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# Mathematical modeling in neuroscience: collective behavior of neuronal networks & the role of local homeoproteins diffusion in morphogenesis

Cristobal Quininao

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**Thèse de Doctorat de  
l'Université Pierre et Marie Curie**

Spécialité Mathématiques

École Doctorale de Sciences Mathématiques de Paris Centre

par

Cristóbal QUIÑINAO

pour obtenir le grade de

DOCTEUR de l'UNIVERSITÉ PIERRE ET MARIE CURIE

**Mathematical modeling in Neuroscience: collective behavior of  
neuronal networks & the role of local homeoproteins diffusion in  
morphogenesis**

*Modélisation mathématique en neuroscience: comportement collectif des réseaux  
neuronaux & rôle de la diffusion locale des homéoprotéines dans la morphogénèse.*

dirigée par Benoît PERTHAME, Stéphane MISCHLER et Jonathan TOUBOUL

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# General Introduction

## 1.1 Presentation

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The text you are holding in your hands is a summary of the labor I have been doing the past few years, which is related to mathematical models motivated by neuroscience. Working in a multidisciplinary environment encompasses a great amount of unexpected difficulties: *even the language can be misunderstood!* Nevertheless, I have learned that such diversity is translated into infinite possibilities. My research activity has been principally related to mathematical questions arising from the modeling of biological systems combining analytic and probabilistic tools. The main issue consists in understanding the long time behaviour of those systems, and the structure of the set of stationary solutions under different parameters regime. The results provided here are related to three major elements: (1) the mathematical modeling and analysis of neuronal networks, (2) the role of homeoproteins local diffusion in pattern formation, and (3) an individual base model for a subcritical Keller-Segel equation. To simplify the presentation, the manuscript is divided in three parts:

### 1.1.1 Part I: Neuronal networks

The first part of the text is related to theoretical neuroscience, specifically with some networks of interconnected neurons. One of the most remarkable and celebrated models for isolated neurons is due to Alan Hodgkin and Andrew Huxley [75]. In their outstanding paper, authors planted the seed of any latter attempt to model the brain. However, it is estimated that the human brain is composed by 100 billion interacting cells. Therefore, even having such a precise model for a single neuron, the collective behaviour is not completely understood.

The approach followed here undertakes the analysis of mean-field equations arising in the modeling of the macroscopic activity of the brain. The equations describe the large-scale dynamics of the central nervous system, taking into account the fact that it is composed of a very large number of interconnected cells that manifest highly nonlinear dynamics and are subject to noise. Non-linearities in the intrinsic dynamics of individual cells are an essential element of the neural code: nerve cells constantly regulate

their electrical potential depending on the input they receive. Our models describe a particle network at a macroscopic level and take into account two mechanisms:

- ▷ the intrinsic dynamic of individuals, which eventually lead to cyclic solutions;
- ▷ a nonlinear mean-field interaction (or coupling) between individuals which can take into account some delay term;

The general mathematical properties observed are: on one hand the existence of steady states (whatever are the coefficients) and discrete principal spectrum of the linearized operator associated to the mean-field equations, and on the other hand, the uniqueness of the steady state and nonlinear exponential stability of this one in the weak connectivity regime.

### **1.1.2 Part II: The role of homeoprotein diffusion in morphogenesis**

The second part of the text is related to a developmental biology problem called morphogenesis. The question here is to explain how a system starting with almost identical cells results in a well-defined spatial pattern and defining a set of specific cellular states. This problem can be addressed in two complementary perspectives: on one hand, there is the variety of cells as the result of the growth of a single one (process driven by local interaction); and on the other hand, the regulation on an ensemble of cells to produce different functional areas (process driven by global interaction). Moreover, boundaries in the developing organism decides on the position and size of compartments in the adult. Therefore, the stability and regularity of those boundaries is key element on the development of a healthy individual. The emergence of compartments in the cerebral cortex or in the spinal cord is a paradigmatic example of this process. From a theoretical perspective, the specification of territories in the nervous system represents a particular case of the general phenomenon of patterning. In contemporary terms, the differentiation process is driven by the presence of a morphogen, and a response to the morphogen concentration characterized by the expression of cell autonomous transcription factors, very often of the homeoprotein family.

Starting from two very different theories of neurogenesis, we claim that they are not necessarily opposing. Moreover we show both numerically and analytically that the presence of homeoproteins arbitrarily small diffusion, leads to a dramatic stabilization of the positioning of the boundary, even when other parameters are significantly modified. This novel combined model we propose has thus an important theoretical consequence for our understanding of the role of homeoproteins intercellular diffusion in developmental robustness and of the changes that took place in the course of evolution.

### **1.1.3 Part III: On a subcritical Keller-Segel equation**

Finally, the third part of this manuscript constitutes a complementary work. It deals with a modified version of the Keller-Segel (KS) equation. A main property of the standard KS equation is that the force kernel is singular at the origin. It describes a model of chemotaxis: the movement of cells, usually bacteria or amoebae, which are attracted by some chemical substance. The microscopic model of chemotaxis and

the convergence of those systems, has become a very interesting subject in the past years [142, 71]. One of the reasons is that the classical formulation of the KS equation in two dimensions can be naturally related to a mean field limit. Nevertheless, the evaluation of the force kernel on the distance between the particles has to be treated carefully to avoid blow-up in finite time.

The approach followed here undertakes the analysis of a microscopic system for the subcritical KS equation. Thanks to the subcritical exponent, we prove that the particles never collide. As a consequence, we get the chaos propagation property and the consistence of the microscopic particle system with the mean-field limit equation.

#### 1.1.4 Plan of the Thesis

The present text is organised as follows: in the rest of this introduction we describe the most recurrent mathematical tools we use throughout the following chapters. We also provide some biological background to the problems motivating the mathematical work. In the final section of this introduction, we describe the main results and present the main ideas of the proofs.

Chapter 2 deals with the limits of a general model of neuronal networks with delays and random architectures. We prove the classical propagation of chaos property and study a completely solvable toy model. Next, in Chapter 3, we show the non exponential convergence to a non trivial steady state for a kinetic FitzHugh-Nagumo equation. This equation is obtained as the mean-field limit of a FitzHugh-Nagumo neuronal network.

The second part of the thesis is composed by two chapters. In Chapter 4 we present the general model of neuronal morphogenesis we propose. We study the set of stationary solutions and the effects of the diffusion operator on them. In Chapter 5, we analyse the previous model in the one dimensional case, and prove that, when the diffusivity coefficient goes to zero, the stationary solutions converge to a unique solution of an autonomous dynamical system with a unique discontinuity point.

Finally, Chapter 6 deals again with the propagation of chaos property for a subcritical Keller-Segel equation. Using a combination of PDE and SDE tools, we also prove the more strong notion of entropic chaos propagation.

## 1.2 Mathematical toolbox ---

In this section we describe the two most recurrent mathematical tools used throughout the memoir. We pay special attention to the chaos propagation property (c.p.p.) and the semigroup decomposition technique (s.d.t). The c.p.p. will allow us to justify the passage from Individual Based models (IBM) to their description in terms of a mean-field equation. The s.d.t. will be useful to describe the spectrum the linearised operators and eventually, using a perturbation argument, the convergence of the nonlinear operator on a small parameter regime.

### 1.2.1 Mean-field macroscopic equations: propagation of chaos property

The first question we treat is the justification of the mean-field limits. To that aim it is necessary to pass from Individual Based Models (IBM) to the network activity in terms of a nonlinear McKean-Vlasov equation describing the law of independent particles. This property, called usually *chaoticity* or *propagation of chaos*, is a very well known and popular topic since the seminal works of Kac [82], McKean [104, 103], and Sznitzman [145]. To fix ideas, let us consider a generic toy neuronal network, composed by  $N$  individuals. The state of the neuron  $i$  is given by a  $\mathbb{R}^d$ -random process (e.g. the membrane voltage, ionic concentrations, etc) solving:

$$X_t^{i,N} = X_0^{i,N} + \int_0^t f(s, X_s^{i,N}) ds + \frac{1}{N} \sum_{j=1}^N \int_0^t g(s, X_s^{i,N}, X_s^{j,N}) ds + \sqrt{2\sigma} B_t^i, \quad (1.2.1)$$

where  $f$  is the intrinsic dynamic of any neuron,  $g$  is the interaction function, and  $B_t^i$  is a family of independent Brownian motions modeling the natural random component of the dynamics.

We can summarise the chaos propagation property by: *when the number of particles is going to infinity, each one of them behaves as independent copies of the solution of a mean field equation.* The nonlinearity is characterised by the presence of the law itself in the dynamics on the process, i.e., an integro-differential nonlinear equation. To justify the limit we mainly use the coupling method which is a very intuitive idea and apply to a wide range of applications. In the case of equation (1.2.1) the limit equation is given by

$$X_t = X_0 + \int_0^t f(s, X_s) ds + \int_{\mathbb{R}^d} \int_0^t g(s, X_s, y) f_s(dy) ds + \sqrt{2\sigma} B_t, \quad (1.2.2)$$

where  $f_t = \mathcal{L}(X_t)$  is the law of  $X_t$ . Therefore, the propagation of chaos property means that any finite set of neurons  $(X^{i_1}, \dots, X^{i_l})$  converges in law to  $l$  independent copies of the solution of (1.2.2).

Let us consider  $E$  a Banach space, for  $N \geq 2$ , we denote by  $\mathbb{P}_{sym}(E^N)$  the set of symmetric probability measures on  $E^N$ , i.e. the set of probability measures which are laws of exchangeable  $E^N$ -valued random variables.

We consider for any  $F \in \mathbb{P}_{sym}((\mathbb{R}^d)^N)$  with a density and a finite moment of positive order, the Boltzmann entropy and the Fisher information which are defined by

$$H(F) := \frac{1}{N} \int_{(\mathbb{R}^d)^N} F(x) \log F(x) dx \quad \text{and} \quad I(F) := \frac{1}{N} \int_{(\mathbb{R}^d)^N} \frac{|\nabla F(x)|^2}{F(x)} dx.$$

If  $x_i \in \mathbb{R}^d$ , stands for the  $i$ -th coordinate of  $x \in (\mathbb{R}^d)^N$ , we define for  $k \geq 0$ ,

$$M_k(F) := \frac{1}{N} \int_{(\mathbb{R}^d)^N} \sum_{i=1}^N |x_i|^k F(dx).$$

Observe that we proceed to the normalization by  $1/N$  in order to have, for any  $f \in \mathbb{P}(\mathbb{R}^d)$ ,

$$H(f^{\otimes N}) = H(f), \quad I(f^{\otimes N}) = I(f) \quad \text{and} \quad M_k(f^{\otimes N}) = M_k(f).$$

We introduce the space  $\mathbb{P}_1(\mathbb{R}^d) := \{f \in \mathbb{P}(\mathbb{R}^d), M_1(f) < \infty\}$  and we recall the definition of the Wasserstein distance: if  $f, g \in \mathbb{P}_1(\mathbb{R}^d)$ ,

$$\mathcal{W}_1(f, g) = \inf \left\{ \int_{\mathbb{R}^d \times \mathbb{R}^d} |x - y| R(dx, dy) \right\},$$

where the infimum is taken over all probability measures  $R$  on  $\mathbb{R}^d \times \mathbb{R}^d$  with  $f$  for first marginal and  $g$  for second marginal. It is known that the infimum is reached. See e.g. Villani [158] for many details on the subject.

The notion of propagation of chaos is rigorously defined by

**Definition 1.2.1.** *Let  $X$  be some  $\mathbb{R}^d$ -valued random variable. A sequence  $(X^{1,N}, \dots, X^{N,N})$  of exchangeable  $\mathbb{R}^d$ -valued random variables is said to be  $X$ -chaotic if one of the three following equivalent conditions is satisfied:*

- (i)  $(X^{1,N}, X^{2,N})$  goes in law to 2 independent copies of  $X$  as  $N$  goes towards  $+\infty$ ;
- (ii) for all  $j \geq 0$ ,  $(X^{1,N}, \dots, X^{j,N})$  goes in law to  $j$  independent copies of  $X$  as  $N$  goes towards  $+\infty$ ;
- (iii) the empirical measure  $\mu_{X^N}^N := \frac{1}{N} \sum_{i=1}^N \delta_{X^{i,N}} \in \mathbb{P}(\mathbb{R}^d)$  goes in law to the constant  $\mathcal{L}(X)$  as  $N$  goes towards  $+\infty$ .

Let us remark that the key points on the propagation of chaos property are: the existence of a unique solution to the particle system (1.2.1), the existence and uniqueness of the solutions to the mean-field nonlinear equation (1.2.2), and the consistence between the particle system and the limit equation. To prove the third point, we can use the *coupling method* (or in general any other compactness method), which consist in use the well-posedness of both equations to control the distance of the paths of a finite set of particles as  $N$  is going to  $+\infty$ .

**Example 1.2.2.** *In our toy model (1.2.1), let us assume that  $d = 1$ , and fix a family of Brownian motions  $B_t^i$  driving the solutions of the particle system. Consider  $(Y^{i,N}, \dots, Y^{N,N})$  a family of solutions to the nonlinear mean-field equations*

$$Y_t^{i,N} = X_0^{i,N} + \int_0^t f(s, Y_s^{i,N}) ds + \int_0^t \mathbb{E}_Z [g(s, Y_s^{i,N}, Z_s)] ds + \sqrt{2\sigma} B_t^i,$$

where  $Z$  is a independent copy of the unique solution to (1.2.2). We see that, since we use the same initial condition and Brownian motions, the random processes  $Y^{i,N}$  are “coupled” to the  $X^{i,N}$  processes. For any  $i \in \mathbb{N}$  fixed, the difference between  $X^{i,N}$  and  $Y^{i,N}$  is such that

$$\begin{aligned} \mathbb{E}[|X_t^{i,N} - Y_t^{i,N}|] &\leq \int_0^t \mathbb{E}[|f(s, X_s^{i,N}) - f(s, Y_s^{i,N})|] ds \\ &\quad + \frac{1}{N} \sum_{j=1}^N \int_0^t \mathbb{E} \left[ |g(s, X_s^{i,N}, X_s^{j,N}) - \mathbb{E}_Z [g(s, Y_s^{i,N}, Z_s)]| \right] ds. \end{aligned}$$

If the dynamic  $f$  and the interaction  $g$  are  $L$ -Lipchitz continuous functions, it follows that

$$\begin{aligned} \mathbb{E}[|X_t^{i,N} - Y_t^{i,N}|] &\leq 2L \int_0^t \mathbb{E}[|X_s^{i,N} - Y_s^{i,N}|] ds + L \int_0^t \mathbb{E} \left[ \max_{j=1, \dots, N} |X_s^{j,N} - Y_s^{j,N}| \right] ds \\ &\quad + \frac{1}{N} \sum_{j=1}^N \int_0^t \mathbb{E} \left[ |g(s, Y_s^{i,N}, Y_s^{j,N}) - \mathbb{E}_Z [g(s, Y_s^{i,N}, Z_s)]| \right] ds. \end{aligned}$$

Let us further assume that the interaction function  $g$  is upper bounded by  $C$ , then we get

$$\sum_{j=1}^N \int_0^t \mathbb{E}[|g(s, Y_s^{i,N}, Y_s^{j,N}) - \mathbb{E}_Z[g(s, Y_s^{i,N}, Z_s)]|] ds \leq 2tC\sqrt{N} := C_t\sqrt{N},$$

and by consequence

$$\forall i \in \{1, \dots, N\} \quad \mathbb{E}[|X_t^{i,N} - Y_t^{i,N}|] \leq 3L \int_0^t \mathbb{E}[\max_{j=1, \dots, N} |X_s^{j,N} - Y_s^{j,N}|] ds + \frac{C_t}{\sqrt{N}}.$$

Since  $N$  is fixed, we can apply Gronwall's lemma to deduce that for all  $s \in [0, t]$

$$\mathbb{E}[|X_s^{i,N} - Y_s^{i,N}|] \leq \mathbb{E}[\max_{j=1, \dots, N} |X_s^{j,N} - Y_s^{j,N}|] \leq \frac{C_t e^{3Lt}}{\sqrt{N}}.$$

From the last inequality we have easily the propagation of chaos property. Fixing a finite set of neurons  $(1, \dots, l)$ , then

$$\mathbb{E}[|(X_s^{1,N}, \dots, X_s^{l,N}) - (Y_s^1, \dots, Y_s^l)|] \leq \frac{lC_t e^{3Lt}}{\sqrt{N}},$$

hence

$$(X_s^{1,N}, \dots, X_s^{l,N}) \xrightarrow{\mathcal{L}} (Y_s^1, \dots, Y_s^l),$$

this implies that the vector  $(X_s^{1,N}, \dots, X_s^{l,N})$  converges in law towards  $l$  independent copies of  $Y$  as  $N$  goes to  $+\infty$

We finally recall a stronger (see [72]) sense of chaos introduced by Kac in [82] and formalized recently in [35]: the entropic chaos.

**Definition 1.2.3.** Let  $f$  be some probability measure on  $E$ . A sequence  $(F^N)$  of symmetric probability measures on  $E^N$  is said to be entropically  $f$ -chaotic if

$$F_1^N \rightarrow f \quad \text{weakly in } \mathbb{P}(E) \quad \text{and} \quad H(F^N) \rightarrow H(f) \quad \text{as } N \rightarrow \infty,$$

where  $F_1^N$  stands for the first marginal of  $F^N$ .

We can observe that since the entropy is lower semi continuous (so that  $H(f) \leq \liminf_N H(F^N)$ ) and is convex, the entropic chaos (which requires  $\lim_N H(F^N) = H(f)$ ) is a stronger notion of convergence which implies that for all  $j \geq 1$ , the density of the law of  $(X_1^N, \dots, X_j^N)$  goes to  $f^{\otimes j}$  strongly in  $L^1$  as  $N \rightarrow \infty$  (see [23]).

## 1.2.2 Uniqueness of stationary solutions and nonlinear convergence: semi-group decomposition method

Once the derivation of the limit equation is well justified, several questions arise: what is the role of parameters? are there stationary (stable) solutions? does the system exhibit bifurcations? The second problem addressed in the manuscript is the nonlinear convergence to the equilibrium of a macroscopic mean-field equation. In particular, we study the limit equation of a neural network such that the individual dynamic is given by the FitzHugh-Nagumo model. We uncover the structure of the related linearised operator and apply the semigroup factorisation method to prove the exponential decay to a

unique stationary solution when the interaction between particles is small. Moreover, as the interaction gets stronger, we show numerically that an oscillatory regime emerges.

Of course, the previous paragraph remains very cryptic. We prepare to the study by introducing a few useful notations. For two given Banach spaces  $(E, \|\cdot\|_E)$  and  $(\mathcal{E}, \|\cdot\|_{\mathcal{E}})$ , we denote by  $\mathcal{B}(E, \mathcal{E})$  the space of bounded linear operators from  $E$  to  $\mathcal{E}$  and we denote by  $\|\cdot\|_{\mathcal{B}(E, \mathcal{E})}$  the associated operator norm. The set of closed unbounded linear operators from  $E$  to  $\mathcal{E}$  with dense domain is denoted by  $\mathcal{C}(E, \mathcal{E})$ . In the special case when  $E = \mathcal{E}$ , we simply write  $\mathcal{B}(E) = \mathcal{B}(E, E)$  and  $\mathcal{C}(E) = \mathcal{C}(E, E)$ .

For a given Banach space  $X$  and  $\Lambda \in \mathcal{C}(X)$  which generates a semigroup, we denote this associated semigroup by  $(S_\Lambda(t), t \geq 0)$ , by  $D(\Lambda)$  its domain, by  $N(\Lambda)$  its null space, by  $R(\Lambda)$  its range, and by  $\Sigma(\Lambda)$  its spectrum. On the resolvent set  $\rho(\Lambda) = \mathbb{C} \setminus \Sigma(\Lambda)$  we may define the resolvent operator  $\mathcal{R}(\Lambda)$  by

$$\forall z \in \mathbb{C}, \quad \mathcal{R}_\Lambda(z) := (\Lambda - z)^{-1}.$$

Moreover,  $\mathcal{R}_\Lambda(z) \in \mathcal{B}(X)$  and has range equal to  $D(\Lambda)$ . We recall that  $\xi \in \Sigma(\Lambda)$  is called an eigenvalue of  $\Lambda$  if  $N(\Lambda - \xi) \neq \{0\}$ , and it called an isolated eigenvalue if there exists  $r > 0$  such that

$$\Sigma(\Lambda) \cap \{z \in \mathbb{C}, |z - \xi| < r\} = \{\xi\}.$$

The notion of convolution of semigroups will be also required. Let us consider some Banach spaces  $X_1, X_2$  and  $X_3$  and two given functions

$$S_1 \in L^1([0, \infty); \mathcal{B}(X_1, X_2)) \quad \text{and} \quad S_2 \in L^1([0, \infty); \mathcal{B}(X_2, X_3)),$$

one can define  $S_2 * S_1 \in L^1([0, \infty); \mathcal{B}(X_1, X_3))$  by

$$(S_2 * S_1)(t) := \int_0^t S_2(t-s)S_1(s) ds, \quad \forall t \geq 0.$$

In the special case  $S_1 = S_2$  and  $X_1 = X_2 = X_3$ ,  $S^{(*n)}$  is defined recursively by  $S^{(*1)} = S$  and  $S^{(*n)} = S * S^{(*(n-1))}$  for  $n > 1$ .

To illustrate the ideas we use in the following, let us assume that an operator  $\Lambda$  on a Banach space  $X$  can be written as

$$\Lambda = \mathcal{A} + \mathcal{B},$$

where  $\mathcal{B}$  has some dissipative property and  $\mathcal{A}$  is much more regular than  $\mathcal{B}$ . Under some additional positivity assumption on the generator  $\Lambda$ , the principal part of spectrum is a simple real eigenvalue. This is known as the Krein-Rutman theorem. We state below a recent version picked up from [113],

**Theorem 1.2.4.** *We consider a semigroup generator  $\Lambda$  on a Banach lattice of functions  $X$ , and we assume that*

1. *there exists some  $\alpha^* \in \mathbb{R}$  and two operators  $\mathcal{A}, \mathcal{B} \in \mathcal{C}(X)$ , such that  $\Lambda = \mathcal{A} + \mathcal{B}$  and*

(a) *for any  $\alpha > \alpha^*, \ell \geq 0$ , there exists a constant  $C_{\alpha, \ell} > 0$  such that*

$$\forall t \geq 0, \quad \|S_{\mathcal{B}} * (\mathcal{A}S_{\mathcal{B}})^{(*\ell)}(t)\|_{\mathcal{B}(X)} \leq C_{\alpha, \ell} e^{\alpha t}.$$



(b)  $\mathcal{A}$  is bounded, and there exists an integer  $n \geq 1$  such that for any  $\alpha > \alpha^*$ , there exists a constant  $C_{\alpha,n} > 0$  such that

$$\forall t \geq 0, \quad \|(\mathcal{A}S_{\mathcal{B}})^{(*n)}(t)\|_{\mathcal{B}(X,Y)} \leq C_{\alpha,n}e^{\alpha t},$$

with  $Y \subset D(\Lambda)$  and  $Y \subset X$  with compact embedding;

2. for  $\Lambda^*$  the dual operator of  $\Lambda$  defined in  $X'$ , there exists  $\beta > \alpha^*$  and  $\psi \in D(\Lambda^*) \cap X'_+ \setminus \{0\}$  such that  $\Lambda^*\psi \geq \beta\psi$ ;
3.  $S_{\Lambda}(t)$  is a positive semigroup and  $\Lambda$  satisfies Kato's inequality, i.e.,  $\forall f \in D(\Lambda)$  it holds  $\Lambda|f| \geq \text{sign}(f)\Lambda f$ .
4.  $-\Lambda$  satisfies a strong maximum principle: for any given  $f$  and  $\gamma \in \mathbb{R}$ , there holds,

$$f \in D(\Lambda) \setminus \{0\}, f \geq 0 \text{ and } (-\Lambda + \gamma)f \geq 0 \quad \text{imply} \quad f > 0,$$

and there exists an integer  $m$  such that

$$f \in D(\Lambda^m) \text{ and } |f| > 0 \quad \text{imply} \quad f > 0 \text{ or } f < 0.$$

*Defining*

$$\lambda := s(\Lambda) = \sup \{(\xi) : \xi \in \Sigma(\Lambda)\},$$

there exists  $0 < f_{\infty} \in D(\Lambda)$  and  $0 < \phi \in D(\Lambda^*)$  such that

$$\Lambda f_{\infty} = \lambda f_{\infty}, \quad \Lambda^*\phi = \lambda \phi.$$

Moreover, there is some  $\alpha' \in (\alpha^*, \lambda)$  and  $C > 0$  such that for any  $f_0 \in X$

$$\|S_{\Lambda}(t)f_0 - e^{\lambda t}\langle f_0, \phi \rangle f_{\infty}\|_X \leq Ce^{\alpha' t}\|f_0 - \langle f_0, \phi \rangle f_{\infty}\|_X. \quad (1.2.3)$$

Let us explain some implications of inequality (3.4.30). Assume that the operator  $\Lambda$  has the good decomposition  $\mathcal{A}$  and  $\mathcal{B}$ , and that  $\lambda = 0$ . Then for any initial condition, we have that the difference between the solution to the equation

$$\partial_t f(t) = \Lambda f(t), \quad f(0) = f_0, \quad (1.2.4)$$

which is exactly  $S(t)f_0$ , and the projection of the initial condition on the space related to the first eigenvalue  $\lambda$ , is such that

$$\|f(t) - \langle f_0, \phi \rangle f_{\infty}\|_X \leq Ce^{\alpha' t}\|f_0 - \langle f_0, \phi \rangle f_{\infty}\|_X.$$

Moreover, we know that necessarily  $\alpha' < 0$ , then we conclude that  $f(t)$  is converging to  $\langle f_0, \phi \rangle f_{\infty}$ . In the special case that  $f_0$  is a probability measure and  $\phi = 1$ , we readily obtain that the convergence is always to the unique eigenvector  $f_{\infty}$ .

The previous result is remarkable, and allows us to pass to the limit (in time) with very few (and somehow natural) hypotheses on the operator driving the evolutionary problem. We use it to describe

the convergence to a steady state of a linearised equation. Moreover, in small connectivity regime (i.e. the nonlinear case with a small parameter multiplying the nonlinearity) we use a perturbation argument to show that the convergence still hold.

We are interested in the extrapolation of the convergence results of the heat equation to some mean-field problems that are almost dissipative. In particular, we recall the abstract notion of *hypodissipative operators*:

**Definition 1.2.5.** *Considering a Banach space  $(X, \|\cdot\|_X)$ , a real number  $\alpha \in \mathbb{R}$  and an operator  $\Lambda \in \mathcal{C}(X)$ ,  $(\Lambda - \alpha)$  is said to be hypodissipative on  $X$  if there exists some norm  $\|\cdot\|_X$  on  $X$  equivalent to the usual norm  $\|\cdot\|_X$  such that*

$$\forall f \in D(\Lambda), \quad \exists \phi \in F(f) \quad \text{such that} \quad \langle \phi, (\Lambda - \alpha)f \rangle \leq 0,$$

where  $\langle \cdot, \cdot \rangle$  is the duality bracket in  $X$  and  $X^*$  and  $F(f) \subset X^*$  is the dual set of  $f$  defined by

$$F(f) = F_{\|\cdot\|_X}(f) := \{\phi \in X^*, \quad \langle \phi, f \rangle = \|f\|_X^2 = \|\phi\|_{X^*}^2\}.$$

One classically sees (we refer to for example [70, Subsection 2.3]) that when  $\Lambda$  is the generator of a semigroup  $S_\Lambda$ , for given  $\alpha \in \mathbb{R}$  and  $C > 0$  constants, the following assertions are equivalent:

- (a)  $(\Lambda - \alpha)$  is hypodissipative;
- (b) the semigroup satisfies the growth estimate  $\|S_\Lambda(t)\|_{\mathcal{B}(X)} \leq Ce^{\alpha t}$ ,  $t \geq 0$ .

Finally, we present an example that highlights the relationship between an hypodissipative operator and the decomposition method:

**Example 1.2.6.** *Let us consider  $\Lambda$  the differential operator related to the equation*

$$\frac{\partial}{\partial t} f = \Lambda f := \Delta f + \nabla \cdot (xf), \quad x \in \mathbb{R}. \quad (1.2.5)$$

and the associated semigroup  $S_\Lambda(t)$ . We see clearly that equation (1.2.5) is given in divergence form, therefore, it preserves the mass and the positivity of the solutions. Fix some  $f_0 \in L^1(\mathbb{R}) \cap \mathbb{P}_2(\mathbb{R})$ , then we have that

$$\frac{d}{dt} \int_{\mathbb{R}} |S_\Lambda(t)f_0|(1+x^2)dx = \int_{\mathbb{R}} \Lambda f(t)(1+x^2)dx = \int_{\mathbb{R}} p(x)f dx \quad (1.2.6)$$

with  $p(x) = 2(1-x^2)$ . A nice decomposition of the operator  $\Lambda$  is given by

$$\mathcal{A} = M\chi_R, \quad \mathcal{B} = \Lambda - \mathcal{A},$$

with  $M \geq 0$ ,  $\chi_R(x) = \chi(x/R)$  regular, and  $\mathbf{1}_{\{|x|<1\}} \leq \chi(x) \leq \mathbf{1}_{\{|x|\leq 2\}}$ . Indeed, the idea is to “remove” the positive contribution of  $p(x)$  on the righthand side of (1.2.6) to get

$$\frac{d}{dt} \int_{\mathbb{R}^d} S_{\mathcal{B}}(t)f_0(1+x^2)dx = \int_{\mathbb{R}^d} (\Lambda - \mathcal{A})S_{\mathcal{B}}(t)f_0(1+x^2)dx \leq \int_{\mathbb{R}^d} (p(x) - M\chi_R) S_\Lambda(t)f_0 dx.$$

For  $M$  and  $R$  large enough we conclude that the operator  $\mathcal{B}$  is hypodissipative. Since  $\mathcal{A}f$  is positive and lies in a compact, the split  $\mathcal{A}$  and  $\mathcal{B}$  has the required properties.

In Chapter 3 we analyse the decomposition provided in the previous example and we find that hypotheses of Theorem 1.2.4 hold.

## 1.3 Biomathematical background ---

For completeness of the text, before passing to the presentation of the main mathematical results, we review some basic facts about the biological background. The aim of the discussion presented here is not to give a comprehensive description of such complex structures such as the brain, or of the problem of morphogenesis. Nevertheless, we want to provide some basic concepts that will explain the motivations behind our models and their biological interest. Notwithstanding, this information is not necessary to the understanding of the mathematical developments and contributions of the thesis.

### Part I: Theoretical neuroscience ---

The ability to exploit and transform the environment is remarkable characteristic of humans and it has been well established that this ability is due to a very evolved nervous system [83]. One of the principal organs of the nervous system is the brain which, roughly speaking, can be considered as a complex and very sophisticated machine with an array of sensorial receptors connected to it.

When modeling the activity of the brain one can consider different scales. If the emphasis is made on the microscopic dynamics, then the basic element is the neuron. The morphology of neural cells is relatively simple and the basic architecture is shared for all neurons. The main characteristic is the presence of dendrites and axons, both related to the “transmission of information” which is coded in electrical signals known as action potentials. Dendrites take information towards the cells, while axons take the information away from the cell. Moreover, nerve cells constantly regulate their electrical potential depending on the input they receive. This regulation results from intense ionic exchanges through the cellular membranes giving rise to a complex electrochemical process.

From the macroscopic viewpoint, the brain is composed of a very large number of interconnected cells (approximately 100 billion neurons in the human brain) and each one of them manifests highly nonlinear dynamics and are subject to noise. The complexity of human behaviour (i.e. our responses to environmental stimulus) depends more on the precise anatomical circuits conforming the brain, and less on the particularities of individual neural cells. Indeed, a main observation, is that nerve cells with similar properties can act very different depending on the way they are connected with its neighbours and with long range sensory receptors. Therefore, even if is important to understand the models for isolated entities, it is also important to uncover the complexity of the network's architecture they belong to. The most important features of the nervous system can be summarised by: (1) the mechanism by which neural cells produce signals, (2) the pattern of connections, (3) the relationship between the patterns of interconnections and the mechanical/sensorial response, and (4) how experience can modify neurons and their interconnectivity.

Because of the complexity of the human nervous system, in the text we only focused on the first two points. In particular we will study models for isolated neurons and networks, and also, the importance

of the level of connectivity on the solutions to those systems.

### The FitzHugh-Nagumo model

One of the most complete and celebrated descriptions of the generation of action potentials is given by the Hodgkin-Huxley (HH) model [75]. It establishes a very precise description of the ion exchanges through the membrane and their effects on the cell voltage. However, the nonlinearities driven the HH dynamics make difficult the analysis of complex HH neuronal networks. A simplification of this model conserving the most prominent aspects of the HH model, the Fitzhugh-Nagumo (FhN) model [59, 116], and has gained the status of canonical model of excitable cells in neuroscience.

Let us consider a generic 2 set of equations of the type

$$\begin{cases} \dot{V}_M(t) &= F(V_M(t)) - w(t) + I \\ \dot{w}(t) &= \tau(V_M(t) + a - bw(t)), \end{cases} \quad (1.3.7)$$

where  $\tau, a$  and  $b$  are nonnegative constants. The first equation describe the dynamics of the membrane potential, and the second one is usually called the recovery variable. Moreover,  $\tau$  is a slow-fast parameter, making the dynamics of both equations have different time scales. The role of the second variable is to model the adaptation of the cell to an external current.

The name of the model is due to the contribution of two independent publications. In 1981, Richard FitzHugh proposed, as a modification of the van der Pol equation, that the action potential was given by a system of the type (1.3.7), for a cubic nonlinear function  $F$  such as

$$F(V_M(t)) = V_M(t)(V_M(t) - a)(1 - V_M(t)), \quad 0 \leq a \leq 1.$$

One year later, J. Nagumo and colleagues proposed a very similar electrical circuit to describe prototype of an excitable system. The applications of FhN equations are very varied, specially for excitability systems such as the heart muscle. One main feature of the model is the presence of a Hopf's bifurcation (and therefore cycle limits) for a well tuned set of parameters. In figure 1.1 we show the time evolution of the voltage variable in the FhN model and some trajectories for different initial points on the phase plane. The transition from a unique stable solution to a cycle limit is a consequence of increasing the input current (Hopf's bifurcation). Therefore, a strong step input current injected to the system, will sustain a train of spikes that disappears as soon as the current is reduced. The image at the right of figure 1.1 is a clear example: the system goes from a resting state to a train of spikes and back to the resting state.

### Brain functional areas

As we said before, the brain is the central object of study for neural science. Indeed, neuroscience approach is based on the view that all behaviour is the result of brain function [83]. The claim is actually controversial because it is assumed that not only simple motor actions (e.g. to walk and to eat chewing

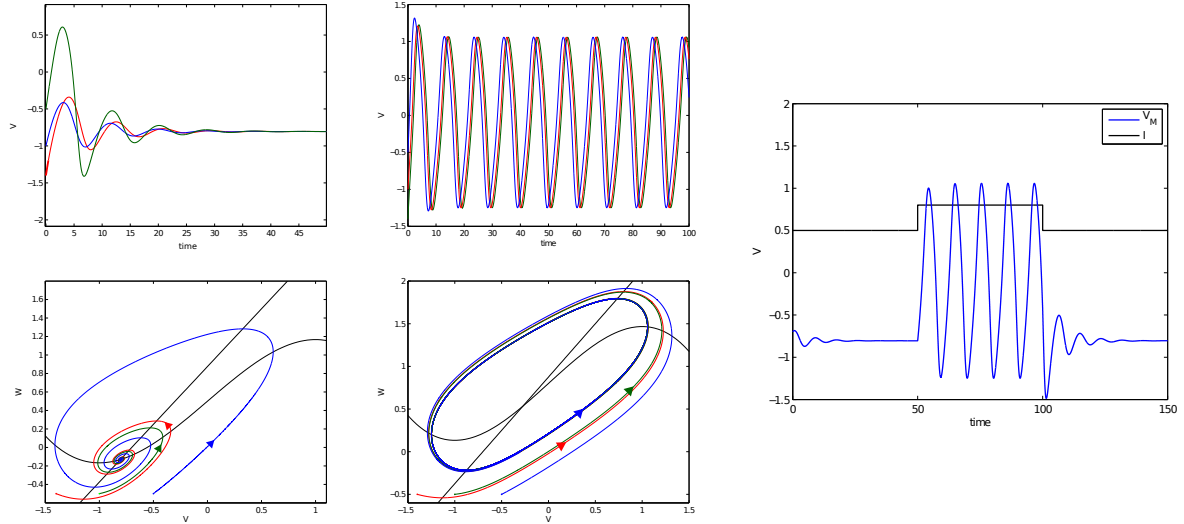


Figure 1.1: Time evolution of the voltage variable on the FitzHugh-Nagumo equations and some trajectories of different solutions on the phase plane, in the case of one stable steady state (left), a stable limit cycle (center) and a strong step current (right). For  $F(v) = v - \frac{v^3}{3}$ ,  $a = 0.7$ ,  $b = 0.8$  and  $\tau = 0.8$ . In all cases the nullclines intersect in only one point. Arrows indicate the sense of the time evolution. Figures on the left row correspond to  $I = 0.5$ , and figures on the center row correspond to  $I = 0.8$ . Figure on the right corresponds to an step function (black solid line) equal to  $I = 0.8$  for  $50 \text{ ms} < t < 100 \text{ ms}$  and  $I = 0.5$  otherwise.

gum at the same time), but complex cognitive actions (e.g. have feelings), underlie on the activity of the brain. Therefore, the task is to explain behaviour (and finally human behaviour) in terms of the activity of the brain. If the hypothesis (brain activities  $\Leftrightarrow$  behavior) is accepted, a second fundamental problem is whether the mental processes depend on specific functional areas, or on a collective property of the whole brain.

In last years of the eighteenth century, the german physician and neuroanatomist Franz J. Gall proposed that the brain was divided in several “organs” coding the different mental faculties, and that they grew with use. This doctrine became very popular in the nineteenth century and gave birth to the study of the bumps of the skulls known as *phrenology*. However, by removing parts of the brains of animals, scientists tried to isolate the contributions of Gall's cerebral organs, concluding that any part of a determined hemisphere was able to participate in all respective functions of the hemisphere. However, in the second part of the nineteenth century, several studies, agreed with the view that the brain had a *cellular-collectionism* structure and not a *aggregate-field* one. In particular, studies of local epilepsy showed that specific motor and sensory functions can be traced down to different parts of the cerebral cortex [83]. Nevertheless, it was only by the beginning of the twentieth century that there was enough biological evidence to support the existence of different discrete areas in the cortex, related to specialised roles in behaviour. For example, the precise map to the body of a cat in specific parts of the cerebral cortex *somatotopy* established by Wade Marshall and Philip Bard in the 1930s. This observation is more

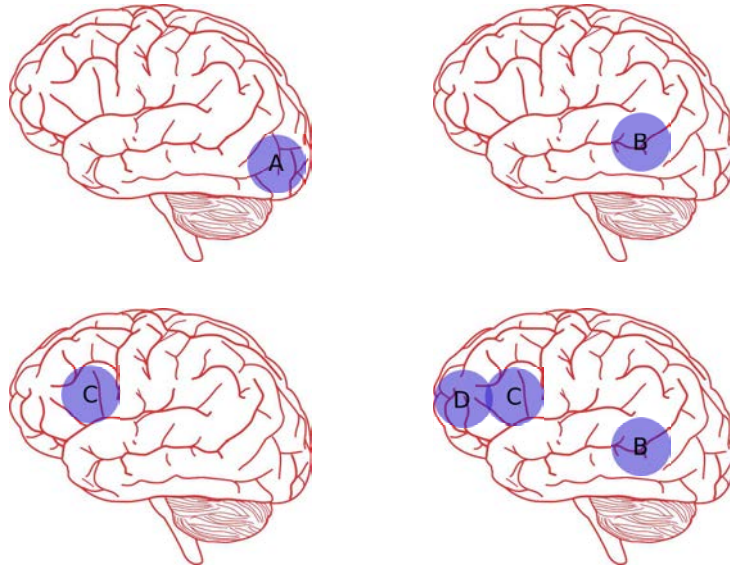


Figure 1.2: Schematic specific regions of the cortex while reacting to a single word (based on [83]). Blue coloured circles represent high activity. (A) Reading a word is related to the V1, (B) hearing is located in the temporal cortex (C), repeating a word is related to a motor area, and (D) thinking of words triggers activity in the regions related to (B) and (C) and with the frontal cortex.

accurate if we look the example of language. Using PET scanning, one can observe which parts of the cerebral cortex are reacting (showing high electrical activity) in the recognition of a spoken or written word. This is depicted in figure 1.2. The reading of a single word triggers action potentials in the primary visual (V1) cortex. Hearing words activates a different part called temporal lobe. Speaking is related to a supplementary motor area on the medial frontal cortex. But, responses to a particular word activates (B), (C) and the frontal cortex at the same time. Moreover, it has been reported that damages on the (B) part result on effortful speech but relatively good oral comprehension. On the contrary, damages on the (C) part result on difficulties understanding sentences, but fluent speech [83].

The questions we study in the first part of the text are motivated for the connectivity level in neuronal networks. In particular, we are concerned with the emergence of synchronised activity for highly connected networks, and the convergence to an equilibrium when the connectivity level and external inputs are small.

## Summary

To construct reasonable neuronal networks we have to keep in mind at least the following restrictions: (1) the brain is composed by a large number of interconnected neurons; (2) the behaviour depends more on the neuronal networks and discrete areas, and less on the particular dynamics of each cell; (3) the system is intrinsically stochastic; and (4) cortical networks tend to display complex network topologies, and typical cortical networks tend favour local connectivity.

## Part II: Morphogenesis

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In the first part of this manuscript we work under the hypothesis that the neural networks of the adult hemispheres are the responsible of most (if not all) human behaviour. But despite the complexity on the structure of the brain, it start off as a simple sheet of neuroepithelial cells during the first stages of neurogenesis. How is that possible?

To answer that question we need to take a quick view to developmental biology (DB). The three major axes of DB are morphogenesis, the control of cell growth and cellular differentiation. Among these axes, it is morphogenesis the one who deals with the processes causing an organism have a particular shape, as well as, the formation and development of identifiable and robust functional areas. It is important to remark that morphogenesis is not only concerned with a purely descriptive study of the shape of living things, but also with the laws driving the morphological differentiation. Of course, in living organisms, the mechanical constraints and forces are not enough to explain the diversity of cell types. Moreover, those mechanisms are unable to fully explain the robustness of the boundary positions of functional areas. To bring light to the subject, it becomes necessary to consider the complex relationships between the DNA structure, proteins transcription and gene expression. Nevertheless, to understand properly contemporary discoveries, we have to go back in time and start with the very abstract definition of *morphogen* which was primary introduced in 1950s by Alan Turing in [155], and then restated by Lewis Wolpert [164].

## Two different definitions or morphogen

### Turing's definition of morphogen

In the outstanding paper *The chemical basis of morphogenesis*, the author stated a first rigorous definition of morphogen. Starting from the principle that it was more important to consider the substances that are reacting chemically, than the non-growing masses of tissues through they diffuse [155], it was proposed a theory where patterning was due to local interactions. Alan Turing defined a morphogen as a substance (gens, skin pigments or/and hormones) that is diffusing and reacting chemically as catalyst or inhibitor.

### Wolpert's definition of morphogen

Thirty years later, and based on several studies showing that spatial patterns of differentiation were capable of considerable regulation when disturbed [164], Lewis Wolpert came up with a different theory of morphogenesis. The main concept of his theory is the positional information (PI). Since patterning in Turing's model is driven by instabilities the regulation mechanism of development was not incorporated. Moreover, considerable attention was given to the molecular characterisation of differentiation, but very few of to the global regulation of spatial patterning.

The solution proposed by Lewis Wolpert was based on the assumption that there are mechanisms whereby cells have their position specified. The fate of the cell, i.e., its molecular differentiation, is therefore determined by its position on the field as a result of the *interpretation of the PI*. Moreover, since several points can determinate the position of a particular cell, it is necessary to specify the *polarity* or the direction in which measurement must occur. It is important to remark that, Wolpert was not the first one in proposing a mechanism as PI in the core of development. In fact, some similar ideas were already introduced in the 50's by Dalcq (double gradient [40, 41]), and by Stern [140] and Kroegeer [93] with the concept of pre-patterning. The novelty of PI was first its universality, and second that it was applicable in both development and regeneration context.

### The french flag problem

We own to Wolpert not only the concept of PI but also the well-posedness and a first satisfactory solution to the French Flag Problem (FFP) that we state now

**Problem 1.3.7.** *Let us consider a field of  $N$  cells in a line, where each one of them is capable of molecular differentiation. Assumed that this differentiation is related with the secretion of blue, white and red pigments changing the appearance of the cell. Describe a mechanism by which the first third of cells differentiate as blue cells, the second third as white cells, and the last one as red cells.*

A typical solution to the FFP is depicted in figure 1.3. A gradient of morphogen determines the position of the cells inside the field (a straight line of cells) and thresholds determine the fate of a particular individual. We remark that this theoretical solution to the FFP is characterized by the combination of a continuous gradient and thresholds. Some studies suggest that this sole mechanism results in the formation of boundaries of imprecise shapes and positions (for a detailed discussion see Chapter 4). This model has since evolved considerably to take into account the complexity of the cellular environment, and new versions include for example, later cell migration and/or death to get sharp and well-defined boundaries.

The solution proposed by Wolpert (also known as the French Flag Model FFM), can be applied to different scenarios, in particular, it serves to explain an invariant size system (changing the number  $N$  of cells does not varies the organisation of blue-white-red) or the fixed size case. In the first case a simple unipolar solution can be provided by assuming that cells differentiate according to their distances to the polarity point (see figure 1.4 up). However, since embryos regulate themselves in a size invariant context (two organisms can have different size but a similar proportionality between body parts), a more reasonable solution is a bipolar system (see figure 1.4 bottom).

### Morphogens in contemporary terms

It has become evident that the only presence of a morphogen is not enough to generate the whole mosaic of cell types. In contrast, it has been observed that morphogens act upon pre-patterns of tissues [133]. However, as the FFM predicted, the main property of a morphogen is that cell fates depend



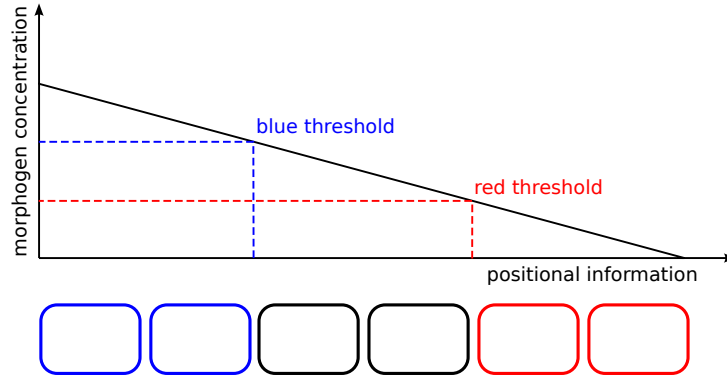


Figure 1.3: The French flag model (FFM) and pattern formation driven by global interaction. At the beginning cells are aligned and have the potential to develop as blue, white and red. The presence of a gradient of morphogen defines the position of each cell within the field. The positional information is then interpreted and cells differentiate forming a pattern deciding their fates according to predefined thresholds.

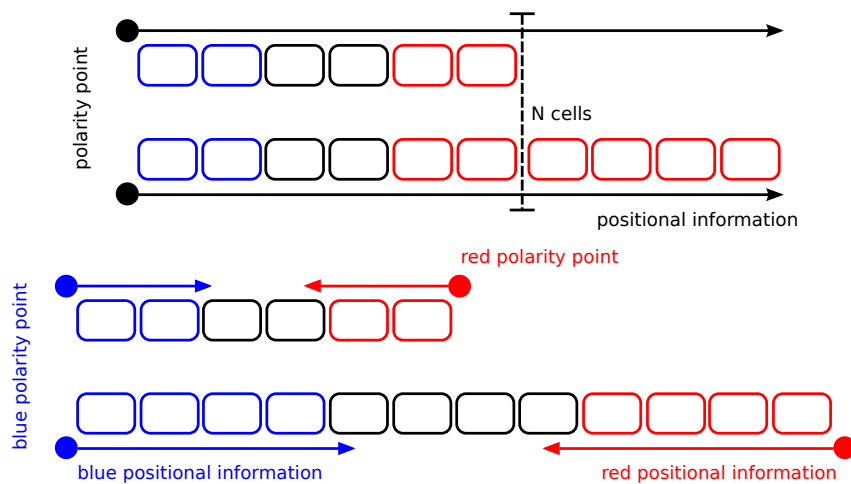


Figure 1.4: The FFM in a size invariant and a non size invariant context. The coloured dots correspond to the polarity points and the arrows to the direction of PI. The morphogens are secreted from the polarity points and free diffusion forms the gradients of concentration (up) Unipolar system. The fate of the cell is only determined by the concentration of a generic black morphogen, by expressing different pigments according to three thresholds. If a cell is close to the polarity point, then the concentration of the morphogen is high and it expresses the blue pigment. Medium and low concentrations result on white or red pigments respectively. If the number of cells is increased, any cell with a position larger than  $N$  will secrete the red pigment due to the low concentration of morphogen. (bottom) Bipolar version. The fate of the cell is decided by the combination of the concentration of black and red morphogen according to its rate. If the rate blue/red is high, then the PI indicates proximity to the blue polarity point and blue pigment is secreted. Same for low rate blue/red and red pigment. In any other case the cell differentiate as a white cell. Changes on the large of the cell field do not modify the sequence nor the proportion of colours

on the concentration of them. Prior to the formation of well defined boundaries and functional areas, some specific sets of proteins are expressed in a sort of pre-patterning. These proteins are mostly of the family of the *transcript or factors (TFs)* and correspond to the transcription of PI mechanism predicted by Wolpert. The TFs are involved in the process of converting, or transcribing, DNA into RNA. Some distinct features of them are that they have a DNA-binding domains providing them the ability to bind to specific sequences of DNA called enhancer. Some of TFs bind to regulatory sequences and can either stimulate or repress the transcription of the related gene.

We can summarise the general principles of morphogens gradient patterning by: (1) they are released from spatially localised sources. Whether they diffuse free or are other transport mechanisms forming the gradient is an active source of discussion [77, 95]. (2) Morphogen concentration is transmitted to intracellular molecules resulting in the expression of particular sets of TFs. (3) TFs regulate complex cascade effects in the cells by self stimulating its own expression and inhibiting the expression of others TFs. (4) Feedback mechanisms stabilise fluctuations in morphogen production, regulate signalling and confer stability to morphogen-mediated patterning. In this text is mainly concerned with a particular family of TFs called *homeoproteins (HP)*:

**Definition 1.3.8.** *HPs are specific proteins encoded by homeobox genes that exhibit structural similarity to certain prokaryotic and eukaryotic DNA-binding proteins. They are involved in the control of gene expression during morphogenesis and development.*

The particularity of HPs is that recent data support the view that they can be transferred from cell to cell and have direct non-cell-autonomous activities [96, 138, 85, 80]. This is a very important remark because HPs are very ancient molecules present in almost all phyla, therefore can have played a role in the course of evolution of multicellular organisms.

## Part III: Microscopic viewpoint of chemotaxis ---

In the math-bio community, chemotaxis is probably one of the most well known and studied subjects, and still encompasses a large quantity of unsolved problems. Since the seminal publication of the Keller-Segel model [88], mathematicians have been interested by different aspects of this remarkable equation, but the work has not been finished.

The microscopic description of the Keller-Segel system has been a very popular field of research in the past few years. In [142], Stevens studies a particle system with two kinds of particles corresponding to bacteria and chemical substance. The author shows convergence of the system for smooth initial data (lying in  $C_b^3(\mathbb{R}^d)$ ) and for regular kernels (continuously differentiable and bounded together with their derivatives). In [71], a kernel with a cutoff parameter  $K_\epsilon(x) = \frac{x}{|x|(|x|+\epsilon)}$  is considered. Some well-posedness result for the particle system are given and the weak convergence of subsequences due to a tightness result is showed. In a recent work [34], authors investigate a one-dimensional Keller-Segel model and a dynamical particle system for which there is a global existence result under some assumptions on

the initial distribution of the particles that prevents collisions. It is also given two blow-up criteria for the particle system but the convergence result is not stated.

But what do we mean by chemotaxis? and why are we interested in microscopic descriptions of that biological system? To answer that questions we recall that live organisms are in constantly movement, we refer to chemotaxis when this movement is the response to a chemical stimulus. In the case of a positive chemotaxis, i.e. when an organism or a cell is induced to migrate toward the chemical signal, this factor is called *chemoattractant*. Chemoattractants can be secreted by the same population of organisms, and/or by a different one.

### Self-induced chemotaxis

The slime mold or *Dictyostelium discoideum* is a very nice example of self induced chemotaxis. This amoeba belongs to a diverse group of motile unicellular eukariotic organisms. This protozoa is commonly found in soil and water. The main particularity of this specie is its transition from a unicellular amoeba into a multicellular organism. Let us describe the lifecycle of *Dictyostelium discoideum* and the role of chemotaxis in it: as long as the food is present, individual cells of *Dictyostelium discoideum* live as independent individuals. As soon as the food becomes scarce, cells start a process of aggregation (and cellular differentiation) resulting in a multicellular organism. Roughly speaking, the starving cells secrete waves of a chemical signalling called *cyclic adenosine monophosphate* (cAMP) that indicate to surrounding cells the center of territories. The amoebas migrate and gather resulting is a multicellular organism with a body and spores that are dispersed to reset the life cycle.

### Chemotaxis induced by external populations

An example of chemotaxis induced by external populations is the formation of new blood vessels in cancer, process known as *angiogenesis* [36]. In early stages of cancer, the growth of cells is limited (up to 1-2 mm) by the availability of nutrients on the hosting tissue. Indeed, while the growth is volumetric, the amount of nutrients is proportional to the area. Naturally, the nutrients become scarce, and the tumour requires new blood vessels to sustain the demand of oxygen and glucose, and to avoid hypoxia. Therefore, quiescent cells secrete a chemoattractant called *vascular endothelial growth factor* (VEGF) which is the key mediator of angiogenesis in cancer. Surrounding blood vessels react to the gradient of VEGF and new vasculature is formed. The final result is a vascularised tumour and metastasis.

### The Keller-Segel equation

The most celebrated model for chemotaxis was proposed in the 1970s by Evelyn Keller and Lee Segel when they were studying the slime mold [88]. The model classically writes

$$\begin{cases} \partial_t n(t, x) - \Delta n(t, x) + \operatorname{div}(n(t, x)\chi \nabla c(t, x)) = 0, \\ -\Delta c(t, x) = n(t, x), \end{cases} \quad (1.3.8)$$

where the parameter  $\chi$  is the sensitivity of cells to the chemoattractant,  $c(t, x)$  is the concentration of chemoattractant, and  $n(t, x)$  is the density of cells at time  $t$  and position  $x$ . We see that this is a case of self-induced positive chemotaxis.

In the two dimensional, system of equations (1.3.8) can be simplify, by solving explicitly the second equation, to get

$$\frac{\partial n(t, x)}{\partial t} = \frac{\chi}{2\pi} \nabla \cdot \left( n(t, x) \int_{\mathbb{R}^2} n(t, y) \frac{x-y}{|x-y|^2} dy \right) + \Delta n(t, x). \quad (1.3.9)$$

Equation (1.3.9) is a nonlocal equation. Moreover, if we consider the case when  $n_0(t, x)$  has unitary mass, then equation (1.3.9) is describing the time evolution of a probability density. The parallel with the chaos propagation property we study in the first part of the text is remarkable. However, since the force kernel is singular at 0, several technical difficulties arise.

## 1.4 Main results

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### Part I: Main results

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Chapter 2 and 3 are related to theoretical neuroscience. In Chapter 2 we study the limits of a general model of neuronal networks at two different scales: macroscopic and mesoscopic. We also study the solutions in a particular solvable case, and the importance of the connectivity level in the emergence of synchronisation states. Next, in Chapter 3, we study a kinetic mean field equation related to the FitzHugh-Nagumo model. In particular, we are concerned with the exponential nonlinear stability of the stationary solutions.

#### 1.4.1 Randomly connected neuronal networks with delays

We analyse a general model of neuronal networks at different scales: (1) the *macroscopic scale* where neurons gather into a few populations  $P(N) = P$  fixed, corresponding to coarse-grained descriptions of neural activity [79]; and (2) the *mesoscopic scale*, or neural-field limit, where the number of populations tends to infinity and the area described covers a continuous piece of cortex  $\Gamma \subset \mathbb{R}^p$  with  $p \in \mathbb{N}^*$  [150, 151].

The state of a neuron  $i$  is described by a  $d$ -dimensional variable  $X^{i,N} \in E$ . The networks are composed of  $N$  neurons falling into  $P(N)$  populations labeled  $\alpha \in \{1, \dots, P(N)\}$  and composed of  $N_\alpha$  neurons, and the convention  $\alpha = p(i)$  defines the population neuron  $i$  belongs to. The evolution state  $X_t^{i,N}$  of neuron  $i$  in the population  $\alpha \in \{1, \dots, P\}$  is governed by a stochastic differential equation. The intrinsic dynamics of the neuron is governed by a function  $f_\alpha : \mathbb{R}_+ \times E \mapsto E$ . This evolution is stochastic, driven by independent  $m$ -dimensional Brownian motions  $(W_t^i)$  through a diffusion coefficient  $g_\alpha : \mathbb{R}_+ \times E \mapsto \mathbb{R}^{d \times m}$ . The neuron  $i$  receives inputs from other neurons in the network, which affect its

state through an interaction function  $b_{\alpha\gamma} : \mathbb{R} \times E \times E \mapsto E$  depending on the synaptic weight  $w_{ij} \in \mathbb{R}$ , and the state of both neurons  $i$  and  $j$ . Moreover, these interactions take place after a delay  $\tau_{ij} > 0$ .

The dynamic of neuron  $i$  in population  $\alpha$  is given by:

$$dX_t^{i,N} = \left( f_\alpha(t, X_t^{i,N}) + \sum_{\gamma=1}^{P(N)} \sum_{p(j)=\gamma} \frac{1}{N^\gamma} b_{\alpha\gamma}(w_{ij}, X_t^{i,N}, X_{t-\tau_{ij}}^{j,N}) \right) dt + g_\alpha(t, X_t^{i,N}) \cdot dW_t^i, \quad (1.4.10)$$

under the assumption that  $b(0, x, y) = 0$  and the fact that the synaptic weight  $w_{ij}$  is assumed zero when no link from  $j$  to  $i$ .

We are concerned on the convergence of the solutions when the number of neurons goes to infinity (under some assumption to be precise latter on). In particular, when  $N \rightarrow \infty$ , then

- ▷ for almost any realization of the transmission delays  $\tau_{ij}$  and synaptic weights  $w_{ij}$  in the translation-invariant case or
- ▷ averaged across all realizations of the disorder in the general case,

the propagation of chaos property holds: *if the initial conditions are chaotic, then the states of a finite number of neurons are independent for all times when  $N \rightarrow \infty$ .*

In both cases, the proof of the convergence and propagation of chaos will use the coupling method already described. The proof is in two steps: (i) we prove that the limit equation (see equation (2.3.2) below) has an unique solution, and (ii) that the law of  $X_t^{i,N}$  converges towards the law of (2.3.2). In this mesoscopic scale, when the number of populations is also going to infinity, the notion of solution is more complex, as one obtains a process depending on space but which is not measurable with respect to the spatial variable. To help the lecture, we focused on the first case  $P$  fixed and, will be briefly discussed how to adapt the results of [151] to our context in section 2.7.

We start by showing the well-posedness of the network system:

**Proposition 1.4.9.** *Let  $X_0$ , a square integrable stochastic process from  $[-\tau, 0]$  to  $E^N$ , be the initial condition of the network system. For any  $(\alpha, \gamma) \in \{1, \dots, P(N)\}^2$ , assume that:*

- (H1).  *$f_\alpha$  and  $g_\alpha$  are uniformly (in time) Lipschitz-continuous functions with respect to their second variable.*
- (H2). *For almost all  $w \in \mathbb{R}$ ,  $b_{\alpha\gamma}(w, \cdot, \cdot)$  is  $L_{\alpha\gamma}$ -Lipschitz-continuous with respect of both variables.*
- (H3). *There exists functions  $\bar{K}_{\alpha\gamma} : \mathbb{R} \mapsto \mathbb{R}^+$  such that for any  $(\alpha, \gamma) \in \{1, \dots, P(N)\}^2$ ,*

$$|b_{\alpha\gamma}(w, x, y)|^2 \leq \bar{K}_{\alpha\gamma}(w) \quad \text{and} \quad \mathbb{E}[\bar{K}_{\alpha\gamma}(w)] \leq \bar{k} < \infty.$$

- (H4). *The drift and diffusion functions satisfy the monotone growth condition: there exists a positive constant  $K$  depending on  $f$  and  $g$  such that:*

$$x^T f_\alpha(t, x) + \frac{1}{2} |g_\alpha(t, x)|^2 \leq K(1 + |x|^2).$$

Then for almost all realization of the synaptic weights  $w_{ij} \in \mathbb{R}$  and the delays  $\tau_{ij} \in [-\tau, 0]$ , we have existence and uniqueness of solutions to the network equations (1.4.10).

The proof is based on the *a priori* bounds on the solutions and the Lipschitz continuity of the functions. Even if the ideas used to the proof are simple, they allow us to conclude almost directly that the limit mean-field equation is also well posed when the number of populations is fixed. More precisely, let  $P(N) = P$  be fixed and independent of  $N$ . In this case, we will show that the network equation converges (in a sense to be precised in each case) towards the solution of a well-posed McKean-Vlasov equation given by:

$$d\bar{X}_t^\alpha = f_\alpha(t, \bar{X}_t^\alpha) dt + g_\alpha(t, \bar{X}_t^\alpha) \cdot dW_t^\alpha + \left( \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} \mathbb{E}_{\bar{Y}} [b_{\alpha\gamma}(w, \bar{X}_t^\alpha, \bar{Y}_{t+s}^\gamma)] d\Lambda_{\alpha\gamma}(s, w) \right) dt, \quad (1.4.11)$$

where  $\bar{Y}$  is a process independent of  $\bar{X}$  that has the same law,  $\mathbb{E}_{\bar{Y}}$  the expectation under the law of  $\bar{Y}$ , and  $W_t^\alpha$  are independent adapted standard Brownian motions of dimension  $d \times m$ . In equation (1.4.11),  $\Lambda_{ip(j)}$  is the distribution of the variables  $(w_{ij}, \tau_{ij})$  and it is assumed to depend only on the population the particle  $i$  belongs to (translation invariant property). In that case we have the

**Theorem 1.4.10.** *Under the hypotheses of Proposition 1.4.24 and for any  $\zeta_0$  a square integrable process, the mean-field equations (1.4.11) with initial condition  $\zeta_0$  have a unique strong solution on  $[-\tau, T]$  for any time horizon  $T > 0$ .*

The proof of Theorem 1.4.20 is based on the *a priori* bounds “inherited” from the particle system, and a Picard's iteration argument.

Let  $i \in \mathbb{N}$  such that  $p(i) = \alpha$ . We define the process  $\bar{X}^i$  solution of (1.4.11), driven by the Brownian motions  $(W_t^i)$  that governs  $X^i$ , and having the same initial condition as neuron  $i$  in the network,  $\zeta_0^i$ :

$$\begin{cases} d\bar{X}_t^i = f_\alpha(t, \bar{X}_t^i) dt + g_\alpha(t, \bar{X}_t^i) \cdot dW_t^i \\ \quad + \left( \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} \mathbb{E}_Z [b_{\alpha\gamma}(w, \bar{X}_t^i, Z_{t+s}^\gamma)] d\Lambda_{\alpha\gamma}(s, w) \right) dt, \quad t \geq 0 \\ \bar{X}_t^i = \zeta_0^i(t), \quad t \in [-\tau, 0]. \end{cases} \quad (1.4.12)$$

By definition, the processes  $(Z_t^1, \dots, Z_t^P)$  are a collection of processes independent of  $(\bar{X}_t^i)_{i=1, \dots, N}$  and have the distribution  $m_t^1 \otimes \dots \otimes m_t^P$ , where  $m_t^\alpha$  is the probability distribution of  $\bar{X}_t^\alpha$  (unique solution of the equation (1.4.11)). One of the main results of the chapter is the

**Theorem 1.4.11 (Quenched convergence).** *Under assumptions (H1)-(H4) and chaotic square integrable initial conditions. The process  $(X_t^{i,N}, -\tau \leq t \leq T)$  for  $i \in \mathbb{N}$  fixed, solution of the network equations (1.4.10), converges almost surely towards the process  $(\bar{X}_t^i, -\tau \leq t \leq T)$  solution of the mean-field equations (1.4.12). This implies in particular convergence in law of the process  $(X_t^{i,N}, -\tau \leq t \leq T)$  towards  $(\bar{X}_t^\alpha, -\tau \leq t \leq T)$  solution of the mean-field equations (1.4.11).*

The proof of Theorem 1.4.11 is quite interesting and clarifies the coupling method. Indeed, we only need to control the square difference of the solutions to (1.4.10) and (1.4.12). Most of the terms are easily upper bounded by using the Lipschitz continuity of the functions except for the contribution of the

delays. In that case, the key remark is that the Cauchy-Schwartz and the triangular inequalities imply that

$$\mathcal{E}[\mathbb{E}[\sup_{0 \leq s \leq t} |E_s(N)|^2]] \leq TP \sum_{\gamma=1}^P \int_0^t \mathcal{E} \left[ \left[ \mathbb{E} \left[ \left| \frac{1}{N_\gamma} \sum_{p(j)=\gamma} \left( b_{\alpha\gamma}(w_{ij}, \bar{X}_s^i, \bar{X}_{s-\tau_{ij}}^j) - \int_{-\tau}^0 \int_{\mathbb{R}} \mathbb{E}_Z [b_{\alpha\gamma}(w, \bar{X}_s^i, Z_{s+u}^\gamma)] d\Lambda_{\alpha\gamma}(u, w) \right) \right|^2 \right] \right] ds, \quad (1.4.13)$$

where  $\mathcal{E}$  stands for the expectation over the random architecture of the network. The important remark is that we assume that for fixed  $i$ , sequences  $(\tau_{ij})_{j=1, \dots, N}$  and  $(w_{ij})_{j=1, \dots, N}$  are considered independent and identically distributed population-wise. Therefore, the previous expression is of order  $1/\min(N_\gamma)$ , and by consequence, going to 0 as  $N$  goes to infinity.

Finally, in the case that  $\Lambda_{ip(j)}$  depend on the precise position of the neuron  $i$  and not only on the population (non translation invariant case), a different chaos propagation property is proved. Denoting  $\mathcal{E}_i$  the expectation over all possible distributions  $\Lambda_{i\gamma}$ , and modifying accordingly the respective proof, we have the

**Theorem 1.4.12 (Annealed convergence).** *We assume that (H1)-(H4) are valid, that network initial conditions are chaotic and square integrable, and that the interaction does not depend on the postsynaptic neuron state (i.e.,  $b(w, x, y) = \ell(w, y)$ ). Let us fix  $i \in \mathbb{N}$ , then the law of process  $(X_t^{i,N}, -\tau \leq t \leq T)$  solution to the network equations (1.4.10) averaged over all the possibles realizations of the disorder, converge almost surely towards the process  $(\bar{X}_t^i, -\tau \leq t \leq T)$  solution to the mean field equations (1.4.11). This implies in particular the convergence in law of  $(\mathcal{E}_i[X_t^{i,N}], -\tau \leq t \leq T)$  towards  $(\bar{X}_t^\alpha, -\tau \leq t \leq T)$  solution of the mean field equations (1.4.11).*

The previous setting can be fully understood in the special case of a one population firing-rate neuron network.

### Application: dynamics of the firing-rate model with random connectivity

A particularly suitable framework to solve the question of the role of the random architecture is provided by the classical firing-rate model (see e.g. [151]). For that dynamics, we can show that the solution to the mean-field equations (1.4.11) is exponentially attracted to a Gaussian, whose mean and standard deviation are solution of simpler dynamical system. Moreover, we prove that the connectivity level of the network plays a role on the emergence of synchronisation of the solutions.

For the firing-rate model, the solution of (1.4.11) satisfies the implicit equation:

$$\begin{aligned} \bar{X}_t^\alpha &= \bar{X}_0^\alpha e^{-t/\theta_\alpha} + \int_0^t e^{-(t-s)/\theta_\alpha} \left( -\frac{\bar{X}_s^\alpha}{\theta_\alpha} + I_\alpha(s) \right. \\ &\quad \left. + \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} J_{\alpha\gamma}(w) \mathbb{E}_{\bar{Y}} [S(Y_{s+r}^\gamma)] d\Lambda_{\alpha\gamma}(r, w) \right) ds + \int_0^t e^{-(t-s)/\theta_\alpha} \lambda_\alpha dW_s^\alpha \end{aligned}$$

which is composed of Gaussian terms and the initial condition  $\bar{X}_0^\alpha e^{-t/\theta_\alpha}$  vanishing at an exponential rate. Therefore, taking expectation and covariance we get that the mean and the variance of the solution

satisfy the following well-posed system of delayed differential equations:

$$\begin{cases} \dot{u}_\alpha = -u_\alpha/\theta_\alpha + \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} J_{\alpha\gamma}(w) \mathbb{E}_Y [S(Y_{t+s}^\gamma)] d\Lambda_{\alpha\gamma}(s, w) \\ \dot{v}_\alpha = -2v_\alpha/\theta_\alpha + \lambda_\alpha^2. \end{cases}$$

Here we see that there is a unique stable steady state for the variance. Moreover, in we take  $S$  as the erf function, we can interchange  $\mathbb{E}$  with  $S$ , and find an implicit equation for the mean of the system. Further simplifications on the number of populations, allow us to write that if  $P = 1$ , then the mean solves

$$\dot{u}(t) = -\frac{u(t)}{\theta} + \int_{-\tau}^0 \int_{\mathbb{R}} J(w) \frac{1}{\sqrt{2\pi(1+v^*)}} u(t+s) d\Lambda(s, w), \quad (1.4.14)$$

and by consequence, the stability of the fixed point only depends on the dispersion relationship:

$$\xi = -\frac{1}{\theta} + \frac{1}{\sqrt{2\pi(1+v^*)}} \int_{-\tau}^0 \int_{\mathbb{R}} J(w) e^{\xi s} d\Lambda_{\alpha\gamma}(s, w), \quad (1.4.15)$$

which is nothing more than looking for solutions of the form  $u = e^{\xi t}$  in (1.4.14).

Equipped with (1.4.15) we show that in the small-world type of architectures, and one dimensional model, variations on the extension of the neural field induce a transition from a stationary solution, to an oscillatory regime and back to the stationary solution, when all other parameters remain unchanged. On the other hand, increasing the value of the connectivity of the network favors the apparition of these oscillatory solutions. We conclude that: *the topology of the network strongly impacts the collective behavior of the solutions. For a fixed value of the connectivity parameter, there exists an optimal neural field size for synchronization. At this size, the constant delays necessary to induce oscillations is minimal. In contrast, at fixed values of the extension of the field: fully connected networks synchronize more easily. In the cortex, for energetic reasons, full connectivity is not favored, and therefore this indicates optimal cluster sizes for synchronization.*

All the technical details of this work are presented in the Chapter 2 of this memoir, which is included in [128] written in collaboration with J. Touboul and published in Acta Applicandae Mathematicae.

## 1.4.2 On a kinetic FitzHugh-Nagumo equation

Chapter 3 is probably the most technical and the main interesting mathematical contribution of this dissertation. It deals with an FitzHugh-Nagumo model, which constitutes a very good compromise between versatility and accuracy of its dynamics compared to biological neurons on the one hand, and relative mathematical simplicity on the other hand. It describes the evolution of the membrane potential  $v$  of a cell coupled to an auxiliary variable  $x$ , modeling the adaptation to external inputs. The evolution of the the state  $(x, v)$  of each cell  $i$  belonging to a set of  $n$  FitzHugh-Nagumo neurons satisfies:

$$\begin{cases} dv_t^i = \left( v_t^i (v_t^i - \lambda) (1 - v_t^i) - x_t^i + \sum_{j=1}^n J_{ij} (v_t^i - v_t^j) + I_t \right) dt + \sigma dW_t^i \\ dx_t^i = (-ax_t^i + bv_t^i) dt, \end{cases} \quad (1.4.16)$$



where the  $I_t$  is the input level,  $a$  and  $b$  are positive constants, and the processes  $\{(W_t^i)_{t \geq 0}, 1 \leq i \leq n\}$  are independent Brownian motions. For sake of simplicity, we assume that  $\sigma^2 = 2$  and  $I_t = I_0 \in \mathbb{R}$  constant. The positive coefficients  $J_{ij}$  represent the effect of the interconnection of cell  $j$  onto cell  $i$ . Under relatively weak assumptions on the distribution of these coefficients, we show that the system enjoys propagation of chaos property towards a process whose density solves, on  $(0, \infty) \times \mathbb{R}^2$ , the McKean-Vlasov evolution PDE

$$\left\{ \begin{array}{l} \partial_t f = Q_\varepsilon[\mathcal{J}_f] f := \partial_x(Af) + \partial_v(B_\varepsilon(\mathcal{J}_f)f) + \partial_{vv}^2 f \\ A = A(x, v) = ax - bv, \\ B_\varepsilon(\mathcal{J}_f) = B(x, v; \varepsilon, \mathcal{J}_f), \\ B(x, v; \varepsilon, j) = v(v - \lambda)(v - 1) + x - \varepsilon(v - j) + I_0, \\ \mathcal{J}_f = \mathcal{J}(f) = \int_{\mathbb{R}^2} v f(x, v) dv dx. \end{array} \right. \quad (1.4.17)$$

This is a nonlinear nonlocal PDE, with non bounded coefficients and such that the related differential operator is hypodissipative and non Lipschitz. Therefore, even if the particle system seems to be mathematically simple, the limit equation is not easy to analyze. Nevertheless, we observe that the equation is given in a divergence form, then the mass and the positivity of the initial condition are conserved as long as a solution exists. The first main result we get is related to the existence of solutions to (1.4.17) and the respective *a priori* bounds:

**Theorem 1.4.13.** *For any  $f_0 \in L^1(M^2) \cap L^1 \log L^1 \cap \mathbb{P}(\mathbb{R}^2)$ , there exists a unique global weak solution  $f_t$  to the FhN equation (3.1.2), that moreover satisfies*

$$\|f_t\|_{L^1(M)} \leq \max(C_0, \|f_0\|_{L^1(M)}), \quad (1.4.18)$$

and depends continuously in  $L^1(M)$  to the initial datum.

Furthermore, there exist two norms  $\|\cdot\|_{\mathcal{H}^1}$  and  $\|\cdot\|_{\mathcal{H}_v^2}$  equivalent respectively to  $\|\cdot\|_{H^1(m)}$  and  $\|\cdot\|_{H_v^2(m)}$ , such that the following estimates hold true:

$$\|f_t\|_{L^1(m)} \leq \max(C_1, \|f_0\|_{L^1(m)}), \quad (1.4.19)$$

as well as

$$\|f_t\|_{\mathcal{H}^1} \leq \max(C_2, \|f_0\|_{\mathcal{H}^1}), \quad (1.4.20)$$

and

$$\|f_t\|_{\mathcal{H}_v^2} \leq \max(C_3, \|f_0\|_{\mathcal{H}_v^2}), \quad (1.4.21)$$

where  $C_1, C_2, C_3$  are positive constants.

We recall, from classical literature, that  $L^1 \log L^1$  is the space of function with finite entropy,  $M$  (respectively  $m$ ) is a polynomial (respectively exponential of a polynomial) weight function,  $L^1(M)$ ,  $H^1(m)$  are Sobolev weighted spaces, and that  $H_v^2(m)$  is the set of functions of  $H^1(m)$  such that the second  $v$  derivative exists and belong to  $L^2(m)$ . The proof of the Theorem 1.4.13 is based on the bounds on the solutions. We start by noticing that the nonlocal term is upper bounded uniformly on time. This

allow us to replace  $\mathcal{J}(f_t)$  by a constant  $\mathcal{J} \in \mathbb{R}$  when proving (1.4.19), (1.4.20) and (1.4.21). More precisely, to find inequality (1.4.18), we use the definition of  $A$  and  $B_\varepsilon$ , to get

$$\frac{d}{dt} \int_{\mathbb{R}^2} f_t M dx dv \leq K_1 - K_2 \int_{\mathbb{R}^2} f_t M dx dv, \quad (1.4.22)$$

where  $K_1$  and  $K_2$  are generic constants depending only on the parameters of the system. To prove (1.4.19) we simply use that  $\text{sign}(f)\partial_{vv}^2 f \leq \partial_{vv}^2 |f|$ , to get an inequality of the type (1.4.22).

The other two inequalities are much more delicate. Indeed, since the operator is hypodissipative we cannot use the standard arguments of parabolic equations to upper bound the  $H^1$  norm. Instead we use the ideas of Villani [158] and study a “shifted” norm equivalent to the usual norm on  $H^1$ . More, precisely we get the

**Lemma 1.4.14.** *Let us consider two exponential weight functions  $m_1 < m_2$ . For any  $\mathcal{J} \in \mathbb{R}$  fixed, there exist  $K_1, K_2 > 0$  and  $\delta \in (0, 1)$  constants such that*

$$\langle Q_\varepsilon[\mathcal{J}]f, f \rangle_{\mathcal{H}^1} \leq K_1 \|f\|_{L^2(\mathbb{R}^2)}^2 - K_2 \|f\|_{\mathcal{H}^1}^2, \quad \forall f \in H^1(m_2), \quad (1.4.23)$$

where  $\langle \cdot, \cdot \rangle_{\mathcal{H}^1}$  is the scalar product related to the Hilbert norm

$$\|f\|_{\mathcal{H}^1}^2 := \|f\|_{L^2(m_2)}^2 + \delta^{3/2} \|\partial_x f\|_{L^2(m_2)}^2 + \delta^{4/3} \langle \partial_x f, \partial_v f \rangle_{L^2(m_1)} + \delta \|\partial_v f\|_{L^2(m_2)}^2.$$

The proof of Lemma 1.4.23 is based on control the extra contribution of the  $x$ -derivative thanks to the presence of the cross derivative term. In particular we prove an inequality of the type

$$\langle \partial_x(Q_\varepsilon f), \partial_x f \rangle_{L^2(m_2)} \leq K \|\partial_x f\|_{L^2(\mathbb{R}^2)}^2 + (\text{other terms}),$$

with  $K$  a constant, and

$$\langle \partial_x Q_\varepsilon f, \partial_v f \rangle_{L^2(m_1)} + \langle \partial_v Q_\varepsilon f, \partial_x f \rangle_{L^2(m_1)} \leq -b \|\partial_x f\|_{L^2(m_1)}^2 + (\text{other terms}),$$

where all the other terms can be easily upper bounded. The choice of the exponent of  $\delta$  in the definition of the  $\|\cdot\|_{\mathcal{H}^1}$  norm is such that for  $\delta > 0$  small enough

$$\delta^{3/2} K \|\partial_x f\|_{L^2(\mathbb{R}^2)}^2 - \delta^{4/3} b \|\partial_x f\|_{L^2(m_1)}^2 \leq 0.$$

Finally, we use that  $\mathcal{J}(f_t)$  is uniformly upper bounded to find  $K_1, K_2$  and  $\delta$  in Lemma 1.4.14 such that

$$\frac{d}{dt} \|f_t\|_{\mathcal{H}^1}^2 \leq K_1 \|f_t\|_{L^2(\mathbb{R}^2)}^2 - K_2 \|f_t\|_{\mathcal{H}^1}^2,$$

with  $f_t$  any solution to (1.4.17). To finally obtain (1.4.20), we recall Nash's inequality

$$\|f\|_{L^2(\mathbb{R}^2)}^2 \leq C \|f\|_{L^1(\mathbb{R}^2)} \|D_{x,v} f\|_{L^2(\mathbb{R}^2)}, \quad (1.4.24)$$

and use that  $f_t$  has unitary mass. Inequality (1.4.21) follows the same schema of proof. Equipped with these inequalities the existence of a solution (at least in a weak sense) can be obtained by using a fixed point argument. Nevertheless, the uniqueness result requires to work in a smaller space. To that aim we simply use the definition of  $A$  and  $B_\varepsilon$ , to prove that for any  $f_0 \in L^1(M) \cap L^1 \log L^1 \cap \mathbb{P}(\mathbb{R}^2)$ , it holds

$$\sup_{t \in [0, T]} \int_{\mathbb{R}^2} f_t \log(f_t) dx dv + \int_0^t \int_{\mathbb{R}^2} \frac{|\partial_v f_s|^2}{f_t} dx dv ds \leq C(T), \quad (1.4.25)$$

where  $C(T)$  depend on  $f_0$  and the coefficients of the problem.

It is important to remark that the inequality (1.4.25) includes the entropy of the solution and a quantity that it is not the classical Fisher's information but only a partial  $v$ -derivative Fisher's information. This is related to the hypodissipativity of the operator. At this point the uniqueness (and by consequence the well-posedness of (1.4.17)) are obtained by putting together all the *a priori* bounds.

The second main result of the chapter is the

**Theorem 1.4.15.** *For any  $\varepsilon \geq 0$ , there exists at least one stationary solution  $G_\varepsilon$  to the FhN statistical equation (1.4.17). Moreover, there exists an increasing function  $\eta : \mathbb{R}_+ \rightarrow \mathbb{R}$  such that  $\eta(\varepsilon) \xrightarrow{\varepsilon \rightarrow 0} 0$  and such that any stationary solution  $G_\varepsilon$  satisfies*

$$\|G_\varepsilon - G_0\|_{L^2(m)} \leq \eta(\varepsilon),$$

where  $G_0$  is the unique stationary solution corresponding to the case  $\varepsilon = 0$ .

The existence part of Theorem 1.4.15 is obtained using a classic Brouwer fixed point argument. The stability part is much more complicated and requires to analyse first the linearized equation. To that aim we use the decomposition technique. Around any stationary solution  $G_\varepsilon$ , we consider the linearized operator

$$\mathcal{L}_\varepsilon h = Q_\varepsilon(\mathcal{J}(G_\varepsilon))h + \varepsilon \mathcal{J}(h)\partial_v G_\varepsilon.$$

Next, we fix a constant  $N > 0$ , and in the same sense that we did in the Example 1.2.6, we define

$$\mathcal{B}_\varepsilon := \mathcal{L}_\varepsilon - \mathcal{A}, \quad \text{where } \mathcal{A} = N \chi_R(x, v). \quad (1.4.26)$$

The split (1.4.26) is such that the hypotheses (1.a) and (1.b) of the Krein-Rutmann abstract Theorem 1.2.4 hold. In particular, we have that for  $N$  and  $R$  large enough,  $(\mathcal{B}_\varepsilon + 1)$  is hypodissipative in  $H_v^2(m)$  and the

**Lemma 1.4.16.** *There are positive constants  $N, R$  large enough and some  $C_{\mathcal{B}_\varepsilon} > 0$ , such that the semigroup  $S_{\mathcal{B}_\varepsilon}$  satisfies*

$$\|S_{\mathcal{B}_\varepsilon}(t)h\|_{H_v^2(m_1)} \leq C_{\mathcal{B}_\varepsilon} t^{-9/2} \|h\|_{L^2(m_2)}, \quad \forall t \in (0, 1].$$

As a consequence, for any  $\alpha > -1$ , and any exponential weight  $m$ , there exists  $n \geq 1$  and  $C_{n,\varepsilon}$  such that of any  $t > 0$  it holds

$$\|(\mathcal{A}S_{\mathcal{B}_\varepsilon})^{(*n)}(t)h\|_{H_v^2(m)} \leq C_{n,\varepsilon} e^{\alpha t} \|h\|_{L^2(m)}. \quad (1.4.27)$$

The proof of the hypodissipativity of  $\mathcal{B}_\varepsilon + 1$  uses the idea of “removing” the positive parts of the  $\mathcal{H}_v^2$  inequality obtained for  $Q_\varepsilon$ . The key point is to define a new norm

$$\|h\|_{\tilde{H}_v^2(m)}^2 := \|h\|_{L^2(m)}^2 + \delta \|D_{x,v}h\|_{L^2(m)}^2 + \delta^2 \|\partial_{vv}^2 h\|_{L^2(m)}^2,$$

and choose  $\delta > 0$  small enough, to conclude that for any  $\alpha \in (0, 1]$  there is  $\delta_\alpha$  such that

$$\langle \mathcal{B}_\varepsilon h, h \rangle_{\tilde{H}_v^2(m)} \leq -\alpha \|h\|_{\tilde{H}_v^2(m)}^2.$$

Since the norm related to  $\bar{H}_v^2(m)$  is equivalent to the usual norm in  $H_v^2(m)$ , we can conclude the hypodissipative of  $\mathcal{B}_\varepsilon$ .

The proof of Lemma 1.4.16 is more technical. We first state some sharper estimates on the  $H_v^2(m)$  norm of  $\mathcal{B}_\varepsilon h$ , and next define a real function  $\mathcal{F}(t, h)$  by the formula

$$\begin{aligned} \mathcal{F}(h, t) := & \|h\|_{L^2(m_2)}^2 + c_1 t^3 \|\partial_x h\|_{L^2(m_1)}^2 + c_2 t \|\partial_v h\|_{L^2(m_1)}^2 \\ & + c_3 t^2 \langle \partial_x h, \partial_v h \rangle_{L^2(m_1)} + c_4 t^4 \|\partial_{vv}^2 h\|_{L^2(m_1)}^2. \end{aligned} \quad (1.4.28)$$

This is usually called the Hörmander-Hérau technique. When  $\mathcal{F}$  is evaluated on  $h_t = S_{\mathcal{B}_\varepsilon(t)} h$ , the sharper estimates on  $h_t$  allow us to conclude that for a well chosen family of  $c_i$ ,  $\mathcal{F}(t, h_t)$  is a decreasing function and then

$$C^{-1} t^{9/2} \left( \|\partial_{x,v} h_t\|_{L^2(m_1)}^2 + \|\partial_{vv}^2 h_t\|_{L^2(m_1)}^2 \right) \leq \|h_0\|_{L^2(m_2)}^2.$$

for some constant  $C$ . Finally, thanks to the fact that  $\mathcal{A}$  lies within a compact, we get that

$$\|\mathcal{A} S_{\mathcal{B}_\varepsilon(t)} h\|_{H_v^2(m)} \leq C' t^{-9/2} e^{-t} \|h\|_{L^2(m)}, \quad \forall t \in (0, 1],$$

for any exponential weight  $m$ .

Finally, thanks to the general Krein-Rutman's theorem, an induction argument, and the properties of the split (1.4.26) we deduce that in the linear case  $\varepsilon = 0$  the spectrum of the operator  $Q_0 = \mathcal{L}_0$ , is such that

**Proposition 1.4.17.**

(i) *There exists  $\bar{\alpha} < 0$  such that the spectrum  $\Sigma(\mathcal{L}_0)$  of  $\mathcal{L}_0$  in  $L^2(m)$  writes*

$$\Sigma(\mathcal{L}_0) \cap \Delta_{\bar{\alpha}} = \{0\},$$

*and 0 is simple.*

(ii) *For any  $\alpha > \bar{\alpha}$ , there exists a constant  $C_{H_v^1} > 0$  depending on  $(\alpha - \bar{\alpha})$ , such that*

$$\|\mathcal{R}_{\mathcal{L}_0}(z)\|_{\mathcal{B}(L^2(m), H_v^1(m))} \leq C_{H_v^1} (1 + |z|^{-1}), \quad \forall z \in \mathbb{C} \setminus \{0\}, \operatorname{Re}(z) > \alpha.$$

Proposition 1.4.17 implies two things: first, the operator  $\mathcal{L}_0$  is invertible in  $L^2(m)$  for functions with zero mean; and second, the stability part of Theorem 1.4.15 holds.

The third main result of the chapter is the

**Theorem 1.4.18.** *There exists  $\varepsilon^* > 0$  such that, in the small connectivity regime  $\varepsilon \in (0, \varepsilon^*)$ , the stationary solution is unique and exponentially stable. More precisely, there exist  $\alpha^* < 0$  and  $\eta^*(\varepsilon) : \mathbb{R}_+ \rightarrow \mathbb{R}$ , with  $\eta^*(\varepsilon) \xrightarrow{\varepsilon \rightarrow 0} \infty$ , such that if*

$$f_0 \in H^1(m) \cap \mathbb{P}(\mathbb{R}^2) \quad \text{and} \quad \|f_0 - G\|_{H^1(m)} \leq \eta^*(\varepsilon),$$

*then there exists  $C^* = C^*(f_0, \varepsilon^*, \varepsilon) > 0$ , such that*

$$\|f_t - G\|_{L^2(m)} \leq C^* e^{\alpha^* t}, \quad \forall t \geq 0,$$

*where  $f_t$  is the solution to (1.4.17) with initial condition  $f_0$ .*

The uniqueness is once again a result of the invertibility of  $\mathcal{L}_0$  on  $L^2(m)$  for functions with zero mean and an inequality of the type

$$\|f\|_{\mathcal{V}} := \|f\|_{L^2(Mm)} + \|\nabla_v f\|_{L^2(M^{1/2}m)} \leq C_{\mathcal{V}} \|g\|_{L^2(m)}. \quad (1.4.29)$$

for a constant  $C_{\mathcal{V}}$  and any  $g$  with zero mean such that  $\mathcal{L}_0 f = g$ . Inequality 1.4.29 implies that there is a constant  $C$  such that for any two stationary solutions of (1.4.17)  $F_{\varepsilon}$  and  $G_{\varepsilon}$  it holds

$$\|F_{\varepsilon} - G_{\varepsilon}\|_{\mathcal{V}} \leq \varepsilon C \|F_{\varepsilon} - G_{\varepsilon}\|_{\mathcal{V}}, \quad (1.4.30)$$

then for  $\varepsilon$  small enough we get the uniqueness of the stationary state.

The nonlinear exponential convergence uses a perturbation argument on the spectrum of  $\mathcal{L}_0$  to find the

**Theorem 1.4.19.** *Let us fix  $\alpha$  negative and close to 0. Then there exists  $\varepsilon_2 \in (0, \varepsilon_1)$  such that for any  $\varepsilon \in [0, \varepsilon_2]$ , there hold*

(i) *The spectrum  $\Sigma(\mathcal{L}_{\varepsilon})$  of  $\mathcal{L}_{\varepsilon}$  in  $L^2(m)$  writes*

$$\Sigma(\mathcal{L}_{\varepsilon}) \cup \Delta_{\alpha} = \{0\},$$

*and 0 is a simple eigenvalue.*

(ii) *The linear semigroup  $S_{\mathcal{L}_{\varepsilon}}(t)$  associated to  $\mathcal{L}_{\varepsilon}$  in  $L^2(m)$  writes*

$$S_{\mathcal{L}_{\varepsilon}}(t) = \Pi_{\varepsilon} + R_{\varepsilon}(t),$$

*where  $\Pi_{\varepsilon}$  is the projection on the eigenspace associated to 0 and where  $R_{\varepsilon}(t)$  is a semigroup which satisfies*

$$\|R_{\varepsilon}(t)\|_{\mathcal{B}(L^2(m))} \leq C_{\mathcal{L}_{\varepsilon_1}} e^{\alpha t},$$

*for some positive constant  $C_{\mathcal{L}_{\varepsilon_1}}$  independent of  $\varepsilon$ .*

The proof of Theorem 1.4.19 consists in finding  $\eta_2(\varepsilon) \xrightarrow{\varepsilon \rightarrow 0} 0$ , such that  $\Sigma(\mathcal{L}_{\varepsilon}) \cap \Delta_{\alpha} \subset B(0, \eta_2(\varepsilon))$ , which is done by computing exactly the inverse of  $\mathcal{L}_{\varepsilon} - z$  for  $z \neq 0$ ,  $\text{Re}(z) > \alpha$ . A direct consequence of this result is that the conclusion of Theorem 1.4.18 is an application of the Duhamel's formula for the linear semigroup  $S_{\mathcal{L}_{\varepsilon}}$ , and to control correctly the nonlinear extra term.

All the technical details of this work are presented in the Chapter 3 of this text, which is included in a very recent pre-publication [112] (submitted), work done in collaboration with S. Mischler and J. Touboul.

## Part II: Main mathematical results ---

The second biological problem we study is presented in Chapter 4 and Chapter 5, and it no more deals with neuronal activity but with the structuring of neuronal areas. In Chapter 4 we present the model and

provide a biological relevant discussion of the results obtained. This model of neuronal differentiation was proposed with the help of the experimental biologist Professor Alan Prochiantz. In Chapter 5 we consider a general version of the model of neuronal differentiation in a one dimensional case. There, we prove rigorously the idea of the convergence of the family of stationary solutions when the diffusive operator is going to zero.

### 1.4.3 Competition and boundary formation in heterogeneous media: application to neuronal differentiation

Our model falls in the frame of the competition of two diffusing species  $A$  and  $B$  that are reciprocal inhibitor and self-activating, with saturation and spatially heterogeneous production rates  $H_A(x, A, B)$  and  $H_B(x, A, B)$ . In neurodevelopmental terms, transcription factors expressed by two genes  $G_A$  and  $G_B$  constitute our two competing species, and the space heterogeneity corresponds to the graded concentration of morphogens. For simplicity, we present the framework a one-dimensional case in which the differentiating tissue is along the interval  $[0, 1]$ .

Abstracting the problems that we will see in Chapter 4, it is natural to consider the following system of reaction-diffusion equations:

$$\begin{cases} \partial_t A - \varepsilon d_A \Delta A = A H_A(x, A, B), & 0 < x < 1, \\ \partial_t B - \varepsilon d_B \Delta B = B H_B(x, A, B), \end{cases} \quad (1.4.31)$$

with some boundary conditions to be preciser later.

Here  $H_A$  and  $H_B$  are maps from  $[0, 1] \times \mathbb{R}_+ \times \mathbb{R}_+$  on  $\mathbb{R}$ , assumed to be of class  $C^2$ . We assume that

$$\begin{cases} H_A(x, 0, 0) > 0, & H_B(x, 0, 0) > 0, \\ \partial_x H_A(x, A, B) < 0, & \partial_x H_B(x, A, B) > 0, \\ \partial_B H_A(x, A, B) < 0, & \partial_A H_B(x, A, B) < 0, \end{cases} \quad (1.4.32)$$

which can be interpreted as follows: on the one hand, the morphogen gradients do not vanish and vary monotonically, on the other hand the system expresses competition between species  $A$  and  $B$ .

Because, we are interested in the limit  $\varepsilon = 0$ , the stationary solutions of (1.4.31) in the absence of diffusion are useful. We assume that there exists two solutions  $(F_A(x) > 0, 0)$  and  $(0, F_B(x) > 0)$  such that

$$H_A(x, F_A(x), 0) = 0, \quad H_B(x, 0, F_B(x)) = 0, \quad (1.4.33)$$

and that they are respectively stable for  $x \in (0, x_a)$  and for  $x \in (x_b, 1)$ , with  $x_a > x_b$ . Therefore, for any fixed  $x \in (x_b, x_a)$ , the system is a bistable ODE. We further assume

$$H_B(x, F_A(x), 0) > 0 \text{ for } x > x_a > x_b, \quad H_A(x, 0, F_B(x)) > 0 \text{ for } x < x_b < x_a. \quad (1.4.34)$$

Finally, we assume that there exists a unique additional solution  $(A^*(x) > 0, B^*(x) > 0)$  in the interval  $(x_b, x_a)$  which is a saddle. In order to complete the definition of our system (1.4.31), we consider the Robin (also called third type) boundary conditions:

$$\begin{cases} A(0) - \sqrt{\varepsilon} \frac{\partial}{\partial x} A(0) = F_A(0), & A(1) + \sqrt{\varepsilon} \frac{\partial}{\partial x} A(1) = 0, \\ B(0) - \sqrt{\varepsilon} \frac{\partial}{\partial x} B(0) = 0, & B(1) + \sqrt{\varepsilon} \frac{\partial}{\partial x} B(1) = F_B(1). \end{cases} \quad (1.4.35)$$

At this level of generality, assumptions (1.4.32)–(1.4.34) may appear formal. These are actually very natural, as we will see in the Chapter 4.

The main result that we will demonstrate is the fact that in the presence of small diffusion, a clear boundary between two differentiated domains exists and is unique, and may be characterized univocally. In detail, we prove the

**Theorem 1.4.20.** *Under assumptions 1.4.32–1.4.34, there exists a classical stationary solution  $(A_\varepsilon, B_\varepsilon)$  of (1.4.31) which satisfies*

$$\frac{d}{dx} A_\varepsilon(x) < 0, \quad \frac{d}{dx} B_\varepsilon(x) > 0, \quad (1.4.36)$$

and is obtained as  $t \rightarrow \infty$  in the corresponding parabolic equation. Moreover

(i) *As  $\varepsilon \rightarrow 0$ ,  $(A_\varepsilon, B_\varepsilon)$  converges a.e. towards a pair  $(A_0, B_0)$ . These maps are discontinuous at some point  $x^* \in [x_b, x_a]$  and have disjoint supports*

$$\text{supp}(A_0) = [0, x^*] \quad \text{and} \quad \text{supp}(B_0) = [x^*, 1].$$

(ii) *The point  $x^*$  is characterized by the relation  $c(x^*) = 0$  where  $c(\cdot)$  represents the speed of propagation of a traveling wave problem parametrized by  $x$ .*

The proof of Theorem 1.4.20 uses arguments of viscosity solutions and travelling waves. The first step is to characterise the stationary functions  $F_A$ ,  $F_B$  and  $(A^*, B^*)$ . Using the hypotheses on the spatially heterogeneous production rates, we can readily prove that the functions defined in (1.4.33) and (1.4.34) satisfy

$$\frac{d}{dx} F_A(x) < 0 \quad \text{for } x \in [0, x_a), \quad \frac{d}{dx} F_B(x) > 0 \quad \text{for } x \in (x_b, 1], \quad (1.4.37)$$

$$\frac{d}{dx} A^*(x) > 0 \quad \text{and} \quad \frac{d}{dx} B^*(x) < 0, \quad x_b < x < x_a. \quad (1.4.38)$$

The next step is to prove that solutions to the parabolic problem are monotone for well chosen initial conditions. To that aim we start by fixing two nonnegative decreasing sub-solution (respectively increasing super-solution) for  $A$  (respectively  $B$ ). In that case, we prove the

**Lemma 1.4.21.** *For all  $t \geq 0$  and  $x \in [0, 1]$ , we have that  $(A_\varepsilon, B_\varepsilon)$  solution to (1.4.31), are such that  $\partial_t A_\varepsilon(t, x) \geq 0$  and  $\partial_t B_\varepsilon(t, x) \leq 0$ .*

and the

**Lemma 1.4.22.** *For any  $\varepsilon > 0$  fixed, let us consider any solution  $(A_\varepsilon, B_\varepsilon)$  of (1.4.31) with initial conditions  $A(0, x)$  decreasing and  $B(0, x)$  increasing. If the solutions are uniformly bounded on space and*

time, we have for all  $t \geq 0$

$$\frac{\partial}{\partial x} A_\varepsilon(t, x) \leq 0 \quad \text{and} \quad \frac{\partial}{\partial x} B_\varepsilon(t, x) \geq 0, \quad 0 \leq x \leq 1.$$

Both previous lemmas are interesting because the proof is based on the *a priori bounds* of the parabolic system. In particular, we use the temporal and spatial derivatives of equations (1.4.31), to get the monotonicity results stated.

At this point a bootstrap argument allows us to conclude that there exists  $A_\varepsilon(x), B_\varepsilon(x)$  regular stationary solutions of (1.4.31), and then the first part of Theorem 1.4.20 is valid. To continue we provide sharper estimates of the stationary solutions to control  $A_\varepsilon(0)$  and  $B_\varepsilon(1)$  away from zero. More precisely, we prove the

**Proposition 1.4.23.** *There exists  $\varepsilon_0 > 0$  such that for any  $\varepsilon < \varepsilon_0$ , the stationary solution  $A_\varepsilon$  is strictly positive and  $A_\varepsilon(0)$  is, uniformly in  $\varepsilon$ , larger than some  $\delta_A > 0$ . The same holds for  $B_\varepsilon$  and  $B_\varepsilon(1)$ .*

The proof of Proposition 1.4.23 consists in finding a strictly positive sub-solution for

$$-\varepsilon d_A \frac{d^2}{dx^2} \phi_A = H_A(x, \phi_A(x), B_\varepsilon(x)) \phi_A, \quad (1.4.39)$$

which can be done explicitly. Equipped with this result, and since the total variation of the stationary solutions  $A_\varepsilon$  and  $B_\varepsilon$  is uniformly bounded in  $\varepsilon$ , we can pass to the limit and find a pair  $(A_0, B_0)$  that satisfies, almost everywhere,

$$\begin{cases} A_0 H_A(x, A_0(x), B_0(x)) = 0, \\ B_0 H_B(x, A_0(x), B_0(x)) = 0. \end{cases} \quad (1.4.40)$$

Since we know from the hypotheses the possible solutions to the autonomous system (1.4.40) for each  $x$  fixed, it only remains to prove that they define a pair  $(A_0(x), B_0(x))$  as the Theorem 1.4.20 states. The previous condition is reduced to find  $x^*$  such that  $(A_0(x), B_0(x)) = (F_A(x), 0)$ , for  $x < x^*$  and  $(A_0(x), B_0(x)) = (0, F_B(x))$ , for  $x > x^*$ . To that aim, we use a WKB change of unknown ( $\varphi_A^\varepsilon := -\sqrt{\varepsilon} \log(A_\varepsilon)$ ), and thanks to the sharper estimates given by Proposition 1.4.23 we get the

**Lemma 1.4.24.** *There exists two non empty intervals, namely  $I_b$  and  $I_a = [0, 1] \setminus I_b$ , such that  $B_0 \equiv 0$  in  $I_b$  and  $A_0 \equiv 0$  in  $I_a$ . Moreover,*

$$[0, x_b) \subset I_b \quad \text{and} \quad (x_a, 1] \subset I_a.$$

Finally, we would like to characterise the limit  $(A_0, B_0)$ . Under the change of variables  $y = (x - x_\varepsilon^*)/\sqrt{\varepsilon}$ , and define  $a_\varepsilon(y) = A_\varepsilon(x_\varepsilon^* + \sqrt{\varepsilon}y)$  and  $b_\varepsilon$  in the same way. We pass to the limit  $\varepsilon \rightarrow 0$  in the stationary version of (1.4.31) to find that  $(a_0, b_0)$ , is solution of

$$\begin{cases} -d_A \frac{d^2}{dy^2} a_0(y) = a_0(y) H_A(x^*, a_0(y), b_0(y)), & \partial_y a_0(y) \leq 0, \\ -d_B \frac{d^2}{dy^2} b_0(y) = b_0(y) H_B(x^*, a_0(y), b_0(y)), & \partial_y b_0(y) \geq 0, \\ a_0(0) = b_0(0). \end{cases} \quad (1.4.41)$$

This solution is characterized as follows:



**Theorem 1.4.25.** *The limits satisfy  $a_0 \neq 0$ ,  $b_0 \neq 0$  and there exists a unique value  $x^*$  such that the system (1.4.41) has a non-trivial solution. This solution is the unique traveling wave defined as*

$$\begin{cases} -c(x)\frac{\partial}{\partial y}a(y;x) - d_A\frac{\partial^2}{\partial y^2}a(y;x) = a(y;x)H_A(x, a(y;x), b(y;x)), & y \in \mathbb{R}, \\ -c(x)\frac{\partial}{\partial y}b(y;x) - d_B\frac{\partial^2}{\partial y^2}b(y;x) = b(y;x)H_B(x, a(y;x), b(y;x)), \\ \lim_{y \rightarrow -\infty} a(y;x) = F_A(x), & \lim_{y \rightarrow +\infty} a(y;x) = 0, \\ \lim_{y \rightarrow +\infty} b(y;x) = F_B(x), & \lim_{y \rightarrow -\infty} b(y;x) = 0, \end{cases} \quad (1.4.42)$$

with speed zero, that is  $c(x^*) = 0$ , and connecting  $(F_A(x^*), 0)$  to  $(0, F_B(x^*))$ .

The proof of Theorem 1.4.42 is split into three steps. First we show that functions  $a_\varepsilon$  and  $b_\varepsilon$  cannot converge both at the same time to the zero function. Then, using that  $a_0$  and  $b_0$  converge at  $-\infty$  to solutions of (1.4.40), we show that limit conditions of (1.4.42) are satisfied. Finally, thanks to a monotonicity argument on the speed  $c(x)$ , we show that  $(a_0, b_0)$  are in fact the unique traveling wave solutions of (1.4.42) such that  $c(\cdot) = 0$ .

## Part III: Main results

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Finally, we discuss the convergence results obtained for the subcritical Keller-Segel particle system. In particular, we prove chaos and entropic chaos propagation without the use of a truncation and/or regularisation version of the related kernel. Eventually, by the use of a combined PDE/Probabilistic approach we prove the entropic chaos propagation property.

### 1.4.4 On a subcritical Keller-Segel equation

We consider the following system of particles

$$\forall i = 1, \dots, N, \quad X_t^{i,N} = X_0^{i,N} - \frac{\chi}{N} \sum_{j=1, j \neq i}^N \int_0^t K(X_s^{i,N} - X_s^{j,N}) ds + \sqrt{2} B_t^i, \quad (1.4.43)$$

where  $(B^i)_{i=1, \dots, N}$  is an independent family of 2D standard Brownian motions and the force field kernel  $K : \mathbb{R}^2 \rightarrow \mathbb{R}^2$  comes from an attractive potential  $\Phi : \mathbb{R}^2 \rightarrow \mathbb{R}$  and is defined by

$$K(x) := \frac{x}{|x|^{\alpha+1}} = -\nabla \underbrace{\left( \frac{1}{\alpha-1} |x|^{1-\alpha} \right)}_{\Phi(x)}, \quad \alpha \in (0, 1). \quad (1.4.44)$$

Our goal is to prove that there is propagation of chaos to the solution of the following nonlinear SDE

$$X_t = X_0 - \chi \int_0^t \int_{\mathbb{R}^2} K(X_s - x) f_s(dx) ds + \sqrt{2} B_t, \quad (1.4.45)$$

where  $f_t = \mathcal{L}(X_t)$  is the law of  $X_t$ . Moreover, it is classical to show that if  $(X_t)_{t \geq 0}$  is a solution to (1.4.45), then  $(f_t)_{t \geq 0}$  is a weak solution of

$$\frac{\partial f_t(x)}{\partial t} = \chi \nabla_x \cdot ((K * f_t)(x)) f_t(x) + \Delta_x f_t(x). \quad (1.4.46)$$

The main result that we obtained on this Chapter is the following:

**Theorem 1.4.26.** *Let  $\alpha \in (0, 1)$ . Assume that initial condition is such that*

$$\begin{cases} F_0^N \in \mathbb{P}_{sym}((\mathbb{R}^2)^N) \text{ is } f_0\text{-chaotic;} \\ \sup_{N \geq 2} M_1(F_0^N) < \infty, \quad \sup_{N \geq 2} H(F_0^N) < \infty. \end{cases} \quad (1.4.47)$$

For each  $N \geq 2$ , consider the unique solution  $(X_t^{i,N})_{i=1,\dots,N,t \geq 0}$  to (1.4.43). Let  $(X_t)_{t \geq 0}$  be the unique solution to (1.4.45).

(i) The sequence  $(X_t^{i,N})_{i=1,\dots,N,t \geq 0}$  is  $(X_t)_{t \geq 0}$ -chaotic. In particular, the empirical measure  $Q^N := \frac{1}{N} \sum_{i=1}^N \delta_{(X_t^{i,N})_{t \geq 0}}$  goes in law to  $\mathcal{L}((X_t)_{t \geq 0})$  in  $\mathbb{P}(C((0, \infty), \mathbb{R}^2))$ .

(ii) Assume furthermore that  $\lim_N H(F_0^N) = H(f_0)$ . For all  $t \geq 0$ , the sequence  $(X_t^{i,N})_{i=1,\dots,N}$  is then  $X_t$ -entropically chaotic. In particular, for any  $j \geq 1$  and any  $t \geq 0$ , denoting by  $F_{tj}^N$  the density of the law of  $(X_t^{1,N}, \dots, X_t^{j,N})$ , it holds that

$$\lim_{N \rightarrow \infty} \|F_{tj}^N - f_t^{\otimes j}\|_{L^1((\mathbb{R}^2)^j)} = 0.$$

The proof of Theorem 1.4.26 is based on the tightness of the empirical measure  $Q^N$ . However, since the force kernel is singular and the limit equation is nonlinear and nonlocal, the well posedness of the particle system (1.4.43) and the mean-field equation (1.4.45) are not direct.

To avoid the singularity at 0, we first analyse a regularized version of the equations and then pass to the limit. For  $\epsilon \in (0, 1)$ , we set

$$K_\epsilon(x) = \frac{x}{\max(|x|, \epsilon)^{\alpha+1}}, \quad (1.4.48)$$

which obviously satisfies  $|K_\epsilon(x) - K_\epsilon(y)| \leq C_{\alpha,\epsilon}|x - y|$ . Therefore, the following system of S.D.E.s

$$\forall i = 1, \dots, N, \quad X_t^{i,N,\epsilon} = X_0^{i,N} - \frac{\chi}{N} \sum_{j=1, j \neq i}^N \int_0^t K_\epsilon(X_s^{i,N,\epsilon} - X_s^{j,N,\epsilon}) ds + \sqrt{2} B_t^i, \quad (1.4.49)$$

is such that strong existence and uniqueness of the solution hold. Moreover, we notice that the entropy, the first moment, and the Fisher's information of the solutions to the system (1.4.48) are upper bounded uniformly in  $\epsilon$ . In particular we show the:

**Proposition 1.4.27.** *Let  $\alpha \in (0, 1)$ .*

(i) Let  $N \geq 2$  be fixed. Assume that  $M_1(F_0^N) < \infty$  and  $H(F_0^N) < \infty$ . For all  $t \geq 0$ , we denote by  $F_t^{N,\epsilon} \in \mathbb{P}_{sym}((\mathbb{R}^2)^N)$  the law of  $(X_t^{i,N,\epsilon})_{i=1,\dots,N}$ . Then

$$\begin{aligned} H(F_t^{N,\epsilon}) = & H(F_0^N) + \frac{\chi}{N^2} \sum_{i \neq j} \int_0^t \int_{(\mathbb{R}^2)^N} \operatorname{div} K_\epsilon(x_i - x_j) F_s^{N,\epsilon}(x) ds dx \\ & - \int_0^t I(F_s^{N,\epsilon}) ds. \end{aligned} \quad (1.4.50)$$

(ii) There exists a constant  $C$  which depends on  $\chi$ ,  $H(F_0^N)$  and  $M_1(F_0^N)$  (but not on  $\epsilon$ ) such that for all  $t \geq 0$  and  $N \geq 2$ ,

$$H(F_t^{N,\epsilon}) \leq C(1+t), \quad M_1(F_t^{N,\epsilon}) \leq C(1+t), \quad \int_0^t I(F_s^{N,\epsilon}) ds \leq C(1+t). \quad (1.4.51)$$

Furthermore,

$$\mathbb{E} \left[ \sup_{[0, T]} |X_t^{1, N, \epsilon}| \right] \leq C(1 + T). \quad (1.4.52)$$

The proof of Proposition 1.4.27 is based on the ideas of [62, Proposition 5.1], that we adapt using the fact that the kernel is no more divergence free. Therefore, there is an additional term in the dissipation of entropy formula (1.4.50) that necessitate to be specifically controlled. This is a technical problem, but using classical properties of the Brownian motions it is possible to get the stated result.

To prove the well posedness of (1.4.43) the key point is to show that particles almost surely never collide. To this purpose we first notice that this result holds for (1.4.49). Since  $K_\epsilon$  and  $K$  coincide as long as the distance between any two particles of (1.4.43) is larger than  $\epsilon$ , we deduce first that the particles of true system (1.4.43) also never collide, and second the global existence and uniqueness for (1.4.43). Finally, we establish the estimates about the entropy, Fisher information and the first moment by passing to the limit in (1.4.51).

In a second part of the chapter, we deal with the tightness and the consistency of the particle system with respect to the SDE (1.4.45). In particular we show the

**Lemma 1.4.28.** *Let  $\alpha \in (0, 1)$ . Assume (1.4.47). For each  $N \geq 2$ , let  $(X_t^{i, N})_{i=1, \dots, N}$  be the unique solution to (6.1.3) and  $Q^N := \frac{1}{N} \sum_{i=1}^N \delta_{(X_t^{i, N})_{t \geq 0}}$ , then*

▷ *the family  $\{\mathcal{L}((X_t^{1, N})_{t \geq 0}), N \geq 2\}$  is tight in  $\mathbb{P}(C([0, \infty), \mathbb{R}^2))$ ;*

▷ *the family  $\{\mathcal{L}(Q^N), N \geq 2\}$  is tight in  $\mathbb{P}(\mathbb{P}(C([0, \infty), \mathbb{R}^2)))$ .*

and, defining  $\mathcal{S}$  as the set of all probability measures  $f \in \mathbb{P}(C([0, \infty), \mathbb{R}^2))$  such that  $f$  is the law of  $(X_t)_{t \geq 0}$  solution to (1.4.45) with locally (in time) integrable Fisher information and locally (in time) bounded first moment, we have the

**Proposition 1.4.29.** *Let  $\alpha \in (0, 1)$  and assume (1.4.47). For each  $N \geq 2$ , let  $(X_0^{i, N})_{i=1, \dots, N}$  be  $F_0^N$ -distributed and consider the solution  $(X_t^{i, N})_{i=1, \dots, N, t \geq 0}$  to (1.4.43). Assume that there is a subsequence of  $Q^N := \frac{1}{N} \sum_{i=1}^N \delta_{(X_t^{i, N})_{t \geq 0}}$  going in law to some  $\mathbb{P}(C([0, \infty), \mathbb{R}^2))$ -valued random variable  $Q$ . Then  $Q$  a.s. belongs to  $\mathcal{S}$ .*

The proof of these results is classical and it is mainly based on the a priori bounds of the solutions and Itô's formula. As a direct consequence we find a weak solution to the limit mean-field SDE (1.4.45). To find a strong solution and the uniqueness required to the propagation of chaos result, it is necessary to analyse the set of weak solutions to the equation (1.4.46) when initial conditions have bounded entropy. In particular, we show that if  $p > 2/(1 - \alpha)$  and any weak solution  $(f_t)_{t \geq 0}$  to (1.4.46) lying in  $L_{loc}^\infty([0, \infty), \mathbb{P}_1(\mathbb{R}^2)) \cap L_{loc}^1([0, \infty); L^p(\mathbb{R}^2))$  is unique.

The proof uses the related martingale problem, and the fact that for deterministic initial conditions, there exists a unique solution to it. All the previous analysis imply the validity of (i) in the Theorem 1.4.26. To prove the entropic chaos propagation (ii), we use the notion of renormalised solutions. To that aim, we first show that the strong solution to the mean-field system coincide with the unique solution given by the

**Theorem 1.4.30.** *Let  $\alpha \in (0, 1)$ . Assume that  $f_0 \in \mathbb{P}_1(\mathbb{R}^2)$  is such that  $H(f_0) < \infty$ .*

(i) *There exists a unique weak solution  $f$  to (1.4.46) such that*

$$f \in L_{loc}^\infty([0, \infty), \mathbb{P}_1(\mathbb{R}^2)) \cap L_{loc}^1([0, \infty); L^p(\mathbb{R}^2)) \quad \text{for some } p > \frac{2}{1-\alpha}. \quad (1.4.53)$$

(ii) *This solution furthermore satisfies that for all  $T > 0$ ,*

$$\int_0^T I(f_s) ds < \infty, \quad (1.4.54)$$

*for any  $q \in [1, 2)$  and for all  $T > 0$ ,*

$$\nabla_x f \in L^{2q/(3q-2)}(0, T; L^q(\mathbb{R}^2)), \quad (1.4.55)$$

*for any  $p \geq 1$ ,*

$$f \in C([0, \infty); L^1(\mathbb{R}^2)) \cap C((0, \infty); L^p(\mathbb{R}^2)), \quad (1.4.56)$$

*and that for any  $\beta \in C^1(\mathbb{R}) \cap W_{loc}^{2,\infty}(\mathbb{R})$  such that  $\beta''$  is piecewise continuous and vanishes outside a compact set,*

$$\begin{aligned} \partial_t \beta(f) = & \chi(K * f) \cdot \nabla_x(\beta(f)) + \Delta_x \beta(f) \\ & - \beta''(f) |\nabla_x f|^2 + \chi \beta'(f_s) f_s (\nabla_x \cdot K * f_s), \end{aligned} \quad (1.4.57)$$

*on  $[0, \infty) \times \mathbb{R}^2$  in the distributional sense.*

Notice that here the notion of weak solution makes reference to the deterministic notion of weak solutions, i.e., in a PDE context. The proof of Theorem 1.4.30 uses first the Hardy-Littlewood-Sobolev inequality to prove that the convolution term  $K * f$  is bounded in some specific  $L^p(0, T; L^q(\mathbb{R}^2))$  spaces. Thanks to this remark, one can use a sequence of mollifiers to prove that inequality (1.4.57) holds, and using a bootstrap argument we get the maximal regularity of the solution (1.4.56) and its derivatives (1.4.55). Choosing a well sequence of test functions  $\beta_m$  functions converging to  $H$ , one can finally pass to the limit and deduce the entropic propagation of chaos property.

All the technical details and calculations are presented in the Chapter 6 of this manuscript. This is the object of [66] written in collaboration with D. Godinho to appear in *Annales de l'Institut Henri Poincaré*.

## 1.5 Perspectives and open problems ---

We finish this introductory chapter by discussing a complementary problem related to the chaos propagation for a Poisson coupling model and a couple of open problems that constitute the direct perspectives of this work.

### 1.5.1 A microscopic spiking neuronal network for the age-structured model

Regarding the chaos propagation method, in a series of outstanding papers, Pakdaman, Perthame and Salort (PPS) [121, 122, 123] introduced a very versatile model for the large-scale dynamics of neuronal

networks. These equations describe the probability distribution of the time elapsed since the last spike fired as an age-structured nonlinear PDE. Inspired by the dynamics of these macroscopic equations, we work on a microscopic model describing the dynamics of a finite number of neurons, and that provides a realistic neural network model consistent with the PPS model, in the sense that in the thermodynamic limit, propagation of chaos and convergence to the PPS equation is proved.

In this model, the state of each neuron  $i$  is described by a  $\mathbb{R}_+$ -valued variable  $X_t^{i,N}$  corresponding to the time elapsed since last discharge. Of course, this approach is quite different from classical literature, where the key variable is the voltage: this is an important originality of the PPS model. The spiking interaction between neurons is considered as a the global activity  $M$  at the network level. Specifically, a neuron with age  $x$  (duration since it fired its last spike) fires a spike with an instantaneous intensity  $a(x, M)$  where  $M$  is the global activity of the network. Subsequently to the spike emission, two things happen: the age of the spiking neuron is reset to 0, and the global variable  $M$  increases its value by an extra value of  $J/N$ . The coefficient  $J$  represents the mean connectivity of the network.

For each  $N \in \mathbb{N}$ , let us consider a family  $(\mathcal{N}_t^1, \dots, \mathcal{N}_t^N)_{t \geq 0}$  of i.i.d. standard Poisson processes. Let us also consider a family  $(\tau_1, \dots, \tau_N)$  of i.i.d. real valued random variables with probability law  $b$ . These coefficients represent delays in the transmission of information from the cell to whole network. Furthermore, we assume that the family of delays is independent of the Poisson processes and the initial conditions.

As always in the propagation of chaos framework, we assume chaotic initial conditions, in the sense that the initial state of the neurons are independent and identically distributed random variables. Therefore, for  $g_0$  and  $m_0$  two independent probability measures on  $\mathbb{R}_+$ ,  $(g_0, m_0)$ -chaotic initial states consists in setting i.i.d. initial conditions for all neurons with common law equal to  $g_0$ , and setting independently, for the global activity, another random variable distributed as  $m_0$ .

The main idea is to understand the convergence of the  $\mathbb{R}_+$ -valued Markov processes

$$(X_t^N)_{t \geq 0} = (X^{1,N}, \dots, X^{N,N})_{t \geq 0},$$

solving, for each  $i = 1, \dots, N$  and any  $t \geq 0$ :

$$X_t^{i,N} = X_0^{i,N} + t - \int_0^t X_{s-}^{i,N} \int_0^\infty \mathbf{1}_{\{u \leq a(X_{s-}^{i,N}, M_{s-}^N)\}} \mathcal{N}^i(du, ds), \quad (1.5.58)$$

with the coupling given by the global variable

$$M_t^N = M_0^N - \alpha \left[ \int_0^t M_s^N ds - \frac{J}{N} \sum_{j=1}^N \int_0^t \int_0^\infty \mathbf{1}_{\{u \leq a(X_{s-\tau_j}^{j,N}, M_{s-\tau_j}^N)\}} \tilde{\mathcal{N}}^j(du, ds) \right], \quad (1.5.59)$$

where  $\tilde{\mathcal{N}}_t^j$  is the shifted (in time) process  $\mathcal{N}_{t-\tau_j}^j$  extended by 0 for negative values of the time. These processes are a consistency restriction on the spiking times: *when a neuron  $j$  sends a signal at a time  $t \geq 0$ , the global variable receives it only at instant  $t + \tau_j$ .*

Finally, we make the following physically reasonable assumption on the intensity spike function of the

system:

$$\begin{cases} a(\cdot, \cdot) \text{ is a continuous non decreasing function in both variables,} \\ a(0, \cdot) = 0, \quad a(\cdot, 0) > 0 \\ a(x, m) \xrightarrow{x \rightarrow \infty} \infty, \quad \forall m \in \overline{\mathbb{R}}_+, \end{cases} \quad (1.5.60)$$

and impose a second consistency restriction

$$(\forall \delta > 0)(\exists x_\delta^* > 0) \text{ such that } a(x, m) \leq \delta, \quad \forall m \in \mathbb{R}_+ \quad (1.5.61)$$

representing that, independently of the level of the network activity, a neuron cannot spike two times in an arbitrary small period of time. The well-posedness of the particle system under these set of hypotheses is direct.

Under suitable conditions, it is likely that the solution  $(X_t^N)_{t \geq 0}$  behave, for large values of  $N$ , as  $N$  independent copies of the solution to a *nonlinear* SDE. Let  $Y_0$  (respectively  $M_0$ ) be a  $g_0$ -distributed random variable (resp.  $m_0$ ) and  $\mathcal{N}_t$  a standard Poisson process independent of  $Y_0$  and  $M_0$ . Then we look for  $\mathbb{R}_+$ -valued *càdlàg* adapted process  $(Y_t, M_t)_{t \geq 0}$  solving for any  $t \geq 0$

$$Y_t = Y_0 + t - \int_0^t Y_{s-} \int_0^\infty \mathbf{1}_{\{u \leq a(Y_{s-}, M_{s-})\}} \mathcal{N}(du, ds), \quad (1.5.62)$$

and

$$M_t = M_0 - \alpha \left[ \int_0^t M_s ds - J \int_0^t \int_0^s \mathbb{E}[a(Y_{s-w}, M_{s-w})] b(dw) ds \right]. \quad (1.5.63)$$

Indeed, it is not difficult to prove, using a tightness and a consistency method, the

**Theorem 1.5.31.** *Let us assume that hypotheses (1.5.60)–(1.5.61) hold, then there exists a weak solution  $(Y_t, M_t)_{t \geq 0}$  to (1.5.62)–(1.5.63) such that*

$$\int_0^t \int_0^s \mathbb{E}[a(Y_{s-w}, M_{s-w})] b(dw) ds < \infty, \quad \forall t \geq 0. \quad (1.5.64)$$

On the other hand, let us consider the growing restriction

$$(\exists \xi > 2)(\exists 0 < \rho < 1)(\exists C_\xi, c_\rho > 0) : c_\rho x^{\frac{1+\rho}{1-\rho}} \leq a(x, m) \leq C_\xi(1 + x^{\xi-2} + m^{\xi-2}), \quad (1.5.65)$$

and suppose that initial condition has bounded exponential moments

$$\mathbb{E}[e^{\omega(Y^\xi + M^\xi)}] < \infty, \quad \omega > 0. \quad (1.5.66)$$

then it is likely to have the

**Theorem 1.5.32.** *There exists a unique strong solution  $(Y_t, M_t)_{t \geq 0}$  to (1.5.62)–(1.5.63) in the class of functions of locally bounded exponential moments (1.5.66).*

and the

**Theorem 1.5.33.** *Let us assume that hypotheses (1.5.60)–(1.5.61) hold, and that the law of  $(Y_0, M_0)$  is compactly supported, then the sequence of empirical processes  $\mu_N(t)$  converges in distribution to the law of the unique process  $(Y_t, M_t)_{t \geq 0}$  with  $(g_0, m_0)$ -chaotic initial states solution to (1.5.62)–(1.5.63).*

If the initial datum has a fast decay (in the sense described in Theorem 1.5.32), and if moreover there is a positive constant  $C_0$  such that

$$|a(x, m) - a(x', m')| \leq C_0 [a(x, m) \wedge a(x', m') |x - x'| + |m - m'|], \quad (1.5.67)$$

for all  $x, x', m, m' \in \mathbb{R}_+$ . Then the convergence of  $\mu_N(t)$  remains true.

In the weak connectivity case, i.e.  $\varepsilon \in [0, \varepsilon_0)$  for  $\varepsilon_0$  small enough, hypothesis (1.5.67) can be replaced by

$$|a(x, m) - a(x + h, m + h)| \leq C_0 a(x, m) h, \quad (1.5.68)$$

for all  $x, m \in \mathbb{R}_+$  and any  $h \in [0, 1]$ .

At this moment, Theorems 1.5.32 and 1.5.33 are mere conjectures, but there is strong evidence to think that they are indeed true. For start, by using some arguments of Chapter 2 and Chapter 6, the existence of weak solutions can be completely justified along with the path-wise uniqueness in the cases of compactly supported initial datum and fast decay at infinite also. The chaos propagation argument, using the coupling method indeed works. The only remaining *Open Problem* is to prove that any two weak solutions to the limit problem are necessarily the same when the initial data decays vastly at infinite which seems to be the case.

## 1.5.2 On the statistical description of neuron networks: the weak connectivity conjecture

Most large-scale neuronal networks can be described by a density function  $f = f(t, \xi) \geq 0$  describing the probability density of finding neurons in some state  $\xi \in \Xi$  (typically  $\xi$  stands for an intern neuron time, the membrane voltage or the couple voltage-conductance of the neuron in the FhN model) at time  $t \geq 0$ . The density  $f$  evolves according to an integral and/or partial differential equation

$$\partial_t f = \mathcal{L}_{M(t)} f, \quad f(0, \cdot) = f_0, \quad (1.5.69)$$

where the operator  $f \mapsto \mathcal{L}_m f$  is linear for any given network state  $m \in \mathbb{R}$ , and the evolution of  $M(t)$  is also given by some constraints, differential or delay equation

$$M(t) = \mathcal{M}[f] = \mathcal{M}[(f(s))_{s \in [0, t]}]. \quad (1.5.70)$$

The fundamental property of the dynamics is that the total number of neurons is conserved so that the (mass) conservation equation

$$\int_{\Xi} f(t, \xi) d\xi = \int_{\Xi} f_0(\xi) d\xi = 1 \quad \forall t \geq 0$$

holds (or a slightly modified version of that mass conservation equation holds).

As a first step we consider the stationary problem: we search a time independent couple  $(F, M)$  such that

$$\mathcal{L}_M F = 0, \quad \int_{\Xi} F d\xi = 1 \quad \text{and} \quad M = \mathcal{M}[F]. \quad (1.5.71)$$

That system of equations seem to be solvable by using a Brouwer fixed point type theorem or by solving (explicitly or using a Perron-Frobenius type theorem) the linear problem  $0 = \mathcal{L}_m f_m$  for any given  $m$  and then fixing the appropriate parameter  $m$  by using an intermediate value theorem for the real valued function  $m \mapsto \mathcal{M}[f_m] - m$ .

As a second step we linearize the equation around a stationary state  $(F, M)$ . The linearized equation on a variation  $(g, m)$  reads

$$\partial_t g = \mathcal{L}_M g + (\mathcal{L}'_M F) m = \Lambda g, \quad m(t) = \mathcal{M}[g],$$

and the above operator should split as

$$\Lambda = \mathcal{A} + \mathcal{B}$$

for some  $\alpha$ -dissipative operator  $\mathcal{B}$ ,  $\alpha < 0$ , and some “ $\mathcal{B}$ -power regular” operator  $\mathcal{A}$ . In this case we may deduce that the principal (those which are the most at the right hand side) spectral values of  $\Lambda$  are discrete eigenvalues. We claim that the following first result holds:

**Meta Theorem 1.5.34.** *For any  $f_0 \in X \subset \mathbb{P}(\Xi)$  there exists a solution  $f$  to the equation (1.5.69). There exists at least one steady state  $(F, M)$  solution to (1.5.71) and the associated linearized operator  $\Lambda$  is such that*

$$\Sigma(\Lambda) \cap \Delta_\alpha = \{\xi_1, \dots, \xi_j\} \subset \Sigma_d(\Lambda),$$

for some real number  $\alpha < 0$  and some integer  $j \in \mathbb{N}$ , where  $\Delta_\alpha := \{z \in \mathbb{C}, \Re z > \alpha\}$ .

Next, we consider the weakly connectivity regime. Introducing a (small connectivity) parameter  $\varepsilon > 0$ , the evolution equation can be written as

$$\partial_t f = \mathcal{L}_{\varepsilon M(t)} f, \quad f(0, \cdot) = f_0, \tag{1.5.72}$$

We claim that, in the same sense that we did for the FitzHugh-Nagumo equation (1.4.17), the following second result should hold:

**Meta Theorem 1.5.35.** *There exists  $\varepsilon_0 > 0$  such that for any  $\varepsilon \in (0, \varepsilon_0)$  the steady state  $(F, M)$  is unique and there exist some constants  $\alpha < 0 < C$  such that for any  $f_0 \in X \subset \mathbb{P}(\Xi)$  the solution  $f$  to the evolution equation (1.5.69) satisfies*

$$\|f(t) - F\|_X \leq C_{f_0} e^{\alpha t}.$$

The main conclusion of this systematic description of these neuron population models is that convergence to a steady state is not a consequence of the modeling of the intrinsic properties of neurons taken individually but clearly a consequence of the nonlinear coupling in the network. The same remark can be done for desynchronization/oscillation phenomena observed in nature and numerical simulations of finite networks. A second interesting problem is the

**Open Problem 1.5.36.** *Is possible to build some oscillating particular solutions for large enough connectivity parameter?*





## Part I

# Neuronal networks



# Limits on randomly connected neuronal networks

Networks of the brain are composed of a very large number of neurons connected through a random graph and interacting after random delays that both depend on the anatomical distance between cells. In order to comprehend the role of these random architectures on the dynamics of such networks, we analyze the mesoscopic and macroscopic limits of networks with random correlated connectivity weights and delays. We address both averaged and quenched limits, and show propagation of chaos and convergence to a complex integral McKean-Vlasov equations with distributed delays. We then instantiate a completely solvable model illustrating the role of such random architectures in the emerging macroscopic activity. We particularly focus on the role of connectivity levels in the emergence of periodic solutions.

This chapter is included in [128] written in collaboration with J. Touboul published in *Acta Applicandae Mathematicae*. (2015) 136:1, 167-192.

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## 2.1 Introduction

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Neuronal networks in the cortex are composed of large structures, called cortical columns, that are in charge of collective information processing. Neurons are characterized by a nonlinear activity subject to an intense noise. They interact by sending action potentials (spikes) to those neurons they are connected to. The transmission of the information takes a specific time, related to the characteristic time of the synaptic chemical machinery and to the transport of signals at finite speed through the axons (and therefore function of the anatomical distance between the cells).

The macroscopic behaviors emerging from such large-scale systems provide relevant signals that are recorded by usual imaging techniques and from which physicians can infer hallmarks of function and dysfunction. Large-scale networks are therefore adequate scales to uncover the function of the cells, and as such have attracted much work in the past few years. Indeed, while properties of single cells have been well known since the seminal works of Hodgkin and Huxley [74, 75], models of macroscopic behaviors are less understood and computational studies have mainly relied on heuristic descriptions of macroscopic behaviors through firing-rate models, following the important work of Wilson and Cowan (WC) [161, 162]. In this class of models, we will make a distinction between macroscopic models in which the activity considered describes a whole brain area (which correspond to finite-dimensional WC systems) and mesoscopic models that describe macroscopic variables at a finer scale at which averaging effects occur but where we can resolve finer structure of the brain (e.g., WC integro-differential neural field equations). WC models have been very successful in reproducing a number of relevant phenomena in the cortex such as visual hallucinations, which was related to symmetry breaking and pattern formation in the neural field equation [53] and binocular rivalry in macroscopic models [136], see [22] for a recent review. WC model describes the evolution of a macroscopic variable, the population-averaged firing-rate, as a deterministic variable, which satisfies a delayed differential (macroscopic scale) or integro-differential (mesoscopic scale) equation. The success of these models prompted much work in order to provide a link between such macroscopic regimes and the noisy activity of individual cells. Mean-field methods based on the statistical physics theory of gases was also used for biologically relevant neuronal models [150, 149] including noisy input or noisy synaptic transmission and delays. Similarly to the molecular description of gases, it is shown that the propagation of chaos property takes place and that the system converges to a particular class of McKean-Vlasov equations.

In the vast majority of these studies, networks are assumed to be fully connected (i.e. all cells interact together), and no specific topology is taken into account. If this assumption is relevant in the molecular theory of gases, such architectures are not germane to neuronal networks. Indeed, cortical networks tend to rather display complex network topologies [20]. Typical cortical networks tend favor local connectivity: they present a short path length (associated with global efficacy of information transfer), high clustering (associated to resilience to noise) which are rather compatible with small-world topologies and that ensure important function (see [14], and [30] for a review). Moreover, some experimental studies tend to relate typical connectivity patterns with collective qualitative properties of the networks in physiological situations [67], and in particular in relationship with the emergence of synchronized

activity. The question we may ask here is whether such random architectures, in which neurons connect to their nearest neighbors with higher probability than to more remote cells, have qualitative properties different from fully connected networks.

The topic of this paper is precisely to investigate the role of network topology in the macroscopic or mesoscopic activity of cortical networks. From a mathematical viewpoint, heterogeneous connections break down the interchangeability assumption usually instrumental in order to prove mean-field limits (see e.g. [145]). However, the classical coupling method readily extends, as we show here, to networks with specific random topologies. In detail, a weak notion of exchangeability under a certain probability law (that of the connectivity weights and delays) is enough. We will address here both annealed (i.e. averaged over all possible connectivity patterns) and quenched convergence along subsequences, of networks with random architectures and random delays in a general setting encompassing the classical models of Hodgkin-Huxley and Fitzhugh-Nagumo neurons [54]. In order to uncover the role of random connectivities in the qualitative behavior of the network, we will instantiate a simple model, the WC firing-rate model with noise as a benchmark of single neurons behaviors. This model has the interest (see [152]) to have Gaussian solutions whose mean and standard deviation satisfy a dynamical system which will be analyzed using the bifurcation theory. The rigorous analysis of this model will lead us to conclude that in our models, random connectivities affect the network only when these are correlated with the delays (which is the case in neuronal network models since the connectivity probability, as well as the interaction delays are functions of the distance between two cells), and that these topologies govern the response of the network.

The paper is organized as follows. We start by introducing in section 2.2 the formalism and the network under consideration. In section 2.3 we present the main theoretical results for finite-populations networks on which our developments are based. Appendix 2.7 extends these results to neural fields where the number of different neuronal populations tends to infinity. The proof of these results are extension of previous works [150, 149], and are therefore postponed in section 2.5. Section 2.4 is devoted to the qualitative analysis of the nature of the solutions in the case of the firing-rate model, and exhibits the relationship between network topology and macroscopic dynamics.

## 2.2 Setting of the problem

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We now introduce the mathematical formalism used throughout the paper. We work in a complete probability space  $(\Omega, \mathcal{F}, \mathbb{P})$  satisfying the usual conditions. We will analyze the dynamics of a neuronal network model composed of  $N$  neurons, in an abstract setting valid for most usual models used in computational neuroscience such as the Hodgkin-Huxley [75] or Fitzhugh-Nagumo [59] models. In this model, the state of each neuron  $i$  is described by a  $d$ -dimensional variable  $X^{i,N} \in E$  (typically in  $E \subset \mathbb{R}^d$ ) corresponding to the membrane potential, ionic concentration and gated channels (see e.g. [54]).

The networks are composed of  $N$  neurons falling into  $P(N)$  populations labeled  $\alpha \in \{1, \dots, P(N)\}$

and composed of  $N_\alpha$  neurons, and the convention  $\alpha = p(i)$  defines the population neuron  $i$  belongs to. The level of description chosen governs the choice of the asymptotic regime analyzed. Here, we will consider two main different cases:

- The *macroscopic scale* where neurons gather into a few populations  $P(N) = P$  fixed, corresponding to coarse-grained descriptions of neural activity, generally called in the neuroscience domain neural mass models [79]
- The *mesoscopic scale*, or neural-field limit, where the number of populations tends to infinity and the area described covers a continuous piece of cortex  $\Gamma \subset \mathbb{R}^p$  with  $p \in \mathbb{N}^*$ . This description correspond to finer scale descriptions at which averaging effects occur, but fine enough to resolve the spatial structure of the cortex [149].

In each population, neurons have different intrinsic properties, receive different inputs and present a specific connectivity map with neurons in the other populations. Macroscopic or mesoscopic behavior correspond to the network's properties when the number of neurons in each population tends to infinity. This limit will be denoted with a slight abuse of notation  $N \rightarrow \infty$ . To fix ideas, we make the following assumption in the macroscopic scale case:

(H0). *There exists a sequence of positive real numbers  $r_1, \dots, r_P \in (0, 1)^P$  with  $\sum_{\alpha=1}^P r_\alpha = 1$  such that for all  $\alpha \in \{1, \dots, P\}$ ,*

$$N_\alpha/N \longrightarrow r_\alpha,$$

when  $N \rightarrow \infty$ .

In other words, we are assuming that the fraction of neurons belonging to a given population remains non trivial in the limit  $N \rightarrow \infty$ .

The evolution state  $X_t^{i,N}$  of neuron  $i$  in the population  $\alpha \in \{1, \dots, P\}$  is governed by a stochastic differential equation. The intrinsic dynamics of the neuron is governed by a function  $f_\alpha : \mathbb{R}_+ \times E \mapsto E$ . This evolution is stochastic, driven by independent  $m$ -dimensional Brownian motions  $(W_t^i)$  through a diffusion coefficient  $g_\alpha : \mathbb{R}_+ \times E \mapsto \mathbb{R}^{d \times m}$ . The neuron  $i$  receives inputs from other neurons in the network, which affect its state through an interaction function  $b_{\alpha\gamma} : \mathbb{R} \times E \times E \mapsto E$  depending on

- The synaptic weight  $w_{ij} \in \mathbb{R}$  between neurons  $i$  in population  $\alpha$  and  $j$  in population  $\gamma$  controlling the topology of the network: these are zero when there is no connection between  $i$  and  $j$ , positive when the connection is excitatory and negative when inhibitory.
- the state of both neurons  $i$  and  $j$ .

These interactions take place after a delay  $\tau_{ij} > 0$ .

The dynamics of neuron  $i$  in population  $\alpha$  is given by:

$$dX_t^{i,N} = \left( f_\alpha(t, X_t^{i,N}) + \sum_{\gamma=1}^{P(N)} \sum_{p(j)=\gamma} \frac{1}{N_\gamma} b_{\alpha\gamma}(w_{ij}, X_t^{i,N}, X_{t-\tau_{ij}}^{j,N}) \right) dt + g_\alpha(t, X_t^{i,N}) \cdot dW_t^i, \quad (2.2.1)$$



under the assumption that  $b(0, x, y) = 0$  and the fact that the synaptic weight  $w_{ij}$  is assumed zero when no link from  $j$  to  $i$ . In these notations, the architecture of the network is completely integrated in the choice of the synaptic coefficients  $w_{ij}$ . In our purpose to analyze networks on random graphs, we will consider that the synaptic weights  $w_{ij}$  and delays  $\tau_{ij}$  are non-negative random variables, drawn in a distinct probability space  $(\Omega', \mathcal{F}', \mathcal{P})$  at the beginning of the evolution and frozen. We generically denote by  $\mathbb{E}$  the expectation with respect to the processes (i.e., under the probability  $\mathbb{P}$ ) and by  $\mathbb{E}$  the expectation of random variables or processes with respect to the environment (i.e. under  $\mathcal{P}$ ). One realization of these weights corresponds to one network with prescribed architecture. In realistic settings, both connectivity weight and delay are related to the distance between the cells, and therefore are generally correlated. A specific choice relevant to biology is discussed in section 2.4, in which connectivity probability as well as delays are deterministic functions of the random respective locations of the cells (yielding a specific strong correlation between the two variables).

While the random variables  $w_{ij}$  and  $\tau_{ij}$  are correlated, an important hypothesis is that for fixed  $i$ , sequences  $(\tau_{ij}, j = 1 \dots N)$  and  $(w_{ij}, j = 1 \dots N)$  are considered independent and identically distributed population-wise, i.e. they have the same distribution for all  $j$  belonging to a given population<sup>1</sup>. For fixed  $i \in \{1, \dots, N\}$ , we can therefore denote  $\Lambda_{ip(j)}$  the distribution of the variables  $(w_{ij}, \tau_{ij})$ .

The piece of cortex considered will be said invariant by translations if the joint distribution of weights and delays  $(w_{ij}, \tau_{ij})$  for  $p(j) = \gamma$  does not depend on the specific neuron  $i$  considered but only on the population  $\alpha$  the neuron  $i$  belongs to<sup>2</sup>. In that case, we will denote  $\Lambda_{\alpha\gamma}$  the joint law of weights and delays. In the *general case*, we assume that the laws  $\Lambda_{i\gamma}$  are independently drawn from a distribution of measures centered at a specific one  $\Lambda_{\alpha\gamma}$ . For instance, when delays and connectivity depend on the distance between cells, the distribution  $\Lambda_{i\gamma}$  depends on the position  $r_i$  of neuron  $i$ . If cells of population  $\alpha$  are distributed on a space  $D$  with density  $p$ , and the weights and delays have a density  $\lambda_{r_i}(s, t)$ ,  $\Lambda_{\alpha\gamma}$  is the law with density  $\int_D \lambda_r(s, t) dp(r)$ .

Let us denote by  $\tau$  the maximal possible delay  $\tau_{ij}$  which we assume finite<sup>3</sup>. Equations (2.2.1) are stochastic differential equations on the infinite-dimensional space of functions  $C([-\tau, 0], E)$  (i.e. on the variable  $\tilde{X}_t = (X_s, s \in [t - \tau, t])$ , see e.g. [39, 100]).

Finally, we consider that the network has chaotic initial states, in the sense that they have independent and population-wise identically distributed initial conditions. In detail, we denote  $C_\tau = C([-\tau, 0], E^P)$  and set  $(\zeta_0^\alpha(t)) \in C_\tau$  a stochastic process with independent components. Chaotic initial condition on the network consists in setting independent initial condition for all neurons, with distribution for neurons of

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<sup>1</sup>Note that the whole sequence of weights  $(w_{ij}; 1 \leq i, j \leq N)$  as well as the delays  $(\tau_{ij}; 1 \leq i, j \leq N)$  might be correlated. When these are related to the distance  $r_{ij}$  between  $i$  and  $j$ , correlations may arise from symmetry ( $r_{ij} = r_{ji}$ ) or triangular inequality  $r_{ij} \leq r_{ik} + r_{kj}$ . The independence assumption is nevertheless valid in that setting provided that the locations of the different cells are independent and identically distributed random variables

<sup>2</sup>The term *invariant by translation* is chosen in reference to random variables  $\tau_{ij}$  and  $w_{ij}$  function of the distance  $r_{ij}$  between neuron  $i$  and  $j$ : this distance is independent of the particular choice of neuron  $i$  (and of its location) if the neural field is invariant by translation in the usual sense

<sup>3</sup>This is always the case when considering bounded neural fields.

population  $\alpha$  equal to that of  $\zeta_0^\alpha$ .

In what follows, we note  $\mathcal{M}^2(C([- \tau, 0], E^N))$  the space of square integrable stochastic processes on  $[- \tau, 0]$  with values in  $E^N$ ,  $\mathcal{M}(\mathcal{C})$  the set of probability distributions on  $\mathcal{C}$  the set continuous functions  $[- \tau, T] \mapsto E^P$ , and  $\mathcal{M}^2(\mathcal{C})$  the space of square-integrable processes.

## 2.3 Main results

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In this section, we state and discuss the main mathematical results on the convergence of the above described process as the network size goes to infinity. Interestingly, even if the network considered has a complex random topology in which connectivity map as well as delays are correlated, methods developed in the case of fully connected architectures [150, 149] extend to this more complex case. Proofs are provided for completeness in section 2.5.

Let us first state the following proposition ensuring well-posedness of the network system:

**Proposition 2.3.37.** *Let  $X_0 \in \mathcal{M}^2(C([- \tau, 0], E^N))$  an initial condition of the network system. For any  $(\alpha, \gamma) \in \{1, \dots, P(N)\}^2$ , assume that:*

(H1).  *$f_\alpha$  and  $g_\alpha$  are uniformly in time Lipschitz-continuous functions with respect to their second variable.*

(H2). *For almost all  $w \in \mathbb{R}$ ,  $b_{\alpha\gamma}(w, \cdot, \cdot)$  is  $L_{\alpha\gamma}$ -Lipschitz-continuous with respect of both variables.*

(H3). *There exists functions  $\bar{K}_{\alpha\gamma} : \mathbb{R} \mapsto \mathbb{R}^+$  such that for any  $(\alpha, \gamma) \in \{1, \dots, P(N)\}^2$ ,*

$$|b_{\alpha\gamma}(w, x, y)|^2 \leq \bar{K}_{\alpha\gamma}(w) \quad \text{and} \quad \mathbb{E}[\bar{K}_{\alpha\gamma}(w)] \leq \bar{k} < \infty.$$

(H4). *The drift and diffusion functions satisfy the monotone growth condition: there exists a positive constant  $K$  depending on  $f$  and  $g$  such that:*

$$x^T f_\alpha(t, x) + \frac{1}{2} |g_\alpha(t, x)|^2 \leq K(1 + |x|^2).$$

*Then for almost all realization of the synaptic weights  $w_{ij} \in \mathbb{R}$  and the delays  $\tau_{ij} \in [- \tau, 0]$ , we have existence and uniqueness of solutions to the network equations (2.2.1).*

This property results from the application of standard theory of stochastic delayed differential equations. We provide a sense of the proof in section 2.5: the details of the proof of this elementary proposition will largely simplify the analysis of the limit equations.

When the number of neurons goes to infinity (under assumption (H0)) then

- for almost any realization of the transmission delays  $\tau_{ij}$  and synaptic weights  $w_{ij}$  in the translation-invariant case or
- averaged across all realizations of the disorder in the general case,

the propagation of chaos property holds: *if the initial conditions are chaotic, then the states of a finite number of neurons are independent for all times when  $N \rightarrow \infty$ .* Their law is given by a nonlinear McKean-Vlasov equation that depends on the neural population they belong to. Similar results hold for mesoscopic limits of neural field models, i.e. in situations in which the number of populations  $P(N)$  diverges as  $N \rightarrow \infty$ . In this case, the notion of solution is much more complex, as one obtains a process depending on space but which is not measurable with respect to the spatial variable. These questions, addressed in [149], will be briefly discussed in our context in appendix 2.7.

In both cases, the proof of the convergence and propagation of chaos will use the powerful coupling method (see [145]). The proof is in two steps: (i) we prove that the limit equation (see equation (2.3.2) below) has an unique solution, and (ii) that the law of  $X_t^{i,N}$  converges towards the law of (2.3.2)<sup>4</sup>.

### 2.3.1 Randomly connected neural mass models

Let  $P(N) = P$  be fixed and independent of  $N$ . In this case, we will show that the network equation converges (in a sense to be defined in each sub case) towards the solution of a well-posed McKean-Vlasov equation given by:

$$d\bar{X}_t^\alpha = f_\alpha(t, \bar{X}_t^\alpha) dt + g_\alpha(t, \bar{X}_t^\alpha) \cdot dW_t^\alpha + \left( \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} \mathbb{E}_{\bar{Y}} [b_{\alpha\gamma}(w, \bar{X}_t^\alpha, \bar{Y}_{t+s}^\gamma)] d\Lambda_{\alpha\gamma}(s, w) \right) dt, \quad (2.3.2)$$

where  $\bar{Y}$  is a process independent of  $\bar{X}$  that has the same law,  $\mathbb{E}_{\bar{Y}}$  the expectation under the law of  $\bar{Y}$ , and  $W_t^\alpha$  are independent adapted standard Brownian motions of dimension  $d \times m$ . Denoting by  $m_t^\gamma(dx)$  the law of  $\bar{X}_t^\gamma$  the equation (2.3.2) is nothing but

$$d\bar{X}_t^\alpha = f_\alpha(t, \bar{X}_t^\alpha) dt + g_\alpha(t, \bar{X}_t^\alpha) \cdot dW_t^\alpha + \left( \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} \int_E [b_{\alpha\gamma}(w, \bar{X}_t^\alpha, y)] m_{t+s}^\gamma(dy) d\Lambda_{\alpha\gamma}(s, w) \right) dt, \quad (2.3.3)$$

The hypotheses made in Proposition 2.3.37 also ensure existence and uniqueness of solutions as we now state in the following:

**Theorem 2.3.38.** *Under the hypotheses of Proposition 2.3.37 and for any  $\zeta_0 \in \mathcal{M}(C([-\tau, 0], E^P))$  a square integrable process, the mean-field equations (2.3.3) with initial condition  $\zeta_0$  have a unique strong solution on  $[-\tau, T]$  for any time horizon  $T > 0$ .*

In order to demonstrate the convergence of the network equation and the propagation of chaos when the number of neurons goes to infinity, we use Dobrushin's coupling approach [48, 144, 145, 147] in the same fashion as done in [150, 149] in the context of neurosciences, the only difference being the random environment nature of the network equation related to the random structure of the synaptic coefficients.

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<sup>4</sup>More precisely, taking a finite set of neurons  $\{i_1, \dots, i_k\}$  the law of the process  $(X_t^{i_1, N}, \dots, X_t^{i_k, N}, t \in [-\tau, T])$  converge in probability towards a vector  $(\bar{X}_t^{i_1}, \dots, \bar{X}_t^{i_k}, t \in [-\tau, T])$ , where the processes  $\bar{X}^l$  are independent and have the law of  $X^{P(i_l)}$  given by (2.3.2).

### 2.3.2 Quenched convergence and propagation of chaos in the translation invariant case

The translation invariant case correspond to the situation where the laws  $\Lambda_{i\gamma}$  for  $i$  such that  $p(i) = \alpha$  are identical and only depend on  $\alpha$ .

Let  $i \in \mathbb{N}$  such that  $p(i) = \alpha$ . We define the process  $\bar{X}^i$  solution of (2.3.2), driven by the Brownian motions  $(W_t^i)$  that governs  $X^i$ , and having the same initial condition as neuron  $i$  in the network,  $\zeta_0^i \in \mathcal{M}^2(\mathcal{C})$ :

$$\begin{cases} d\bar{X}_t^i &= f_\alpha(t, \bar{X}_t^i)dt + g_\alpha(t, \bar{X}_t^i) \cdot dW_t^i \\ &+ \left( \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} \mathbb{E}_Z [b_{\alpha\gamma}(w, \bar{X}_t^i, Z_{t+s}^\gamma)] d\Lambda_{\alpha\gamma}(s, w) \right) dt, \quad t \geq 0 \\ \bar{X}_t^i &= \zeta_0^i(t), \quad t \in [-\tau, 0]. \end{cases} \quad (2.3.4)$$

By definition, the processes  $(Z_t^1, \dots, Z_t^P)$  are a collection of processes independent of  $(\bar{X}_t^i)_{i=1, \dots, N}$  and have the distribution  $m_t^1 \otimes \dots \otimes m_t^P$ , where  $m_t^\alpha$  is the probability distribution of  $\bar{X}_t^\alpha$  (unique solution of the equation (2.3.2)).

Theorem 2.3.38 ensures well posedness of these equations, and therefore  $(\bar{X}_t^i)_{i \in \mathbb{N}}$  constitute a sequence of independent processes with law  $\bar{X}^{p(i)}$ .

**Theorem 2.3.39** (Quenched Convergence). *Under assumptions (H1)-(H4) and chaotic initial conditions in  $\mathcal{M}^2(\mathcal{C})$ . The process  $(X_t^{i,N}, -\tau \leq t \leq T)$  for  $i \in \mathbb{N}$  fixed, solution of the network equations (2.2.1), converges almost surely towards the process  $(\bar{X}_t^i, -\tau \leq t \leq T)$  solution of the mean-field equations (2.3.4). This implies in particular convergence in law of the process  $(X_t^{i,N}, -\tau \leq t \leq T)$  towards  $(\bar{X}_t^i, -\tau \leq t \leq T)$  solution of the mean-field equations (2.3.2).*

### 2.3.3 Annealed convergence and propagation of chaos in the general case

We now turn our attention to the case of non-translation invariant networks where the law of delays and synaptic weights depend on the index of neuron  $i$  in population  $\alpha$ . In this case we will see that the propagation of chaos property remains valid as well as convergence to the mean-field equations (2.3.2), no more for almost all realization of the disorder, but in average across all possible configurations. Denoting  $\mathcal{E}_i$  the expectation over all possible distributions  $\Lambda_{i\gamma}$ , we have:

**Theorem 2.3.40** (Annealed convergence in the general case). *We assume that (H1)-(H4) are valid and that network initial conditions are chaotic in  $\mathcal{M}^2(\mathcal{C})$ , and that the interaction does not depend on the postsynaptic neuron state (i.e.,  $b(w, x, y) = \ell(w, y)$ ). Let us fix  $i \in \mathbb{N}$ , then the law of process  $(X_t^{i,N}, -\tau \leq t \leq T)$  solution to the network equations (2.2.1) averaged over all the possibles realizations of the disorder, converge almost surely towards the process  $(\bar{X}_t^i, -\tau \leq t \leq T)$  solution to the mean field equations (2.3.2). This implies in particular the convergence in law of  $(\mathcal{E}_i[X_t^{i,N}], -\tau \leq t \leq T)$  towards  $(\bar{X}_t^\alpha, -\tau \leq t \leq T)$  solution of the mean field equations (2.3.2).*

Extensions to the spatially extended neural field case are discussed in Appendix 2.7.

## 2.4 Application: dynamics of the firing-rate model with random connectivity

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In the previous section, we derived limit equations for networks with random connectivities and synaptic weights. The motivation of these mathematical developments is to understand the role of specific connectivity and delays patterns arising in plausible neuronal networks. More precisely, it is known that anatomical properties of neuronal networks affect both connectivities and delays, and we will specifically consider the two following facts:

- Neurons connect preferentially to those anatomically close.
- Delays are proportional to the distance between cells.

At the level of generality of the previous sections, we obtained very complex equations, from which it is very hard to uncover the role of random architectures. However, as we already showed in previous works [152], a particularly suitable framework to solve these questions is provided by the classical firing-rate model. In that case, we showed in different contexts that the solution to the mean-field equations is Gaussian, whose mean and standard deviation are solution of simpler dynamical system.

### 2.4.1 Reduction to distributed delays differential equations

In the firing-rate model, the intrinsic dynamics of each neuron is given by

$$f_\alpha(t, x) = -x/\theta_\alpha + I_\alpha(t),$$

where  $I_\alpha(t)$  is the external input of the system, and the diffusion function  $g_\alpha(t, x) = \lambda_\alpha$  is constant. The interaction only depends in a nonlinear transform of the membrane potential of the pre-synaptic neuron multiplied by the synaptic weight:  $b_{\alpha\gamma}(w, x, y) = J_{\alpha\gamma}(w)S(y)$ . We also assume, in order to satisfy the assumptions of the Theorems 2.3.39 and 2.3.40, that the functions  $J_{\alpha\gamma} \in L^\infty(\mathbb{R})$  and  $S \in W^{1,\infty}(E^d)$ . Therefore, when considering the delays and the synaptic weights only depending on  $p(i)$ , we have propagation of chaos and almost sure convergence (quenched) towards the mean-field equations:

$$\begin{aligned} d\bar{X}_t^\alpha &= \left( -\frac{\bar{X}_t^\alpha}{\theta_\alpha} + I_\alpha(t) + \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} J_{\alpha\gamma}(w) \mathbb{E}_Y [S(Y_{t+s}^\gamma)] d\Lambda_{\alpha\gamma}(s, w) \right) dt \\ &\quad + \lambda_\alpha dW_t^\alpha, \end{aligned} \tag{2.4.5}$$

and in the general case, the same result holds in an averaged sense.

**Remark 2.4.41.** Let us note that if the synaptic weights and the delays are independent, it is very easy to see that the network converges towards an effective mean-field equation where the disorder in the connectivity weights disappears and the mean-field equation obtained reduces to

$$d\bar{X}_t^\alpha = \left( -\frac{\bar{X}_t^\alpha}{\theta_\alpha} + I_\alpha(t) + \sum_{\gamma=1}^P \bar{J}_{\alpha\gamma} \int_{-\tau}^0 \mathbb{E}_Y [S(Y_{t+s}^\gamma)] d\rho_{\alpha\gamma}(s) \right) dt + \lambda_\alpha dW_t^\alpha,$$

where  $\rho_{\alpha\gamma}$  is the marginal density of delays of  $\Lambda_{\alpha\gamma}$  and  $\bar{J}_{\alpha\gamma}$  is the averaged synaptic weight. This is exactly the same equation as would arise from a non-disordered network equation where all connectivity weights are deterministic:  $J_{ij} = \bar{J}_{\alpha\gamma}/N_\gamma$ . Therefore, the architecture plays a role in the dynamics only when the synaptic weights and the delays are correlated, as is the case of the cortex.

We will therefore focus on more realistic models where delays and connectivity weights are correlated. It is very easy to see, integrating equation (2.4.5), that the solution satisfies the implicit equation:

$$\begin{aligned} \bar{X}_t^\alpha &= \bar{X}_0^\alpha e^{-t/\theta_\alpha} + \int_0^t e^{-(t-s)/\theta_\alpha} \left( -\frac{\bar{X}_s^\alpha}{\theta_\alpha} + I_\alpha(s) \right. \\ &\quad \left. + \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} J_{\alpha\gamma}(w) \mathbb{E}_{\bar{Y}} [S(Y_{s+r}^\gamma)] d\Lambda_{\alpha\gamma}(r, w) \right) ds + \int_0^t e^{-(t-s)/\theta_\alpha} \lambda_\alpha dW_s^\alpha \end{aligned}$$

which is composed of Gaussian terms and the initial condition  $\bar{X}_0^\alpha e^{-t/\theta_\alpha}$  vanishing at an exponential rate. Therefore, when the initial conditions are Gaussian processes<sup>5</sup>, the solution is also Gaussian with mean  $u_\alpha$  and variance  $v_\alpha$ . Taking expectation and covariance we get that the mean and the variance of the solution satisfy the following well-posed system of delayed differential equations:

$$\begin{cases} \dot{u}_\alpha = -u_\alpha/\theta_\alpha + \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} J_{\alpha\gamma}(w) \mathbb{E}_Y [S(Y_{t+s}^\gamma)] d\Lambda_{\alpha\gamma}(s, w) \\ \dot{v}_\alpha = -2v_\alpha/\theta_\alpha + \lambda_\alpha^2. \end{cases} \quad (2.4.6)$$

In the firing-rate case, we hence have an important reduction of complexity. This simpler form allows us to use bifurcation theory in order to understand the role of the parameters on the qualitative properties of the solutions. This theory has been widely used in neuroscience in order to uncover, in single cells models, the emergence of periodic spiking or bursting [54], and for heuristic macroscopic models, formation of patterns of activity [22] or visual hallucinations [53]. Here, the theory of delayed differential equations (see e.g. [53]) allows us to uncover the role of the randomness of the architecture and delays in shaping the collective behavior of the network. In order to analyze this dependence, we consider the system in the absence of external input  $I = 0$  and

$$S(x) := \frac{1}{\sqrt{2\pi}} \int_0^x e^{-s^2/2} ds,$$

which has the property that a simple change of variables yields (see [152, Appendix A]):

$$\mathbb{E}_Y [S(Y_t^\gamma)] = \mathbb{E}_Y [S(Y_t^\gamma)] = S\left(\frac{u_\gamma(t)}{\sqrt{1+v_\gamma(t)}}\right)$$

In that simplified case, a stationary solution of the system is given by  $(u_\alpha^*, v_\alpha^*) = (0, \lambda_\alpha^2 \theta_\alpha / 2)$ . The solution to the variance equation is

$$v_\alpha(t) = \frac{1}{2} (\lambda_\alpha^2 \theta_\alpha + e^{-2t/\theta_\alpha}) = v_\alpha^* + \frac{1}{2} e^{-2t/\theta_\alpha},$$

then the stability of the fixed point only depends on the delayed linear equation to the mean, which is:

$$\dot{u}_\alpha(t) = -\frac{u_\alpha(t)}{\theta_\alpha} + \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} J_{\alpha\gamma}(w) \frac{1}{\sqrt{2\pi(1+v_\gamma^*)}} u_\gamma(t+s) d\Lambda_{\alpha\gamma}(s, w).$$

---

<sup>5</sup>If the initial condition is not Gaussian, the solution to the mean-field equation will nevertheless be attracted exponentially fast towards the Gaussian solution described.

If only one population is considered, then dropping the index for the population lead us to:

$$\dot{u}(t) = -\frac{u(t)}{\theta} + \int_{-\tau}^0 \int_{\mathbb{R}} J(w) \frac{1}{\sqrt{2\pi(1+v^*)}} u(t+s) d\Lambda(s, w). \quad (2.4.7)$$

The stability of the fixed point only depends on the dispersion relationship:

$$\xi = -\frac{1}{\theta} + \frac{1}{\sqrt{2\pi(1+v^*)}} \int_{-\tau}^0 \int_{\mathbb{R}} J(w) e^{\xi s} d\Lambda_{\alpha\gamma}(s, w), \quad (2.4.8)$$

which is nothing more that looking for solutions of the form  $u = \exp(\xi t)$  in (2.4.7).

The solutions of this equations are the characteristic exponents of the system, and relate directly the stability of the fixed point considered. If all characteristic exponents have negative real part, the equilibrium is asymptotically exponentially stable, but if there exists a characteristic exponent with strictly positive real part, the equilibrium is unstable. Turing-Hopf bifurcations occur when the system has a pair of complex conjugate characteristic exponents with non-zero imaginary part crossing the imaginary axis.

## 2.4.2 Small-world type model and correlated delays

As we stated before one interesting situation arising in neuroscience is the case where synaptic weights and the delays are function of the distance between neurons. Without loss of generality, we assume the signal transmission speed is unitary, then the delay  $\tau_{ij}$  between the neuron  $i$  at location  $r_i$  and a neuron  $j$  at location  $r_j$  is simply modeled by

$$\tau_{ij} = |r_i - r_j| + \tau_s,$$

where  $\tau_s$  is the minimum value corresponding to the transmission of the information at the synapse. We further assume that the synaptic links are drawn according to a Bernoulli random variable:

$$w_{ij} = \begin{cases} 1 & \text{with probability } b(|r_i - r_j|) := e^{-\beta|r_i - r_j|} \\ 0 & \text{with probability } 1 - b(|r_i - r_j|), \end{cases}$$

with  $\beta > 0$ . The synaptic weights are given by  $J(w_{ij})$  with

$$J(x) = \begin{cases} \bar{J} & \text{if } x = 1 \\ 0 & \text{if } x = 0 \end{cases}.$$

In this model, the total connectivity level of the system decreases when  $\beta$  is increased. When neurons are uniformly distributed in the interval  $[0, a]$ , the averaged law density can be easily computed and is given by:

$$dp(r) = \left( \frac{2}{a} - \frac{2r}{a^2} \right) dr,$$

and thanks to conditional expectation we find that (2.4.8) is nothing but

$$\begin{aligned} \xi &= -\frac{1}{\theta} + \frac{1}{\sqrt{2\pi(1+v^*)}} \mathbb{E}[\mathbb{E}[J(w)e^{\xi u} | r]] \\ &= -\frac{1}{\theta} + \frac{1}{\sqrt{2\pi(1+v^*)}} \mathbb{E}[\mathbb{E}[J(w) | r] e^{-\xi(\tau_s+r)}] \\ &= -\frac{1}{\theta} + \frac{\bar{J}e^{-\xi\tau_s}}{\sqrt{2\pi(1+v^*)}} \int_0^a e^{-(\beta+\xi)r} \left( \frac{2}{a} - \frac{2r}{a^2} \right) dr. \end{aligned}$$

Turing bifurcations arise for parameters such that there exists a purely imaginary characteristic root (solution of the above equation)  $\xi = i\omega$ . These occur when one can find  $\omega > 0$  such that:

$$i\omega = -\frac{1}{\theta} + \frac{2\bar{J}}{\sqrt{2\pi(1+v^*)}} \times \frac{1}{a(\beta+i\omega)} \left( 1 - \frac{1}{a(\beta+i\omega)} + \frac{e^{-a(\beta+i\omega)}}{a(\beta+i\omega)} \right) e^{-i\omega\tau_s}. \quad (2.4.9)$$

Since (2.4.9) depend on many parameters, in order to understand the solutions we study the system decoupling the size of the neural field with respect to the connectivity parameter  $\beta$  and the size  $a$ .

### The effect of the extension of the neural field.

We first fix  $\beta > 0$  and make the change of variables  $\Omega = a\omega$ ,  $B = a\beta$ . Defining

$$Z(\Omega, B) = \frac{2\bar{J}}{\sqrt{2\pi(1+v^*)}} \frac{1}{B+i\Omega} \left( 1 - \frac{1}{B+i\Omega} + \frac{e^{-(B+i\Omega)}}{B+i\Omega} \right),$$

then (2.4.9) is reduced to solve the system

$$\begin{cases} a^2 = \Omega^2 (|Z(B, \Omega)|^2 - \frac{1}{\theta^2})^{-1}, \\ \tau_s = (\text{Arg}(Z(\Omega, B)) - \text{Arg}(1 + \frac{i\Omega}{a}) + 2k\pi) \frac{a}{\Omega}, \\ B = \beta a \end{cases} \quad (2.4.10)$$

which can be seen as a intersection of two surfaces in the space  $(a, B, \tau_s)$ :

$$S_1 : \begin{cases} \mathbb{R} \times \mathbb{R}_+ & \rightarrow & \mathbb{R}^3 \\ (\Omega, B) & \mapsto & (a(\Omega, B), B, \tau_s(\Omega, B)) \end{cases} \quad S_2 : \begin{cases} \mathbb{R}_+ \times \mathbb{R} & \rightarrow & \mathbb{R}^3 \\ (a, \tau_s) & \mapsto & (a, \beta a, \tau_s) \end{cases},$$

where  $a(\Omega, B)$  and  $\tau_s(\Omega, B)$  are the solutions of (2.4.10) for  $B$  given. We obtain a sequence of Turing-Hopf bifurcations indexed by  $k$ , and the first bifurcation is responsible for oscillations appearing in the system.

In figure 2.1, we represent the curve of Hopf bifurcation given by (2.4.10) for a fixed value of the parameter  $\beta$ . This bifurcation diagram separates the parameter space  $(a, \tau_s)$  into a region of oscillatory regime and a region of stationary behavior. The typical shape of the Hopf bifurcation curve is a parabola, displaying a unique minimum for a value that we denote by  $(a^m, \tau_s^m)$ . We denote  $\tau_s^0$  the value of the Hopf bifurcation curve for  $a = 0$  (i.e. fully connected network with deterministic delays  $\tau_s$ ). For  $a = 0$ , the system depends on the delays in the following fashion: for any  $\tau_s < \tau_s^0$ , the system converges towards stationary behaviours, and for  $\tau_s > \tau_s^0$ , the system displays periodic behaviors.

For  $\tau_s > \tau_s^0$  fixed, long-range connectivities (corresponding to small values of  $\beta$ ) produce synchronized periodic behaviors that disappear when the network becomes less connected, until a specific value of  $\beta$  corresponding to the unique intersection of the Hopf curve with the line of constant  $\tau_s$ . For  $\tau_s^0 < \tau_s < \tau_s^m$ , the long-range (small  $\beta$  or small  $a$ ) and short-range (large  $\beta$  or large  $a$ ) connectivity models correspond to stationary behaviors, and for values of the network length  $a$  (or range  $\beta$ ) in a specific interval, the system will display synchronized behaviors. Eventually, for  $\tau_s < \tau_s^m$ , the system only displays stationary solutions whatever the length of the network  $a$  or the range  $\beta$ .



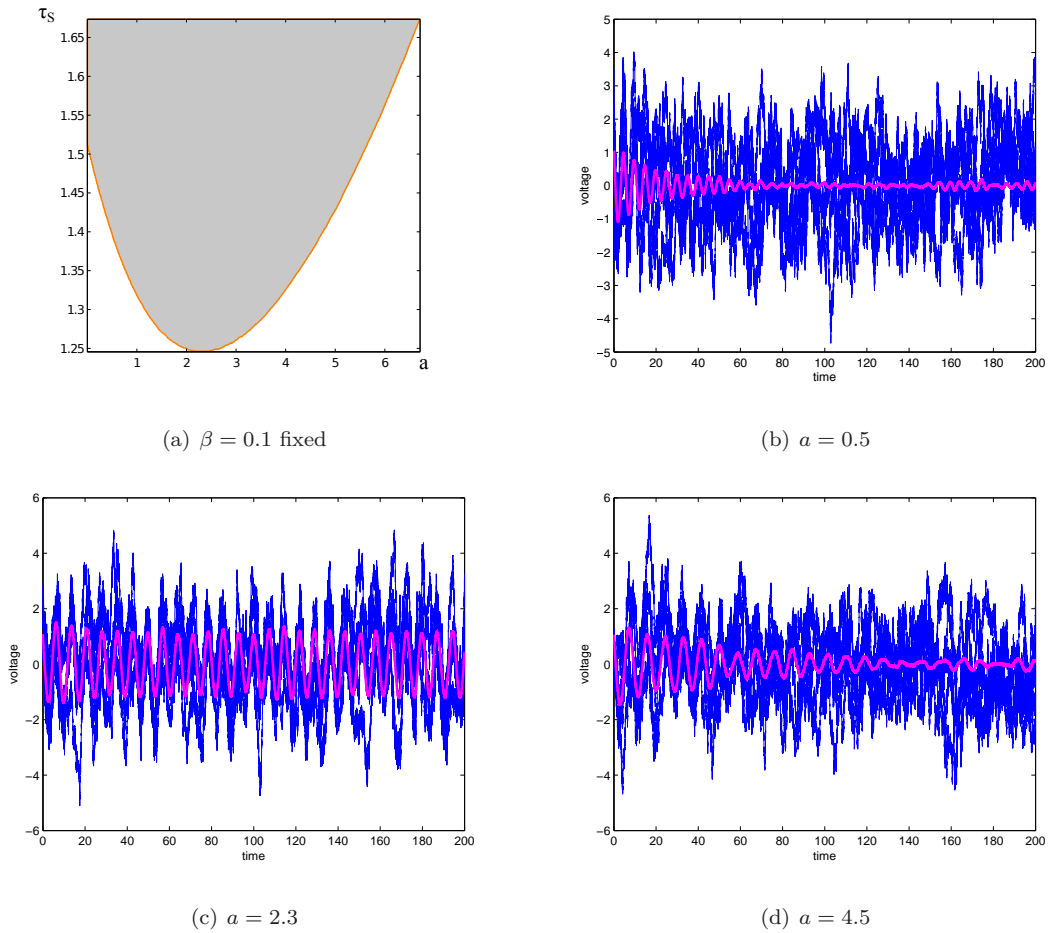


Figure 2.1: Neurons uniformly distributed in  $[0, a]$ . Fixed parameters  $\theta = 3$ ,  $\bar{J} = -5$ ,  $\lambda = 1$ . (a) Bifurcation diagram for  $\beta = 0.1$  in the space  $(a, \tau)$ : gray zone correspond to oscillatory solutions. For  $\tau_s = 1.3$ : (b-d) Increasing the parameter  $a$  (the size of the neural field) induces transition from stationary to periodic and back to stationary. All simulation were made for an Euler explicit method with  $N = 3000$ .

## The effect of the connectivity factor

Let us now fix the size of the interval  $a > 0$ . We investigate the effects of  $\beta$  and  $\tau_s$  on the solution. Equation (2.4.9) can be written in the form:

$$\begin{cases} \omega^2 = -\frac{1}{\theta^2} + |Z(\omega, \beta)|^2, \\ \tau_s = (\text{Arg}(Z(\omega, \beta)) - \text{Arg}(\frac{1}{\theta^2} + i\omega) + 2k\pi) \frac{1}{\omega} \end{cases} \quad (2.4.11)$$

with

$$Z(\omega, \beta) = \frac{2\bar{J}}{\sqrt{2\pi(1+v^*)}} \frac{1}{a(\beta + i\omega)} \left( 1 - \frac{1}{a(\beta + i\omega)} + \frac{e^{-a(\beta + i\omega)}}{a(\beta + i\omega)} \right)$$

We solve this equation by numerically computing the manifold:

$$S_0 := \left\{ (\omega, \beta) \in \mathbb{R} \times \mathbb{R}_+, \text{ such that } \omega^2 + \frac{1}{\theta^2} - |Z(\omega, \beta)|^2 = 0 \right\}$$

from which one can readily compute the delay corresponding to the Hopf bifurcation.

Figure 2.2(a) show the solution to the system (2.4.11) for a fixed value of the spatial extension of the neural field. The curve is relatively different: it now appears to be a monotone non-decreasing map separating oscillatory and stationary behaviors. Qualitatively, the global picture remains unchanged: oscillations vanish as  $\beta$  is increased, i.e. as the network is less connected.

## Discussion

We therefore observe that the topology of the network strongly impacts the collective behavior of the network. For a fixed value of the connectivity parameter, we have seen that there exists an optimal neural field size for synchronization. At this size, the constant delays necessary to induce oscillations is minimal. In contrast, at fixed values of  $a$ , we observe that the optimal connectivity level ensuring minimal constant delay to induce oscillations is zero: fully connected networks synchronize more easily. In the cortex, for energetic reasons, full connectivity is not favored, and therefore this indicates optimal cluster sizes for synchronization.

## 2.5 Proofs

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We start by showing the well-posedness of the network system stated in proposition 2.3.37:

*Proposition 2.3.37.* The proof splits into two main steps: we show *a priori estimates* and define a *contraction map* that implies existence and unicity for a stopped version of the problem.

*A priori estimates* Let us start by showing that all possible solutions of the system have bounded second moment. It is important to remark that the number of particles of the system is fixed. Let  $X^N$

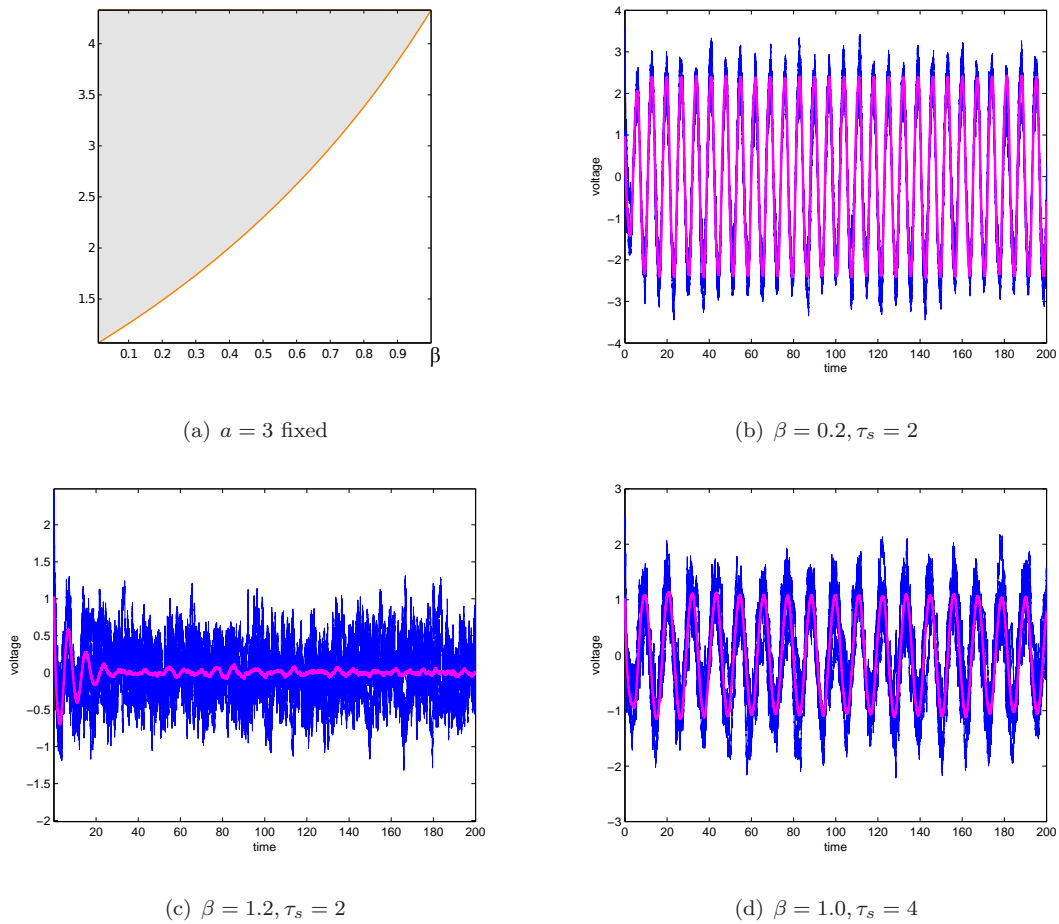


Figure 2.2: Neurons uniformly distributed in  $[0, a]$  for different values of  $\beta$ . Fixed parameters  $\theta = 1$ ,  $\bar{J} = -3.5$ ,  $\lambda = 0.5$ : (a) Hopf bifurcation diagram in the plane  $(\beta, \tau_s)$  for  $a = 3$ . (c-e) Starting from a point inside the oscillation zone increasing one of the parameters  $\beta$  or  $\tau_s$  induces transition to the stationary state. All simulation were made for an Euler explicit method with  $N = 2000$ .

be a solution of (2.2.1) and  $\tau_n$  the first time the process  $|X_t^N|$  exceeds the quantity  $n$ . We look for an upper-bound of the form:

$$\mathbb{E}\left[|X_{t \wedge \tau_n}^N|^2\right] \leq \mathbb{E}\left[|X_0(0)|^2\right] + C \int_0^{t \wedge \tau_n} \mathbb{E}\left[1 + |X_{s \wedge \tau_n}^N|^2\right] ds, \quad (2.5.12)$$

where the positive constant  $C$  does not depend on  $\tilde{X}_t = (X_s, s \in [t - \tau, t])$  nor on  $n$ .

It is clear that Itô's formula is valid for  $|X_{t \wedge \tau_n}^N|^2$  and that we can study each  $i \in \{1, \dots, N\}$  separately. For all  $t > 0$ :

$$\begin{aligned} |X_{t \wedge \tau_n}^{i,N}|^2 &= |X_0^i|^2 + 2 \int_0^{t \wedge \tau_n} (X_s^{i,N})^T g_\alpha(s, X_s^{i,N}) dW_s^i \\ &\quad + 2 \int_0^{t \wedge \tau_n} \left[ (X_s^{i,N})^T f_\alpha(s, X_s^{i,N}) + \frac{1}{2} |g_\alpha(s, X_s^{i,N})|^2 \right. \\ &\quad \left. + (X_s^{i,N})^T \sum_{\gamma=1}^P \sum_{p(j)=\gamma} \frac{1}{N^\gamma} [b_{\alpha\gamma}(w_{ij}, X_s^{i,N}, X_{s-\tau_{ij}}^{j,N})] \right] ds, \end{aligned}$$

The stochastic integral has null expectation and a direct application of (H4) allow us to find upper-bounds for the two first lines of the previous equality. The last term is controlled using (H3):

$$\begin{aligned} &\int_0^{t \wedge \tau_n} (X_s^{i,N})^T \sum_{\gamma=1}^P \sum_{p(j)=\gamma} \frac{1}{N^\gamma} [b_{\alpha\gamma}(w_{ij}, X_s^{i,N}, X_{s-\tau_{ij}}^{j,N})] ds \\ &\leq \int_0^{t \wedge \tau_n} \sum_{\gamma=1}^P \sum_{p(j)=1} \frac{1}{N^\gamma} \left( \bar{K}_{\alpha\gamma}(w_{ij}) + |X_s^{i,N}|^2 \right) ds \\ &\leq P \int_0^{t \wedge \tau_n} \left( \bar{K} + |X_s^{i,N}|^2 \right) ds, \end{aligned}$$

where we have introduced  $\bar{K} := \max_{(\alpha,\gamma)} \max_{(i,j)} \bar{K}_{\alpha\gamma}(w_{ij})$ . Summing over  $i$  yields directly to (2.5.12).

Applying Gronwall's lemma we find a uniform upper bound for the second moment of  $X_{t \wedge \tau_n}$  for any  $t \in [-\tau, T \wedge \tau_n]$ . Finally letting  $n \rightarrow \infty$  provides that for any realization of the synaptic weights and delays the solutions of (2.2.1) have bounded second moment.

*Existence.* Let  $X^0 \in \mathcal{M}^2(C_\tau)$  such that  $X^0|_{[-\tau,0]} \stackrel{\mathcal{L}}{=} X_0$  a given stochastic process. We introduce the map  $\Phi$  given by

$$\Phi : \begin{cases} \mathcal{M}(\mathcal{C}) & \mapsto \mathcal{M}(\mathcal{C}) \\ X & \mapsto (Y_t = \{Y_t^{i,N}, i = 1, \dots, N\}), \text{ with} \\ & Y_t^{i,N} = X_0^{i,N}(0) + \int_0^t \left( f_\alpha(s, X_s^{i,N}) \right. \\ & \quad \left. + \sum_{\gamma=1}^P \sum_{p(j)=\gamma} \frac{1}{N^\gamma} b_{\alpha\gamma}(w_{ij}, X_s^{i,N}, X_{s-\tau_{ij}}^{j,N}) \right) ds \\ & \quad + \int_0^t g_\alpha(s, X_s^{i,N}) \cdot dW_s^i; \quad t > 0 \\ Y_t &= X_0^i(t), \quad t \in [-\tau, 0] \end{cases}$$

and the sequence of processes  $(X^k)_{k \geq 0}$  on  $\mathcal{M}(\mathcal{C})$  given by the induction  $X^{k+1} = \Phi(X^k)$ . Existence and uniqueness are classically shown through a fixed point argument on the map  $\Phi$ .

For compactness of notations, we denote  $X_t^{i,k} \in E$  the  $i$  component of the vector  $X_t^k$ . We decompose the difference into elementary terms:

$$\begin{aligned}
X_t^{i,k+1} - X_t^{i,k} &= \int_0^t (f_\alpha(s, X_s^{i,k}) - f_\alpha(s, X_s^{i,k-1})) ds \\
&\quad + \int_0^t \sum_{\gamma=1}^{P(N)} \sum_{p(j)=\gamma} \frac{1}{N_\gamma} \left[ b_{\alpha\gamma}(w_{ij}, X_s^{i,k}, X_{s-\tau_{ij}}^{j,k}) \right. \\
&\quad \quad \left. - b_{\alpha\gamma}(w_{ij}, X_s^{i,k-1}, X_{s-\tau_{ij}}^{j,k}) \right] ds \\
&\quad + \int_0^t \sum_{\gamma=1}^{P(N)} \sum_{p(j)=\gamma} \frac{1}{N_\gamma} \left[ b_{\alpha\gamma}(w_{ij}, X_s^{i,k-1}, X_{s-\tau_{ij}}^{j,k}) \right. \\
&\quad \quad \left. - b_{\alpha\gamma}(w_{ij}, X_s^{i,k-1}, X_{s-\tau_{ij}}^{j,k-1}) \right] ds \\
&\quad + \int_0^t (g_\alpha(s, X_s^{i,k}) - g_\alpha(s, X_s^{i,k-1})) \cdot dW_s^i \\
&\stackrel{\text{def}}{=} A_t^i + B_t^i + C_t^i + D_t^i,
\end{aligned}$$

where we simply identify each of the four terms  $A_t = (A_t^i, i = 1, \dots, N)$ ,  $B_t$ ,  $C_t$ , and  $D_t$  with their corresponding expression. Using Holder's inequality

$$|X_t^{k+1} - X_t^k|^2 \leq 4(|A_t|^2 + |B_t|^2 + |C_t|^2 + |D_t|^2),$$

and treat each term separately. The first term  $A_t$  and the last term  $D_t$  are easily controlled using standard techniques (Cauchy-Schwarz inequality and Burkholder-Davis-Gundy theorem) and (H1). In  $B_t$  follows

$$\begin{aligned}
&\sum_{i=1}^N \left| \sum_{\gamma=1}^P \sum_{p(j)=\gamma} \int_0^t \frac{1}{N_\gamma} \left[ b_{\alpha\gamma}(w_{ij}, X_s^{i,k}, X_{s-\tau_{ij}}^{j,k}) - b_{\alpha\gamma}(w_{ij}, X_s^{i,k-1}, X_{s-\tau_{ij}}^{j,k}) \right] ds \right|^2 \\
&\leq \sum_{i=1}^N P t \sum_{\gamma=1}^P \sum_{p(j)=\gamma} \int_0^t \left| b_{\alpha\gamma}(w_{ij}, X_s^{i,k}, X_{s-\tau_{ij}}^{j,k}) - b_{\alpha\gamma}(w_{ij}, X_s^{i,k-1}, X_{s-\tau_{ij}}^{j,k}) \right|^2 ds \\
&\leq T P^2 L^2 N \int_0^t |X_s^k - X_s^{k-1}|^2 ds,
\end{aligned}$$

where  $L := \max_{(\alpha,\gamma)} L_{\alpha\gamma}$ . and similarly for  $C_t$ .

The conclusion is easy, at this point we have:

$$\mathbb{E} \left[ \sup_{-\tau < s < t} |X_s^{k+1} - X_s^k|^2 \right] \leq C \int_0^t \mathbb{E} \left[ \sup_{-\tau \leq u \leq s} |X_u^k - X_u^{k-1}|^2 \right] ds, \quad (2.5.13)$$

where  $C > 0$  depends on  $T, K, L$  and  $P$ . Calling

$$M_t^k \stackrel{\text{def}}{=} \mathbb{E} \left[ \sup_{-\tau \leq s \leq t} |X_s^k - X_s^{k-1}|^2 \right],$$

*a priori bounds* ensures that  $M_T^0 < \infty$  and the recursive inequality holds

$$M_t^k \leq C^k \int_0^t \int_0^{s_1} \dots \int_0^{s_{k-1}} M_{s_k}^0 ds_1 \dots ds_k \leq C^k \frac{t^k}{k!} M_T^0,$$

From the last inequality we get that

$$\sum_{n=1}^{\infty} \mathbb{E} \left[ \sup_{-\tau \leq s \leq t} |X_s^{n+1} - X_s^n|^2 \right] < \infty,$$

which implies in particular the almost sure convergence of

$$X_t^0 + \sum_{k=0}^n (X_t^{k+1} - X_t^k) = X_t^n,$$

on  $[-\tau, T]$ . The limit defined  $\bar{X}_t$  is trivially a fixed point of  $\Phi$  and by consequence solution to networks equations (2.2.1).

*Uniqueness.* Starting with two solutions of the network equations (2.2.1) with exactly the same initial condition one can remake the argument used to find (2.5.13) and then the uniqueness follows directly from Gronwall's lemma.  $\square$

$\square$

The proof well-posedness of mean field equation (2.3.3) (Theorem 2.3.38) is very similar:

*Theorem 5.1.78.* It might seem that averaging over the delays and weights could add some new technical difficulties to the upper-bounds for the second moment but thanks to (H3) similar estimates hold.

To illustrate how to deal with our random network framework, let  $X$  be a solution of the mean-field equations and once again  $\tau_n$  the first time that the process  $|X_t|$  exceeds the quantity  $n$ . Applying Itô's formula to  $|X_{t \wedge \tau_n}|^2$  we now find

$$\begin{aligned} |X_{t \wedge \tau_n}^\alpha|^2 &= |\zeta_0^\alpha|^2 + 2 \int_0^{t \wedge \tau_n} \left[ (X_s^\alpha)^T f_\alpha(s, X_s^\alpha) + \frac{1}{2} |g_\alpha(s, X_s^\alpha)|^2 \right. \\ &\quad \left. + (X_s^\alpha)^T \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} \left[ \mathbb{E}_{\bar{Y}} [b_{\alpha\gamma}(w, X_s^\alpha, \bar{Y}_{s+u}^\gamma)] d\Lambda_{\alpha\gamma}(u, w) \right] ds \right. \\ &\quad \left. + 2 \int_0^{t \wedge \tau_n} (X_s^\alpha)^T g_\alpha(s, X_s^\alpha) dW_t^\alpha, \right. \end{aligned}$$

the only interesting term is the one in the second line, using triangular inequality and (H3) we get

$$\begin{aligned} &(X_s^\alpha)^T \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} \left[ \mathbb{E}_{\bar{Y}} [b_{\alpha\gamma}(w, X_s^\alpha, \bar{Y}_{s+u}^\gamma)] d\Lambda_{\alpha\gamma}(u, w) \right] ds \\ &\leq P |X_s^\alpha|^2 + \sum_{\gamma=1}^P \int_{-\tau}^0 \int_{\mathbb{R}} \bar{K}_{\alpha\gamma}(w) d\Lambda_{\alpha\gamma}(u, w) \leq C(\bar{k} + |X_s^\alpha|^2). \end{aligned}$$

Equipped with this estimate, the proof is identical to that of the related property in proposition 2.3.37, i.e., define a contraction mapping which gives the existence and uniqueness of solutions.  $\square$

$\square$

The two following proofs deal with the propagation of chaos property, we first demonstrate Theorem 2.3.39 which states the convergence properties in a quenched sense in the translation invariant case, and we finally explain how to adapt this proof to the general case Theorem 2.3.40, i.e., how to deal with the additional difficulty of averaging over all possible positions of neurons in each population.

*Theorem 2.3.39.* The idea extends standard arguments for propagation of chaos and mean-field limits by considering random correlated coupling and delays. The argument remains to control the difference between the two processes as  $N$  goes to infinity. Decomposing the difference in 5 simpler terms we find:

$$\begin{aligned}
X_t^{i,N} - \bar{X}_t^i &= \int_0^t (f_\alpha(s, X_s^{i,N}) - f_\alpha(s, \bar{X}_s^i)) ds \\
&+ \int_0^t (g_\alpha(s, X_s^{i,N}) - g_\alpha(s, \bar{X}_s^i)) \cdot dW_s^i \\
&+ \sum_{\gamma=1}^P \int_0^t \sum_{p(j)=\gamma} [b_{\alpha\gamma}(w_{ij}, X_s^{i,N}, X_{s-\tau_{ij}}^{j,N}) - b_{\alpha\gamma}(w_{ij}, \bar{X}_s^i, X_{s-\tau_{ij}}^{j,N})] \frac{ds}{N_\gamma} \\
&+ \sum_{\gamma=1}^P \int_0^t \sum_{p(j)=\gamma} [b_{\alpha\gamma}(w_{ij}, \bar{X}_s^i, X_{s-\tau_{ij}}^{j,N}) - b_{\alpha\gamma}(w_{ij}, \bar{X}_s^i, \bar{X}_{s-\tau_{ij}}^j)] \frac{ds}{N_\gamma} \\
&+ \sum_{\gamma=1}^P \int_0^t \left( \frac{1}{N_\gamma} \sum_{p(j)=\gamma} b_{\alpha\gamma}(w_{ij}, \bar{X}_s^i, \bar{X}_{s-\tau_{ij}}^j) \right. \\
&\quad \left. - \int_{-\tau}^0 \int_{\mathbb{R}} \mathbb{E}_Z [b_{\alpha\gamma}(w, \bar{X}_s^i, Z_{s+u}^\gamma)] d\Lambda_{\alpha\gamma}(u, w) \right) ds \\
&:= A_t(N) + B_t(N) + C_t(N) + D_t(N) + E_t(N).
\end{aligned}$$

We are interested in the behavior of  $\mathcal{E}[\mathbb{E}(\sup_{-\tau \leq s \leq T} |X_s^{i,N} - \bar{X}_s^i|^2)]$  as  $N \rightarrow \infty$ . Under the same ideas used in Proposition 5.3.84 and in Theorem 2.3.38, we find:

$$\begin{aligned}
\mathbb{E}[\sup_{0 \leq s \leq t} |A_s(N)|^2] &\leq K'^2 T \int_0^t \mathbb{E}[\sup_{-\tau \leq u \leq s} |X_u^{i,N} - \bar{X}_u^i|^2] ds \\
\mathbb{E}[\sup_{0 \leq s \leq t} |B_s(N)|^2] &\leq 4K'^2 \int_0^t \mathbb{E}[\sup_{-\tau \leq u \leq s} |X_u^{i,N} - \bar{X}_u^i|^2] ds, \\
\mathbb{E}[\sup_{0 \leq s \leq t} |C_s(N)|^2] &\leq TL^2 P^2 \int_0^t \mathbb{E}[\sup_{-\tau \leq u \leq s} |X_u^{i,N} - \bar{X}_u^i|^2] ds \\
\mathbb{E}[\sup_{0 \leq s \leq t} |D_s(N)|^2] &\leq TL^2 P^2 \int_0^t \max_{k=1, \dots, N} \mathbb{E}[\sup_{-\tau \leq u \leq s} |X_u^{k,N} - \bar{X}_u^k|^2] ds,
\end{aligned}$$

where  $L$  is the maximum value of constants  $L_{\alpha\gamma}$  (finite number of populations) and we precise that the 4 in the  $B_t(N)$  upper-bound is found using the Burkholder-David-Gundy Inequality.

For the last term  $E_t(N)$  we start by applying the Cauchy-Schwartz and the triangular inequality:

$$\begin{aligned}
\mathcal{E}[\mathbb{E}[\sup_{0 \leq s \leq t} |E_s(N)|^2]] &\leq TP \sum_{\gamma=1}^P \int_0^t \mathcal{E} \left[ \mathbb{E} \left[ \left| \frac{1}{N_\gamma} \sum_{p(j)=\gamma} \left( b_{\alpha\gamma}(w_{ij}, \bar{X}_s^i, \bar{X}_{s-\tau_{ij}}^j) \right. \right. \right. \right. \\
&\quad \left. \left. \left. - \int_{-\tau}^0 \int_{\mathbb{R}} \mathbb{E}_Z [b_{\alpha\gamma}(w, \bar{X}_s^i, Z_{s+u}^\gamma)] d\Lambda_{\alpha\gamma}(u, w) \right) \right|^2 \right] \right] ds,
\end{aligned}$$

moreover,

$$\begin{aligned}
&\mathcal{E} \left[ \mathbb{E} \left[ \left| \frac{1}{N_\gamma} \sum_{p(j)=\gamma} \left( b_{\alpha\gamma}(w_{ij}, \bar{X}_s^i, \bar{X}_{s-\tau_{ij}}^j) \right. \right. \right. \right. \right. \\
&\quad \left. \left. \left. - \int_{-\tau}^0 \int_{\mathbb{R}} \mathbb{E}_Z [b_{\alpha\gamma}(w, \bar{X}_s^i, Z_{s+u}^\gamma)] d\Lambda_{\alpha\gamma}(u, w) \right) \right|^2 \right] \right] \\
&= \frac{1}{N_\gamma^2} \sum_{p(j)=\gamma} \sum_{p(l)=\gamma} \mathcal{E} \left[ \mathbb{E} \left[ \left( b_{\alpha\gamma}(w_{ij}, \bar{X}_s^i, \bar{X}_{s-\tau_{ij}}^j) - \mathbb{E}_{Z,(\tilde{\tau}, \tilde{w})_{\alpha\gamma}} [b_{\alpha\gamma}(\tilde{w}_{\alpha\gamma}, \bar{X}_s^i, Z_{s-\tilde{\tau}_{\alpha\gamma}}^\gamma)] \right) \right. \right. \right. \\
&\quad \left. \left. \left. \left( b_{\alpha\gamma}(w_{il}, \bar{X}_s^i, \bar{X}_{s-\tau_{il}}^l) - \mathbb{E}_{Z,(\tilde{\tau}, \tilde{w})_{\alpha\gamma}} [b_{\alpha\gamma}(\tilde{w}_{\alpha\gamma}, \bar{X}_s^i, Z_{s-\tilde{\tau}_{\alpha\gamma}}^\gamma)] \right) \right) \right]^2 \right]
\end{aligned}$$

In the above expression,  $(\tilde{\tau}, \tilde{w})_{\alpha\gamma}$  denotes a random variable with law  $\Lambda_{\alpha\gamma}$  independent of the sequence of delays, weights and Brownian motions. We remark that  $\int_{-\tau}^0 \int_{\mathbb{R}} \mathbb{E}_Z [b_{\alpha\gamma}(w, \bar{X}_s^i, Z_{s+u}^\gamma)] d\Lambda_{\alpha\gamma}(u, w)$  is exactly the expectation of  $b_{\alpha\gamma}(w_{ij}, \bar{X}_s^i, \bar{X}_{s-\tau_{ij}}^j)$  under the law of  $\bar{X}^j$  and of the pair delays-weights.

Therefore in the case  $j \neq l$ , the term in the summation vanishes, and in the opposite case  $j = l$  we use the triangular inequality to see that

$$\begin{aligned} & \mathbb{E} \left[ \mathbb{E} \left[ \left| b_{\alpha\gamma}(w_{ij}, \bar{X}_s^i, \bar{X}_{s-\tau_{ij}}^j) - \mathbb{E}_{Z, (\tilde{\tau}, \tilde{w})_{\alpha\gamma}} [b_{\alpha\gamma}(\tilde{w}_{\alpha\gamma}, \bar{X}_s^i, Z_{s-\tilde{\tau}_{\alpha\gamma}}^\gamma)] \right|^2 \right] \right] \\ & \leq 2 \mathcal{E} \left[ \mathbb{E} \left[ \left| b_{\alpha\gamma}(w_{ij}, \bar{X}_s^i, \bar{X}_{s-\tau_{ij}}^j) \right|^2 + \left| \mathbb{E}_{Z, (\tilde{\tau}, \tilde{w})_{\alpha\gamma}} [b_{\alpha\gamma}(\tilde{w}_{\alpha\gamma}, \bar{X}_s^i, Z_{s-\tilde{\tau}_{\alpha\gamma}}^\gamma)] \right|^2 \right] \right] \\ & \leq 2 \mathcal{E} \left[ \mathbb{E} [\bar{K}(w_{ij}) + \bar{k}] \right] \leq 4\bar{k}. \end{aligned}$$

This implies that number of non-null terms in the sum is proportional to  $N_\gamma$  and all of them are bounded by the same quantity. Thus

$$\mathcal{E} \left[ \mathbb{E} \left[ \sup_{0 \leq s \leq t} |E_s(N)|^2 \right] \right] \leq \bar{C}k \sum_{\gamma=1}^P \frac{1}{N_\gamma} \leq \frac{C\bar{k}P}{\min_\gamma(N_\gamma)}.$$

Assembling all the estimates, using that on  $[-\tau, 0]$  both  $X_t^{i,N}$  and  $\bar{X}_t^i$  are equal and denoting by  $C$  any generic constant that does not depend on  $N$  we find

$$\begin{aligned} & \max_{i=1, \dots, N} \mathcal{E} \left[ \mathbb{E} \left[ \sup_{-\tau \leq s \leq t} |X_s^{i,N} - \bar{X}_s^i|^2 \right] \right] \\ & \leq C \int_0^t \max_{k=1, \dots, N} \mathcal{E} \left[ \mathbb{E} \left[ \sup_{-\tau \leq u \leq s} |X_u^{k,N} - \bar{X}_u^k|^2 \right] \right] ds + \frac{C}{\min_\gamma(N_\gamma)}, \end{aligned}$$

by Gronwall's inequality:

$$\max_{i=1, \dots, N} \mathcal{E} \left[ \mathbb{E} \left[ \sup_{-\tau \leq s \leq t} |X_s^{i,N} - \bar{X}_s^i|^2 \right] \right] \leq \frac{Ce^{CT}}{\min_\gamma(N_\gamma)},$$

which tends to zeros as  $N$  goes to infinity by (H0).

As a side result, the almost sure convergence towards the coupled process implies the convergence in law of  $(X_t^{i,N}, -\tau \leq t \leq T)$  towards  $(\bar{X}_t^\alpha, -\tau \leq t \leq T)$ .  $\square$

From the last inequality we have easily the propagation of chaos property. Fixing a finite set of neurons  $(i_1, \dots, i_l) \in \mathbb{N}$ , then if  $f_\alpha$  and  $g_\alpha$  are globally Lipschitz continuous, we have:

$$\max_{i_1, \dots, i_l \in \{1, \dots, N\}^l} \mathcal{E} \left[ \mathbb{E} \left[ \sup_{-\tau \leq s \leq t} |(X_s^{i_1, N}, \dots, X_s^{i_l, N}) - (\bar{X}_s^{i_1}, \dots, \bar{X}_s^{i_l, N})|^2 \right] \right] \leq \frac{lCe^{CT}}{\min_\gamma(N_\gamma)},$$

hence

$$(X_s^{i_1, N}, \dots, X_s^{i_l, N}, -\tau \leq s \leq T) \xrightarrow{\mathcal{L}} (\bar{X}_s^{i_1}, \dots, \bar{X}_s^{i_l, N}, -\tau \leq s \leq T),$$

and truncation argument allows to conclude on the convergence in the locally Lipschitz case. This implies that the vector  $(X_s^{i_1, N}, \dots, X_s^{i_l, N}, -\tau \leq s \leq T)$  converges in law towards  $m^{i_1} \otimes \dots \otimes m^{i_l}$ , readily implying propagation of chaos.



*Theorem 2.3.40.* The proof uses essentially the same arguments as that of theorem 2.3.39. Here, we control the difference between  $\mathcal{E}_i[X_t^{i,N}]$  and  $\bar{X}_t^i$  in the quadratic norm  $\|Z\|^2 := \mathbb{E}[\sup_{-\tau \leq t \leq T} |Z_s|^2]$ . The assumption on  $b$  allow us to separate the distance into only 4 terms similarly to the quenched case. Most terms are handled in a similar fashion, the only difference being the presence of a additional expectation  $\mathcal{E}_i$ . The main difference is to deal with the term corresponding to  $E_t(N)$ , which now reads:

$$\begin{aligned} \mathcal{E} \left[ \mathbb{E} \left[ \sup_{0 \leq s \leq t} |E_s(N)'|^2 \right] \right] = \\ \leq TP \sum_{\gamma=1}^P \int_0^t \mathcal{E} \left[ \mathbb{E} \left[ \left| \frac{1}{N_\gamma} \sum_{p(j)=\gamma} \mathcal{E}_i[\ell_{\alpha\gamma}(w_{ij}, \bar{X}_{s-\tau_{ij}}^j)] \right. \right. \right. \\ \left. \left. \left. - \int_{-\tau}^0 \int_{\mathbb{R}} \mathbb{E}_Z[\ell_{\alpha\gamma}(w, Z_{s+u}^\gamma)] d\Lambda_{\alpha\gamma}(u, w) dr_i \right|^2 ds \right] \right], \end{aligned}$$

Again,

$$\mathcal{E} \left[ \mathbb{E} \left[ \mathcal{E}_i[\ell_{\alpha\gamma}(w_{ij}, \bar{X}_{s-\tau_{ij}}^j)] \right] \right] = \int_{-\tau}^0 \int_{\mathbb{R}} \mathbb{E}_Z[\ell_{\alpha\gamma}(w, Z_{s+u}^\gamma)] d\Lambda_{\alpha\gamma}(u, w)$$

we develop in the same way that Theorem 2.3.39. The key point is that it suffices to find an upper-bound uniformly in the disorder of the system which is trivially found using (H3), i.e.,

$$\mathcal{E} \left[ \mathbb{E} \left[ \left| \mathcal{E}_i[\ell_{\alpha\gamma}(w_{ij}, \bar{X}_{s-\tau_{ij}}^j)] - \mathbb{E}_{Z,(\bar{\tau}, \bar{w})_{\alpha\gamma}}[\ell_{\alpha\gamma}(w_{\alpha\gamma}, Z_{s-\bar{\tau}_{\alpha\gamma}}^\gamma)] \right|^2 \right] \right] \leq 2\bar{k},$$

and we conclude using (H0). □ □

## 2.6 Discussion

---

In this paper, motivated by the structure of interconnection matrix and interactions of neuronal networks of the brain, we analyzed the mean-field limits and dynamics of networks on some random graphs with delays correlated to the synaptic weights. Extending coupling methods to these models, we showed quenched and averaged propagation of chaos, and convergence towards a complex mean-field equation involving distributed delays and averaging with respect to the law of the connectivity. This limit equation is relatively complex in general models, however, they massively simplify for the classical firing-rate model, in which case solutions are exactly reduced to a system of distributed delays integro-differential equations, from which one can infer, using bifurcation theory, the role of random connectivities and delays. This technique led us to demonstrate that typical size of the neuronal area, as well as typical length scale of connectivity, induced or broke synchronization of the neurons. In detail, we showed that depending on the connectivity of the network and the averaged delays the network can either present stationary or a synchronized periodic behavior. In this sense, using a small-world type of model for the value of the weights, we were able to prove that the architecture of the system also plays a role in the dynamics. We also showed that the macroscopic behavior depends on the size of the neural field considered and, more important, on the connectivity of the system measured as the amount of connections over the total possible ones.

### 2.6.1 Relationship with pathological rhythmic brain activity

Synchronized states are ubiquitous and serve essential function in brain such as memory or attention [31]. Impairments of synchronization levels often relate to severe pathological effects such as epilepsy (too much synchronization) or Parkinson’s disease (too little synchronization) [134]. Troubles in oscillatory patterns have also been related to connectivity levels in epilepsy. In detail, the emergence of seizures and abnormal synchronization was hypothesized to be related to an increased functional connectivity, or more recently to the appearance of an increased number of synaptic buttons between cells. The former phenomenon has been reported in various epileptic situations (see e.g. [16]), and the latter was mainly evidenced in hippocampal epilepsy, and is generally referred to as *neosynaptogenesis*, or *sprouting*, see e.g. [8, 115, 117]. Our models provides an elementary account for the fact that indeed, increased connectivity levels (corresponding to small values of  $\beta$ ) tend to favor synchronization for most values of  $\tau_s$ . The model even makes a prediction about some possible parameter regions in which this synchronization may only arise in a particular intermediate interval of connectivity levels  $\beta$ . Disorder also seems to intervene in the emergence of abnormally synchronized oscillations, as evidenced for instance by Aradi and Soltesz [6] who showed that even if average levels of connectivity in rats subjects to febrile epileptic seizures were similar to those of a control population, variance in the connectivities were increased. Our models incorporate the law of the synaptic weights, and therefore all for testing this hypothesis, as well as a number of variations around these models, in a rigorous manner.

### 2.6.2 Cluster size and synchronization in primary visual area

The structure of the primary visual areas are very diverse across species. These areas are composed of cells sensitive to the orientation of visual stimuli. In primates, neurons gather into columns as a function of the orientation they are selective to, and these columns organize spatially creating continuous patterns of a specific anatomical size (see e.g. [20]). In contrast, rodents present no specific organization of neurons selective to the same orientation (salt-and-pepper organization, see [118]). The reason why these architectures are very different across mammals is still poorly understood, and one of the possibles explanations proposed is related to the size of V1: the model tends to show that it is harder to ensure collective synchronization at the level of large cortical areas than locally, phenomenon probably due to the fact that naturally, connectivities are local. This is precisely one of the results of our analysis. In our model, the parameter  $a$  characterizes the size of one cortical column, and the results of the analysis of the model show that increasing the size of a column  $a$  induces transitions from synchronized regimes to stationary regimes, reducing the collective response of neurons.

### 2.6.3 Macroscopic vs Mesoscopic models

The question of which is the proper scale adapted to describe a phenomenon is central in computational neuroscience. Of course, it is tempting to propose large-scale macroscopic models made of homogeneous

neuronal populations, as neuronal networks tend to present a columnar organization made of a large number of strongly connected neurons. Most models use implicitly this kind of structure through neural mass models [161, 79]. Another common approximation is the neural field model (see [22] for a recent review) that describes the cortical activity through integro-differential delayed equations, which could be related to a particular limit of neuronal networks with local homogeneity properties as shown in [149].

The model analyzed sits at an intermediate scale at which homogeneity of connectivity is only true (i) locally an (ii) in a statistical sense. Though these local variations, the model studied in first part of section 2.3, termed *macroscopic*, describes the neural network at a macroscopic scale with a single equation describing the averaged or quenched behavior of one cell in the network. Appendix 2.7 shows that the result persists when considering asymptotically a continuum of neural populations, yielding the *mesoscopic* model. Let us now compare our models to usual neural mass (NM) or neural fields (NF). These latter models are given by the equations (in which  $\Phi$  is a sigmoid transform):

$$\dot{u}_\alpha(t) = -\frac{u_\alpha}{\theta_\alpha}(t) + \sum_{\beta=1}^P \bar{J}_{\alpha\beta} \Phi(u_\beta(t - \tau_{\alpha\beta}))$$

for finite-populations networks (model NM), and in spatial continuous settings (NF) with a single layer:

$$\partial_t u(r, t) = -\frac{u(r, t)}{\theta} + \int_{\Gamma} \bar{J}(r, r') \Phi(u(r', t - \tau(r, r'))) dr'.$$

These two equations are very close from the mean equations we obtained in our mean-field limit. Disregarding stochastic inputs, the macroscopic (mesoscopic) model is an homogenized version of an heterogeneous neural mass (resp, neural field) model. Disregarding the effect of stochastic noise, our macroscopic model therefore tends to correspond to spatially homogeneous solutions of the neural field equations for translation invariant neural fields. Indeed, assuming  $r \in \mathbb{S}_a$  the 1-dimensional torus of length  $a$ , i.e. the periodic interval  $[0, a]$ ,  $J(r, r') = J(r - r')$  and  $\tau(r, r') = \tau_s + |r - r'|$ , spatially homogeneous solutions are functions of time only, satisfying the equations:

$$\dot{\bar{u}}(t) = -\frac{\bar{u}(t)}{\theta} + \int_0^a \bar{J}(\zeta) \Phi(\bar{u}(t - \tau_s - \zeta)) d\zeta$$

(which does not depend on  $r$ ). Our model yields an equation on the mean of the process that corresponds to:

$$\dot{\mu}(t) = -\frac{\mu(t)}{\theta} + \int_0^a \bar{J}\beta(\zeta) f(\mu(t - \tau_s - \zeta), v(t - \tau_s - \zeta)) d\zeta.$$

Therefore, with an appropriate choice of parameters and function, the mean-field macroscopic model represents spatially homogeneous solutions of the Wilson-Cowan neural field equations. The present approach provides a microscopic interpretation of these equations, and the model provides therefore a suitable framework to investigate random individual phenomena arising in large neuronal areas, observed at scales that do not resolve fine structure of the brain, such as the electro-encephalogram method used in epilepsy monitoring.

## 2.6.4 Perspectives

The course of our developments lead us to cast aside the assumption of full connectivity or exchangeability between neurons. Incidentally, this work therefore shows that the notion of exchangeability, widely use in large stochastic particle systems, can be significantly weakened, in favor of statistical equivalent, and more structured global exchangeability properties such as the translation invariance. This opens the way to develop a these ideas towards invariant architectures under the action of specific groups of transformation. This constitute an active research that we are currently developing. This method also has a number of possible implications in neuroscience and in complex systems more generally, and may help understanding the dynamics of large neural networks. Enriching this model considering different populations in the applications section is a straightforward extension of the manuscript, and analyzing those results would allow going even deeper in the analysis of neuronal networks and macroscopic synchronization of them as an effect of random pairs delays and synaptic weights. Considering different kind of architectures is also a possible path to follow and could bring new relationships with the specific cortical functions. A deep question is whether one can obtain information on the microscopic configurations related to the macroscopic regimes observed. This motivates to develop the analysis of the presence of structured activity (localized bumps, traveling waves, traveling pulses) and their probability of appearance as a function of disorder, noise and the parameters of the system. This is an exciting question well worth investigating. One limitation of the qualitative analysis provided here is that the moment reduction is rigorously exact only in very specific models where solutions are Gaussian. Such models do not reproduce the excitability properties of the cells. Extending this analysis to excitable systems, i.e. analyzing equation (2.3.2) with nonlinear dynamics and nonlinear interactions, is a deep and challenging mathematical question in the domain of stochastic processes and functional analysis.

## 2.7 Appendix A: Randomly connected neural fields \_\_\_\_\_

We now extend the above results to the mesoscopic case of spatially-extended neural fields with random correlated connectivity weights and delays. In this case, following [149], we consider that the number of populations in a network of size  $N$  is  $P(N)$ , and this quantity diverges when  $N$  tends to infinity covering, in the limit  $N \rightarrow \infty$ , a piece of cortical tissue  $\Gamma$  which compact set of  $\mathbb{R}^\delta$  (generally  $\delta = 1, 2$ ). In this interpretation, a population index represents the location  $r_\alpha \in \Gamma$  of a microcolumn on the neural field, which are assumed to be independent random variables with distribution  $\lambda$  on  $\Gamma$ . For the sake of simplicity and consistency with other works about neural fields, we include the dependence on the neural populations in the drift and diffusion functions. We therefore introduce three maps:

- the measurable functions  $f : \Gamma \times \mathbb{R} \times E \mapsto E$  and  $g : \Gamma \times \mathbb{R} \times E \mapsto E^m$
- the map  $b : \Gamma \times \Gamma \times \mathbb{R} \times E \times E \mapsto E$  which is assumed measurable,

and rewrite the network equations as:

$$dX_t^{i,N} = f(r_\alpha, t, X_t^{i,N}) + \frac{1}{P(N)} \sum_{\gamma=1}^{P(N)} \sum_{p(j)=\gamma} \frac{1}{N_\gamma} b(r_\alpha, r_\gamma, w_{ij}, X_t^{i,N}, X_{t-\tau_{ij}}^{j,N}) dt + g(r_\alpha, t, X_t^{i,N}) \cdot dW_t^i, \quad (2.7.14)$$

These equations are clearly well-defined as proved in proposition 2.3.37. As described in the macroscopic framework 2.2, the two sequences of random variables  $(w_{ij})$  and  $(\tau_{ij})$  for fixed  $i \in \mathbb{N}$  are independent, and for fixed  $(i, j)$ ,  $\tau_{ij}$  and  $w_{ij}$  are correlated. Their law depend on the locations  $r_\alpha$  and  $r_\gamma$  of the microcolumns neurons  $i$  and  $j$  belong to. We denote  $\Lambda_{r_\alpha, r_\gamma}$  this law. We assume that this law is measurable with respect to the Borel algebra of  $\Gamma$ , i.e. for any  $A \in \mathcal{B}(\mathbb{R} \times \mathbb{R}_+)$  the Borel algebra of  $\mathbb{R} \times \mathbb{R}_+$ , the map  $(r, r') \mapsto \Lambda_{r, r'}(A)$  is measurable with respect to  $\mathcal{B}(\Gamma \times \Gamma)$ . We assume that assumptions (H1)-(H4) are valid uniformly in the space variables, and consider the *neural field limit* given by the condition:

$$\varepsilon(N) = \frac{1}{P(N)} \sum_{\gamma=1}^{P(N)} \frac{1}{N_\gamma} \xrightarrow{N \rightarrow \infty} 0. \quad (2.7.15)$$

Elaborating on the proofs provided (i) in the finite-population case treated in the present manuscript and (ii) in the neural field limit for non random synaptic weights or delays, we will show that the network equations converge towards a spatially-extended McKean-Vlasov equation:

$$dX_t(r) = f(r, t, X_t(r)) dt + g(r, t, X_t(r)) \cdot dW_t(r) + \int_{\Gamma} \int_{\mathbb{R}} \int_{-\tau}^0 \mathbb{E}_Z[b(r, r', j, X_t(r), Z_{t+s}(r'))] d\Lambda_{r, r'}(j, s) d\lambda(r') dt. \quad (2.7.16)$$

In these equations, the process  $(W_t(r))$  is a chaotic Brownian motion (as defined in [149]), i.e. a stochastic process indexed by space  $r \in \Gamma$ , such that for any  $r \in \Gamma$ , the process  $W_t(r)$  is a standard  $m$ -dimensional Brownian motion and for any  $r \neq r' \in \Gamma^2$ ,  $W_t(r)$  and  $W_t(r')$  are independent. These processes are singular functions of space, and in particular not measurable with respect to the Borel algebra of  $\Gamma$ ,  $\mathcal{B}(\Gamma)$ . Therefore, the solutions are themselves not measurable, which raise questions on the definition of the mean-field equation (2.7.16) in particular for the definition of the integral on space of the mean-field term. However, it was shown in [149], making sense of this equation amounts showing that the law of the solution is  $\mathcal{B}(\Gamma)$ -measurable. Once this is proved, the integral is well defined. In the spatial case, we make the following assumptions, that are directly corresponding to the assumptions (H1)-(H4) of the finite-population case:

(H1')  $f$  and  $g$  are uniformly Lipschitz-continuous functions with respect to their last variable.

(H2') For almost all  $w \in \mathbb{R}$  and any  $(r, r') \in \Gamma^2$ ,  $b(r, r', w, \cdot, \cdot)$  is  $L$ -Lipschitz-continuous, i.e. for any  $(x, y)$  and  $(x', y')$  in  $E \times E$ , we have:

$$|b(r, r', w, x, y) - b(r, r', w, x', y')| \leq L(|x - x'| + |y - y'|).$$

(H3') There exists a function  $\bar{K} : \mathbb{R} \mapsto \mathbb{R}^+$  such that for any  $(r, r') \in \Gamma^2$ ,

$$|b(r, r', w, x, y)|^2 \leq \bar{K}(w) \quad \text{and} \quad \mathcal{E}_{\Lambda_{r, r'}}[\bar{K}(w)] \leq \bar{k} < \infty.$$

(H4') The drift and diffusion functions satisfy the uniform (in  $r$ ) monotone growth condition:

$$x^T f(r, t, x) + \frac{1}{2} |g(r, t, x)|^2 \leq K(1 + |x|^2).$$

The initial conditions we consider for the mean-field equations are processes  $(\zeta_t(r), t \in [-\tau, 0]) \in \mathcal{X}_0$  the space of spatially chaotic square integrable process with measurable law, processes such that the regularity conditions are satisfied:

- for any  $r \in \Gamma$ ,  $\zeta_t(r)$  is square integrable in  $\mathcal{C}_\tau$
- for any  $r \neq r'$ , the processes  $\zeta(r)$  and  $\zeta(r')$  are independent
- for fixed  $t \in [-\tau, 0]$ , the law of  $\zeta_t(r)$  is measurable with respect to  $\mathcal{B}(\Gamma)$ , i.e. for any  $A \in \mathcal{B}(E)$ ,  $p_{\zeta_t}(r) = \mathbb{P}(\zeta_t(r) \in A)$  is a measurable function of  $(\Gamma, \mathcal{B}(\Gamma))$  in  $[0, 1]$ .

We will denote  $\mathcal{X}_T$  the set of processes  $(\zeta_t(r), t \in [-\tau, T])$  satisfying the above regularity conditions on  $[-\tau, T]$ .

**Proposition 2.7.42.** *Under assumptions (H1')-(H4'), for any initial condition  $\zeta \in \mathcal{X}$ , there exists a unique, well-defined strong solution to the mean-field equations (2.7.16).*

The proof classically starts by showing square integrability of possible solutions, then considers equation (2.7.16) as a fixed point equation  $X_t = \Phi(X_t)$ , and shows a convergence property of iterates of the map  $\Phi$  starting from an arbitrary chaotic process  $X_t^0(r) \in \mathcal{X}_T$ . It is easy to see that the function  $\Phi$  maps  $\mathcal{X}_T$  in itself. The sequence of processes  $X^k = \Phi^k(X^0)$  is therefore well-defined. Estimates similar to those proved in proposition 5.3.84 and theorem 5.1.78 allow concluding on the existence and uniqueness of solutions. The proof being classical, it is left to the interested reader extending the argument of [149, Theorem 2] to our random environment setting.

The convergence result of the network equations towards the mean-field equations can be stated as follows:

**Theorem 2.7.43.** *Let  $\zeta \in \mathcal{X}_0$  a chaotic process. Consider the process  $(X_t^{i,N}, t \in [-\tau, T])$  solution of the network equations (2.7.14) with independent initial conditions identically distributed for neurons in the same population located at  $r \in \Gamma$  with law equal to  $(\xi_t(r), t \in [-\tau, 0])$ . Under assumptions (H1')-(H4') and the neural field limit assumption (2.7.15), the process  $(X_t^{i,N}, t \in [-\tau, T])$  converges in law towards  $(X_t(r), t \in [-\tau, T])$  solution of the mean-field equations with initial conditions  $\zeta$ .*

The proof of this result proceeds as that of [149, Theorem 3] including the refinements brought in the proof of theorem 2.3.38 to take into account random connectivities and delays.



# On a kinetic FitzHugh-Nagumo equation: exponential nonlinear convergence

In this chapter we investigate existence and uniqueness of solutions of a McKean-Vlasov evolution PDE representing the macroscopic behaviour of interacting Fitzhugh-Nagumo neurons. This equation is hypoelliptic, nonlocal and has unbounded coefficients. We prove existence of a solution to the evolution equation and non trivial stationary solutions. Moreover, we demonstrate uniqueness of the stationary solution in the weakly nonlinear regime. Eventually, using a semigroup factorisation method, we show exponential nonlinear stability in the small connectivity regime. As coupling increases, highly non-trivial phenomena may emerge as nonlinear effects of the McKean-Vlasov equation. In a final section, we numerically explore the dynamics of the Fitzhugh-Nagumo kinetic equation using a Monte-Carlo algorithm. We observe that complex phenomena occur as the coupling is varied: *the stability of stationary solutions may change as a function of connectivity levels, and attractive periodic solution in time may emerge.*

This paper is included in [112] written in collaboration with S. Mischler and J. Touboul (submitted).

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# 3.1 Introduction

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This paper undertakes the analysis of the existence and uniqueness of solutions for a mean-field equation arising in the modeling of the macroscopic activity of the brain. This equation describes the large-scale dynamics of a model of the central nervous system, taking into account the fact that it is composed of a very large number of interconnected cells that manifest highly nonlinear dynamics and are subject to noise. Non-linearities in the intrinsic dynamics of individual cells are an essential element of the neural code. Indeed, nerve cells constantly regulate their electrical potential depending on the input they receive. This regulation results from intense ionic exchanges through the cellular membranes. The modeling of these dynamics led to the development of the celebrated Hodgkin-Huxley model [75], a very precise description of ion exchanges through the membrane and their effects on the cell voltage. A simplification of this model conserving the most prominent aspects of the Hodgkin-Huxley model, the Fitzhugh-Nagumo (FhN) model [59, 116], has gained the status of canonical model of excitable cells in neuroscience. This model constitutes a very good compromise between versatility and accuracy on the one hand, and relative mathematical simplicity on the other hand. It describes the evolution of the membrane potential  $v$  of the cell coupled to an auxiliary variable  $x$ , called the adaptation variable. Different neurons interact through synapses that are either chemical or electrical. In the case of electrical synapses for instance, the evolution of the pair voltage-adaptation for a set of  $n$  neurons  $\{(v_t^i, x_t^i), 1 \leq i \leq n\}$  satisfy the equations:

$$\begin{cases} dv_t^i = \left( v_t^i (v_t^i - \lambda) (1 - v_t^i) - x_t^i + \sum_{j=1}^n J_{ij} (v_t^i - v_t^j) + I_t \right) dt + \sigma dW_t^i \\ dx_t^i = (-ax_t^i + bv_t^i) dt, \end{cases} \quad (3.1.1)$$

where the cubic nonlinearity accounts for the cell excitability,  $I_t$  is the input level,  $a$  and  $b$  are positive constants representing timescale and coupling between the two variables, and the processes  $\{(W_t^i)_{t \geq 0}, 1 \leq i \leq n\}$  are independent Brownian motions accounting for the intrinsic noise at the level of each cell. In the sequel, for sake of simplicity, we assume that  $\sigma^2 = 2$  and  $I_t = I_0 \in \mathbb{R}$  constant, but it is likely that some of our analysis can be extend to  $I_t \in L^\infty(\mathbb{R}_+)$  converging rapidly when  $t$  goes to infinity. The coefficients  $J_{ij}$  represent the effect of the interconnection of cell  $j$  onto cell  $i$ . These coefficients are positive, and incorporate the information of the connectivity map. Under relatively weak assumptions on the distribution of these coefficients (see Appendix 3.7), it is relatively classical to show that the system enjoys propagation of chaos property and finite sets of neurons converge in law towards a process whose density solves the McKean-Vlasov evolution PDE:

$$\partial_t f = Q_\varepsilon[\mathcal{J}_f] f := \partial_x(Af) + \partial_v(B_\varepsilon(\mathcal{J}_f)f) + \partial_{vv}^2 f \quad \text{on } (0, \infty) \times \mathbb{R}^2, \quad (3.1.2)$$

$$A = A(x, v) = ax - bv, \quad B_\varepsilon(\mathcal{J}_f) = B(x, v; \varepsilon, \mathcal{J}_f), \quad (3.1.3)$$

$$B(x, v; \varepsilon, j) = v(v - \lambda)(v - 1) + x - \varepsilon(v - j) + I_0, \quad (3.1.4)$$

$$\mathcal{J}_f = \mathcal{J}(f) = \int_{\mathbb{R}^2} v f(x, v) dv dx, \quad (3.1.5)$$

where  $\varepsilon$  denotes the averaged value of the connectivity coefficients  $J_{ij}$  and  $f = f(t, x, v) \geq 0$  is the

density function of finding neurons with adaptation and voltage  $(x, v) \in \mathbb{R}^2$  at time  $t \geq 0$ . The evolution equation (3.1.2) is complemented by an initial condition

$$f(0, \cdot, \cdot) = f_0(\cdot, \cdot) \geq 0 \quad \text{in } \mathbb{R}^2.$$

Since the PDE can be written in divergence form, the initial normalization of the density is conserved. In particular, consistent with the derivation of the system, we have:

$$\int_{\mathbb{R}^2} f(t, x, v) dx dv = \int_{\mathbb{R}^2} f_0(x, v) dx dv = 1,$$

when  $f_0$  is normalized. Moreover, the nonnegativity is also a classical result of this kind of equations (for a brief discussion see Appendix 3.8), therefore we assume in the sequel that  $f$  is a probability density.

From the mathematical viewpoint, this equation presents several interests. First, the system is not Hamiltonian and the dynamics may present several equilibria, therefore, methods involving a potential and its possible convexity may not be used. Second, intrinsic noise acts as a stochastic input only into the voltage variable (since it modifies the voltage through random fluctuations of the current), leaving the adaptation equation unchanged and yielding to a hypoelliptic equation. From the phenomenological viewpoint, this system is particularly rich. It shows a number of different regimes as parameters are varied, and in particular, as a function of the connectivity level: the system goes from a non-trivial stationary regime in which several stationary solutions may exist for strong coupling, to periodic solutions, and eventually to a unique stationary solution for weak coupling. This is illustrated in section 3.6, in particular, we present some numerical results of (3.1.1) for a large number of interacting neurons.

In order to rigorously analyse equation (3.1.2), we restrict ourself to the latter regime, and we shall demonstrate the existence, uniqueness and stability of solutions to the McKean-Vlasov equation in the limit of weak coupling. More precisely, we shall prove existence of solution and non trivial stationary solution to the evolution equation (3.1.2) without restriction on the connectivity coefficient  $\varepsilon > 0$ , and next uniqueness of the stationary solution and its exponential NL stability in the small excitability regime.

### 3.1.1 Historical overview of macroscopic and kinetic models in neuroscience

As mentioned above, the problem we study lies within a long tradition of works in the domain of the characterization of macroscopic behaviors in large neuronal networks. First efforts to describe the macroscopic activity of large neuron ensemble can be traced back to the work of Amari, Wilson and Cowan in the 1970s [3, 4, 161, 162], where were introduced heuristically derived equations on the averaged membrane potential of a population of neurons. These models made the assumption that populations interact through a macroscopic variable, the averaged firing rate of the population, assumed to be a sigmoidal transform of the mean voltage. This model has been extremely successful in reproducing a number of macroscopic behaviors in the cortex, one of the most striking being related to pattern formation in the cortex associated to visual hallucinations [53] (see also [22] for a recent review on the subject). The relatively simplicity and good agreement with neurological phenomena motivated to understand the relationship between the dynamics of individual cells activity and macroscopic models.

This has been an important piece of work in the 1990s in the bio-physics community, using simplified (non-excitable) models and specific assumptions on the architecture of the network, including the assumption of sparse and balanced connectivity (the sum of all incoming input vanishes). The sparse connectivity assumption was used by the authors to state that the activity was uncorrelated [1, 5, 26], and resulted in characterizing different neuronal states. Alternative approaches were also developed based on population density [33] methods. These yield complex partial differential equations, that were reduced to a set of moment equations from which authors may deduce the behavior of the system. The validity of these moment reduction and their well-posedness is a complex issue debated in the literature, see e.g. [99]. A transition Markov two-states model governing the firing dynamics of the neurons in the network was recently introduced. In these models, the transition probability of the system, written through a master equation, is then handled using different physics techniques including van Kampen expansions or path integral methods. This modeling recently gathered the interest of the community (see for example [29, 21, 52, 153]).

The mathematical community also undertook the analysis of the problem since the beginning of this decade. In that domain, one can distinguish also two distinct approaches: on one side, the development of mathematical models for simplified or phenomenological neuronal models, and on the other side works on the precise neuronal models. The dynamics of solutions of macroscopic limits of phenomenological neuron models is much more developed. The characterization of the stationary (or periodic) solutions was done in a simplified model, the Wilson-Cowan system, which has the important advantage to yield a Gaussian solution whose mean and standard deviation satisfy a deterministic dynamical system that may be studied analytically [149, 152] using the analysis of ordinary differential equations. Artificial spiking neuronal models representing the discontinuous dynamics of the time to the next spike were analyzed in a number of situations, including construction of periodic solutions to the limit equation in the presence of delays [121, 123, 122]. In the same vein, an important result was demonstrated on integrate-and-fire models in the presence of noise and excitation: it was shown that too much excitation could prevent the existence of solutions for all times, as the firing rate blows up in finite time [32]. These approaches make use of functional analysis of PDEs and nonlocal age-structured type of equations.

### 3.1.2 Organization of the paper

The paper is organized as follows. Section 3.2 summarizes our main results that are demonstrated in the rest of the paper. Section 3.3 is interested with the existence, uniqueness and *a priori* estimates on the solutions to the evolution equation, as well as, the existence of stationary solutions. The next sections prove the stability of the unique stationary solution. Our proof uses factorization of the linearized semigroup allowing to prove linear stability, which we complete in section 3.5 by an analysis of the nonlinear stability of the stationary solution. Along the way, a number of open problems were identified beyond the small connectivity regime treated here that we present in section 3.6 together with numerical simulations: we will observe that the stationary solution splits into two stable stationary solutions as connectivity is increased, and in an intermediate regime, periodic solutions emerge. Two appendices

complete the paper. Appendix 3.7 investigates the microscopic system and its convergence towards the mean-field equation (3.1.2) and Appendix 3.8 deals with the strict positivity of stationary solutions.

## 3.2 Summary of the main results ---

### 3.2.1 Functional spaces and norms

We start by introducing the functional framework in which we work throughout the paper. For any exponent  $p \in [1, \infty]$  and any nonnegative weight function  $\omega$ , we denote by  $L^p(\omega)$  the Lebesgue space  $L^p(\mathbb{R}^2; \omega dx dv)$  and for  $k \in \mathbb{N}$  the corresponding Sobolev spaces  $W^{k,p}(\mathbb{R}^2; \omega dx dv)$ . They are associated to the norms

$$\|f\|_{L^p(\omega)} = \|f\omega\|_{L^p}, \quad \|f\|_{W^{k,p}(\omega)}^p = \|f\|_{L^p(\omega)}^p + \sum_{j=1}^k \|D_{x,v}^j f\|_{L^p(\omega)}^p.$$

For  $k \geq 1$ , we define the partial  $v$ -derivative space  $W_v^k(\omega)$  by

$$W_v^k(\omega) := \{f \in W^{k-1,p}(\omega); D_v^k f \in L^p(\omega)\},$$

and it is natural to associate them to the norm

$$\|f\|_{W_v^k(\omega)}^p = \|f\|_{W^{k-1,p}(\omega)}^p + \|D_v^k f\|_{L^p(\omega)}^p.$$

A particularly important space in our analysis, denoted by  $H_v^2(\omega)$ , is

$$H_v^2(\omega) = W_v^{2,2}(\omega) = \{f \in H^1(\omega) \text{ such that } \partial_{vv}^2 f \in L^2(\omega)\},$$

together with the set of functions with finite entropy

$$L^1 \log L^1 := \left\{ f \in L^1(\mathbb{R}^2) \text{ such that } f \geq 0 \text{ and } \mathcal{H}(f) < \infty \right\},$$

where we use the classical notation  $\mathcal{H}(f) := \int_{\mathbb{R}^2} f \log f$ . Finally, for  $\kappa > 0$ , let us introduce the exponential weight function:

$$m = e^{\kappa(M-1)} \quad \text{with} \quad M := 1 + x^2/2 + v^2/2. \tag{3.2.6}$$

In the sequel, we will be brought to vary the constant  $\kappa$  involved in the definition of  $m$ , therefore we introduce the shorthand  $m_i = e^{\kappa_i(M-1)}$ ,  $i \in \mathbb{N}$ . Unless otherwise specified, these sequences are constructed under the assumption that the sequence  $\kappa_i$  is strictly increasing.

### 3.2.2 Main results

We start by stating a result related to the well posedness of (3.1.2) and to the *a priori* bounds on the solution. Using classical theory of renormalized solutions, it is not hard to see that equation (3.1.2) has indeed *weak solutions*, which we naturally define as:

**Definition 3.2.44.** Let  $f_0$  be a normalized nonnegative function defined on  $\mathbb{R}^2$  such that  $\mathcal{J}(f_0)$  is well defined. We say that  $f_t(x, v) := (t, x, v) \mapsto f(t, x, v)$  is a weak solution to (3.1.2) if the following conditions are fulfilled:

- $f \in C([0, \infty); L^1(M^2))$ ;
- for almost any  $t \geq 0$ ,  $f \geq 0$  and

$$\int_{\mathbb{R}^2} f(t, x, v) dx dv = \int_{\mathbb{R}^2} f_0(x, v) dx dv = 1;$$

- for any  $\varphi \in C^1([0, \infty); C_c^\infty(\mathbb{R}^2))$  and any  $t \geq 0$  it holds

$$\int_{\mathbb{R}^2} \varphi f_t = \int_{\mathbb{R}^2} \varphi f_0 + \int_0^t \int_{\mathbb{R}^2} [\partial_t \varphi + \partial_{vv}^2 \varphi - A \partial_x \varphi - B_\varepsilon(\mathcal{J}(f_s)) \partial_v \varphi] f_s. \quad (3.2.7)$$

Equipped with this definition we can state the

**Theorem 3.2.45.** For any  $f_0 \in L^1(M^2) \cap L^1 \log L^1 \cap \mathbb{P}(\mathbb{R}^2)$ , there exists a unique global weak solution  $f_t$  to the FhN equation (3.1.2), that moreover satisfies

$$\|f_t\|_{L^1(M)} \leq \max(C_0, \|f_0\|_{L^1(M)}), \quad (3.2.8)$$

and depends continuously in  $L^1(M)$  to the initial datum. More precisely, if  $f_{n,0} \rightarrow f_0$  in  $L^1(M)$  and  $\mathcal{H}(f_{n,0}) \leq C$  then  $f_{n,t} \rightarrow f_t$  in  $L^1(M)$  for any later time  $t \geq 0$ .

Furthermore, there exist two norms  $\|\cdot\|_{\mathcal{H}^1}$  and  $\|\cdot\|_{\mathcal{H}_v^2}$  equivalent respectively to  $\|\cdot\|_{H^1(m)}$  and  $\|\cdot\|_{H_v^2(m)}$ , such that the following estimates hold true:

$$\|f_t\|_{L^1(m)} \leq \max(C_1, \|f_0\|_{L^1(m)}), \quad (3.2.9)$$

as well as

$$\|f_t\|_{\mathcal{H}^1} \leq \max(C_2, \|f_0\|_{\mathcal{H}^1}), \quad (3.2.10)$$

and

$$\|f_t\|_{\mathcal{H}_v^2} \leq \max(C_3, \|f_0\|_{\mathcal{H}_v^2}), \quad (3.2.11)$$

where  $C_1, C_2, C_3$  are positive constants.

The other two main results of the present work can be summarized in the following

**Theorem 3.2.46.** For any  $\varepsilon \geq 0$ , there exists at least one stationary solution  $G_\varepsilon$  to the FhN statistical equation (3.1.2), that is

$$G_\varepsilon \in H_v^2(m) \cap \mathbb{P}(\mathbb{R}^2), \quad 0 = \partial_x (A G_\varepsilon) + \partial_v (B_\varepsilon(\mathcal{J}_{G_\varepsilon}) G_\varepsilon) + \partial_{vv}^2 G_\varepsilon \quad \text{in } \mathbb{R}^2. \quad (3.2.12)$$

Moreover, there exists an increasing function  $\eta : \mathbb{R}_+ \rightarrow \mathbb{R}$  such that  $\eta(\varepsilon) \xrightarrow{\varepsilon \rightarrow 0} 0$  and such that any solution to (3.2.12) satisfies

$$\|G - G_0\|_{L^2(m)} \leq \eta(\varepsilon),$$

where  $G_0$  is the unique stationary solution corresponding to the case  $\varepsilon = 0$ .

**Theorem 3.2.47.** *There exists  $\varepsilon^* > 0$  such that, in the small connectivity regime  $\varepsilon \in (0, \varepsilon^*)$ , the stationary solution is unique and exponentially stable. More precisely, there exist  $\alpha^* < 0$  and  $\eta^*(\varepsilon) : \mathbb{R}_+ \rightarrow \mathbb{R}$ , with  $\eta^*(\varepsilon) \xrightarrow{\varepsilon \rightarrow 0} \infty$ , such that if*

$$f_0 \in H^1(m) \cap \mathbb{P}(\mathbb{R}^2) \quad \text{and} \quad \|f_0 - G\|_{H^1(m)} \leq \eta^*(\varepsilon),$$

*then there exists  $C^* = C^*(f_0, \varepsilon^*, \varepsilon) > 0$ , such that*

$$\|f_t - G\|_{L^2(m)} \leq C^* e^{\alpha^* t}, \quad \forall t \geq 0,$$

*where  $f_t$  is the solution to (3.1.2) with initial condition  $f_0$ .*

### 3.2.3 Other notations and definitions.

We prepare to the demonstration of these results by introducing a few notations that will be used throughout the paper. For two given Banach spaces  $(E, \|\cdot\|_E)$  and  $(\mathcal{E}, \|\cdot\|_{\mathcal{E}})$ , we denote by  $\mathcal{B}(E, \mathcal{E})$  the space of bounded linear operators from  $E$  to  $\mathcal{E}$  and we denote by  $\|\cdot\|_{\mathcal{B}(E, \mathcal{E})}$  the associated operator norm. The set of closed unbounded linear operators from  $E$  to  $\mathcal{E}$  with dense domain is denoted by  $\mathcal{C}(E, \mathcal{E})$ . In the special case when  $E = \mathcal{E}$ , we simply write  $\mathcal{B}(E) = \mathcal{B}(E, E)$  and  $\mathcal{C}(E) = \mathcal{C}(E, E)$ .

For a given  $\alpha \in \mathbb{R}$ , we define the complex half plane

$$\Delta_\alpha := \{z \in \mathbb{C}, \quad \operatorname{Re}(z) > \alpha\}.$$

For a given Banach space  $X$  and  $\Lambda \in \mathcal{C}(X)$  which generates a semigroup, we denote by  $(S_\Lambda(t), t \geq 0)$  this one, by  $D(\Lambda)$  its domain, by  $N(\Lambda)$  its null space, by  $R(\Lambda)$  its range, and by  $\Sigma(\Lambda)$  its spectrum. On the resolvent set  $\rho(\Lambda) = \mathbb{C} \setminus \Sigma(\Lambda)$  we may define the resolvent operator  $\rho(\Lambda)$  by

$$\forall z \in \mathbb{C}, \quad \mathcal{R}_\Lambda(z) := (\Lambda - z)^{-1}.$$

Moreover,  $\mathcal{R}_\Lambda(z) \in \mathcal{B}(X)$  and has range equal to  $D(\Lambda)$ . We recall that  $\xi \in \Sigma(\Lambda)$  is called an eigenvalue of  $\Lambda$  if  $N(\Lambda - \xi) \neq \{0\}$ , and it called an isolated eigenvalue if there exists  $r > 0$  such that

$$\Sigma(\Lambda) \cap \{z \in \mathbb{C}, |z - \xi| < r\} = \{\xi\}.$$

Since the notion of convolution of semigroups will be required, we recall it here. Let us consider some Banach spaces  $X_1, X_2$  and  $X_3$  and two given functions

$$S_1 \in L^1([0, \infty); \mathcal{B}(X_1, X_2)) \quad \text{and} \quad S_2 \in L^1([0, \infty); \mathcal{B}(X_2, X_3)),$$

one can define  $S_2 * S_1 \in L^1([0, \infty); \mathcal{B}(X_1, X_3))$  by

$$(S_2 * S_1)(t) := \int_0^t S_2(t-s) S_1(s) ds, \quad \forall t \geq 0.$$

In the special case  $S_1 = S_2$  and  $X_1 = X_2 = X_3$ ,  $S^{(*n)}$  is defined recursively by  $S^{(*1)} = S$  and  $S^{(*n)} = S * S^{(*(n-1))}$  for  $n > 1$ . Equipped with this definition, we state the

**Proposition 3.2.48.** *Let  $X, Y$  be two Banach spaces such that  $Y \subset X$ . Let us consider  $S(t)$  a continuous semigroup such that for all  $t \geq 0$*

$$\|S(t)f\|_{\mathcal{B}(\mathcal{X})} \leq C_{\mathcal{X}} e^{\alpha^* t}, \quad \mathcal{X} \in \{X, Y\},$$

*for some  $\alpha^* \in \mathbb{R}$  and positive constants  $C_X$  and  $C_Y$ . If there exists  $\Theta > 0$  and  $C_{X,Y} > 0$  such that*

$$\|S(t)f\|_Y \leq C_{X,Y} t^{-\Theta} e^{\alpha^* t} \|f\|_X, \quad \forall f \in Y, t \in (0, 1],$$

*then, there exists  $n \in \mathbb{N}$ , and a polynomial  $p_n(t)$  such that*

$$\|S^{(*n)}(t)f\|_Y \leq p_n(t) e^{\alpha^* t} \|f\|_X, \quad \forall f \in Y, t > 0. \quad (3.2.13)$$

*In particular, for any  $\alpha > \alpha^*$ , it holds*

$$\|S^{(*n)}(t)f\|_Y \leq C_{\alpha,n} e^{\alpha t} \|f\|_X, \quad \forall f \in Y, t > 0,$$

*for some positive constant  $C_{\alpha,n}$ .*

This general result has been already established and used in [70] and [110], but we give an alternative, and somehow simpler, proof of it.

*Proof.* Let us start by noticing that for  $\mathcal{X} \in \{X, Y\}$ , if

$$\|S^{(*n)}(t)f\|_{\mathcal{X}} \leq p_n^{\mathcal{X}}(t) e^{\alpha^* t} \|f\|_{\mathcal{X}}, \quad \forall t \geq 0, \quad (3.2.14)$$

for  $n \in \mathbb{N}$  and  $p_n^{\mathcal{X}}(t)$  a polynomial, then

$$\|S^{(*n+1)}(t)f\|_{\mathcal{X}} \leq \int_0^t \|S(t-s)S^{(*n)}(s)f\|_{\mathcal{X}} ds \leq p_{n+1}^{\mathcal{X}}(t) e^{\alpha^* t} \|f\|_{\mathcal{X}},$$

for  $p_{n+1}^{\mathcal{X}} = C_{\mathcal{X}} \int_0^t p_n^{\mathcal{X}}(s) ds$ . So, by an immediate induction argument we get (3.2.14) for any  $n \geq 1$  and  $p_n^{\mathcal{X}}(t) := \frac{C_{\mathcal{X}}^n t^{n-1}}{(n-1)!}$ .

Let us now fix  $t \in (0, 1]$  and, without loss of generality, assume that  $\Theta \notin \mathbb{N}$ . In that case, if

$$\|S^{(*n)}(t)f\|_Y \leq C_n t^{-(\Theta-n+1)} e^{\alpha^* t} \|f\|_X, \quad \forall t \in (0, 1], \quad (3.2.15)$$

for some  $n \in \mathbb{N}$  and  $C_n$  a positive constant, then

$$\begin{aligned} \|S^{(*n+1)}(t)f\|_Y &\leq \int_0^{t/2} \|S(t-s)S^{(*n)}(s)f\|_Y ds + \int_{t/2}^t \|S(t-s)S^{(*n)}(s)f\|_Y ds \\ &\leq \int_0^{t/2} C_{X,Y} (t-s)^{-\Theta} e^{\alpha^*(t-s)} \|S^{(*n)}(s)f\|_X ds + \int_{t/2}^t C_Y e^{\alpha^*(t-s)} \|S^{(*n)}(s)f\|_Y ds \\ &\leq \int_0^{t/2} C_{X,Y} (t-s)^{-\Theta} e^{\alpha^* t} p_n^X(s) \|f\|_X ds + \int_{t/2}^t C_Y e^{\alpha^* t} C_n s^{-(\Theta-n+1)} \|f\|_X ds \\ &\leq \frac{C_{X,Y} C_X^n}{(n-1)!} e^{\alpha^* t} \|f\|_X \int_0^{t/2} (t-s)^{-\Theta} s^{n-1} ds + C_Y C_n e^{\alpha^* t} \|f\|_X \int_{t/2}^t s^{-(\Theta-n+1)} ds \\ &\leq C_{n+1} t^{-(\Theta-n)} e^{\alpha^* t} \|f\|_X, \end{aligned}$$

for some  $C_{n+1}$  depending only on  $C_X, C_Y, C_{X,Y}$  and  $C_n$ . Once again, by an induction argument, we get (3.2.15). Moreover, as soon as  $\Theta - n + 1 > 0$ , inequality (3.2.13) holds.



Finally, to get the conclusion in the case  $t > 1$ , it suffices to notice that

$$\|S(t)f\|_Y \leq C_Y C_{X,Y} (t - [t])^{-\Theta} e^{\alpha^* t} \|f\|_X,$$

where  $[t]$  is the largest integer smaller than  $t$ . A similar argument that the one used for  $t \in (0, 1]$ , allows us to find a polynomial  $p_n$  such that (3.2.13) still holds when  $t > 1$ .  $\square$

Finally, we recall the abstract notion of *hypodissipative operators*:

**Definition 3.2.49.** *Considering a Banach space  $(X, \|\cdot\|_X)$ , a real number  $\alpha \in \mathbb{R}$  and an operator  $\Lambda \in \mathcal{C}(X)$ ,  $(\Lambda - \alpha)$  is said to be hypodissipative on  $X$  if there exists some norm  $\|\cdot\|_X$  on  $X$  equivalent to the usual norm  $\|\cdot\|_X$  such that*

$$\forall f \in D(\Lambda), \quad \exists \phi \in F(f) \quad \text{such that} \quad \operatorname{Re}\langle \phi, (\Lambda - \alpha)f \rangle \leq 0,$$

where  $\langle \cdot, \cdot \rangle$  is the duality bracket in  $X$  and  $X^*$  and  $F(f) \subset X^*$  is the dual set of  $f$  defined by

$$F(f) = F_{\|\cdot\|_X}(f) := \{\phi \in X^*, \quad \langle \phi, f \rangle = \|f\|_X^2 = \|\phi\|_{X^*}^2\}.$$

One classically sees (we refer to for example [70, Subsection 2.3]) that when  $\Lambda$  is the generator of a semigroup  $S_\Lambda$ , for given  $\alpha \in \mathbb{R}$  and  $C > 0$  constants, the following assertions are equivalent:

- (a)  $(\Lambda - \alpha)$  is hypodissipative;
- (b) the semigroup satisfies the growth estimate  $\|S_\Lambda(t)\|_{\mathcal{B}(X)} \leq Ce^{\alpha t}$ ,  $t \geq 0$ ;

## 3.3 Analysis of the nonlinear evolution equation ---

This section is concerned with the analysis of the nonlinear evolution equation. We shall prove existence and uniqueness of solutions, and provide some *a priori* estimates on their behavior.

Before going into further details, let us remark that for  $\mathcal{J}$  fixed, the operator  $Q_\varepsilon[\mathcal{J}]$  is linear and writes

$$Q_\varepsilon[\mathcal{J}]f = \partial_x(Af) + \partial_v(B_\varepsilon(\mathcal{J})f) + \partial_{vv}^2 f.$$

In particular, for  $g \in H_v^2(m)$  we have

$$\int_{\mathbb{R}^2} (Q_\varepsilon[\mathcal{J}]f)g \, dv dx = - \int_{\mathbb{R}^2} f (A \partial_x g + B_\varepsilon(\mathcal{J}) \partial_v g - \partial_{vv}^2 g) \, dv dx,$$

therefore, it is natural to define

$$Q_\varepsilon^*[\mathcal{J}]g := -A \partial_x g - B_\varepsilon(\mathcal{J}) \partial_v g + \partial_{vv}^2 g.$$

### 3.3.1 A priori bounds.

We now fix  $\varepsilon_0 > 0$ . The a priori estimates that follow are uniform in  $\varepsilon$  in the bounded connectivity regime  $\varepsilon \in [0, \varepsilon_0)$ , i.e., they involve constants that do not depend on  $\varepsilon$ .

**Lemma 3.3.50.** For  $f_t$  solution to (3.1.2) with  $f_0 \in L^1(M) \cap \mathbb{P}(\mathbb{R}^2)$ , estimate (3.2.8) holds. Moreover, there exists  $C'_0 > 0$  depending on  $a, b, \lambda, I_0, \varepsilon_0$  and  $\|f_0\|_{L^1(M)}$  such that

$$\sup_{t \geq 0} |\mathcal{J}(f_t)| < C'_0. \quad (3.3.16)$$

*Proof.* We first apply Cauchy-Schwartz's inequality to find

$$|\mathcal{J}(f)| \leq \int_{\mathbb{R}^2} |v| f \leq \left( \int_{\mathbb{R}^2} f \right)^{1/2} \left( \int_{\mathbb{R}^2} v^2 f \right)^{1/2} = \left( \int_{\mathbb{R}^2} v^2 f \right)^{1/2}, \quad (3.3.17)$$

for any  $f \in \mathbb{P}(\mathbb{R}^2) \cap L^1(v^2)$ . Now, for  $f_t$  a solution to (3.1.2), we have

$$\begin{aligned} \frac{d}{dt} \int_{\mathbb{R}^2} f_t M &= \int_{\mathbb{R}^2} (Q_\varepsilon[\mathcal{J}f_t] f_t) M = \int_{\mathbb{R}^2} f_t (Q_\varepsilon^*[\mathcal{J}f_t] M) \\ &= \int_{\mathbb{R}^2} (1 - Ax - B_\varepsilon(\mathcal{J}f_t)v) f_t. \end{aligned}$$

Using the definition of  $A$  and  $B_\varepsilon$ , and then (3.3.17), we get

$$\begin{aligned} \frac{d}{dt} \int_{\mathbb{R}^2} f_t M dx dv &\leq - \int_{\mathbb{R}^2} \left( -1 + ax^2 - bxv + v^2(v - \lambda)(v - 1) - \varepsilon v^2 + xv + I_0 v \right) f_t + \varepsilon \mathcal{J}(f_t)^2 \\ &\leq K_1 - K_2 \int_{\mathbb{R}^2} (v^4 + x^2) f_t + \varepsilon \int_{\mathbb{R}^2} v^2 f_t \\ &\leq K_1 - K_2 \int_{\mathbb{R}^2} f_t M dx dv, \end{aligned}$$

where  $K_1$  and  $K_2$  are generic constants depending only on  $a, b, \lambda, I_0$  and  $\varepsilon_0$ . Using Gronwall's lemma we get (3.2.8) for some  $C_0 > 0$ . Finally, coming back to (3.3.17), we get

$$|\mathcal{J}(f_t)|^2 \leq \int_{\mathbb{R}^2} v^2 f_t \leq 2 \|f_t\|_{L^1(M)} \leq 2 \max(C_0, \|f_0\|_{L^1(M)}),$$

which is nothing but (3.3.16).  $\square$

**Lemma 3.3.51.** For any  $\mathcal{J} \in \mathbb{R}$  fixed, there exist some constants  $K_1, K_2 > 0$  depending on  $a, b, \lambda, I_0, \mathcal{J}, \kappa$  and  $\varepsilon_0$  such that

$$\int_{\mathbb{R}^2} Q_\varepsilon[\mathcal{J}] f \cdot \text{sign}(f) m \leq K_1 \|f\|_{L^1(\mathbb{R}^2)} - K_2 \|f\|_{L^1(m)}, \quad \forall f \in L^1(m). \quad (3.3.18)$$

*Proof.* Since  $\mathcal{J} \in \mathbb{R}$  is now fixed, for simplicity of notation, we drop the dependence on this parameter. By Kato's inequality

$$\begin{aligned} \int_{\mathbb{R}^2} Q_\varepsilon f \cdot \text{sign}(f) m &\leq \int_{\mathbb{R}^2} |f| Q_\varepsilon^* m \\ &= -\kappa \int_{\mathbb{R}^2} |f| (Ax + B_\varepsilon v - (1 + \kappa v^2)) m, \end{aligned}$$

thus

$$\int_{\mathbb{R}^2} Q_\varepsilon f \cdot \text{sign}(f) m \leq - \int_{\mathbb{R}^2} p(x, v) |f| m,$$

where  $p(x, v)$  is a polynomial on  $x$  and  $v$  with leading term  $v^4 + x^2$ . Inequality (3.3.18) follows directly.  $\square$

**Corollary 3.3.52.** Estimate (3.2.9) holds.

*Proof.* For  $f_t$  solution to (3.1.2), inequality (3.3.16) tells us that  $|\mathcal{J}(f_t)| \leq C'_0$ . Moreover, since the mass is unitary for almost any  $t \geq 0$ , it holds

$$\frac{d}{dt} \int_{\mathbb{R}^2} |f_t| m = \int_{\mathbb{R}^2} Q_\varepsilon[\mathcal{J}_{f_t}] f_t \cdot \text{sign}(f_t) m \leq K_1 - K_2 \int_{\mathbb{R}^2} |f_t| m,$$

where  $K_1$  and  $K_2$  depend only on  $a, b, \lambda, I, \varepsilon_0$  and  $C'_0$ . Finally, integrating this last inequality, we get

$$\|f_t\|_{L^1(m)} \leq \max(C_1, \|f_0\|_{L^1(m)}), \quad \forall t \geq 0,$$

for some positive constant  $C_1$  depending only on the parameters of the system,  $\varepsilon_0$  and  $C'_0$ .  $\square$

Now we analyse the  $H^1(m)$  and  $H_v^2(m)$  norms of the solutions to (3.1.2), in particular, we prove a priori bounds (3.2.10) and (3.2.11). Since the equation is hypodissipative, we used the ideas of “twisted spaces” and the Nash-Villani’s technique (see e.g. [159]) to control the  $L^2(\mathbb{R}^2)$  contributions in function of the  $L^1(\mathbb{R}^2)$  norm.

**Lemma 3.3.53.** *For  $0 < \kappa_1 < \kappa_2$ , let us consider two exponential weight functions  $m_1$  and  $m_2$  as defined in (3.2.6). For any  $\mathcal{J} \in \mathbb{R}$  fixed, there exist  $K_1, K_2 > 0$  and  $\delta \in (0, 1)$  constants such that*

$$\langle Q_\varepsilon[\mathcal{J}] f, f \rangle_{\mathcal{H}^1} \leq K_1 \|f\|_{L^2(\mathbb{R}^2)}^2 - K_2 \|f\|_{\mathcal{H}^1}^2, \quad \forall f \in H^1(m_2), \quad (3.3.19)$$

where  $\langle \cdot, \cdot \rangle_{\mathcal{H}^1}$  is the scalar product related to the Hilbert norm

$$\|f\|_{\mathcal{H}^1}^2 := \|f\|_{L^2(m_2)}^2 + \delta^{3/2} \|\partial_x f\|_{L^2(m_2)}^2 + \delta^{4/3} \langle \partial_x f, \partial_v f \rangle_{L^2(m_1)} + \delta \|\partial_v f\|_{L^2(m_2)}^2.$$

**Remark 3.3.54.** *It is worth emphasising that for  $\delta \in (0, 1)$  the norm  $\mathcal{H}^1$  is equivalent to the usual norm of  $H^1(m_2)$ . Indeed, the choice of the exponents allows us to write*

$$c_\delta \|f\|_{\mathcal{H}^1}^2 \leq \|f\|_{L^2(m_2)}^2 + \left( \delta^{3/2} - \frac{\delta^{5/3}}{2} \right) \|\partial_x f\|_{L^2(m_2)}^2 + \frac{\delta}{2} \|\partial_v f\|_{L^2(m_2)}^2 \leq \|f\|_{\mathcal{H}^1}^2,$$

for some  $c_\delta > 0$ .

*Proof.* The proof is presented as follows: the first three steps deal with inequalities in  $L^2$  for  $f$  and its derivatives, while the last one combines these inequalities to control the  $\mathcal{H}^1$  norm. Some long and tedious calculations are only outlined for the sake of clarity. In the following we denote by  $k_0, k_1$  and  $k_2$  some unspecified constants and drop the dependance on  $\mathcal{J}$ .

*Step 1.  $L^2(m_2)$  norm.* We start by noticing that

$$\begin{aligned} \langle \partial_{vv}^2 f, f \rangle_{L^2(m_2)} &= - \int_{\mathbb{R}^2} (\partial_v f)^2 m_2^2 + \kappa_2 \int_{\mathbb{R}^2} (1 + 2\kappa_2 v^2) f^2 m_2^2. \\ \langle \partial_x(Af), f \rangle_{L^2(m_2)} &= \frac{1}{2} \int_{\mathbb{R}^2} \left[ \partial_x A - A \frac{\partial_x m_2^2}{m_2^2} \right] f^2 m_2^2 = \frac{1}{2} \int_{\mathbb{R}^2} [a - 2\kappa_2 x(ax - bv)] f^2 m_2^2, \end{aligned}$$

and similarly

$$\langle \partial_v(B_\varepsilon f), f \rangle_{L^2(m_2)} = \frac{1}{2} \int_{\mathbb{R}^2} [3v^2 - 2(1 + \lambda)v + \lambda - \varepsilon - 2\kappa_2 v B_\varepsilon] f^2 m_2^2.$$

Therefore, we get

$$\langle Q_\varepsilon f, f \rangle_{L^2(m_2)} = - \int_{\mathbb{R}^2} p(x, v) f^2 m_2^2 - \|\partial_v f\|_{L^2(m_2)}^2, \quad (3.3.20)$$

where  $p(x, v)$  is a polynomial in  $x$  and  $v$  with leading term  $v^4 + x^2$ . In particular, there exist some positive constants  $k_1$  and  $k_2$  such that

$$\langle Q_\varepsilon f, f \rangle_{L^2(m_2)} \leq k_1 \|f\|_{L^2(\mathbb{R}^2)}^2 - k_2 \|f\|_{L^2(M^{1/2}m_2)}^2 - \|\partial_v f\|_{L^2(m_2)}^2. \quad (3.3.21)$$

*Step 2.  $x$ -derivative bound.* We have

$$\begin{aligned} \langle \partial_x(\partial_x(Af)), \partial_x f \rangle_{L^2(m_2)} &= \frac{1}{2} \int_{\mathbb{R}^2} \left[ 3 \partial_x A - A \frac{\partial_x m_2^2}{m_2^2} \right] (\partial_x f)^2 m_2^2 \\ &= \frac{1}{2} \int_{\mathbb{R}^2} [3a - 2\kappa_2 x(ax - bv)] (\partial_x f)^2 m_2^2, \end{aligned}$$

and

$$\langle \partial_x(\partial_v(B_\varepsilon f)), \partial_x f \rangle_{L^2(m_2)} = \int_{\mathbb{R}^2} [\partial_v B_\varepsilon \partial_x f + \partial_x B_\varepsilon \partial_v f + B_\varepsilon \partial_{xv}^2 f] \partial_x f m_2^2.$$

Since  $\partial_x B_\varepsilon = 1$ , and observing that

$$\int_{\mathbb{R}^2} [\partial_v B_\varepsilon \partial_x f + B_\varepsilon \partial_{xv}^2 f] \partial_x f m_2^2 = \frac{1}{2} \int_{\mathbb{R}^2} \left[ \partial_v B_\varepsilon - B_\varepsilon \frac{\partial_v m_2^2}{m_2^2} \right] (\partial_x f)^2 m_2^2,$$

we get

$$\langle \partial_x(\partial_v(B_\varepsilon f)), \partial_x f \rangle_{L^2(m_2)} \leq \int_{\mathbb{R}^2} |\partial_x f| |\partial_v f| m_2^2 + \frac{1}{2} \int_{\mathbb{R}^2} \left[ \partial_v B_\varepsilon - B_\varepsilon \frac{\partial_v m_2^2}{m_2^2} \right] (\partial_x f)^2 m_2^2.$$

Using that

$$\langle \partial_x \partial_{vv}^2 f, \partial_x f \rangle_{L^2(m_2)} = - \int_{\mathbb{R}^2} |\partial_{xv}^2 f|^2 m_2^2 + \frac{1}{2} \int_{\mathbb{R}^2} (\partial_x f)^2 \partial_{vv}^2 m_2^2.$$

we finally obtain

$$\begin{aligned} \langle \partial_x(Q_\varepsilon f), \partial_x f \rangle_{L^2(m_2)} &\leq k_1 \|\partial_x f\|_{L^2(\mathbb{R}^2)}^2 - k_2 \|\partial_x f\|_{L^2(M^{1/2}m_2)}^2 \\ &\quad - \|\partial_{xv}^2 f\|_{L^2(m_2)}^2 + \int_{\mathbb{R}^2} |\partial_x f| |\partial_v f| m_2^2. \end{aligned} \quad (3.3.22)$$

A similar calculation leads to

$$\begin{aligned} \langle (\partial_v Q_\varepsilon f), \partial_v f \rangle_{L^2(m_2)} &\leq k_1 \|\partial_v f\|_{L^2(\mathbb{R}^2)}^2 - k_2 \|\partial_v f\|_{L^2(M^{1/2}m_2)}^2 \\ &\quad - \|\partial_{vv}^2 f\|_{L^2(m_2)}^2 + b \int_{\mathbb{R}^2} |\partial_x f| |\partial_v f| m_2^2 \\ &\quad + 2\kappa_2(1 + \lambda) \int_{\mathbb{R}^2} v f^2 m_2^2. \end{aligned} \quad (3.3.23)$$

*Step 3. Cross product bound.* The contribution of the cross product term is a little bit more delicate. We decompose it into five quantities and we study them separately:

$$\begin{aligned} &\langle \partial_x Q_\varepsilon f, \partial_v f \rangle_{L^2(m_1)} + \langle \partial_v Q_\varepsilon f, \partial_x f \rangle_{L^2(m_1)} \\ &= \int_{\mathbb{R}^2} [(\partial_x f)(\partial_{vvv}^3 f) + (\partial_v f)(\partial_{xvv}^3 f)] m_1^2 \\ &\quad + \int_{\mathbb{R}^2} [\partial_x A \partial_v f + \partial_v A \partial_x f + A \partial_{vx}^2 f] (\partial_x f) m_1^2 \\ &\quad + \int_{\mathbb{R}^2} [\partial_{vv}^2 B f + 2\partial_v B \partial_v f + B \partial_{vv}^2 f] (\partial_x f) m_1^2 \\ &\quad + \int_{\mathbb{R}^2} [2\partial_x A \partial_x f + A \partial_{xx}^2 f] (\partial_v f) m_1^2 \\ &\quad + \int_{\mathbb{R}^2} [\partial_v B \partial_x f + \partial_x B \partial_v f + B \partial_{xv}^2 f] (\partial_v f) m_1^2 =: \sum_{i=1}^5 \mathcal{T}_i. \end{aligned}$$

We start by handling the first term on the right hand side. Using integration by parts adequately, we get

$$\mathcal{T}_1 = \int_{\mathbb{R}^2} (\partial_x f)(\partial_v f) \partial_{vv}^2 m_1^2 - 2 \int_{\mathbb{R}^2} (\partial_{xv}^2 f)(\partial_{vv}^2 f) m_1^2.$$

Similarly, for the contributions involving  $A$ , we have

$$\mathcal{T}_2 = \frac{1}{2} \int_{\mathbb{R}^2} \left[ \partial_v A - A \frac{\partial_v m_1^2}{m_1^2} \right] (\partial_x f)^2 m_1^2 + a \int_{\mathbb{R}^2} (\partial_x f)(\partial_v f) m_1^2,$$

and

$$\mathcal{T}_4 = \int_{\mathbb{R}^2} \left[ \partial_x A - A \frac{\partial_x m_1^2}{m_1^2} \right] (\partial_x f)(\partial_v f) m_1^2 + \frac{1}{2} \int_{\mathbb{R}^2} \partial_v [A m_1^2] (\partial_x f)^2.$$

Adding these last two expressions, it only remains

$$\int_{\mathbb{R}^2} \partial_v A (\partial_x f)^2 m_1^2 + \int_{\mathbb{R}^2} \left[ 2a - A \frac{\partial_x m_1^2}{m_1^2} \right] (\partial_x f)(\partial_v f) m_1^2 \leq -b \|\partial_x f\|_{L^2(m_1)}^2 + k_0 \int_{\mathbb{R}^2} |\partial_x f| |\partial_v f| M m_1^2,$$

for some constant  $k_0 > 0$ .

For the contributions related to  $B_\varepsilon$ , involved in  $\mathcal{T}_3$  and  $\mathcal{T}_5$ , we have

$$\mathcal{T}_3 = - \int_{\mathbb{R}^2} 2\kappa_1 x (3v - 1 - \lambda) f^2 m_1^2 + 2 \int_{\mathbb{R}^2} \partial_v B_\varepsilon (\partial_x f)(\partial_v f) m_1^2 + \int_{\mathbb{R}^2} B_\varepsilon (\partial_{vv}^2 f)(\partial_x f) m_1^2,$$

and

$$\mathcal{T}_5 = \int_{\mathbb{R}^2} \partial_v B_\varepsilon (\partial_x f)(\partial_v f) m_1^2 + \frac{1}{2} \int_{\mathbb{R}^2} \left[ \partial_x B_\varepsilon - B_\varepsilon \frac{\partial_x m_1^2}{m_1^2} \right] (\partial_v f)^2 m_1^2,$$

Finally, for the last contribution in  $\mathcal{T}_3$ , we have

$$\int_{\mathbb{R}^2} B_\varepsilon (\partial_{vv}^2 f)(\partial_x f) m_1^2 \leq k_0 \int_{\mathbb{R}^2} (\partial_{vv}^2 f)(\partial_x f) M^{3/2} m_1^2,$$

getting that there exists  $k_0 > 0$  such that

$$\begin{aligned} & \langle \partial_x Q_\varepsilon f, \partial_v f \rangle_{L^2(m_1)} + \langle \partial_v Q_\varepsilon f, \partial_x f \rangle_{L^2(m_1)} \\ & \leq k_0 \int_{\mathbb{R}^2} |\partial_x f| |\partial_v f| M m_1^2 + k_0 \int_{\mathbb{R}^2} |\partial_{xv}^2 f| |\partial_{vv}^2 f| m_1^2 \\ & \quad - b \|\partial_x f\|_{L^2(m_1)}^2 + k_0 \int_{\mathbb{R}^2} |\partial_{vv}^2 f| |\partial_x f| M^{3/2} m_1^2 \\ & \quad + k_0 \int_{\mathbb{R}^2} |\partial_v f|^2 M^2 m_1^2 + k_0 \int_{\mathbb{R}^2} f^2 M m_1^2. \end{aligned} \tag{3.3.24}$$

*Step 4. Conclusion.* To get (3.3.19), we just put together (3.3.21), (3.3.22), (3.3.23) and (3.3.24) and we use Young's inequality several times. Indeed, the scalar product  $\langle \cdot, \cdot \rangle_{\mathcal{H}^1}$  applied to any  $f \in H^1(m_2)$  writes

$$\begin{aligned} \langle Q_\varepsilon f, f \rangle_{\mathcal{H}^1} & = \langle Q_\varepsilon f, f \rangle_{L^2(m_2)} \\ & \quad + \delta^{3/2} \langle \partial_x Q_\varepsilon f, \partial_x f \rangle_{L^2(m_2)} + \delta \langle \partial_v Q_\varepsilon f, \partial_v f \rangle_{L^2(m_2)} \\ & \quad + \frac{\delta^{4/3}}{2} \langle \partial_x Q_\varepsilon f, \partial_v f \rangle_{L^2(m_1)} + \frac{\delta^{4/3}}{2} \langle \partial_v Q_\varepsilon f, \partial_x f \rangle_{L^2(m_1)}. \end{aligned}$$

To give an idea of the method, we only explain how to get rid of a few terms. For example, for the positive contribution of (3.3.22), it holds

$$\delta^{3/2} k_1 \|\partial_x f\|_{L^2(\mathbb{R}^2)}^2 + \delta^{3/2} \int |\partial_x f| |\partial_v f| m_2^2 \leq \delta^{3/2} k_1 \|\partial_x f\|_{L^2(\mathbb{R}^2)}^2 + \delta^{7/4} \|\partial_x f\|_{L^2(m_2)}^2 + \delta^{5/4} \|\partial_v f\|_{L^2(m_2)}^2,$$

and for  $\delta > 0$  small enough these terms are annihilated by the quantities

$$-\|\partial_v f\|_{L^2(m_2)}^2 - \delta^{3/2} k_2 \|\partial_x f\|_{L^2(M^{1/2}m_2)}^2 - \frac{\delta^{4/3} b}{2} \|\partial_x f\|_{L^2(m_1)}^2$$

present in the right hand side of (3.3.21), (3.3.22) and (3.3.24).

In (3.3.23), the only delicate contribution is

$$\delta b \int |\partial_x f| |\partial_v f| m_2^2 \leq \frac{\delta^{5/3} b}{2} \|\partial_x f\|_{L^2(m_2)}^2 + \frac{\delta^{1/3} b}{2} \|\partial_v f\|_{L^2(m_2)}^2,$$

but the right hand sides of (3.3.21) and (3.3.22) include

$$-\|\partial_v f\|_{L^2(m_2)}^2 - \delta^{3/2} k_2 \|\partial_x f\|_{L^2(M^{1/2}m_2)}^2,$$

and once again for  $\delta > 0$  small the sum is nonpositive.

The positive part of (3.3.24) is controlled using that  $\kappa_1 < \kappa_2$ . Indeed, in that situation

$$\delta^{4/3} k_0 \int |\partial_{vv}^2 f| |\partial_x f| M^{3/2} m_1^2 \leq \delta^{4/3-1/4} k_0 \|\partial_{vv}^2 f\|_{L^2(m_2)}^2 + \delta^{4/3+1/4} k_0 \|\partial_x f\|_{L^2(m_2)}^2,$$

replacing, if necessary,  $k_0$  by a larger constant. If  $\delta > 0$  is small we get rid of these terms thanks to the presence of

$$-\delta^{3/2} k_2 \|\partial_x f\|_{L^2(M^{1/2}m_2)}^2 - \delta \|\partial_{vv}^2 f\|_{L^2(m_2)}^2,$$

in (3.3.22) and (3.3.23).

All remaining positive contributions can be handled in the same fashion leading to the conclusion that one can find  $K_1, K_2 > 0$  such that

$$\langle Q_\varepsilon f, f \rangle_{\mathcal{H}^1} \leq K_1 \|f\|_{L^2(\mathbb{R}^2)}^2 - K_2 \|f\|_{\mathcal{H}^1}^2.$$

□

**Corollary 3.3.55.** *Estimate (3.2.10) holds.*

*Proof.* Nash's inequality in the 2-dimensional case reads: there exists a constant  $C > 0$ , such that for any  $f \in L^1(\mathbb{R}^2) \cap H^1(\mathbb{R}^2)$ ,

$$\|f\|_{L^2(\mathbb{R}^2)}^2 \leq C \|f\|_{L^1(\mathbb{R}^2)} \|D_{x,v} f\|_{L^2(\mathbb{R}^2)} \leq \frac{C}{2\delta'} \|f\|_{L^1(\mathbb{R}^2)}^2 + \frac{\delta'}{2} \|D_{x,v} f\|_{L^2(\mathbb{R}^2)}^2. \quad (3.3.25)$$

Coming back to the previous lemma, using the equivalence of the norms  $\mathcal{H}^1$  and  $H^1(m_2)$ , together with the fact that a solution  $f_t$  to (3.1.2) is a probability measure, we get that,

$$\frac{d}{dt} \|f_t\|_{\mathcal{H}^1}^2 = \langle Q_\varepsilon[\mathcal{J}_{f_t}] f_t, f_t \rangle_{\mathcal{H}^1} \leq k_1 - k_2 \|f_t\|_{\mathcal{H}^1}^2,$$

for some  $k_1, k_2 > 0$  constants. Finally, integrating in time, we get

$$\|f_t\|_{\mathcal{H}^1} \leq \max(C_2, \|f_0\|_{\mathcal{H}^1}),$$

for some  $C_2 > 0$  depending only on the parameters of the system and the initial condition. □

Let us notice that we can go a little further in the analysis of the regularity of the solutions of (3.1.2). Actually, we can expect that the norm  $H_v^2(m)$  is also bounded. Indeed, there exists  $k_0 > 0$  such that

$$\begin{aligned}
& \langle \partial_{vv}^2 Q_\varepsilon f, \partial_{vv}^2 f \rangle_{L^2(m_2)} \\
&= - \int |\partial_{vvv}^3 f| m_2^2 + \frac{1}{2} \int |\partial_{vv}^2 f|^2 \partial_{vv}^2 m_2^2 \\
&\quad + 2 \int (\partial_v A)(\partial_{vv}^2 f)(\partial_{xv}^2 f) m_2^2 + \frac{1}{2} \int |\partial_{vv}^2 f|^2 \left[ \partial_x A - A \frac{\partial_x m_2^2}{m_2^2} \right] m_2^2 \\
&\quad + \int (\partial_{vvv}^3 B) f (\partial_{vv}^2 f) m_2^2 + 3 \int (\partial_{vv}^2 B)(\partial_v f)(\partial_{vv}^2 f) m_2^2 \\
&\quad + \frac{1}{2} \int |\partial_{vv}^2 f|^2 \left[ 5 \partial_v B_\varepsilon - B_\varepsilon \frac{\partial_v m_2^2}{m_2^2} \right] m_2^2 \\
&\leq k_0 \left[ \int |\partial_{vv}^2 f|^2 + \int |\partial_{xv}^2 f|^2 m_2^2 + \int |f|^2 m_2^2 + \int |\partial_v f|^2 m_2^2 \right].
\end{aligned} \tag{3.3.26}$$

We can therefore state that

**Corollary 3.3.56.** *Estimate (3.2.11) holds.*

*Proof.* The proof follows the same idea already introduced in the proof of Corollary 3.3.55. We consider the norm

$$\|f\|_{\mathcal{H}_v^2}^2 := \|f\|_{\mathcal{H}^1}^2 + \delta^2 \|\partial_{vv}^2 f\|_{L^2(m_2)}^2,$$

and notice that (3.3.21), (3.3.22), (3.3.23) together with (3.3.26) imply that

$$\begin{aligned}
\frac{d}{dt} \|f_t\|_{\mathcal{H}_v^2}^2 &\leq \frac{d}{dt} \|f_t\|_{\mathcal{H}^1}^2 \\
&\quad + 2 \delta^2 k_0 \left[ \int |\partial_{vv}^2 f_t|^2 m_2^2 + \int |\partial_{xv}^2 f_t|^2 m_2^2 + \int |f_t|^2 m_2^2 + \int |\partial_v f_t|^2 m_2^2 \right] \\
&\leq k_1 - k_2 \|f_t\|_{\mathcal{H}_v^2}^2,
\end{aligned}$$

for some  $k_1, k_2 > 0$  depending on some  $\delta > 0$  small and the parameters of the system. Inequality (3.2.11) follows.  $\square$

### 3.3.2 Entropy estimates and uniqueness of the solution

Now we focus our attention on the problem of uniqueness of the solutions to (3.1.2). First, we prove that solutions remain in the space of functions with finite entropy. To that aim, for any positive function  $f$ , we define

$$I_v(f) := \int_{\mathbb{R}^2} \frac{|\partial_v f(x, v)|^2}{f(x, v)} dx dv,$$

which is understood as a *partial Fisher information*. When the previous quantity is not well defined we use the convention  $I_v(f) = +\infty$ . Notice that in any case  $I_v(\cdot) \geq 0$ . Equipped with this definition we can state:

**Lemma 3.3.57.** *For any  $f_0 \in L^1(M) \cap L^1 \log L^1 \cap \mathbb{P}(\mathbb{R}^2)$  we denote by  $f_t$  the associated solution to the FhN statistical equation (3.1.2) with initial condition  $f_0$ . It holds*

$$\sup_{t \in [0, T]} \mathcal{H}(f_t) + \int_0^t I_v(f_s) ds \leq C(T), \tag{3.3.27}$$

where  $C(T)$  depend on  $f_0$  and the coefficients of the problem.

*Proof.* It is well known that for functions with finite moments, the entropy can be bounded from below. Indeed, since

$$r_1 \log r_1 \geq -r_2 + r_1 \log r_2, \quad \forall r_1 \geq 0, r_2 > 0,$$

taking  $r_1 = f(x, v)$  and  $r_2 = e^{-M}$ , it holds

$$0 \geq f \log f \geq -e^{-M} - f M,$$

implying that

$$\mathcal{H}(f_t) \geq - \int_{\mathbb{R}^2} e^{-M} - \int_{\mathbb{R}^2} f_t M \geq -2\pi e^{-1} - \max(C_0, \|f_0\|_{L^1(M)}).$$

On the other hand, for any solution of (3.1.2) with initial datum  $f_0$  there exists a positive constant  $C$ , depending on the parameters of the system,  $\varepsilon_0$  and  $C'_0$ , such that

$$\begin{aligned} \frac{d}{dt} \mathcal{H}(f_t) &= \int (1 + \log(f_t)) Q_\varepsilon[\mathcal{J}_{f_t}] f_t \\ &= -I_v(f_t) + \int (\partial_x A + \partial_v B_\varepsilon(\mathcal{J}_{f_t})) f_t \\ &\leq -I_v(f_t) + C \|f_t\|_{L^1(M)}. \end{aligned}$$

Let us fix  $T > 0$  and take any  $t < T$ , thanks to estimate (3.2.8), we get that

$$\mathcal{H}(f_t) \leq - \int_0^t I_v(f_s) ds + \mathcal{H}(f_0) + C T \max(C_0, \|f_0\|_{L^1(M)}).$$

Since  $\mathcal{H}$  is bounded by below, we get that  $I_v(f_t) \in L^1([0, T])$ . Moreover, taking the supremum on the last relationship, we get

$$\sup_{t \in [0, T]} \mathcal{H}(f_t) \leq \mathcal{H}(f_0) + C T \max(C_0, \|f_0\|_{L^1(M)}).$$

□

**Corollary 3.3.58.** *For any two initial data  $f_0, g_0 \in L^1(M^2) \cap L^1 \log L^1 \cap \mathbb{P}(\mathbb{R}^2)$  the associated solutions  $f$  and  $g$  to the FhN statistical equation (3.1.2), satisfy*

$$\sup_{[0, T]} \|f_t - g_t\|_{L^1(M)} \leq C(T) \|f_0 - g_0\|_{L^1(M)},$$

for some positive  $C(T)$ . In particular, equation (3.1.2) with initial datum in  $L^1(M^2) \cap L^1 \log L^1 \cap \mathbb{P}(\mathbb{R}^2)$  has, at most, one solution.

*Proof of Corollary 3.3.58.* We write

$$\partial_t(f_t - g_t) = Q_\varepsilon[\mathcal{J}(f_t)](f_t - g_t) + \varepsilon \mathcal{J}(f_t - g_t) \partial_v g_t$$

from which we deduce

$$\begin{aligned} \frac{d}{dt} \int_{\mathbb{R}^2} |f_t - g_t| M &\leq K_1 \int_{\mathbb{R}^2} |f_t - g_t| M + \varepsilon |\mathcal{J}(f_t - g_t)| \int_{\mathbb{R}^2} |\partial_v g_t| M \\ &\leq K_1 \int_{\mathbb{R}^2} |f_t - g_t| M + \varepsilon |I(g_t)|^{1/2} \|g_t\|_{L^1(M^2)}^{1/2} \int_{\mathbb{R}^2} |f_t - g_t| M, \end{aligned}$$



where  $K_1$  is the constant introduced in the proof of Lemma 3.3.50. Also, it is not hard to see that

$$\sup_{t \in [0, T]} \|g_t\|_{L^1(M^2)} \leq \|g_0\|_{L^1(M^2)} + 2(K_1 + 1)T \max(C_0, \|g_0\|_{L^1(M)}).$$

The rest of the proof is a direct application of the time integrability of  $I_v(g_t)$  and Gronwall's lemma.  $\square$

Let us finish this section by giving some insights of the proofs of the existence of solutions and stationary solutions to equation (3.1.2) which are, however, classical.

*Proof of Theorem 3.2.45.* Let us consider an exponential weight  $m$  and  $\mathcal{J} \in L^\infty(\mathbb{R}_+)$  such that

$$\sup_{t \geq 0} |\mathcal{J}| \leq C'_0,$$

where  $C'_0$  is given by (3.3.16). First, to avoid the non boundedness of the coefficients of the equation, let us fix  $R > 0$ , and define a regular truncation function

$$\chi_R(x, v) = \chi(x/R, v/R), \quad \chi \in \mathcal{D}(\mathbb{R}^2), \quad \mathbf{1}_{B(0,1)} \leq \chi \leq \mathbf{1}_{B(0,2)}. \quad (3.3.28)$$

Secondly, to avoid the intrinsic degenerate character of (3.1.2), we fix some  $1 > \sigma > 0$ , and define the bilinear form

$$\begin{aligned} a_\sigma(t; f, g) &:= \langle \partial_v f, \partial_v g \rangle_{L^2(m)} + \langle \partial_v f, g \chi_R m^{-2} \partial_v m^2 \rangle_{L^2(m)} \\ &\quad + \sigma \langle \partial_x f, \partial_x g \rangle_{L^2(m)} + \sigma \langle \partial_x f, g \chi_R m^{-2} \partial_x m^2 \rangle_{L^2(m)} \\ &\quad - \frac{1}{2} \langle f, g \chi_R [\partial_x A - A m^{-2} \partial_x m^2] \rangle_{L^2(m)} \\ &\quad - \frac{1}{2} \langle f, g \chi_R [\partial_v B_\varepsilon(\mathcal{J}_t) - B_\varepsilon(\mathcal{J}_t) m^{-2} \partial_v m^2] \rangle_{L^2(m)}. \end{aligned}$$

This bilinear form is obviously well defined, a.e.  $t \geq 0$ , for any  $f, g \in H^1(m)$ . Moreover,  $a_\sigma$  is continuous,

$$|a_\sigma(t; f, g)| \leq C_R \|f\|_{H^1(m)} \|g\|_{H^1(m)},$$

for some positive constant  $C_R$ , and coercive. Indeed, we have from (3.3.21), that

$$a_\sigma(t; f, f) \geq \frac{1}{2} \|\partial_v f\|_{L^2(m)}^2 + \frac{\sigma}{2} \|\partial_x f\|_{L^2(m)}^2 - k_1 \|f\|_{L^2(m)}^2,$$

for some  $k_1 > 0$  not depending on  $t$ , nor on  $R$  and nor on  $\sigma$ . The J. L. Lions theorem [23, Theorem X.9] implies that for any  $f_0 \in L^2(m)$  there exists a unique

$$f \in L^2((0, \infty); H^1(m)) \cap C([0, \infty); L^2(m)); \quad \frac{d}{dt} f \in L^2((0, \infty); H^1(m)')$$

such that  $f(0) = f_0$  and

$$\left\langle \frac{d}{dt} f, g \right\rangle_{L^2(m)} + a_\sigma(f(t), g) = 0, \quad \text{a.e. } t \geq 0, \forall g \in H^1(m).$$

We recall that  $f_- := \min(f, 0)$  belongs to  $H^1(m)$ , therefore we can use it as a test function to find that

$$f_0 \geq 0 \quad \Rightarrow \quad f(t) \geq 0, \quad \text{a.e. } t \geq 0.$$

Let us now fix some  $T > 0$ . Using  $f$  itself as a test function, we get easily that

$$\|f_t\|_{L^2(m)}^2 + \int_0^t \|\partial_v f_s\|_{L^2(m)}^2 ds \leq e^{k_1 t} \|f_0\|_{L^2(m)}^2,$$

therefore, one can take the limits  $\sigma \rightarrow 0$  and  $R \rightarrow \infty$ , to find that for any  $\varphi \in C^1([0, T]; C_c^2(\mathbb{R}^2))$

$$\int_{\mathbb{R}^2} \varphi_t f_t = \int_{\mathbb{R}^2} \varphi_0 f_0 + \int_0^t \int_{\mathbb{R}^2} [\partial_t \varphi_s + \partial_{vv}^2 \varphi_s - A \partial_x \varphi_s - B_\varepsilon(\mathcal{J}_s) \partial_v \varphi_s] f_s ds, \quad 0 < t < T,$$

holds. Taking a well chosen sequence  $\varphi^n \rightarrow M^2$ , we deduce that

$$\sup_{t \in [0, T]} \|f_t\|_{L^1(M^2)} \leq \max(C', \|f_0\|_{L^1(M^2)}),$$

for some positive constant  $C'$  that depends only on the parameters of the system. We also notice that, thanks to renormalisation concepts, we recover the inequality

$$\sup_{t \in [0, T]} \mathcal{H}(f_t) + \int_0^t I_v(f_s) ds \leq \mathcal{H}(f_0) + K_0 T \max(C_0, \|f_0\|_{L^1(M)}).$$

Let us take now  $f_0 \in L^1(M^2) \cap L^1 \log L^1 \cap \mathbb{P}(\mathbb{R}^2)$ , and a sequence  $\{f_{n,0}\} \subset L^2(m)$  such that  $f_{n,0} \rightarrow f_0$  in  $L^1(M)$ . Moreover, let us assume that there is a positive constant  $C > 0$  such that  $\mathcal{H}(f_{n,0}) \leq C$ , for any  $n \in \mathbb{N}$ . From the previous analysis we get a family  $\{f_n\} \in C((0, T); L^1(M))$  of functions related to the initial conditions  $\{f_{n,0}\}$ . Using the Dunford-Pettis criterium we can pass to the limit in  $L^1(M)$  finding a solution to the linear problem

$$\partial_t f = \partial_x(Af) + \partial_v(B_\varepsilon(\mathcal{J}_t)f) + \partial_{vv}^2 f. \quad (3.3.29)$$

that depends continuously to the initial datum (in the sense defined in Theorem 3.2.45). Moreover, from Corollary 3.3.58 we get that this solution is necessarily unique.

Finally, we use again the ideas of Corollary 3.3.58 to find a solution to the NL equation (3.1.2). Indeed, it suffices to notice that the mapping

$$\begin{cases} L^\infty([0, T]) & \longrightarrow C([0, T]; L^1(M^2)) \\ \mathcal{J} & \longmapsto f, \end{cases}$$

with  $f$  solution of (3.3.29) for  $\mathcal{J}$  given, is Lipschitz and contracting when  $T > 0$  is small enough.  $\square$

Existence of stationary solutions will be shown as a result of an abstract version of the Brouwer fixed point theorem (a variant of [55, Theorem 1.2] and [63]):

**Theorem 3.3.59.** *Consider  $\mathcal{Z}$  a convex and compact subset of a Banach space  $X$  and  $S(t)$  a continuous semigroup on  $\mathcal{Z}$ . Let us assume that  $\mathcal{Z}$  is invariant under the action of  $S(t)$  (that is  $S(t)z \in \mathcal{Z}$  for any  $z \in \mathcal{Z}$  and  $t \geq 0$ ). Then, there exists  $z_0 \in \mathcal{Z}$  which is stationary under the action of  $S(t)$ , i.e.,  $S(t)z_0 = z_0$  for any  $t \geq 0$ .*

We present the argument briefly in this section. Our aim is to find a fixed point for the nonlinear semigroup  $S_{Q_\varepsilon}(t)$  related to equation (3.1.2). At this point we do not have any hint on the number of functions solving

$$Q_\varepsilon[\mathcal{J}_F] F = 0,$$

and the nonlinearity could lead to the presence of more than one. However, in the disconnected regime  $\varepsilon = 0$  the nonlinearity disappears, and the multiplicity problem is no longer present.

*Proof of existence of stationary solutions to (3.2.12).* Let us fix  $m$  an exponential weight and define for any  $t \geq 0$

$$S(t) : X \rightarrow X \quad \text{with} \quad X = H_v^2(m) \cap L^1 \log L^1 \cap \mathbb{P}(\mathbb{R}^2),$$

such that  $S(t)f_0$  is the solution to (3.1.2) given by Theorem 3.2.45 associated to the initial condition  $f_0$ . Estimates (3.2.11) and (3.3.27) imply that  $S(t)$  is well defined. Moreover, the continuity of  $S$  in the Banach space  $L^1(\mathbb{R}^2)$  is direct from the definition of weak solutions, in particular,

$$S(t)f_0 \in C([0, \infty); L^1(\mathbb{R}^2)),$$

with the topology of compact subsets in time.

Finally, defining

$$\mathcal{Z} := \mathcal{Z}(\varepsilon) = \{f \in X \text{ such that (3.2.8) and (3.2.11) hold}\} \subset L^1(\mathbb{R}^2),$$

which is invariant under  $S_t$  for any  $t \geq 0$  and convex. Moreover, the compactness of the inclusion  $\mathcal{Z} \subset H^1(m) \hookrightarrow L^1(\mathbb{R}^2)$  allows us to apply Theorem 3.3.59 and find the existence of a fixed point for  $S(t)$  and by consequence a stationary solution to (3.1.2).

It is worth emphasising that the above proof show yet that the map  $\varepsilon \mapsto G_\varepsilon$  is locally bounded in  $[0, \infty)$ , i.e., if  $\varepsilon_0 > 0$  is fixed, then

$$G_\varepsilon \in \mathcal{Z}(\varepsilon_0) \quad \text{for any} \quad \varepsilon \in (0, \varepsilon_0).$$

□

## 3.4 The linearized equation

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The aim of the present section is to uncover the properties of the linearized operator associated to  $Q_\varepsilon$  in the small connectivity case using what we call a *splitting method*. To illustrate the ideas we use in the following, let us assume that an operator  $\Lambda$  on a Banach space  $X$  can be written as

$$\Lambda = \mathcal{A} + \mathcal{B},$$

where  $\mathcal{B}$  has some dissipative property and  $\mathcal{A}$  is much more regular than  $\mathcal{B}$ . Under some additional positivity assumption on the generator  $\Lambda$ , the principal part of spectrum is a simple real eigenvalue. This is known as the Krein-Rutman theorem. We state below a recent version picked up from [113],

**Theorem 3.4.60.** *We consider a semigroup generator  $\Lambda$  on a Banach lattice of functions  $X$ , and we assume that*

1. *there exists some  $\alpha^* \in \mathbb{R}$  and two operators  $\mathcal{A}, \mathcal{B} \in \mathcal{C}(X)$ , such that  $\Lambda = \mathcal{A} + \mathcal{B}$  and*

(a) for any  $\alpha > \alpha^*, \ell \geq 0$ , there exists a constant  $C_{\alpha, \ell} > 0$  such that

$$\forall t \geq 0, \quad \|S_{\mathcal{B}} * (\mathcal{A}S_{\mathcal{B}})^{(*\ell)}(t)\|_{\mathcal{B}(X)} \leq C_{\alpha, \ell} e^{\alpha t}.$$

(b)  $\mathcal{A}$  is bounded, and there exists an integer  $n \geq 1$  such that for any  $\alpha > \alpha^*$ , there exists a constant  $C_{\alpha, n} > 0$  such that

$$\forall t \geq 0, \quad \|(\mathcal{A}S_{\mathcal{B}})^{(*n)}(t)\|_{\mathcal{B}(X, Y)} \leq C_{\alpha, n} e^{\alpha t},$$

with  $Y \subset D(\Lambda)$  and  $Y \subset X$  with compact embedding;

2. for  $\Lambda^*$  the dual operator of  $\Lambda$  defined in  $X'$ , there exists  $\beta > \alpha^*$  and  $\psi \in D(\Lambda^*) \cap X'_+ \setminus \{0\}$  such that  $\Lambda^*\psi \geq \beta\psi$ ;

3.  $S_{\Lambda}(t)$  is a positive semigroup and  $\Lambda$  satisfies Kato's inequality, i.e.,  $\forall f \in D(\Lambda)$  it holds  $\Lambda|f| \geq \text{sign}(f)\Lambda f$ .

4.  $-\Lambda$  satisfies a strong maximum principle: for any given  $f$  and  $\gamma \in \mathbb{R}$ , there holds,

$$f \in D(\Lambda) \setminus \{0\}, f \geq 0 \text{ and } (-\Lambda + \gamma)f \geq 0 \quad \text{imply} \quad f > 0,$$

and there exists an integer  $m$  such that

$$f \in D(\Lambda^m) \text{ and } |f| > 0 \quad \text{imply} \quad f > 0 \text{ or } f < 0.$$

Defining

$$\lambda := s(\Lambda) = \sup \{(\xi) : \xi \in \Sigma(\Lambda)\},$$

there exists  $0 < f_{\infty} \in D(\Lambda)$  and  $0 < \phi \in D(\Lambda^*)$  such that

$$\Lambda f_{\infty} = \lambda f_{\infty}, \quad \Lambda^* \phi = \lambda \phi.$$

Moreover, there is some  $\alpha' \in (\alpha^*, \lambda)$  and  $C > 0$  such that for any  $f_0 \in X$

$$\|S_{\Lambda}(t)f_0 - e^{\lambda t} \langle f_0, \phi \rangle f_{\infty}\|_X \leq C e^{\alpha' t} \|f_0 - \langle f_0, \phi \rangle f_{\infty}\|_X. \quad (3.4.30)$$

From Theorem 3.2.46 we know that for any value of  $\varepsilon$  there exists at least one  $G_{\varepsilon}$  non zero stationary solution of the FhN kinetic equation (3.1.2). The linearized equation, on the variation  $h := f - G_{\varepsilon}$ , induces the linearized operator

$$\mathcal{L}_{\varepsilon} h = Q_{\varepsilon}(\mathcal{J}(G_{\varepsilon}))h + \varepsilon \mathcal{J}(h)\partial_v G_{\varepsilon}.$$

Moreover, let us recall that in Section 3.3 we proved that

$$\langle Q_{\varepsilon}[\mathcal{J}(G_{\varepsilon})]f, f \rangle_{L^2(m)} \leq K_1 \|f\|_{L^2(\mathbb{R}^2)} - K_2 \|f\|_{L^2(m)},$$

if we could make  $K_1 = 0$ , then the operator  $Q_{\varepsilon}$  together with  $\mathcal{L}_{\varepsilon}$  would be dissipative. Since it is not the case, let us fix a constant  $N > 0$  and define

$$\mathcal{B}_{\varepsilon} := \mathcal{L}_{\varepsilon} - \mathcal{A}, \quad \text{where} \quad \mathcal{A} = N \chi_R(x, v); \quad (3.4.31)$$

with  $\chi_R$  given by (3.3.28). We remark that  $\mathcal{A} \in \mathcal{B}(H_v^2(m))$ , and that  $\mathcal{A}f$  vanishes outside a ball of radius  $2R$  for any  $f \in H_v^2(m)$ .

### 3.4.1 Properties of $\mathcal{A}$ and $\mathcal{B}_\varepsilon$

We now precise the dissipative properties of  $\mathcal{L}_\varepsilon$ . In particular, we present two lemmas dealing with the hypodissipativity and regularisation properties of the splitting  $\mathcal{A}$  and  $\mathcal{B}_\varepsilon$ . We use some ideas developed in [111, 70] and [110].

**Lemma 3.4.61.** *For any exponential weight  $m$ , there exist some constants  $N, R > 0$  such that  $(\mathcal{B}_\varepsilon + 1)$  is hypodissipative in  $H_v^2(m)$ .*

*Proof.* From the characterisation of hypodissipativity given in Section 3.2, it suffices to show that there exists a constant  $C > 0$  such that

$$\|S_{\mathcal{B}_\varepsilon}(t)\|_{\mathcal{B}(H_v^2(m))} \leq C e^{-t}, \quad t \geq 0,$$

or simply, to show that for any  $h \in H_v^2(m)$ , it holds

$$\langle \mathcal{B}_\varepsilon h, h \rangle_{\tilde{H}_v^2(m)} \leq -\|h\|_{\tilde{H}_v^2(m)}^2, \quad (3.4.32)$$

for some norm  $\|\cdot\|_{\tilde{H}_v^2(m)}$  equivalent to the usual norm  $\|\cdot\|_{H_v^2(m)}$ .

Let us recall that the operator  $\mathcal{B}_\varepsilon$  writes

$$\mathcal{B}_\varepsilon = \mathcal{L}_\varepsilon - \mathcal{A} = (Q_\varepsilon[\mathcal{J}_{G_\varepsilon}] - N\chi_R)h + \varepsilon \mathcal{J}(h) \partial_v G_\varepsilon,$$

and since  $\mathcal{J}_{G_\varepsilon} \in \mathbb{R}$  is a real constant, we can use all a priori estimates on  $Q_\varepsilon$  directly. As usual, when no confusion is possible, we drop the dependence on  $\mathcal{J}_\varepsilon$ . Three steps complete the proof:

*Step 1. Dissipativity in  $L^2(m)$ .* Let us notice that for any  $h \in L^2(m)$  we have

$$|\mathcal{J}(h)| \leq C \|h\|_{L^2(m)},$$

for some constant  $C > 0$ . It follows that

$$\mathcal{J}(h) \int_{\mathbb{R}^2} (\partial_v G_\varepsilon) h m^2 \leq |\mathcal{J}(h)| \|\partial_v G_\varepsilon\|_{L^2(m)} \|h\|_{L^2(m)} \leq C \|\partial_v G_\varepsilon\|_{L^2(m)} \int_{\mathbb{R}^2} h^2 m^2.$$

Thus, coming back to (3.3.20), we find that for  $N$  and  $R$  large enough one can assume  $k_1 = -1$ , getting

$$\langle \mathcal{B}_\varepsilon h, h \rangle_{L^2(m)} \leq -\|h\|_{L^2(m)}^2 - k_2 \|h\|_{L^2(M^{1/2}m)}^2 - \|\partial_v h\|_{L^2(m)}^2, \quad (3.4.33)$$

as a consequence,  $(\mathcal{B}_\varepsilon + 1)$  is dissipative in  $L^2(m)$ .

*Step 2. Bounds on the derivatives of  $\mathcal{B}_\varepsilon$ .* For the  $x$ -derivative we see that there exists some constant  $C'$  depending on  $\chi_R$  and its derivatives, such that

$$-N \langle \partial_x(\chi_R h), \partial_x h \rangle_{L^2(m)} \leq C' \|h\|_{L^2(m)}^2 - N \|(\partial_x h) \sqrt{\chi_R}\|_{L^2(m)}^2.$$

On the other hand, thanks to Young's inequality, we get

$$\begin{aligned} \mathcal{J}(h) \int_{\mathbb{R}^2} (\partial_{xv}^2 G_\varepsilon)(\partial_x h) m^2 &= -\mathcal{J}(h) \int_{\mathbb{R}^2} \partial_x G_\varepsilon [\partial_{vx}^2 h + 2\kappa v \partial_x h] m^2 \\ &\leq \mathcal{J}(h)^2 \|\partial_v G_\varepsilon\|_{L^2(m)}^2 + \frac{1}{2} \|\partial_{xv}^2 h\|_{L^2(m)}^2 + \|\sqrt{2\kappa v} \partial_x h\|_{L^2(m)}^2. \end{aligned}$$

These two inequalities, together with (3.3.22), imply that for  $N$  and  $R$  large enough

$$\langle \partial_x(\mathcal{B}_\varepsilon h), \partial_x h \rangle_{L^2(m)} \leq -\|\partial_x h\|_{L^2(m)}^2 - \frac{1}{2} \|\partial_{xv}^2 h\|_{L^2(m)}^2 + C' \|h\|_{L^2(m)}^2 + \int_{\mathbb{R}^2} |\partial_x h| |\partial_v h| m^2.$$

Proceeding similarly with the  $v$ -derivative we get

$$\begin{aligned} \mathcal{J}(h) \int_{\mathbb{R}^2} (\partial_{vv}^2 G_\varepsilon)(\partial_v h) m^2 &= |\mathcal{J}(h)| \|\partial_{vv}^2 G_\varepsilon\|_{L^2(m)} \|\partial_v h\|_{L^2(m)} \\ &\leq \frac{1}{2} \|\partial_{vv}^2 G_\varepsilon\|_{L^2(m)} (C' \|h\|_{L^2(m)}^2 + \|\partial_v h\|_{L^2(m)}^2), \end{aligned}$$

then, coming back to (3.3.23), we find  $N, R > 0$  such that

$$\langle \partial_v(\mathcal{B}_\varepsilon h), \partial_v h \rangle_{L^2(m)} \leq -\|\partial_v h\|_{L^2(m)}^2 - \|\partial_{vv}^2 h\|_{L^2(m)}^2 + C' \|h\|_{L^2(m)}^2 + \int_{\mathbb{R}^2} |\partial_x h| |\partial_v h| m^2.$$

Finally, for the second  $v$ -derivative we find  $C'$  such that

$$-N \langle \partial_{vv}^2(\chi_R h), \partial_{vv}^2 h \rangle_{L^2(m)} \leq -N \int_{\mathbb{R}^2} \chi_R (\partial_{vv}^2 h)^2 m^2 + C' \int_{\mathbb{R}^2} (\partial_v h)^2 m^2 + C' \int_{\mathbb{R}^2} h |\partial_{vv}^2 h| m^2,$$

and for any  $\epsilon > 0$

$$\begin{aligned} \mathcal{J}(h) \int_{\mathbb{R}^2} (\partial_{vvv}^3 G_\varepsilon)(\partial_{vv}^2 h) m^2 &\leq \frac{\mathcal{J}(h)^2}{2\epsilon} + \epsilon (\|\partial_{vv}^2 G_\varepsilon\|_{L^2(m)}^2 \|\partial_{vvv}^3 h\|_{L^2(m)}^2 + \\ &\quad + \|\partial_{vv}^2 G_\varepsilon\|_{L^2(m)}^2 \|2\kappa v (\partial_{vv}^2 h)\|_{L^2(m)}^2). \end{aligned}$$

If  $\epsilon > 0$  is small and  $N, R$  large enough, we obtain as an application of (3.3.26), that there is a constant  $C' > 0$  such that

$$\langle \partial_{vv}^2(\mathcal{B}_\varepsilon h), \partial_{vv}^2 h \rangle_{L^2(m)} \leq -\|\partial_{vv}^2 h\|_{L^2(m)}^2 + C' [\|h\|_{L^2(m)}^2 + \|\partial_v h\|_{L^2(m)}^2 + \|\partial_{xv}^2 h\|_{L^2(m)}^2 + \|\partial_{vv}^2 h\|_{L^2(m)}^2].$$

*Step 3. Equivalent norm and conclusion.* Let  $\delta > 0$  and  $h_1, h_2 \in H_v^2(m)$ , we can define the bilinear product

$$\langle h_1, h_2 \rangle_{\bar{H}_v^2(m)} := \langle h_1, h_2 \rangle_{L^2(m)} + \delta \langle \partial_x h_1, \partial_x h_2 \rangle_{L^2(m)} + \delta \langle \partial_v h_1, \partial_v h_2 \rangle_{L^2(m)} + \delta^2 \langle \partial_{vv}^2 h_1, \partial_{vv}^2 h_2 \rangle_{L^2(m)}.$$

and the relative norm

$$\|h\|_{\bar{H}_v^2(m)}^2 := \|h\|_{L^2(m)}^2 + \delta \|D_{x,v} h\|_{L^2(m)}^2 + \delta^2 \|\partial_{vv}^2 h\|_{L^2(m)}^2.$$

Choosing  $\delta > 0$  small enough we conclude that for any  $\alpha \in (0, 1]$  one find  $\delta_\alpha$  such that

$$\langle \mathcal{B}_\varepsilon h, h \rangle_{\bar{H}_v^2(m)} \leq -\alpha \|h\|_{\bar{H}_v^2(m)}^2.$$

Since the norm related to  $\bar{H}_v^2(m)$  is equivalent to the usual norm in  $H_v^2(m)$ , we can conclude that  $(\mathcal{B}_\varepsilon + 1)$  is hypodissipative in  $H_v^2(m)$ .  $\square$

**Lemma 3.4.62.** *There are positive constants  $N, R$  large enough and some  $C_{\mathcal{B}_\varepsilon} > 0$ , such that the semigroup  $S_{\mathcal{B}_\varepsilon}$  satisfies*

$$\|S_{\mathcal{B}_\varepsilon}(t)h\|_{H_v^2(m_1)} \leq C_{\mathcal{B}_\varepsilon} t^{-9/2} \|h\|_{L^2(m_2)}, \quad \forall t \in (0, 1].$$

As a consequence, for any  $\alpha > -1$ , and any exponential weight  $m$ , there exists  $n \geq 1$  and  $C_{n,\varepsilon}$  such that of any  $t > 0$  it holds

$$\|(AS_{\mathcal{B}_\varepsilon})^{(*n)}(t)h\|_{H_v^2(m)} \leq C_{n,\varepsilon} e^{\alpha t} \|h\|_{L^2(m)}. \quad (3.4.34)$$

*Proof.* We split the proof in three steps, in the first one we refine the previous estimates on the norm of the semigroup associated to the operator  $\mathcal{B}_\varepsilon$ , in the second one we use Hormander-Hérau technique (see e.g. [73]) to get the first inequality, and finally we prove (3.4.34).

*Step 1. Sharper estimates on  $\mathcal{B}_\varepsilon$ .* We denote for  $K > 0$  a generic constant. From the proof of the previous Lemma, we know that there are  $N, R$  large enough such that for any  $h \in D(\mathcal{B}_\varepsilon)$ , it holds

$$\begin{aligned} \langle \mathcal{B}_\varepsilon h, h \rangle_{L^2(m_2)} &\leq -K \|h\|_{L^2(m_2)}^2 - \|\partial_v h\|_{L^2(m_2)}^2 \\ \langle \partial_x \mathcal{B}_\varepsilon h, \partial_x h \rangle_{L^2(m_1)} &\leq -\frac{1}{2} \|\partial_x h\|_{L^2(m_1)}^2 - \frac{1}{2} \|\partial_{xv}^2 h\|_{L^2(m_1)}^2 + K \|h\|_{L^2(m_1)}^2 + \frac{1}{2\delta t} \|\partial_v h\|_{L^2(m_1)}^2 \\ \langle \partial_v \mathcal{B}_\varepsilon h, \partial_v h \rangle_{L^2(m_1)} &\leq -\|\partial_{vv}^2 h\|_{L^2(m_1)}^2 + K \|h\|_{L^2(m_1)}^2 + \frac{1}{\delta t} \|\partial_v h\|_{L^2(m_1)}^2 + \delta t \|\partial_x h\|_{L^2(m_1)}^2 \\ \langle \partial_{vv}^2 \mathcal{B}_\varepsilon h, \partial_{vv}^2 h \rangle_{L^2(m_1)} &\leq K \|h\|_{L^2(m_1)}^2 + K \|\partial_v h\|_{L^2(m_1)}^2 + \frac{1}{2t\delta} \|\partial_{xv}^2 h\|_{L^2(m_1)}^2. \end{aligned}$$

We also notice for any  $\delta, t \in (0, 1)$  it holds

$$\begin{aligned} \langle \partial_x (Q_\varepsilon - \mathcal{A})h, \partial_v h \rangle_{L^2(m_1)} + \langle \partial_v (Q_\varepsilon - \mathcal{A})h, \partial_x h \rangle_{L^2(m_1)} &\leq -\frac{b}{2} \|\partial_x h\|_{L^2(m_1)}^2 \\ &\quad + K \|h\|_{L^2(m_2)}^2 + \frac{K}{t\delta} \|\partial_v h\|_{L^2(m_2)}^2 + \frac{K}{t\delta^{1/10}} \|\partial_{vv}^2 h\|_{L^2(m_1)}^2 + K t \delta^{1/10} \|\partial_{xv}^2 h\|_{L^2(m_1)}^2, \\ \langle \mathcal{J}(h) \partial_{xv}^2 G_\varepsilon, \partial_v h \rangle_{L^2(m_1)} + \langle \mathcal{J}(h) \partial_{vv}^2 G_\varepsilon, \partial_x h \rangle_{L^2(m_1)} &\leq \frac{\|\partial_x G_\varepsilon\|_{L^2(m_1)}^2}{2} [2 \mathcal{J}(h)^2 \\ &\quad + \|\partial_{vv}^2 h\|_{L^2(m_1)}^2 + \|\partial_v h\|_{L^2(m_2)}^2] + \frac{\|\partial_{vv}^2 G_\varepsilon\|_{L^2(m_1)}^2}{2} \left[ \frac{\mathcal{J}(h)^2}{t\delta} + t\delta \|\partial_x h\|_{L^2(m_1)}^2 \right], \end{aligned}$$

yielding to

$$\begin{aligned} \langle \partial_x \mathcal{B}_\varepsilon h, \partial_v h \rangle_{L^2(m)} + \langle \partial_v \mathcal{B}_\varepsilon h, \partial_x h \rangle_{L^2(m)} &\leq -\frac{b}{4} \|\partial_x h\|_{L^2(m_1)}^2 + \frac{K}{t\delta} \|h\|_{L^2(m_2)}^2 + \frac{K}{t\delta} \|\partial_v h\|_{L^2(m_2)}^2 \\ &\quad + \frac{K}{t\delta^{1/10}} \|\partial_{vv}^2 h\|_{L^2(m_1)}^2 + K t \delta^{1/10} \|\partial_{xv}^2 h\|_{L^2(m_1)}^2. \end{aligned}$$

*Step 2. Hormander-Hérau technique.* For a given  $h \in H_v^2(m_1) \cap L^2(m_2)$  we denote  $h_t := S_{\mathcal{B}_\varepsilon}(t)h$ , and define  $\mathcal{F}$  by

$$\mathcal{F}(h, t) := \|h\|_{L^2(m_2)}^2 + c_1 t^3 \|\partial_x h\|_{L^2(m_1)}^2 + c_2 t \|\partial_v h\|_{L^2(m_1)}^2 + c_3 t^2 \langle \partial_x h, \partial_v h \rangle_{L^2(m_1)} + c_4 t^4 \|\partial_{vv}^2 h\|_{L^2(m_1)}^2,$$

which, for well chosen parameters, is decreasing. Indeed, thanks to the inequalities found in the first step, we have

$$\frac{d}{dt} \mathcal{F}(t, h_t) \leq \sum_{i=1}^5 \mathcal{T}_i,$$

with

$$\begin{aligned}
\mathcal{T}_1 &= K \int_{\mathbb{R}^2} \left[ -2m_2^2 + 2(c_1 t^3 + c_2 t + c_4 t^4) m_1^2 + \frac{c_3 t}{\delta} m_2^2 \right] h_t^2, \\
\mathcal{T}_2 &= \int_{\mathbb{R}^2} \left[ (3c_1 + 2c_2 \delta - \frac{b}{4} c_3 + 2c_3 \delta) t^2 - c_1 t^3 \right] (\partial_x h_t)^2 m_1^2, \\
\mathcal{T}_3 &= \int_{\mathbb{R}^2} \left[ -2m_2^2 + c_2 m_1^2 + \frac{2c_2}{\delta} m_1^2 + \frac{2c_3}{\delta} m_1^2 + \frac{c_1 t^2}{\delta} m_1^2 + 2c_4 t^4 K m_1^2 + \frac{c_3 t K}{\delta} m_2^2 \right] (\partial_v h_t)^2, \\
\mathcal{T}_4 &= \int_{\mathbb{R}^2} t^3 \left[ -c_1 + \frac{c_4}{\delta} + c_3 K \delta^{1/10} \right] (\partial_{xv}^2 h_t)^2 m_1^2, \\
\mathcal{T}_5 &= \int_{\mathbb{R}^2} \left[ -2c_2 t + \frac{c_3 t K}{\delta^{1/10}} + 4c_4 t^3 \right] (\partial_{vv}^2 h_t)^2 m_1^2.
\end{aligned}$$

Choosing

$$c_1 = \delta^2, \quad c_2 = \delta^{4/3}, \quad c_3 = \delta^{3/2} \quad \text{and} \quad c_4 = \delta^4,$$

we get that for  $\delta \in (0, 1]$  small enough, it holds

$$\frac{d}{dt} \mathcal{F}(t, h_t) \leq 0.$$

for any  $t \in (0, 1]$ . Since  $0 < c_4 \leq c_1 \leq c_3 \leq c_2$  and  $c_1 c_2 \geq c_3^2$ , we finally get that

$$c_4 t^{9/2} \left( \|\partial_{x,v} h_t\|_{L^2(m_1)}^2 + \|\partial_{vv}^2 h_t\|_{L^2(m_1)}^2 \right) \leq \mathcal{F}(t, h_t) \leq F(0, h_0) = \|h_0\|_{L^2(m_2)}^2.$$

*Step 3. Proof of inequality (3.4.34).* From the definition of  $\mathcal{A}$  we notice that

$$\|\mathcal{A} S_{B_\varepsilon}(t) h\|_{H_v^2(m)} \leq C' t^{-9/2} e^{-t} \|h\|_{L^2(m)}, \quad \forall t \in (0, 1],$$

for some constant  $C'$ . It is important to remark that since  $\mathcal{A}$  lies in a compact, we do not need anymore two different weights  $m_1$  and  $m_2$ . Therefore, we apply Proposition 3.2.48 with  $X = L^2(m)$ ,  $Y = H_v^2(m)$ ,  $\Theta = 9/2$  and  $\alpha^* = -1$  to get (3.4.34).  $\square$

### 3.4.2 Spectral analysis on the linear operator in the disconnected case

We consider in this section the disordered case  $\varepsilon = 0$ . The corresponding FhN kinetic equation is linear and writes

$$\begin{aligned}
\partial_t g &= \partial_x (A g) + \partial_v (B_0 g) + \partial_{vv}^2 g \\
B_0 &= v(v - \lambda)(v - 1) + x,
\end{aligned}$$

Theorem 3.2.46 states that there exists at least one function  $G_0 \in \mathbb{P} \cap H_v^2(m)$  which is a solution to the associated (linear) stationary problem

$$\mathcal{L}_0 G_0 = \partial_x (A G_0) + \partial_v (B_0 G_0) + \partial_{vv}^2 G_0 = 0.$$

Since the operator now enjoys a *positive structure* (it generates a positive semigroup  $S_{\mathcal{L}_0}$ ), we can perform a more accurate analysis. Indeed, we can apply the abstract Krein-Rutman theorem 3.4.60 previously stated.



*Proof of the stability around  $\varepsilon = 0$  in Theorem 3.2.46.* Let us assume for a first moment that hypotheses of the abstract Theorem 3.4.60 hold for  $\mathcal{L}_0$  with  $\alpha^* = -1$ . We easily remark that

$$\lambda = 0, \quad f_\infty = G_0 \quad \phi = 1,$$

therefore, there exists  $\bar{\alpha} \in (-1, 0)$  such that

$$\Sigma(\mathcal{L}_0) \cap \Delta_{\bar{\alpha}} = \{0\},$$

and

$$\forall f_0 \in L^2(m), \quad \forall t \geq 0 \quad \|S_{\mathcal{L}_0}(t)f_0 - \langle f_0 \rangle G_0\|_{L^2(m)} \leq C e^{\bar{\alpha}t} \|f_0 - \langle f_0 \rangle G_0\|_{L^2(m)}.$$

Now, for  $\varepsilon > 0$ , we consider  $G_\varepsilon$  such that

$$Q_\varepsilon[\mathcal{J}_{G_\varepsilon}]G_\varepsilon = 0,$$

then, it holds

$$\frac{\partial}{\partial t}(G_\varepsilon - G_0) + \mathcal{L}_0(G_\varepsilon - G_0) = h, \quad h = \varepsilon \partial_v((v - \mathcal{J}(G_\varepsilon))G_\varepsilon),$$

and, thanks to Duhamel's formula, we get that

$$\|G_\varepsilon - G_0\|_{L^2(m)} \leq \|S_{\mathcal{L}_0}(t)(G_\varepsilon - G_0)\|_{L^2(m)} + \int_0^t \|S_{\mathcal{L}_0}(t-s)h\|_{L^2(m)} ds.$$

But  $G_\varepsilon - G_0$  and  $h$  have zero mean, then

$$\|G_\varepsilon - G_0\|_{L^2(m)} \leq C \|G_\varepsilon - G_0\|_{L^2(m)} e^{\bar{\alpha}t} + \varepsilon \frac{C}{|\bar{\alpha}|} \|G_\varepsilon\|_{H_v^1(M^{1/2}m)} (1 - e^{\bar{\alpha}t}).$$

Letting  $t \rightarrow \infty$  we conclude that there exists  $C_{\bar{\alpha}} > 0$  such that

$$\|G_\varepsilon - G_0\|_{L^2(m)} \leq \varepsilon C_{\bar{\alpha}} \|G_\varepsilon\|_{H_v^1(M^{1/2}m)}.$$

Finally, thanks to Corollary 3.3.55, we have

$$0 = \langle Q_\varepsilon[\mathcal{J}_{G_\varepsilon}]G_\varepsilon, G_\varepsilon \rangle_{\mathcal{H}^1} \leq K_1 - K_2 \|G_\varepsilon\|_{\mathcal{H}^1}^2 \leq K_1 - c_\delta K_2 \|G_\varepsilon\|_{H^1(m_2)}^2,$$

for any exponential weight  $m_2$ . If  $\kappa_2 > \kappa$ , we have then

$$\|G_\varepsilon\|_{H_v^1(M^{1/2}m)}^2 \leq C_{\kappa, \kappa_2} \|G_\varepsilon\|_{H^1(m_2)}^2 \leq C_{\kappa, \kappa_2} K_1 / c_\delta K_2,$$

and in the small connectivity regime  $\varepsilon \in (0, \varepsilon_0)$ , constants  $K_1$  and  $K_2$  do not depend on  $\varepsilon$ . Defining  $\eta(\varepsilon) = \varepsilon C_{\bar{\alpha}} C_{\kappa, \kappa_2} K_1 / c_\delta K_2$  we get the stability part of Theorem 3.2.46.

It only remains to verify that the requirement of Theorem 3.4.60 are fulfilled for  $\mathcal{L}_0$  in the Banach lattice  $X = L^2(m)$ .

1. (a) the splitting (3.4.31) has the nice structure. Indeed, the Lemma 3.4.61 implies that  $\mathcal{B}_0 + 1$  is hypodissipative in  $L^2(m)$ , therefore

$$\|S_{\mathcal{B}_0}(t)\|_{\mathcal{B}(L^2(m))} \leq C e^{-t}, \quad \forall t \geq 0,$$

i.e., it suffices to take  $\alpha^* = -1$ .

(b) if  $Y = H_v^2(m)$  and  $X = L^2(m)$ , the desired inequality is consequence of Lemma 3.4.62.

2. The requirement is obtained for  $\beta = 0$  and  $\psi = 1$ . Indeed, in that case

$$\mathcal{L}_0^* \psi = Q_0^* 1 = 0 \geq \beta \psi.$$

3. A side consequence of (3.3.21) is the positivity of the semigroup:

$$f_0 \geq 0 \quad \Rightarrow \quad S_{\mathcal{L}_0} f_0(t) \geq 0, \quad \forall t \geq 0.$$

Moreover, using that  $L^2(m)$  is also a Hilbert space, we deduce the Kato's inequalities.

4. The strict positivity (or strong maximum principle) is a straightforward consequence of Theorem 3.8.73 in Appendix 3.8. □

Let us finish this section by summarizing the properties of the spectrum of  $\mathcal{L}_0$  in the Banach space  $L^2(m)$  and by a useful result on the regularisation properties of  $\mathcal{R}_{\mathcal{L}_0}(z)$ .

**Proposition 3.4.63.**

(i) There exists  $\bar{\alpha} < 0$  such that the spectrum  $\Sigma(\mathcal{L}_0)$  of  $\mathcal{L}_0$  in  $L^2(m)$  writes

$$\Sigma(\mathcal{L}_0) \cap \Delta_{\bar{\alpha}} = \{0\},$$

and 0 is simple.

(ii) For any  $\alpha > \bar{\alpha}$ , there exists a constant  $C_{H_v^1} > 0$  depending on  $(\alpha - \bar{\alpha})$ , such that

$$\|\mathcal{R}_{\mathcal{L}_0}(z)\|_{\mathcal{B}(L^2(m), H_v^1(m))} \leq C_{H_v^1} (1 + |z|^{-1}), \quad \forall z \in \mathbb{C} \setminus \{0\}, \operatorname{Re}(z) > \alpha.$$

*Proof.* It only remains to prove (ii). Let us consider  $z \in \Delta_{\alpha} \setminus \{0\}$ , and take  $f, g \in L^2(m)$  such that

$$(\mathcal{L}_0 - z)f = g.$$

Thanks to Lemma 3.4.61 and the definition of  $\mathcal{A}$ , we get

$$(\operatorname{Re}(z) - \bar{\alpha})\|f\|_{L^2(m)}^2 + \|\partial_v f\|_{L^2(m)}^2 \leq \|g\|_{L^2(m)} \|f\|_{L^2(m)} + N \|f\|_{L^2(m)}^2.$$

Moreover, (i) tells us that 0 is an isolated simple eigenvalue for  $\mathcal{L}_0$  in  $L^2(m)$ , then  $\mathcal{R}_{\mathcal{L}_0}(z)$  writes as the Laurent series (see for example [86, Section 3.5])

$$\mathcal{R}_{\mathcal{L}_0}(z) = \sum_{k=-1}^{\infty} z^k \mathcal{C}_k, \quad \mathcal{C}_k \in \mathcal{B}(L^2(m)),$$

which on a small disc around 0 converges. Thus, there is some  $C^0 > 0$  such that  $\|\mathcal{R}_{\mathcal{L}_0}(z)\|_{\mathcal{B}(L^2(m))} \leq C^0 |z|^{-1}$  for any  $z \in \Delta_{\alpha}$ ,  $z \neq 0$ . Finally, we notice that

$$\min(1, \alpha - \bar{\alpha})\|f\|_{H_v^1(m)} \leq (1 + NC^0 |z|^{-1}) \|g\|_{L^2(m^2)},$$

therefore, it suffices to take  $C_{H_v^1} = 1 + /NC^0 \min(1, \alpha - \bar{\alpha})$ , with  $N$  large enough. □

## 3.5 Stability of the stationary solution in the small connectivity regime

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Now, we establish the exponential convergence of the nonlinear equation. To that aim, we first notice that, in the small connectivity regime, the linear operator  $\mathcal{L}_\varepsilon$  inherits (in a sense that we precise later on) the stability properties of  $\mathcal{L}_0$ .

### 3.5.1 Uniqueness of the stationary solution in the weak connectivity regime

As a first step in the proof of Theorem 3.2.47, we need a uniqueness condition that, for instance, can be settled as a consequence of the following estimate:

**Lemma 3.5.64.** *There exists a constant  $C_V$  such that for any  $g \in L^2(m)$ ,  $\langle g \rangle = 0$  and for the solution  $f \in L^2(m)$  to the linear equation  $\mathcal{L}_0 f = g$  there holds*

$$\|f\|_V := \|f\|_{L^2(Mm)} + \|\nabla_v f\|_{L^2(M^{1/2}m)} \leq C_V \|g\|_{L^2(m)}. \quad (3.5.35)$$

*Proof.* We easily compute

$$\int_{\mathbb{R}^2} (\mathcal{L}_0 f) f M m^2 = - \int_{\mathbb{R}^2} p(x, v) f^2 m^2 - \int_{\mathbb{R}^2} (\partial_v f)^2 M m^2,$$

for some  $p(x, v)$  polynomial in  $x$  and  $v$  with leading term  $v^6 + x^4$ . Therefore, there exists some constants  $K_1 > 0$  and  $0 < K_2 < 1$ , such that

$$\int_{\mathbb{R}^2} (\mathcal{L}_0 f) f M m^2 \leq K_1 \int_{\mathbb{R}^2} f^2 m^2 - K_2 \int_{\mathbb{R}^2} f^2 M^2 m^2 - K_2 \int_{\mathbb{R}^2} (\partial_v f)^2 M m^2.$$

The invertibility of  $\mathcal{L}_0$  in  $L^2(m)$  for zero mean functions, writes

$$\mathcal{L}_0 f = g \in L^2(m), \langle g \rangle = 0 \quad \Rightarrow \quad \|f\|_{L^2(m)} \leq C_{\bar{\alpha}} \|g\|_{L^2(m)},$$

with  $C_{\bar{\alpha}}$  given in the proof of the stability part of Theorem 3.2.46. As a consequence, for any  $f$  and  $g$  as in the statement of the lemma, we have

$$\begin{aligned} \int_{\mathbb{R}^2} f^2 M^2 m^2 + \int_{\mathbb{R}^2} (\partial_v f)^2 M m^2 &\leq -\frac{1}{K_2} \int_{\mathbb{R}^2} g f M m^2 + \frac{K_1}{K_2} \int_{\mathbb{R}^2} f^2 m^2 \\ &\leq \frac{1}{2} \int_{\mathbb{R}^2} f^2 M^2 m^2 + \frac{1}{2K_2^2} \int_{\mathbb{R}^2} g^2 m^2 + \frac{K_1 C}{K_2} \int_{\mathbb{R}^2} g^2 m^2, \end{aligned}$$

from which (3.5.35) immediately follows.  $\square$

**Corollary 3.5.65.** *There exists  $\varepsilon_1 \in (0, \varepsilon_0)$  such that in the small connectivity regime  $\varepsilon \in (0, \varepsilon_1)$  the stationary solution is unique.*

*Proof.* We write

$$\begin{aligned} G_\varepsilon - F_\varepsilon &= \varepsilon \mathcal{L}_0^{-1} \left[ \partial_v \left( (v - \mathcal{J}(F_\varepsilon)) F_\varepsilon - (v - \mathcal{J}(G_\varepsilon)) G_\varepsilon \right) \right] \\ &= \varepsilon \mathcal{L}_0^{-1} \left[ \partial_v \left( (v - \mathcal{J}(F_\varepsilon)) (F_\varepsilon - G_\varepsilon) + (\mathcal{J}(F_\varepsilon) - \mathcal{J}(G_\varepsilon)) G_\varepsilon \right) \right]. \end{aligned} \quad (3.5.36)$$

As a consequence, using the invertibility property of  $\mathcal{L}_0$  for zero mean functions, and the uniform bound (3.2.10) on  $G_\varepsilon, F_\varepsilon$ , we get

$$\begin{aligned} \|F_\varepsilon - G_\varepsilon\|_{\mathcal{V}} &\leq \varepsilon C_{\bar{\alpha}} \left\| \partial_v((v - \mathcal{J}(F_\varepsilon))(F_\varepsilon - G_\varepsilon) + (\mathcal{J}(F_\varepsilon) - \mathcal{J}(G_\varepsilon))G_\varepsilon) \right\|_{L^2(m)} \\ &\leq \varepsilon C \|F_\varepsilon - G_\varepsilon\|_{\mathcal{V}}, \end{aligned}$$

for some  $C$  depending on the parameters of the system and  $\varepsilon_0$ . The previous relationship implies, in particular, that  $\|F_\varepsilon - G_\varepsilon\|_{\mathcal{V}} = 0$  for  $\varepsilon < \varepsilon_1 = 1/C$ .  $\square$

### 3.5.2 Study of the Spectrum and Semigroup for the Linear Problem

We now turn into a generalisation of Proposition 3.4.63 in the case  $\varepsilon > 0$  small. Since the positivity of the operator is lost, Krein-Rutman theory does not apply anymore, however we can prove the following result based on a perturbation argument

**Theorem 3.5.66.** *Let us fix  $\alpha \in (\bar{\alpha}, 0)$ . Then there exists  $\varepsilon_2 \in (0, \varepsilon_1)$  such that for any  $\varepsilon \in [0, \varepsilon_2]$ , there hold*

(i) *The spectrum  $\Sigma(\mathcal{L}_\varepsilon)$  of  $\mathcal{L}_\varepsilon$  in  $L^2(m)$  writes*

$$\Sigma(\mathcal{L}_\varepsilon) \cup \Delta_\alpha = \{\mu_\varepsilon\},$$

*where  $\mu_\varepsilon$  is a eigenvalue simple. Moreover, since  $\mathcal{L}_\varepsilon$  remains in divergence form, we still have*

$$\mathcal{L}_\varepsilon^* 1 = 0$$

*and then  $\mu_\varepsilon = 0$ .*

(ii) *The linear semigroup  $S_{\mathcal{L}_\varepsilon}(t)$  associated to  $\mathcal{L}_\varepsilon$  in  $L^2(m)$  writes*

$$S_{\mathcal{L}_\varepsilon}(t) = e^{\mu_\varepsilon t} \Pi_\varepsilon + R_\varepsilon(t),$$

*where  $\Pi_\varepsilon$  is the projection on the eigenspace associated to  $\mu_\varepsilon$  and where  $R_\varepsilon(t)$  is a semigroup which satisfies*

$$\|R_\varepsilon(t)\|_{\mathcal{B}(L^2(m))} \leq C_{\mathcal{L}_{\varepsilon_1}} e^{\alpha t},$$

*for some positive constant  $C_{\mathcal{L}_{\varepsilon_1}}$  independent of  $\varepsilon$ .*

To enlighten the key points of the proof we present it in three steps: *accurate preliminaries, geometry of the spectrum* of the linear operator in the small connectivity regime and *sharp study of the spectrum close to 0*:

*Step 1. Accurate preliminaries:* Let us introduce the operator

$$P_\varepsilon = \mathcal{L}_\varepsilon - \mathcal{L}_0 = -\varepsilon \partial_v((v - \mathcal{J}(G_\varepsilon)) \cdot) + \varepsilon \mathcal{J}(\cdot) \partial_v G_\varepsilon.$$

Our aim is to estimate the convergence to 0 of this operator in a suitable norm. We notice that, for two exponential weights  $m_1, m_2$  as in (3.2.6) with  $\kappa_1 < \kappa_2$ , it holds

$$\begin{aligned} \|P_\varepsilon h\|_{L^2(m_1)}^2 &\leq C \varepsilon^2 \int_{\mathbb{R}^2} (h^2 + v^2 |\partial_v h|^2) m_1^2 + C \varepsilon^2 \mathcal{J}(h)^2 \\ &\leq C \varepsilon^2 (\|h\|_{L^2(m_1)}^2 + \|\partial_v h\|_{L^2(m_2)}^2), \end{aligned}$$

where  $C$  depends only on the parameters of the system and, in the small connectivity regime, on  $\varepsilon_1$ . Therefore, there exists  $C_{P_{\varepsilon_1}} > 0$  such that

$$\|P_\varepsilon h\|_{L^2(m_1)} \leq C_{P_{\varepsilon_1}} \varepsilon \|h\|_{H_v^1(m_2)}.$$

*Step 2. Geometry of the spectrum of  $\mathcal{L}_\varepsilon$ .*

**Lemma 3.5.67.** *For any  $z \in \Delta_\alpha$ ,  $z \neq 0$  let us define  $K_\varepsilon(z)$  by*

$$K_\varepsilon(z) = -P_\varepsilon \mathcal{R}_{\mathcal{L}_0}(z) \mathcal{A} \mathcal{R}_{\mathcal{B}_\varepsilon}(z).$$

*Then, there exists  $\eta_2(\varepsilon) \xrightarrow{\varepsilon \rightarrow 0} 0$ , such that*

$$\forall z \in \Omega_\varepsilon := \Delta_\alpha \setminus \bar{B}(0, \eta_2(\varepsilon)), \quad \|K_\varepsilon(z)\|_{\mathcal{B}(L^2(m))} \leq \eta_2(\varepsilon)(1 + \eta_2(\varepsilon)).$$

*Moreover, there exists  $\varepsilon_2 \in (0, \varepsilon_1]$  such that for any  $\varepsilon \in [0, \varepsilon_2]$  we have*

1.  $I + K_\varepsilon(z)$  is invertible for any  $z \in \Omega_\varepsilon$
2.  $\mathcal{L}_\varepsilon - z$  is also invertible for any  $z \in \Omega_\varepsilon$  and

$$\forall z \in \Omega_\varepsilon, \quad \mathcal{R}_{\mathcal{L}_\varepsilon}(z) = \mathcal{U}_\varepsilon(z)(I + K_\varepsilon(z))^{-1}$$

where

$$\mathcal{U}_\varepsilon(z) = \mathcal{R}_{\mathcal{B}_\varepsilon}(z) - \mathcal{R}_{\mathcal{L}_0}(z) \mathcal{A} \mathcal{R}_{\mathcal{B}_\varepsilon}(z).$$

We thus deduce that

$$\Sigma(\mathcal{L}_\varepsilon) \cap \Delta_\alpha \subset B(0, \eta_2(\varepsilon)).$$

*Proof.* We define  $m_1$  and  $m_2$  two exponential weights with  $m_1 = m$ . From Lemma 3.4.61, Proposition 3.4.63 and the Step 1 we get that for any  $z \in \Omega_\varepsilon$ , any  $h \in L^2(m)$

$$\begin{aligned} \|K_\varepsilon(z)h\|_{L^2(m)} &\leq \varepsilon C_{P_{\varepsilon_1}} \|\mathcal{R}_{\mathcal{L}_0}(z) \mathcal{A} \mathcal{R}_{\mathcal{B}_\varepsilon}(z)h\|_{H_v^1(m_2)} \\ &\leq \varepsilon C_{P_{\varepsilon_1}} C_{H_v^1}(1 + |z|^{-1}) \|\mathcal{A} \mathcal{R}_{\mathcal{B}_\varepsilon}(z)h\|_{L^2(m_2)} \\ &\leq \varepsilon C_{P_{\varepsilon_1}} C_{H_v^1}(1 + |z|^{-1}) C_{\varepsilon_1} \|h\|_{L^2(m)}, \end{aligned}$$

where  $C_{\varepsilon_1}$  is an upper bound of  $\|\mathcal{A} \mathcal{R}_{\mathcal{B}_\varepsilon}\|_{\mathcal{B}(L^2(m), L^2(m_2))}$  and do not depend on  $\varepsilon$ . Defining

$$\eta_2(\varepsilon) := (\varepsilon C_{P_{\varepsilon_1}} C_{H_v^1} C_{\varepsilon_1})^{1/2},$$

it holds

$$\|K_\varepsilon(z)\|_{\mathcal{B}(L^2(m))} \leq \eta_2(\varepsilon)^2(1 + \eta_2(\varepsilon)^{-1}) = \eta_2(\varepsilon)(1 + \eta_2(\varepsilon)), \quad \forall z \in \Omega_\varepsilon,$$

therefore, fixing  $\varepsilon_2 > 0$  such that

$$\eta_2(\varepsilon) < 1/2, \quad \forall \varepsilon \in (0, \varepsilon_2],$$

we obtain the invertibility of  $I + K_\varepsilon(z)$ .

Finally, for any  $z \in \Omega_\varepsilon$ :

$$(\mathcal{L}_\varepsilon - z)\mathcal{U}_\varepsilon(z) = I + K_\varepsilon(z),$$

then there exists a right inverse of  $\mathcal{L}_\varepsilon - z$ . The rest of the proof is similar to the proof of [154, Lemma 2.16].  $\square$

*Step 3. Sharp study of spectrum close to 0.*

Let us fix  $r \in (0, -\alpha]$  and choose any  $\varepsilon_r \in [0, \varepsilon_2]$  such that  $\eta_2(\varepsilon_r) < r$  in such a way that  $\Sigma(\mathcal{L}_\varepsilon) \cap \Delta_\alpha \subset B(0, r)$  for any  $\varepsilon \in [0, \varepsilon_r]$ . We may define the spectral projection operator

$$\Pi_\varepsilon := -\frac{1}{2\pi i} \int_{|z'|=r} \mathcal{R}_{\mathcal{L}_\varepsilon}(z') dz'.$$

We have then the

**Lemma 3.5.68.** *The operator  $\Pi_\varepsilon$  is well defined and bounded in  $L^2(m)$ . Moreover, for any  $\varepsilon \in [0, \varepsilon_r]$ , it holds*

$$\|\Pi_\varepsilon - \Pi_0\|_{\mathcal{B}(L^2(m))} \leq \eta_3(\varepsilon),$$

for some  $\eta_3(\varepsilon) \xrightarrow{\varepsilon \rightarrow 0} 0$ .

*Proof.* Let us notice that

$$\Pi_0 = -\frac{1}{2\pi i} \int_{|z'|=r} (\mathcal{R}_{\mathcal{B}_0}(z') - \mathcal{R}_{\mathcal{L}_0} \mathcal{A} \mathcal{R}_{\mathcal{B}_0}(z')) dz' = \frac{1}{2\pi i} \int_{|z'|=r} \mathcal{R}_{\mathcal{L}_0} \mathcal{A} \mathcal{R}_{\mathcal{B}_0}(z') dz'$$

and

$$\begin{aligned} \Pi_\varepsilon &= -\frac{1}{2\pi i} \int_{|z'|=r} (\mathcal{R}_{\mathcal{B}_\varepsilon}(z') - \mathcal{R}_{\mathcal{L}_0} \mathcal{A} \mathcal{R}_{\mathcal{B}_\varepsilon}(z')) (I + K_\varepsilon(z'))^{-1} dz' \\ &= \frac{1}{2\pi i} \int_{|z'|=r} \mathcal{R}_{\mathcal{B}_\varepsilon}(z') K_\varepsilon(z') (I + K_\varepsilon(z'))^{-1} dz' \\ &\quad + \frac{1}{2\pi i} \int_{|z'|=r} \mathcal{R}_{\mathcal{L}_0} \mathcal{A} \mathcal{R}_{\mathcal{B}_\varepsilon}(z') (I + K_\varepsilon(z'))^{-1} dz'. \end{aligned}$$

Then, we deduce that

$$\begin{aligned} \Pi_\varepsilon - \Pi_0 &= \frac{1}{2\pi i} \int_{|z'|=r} \mathcal{R}_{\mathcal{B}_\varepsilon}(z') K_\varepsilon(z') (I + K_\varepsilon(z'))^{-1} dz' \\ &\quad + \frac{1}{2\pi i} \int_{|z'|=r} \mathcal{R}_{\mathcal{L}_0} \mathcal{A} (\mathcal{R}_{\mathcal{B}_\varepsilon}(z') - \mathcal{R}_{\mathcal{B}_0}(z')) dz' \\ &\quad + \frac{1}{2\pi i} \int_{|z'|=r} \mathcal{R}_{\mathcal{L}_0} \mathcal{A} \mathcal{R}_{\mathcal{B}_\varepsilon}(z') (I - (I + K_\varepsilon(z'))^{-1}) dz', \end{aligned}$$

here, the first and third terms are going to 0 because of the upper bounds of  $K_\varepsilon(z)$ . For the second term, it suffices to notice that

$$\mathcal{R}_{\mathcal{B}_\varepsilon}(z') - \mathcal{R}_{\mathcal{B}_0}(z') = \mathcal{R}_{\mathcal{B}_0}(z') (\mathcal{B}_\varepsilon - \mathcal{B}_0) \mathcal{R}_{\mathcal{B}_\varepsilon}(z'),$$

and use that  $(\mathcal{B}_\varepsilon - \mathcal{B}_0) = P_\varepsilon$ . □

To conclude the proof we recall the following lemma from [86, paragraph I.4.6]

**Lemma 3.5.69.** *Let  $X$  be a Banach space and  $P, Q$  two projectors in  $\mathcal{B}(X)$  such that  $\|P - Q\|_{\mathcal{B}(X)} < 1$ . Then the ranges of  $P$  and  $Q$  are isomorphic. In particular,  $\dim(R(P)) = \dim(R(Q))$ .*

Provided with this lemma and fixing  $\varepsilon'$  such that  $\eta_3(\varepsilon') < 1$ , we get the

**Corollary 3.5.70.** *There exists  $\varepsilon' > 0$  such that for any  $\varepsilon \in [0, \varepsilon']$  there holds*

$$\Sigma(\mathcal{L}_\varepsilon) \cap \Delta_\alpha = \{\mu_\varepsilon\} \quad \text{and the eigenspace associated to } \mu_\varepsilon \text{ is 1-dimensional.}$$

### 3.5.3 Exponential stability of the NL equation

In the small connectivity regime  $\varepsilon \in (0, \varepsilon')$ , let us consider the variation  $h := f_\varepsilon - G_\varepsilon$ , with  $f_\varepsilon$  the solution to (3.1.2) and  $G_\varepsilon$  the unique solution to (3.2.12) given by Theorem 3.2.46. By definition,  $h$  satisfies the evolution PDE:

$$\partial_t h = \mathcal{L}_0 h - \varepsilon \partial_v(vh) + \varepsilon \mathcal{J}(f_\varepsilon) \partial_v f_\varepsilon - \varepsilon \mathcal{J}(G_\varepsilon) \partial_v G_\varepsilon = \mathcal{L}_\varepsilon h + \varepsilon \mathcal{J}(h) \partial_v h,$$

moreover, the nonlinear part is such that

$$\|\varepsilon \mathcal{J}(h) \partial_v h\|_{L^2(m)} \leq C \varepsilon \|h\|_{L^2(m)} \|\partial_v h\|_{L^2(m)}$$

for some positive constant  $C$ .

*Proof of Theorem 3.2.47.* Let us first notice that, thanks to inequality (3.2.10) and the definition of  $\mathcal{J}(\cdot)$ , we have that

$$\|\varepsilon \mathcal{J}(h) \partial_v h\|_{L^2(m)} \leq C_{NL} \varepsilon \|h\|_{L^2(m)}, \quad \forall h_0 \in H^1(m),$$

where

$$C_{NL} = c_\delta^{-1} \max(C_2, \|h_0\|_{H^1(m)}).$$

On the other hand, Duhamel's formula reads

$$h = S_{\mathcal{L}_\varepsilon}(t) h_0 + \int_0^t S_{\mathcal{L}_\varepsilon}(t-s) (\varepsilon \mathcal{J}(h) \partial_v h) ds,$$

then, we have that

$$\begin{aligned} u(t) := \|h\|_{L^2(m)} &\leq \|S_{\mathcal{L}_\varepsilon}(t) h_0\|_{L^2(m)} + \int_0^t \|S_{\mathcal{L}_\varepsilon}(t-s) (\varepsilon \mathcal{J}(h) \partial_v h)\|_{L^2(m)} ds \\ &\leq C_{\mathcal{L}_{\varepsilon_1}} e^{\alpha t} \|h_0\|_{L^2(m)} + C_{\mathcal{L}_{\varepsilon_1}} C_{NL} \varepsilon \int_0^t e^{\alpha(t-s)} \|h\|_{L^2(m)} ds \\ &= C_{\mathcal{L}_{\varepsilon_1}} e^{\alpha t} u(0) + C_{\mathcal{L}_{\varepsilon_1}} C_{NL} \varepsilon \int_0^t e^{\alpha(t-s)} u(s) ds. \end{aligned}$$

In particular,

$$u(t) \leq C_{\mathcal{L}_1} u(0) e^{(\alpha + C_{\mathcal{L}_{\varepsilon_1}} C_{NL} \varepsilon) t},$$

Summarising, it suffices to define  $\eta^*(\varepsilon) := C_2/\sqrt{\varepsilon}$  to get that for any  $f_0$  such that

$$\|f_0 - G_\varepsilon\|_{H^1(m)} \leq \eta^*(\varepsilon),$$

it holds

$$\|f_\varepsilon(t) - G_\varepsilon\|_{L^2(m)} \leq C_{\mathcal{L}_{\varepsilon_1}} \|f_0 - G_\varepsilon\|_{L^2(m)} e^{\alpha^* t},$$

with

$$\alpha^* = \alpha + C_{\mathcal{L}_{\varepsilon_1}} c_\delta^{-1} C_2 \sqrt{\varepsilon^*} < 0,$$

if  $\varepsilon^*$  is small enough. □

## 3.6 Open problems beyond the weak coupling regime ---

In the weak coupling regime, we have demonstrated that existence and uniqueness of solutions persist. In that regime, noise overcomes nonlinear effects and the system is mixing: one finds a unique distribution with an everywhere strictly positive density. As coupling increases, highly non-trivial phenomena may emerge as nonlinear effects of the McKean-Vlasov equation. For instance, it is likely that in another asymptotic regime in which coupling is non-trivial and noise goes to zero, Dirac-delta distributed solutions shall emerge (in which all neurons are synchronized and their voltage and adaptation variable are equal to one of the stable fixed point of the deterministic Fitzhugh-Nagumo ODE).

Here, we numerically explore the dynamics of the Fitzhugh-Nagumo McKean-Vlasov equation using a Monte-Carlo algorithm. We observe that complex phenomena occur as the coupling is varied. That numerical evidence tends to show that several additional equilibria may emerge, the stability of stationary solutions may change as a function of connectivity levels, and attractive periodic solution in time may emerge. These regimes are particularly interesting from the application viewpoint: indeed, among important collective effects in biology, from large networks often emerge bistable high-state of down-states (characterized by high or low firing rates), and even oscillations. These two phenomena are particularly important in developing and storing memories, and this occurs by slowly reinforcing connections [83]. Interestingly, these two types of behaviors emerge naturally in the FhN McKean Vlasov equation beyond weak coupling. For instance, for fixed  $\sigma = 0.5$ , we present the solutions of the particle system varying the connectivity weight beyond small values, both in the bistable case (in which the FhN model presents two stable attractors) and the excitable regime, the most relevant for biological applications, characterized by a single stable equilibrium and a manifold separating those trajectories doing large excursions (spikes) from those returning to the resting state directly. In both cases, we observe (i) that the unique stationary solution is not centered close from a fixed point of the dynamical system: neurons intermittently fire in an asynchronous manner for small coupling. As coupling increases, a periodic attractive solution emerges, before the appearance of distinct stationary solutions (two in the bistable case, one in the excitable case). These phenomena are depicted in Fig. 3.1. Proving, for larger coupling, the existence and stability of a periodic solution or distinct and multiple stationary solutions constitute exciting perspectives of this work.

These phenomena are actually conjectured to be generic in coupled excitable systems subject to noise.

## 3.7 Appendix A: Mean-Field limit for Fitzhugh-Nagumo neurons ---

Let us start by a well known result with is a simple application of global existence and path wise uniqueness for system of SDE, see [56, Chapter 5, Theorems 3.7 and 3.11] for example. Consider the



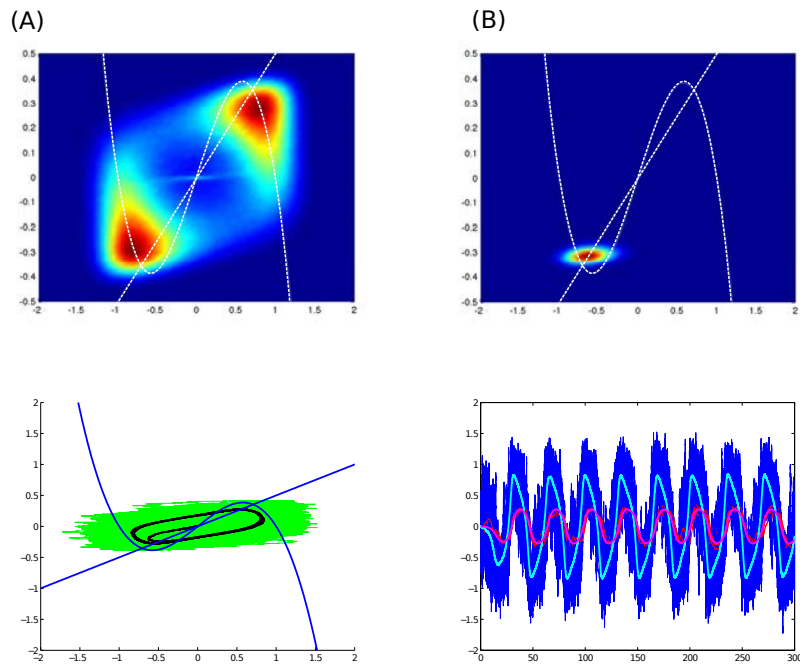


Figure 3.1: Permanent (non-transient) regimes of the FhN particle system for  $N = 2000$ . Top row:  $J = 0.1$  (A) and  $J = 3$  (B), bottom row:  $J = 1$ . The unique stationary solution in the small coupling limit analyzed in the manuscript visits both attractors transiently (A), while in the high coupling regime (B), the system remains around one of the attractors (the system has at least two such solutions). In an intermediate regime, the system shows periodic oscillations (bottom row).

particle system for  $1 \leq i \leq N$ :

$$\begin{cases} dv_t^i = (v_t^i(v_t^i - \lambda)(1 - v_t^i) - x_t^i + I_0) dt + \frac{J}{N} \sum_{j=1}^N (v_t^i - v_t^j) dt + dW_t^i \\ dx_t^i = (-ax_t^i + bv_t^i) dt, \end{cases} \quad (3.7.37)$$

with initial data  $(X_0^i, V_0^i)$  for  $1 \leq i \leq N$  distributed according to  $f_0 \in \mathbb{P}_2(\mathbb{R}^2)$ , i.e., a probability measure in  $\mathbb{R}^2$  with finite second moment. Here the  $(W_t^i)_{t \geq 0}$  are  $n$  independent standard Brownian motions in  $\mathbb{R}$ . This result was stated in [10]. In that paper, the authors use a stopping in the  $n$ -voltage variables which requires finely controlling all trajectories. We prove here a simpler version of the result based on *a-priori* estimates.

**Lemma 3.7.71.** *Let  $f_0 \in \mathbb{P}(\mathbb{R}^2)$  be a probability with finite second moment, and a set of random variables  $(X_0^i, V_0^i)$  with law  $f_0$ . Then (3.7.37) admits a path wise unique global solution with initial datum  $(X_0^i, V_0^i)$  for  $1 \leq i \leq N$ .*

*Proof.* The system (3.7.37) can be written in  $\mathbb{R}^{2N}$  as the SDE

$$d\mathbf{Z}_t^N = \sigma^N d\mathbf{B}_t^N + \mathbf{b}(\mathbf{Z}_t^N) dt,$$

where  $\mathbf{Z}_t^N = (x_t^1, v_t^1, \dots, x_t^N, v_t^N)$ ,  $\sigma^N$  is a constant  $2N \times 2N$  sparse matrix,  $(\mathbf{B}_t^N)_{t \geq 0}$  is a standard Brownian motion on  $\mathbb{R}^{2N}$ , and  $\mathbf{b} : \mathbb{R}^{2N} \rightarrow \mathbb{R}^{2N}$  is a function defined in the obvious way. It is easy to see that  $\mathbf{b}$  is a locally Lipschitz function, moreover, letting  $\langle \cdot, \cdot \rangle$  and  $\|\cdot\|$  the scalar product and the Euclidean norm on  $\mathbb{R}^{2N}$  respectively, then for all  $\mathbf{Z}^N = (x^1, v^1, \dots, x^N, v^N)$ ,

$$\begin{aligned} \langle \mathbf{Z}^N, \mathbf{b}(\mathbf{Z}^N) \rangle &= \sum_{i=1}^N x^i (-ax^i + bv^i) + \sum_{i=1}^N v^i (v^i(v^i - \lambda)(1 - v^i) - x^i + I_0) + \frac{J}{N} \sum_{i,j=1}^N v^i (v^i - v^j) \\ &\leq \sum_{i=1}^N (b-1)x^i v^i + \sum_{i=1}^N (J|v^i|^2 - a|x^i|^2) - \frac{J}{N} \sum_{i,j=1}^N v^i v^j + CN \\ &\leq C(1 + \|\mathbf{Z}^N\|^2). \end{aligned}$$

This is a sufficient condition for global existence and pathwise uniqueness (see e.g. [100]).  $\square$

## Mean-Field limit

Now we turn to the propagation of chaos property. We already know the existence and uniqueness of the particle system (3.7.37), moreover the nonlinear SDE:

$$\begin{cases} d\bar{v}_t = (\bar{v}_t(\bar{v}_t - \lambda)(1 - \bar{v}_t) - \bar{x}_t + I) dt + J \int_{\mathbb{R}^2} (\bar{v}_t - v) df_t(x, v) dt + dW_t, \\ d\bar{x}_t = (-a\bar{x}_t + b\bar{v}_t) dt \\ f_t = \text{law}(\bar{x}_t, \bar{v}_t), \quad \text{law}(\bar{x}_0, \bar{v}_0) = f_0. \end{cases} \quad (3.7.38)$$

is also well-posed for  $f_0 \in L^1(M^2) \cap L^1 \log L^1 \cap \mathbb{P}(\mathbb{R}^2)$ , as a consequence of Theorem 3.2.45. Then, for instance, we can state the

**Theorem 3.7.72.** Let  $f_0$  be a Borel probability measure and  $(X_0^i, V_0^i)$  for  $1 \leq i \leq N$  be  $N$  independent variables with law  $f_0$ . Let us assume that the solutions to (3.7.37) and (3.7.38) with initial data  $(X_0^i, V_0^i)$  and  $f_0$  are well defined on  $[0, T]$  and such that

$$\sup_{[0, T]} \left\{ \int_{\mathbb{R}^2} (|x|^2 + |v|^2) df_t(x, v) \right\} < +\infty, \quad (3.7.39)$$

with  $f_t = \text{law}(\bar{x}_t^i, \bar{v}_t^i)$  (which actually does not depend on  $i$  by exchangeability). Then there exists a constant  $C > 0$  such that

$$\mathbb{E}[|x_t^i - \bar{x}_t^i|^2 + |v_t^i - \bar{v}_t^i|^2] \leq \frac{C}{N} e^{Ct}. \quad (3.7.40)$$

*Proof.* We start by writing  $X_t^i = x_t^i - \bar{x}_t^i$  and  $V_t^i = v_t^i - \bar{v}_t^i$ . For notational convenience we drop the time dependence subindex and take  $J = 1$ . Because  $x_t^i$  and  $\bar{x}_t^i$  are driven by the same Brownian motion, we have that

$$\begin{cases} dV^i = (v^i(v^i - \lambda)(1 - v^i) - \bar{v}^i(\bar{v}^i - \lambda)(1 - \bar{v}^i) - X^i) dt + \frac{1}{N} \sum_{j=1}^N (v_t^i - v_t^j) dt - \int_{\mathbb{R}^2} (\bar{v}^i - v) df_t(x, v) dt \\ dX^i = (-aX^i + bV^i) dt, \end{cases}$$

We define  $\alpha(t) = \mathbb{E}[|X^i|^2 + |V^i|^2]$  which is independent of the label  $i$  by symmetry and exchangeability of the system. It is not hard to see that

$$\frac{1}{2} \frac{d}{dt} \mathbb{E}[|X^i|^2] = \mathbb{E}[b|X^i| |V^i| - a|X^i|^2] \leq \frac{b}{2} \alpha(t),$$

and

$$\begin{aligned} \frac{1}{2} \frac{d}{dt} \mathbb{E}[|V^i|^2] &= \mathbb{E}[V^i(v^i(v^i - \lambda)(1 - v^i) - \bar{v}^i(\bar{v}^i - \lambda)(1 - \bar{v}^i) - X^i)] \\ &\quad + \mathbb{E}\left[\frac{V^i}{N} \sum_{j=1}^N (v_t^i - v_t^j) dt - V^i \int_{\mathbb{R}^2} (\bar{v}^i - v) df_t(x, v)\right] =: \mathcal{S}_1 + \mathcal{S}_2. \end{aligned}$$

*Estimate for  $\mathcal{S}_1$ :* Let us first notice that

$$\begin{aligned} v^i(v^i - \lambda)(1 - v^i) - \bar{v}^i(\bar{v}^i - \lambda)(1 - \bar{v}^i) &= -(|v^i|^3 - |\bar{v}^i|^3) + (1 + \lambda)(|v^i|^2 - |\bar{v}^i|^2) - \lambda V^i \\ &= -V^i(|v^i|^2 + v^i \bar{v}^i + |\bar{v}^i|^2) + (1 + \lambda)V^i(|v^i| + |\bar{v}^i|) - \lambda V^i, \end{aligned}$$

therefore

$$\mathcal{S}_1 = \mathbb{E}[|V^i|^2(-|v^i|^2 - v^i \bar{v}^i - |\bar{v}^i|^2 + (1 + \lambda)(|v^i| + |\bar{v}^i|) - \lambda)] - \mathbb{E}[V^i X^i],$$

and by consequence there is some constant  $C > 0$  such that

$$\mathcal{S}_1 \leq C\alpha(t). \quad (3.7.41)$$

*Estimate for  $\mathcal{S}_2$ :* By definition, it holds

$$\begin{aligned} \mathcal{S}_2 &= \mathbb{E}\left[V^i(v_t^i - \bar{v}^i) - \frac{V^i}{N} \sum_{j=1}^N (v_t^j - \int_{\mathbb{R}^2} v df_t(x, v))\right] \\ &= \mathbb{E}[|V^i|^2] - \frac{1}{N} \mathbb{E}\left[V^i \sum_{j=1}^N (v_t^j - \int_{\mathbb{R}^2} v df_t(x, v))\right]. \end{aligned}$$

Moreover, by symmetry we know that  $\mathcal{S}_2$  does not depend on a particular  $i$ , therefore we take  $i = 1$  to get

$$\mathcal{S}_2 \leq \mathbb{E} [|V^1|^2] + \frac{1}{N} \left( \mathbb{E} [|V^1|^2] \right)^{1/2} \left( \mathbb{E} \left[ \left| \sum_{j=2}^N \left( v_t^j - \int_{\mathbb{R}^2} v df_t(x, v) \right) \right|^2 \right] \right)^{1/2}.$$

Now, defining  $Y^j = v_t^j - \int_{\mathbb{R}^2} v df_t(x, v)$ , for  $j \neq k$ , we find that

$$\mathbb{E}[Y^j Y^k] = \mathbb{E} \left[ \mathbb{E}[Y^j | (\bar{x}^1, \bar{v}^1)] \mathbb{E}[Y^k | (\bar{x}^1, \bar{v}^1)] \right],$$

but

$$\mathbb{E}[Y^j | (\bar{x}^1, \bar{v}^1)] = \mathbb{E} \left[ v_t^j - \int_{\mathbb{R}^2} v df_t(x, v) \right] = 0.$$

Hence, fixing  $j_* \in \{2, \dots, N\}$

$$\begin{aligned} \mathbb{E} \left[ \left| \sum_{j=2}^N \left( v_t^j - \int_{\mathbb{R}^2} v df_t(x, v) \right) \right|^2 \right] &= (N-1) \mathbb{E} \left[ \left| v_t^{j_*} - \int_{\mathbb{R}^2} v df_t(x, v) \right|^2 \right] \\ &= (N-1) \int_{\mathbb{R}^2} \left( w - \int_{\mathbb{R}^2} v df_t(x, v) \right)^2 df_t(y, w) \leq C(N-1), \end{aligned}$$

since the second moment of  $f_t$  is uniformly bounded in  $[0, T]$ . Finally we conclude that

$$\mathcal{S}_2 \leq \alpha(t) + \alpha(t)^{1/2} \frac{C}{\sqrt{N}}. \quad (3.7.42)$$

Finally, going back to the bounds on  $\alpha(t)$ , we put together (3.7.41) and (3.7.42) to find

$$\frac{d}{dt} \alpha(t) \leq C\alpha(t) + 2\alpha(t)^{1/2} \frac{C}{\sqrt{N}} \leq C\alpha(t) + \frac{C}{N},$$

and using Grönwal's Lemma,

$$\alpha(t) \leq \left( \alpha(0) + \frac{C}{N} \right) e^{Ct} = \frac{C}{N} e^{Ct}$$

which finishes the proof.  $\square$

## 3.8 Appendix B: Strong maximum principle for the linearized operator

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In this final appendix we shall extend the result provided in [159, Corollary A.20] to our framework. These local positivity estimates are classical in hypoelliptic equations and they are a necessary condition for Theorem 3.2.46. Here, our result is time dependant and by consequence more general than it is needed in the applications.

In the sequel, we shall use the notation

$$B_r(x_0, v_0) := \{(x, v) \in \mathbb{R}^2; \quad |v - v_0| \leq r, |x - x_0| \leq r^3\},$$

and come back to the classical notation  $\nabla_{x,v} = D_{x,v}$  and  $\partial_{vv}^2 = \Delta_v$ . Also, we simplify the problem by choosing  $a = b = 1$ , but the proof can be easily extended to the general case.

**Theorem 3.8.73.** *Let  $f(t, x, v)$  be a classical nonnegative solution of*

$$\frac{\partial}{\partial t} f - \Delta_v f = A(t, x, v) \nabla_v f + B(x, v) \nabla_x f + C(t, x, v) f \quad (3.8.43)$$

*in  $[0, T) \times \Omega$ , where  $\Omega$  is an open subset of  $\mathbb{R}^2$ , and  $A, C : [0, T) \times \mathbb{R}^2$  and bounded continuous functions and  $B(x, v) = x - v$ . Let  $(x_0, v_0) \in \Omega$  and  $\bar{A}$  and  $\bar{C}$  upper bounds of respectively  $\|A\|_{L^\infty}$  and  $\|C\|_{L^\infty}$ .*

*Then, for any  $r, \tau > 0$  there are constants  $\lambda, K > 0$ , only depending on  $\bar{A}, \bar{C}$  and  $r^2/\tau$  such that the following holds: If  $B_{\lambda r}(x_0, v_0) \subset \Omega$ ,  $\tau < \min(1/2, -\log(r^3/2|x_0 - v_0|))$  and  $f \geq \delta > 0$  in  $[\tau/2, \tau) \times B_r(x_0, v_0)$ , then  $f \geq K\delta$  in  $[\tau/2, \tau) \times B_{2r}(x_0, v_0)$ .*

Theorem 3.8.73 implies, via covering arguments in variables  $t, x, v$  the

**Corollary 3.8.74.** *If  $f \geq 0$  solves (3.8.43) in  $[0, T) \times \Omega$  and  $f \geq \delta > 0$  in  $[0, T) \times B_r(x_0, v_0)$ , then for any compact set  $K \subset \Omega$  containing  $(x_0, v_0)$  and for any  $t_0 \in (0, T)$ , we have  $f \geq \delta' > 0$  in  $[t_0, T) \times K$  where  $\delta'$  only depends on  $\bar{A}, \bar{C}, K, \Omega, x_0, v_0, r, t_0, \delta$ .*

*Proof of Theorem 3.8.73.* We only explain how to adapt the proof of Theorem A.19 given in [159]. Let  $g = e^{\bar{C}t} f(t, x, v)$ ; then  $g \geq f$  and  $\mathcal{L}g \geq 0$  in  $(0, T) \times \Omega$ , where

$$\mathcal{L} = \partial_t + (v - x) \nabla_x - \Delta_v - A(t, x, v) \nabla_v.$$

Next, we construct a particular subsolution for  $\mathcal{L}$ . In the sequel,  $B_r$  stands for  $B_r(x_0, v_0)$  and we define  $X_t(x_0, v_0) = v_0 + (x_0 - v_0)e^{-t}$ .

*Step 1. Construction of the subsolution.*

For  $t \in (0, \tau]$  and  $(x, v) \in \Omega \setminus B_r$  let

$$P(t, x, v) = \alpha \frac{(v - v_0)^2}{2t} - \frac{\beta}{t^2} (v - v_0)(x - X_t) + \gamma \frac{(x - X_t)^2}{2t^3},$$

with  $\alpha, \beta, \gamma > 0$  to be chosen later on. Let further define

$$\varphi(t, x, v) = \delta e^{-\mu P(t, x, v)} - \varepsilon,$$

where  $\mu, \varepsilon > 0$  will also be chosen later on. If we assume that  $\beta^2 < \alpha\gamma$ , then  $P$  is a positive quadratic form in the variables  $v - v_0$  and  $x - X_t$ . Clearly

$$\mathcal{L}\varphi = -\mu \delta e^{-\mu P} \mathcal{E}(P),$$

where

$$\mathcal{E}(P) = \partial_t P + (v - x) \nabla_x P - \Delta_v P + \mu |\nabla_v P|^2 - A(t, x, v) \nabla_v P.$$

By straightforward computation we find that  $\mathcal{E} = \mathcal{E}_1 + \mathcal{E}_2$ , with

$$\begin{aligned} \mathcal{E}_1(P) &= \left( \mu \alpha^2 - \frac{\alpha}{2} - \beta \right) \frac{(v - v_0)^2}{t^2} + 2 \left( \beta + \frac{\gamma}{2} - \mu \alpha \beta \right) \frac{(v - v_0)(x - X_t)}{t^3} \\ &\quad + \left( \mu \beta^2 - \frac{3\gamma}{2} \right) \frac{(x - X_t)^2}{t^4} \end{aligned}$$

and

$$\begin{aligned}\mathcal{E}_2(P) &= \beta \frac{(v-v_0)(x-X_t)}{t^2} - \alpha \frac{1}{t} \\ &\quad - \gamma \frac{(x-X_t)^2}{t^3} - \alpha \frac{A(t,x,v)(v-v_0)}{t} + \beta \frac{A(t,x,v)(x-X_t)}{t^2}.\end{aligned}$$

Now we notice that  $\mathcal{E}_1$  is defined by the quadratic form

$$M_q = \begin{bmatrix} \mu \alpha^2 - \frac{\alpha}{2} - \beta & \beta + \frac{\gamma}{2} - \mu \alpha \beta \\ \beta + \frac{\gamma}{2} - \mu \alpha \beta & \mu \beta^2 - \frac{3\gamma}{2} \end{bmatrix}$$

which is nothing but a quadratic polynomial on  $(v-v_0)/t$  and  $(x-X_t)/t^2$ . As  $\mu \rightarrow \infty$

$$\begin{cases} \text{tr } M_q = \mu(\alpha^2 + \beta^2) + O(1) \\ \det M_q = \mu \left[ \frac{3\alpha\beta^2}{2} + \alpha\beta\gamma - \beta^3 - \frac{3\alpha^2\gamma}{2} \right] + O(1), \end{cases}$$

both positive quantities if  $\beta > \alpha$  and  $\alpha\gamma > \beta^2$ . In particular, for  $\beta = 2\alpha$  and  $\gamma = 8\alpha$ ,

$$\begin{cases} \text{tr } M_q = 5\alpha^2\mu + O(1) \\ \det M_q = 2\alpha^3\mu + O(1), \end{cases}$$

and letting  $\mu \rightarrow \infty$  the eigenvalues of  $M_q$  are of order  $\mu\beta^2$  and  $\beta$ . So, for any fixed  $C > 0$  we may choose  $\alpha, \beta, \gamma$  and  $\mu$  such that

$$\mathcal{E}_1(P) \geq C\beta \left( \frac{(v-v_0)^2}{t^2} + \frac{(x-X_t)^2}{t^4} \right).$$

Second, if  $t \in (0, 1)$  then

$$\mathcal{E}_2(P) \geq -4\beta \frac{(x-X_t)^2}{t^4} - \frac{3\beta(v-v_0)^2}{2} - \frac{3\beta(x-X_t)^2}{2t^4} - 2\beta\bar{A}^2 - \frac{\beta}{2t},$$

and making  $\tau \leq 1$ , we get,

$$\mathcal{E}(P) \geq \text{const} \frac{\beta}{t} \left[ C \left( \frac{(v-v_0)^2}{t} + \frac{(x-X_t)^2}{t^3} \right) - 1 \right],$$

with  $C$  arbitrarily large.

Let us briefly describe the rest of the proof. Recall that  $(x, v) \notin B_r$  so

1. either  $|v-v_0| \geq r$ , then  $\mathcal{E}(P) \geq \text{const} \cdot (\beta/t)[Cr^2/\tau - 1]$ , which is positive for  $C > \tau/r^2$ ;
2. or  $|x-x_0| \geq r^3$ , and then, if  $\tau \leq \frac{1}{2} \min(1, -\log(\frac{r^3}{|x_0-v_0|}))$  then for any  $t \in [0, \tau)$

$$|X_t - x_0| \leq r^3/2 \quad \text{and} \quad \frac{|x-X_t|^2}{t^2} \geq \frac{|x-x_0|^2}{2t^2} - \frac{|X_t-x_0|^2}{t^2} \geq \frac{r^6}{4\tau^2},$$

so  $\mathcal{E}(P) \geq \text{const} \cdot (\beta/t)[Cr^6/4\tau^3 - 1]$ , which is positive as soon as  $C > 4\tau^3/r^6$ .

Summarizing: under the assumptions, we can always choose constants  $\gamma > \beta > \alpha > 1$  and  $\alpha\gamma > \beta^2$ , depending only on  $\bar{A}$  and  $r^2/\tau$ , so that

$$\mathcal{L}\varphi \geq 0, \quad \text{in } [0, \tau) \times (B_{\lambda r} \setminus B_r),$$

as soon as  $\tau < \min(1/2, -\log(r^3/2|x_0 - v_0|))$ .

*Step 2. Boundary conditions.* We now wish to prove that  $\varphi \leq g$  for  $t = 0$  and for any  $(x, v) \in \partial(B_{\lambda r} \setminus B_r)$ ; then classical maximum principle will do the rest.

Let us first notice that the boundary condition at  $t = 0$  is obvious ( $\varphi$  can be extended by continuity by 0 at the initial time). The condition at  $\partial B_r$  is also true since  $\forall (x, v) \in \partial B_r: \varphi \leq \delta \leq g$ .

It remains to fix the remaining parameters in order to conclude that  $\varphi \leq g$  in  $\partial B_{\lambda r}$ . From the choice of  $\alpha, \beta$  and  $\gamma$ , it is easy to see that for any  $(x, v) \in \partial B_{\lambda r}$  :

$$P(t, x, v) \geq \frac{\alpha}{4} \left( \frac{(v - v_0)^2}{t} + \frac{(x - X_t)^2}{t^3} \right) \geq \frac{\alpha}{4} \min \left( \frac{\lambda^2 r^2}{\tau}, \frac{\lambda^6 r^6}{4\tau^3} \right) \geq \frac{\alpha \lambda^2}{16} \min \left( \frac{r^2}{\tau}, \frac{r^6}{\tau^3} \right),$$

notice that we are imposing  $\lambda > 1$ . Choosing

$$\varepsilon = \delta \exp \left( - \frac{\mu \alpha \lambda^2}{16} \min \left( \frac{r^2}{\tau}, \frac{r^6}{\tau^3} \right) \right),$$

we get  $\varphi = \delta e^{-\mu P(t, x, v)} - \varepsilon \leq 0$  on  $\partial B_{\lambda r}$ . By consequence  $\varphi \leq g$  on the whole set  $B_{\lambda r}$ .

Let us finally notice that at this point we have uniform bounds for  $g$  on  $B_{2r} \setminus B_r$  for any  $t \in [\tau/2, \tau)$ . Indeed,

$$P(t, x, v) \leq 2\gamma \left( \frac{(v - v_0)^2}{t} + \frac{(x - X_t)^2}{t^3} \right) \leq 2\gamma \left( \frac{8r^2}{\tau} + \frac{1026r^6}{\tau^3} \right) \leq 2068\gamma \max \left( \frac{r^2}{\tau}, \frac{r^6}{\tau^3} \right)$$

Then, for  $\lambda$  big enough we find  $K_0 > 0$  such that

$$\varphi(t, x, v) \geq \delta \left[ \exp \left( - 2068\mu\gamma \max \left( \frac{r^2}{\tau}, \frac{r^6}{\tau^3} \right) \right) - \exp \left( - \frac{\mu \alpha \lambda^2}{16} \min \left( \frac{r^2}{\tau}, \frac{r^6}{\tau^3} \right) \right) \right] \geq K_0 \delta,$$

because  $\gamma = 8\alpha$ , to find such  $\lambda$  it suffices that

$$2068 \times 16 \times 8 \max \left( \frac{r^2}{\tau}, \frac{r^6}{\tau^3} \right) \leq \lambda^2 \min \left( \frac{r^2}{\tau}, \frac{r^6}{\tau^3} \right),$$

by consequence  $\lambda$  depends only on  $r^2/\tau$ .

Finally, we find  $K, \lambda > 0$  depending on  $\bar{A}, \bar{C}$  and  $r^2/\tau$  such that

$$f \geq K_0 \delta e^{-\tau \bar{C}} \quad \text{on} \quad [\tau/2, \tau) \times (B_{2r} \setminus B_r).$$

□

**Remark 3.8.75.** *Let us notice that we can extend Theorem 3.8.73 to some cases when  $A$  or  $C$  are not necessarily bounded and  $\Omega = \mathbb{R}^2$ . It suffices to take any  $r, \tau > 0$  and fix  $\lambda$  (which as we saw only depends on a numerical constant and the ratio  $r^2/\tau$ ). We can then fix  $R > 0$  big enough, in order to have that  $\lambda r < R$  and study the equation into  $B_R$ , where by continuity  $A$  and  $C$  attain their maximum in the compact set  $[0, \tau] \times \bar{B}_R$ .*

## Part II

# The role of homeoprotein diffusion in morphogenesis





# Local homeoprotein reaction-diffusion can stabilize boundaries generated by graded positional cues

Boundary formation in the developing neuroepithelium decides on the position and size of compartments in the adult nervous system. In this study we start from the French flag model proposed by Lewis Wolpert in which boundaries are formed through the combination of morphogen diffusion and of thresholds in cell responses. In contemporary terms, a response is characterized by the expression of cell autonomous transcription factors, very often of the homeoprotein family. Theoretical studies suggest that this sole mechanism results in the formation of boundaries of imprecise shapes and positions. Turing, on the other hand, proposed a model whereby two morphogens exhibiting self-activation and reciprocal inhibition, uniformly distributed and diffusing at different rates lead to the formation of territories of unpredictable shapes and positions but with sharp boundaries (the leopard spots). Here we have combined the two models and compared the stability of boundaries when the hypothesis of local homeoprotein intercellular diffusion is, or is not, introduced in the equations. We find that the addition of the homeoprotein local diffusion leads to a dramatic stabilization of the positioning of the boundary, even when other parameters are significantly modified. This novel combined model has thus important theoretical consequences for our understanding of the role of homeoproteins intercellular diffusion in developmental robustness and of the changes that take place in the course of evolution.

This paper is included in [127] written in collaboration with A. Prochiantz and J. Touboul to appear in *Development*.

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## 4.1 Introduction

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The specification of territories in the nervous system relies on the precise positioning of boundaries between different functional areas [60, 90, 91]. Each territory is characterized by the expression of a specific combination of molecular marks, including transcription factors (TFs), before developing into areas endowed with specific functions [119, 170]. The emergence of compartments in the cerebral cortex or in the spinal cord is a paradigmatic example of this process. From a theoretical perspective, the specification of territories in the nervous system represents a particular case of the general phenomenon of patterning. We owe to Alan Turing the first theoretical model of how patterns form. In his 1952 seminal article “The chemical basis of morphogenesis” Turing explains how reaction-diffusion properties of two morphogens, in the presence of a catalyst, can lead to the emergence of heterogeneities even if the tissue is initially homogeneous [155]. This universal pattern formation mechanism through Turing instabilities has become increasingly popular in the developmental biology community [84, 101, 135, 130, 167]. In Turing's model and its enriched versions, in particular those proposed by Meinhardt and colleagues [108], the interaction of a limited number of molecular species can create regular spatial patterns, provided that they exhibit different diffusion constants and have auto-activating and reciprocal inhibitory properties. In all cases, Turing-like mechanisms alone do not lead to the emergence of predictable shapes.

Another popular patterning mechanism has been proposed in 1969 by Lewis Wolpert [164] with the concept of Positional Information (PI). This model, also known as the French Flag Model (FFM), requires a continuous morphogen gradient and the existence of thresholds. A typical abstract example is the differentiation of cells into blue, white and red populations when exposed to high, intermediate or low morphogen levels (thus the FFM), each territory corresponding to the expression of specific genes, in many cases transcription factors (TFs) defining specific areas within the neuroepithelium. This model has since evolved considerably to take into account the complexity of the cellular environment [77, 89, 94, 166].

If one compares the two models, Turing's model allows the formation of precise and neat boundaries but suffers from the absence of a historical pre-patterning leading to a lack of reproducibility in their positioning. In contrast the PI model provides a pre-pattern that constrains the positioning, but suffers from fuzziness due to an uncertainty in the morphogen concentration at which a threshold appears (especially when the morphogen slope is shallow). This represents a serious difficulty as discussed by Gregor and colleagues [68]. In addition to the positioning of boundaries, one has to consider the fate of misplaced cells not expressing a TF combination corresponding to their territory. Since in PI models each cell “works for itself”, cells close to thresholds may differentiate into different types, leading to a salt and pepper pattern in the region of the boundary. In the most parsimonious version of the model (no other mechanism added), the only solutions are migration or death of misplaced cells [91, 166], requiring additional mechanisms and information to regulate cell migration/guidance and/or death.

It might thus be useful to verify if recent findings in developmental biology may permit to reconcile the advantages of the two models. In vertebrates the most popular illustration of the PI theory is provided

by the compartmentalization of the neural tube in response to the diffusion of the ventral and dorsal morphogens Sonic Hedgehog (Shh) and Bone Morphogenetic Protein (BMP), respectively [131, 44]. A continuous gradient activates ventral and dorsal genes and territories are formed that express distinct TF subsets [7, 44, 45, 91]. In this model, differentiation is based on the almost general rule that within a developing neuroepithelium, each side of a boundary expresses a TF, in most cases a Homeoprotein (HP) transcription factor, which amplifies its own expression and represses that of its counterpart (on the other side). This is illustrated, among many other examples, by the Pax6/Nkx2.2 dorso-ventral boundary and the Otx2/Gbx2 antero-posterior boundary in the neural tube, or the Emx2/Pax6 boundary in the cortex [24, 25, 81, 119]. An important novelty of this study is to introduce in the calculations the intercellular transfer of HPs allowed by two short peptidic sequences present in their DNA-binding domain [138, 80, 143, 163, 139, 92, 114, 168].

Direct communication between nearby nuclei in the context of cell assemblies is reminiscent of the studies where direct morphogenetic functions were attributed to transcription factors diffusing in the fly embryo at the syncytial stage [49, 50]. The parallel is made even more striking by recent studies suggesting that such local diffusion between nearby nuclei represses developmental noise allowing the precise positioning of transcriptional domains [68, 69]. It is not usual to think of a transcription factor as a morphogen, and if Bicoid was easily labeled “morphogen” in spite of being a HP transcription factor it is rather because of its graded expression and of the fact that the *Drosophila* embryo is a syncytium allowing Bicoid direct transfer from nucleus to nucleus. Therefore, the similarity between the Bicoid model and our own hypothesis is limited to the fact that HP diffusion is involved. Indeed Bicoid in the fly is a morphogen as defined by Wolpert whereas, in our model, HPs are morphogens in the Turing acceptance of the term.

Indeed, their intercellular transfer added to self-amplification and reciprocal inhibition properties may convey to HPs the quality of local Turing’s morphogens. In that sense, nature may have combined Turing’s morphogen diffusion (HPs) with PI provided by classical morphogen gradients (e.g. Shh). This reasoning is at the basis of the parsimonious model presented in this study that takes into account the presence of morphogen gradients, as in the PI theory, but also incorporates a Turing-like mechanism based on the local diffusion of HP transcription factors. A major and counter-intuitive finding of our study is that, even in the limit of infinitesimal diffusion, HP transfer across cells is sufficient to ensure precise boundaries with reliable location. Beyond the case explored here in the context of neural development, this study has led to us to discover an important mathematical property, universal in systems with competing species subject to diffusion, as shown in another study [124]. This paper does not present these formal mathematical details, but illustrates this theory with one minimalistic example that can be precisely analyzed mathematically and simulated.

In conclusion it is demonstrated that the addition of the simple property of HP transfer integrates a local Turing’s mechanism within the PI model first proposed by Wolpert and provides a very parsimonious model for the formation of precise and stable boundaries.

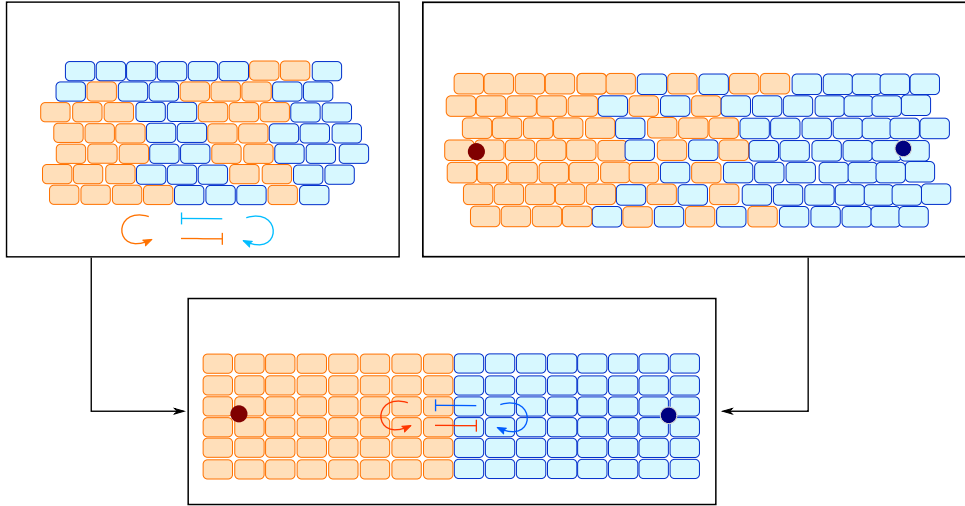


Figure 4.1: Different Models of cell differentiation: Pure gene competition with small diffusion in the absence of spatial cues classically yields to Turing patterns composed of unpredictable abutting territories, while the PI model shows a fixed global patterning driven by the morphogen gradients but with imprecise salt-and-pepper boundaries. The combination of the two phenomena yields precise and predictable patterning.

## 4.2 Model

---

We propose a model that takes into account the basic mechanisms at play during neuroepithelium development when different combinations of genes are expressed in abutting differentiating domains, including HPs, that dictate the morphological and functional fate of territories [91].

The simple and parsimonious model that we propose considers that the differentiation between two areas  $A$  and  $B$  is driven by the dynamical competition between the expression of two homeogenes associated to distinct HPs:  $T_A$  and  $T_B$ . Three important processes propel this mechanism:

1. The presence of one or several morphogens forming gradients along the developmental axis.
2. The competition between the different HPs through autocatalytic activation and reciprocal inhibition
3. The activity of non cell-autonomous HPs captured from the closest neighboring cells (up to three cell ranks) through extracellular diffusion.

As the neuroepithelium develops, epigenetic phenomena take place and modify the homeogene expression repertoire by favoring those that are the most expressed. Eventually, a classical self-limiting process such as saturation within the cell imposes a plateau to gene expression.

All these phenomena provide a well-defined equation for the evolution in time of the HPs in each cell. We provide the detailed mathematical model in the following section. Overall, the model qualitatively

depends on only three effective parameters that are the ratio of (i) the autocatalytic activation rates (ii) the saturation/inhibition rates and (iii) the extracellular diffusion rates.

### 4.2.1 Theoretical Description

The model describes the time evolution of the quantities  $T_A$  and  $T_B$  in a spatially extended neural tissue composed of  $N$  differentiating cells. Their dynamics is the result of cell-autonomous mechanisms and non cell-autonomous diffusion. Specifically, they satisfy the equations:

Time Evolution	Cell-autonomous mechanism	Diffusion
$\frac{d}{dt}T_A$	$D_A(F_A(x) + g_A T_A) - s_A T_A(T_A + T_B)$	$\sigma_A \Delta T_A$
$\frac{d}{dt}T_B$	$D_B(F_B(x) + g_B T_B) - s_B T_B(T_A + T_B)$	$\sigma_B \Delta T_B$

where  $F_A$  and  $F_B$  represent the effect of the external cues (morphogen gradients) on the expression of  $T_A$  and  $T_B$ .

#### Cell-autonomous HP competition

The expression of the genes is the result of the competition between the expression of the two combination of genes modulated in our system by gene expression capacities  $D_A$  and  $D_B$  that evolve according to epigenetic mechanisms that we discuss below. We take into account the following phenomena (described for one combination of gene,  $A$ , the same phenomena being considered for  $B$ ):

- ▷ Morphogens stimulates TF expression:

$$\frac{d}{dt}T_A = D_A F_A(x).$$

The quantity  $F_A(x)$  denotes the rate of production of  $T_A$  induced by the morphogen on cells at location  $x$ . It is a monotonic function along developmental axis (gradient direction of the morphogen).

- ▷ The auto-inducer properties of TFs are taken into account by considering that  $T_A$  stimulates its own expression with a positive rate  $g_A$ . This intensity is modulated also by the gene expression capacity  $D_A$

$$T_A \rightarrow T_A + T_A \quad \Rightarrow \quad \frac{d}{dt}T_A = g_A D_A T_A.$$

- ▷ The cross-inhibition properties imply that the presence of  $T_B$  inhibits the expression of  $T_A$  causing, in the cell, a decrease of the production rate of  $T_A$  at a certain rate  $s_A$ . The simplest way to express this competition is to write:

$$T_A + T_B \rightarrow \emptyset \quad \Rightarrow \quad \frac{d}{dt}T_A = -s_A T_A T_B \text{ and } \frac{d}{dt}T_B = -s_B T_A T_B.$$

▷ Finally, saturation of the number of proteins inside the cell is taken into account by considering that the rate of production of the species decreases when  $T_A$  exceeds a certain level. We choose here the logistic saturation law classical to ecologists:

$$\frac{d}{dt}T_A = -s'_A T_A(1 - T_A).$$

These equations characterize the expression dynamics within a cell. All phenomena requiring gene expression occur at a rate that is scaled by a coefficient  $D_A$  taking into account the epigenetic phenomena. This coefficient accounts for the fact that the more one combination of gene is expressed, the more likely it is to be expressed. This facilitation-inhibition of the transcriptional activity results in the fact that  $D_A$  is an increasing function of  $T_A$  and decreasing function of  $T_B$ :

$$D_A = G(T_A, T_B)$$

where the map  $G$  is such that, by convention:

$$G(0, y) = 0, \quad G(+\infty, y) = 1.$$

In this scaling,  $D_A = 1$  corresponds to a maximal expression activity and  $D_A = 0$  to no gene expression at all.

### Non cell-autonomous transfers

In addition to the cell-autonomous mechanisms, and given that homeoproteins are endowed with direct non-cell-autonomous properties, we include in the set of equations what we called a diffusion operator  $\Delta$ . From a modeling viewpoint, we incorporate in the dynamics of  $T_A$  and  $T_B$  the ability of being transferred to neighboring cells. To emphasize this very local mechanism, we limit this diffusion to one cell in all directions. In detail, the time evolution of the transcription factor level  $T_A(x)$  within the cell at location  $x$  is added a nonlocal term corresponding to the exchange of transcription factors from and towards the set of neighboring cells  $\nu(x)$  (the number of neighbors is denoted  $|\nu(x)|$ ):

$$\frac{d}{dt}T_A(x) = \sigma T_A(x, \nu(x)) := \left( -|\nu(x)|T_A(x) + \sum_{y \in \nu(x)} T_A(y) \right).$$

In other words, TFs have the ability to be transferred to all neighboring cells at a rate  $\sigma$  (the intensity in time of the transfer), creating outward inward fluxes.

## 4.3 Results

---

The problem of boundary formation and stability consists in determining (i) whether the piece of neural tissue clearly splits into separate regions in which cells either express  $T_A$  or  $T_B$  and (ii) the site where this partition takes place as a function of initial conditions and the stability of the boundary position upon random parameter variations.



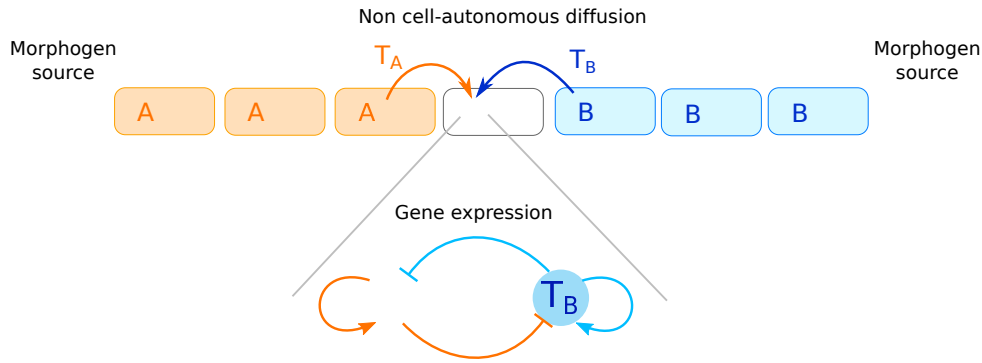


Figure 4.2: Schematic description of the model of neural differentiation: TF synthesis is driven by external morphogens organized along gradients (that form through diffusion from different morphogen sources) and by the dynamical competition of gene expression. Diffusion of HPs to the nearest neighboring cells take into account the non cell-autonomous transfer properties.

### 4.3.1 Ambiguous boundary in the absence of non cell-autonomous processes

In the absence HP diffusion, the behavior of each cell is governed by an autonomous equation (independent of the behavior of the other cells) that depends on the local concentration of morphogen. Within each cell, homeogenes compete for expression, and the outcome of this process is that the “winner-takes-all”: one TF will be expressed at the expense of the other that eventually disappears. The differentiation of a cell into  $A$  or  $B$  depends on their position within the morphogen gradient. We demonstrate in the Supplementary Material that in the regions where the expression of one HP (say,  $T_A$ ) is highly promoted by the morphogen gradients, the cells can only differentiate into type  $A$ : morphogens “select”, in these regions, the winner. However, in the regions of intermediate concentrations of morphogen, the cells can differentiate into  $A$  or  $B$ , and the fate of one cell is governed by initial concentrations of HPs and the transcriptional noise. In other words, there exists a non-trivial set of morphogen concentration levels in which the system has a stochastic patterning. In a differentiating tissue, the region corresponding to these morphogen concentrations is ambiguous: the system displays an exponential number of possible stable differentiated states<sup>1</sup>.

The sensitivity of the differentiation process within the ambiguous region leads, in physiological noisy conditions, to an unpredictable patterning, and a vast majority of the solutions displays an alternation between the two cell types, precluding the definition of smooth boundaries between cells but rather leading to a salt-and-pepper pattern. In the absence of additional processes leading to cell reprogramming, migration or death [91], this salt-and-pepper regime is ubiquitous (see Supplementary Material). This is a property of a wide class of abstract models of cell differentiation where systems of competing species yield two winner-takes-all states which, except in extremely fine tuned situations, do not change stability exactly at the same points in space, and hence are generally both stable in a region of space defined as ambiguous.

<sup>1</sup>If there are  $k$  cells in the ambiguous region, each cell can be of type  $A$  or  $B$  independently, therefore the total number of possible solutions is equal to  $2^k$

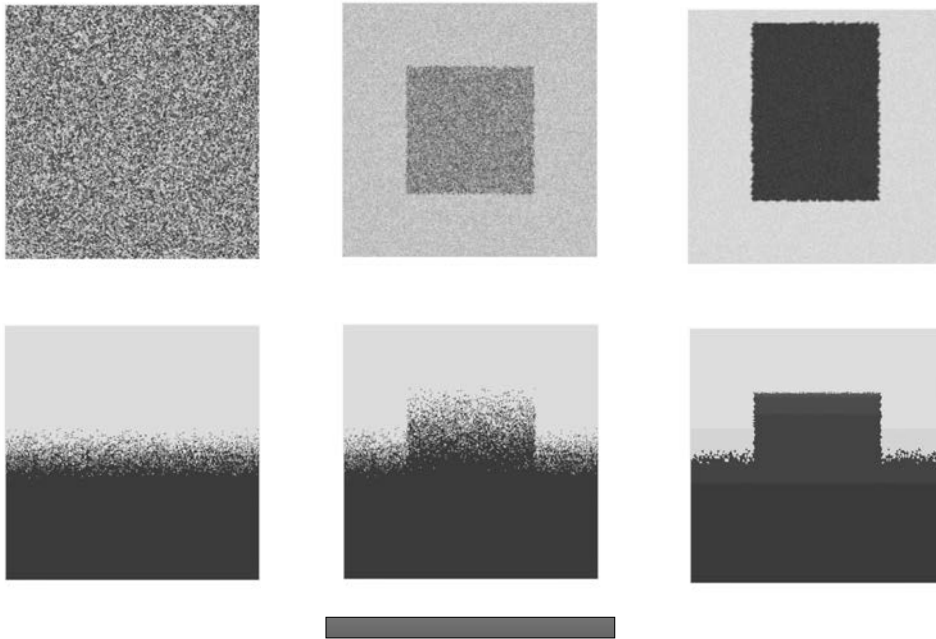


Figure 4.3: Ambiguous boundary in the absence of non cell-autonomous processes. Simulations of the system with distinct initial conditions (top row) in the absence of HP diffusion  $\sigma_A = \sigma_B = 0$ . For each point, the combination of levels of morphogen gradients either corresponds to univocal or ambiguous region (see Appendix and the bifurcation diagram in Supplementary figure 4.7). We chose a simple two-dimensional square topology to illustrate the phenomenon with  $g_A/g_B = 1$  and  $s_A/s_B = 1$  unitary parameters and linear morphogen gradients. (top) From left to right: random initial values; structured initial values with a small predominance of  $T_A$  in a centred square; and a large predominance of  $T_A$  (close to the steady state) in a rectangle that exceeds the ambiguous region. (bottom) End-state of the differentiation process: two differentiated regions emerge with a fuzzy interface; when the initial condition shows a small predominance of  $T_A$ , a clear bias in this region to A type is found and salt-and-pepper interface persists. Important predominance of  $T_A$  leads to a differentiation of all cells in the region into A-cells within the ambiguous region. Salt-and-pepper boundary persists away from the region of high initial  $T_A$ .

This is clearly visible in the numerical simulations of a two-dimensional tissue in figure 4.3 in the two cases, the initial randomness persists in the final state, and the overall shape of the domain dramatically depends on the choice of the initial condition. In all cases we indeed observe the salt-and-pepper type of boundary due to the randomness in the initial condition. In order to illustrate this sensitivity to noise and initial concentrations, we present three examples either presenting no specific initial pattern, or an initial partially or fully differentiated pattern. The end state of the differentiation process always show an imprecise boundary, and we can see the dramatic dependence on the initial condition with, in the three cases, a patterning that is globally very distinct.

All in all, it can be concluded that in the absence of HP diffusion, different steady state solutions appear and remain stable, the differentiated domains are highly irregular and subject to fluctuations

upon variation of the initial conditions and parameters.

### 4.3.2 Unpredictable patterns in the absence of morphogen gradients

We now discuss the behavior of a differentiating tissue within which molecular species diffuse but in the absence of positional information given by morphogen gradients. Turing was the first to suggest that the diffusion of self-activating and reciprocal inhibitor elements is at the basis of boundary formation [155]. In order to support pattern formation, the original Turing model makes the assumption that an additional molecular species plays a catalytic role on the expression of both of  $A$  and  $B$ . This molecular species contrasts with the graded expression of the different morphogens of the PI model on at least two aspects: it has a no spatial source and therefore does not define any preferred place in space for one specie to be expressed, and it promotes the expression of both  $A$  and  $B$ .

A major mathematical finding in this model is the now-called Turing's instability: when the rates of diffusion of the two species are very different, several homogenous “winner-takes-all” abutting territories emerge at random places (the leopard spots, see figure 4.1). The patterns so generated are unpredictable: they are highly sensitive to noise and initial conditions.

In our model, one can consider HPs as Turing's self-activating and reciprocal inhibitor species, and the morphogen showing a graded expression along the differentiating pluricellular tissue (central in Wolpert's French Flag model) plays the role of Turing's catalytic species. But it no more has a spatially homogeneous concentration. Its graded monotonic expression will stabilize the Turing patterns, leading to regular, predictable and highly reproducible boundaries between distinct “winner-takes-all” abutting territories, as we now show.

### 4.3.3 Precise patterning for competitive systems with spatial cues and HP diffusion

From the two above sections, we conclude that HP diffusion in the absence of morphogen gradients (Turing) leads to unpredictable patterning with clearly defined boundaries, while the presence of spatial cues (positional information) in the absence of HP diffusion (Wolpert) yields to a patterning predictable “at large” but with imprecise boundaries. Our model combines both spatial cues (external morphogen gradient) and HP diffusion across cell membranes. The classical morphogen in the Wolpert's definition (e.g. Shh) creates zones of expression of distinct HPs (the French Flag) with blurred and unstable boundaries and HPs are now locally diffusing secondary morphogens in the Turing's definition (self-activation and reciprocal inhibition). These two processes, when combined, lead to smooth and predictable pattern formation and the location of the boundary is very robust to random fluctuations of the initial conditions and parameters, even at very low diffusion levels. This is a surprising property of the equations. Indeed, this stabilization takes place for arbitrarily small values of the diffusion constants, meaning that most solutions present in the case  $\sigma_A = \sigma_B = 0$  disappear in favor of a unique solution with precise front

location. This stabilization property is mathematically demonstrated in our study on general models of competitive-type systems driven by monotonic gradients [124].

In order to illustrate this phenomenon, simulations of the system are provided in figure 4.4. For the sake of consistency with the biological problem, we performed the simulations adopting the topology of a neural tube. Two sources (representing Shh and BMP for instance) are fixed at the floor plate and roof plate respectively, and free diffusion was simulated to form the gradients. The BMP source was arbitrarily chosen stronger than the Shh source (ratio 3:2), and initial HP concentrations were chosen close to zero, with small fluctuations across different cells. In the absence of diffusion emerges a noisy boundary consistent with the previous analysis. But even a very small diffusion leads to a dramatic stabilization and regularization of the boundary, at a location that depends only on the parameters of the system (strength of the gradients and intensities of the reactions) but not on the choice of the initial conditions (see Supplementary material).

This dramatic regularization and stabilization of the boundary position is a direct consequence of HP local diffusion (see figure 4.4, right). First, in contrast with the cell autonomous situation, diffusion prevents the persistence of small isolates of one cell type, say  $B$ , within a large domain of the other cell type, say  $A$ . Would such an isolate appear, diffusions of  $T_B$  and  $T_A$  (out and into the isolate, respectively) would rapidly translate into a “ $T_A$ -takes-all” situation. In addition to forcing isolated cells to adopt the identity of their dominant neighbors, HP diffusion also contributes to the determination of a highly conserved boundary position between territories  $A$  and  $B$ , even for a large range of initial conditions. Indeed, as in the cell autonomous situation, the regions of high morphogen concentration rapidly differentiate into  $A$  or  $B$  type, thus anchoring the differentiation of the field at both of its extremities. Closer to the future boundary, HP diffusion extends the competing domains until the two fronts meet, resulting into continuous and monotonous  $T_A$  and  $T_B$  gradients. Then local competition based on HP local diffusion and the ability of the two HPs to self amplify and to repress each other, will settle a smooth boundary along the level sets of the morphogen gradients.

#### 4.3.4 Stability of the front

In physiological conditions, several phenomena may occur and perturb the position of the front. An important source of variability comes from the heterogeneity of the cell population, and in particular from the fact that the characteristics of gene expression vary from cell to cell. Moreover, noise can arise from cell division, cell death and random movements of the cells that modify the sensed value of the morphogens, which may join their effects to perturb the position of the boundary. Actually, the boundary location predicted in the idealized model proves surprisingly resilient in all these situations, as we now illustrate.

In order to quantify the sensitivity of the boundary location to the heterogeneity of the cell population, we investigated the effect of having heterogeneous rates of self-activation and inhibition between TFs (i.e. varying from cell to cell). These two parameters completely characterize gene expression in a given cell in

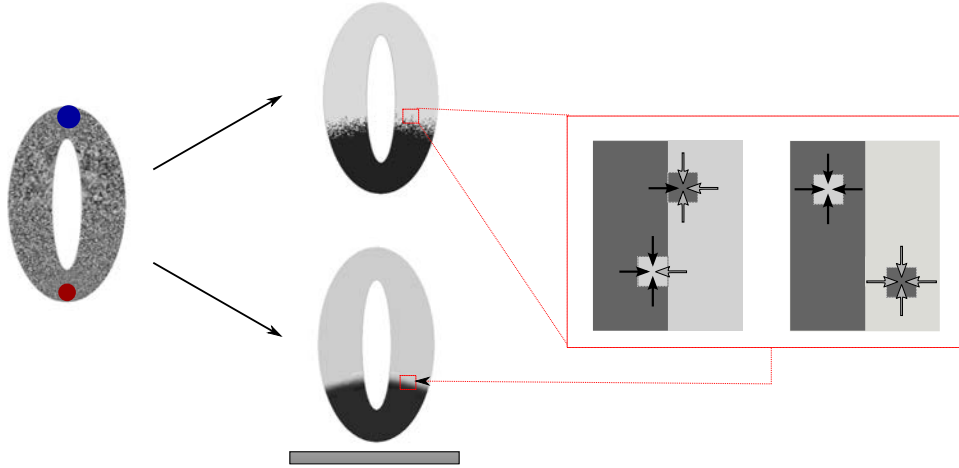


Figure 4.4: Precise patterning for competitive systems with spatial cues and HP diffusion. (left) Simulation of a model of neural tube with Shh (floor plate) and BMP (roof plate) morphogen sources. Gradients formed through diffusion of morphogens, and  $g_A/g_B = 1$  and  $s_A/s_B = 1$ , and symmetry is broken by considering a BMP gradient larger than Shh (ratio between BMP and Shh 3:2). In the absence of HP diffusion salt-and-pepper boundary is found while the presence of HP diffusion ( $\sigma_A = \sigma_B = 10^{-2}$ ) makes the boundary sharp, precise and smooth. Phenomena ensuring this stabilization and regularization only rely on HP diffusion, even limited, and are heuristically depicted on the right: misplaced cells or irregular boundaries will evolve according to the influence of their neighboring cells to yield the unique possible outcome of the differentiation process.

our cell. We considered for instance these rates randomly chosen according to a normal distribution with mean  $g = 1$  and different standard deviations  $\lambda$  (see figure 4.5). The end-state for  $\lambda = 0.05$  is displayed in figure 4.5 (left) superimposed with the end-state in the homogeneous case  $\lambda = 0$  (dashed line). We can observe that even if the precise concentration levels in the different cells are modified compared to the homogeneous predicted solution, the position of the front barely changes. This is due to the very sharp drop of concentration across the boundary. We quantified this stability by looking at the distribution of the front location for 500 independent realizations. The histograms of the front location are displayed in figure 4.5 (right) for different values of the heterogeneity level. Even for large values of the heterogeneity, the position of the front is conserved relatively precisely. For instance, for a noise on the coefficients of  $\lambda = 0.05$ , the front position is barely modified (maximal displacements of 2 cells), and for  $\lambda = 0.2$ , though the solution appears relatively different from realization to realization, the front location remains relatively stable, with maximal errors of 10 cell ranks (on a total of 100 cells).

Cell division occurring during development may also result in variations in the position of the boundary. In order to investigate this effect, we simulate the system with a variable  $N$  that randomly depends on time.  $N$  is set to 100 at initial time, and we consider that one new cell appears as a Poisson process (i.e. cell division occurs at independent exponentially distributed times). When a cell divides, it shares its contents (number of TFs  $T_A$  and  $T_B$ ) between the two new cells which conserve the same epigenetic marks as the mother cell, here transcription intensities  $D_A$  and  $D_B$ . A typical trajectory of the front is

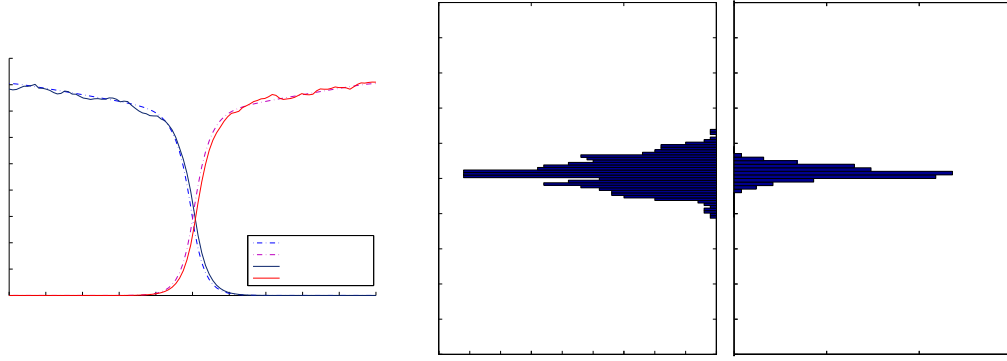


Figure 4.5: Stability of the boundary: one-dimensional field made of 100 cells, diffusion constants  $\sigma_A = \sigma_B = 10^{-4}$  and linear gradients: (left) Stationary solution of the neural differentiation process with constant unit values of  $g_A$  and  $g_B$ , or heterogeneous values centered at 1 with a variance of 0.2 (20%) (right) Histograms of boundary positions for 500 realizations of the process, for heterogeneity level of 100% (variance 1, center) or 20% (right).

depicted in supplementary figure 4.11. Numerical results show that the position of the boundary is barely modified by this process: transient displacements of the boundary that may arise when divisions occur close from the boundary are rapidly overcome, as visible in Supplementary movie 4.6. The stability of the boundary location upon variations of morphogen activity (parameters  $F_A$  and  $F_B$ ) was analyzed in order to account for possible random movements of the cells and fluctuations of the environment (e.g. random arrival of morphogen molecules at their target and readout noise, see [68]). Again, the front remains stable with time, varying at most of a few cell ranks even for large values of the noise (see figure 4.11).

## 4.4 Discussion

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In this paper we describe a parsimonious model for the formation of boundaries within an epithelium. It is in the spirit of the seminal paper where Lewis Wolpert proposed, almost 50 years ago, the French Flag Model (FFM) to explain boundary formation and, in many ways, it extends this model [164]. We started with the idea that the compartments created by a diffusing morphogen as in the FFM are marked by the expression of secondary morphogens (not morphogens in the presently most accepted term, but in the sense coined by Turing) of the HP transcription factor family and introduced two hypotheses: first, that HPs diffuse locally between cells; second, that HPs on either side of a boundary activate themselves and are reciprocal inhibitors (at the transcription level). HP diffusion was indeed demonstrated in a number of biological systems and situations [27, 28, 46, 138, 139, 141, 143, 163, 92, 114, 168]. In addition, the sequences responsible for HP secretion and internalization are highly conserved between HPs, supporting the idea that most HPs are local “Turing” morphogens. The second hypothesis is also supported by a large number of experiments and illustrated by the fact that genetic gain or loss of function of one

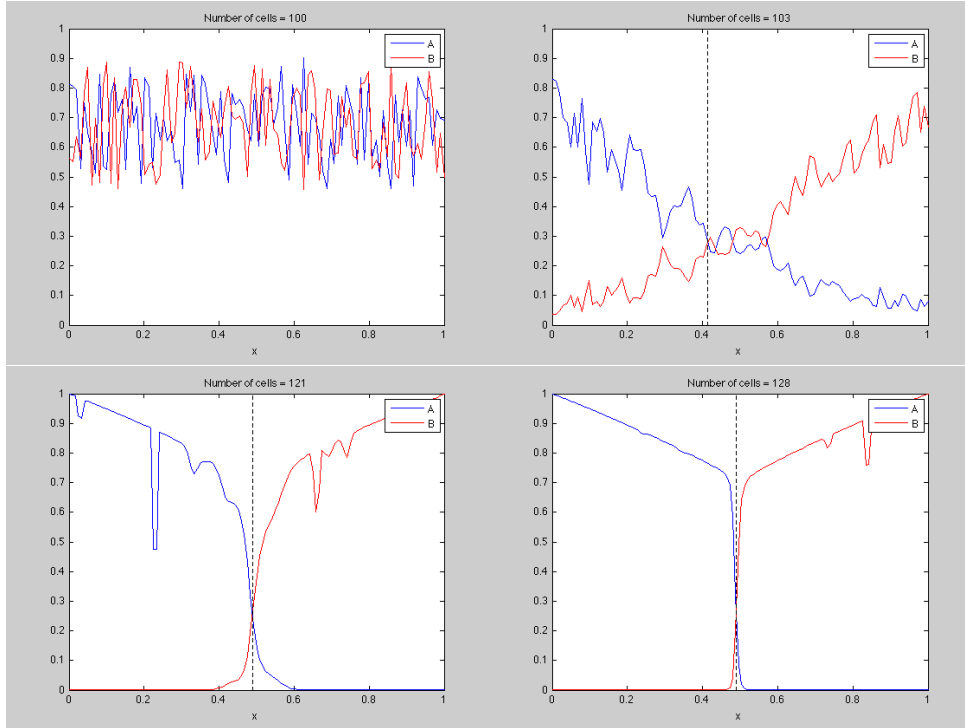


Figure 4.6: Supplementary Movie 1: Random cell division and stability of the front. Cells divide with a frequency of one per unit time, and the two child cells share the content of the mother cell. While concentration locally changes where cells divide, the front remains stable.

of the two “abutting” HPs results in a shift in boundary position [109, 119, 120, 126, 148, 169, 43]. From the mathematical standpoint, the phenomenon of disambiguation and stability of the boundary is relatively surprising, since for arbitrarily small values of the diffusion constants, most solutions present in the case  $\sigma_A = \sigma_B = 0$  (no HP diffusion) disappear in favor of a unique solution with precise boundary location. The characterization of similar phenomena in partial differential equations (PDE) in the small diffusion limit is a very interesting mathematical problem and constitutes an active field of research [9]. It is actually possible to prove that in the continuous limit, the viscosity solutions of this equation (i.e. asymptotic solutions in the limit where the diffusion tends to zero) present a unique and perfectly defined boundary.

Our model requires only 3 molecules to form a boundary (one graded morphogen and two HPs). It is thus as parsimoniously as the FFM, while avoiding the introduction of explicit thresholds. Its main advantage is that the robustness of the positioning of boundaries is highly increased by the diffusion and reciprocal inhibition HP properties. Our model can also be compared to that proposed by Turing in 1952 [155]. Indeed, HPs can be considered as morphogens in the sense of Turing because they amplify their own expression, are reciprocal inhibitors, and have non-local properties. However, in the reaction-diffusion Turing’s model, boundaries appear in a morphogenetic field due to dynamical instabilities arising when the rate of diffusion of the two species in competition are sufficiently different. The mechanisms by which a biological system could be composed of species with very different diffusion constants are still largely unknown. Moreover, when Turing instability forms a pattern, the boundary location is unpredictable.

In sharp contrast, our model forms regular and predictable patterns regardless of the respective value of the diffusion of the two species. In other words, the diffusivity of the species in competition do not need to be different to form a boundary, and moreover, the boundary forms at a precise position and remains stable under variations of the initial conditions and fluctuations of parameters.

By putting aside the ability of HPs themselves to form a gradient through their iterative induction across a large territory that was considered recently [76, 85], we have been able to base our developments only on solidly established data and to neglect several parameters, thus giving direct access to the comparison with the models proposed by Turing and Wolpert. If we think of other models, such as those proposed by Hans Meinhardt, by concentrating on HP local diffusion we could also make the economy of the long range inhibition hypothesis [105, 106, 107, 108]. Indeed, our model does not preclude that such long range inhibitions take place, but does not need it in a first place. Other studies have proposed that bistable dynamics could be the source of reliable patternings [98]. Their model is somewhat simpler in that it only considers auto-activation (and ignores cross inhibition) and the presence of a long-range gradient. But the cells no more respond monotonically to gradients: they have a more complex nonlinear dynamics, which, in a certain range of values of the morphogen gradient, can differentiate into different populations. This bistability is naturally built in our model and emerges from the competition between the two species. Yet, in the absence of diffusion, any bistable system bears ambiguity on the patterning: the boundary will in particular depend on the initial condition (as in our system in the absence of diffusion). However, similarly to what we showed here, adding a diffusion term in bistable models such as [98] would allow stabilizing the boundary.

This is actually a deep mathematical property. From the mathematical viewpoint, the problem of neurodevelopment in the presence of diffusing HPs is one of the seldom examples in which biology led to discover a universal mathematical property. Motivated initially by the mechanism of gene expression described here, we demonstrated that all competitive systems in the presence of monotonic cues yield the formation of a stable and regular boundary between two abutting domains, and that this property is valid even at arbitrarily low levels of diffusion [124]. This mathematical result, beyond applications to other domains, has major implications from the biological viewpoint. Indeed, it ensures that the phenomenon of reliable pattern formation does not depend on the details of the model under consideration, but only on a few qualitative properties that are very natural in the context of neurodevelopment.

Because HPs are very ancient molecules present in all phyla [42] and since transduction takes place in plants and animals, it is speculated that this mode of signaling was operating in the first multicellular organisms. In that sense it may have preceded other signaling mechanisms based on classical signaling entities (e.g. growth factors and their receptors) and pathways. Indeed, reminding of the Bicoid case [51, 102, 132] it was shown that internalized HPs could regulate local translation [2, 141, 168]. The recruitment, later in the evolution of multicellular organisms, of classical signaling pathway is likely to have added robustness to the formation of territories and to other functions involving HP transduction. For example, it was shown that the patterning of terminals from the retinal ganglion cells within the tectum/superior colliculus depends on an interaction between Engrailed HP and Ephrin/Eph signal-



ing [141, 163]. How HP and classical signaling pathways have evolved in parallel and in interaction is of the highest importance to understand the morphogenesis of multicellular organisms and its evolution. In that context, proposing a parsimonious mechanism is a first step in the further analysis of these complex phenomena.

## 4.5 Appendix A: Supplementary material ---

In this supplementary material we provide the details of our mathematical model and the mathematical development supporting our results. We also provide further investigations of the stability of the boundary location between two differentiated domains in noisy situations and details on the hypothesis that led us to the proposed equations.

### 4.5.1 Mathematical Model

#### The general model of neurodevelopment

The model that we study is a particular example taking into account the three cell-autonomous processes of competition and saturation. The properties demonstrated on this particular model actually extend to a wide class of models that can be written as:

$$\begin{cases} \partial_t T_A = T_A H_A(x, T_A, T_B), \\ \partial_t T_B = T_B H_B(x, T_A, T_B), \end{cases} \quad (4.5.1)$$

under the following assumptions on the production rates  $H_A$  and  $H_B$ :

- ▷ External gradients are incorporated by assuming that the map  $x \mapsto H_A(x, T_A, T_B)$  is monotonic along a gradient direction, and the map  $x \mapsto H_B(x, T_A, T_B)$  has the inverse monotonicity. We assume  $H_{A,B}(x, T_A, T_B) \geq 0$ .
- ▷ Competition:  $\partial_{T_B} H_A(x, T_A, T_B) < 0$  and  $\partial_{T_A} H_B(x, T_A, T_B) < 0$
- ▷ Saturation: for any  $(x, T_B)$ , there exists a maximal concentration  $z$  such that for any  $T_A > z$ ,  $H_A(x, T_A, T_B) < 0$  (and similarly for  $H_B$ ).

These abstract equations are studied in [124].

#### Stationary solutions

The problem of boundary formation and stability consists in the determination of (i) whether the piece of neural tissue clearly splits into separate regions in which neurons either express  $T_A$  or  $T_B$  and (ii) the spatial position where this partition takes place and the stability of that boundary as a function of initial conditions or upon random variation of the parameters. To this end, the first step consists in characterizing stationary states of the equations (1)-(2). These are the solutions that do not depend on

time (they are sometimes called equilibrium solutions). A stationary solution is said to be attractive if the system converges towards it for some initial conditions, and stops evolving. This is why these solutions have a major interest: they represent the possible stable outcomes of the differentiation process. In particular, if there exists a unique stationary solution, which is attractive, then differentiation leads to a unique differentiated state, whereas if there exist multiple stable equilibria, the differentiation process is ambiguous. The equilibria do not evolve in time. They are therefore solutions to the equations:

$$\begin{cases} 0 = \sigma_A \Delta A + G(T_A, T_B)(F_A(x) + g_A T_A) - s_A T_A (T_A + T_B), \\ 0 = \sigma_B \Delta B + G(T_B, T_A)(F_B(x) + g_B T_B) - s_B T_B (T_A + T_B), \end{cases} \quad (4.5.2)$$

where we used the fact that necessarily the stationary solutions satisfy  $D_A = G(T_A, T_B)$  and  $D_B = G(T_B, T_A)$ . Equations (4.5.2) constitute a set of  $2N$  algebraic equations. Solving this system is not possible analytically, even in the continuous limit  $N \rightarrow \infty$  where the problem becomes a nonlinear PDE with non-homogeneous coefficients. However, in the cell autonomous case ( $\sigma_A = \sigma_B = 0$ ), the characterization of steady states appears much simpler.

## 4.5.2 Stationary solutions in the cell autonomous case

In this section we describe the stationary solutions of system (4.5.2) in the zero diffusion limit ( $\sigma_A = \sigma_B = 0$ ). This corresponds to the case where transcription factors do not diffuse across cell membranes. From a mathematical viewpoint, this assumption uncouples the equations corresponding to the different cells, and the system is reduced to a set of  $N$  independent ordinary differential equations in dimension 2. Stationary solutions are subject to the following:

**Proposition 4.5.76.** *The stationary solutions of equations (4.5.2) in the zero diffusion limit ( $\sigma_A = \sigma_B = 0$ ) are:*

- ▷ The trivial solution  $T_A = 0, T_B = 0$ , which is always unstable whatever the parameters are,
- ▷  $T_A = 0$  and  $T_B = T_B^x \geq 0$ , given by

$$T_B^x = \frac{\sqrt{(g_B - s_B)^2 + 4s_B F_B(x)} + (g_B - s_B)}{2s_B}. \quad (4.5.3)$$

*This fixed point is stable if and only if  $F_A(x) - s_A T_B (1 + T_B) < 0$ , i.e. when the gradient concentration is small enough compared to the saturation term.*

### Heuristic interpretation of Proposition 4.5.76

In our model, as well as in the general model, if no TF is present, the system does not evolve because the genetic efficacy prevents from synthesizing TFs. This is an unstable equilibrium: since the morphogen concentrations are always strictly positive  $F_A(x) > 0$  (or in the general model, because of the assumption made on  $H_A(x, 0, 0)$ ), the system will always leave the trivial equilibrium meaning that this is not a stable solution.

Two differentiated states appear: they correspond to a case where one of the species does not exist at the advantage of the other. Assuming for instance  $T_B = 0$ , one can find at least one equilibrium solution for  $T_A$  since the map  $H_A(x, T_A, 0)$  is positive for  $T_A = 0$  and negative for  $T_A$  large enough (saturation hypothesis). A stable equilibrium therefore necessarily exists on the line  $T_B = 0$ . This can be stable or unstable depending on the competition between maintaining  $T_A$  at a high level and keeping  $T_B$  at a low level, which is possible when the morphogen gradient is strong enough.

**Remark 4.5.77.** *Rigorously, the system has an additional fixed point, but it is irrelevant for our biological purposes since it corresponds to negative concentrations. This fixed point will never be reached when starting from acceptable initial conditions, i.e. for positive initial values of  $T_A$  and  $T_B$ , because trajectories never cross the axes  $T_A = 0$  or  $T_B = 0$ . Moreover, there exists only one additional stationary solution  $(T_A^*, T_B^*) > 0$  in the parameter regions where both  $(0, T_B^x)$  and  $(T_A^x, 0)$  are stable, but it is unstable. Since this is a non-reachable solution, we do not prove its existence: this state will never be reached in the simulations.*

*Proof of Proposition 4.5.76.* In order to demonstrate the proposition, we need to find all solutions to the pair of equations

$$\begin{cases} \frac{T_A}{1+T_A+T_B}(F_A(x) + g_A T_A) - s_A T_A(T_A + T_B) = 0, \\ \frac{T_B}{1+T_A+T_B}(F_B(x) + g_B T_B) - s_B T_B(T_A + T_B) = 0, \end{cases}$$

and for each solution, find the eigenvalues of the Jacobian matrix at this point. The fixed point is then stable if and only if all eigenvalues have a negative real part.

It is clear that  $T_A = 0$  always solves the first equation and  $T_B = 0$  the second equation. The trivial fixed point  $T_A = 0$  and  $T_B = 0$  is therefore a solution of the system, and the Jacobian matrix at this point is diagonal, with eigenvalues  $F_A(x)$  and  $F_B(x)$  which are both non-negative, hence this fixed point is always unstable. Assuming  $T_A = 0$  only, there exists an additional solution to the system satisfying the quadratic equation:

$$(F_B(x) + g_B T_B) - s_B T_A(1 + T_B) = 0, \quad (4.5.4)$$

which always has a unique non-negative solution given by (4.5.3). The Jacobian matrix at this point is triangular, and the diagonal elements hence correspond to the eigenvalues of the matrix. One of these eigenvalues is given by:

$$\lambda_1 = -\frac{g_B T_B^x + F_B(x)}{(1 + T_B^x)^2} + \frac{T_B^x}{1 + T_B^x} g_B - 2s_B T_B^x,$$

which can be simplified, using equation (4.5.4), into

$$\lambda_1 = -\frac{1}{1 + T_B^x}(F_B(x) + s_B^2),$$

and it is therefore always negative since  $F_B(x)$  and  $s_B^2$  are positive. The second eigenvalue is given by:

$$\lambda_2 = \frac{F_A(x)}{1 + T_B^x} - s_A T_B^x = \frac{1}{1 + T_B^x}(F_A(x) - \frac{s_A}{s_B} F_B(x))$$

which can be either positive or negative depending on the parameters. If  $F_A(x)$  is large enough, we can see that the fixed point is unstable.  $\square$

Supplementary figure 4.7 illustrates this proposition by showing, for a specific type of combination of  $F_A(x)$  and  $F_B(x)$ , the location of the different equilibria and their stability. It shows the presence of a bistable region, formally corresponding to the conditions:

$$F_A(x) - s_A T_B(1 + T_B) < 0 \text{ and } F_B(x) - s_B T_A(1 + T_A) < 0.$$

This bistable regime is at the origin of the indeterminacy of the boundary. This is a general property of models of differentiation, as noted above.

We complement this analysis by providing, for a fixed location inside the cell field (this is nothing but to fix a value of  $x$  and evaluate the morphogen gradients  $F_A(x)$  and  $F_B(x)$ ), a picture of three phase planes of system (4.5.2) in Supplementary figure 4.7 (bottom). The phase plane  $(T_A, T_B)$  represents how variables evolve according to the dynamics, and we show a few typical trajectories.

The stationary solutions of the system (4.5.2) are represented by blue and red squares. A given trajectory converges towards one of the equilibria depending on the initial condition. We have computed the basin of attraction of each equilibrium: any trajectory with initial condition in the blue region will converge to  $(0, T_B^x)$  and will therefore differentiate into a  $B$ -type cell and any trajectory with initial condition in the pink region will converge to  $(T_A^x, 0)$  and differentiate into a  $A$ -type cell. The attraction basins depend on the concentrations of morphogens. If there is an imbalance between the two concentrations, the promoted specie has a larger attraction basin.

### 4.5.3 Uniqueness of the front in the presence of HP diffusion

We now discuss uniqueness and stability of the front in the presence of HP diffusion. We start with mathematical considerations before turning to the numerical confirmation of this result and the testing of its robustness.

#### Existence and Uniqueness of a front at arbitrary low diffusion levels

The rigorous mathematical proof that there exists a unique well defined front for the general model (4.5.1) or for the particular model analyzed here is much more complicated. This is the topic of a companion paper [124], which deals with the general problem. In that paper, we demonstrate that under a few hypotheses, all very natural to the neuronal differentiation process, there exists a unique solution to the differentiation process. This solution persists (and sharpens) even in the limit of infinitesimal diffusion. A case very close from the model under consideration here is treated also in that contribution.

#### Uniqueness of the front

We simulated the system with small diffusions by varying initial conditions (over 100 of experiences varying all parameters and initial conditions) and found no dependence of the stationary solution on the

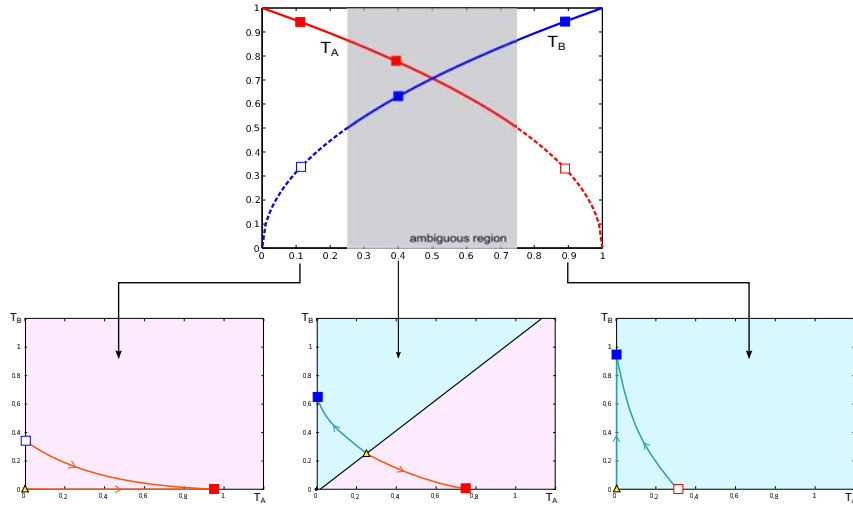


Figure 4.7: Stationary stable solutions in Proposition 4.5.76 and examples of the attraction basins of the stable equilibria for three different concentration of morphogens. In this example we consider all constant equal to 1 and linear gradients  $F_A(x) = x$ ,  $F_B(x) = 1 - x$ . (top) Representation of the solutions  $T_A^x$  (in red) and  $T_B^x$  (in blue). Solutions are depicted in solid line when they are stable and in dashed line otherwise. The grey zone corresponds to the ambiguous region mentioned in the main text. Notice that in that region both solutions are stable with different attraction basins. (bottom) Attraction basins for the solutions for: (left)  $F_A = 0.1, F_B = 0.9$ . In this case the respective solutions given in Proposition 1 are represented by a red square  $T_A^x$ , and a white square  $T_B^x$ ; since the solution in B is unstable, any initial condition goes to  $(T_A^x, 0)$ . (center)  $F_A = 0.4, F_B = 0.6$ , both solutions are stable and represented by a red and a blue square for  $T_A^x$  and  $T_B^x$  respectively; the space is split in two attraction basin colored in soft red and blue. (right)  $F_A = 0.9, F_B = 0.1$ , the same interpretation of the (left) figure holds but interchanging the roles of  $T_A^x$  and  $T_B^x$ .

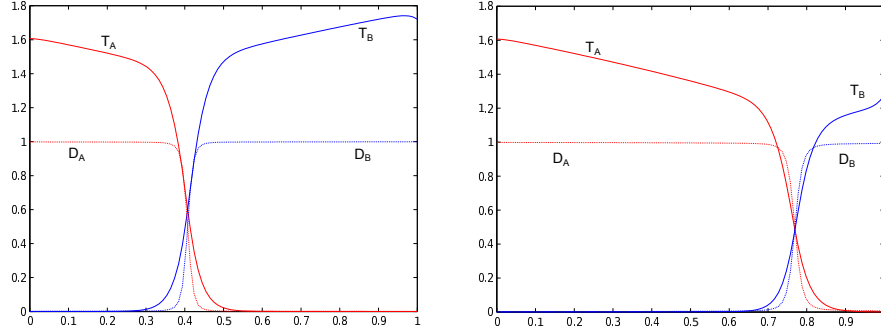


Figure 4.8: Shape of the end-state solution for a one-dimensional tissue for distinct initial conditions show no fluctuation of the profile (and therefore of the boundary) upon variation of the initial condition, but it does depend on the parameters of the system.

initial condition as soon as local HP diffusion is considered ( $\sigma_A, \sigma_B > 0$  arbitrarily small, on the simulations they are of order  $10^{-4}$ ). In order to confirm the apparent identity between stationary states reached from different initial conditions (as plotted in figure 4.3 of the main text), we computed the interface position for 100 different initial conditions for two set of parameters:  $(g_A, g_B, s_A, s_B) = (1, 1, 1, 1.5)$  and  $(g_A, g_B, s_A, s_B) = (1, 1.2, 1, 1)$ . For any set of parameters, the steady state was always the same (see Supplementary figure 4.8). We also performed simulations for the square model considered in figure 4.3 of the main text, and as predicted by the theory we find no difference between the end-states for the different initial conditions chosen that did lead to distinct end-states in the absence of diffusion. As the theory predicts, the position of the boundary does not depend on the initial conditions of the system, but only on the parameters of the system: rate of the diffusion coefficients and the shape of the morphogen gradients.

### Reliability of the boundary location

In order to test the robustness of the front location to noise in the parameters, we intensively simulated the system under two conditions: (i) fluctuation of the positional information, (ii) heterogeneity of the cells rates of TF expression, (iii) cell division and cell death.

Results of (i) and (ii) appear in the main text as well as a description of (iii). Here, we complement these results by showing, in contrast, the high sensitivity of the differentiation process in the absence of HP diffusion. In this case, there is an ambiguity in defining a front, since the values of  $T_A$  and  $T_B$  may not be monotonic and may present several intersections. In order to quantify the error on the front location, we consider two quantities: the leftmost and rightmost intersection of  $T_A$  and  $T_B$ . In the absence of diffusion, the leftmost intersection has a wide distribution (see Supplementary figure 4.10) centered at  $x = 0.428$  with a variance  $1.5 \times 10^{-3}$ , and the rightmost intersection is centered at  $x = 0.58$  with the same variance. This is not the case when considering a small diffusion, in which case the mean value of the leftmost front and the rightmost front differ with a relative error  $10 \times 10^{-4}$ . We observe distributions

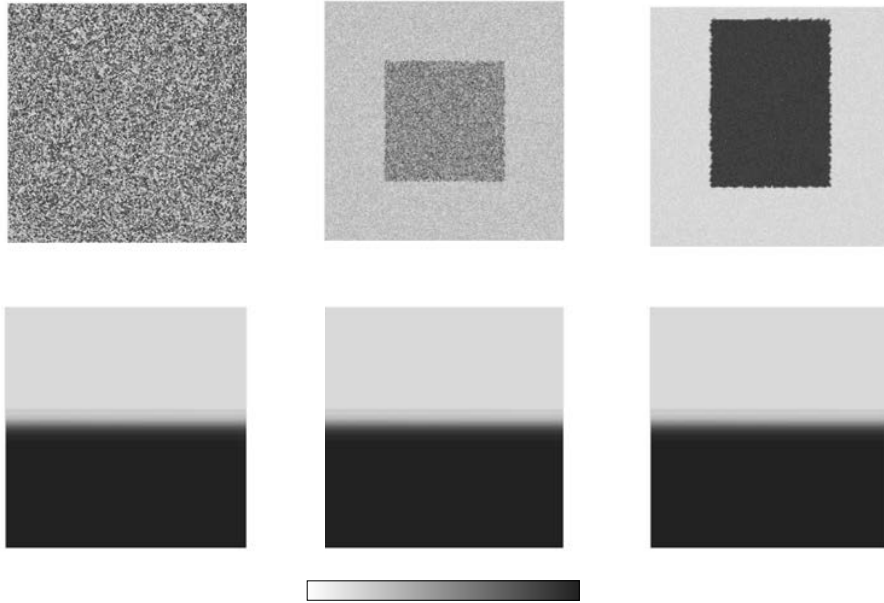


Figure 4.9: Shape of the end-state solution tissue for distinct initial conditions show no fluctuation of the profile (and therefore of the boundary) upon variation of the initial condition. In two dimensions, figure 4.3 showed that the three initial conditions chosen lead to significantly different outcomes of the differentiation. Adding small diffusion ( $\sigma_A, \sigma_B = 10^{-4}$ ) disambiguates the process and we find the same differentiated tissue in all three cases.

peaked at the predicted location of the front.

#### 4.5.4 Movies

Movies of the front location in a one-dimensional neuronal tissue with  $g_A = g_B = s_A = s_B = 1$  in the presence of random cell division and death or in the presence of stochastic variations of the sensed concentration of morphogen  $F_A$  and  $F_B$ .

The process of cell division is explained in the main text. Stochastic variations of the sensed concentration of morphogen were modeled by considering that the effective values of the parameters  $F_A(x)$  and  $F_B(x)$  are stochastic processes (i.e. randomly evolving in time), modeled as an Ornstein-Uhlenbeck process. In detail, we consider:

$$F_A(x) = F_A^*(x) + \xi_A(s, t) \text{ and } F_B(x) = F_B^*(x) + \xi_B(s, t)$$

with  $F_A^*(x)$  and  $F_B^*(x)$  being the mean profile of morphogen gradient and  $\xi_i(x, t)$  the noise at location  $x$ , modeled as a set of independent processes solutions of the equation:

$$d\xi_i(t) = -\xi_i(t) dt + \lambda dW_t^I(x),$$

where  $(W_t^A(x))$  and  $(W_t^B(x))$  are a collection of independent standard Brownian motions.

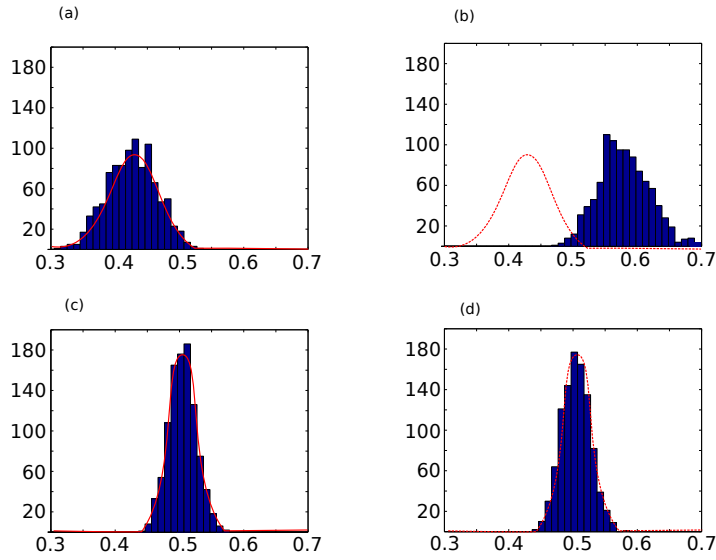


Figure 4.10: Leftmost and Rightmost intersection between  $T_A$  and  $T_B$  in the absence of diffusion (a-b) or in the presence of small diffusion (c-d)  $\sigma_i = 10^{-3}$ : histograms over 200 simulations with random  $g_A(x)$  and  $g_B(x)$  drawn independently for each cell with a uniform distribution with variance 0.5. Red curve indicates approximately the shape of the distribution of the rightmost intersection in the absence of diffusion and is reported, in dashed line, on the histogram of leftmost intersections.

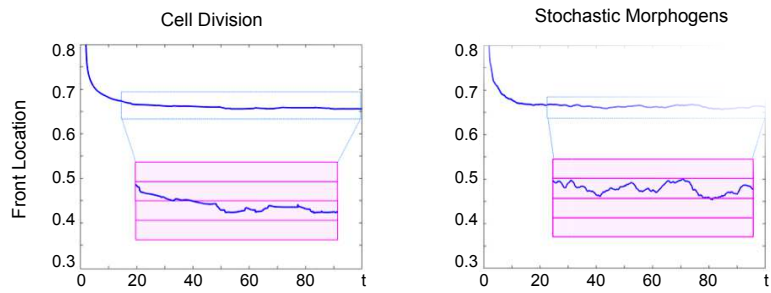


Figure 4.11: Stability of the boundary with random cell division or stochastic morphogen concentration fluctuations. Position of the front as a function of time. Cell division occurred at rate 1 (left) and variance of the morphogen gradient fluctuations are 20% of the maximal value (right). The front globally shows a smooth convergence towards a fixed value with small displacements due to the random phenomena considered. The pink boxes represent cell boundaries. In both simulations, the interpolated front remains within a single cell.





# Competition and boundary formation in heterogeneous media: Application to neuronal differentiation

In this chapter we analyze an inhomogeneous system of coupled reaction-diffusion equations representing the dynamics of gene expression during differentiation of nerve cells. The outcome of this developmental phase is the formation of distinct functional areas separated by sharp and smooth boundaries. It proceeds through the competition between the expression of two genes whose expression is driven by monotonic gradients of chemicals, and the products of gene expression undergo local diffusion and drive gene expression in neighbouring cells. The problem therefore falls in a more general setting of species in competition within a non-homogeneous medium. We show that in the limit of arbitrarily small diffusion, there exists a unique monotonic stationary solution, which splits the neural tissue into two winner-take-all parts at a precise boundary point: on both sides of the boundary, different neuronal types are present. In order to further characterize the location of this boundary, we use a blow-up of the system and define a traveling wave problem parametrized by the position within the monotonic gradient: the precise boundary location is given by the unique point in space at which the speed of the wave vanishes.

This paper is included in [124] written in collaboration with B. Perthame and J. Touboul to appear in M3AS.

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## 5.1

In this paper we undertake a rigorous mathematical analysis of the boundary formation in a model of developing tissue. Our motivation can be traced back to the work of Alan Turing in the middle of last century, that lead to his celebrated theory of instabilities [155]. In his paper, Turing proposed, before substantial knowledge about the development and maturation of living systems was acquired, that the determination of territories was the result of the competition between different chemical substances, he called morphogens, that were reacting together and diffusing, in the presence of a third specie which acts as a catalyst on the expression of both species. In a certain regime of diffusion, these equations yield what we now call *Turing patterns*, that define a partition of the tissue into differentiated areas (expressing one or the other chemical specie), whose exact shape and location are unpredictable and depend on the initial condition.

In contrast to this indeterminacy of the boundary location in Turing's model, morphogenesis in living systems is an extremely reliable process. Actually, precision of the boundary location is crucial from an evolutionary perspective, in that it ensures proper transmission of essential hereditary patterns. Notwithstanding this qualitative distinction, several years after introduction of Turing's model, biological experiments validated Turing's intuition: transcription factors (called homeoproteins) expressed in cells during development have been shown to have self-activating and reciprocal inhibitor properties as in Turing's theory, but moreover, were shown to have the property to exit the cellular nucleus and membrane and enter the neighboring cells nucleus where it exerts its transcriptional properties [125, 96]. However, in contrast to the initial Turing model, the catalyst chemical specie show a specific spatial organization: it forms one-dimensional monotonic gradients of concentration [27]. This arrangement of catalysts along gradients lead to the development of the french flag model (FFM) [164]. This model assumes no diffusion of genetic material, but only all-or-none response to specific thresholds of the catalyst gradient, therefore yielding boundary at a specific location in space. However, this model is relatively sensitive to noise and necessitates to introduce finer mechanisms in order to ensure robustness and accuracy of the boundary location [105, 65].

Combining both phenomena of non cell-autonomous activity (small diffusion of transcription factors, acting as Turing morphogens) and graded expression of a catalyst (FFM-like model) lead to a recently developed minimalistic model of boundary formation [127] reproducing in a parsimonious way both reliability and accuracy of boundary location. This model is given by nonlinear parabolic equations with spatially-dependent coefficients. Simulations indeed showed that in the absence of diffusion, there is no clear separation in two regions, but even very small diffusions disambiguate the differentiation process and lead to a clear definition of the boundary. The object of the paper is to rigorously understand this stabilization in the regime of small diffusions. The mathematical problem we shall be analyzing is actually much more general than the problem of neurodevelopment that motivates the study. Indeed, systems characterized by the competition of two species that are self-activating and reciprocal inhibitor are ubiquitous in life science, and extend to spatially extended population models, large-scale systems of bacterias and social interactions. The particularity of the model we shall analyze, and which may occur

in different situations in the cited domains, is precisely the presence of the non-spatially homogeneous catalyst, producing predictable and reproducible patterns.

Due to the ubiquity of such competing systems in life science, we shall propose here a general model supporting reliable pattern formation, and relevant to biology. To this purpose, we complete this introduction by briefly exposing details on neuronal differentiation, before introducing the model we shall be investigating and summarizing our main mathematical results.

### 5.1.1 Biological motivation

Let us make more precise the model we have in mind in our developments. The central question we shall address the emergence of reliable boundaries in the developing nervous system. The neural tube indeed develops into a complex functional and anatomical architecture endowed with complex connectivity patterns [129]. The size and shape of functional areas in the cortex is of primary importance: it conditions acquisition of functions, and disruptions are associated to severe conditions, including neuropsychiatric and cognitive disorders [156, 64]. In the beginning of this century, biologists analyzed developmental genes transcription factors, and showed that these are endowed with non cell-autonomous activity (they belong the *homeoprotein* family), thanks to two short peptidic sequences present in their DNA-binding domain [80]. These transcription factors have the capability to exit the nucleus of the cells, leave the intracellular medium and penetrate the nucleus of neighboring cells where they exert they transcriptional activity. This direct signaling was experimentally demonstrated in vivo during development in the zebrafish [97, 163], or involved in plasticity of adult networks [17, 143, 138, 27]. The spatial extension and rate of this process are very low: transcription factors can diffuse and reach at most three cell ranks [96], and since the diffusion is passive, important loss reduce the effective number of transcription factors involved. Notwithstanding, it was shown recently [127] in an elementary model of neurodevelopment that even very low diffusion had major effects on the outcome of the differentiation process. Indeed, in the absence of diffusion, there is an ambiguity in the differentiation in a specific region of the neural tissue, which yield imprecise boundaries that are not reproducible, and sensitively depend on initial condition and possible heterogeneity or noise, but in the presence of small diffusion, the location of the boundary is highly reliable, and the differentiation yields a smooth boundary.

Understanding this dramatic regularization is precisely the object of the present paper. This problem falls in the frame of the competition of two diffusing species  $A$  and  $B$  that are reciprocal inhibitor and self-activating, with saturation and spatially heterogeneous production rates  $H_A(x, A, B)$  and  $H_B(x, A, B)$  (depending on the cell location  $x$ ). In the neurodevelopment problem, transcription factors expressed by two genes  $G_A$  and  $G_B$  constitute our two competing species, and the space heterogeneity corresponds to the graded concentration of morphogens. For simplicity, we shall restrict here our analysis to a one-dimensional case<sup>1</sup> in which the differentiating tissue is along the interval  $[0, 1]$ . A schematic version of the model is plotted is Figure 5.1.

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<sup>1</sup>Generalization to higher dimensions in situations where geometry of the space and the spatial variations along gradients are sufficiently simple can be handled in the same manner. In [127], we propose a two-dimensional extension of this property.

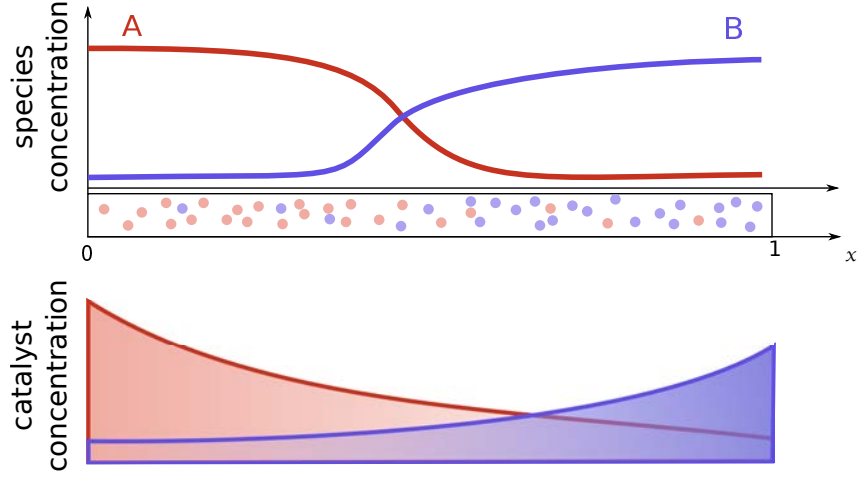


Figure 5.1: Our model describes the dynamics of two species in competition ( $A$ , pink and  $B$ , violet) responding to monotonic resource distributions (bottom line), with reciprocally inhibitory activity and subject to local diffusion.

### 5.1.2 General model and main result

The above description naturally leads to the definition of the following system of reaction-diffusion equations:

$$\begin{cases} -\varepsilon d_A \Delta A = A H_A(x, A, B), & 0 < x < 1, \\ -\varepsilon d_B \Delta B = B H_B(x, A, B), \end{cases} \quad (5.1.1)$$

with Robin type boundary conditions stated below.

Here  $H_A$  and  $H_B$  are maps from  $[0, 1] \times \mathbb{R}_+ \times \mathbb{R}_+$  on  $\mathbb{R}$ , assumed to be of class  $C^2$ . Based on our description of the phenomena, we assume that, for  $0 < x < 1$ ,  $A > 0$ ,  $B > 0$ ,

$$\begin{cases} H_A(x, 0, 0) > 0, & H_B(x, 0, 0) > 0, \\ \partial_x H_A(x, A, B) < 0, & \partial_x H_B(x, A, B) > 0, \\ \partial_B H_A(x, A, B) < 0, & \partial_A H_B(x, A, B) < 0, \end{cases} \quad (5.1.2)$$

which can be interpreted as follows: on the one hand, the morphogen gradients do not vanish and vary monotonically, on the other hand the system expresses competition between species  $A$  and  $B$ .

Because, we are interested in the limit  $\varepsilon = 0$ , the solutions of (5.1.1) in the absence of diffusion are useful. We assume that there exists two solutions  $(F_A(x) > 0, 0)$  and  $(0, F_B(x) > 0)$

$$H_A(x, F_A(x), 0) = 0, \quad H_B(x, 0, F_B(x)) = 0, \quad (5.1.3)$$

and that they are respectively stable for  $x \in (0, x_a)$  and for  $x \in (x_b, 1)$ , with  $x_a > x_b$ , i.e., there exists a bistable zone. It means that the linearized matrix at  $(F_A(x), 0)$  have negative eigenvalues for  $x \in (0, x_a)$ . The same holds at  $(0, F_B(x))$  for  $x \in (x_b, 1)$ . Moreover, we assume

$$H_B(x, F_A(x), 0) > 0 \quad \text{for } x > x_a > x_b, \quad H_A(x, 0, F_B(x)) > 0 \quad \text{for } x < x_b < x_a. \quad (5.1.4)$$

The first inequality, for instance, can be interpreted as follows: for  $x > x_a$ ,  $A$  loses stability because resource concentration of  $B$  overcomes inhibition from  $A$ .

Finally, we assume that there exists a unique additional solution ( $A^*(x) > 0, B^*(x) > 0$ ) in the interval  $(x_b, x_a)$  which is a saddle, i.e.

$$\begin{cases} H_A(x, A^*(x), B^*(x)) = 0, & \text{for } x_b < x < x_a, \\ \partial_A H_A(x, A^*, B^*) \partial_B H_B(x, A^*, B^*) - \partial_B H_A(x, A^*, B^*) \partial_A H_B(x, A^*, B^*) < 0, \\ \partial_A H_A(x, A^*, B^*) < 0, & \partial_B H_B(x, A^*, B^*) < 0 \end{cases} \quad (5.1.5)$$

that simply express the negativity of the determinant of the Jacobian matrix at this point:

$$\begin{vmatrix} A^* \partial_A H_A(x, A^*, B^*) & A^* \partial_B H_A(x, A^*, B^*) \\ B^* \partial_A H_B(x, A^*, B^*) & B^* \partial_B H_B(x, A^*, B^*) \end{vmatrix} < 0.$$

In order to complete the definition of our system (5.1.1), we need to specify the boundary conditions considered. We are interested in solutions in which the system decomposes the domain into two separate areas in which  $A$  or  $B$  dominate. In the limit where  $\varepsilon$  going to zero, it is therefore natural to consider that the system is subject to Dirichlet boundary conditions, but as the diffusion coefficient increases, loss of transcription factor through the boundary becomes increasingly prominent. These mechanisms correspond to Robin (also called third type) boundary conditions:

$$\begin{cases} A(0) - \sqrt{\varepsilon} \frac{\partial}{\partial x} A(0) = F_A(0), & A(1) + \sqrt{\varepsilon} \frac{\partial}{\partial x} A(1) = 0, \\ B(0) - \sqrt{\varepsilon} \frac{\partial}{\partial x} B(0) = 0, & B(1) + \sqrt{\varepsilon} \frac{\partial}{\partial x} B(1) = F_B(1). \end{cases} \quad (5.1.6)$$

At this level of generality, assumptions (5.1.2)–(5.1.5) may appear formal. These are actually very natural, and we refer to Section 5.5.1 for a basic example where they are satisfied. They formulate in a general fashion the elements of our problem: the first assumption expresses the existence of two stable differentiated states at both ends of the differentiating tissue in the absence of diffusion, whose domain of stability may overlap. In other words, in the absence of diffusion, levels of concentration of morphogen are sufficient to support differentiated states at the boundaries of the interval, and there exists generically an overlap between these two regions. Within this overlap (in the bistable regime), a saddle fixed point naturally emerges between the two solutions due to the properties of planar vector fields, and in our system, at this fixed point, concentrations of  $A$  and  $B$  perfectly balance the concentrations of morphogen.

The main result that we will be demonstrating in the present manuscript is the fact that in the presence of small diffusion, a clear boundary between two differentiated domains exists and is unique, and may be characterized univocally. In detail, we shall demonstrate the following:

**Theorem 5.1.78.** *Under assumptions 5.1.2–5.1.5, there exists a classical stationary solution  $(A_\varepsilon, B_\varepsilon)$  of (5.1.1) which satisfies*

$$\frac{d}{dx} A_\varepsilon(x) < 0, \quad \frac{d}{dx} B_\varepsilon(x) > 0, \quad (5.1.7)$$

and is obtained as  $t \rightarrow \infty$  in the corresponding parabolic equation. Moreover

- (i) As  $\varepsilon \rightarrow 0$ ,  $(A_\varepsilon, B_\varepsilon)$  converges a.e. towards a pair  $(A_0, B_0)$ . These maps are discontinuous at some point  $x^* \in [x_b, x_a]$  and have disjoint supports

$$\text{supp}(A_0) = [0, x^*] \quad \text{and} \quad \text{supp}(B_0) = [x^*, 1].$$

- (ii) The point  $x^*$  is characterized by the relation  $c(x^*) = 0$  where  $c(\cdot)$  represents the speed of propagation of a traveling wave problem parametrized by  $x$  (see equation (5.4.23)).

This qualitative result falls in the class of free boundary problems, a well developed asymptotic theory in the frame of homogeneous elliptic or parabolic semilinear equations and systems [37, 61, 57, 11, 12, 137]. As reviewed in [38], these results generally rely on the definition and analysis of viscosity solutions of the resulting Hamilton-Jacobi equation. The second point of the theorem involves a traveling wave with inhomogeneous speed. A vast literature, in particular in the domain of mathematical ecology of competing populations, have been interested in related questions (see e.g. [160, 165]). Most applications of this theory are related to front propagations and rules to compute their speeds and invasion properties in homogeneous or heterogeneous environments [15]. Here, we ask a distinct question concerned with the determination of the precise point where a transition between two stable states occurs.

Theorem 5.1.78 will therefore show the existence of monotonic solutions. The monotonicity is a consequence of analogous properties of the equilibria in the absence of diffusion, which can be readily proved under the current assumptions. Similarly, the monotonicity of equilibria  $A^*(x)$  and  $B^*(x)$  can be characterized. This is the object of the following:

**Lemma 5.1.79.** *Under assumption (5.1.2), the functions defined in (5.1.3) and (5.1.5) satisfy*

$$\frac{d}{dx}F_A(x) < 0 \quad \text{for } x \in [0, x_a), \quad \frac{d}{dx}F_B(x) > 0 \quad \text{for } x \in (x_b, 1], \quad (5.1.8)$$

$$\frac{d}{dx}A^*(x) > 0 \quad \text{and} \quad \frac{d}{dx}B^*(x) < 0, \quad x_b < x < x_a. \quad (5.1.9)$$

*Proof.* Since  $F_A(x)$  is a fixed point of the system in the absence of diffusion, we have:

$$\frac{d}{dx}H_A(x, F_A(x), 0) = \partial_x H_A(x, F_A(x), 0) + \partial_A H_A(x, F_A(x), 0) \frac{d}{dx}F_A(x) = 0,$$

and therefore

$$\frac{d}{dx}F_A(x) = -\frac{\partial_x H_A(x, F_A(x), 0)}{\partial_A H_A(x, F_A(x), 0)}.$$

Assumption (5.1.4) ensures that  $\partial_A H_A(x, F_A(x), 0) < 0$  readily implies that  $\frac{d}{dx}F_A(x) < 0$  for  $x$  in  $[0, x_a)$ . By a similar argument,  $\frac{d}{dx}F_B(x) > 0$  for any  $x$  in  $(x_b, 1]$ .

Hypotheses (5.1.2) and (5.1.5) also constrain the monotonicity of  $A^*$  and  $B^*$ . Indeed, since the vector function  $(H_A, H_B)$  is constant along the curve  $(x, A^*(x), B^*(x))$ , we have

$$\frac{d}{dx}A^*(x) = \frac{\partial_B H_A \partial_x H_B - \partial_x H_A \partial_B H_B}{\partial_A H_A \partial_B H_B - \partial_B H_A \partial_A H_B}, \quad \frac{d}{dx}B^*(x) = \frac{\partial_x H_A \partial_A H_B - \partial_A H_A \partial_x H_B}{\partial_A H_A \partial_B H_B - \partial_B H_A \partial_A H_B}.$$

Using the assumptions (5.1.2) and (5.1.5), we conclude the inequalities (5.1.9).  $\square$



The manuscript is devoted to the demonstration of Theorem 5.1.78, and to the development of an application to a specific model of neuronal differentiation. We shall start by proving the existence of a monotonic solution of the elliptic system (5.1.1), (5.1.6) by analyzing the long-time properties of the associated parabolic system. The proof of the existence of monotonic solutions and the characterization of the boundary combines stability and monotonicity arguments, WKB asymptotics and a suitable dilation of the spatial variable. The proof proceeds as follows: the limit where  $\varepsilon \rightarrow 0$  is investigated in section 5.3 and we will show existence and uniqueness of the boundary point  $x^*$  for small diffusions, and in section 5.4, we characterize the boundary point  $x^*$  as the value when a certain traveling wave problem has zero speed, completing the proof of Theorem 5.1.78. Section 5.5 puts in good use this theory on a simple model of neuronal differentiation.

## 5.2 Analysis of the parabolic problem

We start with the parabolic problem associated with (5.1.1)

$$\begin{cases} \partial_t A - \varepsilon d_A \Delta A = A H_A(x, A, B), & 0 < x < 1, t \geq 0, \\ \partial_t B - \varepsilon d_B \Delta B = B H_B(x, A, B), \end{cases} \quad (5.2.10)$$

completed again with the Robin boundary conditions (5.1.6).

We show that for a well chosen pair of initial conditions, solutions to the parabolic problem (5.2.10)-(5.1.6) are monotonic in time. Since all coefficients are regular, solutions are classical and therefore bounded. From here, the existence of steady states is granted.

Because  $F_B$  is an increasing function in  $(x_b, 1]$  we can expect that any non-negative solution for the second equation of (5.2.10) is upper bounded by  $F_B(1)$ . Under the change of variables  $\mathcal{B} = F_B(1) - B$ , system (5.2.10) becomes

$$\begin{cases} \partial_t A - \varepsilon d_A \Delta A = A H_A(x, A, F_B(1) - \mathcal{B}), & 0 < x < 1, t \geq 0, \\ \partial_t \mathcal{B} - \varepsilon d_B \Delta \mathcal{B} = -(F_B(1) - \mathcal{B}) H_B(x, A, F_B(1) - \mathcal{B}), \end{cases} \quad (5.2.11)$$

with the respective boundary conditions

$$\begin{cases} A(0) - \sqrt{\varepsilon} \frac{\partial}{\partial x} A(0) = F_A(0), & A(1) + \sqrt{\varepsilon} \frac{\partial}{\partial x} A(1) = 0, \\ \mathcal{B}(0) - \sqrt{\varepsilon} \frac{\partial}{\partial x} \mathcal{B}(0) = F_B(1), & \mathcal{B}(1) + \sqrt{\varepsilon} \frac{\partial}{\partial x} \mathcal{B}(1) = 0. \end{cases} \quad (5.2.12)$$

hypothesis 5.1.2, 5.1.3 and 5.1.4 imply that the pair  $(0, 0)$  (respectively  $(F_A(0), F_B(1))$ ) is a sub-solution (resp. super-solution) of the steady state problem related to (5.2.11)-(5.2.12). Therefore, taking  $(0, F_B(1))$  as initial condition in (5.2.10) we have the existence of a regular solution  $(A_\varepsilon(t, x), B_\varepsilon(t, x))$  such that:

$$0 \leq A_\varepsilon(t, x) \leq F_A(0) \quad \text{and} \quad 0 \leq B_\varepsilon(t, x) \leq F_B(1), \quad t \geq 0, 1 \leq x \leq 1. \quad (5.2.13)$$

**Lemma 5.2.80.** *Then for all  $t \geq 0$  and  $x \in [0, 1]$ , we have  $\partial_t A_\varepsilon(t, x) \geq 0$  and  $\partial_t B_\varepsilon(t, x) \leq 0$ .*

*Proof.* Defining  $u := \partial_t A_\varepsilon$  and  $v := \partial_t B_\varepsilon$ , we have

$$\begin{aligned}\partial_t u - d_A \varepsilon \Delta u &= u H_A + A \partial_A H_A u + A \partial_B H_A v, \\ \partial_t v - d_B \varepsilon \Delta v &= v H_B + B \partial_A H_B u + B \partial_B H_B v,\end{aligned}$$

multiplying the first equation by  $u_- := \min\{0, u\}$ , the second one by  $v_+ := \max\{0, v\}$  and integrating over  $[0, 1]$  we get

$$\begin{aligned}\frac{1}{2} \frac{d}{dt} \int u_-^2 + d_A \varepsilon \int |\partial_x u_-|^2 - d_A \varepsilon u_- \partial_x u_- \Big|_0^1 &= \int u_-^2 (H_A + A \partial_A H_A) + \int A \partial_B H_A u_- v, \\ \frac{1}{2} \frac{d}{dt} \int v_+^2 + d_B \varepsilon \int |\partial_x v_+|^2 - d_B \varepsilon v_+ \partial_x v_+ \Big|_0^1 &= \int v_+^2 (H_B + B \partial_B H_B) + \int B \partial_A H_B v_+ u.\end{aligned}$$

Time continuity of  $(A_\varepsilon(t, x), B_\varepsilon(t, x))$  together with initial conditions imply that for any  $x$ :

$$u_-(0, x) = 0 \quad \text{and} \quad v_+(0, x) = 0.$$

Thus, there exists  $C > 0$  such that

$$\frac{d}{dt} \int (u_-^2 + v_+^2) \leq C \int (u_-^2 + v_+^2),$$

with zero initial condition. We conclude using Grönwall's lemma.  $\square$

### 5.2.1 Monotonicity in space

We have shown that the monotonicity property of the maps  $H_A$  and  $H_B$  in space implies monotonicity of  $F_A(x)$  and  $F_B(x)$ , solutions of the zero diffusion problem at location  $x$ . This is also true of the maps  $(A_\varepsilon, B_\varepsilon)$  solutions of the parabolic equation (5.2.10). In detail, we show that monotonic initial conditions ensure monotonic solutions  $(A_\varepsilon, B_\varepsilon)$  in space for all times. This property has two remarkable implications: time dependent solutions belong to the bounded variation class and also their respective steady states.

**Lemma 5.2.81.** *For any  $\varepsilon > 0$  fixed, let us consider any solution  $(A_\varepsilon, B_\varepsilon)$  of (5.2.10)-(5.1.6) with initial conditions  $A(0, x)$  decreasing and  $B(0, x)$  increasing. Under assumption (5.2.13), we have for all  $t \geq 0$*

$$\frac{\partial}{\partial x} A_\varepsilon(t, x) \leq 0 \quad \text{and} \quad \frac{\partial}{\partial x} B_\varepsilon(t, x) \geq 0, \quad 0 \leq x \leq 1.$$

*Proof.* The proof proceeds as that of Lemma 5.2.80: we define  $u := \partial_x A_\varepsilon$  and  $v := \partial_x B_\varepsilon$ , we have

$$\begin{aligned}\partial_t u - d_A \varepsilon \Delta u &= u H_A + A \partial_x H_A + A \partial_A H_A u + A \partial_B H_A v, \\ \partial_t v - d_B \varepsilon \Delta v &= v H_B + B \partial_x H_B + B \partial_A H_B u + B \partial_B H_B v,\end{aligned}$$

multiplying the first equation by  $u_+$  and the second one by  $v_-$ , integrating over  $[0, 1]$  and using that boundary conditions (5.1.6) and (5.2.13), we get

$$\begin{aligned}\frac{1}{2} \frac{d}{dt} \int u_+^2 + d_A \varepsilon \int |\partial_x u_+|^2 - d_A \varepsilon u_+ \partial_x u_+ \Big|_0^1 &= \\ &= \int u_+^2 (H_A + A \partial_A H_A) + \int A \partial_B H_A u_+ v + \int A \partial_x H_A u_+ \leq C \int u_+^2 - C \int u_+ v_-, \\ \frac{1}{2} \frac{d}{dt} \int v_-^2 + d_B \varepsilon \int |\partial_x v_-|^2 - d_B \varepsilon v_- \partial_x v_- \Big|_0^1 &= \\ &= \int v_-^2 (H_B + B \partial_B H_B) + \int B \partial_A H_B v_- u + \int B \partial_x H_B v_- \leq C \int v_-^2 - C \int u_+ v_-, \end{aligned}$$

where we have also used that  $\partial_x H_A \leq 0$  and  $\partial_x H_B \geq 0$ . It is then easy to see that there exists  $C > 0$  such that:

$$\frac{d}{dt} \int (u_+^2 + v_-^2) \leq C \int (u_+^2 + v_-^2),$$

with zero initial condition, and to conclude the proof using Grönwall's lemma.  $\square$

We have therefore constructed a pair  $(A_\varepsilon(t, x), B_\varepsilon(t, x))$  such that (5.2.13) is satisfied. We can apply Lemma 5.2.81 and find that for any time  $A_\varepsilon(t, x)$  is decreasing and  $B_\varepsilon(t, x)$  increasing. Moreover, Lemma 5.2.80 together with (5.2.13) imply that pointwise in space  $A_\varepsilon(t, x)$  (resp.  $B_\varepsilon(t, x)$ ) converges to  $A_\varepsilon(x)$  (reps.  $B_\varepsilon(x)$ ) solution to (5.1.1), together with the boundary condition (5.1.6), in the weak sense. Bootstrap method allows us to conclude that  $A_\varepsilon(x), B_\varepsilon(x) \in C^2(0, 1) \cap C_0([0, 1])$  which proves the first part of Theorem 5.1.78 and (5.1.7).

## 5.2.2 Positivity of the solutions

We now consider the pair  $(A_\varepsilon, B_\varepsilon)$  solution of the stationary problem (5.2.10)-(5.1.6) for  $\varepsilon > 0$  fixed. We now provide finer estimates of sub-solutions in order to control  $A_\varepsilon(0)$  and  $B_\varepsilon(1)$  away from zero.

**Proposition 5.2.82.** *There exists  $\varepsilon_0 > 0$  such that for any  $\varepsilon < \varepsilon_0$ ,  $A_\varepsilon$  is strictly positive and  $A_\varepsilon(0)$  is, uniformly in  $\varepsilon$ , larger than some  $\delta_A > 0$ . The same holds for  $B_\varepsilon$  and  $B_\varepsilon(1)$ .*

*Proof.* The proof consists in finding a strictly positive sub-solution for

$$-\varepsilon d_A \frac{d^2}{dx^2} \phi_A = H_A(x, \phi_A(x), B_\varepsilon(x)) \phi_A, \quad (5.2.14)$$

i.e., the equation for  $A_\varepsilon$  when  $B_\varepsilon$  is fixed. To this purpose, we analyze a completely solvable linear problem related to (5.2.14), whose solution constitutes a sub-solution of (5.2.14) and is defined and strictly positive up to the boundary. This solution can thus be used to find a lower bound for  $A_\varepsilon(0)$ .

Consider the following linear equation

$$-\varepsilon d_A \frac{d^2}{dx^2} \phi_A = \left[ \min_{0 \leq s \leq F_A(0)} H_A(1, s, F_B(1)) \right] \phi_A \quad (5.2.15)$$

with boundary conditions inherited from (5.1.6):

$$\phi_A(0) - \sqrt{\varepsilon} \frac{d}{dx} \phi_A(0) = F_A(0), \quad \phi_A(1) + \sqrt{\varepsilon} \frac{d}{dx} \phi_A(1) = 0. \quad (5.2.16)$$

Clearly, the solution takes the form

$$\phi_A(x) = \alpha_\varepsilon e^{x\sqrt{\mu/\varepsilon}} + \beta_\varepsilon e^{-x\sqrt{\mu/\varepsilon}}, \quad \text{with} \quad d_A \mu = - \left[ \min_{0 \leq s \leq F_A(0)} H_A(1, s, F_B(1)) \right] > 0.$$

Using (5.2.16), one can find the exact values of  $\alpha_\varepsilon$  and  $\beta_\varepsilon$  as a function of the system parameters

$$\frac{\alpha_\varepsilon}{\beta_\varepsilon} = \frac{(\sqrt{\mu} - 1)}{(\sqrt{\mu} + 1)} e^{-2\sqrt{\mu/\varepsilon}} \quad \text{and} \quad \beta_\varepsilon = \frac{F_A(0)}{\sqrt{\mu} + 1} \left[ 1 - \frac{(\sqrt{\mu} - 1)^2}{(\sqrt{\mu} + 1)^2} e^{-2\sqrt{\mu/\varepsilon}} \right]^{-1}.$$

Taking  $\varepsilon \rightarrow 0$ , we immediately compute

$$\alpha_\varepsilon e^{\sqrt{\mu/\varepsilon}} \rightarrow 0 \quad \text{and} \quad \beta_\varepsilon \rightarrow \beta := \frac{F_A(0)}{\sqrt{\mu} + 1},$$

thus, for any  $\varepsilon > 0$  small enough,  $\phi_A$  becomes positive and

$$0 < \min_{0 \leq x \leq 1} \phi_A(x) \leq \max_{0 \leq x \leq 1} \phi_A(x) \leq |\alpha_\varepsilon| e^{\sqrt{\mu/\varepsilon}} + \beta_\varepsilon \leq F_A(0).$$

Then, using that  $H_A$  is decreasing in both  $x$  and  $B$ , we obtain

$$-\varepsilon d_A \frac{d^2}{dx^2} \phi_A = \left[ \min_{0 \leq s \leq F_A(0)} H_A(1, s, F_B(1)) \right] \phi_A \leq H_A(x, \phi_A(x), B_\varepsilon(x)) \phi_A.$$

Therefore,  $\phi_A$  is a sub-solution to (5.2.14) comprised between 0 and  $F_A(0)$ . Since  $A_\varepsilon$  is a solution to the same problem with the same bounds and  $\phi_A(0)$  is converging to  $\beta$ , the existence of  $\delta_A > 0$  follows.  $\square$

## 5.3 Asymptotic analysis as $\varepsilon$ vanishes and front position

We now consider the monotonic stationary solutions  $(A_\varepsilon, B_\varepsilon)$  for  $\varepsilon > 0$  defined in Theorem 5.1.78. Thanks to Proposition 5.2.82, we know that for any  $x \in [0, 1]$

$$0 < A_\varepsilon(x) \leq F_A(0) \quad \text{and} \quad 0 < B_\varepsilon(x) \leq F_B(1). \quad (5.3.17)$$

We are now in a position to demonstrate the convergence of the pair  $(A_\varepsilon, B_\varepsilon)$  as  $\varepsilon \rightarrow 0$  towards a pair  $(A_0, B_0)$  that are discontinuous at the same point  $x^*$  and are characterized by point (i) of Theorem 5.1.78. The proof proceeds as follows. First, using the monotonicity of  $(A_\varepsilon, B_\varepsilon)$  we find the existence of  $A_0$  and  $B_0$ , and we characterize those limits as a family of critical points of (5.1.1) indexed by  $x$ . That characterization gives us three possibilities for the support of  $A_0$ . Using a WKB change of variables and the monotonicity properties of critical points (characterized by lemma 5.1.79), we discard two of them. This allows to conclude on the existence of a unique  $x^* \in [x_b, x_a]$  with the properties stated in Theorem 5.1.78.

### 5.3.1 The limit as $\varepsilon$ vanishes

We recall that by monotonicity and  $L^\infty$  bounds, the total variations of  $A_\varepsilon$  and  $B_\varepsilon$  are uniformly bounded in  $\varepsilon$ . Classical theory of Bounded Variation functions (see for instance [58, Theorem 4, p.176]) ensures that there exists a subsequence  $\varepsilon_k$  and BV-functions  $A_0, B_0$  such that, almost everywhere and in all  $L^p(0, 1)$ ,  $1 \leq p < \infty$ ,

$$\begin{cases} A_{\varepsilon_k} \rightarrow A_0, & 0 \leq A_0(x) \leq F_A(0), & \frac{d}{dx} A_0 \leq 0, \\ B_{\varepsilon_k} \rightarrow B_0, & 0 \leq B_0(x) \leq F_B(1), & \frac{d}{dx} B_0 \geq 0. \end{cases} \quad (5.3.18)$$

Those limits satisfy, almost everywhere,

$$\begin{cases} A_0 H_A(x, A_0(x), B_0(x)) = 0, \\ B_0 H_B(x, A_0(x), B_0(x)) = 0. \end{cases} \quad (5.3.19)$$

This means that at each point  $x$ ,  $(A_0, B_0)$  is one of the four nonnegative equilibrium points;  $(0, 0)$  and those three given by hypotheses (5.1.3), (5.1.5). Because  $A_0$  is decreasing, three possible scenarios arise:

- (a) There exists  $x^*$  such that  $(A_0(x), B_0(x)) = (F_A(x), 0)$ , for  $x < x^*$  and  $(A_0(x), B_0(x)) = (0, F_B(x))$ , for  $x > x^*$ .
- (b) There exists  $x_-^* < x_+^*$  such that  $(A_0(x), B_0(x)) = (F_A(x), 0)$ , for  $x < x_-^*$ ,  $(A_0(x), B_0(x)) = (0, 0)$ , for  $x_-^* < x < x_+^*$ .
- (c) There exists  $x^* \geq x_b$  such that  $(A_0(x), B_0(x)) = (F_A(x), 0)$ , for  $x < x^*$  and  $(A_0(x), B_0(x)) = (A^*, B^*)$  for  $x > x^*$  close enough to  $x^*$ .

Notice that neither (a) nor (b) exclude the possibility that  $A_0$  is identically zero. Indeed, at this stage,  $x^*$  (or  $x_-^*$ ) could be the origin. Our aim now is to show that only the first scenario is possible for some  $x^* \in [x_b, x_a]$  proving part (i) of Theorem 5.1.78.

Scenario (c) can be readily discarded. Indeed, if (c) holds, then the relationship (5.1.9) would be in contradiction with the monotonicity of  $A_0(x)$  in a neighborhood of  $x^*$ .

### 5.3.2 WKB change of unknown

We define  $\varphi_A^\varepsilon := -\sqrt{\varepsilon} \log(A_\varepsilon)$ , which is well defined thanks to Proposition 5.2.82. Furthermore,

$$\frac{d}{dx} \varphi_A^\varepsilon = -\sqrt{\varepsilon} \frac{\frac{d}{dx} A_\varepsilon}{A_\varepsilon} \quad \text{and} \quad \frac{d^2}{dx^2} \varphi_A^\varepsilon = -\sqrt{\varepsilon} \left( \frac{\frac{d^2}{dx^2} A_\varepsilon}{A_\varepsilon} - \frac{|\frac{d}{dx} A_\varepsilon|^2}{A_\varepsilon^2} \right),$$

and we find that  $\varphi_A^\varepsilon$  is solution of the eikonal equation

$$\left| \frac{d}{dx} \varphi_A^\varepsilon \right|^2 - \sqrt{\varepsilon} \frac{d^2}{dx^2} \varphi_A^\varepsilon = -H_A(x, A_\varepsilon, B_\varepsilon),$$

with

$$\frac{d}{dx} \varphi_A^\varepsilon(0) = \frac{F_A(0)}{A_\varepsilon(0)} - 1, \quad \frac{d}{dx} \varphi_A^\varepsilon(1) = 1.$$

The same constructions can be made for  $\varphi_B^\varepsilon$ . If we prove that the family  $(\varphi_A^\varepsilon)$  has some regularity, then we can take let  $\varepsilon$  go to 0 in  $\varphi_A^\varepsilon$  and  $\varphi_B^\varepsilon$ . That is the object of the following:

**Lemma 5.3.83.** *The sequence  $(\varphi_A^\varepsilon)$  is uniformly Lipschitz-continuous with respect to  $\varepsilon$ . Therefore, after extracting a subsequence,  $\varphi_A^{\varepsilon_k} \xrightarrow{\varepsilon_k \rightarrow 0} \varphi_A^0$ , a Lipschitz continuous, non-decreasing viscosity solution of*

$$\left| \frac{d}{dx} \varphi_A^0 \right|^2 = -H_A(x, A_0, B_0). \quad (5.3.20)$$

*The same construction for  $B_\varepsilon$  provides us with a function  $\varphi_B$ , Lipschitz continuous, non-increasing viscosity solution of*

$$\left| \frac{d}{dx} \varphi_B^0 \right|^2 = -H_B(x, A_0, B_0). \quad (5.3.21)$$

*Proof.* Since  $A_\varepsilon \geq 0$  and  $\frac{d}{dx}A_\varepsilon \leq 0$  we get directly that  $\frac{d}{dx}\varphi_A^\varepsilon \geq 0$ . We are going to prove that there exists  $C_{\varepsilon_0}$ , independent of  $\varepsilon$ , such that

$$0 \leq \sup_{x \in [0,1]} \frac{d}{dx}\varphi_A^\varepsilon(x) \leq C_{\varepsilon_0}.$$

Consider  $y$ , one argmax of  $\frac{d}{dx}\varphi_A^\varepsilon(y)$ . If  $0 < y < 1$ , then  $\frac{d^2}{dx^2}\varphi_A^\varepsilon(x) = 0$  and

$$\left| \frac{d}{dx}\varphi_A^\varepsilon \right|^2 = -H_A(x, A_\varepsilon, B_\varepsilon),$$

which is uniformly upper-bounded because  $H_A$  is continuous and evaluated on  $(0, 1) \times (0, F_A(0)) \times (0, F_B(1))$ . The upper bound follows.

If  $y = 0$ , Proposition 5.2.82 tells us that  $A_\varepsilon(0)$  is bounded from below by some positive constant  $\delta_A$  independent from  $\varepsilon$ . Then, we may conclude again because

$$\frac{d}{dx}\varphi_A^\varepsilon(0) = \frac{F_A(0)}{A_\varepsilon(0)} - 1 \leq \frac{F_A(0)}{\delta_A} - 1 < \infty.$$

If  $y = 1$ , we immediately conclude thanks to the boundary condition and thus, we have proved the uniform Lipschitz estimate.

The Ascoli-Arzelà theorem allows us to take a subsequence of  $\varphi_A^\varepsilon$  which converges uniformly and we conclude thanks to the usual theory of viscosity solutions [38, 13]. Note that the viscosity procedure only allows to control the limsup or liminf of the right hand sides of (5.3.20), (5.3.21), and this information sufficient for the conclusion we want to draw.  $\square$

A direct consequence of Lemma 5.3.83 is that scenario (b) cannot hold. Indeed, in that case,

$$\left| \frac{d}{dx}\varphi_A^0 \right|^2 = -H_A(x, 0, 0) < 0, \quad \forall x \in (x_-^*, x_+^*)$$

which is contradictory.

The only possible scenario is therefore (a). In order to conclude the proof, we are left showing that  $x^* \in [x_b, x_a]$ . It suffices to show that  $A_0(x)$  becomes positive when  $x \rightarrow 0$  and the same with  $B_0(x)$  when  $x \rightarrow 1$ .

**Lemma 5.3.84.** *There exists two non empty intervals, namely  $I_b$  and  $I_a = [0, 1] \setminus I_b$ , such that  $B_0 \equiv 0$  in  $I_b$  and  $A_0 \equiv 0$  in  $I_a$ . Moreover,*

$$[0, x_b) \subset I_b \quad \text{and} \quad (x_a, 1] \subset I_a.$$

*Proof.* Let us assume that there exists  $y \in (x_a, 1)$  such that  $A_0(y) > 0$ . We have shown that we are necessarily in scenario (a), which implies that  $B_0(y) = 0$  and by monotonicity

$$B_0(x) = 0, \quad A_0(x) = F_A(x) \quad \text{for } 0 \leq x \leq y.$$

Using the fact that  $(F_A(x), 0)$  is linearly unstable for  $x \in (x_a, 1]$  and that  $\varphi_B^0$  is a viscosity solution of (5.3.21), we have

$$\left| \frac{d}{dx}\varphi_B^0 \right|^2 = -H_B(y, F_A(y), 0) < 0,$$

which is impossible, hence  $A_0 \equiv 0$  on  $(x_a, 1)$ . The same argument ensures us that  $B_0 \equiv 0$  in  $(0, x_b)$ . One can therefore define the intervals  $I_a$  and  $I_b$  by maximality as the supports of  $A_0$  and  $B_0$ .  $\square$

## 5.4 Characterization of the Front

Now that we have proved the existence of a boundary  $x^*$ , we can turn to the characterization of this point. To this purpose, we start defining the point,  $x_\varepsilon^*$  such that

$$A_\varepsilon(x_\varepsilon^*) = B_\varepsilon(x_\varepsilon^*),$$

which, by monotonicity, is unique. We also know, by compactness and unique limit, that  $x_\varepsilon^* \rightarrow x^*$  when  $\varepsilon \rightarrow 0$ .

We perform the change of variables  $y = (x - x_\varepsilon^*)/\sqrt{\varepsilon}$ , and define  $a_\varepsilon(y) = A_\varepsilon(x_\varepsilon^* + \sqrt{\varepsilon}y)$  and  $b_\varepsilon$  in the same way. System (5.1.1) becomes

$$\begin{cases} -d_A \frac{d^2}{dy^2} a_\varepsilon(y) = a_\varepsilon(y) H_A(x_\varepsilon^* + \sqrt{\varepsilon}y, a_\varepsilon(y), b_\varepsilon(y)), \\ -d_B \frac{d^2}{dy^2} b_\varepsilon(y) = b_\varepsilon(y) H_B(x_\varepsilon^* + \sqrt{\varepsilon}y, a_\varepsilon(y), b_\varepsilon(y)), \\ a_\varepsilon(0) = b_\varepsilon(0). \end{cases}$$

Because  $a_\varepsilon$  and  $b_\varepsilon$  are uniformly bounded, by elliptic regularity they are uniformly bounded in  $C^2$  and, after extraction of a subsequence (by uniqueness, as we will show, in fact the full sequence converges), we may take the limit as  $\varepsilon \rightarrow 0$  (which we know is well defined, bounded, Lipschitz-continuous). We find that this limit, denoted  $(a_0, b_0)$ , is solution of

$$\begin{cases} -d_A \frac{d^2}{dy^2} a_0(y) = a_0(y) H_A(x^*, a_0(y), b_0(y)), & \partial_y a_0(y) \leq 0, \\ -d_B \frac{d^2}{dy^2} b_0(y) = b_0(y) H_B(x^*, a_0(y), b_0(y)), & \partial_y b_0(y) \geq 0, \\ a_0(0) = b_0(0). \end{cases} \quad (5.4.22)$$

This solution is characterized as follows:

**Theorem 5.4.85.** *The limits satisfy  $a_0 \neq 0$ ,  $b_0 \neq 0$  and there exists a unique value  $x^*$  such that the system (5.4.22) has a non-trivial solution. This solution is the unique traveling wave defined as*

$$\begin{cases} -c(x) \frac{\partial}{\partial y} a(y; x) - d_A \frac{\partial^2}{\partial y^2} a(y; x) = a(y; x) H_A(x, a(y; x), b(y; x)), & y \in \mathbb{R}, \\ -c(x) \frac{\partial}{\partial y} b(y; x) - d_B \frac{\partial^2}{\partial y^2} b(y; x) = b(y; x) H_B(x, a(y; x), b(y; x)), \\ \lim_{y \rightarrow -\infty} a(y; x) = F_A(x), & \lim_{y \rightarrow +\infty} a(y; x) = 0, \\ \lim_{y \rightarrow +\infty} b(y; x) = F_B(x), & \lim_{y \rightarrow -\infty} b(y; x) = 0, \end{cases} \quad (5.4.23)$$

with speed zero, that is  $c(x^*) = 0$ , and connecting  $(F_A(x^*), 0)$  to  $(0, F_B(x^*))$ .

*Proof.* The proof is split into three steps. First we show that functions  $a_\varepsilon$  and  $b_\varepsilon$  cannot converge both at the same time to the zero function. Then, using that  $a_0$  and  $b_0$  converge at  $-\infty$  to solutions of (5.3.19), we show that limit conditions of (5.4.23) are satisfied. Finally, thanks to a monotonicity argument on the speed  $c(x)$ , we show that  $(a_0, b_0)$  are in fact the unique traveling wave solutions of (5.4.23) such that  $c(\cdot) = 0$ .

*1st step.* The pair  $(a_\varepsilon, b_\varepsilon)$  does not converge to the zero function.

Indeed, for any interval  $(y^-, 0)$  with  $y^- < 0$ , integrating by parts the equation on  $a_\varepsilon$  after dividing it by  $a_\varepsilon$ , we compute

$$\frac{1}{d_A} \int_{y^-}^0 H_A(x_\varepsilon^* + \sqrt{\varepsilon}y, a_\varepsilon(y), b_\varepsilon(y)) dy = - \int_{y^-}^0 \frac{|\frac{d}{dy}a_\varepsilon|^2}{a_\varepsilon^2} dy - \left[ \frac{\frac{d}{dy}a_\varepsilon}{a_\varepsilon} \right]_{y^-}^0 \leq - \frac{\frac{d}{dy}a_\varepsilon(0)}{a_\varepsilon(0)}.$$

Moreover, Lemma 5.3.83 tells us that, for  $\varepsilon < \varepsilon_0$ ,

$$\frac{d}{dx}\varphi_A^\varepsilon = -\sqrt{\varepsilon} \frac{1}{A_\varepsilon} \frac{d}{dx}A_\varepsilon < C_{\varepsilon_0}.$$

This implies directly that for any  $y \in \mathbb{R}$

$$-\frac{\frac{d}{dy}a_\varepsilon(y)}{a_\varepsilon(y)} = -\frac{1}{A_\varepsilon(x_\varepsilon^* + \sqrt{\varepsilon}y)} \frac{d}{dy}A_\varepsilon(x_\varepsilon^* + \sqrt{\varepsilon}y) = -\frac{\sqrt{\varepsilon} \frac{dA_\varepsilon}{dx}(x_\varepsilon^* + \sqrt{\varepsilon}y)}{A_\varepsilon(x_\varepsilon^* + \sqrt{\varepsilon}y)} \leq C_{\varepsilon_0}.$$

Taking the limit  $\varepsilon \rightarrow 0$ , using the continuity of  $H_A$  and that  $(a_\varepsilon, b_\varepsilon) \rightarrow (a_0, b_0)$  uniformly, we find

$$\frac{1}{d_A} \int_{y^-}^0 H_A(x^*, a_0(y), b_0(y)) dy \leq C_{\varepsilon_0}. \quad (5.4.24)$$

If  $(a_0, b_0) \equiv (0, 0)$ , then the left hand side becomes  $|y^-|H_A(x^*, 0, 0)/d_A$  which goes to  $\infty$  when  $y^- \rightarrow -\infty$ . Therefore, one of them, say  $a_0$  is positive in some interval and by the strong maximum principle,  $a_0(y) > 0$  for any  $y \in \mathbb{R}$ . By the condition  $a_0(0) = b_0(0)$ , then  $b_0$  is also positive.

*2nd step.* The pair  $(a_0, b_0)$  satisfies the conditions at infinity in (5.4.23).

We treat for instance the limit at  $-\infty$ . Again by elliptic regularity and thanks to (5.4.24),  $\frac{d^2}{dy^2}a_0(y)$  and  $\frac{d^2}{dy^2}b_0(y)$  vanish at  $-\infty$ . Therefore the limits of  $a_0$  and  $b_0$  are steady state solutions with  $a_0(-\infty) > b_0(-\infty)$ .

The case when this steady state is  $(A^*(x^*), B^*(x^*))$  is discarded by stability hypothesis (5.1.5) and saturation hypothesis (5.1.2). Indeed, we can rewrite the system defining  $\varepsilon_A = A(x^*) - a_0$  and  $\varepsilon_B = b_0 - B(x^*)$ . These functions are always positive and have non negative derivatives. Moreover, both they and their first derivatives, go to zero when  $y \rightarrow -\infty$ . We can write

$$\frac{d^2}{dy^2} \begin{pmatrix} \varepsilon_A(y) \\ \varepsilon_B(y) \end{pmatrix} \approx \begin{pmatrix} -\partial_A H_A/d_A & \partial_B H_A/d_A \\ \partial_A H_B/d_B & -\partial_B H_B/d_B \end{pmatrix} \begin{pmatrix} \varepsilon_A(y) \\ \varepsilon_B(y) \end{pmatrix},$$

where the matrix is evaluated at  $(x^*, A^*(x^*), B^*(x^*))$  and we have neglected the terms of the type  $\varepsilon_A^2, \varepsilon_B^2$  and  $\varepsilon_A \varepsilon_B$  (which do not play a role in the analysis of the signs when  $y \rightarrow -\infty$ ). Integrating between  $-\infty$



and any value  $y \ll -1$  we get

$$0 \leq \frac{d}{dy} \begin{pmatrix} \epsilon_A(y) \\ \epsilon_B(y) \end{pmatrix} \approx \begin{pmatrix} -\partial_A H_A/d_A & \partial_B H_A/d_A \\ \partial_A H_B/d_B & -\partial_B H_B/d_B \end{pmatrix} \begin{pmatrix} \int_{-\infty}^y \epsilon_A \\ \int_{-\infty}^y \epsilon_B \end{pmatrix},$$

which is only possible when  $\partial_A H_A \partial_B H_B - \partial_B H_A \partial_A H_B \geq 0$  contradicting the saddle characterization of  $(A^*(x), B^*(x))$ .

*3rd step.* Finally because the system is competitive, the positive solutions are unique and, in the case at hand, traveling waves with speed 0. We recall why the speed  $c(\cdot)$  is monotonic. Considering the derivatives  $w_a(y) = \frac{\partial}{\partial y} a(y) < 0$ ,  $w_b(y) = \frac{\partial}{\partial y} b(y) > 0$  they satisfy

$$\begin{cases} -c(x) \frac{\partial}{\partial y} w_a(y; x) - d_A \frac{\partial^2}{\partial y^2} w_a(y; x) = M_{11} w_a + M_{12} w_b, \\ -c(x) \frac{\partial}{\partial y} w_b(y; x) - d_B \frac{\partial^2}{\partial y^2} w_b(y; x) = M_{21} w_a + M_{22} w_b. \end{cases}$$

The signs  $M_{12} := \partial_B H_A < 0$  and  $M_{21} := \partial_A H_B < 0$  are compatible with the Krein-Rutman theory, and by consequence the dual problem has a signed solution

$$\begin{cases} c(x) \frac{\partial}{\partial y} \Phi_a(y; x) - d_A \frac{\partial^2}{\partial y^2} \Phi_a(y; x) = M_{11} \Phi_a + M_{21} \Phi_b, & \Phi_a > 0 \\ c(x) \frac{\partial}{\partial y} \Phi_b(y; x) - d_B \frac{\partial^2}{\partial y^2} \Phi_b(y; x) = M_{12} \Phi_a + M_{22} \Phi_b, & \Phi_b < 0. \end{cases}$$

We now consider the  $x$ -derivative:  $z_a(y) = \frac{\partial}{\partial x} w_a(y; x)$  and  $z_b(y) = \frac{\partial}{\partial x} w_b(y; x)$  satisfying

$$\begin{cases} -c(x) \frac{\partial}{\partial y} z_a(y; x) - d_A \frac{\partial^2}{\partial y^2} z_a(y; x) = M_{11} z_a + M_{12} z_b + c'(x) w_a + a \partial_x H_A, \\ -c(x) \frac{\partial}{\partial y} z_b(y; x) - d_B \frac{\partial^2}{\partial y^2} z_b(y; x) = M_{21} z_a + M_{22} z_b + c'(x) w_b + b \partial_x H_B. \end{cases}$$

Integrate in  $y$  against the test function  $\Phi$  and add the two lines, it remains

$$0 = c'(x) \int \underbrace{[w_a \Phi_a + w_b \Phi_b]}_{<0} dy + \int \overbrace{[a \Phi_a \partial_x H_A + b \Phi_b \partial_x H_B]}^{<0} dy, \quad 0 < x < 1,$$

thus  $c' < 0$ . The uniqueness of  $x^*$  follows directly.  $\square$

This result concludes the proof of theorem 5.1.78. We now use this result on a simple model of differentiating neuronal tissue.

## 5.5 Application

---

### 5.5.1 Model

As discussed in [127], a classical illustration of neurodevelopment is provided by the compartmentalization of the neural tube in response to the diffusion of the ventral and dorsal morphogens Sonic Hedgehog

(SHH) and Bone Morphogenetic Protein (BMP), respectively [131, 157]. In this system, a continuous gradient activates ventral and dorsal genes, transcription factors are reciprocal inhibitor and self-activator and diffuse through boundaries. This is well-known to result in the clear definition of territories that express distinct transcription factors subsets [91, 19, 45, 44].

We analyze a simplified version of the model proposed in [127], which includes:

- Epigenetic phenomena: the more a specie has been expressed, the more it is likely to be expressed. This phenomenon scales the production rate with a coefficient  $\alpha_i(A, B)$ .
- The presence of morphogens with a graded concentration along the neural tissue,  $F_i(x)$ ,  $i \in \{A, B\}$ ,
- The self-activation of transcription factors
- and the saturation effects, limiting the production rate of each species proportionally to the total concentration within a cell.
- Eventually, diffusion of homeoproteins will be considered, through a small diffusion parameter  $\varepsilon \ll 1$ .

We will show that these four mechanisms regulating the gene expression (response to gradients, self-activation, reciprocal inhibition and saturation) precisely correspond to our theoretical assumptions. Assuming that the number of cells is large, we consider a space-continuous description of the system, and we denote by  $A(x)$  and  $B(x)$  the concentrations of transcription factors at location  $x$  on the neural tissue. The system described above readily translates into the system of parabolic equations:

$$\partial_t A - \varepsilon d_A \Delta A = \alpha_A A (F_A(x) + A) - \beta_A A (A + B), \quad 0 < x < 1,$$

and a similar equation for  $B$ . In this equation, we considered epigenetic phenomena to have linear effects:  $\alpha_A(A, B) = \alpha_A A$ . Therefore, the term  $\alpha_A A$  is the transcriptional intensity,  $\beta_A$  is the saturation parameter, and we assume  $0 < \alpha_A < \beta_A$  because saturation will overcome necessarily the self-activation. The parameter  $d_A$  incorporates the relative level of diffusion of the parameter  $A$  compared to that of  $B$  (at least one of these constants can be incorporated in the  $\varepsilon$ ). We shall assume that the system is subject to Robin type boundary conditions (5.1.6).

It is not hard to rescale the system so as to write the stationary solutions in the form:

$$\begin{cases} -\varepsilon d_A \Delta A = A (F_A(x) - A - s_A B), & 0 < x < 1, \\ -\varepsilon d_B \Delta B = B (F_B(x) - B - s_B A), \end{cases} \quad (5.5.25)$$

where, for simplicity of notation, we use the same terms  $F_A(x)$  and  $F_B(x)$  to represent the rescaled action of external morphogen gradients. We introduce the parameters  $s_i$  as positive constants taking into account the relation between  $\alpha_i$  and  $\beta_i$ :

$$s_A = \frac{\beta_A}{\beta_A - \alpha_A} > 1 \quad \text{and} \quad s_B = \frac{\beta_B}{\beta_B - \alpha_B} > 1.$$

In the limit  $\varepsilon$  goes to 0, we look for a decreasing solution  $A$  connecting the value  $F_A(0)$  with 0. The morphogen gradients are monotonic and smooth, assumed to be twice differentiable, defined on the

closure of the domain, strictly positive and monotonic. Summarizing, there exists  $\delta > 0$  such that for any  $0 \leq x \leq 1$

$$F_A(x) > \delta, \quad \frac{d}{dx}F_A(x) < 0, \quad F_B(x) > \delta, \quad \frac{d}{dx}F_B(x) > 0. \quad (5.5.26)$$

We have mentioned that diffusion is extremely small. Non-trivial differentiation at these levels of diffusion would require that steady states for  $\varepsilon = 0$  are non-trivial as well. This is why we shall assume that:

$$\exists (x_a, x_b) \in I, \quad x_b < x_a \quad \text{such that} \quad F_A(x_b) = s_A F_B(x_b), \quad F_B(x_a) = s_B F_A(x_a). \quad (5.5.27)$$

A first remark is that combining assumptions (5.5.26) and (5.5.27) we get that

$$\begin{cases} F_B(x) < F_B(x_a) = s_B F_A(x_a) < s_B F_A(x), & \text{for } x \in [0, x_a), \\ F_A(x) < F_A(x_b) = s_A F_B(x_b) < s_A F_B(x), & \text{for } x \in (x_b, 1]. \end{cases} \quad (5.5.28)$$

We have already noticed that both saturation coefficients  $s_A$  and  $s_B$  are greater than 1. For the sake of generality, we make the weaker assumption:

$$s_A s_B > 1. \quad (5.5.29)$$

Of course, in these notations, the parabolic system reads:

$$\begin{cases} \partial_t A - \varepsilon d_A \Delta A = A(F_A - A - s_A B), & 0 < x < 1, t \geq 0, \\ \partial_t B - \varepsilon d_B \Delta B = B(F_B - B - s_B A), \end{cases} \quad (5.5.30)$$

with the Robin boundary conditions (5.1.6). If (5.1.2)–(5.1.5) are met for these  $H_A$  and  $H_B$ , then Theorem 5.1.78 allow us to say that starting with monotonic initial conditions, then solution to (5.5.30) defines a unique point  $x^*$  as a boundary between the two functional areas considered, disambiguating the boundary location.

To start with, note that assumption (5.1.2) is valid thanks to (5.5.26) and that they fit the interpretation for neurodevelopment. They are trivially checked in our case since the maps  $H_A(x, A, B)$  and  $H_B(x, A, B)$  are linear. We are therefore left to characterizing the equilibria of the system and their stability.

**Lemma 5.5.86.** *The properties (5.1.3)–(5.1.5) are valid for our model (see Fig. 5.2). In details, under assumptions (5.5.26), (5.5.27) and (5.5.29) and in the absence of diffusion, we have*

- i.  $(F_A(x), 0)$  is a stable fixed point for  $x \in [0, x_a)$ ,
- ii.  $(0, F_B(x))$  is a stable fixed point for  $x \in (x_b, 1]$ ,
- iii. and there exists an additional solution, which is saddle, in  $(x_a, x_b)$ .

*Proof.* First two fixed points are trivial solutions, and their stability is obtained by investigating the eigenvalues of the Jacobian matrix at these points

i. At  $(F_A(x), 0)$ , the Jacobian matrix reads

$$\begin{bmatrix} -F_A(x) & -s_A F_A(x) \\ 0 & F_B(x) - s_B F_A(x) \end{bmatrix},$$

and (5.5.28) ensures us that this point is stable only on the region  $[0, x_a)$ .

ii. The pair  $(0, F_B(x))$  which is analogous to the previous point and stable on  $(x_b, 1]$ .

iii. Because of hypothesis (5.5.29), there is an extra fixed point  $(A^*, B^*)$  given by

$$A^* = \frac{s_A F_B - F_A}{s_A s_B - 1}, \quad B^* = \frac{s_B F_A - F_B}{s_A s_B - 1}.$$

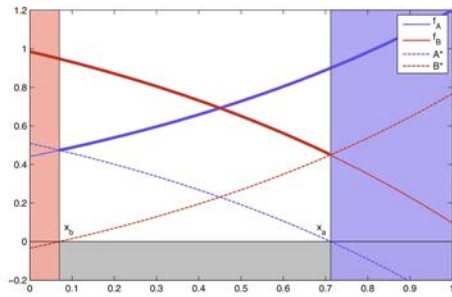
From (5.5.28) and (5.5.29), we get that  $(A^*, B^*)$  is admissible (i.e. both coordinates are non-negative) only in the region  $[x_b, x_a]$ . Monotonicity properties are trivial from the explicit expression, and the stability is governed by the eigenvalues of the Jacobian matrix

$$\text{Jac}(A^*, B^*) = - \begin{bmatrix} A^* & s_A A^* \\ s_B B^* & B^* \end{bmatrix},$$

which has negative determinant (as a consequence of assumption (5.5.29)). Therefore, its eigenvalues are real with opposite signs, i.e. the point  $(A^*, B^*)$  is a saddle fixed point, completing the proof. □

**Remark 5.5.87.** *Let us eventually notice the following fact explaining the topology of the phase plane for  $x \in (x_b, x_a)$ . The space  $\mathbb{R}_+ \times \mathbb{R}_+$  is partitioned into the attraction basin of  $(F_A(x), 0)$  and that of  $(0, F_B(x))$ , in addition to lower-dimensional invariant manifolds. The attraction basins of the fixed point are separated by the one-dimensional stable manifold of the saddle fixed point  $(A^*(x), B^*(x))$ , which is an invariance manifold serving as a separatrix between those trajectories converging to  $(F_A, 0)$  and  $(0, F_B)$ .*

By a direct application of Theorem 5.1.78, the system has a unique differentiated solution in the limit of small diffusion. But when considering only cell-autonomous mechanisms, the bistable region  $x \in (x_b, x_a)$  induces an indeterminacy in the differentiation between two domains: cells may choose independently to differentiate into type  $A$  or type  $B$ , yielding irregular and non-reproducible boundaries depending on the initial condition. This phenomenon is illustrated in Figure 5.2, right panel: in the absence of diffusion, the region within the interval  $(x_b, x_a)$  has an unpredictable behavior that depends on space, while in the presence of even a very small diffusion, ambiguity disappears and a unique steady state emerges (see Figure 5.2). In that sense, a small diffusion suffices to stabilize the transition. From an evolutionary viewpoint, endowing developmental transcription factors with non diffusion properties is a simple mechanism ensuring dramatic stabilization and robustness of the differentiation process. These numerical simulations further open some new perspectives. Indeed, we observe that the convergence towards the monotonic differentiated solutions seem to occur even when we relax the initial condition monotonicity hypothesis of Theorem 5.1.78. Moreover, with random initial conditions, we numerically observe that for small times,  $A$  converges rapidly to  $F_A$  in  $[0, x_b)$  and  $B$  to  $F_B$  in  $(x_a, 1]$ , before the appearance of two abutting traveling fronts that develop toward the center of the coexistence zone,



(a) The morphogen gradients and steady states

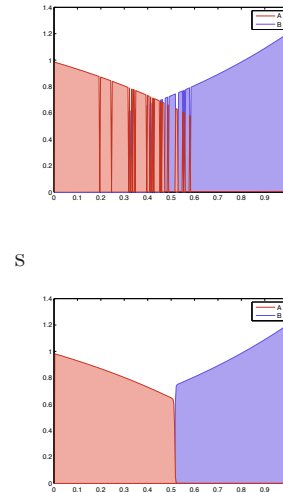


Figure 5.2: Morphogenesis model with exponential morphogen gradients  $F_A(x)$  and  $F_B(x)$  (not shown) and  $s_A = s_B = 2$ . (Left) Equilibria of the system in the absence of diffusion together with their stability (thick solid line: stable, thin solid line: repulsive, dashed: saddle). (Right) Numerical simulations of stationary states of the system (5.5.30)-(5.1.6) shows (top) the ambiguity of boundary location for  $\varepsilon = 0$  and (bottom) the disambiguation for small diffusion  $\varepsilon = 10^{-6}$ .

whose speed decreases as the solution converge. Proving that the theorem persists for general initial conditions remains an open problem.

## Part III

# On a sub-critical model of chemotaxis



# On a subcritical Keller-Segel equation: chaos and entropic chaos propagation

In this last chapter we deal with a subcritical Keller-Segel equation. Starting from the stochastic particle system associated with it, we show well-posedness results and the propagation of chaos property. More precisely, we show that the empirical measure of the system tends towards the unique solution of the limit equation as the number of particles goes to infinity. The main novelty is that we only ask for locally Lipschitz coefficients and the proof of path-wise uniqueness allow us to consider a more general initial conditions than we could use in a more classical framework.

This chapter is included in [66] written in collaboration with D. Godinho to appear on *Annales de l'Institut Henri Poincaré*.

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# 6.1 Introduction and main results

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The subject of this paper is the convergence of a stochastic particle system to a nonlinear and nonlocal equation which can be seen as a subcritical version of the classical Keller-Segel equation.

## 6.1.1 The subcritical Keller-Segel Equation

Consider the equation:

$$\frac{\partial f_t(x)}{\partial t} = \chi \nabla_x \cdot ((K * f_t)(x))f_t(x) + \Delta_x f_t(x), \quad (6.1.1)$$

where  $f : \mathbb{R}_+ \times \mathbb{R}^2 \rightarrow \mathbb{R}$  and  $\chi > 0$ . The force field kernel  $K : \mathbb{R}^2 \rightarrow \mathbb{R}^2$  comes from an attractive potential  $\Phi : \mathbb{R}^2 \rightarrow \mathbb{R}$  and is defined by

$$K(x) := \frac{x}{|x|^{\alpha+1}} = -\nabla \underbrace{\left( \frac{1}{\alpha-1} |x|^{1-\alpha} \right)}_{\Phi(x)}, \quad \alpha \in (0, 1). \quad (6.1.2)$$

The standard Keller-Segel equation correspond to the critical case  $K(x) = x/|x|^2$  (i.e., more singular at  $x = 0$ ) and it describes a model of chemotaxis, i.e., the movement of cells (usually bacteria or amoebae) which are attracted by some chemical substance that they produce. This equation has been first introduced by Keller and Segel in [87, 88]. Blanchet-Dolbeault-Perthame showed in [19] some nice results on existence of global weak solutions if the nonnegative parameter  $\chi$  (which is the sensitivity of the bacteria to the chemo-attractant) is smaller than  $8\pi/M$  where  $M$  is the initial mass (here  $M$  will always be 1 since we will deal with probability measures). For more details on the subject, see [78].

## 6.1.2 The particle system

We consider the following system of particles

$$\forall i = 1, \dots, N, \quad X_t^{i,N} = X_0^{i,N} - \frac{\chi}{N} \sum_{j=1, j \neq i}^N \int_0^t K(X_s^{i,N} - X_s^{j,N}) ds + \sqrt{2} B_t^i, \quad (6.1.3)$$

where  $(B^i)_{i=1, \dots, N}$  is an independent family of 2D standard Brownian motions and  $K$  is defined in (6.1.2). We will show in the sequel that there is propagation of chaos to the solution of the following nonlinear S.D.E linked with (6.1.1) (see the next paragraph)

$$X_t = X_0 - \chi \int_0^t \int_{\mathbb{R}^2} K(X_s - x) f_s(dx) ds + \sqrt{2} B_t, \quad (6.1.4)$$

where  $f_t = \mathcal{L}(X_t)$  ( $\mathcal{L}(X_t)$  denotes the law of  $X_t$ ).

## 6.1.3 Weak solution for the P.D.E

For any Polish space  $E$ , we denote by  $\mathbb{P}(E)$  the set of all probability measures on  $E$  which we endow with the topology of weak convergence defined by duality against functions of  $C_b(E)$ . We give the notion of weak solution that we use in this paper.

**Definition 6.1.88.** We say that  $f = (f_t)_{t \geq 0} \in C([0, \infty), \mathbf{P}(\mathbb{R}^2))$  is a weak solution to (6.1.1) if

$$\forall T > 0, \quad \int_0^T \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} |K(x-y)| f_s(dx) f_s(dy) ds < \infty, \quad (6.1.5)$$

and if for all  $\varphi \in C_b^2(\mathbb{R}^2)$ , all  $t \geq 0$ ,

$$\begin{aligned} \int_{\mathbb{R}^2} \varphi(x) f_t(dx) &= \int_{\mathbb{R}^2} \varphi(x) f_0(dx) + \int_0^t \int_{\mathbb{R}^2} \Delta_x \varphi(x) f_s(dx) ds \\ &\quad - \chi \int_0^t \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} K(x-y) \cdot \nabla_x \varphi(x) f_s(dy) f_s(dx) ds. \end{aligned} \quad (6.1.6)$$

**Remark 6.1.89.** We can see easily that if  $(X_t)_{t \geq 0}$  is a solution to (6.1.4), then setting  $f_t = \mathcal{L}(X_t)$  for any  $t \geq 0$ ,  $(f_t)_{t \geq 0}$  is a weak solution of (6.1.1) in the sense of Definition 6.1.88 provided it satisfies (6.1.5). Indeed, by Itô's formula, we find that for  $\varphi \in C_b^2(\mathbb{R}^2)$ ,

$$\begin{aligned} \varphi(X_t) &= \varphi(X_0) - \chi \int_0^t \nabla_x \varphi(X_s) \cdot \int_{\mathbb{R}^2} K(X_s - y) f_s(dy) ds \\ &\quad + \int_0^t \sqrt{2} \nabla_x \varphi(X_s) \cdot dB_s + \int_0^t \Delta_x \varphi(X_s) ds. \end{aligned}$$

Taking expectations, we get (6.1.6).

#### 6.1.4 Notation and propagation of chaos

For  $N \geq 2$ , we denote by  $\mathbb{P}_{sym}(E^N)$  the set of symmetric probability measures on  $E^N$ , i.e. the set of probability measures which are laws of exchangeable  $E^N$ -valued random variables.

We consider for any  $F \in \mathbb{P}_{sym}((\mathbb{R}^2)^N)$  with a density (a finite moment of positive order is also required in order to define the entropy) the Boltzmann entropy and the Fisher information which are defined by

$$H(F) := \frac{1}{N} \int_{(\mathbb{R}^2)^N} F(x) \log F(x) dx \quad \text{and} \quad I(F) := \frac{1}{N} \int_{(\mathbb{R}^2)^N} \frac{|\nabla F(x)|^2}{F(x)} dx.$$

We also define  $(x_i \in \mathbb{R}^2)$  stands for the  $i$ -th coordinate of  $x \in (\mathbb{R}^2)^N$ , for  $k \geq 0$ ,

$$M_k(F) := \frac{1}{N} \int_{(\mathbb{R}^2)^N} \sum_{i=1}^N |x_i|^k F(dx).$$

Observe that we proceed to the normalization by  $1/N$  in order to have, for any  $f \in \mathbb{P}(\mathbb{R}^2)$ ,

$$H(f^{\otimes N}) = H(f), \quad I(f^{\otimes N}) = I(f) \quad \text{and} \quad M_k(f^{\otimes N}) = M_k(f).$$

We introduce the space  $\mathbb{P}_1(\mathbb{R}^2) := \{f \in \mathbb{P}(\mathbb{R}^2), M_1(f) < \infty\}$  and we recall the definition of the Wasserstein distance: if  $f, g \in \mathbb{P}_1(\mathbb{R}^2)$ ,

$$\mathcal{W}_1(f, g) = \inf \left\{ \int_{\mathbb{R}^2 \times \mathbb{R}^2} |x - y| R(dx, dy) \right\},$$

where the infimum is taken over all probability measures  $R$  on  $\mathbb{R}^2 \times \mathbb{R}^2$  with  $f$  for first marginal and  $g$  for second marginal. It is known that the infimum is reached. See e.g. Villani [158] for many details on the subject.

We now define the notion of propagation of chaos.

**Definition 6.1.90.** Let  $X$  be some  $E$ -valued random variable. A sequence  $(X_1^N, \dots, X_N^N)$  of exchangeable  $E$ -valued random variables is said to be  $X$ -chaotic if one of the three following equivalent conditions is satisfied:

- (i)  $(X_1^N, X_2^N)$  goes in law to 2 independent copies of  $X$  as  $N \rightarrow +\infty$ ;
- (ii) for all  $j \geq 1$ ,  $(X_1^N, \dots, X_j^N)$  goes in law to  $j$  independent copies of  $X$  as  $N \rightarrow +\infty$ ;
- (iii) the empirical measure  $\mu_{X^N}^N := \frac{1}{N} \sum_{i=1}^N \delta_{X_i^N} \in \mathbb{P}(E)$  goes in law to the constant  $\mathcal{L}(X)$  as  $N \rightarrow +\infty$ .

We refer to [145] for the equivalence of the three conditions or [72, Theorem 1.2] where the equivalence is established in a quantitative way.

Propagation of chaos in the sense of Sznitman holds for a system of  $N$  exchangeable particles evolving in time if when the initial conditions  $(X_0^{1,N}, X_0^{2,N}, \dots, X_0^{N,N})$  are  $X_0$ -chaotic, the trajectories  $((X_t^{1,N})_{t \geq 0}, \dots, (X_t^{N,N})_{t \geq 0})$  are  $(X_t)_{t \geq 0}$ -chaotic, where  $(X_t)_{t \geq 0}$  is the (unique) solution of the expected (one-particle) limit model.

We finally recall a stronger (see [72]) sense of chaos introduced by Kac in [82] and formalized recently in [35]: the entropic chaos.

**Definition 6.1.91.** Let  $f$  be some probability measure on  $E$ . A sequence  $(F^N)$  of symmetric probability measures on  $E^N$  is said to be entropically  $f$ -chaotic if

$$F_1^N \rightarrow f \text{ weakly in } \mathbb{P}(E) \text{ and } H(F^N) \rightarrow H(f) \text{ as } N \rightarrow \infty,$$

where  $F_1^N$  stands for the first marginal of  $F^N$ .

We can observe that since the entropy is lower semi continuous (so that  $H(f) \leq \liminf_N H(F^N)$ ) and is convex, the entropic chaos (which requires  $\lim_N H(F^N) = H(f)$ ) is a stronger notion of convergence which implies that for all  $j \geq 1$ , the density of the law of  $(X_1^N, \dots, X_j^N)$  goes to  $f^{\otimes j}$  strongly in  $L^1$  as  $N \rightarrow \infty$  (see [23]).

## 6.1.5 Main results

We first give a result of existence and uniqueness for (6.1.1).

**Theorem 6.1.92.** Let  $\alpha \in (0, 1)$ . Assume that  $f_0 \in \mathbb{P}_1(\mathbb{R}^2)$  is such that  $H(f_0) < \infty$ .

(i) There exists a unique weak solution  $f$  to (6.1.1) such that

$$f \in L_{loc}^\infty([0, \infty), \mathbb{P}_1(\mathbb{R}^2)) \cap L_{loc}^1([0, \infty); L^p(\mathbb{R}^2)) \text{ for some } p > \frac{2}{1-\alpha}. \quad (6.1.7)$$

(ii) This solution furthermore satisfies that for all  $T > 0$ ,

$$\int_0^T I(f_s) ds < \infty, \quad (6.1.8)$$

for any  $q \in [1, 2)$  and for all  $T > 0$ ,

$$\nabla_x f \in L^{2q/(3q-2)}(0, T; L^q(\mathbb{R}^2)), \quad (6.1.9)$$

for any  $p \geq 1$ ,

$$f \in C([0, \infty); L^1(\mathbb{R}^2)) \cap C((0, \infty); L^p(\mathbb{R}^2)), \quad (6.1.10)$$

and that for any  $\beta \in C^1(\mathbb{R}) \cap W_{loc}^{2,\infty}(\mathbb{R})$  such that  $\beta''$  is piecewise continuous and vanishes outside a compact set,

$$\begin{aligned} \partial_t \beta(f) = & \chi(K * f) \cdot \nabla_x(\beta(f)) + \Delta_x \beta(f) \\ & - \beta''(f) |\nabla_x f|^2 + \chi \beta'(f_s) f_s (\nabla_x \cdot K * f_s), \end{aligned} \quad (6.1.11)$$

on  $[0, \infty) \times \mathbb{R}^2$  in the distributional sense.

We denote by  $F_0^N$  the law of  $(X_0^{i,N})_{i=1,\dots,N}$ . We assume that for some  $f_0 \in \mathbb{P}(\mathbb{R}^2)$ ,

$$\begin{cases} F_0^N \in \mathbb{P}_{sym}((\mathbb{R}^2)^N) \text{ is } f_0\text{-chaotic;} \\ \sup_{N \geq 2} M_1(F_0^N) < \infty, \quad \sup_{N \geq 2} H(F_0^N) < \infty. \end{cases} \quad (6.1.12)$$

Observe that this condition is satisfied if the random variables  $(X_0^{i,N})_{i=1,\dots,N}$  are i.i.d. with law  $f_0 \in \mathbb{P}_1(\mathbb{R}^2)$  such that  $H(f_0) < \infty$ . The next result states the well-posedness for the particle system (6.1.3).

**Theorem 6.1.93.** *Let  $\alpha \in (0, 1)$ .*

(i) *Let  $N \geq 2$  be fixed and assume that  $M_1(F_0^N) < \infty$  and  $H(F_0^N) < \infty$ . There exists a unique strong solution  $(X_t^{i,N})_{t \geq 0, i=1,\dots,N}$  to (6.1.3). Furthermore, the particles a.s. never collapse i.e. it holds that a.s., for any  $t \geq 0$  and  $i \neq j$ ,  $X_t^{i,N} \neq X_t^{j,N}$ .*

(ii) *Assume (6.1.12). If for all  $t \geq 0$ , we denote by  $F_t^N \in \mathbb{P}_{sym}((\mathbb{R}^2)^N)$  the law of  $(X_t^{i,N})_{i=1,\dots,N}$ , then there exists a constant  $C$  depending on  $\chi$ ,  $\sup_{N \geq 2} H(F_0^N)$  and  $\sup_{N \geq 2} M_1(F_0^N)$  such that for all  $t \geq 0$  and  $N \geq 2$*

$$H(F_t^N) \leq C(1+t), \quad M_1(F_t^N) \leq C(1+t), \quad \int_0^t I(F_s^N) ds \leq C(1+t).$$

Furthermore for any  $T > 0$ ,

$$\mathbb{E} \left[ \sup_{t \in [0, T]} |X_t^{1,N}| \right] \leq C(1+T). \quad (6.1.13)$$

We also have

$$H(F_t^N) + \int_0^t I(F_s^N) ds \leq H(F_0^N) + \frac{\chi}{N^2} \sum_{i \neq j} \int_0^t \mathbb{E} [\operatorname{div} K(X_s^{i,N} - X_s^{j,N})] ds. \quad (6.1.14)$$

We next state a well-posedness result for the nonlinear S.D.E. (6.1.4).

**Theorem 6.1.94.** *Let  $\alpha \in (0, 1)$  and  $f_0 \in \mathbb{P}_1(\mathbb{R}^2)$  such that  $H(f_0) < \infty$ . There exists a unique strong solution  $(X_t)_{t \geq 0}$  to (6.1.4) such that for some  $p > 2/(1-\alpha)$ ,*

$$(f_t)_{t \geq 0} \in L_{loc}^\infty([0, \infty), \mathbb{P}_1(\mathbb{R}^2)) \cap L_{loc}^1([0, \infty); L^p(\mathbb{R}^2)), \quad (6.1.15)$$

where  $f_t$  is the law of  $X_t$ . Furthermore,  $(f_t)_{t \geq 0}$  is the unique solution to (6.1.1) given in Theorem 6.1.92.

We finally give the result about propagation of chaos.

**Theorem 6.1.95.** *Let  $\alpha \in (0, 1)$ . Assume (6.1.12). For each  $N \geq 2$ , consider the unique solution  $(X_t^{i,N})_{i=1,\dots,N, t \geq 0}$  to (6.1.3). Let  $(X_t)_{t \geq 0}$  be the unique solution to (6.1.4).*

(i) *The sequence  $(X_t^{i,N})_{i=1,\dots,N, t \geq 0}$  is  $(X_t)_{t \geq 0}$ -chaotic. In particular, the empirical measure  $Q^N :=$*

$\frac{1}{N} \sum_{i=1}^N \delta_{(X_t^{i,N})_{t \geq 0}}$  goes in law to  $\mathcal{L}((X_t)_{t \geq 0})$  in  $\mathbb{P}(C((0, \infty), \mathbb{R}^2))$ .

(ii) Assume furthermore that  $\lim_N H(F_0^N) = H(f_0)$ . For all  $t \geq 0$ , the sequence  $(X_t^{i,N})_{i=1, \dots, N}$  is then  $X_t$ -entropically chaotic. In particular, for any  $j \geq 1$  and any  $t \geq 0$ , denoting by  $F_{tj}^N$  the density of the law of  $(X_t^{1,N}, \dots, X_t^{j,N})$ , it holds that

$$\lim_{N \rightarrow \infty} \|F_{tj}^N - f_t^{\otimes j}\|_{L^1((\mathbb{R}^2)^j)} = 0.$$

We can observe that the condition  $\lim_N H(F_0^N) = H(f_0)$  is satisfied if the random variables  $(X_0^{i,N})_{i=1, \dots, N}$  are i.i.d. with law  $f_0$  such that  $H(f_0) < \infty$ .

### 6.1.6 Comments

This paper is some kind of adaptation of the work of Fournier-Hauray-Mischler in [62] where they show the propagation of chaos of some particle system for the 2D viscous vortex model. We use the same methods for a subcritical Keller-Segel equation. The proofs are thus sometimes very similar to those in [62] but there are some differences due to the facts that i) there are no circulation parameter ( $\mathcal{M}_i^N$  in [62]): this simplify the situation since we thus deal with solutions which are probabilities and ii) the kernel is not the same: it is not divergence-free and we thus have to deal with some additional terms in our computations (see the comments before Proposition 6.3.101 and in the proof of the point ii) of Theorem 6.1.92 in Section 6). We can also notice that due to this fact, we have no already known result for the existence and uniqueness of the particle system that we consider. The methods used to prove uniqueness for the Keller-Segel equation (6.1.1) and its associated S.D.E. (6.1.4), and to prove the entropic chaos are also different.

The proof of Theorem 6.1.92 follows the ideas of renormalisation solutions to a PDE introduced by Di Perna and Lions in [47] and developed since then. The key point is to be able to find good *a priori* estimates which allow us to approximate the weak solutions by regular functions, i.e., to use  $C^k$  functions instead of  $L^1$ . Then, using these estimates, one can pass to the limit and go back to the initial problem. One can further see that the uniqueness result is proven based on coupling methods and the Wasserstein distance. This will allow us to use more general initial conditions than we could use in a strictly deterministic framework.

The proof of existence and uniqueness for the particle system (6.1.3) (Theorem 6.1.93) use some nice arguments. Like for S.D.Es with locally Lipschitz coefficients, we show existence and uniqueness up to an explosion time and the interesting part of the proof is to show that this explosion time is infinite a.s.

To our knowledge, there is no other work that give a convergence result of some particle system for a chemotaxis model with a singular kernel  $K$  and without cutoff parameter. In [142], Stevens studies a particle system with two kinds of particles corresponding to bacteria and chemical substance. She shows convergence of the system for smooth initial data (lying in  $C_b^3(\mathbb{R}^d)$ ) and for regular kernels (continuously differentiable and bounded together with their derivatives). In [71], Haskovec and Schmeiser consider a kernel with a cutoff parameter  $K_\epsilon(x) = \frac{x}{|x|(|x|+\epsilon)}$ . They get some well-posedness result for the particle

system and they show the weak convergence of subsequences due to a tightness result (observe that here we have propagation of chaos and also entropic chaos). In a recent work [34], Calvez and Corrias work on some one-dimensional Keller-Segel model. They study a dynamical particle system for which they give a global existence result under some assumptions on the initial distribution of the particles that prevents collisions. They also give two blow-up criteria for the particle system they do not state a convergence result for this system.

Finally, it is important to notice that the present method can not be directly adapted for the standard case  $\alpha = 1$  because in this last situation the entropy and the Fisher information are not controlled.

### 6.1.7 Plan of the paper

In the next section, we give some preliminary results. In Section 3, we establish the well-posedness of the particle system (6.1.3). In Section 4, we prove the tightness of the particle system and we show that any limit point belongs to the set of solutions to the nonlinear S.D.E. (6.1.4). In Section 5, we show that the P.D.E. (6.1.1) and the nonlinear S.D.E. (6.1.4) are well-posed and we show the propagation of chaos. Finally, in the last section, we improve the regularity of the solution, give some renormalization results for the solution to (6.1.1) and we conclude with the entropic chaos.

## 6.2 Preliminaries

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In this section, we recall some lemmas stated in [62] and [72] and we state a result on the regularity of the kernel  $K$  defined in (6.1.2). The first result tells us that pairs of particles which law have finite Fisher information cannot be too close.

**Lemma 6.2.96.** (*[62, Lemma 3.3]*) *Consider  $F \in \mathbb{P}(\mathbb{R}^2 \times \mathbb{R}^2)$  with finite Fisher information and  $(X_1, X_2)$  a random variable with law  $F$ . Then for any  $\gamma \in (0, 2)$  and any  $\beta > \gamma/2$  there exists  $C_{\gamma, \beta}$  so that*

$$\mathbb{E}[|X_1 - X_2|^{-\gamma}] = \int_{\mathbb{R}^2 \times \mathbb{R}^2} \frac{F(x_1, x_2)}{|x_1 - x_2|^\gamma} dx_1 dx_2 \leq C_{\gamma, \beta} (I(F)^\beta + 1).$$

In the next lemma, we see that the Fisher information of the marginals of some  $F \in \mathbb{P}_{sym}((\mathbb{R}^2)^N)$  is smaller than the Fisher information of  $F$ .

**Lemma 6.2.97.** (*[72, Lemma 3.7]*) *For any  $F \in \mathbb{P}_{sym}((\mathbb{R}^2)^N)$  and  $1 \leq l \leq N$ ,  $I(F_l) \leq I(F)$ , where  $F_l \in \mathbb{P}_{sym}((\mathbb{R}^2)^l)$  denotes the marginal probability of  $F$  on the  $l$ -th block of variables.*

The following lemma allows us to control from below the entropy of some  $F \in \mathbb{P}_k((\mathbb{R}^2)^N)$  by its moment of order  $k$  for any  $k > 0$ .

**Lemma 6.2.98.** (*[62, Lemma 3.1]*) *For any  $k, \lambda \in (0, \infty)$ , there is a constant  $C_{k, \lambda} \in \mathbb{R}$  such that for any  $N \geq 1$ , any  $F \in \mathbb{P}_k((\mathbb{R}^2)^N)$ ,*

$$H(F) \geq -C_{k, \lambda} - \lambda M_k(F).$$

The next result tells us that a probability measure on  $\mathbb{R}^2$  with finite Fisher information belongs to  $L^p$  for any  $p \geq 1$  and its derivatives, to  $L^q$  for any  $q \in [1, 2)$ .

**Lemma 6.2.99.** ([62, Lemma 3.2]) *For any  $f \in \mathbb{P}(\mathbb{R}^2)$  with finite Fisher information, there holds*

$$\begin{aligned} \forall p \in [1, \infty), \quad \|f\|_{L^p(\mathbb{R}^2)} &\leq C_p I(f)^{1-1/p}, \\ \forall q \in [1, 2), \quad \|\nabla_x f\|_{L^q(\mathbb{R}^2)} &\leq C_q I(f)^{3/2-1/q}. \end{aligned}$$

We end this section with the following result on  $K$ .

**Lemma 6.2.100.** *Let  $\alpha \in (0, 1)$ . There exists a constant  $C_\alpha$  such that for all  $x, y \in \mathbb{R}^2$*

$$|K(x) - K(y)| \leq C_\alpha |x - y| \left( \frac{1}{|x|^{\alpha+1}} + \frac{1}{|y|^{\alpha+1}} \right).$$

**Proof.** We have

$$\begin{aligned} |K(x) - K(y)| &= \left| x \left( \frac{1}{|x|^{\alpha+1}} - \frac{1}{|y|^{\alpha+1}} \right) + \frac{x-y}{|y|^{\alpha+1}} \right| \\ &\leq |x| |x-y| (\alpha+1) \max \left( \frac{1}{|x|^{\alpha+2}}, \frac{1}{|y|^{\alpha+2}} \right) + \frac{|x-y|}{|y|^{\alpha+1}}. \end{aligned}$$

By symmetry, we also have

$$|K(x) - K(y)| \leq |y| |x-y| (\alpha+1) \max \left( \frac{1}{|x|^{\alpha+2}}, \frac{1}{|y|^{\alpha+2}} \right) + \frac{|x-y|}{|x|^{\alpha+1}}.$$

So we deduce that

$$\begin{aligned} |K(x) - K(y)| &\leq |x-y| \left[ (\alpha+1) \min(|x|, |y|) \max \left( \frac{1}{|x|^{\alpha+2}}, \frac{1}{|y|^{\alpha+2}} \right) \right. \\ &\quad \left. + \frac{1}{|x|^{\alpha+1}} + \frac{1}{|y|^{\alpha+1}} \right] \\ &\leq |x-y| \left[ (\alpha+1) \frac{1}{\min(|x|, |y|)^{\alpha+1}} + \frac{1}{|x|^{\alpha+1}} + \frac{1}{|y|^{\alpha+1}} \right] \\ &\leq (\alpha+2) |x-y| \left( \frac{1}{|x|^{\alpha+1}} + \frac{1}{|y|^{\alpha+1}} \right). \end{aligned}$$

which concludes the proof.  $\square$

## 6.3 Well-posedness for the system of particles ---

Let's now introduce another particle system with a regularized kernel. We set, for  $\epsilon \in (0, 1)$ ,

$$K_\epsilon(x) = \frac{x}{\max(|x|, \epsilon)^{\alpha+1}}, \tag{6.3.16}$$

which obviously satisfies  $|K_\epsilon(x) - K_\epsilon(y)| \leq C_{\alpha, \epsilon} |x - y|$  and we consider the following system of S.D.E.s

$$\forall i = 1, \dots, N, \quad X_t^{i, N, \epsilon} = X_0^{i, N} - \frac{\chi}{N} \sum_{j=1, j \neq i}^N \int_0^t K_\epsilon(X_s^{i, N, \epsilon} - X_s^{j, N, \epsilon}) ds + \sqrt{2} B_t^i, \tag{6.3.17}$$

for which strong existence and uniqueness thus holds.

The following result will be useful for the proof of Theorem 6.1.93. Its proof is very similar to the proof of [62, Proposition 5.1]. Nevertheless, due to the fact that the kernel is not divergence-free, there is an additional term in the dissipation of entropy's formula (6.3.18) which will lead to additional computations to control it.

**Proposition 6.3.101.** *Let  $\alpha \in (0, 1)$ .*

(i) *Let  $N \geq 2$  be fixed. Assume that  $M_1(F_0^N) < \infty$  and  $H(F_0^N) < \infty$ . For all  $t \geq 0$ , we denote by  $F_t^{N,\epsilon} \in \mathbb{P}_{sym}((\mathbb{R}^2)^N)$  the law of  $(X_t^{i,N,\epsilon})_{i=1,\dots,N}$ . Then*

$$H(F_t^{N,\epsilon}) = H(F_0^N) + \frac{\chi}{N^2} \sum_{i \neq j} \int_0^t \int_{(\mathbb{R}^2)^N} \operatorname{div} K_\epsilon(x_i - x_j) F_s^{N,\epsilon}(x) ds dx - \int_0^t I(F_s^{N,\epsilon}) ds. \quad (6.3.18)$$

(ii) *There exists a constant  $C$  which depends on  $\chi$ ,  $H(F_0^N)$  and  $M_1(F_0^N)$  (but not on  $\epsilon$ ) such that for all  $t \geq 0$  and  $N \geq 2$ ,*

$$H(F_t^{N,\epsilon}) \leq C(1+t), \quad M_1(F_t^{N,\epsilon}) \leq C(1+t), \quad \int_0^t I(F_s^{N,\epsilon}) ds \leq C(1+t). \quad (6.3.19)$$

Furthermore,

$$\mathbb{E} \left[ \sup_{[0,T]} |X_t^{1,N,\epsilon}| \right] \leq C(1+T). \quad (6.3.20)$$

**Proof.** Let  $\varphi \in C_b^2((\mathbb{R}^2)^N)$ , and  $t \geq 0$  be fixed. Using Itô's formula, we compute the expectation of  $\varphi(X_t^{1,N,\epsilon}, \dots, X_t^{N,N,\epsilon})$  and get (recall that  $x_i \in \mathbb{R}^2$  stands for the  $i$ -th coordinate of  $x \in (\mathbb{R}^2)^N$ )

$$\begin{aligned} \frac{d}{dt} \int_{(\mathbb{R}^2)^N} \varphi(x) F_t^{N,\epsilon}(dx) &= -\frac{\chi}{N} \int_{(\mathbb{R}^2)^N} \sum_{i \neq j} K_\epsilon(x_i - x_j) \cdot \nabla_{x_i} \varphi(x) F_t^{N,\epsilon}(dx) \\ &\quad + \int_{(\mathbb{R}^2)^N} \Delta_x \varphi(x) F_t^{N,\epsilon}(dx). \end{aligned} \quad (6.3.21)$$

We deduce that  $F^{N,\epsilon}$  is a weak solution to

$$\partial_t F_t^{N,\epsilon}(x) = \frac{\chi}{N} \sum_{i \neq j} \operatorname{div}_{x_i} (F_t^{N,\epsilon}(x) K_\epsilon(x_i - x_j)) + \Delta_x F_t^{N,\epsilon}(x). \quad (6.3.22)$$

We are now able to compute the evolution of the entropy.

$$\begin{aligned} \frac{d}{dt} H(F_t^{N,\epsilon}) &= \frac{1}{N} \int_{(\mathbb{R}^2)^N} \partial_t F_t^{N,\epsilon}(x) (1 + \log F_t^{N,\epsilon}(x)) dx \\ &= \frac{\chi}{N^2} \sum_{i \neq j} \int_{(\mathbb{R}^2)^N} \operatorname{div}_{x_i} (F_t^{N,\epsilon}(x) K_\epsilon(x_i - x_j)) (1 + \log F_t^{N,\epsilon}(x)) dx \\ &\quad + \frac{1}{N} \int_{(\mathbb{R}^2)^N} \Delta_x F_t^{N,\epsilon}(x) (1 + \log F_t^{N,\epsilon}(x)) dx. \end{aligned}$$

Performing some integrations by parts, we get

$$\begin{aligned} \frac{d}{dt} H(F_t^{N,\epsilon}) &= -\frac{\chi}{N^2} \sum_{i \neq j} \int_{(\mathbb{R}^2)^N} K_\epsilon(x_i - x_j) \cdot \nabla_{x_i} F_t^{N,\epsilon}(x) dx - I(F_t^{N,\epsilon}) \\ &= \frac{\chi}{N^2} \sum_{i \neq j} \int_{(\mathbb{R}^2)^N} \operatorname{div} K_\epsilon(x_i - x_j) F_t^{N,\epsilon}(x) dx - I(F_t^{N,\epsilon}), \end{aligned}$$



and (6.3.18) follows. Using that  $\operatorname{div} K_\epsilon(x) = \frac{1-\alpha}{|x|^{\alpha+1}} \mathbf{1}_{\{|x| \geq \epsilon\}} + \frac{2}{\epsilon^{\alpha+1}} \mathbf{1}_{\{|x| < \epsilon\}} \leq \frac{2}{|x|^{\alpha+1}}$  and the exchangeability of the particles, we get

$$\begin{aligned} \frac{d}{dt} H(F_t^{N,\epsilon}) &\leq \frac{2\chi}{N^2} \sum_{i \neq j} \int_{(\mathbb{R}^2)^N} \frac{F_t^{N,\epsilon}(x)}{|x_i - x_j|^{\alpha+1}} dx - I(F_t^{N,\epsilon}) \\ &\leq 2\chi \int_{(\mathbb{R}^2)^N} \frac{F_t^{N,\epsilon}(x)}{|x_1 - x_2|^{\alpha+1}} dx - I(F_t^{N,\epsilon}). \end{aligned}$$

Since  $\alpha \in (0, 1)$ , we can use Lemma 6.2.96 with  $\gamma = \alpha + 1$  and  $\beta$  such that  $\frac{\alpha+1}{2} < \beta < 1$ , which gives

$$\int_{(\mathbb{R}^2)^N} \frac{F_t^{N,\epsilon}(x) dx}{|x_1 - x_2|^{\alpha+1}} \leq C(I(F_{t_2}^{N,\epsilon})^\beta + 1),$$

where  $F_{t_2}^{N,\epsilon}$  is the two-marginal of  $F_t^{N,\epsilon}$ . By Lemma 6.2.97, we have  $I(F_{t_2}^{N,\epsilon}) \leq I(F_t^{N,\epsilon})$ . Using that  $Cx^\beta \leq C' + \frac{x}{6\chi}$  for a constant  $C'$  sufficiently large, we thus get

$$\frac{d}{dt} H(F_t^{N,\epsilon}) \leq C - \frac{2}{3} I(F_t^{N,\epsilon}),$$

and thus

$$H(F_t^{N,\epsilon}) + \frac{2}{3} \int_0^t I(F_s^{N,\epsilon}) ds \leq H(F_0^N) + Ct. \quad (6.3.23)$$

We now compute  $M_1(F_t^{N,\epsilon})$ . We first observe that

$$M_1(F_t^{N,\epsilon}) = \frac{1}{N} \int_{(\mathbb{R}^2)^N} \sum_{i=1}^N |x_i| F_t^{N,\epsilon}(dx) = \mathbb{E}[|X_t^{1,N,\epsilon}|],$$

since the particles are exchangeable. We will need to control  $\mathbb{E}[\sup_{[0,T]} |X_t^{1,N,\epsilon}|]$  in the sequel. We have

$$\begin{aligned} \mathbb{E} \left[ \sup_{[0,T]} |X_t^{1,N,\epsilon}| \right] &\leq C \left( \mathbb{E}[|X_0^1|] + \mathbb{E} \left[ \sup_{[0,T]} |B_t^1| \right] \right) \\ &\quad + \mathbb{E} \left[ \sup_{t \in [0,T]} \left| \frac{1}{N} \sum_{j \neq 1} \int_0^t K_\epsilon(X_s^{1,N,\epsilon} - X_s^{j,N,\epsilon}) ds \right| \right] \\ &\leq C \left( \mathbb{E}[|X_0^1|] + T + \frac{1}{N} \sum_{j \neq 1} \int_0^T \mathbb{E}[|K_\epsilon(X_s^{1,N,\epsilon} - X_s^{j,N,\epsilon})|] ds \right) \\ &\leq C \left( \mathbb{E}[|X_0^1|] + T + \int_0^T \mathbb{E} \left[ \frac{1}{|X_s^{1,N,\epsilon} - X_s^{2,N,\epsilon}|^\alpha} \right] ds \right). \end{aligned} \quad (6.3.24)$$

Using Lemma 6.2.96 with  $\gamma = \alpha$  and  $\beta$  such that  $\frac{\alpha}{2} < \beta < 1$  and recalling that  $I(F_{t_2}^{N,\epsilon}) \leq I(F_t^{N,\epsilon})$ , we get

$$\begin{aligned} M_1(F_t^{N,\epsilon}) &\leq C \left( M_1(F_0^N) + T + \int_0^t I(F_s^{N,\epsilon})^\beta ds \right) \\ &\leq C \left( M_1(F_0^N) + T \right) + \frac{1}{3} \int_0^t I(F_s^{N,\epsilon}) ds, \end{aligned} \quad (6.3.25)$$

where we used that  $Cx^\beta \leq C' + \frac{x}{3}$  for a constant  $C'$  sufficiently large. Summing (6.3.23) and (6.3.25), we thus find

$$H(F_t^{N,\epsilon}) + M_1(F_t^{N,\epsilon}) + \frac{1}{3} \int_0^t I(F_s^{N,\epsilon}) ds \leq H(F_0^N) + Ct + C(1 + M_1(F_0^N)).$$

Since the quantities  $M_1$  and  $I$  are positive, we immediately get  $H(F_t^{N,\epsilon}) \leq C(1+t)$ . Using Lemma 6.2.98, we have  $H(F_t^{N,\epsilon}) \geq -C - M_1(F_t^{N,\epsilon})/2$ , so that

$$M_1(F_t^{N,\epsilon}) + \frac{1}{3} \int_0^t I(F_s^{N,\epsilon}) ds \leq C(1+t) + M_1(F_t^{N,\epsilon})/2.$$

Using again the positivity of  $M_1$  and  $I$ , we easily get (6.3.19). Coming back to (6.3.24), we finally observe that

$$\mathbb{E} \left[ \sup_{[0,T]} |X_t^{1,N,\epsilon}| \right] \leq C \left( \mathbb{E}[|X_0^1|] + T + \int_0^T I(F_s^{N,\epsilon}) ds \right) \leq C(1 + \mathbb{E}[|X_0^1|] + T),$$

which gives (6.3.20) and concludes the proof.  $\square$

We can now give the proof of existence and uniqueness for the particle system (6.1.3).

**Proof of Theorem 6.1.93.** Like in [146], the key point of the proof is to show that particles of the system (6.1.3) a.s. never collide. We divide the proof in three steps. The first step consists in showing that a.s. there are no collisions between particles for the system (6.3.17). In the second step, we deduce that the particles of the system (6.1.3) also never collide, which ensures global existence and uniqueness for (6.1.3). In the last step, we establish the estimates about the entropy, Fisher information and the first moment. We fix  $N \geq 2$  and for all  $\epsilon \in (0, 1)$ , we consider  $(X_t^{i,N,\epsilon})_{i=1,\dots,N,t \geq 0}$  the unique solution to (6.3.17).

*Step 1.* Let  $\tau_\epsilon := \inf\{t \geq 0, \exists i \neq j, |X_t^{i,N,\epsilon} - X_t^{j,N,\epsilon}| \leq \epsilon\}$ . The aim of this step is to prove that  $\lim_{\epsilon \rightarrow 0} \mathbb{P}[\tau_\epsilon < T] = 0$  for all  $T > 0$ . We fix  $T > 0$  and introduce

$$S_t^\epsilon := \frac{1}{N^2} \sum_{i \neq j} \log |X_t^{i,N,\epsilon} - X_t^{j,N,\epsilon}|. \quad (6.3.26)$$

For any  $A > 1$ , we have

$$\begin{aligned} \mathbb{P}[\tau_\epsilon < T] &\leq \mathbb{P} \left[ \inf_{[0,T]} S_{t \wedge \tau_\epsilon}^\epsilon \leq S_{\tau_\epsilon}^\epsilon \right] \\ &\leq \mathbb{P}[\exists i, \exists t \in [0, T], |X_t^{i,N,\epsilon}| > A] \\ &\quad + \mathbb{P} \left[ \forall i, \forall t \in [0, T], |X_t^{i,N,\epsilon}| \leq A, \inf_{[0,T]} S_{t \wedge \tau_\epsilon}^\epsilon \leq S_{\tau_\epsilon}^\epsilon \right] \\ &\leq \frac{N \mathbb{E} \left[ \sup_{[0,T]} |X_t^{1,N,\epsilon}| \right]}{A} + \mathbb{P} \left[ \inf_{[0,T]} S_{t \wedge \tau_\epsilon}^\epsilon \leq \frac{\log \epsilon}{N^2} + \log 2A \right] \\ &\leq \frac{C(1+T)N}{A} + \mathbb{P} \left[ \inf_{[0,T]} S_{t \wedge \tau_\epsilon}^\epsilon \leq \frac{\log \epsilon}{N^2} + \log 2A \right], \end{aligned} \quad (6.3.27)$$

where we used (6.3.20). We thus want to compute  $\mathbb{P} \left[ \inf_{[0,T]} S_{t \wedge \tau_\epsilon}^\epsilon \leq -M \right]$  for all (large)  $M > 0$ . Using Itô's formula, that  $K_\epsilon(x) = K(x)$  for any  $|x| \geq \epsilon$  (see (6.3.16)) and that  $\Delta(\log|x|) = 0$  on

$\{x \in \mathbb{R}^2, |x| > \epsilon\}$ , we have

$$\begin{aligned} \log |X_{t \wedge \tau_\epsilon}^{i,N,\epsilon} - X_{t \wedge \tau_\epsilon}^{j,N,\epsilon}| &= \log |X_0^{i,N} - X_0^{j,N}| + M_{t \wedge \tau_\epsilon}^{i,j,\epsilon} \\ &\quad - \frac{\chi}{N} \int_0^{t \wedge \tau_\epsilon} \left[ \sum_{k \neq i,j} \left( K(X_s^{i,N,\epsilon} - X_s^{k,N,\epsilon}) - K(X_s^{j,N,\epsilon} - X_s^{k,N,\epsilon}) \right) \right. \\ &\quad \left. + 2K(X_s^{i,N,\epsilon} - X_s^{j,N,\epsilon}) \right] \cdot \frac{X_s^{i,N,\epsilon} - X_s^{j,N,\epsilon}}{|X_s^{i,N,\epsilon} - X_s^{j,N,\epsilon}|^2} ds \\ &=: \log |X_0^{i,N} - X_0^{j,N}| + M_{t \wedge \tau_\epsilon}^{i,j,\epsilon} + R_{t \wedge \tau_\epsilon}^{i,j,\epsilon}, \end{aligned}$$

where  $M_t^{i,j,\epsilon}$  is a martingale. Setting  $S_0 := \frac{1}{N^2} \sum_{i \neq j} \log |X_0^{i,N} - X_0^{j,N}|$ ,  $M_t^\epsilon := \frac{1}{N^2} \sum_{i \neq j} M_{t \wedge \tau_\epsilon}^{i,j,\epsilon}$  and  $R_t^\epsilon := \frac{1}{N^2} \sum_{i \neq j} R_{t \wedge \tau_\epsilon}^{i,j,\epsilon}$ , we thus have

$$S_{t \wedge \tau_\epsilon}^\epsilon = S_0 + M_t^\epsilon + R_t^\epsilon,$$

so that

$$\begin{aligned} \mathbb{P}(\inf_{[0,T]} S_{t \wedge \tau_\epsilon}^\epsilon \leq -M) &\leq \mathbb{P}(S_0 \leq -M/3) + \mathbb{P}(\inf_{[0,T]} M_t^\epsilon \leq -M/3) \\ &\quad + \mathbb{P}(\inf_{[0,T]} R_t^\epsilon \leq -M/3). \end{aligned} \tag{6.3.28}$$

Using first Lemma 6.2.100 and that  $|K(x)| = |x|^{-\alpha}$ , and then exchangeability, we clearly have for some constant  $C$  independent of  $N$  and  $\epsilon$ ,

$$\begin{aligned} \mathbb{E}[\sup_{[0,T]} |R_t^\epsilon|] &\leq \frac{C}{\chi N^3} \sum_{i \neq j} \sum_{k \neq i,j} \left( \mathbb{E} \left[ \frac{1}{|X_s^{i,N,\epsilon} - X_s^{k,N,\epsilon}|^{\alpha+1}} \right] + \mathbb{E} \left[ \frac{1}{|X_s^{j,N,\epsilon} - X_s^{k,N,\epsilon}|^{\alpha+1}} \right] \right. \\ &\quad \left. + \mathbb{E} \left[ \frac{1}{|X_s^{i,N,\epsilon} - X_s^{j,N,\epsilon}|^{\alpha+1}} \right] \right) ds \\ &\leq C\chi \int_0^T \mathbb{E} \left[ \frac{1}{|X_s^{1,N,\epsilon} - X_s^{2,N,\epsilon}|^{\alpha+1}} \right] ds \\ &\leq C\chi \int_0^T (1 + I(F_{s^2}^{N,\epsilon})) ds \\ &\leq C(1 + T), \end{aligned} \tag{6.3.29}$$

where we used Lemma 6.2.96, the fact that  $I(F_{t^2}^{N,\epsilon}) \leq I(F_t^{N,\epsilon})$  by Lemma 6.2.97, and finally Proposition 6.3.101. We thus get

$$\mathbb{P}(\inf_{[0,T]} R_t^\epsilon \leq -M/3) \leq \mathbb{P}(\sup_{[0,T]} |R_t^\epsilon| \geq M/3) \leq \frac{C(1+T)}{M}. \tag{6.3.30}$$

We now want to compute  $\mathbb{P}(\inf_{[0,T]} M_t^\epsilon \leq -M/3)$ . Using that  $\log |x| \leq |x|$ , we have

$$S_t^\epsilon \leq \frac{1}{N^2} \sum_{i \neq j} (|X_t^{i,N,\epsilon}| + |X_t^{j,N,\epsilon}|) \leq \frac{2}{N} \sum_i |X_t^{i,N,\epsilon}|.$$

Consequently,

$$\begin{aligned} M_t^\epsilon &\leq S_{t \wedge \tau_\epsilon}^\epsilon + \sup_{s \in [0,T]} |R_s^\epsilon| - S_0 \\ &\leq \frac{2}{N} \sum_i \sup_{s \in [0,T]} |X_s^{i,N,\epsilon}| + \sup_{s \in [0,T]} |R_s^\epsilon| - S_0 =: K^\epsilon - S_0 =: Z^\epsilon. \end{aligned}$$

We have

$$\mathbb{P}(\inf_{[0,T]} M_t^\epsilon \leq -M/3) \leq \mathbb{P}(Z^\epsilon \geq \sqrt{M/3}) + \mathbb{P}(\inf_{[0,T]} M_t^\epsilon \leq -M/3, Z^\epsilon < \sqrt{M/3}). \quad (6.3.31)$$

Since  $(M_t^\epsilon)_{t \geq 0}$  is a continuous local martingale, there exists a Brownian Motion  $\beta$  such that  $M_t^\epsilon = \beta_{\langle M^\epsilon \rangle_t}$ . For  $x \in \mathbb{R}$ , we set  $\sigma_x := \inf\{t \geq 0, \beta_t = x\}$ . Using that  $\sup_{[0,T]} M_t^\epsilon \leq Z^\epsilon$  a.s.,

$$\begin{aligned} \mathbb{P}(\inf_{[0,T]} M_t^\epsilon \leq -M/3, Z^\epsilon < \sqrt{M/3}) &\leq \mathbb{P}(\inf_{[0,T]} M_t^\epsilon \leq -M/3, \sup_{[0,T]} M_t^\epsilon < \sqrt{M/3}) \\ &\leq \mathbb{P}(\sigma_{-M/3} \leq \sigma_{\sqrt{M/3}}) \\ &= \frac{\sqrt{M/3}}{M/3 + \sqrt{M/3}} \leq \sqrt{\frac{3}{M}}, \end{aligned} \quad (6.3.32)$$

by classical results on the Brownian Motion. Using (6.3.20) and (6.3.29), we get that  $\mathbb{E}[K^\epsilon] \leq C(1+T)$  where  $C$  does not depend on  $\epsilon$ . So using the Markov inequality,

$$\begin{aligned} \mathbb{P}(Z^\epsilon \geq \sqrt{M/3}) &= \mathbb{P}(K^\epsilon - S_0 \geq \sqrt{M/3}) \\ &\leq \mathbb{P}(K^\epsilon \geq \sqrt{M/12}) + \mathbb{P}(-S_0 \geq \sqrt{M/12}) \\ &\leq \frac{C(1+T)}{\sqrt{M}} + \mathbb{P}(-S_0 \geq \sqrt{M/12}). \end{aligned} \quad (6.3.33)$$

Gathering (6.3.31), (6.3.32) and (6.3.33), we find that

$$\mathbb{P}(\inf_{[0,T]} M_t^\epsilon \leq -M/3) \leq \frac{C(1+T)}{\sqrt{M}} + \mathbb{P}(-S_0 \geq \sqrt{M/12}). \quad (6.3.34)$$

Coming back to (6.3.27) and (6.3.28), using (6.3.30) and (6.3.34) with  $M = -\frac{\log \epsilon}{N^2} - \log 2A$ , we finally get that for any  $\epsilon \in (0, 1)$ , any  $A > 1$  such that  $\frac{\log \epsilon}{N^2} + \log 2A < 0$ ,

$$\begin{aligned} \mathbb{P}(\tau_\epsilon < T) &\leq \frac{C(1+T)N}{A} + \mathbb{P}\left(S_0 \leq \left(\frac{\log \epsilon}{N^2} + \log 2A\right)/3\right) \\ &\quad + \frac{C(1+T)}{-\frac{\log \epsilon}{N^2} - \log 2A} + \frac{C(1+T)}{\sqrt{-\frac{\log \epsilon}{N^2} - \log 2A}} \\ &\quad + \mathbb{P}\left(S_0 \leq -\sqrt{\left(-\frac{\log \epsilon}{N^2} - \log 2A\right)/12}\right). \end{aligned}$$

Observe finally that  $S_0 > -\infty$  a.s. (because  $F_0^N$  has a density since  $H(F_0^N) < \infty$ ) so that  $\lim_{M \rightarrow +\infty} \mathbb{P}(S_0 < -M) = 0$ . Letting  $\epsilon \rightarrow 0$  in the above formula, we get that for all  $A > 1$ ,

$$\limsup_{\epsilon} \mathbb{P}(\tau_\epsilon < T) \leq \frac{C(1+T)N}{A}.$$

It only remains to make  $A$  go to  $\infty$  to conclude this step.

*Step 2.* Since  $K$  is Lipschitz-continuous outside 0, classical arguments give existence and uniqueness of a solution to (6.1.3) until the explosion time  $\tau = \inf\{t \geq 0, \exists i \neq j, X_t^{i,N} = X_t^{j,N}\}$ . We can observe that since  $K_\epsilon(x) = K(x)$  for any  $|x| \geq \epsilon$ ,  $(X^{i,N,\epsilon})_{i=1,\dots,N}$  is solution to (6.1.3) on  $[0, \tau_\epsilon]$  so that for any  $i = 1, \dots, N$ ,  $X_t^{i,N} = X_t^{i,N,\epsilon}$  on  $[0, \tau_\epsilon]$ . We thus have  $\tau_\epsilon < \tau$  for any  $\epsilon \in (0, 1)$  a.s. so that, using Step 1, we have for any  $T > 0$

$$\mathbb{P}(\tau < T) \leq \mathbb{P}(\tau_\epsilon < T) \xrightarrow{\epsilon \rightarrow 0} 0.$$

Thus  $\tau = \infty$  a.s. which proves global existence and uniqueness for (6.1.3).

*Step 3.* Using that the functionals  $H$ ,  $I$  and  $M_1$  are lower semi-continuous and Proposition 6.3.101, we have

$$\begin{aligned} H(F_t^N) &\leq \liminf_{\epsilon} H(F_t^{N,\epsilon}) \leq C(1+t), \\ \int_0^t I(F_s^N) ds &\leq \liminf_{\epsilon} \int_0^t I(F_s^{N,\epsilon}) ds \leq C(1+t), \end{aligned} \quad (6.3.35)$$

and

$$M_1(F_t^N) \leq \liminf_{\epsilon} M_1(F_t^{N,\epsilon}) \leq C(1+t).$$

Using Fatou's lemma and (6.3.20), we get

$$\mathbb{E} \left[ \sup_{[0,T]} |X_t^{1,N}| \right] \leq \liminf_{\epsilon} \mathbb{E} \left[ \sup_{[0,T]} |X_t^{1,N,\epsilon}| \right] \leq C(1+T),$$

and (6.1.13) is proven. It remains to prove (6.1.14). Using again that the functionals  $H$  and  $I$  are lower semi-continuous and using (6.3.18), we get

$$\begin{aligned} H(F_t^N) + \int_0^t I(F_s^N) ds &\leq \liminf_{\epsilon} \left[ H(F_t^{N,\epsilon}) + \int_0^t I(F_s^{N,\epsilon}) ds \right] \\ &\leq H(F_0^N) + \liminf_{\epsilon} \frac{\chi}{N^2} \int_0^t \sum_{i \neq j} \mathbb{E}[\operatorname{div} K_{\epsilon}(X_s^{i,N,\epsilon} - X_s^{j,N,\epsilon})] ds. \end{aligned}$$

By exchangeability, it suffices to prove that, as  $\epsilon \rightarrow 0$ ,

$$D_{\epsilon} := \int_0^t \mathbb{E}[\operatorname{div} K_{\epsilon}(X_s^{1,N,\epsilon} - X_s^{2,N,\epsilon})] ds \rightarrow \int_0^t \mathbb{E}[\operatorname{div} K(X_s^{1,N} - X_s^{2,N})] ds =: D.$$

By Step 2, we have  $X_s^{i,N} = X_s^{i,N,\epsilon}$  for any  $i$  and  $s \leq \tau_{\epsilon}$  and thus recalling that  $K_{\epsilon}(x) = K(x)$  for any  $|x| \geq \epsilon$ , we get that a.s. for any  $s < \tau_{\epsilon}$

$$\operatorname{div} K_{\epsilon}(X_s^{1,N,\epsilon} - X_s^{2,N,\epsilon}) = \operatorname{div} K(X_s^{1,N,\epsilon} - X_s^{2,N,\epsilon}) = \operatorname{div} K(X_s^{1,N} - X_s^{2,N}).$$

So using that  $\operatorname{div} K(x) \leq 2|x|^{-\alpha-1}$  and  $\operatorname{div} K_{\epsilon}(x) \leq 2|x|^{-\alpha-1}$ , we get

$$|D - D_{\epsilon}| \leq C \int_0^t \mathbb{E} \left[ \mathbf{1}_{\{\tau_{\epsilon} < s\}} \left( \frac{1}{|X_s^{1,N,\epsilon} - X_s^{2,N,\epsilon}|^{\alpha+1}} + \frac{1}{|X_s^{1,N} - X_s^{2,N}|^{\alpha+1}} \right) \right] ds.$$

Let  $a \in \left(0, \frac{1-\alpha}{1+\alpha}\right)$  (in order to have  $(1+a)(\alpha+1) < 2$ ). Using first the Hölder inequality with  $p = 1+a$  and  $q$  such that  $1/p + 1/q = 1$ , and then Lemma 6.2.96 with  $\beta = 1$ , we get

$$\begin{aligned} |D - D_{\epsilon}| &\leq C \int_0^t \mathbb{P}(\tau_{\epsilon} < s)^{1/q} \mathbb{E} \left[ \left( \frac{1}{|X_s^{1,N,\epsilon} - X_s^{2,N,\epsilon}|^{(\alpha+1)(1+a)}} \right. \right. \\ &\quad \left. \left. + \frac{1}{|X_s^{1,N} - X_s^{2,N}|^{(\alpha+1)(1+a)}} \right) \right]^{1/p} ds \\ &\leq C \mathbb{P}(\tau_{\epsilon} < t)^{1/q} \int_0^t [1 + I(F_s^{N,\epsilon}) + I(F_s^N)] ds \\ &\leq C(1+t) \mathbb{P}(\tau_{\epsilon} < t)^{1/q}, \end{aligned}$$

by (6.3.19) and (6.3.35). This tends to 0 as  $\epsilon \rightarrow 0$  by Step 1 and concludes the proof.  $\square$

## 6.4 Convergence of the particle system

We start this section with a tightness result for the particle system (6.1.3).

**Lemma 6.4.102.** *Let  $\alpha \in (0, 1)$ . Assume (6.1.12). For each  $N \geq 2$ , let  $(X_t^{i,N})_{i=1,\dots,N}$  be the unique solution to (6.1.3) and  $Q^N := \frac{1}{N} \sum_{i=1}^N \delta_{(X_t^{i,N})_{t \geq 0}}$ .*

(i) *The family  $\{\mathcal{L}((X_t^{1,N})_{t \geq 0}), N \geq 2\}$  is tight in  $\mathbb{P}(C([0, \infty), \mathbb{R}^2))$ .*

(ii) *The family  $\{\mathcal{L}(Q^N), N \geq 2\}$  is tight in  $\mathbb{P}(\mathbb{P}(C([0, \infty), \mathbb{R}^2)))$ .*

**Proof.** Since the system is exchangeable, we deduce (ii) from (i) by [145, Proposition 2.2]. Let's prove (i). Let thus  $\eta > 0$  and  $T > 0$  be fixed. To prove the tightness of  $\{\mathcal{L}((X_t^{1,N})_{t \geq 0}), N \geq 2\}$  in  $\mathbb{P}(C([0, \infty), \mathbb{R}^2))$ , we have to find a compact subset  $\mathcal{K}_{\eta,T}$  of  $C([0, T], \mathbb{R}^2)$  such that  $\sup_N \mathbb{P}[(X_t^{1,N})_{t \in [0, T]} \notin \mathcal{K}_{\eta,T}] \leq \eta$ . We first set  $Z_T := \sup_{0 < s < t < T} \sqrt{2}|B_t^1 - B_s^1|/|t - s|^{1/3}$ . This random variable is a.s. finite since the paths of a Brownian motion are a.s. Hölder continuous with index  $1/3$ . We can also notice that the law of  $Z_T$  does not depend on  $N$ . Using the Hölder inequality with  $p = 3$  and  $q = 3/2$ , we get that for all  $0 < s < t < T$ ,

$$\begin{aligned} \left| \frac{\chi}{N} \sum_{j=2}^N \int_s^t K(X_u^{1,N} - X_u^{j,N}) du \right| &\leq \frac{\chi}{N} \sum_{j=2}^N \int_s^t \frac{du}{|X_u^{1,N} - X_u^{j,N}|^\alpha} \\ &\leq \frac{\chi}{N} (t-s)^{1/3} \sum_{j=2}^N \left( \int_0^T \frac{du}{|X_u^{1,N} - X_u^{j,N}|^{3\alpha/2}} \right)^{2/3} \\ &\leq (t-s)^{1/3} \left( \chi + \frac{\chi}{N} \sum_{j=2}^N \int_0^T \frac{du}{|X_u^{1,N} - X_u^{j,N}|^{3\alpha/2}} \right) \\ &=: (t-s)^{1/3} U_T^N. \end{aligned}$$

Using Lemma 6.2.96 with  $\gamma = 3\alpha/2$  and  $\beta = 1$ , the exchangeability of the system of particles, and denoting by  $F_{u_2}^N$  the two-marginal of  $F_u^N$ , we have

$$\begin{aligned} \mathbb{E}(U_T^N) &= \chi + \chi \frac{N-1}{N} \int_0^T \mathbb{E} \left( \frac{1}{|X_u^{1,N} - X_u^{2,N}|^{3\alpha/2}} \right) du \leq \chi + C \int_0^T (1 + I(F_{u_2}^N)) du \\ &\leq \chi + C \int_0^T (1 + I(F_u^N)) du \\ &\leq C(1+T), \end{aligned}$$

where we used that  $I(F_{t_2}^N) \leq I(F_t^N)$  by Lemma 6.2.97 and Theorem 6.1.93. We thus have  $\sup_{N \geq 2} \mathbb{E}(U_T^N) < \infty$ . Furthermore,  $Z_T$  is also a.s. finite so that we can find  $R > 0$  such that  $\mathbb{P}(Z_T + U_T^N > R) \leq \eta/2$  for all  $N \geq 2$ . Recalling (6.1.12), we can also find  $a > 0$  such that  $\sup_{N \geq 2} \mathbb{P}(X_0^{1,N} > a) \leq \eta/2$ . We now consider

$$\mathcal{K}_{\eta,T} := \{f \in C([0, T], \mathbb{R}^2), |f(0)| \leq a, |f(t) - f(s)| \leq R(t-s)^{1/3} \forall 0 < s < t < T\},$$

which is a compact subset of  $C([0, T], \mathbb{R}^2)$  by Ascoli's theorem. Observing that for all  $0 < s < t < T$ ,  $|X_t^{1,N} - X_s^{1,N}| \leq (Z_T + U_t^N)(t-s)^{1/3}$ , we get

$$\mathbb{P}[(X_t^{1,N})_{t \in [0, T]} \notin \mathcal{K}_{\eta,T}] \leq \mathbb{P}(|X_0^{1,N}| > a) + \mathbb{P}(Z_T + U_T^N > R) \leq \eta,$$

which concludes the proof.  $\square$

We define  $\mathcal{S}$  as the set of all probability measures  $f \in \mathbb{P}(C([0, \infty), \mathbb{R}^2))$  such that  $f$  is the law of  $(X_t)_{t \geq 0}$  solution to (6.1.4) satisfying (setting  $f_t = \mathcal{L}(X_t)$ )

$$\forall T > 0, \quad \int_0^T I(f_s) ds < \infty \quad \text{and} \quad \sup_{[0, T]} M_1(f_s) < \infty. \quad (6.4.36)$$

Observe that by Lemma 6.2.99, (6.4.36) implies (6.1.7). The condition  $p > \frac{2}{1-\alpha}$  in (6.1.7) is asked in order to use (6.5.37) with  $\gamma = -(\alpha + 1)$  (see the beginning of Section 5).

**Proposition 6.4.103.** *Let  $\alpha \in (0, 1)$  and assume (6.1.12). For each  $N \geq 2$ , let  $(X_0^{i, N})_{i=1, \dots, N}$  be  $F_0^N$ -distributed and consider the solution  $(X_t^{i, N})_{i=1, \dots, N, t \geq 0}$  to (6.1.3). Assume that there is a subsequence of  $\mathcal{Q}^N := \frac{1}{N} \sum_{i=1}^N \delta_{(X_t^{i, N})_{t \geq 0}}$  going in law to some  $\mathbb{P}(C([0, \infty), \mathbb{R}^2))$ -valued random variable  $\mathcal{Q}$ . Then  $\mathcal{Q}$  a.s. belongs to  $\mathcal{S}$ .*

**Proof.** We consider a (not relabelled) subsequence of  $\mathcal{Q}^N$  going in law to some  $\mathcal{Q}$  and we introduce the identity map  $\psi : C([0, \infty); \mathbb{R}^2) \rightarrow C([0, \infty); \mathbb{R}^2)$ . Using the arguments of [62, Proposition 6.1], we have to prove that  $\mathcal{Q}$  a.s. satisfies

- (a)  $\mathcal{Q} \circ (\psi(0))^{-1} = f_0$ ;
- (b) setting  $\mathcal{Q}_t = \mathcal{Q} \circ (\psi(t))^{-1}$ ,  $(\mathcal{Q}_t)_{t \geq 0}$  satisfies (6.4.36);
- (c) for all  $0 < t_0 < \dots < t_k < s < t$ ,  $\varphi_1, \dots, \varphi_k \in C_b(\mathbb{R}^2)$ ,  $\varphi \in C_b^2(\mathbb{R}^2)$ ,  $\mathcal{F}(\mathcal{Q}) = 0$  where, for  $f \in \mathbb{P}(C([0, \infty), \mathbb{R}^2))$ ,

$$\begin{aligned} \mathcal{F}(f) := & \iint f(d\gamma) f(d\tilde{\gamma}) \varphi_1(\gamma_{t_1}) \dots \varphi_k(\gamma_{t_k}) \\ & \left[ \varphi(\gamma_t) - \varphi(\gamma_s) + \chi \int_s^t \nabla_x \varphi(\gamma_u) \cdot K(\gamma_u - \tilde{\gamma}_u) du - \int_s^t \Delta_x \varphi(\gamma_u) du \right]. \end{aligned}$$

For simplicity, we split the proof in many steps.

*Step 1.* By assumption (6.1.12), we have that  $F_0^N$  is  $f_0$ -chaotic which implies that  $\mathcal{Q}_0^N = \mathcal{Q}^N \circ \psi(0)^{-1}$  goes weakly to  $f_0$  in law, and, since  $f_0$  is deterministic, also in probability. Hence  $\mathcal{Q}_0 = f_0$  a.s. and thus  $f \circ \psi(0)^{-1} = f_0$ . Thus  $\mathcal{Q}$  a.s. satisfies (a).

*Step 2.* Since  $\frac{1}{N} \sum_{i=1}^N \delta_{X_t^{i, N}}$  goes weakly to  $\mathcal{Q}_t$ , for all  $j \geq 1$ ,  $F_{t_j}^N$  goes weakly to  $\pi_{t_j}$ , where  $\pi_t := \mathcal{L}(\mathcal{Q}_t)$  and  $\pi_{t_j} := \int_{\mathbb{P}(\mathbb{R}^2)} f^{\otimes j} \pi_t(df)$ . We can thus apply [72, Theorem 5.7] (and then Fatou's Lemma) to get

$$\begin{aligned} \mathbb{E} \left[ \int_0^T I(\mathcal{Q}_s) ds \right] &= \int_0^T \mathbb{E}[I(\mathcal{Q}_s)] ds \leq \int_0^T \liminf_N I(F_s^N) ds \\ &\leq \liminf_N \int_0^T I(F_s^N) ds, \end{aligned}$$

which is finite by Theorem 6.1.93. We conclude that  $\int_0^T I(\mathcal{Q}_s) ds < \infty$  a.s. We also have, using Fatou's

lemma and the exchangeability of the particles,

$$\begin{aligned}\mathbb{E}\left[\sup_{[0,T]} M_1(\mathcal{Q}_t)\right] &\leq \mathbb{E}\left[\liminf_N \sup_{[0,T]} M_1(\mathcal{Q}_t^N)\right] \\ &\leq \liminf_N \mathbb{E}\left[\sup_{[0,T]} \frac{1}{N} \sum_{i=1}^N |X_t^{i,N}|\right] \\ &\leq \liminf_N \mathbb{E}\left[\sup_{[0,T]} |X_t^{1,N}|\right] \leq C(1+T),\end{aligned}$$

by (6.1.13), so that  $\sup_{[0,T]} M_1(\mathcal{Q}_t) < \infty$  a.s. Consequently,  $\mathcal{Q}$  a.s. satisfies (b).

*Step 3.1.* Using Itô's formula

$$\begin{aligned}O_t^i &:= \varphi(X_s^{i,N}) + \frac{\chi}{N} \sum_{j \neq i} \int_0^t \nabla_x \varphi(X_s^{i,N}) \cdot K(X_s^{i,N} - X_s^{j,N}) ds - \int_0^t \Delta_x \varphi(X_s^{i,N}) ds \\ &= \varphi(X_0^{i,N}) + \sqrt{2} \int_0^t \nabla_x \varphi(X_s^{i,N}) \cdot dB_s^i.\end{aligned}$$

But, using the last equality, we see that

$$\begin{aligned}\mathcal{F}(\mathcal{Q}^N) &= \frac{1}{N} \sum_{i=1}^N \varphi_1(X_{t_1}^{i,N}) \dots \varphi_k(X_{t_k}^{i,N}) [O_t^i - O_s^i] \\ &= \frac{\sqrt{2}}{N} \sum_{i=1}^N \varphi_1(X_{t_1}^{i,N}) \dots \varphi_k(X_{t_k}^{i,N}) \int_s^t \nabla_x \varphi(X_u^{i,N}) \cdot dB_u^i.\end{aligned}$$

From there, and thanks to the independence of the Brownian motions we conclude that (recall that the functions  $\varphi_1, \dots, \varphi_k, \nabla_x \varphi$  are bounded)

$$\mathbb{E}[(\mathcal{F}(\mathcal{Q}^N))^2] \leq \frac{C}{N}.$$

*Step 3.2.* We also introduce the regularized version of  $\mathcal{F}$ . For  $\varepsilon \in (0, 1)$ , we define  $\mathcal{F}_\varepsilon$  replacing  $K$  by  $K_\varepsilon$  defined by (6.3.16). Since  $f \mapsto \mathcal{F}_\varepsilon(f)$  is continuous and bounded from  $\mathbf{P}(C([0, \infty); \mathbb{R}^2))$  to  $\mathbb{R}$  and since  $\mathcal{Q}^N$  goes in law to  $\mathcal{Q}$ , we deduce that for any  $\varepsilon \in (0, 1)$ ,

$$\mathbb{E}[|\mathcal{F}_\varepsilon(\mathcal{Q})|] = \lim_N \mathbb{E}[|\mathcal{F}_\varepsilon(\mathcal{Q}^N)|].$$

*Step 3.3.* Using that all the functions and their derivatives involved in  $\mathcal{F}$  are bounded and that  $|K_\varepsilon(x) - K(x)| \leq |x|^{-\alpha} \mathbf{1}_{0 \leq |x| \leq \varepsilon}$ , we get

$$\begin{aligned}|\mathcal{F}(f) - \mathcal{F}_\varepsilon(f)| &\leq \chi C \iiint_0^t |\gamma(u) - \tilde{\gamma}(u)|^{-\alpha} \mathbf{1}_{0 < |\gamma(u) - \tilde{\gamma}(u)| < \varepsilon} du f(d\gamma) f(d\tilde{\gamma}) \\ &\leq C\varepsilon^{3/2-\alpha} \iiint_0^t |\gamma(u) - \tilde{\gamma}(u)|^{-3/2} \mathbf{1}_{\gamma(u) \neq \tilde{\gamma}(u)} du f(d\gamma) f(d\tilde{\gamma}).\end{aligned}$$

Thus,

$$|\mathcal{F}(\mathcal{Q}^N) - \mathcal{F}_\varepsilon(\mathcal{Q}^N)| \leq \frac{C\varepsilon^{3/2-\alpha}}{N^2} \sum_{i \neq j} \int_0^t |X_u^{i,N} - X_u^{j,N}|^{-3/2} du,$$

and by exchangeability

$$\mathbb{E}[|\mathcal{F}(\mathcal{Q}^N) - \mathcal{F}_\varepsilon(\mathcal{Q}^N)|] \leq C\varepsilon^{3/2-\alpha} \int_0^t \mathbb{E}[|X_u^{1,N} - X_u^{2,N}|^{-3/2}] du.$$



Using Lemma 6.2.96 with  $\gamma = 3/2$  and  $\beta = 1$  and denoting by  $F_{u2}^N$  the two-marginal of  $F_u^N$ , we have

$$\mathbb{E} [|\mathcal{F}(\mathcal{Q}^N) - \mathcal{F}_\varepsilon(\mathcal{Q}^N)|] \leq C\varepsilon^{3/2-\alpha} \int_0^t I(F_{u2}^N) du.$$

Using that  $I(F_{t2}^N) \leq I(F_t^N)$  by Lemma 6.2.97 and Theorem 6.1.93 we conclude that

$$\mathbb{E} [|\mathcal{F}(\mathcal{Q}^N) - \mathcal{F}_\varepsilon(\mathcal{Q}^N)|] \leq C\varepsilon^{3/2-\alpha}.$$

*Step 3.4.* Now we see that

$$|\mathcal{F}(\mathcal{Q}) - \mathcal{F}_\varepsilon(\mathcal{Q})| \leq C\varepsilon^{3/2-\alpha} \int_0^t \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} |x-y|^{-3/2} \mathcal{Q}_s(dx) \mathcal{Q}_s(dy) ds.$$

Step 2 says that (6.4.36) holds true for  $\mathcal{Q}_s$ , then thanks to Lemma 6.2.99 we get that a.s.,  $\nabla_x \mathcal{Q}_s \in L^{2q/(3q-2)}(0, T; L^q(\mathbb{R}^2))$  for all  $q \in [1, 2)$ . Then using [62, Lemma 3.5] for  $\gamma = 3/2$  we deduce that a.s.

$$\lim_{\varepsilon \rightarrow 0} |\mathcal{F}(\mathcal{Q}) - \mathcal{F}_\varepsilon(\mathcal{Q})| = 0.$$

*Step 3.5.* Using Steps 3.1, 3.2 and 3.3, we finally observe, using the same arguments as in [62, Proposition 6.1, Step 4.5], that

$$\mathbb{E}[|\mathcal{F}(\mathcal{Q})| \wedge 1] \leq C\varepsilon^{3/2-\alpha} + \mathbb{E}[|\mathcal{F}(\mathcal{Q}) - \mathcal{F}_\varepsilon(\mathcal{Q})| \wedge 1],$$

so that  $\mathcal{F}(\mathcal{Q}) = 0$  a.s. by Step 3.4 thanks to dominated convergence and  $\mathcal{Q}$  a.s. satisfies (c) which concludes the proof.  $\square$

## 6.5 Well-posedness and propagation of chaos ---

We start this section with the proof of existence and uniqueness for the nonlinear S.D.E. (6.1.4). We will use that for  $\gamma \in (-2, 0)$ , for  $p \in (2/(2+\gamma), \infty]$  and for any  $h \in \mathbb{P}(\mathbb{R}^2) \cap L^p(\mathbb{R}^2)$ ,

$$\begin{aligned} \sup_{v \in \mathbb{R}^2} \int_{\mathbb{R}^2} h(v_*) |v - v_*|^\gamma dv_* &\leq \sup_{v \in \mathbb{R}^2} \int_{|v_* - v| < 1} h(v_*) |v - v_*|^\gamma dv_* \\ &\quad + \sup_{v \in \mathbb{R}^2} \int_{|v_* - v| \geq 1} h(v_*) dv_* \\ &\leq C_{\gamma, p} \|h\|_{L^p(\mathbb{R}^2)} + 1, \end{aligned} \tag{6.5.37}$$

where

$$C_{\gamma, p} = \left[ \int_{|v_*| \leq 1} |v_*|^{\gamma p / (p-1)} dv_* \right]^{(p-1)/p} < \infty,$$

since by assumption  $\gamma p / (p-1) > -2$ .

**Proof of Theorem 6.1.94.** The existence in law follows from Proposition 6.4.103 and Lemma 6.4.102 (see the comment after (6.4.36)). We now prove pathwise uniqueness which will also imply the strong existence. To this aim, we consider  $(X_t)_{t \geq 0}$  and  $(Y_t)_{t \geq 0}$  two solutions of (6.1.4) driven by the same Brownian motion and with same initial condition such that, setting  $f_s := \mathcal{L}(X_s)$  and  $g_s := \mathcal{L}(Y_s)$ ,

$(f_t)_{t \geq 0}$  and  $(g_t)_{t \geq 0}$  are in  $L_{loc}^\infty([0, \infty), \mathbb{P}_1(\mathbb{R}^2)) \cap L_{loc}^1([0, \infty); L^p(\mathbb{R}^2))$  for some  $p > \frac{2}{1-\alpha}$ . For any  $s > 0$ , we consider the probability measure  $R_s$  on  $\mathbb{R}^2 \times \mathbb{R}^2$  with first (respectively second) marginal equal to  $f_s$  (resp.  $g_s$ ) such that

$$\mathcal{W}_1(f_s, g_s) = \int_{\mathbb{R}^2 \times \mathbb{R}^2} |x - y| R_s(dx, dy).$$

We have

$$\begin{aligned} X_t - Y_t &= -\chi \left( \int_0^t \int_{\mathbb{R}^2} K(X_s - x) f_s(dx) ds - \int_0^t \int_{\mathbb{R}^2} K(Y_s - y) g_s(dy) ds \right) \\ &= -\chi \int_0^t \int_{\mathbb{R}^2 \times \mathbb{R}^2} [K(X_s - x) - K(Y_s - y)] R_s(dx, dy). \end{aligned}$$

Using Lemma 6.2.100 and recalling that  $\mathcal{L}(X_t) = f_t$ ,  $\mathcal{L}(Y_t) = g_t$ , and that  $R_t$  has marginals  $f_t$  and  $g_t$ , this gives

$$\begin{aligned} \mathbb{E}[\sup_{[0, T]} |X_t - Y_t|] &\leq C_\alpha \chi \int_0^T \int_{\mathbb{R}^2 \times \mathbb{R}^2} \mathbb{E} \left[ (|X_s - Y_s| + |x - y|) \left( \frac{1}{|X_s - x|^{\alpha+1}} \right. \right. \\ &\quad \left. \left. + \frac{1}{|Y_s - y|^{\alpha+1}} \right) \right] R_s(dx, dy) ds \\ &\leq C_\alpha \chi \int_0^T \mathbb{E} \left[ |X_s - Y_s| \left( \int_{\mathbb{R}^2} \frac{1}{|X_s - x|^{\alpha+1}} f_s(dx) \right. \right. \\ &\quad \left. \left. + \int_{\mathbb{R}^2} \frac{1}{|Y_s - y|^{\alpha+1}} g_s(dy) \right) \right] ds \\ &\quad + C_\alpha \chi \int_0^T \int_{\mathbb{R}^2 \times \mathbb{R}^2} |x - y| \mathbb{E} \left[ \frac{1}{|X_s - x|^{\alpha+1}} \right. \\ &\quad \left. + \frac{1}{|Y_s - y|^{\alpha+1}} \right] R_s(dx, dy) ds. \end{aligned}$$

Using (6.5.37), we thus have, since  $\int_{\mathbb{R}^2 \times \mathbb{R}^2} |x - y| R_s(dx, dy) = \mathcal{W}_1(f_s, g_s) \leq \mathbb{E}[|X_s - Y_s|]$  by definition of  $\mathcal{W}_1$ ,

$$\begin{aligned} \mathbb{E}[\sup_{[0, T]} |X_t - Y_t|] &\leq C \int_0^T \mathbb{E}[|X_s - Y_s|] (1 + \|f_s\|_{L^p} + \|g_s\|_{L^p}) ds \\ &\quad + C \int_0^T \int_{\mathbb{R}^2 \times \mathbb{R}^2} |x - y| (1 + \|f_s\|_{L^p} + \|g_s\|_{L^p}) R_s(dx, dy) ds \\ &\leq C \int_0^T \mathbb{E}[|X_s - Y_s|] (1 + \|f_s\|_{L^p} + \|g_s\|_{L^p}) ds. \end{aligned}$$

By Grönwall's Lemma, we thus get  $\mathbb{E}(\sup_{[0, T]} |X_t - Y_t|) = 0$  and pathwise uniqueness is proven.  $\square$

The following lemma is useful for the uniqueness of (6.1.1).

**Lemma 6.5.104.** *Let  $p > 2/(1-\alpha)$  and consider a weak solution  $(f_t)_{t \geq 0}$  to (6.1.1) lying in  $L_{loc}^\infty([0, \infty), \mathbb{P}_1(\mathbb{R}^2)) \cap L_{loc}^1([0, \infty); L^p(\mathbb{R}^2))$ . Assume that for some  $h = (h_t)_{t \geq 0}$  lying in  $L_{loc}^\infty([0, \infty), \mathbb{P}_1(\mathbb{R}^2)) \cap L_{loc}^1([0, \infty); L^p(\mathbb{R}^2))$ , for all  $\varphi \in C_c^2(\mathbb{R}^2)$ , all  $t \geq 0$ ,*

$$\begin{aligned} \int_{\mathbb{R}^2} \varphi(x) h_t(dx) &= \int_{\mathbb{R}^2} \varphi(x) f_0(dx) + \int_0^t \int_{\mathbb{R}^2} \Delta_x \varphi(x) h_s(dx) ds \\ &\quad - \chi \int_0^t \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} K(x - y) \cdot \nabla_x \varphi(x) f_s(dy) h_s(dx) ds. \end{aligned} \tag{6.5.38}$$

Then  $h = f$ .

**Proof.** For any  $\varphi \in C_c^2(\mathbb{R}^2)$  and any  $t \geq 0$ , we set

$$\mathcal{A}_t \varphi(x) = \Delta_x \varphi(x) - \chi \int_{\mathbb{R}^2} K(x-y) \cdot \nabla_x \varphi(x) f_t(dy).$$

We will prove that for any  $\mu \in \mathbb{P}_1(\mathbb{R}^2)$ , there exists at most one  $h$  lying in  $L_{loc}^\infty([0, \infty), \mathbb{P}_1(\mathbb{R}^2)) \cap L_{loc}^1([0, \infty); L^p(\mathbb{R}^2))$  such that for all  $t \geq 0$ ,  $\varphi \in C_c^2(\mathbb{R}^2)$ ,

$$\int_{\mathbb{R}^2} \varphi(x) h_t(dx) = \int_{\mathbb{R}^2} \varphi(x) \mu(dx) + \int_0^t \int_{\mathbb{R}^2} \mathcal{A}_s \varphi(x) h_s(dx) ds. \quad (6.5.39)$$

This will conclude the proof since  $f$  and  $h$  solve this equation with  $\mu = f_0$  by assumption.

*Step 1.* Let  $\mu \in \mathbb{P}_1(\mathbb{R}^2)$ . A continuous adapted  $\mathbb{R}^2$ -valued process  $(X_t)_{t \geq 0}$  on some filtered probability space  $(\Omega, \mathcal{F}, (\mathcal{F}_t)_{t \geq 0}, P)$  is said to solve the martingale problem  $MP((\mathcal{A}_t)_{t \geq 0}, \mu)$  if  $P \circ X_0^{-1} = \mu$  and if for all  $\varphi \in C_c^2(\mathbb{R}^2)$ ,  $(M_t^\varphi)_{t \geq 0}$  is a  $(\Omega, \mathcal{F}, (\mathcal{F}_t)_{t \geq 0}, P)$ -martingale, where

$$M_t^\varphi = \varphi(X_t) - \int_0^t \mathcal{A}_s \varphi(X_s) ds.$$

Using Bhatt-Karandikar [18, Theorem 5.2] (see also Remark 3.1 in [18]), uniqueness for (6.5.39) holds if

- (i) there exists a countable subset  $(\varphi_k)_{k \geq 1} \subset C_c^2$  such that for all  $t \geq 0$ , the closure (for the bounded pointwise convergence) of  $\{(\varphi_k, \mathcal{A}_t \varphi_k), k \geq 1\}$  contains  $\{(\varphi, \mathcal{A}_t \varphi), \varphi \in C_c^2\}$ ,
- (ii) for each  $x_0 \in \mathbb{R}^2$ , there exists a solution to  $MP((\mathcal{A}_t)_{t \geq 0}, \delta_{x_0})$ ,
- (iii) for each  $x_0 \in \mathbb{R}^2$ , uniqueness (in law) holds for  $MP((\mathcal{A}_t)_{t \geq 0}, \delta_{x_0})$ .

*Step 2.* We first prove (i). Consider thus some countable  $(\varphi_k)_{k \geq 1} \subset C_c^2$  dense in  $C_c^2$ , in the sense that for  $\psi \in C_c^2$ , there exists a subsequence  $\varphi_{k_n}$  such that  $\lim_{n \rightarrow \infty} (\|\psi - \varphi_{k_n}\|_\infty + \|\psi' - \varphi'_{k_n}\|_\infty + \|\psi'' - \varphi''_{k_n}\|_\infty) = 0$ . We then have to prove that, for  $t \geq 0$ ,

- (a)  $\mathcal{A}_t \varphi_{k_n}(x)$  tends to  $\mathcal{A}_t \psi(x)$  for all  $x \in \mathbb{R}^2$ ,
- (b)  $\sup_n \|\mathcal{A}_t \varphi_{k_n}\|_\infty < \infty$ .

Let  $x \in \mathbb{R}^2$ . Using that  $|K(x)| = \frac{1}{|x|^\alpha}$ , we have

$$|\mathcal{A}_t \varphi_{k_n}(x) - \mathcal{A}_t \psi(x)| \leq \|\psi'' - \varphi''_{k_n}\|_\infty + \chi \|\psi' - \varphi'_{k_n}\|_\infty \int_{\mathbb{R}^2} \frac{1}{|x-y|^\alpha} f_t(dy) \rightarrow 0,$$

since  $\int_{\mathbb{R}^2} \frac{1}{|x-y|^\alpha} f_t(dy) \leq C(1 + \|f_t\|_{L^p})$  by (6.5.37). For (b), we can observe that setting  $A := \sup_n (\|\varphi_{k_n}\|_\infty + \|\varphi'_{k_n}\|_\infty + \|\varphi''_{k_n}\|_\infty)$

$$|\mathcal{A}_t \varphi_{k_n}| \leq A + \chi A \int_{\mathbb{R}^2} \frac{1}{|x-y|^\alpha} f_t(dy) \leq A + CA(1 + \|f_t\|_{L^p}),$$

which concludes this step.

*Step 3.* Using classical arguments, we observe that a process  $(X_t)_{t \geq 0}$  is a solution to  $MP((\mathcal{A}_t)_{t \geq 0}, \delta_{x_0})$  if and only if there exists, on a possibly enlarged probability space, a  $(\mathcal{F}_t)_{t \geq 0}$ -Brownian motion  $(B_t)_{t \geq 0}$  such that

$$X_t = x_0 - \chi \int_0^t \int_{\mathbb{R}^2} K(X_s - x) f_s(dx) ds + \sqrt{2} B_t. \quad (6.5.40)$$

It thus suffices to prove existence and uniqueness in law for solutions to (6.5.40) to get (ii) and (iii).

*Step 4.* The proof of (pathwise) uniqueness for (6.5.40) is very similar with the proof of uniqueness for (6.1.4) which has already been done and we leave it to the reader.

*Step 5.* It remains to check (ii) to conclude. We thus have to prove the existence of a solution to (6.5.40). To this aim, we use a Picard iteration. We thus consider the constant process  $X_t^0 = x_0$  and define recursively

$$X_t^{n+1} = x_0 - \chi \int_0^t \int_{\mathbb{R}^2} K(X_s^n - x) f_s(dx) ds + \sqrt{2} B_t.$$

Using the same kind of arguments as in the proof of Theorem 6.1.94, we get

$$\mathbb{E}(\sup_{[0,T]} |X_t^{n+1} - X_t^n|) \leq C \int_0^T \mathbb{E}[|X_s^n - X_s^{n-1}|] (1 + \|f_s\|_{L^p}) ds.$$

Since  $\int_0^T (1 + \|f_s\|_{L^p}) ds < \infty$ , we classically deduce that  $\sum_n \mathbb{E}(\sup_{[0,T]} |X_t^{n+1} - X_t^n|) < \infty$ , so that there is a continuous adapted process  $(X_t)_{t \geq 0}$  such that for all  $T > 0$ ,  $\lim_n \mathbb{E}[\sup_{[0,T]} |X_t - X_t^n|] = 0$ . This  $L^1$  convergence implies that  $(X_t)_{t \geq 0}$  is solution to (6.5.40), which concludes the proof.  $\square$

The following result ensures that uniqueness holds for (6.1.1).

**Theorem 6.5.105.** *Let  $f_0$  and  $g_0$  be two probability measures with finite first moment. Let  $(f_t)_{t \geq 0}$  and  $(g_t)_{t \geq 0}$  be two solutions to (6.1.1) lying in  $L_{loc}^\infty([0, \infty), \mathbb{P}_1(\mathbb{R}^2)) \cap L_{loc}^1([0, \infty); L^p(\mathbb{R}^2))$  for some  $p > 2/(1 - \alpha)$  starting from  $f_0$  and  $g_0$  respectively. Then*

$$\mathcal{W}_1(f_t, g_t) \leq \mathcal{W}_1(f_0, g_0) \exp\left(C \int_0^t (1 + \|f_s\|_{L^p} + \|g_s\|_{L^p}) ds\right).$$

**Proof.** Let thus  $p > 2/(1 - \alpha)$ ,  $(f_t)_{t \geq 0}$  and  $(g_t)_{t \geq 0}$  be two solutions to (6.1.1) lying in  $L_{loc}^\infty([0, \infty), \mathbb{P}_1(\mathbb{R}^2)) \cap L_{loc}^1([0, \infty); L^p(\mathbb{R}^2))$ . For any  $s \geq 0$ , we consider the probability measure  $R_s$  on  $\mathbb{R}^2 \times \mathbb{R}^2$  with first (respectively second) marginal equal to  $f_s$  (resp.  $g_s$ ) such that

$$\mathcal{W}_1(f_s, g_s) = \int_{\mathbb{R}^2 \times \mathbb{R}^2} |x - y| R_s(dx, dy),$$

and we consider  $(X_0, Y_0)$  with law  $R_0$ . We finally set

$$\begin{aligned} X_t &= X_0 - \chi \int_0^t \int_{\mathbb{R}^2} K(X_s - x) f_s(dx) ds + \sqrt{2} B_t, \\ Y_t &= Y_0 - \chi \int_0^t \int_{\mathbb{R}^2} K(Y_s - x) g_s(dx) ds + \sqrt{2} B_t. \end{aligned}$$

Using Itô's formula, we see that  $h$  defined by  $h_t := \mathcal{L}(X_t)$  satisfies (6.5.38) and Lemma 6.5.104 ensures us that  $\mathcal{L}(X_t) = f_t$ . Similarly, we also have  $\mathcal{L}(Y_t) = g_t$ . Using the same arguments as in the proof of Theorem 6.1.94, we easily get

$$\mathbb{E}(|X_t - Y_t|) \leq \mathbb{E}[|X_0 - Y_0|] + C \int_0^t \mathbb{E}[|X_s - Y_s|] (1 + \|f_s\|_{L^p} + \|g_s\|_{L^p}) ds.$$

Using the Grönwall's Lemma and recalling that  $\mathbb{E}[|X_0 - Y_0|] = \mathcal{W}_1(f_0, g_0)$ , we get

$$\mathbb{E}(|X_t - Y_t|) \leq \mathcal{W}_1(f_0, g_0) \exp\left(C \int_0^t (1 + \|f_s\|_{L^p} + \|g_s\|_{L^p}) ds\right),$$

which concludes the proof since  $\mathcal{W}_1(f_t, g_t) \leq \mathbb{E}(|X_t - Y_t|)$ .  $\square$

We can now give the proof of our well-posedness result for (6.1.1).

**Proof of Theorem 6.1.92 (i).** The existence follows by Theorem 6.1.94. Indeed consider  $(X_t)_{t \geq 0}$  the unique solution of (6.1.4) with initial law  $f_0$  and set for  $t \geq 0$   $f_t := \mathcal{L}(X_t)$ . Thanks to the Remark 6.1.89,  $f_t$  is a weak solution to (6.1.1) in the sense given by Definition 6.1.88 and (6.1.15) is exactly (6.1.7).

For uniqueness, consider two weak solutions  $(f_t)_{t \geq 0}$  and  $(g_t)_{t \geq 0}$  of (6.1.1) satisfying (6.1.7) with the same initial condition  $f_0 \in \mathbb{P}_1(\mathbb{R}^2)$ . Then Theorem 6.5.105 ensures that  $\mathcal{W}_1(f_t, g_t) = 0$  for any  $t \geq 0$  which concludes the proof.  $\square$

We end this section with the proof of our propagation of chaos result.

**Proof of Theorem 6.1.95 (i).** We consider  $Q^N := \frac{1}{N} \sum_{i=1}^N \delta_{(X_t^{i,N})_{t \geq 0}}$ . By Lemma 6.4.102, the family  $\{\mathcal{L}(Q^N), N \geq 2\}$  is tight in  $\mathbb{P}(\mathbb{P}(C([0, \infty), \mathbb{R}^2)))$ . Furthermore, by proposition 6.4.103, any limit point of  $Q^N$  belongs a.s. to the set of all probability measures  $f \in \mathbb{P}(C([0, \infty), \mathbb{R}^2))$  such that  $f$  is the law of a solution to (6.1.4) satisfying (6.1.9). But by Theorem 6.1.94, this set is reduced to  $\mathcal{L}((X_t)_{t \geq 0}) =: f$ . We thus deduce that  $Q^N$  goes in law to  $f$  as  $N \rightarrow \infty$  which concludes the proof of (i).

## 6.6 Renormalization and entropic chaos

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In this section, we first deal with the renormalization which will give us the dissipation of entropy for the solution to (6.1.1). From this, we will be able to show the entropic chaos for the system (6.1.3), which will conclude this paper.

**Proof of Theorem 6.1.92 (ii).** We adapt the ideas used in [62] for the 2D vortex model to our case, which in particular has a non divergence free kernel. We split the proof in four steps plus a Step 0 which is nothing but direct results of what we have already done. We consider the unique weak solution  $f = (f_t)_{t \geq 0}$  of (6.1.1). In step 1 we deal with the necessary estimates on  $K * f$  and  $\nabla \cdot (K * f)$  to regularize  $f$ . In step 2 we show the convergence of a regular version of  $f$  towards  $f$ . In step 3, we improve the regularity of the solution using a well-known bootstrap argument. Finally, in step 4 we prove the renormalization property.

We first observe that by construction,  $f$  satisfies (6.1.8). Indeed, for any  $t \geq 0$ , we considered  $f_t$  as the law of  $X_t$ , where  $(X_t)_{t \geq 0}$  is the unique solution to (6.1.4), obtained by Proposition 6.4.103 and Lemma 6.4.102, so that (6.4.36) (which englobes (6.1.8)) is satisfied.

*Step 0. Direct Estimates.* We start by noticing that Lemma 6.2.99 and (6.1.8) implies directly (6.1.9)

and also that for any  $p \in [1, \infty)$  and all  $T > 0$ ,

$$f \in L^{p/(p-1)}(0, T; L^p(\mathbb{R}^2)). \quad (6.6.41)$$

*Step 1. First Estimates.* The aim of this step is to prove that for any  $q > 2/\alpha$  and all  $T > 0$ :

$$(K * f) \in L^{2q/(\alpha q - 2)}(0, T; L^q(\mathbb{R}^2)), \quad (6.6.42)$$

and

$$\nabla_x \cdot (K * f) = K * (\nabla_x \cdot f) \in L^{2q/(q(1+\alpha) - 2)}(0, T; L^q(\mathbb{R}^2)). \quad (6.6.43)$$

Let us remember the Hardy-Littlewood-Sobolev inequality in 2D: for  $1 \leq p < 2/(2 - \alpha)$ ,

$$\left\| \int_{\mathbb{R}^2} \frac{f(y)}{|\cdot - y|^{2 - (2 - \alpha)}} dy \right\|_{2p/(2 - (2 - \alpha)p)} \leq C_{\alpha, p} \|f\|_p.$$

Using (6.6.41) we get that for any  $p \in (1, 2/(2 - \alpha))$  and all  $T > 0$ ,

$$(K * f) \in L^{p/(p-1)}(0, T; L^{2p/(2 - (2 - \alpha)p)}(\mathbb{R}^2)),$$

and under the change of variables  $q = 2p/(2 - (2 - \alpha)p)$  we easily deduce (6.6.42).

Similarly, but using (6.1.9) instead of (6.6.41), we get that for any  $p \in (1, 2/(2 - \alpha))$  and all  $T > 0$ ,

$$\nabla_x \cdot (K * f) \in L^{2p/(3p-2)}(0, T; L^{2p/(2 - (2 - \alpha)p)}(\mathbb{R}^2)),$$

applying the same change of variables  $q = 2p/(2 - (2 - \alpha)p)$  we get (6.6.43).

*Step 2. Continuity.* Consider  $T > 0$  fixed. For  $q > 2/\alpha$  we have that  $2q/(q(1+\alpha) - 2) > q/(q-1)$ , then using (6.6.41) with  $p_* = q/(q-1) > 1$ , and (6.6.43), we get that  $f \nabla_x \cdot (K * f)$  belongs to  $L^1(0, T; L^1(\mathbb{R}^2))$ .

The following lemma follows directly:

**Lemma 6.6.106.** *Consider a mollifier sequence  $(\rho_n)$  on  $\mathbb{R}^2$  and introduce the mollified function  $f_t^n := f_t * \rho_n$ . Clearly,  $f_t^n \in C([0, \infty), L^1(\mathbb{R}^2))$ . For all  $T > 0$ , there exists  $r^n \in L^1(0, T; L^1_{loc}(\mathbb{R}^2))$  that goes to 0 when  $n \rightarrow \infty$ , and such that*

$$\partial_t f^n - \chi \nabla_x \cdot ((K * f) f^n) - \Delta_x f^n = r^n. \quad (6.6.44)$$

**Remark 6.6.107.** *The proof of the previous lemma is a modification of [47, Lemma II.1.(ii) and Remark 4]. In fact, for all  $T > 0$ ,  $f \in L^\infty(0, T; L^1(\mathbb{R}^2))$  and for any  $q > 2/\alpha$ ,  $(K * f) \in L^1(0, T; L^q(\mathbb{R}^2))$ . That suffices for the existence of  $r^n$  given by*

$$r^n := \chi[(\nabla \cdot ((K * f) f)) * \rho^n - \nabla \cdot ((K * f) f^n)],$$

*which goes to 0 if  $n \rightarrow \infty$  in  $L^1(0, T; L^1_{loc}(\mathbb{R}^2))$ .*

As a consequence of Lemma 6.6.106, the chain rule applied to the smooth  $f^n$  reads

$$\begin{aligned} \partial_t \beta(f^n) = & \chi [(K * f) \cdot \nabla_x \beta(f^n) + \beta'(f^n) f^n \nabla_x \cdot (K * f)] \\ & + \Delta_x \beta(f^n) - \beta''(f^n) |\nabla_x f^n|^2 + \beta'(f^n) r^n, \end{aligned} \quad (6.6.45)$$

for any  $\beta \in C^1(\mathbb{R}) \cap W_{loc}^{2,\infty}(\mathbb{R})$  such that  $\beta''$  is piecewise continuous and vanishes outside of a compact set. Since the equation (6.6.44) with  $(K * f)$  fixed is linear in  $f^n$ , the difference  $f^{n,k} := f^n - f^k$  satisfies (6.6.44) with  $r^n$  replaced by  $r^{n,k} := r^n - r^k \rightarrow 0$  in  $L^1(0, T; L_{loc}^1(\mathbb{R}^2))$  and then also (6.6.45) (with again  $f^n$  and  $r^n$  changed in  $f^{n,k}$  and  $r^{n,k}$ ). Observe that the term  $\beta'(f^n) f^n \nabla_x \cdot (K * f)$  comes from the fact that the kernel is not divergence-free (it is equal to 0 in [62]).

Now, choosing  $\beta(s) = \beta_1(s)$  where  $\beta_1(s) = s^2/2$  for  $|s| \leq 1$  and  $\beta_1(s) = |s| - 1/2$  for  $|s| \geq 1$ . It is clear that  $\beta \in C^1(\mathbb{R})$ , that  $\beta', \beta'' \in L^\infty(\mathbb{R})$  and that the second derivative has compact support. For any nonnegative  $\psi \in C_c^2(\mathbb{R}^2)$ , we obtain

$$\begin{aligned} & \frac{d}{dt} \int_{\mathbb{R}^2} \beta_1(f^{n,k}(t, x)) \psi(x) dx \\ &= \int_{\mathbb{R}^2} \chi [(K * f) \cdot \nabla_x \beta_1(f^{n,k}) + \beta_1'(f^{n,k}) f^{n,k} \nabla_x \cdot (K * f)] \psi(x) dx \\ &+ \int_{\mathbb{R}^2} [\Delta_x \beta_1(f^{n,k}) - \beta_1''(f^{n,k}) |\nabla_x f^{n,k}|^2 + \beta_1'(f^{n,k}) r^{n,k}] \psi(x) dx \\ &\leq \int_{\mathbb{R}^2} |r^{n,k}(t, x)| \psi(x) dx + \int_{\mathbb{R}^2} \beta_1(f^{n,k}) \Delta_x \psi dx \\ &+ \chi \int_{\mathbb{R}^2} |f^{n,k} \nabla_x \cdot (K * f)| \psi(x) dx - \chi \int_{\mathbb{R}^2} \beta_1(f^{n,k}) \nabla_x \cdot ((K * f) \psi(x)) dx, \end{aligned}$$

where we have used that  $|\beta_1'| \leq 1$  and that  $\beta_1'' \geq 0$ . We know that  $f_0 \in L^1(\mathbb{R}^2)$  then  $f^{n,k}(0) \rightarrow 0$  in  $L^1(\mathbb{R}^2)$ , also that  $r^{n,k} \rightarrow 0$  in  $L^1(0, T; L_{loc}^1(\mathbb{R}^2))$ . It is not difficult to see that  $\beta_1(f^{n,k})(K * f) \rightarrow 0$  in  $L^1(0, T; L_{loc}^1(\mathbb{R}^2))$ , (because  $\beta_1$  is sub-linear, and for all  $0 < \alpha < 1$  there is  $q := p/(p-1) > 2/\alpha$ , then using (6.6.41) and (6.6.42):  $f^{n,k} \rightarrow 0$  in  $L^{p/(p-1)}(0, T; L^p(\mathbb{R}^2))$ , and  $(K * f) \in L^{q/(q-1)}(0, T; L^q(\mathbb{R}^2))$ ).

The same arguments apply to  $\beta_1(f^{n,k}) \nabla_x \cdot (K * f)$  and  $|f^{n,k} \nabla_x \cdot (K * f)|$ , and then both goes to 0 as  $n, k \rightarrow \infty$  in  $L^1(0, T; L_{loc}^1(\mathbb{R}^2))$ . Finally, we get

$$\sup_{t \in [0, T]} \int_{\mathbb{R}^2} \beta_1(f^{n,k}(t, x)) \psi(x) dx \xrightarrow{n, k \rightarrow \infty} 0.$$

Since  $\psi$  is arbitrary, we deduce that there exists  $\bar{f} \in C([0, \infty); L_{loc}^1(\mathbb{R}^2))$  so that  $f^n \rightarrow \bar{f}$  in  $C([0, \infty); L_{loc}^1(\mathbb{R}^2))$  with the topology of the uniform convergence on any compact subset in time. Together with the convergence  $f^n \rightarrow f$  in  $C([0, \infty); \mathbf{P}(\mathbb{R}^2))$  we get that  $f = \bar{f}$ . We end this Step by concluding that, with the same convention for the notion of convergence on  $[0, \infty)$ :  $f^n \rightarrow f$  in  $C([0, \infty); L^1(\mathbb{R}^2))$ .

*Step 3. Additional estimates.* From (6.6.45), we know that for all  $0 < t_0 < t_1$ , all  $\psi \in C_c^2(\mathbb{R}^2)$ ,

$$\begin{aligned}
& \int_{\mathbb{R}^2} \beta(f_{t_1}^n) \psi(x) dx + \int_{t_0}^{t_1} \int_{\mathbb{R}^2} \beta''(f_s^n) |\nabla_x f_s^n|^2 \psi(x) dx ds \\
&= \int_{\mathbb{R}^2} \beta(f_{t_0}^n) \psi(x) dx + \int_{t_0}^{t_1} \int_{\mathbb{R}^2} \beta'(f_s^n) r^n \psi(x) dx ds \\
&+ \int_{t_0}^{t_1} \int_{\mathbb{R}^2} \beta(f_s^n) [\Delta_x \psi(x) - \chi(K * f) \nabla_x \psi(x)] dx ds \\
&+ \chi \int_{t_0}^{t_1} \int_{\mathbb{R}^2} [\beta'(f_s^n) f_s^n - \beta(f_s^n)] \psi(x) \nabla_x \cdot (K * f) dx ds.
\end{aligned} \tag{6.6.46}$$

The last term appears because the kernel is not divergence-free. Due to it, we have to be careful with the choice of the functions  $\beta$  admissible (in order to have the last term bounded). Let us choose  $0 \leq \psi \in C_c^2(\mathbb{R}^2)$  and  $\beta \in C^1(\mathbb{R}) \cap W_{loc}^{2,\infty}(\mathbb{R})$  convex such that  $\beta''$  is nonnegative and vanishes outside of a compact set (notice that, there is a constant  $C > 0$  such that  $s\beta'(s) \leq C\beta(s)$ ). We can pass to the limit as  $n \rightarrow \infty$  (for details see step 2) to get

$$\begin{aligned}
\int_{\mathbb{R}^2} \beta(f_{t_1}) \psi(x) dx &\leq \int_{\mathbb{R}^2} \beta(f_{t_0}) \psi(x) dx \\
&+ \int_{t_0}^{t_1} \int_{\mathbb{R}^2} \beta(f_s) [\Delta_x \psi(x) - \chi(K * f) \nabla_x \psi(x)] dx ds \\
&+ \chi \int_{t_0}^{t_1} \int_{\mathbb{R}^2} [-\beta(f_s) + \beta'(f_s) f_s] \psi(x) \nabla_x \cdot (K * f) dx ds.
\end{aligned}$$

It is not hard to deduce, by approximating  $\psi \equiv 1$  by a well-chosen sequence  $\psi_R$  that

$$\int_{\mathbb{R}^2} \beta(f_{t_1}) dx \leq \int_{\mathbb{R}^2} \beta(f_{t_0}) dx + \chi \int_{t_0}^{t_1} \int_{\mathbb{R}^2} [-\beta(f_s) + \beta'(f_s) f_s] \nabla_x \cdot (K * f) dx ds.$$

whenever  $\beta$  is admissible.

Now we deal with the regularity in space of (6.1.10). Let us start by noticing that

$$\nabla_x (K * f)(x) = \int_{\mathbb{R}^2} \frac{(1-\alpha)f(y)}{|x-y|^{1+\alpha}} dy, \tag{6.6.47}$$

so that taking  $p > 2/(1-\alpha)$  and using (6.5.37),

$$\int_0^T \|\nabla_x (K * f_s)\|_{L^\infty(\mathbb{R}^2)} \leq C(\alpha, p) \int_0^T (\|f_s\|_{L^p(\mathbb{R}^2)} + 1) < \infty,$$

and due to the fact that  $s\beta'(s) \leq C\beta(s)$ , we get

$$\begin{aligned}
\int_{\mathbb{R}^2} \beta(f_{t_1}) dx &\leq \int_{\mathbb{R}^2} \beta(f_{t_0}) dx \\
&+ (C+1) \chi \int_{t_0}^{t_1} \|\nabla_x (K * f)(x)\|_{L^\infty(\mathbb{R}^2)} \int_{\mathbb{R}^2} \beta(f_s) dx ds.
\end{aligned}$$

Then Grönwall's lemma implies that for all  $0 < t_0 < t_1 < T$ ,

$$\int_{\mathbb{R}^2} \beta(f_{t_1}) dx \leq C(\alpha, T) \int_{\mathbb{R}^2} \beta(f_{t_0}) dx.$$

Finally letting  $\beta(s) \rightarrow |s|^q/q$ , we get that for all  $q \geq 1$  and all  $0 < t_0 < t_1 < T$ ,

$$\|f(t_1, \cdot)\|_{L^q(\mathbb{R}^2)} \leq C(q, \alpha, T) \|f(t_0, \cdot)\|_{L^q(\mathbb{R}^2)}. \tag{6.6.48}$$



Coming back to (6.6.46) and using  $\beta_M(s) = s^2/2$  for  $|s| \leq M$  and  $\beta_M(s) = M|s| - M^2/2$  for  $|s| \geq M$ , we have

$$\begin{aligned} & \int_{\mathbb{R}^2} \beta_M(f_{t_1}^n) \psi \, dx + \int_{t_0}^{t_1} \int_{\mathbb{R}^2} \mathbf{1}_{|f_s| \leq M} |\nabla_x f_s^n|^2 \psi \, dx \, ds \\ &= \int_{\mathbb{R}^2} \beta_M(f_{t_0}^n) \psi \, dx + \int_{t_0}^{t_1} \int_{\mathbb{R}^2} \beta'_M(f_s^n) r^n \psi(x) \, dx \, ds \\ & \quad + \int_{t_0}^{t_1} \int_{\mathbb{R}^2} \beta_M(f_s^n) [\Delta \psi(x) - \chi(K * w) \nabla_x \psi(x)] \, dx \, ds \\ & \quad + \chi \int_{t_0}^{t_1} \int_{\mathbb{R}^2} [\beta'_M(f_s^n) f_s^n - \beta_M(f_s^n)] \psi(x) \nabla_x \cdot (K * f) \, dx \, ds, \end{aligned}$$

similarly as above we first make  $n \rightarrow \infty$ , then we approximate  $\psi \equiv 1$  by a well-chosen sequence  $\psi_R$  and make  $R \rightarrow \infty$ , and finally make the limit  $M \rightarrow \infty$  to find that for every  $T \geq t_1 \geq t_0 \geq 0$ :

$$\begin{aligned} & \int_{\mathbb{R}^2} |f_{t_1}|^2 \, dx + \int_{t_0}^{t_1} \int_{\mathbb{R}^2} |\nabla_x f_s|^2 \, dx \, ds \\ & \leq \int_{\mathbb{R}^2} |f_{t_0}|^2 \, dx + \chi \int_{t_0}^{t_1} \|\nabla_x (K * f)(x)\|_{L^\infty(\mathbb{R}^2)} \int_{\mathbb{R}^2} |f_s|^2 \, dx \, ds. \end{aligned}$$

We conclude, using (6.6.48), that for all  $0 < t_0 < T$  and any  $q \in [1, \infty)$ :

$$f \in L^\infty(t_0, T; L^q(\mathbb{R}^2)) \quad \text{and} \quad \nabla_x f \in L^2((t_0, T) \times \mathbb{R}^2). \quad (6.6.49)$$

To get the continuity in time of (6.1.10), we need to improve even more the estimates on  $f$  which will be achieved using a bootstrap argument. First, fixing  $p > 2/(2 - \alpha)$  we notice that for all  $t_0 > 0$

$$\|K * f_t\|_{L^\infty} \leq C(p)(1 + \|f_t\|_{L^p}) \Rightarrow K * f_t \in L^\infty(t_0, T; L^\infty(\mathbb{R}^2)),$$

and thanks to (6.6.47) and (6.6.49):

$$\|\nabla_x (K * f_t)\|_{L^\infty} \leq C(p)(1 + \|f_t\|_{L^p}) \Rightarrow \nabla_x (K * f_t) \in L^\infty(t_0, T; L^\infty(\mathbb{R}^2)),$$

we thus have

$$\partial_t f - \Delta_x f = [\chi f \nabla_x \cdot (K * f) + (K * f) \cdot \nabla_x f] \in L^2((t_0, T) \times \mathbb{R}^2),$$

and [23, Theorem X.11] provides the maximal regularity in  $L^2$  spaces for the heat equation, in other words: for all  $t_0 > 0$

$$f \in L^\infty(t_0, T; H^1(\mathbb{R}^2)) \cap L^2(t_0, T; H^2(\mathbb{R}^2)).$$

**Remark 6.6.108.** *We emphasize that the previous bound is true for all  $t_0$ . In fact, when  $f_{t_0} \in H^1(\mathbb{R}^2)$ , the maximal regularity implies the above bound in the time interval  $[t_0, \infty)$ . But thanks to (6.6.49), we can find  $t_0$  arbitrary close to 0 such that  $f_{t_0/2} \in H^1(\mathbb{R}^2)$ , then we get the conclusion.*

Using now the interpolation inequality, there exists a constant  $C > 0$  such that

$$\|\nabla_x f\|_{L^3(\mathbb{R}^2)} \leq C \|D^2 f\|_{L^2(\mathbb{R}^2)}^{2/3} \|f\|_{L^2(\mathbb{R}^2)}^{1/3},$$

which implies

$$\int_{t_0}^T \|\nabla_x f\|_{L^3(\mathbb{R}^2)}^3 \, ds \leq C \int_{t_0}^T \|D^2 f\|_{L^2(\mathbb{R}^2)}^2 \|f\|_{L^2(\mathbb{R}^2)} \, ds < \infty.$$

Thanks to the previous calculus and again [23, Theorem X.12] we conclude that  $\partial_t f, \nabla_x f \in L^3((t_0, T) \times \mathbb{R}^2)$  and then Morrey's inequality implies that for all  $t_0 > 0$

$$f \in C^0((t_0, T) \times \mathbb{R}^2),$$

all together allow us to deduce that

$$f \in C([0, T]; L^1(\mathbb{R}^2)) \cap C((0, T); L^2(\mathbb{R}^2)).$$

We can go even further iterating this argument, using the interpolation inequality and the Sobolev inequality, to deduce that  $\nabla_x f \in L^p((t_0, T) \times \mathbb{R}^2)$  for any  $1 < p < \infty$ ,  $[\chi f \nabla_x \cdot (K * f) + (K * f) \cdot \nabla_x f] \in L^p((t_0, T) \times \mathbb{R}^2)$  for all  $t_0 > 0$ . Then the maximal regularity of the heat equation in  $L^p$  spaces (see [23, Theorem X.12]) implies that for all  $t_0 > 0$

$$\partial_t f, \nabla_x f \in L^p((t_0, T) \times \mathbb{R}^2),$$

and then using again Morrey's inequality:  $f \in C^{0,\alpha}((t_0, T) \times \mathbb{R}^2)$  for any  $0 < \alpha < 1$ , and any  $t_0 > 0$ . All together allow us to prove (6.1.10).

*Step 4. Renormalization.* To end the proof we show (6.1.11). Let thus  $\beta \in C^1(\mathbb{R}) \cap W_{loc}^{2,\infty}(\mathbb{R})$  sub-linear, such that  $\beta''$  is piecewise continuous and vanishes outside of a compact set. Thanks to (6.6.49), we can pass to the limit in the similar identity as (6.6.46) obtained for time dependent test functions  $\psi \in C_c^2([0, \infty) \times \mathbb{R}^2)$  to get

$$\begin{aligned} \int_{t_0}^{\infty} \int_{\mathbb{R}^2} \beta''(f_s) |\nabla_x f_s|^2 \psi_s dx ds &= \int_{\mathbb{R}^2} \beta(f_{t_0}) \psi_{t_0} dx \\ &- \chi \int_{t_0}^{\infty} \int_{\mathbb{R}^2} \psi_s(x) \nabla_x \cdot (K * f) (f_s \beta'(f_s) - \beta(f_s)) dx ds \\ &+ \int_{t_0}^{\infty} \int_{\mathbb{R}^2} \beta(f_s) (\Delta_x \psi_s(x) - (K * f) \nabla_x \psi_s(x) + \partial_t \psi_s(x)) dx ds. \end{aligned} \quad (6.6.50)$$

In the case  $\psi \geq 0$  and  $\beta'' \geq 0$  we can pass to the limit  $t_0 \rightarrow 0$  thanks to monotonous convergence in the first term, the continuity property obtained in Step 2 in the second term, and the monotonous convergence in the other terms (recall that  $s\beta'(s) \leq \beta(s)$ ,  $\beta$  is sub-linear and  $|f|(1 + |K * f| + |\nabla \cdot (K * f)|)$  belongs to  $L^1(0, T; L^1(\mathbb{R}^2))$  thanks to (6.6.42) and (6.6.43)). We get

$$\begin{aligned} \int_0^{\infty} \int_{\mathbb{R}^2} \beta''(f_s) |\nabla_x f_s|^2 \psi_s dx ds &= \int_{\mathbb{R}^2} \beta(f_0) \psi_0 dx \\ &+ \int_0^{\infty} \int_{\mathbb{R}^2} \beta(f_s) [\Delta_x \psi_s - \chi \nabla_x \cdot (K * f) \cdot \psi_s + \partial_t \psi_s] dx ds \\ &+ \chi \int_0^{\infty} \int_{\mathbb{R}^2} \beta'(f_s) f_s \psi_s(x) \nabla_x \cdot (K * f) dx ds, \end{aligned} \quad (6.6.51)$$

and the bound given by (6.6.51) implies directly that we can pass to the limit  $t_0 \rightarrow 0$  in the general case for  $\psi$  in (6.6.50) which is nothing but (6.1.11) in the distributional sense.  $\square$

We now give a useful lemma for the entropic chaos.

**Lemma 6.6.109.** *Let  $\alpha \in (0, 1)$  and  $f_0 \in \mathbb{P}_1(\mathbb{R}^2)$  such that  $H(f_0) < \infty$ . Let  $(f_t)_{t \geq 0}$  be the unique solution of (6.1.1) satisfying (6.1.7). Then*

$$H(f_t) + \int_0^t I(f_s) ds = H(f_0) + \chi(1 - \alpha) \int_0^t \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} \frac{f_s(dx) f_s(dy)}{|x - y|^{\alpha+1}} ds. \quad (6.6.52)$$

**Proof.** For  $m > 1$ , let us take  $\beta_m \in C^1(\mathbb{R}) \cap W_{loc}^{2, \infty}(\mathbb{R})$  given by

$$\beta_m(s) = \begin{cases} s \log(s) + (1 - s)/m & \text{for } m^{-1} \leq s \leq m, \\ \beta_m(m_-) + \beta'_m(m_-)(s - m) & \text{for } s > m, \\ \beta_m(m_+^{-1}) + \beta'_m(m_+^{-1})(s - m^{-1}) & \text{for } s < m^{-1}, \end{cases}$$

so that  $\beta_m(s) \leq Cs$  and  $\beta_m \rightarrow s \log(s)$  for any  $s > 0$ .

Since  $\beta_m$  is admissible (in the sense of Theorem 6.1.92), then using (6.1.11) we get that for any  $\psi \in C_c^\infty(\mathbb{R}^2)$ ,

$$\begin{aligned} \int \beta_m(f_t) \psi dx - \int \beta_m(f_0) \psi dx &= \chi \int_0^t \int \nabla_x \cdot (K * f) (f \beta'_m(f) - \beta_m(f)) \psi dx ds \\ &\quad + \int_0^t \int \beta_m(f) (\Delta_x \psi - \chi(K * f) \cdot \nabla_x \psi) dx ds \\ &\quad - \int_0^t \int \beta''_m(f) |\nabla_x f|^2 \psi dx ds, \end{aligned}$$

using that  $\beta''_m(s)$  is nonnegative, that  $\beta_m$  grows linearly at  $+\infty$  and that  $(f_s)_{s \geq 0}$  is nonnegative we can make  $\psi \rightarrow 1$  to get

$$\begin{aligned} \int \beta_m(f_t) dx - \int \beta_m(f_0) dx &= \chi \int_0^t \int \nabla_x \cdot (K * f) (f \beta'_m(f) - \beta_m(f)) dx ds \\ &\quad - \int_0^t \int \beta''_m(f) |\nabla_x f|^2 dx ds. \end{aligned}$$

In fact, the first and the second terms converge thanks to monotonous convergence and that  $|\beta_m(s)| \leq C|s|$ . The third term is a consequence of the monotonous convergence, that  $\beta'_m(s)$  is bounded, and that  $f \nabla \cdot (K * f)$  (resp.  $|f(K * f)|$  for the fourth term) is integrable by (6.6.43) (resp. (6.6.42)). The last term is a consequence of (6.4.36).

Finally, we notice that in the interval  $(0, 1]$  the function  $-\beta_m$  increases to  $-s \log(s)$  while in the interval  $[1, \infty)$ ,  $\beta_m(s)$  increases to  $s \log(s)$ . Thanks to the monotonous convergence we can make  $m \rightarrow \infty$  and using the integrability of all the limits we get (6.6.52).  $\square$

It remains to conclude with the proof of the entropic chaos.

**Proof of Theorem 6.1.95 (ii).** We only have to prove that for each  $t \geq 0$ ,  $H(F_t^N)$  tends to  $H(f_t)$ . To this aim, we first show that for any  $t \geq 0$

$$L := \limsup_N \left[ H(F_t^N) + \int_0^t I(F_s^N) ds \right] \leq H(f_t) + \int_0^t I(f_s) ds. \quad (6.6.53)$$

Let  $t \geq 0$  be fixed. Using (6.1.14) and recalling that  $H(F_0^N) \rightarrow H(f_0)$  by assumption, we have

$$L \leq H(f_0) + \limsup_N \frac{\chi(1-\alpha)}{N^2} \sum_{i \neq j} \int_0^t \mathbb{E} \left[ \frac{1}{|X_s^{i,N} - X_s^{j,N}|^{\alpha+1}} \right] ds,$$

so that using that  $H(f_t) + \int_0^t I(f_s) ds = H(f_0) + \chi(1-\alpha) \int_0^t \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} \frac{f_s(dx) f_s(dy)}{|x-y|^{\alpha+1}} ds$  by Lemma 6.6.109, we only have to prove that

$$\lim_{N \rightarrow \infty} \frac{1}{N^2} \int_0^t \mathbb{E} \left[ \sum_{i \neq j} \frac{1}{|X_s^{i,N} - X_s^{j,N}|^{\alpha+1}} \right] ds = \int_0^t \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} \frac{f_s(dx) f_s(dy)}{|x-y|^{\alpha+1}} ds.$$

By exchangeability, it suffices to prove that, as  $N \rightarrow \infty$ ,

$$D_N := \int_0^t \mathbb{E} \left[ \frac{1}{|X_s^{1,N} - X_s^{2,N}|^{\alpha+1}} \right] ds \rightarrow \int_0^t \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} \frac{f_s(dx) f_s(dy)}{|x-y|^{\alpha+1}} ds =: D.$$

For any  $\epsilon > 0$ , we have

$$|D - D_N| \leq |D - D_\epsilon| + |D_\epsilon - D_{N,\epsilon}| + |D_{N,\epsilon} - D_N|,$$

where  $D_{N,\epsilon} = \int_0^t \mathbb{E} \left[ \frac{1}{(|X_s^{1,N} - X_s^{2,N}| \vee \epsilon)^{\alpha+1}} \right] ds$  and  $D_\epsilon = \int_0^t \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} \frac{f_s(dx) f_s(dy)}{(|x-y| \vee \epsilon)^{\alpha+1}} ds$ . Using that for any  $\epsilon > 0$  fixed, the function  $(x, y) \mapsto (|x-y| \vee \epsilon)^{-\alpha-1}$  is bounded continuous and that  $\mathcal{L}(X_s^{1,N}, X_s^{2,N})$  goes weakly to  $f_s \otimes f_s$  for any  $s \geq 0$ , we have  $\lim_N \mathbb{E} \left[ \frac{1}{(|X_s^{1,N} - X_s^{2,N}| \vee \epsilon)^{\alpha+1}} \right] = \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} \frac{f_s(dx) f_s(dy)}{(|x-y| \vee \epsilon)^{\alpha+1}}$ . By dominated convergence, we thus get that  $\lim_N |D_\epsilon - D_{N,\epsilon}| = 0$ . We thus have

$$\limsup_N |D - D_N| \leq |D - D_\epsilon| + \limsup_N |D_{N,\epsilon} - D_N| \quad \forall \epsilon > 0.$$

Let  $\tilde{\alpha}$  be such that  $\alpha + 1 < \tilde{\alpha} < 2$ . We have

$$\begin{aligned} |D - D_\epsilon| &\leq 2 \int_0^t \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} \frac{f_s(dx) f_s(dy)}{|x-y|^{\alpha+1}} \mathbf{1}_{\{|x-y| < \epsilon\}} ds \\ &\leq 2\epsilon^{\tilde{\alpha}-\alpha-1} \int_0^t \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} \frac{f_s(dx) f_s(dy)}{|x-y|^{\tilde{\alpha}}} ds \\ &\leq C\epsilon^{\tilde{\alpha}-\alpha-1} \int_0^t (1 + I(f_s)) ds \leq C(1+t)\epsilon^{\tilde{\alpha}-\alpha-1}, \end{aligned}$$

by Lemma 6.2.96 (applied with  $F = f_s \otimes f_s$ , for which  $I(F_s) = I(f_s)$ ) and (6.1.8). Using the same arguments, we also have for any  $N \geq 2$ ,

$$|D_{N,\epsilon} - D_N| \leq C\epsilon^{\tilde{\alpha}-\alpha-1} \int_0^t (1 + I(F_s^N)) ds \leq C(1+t)\epsilon^{\tilde{\alpha}-\alpha-1}.$$

We thus get that  $\limsup_N |D - D_N| = 0$  and (6.6.53) is proven.

Using [72, Theorem 3.4 and Theorem 5.7], we have

$$\liminf_N H(F_t^N) \geq H(f_t) \quad \text{and} \quad \liminf_N \int_0^t I(F_s^N) ds \geq \int_0^t I(f_s) ds. \quad (6.6.54)$$

Using (6.6.53) and (6.6.54), we easily conclude that

$$\lim_N H(F_t^N) = H(f_t) \quad \text{and} \quad \lim_N \int_0^t I(F_s^N) ds = \int_0^t I(f_s) ds,$$

which concludes the proof.  $\square$



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## Résumé

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Ce travail est consacré à l'étude de quelques questions mathématiques issues de la modélisation des systèmes biologiques en combinant des outils analytiques et probabilistes. Il est principalement lié à: (1) la modélisation mathématique et l'analyse des réseaux neuronaux, (2) le rôle de la diffusion des homéoprotéines dans la morphogenèse et (3) la propriété de propagation du chaos pour un système de particules pour une équation de Keller-Segel sous-critique.

Dans la première partie, nous nous intéressons à la propagation du chaos et au comportement en temps long des solutions des équations de champ moyen. Plus précisément, nous nous intéressons à la dérivation des équations de champ moyen associées aux réseaux de neurones, ainsi qu'à l'étude de la convergence vers l'équilibre des solutions des équations limites. Tout d'abord, dans le Chapitre 2, nous utilisons la méthode de couplage pour démontrer la propagation du chaos pour un réseaux neuronal avec délais et avec une architecture aléatoire. La principale nouveauté est de considérer délais et poids synaptiques corrélés, comme ceci est le cas dans les réseaux biologiques où les neurones proches anatomiquement sont plus fortement connectés. Ceci nous permet de montrer, dans le cas d'une dynamique de type taux de décharge, que le niveau de connectivité joue un rôle remarquable dans l'émergence de solutions oscillantes synchronisées. Dans le Chapitre 3, nous considérons une équation cinétique du type FitzHugh-Nagumo. Nous analysons l'existence de solutions à cette équation et, en utilisant un argument de perturbation, prouvons la convergence exponentielle de l'équation non linéaire dans les régimes de faible connectivité. Enfin, en utilisant l'unicité de la solution faible, nous justifions la propagation du chaos. Il est à noter que les coefficients de l'équation de champ moyen ne sont pas globalement Lipschitziens, ce qui améliore en particulier les résultats classiques. En outre, l'opérateur différentiel est hypodissipatif: nous utilisons un argument de décomposition du semigroupe pour prouver la convergence de l'équation linéaire.

Dans la deuxième partie, nous étudions le rôle des homeoprotéines (HPs) sur la robustesse des bords des aires fonctionnelles. Les HPs sont des facteurs de transcription des gènes du développement connus pour avoir une activité non-autonome et la possibilité de se faire exprimer dans les cellules voisines par diffusion. Dans le Chapitre 4, nous proposons, sur la base de deux théories classiques de la morphogenèse, un modèle général du développement neuronal. Le modèle décrit la compétition entre deux HPs avec faible diffusion. Par l'analyse des solutions stationnaires dans le cas autonome, nous prouvons qu'en l'absence de diffusion, les HPs sont exprimées différenciellement dans des régions irrégulières. Mais en présence de diffusion, même arbitrairement faible, des frontières bien définies entre les différentes zones fonctionnelles émergent. Dans le Chapitre 5, nous considérons le modèle général dans le cas unidimensionnel et prouvons l'existence de solutions stationnaires monotones définissant un point d'intersection unique aussi faible que soit le coefficient de diffusion. De plus, quand le coefficient de diffusion tend vers zéro, nous prouvons que les solutions stationnaires convergent vers une solution d'un système dynamique autonome qui a un unique point de discontinuité caractérisé comme l'unique point de l'espace où la vitesse d'une onde progressive particulière s'annule.

Enfin, dans la troisième partie, nous étudions un système de particules pour une équation de Keller-Segel sous-critique. Nous démontrons la propagation du chaos sans aucune restriction sur le noyau de force. En outre, en utilisant la notion de solutions de renormalisation pour les EDP, nous démontrons que la propagation du chaos a lieu dans le sens plus fort de chaos entropique.

**Mots-clés :** équation de champ moyen, équation cinétique, modèle de FitzHugh-Nagumo, propagation du chaos, propagation du chaos entropique, solutions de renormalisation, équation de Keller-Segel sous-critique, modélisation de la morphogenèse, diffusion des homéoprotéines, décomposition de semi-groupe.

## Summary

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This work is devoted to the study of mathematical questions arising from the modeling of biological systems combining analytic and probabilistic tools. It is principally related to: (1) the mathematical modeling and analysis of neuronal networks, (2) the role of homeoproteins diffusion in morphogenesis, and (3) the chaos propagation property for a particle system for a subcritical Keller-Segel equation.

In the first part, we are concerned with the chaos propagation and long time behaviour of the solutions of some mean-field equations. More precisely, we are interested in the derivation of the mean-field equations related to neuronal networks, and in the study of the convergence to the equilibria of the solutions to those limit equations. First, in Chapter 2, we use the coupling method to prove the chaos propagation for a neuronal network with delays and random architecture. The main novelty is to consider the delays and the synaptic weights correlated, which is the case of biological networks where the anatomically close neurons are strongly connected. We find, in the case of a firing rate dynamic, that the level of connectivity plays a remarkable role in the emergence of synchronized oscillatory solutions. In Chapter 3, we consider a kinetic FitzHugh-Nagumo equation. We analyze the existence of solutions to this equation and, by using a perturbation argument, we prove the nonlinear exponential convergence of the solutions in the weak connectivity regime. Finally, by using the uniqueness of weak solutions, we justify the chaos propagation property. We remark that the coefficients of the mean-field equation are not globally Lipschitz, which, in particular, improve the classical results. Moreover, the differential operator is hypodissipative: we use an argument of semigroup decomposition to prove the convergence of the linear equation.

In the second part, we study the role of homeoproteins (HPs) on the robustness of boundaries of functional areas. The HPs are transcriptional factors of developmental gens, known for having a non-autonomous activity and the possibility of expressing themselves in neighbouring allowing them to diffuse to neighboring cells by diffusion. In Chapter 4, we propose, based on two classical theories of morphogenesis, a general model for neuronal development. The model describes the competition between two HPs with weak diffusivity. By the analysis of the stationary solutions in the autonomous case, we prove that in the absence of diffusion, the HPs are expressed on irregular areas. But in presence of diffusion, even arbitrarily small, boundaries well defined emerge. In Chapter 5, we consider the general model in the one dimensional case and prove the existence of monotonic stationary solutions defining a unique intersection point. Moreover, when the diffusivity coefficient goes to zero, we prove that the stationary solutions converge to a unique solution of an autonomous dynamical system with a unique discontinuity point. We characterise this discontinuity point as the only spatial point where the speed of a particular traveling wave is zero.

Finally, in the third part, we study a particle system for a subcritical Keller-Segel equation. We show the chaos propagation without any restriction on the force kernel. Moreover, by using the notion of renormalised solutions of PDEs, we demonstrate that the propagation of chaos is in the stronger sense of

entropic chaos propagation.

**Keywords:** Mean-field equation, kinetic equation, FitzHugh-Nagumo model, chaos propagation, entropic chaos propagation, renormalisation solutions, subcritical Keller-Segel equation, morphogenesis modeling, homeoproteins diffusion, semigroup decomposition.