

2025 Activity Report

RESEARCH CENTRE: Inria Lyon Centre

IN PARTNERSHIP WITH: Université Claude Bernard (Lyon 1), CNRS, Ecole normale supérieure de Lyon

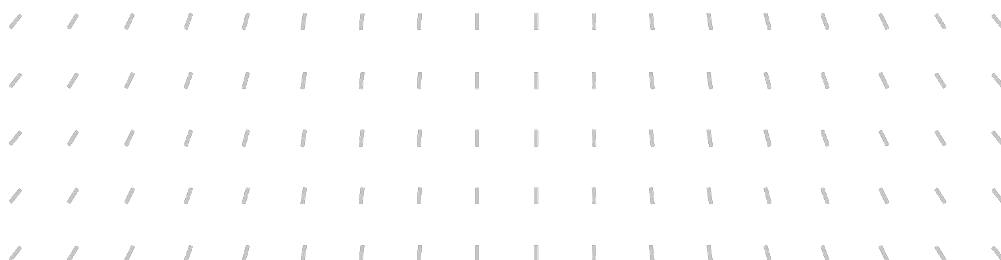

Project-Team

MUSICS

MULTIscale Interacting Cell Systems



In collaboration with Institut Camille Jordan, Laboratoire de Biologie et Modélisation de la Cellule



Project-Team MUSICS

Creation of the Project-Team: 2024 July 01

Each year, Inria research teams publish an Activity Report presenting their work and results over the reporting period. These reports follow a common structure, with some optional sections depending on the specific team. They typically begin by outlining the overall objectives and research programme, including the main research themes, goals, and methodological approaches. They also describe the application domains targeted by the team, highlighting the scientific or societal contexts in which their work is situated. The reports then present the highlights of the year, covering major scientific achievements, software developments, or teaching contributions. When relevant, they include sections on software, platforms, and open data, detailing the tools developed and how they are shared. A substantial part is dedicated to new results, where scientific contributions are described in detail, often with subsections specifying participants and associated keywords. Finally, the Activity Report addresses funding, contracts, partnerships, and collaborations at various levels, from industrial agreements to international cooperations. It also covers dissemination and teaching activities, such as participation in scientific events, outreach, and supervision. The document concludes with a presentation of scientific production, including major publications and those produced during the year.

Keywords

Computer sciences and digital sciences

- 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
 - A6.2. – Scientific computing, Numerical Analysis & Optimization
 - A6.2.1. – Numerical analysis of PDE and ODE
 - A6.2.3. – Probabilistic methods
 - A6.2.4. – Statistical methods
 - A6.3.1. – Inverse problems
 - A6.3.3. – Data processing
- A8.12. – Optimal transport

Other research topics and application domains

- B1. – Life sciences
 - B1.1. – Biology
 - B1.1.3. – Developmental biology
 - B1.1.4. – Genetics and genomics
 - B1.1.5. – Immunology
 - B1.1.7. – Bioinformatics
 - B1.1.8. – Mathematical biology
 - B1.1.10. – Systems and synthetic biology
 - B2.2.3. – Cancer
 - B2.2.4. – Infectious diseases, Virology
 - B2.2.6. – Neurodegenerative diseases
- B2.3. – Epidemiology
- B2.6. – Biological and medical imaging
 - B2.6.3. – Biological Imaging

Contents

Project-Team MUSICS	1
1 Team members, visitors, external collaborators	5
2 Overall objectives	6
3 Research program	6
4 Application domains	7
5 Highlights of the year	7
6 Latest software developments, platforms, open data	8
6.1 Latest software developments	8
6.1.1 Simuscale	8
7 New results	9
7.1 Multiscale modeling of the spatial structure of stem cells in neuroblastoma patient-derived tumoroids reveals a critical role for a short-range diffusive process	9
7.2 Inferring and simulating a gene regulatory network for the sympathoadrenal differentiation from single-cell transcriptomics in human.	9
7.3 A refractory density approach to a multi-scale SEIRS epidemic model	10
7.4 Mast cells act as pro-angiogenic and pro-tumorigenic players in pituitary gonadotroph tumors	10
7.5 Mathematical modeling of the feather follicle morphogenetic wave in birds	10
7.6 Multi-serotype nested immuno-epidemiological model for dengue hemorrhagic fever involving backward bifurcation and serotype invasion	11
7.7 Uncovering candidate Nanog-Helper genes in early mouse embryo differentiation using differential entropy and network inference	11
7.8 Modelling of anti-inflammatory treatment in the Alzheimer disease: optimal regimen and outcome	11
7.9 A temporary challenge by tumor cells can lead to a permanent partial-impairment of memory CD8 T cell function	12
7.10 Spatial pattern analysis of A $A\beta$ -monomer model with inflammation processes for Alzheimer's disease	12
7.11 Velocity Trapping in the Lifted Totally Asymmetric Simple Exclusion Process and the True Self-Avoiding Random Walk	13
7.12 Cell Trajectory Inference based on Schrödinger Problem and a Mechanistic Model of Stochastic Gene Expression	13
7.13 A mathematical model to the melanoma dynamics involving CAR T-cells	13
7.14 Steady state large deviations for one-dimensional, symmetric exclusion processes in weak contact with reservoirs	14
7.15 Scaling relations for the CLG's critical exponents	14
7.16 Quantifying uncertainty and sensitivity in an Alzheimer's disease model: A mathematical approach	14
7.17 A reaction telegraph model reveals synergy between motility strategies in <i>Myxococcus xanthus</i> predation	15
7.18 Mixed precision implicit numerical schemes for systems of ordinary differential equations	15
7.19 Spatial pattern analysis of an $A\beta$ -monomer model with inflammation processes for Alzheimer's disease	15
7.20 Analysis of a polarization model with exchange at the boundary	16
7.21 Global stability and periodicity in a delay differential model	16
7.22 Regional Control Strategies for a Spatiotemporal SQEIR Epidemic Model: Application to COVID-19	16

7.23	Exploring well-posedness and asymptotic behavior in an Advection Diffusion Reaction (ADR) model	17
7.24	Optimal control of an impulsive VS-EIAR epidemic model with applications to COVID-19	17
7.25	Analytical derivation of delayed prey-predator model with hunting-and-resting delay	17
7.26	Traveling Waves in a Hybrid Reaction-Diffusion-Difference SEIR Epidemic Model With Nonlocal Transmission and Protection Phase With Delay	18
7.27	Three-State Gene Expression Model Parameterized for Single-Cell Multi-Omics Data	18
7.28	Subdiffusive fractional limit of a jump-renewal equation	18
8	Partnerships and cooperations	19
8.1	International initiatives	19
8.1.1	Associate Teams in the framework of an Inria International Lab or in the framework of an Inria International Program	19
8.1.2	Inria associate team not involved in an IIL or an international program	19
8.2	International research visitors	19
8.2.1	Visits to international teams	19
8.3	National initiatives	19
8.4	Regional initiatives	21
9	Dissemination	22
9.1	Promoting scientific activities	22
9.1.1	Journal	22
9.1.2	Invited talks	22
9.1.3	Research administration	23
9.2	Teaching - Supervision - Juries - Educational and pedagogical outreach	23
9.2.1	Teaching	23
9.2.2	Supervision	24
9.2.3	Juries	25
9.3	Popularization	25
9.3.1	Participation in Live events	25
10	Scientific production	25
10.1	Publications of the year	25
10.2	Cited publications	28

1 Team members, visitors, external collaborators

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2 Overall objectives

MUtiScale Interacting Cell Systems, or MUSICS, is a newly created Inria team at the Centre Inria de Lyon devoted to the multiscale modelling and analysis of cellular dynamics. It is jointly supported by members of the ICJ (Institut Camille Jordan, University Lyon 1, CNRS and Inria), and the LBMC (ENS Lyon, CNRS) under the leadership of Thomas Lepoutre (Inria and ICJ). MUSICS inherits in part the staff and the research topics of the late Inria team Dracula, headed by Mostafa Adimy, that was set up in 2011.

3 Research program

Biological systems can be described at many organization scales, starting from the molecular level, to cellular, whole body, and all the way up to the population level. Each scale is rich and complex in its own right, but also interact with other scales and this is a crucial feature.

Yet it contains a much higher level of complexity, both in terms of computations and modelling. The historical, reductionist approach that has been used in molecular biology for the past 30 years consists in inferring the biological function, often at the tissue or whole body level, from molecular observations. There are several areas where this approach does not work so well. If the average cellular phenotype is not representative of the whole population phenotype, no matter how finely individual cells will be characterised, there will be a mismatch between the prediction and the observation. For the reductionist approach to work, it must take into account what happens when cells are brought together, that is, the tissue ecology. Cell population dynamics, in a broad sense, is the study of the phenomena that occur when many cells are brought in together, interact, proliferate, differentiate and die. One major difficulty that arises when analyzing such systems stems from the fact that those different scales do not behave independently but display strong, constant and dynamic interactions. In this context, the idea of a privileged level of causation loses its meaning, calling for new formal tools and approaches that aim at capturing the so-called “circular causality”, where causation moves both upward and downward [38]. Upward causation is the set of processes by which the elements at lower levels interact and produce changes at higher levels. For example, a modification in the function of a gene product will alter the proliferation capacity of a cell that will alter the tissue composition. Downward causation is the set of constraints imposed by the higher levels on the dynamics at lower levels. For example, the generation at the tissue level of a gradient of a morphogen will result in a change in gene expression in individual cells. The gradient is a property of the tissue, not individual cells. Despite the variety of existing techniques to handle causality, this complexity of living systems poses new challenges and calls for the development of new tools. The MUSICS project is devoted to the development of tools and methods to study **multiscale processes in biology with potential applications in medicine**.

MUSICS will mainly focus on the **cellular level**, taking into account interactions at smaller spatial (and faster) scales (e.g. cellular content, gene expression), or at larger spatial scales (e.g. tissue, organism). The **cell**, as the structural unit of living organisms, has always played a key role in biology. With the rise of molecular biology and genomics, the role of the cell had been somewhat relegated to the background, in favour of molecular data acquired on large numbers of cells. The existence, extent and role of intercellular diversity was largely underestimated. Molecular biology was until recently based upon the assumption (or approximation) of the existence of an “average cell” that could be characterised from population measurements. This view proved to be not only wrong, but irrelevant [37]. **Rather, cellular diversity seems to be a key feature to understand biological systems and dynamics.**

What has dramatically changed in the last decade is the access to this diversity, notably through the revolution of **single cell data**. We now have access to gene expression at the resolution of the (single) cell for a large number of genes (thousands) in a large number of (individual) cells (up to millions) [41]. The recent years have witnessed an explosion in both the amount and the diversity of single-cell omics data. This has

led to new opportunities to develop computationally efficient and statistically sound models and methods, with many challenges ahead [35].

One of the main drivers for cellular variability lies within the **gene expression** process that is intrinsically stochastic [34]. Notably, the observable regime for gene expression, when analysed at the single cell level, can be characterised as bursty [40]. This means that mRNA production occurs in brief episodes (bursts), generating a characteristic gamma distribution of mRNA transcripts when analysed over a sufficiently large amount of individual cells [36]. Such variability is often not taken into account at all in current modelling schemes. For example in a recent paper which developed a model of multicellular gene expression that accounts for intra- and intercellular gene regulation [39], gene expression is reduced to a binary variable.

It is therefore critical to develop new modelling approaches in which the molecular-based variability is correctly taken into account at the molecular level, so that its impact at higher levels (cellular and tissular) can be analysed.

Similarly, the way such molecular variability is constrained by higher levels should also be incorporated into the modelling process. Finally, we will build on our expertise in developing population models that can be analysed mathematically in order to be able to derive relevant predictions in simplified situations (corresponding to mean-field limits, for instance). This leads to a structure of the project into three thematic axes of different size (more members in the first one, and fewer in the two others).

Axis 1 Modelling and theoretical analysis in population dynamics. This methodological axis concerns population dynamics in general. This leads to the study of questions related to existence, uniqueness and asymptotic behaviour for population models, described in terms of **partial differential equations** (PDEs), **integro-differential equations**, or **delay differential equations**. Moreover, we have a strong focus on an intermediate description: structured population dynamics. This is the biggest axis and concerns most members of the teams.

Axis 2 Simulate efficiently large populations of individuals with internal dynamics influenced by the population (chemical signalling, overcrowding . . .). This approach is not only adapted when the coupling of scales is strong but can also be used to test the validity approximation of weak coupling used in population models. This can also guide the construction of new simplified models (based on numerical observations). Moreover, internal dynamics assessed on the data will be encoded in the simulation tool with the addition of nonlinear feedback loops. The axis is notably computational but contains also the analysis of large population limit.

Axis 3 Understand, analyse and infer the internal dynamics from data with a mechanistic description. This challenge is more related to statistical inference (mechanistic description has consequences on the structure of the noise) and leads to difficult questions linked to large deviations and optimal transportation. Axis 3 mixes some deep theoretical questions related to stochastic hybrid models with direct confrontations to data.

Only such multiscale modelling approaches will allow to investigate one of the most challenging characteristics of living systems, namely the circular causality that drives them [38].

4 Application domains

Detailed in the research program

5 Highlights of the year

Both Leon Tine [22] and Clément Erignoux [21] both defended their HDR this year.

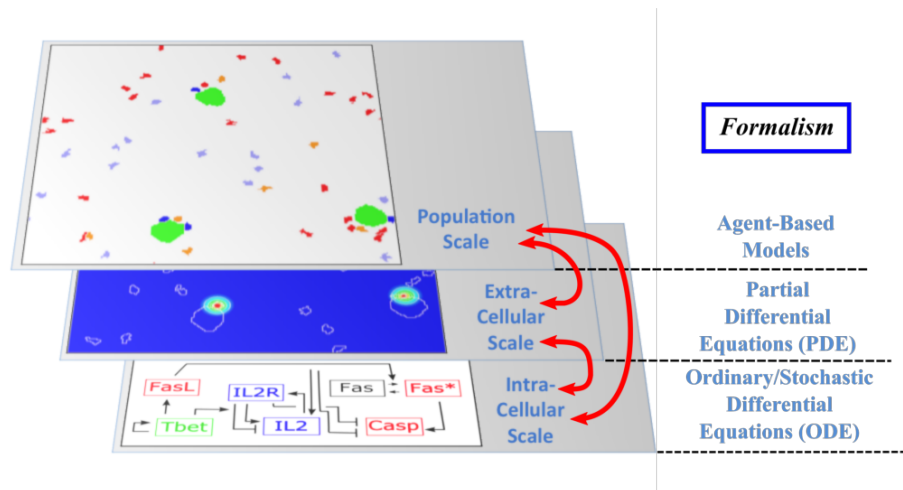


Figure 1: Non-exhaustive view of interacting scales.

6 Latest software developments, platforms, open data

6.1 Latest software developments

6.1.1 Simuscale

Name: Multiscale simulation of cell populations

Keywords: Ode, Simulation, Multiscale, Multi-agent

Scientific Description: SiMuScale is a C++ simulation framework that models both intra- and extra-cellular processes at different time scales. Its decoupled architecture allows for an easy and parsimonious extension of the model with e.g. a new kind of intra-cellular formalism.

Functional Description: Simuscale is a multiscale, individual-based modelling platform written in C++ for performing numerical simulations of heterogeneous populations of individual cells evolving in time and interacting physically and biochemically. Models are described at two levels: cellular level and population level. The cellular level describes the dynamics of single cells, as defined by the modeller. Cells have an internal state that includes default properties such as cell size and position, and may also include any other cell-specific state, such as gene or protein expression. The population level describes the mechanical constraints and biochemical interactions between cells. Cells evolve in bounded 3D domain, and can divide or die. Simuscale implements the physical simulator that manages the simulations at the population level. It delegates the details of cellular dynamics to each cell. This makes Simuscale modular, as it can accommodate any number of cell models with the same simulation, including models with different modelling formalisms. Biochemical interactions occur between cells that are in contact with each other, through intercellular signals. Intercellular signals can be known to all or to a subset of the cells only. Simuscale expects an input file describing the initial cell population and numerical options, it runs a simulation over a specified time interval, updating the cell population at given time steps, and generates an output file containing the state of each cell at each time step, and the tree of cell divisions and deaths.

Release Contributions: Includes diffusive signals (nonlocal) across the whole simulation domain

URL: <https://gitlab.inria.fr/bernard1/simuscale>

Publications: [hal-04489553](#), [hal-04400510](#)

Contact: Samuel Bernard

Participants: Carole Knibbe, David Parsons, Fabien Crauste, Olivier Gandrillon, Samuel Bernard, an anonymous participant

Partners: CNRS, UCBL Lyon 1

7 New results

In this section, we briefly present the results obtained by members of the team this year. In each case, only the members of the team are indicated as participants, not the full list of authors.

7.1 Multiscale modeling of the spatial structure of stem cells in neuroblastoma patient-derived tumoroids reveals a critical role for a short-range diffusive process

Participants: Thi Nhu Thao Nguyen, Samuel Bernard, Olivier Gandrillon.

Neuroblastomas are heterogeneous pediatric tumors of the sympathetic nervous system for which treatments are still limited. Fundamental and applied approaches have been enabled thanks to the generation of patient-derived tumoroids (PDTs), ex vivo 3D structures used as avatars of the original tumor. In [32], we generated neuroblastoma PDTs and quantified the spatial distribution of CD133 + cancer stem cells using immunohistochemistry. We observed that those cells tend to aggregate in the PDT. In order to better understand the set of rules needed for generating such structures, we implemented a multiscale agent-based neuroblastoma tumoroid model. Model rules specify single cell's fate based on its intracellular content, which dynamically evolves according to a stochastic gene regulatory network. The state of this network can be modulated by cell-to-cell signalling through neighbor cells fate decisions and, possibly, spatial location. We first observed that in the absence of any spatial rules for inter-cellular interactions, no spatial structure emerged. The addition of simple rules (signalling by cell-to-cell contact or differential cell adhesion) only marginally improved the quantitative agreement to the experimental dataset. In sharp contrast, the addition of short-range pro-stem cell diffusive signalling among stem cells produced very realistic 3D PDT-like structures. This work highlights the power of our multiscale approach to discard too simplistic rules and to propose a minimal set of hypotheses required to reproduce qualitatively and quantitatively experimentally observed spatial structures. In the case of neuroblastomas-derived PDTs, short-range spatial diffusion of stem-to-stem cell signalling proved to play a key role in successfully reconstructing the spatial structure.

7.2 Inferring and simulating a gene regulatory network for the sympathoadrenal differentiation from single-cell transcriptomics in human.

Participants: Olivier Gandrillon.

Neuroblastoma is a malignant childhood cancer with significant interand inpatient heterogeneity arising from the abnormal differentiation of neural crest cells into sympathetic neurons. The lack of actionable mutations limits therapeutic options, highlighting the need to better understand the molecular mechanisms that drive this differentiation. Although RNA velocity has provided some insights, modeling regulatory relationships is limited.

Methods: To address this, we applied in [13] our integrated gene regulatory network (GRNs) inference (CARDAMOM) and simulation (HARISSA) tools using a published single-cell RNAseq dataset from human sympathoadrenal differentiation

Results: Our analysis identified a 97-gene GRN that drives the transition from Schwann cell precursors to chromaffin cells and sympathoblasts, highlighting dynamic interactions such as self-reinforcing loops and toggle switches. The simulation of that GRN was able to reproduce very satisfactorily the experimentally observed gene expression distributions

7.3 A refractory density approach to a multi-scale SEIRS epidemic model

Participants: Laurent Pujo-Menjouet.

In [5], we propose a novel multi-scale modeling framework for infectious disease spreading, borrowing ideas and modeling tools from the so-called Refractory Density (RD) approach. We introduce a microscopic model that describes the probability of infection for a single individual and the evolution of the disease within their body. From the individual-level description, we then present the corresponding population-level model of epidemic spreading on the mesoscopic and macroscopic scale. We conclude with numerical illustrations, taking into account either a white Gaussian noise or an escape noise to showcase the potential of our approach in producing both transient and asymptotic complex dynamics as well as finite-size fluctuations consistently across multiple scales. A comparison with the epidemiology of coronaviruses is also given to corroborate the qualitative relevance of our new approach.

7.4 Mast cells act as pro-angiogenic and pro-tumorigenic players in pituitary gonadotroph tumors

Participants: Olivier Gandrillon.

Background – The tumor microenvironment (TME) represents a promising avenue to understand gonadotroph tumors and develop therapeutic tools. In [14], we aimed to gain insight into the tumorigenesis mechanisms driven by the gonadotroph TME. Methods Single-cell and spatial-omics were combined with histological analysis. Mice engrafted with tumor cells were used for functional validation.

Results – Using single-cell and spatial transcriptomic data from gonadotroph tumors and normal tissues, we identified mast cells in the microenvironment of gonadotroph tumors and confirmed their physical and functional interaction with endothelial cells. Quantification of mast cells in 40 patients suggested their pro-tumoral role as tumors relapsing after surgery harbored more mast cells. More interestingly, the distribution of mast cells was associated with the presence of a higher number of blood vessels, with an increased microvessel density (MVD), and with blood vessels with thicker walls. Ligand-receptor network analysis highlighted VEGFA as a modulator of mast/endothelial cell communication, a result confirmed by the identification of intratumoral mast cells expressing VEGFA in mouse and human gonadotroph tumors. Finally, using mice engrafted with gonadotroph tumor cells, we demonstrated that the depletion of mast cells reduces tumor volume through increased apoptosis. These observations were associated with increased hemorrhagic areas and a significant reduction of the number of blood vessels and MVD as evidenced in human gonadotroph tumors.

Conclusion – we demonstrate that mast cells represent a new actor of the gonadotroph TME, and highlight their pro-angiogenic and pro-tumorigenic roles as potential targets for the therapeutic treatment of gonadotroph tumors.

7.5 Mathematical modeling of the feather follicle morphogenetic wave in birds

Participants: Maxime Estavoyer, Thomas Lepoutre.

During the development of the avian skin, feather follicles are produced in a medio-lateral morphogenetic wave that results in their spatial arrangement in typical patterns. This wave involves the timely acquisition of pattern-forming competence followed by a row-by-row production of feather follicles. While several mathematical models combining self-organizing systems accurately reproduced dynamics of feather follicle pattern formation, the events that control timely parameters of wave propagation remain poorly understood. In [10], we built on previous modeling work to theoretically calculate the speed at which tissue competence

progresses. Using a weakly non-linear analysis, we calculated the speed at which follicles emerge once competence is attained. We produced numerical simulations of our model to predict the respective influences of competence acquisition and follicle emergence on each other and on wave propagation. Our results show that the theoretical speed of follicle emergence is limited by competence acquisition, but that, in turn, competence acquisition is not constrained by follicle emergence. This modeling work provides an approximation of the timely parameters of the morphogenetic wave, and sheds light on the interplay between competence and patterning events in the developing skin.

7.6 Multi-serotype nested immuno-epidemiological model for dengue hemorrhagic fever involving backward bifurcation and serotype invasion

Participants: Mostafa Adimy, Charlotte Dugourd-Camus, Ruben Taieb.

Reinfection with the same dengue serotype is generally benign, as individuals develop protective immunity. On the other hand, in the case of reinfection with a different serotype, pre-existing antibodies can increase the risk of developing Dengue Hemorrhagic Fever (DHF), by inducing Antibody-Dependent Enhancement (ADE). To model this dynamic, we introduce in [24] a multi-scale immuno-epidemiological system. The immunological part is described by a system of ODEs representing the interaction between two antibodies (from previous and current infection) and the virus. The epidemiological part is represented by an infection-age structured SIRS system (for both the primary and secondary infections) and a recovery-age structured equation (for the first infection). A detailed mathematical analysis of the equilibrium points of the multi-scale reinfection model, including disease-free, mono-endemic and bi-endemic states, is performed. We establish necessary and sufficient conditions for the existence of backward bifurcations and derive an expression for the invasion reproduction number, which shows that the second serotype can invade the population after a mono-endemic first serotype. We also investigate the dependence of the basic and invasion reproduction numbers on the immunological parameters of the first and second infections. This gives us a better understanding of the relationship between DHF and ADE during secondary infection.

7.7 Uncovering candidate Nanog-Helper genes in early mouse embryo differentiation using differential entropy and network inference

Participants: Olivier Gandrillon.

In the preimplantation mammalian embryo, stochastic cell-to-cell expression heterogeneity is followed by signal reinforcement to initiate the specification of Inner Cell Mass (ICM) cells into Epiblast (Epi). The expression of NANOG, the key transcription factor for the Epi fate, is necessary but not sufficient: coincident expression of other factors is required. To identify possible Nanog-helper genes, we analyzed in [17] gene expression variability in five time-stamped single-cell transcriptomic datasets using differential entropy, a quantitative measure of cell-to-cell heterogeneity. The entropy of Nanog displays a peak-shaped temporal pattern from the 16-cell to the 64-cell stage, consistent with its key role in Epi specification. By estimating the entropy profiles of the 21 genes common to all five datasets, we identified three genes - Pecam1, Sox2, and Hnf4a - whose variability in expression patterns mirrors that of Nanog. We further performed gene regulatory network inference using CARDAMOM, an algorithm that exploits temporal dynamics and transcriptional bursting. The results revealed that these three genes exhibit reciprocal activation with Nanog at the 32-cell stage. This regulatory motif reinforces fate-switching decisions and co-expression states. Our innovative analysis of single-cell transcriptomic data thus uncovers a likely role for Pecam1, Sox2, and Hnf4a as key genes that, when coincidentally expressed with Nanog, initiate ICM differentiation.

7.8 Modelling of anti-inflammatory treatment in the Alzheimer disease: optimal regimen and outcome

Participants: Laurent Pujo-Menjouet, Léon Tine.

The application of non-steroidal anti-inflammatory drugs (NSAIDs) for Alzheimer's disease is considered to be a promising therapeutic approach. Epidemiological studies suggest potential benefits of NSAIDs; however, these findings are not consistently supported by clinical trials. This long-standing discrepancy has persisted for decades and remains a significant barrier to developing effective treatment strategies. To assess the efficacy of NSAIDs in Alzheimer's disease, we have developed in [7] a mathematical model based on a system of ordinary differential equations. The model captures the dynamics of key players in disease progression, including $A\beta$ -monomers, oligomers, proinflammatory mediators (M1 microglial cells and pro-inflammatory cytokines), and anti-inflammatory mediators (M2 microglial cells and anti-inflammatory cytokines). The effects of NSAIDs are modeled through a reduction in the production rate of inflammatory cytokines (IC). While a single NSAID administration temporarily reduces IC levels, their concentration eventually returns to baseline due to drug elimination. The return time depends on the drug dose, resulting in a patient-specific return time function. By analyzing this function, we propose an optimal treatment regimen and identify conditions under which NSAID treatment is most effective in reducing IC levels. Our results suggest that NSAID efficacy in Alzheimer's disease is influenced by the stage of the disease (with earlier intervention being more effective), patient-specific parameters, and the treatment regimen. The approach developed here can also be generalized to evaluate the efficacy of anti-inflammatory treatments for other diseases.

7.9 A temporary challenge by tumor cells can lead to a permanent partial-impairment of memory CD8 T cell function

Participants: Olivier Gandrillon.

Memory CD8 T cells typically exhibit improved effector functions compared to their naive counterparts. However, under certain activation conditions, such as chronic viral infections or cancer, these cells may develop functional defects. In [29], we compared the functional quality of memory CD8 T cells generated following tumor rejection with those arising from an acute viral infection. We found that tumor-induced (Tum-CD8) memory cells exhibited a distinct phenotype and transcriptomic profile compared with viral-induced (Vir-CD8) memory cells. These memory cells are characterized by the expression of inhibitory receptors and displayed altered functions including reduced $IFN\gamma$ and $TNF\alpha$ production as well as changes in integrin expression. Additionally, the protective capacity of Tum-CD8 memory cells was flawed relative to that of Vir-CD8 memory cells. Importantly, the functional defects of Tum-CD8 persisted upon viral recall. Together, these findings indicate that transient tumoral stimulation can imprint a stable partial exhaustion-like program on memory CD8 T cells.

7.10 Spatial pattern analysis of A $A\beta$ -monomer model with inflammation processes for Alzheimer's disease

Participants: Maxime Estavoyer, Laurent Pujo-Menjouet.

We study the emergence of spatial patterns for a system of reaction-diffusion equations, modeling the progression of Alzheimer's disease through the interaction of $A\beta$ -monomers, oligomers, microglial cells, and interleukins with neurons. In our work, these spatial patterns stand for inert amyloid plaques, which are extracellular deposits of $A\beta$ -proteins and a characteristic feature of this neurodegenerative disease. Using linear analysis and numerical simulations, we show in [11] the existence of spatially heterogeneous solutions and exhibit a wide variety of possible spatially-dependent solutions: time-oscillating, low-amplitude, and high-amplitude patterns. Moreover, we carry out an extensive analysis of high-amplitude patterns in the

one- and two-dimensional domains. In particular, we study the stability of branches of heterogeneous steady states through bifurcation diagrams and their selection. From this numerical bifurcation analysis, we develop some conjectures concerning the influence of inflammation and microglial cells in the formation of amyloid plaques. These findings offer insights into potential anti-inflammatory treatments that might be used to mitigate the progression of Alzheimer's disease and the emergence of inert amyloid plaques.

7.11 Velocity Trapping in the Lifted Totally Asymmetric Simple Exclusion Process and the True Self-Avoiding Random Walk

Participants: Brune Massoulié, Clément Erignoux.

We discuss in [15] nonreversible Markov-chain Monte Carlo algorithms that, for particle systems, rigorously sample the positional Boltzmann distribution and that have faster than physical dynamics. These algorithms all feature a nonthermal velocity distribution. They are exemplified by the lifted totally asymmetric simple exclusion process (lifted TASEP), a one-dimensional lattice reduction of event-chain Monte Carlo. We analyze its dynamics in terms of a velocity trapping that arises from correlations between the local density and the particle velocities. This allows us to formulate a conjecture for its out-of-equilibrium mixing timescale, and to rationalize its equilibrium superdiffusive timescale. Both scales are faster than for the (unlifted) TASEP. They are further justified by our analysis of the lifted TASEP in terms of many-particle realizations of true self-avoiding random walks. We discuss velocity trapping beyond the case of one-dimensional lattice models and in more than one physical dimensions. Possible applications beyond physics are pointed out.

7.12 Cell Trajectory Inference based on Schrödinger Problem and a Mechanistic Model of Stochastic Gene Expression

Participants: Clémence Fournié, Aymeric Baradat, Olivier GandrillonFabien Crauste.

Cellular differentiation is the biological process that leads a cell to opt for a particular cellular identity. Recently, single-cell RNA-sequencing has enabled the simultaneous measurement of gene expression levels at specific times for a large number of individual cells and a large number of genes. Repeating such measurements at different time points gives then access to the temporal variation, or transport, of a distribution on a gene expression space. The whole temporal trajectory of distributions thus characterizes the differentiation process at population level, but trajectories of individual cells are still out of reach since most measurement techniques are destructive. The optimal transport theory that has been used so far to infer cellular differentiation trajectories from time-stamped single-cell RNA-seq data involves solving the so-called Schrödinger problem in its most common version. This implies assuming that cells move, in the gene expression space, by diffusion. Yet, real gene dynamics are much more complex. In [28], we assume that mRNA dynamics are characterized by brief and important production of RNA, with long periods of inactivity in between, and consider the so-called Bursty model of gene dynamics. We use this model to define a reference process for the Schrödinger problem. By comparing the solutions of the Schrödinger problems with a Diffusive and a Bursty reference process, under different conditions, we show that the Bursty model provides a better approximation of the underlying gene dynamics than the standard Diffusive process when inferring cell trajectories.

7.13 A mathematical model to the melanoma dynamics involving CAR T-cells

Participants: Mostafa Adimy.

Melanoma is one of the most aggressive types of cancer. Although it has a low percentage of incidence in the population, a high degree of lethality is observed due to its rapid metastasis. As melanoma is a highly immunogenic cancer, it has been used as an experimental model in several studies aimed at developing therapies, such as immunotherapy with Chimeric Antigen Receptor (CAR) T-cells. We propose in [18] a mathematical model of three ordinary differential equations to describe the dynamics of melanoma in the presence of Tumor-Associated Macrophages (TAMs) and CAR T-cell therapy, to assess the role of TAMs cells in the failure of this melanoma therapy. We examine the existence and asymptotic stability of equilibrium points of this system, giving a biological interpretation to each of them. Based on our theoretical and numerical results, we conclude that immunosuppression has a negative impact on CAR T-cell immunotherapy and that increasing the immunotherapy dose can improve tumor control. Furthermore, an increase in the action of the TAMs population on tumor proliferation can induce oscillations that eventually become periodic.

7.14 Steady state large deviations for one-dimensional, symmetric exclusion processes in weak contact with reservoirs

Participants: Clément Erignoux.

Consider the symmetric exclusion process evolving on an interval and weakly interacting at the end-points with reservoirs. Denote by $I_{[0,T]}(\cdot)$ its dynamical large deviations functional and by $V(\cdot)$ the associated quasi-potential, defined as $V(\gamma) = \inf_{T>0} \inf_u I_{[0,T]}(u)$, where the infimum is carried over all trajectories u such that $u(0) = \bar{\rho}$, $u(T) = \gamma$, and $\bar{\rho}$ is the stationary density profile. We derive in [4] the partial differential equation which describes the evolution of the optimal trajectory, and deduce from this result the formula obtained by Derrida, Hirschberg and Sadhu [33] for the quasi-potential through the representation of the steady state as a product of matrices.

7.15 Scaling relations for the CLG's critical exponents

Participants: Clément Erignoux.

In [26] we consider, in any dimension, the constrained lattice gas introduced by Rossi et al., which is an exclusion process on a d-dimensional lattice following the additional constraint that only particles with at least one occupied neighbour can jump. In dimension $d=2$, this model features self-organized criticality at some critical density of particles. Numerical simulations predict the existence of scaling exponents close to criticality, and several relations can be derived between these exponents. The goal of this article is to give a mathematical framework for these relations, which have been numerically established in a companion article.

7.16 Quantifying uncertainty and sensitivity in an Alzheimer's disease model: A mathematical approach

Participants: Laurent Pujon-Menjouet.

To understand the dynamics of Alzheimer's disease, we formulate in [31] a generalized mathematical model based on three events: aggregation of disease-related proteins, activation of immune cells, and initiation of inflammation. We incorporate functional forms in the model to represent the complex biological interactions between components related to Alzheimer's disease. We take explicit forms depending on the properties of functions in the model. We describe the system dynamics by locating biologically feasible steady states, determining stability properties, and identifying the effective parameters. Parameters are estimated using two methods: biological literature and data fitting. We perform sensitivity and uncertainty analyses to identify the most influential parameters. Partial Rank Correlation Coefficient and scatter plots

are used to visualize global sensitivity. Our results reveal that lower activation rate and higher proliferation rate of microglia may contribute to a reduction in toxic protein aggregate levels, thus slowing the disease progression.

7.17 A reaction telegraph model reveals synergy between motility strategies in *Myxococcus xanthus* predation

Participants: Maxime Estavoyer.

The predatory bacterium *Myxococcus xanthus* can invade prey bacteria using two distinct motility apparatuses. It is commonly acknowledged that adventurous motility is used for isolated bacteria, while social motility corresponds to bacterial clusters. Inspired by recent biological findings, we propose in [27] a simple model of predatory invasion focusing on the co-occurrence of these two mechanisms and their possible synergistic effects. At microscopic scale, cell motion is persistent; therefore, we opt for a transport-reaction model, extending previous reaction-diffusion models. Another specificity is the structuration of the bacterial population into clusters with varying speeds and persistence times. In the linear regime, we find a transition from normal speed to anomalous speed, consistent with reaction-diffusion theory but with specificities due to the hyperbolic nature of the model. For the nonlinear regime, we numerically observe and study the existence of transitions between pulled and pushed fronts. Finally, we reproduced biological experiments with mutants lacking each of the motility apparatuses based on relevant modifications of the model. Moreover, we propose a rational basis for the reported synergistic effects. Our work paves the way for a better understanding of the complex waves of bacterial population advance, which are precursors to biofilm formation.

7.18 Mixed precision implicit numerical schemes for systems of ordinary differential equations

Participants: Mouhamad Al Sayed Ali, Samuel Bernard, Arsène Marzorati.

Ordinary differential equations (ODEs) are widely used to model complex systems in biology, which result from the interactions of a large number of cells or organisms. This can lead to a substantial system size. These complex interactions can quickly alter their behavior, and some biological systems are stiff when represented as ODEs. Therefore, these stiff ODEs could benefit from implicit numerical schemes. However, each iteration of these schemes involves solving a large nonlinear system, typically using the Newton method. To guarantee the global convergence of this method, we use line search (LS) and trust region (TR) algorithms. In [2], we introduce a new approach to accelerate the computation of the implicit schemes by using mixed precision arithmetic, combining float and double precision, within the LS and TR algorithms, as well as in the Newton method. This approach aims at balancing the performance of lower precision arithmetic with the accuracy of higher precision arithmetic. We give theoretical results that show the efficiency of our approach. Numerical experiments show that our approach, running in either sequential or in parallel with MPI, is up to twice as fast as the double precision approach with the same level of accuracy. These experiments also show that increasing the size of the ODEs does not impact the quality of our mixed precision solution.

7.19 Spatial pattern analysis of an $A\beta$ -monomer model with inflammation processes for Alzheimer's disease

Participants: Maxime Estavoyer, Laurent Pujo-Menjouet.

We study in [12] the emergence of spatial patterns for a system of reaction-diffusion equations, modeling the progression of Alzheimer's disease through the interaction of $A\beta$ -monomers, oligomers, microglial

cells, and interleukins with neurons. In our work, these spatial patterns stand for inert amyloid plaques, which are extracellular deposits of $A\beta$ -proteins and a characteristic feature of this neurodegenerative disease. Using linear analysis and numerical simulations, we show the existence of spatially heterogeneous solutions and exhibit a wide variety of possible spatially dependent solutions: time-oscillating, low-amplitude, and high-amplitude patterns. Moreover, we carry out an extensive analysis of high-amplitude patterns in the one- and two-dimensional domains. In particular, we study the stability of branches of heterogeneous steady states through bifurcation diagrams and their selection. From these numerical simulations, we develop some conjectures concerning the influence of inflammation and microglial cells in the formation of amyloid plaques. These findings offer insights into potential anti-inflammatory treatments that might be used to mitigate the progression of Alzheimer's disease and the emergence of inert amyloid plaques.

7.20 Analysis of a polarization model with exchange at the boundary

Participants: Thomas Lepoutre.

We analyze in [30] a drift-diffusion model on the half-line. The drift is linked to exchanges at 0. This corresponds to the modeling of filament generation following protein exchanges between the membrane and the cytoplasm of a cell. This model has a critical mass and the asymptotic behaviors can be divided into three categories. In subcritical mass regime, diffusive behavior dominates and convergence in self-similar variables can be obtained with parabolic scaling. In supercritical mass regime, drift compensates for diffusion and convergence towards equilibrium distributions occurs. In the critical case, convergence towards 0 for the drift occurs over a long period of time, the behavior exhibits a distinct relevant scaling. We quantify the convergences in the relevant variables in the three regimes.

7.21 Global stability and periodicity in a delay differential model

Participants: Mostafa Adimy, Laurent Pujo-Menjouet.

Simple form delay differential equation (DDE) is considered in [23] as a mathematical model of several biological processes. The problems of the global asymptotic stability (GAS) of the unique positive equilibrium and the existence of periodic solutions slowly oscillating about this equilibrium are studied. Sufficient conditions for the GAS are derived in terms of the global attractivity of the unique fixed point of induced interval maps, one set being delay independent conditions and the other one dependent on the size of the delay. Slowly oscillating periodic solutions always exist when the linearized about the equilibrium DDE is unstable. The theoretical results are demonstrated by extensive numerical simulations.

7.22 Regional Control Strategies for a Spatiotemporal SQEIR Epidemic Model: Application to COVID-19

Participants: Mohammed Elghandouri.

In [8], we develop a spatial SEIAR-type epidemic model considering a quarantined population (denoted as Q), which we call the SQEIR model. The dynamics of the SQEIR model are described by six Partial Differential Equations (PDEs) that represent the changes in the susceptible, quarantined, exposed, asymptomatic, infected, and recovered populations. Our goal is to reduce the number of susceptible, exposed, asymptomatic, and infected individuals while accounting for the environment, which plays a critical role in the spread of epidemics. We then propose a novel strategy for epidemic control, incorporating two key control measures: regional quarantine for the susceptible population and treatment for the infected. This approach serves as an alternative to widespread quarantine, minimizing the economic, social, and other

potential impacts. Additionally, we consider the possibility of re-infection among recovered individuals, a common occurrence in many diseases. To demonstrate the practical utility of our results, a numerical example centered on COVID-19 is presented.

7.23 Exploring well-posedness and asymptotic behavior in an Advection Diffusion Reaction (ADR) model

Participants: Mohammed Elghandouri.

In [9], the existence, uniqueness, and positivity of solutions, as well as the asymptotic behavior through a finite fractal dimensional global attractor for a general Advection-Diffusion-Reaction (ADR) equation, are investigated. Our findings are innovative, as we employ semigroups and global attractors theories to achieve these results. Also, an analytical solution of a two-dimensional Advection-Diffusion Equation is presented. And finally, two Explicit Finite Difference schemes are used to simulate solutions in the two- and three-dimensional cases. The numerical simulations are conducted with predefined initial and Dirichlet boundary conditions.

7.24 Optimal control of an impulsive VS-EIAR epidemic model with applications to COVID-19

Participants: Mohammed Elghandouri.

In [6], we investigate a VS-EIAR epidemiological model that incorporates vaccinated individuals $V_i : i = 1, \dots, n$, where $n \in \mathbb{N}^*$. The dynamics of the VS-EIAR model are governed by a system of ordinary differential equations describing the evolution of vaccinated, susceptible, exposed, infected, asymptomatic, and deceased population groups. Our primary objective is to minimize the number of susceptible, exposed, infected, and asymptomatic individuals by administering vaccination doses to susceptible individuals and providing treatment to the infected population. To achieve this, we employ optimal control theory to regulate the epidemic dynamics within an optimal terminal time τ^* . Using Pontryagin's Maximum Principle (PMP), we establish the existence of an optimal control pair $(v^*(t), u^*(t))$. Additionally, we extend the model to an impulsive VS-EIAR framework, with particular emphasis on the impact of immigration and population movement. Finally, we present numerical simulations to validate the theoretical results and demonstrate their practical applicability.

7.25 Analytical derivation of delayed prey-predator model with hunting-and-resting delay

Participants: Mostafa Adimy.

We investigate in [1] a prey-predator model based on a general Gause type system. We take for the predator two phases into account, the hunting phase and the resting one. We suppose that the predators stop hunting after they catch the prey. Then they enter the resting phase where they stay for a fixed limited time. The resulting mathematical model is a system of two age-structured partial differential equations. By integrating this system over age and using the characteristics method, we reduce it to a delay differential system, and we investigate the existence and stability of the steady states. In particular, we have shown that the introduction of the delay (the duration of the resting phase) stabilizes the coexistence equilibrium.

7.26 Traveling Waves in a Hybrid Reaction-Diffusion-Difference SEIR Epidemic Model With Nonlocal Transmission and Protection Phase With Delay

Participants: Mostafa Adimy.

In [16] we study the existence and non-existence of traveling waves for a SEIR epidemic model with diffusion. This system is coupled to an age-structured protection equation that takes into account a proportion of susceptible individuals who protect themselves from the disease through medical treatment or vaccination with temporary immunity, for example. The model includes a compartment of exposed individuals to represent diseases with an incubation period. In addition, the model contains a nonlinear saturated incidence rate to describe the interaction between susceptible and infected individuals. By solving the equation associated with the exposed compartment, we obtain a nonlocal integral representation of the exposed population as a function of the nonlinear incidence rate. This reformulation reduces the model to an hybrid system of reaction-diffusion equations coupled to a continuous difference equation that includes a delay and a nonlocal term, reflecting the movement of individuals during the protection and exposure phases. For wave speeds above a certain threshold, we construct lower and upper solutions for the resulting hybrid system. Finally, we apply Schauder's fixed point theorem in an appropriate function space to establish the existence of progressive wave solutions.

7.27 Three-State Gene Expression Model Parameterized for Single-Cell Multi-Omics Data

Participants: Thomas Lepoutre.

We present in [19] a novel three-state gene expression model designed to elucidate the underlying mechanisms of mRNA transcription and its regulation. Our model incorporates gene regulatory processes by explicitly including a transcription factor-bound state, thereby capturing the dynamic interplay between transcription activation and chromatin dynamics. We fit the model to paired single-cell ATAC-seq and single-cell RNA-seq data, as these data give us simultaneous information on a gene's transcriptional state and its accompanying chromatin state. Working at the pseudo-bulk level, we extract biologically meaningful high-level descriptors from homogeneous cell (sub)populations, such as the mean and variance of gene expression as well as the fraction of accessible chromatin. Crucial to the computational feasibility of our approach, these descriptors can be analytically related to our model parameters. Despite the increased complexity needed to capture regulatory processes in our model, it remains sufficiently parsimonious to infer parameters reliably from experimental data. Each parameter has a clear biological interpretation, reflecting properties such as burst frequency, chromatin opening and closing dynamics, and basal or regulated expression. Fitting the model to a large collection of genes allows us to analyze the parameters and distinguish so-called gene expression strategies. The model parameters reveal a small number of distinct expression strategies among gene clusters, providing data-driven novel insight into context-dependent regulation of gene expression.

7.28 Subdiffusive fractional limit of a jump-renewal equation

Participants: Thomas Lepoutre.

We present in [25] an age-structured jump model that arises as a description of continuous time random walks with infinite mean waiting time between jumps. We prove that under a suitable rescaling, this equation converges in the long time large scale limit to a time fractional subdiffusion equation.

8 Partnerships and cooperations

8.1 International initiatives

8.1.1 Associate Teams in the framework of an Inria International Lab or in the framework of an Inria International Program

Participants: Mostafa Adimy, , Charlotte Camus, , Gregoire Ranson, , Laurent Pujomenjouet, , Leon Tiné. .

Title: Associated team DIFAIRE – “Infectious disease prevention: a multi-scale approach combining crowd dynamics and immuno-epidemiology”,

Partner Institution(s): Partner Institution(s): Centre de Recherche Systèmes Complexes et Interactions de Ecole Centrale de Casablanca (A. Jebrane [Coordinator]) Laboratoire d’Étude et de Recherche en Mathématiques Appliquées (LEREMA), École Mohammedia d’Ingénieurs, Université Mohammed V, Rabat.

Date/Duration: 2024-2026.

Additional info/keywords: The aim is to use a crowd movement model adapted to each social context to simulate contact dynamics (contact matrices) and evaluate the risk of pathogen transmission. This approach takes into account the behavioral, demographic and environmental characteristics of populations, as well as the different transmission routes (direct and indirect contact). The process involves simulating activity locations separately, initially focusing on residential areas as a case study. Expected results include the reproduction of population interactions and the generation of contact matrices to provide information for the macroscopic epidemiological model.

8.1.2 Inria associate team not involved in an IIL or an international program

Participants: Mostafa Adimy, Charlotte Camus.

Title: Associated team MoCoVec "Modelling and Biological Control of Vector-Borne Diseases: the case of Malaria and Dengue"

Partner Institution(s): MAMBA Inria, Paris (P.A. Bliman [Coordinator]) FAPESP São Paulo, Brazil.

Date/Duration: 2022-2025.

Additional info/keywords: 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

8.2 International research visitors

8.2.1 Visits to international teams

Research stays abroad Mostafa Adimy France-Brazil Chair (UNESP): "Nested immuno-epidemiological modeling of intra- and inter-host infection dynamics," two-month stay in São Paulo, October-November, 2025.

8.3 National initiatives

ANR Prio Diff

Participants: Laurent Pujomenjouet, Léon Tine.

Title: Impact of replication and structural diversification of prions on their cerebral dissemination

Partner Institution(s): • Inrae Jouy-en-Josas, France

- Inrae Toulouse, France
- CEA, Fontenay aux Roses, France
- Institut Camille Jordan, France

Date/Duration: July 2021-June 2025

Additional info/keywords: Prions are lethal proteinaceous pathogens with major public-health risks due to their zoonotic and iatrogenic potential. They are composed of aggregated, misfolded conformers of the host-encoded prion protein that progressively deposit in the brain by a self-perpetuating reaction. The underlying molecular mechanisms of replication and tissue dissemination remain mostly elusive. Our objective is to model these processes entirely based on recent advances that prion aggregates are conformationally heterogeneous and dynamic rather than uniform and static. To achieve this, we will map in prion-infected brain the structural diversification-to-bioactivity/neurotoxicity landscape of prion assemblies in a spatiotemporal manner and mathematically build a multiscale model of diversification and lesion spreading. The goal is to generate an open access model capable of predicting the disease progression and identify key elementary process for therapeutics intervention and early diagnostics.

Keywords: interactions hôtes pathogènes, infectiologie, modélisation prion, tissue diffusion, neuro-tropism.

ANR PLUME

Participants: Thomas Lepoutre, Maxime Estavoyer.

Title: Molecular and morphogenetic control of feather pattern formation

Partner Institution(s):

- Centre interdisciplinaire de recherche en biologie (M. Manceau [Coordinator])
- Institut de Biologie du Développement de Marseille
- Brandeis University.

Date/Duration:2021-2025

Additional info/keywords: The objectives are to identify the hierarchy of pattern forming mechanisms establishing initial patterning spaces, characterise material properties and mechanical stresses controlling primordia self-organisation, and uncover how cell and mechanical dynamics control the timely wave of primordia production. This work will shed light on the mechanisms governing pattern variation and fidelity in nature.

PEPR Santé Numérique , project AI4scMed

Participants: Olivier Gandrillon, Thi Nhu Thao Nguyen, Thomas Lepoutre.

Title: PEPR Santé Numérique , project AI4scMed (Multiscale AI for single-cell-based precision medicine)

Partner Institution(s):

- Inria
- Inserm
- CNRS

Date/Duration: since 2023

Additional info/keywords: We are concerned by WP4: “Towards multiscale mechanistic models for innovative treatments” in collaboration with CNRS (F. Crauste) and Inria team MUSCA (F. Clément). Coordinator: F. Picard (CNRS, ENS Lyon).

PEPR MathsVives, project MAMUTCELL

Participants: Michele Romanos, Thomas Lepoutre.

Title: PEPR MathsVives, project MAMUTCELL

Partner Institution(s): • Université Claude Bernard

- ENS Lyon
- CNRS
- Université Brest, Bretagne Occidentale
- Aix-Marseille Université

Date/Duration: since 2025

PEPR MathsVives, project PREMMOVE

Participants: Michele Romanos.

Title: PEPR MathsVives, Predictive Morphogenesis and mathematical Modeling of Vertebrate Embryos

Partner Institution(s): • Université Claude Bernard (ICJ)

- MCD (Toulouse, UMR CNRS Biology)
- CNRS
- LAAS
- Université de Toulouse

Date/Duration: since 2025

MITI CNRS:

Participants: Michele Romanos.

Title: Interactions complexes et comportements collectifs

Partner Institution(s): • CNRS

Date/Duration: since 2025

Additional info/keywords: This project studies the collective patterning and dynamics of a colony of single cells under self-generated gradients. collaboration with ILM (LYon) UBO (Brest) and ICJ (Lyon)

8.4 Regional initiatives

IXXI Project

Participants: Thomas Lepoutre, Michèle Romanos.

Title: Modeling and characterizing migration in glioblastoma, modeling sensitive and resistant cells in interaction

Partner Institution(s): Centre de recherche en Cancérologie de Lyon (CRCL, Erika Cosset).

Date/Duration:2021-2025

Additional info/keywords: The aim of this project is to develop a simple model of cell migration that can be parameterized with respect to homogeneous data. Once such a model has been characterized, we'll be able to build a strain-mixing model to propose a description of the effect of resistant cells on susceptible cells (which can become resistant in the presence of stress and resistant cells).

9 Dissemination

9.1 Promoting scientific activities

Member of the organizing committees

- Thomas Lepoutre in in the organizing committee of [Mathematics of Single-Cell Data-Analysis au CIRM à Marseille](#)

Member of the conference program committees

- Thomas Lepoutre is a member of the program committee for [JMBS 2025](#)

9.1.1 Journal

Member of the editorial boards Laurent Pujou-Menjouet is member of the editorial board of:

- Journal of Theoretical Biology,
- Mathematical Modelling of Natural Phenomena
- Plos One

Reviewer - reviewing activities All permanent members of the MUSICS team frequently work as reviewers for the main scientific publications in their respective fields. We chose not to list each of these publications here.

9.1.2 Invited talks

Here is a short selection of invited talk given by members of the team this year:

- Thomas Lepoutre Saint Etienne : Mathematical modelling and health: biomechanics, hemodynamics, aggregation phenomena.
- Mostafa Adimy: São Paulo, October 2025: Multi-serotype nested immuno-epidemiological PDE model for dengue hemorrhagic fever with backward bifurcation and serotype invasion.
- Mostafa Adimy: Casablanca, May 2025: Continuous-time differential-difference models in population dynamics and epidemiology.
- Clément Erignoux: Oberwolfach Workshop 2536, August 2025, Large Scale Stochastic Dynamics, Transience and mixing time for the FEP and the SSEP with traps.
- Clément Erignoux: PSPDE XIII, Modena, November 2025: Hydrostatic and hydrodynamic behavior of SSEP with non-reversible boundary dynamics.

9.1.3 Research administration

- Thomas Lepoutre is member of the board of Insitut Camille Jordan
- Thomas Lepoutre is member of the scientific council of Insitut Camille Jordan
- Thomas Lepoutre is member of the scientific council of Réseau Thématique Math-Bio-Santé.
- Starting 2025, Clément Erignoux is the local correspondant for the Lyon center's Radar campaign.

9.2 Teaching - Supervision - Juries - Educational and pedagogical outreach

9.2.1 Teaching

- Laurent Pujo-Menjouet: MD Sciences pour la santé in PASS,
- Michele Romanos: Renforcement in Cursus prépa Polytech 1A,
- Samuel Bernard: Processus stochastiques in Cycle ingénieur INSA Dept Biotechnologies Bioinformatique,
- Samuel Bernard: Remise à niveau en mathématiques in Cycle ingénieur INSA Dept Biotechnologies Bioinformatique,
- Samuel Bernard: Modélisation EDP in Cycle ingénieur INSA Dept Biotechnologies Bioinformatique,
- Samuel Bernard: Modélisation EDO avancée in Cycle ingénieur INSA Dept Biotechnologies Bioinformatique,
- Samuel Bernard: Modélisation EDO avancée in Cycle ingénieur INSA Dept Biotechnologies Bioinformatique,
- Samuel Bernard: Algèbre pour l'analyse de données in Cycle ingénieur INSA Dept Biotechnologies Bioinformatique,
- Thibault Espinasse: Analyse des données in L3 double licence Maths-Eco,
- Clement Erignoux: Probabilités in Double Licence Mathématiques - Physique 3A,
- Laurent Pujo-Menjouet: fondamentaux des maths pour la santé in F.G.S.M.2 (Lyon Est),
- Michele Romanos: Algèbre 2 in L1 Mathématiques informatique,
- Charlotte Camus: Algèbre 2 in L1 Mathématiques informatique,
- Leon Tine: Algèbre 2 in L1 Mathématiques informatique,
- Laurent Pujo-Menjouet: Math et Stat appliquées à la santé 1 in L1 Sciences pour la santé,
- Leon Tine: Analyse matricielle et algèbre linéaire in L2 Informatique,
- Thibault Espinasse: Probas Stats 2 in L2 Mathématiques,
- Leon Tine: Compléments mathématiques in L2 Mathématiques,
- Leon Tine: Mathématiques 3 in L2 Physique,
- Leon Tine: Mathématiques 4 in L2 Physique,
- Laurent Pujo-Menjouet: Math et Stat appliquées à la santé 2 in L2 Sciences pour la santé,
- Laurent Pujo-Menjouet: Biomathématiques et modélisation in L3 SV prcs bio informatique, statistique et modélisation,

- Laurent Pujo-Menjouet: Math et Stat appliquées à la santé 3 in L3 Sciences pour la santé prcs objets connectés,
- Laurent Pujo-Menjouet: Parcours personnel et professionnel in Licence STS,
- Thibault Espinasse: Graphes et réseaux en écologie in M2 Maths en action,
- Laurent Pujo-Menjouet: Systèmes dynamiques in M1 Mathématiques appliquées, statistiques,
- Thibault Espinasse: Statistique bayésienne in M1 MAS,
- Thibault Espinasse: Classification et réseaux de neurones in M1 MAS,
- Thibault Espinasse: Cas pratiques in M1 MAS,
- Thomas Thomas: Sciences Fondamentales pour le vivant in M1 Santé publique, Initiation à la recherche ,
- Michele Romanos: Systems Biology in M2 BMC Génétique de la cellule et pathologie,
- Samuel Bernard: Dynamique cellulaire et systèmes complexes in M2 Maths en Action ,
- Laurent Pujo-Menjouet: Mathématiques et statistique pour la santé in M2 Stats, Modèles et Sciences des données,
- Thibault Espinasse: Remise à niveau en statistique in M2 Stats, Modèles et Sciences des données,
- Thibault Espinasse: Méthodes en apprentissage statistique in M2 Stats, Modèles et Sciences des données,
- Aymeric Baradat: Transport optimal pour l'apprentissage in M2 Maths en action,
- Thomas Lepoutre: Cours fondamental in M2 Mathématiques avancées,
- Clement Erignoux: Cours avancé in M2 Mathématiques avancées,
- Laurent Pujo-Menjouet: Du modèle biologique au modèle statistique in M2 Santé publique prcs Biostat, Bioinfo, Biomath for health,
- Laurent Pujo-Menjouet: Modeling in biology and medicine in M2 Sciences de la matière,
- Laurent Pujo-Menjouet: Modeling in biology and medicine in M2 Sciences de la matière,
- Mostafa Adimy: An introduction to delay differential equations with applications in population dynamics and epidemiology, for undergraduate and postgraduate students, Institute of Biosciences, Botucatu (UNESP), São Paulo, Brazil.

9.2.2 Supervision

- PhD defended: Charlotte Camus, "Nested Immuno-epidemiological modeling of the dynamics of intra- and inter-host infections", Université Lyon 1, since October 01, 2022, supervisor: Mostafa Adimy .
- PhD defended: Basile Fornara, "Mécanismes de dissémination des prions dans les tissus cérébraux : une approche synthétique", Université Paris Cité, since October 21, 2022, supervisors: Human Rezaei and Laurent Pujo-Menjouet .
- PhD in progress: Grégoire Ranson, "Mathematical modeling of epidemics spreading dealing with temporary treatment efficiency" , since January 1st, 2022, supervisors Mostafa Adimy , Laurent Pujo-Menjouet , Jianhonw Wu (York university) **funded by SANOFI**
- PhD in progress: Théo Loureaux, "Contribution to the study of neurodegenerative diseases", since January 1st, 2023, supervisors Laurent Pujo-Menjouet , Suzanne Sindi (UC Merced)

- PhD in progress: Ruben Taieb, supervisor Mostafa Adimy (with Arnaud Ducrot, Le Havre)
- PhD in progress : Clemence Fournie, supervisor Olivier Gandrillon (co-supervision with Fabien Crauste, Paris)
- Post-doc: Thao Nguyen Thi Nhu, supervisors: Olivier Gandrillon
- Post-doc: Mohammed Elghandouri, supervisor Mostafa Adimy
- PhD defended: Arsène Marzorati, "Mixed floating precision schemes for ODEs in large dimensions", supervisors Samuel Bernard (co-supervisor Jonathan Rouzaud-Cornabas)
- PhD in progress: Clémence Métayer, "Machine learning for the dynamics of interactions between the NLRP3 immune receptor, DNA repair and the circadian clock for lung cancer treatment optimisation", co-supervisor Samuel Bernard (supervisor A Ballesta)
- PhD in progress : Brune Massoulié, "Macroscopic behavior and timescales for kinetically constrained lattice gases", supervisor Clément Erignoux (co-supervision with Cristina Toninelli, Paris)
- PhD in progress : Hugo Da Cunha, "Macroscopic behavior of non-equilibrium facilitated exclusion processes", supervisor Clément Erignoux (co-supervision with Marielle Simon, Lyon)

9.2.3 Juries

- Thomas Lepoutre was examiner in the PhD jury of Coline Hermine CIRB (collège de France, biology), "Origine et formation des motifs périodiques de couleurs chez les oiseaux".
- Thomas Lepoutre was referee for the PhD of Saoussen Latrach LAGA (PSL), "Analyse mathématique du blocage de phénomènes d'invasion ; applications aux maladies inflammatoires et au remplacement de populations".

9.3 Popularization

9.3.1 Participation in Live events

- Thomas Lepoutre has participated to the ICJ stand at Fête de la science

10 Scientific production

10.1 Publications of the year

International journals

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- [8] M. Elghandouri, K. Ezzinbi and Y. Mezzan. ‘Regional Control Strategies for a Spatiotemporal SQEIAR Epidemic Model: Application to COVID-19’. In: *International Journal of Control* (24th Jan. 2025), pp. 1–19. DOI: [10.1080/00207179.2025.2456036](https://doi.org/10.1080/00207179.2025.2456036). URL: <https://hal.science/hal-05045576> (cit. on p. 16).
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- [16] H. Meghelli, A. Chekroun and M. Adimy. ‘Traveling Waves in a Hybrid Reaction-Diffusion-Difference SEIR Epidemic Model With Nonlocal Transmission and Protection Phase With Delay’. In: *Mathematical Methods in the Applied Sciences* 48.14 (3rd June 2025), pp. 13380–13398. DOI: [10.1002/mma.11110](https://doi.org/10.1002/mma.11110). URL: <https://inria.hal.science/hal-05447865> (cit. on p. 18).
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- [19] T. Peyric, T. Lepoutre, A. Crombach and T. Guyet. ‘Three-State Gene Expression Model Parameterized for Single-Cell Multi-Omics Data’. In: 23rd International Conference on Computational Methods in Systems Biology (CMSB 2025). Lyon, France, 19th July 2025. DOI: [10.1101/2025.07.16.665109](https://doi.org/10.1101/2025.07.16.665109). URL: <https://hal.science/hal-05180519> (cit. on p. 18).

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- [20] C. Dugourd-Camus. ‘Nested immuno-epidemiological modeling of the dynamics of intra- and inter-host infections: application to Dengue Hemorrhagic Fever’. Université Claude Bernard Lyon 1, 4th Dec. 2025. URL: <https://inria.hal.science/tel-05443140>.
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- [22] L. M. TINE. ‘Contribution à la modélisation mathématique et au calcul scientifique: Dynamique de population, Modeles structurés pour la maladie d’Alzheimer, Schémas numériques, Problemes inverses et Contrôle optimal pour l’estimation de parametres’. Université Claude Bernard Lyon 1, 9th Jan. 2025. URL: <https://hal.science/tel-05450259> (cit. on p. 7).

Reports & preprints

- [23] M. Adimy, F. Crauste, A. Ivanov and L. Pujo-Menjouet. *Global stability and periodicity in a delay differential model*. 3rd Sept. 2025. URL: <https://hal.science/hal-05363003> (cit. on p. 16).
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- [25] H. Berry, P. Gabriel, T. Lepoutre and N. Quiblier. *Subdiffusive fractional limit of a jump-renewal equation*. 13th Jan. 2026. URL: <https://hal.science/hal-05456904> (cit. on p. 18).
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- [27] M. Estavoyer. *A reaction telegraph model reveals synergy between motility strategies in Myxococcus xanthus predation*. 31st Dec. 2025. URL: <https://inria.hal.science/hal-04699047> (cit. on p. 15).
- [28] C. Fournié, E. Ventre, U. Herbach, A. Baradat, O. Gandrillon and F. Crauste. *Cell Trajectory Inference based on Schrödinger Problem and a Mechanistic Model of Stochastic Gene Expression*. Nov. 2025. URL: <https://hal.science/hal-05376256> (cit. on p. 13).
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