RESEARCH CENTRE

Inria Saclay Centre at Institut Polytechnique de Paris

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2023 ACTIVITY REPORT

Project-Team MERGE

Mathematics for Evolution, Reproduction, Growth and Emergence

IN COLLABORATION WITH: Centre de Mathématiques Appliquées (CMAP)

DOMAIN

Digital Health, Biology and Earth

THEME

Computational Biology

Inria

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Project-Team MERGE

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Computer sciences and digital sciences

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A6.1.4. – Multiscale modeling

A6.2.1. – Numerical analysis of PDE and ODE

A6.2.3. – Probabilistic methods

A6.2.4. – Statistical methods

A6.3.1. – Inverse problems

Other research topics and application domains

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1 Team members, visitors, external collaborators

Research Scientists

- Marie Doumic-Jauffret [Team leader, Inria, Senior Researcher, HDR]
- Gael Raoul [CNRS, Researcher]
- Milica Tomasevic [CNRS, Researcher]

Faculty Member

- Vincent Bansaye [Ecole Polytechnique, Professor, HDR]

Post-Doctoral Fellow

- Laetitia Colombani [Ecole Polytechnique, from Sep 2023]

PhD Students

- Sirine Boucenna [Ecole Polytechnique]
- Claire Ecotière [Ecole Polytechnique, until Oct 2023]
- Ana Fernandez Baranda [Ecole Polytechnique]
- Guillaume Garnier [Inria]
- Madeleine Kubasch [Ecole Polytechnique]
- Maxime Ligonnière [Ecole Polytechnique]
- Ignacio Madrid Canales [Ecole Polytechnique]
- Jules Olayé [Ecole Polytechnique]
- Alexandre Perrin [Ecole Polytechnique, from Oct 2023]
- Anaïs Rat [Inria, until Mar 2023]

Administrative Assistant

- Anna Dib [INRIA]

2 Overall objectives

The wide domain of population dynamics has had many developments in recent years, in probability with the study of stochastic integro-differential equations [36] as well as in PDE analysis [108, 107]. The two approaches are combined more and more frequently, for model analysis [51, 35] as well as for estimation problems [19]. In biology, many new questions have appeared, and the very recent development, over the last decade, of the so-called "single cell" or micro-fluidic methods [124, 75, 89, 39] make these models all the more topical as they can now be quantitatively compared with the data microscopically as well as macroscopically. Many essential medical and social applications are closely related to our research, *e.g.* cancer treatment (see Section 4.1), biotechnologies (Section 4.3), antibiotic resistance (Section 4.1), species extinction (Section 4.4). Our main theoretical guideline, which can have applications in other fields (SPDE, propagation of uncertainty, PDE analysis...), is to reconcile PDE approaches with stochastic ones, in situations where the two types of dynamics play a fundamental role at different scales. Our main application guideline is to study problems directly inspired by our biologist collaborators' questions, so that even our most theoretical work could have an impact also in biology or medicine.

The applications drive our mathematical research, including the most theoretical ones. Many of our models have several possible applications so that the interests of MERGE members converge, since for instance we are interested in modelling mutations both for bacteria and for leukemic cells; emergence of survivors for senescent yeasts as well as for bacteria under antibiotic treatments; evolutionary questions for bacterial populations as well as tree populations submitted to the climate change. Moreover, most of our mathematical models have even wider applications than in biology - among many other possible examples, fragmentation processes occur in mineral crushing in the mining industry, cell division models are close to models for the TCP-IP protocol. The main application domain, shared by all team members, concerns unicellular organism populations.

Our research program is organised along three main axes. First, the study of "models through scales", *i.e.* the links between various stochastic or PDE models through convergence analysis of individual-based models towards mesoscopic or macroscopic ones, is essential for our models to have a solid foundation. The second axis is their mathematical analysis, which allows one to qualitatively compare them to biological systems and use them as predictive and exploration tools, whereas the third one develops methods for their quantitative comparison to data. For each research axis, we outline what we consider to be the major current research issues of the field, and then use a few non exhaustive examples of work in progress to give a concrete description of our work programme in the short and medium term.

To make the links between our research program and the applications more obvious, we have specified the main research axes concerned for each application.

3 Research program

Our research program is entirely devoted to the modelling and study of interacting populations. In many cases, we will also develop methods for quantitative model-data comparison through estimation methods and inverse problems.

The first research axis, "Models through scales", is devoted to mathematical problems which appear in order to obtain rigorous links between microscopic, mesoscopic and macroscopic models. These questions are closely related to the modelling work, which we have not detailed in a specific section, as it is carried out through exchanges with our medical doctors and biologists collaborators and is a direct continuation of the application questions outlined above. The second axis gathers qualitative analysis problems for the structured population models that we wrote during such modelling work, or inspired by our interdisciplinary discussions. The third axis, "Model-data comparison", goes back to the data, through inverse problems theoretical and numerical solution.

3.1 Axis 1: Models through scales

Permament members: Vincent Bansaye, Marie Doumic, Sylvie Méléard, Gaël Raoul, Milica Tomašević

When we describe non-interacting populations which undergo mutations, growth, movement, division and death, the stochastic branching process modelling each individual behaviour may be translated to a structured population equation or system in a rather direct way, by the use of random measures [19] or from the expectation of the empirical measure linked to the branching tree and so-called many-to-one formulae [57]. This is no more true once interaction between the cells or with the environment is considered: in such cases, mean-field limits have to be derived [78], by making the number of individuals in the population tend to infinity. Making such limits rigorous, and relating the asymptotic models to specific parameter regimes, is a very active research field not only for structured populations but also in physics. One faces several fundamental questions: how to describe and quantify the emergence of an initially very small number of individuals, inside multi-species interacting populations which, depending on available resources and space, will finally succeed to become dominant? How to keep track of microscopic fluctuation at the macroscopic level? How to perform a macroscopic limit when each individual interacts only with its closest neighbours rather than with the overall population? Finally, how stochasticity and heterogeneity between individuals impact macroscopic behaviours? These issues drive our work. Let us now detail some more specific problems we want to study.

From stochastic processes to constrained Hamilton-Jacobi (HJ) equations.
Permanent members: Sylvie Méléard, Gaël Raoul

Most models, for instance for the "normal" bacterial division cycle [68], consider asexual populations with clonal reproduction and vertical inheritance. We want to consider here a more general model with a transfer term, justified by biological considerations in the case of bacterial transfer [74] (see also the application section 4.1). The individual-based population process is given for any K by the jump point-measure Markov process $(\mu_t^K)_t$ on a trait subset of $\mathbb{R}^d$ weighted by $1/K$. An individual with trait x gives birth to a new individual with rate $b(x)$. With probability $1-p_K$, the new individual carries the trait x and with probability p_K, it carries a mutant trait z chosen according to the distribution $m(x,z)dz$. An individual with trait x in the population μ^K dies with death rate $d(x)+C\langle\mu^K(t),1\rangle$. Further an individual with trait x chooses a partner with trait y at rate $h_K(x,y,\mu^K)=\tau(x,y)/K\langle\mu^K,1\rangle$ and after transfer, the couple (x,y) becomes (x,x). Then for any "good" test function φ, we have

$$\begin{aligned}\langle\mu_t^K,\varphi\rangle =&\langle\mu_0^K,\varphi\rangle+\int_0^t\int_{\mathbb{R}}\Big\{\Big(b(x)-d(x)-C\langle\mu_s^K,1\rangle\Big)\varphi(x)+p_K b(x)\int_{\mathbb{R}}\big(\varphi(z)-\varphi(x)\big)m(x,z)dz\Big\}\mu_s^K(dx)ds\\&+\int_0^t\int_{\mathbb{R}}\frac{\tau(x,y)}{\langle\mu_s^K,1\rangle}\big(\varphi(x)-\varphi(y)\big)\mu_s^K(dx)\mu_s^K(dy)ds+M^{K,\varphi}(t),\end{aligned}\tag{1}$$

where $M^{K,\varphi}$ is a square integrable martingale whose quadratic variation can be easily made explicit. By letting K go to infinity, and p_K go to p, we can derive an integro-differential equation with non local non linearities due to both competition and transfer. Uniqueness of its solution is obvious but its long-time behaviour is unknown, as well as the existence of stationary solutions. Formally, applying a limiting procedure for small mutations and time rescaling usually leads to a HJ type equation with constraints, in the formalism introduced in [63], successfully developed in [41, 109, 40], and in many extensions so far. Concentrations in such equations are too fast for realistic evolution [110]. Indeed the evolutionary dynamics strongly depend on the positivity of the density although it is exponentially small for some traits. Different papers [110, 84, 100] proposed to slow down the concentration speed by the addition of artificial terms. With Nicolas Champagnat, Sylvie Méléard introduced another point of view. The rare mutation assumption introduced in [50] allowed to obtain a time scale separation between demography and mutation. Under this assumption, they were able to characterize rigorously a general evolutionary jump process describing the successive evolutionary population states [52]. This approach was very fruitful and allowed to quantify the complete scheme from individuals to macroscopic behaviors as suggested in [97] and [62]. Nevertheless, the assumptions imposed very small mutation rates considered too slow to explain evolution (especially for microorganisms), but also too slow to capture the concentration effects of the HJ equations. At this point one may recall the usual critics by some biologists [125], of unrealistic evolutionary time scale, at least for certain species.

The first task in this study is to integrate fast mutation time scales and to show how stochastic models based on logarithmic scales can capture small populations in large approximations and explain deterministic concentration phenomena. In particular we aim to obtain new singular and constrained HJ equations taking into account the local population extinctions. We hope that these new scales will provide an intermediate approach consistent with biological observations.

The second task is to characterize the different asymptotic behaviors in the Hamilton-Jacobi equation and to understand the role of the trade-off between demography and transfer.

Space-and-trait structured models

Permanent members: Vincent Bansaye, Marie Doumic, Gaël Raoul

Effects of spatial heterogeneity on structured population dynamics need to be studied for many applications, in ecology as well as in microbiology. Here again, relating macroscopic to individual-based models is of key importance for a correct interpretation of macroscopically observed phenomena such as morphogenesis or front propagation. Let us develop two examples: size-and-space structured models and phenotypic trait-and-space structured models.

Microcolony morphogenesis. A bacterial microcolony may form out of one single cell, growing and dividing in a petri dish without movement except due to the growth. We can describe it by an individual-based model, where each cell repulses and maybe attracts its neighbours, but how do these local interaction forces influence the overall shape of the microcolony? When and how do specific patterns emerge? Do the bacteria only repulse each other or is attraction possible? Which mesoscopic or macroscopic description would be valid? These are some of the questions we want to address.

As a first step, in [70], Marie Doumic, Sophie Hecht and Diane Peurichard proposed a purely-repulsive individual-based model of rod-shaped bacteria, where growth, division and repulsion were sufficient to explain the main characteristics of microcolonies observed.

A first research direction consists in deriving rigorously a kinetic model, including both a spatial structure and a structuring trait such as size. For a model with spherical 2D-cells dividing into equally-sized daughters, with an interaction force ϕ, an example of limit model satisfied by $u(t,x,r)$ the density of cells at time t, position x and radius r is as follows

$$\begin{aligned} \tfrac{\partial}{\partial t}u(t,x,r) \quad &+\tfrac{\partial}{\partial r}\left(g(r)u\right)+\nabla\cdot(G[u]u)+\beta(r)u \\ &= 2\sqrt{2}\beta(\sqrt{2}r)\int_0^1 \kappa(\theta)u(t,x+\alpha r\,(\cos(2\pi\theta),\sin(2\pi\theta)),\sqrt{2}r)d\theta, \quad t\geq 0,\ x\in\Omega,\ r>0, \qquad (2) \\ u(0,x) \quad &= u_0(x), \qquad g(0)u(t,x,0)=0, \qquad G[u]=-\textstyle\int_{\Omega\times(0,\infty)}\phi(|\frac{x-x'}{r+r'}|^2)(x-x')u(dx',dr'). \end{aligned}$$

This should generalize the model proposed in [102]. However, the main drawback is that to prove rigorously this limit, departing from a stochastic differential equation of the same kind as (1) when the number of cells K tends to infinity, one needs to assume a nonlocal interaction kernel G, so that at the limit each cell interacts with infinitely many others. This is false for many applications and in particular for morphogenesis. We thus want to derive, from (2), a macroscopic model where the nonlocal interaction kernel G boils down to a local one, cells interacting only with the ones at the same macroscopic position x [49]. However, even for simpler cases - for instance forgetting with the growth and division terms - many difficulties appear, since existing methods [105, 104], based on energy inequalities and compactness embeddings [88, 93], cannot apply due to the lack of compactness in the size variable.

Another research direction, for not isotropic cells but rather rod-shaped bacteria like *E. coli*, is to include a direction for each individual. In this spirit, nematic liquid crystal models [32, 92] have been proposed to describe a variety of biological active fluids, *e.g.* cellular monolayers [66, 123, 126]; though, how they may be derived from individual-based models such as the hard-rod model of [126, 70] or the models of [55, 123] remains unclear. We aim at deriving, formally and then - on simplified versions of the model - rigorously, a continuous model of liquid crystal type.This could then be a step towards the reverse question: how to estimate the *microscopic* interaction function from a *macroscopic* picture of the colony at a given time, see Section 3.3.

Space and phenotype species models. Sexual reproductions imply the recombination of DNA during reproductions. The models describing the effect of recombinations on trait-structured species can be divided into two classes: the ones describing the dynamics of a small number of loci (typically less than 3), and the ones considering an infinite number of loci. In the latter case, the main model used is the so-called infinitesimal model, that was developed by Fisher in 1919 [76]. This model is reminiscent of collision models from statistical physics, which provides an interesting perspective to study the dynamics of these models, in particular when this phenotypic structure is coupled to a distribution of the species in space.

Our first goal will be to generalize the derivation of mascroscopic limits[101, 43] to situations where a finite (but large) number of loci are present, and/or where the reproduction is partially asexual. We would like to study the spatial dynamics of such species compare to asexual species on one side, and to the infinitesimal model case on the other side. From a ecological stand point, this would help us understand the impact of recombination on species' range.

Our second goal will be to use these macroscopic limits to build travelling waves for the structured population models. We would then take advantage of the diffusion operator that represents the effect of the spatial dispersion of individuals. The main roadblock here will be to develop a good framework for

the macroscopic travelling waves [98]. This is difficult because the macroscopic equations (describing the population by its size and mean phenotypic trait in each location) involves a so-called gene flow term, that we do not fully apprehend yet. This difficulty is directly related to ecological questions: gene flow is an important effect of sexual reproduction on a species' evolutionary dynamics.

The last objective on this topic would be to develop a software able to simulate the dynamics of a species' range. Based on the travelling wave analysis we have developed [27], we believe we could use recently developed fast-marching algorithms [99] to propose a description of the effect of climate change on a given species.

From local interaction models to cross-diffusion equations. Many interactions of species and cells are local, which means that they occur when individuals are close enough, at a distance negligible for the macroscopic scale. Going from the individual level to macroscopic models raises several mathematical challenges linked in particular to the control of the non linearity in the motion component [77]. This issue is linked to the control of the limiting PDE (stability, non-explosion, invariant distribution, entropic structure) and the distance involved in the convergence of the stochastic process. Vincent Bansaye, Ayman Moussa and Felipe Munoz have developed duality estimates to prove stability of the limit and get a strong convergence of the stochastic model seen as a random perturbation [37].

Non-markovian interactions: from local interaction model to the parabolic-parabolic Keller-Segel system

Permanent members: Milica Tomašević

An important mathematical challenge is to derive mean-field limits for *non-Markovian* interaction, *i.e.,* when the past also needs to be taken into account. Such models appear for instance in neuroscience [54, 53] and chemotaxis. To model chemotaxis, the parabolic-parabolic Keller-Segel model has been stated phenomenologically, but to interpret it we need to introduce interaction memory, which provides tremendous analysis difficulties since particles are now non-markovian both in time and space. New methods have been proposed by Milica Tomašević, with a stochastic representation of the *mild* formulation of the equation and a particle approximation [114, 118, 116]. The equations obtained have been little studied before Milica Tomašević's Ph.D thesis, so that many questions remain open. Concerning the convergence of the particle systems towards the Keller-Segel model, an important problem is the obtention of explicit convergence rates, when the number of particles tends to infinity, for the propagation of chaos of the particle system in 1D. A possible way is to extend techniques developed by Jabin and Wang [85] for the quantitative study of the mean-field boundaries of particle systems in non-regular Markovian interaction. The aim is to control the relative entropy between the joint law of the particles and the law of N independent copies of the Keller-Segel system. By exploiting the results on the Keller-Segel nonlinearity in 1 dimension and on the Sobolev type estimation on the densities of the system (chapter 4 in [117]), a regularization of the interaction kernel of the particles allows to obtain a first convergence rate for the marginal laws in time of an arbitrary particle, explicit but suboptimal (due to the regularization procedure). To obtain the optimal convergence rate, we think to develop an essentially probabilistic approach suggested by the recent works of Veretennikov [122] and Lacker [91] as well as by the partial Girsanov transformations introduced in [86].

3.2 Axis 2: Qualitative analysis of structured populations

Diffusion-growth-fragmentation processes and equations

Permanent members: Marie Doumic, Sylvie Méléard

To model the growth of a bacterial population in a chemostat, a new model of growth and fragmentation, coupled to a differential equation for the resource, was proposed by Josué Tchouanti in his thesis [115]. Using a combination of probabilistic and analytical methods, he proved the existence,

uniqueness and regularity of solutions, as well as the convergence in large populations of the individual-based model. This model also present similiarities with the proliferation of parasites in dividing cells studied by Vincent Bansaye [38, 34].

One of the very interesting novelties of this model is to consider the growth not as a purely deterministic process, leading to a transport term in the size structured equation $\frac{\partial}{\partial x}(\tau(x)u(t,x))$, but to take into account the intrinsic stochasticity in growth, so that a diffusion-type term $\frac{\partial^2}{\partial x^2}(D(x)u(t,x))$ is added, which degenerates at the boundary $x = 0$. We thus want to study further this equation, its long-time dynamics with and without interaction (*i.e.* in the linear case as well as with nonlinear couplings), how it differs from the much more studied growth-fragmentation equation, and which model seems more relevant in which applicative case. We also want to adapt the model to metabolic heterogeneity cases, *i.e.* when we model the capacity for bacteria to feed on two distinct nutrients, which leads to distinguish two populations competing for two resources.

Ergodicity analysis and exponential convergence for multi-dimensional growth-fragmentation processes and equations

Permanent members: Vincent Bansaye, Sylvie Méléard, Milica Tomašević

Based on data from the Edinburgh's lab of Meriem El Karoui, Ignacio Madrid Canales introduced during his thesis an adder growth-fragmentation stochastic process modelling the growth of bacteria. He studied its long time behaviour and proved that conveniently renormalized, the associated semigroup converges exponentially to a well defined measure. The aim is now to generalize this result in higher dimensions, motivated by the different growth strategies that bacteria can have under stress. Mathematically the question is also largely open.

Understanding the links between genealogical and population behaviours

Permanent members: Vincent Bansaye, Marie Doumic and Sylvie Méléard

Microfluidic experiments allow one to follow a genealogical lineage of cells, whereas most previous experiments as well as "natural" conditions consist in observing a full population dynamics. The natural question then comes to relate the two models, and to understand how certain phenomena may be observed in one setting but not in the other - for instance, how a few individuals may finally invade the whole population; how survivor cells may emerge from a senescent population; or yet, how to find the "signature" of a phenomenon that happened in the past from the observation of a population at a fixed time.

Differential influence of the initial condition Time to extinction in the case of genealogical data differs drastically from time to extinction for a dividing whole population, so that observing the first occurs at a much faster timescale than the second. Relating the two in simple models like the Galton-Watson tree is straightforward, but much more involved in more complex cases [36], especially if rare mutation events occur (see Section 3.1). With a view towards telomere shortening models and the interpretation of experiments carried out by Teresa Teixeira's lab, we want to assess rigorously the relations between these two observation cases in increasingly complex models. Reversing time in population models which are in a stationary regime has been well developed during the past decades, using coalescent and duality theories, in particular in the case of fixed population size. Understanding the genealogical structure in transitory regime (such as growth), keeping track of the initial conditions (in particular in finite window size of experiments or cancer treatment or epidemics) or capturing the effect of variations of the populations raise new and fundamental mathematical issues. For that purpose, we aim at developing spinal approaches, which consist in a forward construction distinguishing an individual bound to be the sample at a future time.

Time reversed trajectories. A natural question is to get information on individuals from observation on the whole population at a given time. More precisely, given a finite sample of living individuals, we aim first, to find their genealogical and trait's history and second, to find the explicit time reversed path

from a sampled individual to its ancestor. A particularly interesting case is the one when the initial density of the whole stochastic process is close to a Dirac measure. This question motivated an abundant literature in population genetics with the so-called Kingman coalescent (see [90], [44] and references therein), or lookdown processes [65], [73] in a context of fixed and small population size, almost neutrality and individuals independence. Genealogy of branching processes models have also been introduced, allowing demographic structure but no interactions (cf. [94]). Our framework is different: we focus on bacteria or cells which form large populations and for which assumptions of neutrality, extrinsic control of population size or non-interacting individuals are violated. Developing methods which relax such hypotheses is a contemporary challenge, which could be used in different contexts (see below how this point of view can be of particular relevance to study the individuals responsible of the population survival in case of environmental changes). Inspired by Perkins [106], Sylvie Méléard and Viet Chi Tran constructed in [96] a nonlinear historical super-process with values in a paths measure space, capturing the history of a large population. It is a heavy object which might not be tractable for our goal.

Our purpose is to introduce more tractable tools, exploiting the large population assumption ($K \to \infty$) and the spinal techniques developed for branching processes (cf [82, 81], [94] and references therein). We have seen that the stochastic process (1) is close to the solution of an integro-differential equation. Therefore, we can construct for large K a coupling between the stochastic process and a non-homogeneous structured branching process where the interaction terms have been replaced by their deterministic approximation. We should obtain some non-homogeneous biased Markov process by giving its associated infinitesimal generator. The next step would consist in finding the time reversed trajectory of a sample individual. This will be done using time reversal theory for non-homogeneous Markov processes, see [56, 103]. This program has already been developed in the Gaussian case [48] and lead to a precise quantitative description of the reverse trajectories explaining the genetic or phenotypic characteristics of a living individual.

3.3 Axis 3: Model-data comparison

Permanent members: Marie Doumic, Sylvie Méléard, Milica Tomašević

Comparing models to data, either qualitatively or quantitatively, is an essential step for all the previously seen tasks, especially the asymptotic studies through scales. It is often done in a purely informal way, by recursive discussions with our biologists collaborators and qualitative comparison, see Section 4 and for examples of models we design in such interdisciplinary work [30, 45, 46, 69]. It may also be carried out with the use of theoretical analysis as in Axis 2, or by sensitivity analysis on the parameters (as for instance in [33, 79, 120]), or by relatively standard data analysis tools , as has been done for instance in [42, 47, 95] by various members of the team; our added value then lies in the biological conclusions and models conception rather than in methodological novelties. In other cases however, no standard method is available, or yet, we are led by experimentalists to formulate new inverse problem questions, see for instance [19] for a review of the estimation of the division rate in structured population equations, or yet [29, 71] for the study of inverse problems formulated with biologists.

In this section, we thus explain some of the methodological developments that will be carried out in MERGE in this field of ("deterministic" or "statistical") inverse problems. The underlying question, throughout the section, is to estimate growth and division functional parameters of the individuals. Though we work with external collaborators who are experts in statistics, our team would greatly benefit from the recruitment of a statistician, in order to stay at the cutting edge of new methods like bayesian approaches or machine learning.

Estimate growth, division, interaction features in structured populations

The estimation of the division rate in non-interacting populations has been developed in a series of papers over the last decade [19]. The question we want to address now is whether growth and division rates are modified by cell-to-cell interaction (or yet by antibiotic resistance or by competition), and reciprocally, how distributed growth and division rates may have an influence on the morphogenesis of the bacterial microcolony. In this task, we aim to provide answers based on more realistic individual-based models. We plan the following steps:

- Develop parametric and non-parametric inference of the interaction function from single individual tracking. A similar study has been carried out by Laetitia Della Maestra and Marc Hoffmann [61] for Mc-Kean-Vlasov equation; we would like to add a size structure and a non-constant number of individuals. We will first assume that the growth and division rates do *not* depend on the interaction between cells, so that prior to this step we have used the methods already developed to infer these functional parameters. We may also build upon biophysical studies such as in [127].

- Develop statistical hypothesis testing to accept or reject the assumption made in the previous step that division and growth are not influenced by the interaction inferred. Reciprocally, test whether different division or growth rates would give rise to different morphogenesis.

- Generalise the methods and adapt them to new problems, in particular the mycelial networks [64].

Estimate mutation or fragmentation kernel density

The question of estimating the fragmentation kernel in polymer breakage experiments [67] surprisingly rejoins the question of estimating the so-called *Distribution of Fitness Effects* (DFE) which characterizes the accumulation of mutations in bacteria [111]. As shown in [67], these are so-called *severely ill-posed* inverse problems, for which we aim at developing new approaches, two in particular: rely on short-time instead of long-term behaviour, adapt statistical methods developed for decoumpounding Poisson processes and deconvolution [72].

State estimation and observation inequalities for depolymerisation models

In depolymerisation experiments, prior to parameter estimation, we began to address the question of state estimation, *i.e.* how to infer the initial condition out of measurements of moments time dynamics. Whereas it is relatively straightforward if we approximate the discrete system by a backward transport equation [29], we address the question of estimating it from the next order approximation, namely a transport-diffusion equation; this new problem is closer to the experimental system but gives rise to a severely ill-posed inverse problem, for which we want to find an observation inequality thanks to Carleman estimates [59, 58].

Calibrating the mycelial network model

The model developed in [119] paves the way to new parametric calibration methods that we wish to confront with the real observations made by mycological colleagues of the LIED laboratory (Paris Diderot University), as well as with their empirical results.

The parametric calibration based on the solutions of the spectral problem can lead to new simple descriptors that characterize the growth of the fungus.

The first objective is to see how values obtained in [64] for the exponential growth rates compare with the one obtained in [119] as a solution of the spectral problem related to the corresponding growth and fragmentation equation. For the latter, there is an interpretation through the main characteristics of the network (ratio between the number of external nodes and the total length of the network at a sufficiently large time t).

Then, we could test how these descriptors change in different growth environments. This will allow us to quantify the impact of various forms of stress (nutrient depletion, pH, ...).

From a theoretical point of view, we would have to justify this empirical approach and demonstrate a "many to one" formula to be able to correctly sample our model. It should also be proved that the estimators thus constructed are consistent and converge, when $t \to \infty$, to the quantities they are supposed to approximate.

3.4 Software development and dissemination

Permanent members: Marie Doumic, Milica Tomašević

3.5 CellDiv: a platform for biologists to estimate cell division rates

The CellDiv plateform has been developed by Cédric Doucet and Adeline Fermanian and is already available at . It allows a biologist to upload experimental data of dividing cells, either along a genealogical lineage (microfluidic experiments) or inside an exponentially growing culture (petri dish case), and to get the best-fit estimation of the division rate, according to estimation methods combining statistics and PDE analysis [19].

This plateform will be maintained and completed, to accept other types of data (for instance cells dividing into unequal daughters or with heterogeneous growth rates), estimate the division in more general structured population models, and add statistical tests to select the best-fit model. To date, only Marie Doumic being involved in this project, we need to hire an engineer to continue to develop it - a short term goal being to write a proposal for the help of an engineer from SED.

4 Application domains

Unicellular organisms population models are a transversal application of our work, in various aspects and with different biologists collaborators that we detail below. There are many fascinating issues raised by the understanding of their growth and evolutionary mechanisms, which have prominent societal and health impact - cancer treatment, prevention of antibiotic resistance, aging diseases, control and evolution of epidemics, population viability analysis.

4.1 Bacterial growth

Permanent members: Vincent Bansaye, Marie Doumic, Sylvie Méléard, Gaël Raoul

Biologists collaborators: Meriem El Karoui (Ecole polytechnique and University of Edinburgh), Lydia Robert (INRAe), Charles Baroud (Institut Pasteur and Ecole polytechnique)

Possible new collaborations (first contacts made): Nicolas Desprat (ENS Paris), Claude Loverdo (Sorbonne University)

Bacteria are ubiquitous unicellular organisms, present in most parts of earth, and among the first living beings in evolution. Most animals carry millions of bacteria- one human possesses as many bacteria as one's own cells. They are vital, for instance the ones of the gut for facilitating digestion, and very useful in industry (biofilms, sewage treatment, cheese production...) as well as potentially pathogenic, causing infectious diseases, increasingly more difficult to treat due to their high capacity of developing resistance to antibiotics. Here are some of the questions we want to tackle concerning bacterial growth.

The bacterial cell cycle Coordination between cell growth and division is often carried out by 'size control' mechanisms, where the cell size has to reach a certain threshold to trigger some event of the cell cycle, such as DNA replication or cell division. Concerning bacteria, recent articles [28, 113] stated the excellent adequacy of the so-called "incremental model", where the structuring variable which triggers division is the size increase of the bacteria since birth, to experimental data. This opens up new questions to refine and analyse this model, test its validity in extreme growth conditions such as antibiotic treatments, and understand its links with intracellular mechanisms. *Main research axis: 3, and the CellDiv platform.*

Antibiotic response and resistance emergence To address the emergence of antibiotic-resistant strains of bacteria, it is essential to understand quantitatively the response of bacteria to antibiotic treatments. Under the action of an antibiotic that causes damage to cellular DNA, bacteria change their growth strategy and do not respond homogeneously to this stress. Of particular importance is the so-called SOS response: in response to DNA damage induced by antibiotic treatments, the cell cycle is arrested and DNA repair and mutagenesis are induced (cf. [31]). Cells with high SOS response will grow for an abnormal duration, producing long filaments that are impervious to antibiotics. Understanding the distribution of sizes in the population of bacteria will allow a better quanitfication of antibiotics effects.

On this subject, we work with Meriem El Karoui who carries out microfluidic experiments in Edinburg university. *Main research axis: 2.*

Microcolony morphogenesis When bacterial microcolonies grow, they can aggregate to one another and form a biofilm. How do they interact? How do their growth and division characteristics translate into the shape of the colony? Inside the gut, it has been proved that the immune response acts not by killing bacteria but by making them aggregate after division; how do these aggregates form and break is another question tackled by Claude Loverdo at Lab. Jean Perrin (Sorbonne). *Main research axis: 1 (short term in collaboration with Diane Peurichard and Sophie Hecht).*

Bacterial growth in a chemostat; the gut as a chemostat A chemostat is a specific experiment, where the number of bacteria is let constant by a permanent influx and outflux. The functional mechanism of the very gut could be modeled as a chemostat. *Main research axis: 2 (mid to long term / only first contacts made).*

Mutations The pace of evolution and possible trajectories depend on the dynamics of mutation incidence and the effects of mutations on fitness. Mutation dynamics has been for the first time analyzed directly by Lydia Robert and co-authors [111], using two different microfluidic experiments which led them to the conclusion of a Poissonnian appearance of bacterial mutations, and to a first parametric estimation of the so-called "distribution of fitness effects" (DFE) of mutations. How to assess better the shape of the DFE, and apply the method not only to deleterious or neutral but also to possibly beneficial mutations, is one of our goals. *Main research axis: 3, short term (Guillaume Garnier's ongoing Ph.D).*

Horizontal gene transfer Microorganisms such as bacteria tend to exhibit a relatively large "evolution speed". They have also the particularity to exchange genes by direct cell-to-cell contact. We are particularly interested in plasmids horizontal gene transfer (HGT): plasmids carry pathogens or genes coding for antibiotics resistances, and plasmid exchange is considered by biologists as the primary reason for antibiotics resistance. *Main research axis: 1, both short and long-term research, included in the ERC project SINGER.*

4.2 Cancer and aging

MERGE members involved: Vincent Bansaye, Marie Doumic, Sylvie Méléard

Medical doctors and biologists collaborators: Stéphane Giraudier and Raphael tzykson (St Louis hospital), Teresa Teixeira (IBPC), Zhou Xu (Sorbonne University), Michael Rera (CRI)

Cell division dynamics combine several fundamental processes that are involved in aging and cancers, such as replication and mutation, differentiation and proliferation, quiescence. The main research axis concerned by these applications is axis 2, together with an important modelling work performed through interdisciplinary discussions with MD and biologists.

Leukemic mutations and hematopoeisis Hematopoiesis is the process of producing blood cells from stem cells and progenitors. These highly regulated mechanisms keep at equilibrium the number of blood cells such as red blood cells, white blood cells and platelets (mature cells). We want to understand the emergence of leukaemia or resistance to chemotherapy through the mechanisms of erythropoiesis (production of red blood cells) and leukopoiesis (white blood cell formation). *This application also rejoins the application 3.1.*

Senescence by telomere shortening Telomeres cap the ends of linear chromosomes, and help maintain genome integrity by preventing the ends being recognized and processed as accidental chromosomal breaks. When telomeres fall below a critical length, cells enter replicative senescence. However, the exact structure(s) of the short or dysfunctional telomeres either triggering permanent replicative senescence or promoting genome instability remains to be defined; this is the main focus of Teresa Teixeira's lab at IBPC,

which has developed microfluidic as well as population experiments to follow senescence triggering in yeast cells. *Main research axis: 1 and 2. This application is both a long-term goal, in a long-lasting collaboration with Teresa Teixeira and Zhou Xu, and has short and mid-terms objectives, through Anaïs Rat's finishing Ph.D and Jules Olayé forthcoming Ph.D (co-supervised by Milica Tomašević and Marie Doumic).*

Ageing in drosophyla Ageing's sensitivity to natural selection has long been discussed because of its apparent negative effect on an individual's fitness. In the recent years, a new 2-phases model of ageing has been proposed by Hervé Tricoire and Michael Rera [60, 121], describing the ageing process not as being continuous but as made of at least 2 consecutive phases separated by a dramatic transition. It was first observed in drosophila, and then shown to be evolutionary conserved; this raises the question of an active selection of the underlying mechanisms throughout evolution. *Main research axis: 2 and 3.*

4.3 Fragmentation, aggregation, filamentation phenomena

Permanent members: Vincent Bansaye, Marie Doumic, Milica Tomašević

Biologist collaborators: Human Rezaei (INRAe), Florence Chapeland-Leclerc and Eric Herbert (LIED, Univ. Paris Diderot), Sascha Martens (Vienna University), Wei-Feng Xue (Univ. of Kent)

Protein polymerisation: amyloid formation and autophagy

Protein polymerisation occurs in many different situations, from functional situations (actin filaments, autophagy) to toxic ones (amyloid diseases). It involves complex reaction networks, making it a challenge to identify the key mechanisms, for instance which mechanisms lead to the initial formation of polymers during the first reaction steps (nucleation), how and where the polymers break, or yet the aggregates formation, out of (at least) two different proteins, in autophagy. With our biologist collaborators, our aim in these applications is to isolate the most meaningful reactions, study their behaviour *(Research axis 2)*, and compare them - qualitatively and, if possible, quantitatively - with experimental data.

Mycelial network

Filamentous fungi are complex expanding organisms that are omnipresent in nature. They form filamentous structures, growing and branching to create huge networks called *mycelia*. We aim at modelling, understanding and estimating the main mechanisms of mycelial formation. We have already studied a first model without interactions and we will now study the impact of fusion of filaments on the growth of the network. *Main research axes: 2 and 3.*

4.4 Evolutionary epidemiology and ecology

Permanent members: Vincent Bansaye, Gaël Raoul

Biologists collaborators: Sylvain Billiard, Nicolas Lœuille (Institute of Ecology and Environmental Sciences, Paris), François Massol (Center for Infection and Immunity of Lille), Ophélie Ronce (ISEM, Montpellier), François Deslandes (INRAe), Sylvain Gandon (CEFE Montpellier), Elisabeta Vergu (INRAe)

In ecology, the influence of a spatially heterogeneous environment and of different contact structures is at the heart of current problems (biological invasions, epidemiology, etc.), as well as the interaction between different species. The questions we look at concern how a species can invade the range of another one, leading to its extinction; how an epidemics spreading is influenced by contact structures; resilience and tipping points in ecosystems. Applications are as varied as the links between light and plankton species evolution in shallow water lakes, the replacement of red squirrels by grey squirrels, or the current pandemics. *Main research axis: 1.*

Emergence of bacterial resistance in heterogeneous environments

When an antibiotic treatment is applied to a population, bacteria resistant to the treatment have an opportunity to develop. If several treatments are used, life threatening multi-resistant bacteria can appear. Understand the dynamics of bacterial populations in such heterogeneous environments would provide interesting perspectives to improve treatments and keep antibiotic resistance in control. On this topic, we will collaborate with S. Gandon lab at CEFE, that tackles this problem with a combination of theory and experiments. *This also rejoins the application domain 3.1., and the main research axis is axis 2.*

Dynamics of species submitted to climate change

The impact of climate change on natural species is a complicated matter. An important research effort has been made on the modification of species' niche in coming years, but this is only a partial clue for the future of species. In collaboration with Ophélie Ronce at ISEM, we will investigate how the local adaptation of species will is shook by global changes. With François Massol in CIIL and Nicolas Loeuille in IEES, we will focus on the impact of interspecies effects: predation, parasitism, cooperation, etc. *Main research axis: 1.*

Contacts structured by graphs

In the context of spatial ecology and epidemiology, the contacts between individuals leading to predation or transmission of a desease are often modeled by graph. It may represent the connected sites (metapopulations) or the nature of the contacts (multilevel contact structure) between individuals. The description of the population dynamics is important for prediction : stability, explosion, coexistence... The macroscopic approximation when the population and the graph are large is a key question for model reduction and analysis of these models. The mathematical challenges raised are linked to homogeneisation and spatial random graphs, multiscale modelling and local interactions. Collaborations with Sylvain Billiard (Lille, biologist) and Elisebeta Vergu (INRAe, epidemiologist) and Michele Salvi (Roma, mathematician) and Ayman Moussa (Paris Sorbonne, mathematician). *Main research axis: 1.*

5 Social and environmental responsibility

The MERGE project-team brings together mathematicians with complementary competences and interests, in order to integrate at a high level different areas of mathematical analysis (multiscale stochastic processes, partial or integro-differential equations) and microbiology, ecology, cancer medicine. If successful, this research can have fundamental impacts in these fields. General mathematical frameworks unifying different biological questions from single cell to ecological problems not only can improve modelling and simulations but also create a considerable synergy in all these scientific communities. It will also create collaborations between mathematicians (the links between models through scales, taking into account varying environment, interaction between cells...) which could have potential applications in other domains, beyond biology and ecology. In Mathematics, this research tackles fundamental problems from the representation of stochastic microscopic effects in large approximations to macroscopic representations. Successful results would open a new area of research at the interface of probability and analysis, tracking the rare but fundamental effects.

In Biology, this research addresses fundamental questions of growth, mutation and resistance. Successful results will offer interesting opportunities for medical innovations based on evolutionary or adaptive strategies.

6 Highlights of the year

Sylvie Méléard received the « Médaillon Lecture » of the IMS at the conference INFORMS, NANCY 2023. Together with 16 speakers, including 7 Fields Medal, she has given an invited talk at the Conference "Panorama of Mathematics", Hausdorff Center, Bonn 2023.

7 New software, platforms, open data

When simulations have been carried out, the source codes have been systematically published, in a "reproducible research" perspective.

For the simulations done in the submitted article [25], the codes and software are publicly available on Anais Rat's github project "telomeres".

8 New results

8.1 Axis 1: Models through scales

We refer to 3.1 for a presentation of the research program in this direction.

8.1.1 From the distributions of times of interactions to preys and predators dynamical systems

Participants: Vincent Bansaye, Bertrand Cloez.

In [6], we consider a stochastic individual based model where each predator searches during a random time and then manipulates its prey or rests. The time distributions may be non-exponential. An age structure allows to describe these interactions and get a Markovian setting. The process is characterized by a measure-valued stochastic differential equation. We prove averaging results in this infinite dimensional setting and get the convergence of the slow-fast macroscopic prey predator process to a two dimensional dynamical system. We recover classical functional responses. We also get new forms arising in particular when births and deaths of predators are affected by the lack of food.

8.1.2 Scaling limit of bisexual Galton-Watson process

Participants: Vincent Bansaye, Maria-Emilia Caballero, Jaime San Martin, Sylvie Méléard.

Bisexual Galton-Watson processes are discrete Markov chains where reproduction events are due to mating of males and females. Owing to this interaction, the standard branching property of Galton-Watson processes is lost. In [5], we prove tightness for conveniently rescaled bisexual Galton-Watson processes, based on recent techniques developed by Bansaye, Caballero and Méléard. We also identify the possible limits of these rescaled processes as solutions of a stochastic system, coupling two equations through singular coefficients in Poisson terms added to square roots as coefficients of Brownian motions. Under some additional integrability assumptions, pathwise uniqueness of this limiting system of stochastic differential equations and convergence of the rescaled processes are obtained. Two examples corresponding to mutual fidelity are considered.

8.1.3 From individual-based evolutionary models to Hamilton-Jacobi equations

Participants: Nicolas Champagnat, Sylvie Méléard, Sepideh Mirrahimi, Viet Chi Tran.

In [2], we consider a stochastic model for the evolution of a discrete population structured by a trait with values on a finite grid of the torus, and with mutation and selection. Traits are vertically inherited unless a mutation occurs, and influence the birth and death rates. We focus on a parameter scaling where population is large, individual mutations are small but not rare, and the grid mesh for the trait values is much smaller than the size of mutation steps. When considering the evolution of the population in a long time scale, the contribution of small sub-populations may strongly influence the dynamics. Our main

result quantifies the asymptotic dynamics of sub-population sizes on a logarithmic scale. We establish that under the parameter scaling the logarithm of the stochastic population size process, conveniently normalized, converges to the unique viscosity solution of a Hamilton-Jacobi equation. Such Hamilton-Jacobi equations have already been derived from parabolic integro-differential equations and have been widely developed in the study of adaptation of quantitative traits. Our work provides a justification of this framework directly from a stochastic individual based model, leading to a better understanding of the results obtained within this approach. The proof makes use of almost sure maximum principles and careful controls of the martingale parts. We have thus provided a first answer to a question that has been open for a long time, and we continue to progress in order to generalise these results.

8.1.4 Multispecies cross diffusion

Participants: Marie Doumic, Sophie Hecht, Benoit Perthame, Diane Peurichard.

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 the article [23], to be published in the Journal of Differential Equations, we establish 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, at odd with the existing literature. The central compactness result is provided by 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.

8.1.5 Particle approximation of the doubly parabolic Keller-Segel equation

Participants: Nicolas Fournier, Milica Tomašević.

In [3], we study a stochastic system of N particles associated with the parabolic-parabolic Keller-Segel system. This particle system is singular and non Markovian in that its drift term depends on the past of the particles. When the sensitivity parameter is sufficiently small, we show that this particle system indeed exists for any , we show tightness in N of its empirical measure, and that any weak limit point of this empirical measure, as , solves some nonlinear martingale problem, which in particular implies that its family of time-marginals solves the parabolic-parabolic Keller-Segel system in some weak sense. The main argument of the proof consists of a Markovianization of the interaction kernel: We show that, in some loose sense, the two-by-two path-dependant interaction can be controlled by a two-by-two Coulomb interaction, as in the parabolic-elliptic case.

8.2 Axis 2: qualitative analysis of structured populations

We refer to 3.2 for a presentation of the research program in this direction.

8.2.1 Claire Ecotiere's PhD

Participants: Claire Ecotière, Sylvie Méléard, Régis Ferrière.

Claire Ecotiere's thesis focuses on the stochastic modeling of human behavior in the face of environmental change and the study of related mathematical models. She has mainly developed a stochastic model describing the coupled dynamics of the environment and the population, through the proportion of active individuals facing the environment, in a population composed of active and passive individuals.

Individuals can switch from one behavior to another through social interactions or their own assessment of environmental degradation. Active behavior contributes less to environmental degradation, but is more costly to adopt than passive behavior. The stochastic model and its behavior in long time are studied as well as its approximation in large population leading to a deterministic system.

8.2.2 Evolutionary dynamics

Participants: Sirine Boucenna, Vasilis Dakos, Quentin Griette, Sylvie Alfaro, Sylvain Gandon, Gaël Raoul.

The article [80] has been accepted in Evolution Letters. In this article, we have analysed the evolutionary dynamics of pathogens spreading in a heterogeneous host population where selection varies periodically in space. We study both the transient dynamics taking place at the front of the epidemic and the long-term evolution far behind the front. In particular, we identify the conditions where a generalist pathogen carrying multiple adaptations can outrace a coalition of specialist pathogens. We also show that finite host populations promote the spread of generalist pathogens because demographic stochasticity enhances the extinction of locally maladapted pathogens.

The article [112] is in revision for Theoretical Population Biology. Shallow lakes ecosystems may experience abrupt shifts (ie tipping points) from one state to a contrasting degraded alternative state as a result of gradual environmental changes. It is crucial to elucidate how eco-evolutionary feedbacks affect abrupt ecological transitions in shallow lakes. We explore the eco-evolutionary dynamics of submerged and floating macrophytes in a shallow lake ecosystem under asymmetric competition for nutrients and light. We show how rapid trait evolution can result in complex dynamics including evolutionary oscillations, extensive diversification and evolutionary suicide. Overall, this study shows that evolution can have strong effects in the ecological dynamics of bistable ecosystems.

8.2.3 A growth-fragmentation-isolation process on random recursive trees and contact tracing

Participants: Vincent Bansaye, Chenlin Gu, Linglong Yuan.

In [7], we consider a random process on recursive trees, with three types of events. Vertices give birth at a constant rate (growth), each edge may be removed independently (fragmentation of the tree) and clusters (or trees) are frozen with a rate proportional to their sizes (isolation of connected component). A phase transition occurs when the isolation is able to stop the growth fragmentation process and cause extinction. When the process survives, the number of clusters increases exponentially and we prove that the normalized empirical measure of clusters a.s. converges to a limit law on recursive trees. We exploit the branching structure associated with the size of clusters, which is inherited from the splitting property of random recursive trees. This work is motivated by the control of epidemics and contact tracing where clusters correspond to trees of infected individuals that can be identified and isolated. We complement this work by providing results on the Malthusian exponent to describe the effect of control policies on epidemics.

8.2.4 Propagation of chaos for stochastic particle systems with singular mean-field interaction of $L^q - L^p$ type

Participants: Milica Tomašević.

In this work [14], we prove the well-posedness and propagation of chaos for a stochastic particle system in mean-field interaction under the assumption that the interacting kernel belongs to a suitable $L^q_t - L^p_x$ space. Contrary to the large deviation principle approach recently proposed in [83], the main

ingredient of the proof here are the Partial Girsanov transformations introduced in [87] and developed in a general setting in this work.

8.2.5 Blow-up for a stochastic model of chemotaxis driven by conservative noise on $\mathbb{R}^2$

Participants: Avi Mayorcas, Milica Tomašević.

In [13], we establish criteria on the chemotactic sensitivity χ for the non-existence of global weak solutions (i.e., blow-up in finite time) to a stochastic Keller–Segel model with spatially inhomogeneous, conservative noise on $\mathbb{R}^2$. We show that if χ is sufficiently large then blow-up occurs with probability 1. In this regime, our criterion agrees with that of a deterministic Keller–Segel model with increased viscosity. However, for χ in an intermediate regime, determined by the variance of the initial data and the spatial correlation of the noise, we show that blow-up occurs with positive probability.

8.2.6 Reducing exit-times of diffusions with repulsive interactions

Participants: Paul-Eric Chaudru de Reynal, Pierre Monmarché, Milica Tomašević, Julian Tugaut.

In this work [9], we prove a Kramers' type law for the low-temperature behavior of the exittimes from a metastable state for a class of self-interacting nonlinear diffusion processes. Contrary to previous works, the interaction is not assumed to be convex, which means that this result covers cases where the exit-time for the interacting process is smaller than the exit-time for the associated non-interacting process. The technique of the proof is based on the fact that, under an appropriate contraction condition, the interacting process is conveniently coupled with a non-interacting (linear) Markov process where the interacting law is replaced by a constant Dirac mass at the fixed point of the deterministic zero-temperature process.

8.3 Axis 3: Model-data comparison

We refer to 3.3 for a presentation of the research program in this direction.

8.3.1 Telomere shortening, a unifying model

Participants: Anaïs Rat, Marie Doumic, Teresa Teixeira, Zhou Xu.

Progressive shortening of telomeres ultimately causes replicative senescence and is linked with aging and tumor suppression. Studying the intricate link between telomere shortening and senescence at the molecular level and its population-scale effects over time is challenging with current approaches but crucial for understanding behavior at the organ or tissue level. In the submitted article [4], we developed a mathematical model for telomere shortening and the onset of replicative senescence using data from Saccharomyces cerevisiae without telomerase. Our model tracks individual cell states, their telomere length dynamics, and lifespan over time, revealing selection forces within a population. We discovered that both cell genealogy and global telomere length distribution are key to determine the population proliferation capacity. We also discovered that cell growth defects unrelated to telomeres also affect subsequent proliferation and may act as confounding variables in replicative senescence assays. Overall, while there is a deterministic limit for the shortest telomere length, the stochastic occurrence of non-terminal arrests drive cells into a totally different regime, which may promote genome instability and senescence escape. Our results offer a comprehensive framework for investigating the implications of telomere length on human diseases.

8.3.2 Calibrating division rates in population dynamics

Participants: Marie Doumic, Marc Hoffmann.

Modelling, analysing and inferring triggering mechanisms in population reproduction is fundamental in many biological applications. It is also an active and growing research domain in mathematical biology. In the book chapter [19], we review the main results developed over the last decade for the estimation of the division rate in growing and dividing populations in a steady environment. These methods combine tools borrowed from PDE's and stochastic processes, with a certain view that emerges from mathematical statistics. A focus on the application to the bacterial cell division cycle provides a concrete presentation, and may help the reader to identify major new challenges in the field.

8.3.3 Fragmentation estimation through short-time dynamics

Participants: Marie Doumic, Miguel Escobedo, Magali Tournus.

Given a phenomenon described by a self-similar fragmentation equation, how to infer the fragmentation kernel from experimental measurements of the solution ? To answer this question at the basis of our work, a formal asymptotic expansion suggested us that using short-time observations and initial data close to a Dirac measure should be a well-adapted strategy. We prove error estimates in Total Variation and Bounded Lipshitz norms; this gives a quantitative meaning to what a "short" time observation is. Our analysis is complemented by a numerical investigation.

9 Partnerships and cooperations

Sylvie Méléard has a regular partnership with the CMM (Chile), mainly with Servet Martinez, Joaquin Fontbona and Jaime San Martin.

Gaël Raoul has a regular collaboration with research groups in Vietnam:

- with Marc Choisy and Pham Thanh Duy, Oxford Clinical Research Unit, Ho Chi Minh city, Vietnam. They work on the multi-drug resistance of Klebsiella pneumoniae.

- with Vo Hoang Hung, Saigon University, Ho Chi Minh city, Vietnam. They work on the effect of an age structure on the propagation of population in the context of climate change.

9.1 International initiatives

Milica Tomašević participates in two international projects, in the France-Japan program Sakura (headed by K. Fujie in Japan and Julian Tugaut in France) and in a franco-brasilian ANR project, ANR PRCI FAPESP SDAIM : Stochastic and Deterministic Analysis of Irregular Models, 2023-2027, PI : F. Russo (ENSTA).

9.2 International research visitors

9.2.1 Visits of international scientists

Other international visits to the team Juan Velazquez visited the team for one week in September, and gave a talk at the CMAP.

9.2.2 Visits to international teams

Research stays abroad Sylvie Méléard spent 2 weeks at Santiago (Chile).

9.3 European initiatives

9.3.1 Horizon Europe

The ERC Advanced Grant SINGER (Stochastic dynamics of sINgle cells; Growth, Emergence and Resistance) 2022-2027, headed by Sylvie Méléard, involves all members of MERGE and several of our collaborators (Sepideh Mirrahimi in Toulouse, Nicolas Champagnat in BIGS, Viet-Chi Tran in Univ. G. Eiffel). Amount: 2M€.

9.4 National initiatives

- The MMB Chaire, *Modélisation Mathématique et Biodiversité*, headed by Sylvie Méléard since 2009, has been renewed till 2027. It funds PhD and post-doctoral grants, a yearly summer school and scientific meetings every two month. This has a great role in uniting our community.
- Our research on telomere shortening modelling is structured around several fundings:
  - The INCa Projet *TheFinalCut*, headed by Teresa Teixeira (total: 0,78 M€), 2020–2024
  - Following the funding of the PEPR MathVives, a project on telomere shortening modelling, DyLT (approx. 1MEuro), *Influence of telomere length dynamics and environmental conditions on biological and clinical aspects of aging*, has been accepted. Headed by Nicolas Champagnat (Inria project-team TOSCA), and Marie Doumic being the head of Axis 2 of the project, it will be a meeting place for mathematicians and biologists in this field and will be an important opportunity for the pooling of forces on this important topic.
  - Jules Olayé's Ph.D, co-supervised by Milica Tomašević and Marie Doumic, has been funded by the EDMH.
- We are part of many ANR projects: Marie Doumic participates to the ANR ODISSE (411 k€), 2019–2023 on *Synthèse d'observateur pour des systèmes de dimension infinie*, headed by Vincent Andrieu, and to a newly funded ANR project ENERGENCE (433 k€), 2022–2026, *ENERgy driven modelling of tissue architecture emerGENCE and homeorhesis*, headed by Diane Peurichard. Gaël Raoul participates in the ANR DEEV (159 k€), 2020–2023 on *Integro-Differential Equations from EVolutionary biology*, headed by Sepideh Mirrahimi. Milica Tomašević participates to the ANR project METANOLIN (87 k€), 2019–2023 on *Metastability for nonlinear processes*, headed by Julian Tugaut, and to the ANR project NEMATIC (367 k€), 2021–2025 on *Analyse Modelisation et Simulation Multi-échelle*, headed by Eric Herbert.
- Sylvie Méléard is the P.I. of a newly funded Aviesan-Inserm ITMO Cancer project (261 k€), 2022–2026 on *Mathématiques pour une meilleure compréhension des néoplasmes myélo-prolifératifs et leurs thérapeutiques*.

10 Dissemination

Participants: Vincent Bansaye, Marie Doumic, Sylvie Méléard, Gaël Raoul, Milica Tomašević.

10.1 Promoting scientific activities

10.1.1 Scientific events: organisation

Principle organisation of events Vincent Bansaye, Sylvie Méléard and Milica Tomašević co-organise the summer school of the MMB chaire, headed by Sylvie Méléard, which takes place every June in Aussois.

Milica Tomašević co-organised the conference in honour of Denis Talay at CIRM, Marseille.

Vincent Bansaye organised an invited session in the SPA Conference "Stochastic models for epidemiology and evolution", Lisboa, July 2023.

Member of scientific committees Sylvie Méléard has been a member of the scientific committee of ICIAM 2023 and of the conference in honour of Denis Talay at CIRM, Marseille.

10.1.2 Journal

Member of the editorial boards Vincent Bansaye has been Guest Editor for the special issue "Mathematics and biology" of the journal Maths in Action (SMAI).

Marie Doumic is editor in chief of ESAIM Proceedings and Surveys, and associate editor of the Journal of Mathematical Biology, Kinetic and Related Models and le Bulletin des sciences mathématiques.

Sylvie Méléard is associate editor of the Comptes-Rendus de l'Académie des Sciences, of Stochastic Processes and their Applications, and of the Lecture Notes on mathematical Modelling in the Life Sciences.

10.1.3 Invited talks

Vincent Bansaye gave invited talks at the Conference on "Branching Processes and applications", Angers, may 23rd; on the Journée Analyse Appliquée Hauts de France, October 17th; at the Evolution Everevol Conference, Grenoble, December 14th.

Marie Doumic gave an invited talk at the 5th International Symposium on Pathomechanisms of Amyloid Diseases, Bordeaux, September 5-7 ; at the workshop "Topics on Neuroscience, Collective Migration and Parameter Estimation", Oxford, July 3-7 ; at the "Journées EDP", Aussois, June 19-23 ; at the READINET conference, Orsay, January 3-6.

Sylvie Méléard gave 12 invited talks, including 7 abroad.

Milica Tomašević gave invited talks at the Mean field interactions with singular kernels and their approximations workshop, IHP Paris 18-22 déc 2023 ; at the Conference Stochastic Flows, thematic program Order and Randomness in Partial Differential Equations, Institut Mittag-Leffler, nov 2023 ; at the Second Berlin-Leipzig Workshop on Fluctuating Hydrodynamics, Freie University, Berlin September 19-20, 2023; at the Conference "A random walk in the land of stochastic processes and numerical probability", CIRM sept 2023 ; at the Conference Mean Field Models, Rennes, 12 juin - 16 juin 2023 ; and 4 seminar talks.

10.1.4 Leadership within the scientific community

Vincent Bansaye has become vice president of the applied mathematics department of Ecole Polytechnique and vice director of the Fondation Mathématiques Jacques Hadamard (FMJH) since September 2023.

Sylvie Méléard leads the Chaire MMB, joint between École Polytechnique, the Muséum national d'Histoire naturelle, the Fondation de l'École Polytechnique and VEOLIA Environnement. It is a major player in bringing together our community of mathematicians, modellers and ecologists, and funds several PhD and post-doctoral grants.

10.1.5 Scientific expertise

Vincent Bansaye is a member of the scientific council of ModCov19.

Marie Doumic has been a member of the CID51 of CNRS (hiring committees for junior and senior research scientists of CNRS), and has been a member for the hiring committee of an associate professor at ENSTA.

10.1.6 Research administration

Vincent Bansaye is a member of the steering committee of the MMB Chaire.

Marie Doumic is a member of the scientific committee of INSMI, of Inria Saclay and of the steering committee of FMJH.

Sylvie Méléard has been a member of the Evaluation Committee of Inria till September 2023, and is a member of the scientific committees of CRM (Montreal), Hausdorff Center (Bonn, Germany) and CMM (Chile), and of the steering committees of FMJH and E4H.

10.2 Teaching - Supervision - Juries

10.2.1 Supervision

Claire Ecotière defended her Ph.D on October 18th, 2023, on the *Study and stochastic modelling of human behaviour in the face of environmental change*, under the supervision of Sylvie Méléard and Régis Ferrière.

Anaïs Rat defended her Ph.D on May 31st, 2023, on *Structured population dynamics: theory, asymptotic and numerical analysis. Application to populations with heterogeneous growth rates and to replicative senescence*, under the supervision of Magali Tournus and Marie Doumic.

10.2.2 Juries

Marie Doumic has been a member of the Ph.D thesis committees for Darryl Ondoua (under Yvon Maday's supervision), Léo Meyer (under Magali Ribot and Romain Yvinec's supervision), and for the habilitation thesis of Bertrand Cloez (January 5, 2023).

Sylvie Méléard has been a member for the Marc Yor 2023 prize and the Dargelos 2023 prize committees.

10.3 Popularization

10.3.1 Interventions for undergraduate and highschool students

Marie Doumic gave a talk "Chiche!" at Inria, December 4, 2023, and a talk for high school students at the SMAI/MAM Musée des Arts et Métiers, Paris, March 9.

Sylvie Méléard gave a talk to the Math-Club, Université Paris Cité (bachelor students) and a "Maths en Jeans" conference at Potsdam University in March 2023, organised by the Berlin lycée français and Potsdam University.

10.3.2 General audience talks

Sylvie Méléard gave a talk for her Conférence entry as a foreign correspondent to the Chilean Academy of Sciences, January 2023, and a talk at the actuaries meeting, SCOR Foundation, December 2023.

11 Scientific production

11.1 Major publications

[1] V. Bansaye, C. Gu and L. Yuan. 'A growth-fragmentation-isolation process on random recursive trees and contact tracing'. In: *The Annals of Applied Probability* 33.6B (2023), pp. 5233–5278. DOI: 10.1214/23-AAP1947. URL: https://hal.science/hal-04406491.

[2] N. Champagnat, S. Méléard, S. Mirrahimi and V. Chi Tran. 'Filling the gap between individual-based evolutionary models and Hamilton-Jacobi equations'. In: *Journal de l'École polytechnique — Mathématiques* 10 (2023), pp. 1247–1275. DOI: 10.5802/jep.244. URL: https://hal.science/hal-03656608.

[3] N. Fournier and M. Tomašević. 'Particle approximation of the doubly parabolic Keller-Segel equation in the plane'. In: *Journal of Functional Analysis* 285.7 (2023), p. 110064. DOI: 10.1016/j.jfa.2023.110064. URL: https://hal.science/hal-03855110.

[4] A. Rat, M. Doumic, M. T. Teixeira and Z. Xu. *Individual cell fate and population dynamics revealed by a mathematical model linking telomere length and replicative senescence*. 22nd Nov. 2023. DOI: 10.1101/2023.11.22.568287. URL: https://hal.science/hal-04305005.

11.2 Publications of the year

International journals

[5] V. Bansaye, M.-E. Caballero, S. Méléard and J. San Martín. 'Scaling limits of bisexual Galton-Watson processes'. In: *Stochastics: An International Journal of Probability and Stochastic Processes* 95.5 (6th Feb. 2023), pp. 749–784. DOI: 10.1080/17442508.2022.2123706. URL: https://hal.science/hal-02859954.

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[9] P.-E. Chaudru de Raynal, M. H. Duong, P. Monmarché, M. Tomašević and J. Tugaut. 'Reducing exit-times of diffusions with repulsive interactions'. In: *ESAIM: Probability and Statistics* 27 (2023), pp. 723–748. DOI: 10.1051/ps/2023012. URL: https://hal.science/hal-03762603.

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[11] N. Fournier and M. Tomašević. 'Particle approximation of the doubly parabolic Keller-Segel equation in the plane'. In: *Journal of Functional Analysis* 285.7 (2023), p. 110064. DOI: 10.1016/j.jfa.2023.110064. URL: https://hal.science/hal-03855110.

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[15] M. Kubasch. 'Large population limit for a multilayer SIR model including households and workplaces'. In: Rencontres Mathématiques de Rouen. Rouen, France, 28th June 2023. URL: https://hal.science/hal-04366603.

[16] M. Kubasch, V. Bansaye, F. Deslandes and E. Vergu. 'A tribute to Elisabeta Vergu: Multi-level contact models of epidemics'. In: Journées 2023 de l'Action Coordonnée "Modélisation des Maladies Infectieuses". Paris, France, 24th Oct. 2023. URL: https://hal.science/hal-04366616.

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Scientific book chapters

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Reports & preprints

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[22] V. Bansaye, X. Erny and S. Méléard. *Sharp approximation and hitting times for stochastic invasion processes*. 11th Dec. 2023. URL: https://hal.science/hal-03915479.

[23] 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*. 26th May 2023. URL: https://hal.science/hal-04108050.

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