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ACTIVITY REPORT

Project-Team
MUSCLEES

**Mathematical Understanding across Scales
of Complex Living Ecosystems with
Emerging Structures**

IN COLLABORATION WITH: Laboratoire Jacques-Louis Lions (LJLL)

DOMAIN

Digital Health, Biology and Earth

THEME

Modeling and Control for Life Sciences

Inria

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Project-Team MUSCLEES

Creation of the Project-Team: 2024 June 01

Keywords

Computer sciences and digital sciences

- A3. – Data and knowledge
 - A3.1. – Data
 - A3.1.1. – Modeling, representation
 - A3.4. – Machine learning and statistics
 - A3.4.6. – Neural networks
 - A3.4.7. – Kernel methods
- A6. – Modeling, simulation and control
 - A6.1. – Methods in mathematical modeling
 - A6.1.1. – Continuous Modeling (PDE, ODE)
 - A6.1.2. – Stochastic Modeling
 - A6.1.3. – Discrete Modeling (multi-agent, people centered)
 - A6.1.4. – Multiscale modeling
 - A6.1.5. – Multiphysics modeling
 - A6.2. – Scientific computing, Numerical Analysis & Optimization
 - A6.2.1. – Numerical analysis of PDE and ODE
 - A6.2.2. – Numerical probability
 - A6.2.3. – Probabilistic methods
 - A6.2.4. – Statistical methods
 - A6.2.6. – Optimization
 - A6.3. – Computation-data interaction
 - A6.3.1. – Inverse problems
 - A6.3.2. – Data assimilation
 - A6.4. – Automatic control
 - A6.4.1. – Deterministic control
 - A6.4.4. – Stability and Stabilization
 - A6.4.6. – Optimal control

Other research topics and application domains

- B1.1.2. – Molecular and cellular biology
- B1.1.5. – Immunology
- B1.1.6. – Evolutionary biology
- B1.1.7. – Bioinformatics
- B1.1.8. – Mathematical biology

B1.2. – Neuroscience and cognitive science

B2. – Health

B2.2. – Physiology and diseases

B2.2.3. – Cancer

B2.2.4. – Infectious diseases, Virology

B2.2.6. – Neurodegenerative diseases

B2.3. – Epidemiology

B2.4. – Therapies

B2.4.1. – Pharmacokinetics and dynamics

B2.4.2. – Drug resistance

B2.6.3. – Biological Imaging

B9.6.4. – Management science

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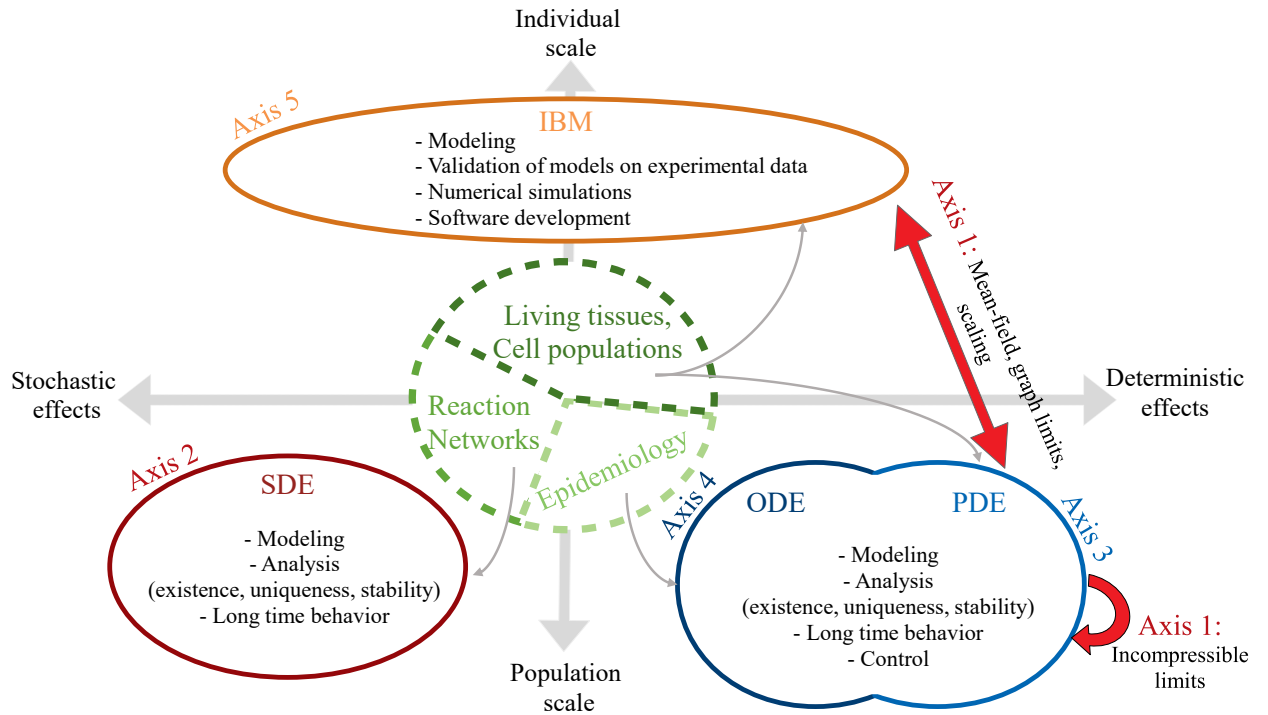


Figure 1: Scheme of the team activities

2 Overall objectives

MUSCLEES is the evolution of the MAMBA Inria project-team, headed by Marie Doumic (now head of the Inria project-team MERGE in Saclay) during 9 years (2014-2022); which was in turn a continuation of the BANG Inria project-team, headed by Benoît Perthame during 11 years (2003-2013). Just as its scientific ascendants, this new project-team aims at developing, analyzing, controlling, observing, identifying and simulating models involving dynamics of phenomena encountered in various biological systems.

The nature of the corresponding populations involved is very diverse, as well as the nature of the interactions between their members. They may contain chemical species, cells, molecules, neurons, bacteria, (human or animal) individuals. We are interested for example in cell motion, (physiological or tumor) cell development, binding/unbinding of macro-molecules, bacteria micro-colony growth, tissue development, repair, ageing and degeneration, epidemic spread, vector control, together with methodological questions related to these aspects.

In accordance with the context, we will use stochastic or deterministic models, systems of ordinary (possibly defined on graphs) or partial differential equations, and agent-based approaches. We will also consider the link between models of different types, exploring the behavior across different scales, and will appeal to tools from control theory to treat issues of (optimal or non-optimal) control, state observation or parametric identification.

In Fig. 1, we give an overview of the different research axes of the MUSCLEES team. The horizontal axis distinguishes schematically between the stochastic and deterministic descriptions, while the vertical axis indicates the description scale. At the heart of our research lie the different applications that drive our mathematical studies: living tissues/cell populations, reaction networks and epidemiology (in green in Fig. 1). All our efforts, even the most theoretical ones, will be motivated by biological questions/challenges with applications in these different fields. The MUSCLEES team proposes to tackle these challenges from different and complementary angles, attempting to provide generalizations and unified points of view in the study of biological systems: Axis 2 (in dark red in Fig. 1) is devoted to the understanding of the role of stochasticity in biological systems through the development and analysis of Stochastic Differential Equations (SDE) for reaction networks; Axes 3 and 4 (in blue in Fig. 1) aim to provide a theoretical understanding of continuum models widely used to describe biological systems at the

population scale, essentially by use of Ordinary Differential Equations (ODE) for the applications to mathematical epidemiology (dark blue in Fig. 1), or of Partial Differential Equations (PDE) for various applications (in light blue in Fig. 1); and Axis 5, the most interdisciplinary axis of our research team, is entirely devoted to the development of valid agent-based models directly confronted to in vitro/in vivo data for bacterial growth and tissue development and ageing (orange in Fig. 1). Lastly, Axis 1 (in red arrows in Fig. 1) represents one of the fundamental perspectives to link all our research activities. It is devoted to establishing the link between the various modelling viewpoints taken in the other research axes, by deriving, as rigorously as possible, the continuum (ODE, SDE, PDE) models from microscopic agent-based descriptions.

The MUSCLEES project-team gathers researchers with complementary skills and interests in applied mathematics (partial differential equations, stochastic processes, control theory). Our goal is to incorporate the different knowledges present in the team as well as expertise obtained from first hand collaborators specialists of the considered applications, in order to provide firm mathematical ground to the representation, understanding, numerical assessment and control of the biological systems of interest. As a peculiarity, we also intend to locate these questions in the larger framework of analysis methods. We will always attempt to unify as much as possible the specific application domains within a common formalism, with scales ranging from individual decision to collective behaviour: this vision and methodology go far beyond the specific applications we have listed. Altogether, the team ambitions to provide a deep **Mathematical Understanding across Scales of Complex Living Ecosystems with Emerging Structures**, whence the acronym: **MUSCLEES**. Our planned activities are exposed below. As a rule, they are activities already currently in progress or whose realisation will be undertaken soon. Longer-term actions or perspectives are mentioned specifically, whenever needed.

3 Research program

The research program is organized along the five following axes.

- Axis 1 – Multiscale study of interacting particle systems
- Axis 2 – Stochastic models for biological systems
- Axis 3 – Theoretical analysis of nonlinear partial differential equations (PDE) modelling various structured population dynamics
- Axis 4 – Mathematical epidemiology
- Axis 5 – Development and analysis of mathematical models for biological tissues confronted to experimental data

The logic of this structure is as follows. A first perspective is related to the various *scales*. Axis 1 is related to the passage from microscopic to mesoscopic scales (these terms are recalled in the beginning of the Section 3.1). The passage to the macroscopic scale and/or the study of the corresponding models is the core of the Axes 2 (stochastic models), 3 (deterministic PDEs) and 4 (deterministic ODEs). In this respect, Axis 5 holds a special place, as it is devoted to the precise confrontation of measured data and model, for some of the problems studied in Axis 3. In a complementary manner, Axes 1, 2 and 3 are of a more theoretical nature, and Axes 4 and 5 more focused on specific applications.

3.1 Axis 1 – Multiscale study of interacting particle systems

MUSCLEES permanent members involved: Pierre-Alexandre Bliman, Sophie Hecht, Benoît Perthame, Diane Peurichard, Nastassia Pouradier Duteil

A growing literature has been devoted to the precise mathematical understanding of the mechanisms subtending pattern formation in multi-agent systems. This subject was initially brought forth by pioneering articles on statistical physics-oriented models for biological systems, and subsequently cemented by a wealth of contributions in the fields of automation theory and engineering. In the midst of this

broad academical trend, a research current led by the works of Hegselman and Krause [112] on bounded confidence models, and the groundbreaking papers of Cucker and Smale [82] on emergent behaviours, started to focus more specifically on the problems of *consensus* or *alignment*.

Multi-agent systems refer to systems of $N \in \mathbb{N}$ agents represented by points in a given configuration space (most often, the Euclidean space \mathbb{R}^d), which evolve according to coupled dynamics of the form

$$\dot{x}_i(t) = \frac{1}{N} \sum_{j=1}^N \phi_{ij}(x_j(t) - x_i(t)). \quad (1)$$

Here, the vector $(x_1(t), \dots, x_N(t)) \in (\mathbb{R}^d)^N$ represents the collection of all the states of the agents at some time $t \geq 0$, while the maps $\phi_{ij} : \mathbb{R}^d \rightarrow \mathbb{R}^d$, encode pairwise interactions between agents, which usually depend on their relative distance and orientation, but could also depend on the individual nature of the agents, which is encoded in the indexing ϕ_{ij} .

Depending on the nature of the interaction functions ϕ_{ij} , these models can be roughly classified in two categories. In the first one, interactions are pre-determined by a given interaction network, which represents the inherent structure of the population's interactions. Then each pairwise interaction ϕ_{ij} is non-zero if and only if the edge (i, j) is part of the underlying graph of interactions. The second approach considers the particle interactions as functions only of the particle's positions: $\phi_{ij} := \phi$. In this case, there is no underlying network.

Mathematically, one of the main challenges in the study of these systems is their multi-scale aspect. Indeed, the reason that such systems have been introduced is to link *local* interactions to *global* behavior. Moreover, in numerous applications these systems are very high dimensional, as they are composed of many individuals, all potentially interacting. Studying and simulating interacting particle systems becomes a particularly challenging problem when the dimension of the system increases. This is referred to as the “curse of dimensionality”, a term coined by Bellman in the context of dynamic optimization of high-dimensional systems. One way around this problem is to move away from the microscopic viewpoint where each agent is considered individually, and consider instead the mean-field limit, which provides a kinetic description of the system. This approach consists of approximating the influence of all agents on any given individual by one averaged effect, which amounts to studying a single partial differential equation (PDE), instead of a large system of coupled ordinary differential equations (ODE).

As several limiting processes can be considered when one passes from an ‘agent-based’ description of a system to a ‘continuous’ one, let us make clear some nomenclature that we will employ throughout this document. We will refer to as ‘microscopic’ the models of agent-based type, i.e systems of ODE that describe the evolution of each agent in a population (each described by individual variables such as position, speed, size, etc). We will first be interested in taking the limit of large number of individuals from our agent-based models, leading to continuum (possibly non-local) PDE models describing the evolution of the agents’ probability distribution (structured in space, time, possibly size etc). We will refer to these models as ‘mesoscopic’, where ‘mesoscopic’ is to be understood here as an intermediate scale, describing populations composed of an ideally infinite number of agents but still expressed at the individual scale (no rescaling of time or space, i.e interactions still expressed at the agents’ scale). On the other hand, we will refer to as ‘macroscopic’ the PDE models obtained after rescaling in time and space the mesoscopic models, in various regimes (diffusion limit, hydrodynamic limit etc) and under proper assumptions on the order of the agents’ interactions. According to the assumptions made on the interactions, these ‘macroscopic’ models will correspond to different microscopic dynamics.

3.1.1 Micro-Meso: Graph limits

MUSCLEES permanent members involved: Pierre-Alexandre Bliman, Nastassia Pouradier Duteil

In 2014, Medvedev used techniques from the recent theory of graph limit to derive rigorously the continuum limit of dynamical models on deterministic graphs [134]. The limiting equation, so-called “graphon equation” now describes the evolution of the particle's positions $x(t, s)$ as a function of time t and of the “continuous index” $s \in I$ (representing the particle's individual identities, in an infinite population):

$$\partial_t x(t, s) = \int_I \phi(s, s', x(t, s') - x(t, s)) . ds' \quad (2)$$

In [56], we extended this idea to a collective dynamics model with time-varying weights, adopting the graph point of view described above. We showed that this approach is more general than the mean-field one, and the Graph Limit can be derived for a much greater variety of models.

Our work will involve deriving graph limits for systems of particles that can be structured along a trait that characterizes their interactions, such as volume, mass or phenotype. Among the open problems that we aim to address in collaboration with Nathalie Ayi (LJLL, Sorbonne University), one of them concerns the graph limit for multi-agent systems evolving on weighted random graphs. More specifically, we will consider that the interactions between agents are given by $\phi_{ij}(x_j(t) - x_i(t)) := \xi_{ij}\phi(x_j(t) - x_i(t))$, where $(\xi_{ij})_{i,j}$ are random variables whose laws are probability distributions on \mathbb{R}_+ that depend on the indices i, j . Graphs with random topologies are often used to model systems such as neuronal networks, coupled lasers and communication or power networks. In [134], the continuum limit of collective dynamics on random graphs was derived for graphs whose edge weights ξ_{ij} can be either 0 (i.e. there is no edge) or 1. Our aim will be to generalize this results to random *weighted* graphs, whose weights can be given by any positive real number. Results will then possibly be extended to *temporal* random graphs, whose edge weights evolve in time as in blinking systems.

In a parallel direction, we will explore the possibilities of the graph-limit formalism in the framework of epidemiological models on graph. A first step was done in [92] by deriving the graph limit of an epidemiological model on graphs, which results in a system of coupled structured PDEs for the susceptible, infected and recovered populations. The graph-limit approach will allow us to ask ourselves fundamental analytical and modeling questions regarding the role of the interaction network in the spread of an epidemic. It will also give us the possibility to address control and optimal control problems aiming to minimize the infected population by controlling the graphon (i.e. the continuous interaction network). Another possibility will be to address inverse problems in order to infer the graph structure based on the epidemic spread. This project will link the research of team members involved in Sections 3.1 and 3.4.

3.1.2 Micro-Meso: Beyond mean-field limits

MUSCLEES permanent members involved: Sophie Hecht, Diane Peurichard, Nastassia Pouradier Duteil

When the interaction between particles is independent of each particle's individual nature, i.e. $\phi_{ij} = \phi$, the particles are said to be *exchangeable*, or *indistinguishable*. In this case, the classical approach to link microscopic and mesoscopic models is a limit process called “mean-field limit”, and consists of approximating the population by a sum of localized point masses, and then of sending the number of agents to infinity, while sending each individual mass to zero [94]. In this way, the total mass of the population is conserved throughout the limit process, and everything can be done in the framework of probability measures. The limit PDE is typically a non-linear transport equation of the type

$$\partial_t \mu(t, x) + \nabla \cdot (V[\mu(t, \cdot)](x) \mu(t, x)) = 0, \quad V[\mu(t, \cdot)](x) = \int_{\mathbb{R}^d} \phi(y - x) d\mu(t, y),$$

in which $\mu(t, \cdot) \in \mathcal{P}(\mathbb{R}^d)$ represents the particle distribution at time t , and the non-local velocity $V[\mu_t]$ represents the averaged effect of the whole population on each individual. However, this approach has a main drawback: it does not take into account the intrinsic volume of the individuals, since they are approximated by their centers of mass. As a result, in many cases the limiting PDE fails to reproduce the behavior of the microscopic system, in particular when modeling congestion effects due to size constraints.

This is a major modeling limitation, and resolving it is crucial. Several works have highlighted a discrepancy between the microscopic and continuum modeling approaches. For instance, in the context of emergency crowd evacuation, microscopic models are able to reproduce the well-known effect of arch formation in front of exits, resulting in congestion and dramatic slow-down of the crowd's evacuation [132]. This effect still eludes all natural continuum limits. Another example can be found in the modeling of cell division: microscopic models capture the fact that the cell population is naturally pushed outwards at the birth of a new daughter cell because of its added volume. This effect is lost in continuum models, as there is no concept of individual size.

The goal of this part of the project is to address this issue. We will first focus on the simple situation of a population of agents whose only interactions are due to “non-overlapping” constraints: if two agents

are within a certain distance (representing their diameter), they exert a repulsive force on each other; if their distance is greater than this diameter, there is no interaction. Despite the simplicity of this setting, the micro-macro limit is highly non-trivial due to the role of the agents' size in the dynamics. Indeed, in the continuum description, the information on the agents' size is lost, and the condition on the agent-to-agent distance no longer makes sense, as the concept of individual agents is gone. However, intuitively, one would expect that this distance condition would correspond to a density condition in the continuum setting: interactions take place if and only if the local density is above a critical threshold. We will explore these questions on systems with identical particles (same and fixed sizes), and take a particular interest in how non-overlapping configurations translate into local density constraints at the population level.

In order to gain insights into the role of the individual particle sizes and shapes on the macroscopic structures generated at the population level, we will consider another approach where the particle density distribution for the mean-field limit is structured in space and sizes. In current works (to be submitted), we showed that under reasonable assumptions for the interaction kernel $\psi_{r,s}$, the limit PDE describing the particle distribution $\mu(t, x, r)$ (depending on time, space and radius) is of the type:

$$\partial_t \mu(t, x, r) - \nabla_x \cdot (\mu(t, x, r) \nabla_x \int_{\mathbb{R}_+} \psi_{r,s} * \mu(t, x, s) ds) - \sigma \Delta_x \mu(t, x, r) = 0. \quad (3)$$

Proving the convergence of the particle system to the limit PDE with the added radial structure in the density distribution is challenging and is a work in collaboration with Marc Hoffman (Université Paris Dauphine).

3.1.3 Scaling limits

MUSCLEES permanent members involved: Sophie Hecht, Benoît Perthame, Diane Peurichard, Nastassia Pouradier Duteil

In order to link the mesoscopic and the macroscopic model it is common to consider a scaling limit. Depending of the variable of the system the scaling can vary (small particle compared to space, slow division compared to the mechanical interaction, etc).

Meso-Macro: the limit of small particles – compressible case Going back to the mesoscopic equation (3) structured in size and space, we will consider a scaling where the size of the particles becomes small compared to the space itself, while keeping the interaction of order 1 (compressible limit). Under these scaling assumptions, we can formally compute that the equation becomes:

$$\partial_t n(t, x, r) - \nabla_x \cdot (n(t, x, r) \int \alpha_{r,s} \nabla_x n(t, x, s) ds) - \sigma \Delta_x n(t, x, r) = 0 \quad \text{with} \quad \alpha_{r,s} = \int \psi_{r,s}(x) dx,$$

where the particle distribution is now denoted by $n(t, x, r)$. The tools to rigorously derive the macroscopic equation requires compacity for the density. Thanks to the diffusion term we can easily find space compacity, and in the case where $\sigma = 0$, energy estimates can allow to recover the result. The difficulty for the convergence resides in finding the compacity according to the size variable density. A recent idea allowed us to circumvent this problem. We now aim to extend the result when considering particle growth and division. In order to do this we will focus on the fact that the equation is a mixed between a reaction diffusion equation and a growth-fragmentation equation.

Meso-macro: The incompressible limit Another limiting process that can be considered is the so-called 'incompressible limit', where the pressure of the system is scaled to become singular. A possible way to study such regime is to work directly at the continuum (macroscopic) level and consider the continuous equation

$$\partial_t n(t, x) - \nabla_x \cdot (n(t, x) \nabla_x p(n(t, x))) = 0,$$

where p represents the pressure of the system depending of the density, the incompressible limit consists in rendering p singular. A classical example is the choice $p(n) = \frac{\gamma}{\gamma-1} n^{\gamma-1}$ with $\gamma \rightarrow +\infty$. This type of limit has been widely studied in the past decade [57, 58, 70] and still provides interesting and difficult problems. For one species we can note the case where the velocity of the system in the Brinkman case

allows a rotational component. In the multiple-species case we can consider the case where the motility rate of the species are different.

Meso-Macro: the link between compressible and incompressible limits This part of the project will be devoted to the study of the link between the two types of limits considered previously, namely the compressible and incompressible limits of mesoscopic models. To this aim, we will consider as starting point multiphase flow models for tumor growth based on mixture theory, well studied by members of the teams. According to the mixture theory, a tissue is modeled as a multiphase flow (different types of cells, liquid, molecules) through a porous media (extra-cellular matrix). In mathematical terms, this leads to strongly nonlinear degenerate parabolic Cahn-Hilliard equations [151] for the cell density $\varphi(t, x)$ as

$$\partial_t \varphi(t, x) + \operatorname{div}[\varphi(t, x)M(\varphi(t, x))\nabla v(t, x)] = 0, \quad v = \nabla V(\varphi) + \delta \Delta \varphi,$$

where M represents the mobility, V describes the interactions between cells, and δ is the surface tension parameter. Our aim is to derive such equations from mesoscopic (kinetic) models and to understand relations between compressible and incompressible models.

Cells may also change their phenotype. Migration, invasion and the epithelial-mesenchymal transition (EMT) are basic principles of the way cells can initiate a collective movement in a living tissue as described above. This is particularly important for the initialisation of metastases in cancer. With the Inserm team, Laboratoire de Biologie du Cancer et Thérapeutique, Saint-Antoine hospital, we will develop a model of invasion through membranes in breast cancer.

3.2 Axis 2 – Stochastic models for biological systems

MUSCLEES permanent members involved: Benoît Perthame, Philippe Robert

This line of research investigates models where a stochastic component, the so-called, and somewhat ambiguous notion, “noise” of the biological literature, plays an important role. This is for example the case for gene expression in bacterial cells, see [158], or in some neural networks to represent the occurrence of spiking events, see [160]. The stochastic framework is due to dynamics of binding/unbinding of pairs of macro-molecules within biological cells. It can be also when a small subset of enzymes has an important impact on the dynamic of the macromolecules, so that the classical law of mass action is not anymore relevant to represent the system. This is a quite different perspective from classical mathematical biological models for population processes where, essentially, a macroscopic view is used, with branching processes in particular.

Scaling approaches are used to investigate these models. The scaling parameter being either the total number of interacting macromolecules, the number of cells, or the factor of the time-scale of fast processes ... Functional laws of large numbers, functional central limit theorems, and averaging principles are the main technical results which can be proved to have a qualitative description of these systems.

3.2.1 Regulation Mechanisms of Gene Expression

MUSCLEES permanent members involved: Philippe Robert

The central dogma of molecular biology states that the genetic information flows only in one way, from DNA to RNAs, and to proteins. The production of proteins is a central process of biological cells. It can be described as a two-step process. In the first step, macro-molecules *polymerases* produce RNAs with genes of the DNA. This is the *transcription* step. The second step is the production of proteins itself from mRNAs, *messenger RNAs*, a subset of RNAs, with macro-molecules *ribosomes*. This is the *translation* step. An additional feature of this process is that it is consuming an important fraction of energy resources of the cell, to build chains of amino-acids or chains of nucleotides in particular. See [62, 150, 158].

In the context of prokaryotic cells, like bacterial cells or archaeal cells. The *cytoplasm* of these cells is not as structured as eukaryotic cells, like mammalian cells for example, so that most of the macro-molecules of these cells can potentially collide with each other. This key biological process can be, roughly,

described as resulting of multiple encounters/collisions of several types of macro-molecules of the cell: *polymerases* with DNA, *ribosomes* with *mRNAs*, or *proteins* with DNA, ...

The fact that the cytoplasm of a bacterial cell is a disorganized medium has important implications on the internal dynamics of these organisms. Numerous events are triggered by random events associated to thermal noise. When the external conditions are favorable, these cells can nevertheless multiply via division at a steady pace. A central question is of understanding how the cell adapts to different environments (scarce resources or rich environment).

Important regulation mechanisms of gene expression of bacterial cells are achieved with RNAs. Up to now little is known on the efficiency of this type of regulation from a quantitative point of view. The ambitious goal is of designing and investigating stochastic models integrating the transcription and translation steps as well as the flows of amino-acids within the cell. One of the difficulties is the number of different chemical species involved: genes, RNAs, tRNAs, sRNAs, rRNAs, proteins, Amino-acids, ppGpp, RelA, ... All of them having an important role in this regulation. A scaling approach is investigated to study these multi-dimensional Markov processes. This is a collaboration with Vincent Fromion of the laboratory BioSys "Biology of systems" of Inrae. The main goal of these studies is to evaluate the efficiency of these regulation mechanisms in the cell for the adaptation to changes of environment: switching times, impact of the variation of the flows of amino-acids, ..., and the dependence on the production rates of ppGpp, RelA and sRNAs among others.

3.2.2 Stochastic Chemical Reaction Networks

MUSCLEES permanent members involved: Philippe Robert

The goal of the research project of this section is of investigating a generalization of the law of mass action for biological systems.

For example, if three chemical species \mathcal{A} , \mathcal{B} and \mathcal{C} are involved in a chemical reaction of the type,



the classical *law of mass action* states that the concentration $x_M(t)$ of the chemical specy M at time t satisfies the relation

$$\frac{dx_C(t)}{dt} = kx_A(t)x_B(t).$$

The ODE in this case is a quadratic functional of the state vector. In a deterministic context, the famous results by Horn, Johnson and Feinberg give, for some specific topologies, a satisfactory description of the stable states of these networks. See [105] for example. It turns that this description is suitable for systems for which the orders of magnitude of the different chemical species are comparable and that the stochastic components merely vanish. These assumptions are nevertheless not true in some biological settings, when, for example, reactions are driven by a small number of enzymes but with a large reaction rate.

As already mentioned, due to dynamics of binding/unbinding of pairs of macro-molecules within biological cells, it is natural to consider models of chemical reaction networks for which collisions of chemical species occur in a random way. In the above example, it will be assumed that a given couple of A and B particles will collide at rate k , so that if $X_M(t)$ is the number of particles of type M at time t , then, at time t , a particle of type C is created at rate $kX_A(t)X_B(t)$. The process $(X_A(t), X_B(t), X_C(t))$ is a Markov process, if we assume that there are external arrivals of A and B particles, it is natural to study the convergence in distribution of this Markov process. There are several conjectures in this domain.

Up to now there are few results in such a random context. The reference [47] shows, by using the results of the deterministic case that the invariant distribution has a product form expression for a specific set of topologies. A challenging question is of extending stability results for networks for which no such product formula holds. New tools, such as scaling techniques, have to be developed to study these important problems.

3.2.3 Neural Networks

MUSCLEES permanent members involved: Benoît Perthame, Philippe Robert

This application domain of this line of research is described in the subsection “Neuroscience” of Section 4.1.

Interacting Hawkes processes When the number of nodes of a neural network is fixed (i.e. not large), one of the challenging questions is of determining the asymptotic, temporal, behavior of a neural network composed of inhibitory and excitatory neural cells. In general mathematical models of neural networks assume excitatory nodes. A classical example is the self-excitatory neural cell, the integrate and fire model. However, experiments have shown that inhibitory cells play a key role in the procedures of learning. See [176] for example.

A typical, simple, evolution of a node i of the network \mathcal{R} could be of the form

$$\begin{cases} dX_i(t) = -X_i(t)dt + \sum_{j \in \mathcal{R} \setminus \{i\}} W_{ji}(t-) \mathcal{N}_j(dt) - X_i(t-) \mathcal{N}_i(dt) \\ dZ_i(t) = -\gamma Z_i(t)dt + \mathcal{N}_i(dt), \\ dW_{ij}(t) = B_i Z_i(t-) \mathcal{N}_j(dt) + B_j Z_j(t-) \mathcal{N}_i(dt) - \delta W_{ij}(t)dt, \end{cases}$$

where $B_i \in \mathbb{R}$, $B_i > 0$ if i is excitatory and inhibitory otherwise.

- $X_i(t)$ is the membrane potential of i at time t ;
- $W_{ij}(t)$ is the synaptic weight of the link $i - j$ at time t ;
- $\mathcal{N}_i(dt)$ is a point process with intensity $\beta(X_i(t))$, it is associated to the spike train of i ;
- $Z_i(t)$ encodes the past spiking activity of node i at time t .

The asymptotic of the matrix of synaptic weights ($W_{ij}(t)$) when t gets large is the main quantity of interest. Up to now there are few theoretical results to determine the conditions under which a given link is asymptotically “weak”, when its weight converges to 0, or “strong” when it grows without bound.

Mean-field neural networks For large neural networks as described before, mean-field limits have been established in a number of situations. The resulting probability distributions satisfy nonlinear PDEs which can be of Integrate&Fire type, renewal type or combinations. The specific non-linearities raise severe difficulties in terms of analysis and numerics, as global existence vs finite blow-up, asymptotic analysis, understanding of synchronisation or convergence to steady state. Motivated either by their mathematical interest of questions asked by biologists, we will continue our analysis of this large class of problems (see, e.g., [118]) in several directions:

- analyze the current models introduced in biophysics (N. Brunel) to take into account spike-triggered adaptation. The difficulty here is the degeneracy of the equations, which leads to several long term problems involving a PhD thesis,
- define solutions of structured equations (see Section 3.3) with infinite number of variables, in relations to Wold processes (in the spirit described above for Hawkes processes, a short term programm),
- explain anti-phase synchronisation in networks à la Wilson-Cowan vs experimental observations. A collaboration with D. Avitabile and D. Salort has begun and results are encouraging.

3.3 Axis 3 – Theoretical analysis of nonlinear partial differential equations (PDE) modelling various structured population dynamics

MUSCLEES permanent members involved: Luca Alasio, Jean Clairambault, Benoît Perthame, Nastassia Pouradier Duteil

Since the seminal paper by McKendrick for medical applications [35], to account for relevant heterogeneity in the variables under study (most often populations of individuals such as proteins, cells, animal species, etc.), continuous models in biology rely on equations structured by different variables, age, size,

physiological trait... The interest of studying these equations stems from the mathematical structure of these equations (which are neither conservative, nor self-adjoint), their non-linearities and the complex behaviour of solutions.

3.3.1 Adaptive phenotype-structured cell population dynamics

MUSCLEES permanent members involved: Jean Clairambault, Benoît Perthame, Nastassia Pouradier Duteil

Initially developed for adaptive dynamics in theoretical ecology and cell population biology models in [87] and in [89], phenotype-structured equations are here studied in the context of cell populations confronted to a changing environment, in particular in the case of cancer and its treatments. Some of these models, developed within the former Inria team, have been reviewed in the survey [79]. A more general and extended recent state of the art on phenotype-structured population dynamics is reported in [128].

Our research will focus on the analysis of such phenotype-structured equations, and more particularly, on their long-time behavior, of which little is known. Indeed, the different mathematical terms such as advection (modeling cell differentiation), diffusion (modeling epimutations) and non-local source terms (modeling population growth and phenotype selection) tend to have antagonistic effects. One of the main mathematical challenges consists of understanding the effect of coupling such phenomena on the long-time behavior of the solution.

Interacting cell populations: Tumour-immune interactions Preferred models rely on structured equations of the nonlocal Lotka-Volterra type with exchanges of bidirectional inhibitory messages between the two populations in the form of weighted integrals acting as added death terms in the logistic part of the net proliferation rate (i.e., nonlocal death term in the net rate ‘birth minus death’). The heterogeneous tumour cell population density $n(t, x)$ is structured according to a *tumour malignancy* continuous phenotype x , here identified to ‘stemness’. Focusing for the sake of this presentation on adaptive immunity, the effector cells, at contact with tumour cells, T-cell population density $\ell(t, y)$ and the naive cells, present in lymphoid organs, T-cell population density $p(t, y)$, unique source term of the effector T-cell population $\ell(t, y)$, are structured according to an *anti-tumour efficacy* phenotype y . The action of Antigen Presenting Cells (APCs), which instruct naive T-cells with the tumour aggressiveness phenotype x is represented below by the weighted integral $\chi(t, y)$. The model runs as follows:

$$\begin{cases} \frac{\partial n}{\partial t}(t, x) = [R(x, \rho(t)) - \mu(x)\varphi(t, x)] n(t, x) \\ \frac{\partial \ell}{\partial t}(t, y) = p(t, y) - \left(\frac{v(y)\rho(t)}{1 + h \cdot ICI(t)} + k_1 \right) \ell(t, y), \\ \frac{\partial p}{\partial t}(t, y) = \alpha \chi(t, y) p(t, y) - k_2 p^2(t, y), \end{cases}$$

with total tumour cell mass at time t

$$\rho(t) = \int_0^1 n(t, x) dx,$$

and

$$\varphi(t, x) = \int_0^1 \psi(x, y) \ell(t, y) dy, \quad \chi(t, y) = \int_0^1 \omega(x, y) n(t, x) dx, \quad \omega(x, y) = \frac{1}{s} e^{-|x-y|/s}, \quad \psi(x, y) = \frac{1}{s_1} e^{-|x-y|/s_1}.$$

We study this system in the framework of the PhD thesis of Zineb Kaid at Tlemcen University, Algeria, and of a collaboration with Camille Pouchol at Université Paris-Cité. The first question concerns the large time behaviour of the system, depending in particular on functions $\mu(x)$ (sensitivity of tumour cells to the action of T-cells) and $v(y)$ (sensitivity of T-cells to PD-ligands), without treatment. We also study its behaviour with added constant control *ICI* (for Immune Checkpoint Inhibitors, see 4.2, Tumour-immune cell interactions), aiming in particular at representing reversal from escape to extinction or equilibrium in the cancer cell population. Some analytical results on phenotype concentration in x have been reached

already in the case where $\varphi = \varphi(t)$ is independent of x (then representing more innate, due to NK-lymphocytes, than adaptive immunity), however the general case remains to be fully explored. Adding the effect of time-scheduled immunotherapies (in particular anti-PD1 immune checkpoint inhibitors $ICI(t)$) and their optimisation, following the optimal control methodology of [156], will be the ultimate object of this study. We may also include small parameters, e.g. in the initial distributions, and study the limiting constrained Hamilton-Jacobi equation (see below).

Asymptotics: population convergence, trait divergence and trait concentration Plasticity, and ‘bet hedging’ in cancer have been modelled, in the framework of Frank Ernesto Alvarez Borges’s PhD thesis at Paris-Dauphine University, by a phenotype-structured reaction-advection-diffusion equation [46] in which the structure variables are viability, fecundity - with a trade-off condition between them - and plasticity, this last variable tuning in a nondecreasing mode a Laplacian that represents nongenetic instability of the other two phenotype variables. The asymptotics of the model, which has been inspired by the Bouin-Calvez cane toad equation, yields phenotypic divergence between viability and fecundity traits, while the plasticity trait asymptotically decreases. The main equation, where $z = (x, y, \theta)$ with x =viability, y =fecundity, θ =plasticity, runs as:

$$\partial_t n + \nabla \cdot \{Vn - A(\theta)\nabla n\} = (r(z) - d(z)\rho(t))n,$$

where

$$(Vn - A(\theta)\nabla n) \cdot \mathbf{n} = 0 \text{ for all } z \in \partial D$$

and

$$n(0, z) = n_0(z) \text{ for all } z \in D = \Omega \times [0, 1], \text{ with } \Omega := \{C(x, y) \leq K\},$$

defining a trade-off between traits x and y .

This model, applied with the aim to investigate the emergence of dimorphism in trait-monomorphic cell populations, is intended to represent both ‘bet hedging’ in cancer populations exposed to cellular stress, and emergence of multicellularity in evolution/development, in the perspective of the atavistic theory of cancer (see above Sec 4.2). This reaction-advection-diffusion setting explores the frequent and *reversible* phenomenon of *epimutations* (due in particular to the reversible graft of methyl and acetyl radicals on DNA and histones, changing the expression of genes without altering the DNA by any mutation in the sequence of bases) in very plastic cancer cell populations - and also, in the early stages of animal development from a zygote to a multicellular individual, when evolving cell populations are also plastic, i.e., frequently capable of differentiations, de-differentiations and transdifferentiations, all reversible phenomena - in isogenic cell populations, i.e., without mutations. How such (usually costly, responding to life-threatening cellular stress) reversible phenomena may, under prolonged environmental evolutionary pressure, lead to rare mutations yielding - usually locally in Cartesian space - new strains actually found in tumours, is to the best of our knowledge a completely open domain of research. In principle, transitions from frequent reversible epimutations to rare established mutations could naturally be studied by piecewise deterministic Markov processes (PDMPs). Using the framework of constrained Hamilton-Jacobi equations mentioned below is another possibility, developed in the next paragraph.

The constrained Hamilton-Jacobi equation. For phenotypically structured equations representing large populations under the pressure of selection, it has been established that a class of asymptotic limits are the constrained Hamilton-Jacobi equations [152, 74]. This is the case for the rare mutations limit or for highly concentrated initial data in models as (5). In that case, and including mutations, the problem is to find the solution $S(t, x)$, and the Lagrange multipliers $(\rho(t), \varphi(t))$ such that

$$\partial_t S(t, x) = R(x, \rho(t), \varphi(t)) + |\nabla S(t, x)|^2, \quad \max_x S(t, x) = 0, \quad \forall t \geq 0.$$

In this framework, an open question is to understand how this limit equation is able to represent the transition from monomorphic (the maximum of $S(t, \cdot)$ is achieved at a single point) to dimorphic populations (the maximum of $S(t, \cdot)$ is achieved at two points). Is this as smooth as observed in numerical simulations including mutations or does branching emerge from a small, but growing mutant population?

3.3.2 Around graphon dynamics

MUSCLEES permanent members involved: Nastassia Pouradier Duteil

As introduced in Section 3.1.1, a possible way to describe infinite-dimensional non-exchangeable particle systems is the so-called graphon equation (2). In this equation, the particles' non-exchangeable nature comes from the dependence of the interaction function ϕ on the particles' "continuous index" s : often, $\phi(s, s', x(t, s') - x(t, s)) = \sigma(s, s')\tilde{\phi}(x(t, s') - x(t, s))$, where the function σ , known as "graphon", encodes the graph relation between the continuous particles. Whereas in Section 3.1.1, we focus on deriving the graph limit equation as a mesoscopic limit of particle systems, here we propose to analyse further this graph-limit framework, and to use it to investigate open problems (more specifically, in control theory) that have so far eluded the community in other frameworks.

Graphon Control for Consensus. One of the main questions regarding the finite-dimensional particle system (1) involves understanding its large-time asymptotics, and, more specifically, finding necessary and sufficient conditions on the underlying network (encoded in the functions $\phi_{ij}(x_j - x_i) = \sigma_{ij}\tilde{\phi}(x_j - x_i)$) for convergence to consensus. This is a highly non-trivial problem, even if sufficient conditions are known (for instance, connectedness of the underlying graph). Related to this problem, many communities are interested in *controlling* system (1) in order to achieve consensus. Generally, the control is introduced as an additive term u_i , so that (1) becomes: $\dot{x}_i(t) = \frac{1}{N} \sum_{j=1}^N \phi_{ij}(x_j(t) - x_i(t)) + u_i(t)$. This amounts to influencing each individual's trajectory (or that of a selection of individuals, referred to as "leaders") in order to drive the group to the desired state. However, here, we propose to embrace a different approach and act instead on the network itself, that is on the coefficients σ_{ij} . Due to the combinatorial complexity of the problem in its discrete setting (1), we will instead study the continuous graphon dynamics (2) and consider the following control problem: Which interaction functions $\sigma(s, s')$ allow to reach consensus most efficiently? This work is conducted in collaboration with Nathalie Ayi, Laurent Boudin and Emmanuel Trélat of Sorbonne University's Jacques-Louis Lions Laboratory.

Measure theoretic generalisation of graphon dynamics. Another description of system (2) would involve introducing a particle density $\mu(t, x, s)$ describing the probability of finding particle with continuous index s at position x at time t . Given a reference measure $\omega \in \mathcal{P}(I)$ encoding the individual statuses of the initial distribution of agents, we define measure graphons as Cauchy problems of the form

$$\partial_t \mu(t, x, s) + \nabla_x \cdot (v(t, \mu(t, \cdot, \cdot), x, s) \mu(t, x, s)) = 0,$$

with $\mu(0, \cdot, \cdot) = \mu_0 \in \mathcal{P}(I)$ satisfying $\pi_I \# \mu_0 = \omega$ ($\pi_I \#$ denoting the projection onto the first marginal), and $v : [0, T] \times \mathcal{P}(I \times \mathbb{R}^d) \times I \times \mathbb{R}^d$ is a non-local velocity field. If the reference measure is given by $\omega(s) = \frac{1}{N} \sum_{i=1}^N \delta(\frac{i}{N} - s)$, one recovers a discrete particle system of the form (1). On the other hand, if the reference measure is given by the Lebesgue measure $d\lambda$ on I , μ_0 models a continuum of agents with evenly distributed weights. The flexibility of this modeling approach is that it can allow us to model situations in which agents are given different weights, for instance $\omega(s) = \psi(s)d\lambda(s)$, for some function ψ . It also allows to model a crowd composed of leaders and followers, for instance with $\omega(s) = \frac{1}{N} \sum_{i=1}^N \delta(s - \frac{i}{N}) + d\lambda(s)$. The first aim of this project, conducted in collaboration with Benoît Bonnet (LAAS-CNRS, Université de Toulouse) will be to prove the well-posedness of such an equation, which is not straightforward as we impose no regularity of the vector field v with respect to the continuous index s . We will also extend this model to describe population transfers, by introducing a source term in the right-hand side.

3.3.3 Analysis of non-local advection-diffusion models for active particles

MUSCLEES permanent members involved: Luca Alasio

Systems of self-propelled interacting particles provide an individual-based description of the motion of agents ranging from bacteria to colloidal surfers [148, 170]. Different approaches to the derivation of macroscopic equations from particle dynamics have been considered, and the corresponding limit PDEs exhibit a variety of possible structures and behaviours [69]. This work is concerned with the analytical

study of some of the above-mentioned PDE models, focusing on regularity and convergence to stationary states. The simplest example is given by the following non-local advection-diffusion equation:

$$\partial_t f + \text{Pe} \operatorname{div}((1 - \rho) f \mathbf{e}(\theta)) = D_e \Delta f + \partial_\theta^2 f, \quad (5)$$

where $\rho(t, x) = \int_0^{2\pi} f(t, x, \theta) d\theta$ is the *angle-independent density* and $\mathbf{e}(\theta) = (\cos \theta, \sin \theta)$, with periodic boundary conditions both in the space variable $x \in (0, 2\pi)^2$ and the angle variable $\theta \in (0, 2\pi)$. The constant parameters $\text{Pe} \in \mathbb{R}$ and $D_e > 0$ are called the *Péclet number* and *spatial diffusion coefficient*, respectively. Further details and a preliminary existence theory can be found in [68]. In collaboration with Simon Schulz (SNS Pisa) and Jessica Guerand (U. Montpellier), we have proven regularity properties, the Harnack inequality, and exponential convergence to stationary states for weak solutions of equation (5). We apply De Giorgi's method and differentiate the equation with respect to the time variable iteratively to show that weak solutions become smooth away from the initial time. This strategy requires that we obtain improved integrability estimates in order to cater for the presence of the non-local drift. The instantaneous smoothing effect observed for weak solutions is shown to also hold for very weak solutions arising from merely distributional initial data; the proof of this result relies on a uniqueness theorem *à la* Michel Pierre for low-regularity solutions. The convergence to stationary states is proved using the method of contractive stochastic semigroups (Doebelin–Harris approach), taking advantage of the aforementioned Harnack inequality. This is the first step towards the study of more sophisticated models, for example we are interested in the following:

$$\partial_t f + \text{Pe} \operatorname{div}((1 - \rho) f \mathbf{e}(\theta)) = D_e \operatorname{div}((1 - \rho) \nabla f + f \nabla \rho) + \partial_\theta^2 f, \quad (6)$$

where the diffusion terms may degenerate to zero. Its microscopic dynamics corresponds to a discrete jump process in position and a continuous Brownian motion in angle. The numerical exploration in [69] shows interesting phase separation effects which connote further analytical challenges.

3.3.4 Analysis of systems with cross-diffusion

MUSCLEES permanent members involved: Luca Alasio

Cross-diffusion systems are related to several models in Mathematical Biology and in Kinetic Theory, for example the SKT model in Population Dynamics [166], tumour growth models [81], and multi-species agent-based models [40]. In collaboration with M. Bruna, S. Fagioli and S. Schulz, we have been studying a family of PDE systems with dominant degenerate diffusion, plus cross-diffusion and drift terms. Existence, uniqueness, stability and long-time asymptotics for related systems with standard diffusion have been established in the literature, however the case of degenerate diffusion is considerably harder and requires the development of new techniques. For example, a class of systems with degenerate diffusion has been recently studied taking advantage of their gradient flow structure (in the Wasserstein sense) [114, 73]. This structural condition is not always satisfied and we aim to develop alternative approaches under less restrictive assumptions. This is possible thanks to the combination of functional analytic techniques (compactness, lower semi-continuity), Lyapunov functionals, and fixed point results. Study of the long-time asymptotics and stationary states is ongoing. The next steps include further exploration of the connections between degenerate-parabolic and hyperbolic systems. Splitting methods constitute a promising research direction, leading to challenging questions on suitable BV estimates for the solution. We also consider the behaviour of solutions when one species is “frozen”, i.e. it does not evolve in time. Such species acts as a spatially heterogeneous obstacle to the evolution of the other components. Finally, efficient model comparison requires new continuous dependence results allowing the study of non-local terms such as interaction potentials describing collective behaviour (in the absence of strong parabolicity).

3.4 Axis 4 – Mathematical epidemiology

MUSCLEES permanent members involved: Pierre-Alexandre Bliman, Benoît Perthame

Epidemiology is “the study of the spread of diseases, in space and time, with the objective to trace factors that are responsible for, or contribute to, their occurrence” [88]. We address here this issue with a

specific control-theoretic flavor: we are interested not only on modeling of infectious diseases [48, 117, 67], but also control and observation issues. Two different directions of research are developed below, corresponding to the two topics described in Section 4.3.

3.4.1 Vector-borne diseases

MUSCLEES permanent members involved: Pierre-Alexandre Bliman, Benoît Perthame

Modeling, analysis and control design of release strategies in metapopulation setting In order to take into account the disturbing effects of migration of mosquitoes between treated and untreated areas, we plan to study multi-site configurations, in meta-population approach. A meta-population is ‘a set of local populations within some larger area, where typically migration, from one local population to at least some other patches, is possible’ [110]. The meta-population models are systems of differential equations defined on graphs whose vertices represent the different patches, and whose edges specify the population transfers [50]. So far, such setting has been used mainly to model human movements [54, 65], the latter being usually responsible for disease transport at a much greater distance than mosquitoes. While most studies focus on the analysis of epidemiological models according to the values of their parameters, fewer study the issues related to disease control through elaborated actions, specified through either open- or closed-loop (i.e. based on measurement) strategies. We will adopt this perspective to define effective methods of release of sterile males, or of mosquitoes infected on purpose by the bacterium *Wolbachia*.

We consider a class of controlled meta-population models under the general form

$$\dot{x}_i = F_i(x_i, x_{S,i})x_i - ((L \otimes I)x)_i + m_i(t), \quad \dot{x}_{S,i} = \Lambda_i(t) + F_{S,i}(x_i, x_{S,i})x_i - ((L_S \otimes I)x_S)_i + m_{S,i}(t), \quad (7)$$

$i = 1, \dots, n$. For studying e.g. the Sterile Insect Technique (see [64]), x_i and $x_{S,i}$ are vectors whose components represent the numbers of wild and sterile mosquitoes in the patch i , according to their sex and life stage. The matrix-valued functions $F_i, F_{S,i}$ represent globally the birth and death processes as they occur locally in patch i , including the effects of interaction between the two populations (during mating and early development), which allows to envision reduction or extinction of the targeted population. The $n \times n$ -matrices L, L_S are Laplacian matrices that model the displacement of the mosquitoes from one patch to the others, and external migrations are modeled as additive perturbations $m_i, m_{S,i}$.

The rate of release of sterile males in patch i per time unit is $\Lambda_i(t) \geq 0$. Generally speaking, our objective is to derive release strategies ensuring elimination or control of the population under certain level in some of the targeted patches, and fulfilling adequate constraints (due e.g. to limited production rate). This amounts to determine the number of sterile males to release in these specific subdomains, but also possibly in connected subdomains playing the role of ‘buffer zones’. The basic reproduction number, which must be kept low to avoid epidemic burst, is related to the linearized behavior of the system in the vicinity of the disease-free trajectory. Seeing migration as a structured perturbation of this linear system, we intend to analyze the robustness of thresholds defined based on this number, and to propose control laws aiming at allocating the releases in a complex, heterogeneous, metapopulation model, so that they reduce the epidemiological risk in the worst perturbation configuration. We plan to exploit the peculiarities of the positive systems to tackle these robust control issues [167, 101, 80].

Optimization of killing and replacement policies in heterogeneous contexts Most mathematical modeling of killing and replacement strategies, as the use of the bacterium *Wolbachia*, focus on spatially homogeneous systems and propose to model the time dynamics of mosquito populations thanks to the study of differential systems. In this setting, the influence of the releases on the time dynamics of mosquito populations has already been extensively studied (see e.g. [45] for SIT (Sterile Insect Technique) and [106, 104] for replacement strategy by *Wolbachia*). However, for practical applications, it is important to take into account the space variables and other phenomena like seasonality, heterogeneities, migration... Moreover, the use of optimal control theory in coordination with actors in the field should be very interesting to improve the efficiency of the strategies and to minimize their cost.

The study of the dynamics taking into account the spatial variable has started only recently. For the replacement strategy a first simple model of the spatial spread of *Wolbachia* was proposed by Barton

& Turelli in [60]. In their simplified approach, the total population is assumed to be constant and the dynamics of the proportion of infected mosquitoes $u \in [0, 1]$ is governed by a bistable reaction-diffusion equation. Using such a simple one-dimensional model, a first attempt to study the influence of spatial heterogeneities in the spread has been proposed in [143]; in particular, it has been proved that strong variations in the densities of wild mosquitoes, due for instance to vegetation, may block replacement. Up to our knowledge this is the only study of this kind for replacement strategy.

Our aim here is to perform well-fitted killing or sterile insect strategies so that blocking phenomenon occurs. In a mathematical language, we consider the following bistable reaction-diffusion equation

$$\partial_t u - \partial_{xx} u = g(u) - \mu(x)u \mathbf{1}_{\{0 < x < L\}} \text{ in } (0, \infty) \times \mathbb{R} \quad (8)$$

where g is a bistable reaction term (such as $g(u) := u(1-u)(u-\theta)$ for example), and the killing term $\mu(x)\mathbf{1}_{\{0 < x < L\}}$ represents a killing strategy with a rate $\mu(x)$ over $(0, L)$.

When $\mu(x) = C$ is constant over $(0, L)$, it has been proved in [43] that if C is large enough, that is, if one performs a sufficiently sharp killing strategy in a localized area, then there exists a heteroclinic steady state connecting 1 to 0, that is, a blocking phenomenon occurs. We then have two questions that come up very naturally : one concerning how to optimize this strategy, and a second concerning how to extend these results to higher dimensions.

In particular the two-dimensional problem is very relevant for field interventions where one would have to protect a certain area (e.g. a village) from a wave of mosquitoes arriving from an infected area (e.g. a swamp). Beyond the construction of a static barrier in the two-dimensional setting, it would be interesting to show the effectiveness of a rolling carpet strategy (generalizing the results of [43]) to expand a mosquito free area and progressively clear the mosquito population in a region (for instance a whole island or a pre-defined intervention region).

In order to optimize the killing strategies, we need to determine what is the best μ , among the class of admissible death rates satisfying $0 \leq \mu \leq C$, guaranteeing the existence of a heteroclinic solution connecting 0 to 1, and with minimal integral $\int_0^L \mu$? Does it exist? Is it "bang-bang" (that is, $\mu = 0$ or C almost everywhere)? This problem has recently been solved when there is no constraint on the support (that is, $L = +\infty$) in [34]. We want to address it when $L < +\infty$ and with direct methods, enabling us to consider more general dependence with respect to the growth rate.

In a second step, we would like to optimize the sterile male strategy. The mathematical model for this strategy is

$$\partial_t u - \partial_{xx} u = \frac{u}{u + \mu(x)\mathbf{1}_{\{0 < x < L\}}} g(u) \text{ in } (0, \infty) \times \mathbb{R}, \quad (9)$$

that is, $\mu(x)$ represents our input of sterile males, that decreases the fecundity.

We aim at using our recent progress on similar topics in order to solve these questions [99, 133, 144].

Optimisation of release strategies in time-varying setting - seasonality We now want to take into account seasonality (i.e. rainfall, humidity and temperature variations) in our models, since it is known to play a key role in the dynamics of mosquito populations.

Some weather dependent mosquito models have been developed, mainly with Temperature-dependent parameters (see for instance [98, 75] and references therein) and very few with temperature and rainfall-dependent parameters (see [172] and references therein). However, in general, these last models are quite complex: they relied on statistical approaches, and on the user's subjective choices, such that the calibration (of many parameters), with respect to the environmental parameters, is not generic and might not be able to provide a unique set of valuable values. We firmly believe that simple (but not too simple) models can rapidly provide useful and reliable information to help field experts to manage vector control campaigns.

We will first adapt the Barton-Turelli model [60] in order to take into account seasonality effects. This leads to the equation

$$u_t - u_{xx} = \mu(t)g(u),$$

where g is a bistable reaction term and μ is T -periodic and positive. Alikakos, Bates and Chen [42] proved the existence and attractivity of pulsating traveling waves, that is, time-global solutions of the form $u(t, x) = U(x - ct, t)$ with $U(-\infty, t) = 1$, $U(+\infty, t) = 0$, and $t \mapsto U(z, t)$ is T -periodic for all $z \in \mathbb{R}$,

under some hypothesis on the non-existence and stability of intermediate steady states, that we believed to be satisfied in our framework.

Ding and Matano [91, 90] recently proved that the solutions of the Cauchy problem always converges as $t \rightarrow +\infty$ for compactly supported initial data. Moreover, Polacik described further [154] the basins of attraction of the steady states. Namely, consider an initial datum $1_{[-L, L]}$ at time t_0 (more general families of initial data could be considered), then there exists a critical size $L = L^*(t_0)$ such that the solution of the Cauchy problem converges to 1 at large times if $L > L^*(t_0)$, while it converges to 0 if $L < L^*(t_0)$.

We will then investigate the dependence of this critical size $L^*(t_0)$ with respect to t_0 and try to characterize the best time of the year to release Wolbachia infected mosquitoes, that is, the t_0 minimizing $L^*(t_0)$. This is a difficult problem, since $L^*(t_0)$ is defined implicitly. First, we believe we could characterize the quantity $L^*(t_0)$ through some adjoint function by using some Pontryagin maximum principle style arguments. Second, such a characterization might help to construct a relevant algorithm in order to investigate this problem numerically. Lastly, we could investigate the following related problem: maximize $\int_{\mathbb{R}} u(t_0 + T, x) dx$ with respect to $u(t_0)$ in a given class of functions. This problem has been addressed in the homogeneous framework by Nadin and Toledo [144].

3.4.2 Infectious diseases

MUSCLEES permanent members involved: Pierre-Alexandre Bliman

Using reinfections for identifiability and observability While the loss of immunity has been modeled and studied in the framework of compartmental models, the phenomena of reinfection, and particularly the counting of the number of reinfections, have been little studied to date. Dynamics induced by reinfections with different strains [49, 36], in presence of vaccination of incomplete efficiency [51] or with partial and temporary immunity [109] have been studied. A modified SIRS system was proposed in [116] with an infinite set of differential equations capable of counting the number of reinfections, that we extended and studied in [103]¹. In the simple case of an SIS model, this consists in ‘unfolding’ the system

$$\dot{S} = \mu N - \beta S \frac{I}{N} + \gamma I - \mu S, \quad \dot{I} = \beta S \frac{I}{N} - (\gamma + \mu) I, \quad (10)$$

where $N(t)$ represents the total population $S(t) + I(t)$, in

$$\dot{S}_i = \gamma I_{i-1} - \beta S_i \frac{I}{N} - \mu S_i, \quad \dot{I}_i = \beta S_i \frac{I}{N} - (\gamma + \mu) I_i, \quad i \geq 1, \quad (11)$$

with here $I(t) := \sum_{i \geq 1} I_i(t)$, $N(t) := \sum_{i \geq 1} (S_i(t) + I_i(t))$ and by convention $\gamma R_0(t) := \mu N(t)$. This ‘microscopic’ interpretation of the ‘macroscopic’ behavior in (10) keeps track of the number of reinfections, accounted for by the index i .

We have shown [103] that revealing this underlying structure allows to access many information on the structure of the infection numbers in the population at endemic equilibrium, and enriches drastically the capacity to identify and observe system (10). Our plan is to extend this work and study the effects of disease characteristics (susceptibility, infectivity, waning immunity...) depending upon the past number of infections, on the dynamics of the epidemics. In particular, one is interested in understanding what knowledge on these quantities can be gained by appropriate measurements. This topic is part of a more general reflection that we intend to pursue, on the observability and identifiability issues in epidemiology. Seroprevalence data are other nonstandard data of which we plan to study the benefit.

Multi-strain problems: modelling and analysis The Covid-19 pandemic has revived, by enriching and renewing them, many questions relating to understanding the dynamics of infectious diseases and the means of combating them [93]. Rapidly, the evolution of the pandemic has been shaped by two different phenomena: the appearance of variant viruses competing with the ‘historic’ virus; and the progress of the vaccination campaigns. We are interested here in analyzing the corresponding dynamics. Related contributions have been published before the appearance of Covid-19, seeking to characterize endemic

¹This type of infinite-dimensional systems is reminiscent of Becker-Döring system [96].

behavior in long time [115, 147, 59]. The first contributions published after the emergence of Covid-19 [107, 53] (see also [145]) consider, on the contrary, the shorter time scale of an epidemic episode, but describe incompletely the complex cross-immunity (complete or partial, permanent or transient) which however seems crucial.

We will also be interested by the interplay of vaccination. Usually the influence of the latter is considered on the long duration of an endemic infection [51, 66]. On the contrary, our approach here will be oriented towards the control of an epidemic outbreak. Drawing inspiration from the current pandemic, we will consider a vaccine providing an immunity different for every strain of infection, as well as the possibility of a waning protection.

We will also be interested by heterogeneous population models [95], structured in susceptibility and/or infectivity, or in number of individual contacts (for example from models of ‘effective contacts’, see [136]).

Modelling and analysis issues of the commutations in complex urban environments Modeling in pertinent and efficient way how the spread of an infection is influenced and shaped by the fact that the effective individuals are in fact individualized, is a considerable issue in mathematical epidemiology. The basic deterministic compartmental models, like the SIR model, take the step to consider homogeneous, perfectly mixed, populations, where the probability of encounter between two individuals is uniform. This ‘gas theory model’ is simple, but unrealistic when the size or the spatial extension of the population is large (which is precisely the assumptions permitting to consider deterministic models rather than stochastic ones...). Heterogeneity cannot be ignored.

Alternative points of view exist [117, 52, 50], which basically transfer the homogeneity and perfect-mixing assumption to sub-populations, defined by some structuring trait, e.g. their age, susceptibility, infectiousness, contact numbers, place of residence, etc. Adopting such point of view amounts in fact to consider perfect mixing of homogeneous sub-populations.

We are particularly interested here in how to render *mobility*, typically urban mobility, whose regular patterns aggregate various characteristics, e.g. social class, age, residence... Usually, modelling mobility is done through an Eulerian description: infection is described in every location, with sub-populations transferred from other places, leading to meta-population setting much in the spirit of (7) (but with only host population). This makes it complicated to follow the individuals of a given group along their displacements, once they have been mixed with other groups. To have this ability, it is natural to consider the groups of individuals with a given infectious status that come from location i and are present at location j at time t . This is indeed neither simple, nor economical.

In fact a Lagrangian setting seems more natural. We will adopt this view, and focus on the description, and the analysis, of epidemic spread during the perfect mixing of different homogeneous classes of the population, indexed by $p \in \mathcal{P}$. The displacements of any class $p \in \mathcal{P}$, are now integrally described by a function $l_p(t)$ that give the location of sub-population p at time t , and each class then evolves according to the presence of the other sub-populations present together at the same point, with whom cross-infection is possible. The effective location of their encounter is quite abstract: physically, it may be as well a public transport system.

We want to compare the complexity of the different modelling settings and achieve comparative study of their behavior, with regard to the value of the basic offspring number, the epidemic final size, the level of endemic equilibrium and so on.

3.5 Axis 5 – Development and analysis of mathematical models for living systems confronted with experimental data

MUSCLEES permanent members involved: Luca Alasio, Sophie Hecht, Diane Peurichard, Nastassia Pouradier Duteil

3.5.1 Individual-based models for micro-colony growth

MUSCLEES permanent members involved: Sophie Hecht, Diane Peurichard

Individual-based models allow the description of a population at the microscopic level. These models consider each particle as autonomous entities and define their dynamics according to their local environments. For this reason it is an ideal tool to confront mathematical models and experimental data. In a previous work [97], we have developed a model to study growth of micro-colonies of elongated bacteria such as *E. coli*. In this paper, bacteria are represented by spherocylinders characterized by their length, their orientation and the position of their center of mass. The motion of bacteria is supposed to be only due to steric interaction with their close neighbors to prevent the overlapping of cells during growth and division (passive motion). This repulsion is realized via a potential based on Hertzian theory. Fragmentation occurs when the increment of length of a bacteria reaches a given threshold, distributed according to an experimental law. A key aspect of the paper is to propose a model taking into account asymmetric friction and a non-uniform distribution of mass along the length of bacteria, which impact the movement of particles. These two mechanisms were shown to improve significantly the comparison between experimental data and numerical simulations, yet we failed to reproduce one of the primordial characteristics such as the high density of bacteria in the microcolony (where all the space within the convex envelope of the colony seems occupied). This property is not reproduced to date in the models proposed in the literature [97, 100].

A discussion with the experimenter Nicolas Desprat (ABCD biophysics Lab - ENS) highlighted the possible impact of the deformation of bacteria in a micro-colony. After observation, it appears that at the point of inflexion in the colony, bacteria are often curved. The small deformation observed could be the key to the dense character of the colonies and modify their global organisations. It is therefore interesting to consider the deformable character of bacteria in order to best reproduce the organization observed experimentally. To do this, many approaches are possible [113, 135]. We will consider an individual-based model where each bacterium is modeled by a string of spheres linked with spring and angular spring. This description will allow local bending for the bacterium. We will then test different modelling assumptions in order to reproduce as close as possible observed phenomena during the micro-colony growth.

After deriving the new model, we will study the influence of the different parameters and compare numerical simulations with experimental data. This work will be a collaboration with the biophysics laboratory of Nicolas Desprat, giving us access to datasets of micro-colony of strains of *Escherichia coli* and *Pseudomonas aeruginosa* growing between glass and agarose. On these datasets, segmentation has been previously performed to track individual bacteria as spherocylinder. However, the purpose of this study requires to identify bacteria as deformable solids. Thus, a first step to compare experimental data to numerical simulations will be to develop new segmentation process, adapting techniques existing for clustered nuclei. In a second part, the comparison will require the development of new tools to better quantify the evolution of the colony. Among the quantifiers we found to study the growth of bacterial structure, we found the one related to the shape of the colony. In the literature, the quantifiers used to characterize the shape often consist in comparing the colony to an ellipse. However, the colonies, although elongated, have shapes that are not necessarily ellipsoidal. To develop a new sophisticated quantifier an idea is to consider the modes of the elliptical Fourier transform of the envelope of a colony in order to characterize its shape [37]. Similar work will be done on other quantifiers characterising the local organisation, bending, four cell array arrangement, etc...

3.5.2 Energy-driven models of tissue organisation and architecture

MUSCLEES permanent members involved: Sophie Hecht, Diane Peurichard

This research axis is in the frame of a long standing collaboration with a team of biologists from RESTORE (Toulouse), which led to the ANR grant ENERGENCE (2023-2026) recently awarded to D. Peurichard. The goal here is to propose a general framework to understand the combined role of mechanics and energy exchanges in tissue development, repair and decline. To our knowledge, very few mathematical models have been proposed for tissue organization combining both energetical and mechanical interactions, while numerous evidences suggest that energy exchanges and mechanical forces can feed-back on each other at different stages of tissue life, and that large perturbations of one or the other are associated with degeneration and diseases. Therefore, we propose to build a complete framework to theoretically and numerically model the complex interplay between energy and mechanics at different spatiotemporal scales. We will focus on adipose tissue (AT) as a relevant biological model because its

architecture is relatively simple and largely dependent on energy exchanges (food supplies), and as a target with the world-wide development of obesity's epidemic.

This project will rely on a synthetic approach based on a dual use of mathematical modelling and in-vitro/in-vivo experiments. We will propose a new view of biological tissues as complex ecological/social systems whose architecture emergence is driven by few key determinants, interacting together mechanically and constantly exchanging energy/matter with their environment. We will aim to first develop individual-based models (IBM), which promises exciting theoretical and experimental challenges such as the determination of complex feedback loops between energy intakes and local growth laws, and the study of metastable states and phase transitions applied to changes in energy fluxes, modelling cafeteria diet and food deprivation. The biological calibration of the IBM via in vitro and in vivo experiments (performed at the RESTORE lab) will go through determining how energy is distributed among the different agents and their interactions. A user-friendly interface will also be developed based on the IBM and will be used to resolve some unsolved questions such as how the AT architecture is modified by the amplitude, frequency and length of energy intake modifications.

In a second aspect of the ENERGENCE project, we will tackle the important challenges contained in the derivation of a Continuum Model (CM) from our IBM, in order to obtain a computationally efficient CM containing as much as possible the mechanisms of the microscale. Numerous technical and conceptual barriers will have to be lifted in this more theoretical part of the project, due to the nature of our IBM, the presence of correlations between the agents at the microscale and the complex mechanical and energetical feedback loops. If successful, this model will be the first continuum description of two immiscible fluids composed of cells and (anisotropic) fiber elements obtained from an agent-based description, and promises exciting new and invaluable insights into how specific microscopic effects translate at the macroscale. Our CM will rely on the complete and valid IBM and, if successful, will enable to study the interplay between energy balance and whole tissue architecture during a lifespan and at the organ scale (long-term and large-scale effects).

The impacts of the highly interdisciplinary ANR project ENERGENCE are twofold. On the biological viewpoint, the energy/mechanics coupling view of tissue emergence and changes will provide a new understanding of aging at different spatio-temporal scales that will pave the way for new rejuvenative therapies to treat age-related dysfunctions, and also impact the tissue engineering field in which metabolism remains often overlooked. On the mathematical viewpoint, the ENERGENCE project will provide involved numerical treatments and innovative sensitivity analysis methods for IBM, and tackle important theoretical challenges related to the derivation of continuous biphasic fluid models from IBM, promising exciting new understanding of the micro- macro- link. Although focused on adipose tissue, the theory and the mathematical modelling developed in this project will be general enough to apply to other biological systems such as muscle tissues and, if successful, will constitute the basis for collaborations with other European research teams through the building of an ERC Synergy.

The ENERGENCE project involves several members of our project team MUSCLEES and will be completely integrated in the team activities: the development and parametric analysis of Agent-Based Models will rely on the expertise of S. Hecht together with D. Peurichard, the challenges of deriving PDE models from IBM will be completely integrated in Axis 1 of the team (together with S. Hecht, N. Pouradier-Duteil, B. Perthame), and the analysis of the resulting PDE models will be enriched by the results of the team in Axes 2 and 3. By combining biological experiments and mathematical modelling to study the multi-scale and temporal effects of metabolism and mechanics, the ENERGENCE project will be one of the most applicative activities of MUSCLEES, and, if successful, will represent a significant step forward to understand the emergence of metastable organized structures in living matter.

3.5.3 A traffic model for the interkinetic nuclear migration (IKNM)

MUSCLEES permanent members involved: Sophie Hecht

In the past years, members of MUSCLEES have studied the cell cycle with age structured transport equations [78, 63]. These models considered the transition between the different phases of the cell cycle depending of the cell age. However, recent works [111] have highlighted that the transition between these phases are likely to be impacted by the moving positions of the nuclei. Thus, we will introduce a space structured model in order to consider the influence of the movement of nuclei on the cell cycle and its

transition.

As mentioned in section 4.2, in pseudo-stratified epithelium, nuclei undergo IKNM during the cell cycle. Namely, nuclei in the phase G2 move toward the apical membrane to divide while nuclei in G1 move in the opposite direction to return in the depth of the tissue. The nuclei in S do not have a clear direction in their motion. This phenomenon can be viewed as a one-dimensional traffic problem. Therefore we will model this system with a 3 species, bidirectional PDE system. The transition between the phases will be modeled by reaction terms and boundary conditions. We will study the new system of equations and answer the classical question of existence and uniqueness. Additionally we will focus on the long time behaviour, understanding the range of parameters leading to a slowdown of growth with realistic distributions of the nuclei in the different cell phases.

The model will be compared to experimental data provided by Jean-Paul Vincent's laboratory in the Francis Crick Institute (Epithelial Cell Interactions Laboratory). Existing data of the distribution of the nuclei in the different phases in the apical/basal axis at different times of development will allow to tune the different parameters of the model. The model will then allow us to test hypothesis proposed in a previous work [111] where we developed a microscopic model. In this paper, we conjectured a mechanism to explain the transition between G1 and S phase but were limited in the test due to the small number of nuclei we could consider due to computational cost. The new model we proposed would allow a further study of the influence of this mechanism.

3.5.4 Models for collective behavior in gregarious fish

MUSCLEES permanent members involved: Nastassia Pouradier Duteil

Many living systems exhibit fascinating dynamics of collective behavior during locomotion, from bacterial colonies to human crowds. The emergence of such complex spatio-temporal patterns can be described using local, short-range interactions between nearest neighbours. Fish schools are a typical example of this kind of self-organization: in order to perceive the position or kinematics of close neighbors, fish rely essentially on vision and sensing of hydrodynamic disturbances. However, the role of each of these senses is not clearly elucidated today. Our objective is to model the visual interaction within a group of animals experiencing a dynamic visual disturbance (temporal variation of the ambient light intensity). Previous experiments have revealed a correlation between illumination and group cohesion, measured in terms of geometric parameters (polarization, rotational moment, nearest-neighbour distance).

In collaboration with a team of experimental physicists of the PMMH laboratory of ESPCI and Sorbonne University, we aim to study this behaviour using mathematical models of collective motion. Numerical simulations could elucidate the influence of illumination on the field of view of the fish (distance or angle of the cone of vision), and the role of density in the emergence or not of strong rotational motion when increasing light intensity. The model used will be a variation of the Persistent Turning Walker model, a system of coupled ordinary differential equations in which each fish's angular velocity evolves in time due to alignment with its closest neighbors, attraction towards the group, and random perturbations.

3.5.5 Mathematical models of retinal biochemistry

MUSCLEES permanent members involved: Luca Alasio, Benoît Perthame, Philippe Robert

Modelling the canonical visual cycle. The visual cycle is the process allowing rod cells to return to the dark state after exposure to light. The main biochemical contributors are: (1) isomers of *vitamin A*, which is the essential photosensitive molecules [120]. They interact with RPE enzymes and they are transported back to the rod, where they recombine with opsins; (2) *rhodopsins* (densely packed membrane proteins), consist of an opsin, embedded in the lipid bilayer of cell membranes, forming a pocket where vitamin A lies; all-trans retinal dissociates after photo-excitation [141]; (3) *enzymes, binding proteins and membrane transporters* responsible for the main steps of the visual cycle (further details in [120]). The current “gold standard” in terms of mathematical description of the visual cycle was established in [122], where Lamb and Pugh derived a simplified ODE system for the evolution of the concentration of rhodopsin. The only two unknowns in their model are total concentrations of opsin and of 11-cis-retinal (no space

dependence). The specific geometry of photoreceptors requires a more sophisticated model to represent the visual cycle accurately. The derivation of new models for AMD and STGD will have the model in [39] as starting point. Our model refinement will provide an improved description of all-trans-retinal diffusivity, which is hydrophobic and can diffuse freely into the aqueous cytoplasm only in presence of a suitable binder. On the other hand, all-trans-retinal can diffuse on the lipid membrane discs. We plan to derive effective equations independent of single membrane discs (starting from the homogenisation results in [108]). The non-uniform distribution of rhodopsins and illumination will reflect into non-uniform and/or stochastic terms at the level of membrane discs.

Modelling the formation of A2E. A2E is a toxic byproduct of the visual cycle. We plan to study both individual-based models and macroscopic differential equations representing the condensation of retinal near membrane discs. We plan to strengthen our collaboration with C. Schwarz (U. Tübingen) with regards to new measurements from two-photon ophthalmoscopy. We plan to derive a stochastic model for the evolution of the concentration of A2E in membrane discs, outer segments and RPE cells. Two molecules of vitamin A are needed for A2E production, hence quadratic reaction terms are expected. Rescaling the model in time appears to be necessary since the probability of formation of A2E is low and accumulation takes place over long time scales (years). This relates to the long-time asymptotic analysis, with a possible reformulation in terms of ODEs/PDEs and coupling with our model of the visual cycle. Accumulation of A2E in RPE cells is a consequence of phagocytosis of outer segments, thus it will be useful to couple our model with those obtained in [129] for retinal metabolic regulation. The starting point will be a numerical exploration, setting the base for parameter tuning.

3.5.6 Modelling the Retinal Pigment Epithelium in Age-Related Macular Degeneration

MUSCLEES permanent members involved: Luca Alasio, Benoît Perthame

Biomedical context. We visually perceive the world in a way that is heavily dependent on sophisticated and delicate biochemical mechanisms, and their disruption has a detrimental impact on a human's life. *Age-related Macular Degeneration* (AMD) affects the centre of the visual field and it has become increasingly prevalent in our ageing society, thus causing a spike of academic and pharmaceutical interest. Globally, there will be nearly 300 million AMD patients by 2040 [178], resulting in a major public health problem (we focus on dry, non-neovascular AMD, not on the wet, vascular type). Interdisciplinary collaboration is crucial in order to deepen the understanding of AMD; we are currently working with M. Paques (H. Quinze-Vingts, SU) and his group, L. Almeida (CNRS, LJLL). We focus on the layer of *retinal pigment epithelium* (RPE) in the retina.

The RPE cell layer supports photoreceptors providing nutrients, contributing to the visual cycle and to phagocytosis of outer segments [139]. RPE cells enable photoreceptor cell renewal, which is essential because outer segments contain high levels of unsaturated lipids, [61] subject to oxidation in the presence of light, as well as other (potentially harmful) photo-reactive molecules [123, 72]. Our goals include: (1) modelling RPE senescence, discontinuity and degeneration in AMD; (2) studying the actin cable dynamics for the closure of small lesions; (3) exploring the hypothesis of myosin inhibition and senescence to explain large lesions; (4) exploring the links with drusen formation and A2E accumulation, which have been connected to macular degeneration and other lesions [168], as well as changes in RPE cell morphology and organisation [171].

Modelling and simulation of the RPE mosaic in AMD. As AMD progresses, the tissue deteriorates and larger, permanent lesions can occur. We are working under the hypothesis that the discontinuity enlargement is related to the cumulative effect of the tissue bio-mechanics and retraction forces of each cell around the lesions. RPE cells do not typically reproduce and, in normal conditions, if one of them dies the neighbours expand to fill the gap to maintain the tissue integrity. We will model the formation of lesions and explore how RPE dysfunction, oxidative stress, and chronic inflammation contribute to the development and growth of lesions. The model will include the evolution and impact of varying lesion sizes, as well as the role of drusen. A suitable starting point for the model derivation are the so-called *multi-phase thresholding scheme* (first introduced for one phase by Merriman, Bence and Osher in 1992),

representing the tensions and the actin cable dynamics through motion by mean curvature (see e.g. [138, 102]). A complementary modelling approach is related to a new family of structured models obtained by S. Hecht and D. Peurichard involving both position and radius variables for each cell.

The group of Prof. Michel Paques (Hopital National de la vision Quinze-Vingts) is performing experiments and collecting data from high resolution in-vivo and ex-vivo retinal imaging, in animals and humans [149]. These include histological markings allowing to detail the size and morphology of each cell of the retinal pigment epithelium that can be used for a direct comparison with in silico models. AMD can be studied at different space and time scales. The connection between different scales will be modelled taking into account several contributing factors, including the following: (1) regions of hypo- and hyper- contracted cells will be studied in relation to myosin dysfunction; (2) feedback between inflammatory host response and accumulation of molecular damage [163]; (3) migration of peripheral RPE cells to compensate for the loss of central RPE cells due to ageing [86]; (4) detrimental effects of excessive concentrations of all-trans retinal and A2E [169, 38, 130]; (5) distinction between normal ageing effects, senescence, and pathological formation of drusen [137].

4 Application domains

- Section 4.1 explores general questions related to the *Emergence of collective phenomena*;
- Section 4.2 considers special occurrences of these questions in the context of *Living biological tissues*, particularly for tissue growth and development and cancer cell proliferation;
- Section 4.3 presents *Mathematical models for epidemic spread*.

These three sections are of course not airtight, and multiple links can be drawn between them. Indeed, Section 4.2 is concerned with *Living biological tissues*, whose behaviour by nature also contain aspects of collective dynamics (Section 4.1). Similarly, collective behaviour is present in the epidemiological issues developed in Section 4.3. We have in mind to exploit and deepen the corresponding ties, between different topics and between the team members.

4.1 Emergence of collective phenomena

How do globally organized patterns emerge in a system driven only by local interactions? Such behavior is ubiquitous in many systems, and understanding the emergence of patterns has numerous applications in biological or social networks, cells' organization in tissues, and neurosciences. Collective dynamics models have been developed to explain the emergence of global patterns in a population from local interaction rules between neighboring agents — a fascinating effect called “self-organization” (see [55, 82, 85, 112, 174] and references within). This general topic breaks down in several more precise subjects.

Biological and social networks Collective phenomena can emerge from local interactions in biological and social networks. Social animals tend to organize themselves into highly coherent groups, such as schools of fish, bird flocks, swarms of insects, herds of sheep, or even human crowds. Much research is currently undertaken in various scientific communities (including biologists, sociologists, computer scientists and mathematicians) to understand how and why certain types of collective behavior (such as flocking [82], alignment [174], or consensus [112]) are observed. Despite this surge of interest, many questions remain open and our research aims to address some of them. In particular, can the emergence of global behavior such as consensus be predicted from initial conditions? Are there sufficient or necessary conditions on the interaction network ensuring convergence to a coherent asymptotic state?

Bacterium colony growth Bacteria are unicellular organisms, whose biomass exceeds that of all other living organisms, and on which our survival is dependent. In the human body, the number of bacteria almost equals the one of cells. Despite the fact that most of the bacteria are harmless, some pathogenic strains are the cause of infectious diseases such as tuberculosis, cholera, bacterial meningitis, and salmonella among others. It makes it essential to understand in which way bacteria multiply and disrupt the normal functions of our bodies. Numerous studies have been done to grasp how a bacterium,

from a single organism, develops into organized micro-colonies and biofilm structures [97, 100]. Still, some phenomena are not explained. At early stages of the development, going from one bacterium to a structured micro-colony, we will investigate mechanisms leading to poorly understood properties, such as the elongated shape of the colonies, the four cell arrays arrangement and the high density [164]. At latter stages of development, we will question the impact of these microscopic phenomena on macroscopic structures.

Cell population dynamics: the classic homogeneous case Self-organization is often observed in cell population dynamics, both within a single cell population or between two or more distinct populations. Interestingly, the forward and backward epithelial-mesenchymal cellular transitions (EMT-MET), which play a crucial role in embryonic development, tissue repair and cancer metastasis, can be modeled either as a transition between three homogeneous cell populations (epithelial, mesenchymal and hybrid), or as the evolution of a single heterogeneous cell population, structured by an epithelial-to-mesenchymal phenotype. In order to achieve self-organization, cell populations often display local communication strategies, whether it be within a cell population or between different cell types. For instance, *chemotaxis* refers to the directed movement of cells in response to a chemical gradient produced by neighbouring cells (Keller-Segel-type models). *Mechanosensing* is another well-established cell-cell communication strategy, that relies simply on mechanical constraints. Communication between cells can also be driven by the secretion and subsequent *binding of ligands*, as in the case of the EMT-MET [173].

When considering interactions between several cell populations, interactions may be mutualistic as in the case of cancer cell populations and trophic healthy cell populations (breast cancer and adipocytes [155], or leukaemic cells and supporting somatic cells [146] for instance), or cells can be in competition (in particular tumour-immune interactions [44, 127]). This latter aspect will continue to be one of our present objectives in modelling cancer cell populations. We will address it in the sequel in the adapted framework of heterogeneous cell populations.

Cell population dynamics: heterogeneous cell populations and trait-structured models One of the main challenges when modeling a single cell population is to take into account the biological variability, aka intrinsic *heterogeneity*, of the population. A now classic way of modelling, introduced in adaptive dynamics, firstly in theoretical ecology, then in cell population dynamics, is to use continuous trait (or phenotype)-structured population dynamics settings.

How to deal with them depends on the heterogeneity question at stake and on the choice of traits used to structure an adaptive cell population: should they be well-identified biological molecules or gene expression determinants, (e.g., specific to a given drug and a given population under drug exposure [157])? Or should they be hidden, but general and linked to cell fates, in other words *potentials to develop such and such a trait or phenotype* [46, 76, 77, 121, 165], as in theoretical ecology models (viability, fecundity, plasticity of individuals)?

Due to the lack of measurable markers of relevant biological variability (i.e., heterogeneity) recorded in continuous time from experimental teams, we are often bound to stick to their more hidden and abstract version. However, this will certainly never free us from keeping watch over incoming biological developments amenable to at least partly identify possible molecular markers of such *a priori* abstract phenotypes.

Of note, in the framework of adaptive structured cell population dynamics, emergence of phenotypes is always *reversible*. Which means that, according to changes in the cell population environment, new phenotypes may appear, and they can equally disappear if the environment changes. In other words, we address the question of cell *differentiations*, not mutations, recalling that cell differentiations occur in an *isogenic* cell population, not modifying its genome, only gene expressions due to the action of epigenetic enzymes, whereas mutations change the genome by modifying its constituting base pairs in the sequences ATGC.

Some of the questions that we aim to address by means of mathematical modelling by structured population models, in particular in the context of the EMT-MET (reversible phenotype transition) and phenotype divergence (reversible evolution between phenotype monomorphism and dimorphism) are the following: Can different cell phenotypes co-exist at the same time in a population, and if only some of them persist, which are they? What effect do growth and death of the population have on the phenotype

distribution of the population? What effect do growth and environmental changes have on transient phenomena, such as the hysteretic behaviour observed in the Epithelial-Mesenchymal Transition, and on asymptotic behaviour of the cell populations? What role can be attributed to phenotype *plasticity* in such transient or established phenomena?

Neuroscience In neuroscience, learning and memory are usually associated with long-term changes of connection strength between neurons. In this context, *synaptic plasticity* refers to the set of mechanisms driving the dynamics of neuronal connections, called *synapses* and represented by a scalar value, the *synaptic weight*. A Spike-Timing Dependent Plasticity (STDP) rule is a biologically-based model representing the time evolution of the synaptic weight as a functional of the past spiking activity of adjacent neurons.

There is a rich mathematical literature on biological neural networks but mainly when the connectivity of the network is fixed, i.e. when the synaptic weights are constant. In a series of articles [160, 161, 159, 175], a new, general, mathematical framework to study the phenomenon of synaptic plasticity associated to STDP rules has been introduced and analyzed for a system composed of two neuronal cells connected by a single synapse whose weight is time-varying.

Experiments show that long-term synaptic plasticity evolves on a much slower timescale than the cellular mechanisms driving the activity of neuronal cells. A scaling model has been introduced and limiting results have been proved. The central result obtained is an averaging principle for the stochastic process associated to the synaptic weight.

We plan to investigate mathematical models of plastic synapticity in a more general network. The question is of determining under which conditions the coordinates of the matrix of synaptic weights of a given subset S of cells grow without bound or not. This property can be expressed by the fact that the cells of S exhibit a collective behavior.

A difficult modelling problem in this context is of having a priori two scaling parameters with two different types of convergence: Averaging principles or mean-field approximations.

1. The factor of the time-scale of fast cellular processes;
The main assumption is that the timescale of the time evolution of the synaptic weights is slow. This is the framework of [159]. This scaling leads to a possible averaging principle.
2. The number of nodes of the network.
A given neural cell receives an input from a large number of cells and to each of them is associated a synaptic weight. This scaling, with appropriate symmetry properties of the topology, may give a mean-field approximation of the network.

Both of these parameters should be large, and are a priori uncorrelated. A central question is to determine how possible scaling results can give an insight on the plastic synapticity at the level of such a network.

4.2 Living biological tissues

Pseudo-stratified epithelial tissue development Understanding how tissue growth and development is regulated is crucial in biology. Both proliferation and regulation of cells' growth are fundamental for the development of healthy tissues in animals and plants. Pseudo-stratified epithelium tissues are composed of narrow and elongated cells arranged in a packed one-layer tissue. The positions of the nuclei are variable along the depth of the tissue. Each cell is connected to the so-called basal and apical surface. During development, each cell follows a series of events leading to cell division. This process, known as the cell cycle, is composed of four steps: G1, where the cell prepares for DNA replication; S, where the DNA is replicated; G2, where the cell prepares to divide; and mitosis M, where the cell divides. In pseudostratified epithelia, the nuclei move along the apical/basal axis during the inter-kinetic phases G1 and G2 [71]. This motion is called inter-kinetic nuclear migration (IKNM). The IKNM has become a point of interest in the past years with numerous studies being published [119]. Some of the questions we will aim to answer with the development and analysis of mathematical models are the following. Are the motions in G1 and G2 active or passive motions? How is the IKNM impacted by the increase of crowding during the tissue development? Which mechanism allows the transition of the cell in the different phases of the cell cycle?

Energy driven development of tissue architecture One of the main socio-economic challenges in the twenty-first century is to ensure that increasing lifespan is accompanied by the prevention of decline to achieve similar or greater increases in health. Organized architecture that supports organ function emerges rapidly and locally during the first period of life (during development), where the extracellular matrix (ECM) plays a key role by giving rise to the mechanical macrostructure. This 3D architecture is then globally maintained during the maturity period, before progressively declining corresponding to degeneration and loss of functions. Throughout all these steps, the evolving architecture and its constant turn-over is powered by energy exchanges through metabolism. Numerous evidences suggest that energy exchanges and mechanical forces can feedback on each other and that large perturbations of one or the other are associated with degeneration and diseases. Therefore, **understanding the dynamics of biological tissues at different spatiotemporal scales requires to account simultaneously for energy exchanges and mechanical considerations, a view that is currently lacking.** We will aim to bridge this gap by taking a particular focus on the complex interplay between metabolism and mechanics in tissue development and ageing via the dual use of mathematical modelling and in vitro/in vivo experiments.

Living tissues as multiphase flows At the continuum (macroscopic) level, a living tissue might be seen as a multiphase flow (different types of cells, liquid, molecules) through a porous media (extra-cellular matrix), a view encompassed in the so-called mixture theory (see [83]). In mathematical terms, this leads to strongly nonlinear degenerate parabolic Cahn-Hilliard (PDE) equations [151]. Although widely used in the literature to describe the mechanical properties of living tissues, it remains unclear how these continuum models (at the population level) can be obtained from a mechanical description at the cell level. We will take an interest in the derivation of such models from mesoscopic (kinetic) models, in order to understand the relation between compressible and incompressible porous-medium models.

Tumour-immune cell interactions and immunotherapies In a model of tumour-immune cell interactions under development, the behaviour of interacting heterogeneous cell populations is described by a set of coupled PDEs of the nonlocal Lotka-Volterra type. The cell population densities are structured by a continuous trait (aka phenotype) standing for malignancy identified to a potential of de-differentiation (so-called ‘stemness’), in tumour cells, and, similarly, a continuous trait representing anti-tumour aggressiveness in immune cells. As modern immunotherapeutic drugs, in particular *Immune Checkpoint Inhibitors*, have recently been introduced as boosters of such aggressiveness, i.e., of cancer cell kill by T-lymphocytes, and even more recently also by NK-lymphocytes, their impact on tumour-immune interactions is represented in the present model under development by a target in the effector lymphocyte population. Questions at stake are: Can we model in a relevant way and mathematically analyse these interactions between cell populations, so as to obtain a qualitative description of the so-called *immunoediting*, that is known to yield extinction, equilibrium or escape in the tumour cell population? Can we show ‘proof of concept’ situations in which the impact of immunotherapies can reverse tumour escape towards extinction, or at least equilibrium? Can we design theoretical optimised strategies to deliver time-scheduled immunotherapies to attain this goal? Can we analyse these interactions and their therapeutic control by immunotherapies in terms of concentration (or not) of the traits?

Phenotypic divergence in cancer and in the emergence of multicellularity The question of understanding the cancer disease from an integrative physiology and long-time evolution point of view has stimulated many authors for quite a long time. In this respect, the atavistic theory of cancer, presented in [84, 177], proposes that tumours represent, roughly speaking, a reverse evolution to a previous, incoherent, disorganised and very *plastic* state of multicellularity in animals, which the authors call *Metazoa 1.0*. This theory involves a billion year-long evolutionary perspective of the emergence of multicellularity from collections of unicellular beings to the first organised animals, so-called *Urmetazoa* [142]. Phenotypic divergence under environmental constraints is involved in both evolutionary/developmental and cancer biology. In the former, it is the fundamental phenomenon by which cell differentiation yields new cell types with emerging functions, leading in particular to multicellular beings such as animals (aka metazoa). In the latter, the process of *bet hedging* in cancer is a response to cellular stress to describe the multiple fates of a *plastic* cancer cell population as a fail-safe strategy to face deadly insults, e.g., due to anticancer drugs. The question of phenotypic divergence in an isogenic cell population is thus crucial. We will

address it by phenotype-structured PDEs of the reaction-advection-diffusion type [46, 76, 77, 121, 165], and explore what mechanisms (mutations, differentiation, selection) are responsible for concentration of the population around a unique phenotype (a singleton in phenotypic space); or, on the contrary, for continuous or discrete heterogeneity of the population, the discrete cases being represented by discrete sets of phenotypes, cases among which divergence *stricto sensu*, leading to a doubleton (phenotypic dimorphism), is the simplest one.

Elastic description of the Retinal Pigment Epithelium (RPE). A further modelling effort is necessary in order to capture both biological and mechanical features of the RPE monolayer, with specific attention to topological changes such as lesion formation, closure and fusion. So far, hybrid models combining elastic deformations and motion by mean curvature seem very promising in terms of analysis, simulation, and qualitative adherence to experimental data.

4.3 Mathematical models for epidemic spread

The still lasting pandemic of Covid-19, coming after the pandemic of H1N1 (2009) and outbreaks of other severe infectious diseases such as SRAS, MERS and Ebola fever, as well as the spread of viruliferous mosquitoes in temperate regions of the world and the increase of the corresponding health risk, tragically illustrates the importance of emerging and reemerging infectious diseases. As noticed by the epidemiologist S. Morse [140], “most emergent viruses are zoonotic, with natural animal reservoirs a more frequent source of new viruses than is the sudden evolution of a new entity. The most frequent factor in emergence is human behavior that increases the probability of transfer of viruses from their endogenous animal hosts to man”. This increase is likely to continue in the near future, due to destruction of ecosystems by deforestation, urbanization, industrial agriculture and economic globalization [162], requiring new efforts for understanding the spread of infectious diseases and for improving their control.

Vector-borne epidemics Every year, around 700,000 deaths are due to diseases transmitted by (female) mosquitoes, like malaria, yellow fever, dengue, Zika, chikungunya, Nile virus... They are indeed the most dangerous animals for humankind. For many of these diseases, no efficient remedy or vaccine presently exists, and an essential strategy to control vector-borne disease outbreaks consists in the control of mosquito vector populations that transmit these diseases (*Aedes* species for the diseases previously cited).

The insecticides, which have non-specific actions and strongly affect biodiversity, are now recognized as a highly unsatisfying solution, and innovative methods of biological control are being searched for and tested. Among these, the sterile or incompatible insect techniques (SIT/IIT) and replacement strategies (*Wolbachia*) attract strong attention. SIT is based on the release of male insects after their sterilization (traditionally by means of irradiation): sterile males will mate with wild females without producing any offspring, reducing or suppressing the wild population. The sterile insects are not self-replicating and, therefore, cannot become established in the environment. On the other hand, *Wolbachia* is a natural intracellular bacterial symbiont, maternally transmitted to offspring. Some of its strains cause a drastic decrease in the capacity to transmit dengue, zika or chikungunya of the mosquitoes, directly (by interfering with their vector competence) or indirectly (by shortening lifespan, etc.). Contrary to SIT, this offers theoretically a permanent protection against the outbreaks.

The application in the field of these promising techniques to control mosquitoes is not easy, and models are a useful tool to study the various issues at stake, and to propose and scale control strategies. In particular, it is important to take into account the spatial extension (and possible heterogeneities) of the operation and other aspects like the seasonality, migration from outside the treated domain, release of mosquitoes imperfectly treated, effects of the treatment on the epidemic risk and so on. The uncertainties on the biological processes and the imprecision of the measures make the whole issue quite intricate, and we intend to see what control science has to say to solve the related problems.

Infectious diseases The progress of the pandemic of Covid-19 has highlighted on a scale never seen before the complexity and intricateness of the factors that shape the spread of an epidemic, from the biological aspects at various scales (from virus to world population), to the economic, social and politic

aspects, without forgetting the many feedback loops binding them². Our interest is to participate to the understanding and disentanglement of the important factors, to the design and analysis of relevant mathematical models, and to their use to shape adequate control strategies.

For the accomplishment of this task, we plan to take advantage of a reservoir of tools and ideas from control theory, in addition to the more classical techniques developed in mathematical epidemiology. This is a point in common with our other topic of interest previously mentioned, the vector-borne diseases. First, we will routinely consider **control issues** — not only in the sense of controlling a disease, but using the term as in “control theory”. The *control inputs* we will encounter represent the available “means of action” on the epidemic, typically vaccination campaigns or social distancing measures (or sterile mosquito releases in the case of vector-borne diseases previously mentioned). *Constraints* on the intensity of the input variables like the duration of lockdown periods are pertinent (total number of released mosquitoes for the control of vector-borne diseases), but also on the state variables, e.g. on a maximal room occupancy rate in Intensive Treatment Units (maximal number of female mosquitoes, to limit both nuisance and epidemiological risk in the vector-borne diseases context). Optimal control involves non-conventional cost functions, such as the *peak* of infectious people (peak of female mosquito population...) or the time spent above a given value, which do not lead to Bolza problem. Robustness issues are also important in this context where the reality is imperfectly described by approximate models.

Second, we will pay particular attention to **the models, the data and their cross-relations**. Contrary to the engineering sciences, where models come from a combination of general principles and empirical laws, there is no such situation in mathematical epidemiology. In fact, it is not fully clear what are the key phenomena and quantities that influence decisively such complex situations, and thus deserve to be included in a model. On the other hand, the data themselves are imprecise and questionable, due to reasons that range from the evolving biological reality and our imperfect knowledge, to the characteristics of the data collection process by the Health system. In this context, we will be specially interested in questions of *observability* and *identifiability* (“given a model of the system and specific input-output experiments supposed error free, is it possible to determine uniquely the actual system state value and the parameters of the model?”), and of *observation* and *identification*, their realization counterparts (“given a model observable or identifiable, how to practically estimate the state or parameter values?”).

5 Social and environmental responsibility

5.1 Footprint of research activities

All members of the team decided to carefully review his or her trip policy (especially by air), in order to reduce carbon footprint.

5.2 Social responsibilities within the community

Several members of MUSCLEES are active in the “Pôle écoute” of the Jacques-Louis Lions laboratory.

Nastassia Pouradier Duteil is part of the mentoring program of Ecole Polytechnique for PhD students organized by “Association Femmes et Sciences”.

6 Highlights of the year

Note : Readers are advised that the Institute does not endorse the text in the “Highlights of the year” section, which is the sole responsibility of the team leader.

- Benoit Perthame has been elected president of the European Society for Mathematical and Theoretical Biology (ESMTB).
- Charles Elbar has defended his PhD thesis “Etude mathématique d’équations de type Cahn-Hilliard dégénérées” at Laboratoire Jacques-Louis Lions, Sorbonne Université in May.

²A new trans-disciplinary research domain has recently emerged, termed *Behavioural Epidemiology of Infectious Diseases* [131]. The referred ‘behaviour’ includes the spontaneous changes at individual and collective, but also the political decisions and their consequences.

- Elena Ambroggi has defended her PhD thesis “PDEs for Neural Networks with internal states” at Laboratoire Jacques-Louis Lions, Sorbonne Université in June.
- Nga Nguyen has defended her PhD thesis “Spatial modeling of invasion dynamics: applications to biological control of *Aedes* spp.(Diptera culicidae)” at Université Sorbonne Paris Nord in June.
- Marcel Fang has defended his PhD thesis “Modelling, Analysis, Observability and Identifiability of Epidemic Dynamics with Reinfections” at Laboratoire Jacques-Louis Lions, Sorbonne Université in December.
- Assane Savadogo has defended his PhD thesis “Etude et simulation numérique de modèles mathématiques sur les maladies infectieuses et de modèles éco-épidémiologiques” at Université Nazi Boni (Bobo Dioulasso, Burkina) in December.
- Lucie Laurence has defended her PhD thesis “A Scaling Approach to Stochastic Chemical Reaction Networks” at Inria in December.
- The team got a project (*FISH*) accepted at last ANR JCJC. It will last three years (2025-2027).

At the end of 2024, Inria’s top management enacted a new “contrat d’objectifs, de moyens et de performance” (COMP), which defines Inria’s objectives for the period 2024–2028. **We are very unhappy and concerned** about the content of this document and the way it was imposed.

- Neither the staff nor their representative bodies were given the opportunity to participate in (or influence) the drafting of this document.
- The document defines Inria’s main mission as “contributing to the digital sovereignty of the Nation through research and innovation” and proposes to amend Inria’s founding decree to reflect this new definition. We strongly believe that our primary mission is (and should remain) the advancement of human knowledge through research. Research is not a means to achieve “digital sovereignty”, whatever that may mean. Research should not be associated with any particular nation, whatever that nation may be.
- The document announces the creation of a funding agency within Inria. France already has an independent funding agency, the ANR. The creation of a new funding agency within a research institute is unnecessary and a waste of resources. It is also likely to create confusion, opacity, and conflicts of interest.
- Many aspects of the document reflect a desire to drive research in a top-down manner, for example through the selection of “strategic partner institutions” and “strategic themes”. This threatens the fundamental freedom of researchers to choose their research topics and collaborations. underestimated.
- The document indicates that all of Inria’s research should have “dual nature”, that is, both civilian and military applications. While some of the institute’s research may have military applications, the vast majority of it is independent of the military, and should remain so.
- The document announces a desire to place all of Inria in a “restricted regime area” (ZRR), which means that the hiring of researchers and interns will be reviewed and possibly vetoed by the Fonctionnaire Sécurité Défense. This creates administrative delays, subjects hiring to opaque criteria, and discourages the hiring of foreign nationals, thus harming research and collaboration.
- Staff opposition to these policies, which has been expressed in several votes and petitions, has been largely ignored.

7 New results

7.1 Axis 1 – Multiscale study of interacting particle systems

Participants: Nastassia Pouradier Duteil, Diane Peurichard, Sophie Hecht, Benoit Perthame.

7.1.1 Large-population limits

Participants: Nastassia Pouradier Duteil.

Mean-field limit of non-exchangeable multi-agent systems over hypergraphs with unbounded rank.

Interacting particle systems are known for their ability to generate large-scale self-organized structures from simple local interaction rules between each agent and its neighbors. In addition to studying their emergent behavior, a main focus of the mathematical community has been concentrated on deriving their large-population limit. In particular, the mean-field limit consists of describing the limit system by its population density in the product space of positions and labels. The strategy to derive such limits is often based on a careful combination of methods ranging from analysis of PDEs and stochastic analysis, to kinetic equations and graph theory. In this article, we focus on a generalization of multi-agent systems that includes higher-order interactions, which has largely captured the attention of the applied community in the last years. In such models, interactions between individuals are no longer assumed to be binary (*i.e.* between a pair of particles). Instead, individuals are allowed to interact by groups so that a full group jointly generates a non-linear force on any given individual. The underlying graph of connections is then replaced by a hypergraph, which we assume to be dense, but possibly non-uniform and of unbounded rank. For the first time in the literature, we show that when the interaction kernels are regular enough, then the mean-field limit is determined by a limiting Vlasov-type equation, where the hypergraph limit is encoded by a so-called UR-hypergraphon (unbounded-rank hypergraphon), and where the resulting mean-field force admits infinitely-many orders of interactions. This work, in collaboration with David Poyato (University of Granada) and Nathalie Ayi, (Sorbonne University) is presented in the pre-publication [23].

Large-population limits of non-exchangeable particle systems. A particle system is said to be non-exchangeable if two particles cannot be exchanged without modifying the overall dynamics. Because of this property, the classical mean-field approach fails to provide a limit equation when the number of particles tends to infinity. In this review, we present novel approaches for the large-population limit of non-exchangeable particle systems, based on the idea of keeping track of the identities of the particles. These can be classified in two categories. The non-exchangeable mean-field limit describes the evolution of the particle density on the product space of particle positions and labels. Instead, the continuum limit allows to obtain an equation for the evolution of each particle's position as a function of its (continuous) label. In the review article [22], we expose each of these approaches in the frameworks of static and adaptive networks.

7.1.2 Scaling limits

Participants: Sophie Hecht, Benoit Perthame, Diane Peurichard.

From a nonlocal mean-field to a porous medium system without self-diffusion Systems describing the long-range interaction between individuals have attracted a lot of attention in the last years, in particular in relation with living systems. These systems are quadratic, written under the form of transport equations

with a nonlocal self-generated drift. In [8], we established the localisation limit, that is the convergence of nonlocal to local systems, when the range of interaction tends to 0. These theoretical results are sustained by numerical simulations. The major new feature in our analysis is that we do not need diffusion to gain compactness, but we rely on a full rank assumption on the interaction kernels. In turn, we prove existence of weak solutions for the resulting system, a cross-diffusion system of quadratic type.

Scaling limits for a model with growth, division and cross-diffusion Originally motivated by the morphogenesis of bacterial microcolonies, we explore in [27] models through different scales for a spatial population of interacting, growing and dividing particles. We start from a microscopic stochastic model, write the corresponding stochastic differential equation satisfied by the empirical measure, and rigorously derive its mesoscopic (mean-field) limit. Under smoothness and symmetry assumptions for the interaction kernel, we then obtain entropy estimates, which provide us with a localization limit at the macroscopic level. Finally, we perform a thorough numerical study in order to compare the three modeling scales.

A Hamilton-Jacobi approach to nonlocal kinetic equations In [14], highly concentrated patterns have been observed which occur in a spatially heterogeneous, nonlocal, model of BGK type implementing a velocity-jump process. We study both a linear and a nonlinear case and describe the concentration profile. In particular, we analyse a hyperbolic (or high frequency) regime that can be interpreted both as a local (microscopic) or as a nonlocal (macroscopic) rescaling. We consider a Hopf-Cole transform and derive a Hamilton-Jacobi equation. The concentrations are then explained as a consequence of the stationary points of the Hamiltonian that is spatially heterogeneous like the velocity-jump process.

Nonlocal Cahn-Hilliard equation with degenerate mobility: Incompressible limit and convergence to stationary states The link between compressible models of tissue growth and the Hele-Shaw free boundary problem of fluid mechanics has recently attracted a lot of attention. In most of these models, only repulsive forces and advection terms are taken into account. In order to take into account long range interactions, in [9], we include for the first time a surface tension effect by adding a nonlocal term which leads to the degenerate nonlocal Cahn-Hilliard equation, and study the incompressible limit of the system. The degeneracy and the source term are the main difficulties.

7.2 Axis 2 – Stochastic models for biological and chemical systems

Participants: Lucie Laurence, Philippe Robert.

A Scaling Approach to Stochastic Chemical Reaction Networks. In [124], we have investigated the asymptotic properties of Markov processes associated to stochastic chemical reaction networks (CRNs) driven by the kinetics of the law of mass action. Their transition rates exhibit a polynomial dependence on the state variable, with possible discontinuities of the dynamics along the boundary of the state space. As a natural choice to study stability properties of CRNs, the scaling parameter considered in this paper is the norm of the initial state. Compared to existing scalings of the literature, this scaling does not change neither the topology of a CRN, nor its reactions constants. Functional limit theorems with this scaling parameter can be used to prove positive recurrence of the Markov process. This scaling approach also gives interesting insights on the transient behavior of these networks, to describe how multiple time scales drive the time evolution of their sample paths for example. General stability criteria are presented as well as a possible framework for scaling analyses. Several simple examples of CRNs are investigated with this approach. A detailed stability and scaling analyses of a CRN with slow and fast timescales is worked out.

Analysis of Stochastic Chemical Reaction Networks with a Hierarchy of Timescales In [125] we investigate a class of stochastic chemical reaction networks with $n \geq 1$ chemical species S_1, \dots, S_n , and whose

complexes are only of the form $k_i S_i$, $i=1, \dots, n$, where (k_i) are integers. The time evolution of these CRNs is driven by the kinetics of the law of mass action. A scaling analysis is done when the rates of external arrivals of chemical species are proportional to a large scaling parameter N . A natural hierarchy of fast processes, a subset of the coordinates of $(X_i(t))$, is determined by the values of the mapping $i \rightarrow k_i$. We show that the scaled vector of coordinates i such that $k_i=1$ and the scaled occupation measure of the other coordinates are converging in distribution to a deterministic limit as N gets large. The proof of this result is obtained by establishing a functional equation for the limiting points of the occupation measure, by an induction on the hierarchy of timescales and with relative entropy functions.

Stochastic Chemical Reaction Networks with Discontinuous Limits and AIMD processes In [126] we study a class of stochastic chemical reaction networks (CRNs) for which chemical species are created by a sequence of chain reactions. We prove that under some convenient conditions on the initial state, some of these networks exhibit a discrete-induced transitions (DIT) property: isolated, random, events have a direct impact on the macroscopic state of the process. If this phenomenon has already been noticed in several CRNs, in auto-catalytic networks in the literature of physics in particular, there are up to now few rigorous studies in this domain. A scaling analysis of several cases of such CRNs with several classes of initial states is achieved. The DIT property is investigated for the case of a CRN with four nodes. We show that on the normal timescale and for a subset of (large) initial states and for convenient Skorohod topologies, the scaled process converges in distribution to a Markov process with jumps, an Additive Increase/Multiplicative Decrease (AIMD) process. This asymptotically discontinuous limiting behavior is a consequence of a DIT property due to random, local, blowups of jumps occurring during small time intervals. With an explicit representation of invariant measures of AIMD processes and time-change arguments, we show that, with a speed-up of the timescale, the scaled process is converging in distribution to a continuous deterministic function. The DIT property analyzed in this paper is connected to a simple chain reaction between three chemical species and is therefore likely to be a quite generic phenomenon for a large class of CRNs.

7.3 Axis 3 – Theoretical analysis of nonlinear partial differential equations (PDE) modelling various structured population dynamics

Participants: Jean Clairambault, Benoît Perthame, Nastassia Pouradier Duteil, Lia Sela.

7.3.1 Modelling phenotypic divergence in cancer and in the emergence of multicellularity by phenotype-structured equations of cell population dynamics

Participants: Jean Clairambault, Lia Sela.

Phenotype divergence and cooperation. The question of understanding the cancer disease from an integrative physiology and long-time evolution point of view has stimulated many authors for quite a long time. In this respect, the atavistic theory of cancer - to which we do not limit our point view, but which offers a coherent framework for our theoretical developments - proposes that tumours represent, roughly speaking, a reverse evolution to a previous, incoherent, disorganised and very plastic state of multicellularity in animals, which the authors call Metazoa 1.0. This theory involves a billion year-long evolutionary perspective of the emergence of multicellularity from collections of unicellular beings to the first organised animals, so-called Urmetazoa. Phenotypic divergence under environmental constraints is involved in both evolutionary/developmental and cancer biology. In the former, it is the fundamental phenomenon by which cell differentiation yields new cell types with emerging functions, leading in particular to multicellular beings such as animals (aka metazoa). In the latter, the process of bet hedging in cancer is a response to cellular stress to describe the multiple fates of a plastic cancer cell population

as a fail-safe strategy to face deadly insults, e.g., due to anticancer drugs. The question of phenotypic divergence in an isogenic cell population is thus crucial. We address it by phenotype-structured PDEs of the reaction-advection-diffusion type, and explore what mechanisms (mutations, differentiation, selection) are responsible for concentration of the population around a unique phenotype (a singleton in phenotypic space); or, on the contrary, for continuous or discrete heterogeneity of the population, the discrete cases being represented by discrete sets of phenotypes, cases among which divergence *stricto sensu*, leading to a doubleton (phenotypic dimorphism), is the simplest one. To this principle of phenotype divergence has been added in [10] a point of view on cooperation between divergent cell species, following prisoner's dilemma settings, largely due to Frank Ernesto Alvarez Borges - it was a chapter of his PhD thesis, defended in December 2023 under the supervision of Stephane Mischler, Dauphine University. This point of view, as mentioned above, applies to both cancer and the constitution of animal multicellularity in evolutionary biology. To clarify the connections between these two fields of research - often mentioned in the scientific literature on cancer, seldom developed -, the notion of animal body plan (Bauplan, plan corporel/organisationnel) is studied in a popularisation paper (in French, with English abstract) [33]. The question of interactions between phenotype-structured cell populations has given rise to the PhD thesis of Lia Sela, begun in October 2024, supervised by Emmanuel Trelat (LJLL), Jean Clairambault and Jean-Philippe Foy (CRSA, INSERM, St Antoine Hospital), in the framework of the Programme Doctoral Interdisciplinaire en Cancerologie (PDIC) of Sorbonne University. The two cell populations considered are oral epithelial cells, subject to possible - but not mandatory - cancerisation on the one hand, and on the other hand, populations of resident macrophages in the oral cavity. The simplified continuous phenotypes considered in a first step are a global malignancy one for epithelial cells, and a M2/M1 axis characterisation for macrophages.

7.3.2 Analysis of non-local advection-diffusion models for active particles

Participants: Luca Alasio.

Existence and regularity results. In connection with section 3.3.3 of the Research Program, new results have been obtained in the study of two models for the evolution of the density of active particles in a periodic setting. In both models, the unknown densities depend on time, space and angle, where the latter is considered as a structure variable.

In a first work in collaboration with S. Schulz and J. Guerand [21], we establish regularity and, under suitable assumptions, convergence to stationary states for weak solutions of a parabolic equation with a non-linear non-local drift term. We apply De Giorgi's method and differentiate the equation with respect to the time variable iteratively to show that weak solutions become smooth away from the initial time. This strategy requires that we obtain improved integrability estimates in order to cater for the presence of the non-local drift. The instantaneous smoothing effect observed for weak solutions is shown to also hold for very weak solutions arising from distributional initial data; the proof of this result relies on a uniqueness theorem in the style of M. Pierre for low-regularity solutions. The convergence to stationary states is proved under a smallness assumption on the drift term.

In a second work with S. Schulz [41], we study regularity and uniqueness of weak solutions of a degenerate parabolic equation, arising as the limit of a stochastic lattice model of self-propelled particles. The angle-average of the solution appears as a coefficient in the diffusive and drift terms, making the equation nonlocal. We prove that, under unrestrictive non-degeneracy assumptions on the initial data, weak solutions are smooth for positive times. Our method rests on deriving a drift-diffusion equation for a particular function of the angle-averaged density and applying De Giorgi's method to show that the original equation is uniformly parabolic for positive times. We employ a Galerkin approximation to justify rigorously the passage from divergence to non-divergence form of the equation, which yields improved estimates by exploiting a cancellation. By imposing stronger constraints on the initial data, we prove the uniqueness of the weak solution, which relies on Duhamel's principle and gradient estimates for the periodic heat kernel to derive L^∞ estimates for the angle-averaged density.

7.4 Axis 4 – Mathematical epidemiology

Participants: Pierre-Alexandre Bliman, Marcel Fang, Nga Nguyen, Assane Savadogo, Manon de la Tousche.

7.4.1 Biological control of vectors

Participants: Pierre-Alexandre Bliman, Nga Nguyen, Manon de la Tousche.

Efficacy of the Sterile Insect Technique in the presence of inaccessible areas: A study using two-patch models The Sterile Insect Technique (SIT) is one of the sustainable strategies for the control of disease vectors, which consists of releasing sterilized males that will mate with the wild females, resulting in a reduction and, eventually a local elimination, of the wild population. The implementation of the SIT in the field can become problematic when there are inaccessible areas where the release of sterile insects cannot be carried out directly, and the migration of wild insects from these areas to the treated zone may influence the efficacy of this technique. However, we can also take advantage of the movement of sterile individuals to control the wild population in these unreachable places. In [3], we derived a two-patch model for *Aedes* mosquitoes with discrete diffusion between the treated area and the inaccessible zone. We investigated two different release strategies (constant and impulsive periodic releases), and by using the monotonicity of the model, we showed that if the number of released sterile males exceeds some threshold, the technique succeeds in driving the whole population in both areas to extinction. This threshold depends not only on the biological parameters of the population but also on the diffusion between the two patches.

Basic offspring number and robust feedback design for the biological control of vectors by sterile insect release technique Sterile Insect Technique (SIT) is a promising control method against insect pests and insect vectors. It consists in releasing males previously sterilized in laboratory, in order to reduce or eliminate a specific wild population. We studied in [24] the implementation by feedback control of SIT-based elimination campaign of *Aedes* mosquitoes. We provided state-feedback and output-feedback control laws and establish their convergence, as well as their robustness properties. In this design procedure, a pivotal role is played by the average number of secondary female insects produced by a single female insect, called basic offspring number, and by the use of properties of monotone systems. Illustrative simulations were provided.

Optimal Control Approach for Implementation of Sterile Insect Techniques The vector or pest control is essential to reduce the risk of vector-borne diseases or crop losses. Among the available biological control tools, the sterile insect technique (SIT) is one of the most promising. However, SIT-control campaigns must be carefully planned in advance in order to render desirable outcomes. In [2], we designed SIT-control intervention programs that can avoid the real-time monitoring of the wild population and require to mass-rear a minimal overall number of sterile insects, in order to induce a local elimination of the wild population in the shortest time. Continuous-time release programs were obtained by applying an optimal control approach, and then laying the groundwork of more practical SIT-control programs consisting of periodic impulsive releases.

Feasibility and optimization results for elimination by mass-trapping in a metapopulation model Having in mind the issue of control of insects vectors or insects pests, we considered in [4] a metapopulation model with patches linearly interconnected, and explore the global effects of the (on purpose) increase of mortality in some of them. Based on previous results by Y. Takeuchi et al., we showed that under appropriate conditions, the sign of the stability modulus of the Jacobian of the system at the origin determines the asymptotic behaviour of the solutions. If it is non-positive, then the population becomes extinct in every patch. Conversely, if it is positive, then there exists a unique nonnegative equilibrium,

which is positive and globally asymptotically stable. In the latter case, given a subset of 'controlled' patches where human intervention is allowed, through mass-trapping for instance, we studied whether the introduction of additional linear mortality in some of them can result in population elimination in every patch. We characterized this possibility by an algebraic property on the Jacobian at the origin of a so-called residual system. We then assessed the minimal globally asymptotically stable equilibrium that may be attained in this way, and when elimination is possible, we studied the optimization problem consisting in achieving this task while minimizing a certain cost function, chosen as a nondecreasing and convex function of the mortality rates added in the controlled patches. We showed that such minimization problem admits a global minimizer, which is unique in the relevant cases. An interior point algorithm was proposed to compute the numerical solution.

7.4.2 Control of infectious diseases

Participants: Pierre-Alexandre Bliman, Marcel Fang, Assane Savadogo.

A framework for the modelling and the analysis of epidemiological spread in commuting populations
In [25], we established a framework for the mathematical modelling and the analysis of the spread of an epidemic in a large population commuting regularly, typically along a time-periodic pattern, as is roughly speaking the case in populous urban center. We consider a large number of distinct homogeneous groups of individuals of various sizes, called subpopulations, and focus on the modelling of the changing conditions of their mixing along time and of the induced disease transmission. We propose a general class of models in which the 'force of infection' plays a central role, which attempts to 'reconcile' the classical modelling approaches in mathematical epidemiology, based on compartmental models, with some widely used analysis results (including those by P. van den Driessche and J. Watmough in 2002), established for apparently less structured systems of nonlinear ordinary-differential equations. We take special care in explaining the modelling approach in details, and provide analysis results that allow to compute or estimate the value of the basic reproduction number for such general periodic epidemic systems.

7.5 Axis 5 – Development and analysis of mathematical models for biological tissues confronted to experimental data

Participants: Nastassia Pouradier Duteil, Diane Peurichard.

7.5.1 Modeling of milling and schooling in gregarious fish.

Participants: Nastassia Pouradier Duteil.

The study of collective behavior has attracted much attention in the last twenty years, both among mathematicians and experimentalists, with the aim of explaining how local interactions between the group members lead to the emergence of global patterns, a phenomenon referred to as *self-organization*. Importantly, a group's capacity to transition between different global configurations is related to its survival capacity. For example, fish schools adopt different collective behaviors when foraging for food or facing predators.

However, the mechanisms provoking phase transition in a group of interacting agents are often difficult to identify experimentally. We have initiated a collaboration with R. Godoy-Diana and B. Thiria of the laboratory PMMH of ESPCI, in order to focus on exploring the effect of two main mechanisms in the collective behavior of gregarious fish (*Hemigramus rhodostomus*): (i) the individuals' **fields of**

vision; and (ii) the population's **heterogeneity**. Both mechanisms are particularly challenging to study exclusively through numerical experiments, which justifies the tight collaboration between the two teams. First results were obtained during the internship of A. Savalle (May-July 2024). We proved that a simple agent-based model with just two forces (self-propulsion and alignment dynamics) is able to reproduce the milling behavior of the group when the interactions are non-symmetric, due to the directed field of vision of each individual.

7.5.2 3D Modeling of biological tissue emergence and repair

Participants: Diane Peurichard.

A combined in-silico / in-vivo approach reveals that an early transient decrease in fiber cross-linking unlocks adult regeneration. The decline in regeneration efficiency after birth in mammals is a significant roadblock for regenerative medicine in tissue repair. We previously developed a computational agent based-model (ABM, cf [153]) that recapitulates mechanical interactions between cells and the extracellular-matrix (ECM), to investigate key drivers of tissue repair in adults. In [15], we perform a time calibration alongside a parameter sensitivity analysis of the model to discover that an early and transient decrease in ECM cross-linking guides tissue repair toward regeneration. Consistent with the computational model, transient inhibition or stimulation of fiber cross-linking for the first six days after subcutaneous adipose tissue (AT) resection in adult mice led to regenerative or scar healing, respectively. Therefore, this work positions the computational model as a predictive tool for tissue regeneration that with further development will behave as a digital twin of our in vivo model. In addition, it opens new therapeutic approaches targeting ECM cross-linking to induce tissue regeneration in adult mammals.

Modeling of spinal cord regeneration in axolotl. Axolotls are uniquely able to completely regenerate the spinal cord after amputation. The underlying governing mechanisms of this regenerative response have not yet been fully elucidated. We previously found that spinal cord regeneration is mainly driven by cell-cycle acceleration of ependymal cells, recruited by a hypothetical signal propagating from the injury. However, the nature of the signal and its propagation remain unknown. In [5], we developed and analyzed a computational model to investigate whether the regeneration-inducing signal can follow a reaction-diffusion process. By developing a theory of the regenerating outgrowth in the limit of fast reaction-diffusion, we demonstrated that control of regenerative response solely relies on cell-to-signal sensitivity and the signal reaction-diffusion characteristic length. This study lays foundations for further identification of the signal controlling regeneration of the spinal cord.

3D modelling of fiber networks. The extracellular-matrix (ECM) is a complex interconnected three-dimensional network that provides structural support for the cells and tissues and defines organ architecture as key for their healthy functioning. However, the intimate mechanisms by which ECM acquire their three-dimensional architecture are still largely unknown. In [6], we studied this question by means of a simple three-dimensional individual based model of interacting fibres able to spontaneously crosslink or unlink to each other and align at the crosslinks. We show that such systems are able to spontaneously generate different types of architectures. We provide a thorough analysis of the emerging structures by an exhaustive parametric analysis and the use of appropriate visualization tools and quantifiers in three dimensions. The most striking result is that the emergence of ordered structures can be fully explained by a single emerging variable: the number of links per fibre in the network. If validated on real tissues, this simple variable could become an important putative target to control and predict the structuring of biological tissues, to suggest possible new therapeutic strategies to restore tissue functions after disruption, and to help in the development of collagen-based scaffolds for tissue engineering. Moreover, the model reveals that the emergence of architecture is a spatially homogeneous process following a unique evolutionary path, and highlights the essential role of dynamical crosslinking in tissue structuring.

7.5.3 Modelling the Retinal Pigment Epithelium in Age-Related Macular Degeneration

Participants: Luca Alasio.

Towards a mechanistic approach to study the growth of lesions. In agreement with section 3.5.6 of the Research Program, we are collaborating with the group of Prof. M. Pâques at Hôpital National des Quinze-Vingts in order to model the evolution and growth of lesions in dry Age-Related Macular Degeneration. During a short visit in spring 2024, S. Gazzoni contributed to the numerical exploration of viscoelastic effects in the Retinal Pigment Epithelium (RPE). The PhD project of N. Cresson, co-supervised by Dr. L. Alasio and Prof. M. Szopos (Université Paris Cité), is aligned with this research direction. We are currently working on the refinement of macroscopic (elastic) models reproducing RPE deformations qualitatively, as well as on the rigorous framework and well-posedness analysis of the corresponding nonlinear system of PDEs. We continue the study of efficient and robust methods for numerical simulations, with particular attention to parameter calibration and to integration of clinical data in the model. We obtained very encouraging preliminary results with simulations in FreeFEM of significant cases involving fusion of lesions, asymmetric growth and foveal sparing.

7.5.4 Mathematical models of retinal biochemistry

Participants: Luca Alasio.

Towards better models for the visual cycle. In agreement with section 3.5.5 of the Research Program, we are investigating improved models for the dynamics of the visual cycle in photoreceptors. In the summer of 2024, L. Alasio supervised the internship of N. Antonelli-Dziri (L3 student, Sorbonne Polytech). The internship focused on simulation and comparison of different ODE models for the key biochemical steps in the visual cycle. Preliminary results obtained in this context have promoted an ongoing collaboration with Dr. C. Schwarz (University of Tübingen), who contributed to the formulation of ODE models for the visual cycle in the past, and is currently planning new experiments with the aim of making the study of such biochemical phenomena more quantitative. Further analysis is required, but the current results are encouraging.

8 Partnerships and cooperations

8.1 International initiatives

8.1.1 Inria associate team not involved in an ILL or an international program

MOCOVEC

Title: Modelling and Biological Control of Vector-Borne Diseases: the case of Malaria and Dengue

Program: Associate Team

Duration: 5 years – (2020-2024)

Local supervisor: Pierre-Alexandre Bliman

Participants: Pierre-Alexandre Bliman.

Partners: • Centres Inria de Paris, Lyon, Nancy-Grand Est

- Department of Biostatistics, Institute of Biosciences, Unesp, Brazil
- Institute for Theoretical Physics, Unesp, Brazil
- Center of Mathematics, Computation and Cognition, UFABC, Brazil
- Institute of Mathematics and Statistics, USP, Brazil

Summary Taking into account all the infectious disease spread worldwide, vector-borne diseases account for over 17%. For a huge part of them, no efficient vaccine is available, and control efforts must be done on the vector population. Focusing on dengue and malaria, two diseases transmitted by vector mosquito and which cause high morbidity and mortality around the world, this project aims to model disease transmission, its spread and control, in a context of climatic and environmental change. For this, the main drives of disease transmission will be addressed to understand which factors modulate the spatio-temporal patterns observed, especially in Brazil. Combining techniques of data analysis with mathematical models and control theory, the plan is to work on data analysis to define potential biotic and abiotic factors that drives malaria and dengue disease dynamics; to study and model the effects of seasonality on the spread of the diseases; to understand spatial aspects of the transmission through the setup of models capable to account for nonlocal and heterogeneous aspect; and to analyse alternative approaches of mosquito control, especially the biological control methods based on sterile mosquitoes or on infection by bacterium that reduces the vectorial capacity.

8.1.2 STIC/MATH/CLIMAT AmSud projects

BIO-CIVIP

Title: Biological Control of Insect Vectors and Insect Pests

Program: STIC-AmSud

Duration: 2 years – (2024-2025)

Local supervisor: Pierre-Alexandre Bliman

Participants: Pierre-Alexandre Bliman, Nga Nguyen, Manon de la Tousche.

Partners:

- **Brazil**
 - Universidade Federal Fluminense, Niteroi
 - Universidade Estadual Paulista “Júlio de Mesquita Filho”, Câmpus de Botucatu
 - Universidade de São Paulo
 - Universidade Federal de Rio de Janeiro
 - Fundação Oswaldo Cruz, Rio de Janeiro
- **Chile**
 - Universidad de Chile, Santiago
 - Universidad Técnica Federico Santa Maria, Valparaiso
- **Colombia**
 - Universidad Autónoma de Occidente, Cali
 - Universidad del Valle, Cali
- **France**
 - Institut de Mathématiques de Bordeaux - UMR 5152
 - Laboratoire Jacques-Louis Lions, UMR 7598

- Laboratoire de Mathématiques et Applications, UMR 7348
- Laboratoire d’analyse, géométrie et application, UMR 7539
- Centres de recherche Inria Paris, Nancy-Grand Est, Lyon
- CIRAD, Montpellier
- UMR MISTEA (INRAE/SupAgro), Montpellier
- **Paraguay**
 - LCCA-NIDTEC, Polytechnic School, National University of Asuncion

Inria contact: Pierre-Alexandre Bliman

Summary: The project BIO-CIVIP is concerned with the mathematical study of new biological control strategies. It concerns on the one hand insect vectors of important diseases that put at risk considerable portions of the human population, and on the other hand insect pests that damage crops and food production. Generally speaking, biological control methods aim at controlling pests or vectors using other organisms. Building on the similarities of the control methods and the potential synergy between the two fields, our goal is to elaborate and analyze mathematical models adapted to several specific applications of interest, and to evaluate qualitatively and quantitatively different control strategies. Our efforts will aim in particular at understanding the key aspects and parameters of insect vector and pest dynamics in their temporal and spatial spread, testing control principles and concepts, estimating feasibility and robustness, identifying risks and reducing cost.

9 Dissemination

9.1 Promoting scientific activities

9.1.1 Scientific events: selection

Reviewer Pierre-Alexandre Bliman has been reviewer for the conference *European Control Conference 2024*.

9.1.2 Journal

Member of the editorial boards Philippe Robert is Associate Editor of the journal “Stochastic Models”
Jean Clairambault is member of the editorial board of the journal “Mathematical Modelling of Natural Phenomena”

Reviewer - reviewing activities Pierre-Alexandre Bliman has been reviewer for the journals *Automatica*, *Bulletin of Mathematical Biology*, *IEEE Control Systems Letters (L-CSS)*, *Mathematical Methods in the Applied Sciences*, *Nonlinear Analysis: Hybrid Systems*, *Systems and Control Letters*.

Nastassia Pouradier Duteil has been reviewer for the journals *Kinetic and Related Models*, *Mathematical Control and Related Fields*, *Foundations of Computational Mathematics*, *Networks and Heterogeneous Media*.

Diane Peurichard has been reviewer for the journals *MATCOM*, *Nonlinearity*, *Journal of Physics A*, *Journal of the Royal Society Interface*

Jean Clairambault has been reviewer for the journals *Applied Mathematical Modelling*, *Cancers*, *Journal of Mathematical Biology*, *Mathematical Medicine and Biology*, *Molecular Medicine*, *npj Systems Biology and Applications*, *PLoS Computational Biology*, *Scientific Reports*

9.1.3 Invited talks

Lucie Laurence has given a talk at the SPT-CRN conference in Pulla, Italia, 10/06-14/06.

Philippe Robert has given a seminar at Toulouse at the IRIT on September 13, in Toledo, for the ECMTB conference, 22/07-26/07 and at the online seminar Morn Seminar 23/05. Philippe Robert has given lectures at the Journées Math Bio Santé 2024, Nantes, 24/06-28/06.

Marcel Fang presented a contribution at the 15th Conference on Dynamical Systems Applied to Biology and Natural Sciences, DSABNS 2024, in February.

Manon De La Tousche presented a contribution at the 15th Conference on Dynamical Systems Applied to Biology and Natural Sciences, DSABNS 2024, in February.

Pierre-Alexandre Bliman gave seminars at Université Mohamed 6 Polytechnique, Maroc in July; and at Department of Mathematics and Applications, University of Naples Federico II in September. He presented contributions at the conference “Numerical Analysis and Modelling in Applied Sciences (NA-MAS)”, Gaeta, Italy, in September, and (online) in the Conférence Maths and Decision: Mini-Symposium Biologiactal Complex Systems, Rabat, Marocco (online) in December.

Nastassia Pouradier Duteil gave presentations at the workshops “Alhambra PDE days” (University of Granada), “Collective models for networked particle systems” (University of Pavia), “Variational Analysis, Models and Methods in Measure Spaces” (CIRM). She gave a course at the Kinmat Summer School “Kinetic description of collective dynamics and related emergent phenomena” (Bedlewo, Poland). She also gave a seminar at the “Laurent Schwarz seminars” at Ecole Polytechnique.

Diane Peurichard gave presentations at the conferences GIMC SIMAI Young (Naples, Italy), ECMTB2024 (Toledo, Spain), ‘International Summer school on mathematical biology’ (Shanghai, China), workshop MATIDY (IHP, Paris), Plant Biology Workshop (Lyon), GDR Mecanobiology (Metz).

Jean Clairambault has given an in-presence talk to the on-invitation workshop “Modelling Complexity in Mechanics and Applied Mathematics: Theory, Experiments, and Simulations” in Ortigia, Syracuse, Italy, September 2024, and another one to the online “Mathematical Modelling in Biomedicine” scientific seminar, RUDN University, Moscow, February 2024.

Sophie Hecht gave a presentation at the GdT Normand on biomathematics in May 2024.

9.1.4 Scientific expertise

Diane Peurichard is member of the commission d’évaluation (CE) Inria, of the commission des emplois scientifiques (CES) Inria Paris, of the comité de suivi doctoral (CSD) Inria Paris, and of the pole ecoute, LJLL, Sorbonne Université.

9.1.5 Research administration

Diane Peurichard is coordinator of the ANR project ENERGENCE.

Nastassia Pouradier Duteil is coordinator of the ANR project FISH.

Pierre-Alexandre Bliman is coordinator of the ANR project NOCIME and of the STIC AMSUd project BIO-CIVIP.

9.2 Teaching - Supervision - Juries

Lucie Laurence is teaching assistant in the course “Mathematics for scientists”, in L1 at Jussieu.

Marcel Fang has been teaching assistant in Licence at Sorbonne Université.

Manon de la Tousche has been teaching assistant in Licence at Sorbonne Université.

Philippe Robert is teaching the master M2 course ‘Modèles Stochastiques de la Biologie Moléculaire’ at Sorbonne Université.

Nastassia Pouradier Duteil has been teaching the M1 course “Ordinary Differential Equations : Theory and Numerical Approximation” at the ISMP institute of Porto Novo, Benin. She has been teaching the course “Essential Mathematics” within the DU “Retour aux Etudes Supérieures pour les Personne Exilées” (Sorbonne University). She also supervised an M1-research project for the course “Travaux Encadrés de Recherche” (Sorbonne University).

Diane Peurichard has given a M2 course (4h) at Université de Strasbourg in the master Physique Cellulaire, a 4h M2 course in the master M2 Biosanté (CARE, Toulouse). She also did exercise course (L1) at Sorbonne university and supervised student project (L3) at Sorbonne university.

Sophie Hecht has been teaching a teaching assistant in L1 and L3 at Sorbonne Université and has given ‘colle’ in classe preparatoire Henri IV.

9.2.1 Supervision

Pierre-Alexandre Bliman has been PhD supervisor of Marcel Fang, Assane Savadogo and Manon De La Tousse.

Nastassia Pouradier Duteil has supervised the M2-level internship of A. Savalle.

Diane Peurichard has supervised the post-doctorate of S. Toste (co-supervised with RESTORE, Toulouse) and the post-doctorate of H. Horii (together with Sophie Hecht).

Sophie Hecht has supervised the post-doctorate of H. Horii (together with Diane Peurichard).

9.2.2 Juries

Philippe Robert has been a reviewer of the PhD document “Stochastic analysis of unreliable large-scale storage systems” by Soukaina El Masmari, University of Casablanca, Morocco. He has been a member of the jury for the PhD defense of Lucie Laurence in December

Diane Peurichard has been in the CRCN/ISFP juries for Inria Saclay and Inria Nancy as a member of the commission d'évaluation (CE), campaign 2024. She was also member of the jury for the Prix Junior Maryam Mirzakhani 2024 of the fondation Hadamar, rewarding three young students (license, master) for a first research work.

Sophie Hecht has been in the jury for the recruitment of a MdC at Université Paris Nord.

9.3 Popularization

Sophie Hecht has given an outreach presentation at the Lycée Viollet Le Duc to highschool students.

Diane Peurichard participated in the RJMI (Rendez-Vous des Jeunes Mathématiciennes et Informaticiennes) in the form of 'Speed meetings' with several groups of young students (Inria Paris). She also participated in online speed meetings with young students (lycéennes) with the association 'femmes et mathématiques'

9.3.1 Productions (articles, videos, podcasts, serious games, ...)

Nastassia Pouradier Duteil was the first guest in Nathalie Ayi's podcast “Tête-à-tête chercheuse(s)”, seeking to promote a diversified image of mathematical researchers. She is now one of the permanent hosts of the podcast.

9.3.2 Participation in Live events

Nastassia Pouradier Duteil gave an outreach presentation for high school and university students at the Classes Préparatoires “Les Lazaristes”.

10 Scientific production

10.1 Major publications

- [1] P. Degond, G. Dimarco, M. A. Ferreira and S. Hecht. ‘Modeling ballistic aggregation by time stepping approaches’. In: *SIAM Journal on Applied Dynamical Systems* 24.01 (2025), pp. 710–743. URL: <https://hal.science/hal-04211646>.

10.2 Publications of the year

International journals

- [2] P.-A. Bliman, D. Cardona-Salgado, Y. Dumont and O. Vasilieva. ‘Optimal Control Approach for Implementation of Sterile Insect Techniques’. In: *Journal of Mathematical Sciences* 279.5 (Mar. 2024), pp. 607–622. DOI: [10.1007/s10958-024-07042-y](https://doi.org/10.1007/s10958-024-07042-y). URL: <https://inria.hal.science/hal-02418508> (cit. on p. 35).

- [3] P.-A. Bliman, N. Nguyen and N. Vauchelet. ‘Efficacy of the Sterile Insect Technique in the presence of inaccessible areas: A study using two-patch models’. In: *Mathematical Biosciences* (Nov. 2024), p. 109290. DOI: [10.1016/j.mbs.2024.109290](https://doi.org/10.1016/j.mbs.2024.109290). URL: <https://hal.science/hal-04525237>. In press (cit. on p. 35).
- [4] P.-A. Bliman, M. de la Tousche and Y. Dumont. ‘Feasibility and optimization results for elimination by mass-trapping in a metapopulation model’. In: *Applied Mathematical Modelling* 144 (5th Mar. 2025), p. 116047. DOI: [10.1016/j.apm.2025.116047](https://doi.org/10.1016/j.apm.2025.116047). URL: <https://hal.science/hal-04688245> (cit. on p. 35).
- [5] V. Caliaro, D. Peurichard and O. Chara. ‘How a reaction-diffusion signal can control spinal cord regeneration in axolotls: A modeling study’. In: *iScience* 27.7 (July 2024), p. 110197. DOI: [10.1016/j.isci.2024.110197](https://doi.org/10.1016/j.isci.2024.110197). URL: <https://hal.science/hal-04715240> (cit. on p. 37).
- [6] P. Chassonnery, J. Paupert, A. Lorisgnol, C. Séverac, M. Ousset, P. Degond, L. Casteilla and D. Peurichard. ‘Fibre crosslinking drives the emergence of order in a three-dimensional dynamical network model’. In: *Royal Society Open Science* 11.1 (2024), p. 231456. DOI: [10.1098/rsos.231456](https://doi.org/10.1098/rsos.231456). URL: <https://hal.science/hal-04618698> (cit. on p. 37).
- [7] G. Ciavolella, N. Ferrand, M. Sabbah, B. Perthame and R. Natalini. ‘A model for membrane degradation using a gelatin invadopodia assay’. In: *Bulletin of Mathematical Biology* 86.3 (5th Jan. 2024), p. 30. DOI: [10.1007/s11538-024-01260-w](https://doi.org/10.1007/s11538-024-01260-w). URL: <https://inria.hal.science/hal-04446414>.
- [8] M. Doumic, S. Hecht, B. Perthame and D. Peurichard. ‘Multispecies cross-diffusions: from a nonlocal mean-field to a porous medium system without self-diffusion’. In: *Journal of Differential Equations* 389 (25th Apr. 2024), pp. 228–256. DOI: [10.1016/j.jde.2024.01.017](https://doi.org/10.1016/j.jde.2024.01.017). URL: <https://hal.science/hal-04108050>. In press (cit. on p. 32).
- [9] C. Elbar, B. Perthame, A. Poiatti and J. Skrzeczkowski. ‘Nonlocal Cahn-Hilliard equation with degenerate mobility: Incompressible limit and convergence to stationary states’. In: *Archive for Rational Mechanics and Analysis* 248.3 (13th May 2024), p. 41. DOI: [10.1007/s00205-024-01990-0](https://doi.org/10.1007/s00205-024-01990-0). URL: <https://hal.science/hal-04094130> (cit. on p. 32).
- [10] F. Ernesto Alvarez and J. Clairambault. ‘Phenotype divergence and cooperation in isogenic multicellularity and in cancer’. In: *Mathematical Medicine and Biology* (7th July 2024). DOI: [10.1093/imammb/dqae005](https://doi.org/10.1093/imammb/dqae005). URL: <https://hal.science/hal-04638544> (cit. on p. 34).
- [11] V. Fromion, P. Robert and J. Zaherddine. ‘A Stochastic Analysis of Particle Systems with Pairing’. In: *Stochastic Processes and their Applications* 178 (Sept. 2024), p. 104480. DOI: [10.1016/j.spa.2024.104480](https://doi.org/10.1016/j.spa.2024.104480). URL: <https://inria.hal.science/hal-04234301>.
- [12] M. Herda, P. Monmarché and B. Perthame. ‘Wasserstein contraction for the stochastic Morris-Lecar neuron model’. In: *Kinetic and Related Models* 18.1 (Feb. 2025), pp. 1–18. DOI: [10.3934/krm.2024009](https://doi.org/10.3934/krm.2024009). URL: <https://hal.science/hal-04170316>.
- [13] L. Kanzler, B. Perthame and B. Sarels. ‘Structured Model Conserving Biomass for the Size-spectrum Evolution in Aquatic Ecosystems’. In: *Journal of Mathematical Biology* 88.3 (7th Feb. 2024), p. 26. DOI: [10.1007/s00285-023-02043-y](https://doi.org/10.1007/s00285-023-02043-y). URL: <https://hal.science/hal-03895919>.
- [14] N. Loy and B. Perthame. ‘A Hamilton-Jacobi approach to nonlocal kinetic equations’. In: *Nonlinearity* 37.10 (13th Sept. 2024), p. 105019. DOI: [10.1088/1361-6544/ad75dd](https://doi.org/10.1088/1361-6544/ad75dd). URL: <https://cnrs.hal.science/hal-04428238> (cit. on p. 32).
- [15] A. Pacary, D. Peurichard, L. Vaysse, P. Monsarrat, C. Bolut, A. Girel, C. Guissard, A. Lorisgnol, V. Planat-Benard, J. Paupert, M. Ousset and L. Casteilla. ‘A computational model reveals an early transient decrease in fiber cross-linking that unlocks adult regeneration’. In: *NPJ Regenerative medicine* 9.1 (15th Oct. 2024), p. 29. DOI: [10.1038/s41536-024-00373-z](https://doi.org/10.1038/s41536-024-00373-z). URL: <https://hal.science/hal-04821044> (cit. on p. 37).
- [16] P. Robert and G. Vignoud. ‘A Palm Space Approach to Non-Linear Hawkes Processes’. In: *Electronic Journal of Probability* 29.none (10th Jan. 2024), pp. 1–37. DOI: [10.1214/23-EJP1063](https://doi.org/10.1214/23-EJP1063). URL: <https://inria.hal.science/hal-03911583>.

International peer-reviewed conferences

- [17] P.-A. Bliman and M. Fang. ‘A two-stage seirs reinfection model with multiple endemic equilibria’. In: 15th Conference on Dynamical Systems Applied to Biology and Natural Sciences, DSABNS 2024. Lisbonne, Portugal, 2024. URL: <https://hal.science/hal-04526417>.
- [18] M. de la Tousche, P.-A. Bliman and Y. Dumont. ‘Modeling population dynamics and control strategies for a unique species evolving in heterogenous landscape’. In: 15 th Conference on Dynamical Systems Applied to Biology and Natural Sciences (DSABNS 2024). Lisbonne, Portugal, 2024, p. 194. URL: <https://hal.inrae.fr/hal-04495187>.

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