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Modélisation stochastique de systèmes biologiques multi-échelles et inhomogènes en espace

Mac Jugal Nguepedja Nankep

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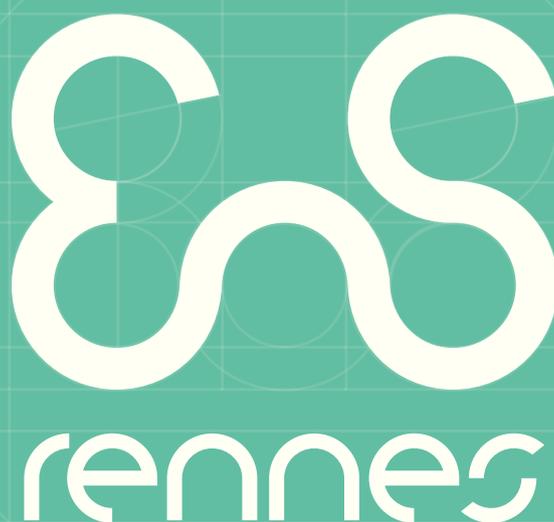
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Université Bretagne Loire

pour obtenir le titre de

DOCTEUR DE L'ÉCOLE NORMALE SUPÉRIEURE DE RENNES

Mention : Mathématiques et leurs interactions

École doctorale MathSTIC

présentée par

Mac Jugal Nguapedja Nankep

Préparée à l'unité mixte de recherche 6625

Institut de recherche mathématique de Rennes

Modélisation stochastique de systèmes biologiques multi-échelles et inhomogènes en espace

Thèse soutenue le 22 mars 2018

devant le jury composé de :

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Titre

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multi-échelles et inhomogènes en espace**

sous la direction de Arnaud DEBUSSCHE

soutenance le 22 mars 2018

Jury

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L'idée d'un modèle n'est pas un modèle de l'idée.

*La famille NGUEPEDJA,
Meudjieu, BANGOU.*

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Résumé

Les besoins grandissants de prévisions robustes pour des systèmes complexes conduisent à introduire des modèles mathématiques considérant un nombre croissant de paramètres. Au temps s'ajoutent, l'espace, l'aléa, les échelles de dynamiques, donnant lieu à des modèles stochastiques multi-échelles avec dépendance spatiale (modèles spatiaux). Cependant, l'explosion du temps de simulation de tels modèles complique leur utilisation. Leur analyse difficile a néanmoins permis, pour les modèles à une échelle, de développer des outils puissants: loi des grands nombres (LGN), théorème central limite (TCL), ..., puis d'en dériver des modèles simplifiés et algorithmes accélérés. Dans le processus de dérivation, des modèles et algorithmes dits hybrides ont vu le jour dans le cas multi-échelle, mais sans analyse rigoureuse préalable, soulevant ainsi la question d'approximation hybride dont la consistance constitue l'une des motivations principales de cette thèse.

En 2012, Crudu, Debussche, Muller et Radulescu établissent des critères d'approximation hybride pour des modèles homogènes en espace de réseaux de régulation de gènes. Le but de cette thèse est de compléter leur travail et le généraliser à un cadre spatial.

Nous avons développé et simplifié différents modèles, tous des processus de Markov de sauts pures à temps continu. La démarche met en avant, d'une part, des conditions d'approximations déterministes par des solutions d'équations d'évolution (type réaction-advection-diffusion), et, d'autre part, des conditions d'approximations hybrides par des processus stochastiques hybrides. Dans le cadre des réseaux de réactions biochimiques, un TCL est établi. Il correspond à une approximation hybride d'un modèle homogène simplifié à deux échelles de temps (suivant Crudu et al.). Puis, une LGN est obtenue pour un modèle spatial à deux échelles de temps. Ensuite, une approximation hybride est établie pour un modèle spatial à deux échelles de dynamique en temps et en espace. Enfin, des comportements asymptotiques en grandes populations et en temps long sont présentés pour un modèle d'épidémie de choléra, via une LGN suivie d'une borne supérieure pour les sous-ensembles compacts, dans le cadre d'un principe de grande déviation (PGD) correspondant.

À l'avenir, il serait intéressant, entre autres, de varier la géométrie spatiale, de généraliser le TCL, de compléter les estimations du PGD, et d'explorer des systèmes complexes issus d'autres domaines.

Mots clés: Systèmes complexes multi-échelles; Réaction-advection-diffusion stochastique; Processus de Markov; Théorèmes limites fonctionnels; Approximation par des systèmes hybrides stochastiques en dimension infinie; Générateurs et problème de martingale; Différences finies.

Abstract

The growing needs of precise predictions for complex systems lead to introducing stronger mathematical models, taking into account an increasing number of parameters added to time: space, stochasticity, scales of dynamics. Combining these parameters gives rise to spatial — or spatially inhomogeneous— multiscale stochastic models. However, such models are difficult to study and their simulation is extremely time consuming, making their use not easy. Still, their analysis has allowed one to develop powerful tools for one scale models, among which are the law of large numbers (LLN) and the central limit theorem (CLT), and, afterward, to derive simpler models and accelerated algorithms. In that deduction process, the so-called hybrid models and algorithms have arisen in the multiscale case, but without any prior rigorous analysis. The question of hybrid approximation then shows up, and its consistency is a particularly important motivation of this PhD thesis.

In 2012, criteria for hybrid approximations of some homogeneous regulation gene network models were established by Crudu, Debussche, Muller and Radulescu. The aim of this PhD thesis is to complete their work and generalize it afterward to a spatial framework.

We have developed and simplified different models. They all are time continuous pure jump Markov processes. The approach points out the conditions allowing on the one hand deterministic approximations by solutions of evolution equations, and, on the other hand, hybrid approximations by hybrid stochastic processes. In the field of biochemical reaction networks, we establish a CLT. It corresponds to a hybrid approximation of a simplified homogeneous model (due to Crudu *et al.*). Then a LLN is obtained for a spatial model with two time scales. Afterward, a hybrid approximation is established, for a two time-space scales spatial model. Finally, the asymptotic behaviour in large population and long time are respectively presented for a model of cholera epidemic, through a LLN followed by the upper bound for compact sets, in the context of a corresponding large deviation principle (LDP).

Interesting future works would be, among others, to study other spatial geometries, to generalize the CLT, to complete the LDP estimates, and to study complex systems from other fields.

Keywords: Multiscale complex systems; stochastic reaction-advection-diffusion; Markov process; functional limit theorems; Approximation by infinite dimensional stochastic hybrid systems; Generators and martingale problem; Finite difference method.

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CONTENTS

Some general notation

Let $(Z, \|\cdot\|_Z)$ and $(\tilde{Z}, \|\cdot\|_{\tilde{Z}})$ be Banach spaces. The product space $Z \times \tilde{Z}$ is equipped with the norm $\|\cdot\|_Z + \|\cdot\|_{\tilde{Z}}$. We introduce:

- $\mathcal{L}(Z, \tilde{Z})$: the space of continuous linear maps from Z to \tilde{Z} . If $Z = \tilde{Z}$, one simply writes $\mathcal{L}(Z)$. The operator norm is denoted $\|\cdot\|_{Z \rightarrow \tilde{Z}}$ and when there is no risk of confusion, we denote it $\|\cdot\|$.
- Z' : the space of continuous linear forms on Z . It is the topological dual space of Z .
- $\mathfrak{B}(Z)$ (resp. $\mathfrak{B}_b(Z)$): the space of Borel-measurable (resp. bounded Borel-measurable) real valued functions on Z . The space $\mathfrak{B}_b(Z)$ is endowed with the supremum norm

$$\|f\|_{\mathfrak{B}_b(Z)} = \sup_{x \in Z} |f(x)| = \|f\|_{\infty}.$$

- $C_b^k(Z)$, $k \in \mathbb{N}$: the space of real valued functions of class C^k , i.e. k -continuously Fréchet differentiable, on Z which are bounded and have uniformly bounded successive differentials. It is equipped with the norm

$$\|f\|_{C_b^k(Z)} = \sum_{i=0}^k \|D^i f\|_{\infty} =: \sum_{i=0}^k \|f\|_{i,\infty},$$

where $D^i f$ is the i -th differential of $f \in C_b^k(Z)$, $C_b^0(Z) = C_b(Z)$ is the set of bounded continuous real valued functions on Z , and we are using the notation $\|f\|_{i,\infty} := \|D^i f\|_{\infty}$.

- $C^{l,k}(Z \times \tilde{Z})$, $l, k \in \mathbb{N}$: the set of real valued functions φ of class C^l w.r.t. the first variable and of class C^k w.r.t. the second. In particular, $C^{0,0}(Z \times \tilde{Z}) = C(Z \times \tilde{Z})$.

For $(z, \tilde{z}) \in Z \times \tilde{Z}$, we denote by $D^{l,k}\varphi(z, \tilde{z})$ the (Fréchet) differential of φ , of order l w.r.t. z and of order k w.r.t. \tilde{z} , computed at (z, \tilde{z}) .

Also, a subscript b can be added - to obtain $C_b^{l,k}(Z \times \tilde{Z})$ - in order to specify that the functions and their successive differentials are uniformly bounded.

- $D(I)$: the set of right-continuous, left-limited (or *càdlàg*¹) real valued functions defined on $I = [0, 1]$. It is endowed with the Skorohod topology.

¹From French *continu à droite et admettant une limite à gauche*.

- $C(I)$ (resp. $C^k(I)$): the set of periodic continuous (resp. C^k) real valued functions defined on $I = [0, 1]$.
- $C_p(I)$: the set of piecewise continuous real valued functions defined on $I = [0, 1]$. It is equipped with the supremum norm.
- $C(\mathbb{R}_+, Z)$: the set of continuous processes defined on \mathbb{R}_+ with values in Z .
- $\mathcal{AC}(\mathbb{R}_+, Z)$: the set of absolutely continuous processes (or functions) defined on \mathbb{R}_+ and taking values in Z .
- $D(\mathbb{R}_+, Z)$: the set of *càdlàg* processes defined on \mathbb{R}_+ and taking values in Z . It is endowed with the Skorohod topologie.

CHAPTER 0

Introduction

La cellule est l'unité biologique structurelle et fonctionnelle fondamentale de tous les êtres vivants connus [Wik]. Au coeur de son fonctionnement, se trouvent les gènes¹, qui en constituent la source d'information génétique nécessaire [Sau17]. Sa vie est régie par des machineries moléculaires complexes. Elles interviennent, d'une part, dans la transmission de l'information portée par le gène d'une cellule mère à sa descendance pendant la division cellulaire: la succession des bases de l'ADN est recopiée de façon très fidèle (réplication de l'ADN), et, d'autre part, lors de l'expression de cette information au cours de la vie cellulaire: les gènes sont codés en ARNm (transcription de l'ADN), puis l'information génétique est convertie en outil fonctionnel (traduction de l'ARNm en protéine).

L'expression des gènes est contrôlée en amont, par une batterie de protéines mobiles (activateurs, repressors) qui s'attachent à l'ADN, lui aussi mobile, et stimulent ou au contraire empêchent l'initiation de la transcription. Il y a auto-régulation. D'autres systèmes de contrôle traquent la survenue de mutations et veillent à la correction d'erreurs potentielles de codage lors de la réplication. Certaines mutations de l'ADN ou erreurs de transcription/traduction sont sans conséquence. D'autres en revanche peuvent conduire à la production de protéines inactives et générer un défaut partiel du fonctionnement de la cellule (inhibition de l'apoptose² par exemple). Cela peut provoquer la perte de contrôle de l'expression d'un gène ou d'un groupe de gènes, et, dans une situation extrême, déclencher la prolifération cellulaire et l'apparition d'un cancer.

Les réseaux de surveillance et de régulation sont donc primordiaux pour assurer le cours normal de la vie cellulaire. Ils permettent non seulement d'assurer la production de protéines actives en quantités voulues et au moment opportun, en réponse à des besoins d'origine interne ou externe à la cellule, mais aussi d'assurer la pérennité du patrimoine génétique. Si les biologistes représentent ces réseaux à l'aide de diagrammes expliqués et interprétés à partir d'observations expérimentales, leurs intuitions sont rapidement dépassées par la taille et la complexité grandissantes des réseaux, au fil des progrès scientifiques. La mise en place de modèles de représentations plus élaborés devient alors indispensable.

¹Un gène est une petite portion, une unité opérationnelle d'information stockée dans l'ADN.

²L'apoptose est le processus par lequel une cellule déclenche son auto-destruction en réponse à un signal. On parle aussi de mort cellulaire programmée.

Ainsi, la biologie moléculaire moderne met l'accent sur l'importance de la modélisation mathématique et la simulation des réseaux de régulation de gènes [DL05], [SL05], [MW11], [EO14]. Il s'agit de comprendre les mécanismes et contraintes physiques sous-jacents à des phénomènes importants tels que la division cellulaire de bactéries [FE06] ou le développement embryonnaire [GTWB07]. Comme plusieurs systèmes dynamiques dans des branches aussi variées que la biochimie, l'épidémiologie, l'écologie, la microfluidique, les finances, la sociologie, ... les réseaux de régulation de gènes font partie de la grande classe des systèmes de réactions chimiques (ou biologiques, ou biochimiques) ou encore systèmes complexes [Hak78],[NP77]. Aussi, le terme système est parfois remplacé par le terme réseaux dans ces terminologies.

Dans le processus de modélisation, un niveau d'observation doit être fixé d'emblée, afin d'identifier les entités qui interagissent. Pour les réseaux de gènes par exemples, nous nous plaçons au niveau intra-cellulaire. Il est intéressant de noter que les modèles développés s'adaptent facilement à des niveaux différents, allant des moléculaires (réactions biochimiques intra-cellulaire) aux organismes entiers (dynamique de populations, épidémiologie). Aussi, des choix d'optimisation s'imposent sur la robustesse ou le réalisme du modèle, et sa simplicité en terme d'analyse et d'interprétation. Enfin, des simulations sont effectuées afin de confronter les prédictions du modèle avec les observations expérimentales.

0.1 Une revue des modèles mathématiques de réseaux de réactions biochimiques

Différentes approches existent dans la modélisation mathématique des systèmes de réactions biochimiques. D'un côté il existe des modèles qualitatifs souvent utilisés par les biologistes et les informaticiens [dJ02], [BdJG⁺06]. Ils sont discrets, graphiques. Beaucoup reposent sur les réseaux de Thomas [Tho73, Tho83], [CTEFT09], d'autres sont liés au réseaux de Petri [VLM96], [CRRT04]. Pour la régulation des gènes par exemple, ils capturent des niveaux d'expression de gènes. Ces modèles sont adaptés aux situations de données expérimentales manquantes, ils requièrent peu de paramètre mais son plutôt simplifiés par rapport à la réalité.

D'un autre côté, on a les modèles quantitatifs, privilégiés par les mathématiciens. Ils peuvent être discrets (certains modèles stochastiques par exemples) ou continus (utilisent des équations différentielles). Si ces modèles sont très robustes, ils souffrent parfois du manque de données expérimentales pour des simulations, car ils tiennent compte de beaucoup de paramètres. Ils restent néanmoins les plus courants, car ils sont précis et faciles à interpréter, étant donné que les variables considérées sont en même temps les variables d'intérêt biologique (concentrations, proportions, nombre d'individus de chaque espèce), et les paramètres pris en compte sont ceux qui régissent les interactions.

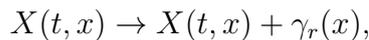
Nous nous intéressons aux modèles quantitatifs de réactions chimiques dans la suite. En plus d'être robustes et réalistes, ces modèles ont à disposition une panoplie d'outils analytiques mathématiques et même informatiques. Les modèles mathématiques de réactions chimiques ont été décrits par [GMWM76] [NP77],[Hak78] et [Arn80], entre autres. Nous commençons par en présenter l'abstraction courante.

0.1.1 Abstraction et formalisme général

Un système de réactions biochimiques est la donnée d'un domaine spatial $I \subset \mathbb{R}^d$ pouvant être borné ou pas, d'un ensemble fini d'espèces chimiques mobiles, indexées par $i = 1, \dots, M$, $M \in \mathbb{N}^*$, et d'un ensemble fini $\mathfrak{R} = \{r \in \mathfrak{R}\}$ de réactions chimiques possibles. On peut penser au domaine I comme la cellule, aux espèces chimiques comme les gènes et/ou les produits de régulation (ARN, protéines,...), et enfin, aux réactions chimiques comme les différents mécanismes qui font varier le nombre de représentants des différentes espèces présentes dans la cellule (synthèse d'une protéine ou destruction d'une protéine en réponse à un signal, mort naturelle d'une protéine...).

Les variables $t \in \mathbb{R}_+$ et $x \in I$ désignent respectivement le temps et une position (ou coordonnée) dans le domaine spatial I . Pour toute espèce $i = 1, \dots, M$, pour tout couple (x, t) de coordonnée espace-temps, parfois noté (t, x) , désignons par $X_i(t, x)$ l'état moléculaire (nombre d'individus, concentration ou proportion) de l'espèce i à l'instant t et à la position x dans la cellule, et soit $X(t, x) = (X_1(t, x), \dots, X_M(t, x))$ le vecteur de \mathbb{N}^M qui donne l'état ou encore la composition moléculaire spatio-temporelle de la cellule ou du système, en (t, x) .

D'une part, si à un instant t une réaction chimique $r \in \mathfrak{R}$ se produit à la position x , alors l'état du système évolue à cet endroit, selon

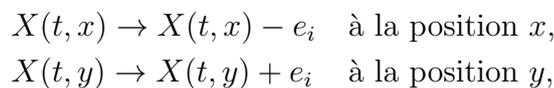


où $\gamma_r(x) = (\gamma_{r,1}(x), \dots, \gamma_{r,M}(x)) \in \mathbb{Z}^M$ est le vecteur stœchiométrique associé à la réaction r lorsqu'elle se produit à la position x . Il décrit comment la composition moléculaire est affectée par la réaction r . L'état $X_i(t, x)$ de l'espèce i varie de la quantité $\gamma_{r,i}(x)$. Si cette quantité est négative, alors la réaction r consomme (ou tue) des molécules ou de la quantité de matière de l'espèce i lorsqu'elle se produit en x . Dans le cas contraire, elle en produit (fait naître) plutôt. Les réactions chimiques consistent donc en des processus de naissance et de mort.

D'autre part, si à un instant t une molécule ou de la quantité de matière d'une espèce i se déplace d'une position x à une autre y , alors la distribution spatiale de l'espèce i change, notamment en x et en y selon



L'état du système en est affectée suivant les relations



où e_i est le i ème vecteur de la base canonique de \mathbb{R}^M ; toutes ses composantes sont nulles, exceptée la i ème qui vaut 1. Dans ce transport de matière, les vecteurs stœchiométriques $\gamma_{x \rightarrow y}(x)$ et $\gamma_{x \rightarrow y}(y)$ en x et y sont explicites et valent $-e_i$ et $+e_i$ respectivement. Les indexations par " $x \rightarrow y$ " indiquent que les vecteurs stœchiométrique dépendent de l'événement qui s'est produit.

Ce type d'événement est appelé *transport*. Le transport peut être de nature *advective* (ou *convective*) lorsque le milieu ambiant se meut et transporte, dans son mouvement, des molécules ou de la matière relative aux espèces présentes (une protéine ou une masse

peut être transportée par le mouvement du cytoplasme à l'intérieur de la cellule par exemple). Si au contraire, des molécules (ou de la masse des espèces présentes) se déplacent "d'elles même" indépendamment d'une éventuelle mobilité de l'environnement ambiant (sous l'effet de l'agitation thermique), alors le transport est de nature *diffusive*.

La description générale du modèle devient quasi-complète si on spécifie les règles qui régissent l'arrivée des événements (réactions chimiques et transports). On définit le *taux instantané* (ou simplement *taux*, ou *intensité*) d'un événement comme étant le nombre de fois que cet événement se produit par unité de temps. C'est un paramètre essentiel dans la modélisation. Il est estimé par des méthodes statistiques, à partir de mesures et observations expérimentales de biologistes. Tout comme le vecteur stœchiométrique, l'intensité d'un événement dépend de l'événement en question et du lieu où il se produit. Elle est en plus, une fonction scalaire positive de l'état du système (la composition moléculaire du système), au moment où la réaction se produit. Ainsi, la description du modèle est complète si l'état initial du système est précisé.

Objectif général. Partant d'une distribution spatiale initiale (instant $t = 0$) des molécules des différentes espèces dans la cellule, on s'intéresse à l'évolution de la composition moléculaire de la cellule dans le temps et dans l'espace, à mesurer que les événements se produisent. Autrement dit, étant donné un état ou une configuration $\{X(0, x), x \in I\}$ du système, on souhaite évaluer précisément $X(t, x)$ pour tout $(t, x) \in \mathbb{R}_+^* \times I$, au fil des réactions chimiques et du transport des molécules.

Definition 0.1.1. (*Fonction débit*)

Nous définissons le *débit d'un événement* comme étant la fluctuation de l'état du système due à cet événement, par unité de temps. Dans notre formalisme, il correspond au produit du taux de ladite réaction avec le vecteur stœchiométrique associé, ou encore, en d'autres termes, c'est le vecteur stœchiométrique pondéré par le taux correspondant. Par exemple, si $\lambda_r(X(t, x))$ et $\gamma_r(x)$ sont respectivement le taux et le coefficient d'une réaction $r \in \mathfrak{R}$, alors le débit de cette réaction vaut $\lambda_r(X(t, x))\gamma_r(x)$ que nous notons souvent $\gamma_r(x)\lambda_r(X(t, x))$. Ensuite, nous définissons le débit d'un ensemble d'événements comme la somme des débits des différents événements considérés. Dans la suite de l'exemple précédent, le débit de l'ensemble \mathfrak{R} de toutes les réactions chimiques vaut $\sum_{r \in \mathfrak{R}} \gamma_r(x)\lambda_r(X(t, x))$. La notion de débit apparaîtra naturellement dans la suite, dans les équations décrivant les évolutions des différents modèles que nous présenterons.

Suivant [NP77, Hak78, Arn80], il existe deux principaux critères selon lesquels les réseaux biochimiques sont modélisés: l'*aléa*, qui permet de distinguer les modèles déterministes des modèles stochastiques, puis, l'*homogénéité*, qui met en avant les modèles homogènes en espace ou tout simplement homogènes et les modèles inhomogènes en espace encore appelés modèles spatiaux. La combinaison de ces deux critères permet d'obtenir quatre modèles mathématiques.

0.1.2 Homogénéité et Modélisation spatiale

L'homogénéité en espace signifie que le système est bien mélangé. Elle se traduit par

$$X(t, x) = X(t) \quad \forall (t, x) \in \mathbb{R}_+ \times I.$$

0.1 Une revue des modèles mathématiques de réseaux de réactions biochimiques

Ainsi, qu'il soit déterministe ou stochastique, le modèle ne dépend que de la variable temporelle et plus de la variable spatiale. Cela suppose que, spatialement, les molécules sont uniformément réparties dans le système. Une description globale du système devient suffisante, donnant la concentration globale de chaque espèce. De telles conditions sont satisfaites lorsque le taux de transport moléculaire est beaucoup plus important que le taux de réactions chimiques. Sous cette condition, Arnold montre dans [Arn80], que le modèle spatial coïncide avec le modèle homogène, justifiant ainsi la consistance de ces modèles.

Tandis que le modèle homogène est encore dit global, le modèle spatial est dit local. La modélisation spatiale est devenue importante dans l'étude de l'influence du transport des molécules sur le comportement des systèmes biologiques. On a des modèles spatiaux de morphogenèse (ou d'effets de communauté) [Bat14], [Mur07] en biologie moléculaire. Ils ont été introduits par Turing en 1952 [Tur52], puis développés par Prigogine et ses co-auteurs [NP77]. En neuroscience, on peut citer des extensions spatiales [Kat66b], [NL91], [Aus08], [Rie11], [Gén13], du modèle de Hodgkin et Huxley pour la propagation de potentiels d'action dans les neurones. En plus, des modèles en épidémiologie et écologie sont proposés par [MPV08] and [BCG⁺10]. Les modèles spatiaux retiendront plus particulièrement notre attention dans la suite. En absence de précision, le terme modèle est utilisé pour désigner un modèle spatial. Dans les sections suivantes, nous discutons des modèles dérivés du premier critère, l'aléa.

0.1.3 Modélisation déterministe

Les modèles déterministes rendent compte d'un comportement moyen observé à un niveau macroscopique. Ils décrivent notamment l'évolution des concentrations des différentes espèces, par des équations différentielles dont les champs de vecteurs sont les débits de tous les événements impliqués dans la dynamique. Les modèles déterministes sont encore appelés modèles macroscopiques. Dans ce contexte, les molécules, qui se situent à un niveau microscopique, ne sont pas observées. On parlera donc de transport de quantité de matière ou de masse, en ce qui concerne les événements de type transport. Pour chaque $i = 1, \dots, N$, $X_i(t, x)$ désigne donc la concentration de l'espèce i à l'instant t et à la position x et le modèle, l'état du système $X(t, x) = (X_i(t, x))_{1 \leq i \leq M}$ donne la distribution de toutes les concentrations. Selon le critère d'homogénéité, on distingue deux cas.

Modèle déterministe homogène

Le modèle global satisfait $X(t, x) = X(t)$. Les seuls événements qui font varier les concentrations sont les réactions chimiques. À chaque instant t , une réaction $r \in \mathfrak{R}$ se produit à un taux instantané $\lambda_r(X(t))$ et change l'état du système d'un vecteur stœchiométrique γ_r . L'évolution de $X(t)$ sur une courte durée $\Delta t > 0$ est alors quantifié par $\Delta t \lambda_r(X(t)) \gamma_r$, de sorte que $X(t + \Delta t) - X(t) = \Delta t \lambda_r(X(t)) \gamma_r$. Ainsi, l'évaluation de la variation sur une durée infinitésimale montre que le modèle évolue suivant l'Équation Différentielle Ordinaire (ÉDO)

$$\frac{dX(t)}{dt} = R(X(t)),$$

où le champ de vecteur R , de \mathbb{R}^M , est le débit des réactions chimiques: $R(y) = \sum_{r \in \mathfrak{R}} \gamma_r \lambda_r(y)$ pour tout $y \in \mathbb{R}^M$.

Notons qu'en pratique, le calcul limite effectué ci-dessus n'est valide que si les taux des réactions sont assez élevés et les réactions assez rapides, pour se produire continuellement sur des durées de temps infinitésimales. En outre, les équations de réactions étant décrites à l'état d'équilibre, selon la loi d'action des masses, les vitesses des réactions chimiques sont de l'ordre des concentrations des réactifs, lorsque les réactions sont assez rapides. Autrement dit, les taux des réactions sont proportionnels aux concentrations des réactifs, et ces grandeurs doivent être élevées. Ainsi, le modèle décrit ci-dessus n'est adapté que lorsque les différentes espèces chimiques présentes sont suffisamment abondantes et les réactions assez fréquentes et rapides. Si certaines espèces sont peu concentrées, ce qui est le cas pour une classe suffisamment importante de systèmes biologiques, alors le modèle rend mal compte de leur évolution effective, et n'est plus adapté du tout.

Modèle déterministe spatial

Une description locale de l'évolution du système est effectuée. Le principe repose à nouveau sur de la discrétisation. On commence par subdiviser le domaine spatial, de façon régulière, en N sous-domaine. Ces derniers ont la même taille et sont considérés comme des systèmes homogènes qui évoluent au fil des réactions chimiques, suivant le mécanisme décrit précédemment. En outre, un échange de matière s'effectue entre les sous-domaines voisins, par transport advectif et/ou diffusif de matière, avec un taux de l'ordre de N^2 . Des conditions limites (au bord du domaine spatial entier) doivent être spécifiées afin de décrire le phénomène de transport dans ces régions limites. Ensuite, pour recouvrir la continuité en espace, on passe à la limite $N \rightarrow \infty$ en rendant les domaines locaux de plus en plus petits. La composition moléculaire évolue alors suivant l'Équation aux Dérivées Partielles (ÉDP)

$$\frac{\partial X(t, x)}{\partial t} = -\nu(\nabla \cdot X(t, x)) + \mathcal{D}\Delta X(t, x) + R(X(t, x)),$$

où $\nu(\nabla \cdot X(t, x))$, est le débit local des transports advectifs, $\mathcal{D}\Delta X(t, x)$ le débit local des transports diffusifs, et $R(X(t, x))$ le débit local des réactions chimiques. Les opérateurs ∇ et Δ sont le gradient et le Laplacien respectivement, ν est la vitesse de déplacement du milieu, c'est le coefficient d'advection ou de convection, et \mathcal{D} est le coefficient de diffusion. Dans le modèle d'épidémiologie du choléra [BCG⁺10] de Bertuzzo *et al.*, ces deux coefficients sont non nuls. L'ÉDP d'évolution est alors dite de réaction-advection/convection-diffusion. Lorsque le terme de convection n'apparaît pas, c'est le cas de nombreux modèles [Kat66b, NL91, Aus08, Hak78], l'ÉDP d'évolution est dite de réaction-diffusion. Cela peut être interprété par le fait qu'il n'y a effectivement pas d'advection (si le milieu n'est pas fluide ou gazeux par exemple), ou alors, que l'advection est négligeable devant la diffusion, et on considère $\nu = 0$.

La modélisation spatiale est plus précise et apporte de la lumière dans le processus de formation de motifs spatiaux (morphogénèse), notamment par la description des mécanismes classiques qui conduisent à ces motifs: les instabilités de Turing pour les transports diffusifs [Tur52], [Mur07], et les instabilités de flots différentiels pour des transports advectifs [MPV08]. Néanmoins, de l'homogénéité locale en espace est requise dans les modèles spatiaux. Cela signifie que localement, le système est supposé

bien mélangé, les différentes espèces sont abondantes et les taux et vitesses de réactions élevés. De plus, les concentrations doivent être suffisamment importantes et les réactions fréquentes et rapides, pour que l'approximation du continu soit valide. Cette approximation est nettement moins précise dans des régions de faibles concentrations. Le champ d'application des modèles macroscopiques aux processus physiques est plutôt restreint, ce qui renforce l'intérêt d'une description microscopique [SPT10].

0.1.4 Modélisation stochastique

De nombreuses observations conduisent à introduire une approche stochastique plus approfondie dans la dynamique des réseaux de gènes en biologie moléculaire [KE01], [KvO07]. Suivant [RMC07a], on peut citer la variabilité épigénétique (niveaux d'expression des gènes dépendant des conditions externes), le faible dosage (gènes de faible activité, haploinsuffisance, promoteurs transcriptionnels de faible activité), la production intermittente par paquets des protéines, les phénomènes de bistabilité, ou la différenciation cellulaire en morphogénèse (Voir [RMC07a] pour des références plus détaillées). Dans le cas du cancer, sous l'incidence du même stimulus, certaines cellules développent le cancer, d'autres non [IMN04]. Par ailleurs, à un niveau microscopique, les observations montrent que les densités ou concentrations évoluent de manière discrète, et conduisent à des fluctuations autour du comportement moyen décrit de manière continue au niveau macroscopique. Cela rend davantage compte du caractère stochastique de la dynamique des réseaux de réactions biochimiques, notamment au niveau microscopique des molécules, ce qui motive davantage la modélisation stochastique de tels systèmes.

Sur les sources d'aléa

Il est utile d'identifier les natures et origines des fluctuations ou du bruit au niveau microscopique dans ces systèmes de réactions chimiques [SPT10]. On distingue ([vK92], [SES02]): le bruit intrinsèque ou interne, provenant des interactions stochastiques internes entre les individus ou molécules, et, le bruit extrinsèque ou externe ou environnemental, dû aux échanges potentiels du système avec l'environnement extérieur. Les fluctuations environnementales sont intégrées dans la modélisation comme un bruit multiplicatif dans une Équation Différentielle Stochastique (ÉDS) pour un modèle homogène, ou une Équation aux Dérivées Partielles Stochastique (ÉDPS) pour un modèle spatial [GOS99],[DHI13]. Le bruit externe s'illustre bien dans le cadre de la variabilité épigénétique, où on observe que les niveaux d'expression des gènes dépendent des conditions externes [RWA02]. Les fluctuations internes, quant à elles, sont intégrées dans la modélisation en terme de loi de probabilité de l'état du système, utilisant l'équation maîtresse de réaction-transport [vK92, vK07],[BM98],[Gar04]. L'état du système est alors décrit par un processus de Markov [Arn80].

Tel que souligné dans [SPT10], des progrès considérables ont été faits concernant la modélisation du bruit externe, dans la caractérisation, l'approximation et la simulation des ÉDPSs [GOS99, Sha05, MPV08]. Cependant, très peu de travaux vont dans le sens de la modélisation du bruit intrinsèque. De nouvelles méthodes expérimentales mettent l'accent sur le rôle important du contrôle des fluctuations internes dans le développement embryonnaire [GTWB07] et la propagation de front [KL98, HNL06, HHRN07]. Selon [TvO01], l'analyse des fluctuations internes révèle les rôles biologiques des réseaux de

gènes et peut éclairer sur leur origine évolutive. Dans le cadre homogène, cette analyse donne lieu à des comportements nouveaux, qui n'ont pas encore été observés dans les modèles déterministes correspondants [WL03, SHI07]. Les cas les plus marquants sont ceux où les fluctuations engendrent des dynamiques plutôt ordonnées, comme des oscillations régulières de systèmes déterministiquement stables [SZK03, MN05, KGG07, PKBDD07], ou les switching stochastiques entre différents états déterministes stables fixés [WOW05], [RMC07a, CDR09]. Dans le cadre inhomogène, l'ajout du degré de liberté spatial offre encore plus de possibilités, parmi lesquelles de nouveaux états stables [TK04], les phases de séparation dans les systèmes bistables [EE04], et, un cas particulièrement important, la formation de motifs spatiaux (morphogenèse) pour des modèles de réaction-diffusion déterministiquement stables [HR03, MN04, FE06, BG09, BFDP10]. Cette thèse s'inscrit dans l'élan de modélisation du bruit interne.

Les modèles stochastiques classiques sont markoviens. Partant des idées pionnières de Delbrück en 1940 [Del40], ils ont été formalisés plus tard par Rényi [Ré54] et Bartholomay [Bar57]. Les événements (réaction chimique entre les molécules ou transport des molécules) sont discrets et sont aussi appelés sauts. L'aléa se situe à deux niveaux indépendants: les événements qui se produisent, et, les instants auxquels ils se produisent ou de manière équivalente, le délai (temps d'attente) entre deux événements consécutifs. Les événements sont identifiés de sorte que deux événements distincts se produisent simultanément avec une probabilité nulle. En d'autres termes, presque sûrement, un seul événement arrive à la fois. Dans les prochaines sections, nous présentons les modèles stochastiques selon le critère d'homogénéité.

Modèle stochastique homogène

Le système évolue suivant des processus de naissance et de mort à travers les réactions chimiques, et on a $X(t, x) = X(t)$. Partant d'un état $X(0)$, on attend le premier instant de saut T_1 . L'état du système reste constant jusqu'à l'instant T_1^- avant le saut: $X(t) = X(0)$ pour tout $t \in [0, T_1^-)$. À l'instant T_1 , une réaction $r \in \mathfrak{R}$ est choisie avec probabilité

$$\mathbb{P}\{\text{choisir la réaction } r\} = \frac{\text{taux de la réaction } r}{\text{taux global des réactions}} = \frac{\lambda_r(X(t))}{\lambda(X(t))},$$

où $\lambda(X(t)) = \sum_{r \in \mathfrak{R}} \lambda_r(X(t))$. L'instant de saut T_1 est une variable aléatoire exponentielle de paramètre $\lambda(X(T_1^-)) = \lambda(X(0))$. Sa fonction de survie est donnée par

$$H(t) = \mathbb{P}\{T_1 > t\} = \exp\left(-\int_0^t \lambda(X(s)) ds\right) = e^{-t\lambda_r(X(0))}.$$

Après ce premier saut, la composition moléculaire passe à un nouvel état $X(T_1)$. Puis on attend le prochain événement partant de là. Dans ce procédé, les instants de sauts sont strictement croissants et les délais entre les sauts sont des variables aléatoires indépendantes. L'évolution future de l'état du système ne dépend de ses états passés que par son état présent. Le processus est alors *sans mémoire*, propriété qu'il hérite de la loi exponentielle choisie pour les délais d'attente. Le modèle est alors un processus markovien de sauts à temps continu, à valeurs dans \mathbb{N}^M (espace d'états). La loi d'un tel processus est caractérisée par son générateur infinitésimal [EK86, Dav93], ou alors par l'équation maîtresse des réactions chimiques [Hak78, Arn80, vK07], par dualité.

Modèle stochastique spatial

En plus des réactions chimiques, les transports de molécules entrent en jeu. Le schéma est le même que dans le cadre déterministe. Le domaine spatial I est discrétisé de façon régulière, en N sous domaines I_j , $j = 1, \dots, N$ appelés sites. Ces derniers sont supposés homogènes et évoluent au fil des réactions chimiques. Parallèlement, mais indépendamment, les molécules sont transportées entre les différents sous domaines suivant des processus de marche aléatoire. Le principe d'évolution du système est le même que dans le cadre stochastique homogène, où il faut remplacer "réaction chimique" par "événement", car il y a aussi des transports dans le cas présent.

Pour chaque $i = 1, \dots, M$, $j = 1, \dots, N$ on note $\tilde{X}_{ij}(t)$ le nombre de molécules de l'espèce i sur le site j à l'instant t . Le nombre de molécules de l'espèce i sur le domaine spatial tout entier est alors donné par $\tilde{X}_i(t) = (\tilde{X}_{ij}(t))_{1 \leq j \leq N}$. C'est un vecteur à valeurs dans \mathbb{N}^N . On remonte alors jusqu'à l'état complet de tout le système $\tilde{X}(t) = (\tilde{X}_i(t))_{1 \leq i \leq M}$, qui est un vecteur à valeurs dans $\mathbb{N}^{M \times N}$. Le modèle $\tilde{X}(t)$ ainsi obtenu représente entièrement la dynamique stochastique. C'est un processus markovien de sauts à temps continu, à espace d'états $\mathbb{N}^{M \times N}$. Sa loi peut également être caractérisée par son générateur infinitésimal [Kot88b, Gar04] ou par l'équation maîtresse de reaction-transport [vK92, BM98, vK07].

Le modèle intermédiaire $\tilde{X}(t)$ est équivalent au modèle de départ $X(t, x)$ dans lequel la coordonnée spatiale x apparaissait clairement. En effet, toute coordonnée $x \in I$ se trouve sur un unique site I_j , de sorte que pour chaque espèce i , $X_i(t, x) = \tilde{X}_{ij}(t)$, pour $x \in I_j$. Il est alors commode d'introduire la définition générale

$$X_i(t, x) = \sum_{j=1}^N \tilde{X}_{ij}(t) \mathbb{1}_{I_j}(x),$$

où $\mathbb{1}_{I_j}(x)$ vaut 1 si $x \in I_j$ et 0 sinon, est la fonction indicatrice du domaine local I_j . Ainsi, le modèle de départ $X(t, x) = (X_i(t, x))_i$ définit un processus markovien de sauts en temps et en espace, à valeurs dans \mathbb{N} . Ensuite, ce dernier est identifiable à un processus markovien de sauts $X(t)$ en temps seulement, mais à valeurs dans un espace fonctionnel, notamment l'espace des fonctions étagées définies sur le domaine I , et ayant exactement N valeurs vectorielles dans \mathbb{N}^M . Ce dernier espace étant isomorphe à $\mathbb{N}^{M \times N}$, les processus $X(t)$ et $\tilde{X}(t)$ s'identifient très bien.

0.2 Modélisation multi-échelle, approximation hybride

0.2.1 Approximation, quasi-approximation, simulation

Des théorèmes mathématiques d'approximation permettent de simplifier les modèles stochastiques. La Loi des Grands Nombres (LGN) stipule qu'une fois remis à échelle (renormalisés suivant l'ordre de grandeur des populations), les modèles stochastiques sont des perturbations sans conséquence des modèles déterministes correspondants, lorsque les molécules des différentes espèces sont abondantes. En poussant l'approximation à

l'ordre suivant, sous les mêmes conditions, le Théorème Central Limite (TCL) permet d'obtenir une vitesse de convergence dans la LGN et stipule qu'à l'échelle de cette vitesse, les fluctuations du modèle stochastique renormalisé sont gaussiennes. D'après le TCL, le modèle stochastique est proche d'une diffusion solution de l'équation de Langevin. Une alternative au TCL est une approximation de diffusion. Elle consiste à montrer que le modèle stochastique est proche d'une diffusion obtenue à partir d'un développement de Taylor tronqué de son générateur infinitésimal, et permet aussi d'obtenir des vitesses de convergence. Pour ces différents résultats, on peut citer plusieurs travaux: [Kur70, Kur71, EK86, BKPR06] dans le cadre homogène, et [AT80, Kot86b, Kot88a, Blo93, Blo96] dans le cadre spatial. Ces approximations permettent de dire que le modèle stochastique bien que discret, est proche d'un modèle continu. Toutefois, elles restent valides uniquement en grandes populations.

D'un point de vue numérique, des solveurs permettent de calculer ou d'approcher assez rapidement la solution des équations différentielles obtenues par la modélisation déterministe des réseaux de réactions biochimiques. Notons tout de même que les temps de calculs sont beaucoup plus importants en cas d'inhomogénéité spatiale, ce qui n'est pas surprenant, avec une variable à discrétiser en plus. Cependant, l'implémentation des solveurs repose sur des méthodes mathématiques de discrétisation-approximation du continu, comme celles utilisées pour construire les modèles mathématiques macroscopiques. Dès lors, ces solveurs souffrent de n'être adaptées qu'à des situations où toutes les espèces sont abondantes, comme souligné plus haut.

Plusieurs méthodes de simulation des modèles stochastiques ont vu le jour: les algorithmes de simulation stochastiques (Stochastic Simulation Algorithm-SSA) encore appelés *First Reaction method* de Gillespie [Gil76, Gil77] dans le cadre homogène, basés sur l'équation maîtresse CME. Puis, [ABDV+04, EE04, LGP09] dans le cadre inhomogène. S'ils sont adaptés dans des situations exclusives de faibles concentrations et interactions, un problème d'envergure est que ces algorithmes de simulation directe (ou exacte) sont extrêmement coûteux en temps dès que le nombre d'individus est grand et les réactions rapides par conséquent, même pour les modèles homogènes les plus simples. Pour se faire une idée, le module de production d'une seule protéine, par exemple, implique des dizaines de variables et réactions biochimiques, et un nombre équivalent de paramètres [KZZ01, KBR05]. Et c'est bien pire encore, concernant les modèles inhomogènes.

De nombreuses améliorations sont proposées. Pour SSA, on peut citer [LSH+98] pour le cas particulier mais important des réactions de surface, [GB00] qui introduit l'algorithme *Next Reaction method*. D'autres traitent le modèle stochastique comme un modèle continu mais qui reste stochastique: [Gil01] avec l'algorithme τ -leap qui utilise l'équation de Langevin obtenu par approximation à partir du TCL. Le champ d'application des résultats d'approximation étant limité à des cas de grandes populations et réactions rapides, des algorithmes dit hybrides ont été introduits. Ces derniers prennent en compte les différences d'abondance entre les espèces qui interagissent. Citons [PK04] avec l'algorithme *Maximal Time Step Method*, qui combine τ -leap pour simuler les réactions *rapides* (réactions à taux élevé) et *Next Reaction method* pour les réactions *lentes* (à faible taux). Une autre approche hybride repose sur la LGN. Elle consiste à simuler les réactions *rapides* suivant des équations différentielles déterministes [RMC07a, CDR09, ZFWL08]. Les algorithmes hybrides sont en plein essor en biologie moléculaire. Ceci vaut également pour les modèles spatialement inhomogènes: [FME12, FWLP14,

[SGA⁺15, SGL⁺16, NCS15]. Les défis sont bien plus grands dans ce contexte, car il faut bien choisir les approximations à considérer, sachant qu'elles peuvent ne pas être les mêmes d'une région à une autre.

La simulation d'un modèle stochastique par des équations différentielles (resp. diffusions) repose sur la LGN (resp. TCL), lorsque les conditions requises sont satisfaites. Les algorithmes hybrides sont fortement inspirés de ces théorèmes limites classiques en mathématiques. Ils produisent des résultats plutôt satisfaisants, qui corroborent les observations expérimentales. Cependant, il n'existe en général pas de cadre théorique rigoureux soutenant les approximations effectuées en amont. Deux questions à propos des modèles hybrides dérivés et simulés méritent réflexion:

- 1) Les modèles hybrides dérivés restent-ils markoviens?
- 2) Les modèles hybrides dérivés sont-ils effectivement proches des modèles stochastiques initialement construits?

Même si intuitivement les réponses semblent évidentes et affirmatives, des investigations théoriques rigoureuses manquent en amont, concernant ces questions qui sont très importantes dans l'implémentation des algorithmes hybrides, d'un point de vue approximation (première question) et d'un point de vue méthode numérique (deuxième question).

(1) Propriété de Markov pour les modèles hybrides dérivés. La réponse à la question (1) est "oui". Elle repose essentiellement sur la théorie des processus de Markov déterministes par morceaux (Piecewise Deterministic Markov Processes-PDMPs). Cette théorie a été développée par Davis [Dav84, Dav93] en dimension finie et est bien adaptée aux modèles homogènes de réseaux de gènes. Les PDMPs ont été utilisés et développés davantage un peu plus tôt en recherche opérationnelle en relation avec le control optimal, dans les transport aériens, et dans beaucoup d'autres applications technologiques [BL04, GB05a, BKP05, BLE06, CE06]. La notion plus générale de processus stochastiques hybrides a été introduite et inclue des processus diffusifs par morceaux. Typiquement, dans les cas d'algorithmes hybrides cités ci-dessus, ceux basés sur la LGN ont des PDMPs comme modèles hybrides dérivés, tandis que ceux basés sur le TCL conduisent à des processus diffusifs par morceaux. Dans le cadre spatialement inhomogène, le formalisme des PDMPs de Davis en dimension finie ne suffit plus. La réponse est apportée par Buckwar et Riedler [BR11, Rie11, RTW12], qui ont généralisé le formalisme des PDMPs à la dimension infinie, pour des applications en neurosciences.

Les modèles hybrides sont encore appelés modèles mésoscopiques, ou modèles multi-échelles, car ils combinent des dynamiques à la fois macroscopiques et microscopiques. Une réponse affirmative à la question (1) n'est pas suffisante à elle seule, pour donner de la consistance aux approximations hybrides computationnelles ou mathématiques souvent effectuées. Par contre, elle permet d'obtenir des propriétés capitales du modèle hybride, par exemple la propriété de Markov forte qui est utile dans les méthodes de simulation. Cette propriété de Markov forte s'avèrera aussi très utile pour répondre à la question (2).

(2) Consistance de l'approximation hybride. Dans le contexte d'homogénéité spatiale, l'approximation de la dynamique des réseaux de gènes par des PDMPs a été proposée par Radulescu, Muller et Crudu [RMC07a], puis Crudu, Debussche et Radulescu [CDR09]. Ensuite, Crudu, Debussche, Muller et Radulescu [CDMR12] le démontrent rigoureusement, apportant ainsi une réponse affirmative à la question (2). Une telle

réponse donne de la consistance à l’usage général des modèles stochastiques hybrides (PDMPs notamment) pour les systèmes biologiques (ou des systèmes équivalents) dans le contexte homogène. Le point de départ pour y arriver a été la considération effective de la différence d’abondance des différentes molécules, et de la différence d’échelle des vitesses et des taux des événements. Ces considérations sont faites dès la modélisation mathématique stochastique initiale, et le système est séparé en fonction de ces échelles. On parle alors de modélisation stochastique multi-échelles, avec des échelles différentes d’évolution en espace et en temps.

La question (2) demeure toutefois ouverte, en ce qui concerne les modèles spatiaux. Une réponse affirmative donnerait, de la consistance à l’usage des modèles hybrides pour les systèmes biologiques ou des systèmes équivalents, avec dépendance spatiale. Les challenges allant de pair avec la robustesse des modèles, ils sont de loin plus nombreux et plus grands dans ce contexte. Au niveau de la modélisation par exemple, les possibilités sont décuplées même pour les modèles déterministes. S’agissant des défis mathématiques, beaucoup découlent du passage de la dimension finie à la dimension infinie. Dans le premier cadre, les éléments de réponses à des questions mathématiques telles que la convergence de suites, la compacité d’ensembles, les propriétés d’opérateurs linéaires, l’existence et d’unicité de solutions d’équations différentielles, les méthodes numériques ... sont relativement simples et plutôt bien compris, et les usages sont assez rodés. En dimension infinie en revanche, les mêmes questions sont d’un tout autre ordre. Elles requièrent l’usage d’outils d’analyse beaucoup plus élaborés et en plein essor.

0.2.2 Objectif de la thèse

Le but de cette thèse est d’établir une base théorique mathématique renforcée, de modélisation stochastique, d’analyse et de réductions consistantes des modèles en vue de simulations plus efficaces, pour des systèmes multi-échelles de réactions biochimiques avec dépendance spatiale. Sur la base de critères variés, différents modèles sont développés. Des méthodes adéquates sont élaborées afin d’étudier et de simplifier ces modèles. La démarche suivie nous permet d’apporter une réponse assez précise à la question (2) posée ci-dessus. Notamment, des critères d’approximations hybrides de modèles stochastiques multi-échelles spatiaux sont mis en avant.

0.2.3 Des champs d’application

Les systèmes de référence dans le présent travail sont les réseaux de régulation génique. Cependant, nous insistons sur le fait que le champ d’application des modèles développés et proposés ne s’y restreint pas. Leur portée va bien au-delà de la biologie moléculaire, et, moyennant quelques adaptations éventuellement, ils peuvent être exploités pour la modélisation des systèmes complexes dans des domaines très variés: épidémiologie, micro-fluidique, trafic aérien, écologie, toxicocinétique, finances, assurance, démographie, hydrologie, les sciences sociales, les écosystèmes, les processus de matériaux, ...

0.3 Présentation des résultats

Dans cette section, nous présentons les résultats obtenus durant la thèse. Ils sont répartis dans les différents chapitres qui meublent le présent manuscrit, à la suite de ce chapitre introductif. Chaque chapitre est autonome et possède les définitions et les propriétés des outils mathématiques utiles pour répondre aux questions qu’il traite. Pour les modèles spatiaux, nous travaillons dans le cadre simplifié unidimensionnel ($d = 1$), le domaine spatial est projeté sur le segment unité ($I = [0, 1]$) et des conditions périodiques sont considérées sur le bord. Le caractère Markovien et l’existence des processus stochastiques manipulés relèvent de leur construction (voir Section 0.1.4). De tels processus sont bien définis (cf. [EK86, Kot88b]) jusqu’à un temps d’explosion potentiel, à partir duquel il prennent des valeurs cimetières. Toutefois, par les nombreuses LGNs [Kur70, AT80, Kot86a, Blo92], on sait que les modèles stochastiques convergent vers les modèles déterministes. Donc pour N assez grand, les processus n’explorent pas si leur limites n’explorent pas. De plus, des hypothèses naturelles sur leur taux de sauts permettent de garantir la positivité des grandeurs évaluées (nombre d’individus, proportions, concentrations) si ces dernières sont positives à l’état initial.

0.3.1 TCL dans le cas homogène

Dans le chapitre 1 de cette thèse, un TCL est obtenu dans le cadre homogène pour un modèle stochastique multi-échelle simplifié de réseaux de réactions biochimiques. On reste en dimension finie. Le résultat obtenu est très différent des résultats usuels obtenus pour des LGNs classiques. Les fluctuations du modèle multi-échelles initial autour de l’approximation hybride sont décrites par un processus de Markov diffusifs par morceaux (Piecewise Diffusion Markov Process - PDifMP). Les PDifMPs sont une généralisation des PDMPs au cas où entre deux sauts consécutifs, le processus évolue suivant une ÉDS à la place d’une ÉDO [BLE06, GB05a]. Ces processus sont bien définis et entièrement caractérisés par leur générateur étendu. Ils sont dit réguliers ou standards lorsqu’ils n’explorent pas. Nous ne considérons que des processus hybrides standards.

Le point de départ pour le TCL présenté dans ce chapitre est l’approximation hybride de modèles multi-échelles homogènes de réseaux de gènes par des PDMPs, due à Crudu, Debussche, Muller et Radulescu [CDMR12]. Le cadre général est celui introduit à la Section 0.1.4: $M \geq 1$ espèces chimiques interagissent suivant un nombre fini de réactions chimiques dans un ensemble \mathfrak{R} . Il y a un nombre M_C d’espèces abondantes de l’ordre d’un N , elles sont dites continues, et un nombre M_D d’espèces rares de l’ordre de 1, dites discrètes. L’indice C fait référence au premier groupe et l’indice D au second. Le vecteur X qui décrit l’état du système s’écrit $X = (X_C, X_D)$, le vecteur stœchiométrique s’écrit $\gamma_r = (\gamma_r^C, \gamma_r^D)$ pour la réaction $r \in \mathfrak{R}$. On pose $x_C^N = N^{-1}X_C$ et $x_D^N = X_D$. Le processus remis à échelle $x^N = (x_C^N, x_D^N)$ vit dans $E = \mathbb{R}^{M_C} \times \mathbb{N}^{M_D}$.

L’ensemble \mathfrak{R} est divisé en trois sous-ensembles

$$\mathfrak{R} = \mathfrak{R}_C \cup \mathfrak{R}_{DC} \cup \mathfrak{R}_D.$$

Les réactions dans \mathfrak{R}_C (resp. \mathfrak{R}_D) impliquent uniquement les molécules de C (resp. D), sont rapides (resp. lentes). Celles dans \mathfrak{R}_{DC} impliquent les deux espèces. Il faut ensuite spécifier les différentes réactions. On fait l’hypothèse suivante.

Hypothèse 0.3.1.

(i) Il y a de la dépendance à la densité pour les réactions dans \mathfrak{R}_C : pour tout $r \in \mathfrak{R}_C$, il existe $\tilde{\lambda}_r$ telle que $\lambda_r(X_C, X_D) = N\tilde{\lambda}_r\left(\frac{X_C}{N}, X_D\right)$.

(ii) Il existe $S_1 \subset \mathfrak{R}_{DC}$ tel que pour tout $r \in S_1$: $\gamma_r^D = 0$ et il existe $\tilde{\lambda}_r$ vérifiant $\lambda_r(X_C N, X_D^N) = \mu\tilde{\lambda}_r\left(\frac{X_C^N}{\mu}, X_D^N\right)$.

(iii) Les réactions dans $(\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D$ sont lentes.

En particulier, les réactions $r \in \mathfrak{R}_C \cup S_1$ sont rapides.

En passant à la limite dans l'expression du générateur infinitésimal du processus remis à échelle x^N , on obtient formellement le générateur d'un PDMP continu et avec switching $x = (x_C, X_D)$, suggérant ainsi que x^N converge vers x en loi. Cette convergence est justifiée rigoureusement par Crudu *et al.*, et a lieu dans l'espace de Skorohod $D(\mathbb{R}_+, E)$ (Theorem 3.1 [CDMR12]).

Le TCL obtenu dans ce cas n'est pas standard. La méthode utilisée par Kurtz [EK86] pour prouver le TCL dans le cadre d'une LGN pour un modèle à une échelle ne marche plus. Les raisons sont liées à la nature stochastique de la limite et la présence de deux échelles de dynamique. La LGN obtenue pour la composante rapide suggère pour cette dernière un TCL. Seulement, le couplage de la dynamique rapide avec la dynamique lente crée des difficultés mathématiques, car les composantes associées ne convergent pas à la même vitesse. En effet, dans les développements, une vitesse de convergence choisie pour la variable rapide se retrouve comme coefficient de la variable lente, créant ainsi un terme qui diverge. Une autre difficulté majeure est de pouvoir obtenir, d'emblée, une convergence forte (presque sûre) pour le processus vectoriel formé du processus initial, et de la partie martingale renormalisée de sa composante continue.

Le premier résultat implique en particulier un TCL partiel pour la martingale mentionnée ci-dessus. Il permet aussi d'apporter une solution au problème de convergence forte mis en avant. La partie martingale de la composante rapide x_C s'écrit (voir [Kur71])

$$Z_C^N(t) = x_C^N(t) - x_C^N(0) - \int_0^t F^N(x^N(s)) ds$$

où, pour $(y_C, y_D) \in \mathbb{R}^{M_C + M_D}$, $F^N = F + F_1^N$ est le débit des réactions qui affectent l'espèce continue, avec

$$F(y_C, y_D) = \sum_{r \in \mathfrak{R}_C} \gamma_r^C \lambda_r(y_C) + \sum_{r \in S_1} \gamma_r^C \lambda_r(y_C, y_D)$$

comme débit des réactions rapides, et

$$F_1^N(y_C, y_D) = \frac{1}{N} \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \gamma_r^C \lambda_r(y_C, y_D),$$

celui des réactions lentes impliquant l'espèce abondante.

On s'intéresse ensuite au processus $U_C^N(t) = \sqrt{N}Z_C^N(t)$ et $Y^N = (x_C^N, X_D^N, U_C^N)$. On prouve que Y^N converge vers un PDifMP avec switching $Y = (x_C, X_D, U_C)$, qui hérite de la nature hybride du PDMP (x_C, X_D) . Entre deux sauts consécutifs de X_D lorsque

0.3 Présentation des résultats

ce dernier a pris une valeur ν , le couple (x_C, U_C) évolue suivant le système stochastique diffusif

$$\begin{cases} \dot{x}_C(t) = F(x_C(t), \nu) \\ dU_C(t) = \sum_{r \in \mathfrak{R}_C} a_r(x_C(t), \nu) dB_r(t) + \sum_{r \in S_1} a_r(x_C(t), \nu) dB_r(t), \end{cases}$$

où B_r , $r \in \mathfrak{R}_C \cup S_1$, sont des mouvements browniens vectoriels standards et indépendants, et chaque matrice de diffusion $a_r(x_C(t), \nu)$ satisfait

$$(a_r a_r^T)_{ij}(y_C, y_D) = \begin{cases} \gamma_{r,i}^C \gamma_{r,j}^C \lambda_r(y_C) & \text{if } r \in \mathfrak{R}_C \\ \gamma_{r,i}^C \gamma_{r,j}^C \lambda_r(y_C, y_D) & \text{if } r \in S_1, \end{cases}$$

pour $(y_C, y_D) \in \mathbb{R}^{M_C + M_D}$.

Le système limite est clairement et facilement identifié, en calculant formellement le générateur limite du processus markovien de saut Y^N . On prouve plus précisément ce qui suit.

Théorème 0.3.1. *On suppose que les taux des réactions sont bornés, et que le débit F des réactions rapides est une fonction Lipschitz de sa première variable. Alors, quand $N \rightarrow \infty$,*

$$Y^N \Longrightarrow Y \text{ dans } D([0, T], \mathbb{R}^{M_C + M_D + M_C}).$$

En particulier, on a un TCL pour la martingale Z_C^N . Il est donné par

$$U_C^N \Longrightarrow U_C \text{ dans } D([0, T], \mathbb{R}^{M_C}).$$

La preuve s'inscrit dans une démarche classique à trois étapes. On commence par montrer la tension du processus Y^N en s'appuyant sur les travaux de [CDMR12] pour le couple (x_C^N, X_D^N) , puis sur les travaux de [Kur71] pour U_C . On obtient la tension pour le triplet par des résultats de [JS87]. À la deuxième étape, on identifie la limite par passage à la limite dans le problème de martingale. On conclut enfin en montrant que le problème de martingale limite est bien posé.

Une conséquence immédiate du Théorème 0.3.1 et du théorème de représentation de Skorohod est qu'on obtient une convergence presque sûre d'une version de Y^N vers une version de Y , moyennant éventuellement un grossissement de l'espace de probabilité. Ainsi, on considère dans la suite que la convergence de Y^N vers Y est presque sûre.

Pour résoudre le problème lié aux échelles, l'idée est de faire un changement de temps aléatoire pour lequel la limite X_D de la composante discrète X_D^N coïncide avec cette dernière. Nous y parvenons pour l'instant, en supposant qu'une seule réaction lente existe. On note λ_1 son taux, et on suppose en plus que la fonction λ_1 est minoré par une constante strictement positive λ_0 . En s'appuyant sur le changement de temps aléatoire introduit par [EK86], on construit alors une fonction g_N telle que

$$\int_0^{g_N(t)} \lambda_1(x_C(s), X_D(s)) ds = \int_0^t \lambda_1(x_C^N(s), X_D^N(s)) ds,$$

de sorte que $X_D(g_N(t)) = X_D^N(t)$.

On considère ensuite les processus v_C^N et h^N définis par

$$v_C^N(t) = \sqrt{N}(x_C^N(t) - x_C(t)) \quad \text{et} \quad h^N(t) = \sqrt{N}(g_N(t) - t).$$

Alors, v_C^N se met sous la forme $v_C^N(t) = v_C^N(0) + U_C^N(t) + A_C^N(t)$, où

$$A_C^N(t) = \int_0^t \sqrt{N} [F(x_C^N(s), X_D^N(s)) - F(x_C(s), X_D(s))] ds.$$

Un développement limité permet de voir que ces processus sont solution d'un système de deux équations couplées, qui suggère pour (v_C^N, h^N) , le couple limite (v_C, h) , où

$$h(t) = \int_0^t \frac{D^{1,0} \lambda_1(x_C(s), X_D(s))}{\lambda_1(x_C(s), X_D(s))} [v_C(s) - F(x_C(s), X_D(s))h(s)] ds,$$

et

$$\begin{aligned} v_C(t) &= v_C(0) + U_C(t) + \int_0^t D^{1,0} F(x_C(s), X_D(s)) v_C(s) ds \\ &\quad - \int_0^t D^{1,0} F(x_C(s), X_D(s)) F(x_C(s), X_D(s)) h(s) ds \\ &\quad - \int_0^t F(x_C(s), X_D(s)) \frac{D^{1,0} \lambda_1(x_C(s), X_D(s))}{\lambda_1(x_C(s), X_D(s))} \\ &\quad \quad \quad \times [v_C(s) - F(x_C(s), X_D(s))h(s)] ds \\ &\quad + F(x_C(t), X_D(t))h(t). \end{aligned}$$

On observe que le problème à la limite est bien posé, car $(v_C, h, x_C, X_D) = (V_C, X_D)$ est un PDifMP à valeurs dans $\mathbb{R}^{2M_C+1} \times \mathbb{N}^{M_D}$.

En absence d'espèces discrètes, le TCL standard (voir [EK86]) se fait uniquement avec le processus v_C^N , et sa limite est une diffusion donnée par les trois premiers termes dans l'expression de v_C ci dessus. En présence d'espèces discrètes, des termes additionnels non intuitifs doivent être pris en compte. Le résultat prouvé est le suivant.

Théorème 0.3.2. *On suppose que l'ensemble $(\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D$ contient une seule réaction r_1 , de taux λ_1 minoré par une constante $\lambda_0 > 0$. On suppose aussi que:*

- (i) *les taux de sauts sont bornés, continus par rapport à la seconde variable, de classe C^1 par rapport à la première variable,*
- (ii) *leurs dérivées par rapport à la première variable sont bornées et sont aussi continues par rapport à la seconde variable.*

Si $v_C^N(0) \rightarrow v_{C,0} \in \mathbb{R}^{M_C}$ en probabilité, alors pour tout $T > 0$,

$$(v_C^N, h^N) \Longrightarrow (v_C, h), \quad \text{dans } D([0, T], \mathbb{R}^{M_C+1}), \quad \text{quand } N \rightarrow \infty.$$

La preuve est relativement simple. En utilisant des propriétés de la dérivée (faible) du changement de temps g_N , on montre d'abord que la suite v^N est bornée uniformément en temps. La diffusion U_C étant continue et g_N uniformément proche de l'identité sur $[0, T]$, un lemme de Gronwall permet ensuite de conclure.

0.3.2 Un modèle spatial multi-échelle: limite déterministe

Au chapitre 2, une LGN non usuelle est obtenue en norme infinie, pour un premier modèle spatial multi-échelle de réactions biochimiques. Nous commençons par préciser les modèles spatiaux déterministe et stochastique à une échelle. Dans ces cas, les concentrations de toutes les espèces ont la même dynamique et il est commode de n'en considérer qu'une seule: on prend $M = 1$.

Modèle déterministe. Les réseaux de régulation génique sont très souvent modélisés dans le cadre macroscopique spatial, par l'équation de réaction-diffusion:

$$\partial_t v = \mathcal{D} \Delta_x v + R(v), \quad (0.3.1)$$

L'inconnue $v = v(t, x) \in \mathbb{R}^M$ décrit les concentrations locales du réactif, $t \geq 0$ (resp. $x \in I$) est la coordonnée temporelle (resp. spatiale), Δ est le laplacien et \mathcal{D} le coefficient de diffusion. Dans la suite, on considère $\mathcal{D} = 1$. Enfin, R représente les fluctuations dues aux réactions chimiques. C'est un polynôme de la forme

$$R(y) = \sum_{k=1}^n a_k y^k = b(y) - d(y),$$

où b (resp. d) est un polynôme traduisant les variations dues aux naissances (resp. morts) du réactif.

Pour l'existence et l'unicité, on suppose que $d(0) = 0$ et $a_n < 0$. Par le principe du maximum, la première (resp. deuxième) condition assure que les concentrations restent positives (resp. bornées) si elles le sont initialement. Ainsi, pour toute condition initiale $v(0) = v_0 \in C^3(I)$ telle que $0 \leq v_0(x) \leq \rho_1 < \infty$, il est bien connu (voir par exemple [Kot86a]) que le problème de Cauchy associé à (0.3.1) admet une unique solution mild $v \in C(\mathbb{R}_+; C^3(I))$ qui s'écrit

$$v(t) = T(t)v_0 + \int_0^t T(t-s)R(v(s))ds$$

et telle que $0 \leq v(t, x) < \rho(\rho_1, \rho_2) < \infty$, pour tout t, x . Ici, $T(t) = e^{\Delta t}$ est le semigroupe engendré par le Laplacien.

Par des arguments heuristiques probabilistes on obtient facilement que le générateur infinitésimal de l'EDP (0.3.1) est formellement donné par

$$\mathcal{A}\varphi(u) = \langle D\varphi(u), \Delta u + R(u) \rangle_2,$$

où $\langle \cdot, \cdot \rangle_2$ est le produit scalaire $L^2(I)$. Enfin, le débit s'écrit $\Psi(u) = \Delta u + R(u)$.

Modèle stochastique. Pour une modélisation stochastique, suivant [AT80], on discrétise le segment unité en N sites $I_j = (\frac{j-1}{N}, \frac{j}{N}]$, $j = 1, \dots, N$ de longueur $\frac{1}{N}$. On définit X_j^N le nombre de molécules sur le site j , $X^N = (X_j^N)_j$ le vecteur qui donne l'état du système, et \mathfrak{R} l'ensemble supposé fini des réactions chimiques possibles. Il est standard (voir [Kur70, Kur71, EK86]) que $\{X^N(t), t \geq 0\}$ est un processus de Markov à sauts

homogène, à temps continu, à valeurs dans \mathbb{N}^N , et admettant les transitions

$$\begin{cases} X^N \longrightarrow X^N + \gamma_{j,r}e_j & \text{au taux } \lambda_r(X_j^N), \\ X^N \longrightarrow X^N + e_{j-1} - e_j & \text{au taux } N^2X_j^N \\ X^N \longrightarrow X^N + e_{j+1} - e_j & \text{au taux } N^2X_j^N, \end{cases}$$

pour $r \in \mathfrak{R}$ et $j = 1, \dots, N$, où $\{e_j, j = 1, \dots, N\}$ est la base canonique de \mathbb{R}^N . Par périodicité, on considère que $X_{j+N}^N = X_j^N$ pour tout j .

On suppose que chaque X_j^N est de l'ordre d'un paramètre μ grand, et que les taux des réactions dépendent des densités: pour tout $r \in \mathfrak{R}$, il existe une fonction $\tilde{\lambda}_r$ telle que

$$\lambda_r(X_j^N) = \mu \tilde{\lambda}_r \left(\frac{X_j^N}{\mu} \right) \quad \text{pour tout } j = 1, \dots, N.$$

Comme μ est grand, toutes les réactions sont rapides. On suppose alors que toutes les réactions sont homogènes en espace, ie

$$\gamma_{j,r} = \gamma_r, \quad \forall r \in \mathfrak{R}.$$

En général, μ dépend de N , mais on omet de mentionner la dépendance en μ dans les notations. Le processus à échelle

$$U^N = U^{N,\mu} = \frac{X^N}{\mu}$$

a les sauts $\frac{x}{\mu}$ et prend ses valeurs dans \mathbb{R}^N .

Le modèle spatial homologue du modèle déterministe précédent est alors

$$u^N(t, x) = \sum_{j=1}^N U_j^N(t) \mathbb{1}_j(x), \quad t \geq 0, \quad x \in I_j, \quad (0.3.2)$$

où $\mathbb{1}_j(\cdot) := \mathbb{1}_{I_j}(\cdot)$ est la fonction indicatrice du j -ème site I_j . Par l'identification standard $u^N(t) = u^N(t, \cdot)$, le processus $u^N = \{u^N(t), t \geq 0\}$ est à valeurs dans l'espace \mathbb{H}^N des fonctions 1-périodiques de $L^2(I)$ qui sont constantes sur les intervalles I_j . Ses transitions sont:

$$\begin{cases} u^N \longrightarrow u^N + \frac{\gamma_r}{\mu} \mathbb{1}_j, & \text{au taux } \mu \tilde{\lambda}_r(u_j^N), \quad \text{pour } r \in \mathfrak{R}, \\ u^N \longrightarrow u^N + \frac{\mathbb{1}_{j-1} - \mathbb{1}_j}{\mu}, & \text{au taux } \mu N^2 u_j^N, \quad \text{pour } 1 \leq j \leq N, \\ u^N \longrightarrow u^N + \frac{\mathbb{1}_{j+1} - \mathbb{1}_j}{\mu}, & \text{au taux } \mu N^2 u_j^N, \quad \text{pour } 1 \leq j \leq N, \end{cases}$$

où $u_j^N = U_j^N$ est la j -ème coordonnée de u^N obtenue par la projection canonique

$$P_N : L^2 \longrightarrow \mathbb{H}^N \\ u \longmapsto P_N u = \sum_{j=1}^N u_j \mathbb{1}_j, \quad \text{where } u_j := N \int_{I_j} u(x) dx. \quad (0.3.3)$$

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La LGN peut à nouveau être justifiée de manière heuristique par un développement de Taylor dans le générateur infinitésimal de u^N . En effet, on voit que ce générateur converge formellement vers celui du modèle déterministe v .

Multiscaling. Nous présentons maintenant le cadre général de nos modèles. Comme il sont multi-échelle, plusieurs espèces sont indispensables ($M \geq 2$). Pour simplifier, deux espèces C et D sont considérées ($M = 2$). La première est abondante et dite continue, la deuxième est plus faiblement concentrée, et dite discrète. Suivant [CDMR12], l'ensemble \mathfrak{R} des réactions possibles est divisé en trois sous-ensembles

$$\mathfrak{R} = \mathfrak{R}_C \cup \mathfrak{R}_{DC} \cup \mathfrak{R}_D.$$

Les réactions dans \mathfrak{R}_C (resp. \mathfrak{R}_D) impliquent uniquement les molécules de C (resp. D). Celles dans \mathfrak{R}_{DC} impliquent les deux espèces. Le vecteur stœchiométrique de la réaction r qui affecte C (resp. D) sur le site j est noté $\gamma_{j,r}^C$ (resp. $\gamma_{j,r}^D$).

On définit $X_j^{N,C}$ (resp. $X_j^{N,D}$) le nombre de molécules de C (resp. D) sur le site j , ensuite les compositions moléculaires $X_C^N := (X_j^{N,C})_j$ et $X_D^N := (X_j^{N,D})_j$ de chaque espèce, puis l'état global $X^N := (X_C^N, X_D^N)$ du système. Les échelles sont telles que pour chaque j , $X_j^{N,C} \sim \mu$ tandis que $X_j^{N,D} \sim \kappa$, avec $\mu \gg \kappa$. Comme précédemment, on remet le processus à l'échelle et on définit le modèle spatial $u^N = (u_C^N, u_D^N)$ à valeurs dans $\mathbb{H}^N \times \mathbb{H}^N$, par

$$u_C^N(t, x) = \sum_{j=1}^N u_j^{N,C}(t) \mathbb{1}_j(x) \quad \text{et} \quad u_D^N(t, x) = \sum_{j=1}^N u_j^{N,D}(t) \mathbb{1}_j(x), \quad (0.3.4)$$

où $u_j^{N,C}(t) := P_N u_C^N(t) = N \int_{I_j} u_C^N(t, x) dx$, et $u_j^{N,D}$ est défini de façon analogue.

Spécifions à présent les différents types de réactions. On suppose que:

Hypothèse 0.3.2.

(i) Il y a de la dépendance à la densité pour les réactions dans \mathfrak{R}_C : Pour tout $r \in \mathfrak{R}_C$, il existe $\tilde{\lambda}_r$ telle que $\lambda_r(X_j^{N,C}) = \mu \tilde{\lambda}_r \left(\frac{X_j^{N,C}}{\mu} \right)$ pour tout j .

(ii) Il existe $S_1 \subset \mathfrak{R}_{DC}$ tel que pour tout $r \in S_1$: $\gamma_{j,r}^D = 0$ et il existe $\tilde{\lambda}_r$ vérifiant $\lambda_r(X_j^{N,C}, X_j^{N,D}) = \mu \tilde{\lambda}_r \left(\frac{X_j^{N,C}}{\mu}, X_j^{N,D} \right)$, pour tout j .

(iii) Les réactions dans $(\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D$ sont lentes.

En particulier, les réactions $r \in \mathfrak{R}_C \cup S_1$ sont rapides. Comme précédemment, on les

suppose homogènes en espace ($\gamma_{j,r}^C = \gamma_r^C$). Les transitions du processus u^N s'écrivent:

$$\left\{ \begin{array}{l} (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\gamma_r^C}{\mu} \mathbf{1}_j, u_D^N \right), \text{ au taux } \mu \tilde{\lambda}_r \left(u_j^{N,C} \right), r \in \mathfrak{R}_C, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\gamma_r^C}{\mu} \mathbf{1}_j, u_D^N \mathbf{1}_j \right), \text{ au taux } \mu \tilde{\lambda}_r \left(u_j^{N,C}, u_j^{N,D} \right), r \in S_1, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\gamma_{j,r}^C}{\mu} \mathbf{1}_j, u_D^N + \gamma_{j,r}^D \mathbf{1}_j \right), \text{ au taux } \lambda_r \left(u_j^{N,C}, u_j^{N,D} \right), r \in \mathfrak{R}_{DC} \setminus S_1, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N, u_D^N + \gamma_{j,r}^D \mathbf{1}_j \right), \text{ au taux } \lambda_r \left(u_j^{N,D} \right), r \in \mathfrak{R}_D, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\mathbf{1}_{j-1} - \mathbf{1}_j}{\mu}, u_D^N \right), \text{ au taux } N^2 u_j^{N,C}, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\mathbf{1}_{j+1} - \mathbf{1}_j}{\mu}, u_D^N \right), \text{ au taux } N^2 u_j^{N,C}. \end{array} \right. \quad (0.3.5)$$

À ce stade, la limite $N \rightarrow \infty$ pose des difficultés mathématiques à cause des réactions lentes. Si on les suppose homogènes en espace, on s'en rend bien compte. À moins d'avoir $u_j^{N,D} = 0$ pour presque tout j , l'espèce discrète D est en fait globalement abondante avec une population totale de l'ordre de N , de sorte que la composante u_D^N converge aussi vers un model continu. La limite attendue pour u^N est une EDP pour u_C couplée à une EDO pour u_D . Cependant la convergence semble se produire dans des espaces irréguliers (de distributions) avec tes topologies faibles. On introduit alors de la dépendance spatiale pour ces réactions, en considérant qu'elles déclenchent des réactions simultanées sur les sites voisins de sa source. Il faut alors faire attention à ce que les proportions et nombres de molécules restent des quantités positives. De tels phénomènes précèdent l'activation d'un gène sur l'ADN. On obtient à la limite une EDP couplée avec une EDO non locale.

Dans ce chapitre, on suppose que:

Hypothèse 0.3.3. Une réaction $r \in (\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D$ qui se produit sur le site j affecte ses voisins suivant $(u_C^N, u_D^N) \rightarrow (u_C^N + \gamma_{j,r}^{N,C}, u_D^N + \gamma_{j,r}^{N,D})$, où

$$\gamma_{j,r}^{N,C} \equiv \gamma_{j,r}^{N,C}(u_C^N, u_D^N) := \frac{\gamma_r^C}{\mu} \sum_{i=1}^N \gamma_{ij}^N \mathbf{1}_i \theta_{ij}^r(u_i^{N,C}, u_i^{N,D}),$$

$$\gamma_{j,r}^{N,D} \equiv \gamma_{j,r}^{N,D}(u_C^N, u_D^N) := \gamma_r^D \sum_{i=1}^N \gamma_{ij}^N \mathbf{1}_i \theta_{ij}^r(u_i^{N,C}, u_i^{N,D}),$$

avec

$$\gamma_{ij}^N := \int_{I_i} a \left(x - \frac{j}{N} \right) dx \quad \text{et} \quad \theta_{ij}^r(u_i^{N,C}, u_i^{N,D}) = \theta(u_i^{N,C} + \frac{\gamma_r^C}{\mu} \gamma_{ij}^N) \theta(u_i^{N,D} + \gamma_r^D \gamma_{ij}^N).$$

Les réactions lentes ont donc des sauts de l'ordre de N^{-1} sur chaque site, avec un effet global de l'ordre de 1. La fonction a dans l'expression de γ_{ij}^N décrit l'intensité avec laquelle l'effet de ces réactions se propage. C'est une fonction $C_p(I)$, 1-périodique et positive. Il est naturel de la considérer maximale en 0 et décroissante en $|x|$ pour que l'effet de la réaction s'amenuise à mesure qu'on s'éloigne de la source. La fonction θ est

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une fonction lisse nulle sur $(-\infty, 0]$, égale à 1 sur $[1, \infty)$ et croissante sur $[0, 1]$. Elle garantit la positivité des proportions.

Un développement de Taylor dans le générateur du processus $u^N = (u_C^N, u_D^N)$ permet d'obtenir une limite formelle $v = (v_C, v_D)$, solution du système

$$\frac{\partial v_C}{\partial t} = \Delta_x v_C + F(v_C, v_D) \quad (\text{PDE}) \quad \text{couplée à} \quad (\text{ODE}) \quad \frac{dv_D}{dt} = G(v_C, v_D),$$

où F est la limite du débit des réactions qui affectent C , et G est la limite du débit des réactions qui affectent D . Le premier correspond au débit des réactions rapides et est donné par

$$F(u_C, u_D) = \sum_{r \in \mathfrak{R}_C} \gamma_r^C \tilde{\lambda}_r(u_C) + \sum_{r \in \mathfrak{S}_1} \gamma_r^C \tilde{\lambda}_r(u_C, u_D),$$

et le second est donné par

$$G(u_C, u_D)(x) := \theta(u_C(x))\theta(u_D(x)) \int_0^1 g(u_C, u_D)(y) a(x-y) dy \quad (0.3.6)$$

pour tout $x \in I$, avec

$$g(u_C, u_D) = \sum_{r \in \mathfrak{R}_{DC} \setminus \mathfrak{S}_1} \gamma_r^D \lambda_r(u_C, u_D) + \sum_{r \in \mathfrak{R}_D} \gamma_r^D \lambda_r(u_D).$$

Dans cette limite déterministe, pour l'instant formelle, on voit que la composante continue u_C^N converge vers le correspondant déterministe qui évolue suivant l'équation de réaction-diffusion. On remarque aussi que la composante discrète se régularise et perd les sauts. Le fait que l'espèce D soit en petit nombre est compensé par le fait qu'il y a un grand nombre de sites. Les réactions lentes se produisent finalement assez fréquemment et l'aléa est moyenné comme dans le cas d'une seule échelle, et la limite évolue suivant des ÉDOs locales, puisqu'il n'y a pas de transport des molécules de D .

De plus, cette limite formelle montre qu'une convergence éventuelle est possible dans l'espace $L^2(I)$, avec la condition $\mu^{-1}N^2 \rightarrow 0$. Dans le cas à une échelle, ce résultat est prouvé par [AT80, Kot86b]. [Kot86b, Blo87] montrent que la convergence peut avoir lieu dans des espaces duaux d'espaces de Sobolev abstraits, ceux-ci obtenus comme domaines de puissances du Laplacien. Les conditions sont discutées selon la puissance considérée. Ces espaces duaux sont des espaces de fonctions à régularité négative, dont le cadre n'est pas adapté aux problèmes non linéaires auxquels nous sommes confrontés. Ensuite dans [Blo92], Blount prouve le résultat en norme uniforme en espace, sous la condition plutôt faible $\mu^{-1} \log N \rightarrow 0$. Nous généralisons [Blo92] au cas multi-échelle.

Pour ce qui est de la résolution du problème limite, on garde des conditions périodiques sur les bords. Des hypothèses générales telles que l'hypothèse 0.3.3 sont possibles pour la fonction F qui est la même que celle du modèle déterministe correspondant. Ce n'est pas le cas de la fonction G qui est une convolution. On considère plutôt l'hypothèse moins générale des accroissements linéaires. On introduit la fonction

$$|g|(u_C, u_D) = \sum_{r \in \mathfrak{R}_{DC} \setminus \mathfrak{S}_1} |\gamma_r^D| \lambda_r(u_C, u_D) + \sum_{r \in \mathfrak{R}_D} |\gamma_r^D| \lambda_r(u_D),$$

et on suppose:

Hypothèse 0.3.4.

(C1) F est localement Lipschitz et pour $y = (y_1, y_2) \in \mathbb{R}^2$ tel que $y_1 = 0$, $F(y) \geq 0$.
(C2) Il existe $0 < \rho_C < \infty$ tel que $|y| > \rho_C$ entraîne $F(y) < 0$ pour tout $y \in \mathbb{R}^m$.

(D1) $\theta(y) = 0$ pour $y \leq 0$.

(D2) g est localement Lipschitz, et $|g|$ est à accroissement au plus linéaire par rapport à sa seconde variable: pour tout $\bar{c} > 0$ il existe $M_1(\bar{c}) \geq 0$ tel que pour $|y_1| \leq \bar{c}$, $|g|(y_1, y_2) \leq M_1(\bar{c})(|y_2| + 1)$.

Pour toute condition initiale $v_0 = (v_{C,0}, v_{D,0}) \in C^3(I) \times C^3(I)$ dont les composantes sont à valeurs positives et bornées, par une application directe de [Kot86a], le problème de Cauchy associé au système limite admet une unique solution mild $v = (v_C, v_D) \in C(\mathbb{R}_+; C^3(I) \times C^3(I))$ dont les composantes sont à valeurs positives et bornées uniformément en espace.

On considère la norme $\|(f, h)\|_{\infty, \infty} = \|f\|_{\infty} + \|h\|_{\infty}$. Le résultat principal est le suivant.

Théorème 0.3.3. *On considère l'Hypothèse 0.3.4 et on suppose en plus que*

(i) $N, \mu \rightarrow \infty$ avec $\mu^{-1} \log N \rightarrow 0$,

(ii) $u_C^N(0) \geq 0$, $u_D^N(0) \geq 0$ et $\|u^N(0) - v(0)\|_{\infty, \infty} \rightarrow 0$ en probabilité.

Alors, pour tout $T > 0$,

$$\sup_{t \leq T} \|u^N(t) - v(t)\|_{\infty, \infty} \rightarrow 0 \quad \text{en probabilité.}$$

La preuve est basée sur celle de [Blo92], dont nous reprenons une partie. Elle se fait en trois étapes principales. Dans un premier temps, on construit par différence finie une approximation discrète $v^N = (v_C^N, v_D^N) \in C(\mathbb{R}_+; \mathbb{H}^N \times \mathbb{H}^N)$ du problème limite telle que

$$\sup_{t \leq T} \|v^N(t) - v(t)\|_{\infty, \infty} \rightarrow 0.$$

La preuve du Théorème 0.3.3 se ramène alors à comparer u^N et v^N .

Ensuite, on tronque le processus en rapport avec v^N qui est borné. Le processus tronqué \bar{u}^N est alors borné et on montre qu'il suffit de le comparer avec v^N . Le contrôle de la composante continue est identique à celle de [Blo92] et basée sur le principe du maximum discret. L'hypothèse des accroissements au plus linéaires sert ensuite à contrôler la composante discrète. De plus, le contrôle sur les sauts de \bar{u}^N permet d'exploiter différentes martingales associées à un processus de Markov et à ses sauts [Kur71, Kot86b, Blo87].

On peut alors conclure par un lemme de Gronwall à partir des représentations milds du processus tronqué et de l'approximation discrète du processus limite. Une première différence avec le cas à une échelle est le besoin de la convergence de la fonction débit G^N relative à l'espèce discrète. Le plus intéressant est de montrer que la partie martingale tend vers zéro. Ce terme est une intégrale stochastique de type convolution (voir [Kot86a]) contre l'une des martingales exhibées plus haut. La clé est un lemme de [Blo92] qui permet d'avoir un contrôle de l'espérance d'une classe particulière de martingales, en terme d'exponentielle des débits associés au processus défini par la somme des carrés des sauts de ces martingales. C'est essentiellement de là que provient la condition simplifiée $\mu^{-1} \log N$. Mais alors, on utilise de manière cruciale le contrôle des sauts de la

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composante continue par μ^{-1} comme dans [Blo92], et ceux de la composante discrète par N^{-1} dans le cas multi-échelle. Nous reprenons la construction de la martingale utilisée de manière déterminante à ce stade, pour la composante continue. Les arguments de [Blo92] ne sont pas détaillés et il semble manquer des étapes. Nous proposons une preuve détaillée.

0.3.3 Un modèle spatial multi-échelle: limite PDMP

À l’opposé du chapitre 1 où une limite déterministe est obtenue, le chapitre 3 présente un résultat d’approximation d’un modèle spatial multi-échelle par un processus hybride: un PDMP continu avec switching, à valeurs dans un espace de Banach de dimension infinie. Des arguments de bonne définition et de caractérisation d’un tel processus par son générateur étendu sont donnés dans [Rie11, BR11].

Le modèle de ce chapitre et le précédent partagent bien des aspects, mais plusieurs difficultés supplémentaires sont rencontrées dans le cas présent. Premièrement, la mise en place d’un modèle consistant pour lequel on garde des sauts à la limite. En particulier, il faut s’assurer que la limite obtenue est bien définie et le problème limite bien posé. Par exemple, on s’attend à un processus dont la composante discrète vit dans un ensemble dénombrable. De plus, montrer que le problème limite est bien posé est compliqué par l’irrégularité du processus limite. Ensuite, comme la limite est stochastique il faut prouver la tension. Cependant, les diffusions se font à des taux non bornés et la troncature classique ne marche pas, car le processus est non borné. Le passage à la limite à l’étape d’après est difficile pour la même raison, à laquelle s’ajoute l’irrégularité en espace du processus.

Le modèle est le suivant. On reprend le cadre général de modélisation multi-échelle introduit au chapitre 2. On considère le processus $u^N = (u_C^N, u_D^N)$ donné par (0.3.4). On garde l’Hypothèse 0.3.2, de sorte que les transitions du processus u^N sont données par (0.3.5). Rappelons (confère chapitre 2) qu’à ce stade, le passage à la limite pose des difficultés mathématiques.

Au chapitre 2, une certaine dépendance spatiale a été introduite, conduisant à une EDP couplée avec une EDO non locale à la limite.

Dans ce chapitre, une situation différente est considérée, où l’espèce D reste discrète à la limite. Une hypothèse de *multiscaling* en espace est introduite: le domaine spatial I est divisé en un nombre fini de macrosites J_1, \dots, J_k , où $k \in \mathbb{N}^*$, et la population de u_D est observée à l’échelle spatiale des J_ℓ . Un tel cadre décrit une situation dans laquelle l’espèce discrète D est de taille plus grande que l’espèce continue C .

Pour simplifier les notations, on suppose que les macrosites sont de même taille et on considère N comme un multiple de k . Ainsi, chaque macrosite J_ℓ est une réunion de microsites

$$J_\ell = \bigcup_{j=N_{\ell-1}+1}^{N_\ell} I_j, \quad \ell = 1, \dots, k,$$

avec $N_\ell = \ell N/k$. La composante discrète u_D^N est homogène sur chaque J_ℓ , et donnée par

$$u_D^N(t, x) = \sum_{\ell=1}^k u_\ell^{N,D}(t) \mathbb{1}^\ell(x),$$

où $\mathbf{1}^\ell = \mathbf{1}_{J_\ell}$ est la fonction indicatrice du ℓ -ème macrosite J_ℓ . Par conséquent, l'espace de phase s'identifie bien à $\mathbb{H}^N \times \mathbb{N}^k \subset \mathbb{H}^N \times \mathbb{R}^k$.

On suppose que:

Hypothèse 0.3.5. Une réaction $r \in (\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D$ qui se produit sur J_ℓ affecte le macrosite comme suit:

- $(u_C^N, u_D^N) \rightarrow \left(u_C^N + \frac{\gamma_{r,\ell}^{C,N}}{\mu}, u_D^N + \gamma_r^D \mathbf{1}^\ell \right)$ au taux $\lambda_r \left(\sum_{j=N_{\ell-1}+1}^{N_\ell} a_{j,N}^r u_j^{N,C}, u_\ell^{N,D} \right)$ pour $r \in \mathfrak{R}_{DC} \setminus S_1$,
- $(u_C^N, u_D^N) \rightarrow (u_C^N, u_D^N + \gamma_r^D \mathbf{1}^\ell)$ au taux $\lambda_r (u_\ell^{N,D})$, pour $r \in \mathfrak{R}_D$.

Ici,

$$a_{j,N}^r = \int_{I_j} a^r(x) dx \quad \text{et} \quad \gamma_{r,\ell}^{C,N} = \gamma_r^C \sum_{j=N_{\ell-1}+1}^{N_\ell} b_{j,N}^r \mathbf{1}_j \quad \text{avec} \quad b_{j,N}^r = N \int_{I_j} b^r(x) dx,$$

pour des fonctions positives $a^r, b^r \in C([0, 1])$, avec $\int_0^1 a^r(x) dx = 1$.

Il est naturel de considérer que les réactions $r \in \mathfrak{R}_{DC} \setminus S_1$ qui se déclenchent sur J_ℓ affectent l'espèce C sur J_ℓ tout entier. Les fonctions b^r décrivent les effets de telles réactions à l'échelle microscopique. Leurs taux dépendent de $u_\ell^{N,D}$, et de moyennes locales des valeurs $u_j^{N,C}$ prises par u_C^N sur J_ℓ tout entier. Ces moyennes sont calculées avec des pondérations données par les fonctions a^r .

Dans ce modèle, les réactions lentes sont indépendantes de la discrétisation initiale du domaine spatial I , de sorte que la limite $N \rightarrow \infty$ est sans effet sur leur fréquence, même d'un point de vue spatial. Ces réactions restent peu fréquentes et la composante discrète garde les sauts à la limite.

Formellement, le générateur de u^N converge vers celui d'un PDMP $v = (v_C, v_D)$ à valeurs dans $E = C(I) \times K$ (on s'appuie sur [BR11]). Étant donné $v_D^N(0) = v_{D,0}$, les valeurs possibles de v_D sont de la forme

$$v_D = v_D(0) + \sum_{m=1}^M \sum_{r \in (\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D} \sum_{\ell=1}^k \alpha_{\ell,r}^m \gamma_r^D \mathbf{1}^\ell,$$

où les coefficients $\alpha_{\ell,r}^m$ sont des entiers. On voit que K est dénombrable.

Pour toute valeur ν prise par v_D^N , la composante continue est solution de

$$\frac{d}{dt} v_C(t) = \Delta v_C(t) + F(v_C(t), \nu). \quad (0.3.7)$$

Avec des conditions limites périodiques, on résout (0.3.7) sous l'Hypothèse 0.3.4 (C1) et (C2), et une condition initiale positive et bornée $v_{C,0} \in C^2(I) \subset W^{2,\infty}(I)$. À l'aide des propriétés du noyau de la chaleur, on obtient une solution unique globale *mild* $v_C \in C([0, T]; W^{2,\infty}(I))$, positive et bornée.

Le PDMP v démarre en $v_0 = (v_{C,0}, v_{D,0})$. Le résultat obtenu est le suivant.

Théorème 0.3.4. On suppose que F satisfait l'Hypothèse 0.3.4 (C1) et (C2). On suppose en plus: (i) $N, \mu \rightarrow \infty$ avec $\mu^{-1} \log N \rightarrow 0$,

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(ii) $\|u^N(0) - v_0\|_{\infty, \infty} \rightarrow 0$ en probabilité.

Alors, pour tout $T > 0$,

$$u^N \Longrightarrow v \quad \text{dans } D([0, T]; D(I) \times K).$$

La preuve est basée sur celle de [CDMR12], Theorem 3.1, mais la démarche est beaucoup plus compliquée. L'idée est de montrer la tension dans l'espace des fonctions càdlàg, puis identifier la limite dans le problème de martingales. L'unicité de la solution du problème de martingale limite entraîne celle de la limite et permet de conclure.

Tout d'abord on montre l'unicité de la solution du problème de martingale pour un PDMP en dimension infinie, suivant [CDMR12]. Une première différence est qu'à la place du générateur infinitésimal nous considérons le générateur plein (*full generator*, [EK86]) dont le domaine caractérise le problème de martingale. L'avantage d'utiliser ce dernier est qu'il a un domaine plus gros. D'autre part, le domaine considéré est affiné du fait de la dimension infinie. Si dans [CDMR12] des fonctions tests $C_b^{1,0}$ suffisent, ici des différentielles H^1 en la première variable sont requises en plus, afin avoir une expression adéquate du générateur, conformément à [BR11].

Pour montrer la tension, on combine des idées de [Blo92, DN17] et des arguments spécifiques à la dimension infinie, notamment pour la composante continue u_C^N . Comme indiqué plus haut, les arguments de troncature classique ne marchent pas: les taux des diffusions explosent et u_C^N n'est pas borné. On tronque les taux des réactions, puis on arrête u_C^N et on montre sa tension à l'aide du processus arrêté \bar{u}_C^N et d'une version discrète v_C^N bien choisie de la limite formelle de u_C^N , i.e. la composante continue du PDMP (voir [Blo92, DN17]).

Le processus arrêté \bar{u}_C^N s'écrit comme somme de deux termes. Le premier converge vers 0 en probabilité par les arguments de [Blo92, DN17]. Le second, qui est étagé, est uniformément approché par des fonctions continues linéaires par morceaux, de sorte que la tension est ramenée à ces dernières. Comme elles sont C^1 au sens faible, elles vivent dans l'espace $W^{1,\infty}(I)$ des fonctions Lipschitz. Puis, on utilise l'injection compacte de ce dernier dans $C(I)$, due au théorème d'Ascoli.

Que la composante discrète soit tendue repose sur sa représentation en changement de temps à l'aide de processus de Poissons indépendants ([EK86]), et la tension de ces derniers.

La tension prouve l'existence d'une sous-suite convergente dans l'espace de Skorohod. On veut passer à la limite dans le problème de martingale pour cette sous-suite. Cela pose des soucis à plusieurs niveaux. La martingale considérée contient le terme de diffusion qui est linéaire en u^N . Il est difficile d'avoir sa limite dans l'espérance, car on n'a pas d'estimée des moments de u^N , la tension étant obtenue à l'aide de bornes en probabilité. On introduit alors le processus $w^N = (v_C^N, u_C^N, u_D^N)$. On remarque assez facilement ([Dav93]) que w^N est un PDMP de dimension finie (v_C^N est solution d'une EDO). En observant que $\{w^N\}_N$ est tendue, on ramène le problème de martingale pour la sous-suite précédente à ce dernier, qui a la particularité que ses points d'accumulations ont leur deux premières composantes égales. Puis on passe à la limite pour des fonctions test ne dépendant que de $v^N = (v_C^N, u_D^N)$.

Cette nouvelle limite fait face au terme $\Delta_N v_C^N(t)$ qui converge vers $\Delta v_C(t)$ mais pour des topologies très faibles et inappropriées. La raison est que v_C^N converge dans l'espace

de Skorohod. Une solution est de régulariser v_C^N par une perturbation des fonctions tests. L'opérateur régularisant

$$A_\epsilon = (I_d - \epsilon\Delta)^{-2}$$

est alors introduit, et les fonctions tests φ sont perturbées comme suit:

$$\varphi_\epsilon(u_C, u_D) = \varphi(A_\epsilon u_C, u_D).$$

On passe une première fois à la limite quand $l \rightarrow \infty$ dans le problème de martingale avec les fonctions test perturbées. Puis une seconde fois quand $\epsilon \rightarrow 0$, en s'appuyant sur les propriétés régularisantes du semigroupe de la chaleur.

Pour conclure la preuve du Théorème 0.3.4, on lève l'hypothèse de troncature sur les taux des réactions, avec les arguments de [CDMR12].

0.3.4 Un modèle issu de l'épidémiologie

Le chapitre 4 à pour but essentiel de prouver une LGN puis d'investir un principe de grande déviation (PGD) pour un modèle spatial explicite d'épidémie de choléra. C'est un travail en collaboration avec Boris KOUEGOU KAMEN de Marseille.

Le choléra est une infection intestinale aigüe causée par une bactérie appelée *vibrio cholerae* et transmise oralement, par ingestion d'eau ou d'aliment souillé, ou par contact avec un liquide provenant d'une personne infectée (salive, sueur, etc...). Le *vibrio cholerae* vit et se diffuse préférentiellement dans des réservoirs d'eau souillés, où elle est dotée d'une incroyable capacité de survie.

Nous partons du modèle déterministe spatial de [BCG+10]. C'est un modèle SIRB. Les susceptibles (S) peuvent être infectés directement au contact des bactéries (B) ou des infectés (I), les infectés peuvent guérir et sont dit remis (R), et ces derniers sont immunisés pendant un certain temps. Les auteurs se concentrent sur la période épidémique de la maladie et cette dernière est plus courte que le temps avant la perte d'immunité. Par conséquent, la classe (R) n'est pas considérée. En vue du PDG, nous sommes intéressé par des temps longs, donc nous considérons le compartiment (R). En outre, les transports des bactéries sont orientés, donc les probabilités et les taux de transport ne sont pas les mêmes dans toutes les directions. Le modèle possède deux échelles de population, celle des humains que nous notons H , et celle des bactéries que nous notons K . Ce sont les paramètres de renormalisation et remise à échelle.

Dans une première partie, une loi des grands nombres (LGN) est obtenue en exploitant les techniques du chapitre 1. La grosse différence est que dans le chapitre 1, on a un modèle de réaction-diffusion, alors que dans le cas présent, il y a de l'advection en plus. On montre que si le rapport $\frac{H}{K}$ est constant et tel que $H^{-1} \log N \rightarrow 0$, alors le modèle stochastique converge vers le modèle déterministe correspondant. D'autres asymptotiques intéressantes paraissent clairement suivant la valeur du rapport des deux échelles, et sont discutées. Nous commençons par présenter les modèles. Ils sont très proches de ceux étudiés aux chapitres 1 et 2.

Modèle déterministe. C'est un vecteur $v = (S, I, R, B)$ qui donne les proportions des différents compartiments dans l'ensemble de la population et du domaine spatial (voir

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[BCG⁺10]). Comme dans les chapitres précédents, nous nous plaçons en dimension 1 en espace, sur le segment unité $J = [0, 1]$. Le modèle $v = v(t, x)$ évolue alors suivant le système

$$\begin{cases} \frac{\partial S(t, x)}{\partial t} &= \mu I(t, x) + (\mu + \rho)R(t, x) - \beta \frac{B(t, x)}{1 + B(t, x)} S(t, x) \\ \frac{\partial I(t, x)}{\partial t} &= \beta \frac{B(t, x)}{1 + B(t, x)} S(t, x) - (\gamma + \alpha + \mu)I(t, x) \\ \frac{\partial R(t, x)}{\partial t} &= \gamma I(t, x) - (\rho + \mu)R(t, x) \\ \frac{\partial B(t, x)}{\partial t} &= -\mu_B B(t, x) + \frac{Hp}{KW} I(t, x) - \nu \frac{\partial B(t, x)}{\partial x} + \mathfrak{D} \frac{\partial^2 B(t, x)}{\partial x^2}, \end{cases} \quad (0.3.8)$$

où $\mathfrak{D} > 0$ et $\nu > 0$ sont respectivement le coefficient de diffusion et la vitesse d'advection des bactéries, $\mu, \rho, \beta, \gamma, \alpha, \mu_B$ et p/W sont des coefficients positifs qui correspondent essentiellement à des taux individuels suivant lesquels les processus de naissances et de morts (les échanges entre compartiments sont inclus) affectant les populations des différents compartiments évoluent.

Sous une forme compacte, le système (0.3.8) s'écrit

$$\frac{dv(t)}{dt} = \tilde{A}v(t) + F(v(t)), \quad (0.3.9)$$

où $F = (F_S, F_I, F_R, F_B)$ est le débit des interactions non spatiales du modèle, $\tilde{A}v(t)$ est le débit des transports, \tilde{A} est l'opérateur matriciel de taille 4

$$\tilde{A} = \text{diag}(0, 0, 0, A) \quad \text{avec} \quad A = -\nu \nabla + \mathfrak{D} \Delta$$

sur $(L^2)^4 = (L^2(J))^4$, 0 étant l'opérateur identité.

L'opérateur \tilde{A} , sur $C(J)$, hérite des bonnes propriétés de l'opérateur A , et engendre un semigroupe analytique de contraction $\tilde{T}(t) = e^{\tilde{A}t}$, de sorte qu'une résolution *mild* de l'ÉDP parabolique de réaction-advection-diffusion (0.3.9) comme au chapitre 1 est possible. Pour $v_0 = v(0) \in (C^3(J))^4$ positive et bornée, on obtient une solution *mild* globale $v \in C(\mathbb{R}_+; (C^3(J))^4)$, positive et bornée, et satisfaisant

$$v(t) = \tilde{T}(t)v_0 + \int_0^t \tilde{T}(t-s)R(v(s))ds \quad \forall t.$$

On dérive de même, respectivement, le générateur infinitésimal et le débit associés:

$$\mathcal{A}\varphi(u) = \langle D\varphi(u), \tilde{A}u + F(u) \rangle \quad \text{et} \quad \psi(u) = \tilde{A}u + F(u).$$

Modèle stochastique. Le principe est le même qu'aux chapitres 1 et 2. On procède à une discrétisation régulière du segment unité J en N sites indexés par $i = 1, \dots, N$ et notés J_i . On regarde les proportions d'individus de chaque compartiment sur chaque site: $u_{S,i}^N, u_{I,i}^N, u_{R,i}^N$ et $u_{B,i}^N$ pour les susceptibles, les infectés, les remis et les bactéries,

respectivement. L'évolution du système est homogène sur chaque site, et les bactéries peuvent diffuser entre les sites. On définit les processus "spatiaux" par

$$u_S^N(t, x) = \sum_{i=1}^N u_{S,i}^N(t) \mathbb{1}_i(x),$$

pour les susceptibles, et de manière conçoordante pour les autres compartiments. Le modèle spatial global est alors donné par $u^N = (u_S^N, u_I^N, u_R^N, u_B^N)$. Son espace d'états est $(L^2(J))^4$.

Le générateur infinitésimal et le débit sont déduits selon les même principes que dans les chapitres précédents, de même que les heuristiques pour la LGN dans la limite $N, H, K \rightarrow \infty$. Le terme $\frac{Hp}{KW}$ dans l'équation limite (0.3.8) suggère un rapport H/K constant et positif à la limite. S'ajoute à cela la condition $K^{-1} \log N \rightarrow 0$ comme dans la LGN du chapitre 1 (voir Théorème 0.3.3), qui dans ces conditions est équivalente à $H^{-1} \log N \rightarrow 0$. Le résultat est le suivant.

Théorème 0.3.5. *On suppose que:*

- (i) *Le problème limite (0.3.9) est bien posé.*
 - (ii) *$N, H, K \rightarrow \infty$ de sorte que le rapport H/K reste constant et positif à la limite, et $K^{-1} \log N \rightarrow 0$.*
 - (iii) *$u^N(0) \in (H^{-1}\mathbb{N})^3 \times K^{-1}\mathbb{N}$ et $\|u^N(0) - v(0)\|_\infty \rightarrow 0$ en probabilité.*
- Alors, pour tout $T > 0$,*

$$\sup_{t \leq T} \|u^N(t) - v(t)\|_\infty \longrightarrow 0 \text{ en probabilité.}$$

Ici, la norme $\|\cdot\|_\infty$ est la somme des normes infinies des différentes composantes du processus.

La preuve du Théorème 0.3.5 est une adaptation de celle du Théorème 0.3.3.

Dans une seconde partie, nous investissons un PGD, correspondant à la LGN obtenue ci-dessus, pour $\frac{H}{K} > 0$ constant. Il s'agit d'établir des estimées de la probabilité, bien que faible étant donné la LGN, que notre modèle stochastique s'éloigne de sa limite déterministe. Pour ce faire, nous utilisons les outils usuels des grandes déviations, et en particulier l'approche convergence faible. Ce travail est inspiré par ceux de [DEW91, DK95, KL95, KOV89, PSK17, KP16, JLLV93, Tra06], qui traitent de modèles à valeurs mesures, et se rapprochent du notre, entre autres, par une variable d'évolution en plus du temps et par la dimension infinie de l'espace des états.

Un PGD est en général satisfait à travers deux conditions: une borne supérieure (borne sup) pour les sous ensembles fermés, et une borne inférieure (borne inf) pour les sous ensembles ouverts. Ces bornes sont estimées à partir d'une fonctionnelle appelée fonction(nelle) de taux. Dans le schéma classique, on identifie une fonction de taux, on retrouve les différentes formes qu'elle peut prendre (voir par exemple [DK95]), on s'assure qu'elle est une "bonne fonction de taux" (BFT) en utilisant sa forme la plus appropriée, et, à partir de la forme la plus adéquate on établit les estimées de grandes déviations.

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Dans le présent travail, nous parvenons à établir une borne sup pour les sous ensembles compacts. La borne sup pour les sous ensembles fermés s'en déduit facilement, s'il est prouvé, en plus, que le processus est exponentiellement tendu. Des efforts supplémentaires sont requis pour obtenir la tension exponentielle dans notre cas.

Remarque. Les techniques usuelles pour la tension exponentielle ne marchent pas, notamment à cause des taux de diffusion qui sont de l'ordre de N^2 et font exploser le processus. La grosse difficulté est d'obtenir une borne exponentielle du processus, en probabilité, de l'ordre de e^{-NH} . Pour se faire une idée du challenge, une borne similaire a été obtenue dans la preuve de la LGN, mais dans ce cas là, la borne est de l'ordre de e^{-H} , ce qui a permis d'utiliser la condition $H^{-1} \log N \rightarrow 0$ pour la LGN. Afin de gérer les diffusions, l'argument a été d'accélérer le temps en observant la dynamique sur des intervalles de temps de longueur N^{-2} . Cependant la démarche ne semble pas s'adapter facilement dans le nouveau cadre mais encore, il n'est pas garanti que la méthode fournisse un ordre de grandeur satisfaisant.

Nous commençons par représenter le processus u^N avec le changement de temps aléatoire présenté dans [EK86]:

$$u_t^N = u_0^N + \frac{1}{H} \sum_{i=1}^N \sum_{j=1}^{14} \tilde{g}_{i,j} P_{i,j} \left(H \int_0^t \beta_{i,j}^N(u_s^N) ds \right), \quad (0.3.10)$$

où les $(P_{i,j})_{i,j}$ sont des processus de Poisson standards mutuellement indépendants. On note

$$P_{i,13} := P_{i \rightarrow i+1,13} \text{ et } P_{i \rightarrow i-1,14} := P_{i,14}$$

les processus de Poisson capturant les transferts spatiaux des bactéries, $M_{i,j}(a) = P_{i,j}(a) - a$ les processus de Poisson compensés (qui sont en fait des martingales centrées).

On distingue, d'une part, les **directions de sauts compartimentales**

$$\begin{aligned} g_1 &:= (1, 0, 0, 0) & g_2 &:= (1, 0, 0, 0) & g_3 &:= (1, 0, 0, 0) & g_4 &:= (-1, 0, 0, 0) \\ g_5 &:= (-1, 1, 0, 0) & g_6 &:= (0, -1, 0, 0) & g_7 &:= (0, -1, 0, 0) & g_8 &:= (0, -1, 1, 0) \\ g_9 &:= (0, 0, -1, 0) & g_{10} &:= (1, 0, -1, 0) & g_{11} &:= (0, 0, 0, -\frac{1}{\mathcal{R}}) & g_{12} &:= (0, 0, 0, \frac{1}{\mathcal{R}}) \\ g_{13} &:= (0, 0, 0, \frac{1}{\mathcal{R}}), \end{aligned}$$

et, d'autre part, les **directions de sauts spatio-compartimentales**

$$\tilde{g}_{i,j} = \begin{cases} g_j \mathbb{1}_i & \text{pour } j = 1, \dots, 12 \\ (\mathbb{1}_{i+1} - \mathbb{1}_i) g_{13} & \text{si } j = 13 \\ (\mathbb{1}_{i-1} - \mathbb{1}_i) g_{13} & \text{si } j = 14, \end{cases}$$

pour $i = 1, \dots, N$. Le paramètre d'échelle \mathcal{R} apparaissant dans les directions des sauts qui modifient le compartiment des bactéries est dû au *scaling* $H/K =: \mathcal{R}^{-1}$.

Les taux de sauts $\beta_{i,j}^N : (\mathbb{H}^N)^4 \rightarrow \mathbb{R}_+$ sont des fonctions positives définies par

$$\beta_{i,j}^N(u^N) = \beta_j^N(u^N(i)) \quad \forall j = 1, \dots, k,$$

pour tout $u^N = (u_S^N, u_I^N, u_R^N, u_B^N) \in (\mathbb{H}^N)^4$, où les $\beta_j^N : \mathbb{R}_+^4 \rightarrow \mathbb{R}_+$ sont des fonctions positives explicites définies comme suit: pour tout $y = (y_1, y_2, y_3, y_4) \in \mathbb{R}_+^4$,

$$\begin{aligned} \beta_1^N(y) &= \mu y_1 & \beta_2^N(y) &= \mu y_2 & \beta_3^N(y) &= \mu y_3 & \beta_4^N(y) &= \mu y_1 & \beta_5^N(y) &= \beta \frac{y_4}{1+y_4} y_1 \\ \beta_6^N(y) &= \mu y_2 & \beta_7^N(y) &= \alpha y_3 & \beta_8^N(y) &= \gamma y_2 & \beta_9^N(y) &= \mu y_3 & \beta_{10}^N(y) &= \rho y_3 \\ \beta_{11}^N(y) &= \mu_B y_4 & \beta_{12}^N(y) &= \frac{P}{W} y_2 & \beta_{13}^N(y) &= \ell \mathcal{P}_{out} y_4 & \beta_{14}^N(y) &= \ell \mathcal{P}_{in} y_4. \end{aligned} \quad (0.3.11)$$

On remarque que les taux de sauts **non spatiaux** β_j^N , $j = 1, \dots, 12$, ne dépendent pas de N . Ils s'étendent à $(L^2([0, 1]))^4$:

$$\beta_j(\phi)(x) = \beta_j^N(\phi(x)), \quad \forall \phi \in (L^2([0, 1]))^4. \quad (0.3.12)$$

On fixe $T > 0$. Rappelons que u^N est càdlàg, à valeurs $D([0, T]; (L^2[0, 1])^4)$, et sa limite LGN v est absolument continue, à valeurs $\mathcal{AC}([0, T]; (\mathcal{C}^3[0, 1])^4)$. Pour $\phi \in \mathcal{AC}([0, T]; (L^2[0, 1])^4)$, on note $\dot{\phi}(t, \cdot) = \dot{\phi}_t(\cdot)$ la dérivée faible de ϕ en t . Notre première forme de la fonctionnelle de taux est

$$I_T(\phi) = \begin{cases} \int_0^T L(\phi_t, \dot{\phi}_t) dt & \text{si } \phi \in \mathcal{AC}([0, T]; (\mathcal{C}[0, 1])^4) \\ +\infty & \text{sinon,} \end{cases} \quad (0.3.13)$$

avec

$$L(\phi_t, \dot{\phi}_t) = \sup_{f \in (\mathcal{C}^3[0, 1])^4} \{ \langle \dot{\phi}_t, f \rangle - \Lambda(\phi_t, f) \},$$

où

$$\Lambda(\phi_t, f) = \sum_{j=1}^{12} \langle \beta_j(\phi_t), e^{(g_j|f)} - \mathbf{1} \rangle + \langle (g_{13} | \phi_t), e^{-(g_{13}|f)} A^* e^{(g_{13}|f)} \rangle, \quad (0.3.14)$$

$\langle \cdot, \cdot \rangle$ étant le produit scalaire sur $L^2[0, 1]$ ou sur $(L^2[0, 1])^4$, de façon conséquente. On note que $I_T(\phi) = 0$ si ϕ est solution de l'équation limite (0.3.9). Même si elle suit la démarche classique qui consiste à calculer la transformée de Legendre de l'Hamiltonien du système, l'identification de I_T n'est pas évidente. Avant de procéder aux estimées annoncées, on introduit la notation

$$I_T(B) := \inf_{\phi \in B} I_T(\phi), \quad \forall B \subset D([0, T]; (L^2[0, 1])^4).$$

Ensuite, à partir d'un résultat utile plutôt classique de la théorie du contrôle et de la formule d'Itô comme notre processus est à variation bornée, on retrouve une forme plus adéquate de la fonction de taux, en permutant le symbole \sum et l'intégrale dans (0.3.13): pour $\phi \in \mathcal{AC}([0, T]; (\mathcal{C}[0, 1])^4)$,

$$I_T(\phi) = \sup_{f \in \mathcal{C}^{1,3}([0, T] \times [0, 1])} \left\{ \langle \phi_T, f_T \rangle - \langle \phi_0, f_0 \rangle - \int_0^T \langle \phi_t, \frac{\partial f_t}{\partial t} \rangle dt - \int_0^T \Lambda(\phi_t, f_t) dt \right\}. \quad (0.3.15)$$

0.4 Perspectives

À ce stade, il n'est pas difficile de voir que la fonction I_T est positive et semicontinue inférieurement.

La borne sup du PGD pour les compacts est donnée par le résultat suivant, où $u^{N,H} \equiv u^N$.

Theorem 0.3.1. *Soit \mathbf{K} un sous ensemble compact de $D\left([0, T]; (L^2[0, 1])^4\right)$.*

Si $u_0 \in (L^2([0, 1]))^4$ est tel que

$$\lim_{N, H \rightarrow \infty} \|u^{N,H}(0) - u_0\|_2 = 0$$

et

$$\sup_{N \in \mathbb{N}} \|u_0^N\|_{0,\infty} \leq C_0 \quad \text{pour un } C_0 > 0, \quad (0.3.16)$$

alors

$$\limsup_{H, N \rightarrow \infty} \frac{1}{NH} \log \mathbb{P} [u^N \in \mathbf{K}] \leq -I_T(\mathbf{K}) \quad (0.3.17)$$

Ici, $\|\cdot\|_2$ est la somme des normes L^2 des différentes composantes.

Le schéma de preuve demeure plutôt classique. On commence par retrouver certaines martingales exponentielles associées au processus et faisant intervenir la fonction de Young $\tau(x) = e^x - 1 - x$. On en déduit une borne sup dite locale. Il s'agit de montrer que pour toute trajectoire càdlàg ϕ et toute perturbation d'ordre $\delta > 0$ de la fonction de taux, on sait construire un voisinage ouvert $U_{\phi,\delta}$ de la trajectoire, pour lequel une borne sup est satisfaite, avec la fonction de taux perturbée. L'obtention de la borne sup pour les sous-ensembles compacts s'en déduit relativement facilement.

0.4 Perspectives

Conditions aux limites spatiales. Nous travaillons avec une condition périodique au bord de notre domaine spatial. D'autres conditions aux limites peuvent être explorées. Par exemple, la condition de Dirichlet (voir [Arn80]) pour laquelle on s'intéresse aux solutions d'ÉDPs nulles (ou plus généralement constantes) sur le bord, ou la condition de Neumann (voir [Kot88a]) pour laquelle les solutions admissibles sont de dérivée nulle (ou plus généralement, constantes) sur le bord. Selon la problématique abordée, l'une ou l'autre de ces conditions pourrait être plus appropriée.

Dimensions supérieures en espace. Il serait également intéressant d'étendre les modèles à la dimension 2, puis 3, en espace, afin de les rendre plus réalistes. Nous pensons cela possible sans trop d'effort, mais au moins au prix de notations beaucoup plus complexes. Il faudra aussi faire attention aux résolutions des ÉDPs dans les différents chapitres concernés. Pour des travaux dans ce sens nous renvoyons à [Kot88a, Blo94].

Autres géométries spatiales. Les modèles pourraient aussi être généralisé à d'autres types de géométrie spatiale: disque, cylindre, sphère, etc ... Ce point vient en quelque sorte compléter les deux précédents.

Approximations d'ordre 2. Une question naturelle après des approximations d'ordre 1 telles que développées pour les modèles spatiaux (résultats de type LGN) est celle des approximations à l'ordre suivant. Tout d'abord, améliorer le TCL obtenu dans le cadre homogène (chapitre 1) à des cas à plusieurs réactions lentes.

Puis un TCL peut être investi pour la limite déterministe obtenue au chapitre 2 et la limite hybride du chapitre 2. Par ailleurs des approximations par des diffusions seraient aussi intéressantes. Heuristiquement, ces dernières sont obtenues à partir d'un développement de Taylor dans le générateur infinitésimal, en remarquant que le générateur tronqué à l'ordre deux est celui d'une diffusion (voir [EK86], chap. 11).

Autres types d'interactions. Après avoir séparé l'ensemble des réactions $\mathfrak{R} = \mathfrak{R}_C \cup \mathfrak{R}_{DC} \cup \mathfrak{R}_D$ selon les espèces qu'elles induisent dans la modélisation multi-échelle, plusieurs cas d'interactions sont envisageables pour les réactions mixtes $r \in \mathfrak{R}_{DC}$. Dans cette thèse, nous avons considéré le cas d'interactions où certaines de ces réactions, dans un ensemble S_1 sont rapides et affectent seulement l'espèce continue C , tandis que les autres sont lentes et affectent C et D (voir Hypothèse 0.3.1 pour le chapitre 1, et Hypothèse 0.3.2 pour les chapitres 2 et 3).

Cela correspond au cas où un PDMP continu est obtenu à la limite dans [CDMR12]. D'autres cas y sont discutés. Par exemple, en considérant que les réactions mixtes dans S_1 affectent aussi l'espèce discrète D (ie $\gamma_r^D \neq 0$, $r \in S_1$), les résultats obtenus ne sont plus valides. La limite formelle du générateur n'est plus possible car la variable discrète X_D a désormais une dynamique rapide. Pour simplifier un tel modèle combinant les dynamiques lentes et rapides, l'idée est de faire de la moyennisation en la variable X_D .

Obtenir un PGD complet. Il s'agit tout d'abord de généraliser aux sous ensembles fermés la borne sup obtenues pour les compacts, en prouvant la tension exponentielle de la suite de processus.

Puis c'est au tour de la borne inf, qui est assez souvent la partie la plus difficile dans l'établissement d'un PGD. L'approche standard consiste à obtenir une forme "non-variationnelle" de la fonction de taux, puis d'appliquer un changement de mesure de probabilité de Girsanov adéquat pour conclure. La pratique usuelle pour avoir cette forme non-variationnelle ([PSK17, KP16, Tra06, KL95, DK95]) consiste à utiliser un théorème de représentation (de Riesz, généralisé parfois) sur des espaces tels que l'espace d'Orlicz. Nous n'y sommes pas arrivés, mais pensons que cela est possible.

Une autre approche ([KOV89, JLLV93]) consiste à perturber le modèle initial, notamment ses taux, et à établir une borne inf correspondant. Les taux sont perturbés en vue du changement de mesure de Girsanov, de sorte que tout se passe bien. La perturbation arrive avec de nouveaux challenges. Il faut s'assurer que le problème limite perturbé est bien posé, et qu'une LGN est toujours satisfaite pour le modèle perturbé. Cette approche nous paraît la plus appropriée.

Plus encore sur les temps longs. On pourrait s'intéresser aux différentes approximations en grandes populations, mais pour des observations du processus sur des fenêtres de temps $[0, T]$, lorsque $T = +\infty$.

Simulation. Des exploitations pour dériver de nouveaux algorithmes.

0.4 Perspectives

Extension à d'autres domaines. Idéalement, nous visons une base beaucoup plus générale de modélisation, intégrant des systèmes complexes issus d'autres domaines que nous n'avons pas abordés ici, chacun avec ses spécificités (voir par exemple les champs d'application, Section [0.2.3](#)).

CHAPTER 1

Central limit theorem for a multiscale stochastic homogeneous gene network

Abstract. In a recent work, a multiscale stochastic homogeneous gene network has been rigorously approximated by a continuous piecewise deterministic Markov process. In this chapter, a central limit theorem is performed for that hybrid approximation. The classical methods that are used to derive central limit theorems corresponding to the standard laws of large numbers in the one scale case fail in the multiscale context, due to the presence of discrete species. A time change is introduced, in order for the discrete component to coincide with its limit. A unique slow reaction is considered, and an unexpected central limit theorem is obtained, with many additional terms compared to the usual case. The limiting process is a part of an easily identified piecewise diffusion Markov process with jumps.

1.1 Introduction

The importance of stochastic modeling for gene regulatory networks has become an evidence, as pointed out by [KE01], [KvO07] and [RMC07b]. One of the great challenges when dealing with the related stochastic models is their simulation, which appears very often to be very prohibitive when using directly stochastic simulation algorithms (SSA) of Gillespie [Gil76]. We refer, for instance, to [KZZ01] and [KBR05]. Different solutions are then proposed. Some of them are based on mathematical simplification theorems such as the Law of Large Numbers (LLN), the Central Limit Theorem (CLT) and diffusion approximation. Others rely on different algorithmic acceleration techniques.

A gene network can be modeled as a biochemical system of interacting molecules that can move within a spatial domain (see e.g. [SHMC13] or [RMC07b, CDR09, CDMR12]). Following pioneer works of Delbrück [Del40], the standard stochastic models are markovian. We are interested in systems with the homogeneous and multiscale properties. Homogeneity is related to the space. It holds when the spatial effects are negligible beside the interactions between the molecules. Multiscaling takes into account the difference of abundance between the molecules. In standard one scale systems, all the molecules have the same order of population. In order to simplify the model, we study the behaviour of such systems, when the global initial population is large.

First order approximations of one scale large population stochastic biochemical systems usually lead to deterministic limits. The principle behind these results is known as the LLN. This latter states that, with an appropriate renormalization, the stochastic model asymptotically behaves like its deterministic counterpart, in a large population limit. A CLT often

follows a LLN and is complementary to it. It is a second order approximation result which gives the speed of the convergence indicated by the LLN. The CLT captures the fluctuations of the stochastic model around its deterministic homologue. It is a very useful tool when dealing with the question of quantifying what size of the population is "large enough" in order to get a LLN, and a very powerful tool in statistics. The LLN as well as the corresponding CLT have been investigated and established by Thomas G. Kurtz in several papers, for one scale homogeneous models (see [Kur70, Kur71, Kur81, EK86]). Application fields are various, and include chemical reaction systems, epidemiology and finance.

The multiscale framework started being investigated later and is still being explored (see e.g. [AEZ16] for cell regulatory networks and enzyme cascade, or [NCS15] for molecular communication). Widely motivated by computational and optimal control purposes, its expansion has given birth to the concepts of hybrid algorithm and hybrid approximation. Several hybrid algorithms are accelerated by treating fast biochemical reactions as continuous variables ([HR02], [ACT⁺04]). This is motivated by the LLN, by the Langevin's approximation which is related to the CLT, and/or by the diffusion approximation for Markov processes [BKPR06].

In [RMC07b, CDR09], the authors proposed that the dynamic of gene networks with well-separated abundances can be well approximated by Piecewise Deterministic Markov Processes (PDMPs). These latter were introduced by Davis [Dav84, Dav93]. They are used in operational research, in relation with optimal control and various technological applications. They are generalized by Stochastic Hybrid Systems (SHS) [PBLB03, BL04, BLE06, CE06], which provide a natural way of approximating and thus modeling multiscale systems. However, the justification of that consideration is not always rigorous.

In a recent work [CDMR12], the authors of [RMC07b, CDR09] have rigorously approximated a multiscale stochastic homogeneous gene network by a continuous PDMP. Though it is a first order approximation result, this hybrid approximation differs from a classical LLN in that the limit remains a stochastic process. The aim of this chapter is to proceed to the approximation at the second order in the case of that hybrid approximation. That is we give a corresponding CLT.

Compared to the classical LLNs obtained in one scale contexts, there are two main difficulties in the present multiscale context. They are related to the stochastic nature of the dynamic of the low scale component at the limit. The first difficulty is to obtain, on the same probability space, an almost sure convergence for both components and the martingale defined by the jumps of the high scale one. Secondly, one naturally expects a CLT for the high scale component whose limit behavior is deterministic. The problem is then the coupling between the dynamics of both components which have different speeds of convergence. In fact, a chosen speed of convergence for the high scale component creates a term of the product of that speed with the low scale component, and that term diverges. We handle this problem with a time change that we introduce in order for the low scale component to coincide with its limit. This somehow accelerates the slow dynamic which reaches its limit faster. However, we can only proceed when the model has a unique slow reaction.

The rest of this chapter is structured as follows. In section 2, we briefly discuss some classes of Stochastic Hybrid Systems we are interested in. Section 3 is devoted to the different hybrid approximation results. We first recall the hybrid approximation of [CDMR12]. Afterward, we prove a weak convergence for the process whose components are the initial model and the martingale defined by the jumps of its high scale component. This provides a solution to the first difficulty mentioned above. It also provides a partial CLT for the related martingale. We finally state and prove a more general CLT for the high scale component of the model.

1.2 Stochastic Hybrid Systems in finite dimension

We discuss two particular classes of General Stochastic Hybrid Systems (GSHS) in finite dimension: Piecewise Deterministic Processes (PDPs) and Switching Diffusion Systems (SDS) that we call Piecewise Diffusion Processes (PDifPs). We give summary descriptions. For in depth discussions, we refer to [Dav93] for PDPs in particular, and, to [BLE06], [CE06] or [Bec07] for GSHS in general, among others. The formalism of Blom, Lygeros and co-authors in [BLE06] is sufficient for our purpose, since we are not concerned with jump diffusions as Lévy processes in this work (that case is treated in [CE06]). The approach is based on a construction as in [Dav93], and the idea is to extend Davis' considerations, allowing "continuous" diffusions, in addition to deterministic motions between consecutive jumps.

1.2.1 Piecewise Deterministic Processes

We start with PDPs on which we collect useful results. Let $(\Omega, \mathcal{F}, (\mathcal{F}_t)_{t \geq 0}, \mathbb{P})$ denote a filtered probability space. We define a standard PDP with values in $E = \mathbb{R}^n \times \mathbb{N}^d$ as a non-exploding stochastic process $(x(t))_{t \geq 0} = (x_C(t), X_D(t))_{t \geq 0}$ determined by its three characteristics:

(1) *Vector fields.* For all $\nu \in \mathbb{N}^d$, there exists a vector field F_ν of class C^1 in \mathbb{R}^n , which determines a unique global flow $\phi_\nu(t, y)$ in \mathbb{R}^n such that, for $t > 0$,

$$\frac{d}{dt} \phi_\nu(t, y) = F_\nu(\phi_\nu(t, y)), \quad \phi_\nu(0, y) = y \quad \forall y \in \mathbb{R}^n. \quad (1.2.1)$$

We often use the notation: $F(y, \nu) = F_\nu(y)$ and $\Phi_\nu(t, y) = \Phi(t, y, \nu)$.

(2) *A jump rate.* $\lambda : E \rightarrow \mathbb{R}_+$ measurable, and $\forall x = (y, \nu) \in E, \forall T \in \mathbb{R}_+^*$

$$\int_0^\infty \lambda(\phi_\nu(t, y), \nu) dt = \infty \quad \text{while} \quad \int_0^T \lambda(\phi_\nu(t, y), \nu) dt < \infty.$$

Often, we also use the notation $\lambda_\nu(y) = \lambda(y, \nu)$.

(3) *A transition measure.* $Q : E \rightarrow \mathcal{P}(E)$, $x \mapsto Q(\cdot; x)$, where $\mathcal{P}(E)$ denotes the set of probability measures on E . We assume that $Q(\{x\}; x) = 0$ for each $x \in E$, and $Q(A; \cdot)$ is measurable as a mapping $x = (y, \nu) \mapsto Q(A; x)$, for every fixed Borel subset A of E . We may also use the notation $Q_\nu(A; y) = Q(A; y, \nu)$.

Between jumps, $x = (x_C, X_D)$ has a deterministic dynamic. While X_D is constant, x_C evolves according to the flow satisfying (1.2.1). Then, a jump occurs with respect to the jump rate, and the target state after a jump is determined by the transition measure.

Existence and extended generator. A càdlàg sample path $\{x(t), t > 0\}$ starting at $x(0) = (x_C(0), x_D(0)) = (y, \nu) = x_0^1 \in E$ can be constructed for such a process with usual methods. The process is given by $x(t) = (\phi_\nu(t, x), \nu)$ for $0 \leq t < T_1$, where T_1 is the first jump time. Denoting τ_1 the waiting time of the first jump, $\tau_1 = T_1$ and

$$\mathbb{P}_{x_0}(\tau_1 > t) = \exp\left(-\int_0^t \lambda(\phi_\nu(s, y), \nu) ds\right) =: H_1(t, x_0), \quad t \in \mathbb{R}_+. \quad (1.2.2)$$

At time $t = T_1^-$, $x(T_1^-) = (\phi_\nu(T_1, y), \nu)$. Next, the target state $x(T_1)$ has the distribution

$$\mathbb{P}_{x_0}\{x(T_1) \in A | T_1 = t\} = Q(A; (\phi_\nu(t, y), \nu)),$$

¹ x_0 can be either an \mathcal{F}_0 -measurable random variable or a constant

for every Borel set A of E , and $t > 0$. Afterward the process restarts at $x(T_1)$, and one proceeds recursively according to the same procedure to obtain a sequence of independent jump waiting times τ_1, τ_2, \dots , a sequence of jump times T_1, T_2, \dots , with $T_k = \tau_1 + \dots + \tau_k$ for all $k \geq 1$.

Such a process is a PDP. The number of jumps that occur between the times 0 and t is denoted by

$$N_t = \sum_{k \geq 1} \mathbb{1}_{(T_k \leq t)}.$$

Non-explosion is insured (see [Dav93], p.60) by

Assumption 1.2.1. $\mathbb{E}_x[N_t] := \mathbb{E}[N_t | x(0) = x] < \infty, \quad \forall x \in E \quad \forall t \geq 0.$

Furthermore, a PDP can be constructed as above in some probability space, to be a strong Markov càdlàg process (see [Dav93], p.62-64 and Theorem 25.5). Thus it is called a Piecewise Deterministic Markov Process (PDMP). Its extended generator \mathcal{A} is then given by

$$\mathcal{A}f(x) = \nabla_y f(x) \cdot F(x) + \lambda(x) \int_E (f(z) - f(x)) Q(dz; x), \quad (1.2.3)$$

for $x = (y, \nu) \in E$, for test functions $f : E \rightarrow \mathbb{R}$ of class C^1 w.r.t. y . Here, ∇_y is the gradient w.r.t. the variable $y \in \mathbb{R}^n$. We do not need to consider the whole domain of the operator \mathcal{A} , and just note that \mathcal{A} is well defined for $f \in C_b^{1,0}(E)$ as considered in [CDMR12]. Still, the generator has a much larger domain as shown by Davis in [Dav93], Section 26.

Remark 1.2.1. The PDMPs we have described are quite general, in the sense that they allow jumps for both components. When the continuous component has continuous trajectories, the PDMP is said to be continuous. Otherwise, it is a jumping PDMP. One can distinguish other levels of specificity for PDMPs (see e.g. [CDR09, CDMR12]).

1.2.2 Piecewise Diffusion Processes

Here, we briefly present GSHS (see [BLE06, CE06, Bec07]). We call them Piecewise Diffusion Processes (PDifPs) in comparison with PDPs introduced in the previous section.

Let $(\Omega, \mathcal{F}, (\mathcal{F})_{t \geq 0}, \mathbb{P})$ denote a filtered probability space. We define a standard PDifP with values in $E = \mathbb{R}^n \times \mathbb{N}^d$ as a non-exploding stochastic process $(x(t))_{t \geq 0} = (x_C(t), X_D(t))_{t \geq 0}$ determined by its three characteristics:

(1) *A family of drift and diffusion coefficients.* For all $\nu \in \mathbb{N}^d$, there exists a vector field b_ν in \mathbb{R}^n and an $n \times n$ matrix a_ν with real coefficients, which determine a unique Itô diffusion flow $\Phi_\nu(t, y) = \Phi(t, y, \nu) \in \mathbb{R}^n$, solution to the initial value SDE

$$\begin{cases} \partial_t \Phi_\nu(t, y) = b_\nu(\Phi_\nu(t, y)) dt + a_\nu(\Phi_\nu(t, y)) dW(t) \\ \Phi_\nu(0, y) = y, \end{cases} \quad (1.2.4)$$

given any initial data $y \in \mathbb{R}^n$. Here, $W = (W(t), t \geq 0)$ is the standard n -dimensional brownian motion. We often adopt the notation $b_\nu(y) = b(y, \nu)$ and $a_\nu(y) = a(y, \nu)$ for $(y, \nu) \in E$, considering b and a as functions defined on E . It is well known (see e.g. [Arn74] or [Kun90]) that the flow satisfying (1.2.4) exists and is unique when the drift vector b and the diffusion matrix a are Lipschitz continuous in their first variable y , for instance.

(2) *A jump rate.* $\lambda : E \rightarrow \mathbb{R}_+$ measurable, and such that $\forall x = (y, \nu) \in E, \forall T \in \mathbb{R}_+^*$,

$$\int_0^T \lambda(\Phi_\nu(t, y), \nu) dt < \infty \quad \text{while} \quad \int_0^\infty \lambda(\Phi_\nu(t, y), \nu) dt = \infty.$$

1.2 Stochastic Hybrid Systems in finite dimension

The notation $\lambda_\nu(y) = \lambda(y, \nu)$ is also used often.

(3) *A transition measure.* $Q : E \rightarrow \mathcal{P}(\mathbb{N}^d)$, where $\mathcal{P}(\mathbb{N}^d)$ denotes the set of probability measures on \mathbb{N}^d equipped with the discrete topology. We assume that $Q(\{x\}; x) = 0$ for each $x \in E$, and $Q(A; \cdot)$ is measurable as a mapping $x = (y, \nu) \mapsto Q(A; x)$, for every fixed Borel subset A of E . We may also use the notation $Q_\nu(A; y) = Q(A; y, \nu)$.

Between jumps, $x = (x_C, X_D)$ has a diffusion dynamic. While X_D is constant, x_C evolves according to the flow satisfying (1.2.4). Then, a jump occurs with respect to the jump rate, and the target state after a jump is determined by the transition measure.

Existence and extended generator. A càdlàg sample path $\{x(t), t > 0\}$ for such a process can be constructed as follows.

- One starts from an initial value $x(0) = (x_C(0), X_D(0)) = (y, \nu) = x_0 \in E$ which can be an \mathcal{F}_0 -measurable random variable or deterministic. Then, for $t \in [0, T_1)$, $X_D(t) = \nu$ is constant and $x_C(t)$ satisfies

$$\begin{cases} dx_C(t) = b(x_C(t), \nu)dt + a(x_C(t), \nu)dW(t) \\ x_C(0) = y, \end{cases}$$

that is

$$x_C(t) = \Phi(t, y, \nu) = \Phi_\nu(t, y), \quad \forall t \in [0, T_1).$$

Here T_1 is the time of the first transition. The corresponding waiting time τ_1 satisfies $\tau_1 = T_1$ and has the survivor function

$$\mathbb{P}_{x_0}(\tau_1 > t) = \exp\left(-\int_0^t \lambda(\Phi_\nu(s, y), \nu_0)ds\right) =: H_2(t, x_0), \quad (1.2.5)$$

defined for all $(t, x) \in \mathbb{R}_+ \times E$.

- At time $t = T_1^-$, $x(T_1^-) = (\Phi_\nu(T_1, y), \nu)$. When a transition occurs at time T_1 , the target state $x(T_1) = (x_C(T_1), X_D(T_1))$ is determined by the target state of $X_D(T_1)$ (which is the only jumping component). It has the distribution

$$\mathbb{P}_{x_0}(X_D(T_1) \in A | T_1 = t) = Q_\nu(A; \Phi_\nu(t^-, y), \nu),$$

for all $A \subset \mathbb{N}^d$, $t > 0$.

- We then restart the process at $x(T_1)$ and proceed recursively according to the same procedure to obtain a sequence of independent transition waiting times τ_1, τ_2, \dots , and a sequence of times of transition T_1, T_2, \dots , satisfying $T_k = \tau_1 + \dots + \tau_k$ for all $k \geq 1$.

Such a process is a PDiFP. The number of jumps that occur between the times 0 and t is denoted by

$$N_t = \sum_k \mathbb{1}_{(T_k \leq t)}.$$

Again we ensure non-explosion by assuming, as a standard condition:

Assumption 1.2.2. $\mathbb{E}_x[N_t] := \mathbb{E}[N_t | x(0) = x] < \infty, \quad \forall x \in E \quad \forall t \in \mathbb{R}_+^*.$

Also, a PDiFP can be constructed as above in some probability space, to be a strong Markov càdlàg process (see Proposition 5, Section 4, Chapter 1 of [BLE06]). We then call it a Piecewise Diffusion Markov Process (PDifMP). Its extended generator \mathcal{A} reads

$$\mathcal{A}f(y, \nu) = \mathcal{A}_{diff}f(y, \nu) + \lambda(y, \nu) \int_{\mathbb{N}^d} (f(y, \xi) - f(y, \nu))Q(d\xi; y, \nu), \quad (1.2.6)$$

for all $(y, \nu) \in E$, for test functions f of class C^2 w.r.t. y . Here, setting $x = (y, \nu)$,

$$\begin{aligned} \mathcal{A}_{dif}f(x) &= \sum_{i=1}^n b_i(x) \partial_i f(x) + \frac{1}{2} \sum_{i,j=1}^n (aa^T)_{ij}(x) \partial_i \partial_j f(x) \\ &= \nabla_y f(x) \cdot b(x) + \frac{1}{2} \text{Tr} [(aa^T)(x)(\nabla_y \nabla_y^T) f(x)] = \mathcal{A}_{dif}f(y, \nu) \end{aligned} \quad (1.2.7)$$

where $\nabla_y f(x) = (\partial_i f(x))_{i \leq i \leq n}$, with

$$\partial_i f(x) = \partial_i f(y, \nu) = \partial_i f_\nu(y) = \frac{\partial f_\nu}{\partial y_i}(y)$$

for $y = (y_1, \dots, y_n)$, for all $i = 1, \dots, n$. Next, $\nabla_y f(x) \cdot b(x)$ is the inner product between the two vectors of \mathbb{R}^n , $a(x)^T$ is the transpose matrix of $a(x)$, ∇_y^T is the transpose vector operator of ∇_y , and

$$(\nabla_y \nabla_y^T) f(x) = (\partial_i \partial_j f(x))_{i,j=1, \dots, n} = \left(\frac{\partial^2 f_\nu}{\partial y_i \partial y_j}(y) \right)_{i,j=1, \dots, n}$$

is the Hamilton operator.

Remark 1.2.2. As one would expect, PDifMPs extend PDMPs in that the latter is formally obtained from the former by letting the diffusion matrix a vanish. The drift vector of the PDifMP are exactly the vector fields of the PDMP. More rigorous comparisons are made in [PBLB03]. As for PDMPs, when the continuous component of a PDifMP has continuous trajectories, that PDifMP is said to be continuous. Otherwise, it is a jumping PDifMP. The different states of the discrete component X_D are often denoted *modes* (see e.g. [BLE06, CE06]). When X_D jumps from one mode to another, the dynamic of the continuous component x_C changes. This phenomenon is usually called a *switching*.

1.2.3 Multiscale homogeneous stochastic regulatory networks

We present a multiscale stochastic homogeneous model for gene regulatory networks. It is a real vector valued pure jump Markov process, and thus, in particular, a very simple example of a jump PDMP with a zero vector field.

Markov jump model: known results. We consider a finite set of chemical reactions $r \in \mathfrak{R}$, involving species indexed by a set $S = 1, \dots, M$. The population size of the species i is denoted by n_i , and $X \in \mathbb{N}^M$ is the vector consisting of the n_i 's. Each reaction r has a rate $\lambda_r(X)$ which depends on the state of the system, described by X , and corresponds to a change $X \rightarrow X + \gamma_r$; $\gamma_r \in \mathbb{Z}^M$ gives informations about the stocheometric coefficients of the reaction r . We call γ_r the jump height associated to the reaction r , and $x \mapsto \Psi_r(x) = \gamma_r \lambda_r(x)$ is the debit associated with r . The vector field $\Psi : \mathbb{R}^M \rightarrow \mathbb{R}^M$ defined by

$$\Psi(x) = \sum_{r \in \mathfrak{R}} \gamma_r \lambda_r(x) \quad (1.2.8)$$

is the global debit function of the model.

Mathematically, this evolution can be described by a Markov jump process based on a sequence $(\sigma_i)_{i \geq 1}$ of random waiting times with exponential distribution. Setting $S_0 = 0$,

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$S_k = \sigma_1 + \dots + \sigma_k$, X is constant on $[S_{k-1}, S_k)$ and has a jump at S_k . The parameter of τ_k is given by $\sum_{r \in \mathfrak{R}} \lambda_r(X(S_{k-1}))$, and one has

$$\mathbb{P}(\sigma_k > t) = \exp\left(-\sum_{r \in \mathfrak{R}} \lambda_r(X(S_{k-1}))t\right).$$

At time S_k , a reaction $r \in \mathfrak{R}$ is chosen with probability $\lambda_r(X(S_{k-1})) / \sum_{r \in \mathfrak{R}} \lambda_r(X(S_{k-1}))$, and the state changes according to $X \rightarrow X + \gamma_r$, that is $X(S_k) = X(S_{k-1}) + \gamma_r$. Such a Markov process admits the infinitesimal generator

$$Af(\nu) = \sum_{r \in \mathfrak{R}} [f(\nu + \gamma_r) - f(\nu)] \lambda_r(\nu),$$

for test functions $f \in C_b(\mathbb{R}^M)$ (see [EK86]).

Multiscaling. Now, we take into account the fact that the populations may have different size scales. Some species may be abundant while others may not. Accordingly, we divide the set of species in two sets C and D , with cardinals M_C and M_D respectively. This induces the decompositions $\mathbb{N}^M = \mathbb{N}^{M_C} \times \mathbb{N}^{M_D}$, $X = (X_C, X_D)$, $\gamma_r = (\gamma_r^C, \gamma_r^D)$. For $i \in D$, n_i is of order 1 whereas for $i \in C$, n_i is proportional to a large number N . For $i \in C$, setting $n_i^N = n_i/N$, n_i^N is of order 1. We define $x_C^N = N^{-1}X_C$, $X_D^N = X_D$ and $x^N = (x_C^N, X_D^N)$. Then $x^N \in E = \mathbb{R}^{M_C} \times \mathbb{N}^{M_D}$ and species in C (resp. D) are said to be continuous (resp. discrete). As it lies in a continuous (resp. discrete) space, x_C^N (resp. X_D^N) is called the continuous (resp. discrete) component of the scaled process.

We also decompose the set of reactions according to the species involved:

$$\mathfrak{R} = \mathfrak{R}_C \cup \mathfrak{R}_{DC} \cup \mathfrak{R}_D.$$

Reactions in \mathfrak{R}_C (resp. \mathfrak{R}_D) as well as their rates depend only on X_C (resp. X_D), and they are fast (resp. slow). We call \mathfrak{R}_C (resp. \mathfrak{R}_D) the set of pure fast reactions (resp. pure slow reactions). On the contrary, reactions in \mathfrak{R}_{DC} have rates depending on both X_C and X_D . They produce or consume species from C , D or both. The set \mathfrak{R}_{DC} is that of mixed reactions. These reactions can be either fast or slow, depending on their specificities, in relation to a specific model.

We assume the following.

Assumption 1.2.3. *Density dependence holds for fast reactions. Namely, if a reaction $r \in \mathfrak{R}$ is fast, then there exist a function $\tilde{\lambda}_r$ such that the rate λ_r of r satisfies*

$$\lambda_r(X) = \lambda_r(X_C, X_D) = N\tilde{\lambda}_r\left(\frac{X_C}{N}, X_D\right) = N\tilde{\lambda}_r(x_C^N, X_D^N) = N\tilde{\lambda}_r(x^N),$$

so that the rate of the reaction r for the rescaled process is $N\tilde{\lambda}_r(x_C^N, X_D^N) = N\tilde{\lambda}_r(x^N)$.

Below, we omit the "tilde" ($\tilde{}$) in our notation. The rate of a fast reaction can be recognized with its proportionality to the parameter N , thanks to *Assumption 2.2.2*. In particular, the rate remains $\lambda_r(X_D^N)$ for a reaction $r \in \mathfrak{R}_D$, while it becomes $N\lambda_r(x_C^N)$ for a reaction $r \in \mathfrak{R}_C$, since reactions of the latter set are fast while those of the former set are slow. In addition, the jump heights of the rescaled component x_C^N are $N^{-1}\gamma_r^C$, for reactions $r \in \mathfrak{R}$ which affect species in C .

The generator of the rescaled process x^N has the form

$$\begin{aligned} \mathcal{A}f(y, \nu) &= \sum_{r \in \mathfrak{R}_C} \left[f\left(y + \frac{1}{N}\gamma_r^C, \nu\right) - f(y, \nu) \right] N\lambda_r(y) \\ &\quad + \sum_{r \in \mathfrak{R}_{DC}} \left[f\left(y + \frac{1}{N}\gamma_r^C, \nu + \gamma_r^D\right) - f(y, \nu) \right] \lambda_r(y, \nu) \\ &\quad + \sum_{r \in \mathfrak{R}_D} [f(y, \nu + \gamma_r^D) - f(y, \nu)] \lambda_r(\nu). \end{aligned}$$

It is not difficult to see that the two sets of species decouple in the limit $N \rightarrow \infty$, if the scaled rates $(\lambda_r)_r$ are continuous with respect to the first variable y . In fact, the limit is simply a set of differential equations for the continuous variable y , evolving without any influence of ν . This result has been shown by Kurtz in models with a unique large scale population size (see [Kur71, Kur78]), and is known as the Law of Large Numbers (LLN). By its side, the discrete component has its own dynamic made of jumps, with some rates depending on both y and ν . The two dynamics decouple because reactions in \mathfrak{R}_{DC} do not happen sufficiently often to considerably change the continuous component. Below, we discuss a situation where some reactions $r \in \mathfrak{R}_{DC}$ are such that λ_r needs to be rescaled.

1.3 Approximation of multiscale homogeneous stochastic gene networks

From now on, we fix $T > 0$ and consider our processes within the time window $[0, T]$.

We are interested in the asymptotic behavior of the rescaled process x^N , as $N \rightarrow \infty$. We rely on the study in [CDMR12] and focus on the case of continuous PDMPs with switching. A LLN-type result was given in [CDMR12], and we are seeking for the corresponding Central Limit Theorem (CLT). Unless we specify a different one, any limit is taken w.r.t. N .

1.3.1 Law of large numbers: toward a continuous PDMP

We first make the following

Assumption 1.3.1. *There is a subset of reactions $S_1 \subset \mathfrak{R}_{DC}$ such that:*

- $(x_C^N, X_D^N) \longrightarrow \left(x_C^N + \frac{1}{N}\gamma_r^C, X_D^N\right)$, at rate $N\lambda_r(x_C^N, X_D^N)$, for $r \in S_1$.
- $(x_C^N, X_D^N) \longrightarrow \left(x_C^N + \frac{1}{N}\gamma_r^C, X_D^N + \gamma_r^D\right)$, at rate $\lambda_r(x_C^N, X_D^N)$, for $r \in \mathfrak{R}_{DC} \setminus S_1$.

Reactions in S_1 are fast and called mixed fast reactions. They affect only continuous species. On the opposite, reactions in $\mathfrak{R}_{DC} \setminus S_1$ are slow and called mixed slow reactions. They affect species of both C and D . Note that this situation is possible and even frequent in molecular biology, meaning that reactions of the type S_1 recover the reactant, like in the reaction $A \rightarrow A + B$, with A discrete and B continuous.

The new scaled generator now has the form

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$$\begin{aligned}
\mathcal{A}^N f(y, \nu) &= \sum_{r \in \mathfrak{R}_C} \left[f\left(y + \frac{1}{N} \gamma_r^C, \nu\right) - f(y, \nu) \right] N \lambda_r(y) \\
&\quad + \sum_{r \in S_1} \left[f\left(y + \frac{1}{N} \gamma_r^C, \nu\right) - f(y, \nu) \right] N \lambda_r(y, \nu) \\
&\quad + \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \left[f\left(y + \frac{1}{N} \gamma_r^C, \nu + \gamma_r^D\right) - f(y, \nu) \right] \lambda_r(y, \nu) \\
&\quad + \sum_{r \in \mathfrak{R}_D} [f(y, \nu + \gamma_r^D) - f(y, \nu)] \lambda_r(\nu).
\end{aligned} \tag{1.3.1}$$

For $f \in C_b^1(E)$, we may let $N \rightarrow \infty$ and obtain the limiting generator

$$\begin{aligned}
\mathcal{A}^\infty f(y, \nu) &= \nabla_y f(y, \nu) \cdot \left(\sum_{r \in \mathfrak{R}_C} \gamma_r^C \lambda_r(y) + \sum_{r \in S_1} \gamma_r^C \lambda_r(y, \nu) \right) \\
&\quad + \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} [f(y, \nu + \gamma_r^D) - f(y, \nu)] \lambda_r(y, \nu) \\
&\quad + \sum_{r \in \mathfrak{R}_D} [f(y, \nu + \gamma_r^D) - f(y, \nu)] \lambda_r(\nu).
\end{aligned} \tag{1.3.2}$$

From (1.2.3), we know that \mathcal{A}^∞ is the generator of a continuous PDMP with switching, and whose characteristics are (F, Λ, Q) : for $x = (y, \nu) \in E$, $f \in C_b^1(E)$, the vector field F is given by

$$F(y, \nu) = \sum_{r \in \mathfrak{R}_C} \lambda_r(y) \gamma_r^C + \sum_{r \in S_1} \lambda_r(y, \nu) \gamma_r^C, \tag{1.3.3}$$

the jump intensity Λ is given by

$$\Lambda(x) = \sum_{r \in (\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D} \lambda_r(x), \tag{1.3.4}$$

and finally, the transition measure Q is given by

$$\begin{aligned}
&\int_E f(y, \xi) Q(d\xi; y, \nu) \\
&= \frac{1}{\Lambda(x)} \left(\sum_{r \in \mathfrak{R}_{DC} \setminus S_1} f(y, \nu + \gamma_r^C) \lambda_r(y, \nu) + \sum_{r \in \mathfrak{R}_D} f(y, \nu + \gamma_r^C) \lambda_r(\nu) \right).
\end{aligned} \tag{1.3.5}$$

This formal argument indicates that x^N converges to a continuous PDMP with switching. The following result rigorously justifies it.

Theorem 1.3.1. (*[CDMR12], Theorem 3.1*)

Let $x^N = (x_C^N, X_D^N)$ be a sequence of $E = \mathbb{R}^{M_C} \times \mathbb{N}^{M_D}$ -valued jump Markov processes starting from $x^N(0) = (x_C^N(0), X_D^N(0))$, and with the infinitesimal generator \mathcal{A}^N given by (1.3.1). Assume the jump rates λ_r , $r \in \mathfrak{R}_C \cup S_1$ and λ_r , $r \in \mathfrak{R}_{DC} \setminus S_1$ are C^1 functions of their first variable $y \in \mathbb{R}^{M_C}$.

Now, let $x = (x_C, X_D)$ be the PDMP starting at $x_0 = (x_{C,0}, X_{D,0}) \in E$ and with the generator \mathcal{A}^∞ given by (1.3.2), and denote by P_{x_0} its law. Suppose that Assumption 1.2.1 holds, and $x^N(0) \Rightarrow x_0$ (weak convergence) as $N \rightarrow \infty$.

Then,

$$x^N \Rightarrow x \text{ in } D([0, T], E), \text{ as } N \rightarrow \infty$$

for every fixed $T > 0$.

Comments. It is well known (see e.g. [Kur71] Proposition 2.1) that the process

$$Z^N(t) = x^N(t) - x^N(0) - \int_0^t \Psi^N(x^N(s)) ds$$

defines an \mathbb{R}^M -valued martingale –under additional assumptions such as bounded jump rates–, where $\Psi^N = (F^N, G)$ is the debit of the process x^N . Here, for $(y_C, y_D) \in \mathbb{R}^{M_C+M_D}$,

$$G(y_C, y_D) := \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \gamma_r^D \lambda_r(y_C, y_D) + \sum_{r \in \mathfrak{R}_D} \gamma_r^D \lambda_r(y_D)$$

is the debit of reactions affecting the discrete species –they are all slow–, and $F^N = F + F_1^N$ is the debit of reactions affecting the continuous species, with F given by (1.3.3) standing as the debit of fast reactions, and

$$F_1^N(y_C, y_D) = \frac{1}{N} \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \gamma_r^C \lambda_r(y_C, y_D), \quad (1.3.6)$$

the debit of slow reactions involving abundant species.

Thus, $Z^N(t) = (Z_C^N(t), Z_D^N(t)) \in \mathbb{R}^{M_C+M_D}$, and $x^N(t) = (x_C^N(t), X_D^N(t))$ is solution of the system of stochastic differential equations (SDEs)

$$\begin{cases} x_C^N(t) = x_C^N(0) + \int_0^t F^N(x_C^N(s), X_D^N(s)) ds + Z_C^N(t) \\ X_D^N(t) = X_D^N(0) + \int_0^t G(x_C^N(s), X_D^N(s)) ds + Z_D^N(t). \end{cases}$$

The counterpart of this system of SDEs at the limit reads

$$\begin{cases} x_C(t) = x_{C,0} + \int_0^t F(x_C(s), X_D(s)) ds \\ X_D(t) = X_{D,0} + \int_0^t G(x_C(s), X_D(s)) ds + Z_D(t), \end{cases}$$

where Z_D is an \mathbb{R}^{M_D} -valued martingale defined by the relation in which it appears here above, with the PDMP $x = (x_C, X_D)$ given in advance.

Hence, a formal understanding of Theorem 1.3.1 is that the continuous component x_C^N of the scaled jump Markov process x^N asymptotically follows a LLN, while the dynamic of the discrete component X_D^N does not change basically and remains stochastic. We have in particular that the continuous marginal Z_C^N of the accompanying martingale vanishes in that limit, realizing in turn a LLN, while the discrete marginal Z_D^N converges to another martingale Z_D and keeps jumps.

All these lead to seek for a CLT for Z_C^N , and more generally for x_C^N , as it is usually suggested by a LLN. These will be the aims of the next two sections.

In the sequel, we assume that $x^N(0) \implies x_0$.

1.3.2 A martingale central limit theorem: toward a diffusion

In this section, we show that the continuous component Z_C^N of the martingale Z^N accompanying our jump Markov process x^N converges to a diffusion, when suitably renormalized.

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Recall Z_C^N is given by

$$Z_C^N(t) = x_C^N(t) - x_C^N(0) - \int_0^t F^N(x_C^N(s), X_D^N(s)) ds. \quad (1.3.7)$$

More specifically, setting

$$U_C^N(t) = \sqrt{N} Z_C^N(t),$$

we prove the stronger result stating that the Markov jump process $Y^N := (x_C^N, X_D^N, U_C^N)$ weakly converges to a continuous PDifMP with switching. This implies in particular that U_C^N weakly converges to a diffusion obtained by interlacing pieces of diffusion processes.

Some heuristics. Let us denote by $\tilde{\mathcal{A}}^N$ the generator of Y^N . Then,

$$\begin{aligned} & \tilde{\mathcal{A}}^N \varphi(y_C, y_D, z_C) \\ &= \sum_{r \in \mathfrak{R}_C} \left[\varphi \left(y_C + \frac{\gamma_r^C}{N}, y_D, z_C + \frac{\gamma_r^C}{\sqrt{N}} \right) - \varphi(y_C, y_D, z_C) \right] N \lambda_r(y_C) \\ &+ \sum_{r \in S_1} \left[\varphi \left(y_C + \frac{\gamma_r^C}{N}, y_D, z_C + \frac{\gamma_r^C}{\sqrt{N}} \right) - \varphi(y_C, y_D, z_C) \right] N \lambda_r(y_C, y_D) \\ &+ \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \left[\varphi \left(y_C + \frac{\gamma_r^C}{N}, y_D + \gamma_r^D, z_C + \frac{\gamma_r^C}{\sqrt{N}} \right) - \varphi(y_C, y_D, z_C) \right] \lambda_r(y_C, y_D) \\ &+ \sum_{r \in \mathfrak{R}_D} \left[\varphi(y_C, y_D + \gamma_r^D, z_C) - \varphi(y_C, y_D, z_C) \right] \lambda_r(y_D) \\ &- \left\langle D_{z_C} \varphi(y_C, y_D, z_C), \sqrt{N} F^N(y_C, y_D) \right\rangle, \end{aligned} \quad (1.3.8)$$

for $\varphi \in C_b^{0,0,1}(\mathbb{R}^{M_C+M_D+M_C})$ the space of functions that are bounded, continuous w.r.t. the first and second variables, of class C^1 w.r.t. the third variable, with bounded differentials. Here, $\langle \cdot, \cdot \rangle$ is the inner product of \mathbb{R}^{M_C} .

It is not difficult to see that $\tilde{\mathcal{A}}^N$ admits the limit

$$\begin{aligned} & \tilde{\mathcal{A}}^\infty \varphi(y_C, y_D, z_C) \\ &= \langle D^{1,0,0} \varphi(y_C, y_D, z_C), F(y_C, y_D) \rangle \\ &+ \sum_{r \in \mathfrak{R}_C} \frac{1}{2} D^{0,0,2} \varphi(y_C, y_D, z_C) \cdot (\gamma_r^C, \gamma_r^C) \lambda_r(y_C) \\ &+ \sum_{r \in S_1} \frac{1}{2} D^{0,0,2} \varphi(y_C, y_D, z_C) \cdot (\gamma_r^C, \gamma_r^C) \lambda_r(y_C, y_D) \\ &+ \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \left[\varphi(y_C, y_D + \gamma_r^D, z_C) - \varphi(y_C, y_D, z_C) \right] \lambda_r(y_C, y_D) \\ &+ \sum_{r \in \mathfrak{R}_D} \left[\varphi(y_C, y_D + \gamma_r^D, z_C) - \varphi(y_C, y_D, z_C) \right] \lambda_r(y_D), \end{aligned} \quad (1.3.9)$$

on the domain $\mathcal{T} = C_b^{1,0,2}(\mathbb{R}^{M_C+M_D+M_C})$ of test functions that are bounded, C^1 w.r.t. the first variable, continuous w.r.t the second variable, C^2 w.r.t. the third variable, and have bounded successive differentials.

This limit suggests the weak convergence of Y^N to some process $Y = (x_C, X_D, U_C)$, whose generator is given by $\tilde{\mathcal{A}}^\infty$. It may be convenient to switch the second and third coordinates,

and on the one hand, identify Y^N with (x_C^N, U_C^N, X_D^N) , and, on the other hand, identify Y with (x_C, U_C, X_D) .

With that configuration, Y clearly appears to be a PDifMP as introduced in Section 1.2.2. Its discrete component is X_D , the discrete component of the PDMP $x = (x_C, X_D)$ previously obtained as the limit of $x^N = (x_C^N, X_D^N)$. The continuous component of the PDifMP Y is the couple (x_C, U_C) . For any value ν taken by X_D between two of its consecutive jumps, (x_C, U_C) evolves according to the system of differential equations

$$\begin{cases} \dot{x}_C(t) = F(x_C(t), \nu) \\ dU_C(t) = \sum_{r \in \mathfrak{R}_C} a_r(x_C(t), \nu) dB_r(t) + \sum_{r \in S_1} a_r(x_C(t), \nu) dB_r(t), \end{cases} \quad (1.3.10)$$

where B_r , $r \in \mathfrak{R}_C \cup S_1$ are independent standard M_C -dimensional brownian motions, and $a_r(x_C(t), \nu)$ is a real coefficient $M_C \times M_C$ matrix satisfying

$$(a_r a_r^T)_{ij}(y_C, y_D) = \begin{cases} \gamma_{r,i}^C \gamma_{r,j}^C \lambda_r(y_C) & \text{if } r \in \mathfrak{R}_C \\ \gamma_{r,i}^C \gamma_{r,j}^C \lambda_r(y_C, y_D) & \text{if } r \in S_1, \end{cases}$$

for $(y_C, y_D) \in \mathbb{R}^{M_C + M_D}$.

As (x_C, U_C) does not jump, Y is a continuous PDifMP with switching.

In order for (1.3.10) to be well posed given an initial condition, we make the

Assumption 1.3.2.

- (i) Reaction rates are bounded with upper bound $\bar{\lambda}$.
- (ii) F is Lipschitz continuous w.r.t. the first variable, with constant L_F .

Remark 1.3.1. It should be emphasized that (1.3.10) indicates that U_C is a diffusion which is entirely determined by the PDMP (x_C, X_D) .

The result is the following.

Theorem 1.3.2. (A martingale Central Limit Theorem)

We consider the Markov process $Y^N = (x_C^N, X_D^N, U_C^N)$ whose generator is given by (1.3.8), and the PDifMP $Y = (x_C, X_D, U_C)$ with generator given by (1.3.9).

Then under Assumption 1.3.2 and Assumption 1.2.2,

$$Y^N \Longrightarrow Y \text{ in } D([0, T], \mathbb{R}^{M_C + M_D + M_C}), \text{ as } N \rightarrow \infty.$$

In particular, the central limit theorem for the martingale Z_C^N given by (1.3.7) reads

$$U_C^N \Longrightarrow U_C \text{ in } D([0, T], \mathbb{R}^{M_C}), \text{ as } N \rightarrow \infty.$$

Proof. The idea follows that of [CDMR12], Theorem 3.1, and is divided in three steps. We first prove the tightness of $\{Y^N\}_N$ in $D([0, T], \mathbb{R}^{M_C + M_D + M_C})$. Afterward, we identify the limit through the associated sequence of martingale problems. We then conclude by showing well-posedness for the limiting martingale problem.

Before getting started, we use Skorohod representation theorem and consider that the convergence of x^N to x is a.s. This causes no problem since we are interested in the laws of our processes, and implies in particular, that Z_C^N vanishes a.s.

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Tightness. From [CDMR12], we already know that $\{x_C^N\}_N$ is C -tight in $D([0, T]; \mathbb{R}^{M_C})$ and $\{X_D^N\}_N$ is tight in $D([0, T]; \mathbb{R}^{M_D})$. Now, we show that $\{U_C^N\}_N$ is tight in $D([0, T]; \mathbb{R}^{M_C})$, using arguments of [Kur71], section 2 essentially.

By martingale inequalities, for all $\delta > 0$,

$$\begin{aligned} \mathbb{P} \left\{ \sup_{s \leq t} |U_C^N(s)| > \delta \right\} &= \mathbb{P} \left\{ \sup_{s \leq t} |Z_C^N(s)| > \delta/\sqrt{N} \right\} \\ &\leq \left[\phi(\delta/\sqrt{N}) \right]^{-1} \mathbb{E} [\phi(Z_C^N(t))], \end{aligned}$$

for every $0 \leq t \leq T$ and every convex function ϕ . Next, one has to estimate the expectation on the r.h.s.

We notice that (x_C^N, X_D^N, Z_C^N) almost has the same generator as Y^N . The difference is that the jumps of Z_C^N are γ_r^C/N while those of U_C^N are γ_r^C/\sqrt{N} . Thus, taking $C_b^{1,0,2}$ test functions $\varphi \in \mathcal{T}$ satisfying $\varphi(y_C, y_D, z_C) = \varphi(z_C)$, we easily get from (1.3.8), that the generator $\hat{\mathcal{A}}^N$ of (x_C^N, X_D^N, Z_C^N) reads

$$\begin{aligned} &\hat{\mathcal{A}}^N \varphi(y_C, y_D, z_C) \\ &= \sum_{r \in \mathfrak{R}_C} \left[\varphi \left(z_C + \frac{\gamma_r^C}{N} \right) - \varphi(z_C) - D\varphi(z_C) \cdot \frac{\gamma_r^C}{N} \right] N \lambda_r(y_C) \\ &\quad + \sum_{r \in \mathfrak{S}_1} \left[\varphi \left(z_C + \frac{\gamma_r^C}{N} \right) - \varphi(z_C) - D\varphi(z_C) \cdot \frac{\gamma_r^C}{N} \right] N \lambda_r(y_C, y_D) \\ &\quad + \sum_{r \in \mathfrak{R}_{DC} \setminus \mathfrak{S}_1} \left[\varphi \left(z_C + \frac{\gamma_r^C}{N} \right) - \varphi(z_C) - D\varphi(z_C) \cdot \frac{\gamma_r^C}{N} \right] \lambda_r(y_C, y_D). \end{aligned} \tag{1.3.11}$$

Furthermore, for such test functions that are non-negative and convex, one has (see Lemma (2.9) of [Kur71])

$$\mathbb{E} [\varphi(Z_C^N(t))] - \varphi(0) = \int_0^t \mathbb{E} [\hat{\mathcal{A}}^N \varphi(x^N(s), Z_C^N(s))] ds. \tag{1.3.12}$$

Choosing in particular the convex test functions

$$\phi(u) = u^2 \quad \text{and} \quad \varphi(z_C) = \phi(|z_C|)$$

respectively, one has

$$\varphi \left(z_C + \frac{\gamma_r^C}{N} \right) - \varphi(z_C) - D\varphi(z_C) \cdot \frac{\gamma_r^C}{N} = \frac{1}{2} D^2 \varphi(z_C) \cdot \left(\frac{\gamma_r^C}{N}, \frac{\gamma_r^C}{N} \right) = \frac{|\gamma_r^C|^2}{N^2}$$

for all $r \in \mathfrak{R}_C \cup \mathfrak{R}_{DC}$.

Therefore, since there is a finite number of reactions and since $\sup_{t \leq T} |Z_C^N(t)| \rightarrow 0$ a.s. —this follows from $x^N \rightarrow x$ a.s. in $D([0, T]; E)$ —, by dominated convergence, (1.3.12) yields

$$\begin{aligned} \mathbb{E} [|Z_C^N(t)|^2] &= \int_0^t \mathbb{E} [\hat{\mathcal{A}}^N \varphi(x_C^N(s), X_D^N(s), Z_C^N(s))] ds \\ &= \frac{1}{N} \int_0^t \left\{ \sum_{r \in \mathfrak{R}_C} |\gamma_r^C|^2 \mathbb{E} [\lambda_r(x_C^N(s))] + \sum_{r \in \mathfrak{S}_1} |\gamma_r^C|^2 \mathbb{E} [\lambda_r(x_C^N(s), X_D^N(s))] \right. \\ &\quad \left. + \sum_{r \in \mathfrak{R}_{DC} \setminus \mathfrak{S}_1} \frac{|\gamma_r^C|^2}{N} \mathbb{E} [\lambda_r(x_C^N(s), X_D^N(s))] \right\} ds \\ &\leq \frac{ct \bar{\lambda} \bar{\gamma}^2}{N} \left(1 + \frac{1}{N} \right) \leq \frac{ct}{N}, \end{aligned}$$

for $0 \leq t \leq T$, where c is a generic constant and $\bar{\gamma} = \max\{|\gamma_r^C|, |\gamma_r^D|, r \in \mathfrak{R}\}$.

Hence,

$$\mathbb{P} \left\{ \sup_{s \leq t} |U_C^N(s)| > \delta \right\} \leq \frac{N}{\delta^2} \times \frac{ct}{N} \leq \frac{ct}{\delta^2} \quad (1.3.13)$$

for every $\delta > 0$. C -tightness is then easily derived for $\{U_C^N\}_N$ using Aldous' criterion. Indeed, on the one hand, for all $\epsilon > 0$, we choose $A := \sqrt{cT}/\sqrt{\epsilon}$ and get that for every $a > A$,

$$\limsup_N \mathbb{P} \left\{ \sup_{t \leq T} |U_C^N(t)| \geq a \right\} < \epsilon,$$

thanks to (1.3.13). On the other hand, we denote the jump by $\delta U_C^N(t) := U_C^N(t) - U_C^N(t^-)$. Note that $\delta U_C^N(t) = \sqrt{N} \delta x_C^N(t)$. Now, let τ be a stopping time such that $\tau \leq T$. Then by the strong Markov property, for all $\epsilon, \eta > 0$, choosing $\beta_0 := \eta \epsilon^2 / c$, we get that for every $\beta \leq \beta_0$ and every N ,

$$\begin{aligned} & \mathbb{P} \left\{ |U_C^N(\tau + \beta) - U_C^N(\beta)| \geq \epsilon \right\} \\ &= \mathbb{P} \left\{ \left| \int_{\tau}^{\tau+\beta} F^N(x_C^N(s), X_D^N(s)) ds + \sum_{\tau \leq s \leq \tau+\beta} \delta x_C^N(s) \right| \geq \epsilon \right\} \\ &= \mathbb{P} \left\{ \left| \int_0^{\beta} F^N(x_C^N(s), X_D^N(s)) ds + \sum_{0 \leq s \leq \beta} \delta x_C^N(s) \right| \geq \epsilon \right\} \\ &= \mathbb{P} \left\{ |U_C^N(\beta) - U_C^N(0)| \geq \epsilon \right\} \\ &\leq \mathbb{P} \left\{ \sup_{s \leq \beta} |U_C^N(s)| \geq \epsilon \right\} \leq \eta, \end{aligned}$$

since $U_C^N(0) = 0$ and thanks to (1.3.13). This yields the tightness of $\{U_C^N\}_N$.

We finally get the tightness of $\{X_D^N, U_C^N\}_N$ in $D([0, T]; \mathbb{R}^{M_D+M_C})$ since

$$\sup_{t \leq T} |\delta U_C^N(t)| \leq \frac{\bar{\gamma}}{\sqrt{N}} \rightarrow 0,$$

and then the tightness of the whole process $\{Y^N\}_N$, thanks to [JS87], Chapter 6, Lemma 3.32 and Corollary 3.33, respectively.

Identification of the limit. On $D([0, T]; \mathbb{R}^{M_C+M_D+M_C})$, let $w = \{w_t, t \geq 0\}$ be the canonical process and let P_N be the law of $Y^N = (x_C^N, X_D^N, U_C^N)$ on this space. We know (see e.g. [EK86]) that for each N , P_N is solution of the martingale problem for \tilde{A}^N on the domain \mathcal{T} . That is for all $\varphi \in \mathcal{T}$,

$$\varphi(w_t) - \varphi(w_0) - \int_0^t \tilde{A}^N \varphi(w_s) ds$$

is a P_N -martingale. Equivalently, for each $n \in \mathbb{N}^*$, $t_1, \dots, t_n \in [0, s]$, $0 \leq s \leq t$, $\psi \in (C_b(\mathbb{R}^{M_C+M_D+M_C}))^n$ and $\varphi \in \mathcal{T}$,

$$\begin{aligned} & \mathbb{E}_{P_N} \left[\left(\varphi(w_t) - \varphi(w_0) - \int_0^t \tilde{A}^N \varphi(w_\sigma) d\sigma \right) \psi(w_{t_1}, \dots, w_{t_n}) \right] \\ &= \mathbb{E}_{P_N} \left[\left(\varphi(w_s) - \varphi(w_0) - \int_0^s \tilde{A}^N \varphi(w_\sigma) d\sigma \right) \psi(w_{t_1}, \dots, w_{t_n}) \right]. \end{aligned} \quad (1.3.14)$$

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We consider a subsequence $(P_{N_k})_k$ weakly converging on $D([0, T]; \mathbb{R}^{M_C+M_D+M_C})$ to a probability measure P_∞ , the law of some process $Y^\infty = (x_C^\infty, X_D^\infty, U_C^\infty)$ on that space, with $Y^\infty(0) = (x_{C,0}, X_{D,0}, 0)$. We know that w is P_∞ -almost surely continuous at every t except for a countable set D_{P_∞} and that for t_1, \dots, t_n outside D_{P_∞} , $P_{N_k} \pi_{t_1 \dots t_n}^{-1}$ converges weakly to $P_\infty \pi_{t_1 \dots t_n}^{-1}$, where $\pi_{t_1 \dots t_n}$ is the canonical projection that carries the point $x \in D([0, T]; \mathbb{R}^{M_C+M_D+M_D})$ to the point $(x_{t_1}, \dots, x_{t_n})$ on \mathbb{R}^n .

Therefore, it is not difficult, using the dominated convergence and weak convergence properties, to let $k \rightarrow \infty$ in (1.3.14) and obtain for t, t_1, \dots, t_n, s outside D_{P_∞} :

$$\begin{aligned} \mathbb{E}_{P_\infty} \left[\left(\varphi(w_t) - \varphi(w_0) - \int_0^t \tilde{\mathcal{A}}^\infty \varphi(w_\sigma) d\sigma \right) \psi(w_{t_1}, \dots, w_{t_n}) \right] \\ = \mathbb{E}_{P_\infty} \left[\left(\varphi(w_s) - \varphi(w_0) - \int_0^t \tilde{\mathcal{A}}^\infty \varphi(w_\sigma) d\sigma \right) \psi(w_{t_1}, \dots, w_{t_n}) \right]. \end{aligned} \quad (1.3.15)$$

If $t \in D_{P_\infty}$, we choose a sequence (t^k) outside D_{P_∞} such that $t^k \rightarrow t$ with $t^k > t$. Then $P_\infty \pi_{t^k}^{-1}$ converges weakly to $P_\infty \pi_t^{-1}$ since w is P_∞ -a.s. right-continuous in t and w_{t^k} converges almost surely to w_t . Then, we use (1.3.15) with t^k instead of t , let $k \rightarrow \infty$ and deduce that (1.3.15) also holds for $t \in D_{P_\infty}$. Similarly, we show that t_1, \dots, t_n, s may be taken in D_{P_∞} .

This shows that P_∞ –and thus Y^∞ – is a solution of the martingale problem associated to the generator $\tilde{\mathcal{A}}^\infty$ on the domain \mathcal{T} .

Conclusion. We conclude by showing that on $D([0, T]; \mathbb{R}^{M_C+M_D+M_C})$, the law P of the PDifMP $Y = (x_C, X_D, U_C)$ is the unique solution of the martingale problem for $\tilde{\mathcal{A}}^\infty$ on \mathcal{T} , with the initial state $Y(0) = (x_{C,0}, X_{D,0}, 0)$. This is equivalent to showing that the process Y is the unique solution of the specified martingale problem.

Clearly, Y is solution of that martingale problem. Another meaning of this is: for all $\varphi \in \mathcal{T}$,

$$\varphi(x_C(t), X_D(t), U_C(t)) - \varphi(x_{C,0}, X_{D,0}, 0) - \int_0^t \tilde{\mathcal{A}}^\infty \varphi(x_C(s), X_D(s), U_C(s)) ds \quad (1.3.16)$$

defines a \mathbb{P} -martingale.

Let a process $\bar{Y} = (\bar{x}_C, \bar{X}_D, \bar{U}_C)$ be another solution such that $\bar{Y}(0) = (x_{C,0}, X_{D,0}, 0)$.

On the one hand, we identify $\mathcal{E} := C_b^{1,0}$ with $C_b^{1,0,\infty}$, and view \mathcal{E} as a subspace of $C_b^{1,0,2} = \mathcal{T}$. It is the subspace of test functions in \mathcal{T} that are independent of the third variable. Then, we observe that the generator \mathcal{A}^∞ of the PDMP $x = (x_C, X_D)$ given by (1.3.2), coincides with the restriction to \mathcal{E} of the generator $\tilde{\mathcal{A}}^\infty$ given by (1.3.9).

Therefore, it is clear that the marginals $\bar{x} := (\bar{x}_C, \bar{X}_D)$ of \bar{Y} is a solution of the martingale problem associated with the generator \mathcal{A}^∞ on the domain \mathcal{E} . Indeed, with the preceding remark, (1.3.16) written with test functions $\varphi \in \mathcal{T}$ such that $\varphi(y_C, y_D, z_C) = \varphi(y_C, y_D)$ for $(y_C, y_D, z_C) \in \mathbb{R}^{M_C+M_D+M_C}$ reads

$$\varphi(\bar{x}_C(t), \bar{X}_D(t)) - \varphi(\bar{x}_{C,0}, \bar{X}_{D,0}) - \int_0^t \mathcal{A}^\infty \varphi(\bar{x}_C(s), \bar{X}_D(s)) ds$$

is a \mathbb{P} -martingale. Our claim then holds, thanks to the identification introduced above.

Hence, \bar{x} has the same law as the PDMP x , since this latter is the unique solution of the martingale problem associated with \mathcal{A}^∞ on \mathcal{E} (see [CDMR12], Theorem 2.5). In other words, on an eventually different probability space, (\bar{x}_C, \bar{X}_D) is a PDMP with the same characteristics (F, Λ, Q) as (x_C, X_D) .

On the other hand, using the same reasoning as previously, we identify $C_b^2(\mathbb{R}^{M_C})$ with $C_b^{\infty,\infty,2}(\mathbb{R}^{M_C+M_D+M_C})$ and consider test functions $\varphi(y_C, y_D, z_C) = \varphi(z_C)$. Thus, we obtain

that

$$\varphi(\bar{U}_C(t)) - \int_0^t \mathcal{A}_{(\bar{x}_C(s), \bar{X}_D(s))}^\infty \varphi(\bar{U}_C(s)) ds$$

is a \mathbb{P} -martingale, where for all $(y_C, y_D) \in \mathbb{R}^{M_C + M_D}$, $z_C \in \mathbb{R}^{M_C}$,

$$\begin{aligned} \mathcal{A}_{(y_C, y_D)}^\infty \varphi(z_C) &= \sum_{r \in \mathfrak{R}_C} \frac{1}{2} D^2 \varphi(z_C) \cdot (\gamma_r^C, \gamma_r^C) \lambda_r(y_C) \\ &\quad + \sum_{r \in S_1} \frac{1}{2} D^2 \varphi(z_C) \cdot (\gamma_r^C, \gamma_r^C) \lambda_r(y_C, y_D) \\ &= \sum_{r \in \mathfrak{R}_C} \frac{1}{2} \sum_{i,j=1}^{M_C} \gamma_{r,i}^C \gamma_{r,j}^C \lambda_r(y_C) \partial_i \partial_j \varphi(z_C) \\ &\quad + \sum_{r \in S_1} \frac{1}{2} \sum_{i,j=1}^{M_C} \gamma_{r,i}^C \gamma_{r,j}^C \lambda_r(y_C, y_D) \partial_i \partial_j \varphi(z_C), \end{aligned} \tag{1.3.17}$$

is the generator of a continuous process. Two particular types of test functions are used in order to successively derive the martingale property of \bar{U}_C and the associated quadratic variation and cross-variations.

Firstly, we consider the test functions $\varphi_\alpha(z_C) = \langle z_C, \alpha \rangle$, $\alpha \in \mathbb{R}^{M_C}$ where $\langle \cdot, \cdot \rangle$ stands for the \mathbb{R}^{M_C} inner product. Observing that $D\varphi_\alpha(z_C) \cdot h = \langle h, \alpha \rangle$ and $D^2\varphi_\alpha(z_C) \equiv 0$, the above martingale problem states that $\langle \bar{U}_C(t), \alpha \rangle$ is a \mathbb{P} -martingale for every $\alpha \in \mathbb{R}^{M_C}$. Thus, taking α within the vectors (e_i) of the canonical basis of \mathbb{R}^{M_C} successively, one easily sees that \bar{U}_C is a martingale.

Therefore, given the PDMP $\bar{x} = (\bar{x}_C, \bar{X}_D)$, \bar{U}_C is a centered continuous martingale.

Secondly, we consider the test functions $\varphi_\alpha(z_C) = \langle z_C, \alpha \rangle^2$. Observing that $D\varphi_\alpha(z_C) \cdot h = 2\langle h, \alpha \rangle \langle z_C, \alpha \rangle$ and $D^2\varphi_\alpha(z_C) \cdot (h, k) = 2\langle h, \alpha \rangle \langle k, \alpha \rangle$, the above martingale problem then states that

$$\langle \bar{U}_C(t), \alpha \rangle^2 - \int_0^t \left(\sum_{r \in \mathfrak{R}_C} \langle \gamma_r^C, \alpha \rangle^2 \lambda_r(\bar{x}_C(s)) + \sum_{r \in S_1} \langle \gamma_r^C, \alpha \rangle^2 \lambda_r(\bar{x}_C(s), \bar{X}_D(s)) \right) ds$$

is a \mathbb{P} -martingale for every α .

This says –having the previous type of test functions in mind–, that for every α , the quadratic variation of the martingale $\langle \bar{U}_C(t), \alpha \rangle$ is given by

$$\langle \langle \bar{U}_C(\cdot), \alpha \rangle \rangle_t = \int_0^t \left(\sum_{r \in \mathfrak{R}_C} \langle \gamma_r^C, \alpha \rangle^2 \lambda_r(\bar{x}_C(s)) + \sum_{r \in S_1} \langle \gamma_r^C, \alpha \rangle^2 \lambda_r(\bar{x}_C(s), \bar{X}_D(s)) \right) ds.$$

Thus, for all $i, j = 1, \dots, M_C$, for convenient choices of α , namely $\alpha = (e_i \pm e_j)/2$, and, using the identity

$$\bar{U}_{Ci}(t) \bar{U}_{Cj}(t) = \frac{1}{4} \left[(\bar{U}_{Ci}(t) + \bar{U}_{Cj}(t))^2 - (\bar{U}_{Ci}(t) - \bar{U}_{Cj}(t))^2 \right]$$

and the same identity with $\bar{U}_C(t)$ replaced by γ_r^C , we get the cross-variations

$$\langle \bar{U}_{Ci}, \bar{U}_{Cj} \rangle_t = \int_0^t \left(\sum_{r \in \mathfrak{R}_C} \gamma_{ri}^C \gamma_{rj}^C \lambda_r(\bar{x}_C(s)) + \sum_{r \in S_1} \gamma_{ri}^C \gamma_{rj}^C \lambda_r(\bar{x}_C(s), \bar{X}_D(s)) \right) ds \tag{1.3.18}$$

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for the vector valued process \bar{U}_C . As these are \mathbb{P} -almost surely absolutely continuous functions of t , we know from the martingale representation theorem (see e.g. Theorem 4.2 of [KS91]) that on some extended probability space $(\tilde{\Omega}, \tilde{\mathcal{F}}, \tilde{\mathbb{P}})$, are defined independent M_C -dimensional standard Brownian motions \bar{B}_r , $r \in \mathbb{R}_C \cup S_1$ with a corresponding associated filtration $\tilde{\mathcal{F}}_t$, and some $M_C \times M_C$ matrix $\sigma_r(\bar{x}_C(t), \bar{X}_D(t)) = (\sigma_{r,ij}(\bar{x}_C(t), \bar{X}_D(t)))_{i,j}$, $r \in \mathfrak{R}_C \cup S_1$, of measurable and $\tilde{\mathcal{F}}_t$ -adapted processes with

$$\tilde{\mathbb{P}} \left\{ \int_0^t (\sigma_{r,ij}(\bar{x}_C(s), \bar{X}_D(s)))^2 ds < \infty \right\} = 1, \quad i, j = 1, \dots, M_C, \quad 0 \leq t \leq T,$$

such that we have, $\tilde{\mathbb{P}}$ -almost surely, the representations

$$\bar{U}_C(t) = \sum_{r \in \mathfrak{R}_C} \int_0^t \sigma_r(\bar{x}_C(s), \bar{X}_D(s)) d\bar{B}_r(s) + \sum_{r \in S_1} \int_0^t \sigma_r(\bar{x}_C(s), \bar{X}_D(s)) d\bar{B}_r(s) \quad (1.3.19)$$

for \bar{U}_C , and

$$\langle \bar{U}_{Ci}, \bar{U}_{Cj} \rangle = \sum_{r \in \mathfrak{R}_C} \int_0^t (\sigma_r \sigma_r^T)_{ij}(\bar{x}_C(s), \bar{X}_D(s)) ds + \sum_{r \in S_1} \int_0^t (\sigma_r \sigma_r^T)_{ij}(\bar{x}_C(s), \bar{X}_D(s)) ds \quad (1.3.20)$$

for the cross-variations.

From (1.3.20) and (1.3.18), it is clear that

$$(\sigma_r \sigma_r^T)_{ij}(y_C, y_D) = \begin{cases} \gamma_{r,i}^C \gamma_{r,j}^C \lambda_r(y_C) & \text{if } r \in \mathfrak{R}_C \\ \gamma_{r,i}^C \gamma_{r,j}^C \lambda_r(y_C, y_D) & \text{if } r \in S_1, \end{cases}$$

for $(y_C, y_D) \in \mathbb{R}^{M_C \times M_D}$.

Hence, the matrices $(\sigma_r)_r$ are the same as the matrix $(a_r)_r$ driving the evolution of U_C and defined by (1.3.10). Furthermore, between two consecutive jumps of the discrete component \bar{X}_D of the PDMP $\bar{x} = (\bar{x}_C, \bar{X}_D)$, where $\bar{X}_D = \nu \in \mathbb{R}^{M_D}$, it is not difficult to see that \bar{U}_D weakly satisfies —as \bar{x}_C has the same law as x_C — the same SDE as U_D . That SDE is given by (1.3.10) and has a unique weak solution under Assumption 1.3.2.

Therefore, conditionally to the PDMP (\bar{x}_C, \bar{X}_D) which has the same law as (x_C, X_D) , the process \bar{U}_C has the same law as U_C , and is a diffusion. It follows that the process $\bar{Y} = (\bar{x}_C, \bar{X}_D, \bar{U}_C)$ is a PDifMP, with the same characteristics as $Y = (x_C, X_D, Z_D)$. Since they both start at $(x_{C,0}, X_{D,0}, 0)$, they have the same law, and this concludes the proof of Theorem 1.3.2. \square

We now emphasize a trivial consequence of Theorem 1.3.2, resulting from a direct application of the Skorohod's representation theorem.

Corollary 1.3.1. *One can always assume that $Y^N = (x_C^N, X_D^N, U_C^N)$ converges almost surely to $Y = (x_C, X_D, U_C)$, in $D([0, T], \mathbb{R}^{M_C + M_D + M_C})$, as $N \rightarrow \infty$, with an appropriate change of probability space.*

In the sequel, we use Corollary 1.3.1 and choose our original probability space $(\Omega, \mathcal{F}, \mathbb{P})$ such that the convergence of $Y^N = (x_C^N, X_D^N, Z_D^N)$ to $Y = (x_C, X_D, Z_D)$ is \mathbb{P} -almost sure.

1.3.3 A more general central limit theorem : toward a jumping PDifMP

In this section, we establish a CLT for the continuous component x_C^N of the scaled jump Markov process $x^N = (x_C^N, X_D^N)$. More specifically, we prove that the process defined by

$$v_C^N(t) = \sqrt{N}(x_C^N(t) - x_C(t))$$

admits a weak limit that we clearly identify and characterize.

We make use of the time change representation that was used in the proof of Theorem 1.3.1 for x^N . We denote that representation \underline{x}^N . In what follows, underlined objects are defined on that time change probability space. In fact, from Theorem 4.1 of Chapter 6 in [EK86], we know that given any sequence Y_r , $r \in \mathfrak{R}$ of independant standard Poisson processes, there exists, on some probability space $(\underline{\Omega}, \underline{\mathcal{F}}, \underline{\mathbb{P}})$, a version $\underline{x}^N = (\underline{x}_C^N, \underline{X}_D^N)$ of x^N , satisfying

$$\begin{aligned} \underline{x}_C^N(t) &= \underline{x}_C^N(0) + \sum_{r \in \mathfrak{R}_C} \frac{\gamma_r^C}{N} \tilde{Y}_r \left(N \int_0^t \lambda_r(\underline{x}_C^N(s)) ds \right) \\ &+ \sum_{r \in S_1} \frac{\gamma_r^C}{N} \tilde{Y}_r \left(N \int_0^t \lambda_r(\underline{x}_C^N(s), \underline{X}_D^N(s)) ds \right) + \int_0^t F(\underline{x}_C^N(s), \underline{X}_D^N(s)) ds \\ &+ \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \frac{\gamma_r^C}{N} Y_r \left(\int_0^t \lambda_r(\underline{x}_C^N(s), \underline{X}_D^N(s)) ds \right) \end{aligned} \quad (1.3.21)$$

and

$$\begin{aligned} \underline{X}_D^N(t) &= \underline{X}_D^N(0) + \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \gamma_r^D Y_r \left(\int_0^t \lambda_r(\underline{x}_C^N(s), \underline{X}_D^N(s)) ds \right) \\ &+ \sum_{r \in \mathfrak{R}_D} \gamma_r^D Y_r \left(\int_0^t \lambda_r(\underline{X}_D^N(s)) ds \right), \end{aligned} \quad (1.3.22)$$

where $\tilde{Y}_r : u \mapsto Y_r(u) - u$ is the centered (or compensated) Poisson process associated with Y_r , and F given by (1.3.3) is the debit function for x^N corresponding to the fast reactions.

Using the same arguments, the limiting PDMP $x = (x_C, X_D)$ has a version $\underline{x} = (\underline{x}_C, \underline{X}_D)$ satisfying

$$\underline{x}_C(t) = x_{C,0} + \int_0^t F(\underline{x}_C(s), \underline{X}_D(s)) ds \quad (1.3.23)$$

and

$$\begin{aligned} \underline{X}_D(t) &= X_{D,0} + \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \gamma_r^D Y_r \left(\int_0^t \lambda_r(\underline{x}_C(s), \underline{X}_D(s)) ds \right) \\ &+ \sum_{r \in \mathfrak{R}_D} \gamma_r^D Y_r \left(\int_0^t \lambda_r(\underline{X}_D(s)) ds \right). \end{aligned} \quad (1.3.24)$$

Let us introduce $W_r^N(t) = \frac{\tilde{Y}_r(Nt)}{\sqrt{N}}$ for $r \in \mathfrak{R}_C \cup S_1$, $0 \leq t \leq T$. From the very standard CLT for Poisson processes,

$$W_r^N \Longrightarrow W_r \quad \text{as } N \rightarrow \infty, \quad (1.3.25)$$

where W_r , $r \in \mathfrak{R}_C \cup S_1$ are independent standard Brownian motions. We then set

$$\underline{v}_C^N(t) = \sqrt{N}(\underline{x}_C^N(t) - \underline{x}_C(t)),$$

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for $0 \leq t \leq T$. From (1.3.21) and (1.3.22),

$$v_C^N(t) = \underline{v}_C^N(0) + \underline{A}_C^N(t) + \underline{U}_C^N(t), \quad (1.3.26)$$

where

$$\begin{aligned} \underline{A}_C^N(t) &= \sqrt{N} \int_0^t F(\underline{x}_C^N(s), \underline{X}_D^N(s)) - F(\underline{x}_C(s), \underline{X}_D(s)) ds, \\ \underline{U}_C^N(t) &= \sum_{r \in \mathfrak{R}_C} \gamma_r^C W_r^N \left(\int_0^t \lambda_r(\underline{x}_C^N(s)) ds \right) + \sum_{r \in S_1} \gamma_r^C W_r^N \left(\int_0^t \lambda_r(\underline{x}_C^N(s), \underline{X}_D^N(s)) ds \right) \\ &\quad + \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \frac{\gamma_r^C}{\sqrt{N}} Y_r \left(\int_0^t \lambda_r(\underline{x}_C^N(s), \underline{X}_D^N(s)) ds \right) \end{aligned}$$

and $\underline{v}_C^N(0) = \sqrt{N}(\underline{x}_C^N(0) - x_{C,0})$.

Remark 1.3.2. *It should be emphasized that, thanks to Theorem 1.3.2, $(\underline{x}_C^N, \underline{X}_D^N, \underline{U}_C^N)$ weakly converges to some PDifMP $(\underline{x}_C, \underline{X}_D, \underline{U}_C)$, where $(\underline{x}_C, \underline{X}_D)$ has the same law as our PDMP (x_C, X_D) , and \underline{U}_C is some diffusion process uniquely determined by $(\underline{x}_C, \underline{X}_D)$, and defined on the space $(\underline{\Omega}, \underline{\mathcal{F}}, \underline{\mathbb{P}})$.*

In one scale models, there is no discrete component and the limit—in the LLN—is almost sure and globally deterministic (see [EK86], Part 11, Theorem 2.1). In that situation, observing that $\mathbf{x}_C^N = \mathbf{x}_C + N^{-1}\mathbf{v}_C^N$ one can write a Taylor expansion at order 1 of F in the integrand on the r.h.s. of (1.3.26). All these combined with (1.3.25) suggest the following weak limit equation for (1.3.26):

$$\mathbf{v}_C(t) = \mathbf{v}_C(0) + \mathbf{A}_C(t) + \mathbf{U}_C(t), \quad (1.3.27)$$

where $\mathbf{v}_C(0)$ stands for the limit in distribution of $\mathbf{v}_C^N(0)$,

$$\mathbf{A}_C(t) = \int_0^t D^{1,0} F(\mathbf{x}_C(s)) \mathbf{v}_C(s) ds,$$

and

$$\mathbf{U}_C(t) = \sum_{r \in \mathfrak{R}_C} \gamma_r^C W_r \left(\int_0^t \lambda_r(\mathbf{x}_C(s)) ds \right) + \sum_{r \in S_1} \gamma_r^C W_r \left(\int_0^t \lambda_r(\mathbf{x}_C(s)) ds \right).$$

In our notation, for all $(y, \nu) \in E$,

$$D^{1,0} F(y, \nu) = (\partial_j F_i(y, \nu))_{1 \leq i, j \leq M_C}$$

is a square matrix of size M_C , with real coefficients. Recall that given any $\nu \in \mathbb{N}^{M_D}$, $y \mapsto F_\nu(y) = F(y, \nu)$ is a—smooth—vector field in \mathbb{R}^{M_C} . For $1 \leq i, j \leq M_C$, $\partial_j F_i(y, \nu)$ is the partial derivative of the i -th component of the image vector $F(y, \nu)$, with respect to the j -th component of the vector y .

The limit (1.3.27) is no more adapted to the present multiscale situation. Indeed, the convergence in the LLN-type approximation only happens in distribution, so it is weak. Moreover, a Taylor expansion at order 1 of F lets the factor $\sqrt{N}(\underline{X}_D^N - \underline{X}_D)$ appear, and this latter diverges in the limit $N \rightarrow \infty$. Furthermore, a bound of v_C^N is hardly obtained by direct methods. We overcome these difficulties and show that when fast and slow dynamics are coupled, complementary terms appear at the limit corresponding to (1.3.27).

Consider the following

Assumption 1.3.3.

(i) The set $(\mathfrak{R}_{DC} \setminus \mathcal{S}_1) \cup \mathfrak{R}_D$ of slow reactions contains a unique reaction. We denote it r_1 and denote its rate λ_1 .

(ii) There exists $\lambda_0 > 0$ such that $\lambda_1 \geq \lambda_0$.

(iii) Reaction rates: are bounded, continuous w.r.t. their second variable, of class C^1 w.r.t. their first variable, and, they have uniformly bounded first differentials that are also continuous w.r.t. the second variable.

When Assumption 1.3.3 is satisfied, F is bounded and Lipschitz w.r.t. its first component. We let M_F be a uniform bound of F , and let L_F be a uniform bound of its differential $D^{1,0}F$. The rate λ_1 is also Lipschitz, and we introduce the Lipschitz constant L_1 for it. Finally, we denote by $\bar{\lambda}$ a bound common to all the reaction rates.

In what follows, c denotes a generic constant independent of N and $t \in [0, T]$, but that may depend on T , L_F , M_F and L_1 eventually.

Since it is usually assumed that the initial value $\underline{X}_D^N(0)$ converges to $X_{D,0}$, we may also assume for simplicity, that $\underline{X}_D^N(0) = X_{D,0}$. Therefore, the time change representations corresponding to (1.3.22) and (1.3.24) are respectively

$$\underline{X}_D^N(t) = X_{D,0} + \gamma_1^D Y_1 \left(\int_0^t \lambda_1(\underline{x}_C^N(s), \underline{X}_D^N(s)) ds \right), \quad (1.3.28)$$

and

$$\underline{X}_D(t) = X_{D,0} + \gamma_1^D Y_1 \left(\int_0^t \lambda_1(\underline{x}_C(s), \underline{X}_D(s)) ds \right), \quad (1.3.29)$$

where $\gamma_1^D = \gamma_{r_1}^D$, $Y_1 = Y_{r_1}$, and $\lambda_1 = \lambda_{r_1}$.

Identification of the limit

On $(\underline{\Omega}, \underline{\mathcal{F}}, \underline{\mathbb{P}})$, consider the initial condition problem:

$$\begin{cases} \underline{g}'_N(t) = \frac{\lambda_1(\underline{x}_C^N(t), \underline{X}_D^N(t))}{\lambda_1(\underline{x}_C(\underline{g}_N(t)), \underline{X}_D(\underline{g}_N(t)))}, & t > 0, \\ \underline{g}_N(0) = 0, \end{cases} \quad (1.3.30)$$

on \mathbb{R}_+ . Under Assumption 1.3.3 and since the processes $\underline{x}^N = (\underline{x}_C^N, \underline{X}_D^N)$ and $\underline{x} = (\underline{x}_C, \underline{X}_D)$ are càdlàg, (1.3.30) admits a weak² local solution \underline{g}_N which is an \mathbb{R}_+ -valued random function that is piecewise C^1 and piecewise satisfies,

$$\begin{cases} \int_0^{\underline{g}_N(t)} \lambda_1(\underline{x}_C(s), \underline{X}_D(s)) ds = \int_0^t \lambda_1(\underline{x}_C^N(s), \underline{X}_D^N(s)) ds \\ \underline{X}_D(\underline{g}_N(t)) = \underline{X}_D^N(t). \end{cases} \quad (1.3.31)$$

By Assumption 1.3.3 (ii), the map $t \rightarrow \int_0^t \lambda_1(\underline{x}_C^N(s), \underline{X}_D^N(s)) ds$ is non decreasing. Therefore, $\underline{g}'_N(t) > 0$ and thus, the solution \underline{g}_N is non decreasing, uniquely defined up to equivalence class, piecewise bijective and global. Below, we consider –by abuse– that \underline{g}'_N is simply the derivative of \underline{g}_N . We also consider its piecewise inverse function $\tilde{\underline{g}}_N(t) := \underline{g}_N^{-1}(t)$ as its inverse function. Then $\tilde{\underline{g}}_N$ is also piecewise C^1 and as for \underline{g}_N , we denote $\tilde{\underline{g}}'_N$ its derivative. Hence, we proceed to changes of variable by abuse, since these are actually piecewise possible only. Clearly, $\tilde{\underline{g}}_N(0) = 0$.

²Not weak in the stochastic sense, but in the sense of deterministic differential equations.

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Let us switch now to the initial space $(\Omega, \mathcal{F}, \mathbb{P})$, and consider the counterpart

$$\begin{cases} g'_N(t) = \frac{\lambda_1(x_C^N(t), X_D^N(t))}{\lambda_1(x_C(g_N(t)), X_D(g_N(t)))}, & t > 0, \\ g_N(0) = 0, \end{cases} \quad (1.3.32)$$

of (1.3.30). Obviously, the solution g_N of (1.3.32) has the same regularity as \underline{g}_N the solution of the former problem. In particular,

$$\int_0^{g_N(t)} \lambda_1(x_C(s), X_D(s)) ds = \int_0^t \lambda_1(x_C^N(s), X_D^N(s)) ds,$$

and it is not difficult to see that g_N has the same law as \underline{g}_N .

Thus,

$$1 = \mathbb{P} \left\{ \underline{X}_D(\underline{g}_N(t)) = \underline{X}_D^N(t) \right\} = \mathbb{P} \left\{ X_D(g_N(t)) = X_D^N(t) \right\},$$

and

$$X_D(g_N(t)) = X_D^N(t) \quad \mathbb{P} - a.s., \quad \text{for all } t \geq 0. \quad (1.3.33)$$

The above discussion shows that computations as above can be made either on the time change representation space $(\underline{\Omega}, \underline{\mathcal{F}}, \underline{\mathbb{P}})$, or on the original space $(\Omega, \mathcal{F}, \mathbb{P})$. From now on, this latter space is considered, where the whole process Y^N is assumed to converge \mathbb{P} -a.s. Due to (1.3.33), most of our considerations hold \mathbb{P} -a.s. However, that is sufficient for our purpose.

Further computations (see the proof of Lemma 1.3.1) show that

$$|g_N(t) - t| \leq c_T \int_0^t |x_C^N(s) - x_C(s)| ds \quad (1.3.34)$$

for all $t \in [0, T]$, for some constant c_T independent of N . A similar inequality also holds for \tilde{g}_N , the inverse of g_N . Since $x_C^N \rightarrow x_C$ a.s. in $D([0, T], \mathbb{R}^{M_C})$ as $N \rightarrow \infty$, and since x_C is continuous, the almost sure convergence $x_C^N \rightarrow x_C$ is uniform (see [Bil99], p. 124). Hence,

$$\sup_{t \leq T} |g_N(t) - t| \rightarrow 0 \quad \text{and} \quad \sup_{t \leq T} |\tilde{g}_N(t) - t| \rightarrow 0 \quad (1.3.35)$$

as $N \rightarrow \infty$.

A limit candidate. By a change of variable, \mathbb{P} -a.s.,

$$\int_0^t F(x_C(s), X_D(s)) ds = \int_0^{\tilde{g}_N(t)} F(x_C(g_N(s)), X_D^N(s)) g'_N(s) ds.$$

Thus, \mathbb{P} -a.s.,

$$\begin{aligned} \frac{A_C^N(t)}{\sqrt{N}} &= \int_0^t F(x_C^N(s), X_D^N(s)) - F(x_C(s), X_D(s)) ds \\ &= \int_0^t F(x_C^N(s), X_D^N(s)) - F(x_C(s), X_D^N(s)) ds \\ &\quad - \int_0^t F(x_C(g_N(s)), X_D^N(s)) - F(x_C(s), X_D^N(s)) ds \\ &\quad - \int_0^t F(x_C(g_N(s)), X_D^N(s)) (g'_N(s) - 1) ds \\ &\quad + F(x_C(t), X_D(t)) (g_N(t) - t) \\ &\quad - \int_{g_N(t)}^t F(x_C(s), X_D(s)) - F(x_C(t), X_D(t)) ds. \end{aligned} \quad (1.3.36)$$

From (1.3.36), we see that the evolution of v_C^N depends on that of the quantity

$$h^N(t) = \sqrt{N}(g_N(t) - t).$$

Thus we may consider h_N together with v_C^N . Furthermore, a Taylor expansion of $v_C^N(t)$ shows that we may need to control

$$u_C^N(t) := \sqrt{N}(x_C(g_N(t)) - x_C(t)).$$

However this latter can be controled as soon as h^N does. In fact,

$$|x_C(t) - x_C(g_N(t))| \leq \int_{g_N(t)}^t |F(x_C(s), X_D(s))| ds \leq M_F |g_N(t) - t|$$

easily follows from (1.3.23). Hence, we only need to consider the couple (v_C^N, h^N) which is an \mathbb{R}^{M_C+1} -valued process.

Now, since

$$\begin{aligned} g'_N(t) - 1 &= \frac{\lambda_1(x_C^N(t), X_D^N(t)) - \lambda_1(x_C(g_N(t)), X_D^N(t))}{\lambda_1(x_C(g_N(t)), X_D^N(t))} \\ &= \frac{1}{\sqrt{N}} \frac{D^{1,0}\lambda_1(x_C(t), X_D^N(t))}{\lambda_1(x_C(g_N(t)), X_D^N(t))} \\ &\quad \times [v_C^N(t) - F(x_C(t), X_D(t))h^N(t) + o(h^N(t))] + o(v_C^N(t)), \end{aligned}$$

\mathbb{P} -a.s., we obtain that v_C^N satisfies \mathbb{P} -a.s.

$$\begin{aligned} v_C^N(t) &= v_C^N(0) + U_C^N(t) \\ &\quad + \int_0^t D^{1,0}F(x_C(s), X_D^N(s))v_C^N(s) + o(v_C^N(s))ds \\ &\quad - \int_0^t D^{1,0}F(x_C(s), X_D^N(s))F(x_C(s), X_D(s))h^N(s) + o(h^N(s))ds \\ &\quad - \int_0^t F(x_C(g_N(s)), X_D^N(s)) \frac{D^{1,0}\lambda_1(x_C(s), X_D^N(s))}{\lambda_1(x_C(g_N(s)), X_D^N(s))} \\ &\quad \quad \times [v_C^N(s) - F(x_C(s), X_D(s))h^N(s) + o(h^N(s))] + o(u^N(s))ds \\ &\quad + F(x_C(t), X_D(t))h^N(t) - \sqrt{N} \int_{g_N(t)}^t F(x_C(s), X_D(s)) - F(x_C(t), X_D(t))ds, \end{aligned} \tag{1.3.37}$$

and h^N satisfies \mathbb{P} -a.s.

$$\begin{aligned} h^N(t) &= \int_0^t \frac{D^{1,0}\lambda_1(x_C(s), X_D^N(s))}{\lambda_1(x_C(g_N(s)), X_D^N(s))} \\ &\quad \times [v_C^N(s) - F(x_C(s), X_D(s))h^N(s) + o(h^N(s))] + o(u^N(s))ds. \end{aligned} \tag{1.3.38}$$

Both evolutions are coupled, and from what precedes, a suggested limiting system of equations for (1.3.26) may be

$$v_C(t) = v_C(0) + U_C(t) + A_C(t), \tag{1.3.39}$$

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where U_C is the limit of $U_C^N = \sqrt{N}Z_C^N$ given by Theorem 1.3.2,

$$\begin{aligned} A_C(t) &= \int_0^t D^{1,0}F(x_C(s), X_D(s))v_C(s)ds \\ &\quad - \int_0^t D^{1,0}F(x_C(s), X_D(s))F(x_C(s), X_D(s))h(s)ds \\ &\quad - \int_0^t F(x_C(s), X_D(s))\frac{D^{1,0}\lambda_1(x_C(s), X_D(s))}{\lambda_1(x_C(s), X_D(s))} \\ &\quad \quad \quad \times [v_C(s) - F(x_C(s), X_D(s))h(s)]ds \\ &\quad + F(x_C(t), X_D(t))h(t), \end{aligned}$$

and

$$h(t) = \int_0^t \frac{D^{1,0}\lambda_1(x_C(s), X_D(s))}{\lambda_1(x_C(s), X_D(s))} [v_C(s) - F(x_C(s), X_D(s))h(s)] ds. \quad (1.3.40)$$

Well-posedness. The system of equations (1.3.39)-(1.3.40) has a unique solution. This relies on the piecewise deterministic nature of $x = (x_C, X_D)$ and the fact that U_C is an interlacing of diffusions. A solution can be uniquely constructed as follows. Between two consecutive jumps of X_D , this latter is constant: $X_D(t) = \nu \in \mathbb{N}^{M_D}$, and (1.3.39)-(1.3.40) is a quite standard SDE in \mathbb{R}^{M_C+1} , which is linear w.r.t. v_C and h_C . Under Assumption 1.3.3, F , λ_1 , $D^{1,0}F$ and $D^{1,0}\lambda_1$ are bounded, and continuous w.r.t. their first variable. This ensures the existence of a unique solution $(v_{C,\nu}, h_\nu)$ to that system of linear equations (see e.g. Theorem 8.1.5, Chapter 8 of [Arn74], or [GB05b]), and that solution is a diffusion. At a jump time of X_D , since h is continuous, only v_C switches to another mode because of the last term of $A_C(t)$. A new equation is obtained and solved similarly and independently, starting from the new state. The global solution (v_C, h) is the pieced together process, obtained by concatenating the $((v_{C,\nu}, h_\nu))_\nu$.

Link with PDifMPs. Now, we consider the process $\mathbf{V} = (v_C, h, x_C, X_D)$ with state space $\mathbf{E} = \mathbb{R}^{M_C+1+M_C} \times \mathbb{N}^{M_D}$, and write it as

$$\mathbf{V}(t) = (\mathbf{V}_C(t), X_D(t)), \quad \text{where } \mathbf{V}_C(t) = (v_C(t), h(t), x_C(t)).$$

From the discussion above, one easily sees that \mathbf{V} is a jumping PDifMP with switching as discussed in Section 1.2.2. Its discrete component is $X_D \in \mathbb{N}^{M_D}$, the same as that of the PDMP $x = (x_C, X_D)$. Its continuous component is $\mathbf{V}_C = (v_C, h, x_C) \in \mathbb{R}^{2M_C+1}$. This latter has discontinuous trajectories since v_C jumps with X_D , and, between the jumps, it satisfies systems of equations made of an SDE satisfied by v_C , coupled with two ODEs satisfied by h and by x_C respectively. We could as well construct the solution relying on PDifPs theory, instead of PDPs one.

The general central limit theorem

In this section, a CLT is proved. It corresponds to the LLN-type result of Theorem 1.3.1. Let us introduce the processes

$$V_C^N = (v_C^N, h^N) \quad \text{and} \quad V_C = (v_C, h).$$

We will need the following

Lemma 1.3.1. *There exists a constant c_T independent of N , depending on T , L_1 , L_F and M_F , such that*

$$\sup_{t \leq T} |V_C^N(t)| := \sup_{t \leq T} (|v_C^N(t)| + |h^N(t)|) \leq c_T \text{ in probability.}$$

Proof. Throughout this proof, the constants c_i , $i = 1, 2, \dots$ are generic, independent of N and t , but eventually dependent of T , L_F , M_F and L_1 .

Let $t \in [0, T]$. We already know that

$$|x_C(t) - x_C(g_N(t))| \leq M_F |g_N(t) - t|,$$

from (1.3.23). Then, (1.3.32), Assumption 1.3.3 (ii) and Gronwall lemma lead to

$$\begin{aligned} |g'_N(t) - 1| &\leq \lambda_0^{-1} L_1 |x_C^N(t) - x_C(g_N(t))| \\ &\leq c_1 \int_0^t |x_C^N(s) - x_C(s)| ds + c_1 M_F \int_0^t |g_N(s) - s| ds \\ &\leq \frac{c_1}{\sqrt{N}} \int_0^t |v_C^N(s)| ds + c_1 T \int_0^t |g'_N(s) - 1| ds \leq \left(\frac{c_1}{\sqrt{N}} \int_0^t |v_C^N(s)| ds \right) e^{c_1 T^2} \\ &\leq \frac{c_1}{\sqrt{N}} \int_0^t |v_C^N(s)| ds. \end{aligned}$$

Therefore,

$$\begin{aligned} |h^N(t)| = \sqrt{N} |g_N(t) - t| &\leq \sqrt{N} \int_0^t |g'_N(s) - 1| ds \leq c_1 T \int_0^t |v_C^N(s)| ds \\ &\leq c_2 \int_0^t |v_C^N(s)| ds. \end{aligned}$$

Afterward, from (1.3.36), it is not difficult to see that

$$\begin{aligned} |A_C^N(t)| &\leq L_F \int_0^t |v_C^N(s)| + |x_C(s) - x_C(g_N(s))| ds + 3M_F |h^N(t)| \\ &\leq c_3 \int_0^t |v_C^N(s)| ds. \end{aligned}$$

Now by assumption, $v_C^N(0) \leq c_4$ in probability for some constant c_4 depending on $v_C(0)$. Moreover, $U_C^N(t) \leq c_5$ a.s., uniformly in t on $[0, T]$, for some constant c_5 depending on T . This follows from the convergence of U_C^N to the diffusion U_C , which is continuous.

Hence,

$$|v_C^N(t)| + |h^N(t)| \leq (c_4 + c_5) + (c_2 + c_3) \int_0^t |v_C^N(s)| ds$$

in probability. The proof of Lemma 1.3.1 is completed by Gronwall lemma, with $c_T = (c_4 + c_5)e^{(c_2+c_3)T}$. □

We now state and prove the general CLT.

Theorem 1.3.3. (The general Central Limit Theorem)

Consider the PDMP $x = (x_C, X_D)$, the processes $x^N = (x_C^N, X_D^N)$, $V_C^N = (v_C^N, h^N)$ and $V_C = (v_C, h)$. Assume that Assumption 1.2.1 and Assumption 1.3.3 hold, and $v_C^N(0) \rightarrow v_{C,0}$ in probability as $N \rightarrow \infty$, for some $v_{C,0} \in \mathbb{R}^{M_C}$. Then for all $T > 0$,

$$V_C^N \rightarrow V_C \text{ in probability, in } D([0, T], \mathbb{R}^{M_C+1}),$$

as $N \rightarrow \infty$.

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Proof of Theorem 1.3.3

We want to estimate

$$|V_C^N(t) - V_C(t)| = |v_C^N(t) - v_C(t)| + |h^N(t) - h(t)|.$$

From (1.3.37) and (1.3.39), resp. (1.3.38) and (1.3.40),

$$|v_C^N(t) - v_C(t)| \leq |v_C^N(0) - v_C(0)| + |U_C^N(t) - U_C(t)| + |A_C^N(t) - A_C(t)|.$$

We set

$$\varepsilon_1^N(t) := |v_C^N(0) - v_C(0)| \quad \text{and} \quad \varepsilon_2^N(t) := |U_C^N(t) - U_C(t)|.$$

By assumption, $\varepsilon_1^N(t) \rightarrow 0$ in probability, uniformly in t on $[0, T]$. Also, $\varepsilon_2^N(t) \rightarrow 0$ a.s., and the convergence is uniform in t on $[0, T]$, since U_C is continuous. We recall that

$$u_C^N(t) = \sqrt{N}(x_C(g_N(t)) - x_C(t)).$$

One has

$$\begin{aligned} & |A_C^N(t) - A_C(t)| \\ & \leq \int_0^t |D^{1,0}F(x_C(s), X_D^N(s))v_C^N(s) - D^{1,0}F(x_C(s), X_D(s))v_C(s)| ds \\ & \quad + \int_0^t |D^{1,0}F(x_C(s), X_D^N(s))F(x_C(s), X_D(s))h^N(s) \\ & \quad \quad - D^{1,0}F(x_C(s), X_D(s))F(x_C(s), X_D(s))h(s)| ds \\ & \quad + \int_0^t \left| F(x_C(g_N(s)), X_D^N(s)) \frac{D^{1,0}\lambda_1(x_C(s), X_D^N(s))}{\lambda_1(x_C(g_N(s)), X_D^N(s))} \right. \\ & \quad \quad \quad \times [v_C^N(s) - F(x_C(s), X_D(s))h^N(s)] \\ & \quad \quad - F(x_C(s), X_D(s)) \frac{D^{1,0}\lambda_1(x_C(s), X_D(s))}{\lambda_1(x_C(s), X_D(s))} \\ & \quad \quad \quad \times [v_C(s) - F(x_C(s), X_D(s))h(s)] \Big| ds \\ & + R^N(t) + \varepsilon_3^N(t) + \varepsilon_4^N(t) + \varepsilon_5^N(t) + \varepsilon_6^N(t) + \varepsilon_7^N(t), \end{aligned}$$

and

$$\begin{aligned} & |h^N(t) - h(t)| \\ & \leq \int_0^t \left| F(x_C(g_N(s)), X_D^N(s)) \frac{D^{1,0}\lambda_1(x_C(s), X_D^N(s))}{\lambda_1(x_C(g_N(s)), X_D^N(s))} \right. \\ & \quad \quad \quad \times [v_C^N(s) - F(x_C(s), X_D(s))h^N(s)] \\ & \quad \quad - F(x_C(s), X_D(s)) \frac{D^{1,0}\lambda_1(x_C(s), X_D(s))}{\lambda_1(x_C(s), X_D(s))} \\ & \quad \quad \quad \times [v_C(s) - F(x_C(s), X_D(s))h(s)] \Big| ds \\ & + \varepsilon_8^N(t) + \varepsilon_9^N(t) + \varepsilon_{10}^N(t), \end{aligned}$$

where the constant c_T is given by Lemma 1.3.1,

$$R^N(t) = \sqrt{N} \int_{g_N(t)}^t |F(x_C(t), X_D(t)) - F(x_C(s), X_D(s))| ds,$$

$$\begin{aligned}
 \varepsilon_3^N(t) &= c_T \int_0^t \frac{\sqrt{N}}{|v_C^N(s)|} \left| F(x_C^N(s), X_D^N(s)) - F(x_C(s), X_D^N(s)) \right. \\
 &\quad \left. - \frac{1}{\sqrt{N}} D^{1,0} F(x_C(s), X_D^N(s)) v_C^N(s) \right| ds, \\
 \varepsilon_4^N(t) &= c_T \int_0^t \frac{\sqrt{N}}{|u_C^N(s)|} \left| F(x_C(g_N(s)), X_D^N(s)) - F(x_C(s), X_D^N(s)) \right. \\
 &\quad \left. - \frac{1}{\sqrt{N}} D^{1,0} F(x_C(s), X_D^N(s)) u_C^N(s) \right| ds, \\
 \varepsilon_5^N(t) &= L_F c_T \int_0^t \frac{\sqrt{N}}{|h^N(s)|} \left| x_C(g_N(s)) - x_C(s) - \frac{1}{\sqrt{N}} F(x_C(s), X_D(s)) h^N(s) \right| ds, \\
 \varepsilon_6^N(t) &= \lambda_0^{-1} M_F c_T \int_0^t \frac{\sqrt{N}}{|v_C^N(s)|} \left| \lambda_1(x_C^N(s), X_D^N(s)) - \lambda_1(x_C(s), X_D^N(s)) \right. \\
 &\quad \left. - \frac{1}{\sqrt{N}} D^{1,0} \lambda_1(x_C(s), X_D^N(s)) v_C^N(s) \right| \\
 &\quad + \frac{\sqrt{N}}{|u_C^N(s)|} \left| \lambda_1(x_C(g_N(s)), X_D^N(s)) - \lambda_1(x_C(s), X_D^N(s)) \right. \\
 &\quad \left. - \frac{1}{\sqrt{N}} D^{1,0} \lambda_1(x_C(s), X_D^N(s)) u_C^N(s) \right| ds, \\
 \varepsilon_7^N(t) &= \lambda_0^{-1} M_F L_1 c_T \int_0^t \frac{\sqrt{N}}{|h^N(s)|} \left| x_C(g_N(s)) - x_C(s) - \frac{1}{\sqrt{N}} F(x_C(s), X_D(s)) h^N(s) \right| ds, \\
 \varepsilon_8^N(t) &= M_F^{-1} \varepsilon_5^N(t), \quad \varepsilon_9^N(t) = M_F^{-1} \varepsilon_6^N(t) \quad \text{and} \quad \varepsilon_{10}^N(t) = M_F^{-1} \varepsilon_7^N(t).
 \end{aligned}$$

By definition of the differential and dominated convergence, every $\varepsilon_i^N(t), i = 3, \dots, 14$ converges to zero a.s., and the convergence is uniform in t on $[0, T]$ by Dini theorem, since every $\varepsilon_i^N, i = 3, \dots, 14$ is an increasing function.

Firstly observe that

$$\begin{aligned}
 &\int_0^t |D^{1,0} F(x_C(s), X_D^N(s)) v_C^N(s) - D^{1,0} F(x_C(s), X_D(s)) v_C(s)| ds \\
 &\leq \int_0^t |D^{1,0} F(x_C(s), X_D^N(s)) [v_C^N(s) - v_C(s)]| \\
 &\quad + |[D^{1,0} F(x_C(s), X_D^N(s)) - D^{1,0} F(x_C(s), X_D(s))] v_C(s)| ds \\
 &\leq L_F \int_0^t |v_C^N(s) - v_C(s)| ds + \varepsilon_{11}^N(t).
 \end{aligned}$$

Secondly,

$$\begin{aligned}
 &\int_0^t |D^{1,0} F(x_C(s), X_D^N(s)) F(x_C(s), X_D(s)) h^N(s) \\
 &\quad - D^{1,0} F(x_C(s), X_D(s)) F(x_C(s), X_D(s)) h(s)| ds \\
 &\leq \int_0^t |D^{1,0} F(x_C(s), X_D^N(s)) F(x_C(s), X_D(s)) [h^N(s) - h(s)]| \\
 &\quad + |[D^{1,0} F(x_C(s), X_D^N(s)) - D^{1,0} F(x_C(s), X_D(s))] F(x_C(s), X_D(s)) h(s)| ds \\
 &\leq L_F \int_0^t |h^N(s) - h(s)| ds + \varepsilon_{12}^N(t).
 \end{aligned}$$

1.3 Approximation of multiscale homogeneous stochastic gene networks

Thirdly, with the same principle,

$$\begin{aligned}
& \int_0^t \left| F(x_C(g_N(s)), X_D^N(s)) \frac{D^{1,0}\lambda_1(x_C(s), X_D^N(s))}{\lambda_1(x_C(g_N(s)), X_D^N(s))} \right. \\
& \quad \times [v_C^N(s) - F(x_C(s), X_D(s))h^N(s)] \\
& \quad \left. - F(x_C(s), X_D(s)) \frac{D^{1,0}\lambda_1(x_C(s), X_D(s))}{\lambda_1(x_C(s), X_D(s))} \right. \\
& \quad \left. \times [v_C(s) - F(x_C(s), X_D(s))h(s)] \right| ds \\
& \leq \lambda_0^{-1} M_F L_1 \int_0^t |v_C^N(s) - v_C(s)| + |h^N(s) - h(s)| ds + \varepsilon_{13}^N(t) + \varepsilon_{14}^N(t) \\
& \leq \lambda_0^{-1} M_F L_1 \int_0^t |V_C^N(s) - V_C(s)| ds + \varepsilon_{13}^N(t) + \varepsilon_{14}^N(t),
\end{aligned}$$

where

$$\begin{aligned}
\varepsilon_{11}^N(t) &= \int_0^t |[D^{1,0}F(x_C(s), X_D^N(s)) - D^{1,0}F(x_C(s), X_D(s))] v_C(s)| ds, \\
\varepsilon_{12}^N(t) &= \int_0^t |[D^{1,0}F(x_C(s), X_D^N(s)) - D^{1,0}F(x_C(s), X_D(s))] F(x_C(s), X_D(s))h(s)| ds, \\
\varepsilon_{13}^N(t) &= \int_0^t \left| \left[F(x_C(g_N(s)), X_D^N(s)) \frac{D^{1,0}\lambda_1(x_C(s), X_D^N(s))}{\lambda_1(x_C(g_N(s)), X_D^N(s))} \right. \right. \\
& \quad \left. \left. - F(x_C(s), X_D(s)) \frac{D^{1,0}\lambda_1(x_C(s), X_D(s))}{\lambda_1(x_C(s), X_D(s))} \right] v_C(s) \right| ds
\end{aligned}$$

and

$$\varepsilon_{14}^N(t) = \int_0^t \left| \left[F(x_C(g_N(s)), X_D^N(s)) \frac{D^{1,0}\lambda_1(x_C(s), X_D^N(s))}{\lambda_1(x_C(g_N(s)), X_D^N(s))} F(x_C(s), X_D(s)) \right. \right. \\
\left. \left. - F(x_C(s), X_D(s)) \frac{D^{1,0}\lambda_1(x_C(s), X_D(s))}{\lambda_1(x_C(s), X_D(s))} F(x_C(s), X_D(s)) \right] h(s) \right| ds.$$

By Assumption 1.3.3 (iii) and dominated convergence, the terms $\varepsilon_i^N(t), i = 11, \dots, 14$ vanish as $N \rightarrow \infty$, and again, as these are increasing functions of t , their convergences are uniform in t on $[0, T]$, by Dini theorem.

Now, put

$$\varepsilon^N(t) = \sum_{i=1}^{14} \varepsilon_i^N(t) \quad \text{and} \quad \varepsilon^N = \sup_{t \leq T} \varepsilon^N(t),$$

and let c denote a generic positive constant independent of N and t , but eventually dependent of T, L_F, M_F and L_1 . From what precedes,

$$|V_C^N(t) - V_C(t)| \leq R^N(t) + \varepsilon^N(t) + c \int_0^t |V_C^N(s) - V_C(s)| ds$$

and by Gronwall lemma,

$$\sup_{t \leq T} |V_C^N(t) - V_C(t)| \leq (R^N + \varepsilon^N) e^{cT},$$

where $R^N = \sup_{t \leq T} R^N(t)$. Hence, the proof of Theorem 1.3.3 ends if we show that $R^N \rightarrow 0$. One has

$$\begin{aligned} R^N(t) &\leq \sqrt{N} \int_{g_N(t)}^t |F(x_C(s), X_D(s)) - F(x_C(t), X_D(s))| ds \\ &\quad + \sqrt{N} \int_{g_N(t)}^t |F(x_C(t), X_D(s)) - F(x_C(t), X_D(t))| ds. \\ &= R_1^N(t) + R_2^N(t). \end{aligned}$$

The uniform convergence of $R_2^N(t)$ follows from $R_2^N(t) = 0$ as the integrand is zero, for N large enough, thanks to (1.3.35). Our claim is clear if X_D does not jump at t . If t is a jump time of X_D , since $t \mapsto R_2^N(t)$ is càdlàg, we approximate t from above by a sequence $(t_k)_k$ in $[0, T]$ such that for all k , $t_k \geq t$ and X_D is continuous at t_k . Our claim is justified for the sequence and at the limit $k \rightarrow \infty$. We then conclude by density, since the set of jump times of a càdlàg process is countable -it is even finite on every finite time window- and therefore, its complementary set is dense.

Recall that $\tilde{g}_N = g_N^{-1}$. Then using a change of variable,

$$\begin{aligned} R_1^N(t) &\leq L_F \int_t^{\tilde{g}_N(t)} M_F \sqrt{N} |g_N(s) - t| + o(\sqrt{N} |g_N(s) - t|) ds \\ &\leq c |\tilde{g}_N(t) - t| + o(|\tilde{g}_N(t) - t|) \rightarrow 0 \end{aligned}$$

uniformly in, on $[0, T]$, thanks to (1.3.35). This completes the proof of Theorem 1.3.3. ■

CHAPTER 2

A law of large numbers in the supremum norm for a multiscale stochastic spatial gene network

Abstract. In this chapter, we study the asymptotic behavior of multiscale stochastic spatial gene networks. One major difference with chapter 1 is the modeling of space. Multiscaling takes into account the difference of abundance between molecules, and captures the dynamic of rare species at a mesoscopic level. We introduce an assumption of spatial correlations for reactions involving rare species and a new law of large numbers is obtained. According to the scales, the whole system splits into two parts with different but coupled dynamics. The high scale component converges to the usual spatial model which is the solution of a partial differential equation, whereas, the low scale component converges to the usual homogeneous model which is the solution of an ordinary differential equation. Comparisons are made in the supremum norm.

This chapter is the object of a submitted article (Cf. [arXiv:1711.06010](#), [[DN17](#)]).

2.1 Introduction

Modern molecular biology emphasizes the important role of the gene regulatory networks in the functioning of living organisms (see [[DL05](#)], [[SL05](#)] or [[MW11](#)]). As many other dynamical systems in a great variety of fields (e.g. biology, chemistry, epidemic theory or physics), gene regulatory networks belong to the large family of chemical reaction systems, which has been highly investigated in mathematics, for modeling. We refer to [[Kur70](#), [Kur71](#)], [[AT80](#)], [[Arn80](#)], [[EK86](#)], [[ET89](#)], [[RMC07b](#)], [[CDR09](#)], [[CDMR12](#)], and many other references therein. Following Arnold in [[Arn80](#)], there are two main criteria according to which reactions in a spatial domain are modeled:

(C1) global description (spatially homogeneous, "well-stirred" case excluding diffusion) versus local description (spatially inhomogeneous, "spatial model" including diffusion);

(C2) deterministic description (macroscopic, phenomenological, in terms of concentrations) versus stochastic description (mesoscopic, taking into account fluctuations, at the level of particles or molecules).

The combination of these two criteria gives rise to four mathematical models:

- Deterministic-Homogeneous: the concentration is solution to an Ordinary Differential Equation (ODE).
- Stochastic-Homogeneous: the number of particles is a (time) jump Markov process.
- Deterministic-Spatial: the concentration is solution to a Partial Differential Equation (PDE).
- Stochastic-Spatial: the number of particles is a (space-time) jump Markov process.

There is a restrictive assumption for deterministic and many of the stochastic models, in the literature. Namely, the different species (or reactants) have the same order of population size, which is large, meaning that the whole system has a fast dynamic. There are many biological situations for which this is not true. In some situations (gene regulatory networks are typical), some molecules are present in much greater quantity than others, and reactions rate constants can vary over several orders of magnitude (see [CDMR12] or [BKPR06]). A third criterion of modeling then shows up:

(C3) one scale description with a unique and large population size scale, with only high reaction rates and fast dynamics, versus multiscale description with at least two population size scales, with high and low reaction rates, and, fast and slow dynamics.

Now, with the three criteria **(C1)**, **(C2)**, and **(C3)** in hands, we can derive: the

- | | |
|-------------|--|
| (M1) | Deterministic Homogeneous Model, |
| (M2) | Deterministic Spatial Model, |
| (M3) | Stochastic Homogeneous Model, |
| (M4) | Stochastic Spatial Model, |
| (M5) | Multiscale Stochastic Homogeneous Model, |
| (M6) | Multiscale Stochastic Spatial Model. |

It should be emphasized that criterion **(C3)** has been introduced at the mesoscopic level and thus suggests to preferentially consider a stochastic description for multiscale modeling. This stresses the importance of, and our focus on, the multiscale stochastic modeling.

All these models are not independent one from another. The relation between **(M1)** and **(M3)** has been thoroughly investigated by Kurtz (among others, see [Kur70, Kur71] or [EK86] with Ethier). A law of large numbers (LLN) and the corresponding central limit theorem (CTL) have been proved, showing convergence of **(M3)** to **(M1)**. The consistency of **(M1)** and **(M2)** as well as of **(M3)** and **(M4)** have been proved in [Arn80]. In [AT80], Arnold and Theodosopulu compared **(M2)** and **(M4)** in the L^2 norm, through a LLN. Blount after Kotelenez did the same comparison, but much more extensively. Under more and more relaxed assumptions, they proved different LLNs and the associated CLTs in spaces of distributions. Blount showed a LLN in the supremum norm. We refer to [Kot86a, Kot86b, Kot87, Kot88a], [Blo87, Blo92, Blo93, Blo94] among others.

In [RMC07b], [CDR09] and [CDMR12], Crudu, Debussche, Muller and Radulescu studied **(M5)**. In the latter article, they proved that the model (weakly) converges to a finite-dimensional Piecewise Deterministic Markov Process (PDMP). In finite dimension, PDMPs are hybrid processes which follow between consecutive jumps, the flows of ODEs whose parameters can jump. They have been well formalised and studied by Davis in [Dav93]. Depending on the interactions and the scaling, Crudu *et al.* distinguished various types of limiting PDMPs. Stochasticity does not disappear in that hybrid simplification, and multiscale modeling appears to be a tool for estimating asymptotically at the first order, the noise lost in the LLN. Furthermore, PDMPs increase computational efficiency. This is very useful, since direct simulation of Markov processes is extremely time consuming for models we are dealing with (see [CDR09] or [Gil76]).

In this chapter, we start the study of **(M6)** and generalize Crudu *et al.* to a spatially

2.2 Modeling and Asymptotics

dependent situation. Depending on their abundance, we distinguish abundant ("continuous") and rare ("discrete") species. Also, there are different speeds of reactions, according to their rate scale and the species involved. When only abundant (resp. rare) species are involved, the reaction is fast (resp. slow). Otherwise, the speed depends on the specification of the rate scale. We assume that only abundant reactants diffuse. Also, a spatial correlation for slow reactions is considered. Its effects are inversely proportional to the distance to the location where the reaction occurred. In this context, we prove a new law of large numbers, showing the convergence of (M6) to (M2) coupled with (M1), in the supremum norm.

The structure for the rest of the chapter is as follows. In Section 2, we present local models, starting with the existing ones. We emphasize the notions of infinitesimal generator, debit functions, scaling and density dependence. Then we present our model of interest (M6). Afterwards, we identify its limit through the asymptotics of its debit function and of its generator. We state and prove our main result in Section 3. Finally, Section 4 is dedicated to the proofs of some intermediate results.

2.2 Modeling and Asymptotics

2.2.1 One scale spatial models

Since we are not concerned with the homogeneous models, we only review the mathematical details of the local models as given by Arnold and Theodosopulu in [AT80].

Deterministic Spatial Model

One scale chemical reactions with diffusion in a spatial domain $I \subset \mathbb{R}^d$ are modeled deterministically, at a macroscopic level, by the reaction-diffusion equation

$$\frac{\partial v}{\partial t} = D\Delta v + R(v), \quad (2.2.1)$$

where $v = v(t, x)$ is an M -dimensional real vector which gives the concentrations for the $M \geq 1$ reactants involved in the interactions, $x \in I$ is the spatial coordinate, $t \geq 0$ is the time. The domain I can be bounded or unbounded, v is subjected to boundary and initial conditions, Δ is the Laplace operator, D is a diagonal matrix of size M , with non-negative coefficients on the diagonal, called the diffusion matrix. As it is often the case, we consider for simplicity $D = I_d$, the identity matrix (in the sequel, D is the differential operator). Reactions are represented by R , a polynomial vector field in \mathbb{R}^M , defined by

$$R(y) = (R_1(y), \dots, R_M(y)) \quad \text{with} \quad R_i(y) := \sum_{|\alpha| \leq n} a_{\alpha}^i y^{\alpha},$$

where $n \in \mathbb{N}^*$, $\alpha = (\alpha_1, \dots, \alpha_M) \in \mathbb{N}^M$ is a multi-index, $|\alpha| := \alpha_1 + \dots + \alpha_M$, $a_{\alpha}^i \in \mathbb{R}$, $y = (y_1, \dots, y_M) \in \mathbb{R}^M$ and $y^{\alpha} := y_1^{\alpha_1} \dots y_M^{\alpha_M}$.

Well-posedness, generator and debit function. For simplicity, we work on a one dimensional domain, $d = 1$, that we project on the unit interval $I = [0, 1]$ with periodic boundary conditions: $v(t, 0) = v(t, 1)$, $\forall t \geq 0$. Since concentrations are positive quantities, a positive initial data is considered: $\forall x \in I$, $v(0, x) \geq 0$ in the sense $v_i(0, x) \geq 0$, $\forall 1 \leq i \leq M$. In order to have some control on the concentrations, it is assumed that $v(0) = v(0, \cdot)$ is bounded: $v(0, x) < \rho_1 < \infty$, $\forall x \in I$, for some $\rho_1 > 0$, and that:

Assumption 2.2.1.

- (i) For all $y = (y_1, \dots, y_M) \in \mathbb{R}^M$, $R_i(y) \geq 0$ when $y_i = 0$ for some $1 \leq i \leq M$.
 (ii) There exists $\rho_2 > 0$ such that $\langle R(y), y \rangle < 0$ for all $y \in \mathbb{R}^M$ satisfying $|y| > \rho_2$.

We have denoted by $|\cdot|$ and $\langle \cdot, \cdot \rangle$ the vector norm and the inner product of \mathbb{R}^M respectively. Assumption 2.2.1 is natural, and ensures the consistency of the model through *a priori* estimates for (2.2.1). In fact, (i) yields positiveness: $v_i(t, x) \geq 0$, $\forall t, x, \forall i$, whereas (ii) yields boundedness: $v(t, x) \leq \rho$, $\forall t > 0, \forall x$ with $\rho := \max(\rho_1, \rho_2) + 1$, thanks to the maximum principle.

As species all have the same dynamic in one scale models, a unique reactant is often considered, i.e. $M = 1$. The function R is written in the form $R(y) = b(y) - d(y)$, where b and d refer to variations due to births and deaths respectively. They are real valued polynomials with non-negative coefficients, such that $d(0) = 0$ and $a_n < 0$. We consider this case in this section.

We now consider an initial condition $v(0) = v_0 \in C^3(I)$. In [Kot86a], Kotelenez showed that, under the preceding conditions, the Cauchy problem associated with (2.2.1) has a unique mild solution $v \in C(\mathbb{R}_+; C^3(I))$ satisfying

$$v(t) = T(t)v_0 + \int_0^t T(t-s)R(v(s))ds,$$

and $0 \leq v(t) < \rho$ for all $t \geq 0$. Here, $T(t) := e^{\Delta t}$ is the semigroup associated with the Laplace operator Δ . We notice that $v_0 \in C^3(I)$ is not necessary if the purpose is to solve the equation. Well-posedness still holds for much more general v_0 . For more details, see [CH98], Section 5, or [AT80], Lemma 2 (based on [Kui77]).

Informally, the (weak) infinitesimal generator of the PDE (2.2.1) reads

$$\mathcal{A}\varphi(u) = (D_u\varphi(u), \Delta u + R(u)) = \langle D_u\varphi(u), \Delta u + R(u) \rangle_2, \quad (2.2.2)$$

for test functions $\varphi \in C_b^1(C^1(I))$. The bracket $\langle \cdot, \cdot \rangle_2$ is the inner product of $L^2 := L^2(I)$, the space of square integrable real valued functions on I , and (\cdot, \cdot) denotes the duality pairing. We give some probabilistic heuristics for understanding (2.2.2). Let $X(\cdot)$ be a solution to (2.2.1), and denote by $\Phi(\cdot, u)$ the solution starting at $u \in C^3(I)$. Viewing $(X(t))_{t \geq 0}$ as a $C^3(I)$ -valued deterministic - thus Markov - process on some filtered probability space $(\Omega, \mathcal{F}, (\mathcal{F}_t)_{t \geq 0}, \mathbb{P})$, its semigroup $(P_t)_{t \geq 0}$ on $\mathfrak{B}(C^3(I))$ reads

$$P_t\varphi(u) := \mathbb{E}[\varphi(X(t)) | X(0) = u] = \varphi(\Phi(t, u)).$$

Then as usual, we interpret the generator \mathcal{A} as the derivative of the semigroup w.r.t. t , at $t = 0$. Thus, for every test function $\varphi \in C_b^1(C^1(I))$, the chain rule leads to

$$\mathcal{A}\varphi(u) := \left. \frac{\partial}{\partial t} \varphi(\Phi(t, u)) \right|_{t=0} = (D\varphi(u), \Delta u + R(u)).$$

Finally, $D\varphi(u)$ being the differential of φ at u , it belongs to $(C^1(I))'$. We identify it with the (abstract) gradient of φ at u since $C^1(I) \subset L^2$, and write

$$(D\varphi(u), \Delta u + R(u)) = \langle D\varphi(u), \Delta u + R(u) \rangle_2,$$

thanks to the Riesz representation theorem. Relation (2.2.2) then follows. \square

After all, we define the corresponding debit function as

$$\psi(u) = \Delta u + R(u).$$

It is the vector field, in $C^1(I)$ here, determining the flow of the equation. More precisely, $u \mapsto \Delta u$ (resp. $u \mapsto R(u)$) is the debit function related to diffusions (resp. reactions).

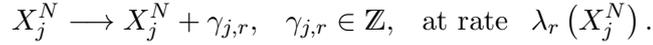
Stochastic Spatial Model

Following [AT80], we divide the unit interval into N smaller intervals of equal length N^{-1} : $I_j = ((j-1)N^{-1}, jN^{-1}]$, for $j = 1, \dots, N$, called **sites**. Molecules are produced - birth - or removed - death - on each site according to chemical reactions. They also diffuse between sites by simple random walks, at rates proportional to N^2 . This couples the site reactants and extends Kurtz's model (M3) to the spatially inhomogeneous case (M4). Define:

- X_j^N : the number of molecules on site j , $j = 1, \dots, N$,
- $X^N = (X_j^N)_{1 \leq j \leq N} \in \mathbb{N}^N$: the molecular composition of the whole system,
- \mathfrak{R} : the set of possible onsite reactions (we assume that \mathfrak{R} is finite).

Consider the natural completed filtration $\{\mathcal{F}_t^N, t \geq 0\}$, where \mathcal{F}_t^N is the completion of the σ -algebra $\sigma(\{X^N(s) : s \leq t\})$ with null probability measure sets. That will be the filtration considered by default, for each process we will define. From [Kur70, Kur71] or Chapter4, Section2, p.162-164 of [EK86], we know that $\{X^N(t), t \geq 0\}$ is a time homogeneous \mathbb{N}^N -valued jump Markov process, with the following transitions on any j :

Onsite reactions. A chemical reaction $r \in \mathfrak{R}$ occurs on the site j :



Diffusions. A molecule moves from the site j to the site $j-1$ or to the site $j+1$:

$$\begin{cases} (X_{j-1}^N, X_j^N) \longrightarrow (X_{j-1}^N + 1, X_j^N - 1), & \text{at rate } N^2 X_j^N, \\ (X_j^N, X_{j+1}^N) \longrightarrow (X_j^N - 1, X_{j+1}^N + 1), & \text{at rate } N^2 X_j^N. \end{cases}$$

At the level of the whole vector, we get for $1 \leq j \leq N$

$$\begin{cases} X^N \longrightarrow X^N + \gamma_{j,r} e_j & \text{at rate } \lambda_r(X_j^N), \\ X^N \longrightarrow X^N + e_{j-1} - e_j & \text{at rate } N^2 X_j^N \\ X^N \longrightarrow X^N + e_{j+1} - e_j & \text{at rate } N^2 X_j^N, \end{cases}$$

where $\{e_j, j = 1, \dots, N\}$ is the canonical basis of \mathbb{R}^N .

In all the article, we assume that the rates of onsite reactions are polynomial functions and that there are a finite number of reaction in \mathfrak{R} .

Two types of events are clearly distinguishable: onsite or chemical reactions, and diffusions. We sometimes say reaction for each of them, but we avoid any possibility of confusion. The vectors $\gamma_{j,r} e_j, e_{j-1} - e_j, \dots$ appearing in the transitions are the stocheometric coefficients of the corresponding event. They point out the different possible directions that the jump due to an event can take. We also denote them by jump height or simply jump.

We insist on the fact that the directions of jumps are actually characterized by two parameters: a "true" event - reaction or diffusion - and a location - site - where that event occurs. Furthermore, they are independently chosen and the total jump rate, denoted by λ^N , is the sum of the rates over all the possible directions of jump:

$$\lambda^N(X^N) = \sum_{j=1}^N \left[\sum_{r \in \mathfrak{R}} \lambda_r(X_j^N) + N^2 (X_{j-1}^N + 2X_j^N + X_{j+1}^N) \right].$$

In general, the jump height of an onsite reaction may depend both on that reaction and on the site where it occurs. In the present model, onsite reactions are assumed to be spatially homogeneous, that is

$$\gamma_{j,r} = \gamma_r \quad \text{for all } 1 \leq j \leq N.$$

Well-posedness, generator and debit function. Such a Markov process can be constructed, relying on a sequence $(\tau_i)_{i \geq 1}$ of independent random waiting times with exponential distributions. We set $T_0 = 0$ and $T_k = \tau_1 + \dots + \tau_k$ for $k \geq 1$. $\{T_k, k \geq 1\}$ is a family of $\{\mathcal{F}_t^N\}$ -stopping times such that X^N is constant on each $[T_{k-1}, T_k)$, and has a jump at T_k . The parameter of τ_k is the total jump rate $\lambda^N(X^N(T_{k-1}))$, at time T_{k-1} . For $t > 0$,

$$\mathbb{P}\{\tau_k > t | T_{k-1}\} = \exp\{-t\lambda^N(X^N(T_{k-1}))\}.$$

At time T_k , a given event (or direction of jump) is chosen with probability

$$\frac{\text{"rate of the direction of jump at time } T_{k-1}\text{"}}{\text{"total rate of jump at time } T_{k-1}\text{"}}.$$

Periodic boundary conditions are considered on the spatial domain, and X_j^N is viewed as a sequence satisfying $X_{j+N}^N = X_j^N$ for all j (as in [Blo87], see p.10). The infinitesimal generator of our jump Markov process then reads

$$\begin{aligned} \mathcal{A}^N \varphi(X) &:= \left. \frac{d}{dt} \mathbb{E}_X [\varphi(X^N(t))] \right|_{t=0} := \lim_{t \rightarrow 0} \frac{1}{t} \mathbb{E}_X [\varphi(X^N(t)) - \varphi(X)] \\ &= \sum_{j=1}^N \sum_{r \in \mathfrak{R}} [\varphi(X + \gamma_r e_j) - \varphi(X)] \lambda_r(X_j) \\ &\quad + \sum_{j=1}^N [\varphi(X + e_{j-1} - e_j) + \varphi(X + e_{j+1} - e_j) - 2\varphi(X)] N^2 X_j. \end{aligned} \tag{2.2.3}$$

We need not specify the complete domain of the generator \mathcal{A}^N . The limit above holds, for test functions $\varphi \in C_b(\mathbb{R}^N)$ (see [EK86] p.162-164).

In this stochastic description, the global debit is the function which sums the jump heights weighted with the corresponding rates, under the possible directions of jump. It is a vector field in the state space. If we denote it by Ψ^N , then

$$\begin{aligned} \Psi^N(X) &:= \sum_{j=1}^N \sum_{r \in \mathfrak{R}} \gamma_r \lambda_r(X_j) e_j + N^2 (e_{j-1} - 2e_j + e_{j+1}) X_j \\ &= \sum_{j=1}^N \left(\sum_{r \in \mathfrak{R}} \gamma_r \lambda_r(X_j) + N^2 (X_{j-1} - 2X_j + X_{j+1}) \right) e_j \end{aligned} \tag{2.2.4}$$

for $X \in \mathbb{N}^N$, thanks to periodicity and a change of subscript. We clearly identify the debit of onsite reactions, and that of diffusions. The latter, the linear part in X , defines a discrete Laplace operator that we introduce later.

Scaling and density dependence: The following are parts of the main assumptions in the framework of one scale models.

- On each site, the reactant has a population size of order μ . Typically, μ is large and represents the initial average number of particles on each site.
- Density dependence holds for the reaction rates. That is: for all $r \in \mathfrak{R}$, there exists $\tilde{\lambda}_r$ satisfying

$$\lambda_r(X_j^N) = \mu \tilde{\lambda}_r \left(\frac{X_j^N}{\mu} \right) \quad \text{for all } j = 1, \dots, N.$$

2.2 Modeling and Asymptotics

Density dependence is a natural assumption when dealing with chemical reaction systems (see [Kur70], or Chapter 11 of [EK86]). It clearly holds for linear rates for instance, and can be understood as the fact that reducing the scale is somehow increasing the density, and results in speeding up the dynamic.

In general μ depends on N and we omit to mention the dependence on μ .

We rescale our process, setting

$$U_j^N := U_j^{N,\mu} := \frac{X_j^N}{\mu}, \quad \text{and} \quad U^N := (U_j^N)_{1 \leq j \leq N},$$

and do not distinguish λ_r from $\tilde{\lambda}_r$ in the sequel, for all $r \in \mathfrak{R}$. The new scaled process U^N has values in \mathbb{R}^N and gives the proportions of the reactant on each site. With some abuse, we often say concentration instead of proportion.

In order to achieve a pointwise modeling over the whole spatial domain, a space-time jump Markov process is constructed, which is the stochastic counterpart of the solution to (2.2.1). As in [AT80], [Kot86b] or [Blo87, Blo92], we introduce the step function

$$u^N(t, x) = \sum_{j=1}^N U_j^N(t) \mathbb{1}_j(x), \quad t \geq 0, \quad x \in I_j, \quad (2.2.5)$$

where $\mathbb{1}_j(\cdot) := \mathbb{1}_{I_j}(\cdot)$ is the indicator function of the j -th site I_j . Note that for all $t \geq 0$, $N \geq 1$, the function $u^N(t, \cdot)$ can be identified with the vector $U^N(t)$ of \mathbb{R}^N . Furthermore, since we consider a periodic framework we have $U_{j+N}^N(t) = U_j^N(t)$ and $u^N(t, \cdot)$ is 1-periodic. Below, we use the standard identification $u^N(t) := u^N(t, \cdot)$.

Let \mathbb{H}^N denote the subspace of L^2 which consists of real-valued and 1-periodic step functions that are constant on the intervals I_j , $1 \leq j \leq N$. Therefore, $u^N := \{u^N(t), t \geq 0\}$ is a càdlàg (time-space) Markov process, with values in \mathbb{H}^N and jumps given by:

$$\begin{cases} u^N \longrightarrow u^N + \frac{\gamma_r}{\mu} \mathbb{1}_j, & \text{at rate } \mu \lambda_r(u_j^N), \text{ for } r \in \mathfrak{R}, \\ u^N \longrightarrow u^N + \frac{\mathbb{1}_{j-1} - \mathbb{1}_j}{\mu}, & \text{at rate } \mu N^2 u_j^N, \text{ for } 1 \leq j \leq N, \\ u^N \longrightarrow u^N + \frac{\mathbb{1}_{j+1} - \mathbb{1}_j}{\mu}, & \text{at rate } \mu N^2 u_j^N, \text{ for } 1 \leq j \leq N. \end{cases}$$

Here, $u_j^N = U_j^N$ is the j -th "coordinate" of u^N , obtained by the canonical projection

$$\begin{aligned} P_N &: L^2 \longrightarrow \mathbb{H}^N \\ u &\longmapsto P_N u = \sum_{j=1}^N u_j \mathbb{1}_j, \quad \text{where } u_j := N \int_{I_j} u(x) dx. \end{aligned} \quad (2.2.6)$$

The infinitesimal generator $\mathcal{A}^N := \mathcal{A}^{N,\mu}$ of u^N is given by

$$\begin{aligned} \mathcal{A}^N \varphi(u) &= \sum_{j=1}^N \sum_{r \in \mathfrak{R}} \left[\varphi \left(u + \frac{\gamma_r}{\mu} \mathbb{1}_j \right) - \varphi(u) \right] \mu \lambda_r(u_j) \\ &+ \sum_{j=1}^N \left[\varphi \left(u + \frac{\mathbb{1}_{j-1} - \mathbb{1}_j}{\mu} \right) + \varphi \left(u + \frac{\mathbb{1}_{j+1} - \mathbb{1}_j}{\mu} \right) - 2\varphi(u) \right] \mu N^2 u_j, \end{aligned} \quad (2.2.7)$$

on the domain $C_b(\mathbb{H}^N)$. It can be extended to $C_b(L^2)$ by

$$\bar{\mathcal{A}}^N \varphi(u) := \mathcal{A}^N \varphi(P_N u).$$

Such a Markov process does exist and is unique (see [Kot88b] whose result is based on [EK86]) until a possible blow-up time. In addition, under natural assumptions on the reaction rates, we have $u^N(t) \geq 0$ for all t , as soon as $u^N(0) \geq 0$.

As already mentioned, the convergence of u^N to u solution of (2.2.1) has been the object of several articles. This implies in particular that for N large enough there is no blow-up.

For $f, g \in \mathbb{H}^N$, the L^2 inner product reads $\langle f, g \rangle_2 = N^{-1} \sum_{j=1}^N f_j g_j$. We denote by $\|\cdot\|_2$ the L^2 norm. Also, the supremum norm is given by $\|f\|_\infty = \sup_{1 \leq j \leq N} |f_j|$. Setting $\mathbb{H} := \cup_{N \geq 1} \mathbb{H}^N$, the following obviously holds.

Proposition 2.2.1.

- (i) $(\mathbb{H}^N, \langle \cdot, \cdot \rangle_2)$ is a finite dimensional Hilbert space with $\{\sqrt{N} \mathbf{1}_j, 1 \leq j \leq N\}$ as an orthonormal basis.
- (ii) $\lim_{N \rightarrow \infty} \|P_N u - u\|_2 \rightarrow 0$ for $u \in L^2$, and $(\mathbb{H}, \|\cdot\|_2)$ is dense in $(L^2, \|\cdot\|_2)$.
- (iii) P_N is a contracting linear continuous operator on $(C_p(I), \|\cdot\|_\infty)$ such that $\lim_{N \rightarrow \infty} \|P_N u - u\|_\infty \rightarrow 0$ for $u \in C_p(I)$, and $(\mathbb{H}, \|\cdot\|_\infty)$ is dense in $(C_p(I), \|\cdot\|_\infty)$.

2.2.2 Multiscale Stochastic Spatial Model

Now we wish to generalize [CDMR12] to a spatially dependent context. We consider two orders of population sizes and repeat the previous procedure. Note that at least two types of reactants are needed, i.e. $M \geq 2$ is necessary. For simplicity, we consider exactly two reactants, i.e. we take $M = 2$, that we denote by C and D . The former is abundant and the latter is rare. Henceforth, the super/subscript C (resp. D) refers to the species C (resp. D).

The set \mathfrak{R} of possible onsite reactions is divided in three disjoint subsets

$$\mathfrak{R} = \mathfrak{R}_C \cup \mathfrak{R}_{DC} \cup \mathfrak{R}_D.$$

Reactions in \mathfrak{R}_C (resp. \mathfrak{R}_D) involve only molecules of C (resp. D) as reactants and products, whereas, reactions in \mathfrak{R}_{DC} involve both types of reactants and/or products. We assume:

Assumption 2.2.2.

- (i) Density dependence holds for reactions in \mathfrak{R}_C .
- (ii) Reactions $r \in \mathfrak{R}_C$ are spatially homogeneous and fast ("pure fast reactions"), while reactions $r \in \mathfrak{R}_D$ are slow ("pure slow reactions").
- (iii) The molecules of C diffuse, while those of D do not.

Now, we define

- $X_j^{N,C}$ (resp. $X_j^{N,D}$) as the number of molecules of C (resp. D) on the site j ,
- $X_C^N := (X_j^{N,C})_{1 \leq j \leq N}$, $X_D^N := (X_j^{N,D})_{1 \leq j \leq N}$ and $X^N := (X_C^N, X_D^N) \in \mathbb{N}^{2N}$.

Scales are set such that on every site, the initial average number of molecules for C is of order μ , while it is of order κ for D , with $\mu \gg \kappa$. Namely, if the total initial population is $\mathfrak{M} = \mathfrak{M}_C + \mathfrak{M}_D$, then $\mathfrak{M}_C \approx N \times \mu$ while $\mathfrak{M}_D \approx N \times \kappa$. We set

2.2 Modeling and Asymptotics

$$U_j^{N,C} := U_j^{N,\mu,C} := \frac{X_j^{N,C}}{\mu}, \quad U_j^{N,D} := U_j^{N,\mu,D} := X_j^{N,D},$$

$$U_C^N := \left(U_j^{N,C} \right)_{1 \leq j \leq N}, \quad U_D^N := \left(U_j^{N,D} \right)_{1 \leq j \leq N},$$

and finally

$$U^{N,\mu} =: U^N := (U_C^N, U_D^N).$$

The new scaled process U^N has values in $\mathbb{R}^N \times \mathbb{N}^N$. Its generator has the form

$$\begin{aligned} & \mathcal{A}^{N,\mu} \varphi(U_C, U_D) \\ &= \sum_{j=1}^N \left\{ \sum_{r \in \mathfrak{R}_C} \left[\varphi \left(U_C + \frac{\gamma_{j,r}^C}{\mu} e_j, U_D \right) - \varphi(U_C, U_D) \right] \mu \lambda_r(U_j^C) \right. \\ & \quad + \sum_{r \in \mathfrak{R}_{DC}} \left[\varphi \left(U_C + \frac{\gamma_{j,r}^C}{\mu} e_j, U_D + \gamma_{j,r}^D e_j \right) - \varphi(U_C, U_D) \right] \lambda_r(U_j^C, U_j^D) \\ & \quad \left. + \sum_{r \in \mathfrak{R}_D} \left[\varphi(U_C, U_D + \gamma_{j,r}^D e_j) - \varphi(U_C, U_D) \right] \lambda_r(U_j^D) \right\} \\ & + \sum_{j=1}^N \left\{ \left[\varphi \left(U_C + \frac{e_{j-1} - e_j}{\mu}, U_D \right) + \varphi \left(U_C + \frac{e_{j+1} - e_j}{\mu}, U_D \right) - 2\varphi(U_C, U_D) \right] \mu N^2 U_j^C \right\} \end{aligned}$$

for test functions $\varphi \in C_b(\mathbb{R}^{2N})$ and $U = (U_C, U_D) \in \mathbb{R}^{2N}$.

Below, we discuss the nature of the reactions in \mathfrak{R}_{DC} , and consider situations where $\gamma_j^{r,D}$ and λ_r need to be rescaled, for $r \in \mathfrak{R}_D$ and some $r \in \mathfrak{R}_{DC}$.

Next, we introduce the step function

$$u^N(t, x) = \sum_{j=1}^N U_j^N(t) \mathbf{1}_j(x), \quad t \geq 0, \quad x \in I_j, \quad (2.2.8)$$

which belongs to $\mathbb{H}^N \times \mathbb{H}^N$. It involves the following functions for each component

$$u_C^N(t, x) = \sum_{j=1}^N u_j^{N,C}(t) \mathbf{1}_j(x) \quad \text{and} \quad u_D^N(t, x) = \sum_{j=1}^N u_j^{N,D}(t) \mathbf{1}_j(x),$$

where

$$u_j^{N,C}(t) := P_N u_C^N(t) = N \int_{I_j} u_C^N(t, x) dx = U_j^{N,C}(t),$$

and a similar relation holds for the reactant D . Therefore, $u^N := \{u^N(t), t \geq 0\}$ is a $\mathbb{H}^N \times \mathbb{H}^N$ -

valued càdlàg jump Markov process, with the transitions:

$$\left\{ \begin{array}{l} (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\gamma_{j,r}^C}{\mu} \mathbb{1}_j, u_D^N \right), \text{ at rate } \mu \lambda_r \left(u_j^{N,C} \right), \text{ for } r \in \mathfrak{R}_C, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\gamma_{j,r}^C}{\mu} \mathbb{1}_j, u_D^N + \gamma_{j,r}^D \mathbb{1}_j \right), \text{ at rate } \lambda_r \left(u_j^{N,C}, u_j^{N,D} \right), r \in \mathfrak{R}_{DC}, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N, u_D^N + \gamma_{j,r}^D \mathbb{1}_j \right), \text{ at rate } \lambda_r \left(u_j^{N,D} \right), \text{ for } r \in \mathfrak{R}_D, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\mathbb{1}_{j-1} - \mathbb{1}_j}{\mu}, u_D^N \right), \text{ at rate } N^2 u_j^{N,C}, \text{ for } 1 \leq j \leq N, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\mathbb{1}_{j+1} - \mathbb{1}_j}{\mu}, u_D^N \right), \text{ at rate } N^2 u_j^{N,C}, \text{ for } 1 \leq j \leq N, \end{array} \right. \quad (2.2.9)$$

We endow $\mathbb{H}^N \times \mathbb{H}^N$ with the norm

$$\|(f_1, f_2)\|_{\infty, \infty} := \|f_1\|_{\infty} + \|f_2\|_{\infty}, \quad \text{for } f_1, f_2 \in \mathbb{H}^N.$$

As before, we assume that onsite reactions in \mathfrak{R}_C are spatially homogeneous, that is

$$\gamma_{j,r}^C = \gamma_r^C \quad \text{for all } 1 \leq j \leq N, r \in \mathfrak{R}_C.$$

Let us specify the description of the mixed reactions.

Assumption 2.2.3. *In some $S_1 \subset \mathfrak{R}_{DC}$, reactions are spatially homogeneous, fast and do not affect the discrete species:*

- $\gamma_{j,r}^D = 0$ and the rate is $\mu \tilde{\lambda}_r \left(u_j^{N,C}, u_j^{N,D} \right)$ for $r \in S_1 \subset \mathfrak{R}_{DC}$

Again we omit the tilde below.

The limit $N \rightarrow \infty$ of the above system creates mathematical difficulties (see Remark 2.3.3 and Remark 2.4.1 below). We introduce some spatial correlations for reactions in $(\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D$.

All reactions in $(\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D$ are slow. We assume that when such a reaction occurs on a site, it affects the neighboring sites. A natural way to do this is to assume that when the reaction $r \in (\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D$ occurs at a site $j \in \{1, \dots, N\}$, each site $i \in \{1, \dots, N\}$, is affected in the following way:

$$(u_j^{N,C}, u_j^{N,D}) \longrightarrow \left(u_j^{N,C} + \frac{\gamma_r^C}{\mu} \gamma_{ij}^N, u_j^{N,D} + \gamma_r^D \gamma_{ij}^N \right). \quad (2.2.10)$$

A first possibility is to take $\gamma_{ij}^N = \frac{1}{A}$ for $|i - j| < A$, describing the case when a reaction at site i triggers simultaneously the same reaction at sites at distance less than $\frac{A}{N}$, while keeping the global effect of order 1. The above model corresponds to $A = 1$ but below we assume that A has the same order as N . More generally, we choose a 1-periodic $C_p(I)$ function a and choose:

$$\gamma_{ij}^N = \int_{I_i} a \left(x - \frac{j}{N} \right) dx.$$

It is natural to assume that a is maximum at zero, and is even decaying with respect to $|x|$. The preceding case is recovered with a being an indicator function. Note that we should require that $\gamma_r^D \gamma_{ij}^N$ is an integer, but it is complicated to write general conditions to ensure this.

2.2 Modeling and Asymptotics

This modeling has a problem. Indeed, the positivity of the proportion of molecules is ensured by the fact that the rate vanishes when the proportion vanishes, but now, since we have a nonlocal effect this is not true. It would not be realistic to consider a rate which depends on the proportion at all neighboring sites. Instead, we simply assume that when a reaction occurs at site j , it has an effect at a site i only if the reaction is possible. Thus we would like to replace (2.2.10) by

$$(u_j^{N,C}, u_j^{N,D}) \longrightarrow \left(u_j^{N,C} + \frac{\gamma_r^C}{\mu} \gamma_{ij}^N \theta_{ij}^r, u_j^{N,D} + \gamma_r^D \gamma_{ij}^N \theta_{ij}^r \right) \quad (2.2.11)$$

with $\theta_{ij}^r = \theta_{ij}^r(u_j^{N,C}, u_j^{N,D}) = \mathbb{1}_{u_j^{N,C} + \frac{\gamma_r^C}{\mu} \gamma_{ij}^N \geq 0} \mathbb{1}_{u_j^{N,D} + \gamma_r^D \gamma_{ij}^N \geq 0}$, where $\gamma_r^C = 0$ for $r \in \mathfrak{R}_D$. Again, this creates mathematical difficulties, since the indicator function is not smooth. We replace it by a smooth function θ equal to 0 on $(-\infty, 0]$, to 1 on $[1, \infty)$ and smoothly increasing on $[0, 1]$. We are now able to write the multiscale model we consider.

Assumption 2.2.4. *When a slow reaction $r \in (\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D$ occurs on a site j , it affects C and D on a site $1 \leq i \leq N$ in the following way:*

$$\gamma_{j,r}^C \equiv \gamma_{j,r}^{N,C}(u_C^N, u_D^N) := \gamma_r^C \sum_{i=1}^N \gamma_{ij}^N \mathbb{1}_i \theta_{ij}^r(u_i^{N,C}, u_i^{N,D})$$

and

$$\gamma_{j,r}^D \equiv \gamma_{j,r}^{N,D}(u_C^N, u_D^N) := \gamma_r^D \sum_{i=1}^N \gamma_{ij}^N \mathbb{1}_i \theta_{ij}^r(u_i^{N,C}, u_i^{N,D}),$$

where $\gamma_{ij}^N := \int_{I_i} a \left(x - \frac{j}{N} \right) dx$, and $\theta_{ij}^r(u_i^{N,C}, u_i^{N,D}) = \theta \left(u_i^{N,C} + \frac{\gamma_r^C}{\mu} \gamma_{ij}^N \right) \theta \left(u_i^{N,D} + \gamma_r^D \gamma_{ij}^N \right)$.

Remark 2.2.1. *Assumption 2.2.4 points out some spatial correlation for slow reactions. These latter start on a source site j , and then, their effect spreads inside the system. This is a natural assumption in molecular biologie. In the cell, the synthesis of some rare proteins is the launch for a sequence of chemical reactions in chain. This kind of phenomenon precedes the activation of a gene on DNA (DeoxyriboNucleic Acid) for instance.*

Since $\mathbb{1}_i(x)$ is nonzero only on I_i and $\gamma_{ij}^N \leq \frac{a(0)}{N}$, we clearly have:

$$\left\| \gamma_{j,r}^{N,C}(u_C^N, u_D^N) \right\|_{\infty} \leq \frac{|\gamma_r^C| a(0)}{N} \quad \text{and} \quad \left\| \gamma_{j,r}^{N,D}(u_C^N, u_D^N) \right\|_{\infty} \leq \frac{|\gamma_r^D| a(0)}{N} \quad (2.2.12)$$

The infinitesimal generator of u^N on $C_b(\mathbb{H}^N \times \mathbb{H}^N)$ then reads

$$\begin{aligned}
 & \mathcal{A}^N \varphi(u_C, u_D) \\
 &= \sum_{j=1}^N \left\{ \sum_{r \in \mathfrak{R}_C} \left[\varphi \left(u_C + \frac{\gamma_r^C}{\mu} \mathbf{1}_j, u_D \right) - \varphi(u_C, u_D) \right] \mu \lambda_r(u_j^C) \right. \\
 & \quad + \sum_{r \in \mathfrak{S}_1} \left[\varphi \left(u_C + \frac{\gamma_r^C}{\mu} \mathbf{1}_j, u_D \right) - \varphi(u_C, u_D) \right] \mu \lambda_r(u_j^C, u_j^D) \\
 & \quad + \sum_{r \in \mathfrak{R}_{DC} \setminus \mathfrak{S}_1} \left[\varphi \left(u_C + \frac{\gamma_{j,r}^{N,C}(u_C, u_D)}{\mu}, u_D + \gamma_{j,r}^{N,D}(u_C, u_D) \right) - \varphi(u_C, u_D) \right] \\
 & \quad \left. \times \lambda_r(u_j^C, u_j^D) \right. \\
 & \quad \left. + \sum_{r \in \mathfrak{R}_D} \left[\varphi \left(u_C, u_D + \gamma_{j,r}^{N,D}(u_C, u_D) \right) - \varphi(u_C, u_D) \right] \lambda_r(u_j^D) \right\} \\
 & + \sum_{j=1}^N \left[\varphi \left(u_C + \frac{\mathbf{1}_{j-1} - \mathbf{1}_j}{\mu}, u_D \right) + \varphi \left(u_C + \frac{\mathbf{1}_{j+1} - \mathbf{1}_j}{\mu}, u_D \right) - 2\varphi(u_C, u_D) \right] \mu N^2 u_j^C
 \end{aligned} \tag{2.2.13}$$

It can be extended to $C_b(L^2 \times L^2)$ by

$$\mathcal{A}^N \varphi(u_C, u_D) := \mathcal{A}^{N,\mu} \varphi(P_N u_C, P_N u_D).$$

For $u := (u_C, u_D) \in L^2 \times L^2$, we may often use the notation $\tilde{P}_N u := (P_N u_C, P_N u_D)$.

Again, such a process exists until a possible blow-up time. If the process blows up, we say that from this time it takes a cemetery value $\bar{\Delta}$ whose distance to any point is 1.

2.2.3 Convergence of (M6)

We discuss the asymptotic behavior of the sequence u^N of Markov processes representing (M6), as N and μ go to the infinity, for polynomial (onsite) reaction rates.

Identification of the limit

Some preliminaries: a discrete Laplace. For $f \in C_p(I)$ and for $x \in [0, 1]$, we set

$$\nabla_N^+ f(x) := N \left[f \left(x + \frac{1}{N} \right) - f(x) \right] \quad \text{and} \quad \nabla_N^- f(x) := N \left[f(x) - f \left(x - \frac{1}{N} \right) \right].$$

Then, we define the discrete Laplace

$$\begin{aligned}
 \Delta_N f(x) &:= \nabla_N^+ \nabla_N^- f(x) \\
 &= \nabla_N^- \nabla_N^+ f(x) = N^2 \left[f \left(x - \frac{1}{N} \right) - 2f(x) + f \left(x + \frac{1}{N} \right) \right].
 \end{aligned}$$

If $f \in \mathbb{H}^N$ in particular, then

$$\Delta_N f(x) = \sum_{j=1}^N [N^2(f_{j-1} - 2f_j + f_{j+1})] \mathbf{1}_j(x).$$

2.2 Modeling and Asymptotics

From the spectral analysis of Δ_N , it is well known that, if N is an odd integer, letting $0 \leq m \leq N - 1$ with m even, letting $\varphi_{0,N} \equiv 1$, $\varphi_{m,N}(x) = \sqrt{2}\cos(\pi m j N^{-1})$ and $\psi_{m,N}(x) = \sqrt{2}\sin(\pi m j N^{-1})$ for $x \in I_j$, then, $\{\varphi_{m,N}, \psi_{m,N}\}$ are eigenfunctions of Δ_N with eigenvalues given by $-\beta_{m,N} = -2N^2(1 - \cos(\pi m N^{-1})) \leq 0$. If N is even, we need the additional eigenfunction $\varphi_{N,N} = \cos(\pi j)$ for $x \in I_j$. The following (classical) properties are derived from [Blo87], Lemma 2.12 p.12, [Blo92], Lemma 4.2 for the parts (i)-(vi), and from [Kat66a], chapter 9, Section 3 for the part (vi).

Proposition 2.2.2. (Some properties of the discrete Laplace)

(i) The family $\{\varphi_{m,N}, \psi_{m,N}\}$ forms an orthonormal basis of $(\mathbb{H}^N, \langle \cdot, \cdot \rangle_2)$.

Consider $f, g \in \mathbb{H}^N$ and let $T_N(t) = e^{\Delta_N t}$ denote the semigroup on \mathbb{H}^N generated by Δ_N .

(ii) $T_N(t)f = \sum_m e^{-\beta_{m,N}t} (\langle f, \varphi_{m,N} \rangle_2 \varphi_{m,N} + \langle f, \psi_{m,N} \rangle_2 \psi_{m,N})$.

(iii) $\langle \nabla_N^+ f, g \rangle_2 = \langle f, \nabla_N^- g \rangle_2$ and $T_N(t)\Delta_N f = \Delta_N T_N(t)f$.

(iv) Δ_N and $T_N(t)$ are self-adjoint on $(\mathbb{H}^N, \langle \cdot, \cdot \rangle_2)$.

(v) $T_N(t)$ is a positive contraction semigroup on both $(\mathbb{H}^N, \langle \cdot, \cdot \rangle_2)$ and $(\mathbb{H}^N, \|\cdot\|_\infty)$.

(vi) The projection P_N commutes with Δ_N , and $\forall T > 0, f \in C^3(I)$,

$$\begin{cases} \|\Delta_N f - \Delta f\|_\infty \longrightarrow 0 & \text{as } N \rightarrow \infty, \\ \|\Delta_N P_N f - \Delta f\|_\infty \longrightarrow 0 & \text{as } N \rightarrow \infty, \\ \sup_{t \in [0, T]} \|T_N(t)P_N f - T(t)f\|_\infty \longrightarrow 0 & \text{as } N \rightarrow \infty. \end{cases}$$

We introduce the operator $\tilde{\Delta}_N := \begin{pmatrix} \Delta_N & 0 \\ 0 & 0 \end{pmatrix}$ on $\mathbb{H}^N \times \mathbb{H}^N$, and denote by $\tilde{T}_N(t) := e^{\tilde{\Delta}_N t}$ the associated semigroup.

(vii) $\tilde{\Delta}_N$ is a bounded linear operator on $(\mathbb{H}^N \times \mathbb{H}^N, \|\cdot\|_{\infty, \infty})$.

(viii) $\tilde{T}_N(t) = \begin{pmatrix} T_N(t) & 0 \\ 0 & I_d \end{pmatrix}$, and defines a bounded positive contraction semigroup on $(\mathbb{H}^N \times \mathbb{H}^N, \|\cdot\|_{\infty, \infty})$. We have denoted by I_d is the identity operator on \mathbb{H}^N .

Debit functions and formal limit of the generator. We consider the generator \mathcal{A}^N of (M6) given by (2.2.13), applied to a $C_b^2(\mathbb{H}^N \times \mathbb{H}^N)$ test function φ . We use a Taylor expansion of order 2 of φ . From Section 2.2.1, we know that the generator is (informally) obtained as the image of the corresponding debit by the differential of the test function.

In Section 2.4.1, we give heuristics showing that the terms related to the second order of the Taylor expansion vanish, under the very strong condition $\mu^{-1}N^2 \rightarrow 0$ as $N, \mu \rightarrow \infty$. In our rigorous proof below, we only assume $\mu^{-1} \log N \rightarrow 0$.

Concerning the first order terms, we identify the differential operator with the gradient as usual, and get

$$\begin{aligned} & (D\varphi(u_C, u_D), \Psi^N(u_C, u_D)) \\ &= \left\langle D^{1,0}\varphi(u_C, u_D), \sum_{j=1}^N \left(\sum_{r \in \mathfrak{R}_C} \gamma_r^C \lambda_r(u_j^C) + \sum_{r \in S_1} \gamma_r^C \lambda_r(u_j^C, u_j^D) \right) \mathbf{1}_j \right\rangle_2 \end{aligned}$$

$$\begin{aligned}
 & + \left\langle D^{1,0} \varphi(u_C, u_D), \sum_{j=1}^N \left(\sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \frac{\gamma_{j,r}^{N,C}(u_C, u_D)}{\mu} \lambda_r(u_j^C, u_j^D) \right) \mathbf{1}_j \right\rangle_2 \\
 & + \left\langle D^{1,0} \varphi(u_C, u_D), \sum_{j=1}^N N^2 (\mathbf{1}_{j-1} - 2\mathbf{1}_j + \mathbf{1}_{j+1}) u_j^C \right\rangle_2 \\
 & + \left\langle D^{0,1} \varphi(u_C, u_D), \sum_{j=1}^N \left(\sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \gamma_{j,r}^{N,D}(u_C, u_D) \lambda_r(u_j^C, u_j^D) + \sum_{r \in \mathfrak{R}_D} \gamma_{j,r}^{N,D}(u_C, u_D) \lambda_r(u_j^D) \right) \right\rangle_2,
 \end{aligned}$$

where $D^{1,0}$ (resp. $D^{0,1}$) denotes the differential with respect to u_C (resp. u_D).

On the one hand, we derive the debit function $\Psi_C^N : \mathbb{H}^N \times \mathbb{H}^N \rightarrow \mathbb{H}^N$, related to the reactant C and defined by

$$\Psi_C^N(u_C, u_D) := \Delta_N u_C + F(u_C, u_D) + F_1^N(u_C, u_D). \quad (2.2.14)$$

The first term on the r.h.s. is the debit of the diffusions of molecules of C . As in (2.2.4), it is obtained using the periodicity and a change of index:

$$\sum_{j=1}^N N^2 (\mathbf{1}_{j-1} - 2\mathbf{1}_j + \mathbf{1}_{j+1}) u_j^C = \sum_{j=1}^N N^2 (u_{j+1}^C - 2u_j^C + u_{j-1}^C) \mathbf{1}_j = \Delta_N u_C. \quad (2.2.15)$$

The second term is associated with fast onsite reactions (they all influence C). It is given by

$$\begin{aligned}
 F(u_C, u_D) & = \sum_{j=1}^N \left(\sum_{r \in \mathfrak{R}_C} \gamma_r^C \lambda_r(u_j^C) + \sum_{r \in S_1} \gamma_r^C \lambda_r(u_j^C, u_j^D) \right) \mathbf{1}_j \\
 & = \sum_{r \in \mathfrak{R}_C} \gamma_r^C \lambda_r(u_C) + \sum_{r \in S_1} \gamma_r^C \lambda_r(u_C, u_D).
 \end{aligned} \quad (2.2.16)$$

The third term corresponds to slow onsite reactions influencing C and vanishes at the limit. It is defined by

$$F_1^N(u_C, u_D) = \frac{1}{\mu} \sum_{j=1}^N \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \gamma_r^C \sum_{i=1}^N \gamma_{ij}^N \mathbf{1}_i \theta_{ij}^r(u_i^C, u_i^D) \lambda_r(u_j^C, u_j^D) \quad (2.2.17)$$

On the other hand, we have $\Psi_D^N : \mathbb{H}^N \times \mathbb{H}^N \rightarrow \mathbb{H}^N$, the debit related to D . It corresponds to slow onsite reactions - only them has an effect on D - and is given by

$$\Psi_D^N(u_C, u_D) = \sum_{j=1}^N \sum_{i=1}^N \gamma_{ij}^N \mathbf{1}_i g_{ij}(u_C, u_D) =: G^N(u_C, u_D), \quad (2.2.18)$$

where

$$g_{ij}(u_C, u_D) = \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \gamma_r^D \theta_{ij}^r(u_i^C, u_i^D) \lambda_r(u_j^C, u_j^D) + \sum_{r \in \mathfrak{R}_D} \gamma_r^D \theta_{ij}^r(u_i^C, u_i^D) \lambda_r(u_j^D).$$

The global debit on $\mathbb{H}^N \times \mathbb{H}^N$ then reads

$$\Psi^N(u_C, u_D) = (\Psi_C^N(u_C, u_D), \Psi_D^N(u_C, u_D)).$$

2.2 Modeling and Asymptotics

We finally define the extra debit type function $G : C_p(I) \times C_p(I) \longrightarrow C_p(I)$, by

$$G(u_C, u_D)(x) := \theta(u_C(x))\theta(u_D(x)) \int_0^1 g(u_C, u_D)(y)a(x-y)dy \quad (2.2.19)$$

for all $x \in I$. It is the limit of G^N (see Section 2.4.4). Here,

$$g(u_C, u_D) = \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \gamma_r^D \lambda_r(u_C, u_D) + \sum_{r \in \mathfrak{R}_D} \gamma_r^D \lambda_r(u_D).$$

Remark 2.2.2. We notice that Δ_N , F , F_1^N and G^N map $C_p(I) \times C_p(I)$ on $C_p(I)$. This follows from the definition of the discrete Laplace, and from we are considering polynomial reaction rates. Here above, we have considered these three functions on $\mathbb{H}^N \times \mathbb{H}^N$, as they were introduced to define the debit function, on $\mathbb{H}^N \times \mathbb{H}^N$.

Besides, the debit can be extended to $C_p(I) \times C_p(I)$, not by taking Δ_N , F , F_1^N and G^N as maps on $C_p(I) \times C_p(I)$, but using the projection P_N introduced earlier, in a similar way as for extending the generator. Namely, the global debit extends to

$$(u_C, u_D) \mapsto (\Psi_C^N(P_N u_C, P_N u_D), \Psi_D^N(P_N u_C, P_N u_D)).$$

Furthermore, it should be emphasized that each of F , F_1^N and λ_r , $r \in \mathfrak{R}$ is a function of real variables, actually. Still, we use the notation $F(u)$ for $u \in C_p(I) \times C_p(I)$. That is, for a given u , we define a function $f(u) : I \rightarrow \mathbb{R}$ by

$$f(u)(x) = F(u(x)), \quad \forall x \in [0, 1].$$

If F is (locally) Lipschitz, then f is (locally) Lipschitz too, accordingly, with the corresponding norms. We do not distinguish between F and f in our notation, and do the same for the functions F_1^N and λ_r , $r \in \mathfrak{R}$.

Fix $u = (u_C, u_D) \in C_p(I) \times C_p(I)$ and let $N, \mu \rightarrow \infty$. Clearly, $F_1^N(\tilde{P}_N u) \rightarrow 0$. From Proposition 3.2.1 and the continuity of F , $F(\tilde{P}_N u) \rightarrow F(u)$. Therefore, if $u_C \in C^3(I)$, $\Psi_C^N(\tilde{P}_N u) \rightarrow \Delta u_C + F(u)$ thanks to Proposition 3.2.2 (vi). We also prove below that $\Psi_D^N(\tilde{P}_N u) = G^N(\tilde{P}_N u) \rightarrow G(u)$. Therefore, under the strong assumption $\mu^{-1}N^2 \rightarrow 0$ and $u_C \in C^3(I)$, we obtain the limit generator

$$\begin{aligned} \mathcal{A}^\infty \varphi(u_C, u_D) &= \langle D^{1,0} \varphi(u_C, u_D), \Delta u_C + F(u_C, u_D) \rangle_2 \\ &\quad + \langle D^{0,1} \varphi(u_C, u_D), G(u_C, u_D) \rangle_2. \end{aligned} \quad (2.2.20)$$

The condition $\mu^{-1}N^2 \rightarrow 0$ was used By Arnold and Theodosopulu in [AT80], to prove a LLN for (M4) in the L^2 norm. However, that condition is not optimal. Indeed, in [Blo92], Blount proved a LLN for (M4) in the supremum norm, requiring only $\mu^{-1} \log N \rightarrow 0$. Our convergence result for (M6) falls within the latter framework.

We now look for a process admitting \mathcal{A}^∞ defined by (2.2.20) as infinitesimal generator.

The limiting problem

Well-posedness. Proceeding as in Section 2.2.1, we see that to \mathcal{A}^∞ , corresponds

$$\frac{\partial v_C}{\partial t} = \Delta v_C + F(v_C, v_D) \quad (\text{PDE}) \quad \text{coupled to} \quad (\text{ODE}) \quad \frac{dv_D}{dt} = G(v_C, v_D).$$

Hence, we shall consider the following system of differential equations, for $x \in I$, $t \geq 0$, with periodic boundary conditions and initial data $v_0 = (v_0^C, v_0^D)$:

$$\begin{cases} \frac{\partial}{\partial t} v_C(t, x) = \Delta v_C(t, x) + F(v_C(t, x), v_D(t, x)) \\ \frac{\partial}{\partial t} v_D(t, x) = G(v_C(t, x), v_D(t, x)) \\ v_C(t, 0) = v_C(t, 1) \quad \text{and} \quad v_D(t, 0) = v_D(t, 1) \quad \forall t \geq 0 \\ v_C(0, x) = v_0^C(x) \geq 0 \quad \text{and} \quad v_D(0, x) = v_0^D(x) \geq 0 \quad \forall x. \end{cases}$$

A compact form of the system is:

$$\begin{cases} \frac{d}{dt} v(t) = \tilde{\Delta} v(t) + R(v(t)) \\ v(t, 0) = v(t, 1) \quad \forall t \geq 0 \\ v(0) = v_0 \geq 0, \end{cases} \quad (2.2.21)$$

where $\tilde{\Delta} = \begin{pmatrix} \Delta & 0 \\ 0 & 0 \end{pmatrix} : C_p(I) \times C_p(I) \rightarrow C_p(I)$ is a linear operator we define on the domain $C^2(I) \times C_p(I)$, and whose associated semigroup $\tilde{T}(t) := e^{\tilde{\Delta}t}$ is of contraction. For $u \in C_p(I) \times C_p(I)$, $R(u) = \begin{pmatrix} F(u) \\ G(u) \end{pmatrix}$, with $G(u) = \theta(u_C)\theta(u_D)a * g(u)$.

Before, we give the counterpart of *Assumption 2.2.1* for (2.2.21), let us introduce the \mathbb{H}^N -valued function $|g|$ defined by $|g|(u) := \sum_{j=1}^N |g|_j(u) \mathbf{1}_j$ for $u = (u_C, u_D) \in C_p(I) \times C_p(I)$, where

$$|g|_j(u_C, u_D) := \sum_{r \in \mathcal{R}_{DC} \setminus S_1} |\gamma_r^D| \lambda_r(u_j^C, u_j^D) + \sum_{r \in \mathcal{R}_D} |\gamma_r^D| \lambda_r(u_j^D),$$

so that

$$|g|(u) = \sum_{r \in \mathcal{R}_{DC} \setminus S_1} |\gamma_r^D| \lambda_r(u_C, u_D) + \sum_{r \in \mathcal{R}_D} |\gamma_r^D| \lambda_r(u_D).$$

Below, we introduce different quantities and functions such as $|g|$, related to debit type functions, and explain the intuition behind them. We call $|g|$ the "amplitude function" associated with the debit type function g . Then as usual, we may view $|g|$ as a real valued function defined on \mathbb{R}^2 . Now, we make the following

Assumption 2.2.5.

(C1) F is locally Lipschitz and $F(y) \geq 0$ for $y = (y_1, y_2) \in \mathbb{R}^2$ such that $y_1 = 0$.

(C2) There exists $0 < \rho_C < \infty$ such that $|y| > \rho_C$ yields $F(y) < 0$ for all $y \in \mathbb{R}^m$.

(D1) $\theta(y) = 0$ for $y \leq 0$.

(D2) g is locally Lipschitz, and $|g|$ has at most linear growth w.r.t. its second variable: for all $\bar{c} > 0$ there exists $M_1(\bar{c}) \geq 0$ such that, for $|y_1| \leq \bar{c}$, $|g|(y_1, y_2) \leq M_1(\bar{c})(|y_2| + 1)$.

2.2 Modeling and Asymptotics

Concerning the reactant C , Assumption 2.2.5 (C1) and (C2) correspond to Assumption 2.2.1. These conditions are met in particular, as soon as the rate of each fast reaction satisfies (C1) and (C2) in the place of F . Yet, there is difference with D . First of all, in order to ensure positivity for its concentration, we have introduced the function θ in Assumption 2.2.4. Moreover, the debit associated with D involves a convolution product at the limit. It seems difficult to write an assumption similar to (C2) and we assume linear growth which is less general.

The upcoming result states that \mathcal{A}^∞ is the generator of a unique process. It is a straightforward adaptation of the result of Kotelenz in [Kot86a], about well-posedness for the one scale deterministic spatial model.

Proposition 2.2.3. *Assume that:*

- (i) *the rates of onsite reactions are polynomial and such that Assumption 2.2.5 holds,*
- (ii) $v_0 = (v_0^C, v_0^D) \in C^3(I) \times C^3(I)$,
- (iii) $\rho_C, \rho_D \gg 1$ such that $\|v_0^C\|_\infty < \rho_C < \infty$ and $\|v_0^D\|_\infty < \rho_D < \infty$.

Then, (2.2.21) has a unique global mild solution $v := v(t, v_0)$ satisfying

$$v = (v_C, v_D) \in C(\mathbb{R}_+; C^3(I) \times C^3(I)) \quad (2.2.22)$$

and

$$v(t) = \tilde{T}(t)v_0 + \int_0^t \tilde{T}(t-s)R(v(s))ds \quad \forall t \geq 0. \quad (2.2.23)$$

Moreover,

$$\begin{cases} v_C(t) \geq 0, & v_D(t) \geq 0 & \forall t \geq 0, \\ \|v_C(t)\|_\infty \leq \rho_C & \forall t \geq 0, \\ \|v_D(t)\|_\infty \leq (\rho_D + 1)e^{a(0)M_1(\rho_C)t} & \forall t \geq 0. \end{cases} \quad (2.2.24)$$

A discretization of the limit. We define a discrete version $v^N = (v_C^N, v_D^N)$ of the limiting problem. Henceforth, $v = (v_C, v_D)$ denotes the solution to (2.2.21) given by Proposition 2.2.3. For $x \in I$, $t \geq 0$, we consider the system:

$$\begin{cases} \frac{\partial}{\partial t} v_C^N(t, x) = \Delta_N v_C^N(t, x) + F(v_C^N(t, x), v_D^N(t, x)) \\ \frac{\partial}{\partial t} v_D^N(t, x) = G(v_C^N(t, x), v_D^N(t, x)), \\ v_C^N(t, 0) = v_C^N(t, 1) \text{ and } v_D^N(t, 0) = v_D^N(t, 1), \\ v_C^N(0, x) = P_N v_C(0) \text{ and } v_D^N(0) := P_N v_D(0). \end{cases}$$

Note that $v^N(0) = \tilde{P}_N v(0)$, where we recall $\tilde{P}_N v := (P_N v_C, P_N v_D)$. Using the operators introduced in Proposition 3.2.2, a compact version for this system of ODEs reads

$$\begin{cases} \frac{d}{dt} v^N(t) = \tilde{\Delta}_N v^N(t) + R(v^N(t), v^N(t)) \\ v^N(t, 0) = v^N(t, 1) \\ v^N(0) = \tilde{P}_N v(0). \end{cases} \quad (2.2.25)$$

The next result gives a relation between the limiting problem and its discretization. Its proof is reported to Appendix 2.4.2.

Theorem 2.2.1. *If the rates of onsite reactions are polynomial and Assumption 2.2.5 holds, then (2.2.25) has a unique global mild solution $v^N = (v_C^N, v_D^N) \in C(\mathbb{R}_+; \mathbb{H}^N \times \mathbb{H}^N)$ satisfying*

$$v^N(t) = \tilde{T}_N(t)\tilde{P}_N v(0) + \int_0^t \tilde{T}_N(t-s) \begin{pmatrix} F(v^N(s)) \\ G(v^N(s)) \end{pmatrix} ds \quad (2.2.26)$$

for all $t \geq 0$. Furthermore, for any fixed $T > 0$,

$$\begin{cases} \|v_C^N(t)\|_\infty \leq (\rho + 1)/2 & \forall t \geq 0, \\ \|v_D^N(t)\|_\infty \leq \bar{c}_D = \bar{c}_D(M_1, T, a(0)), & \forall 0 \leq t \leq T, \end{cases} \quad (2.2.27)$$

and

$$\sup_{t \in [0, T]} \|v^N(t) - v(t)\|_{\infty, \infty} \longrightarrow 0. \quad (2.2.28)$$

2.3 The Law of Large Numbers

Now, we state and prove our main result.

Theorem 2.3.1. *Consider a sequence $u^N = (u_C^N, u_D^N)$ of Markov processes starting at $u^N(0) = (u_C^N(0), u_D^N(0))$, with infinitesimal generators \mathcal{A}^N given by (2.2.7). Assume that the assumptions of Proposition 2.2.3 hold and:*

- (i) $N, \mu \longrightarrow \infty$ in such a way that $\mu^{-1} \log N \longrightarrow 0$,
- (ii) $u^N(0) \geq 0$ and $\|u^N(0) - v(0)\|_{\infty, \infty} \longrightarrow 0$ in probability.

Then, for all $T > 0$,

$$\sup_{t \in [0, T]} \|u^N(t) - v(t)\|_{\infty, \infty} \longrightarrow 0 \quad \text{in probability.} \quad (2.3.1)$$

Proof. Let $T > 0$ be fixed. Our goal is to show that,

$$\forall \epsilon > 0, \quad \mathbb{P} \left\{ \sup_{[0, T]} \|u^N(t) - v(t)\|_{\infty, \infty} > \epsilon \right\} \longrightarrow 0.$$

It follows from Theorem 2.2.1 that it is sufficient to prove

$$\forall \epsilon > 0, \quad \mathbb{P} \left\{ \sup_{[0, T]} \|u^N(t) - v^N(t)\|_{\infty, \infty} > \epsilon \right\} \longrightarrow 0. \quad (2.3.2)$$

The rest of the proof is divided in two principal steps. In the first step, we successively consider some martingales associated to our model (M6) and, an adequate truncation of our process in time, using the properties of these martingales. The aim is to work only with the truncated model in the place of the initial one. Next, we conclude using a Gronwall-Bellman argument.

2.3 The Law of Large Numbers

2.3.1 Accompanying martingales

Different types of martingales are associated to jump Markov processes such as u^N . Before specifying some of them, we introduce:

Some useful notation. Let $j = 1, \dots, N$ and $u = (u_C, u_D) \in C_p(I) \times C_p(I)$ be fixed.

- $\lambda_j^C(u)$ (resp. $\lambda_j^D(u)$) is the rate for fast (resp. slow) reactions on site j :

$$\lambda_j^C(u_C, u_D) = \mu \left(\sum_{r \in \mathfrak{R}_C} \lambda_r(u_j^C) + \sum_{r \in S_1} \lambda_r(u_j^C, u_j^D) + 2N^2 u_j^C \right),$$

and

$$\lambda_j^D(u_C, u_D) = \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \lambda_r(u_j^C, u_j^D) + \sum_{r \in \mathfrak{R}_D} \lambda_r(u_j^D).$$

- $\lambda_j(u) := \lambda_j^C(u) + \lambda_j^D(u)$ is the total rate for reactions on site j .
- $\lambda^N(u) := \sum_{j=1}^N \lambda_j(u)$ is the total rate for reactions in the system:

$$\begin{aligned} \lambda^N(u_C, u_D) = & \mu \sum_{j=1}^N \left(\sum_{r \in \mathfrak{R}_C} \lambda_r(u_j^C) + \sum_{r \in S_1} \lambda_r(u_j^C, u_j^D) + 2N^2 u_j^C \right) \\ & + \sum_{j=1}^N \left(\sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \lambda_r(u_j^C, u_j^D) + \sum_{r \in \mathfrak{R}_D} \lambda_r(u_j^D) \right). \end{aligned}$$

- If the reaction rates are bounded, we set $\bar{\lambda} := \max(\bar{\lambda}_C, \bar{\lambda}_D)$ where,

$$\bar{\lambda}_C = \sum_{r \in \mathfrak{R}_C \cup S_1} \|\lambda^C\|_\infty \quad \text{with} \quad \|\lambda^C\|_\infty := \sup \{ \|\lambda_r\|_\infty, r \in \mathfrak{R}_C \cup S_1 \}.$$

The notation $\bar{\lambda}_D$ is the counterpart of $\bar{\lambda}_C$ for slow reactions.

- $|\gamma| := \max(|\gamma^C|, |\gamma^D|)$ and $\bar{\gamma} := \max(\bar{\gamma}_C, \bar{\gamma}_D)$.

$$\bar{\gamma}_D := \max \left(\sum_{r \in \mathfrak{R}_{DC} \setminus S_1} |\gamma^D|, \sum_{r \in \mathfrak{R}_D} |\gamma^D| \right), \quad \text{with} \quad |\gamma^D| := \sup_{r \in (\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D} |\gamma_r^D|.$$

The notation $\bar{\gamma}_C$ and $|\gamma^C|$ are the counterparts for fast reactions.

Recall that the debit of a process is defined as the sum of its jumps weighted by the corresponding rates, over all its possible jump directions. Let

$$\delta u_j^N(t) := u_j^N(t) - u_j^N(t^-)$$

be the jump of u_j^N at time t , and denote by $|\delta u_j^N(t)|$ the amplitude of that jump, where $|(y_1, y_2)| = |y_1| + |y_2|$. Firstly, we define the "amplitude" $|\Psi_C^N|_j$ (resp. $|\Psi_D^N|_j$) of the debit $\Psi_j^{N,C}$ (resp. $\Psi_j^{N,D}$), as the debit function of the process

$$\left(\sum_{s \leq t} |\delta u_j^{N,C}(t)| \right)_{t \geq 0} \quad \left[\text{resp.} \quad \left(\sum_{s \leq t} |\delta u_j^{N,D}(t)| \right)_{t \geq 0} \right].$$

As a fact, that notion of "amplitude" is perfectly adapted to any of the specific debit functions Δ_N , F , F_1^N , or G^N . Especially, we have for the part related to C :

- $|\Delta_N|_j(u_C) = N^2 (u_{j-1}^C + 2u_j^C + u_{j+1}^C)$,
- $|F|_j(u_C, u_D) = \sum_{r \in \mathfrak{R}_C} |\gamma_r^C| \lambda_r(u_j^C) + \sum_{r \in S_1} |\gamma_r^C| \lambda_r(u_j^C, u_j^D)$,
- $|F_1^N|_j(u_C, u_D) = \frac{1}{\mu} \sum_{i=1}^N \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} |\gamma_{ij}^N| \theta_{ij}^r(u_i^C, u_i^D) \lambda_r(u_j^C, u_j^D)$,
- $|\Psi_C^N|_j(u_C, u_D) = |\Delta_N|_j(u) + |F|_j(u) + |F_1^N|_j(u_C, u_D)$.

For the part related to the reactant D , we have

- $|g|_{ij}(u_C, u_D) = \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} |\gamma_r^D| \theta_{ij}^r(u_i^C, u_i^D) \lambda_r(u_j^C, u_j^D) + \sum_{r \in \mathfrak{R}_D} |\gamma_r^D| \theta_{ij}^r(u_i^C, u_i^D) \lambda_r(u_j^D)$,

for all $1 \leq i \leq N$,

- $|\Psi_D^N|_j(u_C, u_D) = \sum_{i=1}^N |\gamma_{ij}^N| |g|_{ij}(u_C, u_D) =: |G^N|_j(u_C, u_D)$.

Then we set $|\Psi^N|_j(u) := |\Psi_C^N|_j(u) + |\Psi_D^N|_j(u)$ and $|\Psi^N|(u) := \sum_{j=1}^N |\Psi^N|_j(u)$.

Next, we analogously define the "square amplitude" $|\Psi_C^N|_j^2$ (resp. $|\Psi_D^N|_j^2$) of $\Psi_j^{N,C}$ (resp. $\Psi_j^{N,D}$), as the debit function of the process

$$\left(\sum_{s \leq t} |\delta u_j^{N,C}(t)|^2 \right)_{t \geq 0} \quad \left[\text{resp.} \quad \left(\sum_{s \leq t} |\delta u_j^{N,D}(t)|^2 \right)_{t \geq 0} \right].$$

Then,

- $|\Delta_N|_j^2(u_C) := N^2 (u_{j-1}^C + 2u_j^C + u_{j+1}^C)$,
- $|F|_j^2(u_C, u_D) = \sum_{r \in \mathfrak{R}_C} |\gamma_r^C|^2 \lambda_r(u_j^C) + \sum_{r \in S_1} |\gamma_r^C|^2 \lambda_r(u_j^C, u_j^D)$,
- $|F_1^N|_j^2(u_C, u_D) = \frac{1}{\mu^2} \sum_{i=1}^N \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} |\gamma_{ij}^N|^2 |\theta_{ij}^r(u_i^C, u_i^D)|^2 \lambda_r(u_j^C, u_j^D)$,
- $|\Psi_C^N|_j^2(u) = |\Delta_N|_j^2(u) + |F|_j^2(u) + |F_1^N|_j^2(u_C, u_D)$.
- $|g|_{ij}^2(u_C, u_D) = \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} |\gamma_r^D|^2 |\theta_{ij}^r(u_i^C, u_i^D)|^2 \lambda_r(u_j^C, u_j^D) + \sum_{r \in \mathfrak{R}_D} |\gamma_r^D|^2 |\theta_{ij}^r(u_i^C, u_i^D)|^2 \lambda_r(u_j^D)$,

for all $1 \leq i \leq N$,

- $|\Psi_D^N|_j^2(u_C, u_D) = \sum_{i=1}^N |\gamma_{ij}^N|^2 |g|_{ij}^2(u_C, u_D) =: |G^N|_j^2(u_C, u_D)$.

And we set $|\Psi^N|_j^2(u) := |\Psi_C^N|_j^2(u) + |\Psi_D^N|_j^2(u)$ and $|\Psi^N|^2(u) := \sum_{j=1}^N |\Psi^N|_j^2(u)$.

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In addition, we introduce at last, the very useful "square amplitude function" associated with the debit Ψ^N . It is defined by

$$|\Psi^N|^2(u) = \sum_{j=1}^N |\Psi_j^N|^2(u) \mathbf{1}_j.$$

We also denote it by $|\Psi^N|^2$, as the "square amplitude". Both functions are defined on $\mathbb{H}^N \times \mathbb{H}^N$. But still, if the former is \mathbb{H}^N -valued, the latter has non-negative real values. In order to avoid any confusion in the sequel, the notation $|\Psi^N|^2$ refers to the "square amplitude function", unless another precision is made.

Moreover, as for the "square amplitude" introduced first, the "square amplitude function" can be easily derived for each of the specific debit functions we have introduced above. For instance, the "square amplitude function" corresponding to F is just

$$|F|^2(u) := \sum_{j=1}^N |F_j|^2(u) \mathbf{1}_j.$$

The so-called accompanying martingales. It is well known from [Kur70] or Proposition 2.1 of [Kur71] that, if the total reaction rate λ^N and the global "amplitude" - that of the global debit Ψ^N - of u^N are bounded, or in other words if

$$\sup_{(u) \in \mathbb{H}^N \times \mathbb{H}^N} \lambda^N(u) < \infty \quad \text{and} \quad \sup_{(u) \in \mathbb{H}^N \times \mathbb{H}^N} |\Psi^N(u)| < \infty \quad (2.3.3)$$

respectively, then the processes defined by

$$\begin{cases} Z^N(t) = u^N(t) - u^N(0) - \int_0^t \Psi^N(u^N(s)) ds \\ Z_C^N(t) := u_C^N(t) - u_C^N(0) - \int_0^t \Psi_C^N(u^N(s)) ds \\ Z_D^N(t) := u_D^N(t) - u_D^N(0) - \int_0^t \Psi_D^N(u^N(s)) ds \end{cases} \quad (2.3.4)$$

are $\mathcal{F}_t^N = \mathcal{F}_t^{N,\mu}$ -martingales, with $Z^N(t) = (Z_C^N(t), Z_D^N(t))$ taking values in $\mathbb{H}^N \times \mathbb{H}^N$, for all $t \geq 0$. Note that (2.3.3) holds when the reaction rates are bounded for instance. Furthermore, if τ is a \mathcal{F}_t^N -stopping time such that

$$\sup_{[0,T]} \|u^N(t \wedge \tau)\|_{\infty, \infty} \leq C(T, N, \mu) < \infty, \quad (2.3.5)$$

then $u^N(t \wedge \tau)$ has a bounded total jump rate, and $Z^N(t \wedge \tau)$, $Z_C^N(t \wedge \tau)$ and $Z_D^N(t \wedge \tau)$ are martingales. In all these, $t \wedge \tau$ denotes the infimum between t and τ .

The following result is similar to Lemma 2.2, p.8. in [Blo87]. It presents a first type of martingales related to u^N . We give its proof in Section 2.4.3.

Lemma 2.3.1. *Assume there exists τ satisfying (2.3.5). Then, for all $j \in \{1, \dots, N\}$ and all $t \geq 0$, the following define mean zero \mathcal{F}_t^N -martingales:*

$$(Mg1) \quad \sum_{s \leq t \wedge \tau} \left[\delta u_j^{N,C}(s) \right]^2 - \frac{1}{\mu} \int_0^{t \wedge \tau} \left(|\Delta|_j^2 + |F|_j^2 + \mu |F_1^N|^2 \right) (u^N(s)) ds,$$

$$(Mg2)-(Mg3) \quad \sum_{s \leq t \wedge \tau} \left[\delta u_j^{N,C}(s) \right] \left[\delta u_{j \pm 1}^{N,C}(s) \right] + \frac{1}{\mu} \int_0^{t \wedge \tau} N^2 \left(u_j^{N,C}(s) + u_{j \pm 1}^{N,C}(s) \right) ds,$$

$$(Mg4) \quad \sum_{s \leq t \wedge \tau} \left[\delta u_j^{N,D}(s) \right]^2 - \int_0^{t \wedge \tau} \left| \Psi_j^{N,D} \right|^2 (u^N(s)) ds.$$

We move on to the second martingale type. The result is a variant of Lemma 2.16, p.19 in [Blo87], and Lemma 1.1 in [Kot86b]. Find the proof in Section 2.4.3.

Lemma 2.3.2. *Consider $\varphi \in \mathbb{H}^N$ and τ satisfying (2.3.5). Then for $t \geq 0$, the following are mean 0 martingales:*

$$(Mg5) \quad \sum_{s \leq t \wedge \tau} \left[\delta \langle Z_C^N(s), \varphi \rangle_2 \right]^2 - \frac{1}{N\mu} \int_0^{t \wedge \tau} \left[\langle u_C^N(s), (\nabla_N^+ \varphi)^2 + (\nabla_N^- \varphi)^2 \rangle_2 + \left\langle \left(|F|^2 + \mu |F_1^N|^2 \right) (u^N(s)), \varphi^2 \right\rangle_2 \right] ds,$$

$$(Mg6) \quad \sum_{s \leq t \wedge \tau} \left[\delta \langle Z_D^N(s), \varphi(s) \rangle_2 \right]^2 - \frac{1}{N} \int_0^{t \wedge \tau} \left\langle |\Psi_D^N|^2 (u^N(s)), \varphi^2 \right\rangle_2 ds.$$

Now we look for a stopping time with the same properties as at (2.3.5).

2.3.2 Truncation

Set

$$\tau := \tau(N, \epsilon_0) = \inf \left\{ t \geq 0 : \|u^N(t) - v^N(t)\|_{\infty, \infty} > \epsilon_0 \right\},$$

for fixed $\epsilon_0 \in]0, 1[$. By definition of τ , the process u^N exists and takes finite value on $[0, \tau]$. Now, define $\bar{u}^N = (\bar{u}_C^N, \bar{u}_D^N)$ by

$$\begin{cases} \bar{u}^N(t) = u^N(t \wedge \tau) & \text{for } 0 \leq t \leq \tau \leq \infty, \\ \bar{u}^N(t) = u^N(t \wedge \tau) + \int_{t \wedge \tau}^t \left(\tilde{\Delta}_N \bar{u}^N(s) + R^N(\bar{u}^N(s)) \right) ds & \text{for } \tau < t < \infty, \end{cases} \quad (2.3.6)$$

where $R^N(u) := \begin{pmatrix} F(u) \\ G^N(u) \end{pmatrix}$ for $u \in C_p(I) \times C_p(I)$. The process \bar{u}^N is obtained by running u^N until time τ and then running it deterministically afterwards, if $\tau < \infty$.

Note that τ is a stopping time such that

$$\begin{aligned} \mathbb{P} \left\{ \sup_{[0, T]} \|u^N(t) - v^N(t)\|_{\infty, \infty} > \epsilon_0 \right\} &\leq \mathbb{P} \left\{ \sup_{[0, T]} \|u^N(t \wedge \tau) - v^N(t \wedge \tau)\|_{\infty, \infty} \geq \epsilon_0 \right\} \\ &\leq \mathbb{P} \left\{ \sup_{[0, T]} \|\bar{u}^N(t) - v^N(t)\|_{\infty, \infty} \geq \epsilon_0 \right\}. \end{aligned}$$

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Therefore, it follows from (2.3.2) that showing

$$\mathbb{P} \left\{ \sup_{[0,T]} \|\bar{u}^N(t) - v^N(t)\|_{\infty, \infty} > \epsilon_0 \right\} \longrightarrow 0 \quad (2.3.7)$$

is sufficient for proving the main result.

Boundedness. From Proposition 2.2.3, we know that $\|v(t)\|_{\infty, \infty} < \rho_T$ with $\rho_T = \rho_C + (\rho_D + 1)e^{a(0)M_1(\rho_C)T}$ for all $t \in [0, T]$. Since we are assuming $\|u^N(0) - v(0)\|_{\infty, \infty} \rightarrow 0$ in probability, we may, by conditioning on $\|u^N(0)\|_{\infty, \infty} < \rho_T + 1$ if necessary, assume without loss of generality that

$$\|u^N(0)\|_{\infty, \infty} < \rho_T + 1 \quad \text{for all } N. \quad (2.3.8)$$

From Theorem 2.2.1, we also have

$$\sup_{t \in [0, T]} \|v_C^N(t)\|_{\infty} \leq \rho_C, \quad \sup_{t \in [0, T]} \|v_D^N(t)\|_{\infty} \leq (\rho_D + 1)e^{a(0)M_1(\rho_C)T}.$$

Therefore, by definition of τ , for $\epsilon_0 \leq 1$,

$$\|u_D^N(t \wedge \tau)\|_{\infty, \infty} < \rho_C + 1, \quad \|u_D^N(t \wedge \tau)\|_{\infty, \infty} < (\rho_D + 1)e^{a(0)M_1(\rho_C)T} + 1 \quad \text{for } 0 \leq t \leq T. \quad (2.3.9)$$

Thanks to Assumption 2.2.5, we obtain

$$\|\bar{u}^N(t)\|_{\infty, \infty} \leq \tilde{\rho}_T = \rho_C + 1 + (\rho_D + 2)e^{a(0)M_1(\rho_C + 1)T} \quad \text{for } 0 \leq t \leq T. \quad (2.3.10)$$

Indeed, given (2.3.9), we prove (2.3.10) if for $\tau < t \leq T$, we show the inequalities

$$\begin{cases} \|\bar{u}_C^N(t)\|_{\infty} \leq \rho_C + 1 & (C\star) \\ \|\bar{u}_D^N(t)\|_{\infty} \leq (\rho_D + 2)e^{2a(0)M_1(\rho_C + 1)T} & (D\star). \end{cases}$$

Suppose that $\bar{u}_j^{N,C}(t) > \rho_C + 1$ for some $t \in [\tau, T]$, $1 \leq j \leq N$. Since $\bar{u}_C^N(t) \in \mathbb{H}^N$, there is $1 \leq i \leq N$ and t_0 satisfying

$$\bar{u}_i^{N,C}(t_0) = \sup_{s \in [\tau, T]} \|\bar{u}_C^N(s)\|_{\infty} \geq \bar{u}_j^{N,C}(t) > \rho_C + 1.$$

Therefore, Assumption 2.2.5 (i) yields

$$F(\bar{u}_i^N(t_0)) = F(\bar{u}_i^{N,C}(t_0), \bar{u}_i^{N,D}(t_0)) < 0.$$

Moreover

$$\Delta_N \bar{u}_i^{N,C}(t_0) = \bar{u}_{i+1}^{N,C}(t_0) - 2\bar{u}_i^{N,C}(t_0) + \bar{u}_{i-1}^{N,C}(t_0) < 0.$$

Combining these two arguments with (2.3.6), we get

$$\frac{d}{dt} \bar{u}_i^{N,C}(t_0) = \Delta_N \bar{u}_i^{N,C}(t_0) + F(\bar{u}_i^N(t_0)) < 0.$$

By (2.3.9) $t_0 > \tau$ and necessarily $\frac{d}{dt}\bar{u}_i^{N,C}(t_0) \geq 0$ in contradiction with the above. Thus, (C \star) follows.

Now, let $\tau < t \leq T$ and $1 \leq i \leq N$ be fixed. Let $\tau \leq s \leq t$. Observing that $|g_{ij}(u^N(s))| \leq \| |g|(u^N(s)) \|_\infty$, Assumption 2.2.5 (ii) and (C \star) yield

$$\begin{aligned} \left| G^N(\bar{u}_i^{N,D}(s)) \right| &\leq \sum_{j=1}^N |\gamma_{ij}^N| |g_{ij}(u^N(s))| \leq \sum_{j=1}^N \frac{a(0)}{N} \| |g|(u^N(s)) \|_\infty \\ &\leq a(0)M_1(\rho_C + 1)(\|\bar{u}_D^N(s)\|_\infty + 1). \end{aligned}$$

Thus, $\|G^N(\bar{u}_D^N(s))\|_\infty \leq a(0)M_1(\rho_C + 1)(\|\bar{u}_D^N(s)\|_\infty + 1)$, and, (2.3.6) with (2.3.9) lead to

$$\begin{aligned} \|\bar{u}_D^N(t)\|_\infty &\leq \|u_D^N(t \wedge \tau)\|_\infty + \int_\tau^t \|G^N(\bar{u}_i^{N,D}(s))\|_\infty ds \\ &\leq (\rho_D + 1)e^{a(0)M_1(\rho_C)T} + 1 + M_1(\rho_C + 1)a(0) \int_\tau^t \|\bar{u}_D^N(s)\|_\infty + 1 ds \end{aligned}$$

The result follows from Gronwall lemma. (D \star) follows, and (2.3.10) is proved. \square

In the sequel, we consider \bar{c} as a generic constant depending on $\tilde{\rho}_T$ and T .

Remark 2.3.1. *As we are considering the truncated process \bar{u}^N in the following, we consider that reaction rates are bounded and Lipschitz as functions defined on \mathbb{R}^2 . Indeed, thanks to (2.3.10), we know that the family $\{\bar{u}^N(t), t \geq 0\}_N$ lies in the bounded set*

$$\mathfrak{S}_{\tilde{\rho}_T} := \{u \in \mathbb{H}^N \times \mathbb{H}^N : \|u\|_{\infty, \infty} \leq \tilde{\rho}_T\}.$$

Thus $\{\bar{u}^N(t, x), t \geq 0, x \in I\}_N \subset \bar{B}(0, \tilde{\rho}_T)$, where $\bar{B}(0, \tilde{\rho}_T)$, the closed ball of \mathbb{R}^2 of radius $\tilde{\rho}_T$, and centered at zero. Now, since reaction rates are functions of the concentrations of the truncated process, we only consider their restrictions to the compact $\bar{B}(0, \tilde{\rho}_T)$. These latter are bounded and Lipschitz, as the rates are polynomial. Their bounds depend on $\tilde{\rho}_T$ and are also denoted $\bar{\lambda}(\tilde{\rho}_T)$. \square

We have the following result, proved in Section 2.4.4.

Proposition 2.3.1.

- (i) *The debit functions F , F_1^N , G and G^N are Lipschitz.*
- (ii) *For all $u \in C(I) \times C(I)$, $\|G^N(u) - G(u)\|_\infty \rightarrow 0$.*

Martingale and jumps. The stopping time τ satisfies (2.3.5). Thus,

$$Z^N(t \wedge \tau) := u^N(t \wedge \tau) - u^N(0) - \int_0^{t \wedge \tau} \left(\tilde{\Delta}_N u^N(s) + R^N(u^N(s)) \right) ds$$

is a mean 0 martingale. From the definition of \bar{u}^N ,

$$\bar{u}^N(t) = u^N(0) + \int_0^t \left(\tilde{\Delta}_N \bar{u}^N(s) + R^N(\bar{u}^N(s)) \right) ds + Z^N(t \wedge \tau). \quad (2.3.11)$$

In fact, if $t \leq \tau$, then

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$$\begin{aligned}
\bar{u}^N(t) - u^N(0) &= \int_0^t \left(\tilde{\Delta}_N \bar{u}^N(s) + R^N(\bar{u}^N(s)) \right) ds \\
&:= u^N(t \wedge \tau) - u^N(0) - \int_0^t \left(\tilde{\Delta}_N u^N(s \wedge \tau) + R^N(u^N(s \wedge \tau)) \right) ds \\
&= u^N(t \wedge \tau) - u^N(0) - \int_0^{t \wedge \tau} \left(\tilde{\Delta}_N u^N(s) + R^N(u^N(s)) \right) ds = Z^N(t \wedge \tau).
\end{aligned}$$

Otherwise $t > \tau$ and, since \bar{u}^N and u^N are the same before time τ ,

$$\begin{aligned}
\bar{u}^N(t) - u^N(0) &= \int_0^t \left(\tilde{\Delta}_N \bar{u}^N(s) + R^N(\bar{u}^N(s)) \right) ds \\
&:= u^N(t \wedge \tau) + \int_{t \wedge \tau}^t \left(\tilde{\Delta}_N \bar{u}^N(s) + R^N(\bar{u}^N(s)) \right) ds \\
&\quad - u^N(0) - \int_0^{t \wedge \tau} \left(\tilde{\Delta}_N \bar{u}^N(s) + R^N(\bar{u}^N(s)) \right) ds \\
&= u^N(t \wedge \tau) - u^N(0) - \int_0^{t \wedge \tau} \left(\tilde{\Delta}_N \bar{u}^N(s) + R^N(\bar{u}^N(s)) \right) ds \\
&= u^N(t \wedge \tau) - u^N(0) - \int_0^{t \wedge \tau} \left(\tilde{\Delta}_N u^N(s) + R^N(u^N(s)) \right) ds = Z^N(t \wedge \tau). \quad \square
\end{aligned}$$

Also, setting $\delta f := (\delta f_j)_{1 \leq j \leq N}$ for $f \in \mathbb{H}^N$, the jumps related to u^N and \bar{u}^N satisfy

$$\begin{cases} \|\delta \bar{u}_C^N(t)\|_\infty = \|\delta Z_C^N(t \wedge \tau)\|_\infty = \|\delta u_C^N(t \wedge \tau)\|_\infty \leq (1 \vee \bar{\gamma}_C) \mu^{-1} \leq \gamma \mu^{-1} \\ \|\delta \bar{u}_D^N(t)\|_\infty = \|\delta Z_D^N(t \wedge \tau)\|_\infty = \|\delta u_D^N(t \wedge \tau)\|_\infty \leq \bar{\gamma}_D a(0) N^{-1} \leq \gamma N^{-1} \end{cases} \quad (2.3.12)$$

for all $t \geq 0$, for some constant $\gamma > 0$. We refer to (2.2.12) in particular for the bound related to D .

2.3.3 A Gronwall-Bellman argument

We want to study the difference

$$\bar{u}^N(t) - v^N(t) = (\bar{u}_C^N(t) - v_C^N(t), \bar{u}_D^N(t) - v_D^N(t)).$$

Using variation of constant at (2.3.11), we get

$$\bar{u}^N(t) = \tilde{T}_N(t) u^N(0) + \int_0^t \tilde{T}_N(t-s) \begin{pmatrix} F(\bar{u}^N(s)) \\ G^N(\bar{u}^N(s)) \end{pmatrix} ds + Y^N(t), \quad (2.3.13)$$

where $Y^N(t) = \int_0^t \tilde{T}_N(t-s) dZ^N(s \wedge \tau)$. Note that $Z^N\left(s \wedge \tau, \frac{j}{N}\right) := \begin{pmatrix} Z_C^N(s \wedge \tau, \frac{j}{N}) \\ Z_D^N(s \wedge \tau, \frac{j}{N}) \end{pmatrix}$, $1 \leq j \leq N$, is of bounded variation in s , and \tilde{T}_N may be viewed as a $2N \times 2N$ matrix-valued function. T_N is indeed identified to an $N \times N$ matrix-valued function. Hence, $Y^N\left(t, \frac{j}{N}\right)$, $1 \leq j \leq N$, is defined as a Stieltjes integral. From the mild forms of v^N and \bar{u}^N at (2.2.26) and (2.3.13) respectively,

$$\begin{aligned}\bar{u}^N(t) - v^N(t) &= \tilde{T}_N(t) (u^N(0) - v^N(0)) \\ &\quad + \int_0^t \tilde{T}_N(t-s) \begin{pmatrix} F(\bar{u}^N(s)) - F(v^N(s)) \\ G^N(\bar{u}^N(s)) - G(v^N(s)) \end{pmatrix} + Y^N(t).\end{aligned}$$

Since the semigroup $\tilde{T}_N(t)$ is of contraction,

$$\begin{aligned}\|\bar{u}^N(t) - v^N(t)\|_{\infty, \infty} &\leq \|u^N(0) - v^N(0)\|_{\infty, \infty} + \|Y^N(t)\|_{\infty, \infty} \\ &\quad + \int_0^t \left\| \begin{pmatrix} F(\bar{u}^N(s)) - F(v^N(s)) \\ G^N(\bar{u}^N(s)) - G^N(v^N(s)) \end{pmatrix} \right\|_{\infty, \infty} + \left\| \begin{pmatrix} 0 \\ G^N(v^N(s)) - G(v^N(s)) \end{pmatrix} \right\|_{\infty, \infty} ds.\end{aligned}$$

We have

$$\left\| \begin{pmatrix} F(\bar{u}^N(s)) - F(v^N(s)) \\ G^N(\bar{u}^N(s)) - G^N(v^N(s)) \end{pmatrix} \right\|_{\infty, \infty} \leq 2L \|\bar{u}^N(s) - v^N(s)\|_{\infty, \infty},$$

and

$$\begin{aligned}\left\| \begin{pmatrix} 0 \\ G^N(v^N(s)) - G(v^N(s)) \end{pmatrix} \right\|_{\infty, \infty} &= \|G^N(v^N(s)) - G(v^N(s))\|_{\infty} \\ &\leq \|G^N(v^N(s)) - G^N(v(s))\|_{\infty} + \|G^N(v(s)) - G(v(s))\|_{\infty} \\ &\quad + \|G(v(s)) - G(v^N(s))\|_{\infty} \\ &\leq 2L \|v^N(s) - v(s)\|_{\infty, \infty} + \|G^N(v(s)) - G(v(s))\|_{\infty}.\end{aligned}$$

where L is a Lipschitz constant common to F , G and G^N . Therefore,

$$\begin{aligned}\|\bar{u}^N(t) - v^N(t)\|_{\infty, \infty} &\leq \|u^N(0) - v^N(0)\|_{\infty, \infty} + \|Y^N(t)\|_{\infty, \infty} + 2L \int_0^t \|\bar{u}^N(s) - v^N(s)\|_{\infty, \infty} ds \\ &\quad + \int_0^t \left(2L \|v^N(s) - v(s)\|_{\infty, \infty} + \|G^N(v(s)) - G(v(s))\|_{\infty} \right) ds\end{aligned}$$

Taking the supremum in time on $[0, T]$ and applying Gronwall lemma, we obtain

$$\begin{aligned}\sup_{[0, T]} \|\bar{u}^N(t) - v^N(t)\|_{\infty, \infty} &\leq \left\{ \|u^N(0) - v^N(0)\|_{\infty, \infty} + \sup_{[0, T]} \|Y^N(t)\|_{\infty, \infty} \right. \\ &\quad \left. + 2LT \sup_{[0, T]} \|v^N(t) - v(t)\|_{\infty, \infty} + \int_0^T \|G^N(v(s)) - G(v(s))\|_{\infty} ds \right\} \times e^{2LT}.\end{aligned}\tag{2.3.14}$$

2.3 The Law of Large Numbers

Now, by assumption,

$$\|u^N(0) - v^N(0)\|_{\infty, \infty} \leq \|u^N(0) - v(0)\|_{\infty, \infty} + \|\tilde{P}_N v(0) - v(0)\|_{\infty, \infty} \longrightarrow 0$$

in probability. Also, $\int_0^T \|G^N(v(s)) - G(v(s))\|_{\infty} \longrightarrow 0$, thanks to Proposition 2.3.1 and dominated convergence. Moreover, Theorem 2.2.1 yields $\sup_{[0, T]} \|v^N(t) - v(t)\|_{\infty, \infty} \longrightarrow 0$.

Finally, we claim that:

$$\sup_{[0, T]} \|Y^N(t)\|_{\infty, \infty} \longrightarrow 0 \text{ in probability.} \quad (2.3.15)$$

The proof of Theorem 2.3.1 is completed, if our claim is justified. We write

$$Y^N(t) = \int_0^t \tilde{T}_N(t-s) d \begin{pmatrix} Z_C^N(s \wedge \tau) \\ Z_D^N(s \wedge \tau) \end{pmatrix} = \begin{pmatrix} \int_0^t T_N(t-s) dZ_C^N(s \wedge \tau) \\ Z_D^N(t \wedge \tau) \end{pmatrix} =: \begin{pmatrix} Y_C^N(t) \\ Y_D^N(t) \end{pmatrix},$$

where $Z_C^N(t \wedge \tau)$ and $Z_D^N(t \wedge \tau)$ are \mathbb{H}^N -valued martingales. It follows that

$$\sup_{[0, T]} \|Y^N(t)\|_{\infty, \infty} \leq \sup_{[0, T]} \|Y_C^N(t)\|_{\infty} + \sup_{[0, T]} \|Z_D^N(t \wedge \tau)\|_{\infty}.$$

Therefore, it is sufficient to show that each term on the r.h.s. of the inequality converges to zero in probability. For that purpose, we need the subsequent results, whose proofs are deferred to Section 2.4.5.

Lemma 2.3.3. (*Lemma 4.3, [Blo92]*) *Set $f = N\mathbf{1}_j$. Then*

$$\left\langle (\nabla_N^+ T_N(t)f)^2 + (\nabla_N^- T_N(t)f)^2 + (T_N(t)f)^2, 1 \right\rangle_2 \leq h_N(t), \text{ with } \int_0^t h_N(s) ds \leq KN + t.$$

Lemma 2.3.4. (*Lemma 4.4, [Blo92]*) *Let $m(t)$ be a bounded martingale of finite variation defined on $[t_0, t_1]$, with $m(t_0) = 0$, and satisfying:*

(i) *m is right-continuous with left limits.*

(ii) *$|\delta m(t)| \leq 1$ for $t_0 \leq t \leq t_1$.*

(iii) *$\sum_{t_0 \leq s \leq t} [\delta m(s)]^2 - \int_{t_0}^t g(s) ds$ is a mean 0 martingale with $0 \leq g(s) \leq h(s)$, where*

$h(s)$ is a bounded deterministic function and $g(s)$ is \mathcal{F}_t^N -adapted.

Then,

$$\mathbb{E} [e^{m(t_1)}] \leq \exp \left(\frac{3}{2} \int_{t_0}^{t_1} h(s) ds \right).$$

Let us go back to the proof of 2.3.15.

Martingale continuous component term

We want to show that

$$\mathbb{P} \left\{ \sup_{[0, T]} \|Y_C^N(t)\|_{\infty} > \epsilon_0 \right\} \longrightarrow 0.$$

Fix $\bar{t} \in (0, T]$ and $j \in \{1, \dots, N\}$. For $0 \leq t \leq \bar{t}$, set

$$f := N\mathbf{1}_j, \quad \text{and} \quad \bar{m}_C(t) := \left\langle \int_0^t T_N(\bar{t} - s) dZ_C^N(s \wedge \tau), f \right\rangle_2.$$

Then, $\bar{m}_C := \{\bar{m}_C(t), 0 \leq t \leq \bar{t}\}$ is a mean zero martingale such that

$$\begin{aligned} \bar{m}_C(\bar{t}) &= N \int_0^1 \int_0^{\bar{t}} T_N(\bar{t} - s) dZ_C^N(s \wedge \tau, x) \mathbf{1}_j(x) dx \\ &= \int_0^{\bar{t}} T_N(\bar{t} - s) dZ_C^N\left(s \wedge \tau, \frac{j}{N}\right) = Y_C^N\left(\bar{t}, \frac{j}{N}\right). \end{aligned}$$

We need the additional upcoming result, that we prove in Section 2.4.5.

Lemma 2.3.5. *(A third type of accompanying martingale)*

$$\begin{aligned} &\sum_{s \leq t \wedge \tau} [\delta \bar{m}_C(s)]^2 \\ &\quad - \frac{1}{N\mu} \int_0^{t \wedge \tau} \left[\left\langle u_C^N(s), (\nabla_N^+ T_N(\bar{t} - s)f)^2 + (\nabla_N^- T_N(\bar{t} - s)f)^2 \right\rangle_2 \right. \\ &\quad \quad \left. + \left\langle (|F|^2 + \mu|F_1^N|^2)(u^N(s)), (T_N(\bar{t} - s)f)^2 \right\rangle_2 \right] ds \end{aligned}$$

defines a mean 0 càdlàg martingale for $0 \leq t \leq \bar{t}$.

Remark 2.3.2. In [Blo92], Blount uses this result and claims that it is a consequence of Lemma 2.3.2, whose proof uses Lemma 2.3.1. We have not been able to reproduce his proof. Our proof uses Lemma 2.3.1 directly.

From (3.2.2), we know that $T_N(t)$ is a contraction on $(\mathbb{H}^N, \|\cdot\|_\infty)$. Thus, (2.3.12) yields

$$\begin{aligned} |\delta \bar{m}_C(t)| &= \left| T_N(\bar{t} - t) \delta Z_C^N\left(t \wedge \tau, \frac{j}{N}\right) \right| \leq \|T_N(\bar{t} - t) \delta Z_C^N(t \wedge \tau)\|_\infty \\ &\leq \|\delta Z_C^N(t \wedge \tau)\|_\infty = \|\delta u_C^N(t \wedge \tau)\|_\infty \leq \gamma \mu^{-1}. \end{aligned}$$

For $\bar{\theta} \in [0, \gamma^{-1}]$, the process m_C defined by

$$m_C(t) := \bar{\theta} \mu \bar{m}_C(t) \quad \text{for} \quad 0 \leq t \leq \bar{t}$$

is a mean 0 càdlàg martingale such that $|\delta m_C(t)| = \bar{\theta} \mu |\delta \bar{m}_C(s)| \leq 1$. Thus,

$$\sum_{s \leq t \wedge \tau} [\delta m_C(s)]^2 - \int_0^{t \wedge \tau} g_C^N(s) ds$$

is a mean 0 càdlàg martingale thanks to Lemma 2.3.5, where for $0 \leq s \leq t \wedge \tau$,

$$\begin{aligned} g_C^N(s) &= \frac{\bar{\theta}^2 \mu}{N} \left[\left\langle u_C^N(s), (\nabla_N^+ T_N(\bar{t} - s)f)^2 + (\nabla_N^- T_N(\bar{t} - s)f)^2 \right\rangle_2 \right. \\ &\quad \left. + \left\langle (|F|^2 + \mu|F_1^N|^2)(u^N(s)), (T_N(\bar{t} - s)f)^2 \right\rangle_2 \right]. \end{aligned}$$

2.3 The Law of Large Numbers

Since u_C^N is positive and the reaction rates are bounded, (2.3.9) and Lemma 4.3.3 yield

$$\begin{aligned} g_C^N(s) &\leq \frac{\bar{\theta}^2 \mu}{N} \bar{c} \left\langle 1, (\nabla_N^+ T_N(\bar{t} - s)f)^2 + (\nabla_N^- T_N(\bar{t} - s)f)^2 + (T_N(\bar{t} - s)f)^2 \right\rangle_2 \\ &\leq \frac{\bar{\theta}^2 \mu}{N} \bar{c} h_1^{N,C}(\bar{t} - s), \end{aligned}$$

where we know from (2.4.1) that we can take $h_1^{N,C}(t) = 1 + 4 \sum_{m>0} e^{-2\beta_{m,N}(\bar{t}-t)} (\beta_{m,N} + 1)$,

and it satisfies $\int_0^t h_1^{N,C}(\bar{t} - s) ds \leq KN + t$, for $0 \leq t \leq \bar{t}$. Hence, g_C^N is an \mathcal{F}_t^N -adapted process such that

$$0 \leq g_C^N(s) \leq h_C^N(s),$$

where $h_C^N(s) = \bar{c} \frac{\bar{\theta}^2 \mu}{N} h_1^{N,C}(\bar{t} - s)$ is a bounded deterministic function on $[0, \bar{t}]$. Since $N \rightarrow \infty$ and $\bar{t} \leq T < \infty$, we may assume $\bar{t}N^{-1} \leq 1$ and get

$$\int_0^{\bar{t}} h_C^N(s) ds \leq \bar{c} \bar{\theta}^2 \mu (K + \bar{t}N^{-1}) \leq \bar{c} \bar{\theta}^2 \mu.$$

Therefore, Lemma 2.3.4 implies $\mathbb{E} [e^{m_C(\bar{t})}] \leq \exp(\bar{c} \bar{\theta}^2 \mu)$. By Markov's inequality,

$$\begin{aligned} \mathbb{P} \left\{ Y_C^N \left(\bar{t}, \frac{j}{N} \right) > \epsilon_0 \right\} &= \mathbb{P} \{ \bar{m}_C(\bar{t}) > \epsilon_0 \} = \mathbb{P} \{ m_C(\bar{t}) > \bar{\theta} \mu \epsilon_0 \} = \mathbb{P} \left\{ e^{m_C(\bar{t})} > e^{\bar{\theta} \mu \epsilon_0} \right\} \\ &\leq e^{-\bar{\theta} \mu \epsilon_0} \mathbb{E} [e^{m_C(\bar{t})}] \leq \exp[\bar{\theta} \mu (\bar{c} \bar{\theta} - \epsilon_0)]. \end{aligned}$$

Thus we can choose $\bar{\theta}$ such that

$$\mathbb{P} \left\{ Y_C^N \left(\bar{t}, \frac{j}{N} \right) > \epsilon_0 \right\} \leq e^{-\alpha \epsilon_0^2 \mu}, \quad \text{for } \alpha = \bar{c}(\bar{\rho}_T, T) > 0,$$

independently of N , μ , j and \bar{t} (one may solve $\bar{c} \bar{\theta}^2 - \epsilon_0 \bar{\theta} + \alpha \epsilon_0^2 \leq 0$ in $\bar{\theta}$). The same relation holds for $\mathbb{P} \left\{ -Y_C^N \left(\bar{t}, \frac{j}{N} \right) > \epsilon_0 \right\}$, by replacing the processes \bar{m}_C and Y_C^N by their opposites $-\bar{m}_C$ and $-Y_C^N$ respectively, and repeating the argument. Therefore,

$$\mathbb{P} \left\{ \left| Y_C^N \left(t, \frac{j}{N} \right) \right| > \epsilon_0 \right\} \leq 2e^{-\alpha \epsilon_0^2 \mu}, \quad \text{for } 0 < t \leq T \quad \text{and } j \in \{1, \dots, N\}.$$

Since $\|Y_C^N(t)\|_\infty = \sup_{1 \leq j \leq N} \left| Y_C^N \left(t, \frac{j}{N} \right) \right|$ and $Y_C^N(0) = 0$,

$$\begin{aligned} \mathbb{P} \{ \|Y_C^N(t)\|_\infty > \epsilon_0 \} &= \mathbb{P} \left\{ \exists j \in \{1, \dots, N\} : \left| Y_C^N \left(t, \frac{j}{N} \right) \right| > \epsilon_0 \right\} \\ &\leq \sum_{1 \leq j \leq N} \mathbb{P} \left\{ \left| Y_C^N \left(t, \frac{j}{N} \right) \right| > \epsilon_0 \right\} \leq 2Ne^{-\alpha \epsilon_0^2 \mu} \end{aligned} \tag{2.3.16}$$

for $0 \leq t \leq T$, $\alpha = \alpha(\rho) > 0$. We now show that (2.3.16) holds with $\|Y_C^N(t)\|_\infty$ replaced by $\sup_{[0,T]} \|Y_C^N(t)\|_\infty$ and N - on the r.h.s. - replaced by N^3 . From Duhamel formula,

$Y_C^N(t) = \int_0^t T_N(t-s) dZ_C^N(s \wedge \tau)$ satisfies the Stochastic Differential Equation (SDE)

$$dY_C^N(t) = \Delta_N Y_C^N(t) + dZ_C^N(t \wedge \tau).$$

whose integral form is

$$Y_C^N(t) = Z_C^N(t \wedge \tau) + \int_0^t \Delta_N Y_C^N(s) ds. \quad (2.3.17)$$

We subdivide $[0, T]$ into N^2 subintervals $I_n(T) := \left[\frac{nT}{N^2}, \frac{(n+1)T}{N^2} \right]$, $0 \leq n \leq N^2 - 1$. Then taking $t = \frac{nT}{N^2}$ in (2.3.17) yields

$$Y_C^N\left(\frac{nT}{N^2}\right) = Z_C^N\left(\frac{nT}{N^2} \wedge \tau\right) + \int_0^{\frac{nT}{N^2}} \Delta_N Y_C^N(s) ds.$$

One writes

$$\begin{aligned} Y_C^N(t) &= Z_C^N(t \wedge \tau) + \int_0^{\frac{nT}{N^2}} \Delta_N Y_C^N(s) ds + \int_{\frac{nT}{N^2}}^t \Delta_N Y_C^N(s) ds \\ &= Z_C^N(t \wedge \tau) + \left[Y_C^N\left(\frac{nT}{N^2}\right) - Z_C^N\left(\frac{nT}{N^2} \wedge \tau\right) \right] + \int_{\frac{nT}{N^2}}^t \Delta_N Y_C^N(s) ds \\ &= Y_C^N\left(\frac{nT}{N^2}\right) + \int_{\frac{nT}{N^2}}^t \Delta_N Y_C^N(s) ds + \tilde{m}_C(t), \end{aligned}$$

where

$$\tilde{m}_C(t) = Z_C^N(t \wedge \tau) - Z_C^N\left(\frac{nT}{N^2} \wedge \tau\right)$$

defines a mean 0 martingale, for $t \in I_n(T)$. Thus,

$$\|Y_C^N(t)\|_\infty \leq \left\| Y_C^N\left(\frac{nT}{N^2}\right) \right\|_\infty + 4N^2 \int_{\frac{nT}{N^2}}^t \|Y_C^N(s)\|_\infty ds + \|\tilde{m}_C(t)\|_\infty$$

since $\|\Delta_N\|_\infty \leq 4N^2$. With the notation $\sup_{t \in I_n(T)} \equiv \sup_{I_n(T)}$, a Gronwall argument leads to

$$\sup_{I_n(T)} \|Y_C^N(t)\|_\infty \leq \left(\left\| Y_C^N\left(\frac{nT}{N^2}\right) \right\|_\infty + \sup_{I_n(T)} \|\tilde{m}_C(t)\|_\infty \right) e^{4T}. \quad (2.3.18)$$

We now want to proceed as previously, by finding a suitable martingale associated with \tilde{m}_C . Fix $j \in \{1, \dots, N\}$, $\bar{\theta} \in [0, |\gamma|^{-1}]$ and set

$$m_C(t) = \bar{\theta} \mu \tilde{m}_C\left(t, \frac{j}{N}\right), \quad \text{for } t \in I_n(T) = \left[\frac{nT}{N^2}, \frac{(n+1)T}{N^2} \right].$$

For $s \in I_n(T)$, $s \geq \frac{nT}{N^2}$ yields $|\delta m_C(s)| = \bar{\theta} \mu |\delta \tilde{m}_C(s)| = \bar{\theta} \mu \left| \delta Z_j^{N,C}(s \wedge \tau) \right| \leq 1$. By Lemma 2.3.2,

$$\sum_{\frac{nT}{N^2} \wedge \tau \leq s \leq t \wedge \tau} [\delta m_C(s)]^2 - \int_{\frac{nT}{N^2} \wedge \tau}^{t \wedge \tau} g_C^N(s) ds$$

2.3 The Law of Large Numbers

is a mean 0 martingale for $t \in I_n(T)$, where

$$g_C^N(s) = \bar{\theta}^2 \mu \left[N^2 \left(u_{j-1}^{N,C}(s) + 2u_j^{N,C}(s) + u_{j+1}^{N,C}(s) \right) + \left(|F|_j^2 + \mu |F_1^N|_j^2 \right) \left(u^N(s) \right) \right].$$

Now, $0 \leq g_C^N(s) \leq h_C^N(s)$ by (2.3.9) and the local boundedness of the reaction rates, where

$$h_C^N(s) = \bar{\theta}^2 \mu (4N^2 \tilde{\rho}_T + \bar{\gamma}_C \bar{\lambda}(\tilde{\rho}_T)) \quad \text{satisfies} \quad \int_{\frac{nT}{N^2} \wedge \tau}^{t \wedge \tau} h_C^N(s) \leq \bar{c} \bar{\theta}^2 \mu T.$$

Lemma 2.3.4 then implies

$$\mathbb{E} \left[\exp \left\{ m_C \left(\frac{(n+1)T}{N^2} \right) \right\} \right] \leq \exp(\bar{c} \bar{\theta}^2 \mu T).$$

Applying Doob's inequalities, we have

$$\begin{aligned} \mathbb{P} \left\{ \sup_{I_n(T)} \tilde{m}_C \left(t, \frac{j}{N} \right) > \epsilon_0 \right\} &\leq e^{-\bar{\theta} \mu \epsilon_0} \mathbb{E} \left[\exp \left\{ m_C \left(\frac{(n+1)T}{N^2} \right) \right\} \right] \\ &\leq \exp[\bar{\theta} \mu (\bar{c} \bar{\theta} - \epsilon_0)] \leq e^{-\alpha \epsilon_0^2 \mu}, \end{aligned}$$

where $\alpha = \bar{c}(\tilde{\rho}_T, T) > 0$, independently of N , μ and j . We have chosen a suitable $\bar{\theta}$ as previously. Again, the same inequality holds for $-\tilde{m}_C \left(t, \frac{j}{N} \right)$ and consequently,

$$\mathbb{P} \left\{ \sup_{I_n(T)} \|\tilde{m}_C(t)\|_\infty > \epsilon_0 \right\} \leq 2N e^{-\alpha \epsilon_0^2 \mu}. \quad (2.3.19)$$

From (2.3.16), (2.3.18) and (2.3.19),

$$\begin{aligned} \mathbb{P} \left\{ e^{-4T} \sup_{I_n(T)} \|Y_C^N(t)\|_\infty > \epsilon_0 \right\} &\leq \mathbb{P} \left\{ \left\| Y_C^N \left(\frac{nT}{N^2} \right) \right\|_\infty + \sup_{I_n(T)} \|\tilde{m}_C(t)\|_\infty > \epsilon_0 \right\} \\ &\leq \mathbb{P} \left\{ \left\| Y_C^N \left(\frac{nT}{N^2} \right) \right\|_\infty > \frac{\epsilon_0}{2} \right\} + \mathbb{P} \left\{ \sup_{I_n(T)} \|\tilde{m}_C(t)\|_\infty > \frac{\epsilon_0}{2} \right\} \\ &\leq 2N e^{-\alpha \frac{\epsilon_0^2}{4} \mu} + 2N e^{-\alpha \frac{\epsilon_0^2}{4} \mu} = 4N e^{-\alpha \frac{\epsilon_0^2}{4} \mu} \leq 4N e^{-\alpha \epsilon_0^2 \mu}. \end{aligned} \quad (2.3.20)$$

Hence,

$$\mathbb{P} \left\{ e^{-4T} \sup_{[0,T]} \|Y_C^N(t)\|_\infty > \epsilon_0 \right\} \leq \sum_{n=0}^{N^2-1} \mathbb{P} \left\{ e^{-4T} \sup_{I_n(T)} \|Y_C^N(t)\|_\infty > \epsilon_0 \right\} \leq 4N^3 e^{-\alpha \epsilon_0^2 \mu},$$

where $\alpha = \alpha(\tilde{\rho}_T, T) > 0$. We deduce

$$\mathbb{P} \left\{ \sup_{[0,T]} \|Y_C^N(t)\|_\infty > \epsilon_0 \right\} \leq 4N^3 \exp\left(-\alpha e^{-16T^2} \epsilon_0^2 \mu\right) \leq \exp(\log 4 + 3 \log N - \alpha \mu),$$

with $\alpha = \alpha(\tilde{\rho}_T, T, \epsilon_0)$. The r.h.s. vanishes, since we are assuming $\mu^{-1} \log N \rightarrow 0$. This proves the convergence of the continuous part. \square

Martingale discrete component term

We want to show that

$$\mathbb{P} \left\{ \sup_{[0, T]} \|Y_D^N(t)\|_\infty > \epsilon_0 \right\} \longrightarrow 0.$$

We use the same procedure as for the continuous part. Fix $\bar{t} \in (0, T]$ and $j \in \{1, \dots, N\}$. For $0 \leq t \leq \bar{t}$, set

$$f := N\mathbb{1}_j, \quad \text{and} \quad \bar{m}_D(t) := \langle Z_D^N(t \wedge \tau), f \rangle_2.$$

Then, the process $\bar{m}_D := \{\bar{m}_D(t), 0 \leq t \leq \bar{t}\}$ defines a mean zero martingale, such that $\bar{m}_D(\bar{t}) = Y_D^N\left(\bar{t}, \frac{j}{N}\right)$. Taking $\varphi = f$ in Lemma 2.3.2 yields

$$\sum_{s \leq t \wedge \tau} [\delta \bar{m}_D(s)]^2 - \frac{1}{N} \int_0^{t \wedge \tau} \langle |G^N|^2(u^N(s)), f^2 \rangle_2 ds \quad (2.3.21)$$

is a mean 0 martingale for $0 \leq t \leq \bar{t}$. From (2.3.12),

$$|\delta \bar{m}_D(t)| = \left| \delta Z_D^N\left(t \wedge \tau, \frac{j}{N}\right) \right| \leq \|\delta Z_D^N(t \wedge \tau)\|_\infty = \|\delta u_D^N(t \wedge \tau)\|_\infty \leq \gamma N^{-1}.$$

Since $N \rightarrow \infty$, we may assume $N^{-1} \leq 1$. Then, For $\bar{\theta} \in [0, \gamma^{-1}]$,

$$m_D(t) = \bar{\theta} N \bar{m}_D(t)$$

defines a mean 0 càdlàg martingale such that $|\delta m_D(t)| \leq 1$ and $[\delta m_D(s)]^2 = \bar{\theta}^2 N^2 [\delta \bar{m}_D(s)]^2$ for $0 \leq t \leq \bar{t}$. Thus, from Lemma 2.3.2,

$$\sum_{s \leq t} [\delta m_D(s)]^2 - \int_0^{t \wedge \tau} g_D^N(s) ds$$

is a mean 0 càdlàg martingale, where

$$\begin{aligned} g_D^N(s) &:= \bar{\theta}^2 N \langle |G^N|(u^N(s)), f^2 \rangle_2 = \bar{\theta}^2 N^2 |G_j^N|^2(u^N(s)) \\ &= \bar{\theta}^2 N^2 \sum_{i=1}^N |\gamma_{ij}^N|^2 |g_{ij}^2(u^N(s))| \leq \bar{\theta}^2 \bar{c} N, \end{aligned}$$

thanks to the boundedness of the reaction rates. It follows that $0 \leq g_D^N(s) \leq h_D^N(s)$, where $h_D^N(s) := \bar{\theta}^2 \bar{c} N$ satisfies $\int_0^t h_D^N(s) ds \leq \bar{\theta}^2 \bar{c} N$ for $0 \leq t \leq \bar{t} \leq T$. Therefore, Lemma 2.3.4 implies $\mathbb{E} \left[e^{m_D(\bar{t})} \right] \leq \exp(\bar{\theta}^2 \bar{c} N)$. Markov's inequality yields

$$\begin{aligned} \mathbb{P} \left\{ Y_D^N\left(\bar{t}, \frac{j}{N}\right) > \epsilon_0 \right\} &= \mathbb{P} \{ \bar{m}_D(\bar{t}) > \epsilon_0 \} = \mathbb{P} \{ m_D(\bar{t}) > \bar{\theta} N \epsilon_0 \} = \mathbb{P} \left\{ e^{m_D(\bar{t})} > e^{\bar{\theta} N \epsilon_0} \right\} \\ &\leq e^{-\bar{\theta} N \epsilon_0} \mathbb{E} \left[e^{m_D(\bar{t})} \right] \leq \exp[\bar{\theta} N (\bar{c} \bar{\theta} - \epsilon_0)]. \end{aligned}$$

2.3 The Law of Large Numbers

We can choose $\bar{\theta}$ such that

$$\mathbb{P} \left\{ Y_D^N \left(\bar{t}, \frac{j}{N} \right) > \epsilon_0 \right\} \leq e^{-\alpha \epsilon_0^2 N}, \quad \text{for } \alpha = \bar{c}(M_1, \rho, T) > 0,$$

independently of N , μ , j and \bar{t} . The same relation holds for $\mathbb{P} \left\{ -Y_D^N \left(\bar{t}, \frac{j}{N} \right) > \epsilon_0 \right\}$. Therefore,

$$\mathbb{P} \left\{ \left| Y_D^N \left(t, \frac{j}{N} \right) \right| > \epsilon_0 \right\} \leq 2e^{-\alpha \epsilon_0^2 N} \quad \text{for } 0 < t \leq T \quad \text{and } j \in \{1, \dots, N\}.$$

Since $\|Y_D^N(t)\|_\infty = \sup_{1 \leq j \leq N} \left| Y_D^N \left(t, \frac{j}{N} \right) \right|$ and $Y_D^N(0) = 0$,

$$\begin{aligned} \mathbb{P} \left\{ \|Y_D^N(t)\|_\infty > \epsilon_0 \right\} &= \mathbb{P} \left\{ \exists j \in \{1, \dots, N\} : \left| Y_D^N \left(t, \frac{j}{N} \right) \right| > \epsilon_0 \right\} \\ &\leq \sum_{1 \leq j \leq N} \mathbb{P} \left\{ \left| Y_D^N \left(t, \frac{j}{N} \right) \right| > \epsilon_0 \right\} \leq 2Ne^{-\alpha \epsilon_0^2 N} \end{aligned} \quad (2.3.22)$$

for $0 \leq t \leq T$. We now show that (2.3.22) holds with $\|Y_D^N(t)\|_\infty$ replaced by $\sup_{[0, T]} \|Y_D^N(t)\|_\infty$ and N (on the right) replaced by N^3 . With the introduced subdivision of $[0, T]$ into N^2 subintervals $I_n(T) = \left[\frac{nT}{N^2}, \frac{(n+1)T}{N^2} \right]$, $0 \leq n \leq N^2 - 1$, one can always write

$$Y_D^N(t) = \tilde{m}_D(t) + Z_D^N \left(\frac{nT}{N^2} \wedge \tau \right) = \tilde{m}_D(t) + Y_D^N \left(\frac{nT}{N^2} \right),$$

where $\tilde{m}_D(t) := Z_D^N(t \wedge \tau) - Z_D^N \left(\frac{nT}{N^2} \wedge \tau \right)$ is a mean zero martingale for $t \in I_n(T)$. Thus,

$$\sup_{I_n(T)} \|Y_D^N(t)\|_\infty \leq \sup_{I_n(T)} \|\tilde{m}_D(t)\|_\infty + \left\| Y_D^N \left(\frac{nT}{N^2} \right) \right\|_\infty. \quad (2.3.23)$$

As previously, we now want to find a suitable martingale associated with \tilde{m}_D . Fix $j \in \{1, \dots, N\}$, $\bar{\theta} \in [0, \gamma^{-1}]$ and set

$$m_D(t) = \bar{\theta} N \tilde{m}_D \left(t, \frac{j}{N} \right), \quad \text{for } t \in I_n(T) = \left[\frac{nT}{N^2}, \frac{(n+1)T}{N^2} \right].$$

For $s \in I_n(T)$, $s \geq \frac{nT}{N^2}$ yields $|\delta m_D(s)| = \bar{\theta} N \left| \delta Z_j^{N,D}(s \wedge \tau) \right| \leq 1$. From Lemma 2.3.2,

$$\sum_{\frac{nT}{N^2} \leq s \leq t \wedge \tau} [\delta m_D(s)]^2 - \int_{\frac{nT}{N^2} \wedge \tau}^{t \wedge \tau} g_D^N(s) ds$$

is a mean 0 martingale, with $g_D^N(s) = \bar{\theta}^2 N^2 |G^N|_j^2(u^N(s)) \leq \bar{\theta}^2 \bar{c} N$. Since reaction rates are bounded, $0 \leq g_D^N(s) \leq h_D^N(s)$, where $h_D^N(s) = \bar{\theta}^2 \bar{c} N$ satisfies $\int_{\frac{nT}{N^2} \wedge \tau}^{t \wedge \tau} h_D^N(s) \leq \bar{c} \bar{\theta}^2 N$.

Thus, Lemma 2.3.4 implies $\mathbb{E} \left[\exp \left\{ m_D \left(\frac{(n+1)T}{N^2} \right) \right\} \right] \leq \exp(\bar{c}\bar{\theta}^2 N)$. Doob's inequalities, lead to

$$\begin{aligned} \mathbb{P} \left\{ \sup_{I_n(T)} \tilde{m}_D \left(t, \frac{j}{N} \right) > \epsilon_0 \right\} &\leq e^{-\bar{\theta} N \epsilon_0} \mathbb{E} \left[\exp \left\{ m_D \left(\frac{(n+1)T}{N^2} \right) \right\} \right] \\ &\leq \exp [\bar{\theta} N (\bar{c}\bar{\theta} - \epsilon_0)] \leq e^{-\alpha \epsilon_0^2 N}, \end{aligned}$$

where $\alpha = \bar{c}(\bar{\rho}_T, T) > 0$, independently of N , μ and j . We have chosen a suitable $\bar{\theta}$ as previously. Also, the same holds for $-\tilde{m}_D \left(t, \frac{j}{N} \right)$. This shows that

$$\mathbb{P} \left\{ \sup_{I_n(T)} \|\tilde{m}_D(t)\|_\infty > \epsilon_0 \right\} \leq 2N e^{-\alpha \epsilon_0^2 N}. \quad (2.3.24)$$

From (2.3.22), (2.3.23) and (2.3.24), we have

$$\begin{aligned} \mathbb{P} \left\{ e^{-4T} \sup_{I_n(T)} \|Y_D^N(t)\|_\infty > \epsilon_0 \right\} &\leq \mathbb{P} \left\{ \left\| Y_D^N \left(\frac{nT}{N^2} \right) \right\|_\infty + \sup_{I_n(T)} \|\tilde{m}_D(t)\|_\infty > \epsilon_0 \right\} \\ &\leq \mathbb{P} \left\{ \left\| Y_D^N \left(\frac{nT}{N^2} \right) \right\|_\infty > \frac{\epsilon_0}{2} \right\} + \mathbb{P} \left\{ \sup_{I_n(T)} \|\tilde{m}_D(t)\|_\infty > \frac{\epsilon_0}{2} \right\} \quad (2.3.25) \\ &\leq 2N e^{-\alpha \frac{\epsilon_0^2}{2} N} + 2N e^{-\alpha \frac{\epsilon_0^2}{2} N} \leq 4N e^{-\alpha \epsilon_0^2 N}. \end{aligned}$$

Hence,

$$\mathbb{P} \left\{ e^{-4T} \sup_{[0,T]} \|Y_D^N(t)\|_\infty > \epsilon_0 \right\} \leq \sum_{n=0}^{N^2-1} \mathbb{P} \left\{ e^{-4T} \sup_{I_n(T)} \|Y_D^N(t)\|_\infty > \epsilon_0 \right\} \leq 4N^3 e^{-\alpha \epsilon_0^2 N}.$$

Setting $c := \alpha e^{-4T} \epsilon_0 > 0$, it follows that

$$\mathbb{P} \left\{ \sup_{[0,T]} \|Y_D^N(t)\|_\infty > \epsilon_0 \right\} \leq 4N^3 e^{-cN} \rightarrow 0 \quad \text{as } N \rightarrow \infty,$$

which shows the convergence for the discrete part. This completes the proof of (2.3.15) and ends the proof of Theorem 2.3.1. ■

Remark 2.3.3. *In this proof we have used in a crucial way that at each point, the jump of the discrete component is of order $\frac{1}{N}$. For the original model, without spatial correlation of the slow reactions, this does not hold since the jump of discrete components are of order 1.*

Concluding remarks.

The law of large numbers we present in this chapter differs from the existing one, essentially with the additional presence of discrete species, which leads to multiscaling. That consideration complements classical one scale stochastic spatial models, which were already very useful, to a more realistic model.

2.4 Appendix

We believe the multiscale model can be extended to higher dimensions at the level of both the space and the number of species, at the prize of very cumbersome notation. That will be one of the directions for future works, the extension to a larger number of species being more or less trivial. For spatial higher dimensions, one has to be careful about particular points such as the resolution of partial differential equations.

The possibility of a spatial correlation for slow reactions, as considered, supposes that the discrete species is present enough to react sufficiently frequently and get homogenized as the sites get closer.

If the initial model (M6) is a typical hybrid stochastic system, its limit looks like one, but this latter has no discrete variable anymore, and jumps totally disappear. In forthcoming works, we will study the fluctuations of the model around its deterministic limit, in order to get the speeds of the convergence of the initial fast and slow dynamics, through a central limit theorem.

Also, we will present other multiscale stochastic spatial models, with a stronger stochasticity that does not vanishes in the approximation at the first order. The limit will remain a stochastic hybrid system.

2.4 Appendix

2.4.1 Formal limit of the generator

We consider the sequence $\mathcal{A}^N = \mathcal{A}^{N,\mu}$ of generators defined by (2.2.13). We consider a $L^2(I)$ framework and consider test functions $\varphi \in C_b^2(L^2(I) \times L^2(I))$. Each line is expanded at order two thanks to Taylor expansion. The first order expansion has already been examined to understand the limiting generator. For $k = 1, \dots, 5$, denote by $T_k(N)$ the second order term corresponding to the k -th line in the expression of the generator. Let $u = (u_C, u_D) \in C_p(I) \times C_p(I)$ be fixed and let $N, \mu \rightarrow \infty$. We assume that the reaction rates are bounded.

At order 1. We already know that the whole terms together read

$$\begin{aligned} \mathcal{A}_1^N \varphi(\tilde{P}_N u) &= \left\langle D^{1,0} \varphi(\tilde{P}_N u), \Delta_N P_N u_C + F(\tilde{P}_N u) + F_1^N(\tilde{P}_N u) \right\rangle_2 \\ &\quad + \left\langle D^{0,1} \varphi(\tilde{P}_N u), G^N(\tilde{P}_N u) \right\rangle_2. \end{aligned}$$

For $u_C \in C^3(I)$, it converges to

$$\mathcal{A}^\infty \varphi(u) = \left\langle D^{1,0} \varphi(u), \Delta u_C + F(u) \right\rangle_2 + \left\langle D^{0,1} \varphi(u), G(u) \right\rangle_2,$$

requiring $G^N(\tilde{P}_N u) \rightarrow G(u)$, which follows from Proposition 3.2.1, Proposition 2.3.1 and

$$\begin{aligned} \left\| G^N(\tilde{P}_N u) - G(u) \right\|_\infty &\leq \left\| G^N(\tilde{P}_N u) - G^N(u) \right\|_\infty + \left\| G^N(u) - G(u) \right\|_\infty \\ &\leq L_0 \|P_N u - u\|_{\infty, \infty} + \left\| G^N(u) - G(u) \right\|_\infty, \end{aligned}$$

where we use the same notation as in Section 2.4.4.

At order 2. We introduce $e_j := \sqrt{N}\mathbf{1}_j$, for $1 \leq j \leq N$. Since the functions $(\mathbf{1}_j)_{1 \leq j \leq N}$ are pairwise orthogonal in L^2 and of norm $\|\mathbf{1}_j\|_2 = \frac{1}{\sqrt{N}}$, the family $\{e_j, 1 \leq j \leq N\}$ forms an orthonormal basis of $(\mathbb{H}^N, \|\cdot\|_2)$. Also, c denotes a generic constant and $\|D^{l,k}\varphi\|_\infty$ denotes a uniform bound of $D^{l,k}\varphi$, for $0 \leq l, k \leq 2$, $l+k \leq 2$. Let us treat the term appearing from the second line,

$$\begin{aligned} T_2(N) &= \frac{1}{2} \sum_{r \in S_1} \sum_{j=1}^N D^{2,0}\varphi(\tilde{P}_N u) \cdot \left\langle \frac{\gamma_r^C}{\mu} \mathbf{1}_j, \frac{\gamma_r^C}{\mu} \mathbf{1}_j \right\rangle_2 \mu \lambda_r(u_j^C, u_j^D) \\ &\leq \frac{\bar{\gamma}^2 \bar{\lambda}}{2} \|D^{2,0}\varphi\|_\infty \frac{1}{N\mu} \sum_{j=1}^N \|e_j\|_2^2 \leq \frac{c}{\mu} \rightarrow 0. \end{aligned}$$

The first term is similar and also vanishes at the limit, using the same argument. Next, the third term reads

$$\begin{aligned} T_3(N) &= \frac{1}{2} \sum_{r \in \mathfrak{A}_{DC} \setminus S_1} \sum_{j=1}^N D^{2,0}\varphi(\tilde{P}_N u) \cdot \left\langle \frac{\gamma_r^C}{\mu} \mathbf{1}_j, \frac{\gamma_r^C}{\mu} \mathbf{1}_j \right\rangle_2 \lambda_r(u_j) \\ &\quad + \frac{1}{2} \sum_{r \in \mathfrak{A}_{DC} \setminus S_1} \sum_{j=1}^N D^{1,1}\varphi(\tilde{P}_N u) \cdot \left\langle \frac{\gamma_r^C}{\mu} \mathbf{1}_j, \gamma_{j,r}^{N,D}(\tilde{P}_N u) \right\rangle_2 \lambda_r(u_j) \\ &\quad + \frac{1}{2} \sum_{r \in \mathfrak{A}_{DC} \setminus S_1} \sum_{j=1}^N D^{0,2}\varphi(\tilde{P}_N u) \cdot \left\langle \gamma_{j,r}^{N,D}(P_N u_D), \gamma_{j,r}^{N,D}(\tilde{P}_N u) \right\rangle_2 \lambda_r(u_j). \end{aligned}$$

We have

$$\begin{aligned} T_{31}(N) &:= \frac{1}{2N} \sum_{r \in \mathfrak{A}_{DC} \setminus S_1} \sum_{j=1}^N D^{2,0}\varphi(\tilde{P}_N u) \cdot \left\langle \frac{\gamma_r^C}{\mu} e_j, \frac{\gamma_r^C}{\mu} e_j \right\rangle_2 \lambda_r(u_j) \\ &\leq c \|D^{2,0}\varphi\|_\infty \frac{1}{N\mu^2} \sum_{j=1}^N \|e_j\|_2^2 \leq \frac{c}{\mu^2} \rightarrow 0. \end{aligned}$$

Observing that

$$\left\| \gamma_{j,r}^{N,D}(\tilde{P}_N u) \right\|_2 \leq |\gamma_r^D| \sum_{i=1}^N |\gamma_{ij}(N)| \|\mathbf{1}_i\|_2 \leq |\gamma_r^D| \frac{a(0)}{\sqrt{N}}$$

for all $1 \leq j \leq N$, we deduce from the inequality of Cauchy-Schwarz

$$\begin{aligned} T_{32}(N) &:= \frac{1}{2\sqrt{N}} \sum_{r \in \mathfrak{A}_{DC} \setminus S_1} \sum_{j=1}^N D^{1,1}\varphi(\tilde{P}_N u) \cdot \left\langle \frac{\gamma_r^C}{\mu} e_j, \gamma_{j,r}^{N,D}(\tilde{P}_N u) \right\rangle_2 \lambda_r(u_j) \\ &\leq c \|D^{1,1}\varphi\|_\infty \frac{1}{\sqrt{N}\mu} \sum_{j=1}^N \|e_j\|_2 \left\| \gamma_{j,r}^{N,D}(\tilde{P}_N u) \right\|_2 \leq \frac{c}{\sqrt{N}\mu} \rightarrow 0, \end{aligned}$$

on the one hand, and, on the other hand

$$T_{33}(N) := \frac{1}{2} \sum_{r \in \mathfrak{A}_{DC} \setminus S_1} \sum_{j=1}^N D^{0,2}\varphi(\tilde{P}_N u) \cdot \left\langle \gamma_{j,r}^{N,D}(\tilde{P}_N u), \gamma_{j,r}^{N,D}(\tilde{P}_N u) \right\rangle_2 \lambda_r(u_j)$$

2.4 Appendix

Recall that, setting $\tilde{P}_N u = u^N$,

$$\gamma_{j,r}^{N,D}(u_C^N, u_D^N) := \gamma_r^D \sum_{i=1}^N \gamma_{ij}^N \mathbb{1}_i \theta_{ij}^r(u_i^{N,C}, u_i^{N,D}),$$

where $\gamma_{ij}^N := \int_{I_i} a\left(x - \frac{j}{N}\right) dx$, and $\theta_{ij}^r(u_i^{N,C}, u_i^{N,D}) = \theta(u_i^{N,C} + \frac{\gamma_r^C}{\mu} \gamma_{ij}^N) \theta(u_i^{N,D} + \gamma_r^D \gamma_{ij}^N)$. Define the operator A_r by:

$$A_r e_j = \sqrt{N} \sqrt{\lambda_r(u_j^N)} \gamma_{j,r}^{N,D} = \gamma_r^D \sum_{i=1}^N \gamma_{ij}^N \theta_{ij}^r(u_i^N) \sqrt{\lambda_r(u_j^N)} e_i.$$

Then, using standard property of the trace,

$$\begin{aligned} T_{33}(N) &= \frac{1}{2N} \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \sum_{j=1}^N D^{0,2} \varphi(u^N) \cdot \langle A_r e_j, A_r e_j \rangle_2 \\ &= \frac{1}{2N} \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \text{Tr} (A_r^* D^{0,2} \varphi(u^N) A_r) \\ &\leq \frac{1}{2N} \|D^{0,2} \varphi(u^N)\|_\infty \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \text{Tr} (A_r^* A_r). \end{aligned}$$

Also

$$\text{Tr} (A_r^* A_r) = \sum_{j=1}^N \|A_r e_j\|_2^2 \leq \bar{\lambda}(\tilde{\rho}_T) \bar{\gamma}^2 \sum_{i,j} |\gamma_{ij}^N|^2$$

and since $|\gamma_{ij}^N|^2 = \int_{I_i} a\left(x - \frac{j}{N}\right) dx = \frac{1}{\sqrt{N}} \left\langle a\left(\cdot - \frac{j}{N}\right), e_i \right\rangle_2^2$ we have by Parseval identity:

$$\sum_i |\gamma_{ij}^N|^2 = \frac{1}{N} \left\| a\left(\cdot - \frac{j}{N}\right) \right\|_2^2 = \frac{1}{N} \|a\|_2^2.$$

It follows that

$$\text{Tr} (A_r^* A_r) \leq \bar{\lambda} \bar{\gamma}^2 \|a\|_2^2,$$

and as a result, $T_3(N) \rightarrow 0$. The fourth term also vanishes at the limit, using the same argument.

Remark 2.4.1. *Again, we see why we had to consider some spatial correlation in our model. Indeed, the case without spatial correlation for the discrete species corresponds to $\gamma_{ij}^N = 1$ for $i = j$ and is 0 otherwise, obtained with a being the Dirac mass. In this case $\text{Tr} (A_r^* A_r)$ is of order N and $T_3(N)$ does not converge to 0.*

Let us consider the fifth. From

$$\|\mathbb{1}_{j+1} - \mathbb{1}_j\|_2^2 = \frac{2}{N} = \|\mathbb{1}_{j-1} - \mathbb{1}_j\|_2^2,$$

we have

$$\begin{aligned}
 T_5(N) &= \frac{1}{2} \sum_{j=1}^N \left[D^{2,0} \varphi(\tilde{P}_N u) \cdot \left\langle \frac{\mathbf{1}_{j+1} - \mathbf{1}_j}{\mu}, \frac{\mathbf{1}_{j+1} - \mathbf{1}_j}{\mu} \right\rangle_2 \right. \\
 &\quad \left. + D^{2,0} \varphi(\tilde{P}_N u) \cdot \left\langle \frac{\mathbf{1}_{j-1} - \mathbf{1}_j}{\mu}, \frac{\mathbf{1}_{j-1} - \mathbf{1}_j}{\mu} \right\rangle_2 \right] \mu N^2 u_j^C \\
 &\leq \frac{\|u_C\|_\infty}{2} \|D^2 \varphi\|_\infty \frac{N^2}{\mu} \sum_{j=1}^N (\|\mathbf{1}_{j+1} - \mathbf{1}_j\|_2^2 + \|\mathbf{1}_{j-1} - \mathbf{1}_j\|_2^2) \\
 &\leq c \mu^{-1} N^2 \rightarrow 0,
 \end{aligned}$$

if $\mu^{-1} N^2 \rightarrow 0$ as $N, \mu \rightarrow \infty$.

Hence, under the additional condition $\mu^{-1} N^2 \rightarrow 0$, all the terms of the second order in the Taylor expansion vanish at the limit and hence, \mathcal{A}^∞ is indeed formally the limit of \mathcal{A}^N . \square

2.4.2 Relation between the limit and its discretization

Proof of Theorem 2.2.1. Let $T > 0$ be fixed. Since the operator $\tilde{\Delta}_N$ is linear, it is Lipschitz. Next, the vector field $R = (F, G)$ is locally Lipschitz continuous. Therefore, the initial value problem (2.2.25) has a unique local solution v^N thanks to the Picard-Lindelöf theorem. The bounds (2.2.27) are proved thanks to the discrete maximum principle and Gronwall lemma as in section 2.3.2 and we deduce that v^N is in fact a global solution.

Thanks to (2.2.27) and (2.2.24), we may assume that F and G are globally Lipschitz and we choose L such that

$$\|F(u_C^1, u_D^1) - F(u_C^2, u_D^2)\|_\infty \leq L \|(u_C^1, u_D^1) - (u_C^2, u_D^2)\|_{\infty, \infty},$$

$$\|G(u_C^1, u_D^1) - G(u_C^2, u_D^2)\|_\infty \leq L \|(u_C^1, u_D^1) - (u_C^2, u_D^2)\|_{\infty, \infty},$$

provided $\|u_C\|_\infty \leq \rho_C$, $\|u_D\|_\infty \leq (\rho_D + 1)e^{a(0)M_1(\rho_C)T}$.

we have

$$\begin{aligned}
 v^N(t) - u(t) &= \tilde{T}_N(t) \tilde{P}_N u(0) - \tilde{T}(t) u(0) \\
 &\quad + \int_0^t \tilde{T}_N(t-s) \begin{pmatrix} F(v^N(s)) \\ G(v^N(s)) \end{pmatrix} - \tilde{T}(t-s) \begin{pmatrix} F(u(s)) \\ G(u(s)) \end{pmatrix} ds.
 \end{aligned}$$

for all $t \geq 0$. Then,

$$\begin{aligned}
 &\|v^N(t) - u(t)\|_{\infty, \infty} \\
 &\leq \left\| \tilde{T}_N(t) \tilde{P}_N u(0) - \tilde{T}(t) u(0) \right\|_{\infty, \infty} \\
 &\quad + \int_0^t \left\| \tilde{T}_N(t-s) \begin{pmatrix} F(v^N(s)) \\ G(v^N(s)) \end{pmatrix} - \tilde{P}_N \begin{pmatrix} F(v(s)) \\ G(v(s)) \end{pmatrix} \right\|_{\infty, \infty} ds \\
 &\quad + \int_0^t \left\| \tilde{T}_N(t-s) \tilde{P}_N \begin{pmatrix} F(u(s)) \\ G(u(s)) \end{pmatrix} - \tilde{T}(t-s) \begin{pmatrix} F(u(s)) \\ G(u(s)) \end{pmatrix} \right\|_{\infty, \infty} ds.
 \end{aligned}$$

2.4 Appendix

Since \mathbb{H}^N is stable by F and G , we rely on [Proposition 3.2.1](#) and [Proposition 3.2.2](#) to find an upper bound for each term on the right hand side of the inequality above.

$$T_2(N) \leq \int_0^t \left\| \tilde{P}_N \begin{pmatrix} F(v^N(s)) - F(v(s)) \\ G(v^N(s)) - G(v(s)) \end{pmatrix} \right\|_{\infty, \infty} ds \leq 2L \int_0^t \|v^N(s) - v(s)\|_{\infty, \infty} ds,$$

and

$$T_3(N) = \int_0^t \|T_N(t-s)P_N F(u(s)) - T(t-s)F(u(s))\|_{\infty} ds.$$

Hence,

$$\begin{aligned} \|v^N(t) - v(t)\|_{\infty, \infty} &\leq \left\| \tilde{T}_N(t)\tilde{P}_N v(0) - \tilde{T}(t)v(0) \right\|_{\infty, \infty} \\ &\quad + \int_0^t \|T_N(t-s)P_N F(v(s)) - T(t-s)F(v(s))\|_{\infty} ds \\ &\quad + 2L \int_0^t \|v^N(s) - v(s)\|_{\infty, \infty} ds. \end{aligned}$$

Taking the supremum in t on $[0, T]$ and using Gronwall lemma leads to

$$\begin{aligned} &\sup_{[0, T]} \|v^N(t) - v(t)\|_{\infty, \infty} \\ &\leq \left(\sup_{[0, T]} \left\| \tilde{T}_N(t)\tilde{P}_N v(0) - \tilde{T}(t)v(0) \right\|_{\infty, \infty} \right. \\ &\quad \left. + \int_0^T \sup_{t \in [0, T]} (\|T_N(t-s)P_N F(v(s)) - T(t-s)F(v(s))\|_{\infty} \mathbf{1}_{(s \leq t)}) ds \right) \times e^{2LT}. \end{aligned}$$

Firstly,

$$\begin{aligned} &\sup_{[0, T]} \left\| \tilde{T}_N(t)\tilde{P}_N v(0) - \tilde{T}(t)v(0) \right\|_{\infty, \infty} \\ &\leq \sup_{[0, T]} \|T_N(t)P_N u_C(0) - T(t)u_C(0)\|_{\infty} + \|P_N u_D(0) - u_D(0)\|_{\infty} \longrightarrow 0, \end{aligned}$$

where the first term vanishes thanks to [Proposition 3.2.2](#) (vi), since $u_C(0) \in C^3(I)$. Secondly, we fix $t \in [0, T]$ and $s \in [0, t]$. Since $F(u(s)) \in C^3(I)$, we have

$$\|T_N(t-s)P_N F(u(s)) - T(t-s)F(u(s))\|_{\infty} \longrightarrow 0,$$

thanks to [Proposition 3.2.2](#) (vi) again. Moreover, the convergence is uniform with respect to t , on $[0, T]$. Thus,

$$\sup_{t \in [0, T]} (\|T_N(t-s)P_N F(u(s)) - T(t-s)F(u(s))\|_{\infty} \mathbf{1}_{(s \leq t)}) \longrightarrow 0.$$

$$\text{Hence, } \int_0^T \sup_{t \in [0, T]} (\|T_N(t-s)P_N F(u(s)) - T(t-s)F(u(s))\|_{\infty} \mathbf{1}_{(s \leq t)}) ds \longrightarrow 0,$$

thanks to the dominated convergence theorem. \square

2.4.3 The accompanying martingales

Proof of Lemma 2.3.1. Fix $1 \leq j \leq N$ and define $Y^N(t) = (Y_1^N(t), \dots, Y_{N+4}^N(t))$ by

$$\left\{ \begin{array}{l} Y_k^N(t) := u_k^N(t) \quad \text{for } 1 \leq k \leq N, \\ Y_{N+1}^N(t) := \sum_{s \leq t} [\delta u_{j-1}^{N,C}(s)] [\delta u_j^{N,C}(s)] \\ Y_{N+2}^N(t) := \sum_{s \leq t} [\delta u_j^{N,C}(s)]^2 \\ Y_{N+3}^N(t) := \sum_{s \leq t} [\delta u_j^{N,C}(s)] [\delta u_{j+1}^{N,C}(s)] \\ Y_{N+4}^N(t) := \sum_{s \leq t} [\delta u_j^{N,D}(s)]^2. \end{array} \right.$$

Y^N is a Markov process with values in \mathbb{R}^{2N+4} . From (2.2.9), Assumptions 2.2.3 and 2.2.4, we know that Y^N enjoys the following transitions:

$Y_{N+1}^N \longrightarrow Y_{N+1}^N - \frac{1}{\mu^2}$ at rate $\mu N^2 (u_{j-1}^{N,C} + u_j^{N,C})$ so that the corresponding debit is

$$-\frac{N^2}{\mu} (u_{j-1}^C + u_j^C) =: |\Psi_-^{N,C}|_j^2(u).$$

Similarly, $Y_{N+3}^N \longrightarrow Y_{N+3}^N - \frac{1}{\mu^2}$ at rate $\mu N^2 (u_j^{N,C} + u_{j+1}^{N,C})$, and the associated debit is

$$-\frac{N^2}{\mu} (u_j^C + u_{j+1}^C) =: |\Psi_+^{N,C}|_j^2(u_j).$$

Now,

$$Y_{N+2}^N \rightarrow Y_{N+2}^N + \frac{|\gamma_r^C|^2}{\mu^2} \text{ at rate } \begin{cases} \mu \lambda_r (u_j^{N,C}) & \text{for } r \in \mathfrak{R}_C \\ \mu \lambda_r (u_j^{N,C}, u_j^{N,D}) & \text{for } r \in S_1, \end{cases}$$

$$Y_{N+2}^N \rightarrow Y_{N+2}^N + \frac{|\gamma_r^C|^2}{\mu^2} \text{ at rate } \lambda_r (u_j^{N,C}, u_j^{N,D}) \text{ for } r \in \mathfrak{R}_{DC} \setminus S_1$$

$$Y_{N+2}^N \rightarrow Y_{N+2}^N + \frac{1}{\mu^2} \text{ at rate } \mu N^2 (u_{j-1}^{N,C} + 2u_j^{N,C} + u_{j+1}^{N,C}) \text{ for a diffusion.}$$

The joined debit is

$$\begin{aligned} & \frac{1}{\mu} \left[N^2 (u_{j-1}^C + 2u_j^C + u_{j+1}^C) + \sum_{r \in \mathfrak{R}_C} |\gamma_r^C|^2 \lambda_r (u_j^C) + \sum_{r \in S_1} |\gamma_r^C|^2 \lambda_r (u_j^C, u_j^D) \right. \\ & \quad \left. + \frac{1}{\mu} \sum_{i=1}^N \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} |\gamma_{ji}^N|^2 |\theta_{ji}^r(u_j^C, u_j^D)|^2 \lambda_r (u_j^C, u_j^D) \right] \\ & = \frac{1}{\mu} \left(|\Delta_N|^2 (u_j^C) + |F|_j^2(u_C, u_D) + |F_1^N|_j^2(u_C, u_D) \right) = \frac{1}{\mu} |\Psi_C^N|_j^2(u_C, u_D). \end{aligned}$$

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Finally, for $i = 1, \dots, N$, $Y_{N+4}^N \longrightarrow Y_{N+4}^N + |\gamma_{ij}(N)|^2 |\gamma_r^D|^2 |\theta_{ij}^r(u_i^C, u_i^D)|^2$ at rate

$$\begin{cases} \lambda_r \left(u_j^{N,C}, u_j^{N,D} \right) & \text{for } r \in \mathfrak{R}_{DC} \setminus S_1 \\ \lambda_r \left(u_j^{N,D} \right) & \text{for } r \in \mathfrak{R}_D. \end{cases}$$

Theses transitions admit as debit function

$$|\Psi_D^N|_j^2(u_C, u_D) = \sum_{i=1}^N |\gamma_{ij}^N|^2 |g_{ij}^2(u_C, u_D)| =: |G^N|_j^2(u_C, u_D).$$

Furthermore,

$$\begin{aligned} \sup_{[0,T]} \sup_{1 \leq k \leq N} |Y_k^N(t \wedge \tau)| &= \sup_{[0,T]} \sup_{1 \leq k \leq N} |u_k^N(t \wedge \tau)| \\ &\leq c \sup_{[0,T]} \max \left(\|u_C^N(t \wedge \tau)\|_\infty, \|u_D^N(t \wedge \tau)\|_\infty \right) \\ &\leq c \sup_{[0,T]} \|u^N(t \wedge \tau)\|_{\infty, \infty} \leq C(T_N, \mu) \end{aligned}$$

since u^N satisfies (2.3.5). Therefore, Y^N satisfies (2.3.5) too, and has a bounded total jump rates when stopped at τ . Applying Proposition 2.1 of [Kur71] to Y^N ends the proof. \square

Proof of Lemma 2.3.2. Set $\varphi_j := \varphi \left(\frac{j}{N} \right)$ for $1 \leq j \leq N$. Since Z_C^N has the same jumps as u_C^N ,

$$\begin{aligned} \delta \langle Z_C^N(s), \varphi \rangle_2 &= \delta \left[\frac{1}{N} \sum_{j=1}^N Z_C^N \left(s, \frac{j}{N} \right) \varphi \left(\frac{j}{N} \right) \right] \\ &= \frac{1}{N} \sum_{j=1}^N \delta Z_j^{N,C}(s) \varphi_j = \frac{1}{N} \sum_{j=1}^N \delta u_j^{N,C}(s) \varphi_j. \end{aligned}$$

Recall that $[\delta u_j^{N,C}(s)] [\delta u_k^{N,C}(s)] = 0$ for $k \notin \{j-1, j, j+1\}$. Thus,

$$\begin{aligned} [\delta \langle Z_C^N(s), \varphi \rangle_2]^2 &= \frac{1}{N^2} \sum_{j=1}^N \left([\delta u_{j-1}^{N,C}(s)] [\delta u_j^{N,C}(s)] \varphi_{j-1} \varphi_j + [\delta u_j^{N,C}(s)]^2 \varphi_j^2 \right. \\ &\quad \left. + [\delta u_j^{N,C}(s)] [\delta u_{j+1}^{N,C}(s)] \varphi_j \varphi_{j+1} \right). \end{aligned}$$

By Lemma 2.3.1,

$$\begin{aligned} &\sum_{s \leq t \wedge \tau} [\delta \langle Z_C^N(s), \varphi \rangle_2]^2 \\ &= \frac{1}{N^2 \mu} \sum_{j=1}^N \left\{ \varphi_j^2 \int_0^{t \wedge \tau} \left[N^2 \left(u_{j+1}^{N,C}(s) + 2u_j^{N,C}(s) + u_{j-1}^{N,C}(s) \right) \right. \right. \\ &\quad \left. \left. + \left(|F_j|^2 + \mu |F_1^N|_j^2 \right) \left(u^N(s) \right) \right] ds \right. \\ &\quad \left. - \varphi_j \varphi_{j-1} \int_0^{t \wedge \tau} N^2 \left(u_j^{N,C}(s) + u_{j-1}^{N,C}(s) \right) ds \right. \end{aligned}$$

$$-\varphi_j \varphi_{j+1} \int_0^{t \wedge \tau} N^2 \left(u_j^{N,C}(s) + u_{j+1}^{N,C}(s) \right) ds \Big\} + M(t),$$

where $M(t)$ is a martingale. Therefore, using the 1-periodicity of our processes with respect to the space variable and proceeding to a change of superscript in j , we get

$$\begin{aligned} & \sum_{s \leq t \wedge \tau} \left[\delta \left\langle Z_j^{N,C}(s), \varphi \right\rangle_2 \right]^2 \\ &= \frac{1}{N^2 \mu} \int_0^{t \wedge \tau} \left[\sum_{j=1}^N u_j^{N,C}(s) N^2 (\varphi_{j-1}^2 + 2\varphi_j^2 + \varphi_{j+1}^2 - 2\varphi_{j-1}\varphi_j - 2\varphi_j\varphi_{j+1}) \right. \\ & \quad \left. + \sum_{j=1}^N \left(|F|_j^2 + \mu |F_1^N|_j^2 \right) (u^N(s)) \varphi_j^2 \right] ds + M(t) \\ &= \frac{1}{N\mu} \int_0^{t \wedge \tau} \left[\frac{1}{N} \sum_{j=1}^N u_j^{N,C}(s) \left([N(\varphi_{j-1} - \varphi_j)]^2 + [N(\varphi_{j+1} - \varphi_j)]^2 \right) \right. \\ & \quad \left. + \frac{1}{N} \sum_{j=1}^N \left(|F|_j^2 + \mu |F_1^N|_j^2 \right) (u^N(s)) \varphi_j^2 \right] ds + M(t) \\ &= \frac{1}{N\mu} \int_0^{t \wedge \tau} \left[\left\langle u_C^N(s), (\nabla_N^+ \varphi)^2 + (\nabla_N^- \varphi)^2 \right\rangle_2 \right. \\ & \quad \left. + \left\langle \left(|F|^2 + \mu |F_1^N|^2 \right) (u^N(s)), \varphi^2 \right\rangle_2 \right] ds + M(t). \end{aligned}$$

This shows that (Mg5) defines a martingale. The case of (Mg6) is treated similarly, replacing $|F|^2$ by $|G^N|^2$. There is no term with the discrete gradient. \square

2.4.4 Regularity and convergence of the debits

Proof of Proposition 2.3.1. Denote by L_λ the Lipschitz constant common to all the reactions rates. Fix $u = (u_C, u_D), v = (v_C, v_D) \in C_p(I) \times C_p(I)$.

We start with the debit F defined by (2.2.16).

$$\begin{aligned} & |F(u(x)) - F(v(x))| \\ & \leq \sum_{r \in \mathfrak{R}_C} |\gamma_r^C| |\lambda_r(u_C(x)) - \lambda_r(v_C(x))| + \sum_{r \in \mathfrak{S}_1} |\gamma_r^C| |\lambda_r(u(x)) - \lambda_r(v(x))| \\ & \leq L_\lambda \left(|u_C(x) - v_C(x)| \sum_{r \in \mathfrak{R}_C} |\gamma_r^C| + |u(x) - v(x)| \sum_{r \in \mathfrak{S}_1} |\gamma_r^C| \right) \\ & \leq L_\lambda \bar{\gamma}_C [|u_C(x) - v_C(x)| + |u_D(x) - v_D(x)| + |u_D(x) - v_D(x)|] \\ & \leq L_F (\|u_C - v_C\|_\infty + \|u_D - v_D\|_\infty) = L_F \|u - v\|_{\infty, \infty}. \end{aligned}$$

Thus, F is Lipschitz. The Lipschitz property of the debit F_1^N given by (2.2.17) immediately follows from that of the reaction rates, as F_1^N is a linear combination of some of them.

2.4 Appendix

The function g defined by (2.2.19) is Lipschitz. Indeed,

$$\begin{aligned}
& |g(u(x)) - g(v(x))| \\
& \leq \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} |\gamma_r^D| |\lambda_r(u(x)) - \lambda_r(v(x))| + \sum_{r \in \mathfrak{R}_D} |\gamma_r^D| |\lambda_r(u_D(x)) - \lambda_r(v_D(x))| \\
& \leq L_\lambda \bar{\gamma}_D [|u_C(x) - v_C(x)| + |u_D(x) - v_D(x)| + |u_D(x) - v_D(x)|] \\
& \leq L_g (\|u_C - v_C\|_\infty + \|u_D - v_D\|_\infty) = L_g \|u - v\|_{\infty, \infty},
\end{aligned}$$

and g is Lipschitz. As a result, it follows easily that G is Lipschitz.

Recall

$$G^N(u) = \sum_{i,j} \gamma_{ij}^N g_{ij}(u) \mathbf{1}_i, \quad \text{where} \quad g_{ij}(u) = \sum_r \gamma_r^D \theta_{ij}^r(u_i) \lambda_r(u_i),$$

with $j, i = 1, \dots, N$ and $r \in (\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D$. Fix j, i , let $x \in I_i$ and let L_θ be a Lipschitz constant for the function θ . We successively have

$$\begin{aligned}
|\theta_{ij}^r(u_i) - \theta_{ij}^r(v_i)| & \leq \left| \theta(u_i^C + \frac{\gamma_r^C}{\mu} \gamma_{ij}^N) - \theta(v_i^C + \frac{\gamma_r^C}{\mu} \gamma_{ij}^N) \right| \theta(u_i^C + \gamma_r^D \gamma_{ij}^N) \\
& \quad + \theta(v_i^C + \frac{\gamma_r^C}{\mu} \gamma_{ij}^N) \left| \theta(u_i^C + \gamma_r^D \gamma_{ij}^N) - \theta(v_i^C + \gamma_r^D \gamma_{ij}^N) \right| \\
& \leq L_\theta (|u_i^C - v_i^C| + |u_i^D - v_i^D|) \leq L_\theta \|u - v\|_{\infty, \infty},
\end{aligned}$$

$$\begin{aligned}
|g_{ij}(u) - g_{ij}(v)| & \leq \sum_r |\gamma_r^D| [|\theta_{ij}^r(u_i) - \theta_{ij}^r(v_i)| \lambda_r(u_j) + \theta_{ij}^r(v_i) |\lambda_r(u_j) - \lambda_r(v_j)|] \\
& \leq L_\theta \bar{\gamma} \bar{\lambda}(\tilde{\rho}_T) \|u - v\|_{\infty, \infty} + L_\lambda \bar{\gamma} |u_j - v_j| \bar{c} \|u - v\|_{\infty, \infty},
\end{aligned}$$

and it easily follows that G^N is Lipschitz uniformly in N .

Since G^N and G are Lipschitz with a uniform constant and using a density argument, we may assume that $u = (u_C, u_D) \in C^1(I) \times C^1(I)$. Also, G and G^N are continuous with respect to a for the L^1 topology. Indeed, since θ is bounded by 1 and g is a bounded function

$$\|G^N(u)\|_\infty \leq \bar{\gamma} \bar{\lambda}(\tilde{\rho}_T) \max_{i=1, \dots, N} \sum_{j=1}^N N \int_{I_j} \int_{I_i} a \left(z - \frac{j}{N} \right) dz dy = \|g\|_\infty \|a\|_{L^1(I)}.$$

The same bound holds for G and by linearity, we deduce the continuity property. By density of periodic $C^1(I)$ function in $L^1(I)$, we may assume that $a \in C^1(I)$.

Write for $x \in I_i$, and r varying over $(\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D$:

$$G^N(u)(x) = \sum_{j=1}^N \sum_r \gamma_r^D \theta(u_i^C + \frac{\gamma_r^C}{\mu} \gamma_{ij}^N) \theta(u_i^D + \gamma_r^D \gamma_{ij}^N) N \int_{I_j} \lambda_r(u_j) \int_{I_i} a \left(z - \frac{j}{N} \right) dz dy,$$

and

$$G(u)(x) = \sum_{j=1}^N \sum_r \gamma_r^D \theta(u_C(x)) \theta(u_D(x)) N \int_{I_j} \lambda_r(u(y)) \int_{I_i} a(x-y) dz dy.$$

Thus, since θ is bounded by 1, a by $a(0)$ and is a bounded function,

$$\begin{aligned} & |G^N(u)(x) - G(u)(x)| \\ & \leq a(0) \sum_r |\gamma_r^D| \sum_{j=1}^N \int_{I_j} |g(u_j) - g(u(y))| dy \\ & \quad + a(0) \bar{\gamma} \bar{\lambda}(\tilde{\rho}_T) \left| \theta(u_i^C + \frac{\gamma_r^C}{\mu} \gamma_{ij}^N) \theta(u_i^D + \gamma_r^D \gamma_{ij}^N) - \theta(u^C(x)) \theta(u^D(x)) \right| \\ & \quad + \bar{\gamma} \bar{\lambda}(\tilde{\rho}_T) \sum_{j=1}^N N \int_{I_j} \int_{I_i} \left| a\left(z - \frac{j}{N}\right) - a(x-y) \right| dz dy \end{aligned}$$

This clearly goes to zero when $N \rightarrow \infty$ thanks to (2.3.12) and the Lipschitz property of θ , g , a and u . \square

2.4.5 On the Gronwall-Bellman argument

Proof of Lemma 4.3.3. From Proposition 3.2.2 and the observations at the beginning of Section 2.2.3,

$$\begin{aligned} \left\langle (\nabla_N^\pm T_N(t)f)^2, 1 \right\rangle_2 &= \langle T_N(2t)f, \Delta_N f \rangle_2 \\ &= \sum_m \left[\langle |f, \varphi_{m,N} \rangle_2|^2 + \langle |f, \psi_{m,N} \rangle_2|^2 \right] e^{-2\beta_{m,N}t} \beta_{m,N} \\ &= \sum_m \left(\varphi_{m,N}^2 \left(\frac{j}{N}\right) + \psi_{m,N}^2 \left(\frac{j}{N}\right) \right) e^{-2\beta_{m,N}t} \beta_{m,N} \\ &\leq 2 \sum_m e^{-2\beta_{m,N}t} \beta_{m,N}. \end{aligned}$$

Similarly,

$$\left\langle (T_N(t)f)^2, 1 \right\rangle_2 \leq 1 + 2 \sum_{m>0} e^{-2\beta_{m,N}t}.$$

The result then holds for

$$h_N(t) = 1 + 4 \sum_{m>0} e^{-2\beta_{m,N}t} (\beta_{m,N} + 1), \quad (2.4.1)$$

since $\beta_{0,N} = 0$ and $\beta_{m,N} > cm^2$ for $m > 0$ and $c > 0$, where c is independent of m and N . \square

Proof of Lemma 2.3.4. Let $f(x) = e^x$ and note

$$0 \leq f''(x+y) = f(x)f(y) \leq 3f(x) \quad \text{if } |y| \leq 1.$$

Using change of variables for functions of bounded variation, we have for $t_0 \leq t \leq t_1$,

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$$\begin{aligned}
f(m(t)) &= 1 + \int_{t_0}^t f'(m(s^-)) dm(s) \\
&\quad + \sum_{t_0 \leq s \leq t} [f(m(s)) - f(m(s^-)) - f'(m(s^-)) \delta m(s)] \\
&\leq 1 + \int_{t_0}^t f'(m(s^-)) dm(s) + \frac{3}{2} \sum_{t_0 \leq s \leq t} f(m(s^-)) (\delta m(s))^2,
\end{aligned}$$

by Taylor's theorem, (ii) of Lemma 2.3.4 and our observations at the start of the proof. Note that $\int_{t_0}^t f'(m(s^-)) dm(s)$ has mean 0 and after applying (iii) of Lemma 2.3.4 and taking expectations, we have

$$\mathbb{E}f(m(t)) \leq 1 + \frac{3}{2} \int_{t_0}^t \mathbb{E}f(m(s)) h(s) ds.$$

The result then follows from Gronwall's inequality. \square

Proof of Lemma 2.3.5. We want to identify the martingale part of $\sum_{s \leq t} [\delta \bar{m}_C(t)]^2$. Integrating $\bar{m}_C(t)$ by parts leads to

$$\begin{aligned}
\bar{m}_C(t) &= \left\langle T_N(\bar{t} - t) Z_C^N(t \wedge \tau) + \int_0^t \Delta_N T_N(\bar{t} - s) Z_C^N(s \wedge \tau) ds, f \right\rangle_2 \\
&= \left\langle T_N(\bar{t} - t) Z_C^N(t \wedge \tau), f \right\rangle_2 + \left\langle \int_0^t \Delta_N T_N(\bar{t} - s) Z_C^N(s \wedge \tau) ds, f \right\rangle_2.
\end{aligned}$$

Since $t \mapsto \int_0^t \Delta_N T_N(\bar{t} - s) Z_C^N(s \wedge \tau) ds$ is continuous, the corresponding term does not jump and consequently

$$\delta \bar{m}_C(t) = \delta \left\langle T_N(\bar{t} - t) Z_C^N(t \wedge \tau), f \right\rangle_2 = [\delta T_N(\bar{t} - t) u_C^N(t \wedge \tau)]_j,$$

where j has been fixed within $\{1, \dots, N\}$. Observing that

$$[T_N(\bar{t} - t) u_C^N(t)]_j = \sum_{i=1}^N u_i^{N,C}(t) [T_N(\bar{t} - t) \mathbf{1}_i]_j,$$

we have

$$\begin{aligned}
[\delta T_N(\bar{t} - t) u_C^N(t)]_j^2 &= \left(\sum_{i=1}^N [\delta u_i^{N,C}(t)] [T_N(\bar{t} - t) \mathbf{1}_i]_j \right)^2 \\
&= \sum_{i=1}^N \left([\delta u_i^{N,C}(t)]^2 [T_N(\bar{t} - t) \mathbf{1}_i]_j^2 \right. \\
&\quad + [\delta u_i^{N,C}(t)] [\delta u_{i-1}^{N,C}(t)] [T_N(\bar{t} - t) \mathbf{1}_i]_j [T_N(\bar{t} - t) \mathbf{1}_{i-1}]_j \\
&\quad \left. + [\delta u_i^{N,C}(t)] [\delta u_{i+1}^{N,C}(t)] [T_N(\bar{t} - t) \mathbf{1}_i]_j [T_N(\bar{t} - t) \mathbf{1}_{i+1}]_j \right)
\end{aligned}$$

We need the forthcoming.

Lemma 2.4.1. *We have $[T_N(t)\mathbf{1}_i]_j = [T_N(t)\mathbf{1}_j]_i$ for all $1 \leq i \leq N$.*

Proof. Let $1 \leq i \leq N$ and $t \geq 0$ be fixed. We first remark that

$$\langle \mathbf{1}_i, \varphi \rangle_2 = \varphi_j = v(j/N) \quad \forall \varphi \in \mathbb{H}^N.$$

Then, from the spectral decomposition of $T_N(t)$ on $(\mathbb{H}^N, \langle \cdot, \cdot \rangle_2)$ (see Proposition 3.2.2),

$$\begin{aligned} [T_N(t)\mathbf{1}_i]_j &= \sum_m e^{-\beta_{m,N}t} (\langle \mathbf{1}_i, \varphi_{m,N} \rangle_2 \varphi_{m,N}^j + \langle \mathbf{1}_i, \psi_{m,N} \rangle_2 \psi_{m,N}^j) \\ &= \sum_m e^{-\beta_{m,N}t} (\varphi_{m,N}^i \langle \mathbf{1}_j, \varphi_{m,N} \rangle_2 + \psi_{m,N}^i \langle \mathbf{1}_j, \psi_{m,N} \rangle_2) = [T_N(t)\mathbf{1}_j]_i. \quad \square \end{aligned}$$

Now, from Lemma 2.3.1, there exists a martingale $M(t)$ such that, using periodicity and Lemma 2.4.1, we get

$$\begin{aligned} & \sum_{s \leq t} [\delta T_N(\bar{t} - s)u_C^N(t)]_j^2 \\ &= \sum_{i=1}^N \frac{1}{\mu} \int_0^{t \wedge \tau} \left\{ \left[N^2(u_{i+1}^{N,C}(s) + 2u_i^{N,C}(s)u_{i-1}^N(s)) \right. \right. \\ & \quad \left. \left. + \left(|F|_i^2 + \mu |F_1^N|_i^2 \right) (u^N(s)) \right] [T_N(\bar{t} - s)\mathbf{1}_i]_j^2 \right. \\ & \quad \left. - N^2(u_i^{N,C}(s) + u_{i-1}^{N,C}(s)) [T_N(\bar{t} - s)\mathbf{1}_i]_j [T_N(\bar{t} - s)\mathbf{1}_{i-1}]_j \right. \\ & \quad \left. - N^2(u_i^{N,C}(s) + u_{i+1}^{N,C}(s)) [T_N(\bar{t} - s)\mathbf{1}_i]_j [T_N(\bar{t} - s)\mathbf{1}_{i+1}]_j \right\} ds + M(t) \\ &= \frac{1}{\mu} \int_0^{t \wedge \tau} \left\{ \sum_{i=1}^N u_i^{N,C}(s) N^2 \left([T_N(\bar{t} - s)\mathbf{1}_{i-1}]_j^2 + 2[T_N(\bar{t} - s)\mathbf{1}_i]_j^2 + [T_N(\bar{t} - s)\mathbf{1}_{i+1}]_j^2 \right. \right. \\ & \quad \left. \left. - 2[T_N(\bar{t} - s)\mathbf{1}_i]_j [T_N(\bar{t} - s)\mathbf{1}_{i-1}]_j \right. \right. \\ & \quad \left. \left. - 2[T_N(\bar{t} - s)\mathbf{1}_{i+1}]_j [T_N(\bar{t} - s)\mathbf{1}_i]_j \right) \right. \\ & \quad \left. + \sum_{i=1}^N \left(|F|_i^2 + \mu |F_1^N|_i^2 \right) (u^N(s)) [T_N(\bar{t} - s)\mathbf{1}_i]_j^2 \right\} ds + M(t) \\ &= \frac{1}{\mu N} \int_0^{t \wedge \tau} \left\{ \frac{1}{N} \sum_{i=1}^N \left(N [T_N(\bar{t} - s)N\mathbf{1}_j]_{i+1} - [T_N(\bar{t} - s)N\mathbf{1}_j]_i \right)^2 \right. \\ & \quad \left. + \left(N [T_N(\bar{t} - s)N\mathbf{1}_j]_i - [T_N(\bar{t} - s)N\mathbf{1}_j]_{i-1} \right)^2 \right. \\ & \quad \left. + \frac{1}{N} \sum_{i=1}^N \left(|F|_i^2 + \mu |F_1^N|_i^2 \right) (u^N(s)) [T_N(\bar{t} - s)N\mathbf{1}_i]_j^2 \right\} ds + M(t) \\ &= \frac{1}{\mu N} \int_0^{t \wedge \tau} \left[\left\langle u_C^N(s), (\nabla_N^+ T_N(\bar{t} - s)f)^2 + (\nabla_N^- T_N(\bar{t} - s)f)^2 \right\rangle_2 \right. \\ & \quad \left. + \left\langle \left(|F|^2 + \mu |F_1^N|^2 \right) (u^N(s)), (T_N(\bar{t} - s)f)^2 \right\rangle_2 \right] ds + M(t). \quad \square \end{aligned}$$

CHAPTER 3

A piecewise deterministic limit in the supremum norm for a multiscale stochastic spatial gene network

Abstract. We perform in this chapter a hybrid approximation in the supremum norm, for a multiscale stochastic spatial gene networks involving chemical reactions and diffusions. As in chapter 2, the model is Markovian and the transitions are driven by Poisson process clocks. We consider that the slow dynamics are spatially localized at a macroscopic level, on the opposite of chapter 2 where the whole spatial dynamics were happening at a microscopic level. We prove that in a large global population weak asymptotic, in this new context, the part of the system involved in the slow dynamics is not affected too much, and stochastic jumps are kept with the same driving clocks. Contrarywise, the part corresponding to the fast dynamics converges to the solution of a reaction-diffusion equation, which is deterministic. This is not really surprising as in chapter 2. However, the two dynamics are coupled so that the global weak limit is an infinite dimensional continuous piecewise deterministic Markov process.

3.1 Introduction

Within the last decades, the importance of spatial and stochastic modeling has been widely motivated for systems of biochemical reactions. A commonly used model is the reaction-diffusion one, where reactants undergo chemical reactions and can diffuse in the considered spatial domain. It is used either deterministically or stochastically. Deterministic models are solutions of the so-called reaction-diffusion equations, which are partial differential equations (PDEs). These equations are solved analytically, and/or simulated numerically in which case results are obtained relatively fast.

However, these models capture a macroscopic dynamic and are valid only in high concentrations contexts. When some of the interacting species are present in small quantity, a stochastic description is much more accurate. Still, the direct computation of stochastic models is extremely time consuming. Therefore, in order to speed up these latter simulations, it is usual to compute abundant species as continuous variables that follow deterministic motions. Species in low number are directly simulated and one talks about hybrid approximation. Lately, hybrid algorithms have been proposed for the simulation of multiscale spatial models arising from cellular biology or related fields. We refer to [AEZ16] for cell regulatory networks and enzyme cascades, or [NCS15] for molecular communication.

Stochastic hybrid systems (SHS), and especially piecewise deterministic Markov processes (PDMPs), form a class of systems that has got very popular throughout the past decade, as it proposes a quite natural simplification of multiscale systems. PDMPs theory was initiated in

finite dimension by Davis [Dav84, Dav93] and is adapted to spatially homogeneous situations. Recently, Buckwar and Riedler [BR11, Rie11] have extended PDMPs to the infinite dimensional case, in order to model the propagation of action potentials in neurons (see also [RTW12, Gén13]). Mathematical settings about stochastic hybrid systems rigorously ensure existence, well-definiteness and, more importantly Markov property, for the hybrid systems considered in hybrid simulations.

Such rigorous mathematical considerations are missing, concerning the fact that these well defined hybrid systems approximate indeed, or not always, multiscale stochastic systems. For an analogy, we know that the law of large numbers allows one to approach a one scale stochastic system by a corresponding deterministic version, in the presence of many individuals. Radulescu, Muller and Crudu in [RMC07a], then Crudu, Debussche and Radulescu in [CDR09] have proposed hybrid approximations by finite dimensional PDMPs, for some multiscale stochastic homogeneous gene networks. Afterward, the four authors rigorously proved these approximations in [CDMR12].

The question is more complicated in the spatially inhomogeneous case, where there are much more possibilities of modeling. In chapter 2, assumptions of spatial correlations for reactions involving low numbered species were introduced, and a deterministic approximation was obtained for a multiscale spatial biochemical reaction system. The limit was a reaction-diffusion PDE for the continuous component modeling abundant species, coupled to an ordinary differential equation (ODE) driving the discrete component modeling species in low numbers.

In this chapter, we give a new set of conditions, under which a hybrid approximation holds for a model such as the previous. Unlike in chapter 2, an essential element here is that the system has two spatial scales. While the abundant species evolves at a microscopic spatial level, the discrete species is of larger size and evolves at a macroscopic spatial level. With similar, but more suitable, spatial correlations compared to chapter 2, the obtained limit here is a continuous infinite dimensional PDMP. Its continuous component satisfies, between the jumps of its discrete component, a reaction-diffusion equation parametrized by the value of the discrete component between the considered jumps.

The rest of this chapter is organized as follows. In section 2, we briefly recall the definition of an infinite dimensional PDMP and collect some useful result about them. Then, we develop our model of interest and present heuristics allowing to identify its limit. The main result of convergence is stated and proved in section 3. The tightness of the process is proved first, then the limit is rigorously identified through the martingale problem, and we conclude by a truncation argument. Section 4 is an appendix where intermediate technical computations and proves have been postponed.

3.2 Modeling and asymptotics

3.2.1 Infinite dimensional Piecewise Deterministic Processes

Piecewise deterministic processes (PDPs) form a class of processes that has been formalized in the finite dimensional case in [Dav84, Dav93] among others. We briefly define infinite dimensional (continuous) PDPs and give some useful results about them. We refer to [Rie11] or [BR11] for an in depth presentation.

Consider a Banach space B endowed with a norm $\|\cdot\|_B$, a countable set of isolated states K equipped with the discrete topology, and set $E := B \times K$. Then, let $(\Omega, \mathfrak{F}, (\mathfrak{F}_t)_{t \geq 0}, \mathbb{P})$ denote a filtered probability space satisfying the usual conditions.

In this article, a standard "continuous" PDP with values in E is a non exploding càdlàg

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stochastic process $\{u(t) = (u_C(t), u_D(t)), t \geq 0\}$, determined by its four characteristics:

(1)-(2) Linear and nonlinear operators: for every $\nu \in K$, there is given an abstract evolution equation

$$\frac{d}{dt}u_C(t) = L_\nu u_C(t) + F_\nu(u_C(t)), \quad (3.2.1)$$

where $F_\nu : B \rightarrow B$ is a (possibly nonlinear) operator and $L_\nu : B \rightarrow B$ is an unbounded linear operator, which is m -dissipative with dense domain. Let $\{S_\nu(t) := e^{L_\nu t}, t \geq 0\}$ be the semigroup generated by L . We assume that there exists a unique global mild flow $\phi_\nu(\cdot, \alpha)$ to (3.2.1), satisfying $\phi_\nu(\cdot, \alpha) \in C(\mathbb{R}_+, B)$ and

$$\phi_\nu(t, \alpha) = S_\nu(t)\alpha + \int_0^t S_\nu(t-s)F_\nu(\phi_\nu(s, \alpha))ds,$$

for periodic boundary conditions, every initial value $\alpha \in B$, and all $\nu \in K$. We often use the notation $L_\nu(\alpha) = L(\alpha, \nu)$, $F_\nu(\alpha) = F(\alpha, \nu)$ and $\phi_\nu(\cdot, \alpha) = \phi(\cdot, \alpha, \nu)$.

(3) A jump rate: $\Lambda : E \rightarrow \mathbb{R}_+$, which is measurable, and such that for all $(\alpha, \nu) \in E$, the function $t \mapsto \Lambda(\phi_\nu(t, \alpha), \nu)$ is integrable over every finite time interval, but divergent over \mathbb{R}_+ . In other words, $\forall(\alpha, \nu) \in E, \forall T > 0$,

$$\int_0^T \Lambda(\phi_\nu(t, \alpha), \nu)dt < \infty \quad \text{while} \quad \int_0^\infty \Lambda(\phi_\nu(t, \alpha), \nu)dt = \infty.$$

Also, we often use the notation $\Lambda_\nu(\phi_\nu(t, \alpha)) = \Lambda(\phi_\nu(t, \alpha), \nu)$.

(4) A transition measure: $Q : E \rightarrow \mathcal{P}(K)$ which is measurable, such that for every fixed $A \subset K$, the function $(\alpha, \nu) \mapsto Q_\nu(A; \alpha)$ is measurable, and satisfies $Q_\nu(\{\nu\}; \alpha) = 0$ for all $(\alpha, \nu) \in E$. Again, we often denote $Q_\nu(A; \alpha) = Q(A; \alpha, \nu)$.

The second component u_D of the PDP takes (discrete) values in K , and is called the discrete component. It has right continuous piecewise constant sample paths and is often denoted the piecewise constant or jump component. The first component u_C takes (continuous) values in B , and is called the continuous component. It has continuous sample paths and justifies the name "continuous" PDP. The mechanism which governs the evolution of the process is as follows. While u_D is constant, u_C evolves according to the flow determined by the operators L and F through (3.2.1) with $u_D = \nu$. Then, a jump occurs at a random time with the jump rate Λ , and the target state after that jump is determined by the transition measure Q .

Construction. A càdlàg sample path $\{v(t), t \geq 0\}$ starting at

$$v(0) = (v_C(0), v_D(0)) = (\alpha, \nu) = v_0 \in E$$

can be constructed for such a process as follows.

- For all $t \in [0, T_1)$,

$$v(t) = (\phi_\nu(t, \alpha), \nu),$$

where T_1 is the first jump time of v_D . Denote by τ_1 the waiting time of the first transition. Then $\tau_1 = T_1$, and, conditionally to the starting point, τ_1 has an exponential distribution. Its survivor function $H_\nu : \mathbb{R}_+ \times B \rightarrow \mathbb{R}_+$, is defined by

$$H_\nu(t, \alpha) := \mathbb{P}_{v_0}\{\tau_1 > t\} = \exp\left(-\int_0^t \Lambda(\phi_\nu(s, \alpha), \nu)ds\right). \quad (3.2.2)$$

It is often convenient to use the notation $H(t, \alpha, \nu) = H_\nu(t, \alpha)$.

- At time T_1^- ,

$$v(T_1^-) = (\phi_\nu(T_1, \alpha), \nu).$$

- A transition occurs at time T_1 . The target state $v(T_1) = (v_C(T_1), v_D(T_1))$ satisfies

$$v_C(T_1) = \phi_\nu(T_1, \alpha) = v_C(T_1^-) = \alpha_1,$$

and $v_D(T_1)$ has the distribution

$$\mathbb{P}_{v_0}\{v_D(T_1) \in A | T_1 = t\} = Q_\nu(A; \phi_\nu(t, \alpha)),$$

for every measurable subset $A \subset K$, and $t > 0$.

• After that first transition, the jump component v_D remains constant and equal to the chosen target state $v_D(T_1) = \nu_1$, until its next jump. The continuous component v_C then evolves according to the "updated" abstract evolution equation, starting from $v_C(T_1) = \alpha_1$ with $v_D = \nu_1$. The procedure is repeated independently starting from (α_1, ν_1) , and the process is recursively constructed. One obtains a sequence τ_1, τ_2, \dots of independent transition waiting times and a sequence of jump times T_1, T_2, \dots , with $T_i = \tau_1 + \dots + \tau_i$ for all $i \geq 1$.

The constructed process is a "continuous" PDP. The number of jumps that occur between times 0 and t is

$$N_t = \sum_{i \geq 1} \mathbf{1}_{(T_i \leq t)}.$$

The non explosion of the process is usually referred to, as the regularity of the PDP. It means an almost sure finite number of jumps until finite times, and is characterized by $T_i \rightarrow \infty$ as $i \rightarrow \infty$. However, that condition is not easy to check in practice. Still, it is satisfied in particular when the expected number of jumps is finite on any finite time interval (see [Dav93], p.60). Therefore, in order to make sure our PDP is regular, we assume, as part of the standard conditions, that

Assumption 3.2.1. $\mathbb{E}_{(\alpha, \nu)}[N_t] < \infty, \quad \forall (\alpha, \nu) \in E, t \geq 0.$

Next, a PDP characterized by a quadruple (L, F, Λ, Q) can be constructed as above in some probability space, to be a strong Markov *càdlàg* process ([BR11], Theorem 4). It is then called a PDMP, meaning piecewise deterministic Markov process. Only standard PDMPs are considered in the sequel.

The full generator and the martingale problem. Consider a PDMP $v = (v_C, v_D)$ with the characteristics (L, F, Λ, Q) and let $(P_t) \equiv (P_t)_{t \geq 0}$ be the corresponding semigroup on $E = B \times K$. For all $t \geq 0$, $P_t : \mathfrak{B}_b(E) \rightarrow \mathfrak{B}_b(E)$, and

$$P_t \varphi(\alpha, \nu) = \mathbb{E}_{(\alpha, \nu)}[\varphi(u(t))]$$

for all $\varphi \in \mathfrak{B}_b(E)$, $(\alpha, \nu) \in E$. We have denoted by $\mathbb{E}_{(\alpha, \nu)}$ the conditional expectation given $u(0) = (\alpha, \nu)$. Clearly, (P_t) is a semigroup of contraction and is measurable in the sense that the map $t \mapsto P_t \varphi$ is measurable for all $\varphi \in \mathfrak{B}_b(E)$. Associated with (P_t) is its full generator

$$\hat{A} = \left\{ (\varphi, \psi) \in \mathfrak{B}_b(E) \times \mathfrak{B}_b(E) : P_t \varphi - \varphi = \int_0^t P_s \psi ds \right\}.$$

This operator is in general multi-valued, i.e. given any φ , there needs not be a unique ψ such that $(\varphi, \psi) \in \hat{A}$. Hence, for a given semigroup, the associated full generator can not be viewed as an operator on $\mathfrak{B}_b(E)$ in general. Find more details in [EK86], Part 1, Section 5. However, we show below that PDMP semigroups are part of exceptions.

3.2 Modeling and asymptotics

Now, denote by P_{v_0} the law of the PDMP v when it starts from $v_0 \in E$. It is well known that P_{v_0} is a solution of the martingale problem associated with $\hat{\mathcal{A}}$ in the sense:

$$\varphi(w(t)) - \varphi(v_0) - \int_0^t \psi(w(s)) ds$$

defines a P_{v_0} -martingale, for all $(\varphi, \psi) \in \hat{\mathcal{A}}$. We have denoted by $\{w(t), t \geq 0\}$ the canonical process on the probability space $(D(\mathbb{R}_+, E), \mathcal{D}_E, P_{v_0})$. An equivalent formulation is:

$$N_\varphi(t) := \varphi(v(t)) - \varphi(v_0) - \int_0^t \psi(v(s)) ds \quad (3.2.3)$$

defines a \mathbb{P}_{v_0} -martingale, for all $(\varphi, \psi) \in \hat{\mathcal{A}}$. One is easily convinced that the full generator $\hat{\mathcal{A}}$ is exactly the subset of all the couples $(\varphi, \psi) \in \mathfrak{B}_b(E) \times \mathfrak{B}_b(E)$ for which the martingale problem above is satisfied.

The extended generator. We notice that the martingale problem is an essential tool for characterizing the law of a PDMP. However, it is directly related to the full generator of the process, which in turn is very often not easy to determine explicitly. With that idea in mind, the extended generator associated with the PDMP is considered, which is the operator $\bar{\mathcal{A}}$, whose domain is

$$\mathcal{D}(\bar{\mathcal{A}}) := \left\{ \varphi \in \mathfrak{B}(E), \exists \psi \in \mathfrak{B}(E) : N_\varphi(t) \text{ defines a } \mathbb{P}_{v_0} - \text{local martingale} \right\},$$

where again

$$N_\varphi(t) := \varphi(v(t)) - \varphi(v_0) - \int_0^t \psi(v(s)) ds. \quad (3.2.4)$$

Clearly, it is an extension of the full generator. This justifies the name "extended" generator.

It should be emphasized, see [Dav93] pp 32-33, that the extended generator is a single-valued operator on $\mathfrak{B}(E)$, up to sets of *zero potential*, these are sets $A \subset \mathfrak{B}(E)$ such that

$$\int_0^\infty \mathbb{1}_A(v(s)) ds = 0 \quad \mathbb{P}_{v_0} - a.s. \quad \text{for every } v_0 \in E.$$

The process "spends no time" in A , regardless of the starting point. Thus, we can set: $\bar{\mathcal{A}}\varphi = \psi$.

Therefore, the full generator is in particular also single-valued up to sets of *zero potential*. Thus, it may be considered as an operator $\hat{\mathcal{A}}$ on $\mathfrak{B}(E)$, with the domain

$$\mathcal{D}(\hat{\mathcal{A}}) = \left\{ \varphi \in \mathfrak{B}(E) : P_t \varphi - \varphi = \int_0^t P_s \hat{\mathcal{A}} \varphi ds \right\}.$$

Furthermore, if the test function φ is such that $N_\varphi(t)$ given by (3.2.4) is bounded, then $N_\varphi(t)$ defines a martingale and hence, the restriction of $\bar{\mathcal{A}}$ to such test functions coincides with $\hat{\mathcal{A}}$.

The domain of the extended generator is characterized in [Dav93], Theorem 26.14, for finite dimensional PDMPs. The infinite dimensional case is considered in [BR11], Theorem 4. Following their arguments, we know that, for well chosen test functions φ , the generator may be identified with the operator

$$\begin{aligned} \mathcal{A}\varphi(\alpha, \nu) = & \langle D^{1,0}\varphi(\alpha, \nu), L(\alpha, \nu) + F(\alpha, \nu) \rangle \\ & + \Lambda(\alpha, \nu) \int_K [\varphi(\alpha, \xi) - \varphi(\alpha, \nu)] Q(d\xi, \alpha, \nu), \end{aligned} \quad (3.2.5)$$

where $\langle \cdot, \cdot \rangle$ is the duality pairing between B and its topological dual B' , and $D^{1,0}\varphi(\alpha, \nu)$ the Fréchet differential of φ w.r.t. its first variable.

In the case when there is an underlying Hilbert space H such that $B \subset H$, one identifies $D^{1,0}\varphi(\alpha, \nu)$ with the corresponding gradient, and the duality pairing with the inner product $\langle \cdot, \cdot \rangle$ of H . The main difference with the finite dimensional case is that the expression above contains an unbounded operator and in general $L(\alpha, \nu)$ is not in B . We need to restrict the test functions so that the duality pairing $\langle D^{1,0}\varphi(\alpha, \nu), L(\alpha, \nu) \rangle$ is meaningful. Another possibility is to restrict the values of α to a smaller set than B .

Below, we identify a subset \mathcal{E} of the domain of \mathcal{A} such that for $\varphi \in \mathcal{E}$ equation (3.2.5) holds.

3.2.2 Multiscale stochastic spatial regulatory networks with a slow dynamic independent of the space discretization

Molecules of two species C and D are submitted to reactions and diffusions in the unit interval, the spatial domain I . Following [AT80], we divide I into N smaller intervals, called *sites*, of equal length N^{-1} : $I_j = ((j-1)N^{-1}, jN^{-1}]$, for $j = 1, \dots, N$. Molecules are produced (birth) or removed (death) on sites at rates which depend on the local current number of particles. Moreover, molecules of C can diffuse between sites by simple random walks (one at once), with jump rates proportional to N^2 and linearly depending on the current local state. In this framework, an event can be either an onsite chemical reaction or a diffusion. We often say "reaction" for "event", and use the super/subscript C (resp. D) in reference to C (resp. D).

The species C has a large population size scale while that of D is small. Molecules of D do not diffuse. As in [CDMR12], we divide the set \mathfrak{R} of possible onsite reactions in three disjoint subsets:

$$\mathfrak{R} = \mathfrak{R}_C \cup \mathfrak{R}_{DC} \cup \mathfrak{R}_D.$$

Reactions in \mathfrak{R}_C (resp. \mathfrak{R}_D) involve only reactants and products of type C (resp. D), whereas, reactions in \mathfrak{R}_{DC} involve both types of reactants and/or products. Also,

- $X_j^{N,C}$ (resp. $X_j^{N,D}$) is the number of molecules of C (resp. D) on the site j ;
- $X_C^N := \left(X_j^{N,C} \right)_{1 \leq j \leq N}$, $X_D^N := \left(X_j^{N,D} \right)_{1 \leq j \leq N}$ and $X^N := (X_C^N, X_D^N) \in \mathbb{N}^{2N}$.

We consider periodic boundary conditions, extended to $X_{j+N}^N = X_j^N, \forall j$. Hence, the molecular composition of the system $X^N := \{X^N(t), t \geq 0\}$ is a \mathbb{N}^{2N} -valued Markov process with the transitions:

$$\left\{ \begin{array}{l} (X_C^N, X_D^N) \longrightarrow (X_C^N + \gamma_{j,r}^C e_j, X_D^N) \text{ at rate } \lambda_r \left(X_j^{N,C} \right), \text{ for } r \in \mathfrak{R}_C, \\ (X_C^N, X_D^N) \longrightarrow (X_C^N + \gamma_{j,r}^C e_j, X_D^N + \gamma_{j,r}^D e_j) \text{ at rate } \lambda_r \left(X_j^{N,C}, X_j^{N,D} \right), \text{ for } r \in \mathfrak{R}_{DC}, \\ (X_C^N, X_D^N) \longrightarrow (X_C^N, X_D^N + \gamma_{j,r}^D e_j) \text{ at rate } \lambda_r \left(X_j^{N,D} \right), \text{ for } r \in \mathfrak{R}_D, \\ (X_C^N, X_D^N) \longrightarrow (X_C^N + e_{j-1} - e_j, X_D^N) \text{ at rate } N^2 X_j^{N,C}, \text{ for a diffusion } j \rightarrow j+1, \\ (X_C^N, X_D^N) \longrightarrow (X_C^N + e_{j+1} - e_j, X_D^N) \text{ at rate } N^2 X_j^{N,C}, \text{ for a diffusion } j \rightarrow j-1, \end{array} \right.$$

where $\{e_j, j = 1, \dots, N\}$ is the canonical basis of \mathbb{R}^N , and $\gamma_{j,r}^C, \gamma_{j,r}^D \in \mathbb{Z}, \forall r \in \mathfrak{R}, \forall 1 \leq j \leq N$.

Scaling and Density dependence. We reset scales so that on every site, the initial average number of molecules for C is of order μ with μ large. Namely, if $\mathfrak{M} = \mathfrak{M}_C + \mathfrak{M}_D$ is the total initial number of molecules, then $\mathfrak{M}_C \approx N \times \mu$. The size of \mathfrak{M}_D is precised below.

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Then, we make the

Assumption 3.2.2.

(i) *Density dependence holds for the rates of reactions in \mathfrak{R}_C . That is, for all $r \in \mathfrak{R}_C$, there exists $\tilde{\lambda}_r$ satisfying*

$$\lambda_r \left(X_j^{N,C} \right) = \mu \tilde{\lambda}_r \left(\frac{X_j^{N,C}}{\mu} \right) \quad \text{for all } j = 1, \dots, N.$$

(ii) *Reactions $r \in \mathfrak{R}$ are spatially homogeneous: $\gamma_{j,r}^C = \gamma_r^C$, $\gamma_{j,r}^D = \gamma_r^D$.*

(iii) *The molecules of C diffuse, while those of D do not.*

It follows that reactions in \mathfrak{R}_C are fast ("pure fast reactions"), while reactions in \mathfrak{R}_D are slow ("pure slow reactions"). Below, we will distinguish two types of mixed reactions in \mathfrak{R}_{DC} , some will be fast.

For notational convenience, we omit the tilde for reaction rates obtained by density dependence, as described in Assumption 3.2.2 (i). Moreover, we consider the parameter μ as a function of N which grows to the infinity with N , and omit the superscript μ when it should appear with N .

The assumption of spatial homogeneity is not essential and allows to simplify notation.

Now, we rescale X^N by setting

$$U_j^{N,C} := U_j^{N,\mu,C} := \frac{X_j^{N,C}}{\mu}, \quad U_j^{N,D} := U_j^{N,\mu,D} := X_j^{N,D},$$

then,

$$U_C^N := \left(U_j^{N,C} \right)_{1 \leq j \leq N}, \quad U_D^N := \left(U_j^{N,D} \right)_{1 \leq j \leq N},$$

and

$$U^{N,\mu} := U^N := (U_C^N, U_D^N) \in \mathbb{R}^N \times \mathbb{N}^N.$$

As U_C^N (resp. U_D^N) has continuous (resp. discrete) values, C (resp. D) is said to be continuous (resp. discrete). The generator of the new scaled process U^N is given by

$$\begin{aligned} \mathcal{A}_0^N \varphi(U) &:= \left. \frac{d}{dt} \mathbb{E}_U [\varphi(U^N(t))] \right|_{t=0} := \lim_{t \rightarrow 0} \frac{1}{t} \mathbb{E}_U [\varphi(U^N(t)) - \varphi(U)] \\ &= \sum_{j=1}^N \left\{ \sum_{r \in \mathfrak{R}_C} \left[\varphi \left(U_C + \frac{\gamma_r^C}{\mu} e_j, U_D \right) - \varphi(U_C, U_D) \right] \mu \lambda_r(U_j^C) \right. \\ &\quad + \sum_{r \in \mathfrak{R}_{DC}} \left[\varphi \left(U_C + \frac{\gamma_r^C}{\mu} e_j, U_D + \gamma_r^D e_j \right) - \varphi(U_C, U_D) \right] \lambda_r(U_j^C, U_j^D) \\ &\quad \left. + \sum_{r \in \mathfrak{R}_D} \left[\varphi(U_C, U_D + \gamma_r^D e_j) - \varphi(U_C, U_D) \right] \lambda_r(U_j^D) \right\} \\ &+ \sum_{j=1}^N \left\{ \left[\varphi \left(U_C + \frac{e_{j-1} - e_j}{\mu}, U_D \right) + \varphi \left(U_C + \frac{e_{j+1} - e_j}{\mu}, U_D \right) - 2\varphi(U_C, U_D) \right] \mu N^2 U_j^C \right\}, \end{aligned}$$

on the domain $\mathfrak{B}_b(\mathbb{R}^{2N})$ (see [Kur71] or [EK86] pp162-164).

In order to achieve a pointwise modeling over the whole spatial domain, we introduce the step function

$$u^N(t, x) = \sum_{j=1}^N U_j^N(t) \mathbf{1}_j(x), \quad t \geq 0, \quad x \in I_j, \quad (3.2.6)$$

where $\mathbb{1}_j(\cdot) := \mathbb{1}_{I_j}(\cdot)$ is the indicator function of the j -th site I_j . Note that for all $t \geq 0$, the function $u^N(t) = u^N(t, \cdot)$ can be identified with the vector $U^N(t)$ of \mathbb{R}^{2N} . It is a 1-periodic function, since $U_{j+N}^N = U_j^N$ for all j . Now, let \mathbb{H}^N denote the subspace of $L^2(I)$ which consists in real-valued step functions defined on I , and constant on every site I_j , $1 \leq j \leq N$. We extend functions in \mathbb{H}^N to be periodic. Moreover, consider the canonical projection

$$\begin{aligned} P_N &: L^2(I) \longrightarrow \mathbb{H}^N \\ u &\longmapsto P_N u = \sum_{j=1}^N u_j \mathbb{1}_j, \quad \text{with } u_j := N \int_{I_j} u(x) dx. \end{aligned} \quad (3.2.7)$$

Then,

$$u_C^N(t, x) = \sum_{j=1}^N u_j^{N,C}(t) \mathbb{1}_j(x) \quad \text{and} \quad u_D^N(t, x) = \sum_{j=1}^N u_j^{N,D}(t) \mathbb{1}_j(x),$$

where

$$u_j^{N,C}(t) := P_N u_C^N(t) = N \int_{I_j} u_C^N(t, x) dx = U_j^{N,C}(t),$$

and a similar relation holds for D . The process, $u^N := \{u^N(t), t \geq 0\}$ is a $\mathbb{H}^N \times \mathbb{H}^N$ -valued càdlàg Markov process, with the transitions:

$$\left\{ \begin{array}{l} (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\gamma_r^C}{\mu} \mathbb{1}_j, u_D^N \right), \text{ at rate } \mu \lambda_r \left(u_j^{N,C} \right), \text{ for } r \in \mathfrak{R}_C, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\gamma_r^C}{\mu} \mathbb{1}_j, u_D^N + \gamma_r^D \mathbb{1}_j \right), \text{ at rate } \lambda_r \left(u_j^{N,C}, u_j^{N,D} \right), r \in \mathfrak{R}_{DC}, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N, u_D^N + \gamma_r^D \mathbb{1}_j \right), \text{ at rate } \lambda_r \left(u_j^{N,D} \right), \text{ for } r \in \mathfrak{R}_D, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\mathbb{1}_{j-1} - \mathbb{1}_j}{\mu}, u_D^N \right), \text{ at rate } \mu N^2 u_j^{N,C}, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\mathbb{1}_{j+1} - \mathbb{1}_j}{\mu}, u_D^N \right), \text{ at rate } \mu N^2 u_j^{N,C}. \end{array} \right. \quad (3.2.8)$$

Such a Markov process does exist and is unique (see [Kot88b], which is based on [EK86]) until a possible blow-up time. In addition, under natural assumptions on the reaction rates, we have $u^N(t) \geq 0$ for all t , as soon as $u^N(0) \geq 0$.

We now specify the description of the mixed reactions $r \in \mathfrak{R}_{DC}$.

Assumption 3.2.3. *In some $S_1 \subset \mathfrak{R}_{DC}$, reactions are spatially homogeneous, fast and do not affect the discrete species:*

• $\gamma_r^D = 0$ and the rate is $\lambda_r \left(u_j^{N,C}, u_j^{N,D} \right) = \mu \tilde{\lambda}_r \left(u_j^{N,C}, u_j^{N,D} \right)$, for $r \in S_1$ (fast mixed reactions).

Again, below we omit the tildes.

This model leads to mathematical difficulties as explained in chapter 2. Unless $u_j^{N,D}$ is zero for almost all j , the discrete species are in fact also abundant since the total number is of order N , hence they also converge to a continuous model. The limit model is expected to be a PDE for u_C coupled to an ODE for u_D . As explained in chapter 2 the difficulty is that the convergence seems to hold in bad topologies, and this limit is probably difficult to justify for nonlinear reaction rates. Thus, in chapter 2, a spatial correlation in the reaction involving the discrete species has been introduced and the limit model is described by a PDE coupled to a nonlocal differential equation.

3.2 Modeling and asymptotics

In this chapter, we introduce another situation where the discrete species remain discrete at the limit. We introduce an assumption of spatial multiscaling: the spatial domain I is split into a finite number of macrosites J_1, \dots, J_k , where k is a fixed finite number, and u_D is constant in each J_ℓ . This describes a situation where the discrete species are of much larger size than the continuous species.

In order to avoid complicated notation, we assume for simplicity that all J_ℓ has the same length and consider N as multiples of k . Thus each J_ℓ is the union of microsites:

$$J_\ell = \bigcup_{j=N_{\ell-1}+1}^{N_\ell} I_j, \quad \ell = 1, \dots, k,$$

with $N_\ell = \frac{\ell N}{k}$. On each J_ℓ , u_D^N is constant and takes the value $u_\ell^{N,D}$:

$$u_D^N(t, x) = \sum_{\ell=1}^k u_\ell^{N,D}(t) \mathbb{1}^\ell(x),$$

where $\mathbb{1}^\ell = \mathbb{1}_{J_\ell}$ is the indicator function of the ℓ -th macrosite J_ℓ .

It is then natural to consider that when there is a slow reaction between discrete and continuous species, *i.e.* in $\mathfrak{R}_{DC} \setminus \mathcal{S}_1$, on J_ℓ , it may affect u_C on all J_ℓ :

$$(u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\gamma_r^C}{\mu} \sum_{j=N_{\ell-1}+1}^{N_\ell} b_{j,N}^r \mathbb{1}_j, u_D^N + \gamma_r^D \mathbb{1}^\ell \right),$$

for some non negative $b_{j,N}^r$. Below we use the notation:

$$\gamma_{r,\ell}^{C,N} = \gamma_r^C \sum_{j=N_{\ell-1}+1}^{N_\ell} b_{j,N}^r \mathbb{1}_j.$$

We choose $b_{j,N}^r = N \int_{I_j} b^r(x) dx$ for some positive function $b^r \in C([0, 1])$.

We also assume that the rate of such reaction depends on $u_\ell^{N,D}$, and on u_C^N (considered all over J_ℓ) through a local average. In other words, the rate of such reaction is of the form $\lambda_r \left(\sum_{j=N_{\ell-1}+1}^{N_\ell} a_{j,N}^r u_j^{N,C}, u_\ell^{N,D} \right)$ where $a_{j,N}^r$ are non negative numbers summing to 1: $\sum_{j=N_{\ell-1}+1}^{N_\ell} a_{j,N}^r = 1$. We choose $a_{j,N}^r = \int_{I_j} a^r(x) dx$ for some positive function $a^r \in C([0, 1])$ such that $\int_0^1 a^r(x) dx = 1$.

In this framework , (3.2.8) becomes

$$\left\{ \begin{array}{l} (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\gamma_r^C}{\mu} \mathbb{1}_j, u_D^N \right), \text{ at rate } \mu \lambda_r \left(u_j^{N,C} \right), \text{ for } r \in \mathfrak{R}_C, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\gamma_r^C}{\mu} \mathbb{1}_j, u_D^N \right), \text{ at rate } \mu \lambda_r \left(u_j^{N,C}, u_{\ell_j}^{N,D} \right), \text{ for } r \in S_1, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\gamma_{r,\ell}^{C,N}}{\mu}, u_D^N + \gamma_r^D \mathbb{1}^\ell \right), \text{ at rate } \lambda_r \left(\sum_{j=N_{\ell-1}+1}^{N_\ell} a_{j,N}^r u_j^{N,C}, u_\ell^{N,D} \right), \\ \hspace{15em} \text{for } r \in \mathfrak{R}_{DC} \setminus S_1, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N, u_D^N + \gamma_r^D \mathbb{1}^\ell \right), \text{ at rate } \lambda_r \left(u_\ell^{N,D} \right), \text{ for } r \in \mathfrak{R}_D, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\mathbb{1}_{j-1} - \mathbb{1}_j}{\mu}, u_D^N \right), \text{ at rate } \mu N^2 u_j^{N,C}, \\ (u_C^N, u_D^N) \longrightarrow \left(u_C^N + \frac{\mathbb{1}_{j+1} - \mathbb{1}_j}{\mu}, u_D^N \right), \text{ at rate } \mu N^2 u_j^{N,C}, \end{array} \right. \quad (3.2.9)$$

where here and below ℓ_j is the upper integer part of $\frac{j^k}{N}$. In other words: $N_{\ell_j-1} + 1 \leq j \leq N_{\ell_j}$.

Note that this system has a problem since it does not ensure positivity of u_C^N . In general, this is ensured by the fact that the rate vanishes when the concentration vanishes. But this is not possible for the type of rate considered for the mixed reactions in $\mathfrak{R}_{DC} \setminus S_1$. A more realistic rate for such reactions would be:

$$\lambda_r \left(\sum_{j=N_{\ell-1}+1}^{N_\ell} a_{j,N}^r u_j^{N,C}, u_\ell^{N,D} \right) \prod_{j=N_{\ell-1}+1}^{N_\ell} \mathbb{1}_{u_j^{N,C} + \frac{\gamma_C^r b_{j,N}^r}{\mu} \geq 0}$$

When $\mu \rightarrow \infty$, this further factor converges to $\prod_{j=N_{\ell-1}+1}^{N_\ell} \mathbb{1}_{u_j^{N,C} \geq 0}$ or $\prod_{j=N_{\ell-1}+1}^{N_\ell} \mathbb{1}_{u_j^{N,C} > 0}$ depending on the sign of γ_C^r . This extra factor has no effect at the limit since u_C is positive for $\mu = \infty$. Indeed, positivity is ensured by the other reactions acting on the continuous component.

Moreover, due to the lack of smoothness of the indicator function, we should replace $\mathbb{1}_{u \geq 0}$ by a smooth function approximating it. This creates further notational complexity but no mathematical problems (see chapter 2) and we do not consider such extra factor.

We follow the spatial distribution of the discrete component at the level of the macrosites J_ℓ . We may identify the space of such functions with \mathbb{R}^k thanks to the formula: $u_D(t, x) = \sum_{\ell=1}^k u_\ell^D(t) \mathbb{1}^\ell(x)$. Thus, with this new framework, the phase space is $\mathbb{H}^N \times \mathbb{N}^k \subset \mathbb{H}^N \times \mathbb{R}^k$ and the infinitesimal generator for u^N has the form

$$\begin{aligned} & \mathcal{A}^N \varphi(u_C, u_D) \\ &= \sum_{j=1}^N \left\{ \sum_{r \in \mathfrak{R}_C} \left[\varphi \left(u_C + \frac{\gamma_r^C}{\mu} \mathbb{1}_j, u_D \right) - \varphi(u_C, u_D) \right] \mu \lambda_r \left(u_j^C \right) \right. \\ & \quad \left. + \sum_{r \in S_1} \left[\varphi \left(u_C + \frac{\gamma_r^C}{\mu} \mathbb{1}_j, u_D \right) - \varphi(u_C, u_D) \right] \mu \lambda_r \left(u_j^C, u_{\ell_j}^D \right) \right\} \\ & + \sum_{j=1}^N \left\{ \left[\varphi \left(u_C + \frac{\mathbb{1}_{j-1} - \mathbb{1}_j}{\mu}, u_D \right) + \varphi \left(u_C + \frac{\mathbb{1}_{j+1} - \mathbb{1}_j}{\mu}, u_D \right) - 2\varphi(u_C, u_D) \right] \mu N^2 u_j^C \right\} \end{aligned}$$

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$$\begin{aligned}
& + \sum_{\ell=1}^k \left\{ \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \left[\varphi \left(u_C + \frac{\gamma_r^{C,N}}{\mu}, u_D + \gamma_r^D \mathbf{1}^\ell \right) - \varphi(u_C, u_D) \right] \lambda_r \left(\sum_{j=N_{\ell-1}+1}^{N_\ell} a_{j,N}^r u_j^C, u_\ell^D \right) \right. \\
& \quad \left. + \sum_{r \in \mathfrak{R}_D} \left[\varphi \left(u_C, u_D + \gamma_r^D \mathbf{1}^\ell \right) - \varphi(u_C, u_D) \right] \lambda_r(u_\ell^D) \right\}
\end{aligned} \tag{3.2.10}$$

on the domain $C_b(\mathbb{H}^N \times \mathbb{R}^k)$. It can be extended to an $\tilde{\mathcal{A}}^N$ on $C_b(L^2(I) \times \mathbb{R}^k)$ by

$$\tilde{\mathcal{A}}^N \varphi(u_C, u_D) = \mathcal{A}^N \varphi(P_N u_C, u_D). \tag{3.2.11}$$

Again, we omit the tildes: $\tilde{\mathcal{A}}^N = \mathcal{A}^N$. Also we write $\tilde{P}_N u := (P_N u_C, \sum_{\ell=1}^k u_\ell^D \mathbf{1}^\ell)$ for $u = (u_C, u_D) \in L^2(I) \times \mathbb{R}^k$.

For $f, g \in \mathbb{H}^N$, the L^2 inner product reads $\langle f, g \rangle_2 = N^{-1} \sum_{j=1}^N f_j g_j$, and the supremum norm is given by $\|f\|_\infty = \max_{1 \leq j \leq N} |f_j|$.

Proposition 3.2.1.

(i) $(\mathbb{H}^N, \langle \cdot, \cdot \rangle_2)$ is a finite dimensional Hilbert space with $\{\sqrt{N} \mathbf{1}_j, 1 \leq j \leq N\}$ as an orthonormal basis.

(ii) $\lim_{N \rightarrow \infty} \|P_N f - f\|_2 \rightarrow 0$ for $f \in L^2$,

(iii) $\lim_{N \rightarrow \infty} \|P_N f - f\|_\infty \rightarrow 0$, for $f \in C(I)$.

Henceforth, $\mathbb{H}^N \times \mathbb{R}^k$ is endowed with the norm

$$\|(f, g)\|_{\infty, \infty} := \|f\|_\infty + \|g\|_\infty, \quad \text{for } f \in \mathbb{H}^N, g \in \mathbb{R}^k.$$

3.2.3 Convergence tools

Formal limit of the generator

We seek for the asymptotic behavior of the process u^N presented above, as $N, \mu \rightarrow \infty$.

Some preliminaries: a discrete Laplace. For $f \in D(I)$ and for $x \in [0, 1]$, we set

$$\nabla_N^+ f(x) := N \left[f \left(x + \frac{1}{N} \right) - f(x) \right] \quad \text{and} \quad \nabla_N^- f(x) := N \left[f(x) - f \left(x - \frac{1}{N} \right) \right].$$

Then, we define the discrete Laplace on $D(I)$ by

$$\begin{aligned}
\Delta_N f(x) & := \nabla_N^+ \nabla_N^- f(x) \\
& = \nabla_N^- \nabla_N^+ f(x) = N^2 \left[f \left(x - \frac{1}{N} \right) - 2f(x) + f \left(x + \frac{1}{N} \right) \right].
\end{aligned}$$

If $f \in \mathbb{H}^N$ in particular, then

$$\Delta_N f(x) = \sum_{j=1}^N [N^2 (f_{j-1} - 2f_j + f_{j+1})] \mathbf{1}_j(x).$$

From the spectral analysis of Δ_N , it is well known that, if N is an odd integer, letting $0 \leq m \leq N - 1$ with m even, letting $\varphi_{0,N} \equiv 1$, $\varphi_{m,N}(x) = \sqrt{2} \cos(\pi m j N^{-1})$ and

$\psi_{m,N}(x) = \sqrt{2} \sin(\pi m j N^{-1})$ for $x \in I_j$, then, $\{\varphi_{m,N}, \psi_{m,N}\}$ are eigenfunctions of Δ_N with eigenvalues given by $-\beta_{m,N} = -2N^2(1 - \cos(\pi m N^{-1})) \leq 0$. If N is even, we need the additional eigenfunction $\varphi_{N,N} = \cos(\pi j)$ for $x \in I_j$. The following (classical) properties are derived from [Blo87], Lemma 2.12 p.12, [Blo92], Lemma 4.2 for the parts (i)-(v), from [Kat66a], Chapter 9, Section 3 for the part (vi), and from [Hen81], Chapter 1, Sections 1.3 and 1.4 for the parts (viii)-(ix). Consider $f, g \in \mathbb{H}^N$ and let $T_N(t) = e^{\Delta_N t}$ denote the semigroup on \mathbb{H}^N generated by Δ_N .

Proposition 3.2.2. *(Some properties of the discrete Laplace)*

(i) The family $\{\varphi_{m,N}, \psi_{m,N}\}$ forms an orthonormal basis of $(\mathbb{H}^N, \langle \cdot, \cdot \rangle_2)$.

(ii) $T_N(t)f = \sum_m e^{-\beta_{m,N}t} (\langle f, \varphi_{m,N} \rangle_2 \varphi_{m,N} + \langle f, \psi_{m,N} \rangle_2 \psi_{m,N})$.

(iii) $\langle \nabla_N^+ f, g \rangle_2 = \langle f, \nabla_N^- g \rangle_2$ and $T_N(t)\Delta_N f = \Delta_N T_N(t)f$.

(iv) Δ_N and $T_N(t)$ are self-adjoint on $(\mathbb{H}^N, \langle \cdot, \cdot \rangle_2)$.

(v) $T_N(t)$ is a positive contraction semigroup on both $(\mathbb{H}^N, \langle \cdot, \cdot \rangle_2)$ and $(\mathbb{H}^N, \|\cdot\|_\infty)$.

(vi) The projection P_N commutes with Δ_N , and $\forall f \in C^2(I)$, $t \geq 0$,

$$\begin{cases} \|\Delta_N f - \Delta f\|_\infty \rightarrow 0 & \text{as } N \rightarrow \infty, \\ \|\Delta_N P_N f - \Delta f\|_\infty \rightarrow 0 & \text{as } N \rightarrow \infty, \\ \|T_N(t)P_N f - T(t)f\|_\infty \rightarrow 0 & \text{as } N \rightarrow \infty. \end{cases}$$

(vii) Let $f_N, f \in C^2(I)$.

$$\text{If } \lim_{N \rightarrow \infty} \|f_N - f\|_{C^2(I)} \rightarrow \infty, \quad \text{then } \lim_{N \rightarrow \infty} \|\Delta_N f_N - \Delta f\|_\infty \rightarrow 0.$$

(viii) For all $\eta \geq 0$, there exist a constant $c_1 = c_1(\eta) > 0$ independent of N , such that

$$\|T_N(t)(-\Delta_N)^\eta\|_{L^\infty(I) \rightarrow L^\infty(I)} \leq c_1 t^{-\eta} \quad \text{for } t > 0.$$

(ix) For all $0 < \eta \leq 1$, there exists $c_2 = c_2(\eta) > 0$ independent of N , such that

$$\|(T_N(t) - I_d)(-\Delta_N)^{-\eta}\|_{L^\infty(I) \rightarrow L^\infty(I)} \leq c_2 t^\eta \quad \text{for } t \geq 0.$$

We wish to identify the limit as $N, \mu \rightarrow \infty$, of our sequence u^N of Markov processes with generators \mathcal{A} given by (3.2.10), we compute a formal limit of the sequence of the extended generators defined by (3.2.10), for test functions $\varphi \in C_b^{2,0}(L^2(I) \times \mathbb{R}^k)$. As already mentioned the rigorous proof below is done for a stronger topology than $L^2(I)$, but this latter space being Hilbert the formal argument is clearer.

We first proceed to a Taylor expansion at order 2 of φ for the part of the generator corresponding to the fast dynamic, that is the first three terms in the right hand side of (3.2.10). We identify the differential with the corresponding gradient, the debit functions appear naturally. With the notation $u = (u_C, u_D)$, we have:

For the first order terms.

$$\begin{aligned} T_{fast}^{(1)}(N) = & \left\langle D^{1,0} \varphi(\tilde{P}_N u), \sum_{j=1}^N \left(\sum_{r \in \mathfrak{R}_C} \gamma_r^C \lambda_r(u_j^C) + \sum_{r \in S_1} \gamma_r^C \lambda_r(u_j^C, u_{\ell_j}^D) \right) \mathbb{1}_j \right\rangle_2, \\ & + \left\langle D^{1,0} \varphi(\tilde{P}_N u), \sum_{j=1}^N N^2 (\mathbb{1}_{j-1} - 2\mathbb{1}_j + \mathbb{1}_{j+1}) u_j^C \right\rangle_2 \end{aligned}$$

3.2 Modeling and asymptotics

$$= \left\langle D^{1,0}\varphi(\tilde{P}_N u), F(\tilde{P}_N u) + \Delta_N P_N u_C \right\rangle_2.$$

Here Δ_N is the discrete Laplace introduced above and corresponds to the debit function corresponding to the diffusions. Its expression is obtained using a change of index and periodicity. The function F is the debit related to fast onsite reactions. It also maps $D(I) \times \mathbb{R}^k$ on $D(I)$, and is given by

$$F(u_C, u_D) = \sum_{r \in \mathfrak{R}_C} \gamma_r^C \lambda_r(u_C) + \sum_{r \in \mathfrak{S}_1} \gamma_r^C \lambda_r(u_C, u_D). \quad (3.2.12)$$

These allow to define the debit of the whole fast dynamic $(u_C, u_D) \mapsto \Delta_N P_N u_C + F(\tilde{P}_N u)$ on $D(I) \times \mathbb{R}^k$. If F is continuous, then for $u_C \in C^2(I)$,

$$T_{fast}^{(1)}(N) \longrightarrow \left\langle D^{1,0}\varphi(u_C, u_D), \Delta u_C + F(u_C, u_D) \right\rangle_2 =: \mathcal{A}_{fast}^\infty \quad (3.2.13)$$

as $N \rightarrow \infty$, thanks to *Proposition 3.2.2* (vi) and *Proposition 3.2.1* (iii).

For the terms of order 2. We give heuristics indicating that they converge to zero in the $L^2(I)$ topology. For these heuristics, we assume that the concentration of the species C is bounded (uniformly in N) on every site. Say $0 \leq u_C(x) \leq \rho$ for all $x \in I$ for some $\rho > 0$. Then in particular, the rates of fast onsite reactions are bounded too, if these latter are continuous. Let us introduce $e_j := \sqrt{N} \mathbf{1}_j$, for $1 \leq j \leq N$. Since the functions $(\mathbf{1}_j)_{1 \leq j \leq N}$ are pairwise orthogonal in $L^2(I)$ and of norm $\|\mathbf{1}_j\|_2 = N^{-1/2}$, the family $\{e_j, 1 \leq j \leq N\}$ forms an orthonormal basis of $(\mathbb{H}^N, \|\cdot\|_2)$. Also, c denotes a generic constant and $\|D^{2,0}\varphi\|_\infty$ denotes a uniform bound on the norm of $D^{2,0}\varphi(u)$ as a bilinear operator on $L^2(I)$ for $u \in L^2(I) \times \mathbb{R}^k$.

For fast onsite reactions, we have the following term for the second order term in the Taylor expansion

$$\begin{aligned} T_{fastOn}^{(2)}(N) &= \frac{1}{2} \sum_{j=1}^N \left(\sum_{r \in \mathfrak{R}_C} D^{2,0}\varphi(\tilde{P}_N u) \cdot \left\langle \frac{\gamma_r^C}{\mu} \mathbf{1}_j, \frac{\gamma_r^C}{\mu} \mathbf{1}_j \right\rangle_2 \mu \lambda_r(u_j^C) \right. \\ &\quad \left. + \sum_{r \in \mathfrak{S}_1} D^{2,0}\varphi(\tilde{P}_N u) \cdot \left\langle \frac{\gamma_r^C}{\mu} \mathbf{1}_j, \frac{\gamma_r^C}{\mu} \mathbf{1}_j \right\rangle_2 \mu \lambda_r(u_j^C, u_{\ell_j}^D) \right) \\ &\leq c \bar{\gamma}_C^2 \bar{\lambda}_C \|D^{2,0}\varphi\|_\infty \frac{1}{N\mu} \sum_{j=1}^N \|e_j\|_2^2 \leq \frac{c}{\mu} \longrightarrow 0. \end{aligned}$$

Here, $\bar{\gamma}_C$ is an upper bound for the amplitudes of fast onsite reactions and $\bar{\lambda}_C$ is an upper bound for the rates of fast onsite reactions.

We now treat the diffusion part. From $\|\mathbf{1}_{j+1} - \mathbf{1}_j\|_2^2 = 2N^{-1} = \|\mathbf{1}_{j-1} - \mathbf{1}_j\|_2^2$,

$$\begin{aligned} T_{fastDiff}^{(2)}(N) &= \frac{1}{2} \sum_{j=1}^N \left[D^{2,0}\varphi(\tilde{P}_N u) \cdot \left\langle \frac{\mathbf{1}_{j-1} - \mathbf{1}_j}{\mu}, \frac{\mathbf{1}_{j-1} - \mathbf{1}_j}{\mu} \right\rangle_2 \right] \mu N^2 u_j^C \\ &\leq c \rho \|D^{2,0}\varphi\|_\infty \frac{N^2}{\mu} \sum_{j=1}^N \|\mathbf{1}_{j-1} - \mathbf{1}_j\|_2^2 \\ &\leq c \mu^{-1} N^2 \longrightarrow 0, \end{aligned}$$

if $\mu^{-1} N^2 \rightarrow 0$ as $N, \mu \rightarrow \infty$. The other term related to diffusions converges to zero, using the same argument.

Below, we will see that the condition $\mu^{-1}N^2 \rightarrow \infty$ can be weakened, even in the supremum norm framework.

Let us then treat the slow dynamic part. With our choice of $b_{j,N}^r, \gamma_{r,\ell}^{C,N}$ are clearly bounded and $\frac{\gamma_{r,\ell}^{C,N}}{\mu} \rightarrow 0$. Also, since a^r is continuous, it is not difficult to see that if u_C^N and $u_\ell^{N,D}$ converge to u_C and $u_{D,\ell}$ respectively, then $\lambda_r \left(\sum_{j=N_{\ell-1}+1}^{N_\ell} a_{j,N}^r u_j^{N,C}, u_\ell^{N,D} \right)$ converges to $\lambda_r \left(\int_{J_\ell} a^r(x) u_C(x) dx, u_{D,\ell} \right)$. Since here, we work at a formal level, we do not need to precise in which sense the convergences hold.

We deduce that the limit generator is given by

$$\begin{aligned} \mathcal{A}^\infty \varphi(u_C, u_D) &= \langle D_{u_C} \varphi(u_C, u_D), \Delta u_C + F(u_C, u_D) \rangle_2 \\ &+ \sum_{\ell=1}^k \left\{ \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \left[\varphi(u_C, u_D + \gamma_r^D \mathbf{1}^\ell) - \varphi(u_C, u_D) \right] \lambda_r \left(\int_{J_\ell} a^r(x) u_C(x) dx, u_{D,\ell} \right) \right. \\ &\quad \left. + \sum_{r \in \mathfrak{R}_D} \left[\varphi(u_C, u_D + \gamma_r^D \mathbf{1}^\ell) - \varphi(u_C, u_D) \right] \lambda_r(u_{D,\ell}) \right\} \end{aligned} \quad (3.2.14)$$

As seen above, this is the generator of a continuous PDMP.

The problem at the limit

From *Section 3.2.1*, we know that (3.2.14) is the (extended) generator of a continuous PDMP $v := \{v(t) = (v_C(t), v_D(t)), t \geq 0\}$ as given by (3.2.5). The evolution of its discrete component $v_D(t)$ is governed by the slow dynamic part in the limiting generator. It is a jump process, and some of its jump rates depend on both components. The possible values of $v_D(t)$ are of the form

$$v_D = v_D(0) + \sum_{m=1}^M \sum_{r \in (\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D} \sum_{\ell=1}^k \alpha_{\ell,r}^m \gamma_r^D \mathbf{1}^\ell,$$

where the coefficients $\alpha_{\ell,r}^m$ are integers. This describes a countable set denoted by K .

Contrariwise, the continuous component $v_C(t)$ has values in $C(I)$, and has continuous trajectories. More precisely, for any value $\nu \in K$ of $v_D(t)$ —fixed between two consecutive jumps of this latter—, $v_C(t)$ evolves according to

$$\frac{d}{dt} v_C(t) = \Delta v_C(t) + F(v_C(t), \nu), \quad (3.2.15)$$

the reaction-diffusion equation with a parameter ν . It is supplemented with periodic boundary conditions. We use the same symbol for the Laplace operator Δ as an operator in the C -theory framework, w.r.t. the terminology used in [CH98] (Chapter 2, Section 6), where Dirichlet boundary conditions are considered, the case of periodic boundary conditions considered here is similar. In other words, we consider the Laplace is defined on $C(I)$ and its domain is

$$\{u \in C(I) : \Delta u \in C(I)\}.$$

This latter domain is dense, and the Laplace is also m -dissipative. We use the same notation for this unbounded operator and the differential operator.

3.2 Modeling and asymptotics

Henceforth, unless other precisions are made, we define the Laplace on $C(I)$. From Hille-Yosida-Phillips theorem, it is well known that the Laplace generates on $C(I)$ a strongly continuous semigroup of contraction we denote $\{T(t)\} = \{T(t) = e^{\Delta t}, t \geq 0\}$.

Consider the

Assumption 3.2.4.

- (i) For all $y = (y_1, y_2) \in \mathbb{R}^2$, $F(y) \geq 0$ if $y_1 = 0$.
- (ii) There exists $\rho_1 > 0$ such that $F(y) < 0$ for all $y \in \mathbb{R}^2$ satisfying $|y_1| > \rho_1$.

Under Assumption 3.2.4, and given any initial condition $v_C(0) = v_{C,0} \in C(I)$ such that $0 \leq v_{C,0}(x) \leq \rho_2$, for all $x \in I$, for some $\rho_2 > 0$, there exists a unique global mild solution v_C to (3.2.15), satisfying $v_C \in C(\mathbb{R}_+; C(I))$, and $0 \leq v_C(t, x) < \rho = (\rho_1 \vee \rho_2) + 1$: for all $t \geq 0$, $x \in I$.

By mild solution, we mean for all $t \geq 0$:

$$v_C(t) = T(t)v_{C,0} + \int_0^t T(t-s)F(v_C(s), \nu)ds.$$

Recall that F is polynomial. It is classical that for all $\nu \in \mathbb{R}^k$ this equation has a unique solution in $C(\mathbb{R}^+ \times I)$ for any initial data $v_{C,0} \in C(I)$. We use the notation $v_C(t) = \phi_\nu(t)v_{C,0}$ for the associated flow.

Then henceforth, we consider that the "limiting" PDMP $v = (v_C, v_D)$ starts at $v_0 = (v_{C,0}, v_{D,0}) \in C(I) \times \mathbb{R}^k$, has values in

$$E := C(I) \times K \quad \text{endowed with the norm } \|\cdot, \cdot\|_{\infty, \infty},$$

and the following characteristics: the *linear and nonlinear operators* are respectively the Laplace operator Δ and the debit of fast onsite reactions F given by (3.2.12), the *transition rate* Λ , defined by

$$\Lambda(u_C, u_D) := \sum_{\ell=1}^k \left\{ \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \lambda_r \left(\int_{J_\ell} a^r(y) u_C(y) dy, u_{D,\ell} \right) + \sum_{r \in \mathfrak{R}_D} \lambda_r(u_{D,\ell}) \right\}, \quad (3.2.16)$$

and, the *transition measure* Q , defined by

$$\begin{aligned} & \int_K \varphi(u_C, \nu) Q(d\nu; (u_C, u_D)) \\ &= \frac{1}{\Lambda(u_C, u_D)} \sum_{\ell=1}^k \left\{ \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \varphi(u_C, u_D + \gamma_r^D \mathbf{1}^\ell) \lambda_r \left(\int_{J_\ell} a^r(y) u_C(y) dy, u_{D,\ell} \right) \right. \\ & \quad \left. + \sum_{r \in \mathfrak{R}_D} \varphi(u_C, u_D + \gamma_r^D \mathbf{1}^\ell) \lambda_r(u_{D,\ell}) \right\}. \end{aligned} \quad (3.2.17)$$

We assume that Assumption 3.2.1 holds. Then, v_D is a càdlàg process which is almost surely in $D([0, T], \mathbb{R}^k)$. Using Assumption 3.2.4, it is classical that the continuous component v_C which solves equation (3.2.15) with $\nu = v_D(t)$ is uniquely defined and belongs to $C([0, T] \times I)$. Note that if $v_{C,0} \in W^{2,\infty}(I)$ then v_C belongs to $C([0, T]; W^{2,\infty}(I))$. This can be seen from Assumption 3.2.4 using standard properties of the heat kernel. Moreover, there exists a constant depending on ρ and F such that:

$$\|v_C(t)\|_{W^{2,\infty}} \leq c(\rho, F, \|v_{C,0}\|_{W^{2,\infty}}), \quad t \geq 0. \quad (3.2.18)$$

Below, during the main proof, we take the additional assumption that all reaction rates are bounded. Then, arguing as in [Dav93] or [BR11], we prove that the law of (v_C, v_D) solves the martingale problem in the sense that for all $\varphi \in \mathcal{E}$:

$$\varphi(v_C(t), v_D(t)) - \varphi(v_{C,0}, v_{D,0}) - \int_0^t \mathcal{A}^\infty \varphi(v_C(s), v_D(s)) ds$$

is a martingale. The set of test functions \mathcal{E} is the set of functions φ on $E = C(I) \times \mathbb{R}^k$ which are bounded, continuous with respect to the second variable, differentiable with bounded differential with respect to the first variable and such that the differential can be extended continuously to $H^{-1}(I)$. Recall that this is the dual space of $H_0^1(I)$, and there exists c_φ such that

$$|D_{u_C} \varphi(u_C, u_D) \cdot h| = |\langle D_{u_C} \varphi(u_C, u_D), h \rangle_2| \leq c_\varphi \|h\|_{H^{-1}(I)}$$

for all $(u_C, u_D) \in C(I) \times \mathbb{R}^k$, $h \in L^\infty(I)$. We denote by $|\varphi|_\mathcal{E}$ the smallest constant c_φ such that the above inequality holds and

$$\|\varphi\|_\mathcal{E} = \|\varphi\|_{C_b^{1,0}(C(I) \times \mathbb{R}^k)} + |\varphi|_\mathcal{E}.$$

The forthcoming result states that, under the boundedness assumption, the martingale problem for \mathcal{A}^∞ is well-posed.

Theorem 3.2.1. *Assume that the reaction rates are bounded, the (law of the) PDMP v is the unique solution of the martingale problem associated with \mathcal{A}^∞ on \mathcal{E} .*

The proof is postponed to Appendix 3.4.1. It relies on that of Theorem 2.5 of [CDMR12].

3.3 A Piecewise deterministic limit

The following is our main result.

Theorem 3.3.1. (Hybrid simplification)

Let $u^N = (u_C^N, u_D^N)$ define a sequence of Markov processes as above, starting at $u^N(0) = (u_C^N(0), u_D^N(0)) \in \mathbb{H}^N \times K$, with the corresponding sequence of infinitesimal generators \mathcal{A}^N , defined by (3.2.10). Assume the jump rates λ_r , $r \in \mathfrak{R}$ are polynomial, and the rates λ_r , $r \in \mathfrak{R}_C \cup S_1$ are such that F satisfies Assumption 3.2.4.

Now, consider the E -valued PDMP $v = (v_C, v_D)$ started from $v_0 = (v_0^C, v_0^D) \in C^2(I) \times K$, whose characteristics are $(\Delta, F, \lambda^D, Q)$. Assume Assumption 3.2.1 holds so that the PDMP is standard.

In addition, assume that: (i) $N, \mu \rightarrow \infty$ such that $\mu^{-1} \log N \rightarrow 0$.

(ii) $\|u^N(0) - v_0\|_{\infty, \infty} \rightarrow 0$ in probability.

Then for all $T > 0$,

$$u^N \Longrightarrow v \quad \text{in } D([0, T]; D(I) \times K),$$

where \Longrightarrow means convergence in law.

Proof. Relying on the proof of Theorem 3.1 in [CDMR12], we proceed as follows. We first assume that the reaction rates corresponding to onsite reactions are bounded, as well as their derivatives with respect to their first variable. In this case, we prove tightness for the sequence of Markov processes and identify its limit through the associated sequence of martingale problems.

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At the end of the proof, we relax the additional hypothesis of boundedness and conclude by a truncation argument.

In the whole proof, $T > 0$ is fixed and we take all the limits as $N \rightarrow \infty$ if there is no further precision.

3.3.1 Tightness

We want to show that the family of processes $\{u^N = (u_C^N, u_D^N)\}_N$ is tight in the Skorohod's space $D([0, T], D(I) \times \mathbb{R}^k)$. This has to be understood in the sense that the family $\{P_N\}_N$ of their laws —where P_N is the law of u^N for all N — is tight in the space $\mathcal{P}(D([0, T], D(I) \times \mathbb{R}^k))$ of probability measures (see [Bil99], page 8). We treat both components one after another, starting with the continuous one.

Tightness for the continuous component

We first prove that $\{u_C^N\}_N$ is C -tight. That is (see [JS87], Chapter 6, Section 3, Definition 3.25, page 351), the family is tight in $D([0, T], D(I))$, and each converging subsequence converges to a limit whose law has its support in $C([0, T], D(I))$, *i.e.* the limiting law charges only continuous trajectories. In fact we even prove that each limit point has support in $C([0, T], C(I))$.

From Proposition 2.1 of [Kur71], we know that u_C^N is solution to the SDE

$$u_C^N(t) := u_C^N(0) + \int_0^t \Delta_N u_C^N(s) + F(u^N(s)) ds + Z_C^N(t),$$

where Z_C^N is a \mathbb{H}^N -valued martingale on $[0, T]$.

Duhamel's formula yields

$$u_C^N(t) = T_N(t)u_C^N(0) + \int_0^t T_N(t-s)F(u^N(s))ds + Y_C^N(t),$$

where $Y_C^N(t) = \int_0^t T_N(t-s)dZ_C^N(s)$ is a stochastic convolution.

As in [Blo92] and chapter 2, we need to introduce a stopping time to control Y_C^N . Define v^N by

$$v_C^N(t) = T_N(t)u_C^N(0) + \int_0^t T_N(t-s)F(v_C^N(s), u_D^N(s))ds. \quad (3.3.1)$$

It is classical to prove that v_C^N exists on \mathbb{R}^+ and since F is bounded and $(T_N(t))_t$ is a contraction semigroup, we have:

$$\|v_C^N(t)\|_\infty \leq \|u_C^N(0)\|_\infty + TM_F, \quad t \in [0, T], \quad (3.3.2)$$

where M_F is a bound on F .

We also introduce

$$\bar{u}_C^N(t) = T_N(t)u_C^N(0) + \int_0^t T_N(t-s)F(\bar{u}_C^N(s), u_D^N(s))ds + Y_C^N(t)\mathbb{1}_{t \leq \tau_N} \quad (3.3.3)$$

where the stopping time τ_N is defined by

$$\tau_N = \inf\{t \geq 0, \|u_C^N(t) - v_C^N(t)\|_\infty \geq 1\}.$$

Using the same arguments as in [Blo92] and chapter 2, we prove

$$\sup_{t \in [0, T \wedge \tau_N]} \|Y_C^N(t)\|_\infty \longrightarrow 0 \quad \text{in probability,}$$

under the assumptions of Theorem 3.3.1. Using a Gronwall type argument, we deduce:

$$\sup_{t \in [0, T]} \|\bar{u}_C^N(t) - v_C^N(t)\|_\infty \longrightarrow 0 \quad \text{in probability.}$$

Then, we write

$$\mathbb{P} \left(\sup_{t \in [0, T]} \|\bar{u}_C^N(t) - u_C^N(t)\|_\infty > \epsilon \right) \leq \mathbb{P} \left(\sup_{t \in [0, T]} \|\bar{u}_C^N(t) - v_C^N(t)\|_\infty > 1 \right) \rightarrow 0,$$

when $N \rightarrow \infty$ and, by Lemma 3.31, Section 3, Chapter 6 of [JS87], tightness of $\{u_C^N\}_N$ follows from tightness of $\{\bar{u}_C^N\}_N$

Let us write the first term of $\bar{u}_C^N(t)$ as

$$T_N(t)u_C^N(0) = T_N(t) (u_C^N(0) - P_N v_C(0)) + T_N(t)P_N v_C(0),$$

and note that

$$\begin{aligned} \sup_{t \in [0, T]} \|T_N(t) (u_C^N(0) - P_N v_C(0))\|_\infty &\leq \|u_C^N(0) - P_N v_C(0)\|_\infty \\ &\leq \|u_C^N(0) - v_C(0)\|_\infty + \|v_C(0) - P_N v_C(0)\|_\infty \longrightarrow 0, \end{aligned}$$

by assumption (ii) of Theorem 3.3.1, and the contraction property of the semigroup $T_N(t)$. Therefore

$$\sup_{t \in [0, T]} \|B_C^N(t)\|_\infty \longrightarrow 0 \quad \text{in probability,} \quad (3.3.4)$$

where $B_C^N(t) = T_N(t) (u_C^N(0) - P_N v_C(0)) + Y_C^N(t)\mathbf{1}_{t \leq \tau_N}$.

Now, set $A_C^N(t) := a_C^N(t) + b^N(t)$, with

$$a_C^N(t) := T_N(t)P_N v_C(0) \quad \text{and} \quad b^N(t) := \int_0^t T_N(t-s)F(\bar{u}^N(s), u_D^N(s))ds.$$

With these settings and results in hand, equation (3.3.3) reads

$$\bar{u}_C^N(t) = A_C^N(t) + B_C^N(t),$$

and it remains to prove that the family $\{A_C^N\}_N$ is tight. Tightness for $\{\bar{u}_C^N\}_N$, and thus of $\{u_C^N\}_N$ and $\{v_C^N\}_N$, will then follow again from (3.3.4) and Lemma 3.31, Section 3, Chapter 6 of [JS87]. Moreover, the laws of three sequences have the same limit points.

Since $A_C^N \in C([0, T], D(I))$ for all N , we use Arzelà-Ascoli theorem to get relative compactness and derive tightness from Prohorov theorem, since $C([0, T], D(I))$ is separable and complete.

Seeking for equicontinuity (in time). Fix $t_1, t_2 \in [0, T]$. For all $t \in [0, T]$,

$$\left\{ \begin{array}{l} \frac{d}{dt} a_C^N(t) = \Delta_N a_C^N(t) \\ a_C^N(0) = P_N v_C(0), \end{array} \right. \quad \text{and} \quad \left\{ \begin{array}{l} \frac{d}{dt} \Delta_N a_C^N(t) = \Delta_N (\Delta_N a_C^N(t)) \\ \Delta_N a_C^N(0) = \Delta_N P_N v_C(0). \end{array} \right.$$

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The second equation yields

$$\sup_{t \in [0, T_0]} \|\Delta_N a_C^N(t)\|_\infty = \|\Delta_N a_C^N(0)\|_\infty = \|\Delta_N P_N v_C(0)\|_\infty,$$

thanks to the discrete maximum principle. Together with the first equation, we derive

$$\begin{aligned} \|a_C^N(t_2) - a_C^N(t_1)\|_\infty &\leq \int_{t_1}^{t_2} \left\| \frac{d}{dt} a_C^N(t) \right\|_\infty dt \leq |t_2 - t_1| \|\Delta_N P_N v_C(0)\|_\infty \\ &\leq c|t_2 - t_1|, \end{aligned}$$

where the constant $c = c(v_C''(0)) > 0$ is independent of N , and exists thanks to Proposition 3.2.2 (vi). Hence, since $\|\cdot\|_\infty$ defines a stronger distance than the Skohorod distance on $D(I)$, uniform equicontinuity holds for $\{a_C^N\}_N$ in $D(I)$.

Henceforth, we may consider only generic constants, when these do not depend on N . Let I_d be the identity operator on $D(I)$, and let $0 < \eta < 1$ be a real number. We have

$$\begin{aligned} b^N(t_2) - b^N(t_1) &= \int_0^{t_1} (T_N(t_2 - t_1) - I_d) T_N(t_1 - s) F(\bar{u}_C^N(s), u_D^N(s)) ds \\ &\quad + \int_{t_1}^{t_2} T_N(t_2) F(\bar{u}_C^N(s), u_D^N(s)) ds \end{aligned}$$

Under the additional assumption of boundedness for the reaction rates and their derivatives, we know that the function F is bounded by a constant M_F . From Proposition 3.2.2 (iii), (viii) and (ix),

$$\begin{aligned} &\|b^N(t_2) - b^N(t_1)\|_\infty \\ &\leq \int_0^{t_1} \left\| (T_N(t_2 - t_1) - I_d) [(-\Delta_N)^{-\eta}] [(-\Delta_N)^\eta] T_N(t_1 - s) F(\bar{u}_C^N(s), u_D^N(s)) \right\|_\infty ds \\ &\quad + \int_{t_1}^{t_2} \|T_N(t_2) F(\bar{u}_C^N(s), u_D^N(s))\|_\infty ds \\ &\leq c_2 |t_2 - t_1|^\eta M_F \int_0^{t_1} c_1 (t_1 - s)^{-\eta} ds + |t_2 - t_1| M_F, \quad \forall 0 < \eta < 1, \\ &\leq c |t_2 - t_1|^\eta M_F \left(\frac{t_1^\eta}{1 - \eta} + |t_2 - t_1|^{1-\eta} \right), \quad c = c_1 \vee c_2 = \max(c_1, c_2) \\ &\leq c |t_2 - t_1|^\eta, \quad c = (M_F, c_1, c_2, T), \end{aligned}$$

and the family $\{b^N\}_N$ is uniformly equicontinuous.

To conclude about equicontinuity, we have

$$\|A_C^N(t_2) - A_C^N(t_1)\|_\infty \leq c |t_2 - t_1|^\eta, \quad 0 < \eta < 1 \quad (3.3.5)$$

and it follows that $\{A_C^N\}_N$ is uniformly equicontinuous with values in $D(I)$.

Seeking for compactness (in space). Fix $t \in [0, T]$. Recall that $A_C^N(t) \in \mathbb{H}^N$, it is a piecewise constant function of the spatial variable. We approximate it by a continuous function of the spatial variable $\tilde{A}_C^N(t) \in C(I)$, using piecewise linear interpolation.

We first prove compactness for $\{\tilde{A}_C^N(t)\}_N$ in $C(I)$.

To that aim, we use Sobolev injections. In particular, we are interested in the space $W^{1,\infty}(I)$, of functions of $L^\infty(I)$ which are Lipschitz. It is equipped with the norm

$$\|f\|_{W^{1,\infty}(I)} := \|f\|_{L^\infty(I)} + \|\nabla f\|_{L^\infty(I)},$$

for $f \in W^{1,\infty}(I)$. We have denoted by $L^\infty(I)$ the usual space of essentially bounded real functions measurable on I , and ∇f is the (weak) derivative of f . We refer to [Bre11], Chapter 4; and Section 8.2 in Chapter 8, for more details. Moreover, from Theorem 8.8, Chapter 8 in the same book, we know that $W^{1,\infty}(I)$ is compactly injected in $C(I)$, as I is bounded. Therefore, we end by proving boundedness in $W^{1,\infty}(I)$, which is sufficient for getting compactness on $C(I)$.

Observe that

$$\left\| \tilde{A}_C^N(t) \right\|_\infty = \sup_{x \in I} |\tilde{A}_C^N(t, x)| = \sup_{1 \leq j \leq N} |A_j^{N,C}(t)| = \|A_C^N(t)\|_\infty.$$

In addition, $\tilde{A}_C^N(t)$ is piecewise C^1 on I . It is then in $W^{1,\infty}(I)$ and one has $\nabla \tilde{A}_C^N(t) = \nabla_N^+ A_C^N(t)$. Thus,

$$\left\| \tilde{A}_C^N(t) \right\|_{W^{1,\infty}(I)} = \|A_C^N(t)\|_\infty + \|\nabla_N^+ A_C^N(t)\|_\infty.$$

Then, it only remains to find an upper bound which is uniform in N , for each term in the r.h.s. This is the content of the following.

Lemma 3.3.1. *There exists constants $c_3, c_4, c_5, c_6 > 0$ independent of N (but which may depend on T), such that:*

$$\begin{aligned} (i) \quad \sup_{t \in [0, T]} \|a_C^N(t)\|_\infty &\leq c_3, & (ii) \quad \sup_{t \in [0, T]} \|\nabla_N^+ a_C^N(t)\|_\infty &\leq c_4. \\ (iii) \quad \sup_{t \in [0, T]} \|b^N(t)\|_\infty &\leq c_5, & (iv) \quad \sup_{t \in [0, T]} \|\nabla_N^+ b^N(t)\|_\infty &\leq c_6. \end{aligned}$$

The proof is reported to Appendix 3.4.2.

With Lemma 3.3.1 in hands, the family $\{\tilde{A}_C^N(t)\}_N$ is tight in $C(I)$.

Lemma 3.3.2. $\sup_{t \in [0, T]} \|A_C^N(t) - \tilde{A}_C^N(t)\|_\infty \rightarrow 0$, as $N \rightarrow \infty$.

The proof of this result is an immediate consequence of

$$\left\| A_C^N(t) - \tilde{A}_C^N(t) \right\|_\infty \leq \frac{1}{N} \|\nabla_N^+ A_C^N(t)\|_\infty$$

and of Lemma 3.3.1.

Tightness follows for $\{A_C^N\}_N$ in $C([0, T]; D(I))$. Hence, it finally follows that $\{\tilde{u}_C^N\}_N$ is C -tight and as claimed the limit points are in $C([0, T], C(I))$.

Tightness for the discrete component

We prove that $\{u_D^N\}_N$ is tight. Let $(\Omega, \mathcal{F}, \mathbb{P})$ be the abstract probability space where our stochastic processes u^N are defined. Let $\{Y_{j+}, Y_{j-}, Y_{j,r}, Y_{k,r}, 1 \leq j \leq N, 1 \leq k \leq m, r \in \mathfrak{R}\}$ be a family of independent standard Poisson processes. We know that for all N , the Markov process $u^N = \{u^N(t), t \geq 0\}$ is progressive, since it is càdlàg. Moreover, its generator is \mathcal{A}^N . Thus, by Proposition 1.7, Part 4 of [EK86], u^N is solution to the martingale problem associated

3.3 A Piecewise deterministic limit

with \mathcal{A}^N (on the specified domain), in the sense that for all measurable and bounded φ , the process M_φ defined by

$$M_\varphi^N(t) = \varphi(u^N(t)) - \varphi(u^N(0)) - \int_0^t \mathcal{A}^N \varphi(u^N(s)) ds \quad (3.3.6)$$

for all $t \geq 0$, is a \mathbb{P} -martingale with respect to the (usual) natural associated filtration.

In addition, \mathcal{A}^N is bounded on the domain consisting of bounded measurable functions, since reaction rates are bounded. Hence, by Theorem 4.1, Part 6, of [EK86], we know that, there exists a sequence $(\hat{u}^N = (\hat{u}_C^N, \hat{u}_D^N))_N$ of càdlàg stochastic processes in $D([0, T], D(I) \times \mathbb{R}^k)$ such that

$$\begin{aligned} \hat{u}^N(t) = \hat{u}^N(0) &+ \sum_{j=1}^N \left\{ \sum_{r \in \mathfrak{R}_C \cup S_1} \gamma_{j,r}^N Y_{j,r} \left(\int_0^t \hat{\beta}_{j,r}^N(\hat{u}^N(s)) ds \right) \right. \\ &\quad \left. + \gamma_{j+}^N Y_{j+} \left(\int_0^t \hat{\beta}_{j+}^N(\hat{u}^N(s)) ds \right) + \gamma_{j-}^N Y_{j-} \left(\int_0^t \hat{\beta}_{j-}^N(\hat{u}^N(s)) ds \right) \right\} \\ &+ \sum_{\ell=1}^k \sum_{r \in (\mathfrak{R}_{DC} \setminus S_1) \cup \mathfrak{R}_D} \gamma_{\ell,r}^N Y_{\ell,r} \left(\int_0^t \hat{\beta}_{\ell,r}^N(\hat{u}^N(s)) ds \right), \end{aligned}$$

for $t \geq 0$. Moreover, for each N , u^N and \hat{u}^N have the same distribution. In that representation of u^N as multiparameter random time changes,

- $\gamma_{j\pm}^N$ and $\hat{\beta}_{j\pm}^N$ are respectively the jump height of the process u^N , and the corresponding rates, relative to diffusions of reactants from the microsite j onto the microsite $j \pm 1$,
- $\gamma_{j,r}^N$ and $\hat{\beta}_{j,r}^N$ are respectively the jump height of the process u^N , and the corresponding rates, relative to the fast (onsite) reactions on the microsite j ,
- $\gamma_{\ell,r}^N$ and $\hat{\beta}_{\ell,r}^N$ are respectively the jump height of the process u^N , and the corresponding rates, relative to slow reactions having their source on the macrosite ℓ .

Since we are interested only in the distributions of the processes, we only consider the version \hat{u}^N in the following, and use the same notation for both processes. Using the decomposition $u^N = (u_C^N, u_D^N)$, one can represent each component as a multiparameter random time changes. However, since we want to prove tightness for $\{u_D^N\}_N$, we write out only its representation :

$$\begin{aligned} u_D^N(t) = u_D^N(0) &+ \sum_{\ell=1}^k \left\{ \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \gamma_r^D \mathbb{1}^\ell Y_{\ell,r} \left(\int_0^t \lambda_r \left(\sum_{j=N_{\ell-1}+1}^{N_\ell} a_{j,N}^r u_j^{N,C}(s), u_\ell^{N,D}(s) \right) ds \right) \right. \\ &\quad \left. + \sum_{r \in \mathfrak{R}_D} \gamma_r^D \mathbb{1}^\ell Y_{\ell,r} \left(\int_0^t \lambda_r \left(u_\ell^{N,D}(s) \right) ds \right) \right\}. \end{aligned}$$

Let us show that for each ℓ, r , the laws of $Z_{\ell,r}^N(t) = Y_{\ell,r}(\int_0^t \tilde{\lambda}_r^N(s) ds)$ for $N \in \mathbb{N}$ are tight in $D([0, T], \mathbb{R})$ where $\tilde{\lambda}_r^N(s)$ is either $\lambda_r \left(\sum_{j=N_{\ell-1}+1}^{N_\ell} a_{j,N}^r u_j^{N,C}(s), u_\ell^{N,D}(s) \right)$ or $\lambda_r \left(u_\ell^{N,D}(s) \right)$.

From Theorem 1.3, Section 1, Chapter 1 of [Bil99], we know that the law $Y_{\ell,r}$ is tight in $D([0, T]; \mathbb{R})$ for all $T \geq 0$. Hence, for every $\varepsilon > 0$, there exists a compact set K_ε^T in $D([0, T]; \mathbb{R})$ such that

$$\mathbb{P}(Y_{\ell,r} \in K_\varepsilon^T) \geq 1 - \varepsilon.$$

From Theorem 6.3, Remark 6.4, part 3 in [EK86], we may assume that

$$K_\varepsilon^T = \{f \in D([0, T]; \mathbb{R}) : |f(t)| \leq M_\varepsilon^T, w'(f, \delta, T) \leq \alpha_\varepsilon^T(\delta) \text{ for all } \delta > 0\},$$

with $\lim_{\delta \rightarrow 0} \alpha_\varepsilon^T(\delta) = 0$. The modulus of continuity w' is defined in section 6, part 3 of [EK86]. Since $w'(Z_{\ell, r}^N, \delta, T) \leq w'(Y_{\ell, r}, \bar{\lambda}\delta, \bar{\lambda}T)$, where $\bar{\lambda}$ is an upper bound of all reaction rates, we deduce that

$$\mathbb{P}(Z_{\ell, r}^N \in \tilde{K}_\varepsilon^T) \geq 1 - \epsilon$$

with

$$\tilde{K}_\varepsilon^T = \{f \in D([0, T]; \mathbb{R}) : |f(t)| \leq M_\varepsilon^T, w'(f, \delta, T) \leq \alpha_\varepsilon^T(\bar{\lambda}\delta) \text{ for all } \delta > 0\}$$

which is a compact set in $D([0, T]; \mathbb{R})$.

Since $u_D^N(0)$ converges in probability, we deduce that the laws of u_D^N for $N \in \mathbb{N}$ are tight in $D([0, T], \mathbb{R}^k)$.

Conclusion about tightness

From Corollary 3.33, Section 3, Chapter 6 of [JS87], we derive that $\{u^N = (u_C^N, u_D^N)\}_N$ is tight in $D([0, T], D(I)) \times D([0, T], \mathbb{R}^k) \equiv D([0, T], D(I) \times \mathbb{R}^k)$. In other words, $\{P_N\}_N$ is tight in $\mathcal{P}(D([0, T], D(I) \times \mathbb{R}^k))$.

3.3.2 Identification of the limit

For all N , u^N is a Markov jump process, and thus, is solution to the martingale problem associated with its generator \mathcal{A}^N , in the sense given by (3.3.6). In particular, for all $\varphi \in \mathcal{E}$ for all $n \geq 1$, for all $0 \leq t_1, \dots, t_n \leq s \leq t \leq T$, and for all $\psi \in C_b((D(I) \times \mathbb{R}^k)^n)$,

$$\begin{aligned} & \mathbb{E}_{\mathbb{P}} [M_\varphi^N(t) \psi(u^N(t_1), \dots, u^N(t_n))] \\ &= \mathbb{E}_{\mathbb{P}} [M_\varphi(s)^N \psi(u^N(t_1), \dots, u^N(t_n))], \end{aligned}$$

where

$$M_\varphi^N(t) = \varphi(u^N(t)) - \varphi(u^N(0)) - \int_0^t \mathcal{A}^N \varphi(u^N(s)) ds.$$

Since the family $\{P_N\}_N$ is tight in $\mathcal{P}(D([0, T], D(I) \times \mathbb{R}^k))$, it is relatively compact there, by Prohorov theorem. Therefore, there exists a subsequence $(P_{N_l})_l$ and a probability measure $P \in \mathcal{P}(D([0, T], D(I) \times \mathbb{R}^k))$, such that

$$P_{N_l} \Longrightarrow P \quad (\text{weakly}) \text{ as } l \rightarrow \infty.$$

Equivalently, there exists a process u with sample paths in $D([0, T], D(I) \times \mathbb{R}^k)$ and whose law is P , such that the subsequence $(u^{N_l})_l$ satisfies $u^{N_l} \Longrightarrow u$ as $l \rightarrow \infty$. The law of u^{N_l} is denoted by P_{N_l} for each l . The induced subsequence of martingale problems reads

$$\begin{aligned} & \mathbb{E}_{\mathbb{P}} [M_\varphi^{N_l}(t) \psi(u^{N_l}(t_1), \dots, u^{N_l}(t_n))] \\ &= \mathbb{E}_{\mathbb{P}} [M_\varphi^{N_l}(s) \psi(u^{N_l}(t_1), \dots, u^{N_l}(t_n))]. \end{aligned} \tag{3.3.7}$$

There are several difficulties if we try to take the limit in (3.3.7), as $l \rightarrow \infty$. In particular, $M_\varphi^{N_l}$ contains the diffusion term which is linear in u^N . This creates difficulties when taking limits inside the expectation since we do not have any estimates on the moments of u^N . Tightness was obtained through bounds in probability.

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To avoid this problem, we consider the process $w^N = (v_C^N, u_C^N, u_D^N)$, where v_C^N was introduced in Section 3.3.1. It is a Markov process. In fact it is a finite dimensional PDMP with generator

$$\begin{aligned}
& \tilde{\mathcal{A}}^N \varphi(v_C^N, u_C^N, u_D^N) \\
&= \left\langle D_{v_C^N} \varphi(v_C^N, u_C^N, u_D^N), \Delta_N v_C^N + F(v_C^N, u_C^N, u_D^N) \right\rangle_2 \\
&+ \sum_{j=1}^N \left\{ \sum_{r \in \mathfrak{R}_C} \left[\varphi \left(v_C^N, u_C^N + \frac{\gamma_r^C}{\mu} \mathbf{1}_j, u_D^N \right) - \varphi(v_C^N, u_C^N, u_D^N) \right] \mu \lambda_r \left(u_j^{N,C} \right) \right. \\
&\quad \left. + \sum_{r \in S_1} \left[\varphi \left(v_C^N, u_C^N + \frac{\gamma_r^C}{\mu} \mathbf{1}_j, u_D^N \right) - \varphi(v_C^N, u_C^N, u_D^N) \right] \mu \lambda_r \left(u_j^{N,C}, u_{\ell_j}^{N,D} \right) \right\} \\
&+ \sum_{j=1}^N \left\{ \left[\varphi \left(v_C^N, u_C^N + \frac{\mathbf{1}_{j-1} - \mathbf{1}_j}{\mu}, u_D^N \right) - \varphi(v_C^N, u_C^N, u_D^N) \right] \mu N^2 u_j^{N,C} \right. \\
&\quad \left. + \left[\varphi \left(v_C^N, u_C^N + \frac{\mathbf{1}_{j+1} - \mathbf{1}_j}{\mu}, u_D^N \right) - 2\varphi(v_C^N, u_C^N, u_D^N) \right] \mu N^2 u_j^{N,C} \right\} \\
&+ \sum_{\ell=1}^k \left\{ \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \left[\varphi \left(v_C^N, u_C^N + \frac{\gamma_r^{C,N}}{\mu}, u_D^N + \gamma_r^D \mathbf{1}^\ell \right) - \varphi(v_C^N, u_C^N, u_D^N) \right] \right. \\
&\quad \left. \times \lambda_r \left(\sum_{j=N_{\ell-1}+1}^{N_\ell} a_{j,N} u_j^{N,C}, u_\ell^{N,D} \right) \right\} \\
&+ \sum_{r \in \mathfrak{R}_D} \left[\varphi \left(v_C^N, u_C^N, u_D^N + \gamma_r^D \mathbf{1}^\ell \right) - \varphi(v_C^N, u_C^N, u_D^N) \right] \lambda_r \left(u_\ell^{N,D} \right) \left. \right\}.
\end{aligned}$$

The laws of w^N are tight in $D([0, T]; D(I) \times D(I) \times \mathbb{R}^k)$. By the discussion of the beginning of Section 3.3.1, we know that the limit points are concentrated on the set $\{(u_C, v_C, u_D) \in C([0, T]; C(I) \times C(I)) \times D([0, T]; \mathbb{R}^k) : u_C = v_C\}$. We repeat the argument above for w^N and deduce the existence of a subsequence such that $w^{N_l} \Rightarrow w$ as $l \rightarrow \infty$

Using the representation theorem of Skorohod, there exist versions of the stochastic processes, $\tilde{w}^{N_l}, \tilde{w}$ on a probability space $(\tilde{\Omega}, \tilde{\mathcal{F}}, \tilde{\mathbb{P}})$, such that

$$\tilde{w}^{N_l} \longrightarrow \tilde{w} \quad \tilde{\mathbb{P}} - a.s.^1$$

in the Skorohod topology. Also, we know that \tilde{w} is of the form $(\tilde{u}_C, \tilde{u}_C, \tilde{u}_D)$ for some processes \tilde{u}_C, \tilde{u}_D in $C([0, T]; C(I))$ and $D([0, T]; \mathbb{R}^k)$. Below, we write $\tilde{v} = (\tilde{u}_C, \tilde{u}_D)$.

Since we are interested in the laws of the processes, we consider these new versions in the sequel, and conserve the initial notation (without the "tilde"). Moreover, there exists a subset $\underline{\Omega} \subset \Omega$ such that $\mathbb{P}(\underline{\Omega}) = 1$ and for all $\omega \in \underline{\Omega}$, $w^{N_k}(\omega) \rightarrow w(\omega)$ in the Skorohod topology.

In addition, we know that $\|w^{N_l}(t) - w(t)\|_\infty \rightarrow 0$ if and only if w is continuous at $t \in [0, T]$ (see Section 12, Chapter 3 of [Bil99]). Thus this holds almost everywhere in $(t, \omega) \in [0, T] \times \Omega$. Also, from Lemma 1, Section 12, Chapter 3 of [Bil99], w is \mathbb{P} -a.s. continuous at every t , except for a countable set $D_P = D_{\mathbb{P}}(w)$. The set D_P is the complementary of

$$T_P = T_{\mathbb{P}}(w) := \{t \in [0, T] : \mathbb{P}(w(t) = w(t^-)) = 1\}.$$

Thus, for all $t \in T_P$, there is a subset $\Omega_t \subset \Omega$ with $\mathbb{P}(\Omega_t) = 1$, such that $w(\omega)$ is continuous at t for all $\omega \in \Omega_t$. Note that $0, T \in T_P$.

¹abbreviation for almost surely.

To consider the limit $l \rightarrow \infty$, we consider particular test functions depending only on $v^N = (v_C^N, u_D^N)$. For such functions we have the following expression for the generator:

$$\begin{aligned} & \tilde{\mathcal{A}}^N \varphi(v_C^N, u_C^N, u_D^N) \\ &= \left\langle D_{v_C^N} \varphi(v_C^N, u_D^N), \Delta_N v_C^N + F(v_C^N, u_D^N) \right\rangle_2 \\ &+ \sum_{\ell=1}^k \left\{ \sum_{r \in \mathfrak{R}_{DC} \setminus S_1} \left[\varphi(v_C^N, u_D^N + \gamma_r^D \mathbf{1}^\ell) - \varphi(v_C^N, u_D^N) \right] \lambda_r \left(\sum_{j=N_{\ell-1}+1}^{N_\ell} a_{j,N}^r u_j^{N,C}, u_\ell^{N,D} \right) \right. \\ &\quad \left. + \sum_{r \in \mathfrak{R}_D} \left[\varphi(v_C^N, u_D^N + \gamma_r^D \mathbf{1}^\ell) - \varphi(v_C^N, u_D^N) \right] \lambda_r(u_\ell^{N,D}) \right\} \end{aligned} \quad (3.3.8)$$

In particular, for all $\varphi \in \mathcal{E}$ for all $n \geq 1$, for all $0 \leq t_1, \dots, t_n \leq s \leq t \leq T$, and for all $\psi \in C_b((D(I) \times \mathbb{R}^k)^n)$,

$$\begin{aligned} & \mathbb{E}_{\mathbb{P}} \left[\tilde{M}_\varphi^N(t) \psi(v^N(t_1), \dots, v^N(t_n)) \right] \\ &= \mathbb{E}_{\mathbb{P}} \left[\tilde{M}_\varphi^N(s) \psi(v^N(t_1), \dots, v^N(t_n)) \right], \end{aligned} \quad (3.3.9)$$

where

$$\tilde{M}_\varphi^N(t) = \varphi(v^N(t)) - \varphi(v^N(0)) - \int_0^t \tilde{\mathcal{A}}^N \varphi(w^N(s)) ds.$$

This follows from the fact that functions in \mathcal{E} are in the domain of the finite dimensional PDMP w^N (see [CDMR12]).

For $t_1, \dots, t_n, s, t \in T_P$, the set

$$\tilde{\Omega} = \left(\bigcup_{i=1}^n \Omega_{t_i} \right) \cup (\Omega_s \cup \Omega_t \cup \underline{\Omega})$$

is of probability 1, and, working ω by ω on that set, we have the following asymptotics as $l \rightarrow \infty$.

- Firstly, $\psi(v^{N_l}(t_1), \dots, v^{N_l}(t_n)) \rightarrow_l \psi(v(t_1), \dots, v(t_n))$, since $v^{N_k}(t_i) \rightarrow_l v(t_i)$ for all $i = 1, \dots, n$, and ψ is continuous.
- Secondly, $v^{N_l}(0) \rightarrow_l v(0)$ and $\varphi(v^{N_l}(0)) \rightarrow_l \varphi(v(0))$, since φ is continuous. By the assumption (ii) of Theorem 3.3.1, we necessarily have $v(0) = v_0$.
- Similarly, $v^{N_l}(t) \rightarrow_l v(t)$ and $\varphi(v^{N_l}(t)) \rightarrow_l \varphi(v(t))$. The same results hold when t is replaced by s .

We cannot let $l \rightarrow \infty$ directly in (3.3.9). Indeed $\tilde{\mathcal{A}}^{N_l} \varphi(w^{N_l}(t))$ contains the term $\Delta_{N_l} v_C^{N_l}(t)$ which converges to $\Delta v_C(t)$ but in very bad topologies. This is because the convergence of $v_C^{N_l}$ holds only in $D(I)$.

In order to overcome this difficulty, we regularize v_C^N through a disturbance of the test functions.

Regularization. For all $\varphi \in \mathcal{E}$ and $\varepsilon > 0$, we introduce the linear operator A_ε on $D(I)$, and the function $\varphi_\varepsilon : D(I) \times \mathbb{R}^k \rightarrow \mathbb{R}$, defined by

$$A_\varepsilon := (I_d - \varepsilon \Delta)^{-2} \quad \text{and} \quad \varphi_\varepsilon := \varphi \circ (A_\varepsilon \otimes I_d), \quad (3.3.10)$$

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where $A_\varepsilon \otimes I_d : D(I) \times \mathbb{R}^k \rightarrow D(I) \times \mathbb{R}^k$ denotes the tensor product defined by

$$A_\varepsilon \otimes I_d(f, g) = (A_\varepsilon f, g) \quad \forall (f, g) \in D(I) \times \mathbb{R}^k.$$

Remark 3.3.1. Recall that in the definition of A_ε , we consider the Laplace defined in the C -theory with periodic boundary conditions.

It is well known that A_ε is a bounded linear operator of contraction (see e.g. [CH98], Chapter 2). Also, it commutes with Δ and with Δ_N , and is self-adjoint in L^2 -theory. Moreover, it maps $L^\infty(I)$, and in particular $D(I)$, into $W^{4,\infty}(I)$. The following result states further properties fulfilled by A_ε and φ_ε .

Lemma 3.3.3.

For all $g_N, g \in D(I)$ such that $\|g_N - g\|_\infty \rightarrow 0$ as $N \rightarrow \infty$,

$$(i) \|A_\varepsilon g_N - A_\varepsilon g\|_{C^2(I)} \rightarrow 0 \text{ as } N \rightarrow \infty,$$

$$(ii) \|\Delta_N A_\varepsilon g_N - \Delta A_\varepsilon g\|_\infty \rightarrow 0 \text{ as } N \rightarrow \infty.$$

The second point (ii) immediately follows from the first (i), thanks to *Proposition 3.2.2* (vii). Point (i) is a consequence of the fact that A_ε is a continuous operator from $L^\infty(I)$ to $W^{4,\infty}$ and therefore to $C^2(I)$.

Let us consider (3.3.9), with the disturbed test function φ_ε rather than φ . Explicitely,

$$\begin{aligned} \mathbb{E}_\mathbb{P} \left[\widetilde{M}_{\varphi_\varepsilon}^{N_l}(t) \psi(v^{N_l}(t_1), \dots, v^{N_l}(t_n)) \right] \\ = \mathbb{E}_\mathbb{P} \left[\widetilde{M}_{\varphi_\varepsilon}^{N_l}(s) \psi(v^{N_l}(t_1), \dots, v^{N_l}(t_n)) \right], \end{aligned} \quad (3.3.11)$$

where

$$\widetilde{M}_{\varphi_\varepsilon}^{N_l}(t) = \varphi_\varepsilon(v^{N_l}(t)) - \varphi_\varepsilon(v^{N_l}(0)) - \int_0^t \widetilde{\mathcal{A}}^{N_l} \varphi_\varepsilon(w^{N_l}(r)) dr.$$

We start keeping ε fixed, and let $l \rightarrow \infty$. Clearly, φ_ε is continuous on $D(I)$. Since $s, t \in T_P$, it follows from the preceding discussion that

$$\begin{cases} \varphi_\varepsilon(v^{N_l}(0)) \rightarrow_l \varphi_\varepsilon(v_0) \text{ a.s.} \\ \varphi_\varepsilon(v^{N_l}(s)) \rightarrow_l \varphi_\varepsilon(v(s)) \text{ a.s.} \\ \varphi_\varepsilon(v^{N_l}(t)) \rightarrow_l \varphi_\varepsilon(v(t)) \text{ a.s.} \end{cases}$$

It is rather straightforward to prove that $\widetilde{\mathcal{A}}^{N_l} \varphi_\varepsilon(w^{N_l}(t)) \rightarrow_l \mathcal{A}^\infty \varphi_\varepsilon(v(t))$. Also, it is uniformly bounded in N on $[0, T]$. This follows from the boundedness of the reaction rates, the bound (3.3.2) and the fact that A_ε is a bounded operator on $D(I)$.

Therefore, by dominated convergence, we may let $l \rightarrow \infty$ in equation (3.3.11) and obtain

$$\begin{aligned} \mathbb{E}_\mathbb{P} \left[M_{\varphi_\varepsilon}^\infty(t) \psi(v(t_1), \dots, v(t_n)) \right] \\ = \mathbb{E}_\mathbb{P} \left[M_{\varphi_\varepsilon}^\infty(s) \psi(v(t_1), \dots, v(t_n)) \right], \end{aligned} \quad (3.3.12)$$

with

$$M_{\varphi_\varepsilon}^\infty(t) = \varphi_\varepsilon(v(t)) - \varphi_\varepsilon(v_0) - \int_0^t \mathcal{A}^\infty \varphi_\varepsilon(v(r)) dr, \quad (3.3.13)$$

where \mathcal{A}^∞ is the generator defined by (3.2.14).

We now want to let $\varepsilon \rightarrow 0$. Except for the one containing the Laplace operator, all terms in the (3.3.12) are easily seen to converge. To treat the remaining term, we observe that we

may take the limit in equation (3.3.1) along the subsequence N_l and deduce that u_C satisfies almost surely:

$$u_C(t) = T(t)v_{C,0} + \int_0^t T(t-s)F(u_C(s), u_D(s))ds, \text{ a.s.}$$

The easiest way to do this is to take the limit in the weak form of the equation. From the smoothing property of $T(t)$:

$$\|T(t)\|_{L^\infty(I) \rightarrow W^{1,\infty}(I)} \leq c(t^{-\frac{1}{2}} + 1), \quad t \geq 0,$$

we deduce that $u_C(t)$ is bounded uniformly in $W^{1,\infty}(I)$, and in particular in $H_0^1(I)$ for $t \in [0, T]$ and $\omega \in \underline{\Omega}$. We deduce that $\Delta u_C(t)$ is bounded uniformly in H^{-1} and thanks to the property of the differential of functions in \mathcal{E} we may let $\varepsilon \rightarrow 0$ in the term containing the Laplace operator.

We obtain:

$$\begin{aligned} \mathbb{E}_{\mathbb{P}} [M_\varphi^\infty(t)\psi(v(t_1), \dots, v(t_n))] \\ = \mathbb{E}_{\mathbb{P}} [M_\varphi^\infty(s)\psi(v(t_1), \dots, v(t_n))], \end{aligned} \quad (3.3.14)$$

with

$$M_\varphi^\infty(t) = \varphi(v(t)) - \varphi(v_0) - \int_0^t \mathcal{A}^\infty \varphi(v(r))dr, \quad (3.3.15)$$

for all $\varphi \in \mathcal{E}$.

Now, if any of t_1, \dots, t_n, s, t does not lie in T_P , let us say $t \notin T_P$ for instance, we choose a sequence $(t^l)_l$ in T_P such that $t^l \rightarrow_l t$ with $t^l > t$. Since v is càdlàg, it is right-continuous at t , and $v(t^l) \rightarrow_l v(t)$. Then, we use (3.3.15) with t^l instead of t , let $l \rightarrow \infty$ and deduce that (3.3.15) also holds for $t \notin T_P$.

We have proved that the probability measure P , the law of v , is a solution of the martingale problem associated with the generator \mathcal{A}^∞ on the domain \mathcal{E} . Since the reaction rates are bounded as well as their derivatives, Theorem 3.2.1 holds and the martingale problem for \mathcal{A}^∞ —restricted to \mathcal{E} —admits a unique solution, which is the law P_{v_0} of the PDMP v characterized by $(\Delta, F, \lambda^D, Q)$, and which starts at v_0 . It follows that $P = P_{v_0}$, and the whole sequence of the laws of v^N converges to P_{v_0} . This implies the convergence of $(P_N)_N$ to P_{v_0} .

3.3.3 Conclusion

Now, we free ourselves from the additional assumption of boundedness of the process, and prove Theorem 3.3.1 by a truncation argument.

Let $\eta \in C^\infty(\mathbb{R}_+)$ such that

$$\begin{cases} \eta(y) = 1, & y \in [0, 1], \\ \eta(y) = 0, & y \in [2, \infty). \end{cases}$$

For $n \geq 1$ and $r \in \mathfrak{R}$, define

$$\eta_n(y) = \eta\left(\frac{|y|^2}{n^2}\right) \quad \text{and} \quad \lambda_r^n(y) = \eta_n(y)\lambda_r(y)$$

for $y \in \mathbb{R}^2$. Since (we have in particular) $y \mapsto |y|^2$ belongs to $C^1(\mathbb{R}^2)$ and $\eta \in C_b^1(\mathbb{R}_+)$, we also have $\eta_n \in C_b^1(\mathbb{R}_+)$. Furthermore, η_n and its derivative vanish outside the compact $\bar{B}(0, n)$, which is the closed ball in \mathbb{R}^2 centered at 0 and of radius n . Then, the problem with λ_r^n instead of λ_r fulfills the additional assumptions of the previous steps,.

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We define $u_n^N = (u_C^{N,n}, u_D^{N,n})$ the (truncated) jump Markov process associated to the (truncated) jump intensities λ_r^n , and starting at $u^N(0)$. By the preceding results, we know that, for all $n \geq 1$,

$$u^{N,n} \Longrightarrow_N v^n, \text{ in } D(\mathbb{R}_+; E),$$

where v^n is the (truncated) PDMP whose (truncated) characteristics $(\Delta, F_n, \lambda_n^D, Q_n)$ are obviously defined, w.r.t. the truncation.

It remains to argue as in [CDMR12] to conclude and to end the proof of Theorem 3.3.1. ■

3.4 Appendix

3.4.1 Well-posedness of the martingale problem for the generator of an infinite dimensional PDMP

Proof of Theorem 3.2.1. Let $(P_t) := (P_t)_{t \geq 0}$ be the semigroup on $E = C(I) \times \mathbb{R}^k$ associated to the PDMP $\{v(t) = (v_C(t), v_D(t)), t \geq 0\}$ starting at $(v_{C,0}, v_{D,0})$. We need the following:

Lemma 3.4.1. *For all $t \geq 0$, $\varphi \in \mathcal{E}$, $P_t \varphi$ is bounded differentiable with respect to the first variable on $C(I)$ and satisfies:*

$$\|P_t \varphi\|_\infty \leq \|\varphi\|_\infty, \quad (3.4.1)$$

$$|D_\alpha P_t \varphi(\alpha, \nu) \cdot h| \leq c \|\varphi\|_{\mathcal{E}} e^{Mt} \|h\|_\infty, \quad \alpha \in C(I), \nu \in \mathbb{R}^k, h \in C(I) \quad (3.4.2)$$

for some constants c and M depending only on the characteristics of the PDMP v .

Proof of Lemma 3.4.1. The part (3.4.1) immediately follows, from the definition of the semigroup and the fact that the expectation is increasing. For $\varphi \in \mathcal{E}$ and $\psi \in \mathfrak{B}(\mathbb{R}_+ \times E)$, let us define

$$\begin{aligned} G_\varphi \psi(t, u) &:= \mathbb{E}_u [\varphi(v(t)) \mathbf{1}_{t < T_1} + \psi(t - T_1, v(T_1)) \mathbf{1}_{t \geq T_1}] \\ &= \varphi(\phi_\nu(t, \alpha), \nu) H(t, u) \\ &\quad + \int_0^t \int_K \psi(t - s, \alpha, \xi) Q(d\xi; \phi_\nu(s, \alpha), \nu) \Lambda(\phi_\nu(s, \alpha), \nu) H(s, u) ds \end{aligned}$$

for $(t, u) \in \mathbb{R}_+ \times E$, with $u = (\alpha, \nu)$ and v the PDMP starting at u . Then, according to Lemma 27.3 of [Dav93],

$$G_\varphi^n \psi(t, u) = \mathbb{E}_u [\varphi(v(t)) \mathbf{1}_{t < T_n} + \psi(t - T_n, v(T_n)) \mathbf{1}_{t \geq T_n}]$$

and

$$\lim_{n \rightarrow \infty} G_\varphi^n \psi(t, u) = P_t \varphi(u),$$

where

$$\begin{aligned} G_\varphi^n \psi(t, u) &:= G_\varphi(G_\varphi^{n-1} \psi(t, u)) \\ &= \varphi(\phi_\nu(t, \alpha), \nu) H(t, u) \\ &\quad + \int_0^t H(s, u) \left[\int_K \Lambda_\nu(\phi_\nu(s, \alpha)) G_\varphi^{n-1} \psi(t - s, \alpha, \xi) Q(d\xi; \phi_\nu(s, \alpha), \nu) \right] ds. \end{aligned}$$

Thus, our assumptions allow us to use dominated convergence, and we deduce

$$\begin{aligned} P_t\varphi(u) &= \varphi(\phi_\nu(t, \alpha), \nu)H(t, u) \\ &\quad + \int_0^t \int_K P_{t-s}\varphi(\alpha, \xi)Q(d\xi; \phi_\nu(s, \alpha), \nu)\Lambda(\phi_\nu(s, \alpha), \nu)H(s, u)ds. \end{aligned} \quad (3.4.3)$$

That is, $P_t\varphi : t \mapsto P_t\varphi$ is a fixed point of G_φ .

For $T > 0$, we introduce the Banach space $\mathcal{E}_T := L^\infty([0, T], C_b^{1,0}(C(I) \times \mathbb{R}^k))$, with the norm

$$\|\psi\|_{\mathcal{E}_T} = \sup_{t \in [0, T]} e^{-\beta t} (\|\psi(t, \cdot)\|_\infty + \|D_\alpha \psi(t, \cdot)\|_\infty),$$

where β will be fixed hereafter.

For $t \in [0, T]$, $(\alpha, \nu) \in E$, set

$$q_\varphi(t, \alpha, \nu) = \varphi(\phi_\nu(t, \alpha), \nu)H(t, \alpha, \nu).$$

We claim that

$$q_\varphi : t \mapsto q_\varphi(t, \cdot) \text{ is in } \mathcal{E}_T. \quad (3.4.4)$$

Indeed, let $0 \leq t \leq T$, $u = (\alpha, \nu) \in E$ be fixed. Then

$$|H(t, \alpha, \nu)| \leq 1,$$

from the definition of the survivor function H by (3.2.2). Since φ is bounded, we have

$$\|q_\varphi(t, \cdot)\|_\infty \leq \|\varphi\|_\infty \quad \text{and} \quad q_\varphi(t, \cdot) \in \mathfrak{B}_b(E).$$

Next, we show that $q_\varphi(t, \cdot) \in \mathcal{E}$. Let D_α denote the differential operator w.r.t. the variable α , and set

$$\Psi_\nu(t) \cdot h = D_\alpha \phi_\nu(t, \alpha) \cdot h.$$

From our assumptions, $F \in C_b^{1,0}(E)$. It follows that for $h \in C(I)$ the map $t \mapsto \Psi_\nu(t) \cdot h$ is a global mild solution of

$$\begin{cases} \frac{\partial}{\partial t} \Psi_\nu(t) \cdot h = \Delta \Psi_\nu(t) \cdot h + D_\alpha F_\nu(\phi_\nu(t, \alpha)) \circ \Psi_\nu(t) \cdot h \\ \Psi_\nu(0) \cdot h = h. \end{cases} \quad (3.4.5)$$

It satisfies

$$\Psi_\nu(t) \cdot h = T(t)h + \int_0^t T(t-s)D_\alpha F_\nu(\phi_\nu(s, \alpha)) \circ \Psi_\nu(s) \cdot h ds.$$

Since the semigroup $\{T(t)\}$ of Δ is of contraction, the Gronwall Lemma yield,

$$\|\Psi_\nu(t) \cdot h\|_\infty \leq \|h\|_\infty + L_F \int_0^t \|\Psi_\nu(s) \cdot h\|_\infty ds \leq e^{L_F t} \|h\|_\infty.$$

Thus,

$$\|D_\alpha \phi_\nu(t, \alpha) \cdot h\|_\infty \leq e^{L_F t} \|h\|_\infty.$$

The chain rule leads to

$$\begin{aligned} \|D_\alpha H(t, \alpha, \nu) \cdot h\|_\infty &\leq \int_0^t \|D_\alpha [\Lambda(\phi_\nu(s, \alpha), \nu)] \cdot h\|_\infty ds \leq L_\Lambda \int_0^t \|D_\alpha \phi_\nu(s, \alpha) \cdot h\|_\infty ds \\ &\leq \frac{L_\Lambda}{L_F} (e^{L_F t} - 1) \|h\|_\infty. \end{aligned}$$

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Therefore $q_\varphi(t, \cdot) \in \mathcal{E}$, since

$$\begin{aligned} \|D_\alpha q_\varphi(t, \alpha, \nu) \cdot h\|_\infty &\leq \|D_\alpha \varphi(\phi_\nu(t, \alpha), \nu) \cdot h\|_\infty + \|D_\alpha H(t, \alpha, \nu) \cdot h\|_\infty \\ &\leq \left(\|D_\alpha \varphi\|_\infty + \frac{L_\Lambda}{L_F} (e^{L_F t} - 1) \right) \|h\|_\infty. \end{aligned}$$

Finally, for $\beta > L_F$,

$$\|q_\varphi\|_{\mathcal{E}_T} \leq \|\varphi\|_\infty + \left(\|D_\alpha \varphi\|_\infty + \|\varphi\|_\infty \frac{L_\Lambda}{L_F} \right). \quad (3.4.6)$$

Similar arguments will allow us to get the upcoming upper bounds. If $\psi \in \mathcal{E}_T$, then $G_\varphi \psi \in \mathcal{E}_T$. In fact,

$$G_\varphi \psi(t, \alpha, \nu) = q_\varphi(t, \alpha, \nu) + \tilde{q}_\psi(t, \alpha, \nu),$$

with

$$\tilde{q}_\psi(t, \alpha, \nu) = \int_0^t H(s, \alpha, \nu) \left[\Lambda(\phi_\nu(s, \alpha), \nu) \int_K \psi(t-s, \alpha, \xi) Q_\nu(d\xi; \phi_\nu(s, \alpha)) \right] ds.$$

It is standard to prove that this defines a function in \mathcal{E}_T . Moreover, observing that $\|\tilde{q}_\psi(t, \cdot)\|_\infty \leq M_\Lambda \|\psi\|_\infty t \leq c_1 t$, and recalling the definition of Λ and Q (see (3.2.16) and (3.2.17)), which in particular imply their differentiability,

$$\|D_\alpha \tilde{q}_\psi(t, \alpha, \nu) \cdot h\|_\infty \leq \int_0^t \left[\frac{L_\Lambda}{L_F} (e^{L_F s} - 1) M_\Lambda \|\psi(t-s, \cdot)\|_\infty + L_Q \|\psi\|_{\mathcal{E}_T} \right] ds \|h\|_\infty,$$

it follows from (3.4.6) and (3.4.1) that

$$\begin{aligned} \|D_\alpha G_\varphi \psi(t, \alpha, \nu) \cdot h\|_\infty &\leq \left(\|D_\alpha \varphi\|_\infty + \|\varphi\|_\infty \frac{L_\Lambda}{L_F} e^{L_F t} \right. \\ &\quad \left. + \left(\frac{L_\Lambda}{L_F} M_\Lambda + \frac{L_Q}{L_F} \right) \|\varphi\|_\infty e^{L_F t} + L_Q \int_0^t L_{\psi(t-s, \cdot)} ds \right) \|h\|_\infty, \end{aligned}$$

which yields (using Gronwall lemma)

$$\|D_\alpha G_\varphi \psi(t, \cdot)\|_\infty \leq c \|\varphi\|_{C_b^{1,0}(C(I) \times \mathbb{R}^k)} e^{L_F t} + L_Q \int_0^t \|D_\alpha \psi(s, \cdot)\|_\infty ds \leq c \|\varphi\|_{C_b^{1,0}(C(I) \times \mathbb{R}^k)} e^{Mt}, \quad (3.4.7)$$

and we conclude that G_φ maps \mathcal{E}_T into itself. The constants c and M depend only on (L, F, Λ, Q) and will turn out to be the constants appearing in (3.4.2).

Moreover, if $\psi_1, \psi_2 \in \mathcal{E}_T$, we prove similarly

$$\begin{aligned} \|G_\varphi \psi_1(t, \cdot) - G_\varphi \psi_2(t, \cdot)\|_\infty &\leq M_\Lambda \int_0^t \|\psi_1(t-s, \cdot) - \psi_2(t-s, \cdot)\|_\infty ds, \\ \|D_\alpha G_\varphi \psi_1(t, \cdot) - D_\alpha G_\varphi \psi_2(t, \cdot)\|_\infty &\leq \kappa_1 \int_0^t e^{L_F s} \|\psi_1(t-s, \cdot) - \psi_2(t-s, \cdot)\|_{C_b^{1,0}(C(I) \times \mathbb{R}^k)} ds, \end{aligned}$$

where κ_1 is a constant depending only on (L, F, Λ, Q) .

Then, it is not difficult to deduce that

$$\begin{aligned} \|G_\varphi \psi_1 - G_\varphi \psi_2\|_{\mathcal{E}_T} &\leq \kappa_2 \sup_{t \in [0, T]} e^{-\beta t} \left(\int_0^t e^{\beta(t-s)} ds + \int_0^t e^{\beta(t-s)} e^{L_F s} ds \right) \|\psi_1 - \psi_2\|_{\mathcal{E}_T} \\ &\leq \kappa_2 \left(\frac{1}{\beta} + \frac{1}{\beta - L_F} \right) \|\psi_1 - \psi_2\|_{\mathcal{E}_T}, \end{aligned}$$

where again, κ_2 depends only on (L, F, Λ, Q) . We now choose β sufficiently large and deduce from the Picard theorem that G_φ has a unique fixed point in \mathcal{E}_T . This fixed point is the limit of $G_\varphi^n \psi$ for any $\psi \in \mathcal{E}_T$. Thus, $P_t \varphi \mapsto P_t \varphi$ is that fixed point.

The Lipschitz constant $L_{P_t \varphi}$ of $P_t \varphi$ is obtained from (3.4.7), by taking $\psi = P_t \varphi$. \square

Lemma 3.4.2. *For all $t \geq 0$, $\varphi \in \mathcal{E}$, $P_t \varphi \in \mathcal{E}$ and satisfies:*

$$|D_\alpha P_t \varphi(\alpha, \nu) \cdot h| \leq \tilde{c}(t^{-\frac{3}{4}} + 1)e^{\tilde{M}t} \|\varphi\|_{\mathcal{E}} \|h\|_{H^{-1}}, \quad \alpha \in C(I), \nu \in \mathbb{R}^k, h \in C(I) \quad (3.4.8)$$

for some constants \tilde{c} and \tilde{M} depending only on the characteristics of the PDMP v .

Proof. If we prove (3.4.8), it follows that $D_\alpha P_t \varphi$ can be extended to $H^{-1}(I)$ and using Lemma 3.4.1 the result follows. The proof of (3.4.8) relies on the smoothing properties of the heat kernel. Indeed, we have for $t > 0$

$$\|T(t)\|_{H^{-1}(I) \rightarrow L^\infty(I)} \leq c(t^{-\frac{3}{4}} + 1)$$

for some constant $c > 0$. It follows:

$$\|\Psi_\nu(t) \cdot h\|_\infty \leq c(t^{-\frac{3}{4}} + 1) \|h\|_{H^{-1}(I)} + L_F \int_0^t \|\Psi_\nu(s) \cdot h\|_\infty ds$$

and by Gronwall Lemma:

$$\|\Psi_\nu(t) \cdot h\|_\infty \leq c(t^{-\frac{3}{4}} + 1)e^{(L_F+1)t} \|h\|_{H^{-1}(I)}, \quad t \in (0, T].$$

We end the proof with similar computations as in the proof of Lemma 3.4.1. \square

Remark 3.4.1. *In fact, we have proved a slightly stronger result. Indeed, we have not used that $\varphi \in \mathcal{E}$ but only that $\varphi \in C_b^{1,0}(C(I) \times \mathbb{R}^k)$. Therefore for $t > 0$, P_t maps $C_b^{1,0}(C(I) \times \mathbb{R}^k)$ into \mathcal{E} .*

Corollary 3.4.1. *(One more characterization of \mathcal{A}^∞)*

(i) *For all $\mu > 0$, $\mathbb{R}(\mu - \mathcal{A}^\infty) = \mathcal{E}$, and*

$$(\mu - \mathcal{A}^\infty)^{-1} \varphi = \int_0^\infty e^{-\mu t} P_t \varphi dt \quad \forall \varphi \in \mathcal{E}.$$

(ii) *If $\mu > K = \max\{M, \tilde{M}\}$, then for all $\varphi \in \mathcal{E}$, $\psi := (\mu - \mathcal{A}^\infty)^{-1} \varphi \in \mathcal{E}$.*

Proof. Since the domain of \mathcal{A}^∞ is \mathcal{E} , under our assumption we already know that

$$\bar{\mathcal{A}}^\infty \varphi(u) = \mathcal{A}^\infty \varphi(u) = \hat{\mathcal{A}}^\infty \varphi(u), \quad \forall \varphi \in \mathcal{E}, u \in E.$$

Therefore, we conclude the part (i) by the Proposition 5.1, Section 5, Part 1 of [EK86], since the semigroup (P_t) is measurable and of contraction on \mathcal{E} by Lemma 3.4.1, and observing that, thanks to Fubini theorem, the condition

$$P_s \int_0^\infty e^{-\mu t} P_t \varphi dt = \int_0^\infty e^{-\mu t} P_{s+t} \varphi dt$$

holds for all $\varphi \in \mathcal{E}$, $\mu > 0$ and $s \geq 0$.

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Concerning the part (ii), take $\varphi \in \mathcal{E}$. From (ii), it is clear that $\psi := (\mu - \mathcal{A}^\infty)^{-1}$ is bounded. Moreover, a derivation under the integral shows that ψ is of class C^1 w.r.t. its first variable. At last, for all $\alpha \in B$ and $\nu \in K$, it follows from *Lemma 3.4.1* that

$$\begin{aligned} |D_\alpha \psi(\alpha, \nu) \cdot h| &= \left| \int_0^\infty e^{-\mu t} D_\alpha P_t \psi(\alpha, \nu) \cdot h dt \right| \\ &\leq c \|\psi\|_{\mathcal{E}} \left(\int_0^\infty e^{-(\mu-M)t} dt \right) \|h\|_\infty \\ &\leq c \|\psi\|_{\mathcal{E}} \frac{1}{\mu - M} \|h\|_\infty, \end{aligned}$$

which yields boundedness for the differential of ψ . Similarly:

$$\begin{aligned} |D_\alpha \psi(\alpha, \nu) \cdot h| &\leq \tilde{c} \|\psi\|_{\mathcal{E}} \left(\int_0^\infty (t^{-\frac{3}{4}} + 1) e^{-(\mu-\tilde{M})t} dt \right) \|h\|_{H^{-1}(I)} \\ &\leq C \|\psi\|_{\mathcal{E}} \frac{1}{(\mu - \tilde{M})^{\frac{1}{4}}} \|h\|_{H^{-1}(I)}, \end{aligned}$$

for some constant C . \square

We now use a classical argument to prove uniqueness. Let \tilde{P}_u be another solution of the martingale problem for \mathcal{A}^∞ . Let $\varphi \in \mathcal{E}$, $\mu \in K$ and $\psi := (\mu - \mathcal{A}^\infty)^{-1}\varphi$. Then

$$\psi(v(t)) - \psi(u) - \int_0^t \mathcal{A}^\infty \psi(v(s)) ds$$

is a \tilde{P}_u -martingale. In particular,

$$\tilde{\mathbb{E}}_u \left(\psi(v(t)) - \int_0^t \mathcal{A}^\infty \psi(v(s)) ds \right) = \psi(u).$$

Multiply this identity by $\mu e^{-\mu t}$ and integrate on $[0, \infty)$ yield

$$\tilde{\mathbb{E}}_u \left(\int_0^\infty e^{-\mu t} \varphi(v(t)) dt \right) = \psi(u) = \int_0^\infty e^{-\mu t} P_t \varphi(u) dt,$$

for $\mu > K$, since \mathcal{A}^∞ is the full generator $\hat{\mathcal{A}}^\infty$. By injectivity of the Laplace transform, this implies

$$\tilde{\mathbb{E}}_u[\varphi(v(t))] = P_t \varphi(u) = \mathbb{E}_u[\varphi(v(t))],$$

for almost all $t \geq 0$.

We have proved that the laws of the solutions to the martingale problem are the same at every fixed time t in a dense set of \mathbb{R}_+ . This implies uniqueness for the martingale problem (see [Bil99], Section 14), and the proof of *Theorem 3.2.1* ends. \blacksquare

3.4.2 About tightness

Proof of Lemma 3.3.1. Recall that

$$a_C^N(t) = T_N(t) P_N v_C(0) \quad \text{and} \quad b^N(t) = \int_0^t T_N(t-s) F(\bar{u}_C^N(s), u_D^N(s)) ds.$$

Part (i). Since the semigroup $\{T_N(t)\}$ is contracting on $(\mathbb{H}^N, \|\cdot\|_\infty)$, it easily follows from Proposition 3.2.1 (iii), that

$$\sup_{t \in [0, T_0]} \|a_C^N(t)\|_\infty \leq \|P_N v_C(0)\|_\infty \leq c_3,$$

where c_3 is a constant independent of N .

Part (ii). Now, $\nabla_N^+ a_C^N(t)$ satisfies on \mathbb{H}^N the initial condition problem

$$\begin{cases} \frac{d}{dt} \nabla_N^+ a_C^N(t) = \Delta_N \nabla_N^+ a_C^N(t) \\ \nabla_N^+ a_C^N(0) = \nabla_N^+ P_N v_C(0). \end{cases}$$

From the maximum principle, we have

$$\sup_{t \in [0, T]} \|\nabla_N^+ a_C^N(t)\|_\infty = \|\nabla_N^+ P_N v_C(0)\|_\infty \leq c_4,$$

where c_4 is some constant independent of N since $v_C(0)$ is $C^1(I)$.

Part (iii). Under the additional assumption of boundedness for the reaction rates and their derivatives, we know that the function F is bounded by a constant M_F . Using the contraction property of $T_N(t)$ we get

$$\sup_{t \in [0, T]} \|b^N(t)\|_\infty \leq T M_F =: c_5.$$

Part (iv). An elementary proof shows that there exists a constant c such that, for all $v \in \mathbb{H}^N$, $\|\nabla_N^+ v\|_\infty \leq c \|v\|_\infty^{1/2} \|\Delta_N v\|_\infty^{1/2}$. By Proposition 3.2.2 (viii), we deduce that for all $t > 0$, $\|\nabla_N^+ T_N(t)\|_{L^\infty(I) \rightarrow L^\infty(I)} \leq c t^{-1/2}$ for some constant c independent of N . Since F is bounded, we have

$$\begin{aligned} \|\nabla_N^+ b^N(t)\|_\infty &\leq \int_0^t \|\nabla_N^+ T_N(t-s) F(\bar{u}_C^N(s), u_D^N(s))\|_\infty ds \\ &\leq \int_0^t \|\nabla_N^+ T_N(t-s)\|_{L^\infty(I) \rightarrow L^\infty(I)} |F(\bar{u}_C^N(s), u_D^N(s))| ds \\ &\leq c M_F \int_0^t (t-s)^{-1/2} ds \\ &\leq c M_F \sqrt{t} \end{aligned}$$

and we can conclude, with $c_6 = c M_F \sqrt{T}$. \square

CHAPTER 4

A spatial model of cholera epidemic: large population and long time behaviour

Abstract. This chapter is devoted to some applications of chapters 2 and 3 in the field of epidemiology, with an extension to some study of the long time behavior. We develop a more specific model of interactions, compared to those of chapters 2 and 3. It is actually a stochastic spatial model of cholera epidemic, where three types of human populations (susceptibles, infectious and recovered) are interacting with a population of bacteria in some spatial domain. Moreover, the system is multiscale since human population scales differently from bacteria. Jump intensities and stoichiometric vectors now have determined parametric forms. The spatial transport is not symmetric, and this creates a gradient additional term. We are interested in the large population and the long time asymptotic behaviours of the system. With respect to the former, different configurations of scaling are pointed out and their corresponding to either a deterministic or a hybrid approximation is argued, relying on chapters 2 and 3. Using the technics of chapter 2, we rigorously prove a law of large numbers with details, in the particular case when the two population scales are proportional. Afterward, study the long time behaviour of the system in that case. More specifically, we establish an upper bound for compact sets, in the sense of a weak large deviation principle.

This chapter is the result of a conjoint work with KOUEGOU KAMEN Boris (I2M, Marseille).

4.1 Introduction

We are interested in modeling the spreading of Cholera in an endemic area where it is usually known there is little hydraulic hygiene. Cholera is an acute intestinal infection caused by a bacterium called *vibro cholerae* which is most commonly transmitted orally by ingestion of water or contaminated food, or by contact with any liquid of an infected host (saliva, sweat, etc...). *Vibro cholerae* lives and spreads in the water where she's endowed with an incredible capacity for survival. Rivers, streams and groundwater or any source of water contaminated by Human defects are its preferred reservoirs. Several deterministic works showed the importance

of the spatial distribution of humans and reservoirs in the spread of this disease in endemic areas.

A deterministic model is proposed by [BCG⁺10], where spatial dynamic is effectively considered for bacteria only, through water reservoirs. As their spatial transport is asymmetric, bacteria population evolves according to a reaction-advection-diffusion partial differential equation. The model is of type SIRSB, where susceptible (S) can be infected directly by contact with bacteria (B) or infectious (I). Infectious can recover and are called recovered (R). These latter are immune within a period. In [BCG⁺10], the authors focus on the epidemic period of the disease, which is shorter than the period of immunity, so that they need not consider the compartment (R) of recovered people. Furthermore, bacteria transportation are oriented and their probabilities and rates depend on the directions.

In this chapter, the stochastic counterpart of the model of [BCG⁺10] is developed. We study its large population and long time asymptotic behaviours. With respect to the long time behaviour, we explicitly consider the compartment (R) of recovered people, since they can lose their immunity with time, and become susceptible again. The model has two population time scales, the one of humans denoted H , and the one of bacteria denoted K . The main results are stated under the condition that H scales with K . However, other possibilities are discussed and other deterministic limits are identified as well as hybrid limits.

The rest of the chapter is organised as follows. Section 2 is devoted to modeling. After recalling the model of [BCG⁺10], we present our model, which is its stochastic counterpart. In section 3, a law of large numbers (LLN) is established. Relying on chapter 2 or [Blo92], we prove that the stochastic model well renormalized converges, in large populations limit, to its deterministic corresponding, in the supremum norm. In section 4, a corresponding large deviation principle (LDP) is investigated. We first present a rate function candidate. Then, we proceed to the upper bound estimates. Technical computations are postponed to the Appendix section at the end.

4.2 Modeling and convergence tools

We first present existing deterministic models as given in [BCG⁺10], where the authors study the disease spread in a population of Humans interacting with a population of bacteria in reservoirs, in some endemic area $J \subset \mathbb{R}^d$. We consider a one dimensional spatial domain - $d = 1$ - and take $J = [0, 1]$, the unit interval. We also consider periodic boundary conditions. That is we are interested in functions that are 1-periodic w.r.t. the space variable.

Given any spatio-temporal coordinate $(t, x) \in \mathbb{R}_+ \times J$, human living population is subdivided into classes, according to their disease status:

- $S(t, x)$: is the number of humans who are susceptible to catch the disease,
- $I(t, x)$: is the number of humans who are infected and therefore are infectious too,
- $R(t, x)$: is the number of infected humans who received treatment and are still alive.

Human total population is $\mathbf{H}(t, x) = S(t, x) + I(t, x) + R(t, x)$. Its average initial value

$$H := \int_J \mathbf{H}(0, x) dx$$

will turn out to be of particular importance. In addition, we denote by $B(t, x)$ the population of *vibrio cholerae* for every time-space coordinate $(t, x) \in \mathbb{R}_+ \times J$. Bacteria live in water reservoirs. Commonly, S , I , R and B are referred to, as the compartments of the model. We often use the notation $S(t) = S(t, \cdot)$, and similar notation for the other compartments. The functions $S(t)$, $I(t)$, $R(t)$ and $B(t)$ are considered to be periodic, of period 1.

4.2 Modeling and convergence tools

In [BCG⁺10], the class R of recovered is not considered, since the authors focus on the population behavior over the epidemic period, and this latter is less important than the time before the loss of immunity. Contrariwise, we have to consider that class, as we are interested in large deviations study, which involves a long time behavior.

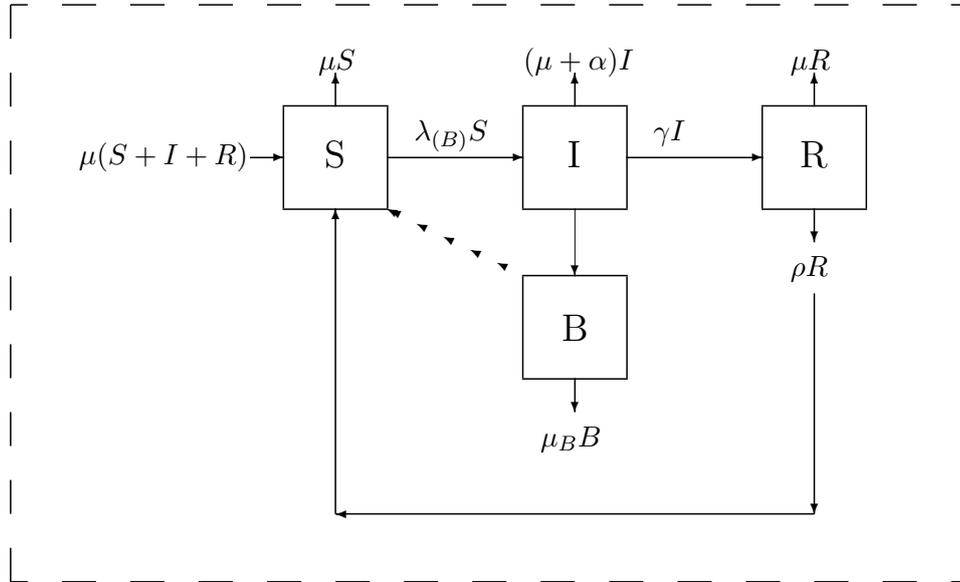
4.2.1 Deterministic models

Deterministic homogeneous model

Only a global description of the system is needed, and the quantities of interest are concentrations. Human and bacteria are assumed to be spatially homogeneous, meaning that for all $(t, x) \in \mathbb{R}_+ \times J$, one has $S(t, x) = S(t)$. A similar relation holds for I , R , and B . In this context, the human average initial population is simply the human total initial total population:

$$H = \mathbf{H}(0).$$

The figure below describes the transition mechanisms that the different compartments undergo.



Here,

- μ is the natural death and birth rate per human.
- α is the cholera-mortality rate per infected.
- γ is the rate at which infected recover health.
- ρ is the rate at which a recovered loses his immunity.
- p/W is the rate at which an infected contributes to the concentration of vibrios. Bacteria produced by an infected person reach and contaminate a water reservoir of volume W , at rate p .
- $\lambda_{(B)}(t) = \beta \frac{B(t)}{K+B(t)}$ is the rate at which susceptible people become infected. Therein, β is the rate of contacts with contaminated water per susceptible, K is the capacity of bacteria concentration in the area, and $\frac{B(t)}{K+B(t)}$ is the logistic dose-response curve. Such a curve links the probability of becoming infected to the concentration of vibrios B in water (see [Cod01]).
- μ_B is the death rate per *vibrio cholerae*. This parameter actually takes into account both the reproduction and the death of free-living vibrios. However, these latter reproduce in water at a smaller rate than that of their mortality. So basically, they "only" die.

In such context, the spread of the disease is described by the system of ordinary differential equations (ODEs) of concentrations:

$$\begin{cases} \frac{dS(t)}{dt} = \mu I(t) + (\mu + \rho)R(t) - \lambda_{(B)}(t)S(t) \\ \frac{dI(t)}{dt} = \lambda_{(B)}(t)S(t) - (\gamma + \alpha + \mu)I(t) \\ \frac{dR(t)}{dt} = \gamma I(t) - (\mu + \rho)R(t) \\ \frac{dB(t)}{dt} = -\mu_B B(t) + \frac{p}{KW}I(t). \end{cases} \quad (4.2.1)$$

Renormalization. Proportions are often described in practice, in the place of the number of individuals. One switches from the latter to the former by setting

$$S^*(t) = \frac{S(t)}{H}, \quad I^*(t) = \frac{I(t)}{H}, \quad R^*(t) = \frac{R(t)}{H} \quad \text{and} \quad B^*(t) = \frac{B(t)}{K}.$$

As a result, the rates of events for the rescaled variable are of order H (resp. K) for humans (resp. bacteria). The rescaled variables also depend on the parameters H and K , but we do not mention these latter throughout this work. The renormalized version of (4.2.1) is given by

$$\begin{cases} \frac{dS^*(t)}{dt} = \mu I^*(t) + (\mu + \rho)R^*(t) - \lambda_{(B^*)}(t)S^*(t) \\ \frac{dI^*(t)}{dt} = \lambda_{(B^*)}(t)S^*(t) - (\gamma + \alpha + \mu)I^*(t) \\ \frac{dR^*(t)}{dt} = \gamma I^*(t) - (\rho + \mu)R^*(t) \\ \frac{dB^*(t)}{dt} = -\mu_B B^*(t) + \frac{Hp}{KW}I^*(t), \end{cases} \quad (4.2.2)$$

where $\lambda_{(B^*)}(t) = \beta \frac{B^*(t)}{1+B^*(t)}$.

Well-posedness, generator and debit function. Set $X^* = (S^*, I^*, R^*, B^*) \in \mathbb{R}^4$. One puts (4.2.2) on the compact form

$$\frac{dX^*(t)}{dt} = F(X^*(t)), \quad (4.2.3)$$

where $F = (F_S, F_I, F_R, F_B)$ is the vector field in \mathbb{R}^4 given for $y \in (y_1, y_2, y_3, y_4) \in \mathbb{R}^4$ by

$$F(y) = \begin{pmatrix} F_S(y) \\ F_I(y) \\ F_R(y) \\ F_B(y) \end{pmatrix} = \begin{pmatrix} \mu y_2 + (\mu + \rho)y_3 - \beta \frac{y_4}{1+y_4} y_1 \\ \beta \frac{y_4}{1+y_4} y_1 - (\gamma + \alpha + \mu)y_2 \\ \gamma y_2 - (\mu + \rho)y_3 \\ -\mu_B y_4 + \frac{Hp}{KW} y_2 \end{pmatrix}.$$

We say that the vector y is positive and write $y \geq 0$, when $y_i \geq 0$ for $i = 1, \dots, 4$. For consistency, only positive initial conditions are considered. Let $\mathbb{R}_+^4 = \{y \in \mathbb{R}^4 : y \geq 0\}$. Then it is not difficult to see that the restriction of F to \mathbb{R}_+^4 is of class C^∞ . Furthermore, F satisfies

- (i) $F_S(y) \geq 0$ if $y_1 = 0$, $\forall y = (y_1, \dots, y_4) \in \mathbb{R}_+^4$.
- (ii) In (i), (S, y_1) can be replaced by (I, y_2) , (R, y_3) or (B, y_4) .
- (iii) $\exists M > 0$, such that $|F(y)| \leq M|y| \forall y \geq 0$,

4.2 Modeling and convergence tools

where $|\cdot|$ is the norm of \mathbb{R}^4 , and the constant M depends on $\mu, \rho, \beta, \alpha, \gamma, \rho, H/K$ and p/W . Relations (i) and (ii) are trivial. Concerning (iii), for $y = (y_1, \dots, y_4) \geq 0, y_4 \geq 0$ yields $\frac{y_4}{1+y_4} \leq 1$. Then, one easily sees that there exists constants $M_S = M_S(\mu, \rho, \beta)$, $M_I = M_I(\beta, \gamma, \alpha, \mu)$, $M_R = M_R(\gamma, \rho, \mu)$ and $M_B = M_B(\mu_B, \frac{Hp}{KW})$, such that $|F_S(y)| \leq M_S|y|$, $|F_I(y)| \leq M_I|y|$, $|F_R(y)| \leq M_R|y|$ and $|F_B(y)| \leq M_B|y|$, for all $y \geq 0$.

It is very standard that for all $y_0 = (S_0, I_0, R_0, B_0) \in \mathbb{R}_+^4$, the initial condition problem (4.2.3) with $X(0) = y_0$ admits a unique global solution $X \in C^1(\mathbb{R}_+; \mathbb{R}^4)$, satisfying

$$X(t) = y_0 + \int_0^t F(X(s)) ds \quad (4.2.5)$$

and $X(t) \geq 0$ for all $t \geq 0$, and, for all $T > 0$,

$$\sup_{t \leq T} |X(t)| \leq c_T = |y_0| e^{MT}. \quad (4.2.6)$$

The generator and the debit of this model are respectively given by

$$\mathcal{A}\varphi(y) = \langle D\varphi(y), F(y) \rangle \quad \text{and} \quad \psi(y) = F(y) \quad (4.2.7)$$

for $y \in \mathbb{R}^4$ and $\varphi \in C_b^1(\mathbb{R}^4)$. We have denoted $\langle \cdot, \cdot \rangle$ the inner product of \mathbb{R}^4 .

Deterministic spatial model

In this context, a local description is given, and compartments are now functions of the space variable that are not necessary constant. Human and bacteria are initially distributed all over the unit interval J . Periodic boundary conditions are considered. We discretize J w.r.t. the well known one dimensional lattice regular subdivision in N parts. There are N nodes, indexed by i , and the subintervals $J_i = ((i-1)/N, i/N]$, $1 \leq i \leq N$ are called sites. We view each node as a site which has been concentrated at a point in such a way that the distance between two neighboring nodes is constant and equal to the length of each site. We equivalently consider the two notions and say node as well as site.

In accordance with the precedent notation, S_i, I_i, R_i , and B_i are the number of susceptible, infectious, recovered, and bacterium on node i , respectively. Note that these quantities actually depend on the parameter N of the subdivision. Also, on a node i , the human total population is \mathbf{H}_i , and the water volume is W_i . Periodicity at the boundary allows us to consider that $S_{i+N} = S_i$ for all $i \in \mathbb{Z}$. The same holds for I_i, R_i, \dots

As previously, proportions are captured by rescaling. The average initial human total population on each site is

$$H = \frac{1}{N} \sum_{i=1}^N \mathbf{H}_i(0) = \frac{\mathbf{H}(0)}{N},$$

and we set $S_i^*(t) = S_i(t)/H$, $I_i^*(t) = I_i(t)/H$, $R_i^*(t) = R_i(t)/H$, and $B_i^*(t) = B_i(t)/K$. Henceforth, only rescaled variables are considered. Thus, we forget about the superscript $*$ in our notation and write S_i, I_i, \dots , instead of S^*, I^*, \dots . We make the following

Assumption 4.2.1.

(i) *The lattice is oriented and we fix an orientation, in order to perform precise computations: the direction of the edges follows the increasing numerical order of nodes index*

$$\dots (i-1) \longrightarrow i \longrightarrow (i+1) \dots$$

(ii) *Vibrios can move with a certain probability from a node to a connected node, through an inward or an outward edge, at a certain rate ℓ .*

Assumption 4.2.1 is not restrictive from regarding to the dimension of the spatial. In fact, the following tools we introduce are usable in a higher spatial dimensional context. We define:

- $d_{in}(i)$ the number of inward edges of node i ,
- $d_{out}(i)$ the number of outward edges of node i ,
- \mathcal{P}_{in} the transmission probability by an inward edge,
- \mathcal{P}_{out} the transmission probability by an outward edge.

Clearly, $d_{in}(i) = 1 = d_{out}(i)$ for all $i = 1, \dots, N$ in a one dimensional framework.

The probability that a propagule transits from a node i to another one j has the form:

$$\mathcal{P}_{ij} = \begin{cases} \frac{\mathcal{P}_{out}}{\mathcal{P}_{out}d_{out}(i) + \mathcal{P}_{in}d_{in}(i)} & \text{if } i \rightarrow j \\ \frac{\mathcal{P}_{in}}{\mathcal{P}_{out}d_{out}(i) + \mathcal{P}_{in}d_{in}(i)} & \text{if } i \leftarrow j \\ 0 & \text{otherwise.} \end{cases} \quad (4.2.8)$$

Of course, we have $\sum_{j=1}^N \mathcal{P}_{ij} = 1$, since $\mathcal{P}_{in} + \mathcal{P}_{out} = 1$.

Infectious propagules are removed at every node – at rate ℓ – and transported through the network following the transition probabilities (4.2.8). Hence, replacing probabilities with frequencies, the corresponding – in this spatial context – to the rescaled system (4.2.2) reads

$$\begin{cases} \frac{dS_i(t)}{dt} = \mu I_i(t) + (\mu + \rho)R_i(t) - \beta \frac{B_i(t)}{1 + B_i(t)} S_i(t) \\ \frac{dI_i(t)}{dt} = \beta \frac{B_i(t)}{1 + B_i(t)} S_i(t) - (\gamma + \alpha + \mu)I_i(t) \\ \frac{dR_i(t)}{dt} = \gamma I_i(t) - (\mu + \rho)R_i(t) \\ \frac{dB_i(t)}{dt} = -\mu_B B_i(t) + \frac{Hp}{KW_i} I(t) - \ell B_i(t) + \sum_{j=1}^N \ell \mathcal{P}_{ji} B_j(t) \frac{W_j}{W_i}. \end{cases} \quad (4.2.9)$$

In order to derive a continuous-space model, we introduce $b = \mathcal{P}_{out} - \mathcal{P}_{in} = 2\mathcal{P}_{out} - 1$, the bias of the transport to follow the edge direction (the reader is referred to [BCG⁺10] and references therein, for more details about the parameter b). We take the limit $N \rightarrow \infty$ under the conditions:

Assumption 4.2.2.

- (i) Water reservoir volume is constant on each site: $W_i = W$ for all $i = 1, \dots, N$.
- (ii) The transport rate ℓ scales with N^2 and we put $\mathfrak{D} = \ell/2N^2$.
- (iii) The product $b \cdot \ell$ is of order N and we put $\nu = b \cdot \ell/N$.

Then, as the site length goes to zero, we obtain the limit system of partial differential equations (PDEs)

$$\begin{cases} \frac{\partial S(t, x)}{\partial t} = \mu I(t, x) + (\mu + \rho)R(t, x) - \beta \frac{B(t, x)}{1 + B(t, x)} S(t, x) \\ \frac{\partial I(t, x)}{\partial t} = \beta \frac{B(t, x)}{1 + B(t, x)} S(t, x) - (\gamma + \alpha + \mu)I(t, x) \\ \frac{\partial R(t, x)}{\partial t} = \gamma I(t, x) - (\rho + \mu)R(t, x) \\ \frac{\partial B(t, x)}{\partial t} = -\mu_B B(t, x) + \frac{Hp}{KW} I(t, x) - \nu \frac{\partial B(t, x)}{\partial x} + \mathfrak{D} \frac{\partial^2 B(t, x)}{\partial x^2}, \end{cases} \quad (4.2.10)$$

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where $\mathfrak{D} > 0$ and $\nu > 0$ are respectively the diffusion coefficient and the advection velocity of the bacteria.

Well-posedness, generator and debit function. A compact form of (4.2.10) reads

$$\frac{dv(t)}{dt} = \tilde{A}v(t) + F(v(t)), \quad (4.2.11)$$

where $v = (S, I, R, B)$, $F = (F_S, F_I, F_R, F_B)$ is the debit of the homogeneous model and is given by (4.2.3), and, \tilde{A} is the diagonal matrix operator of size 4 on $(L^2)^4 = (L^2(J))^4$, given by

$$\tilde{A} = \text{diag}(0, 0, 0, A) \quad \text{with} \quad A = -\nu\nabla + \mathfrak{D}\Delta.$$

In our notation, 0 is the identically zero operator, ∇ is the gradient, Δ is the Laplace, and $L^2(J)$ is the space of square integrable real valued functions defined and periodic on J . It is endowed with its usual inner product

$$\langle f, g \rangle_2 = \int_J f(x)g(x)dx \quad \text{and the induced norm} \quad \|f\|_2 = \sqrt{\langle f, f \rangle_2}.$$

It is well known (see e.g. [Hen81], Chapter 3, or Chapter 2 of [Dia13]) that the differential operator A generates on $C(J)$ an analytical semigroup $\{T(t) = e^{At}, t \geq 0\}$ which is of contraction. Thus, \tilde{A} also generates an analytical semigroup on $C(J)^4$, and we denote it $\tilde{T}(t) = e^{\tilde{A}t}$. The following result of existence and uniqueness is derived then.

Proposition 4.2.1. *Consider (4.2.11) on $C(J)^4$, with an initial condition $v(0) = v_0 \in C(J)^3 \times C^3(J)$ such that $v_0 \geq 0$ and $\|v_0\|_{C(J)^4} < c_0$ for some $c_0 \gg 1$. We also consider periodic boundary conditions: $v_0(t, 0) = v_0(t, 1)$ for all $t \geq 0$. Then, the described Cauchy problem has a unique global mild solution $v \in C(\mathbb{R}_+; C(J)^3 \times C^3(J))$ satisfying*

$$v(t) = \tilde{T}(t)v_0 + \int_0^t \tilde{T}(t-s)F(v(s))ds \quad (4.2.12)$$

and $v(t) \geq 0$ for all $t \geq 0$, and, for all $T > 0$,

$$\sup_{t \leq T} \|v(t)\|_{C(J)^4} < c_T = c_0 e^{MT}. \quad (4.2.13)$$

We notice that in this context, one has in particular that $v \in \mathcal{AC}(\mathbb{R}_+; C(J)^4)$.

Proof. Positivity follows from (4.2.4) (i)-(ii), $v_0 \geq 0$ and the continuity of any solution. We restrict F to \mathbb{R}_+^4 . Thus, F is locally Lipschitz and from (4.2.4) (iii), there exists a unique local mild solution to (4.2.11), which lies in $C([0, T], C(J)^4)$ for all $T \in (0, T(c_0)]$ for some $T(c_0) > 0$. This follows using a Banach fixed point argument. Then, we obtain the bound (4.2.13) through a Gronwall bellman lemma, thanks to (4.2.4) (iii). Therefore, the solution is global. Finally, the solution actually lies in $C(\mathbb{R}_+; C(J)^3 \times C^3(J))$, since the initial condition satisfies $v_0 \in C(J)^3 \times C^3(J)$ and —the considered restriction of— F is of class C^∞ . \square

The infinitesimal generator of the model, or of (4.2.11), is given by

$$\mathcal{A}\varphi(u) = \langle D\varphi(u), \tilde{A}u + F(u) \rangle, \quad (4.2.14)$$

on the domain $C_b^1(C(J)^3 \times C^3(J))$. The associated debit function is the vector field in $C(J)^4$ defined by

$$\psi(u) = \tilde{A}u + F(u).$$

More precisely, $u \mapsto F(u)$ is the debit related to the fluctuations of v due to events that are spatially homogeneous, while $u \mapsto \tilde{A}u$ is the debit related to the fluctuations created by spatial motions. A much more specific decomposition is possible for ψ . It consists in writing $\psi = (\psi_S, \psi_I, \psi_R, \psi_B)$, where $\psi_S(u) = F_S$, $\psi_I(u) = F_I(u)$, $\psi_R(u) = F_R(u)$ and $\psi_B(u) = Au_B + F_B(u)$ are the debits related to the fluctuations of S , I , R , and B respectively, defined for all $u = (u_S, u_I, u_R, u_B) \in C(J)^3 \times C^3(J)$.

4.2.2 Stochastic spatial model

We now introduce the stochastic counterpart of $v = (S, I, R, B)$. The preceding subdivision of the spatial domain is considered. In order to model event randomness, as it is usual we use Poisson processes as random clock to capture events. For each site $i \in \{1, \dots, N\}$, proportions for compartments are denoted $u_{S,i}^N, u_{I,i}^N, u_{R,i}^N, u_{B,i}^N$. Recall that the parameter of renormalization is K (resp. $H = \mathbf{H}(0)/N$) for bacteria (resp. humans), so that

$$u_{B,i}^N = \frac{\text{number of bacteria on } i}{K}, \quad u_{S,i}^N = \frac{\text{number of susceptible on } i}{H}, \quad \dots$$

We have $u_{S,i}^N, u_{I,i}^N, u_{R,i}^N \in H^{-1}\mathbb{N}$ and $u_{B,i}^N \in K^{-1}\mathbb{N}$, where

$$H^{-1}\mathbb{N} = \{H^{-1}n, n \in \mathbb{N}\} \quad \text{and} \quad K^{-1}\mathbb{N} = \{K^{-1}n, n \in \mathbb{N}\}.$$

As previously, we are omitting the parameters H and K in our notation.

A pointwise modeling over the whole spatial domain is achieved for susceptible through the step function

$$u_S^N(t, x) = \sum_{i=1}^N u_{S,i}^N(t) \mathbf{1}_i(x), \quad t \geq 0, \quad x \in J,$$

where $\mathbf{1}_i(\cdot) = \mathbf{1}_{J_i}(\cdot)$ is the indicator function of the i -th site J_i . For the compartments (infected, recovered and bacteria), $u_S^N(t, x)$, $u_R^N(t, x)$ and $u_B^N(t, x)$ are defined in a similar way as $u_S^N(t, x)$. Using the standard identification $u_S^N(t) := u_S^N(t, \cdot)$, $u_I^N(t) := u_I^N(t, \cdot)$, ... we have $u_S^N(t), u_I^N(t), u_R^N(t), u_B^N(t) \in L^2(J)$. Finally, a global description including all the compartments is given by

$$u^N(t) = (u_S^N(t), u_I^N(t), u_R^N(t), u_B^N(t)),$$

which is our stochastic model. In absence of precision, we consider the natural completed filtration $\{\mathcal{F}_t^N, t \geq 0\}$, where $\mathcal{F}_t^N = \mathcal{F}_t^{N,H,K}$ is the completion of the σ -algebra $\sigma(\{u^N(s) : s \leq t\})$ with null probability measure sets.

Let $\mathbb{H}^N := \mathbb{H}^N(J)$ be the subspace of $L^2(J)$ which consists of real valued step functions that are constant on each site J_i . Introduce the canonical projection

$$\begin{aligned} P_N &: L^2 \longrightarrow \mathbb{H}^N \\ f &\longmapsto P_N f = \sum_{i=1}^N f_i \mathbf{1}_i, \quad \text{where} \quad f_i := N \int_{J_i} f(x) dx. \end{aligned} \tag{4.2.15}$$

Then, $(\mathbb{H}^N, \langle \cdot, \cdot \rangle_2)$ is an N -dimensional Hilbert space. An orthonormal basis of it is $\{e_i := \sqrt{N} \mathbf{1}_i, 1 \leq i \leq N\}$. The restriction on \mathbb{H}^N of the inner product of $L^2(J)$ is $\langle f, g \rangle_2 =$

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$\frac{1}{N} \sum_{i=1}^N f_i g_i$. Setting $\mathbb{H} = \cup_{N \geq 1} \mathbb{H}^N$, it is not difficult to see that $(\mathbb{H}, \langle \cdot, \cdot \rangle_2)$ is dense in $L^2(J)$. Indeed, every function $f \in L^2(J)$ can be approximated by the sequence $(P_N f)_N \subset \mathbb{H}$.

Furthermore, $(\mathbb{H}, \|\cdot\|_\infty)$ is dense in $(C_p(J), \|\cdot\|_\infty)$, the set of piecewise continuous real valued functions defined on J , endowed with the supremum norm $\|f\|_\infty = \sup_{x \in J} |f(x)|$. As our goal is to perform approximations in the supremum norm, we systematically consider $(\mathbb{H}^N, \|\cdot\|_\infty)$, unless we specify another topology.

In addition, we define \tilde{P}_N on $(L^2(J))^4$ by $(u^{(1)}, \dots, u^{(4)}) \mapsto \tilde{P}_N u = (P_N u^{(1)}, \dots, P_N u^{(4)})$, and introduce the notation $E_N = (\mathbb{H}^N)^4$, $E = C(J)^4$, $\tilde{E} = (L^2)^4$. The former and the latter are clearly Hilbert spaces when endowed with the inner product

$$\langle u, \tilde{u} \rangle_{\tilde{E}} = \sum_{j=1}^4 \langle u^{(j)}, \tilde{u}^{(j)} \rangle_2 \quad \text{and the induced norm} \quad \|u\|_{\tilde{E}} = \sum_{j=1}^4 \|u^{(j)}\|_2,$$

defined for $u = (u^{(1)}, \dots, u^{(4)})$, $\tilde{u} = (\tilde{u}^{(1)}, \dots, \tilde{u}^{(4)}) \in \tilde{E}$. Moreover, the space $\cup_{N \geq 1} E_N$ is dense in $(\tilde{E}, \|\cdot\|_{\tilde{E}})$. On the contrary, E_N and E are just Banach spaces, when equipped with the norm

$$\|u\|_E = \sum_{j=1}^4 \|u^{(j)}\|_\infty.$$

Still, density holds for $\cup_{N \geq 1} E_N$ in $(E, \|\cdot\|_E)$. Below, the Banach topology is considered by default.

Now, for all $t \geq 0$, the i -th coordinate of $u^N(t)$ with respect to the projection \tilde{P}_N is

$$u_i^N(t) = N \int_{J_i} u^N(t, x) dx = (u_{S,i}^N(t), u_{I,i}^N(t), u_{R,i}^N(t), u_{B,i}^N(t)),$$

so that $\tilde{P}_N u^N(t) = u^N(t)$ and

$$u^N(t, x) = \sum_{i=1}^N u_i^N(t) \mathbb{1}_i(x), \quad \forall x \in J.$$

Therefore, $u^N = \{u^N(t), t \geq 0\}$ is an E_N -valued jump Markov process. Its infinitesimal generator is given on the domain $C_b(E_N)$ by

$$\begin{aligned} \mathcal{A}^N \varphi(u) &= \mathcal{A}_S^N \varphi(u) + \mathcal{A}_{SI}^N \varphi(u) + \mathcal{A}_I^N \varphi(u) \\ &\quad + \mathcal{A}_{IR}^N \varphi(u) + \mathcal{A}_R^N \varphi(u) + \mathcal{A}_{RS}^N \varphi(u) + \mathcal{A}_B^N \varphi(u), \end{aligned} \quad (4.2.16)$$

where $u = (u_S, u_I, u_R, u_B)$,

$$\begin{aligned} &\mathcal{A}_S^N \varphi(u_S, u_I, u_R, u_B) \\ &= \sum_{i=1}^N \left\{ \left[\varphi \left(u_S + \frac{1}{H} \mathbb{1}_i, u_I, u_R, u_B \right) - \varphi(u_S, u_I, u_R, u_B) \right] H \mu_{u_S, i} \right. \\ &\quad + \left[\varphi \left(u_S + \frac{1}{H} \mathbb{1}_i, u_I, u_R, u_B \right) - \varphi(u_S, u_I, u_R, u_B) \right] H \mu_{u_I, i} \\ &\quad + \left[\varphi \left(u_S + \frac{1}{H} \mathbb{1}_i, u_I, u_R, u_B \right) - \varphi(u_S, u_I, u_R, u_B) \right] H \mu_{u_R, i} \\ &\quad \left. + \left[\varphi \left(u_S - \frac{1}{H} \mathbb{1}_i, u_I, u_R, u_B \right) - \varphi(u_S, u_I, u_R, u_B) \right] H \mu_{u_S, i} \right\}, \end{aligned} \quad (4.2.17)$$

$$\begin{aligned}
 & \mathcal{A}_{SI}^N \varphi(u_S, u_I, u_R, u_B) \\
 &= \sum_{i=1}^N \left[\varphi \left(u_S - \frac{1}{H} \mathbf{1}_i, u_I + \frac{1}{H} \mathbf{1}_i, u_R, u_B \right) - \varphi(u_S, u_I, u_R, u_B) \right] H \beta \frac{u_{B,i}}{1 + u_{B,i}} u_{S,i},
 \end{aligned} \tag{4.2.18}$$

$$\begin{aligned}
 & \mathcal{A}_I^N \varphi(u_S, u_I, u_R, u_B) \\
 &= \sum_{i=1}^N \left\{ \left[\varphi \left(u_S, u_I - \frac{1}{H} \mathbf{1}_i, u_R, u_B \right) - \varphi(u_S, u_I, u_R, u_B) \right] H \mu u_{I,i} \right. \\
 & \quad \left. + \left[\varphi \left(u_S, u_I - \frac{1}{H} \mathbf{1}_i, u_R, u_B \right) - \varphi(u_S, u_I, u_R, u_B) \right] H \alpha u_{I,i} \right\},
 \end{aligned} \tag{4.2.19}$$

$$\begin{aligned}
 & \mathcal{A}_{IR}^N \varphi(u_S, u_I, u_R, u_B) \\
 &= \sum_{i=1}^N \left[\varphi \left(u_S, u_I - \frac{1}{H} \mathbf{1}_i, u_R + \frac{1}{H} \mathbf{1}_i, u_B \right) - \varphi(u_S, u_I, u_R, u_B) \right] H \gamma u_{I,i},
 \end{aligned} \tag{4.2.20}$$

$$\begin{aligned}
 & \mathcal{A}_R^N \varphi(u_S, u_I, u_R, u_B) \\
 &= \sum_{i=1}^N \left[\varphi \left(u_S, u_I, u_R - \frac{1}{H} \mathbf{1}_i, u_B \right) - \varphi(u_S, u_I, u_R, u_B) \right] H \mu u_{R,i},
 \end{aligned} \tag{4.2.21}$$

$$\begin{aligned}
 & \mathcal{A}_{RS}^N \varphi(u_S, u_I, u_R, u_B) \\
 &= \sum_{i=1}^N \left[\varphi \left(u_S + \frac{1}{H} \mathbf{1}_i, u_I, u_R - \frac{1}{H} \mathbf{1}_i, u_B \right) - \varphi(u_S, u_I, u_R, u_B) \right] H \rho u_{R,i},
 \end{aligned} \tag{4.2.22}$$

and finally

$$\begin{aligned}
 & \mathcal{A}_B^N \varphi(u_S, u_I, u_R, u_B) \\
 &= \sum_{i=1}^N \left\{ \left[\varphi \left(u_S, u_I, u_R, u_B - \frac{1}{K} \mathbf{1}_i \right) - \varphi(u_S, u_I, u_R, u_B) \right] K \mu_B u_{B,i} \right. \\
 & \quad + \left[\varphi \left(u_S, u_I, u_R, u_B + \frac{1}{K} \mathbf{1}_i \right) - \varphi(u_S, u_I, u_R, u_B) \right] \frac{H p}{W} u_{I,i} \\
 & \quad + \left[\varphi \left(u_S, u_I, u_R, u_B + \frac{\mathbf{1}_{i+1} - \mathbf{1}_i}{K} \right) - \varphi(u_S, u_I, u_R, u_B) \right] K \ell \mathcal{P}_{out} u_{B,i} \\
 & \quad \left. + \left[\varphi \left(u_S, u_I, u_R, u_B + \frac{\mathbf{1}_{i-1} - \mathbf{1}_i}{K} \right) - \varphi(u_S, u_I, u_R, u_B) \right] K \ell \mathcal{P}_{in} u_{B,i} \right\}.
 \end{aligned} \tag{4.2.23}$$

The generator \mathcal{A}^N can be extended to a generator $\bar{\mathcal{A}}^N$ on $C_b(\tilde{E})$, using the projection \tilde{P}_N as follows:

$$\bar{\mathcal{A}}^N \varphi(u) := \mathcal{A}^N \varphi(\tilde{P}_N u),$$

for $u \in \tilde{E} = (L^2(J))^4$. We do not distinguish between the two generators and use the notation \mathcal{A}^N for both.

By construction, when started at a positive state $u^N(0) \in (H^{-1}\mathbb{N}) \times K^{-1}\mathbb{N}$, the process u^N lies in the same set, and thus keeps positive values. We assume that our process starts from

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such a state in the sequel.

From preceding discussions, we know that the debit function of u^N is the vector field $\psi^N = (\psi_S^N, \psi_I^N, \psi_R^N, \psi_B^N)$ in $E_N = (\mathbb{H}^N)^4$, such that:

$$\begin{aligned}\psi_S^N(u_S, u_I, u_R, u_B) &= \sum_{i=1}^N \left[\mu u_{I,i} + (\mu + \rho) u_{R,i} - \beta \frac{u_{B,i}}{1 + u_{B,i}} u_{S,i} \right] \mathbf{1}_i \\ &= \mu u_I + (\mu + \rho) u_R - \beta \frac{u_B}{1 + u_B} u_S = F_S(u_S, u_I, u_R, u_B)\end{aligned}\quad (4.2.24)$$

is the debit related to susceptibles,

$$\begin{aligned}\psi_I^N(u_S, u_I, u_R, u_B) &= \sum_{i=1}^N \left[\beta \frac{u_{B,i}}{1 + u_{B,i}} u_{S,i} - (\mu + \alpha + \gamma) u_{I,i} \right] \mathbf{1}_i \\ &= \beta \frac{u_B}{1 + u_B} u_S - (\mu + \alpha + \gamma) u_I = F_I(u_S, u_I, u_R, u_B)\end{aligned}\quad (4.2.25)$$

is the debit related to infected,

$$\begin{aligned}\psi_R^N(u_S, u_I, u_R, u_B) &= \sum_{i=1}^N [\gamma u_{I,i} - (\mu + \rho) u_{R,i}] \mathbf{1}_i \\ &= \gamma u_I - (\mu + \rho) u_R = F_R(u_S, u_I, u_R, u_B)\end{aligned}\quad (4.2.26)$$

is the debit related to recovered, and lastly,

$$\begin{aligned}\psi_B^N(u_S, u_I, u_R, u_B) &= \sum_{i=1}^N \left[-\mu_B u_{B,i} \mathbf{1}_i + \frac{Hp}{KW} u_{I,i} \mathbf{1}_i + (\mathbf{1}_{i+1} - \mathbf{1}_i) \ell \mathcal{P}_{out} u_{B,i} + (\mathbf{1}_{i-1} - \mathbf{1}_i) \ell \mathcal{P}_{in} u_{B,i} \right] \\ &= \sum_{i=1}^N \left[-\mu_B u_{B,i} + \frac{Hp}{KW} u_{I,i} + \ell (u_{B,i-1} - u_{B,i}) \mathcal{P}_{out} + \ell (u_{B,i+1} - u_{B,i}) \mathcal{P}_{in} \right] \mathbf{1}_i \\ &= \sum_{i=1}^N \left\{ -\mu_B u_{B,i} + \frac{Hp}{KW} u_{I,i} + \frac{\ell}{2N^2} [N^2 (u_{B,i-1} - 2u_{B,i} + u_{B,i+1})] \right. \\ &\quad \left. - \frac{\ell}{N} (\mathcal{P}_{out} - \mathcal{P}_{in}) \left[\frac{N}{2} (u_{B,i+1} - u_{B,i-1}) \right] \right\} \\ &= -\mu_B u_B + \frac{Hp}{KW} u_I + (-\nu \nabla_N + \mathfrak{D} \Delta_N) u_B = F_B(u_S, u_I, u_R, u_B) + A_N u_B\end{aligned}\quad (4.2.27)$$

is the debit related to bacteria. The second equality of (4.2.27) is obtained using a change of index and periodicity, and the next one follows from the identity $\mathcal{P}_{in} + \mathcal{P}_{out} = 1$. The coefficients $\nu = \ell \cdot b/N$ and $\mathfrak{D} = \ell/2N^2$ are the advection and diffusion coefficients introduced in Assumption 4.2.2. The operator $A_N = -\nu \nabla_N + \mathfrak{D} \Delta_N$ is a discretization of the operator A defined by (4.2.11). Here, ∇_N and Δ_N are respectively the centered, discrete, gradient and Laplace operators, defined on $L^2(J)$. The former is given by

$$\nabla_N f(x) = \frac{N}{2} \left[f \left(x + \frac{1}{N} \right) - f \left(x - \frac{1}{N} \right) \right].$$

Concerning the latter, we first introduce the uncentered discrete gradients

$$\nabla_N^+ f(x) = N \left[f \left(x + \frac{1}{N} \right) - f(x) \right] \quad \text{and} \quad \nabla_N^- f(x) = N \left[f(x) - f \left(x - \frac{1}{N} \right) \right].$$

Then, we define the centered discrete Laplace by

$$\begin{aligned}\Delta_N f(x) &= \nabla_N^+ \nabla_N^- f(x) \\ &= \nabla_N^- \nabla_N^+ f(x) = N^2 \left[f\left(x + \frac{1}{N}\right) - 2f(x) + f\left(x - \frac{1}{N}\right) \right].\end{aligned}$$

If $f \in \mathbb{H}^N$ in particular, then periodicity yields

$$\nabla_N f = \frac{N}{2} \sum_{i=1}^N (f_{i+1} - f_{i-1}) \mathbb{1}_i \quad \text{and} \quad \Delta_N f = N^2 \sum_{i=1}^N (f_{i+1} - 2f_i + f_{i-1}) \mathbb{1}_i.$$

Hence, a compact formulation of the debit is

$$\psi^N(u) = \tilde{A}_N u + F(u)$$

for all $u \in E_N = (\mathbb{H}^N)^4$, where F is the homogeneous case debit given by (4.2.3), and $\tilde{A}_N = \text{diag}(0, 0, 0, A_N)$ is a diagonal matrix operator on E_N . This latter is a discretization of the operator \tilde{A} given by (4.2.11).

The debit ψ^N can also be extended to $\tilde{E} = (L^2(J))^4$, by $u \mapsto \psi^N(\tilde{P}_N u)$.

Formal limit of the generator

We study the asymptotic behavior of the sequence \mathcal{A}^N of generators defined by (4.2.16), as N , $\mathbf{H}(0)$, and K go to infinity, since we are interested in space-continuous and in large population asymptotics. The asymptotic $\mathbf{H}(0) \rightarrow \infty$ is studied through the parameter $H = \mathbf{H}(0)/N$. For a start, we consider $H \rightarrow \infty$ and $H/K \rightarrow \text{constant} > 0$. The former condition means that $\mathbf{H}(0)$ grows to the infinity much faster than N . The latter condition states that human population scales with that of bacteria.

We consider $L^2(J)$ framework, and the domain $\mathcal{T} = C_b^2(\tilde{E})$ of test functions $\varphi \in C_b(\tilde{E})$ such that:

- (T1) φ is twice continuously Fréchet-differentiable w.r.t. each of its variables,
- (T2) φ is bounded and has bounded successive differentials.

For all $\varphi \in \mathcal{T}$, denote by :

- $\|D\varphi\|_\infty$ a uniform bound common to the differentials of φ w.r.t. its variables,
- $\|D^2\varphi\|_\infty$ the counterpart of $\|D\varphi\|_\infty$ for the second differentials of φ .

Then we proceed to a Taylor expansion of the test function $\varphi \in \mathcal{T}$. Then we plug it into the expression of \mathcal{A}^N and derive term by term, a formal limit for this latter. Let $u = (u_S, u_I, u_R, u_B) \in E$ be fixed.

At first order. We already know that all the terms put together correspond to the product of the differential of φ and the debit ψ^N . From (4.2.24)–(4.2.27), we have:

$$\begin{aligned}\mathcal{A}^{N,1}\varphi(u) &= \left\langle D\varphi(\tilde{P}_N u), \psi^N(\tilde{P}_N u) \right\rangle_2 = \left\langle D\varphi(\tilde{P}_N u), \tilde{A}_N \tilde{P}_N u + F(\tilde{P}_N u) \right\rangle_2 \\ &= \left\langle D_{u_S}\varphi(\tilde{P}_N u), F_S(\tilde{P}_N u) \right\rangle_2 + \left\langle D_{u_I}\varphi(\tilde{P}_N u), F_I(\tilde{P}_N u) \right\rangle_2 \\ &\quad + \left\langle D_{u_R}\varphi(\tilde{P}_N u), F_R(\tilde{P}_N u) \right\rangle_2 + \left\langle D_{u_B}\varphi(\tilde{P}_N u), A_N P_N u_B + F_B(\tilde{P}_N u) \right\rangle_2.\end{aligned}$$

4.2 Modeling and convergence tools

If u is $C^3(J)$, then from the continuity of F and that of the differential, $\mathcal{A}^{N,1}\varphi(u)$ converges to

$$\begin{aligned} \mathcal{A}^\infty\varphi(u) &= \langle D_{u_S}\varphi(u), F_S(u) \rangle_2 + \langle D_{u_I}\varphi(u), F_I(u) \rangle_2 \\ &\quad + \langle D_{u_R}\varphi(u), F_R(u) \rangle_2 + \langle D_{u_B}\varphi(u), F_B(u) + Au_B \rangle_2 \\ &= \langle D\varphi(u), \tilde{A}u + F(u) \rangle_2 = \langle D\varphi(u), \psi(u) \rangle_2. \end{aligned} \quad (4.2.28)$$

In the limit above, $N, H, K \rightarrow \infty$ and the ratio $\frac{H}{K}$ remains constant. The second condition gives consistency to the limit obtained in the deterministic spatial model, for the coefficient $\frac{Hp}{KW}$ appearing in the expression of the debit function related to bacteria. That coefficient is involved in the transfer of bacteria from infected people to water reservoirs. It is the rescaled rate at which one person contribute to the population of bacteria.

At the second order. We prove that each term vanishes at the limit, under the additional assumption that $u^N(t)$ is bounded uniformly in N , on each interval $[0, T]$ and denote by \bar{u} an upperbound of the u^N . Further, we free ourselves from that ad hoc assumption which is not needed to prove our result. In the upcoming, c denotes a generic constant. Recall that $e_i = \sqrt{N}\mathbf{1}_i$ is an orthonormal basis of $(\mathbb{H}^N, \langle \cdot, \cdot \rangle_2)$. Let us get started with the part \mathcal{A}_{IR}^N of the generator given by (4.2.20). We have

$$\begin{aligned} \mathcal{A}_{IR}^{N,2}\varphi(u) &= \frac{1}{2} \sum_{i=1}^N \left[D_{u_S}^2\varphi(\tilde{P}_Nu) \cdot \left\langle \frac{1}{H}\mathbf{1}_i, \frac{1}{H}\mathbf{1}_i \right\rangle_2 + D_{u_S u_R}^2\varphi(\tilde{P}_Nu) \cdot \left\langle \frac{1}{H}\mathbf{1}_i, -\frac{1}{H}\mathbf{1}_i \right\rangle_2 \right. \\ &\quad \left. + D_{u_R}^2\varphi(\tilde{P}_Nu) \cdot \left\langle \frac{1}{H}\mathbf{1}_i, \frac{1}{H}\mathbf{1}_i \right\rangle_2 \right] H\gamma u_{R,i} \\ &\leq \frac{\bar{u}\gamma}{2} \|D^2\varphi\|_\infty \frac{1}{HN} \sum_{i=1}^N \|e_i\|_2^2 \leq \frac{c}{H} \rightarrow 0. \end{aligned}$$

The limit above only requires $H \rightarrow \infty$.

The other parts of the generator \mathcal{A}_S^N , \mathcal{A}_{SI}^N , \mathcal{A}_I , \mathcal{A}_R and \mathcal{A}_{RS}^N given by (4.2.17)-(4.2.22), without (4.2.20), are similar and also vanish at the limit $H \rightarrow \infty$, using the same argument.

Now we treat the part \mathcal{A}_B^N given by (4.2.23). For $k = 1, \dots, 4$, denote by $T_{B,k}^N$ the second order term corresponding to the k -th line in its expression. Firstly, $T_{B,1}^N$ vanishes, using the same argument as above, however, requiring $K \rightarrow \infty$ instead of $H \rightarrow \infty$. Next,

$$\begin{aligned} T_{B,2}^N &= \frac{1}{2} \sum_{i=1}^N D_{u_B}^2\varphi(\tilde{P}_Nu) \cdot \left\langle \frac{1}{K}\mathbf{1}_i, \frac{1}{K}\mathbf{1}_i \right\rangle_2 \frac{Hp}{W} u_{I,i} \\ &\leq \frac{\bar{u}p}{2w} \|D^2\varphi\|_\infty \frac{H}{K^2} \frac{1}{N} \sum_{i=1}^N \|e_i\|_2^2 \leq c \frac{H}{K^2} \rightarrow 0. \end{aligned}$$

The limit above holds in particular when H/K is kept constant as $H, K \rightarrow \infty$. Afterwards, observing that $\|\mathbf{1}_{i\pm 1} - \mathbf{1}_i\|_2^2 = 2/N$,

$$\begin{aligned} T_{B,3}^N &= \frac{1}{2} \sum_{i=1}^N D_{u_B}^2\varphi(\tilde{P}_Nu) \cdot \left\langle \frac{\mathbf{1}_{i+1} - \mathbf{1}_i}{K}, \frac{\mathbf{1}_{i+1} - \mathbf{1}_i}{K} \right\rangle_2 K\ell \mathcal{P}_{out} u_{B,i} \\ &\leq \frac{\bar{u}}{2} \|D^2\varphi\|_\infty \frac{\ell}{K} \sum_{i=1}^N \|\mathbf{1}_{i\pm 1} - \mathbf{1}_i\|_2^2 \leq c \frac{\ell}{K} \rightarrow 0, \end{aligned}$$

if $\ell/K \rightarrow 0$ as $K \rightarrow \infty$. According to the considerations in the deterministic model, ℓ should be thought as being of order N^2 . Therefore, the term $T_{B,3}^N$ vanishes if $N^2/K \rightarrow 0$ as $N, K \rightarrow \infty$. The last terms $T_{B,4}^N$ also converges to 0, using exactly the same argument as for $T_{B,3}^N$.

Hence, if $N, H, K \rightarrow \infty$ such that $K^{-1}N^2 \rightarrow 0$ and $H/K > 0$ is kept constant, then all the terms of the second order in the Taylor expansion vanish at the limit and consequently, \mathcal{A}^∞ is the limit of \mathcal{A}^N . Note that the condition $K^{-1}N^2 \rightarrow 0$ is equivalent to $H^{-1}N^2 \rightarrow 0$ as soon as $H/K \rightarrow \text{constant} > 0$. Below, we will see that the preceding condition is not needed at all.

The limiting problem

The limit generator \mathcal{A}^∞ given by (4.2.28) is well defined on the domain $C_b^1(C(J)^3 \times C^3(J))$. It coincides with the generator \mathcal{A} given by (4.2.14). Therefore, the differential equation associated with \mathcal{A}^∞ is the same as equation (4.2.11), and thus, has a unique solution v under the assumptions of Proposition 4.2.1. These observations strongly suggest that the stochastic spatial model u^N converges to the corresponding deterministic spatial model v . We rigorously prove this below, replacing the strong condition $K^{-1}N^2 \rightarrow \infty$ by the much weaker condition $K^{-1} \log N \rightarrow \infty$.

Instead of working directly with v , we consider a discrete version $v^N = (v_S^N, v_I^N, v_R^N, v_B^N)$ of it, defined by the ODE:

$$\begin{cases} \frac{dv^N(t)}{dt} = \tilde{A}_N v^N(t) + F(v^N(t)) \\ v^N(0) = \tilde{P}_N v_0. \end{cases} \quad (4.2.29)$$

Let $T_N(t) = e^{A_N t}$ be the semigroup of A_N , and let $\tilde{T}_N(t) = e^{\tilde{A}_N t}$ be that of \tilde{A}_N . These are of contraction on $(\mathbb{H}^N, \|\cdot\|_\infty)$ and on $(E_N, \|\cdot\|_E)$ respectively, and we claim the following.

Theorem 4.2.1. *The initial condition problem (4.2.29) has a unique global mild solution $v^N \in C(\mathbb{R}_+; E_N)$, satisfying $v^N(t) \geq 0$ and*

$$v^N(t) = \tilde{T}_N(t) \tilde{P}_N v_0 + \int_0^t \tilde{T}_N(t-s) F(v^N(s)) ds \quad (4.2.30)$$

for all $t \geq 0$. Moreover, for every $T > 0$,

$$\sup_{t \leq T} \|v^N(t)\|_E \leq c_T = c_0 e^{MT} \quad (4.2.31)$$

and

$$\lim_{N \rightarrow \infty} \sup_{t \in [0, T]} \|v^N(t) - v(t)\|_E = 0. \quad (4.2.32)$$

The proof is postponed to Section 4.5.1.

4.3 The law of large numbers

We state and prove the result about the convergence of the stochastic spatial model to the corresponding deterministic one.

4.3 The law of large numbers

Theorem 4.3.1. Consider a sequence $u^N = (u_S^N, u_I^N, u_R^N, u_B^N)$ of Markov processes starting at $u^N(0) = (u_S^N(0), u_I^N(0), u_R^N(0), u_B^N(0))$, with the infinitesimal generators \mathcal{A}^N given by (4.2.16). Assume that:

(i) $N, H, K \rightarrow \infty$ in such a way that H/K remains constant and nonnegative, and $K^{-1} \log N \rightarrow 0$ or, equivalently, $H^{-1} \log N \rightarrow 0$.

(ii) The assumptions of Proposition 4.2.1 hold and v is the solution of (4.2.11).

(iii) $u^N(0) \in (H^{-1}\mathbf{N})^3 \times K^{-1}\mathbf{N}$ and $\|u^N(0) - v(0)\|_E \rightarrow 0$ in probability.

Then, for all $T > 0$,

$$\sup_{t \leq T} \|u^N(t) - v(t)\|_E \rightarrow 0 \text{ in probability.}$$

Proof. Fix $T > 0$. We want to prove that for all $\epsilon > 0$,

$$\mathbb{P} \left\{ \sup_{t \leq T} \|u^N(t) - v(t)\|_E > \epsilon \right\} \rightarrow 0.$$

In view of Theorem 4.2.1, we may work with v^N rather than v .

The rest of the proof is divided in two steps. We first truncate the stochastic model and replace it by its truncation. Then, we conclude with a Gronwall argument.

4.3.1 Truncation

Set

$$\tau = \tau(N, \epsilon_0) = \inf \{t \geq 0 : \|u^N(t) - v^N(t)\|_E > \epsilon_0\},$$

for fixed $\epsilon_0 \in (0, 1)$, and define $\bar{u}^N = (\bar{u}_S^N, \bar{u}_I^N, \bar{u}_R^N, \bar{u}_B^N)$ by

$$\begin{cases} \bar{u}^N(t) = u^N(t \wedge \tau) & \text{for } 0 \leq t \leq \tau \leq \infty, \\ \bar{u}^N(t) = u^N(t \wedge \tau) + \int_{t \wedge \tau}^t \left(\tilde{A}_N \bar{u}^N(s) + F(\bar{u}^N(s)) \right) ds & \text{for } \tau < t < \infty. \end{cases} \quad (4.3.1)$$

Then, τ is a stopping time such that

$$\begin{aligned} \mathbb{P} \left\{ \sup_{t \leq T} \|u^N(t) - v^N(t)\|_E > \epsilon_0 \right\} &\leq \mathbb{P} \left\{ \sup_{t \leq T} \|u^N(t \wedge \tau) - v^N(t \wedge \tau)\|_E > \epsilon_0 \right\} \\ &\leq \mathbb{P} \left\{ \sup_{t \leq T} \|\bar{u}^N(t) - v^N(t)\|_E > \epsilon_0 \right\}. \end{aligned}$$

Therefore, we may work with \bar{u}^N instead of u^N .

Boundedness and Lipschitz debits. The truncated process \bar{u}^N has the same dynamic as u^N until time τ , and follows the flow of an ODE after time τ if $\tau < \infty$. We then can derive that,

$$0 \leq \bar{u}^N(t, x) \leq C_T = (c_0 + 1)e^{2MT}, \quad \forall t \leq T, \forall x \in J. \quad (4.3.2)$$

Indeed, $u^N(0) \geq 0$ and from Proposition 4.2.1, we know that $0 \leq v(t, x) \leq c_T = c_0 e^{MT}$ for all $(t, x) \in [0, T] \times J$. Since we are assuming $\|u^N(0) - v(0)\|_E \rightarrow 0$ in probability, we may, by conditioning on $\|u^N(0)\|_E < c_T + 1$ if necessary, assume without loss of generality that

$$0 \leq u^N(0, x) < c_T + 1 \quad \forall x \in J, \forall N.$$

From Proposition 4.2.1 and Theorem 4.2.1, we have $\sup_{t \leq T} \|v^N(t)\|_E \leq c_T + \frac{1}{2}$. Therefore, by definition of τ , for $\epsilon_0 < \frac{1}{2}$,

$$\|u^N(t \wedge \tau, x)\|_E \leq c_T + 1, \quad \text{for } 0 \leq t \leq \tau.$$

Now, if $\tau < T < \infty$, for all $t \in (\tau, T]$, (4.2.4) (iii) yields

$$\|\bar{u}^N(t)\|_E \leq \|\bar{u}^N(\tau)\|_E + M \int_{\tau}^t \|\bar{u}^N(s)\|_E ds \leq (c_T + 1)e^{MT} < (c_0 + 1)e^{2MT},$$

using Gronwall lemma. \square

As a result, we consider the restriction of the function F to the compact set $[0, C_T]^4$ of \mathbb{R}^4 , and consider that F is bounded in the following, by a constant $M_F(C_T) > 0$. Furthermore, F is globally Lipschitz on that compact set and we let $L_F(C_T)$ be a consequent Lipschitz constant.

Accompanying martingales. Let us introduce some useful notions and notation. First, for every node $i = 1, \dots, N$ and all $t \geq 0$, define the jump

$$\delta u_i^N(t) := u_i^N(t) - u_i^N(t^-)$$

of u_i^N at time t . Then denote by $|\delta u_i^N(t)|$ the amplitude of that jump, where $|(y_1, \dots, y_4)| = |y_1| + \dots + |y_4|$. Next, we define the *square amplitude* $|\psi_S^N|_i^2$ (resp. $|\psi_B^N|_i^2$) of $\psi_{S,i}^N$ (resp. $\psi_{B,i}^N$), as the debit function of the process

$$\left(H \sum_{s \leq t} |\delta S_i^N(s)|^2 \right)_{t \geq 0} \quad \left[\text{resp.} \quad \left(K \sum_{s \leq t} |\delta B_i^N(s)|^2 \right)_{t \geq 0} \right].$$

We similarly define the *square amplitudes* related to the compartments of infected and recovered, accordingly. We have:

- $|\psi_S^N|_i^2(u) = |F_S|_i^2(u) = \mu u_{I,i} + (\mu + \rho) u_{R,i} + \beta \frac{u_{B,i}}{1 + u_{B,i}} u_{S,i}$
- $|\psi_I^N|_i^2(u) = |F_I|_i^2(u) = \beta \frac{u_{B,i}}{1 + u_{B,i}} u_{S,i} + (\mu + \alpha + \gamma) u_{I,i}$
- $|\psi_R^N|_i^2(u) = |F_R|_i^2(u) = \gamma u_{I,i} + (\mu + \rho) u_{R,i}$
- $|\psi_B^N|_i^2(u) = |A_N|_i^2(u) + |F_B|_i^2(u),$

where

$$|F_B|_i^2(u) = \mu u_{B,i} + r \frac{p}{W} u_{I,i} \quad \text{and} \quad |A_N|_i^2(u) = \ell(\mathcal{P}_{in} u_{B,i+1} + u_{B,i} + \mathcal{P}_{out} u_{B,i-1}).$$

Also, we set $|\psi^N|_i^2(u) = (|\psi_S^N|_i^2 + |\psi_I^N|_i^2 + |\psi_R^N|_i^2 + |\psi_B^N|_i^2)(u)$.

Therewith, since spatial correlations induce simultaneous jumps on the nodes i and $i \pm 1$, the process

$$\left(K \sum_{s \leq t} [\delta B_i^N(s)] [\delta B_{i \pm 1}^N(s)] \right)_{t \geq 0},$$

with crossed products, is also of interest. Its debit $|\psi_B^N|_i |\psi_B^N|_{i \pm 1}$ is given by

- $|\psi_B^N|_i |\psi_B^N|_{i+1}(u) = -\ell(\mathcal{P}_{out} u_{B,i} + \mathcal{P}_{in} u_{B,i+1})$
- $|\psi_B^N|_i |\psi_B^N|_{i-1}(u) = -\ell(\mathcal{P}_{in} u_{B,i} + \mathcal{P}_{out} u_{B,i-1}).$

4.3 The law of large numbers

In addition, we introduce at last, the *square amplitude function* $|\psi^N|^2$ associated with the debit ψ^N . It is the \mathbb{H}^N -valued function defined by

$$|\psi^N|^2(u) = \sum_{i=1}^N |\psi^N|_i^2(u) \mathbf{1}_i.$$

The *square amplitude function* can be easily derived for each of the specific debit functions introduced above. Concerning $\psi_S^N = F_S$ for instance, it is given by

$$|\psi_S^N|^2(u)(x) = |F_S|^2(u)(x) = \sum_{i=1}^N |F_S|_i^2(u) \mathbf{1}_i(x).$$

The others are derived accordingly.

Now, we move on to the so-called accompanying martingales. As the stopping time τ satisfies

$$\sup_{t \leq T} \|u^N(t \wedge \tau)\|_E \leq \sup_{t \leq T} \|\bar{u}^N(t)\|_E < \infty \leq C_T,$$

various types of martingales can be pointed out, that are associated to the stopped Markov process $u^N(t \wedge \tau)$. Define the process $Z^N = (Z_S^N, Z_I^N, Z_R^N, Z_B^N)$ by

$$Z^N(t) = u^N(t) - u^N(0) - \int_0^t \psi^N(u^N(s)) ds, \quad (4.3.3)$$

where

$$Z_S^N(t) = u_S^N(t) - u_S^N(0) - \int_0^t \psi_S^N(u^N(s)) ds,$$

and the other components are defined accordingly. It is well known that $Z^N(t \wedge \tau)$ defines an E_N -valued mean zero \mathcal{F}_t^N -martingale, so that $Z_S^N(t \wedge \tau)$, $Z_I^N(t \wedge \tau)$, $Z_R^N(t \wedge \tau)$ and $Z_B^N(t \wedge \tau)$ are \mathbb{H}^N -valued mean zero \mathcal{F}_t^N -martingales. We denote these as *Zero-type associated martingales*. In other words, debit functions are martingale parts of the Markov processes they are associated with. This statement is the basis of what follows.

Lemma 4.3.1. (Martingales of type 1)

For every $i = 1, \dots, N$, the following are mean zero \mathcal{F}_t^N -martingales:

- (i) $\sum_{s \leq t \wedge \tau} [\delta u_{S,i}^N(s)]^2 - \frac{1}{H} \int_0^{t \wedge \tau} |\psi_S^N|_i^2(u^N(s)) ds,$
- (ii) $\sum_{s \leq t \wedge \tau} [\delta u_{I,i}^N(s)]^2 - \frac{1}{H} \int_0^{t \wedge \tau} |\psi_I^N|_i^2(u^N(s)) ds,$
- (iii) $\sum_{s \leq t \wedge \tau} [\delta u_{R,i}^N(s)]^2 - \frac{1}{H} \int_0^{t \wedge \tau} |\psi_R^N|_i^2(u^N(s)) ds,$
- (iv) $\sum_{s \leq t \wedge \tau} [\delta u_{B,i}^N(s)]^2 - \frac{1}{K} \int_0^{t \wedge \tau} |\psi_B^N|_i^2(u^N(s)) ds,$
- (v) $\sum_{s \leq t \wedge \tau} [\delta u_{B,i}^N(s)] [\delta u_{B,i \pm 1}^N(s)] - \frac{1}{K} \int_0^{t \wedge \tau} [\psi_B^N]_{i,i \pm 1}(u^N(s)) ds.$

Lemma 4.3.2. (Martingales of type 2)

Let $f \in \mathbb{H}^N$. For all $i = 1, \dots, N$, the following are mean zero \mathcal{F}_t^N -martingales:

$$\begin{aligned}
 (i) \quad & \sum_{s \leq t \wedge \tau} [\delta \langle Z_S^N(s), f \rangle_2]^2 - \frac{1}{NH} \int_0^{t \wedge \tau} \langle |\psi_S^N|^2(u^N(s)), f^2 \rangle_2 ds \\
 (ii) \quad & \sum_{s \leq t \wedge \tau} [\delta \langle Z_I^N(s), f \rangle_2]^2 - \frac{1}{NH} \int_0^{t \wedge \tau} \langle |\psi_I^N|^2(u^N(s)), f^2 \rangle_2 ds \\
 (iii) \quad & \sum_{s \leq t \wedge \tau} [\delta \langle Z_R^N(s), f \rangle_2]^2 - \frac{1}{NH} \int_0^{t \wedge \tau} \langle |\psi_R^N|^2(u^N(s)), f^2 \rangle_2 ds \\
 (iv) \quad & \sum_{s \leq t \wedge \tau} [\delta \langle Z_B^N(s), f \rangle_2]^2 - \frac{1}{NK} \int_0^{t \wedge \tau} \left[\langle u_B^N(s), \mathcal{D} \left((\nabla_N^+ f)^2 \mathcal{P}_{out} + (\nabla_N^- f)^2 \mathcal{P}_{in} \right) \rangle_2 \right. \\
 & \quad \left. + \langle |F_B|^2(u^N(s)), f^2 \rangle_2 \right] ds.
 \end{aligned}$$

The proves of Lemma 4.3.1 and of Lemma 4.3.2 are similar to those of their counterparts in chapter 2: Lemma 2.3.1 and Lemma 2.3.2 respectively.

Jump estimates. By definition, the truncated process satisfies

$$\bar{u}^N(t) = u^N(0) + \int_0^t \left(\tilde{A}_N \bar{u}^N(s) + F(\bar{u}^N(s)) \right) ds + Z^N(t \wedge \tau), \quad (4.3.4)$$

and its jumps have the bounds:

$$\begin{cases}
 \|\delta \bar{u}_S^N(t)\|_\infty = \|\delta Z_S^N(t \wedge \tau)\|_\infty = \|\delta u_{S,i}^N(t \wedge \tau)\|_\infty = H^{-1} \\
 \|\delta \bar{u}_I^N(t)\|_\infty = \|\delta Z_I^N(t \wedge \tau)\|_\infty = \|\delta u_{I,i}^N(t \wedge \tau)\|_\infty = H^{-1} \\
 \|\delta \bar{u}_R^N(t)\|_\infty = \|\delta Z_R^N(t \wedge \tau)\|_\infty = \|\delta u_{R,i}^N(t \wedge \tau)\|_\infty = H^{-1} \\
 \|\delta \bar{u}_B^N(t)\|_\infty = \|\delta Z_B^N(t \wedge \tau)\|_\infty = \|\delta u_{B,i}^N(t \wedge \tau)\|_\infty = K^{-1}
 \end{cases} \quad (4.3.5)$$

for all $t \geq 0$.

From now on, we consider the truncated process and write $\bar{u}^N = u^N$ in order to simplify our notation.

4.3.2 A Gronwall-Bellman argument

We study the difference

$$u^N(t) - v^N(t) = (u_S^N(t) - v_S^N(t), u_I^N(t) - v_I^N(t), u_R^N(t) - v_R^N(t), u_B^N(t) - v_B^N(t)).$$

where we recall u^N is the truncated process. Variation of constant at (4.3.4) yields

$$u^N(t) = \tilde{T}_N(t)u^N(0) + \int_0^t \tilde{T}_N(t-s)F(u^N(s))ds + Y^N(t), \quad (4.3.6)$$

where $Y^N(t) = \int_0^t \tilde{T}_N(t-s)dZ^N(s \wedge \tau)$. It should be noted that $s \mapsto Z^N(s \wedge \tau, \frac{i}{N})$ is of bounded variation for $i = 1, \dots, N$, and \tilde{T}_N may be viewed as a $4N \times 4N$ matrix-valued function. Hence, $Y^N(t, \frac{i}{N})$, $1 \leq i \leq N$, is defined as a Stieltjes integral.

From (4.2.30) and (4.3.6),

$$\begin{aligned}
 u^N(t) - v^N(t) &= \tilde{T}_N(t)(u^N(0) - v^N(0)) \\
 &+ \int_0^t \tilde{T}_N(t-s) [F(u^N(s)) - F(v^N(s))] ds + Y^N(t).
 \end{aligned}$$

4.3 The law of large numbers

Since F is Lipschitz and $\tilde{T}_N(t)$ is of contraction, we get from Gronwall lemma

$$\sup_{t \leq T} \|u^N(t) - v^N(t)\|_E \leq \left(\|u^N(0) - v^N(0)\|_E + \sup_{t \leq T} \|Y^N(t)\|_E \right) e^{TL_F(C_T)}.$$

By assumption,

$$\|u^N(0) - v^N(0)\|_E \leq \|u^N(0) - v(0)\|_E + \|\tilde{P}_N v(0) - v(0)\|_E \longrightarrow 0$$

in probability. Therefore, the proof of Theorem 4.3.1 is completed if we show that

$$\sup_{t \leq T} \|Y^N(t)\|_E \longrightarrow 0 \text{ in probability.} \quad (4.3.7)$$

As $Y^N = (Y_S^N, Y_I^N, Y_R^N, Y_B^N)$, it suffices to prove that

$$\sup_{t \leq T} \|Y_{index}^N(t)\|_E \longrightarrow 0 \text{ in probability, for } index = S, I, R, B,$$

where $Y_{index}^N(t) = Z_{index}^N(t \wedge \tau)$ for $index = S, I, R$, and $Y_B^N(t) = \int_0^t T_N(t-s) dZ_B^N(s \wedge \tau)$.

Below, each component is treated at once.

Components related to human

Let us start with the component Y_S^N related to susceptibles. We want to prove that

$$\mathbb{P} \left\{ \sup_{t \leq T} \|Y_S^N(t)\|_\infty > \epsilon_0 \right\} \longrightarrow 0.$$

Fix $\bar{t} \in (0, T]$, $i \in \{1, \dots, N\}$, and, for $0 \leq t \leq \bar{t}$, set

$$f := N\mathbb{1}_i \quad \text{and} \quad \bar{m}_S(t) = \langle Z_S^N(t \wedge \tau), f \rangle_2.$$

Then, $\bar{m}_S = \{\bar{m}_S(t), 0 \leq t \leq \bar{t}\}$ is a mean zero martingale such that

$$\bar{m}_S(\bar{t}) = Z_{S,i}^N(\bar{t} \wedge \tau) = Y_{S,i}^N(\bar{t}).$$

From Lemma 4.3.2,

$$\sum_{s \leq t \wedge \tau} [\delta \bar{m}_S(s)]^2 - \frac{1}{NH} \int_0^t \langle |F_S|^2(u^N(s)), f^2 \rangle_2 ds$$

is a mean 0 martingale for $0 \leq t \leq \bar{t}$. Now, (4.3.5) yields

$$|\delta \bar{m}_S(t)| \leq \|\delta Z_S^N(t \wedge \tau)\|_\infty = \|\delta u_S^N(t \wedge \tau)\|_\infty \leq H^{-1}.$$

Then, for $\theta \in [0, 1]$,

$$m_S(t) = \theta H \bar{m}_S(t)$$

defines a mean zero càdlàg martingale such that $|\delta m_S(t)| \leq 1$ and $[\delta m_S(s)]^2 = \theta^2 H^2 [\delta \bar{m}_S(s)]^2$.

Thus, from Lemma 4.3.2,

$$\sum_{s \leq t} [\delta m_S(s)]^2 - \int_0^{t \wedge \tau} g_S^N(s) ds$$

defines a mean zero càdlàg martingale, where

$$g_S^N(s) = \frac{\theta^2 H}{N} \langle |F_S|^2(u_S^N(s)), f^2 \rangle_2 = \theta^2 H |F_S|_i^2(u_S^N(s)) \leq c\theta^2 H$$

for $0 \leq s \leq t \wedge \tau$. Here $c = c(\mu, \rho, \beta, C_T)$, and below, c is considered as a generic constant that depends on T . It follows that $0 \leq g_S^N(s) \leq h_S^N(s)$, where $h_S^N(s) = c\theta^2 H$ satisfies $\int_0^t h_S^N(s) ds \leq c\theta^2 H$ for $0 \leq t \leq \bar{t} \leq T$. Therefore, Lemma 2.3.4 implies $\mathbb{E}[e^{m_S(\bar{t})}] \leq \exp(c\theta^2 H)$, and from Markov's inequality,

$$\begin{aligned} \mathbb{P}\{Y_{S,i}^N(\bar{t}) > \epsilon_0\} &= \mathbb{P}\{\bar{m}_S(\bar{t}) > \epsilon_0\} = \mathbb{P}\{m_S(\bar{t}) > \theta H \epsilon_0\} = \mathbb{P}\{e^{m_S(\bar{t})} > e^{\theta H \epsilon_0}\} \\ &\leq e^{-\theta H \epsilon_0} \mathbb{E}[e^{m_S(\bar{t})}] \\ &\leq \exp[\theta H(c\theta^2 H - \epsilon_0)]. \end{aligned}$$

Thus we can choose θ such that

$$\mathbb{P}\{Y_{S,i}^N(\bar{t}) > \epsilon_0\} \leq e^{-\eta \epsilon_0^2 H}, \quad \text{for } \eta = \eta(T, C_T) > 0,$$

independently of N, H, i and \bar{t} . Indeed, one may solve $c\theta^2 H - \epsilon_0 \theta + \eta \epsilon_0^2 H \leq 0$ w.r.t. θ . Below, η is generic. The relation above holds for $\mathbb{P}\{-Y_{S,i}^N(\bar{t}) > \epsilon_0\}$, repeating the argument with the processes \bar{m}_S and Y_S^N replaced by their opposites $-\bar{m}_S$ and $-Y_S^N$. Therefore,

$$\mathbb{P}\{|Y_{S,i}^N(t)| > \epsilon_0\} \leq 2e^{-\eta \epsilon_0^2 H}, \quad \text{for } 0 \leq t \leq T \text{ and } i = 1, \dots, N.$$

Since $\|Y_S^N(t)\|_\infty = \sup_{i=1, \dots, N} |Y_{S,i}^N(t)|$ and $Y_S^N(0) = 0$,

$$\begin{aligned} \mathbb{P}\{\|Y_S^N(t)\|_\infty > \epsilon_0\} &= \mathbb{P}\{\exists i = 1, \dots, N : |Y_{S,i}^N(t)| > \epsilon_0\} \\ &\leq \sum_{i=1}^N \mathbb{P}\{|Y_{S,i}^N(t)| > \epsilon_0\} \\ &\leq 2N e^{-\eta \epsilon_0^2 H} \end{aligned} \tag{4.3.8}$$

for $0 \leq t \leq T, \eta = \eta(C_T) > 0$.

Now, we show that (4.3.8) holds with $\|Y_S^N(t)\|_\infty$ replaced by $\sup_{t \leq T} \|Y_S^N(t)\|_\infty$ and N replaced by N^3 on the r.h.s. Indeed, we subdivide $[0, T]$ into N^2 subintervals denoted $I_n(T) = [\frac{nT}{N^2}, \frac{(n+1)T}{N^2}]$, $0 \leq n \leq N^2 - 1$. Observing that we can always write

$$Y_S^N(t) = \tilde{m}_S(t) + Z_S^N\left(\frac{nT}{N^2} \wedge \tau\right) = \tilde{m}_S(t) + Y_S^N\left(\frac{nT}{N^2}\right),$$

where $\tilde{m}_S(t) = Z_S^N(t \wedge \tau) - Z_S^N\left(\frac{nT}{N^2} \wedge \tau\right)$ is a mean zero martingale for $t \in I_n(T)$, we get

$$\sup_{I_n(T)} \|Y_S^N(t)\|_\infty \leq \sup_{I_n(T)} \|\tilde{m}_S(t)\|_\infty + \left\| Y_S^N\left(\frac{nT}{N^2}\right) \right\|_\infty. \tag{4.3.9}$$

We are using the notation $\sup_{I_n(T)}$ for $\sup_{t \in I_n(T)}$. As previously, we fix $i = 1, \dots, N, \theta \in [0, 1]$ and set $m_S(t) = \theta H \tilde{m}_S\left(t, \frac{i}{N}\right)$ for $t \in I_n(T)$. Thus, for $s \in I_n(T)$, we have $|\delta m_S(s)| \leq 1$, and Lemma 4.3.2 yields

$$\sum_{\frac{nT}{N^2} \wedge \tau \leq s \leq t \wedge \tau} [\delta m_S(t)]^2 - \int_{\frac{nT}{N^2} \wedge \tau}^{t \wedge \tau} g_S^N(s) ds$$

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is a mean 0 martingale, with $g_S^N(s) = \theta^2 H |F_S|^2(u^N(s)) \leq \theta^2 H c = h_S^N(s)$. Then $0 \leq g_S^N(s) \leq h_S^N(s)$ and $\int_{\frac{nT}{N^2} \wedge \tau}^{t \wedge \tau} h_S^N(s) ds \leq \int_{I_n(T)} h_S^N(s) ds \leq c\theta^2 H$ since h_S^N is positive. Thus, Lemma 2.3.4 yields $\mathbb{E}[\exp\{m_S(\frac{(n+1)T}{N^2})\}] \leq \exp(c\theta^2 H)$, and from Doob's inequalities,

$$\begin{aligned} \mathbb{P} \left\{ \sup_{I_n(T)} \tilde{m}_S \left(t, \frac{i}{N} \right) > \epsilon_0 \right\} &\leq e^{-\theta H \epsilon_0} \mathbb{E} \left[\exp \left\{ m_S \left(\frac{(n+1)T}{N^2} \right) \right\} \right] \\ &\leq \exp[\theta H (c\theta - \epsilon_0)] \leq e^{-\eta \epsilon_0 H} \end{aligned}$$

where $\eta = \eta(C_T) > 0$, independently of N , H and i . A suitable θ has been chosen as previously. Also, the same holds for $-\tilde{m}_S(t, \frac{i}{N})$. This shows that

$$\mathbb{P} \left\{ \sup_{I_n(T)} \|\tilde{m}_S(t)\|_\infty > \epsilon_0 \right\} \leq 2N e^{-\eta \epsilon_0^2 H}. \quad (4.3.10)$$

From (4.3.8), (4.3.9) and (4.3.10),

$$\begin{aligned} \mathbb{P} \left\{ \sup_{I_n(T)} \|Y_S^N(t)\|_\infty > \epsilon_0 \right\} &\leq \mathbb{P} \left\{ \left\| Y_S^N \left(\frac{nT}{N^2} \right) \right\|_\infty + \sup_{I_n(T)} \|\tilde{m}_S(t)\|_\infty > \epsilon_0 \right\} \\ &\leq \mathbb{P} \left\{ \left\| Y_S^N \left(\frac{nT}{N^2} \right) \right\|_\infty > \frac{\epsilon_0}{2} \right\} + \mathbb{P} \left\{ \sup_{I_n(T)} \|\tilde{m}_S(t)\|_\infty > \frac{\epsilon_0}{2} \right\} \\ &\leq 2N e^{-\eta H \epsilon_0^2 / 2} + 2N e^{-\eta H \epsilon_0^2 / 2} \\ &\leq 4N e^{-\eta H \epsilon_0^2}. \end{aligned}$$

Hence,

$$\mathbb{P} \left\{ \sup_{t \leq T} \|Y_S^N(t)\|_\infty > \epsilon_0 \right\} \leq \sum_{n=0}^{N^2-1} \mathbb{P} \left\{ \sup_{I_n(T)} \|Y_S^N(t)\|_\infty > \epsilon_0 \right\} \leq 4N^3 e^{-\eta H \epsilon_0^2}$$

and it follows that

$$\mathbb{P} \left\{ \sup_{t \leq T} \|Y_S^N(t)\|_\infty > \epsilon_0 \right\} \leq 4N^3 \exp(-\eta \epsilon_0^2 H) \leq \exp(\log 4 + 3 \log N - \eta H).$$

The r.h.s. in the second inequality vanishes, since we are assuming $H^{-1} \log N \rightarrow 0$. The expected result for the component related to susceptible is then proved. \square

Concerning the other human compartment components Y_I^N and Y_R^N related to infected and recovered respectively, we treat them using exactly the same argument as for Y_S^N , and we prove that they vanish in probability at the limit. \square

Component related to bacteria

Theorem 4.3.1 is proved if we show that

$$\mathbb{P} \left\{ \sup_{t \leq T} \|Y_B^N(t)\|_E > \epsilon_0 \right\} \rightarrow 0.$$

A similar approach to that of the previous section is used. We will need the additional

Lemma 4.3.3. (*Lemma 4.3, [Blo92]*) Set $f = N\mathbb{1}_j$. Then

$$\left\langle (\nabla_N^+ T_N(t)f)^2 + (\nabla_N^- T_N(t)f)^2 + (T_N(t)f)^2, 1 \right\rangle_2 \leq h_N(t), \text{ with } \int_0^t h_N(s)ds \leq \bar{c}N + t.$$

Fix $\bar{t} \in (0, T]$ and $i = 1, \dots, N$. For $0 \leq t \leq \bar{t}$, set

$$f = N\mathbb{1}_i \quad \text{and} \quad \bar{m}_B(t) = \left\langle \int_0^t T_N(\bar{t} - s) dZ_B^N(s \wedge \tau), f \right\rangle_2.$$

The process $\bar{m}_B = \{\bar{m}_B(t), 0 \leq t \leq \bar{t}\}$ is a mean 0 martingale such that

$$\bar{m}_B(\bar{t}) = Y_B^N \left(\bar{t}, \frac{i}{N} \right) = Y_{B,i}^N(\bar{t}).$$

The subsequent result is also needed. It follows from [Blo92] and chapter 2.

Lemma 4.3.4. (*Martingales of type 3*)

$$\begin{aligned} & \sum_{s \leq t \wedge \tau} [\delta \bar{m}_B(s)]^2 \\ & - \frac{1}{N\mu} \int_0^{t \wedge \tau} \left[\left\langle u_B^N(s), \mathcal{D}(\nabla_N^+ T_N(\bar{t} - s)f)^2 \mathcal{P}_{out} + \mathcal{D}(\nabla_N^- T_N(\bar{t} - s)f)^2 \mathcal{P}_{in} \right\rangle_2 \right. \\ & \quad \left. + \left\langle |F_B|^2(u^N(s)), (T_N(\bar{t} - s)f)^2 \right\rangle_2 \right] ds \end{aligned}$$

defines a mean 0 càdlàg martingale for $0 \leq t \leq \bar{t}$.

From (4.3.5), $|\delta \bar{m}_B(t)| \leq \|\delta Z_B^N(t \wedge \tau)\|_\infty = \|\delta u_B^N(t \wedge \tau)\|_\infty \leq K^{-1}$. Thus, for $\theta \in [0, 1]$, the process m_B defined by

$$m_B(t) = \theta K \bar{m}_B(t) \quad \text{for } 0 \leq t \leq \bar{t}$$

is a mean 0 martingale such that $|\delta m_B(t)| \leq 1$. Therefore, from Lemma 4.3.4

$$\sum_{s \leq t} [\delta m_B(s)]^2 - \int_0^{t \wedge \tau} g_B^N(s) ds$$

is a mean 0 càdlàg martingale, where for $0 \leq s \leq t \wedge \tau$,

$$\begin{aligned} g_B^N(s) &= \frac{\theta^2 K}{N} \left[\left\langle u_B^N(s), \mathcal{D}(\nabla_N^+ T_N(\bar{t} - s)f)^2 \mathcal{P}_{out} + \mathcal{D}(\nabla_N^- T_N(\bar{t} - s)f)^2 \mathcal{P}_{in} \right\rangle_2 \right. \\ & \quad \left. + \left\langle |F_B|^2(u^N(s)), (T_N(\bar{t} - s)f)^2 \right\rangle_2 \right] \\ &\leq \frac{\theta^2 K}{N} c \left\langle 1, (\nabla_N^+ T_N(\bar{t} - s)f)^2 + (\nabla_N^- T_N(\bar{t} - s)f)^2 + (T_N(\bar{t} - s)f)^2 \right\rangle_2 \\ &\leq c\theta^2 K h_{C,1}^N(\bar{t} - s) \end{aligned}$$

where $\int_0^t h_{C,1}^N(\bar{t} - s)ds \leq \bar{c}N + t$, thanks to Lemma 4.3.3. The constant c is generic and depends on \mathcal{D} , T , C_T and $M_F(C_T)$. Moreover, from the proof of Lemma 4.3 [Blo92], one can take $h_{C,1}^N(\bar{t} - s) = 1 + 4 \sum_{m>0} e^{-2\beta_{m,N}(\bar{t}-s)} (\beta_{m,N} + 1)$, where $\{-\beta_{m,N} = 2N^2(\cos(\pi m/N) - 1)\}_{m \geq 0}$ are eigen functions of the discrete Laplace Δ_N . More details can be found in [Blo87], Lemma 2.12, p12. Hence, g_B^N defines an \mathcal{F}_t^N -adapted process such that $0 \leq g_B^N(s) \leq h_B^N(s)$, where $h_B^N(s) = \frac{c\theta^2 K}{N} h_{C,1}^N(\bar{t} - s)$ is a bounded deterministic function on $[0, \bar{t}]$. As $N \rightarrow \infty$ and $\bar{t} \leq T <$

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∞ , we may assume $\frac{\bar{t}}{N} \leq 1$ and get $\int_0^{\bar{t}} h_B^N(s) ds \leq c\theta^2 K \left(\bar{c} + \frac{\bar{t}}{N} \right) \leq c\theta^2 K$. Lemma 2.3.4 then implies $\mathbb{E}[e^{m_B(\bar{t})}] \leq \exp(c\theta^2 K)$, and by Markov's inequality,

$$\mathbb{P} \{Y_{B,i}^N(\bar{t}) > \epsilon_0\} \leq e^{-\theta K \epsilon_0} \mathbb{E}[e^{m_B(\bar{t})}] \leq \exp[\theta K(c\theta - \epsilon_0)].$$

Thus, we can choose θ such that

$$\mathbb{P} \{Y_{B,i}^N(\bar{t}) > \epsilon_0\} \leq e^{-\eta \epsilon_0^2 K}, \quad \text{for } \eta = \eta(T, C_T) > 0,$$

independently of N , K , i and \bar{t} . The constant $\eta = \eta(T, C_T)$ is generic in the following. A similar relation is derived, for $-m_B$ and $-Y_B^N$, so that

$$\mathbb{P} \{|Y_{B,i}^N(t)| > \epsilon_0\} \leq 2e^{-\eta \epsilon_0^2 K}, \quad \text{for } 0 \leq t \leq T \text{ and } i = 1, \dots, N.$$

Since $\|Y_B^N(t)\|_\infty = \sup_{i=1, \dots, N} |Y_{B,i}^N(t)|$ and $Y_B^N(0) = 0$,

$$\mathbb{P} \{\|Y_B^N(t)\|_\infty > \epsilon_0\} \leq 2Ne^{-\eta \epsilon_0^2 K}, \quad \text{for } 0 \leq t \leq T. \quad (4.3.11)$$

We now show that (4.3.11) holds when $\|Y_B^N(t)\|_\infty$ is replaced by $\sup_{t \leq T} \|Y_B^N(t)\|_\infty$ and N replaced by N^3 . From Duhamel's formula, $Y_B^N(t) = \int_0^t T_N(t-s) dZ_B^N(s \wedge \tau)$ satisfies the stochastic differential equation (SDE)

$$dY_B^N(t) = A_N Y_B^N(t) + dZ_B^N(t \wedge \tau),$$

whose integral formulation is

$$Y_B^N(t) = Z_B^N(t \wedge \tau) + \int_0^t A_N Y_B^N(s) ds. \quad (4.3.12)$$

We subdivide $[0, T]$ into N^2 subintervals $I_n(T) = [\frac{nT}{N^2}, \frac{(n+1)T}{N^2}]$, $0 \leq n \leq N^2 - 1$. Taking $t = \frac{nT}{N^2}$ in (4.3.12) yields

$$Y_B^N\left(\frac{nT}{N^2}\right) = Z_B^N\left(\frac{nT}{N^2} \wedge \tau\right) + \int_0^{\frac{nT}{N^2}} A_N Y_B^N(s) ds.$$

Thus, we can write

$$\begin{aligned} Y_B^N(t) &= Z_B^N(t \wedge \tau) + \int_0^{\frac{nT}{N^2}} A_N Y_B^N(s) ds + \int_{\frac{nT}{N^2}}^t A_N Y_B^N(s) ds \\ &= Z_B^N(t \wedge \tau) + \left[Y_B^N\left(\frac{nT}{N^2}\right) - Z_B^N\left(\frac{nT}{N^2} \wedge \tau\right) \right] + \int_{\frac{nT}{N^2}}^t A_N Y_B^N(s) ds \\ &= Y_B^N\left(\frac{nT}{N^2}\right) + \int_{\frac{nT}{N^2}}^t A_N Y_B^N(s) ds + \tilde{m}_B(t), \end{aligned}$$

where $\tilde{m}_B(t) = Z_B^N(t \wedge \tau) - Z_B^N\left(\frac{nT}{N^2} \wedge \tau\right)$ defines a mean 0 martingale, for $t \in I_n(T)$, such that $|\delta \tilde{m}_B(t)| \leq K^{-1}$. Thus,

$$\|Y_B^N(t)\|_\infty \leq \left\| Y_B^N\left(\frac{nT}{N^2}\right) \right\|_\infty + cN^2 \int_{\frac{nT}{N^2}}^t \|Y_B^N(s)\|_\infty ds + \|\tilde{m}_B(t)\|_\infty,$$

where c is a constant independent of N , such that $\|A_N\|_\infty \leq cN^2$. From Gronwall lemma,

$$\sup_{I_n(T)} \|Y_B^N(t)\|_\infty \leq \left(\left\| Y_B^N\left(\frac{nT}{N^2}\right) \right\|_\infty + \sup_{I_n(T)} \|\tilde{m}_B(t)\|_\infty \right) e^{cT}. \quad (4.3.13)$$

As previously, for $i = 1, \dots, N$ and $\theta \in [0, 1]$, we set

$$m_B(t) = \theta K \tilde{m}_B \left(t, \frac{i}{N} \right), \quad \text{for } t \in I_n(T) = \left[\frac{nT}{N^2}, \frac{(n+1)T}{N^2} \right].$$

The new defined mean zero martingale m_B satisfies $|\delta m_B(t)| \leq 1$, and by Lemma 4.3.2,

$$\sum_{\frac{nT}{N^2} \wedge \tau \leq s \leq t \wedge \tau} [\delta m_B(s)]^2 - \int_{\frac{nT}{N^2} \wedge \tau}^{t \wedge \tau} g_B^N(s) ds$$

is a mean 0 martingale for $t \in I_n(T)$, where

$$\begin{aligned} g_B^N(s) &= \theta^2 K \left[2DN^2 (\mathcal{P}_{in} u_{B,i+1}^N(s) + u_{B,i}^N(s) \mathcal{P}_{out} u_{B,i-1}^N(s)) + |F_B|_i^2(u^N(s)) \right] \\ &\leq c\theta^2 KN^2 =: h_B^N(s), \end{aligned}$$

and $\int_{\frac{nT}{N^2} \wedge \tau}^{t \wedge \tau} h_B^N(s) ds \leq \int_{I_n(T)} h_B^N(s) ds \leq c\theta^2 KT$ for all $t \in I_n(T)$, since h_B^N is positive. The constant c depends on C_T and $M_F(C_T)$. Lemma 2.3.4 then implies $\mathbb{E} \left[\exp \left\{ m \left(\frac{(n+1)T}{N^2} \right) \right\} \right] \leq \exp(c\theta^2 KT)$. One chooses θ such that

$$\begin{aligned} \mathbb{P} \left\{ \sup_{I_n(T)} \tilde{m}_B \left(t, \frac{i}{N} \right) > \epsilon_0 \right\} &\leq e^{-\theta K \epsilon_0} \mathbb{E} \left[\exp \left\{ m \left(\frac{(n+1)T}{N^2} \right) \right\} \right] \\ &\leq \exp[\theta K (c\theta - \epsilon_0)] \leq e^{-\eta \epsilon_0^2 K}, \end{aligned}$$

applying Doob's inequalities. Here, $\eta = \eta(T, C_T, M_F(C_T)) > 0$ and is going to be generic in the following. A similar inequality is easily derived for $-\tilde{m}_B(t, \frac{i}{N})$. As a result,

$$\mathbb{P} \left\{ \sup_{I_n(T)} \|\tilde{m}_B(t)\|_\infty > \epsilon_0 \right\} \leq 2N e^{-\epsilon_0^2 K}. \quad (4.3.14)$$

From (4.3.11), (4.3.13) and (4.3.14),

$$\begin{aligned} \mathbb{P} \left\{ e^{-cT} \sup_{I_n(T)} \|Y_B^N(t)\|_\infty > \epsilon_0 \right\} &\leq \mathbb{P} \left\{ \left\| Y_B^N \left(\frac{nT}{N^2} \right) \right\|_\infty + \sup_{I_n(T)} \|\tilde{m}_B(t)\|_\infty > \epsilon_0 \right\} \\ &\leq \mathbb{P} \left\{ \left\| Y_B^N \left(\frac{nT}{N^2} \right) \right\|_\infty > \frac{\epsilon_0}{2} \right\} + \mathbb{P} \left\{ \sup_{I_n(T)} \|\tilde{m}_B(t)\|_\infty > \frac{\epsilon_0}{2} \right\} \\ &\leq 4N e^{\eta \epsilon_0^2 K}. \end{aligned}$$

Hence,

$$\mathbb{P} \left\{ e^{-cT} \sup_{[0,T]} \|Y_B^N(t)\|_\infty > \epsilon_0 \right\} \leq \sum_{n=0}^{N^2-1} \mathbb{P} \left\{ e^{-cT} \sup_{I_n(T)} \|Y_B^N(t)\|_\infty > \epsilon_0 \right\} \leq 4N^3 e^{-\alpha \epsilon_0^2 K}$$

and it follows that

$$\mathbb{P} \left\{ \sup_{[0,T]} \|Y_B^N(t)\|_\infty > \epsilon_0 \right\} \leq 4N^3 e^{-\eta K}.$$

The r.h.s. vanishes, as we are assuming that $K^{-1} \log N \rightarrow 0$. This proves the convergence of the part related to bacteria, and the proof of Theorem 4.3.1 ends. ■

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Concluding remarks and further discussion

In the LLN given by Theorem 4.3.1, we consider that

$$H = \frac{\mathbf{H}(0)}{N} \rightarrow \infty, \quad \frac{H}{K} \rightarrow r > 0, \quad \text{and} \quad K^{-1} \log N \rightarrow 0$$

as $\mathbf{H}(0), N, K \rightarrow \infty$. We have seen that due to $r > 0$, the condition $K^{-1} \log N \rightarrow 0$ is equivalent to $H^{-1} \log N \rightarrow 0$. There are many other interesting possibilities of scaling.

The next one we consider is

$$H = \frac{\mathbf{H}(0)}{N} \rightarrow \infty, \quad \frac{H}{K} \rightarrow r = 0, \quad \text{and} \quad K^{-1} \log N \rightarrow 0.$$

This case is very close to the previous one and a similar LLN holds, with two main differences. First of all, the equivalence between $K^{-1} \log N \rightarrow 0$ and $H^{-1} \log N \rightarrow 0$ is lost, since $H/K \rightarrow 0$. Therefore, one needs consider the assumption that both conditions hold, instead of any of them as previously. Furthermore, the limit process changes. In fact, $H/K \rightarrow 0$ means that the human population is negligible besides that of bacteria, and the contribution of the former to the latter vanishes at the limit. The evolution of vibrios population is autonomous and influences that of humans at the limit.

The last case in the context of infinite local human population ($H \rightarrow \infty$) is when $H/K \rightarrow \mathcal{R}^{-1} = \infty$. In this case, the human population is too abundant and their contribution to vibrios population is of order of the infinity. The population of bacteria then explodes and the model does not converges.

Now, we discuss a second class of scaling, when the local human population is of order of a constant: $H \rightarrow h = \text{constant}$. Notice that $h = 0$ would yield $\mathbf{H}(0) = 0$, meaning that there is no human inside the system, which is not really interesting as a situation to model. We shall then assume that $h > 0$. This immediately yields $H/K \rightarrow 0$, and we already know that the contribution of human to vibrio population will vanish at the limit. Thus, the related term disappears in the limit equation. Human compartments need not be renormalized anymore.

The hypothesis $H \rightarrow h = \text{constant} > 0$ we are considering is very realistic actually, and requires a different spatial correlation for humans to be considered, independently of the initial space discretization $(J_i)_i$. In fact, as humans has bigger sizes than bacteria, both species evolve on two different space scales. The scale of the former being larger than that of the latter. A natural way to proceed is to consider human spatial dynamics on a macroscopic discretization of the domain —macrosites may refer to regions in the domain, such as communities in the real life—. On the one hand, every region undergoes independently the interactions (birth, death, infection, recovering) with rates depending on the entire region and with jumps given by a function that depends on the region. On the other hand, the regions communicate in a way that has to be specified. One should also keep in mind that the dynamic of humans remains coupled to that of bacteria.

From Chapter 3, we know that PDMPs shall be obtained at the limit in this context, as soon as the chosen jumps and rates describing human compartments dynamics are convergent. In that limit, human populations follow a pure jump dynamic whose parameters depend on bacteria population. Human compartments then represent the discrete component of the limiting PDMP, while vibrio population represents its continuous component. Between human compartments consecutive jumps, the vibrio population follows an appropriate reaction-advection-diffusion PDE, parametered by the state taken by the human compartments between the considered jumps.

4.4 On Large deviations estimates

In this section we investigate a weak large deviation principle (LDP) for the sequence of stochastic processes $\{u^N\}_N$ defined above, using the weak topology on the 4-vector space $(L^2([0, 1]))^4$ and relying on the Hilbert structure derived from the natural inner product defined on this latter space as introduced in the previous section. We recall that $L^2[0, 1]$ is the space of square integrable 1-periodic functions defined on $[0, 1]$.

A general LDP is usually established through an upper bound for closed sets and a lower bound for open sets. These estimates are made with respect to a function named rate function. A standard way of proceeding is to identify such a function, find its possible representations (see e.g. [DK95]) and choose the most suitable one in order either to verify that it is a *good* rate function or to establish the required estimates indeed.

In the present work, a nice rate function candidate is proposed, and an upper bound for compact sets is performed. The more general upper bound for closed set can be derived easily, if one proves that the sequence of process is exponentially tight. This latter part is not yet ready.

Remark 4.4.1. *Further work is needed in order to prove exponential tightness and achieve an upper bound for closed sets. The principal difficulty to deal with is spatial diffusions which happen at rates of order N^2 . In the proof of the LLN, we have proceeded to an acceleration of time by observing the dynamics over time intervals of length N^{-2} . The approach has led us to obtain an exponential bound of the process u^N in probability, the bound being of order e^{-cH} where c is a constant and H the scale of local human population size. However, these arguments are difficult to use in the present context because of the topology we are working with. Furthermore, they might not be sufficient even. In fact, we are looking for a LDP with speed NH , meaning that we want an exponential bound of order e^{-cNH} this time.*

Our strategy for obtaining upper bound estimates for compact sets is to have some *local upper bound estimates*, which heuristically consists in showing that for every càdlàg trajectory and every perturbation of order $\delta > 0$ of the rate function, one can always find an open neighborhood of the trajectory —depending on δ —, which satisfies an upper bound with the perturbed rate function. To that aim, we will need some standard exponential martingales associated with the process and involving the Young function $\tau(x) = e^x - 1 - x$.

Before we get there, let us recall and specify a bit more, the context we are working in. We want to use the random time change representation of the process u^N , as introduced by [EK86]. As there are two species involved in the system and whose population sizes (H for human and K for bacteria) have the same scale, we make the hypothesis that there is a constant ratio $\mathcal{R}^{-1} = H/K$, $\mathcal{R} > 1$, according to the LLN given by Theorem 4.3.1.

Now from [EK86], it is well known that the process u^N whose generator is given by (4.2.16) admits an explicit version that can be written using independent Poisson processes as clocks to catch the randomness of the events we are studying. As it is standard, these Poisson processes count the number of jumps of our process u^N . By event, we mean any instantaneous event susceptible to change the population of any compartment of either human (S , I and R) or bacteria (B).

We thus keep in mind that we can rewrite u^N on the following form :

$$u_t^N = u_0^N + \frac{1}{H} \sum_{i=1}^N \sum_{j=1}^{14} \tilde{g}_{i,j} P_{i,j} \left(H \int_0^t \beta_{i,j}^N(u_s^N) ds \right) \quad (4.4.1)$$

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$$= u_0^N + \sum_{i=1}^N \sum_{j=1}^{14} \tilde{g}_{i,j} \int_0^t \beta_{i,j}^N(u_s^N) ds + \frac{1}{H} \sum_{i=1}^N \sum_{j=1}^{14} \tilde{g}_{i,j} M_{i,j} \left(H \int_0^t \beta_{i,j}^N(u_s^N) ds \right),$$

where $(P_{i,j})_{i,j}$ are mutually independent standard Poisson processes. Here, we adopt the notation

$$P_{i,13} := P_{i \rightarrow i+1,13} \text{ and } P_{i \rightarrow i-1,14} := P_{i,14}$$

for those Poisson processes counting bacteria transfer between sites according to outward or inward nodes respectively, $M_{i,j}(a) = P_{i,j}(a) - a$ are the associated compensated Poisson processes, which in fact are centered martingales. For $i = 1, \dots, N$, we distinguish, on the one hand, **compartmental jumps directions**, given by

$$\begin{aligned} g_1 &:= (1, 0, 0, 0) & g_2 &:= (1, 0, 0, 0) & g_3 &:= (1, 0, 0, 0) & g_4 &:= (-1, 0, 0, 0) \\ g_5 &:= (-1, 1, 0, 0) & g_6 &:= (0, -1, 0, 0) & g_7 &:= (0, -1, 0, 0) & g_8 &:= (0, -1, 1, 0) \\ g_9 &:= (0, 0, -1, 0) & g_{10} &:= (1, 0, -1, 0) & g_{11} &:= (0, 0, 0, -\frac{1}{\mathcal{R}}) & g_{12} &:= (0, 0, 0, \frac{1}{\mathcal{R}}) \\ g_{13} &:= (0, 0, 0, \frac{1}{\mathcal{R}}), \end{aligned}$$

and, on the other hand, **spatio-compartmental jumps directions**, given by

$$\tilde{g}_{i,j} = \begin{cases} g_j \mathbf{1}_i & \text{for } j = 1, \dots, 12 \\ (\mathbf{1}_{i+1} - \mathbf{1}_i) g_{13} & \text{if } j = 13 \\ (\mathbf{1}_{i-1} - \mathbf{1}_i) g_{13} & \text{if } j = 14. \end{cases}$$

Recall that the scaling $1/\mathcal{R}$ in the jump directions that modify bacteria compartment is due to our scaling $K = \mathcal{R}H$.

The jump rates $\beta_{i,j}^N$ are positive functions defined from $(\mathbb{H}^N)^4$ to \mathbb{R}_+ as follows:

$$\beta_{i,j}^N(u^N) = \beta_j^N(u^N(i)) \quad \forall j = 1, \dots, k \quad (4.4.2)$$

for all $u^N = (u_S^N, u_I^N, u_R^N, u_B^N) \in (\mathbb{H}^N)^4$, where β_j^N are positive functions explicitly defined from \mathbb{R}_+^4 to \mathbb{R}_+ by

$$\begin{aligned} \beta_1^N(y) &= \mu y_1 & \beta_2^N(y) &= \mu y_2 & \beta_3^N(y) &= \mu y_3 & \beta_4^N(y) &= \mu y_1 & \beta_5^N(y) &= \beta \frac{y_4}{1 + y_4} y_1 \\ \beta_6^N(y) &= \mu y_2 & \beta_7^N(y) &= \alpha y_3 & \beta_8^N(y) &= \gamma y_2 & \beta_9^N(y) &= \mu y_3 & \beta_{10}^N(y) &= \rho y_3 \\ \beta_{11}^N(y) &= \mu_B y_4 & \beta_{12}^N(y) &= \frac{p}{W} y_2 & \beta_{13}^N(y) &= \ell \mathcal{P}_{out} y_4 & \beta_{14}^N(y) &= \ell \mathcal{P}_{in} y_4, \end{aligned} \quad (4.4.3)$$

for all $y = (y_1, y_2, y_3, y_4) \in \mathbb{R}_+^4$.

Remark 4.4.2. We note that "non spatial" jump rates β_j^N , $j = 1, \dots, 12$, do not explicitly depend on N . They extend to the space $(L^2([0, 1]))^4$ through $\beta_j : (L^2([0, 1]))^4 \rightarrow (L^2([0, 1]))$, defined by

$$\beta_j(\phi)(x) = \beta_j^N(\phi(x)), \quad (4.4.4)$$

for $\phi \in (L^2([0, 1]))^4$. Furthermore, these "non spatial" jump rates are all linear, except for $j = 5$, both in terms of the β_j s and in terms of the $\beta_{i,j}^N$ s.

Here follows a useful representation of u^N . For $f^N \in \mathcal{C}^1([0, T]; (\mathbb{H}^N)^4)$, for every $s, t \in [0, T]$ we have :

$$\begin{aligned} \langle u_t^N, f_t^N \rangle - \langle u_s^N, f_s^N \rangle &= \frac{1}{N} \sum_{i=1}^N [u_i^N(i) \cdot f_t^N(i) - u_s^N(i) \cdot f_s^N(i)] \\ &= \frac{1}{N} \sum_{i=1}^N \left[\int_s^t u_r^N(i) \cdot \frac{\partial}{\partial r} f_r^N(i) dr + \sum_{s < r \leq t} (u_r^N(i) - u_{r-}^N(i)) \cdot f_r^N(i) \right]. \end{aligned}$$

Furthermore, we have for every i

$$\begin{aligned} \sum_{s < r \leq t} (u_r^N(i) - u_{r-}^N(i)) \cdot f_r^N(i) &= \frac{1}{H} \sum_{j=1}^{12} \int_s^t g_j \cdot f_r^N(i) dP_{i,j} \left(H \int_0^r \beta_{i,j}(u_x^N) dx \right) \\ &\quad + \frac{1}{H} \int_s^t g_{13} \cdot f_r^N(i) dP_{i+1 \rightarrow i, 14} \left(H \int_0^r \beta_{i+1, 14}^N(u_x^N) dx \right) \\ &\quad + \frac{1}{H} \int_s^t g_{13} \cdot f_r^N(i) dP_{i-1 \rightarrow i, 13} \left(H \int_0^r \beta_{i-1, 13}^N(u_x^N) dx \right) \\ &\quad - \frac{1}{H} \int_s^t g_{13} \cdot f_r^N(i) dP_{i \rightarrow i+1, 13} \left(H \int_0^r \beta_{i, 13}^N(u_x^N) dx \right) \\ &\quad - \frac{1}{H} \int_s^t g_{13} \cdot f_r^N(i) dP_{i \rightarrow i-1, 14} \left(H \int_0^r \beta_{i, 14}^N(u_x^N) dx \right). \end{aligned}$$

Therefore, periodicity leads to

$$\begin{aligned} \langle u_t^N, f_t^N \rangle &= \langle u_s^N, f_s^N \rangle + \int_s^t \langle u_r^N, \frac{\partial f_r^N}{\partial r} \rangle dr + \frac{1}{N} \sum_{i=1}^N \sum_{j=1}^{12} \int_s^t g_j \cdot f_r^N(i) \beta_{i,j}^N(u_r^N) dr \\ &\quad + \frac{1}{N} \sum_{i=1}^N \int_s^t g_{13} \cdot (f_r^N(i+1) - f_r^N(i)) \beta_{i,13}(u_r^N) dr \\ &\quad + \frac{1}{N} \sum_{i=1}^N \int_s^t g_{13} \cdot (f_r^N(i-1) - f_r^N(i)) \beta_{i,14}(u_r^N) dr \\ &\quad + \mathcal{M}_{s,t}^{N, f^N} \end{aligned} \tag{4.4.5}$$

where

$$\begin{aligned} \mathcal{M}_{s,t}^{N, f^N} &:= \frac{1}{NH} \sum_{i=1}^N \sum_{j=1}^{12} \int_s^t g_j \cdot f_r^N(i) dM_{i,j} \left(H \int_0^r \beta_{i,j}^N(u_s^N) ds \right) \\ &\quad + \frac{1}{NH} \sum_{i=1}^N \int_s^t g_{13} \cdot (f_r^N(i+1) - f_r^N(i)) dM_{i,13} \left(H \int_0^r \beta_{i,13}(u_s^N) ds \right) \\ &\quad + \frac{1}{NH} \sum_{i=1}^N \int_s^t g_{13} \cdot (f_r^N(i+1) - f_r^N(i)) dM_{i,14} \left(H \int_0^r \beta_{i,14}(u_s^N) ds \right) \end{aligned} \tag{4.4.6}$$

is a mean zero martingale for $t \geq s$ and s fixed.

Note that if $f \in \mathcal{C}([0, T]; (L^2([0, 1]))^4)$, we always have

$$\langle u_t^N, f_t \rangle = \sum_{i=1}^N u_t^N(i) \cdot \int_{J_i} f_t(x) dx = \frac{1}{N} \sum_{i=1}^N u_t^N(i) \cdot P_N f_t(i),$$

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where P_N is the projection defined by (4.2.15) and hence $\langle u^N, f \rangle$ has the same form as in (4.4.5), with $f^N := P_N f$.

4.4.1 The rate function

Here we define a rate function candidate for the large deviations we want to estimate. It is the functional that governs the energy that the system needs to go far away from its deterministic limit prescribed by the LLN in the previous section. We derive that function in a quite non standard way, although we follow the idea of taking the Legendre Transform of the Hamiltonian of the system. Heuristic arguments are given about that, in Section 4.5.2.

We start by adopting formal notation and definitions. Let $T > 0$ be fixed. Recall our process u^N lives in $D([0, T]; (L^2[0, 1])^4)$ and its LLN limit is in $\mathcal{AC}([0, T]; (C[0, 1])^3 \times C^2[0, 1])$. We adopt the convention that for $\phi \in \mathcal{AC}([0, T]; (L^2[0, 1])^4)$, $\dot{\phi}(t, \cdot) = \dot{\phi}_t(\cdot)$ denotes the weak derivatives of ϕ at t which is a 4-vector of $L^2[0, 1]$ components.

Our rate function candidate is the following:

$$I_T(\phi) = \begin{cases} \int_0^T L(\phi_t, \dot{\phi}_t) dt & \text{if } \phi \in \mathcal{AC}([0, T]; (C[0, 1])^4) \\ +\infty & \text{otherwise,} \end{cases} \quad (4.4.7)$$

with

$$L(\phi_t, \dot{\phi}_t) = \sup_{f \in (C^3[0, 1])^4} \Sigma(\phi_t, \dot{\phi}_t; f),$$

where

$$\Sigma(\phi_t, \dot{\phi}_t; f) = \langle \dot{\phi}_t, f \rangle - \Lambda(\phi_t, f)$$

and

$$\Lambda(\phi_t, f) = \sum_{j=1}^{12} \langle \beta_j(\phi_t), e^{(g_j|f)} - \mathbb{1} \rangle + \langle (g_{13} | \phi_t), e^{-(g_{13}|f)} A^* e^{(g_{13}|f)} \rangle. \quad (4.4.8)$$

In our notation, $\langle \cdot, \cdot \rangle$ may denote the inner product either on $L^2([0, 1])$ or on the 4-vector space $(L^2[0, 1])^4$, accordingly.

One can notice that $I_T(\phi) = 0$ if ϕ satisfies the limiting system (4.2.1).

For any subset \mathbf{B} of $D([0, T]; (L^2[0, 1])^4)$ we introduce the notation

$$I_T(\mathbf{B}) := \inf_{\phi \in \mathbf{B}} I_T(\phi).$$

We now rely on a useful result of control theory to prove that we can interchange the supremum and integration in (4.4.7). We found that result very useful since it allows to have an appropriate form for the rate function while proving the Upper bound LDP estimates.

Lemma 4.4.1. *(Interchange supremum and integration)*

Consider the map

$$\begin{aligned} \Phi & : [0, T] \times X \rightarrow \mathbb{R} \quad , \\ & (t, u) \mapsto \Phi(t, u) \end{aligned}$$

where X is a separable normed space and such that: $t \mapsto \Phi(t, u)$ is measurable $\forall u \in X$, and $u \mapsto \Phi(t, u)$ is continuous on X for a.e. t . Then assuming that the set

$\mathcal{L} := \{u(\cdot) \in L^1([0, T]; X) \text{ such that } t \mapsto \Phi(t, u(t)) \text{ is integrable with possibly infinite value}\}$
is nonempty, we have

$$\sup_{u(\cdot) \in \mathcal{L}} \int_0^T \Phi(t, u(t)) dt = \int_0^T \sup_{u \in X} \Phi(t, u) dt. \quad (4.4.9)$$

Proof. Since we obviously have for all $u(\cdot) \in \mathcal{L}$,

$$\int_0^T \Phi(t, u(t)) dt \leq \int_0^T \sup_{u \in X} \Phi(t, u) dt,$$

the first inequality is immediate.

For the other one, as there exists a countable dense subset in X , we will have

$$\sup_{u \in X} \Phi(t, u) = \max_{i \geq 1} \Phi(t, u_i) \quad \forall t.$$

Then $\forall \epsilon, \forall t, \exists i = i(t, \epsilon)$ such that

$$\sup_{u \in X} \Phi(t, u) - \epsilon < \Phi(t, u_i).$$

Fixing ϵ , given t , choose the smallest index $i(t)$ such that the previous inequality holds. Thus the application $t \mapsto u_{i(t)}$ is at least Lebesgue measurable, since

$$\forall v \in X, \exists m(v) \in \mathbb{N} \text{ such that } \{t : u_{i(t)} \leq v\} = \bigcup_{\ell=1}^{m(v)} \{t : u_{i(t)} = u_\ell\}$$

and

$$\{t : u_{i(t)} = u_\ell\} = \bigcap_{k=1}^{\ell-1} \left\{ t : \Phi(t, u_k) + \epsilon \leq \sup_{u \in X} \Phi(t, u) \right\} \cap \left\{ t : \Phi(t, u_\ell) + \epsilon > \sup_{u \in X} \Phi(t, u) \right\}.$$

Let $u^*(\cdot) \in \mathcal{L}$ since this space is assumed to have at least one element, and denote for all n

$$\Gamma_n := \{t \in [0, T] : \|u_{i(t)}\|_X < n\}.$$

Thus we have that

$$\hat{u}(t) := \begin{cases} u_{i(t)} & \text{if } t \in \Gamma_n \\ u^*(t) & \text{else} \end{cases} \quad (4.4.10)$$

belongs to \mathcal{L} and we can compute

$$\begin{aligned} \int_0^T \sup_{u \in X} \Phi(t, u) dt &< \int_0^T \Phi(t, u_{i(t)}) + \epsilon dt \\ &< \int_{\Gamma_n} \Phi(t, \hat{u}(t)) + \epsilon dt + \int_{\Gamma_n^c} \Phi(t, u_{i(t)}) + \epsilon dt \\ &< \int_0^T \Phi(t, \hat{u}(t)) dt + \epsilon T + \int_{\Gamma_n^c} \Phi(t, u_{i(t)}) + \epsilon - \Phi(t, u^*(t)) dt. \end{aligned}$$

Taking n to infinity first, and then letting ϵ go to 0 lead to the result. \square

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We use this lemma with $X = (\mathcal{C}^3[0, 1])^4$ to show that the rate function takes the form

$$I_T(\phi) = \sup_{f \in L^1([0, T]; X)} \int_0^T \Sigma(\phi_t, \dot{\phi}; f_t) dt \quad (4.4.11)$$

$\forall \phi \in \mathcal{AC}([0, T]; X)$.

As $\mathcal{C}^1([0, T]; X)$ is dense in $L^1([0, T]; X)$ and since $f \mapsto \int_0^T \Sigma(\phi, \dot{\phi}; f_t) dt$ is at least lower semicontinuous, the supremum in (4.4.11) can be restricted to smooth functions $t \mapsto f_t$ of t . Therefore (4.4.7) takes the form

$$I_T(\phi) = \sup_{f \in \mathcal{C}^{1,3}([0, T] \times [0, 1])} \tilde{\Sigma}_T(\phi; f) \quad (4.4.12)$$

for $\phi \in \mathcal{AC}([0, T]; (\mathcal{C}[0, 1])^4)$, where

$$\tilde{\Sigma}_T(\phi; f) = \langle \phi_T, f_T \rangle - \langle \phi_0, f_0 \rangle - \int_0^T \langle \phi_t, \frac{\partial f_t}{\partial t} \rangle dt - \int_0^T \Lambda(\phi_t, f_t) dt.$$

Moreover, for every fixed f , the map $\phi \mapsto \tilde{\Sigma}_T(\phi; f)$ is continuous for the Skorohod Topology on $D([0, T]; (L^2[0, 1])^4)$ and the weak topology on $(L^2[0, 1])^4$. This follows, as usual, from the continuity of integration of càdlàg functions.

Furthermore, the rate function I_T is positive and lower-semicontinuous under the weak topology of $L^2[0, 1]$, respectively by its definition at (4.4.7), and, as it is the supremum of lower-semicontinuous functions thanks to the representation (4.4.12).

4.4.2 An exponential local martingale

We start by pointing out a useful standard exponential martingale process, used in the LDP theory, and involving Young function $\tau(x) = e^x - 1 - x$.

Lemma 4.4.2. *Let $f \in \mathcal{C}^1([0, T]; (L^2([0, 1]))^4)$ be fixed. For arbitrary positive constant λ , the process*

$$\mathcal{Z}_t^{N, f, \lambda} := \exp \left\{ \lambda N H \mathcal{M}_{0, t}^{N, f^N} - H G_{0, t}^{N, f^N, \lambda} \right\} \quad (4.4.13)$$

is a mean one martingale, where

$$\begin{aligned} G_{s, t}^{N, f^N, \lambda} &:= \sum_{i=1}^N \sum_{j=1}^{12} \int_s^t \tau(\lambda g_j \cdot f_r^N(i)) \beta_{i, j}^N(u_r^N) dr \\ &+ \sum_{i=1}^N \int_s^t \tau(\lambda g_{13} \cdot (f_r^N(i+1) - f_r^N(i))) \beta_{i, 13}^N(u_r^N) dr \\ &+ \sum_{i=1}^N \int_s^t \tau(\lambda g_{13} \cdot (f_r^N(i-1) - f_r^N(i))) \beta_{i, 14}^N(u_r^N) dr \end{aligned} \quad (4.4.14)$$

where

$$\tau(x) = e^x - 1 - x$$

and $f_t^N := P_N f_t$ denotes the canonical projection of f_t on $(\mathbb{H}^N)^4$ defined by (4.2.15).

Proof. Since $G_t^{N,f^N,\lambda}$ has bounded variation, by Itô's formula

$$\begin{aligned} \mathcal{Z}_t^{N,f,\lambda} &= \mathcal{Z}_0^{N,f,\lambda} + \lambda NH \int_0^t \mathcal{Z}_{r-}^{N,f,\lambda} d\mathcal{M}_{0,r}^{N,f^N} - H \int_0^t \mathcal{Z}_{r-}^{N,f,\lambda} dG_r^{N,f^N} \\ &\quad + \sum_{r \leq t} \left[\mathcal{Z}_r^{N,f,\lambda} - \mathcal{Z}_{r-}^{N,f,\lambda} - \mathcal{Z}_{r-}^{N,f,\lambda} \lambda NH \delta \mathcal{M}_{0,r}^{N,f^N} \right], \end{aligned} \quad (4.4.15)$$

where

$$\delta \mathcal{M}_{0,r}^{N,f^N} = \mathcal{M}_{0,r}^{N,f^N} - \mathcal{M}_{0,r-}^{N,f^N}.$$

Since

$$\delta \mathcal{M}_{0,r}^{N,f^N} = \langle u_r^N - u_{r-}^N, f_r^N \rangle, \quad (4.4.16)$$

and since the jumps of $\langle u^N, f_r \rangle$, according to spatio-compartmental coordinates (i, j) are of the form

$$\frac{1}{H} \langle \tilde{g}_{i,j}, f_r \rangle = \begin{cases} \frac{1}{NH} g_j \cdot f_r^N(i) & \text{if } j = 1, \dots, 12 \\ \frac{1}{NH} g_{13} \cdot (f_r^N(i+1) - f_r^N(i)) & \text{if } j = 13 \\ \frac{1}{NH} g_{14} \cdot (f_r^N(i-1) - f_r^N(i)) & \text{if } j = 14, \end{cases}$$

we can compute the jump terms of (4.4.16):

$$\begin{aligned} &\sum_{r \leq t} \left[\mathcal{Z}_r^{N,f,\lambda} - \mathcal{Z}_{r-}^{N,f,\lambda} - \mathcal{Z}_{r-}^{N,f,\lambda} \lambda NH \delta \mathcal{M}_{0,r}^{N,f^N} \right] \\ &= \sum_{r \leq t} \mathcal{Z}_{r-}^{N,f} \left[e^{\lambda NH \delta \mathcal{M}_{0,r}^{N,f^N}} - 1 - \lambda NH \delta \mathcal{M}_{0,r}^{N,f^N} \right] \\ &= \sum_{i=1}^N \sum_{j=1}^{12} \int_0^t \mathcal{Z}_{r-}^{N,f,\lambda} \tau (\lambda g_j \cdot f_r^N(i)) dP_{i,j} \left(H \int_0^r \beta_{i,j}^N(u_\sigma^N) d\sigma \right) \\ &\quad + \sum_{i=1}^N \int_0^t \mathcal{Z}_{r-}^{N,f,\lambda} \tau (\lambda g_{13} \cdot (f_r^N(i+1) - f_r^N(i))) dP_{i,13} \left(H \int_0^r \beta_{i,13}^N(u_\sigma^N) d\sigma \right) \\ &\quad + \sum_{i=1}^N \int_0^t \mathcal{Z}_{r-}^{N,f,\lambda} \tau (\lambda g_{14} \cdot (f_r^N(i-1) - f_r^N(i))) dP_{i,14} \left(H \int_0^r \beta_{i,14}^N(u_\sigma^N) d\sigma \right) \\ &= \sum_{i=1}^N \sum_{j=1}^{12} \int_0^t \mathcal{Z}_{r-}^{N,f,\lambda} \tau (\lambda g_j \cdot f_r^N(i)) dM_{i,j} \left(H \int_0^r \beta_{i,j}^N(u_\sigma^N) d\sigma \right) \\ &\quad + \sum_{i=1}^N \int_0^t \mathcal{Z}_{r-}^{N,f,\lambda} \tau (\lambda g_j \cdot (f_r^N(i+1) - f_r^N(i))) dM_{i,13} \left(H \int_0^r \beta_{i,13}^N(u_\sigma^N) d\sigma \right) \\ &\quad + \sum_{i=1}^N \int_0^t \mathcal{Z}_{r-}^{N,f,\lambda} \tau (\lambda g_j \cdot (f_r^N(i-1) - f_r^N(i))) dM_{i,14} \left(H \int_0^r \beta_{i,14}^N(u_\sigma^N) d\sigma \right) \\ &\quad + H \int_0^t \mathcal{Z}_{r-}^{N,f,\lambda} dG_r^{N,f^N}. \end{aligned}$$

We then conclude the proof of Lemma 4.4.2 using this in (4.4.15), since the last term above vanishes and the other terms are martingales as integrals against martingales. \square

4.4 On Large deviations estimates

4.4.3 Upper Bound for compact sets

One of the most common approaches for the general upper bound estimates—that is upper bound for closed sets—is to prove the upper bound estimates for compact sets and exponential tightness for the sequence of processes. As mentioned earlier, we only show the first part in the present work, which is already good enough and encouraging for the next step. With respect to the announced strategy, we specify and prove the introduced *local upper bound*.

Lemma 4.4.3. *Let $\phi \in D([0, T]; (L^2[0, 1])^4)$.*

For every $\delta > 0$ we can find an open neighbourhood $U_{\phi; \delta}$ such that

$$\limsup_{N, H \rightarrow +\infty} \frac{1}{NH} \log \mathbb{P} [u^N \in U_{\phi; \delta}] \leq \begin{cases} -I_T(U_{\phi; \delta}) + \delta & \text{if } I_T(\phi) < \infty \\ -\delta & \text{else} \end{cases} \quad (4.4.17)$$

Proof. Let $\delta > 0$ and ϕ be fixed.

Using the fact that for every $f \in \mathcal{C}^{1,3}([0, T] \times [0, 1])$, the map $\phi \mapsto \tilde{\Sigma}_T(\phi; f)$ is continuous on $D([0, T]; (L^2[0, 1])^4)$, there exists a neighbourhood $U_{f, \phi; \delta}$ of ϕ such that

$$\left| \tilde{\Sigma}_T(\phi; f) - \tilde{\Sigma}_T(\psi; f) \right| \leq \delta/3 \quad \text{for all } \psi \in U_{f, \phi; \delta}$$

Let f be fixed and let us note by $f_t^N := P_t^N f$ its projection on $(\mathbb{H}^N)^4$ as define in (4.2.15). Noting that if we denote by

$$\tilde{\Sigma}_T^N(u^N; f^N) := \mathcal{M}_{0, T}^{N, f^N} - G_t^{N, f^N},$$

we have the computations

$$\begin{aligned} 1 &\geq \mathbb{E} \left[\mathcal{Z}_T^{N, f^N} \mathbb{1}_{\{u^N \in U_{f, \phi; \delta}\}} \right] \\ &\geq \mathbb{E} \left[\exp \left\{ NH \left(\tilde{\Sigma}^N(u^N; f^N) - \tilde{\Sigma}(u^N; f) + \tilde{\Sigma}(u^N; f) - \tilde{\Sigma}(\phi; f) + \tilde{\Sigma}(\phi; f) \right) \right\} \mathbb{1}_{\{u^N \in U_{f, \phi; \delta}\}} \right] \end{aligned}$$

thus as we can find a rank N_0 such that

$$\left| \tilde{\Sigma}^N(u^N; f^N) - \tilde{\Sigma}(u^N; f) \right| \leq \delta/3,$$

we have for all $N \geq N_0$

$$\mathbb{P} [u^N \in U_{f, \phi; \delta}] \leq \exp \left\{ NH \left(\frac{2\delta}{3} - \tilde{\Sigma}(\phi; f) \right) \right\}. \quad (4.4.18)$$

If $I_T(\phi) < +\infty$, we can find an f_δ such that

$$I_T(\phi) \leq \tilde{\Sigma}(\phi; f) + \frac{\delta}{3}$$

and then for $N \geq N_0$, (4.4.18) gives the result.

Suppose $I_T(\phi) = +\infty$ then we can find a sequence of $f^{(n)} \in \mathcal{C}^{1,3}([0, T] \times [0, 1])$ such that

$$\tilde{\Sigma}_T(\phi; f^{(n)}) \rightarrow +\infty \quad \text{as } n \rightarrow +\infty.$$

then we have for $n \geq n_0$,

$$\tilde{\Sigma}_T(\phi; f^{(n)}) > 2\delta$$

and the result follows the same taking $U_{f^{(n)}, \phi; \delta}$. □

The next result states the upper bound for compact sets.

Theorem 4.4.1. *Let K be a compact set of $D([0, T]; (L^2[0, 1])^4)$.*

If $u_0 \in (L^2([0, 1]))^4$ is such that

$$\lim_{N, H \rightarrow \infty} \|u^{N, H}(0) - u_0\| = 0$$

and the initial condition satisfies

$$\sup_{N \in \mathbb{N}} \|u_0^N\|_{0, \infty} \leq C_0 \quad \text{for some } C_0 > 0, \quad (4.4.19)$$

then

$$\limsup_{H, N \rightarrow \infty} \frac{1}{NH} \log \mathbb{P} [u^{N, H} \in K] \leq -I_T(K) \quad (4.4.20)$$

proof. Since K is compact, for any fixed $\delta > 0$

$$K \subset \bigcup_{l=1}^m U_{\phi_l; \delta}.$$

and then we have that: $\forall \delta > 0$,

$$\begin{aligned} \limsup_{N, H \rightarrow +\infty} \frac{1}{NH} \log \mathbb{P} [u^N \in K] &\leq \max_{l=1, \dots, m} \limsup_{N, H \rightarrow +\infty} \frac{1}{NH} \log \mathbb{P} [u^N \in U_{\phi_l; \delta}] \\ &\leq \begin{cases} -I_T(K) - \delta & \text{if for some } l, I_T(\phi_l) < +\infty \\ -\delta & \text{else} \end{cases} \end{aligned}$$

and then we conclude. ■

4.5 Appendix

4.5.1 Proof of Theorem 4.2.1

Since $\tilde{A}_N = \text{diag}(0, 0, 0, -\nu \nabla_N + \mathfrak{D} \Delta_N)$ is linear, it is Lipschitz. Next, the vector field $F = (F_S, F_I, F_R, F_B)$ is locally Lipschitz continuous. Thus, the initial value problem (4.2.29) has a unique local solution v^N , thanks to the Picard-Lindelöf theorem. That solution satisfies (4.2.30). The bound (4.2.31) is obtained from (4.2.4) (iii) and Gronwall lemma as in the previous sections, and we deduce that v^N is in fact a global solution.

Now, let $T > 0$ be fixed. From (4.3.2), we may assume that F is globally Lipschitz and we choose L such that $\|F(u) - F(\tilde{u})\|_E \leq L \|u - \tilde{u}\|_E$, provided $\|u\|_E \leq C_T = \max(c_0, 1)e^{2MT}$.

From (4.2.12) and (4.2.30), we have

$$v^N(t) - v(t) = \tilde{T}_N(t) \tilde{P}_N v(0) - \tilde{T}(t) v(0) + \int_0^t \left(\tilde{T}_N(t-s) F(v^N(s)) - \tilde{T}(t-s) F(v(s)) \right) ds$$

for all $t \geq 0$. Then,

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$$\begin{aligned} \|v^N(t) - v(t)\|_{\infty, \infty} &\leq \left\| \tilde{T}_N(t) \tilde{P}_N v(0) - \tilde{T}(t) v(0) \right\|_E \\ &\quad + \int_0^t \left\| \tilde{T}_N(t-s) (F(v^N(s)) - \tilde{P}_N F(v(s))) \right\|_E ds \\ &\quad + \int_0^t \left\| \tilde{T}_N(t-s) \tilde{P}_N F(v(s)) - \tilde{T}(t-s) F(v(s)) \right\|_E ds. \end{aligned}$$

Observing that \mathbb{H}^N is stable by F and the projection \tilde{P}_N is a contracting linear operator on $E = (C_p(J))^4$, the second and third terms on the r.h.s. of the inequality above satisfy

$$T_2(N) \leq \int_0^t \left\| \tilde{P}_N (F(v^N(s)) - F(v(s))) \right\|_E ds \leq L \int_0^t \|v^N(s) - v(s)\|_E ds,$$

and

$$T_3(N) = \int_0^t \|T_N(t-s) P_N F(v(s)) - T(t-s) F(v(s))\|_{\infty} ds.$$

Thus, taking the supremum in t on $[0, T]$ and using Gronwall lemma leads to

$$\begin{aligned} &\sup_{t \leq T} \|v^N(t) - v(t)\|_{\infty, \infty} \\ &\leq \left(\sup_{t \leq T} \left\| \tilde{T}_N(t) \tilde{P}_N v(0) - \tilde{T}(t) v(0) \right\|_E \right. \\ &\quad \left. + \int_0^T \sup_{t \leq T} (\|T_N(t-s) P_N F(v(s)) - T(t-s) F(v(s))\|_{\infty} \mathbf{1}_{(s \leq t)}) ds \right) \times e^{LT}. \end{aligned}$$

Firstly,

$$\sup_{t \leq T} \left\| \tilde{T}_N(t) \tilde{P}_N v(0) - \tilde{T}(t) v(0) \right\|_E \longrightarrow 0,$$

since $v(0) = v_0 \in (C^3(I))^4$ yields $\|\tilde{A}_N \tilde{P}_N v_0 - \tilde{A} v_0\|_E \rightarrow 0$ (see [Kat66a], chapter 9, section 3). Secondly, we fix $t \in [0, T]$ and $s \in [0, t]$. Since $F(v(s)) \in (C^3(I))^4$, the same argument as previously yields

$$\sup_{t \leq T} \|T_N(t-s) P_N F(v(s)) - T(t-s) F(v(s))\|_E \longrightarrow 0,$$

and we conclude by dominated convergence. \square

4.5.2 Heuristics on the Rate function

Remember our process is of the form

$$\begin{aligned} u_t^N &= u_0^N + \frac{1}{H} \sum_{i=1}^N \sum_{j=1}^{14} \tilde{g}_{i,j} P_{i,j} \left(H \int_0^t \beta_{i,j}^N(u_s^N) ds \right) \\ &= u_0^N + \sum_{i=1}^N \sum_{j=1}^{14} \tilde{g}_{i,j} \int_0^t \beta_{i,j}^N(u_s^N) ds + \frac{1}{H} \sum_{i=1}^N \sum_{j=1}^{14} \tilde{g}_{i,j} M_{i,j} \left(H \int_0^t \beta_{i,j}^N(u_s^N) ds \right), \end{aligned} \tag{4.5.1}$$

and we are interested in deriving a rate function for the large deviations principle we want to prove. for every $\phi \in D([0, T]; (L^2[0, 1])^4)$ such that its projection ϕ^N on $(\mathbb{H}^N)^4$ satisfies that

equation, we have at each time t ,

$$\phi_t^N - \phi_{t-}^N = \frac{1}{H} \sum_{i=1}^N \sum_{j=1}^{14} \tilde{g}_{i,j} \left[P_{i,j} \left(H \int_0^t \beta_{i,j}^N(\phi_s^N) ds \right) - P_{i,j} \left(H \int_0^{t-} \beta_{i,j}^N(\phi_s^N) ds \right) \right].$$

In what follows we denote by ϕ both the trajectory ϕ and its projection ϕ^N . But we keep in mind that the notation $\phi_t(i)$ refers to the projection $\phi_t^N(i)$ while $\phi_t(x)$ refers to the original ϕ .

Computing the laplace transform of the variation $\phi_t - \phi_{t-}$ at a jump of ϕ that happens at a time t , we have

$$\mathbb{E} \left[e^{NH \langle \phi_t - \phi_{t-}, f \rangle} \right] = \mathbb{E} \left[\exp \left\{ N \sum_{i=1}^N \sum_{j=1}^{14} \langle \tilde{g}_{i,j}, f \rangle P_{i,j} (H \beta_{i,j}^N(\phi_{t-})) \right\} \right]$$

for all $f \in (\mathcal{C}[0, 1])^4$, and denoting as before $f^N = P_N f$, the projection of f on $(\mathbb{H}^N)^4$.

Then, we use the mutual independance of the Poisson processes $(P_{i,j})_{1 \leq i \leq N, 1 \leq j \leq 14}$ to get

$$\begin{aligned} \mathbb{E} \left[e^{NH \langle \phi_t - \phi_{t-}, f \rangle} \right] &= \left(\prod_{i=1, j=1}^{N, 12} \mathbb{E} \left[\exp \left\{ N \langle \tilde{g}_{i,j}, f \rangle P_{i,j} (H \beta_{i,j}^N(\phi_{t-})) \right\} \right] \right) \\ &\quad \times \prod_{i=1, j=13}^{N, 14} \mathbb{E} \left[\exp \left\{ N \langle \tilde{g}_{i,j}, f \rangle P_{i,j} (H \beta_{i,j}^N(\phi_{t-})) \right\} \right]. \end{aligned}$$

The first term directly comes as follows:

$$\begin{aligned} &\left(\prod_{i=1, j=1}^{N, 12} \mathbb{E} \left[\exp \left\{ \langle \tilde{g}_{i,j}, f \rangle P_{i,j} (H \beta_{i,j}^N(\phi_{t-})) \right\} \right] \right) \\ &= \prod_{i=1, j=1}^{N, 12} \exp \left\{ H \beta_{i,j}^N(\phi_{t-}) \left(e^{(g_j | f^N(i))} - 1 \right) \right\} \\ &= \exp \left\{ \sum_{j=1}^{12} \sum_{i=1}^N H \beta_{i,j}^N(\phi_{t-}) \left(e^{(g_j | f^N(i))} - 1 \right) \right\} \\ &= \exp \left\{ NH \sum_{j=1}^{12} \left[\frac{1}{N} \sum_{i=1}^N \beta_{i,j}^N(\phi_{t-}) \left(e^{(g_j | f^N(i))} - 1 \right) \right] \right\}. \end{aligned}$$

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For the other one, we have :

$$\begin{aligned}
& \prod_{i=1, j=13}^{N, 14} \mathbb{E} \left[\exp \left\{ N \langle \tilde{g}_{i,j}, f \rangle P_{i,j} \left(H \beta_{i,j}^N(\phi_{t-}) \right) \right\} \right] \\
&= \prod_{i=1, j=13}^{N, 14} \exp \left\{ H \beta_{i,j}^N(\phi_{t-}) \left(e^{N \langle \tilde{g}_{i,j}, f \rangle} - 1 \right) \right\} \\
&= \exp \left\{ H \sum_{i=1}^N \phi_{t-}(i) \left[\ell \mathcal{P}_{out} \left(e^{N \langle (\mathbf{1}_{i+1} - \mathbf{1}_i) g_{13}, f \rangle} - 1 \right) + \ell \mathcal{P}_{in} \phi_{t-}(i) \left(e^{N \langle (\mathbf{1}_{i-1} - \mathbf{1}_i) g_{13}, f \rangle} - 1 \right) \right] \right\} \\
&= \exp \left\{ H \sum_{i=1}^N \phi_{t-}(i) \left[\ell \mathcal{P}_{out} \left(e^{(g_{13} | f^N(i+1) - f^N(i))} - 1 \right) + \ell \mathcal{P}_{in} \left(e^{(g_{13} | f^N(i-1) - f^N(i))} - 1 \right) \right] \right\} \\
&= \exp \left\{ H \sum_{i=1}^N \phi_{t-}(i) e^{(g_{13} | f^N(i))} \left[\ell \mathcal{P}_{out} \left(e^{(g_{13} | f^N(i+1))} - e^{(g_{13} | f^N(i))} \right) \right. \right. \\
&\quad \left. \left. + \ell \mathcal{P}_{in} \left(e^{(g_{13} | f^N(i-1))} - e^{(g_{13} | f^N(i))} \right) \right] \right\} \\
&= \exp \left\{ H \sum_{i=1}^N \phi_{t-}(i) e^{(g_{13} | f^N(i))} \left[\ell \frac{\mathcal{P}_{out} + \mathcal{P}_{in}}{2} \left(e^{(g_{13} | f^N(i+1))} - 2e^{(g_{13} | f^N(i))} + e^{(g_{13} | f^N(i-1))} \right) \right. \right. \\
&\quad \left. \left. + \ell (\mathcal{P}_{out} - \mathcal{P}_{in}) \left(\frac{e^{(g_{13} | f^N(i+1))} - e^{(g_{13} | f^N(i-1))}}{2} \right) \right] \right\}
\end{aligned}$$

using the fact that $\ell = 2DN^2$ and $\ell = \nu N$

$$= \exp \left\{ NH \left[\frac{1}{N} \sum_{i=1}^N \phi_{t-}(i) e^{(g_{13} | f^N(i))} \left(\mathcal{D} \Delta_N e^{(g_{13} | f^N)}(i) + \nu \nabla_N e^{(g_{13} | f^N)}(i) \right) \right] \right\}$$

If we show that $\forall j = 1, \dots, 12$

$$\lim_{N \rightarrow +\infty} \frac{1}{N} \sum_{i=1}^N \beta_{i,j}^N(\phi_{t-}) \left(e^{(g_j | f^N(i))} - 1 \right) = \int_0^1 \beta_j(\phi_{t-}(x)) \left(e^{(g_j | f(x))} - 1 \right) dx, \quad (4.5.2)$$

and also that

$$\begin{aligned}
& \lim_{N \rightarrow +\infty} \frac{1}{N} \sum_{i=1}^N \phi_{t-}(i) e^{(g_{13} | f^N(i))} \left(\mathcal{D} \Delta_N e^{(g_{13} | f^N)}(i) + \nu \nabla_N e^{(g_{13} | f^N)}(i) \right) \\
&= \int_0^1 \phi_{t-}(x) e^{(g_{13} | f(x))} \left(D \Delta e^{(g_{13} | f)}(x) + \nu \nabla e^{(g_{13} | f)}(x) \right) dx, \quad (4.5.3)
\end{aligned}$$

then, the log-Laplace transform takes the form given in Section 4.4.1 by (4.4.8).

As it is common in Large deviations theory, the rate function (4.4.7) is obtained by taking the Legendre Transform of the log-Laplace transform. There are other approaches to derive (4.4.8). One of them is somehow to the one we are using. The approach is to derive the Hamiltonian (4.4.8) from the infinitesimal generator of the process (see for instance [KL95], [DK95] and [KOV89]).

It is now left to prove our claims (4.5.2) and (4.5.3) above. For (4.5.2), we use the fact that jump rates have a suitable form and for both claims, we need to assume more regularity in space for test functions f and ϕ_t . $\phi_t \in (\mathcal{C}^1[0, 1])^4$ and $f \in \mathcal{C}^3([0, 1])$. We prove only (4.5.2). The second claim one is treated accordingly.

Recall that the jump rates defined by (4.4.3) and (4.4.4) satisfy

$$\beta_{i,j}(\phi_{t-}) - \beta_j(\phi_{t-}(x)) \leq c^{ste}(\phi) [(\phi_{t-}^1(i) - \phi_{t-}^1(x)) + \cdots + (\phi_{t-}^4(i) - \phi_{t-}^4(x))]$$

for $j = 1, \dots, 12, \forall i = 1, \dots, N$ and $x \in [0, 1]$. Therefore we have that

$$\begin{aligned} & \left| \frac{1}{N} \sum_{i=1}^N \beta_{i,j}^N(\phi_{t-}) \left(e^{(g_j | f^N(i))} - 1 \right) - \int_0^1 \beta_j(\phi_{t-}(x)) \left(e^{(g_j | f(x))} - 1 \right) dx \right| \\ & \leq \left| \sum_{i=1}^N \int_{J_i} \left[\beta_{i,j}^N(\phi_{t-}) \left(e^{(g_j | f^N(i))} - 1 \right) - \beta_j(\phi_{t-}(x)) \left(e^{(g_j | f(x))} - 1 \right) \right] dx \right| \\ & \leq \left| \sum_{i=1}^N \int_{J_i} \left[(\beta_{i,j}^N(\phi_{t-}) - \beta_j(\phi_{t-}(x))) \left(e^{(g_j | f^N(i))} - 1 \right) \right. \right. \\ & \quad \left. \left. + \beta_j(\phi_{t-}(x)) \left(e^{(g_j | f^N(i))} - e^{(g_j | f(x))} \right) \right] dx \right| \\ & \leq c^{ste} \left| \sum_{i=1}^N \int_{J_i} \left(\phi_{t-}^\ell(i) - \phi_{t-}^\ell(x) \right) \left(e^{(g_j | f^N(i))} - 1 \right) dx \right| \\ & \quad + \left| \sum_{i=1}^N \int_{J_i} \beta_j(\phi_{t-}(x)) \left(e^{(g_j | f^N(i))} - e^{(g_j | f(x))} \right) dx \right|, \end{aligned}$$

and we conclude.

4.5 Appendix

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Les besoins grandissants de prévisions robustes pour des systèmes complexes conduisent à introduire des modèles mathématiques considérant un nombre croissant de paramètres. Au temps s'ajoutent, l'espace, l'aléa, les échelles de dynamiques, donnant lieu à des modèles stochastiques multi-échelles avec dépendance spatiale (modèles spatiaux). Cependant, l'explosion du temps de simulation de tels modèles complique leur utilisation. Leur analyse difficile a néanmoins permis, pour les modèles à une échelle, de développer des outils puissants: loi des grands nombres (LGN), théorème central limite (TCL), ..., puis d'en dériver des modèles simplifiés et algorithmes accélérés. Dans le processus de dérivation, des modèles et algorithmes dits hybrides ont vu le jour dans le cas multi-échelle, mais sans analyse rigoureuse préalable, soulevant ainsi la question d'approximation hybride dont la consistance constitue l'une des motivations principales de cette thèse.

En 2012, Crudu, Debussche, Muller et Radulescu établissent des critères d'approximation hybride pour des modèles homogènes en espace de réseaux de régulation de gènes. Le but de cette thèse est de compléter leur travail et le généraliser à un cadre spatial.

Nous avons développé et simplifié différents modèles, tous des processus de Markov de sauts purs à temps continu. La démarche met en avant, d'une part, des conditions d'approximations déterministes par des solutions d'équations d'évolution (type réaction-advection-diffusion), et, d'autre part, des conditions d'approximations hybrides par des processus stochastiques hybrides. Dans le cadre des réseaux de réactions biochimiques, un TCL est établi. Il correspond à une approximation hybride d'un modèle homogène simplifié à deux échelles de temps (suivant Crudu *et al.*). Puis, une LGN est obtenue pour un modèle spatial à deux échelles de temps. Ensuite, une approximation hybride est établie pour un modèle spatial à deux échelles de dynamique en temps et en espace. Enfin, des comportements asymptotiques en grandes populations et en temps long sont présentés pour un modèle d'épidémie de choléra, via une LGN suivie d'une borne supérieure pour les sous-ensembles compacts, dans le cadre d'un principe de grande déviation (PGD) correspondant.

À l'avenir, il serait intéressant, entre autres, de varier la géométrie spatiale, de généraliser le TCL, de compléter les estimations du PGD, et d'explorer des systèmes complexes issus d'autres domaines.

Mots-clés

Systèmes complexes multi-échelles, Réaction-advection-diffusion stochastique, Processus de Markov, Théorèmes limites fonctionnels, Approximation par des systèmes hybrides stochastiques en dimension infinie, Générateurs et problème de martingale, Différences finies.

The growing needs of precise predictions for complex systems lead to introducing stronger mathematical models, taking into account an increasing number of parameters added to time: space, stochasticity, scales of dynamics. Combining these parameters gives rise to spatial --- or spatially inhomogeneous--- multiscale stochastic models. However, such models are difficult to study and their simulation is extremely time consuming, making their use not easy. Still, their analysis has allowed one to develop powerful tools for one scale models, among which are the law of large numbers (LLN) and the central limit theorem (CLT), and, afterward, to derive simpler models and accelerated algorithms. In that deduction process, the so-called hybrid models and algorithms have arisen in the multiscale case, but without any prior rigorous analysis. The question of hybrid approximation then shows up, and its consistency is a particularly important motivation of this PhD thesis.

In 2012, criteria for hybrid approximations of some homogeneous regulation gene network models were established by Crudu, Debussche, Muller and Radulescu. The aim of this PhD thesis is to complete their work and generalize it afterward to a spatial framework.

We have developed and simplified different models. They all are time continuous pure jump Markov processes. The approach points out the conditions allowing on the one hand deterministic approximations by solutions of evolution equations, and, on the other hand, hybrid approximations by hybrid stochastic processes. In the field of biochemical reaction networks, we establish a CLT. It corresponds to a hybrid approximation of a simplified homogeneous model (due to Crudu *et al.*). Then a LLN is obtained for a spatial model with two time scales. Afterward, a hybrid approximation is established, for a two time-space scales spatial model. Finally, the asymptotic behaviour in large population and long time are respectively presented for a model of cholera epidemic, through a LLN followed by the upper bound for compact sets, in the context of a corresponding large deviation principle (LDP).

Interesting future works would be, among others, to study other spatial geometries, to generalize the CLT, to complete the LDP estimates, and to study complex systems from other fields.

Keywords

Multiscale complex systems, Stochastic reaction-advection-diffusion, Markov process, Functional limit theorems, Approximation by infinite dimensional stochastic hybrid systems, Generators and martingale problem, Finite difference method.