ses chances de mourir (incubation). L'équation aux dérivées partielles typique qui intervient est celle de McKendrick (c'est même historiquement la première EDP intervenant en dynamiques de populations) :

$$\begin{cases} \partial_t n(t,x) + \partial_x n(t,x) + d(x) n(t,x) = 0, \\ n(t,0) = \int_0^\infty B(x) n(t,x) dx. \end{cases}$$

  Cette équation modélise l'évolution d'une population qui vieillit (terme de transport $\partial_t + \partial_x$) meurent avec un taux $d(x)$ qui dépend de leur âge et donnent naissance à de nouveaux individus (d'âge 0) avec un taux de naissance $B(x)$ qui dépend de leur âge. C'est à des équations d'évolution de ce type aux coefficients desquelles nous ajoutons une dépendance en temps (i.e., $d(x) \to d(t,x), B(x) \to B(t,x)$ que les deux premiers chapitres de la thèse sont consacrés. Elles sont appelées équations de renouvellement. Elles sont par ailleurs également utilisées en cancérologie dans la modélisation des métastases ([13, 36, 57].
- une autre variable très utilisée en modélisation de la biologie est la taille ou la masse. On peut par exemple représenter la croissance et la division cellulaire symétrique de cellules croissant à vitesse $v(x)$, x étant la taille par l'équation

$$\partial_t n(t,x) + \partial_x [v(x) n(t,x)] + B(x) n(t,x) = 4B(2x) n(t,2x), \tag{1}$$

  complétée si nécessaire par une condition au bord.

On appelle dynamique de populations structurées les EDP de ce type. On peut trouver des approches semi-groupe pour leur étude dans les ouvrages de références [80, 108, 55].

1.2 Comparaison de valeurs propres

Les deux premiers chapitres de cette thèse sont consacrés à des équations ou des systèmes d'équations représentant le cycle de la division cellulaire . Ces équations peuvent se résumer de la façon suivante. On considère un cycle cellulaire sans phase de repos (quiescence), où les individus sont caractérisés par la phase du cycle cellulaire i dans laquelle ils se trouvent et l'âge x qu'ils ont dans cette phase (autrement dit le temps écoulé depuis leur entrée dans la phase). On est donc amené à regarder des densités de populations $n_i(t,x)$, soumises à la dynamique suivante (on considère qu'il y a I phases et on utilise la convention $I+1=1$),

$$\begin{cases} \partial_t n_i(t,x) + \partial_x n_i(t,x) + \big(d_i(t,x) + K_{i\to i+1}(t,x)\big) n_i(t,x) = 0, \quad 1 \le i \le I \\ n_{i+1}(t,0) = \int_0^\infty K_{i\to i+1}(t,x) n_i(t,x) dx, \quad i < I, \\ n_1(t,0) = 2\int_0^\infty K_{I\to 1}(t,x) n_I(t,x) dx. \end{cases} \tag{2}$$

Le modèle peut être décrit de la façon suivante :

- les cellules vieillissent (terme de transport),
- meurent avec un taux $d_i(t,x)$ qui dépend de la phase i, de l'âge x et du temps t,
- passent d'une phase i à la suivante $i+1$ avec un taux $K_{i\to i+1}(t,x)$, où elles entrent à l'âge 0 (le compartiment proliférant du cycle cellulaire est généralement représenté comme divisé en quatre phases),
- la dernière transition correspondant à la mitose (division proprement dite), les cellules quittant la dernière phase donnent deux cellules d'âge 0 dans la première (et non une comme dans les autres cas).

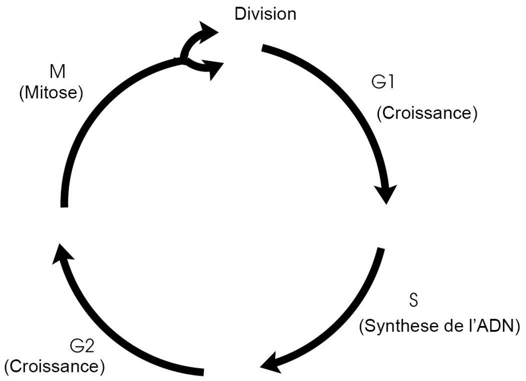

FIG. 1 – Représentation (très) simplifiée du cycle cellulaire modélisée par (2).

Deux remarques sur ce type de modèles s'imposent. Ces modèles sont des cas particuliers de systèmes d'équation de renouvellement,

$$\begin{cases} \partial_t n_i(t,x) + \partial_x n_i(t,x) + d_i(t,x) n_i(t,x) = 0, \quad 1 \le i \le I \\ n_i(t,0) = \sum_j \int_0^\infty B_{ij}(t,x) n_j(t,x) dx. \end{cases} \tag{3}$$

auxquelles nous nous intéressons dans l'annexe B dans toute leur généralité. Un cas particulier de ces équations est donné par l'équation de division cellulaire avec une structure en âge,

$$\begin{cases} \partial_t n(t,x) + \partial_x n(t,x) + K(t,x) n(t,x) = 0, \\ n(t,0) = 2 \int_0^\infty K(t,x) n(t,x) dx, \end{cases} \tag{4}$$

à laquelle est entièrement dédié le chapitre 2 ainsi qu'une bonne partie du chapitre 1. Dans toutes ces équations, nous gardons le même fil directeur : la dynamique asymptotique de tels systèmes est décrite par la valeur propre de Floquet que nous noterons toujours λ_F. Cette valeur propre est caractérisée par l'existence de vecteurs propres positifs et périodiques associés N, ϕ ou $(N_i, \phi_i)_{1\le i\le I}$) (nous les donnons pour le système (2)). Le vecteur $(N_i)_{1\le i\le I}$

étant le vecteur propre direct,

$$\begin{cases} \partial_t N_i(t,x) + \partial_x N_i(t,x) + \big(\lambda_F + d_i(t,x) + K_{i\to i+1}(t,x)\big)N_i(t,x) = 0, \\ N_i(t,0) = \int_0^\infty K_{i-1\to i}(t,x)N_{i-1}(t,x)dx, \quad i \geq 2, \\ N_1(t,0) = 2\int_0^\infty K_{I\to 1}(t,x)N_I(t,x)dx, \\ N_i \geq 0 \quad \text{voire } N_i > 0 \ \text{ dans la plupart des cas,} \\ N_i \quad T\text{-périodique en temps,} \quad i.e., \ N_i(t+T,.) = N_i(t,.), \\ \sum_{i=1}^I \int_0^T \int_0^\infty N_i(t,x)dx = 1, \end{cases} \tag{5}$$

le vecteur $(\phi_i)_{1\leq i\leq I}$ étant le vecteur propre adjoint,

$$\begin{cases} -\partial_t\phi_i(t,x) - \partial_x\phi_i(t,x) + \big(\lambda_F + d_i(t,x) + K_{i\to i+1}(t,x)\big)\phi_i(t,x) = K_{i\to i+1}(t,x)\phi_{i+1}(t,0), \ i < I \\ -\partial_t\phi_I(t,x) - \partial_x\phi_I(t,x) + \big(\lambda_F + d_I(t,x) + K_{I\to 1}(t,x)\big)\phi_I(t,x) = 2K_{I\to 1}(t,x)\phi_1(t,0), \\ \phi_i > 0, \quad T\text{-périodique,} \quad \sum_{i=1}^I \int_0^\infty N_i(t,x)\phi_i(t,x)dx = 1. \end{cases} \tag{6}$$

Ces vecteurs propres gouvernent la dynamique asymptotique du système qui croît en $e^{\lambda_F t}$. On a en effet (voir [82]), d'une part

$$\sum_{i=1}^I \int_0^\infty n_i(t,x)\phi_i(t,x)dx = e^{\lambda_F t}\sum_{i=1}^I \int_0^\infty n_i(0,x)\phi_i(0,x)dx,$$

(on rappelle que les ϕ_i sont positifs stricts et périodiques). On a également l'attraction vers les orbites périodiques

$$\sum_{i=1}^I \int_0^\infty |n_i(t,x)e^{-\lambda_F t} - \rho N_i(t,x)|\phi_i(t,x)dx \to 0,$$

où $\rho = \sum_i \int_0^\infty n_i^0(x)\phi_i(0,x)dx$. La question qui guide les deux premiers chapitres est la suivante : qu'est ce qui change et qu'est ce qui ne change pas lorsqu'on a des coefficients périodiques en temps par rapport au cas où les coefficients ne dépendent pas du temps ?

Avant de s'intéresser directement à la chronothérapie, un des buts de tels modèles était de questionner les résultats obtenus par Filipski et al. dans [45]. Ces résultats tendaient à montrer que les cellules cancéreuses se développaient plus vite lorsqu'elles échappaient au contrôle circadien. Plus précisément, en prenant des souris auxquelles on greffe une tumeur, il a été mis en évidence que plus les rythmes circadiens sont perturbés, plus vite la tumeur se développe. Un des choix de la modélisation était de représenter la perturbation du rythme circadien par la moyennisation des coefficients, i.e., remplacer chaque coefficient $(d_i, K_{i\to i+1})$ par sa moyenne en temps sur une période. Au niveau des valeurs propres, il s'agissait donc de comparer la valeur propre λ_F associée aux coefficients « normaux » (dépendant du temps) à la valeur λ_P correspondant au système moyenné (P pour Perron quoiqu'elle soit notée λ_s pour stationnaire dans l'article dont nous parlons). Le résultat attendu était alors $\lambda_F \leq \lambda_P$, une croissance plus importante pour les cellules non soumises à l'influence circadienne comme dans l'expérience de Filipski. Cependant, le résultat obtenu fut le suivant :

Théorème 1 (Clairambault, Michel et Perthame 2005) *Si les coefficients de transition et division $K_{i\to i+1}$ ne dépendent pas du temps alors*

$$\lambda_F \geq \lambda_P.$$

En d'autres termes, si les rythmes circadiens n'agissent que sur les taux de morts, la population perturbée devrait grandir moins vite ! Dans la première partie, nous confirmons de façon théorique, à l'aide d'un contre-exemple que cette situation ne persiste pas dans le cas de taux de transition dépendant du temps. Le contre-exemple est une simple équation de division sans taux de mort,

$$\begin{cases} \partial_t n(t,x) + \partial_x n(t,x) + \psi(t)\mathbb{1}_{[a,\infty[}(x) n(t,x) = 0, \\ n(t,0) = 2\psi(t)\int_a^\infty n(t,x)dx. \end{cases} \tag{7}$$

Ayant fixé une fonction positive ψ T-périodique non constante de moyenne $\langle\psi\rangle$ et en notant $\lambda_F(a,\psi)$ l'exposant de croissance associé au système (7), on compare au système moyenné arithmétiquement (on prend la moyenne arithmétique partout) dont l'exposant $\lambda_P(a)$ n'est autre que $\lambda_F(a,\langle\psi\rangle)$, et on obtient le résultat suivant :

Théorème 2 (Clairambault, Gaubert et L.) *Étant donné une fonction positive ψ T-périodique non constante, pour a dans un voisinage de T, on a*

$$\begin{aligned} \lambda_F(a,\psi) &= \lambda_P(a), && \textit{pour } a = T, \\ \lambda_F(a,\psi) &> \lambda_P(a) && \textit{si } a < T, \\ \lambda_F(a,\psi) &< \lambda_P(a) && \textit{si } a > T. \end{aligned}$$

Ceci nous donne un exemple simple montrant que lorsque l'on introduit de la périodicité dans les coefficients de transition (ce qui correspond bien au cas du cycle cellulaire [16]), on peut trouver toutes les configurations.

Le résultat énoncé dans le théorème 1 a été expliqué dans [25] par des propriétés de convexité. Si on considère le système

$$\begin{cases} \partial_t n_i(t,x) + \partial_x n_i(t,x) + \big(\langle d_i\rangle(x) + \langle K_{i\to i+1}\rangle(x)\big) n_i(t,x) = 0, \quad 1 \le i \le I \\ n_i(t,0) = \int_0^\infty \langle K_{i\to i+1}\rangle_g(x)(t,x) n_i(t,x)dx, \\ n_1(t,0) = \int_0^\infty \langle K_{I\to 1}\rangle_g n_I(t,x)dx, \end{cases} \tag{8}$$

où

$$\langle f\rangle(x) = \frac{1}{T}\int_0^T f(t,x)dx,$$

désigne la moyenne arithmétique en temps et

$$\langle f\rangle_g(x) = \exp\left(\frac{1}{T}\int_0^T \log f(t,x)dx\right),$$

désigne la moyenne géométrique, on a

Théorème 3 (Clairambault, Gaubert et Perthame 2007) *Si l'on désigne λ_F l'exposant de croissance du système original (2) et λ_g (pour géométrique) celui du système (8), alors on a l'inégalité*

$$\lambda_F \ge \lambda_g.$$

Nous généralisons cette inégalité à tous les systèmes d'équations de renouvellement (3) via le résultat suivant

Théorème 4 (Gaubert et L) *Si l'on définit λ_F comme l'exposant de croissance associé au système (3), alors, sur son domaine de définition, l'application*

$$(d_i, \log B_{ij})_{1\le i,j\le I} \quad \mapsto \quad \lambda_F,$$

est convexe.

Pour l'écrire autrement, si on considère deux jeux de coefficients (ayant la même période) $d_i^{1,2}, B_{ij}^{1,2}$, et les valeurs propres associées $\lambda_F^{1,2}$ et que l'on regarde le système (3) avec des pour coefficients $d_i^\theta = \theta d_i^1 + (1-\theta)d_i^2, B_{ij}^\theta = (B_{ij}^1)^\theta (B_{ij}^2)^{1-\theta}$ (avec $\theta \in [0,1]$, on a, en notant λ_F^θ la valeur propre associée

$$\lambda_F^\theta \leq \theta\lambda_F^1 + (1-\theta)\lambda_F^2. \tag{9}$$

Il est à noter que ce résultat généralise un théorème de Kingman sur la valeur propre dominante des matrices ayant des coefficients hors-diagonaux positifs [62] qui affirme que cette dernière est convexe par rapport aux coefficients diagonaux et convexe par rapport aux logarihtmes des autres. Notons que cette inégalité peut s'interpréter comme un argument positif en faveur de la chronothérapie. Considérons l'effet un traitement n'agissant que de façon cytotoxique (i.e., dont l'effet consiste à tuer des cellules) sur une population de cellules saines. Pour ce faire, on considère que les taux de transition et de division ne sont pas affectés par le traitement, et que l'effet du traitement peut se modéliser par un taux de mort additionnel dans chaque phase (on ajoute ainsi un taux de mort périodique lui aussi $drug_i(t,x)$ au taux de mort naturel). Administrer le traitement θ instants plus tôt revient à regarder l'effet sur la valeur propre de Floquet des taux de mort $drug_i(t-\theta,x)$, on note alors $\lambda_F(drug,\theta)$ la valeur correspondante. On compare cela à un traitement homogène au cours du temps, ce qui correspondrait à remplacer $drug_i(t,x)$ par

$$\langle drug_i \rangle(x) = \frac{1}{T}\int_0^T drug_i(t-\theta,x)d\theta.$$

et on note $\lambda_F(\langle drug \rangle)$ la valeur propre associée. Nous nous intéressons à l'effet sur les cellules saines. La toxicité d'un traitement peut alors se voir sur λ_F. Plus l'exposant de croissance est grand, plus vite la population de cellules saines croît. En conséquence, l'effet d'un traitement sur λ_F est le suivant : plus un traitement est toxique, moins λ_F est élévé. Lorsqu'on souhaite comparer l'effet d'un traitement moyen aux effets des différents traitements périodiques possibles, la version continue l'inégalité de convexité (9) nous donne

$$\lambda_F(\langle drug \rangle) \leq \frac{1}{T}\int_0^T \lambda_F(drug,\theta)d\theta. \tag{10}$$

Le traitement moyen est donc plus toxique que la moyenne des traitements. En conséquence de l'inégalité (10), on est toujours dans une des deux (idéalement les deux) configurations suivantes :

- soit on a $\lambda_F(drug,\theta) \geq \lambda_F(\langle drug \rangle)$ pour la majorité des θ, ce qui signifie que la majorité des traitements disponibles est moins toxique qu'un traitement homogène (autrement dit la probabilité qu'un traitement périodique soit plus efficace que le traitement moyen est plus grande que 1/2),
- soit on a un ensemble de valeurs θ où l'avantage par rapport au traitement homogène est substantiel.

Dans les deux cas, la chronothérapie semble être une bonne approche d'un point de vue de la toxicité minimale pour les cellules saines. On a là un argument théorique en faveur de ce type d'approche thérapeutique.

1.3 Monotonie et asymptotique

Dans le chapitre 2, nous nous focalisons sur l'équation de division pour comprendre les phénomènes que peut faire apparaître l'introduction d'une périodicité temporelle. La plus surprenante est sans doute la suivante :

Théorème 5 (Gaubert et L.) *Il existe des configurations où l'on a*

$$K^1(t,x) \geq K^2(t,x),$$

et en même temps

$$\lambda_F^1 < \lambda_F^2.$$

On peut ainsi trouver des cas où la population qui a le taux de division le plus bas est celle qui prolifère le plus ! De telles situations ne peuvent arriver sans la dépendance en temps. On trouve cependant le critère suivant de type FIFO (First In First Out) pour éviter ce genre de situation,

Théorème 6 (Gaubert et L.) *Si pour tout t*

$$v \mapsto \int_v^t K^1(s, s-v)ds,$$

est une fonction croissante, alors pour tout $K^2 \geq 0$, si $K^1 - K^2$ a un signe, $\lambda^1 - \lambda^2$ a le même.

L'interprétation en termes de probabilités serait la suivante : si deux cellules naissent aux instants $t_1 > t_2$, pour tout temps t, celle qui est né le plus tôt est toujours celle qui a le plus de chances de se diviser avant le temps t.

L'intérêt pour la monotonie est venu d'une recherche de liens avec des systèmes discrets lorsque le taux de division devient très grand.

Théorème 7 (Gaubert et L.) *On considère une équation de division avec un taux de division de la forme*

$$K(t,x) = K\psi(t)\mathbb{1}_{[a,\infty[}, \qquad a > 0, \psi \text{ 1-périodique},$$

- *si ψ est minorée par un réel strictement positif, alors*

  $$\lambda_F \to \log 2/a, \quad \text{quand } K \to \infty,$$

- *si ψ est de la forme $\mathbb{1}_{(0,\tau)+\mathbb{Z}}$ alors la limite pour $K \to \infty$ est donnée par la formule*

  $$\lambda^\infty(a) = \frac{N_a}{\lceil N_a a \rceil}, \quad N_a a = \inf[\tau, 1] + \mathbb{N} \cap \mathbb{N}a,$$

  où $\lceil . \rceil$ désigne la partie entière supérieure.

Pour le deuxième point, on peut déterminer la limite en imaginant que le taux de division prend au final deux valeurs 0 et $+\infty$, et donc la probabilité de se diviser prend donc les valeurs 0 et 1. Si on part d'une cellule d'âge 0 au temps 0, en suivant sa trajectoire, elle se divise à l'instant a si $\psi(a) = 1$, puis à l'instant $2a$ si on a également $2a$ si $\psi(2a) = 1$ et ainsi jusqu'au premier instant $N_a a$ où la cellule est en âge de se diviser (elle s'est divisée à l'instant $(N_a - 1)a$ et a donc l'âge a) mais où la date ne lui permet pas ($\psi(N_a a) = 0$). La cellule devra alors attendre jusqu'au prochain temps entier $\lceil N_a a \rceil$ pour se diviser. Partant d'une cellule d'âge 0 au temps 0, on en obtient donc 2^{N_a} au temps $\lceil N_a a \rceil$. On a donc construit une trajectoire périodique de période $\lceil N_a a \rceil$. La formule pour λ_F s'obtient alors en supposant qu'on a là un vecteur propre (et donc $e^{\lambda_F \lceil N_a a \rceil} = 2^{N_a}$).

1.4 Méthodes utilisées

Mis à part pour la convexité, où les outils essentiels sont les sous vecteurs propres, la clé de toutes les démonstrations concernant les valeurs propres est une reformulation du modèle. Ainsi, dans le chapitre 1, le théorème se prouve en utilisant l'équation à retard vérifiée par le vecteur propre associé à (7). En intégrant l'équation vérifiée par le vecteur propre direct de l'équation (7) entre a et $+\infty$, on obtient l'équation à retard suivante :

$$\frac{dP}{dt} = -(\lambda_F - \psi(t))P(t) + 2\psi(t-a)e^{-\lambda_F a}P(t-a).$$

En dérivant cette équation par rapport à a, on obtient le théorème 2. Autre avantage de cette formulation, elle permet de construire des solution non triviales aux problème au valeurs propres (i.e., dépendant du temps et de l'âge) pour le cycle cellulaire.

Pour prouver l'asymptotique ou la monotonie dans le chapitre 2, l'outil essentiel est une reformulation trajectorielle (générationnelle) de l'équation de division qui permet de suivre l'heuristique dont dérive la formule du théorème 7 et aussi de comprendre ce qui génère les contre exemples. On prend une donnée initiale n^0 et on regarde le système infini d'EDP suivant :

$$\begin{cases} \partial_t n_i + \partial_x n_i + K(t,x)n_i = 0, \qquad i \geq 0, \\ n_{i+1}(t,0) = \displaystyle\int_0^\infty K(t,x)n_i(t,x)dx, \\ n_0(t=0,x) = n^0(x), \qquad n_i(t=0,x) = 0, \quad \text{for } i \geq 1. \end{cases} \tag{11}$$

Au lieu d'étudier un processus de division, on étudie un processus de passage de génération. Les individus de la génération i passent à la génération $i+1$ avec un taux $K(t,x)$. On regarde donc le coefficient K comme le coefficient de transition d'une génération à la suivante. Le lien avec l'équation de division est donné par la remarque suivante :

$$n = \sum_{i=0}^{\infty} 2^i n_i \quad \text{est la solution de l'équation de division (4) avec donnée initiale } n^0.$$

Au lieu de regarder la valeur propre ou la population totale, on va pouvoir étudier à quelle vitesse on passe à la génération i. Les contre-exemples peuvent être vus alors comme des cas où augmenter K accélère (c'est toujours le cas) le passage dans la génération 1, mais pénalise le passage de la génération 1 à 2 (on peut être pénalisé d'être entré trop tôt en génération 1 et se faire enfermer dans une mauvaise trajectoire).

1.5 Prion : des EDO aux EDP

Le chapitre 3 est consacré à la justification de l'utilisation d'EDP pour modéliser la réplication du prion. Nous nous plaçons dans l'hypothèse dite purement protéique introduite par le mathématicien Griffith dans [51] et confortée par les observations de Prusiner [96], c'est à dire qu'on considère que les prions sont des protéines mal repliées. Cette hypothèse suggère que la réplication du prion se fait de manière auto catalytique en changeant la forme saine de la protéine concernée *PrPc* (**Pr**otéine **P**rion **c**ellulaire) forme infectieuse *PrPsc* ou *PrPres* (*sc* pour scrapie, la tremblante du mouton ou *res* pour résistante). La représentation que nous considérons de la dynamique du prion est celle de la polymérisation nucléée. Dans cette approche, les particules infectieuse sont des polymères de *PrPsc* de différentes tailles. L'apparition de tels polymères s'opère par un phénomène de nucléation (très lent). C'est l'agrégation de *PrPsc* qui permet sa stabilisation. La transconformation de *PrPc* en *PrPsc* se fait ensuite par polymérisation. Les modèles suivants ne représentent que ce phénomène (et pas celui de nucléation, en particulier ces modèles ne permettent pas l'apparition spontanée d'un polymères infectieux dans une population saine). En termes de modélisation, cela correspond à considérer une population de monomères et polymères où les monomères sont le compartiment sain (*PrPc*) et les polymères le compartiment infectieux. Ceci est représenté par les équations suivantes introduites dans [79]

$$\begin{cases} \dfrac{\mathrm{d}v}{\mathrm{d}t} = \lambda - \gamma v - v \displaystyle\sum_{i=n_0}^{\infty} \tau_i u_i + 2 \sum_{j \geq n_0} \sum_{i < n_0} i k_{i,j} \beta_j u_j, \\ \dfrac{\mathrm{d}u_i}{\mathrm{d}t} = -\mu_i u_i - \beta_i u_i - v(\tau_i u_i - \tau_{i-1} u_{i-1}) + 2 \displaystyle\sum_{j>i} \beta_j k_{i,j} u_j, \quad \text{for } i \geq n_0, \end{cases} \tag{12}$$

Où v répresente la population de monomères, u_i la population de polymères (donc infectieux) de taille $i \geq n_0$ (on considère que les trop petits polymères ne sont pas stables). Les coefficients représentent les taux de fragmentation (β_i) polymérisation (τ_i), dégradation (γ, μ_i) et répartition des fragments (k_{ij}). Ce modèle a donc un pendant EDP introduit dans [50] qui s'écrit

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \lambda - \gamma V - V \int_{x_0}^{\infty} \tau(x) U(t,x)\,\mathrm{d}x + 2 \int_{x=x_0}^{\infty} \int_{y=0}^{x_0} y k(y,x) \beta(x) U(t,x)\,\mathrm{d}x\,\mathrm{d}y, \tag{13}$$

$$\frac{\partial U}{\partial t} = -\mu(x) U(t,x) - \beta(x) U(t,x) - V \frac{\partial}{\partial x}(\tau U) + 2 \int_{x}^{\infty} \beta(y) k(x,y) U(t,y)\,\mathrm{d}y. \tag{14}$$

Les coefficients gardent la même signification à ceci près qu'on regarde une densité de polymères pour un continuum de tailles possibles (on a $x \in]x_0, +\infty[$ au lieu de $i \in \{n_0, n_0+1 \ldots\}$). L'étude du système permet alors plus naturellement de regarder la distribution en taille des polymères via des problèmes aux valeurs propres [21, 20]. Le problème de Cauchy a été étudié notamment dans [65],[106],[102]. Nous nous sommes posés la question suivante : le système continu (13-14) peut-il se voir comme une approximation du système discret (12) ? Pour y répondre, nous avons adimensionné le système (12) en vue d'identifier les échelles caractéristiques intervenant dans le modèle. Mathématiquement, cela correspond à faire apparaître un petit paramètre ε correspondant au rapport entre la taille des monomères et celle typique des polymères (la taille moyenne par exemple). L'hypothèse de travail sous-jacente est donc que les polymères sont de grande taille. On définit une solution faible de (13-14) de la façon suivante

Définition 8 *On dit que le couple (U, V) est une solution de l'équation préservant les monomères partant des données initiales (U_0, V_0) si elle satisfait* (13)*, si U satisfait (14) sous forme faible : pour tout $\varphi \in \mathcal{C}_c^{\infty}((x_0, \infty))$, on a*

$$\begin{aligned} &\int_0^{\infty} U(t,\,\mathrm{d}x)\varphi(x) - \int_0^{\infty} U_0(\,\mathrm{d}x)\varphi(x) \\ &= -\int_0^t \int_0^{\infty} \mu(x) U(s,\,\mathrm{d}x)\varphi(x)\,\mathrm{d}s - \int_0^t \int_0^{\infty} \beta(x) U(s,\,\mathrm{d}x)\varphi(x)\,\mathrm{d}s \\ &\quad + \int_0^t V(s) \int_0^{\infty} \tau(x) U(s,\,\mathrm{d}x) \partial_x \varphi(x)\,\mathrm{d}s \\ &\quad +2 \int_0^t \int_{x_0}^{\infty} \beta(y) U(s,\,\mathrm{d}y) \int_{x_0}^{y} k(\,\mathrm{d}x, y)\varphi(x)\,\mathrm{d}s, \end{aligned} \tag{15}$$

et le bilan de masse des monomères

$$\begin{aligned} V(t) + \int_{x_0}^{\infty} x U(t,\,\mathrm{d}x) &= V_0 + \int_{x_0}^{\infty} x U_0(\,\mathrm{d}x) \\ &\quad +\lambda t - \int_0^t \gamma V(s)\,\mathrm{d}s - \int_0^t \int_{x_0}^{\infty} x \mu(x) U(s,\,\mathrm{d}x)\,\mathrm{d}s. \end{aligned} \tag{16}$$

On introduit donc un paramètre de taille ε et en notant $v^\varepsilon, u_i^\varepsilon$ les solutions du problème discret pour un paramètre ε fixé, dont les coefficients sont de la forme $O(Ki^m)$ (avec des exposants éventuellement distincts pour μ_i, β_i, τ_i). On a après une mise à l'échelle appropriée et sous des hypothèses de bornes uniformes en ε sur les moments de u^ε que l'on peut résumer ainsi :

$$\int_0^\infty (1 + x^{1+s}) u^\varepsilon(0, x) dx \leq C, \quad \text{C ne dépendant pas de } \varepsilon.$$

une compacité faible qui nous permet d'établir le résultat suivant :

Théorème 9 (Doumic, Goudon et L.) *On définit la fonction u^ε par*

$$u^\varepsilon = \sum_{i=n_0}^{\infty} u_i^\varepsilon \chi_{[i\varepsilon,(i+1)\varepsilon[},$$

alors à extraction près, on a pour tout temps $T > 0$,

$$\begin{cases} u^{\varepsilon_n} \rightharpoonup U, & \textit{in } \mathcal{C}([0,T]; \mathcal{M}^1([0,\infty[-\text{faible}-\star), \\ v^{\varepsilon_n} \rightharpoonup V & \textit{uniformément sur } [0,T], \end{cases}$$

où (V, U) est une solution préservant les monomères de (13-14) (avec des coefficients obtenus également par passage à la limite).

2 Mouvements de populations et ségrégation

2.1 Modèles

Dans la seconde partie de cette thèse, nous nous intéressons à des équations modélisant le mouvement aléatoire (diffusion) d'individus appartenant à plusieurs espèces qui ont tendance à intensifier leur mouvement (diffusent plus en présence de l'autre espèce, d'où le nom de diffusion croisée) dans un espace clos. Au niveau de la population, ce type de modèles dits de diffusion croisée, introduit par Shigezada et Kawasaki dans [100], s'écrit typiquement de la façon suivante : les variables $u_i, i = 1, 2$ représentant les densités spatiales des espèces 1 et 2, Ω étant le domaine considéré

$$\begin{cases} \partial_t u_1 - \Delta[a_1(u_1, u_2)u_1] = f_1(u_1, u_2), & \text{dans } \Omega \\ \partial_t u_2 - \Delta[a_2(u_1, u_2)u_2] = f_2(u_1, u_2), & \text{dans } \Omega \\ \partial_n(a_1(u_1, u_2)u_1) = \partial_n(a_2(u_1, u_2)u_2) = 0, & \text{sur } \partial\Omega \\ u_i^0 \quad \text{données.} \end{cases} \tag{17}$$

Les f_i désignant des termes de réaction (naissances et morts). Ce sont donc des modèles proches des modèles de réaction-diffusion. Habituellement, les auteurs s'intéressent plus à une compétition entre les effets des termes de réaction et les termes de diffusion (croisée ou non) (voir [56, 104, 87] par exemple).

On peut éventuellement écrire ce système sous forme condensée

$$\partial_t U - \Delta A(U) = F(U),$$

la matrice $A'(U)$ n'étant généralement pas elliptique. Une des principales difficultés de ce système réside alors dans la perte du principe du maximum. Des cas avec couplage faible ont été traités dans [66, 67], avec couplage fort dans [22] à chaque fois avec la forme standard des a_i (voir plus bas). Au delà de ces difficultés techniques, il a été mis en évidence que l'introduction de termes de diffusion croisée peut faire apparaître des équilibres inhomogènes stables dans des cas où même en présence de diffusion aucun équilibre inhomogène ne pouvait être stable ([56]). L'objet de notre intérêt est le comportement induit par le seul mouvement (nous regardons donc le cas $f_i = 0$). Dans ce cas, la population totale de chaque espèce reste inchangée au cours du temps.

$$\forall t > 0, \qquad \int_\Omega u_i(t,x)dx = \int_\Omega u_i^0.$$

La question qui se pose naturellement est la suivante : les deux espèces parviennent elles à cohabiter ? Ce qui mathématiquement se formule par la question de la stabilité de l'équilibre homogène $(u_1, u_2) = (\langle u_1\rangle, \langle u_2\rangle)$, où $\langle u\rangle$ désigne la moyenne spatiale de u,

$$\langle u\rangle = \frac{1}{|\Omega|}\int_\Omega u(x)dx.$$

On parlera alors de ségrégation si cet équilibre n'est pas stable.

Le type de coefficients de diffusion croisée habituellement étudié est le suivant :

$$a_i(u_1,u_2) = d_i + \rho_{i1}u_1 + \rho_{i2}u_2,$$

avec $d_i > 0$, $\rho_{ij} \geq 0$. On peut avoir différentes situations : si l'un des deux coefficients de diffusion croisée est nul (cas triangulaire), (ρ_{12} ou ρ_{21}), on n'a pas de ségrégation. Dans le cas où les deux coefficients sont strictement positifs, le cas a été traité dans [22] par l'utilisation d'une entropie. En effet, on a alors l'inégalité suivante

$$\frac{d}{dt}\int_\Omega \frac{d_1}{\rho_{12}}\phi(u_1) + \frac{d_2}{\rho_{21}}\phi(u_2)dx \leq -\int_\Omega \frac{d_1}{\rho_{12}}|\nabla\sqrt{u_1}| + \frac{d_2}{\rho_{21}}|\nabla\sqrt{u_2}| + |\nabla\sqrt{u_1u_2}|^2 dx,$$

qui permet de conclure à la convergence exponentielle vers l'équilibre homogène par inégalité de Sobolev logarithmique (Théorème 1.2 de [22]) :

$$\frac{1}{\langle u_1\rangle}\|u_1(t,.) - \langle u_1\rangle\|_{L^1(\Omega)} + \frac{1}{\langle u_2\rangle}\|u_2(t,.) - \langle u_2\rangle\|_{L^1(\Omega)} \leq Ce^{-rt}, \quad r > 0.$$

Pour le cas général, nous pouvons conclure pour les données petites en dimension 1 :

Théorème 10 (Bendahmane, L. Marrocco et Perthame) *S'il existe* $\nu > 0$ *tel que* $a_i \geq \nu$ *pour tout* i, *et que les* a_i *sont réguliers (*C^1*), alors pour des données initiales petites (en norme en dimension* 1, *on a existence globale et convergence exponentielle vers l'équilibre homogène.*

La présence de la dimension 1 est hélas cruciale (on utilise l'injection $H^1 \hookrightarrow L^\infty$). La raison est que pour des données petites, le système est en fait elliptique.

2.2 Le modèle régularisé

Nous nous sommes intéressés à d'autres types de diffusion croisée, notre cas modèle étant

$$a_1 = 1 + u_2^2, \quad a_2 = 1 + u_1^2.$$

Le manque d'estimations a priori (nous suspectons une explosion en gradient pour certains cas), nous force alors à régulariser le système de la façon suivante. On considère que la diffusion dépend non pas uniquement de la concentration locale mais aussi des voisines de là façon suivante :

$$\begin{cases} \partial_t u_1 - \Delta a_1(\tilde{u}_1, \tilde{u}_2) u_1 = 0, \\ \partial_t u_2 - \Delta a_2(\tilde{u}_1, \tilde{u}_2) u_2 = 0, \\ -\delta^2 \Delta \tilde{u}_1 + \tilde{u}_1 = u_1, \\ -\delta^2 \Delta \tilde{u}_2 + \tilde{u}_2 = u_2, \\ \partial_\nu u_1 = \partial_\nu u_2 = \partial_\nu \tilde{u}_1 = \partial_\nu \tilde{u}_2 = 0, \\ u_i^0 \quad \text{données.} \end{cases} \tag{18}$$

On a alors le théorème d'existence suivant

Théorème 11 (Bendahmane, L., Marrocco et Perthame) *Si les a_i sont réguliers, à croissance sous polynomiale et que $\nabla_u a_i$ est contrôlé par a_i^η pour un $\eta < 1$, alors les estimations a priori permettent d'assurer l'existence et l'unicité globale du système en dimension 1 et 2 pour des domaines réguliers.*

Notons qu'on peut donner une interprétation biologique à une telle régularisation. Comme pour $\mathbb{R}^n$ entier une telle régularisation correspondrait en dimension 1 à effectuer la convolution suivante

$$\tilde{u}(x) = \int_{\mathbb{R}} u(x-y) \frac{e^{-|y|/\delta^2}}{2\delta^2} dy,$$

le paramètre δ^2 représente ainsi la sensibilité aux variations locales de populations.

2.3 Instabilité de Turing et bifurcation

En nous restreignant à des cas sans auto diffusions ($a_1(u_1, u_2) = a_1(u_2)$ et vice versa), on effectue une analyse de Turing, de l'équilibre homogène selon les valeurs de δ. En examinant la stabilité dans la direction des vecteurs propres du Laplacien avec conditions de Neumann, on fait apparaître les matrices

$$M(\delta, \lambda_k) = \begin{pmatrix} a_1(\langle u_2 \rangle) & \dfrac{a_1'(\langle u_2 \rangle)\langle u_1 \rangle}{1 + \delta\lambda_k} \\ \dfrac{a_2'(\langle u_1 \rangle)\langle u_2 \rangle}{1 + \delta\lambda_k} & a_2(\langle u_1 \rangle) \end{pmatrix}$$

et le mode λ_k est instable si $\det(M(\delta, \lambda_k) < 0$. On met alors en évidence une valeur critique δ_0 du paramètre δ, dépendant de $\langle u_1 \rangle, \langle u_2 \rangle$ (et de la forme de a_1, a_2) telles que pour $\delta > \delta_0$ l'équilibre $\langle u_1 \rangle, \langle u_2 \rangle$ est stable, pour $\delta < \delta_0$ il est instable dans la direction du premier vecteur propre w_1 non constant du laplacien avec conditions de Neuman. Le point δ_0 est alors caractérisé par $\det(M(\delta_0, \lambda_1)$. L'importance de ce point critique est vérifié également grâce à la théorie des bifurcations :

Théorème 12 *Si la première valeur propre non nulle du laplacien est simple, alors $(\delta_0, \langle u_1 \rangle, \langle u_2 \rangle)$ est un point de bifurcation pour l'application*

$$(\delta, u, v) \mapsto \Delta \begin{pmatrix} a_1(\tilde{u}_2) u_1 \\ a_2(\tilde{u}_1) u_2 \end{pmatrix}$$

Autrement dit, une nouvelle branche d'équilibres non constants se forme au point $(\delta_0, \langle u_1 \rangle, \langle u_2 \rangle)$.

2.4 Estimations de dualité : l'outil clé

L'outil le plus important dans notre approche est l'estimation en temps-espace qui repose sur la dualité des équations suivantes :

$$\begin{cases} \partial_t u - \Delta a(t,x)u = 0, \\ u^0 \text{donnée}, \\ \partial_n(au) = 0. \end{cases} \tag{19}$$

$$\begin{cases} \partial_t v + a(t,x)\Delta v = F(t,x), \\ v(T) = 0, \\ \partial_n v = 0. \end{cases}$$

On peut déterminer alors (ce qui est fait dans le chapitre 4) en multipliant la première équation par v et la second par u, la borne suivante :

$$\|\sqrt{a}u\|_{L^2(Q_T)} \le C(\Omega)\|u^0\|_{L^2(\Omega)} + 2\langle u\rangle\|\sqrt{a}\|_{L^2(Q_T)}.$$

Cela permet de dériver des estimations a priori pour des modèles généraux de diffusion croisée. Prenons l'exemple d'un modèle avec

$$1 \le a_i(u_1,u_2) \le 1 + |(u_1,u_2)|^p.$$

Si $p < 2$, en sommant les deux estimations a priori, on obtient

$$\|(u_1,u_2)\|_{L^2(Q_T)} \le C(1 + \sqrt{\int_0^T \int_\Omega u_1^p + u_2^p dx},$$

et via une inégalité d'interpolation de L^p entre L^1 et L^2, en utilisant la conservation de la norme L^1, on obtient

$$\|(u_1,u_2)\|_{L^2(Q_T)} \le C(1 + T^{1-p/2}\|(u_1,u_2)\|^{p/2}_{L^2(Q_T)},$$

un argument de bootstrap permet alors d'assurer que $\|(u_1,u_2)\|_{L^2(Q_T)}$ ne peut pas exploser en temps fini. Si explosion il y a, on l'attend ailleurs. Ceci permet d'amorcer la preuve d'existence du système régularisé. En effet, via la régularité elliptique, on va pouvoir contrôler

$$\sqrt{\int_0^T \int_\Omega \tilde{u}_1^p + \tilde{u}_2^p dx},$$

par des normes L^r de u_1, u_2 avec r petit. On aura alors le même type de bootstrap qui nous donne une borne a priori.

Cette estimation est généralisée à des semi-discrétisations en temps dans l'annexe A. Ainsi, en discrétisant l'équation (19) de la façon suivante,

$$\frac{u^{n+1} - u^n}{h} - \Delta a^n u^{n+1} = 0,$$

on obtient l'estimation a priori discrète

$$\sqrt{h}\|\sqrt{a^n}u^{n+1}\|_{l^2(0\ldots N)} \le C(\Omega) + 2\langle u\rangle\sqrt{h}\|\sqrt{a^n}\|_{l^2(0\ldots N)}.$$

Une telle discrétisation a également l'avantage de ne pas poser problème pour ce qui est de la positivité (ce qui n'est pas évident sur le système lui même).

3 Conclusions et perspectives

3.1 Valeurs propres périodiques pour des modèles structurées en taille

Une extension naturelle du travail sur le renouvellement avec périodicité en temps, serait l'étude (pour commencer existence et unicité) de problèmes aux valeurs propres pour d'autres types de populations structurées. Nous avons typiquement en tête les équations structurées en taille comme l'équation de division cellulaire (1) et l'équation d'agrégation-fragmentation correspondant à (14) avec V constant. La motivation est à la fois mathématique (étendre les travaux de Diekmann et al. dans [38] en généralisant ceux de Michel et Doumic et Gabriel [81, 40]) car les équations structurées en taille induisent des difficultés et des questions différentes, dues au caractère non-local plus marqué, et applicative, l'idée serait à terme de pouvoir proposer des protocoles de sonication pour le prion. Des techniques expérimentales visent en effet à accélerer la polymérisation du prion en cassant les gros polymères. Pour schématiser, cela correspond à alterner entre période de fragmentation intense (on diminue la taille des polymères mais on aumgente leur nombre) et repos (on laisse les polymères s'allonger). Ceci se faisant dans un milieu saturé de monomères, cela reviendrait à étudier une version linéarisée de (14) :

$$\partial_t n(t,x) + \partial_x((\tau(x)n(t,x)) + \psi(t)\beta(x)n(t,x) = 2\int_x^\infty \psi(t)\beta(y)k(x,y)dy.$$

Le coefficient d'amplification $\psi(t)$ serait pris périodique (grand pour les périodes de fragmentation intense, petit pendant celles de repos). Produire le plus de prion possibles reviendrait alors à maximiser la valeur de Floquet sous-jacente. On chercherait donc les meilleurs ψ possibles. Ce problème a été en partie traité dans [38], mais il serait utile de généraliser les résultats plus récents de [81, 40]. Une des grosses différences avec les équations structurées en âge est que pour ces dernières le cas stationnaires est assez simple (pour l'équation de renouvellement à coefficients stationnaires, le vecteur propre satisfait en fait une équation différentielle ordinaire), ce qui n'est pas du tout le cas des problèmes structurés en taille (le caractère nonlocal de l'équation fait que le vecteur propre vérifie déjà une équation intégro-différentielle non triviale).

3.2 Cycle cellulaire : couplage et compétition

Plusieurs points restent à étudier concernant le cycle cellulaire. Une première direction consisterait à comprendre de quelle façon l'effet sur les transitions peut être modélisé. On pourrait aussi, plutôt que de regarder les transitions, introduire une vitesse de croissance qui serait la cible de médicaments. Une autre direction pourrait être l'introduction de non-linéarités pour représenter d'une part la compétition pour les ressources entre cellules saines et tumorales, d'autre part la phase quiescente (qui est une forme de contrôle du cycle cellulaire) que nous avons jusqu'ici négligée. Il serait également très utile de pouvoir obtenir des données sur la dynamique du cycle cellulaire (de type durée des phases, variabilité etc.), afin de pouvoir paramétrer de façon pertinente nos modèles, les nouveaux outils de marquage par fluorescence étant très encourageants sur ce point ([98, 99]).

3.3 Diffusion croisée

La question de la stabilité de l'équilibre homogène n'étant actuellement traitée que de façon linéaire, il semble logique de se pencher ensuite sur sa stabilité non-linéaire. Ainsi, nous avons par exemple prouvé que l'équilibre homogène est l'unique équilibre possible pour une régularisation trop forte (chapitre 5), nous aimerions savoir s'il est alors asymptotiquement stable, ce que semblent montrer les simulations numériques. Jusqu'ici, les simulations semblent montrer que le paramètre de régularisation critique définit une frontière entre instabilité et stabilité de l'équilibre homogène, ce dernier étant asymptotiquement stable s'il est localement stable. En ce qui concerne les bifurcations, nous voudrions étudier de façon plus précise et globale les nouvelles branches qui apparaissent. Un autre point important est la compréhension du système non régularisé. L'énergie définie pour notre cas modèle et les simulations numériques nous font envisager qu'il y a bel et bien explosion (ce point n'est pas montré) et que les gradients explosent mais pas la norme L^∞.

Première partie

Dynamique de populations structurées

Chapitre 1

Comparaison de valeurs propres

Ce travail effectué en collaboration avec Jean Clairambault et Stéphane Gaubert a d'abord pour but de répondre à la question de la généralisation ou non de l'inégalité énoncée dans [26] entre les valeurs propres périodiques (Floquet) et stationnaires (Perron). Nous répondons à cette question par la négative en nous basant sur un contre exemple équivalent à une équation à retard discret déjà aperçu dans [14]. Nous donnons ensuite des arguments théoriques en faveur d'une modèlisation multiphases de la chronothérapie. Ce travail reprend l'article [24].

1.1 Cell cycle control and circadian rhythms

The cell division cycle is the process by which the eukaryotic cell duplicates its DNA content and then divides itself in two daughter cells. This process is normally controlled by various physiological mechanisms that ensure homeostasis of healthy tissues, that control genome integrity (e.g. cyclins and cdks, p53, repair enzymes, etc.), launching programmed cell death (apoptosis) if the DNA is irreversibly damaged (see [86] for a complete presentation). The system of control has been extensively studied and modeled (see e.g. [48, 61, 89] or [105]) using ordinary differential equations. The cell division can be modeled through branching processes (see [7]), integral equations, delay differential equations (see [14]) and also many structured PDE models (for an overview, see [6, 8, 80]) where the structuring variables can be age ([87]), size ([92]) or more recently cyclin content ([18, 19, 39]).

Most living organisms exhibit circadian rhythms (from Latin *circa diem*, "roughly a day") which allow them to adapt to an environment that varies with a periodicity of 24h. These rhythms can be observed even in the smallest biological functional unit, the cell. The problem we are studying is the growth of cell populations (undergoing the cell division cycle described above) under the pressure of circadian rhythms. Circadian rhythm effects on the cell cycle turn out to be important in tumor proliferation. This is observed by several experiments involving a major disruption of circadian rhythms in mice. In these experiments it can be seen that the growth of tumors is significantly enhanced in mice in which the pacemaker circadian clock has been drastically perturbed, either through neurosurgery, or through light-dark cycle disruption (see e.g. [46, 45]). Moreover, in the clinic, taking advantage of the influence exerted by circadian clocks on anticancer drug metabolism and on the cell division cycle has led in the past 15 years to successful applications in the *chronotherapy of cancers*, particularly colorectal cancer (see [70]). This motivates modeling the circadian rhythm in simple cell cycle models and studying these effects on the growth rate of a cell population.

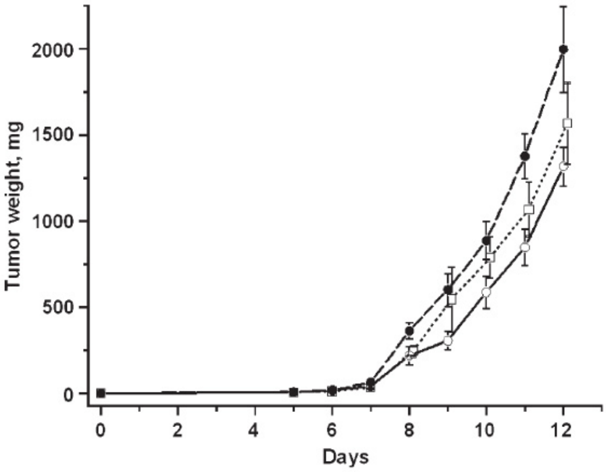

Figure 1.1: Effects of the perturbation of light-dark cycle on tumor proliferation (reproduced from [45]). In clock-perturbed mice (black dots), the tumor proliferates much faster than in control mice (white dots).(By courtesy of Elizabeth Filipski).

Contrary to our first idea, the growth rate of a cell population described by a physiologically structured PDE model with time-periodic control is not necessarily lower than in a model of the same nature, but with a time-averaged control [25, 26, 27].

The goal here is twofold. Firstly we analyze how modeling assumptions lead to define various growth rates under the effects of circadian rhythms. Secondly we model the effect of chronotherapy on these growth rates.

In the second section we recall the definition of these various growth rates, in terms of Perron and Floquet eigenvalues of a linear Von Foerster- Mc-Kendrick model. We also discuss known inequalities between them. In the third section we study a simple division model, for which we establish (in Theorem 1.3.1) strict inequalities comparing the growth rate in the stationary (Perron) and periodic (Floquet) cases. These inequalities are proved by studying a related time delay system (which is similar to the one considered in [14]). This model is used to confirm the impossibility to derive a general comparison between the Perron and Floquet eigenvalues defined in the second section. In the fourth section, we give an argument for using multiphase models to represent chronotherapy, taking better into account the structure of the cell cycle and particularly the existence of various phases. We provide numerical simulations to illustrate our results. In a first appendix, we give the detailed proof of the existence of the solution of the eigenproblem, by applying the Krein-Rutman theorem. In a second appendix, we derive analytical formulæfor the eigenelements in a specific multiphase case, which yield further information on their behavior and can be used to validate numerical experiments.

1.2 The model

1.2.1 The renewal equation

We base our study on a cell population that follows the classical renewal equation structured in age with periodic coefficients representing the effect of circadian rhythms

$$\begin{cases} \frac{\partial}{\partial t}n(t,x) + \frac{\partial}{\partial x}n(t,x) + d(t,x)n(t,x) = 0, \\ n(t,x=0) = \int_0^\infty B(t,x)n(t,x)dx. \end{cases} \tag{1.1}$$

Here $n(t,x)$ represents the density of cells of age x in the cycle at time t, $d(t,x), B(t,x)$ represent respectively the death rate, and the birth rate. Both these coefficients are T-periodic in time. We define the growth rate of the population in terms of an eigenproblem. The growth rate λ_F (F for Floquet as for ODEs with periodic coefficients) is defined as the unique real number λ_F, such that there is a solution N to the problem

$$\begin{cases} \frac{\partial}{\partial t}N(t,x) + \frac{\partial}{\partial x}N(t,x) + [\lambda_F + d(t,x)]N(t,x) = 0, \\ N(t,x=0) = \int_0^\infty B(t,x)N(t,x)dx, \\ N > 0, \qquad T-\text{periodic}. \end{cases} \tag{1.2}$$

We refer to [82] for conditions of existence for λ_F (and to the appendix for the case of division models).

1.2.2 Comparison of eigenvalues

We use the following notations. For a T-periodic function f we define,

$$\begin{aligned} \langle f \rangle &= \frac{1}{T}\int_0^T f(t)dt \qquad \text{the arithmetical average,} \\ \langle f \rangle_g &= \exp\Big(\frac{1}{T}\int_0^T \log f(t)dt\Big) \qquad \text{the geometrical average, when } f > 0. \end{aligned}$$

It may seem natural to introduce the following stationary problem (Perron eigenproblem), in which the death and birth rates are averaged

$$\begin{cases} \frac{d}{dx}N_P(x) + [\lambda_P + \langle d(x) \rangle]N_P(x) = 0, \\ N_P(0) = \int_0^\infty \langle B(x) \rangle N_P(x)dx = 1, \\ N_P(x) > 0. \end{cases} \tag{1.3}$$

It is shown in [26, 27] that, when B does not depend on time, the inequality $\lambda_F \geq \lambda_P$ holds. In the present paper, we show that this inequality does not carry over to the case of a time dependent B. It should be noted, however, that there is a general inequality, established in [25], which relates λ_F with the solution of the following eigenproblem in which an arithmetical average of the death rate is taken, whereas the geometrical average of the birth rate is taken,

$$\begin{cases} \frac{d}{dx}N_g(x) + [\lambda_g + \langle d(x) \rangle]N_g(x) = 0, \\ N_g(0) = \int_0^\infty \langle B(x) \rangle_g N_g(x)dx = 1, \\ N_g(x) > 0. \end{cases} \tag{1.4}$$

Theorem 1.2.1 ([25]) *The eigenvalues defined in (1.2) and (1.4) satisfy*

$$\lambda_F \geq \lambda_g.$$

This result suggests that there is no general inequality between λ_P and λ_F, because the inequality which follows from convexity is $\lambda_F \geq \lambda_g$. Moreover, it follows from the standard arithmetico-geometrical inequality,

$$\lambda_P \geq \lambda_g.$$

Such a general comparison cannot hold between λ_F and λ_P, as shown in the next section. To go further we use a more specific model.

1.3 A simple one-phase division model

1.3.1 Model and main results

We model the cell cycle with the following PDE which is a particular case of (1.1),

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) + \frac{\partial}{\partial x} n(t,x) + [d(t) + K_0\psi(t)\chi_{[a,+\infty[}(x)]n(t,x) = 0, \\ n(t,0) = 2K_0\psi(t)\int_a^\infty n(t,x)dx, \end{cases}$$

where $K_0 > 0$ is a constant, $\psi > 0$ is a T-periodic function with

$$\langle \psi \rangle = 1. \tag{1.5}$$

The term $K_0\psi(t)\chi_{[a,+\infty[}$ represents the division rate, $d(t)$ is the apoptosis rate (we assume it to be T-periodic). We have denoted by χ_E the indicator function of set E. Finally, $\psi(t)$ represents a nonnegative periodic control exerted on division. As before we look for the growth rate λ_F of such a system. It is defined so that there is a solution to the Floquet eigenproblem,

$$\begin{cases} \frac{\partial}{\partial t} N(t,x) + \frac{\partial}{\partial x} N(t,x) + \big[\lambda_F + d(t) + K_0\psi(t)\chi_{[a,+\infty[}(x)\big]N(t,x) = 0, \\ N(t,0) = 2K_0\psi(t)\int_a^\infty N(t,x)dx, \\ N > 0,\ T\text{-periodic}, \end{cases} \tag{1.6}$$

and we normalize N by

$$\int_0^T \int_0^\infty N(t,x)dxdt = 1.$$

As we already know a general comparison result for the geometrical eigenvalue λ_g defined in (1.4), we are now only interested in the comparison of λ_F and λ_P, the latter quantity defined by requiring the existence of a solution to the Perron eigenproblem already defined in (1.3) which here reads

$$\begin{cases} \frac{d}{dx} N_P(x) + [\lambda_P + \langle d \rangle + K_0\chi_{[a,+\infty[}(x)]N_P(x) = 0, \\ N_P(0) = 2K_0\int_a^\infty N_P(x)dx, \\ N_P > 0, \end{cases} \tag{1.7}$$

and we normalize N_P by

$$N_P(0) = 2K_0\int_a^\infty N_P(x)dx = 1.$$

We are interested in evaluating the effect of the periodic control $\psi(t)$ on the growth of the system. Therefore we denote by $\lambda_F(a,\psi)$ and by $\lambda_P(a)$ the above defined eigenelements so as to keep track of the problem parameters.

The following theorem implies that there is no possible general comparison between λ_F and λ_P.

Theorem 1.3.1 *For all continuous positive T-periodic functions ψ satisfying (1.5), we have*

$$\lambda_F(a=T,\psi)=\lambda_P(T)=\lambda_F(a=T,1), \tag{1.8}$$

and for a in a neighborhood of T, we have, provided $\psi \not\equiv 1$

$$\lambda_F(a,\psi)>\lambda_P(a)=\lambda_F(a,1) \quad \textit{for} \quad a<T,$$

$$\lambda_F(a,\psi)<\lambda_P(a)=\lambda_F(a,1) \quad \textit{for} \quad a>T.$$

The proof of this theorem is presented in the next sections. The computations done in section 4.1 insure that, without loss of generality, we can suppose $d\equiv 0$.

Numerical results are presented in figures 1.2 and 1.3 which illustrate this theorem. Graphically, for fixed ψ, this predicts firstly that the curves of $\lambda_F(a,\psi)$ (Floquet curve) and $\lambda_P(a)$ (Perron curve) must cross each other for $a=T$, secondly that the Floquet curve should be above the Perron curve before (i.e., for $a<T$) the crossing and below this curve after it (i.e., for $a>T$). A possible interpretation is that for a better adaptation (in the sense of higher proliferation), the cell cycle should be shorter than 24h; an effect already observed in [14].

1.3.2 Proof of Theorem 2, part 1 (a delay differential equation)

Throughout the proof, we use the shorter notations λ_F and λ_P instead of $\lambda_F(a,\psi)$ and $\lambda_P(a)$ when there is no possible confusion.
To find more information on λ_F we derive a delay differential equation.
We integrate (1.6) with respect to age over $[a,\infty[$. We get

$$\frac{d}{dt}\int_a^\infty N(t,x)dx+N(t,\infty)-N(t,a)+[\lambda_F+K_0\psi(t)]\int_a^\infty N(t,x)dx=0.$$

From the formula of characteristics and the boundary condition in (1.6),

$$\begin{aligned}&N(t,a)=N(t-a,0)e^{-\lambda_F a},\\&N(t,a)=2K_0e^{-\lambda_F a}\psi(t-a)\textstyle\int_a^\infty N(t-a,x)dx.\end{aligned}$$

We set $P(t)=\int_a^\infty N(t,x)dx$. Since we have $N(t,\infty)=0$ (see the appendix) we obtain the delay differential equation

$$\dot P(t)+\Big(\lambda_F+K_0\psi(t)\Big)P(t)=2K_0\psi(t-a)P(t-a)e^{-\lambda_F a}. \tag{1.9}$$

1.3.3 Proof of Theorem 2, part 2 (equality of growth rates for $a=T$)

The comparison between λ_P and λ_F is based on the following formula for λ_P.

Lemma 1.3.2 *For all $a>0$, the Perron eigenvalue λ_P defined in (1.7) satisfies*

$$\frac{\lambda_P+K_0}{2K_0}e^{\lambda_P a}=1. \tag{1.10}$$

Proof. From (1.7), we have, for $x \geq a$, $N_P(x) = e^{-(\lambda_P+K_0)x+K_0a}$. We insert that in the boundary condition and obtain

$$1 = 2K_0 \int_a^\infty e^{-(\lambda_P+K_0)x+K_0a}dx,$$

$$1 = 2K_0 \frac{1}{\lambda_P+K_0} e^{-\lambda_P a}.$$

□

Corollary 1.3.3 *For all $a > 0$, the Perron eigenvalue λ_P defined in (1.7) is strictly positive.*

Proof. This follows from Lemma 1.3.2 and the remark

$$\forall a > 0, \forall \lambda \leq 0, \qquad \frac{\lambda+K_0}{2K_0}e^{\lambda a} \leq \frac{1}{2}.$$

□

To obtain (1.8), we divide (1.9) by P and find

$$\frac{\dot{P}(t)}{P(t)} = -\lambda_F - K_0\psi(t) + 2K_0\psi(t-a)\frac{P(t-a)}{P(t)}e^{-\lambda_F a}.$$

When we take the average over a period, we get (since P is T-periodic in time by its definition as N is)

$$0 = -(\lambda_F+K_0) + 2K_0e^{-\lambda_F a}\left\langle \psi(t-a)\frac{P(t-a)}{P(t)}\right\rangle,$$

$$\frac{\lambda_F+K_0}{2K_0}e^{\lambda_F a} = \left\langle \psi(t-a)\frac{P(t-a)}{P(t)}\right\rangle. \tag{1.11}$$

Now we consider the particular case $a = T$. As P is T-periodic $P(t-a) = P(t)$. Hence, for $a = T$, we arrive at

$$\frac{\lambda_F+K_0}{2K_0}e^{\lambda_F a} = \left\langle \psi(t-a)\frac{P(t-a)}{P(t)}\right\rangle = \langle\psi\rangle = 1. \tag{1.12}$$

This equality is the same for λ_F as the one described in lemma 1 for λ_P. As we know that the mapping

$$\lambda \quad \mapsto \quad \frac{\lambda+K_0}{2K_0}e^{\lambda a}.$$

is increasing on $[-K_0, +\infty[$ from 0 to $+\infty$ and is negative elsewhere, there is only one solution to (1.12) which is also given by (1.10) and the result (1.8) is proved. □

1.3.4 Proof of Theorem 2, part 3 (local comparison around $a = T$)

We fix $\psi \not\equiv 1$. We study the variations of $\frac{\lambda_F+K_0}{2K_0}e^{\lambda_F a}$ around $a = T$. From (1.11), we know:

$$\frac{\lambda_F+K_0}{2K_0}e^{\lambda_F a} = \left\langle \psi(t-a)\frac{P(t-a)}{P(t)}\right\rangle = \left\langle \psi(t)\frac{P(t)}{P(t+a)}\right\rangle,$$

therefore

$$\begin{aligned}\frac{\partial}{\partial a}\frac{\lambda_F+K_0}{2K_0}e^{\lambda_F a} &= \frac{\partial}{\partial a}\left\langle \psi(t)\frac{P(t)}{P(t+a)}\right\rangle, \\ &= \left\langle \psi(t)\frac{\partial P}{\partial a}(t)\frac{1}{P(t+a)}\right\rangle + \left\langle \psi(t)\frac{-P(t)}{P^2(t+a)}\frac{\partial}{\partial a}\big(P(t+a)\big)\right\rangle.\end{aligned}$$

Recalling that P depends on a (as N and λ_F do), we have

$$\frac{\partial}{\partial a} P(t+a) = \frac{\partial P}{\partial a}(t+a) + \dot{P}(t+a).$$

We then split the computations

$$\begin{aligned}
\frac{\partial}{\partial a} \frac{\lambda_F + K_0}{2K_0} e^{\lambda_F a} &= \left\langle \psi(t) \frac{\partial P}{\partial a}(t) \frac{1}{P(t+a)} \right\rangle - \left\langle \psi(t) \frac{P(t)}{P^2(t+a)} \left(\frac{\partial P}{\partial a}(t+a) + \dot{P}(t+a) \right) \right\rangle, \\
&= \left\langle \psi(t) \frac{1}{P(t+a)} \left(\frac{\partial P}{\partial a}(t) - \frac{P(t)}{P(t+a)} \frac{\partial P}{\partial a}(t+a) \right) \right\rangle \\
&\quad - \left\langle \psi(t) \frac{P(t)}{P^2(t+a)} \dot{P}(t+a) \right\rangle.
\end{aligned}$$

For $a = T$, the first term vanishes, and $P(t+a) = P(t)$ i.e.,

$$\frac{\partial}{\partial a} \frac{\lambda_F + K_0}{2K_0} e^{\lambda_F a} = -\left\langle \psi(t) \frac{P(t)}{P^2(t)} \dot{P}(t) \right\rangle = -\left\langle \psi(t) \frac{\dot{P}(t)}{P(t)} \right\rangle.$$

To compute this we again make use of the ODE (1.9) which we multiply by $\frac{\psi}{P}$

$$\psi(t) \frac{\dot{P}(t)}{P(t)} = -\lambda_F \psi(t) - K_0 \psi^2(t) + 2K_0 \psi(t-a) \psi(t) \frac{P(t-a)}{P(t)} e^{-\lambda_F a}.$$

Averaging on a period we still get, for $a = T$,

$$\left\langle \psi(t) \frac{\dot{P}(t)}{P(t)} \right\rangle = -\lambda_F - K_0 \langle \psi^2 \rangle + 2K_0 \langle \psi^2 \rangle e^{-\lambda_F a}.$$

Using (1.12), we arrive at

$$\left\langle \psi(t) \frac{\dot{P}(t)}{P(t)} \right\rangle = -\lambda_F - K_0 \langle \psi^2 \rangle + \langle \psi^2 \rangle (\lambda_F + K_0) = \lambda_F (\langle \psi^2 \rangle - 1).$$

We now have the derivative at $a = T$,

$$\frac{\partial}{\partial a}_{|a=T} \frac{\lambda_F + K_0}{2K_0} e^{\lambda_F a} = -\lambda_F (\langle \psi^2 \rangle - 1). \tag{1.13}$$

We use here the notations $\lambda'_F(T)$ for $\frac{\partial \lambda_F}{\partial a}_{|a=T}$ and $\lambda_F(T) = \lambda_P(T)$ to recall that we are studying the local behavior of λ_F and λ_P around $a = T$, (ψ is fixed). We can directly compute

$$\frac{\partial}{\partial a}_{|a=T} \frac{\lambda_F + K_0}{2K_0} e^{\lambda_F a} = \lambda'_F(T) \frac{e^{\lambda_F(T)T}}{2K_0} + (\lambda'_F(T) T + \lambda_F(T)) \frac{K_0 + \lambda_F(T)}{2K_0} e^{\lambda_F(T)T},$$

Therefore, using (1.8) and (1.10), we obtain

$$\frac{\partial}{\partial a}_{|a=T} \frac{\lambda_F + K_0}{2K_0} e^{\lambda_F a} = \lambda'_F(T) \left(\frac{e^{\lambda_P(T)T}}{2K_0} + T \right) + \lambda_F(T),$$

so that, using (1.8) and (1.13), we have

$$\lambda'_F(T) = \frac{-\lambda_P(T) \langle \psi^2 \rangle}{T + \frac{e^{\lambda_P(T)T}}{2K_0}}.$$

Similarly we have

$$\lambda_P'(T) = \frac{-\lambda_P(T)}{T + \frac{e^{\lambda_P(T)T}}{2K_0}}.$$

Therefore,

$$\lambda_P'(T) - \lambda_F'(T) = \frac{\lambda_P(T)(\langle \psi^2 \rangle - 1)}{T + \frac{e^{\lambda_P(T)T}}{2K_0}}.$$

Thanks to corollary 1.3.3, $\lambda_P(T)$ is positive. The assumption (1.5) leads to

$$\langle \psi^2 \rangle - 1 = \left\langle (\psi - 1)^2 \right\rangle > 0.$$

Finally we obtain

$$\lambda_P'(T) - \lambda_F'(T) > 0, \tag{1.14}$$

and the second statement of the theorem follows then immediately from (1.8) and (1.14). □

1.4 Modeling chronotherapy

In the following we propose a model for chronotherapy by the introduction of a periodic death rate due to the effect of a drug on our cell division cycle model.

1.4.1 Limit of single-phase division models

We consider a population of cells following a general division equation with apoptosis rate d. As above, all coefficients are T-periodic with respect to time.

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) + \frac{\partial}{\partial x} n(t,x) + \big(d(t,x) + K(t,x)\big) n(t,x) = 0, \\ n(t,0) = 2\int_0^\infty K(t,x) n(t,x) dx. \end{cases}$$

We consider the Floquet eigenproblem associated with this equation

$$\begin{cases} \frac{\partial}{\partial t} N(t,x) + \frac{\partial}{\partial x} N(t,x) + \big(d(t,x) + K(t,x) + \lambda_F\big) N(t,x) = 0, \\ N(t,0) = 2\int_0^\infty K(t,x) N(t,x) dx, \\ N > 0, \quad \int_0^T \int_0^\infty N(t,x) dx dt = 1. \end{cases}$$

We propose to model the effect of chronotherapy by adding a time T-periodic, age-independent death rate $\gamma(t)$ representing the effect of a drug (for instance we may consider γ proportional to the quantity of drug in the body). The cell population now follows the equation

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) + \frac{\partial}{\partial x} n(t,x) + [d(t,x) + K(t,x) + \gamma(t)] n(t,x) = 0, \\ n(t,0) = 2\int_0^\infty K(t,x) n(t,x) dx. \end{cases}$$

The Floquet eigenproblem for this equation reads

$$\begin{cases} \frac{\partial}{\partial t} N^\gamma(t,x) + \frac{\partial}{\partial x} N^\gamma(t,x) + \big(d(t,x) + K(t,x) + \gamma(t) + \lambda_F^\gamma\big) N^\gamma(t,x) = 0, \\ N^\gamma(t,0) = 2\int_0^\infty K(t,x) N^\gamma(t,x) dx, \\ N^\gamma > 0, \quad T-\text{periodic} \quad \int_0^T \int_0^\infty N^\gamma(t,x) dx dt = 1. \end{cases}$$

Lemma 1.4.1 *The Floquet eigenvalue* λ_F^γ *defined above satisfies*

$$\lambda_F^\gamma = \lambda_F - \langle\gamma\rangle.$$

Proof. We define $\tilde{\gamma} = \gamma - \langle\gamma\rangle$, $\Gamma(t) = \int_0^t \tilde{\gamma}(s)ds$. Noticing that Γ is T-periodic, we define the function M by $M(t,x) = N(t,x)e^{\Gamma(t)}$. It satisfies

$$\begin{cases} \frac{\partial}{\partial t}M(t,x) + \frac{\partial}{\partial x}M(t,x) + \big(d(t,x) + K(t,x) + \gamma(t) + \lambda_F - \langle\gamma\rangle\big)M(t,x) = 0, \\ M(t,0) = 2\int_0^\infty K(t,x)M(t,x)dx, \\ M > 0, \quad T-\text{periodic}. \end{cases}$$

Therefore $\lambda_F^\gamma = \lambda_F - \langle\gamma\rangle$ and up to a renormalization $M = N^\gamma$. □

This result expresses that with such a simple model, chronotherapy is inefficient, since changing the moment of administration of a drug (in symbols, changing $\gamma(t)$ into $\gamma(t+\theta)$ where θ is a real number) has no effect on the growth rate. In other words, in such one-phase models, this effects depends on $\langle\gamma\rangle$. Only the total daily dose of the drug is relevant!

1.4.2 Using multiphase models

We now consider more realistic multiphase models. We use the additional ingredient that the real cell division cycle is multiphasic because of the existence of checkpoints between phases (mainly at the G1/S and G2/M transitions) at which it can be arrested if genome integrity is not preserved. We consider a cell cycle model with I phases where $I > 1$ (for instance $I = 4$ if we want to represent the classical phases G1-S-G2-M). We study I populations of cells, $n_i(t,x)$ being the density of cells of age x in phase i at time t. We use the convention $I + 1 = 1$

$$\begin{cases} \frac{\partial}{\partial t}n_i(t,x) + \frac{\partial}{\partial x}n_i(t,x) + [K_{i\to i+1}(t,x) + d_i(t,x)]n_i(t,x) = 0, \\ n_{i+1}(t,0) = \int_0^\infty K_{i\to i+1}(t,y)n_i(t,y)dy, \qquad 1 < i \\ n_1(t,0) = 2\int_0^\infty K_{I\to 1}(t,y)n_I(t,y)dy, \\ n_i(0,x) = n_i^0(x) \quad \textit{given}. \end{cases} \tag{1.15}$$

Here $K_{i\to i+1}$ represents the transition rate from phase i to $i+1$. At the end of phase I division occurs with rate $K_{I\to 1}$. To be as general as possible, we have considered death rates d_i in phase i. As above, the coefficients are time T-periodic and we can consider the Floquet eigenproblem

$$\begin{cases} \frac{\partial}{\partial t}N_i(t,x) + \frac{\partial}{\partial x}N_i(t,x) + [K_{i\to i+1}(t,x) + d_i(t,x) + \lambda]N_i(t,x) = 0, \\ N_{i+1}(t,0) = \int_0^\infty K_{i\to i+1}(t,y)N_i(t,y)dy, \qquad 1 < i \\ N_1(t,0) = 2\int_0^\infty K_{I\to 1}(t,y)N_I(t,y)dy, \\ N_i > 0, \quad T-\text{periodic}, \quad \sum\limits_i \int_0^1\int_0^\infty N_i dxdt = 1. \end{cases} \tag{1.16}$$

We also consider the adjoint eigenproblem

$$\begin{cases} \frac{\partial}{\partial t}\phi_i(t,x) + \frac{\partial}{\partial x}\phi_i(t,x) - [K_{i\to i+1}(t,x) + d_i(t,x) + \lambda]\phi_i(t,x) = -K_{i\to i+1}\phi_{i+1}(t,0), \\ \frac{\partial}{\partial t}\phi_I(t,x) + \frac{\partial}{\partial x}\phi_I(t,x) - [K_{I\to 1}(t,x) + d_I(t,x) + \lambda]\phi_I(t,x) = -2K_{I\to 1}\phi_1(t,0), \\ \phi_i > 0, \quad T-\text{periodic}, \quad \sum\limits_i \int_0^\infty N_i\phi_i dxdt = 1. \end{cases} \tag{1.17}$$

To model the effect of chronotherapy, we consider a cytotoxic drug acting only on a specific phase (for instance 5-Fluorouracil acts on S-phase, see [69] for instance and the references therein) and, as in the previous section we represent its action by an additional death rate in phase j, $\gamma(t)$ (we replace in phase j d_j by $d_j+\gamma$) . We also define eigenelements for the modified equation $(\lambda^\gamma, N^\gamma, \phi^\gamma)$. We multiply the first line of (1.16) (version with d_j replaced by $d_j+\gamma$, N_i by N_i^γ and λ by λ^γ) by ϕ_i, and (1.17) by N_i^γ. Summing over i and integrating over age and time, we obtain

$$(\lambda-\lambda^\gamma)\sum_i \int_0^1 \int_0^\infty N_i^\gamma \phi_i dxdt = \int_0^1 \gamma(t) \int_0^\infty N_j^\gamma \phi_j dxdt. \tag{1.18}$$

We shall not have here the problem encountered with one-phase models. We study the effect of a death rate $\gamma(t+\theta)$. We denote $\lambda^{\varepsilon,\theta}, N^{\varepsilon,\theta}$ the eigenelements associated to an additional death rate $\varepsilon\gamma(t+\theta)$ in phase j. We define $F(\varepsilon,\theta)$ by

$$F(\varepsilon,\theta) = \lambda - \lambda^{\varepsilon,\theta} = \frac{\int_0^1 \varepsilon\gamma(t+\theta)\int_0^\infty N_j^{\varepsilon,\theta}\phi_j dxdt}{\sum\limits_i \int_0^1\int_0^\infty N_i^{\varepsilon,\theta}\phi_i dxdt}. \tag{1.19}$$

As we have $\lambda = \lambda^{0,\theta}$ for any θ, $F(0,\theta) \equiv 0$. Particularly it does not depend on θ. The question is: does $F(\varepsilon,\theta)$ depend on θ for fixed ε? To assess this question, we compute using dominated convergence

$$\frac{\partial\lambda(\varepsilon,\theta)}{\partial\varepsilon}\mid_{\varepsilon=0} = \lim_{\varepsilon\to 0}\frac{F(\varepsilon,\theta)}{\varepsilon} = \int_0^1 \gamma(t+\theta)\int_0^\infty N_j\phi_j dxdt. \tag{1.20}$$

Therefore if neither the function $\gamma(.)$ nor the function $\int_0^\infty N_j\phi_j(.,x)dx$ are constant (contrarily to one-phase models, there are no compensating effect making $\int_0^\infty N_j\phi_j(.,x)dx$ constant, see for instance the computations of the appendix), then $\lim\limits_{\varepsilon\to 0}\dfrac{F(\varepsilon,\theta)}{\varepsilon}$ depends on θ (we mean it is not a constant function of θ) and so is (at least for small ε) $F(\varepsilon,.)$. In this case the Taylor first order approximation around 0 of λ: $\lambda(\varepsilon,\theta)\approx\lambda+\varepsilon\int_0^1\gamma(t+\theta)\int_0^\infty N_j\phi_j dxdt$ is not a constant function of θ and neither is $\lambda(\varepsilon,\theta)$, at least for small values of ε. We illustrate this property numerically in the next section (see figure 1.5). It seems that the Taylor first order approximation is a very good approximation of the growth rate for a reasonable range of values of the amplitude ε.

1.5 Numerical simulations

We illustrate the theorems proved above by several numerical simulations. We firstly present the numerical scheme, then we give several algorithmic properties. Finally tests are presented.

1.5.1 Discretization

In our numerical simulations we consider a pure division model :

$$\begin{cases} \frac{\partial}{\partial t}n(t,x) + \frac{\partial}{\partial x}n(t,x) + K_0\psi(t)\chi_{[a,+\infty[}(x)n(t,x) = 0, \\ n(t,0) = 2K_0\psi(t)\int_a^\infty n(t,x)dx. \end{cases} \tag{1.21}$$

Consider time and age increments $\Delta t, \Delta x$ and denote by κ_i and ψ^k, the quantities $\kappa_i = K_0\chi_{[a,+\infty[}(i\Delta x)$ and $\psi^k = \psi(k\Delta t)$. Choosing first order finite differences, we obtain from equation (1.21) the following approximation with an error of order $O(|\Delta t| + |\Delta x|)$

$$\frac{n_i^{k+1}-n_i^k}{\Delta t}+\frac{n_i^k-n_{i-1}^k}{\Delta x}+\kappa_i\psi^{k+1}n_i^{k+1}=0,\quad 1\le i\le I,$$

where $\{0\dots I\}$ is the set of all values of i to be considered in the discretization. Taking $\Delta t=\Delta x$ ($CFL=1$), we obtain the following compact discretization scheme:

$$\begin{cases} n_i^{k+1}=\frac{n_{i-1}^k}{1+\Delta t\kappa_i\psi^{k+1}}, \quad 1\le i\le I,\\ n_0^{k+1}=2\psi^k\sum\limits_{0\le i\le I}\kappa_i n_i^k\Delta t. \end{cases} \tag{1.22}$$

Assume ψ is periodic of period $T\ge 0$ and consider a grid over $[0,T]\times[0,I\Delta t]$, consisting of squares with sides of length $\Delta t=T/N_T$, for some $N_T\in\mathbb{N}$ (and I large enough, particularly $I\Delta t>a$ and $I+1>N_T$). Then, the populations at time $(k+1)\Delta t$ for all ages in $[0,I\Delta t]$ can be obtained from the corresponding populations at time $k\Delta t$ as follows:

$$\begin{pmatrix} n_0^{k+1}\\ n_1^{k+1}\\ \vdots\\ n_I^{k+1}\end{pmatrix}=\begin{pmatrix} 2\psi^k\kappa_0\Delta t & \dots & 2\psi^k\kappa_{I-1}\Delta t & 2\psi^k\kappa_I\Delta t\\ \frac{1}{1+\Delta t\psi^{k+1}\kappa_1} & \dots & 0 & 0\\ \vdots & \ddots & \vdots & \vdots\\ 0 & \dots & \frac{1}{1+\Delta t\psi^{k+1}\kappa_I} & 0\end{pmatrix}\begin{pmatrix} n_0^k\\ n_1^k\\ \vdots\\ n_I^k\end{pmatrix} \tag{1.23}$$

It is clear that the matrix in (1.23) depends only on the time index k and is periodic of period N_T. We denote M_k this matrix and the vectors respectively n^k and n^{k+1}. The equation (1.23) can be written $n^{k+1}=M_kn^k$.

1.5.2 Approximating the eigenvalue

The algorithm has already been discussed in [103]. We recall that the growth rate is defined as the unique real λ_F such that (1.21) admits solutions of the form $N(t,x)e^{\lambda_F t}$ with $N>0$ and $N(.,x)$ is periodic. We can approximate it thanks to:

Lemma 1.5.1 (Discrete Floquet theorem)

There exists a unique real λ *and a unique sequence of vectors* $(\mathcal{N}^k)_{k\in\mathbb{N}}$, $\mathcal{N}^k=\left(\mathcal{N}_i^k\right)_{0\le i\le I}$ *such that*

$$\mathcal{N}_i^k>0,\qquad \sum_{i=0}^{I}\mathcal{N}_i^0=1, \tag{1.24}$$

$$k\mapsto(\mathcal{N}^k)\quad \textit{is}\quad N_T\textit{-periodic}, \tag{1.25}$$

$$n^k,\quad \textit{defined by } n^k=\mathcal{N}^k e^{\lambda.k\Delta t}\quad \textit{is solution to } (1.23). \tag{1.26}$$

Proof. The proof is standard and we recall it for the sake of completeness. It is based on the Perron Frobenius theorem. First we prove uniqueness. Supposing there exists such n^k, we have

$$\begin{aligned} n^1 &= M_0n^0,\\ n^2 &= M_1n^1=M_1M_0n^0,\\ &\dots \qquad\qquad (1.27)\\ n^{k+1} &= M_kn^k=M_kM_{k-1}\dots M_1M_0n^0, \qquad (1.28)\\ &\dots\\ n^{N_T} &= M_{N_T-1}M_{N_T-2}\cdots M_1M_0n^0. \qquad (1.29) \end{aligned}$$

We define

$$\mathbb{M} = M_{N_T-1}M_{N_T-2}\cdots M_1M_0,$$

thus, (1.29) reads $n^{N_T} = \mathbb{M}n^0$. □

Lemma 1.5.2 *The matrix* $\mathbb{M}$ *is nonnegative and primitive (and therefore is irreducible).*

Proof. The nonnegativity is obvious. To prove the primitivity, the key point is $I+1 > N_T$ and $I\Delta t \geq a + 2\Delta t$. For some $\varepsilon > 0$ we have for any k, if we denote by Id_k the identity matrix of order k,

$$M_k \geq \varepsilon \begin{pmatrix} 0\dots 0 & 1\,1 \\ \mathrm{Id}_I & 0 \end{pmatrix} = \varepsilon W.$$

Notice that W is the Wielandt matrix of order $I+1$ which is known to be primitive (see [54]). Therefore for some p, $W^p > 0$ and thus for $qN_T \geq p$,

$$\mathbb{M}^q \geq \varepsilon^{qN_T} W^{qN_T} > 0,$$

which yields the primitivity of $\mathbb{M}$, the spectral radius of which, denoted here by ρ is then positive. We denote by ρ its spectral radius. We have $\rho > 0$.

Back to the proof of the discrete Floquet theorem, we have

$$n^{N_T} = e^{\lambda N_T \Delta t}\mathcal{N}^{N_T} = e^{\lambda T}\mathcal{N}^0 = e^{\lambda T} n^0.$$

Hence we have $\mathbb{M}n^0 = e^{\lambda T}n^0$. This means that n^0 is a positive eigenvector of $\mathbb{M}$ associated to a positive eigenvalue $e^{\lambda T}$. From the Perron-Frobenius theorem, $e^{\lambda T} = \rho$ and $n^0 = \mathcal{N}^0$ is the (unique) associated eigenvector. The solution is unique.

Conversely, if we know the Perron eigenvector V and the Perron eigenvalue ρ of $\mathbb{M}$, then the sequence $\left(\mathcal{N}^k\right)^{k\in\mathbb{N}}$ defined by

$$\begin{cases} \mathcal{N}^0 = V, \\ \mathcal{N}^{k+1} = e^{-\lambda\Delta t}.M_k\mathcal{N}^k, \end{cases}$$

satisfies (1.24),(1.25) and (1.26) for $\lambda = \log(\rho(\mathbb{M}))$. □

For multiphase models, the idea is mainly the same. To compute $\rho = e^{\lambda T}$ the spectral radius of $\mathbb{M}$, the *power algorithm* is used. It converges thanks to the primitivity of $\mathbb{M}$.

1.5.3 Numerical results

First we present some numerical results to illustrate theorem 1.3.1. We scale $T = 1$. We fix the value of K_0 to 2 and test various periodic function ψ. We plot the curves

$$\begin{array}{ccc} a & \rightarrow & \lambda_F(a,\psi), \\ a & \rightarrow & \lambda_P(a). \end{array}$$

We recall that the eigenvalues for the Perron problem can be directly computed thanks to lemma 1.3.2. From theorem 1.3.1, we know that these curves cross for x-coordinate $a = T$, the second part of the theorem tells us that we expect (locally) the curve for λ_F to be above the curve for λ_P for $a < T$ and below it for $a > T$. We plot the curves $\lambda = \lambda_P(a)$ and $\lambda = \lambda_F(a,\psi)$ for our functions ψ and look at the crossing of curves around T (on the simulations, $T = 1$). We also give a more global view of $\lambda_F(a,\psi_{sin})$ and λ_P in figure 1.3 to illustrate the fact that the comparison is only local. Here, the parameters h and δ are respectively set to 3 and 0.3.

Name of the function	Formulation on the interval $[0,1[$	$\langle\psi^2\rangle$
ψ_{sq} (square wave)	$1.8\chi_{[0,1/2[}(t) + 0.1\chi_{[1/2,1[}$	1.81
ψ_{pk} (peak function)	$0.1 + ht/\delta\chi_{[0,\delta[}(t) + (2h - ht/\delta)\chi_{[\delta,2\delta[}(t)$	1.99
ψ_{sin} (sinusoidal)	$1 + 0.9\cos(2\pi t)$	1.405

Table 1.1: Functions ψ for the simulations

From the last part of the demonstration of theorem 1.3.1, we expect,

$$\frac{\partial\lambda_F(a,\psi_{pk})}{\partial a}_{|a=T} > \frac{\partial\lambda_F(a,\psi_{sq})}{\partial a}_{|a=T} > \frac{\partial\lambda_F(a,\psi_{sin})}{\partial a}_{|a=T},$$

we give figure 1.4 as a confirmation. Finally we give some simulations to illustrate our remarks on chronotherapy.

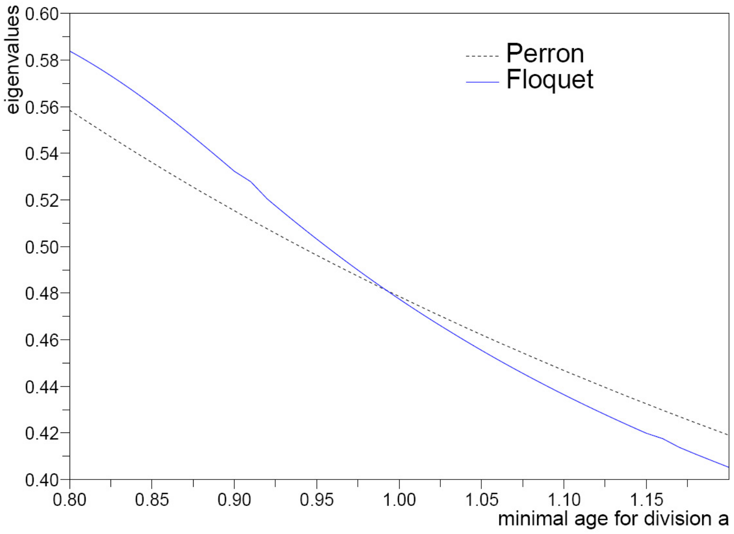

Figure 1.2: Crossing of the Perron and Floquet curves (detail) for $\psi = \psi_{\text{sin}}$.

For the chronotherapy simulation we use the following parameter: we fix $I = 3$ (we consider S and G2 as a single phase). The parameter γ is a periodic function (with strong variations on a period to have a stronger effect of the parameter $\theta \in (0,1)$). We compute the eigenvalue for a death rate in phase 2 (phase S-G2) having the value $\varepsilon\gamma(t+\theta)$. We test several value of ε to determine whether or not the amplitude of the death rate changes the relative behavior of the eigenvalue with respect to θ.The coefficients have the form:

$$K_{i\to i+1}(t,x) = K_i\psi_i(t)\chi_{[a_i,\infty[}(x),$$

where K_i, a_i are positive, ψ_i is a positive 1 periodic function. We give a simulation for the case described in the appendix (a case for which we can compute explicitly $\int_0^\infty N_2\phi_2(t,x)dx$).

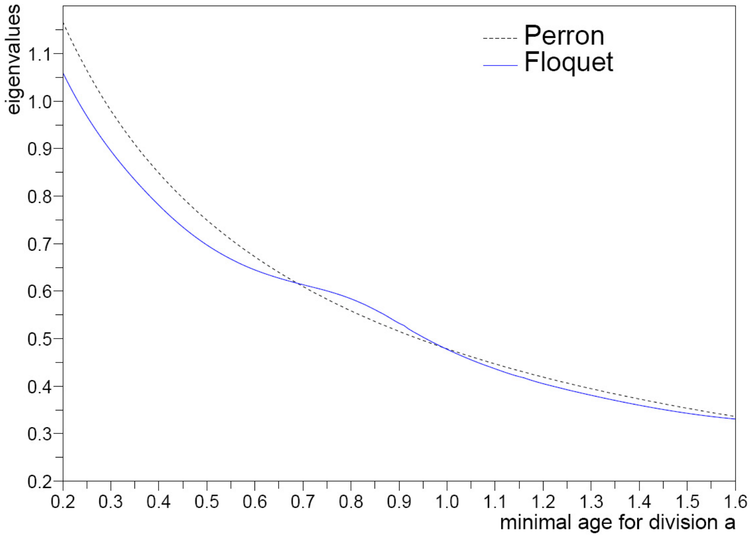

Figure 1.3: Crossing of the Perron and Floquet curves for $\psi = \psi_{\sin}$.

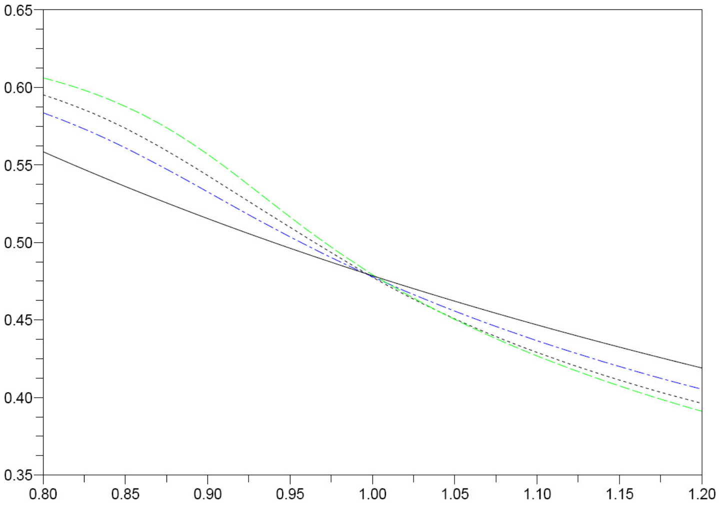

Figure 1.4: Crossing of the Perron and Floquet curves for $\psi = \psi_{\sin}$ (dash dot), ψ_{sq} (dots) and ψ_{pk} (long dash).

We fix $K_i = 10$ for all i, $a_1 = 10/24, a_2 = 12/24 = 0.5, a_3 = 2/24$, $\psi(t) = 1 + 0.9\cos(2\pi t)$ and ψ_i defined from ψ as in the appendix. We choose $\gamma(t) = \cos^6(2\pi t)$. With these choices of coefficients, we compute

$$\int_0^\infty N_2\phi_2(t,x)dx = C - C'\sin(2\pi t),$$

where C and C' are positive constants. Therefore, we have

$$\lim_{\varepsilon\to 0} \frac{\lambda^{\varepsilon,\theta} - \lambda^0}{\varepsilon} = C + C'\sin(2\pi\theta).$$

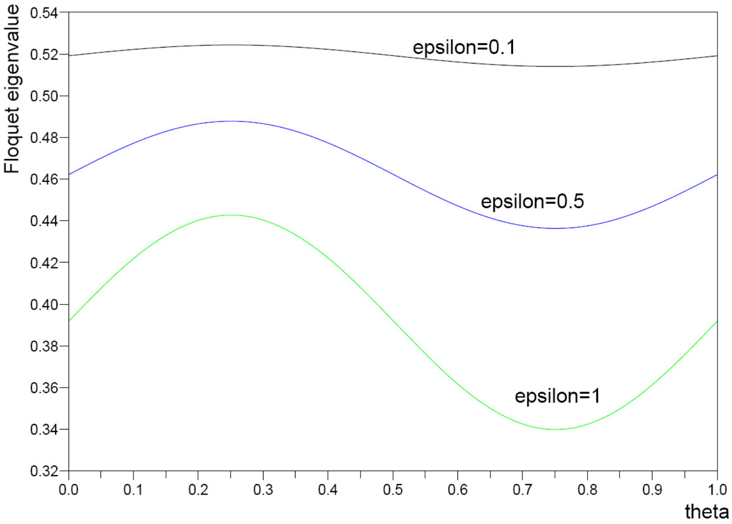

Figure 1.5: Variation of the Floquet eigenvalue with respect to the parameter θ for various amplitude for fixed γ and amplitude $\varepsilon = 0.1, 0.5, 1$ (from left to right).

In figure 1.5, we remark especially that the location of the optimal phase does not depend on ε (since we have $\theta_{\text{optimal}} = \frac{1}{4}$ whatever the value of ε) and corresponds exactly to the value of θ maximizing $\sin(2\pi\theta)$, i.e., minimizing $\int_0^1 \gamma(t+\theta)\int_0^\infty N_2\phi_2 dxdt$.

1.6 Concluding remarks

The results of the present paper show that the periodic control on the transition rate $K_{i\to i+1}$ of cell cycle models yields richer behaviors than in the case in which only the death rates d_i are subject to a periodic control [26, 27]. In particular, the inequality of [26, 27] does not carry over. This is, to our knowledge, the first time that such results are shown -on special cases of the control- analytically, thus confirming numerical results first shown in [26, 27].

Our results also indicate that multiphase cell proliferation models are the simplest candidates to represent the effects of chronotherapy. Indeed, as shown in section 1.4.1, in single-phase models, in the simple case when only death rates d_i are controlled by a periodic forcing term, the growth rate λ is modified by a term depending only on the average over a period of the forcing term, so that no phase of the periodic control function can be relevant to account for differences in the resulting growth rate, contrary to what is observed in chronotherapy [70]. Furthermore such multiphase models take into account the existence of multiple checkpoints , and we know from cell cycle physiology that the minimal number of checkpoints to consider is 2: at G1/S and G2/M.

We performed numerical and graphical results of section 1.5, on a 3-phase model with 1-periodic control on all phase transition functions $K_{i\to i+1}$, where one represents chronotherapy as a 1-periodic death term $\varepsilon\gamma$ of amplitude ε acting on the second phase (S/G2) only. These preliminary computational results, in particular performed in a simple analytically tractable case, seem to indicate that the effect of a chronotherapy on the growth rate $\lambda(\varepsilon,\theta)$ highly depends on the amplitude ε of the death rate but that the optimal phase θ (related to the best peak infusion phase) is independent on ε (see figure 1.5). In future work, we intend to introduce also an effect of chronotherapy on the transition rates $K_{i\to i+1}$.

From a more general point of view (i.e., independently of chronotherapeutic considerations), Theorem 1.3.1 analytically shows, at least in the single-phase case, that under the control of a periodic function exerting its influence on cell division, a selective advantage is given to those cells that are able to divide with a cell cycle duration slightly lower than the control function period. But, as numerically illustrated on Fig. 1.3, this cell cycle duration should be *not too much lower* than the control period, or else the advantage is lost. This leads to a biological speculation (or prediction): in a population of proliferating cells with variable cycle duration times, all being under the control of a common 24 h-periodic circadian clock, those cells that are well controlled by the clock, and endowed with a cycle duration between say 21 h and 23 h should quickly outnumber the others. Hence in proliferating healthy tissues (fast renewing tissues such as gut or bone marrow), an intrinsic cell cycle time of 21 to 23 h should be observed (if such an observation is possible).

Now to explain the initial tumour growth data that first motivated this study, we can speculate in the following way: tumour cells are less sensitive than healthy cells to circadian clock control (indeed it is known from chronotherapeutics in oncology that "in contrast with consistent rhythmic changes in drug tolerability mechanisms in host tissues, tumour rhythms appear heterogeneous with regard to clock gene expression and rhythm in pharmacology determinants as a function of tumour type and stage"[70]), so that their proliferation is more likely to be governed by a simple Perron eigenvalue rather than by one of the Floquet type. Tumour surrounding healthy cells and host immune cells, in contrast with tumour cells, are still under circadian control and they may thus have a selective advantage over cancer cells as long as this circadian control is present. Circadian clock disruption by perturbed light-dark cycle destroys this advantage, and these perturbed host cells oppose in a less efficient way local tissue invasion by cancer cells, hence the resulting curves shown in the introduction. Of course such speculation remains to be documented (in particular by investigating differential circadian clock control on proliferation in tumour and healthy tissues), but this is our best explanation so far for this phenomenon.

1.6.1 Existence theory for λ

This part is dedicated to the demonstration of the existence of the Floquet eigenvalue. Particularly, we try to prove it under general hypothesis on the periodic function ψ. For instance, a short adaptation of the demonstration given in [82] would be sufficient for the case of a positive continuous periodic function ψ, but one would like to have the possibility of studying non smooth functions such as a square wave (which for instance could have value 1 during the day and 0 during the night). We give a proof of the existence of the Floquet eigenvalue in the one-phase model. It can easily be adapted for a multiphase-model with out death rates where the coefficients would have the form $K_{i\to i+1} = K_i\psi_i(t)\chi_{[a_i,+\infty[}$ with the same hypothesis on the functions ψ_i. We prove here existence of a solution to three eigenproblems: the direct eigenproblem

$$\begin{cases} \partial_t N(t,x) + \partial_x N(t,x) + (\lambda + K\psi(t)\chi_{[a,+\infty[}(x))N(t,x) = 0, \\ N(t,0) = 2K\psi(t)\int_a^\infty N(t,x)dx, \\ N \geq 0, \qquad \int_0^\infty N dx = 1, \end{cases} \tag{1.30}$$

the dual eigenproblem

$$\begin{cases} -\partial_t\phi(t,x) - \partial_x\phi(t,x) + (\lambda + K\psi(t)\chi_{[a,+\infty[}(x))\phi(t,x) = 2K\psi(t)\chi_{[a,\infty[}(x)\phi(t,0), \\ \phi > 0, \quad \int_0^\infty N\phi dx = 1, \end{cases} \tag{1.31}$$

and the delay differential equation

$$\dot{P}(t) = -(K\psi(t) + \lambda)P(t) + 2Ke^{-\lambda a}\psi(t-a)P(t-a), \qquad P > 0, \int_0^1 P(t)dt = 1. \tag{1.32}$$

We give a normalization for P to ensure uniqueness.

Theorem 1.6.1 *For any positive T-periodic bounded function $\psi \neq 0$, $a \geq 0$ here exists a unique λ, N, ϕ, P such that $P > 0$ is solution to (1.9) and $N \geq 0$ is solution to (1.6) ($N > 0$ if ψ is positive).*

The proof is based on the Krein-Rutman theorem (see [32] for instance). We consider a T-periodic nonnegative bounded function $\psi \neq 0$. We adapt the proof from [82] to our case. First, using the methods of characteristics for the partial differential equations, we reduce the eigenproblems to integral equations on $N(t,0)$, $\phi(t,0)$ and P. We consider three operators depending on a parameter μ. For a bounded T-periodic function $\mathcal{M}$, we define $\mathcal{N}_i = \mathcal{L}_i(\mathcal{M})$ by

$$\mathcal{N}_1(t) \quad = \quad 2K\int_a^\infty \psi(t-x)e^{-\mu x - K\int_a^x \psi(t-x+s)ds}\mathcal{M}(t-x)dx, \tag{1.33}$$

$$\mathcal{N}_2(t) \quad = \quad 2K\int_a^\infty \psi(t)e^{-\mu x - K\int_a^x \psi(t-x+s)ds}\mathcal{M}(t-x)dx, \tag{1.34}$$

$$\mathcal{N}_3(t) \quad = \quad 2K\int_a^\infty \psi(t+x)e^{-\mu x - K\int_a^x \psi(t+s)ds}\mathcal{M}(t+x)dx. \tag{1.35}$$

These operators are defined such that for $\mu = \lambda$, we get,

$$\begin{aligned} P(t) &= \mathcal{L}_1(P)(t), \\ N(t,0) &= \mathcal{L}_2(N(.,0))(t), \\ \phi(t,0) &= \mathcal{L}_3(\phi(.,0))(t). \end{aligned}$$

This means that the functions should be nonnegative eigenvectors of these three operators associated to the eigenvalue 1.

Lemma 1.6.2 *For $\mu \geq 0$,*

- *$\mathcal{L}_i$ maps $L^\infty_{per}(0,T)$ into itself,*
- *$\mathcal{L}_1, \mathcal{L}_3$ are continuous compact operators on $C_{per}(0,T)$,*
- *$\mathcal{L}_1, \mathcal{L}_3$ are strongly positive and $\mathcal{L}_2$ is nonnegative (strongly positive if $\psi > 0$).*

Proof. For $\mathcal{M}$ bounded, one has, since for $x > a$, $\int_a^x \psi(t)dt \leq \langle\psi\rangle(x-a) + \|\psi\|_\infty T$,

$$\|\mathcal{L}_i(M)\|_\infty \leq 2\frac{\|\psi\|_\infty}{\langle(\psi)\rangle} e^{K\|\psi\|_\infty T}\|\mathcal{M}\|_\infty = C\|\mathcal{M}\|_\infty.$$

For continuity and compactness we only explicit the proof for $i = 1$, the case $i = 3$ is very similar. We consider $\mathcal{M}$ continuous and h small,

$$\begin{aligned}
\mathcal{N}_1(t+h) &= 2K\int_a^\infty \psi(t+h-x)e^{-\mu x - K\int_a^x \psi(t+h-x+s)ds}\mathcal{M}(t+h-x)dx,\\
&= 2K\int_{a-h}^\infty \psi(t-x)e^{-\mu(x+h) - K\int_a^{x+h} \psi(t-x+s)ds}\mathcal{M}(t-x)dx,\\
&= 2K\int_{a-h}^a \psi(t-x)e^{-\mu(x+h) - K\int_a^{x+h} \psi(t-x+s)ds}\mathcal{M}(t-x)dx\\
&+ 2K\int_a^\infty \psi(t-x)e^{-\mu(x+h) - K\int_a^{x+h} \psi(t-x+s)ds}\mathcal{M}(t-x)dx,\\
&= A_h\\
&+ 2K\int_a^\infty \psi(t-x)e^{-\mu x - K\int_a^x \psi(t-x+s)ds}\left(e^{-\mu h - K\int_0^h \psi(t+s)ds} - 1\right)\mathcal{M}(t-x)dx\\
&+ 2K\int_a^\infty \psi(t-x)e^{-\mu x - K\int_a^x \psi(t-x+s)ds}\mathcal{M}(t-x)dx,\\
&= A_h + B_h + \mathcal{N}_1(t).
\end{aligned}$$

We have bounds on A_h and B_h,

$$|A_h| \leq 2K\|\psi\|\|\mathcal{M}\|_\infty h,$$

$$|B_h| \leq K\|\psi\|_\infty h\|\mathcal{N}_1\|_\infty \leq CK\|\psi\|_\infty\|\mathcal{M}\|_\infty h.$$

Therefore, using (1.6.1),(1.6.1), we obtain the continuity and the compactness of operator $\mathcal{L}_1$. Using the same techniques we can prove continuity and compactness of operator $\mathcal{L}_3$. The operator $\mathcal{L}_2$ needs regularity on ψ to be compact (and continuous). All these operators are positive. We can apply the Krein-Rutman theorem (weak form [32]). We denote ρ_1, ρ_3 the spectral radii of respectively $\mathcal{L}_1, \mathcal{L}_3$. They are positive (since $\mathcal{L}(1) \geq \varepsilon > 0$, $\rho_1 \geq \varepsilon$), so are the associated nonnegative eigenfunctions. If $\mathcal{M}_1(t) = 0$, then

$$\psi(t-x)\mathcal{M}_1(t-x) = 0, \qquad \text{for} \quad x \geq a,$$

which leads to $\psi\mathcal{M}_1 \equiv 0$ and $\rho_1\mathcal{M}_1 \equiv 0$.Therefore $\mathcal{M}_1$ and similarly $\mathcal{M}_3$ can not vanish.

Lemma 1.6.3 *We have*

$$\mathcal{L}_2(\psi\mathcal{M}_1) = \rho_1\psi\mathcal{M}_1,$$

$$\rho_1 = \rho_3.$$

Proof. The first point is a straightforward computation. The second point uses the duality of operators $\mathcal{L}_2$ and $\mathcal{L}_3$,

$$\begin{aligned}
\int_0^T \mathcal{L}_2(\psi\mathcal{M}_1)(t), \mathcal{M}_3(t)dt &= \int_0^T \psi(t)\mathcal{M}_1(t)\mathcal{L}_3(\mathcal{M}_3)(t)dt,\\
\rho_1\int_0^T \psi(t)\mathcal{M}_1(t)\mathcal{M}_3(t)dt &= \rho_3\int_0^T \psi(t)\mathcal{M}_1(t)\mathcal{M}_3(t)dt.
\end{aligned}$$

The existence of a solution to (1.9) is equivalent to the existence of a positive fixed point of $\mathcal{L}_1$ for $\mu = \lambda$, therefore, we need to find μ such that $\rho_1(\mu) = 1$. For $\mu = 0$, we have

$$\mathcal{L}_3(1) = 2.$$

Therefore $\rho_1(0) = 2$. As ρ is a decreasing function of μ and $\rho_1(\infty) = 0$, there exists some positive λ such that $\rho_1(\lambda) = 1$. The solution to (1.9) is then given by such λ and $P = \mathcal{M}_1$. Then, the function N defined $N(t,0) = \psi(t)\mathcal{M}_1(t)$ and the characteristics

$$N(t,x) = N(t-x,0)e^{-\lambda x - \int_0^x K\psi(t-x+s)\chi_{[a,\infty[}(s)ds},$$

is solution to (1.6). We remark then, as $\lambda > 0$, that $N(t,\infty) = 0$. Similarly, we define ϕ by

$$\phi(t,x) = \int_x^\infty K\psi(t+y-x)\chi_{[a,\infty[}(y)\phi(t+y-x,0)e^{-\int_x^y \lambda + K\psi(t+s-x)\chi_{[a,\infty[}(s)ds}dy.$$

This is a solution to (1.31).

1.6.2 Explicit solutions for the multiphase eigenproblem

In the following $T = 1$.

We give here explicit solutions to the eigenproblem in the multiple phases case. We do not give details for the demonstration. We consider a 3 phase model without death terms, where the transition terms have the form:

$$K_{i\to i+1}(t,x) = K_i\psi_i(t)\chi_{[a_i,\infty[}(x).$$

Here, ψ_i is a positive 1-periodic function satisfying $\langle\psi_i\rangle = 1$. We consider the following very specific case: we choose $a_1, a_2, a_3 > 0$ such that $a_1 + a_2 + a_3 = 1$, and we choose ψ_i in the following way, for a fixed positive 1-periodic function ψ,

$$\begin{aligned} \psi_1(t) &= \psi(t), \\ \psi_2(t) &= \psi(t-a_2), \\ \psi_3(t) &= \psi(t-a_2-a_3). \end{aligned}$$

To explain the form of the coefficients, we make the following remark: if we denote $P_i(t) = \int_{a_i}^\infty N_i(t,x)dx$ (the same idea as for the one phase model), the 1-periodic functions P_i satisfies a system of delay differential equations and since $a_1 + a_2 + a_3 = 1$, the 1-periodic functions Q_i defined by $Q_1(t) = P_1(t), Q_2(t) = P_2(t+a_2), Q_3(t) = P_3(t+a_2+a_3)$ satisfy a system of ordinary differential equations.

$$\frac{d}{dt}\begin{pmatrix} Q_1(t) \\ Q_2(t) \\ Q_3(t) \end{pmatrix} = \begin{pmatrix} K_1\psi(t)+\lambda & 0 & -2K_3e^{-\lambda a_1}\psi(t) \\ -K_1e^{-\lambda a_2}\psi(t) & K_2\psi(t)+\lambda & 0 \\ 0 & -K_2e^{-\lambda a_3}\psi(t) & K_3\psi(t)+\lambda \end{pmatrix}\begin{pmatrix} Q_1(t) \\ Q_2(t) \\ Q_3(t) \end{pmatrix}.$$

We denote $M(t)$ the above matrix. Due to the special form of the functions ψ_i, we have $M(t)M(t') = M(t')M(t)$, for all t, t'. Therefore we can write

$$Q(t) = \exp\left(\int_0^t M(s)ds\right)Q(0).$$

The vector $Q(t)$ is 1-periodic, thus, $Q(0)$ has to be a positive eigenvector of $\exp(\int_0^1 M(s)ds)$ associated to the eigenvalue 1. The matrix $\exp(\int_0^1 M(s)ds)$ has eigenvalue 1 if and only if

$$(K_1+\lambda)(K_2+\lambda)(K_3+\lambda) - 2K_1K_2K_3e^{-\lambda(a_1+a_2+a_3)} = 0. \tag{1.36}$$

This leads to $Q_i(t) = e^{\lambda \int_0^t \tilde{\psi}(s)ds} Q_i(0)$, where as in section 3, $\tilde{\psi}(s) = \psi(s) - 1$ and $Q(0)$ is a positive vector satisfying $\int_0^1 M(s)dsQ(0) = 0$. Then, we can compute $P_i(t)$ and $N_i(t, 0)$. Finally, using the methods of characteristics, the eigenfunctions N_i are given, up to a normalization, by

$$\begin{aligned}
N_1(t,x) = &\quad 2K_3U_3\psi(t+a_1-x)e^{\lambda \int_0^{t-x+a_1} \tilde{\psi}(s)ds - \lambda x - \int_0^x K_1\psi(t-x+s)\chi_{[a_1,\infty[}(s)ds},\\
N_2(t,x) = &\quad K_1U_1\psi(t-x)e^{\lambda \int_0^{t-x} \tilde{\psi}(s)ds - \lambda x - \int_0^x K_2\psi(t-x+s-a_2)\chi_{[a_2,\infty[}(s)ds},\\
N_3(t,x) = &\quad K_2U_2\psi(t-a_2-x)e^{\lambda \int_0^{t-x-a_2} \tilde{\psi}(s)ds - \lambda x - \int_0^x K_3\psi(t-x+s-a_2-a_3)\chi_{[a_3,\infty[}(s)ds},
\end{aligned}$$

where

$$\begin{pmatrix} U_1 \\ U_2 \\ U_3 \end{pmatrix} = \begin{pmatrix} 1 \\ \frac{K_1 e^{-\lambda a_2}}{K_2+\lambda} \\ \frac{K_1+\lambda}{2K_3 e^{-\lambda a_1}} \end{pmatrix}.$$

The adjoint eigenfunctions are given by the formulas

$$\begin{aligned}
\phi_1(t,x) &= e^{-\lambda \int_0^{t-a_2-a_3-\min(x,a_1)} (\psi(s)-1)ds + \lambda \min(x,a_1)} V_1,\\
\phi_2(t,x) &= e^{-\lambda \int_0^{t-\min(x,a_2)} (\psi(s)-1)ds + \lambda \min(x,a_2)} V_2,\\
\phi_3(t,x) &= e^{-\lambda \int_0^{t-a_2-\min(x,a_3)} (\psi(s)-1)ds + \lambda \min(x,a_3)} V_3,
\end{aligned}$$

where

$$\begin{pmatrix} V_1 \\ V_2 \\ V_3 \end{pmatrix} = \begin{pmatrix} 1 \\ \frac{K_1+\lambda}{K_1 e^{-\lambda a_1}} \\ \frac{2K_3 e^{-\lambda a_3}}{K_3+\lambda} \end{pmatrix}.$$

Basically, the ideas for the computations of ϕ_i are the same, based on the following remark, as

$$\phi_i(t,x) = \int_0^\infty K_{i\to i+1}(t+y, x+y)\phi_{i+1}(t+y, 0)e^{-\int_0^y \lambda + K_{i\to i+1}(t+y', x+y')dy'} dy,$$

(with a factor 2 for $i = 3$), we have $\phi_i(t,x) = \phi_(t, a_i)$ for $a \geq a_i$. This leads to a differential equation for $\phi_i(t, 0)$. Details are left to the reader. In this case, we compute $\int_0^\infty N_i(t,x)\phi_i(t,x)dx$. As we have $\phi_i(t,x) = \phi_i(t,a_i)$ for $x \geq a_i$,

$$\int_0^\infty N_i(t,x)\phi_i(t,x)dx = \int_0^{a_i} N_i(t,x)\phi_i(t,x)dx + \phi_i(t,a_i)\int_{a_i}^\infty N_i(t,x)dx.$$

We have

$$\begin{aligned}
\int_0^\infty N_1(t,x)\phi_1(t,x) &= (K_1+\lambda)e^{\lambda a_1}\int_0^{a_1} \psi(t-x+a_1)dx + U_1V_1e^{\lambda a_1},\\
\int_0^\infty N_2(t,x)\phi_2(t,x)dx &= (K_1+\lambda)e^{\lambda a_1}\int_0^{a_2} \psi(t-x)dx + U_2V_2e^{\lambda a_2},\\
\int_0^\infty N_3(t,x)\phi_3(t,x)dx &= (K_1+\lambda)e^{\lambda a_1}\int_0^{a_3} \psi(t-a_2-x)dx + U_3V_3e^{\lambda a_3}.
\end{aligned}$$

Particularly, in this case, $\int_0^\infty N_i\phi dx$ is not always constant. We denote $\Psi(t) = \int_0^t (\psi(s)-1)ds$, it is a 1 periodic function. We also denote $C_i = U_iV_ie^{\lambda a_i}, C = (K_1+\lambda)e^{\lambda a_1}$, both these constants are positive,

$$\begin{aligned}
\int_0^\infty N_1(t,x)\phi_1(t,x) &= C(a_1+\Psi(t)-\Psi(t+a_1))+C_1,\\
\int_0^\infty N_2(t,x)\phi_2(t,x)dx &= C(a_2+\Psi(t-a_2)-\Psi(t))+C_2,\\
\int_0^\infty N_3(t,x)\phi_3(t,x)dx &= C(a_3+\Psi(t+a_1)-\Psi(t-a_2))+C_3.
\end{aligned}$$

For instance, using the parameters of the simulation, we have, $\Psi(t)=\frac{0.9}{2\pi}\sin(2\pi t)$, $a_2=0.5$,

$$\int_0^\infty N_2\phi_2(t,x)dx=(Ca_2+C_2)-2C\frac{0.9}{2\pi}\sin(2\pi t)=C'-C_2'\sin(2\pi t),$$

$$\int_0^1\gamma(t+\theta)\int_0^\infty N_2\phi_2(t,x)dx=C'\int_0^1\cos^6(2\pi(t+\theta))dt-C_2'\int_0^1\cos^6(2\pi(t+\theta))\sin(2\pi t)dt,$$

a short computation leads to

$$\gamma(t)=\frac{1}{32}\cos(6\pi t)+\frac{3}{24}\cos(4\pi t)+\frac{15}{32}\cos(2\pi t)+\frac{5}{16},$$

therefore,

$$\int_0^1\gamma(t+\theta)\int_0^\infty N_2\phi_2(t,x)dx=C''-C_2''\sin(2\pi\theta),$$

where $C''\geq C_2''>0$. Therefore, in this particular case, we find that

$$\lim\frac{\lambda^{\varepsilon,\theta}-\lambda^0}{\varepsilon}=C_2''\sin(2\pi\theta)-C''.$$

Chapitre 2

Monotonie et asymptotique de la valeur propre de Floquet

Le travail présenté ici a été effectué en collaboration avec Stéphane Gaubert. Le but original était uniquement de déterminer le comportement asymptotique de la valeur propre de Floquet dans des cas dégénérés. En cherchant à prouver les théorèmes de la seconde partie, la nécessité s'est fait sentir de prouver des propriétés de monotonie des équations de division par rapport au taux de division. La non-stationnarité des coefficients s'est avéré pouvoir produire des contre exemples à cette propriété. L'outil introduit pour prouver des conditions suffisantes de monotonie a alors permis d'établir une preuve des résultats asymptotique, en examinant le système d'un point de vue trajectoriel.

2.1 Introduction

Periodicity in populations dynamics The introduction of time periodicity has been quite early studied in population dynamics for describing the seasonal rhythms or cyclic actions. For instance, one can think of the optimal harvesting problem, the spread of diseases transmitted by mosquitoes. Periodicity may also be introduced for modelling a cyclic action on a system which dynamics is not necessarily periodic but can be sensitive to some periodic forcing (see recently [9]). More recently, periodicity appeared also to be relevant at a smaller scale for cell population dynamics, especially in cancer modelling, either by taking advantage of the difference of characteristic times of cancerous and healthy cells for (this is the guideline of resonance therapy [37]) or looking at the importance of the sensitivity of healthy cells to external 24-h rhythms (also called circadian rhythms), both for cancer incidence and cancer therapy (chronotherapy). This motivates a big interest on equations with periodic forcing in population dynamics. The introduction of time periodicity in linear models gives rise to a generalization of Floquet theory for ordinary differential equation and a study of eigenelements of the corresponding equations (see [38, 82] for instance).

The model We consider the renewal-division equation for a population of cells structured in age x described by the density $n(t,x)$, following the pure division model

$$\begin{cases} \dfrac{\partial n}{\partial t} + \dfrac{\partial n}{\partial x} + K(t,x)n(t,x) = 0, \\ n(t,0) = 2\int_0^\infty K(t,x)n(t,x)dx, \\ n(0,x) = n^0(x) \quad \textit{given}. \end{cases} \tag{2.1}$$

The dynamics of a population is governed by its first (Floquet) eigenvalue λ and the associated eigenvectors N, ϕ. The former is the solution of the eigenproblem

$$\begin{cases} \dfrac{\partial N}{\partial t} + \dfrac{\partial N}{\partial x} + (K(t,x)+\lambda)N(t,x) = 0, \\ N(t,0) = 2\int_0^\infty K(t,x)N(t,x)dx, \\ N \geq 0, \quad T-\text{periodic},\ N \not\equiv 0. \end{cases} \tag{2.2}$$

whereas the latter is the solution of the adjoint eigenproblem

$$\begin{cases} \dfrac{\partial \phi}{\partial t} + \dfrac{\partial \phi}{\partial x} - (K(t,x)+\lambda)\phi(t,x) = -2K(t,x)\phi(t,0), \\ \phi > 0, \quad T-\text{periodic}. \end{cases} \tag{2.3}$$

We normalize first the eigenvector N by

$$\int_0^T \int_0^\infty N(s,x)dsdx = 1 \tag{2.4}$$

and then, the adjoint eigenvector ϕ, by requiring

$$\int_0^\infty N(t,x)\phi(t,x)dx = 1, \qquad \forall t \tag{2.5}$$

(the latter integral is easily seen to be independent of t).

The importance of this eigenvalue can be illustrated through the General Relative Entropy theory. We refer the reader to [92, 82] for more background. In particular, the quantity $ne^{-\lambda t}$ satisfies a kind of conservation law

$$\int_0^\infty n(t,x)e^{-\lambda t}\phi(t,x)dx = \int_0^\infty n(0,x)\phi(0,x)dx, \tag{2.6}$$

(and for any integer p, $\int_0^\infty n(pT,x)\phi(0,x)dx = e^{p\lambda T}\int_0^\infty n(0,x)\phi(0,x)dx$, due to the periodicity of ϕ). We also have the following inequality

$$\frac{d}{dt}\int_0^\infty |n(t,x)e^{-\lambda t} - \rho N(t,x)|\phi(t,x)dx \leq 0, \tag{2.7}$$

where $\rho = \int_0^\infty n(0,x)\phi(0,x)dx$. Actually, the latter integral is known to converge to zero as $t \to \infty$[82].

Main results The purpose of the paper is to derive the asymptotics of the growth rate when the division becomes instantaneous, meaning that in the expression $K(t,x) = K\psi(t)B(x)\mathbb{1}_{[a,+\infty[}(x)$ of the division rate, the parameter K tends to ∞.

For that purpose, we study the monotonicity of the eigenvalue λ_F with respect to the division coefficient $K(t,x)$. Surprisingly, increasing $K(.,.)$ is not always a benefit for the growth population.

Theorem 2.1.1 *There exists configurations such that*

$$\forall (t,x), \qquad 0 \le K^1(t,x) \le K^2(t,x),$$

and the corresponding eigenvalues satisfy

$$\lambda_F^1 > \lambda_F^2.$$

We give an explicit counterexample. However, the following theorem identifies a subclass of transition rates for which the Floquet eigenvalue is a monotone function of the transition rate.

Theorem 2.1.2 *If* K^1 *satisfies*

$$v \mapsto \int_v^t K^1(s, s-v)ds \qquad \text{is nondecreasing for any } t,$$

then for all $K^2 \ge 0$,

$$\big(\forall (t,x) K^2(t,x) \ge K^1(t,x)\big) \quad \Rightarrow \quad \lambda_F^2 \ge \lambda_F^1,$$
$$\big(\forall (t,x) K^2(t,x) \le K^1(t,x)\big) \quad \Rightarrow \quad \lambda_F^2 \le \lambda_F^1.$$

A typical division rate may have the form $K(t,x) = K\psi(t)B(x)\mathbb{1}_{[a,+\infty[}(x)$, where $\mathbb{1}_{[a,\infty[}$ denotes the indicator function of the set $[a,\infty[$. Equation (2.1) represents the aging and division of cells. Due to the structure of K, cells can only divide after age a. Then, the division rate is determined in particular by a periodic function $\psi(t)$, which models the circadian control. The period T represents one day.

The function B is assumed to be bounded, positive, of infinite integral,

$$B \in L^\infty(\mathbb{R}^+), \quad B > 0, \quad \int_{\mathbb{R}^+} B = +\infty \tag{2.8}$$

We shall also need the technical condition

$$\tau_h B - B \xrightarrow[h\to 0]{} 0 \text{ in } L^1_{\text{loc}}(\mathbb{R}^+), \tag{2.9}$$

where $\tau_h B(x) = B(x+h)$ if $x+h \ge 0$, 0 otherwise, which is used for the existence theory for the Floquet eigenvalue (see the appendix). The reader should keep in mind for instance that this is satisfied if B is continuous or BV_{loc}.

When $\inf \psi > 0$, the intuition predicts that the growth rate goes to the limit $\log 2/a$, because every cell will divide shortly after reaching age a when the parameter K is large. Our first result shows that this is the case.

Theorem 2.1.3 *Suppose that* ψ *is a bounded* T*-periodic function with* $\inf \psi > 0$, *and that* B *is a positive bounded function satisfying* (2.8),(2.9). *Then, for all* $K > 0$,

$$0 \ \le \lambda_F(K) \le \ \frac{\log(2)}{a}, \tag{2.10}$$

and

$$\lim_{K\to\infty} \lambda_F(K) \ = \ \frac{\log(2)}{a}. \tag{2.11}$$

When ψ vanishes, we show that complex synchronization phenomena appear. We shall assume typically that ψ has a square wave shape, i.e., that ψ is a T-periodic function such that, for some $0 < \tau < T$,

$$\psi(t) = \begin{cases} 1 & \text{for } t \in [0,\tau) \\ 0 & \text{for } t \in [\tau, T) \end{cases}. \tag{2.12}$$

Theorem 2.1.4 (Discrete limit) *Suppose that the division rate is given by* $K(t,x) = K\psi(t)\mathbb{1}_{[a,\infty)}(x)$*, where* ψ *is given by (2.12). Denote* $W_\tau = [\tau, T] + \mathbb{N}T$ *and*

$$N_a a = \min W_\tau \cap \mathbb{N}a,$$

then the limit of $\lambda^K(a)$ *when* $K \to +\infty$ *is given by*

$$\lambda^\infty(a) = \frac{N_a}{\lceil N_a a/T \rceil T}. \tag{2.13}$$

Moreover, we have the estimate

$$\lambda^\infty(a,\tau) \geq \lambda^K(a,\tau) \geq \lambda^\infty(a)\big(1 + \log(1 - e^{-Kr(a)})\big) = \lambda^\infty(a)(1 - e^{-Kr(a)} + o(e^{-Kr(a)})), \tag{2.14}$$

with $0 < r(a) < \lceil N_a a/T \rceil T - N_a a$ *if* $\lceil N_a a/T \rceil T - N_a a > 0$*.*

The formula (2.13) is derived intuitively in Section 2.3.2, by introducing a simple discrete dynamical system, equipped with a multiplicative functional, the asymptotic geometric mean of which yields $\lambda^\infty(a)$. The existence of such a simple asymptotic formula reflects the fact that the Perron-Frobenius operator describing the evolution of the population degenerates as $K \to \infty$. The rate of convergence $r(a)$ appears naturally throughout the proof of convergence. One can remark a particular case where the formula can be rewritten in terms of integer parts. If $\tau/T < 1/2$, and $0 < a = pT + b$ where $p \in \mathbb{N}$ and $0 \leq b < T$, then, we have

$$\lambda^\infty(a) = \frac{\lceil b/\tau \rceil}{\lceil b/\tau \rceil p + 1} \log 2.$$

When ψ vanishes, we may consider $\psi^\varepsilon(t) := \psi(t) + \varepsilon$, with $\varepsilon > 0$, and define the growth rate $\lambda(\epsilon, K)$ with an obvious notation. A comparison of the previous theorems shows that the limits in K and ε do not commute

$$\frac{\log(2)}{a} = \lim_{\varepsilon \to 0} \lim_{K \to \infty} \lambda(\epsilon, K) \neq \lim_{K \to \infty} \lim_{\varepsilon \to 0} \lambda(\epsilon, K) = \lambda^\infty(a) \ .$$

2.2 Monotonicity with respect to the division rate

We first focus on the question of the monotonicity of the Floquet eigenvalue with respect to the division rate. We begin with a counter example.

2.2.1 A counterexample

We next show that increasing the division rate may decrease the growth rate of the population. It will be convenient to write

$$\chi(t) := \mathbb{1}_{[0,\alpha)+\mathbb{Z}}(t) \ ,$$

for some $\alpha \in (0,1)$. We assume that the division rate is of the form

$$K(t,x) = \chi(t-x)K_1(t) + (1 - \chi(t-x))K_2(t) \ .$$

Thus,

- when an individual is born in $[0, \alpha[+\mathbb{Z}$, then the next division occurs with a rate K_1,
- when an individual is born in $[\alpha, 1[+\mathbb{Z}$, then the next division occurs with a rate K_2,

since with the characteristics, one can read this as:

$$n(t,x) = \left\{ \begin{array}{ll} n(t-x,0)e^{-\int_0^x K_1(t+s)ds}, & \text{if} \quad t-x \in [0,\alpha[+\mathbb{Z}, \\ n(t-x,0)e^{-\int_0^x K_2(t+s)ds}, & \text{if} \quad t-x \in [\alpha,1[+\mathbb{Z}. \end{array} \right.$$

We may give some intuitive interpretation: we can for instance consider that $\chi = 1$ during the day and $\chi = 0$ during the night. Being born during the night or the day influences the behaviour. One could then consider that there are actually two subpopulations corresponding respectively to individuals born in $[0,\alpha[+\mathbb{Z}$ (the day), and individuals born in $[\alpha,1[+\mathbb{Z}$ (the night). We have

$$n_1(t,x) = n(t,x)\chi(t-x), \qquad n_2(t,x) = n(t,x)(1-\chi(t-x)).$$

They satisfy the equations:

$$\left\{ \begin{array}{l} \partial_t n_1 + \partial_x n_1 + K_1(t) n_1 = 0, \\ \partial_t n_2 + \partial_x n_2 + K_2(t) n_2 = 0, \\ n_1(t,0) = 2\chi(t) \int_0^\infty (K_1(t) n_1(t,x) + K_2(t) n_2(t,x))dx, \\ n_2(t,0) = 2(1-\chi(t)) \int_0^\infty (K_1(t) n_1(t,x) + K_2(t) n_2(t,x))dx, \end{array} \right.$$

which leads to the following system of ODEs: if $P_i = \int_0^\infty n_i(t,x)dx$,

$$\frac{d}{dt} \left(\begin{array}{c} P_1 \\ P_2 \end{array} \right) = \left(\begin{array}{cc} (2\chi(t)-1)K_1(t) & 2\chi(t)K_2(t) \\ (2-2\chi(t))K_1(t) & (1-2\chi(t))K_2(t) \end{array} \right) \left(\begin{array}{c} P_1 \\ P_2 \end{array} \right)$$

we denote

$$M(t) = \left(\begin{array}{cc} (2\chi(t)-1)K_1(t) & 2\chi(t)K_2(t) \\ (2-2\chi(t))K_1(t) & (1-2\chi(t))K_2(t) \end{array} \right).$$

In order to simplify the computations, we choose K_1, K_2 of the special form

$$K_1(t) = a_1\chi(t) + b_1(1-\chi(t)), \quad K_2(t) = a_2\chi(t) + b_2(1-\chi(t)),$$

and the coefficients a_i, b_i are constant. With this form of the coefficients, we obtain

$$M(t) = \chi(t) \left(\begin{array}{cc} a_1 & 2a_2 \\ 0 & -a_2 \end{array} \right) + (1-\chi(t)) \left(\begin{array}{cc} -b_1 & 0 \\ 2b_1 & b_2 \end{array} \right).$$

An important point here, still with the above interpretation is the following: a_2 and b_1 could be considered here in some sense as transition coefficients between populations n_1 and n_2.

We let the reader check that

$$M_a = \left(\begin{array}{cc} a_1 & 2a_2 \\ 0 & -a_2 \end{array} \right) = \left(\begin{array}{cc} 1 & -1 \\ 0 & \frac{a_2+a_1}{2a_2} \end{array} \right) \left(\begin{array}{cc} a_1 & 0 \\ 0 & -a_2 \end{array} \right) \left(\begin{array}{cc} 1 & \frac{2a_2}{a_2+a_1} \\ 0 & \frac{2a_2}{a_2+a_1} \end{array} \right)$$

$$M_b = \left(\begin{array}{cc} -b_1 & 0 \\ 2b_1 & b_2 \end{array} \right) = \left(\begin{array}{cc} \frac{b_1+b_2}{2b_1} & 0 \\ -1 & 1 \end{array} \right) \left(\begin{array}{cc} -b_1 & 0 \\ 0 & b_2 \end{array} \right) \left(\begin{array}{cc} \frac{2b_1}{b_1+b_2} & 0 \\ \frac{2b_1}{b_1+b_2} & 1 \end{array} \right).$$

Since the linear dynamics $M(t)$ switches between the dynamics M_a (which is exercised during the interval $[0,\alpha)$) and M_b (during the interval $[\alpha,1)$), we get:

$$\left(\begin{array}{c} P_1(1) \\ P_2(1) \end{array} \right) = \exp((1-\alpha)M_b) \exp(\alpha M_a) \left(\begin{array}{c} P_1(0) \\ P_2(0) \end{array} \right).$$

Using the above diagonalization, we compute

$$\exp(\alpha M_a) = \left(\begin{array}{cc} e^{\alpha a_1} & 2a_2 \frac{e^{\alpha a_1} - e^{-\alpha a_2}}{a_1+a_2} \\ 0 & e^{-\alpha a_2} \end{array} \right)$$

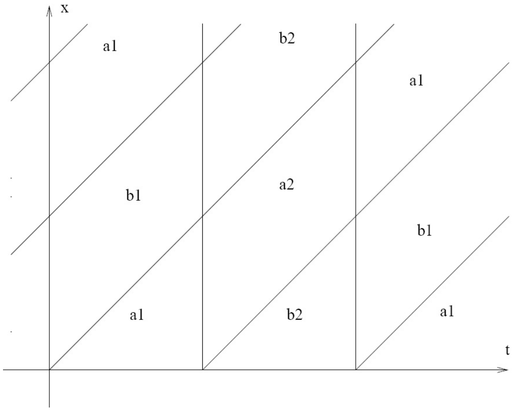

Figure 2.1: Values of K

$$\exp((1-\alpha)M_b) = \begin{pmatrix} e^{-(1-\alpha)b_1} & 0 \\ 2b_1\frac{e^{(1-\alpha)b_2}-e^{-(1-\alpha)b_1}}{b_1+b_2} & e^{(1-\alpha)b_2}. \end{pmatrix}.$$

To make it simpler, we fix $\alpha = \frac{1}{2}$. We let the reader check that denoting $R = \exp(\frac{1}{2}M_b)\exp(\frac{1}{2}M_a)$, we have

$$\det(R) = e^{\frac{a_1-a_2+b_2-b_1}{2}}, \qquad Tr(R) = e^{\frac{a_1-b_1}{2}} + e^{\frac{b_2-a_2}{2}} + 4\frac{a_2b_1}{(a_1+a_2)(b_1+b_2)}(e^{\frac{b_2}{2}} - e^{\frac{-b_1}{2}})(e^{\frac{a_1}{2}} - e^{\frac{-a_2}{2}}).$$

The spectral radius $\rho(a_1, a_2, b_1, b_2)$ is given by

$$\rho(a_1, a_2, b_1, b_2) = \frac{Tr(R) + \sqrt{Tr(R)^2 - 4\det(R)}}{2},$$

and is a continuous function of the coefficients. It is straightforward to see that $\rho(10, 0.1, 0, 0) = e^5$ and that

$$\rho(10, 0.1, \infty, b_2) = e^{\frac{b_2-0.1}{2}} + 4\frac{0.1}{(10.1)}e^{\frac{b_2}{2}}(e^{\frac{10}{2}} - e^{\frac{-0.1}{2}}) \leq e^{b_2/2}(0.96 + 5.84).$$

We may choose b_2 small enough so that $e^{b_2/2}(0.96 + 5.84) < \frac{e^5}{2}$. Then, $\rho(10, 0.1, 0, 0) > \rho(10, 0.1, \infty, b_2)$. By the definition of the latter quantity, we can find $b_1 > 0$ such that $\rho(10, 0.1, 0, 0) > \rho(10, 0.1, b_1, b_2)$. Then, by continuity of ρ, we can find small enough parameters b_1' and b_2', which may chosen less than b_1 and b_2, respectively, such that $\rho(10, 0.1, b_1', b_2') > \rho(10, 0.1, b_1, b_2)$. It follows that ρ is not nondecreasing. $\square$

We give a numerical illustration of this phenomenon.

Remark 2.2.1 *The system does not enter the framework considered in Appendix for the existence of the Floquet eigenvalue. However we did study its behaviour through the study of the spectral radius of R since there exists an adjoint positive eigenvector to $M(t)$ thanks to Floquet theory,*

$$-\frac{d}{dt}\begin{pmatrix} \phi_1 & \phi_2 \end{pmatrix} + \lambda\begin{pmatrix} \phi_1 & \phi_2 \end{pmatrix} + \begin{pmatrix} \phi_1 & \phi_2 \end{pmatrix} M(t) = 0,$$

and we have

$$\frac{d}{dt}(\phi(t), P(t)) = \lambda(\phi(t), P(t))$$

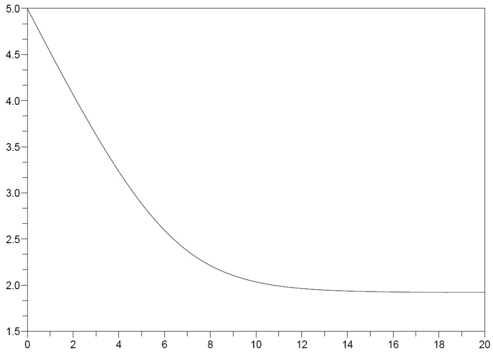

Figure 2.2: Growth exponent as a function of b_1 when $a_1 = 10, a_2 = 0.1, b_2 = 0.01, \alpha = 0.5$. In this case, increasing b_1 (and that way increasing the division rate K) might decrease the growth exponent

which can be read as, denoting $\phi(t,x) = \phi_1(t)\chi(t-x) + \phi_2(t)(1-\chi(t-x))$,

$$\frac{d}{dt}\int_0^\infty n(t,x)\phi(t,x)dx = \lambda \int_0^\infty n(t,x)\phi(t,x)dx,$$

It is straightforward to check that if all the a_{ij} *are positive, so are* ϕ_1, ϕ_2*. In this case, there exists* $M \geq m > 0$ *such that* $m \leq \phi(t,x) \leq M$*, and therefore,*

$$me^{\lambda t}\int n^0 dx \leq \int n(t,x)dx \leq Me^{\lambda t}\int n^0 dx.$$

The eigenvalue λ *determinates the behaviour of the solutions.*

2.2.2 A sufficient condition for monotonicity

To avoid the situation of the above counterexample, we need to forbid the situation of "‘birthday penalty"’. We introduce the following condition on the division coefficient:

$$(t,v) \mapsto \int_v^t K(s,s-v)ds \quad \text{is nonincreasing in } v. \tag{2.15}$$

We can notice that this condition is fulfilled when K depends only on one of the two variables t and x. It is also fulfilled if for any t, $K(t,.)$ is a nondecreasing function (and particularly, in the case of separated variables $K(t,x) = \psi(t)B(x)$ when B is nondecreasing).

Theorem 2.2.2 *Provided* K^1 *or* K^2 *satisfies (2.15) and* $K^1 \geq K^2$*, then, for any* $n^0 \in L^1(\mathbb{R}_+)$*, if we denote* n^i *the solution of (2.1) with* $K = K^i$*, we have, for any* $t \geq 0$*,*

$$\int_0^\infty n^1(t,x)dx \geq \int_0^\infty n^2(t,x)dx.$$

Proof. We consider the following system of PDE:

$$\begin{cases} \partial_t n_i + \partial_x n_i + K(t,x)n_i = 0, & i \geq 0, \\ n_{i+1}(t,0) = \displaystyle\int_0^\infty K(t,x)n_i(t,x)dx, & \\ n_0(t=0,x) = n^0(x), \qquad n_i(t=0,x) = 0, & \text{for } i \geq 1. \end{cases} \tag{2.16}$$

We check easily that $n = \sum 2^i n_i$ is the solution to (2.1) and as before, we denote $(n_i^1)_i$, (resp. $(n_i^2)_i$) the solution to (2.16) with $K = K^1$ (resp. $K = K^2$). We introduce also the quantity S_j:

$$S_j(t) = \sum_{i \geq j} \int_0^\infty n_i(t,x)dx.$$

A short computation leads to

$$\int_0^\infty n(t,x)dx = S_0(t) + \sum_{j=1}^\infty 2^{j-1} S_j(t).$$

Lemma 2.2.3 *We have*

- $S_0(t) = S_0(0) = \int_0^\infty n^0(x)dx$,
- $S_1(t) = \int_0^\infty n^0(x)(1 - e^{-\int_0^t K(s,x+s)ds})dx$,
- $S_j(t) = \int_{v=0}^t n_{j-1}(v,0)(1 - e^{-\int_0^{t-v} K(v+s,s)ds})dv = \int_0^t n_{j-1}(v,0)P(t,v)dv$ *for* $j \geq 2$.

Proof. It is straightforward to show that for any j,

$$\frac{d}{dt} S_j(t) = n_j(t,0) \qquad \text{and therefore,} \quad S_j(t) = \int_0^t n_j(u,0)du$$

This leads immediately to the first statement ($\forall t > 0, n_0(t,0) = 0$). For the second statement, we use the characteristics:

$$n_0(t,x) = 0, \quad \text{if } x \leq t, \qquad n_0(t,x) = n^0(x-t)e^{-\int_0^t K(s,x-t+s)ds}, \quad \text{if } x \geq t.$$

Therefore, we have

$$S_1(t) = \int_0^t \int_u^\infty K(u,x)n^0(x-u)e^{-\int_0^u K(s,x-u+s)ds}dxdu = \int_0^t \int_0^\infty K(u,u+x)n^0(x)e^{-\int_0^u K(s,x+s)ds}dxdu,$$

$$S_1(t) = \int_0^\infty n^0(x) \int_0^t K(u,u+x)e^{-\int_0^u K(s,x+s)ds}dudx = \int_0^\infty n^0(x)(1 - e^{-\int_0^t K(s,x+s)ds})dx,$$

which is the second statement. We consider now $j \geq 2$. Again, using the characteristics, we obtain

$$S_j(t) = \int_0^t \int_0^u K(u,x)n_{j-1}(u-x,0)e^{-\int_0^x K(u-x+s,s)ds}dxdu = \int_{x=0}^t \int_{u=x}^t K(u,x)n_{j-1}(u-x,0)e^{-\int_0^x K(u-x+s,s)ds}dudx.$$

$$S_j(t) = \int_{x=0}^t \int_{v=0}^{t-x} K(v+x,x)n_{j-1}(v,0)e^{-\int_0^x K(v+s,s)ds}dvdx = \int_{v=0}^t n_{j-1}(v,0) \int_{x=0}^{t-v} K(v+x,x)e^{-\int_0^x K(v+s,s)ds}dxdv,$$

which leads to the third statement.

We prove now the lemma implying theorem 2.2.2.

Lemma 2.2.4 *Suppose* K^1 *satisfies (2.15), then*

- *if* $K^2 \geq K^1$, *then* $\forall t, j \quad S_j^2(t) \geq S_j^1(t)$,
- *if* $K^2 \leq K^1$, *then* $\forall t, j \quad S_j^2(t) \leq S_j^1(t)$.

Proof. The proof is performed by induction on j. We remind the notation introduced in lemma 2.2.3:

$$P^k(t,v) = (1 - e^{-\int_0^{t-v} K^k(v+s,s)ds}).$$

It is straightforward thanks to Lemma 2.2.3 to check that it is satisfied for $j = 0, 1$. We use for heredity the following computation for $j \geq 2$:

$$\begin{aligned}
S_j^1(t) - S_j^2(t) &= \textstyle\int_0^t n_{j-1}^1(v,0)P^1(t,v)dv - \int_0^t n_{j-1}^2(v,0)P^2(t,v)dv,\\
&= \textstyle\int_0^t (n_{j-1}^1(v,0) - n_{j-1}^2(v,0))P^1(t,v)dv + \int_0^t n_{j-1}^2(v,0)(P^1(t,v) - P^2(t,v))dv,\\
&= \textstyle[(S_{j-1}^1(v) - S_{j-1}^2(v))P^1(t,v)]_0^t - \int_0^t (S_{j-1}^1(v) - S_{j-1}^2(v))\frac{d}{dv}P^1(t,v)\\
&+ \textstyle\int_0^t n_{j-1}^2(v,0)(P^1(t,v) - P^2(t,v))dv,\\
&= \textstyle-\int_0^t (S_{j-1}^1(v) - S_{j-1}^2(v))\frac{d}{dv}P^1(t,v) + \int_0^t n_{j-1}^2(v,0)(P^1(t,v) - P^2(t,v))dv.
\end{aligned}$$

The condition (2.15) ensures the nonnegativity of $\frac{d}{dv}P^1(t,v)$, we can then conclude since, it is straightforward that $K^2 \geq K^1$ implies $P^2 \geq P^1$.

2.3 Asymptotics of the growth rate

2.3.1 When both ψ and B are positive: proof of theorem 2.1.3

Under conditions we can define as in (2.1) for $K > 0$, the Floquet eigenvalue $\lambda_F(K)$

$$\begin{cases}
\frac{\partial}{\partial t}N^K(t,x) + \frac{\partial}{\partial x}N^K(t,x) + \left[\lambda_F(K) + K\psi(t)B(x)\mathbb{1}_{[a,+\infty[}(x)\right]N^K(t,x) = 0,\\
N^K(t,0) = 2K\psi(t)\int_a^\infty B(x)N^K(t,x)dx,\\
N^K > 0,\ T\text{-periodic.}
\end{cases} \tag{2.17}$$

and we normalize N^K by

$$\int_0^T \int_0^\infty N^K(t,x)dxdt = 1, \tag{2.18}$$

Proof. We introduce the stationary eigenvalues $\lambda_{\min}^K$ and $\bar{\lambda}(K)$ associated respectively to division coefficients $K\min(\psi)B(x)$ and $K\max(\psi)B(x)$. As we have obviously

$$K\min(\psi)B(x) \leq K\psi(t)B(x) \leq K\max(\psi)B(x),$$

we have using the monotonicity property,

$$\underline{\lambda}(K) \leq \lambda_F(K) \leq \bar{\lambda}(K). \tag{2.19}$$

On the other hand, we have,

$$\begin{aligned}
2\int_a^\infty K\min(\psi)B(x)e^{-\underline{\lambda}(K)x - K\min(\psi)\int_a^x B(y)dy} &= 1,\\
2\int_a^\infty K\max(\psi)B(x)e^{-\bar{\lambda}(K)x - K\max(\psi)\int_a^x B(y)dy} &= 1,
\end{aligned}$$

hence,

$$1 \leq e^{-\bar{\lambda}(K)a} 2\int_a^\infty K\max(\psi)B(x)e^{-K\max(\psi)\int_a^x B(y)dy} = 2e^{-\bar{\lambda}(K)a},$$

therefore $\bar{\lambda}(K) \leq \frac{\log(2)}{a}$ which leads to the inequality. On the other hand from integration by parts,

$$1 = 2e^{-\underline{\lambda}(K)a} + \underline{\lambda}(K) \int_a^{\infty} e^{-\underline{\lambda}(K)x - K\min(\psi)\int_a^x B(y)dy} dx,$$

using dominated convergence, as $\underline{\lambda}(K)$ is bounded we have

$$\int_a^{\infty} e^{-\underline{\lambda}(K)x - K\min(\psi)\int_a^x B(y)dy} dx \xrightarrow[K\to+\infty]{} 0$$

and finally

$$2e^{-\underline{\lambda}(K)a} \xrightarrow[K\to+\infty]{} 1,$$

which gives (2.11) and concludes the proof of the theorem.

We give a numerical illustration of this theorem in figure 2.4, in the particular case $B = \mathbb{1}_{[a,+\infty[}$.

2.3.2 When ψ can vanish: proof of theorem 2.1.4

When ψ can vanish, the conclusion of Theorem 2.1.3 fails; its proofs uses strongly that $\min(\psi) > 0$. Here we show that much more complicated behaviours appear. For instance the limits $K \to +\infty$ and $\psi \to 0$ (locally) do not commute!

Intuitive derivation of the formula

We consider the original PDE (2.1), with $d \equiv 0$, (we scale $T = 1$, in all what follows)

$$\begin{cases} \frac{\partial}{\partial t}n(t,x) + \frac{\partial}{\partial x}n(t,x) + K\psi(t)\mathbb{1}_{[a,\infty[}(x)n(t,x) = 0, \\ n(t,0) = 2K\psi(t)\int_a^{\infty} n(t,x)dx. \end{cases} \tag{2.20}$$

where ψ is a 1-periodic square wave, such that if $[t]$ is the integer part of t,

$$\exists\, 0 < \tau < \frac{1}{2}, \quad \psi = t \mapsto \mathbb{1}_{[0,\tau[}(t - [t]). \tag{2.21}$$

We want to derive the limit of the growth rate λ when $K \to +\infty$ (within this section, λ denotes the Floquet eigenvalue $\lambda_F(K)(a,\psi)$). Intuitively, whenever the cell is old enough in the cycle ($x > a$)) and the time is favorable ($0 \leq t - [t] < \tau$) division occurs. The idea is to consider that at time $t = 0$, we have only cells of age 0 ($n(0,.) = \delta_0$) we want to know if for some integer N we have $n(N,.) = \mu\delta_0$ for some $\mu > 0$, if this is the case, the limit of the growth rate λ^{∞} should be $\frac{\log\mu}{N}$.
If we start from age 0 then, a division should occur at any $a, 2a \dots ka$ as long as all these time are favorable. When, for the first time, we reach a possible division $N_a a$ time that is not favorable, then the corresponding division occurs later, namely at the next period : $\lceil N_a a \rceil$ (where $\lceil . \rceil$ denotes the upper integer part. Then, at $\lceil N_a a \rceil$ the population divides (for the N_a^{th} time) and we have $n(\lceil N_a a \rceil, .) = 2^{N_a}\delta_0$. Therefore, we expect

$$e^{\lambda^{\infty}(a)\lceil N_a a \rceil} = 2^{N_a}, \quad \lambda^{\infty}(a) = \frac{N_a}{\lceil N_a a \rceil}\log 2.$$

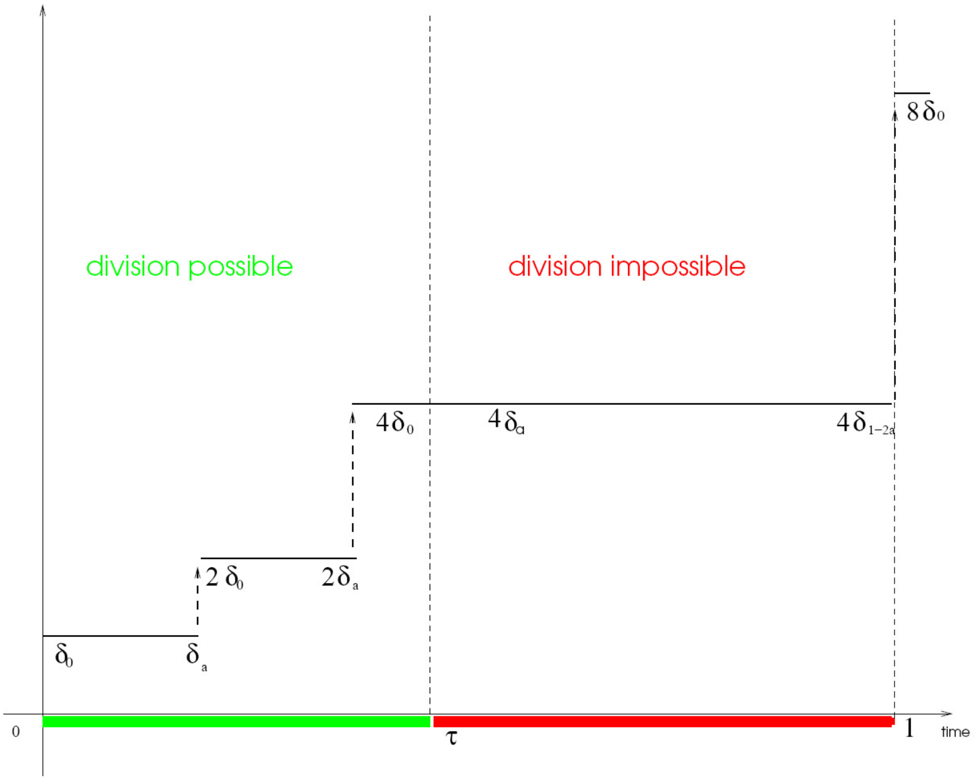

Figure 2.3: Example of the derivation of the formula. Here $2a < \tau < 3a < 1$ and we obtain $n(1,.) = 8n(0,.)$. Hence we expect $\lambda^\infty(a) = 3\log(2)$

Preliminaries: properties of λ^∞ and sketch of the proof

Lemma 2.3.1 *For fixed τ, the limit $l(a) = \lim_{K\to\infty} \lambda^K(a)$ satisfy the following properties:*

$$l(a) = \sup_{K>0} \lambda^K(a),$$

$$a \mapsto l(a),$$

is nondecreasing and rightcontinuous.

We already proved the monotonicity of the eigenvalue with respect to the division rate in our case, we can state the following properties. Since $\lambda^K(a) \leq \log 2/a$, we have always, since $\lambda^K(a)$ is increasing with K,

$$\lambda^\infty(a) = \sup_{K>0} \lambda^K(a).$$

Furthermore, since for any fixed K, $\lambda^K(a)$ is nonincreasing with a, so is $l(a)$. Finally, since for any fixed $K > 0$, $\lambda^K(a)$ is continuous with respect to a, $l(a)$ (seen as the supremum of lower semi continuous functions) is lower semi continuous. Combined with monotonicity, this leads to the very convenient property:

$$\forall a > 0, \qquad l(a) = \liminf_{x\to a} l(x) = \lim_{x\to a+0} l(a).$$

That is, $l(a) = \lim_{K\to\infty} \lambda^K(a)$ is rightcontinuous! $\square$

Lemma 2.3.2 *For any τ , λ^∞ defined as in theorem2.1.4 is rightcontinuous,*

Proof. We remind the definition of λ^∞. Given the set $W_\tau = [\tau, 1] + \mathbb{N}$, we denote

$$N_a a = \inf W_\tau \cap \mathbb{N}a = f(a), \quad \lambda^\infty(a) = \frac{N_a}{\lceil N_a a \rceil} = \frac{f(a)}{a\lceil f(a)\rceil} \log 2.$$

We want to investigate the rightcontinuity of this function. It is sufficient to prove that

$$g(a) = \frac{f(a)}{\lceil f(a)\rceil},$$

is rightcontinuous. If $g(a) \neq 1$, this means that $f(a) \neq \lceil f(a)\rceil$, and therefore, for $\varepsilon > 0$ small enough, we can have $f(a+\varepsilon) = f(a)$, and thereby $g(a+\varepsilon) = g(a)$, which leads to the rightcontinuity of g at a. If $g(a) = 1$, then, choosing $\varepsilon > 0$ small enough, we can have $f(a)$ arbitrary large, and thereby $g(a)$ arbitrary close to 1. $\square$

With this property, we can skip singularities: if we prove that $\lim \lambda^K$ and λ^∞ coincide if $a \notin \mathbb{Q}$, then we can prove using rightcontinuity that they actually coincide everywhere.

We give here also a few hints to understand the proof. A point is important: if $\tau \geq \frac{1}{2}$, we complete the heuristic showing that for any initial data the population is multiplied exactly by 2^{N_a} after time $\lceil N_a a\rceil$. The proof is divided into a few steps:

- prove that the limit is an upper bound for $\lambda^K(a)$,
- fix τ and choose a, such that there is no "singularities" (typically $N_a a \in \mathbb{N}$),
- consider the generational formulation of the division equation with initial data $N^K(0,x)$ and show that at time $\lceil N_a a\rceil$ "‘almost everybody"’ (where almost will be quantified in terms of $1-\varepsilon$ type) has reached generation N_a.
- fill the "‘blanks"’ using rightcontinuity.

2.3.3 Upper bound on λ^K

The fact that the limit is an upper bound is actually a direct consequence of the derivation of the formula. The heuristic gives in fact the earliest possible times for division. It is here convenient to use the generational reformulation of the division equation in order to derive $\lambda^\infty(a)$ as an upper bound. Let $a > 0, \tau \in]0,1[, K > 0$ be fixed. We take the eigenvector as an initial data.

$$\begin{aligned} &\partial_t n_i + \partial_x n_i + K\psi(t)\mathbb{1}_{[a,\infty[}(x) n_i(t,x) = 0,\\ &n_{i+1}(t,0) = K\psi(t) \textstyle\int_a^\infty n_i(t,x)dx, \qquad\qquad .\\ &n_0(x) = N^K(0,x). \end{aligned}$$

We write $I_{max}(t)$ the maximal integer such that $n_i \not\equiv 0$. At time $t = 0$, we have $I_{max}(0) = 0$. Then, because, cells need to have age bigger than a to change generation, we have necessarily $I_{max}(t) \leq 1$ for $t < a$ and more generally,

$$I_{max}(t) \leq n, \qquad \text{if } t < na.$$

$$I_{max}(t) \leq N_a \qquad \text{if } t < (N_a)a.$$

We introduce a notation $p_a + 1 = \lceil N_a a\rceil$. The integers N_a, p_a are then the minimal integers such that

$$p_a + \tau \leq N_a a \leq p_a + 1.$$

We use now the properties of the equation: since no change of generation may occur between times $p_a + \tau$ and $p_a + 1$,we have

$$I_{max}(t) \leq N_a \qquad \text{if } p_a + \tau \leq t < p_a + 1.$$

Now, from the definition of N^K and λ^K, we have

$$\sum_{i=0}^{\infty} 2^i n_i(t,x) = e^{\lambda t} N^K(t,x).$$

In particular, for $t < p_a + 1$, we have

$$\sum_{i=0}^{I_{max}(t)} 2^i n_i(t,x) = \sum_{0}^{N_a} 2^i n_i(t,x) = e^{\lambda t} N^K(t,x).$$

We integrate with respect to x and obtain

$$e^{\lambda t} \int_0^\infty N^K(t,x)dx = \sum_0^{N_a} 2^i \int_0^\infty n_i(t,x)dx \leq 2^{N_a} \sum_0^{N_a} \int_0^\infty n_i(t,x)dx. \tag{2.22}$$

But we also have from the properties of the generational formulation and the definition of I_{max},

$$\sum_0^{N_a} \int_0^\infty n_i(t,x)dx = \sum_0^{\infty} \int_0^\infty n_i(t,x)dx = \int_0^\infty n_0(0,x)dx = \int_0^\infty N^K(0,x)dx. \tag{2.23}$$

Combining (2.22-2.23), we get

$$e^{\lambda t} \int_0^K N^K(t,x)dx \leq 2^{N_a} \int_0^\infty N^K(0,x)dx, \quad t < p_a + 1.$$

As K is fixed, we can use the continuity of $\int_0^\infty N^K(t,x)dx$. We have therefore

$$e^{\lambda^K(p_a+1)} \int_0^\infty N^K(p_a+1,x)dx \leq 2^{N_a} \int_0^\infty N^K(0,x)dx.$$

As $N^K(p_a+1,x) = N^K(0,x)$, we have

$$e^{\lambda^K(p_a+1)} \leq 2^{N_a}.$$

And therefore, as expected

$$\lambda^K(a) \leq \frac{N_a}{p_a+1} \log 2 = \lambda^\infty(a).$$

□

2.3.4 Bounding λ from below

A few more combinatorics We need now to give a lower bound on λ^K. For this purpose, we use the same idea: we consider generational formulation of the division equation with $N^K(0,x)$ as initial data. Above, we prove that cells could enter at most generation N_a before reaching time $p_a + 1$. In the following we prove that for a large parameter K most of the cells enter generation N_a before reaching time $p_a + 1$. The strategy is the following: we prove that even the cells that were the youngest at time 0 are pretty sure to reach generation N_a before reaching time p_a+1. As there can not be any birth between time $-1+\tau$ and 0, we can say, thanks to a short study of the characteristics, that

$$N^K(0,x)=0, \qquad \text{for } 0<x<1-\tau.$$

Therefore,

$$\int_0^\infty N^K(0,x)dx = \int_{1-\tau}^\infty N^K(0,x)dx.$$

For this reason, it is important to study the trajectory of cells that have age $1-\tau$ at time 0.

Let N_a and p_a be defined as in 2.1.4 as the minimal integers such that

$$p_a+\tau \le N_a a \le p_a+1$$

We ask the following question: how many division does a cell undergo before reaching time $t>0$ if it started at age x at time 0 (that is it was born at time $-x$)? We denote this number $D(x,t)$. From the definition and the heuristics for the formula, we already know that

$$D(0,p_a+1)=N_a-1, \qquad D(0,p_a+1+0)=N_a.$$

With the same ideas, it is straightforward that

$$D(a,0+0)=1, \qquad D(a,p_a+1)=N_a, \qquad D(a,p_a+1+0)=N_a+2.$$

Considering the trajectory of cells that have age $1-\tau$ at time 0, we prove the following

Lemma 2.3.3 *Suppose $a\notin\mathbb{Q}$. Let N_a and p_a be defined as the minimal integers such that*

$$p_a+\tau \le (N_a)a \le p_a+1.$$

Let $D(1-\tau,t)$ be defined as above, then ,

$$D(1-\tau,p_a+1)=D(0,p_a+1)+1=N_a.$$

In words, the cells starting at age $1-\tau$ undergo one more division than those starting at age 0.

Proof. First, we consider the case $1-\tau\ge a$. Then from the discussion made in the heuristic justification, a division occurs at time 0^+. We have then

$$D(1-\tau,t)=D(a,t)=D(0,t+1), \qquad \text{for any } t>0.$$

Now we shall consider the case $1-\tau<a$. From a monotonicity argument (older cells divide sooner and therefore $D(x,t)$ is nondecreasing with x), we can claim that

$$D(0,p_a+1)\le D(1-\tau,p_a+1)\le D(a,p_a+1)=D(0,p_a+1)+1.$$

We introduce the notation N_τ, p_τ defined as the minimal integers such that

$$p_\tau+\tau \le N_\tau a-(1-\tau) < p_\tau+1.$$

The reader should keep in mind that time $N_\tau a-(1-\tau)$ corresponds to the first time when cells that had age $(1-\tau)$ at time 0 want to divide and cannot. Notice that after time $p_\tau+1$, they divide and can then follow (with a shift of $p_\tau+1$) the periodic orbit of cells that have age 0 at time 0. We can then predict that these cells will divide again at an integer time at time $(p_\tau+1)+(p_a+1)>p_a+1$. We have two possibilities: either we have $p_a=p_\tau$ either not. If we have $p_a=p_\tau$, then, noticing that since $a\notin\mathbb{Q}$, we have actually

$$p_a+\tau \le N_a a < p_a+1,$$

we also have

$$N_a a - (1-\tau) < p_a + 1 - (1-\tau) = p_a + \tau,$$

and in this case, we know that the N_a^{th} division should occur at time $N_a a-(1-\tau)$. Therefore,

$$D((1-\tau), p_a+1) \geq D((1-\tau), \big(N_a a - (1-\tau)\big)^+) = N_a + 1 = D(0, p_a+1) + 1,$$

we have $D((1-\tau), p_a+1) = D(0, p_a+1)+1$. In the other case, we can insure that the set of integer division times for a cell starting with age $(1-\tau)$, that is, the set $p_\tau + 1 + (p_a+1)\mathbb{N}$ does not contain p_a+1. Therefore there is no division at time p_a+1 for cells starting with age $1-\tau$, which can be read as

$$D((1-\tau), p_a+1) = D((1-\tau), (p_a+1)^+) \geq D(0, (p_a+1)^+) = D(0, p_a+1) + 1$$

and then $D((1-\tau), p_a+1) = D(0, p_a+1)+1$.

□

The proof itself We consider $a \notin \mathbb{Q}$, for sake of simplicity. For fixed τ, we defined N_a, p_a as the minimal integers such that

$$p_a + \tau \leq N_a a \leq p_a + 1$$

as above, we have actually,

$$p_a + \tau \leq N_a a < p_a + 1.$$

It is convenient to introduce (again) some new notations. If we follow heuristically the trajectory of a cell starting with age $1-\tau$, it divides exactly N_a+1 times before time p_a+1. The idea is to compare to a trajectory on which we can give quantitative estimates. Consider $\theta_1, \dots \theta_{N_a}$, satisfying the following properties:

$$\begin{cases} \theta_1 \geq 1 - \tau + a, \\ \forall i \leq N_a - 1, \quad \theta_{i+1} - \theta_i \geq a, \\ \forall i \in \{1 \dots N_a\} \qquad \theta_i < \lfloor \theta_i \rfloor + \tau. \end{cases} \tag{2.24}$$

Note that thanks the study of the trajectory of cells starting with age $1-\tau$, such $(\theta_1, \dots \theta_{N_a})$ exist (we take the division time of cells starting with age $1-\tau$, which gives actually the minimal θ_i satisfying such a constraint) and Θ is not empty. The reader should keep in mind that Θ represents (through the division times) the set of all trajectories allowing N_a divisions before reaching time p_a+1 for a cell starting with age $1-\tau$ at time 0. As for the upper bound, we consider the generational reformulation of the system (2.16) where we take $K(t,x) = K\psi(t)\mathbb{1}_{[a,\infty[}(x)$ and take the eigenvector $N^K(t=0,x)$ as an initial data. We denote $\Theta(a,\tau)$ the set of such θ_i. From the definition, we have

$$\sum_i 2^i n_i(p_a+1, x) = N^K(0,x) e^{\lambda^K(a)(p_a+1)}.$$

Especially,

$$\sum_i 2^i \int_0^\infty n_i(p_a+1, x)dx = e^{\lambda^K(a)(p_a+1)} \int_0^\infty N^K(0,x)dx.$$

We recall that $N^K(0,x) = 0$ for $x \in]0, 1-\tau[$. As we want a bound from below, it is sufficient to look at the individuals that are the youngest at the beginning, that is the individuals starting at age $(1-\tau)$. We can do that thanks to the comparison principle. As

$K(t,x)$ is nondecreasing with respect to x, we know that if we choose $K'(t,x) \leq K(t,x)$, and n_i' with obvious notations, then we have thanks to the comparison principle

$$\sum_i 2^i \int_0^\infty n_i'(p_a+1,x)dx \leq e^{\lambda^K(a)(p_a+1)} \int_0^\infty N^K(0,x)dx.$$

Given a trajectory $(\theta_1 \dots \theta_{N_a}) \in \Theta(a,\tau)$, we denote

$$\varepsilon = \inf_i \frac{\lfloor \theta_i \rfloor + \tau - \theta_i}{i} > 0,$$

(the reader should notice that it is then lower than a), and consider

$$K'(t,x) = \begin{cases} K & \text{if } t \in [\theta_1, \theta_1+\varepsilon], \quad x \geq a \\ K & \text{if } t \in [\theta_i + (i-1)\varepsilon, \theta_i + i\varepsilon], \quad x \geq a, \\ 0 & \text{otherwise.} \end{cases}$$

From the definition of $(\theta_1, \dots \theta_{N_a})$ and ε, we have $K'(t,x) \leq K(t,x)$. We estimate now

$$\sum_i 2^i \int_0^\infty n_i'(p_a+1,x)dx.$$

For sake of simplicity, we omit the $'$ in the following. We look generation by generation. No one can enter generation 1 before time θ_1. We look then at time $\theta_1+\varepsilon$. Thanks to the study of characteristics, and to the fact that from the definition of θ_1, ε, we have

$$n_0(t_1+\varepsilon,x) = n_0(x-t)e^{-K\varepsilon},$$

which leads to

$$\int_0^\infty n_0(t_1+\varepsilon,x)dx = e^{-K\varepsilon} \int_0^\infty N^K(0,x)dx.$$

In words, for K big, at time $t_1+\varepsilon$, there is almost nobody anymore in generation 0. And we have from conservation law

$$\sum_{i=1}^\infty \int_0^\infty n_i(t_1+\varepsilon,x)dx = (1-e^{-K\varepsilon}) \int_0^\infty N^K(0,x)dx.$$

Actually, from the definition of the ε, no cell has time to change twice its generation before reaching time $t_1+\varepsilon$. Therefore, we have

$$\sum_{i=1}^\infty \int_0^\infty n_i(t_1+\varepsilon,x)dx = \int_0^\infty n_1(t_1+\varepsilon) = (1-e^{-K\varepsilon}) \int_0^\infty N^K(0,x)dx.$$

At time $\theta_2+\varepsilon$, since $\theta_2-\theta_1 \geq a$, the cells that have entered generation 1 between time θ_1 and $\theta_1+\varepsilon$, have age greater than a and therefore can change again generation between time $\theta_2+\varepsilon$ and $\theta_2+2\varepsilon$. On the other hand, the other cells (which had staid in generation 0), can not reach generation 2 before time $\theta_2+2\varepsilon$. All the incomers in the generation 2 between time $\theta_2+\varepsilon$ and time $\theta_2+2\varepsilon$ did enter generation 1 between time θ_1 and time $\theta_1+\varepsilon$. This population is represented by the following integral

$$I_1(t) = \int_{t-x \in [\theta_1, \theta_1+\varepsilon]} n_1(t,x)dx.$$

From the previous remark, we deduce that the total number of incomers in generation 2 is given by the loss term in population of cells that did enter generation 1 between time θ_1 and time $\theta_1+\varepsilon$.

$$\int_0^\infty n_2(\theta_2+2\varepsilon,x)dx = I_1(\theta_2+\varepsilon) - I_1(\theta_2+2\varepsilon)$$

As above, from the definition of θ_2 and ε, we have

$$I_1(\theta_2 + 2\varepsilon) = I_1(\theta_2 + \varepsilon)e^{-K\varepsilon},$$

which finally gives

$$\int_0^\infty n_2(\theta_2 + 2\varepsilon, x)dx = (1 - e^{-K\varepsilon})I_1(\theta_2 + \varepsilon) = (1 - e^{-K\varepsilon})^2 \int_0^\infty N^K(0, x)dx.$$

With an induction we obtain for $i \leq N_a$

$$\int_0^\infty n_i(\theta_i + i\varepsilon, x)dx = (1 - e^{-K\varepsilon})^i \int_0^\infty N^K(0, x)dx.$$

This leads to

$$2^{N_a} \int_0^\infty n_{N_a}(p_a + 1, x)dx = (1 - e^{-K\varepsilon})^{N_a} \int_0^\infty N^K(0, x)dx,$$

and then to

$$2^{N_a}(1 - e^{-K\varepsilon})^{N_a} \leq e^{\lambda^K(a)(p_a+1)}.$$

This gives a lower bound

$$\lambda^K(a) \geq \frac{N_a}{p_a + 1} \log 2(1 - K\varepsilon) = \lambda^\infty(a)(1 - \log \frac{2}{1 - K\varepsilon}).$$

□

We choose now $(\theta_1 \dots \theta_{N_a}) \in \Theta$ in order to maximize ε but since

$$\theta_{N_a} \geq N_a a - 1 + \tau,$$

we have, as stated above,

$$\varepsilon \leq \frac{\lceil N_a a \rceil - 1 + \tau - \theta_{N_a}}{N_a} \leq \frac{\lceil N_a a \rceil - N_a a}{N_a}.$$

And therefore, we have the stated bound on $r(a)$. □

2.4 Numerical illustrations

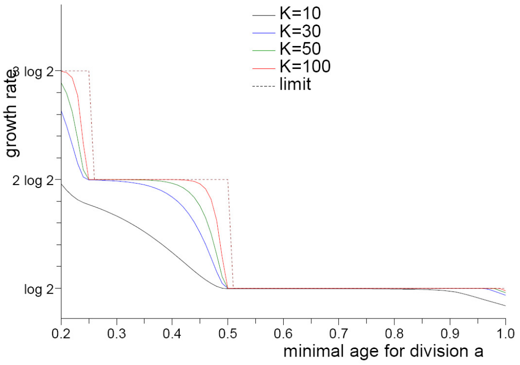

Figure 2.4: Convergence for $\tau = 1/2$.

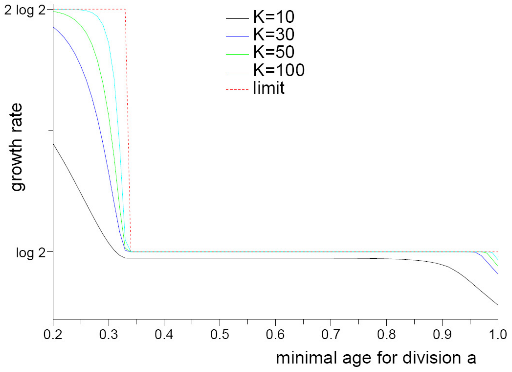

Figure 2.5: Convergence for $\tau = 1/3$

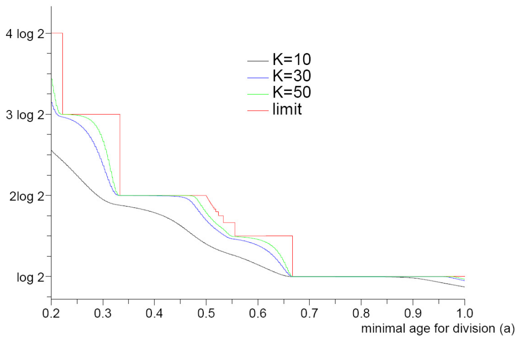

Figure 2.6: Convergence for $\tau = 2/3$

2.5 Appendix

2.5.1 Existence theory for λ

We use the following notations:

- $\tau_h B = x \mapsto B(x+h)$, prolonged by zero on $[0,h]$ if $h<0$,
- $L^\infty_{\text{per}}(0,T,X)$ is the space of bounded T-periodic functions taking values in X, similarly, $C_{\text{per}}(0,T,X)$ is the space of T-periodic continuous (with respect to the time variable) functions taking values in X.

Theorem 2.5.1 *Given $a>0, K>0$, ψ nonnegative, bounded, not identically zero and B positive, bounded satisfying*

$$\forall t, \qquad \int_0^\infty \psi(t-x)B(x)dx = \int_0^\infty \psi(t+x)B(x)dx = +\infty, \tag{2.25}$$

and the following property,

$$\tau_h B - B \xrightarrow[h\to 0]{} 0 \qquad \textit{in } L^1_{loc}(\mathbb{R}^+_*). \tag{2.26}$$

there exists a unique $\lambda_F > 0$ such that there exists (N,ϕ) in $L^\infty_{per}(0,T,L^1(\mathbb{R}^+)) \times C_{per}(0,T,L^\infty(\mathbb{R}^+))$ satisfying (2.2-2.3-2.4-2.5). Furthermore, ϕ is unique.

Before starting the proof, we give a few remarks on the hypothesis:

- we do not need regularity assumptions on the function ψ,
- in the case $\min(\psi) > 0$, the condition (2.25) is equivalent to $\int_0^\infty B = +\infty$, in the case $\min(\psi) = 0$ it is for instance satisfied if $\min(B) > 0$ or at least $\liminf_{+\infty} B > 0$, it is not optimal but other conditions would need assumptions on a and K. It could be replaced for instance by
$$\forall t, \qquad \int_a^\infty K\psi(t-x)B(x)dx, \int_a^\infty K\psi(t+x)B(x)dx > \log 2,$$
but, as we are studying asymptotic properties, we rather restrict the study to a case where existence does not depend on a nor on K,
- the equicontinuity condition (2.26) is used for obtaining compactness of integral operators appearing in the proof, this is satisfied for instance in the following cases: B is continuous and $B \in BV_{\mathrm{loc}}(\mathbb{R}^+)$

Proof. The proof is based on the method of characteristics and Krein Rutman Theorem as in [82] but we need more precisions in order to relax the regularity assumptions on ψ. For the sake of simplicity we take $K = 1$. We denote $P(t) = \int_a^\infty B(x)N(t,x)dx$. Using the methods of characteristics, we have the following integral equations

$$\begin{aligned}
N(t,0) &= 2\int_a^\infty \psi(t)B(x)N(t-x,0)e^{-\lambda x - \int_a^x \psi(t-x+s)B(s)ds}dx = \mathcal{L}_1^\lambda(N(.,0))(t),\\
P(t) &= 2\int_a^\infty \psi(t-x)B(x)P(t-x)e^{-\lambda x - \int_a^x \psi(t-x+s)B(s)ds}dx = \mathcal{L}_2^\lambda(P)(t),\\
\phi(t,0) &= 2\int_a^\infty \psi(t+x)B(x)\phi(t+x,0)e^{-\lambda x - \int_a^x \psi(t+s)B(s)ds}dx = \mathcal{L}_3^\lambda(\phi(.,0))(t).
\end{aligned}$$

We have defined three linear operators on $L^\infty_{per}(0,T)$. These operators are defined for any $\lambda > 0$. Moreover, we can see $\mathcal{L}_2^\lambda$ and $\mathcal{L}_3^\lambda$ as operators on the space $C_{per}(0,T)$ of T-periodic continuous functions. We have

Lemma 2.5.2 *Under assumptions of theorem 2.5.1, for any $\lambda > 0$, $\mathcal{L}_2^\lambda$ and $\mathcal{L}_3^\lambda$ are nonnegative, compact linear operators on $C_{per}(0,T)$.*

Proof. The non negativity and linearity are obvious. The operators Indeed, if we fix $\lambda, a > 0$ then for f continuous and T-periodic with $\|f\| \leq 1$, if we write $g = \mathcal{L}_3^\lambda(f)$, we have

$$g(t+h) = 2\int_{a+h}^\infty \psi(t+x)B(x-h)f(t+x)e^{\lambda h - \lambda x - \int_{a+h}^x \psi(t+s)B(s)ds}dx,$$

$$\begin{aligned}
g(t+h) &= 2\int_a^\infty \psi(t+x)B(x-h)f(t+x)e^{\lambda h - \lambda x - \int_{a+h}^x \psi(t+s)B(s)ds}dx\\
&\quad -2\int_a^{a+h} \psi(t+x)B(x-h)f(t+x)e^{\lambda h - \lambda x - \int_{a+h}^x \psi(t+s)B(s)ds}dx,
\end{aligned}$$

this leads to

$$\begin{aligned} g(t+h)-g(t) &= -2\int_a^{a+h}\psi(t+x)B(x-h)f(t+x)e^{\lambda h-\lambda x-\int_{a+h}^x \psi(t+s)B(s-h)ds}dx \\ &+ 2(e^{\lambda h}-1)\int_a^{\infty}\psi(t+x)B(x-h)f(t+x)e^{-\lambda x-\int_{a+h}^x \psi(t+s)B(s-h)ds}dx \\ &+ 2\int_a^{\infty}\psi(t+x)(B(x-h)-B(x))f(t+x)e^{-\lambda x-\int_{a+h}^x \psi(t+s)B(s-h)ds}dx \\ &+ 2\int_a^{\infty}\psi(t+x)B(x)f(t+x)e^{-\lambda x}\left(e^{-\int_{a+h}^x \psi(t+s)B(s-h)ds}-e^{-\int_a^x \psi(t+s)B(s)ds}\right)dx, \\ &= I_1+I_2+I_3+I_4. \end{aligned}$$

We deal with the I_i separately,

$$|I_1|\le 2\|\psi\|\|B\|e^{\lambda h}h, \tag{2.27}$$

$$|I_2|\le 2\|\psi\|\|B\|(e^{\lambda h}-1)\frac{e^{-\lambda a}}{\lambda}, \tag{2.28}$$

to make I_3 small, we make the following remark: for any $R>a$,

$$|I_3|\le 2\|\psi\|\|\tau_h B-B\|_{L^1([a,R])}+4\|\psi\|\|B\|\int_R^{\infty}e^{-\lambda x}dx,$$

taking R big enough and h small enough, we might prove thanks to (2.26) and positivity of λ, the first term goes to 0 for R fixed and the second goes to 0 when R goes infinite.

$$|I_3|\le\varepsilon \qquad \text{for h small enough,}$$

The same method can be applied to I_4. Finally we have the equicontinuity of $\mathcal{L}_3^\lambda(B)$ where B is the unit ball for the supremum norm. Thanks to Arzela-Ascoli theorem, $\mathcal{L}_3^\lambda$ is compact. We are now in position to apply Krein and Rutman theorem, there exist U_2, U_3 nonnegative eigenvectors of $\mathcal{L}_2^\lambda, \mathcal{L}_3^\lambda$ associated to their respective spectral radii $\rho_2(\lambda), \rho_3(\lambda)$. We have now

Lemma 2.5.3

$$\rho_i(\lambda), U_i>0, \tag{2.29}$$

$$\mathcal{L}_1^\lambda(\psi U_2)=\rho_2(\lambda)\psi U_2, \tag{2.30}$$

$$\rho_3=\rho_2. \tag{2.31}$$

Proof. The second statement is a straightforward computation, we prove the first by contradiction: if U_2 vanishes, then, for some t,

$$2\int_a^{\infty}\psi(t-x)B(x)U_2(t-x)e^{-\lambda x-\int_a^x \psi(t-x+s)B(s)ds}dx=0,$$

as $B>0$, it would mean thanks to T-periodicity $\psi B\equiv 0$ which would lead to $U_2\equiv 0$. Finally, as U_2 does not vanish then $\mathcal{L}_2^\lambda(U_2)>0$ and therefore, $\rho_2(\lambda)>0$. The equality comes from the duality of operators $\mathcal{L}_1$ and $\mathcal{L}_3$, we have

$$\rho_2\int_0^T\psi(t)U_2(t)U_3(t)dt=\int_0^T\mathcal{L}_1(\psi U_2).U_3(t)dt=\int_0^T\psi U_2\mathcal{L}_3(U_3)dt=\rho_3\int_0^T\psi(t)U_2(t)U_3(t)dt,$$

therefore $\rho_2 = \rho_3 = \rho$.
To end the proof, we need to find λ such that $\rho(\lambda) = 1$. Obviously, ρ is a decreasing function that vanishes at infinity. We may also notice thanks to the remark

$$2\int_a^\infty \psi(t+x)B(x)e^{-\int_a^x \psi(t+s)B(s)ds}dx = 2[e^{-\int_a^x \psi(t+s)B(s)ds}]_a^\infty = 2,$$

that $\rho \to 2$ at 0. Therefore there exists a unique λ satisfying $\rho(\lambda) = 1$. Up to a renormalization, ϕ and P are unique, and therefore so is N. This ends the proof of theorem 2.5.1.

Chapitre 3

Passage du discret au continu pour des modèles de dynamique du prion

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Ce travail effectué en collaboration avec Marie Doumic et Thierry Goudon adapte les techniques de [28] au modèle de polymérisation nucléée pour le prion. Nous faisons ici le lien théorique entre les modèles de [79] et [50] par des méthodes de compacité faible. Via une adimensionalisation du système, nous cherchons à mettre en évidence des échelles caractéristiques qui permettent de voir le modèle EDP de [50] comme une approximation du modèle EDO de [79]. Ce travail a été soumis à *Communications in Mathematical Sciences.*

3.1 Introduction

The modelling of intracellular prion infection has been dramatically improved in the past few years according to recent progress in molecular biology of this pathology. Relevant models have been designed to investigate the conversion of the normal monomeric form of the protein (denoted PrPc) into the infectious polymeric form (denoted PrPsc) according to the auto-catalytic process :

$$\mathrm{PrPc} + \mathrm{PrPsc} \longrightarrow 2\mathrm{PrPsc},$$

in fibrillar aggregation of the protein. These models are based on linear growth of PrPsc polymers via an autocatalytic process [42].

The seminal paper by Masel et al. [79] proposed a discrete model where the prion population is described by its distribution with respect to the size of polymer aggregates. The model is an infinite-dimensional system of Ordinary Differential Equations, taking into account nucleated transconformation and polymerization, fragmentation and degradation of the polymers, as well as production of PrPc by the cells. This model consists in an aggregation fragmentation discrete model. In full generality, it writes as follows :

$$\begin{cases} \dfrac{\mathrm{d}v}{\mathrm{d}t} = \lambda - \gamma v - v \displaystyle\sum_{i=n_0}^{\infty} \tau_i u_i + 2 \sum_{j \geq n_0} \sum_{i < n_0} i k_{i,j} \beta_j u_j, \\ \dfrac{\mathrm{d}u_i}{\mathrm{d}t} = -\mu_i u_i - \beta_i u_i - v(\tau_i u_i - \tau_{i-1} u_{i-1}) + 2 \displaystyle\sum_{j > i} \beta_j k_{i,j} u_j, \quad \text{for } i \geq n_0, \end{cases} \tag{3.1}$$

(with the convention $\tau_{n_0-1} u_{n_0-1} = 0$). Here v represents the quantity of healthy monomers (PrPc), u_i the quantity of infectious polymers (PrPsc) of size i, *i.e.* formed by the fibrillar aggregation of i monomers. We thus have $i \geqslant n_0 \geqslant 2$, where n_0 represents the minimal size for polymers : smaller polymers are considered to be unstable and are immediately degraded into monomers, as the last term of Equation (3.1) for v expresses. Parameters γ and μ_i are the degradation rates respectively of monomers and polymers of size i. The parameter λ is a source term : the basal synthesis rate of PrPc. The coefficient β_i is the fragmentation rate of a polymer of size i, and the coefficient $k_{j,i}$ is the repartition function for a polymer of size i dividing into two polymers of smaller sizes j and $i - j$. Finally, the quantity $v\tau_i$ is the aggregation speed of polymers of size i, which is supposed to depend both on the available quantity of monomers v and on a specific aggregation ability τ_i of polymers of size i.

In the original model [79], the degradation rate of polymers μ_i and the aggregation rate τ_i were assumed to be independent of the size i, the fragmentation rate satisfied $\beta_j = \beta(j-1)$ for a constant β and $k_{i,j}$ was a uniform repartition over $\{1, \ldots j-1\}$, i.e., $k_{i,j} = \frac{1}{j-1}$ for $i \in \{1, \ldots j-1\}$, and 0 elsewhere. These laws express that all polymers behave in the same way, and that any joint point of any polymer has the same probability to break. It allowed the authors to close the system into an ODE system of three equations, which is quite simple to analyze. However, following recent experimental results such as in [101], and their mathematical analysis in [21, 20], we prefer here to consider variable coefficients in their full generality. Following the ideas of [30], we can consider, under reasonable growth assumptions on the coefficients, the so called *admissible* solutions, i.e., solutions obtained by taking the limit of truncated systems (see Appendix 3.7.3).

Recent work by Greer *et al.* analyzed this process in a continuous setting [50]. They proposed a Partial Differential Equation to render out the above-mentioned polymerization/fragmentation process. It writes

$$\begin{aligned} \frac{\mathrm{d}V}{\mathrm{d}t} &= \lambda - \gamma V - V \int_{x_0}^{\infty} \tau(x) U(t,x)\, \mathrm{d}x \\ &\quad +2 \int_{x=x_0}^{\infty} \int_{y=0}^{x_0} y k(y,x) \beta(x) U(t,x)\, \mathrm{d}x\, \mathrm{d}y, \end{aligned} \tag{3.2}$$

$$\begin{aligned} \frac{\partial U}{\partial t} &= -\mu(x) U(t,x) - \beta(x) U(t,x) - V \frac{\partial}{\partial x}(\tau U) \\ &\quad +2 \int_x^{\infty} \beta(y) k(x,y) U(t,y)\, \mathrm{d}y. \end{aligned} \tag{3.3}$$

The coefficients of the continuous model (3.2)(3.3) have the same meaning than those of the discrete one (3.1) ; however, some questions about their scaling remain, and in particular about the exact biological interpretation of the variable x.

The aim of this article is to investigate the link between System (3.1) and System (3.2)(3.3). We discuss in details the convenient mathematical assumptions under which we can ensure that the continuous system is the limit of the discrete one and we establish rigorously the convergence statement. We also want to discuss possible biological interpretations of our asymptotic analysis, and see how our work can help to define a proper boundary condition at $x = x_0$ for System (3.2)(3.3). Indeed, Eq. (3.3) holds in the domain $x > x_0$ and, due to the convection term, at least when $V(t)\tau(x_0) > 0$ a boundary condition is necessary to complete the problem.

In Section 3.2, we first recall general properties and previous results on the considered equations. In Section 3.3, we rescale the equations in order to make a small parameter ε appear, and we state the main result : the asymptotic convergence of the rescaled discrete system towards the continuous equations. Section 3.4 is devoted to its proof, based on moments *a priori* estimates. Sections 3.5 and 3.6 discuss how these results can be interpreted on physical grounds. We also comment the issue of the boundary condition for the continuous model.

3.2 Basic properties of the equations

All the considered coefficients are nonnegative. We need some structural hypothesis on k and $k_{j,i}$ to make sense. Obviously, the hypothesis take into account that a polymer can only break into smaller pieces. We also impose symmetry since a given polymer of size y breaks equally into two polymers of size respectively x and $y - x$. Summarizing, we have

$$\begin{array}{ll} k_{i,j} \geq 0, & k(x,y) \geq 0, \\ k_{i,j} = 0 \text{ for } i \geq j & k(x,y) = 0 \text{ for } x > y, \end{array} \tag{3.4}$$

$$k_{i,j} = k_{j-i,i}, \qquad k(x,y) = k(y-x,y), \tag{3.5}$$

$$\sum_{i=1}^{j-1} k_{i,j} = 1, \qquad \int_0^y k(x,y)\,\mathrm{d}x = 1. \tag{3.6}$$

(Note that (3.4) and (3.6) imply that $0 \leq k_{i,j} \leq 1$.) Classically, these two conditions lead to a third one, expressing mass conservation through the fragmentation process :

$$2\sum_{i=1}^{j-1} i k_{i,j} = j, \qquad 2\int_0^y x k(x,y)\,\mathrm{d}x = y. \tag{3.7}$$

The discrete equation belongs to the family of coagulation-fragmentation models (see [10],[11]). Adapting the work of [10, 11] to this system, we obtain the following result. It is not optimal but sufficient for our study.

Theorem 3.2.1 *Let $k_{i.j}$ satisfy Assumptions (3.4)-(3.6). We assume the following growth estimate on the coefficients : there exist $K > 0$, $\alpha \geq 0$, $m \geq 0$ and $0 \leq \theta \leq 1$ such that*

$$0 \leq \beta_i \leq K i^{\alpha}, \qquad 0 \leq \mu_i \leq K i^{m}, \qquad 0 \leq \tau_i \leq K i^{\theta}. \tag{3.8}$$

The initial data $v^0 \geq 0, u_i^0 \geq 0$ satisfies, for $\sigma = \max(1+m, 1+\theta, \alpha)$

$$\sum_{i=n_0}^{\infty} i^{\sigma} u_i^0 < +\infty.$$

Then there exists a unique global solution to (3.1) which satisfies for all $t \geq 0$

$$v(t) + \sum_{i=n_0}^{\infty} i u_i(t) = v^0 + \sum_{i=n_0}^{\infty} i u_i^0 + \lambda t - \int_0^t \gamma v(s)\,\mathrm{d}s - \int_0^t \sum_{i=n_0}^{\infty} i \mu_i u_i(s)\,\mathrm{d}s. \tag{3.9}$$

A sketch of the proof is given in Appendix 3.7.3. Let us introduce the quantity

$$\rho(t) = v(t) + \sum_{i=n_0}^{\infty} i u_i(t), \tag{3.10}$$

which is the total number of monomers in the population. Equation (3.9) is a mass balance equation, which can be written as

$$\frac{\mathrm{d}}{\mathrm{d}t}\rho = \lambda - \gamma v(t) - \sum_{i=n_0}^{\infty} i \mu_i u_i(t). \tag{3.11}$$

Similarly for the continuous model we define

$$\varrho(t) = V(t) + \int_{x_0}^{\infty} x U(t,x)\,\mathrm{d}x.$$

The analogue of (3.11) would be

$$\varrho(t) - \varrho(0) = \lambda t - \int_0^t \gamma V(s)\,\mathrm{d}s - \int_0^t \int_{x_0}^{\infty} x\mu(x) U(t,x)\;\mathrm{d}x. \tag{3.12}$$

In fact, the argument to deduce (3.12) from the system (3.2)(3.3) is two–fold : it relies both on the boundary condition on $\{x = x_0\}$ for (3.3) and on the integrability properties of the fragmentation term

$$x \times \Big(2\int_x^{\infty} \beta(y) k(x,y) U(t,y)\,\mathrm{d}y - \beta(x) U(t,x)\Big),$$

the integral of which has to be combined to (3.2) by virtue of (3.7). The question is actually quite deep, as it is already revealed by the case where $\mu = 0$, $\tau = 0$ and $x_0 = 0$. In this situation it can be shown that (3.3) admits solutions that do not satisfy the conservation law : $\int_0^\infty xU(t,x)\,\mathrm{d}x = \int_0^\infty xU(0,x)\,\mathrm{d}x$, see [41]. Hence, (3.12) has to be incorporated in the model as a constraint to select the physically relevant solution, as suggested in [41] and [65]. Nevertheless, the integrability of the fragmentation term is not a big deal since it can be obtained by imposing boundedness of a large enough moment of the initial data as it will be clear in the discussion below and as it appeared in [41, 65]. More interesting is how to interpret this in terms of boundary conditions ; we shall discuss the point in Section 3.5. (Note that in [65] the problem is completed with the boundary condition $U(t, x_0) = 0$ while $x_0 > 0$, $\tau(x_0) > 0$.) According to [41, 65] we adopt the following definition.

Definition 3.2.2 *We say that the pair (U, V) is a "monomer preserving weak solution of the prion proliferation equations" with initial data (U_0, V_0) if it satisfies (3.2) and if for any $\varphi \in \mathcal{C}_c^\infty((x_0,\infty))$, we have*

$$\begin{aligned}
&\int_0^\infty U(t,\,\mathrm{d}x)\varphi(x) - \int_0^\infty U_0(\mathrm{d}x)\varphi(x)\\
&= -\int_0^t\int_0^\infty \mu(x)U(s,\,\mathrm{d}x)\varphi(x)\,\mathrm{d}s - \int_0^t\int_0^\infty \beta(x)U(s,\,\mathrm{d}x)\varphi(x)\,\mathrm{d}s\\
&\quad + \int_0^t V(s)\int_0^\infty \tau(x)U(s,\,\mathrm{d}x)\partial_x\varphi(x)\,\mathrm{d}s\\
&\quad +2\int_0^t\int_{x_0}^\infty \beta(y)U(s,\,\mathrm{d}y)\int_{x_0}^y k(\mathrm{d}x,y)\varphi(x)\,\mathrm{d}s,
\end{aligned} \tag{3.13}$$

and

$$\begin{aligned} V(t) + \int_{x_0}^{\infty} xU(t,\,\mathrm{d}x) \quad &= \quad V_0 + \int_{x_0}^{\infty} xU_0(\mathrm{d}x) \\ &\quad\; + \lambda t - \int_0^t \gamma V(s)\,\mathrm{d}s - \int_0^t \int_{x_0}^{\infty} x\mu(x)U(s,\,\mathrm{d}x)\,\mathrm{d}s. \end{aligned} \tag{3.14}$$

A break is necessary to discuss the functional framework to be used in Definition 3.2.2. We start with a set up of a few notation. We denote by $\mathcal{M}^1(X)$ the set of bounded Radon measures on a borelian set $X \subset \mathbb{R}$; $\mathcal{M}^1_+(X)$ stands for the positive cone in $\mathcal{M}^1(X)$. The space $\mathcal{M}^1(X)$ identifies as the dual of the space $\mathcal{C}_0(X)$ of continuous functions vanishing at infinity in X,[1] endowed with the supremum norm, see [76]. Given an interval $I \subset \mathbb{R}$, we consider measure valued functions $W : y \in I \mapsto W(y) \in \mathcal{M}^1(X)$. Denoting $W(y,\,\mathrm{d}x) = W(y)(\mathrm{d}x)$, we say that $W \in \mathcal{C}(I;\mathcal{M}^1(X) - \mathrm{weak} - \star)$, if, for any $\varphi \in \mathcal{C}_0(X)$, the function $y \mapsto \int_X \varphi(x)W(y,\,\mathrm{d}x)$ is continuous on I. We are thus led to assume

$$U \in \mathcal{C}([0,T];\mathcal{M}^1_+([0,\infty)) - \mathrm{weak} - \star), \qquad V \in \mathcal{C}([0,T]),$$

with furthermore

$$\mathrm{supp}\big(U(t,.)\big) \subset [x_0,\infty), \qquad \int_{x_0}^{\infty} xU(t,\,\mathrm{d}x) \ < \infty,$$

which corresponds to the physical meaning of the unknowns. Hence, formula (3.13) makes sense for continuous coefficients

$$\mu,\ \beta,\ \tau \in \mathcal{C}([x_0,\infty)).$$

Concerning the fragmentation kernel, it suffices to suppose

$$y \mapsto k(\mathrm{d}x, y) \in \mathcal{C}([x_0,\infty);\mathcal{M}^1_+([0,\infty)) - \mathrm{weak} - \star).$$

3.3 Main result

This section splits into three steps : firstly, we set up precisely the scaling of the equations, secondly we detail the assumptions on the discrete coefficients which will be used to define, through a compactness argument, the coefficients of the limit equations, and thirdly we give the main statement of the paper.

3.3.1 Notations and rescaled equations

We first rewrite system (3.1) in a dimensionless form, as done for instance in [28] (see also [63]). We summarize here all the absolute constants that we will need in the sequel :

- T characteristic time,
- $\mathcal{U}$ characteristic value for the concentration of polymers u_i,
- $\mathcal{V}$ characteristic value for the concentration of monomers v,
- $\mathcal{T}$ characteristic value for the polymerisation rate τ_i,
- B characteristic value for the fragmentation frequency β_i,
- d_0 characteristic value for the degradation frequency of polymers μ_i,
- Γ characteristic value for the degradation frequency of monomers γ,
- L characteristic value for the source term λ,

---

[1] $\phi \in \mathcal{C}_0(X)$ means hat ϕ is continuous and for any $\eta > 0$, there exists a compact set $K \subset X$ such that $\sup_{X\setminus K} |\phi(x)| \leq \eta$. We denote $\mathcal{C}_c(X)$ the space of continuous functions with compact support in X.

The dimensionless quantities are defined by

$$\bar{t}=\frac{t}{T},\qquad \bar{v}(\bar{t})=\frac{v(\bar{t}T)}{\mathcal{V}},\qquad \bar{u}_i(\bar{t})=\frac{u_i(\bar{t}T)}{\mathcal{U}},\qquad \bar{\beta}_i=\frac{\beta_i}{B},\qquad \bar{\tau}_i=\frac{\tau_i}{\mathcal{T}},$$
$$\bar{\mu}_i=\frac{\mu_i}{d_0},\qquad \bar{\lambda}=\frac{\lambda}{L},\qquad \bar{\gamma}=\frac{\gamma}{\Gamma}.$$

We remind that $k_{i,j}$ is already dimensionless. The following dimensionless parameters appear

$$\begin{cases} a=\dfrac{LT}{\mathcal{V}}, \quad b=BT, \quad c=\Gamma T, \quad d=d_0T,\\ s=\dfrac{\mathcal{U}}{\mathcal{V}}, \quad \nu=T\mathcal{T}\mathcal{V}. \end{cases} \tag{3.15}$$

Omitting the overlines, the equation becomes

$$\begin{cases} \dfrac{\mathrm{d}v}{\mathrm{d}t}=a\lambda-c\gamma v-\nu s v\sum \tau_i u_i+2bs\displaystyle\sum_{j\geq n_0}\sum_{i<n_0} i k_{i,j}\beta_j u_j,\\ \dfrac{\mathrm{d}u_i}{\mathrm{d}t}=-d\mu_i u_i-b\beta_i u_i-\nu v(\tau_i u_i-\tau_{i-1}u_{i-1})+2b\sum_{j>i}\beta_j k_{i,j}u_j, \qquad \text{for } i\geq n_0. \end{cases} \tag{3.16}$$

The definition (3.10) of the total mass in dimensionless form becomes

$$v+s\sum_{i=n_0}^{\infty} i u_i=\rho. \tag{3.17}$$

The rationale motivating the scaling can be explained as follows. Let $0<\varepsilon\ll 1$ be a parameter intended to tend to 0. We pass from the discrete model to the continuous model by associating to the u_i's a stepwise constant function, constant on each interval $(\varepsilon i,\varepsilon(i+1))$. Then sums over the index i will be interpreted as Riemann sums which are expected to tend to integrals in the continuum limit while finite differences will give rise to derivatives. Having in mind the case of homogeneous division and polymerization rates $\beta(x)=x^\alpha$, $\tau(x)=x^\theta$, $\mu(x)=x^m$, which generalizes the constant-coefficient case proposed by [50], and their discrete analogue $\beta_i=i^\alpha$, $\tau_i=i^\theta$, $\mu_i=i^m$, we shall assume that the rescaled coefficients β_i,μ_i,τ_i fulfill (3.8). Therefore, we are led to set

$$s=\varepsilon^2,$$

so that (3.17) becomes

$$v+\varepsilon\sum_{i=n_0}^{\infty}\varepsilon i\; u_i=\rho, \tag{3.18}$$

to be compared to the definition of ϱ in (3.12). This scaling means that the typical concentration of any aggregate with size $i>n_0$ is small compared to the monomers concentration, but the total mass of the aggregates is in the order of the mass of monomers. Next, we set

$$a=1,\quad b=\varepsilon^\alpha,\quad c=1,\quad d=\varepsilon^m,\quad \nu=\varepsilon^{\theta-1}.$$

The rescaled equations read

$$\begin{cases} \dfrac{\mathrm{d}v}{\mathrm{d}t}=\lambda-\gamma v-\varepsilon^{\theta+1}v\sum \tau_i u_i+2\varepsilon^{2+\alpha}\displaystyle\sum_{i\geq n_0}\sum_{j<n_0} j k_{j,i}\beta_i u_i,\\ \dfrac{\mathrm{d}u_i}{\mathrm{d}t}=-\varepsilon^m\mu_i u_i-\varepsilon^\alpha\beta_i u_i-\varepsilon^{\theta-1}v(\tau_i u_i-\tau_{i-1}u_{i-1})+2\varepsilon^\alpha\displaystyle\sum_{j>i}\beta_j k_{i,j}u_j, \qquad \text{for } i\geq n_0. \end{cases} \tag{3.19}$$

Eventually, the threshold value n_0 also depends on the scaling parameter and we assume

$$\lim_{\varepsilon \to 0} \varepsilon n_0(\varepsilon) = x_0 \geq 0. \tag{3.20}$$

This choice is discussed in Section 3.6.3.

Equation (3.19) is completed by an initial data $(u_i^{0,\varepsilon}, v^{0,\varepsilon})$ verifying, for some constants $M_0, \rho^0, M_{1+\sigma}$ independent of ε :

$$\begin{cases} v^{0,\varepsilon} + \varepsilon^2 \displaystyle\sum_{i=n_0(\varepsilon)}^{\infty} i u_i^{0,\varepsilon} = \rho^0 < +\infty, \\ \varepsilon \displaystyle\sum_{i=n_0(\varepsilon)}^{\infty} u_i^{0,\varepsilon} \leq M_0 < +\infty, \\ \varepsilon^{2+\sigma} \displaystyle\sum_{i=n_0(\varepsilon)}^{\infty} i^{1+\sigma} u_i^{0,\varepsilon} \leq M_{1+\sigma} < +\infty, \qquad 1+\sigma > \max(1, \alpha, 1+m, 1+\theta). \end{cases} \tag{3.21}$$

For any $0 < T < \infty$, Theorem 3.2.1 guarantees the existence of a solution $(u_i^\varepsilon, v^\varepsilon)$ of (3.19). Let us set

$$\chi_i^\varepsilon(x) = \chi_{[i\varepsilon,(i+1)\varepsilon)}(x),$$

with χ_A the indicator function of a set A. We introduce the piecewise constant function

$$u^\varepsilon(t,x) := \sum_{i=n_0(\varepsilon)}^{\infty} u_i^\varepsilon(t) \chi_i^\varepsilon(x).$$

On the same token, we associate the following functions to the coefficients

$$\begin{aligned} k^\varepsilon(x,y) &:= \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \frac{k_{i,j}}{\varepsilon} \chi_i^\varepsilon(x) \chi_j^\varepsilon(y), \\ \mu^\varepsilon(x) &:= \sum_{i=n_0(\varepsilon)}^{\infty} \varepsilon^m \mu_i \chi_i^\varepsilon(x), \\ \beta^\varepsilon(x) &:= \sum_{i=n_0(\varepsilon)}^{\infty} \varepsilon^\alpha \beta_i \chi_i^\varepsilon(x), \\ \tau^\varepsilon(x) &:= \sum_{i=n_0(\varepsilon)}^{\infty} \varepsilon^\theta \tau_i \chi_i^\varepsilon(x). \end{aligned}$$

This choice is made so that for all y, $k^\varepsilon(\cdot, y)$ is a probability measure on $[0, y]$.

3.3.2 Compactness assumptions on the coefficients

For technical purposes we need further assumptions on the discrete coefficients. Let us collect them as follows : there exists $K > 0$ such that

$$\begin{aligned} \left|\beta_{i+1} - \beta_i\right| &\leq K i^{\alpha-1}, \\ \left|\mu_{i+1} - \mu_i\right| &\leq K i^{m-1}, \\ \left|\tau_{i+1} - \tau_i\right| &\leq K i^{\theta-1}, \end{aligned} \tag{3.22}$$

where the exponents α, θ, m are defined in (3.8). For the fragmentation kernel we assume furthermore that there exists $K > 0$ such that for any i, j

$$\Big| \sum_{p=0}^{i-1} \sum_{r=0}^{p-1} k_{r,j+1} - \sum_{p=0}^{i-1} \sum_{r=0}^{p-1} k_{r,j} \Big| \leq K. \tag{3.23}$$

These assumptions will be helpful for investigating the behavior of (3.19) as ε goes to 0 since they provide compactness properties. We summarize these properties in the following lemmata.

Lemma 3.3.1 *Let $\big(z_i\big)_{i\in\mathbb{N}}$ be a sequence of nonnegative real numbers verifying*

$$0 \leq z_i \leq K i^{\kappa}, \qquad \big| z_{i+1} - z_i \big| \leq K i^{\kappa-1}$$

for some $K > 0$ and $\kappa \geq 0$. For $x \geq 0$, we set $z^{\varepsilon}(x) = \sum_i \varepsilon^{\kappa} z_i \chi_{[\varepsilon i, \varepsilon(i+1))}(x)$. Then there exist a subsequence $\varepsilon_n \to 0$, and a continuous function $z : x \in [0, \infty) \mapsto z(x)$ such that z^{ε_n} converges to z uniformly on $[r, R]$ for any $0 < r < R < \infty$. If $\kappa > 0$, the convergence holds on $[0, R]$ for any $0 < R < \infty$ and we have $z(0) = 0$.

We shall apply this statement to the sequences $\beta^{\varepsilon}, \mu^{\varepsilon}, \tau^{\varepsilon}$. A similar compactness property can be obtained for the fragmentation coefficients.

Lemma 3.3.2 *Let the coefficients $k_{i,j}$ satisfy Assumptions (3.5),(3.6) and (3.23). Then there exist a subsequence $\big(\varepsilon_n\big)_{n\in\mathbb{N}}$ and $k : y \in [0, \infty) \mapsto k(\mathrm{d}x, y) \in \mathcal{M}^1_+([0, \infty))$ which belongs to $\mathcal{C}([0, \infty); \mathcal{M}^1_+([0, \infty)) - \text{weak} - \star)$ satisfying also (3.5) and (3.6) (in their continuous version) and such that k^{ε_n} converges to k in the following sense : for every compactly supported smooth function $\varphi \in \mathcal{C}^{\infty}_c([x_0, \infty))$, denoting*

$$\phi^{\varepsilon_n}(y) = \int_{n_0(\varepsilon_n)\varepsilon_n}^{y} k^{\varepsilon_n}(x, y)\varphi(x)\, \mathrm{d}x, \qquad \phi(y) = \int_{x_0}^{y} k(\mathrm{d}x, y)\varphi(x), \tag{3.24}$$

we have $\phi^{\varepsilon_n} \to \phi$ uniformly locally in $[x_0, +\infty)$.

The detailed proofs of Lemma 3.3.1 and Lemma 3.3.2 are postponed to Appendix 3.7.2.

3.3.3 Main results

We are now ready to state the main results of this article.

Theorem 3.3.3 *Assume* (3.8) *and* (3.22). *Suppose the fragmentation coefficient fulfill* (3.4)–(3.6) *and* (3.23). *Then, there exist a subsequence, denoted $\big(\varepsilon_n\big)_{n\in\mathbb{N}}$, continuous functions μ, τ, β, and a nonnegative measure-valued function $k(\mathrm{d}x, y)$ verifying (3.5) and (3.6), such that*

$$\mu^{\varepsilon_n}, \tau^{\varepsilon_n}, \beta^{\varepsilon_n}, k^{\varepsilon_n} \to \mu, \tau, \beta, k$$

in the sense of Lemma 3.3.1 and Lemma 3.3.2.

Let the initial data satisfy (3.21). *Then we can choose the subsequence $\big(\varepsilon_n\big)_{n\in\mathbb{N}}$ such that there exists (U, V) for which*

$$\begin{cases} u^{\varepsilon_n} \rightharpoonup U, & \text{in } \mathcal{C}([0, T]; \mathcal{M}^1([0, \infty)) - \text{weak} - \star)), \\ v^{\varepsilon_n} \rightharpoonup V & \text{uniformly on } [0, T]. \end{cases}$$

We have $xU(t, \mathrm{d}x) \in \mathcal{M}^1([0, \infty))$, the measure $U(t, \mathrm{d}x)$ has its support included in $[x_0, +\infty)$ for all time $t \geq 0$, and (U, V) satisfies (3.13)–(3.14).

Theorem 3.3.4 *The limit (U, V) exhibited in Theorem 3.3.3 is a monomer preserving weak solution (*i.e. *satisfies also Equation (3.2)) in the following situations :*

i) $x_0 = 0$ and either $\theta > 0$ (so that the limit τ satisfies $\tau(0) = 0$), or the rates $\tau_i = \tau$ are constant.

ii) $x_0 > 0$ and the discrete fragmentation coefficients fulfill the following strengthened assumption : for any i, j we have

$$\left|\sum_{i'\leq i}\Big(k_{i'j+1} - k_{i',j}\Big)\right| \leq \frac{K}{j}, \qquad k_{i,j} \leq \frac{K}{j}. \tag{3.25}$$

3.4 Moment estimates

We start by establishing a priori estimates uniformly with respect to ε. These estimates will induce compactness properties on the sequence of solutions. As described in [64] for general coagulation fragmentation models, the model has the property of propagating moments.

Lemma 3.4.1 *Let the assumptions of Theorem 3.3.3 be fulfilled. Then for any $T > 0$, there exists a constant $C < \infty$ which only depends on $M_0, M_{1+\sigma}, \rho^0, \lambda, K$ and T, such that for any $\varepsilon > 0$:*

$$\sup_{t\in[0,T]} \int_0^\infty (1 + x + x^{1+\sigma}) u^\varepsilon(t, x)\,\mathrm{d}x \leq C, \qquad 0 \leq v^\varepsilon(t) \leq C.$$

Proof. For $r \geq 0$, we denote

$$M_r^\varepsilon(t) = \varepsilon \sum_{i=n_0}^{\infty} (i\varepsilon)^r\ u_i^\varepsilon(t).$$

As in [28], we can notice that

$$\int_0^\infty \left(\frac{x}{2}\right)^r u^\varepsilon(t, x)\,\mathrm{d}x \leq M_r^\varepsilon(t) \leq \int_0^\infty x^r u^\varepsilon(t, x)\,\mathrm{d}x.$$

Therefore, we only need to control $M_0^\varepsilon(t)$, $M_1^\varepsilon(t)$ and $M_{1+\sigma}^\varepsilon(t)$. We notice the obvious but useful inequality, for $0 \leq r \leq 1 + \sigma$,

$$(i\varepsilon)^r \leq 1 + (i\varepsilon)^{1+\sigma},$$

and therefore,

$$|M_r^\varepsilon| \leq |M_0^\varepsilon| + |M_{1+\sigma}^\varepsilon|.$$

In the sequel, we use alternatively two equivalent discrete weak formulations of Equation (3.19) in the spirit of [65]. We multiply the second equation of (3.19) by φ_i and summing over i, we first obtain

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\sum_{i=n_0}^{\infty} u_i^\varepsilon\varphi_i &= -\varepsilon^m \sum_{i=n_0}^{\infty} \mu_i u_i^\varepsilon \varphi_i - \varepsilon^\alpha \sum_{i=n_0}^{\infty} \beta_i u_i^\varepsilon \varphi_i \\ &\quad -\varepsilon^{\theta-1} \sum_{i=n_0}^{\infty} v^\varepsilon(\tau_i u_i^\varepsilon - \tau_{i-1} u_{i-1}^\varepsilon)\varphi_i + 2\varepsilon^\alpha \sum_{i=n_0}^{\infty} \varphi_i \sum_{j>i} \beta_j k_{i,j} u_j^\varepsilon, \\ &= -\varepsilon^m \sum_{i=n_0}^{\infty} \mu_i u_i^\varepsilon \varphi_i - \varepsilon^\alpha \sum_{i=n_0}^{\infty} \beta_i u_i^\varepsilon \varphi_i + \varepsilon^{\theta-1} v^\varepsilon \sum_{i=n_0}^{\infty} \tau_i u_i^\varepsilon (\varphi_{i+1} - \varphi_i) \\ &\quad +2\varepsilon^\alpha \sum_{i=n_0}^{\infty} \varphi_i \sum_{j>i} \beta_j k_{i,j} u_j^\varepsilon.\end{aligned} \tag{3.26}$$

Using the properties of $k_{i,j}$, we rewrite the fragmentation terms as follows

$$\begin{aligned}
\sum_{i=n_0}^{\infty} \beta_i u_i^\varepsilon \varphi_i &= 2\sum_{j=n_0+1}^{\infty} \beta_j \sum_{i=1}^{j-1} i k_{i,j} u_j^\varepsilon \frac{\varphi_j}{j} + \beta_{n_0} u_{n_0}^\varepsilon \varphi_{n_0} \\
&= 2\sum_{j=n_0+1}^{\infty} \sum_{i=n_0}^{j-1} i k_{i,j}\beta_j u_j^\varepsilon \frac{\varphi_j}{j} + 2\sum_{j=n_0+1}^{\infty} \sum_{i=1}^{n_0-1} i k_{i,j}\beta_j u_j^\varepsilon \frac{\varphi_j}{j} + \beta_{n_0} u_{n_0}^\varepsilon \varphi_{n_0}, \\
2\sum_{i=n_0}^{\infty} \varphi_i \sum_{j>i} \beta_j k_{i,j} u_j^\varepsilon &= 2\sum_{j=n_0+1}^{\infty} \sum_{i=n_0}^{j-1} i k_{i,j}\beta_j u_j^\varepsilon \frac{\varphi_i}{i}.
\end{aligned}$$

By using (3.7), we have $n_0 = 2\sum_{i=1}^{n_0-1} i k_{i,n_0}$ and we obtain

$$\begin{aligned}
2\sum_{i=n_0}^{\infty} \varphi_i \sum_{j>i} \beta_j k_{i,j} u_j^\varepsilon - \sum_{i=n_0}^{\infty} \beta_i u_i^\varepsilon \varphi_i &= -2\sum_{j=n_0}^{\infty} \sum_{i=1}^{n_0-1} i k_{i,j}\beta_j u_j^\varepsilon \frac{\varphi_j}{j} \\
&\quad +2\sum_{j=n_0+1}^{\infty} \sum_{i=n_0}^{j-1} i k_{i,j}\beta_j u_j^\varepsilon \left(\frac{\varphi_i}{i} - \frac{\varphi_j}{j}\right).
\end{aligned}$$

Replacing in the weak formulation we get

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t} \sum_{i=n_0}^{\infty} u_i^\varepsilon \varphi_i &= -\varepsilon^m \sum_{i=n_0}^{\infty} \mu_i u_i^\varepsilon \varphi_i + \varepsilon^{\theta-1} v^\varepsilon \sum_{i=n_0}^{\infty} \tau_i u_i^\varepsilon (\varphi_{i+1} - \varphi_i) \\
&\quad +2\varepsilon^\alpha \sum_{j=n_0+1}^{\infty} \sum_{i=n_0}^{j-1} i k_{i,j}\beta_j u_j^\varepsilon \left(\frac{\varphi_i}{i} - \frac{\varphi_j}{j}\right) - 2\varepsilon^\alpha \sum_{j=n_0}^{\infty} \sum_{i=1}^{n_0-1} i k_{i,j}\beta_j u_j^\varepsilon \frac{\varphi_j}{j}.
\end{aligned} \tag{3.27}$$

This last formulation makes the estimates straightforward (the computations are formal but can be understood as uniform bounds on solutions of truncated systems and therefore on any admissible solution). Taking $\phi_i = i\varepsilon$, we obtain the first moment, that is, the previously seen mass balance :

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(v^\varepsilon + \varepsilon^2 \sum_{i=n_0}^{\infty} i u_i^\varepsilon\right) = -\gamma v^\varepsilon - \varepsilon^{2+m} \sum_{i=n_0}^{\infty} \mu_i i u_i^\varepsilon + \lambda \le \lambda. \tag{3.28}$$

Therefore, we get (u_i^ε and v^ε are nonnegative)

$$0 \le v^\varepsilon(t) + M_1^\varepsilon(t) \le \rho^0 + \lambda T \qquad \text{for } 0 \le t \le T < \infty,$$

and

$$\int_0^t \varepsilon^{2+m} \sum_{i=n_0}^{\infty} \mu_i i u_i^\varepsilon(s,x)\,\mathrm{d}s \le \rho^0 + \lambda T \qquad \text{for } 0 \le t \le T < \infty.$$

To obtain an estimate on the 0th order moment, we take $\varphi_i = \varepsilon$. The term with τ_i vanishes. Considering only the nonnegative part of the derivative, we derive from (3.27)

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t} M_0^\varepsilon(t) &\le 2\varepsilon^{1+\alpha} \sum_{j=n_0+1}^{\infty} \sum_{i=n_0}^{j-1} i k_{i,j}\beta_j u_j^\varepsilon \frac{1}{i} \\
&\le 2\varepsilon^{1+\alpha} \sum_{j=n_0+1}^{\infty} \beta_j u_j^\varepsilon \le 2K M_\alpha^\varepsilon(t).
\end{aligned}$$

To give the bound on the $(1+\sigma)$th moment, we choose $\varphi_i = \varepsilon(\varepsilon i)^{1+\sigma}$ in the weak formulation. Thanks to the mean value inequality, we have

$$\big((\varepsilon(i+1))^{1+\sigma} - (\varepsilon i)^{1+\sigma}\big) \le (1+\sigma)\varepsilon(\varepsilon(i+1))^{\sigma} \le (1+\sigma)2^{\sigma}\varepsilon(\varepsilon i)^{\sigma},$$

therefore (3.27) yields

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}M^{\varepsilon}_{1+\sigma}(t) + \varepsilon^{1+m}\sum_{i=n_0}^{\infty}\mu_i(\varepsilon i)^{1+\sigma}u^{\varepsilon}_i &\le \varepsilon^{\theta-1}v^{\varepsilon}\sum_{i=n_0}^{\infty}\tau_i u^{\varepsilon}_i \times \varepsilon \times \big((\varepsilon(i+1))^{1+\sigma} - (\varepsilon i)^{1+\sigma}\big)\\
&\le v^{\varepsilon}(1+\sigma)2^{\sigma}\sum_{i=n_0}^{\infty}\varepsilon^{\theta}\tau_i u^{\varepsilon}_i\varepsilon(\varepsilon i)^{\sigma}\\
&\le K(\rho^0+\lambda T)(1+\sigma)2^{\sigma}M^{\varepsilon}_{\theta+\sigma}(t).
\end{aligned}$$

Since $0 \le \theta \le 1$, and $1+\sigma > \alpha$ (α is the exponent characterizing the growth of the fragmentation coefficient), denoting $C = \max(K(\rho^0+\lambda T)(1+\sigma)2^{\sigma}, 2K)$, we are led to

$$\frac{\mathrm{d}}{\mathrm{d}t}\Big(M^{\varepsilon}_0(t) + M^{\varepsilon}_{1+\sigma}(t)\Big) \le C\Big(M^{\varepsilon}_{\alpha}(t) + M^{\varepsilon}_{\theta+\sigma}(t)\Big) \le 2C\Big(M^{\varepsilon}_0(t) + M^{\varepsilon}_{1+\sigma}(t)\Big),$$

and we conclude by the Gronwall lemma. It ends the proof of Lemma 3.4.1. □

Hereafter, we denote by C a constant depending only on $T, M_0, \rho^0, M_{1+\sigma}, K$ and λ such that

$$M^{\varepsilon}_0, v^{\varepsilon}, M^{\varepsilon}_1, M^{\varepsilon}_{1+\sigma} \le C.$$

Lemma 3.4.2 *Under the assumptions of Lemma 3.4.1, the sequence of monomers concentration* $(v^{\varepsilon})_{\varepsilon>0}$ *is equicontinuous on* $[0,T]$.

Proof. We use the estimates of Lemma 3.4.1 to evaluate the derivative of v^{ε}. We recall the equation satisfied by v^{ε}

$$\frac{\mathrm{d}v^{\varepsilon}}{\mathrm{d}t} = \lambda - \gamma v^{\varepsilon} + \varepsilon^{1+\theta}v^{\varepsilon}\sum \tau_i u^{\varepsilon}_i + 2\varepsilon^{2+\alpha}\sum_{i\ge n_0}\sum_{j<n_0} jk_{j,i}\beta_i u^{\varepsilon}_i,$$

which implies

$$\left|\frac{\mathrm{d}v^{\varepsilon}}{\mathrm{d}t}\right| \le \lambda + \gamma C + KC^2 + 2\varepsilon n_0(\varepsilon)\ KM^{\varepsilon}_{\alpha}.$$

Since the sequence $\big(M^{\varepsilon}_{\alpha}\big)_{\varepsilon>0}$ is uniformly bounded with respect to ε by Lemma 3.4.1 (recall that $\alpha \le 1+\sigma$), the sequence $\big(v^{\varepsilon}\big)_{\varepsilon>0}$ satisfies a uniform Lipschitz criterion on $[0,T]$. This concludes the proof of Lemma 3.4.2. □

Proof of Theorem 3.3.3. By the Arzela-Ascoli theorem and Lemma 3.4.2, there exists a function $V \in \mathcal{C}([0,T])$ and a subsequence that we still denote v^{ε} such that

$$v^{\varepsilon}(t) \longrightarrow V(t) \quad \text{in} \quad \mathcal{C}([0,T]).$$

In the same way, the moment estimates of Lemma 3.4.1 give uniform boundedness for $(1 + x + x^{1+\sigma})u^{\varepsilon}$ in $\mathcal{M}^1([0,\infty))$. Pick a function $\varphi \in \mathcal{C}^{\infty}_c([0,\infty))$. We define

$$\varphi^{\varepsilon}_i = \int_{i\varepsilon}^{(i+1)\varepsilon}\varphi(x)\,\mathrm{d}x,$$

so that $\sum_{n_0\varepsilon}^{\infty} u_i^\varepsilon \varphi_i^\varepsilon = \int_0^\infty u^\varepsilon(t,x)\varphi(x)\,\mathrm{d}x$, and also for $y \in [j\varepsilon,(j+1)\varepsilon[$,

$$\int_0^y k^\varepsilon(x,y)\varphi(x)dx = \int_0^{j\varepsilon} k^\varepsilon(x,j\varepsilon)\varphi(x)dx = \sum_{i=0}^{j} k_{i,j}\frac{\varphi_i^\varepsilon}{\varepsilon}$$

Thanks to the moment estimates of Lemma 3.4.1, and using (3.26), we have

$$\left|\frac{\mathrm{d}}{\mathrm{d}t}\int_0^\infty u^\varepsilon(t,x)\varphi(x)\,\mathrm{d}x\right| \le C(\|\varphi\|_\infty + \|\varphi'\|_\infty) \qquad \text{and} \qquad \left|\int_0^\infty u^\varepsilon(t,x)\varphi(x)\,\mathrm{d}x\right| \le C\|\varphi\|_\infty$$

for some constant C depending only on $K, M_0, M_{1+\sigma}, \rho^0, \lambda, T$. Therefore, for any function $\varphi \in \mathcal{C}_c^\infty([0,\infty))$, the integral $\int u^\varepsilon(\cdot,x)\varphi(x)\,\mathrm{d}x$ is equibounded and equicontinuous. Using a density argument, we can extend this property to $\varphi \in \mathcal{C}_0([0,\infty))$, the space of continuous functions on $[0,\infty)$ that tend to 0 at infinity. This means that $\left(\int_0^\infty u^\varepsilon(.,x)\varphi(x)\,\mathrm{d}x\right)_\varepsilon$ belongs to a compact set of $\mathcal{C}(0,T)$. As in [28], by using the separability of $\mathcal{C}_0([0,\infty))$ and the Cantor diagonal process, we can extract a subsequence u^{ε_n} and $U \in \mathcal{C}([0,T];\mathcal{M}^1([0,\infty))-\text{weak}-\star)$, such that the following convergence

$$\int_0^\infty u^{\varepsilon_n}(t,x)\varphi(x)\,\mathrm{d}x \to \int_0^\infty U(t,\,\mathrm{d}x)\varphi(x),$$

as $\varepsilon_n \to 0$, holds uniformly on $[0,T]$, for any $\varphi \in \mathcal{C}_0([0,\infty))$. As $u^\varepsilon(t,x) = 0$ for $x \le \varepsilon n_0(\varepsilon)$, we check that $U(t,.)$ has its support in $[x_0,\infty[$. It remains to prove that (U,V) satisfies (3.13) (3.14).

Let φ be a smooth function supported in $[\delta, M]$ with $x_0 < \delta < M < +\infty$, choosing $\varepsilon n_0(\varepsilon) + 2\varepsilon < \delta$ (what is possible due to (3.20)). By using Lemma 3.3.1 and Lemma 3.7.1, we check that, for a suitable subsequence, one has

$$\begin{aligned}
\int_0^\infty \mu^{\varepsilon_n}(x)u^{\varepsilon_n}(t,x)\varphi(x)\,\mathrm{d}x \quad &\xrightarrow[\varepsilon_n\to 0]{} \quad \int_0^\infty \mu(x)U(t,\,\mathrm{d}x)\varphi(x),\\
\int_0^\infty \beta^{\varepsilon_n}(x)u^{\varepsilon_n}(t,x)\varphi(x)\,\mathrm{d}x \quad &\xrightarrow[\varepsilon_n\to 0]{} \quad \int_0^\infty \beta(x)U(t,\,\mathrm{d}x)\varphi(x),\\
\int_0^\infty \tau^{\varepsilon_n}(x)u^{\varepsilon_n}(t,x)\varphi(x)\,\mathrm{d}x \quad &\xrightarrow[\varepsilon_n\to 0]{} \quad \int_0^\infty \tau(x)U(t,\,\mathrm{d}x)\varphi(x),
\end{aligned} \tag{3.29}$$

uniformly on $[0,T]$. Equation (3.26) can be recast in the following integral form

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}\int_0^\infty u^\varepsilon(t,x)\varphi(x)\,\mathrm{d}x &= -\int_{x_0}^\infty \mu^\varepsilon u^\varepsilon(t,x)\varphi(x)\,\mathrm{d}x - v^\varepsilon\int_0^\infty \tau^\varepsilon u^\varepsilon \Delta^\varepsilon\varphi(x)\,\mathrm{d}x\\
-\int_0^\infty \beta^\varepsilon u^\varepsilon(t,x)\varphi(x)\,\mathrm{d}x &+ 2\int_0^\infty\int_x^\infty \varphi(x)\beta^\varepsilon(y)u^\varepsilon(t,y)k^\varepsilon(x,y)\,\mathrm{d}x\,\mathrm{d}y
\end{aligned} \tag{3.30}$$

where we have defined

$$\Delta^\varepsilon\varphi(x) = \frac{\varphi(x+\varepsilon)-\varphi(x)}{\varepsilon},$$

and thereby

$$\int_{i\varepsilon}^{(i+1)\varepsilon} \Delta^\varepsilon\varphi(x)\,\mathrm{d}x = \frac{\varphi_{i+1}^\varepsilon - \varphi_i^\varepsilon}{\varepsilon}.$$

In the right hand side of (3.30), the first and third terms are treated in (3.29). Using (3.29) again and remarking that $|\Delta^\varepsilon(x) - \varphi'(x)| \le \varepsilon\|\varphi''\|_\infty$, we have

$$\int_0^\infty \tau^{\varepsilon_n}(x)u^{\varepsilon_n}(t,x)\Delta^{\varepsilon_n}\varphi(x)\,\mathrm{d}x \xrightarrow[\varepsilon_n\to 0]{} \int_0^\infty \tau(x)U(t,\,\mathrm{d}x)\varphi'(x), \tag{3.31}$$

uniformly on $[0,T]$. Let us now study the convergence of the last term in (3.30). To this end, we use the notation ϕ and ϕ^ε as defined in (3.24) of Lemma 3.3.2 and we rewrite

$$2\int_{x_0}^{\infty}\int_{x_0}^{y}\varphi(x)k^\varepsilon(x,y)u^\varepsilon(t,y)\beta^\varepsilon(y)\,\mathrm{d}x\,\mathrm{d}y=2\int_{x_0}^{\infty}u^\varepsilon(t,y)\beta^\varepsilon(y)\phi^\varepsilon(y)\,\mathrm{d}y.$$

Owing to (3.23) we use Lemma 3.3.2 which leads to

$$\phi^{\varepsilon_n}\xrightarrow[\varepsilon_n\to 0]{}\phi\qquad\text{uniformly on}\quad [x_0,R]\ \text{ for any }\ R>0,$$

and thus also

$$\beta^{\varepsilon_n}\phi^{\varepsilon_n}\xrightarrow[\varepsilon_n\to 0]{}\beta\phi\qquad\text{uniformly on}\quad [x_0,R]\ \text{ for any }\ R>0,$$

for a suitable subsequence. Finally, we observe that ϕ^{ε_n} and therefore ϕ are bounded by $\|\varphi\|_\infty$. Thus, by using the boundedness of the higher order moments of u^ε in Lemma 3.4.1 with $1+\sigma>\alpha$, we show that the fragmentation term passes to the limit (see Lemma 3.7.1 in the Appendix). We finally arrive at

$$\begin{aligned}&\int_{x_0}^{\infty}U(t,\,\mathrm{d}x)\varphi(x)-\int_{x_0}^{\infty}U(0,\,\mathrm{d}x)\varphi(x)\\ &=-\int_0^t\int_{x_0}^{\infty}\mu U(t,\,\mathrm{d}x)\varphi(x)-\int_0^t V(s)\int_{x_0}^{\infty}\tau(x)U(s,\,\mathrm{d}x)\varphi'(x)\\ &\quad-\int_0^t\int_{x_0}^{\infty}\beta(x)U(s,\,\mathrm{d}x)(t,x)\varphi(x)+2\int_0^t\int_{x_0}^{\infty}\beta(y)U(s,\,\mathrm{d}y)\int_0^y\varphi(x)k(\mathrm{d}x,y),\end{aligned}$$

which is the weak formulation (3.13). Moreover, (3.28) recasts as

$$\begin{aligned}v^\varepsilon(t)+\int_0^\infty e^\varepsilon(x)u^\varepsilon(t,x)\,\mathrm{d}x\ &=\ v^{0,\varepsilon}(t)+\int_0^\infty e^\varepsilon(x)u^\varepsilon(0,x)\,\mathrm{d}x\\ &\quad+\lambda t-\gamma\int_0^t v^\varepsilon(s)\,\mathrm{d}s-\int_0^t\int_0^\infty e^\varepsilon(x)\mu^\varepsilon(x)u^\varepsilon(s,x)\,\mathrm{d}x\,\mathrm{d}s,\end{aligned}$$

where

$$e^\varepsilon(x)=\sum_{i=0}^{\infty}\varepsilon i\ \chi_{[i\varepsilon,(i+1)\varepsilon)}(x).$$

Clearly $e^\varepsilon(x)$ converges to x uniformly. Using the moment estimate in Lemma 3.4.1, with $\sigma>0$, we obtain

$$v^{\varepsilon_n}(t)+\int_0^\infty e^{\varepsilon_n}(x)u^{\varepsilon_n}(t,x)\,\mathrm{d}x\xrightarrow[\varepsilon_n\to 0]{}V(t)+\int_0^\infty xU(t,\,\mathrm{d}x)$$

uniformly on $[0,T]$ as well as

$$\int_0^t\int_0^\infty e^{\varepsilon_n}(x)\mu^{\varepsilon_n}(x)u^{\varepsilon_n}(s,x)\,\mathrm{d}x\,\mathrm{d}s\xrightarrow[\varepsilon_n\to 0]{}\int_0^t\int_0^\infty x\mu(x)U(s,\,\mathrm{d}x)\,\mathrm{d}s.$$

We refer again to Lemma 3.7.1, or a slight adaptation of it. As $\varepsilon_n\to 0$ we are thus led to (3.14). □

Proof of Theorem 3.3.4. We rewrite the rescaled ODE as

$$\frac{dv^\varepsilon}{dt}=\lambda-\gamma v^\varepsilon-\int_{n_0\varepsilon}^{\infty}\tau^\varepsilon(x)u^\varepsilon(t,x)dx+2\int_{n_0\varepsilon}^{\infty}\beta^\varepsilon(y)u^\varepsilon(t,y)\int_0^{n_0^\varepsilon}e^\varepsilon(x)k^\varepsilon(x,y)dx,$$

Depending on the value of x_0 defined in assumption (3.20), we have to care about the last term ($x_0 > 0$) or the next two last terms ($x_0 = 0$). As already remarked in the proof of Lemma 3.4.2, in case where $x_0 = 0$, the fragmentation term can be dominated by

$$2\varepsilon^{2+\alpha} \sum_{i \geq n_0} \sum_{j < n_0} j k_{j,i} \beta_i u^\varepsilon \leq 2\varepsilon n_0(\varepsilon)\ K M_\alpha^\varepsilon.$$

Hence this contribution vanishes as ε goes to 0 when $\lim_{\varepsilon\to 0} \varepsilon n_0(\varepsilon) = x_0 = 0$. Nevertheless for case i) we still have to justify that $\int_0^\infty \tau^\varepsilon(x) u^\varepsilon(t,x)\,\mathrm{d}x$ passes to the limit. We get

$$\int_{n_0(\varepsilon_n)\varepsilon_n}^\infty \tau^{\varepsilon_n} u^{\varepsilon_n}(t,x)\,\mathrm{d}x \xrightarrow[\varepsilon_n \to 0]{} \int_{x_0}^\infty \tau U(t,\,\mathrm{d}x), \qquad \text{in} \quad \mathcal{C}([0,T]) \tag{3.32}$$

by using the strengthened assumption $0 < \theta \leq 1$ in (3.21). Indeed it implies that $\tau^\varepsilon(x)$ converges uniformly to $\tau(x)$ on any compact set $[0,R]$ while these functions do not grow faster than x at infinity. We can thus use Lemma 3.7.1 to conclude.

In the situation ii), another difficulty comes from the fragmentation term since we have to prove that

$$\begin{aligned} 2\int_{n_0(\varepsilon_n)\varepsilon_n}^\infty \int_0^{n_0(\varepsilon_n)\varepsilon_n} & e^{\varepsilon_n}(x) k^{\varepsilon_n}(x,y)\beta^{\varepsilon_n}(y) u^{\varepsilon_n}(t,y)\,\mathrm{d}x\,\mathrm{d}y \\ & \xrightarrow[\varepsilon_n \to 0]{} 2\int_{x_0}^\infty \int_0^{x_0} x k(\mathrm{d}x,y)\beta(y) U(t,\,\mathrm{d}y). \end{aligned}$$

The stronger compactness assumptions (3.25) are basically Ascoli-type assumptions on the repartition function associated to the kernels k^ε. Denoting, in a similar manner to Appendix 3.7.2 :

$$F^\varepsilon(x,y) = \int_0^x k^\varepsilon(z,y)\,\mathrm{d}z, \qquad G^\varepsilon(x,y) = \int_0^x F^\varepsilon(z,y)\,\mathrm{d}z,$$

Lemma 3.7.7 (see Appendix 3.7.2) ensures that $F^\varepsilon \to F$ uniformly on compact sets of $\mathbb{R}_+ \times [x_0, +\infty)$. We also make the remark that

$$\Big| \int_0^{n_0\varepsilon} e^\varepsilon(x) k^\varepsilon(x,y)\,\mathrm{d}x - \int_0^{n_0\varepsilon} x k^\varepsilon(x,y)\,\mathrm{d}x \Big| \leq \varepsilon,$$

$$\begin{aligned} \int_0^{n_0\varepsilon} x k^\varepsilon(x,y)\,\mathrm{d}x &= \Big[x F^\varepsilon(x,y) \Big]_{x=0}^{x=n_0\varepsilon} - \int_0^{n_0\varepsilon} F^\varepsilon(x,y)\,\mathrm{d}x \\ &= (n_0\varepsilon) F^\varepsilon(n_0\varepsilon, y) - G^\varepsilon(n_0\varepsilon, y). \end{aligned}$$

Thanks to Lemma 3.7.7, we know that the concerned quantities are uniformly bounded and converge uniformly on compact sets, so that

$$\int_0^{n_0\varepsilon_n} e^{\varepsilon_n}(x) k^{\varepsilon_n}(x,y)\,\mathrm{d}x \xrightarrow[\varepsilon_n \to 0]{} \int_0^{x_0} x k(\mathrm{d}x, y) \qquad \text{uniformly on compact sets.}$$

And as before this is sufficient to prove that

$$\begin{aligned} 2\int_{n_0\varepsilon_n}^\infty & \beta^{\varepsilon_n}(y) u^{\varepsilon_n}(t,y) \int_0^{n_0\varepsilon_n} e^{\varepsilon_n}(x) k^{\varepsilon_n}(x,y)\,\mathrm{d}x\,\mathrm{d}y \\ & \xrightarrow[\varepsilon_n \to 0]{} 2\int_{x_0}^\infty \beta(y) U(t,\,\mathrm{d}y) \int_0^{x_0} x k(\mathrm{d}x, y). \end{aligned}$$

□

3.5 Boundary Condition for the Continuous System

The discrete system (3.1) only needs an initial condition prescribing the u_i's and v at time $t = 0$ to be well-posed, as Theorem 3.2.1 states. It is different for the continuous system (3.2)(3.3) : a boundary condition at $x = x_0$ is needed when $\tau(x_0) > 0$ (in which case the characteristics associated to the "velocity" τ are "incoming"). Even when $\tau(x_0) = 0$, difficulties might arise when $x \mapsto \tau(x)$ is not regular enough to define the associated characteristics. However, according to the analysis of [41, 65], we have seen that the notion of "monomer preserving solution" appears naturally, inserting (3.12) as a constraint. It leads to the question of deciding how this condition is related to (3.2) and (3.3) and to determine the corresponding boundary condition to be used at $x = x_0$.

Let (U, V) be a "monomer preserving" solution. In this section we do not care about regularity requirement, and we perform several manipulations on the solution (that is assuming all the necessary integrability conditions). We suppose that the kernel k splits into a Dirac mass at $x = x_0$ and a measure which is diffuse at x_0 :

$$k(\mathrm{d}x, y) = l(\mathrm{d}x, y) + \delta_{x=x_0^+}(\mathrm{d}x)\psi^+(y) + \delta_{x=x_0^-}(\mathrm{d}x)\psi^-(y),$$

where for any $y \geq 0$, $l([x_0 - \eta, x_0 + \eta], y) \to 0$ as η goes to 0. We have defined here $\delta_{x=x_0^\pm}$ by

$$\forall \phi \in \mathcal{C}_b\big([x_0, \infty)\big), \quad < \delta_{x=x_0^+}, \phi >= \phi(x_0); \qquad \forall \phi \in \mathcal{C}_b\big((0, x_0]\big), \quad < \delta_{x=x_0^+}, \phi >= \phi(x_0).$$

Both of them are actually a Dirac mass at x_0, but we have to distinguish between x_0^+ and x_0^- because both their biological and mathematical interpretation are different. The Dirac mass at x_0^+ means that polymers of size x_0 are formed, whereas the Dirac mass at x_0^- is interpreted as breakages of polymers of size x_0 going back to the monomers compartment V. In terms of the asymptotic process, one can think of $\delta_{x_0^-}$ as the Dirac mass at x_0 produced by using information from the left, that is defined from $k^\varepsilon(x, y)\chi_{[0, n_0\varepsilon[}(x)\,\mathrm{d}x$, and $\delta_{x_0^+}$ as the Dirac mass at x_0 produced by $k^\varepsilon(x, y)\chi_{[n_0\varepsilon, y]}(x)\,\mathrm{d}x$ which relies on the information from the right of x_0. To give a simple example, the sequence with $k_{n_0-1,j} = \frac{1}{2}$ and the sequence with $k_{n_0+1,j} = \frac{1}{2}$ would respectively lead to production of $\frac{1}{2}\delta_{x_0^-}$ and $\frac{1}{2}\delta_{x_0^+}$. As shown below, the mathematical treatment of each is different.

The time derivative of (3.14) leads to

$$\frac{\mathrm{d}}{\mathrm{d}t}\varrho = \frac{\mathrm{d}V}{\mathrm{d}t} + \int_{x_0}^{\infty} x \frac{\partial}{\partial t} U(t, x)\,\mathrm{d}x = -\int_{x_0}^{\infty} x\mu(x) U(t, x)\,\mathrm{d}x + \lambda - \gamma V$$

In the left hand side, we can compute the derivative of the moment of U by using (3.3). We get

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\int_{x_0}^{\infty} xU(t, x)\,\mathrm{d}x \quad &= \quad -\int_{x_0}^{\infty} x\beta U\,\mathrm{d}x - \int_{x_0}^{\infty} x\mu U\,\mathrm{d}x \\ &\quad -V\int_{x_0}^{\infty} x\frac{\partial}{\partial x}(\tau U)\,\mathrm{d}x + 2\int_{x_0}^{\infty} x \int_{x}^{\infty} l(\mathrm{d}x, y)\beta(y) U(t, y)\,\mathrm{d}y.\end{aligned}$$

In this equation, since (3.3) is only written for $x > x_0$, only the diffuse part of the kernel k appears. Integrating by parts, the convection term yields

$$\int_{x_0}^{\infty} x\frac{\partial}{\partial x}(\tau U)\,\mathrm{d}x = -x_0\tau(x_0)U(t, x_0) - \int_{x_0}^{\infty} \tau U\,\mathrm{d}x.$$

Now we use (3.2), which writes

$$\begin{aligned}\frac{\mathrm{d}V}{\mathrm{d}t} = \lambda - \gamma V - V\int_{x_0}^{\infty} \tau(x) U(t, x)\,\mathrm{d}x \quad &+2\int_{x=x_0}^{\infty}\int_{y=0}^{x_0} y\, l(\mathrm{d}y, x)\beta(x) U(t, x)\,\mathrm{d}x \\ &+2x_0\int_{x=x_0}^{\infty} \psi^-(x)\beta(x) U(t, x)\,\mathrm{d}x\end{aligned}$$

then we obtain

$$x_0V(t)\tau(x_0)U(t,x_0)-\int_{x_0}^{\infty}x\beta(x)U(t,x)\,\mathrm{d}x$$
$$+2\int_{x_0}^{\infty}\beta(x)U(t,x)\left(\int_0^x yl(\mathrm{d}y,x)+x_0\psi^-(x)\right)\mathrm{d}x=0.$$

However, (3.7) is interpreted as

$$2\int_0^x yl(\mathrm{d}y,x)+2x_0\chi_{[x_0,\infty)}(x)\psi^-(x)+2x_0\chi_{(x_0,\infty)}(x)\psi^+(x)=x.$$

We are thus led to the relation :

$$x_0\left(V(t)\tau(x_0)U(t,x_0)-2\int_{x_0}^{\infty}\psi^+(x)\beta(x)U(t,x)\,\mathrm{d}x\right)=0$$

which suggests the boundary condition

$$x_0V\tau(x_0)U(t,x_0)=2x_0\int_{x_0}^{\infty}\psi^+(x)\beta(x)U(t,x)\,\mathrm{d}x. \tag{3.33}$$

(Note that written in this way it makes sense also when $x_0=0$.)

When $x_0>0$, the above calculation gives solid intuitive ground to choose Equation (3.33) as a boundary condition, defining the incoming flux by means of a weighted average of the solution over the size variable. In particular if the Dirac part vanishes, that is if $\psi^+(x)=0$, we obtain

$$V\tau(x_0)U(t,x_0)=0,$$

the boundary condition proposed in [50], for constant coefficient τ. It is also the boundary condition used in [65].

If $x_0=0$, the problem is still harder, since Equation (3.33) is empty. Dividing it by $x_0>0$ and passing formally to the limit would however give :

$$V\tau(0)U(0)=2\int_0^{\infty}\psi^+(x)\beta(x)U(t,x)\,\mathrm{d}x. \tag{3.34}$$

Here again, it generalizes what has been proposed in [50] for τ constant and $k(x,y)=\frac{1}{y}\chi_{x\le y}$, though without any rigorous justification, and if $\psi^+=0$ it imposes a vanishing incoming flux.

3.6 Discussion on the parameters and choice for ε

The continuous model is easier to deal with than the discrete one, and thus its use is of great interest both for mathematical analysis and numerical simulations. However, as the above derivation shows, it is necessary to check precisely its range of validity. In this section, we try to enlight some of the parameters requirements ; a full biological discussion upon their values can be found in [68]. It is based on [79, 78] and references therein.

3.6.1 Orders of magnitude

To carry out the previous scaling limit theorem, we made the following assumptions :

$$s=\frac{\mathcal{U}}{\mathcal{V}}=\varepsilon^2,\quad \nu=\frac{1}{\varepsilon},\quad \lim\ _{\varepsilon\to 0}\varepsilon n_0(\varepsilon)=x_0,\quad \eta=a=c=d=1.$$

Let us denote i_0 the average size of polymers. Even if there still exists much uncertainty upon its value, we can estimate that the typical size of polymers ranges between 15 and 1000, so we can write

$$\varepsilon_1 = \frac{1}{i_0} \ll 1.$$

It is also known that the "conversion rate" of PrPc is around 5 to 10% at most (depending on the experiment, on the stage of the disease, etc) ; it means that the mass of proteins present in the monomeric form is much larger than the mass of proteins involved in polymers. In terms of characteristic values, it writes

$$\varepsilon_2 = \frac{i_0 \mathcal{U}}{\mathcal{V}} \ll 1.$$

Finally, we get :

$$\varepsilon = \sqrt{\frac{\mathcal{U}}{\mathcal{V}}} = \sqrt{\varepsilon_1 \varepsilon_2} \ll 1.$$

Hence, it legitimates the assumption on the parameters s and ε. Concerning the parameter a, we have $a = \frac{L}{\mathcal{V}} \approx \frac{2400}{500}$, which is in the order of 1. We have only $d_0 \leq 5.10^{-2}$: this should lead to neglect the degradation rate of polymers and simplify the equation.

For the fragmentation frequency, it is in the order of the exponential growth rate, found experimentally to be in the order of 0.1; in the case of Masel's articles [79, 78], it is supposed that $\alpha = 1$, so it seems relevant (it leads to a fragmentation frequency in the order of ε). However, it has to be precisely compared to the other small parameters which are given by the typical size i_0 and the conversion rate to justify the approximation. Moreover, the assumption of a linear fragmentation kernel β has to be confrounted to experiments.

Concerning the aggregation rate $\mathcal{T}$, and its related parameter $\nu = \tau V$, as shown in [68], in most cases we have $\frac{1}{\nu}$ in the range of $[0.01, 0.1]$, so it seems justified to suppose it small; what has to be explored is its link with the other previously seen small parameters.

3.6.2 Discussion on the fragmentation rates $k_{i,j}$

To illustrate the central importance of a good estimate of the orders of magnitude, we exhibit here a case where the limit is not the continuous System (3.2)(3.3), but another one. Our calculation is formal, but a complete proof should be deduced from what preceeds and from [28].

Let us take, instead of $b = \varepsilon^{\alpha}$, the following scaling

$$b = \varepsilon^{\alpha - 1},$$

and suppose also that the fragmentation kernel verifies

$$k_{1,i} = k_{i-1,i} = \tfrac{1}{2}(1 - \varepsilon r_i), \qquad k_{i,j} = \varepsilon k^0_{i,j} r_j, \qquad 2 \leq i \leq j-2,$$

$$\sum_{i=2}^{j-2} k^0_{i,j} = 1, \qquad\qquad k^0_{i,j} = k^0_{j-i,j}.$$

It means that the polymers are much more likely to break at their ends than in the middle of their chain. The rescaled equations (3.19) are replaced by the following ones

$$\begin{cases} \dfrac{\mathrm{d}v}{\mathrm{d}t} = \lambda - \gamma v - \varepsilon^{\theta+1} v \sum \tau_i u_i + 2\varepsilon^{1+\alpha} \displaystyle\sum_{i \geq n_0} \sum_{j < n_0} j k_{j,i} \beta_i u_i, \\ \dfrac{\mathrm{d}u_i}{\mathrm{d}t} = -\varepsilon^m \mu_i u_i - \varepsilon^{\alpha-1} \beta_i u_i - \varepsilon^{\theta-1} v (\tau_i u_i - \tau_{i-1} u_{i-1}) + 2\varepsilon^{\alpha-1} \displaystyle\sum_{j > i} \beta_j k_{i,j} u_j, \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \text{for } i \geq n_0. \end{cases} \tag{3.35}$$

The only changes in Equation (3.35) compared to (3.19) are the fragmentation terms. In order to make their limits clearly appear, we rearrange them as follows. First, in the equation for v, we write

$$\begin{aligned}2\varepsilon^{1+\alpha}\sum_{i\geq n_0}\sum_{j<n_0} jk_{j,i}\beta_i u_i &= \varepsilon^{1+\alpha}\sum_{i\geq n_0}\beta_i u_i + \varepsilon^{1+\alpha}(n_0-1)\beta_{n_0}u_{n_0}\\ &\quad -\varepsilon^{2+\alpha}\sum_{i\geq n_0} r_i\beta_i u_i - \varepsilon^{2+\alpha}(n_0-1)r_{n_0}\beta_{n_0}u_{n_0}\\ &\quad +2\varepsilon^{2+\alpha}\sum_{i\geq n_0}\sum_{j=2}^{\min(n_0-1,i-2)} jk^0_{j,i}r_i\beta_i u_i.\end{aligned}$$

All the terms vanish when ε tends to zero, except the first one, similar to the aggregation term $\varepsilon^{\theta+1}v\sum\tau_i u_i$, and the last one, similar to the usual fragmentation term in Equation (3.19), where $r\beta$ replaces β and k^0 replaces k. We now turn to the equation for u_i, and we get :

$$\begin{aligned}-\varepsilon^{\alpha-1}\beta_i u_i + 2\varepsilon^{\alpha-1}\sum_{j>i}\beta_j k_{i,j}u_j &= -\varepsilon^{\alpha-1}\beta_i u_i + \varepsilon^{\alpha-1}\beta_{i+1}u_{i+1} - \varepsilon^{\alpha}r_{i+1}\beta_{i+1}u_{i+1}\\ &\quad +2\varepsilon^{\alpha}\sum_{j>i+1}k^0_{i,j}r_j\beta_j u_j.\end{aligned}$$

The first two terms can be treated as a derivative, like the aggregation term $-\varepsilon^{\theta-1}v(\tau_i u_i - \tau_{i-1}u_{i-1})$; the last two ones are similar to the usual fragmentation term, where $r\beta$ replaces β and k^0 replaces k.

Hence, under Assumptions (3.23) on $k^0_{i,j}$ and (3.22) on r_j (with a constant as an upper bound, so that its limit r should be in $\mathcal{C}_b$) and β_j, with $\alpha-1\leq 1+\sigma$, denoting respectively k^0, r and β their limits in the sense of Lemma 3.3.1 and Lemma 3.3.2, the limit system writes :

$$\left\{\begin{aligned}\frac{\mathrm{d}v}{\mathrm{d}t} &= \lambda-\gamma v - v\int_{x_0}^{\infty}\tau(x)U(t,x)\,\mathrm{d}x\\ &\qquad +\int_{x_0}^{\infty}\beta(x)U(t,x)\,\mathrm{d}x + 2\int_{x=x_0}^{\infty}\int_{y=0}^{x_0} yk^0(y,x)r(x)\beta(x)U(t,x)\,\mathrm{d}y\,\mathrm{d}x,\\ \frac{\partial u}{\partial t} &= -\mu(x)U(t,x) - r(x)\beta(x)U(t,x) - v\frac{\partial}{\partial x}(\tau U)\\ &\qquad +\frac{\partial}{\partial x}(\beta u) + 2\int_{x}^{\infty} r(y)k^0(x,y)\beta(y)U(t,y)\,\mathrm{d}y.\end{aligned}\right. \tag{3.36}$$

Notice also that (3.36) includes the case of "renewal" type equations (refer to [92] for instance), meaning that the ends of the polymers are more likely to break. A relevant case corresponding to the above setting consists in assuming :

$$\begin{aligned}&k^0_{i-n_0,i} = k^0_{n_0,i} = \frac{m_i}{2}, &&k^0_{i,j} = \tilde{k}_{i,j}(1-m_j) &&\text{for } i\notin\{n_0, j-n_0\},\\ &\sum_{i=2}^{j-2}\tilde{k}_{i,j} = 1, &&\tilde{k}_{i,j} = O(\tfrac{1}{j}),\end{aligned}$$

with (m_i) satisfying the assumptions of Lemma 3.3.1 and $\tilde{k}_{i,j}$ satisfying Assumption (3.23). We also define $m(y)$ as the limit of m^{ε} defined as in Lemma 3.3.1. Then Equation (3.36) remains valid, and as in Section 3.5, the kernel k^0 splits into a Dirac mass at $x=x_0$ and a measure which is diffuse at x_0 :

$$k^0(\mathrm{d}x,y) = \tilde{k}(\mathrm{d}x,y)(1-m(y)) + \delta_{x=x_0^+}(\mathrm{d}x)m(y).$$

We then refer to Section 3.5 for a formal discussion on the choice of Equation (3.34) as a boundary condition. However, Theorems 3.3.3 and 3.3.4 do not apply, since such a fragmentation kernel k does not satisfy Assumption (3.23).

Both of these cases mean that the ends of polymers are more likely to break. What changes is the order of magnitude of what we mean by "more likely to break" : is it in the order of $\frac{1}{\varepsilon}$, in which case System (3.2)(3.3) is (formally) valid, but with a (formal) boundary condition of renewal type (3.34) ? Or is the difference in the order of $\frac{1}{\varepsilon^2}$, in which case Equation (3.36) is more likely ? Refer to [68] for a more complete investigation of what model should be used in what experimental context.

3.6.3 Discussion on the minimal size n_0

We have seen above that to have $x_0 = 0$, it suffices to make Assumption (3.20). Having also seen that the typical size i_0 is large, and that

$$\varepsilon^2 = \frac{1}{i_0}\frac{M}{m_1 V}, \qquad \frac{M}{m_1 V} \ll 1,$$

it is in any case valid to suppose that

$$\frac{1}{i_0} = \varepsilon^c, \qquad 0 < c < 2.$$

Hence, Assumption (3.20) can be reformulated as :

$$n_0 \ll i_0^{\frac{1}{c}}. \tag{3.37}$$

For $c = 1$, it means $n_0 \ll i_0$, which is true. On the contrary, if we suppose that $x_0 > 0$, it means that $n_0 \approx i_0^{\frac{1}{c}}$: in most cases, where for instance $i_0 = 100$ or $i_0 = 1000$, it seems irrelevant.

To conclude this section (or open the debate), it seems that for each specific experiment, like PMCA protocole, *in vitro* or *in vivo* measures, or yet for the case of recombinant *PrP* (see [97]), the orders of magnitude of each parameter should be carefully estimated, in order to adapt the previous model and stick to the biological reality - which proves to be very different in *in vivo*, *ex vivo* or *in vitro* situations, or yet at the beginning (when there are still very few polymers) and at the end of experiments. The previous discussion illustrates this idea, and gives some possible extensions to the model we have studied.

3.7 Appendix

3.7.1 Compactness of the coefficients

Proof of Lemma 3.3.1. We refer to [28] for the case $\kappa = 0$. We prove here the case $\kappa > 0$. First, we show that z^ε is close to a subsequence satisfying the requirements of the Arzela–Ascoli theorem on $[r, R]$. We define $\tilde{z}^\varepsilon$ by

$$\tilde{z}^\varepsilon(x) = \varepsilon^\kappa z_i + \varepsilon^\kappa \frac{z_{i+1} - z_i}{\varepsilon}(x - i\varepsilon) \text{ for } i\varepsilon \leq x \leq (i+1)\varepsilon.$$

We have

$$\begin{aligned} |\tilde{z}^\varepsilon(x) - z^\varepsilon(x)| &= |\varepsilon^\kappa \frac{z_{i+1} - z_i}{\varepsilon}(x - i\varepsilon)|, \\ &\leq \varepsilon^\kappa |z_{i+1} - z_i|, \\ &\leq \varepsilon K(\varepsilon i)^{\kappa-1} \leq 2\varepsilon(K r^{\kappa-1} + K R^{\kappa-1}). \end{aligned}$$

Furthermore $\tilde{z}^\varepsilon$ has a bounded derivative since

$$\begin{aligned}\left|\frac{\mathrm{d}\tilde{z}^\varepsilon}{\mathrm{d}x}\right| &= \varepsilon^\kappa \frac{z_{i+1}-z_i}{\varepsilon},\\ &\leq K(\varepsilon i)^{\kappa-1},\\ &\leq Kr^{\kappa-1}+KR^{\kappa-1}.\end{aligned}$$

Therefore, the family $\tilde{z}^\varepsilon$ satisfies the requirements of the Arzela–Ascoli theorem for any interval $[r,R]$ with $0<r<R<+\infty$. We can extract a subsequence converging uniformly to z. The limit is continuous and satisfies $z(x)\leq Kx^\kappa$. When $\kappa>0$ the convergence extends on $[0,R]$ owing to the remark

$$\sup_{x\in[0,r]} \left|(z^\varepsilon - z)(x)\right| \leq 2Kr.$$

This concludes the proof. □

During the proof of Theorem 3.3.3 and Theorem 3.3.4 we made repeated use of the following claim.

Lemma 3.7.1 *Let* z_n *converge to a continuous function* z *uniformly on* $[0,M]$ *for any* $0<M<\infty$, *with* $|z_n(x)|\leq K(1+x^\kappa)$. *Let* $\big(u_n\big)_{n\in\mathbb{N}}$ *be a sequence of integrable functions which converges to* U *weakly-*$\star$ *in* $\mathcal{M}^1([0,\infty))$. *We suppose furthermore that*

$$\sup_{n\in\mathbb{N}}\int_0^\infty (1+x^\ell)|u_n(x)|\,\mathrm{d}x \leq C<\infty.$$

Assuming $0\leq\kappa<\ell$, *we have*

$$\int_0^\infty z_n(x)u_n(x)\,\mathrm{d}x \xrightarrow[n\to\infty]{} \int_0^\infty z(x)U(\mathrm{d}x).$$

Proof. First we notice that since for any compactly supported continuous function we have

$$\Big|\int_0^\infty (1+x^\ell)u_n(x)\varphi(x)\,\mathrm{d}x\Big| \leq C\|\varphi\|_\infty,$$

we have, from weak star convergence with $(1+x^l)\varphi(x)$ as a test function,

$$\Big|\int_0^\infty (1+x^\ell)\varphi(x)U(\mathrm{d}x)\Big| \leq C\|\varphi\|_\infty,$$

and therefore $(1+x^\ell)U(\mathrm{d}x)$ is a signed measure with total variation

$$\|(1+x^\ell)U(\mathrm{d}x)\|_{VT} = \int_0^\infty (1+x)^\ell\ |U|(\mathrm{d}x)\leq C.$$

We denote as usual $U(\mathrm{d}x)=U^+(\mathrm{d}x)-U^-(\mathrm{d}x)$ and $|U|(\mathrm{d}x)=U^+(\mathrm{d}x)+U^-(\mathrm{d}x)$.

Let $\zeta\in C_c^\infty([0,\infty))$ such that $0\leq\zeta(x)\leq 1$, $\zeta(x)=1$ on $[0,R]$, $0<R<\infty$ and

$\mathrm{supp}(\zeta) \subset [0, 2R]$. We split

$$\begin{aligned}
&\Big| \int_0^\infty z_n(x) u_n(x)\,\mathrm{d}x - \int_0^\infty z(x) U(\mathrm{d}x) \Big| \\
&\quad = \Big| \int_0^\infty z_n(x)\zeta(x) u_n(x)\,\mathrm{d}x - \int_0^\infty z(x)\zeta(x) U(\mathrm{d}x) \\
&\qquad\qquad + \int_0^\infty z_n(x)\big(1-\zeta(x)\big) u_n(x)\,\mathrm{d}x - \int_0^\infty z(x)\big(1-\zeta(x)\big) U(\mathrm{d}x) \Big| \\
&\quad \le \int_0^\infty |z_n(x) - z(x)|\ \zeta(x)\ |u_n(x)|\,\mathrm{d}x \\
&\qquad\qquad + \Big| \int_0^\infty z(x)\zeta(x)\ u_n(x)\,\mathrm{d}x - \int_0^\infty z(x)\zeta(x)\ U(\mathrm{d}x) \Big| \\
&\qquad\qquad + \int_0^\infty |z_n(x)|\ \big(1-\zeta(x)\big)\ |u_n(x)|\,\mathrm{d}x + \int_0^\infty |z(x)|\ \big(1-\zeta(x)\big)\ |U|(\mathrm{d}x).
\end{aligned}$$

The two last integrals can be dominated by

$$\begin{aligned}
&K \sup_{y \ge R} \left(\frac{1+y^\kappa}{1+y^\ell} \right) \left(\sup_n \int_0^\infty (1+x^\ell)(|u_n(x)|\,\mathrm{d}x + \int_0^\infty (1+x^\ell)|U|(\mathrm{d}x) \right) \\
&\qquad\qquad \le 2CK \sup_{y \ge R} \left(\frac{1+y^\kappa}{1+y^\ell} \right).
\end{aligned}$$

Since $0 \le \kappa < \ell$, this contribution can be made arbitrarily small by choosing R large enough, uniformly with respect to n. Moreover, we clearly have

$$\begin{aligned}
0 &\le \int_0^\infty |z_n(x) - z(x)|\ |u_n(x)|\ \zeta(x)\,\mathrm{d}x \\
&\qquad\qquad \le \sup_{0 \le x \le 2R} |z_n(x) - z(x)| \ \sup_m \int_0^\infty |u_m(x)|\,\mathrm{d}x \xrightarrow[n\to\infty]{} 0
\end{aligned}$$

and of course

$$\int_0^\infty z(x)\zeta(x)\ u_n(x)\,\mathrm{d}x - \int_0^\infty z(x)\zeta(x)\ U(\mathrm{d}x) \xrightarrow[n\to\infty]{} 0.$$

Combining all together these informations ends the proof. □

3.7.2 Compactness of the fragmentation kernel

We look for conditions on the coefficients guaranteeing some compactness of k^ε. We use a few classical results of convergence of probability measures (see [15] for instance). Let us introduce a few notations. Given a probability-measure-valued function $y \in \mathbb{R} \mapsto k(., y) \in \mathcal{M}^1(\mathbb{R})$, we denote $F(., y)$ its repartition function : $F(x, y) = \int_{-\infty}^x k(s, y)\,\mathrm{d}s$ and $G(x, y)$ the function $\int_{-\infty}^x F(z, y)\,\mathrm{d}z$. We shall deduce the compactness of k^ε from the compactness of the associated G^ε. To this end, we need several elementary statements.

Lemma 3.7.2 *Let $\{P^n,\ n \in \mathbb{N}\}$ be a family of probability measures on $\mathbb{R}$, having their support included in some interval $[a, b]$. We denote F^n the repartition function of P^n, and G^n the functions defined by $\int_{-\infty}^x F^n(s)\,\mathrm{d}s$. The following assertions are equivalent :*

1. *$P^n \to P$ weakly,* i.e., *$\forall\, f \in \mathcal{C}_b(\mathbb{R})$, $P_n f \to P f$,*
2. *$F^n(x) \to F(x)$ for all x at which F is continuous,*
3. *$G^n \to G$ uniformly locally.*

Lemma 3.7.3 (Conditions for F) *Let F be a nondecreasing function on $\mathbb{R}$. There exists a unique probability measure P on $\mathbb{R}$, such that $F(x) = P(]-\infty, x])$, iff*

- *F is rightcontinuous everywhere,*
- $\lim_{x\to-\infty} F(x) = 0, \lim_{x\to+\infty} F(x) = 1$.

Furthermore P has its support included in $[a, b]$ iff $F \equiv 0$ on $]-\infty, a[$ and $F(b) = 1$.

Lemma 3.7.4 (Conditions for G) *Let G be a convex function on $\mathbb{R}$. There exists a probability measure P on $\mathbb{R}$, having its support included in $[a, b]$, such that $G(x) = \int_{-\infty}^{x} F(s)\,\mathrm{d}s$, where $F(x) = P(]-\infty, x])$, iff*

- *G is increasing,*
- *for $x > b$, $G(x) = G(b) + x$,*
- *$G \equiv 0$ on $]-\infty, a]$.*

Corollary 3.7.5 *Let $\left(G^n\right)_{n\in\mathbb{N}}$ a sequence satisfying the assumptions of lemma 3.7.4. Suppose $G^n \to G$ uniformly locally on $\mathbb{R}$, then G also satisfy these assumptions and we have $P^n \to P$ weakly.*

Proof. We define the function F as $F(x) = \lim_{\delta\to0^+} \frac{G(x+\delta)-G(x)}{\delta}$, it is then easy to check that F satisfies assumptions of lemma 3.7.3, and $G(x) = \int_{-\infty}^{x} F(s)\,\mathrm{d}s$. □

Proof of Lemma 3.3.2. We prove the following result, which contains Lemma 3.3.2.

Lemma 3.7.6 *Suppose that the discrete coefficients satisfy (3.23). Then there exist a subsequence ε_n and $k \in \mathcal{C}([0,\infty), \mathcal{M}^1_+([0,\infty)) - \mathrm{weak} - \star)$ such that*

- *k satisfies (3.6),(3.5) (and therefore (3.7)),*
- *for every $y > 0$, $k^{\varepsilon_n}(.,y) \to k(.,y)$ in law,*
- *for every $\varphi \in \mathcal{C}^\infty_c([0,\infty))$, $\phi^{\varepsilon_n} \to \phi$ uniformly on $[0, R]$ for any $0 < R < \infty$.*

For any $y \geq 0$, $k^\varepsilon(x, y)\,\mathrm{d}x$ defines a probability measure on $[0,\infty)$, supported in $[0, y]$. We set $F^\varepsilon(x, y) = \int_0^x k^\varepsilon(z, y)\,\mathrm{d}z$ and $G^\varepsilon(x, y) = \int_0^x F^\varepsilon(z, y)\,\mathrm{d}z$. Let $\varphi \in C^\infty_c(\mathbb{R}^*_+)$. We start by rewriting, owing to integration by parts,

$$\phi^\varepsilon(y) = \varphi(y) - \int_0^y F^{\varepsilon_n}(x, y)\varphi'(x)\,\mathrm{d}x = \varphi(y) - G^\varepsilon(y, y)\varphi'(y) + \int_0^y G^\varepsilon(x, y)\varphi''(x)\,\mathrm{d}x,$$

where we used the fact that $F^\varepsilon(y, y) = \int_0^y k^\varepsilon(z, y)\,\mathrm{d}z = 1$. The proof is based on the following argument : G^ε is close to a $\tilde{G}^\varepsilon$ which satisfies the assumptions of the Arzela-Ascoli theorem. Given $x, y \geq 0$ and $\varepsilon > 0$, i, j denote the integers satisfying $x \in [i\varepsilon, (i+1)\varepsilon[$, $y \in [j\varepsilon, (j+1)\varepsilon[$ and a short computation leads to

$$\begin{aligned} F^\varepsilon(x, j\varepsilon) &= S_{i,j} + \frac{x - i\varepsilon}{\varepsilon} k_{i,j}, \\ G^\varepsilon(x, j\varepsilon) &= \varepsilon \sum_{p=0}^{i-1} S_{p,j} + (x - i\varepsilon)S_{i,j} + \frac{\varepsilon}{2} S_{i,j} + \frac{(x - i\varepsilon)^2}{2\varepsilon} k_{i,j}, \end{aligned}$$

where

$$S_{i,j} = \sum_{r=0}^{i-1} k_{r,j}. \tag{3.38}$$

We define

$$\tilde{k}^\varepsilon(x, y) = \frac{(j+1)\varepsilon - y}{\varepsilon} k^\varepsilon(x, j\varepsilon) + \frac{y - j\varepsilon}{\varepsilon} k^\varepsilon(x, (j+1)\varepsilon)$$

and we have

$$\tilde{G}^\varepsilon(x, y) = \frac{(j+1)\varepsilon - y}{\varepsilon} G^\varepsilon(x, j\varepsilon) + \frac{y - j\varepsilon}{\varepsilon} G^\varepsilon(x, (j+1)\varepsilon).$$

Observe that

$$\begin{aligned} |\tilde{G}^\varepsilon(x,y) - G^\varepsilon(x,y)| &= \frac{y-j\varepsilon}{\varepsilon}|G^\varepsilon(x,(j+1)\varepsilon) - G^\varepsilon(x,j\varepsilon)| \\ &\le \Big|\varepsilon\sum_{p=0}^{i-1}(S_{p,j+1}-S_{p,j}) + (x-i\varepsilon)(S_{i,j+1}-S_{i,j}) + \frac{\varepsilon}{2}(S_{i,j+1}-S_{i,j}) \\ &\qquad + \frac{(x-i\varepsilon)^2}{2\varepsilon}(k_{i,j+1}-k_{i,j})\Big|. \end{aligned}$$

Due to (3.6), we have $0 \le k_{i,j} \le 1$ and thus $|k_{i,j+1} - k_{i,j}| \le 1$. Similarly $0 \le S_{i,j} \le 1$ and $|S_{i,j+1} - S_{i,j}| \le 1$. Hence, since (3.23) can also be written

$$\Big|\sum_{p=0}^{i-1} S_{p,j+1} - S_{p,j}\Big| \le K,$$

it allows us to obtain

$$|\tilde{G}^\varepsilon(x,y) - G^\varepsilon(x,y)| \le \varepsilon(K+1+1/2+1/2) = \varepsilon(K+2).$$

We also deduce that

$$\big|\partial_y\tilde{G}^\varepsilon(x,y)\big| = \frac{\big|G^\varepsilon(x,j\varepsilon) - G^\varepsilon(x,(j+1)\varepsilon)\big|}{\varepsilon} \le K+2$$

while

$$|\partial_x\tilde{G}^\varepsilon(x,y)| \le 1.$$

Moreover, we have

$$|\tilde{G}^\varepsilon(x,y)| \le 2\varepsilon(i+2)$$

which is bounded uniformly with respect to ε and $0 \le x, y \le R < \infty$. As a consequence of the Arzela-Ascoli theorem we deduce that, for a subsequence, G^{ε_n} converges uniformly to a continuous function $G(x,y)$ on $[0,R]\times[0,R]$ for any $0 < R < \infty$. It follows that

$$\phi^{\varepsilon_n}(y) \xrightarrow[\varepsilon_n\to\infty]{} \phi(y) = \varphi(y) - G(y,y)\varphi'(y) + \int_0^y G(x,y)\varphi''(x)\,\mathrm{d}x$$

uniformly on $[0,R]$. We conclude by applying Lemma 3.7.4 to the function $x \mapsto G(x,y)$, with $y \ge 0$ fixed. □

Lemma 3.7.7 *Suppose that the discrete coefficients satisfy (3.25). Then F^ε and G^ε are uniformly bounded and converge (up to a subsequence) uniformly on compact sets.*

Proof. Assumption (3.25) rewrites

$$\Big|S_{i,j+1} - S_{i,j}\Big| \le \frac{K}{j}, \qquad k_{i,j} \le \frac{K}{j},$$

where S_{ij} is defined as in (3.38). So, with the same notation for $\tilde{F}^\varepsilon$ as for $\tilde{G}^\varepsilon$ and $\tilde{k}^\varepsilon$, we get

$$|F^\varepsilon(x,y) - \tilde{F}^\varepsilon(x,y)| = \frac{y-j\varepsilon}{\varepsilon}|F^\varepsilon(x,(j+1)\varepsilon) - F^\varepsilon(x,j\varepsilon)| \le \frac{2K}{j} \le \frac{3K}{y}\varepsilon.$$

Similar considerations yield

$$|\partial_x\tilde{F}^\varepsilon| \le \frac{(j+1)\varepsilon - y}{\varepsilon}k_{ij} + \frac{y-j\varepsilon}{\varepsilon}k_{i,j+1}\varepsilon \le \frac{2K}{j\varepsilon} \le \frac{2K}{n_0\varepsilon} \le \frac{2K}{x_0},$$

where we have used Assumption (3.20), restricting the discussion to the case $x_0 > 0$ (see case ii) in Theorem 3.3.4) and

$$|\partial_y \tilde{F}^\varepsilon| \leq \frac{1}{\varepsilon}|F^\varepsilon(x,(j+1)\varepsilon) - F^\varepsilon(x,j\varepsilon)| \leq \frac{3K}{y},$$

which leads to Ascoli assumptions and therefore the suitable compactness. □

With such assumptions, we can take into account any k of the form $k(x,y)\,\mathrm{d}x = \frac{1}{y}k_0(x/y)\,\mathrm{d}x$, including Dirac mass. If we consider such a distribution on $[0,1]$ (taken symmetric), then we can define $k_{i,j}$ as

$$\begin{aligned} k_{i,j} = {} & k_0\Big(\Big]\tfrac{i-1}{j-1}, \tfrac{i}{j-1}\Big[\Big) + \tfrac{1}{2}k_0\Big(\Big\{\tfrac{i-1}{j-1}\Big\}\Big) \\ & + \tfrac{1}{2}k_0\Big(\Big\{\tfrac{i}{j-1}\Big\}\Big) + \tfrac{1}{2}k_0\Big(\Big\{0\Big\}\Big)\delta_i^1 + \tfrac{1}{2}k_0\Big(\Big\{0\Big\}\Big)\delta_i^{j-1} \end{aligned}$$

with δ_i^j the Kronecker symbol. With these notations, we have for $p \geq j-2$,

$$S_{p,j} = \sum_{i=0}^{p} k_{i,j} = k_0\Big(\Big[0, \frac{p}{j-1}\Big[\Big) + \frac{1}{2}k_0\Big(\Big\{\frac{p}{j-1}\Big\}\Big)$$

and $S_{j-1,j} = S_{j,j} = 1$, which leads to

$$S_{p,j+1} - S_{p,j} = k_0\Big(\Big[\frac{p}{j}, \frac{p}{j-1}\Big[\Big) + \frac{1}{2}k_0\Big(\Big\{\frac{p}{j}\Big\}\Big) - \frac{1}{2}k_0\Big(\Big\{\frac{p}{j-1}\Big\}\Big), \quad \text{if } p < j-1,$$

$$S_{j-1,j+1} - S_{j-1,j} = -k_0\Big(\Big]\frac{j-1}{j}, 1\Big]\Big) - \frac{1}{2}k_0\Big(\Big\{\frac{j-1}{j}\Big\}\Big), \qquad S_{j,j+1} - S_{j,j} = 0,$$

as $0 \leq i \leq j$, we have for any $p \leq i$,

$$\frac{p-1}{j-1} \leq \frac{p}{j},$$

the intervals $\big[\frac{p}{j}, \frac{p}{j-1}\big[$ and $\big[\frac{p-1}{j}, \frac{p-1}{j-1}\big[$ are disjoint. This leads to

$$\Big|\sum_{p=0}^{i} S_{p,j+1} - S_{p,j}\Big| \leq k_0\Big(\bigcup_{p=0}^{i}\Big[\frac{p}{j}, \frac{p}{j-1}\Big[\Big) + \frac{1}{2}k_0\Big(\bigcup_{p=0}^{i}\Big\{\frac{p}{j}\Big\}\Big) + \frac{1}{2}k_0\Big(\bigcup_{p=0}^{i}\Big\{\frac{p}{j-1}\Big\}\Big) \leq 2,$$

which gives the criterion (3.23). The limit is then obviously given by $k(x,y)dx = \frac{1}{y}k_0(x/y)dx$.

3.7.3 Discrete system

We discuss here briefly the existence theorem for the discrete system. It is mainly an adaptation of theorem 5.1 in [64]. We define the truncated system. Let $N > n_0$, consider the system

$$\left\{\begin{aligned} \frac{\mathrm{d}v}{\mathrm{d}t} &= \lambda - \gamma v - v\sum_{i=n_0}^{N-1}\tau_i u_i + 2\sum_{j=n_0}^{N}\sum_{i<n_0} i k_{i,j}\beta_j u_j, \\ \frac{\mathrm{d}u_{n_0}}{\mathrm{d}t} &= -\mu_{n_0}u_{n_0} - \beta_{n_0}u_{n_0} - v\tau_{n_0} + 2\sum_{j=i+1}^{N}\beta_j k_{n_0,j}u_j, \\ \frac{\mathrm{d}u_i}{\mathrm{d}t} &= -\mu_i u_i - \beta_i u_i - v(\tau_i u_i - \tau_{i-1}u_{i-1}) + 2\sum_{j=i+1}^{N}\beta_j k_{i,j}u_j, \qquad \text{for } n_0 < i < N, \\ \frac{\mathrm{d}u_N}{\mathrm{d}t} &= -\mu_N u_N - \beta_N u_N + v\tau_{N-1}u_{N-1}. \end{aligned}\right. \tag{3.39}$$

Existence, uniqueness and nonnegativity are immediate, we have immediately the weak formulation

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\Big(v(t)\psi + \sum_{i=n_0}^{N} u_i\varphi_i\Big) \quad = \quad & \lambda\psi - \gamma v\psi - v\sum_{i=n_0}^{N}\mu_i u_i\varphi_i + v\sum_{i=n_0}^{N-1}\tau_i u_i(\varphi_{i+1} - \varphi_i - \psi)\\ & +2\sum_{j=n_0+1}^{N}\sum_{i=n_0}^{j-1} ik_{i,j}\beta_j u_j\Big(\frac{\varphi_i}{i} - \frac{\varphi_j}{j}\Big)\\ & +2\sum_{j=n_0}^{N}\sum_{i=1}^{n_0-1} ik_{i,j}\beta_j u_j\big(\psi - \frac{\varphi_j}{j}\big).\end{aligned} \tag{3.40}$$

Let us denote U^N the infinite sequence of functions defined by $U_i^N = u_i^n$ if $n_0 \le i \le N, U_i^N = 0$ otherwise. The weak formulation gives moment estimates (and the moment estimates done in section 4 can then be thought as uniform bounds on truncated systems). This model has the property of propagating moments.

With this type of initial condition, the proof of existence is based on the Ascoli theorem for the continuous functions U_i^N. Thanks all the moments controlled on the initial data and the nice property of propagation of moments, we have bounds on the derivative of v^N, U_i^N and therefore, we can extract convergent subsequence. The limit satisfies the equation in an integral form (see [10] for a definition). For proving uniqueness, the procedure exposed in [10, 64] applies, with a small modification due to death rates (the condition on the moment of order $1+m$ for the initial data insures the convergence of $\sum i\mu_i u_i$).

Deuxième partie

Diffusion croisée et formation de motifs

Chapitre 4

Diffusions croisées et formations de motifs par régularisation

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Le travail présenté ici est issu d'une collaboration avec Mostafa Bendahmane, Americco Morocco et Benoît Perthame. On s'intéresse à des modèles non standards de diffusion croisée en l'absence de termes de réaction. Le but est de déterminer la stabilité de l'équilibre homogène. La clé de voute de ce travail est l'utilisation d'estimation de dualité qui permettent d'amorcer les preuves d'existence dans certains cas. Ce travail a été accepté dans le *Journal des mathématiques pures et appliquées. Nous avons conservé la notation δ^2 pour le paramètre de régularisation comme dans la version publiée. Ce même paramètre est appelée δ dans les autres chapitres.*

4.1 Introduction

The dynamics of interacting population with cross-diffusion have been widely investigated by several researchers. The concept of this phenomena was studied by Levin [72], Levin and Segel, [71], Okubo [91], Mimura and Murray [84], Mimura and Kawasaki [83], Mimura and Yamaguti [85], and many other authors. All these papers base the pattern formation on a reaction term as prey-predator interactions.

Spatial patterns can however emerge from pure diffusions without reaction terms nor oriented drift at the individual level. This is the case of N populations described microscopically by a brownian process which intensity depends upon the macroscopic density $U = (U_1, ..., U_N)$ of the populations

$$dX_k(t) = \sigma_k\big(U(X,t)\big)dW_k(t), \qquad 1 \leq k \leq N.$$

When set on a bounded domain with reflexion on the boundary, the corresponding models for the population density are cross-diffusions

$$\begin{cases} \frac{\partial}{\partial t}U - \Delta A(U) = 0, \quad \text{in } \Omega, \\ \frac{\partial}{\partial n}A(U) = 0 \quad \text{on } \partial\Omega, \end{cases} \tag{4.1}$$

where $U = U(x,t) \in \mathbb{R}^N$, $x \in \Omega$ a smooth bounded domain of $\mathbb{R}^d$, n denotes the outward normal to Ω. Finally $A : \mathbb{R}^N \to \mathbb{R}^N$ is a nonlinearity related to the intensity of the interactions by the relation

$$A_k(U) = U_k a_k(U), \tag{4.2}$$

and $a_k(U) = \frac{1}{2}\sigma_k(U).\sigma_k^t(U)$. We also complete the system with an initial data

$$U(t=0) = U^0 = (U_1^0, ..., U_N^0) \quad \text{with} \;\; U_k^0 \geq 0.$$

The properties, and pattern formation capacity of such systems are better described by introducing the more general form

$$\frac{\partial}{\partial t} U_k - \sum_{l=1}^{N} \text{div}[D_{kl}(U)\nabla U_l] = 0, \tag{4.3}$$

where $D_{kl}(U)$ are the components of a $N \times N$ matrix, the derivative of A in the case (4.1). Boundary conditions have to be imposed and we consider here the case of Neumann conditions

$$D(U).\nabla U.n = 0, \qquad \text{on} \;\; \partial\Omega.$$

For such boundary conditions, mass conservation yields naturally

$$\langle U(t) \rangle = \langle U^0 \rangle, \qquad \forall t \geq 0,$$

where $\langle U^0 \rangle$ denotes the average

$$\langle U \rangle = \frac{1}{|\Omega|} \int_\Omega U(x) dx.$$

The Lotka-Volterra competition with cross-diffusion has recently received great attention. They are many established results concerning the global existence of classical solutions (see [107, 73] and the references therein) where most of the proofs rely on Amann's theorem [2, 3]. We point out that standard parabolic theory is not directly applicable to our model due to the presence of cross-diffusion terms.

In opposition with pattern formations, an important issue has been widely studied which is to know in which circumstances the solutions exist globally and behave like in the case a single heat equation, i.e., relax to a constant state as $t \to \infty$. Typically three kinds of special methods have been helpful in this scope. The first method is to rely on the maximum principle. It can occur on certain combinations of the U_i as in [2, 3, 4]. Entropy methods also applies to particular systems and has also been a useful tool because of the related symmetrization of the system following [60, 34]. It provides a natural method both for existence and relaxation to steady state as in the recent studies in [22, 23] of the Shigezada-Kawasaki prey-predator system [100], or for tumour models [52]. This method typically applies in the special case of the square entropy when D is definite positive meaning that there is $\nu > 0$ such that

$$\sum_{k,l=1}^{N} \xi_k D_{kl}(U) \xi_l \geq \nu |\xi|^2, \quad \forall \xi \in \mathbb{R}^N. \tag{4.4}$$

This strong positivity property gives the energy inequality

$$\frac{1}{2}\frac{d}{dt} \int_\Omega |U(t)|^2 dx = \sum_{k,l=1}^{N} \nabla U_k D_{kl}(U) \nabla U_l \leq -\nu \int_\Omega |\nabla U(t)|^2 dx.$$

The third method, by duality, has been used in [17] on a particular upper-diagonal diffusion with Dirichlet boundary condition; we show here that the method can be extended to very general systems with Neuman conditions.

Concerning instabilities, the interplay between diffusion and reaction terms has raised surprising results in the spirit of the Turing instability mechanism [104]. The question to know if cross-diffusion or self-diffusion gives an advantage to competing species is studied in [74, 75].

Our interest in this paper concerns instability mechanisms that may appear only from the diffusion intensity and the lost of positivity in the second order matrix. We study in which circumstances the increase of this intensity with higher density of the other species can lead to a segregation phenomena. Of course such instability is incompatible with any entropy inequality, and thus (4.4) cannot hold. This raises several mathematical questions which seem to be new in the domain of cross-diffusions. Can it still be that small solutions exist globally even though the maximum principle does not hold in general? For large data, what kind of regularity or 'blow-up' can we expect? Finally, how do regularized systems behave in the 'instability' regime. We will study these questions with a model problem in mind related to Shigezada-Kawasaki's system and that represents two species with stronger interactions

$$\begin{cases} \frac{\partial}{\partial t}U_1 - \Delta[U_1(1 + a_{11}U_1^p + a_{12}U_2^p)] = 0, & x \in \Omega, \\ \frac{\partial}{\partial t}U_2 - \Delta[U_2(1 + a_{21}U_1^p + a_{22}U_2^p)] = 0, \end{cases} \tag{4.5}$$

still with Neumann boundary conditions. One can check that as soon as $p > 1$, the matrix D_{kl} is negative for U large.

We approach these questions both theoretically and numerically. In particular we prove existence for small initial data (section 4.2) and we give a priori bounds in $L^p_{t,x}$ for possible solutions to (4.5) thus showing that the break-down should come from the blow-up of gradient estimates rather than usual L^p norms (section 4.3). Our main tool here is a general estimate due to M. Pierre [94, 93] in the context of semilinear parabolic systems (arising in population dynamics or more generally reaction-diffusion systems) (see also [35]). In section 4.4, these bounds are extended to a relaxation system that takes into account a local measurement of densities; we show that the method is well adapted to general (even not parabolic) cross-diffusions and prove global existence for the relaxation system. For non-parabolic cases, we show that Turing instability occurs in a certain range of data and for small relaxation parameters. Numerical simulations of this relaxation system are performed in section 4.5. They show that the oscillatory initial regime reorganizes to create patches where one species density dominates the other and interfaces are generated which width is related to the relaxation length. The technical and general extension of M. Pierre's estimate to bounded domains for Neumann boundary conditions is kept for an Appendix as well as another remarkable energy estimate which holds for particular cross-diffusion coefficients in (4.5).

4.2 Global solutions for small data

The lack of maximum principle for general diffusion systems is a major difficulty that arises for systems as (4.3). Using stronger H^1 estimates, we can show in one dimension that for small initial data there is global existence. Such solutions decay to the constant state for large time and this is incompatible with the patterns formation we are interested in. This indicates that large initial data are necessary for pattern formation as expected in general.

We consider the system under the form (4.1)–(4.2) and assume that

$$a_k \in C^1(\mathbb{R}^N), \tag{4.6}$$

$$a_k(0) \geq \nu > 0. \tag{4.7}$$

Theorem 4.2.1 (Global small solutions in 1 dimension) *In one dimension, under assumptions (4.6),(4.7), and for an initial data satisfying, with α small enough,*

$$\|U^0\|_{L^\infty(\Omega)} + \|\nabla U^0\|_{L^2(\Omega)} \leq \alpha,$$

there is a global solution $U(t,x)$ to the cross-diffusion system (4.1)–(4.2). It satisfies for all $t > 0$

$$\|U(t)\|_{L^\infty(\Omega)} \leq C\alpha, \qquad \|\nabla U(t)\|_{L^2(\Omega)} \leq \alpha,$$

with C independent of t and

$$U(t) \underset{t\to\infty}{\longrightarrow} \langle U^0\rangle.$$

Proof. Firstly, since $\langle U(t)\rangle$ is a priori conserved, we notice that

$$\|U(t)\|_{L^\infty(\Omega)} \leq \|\langle U^0\rangle\|_{L^\infty(\Omega)} + \sqrt{|\Omega|}\|\nabla U\|_{L^2(\Omega)} \leq \alpha + \sqrt{|\Omega|}\|\nabla U\|_{L^2(\Omega)}.$$

Secondly, we multiply (4.1) by the vector $A'(U)$ and differentiate. We obtain

$$\partial_t \nabla A(U) = \nabla\big(A'(U)\partial_t U\big) = \nabla\big(A'(U)\Delta A(U)\big),$$

we multiply by $\nabla A(U)$ and integrate

$$\frac{d}{dt}\int_\Omega \frac{|\nabla A(U)|^2}{2} = \int_\Omega \nabla A(U)\nabla\big(A'(U)\Delta A(U)\big) = -\int_\Omega \Delta A(U)\ A'(U)\ \Delta A(U). \tag{4.8}$$

But from (4.2) and (4.7), we have $A'(0)_{kl} = a_{kk}(0)\delta_{kl}$, and thus for $\|U\|_{L^\infty(\Omega)} \leq \varepsilon$ small enough, we have

$$XA'(U)X \geq \frac{\nu}{2}\|X\|^2, \qquad \forall X \in \mathbb{R}^N, \tag{4.9}$$

$$|A'(U)X|^2 \geq \frac{\nu^2}{2}\|X\|^2, \qquad \forall X \in \mathbb{R}^N. \tag{4.10}$$

We now consider T^* defined by

$$T^* := \sup\{t \geq 0, \|U(t)\| \leq \varepsilon\}.$$

For $\alpha < \varepsilon$, then $T^* > 0$. Suppose $T^* < \infty$, then for $0 \leq t \leq T^*$, we have, from (4.8) and (4.9),

$$\int_\Omega |\nabla A(U(t))|^2 dx \leq \int_\Omega |\nabla A(U^0)|^2 dx.$$

Therefore,

$$\int_\Omega |A'\big(U(t)\big)\nabla U(t)|^2 \leq \int_\Omega |\nabla A(U^0)|^2 dx.$$

Using (4.10), this leads to

$$\int_\Omega |\nabla U(t)|^2 dx \leq \frac{2}{\nu^2}\int_\Omega |\nabla A(U^0)|^2 dx \leq \frac{2C}{\nu^2}\int_\Omega |\nabla U^0|^2 dx.$$

Now, we choose α such that $\alpha \leq \dfrac{\varepsilon}{3}$ and $\dfrac{\sqrt{2C|\Omega|}}{\nu}\alpha \leq \dfrac{\varepsilon}{3}$, this ensures, $\|U(t)\|_{L^\infty(\Omega)} \leq \frac{2\varepsilon}{3}$ and thus, T^* is not maximal. Therefore $T^* = \infty$.

Finally, the existence of a solution for small times follows from standard parabolic theory and the a priori bound above shows that these are global solutions.

We now prove the time convergence to $\langle U^0\rangle$. Because $\int_\Omega (U-\langle U^0\rangle)^2 = \int_\Omega U^2 - \langle U\rangle^2$, we compute

$$\frac{d}{dt}\int_\Omega (U-\langle U\rangle)^2 = \frac{d}{dt}\int_\Omega U^2 = \int_\Omega \Delta A(U)U = -\int_\Omega A'(U)\nabla U.\nabla U.$$

But as the solution stays in the domain $\|U(t)\|_{L^\infty(\Omega)} \leq \varepsilon$, we have for some constant C_0,

$$\frac{d}{dt}\int_\Omega (U-\langle U^0\rangle)^2 \leq -\frac{\nu}{2}\int_\Omega |\nabla U|^2 \leq -2C_0\int_\Omega (U-\langle U^0\rangle)^2,$$

thanks to the Poincaré Wirtinger inequality. We conclude from Gronwall lemma that

$$\|U-\langle U^0\rangle\|_{L^2(\Omega)} \leq e^{-C_0 t}\|U^0-\langle U^0\rangle\|_{L^2(\Omega)}.$$

□

4.3 A priori bounds for large data

For large initial data and when the condition (4.4) does not hold, we cannot expect in general the existence of solutions for the cross-diffusion system (4.3)–(4.2). For a single equation, the corresponding situation is when $A'(u)$ can be negative on some interval $I \subset \mathbb{R}_+$.

$$\frac{\partial}{\partial t}u - \Delta A(u) = 0.$$

The situation is analyzed in [95, 90, 44] (see also the survey in [43]) and it is better analyzed in term of relaxation systems, an approach which we will follow later. We expect that oscillations or jumps occur at positive times, but a first issue is a priori control in L^∞ for possible solutions. This follows from the maximum principle for a single equation (and possibly from entropy constructions for relaxation systems, see [95]). For systems this is an open question and we give here a first a priori bound

Theorem 4.3.1 *Smooth solutions to (4.3)–(4.2) satisfy the a priori bounds*

$$\Big(\int_0^T\int_\Omega \sum_{k=1}^N A_k(U)\sum_{k=1}^N U_k\,dxdt\Big)^{\frac{1}{2}} \leq C_1(\Omega)\|U^0\|_{L^2(\Omega)} + C_2\big(\Omega, \sum_{k=1}^N\langle U_k^0\rangle\big)\sqrt{T}. \tag{4.11}$$

Therefore if we assume in (4.2) that

$$a_k(U) \geq \nu > 0 \qquad \forall k = 1, ..., N, \tag{4.12}$$

then we also have, with the notation $Q_T = \Omega\times[0,T]$,

$$\nu\|U\|_{L^2(Q_T)} \leq C_1(\Omega)\|U^0\|_{L^2(\Omega)} + C_2(\Omega, \langle U^0\rangle)\sqrt{T}. \tag{4.13}$$

In the particular case of model (4.5), we observe that the larger is p, the best is the bound in (4.11). In particular, $A(U)$ is always integrable. The L^2 estimate in (4.13) is much weaker.

Proof. Our proof is based on a variant of a general duality argument due to [93, 35], that is presented in Appendix A. We denote $w = \sum_{k=1}^N U_k$. We sum up the equations and we find

$$\partial_t w - \Delta\sum_{k=1}^N a_k(U)U_k = 0,$$

which we write

$$\partial_t w - \Delta \alpha(t,x) w = 0, \qquad \alpha(t,x) := \frac{\sum_{k=1}^N a_k(U(t,x))U_k(t,x)}{w(t,x)} = \alpha(U(t,x)).$$

We can use now (4.27) in Appendix A and obtain,

$$\|\sqrt{\alpha}\, w\|_{L^2(Q_T)} \leq C(\Omega)\|w^0\|_{L^2(\Omega)} + 2\langle w^0\rangle \|\sqrt{\alpha}\|_{L^2(Q_T)}. \tag{4.14}$$

In order to control the right hand side by $\|\sqrt{\alpha}\, w\|_{L^2(Q_T)}$, we use a truncation method. Since the coefficients $a_k(U)$ are continuous, and U_k are nonnegative, we may define for any $R > 0$,

$$\sup_{w \leq R} \alpha(U) := M(R) < +\infty.$$

Furthermore, we may truncate w away from values less than R, a parameter to be fixed later on, with the indicator function $\mathbf{I}_{\{w \geq R\}}$ and rewrite (4.14) as

$$\|\sqrt{\alpha}\, w\ \mathbf{I}_{\{w\geq R\}}\|_{L^2(Q_T)} \leq C(\Omega)\|w^0\|_{L^2(\Omega)} + 2\langle w^0\rangle \|\sqrt{\alpha}\mathbf{I}_{\{w\geq R\}}\|_{L^2(Q_T)} + 2\langle w^0\rangle \|\sqrt{\alpha}\ \mathbf{I}_{\{w\leq R\}}\|_{L^2(Q_T)},$$

$$\|\sqrt{\alpha}\, w\ \mathbf{I}_{\{w\geq R\}}\|_{L^2(Q_T)} \leq C(\Omega)\|w^0\|_{L^2(\Omega)} + 2\langle w^0\rangle \|\sqrt{\alpha}\ \frac{w}{R}\ \mathbf{I}_{\{w\geq R\}}\|_{L^2(Q_T)} + 2\langle w^0\rangle \|\sqrt{M(R)}\|_{L^2(Q_T)}.$$

We choose $R = 4\langle w^0\rangle$ and obtain

$$\|\sqrt{\alpha}\, w\ \mathbf{I}_{\{w\geq R\}}\|_{L^2(Q_T)} \leq 2C(\Omega)\|w^0\|_{L^2(\Omega)} + 4\langle w^0\rangle \sqrt{|\Omega|\ T\ M(R)}.$$

Since we also know that

$$\|\sqrt{\alpha} w \mathbf{I}_{\{w\leq R\}}\|_{L^2(Q_T)} \leq R\sqrt{M(R)|\Omega|T} = 4\langle w^0\rangle \sqrt{M(R)|\Omega|T},$$

we conclude

$$\|\sqrt{\alpha}\, w\|_{L^2(Q_T)} \leq 2C(\Omega)\|w^0\|_{L^2(\Omega)} + C_2(\langle w^0\rangle)\sqrt{|\Omega|\ T},$$

with $C_2(\langle w^0\rangle) = 8\langle w^0\rangle \sqrt{M(4\langle w^0\rangle)}$. This is exactly the a priori estimate (4.11).

The other statement is a simple and direct consequence. $\square$

4.4 A relaxation system

If we assume that the intensity of the brownian motion depends on the density of the populations measured with a space scale $\delta > 0$ and not at the exact location x, then the system (4.5) can be replaced by a cross-diffusion relaxation system

$$\begin{cases} \frac{\partial}{\partial t} u_k - \Delta[a_k(\tilde{u})u_k] = 0, \qquad x \in \Omega, \quad k = 1, ..., N, \\ -\delta^2 \Delta \tilde{u}_k + \tilde{u}_k = u_k, \end{cases} \tag{4.15}$$

together with Neumann boundary conditions both on u_k and $\tilde{u}_k$. Relaxation procedures are usual and several other examples for cross-diffusions can be found in [58, 5] and for phase transitions see [56, 43, 95]. In terms of the ecological interpretation, it is also more realistic than the initial system (4.5), because individuals are unlikely to be able to access a pointwise density, but might estimate their environment from sensing at a smaller scale.

We can expect that the system (4.15) is well-posed, and we first study this question. Then we prove uniform bounds independent of δ which indicates that instability should arise from the blow-up of gradients. To tackle the question of instabilities, we show that the system exhibits Turing patterns for δ small, this is our second goal in this section.

We keep in mind the example (4.5) and assume that for some $p > 0$ one has

$$0 < \nu \leq a_k(U) \leq C_0(1 + |U|^p), \qquad \forall k \in \{1, ..., N\}. \tag{4.16}$$

For later purpose, we also introduce the assumption that for some constant $K > 0$ and some $\eta > 0$, we have

$$\left| \frac{\nabla a_k(U)}{a_k^\eta(U)} \right| \leq K |\nabla U|. \tag{4.17}$$

We have in mind coefficients of the form $(1 + \tilde{U}_j^p)$ and then we can take $\eta = \frac{p-1}{p}$.

4.4.1 Uniform estimates for $p < 2$

We first extend the a priori estimate of section 4.3 to this relaxation system. The coupling induces a limitation on the possible growth of the nonlinearities $a_k(U)$ and we have the

Theorem 4.4.1 *Assume that (4.16) holds for some $0 < p < 2$, then, the a priori bound holds for a constant C independent of δ*

$$\|u\|_{L^2(Q_T)} \leq C(\|u^0\|_{L^2(\Omega)}, T), \qquad \forall T > 0.$$

This is weaker than the a priori bound in (4.11). The difficulty in the case at hand comes from the dependency of $a_k(\tilde{u})$ which we cannot lower bound from u itself.

Proof. We denote by $\tilde{a}_k$ the quantity $a_k(\tilde{u})$. The estimate (4.27) of Appendix A gives, for all $k \in \{1, ..., N\}$

$$\|\sqrt{\tilde{a}_k}\, u_k\|_{L^2(Q_T)} \leq C(\Omega)\|u_k^0\|_{L^2(\Omega)} + 2\langle u_k^0 \rangle \|\sqrt{\tilde{a}_k}\|_{L^2(Q_T)}.$$

The last term may be estimated as

$$\|\sqrt{\tilde{a}_k}\|^2_{L^2(Q_T)} = \int_0^T \int_\Omega \tilde{a}_k \leq C_0 \int_0^T \int_\Omega (1 + \sum_l \tilde{u}_l^p).$$

Thanks to Holder inequality and direct estimate on the solution to the elliptic equation on $\tilde{u}_l$, we have,

$$\int_0^T \int_\Omega \tilde{u}_l^p \leq (|\Omega|\, T)^{\frac{2-p}{2}} \|\tilde{u}_l\|^{\frac{p}{2}}_{L^2(Q_T)} \leq C(\Omega) T^{\frac{2-p}{2}} \|u_l\|^p_{L^2(Q_T)}.$$

Finally, back to the original inequality we arrive at

$$\sqrt{\nu}\, \|u_k\|_{L^2(Q_T)} \leq C(\Omega)\|u_k^0\|_{L^2(\Omega)} + 2\sqrt{C_0\, T\, |\Omega|}\langle u_k^0 \rangle + 2\langle u_k^0 \rangle \sqrt{C_0}(|\Omega| T)^{\frac{2-p}{4}} \|u\|^{\frac{p}{2}}_{L^2(Q_T)},$$

which leads to

$$\sqrt{\nu}\|u\|_{L^2(Q_T)} \leq C(\Omega, \|u^0\|_{L^2(\Omega)}, T) + C(\Omega, \langle u^0 \rangle) T^{\frac{2-p}{2}} \|u\|^{\frac{p}{2}}_{L^2(Q_T)}.$$

As $p/2 < 1$, this proves that $\|u\|_{L^2(Q_T)}$ is a priori bounded as by a constant depending only on Ω, T, $\|u^0\|_{L^2(\Omega)}$ and the two constants in (4.16). □

4.4.2 Existence of solutions

We now show stronger estimates from which strong compactness of solutions follows. They use fundamentally the regularity on $\tilde{u}$ in (4.15) by elliptic regularizing effects. Existence of global solutions follow and the details are carried out in annex A.

The main result of this section is the following

Proposition 4.4.2 *Assume that (4.16) holds with $p > 1$, and $p < \frac{2d}{d-2}$ when $d > 2$. Then, the a priori estimate holds*

$$\|\sqrt{\tilde{a}_i}u_i\|_{L^2(Q_T)} \leq C(\delta, \|u^0\|_{L^1 \cap L^2(\Omega)}, T). \tag{4.18}$$

Furthermore, if we assume (4.17) in dimension 1 with any $\eta > 0$, and in dimension 2 with $0 < \eta < 1$, then we have for all $1 \leq q < \infty$,

$$\|u(t)\|_{L^q(\Omega)} \leq C(q, \delta, \|u^0\|_{L^1 \cap L^q(\Omega)}, T), \qquad 0 \leq t \leq T, \tag{4.19}$$

$$\int_0^T \int_\Omega |\nabla u^{q/2}|^2 dxdt \leq C(q, \delta, \|u^0\|_{L^1 \cap L^q(\Omega)}, T). \tag{4.20}$$

Proof. We begin with the proof of (4.18) which improves that of the theorem 4.4.1. We use again the estimate (4.27) applied to u_i which yields

$$\sqrt{\nu}\|u_i\|_{L^2(Q_T)} \leq \|\sqrt{\tilde{a}_i}u_i\|_{L^2(Q_T)} \leq C(\Omega)\|u_i^0\|_{L^2(\Omega)} + 2\langle u_i^0\rangle\|\sqrt{\tilde{a}_i}\|_{L^2(Q_T)}. \tag{4.21}$$

We use the hypothesis (4.16) to get

$$\|\sqrt{\tilde{a}_i}\|_{L^2(Q_T)} \leq \sqrt{C_0|\Omega|\,T + C_0\int_0^T\int_\Omega |\tilde{u}|^p} \leq C'(\Omega)\sqrt{T} + \sqrt{\int_0^T\int_\Omega |\tilde{u}|^p} = \sqrt{C_0|}\big(\sqrt{\Omega|\,T} + \sqrt{\int_0^T \|\tilde{u}\|_p^p}\big).$$

Thanks to elliptic regularity we also have

$$\|\tilde{u}\|_p \leq C(\delta, r)\|u\|_r,$$

for any $r > 1$ satisfying also $\frac{1}{p} \geq \frac{1}{r} - \frac{2}{d}$ (particularly it is true for any r if $d = 1, 2$). Then, using interpolation inequality and choosing $r < 2$, we find successively

$$\|\tilde{u}\|_p \leq C(\delta, r)\|u\|_1^{1-\theta(r)}\|u\|_{L^2(\Omega)}^{\theta(r)} = C(\delta, r)\|u^0\|_1^{1-\theta(r)}\|u\|_{L^2(\Omega)}^{\theta(r)} \qquad \theta(r) = \frac{1 - \frac{1}{r}}{1 - \frac{1}{2}} = 2(1 - \frac{1}{r}),$$

$$\|\sqrt{\tilde{a}_i}\|_{L^2(Q_T)} \leq \sqrt{C_0}\big(\sqrt{\Omega\,T} + \sqrt{\int_0^T C(\delta, r)^p \|u^0\|_1^{(1-\theta(r))p}\|u\|_{L^2(\Omega)}^{p\theta(r)}}\big),$$

$$\|\sqrt{\tilde{a}_i}\|_{L^2(Q_T)} \leq \sqrt{C_0}\big(\sqrt{\Omega\,T} + C(\delta, r)^{p/2}\|u^0\|_1^{(1-\theta(r))p/2}\sqrt{\int_0^T \|u(t)\|_{L^2(\Omega)}^{p\theta(r)}dt}\big). \tag{4.22}$$

Now, if we may choose r such that $\theta(r)p < 2$, we get, thanks to Jensen's inequality

$$\int_0^T \|u(t)\|_{L^2(\Omega)}^{p\theta(r)}dt = \int_0^T \|u(t)\|_{L^2(\Omega)}^{2(p\theta(r)/2)}dt \leq T^{1-p\theta(r)/2}\Big(\int_0^T \|u(t)\|_{L^2(\Omega)}^2 dt\Big)^{p\theta(r)/2},$$

which we rewrite as

$$\int_0^T \|u(t)\|_{L^2(\Omega)}^{p\theta(r)}dt \leq T^{1-p\theta(r)/2}\|u\|_{L^2(Q_T)}^{p\theta(r)}.$$

Replacing in (4.22), we have

$$\|\sqrt{\tilde{a}_i}\|_{L^2(Q_T)} \leq \sqrt{C_0}\sqrt{\Omega T} + C(\delta, r, p, \|u^0\|_1)T^{\frac{2-p\theta(r)}{4}}\|u\|_{L^2(Q_T)}^{\frac{p\theta(r)}{2}}$$

And replacing in (4.21), we obtain

$$\nu\|u\|_{L^2(Q_T)} \leq C(\Omega)\|u^0\|_{L^2(\Omega)} + C'(\Omega)\sqrt{T} + C(\delta, r, p, \|u^0\|_1)T^{\frac{2-p\theta(r)}{4}}\|u\|_{L^2(Q_T)}^{\frac{p\theta(r)}{2}} \tag{4.23}$$

This concludes the first inequality when $p\theta(r)/2 < 1$, and it remains to find the range of p in order to fulfill the constraints. These can be obtained choosing r close enough to 1 for $d = 1, 2$. For $d > 2$, we need the conditions

$$\begin{cases} \frac{1}{p} \geq \frac{1}{r} - \frac{2}{d}, \qquad 1 < r < 2, \\ \frac{p\theta(r)}{2} = p(1 - \frac{1}{r}) < 1. \end{cases}$$

We choose to satisfy the second line $\frac{1}{r} > \frac{p-1}{p}$, but close to equality (which gives $1 < r < 2$ as we check it a posteriori). This leads, in the first line, to the condition $p < \frac{2d}{d-2}$, but close to equality (which imposes $r < \frac{2d}{d+2}$). The bound on $\|u\|_{L^2(Q_T)}$ gives then a bound on $\|\sqrt{\tilde{a}_i}u_i\|_{L^2(Q_T)}$ thus concluding the proof of (4.18).

This estimate leads to the stronger a priori bounds (4.19) that we prove now. We go back to the equation and write

$$\frac{d}{dt}\int u^q + C_q\int \tilde{a}|\nabla u^{q/2}|^2 = -C_q^1\int u^{q/2}\nabla u^{q/2}\nabla\tilde{a}.$$

From this equality, and writing $\tilde{a}|\nabla u^{q/2}| = |\nabla(\tilde{a}^{1/2}u^{q/2}) - u^{q/2}\nabla\tilde{a}^{1/2}|$, we derive directly the inequality

$$\begin{aligned} \tfrac{d}{dt}\textstyle\int u^q + \tfrac{C_q}{3}\textstyle\int \tilde{a}|\nabla u^{q/2}|^2 + \tfrac{C_q}{3}\textstyle\int |\nabla(\tilde{a}^{1/2}u^{q/2})|^2 &\leq C_q^2\textstyle\int u^q\tfrac{|\nabla\tilde{a}|^2}{\tilde{a}} \\ &\leq C_q\textstyle\int u^q|\nabla\tilde{u}|^2\tilde{a}^{2\eta-1}. \end{aligned} \tag{4.24}$$

We show separately how in dimensions 1 and 2 this allows us to control any L^q norm for $q < +\infty$.

The case $d = 1$. The proof is easier for $d = 1$ because there exists a constant C (depending only on δ and Ω) such that

$$\|\tilde{u}\|_{L^\infty(\Omega)} + \|\nabla\tilde{u}\|_{L^\infty(\Omega)} \leq C\int |u| \leq C(\|u^0\|_1).$$

Therefore from (4.24) we deduce

$$\frac{d}{dt}\int u^q \leq C.C_q\int u^q.$$

We conclude thanks to Gronwall lemma.

The case $d = 2$. In dimension 2, we divide the proof into two steps.

Step 1, $1 < q < 2$**.** We first focus on small values of the exponent q namely $1 < q < 2$ and $2\eta < 1 + \frac{q}{2}$ (the limitation $\eta < 1$ comes from choosing q close to 2). From (4.24) and using successively (4.17) and Hölder inequality, we obtain

$$\begin{aligned} \tfrac{d}{dt}\int u^q &\leq C_q^3\int u^q\tilde{a}^{q/2}|\nabla\tilde{u}|^2. \\ &\leq C_q^3\big\|u\sqrt{\tilde{a}}\big\|_{qr}^q\|\nabla\tilde{u}\|_{2r'}^2 \\ &\leq C(q, \delta, r)\big\|u\sqrt{\tilde{a}}\big\|_{qr}^q\|u\|_m^2 \end{aligned}$$

thanks to elliptic regularity, with

$$\frac{1}{m} = \frac{1}{2r'} + \frac{1}{2} = 1 - \frac{1}{2r}.$$

Choosing $r = \frac{2}{q}$ then $\frac{1}{m} = 1 - \frac{q}{4}$ and we arrive at

$$\begin{aligned} \tfrac{d}{dt} \int u^q \quad & \leq C(\delta, r) \|u\sqrt{\tilde{a}}\|_2^q \|u\|_m^2 \\ & \leq C(\delta, r) \|u\sqrt{\tilde{a}}\|_2^q \|u\|_q^{2\theta} \|u\|_{L^2(\Omega)}^{2(1-\theta)} \\ & \leq C(\delta, r) \|u\sqrt{\tilde{a}}\|_2^q \|u\|_q^q \|u\|_{L^2(\Omega)}^{2-q} \end{aligned}$$

because, as we have $\frac{1}{2} < \frac{1}{m} < \frac{1}{q}$, we may interpolate m between q and 2 with

$$\theta = \frac{\frac{1}{m} - \frac{1}{2}}{\frac{1}{q} - \frac{1}{2}} = \frac{\frac{2-q}{4}}{\frac{2-q}{2q}} = \frac{q}{2}.$$

We finally obtain by Young's inequality,

$$\frac{d}{dt} \int u^q \leq C(q, \delta, r) \left[\|u\sqrt{\tilde{a}}\|_2^2 + \|u\|_{L^2(\Omega)}^2 \right] \|u\|_q^q,$$

and we may then conclude with Gronwall lemma using the estimates on $\int_0^T \|u\sqrt{\tilde{a}}\|_2^2$ and $\int_0^T \|u\|_2^2$ in (4.18). By interpolation, this also gives a priori bound for any L^q norm for $q \in [1, 2[$. This ends step 1.

Step 2 We now focus on L^q norms for $q \geq 2$. We notice that now, controlling any L^q norm for $q < 2$, we control by elliptic regularity any L^q norm of $\nabla \tilde{u}$ except the L^∞ norm. We also control the L^∞ norm of $\tilde{u}$ and therefore of $\tilde{a}$. We go back to (4.24) and conclude

$$\begin{aligned} \tfrac{d}{dt} \int u^q + C \int |\nabla u^{q/2}|^2 \quad & \leq C \textstyle\int u^q \frac{|\nabla \tilde{a}|^2}{\tilde{a}} \leq C(\delta, q, T) \textstyle\int u^q |\nabla \tilde{u}|^2 \\ & \leq C(\delta, q, T) \|u\|_{qr}^q \|\nabla \tilde{u}\|_{2r'}^2 \\ & \leq C(\delta, q, r, T) \|u\|_{qr}^q. \end{aligned}$$

We use now interpolation: for any $s > r > 1$, we have

$$\|u\|_{qr} \leq \|u\|_q^{1-\theta} \|u\|_{qs}^\theta \qquad \theta = \frac{\frac{1}{qr} - \frac{1}{qs}}{\frac{1}{q} - \frac{1}{qs}} = \frac{\frac{1}{r} - \frac{1}{s}}{1 - \frac{1}{s}}.$$

Using Young's inequality, we obtain for ε small (to be chosen later)

$$\frac{d}{dt} \int u^q + C \int |\nabla u^{q/2}|^2 \leq C(\delta, q, r, T, \varepsilon) \|u\|_q^q + \varepsilon \|u\|_{qs}^q.$$

We have by Poincaré Wirtinger inequality

$$\begin{aligned} \|u\|_{qs}^q = \|u^{q/2}\|_{2s}^2 \quad & \leq 2\|u^{q/2} - \langle u^{q/2} \rangle\|_{2s}^2 + 2\|\langle u^{q/2} \rangle\|_{2s}^2 \\ & \leq C(\Omega, s, \nu) \textstyle\int_\Omega |\nabla u^{q/2}|^2 + C(\Omega, s) \|u\|_{q/2}^q \\ & \leq C(\Omega, s, \nu) \textstyle\int_\Omega |\nabla u^{q/2}|^2 + C(\Omega, s) \left[\|u\|_1^q + \|u\|_q^q \right], \end{aligned}$$

from interpolation and Young's inequality. We fix s as above, choose ε small enough and we obtain

$$\frac{d}{dt}\int u^q \leq C(\Omega,q)\big[\|u\|_1^q+\|u\|_q^q\big].$$

And we conclude (4.19) by Gronwall lemma. The last estimate (4.20) also follows from (4.24). $\square$

4.4.3 Turing patterns

In order to go further and study the instability occurring in the regularized model, we consider the following particular system:

$$\begin{cases} \partial_t u-\Delta\big(u(1+\tilde v^2)\big)=0,\\ \partial_t v-\Delta\big(v(1+\tilde u^2)\big)=0,\\ -\delta^2\Delta\tilde u+\tilde u=u,\\ -\delta^2\Delta\tilde v+\tilde v=v, \end{cases} \tag{4.25}$$

still with Neumann boundary conditions and initial data u^0, v^0.

It is rather intuitive that for δ large, diffusion is dominant; this is also the case for small initial data thanks to the argument in section 4.2. Therefore, the appearance of patterns depends upon a relation between the average densities of populations u and v and the parameter δ. In order to study this in details, we begin with some notations

- the only possible constant steady state of the system is given by $u=\tilde u=\langle u^0\rangle$ and $v=\tilde v=\langle v^0\rangle$,
- we denote by $(\lambda>0,\ w)$ the non-zero solutions to the Neumann eigenproblem

  $$-\Delta w=\lambda w,\qquad \partial_n w=0\quad\text{on }\partial\Omega$$

  we also denote by λ_1 the first eigenvalue for the Laplacian.

In order to investigate when the (in)stability of the constant steady state occurs, we study the linearized system:

$$\begin{cases} \partial_t u-(1+\langle v^0\rangle^2)\Delta u-2\langle u^0\rangle\langle v^0\rangle\Delta\tilde v=0,\\ \partial_t v-(1+\langle u^0\rangle^2)\Delta v-2\langle u^0\rangle\langle v^0\rangle\Delta\tilde u=0,\\ -\delta^2\Delta\tilde u+\tilde u=u,\\ -\delta^2\Delta\tilde v+\tilde v=v. \end{cases}$$

As usual, we look for solutions of type $e^{\mu t}(a,b,c,d)w$. Such solutions should satisfy

$$\begin{cases} c=\frac{a}{1+\delta^2\lambda},\qquad d=\frac{b}{1+\delta^2\lambda},\\ \mu a+\lambda a(1+\langle v^0\rangle^2)+\lambda 2\langle u^0\rangle\langle v^0\rangle\frac{b}{1+\delta^2\lambda}=0,\\ \mu b+\lambda b(1+\langle u^0\rangle^2)+\lambda 2\langle u^0\rangle\langle v^0\rangle\frac{a}{1+\delta^2\lambda}=0, \end{cases}$$

which may be written under the matrix form

$$\begin{pmatrix} 1+\langle v^0\rangle^2 & \frac{2\langle u^0\rangle\langle v^0\rangle}{1+\delta^2\lambda}\\ \frac{2\langle u^0\rangle\langle v^0\rangle}{1+\delta^2\lambda} & 1+\langle u^0\rangle^2 \end{pmatrix}\begin{pmatrix} a\\ b\end{pmatrix}=-\frac{\mu}{\lambda}\begin{pmatrix} a\\ b\end{pmatrix}.$$

We denote by $M = M(\langle u^0\rangle, \langle v^0\rangle, \delta, \lambda)$ this symmetric matrix.

The question of the stability of the constant steady state can now be formulated in terms of eigenvalues of the matrix M. It is unstable if $\mu > 0$ and thus if M has negative eigenvalues. In this case, local behavior around the equilibrium should lead to segregation since the associated eigenvector to $-\mu/\lambda$ should satisfy $a.b < 0$. We have the following

Lemma 4.4.3 *If the initial populations $\langle u^0\rangle$ and $\langle v^0\rangle$ are large enough and the relaxation parameter δ is small enough, then the constant steady state is linearly unstable. More precisely, it occurs under the conditions*

$$\gamma := 4\langle u^0\rangle^2\langle v^0\rangle^2 - \big(1+\langle u^0\rangle^2\big)\big(1+\langle v^0\rangle^2\big) > 0,$$

$$\delta^2 < \frac{2\langle u^0\rangle\langle v^0\rangle - \sqrt{\big(1+\langle u^0\rangle^2\big)\big(1+\langle v^0\rangle^2\big)}}{\lambda_1\sqrt{\big(1+\langle u^0\rangle^2\big)\big(1+\langle v^0\rangle^2\big)}}. \tag{4.26}$$

The domain influences instability only through the smallness condition on $\delta^2\lambda_1(\Omega)$ when the initial data are such that $\gamma > 0$.

Notice that the first condition ensures that the limiting system ($\delta = 0$) has a negative 'diffusion' matrix D in the setting (4.3).

Proof. As mentioned earlier, the constant steady state is unstable if the symmetric matrix M admits negative eigenvalues, i.e., if $det(M) < 0$. We calculate

$$\det(M) = -\frac{4\langle u^0\rangle^2\langle v^0\rangle^2}{(1+\delta^2\lambda)^2} + (1+\langle u^0\rangle^2)(1+\langle v^0\rangle^2) \geq -\gamma.$$

As $det(M)$ is a non-decreasing function of δ, with limit γ as $\delta \to 0$ we first need $\gamma > 0$ that is our first condition. The second condition gives the upper bound on δ to satisfy this inequality. □

4.5 Numerical results

The theoretical results indicate that solutions of the relaxation system (4.15) remain bounded in L^2. Therefore, we expect that the instability obtained for large initial data or a small δ (through Turing mechanism) should lead to stiff gradients.

We present several numerical tests for the particular cubic system (4.25). They aim at showing that (i) the conditions of Lemma 4.4.3 are accurate and describe the numerical transition to instability, (ii) stationary patterns are indeed obtained in this range of data with stiff gradients. These numerical results also show the variety of possible steady state, an interesting phenomena widely studied theoretically ([75] and the references therein). We have performed both 1D and 2D simulations in the following domains

- In interval $\Omega = [0, 1]$ (1D simulation)
- In rectangle $\Omega = [0, 2] \times [0, 0.5]$ (in both cases $|\Omega| = 1$)
- In unit square $\Omega =]0, 1[^2$

In 2D, the computations use an unstructured grid and a mixed finite element method for space and backward Euler scheme for time. The method is already presented in [77].

We recall the eigenvectors of Laplace operator with Neumann boundary condition: for $\Omega = [0, 1]$, $e_n(x) = \cos(n\pi x)$ and particularly, the first nonzero eigenvalue is π^2, associated to the eigenvector $\cos(\pi * x)$. For $\Omega = [0,2] \times [0,0.5]$, the eigenvectors are given by $e_{n,m}(x,y) = \cos(\frac{n\pi x}{2})\cos(2m\pi y)$, the first nonzero eigenvalue is $\pi^2/4$.

We compare the theoretical formula of Lemma 4.4.3 and the numerical stability of the steady state. In all simulations we take $\langle u^0 \rangle = 2, \langle v^0 \rangle = 1$. In this case, instability might occur, since

$$\gamma = 16 - 10 = 6 > 0$$

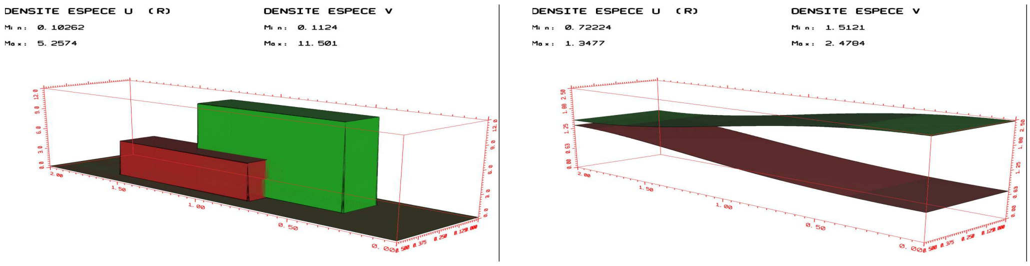
and the limiting values of δ_0 are given in the table 4.1.

Domain	$\Omega =]0,1[$	$\Omega =]0,2[\times]0,0.5[$	$\Omega =]0,1[^2$
Critical value δ_0^2	0.02684	0.1073644	0.02684

Table 4.1: Critical value of the parameter δ_0 for Turing instability, computed from formula (4.26).

Therefore, in a first series of numerical tests, we choose the parameters $\delta^2 = 0.025 < \delta_0^2$ in 1D and for $\delta^2 = 0.1 < \delta_0^2$, and $\delta^2 = 0.11 > \delta_0^2$ in 2D. In both cases, we have obtained relaxation to constant equilibrium when δ is taken larger than the critical value (for all the initial data we have tested), and instability of the constant equilibrium when δ is smaller than the critical value.

We illustrate the instability case with steady states in figure 4.3 for 1D simulations and in figure 4.1 for 2D simulations. For the $1D$ simulation, we took $v^0 \equiv 1$ and $u^0 = 1.9 + 0.2\mathbf{1}_{\{]0.1,0.6[\}}$.

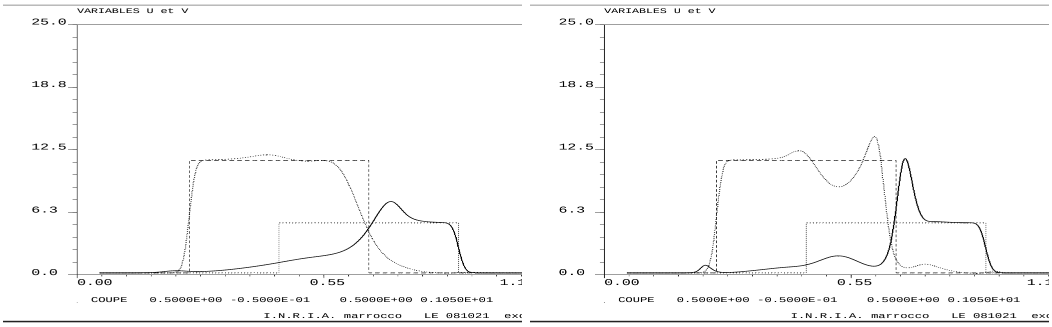


(a) Intital condition

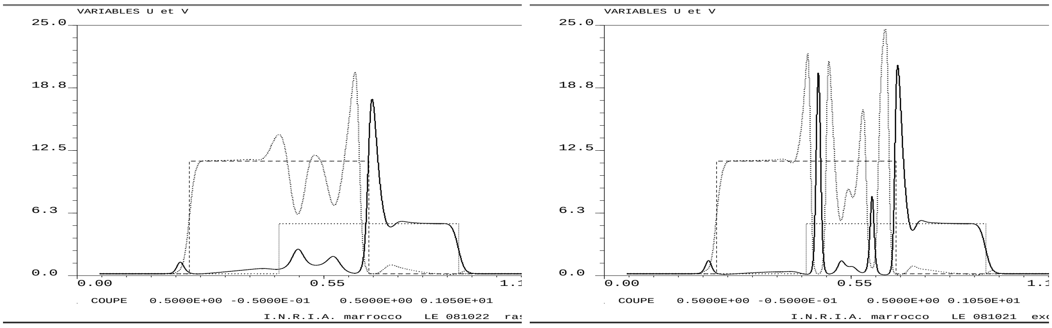
(b) Steady state

Figure 4.1: Initial condition (left) and steady state (right) in 2D simulations. The relaxation parameter $\delta^2 = .1$ is small enough to fulfill condition (4.26). The scales for the solutions are not the same in the two figures.

Next we study the singularity that occurs on the transients for small relaxation parameter δ. Numerical solutions show that strong oscillations occur. In figure 4.2 we depict, for the same initial data, the effect of δ on the solution at a given time.

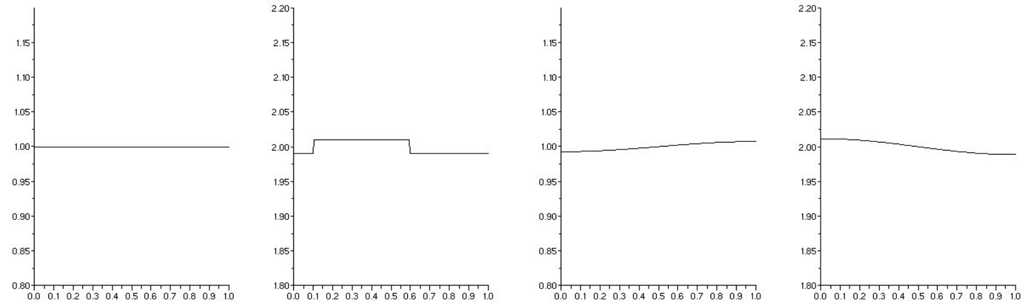


(a) $\delta^2 = 2.\,10^{-3}$ (b) $\delta^2 = 2.\,10^{-4}$

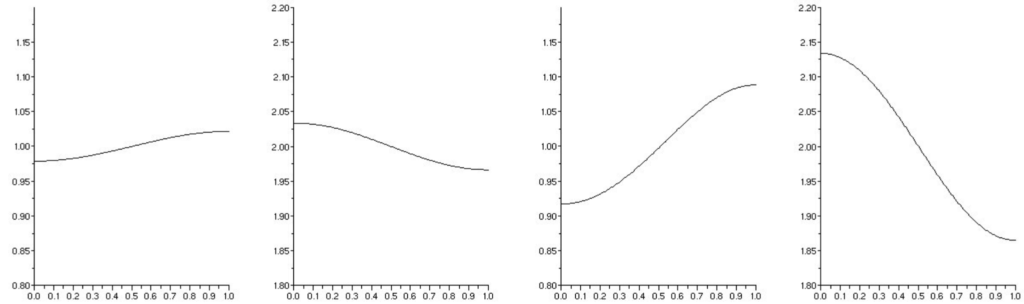


(c) $\delta^2 = 5.\,10^{-5}$ (d) $\delta^2 = 2.\,10^{-5}$

Figure 4.2: Cuts, at a given time, in the y direction and in the middle of the domain $\Omega = (0,1)^2$ in 2D. The piecewise initial condition is also represented in dashed line. As expected strong oscillations occur with species segregation. These oscillations are stronger when δ is smaller.



(a) time $t = 0$ (b) time $t = 2$



(c) time $t = 5$ (d) time $t = 9$

Figure 4.3: Time evolution for a $1D$ simulation for $\delta^2 = 0.025 < \delta_0^2$. This figure shows how a small perturbation is amplified. Because δ is large (close to δ_0) there are not strong oscillations as in the case of smaller values.

4.6 Appendix: Michel Pierre's estimate

Consider the problem

$$\begin{cases} \partial_t u - \Delta[a(t,x)u] = 0, \\ u(t=0) = u^0, \end{cases}$$

together with Neumann boundary condition in a bounded domain Ω. We denote $Q_T = (0,T) \times \Omega$). We assume that $a(t,x) > 0$ is smooth and u is a weak solution. We can also assume withour lack of generality that $\langle u^0 \rangle \geq 0$. Then we have the a priori estimate

Lemma 4.6.1 *For any $T > 0$, we have*

$$\|\sqrt{a}\, u\|_{L^2(Q_T)} \leq C(\Omega)\|u^0\|_{L^2(\Omega)} + 2\langle u^0\rangle \|\sqrt{a}\|_{L^2(Q_T)}, \tag{4.27}$$

where $C(\Omega)$ is the constant of Poincaré Wirtinger's inequality.

Proof. Consider smooth functions $F(t,x)$ and the solutions to the adjoint problem

$$\begin{cases} \partial_t v + a(t,x)\Delta v = F(t,x), \\ v(t=T) = 0, \end{cases} \tag{4.28}$$

still with Neumann conditions. We have

$$\frac{d}{dt}\int_\Omega uv = \int_\Omega Fu,$$

and thanks to the final condition for the adjoint problem,

$$-\int_\Omega u^0 v^0 = \int_0^T \int_\Omega Fu. \tag{4.29}$$

Multiplying (4.28) by Δv, we get

$$\int_\Omega \partial_t v \Delta v + \int_\Omega a|\Delta v|^2 = \int_\Omega F\Delta v,$$

integrating by parts on Ω , we obtain,

$$-\frac{d}{dt}\int_\Omega \frac{|\nabla v|^2}{2} + \int_\Omega a|\Delta v|^2 \leq \int_\Omega (\frac{F^2}{2a} + \frac{a}{2}|\Delta v|^2),$$

which gives after integration in time, using again $v(T) = 0$,

$$\int_\Omega |\nabla v^0|^2 + \int_0^T \int_\Omega a|\Delta v|^2 \leq \int_0^T \int_\Omega \frac{F^2}{a},$$

and by consequence,

$$\|\nabla v^0\|_{L^2(\Omega)} \leq \|\frac{F}{\sqrt{a}}\|_{L^2(Q_T)}, \tag{4.30}$$

$$\|\sqrt{a}\Delta v\|_{L^2(Q_T)} \leq \|\frac{F}{\sqrt{a}}\|_{L^2(Q_T)}. \tag{4.31}$$

We need additionally a bound on $\int v^0$ that we derive as follows. We use again (4.28) to find

$$|\int_\Omega v^0| = |\int_0^T \int_\Omega a\Delta v - F| \leq \int_0^T \int_\Omega \sqrt{a}\Big(\sqrt{a}|\Delta v| + \frac{F}{\sqrt{a}}\Big),$$

which gives, thanks to the Cauchy Schwarz inequality and (4.31),

$$\left|\int_\Omega v^0\right| \leq 2\|\sqrt{a}\|_{L^2(Q_T)}\|\frac{F}{\sqrt{a}}\|_{L^2(Q_T)}. \tag{4.32}$$

Finally, we get using Poincaré-Wirtinger ineqality, (4.32) and then (4.30),

$$\begin{aligned}\left|\int_\Omega u^0 v^0\right| &\leq \left|\int_\Omega u^0(v^0 - \langle v^0\rangle)\right| + |\int_\Omega \langle u^0\rangle v^0| \\ &\leq C(\Omega)\|u^0\|_{L^2(\Omega)}\|\nabla v^0\|_{L^2(\Omega)} + 2\langle u^0\rangle\|\sqrt{a}\|_{L^2(Q_T)}\|\frac{F}{\sqrt{a}}\|_{L^2(Q_T)} \\ &\leq C(\Omega)\|u^0\|_{L^2(\Omega)}\|\frac{F}{\sqrt{a}}\|_{L^2(Q_T)} + 2\langle u^0\rangle\|\sqrt{a}\|_{L^2(Q_T)}\|\frac{F}{\sqrt{a}}\|_{L^2(Q_T)}.\end{aligned}$$

Back to (4.29), we conclude that

$$\left|\int_0^T \int_\Omega Fu\right| = \left|\int_0^T \int_\Omega \frac{F}{\sqrt{a}}\sqrt{a}u\right| \leq \Big(C(\Omega)\|u^0\|_{L^2(\Omega)} + 2\langle u^0\rangle\|\sqrt{a}\|_{L^2(Q_T)}\Big)\|\frac{F}{\sqrt{a}}\|_{L^2(Q_T)},$$

which is equivalent to (4.27). □

4.7 Energy for a particular cross-diffusion system

A particular choice of cross-diffusion terms in (4.5) permits for an energy inequality even for negative second order matrices. This is the case of the system

$$\begin{cases} \partial_t U - \Delta(U(1+V^2)) = 0, \\ \partial_t V - \Delta(V(1+U^2)) = 0, \end{cases} \tag{4.33}$$

still with Neumann boundary conditions and initial data U^0, V^0.

For this system, the energy is given by

$$E(x,t) := (1+U^2)(1+V^2).$$

One can easily check that it holds

$$\frac{\partial}{\partial t}E(x,t) = 2U(1+V^2)\Delta(U(1+V^2)) + 2(V(1+U^2))\Delta(V(1+U^2)),$$

which leads immediately to

$$\frac{d}{dt}\int_\Omega (1+U^2)(1+V^2) = -2\int |\nabla(U(1+V^2))|^2 - 2\int |\nabla(V(1+U^2))|^2 \leq 0.$$

It follows an a priori estimate in the space $L^\infty_t(L^2_x)$ that completes the L^p_{tx} bound proved in section 4.3.

The system (4.33) is not always elliptic. This is related to the non-convexity of this energy (still for large data), an important difference with the Shigezada-Kawasaki prey-predator system which comes with a convex entropy functional ([22]).

Chapitre 5

Solutions stationnaires du système de diffusion croisée régularisé

Nous présentons ici une collaboration entamée avec Salomé Martinez. Nous examinons le système régularisé étudié au chapitre 4 sous l'angle de la théorie des bifurcations.

In this chapter we consider again the relaxed cross diffusion system presented in chapter 4. We adopt the point of view of bifurcation theory. We first prove that, as expected, for large values of the relaxation parameter, only the homogeneous solution is the only steady state. We also prove that the critical value of the relaxation parameter appearing in the Turing analysis determines also a bifurcation point. This open the route of the local analysis of the behaviour of solutions.

5.1 Uniqueness of steady states for large value of the relaxation parameter δ

We consider the steady states of the system

$$\begin{cases} \partial_t U_k - \Delta[a_k(\tilde{U})U_k] = 0, \quad in\ \Omega, \quad 1 \le k \le N \\ -\delta\Delta\tilde{U}_k + \tilde{U}_k = U_k, \quad in\ \Omega \\ \frac{\partial U_k}{\partial n} = \frac{\partial \tilde{U}_k}{\partial n} = 0, \\ U_k(t=0) = U_k^0. \end{cases} \tag{5.1}$$

Here, Ω is a bounded smooth domain. We make the following assumptions on the coefficients a_k.

$$\forall i, \quad a_k \in C^1(\mathbb{R}^N), \quad \exists \nu > 0, \forall k,\ \forall U \in \mathbb{R}^N, \quad a_k(U) \ge \nu. \tag{5.2}$$

The wellposedness of the problem is established under the additional assumptions: the space dimension is 1 or 2 and the a_k satisfy condition (4.16-4.17). We remind a key property of the system: the preservation of population,

$$\forall i, \forall t, \quad \int_\Omega U_k(t,x)dx = \int_\Omega U_k^0(x)dx.$$

We study the steady states of the system (5.3) for given total populations. More precisely we prove

Lemma 5.1.1 *Let the a_k satisfy conditions (5.2) and Ω be a smooth bounded domain. Given $I_k > 0$ (for $1 \le k \le N$), for δ large enough, the constant steady state $(I_k/|\Omega|)_{1\le k\le N}$ is the unique steady state $(V_k)_{1\le k\le N} \in (H^1(\Omega))^N$ of system (5.1) satisfying*

$$\int_\Omega V_k = I_k, \quad 1 \le k \le N.$$

Proof. Let $(V_k)_{1\le k\le N} \in (H^1(\Omega))^N$ be a steady state of the system (5.1). It satisfies

$$\begin{cases} -\Delta[a_k(\tilde{V})V_k] = 0, \quad in\ \Omega, \quad 1 \le i \le N \\ -\delta\Delta\tilde{V}_k + \tilde{V}_k = V_k, \quad in\ \Omega \quad 1 \le i \le N \\ \frac{\partial V_k}{\partial n} = \frac{\partial \tilde{V}_k}{\partial n} = 0, \quad \text{on } \partial\Omega, \quad 1 \le i \le N. \end{cases} \tag{5.3}$$

The steady states of the system should satisfy $\Delta a_k(\tilde{V})V_k = 0$, for any i, and therefore satisfy for certain constants C_k depending on V, such that

$$V_k = \frac{C_k}{a_k(\tilde{V})}.$$

They also satisfy $\int U_k = \int \tilde{U}_k = I_k$. As above, we denote $\langle u\rangle$ the average value of a function u. From Markov inequality, it follows that for any $\alpha > 1$ and any function $u \in L^1(\Omega)$, we have

$$\frac{|u \ge \alpha\langle u\rangle|}{|\Omega|} \le \alpha,$$

and therefore,

$$|u \le \alpha\langle u\rangle| \ge |\Omega|(1-1/\alpha).$$

This gives for the V_k,

$$|\{V_k \le \alpha\langle V_k\rangle\}| \ge |\Omega|(1-1/\alpha).$$

We also have

$$\left|\left\{\sum_{k=1}^N \tilde{V}_k \le \alpha\sum_{k=1}^N \langle V_k\rangle\right\}\right| \ge |\Omega|(1-1/\alpha). \tag{5.4}$$

$$\begin{aligned} I_k = \langle V_k\rangle|\Omega| \quad &= \textstyle\int V_k = \int \frac{C_k}{a_k(\tilde{V})} \\ &\ge \textstyle\int_{\{\sum_{i=1}^N \tilde{V}_i \le \alpha\sum_{i=1}^N \langle V_i\rangle\}} \dfrac{C_k}{a_k(\tilde{V})} \\ &\ge |\Omega|(1-\tfrac{1}{\alpha}) \sup_{\sum_{k=1}^N \tilde{V}_k \le \alpha\sum_{k=1}^N \langle V_k\rangle} \dfrac{C_k}{a_k(\tilde{V})}. \end{aligned}$$

This leads to

$$\forall \alpha > 1, \quad C_k \le \frac{I_k}{|\Omega|}\frac{\alpha}{\alpha-1} \inf_{\sum_{k=1}^N \tilde{V}_k \le \alpha\sum_{k=1}^N \langle V_k\rangle} a_k(\tilde{V}).$$

This gives a bound on C_k depending only on α and $(I_k)_{1\leq k\leq N}$, namely,

$$C_k(V) \leq C_k^0 := \inf_{\alpha>1} \frac{I_k}{|\Omega|}\frac{\alpha}{\alpha-1} \inf_{\sum_{k=1}^N \tilde{V}_k \leq \alpha \sum_{k=1}^N \langle V_k\rangle} a_k(\tilde{V}).$$

By (5.2), we have

$$V_k \leq \frac{C_k^0}{\nu},$$

and by the maximum principle, we also have

$$\tilde{V}_k \leq \frac{C_k^0}{\nu}.$$

Now, we go back to the equation on $\tilde{V}_k$. It can be written in the form

$$-\delta\Delta\tilde{V}_k + \tilde{V}_k = \frac{C_k}{a_k(\tilde{V})},$$

$$-\delta\Delta(\tilde{V}_k - \langle V_k\rangle) + (\tilde{V}_k - \langle V_k\rangle) = \frac{C_k}{a_k(\tilde{V})} - \langle V_k\rangle.$$

Integrating against $(\tilde{V}_k - \langle V_k\rangle)$ gives

$$\delta\int |\nabla(\tilde{V}_k-\langle V_k\rangle)|^2+\int |\tilde{V}_k-\langle V_k\rangle|^2 = \int \left(\frac{C_k}{a_k(\tilde{V})}-\langle V_k\rangle\right)(\tilde{V}_k-\langle V_k\rangle) = \int \left(\frac{C_k}{a_k(\tilde{V})}-C\right)(\tilde{V}_k-\langle V_k\rangle)$$

for any constant C since $\int(\tilde{V}_k - \langle(V_k\rangle) = 0$. We choose

$$C = \frac{C_k}{a_k(\langle V\rangle)}.$$

We have since $V_k, \tilde{V}_k \leq \frac{C_k^0}{\nu}$,

$$\left|\frac{C_k}{a_k(\tilde{V})} - \frac{C_k}{a_k(\langle V\rangle)}\right| \leq K|\tilde{V} - \langle V\rangle|,$$

where

$$K := \sup_{V_k \leq C_k^0/\nu,\quad 1\leq k\leq N} |Da_k(V)|,$$

does not depend on δ and depend only on $(I_k)_{1\leq k\leq N}$. Therefore, summing up,

$$\delta\|\nabla\tilde{V}\|_2^2 + \|\tilde{V} - \langle V\rangle\|_2^2 \leq K\|\tilde{V} - \langle V\rangle\|_2^2.$$

Using Poincaré Wirtinger inequality, we conclude

$$\delta\|\nabla\tilde{V}\|_2^2 + \|\tilde{V} - \langle V\rangle\|_2^2 \geq (1+\delta\lambda_1)\|\tilde{V} - \langle V\rangle\|_2^2,$$

which leads to the inequality

$$(1+\delta\lambda_1)\|\tilde{V} - \langle V\rangle\|_2^2 \leq K\|\tilde{V} - \langle V\rangle\|_2^2,$$

which for δ large (precisely $1 + \delta\lambda_1 > K$), is fulfilled only if

$$\|\tilde{V} - \langle V\rangle\|_2^2 = 0,$$

that is $V \equiv \tilde{V} \equiv \langle V\rangle$. For large values of δ, the homogeneous steady state is the unique steady state of the relaxed system in $(H^1(\Omega))^N$ satisfying for $k = 1\ldots N$, $\int_\Omega V_k = I_k$. $\square$

5.2 From Turing instability to bifurcation

5.2.1 The critical point δ_0

We consider here the following two-species cross diffusion system in a smooth domain Ω

$$\begin{cases} \partial_t u_1 - \Delta a_1(\tilde{u}_2)u_1 = 0, \\ \partial_t u_2 - \Delta a_2(\tilde{u}_1)u_2 = 0, \\ -\delta\Delta\tilde{u}_k + \tilde{u}_k = u_k, \\ \text{with Neumann boundary condition,} \quad u_k^0 \text{ given.} \end{cases} \tag{5.5}$$

The functions a_k satisfy the hypothesis ensuring well posedness of the system, they are, as usual taken nondecreasing. As it was done in chapter 4, one can investigate the linear stability of the homogeneous equilibrium,

$$u_k = \tilde{u}_k = \langle u_k \rangle.$$

As in chapter 4, the linearised system around this equilibrium reads

$$\begin{cases} \partial_t u_1 - \Delta a_1(\langle u_2 \rangle)u_1 - \Delta a_1'(\langle u_2 \rangle)\langle u_1 \rangle \tilde{u}_2 = 0, \\ \partial_t u_2 - \Delta a_2(\langle u_1 \rangle)u_2 - \Delta a_2'(\langle u_1 \rangle)\langle u_2 \rangle \tilde{u}_1 = 0, \\ -\delta\Delta\tilde{u}_k + \tilde{u}_k = u_k, \\ \text{with Neumann boundary condition,.} \end{cases}$$

We look again for solutions of type $(u_1, u_2, \tilde{u}_1, \tilde{u}_2) = e^{\mu t}(\alpha_1, \alpha_2, \beta_1, \beta_2)w$, where w is the first nonconstant eigenvector of the laplacian with Neumann boundary condition (we denote as before λ_1 the associated positive eiegenvalue). Such solutions should satisfy, firstly

$$\beta_k = \frac{1}{1+\delta\lambda_1}\alpha_k,$$

secondly,

$$\begin{cases} \mu\alpha_1 + \lambda_1 a_1(\langle u_2 \rangle)\alpha_1 + \lambda_1 a_1'(\langle u_2 \rangle)\langle u_1 \rangle \frac{\alpha_2}{1+\delta\lambda_1} = 0, \\ \mu\alpha_2 + \lambda_1 a_2(\langle u_1 \rangle)\alpha_2 + \lambda_1 a_2'(\langle u_1 \rangle)\langle u_2 \rangle \frac{\alpha_1}{1+\delta\lambda_1} = 0. \end{cases}$$

That is

$$\begin{pmatrix} a_1(\langle u_2 \rangle) & \frac{a_1'(\langle u_2 \rangle)\langle u_1 \rangle}{1+\delta\lambda_1} \\ \frac{a_2'(\langle u_1 \rangle)\langle u_2 \rangle}{1+\delta\lambda_1} & a_2(\langle u_1 \rangle) \end{pmatrix} \begin{pmatrix} \alpha_1 \\ \alpha_2 \end{pmatrix} = -\frac{\mu}{\lambda_1} \begin{pmatrix} \alpha_1 \\ \alpha_2 \end{pmatrix}.$$

The question of linear stability can now be related to the eigenvalues of the above matrix $M(\delta, \lambda_1)$. As in chapter 4, the steady state is stable if $\mu < 0$ (the matrix has no negative eigenvalue) and unstable if $\mu > 0$ (the matrix has a negative eigenvalue). The matrix $M(\delta, \lambda_1)$ admits a negative eigenvalue if and only if $\det(M(\delta, \lambda_1)) < 0$,

$$a_1(\langle u_2 \rangle)a_2(\langle u_1 \rangle) - \frac{a_1'(\langle u_2 \rangle)a_2'(\langle u_1 \rangle)\langle u_1 \rangle\langle u_2 \rangle}{(1+\delta\lambda_1)^2} < 0.$$

We remark that for fixed $a_k, \langle u_k \rangle$, the function

$$\delta \mapsto \det M(\delta, \lambda_1),$$

decreases from $\det M_0$ to $a_1(\langle u_2 \rangle)a_2(\langle u_1 \rangle) > 0$. If $\det M_0 > 0$ the equilibrium is Turing stable for any $\delta > 0$, otherwise there exists a unique δ_0 such that $\det M_{\delta_0} = 0$. In this case, the homogeneous steady state is stable for $\delta > \delta_0$ and unstable for $\delta < \delta_0$.

5.2.2 Bifurcation at the critical value δ_0

In this section, we prove that the critical value also characterizes the appearance of a new branch of equilibria. We suppose additional smoothness of the functions a_k: at least

$$a_k \in C^2(\mathbb{R}^N).$$

For two give positive constants $\langle u_1\rangle, \langle u_2\rangle$, we denote $w = (w_1, w_2)$ F the function defined by

$$F(\delta, w) = \begin{pmatrix} \Delta a_1(\langle u_2\rangle + \tilde{w}_2)(\langle u_1\rangle + w_1) \\ \Delta a_2(\langle u_1\rangle + \tilde{w}_1)(\langle u_2\rangle + w_2) \end{pmatrix}.$$

We study this function on $\mathbb{R}_+^* \times E^2$, where the space E is defined as

$$E = \{f \in W^{2,2}(\Omega),\ \int_\Omega f = 0,\ \partial_n f = 0\}.$$

In this formula we denote

$$-\delta\Delta\tilde{w} + \tilde{w} = w,$$

and therefore the dependency on δ is hidden in $\tilde{w}_1, \tilde{w}_2$. We remark that for any δ, w satisfying $F(\delta, w) = 0$, if we denote $u_k = \langle u_k\rangle + w_k$, then (u_1, u_2) is a steady state of the system (5.5). The nonnegativity comes from the remark that $F(\delta, w) = 0$ implies

$$a_1(\tilde{u}_2)u_1 = C_1, \qquad a_2(\tilde{u}_1)u_2 = C_2,$$

as we assumed $a_k \geq \nu > 0$, we can claim that u_k has a constant sign, the one of C_k, and since its average $\langle u_k\rangle$ is positive, so is u_k.

We prove now the following theorem

Theorem 5.2.1 *Assume the domain Ω is smooth and that the first nonzero eigenvalue λ_1 of the Neumann-laplacian in Ω is simple. Assume also that for $k = 1, 2$, $a_k \in C^2(\mathbb{R})$ and satisfies (5.2)*

$$a_1(\langle u_2\rangle)a_2(\langle u_1\rangle) - a_1'(\langle u_2\rangle)a_2'(\langle u_1\rangle)\langle u_1\rangle\langle u_2\rangle < 0,$$

(so that δ_0 exists) and let δ_0 be characterized by

$$a_1(\langle u_2\rangle)a_2(\langle u_1\rangle) - \frac{a_1'(\langle u_2\rangle)a_2'(\langle u_1\rangle)\langle u_1\rangle\langle u_2\rangle}{(1+\delta_0\lambda_1)^2} = 0.$$

Then the point $(\delta_0, 0)$ is a bifurcation point for F. That is, in some neighbourhood of $(\delta_0, 0)$, the set $\{(\delta, w); F(\delta, w) = 0\}$ consists of two continuous curves intersecting only at $(\delta_0, 0)$.

Proof. The proof is based on Crandall-Rabinowitz theorem (see [29, 88] for instance). To prove the theorem, we need to prove that, using notation

$$F_z = \frac{\partial F}{\partial z},$$

1. the kernel of $F_w(\delta_0, 0)$ has dimension 1, and is spanned by a vector $\varphi = (\varphi_1, \varphi_2) \in E^2$,
2. the range of $F_w(\delta_0, 0)$ has codimension 1,
3. the cross derivative $F_{\delta,w} = \frac{\partial^2 F}{\partial_\delta \partial_w}$ satisfies $F_{\delta,w}(\delta, 0)(\varphi) \notin R(F_w(\delta_0, 0)$.

Proof of point 1. Linearising the system gives immediately

$$F_w(\delta,0)(v)=\left(\begin{array}{c}\Delta(a_1'(\langle u_2\rangle)\langle u_1\rangle\tilde v_2+\Delta a_2(\langle u_1\rangle)v_1\\ \\ \Delta(a_2'(\langle u_1\rangle)\langle u_2\rangle\tilde v_1+\Delta a_1(\langle u_2\rangle)v_2\end{array}\right).$$

We project on the basis of Neumann-laplacian eigenvectors of the homogeneous space $\dot L^2(\Omega)$, $(e_k)_{k\geq 1}$, (we start at $k=1$ to take into account the fact that for the complete space $L^2(\Omega)$, one should add the constant eigenvector which is associated to the eigenvalue 0). We denote this decomposition

$$v_i=\sum_{k=1}^{\infty}v_i(k)e_k.$$

We have then

$$\tilde v_i(k)=\frac{1}{1+\delta\lambda_k}v_i(k),$$

and thereby,

$$\begin{aligned}F_w(\delta,0)(v)_1(k)&=-\lambda_k\big(a_1'(\langle u_2\rangle)\langle u_1\rangle\tfrac{1}{1+\delta\lambda_k}v_2(k)+a_2(\langle u_1\rangle)v_1(k)\big)\\ F_w(\delta,0)(v)_2(k)&=-\lambda_k\big(a_2'(\langle u_1\rangle)\langle u_2\rangle\tfrac{1}{1+\delta\lambda_k}v_1(k)+a_1(\langle u_2\rangle)v_2(k)\big)\end{aligned}$$

It is here convenient to write it in a matrix way:

$$F_w(\delta,0)(v)=-\sum_{k=1}^{\infty}\lambda_k M(\delta,\lambda_k)\left(\begin{array}{c}v_1(k)\\ v_2(k)\end{array}\right)e_k,$$

where $M(\delta,\lambda_k)$ is the matrix

$$\left(\begin{array}{cc}a_1(\langle u_2\rangle) & \dfrac{a_1'(\langle u_2\rangle)\langle u_1\rangle}{1+\delta\lambda_k}\\ \dfrac{a_2'(\langle u_1\rangle)\langle u_2\rangle}{1+\delta\lambda_k} & a_2(\langle u_1\rangle)\end{array}\right).$$

We want to know the dimension of $\ker(F_w(\delta,0))$. The spectral decomposition gives immediately, since $\lambda_k\neq 0$ for any $k\geq 1$,

$$v\in\ker(F_w(\delta,0))\Leftrightarrow\forall k\geq 1,\left(\begin{array}{c}v_1(k)\\ v_2(k)\end{array}\right)\in\ker M(\delta_0,\lambda_k).$$

The assumption on the simplicity of λ_1 is here crucial: from the definition of δ_0 and since $\lambda_k>\lambda_1$ for $k>1$, it follows that

$$\forall k\geq 2,\quad \det M(\delta_0,\lambda_k)>0.$$

Therefore, for $k\geq 2$, $\ker M(\delta_0,\lambda_k)=\{0\}$. As, from the definition of δ_0, $\det M(\delta_0,\lambda_1)=0$, we know that $\dim\ker M(\delta_0,\lambda_1)\geq 1$ and since it is a 2×2 matrix different of the zero matrix, we have actually $\dim\ker M(\delta_0,\lambda_1)=1$. The kernel can be described as

$$\ker M(\delta_0,\lambda_1)=\text{Span}\left(\begin{array}{c}\alpha_1\\ \alpha_2\end{array}\right),$$

which can be normalized by

$$\alpha_1=1,\quad \alpha_2=-\frac{a_1(\langle u_2\rangle)(1+\delta_0\lambda_1)}{a_1'(\langle u_2\rangle)\langle u_1\rangle}=-\frac{a_2'(\langle u_1\rangle)\langle u_2\rangle}{a_2(\langle u_1\rangle)(1+\delta_0\lambda_1)}\tag{5.6}$$

and therefore we can write,

$$v \in \ker(F_w(\delta,0)) \Leftrightarrow \forall k \geq 2, \begin{pmatrix} v_1(k) \\ v_2(k) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \quad \begin{pmatrix} v_1(1) \\ v_2(1) \end{pmatrix} \in \text{ Span}\begin{pmatrix} \alpha_1 \\ \alpha_2 \end{pmatrix},$$

and finally $\dim\ker(F_w(\delta,0)) = 1$ and

$$\ker(F_w(\delta,0)) = \text{Span}(\varphi), \qquad \varphi = \begin{pmatrix} \alpha_1 \\ \alpha_2 \end{pmatrix} e_1.$$

Proof of point 2.

We focus now on $R(F_w(\delta,0))$. Using the same decomposition, we have immediately,

$$v \in\ R(F_w(\delta,0)) \Leftrightarrow \forall k \geq 1, \begin{pmatrix} v_1(k) \\ v_2(k) \end{pmatrix} \in\ R(M(\delta_0,\lambda_k)).$$

For the very same reason as before, for $k \geq 2$, to impose

$$\begin{pmatrix} v_1(k) \\ v_2(k) \end{pmatrix} \in\ R(M(\delta_0,\lambda_k)) = \mathbb{R}^2,$$

is always possible. Therefore,

$$v \in\ R(F_w(\delta,0)) \Leftrightarrow \begin{pmatrix} v_1(1) \\ v_2(1) \end{pmatrix} \in\ R(M(\delta_0,\lambda_1)).$$

As $\dim\ker R(M(\delta_0,\lambda_1)) = 1$, there exists a unique (up to multiplication by a constant) nonzero real vector (β_1,β_2) such that

$$R(M(\delta_0,\lambda_1)) = (\beta_1,\beta_2)^{\perp},$$

which can be normalized for instance as

$$\beta_1 = 1, \quad \beta_2 = -\frac{a_1(\langle u_2\rangle)(1+\delta_0\lambda_1)}{a_2'(\langle u_1\rangle)\langle u_2\rangle} = -\frac{a_1'(\langle u_2\rangle)\langle u_1\rangle}{a_2(\langle u_1\rangle)(1+\delta_0\lambda_1)}. \tag{5.7}$$

We have then,

$$v \in\ R(F_w(\delta,0)) \Leftrightarrow \forall k \geq 1, \begin{pmatrix} v_1(1) \\ v_2(1) \end{pmatrix} \in\ (\beta_1,\beta_2)^{\perp} \Leftrightarrow v \in (\beta_1 e_1, \beta_2 e_1)^{\perp},$$

and then $R(F_w(\delta,0))$ has codimension 1.

Proof of point 3.

We need now to prove that

$$F_{\delta,w}(\delta,0)(\varphi) \notin R(F_w(\delta,0)).$$

This is equivalent using the above characterization of $R(F_w(\delta,0))$ to

$$(\beta_1 e_1, \beta_2 e_1).F_{\delta,w}(\delta,0)(\varphi) \neq 0.$$

We differentiate $F_w(\delta,0)$ with respect to δ directly in the spectral decomposition

$$F_{\delta,w}(\delta_0,0)(v) = -\sum_{k=1}^{\infty} \lambda_k \frac{\partial}{\partial\delta} M(\delta,\lambda_k) \begin{pmatrix} v_1(k) \\ v_2(k) \end{pmatrix} e_k.$$

We compute then

$$\frac{\partial}{\partial\delta}M(\delta,\lambda_k)=\begin{pmatrix} 0 & \dfrac{-\lambda_k}{(1+\delta\lambda_k)^2}a_1'(\langle u_2\rangle)\langle u_1\rangle \\ \dfrac{-\lambda_k}{(1+\delta\lambda_k)^2}a_2'(\langle u_1\rangle)\langle u_2\rangle & 0 \end{pmatrix}.$$

This leads to

$$F_{\delta,w}(\delta_0,0)(\varphi)=-\frac{\lambda_1^2}{(1+\delta\lambda_1)^2}\begin{pmatrix} 0 & a_1'(\langle u_2\rangle)\langle u_1\rangle \\ a_2'(\langle u_1\rangle)\langle u_2\rangle & 0 \end{pmatrix}\begin{pmatrix}\alpha_1\\ \alpha_2\end{pmatrix},$$

and finally,

$$(\beta_1e_1,\beta_2e_1).F_{\delta,w}(\delta,0)(\varphi)=-\frac{\lambda_1^2}{(1+\delta\lambda_1)^2}\Big(a_1'(\langle u_2\rangle)\langle u_1\rangle\alpha_2\beta_1+a_2'(\langle u_1\rangle)\langle u_2\rangle\alpha_1\beta_2\Big).$$

Using the formulas (5.6,5.7), we have immediately

$$\alpha_1\beta_2<0,\quad \alpha_2\beta_1<0,$$

and since

$$a_1(\langle u_2\rangle)a_2(\langle u_1\rangle)-a_1'(\langle u_2\rangle)a_2'(\langle u_1\rangle)\langle u_1\rangle\langle u_2\rangle<0,$$

we have

$$a_1'(\langle u_2\rangle)>0,\quad a_2'(\langle u_1\rangle)>0.$$

Combining these together we obtain

$$a_1'(\langle u_2\rangle)\langle u_1\rangle\alpha_2\beta_1+a_2'(\langle u_1\rangle)\langle u_2\rangle\alpha_1\beta_2$$

and then as needed

$$(\beta_1e_1,\beta_2e_1).F_{\delta,w}(\delta,0)(\varphi)\neq 0,$$

that is $F_{\delta,w}(\delta_0,0)(\varphi)\notin R(F_w(\delta_0,0))$, which ends the proof of the theorem. □

5.3 Illustrations

We give here numerical illustrations on our model case on the intervall $]0,1[$.

$$a_1(u_2)=1+u_2^2,\quad a_2(u_1)=1+u_1^2.$$

The hypothesis of our theorem are then satisfied.

We choose as in chapter 4 $\langle u_1\rangle=2,\langle u_2\rangle=1$. As in chapter 4, we start from the initial conditions

$$u_1=1.9+0.2\mathbb{1}_{[0.1,0.6]},\quad u_2=1.$$

We plot the final steady state obtained (the smaller δ is, the further the curves are from constant steady state).

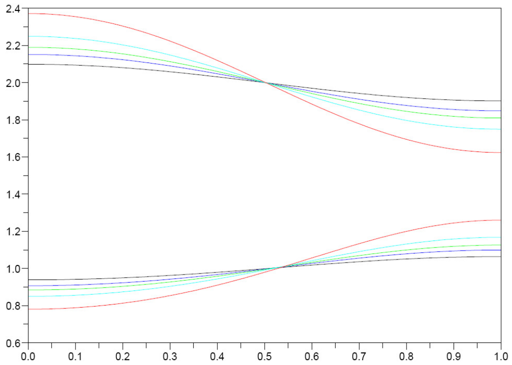


Figure 5.1: Steady states of the function u_1 (upper curves) and u_2 (lower curves). The parameter δ takes values $0.0255, 0.26, 0.261, 0.263, 0.264, 0.265$, the final steady state is closer to the constant steady state when δ is bigger.

Annexe A

Existence et unicité pour le système régularisé

Nous prouvons ici l'existence et l'unicité pour le système de diffusion croisée régularisé. Cette preuve se base sur une discrétisation semi implicite en temps qui conserve les estimations a priori obtenues aux chapitre 4. Ayant prouvé toutes les bornes nécéssaires, on applique le théorème d'Aubin-Lions pour construire une solution. Nous prouvons également l'unicité d'une solution vérifiant les estimations a priori.

We build a solution to the relaxed cross diffusion system (5.3) of chapter 4. We use a time semi discretization. The proof is organized as follows: firstly, we prove that Michel Pierre's estimate derived in chapter 4 has a discrete time analogue. Secondly, we build a discrete time scheme satisfying the bounds derived in chapter 4. Then, we apply compactness result to extract a solution to our system. Finally, we give a proof of uniqueness.

A.1 Adapted time discretization for duality estimates

Suppose the functions a_n are given such that $a_n \geq \nu > 0$, for $n = 0, N-1$ and u_0 is given, nonnegative. We consider the sequence u_n, v_n defined by

$$\begin{cases} \frac{u_{n+1}-u_n}{h} - \Delta(a_n u_{n+1}) = 0, \\ \frac{\partial}{\partial n}(a_n u_{n+1}) = 0, \\ u_0 = u^0 \geq 0 \quad \text{given.} \end{cases} \tag{A.1}$$

A.1.1 Nonnegativity preservation

This scheme is obviously preserving $\int_\Omega u_n$. With this discretization, positive coefficients a_n and initial data u^0 lead to nonnegative solutions: thanks Stampacchia truncation argument, we define $f_- = \min(f, 0)$, we multiply (A.1) by $a_n(u_{n+1})_- = (a_n u_{n+1})_-$ and we obtain

$$\int_\Omega a_n(u_{n+1})_-^2 - \int_\Omega a_n(u_{n+1})_- u_n = -h \int_\Omega |\nabla(a_n u_{n+1})_-|^2.$$

This leads to

$$\int_\Omega a_n(u_{n+1})_-^2 \leq \int_\Omega a_n(u_n)_-^2.$$

A.1.2 Discrete duality estimate

The question is: can we get on estimates analogue to(4.27) for the continuous case on v? The answer is given in the

Lemma A.1.1 *The following a priori estimates holds*

$$\sqrt{h\sum_{n=0}^{N-1}\int_\Omega a_n u_{n+1}^2} \leq C(\Omega)\|u_0\|_{L^2(\Omega)} + 2\langle u^0\rangle\sqrt{h\sum_{n=0}^{N-1}\int_\Omega a_n}. \tag{A.2}$$

Proof. As for the continuous case, the proof is based on a dual problem

$$\begin{cases} \frac{v_{n+1}-v_n}{h} + a_n\Delta v_n = F_{n+1}, \\ \frac{\partial v_n}{\partial n} = 0, \\ v_N = 0, \quad F_{n+1} \quad \text{given.} \end{cases} \tag{A.3}$$

We can notice that both are implicit schemes. We also have,

$$u_{n+1}v_{n+1} - u_n v_n = u_{n+1}(v_{n+1}-v_n) + (u_{n+1}-u_n)v_n = hu_{n+1}F_{n+1} - ha_n u_{n+1}\Delta v_n + hv_n\Delta a_n u_{n+1},$$

Therefore, a space integration leads to

$$\int_\Omega (u_{n+1}v_{n+1} - u_n v_n) = h\int_\Omega u_{n+1}F_{n+1},$$

Summing from 0 to $N-1$ we have, since $v_N = 0$,

$$-\int_\Omega u_0 v_0 = \sum_0^{N-1} h\int_\Omega u_{n+1}F_{n+1}. \tag{A.4}$$

Let us multiply (A.3) by Δv^n and integrate over Ω.

$$\int_\Omega (v_{n+1}-v_n)\Delta v_n + h\int_\Omega a_n|\Delta v_n|^2 = h\int_\Omega F_{n+1}\Delta v_n,$$

we have thanks to Young's inequality,

$$\int_\Omega (v_{n+1}-v_n)\Delta v_n = \int |\nabla v_n|^2 - \nabla v_n \nabla v_{n+1} \geq \int_\Omega \frac{|\nabla v_n|^2}{2} - \frac{|\nabla v_{n+1}|^2}{2}.$$

Which leads to,

$$\begin{aligned} \int_\Omega \tfrac{|\nabla v_n|^2}{2} - \tfrac{|\nabla v_{n+1}|^2}{2} + h\int_\Omega a_n|\Delta v_n|^2 \leq & \quad h\int_\Omega F_{n+1}\Delta v_n, \\ \leq & \quad h\int_\Omega \tfrac{|F_{n+1}|^2}{2a_n} + \tfrac{a_n|\Delta v_n|^2}{2} \end{aligned}$$

After a summation, as $v_N = 0$, we have as for the continuous case,

$$\int_\Omega |\nabla v_0|^2 + \sum_0^{N-1} h\int_\Omega a_n|\Delta v_n|^2 \leq \sum_0^{N-1} h\int_\Omega \frac{|F_{n+1}|^2}{a_n}.$$

We introduce the following notations:

$$\begin{aligned} u^h(t,x) &:= \textstyle\sum_{n=0}^{N-1} u_{n+1}(x)\mathbb{1}_{[nh,(n+1)h[}(t), \\ F^h(t,x) &:= \textstyle\sum_{n=0}^{N-1} F_{n+1}(x)\mathbb{1}_{[nh,(n+1)h[}(t), \\ v^h(t,x) &:= \textstyle\sum_{n=0}^{N-1} v_n(x)\mathbb{1}_{[nh,(n+1)h[}(t), \\ a^h(t,x) &:= \textstyle\sum_{n=0}^{N-1} a_n(x)\mathbb{1}_{[nh,(n+1)h[}(t). \end{aligned} \tag{A.5}$$

If we choose $F_{n+1}(x) = \frac{1}{h}\int_{nh}^{(n+1)h} F(t,x)dt$, we have thanks convexity,

$$F_{n+1}(x)^2 \leq \frac{1}{h}\int_{nh}^{(n+1)h} F(t,x)^2 dt,$$

$$\sum h \int_\Omega \frac{F_{n+1}^2}{a_n} \leq \int_0^T \int_\Omega \frac{F^2}{a^h} \leq \| \frac{F}{\sqrt{a^h}} \|_{L^2(Q_T)}^2,$$

and we have proved

$$\|\sqrt{a^h}\Delta v^h\|_{L^2(Q_T)}, \|\nabla v_0\|_{L^2(\Omega)} \leq \|\frac{F}{\sqrt{a^h}}\|_{L^2(Q_T)}.$$

We have also,

$$\begin{aligned} |\textstyle\int_\Omega v_0| = |\sum h \int_\Omega a_n \Delta v_n - F_{n+1}| &= |\textstyle\int_0^T \int_\Omega a^h \Delta v^h - F|, \\ &\leq \|\sqrt{a^h}\|_{L^2(Q_T)}\Big(\|\sqrt{a^h}\Delta v^h\|_{L^2(Q_T)} + \|\tfrac{F}{\sqrt{a^h}}\|_{L^2(Q_T)}\Big), \\ &\leq 2\|\sqrt{a^h}\|_{L^2(Q_T)}\|\tfrac{F}{\sqrt{a^h}}\|_{L^2(Q_T)}. \end{aligned}$$

As for the continuous case, equation (A.4) reads

$$\int_0^{T=Nh} \int_\Omega u^h F dx dt = -\int_\Omega u_0 v_0.$$

Therefore, we obtain the exact equivalent of Michel Pierre's estimate: since

$$\begin{aligned} |\textstyle\int u_0 v_0| \leq |\int u_0(v_0 - \langle v_0\rangle)| + |\langle u_0\rangle \int v_0| &\leq C(\Omega)\|u_0\|_{L^2(\Omega)}\|\nabla v_0\|_{L^2(\Omega)} + \langle u_0\rangle |\textstyle\int_\Omega v_0|, \\ &\leq (C(\Omega)\|u_0\|_{L^2(\Omega)} + 2\langle u_0\rangle \|\sqrt{a^h}\|_{L^2(Q_T)})\|\tfrac{F}{\sqrt{a^h}}\|_{L^2(Q_T)}. \end{aligned}$$

By duality, we have obtained (A.2). □

A.2 Application to the cross diffusion relaxed system: getting the a priori estimates

Now we apply this to the relaxed cross diffusion system:

$$\begin{cases} \partial_t U^k - \Delta a^k(\tilde{U})U^k = 0, \\ -\delta\Delta\tilde{U}^k + \tilde{U}^k = U^k, \\ \frac{\partial U^k}{\partial n} = \frac{\partial \tilde{U}^k}{\partial n} = 0, \\ U^i(t=0) = U_i^0. \end{cases} \tag{A.6}$$

with the assumptions considered in chapter 4: for $k = 1 \dots N$,

$$\begin{aligned} &a_k \in C^1(\mathbb{R}^N),\ 0 < \nu \leq a_k(U) \leq K(1 + |\tilde{U}|^p), \\ &|\nabla a_k(U)| \leq K a_k^{\eta}(U)|\nabla U| \quad \text{for some } \eta \in [0, 1[. \end{aligned} \tag{A.7}$$

$$\Omega \text{ is a smooth bounded domain in dimension 1 or 2.} \tag{A.8}$$

As for the continuous case, we detail the proof for a single equation, but it extends to As above, we introduce the time semi discretization,

$$\begin{cases} \dfrac{U^i_{n+1} - U^i_n}{h} - \Delta a^i(\tilde{U}_n) U^i_{n+1} = 0, \\ -\delta \Delta \tilde{U}^i + \tilde{U}^i = U^i, \\ U^i_{n=0} = U^i_0 \end{cases}$$

we also use the notations introduced above:

$$U^h(t, x) := \sum_{n \geq 0} U_{n+1}(x) \mathbb{1}_{[nh,(n+1)h[}(t).$$

A.2.1 A priori bounds

As for the continuous case, we treat the case of a single equation (satisfied by a function u), since we only need a summation to adapt the following to the case of systems.

Lemma A.2.1 *With assumptions (A.7),(A.8), we have the following bounds:*

- u^h *is uniformly bounded in* $L^\infty(0, T; L^q(\Omega))$, *for any* $q < +\infty$,
- $\tilde{u}^h$ *is uniformly bounded in* $L^\infty(0, T; W^{2,q}(\Omega))$, *for any* $q < +\infty$,
- $\tilde{u}^h$ *is uniformly bounded in* $L^\infty(0, T; W^{1,\infty}(\Omega))$, *and therefore, so is* a^h,
- u^h *is uniformly bounded in* $L^2(0, T; H^1(\Omega))$,

Proof.
We only need to prove the first and the last bounds, since the second and the third consequence of the first by elliptic regularity and Sobolev embeddings. The second implies the third from Sobolev embeddings (choose $q > 2$). The proof follows the steps of the a priori bounds on solutions derived in chapter 4.

Firstly, we prove a bound on $\|u^h\|_{L^2(Q_T)}$. We introduce the integer N such that $(N-1)h \leq T < Nh$. We have thanks to (A.2),

$$\begin{aligned} \|\sqrt{a^h} u^h\|_{L^2(Q_{Nh})} &\leq C(\Omega)\|u^0\|_{L^2(\Omega)} + 2\langle u^0 \rangle \|\sqrt{a^h}\|_{L^2(Q_{Nh})}, \\ &\leq C(\Omega)\|u^0\|_{L^2(\Omega)} + 2\langle u^0 \rangle K \sqrt{|\Omega| Nh + \textstyle\sum_{n=0}^{N-1} \int_\Omega (\tilde{u}_n)^p dx}, \\ &\leq C(\Omega)\|u^0\|_{L^2(\Omega)} + 2\langle u^0 \rangle K (\sqrt{|\Omega| Nh} + \sqrt{h \|\tilde{u}^0\|_p^p} + \sqrt{\textstyle\int_0^{(N-1)h} \|\tilde{u}^h\|_p^p}), \\ &\leq C(\Omega)\|u^0\|_{L^2(\Omega)} + 2\langle u^0 \rangle K (\sqrt{|\Omega| Nh} + \sqrt{h \|\tilde{u}^0\|_p^p} + \sqrt{\textstyle\int_0^{T} \|\tilde{u}^h\|_p^p}). \end{aligned}$$

Since $Q_T \subset Q_{Nh}$, we also have

$$\|\sqrt{a^h} u^h\|_{L^2(Q_T)} \leq C(\Omega)\|u^0\|_{L^2(\Omega)} + 2\langle u^0 \rangle K (\sqrt{|\Omega| Nh} + \sqrt{h \|\tilde{u}^0\|_p^p} + \sqrt{\int_0^{T} \|\tilde{u}^h\|_p^p}).$$

which can be summarized as

$$\|\sqrt{a^h}u^h\|_{L^2(Q_T)} \quad \leq C(\Omega)\|u^0\|_{L^2(\Omega)} + \sqrt{h}C(\Omega,u^0) + 2\langle u^0\rangle K(\sqrt{|\Omega|T} + \sqrt{\textstyle\int_0^T \|\tilde{u}^h\|_p^p}),$$

with the same constants as for the continuous case (up to the corrective term of order $\sqrt{h}$). With the same computations as in the continuous case, we obtain

$$\nu\|u^h\|_{L^2(Q_T)} \quad \leq C(\Omega)\|u^0\|_{L^2(\Omega)} + C'(\Omega)\sqrt{T} + C(\delta,r,p,\|u^0\|_1)T^{\frac{2-p\theta(r)}{4}}\|u_g^h\|_{L^2(Q_T)}^{p\theta(r)/2}.$$

As in the continuous case, we choose r so that $p\theta(r)/2 < 1$, and obtain

$$\|u^h\|_{L^2(Q_T)} \leq C(\Omega,u^0,\delta,h,T). \tag{A.9}$$

And the constant decreases to a limit when h goes to zero (it should be the constant used for the continuous case). For $q > 1$, we multiply (A.1) by u_{n+1}^{q-1}, we have

$$\begin{aligned}\textstyle\int_\Omega u_{n+1}^q - u_n u_{n+1}^{q-1} \quad &= h\textstyle\int_\Omega u_{n+1}^{q-1}\Delta a_n u_{n+1},\\ &= -h\textstyle\int_\Omega \nabla u_{n+1}^{q-1}\nabla a_n u_{n+1},\end{aligned}$$

We remind that, using Young's inequality, we have for any $p > 1$

$$u_{n+1}^q - u_n u_{n+1}^{q-1} \geq u_{n+1}^q - \frac{u_n^p}{p} - \left(1 - \frac{1}{p}\right)u_{n+1}^{(q-1)p/(p-1)},$$

and choosing $p = q$, we obtain,

$$u_{n+1}^q - u_n u_{n+1}^{q-1} \geq \frac{u_{n+1}^q}{q} - \frac{u_n^q}{q}.$$

Therefore, we have,

$$\begin{aligned}\textstyle\int_\Omega \frac{u_{n+1}^q}{q} - \frac{u_n^q}{q} \quad &\leq -h\textstyle\int_\Omega \nabla u_{n+1}^{q-1}\nabla a_n u_{n+1},\\ &= -h\textstyle\int_\Omega (q-1)u_{n+1}^{q-2}a_n|\nabla u_{n+1}|^2 - h\textstyle\int_\Omega (q-1)u_{n+1}^{q-2}\nabla u_{n+1}\nabla a_n.\end{aligned}$$

We detail now only what differs between the discrete and continuous cases. We arrive (with almost the same constants as the ones involved in the continuous version) to:

$$\frac{1}{h}\int_\Omega (u_{n+1}^q - u_n^q) + \frac{C_q}{3}\int_\Omega a_n|\nabla u_{n+1}^{q/2}|^2 + \frac{C_q}{3}\int_\Omega |\nabla a_n^{1/2}u_{n+1}^{q/2}|^2 \leq C_q^2\int_\Omega u_{n+1}^q|\nabla\tilde{U}_n|^2 a(\tilde{U}_n)^{2\eta-1}.$$

Still almost with the same constant as in the continuous case, we have for $1 < q < 2$ and $\frac{q}{2} > 2\eta - 1$,

$$\begin{aligned}\tfrac{1}{h}\textstyle\int_\Omega (u_{n+1}^q - u_n^q) \quad &\leq C(q,\delta,r)\|\sqrt{a_n}u_{n+1}\|_{qr}^q\|u_n\|_q^q\|u_n\|_2^{2-q}\\ &\leq C(\delta,q)[\|\sqrt{a_n}u_{n+1}\|_2^2 + \|u_n\|_2^2]\|u_n\|_q^q,\end{aligned}$$

which gives an a priori bound thanks to Gronwall lemma (discrete form). We use the same procedure than for the continuous case for bigger exponent $q \geq 2$. We have then proved the first bound. The last bound comes, as for the continuous case, from the case $q = 2$. □

A.2.2 Compactness

We introduce now the interpolated function u_m^h defined by

$$u_m^h(t) = \frac{t-nh}{h} u_{n+1} + \frac{(n+1)h-t}{h} u_n \text{ on } [nh,(n+1)h[.$$

We have then , on $]nh,(n+1)h[$

$$\partial_t u_m^h = \frac{u_{n+1}-u_n}{h} = \Delta a_n u_{n+1} = \Delta a^h u^h. \tag{A.10}$$

We prove the following compactness on u_m^h.

Lemma A.2.2 *The functions $u_m^h, \tilde{u}_m^h$ satisfy:*

- *u_m^h is relatively compact in $C(0,T;H^{-1}(\Omega))$ and in $L^2(0,T;L^2(\Omega))$, where $H^{-1}(\Omega)$ is the dual space of $H^1(\Omega)$,*
- *$\tilde{u}_m^h$ is relatively compact in $C(0,T;C^1(\Omega))$.*

Proof. We first notice that by construction $u_m^h, \tilde{u}_m^h$ are bounded in the same spaces as $u^h, \tilde{u}^h$. Particularly, we have

$$\forall 1 \le q < +\infty, \quad \|u_m^h\|_{L^\infty(0,T;L^q(\Omega))} \le C(q,T), \tag{A.11}$$

$$\forall 1 \le q < +\infty, \quad \|u_m^h\|_{L^\infty(0,T;W^{2,q}(\Omega))} \le C(q,T), \tag{A.12}$$

$$\|u_m^h\|_{L^\infty(0,T;H^1(\Omega))} \le C(T). \tag{A.13}$$

The notation $C(T)$ (resp. $C(q,T)$) denotes any constant depending only on T (resp. T,q) and Ω, δ, u^0. We want to apply Aubin-Lions lemma. Therefore, we need bounds on $\partial_t u_m^h, \partial_t \tilde{u}_m^h$ Equation (A.10) in a weak form reads

$$\int_\Omega \partial_t u_m^h \varphi = -\int_\Omega \nabla a_n u_{n+1} \nabla \varphi,$$

which leads to

$$\|\partial_t u_m^h\|_{H^{-1}(\Omega)} \le \|\nabla a^h u^h\|_{L^2(\Omega)},$$

which gives a uniform bound

$$\|\partial_t u_m^h\|_{L^2(0,T;H^{-1}(\Omega))} \le C(T), \tag{A.14}$$

since a^h is bounded in $L^\infty(0,T;W^{1,\infty}(\Omega)$ and u^h is bounded in $L^2(0,T;H^1(\Omega))$.

Similarly, we have

$$\int_\Omega \delta |\nabla \partial_t \tilde{u}_m^h|^2 + \int_\Omega |\partial_t \tilde{u}_m^h|^2 = -\int_\Omega \nabla a_n u_{n+1} \nabla \partial_t \tilde{u}_m^h$$

which gives

$$\int_\Omega \frac{\delta}{2} |\nabla \partial_t \tilde{u}_m^h|^2 + \int_\Omega |\partial_t \tilde{u}_m^h|^2 \le \frac{1}{2\delta} \int_\Omega |\nabla a_n u_{n+1}|^2$$

we deduce the uniform bound $\partial_t \tilde{u}_m^h$

$$\|\partial_t \tilde{u}_m^h\|_{L^2(0,T;H^1(\Omega))} \le C(T). \tag{A.15}$$

We are in position to apply Aubin-Lions lemma. We summarize the bounds we know on $\tilde{u}_m^h$:

- $\tilde{u}_m^h$ is uniformly bounded in $L^\infty(0,T;W^{2,q}(\Omega))$ for any $q \in]1,\infty[$,
- $\tilde{u}_m^h$ is uniformly bounded in $W^{1,2}(0,T;H^1(\Omega))$,
- u_m^h is uniformly bounded in $L^\infty(0,T;L^q(\Omega))$ for any $q \in]1,\infty[$,
- u_m^h is uniformly bounded in $W^{1,2}(0,T;H^{-1}(\Omega))$.

Let us consider a fixed $q > 2$. Sobolev embeddings give

$$W^{2,q}(\Omega) \hookrightarrow_c C^1(\Omega) \hookrightarrow H^1(\Omega),$$

therefore $\tilde{u}_m^h$ is relatively compact in $C(0,T;C^1(\Omega))$ and also in $C(0,T;H^1(\Omega))$.

Similarly,

$$H^1(\Omega) \hookrightarrow_c L^2(\Omega) \hookrightarrow H^{-1}(\Omega),$$

u_m^h is relatively compact in $L^2(0,T;L^2(\Omega))$ and in $C(0,T;H^{-1}(\Omega))$. □

A.2.3 Extraction of a solution

We first notice that u_m^h is close to u^h is the following sense:

Lemma A.2.3 *We have*

$$\|u^h - u_m^h\|_{L^2(Q_T)} = O(\sqrt{h}),$$

$$\|\tilde{u}^h - \tilde{u}_m^h\|_{L^2(0,T;W^{2,2}(\Omega))} = O(\sqrt{h}).$$

Proof. First, we recall that for $t \in [nh,(n+1)h[$, we have

$$\begin{aligned} \textstyle\int_\Omega |u_m^h - u^h|^2 \leq & \textstyle\int_\Omega (u_{n+1}-u_n)^2, \\ \leq & h \textstyle\int_\Omega \nabla(a_n u_{n+1})\nabla(u_{n+1}-u_n). \end{aligned}$$

Therefore, since a_n is bounded in $L^\infty(C^1(\Omega))$ (by C(T)), we have

$$\int_0^T \int_\Omega |u_m^h - u^h|^2 dxdt \leq C(T)h \sum_{n\geq 1} h \int_\Omega |u_{n+1}||\nabla(u_{n+1}-u_n)| + |\nabla u_{n+1}||\nabla(u_{n+1}-u_n)|dx + h\int_\Omega |u_1-u_0|^2,$$

the right hand side is then controlled by the $L^2(0,T;H^1(\Omega))$ bound on u^h and we have, since u^h is uniformly bounded in $L^2(\Omega)$,

$$h\int_\Omega |u_1 - u_0|^2 \leq C(T)h.$$

Finally we have obtained (we still denote the constant by $C(T)$ even if it also depends on u^0, Ω, δ),

$$\int_0^T \int_\Omega |u_m^h - u^h|^2 dxdt \leq C(T)h,$$

which is the first bound, the second bound is then a consequence of elliptic regularity. □

Lemma A.2.4 *Up to the extraction of a subsequence, we have*

$$\begin{aligned} u_m^h &\to u \quad \textit{in } C(0,T;H^{-1}(\Omega)) \bigcap L^2(0,T;L^2(\Omega)) \quad (\textit{strongly}), \\ u^h &\to u \quad \textit{in } L^2(0,T;L^2(\Omega)) \quad (\textit{strongly}), \\ \tilde{u}_m^h &\to \tilde{u} \quad \textit{in } C(0,T;H^1(\Omega)) \bigcap L^2(0,T;W^{2,2}(\Omega)) \quad (\textit{strongly}), \end{aligned}$$

where u is a solution to (A.6).

Proof. First and last statement are immediate consequences of the compactness result proved in lemma A.2.2 We extract a subsequence such that

$$u_m^h \to u \quad \text{in} \quad C(0,T;H^{-1})\bigcap L^2(0,T;L^2(\Omega)) \quad \text{(strongly)},$$

a consequence of the bound is that

$$u^h \to u \quad \text{in } L^2(0,T;L^2(\Omega)) \quad \text{(strongly)}. \tag{A.16}$$

We can choose the subsequence such that

$$\tilde{u}_m^h \to u \quad \text{in } C(0,T;C^1(\Omega))\bigcap L^2(0,T;H^1(\Omega)) \quad \text{(strongly)}.$$

The bounds on $u^h - u_m^h$ gives then immediately,

$$\tilde{u}^h \to \tilde{u} \quad \text{in } L^2(0,T;H^1(\Omega)) \quad \text{(strongly)}.$$

As u^h is bounded in $L^2(0,T;H^1(\Omega))$, we can choose the subsequence such that

$$u^h \rightharpoonup u \quad \text{in } L^2(0,T;H^1(\Omega)).$$

Furthermore, as $\partial_t u_m^h$ is bounded in $L^2(0,T;H^{-1}(\Omega))$, we also can assume

$$\partial_t u_m h \rightharpoonup \partial_t u \quad \text{in} \quad L^2(0,T;H^{-1}(\Omega)).$$

Now we prove that u is a solution of the equation. We already now that

$$\int_0^T (\partial_t u_m^h, \varphi)dt + \int_\Omega u^0\varphi = -\int_0^T\int_\Omega a^h\nabla u^h\nabla\varphi - \int_0^T\int_\Omega u^h\nabla a^h\nabla\varphi,$$

for any function $\varphi \in H^1(\Omega)$. The notation $(\partial_t u, \varphi)$ is the duality product $H^{-1}\times H^1$. We have then

$$\int_0^T (\partial_t u_m^h, \varphi)dt \to \int_0^T (\partial_t u, \varphi)dt.$$

We have,

$$\textstyle\int_0^T\int_\Omega a^h\nabla u^h\nabla\varphi - \int_0^T\int_\Omega a^h\nabla u^h\nabla\varphi \quad = \int_0^T\int_\Omega (a^h - a)\nabla u^h\nabla\varphi + \int_0^T\int_\Omega a(\nabla u^h - \nabla u)\nabla\varphi$$

The first integral goes to zero thanks the bounds on ∇u^h and the strong convergence of a^h to a in $L^2(0,T;L^2(\Omega))$. The second goes to zero using weak convergence of u^h in $L^2(0,T;H^1(\Omega))$. We have therefore,

$$\int_0^T\int_\Omega a^h\nabla u^h\nabla\varphi \to \int_0^T\int_\Omega a\nabla u\nabla\varphi \quad \text{for any } \varphi\in H^1(\Omega).$$

We need now to prove that

$$\int_0^T\int_\Omega u^h\nabla a^h\nabla\varphi \to \int_0^T\int_\Omega u\nabla a\nabla\varphi \quad \text{for any } \varphi\in H^1(\Omega).$$

This can be reduced, thanks the bounds on a^h and the convergence of u^h to u in $L^2(Q_T)$ to proving

$$\int_0^T\int_\Omega u\nabla a^h\nabla\varphi \to \int_0^T\int_\Omega u\nabla a\nabla\varphi \quad \text{for any } \varphi\in H^1(\Omega).$$

which is obtained using the strong convergence of $\tilde{u}^h \to \tilde{u}$ in $L^2(0,T;H^1(\Omega))$ and of $u^h \to u$. We have build a solution of the equation:

$$u \in L^2(0,T;H^1(\Omega)), \partial_t u \in L^2(0,T;H^{-1}).$$

A.3 Uniqueness

We prove here the uniqueness of the solution build in the above procedure.

Theorem A.3.1 *With the assumptions (4.16) on a_k, for Ω bounded and smooth, there is at most one solution U to (5.3) satisfying*

$$\forall q \in [1, +\infty, \quad U \in \left(L^\infty_{loc}([0, +\infty[; L^q(\Omega)) \right)^N, \tag{A.17}$$

$$U \in \left(L^2_{loc}([0, +\infty[; H^1(\Omega)) \right)^N. \tag{A.18}$$

Proof. The reader may notice, that the solution build using the above procedure also satisfies the a priori bounds derived in chapter 4. We only gave the bounds that are needed to prove uniqueness. The fact that U belongs to those spaces can be written in such a form,

$$\forall T > 0, \ \forall \quad 1 < q < \infty, \quad \|U(t)\|_{L^q(\Omega)} \le C(q, T), \tag{A.19}$$

$$\forall T > 0, \quad \|\nabla U\|_{L^2(Q_T)} \le C(T), \tag{A.20}$$

where the constants $C(q,T), C(T)$ also depend on δ and U^0. We also remind that thanks to elliptic regularity in dimension $1, 2$, we have

$$\forall \quad 1 < q < \infty, \quad \|\nabla \tilde{U}\|_{L^q(\Omega)} \le C(q, \delta) \|U\|_{L^2(\Omega)}$$

$$\|\tilde{U}\|_\infty \le C(\delta) \|U\|_2$$

Finally, we also have a general bound

$$\|\nabla \tilde{U}\|_\infty \le C(T, U^0, \delta)$$

$$\|\nabla U\|_{L^2(Q_T)} \le C(T, U^0)$$

Now, consider two solutions U_1, U_2 of equation (A.6). We may write (we argue again at the level of one equation but a summation is needed at the end).

$$\begin{aligned}
\tfrac{d}{dt} \textstyle\int_\Omega (U_1 - U_2)^2 \quad &= - \textstyle\int_\Omega \nabla(a_1 U_1 - a_2 U_2) \nabla (U_1 - U_2) \\
&= - \textstyle\int_\Omega a_1 |\nabla(U_1 - U_2)|^2 - \int_\Omega (U_1 - U_2) \nabla a_1 \nabla (U_1 - U_2) \\
&- \textstyle\int_\Omega U_2 \nabla(a_1 - a_2) \nabla(U_1 - U_2) - \int_\Omega (a_1 - a_2) \nabla U_2 \nabla (U_1 - U_2) \\
&= -(I_1 + I_2 + I_3 + I_4)
\end{aligned} \tag{A.21}$$

The term I_1 has a sign and plays a crucial role. We have

$$\begin{aligned}
-I_2 \quad &= - \textstyle\int_\Omega (u_1 - u_2) \nabla a_1 \nabla (u_1 - u_2) \\
&\le \textstyle\int_\Omega (u_1 - u_2)^2 \frac{|\nabla a_1|^2}{2\varepsilon a_1} + \varepsilon \int_\Omega a_1 |\nabla (u_1 - u_2)|^2 \\
&\le C(\varepsilon, T, U_0) \textstyle\int_\Omega (u_1 - u_2)^2 + \varepsilon I_1
\end{aligned}$$

This term will be controlled by I_1 and Gronwall lemma. Next, we write

$$\begin{aligned}
-I_3 \quad &= - \textstyle\int_\Omega U_2 \nabla(a_1 - a_2) \nabla (U_1 - U_2) \\
&\le \textstyle\int_\Omega (U_2)^2 \frac{|\nabla a_1 - a_2|^2}{2\varepsilon a_1} + \varepsilon \int_\Omega a_1 |\nabla(U_1 - U_2)|^2 \\
&\le \varepsilon \textstyle\int_\Omega a_1 |\nabla(U_1 - U_2)|^2 + \int_\Omega \frac{U_2^2}{\varepsilon a_1} (|a'(\tilde{U}_1)(\nabla(\tilde{U}_1 - \tilde{U}_2)|^2 + |a'(\tilde{U}_1) - a'(\tilde{U}_2)|^2 |\nabla \tilde{U}_2|^2), \\
&\le \varepsilon I_1 + C(\varepsilon) I_5 + C(\varepsilon) I_6
\end{aligned}$$

where

$$I_5 = \int_\Omega U_2^2(|a'(\tilde{U}_1)(\nabla(\tilde{U}_1 - \tilde{U}_2)|^2,$$

$$I_6 = \int_\Omega U_2^2|a'(\tilde{U}_1) - a'(\tilde{U}_2)|^2|\nabla\tilde{U}_2|^2.$$

Since a is C^1, , then the L^∞ bound on $\tilde{U}$ allows us to write

$$|a'(\tilde{U}_1)\nabla(\tilde{U}_1 - \tilde{U}_2)|^2 \leq C(T)|\nabla(\tilde{U}_1 - \tilde{U}_2)|^2.$$

Therefore,

$$\begin{aligned} I_5 \quad & \leq C(T) \textstyle\int_\Omega u_2^2|\nabla(\tilde{U}_1 - \tilde{U}_2)|^2 \\ & \leq C(T)\|U_2\|_{2p}^2\|\nabla(\tilde{U}_1 - \tilde{U}_2)\|_{2p'}^2 \\ & C'(T, p, U^0)\|\nabla(\tilde{U}_1 - \tilde{U}_2)\|_{2p'}^2 \\ & \leq C'(T, p, U^0)C(\delta, 2p')\|U_1 - U_2\|_2^2. \end{aligned}$$

And thus I_5 will contribute in (A.21) to a Gronwall argument. Finally, we have to control I_6

$$I_6 \leq C(T)\|a'(\tilde{U}_1) - a'(\tilde{U}_2)\|_\infty^2 \leq C'(T, U^0)\|\tilde{U}_1 - \tilde{U}_2\|_\infty^2 \leq C(T, U^0, \delta)\|U_1 - U_2\|_2^2$$

Similarly, we have

$$I_4 \leq \int_\Omega \frac{(a_1 - a_2)^2}{2\varepsilon a_1}|\nabla u_2|^2 + \varepsilon I_1 \leq \varepsilon I_1 + C(T, U^0, \delta)\|U_1 - U_2\|_2^2\|\nabla u_2\|_2^2$$

We might summarize all these inequalities after summation (with a suitable choice of ε in order to get rid of I_1) into

$$\frac{d}{dt}\|U_1 - U_2\|_2^2 \leq C(T, U^0, \delta)(1 + \|\nabla U_2\|_2^2)\|U_1 - U_2\|_2^2$$

As $\|\nabla U_2\|_2^2$ is integrable, we may apply Gronwall lemma so that the solution is unique. □

Annexe B

Convexité de la valeur propre de Floquet

B.1 Context of the result: Kingman's inequality

A theorem of Kingman ([62], see [12] for a proof analogue to this one) on nonnegative matrices, states that, given two nonnegative $d \times d$ matrices A, B, and denoting by $\rho(A), \rho(B)$ their respective spectral radii, by A^α the matrix (A_{ij}^α) for $\alpha \geq 0$ and by $A \circ B$ the Schur product $A_{ij}B_{ij}$, we have

$$\forall \alpha \in [0,1] \rho(A^\alpha \circ B^{1-\alpha}) \leq \rho(A)^\alpha \rho(B)^{1-\alpha}.$$

This result can be extended to essentially nonnegative matrices (matrices with nonnegative offdiagonal entries) in the following way: the dominant eigenvalue $r(A)$ of such a matrix A is defined as the eigenvalue which is real and is bigger than the real part of any other eigenvalue (its existence is insured by Perron Frobenius theorem). It can also be defined as $r(A) = \log(\rho(\exp(A)))$ (essentially nonnegative matrices have nonnegative exponential). Then, we have the following result: given two essentially nonnegative $d \times d$ matrices A, B denoting $r(A)$ and $r(B)$ their respective dominant eigenvalue, for any $\alpha \in [0,1]$, if we define $C(\alpha)$ by

$$C_{ij}(\alpha) = A_{ij}^\alpha B_{ij}^{1-\alpha} \quad \text{if } i \neq j, \qquad C_{ii}(\alpha) = \alpha A_{ii} + (1-\alpha) B_{ii},$$

then we have

$$r(C(\alpha)) \leq \alpha r(A) + (1-\alpha) r(B).$$

We extend this result to the case of periodic dynamical systems. First we extend this to system of ordinary differential equations with periodic coefficients, secondly we extend these results to the case of discrete dynamical systems, thirdly, we generalize this to the case of renewal equations. Finally, we discuss the consequences of such a convexity result. Particularly, this provides a theoretical argument for chronotherapy.

B.2 Differential systems

Let $t \mapsto A^1(t)$, $t \mapsto A^2(t)$ be two periodic maps with value in $\mathbb{R}^{d \times d}$, integrable on $[0,T]$. We assume that for $i \neq j$, we have $A_{ij}^{1,2}(t) \geq 0$ for almost every t. We introduce the (first) Floquet eigenvalue λ_F^k $(k = 1,2)$ which can defined by means of the following eigenproblem: there exists a $T-$periodic function X with values in $\mathbb{R}_+^d$, non identically zero that satisfies

$$\frac{dX^k}{dt} = A^k(t) X^k(t) - \lambda_F^k X^k(t). \tag{B.1}$$

Notice that if A^k satisfies some irreducibility properties, then X is unique up to a normalization. However, it can also be considered as

$$\lambda_F^k = \sup\{\lambda,\ \exists X, \geq 0,\ \text{T-periodic } X \not\equiv 0,\ \dot{X}(t) \leq A^k(t)X(t) - \lambda X(t)\}. \tag{B.2}$$

The inequality holding component by component. We can also define it as

$$\lambda_F^k = \inf\{\lambda,\ \exists X \geq 0,\ \text{T-periodic } X \not\equiv 0,\ \dot{X}(t) \geq A^k(t)X(t) - \lambda X(t)\}. \tag{B.3}$$

With this definition, we do not need irreducibility property. We introduce an averaged version of the systems with matrices A^1, A^2. We define, for $\theta \in [0,1]$, the matrix A^θ by

$$\begin{cases} A^\theta(t)_{ii} = \theta A^1(t)_{ii} + (1-\theta)A^2_{ii}(t), \\ A^\theta(t)_{ij} = (A^1(t)_{ij})^\theta (A^2_{ii}(t))^{(1-\theta)}, \quad \text{if } i \neq j. \end{cases}$$

The map $t \mapsto A^\theta(t)$ satisfies the same hypothesis (except eventual irreducibility properties). We introduce its Floquet eigenvalue λ_F^θ. The result can then be stated as follows:

Theorem B.2.1 *We have always*

$$\lambda_F^\theta \leq \theta\lambda_F^1 + (1-\theta)\lambda_F^2.$$

Proof. The proof is based on the construction of a subsolution to the eigenproblem. We prove the property in the case $A^k_{ij}(t) > 0$ for every t and $i \neq j$. In this case, the eigenfunctions defined in (B.1) satisfy $X_i(t) > 0$ for every t, i. Given the eigenelements λ_F^k, X^k defined in (B.1), we claim the following: let X^θ be defined by $X^\theta(t) = (X^1(t))^\theta (X^2(t))^{1-\theta}$, then, we have

$$\frac{dX^\theta}{dt} \leq A^\theta(t)X^\theta(t) - (\theta\lambda_F^1 + (1-\theta)\lambda_F^2)X^\theta(t).$$

Since, $X_i^k(t) > 0$ for any t, i, we can write the equation on $\ln X_i^k(t)$:

$$\frac{d}{dt}\ln X_i^k(t) = A^k_{ii}(t) - \lambda_F^k + \sum_{j\neq i} A^k_{ij}(t)\frac{X_j^k(t)}{X_i^k(t)}.$$

Since we have

$$\ln X^\theta = \theta \ln X^1 + (1-\theta)\ln X^2,$$

we have

$$\begin{aligned} \tfrac{d}{dt}\ln X_i^\theta(t) &= \theta(A^1_{ii}(t) - \lambda_F^1) + (1-\theta)(A^2_{ii}(t) - \lambda_F^2) + \textstyle\sum_{j\neq i} \theta A^1_{ij}(t)\frac{X_j^1(t)}{X_i^1(t)} + (1-\theta)A^2_{ij}(t)\frac{X_j^2(t)}{X_i^2(t)} \\ &\leq \theta A^1_{ii}(t) + (1-\theta)A^2_{ii}(t) + \textstyle\sum_{j\neq i}\left(A^1_{ij}(t)\frac{X_j^1(t)}{X_i^1(t)}\right)^\theta \left(A^2_{ij}(t)\frac{X_j^2(t)}{X_i^2(t)}\right)^{(1-\theta)}, \end{aligned}$$

thanks to the arithmetic-geometric inequality, which can be formulated as

$$\frac{d}{dt}\ln X^\theta(t)_i \leq A^\theta_{ii}(t) - (\theta\lambda_F^1 + (1-\theta)\lambda_F^2) + \sum_{j\neq i} A^\theta_{ij}(t)\frac{X_j^\theta(t)}{X_i^\theta(t)}.$$

Multiplication the equation by X^θ gives

$$\frac{dX^\theta}{dt} \leq A^\theta(t)X^\theta(t) - (\theta\lambda_F^1 + (1-\theta)\lambda_F^2)X^\theta(t). \tag{B.4}$$

Combining (B.4) and (B.3) leads to the result (if we do not have irreducibility properties, we can state the result by considering $A^k(t) + \varepsilon$ with $\varepsilon > 0$ and let ε go to zero). $\square$

B.3 Discrete dynamical system

The same proof allows to treat discrete dynamical systems. Given two sequences of nonnegative p-periodic matrices $(A^1(n))_{n\in\mathbb{Z}}, (A^2(n))_{n\in\mathbb{Z}}$ with values in $\mathbb{R}^{d\times d}$, we define the averaged sequence of $p-$periodic matrices $(A^\theta(n))_{n\in\mathbb{Z}}$ by the following:

$$\forall n \in \mathbb{Z}, \forall 1 \leq i,j \leq d, \quad (A^\theta(n))_{ij} = (A^1(n))^\theta_{ij}(A^2(n))^{1-\theta}_{ij}.$$

The reader may notice that we take the geometrical average everywhere. We define then respectively λ^1_F, λ^2_F and λ^θ_F as the dominant eigenvalues associated to A^1, A^2 and A^θ. The first Floquet eigenvalue is then defined as the maximal real number such that there exists a non identically zero $p-$periodic solution with values in $\mathbb{R}^d_+$ to the eigenproblem

$$\lambda^k_F X^k(n+1) = A(n)X^k(n). \tag{B.5}$$

We also have discrete equivalent of (B.2),(B.3).

$$\lambda^k_F = \sup\{\lambda,\ \exists X \geq 0,\ \text{p-periodic } X \not\equiv 0,\ \lambda X^k(n+1) \leq A^k(n)X^k(n)\}. \tag{B.6}$$

The inequality holding again component by component.

$$\lambda^k_F = \inf\{\lambda,\ \exists X \geq 0,\ \text{p-periodic } X \not\equiv 0,\ \lambda X^k(n+1) \geq A^k(n)X^k(n)\}. \tag{B.7}$$

The convexity result is then stated as

Theorem B.3.1 *We have again*

$$\lambda^\theta_F \leq \theta\lambda^1_F + (1-\theta)\lambda^2_F.$$

Proof. The proof is actually very similar to the case of differential systems. Since the dominant eigenvalue is a continuous functions of the matrix, it is sufficient to show the inequality when every entry of $A^1(n), A^2(n)$ is positive. In this case, the eigenfunctions X^k ($k = 1,2$) associated to λ^k_F are positive and are unique (up to a normalization). We build again a subsolution X^θ to the eigenproblem. We define X^θ by

$$X^\theta_i(n) = \Big(X^1_i(n)\Big)^\theta \Big(X^2_i(n)\Big)^{1-\theta}.$$

We write the equations satisfied by $X^k_i, k = 1,2, i = 1, \ldots d$.

$$\lambda^k_F X^k_i(n+1) = \sum_{j=1}^d A^k_i(n)X^k_j(n),$$

We divide this equation by $X^k_i(n+1)$ and average.

$$\begin{aligned} \theta\lambda^1_F + (1-\theta)\lambda^2_F \quad &= \textstyle\sum_{j=1}^d \theta A^1_i(n)\frac{X^1_j(n)}{X^1_i(n+1)} + (1-\theta)A^2_i(n)\frac{X^2_j(n)}{X^2_i(n+1)} \\ &\geq \textstyle\sum_{j=1}^d \left(A^1_i(n)\frac{X^1_j(n)}{X^1_i(n+1)}\right)^\theta \left(A^2_i(n)\frac{X^2_j(n)}{X^2_i(n+1)}\right)^{(1-\theta)}, \end{aligned}$$

as before from the arithmetic geometric inequality. This reads again

$$\theta\lambda^1_F + (1-\theta)\lambda^2_F \quad \geq \textstyle\sum_{j=1}^d A^\theta_{ij}(n)\frac{X^\theta_j(n)}{X^\theta_i(n+1)}.$$

And multiplicating it by $X^\theta_i(n+1)$, we obtain

$$\big(\theta\lambda^1_F + (1-\theta)\lambda^2_F\big)X^\theta(n+1) \geq A^\theta(n)X^\theta(n),$$

combining this with (B.7) gives the result. □

B.4 Renewal equations

We consider here the case of renewal equations:

$$\begin{cases} \partial_t n_i(t,x) + \partial_x n_i(t,x) + d_i(t,x) n_i(t,x) = 0, \quad 0 < x, \quad 1 \le i \le I, \\ n_i(t,0) = \int_0^\infty B_{ij}(t,x) n_j(t,x) dx. \end{cases} \tag{B.8}$$

Where the coefficients B_ij and d_i are taken bounded, nonnegative and $T-$periodic with respect to t. For sake of clarity, we write it in a condensed form: $n = (n_i)_{1\le i\le I}$ is the solution vector, $B(t,x) = (B_{ij}(t,x))_{1\le i\le I}$ is the birth rate matrix and $D(t,x)$ is the $I-$diagonal matrix with $D_{ii}(t,x) = d_i(t,x)$. With these notations, the system (B.8) writes in a condensed form

$$\begin{cases} \partial_t n + \partial_x n + Dn = 0, \\ n(t,0) = \int_0^\infty B(t,x) n(t,x) dx. \end{cases}$$

We consider two sets of nonnegative bounded $T-$periodic coefficients (B^1, D^1), (B^2, D^2). We assume there exists positive Floquet eigenelements, that is there exist $\left(\lambda_F^k, N^k, \phi^k\right)$, for $k = 1, 2$ such that

$$\begin{cases} \partial_t N^k + \partial_x N^k + (D^k + \lambda_F^k) N^k = 0, \quad 0 < x, \quad 1 \le i \le I, \\ Nk(t,0) = \int_0^\infty B^k(t,x) N^k(t,x) dx, \\ N_i^k > 0, \quad \text{T-periodic}, \end{cases} \tag{B.9}$$

and N_i^k is integrable over $[0,T] \times [0,+\infty[$. The dual problem writes

$$-\partial_t \phi^k(t,x) - \partial_x \phi^k(t,x) + (D^k(t,x) + \lambda_F^k) \phi^k(t,x) = \phi^k(t,0) B^k(t,x). \tag{B.10}$$

and ϕ_i^k is bounded for every i. Notice that this is satisfied for instance when B_{ij}^k, d_i^k are Lipschitz and

$$\prod_{i=1}^{j} \left(\int_0^\infty \Big(\sum_j \inf_t B_{ij}(t,x) e^{-\int_0^x \sup_t d_j(t,y) dy} \Big) \right) > 1.$$

We define the averaged birth coefficients B^θ by

$$B_{ij}^\theta(t,x) = \left(B_{ij}^1(t,x)\right)^\theta \left(B_{ij}^2(t,x)\right)^{1-\theta},$$

and the averaged death coefficients by

$$d_i^\theta(t,x) = \theta d_i^1(t,x) + (1-\theta) d_i^2(t,x).$$

Here again, we average geometrically the birth rate and arithmetically the death rates. The dominant eigenvalue λ_F^θ of the corresponding system can be defined by the existence of eigenelements N^θ, ϕ^θ satisfying (replacing k by θ everywhere) (B.9),(B.10) or by a Collatz Wielandt type formulation. We say that a triple λ, N, ϕ is a subsolution to the eigenproblem if

$$\lambda \in \mathbb{R} \qquad N > 0 \in (L_{per}^1(0,T; L^1([0,\infty[))^I, \ \phi > 0 \in (L_{per}^\infty(0,T; L^1([0,\infty[))^I, \tag{B.11}$$

satify

$$\begin{cases} \partial_t N(t,x) + \partial_x N(t,x) + (D^\theta(t,x) + \lambda) N(t,x) \ge 0, \\ N(t,0) \ge \int_0^\infty B^\theta(t,x) N(t,x) dx, \\ -\partial_t \phi - \partial_x \phi + (D^\theta + \lambda)\phi \ge \phi(t,0) B^\theta(t,x). \end{cases} \tag{B.12}$$

We may define then λ_F^θ using a Collatz Wielandt type formulation

$$\lambda_F^\theta := \inf\{\lambda, \exists(N,\phi), \quad (\lambda, N, \phi) \text{ satisfy } (B.11),(B.12)\}.$$

Theorem B.4.1 *We have again*

$$\lambda_F^\theta \leq \theta\lambda_F^1 + (1-\theta)\lambda_F^2.$$

Proof. The proof is base on the very same argument as before. Taking the logarithm and averaging, as for the case of differential systems, one can prove easily that if we define N^θ, ϕ^θ as the pointwise geometrical averages of (N^1,ϕ^1) and (N^2,ϕ^2), that $(\theta\lambda_F^1+(1-\theta)\lambda_F^2, N^\theta, \phi^\theta)$ satisfy (B.11),(B.12). Taking the logarithm, one prove immediately that

$$\partial_t N^\theta(t,x) + \partial_x N^\theta(t,x) + (D^\theta(t,x) + \theta\lambda_F^1 + (1-\theta)\lambda_F^2)N^\theta(t,x) = 0.$$

Applying Holder's inequality give also for every $1 \leq j \leq I$,

$$\Big(\textstyle\sum_j \int_0^\infty B_{ij}^1(t,x)N^1(t,x)dx\Big)^\theta \Big(\sum_j \int_0^\infty B_{ij}^2(t,x)N^2(t,x)dx\Big)^{1-\theta}$$
$$\geq \textstyle\sum_j \int_0^\infty \big(B_{ij}^1(t,x)N^1(t,x)\big)^\theta \big(B_{ij}^2(t,x)N^2(t,x)\big)^{1-\theta}dx.$$

This can be written as, using the condensed form,

$$N^\theta(t,0) \geq \int_0^\infty B^\theta(t,x), N^\theta(t,x)dx.$$

For the dual equation we have

$$-\partial_t \ln\phi_i^\theta(t,x) - \partial_x \ln\phi_i^\theta(t,x) + d_i^\theta(t,x) = \sum_j \theta B_{ji}^1(t,x)\frac{\phi_j^1(t,0)}{\phi_i^1(t,x)} + (1-\theta)B_{ji}^2(t,x)\frac{\phi_j^2(t,0)}{\phi_i^2(t,x)}.$$

Then, using the arithmetic geometric inequality, we have

$$\sum_j \theta B_{ji}^1\frac{\phi_j^1(t,0)}{\phi_i^1(t,x)} + (1-\theta)B_{ji}^2\frac{\phi_j^2(t,0)}{\phi_i^2(t,x)} \geq \sum_j \left(B_{ji}^1\frac{\phi_j^1(t,0)}{\phi_i^1(t,x)}\right)^\theta \left(B_{ji}^2\frac{\phi_j^2(t,0)}{\phi_i^2(t,x)}\right)^{(1-\theta)} = \sum_j B_{ji}^\theta\frac{\phi_j^\theta(t,0)}{\phi_i^\theta(t,x)}.$$

Therefore we have

$$-\partial_t \ln\phi_i^\theta(t,x) - \partial_x \ln\phi_i^\theta(t,x) + d_i^\theta(t,x) \geq \sum_j B_{ji}^\theta\frac{\phi_j^\theta(t,0)}{\phi_i^\theta(t,x)},$$

and mutliplicating it by $\phi_i^\theta(t,x)$, we obtain

$$-\partial_t\phi^\theta(t,x) - \partial_x\phi + (D^\theta+\lambda)\phi \geq \big((B^\theta)^*, \phi(t,0)\big),$$

and we have proved that $(\theta\lambda_F^1 + (1-\theta)\lambda_F^2, N, \phi)$ satisfy (B.11),(B.12) which ends the proof of the theorem. □

B.5 Consequences and interpretation of the convexity property

This result is actually an improvement of the results stated in [26, 25], which are special cases of the above inequality. Superconvexity properties of the spectral bound have been firstly stated in [62] for matrices and in [59] for positive operators. The convexity with respect to the death rates in periodic setting is know for reaction diffusion equations ([31]). In this framework, the spectral bound is question of speed of the travelling waves. First we can notice that this generalizes not only Kingman's theorem but also the inequality observed in [25] which gave the result for time averaging instead of simple averaging. That is if we take arithmetical average for diagonal coefficients and geometrical result for offdiagonal coefficients, then the corresponding eigenvalue eigenvalue λ_g satisfies

$$\lambda_g \leq \lambda_F.$$

For instance for the case of ordinary differential equations, with the matrix $A(t)$, we average (continuously) on the matrices $A(t+\alpha)$ over a period.

$$\bar{a}_{ii} = \frac{1}{T}\int_0^T a_{ii}(\alpha)d\alpha, \qquad \bar{a}_{ij} = \exp(\frac{1}{T}\int_0^T \log(a_{ij}(\alpha))d\alpha), i \neq j.$$

If we denote λ_s the eigenvalue associated to $\bar{A}$, we have

$$\lambda_s \leq \frac{1}{T}\int_0^T \lambda_F(\alpha)d\alpha,$$

where $\lambda_F(\alpha)$ is the dominant eigenvalue associated to $A(.+\alpha)$. Since we have obviously $\lambda_F(\alpha)\lambda_F(0)$, the former inequality reads

$$\lambda_s \leq \lambda_F(0),$$

which is exactly the inequality derived in [25].

There is also a possible biological interpretation of these convexity results. Consider a cell cycle system for instance (2). If we want to model the effect of a cytotoxic drug in such a system, we can model it by the introduction of additional death rates d_i. If we are considering the case of chronotherapy such death rates should be taken time $T-$periodic (where the period T is one day). Suppose now that the drug acts only at the level of one phase i. We could compare the effect of the periodic delivery with a shift θ (for instance replacing $d_i(t)$ by $d_i(t-\theta)$, $\theta = 1h$, would represent the fact that the drug is delivered an hour later). As in chapter 1, we denote $\lambda_F(\theta)$ the dominant eigenvalue associated to a shift θ, and we denote $\bar{\lambda}$ the dominant eigenvalue associated to a averaged death rate $\langle d_i \rangle$. The convexity inequality gives us the following comparison:

$$\bar{\lambda} \leq \frac{1}{T}\int_0^T \lambda_F(\theta)d\theta. \tag{B.13}$$

Consequently, we are in one of the following situations

- either for most values of θ, $\lambda_F(\theta) \geq \bar{\lambda}$, that is $|\{\theta \in [0,T], \lambda_F(\theta) \geq \bar{\lambda}\}| \geq T/2$, and it means that it is rare for this type of periodic delivery to be more toxic, (in this case the relative advantage could be small even at maximum see figure B.1),
- or the set of θ satisfying $\lambda_F(\theta) \geq \bar{\lambda}$ is small (that is $|\{\theta \in [0,T], \lambda_F(\theta) < \bar{\lambda}\}| \geq T/2$), in this case, we need a compensation, that is on this set, we need to reach relatively high value for $\lambda_F(\theta)$ in order to achieve the inequality (see figure B.2).

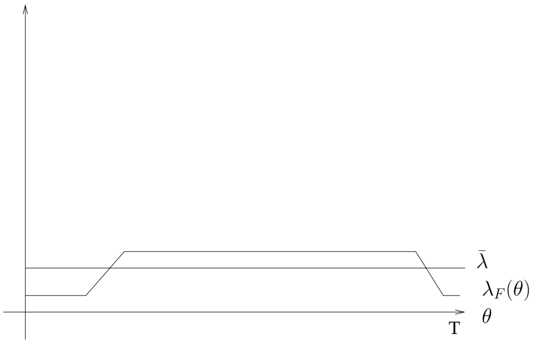


Figure B.1: Long basis, low peak: in this case mose of the θ leads to $\lambda_F(\theta) \geq \bar{\lambda}$.

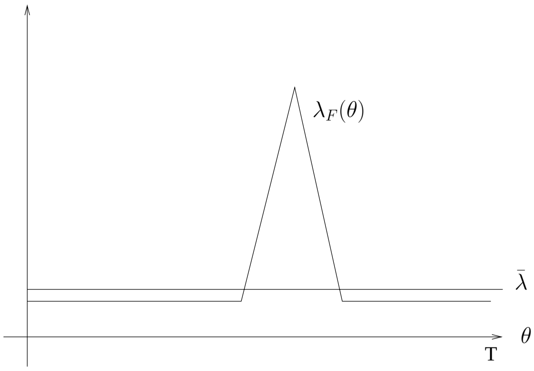


Figure B.2: Short basis, high peak: if the eigenvalue $\lambda_F(\theta)$ is often lower than $\bar{\lambda}$ then on the set where it is bigger, it has to be "really" bigger.

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Résumé

Cette thèse est consacré à l'analyse de modèles de croissance et de mouvement intervenant en biologie et en écologie. Nous regardons en particulier deux types de modèles : des équations de dynamique de populations structurées et des modèles de diffusion croisée.

Dans une première partie consacrée au travail sur les populations structurées, nous étudions d'abord des modèles linéaires de croissance en environnement périodique en temps. Ces modèles sont caractérisés par l'existence d'un exposant de croissance, appelé valeur propre de Floquet, dont nous comparons les propriétés avec celui qui apparaît en environnement stationnaire. Nous mettons en évidence grâce à un contre exemple le fait qu'il n'y a pas de comparaison générale possible entre l'exposant de croissance en milieu périodique et celui associé à un milieu moyenné. Les résultats de convexité de Kingman sur le rayon spectral des matrices positives sont étendus à la valeur propre de Floquet. Nous étudions également le comportement de cette valeur propre dans des cas dégénérés, où certains paramètres peuvent s'annuler ou exploser. Dans cette partie est également exposé une justification de la dérivation d'un modèle d'équations aux dérivées partielles pour la réplication du prion. Ce modèle est vu comme approximation d'un système infini d'équation différentielles ordinaires. Ceci se fait grâce à des résultats de compacité faible et la preuve permet de proposer des pistes pour un modèle plus complet.

La deuxième partie est consacrée à l'étude de modèles de diffusion croisée. Nous nous plaçons dans le cas d'un domaine bornée et en absence de termes de réactions. Le but est de questionner la stabilité de l'équilibre homogène. L'application de techniques de dualité utilisées pour les système de réaction-diffusion permettent d'obtenir des bornes qui servent elles-même ensuite, combinées à la régularité elliptique à obtenir l'existence globale pour une version régularisée du système. Ladite régularisation est dépendante d'un paramètre dont les valeurs déterminent la stabilité ou l'instabilité linéaire de l'équilibre homogène. La valeur critique du paramètre de régularisation est d'ailleurs une valeur de bifurcation pour les équilibres.

Abstract

This work is devoted to the analysis of some growth and collective motion models arising in biology or ecology. We especially investigate two categories of models : structured populations dynamics and cross diffusion models.

The first part focuses on structured population dynamics. We first consider some linear renewal models with periodic forcing. Such models are characterized by a growth exponent called the Floquet eigenvalue. We compare the properties of this exponent with periodic or stationary forcing. We point out, through a counterexample that no general order exists between those two eigenvalues. Kingman's results on the convexity properties of the spectral radius of nonnegative matrices is here extended to the Floquet eigenvalue. We also investigate the behavior of the Floquet eigenvalue in some degenerate cases where parameters can vanish or blow up. In this part, we also present a justification of the derivation of a partial differential equations system modelling the prion replication dynamics. This model is seen as the approximation of a system of infinite number of ordinary differential equations through weak compactness tools. The proof also allows some hints for improving this models.

In the second part we consider cross diffusion models without reaction terms in a bounded domain. The aim is to investigate the stability of the homogeneous steady state. Duality tools used in the framework of reaction diffusion, together with elliptic regularity allow us to derive sufficient a priori estimates to get a global existence theorem in dimension 1,2 for a regularized version of the system. The regularization of the system involves a parameter which value determines the Turing stability or instability of the system. The critical value of this paramater also characterizes a bifurcation point for the steady states.