

2025 Activity Report

RESEARCH CENTRE: Inria Lyon Centre

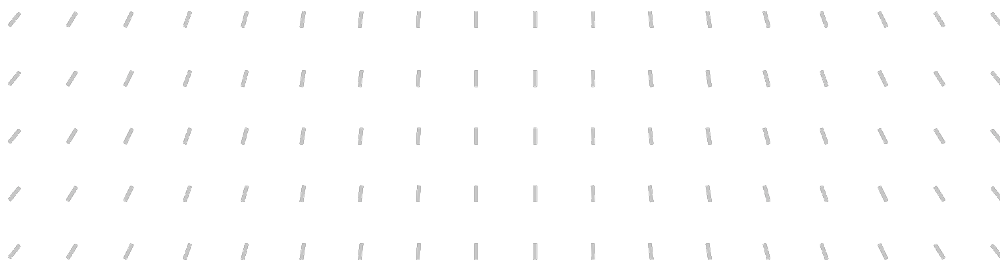
IN PARTNERSHIP WITH: Institut national des sciences appliquées de Lyon

Project-Team

BIOTIC

Computational and Theoretical Biology

In collaboration with Centre d'innovation en télécommunications et intégration de services, Laboratoire de Recherche en Cardiovasculaire, Métabolisme, Diabétologie et Nutrition



Project-Team BIOTIC

Creation of the Project-Team: 2025 August 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

- A3.3. – Data and knowledge analysis
 - A3.3.2. – Data mining
 - A3.3.3. – Big data analysis
- A6.1.1. – Continuous Modeling (PDE, ODE)
- A6.1.3. – Discrete Modeling (multi-agent, people centered)
- A6.1.4. – Multiscale modeling
- A6.2.7. – HPC for machine learning
- A8.1. – Discrete mathematics, combinatorics

Other research topics and application domains

- B1. – Life sciences
 - B1.1. – Biology
 - B1.1.2. – Molecular and cellular biology
 - B1.1.6. – Evolutionary biology
 - B1.1.7. – Bioinformatics
 - B1.1.10. – Systems and synthetic biology
 - B1.1.11. – Plant Biology
 - B3.5. – Agronomy
 - B3.6. – Ecology
 - B3.6.1. – Biodiversity

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1 Team members, visitors, external collaborators

Research Scientists

- Enrico Colizzi [INRIA, Researcher, from Aug 2025]
- Antonius Crombach [INRIA, Researcher, from Aug 2025]
- Clément Moulin-Frier [INRIA, Researcher, from Aug 2025]

Faculty Members

- Guillaume Beslon [Team leader, INSA LYON, Professor, from Aug 2025, HDR]
- Carole Knibbe [INSA LYON, Associate Professor, from Aug 2025, HDR]
- Jonathan Rouzaud-Cornabas [INSA LYON, Associate Professor Delegation, from Sep 2025]
- Jonathan Rouzaud-Cornabas [INSA LYON, Associate Professor, from Aug 2025 until Aug 2025]

Post-Doctoral Fellow

- Hamza Chegraoui [INRIA, Post-Doctoral Fellow, from Aug 2025 until Oct 2025]

PhD Students

- Gabin Calmet [INSA LYON, from Sep 2025]
- Romain Galle [INRIA, from Aug 2025]
- Juliette Luiselli [INSA LYON, from Aug 2025 until Aug 2025]
- Arsene Marzorati [INRIA, from Aug 2025]
- Sofia Pacheco Garcia [INRIA, from Aug 2025]
- Thibaut Peyric [INRIA, from Aug 2025]

Interns and Apprentices

- Gabin Calmet [INRIA, Intern, from Aug 2025 until Aug 2025]

Administrative Assistant

- Laretta Lauret [INRIA, from Jun 2025]

External Collaborator

- Christophe Rigotti [INSA LYON, from Aug 2025, HDR]

2 Overall objectives

The expanded name for the BioTiC team is “Biologie Théorique et Computationnelle” (Computational and Theoretical Biology). We position our research at the interface between biology and computer science, where we contribute new results in biology by modeling biological systems. Our research is based on an interdisciplinary scientific strategy. BioTiC’s members are “computational biologists” who develop computer science formalisms and software to simulate and analyze biological systems.

Biological systems are complex systems composed of myriads of interacting elements. However, among complex systems like global climate, social organizations, and transportation systems, biological systems have several characteristics that make them particularly difficult to study. Indeed, like any complex systems, biological systems are made of a large number of elements at every scale. But they are distinguished by a *heterogeneity* of their elements and by an intertwining of spatial and temporal scales. This is due to the historical nature of these systems. Indeed, they are the result of an evolutionary history whose permanent tinkering results both in many peculiarities, due to contingent events and specific evolutionary conditions, and also many regularities, due to constraints imposed by the physical world in which the system evolves.

In this context, the scientific objective of the BioTiC team is to develop a consistent set of concepts and tools —mainly based on computational science— to contribute to knowledge discovery in biology. Our strategy to achieve the objective is to develop strong interactions with biologists to be active partners in the biological discovery process. Thus, we are neither a computer science team interacting with biologists, nor a team of biologists / bioinformaticians using computer science tools, but our aim is rather to stay in the middle and be a *trading zone*¹ between biology and computer science.

3 Research program

This overall objective of the team requires team members to have skills in computer science *and* life sciences. A direct consequence is that the team restricts its domain of expertise in life sciences by focusing on the cellular scale, a central level of organization in biology. This specific scale is rich in open questions that deserve modeling and simulation approaches. Specifically, we focus on two prominent processes that govern cellular behavior, namely (i) the dynamics of molecular networks, including gene regulatory networks and metabolic networks, and (ii) the evolutionary process and its effect on cell and genome complexity. More precisely, we target questions for which we anticipate that computational approaches (as the ones we are developing in the team) will have a decisive impact:

- In the context of molecular networks, our research aims to elucidate how biological cells acquire, maintain, and —at times— lose their identity. This fundamental question has been profoundly transformed by recent advances in single-cell experimental technologies. Our objective is to contribute to this field by developing computational models and data analysis tools that assist us and our colleagues from biology in interpreting the vast and complex datasets generated by these new techniques.
- In the field of evolution, we study the effects of large-scale mutational events known as chromosomal rearrangements. Although such events are ubiquitous across all domains of life, their consequences remain poorly understood, primarily due to the difficulty of incorporating them into classical mathematical frameworks such as population genetics.

4 Application domains

We do not usually distinguish our research and its application domains. Our shared idea is that the research is oriented by a scientific question, which in case of BioTiC is a multidisciplinary one, most often of biological nature. We do not develop methods or tools independently from this question and then look for applications of those methods and tools (an approach that could be qualified as “Maslow’s hammer”). Instead we collectively work with other disciplines to solve a question, using our competencies.

In consequence the application domains are already listed in the description of our projects and goals and concern mainly functional and evolutionary biology.

¹The concept of interdisciplinary *trading zones* has been coined by Peter Galison in Peter Galison. *Image and logic: A material culture of microphysics*. University of Chicago Press, 1997.

5 Social and environmental responsibility

5.1 Footprint of research activities

We strive to balance the team's carbon footprint with the need for young researchers to develop their international network. This is done in two ways. First, we promote interactions with European laboratories and research groups, ideally for which travel can be done by train. Nevertheless, PhD students and postdocs may undertake longer trips, including visits to laboratories on other continents (America, Asia, etc.), which tends to involve air travel. In such cases, we prefer that students stay longer and amortize the climate impact of transportation. For instance, in 2024, Juliette Luiselli, at that time PhD student with Guillaume Beslon, spent three months at Sherbrooke University (Canada) for a collaboration. This long stay also allowed her to attend two international conferences in Montreal, namely Evolution 2024 (Third Joint Congress on Evolutionary Biology) and ISMB 2024 (International Conference on Intelligent Systems for Molecular Biology). In 2025, Sofia Pacheco-Garcia, PhD student jointly supervised by Anton Crombach and Guillaume Beslon, spent a month at Brown University (US) in order to foster the collaboration with Alexander Fleischmann's lab.

5.2 Impact of research results

BioTiC's research is essentially upstream research and is therefore generally too theoretical to directly consider short-term medical applications. However they open some translational and medical perspectives, particularly in infectious diseases (evolution of microorganisms and antibiotic resistance), oncology (study of the dysregulation of molecular and cellular networks), and neuroscience (development of neurodegenerative diseases).

6 Highlights of the year

2025 was a year of profound change for the BioTiC team. First and foremost, the team itself was officially established on August 1, 2025. This establishment could only take effect, in agreement with INSA Lyon, following the migration on January 1, 2025, of part of the team members (Guillaume Beslon, Jonathan Rouzaud-Cornabas, and Anton Crombach) from the Laboratory of Image and Information Systems (LIRIS) to the Center for Innovation in Telecommunications and Service Integration (CITI). Second, BioTiC has welcomed two new permanent researchers. Sandro Colizzi joined the team in February 2025 after his recruitment as an INRIA CRCN in 2024. Clément Moulin-Frier joined the team in May 2025, following a transfer from the center Inria de Bordeaux (Flowers team). Although it is too early for their arrival to have had a transformative effect on the team, the recruitment of these two researchers naturally expands the area of expertise of the team.

6.1 Awards

- Thibaut Peyric (PhD) and co-authors received the best paper award at the 2025 conference on *Computational Methods for Systems Biology* (CMSB 2025, Lyon, France, September 2025) for his paper "Three-State Gene Expression Model Parameterized for Single-Cell Multi-Omics Data" [12].
- Sofia Pacheco-Garcia (PhD) received a best poster award at CompSysBio2025 (Advanced Lecture Course on Computational Systems Biology, Aussois, France, November 2025).
- Clément Moulin-Frier and co-authors received two Best paper awards (track EvoApp and Best student paper award to the first author Max Taylor-Davis) at the Evostar 2025 conference (Trieste, Italy, April 2025).

7 Latest software developments, platforms, open data

Some of our computational models are specific to a particular question and are developed as single-use prototypes. They are made available to the community, if only for reproducibility. However, when possible, we centralize software development into a few structuring platforms, the most advanced of which is the

Aevol platform. Aevol development efforts have been maintained for many years and it is available as an open-source software. New developments can thus be capitalized on and made available for future use. Such a long-term effort comes at a cost, though. Maintaining such base of code is not trivial, even more so when HPC concerns are at play. The long-term engagement of David P. Parsons, engineer from Inria SED² is therefore of great importance to the team. He enables the team to maintain a high level of development of the Aevol platform, while also helping to establish best practices in software development and project management within the team.

In 2025, we have invested significant effort in developing explainable AI approaches for the analysis of single-cell transcriptomic data. This work has led to the development of new software tools. Two of them, TopShap and GraftBoost, we plan to continue improving in the future. A third tool, XCCSHAP, was developed in collaboration with Ruggero Pensa, who is also its lead developer and maintainer.

Note that, in addition to software, our methodological developments can be disseminated on their own. This is particularly the case in scientific computation where our HPC approach, parallel computing and mixed precision developments open the possibility of collaborations with industrial or academic partners (*e.g.*, in the PEPR Numpex).

Aevol (www.aevol.fr).

Self-assessment:

- Software Family: Vector for Knowledge;
- Audience: Community;
- Evolution and maintenance: LTS, Long Term Support;
- Duration of the Development (Duration): >10 years
- Free Description:

Aevol is a forward-in-time simulator that computes the evolution of a population of haploid organisms through a process of variation and selection. The design of the model focuses on realism of genome structure and the mutational process. Aevol can therefore be used to decipher the effect of chromosomal rearrangements on genome evolution, including their interactions with other types of mutational events.

TopShap (gitlab.inria.fr/topshap).

Self-assessment:

- Software Family: Vehicle for Research;
- Audience: currently at Partners, aim is for Community;
- Evolution and maintenance: LTS, Long Term Support;
- Duration of the Development: 3 years;
- Free Description:

TopShap is an algorithm for explainable machine learning that computes the top-K absolute SHAP values, including their confidence intervals and possible ties. The algorithm is agnostic and can be applied to any kind of machine learning model. TopShap performs an iterative refinement of the set of top-K candidates by interleaving sampling operations to improve SHAP value estimates and pruning steps to eliminate remaining candidates.

GraftBoost (gitlab.inria.fr/hchebraio/graftboost).

Self-assessment:

- Software Family: Vehicle for Research;
- Audience: currently at Personal, aim is for Community;

²Service d'Expérimentation et de Développement.

- Evolution and maintenance: LTS, Long Term Support;
- Duration of the Development: 2 years;
- Free Description:
GraftBoost infers and compares gene regulatory networks across a pair of conditions and highlights their differences. By using transfer-learning during network inference, it shares per target gene the most important TFs between two conditions. In this manner, GraftBoost encourages an explanation where the differential use of a TF is associated with a change in gene expression.

XCCSHAP (github.com/rupensa/xccshap).

Self-assessment:

- Software Family: Vehicle for Research;
- Audience: Partners;
- Evolution and maintenance: Basic maintenance to keep the software alive;
- Duration of the Development: 1 year;
- Free Description:
XCCSHAP is an explanation method that provides surrogate models with competitive fidelity and very compact decision paths to interpret Random Forest and XGBoost predictions. Given a trained model and its corresponding training data, our method exploits SHAP values to extract a co-clustering of data instances and features. It then computes one shallow decision tree per cluster of instances using a subset of features.

Vivarium (github.com/flowersteam/vivarium)

Self-assessment:

- Software Family: Vehicle for Research
- Audience: to be used by people inside and outside the project-team but without a clear and strong dissemination and support action plan;
- Evolution and maintenance: long term support.
- Duration of the Development: 3 years (started by C. Moulin-Frier in 2023 while he was a member of the Flowers team at Inria Bordeaux, now continuing while he is a member of the Biotic team)
- Free Description:
VIVARIUM is a massively multi-agent 2D simulator with realistic physics for research and education in Artificial Intelligence and Artificial Life. It facilitates the design of complex multi-agent ecosystems where thousands of artificial agents interact in a shared environment. The interface is modular, enabling to compose diverse types of agents and entities, each one with its particular dynamics, in a reusable way. It is designed to be usable to a large audience: from high-school students with a code-free web interface, to computer science university students through a pythonic interface enabling real-time interactions, as well to computer science researchers with GPU-accelerated simulation that can run on supercomputers. The core simulator is written in JAX, the web interface with Panel, and the client-server communication relies on gRPC.

Mixed Precision ODE Solver C++ (gitlab.inria.fr/amarzora/perf-arithmetic-cpp).

Self-assessment:

- Software Family: Vehicle for Research;
- Audience: currently at Partners, aim is for Community;
- Evolution and maintenance: LTS, Long Term Support;
- Duration of the Development: 3 years;

- Free Description:
Mixed Precision ODE Solver has been developed by Arsène Marzorati during his PhD. It is a set of ODE Solver dedicated to large scale ODE system. To improve performance, novel algorithms supporting mixed precision arithmetic have been developed and apply to different numerical schemes. Through vectorization, the software is capable to reach very high performance on modern CPU.

Mixed Precision ODE Solver Explicit Fortran: (gitlab.inria.fr/michel.al-sayed-ali/mixed-precision-explicit-numerical-methods).

Self-assessment:

- Software Family: Vehicle for Research;
- Audience: currently at Partners, aim is for Community;
- Evolution and maintenance: no future;
- Duration of the Development: 2 years;
- Free Description:
Mixed Precision ODE Solver has been developed by Mouhamad Al Said Ali during his postdoc. It is a large collections of explicit ODE Solver dedicated to large scale ODE systems. To improve performance, novel algorithms supporting mixed precision arithmetic have been developed and apply to different numerical schemes. Through MPI, the software is capable to run on distributed memory cluster and multi-core CPUs.

Mixed Precision ODE Solver Implicit Fortran: (gitlab.inria.fr/michel.al-sayed-ali/mixed-precision-implicit-numerical-methods).

Self-assessment:

- Software Family: Vehicle for Research;
- Audience: currently at Partners, aim is for Community;
- Evolution and maintenance: no future;
- Duration of the Development: 2 years;
- Free Description:
Mixed Precision ODE Solver has been developed by Mouhamad Al Said Ali during his postdoc. It is a large collections of implicit ODE Solver dedicated to large scale ODE systems. To improve performance, novel algorithms supporting mixed precision arithmetic have been developed and apply to different numerical schemes. Through MPI, the software is capable to run on distributed memory cluster and multi-core CPUs.

8 New results

8.1 Aevol for eukaryotic genomes

Participants: Juliette Luiselli, David Parsons, Romain Gallé, Jonathan Rouzaud-Cornabas, Guillaume Beslon.

Until recently, Aevol was mainly used to study viral and bacterial genomes. In the context of Juliette Luiselli's PhD (defended in June 2025), we developed an eukaryotic version of the model. Aevol_Euk introduces several important elements: linear chromosomes, diploidy, sexual reproduction, and recombination. This version has not been published yet, but it led to an important collaboration with Diala Abu Awad (Université Paris Saclay, France) on the effect of self-fertilization on genome structure. Simultaneously, a huge software engineering work has been conducted, first to get rid of the technical debt necessarily carried by a scientific software developed for more than 10 years, then to integrate this new version of the model. This work, mainly conducted by David P. Parsons, led to the release of Aevol_9 in May 2025 [16].

8.2 Chromosomal rearrangements set an equilibrium fraction of non-coding sequence

Participants: Juliette Luiselli, Guillaume Beslon.

The effect of population size and mutation rate on genome density in Aevol (see above achievement) inspired us to study a probabilistic model of genome evolution. We initiated a collaboration with a mathematician (Olivier Mazet, INSA Toulouse, France) to develop a model linking neutrality of chromosomal rearrangements (CRs) and their fixation probability. We showed that in genomes with a low fraction of non-coding DNA, duplications have a higher probability to be neutral and fix, increasing the fraction of non-coding DNA. Conversely, in genomes with a high fraction of non-coding sequence, deletions have a higher probability of being both neutral and fixed, decreasing the fraction of non-coding sequence. As a result, CRs establish an equilibrium fraction of non-coding DNA, which we demonstrate to depend on the product of the population size and the mutation rate [6].

8.3 Evolution of multicellular reproduction through co-option of ecological interactions

Participants: Enrico Sandro Colizzi.

Multicellular organisms like animals and plants develop by coordinating cell division and behavior to build a complex, functional body from a single progenitor cell. These developmental programs have evolved over time, and originated during the transition from unicellular to multicellular life. What were the first developmental programs built from? Here, we study how ecological interactions among single cells can be transformed into developmental programs at the onset of multicellularity.

We developed a spatially structured evolutionary model based on a hybrid Cellular Potts Model (CPM) in which cells migrate through the environment to locate resources, divide, and adhere to neighbors. Cell behaviour is controlled by an evolvable gene regulatory network (GRN) that integrates information about local resource availability and cell-cell contact to regulate when cells migrate versus when they divide. Mutations introduced during cell division generate heritable variation in these decision rules, while recurrent resource scarcity provides the selective pressure driving evolution.

We found that the spatial distribution of food plays strongly affects what kind of life cycle evolve. Depending on resource structure, we observe both unicellular strategies and diverse multicellular reproductive modes. Notably, multicellular life cycles that reproduce via unicellular propagules, the predominant strategy in extant multicellular life, emerge spontaneously as a dispersal solution in some environments. These propagules are homologous to the lineage's unicellular ancestors, indicating that ancestral cell states mediating ecological interactions can be co-opted as reproductive structures. Once propagule-producing multicellular lineages evolve, they can colonize environments previously dominated by unicellular life. Altogether, our results show how spatial ecology and selection on GRN-controlled migration and division can generate multicellular reproduction and early developmental dynamics [14].

8.4 Three-state model for gene expression

Participants: Thibaud Peyric, Anton Crombach.

As part of the ongoing PhD of Thibaud Peyric and building on the famous two-state model for stochastic gene expression, a novel three-state model was designed for paired single-cell RNA-seq and ATAC-seq data (involving T. Lepoutre of team Musics, [12]). Working at the pseudo-bulk level, the model was fit to a large set of genes and distinguished a small number of distinct expression strategies, providing novel insight into context-dependent regulation of gene expression.

8.5 Explainable ML and network inference

Participants: Lisa Chabrier, Anton Crombach, Christophe Rigotti.

As part of her PhD, Lisa Chabrier developed *TopShap*, an iterative approach to discover the top-k most important features for predictions made by a machine learning (ML) tool. The method is agnostic and thus applicable to any ML tool, and we showed that it drastically cuts computational costs in comparison to the state-of-the-art method, KernelShap. We also showed that TopShap can be applied to network inference from single-cell transcriptomic data in order to detect per cell the transcription factors (TFs) that regulate a target gene (TG). This contrasts ‘standard’ explanations, such as given by PySCENIC, where a single network describes an entire population of cells. With our method, we can dissect the network and zoom in on gene regulation in rare cell types. We tested this idea by applying the method to data on drug-tolerance in lung cancer, as described in Lisa’s thesis (*Efficient approximation method for local explanation of machine learning models, applied to the inference of local activity of gene regulatory networks*, INSA Lyon, defended in April 2025).

8.6 Comparative analysis of networks

Participants: Lisa Chabrier, Sofia Pacheco-Garcia, Hamza Chegraoui, Anton Crombach.

A common experimental setting in biology is to compare two conditions, like healthy/diseased, before/after treatment, and so on. At the level of the transcriptome, the standard analysis in such a case is called differential gene expression. Here we developed two prototypes, *Re_actShap* and *GraftBoost*, to perform similar comparative analyses, but at the gene regulatory level. *Re_actShap* builds on *TopShap* and is tailored to comparing a small set of genes that are considered relevant because of prior information. *GraftBoost*, in contrast, uses transfer learning techniques to provide a global overview of which TFs account most likely for changes in gene regulation. *Re_actShap* was developed by Lisa Chabrier during her PhD [13] and *GraftBoost* by postdoc Hamza Chegraoui (Chegraoui *et al.* in prep). We plan to package, document, and publish the two tools to make them available for the computational biology community.

8.7 Emergence of supercoiling-mediated regulatory networks through the evolution of bacterial chromosome organization

Participants: Guillaume Beslon.

DNA, the carrier of genetic information, is a flexible molecule that can dynamically twist and writhe around itself, a property known as DNA supercoiling. DNA supercoiling plays a particular role in gene regulation, because it can both affect gene transcription and be affected by it in return: genes located in underwound DNA are usually expressed more, and when a gene is being transcribed, DNA both overwinds downstream and underwinds upstream of the gene. We have studied the impact of this coupling between gene regulation and DNA supercoiling on the organization of bacterial genomes. To this aim, we developed a computational model in which simulated bacteria must adapt the expression of their genes, which depends only on supercoiling, to different environments by reordering their genomes through genomic inversions over generations. We show that, in this model, environment-specific gene expression can indeed evolve, and is the result of the formation of specific patterns of gene positions and orientations along the genome, leading to the emergence of supercoiling-sensitive regulatory networks. Altogether, these results suggest that gene regulation via supercoiling can help understand the organization of bacterial genomes through an evolutionary lens, and that this mechanism should be accounted for when designing fine-tuned artificial genetic constructs [5].

8.8 Mammalian olfactory cortex as a ‘missing’ evolutionary link

Participants: Anton Crombach.

Our long-standing collaboration with A. Fleischmann and R. Singh at Brown University (USA) led to an in-depth molecular characterization of neurons in the piriform cortex, also known as olfactory cortex [8]. We generated and analysed paired single-nucleus transcriptome and chromatin accessibility data from three- to six-layered cortical areas of adult mice and across tetrapod species. The core message of this study is that despite over 200 million years of coevolution alongside the neocortex, olfactory cortex neurons retain molecular signatures of ancestral cortical identity. Jupyter notebooks for the advanced analyses of the study were made available via Inria gitlab and via the Fleischmann gitlab.

8.9 Mixed precision for ODE

Participants: Jonathan Rouzaud-Cornabas, Arsène Marzorati, Ali al Sayed.

We were able to establish and facilitate close collaboration between the MUSIC and BioTiC teams via the ExODE AEx. This was achieved through the joint supervision of a research engineer and a PhD. Some of the topics were included in the PEPR NumPEX program. In this context, two journal articles were published [3, 4] and three others are either under review or being finalized. A thesis has been defended in mid-December (Arsène Marzorati). In addition to the knowledge and expertise developed, we have developed several software prototypes. These prototypes will be implemented in computational biology software (Aevol and SimuScale to begin with) in the coming months. This theme will be included in an ANR grant application and is central to new collaborations on regulatory network inference (with INRAE Saclay).

8.10 The cultural evolution of goals: How goals emerge from individual-level mechanisms of generation, selection and transmission

Participants: Clément Moulin-Frier.

Humans pursue goals that are remarkably diverse and vary over time and cultures. These goals shape which behaviors are explored, valued, and socially transmitted, yet most theories of cultural evolution focus on how behaviors evolve while leaving the origins of goals unexamined. We argue that a complete understanding of cultural evolution requires explaining how goals themselves emerge, vary, and persist across generations. Building on studies of motivation and curiosity in cognitive science and artificial intelligence, we introduce the notion of cultural autotelic agents: individuals who actively generate, select, and transmit their own goals within social environments. By highlighting the cognitive and motivational mechanisms that drive goal formation and selection, this framework extends existing models of cultural evolution and helps explain the open-ended, self-propelling character of human culture. A paper is currently under review in a Special Issue of Topics in Cognitive Science (topiCS). Co-authors: Jérémy Perez (1), Cédric Colas (1), Gaia Molinaro (2), Pierre-Yves Oudeyer (1), Maxime Derex (3), Clément Moulin-Frier (4).

- (1) Flowers AI & CogSci Lab, Centre Inria de l’université de Bordeaux, Talence, France
- (2) Department of Psychology, University of California, Berkeley, Berkeley, CA, USA
- (3) Institute for Advanced Study in Toulouse, Toulouse, France
- (4) BioTiC team, Inria, INSA Lyon, CITI, UR3720, 69621 Villeurbanne, France

9 Partnerships and cooperations

9.1 International initiatives

9.1.1 Participation in International Programs

NIH R01 project Paleocortex Formalizing our long-standing collaboration with Alexander Fleischmann and Ritambhara Singh, we obtained joint funding. In this project, we aim to understand how odour learning alters gene expression and regulation at different timescales. We study the olfactory (piriform, PCx) cortex, which plays key roles in odour perception and memory. However, we lack a detailed understanding of its cell types and their molecular adaptations during odour learning. We address this knowledge gap through data analysis of neuron-glia interactions and computational modelling of gene regulation due to neuronal (learning) dynamics.

Participants: Anton Crombach, Sofia Pacheco-Garcia.

Partners: Brown University (USA), Inria

Funding: approximately 2.5 million dollars

Duration: Originally 4 years (2023-2027), but on August 31, 2025 the subaward to BIOTIC was terminated by NIH.

9.1.2 Visits of international scientists

Bram van Dijk

Status: Researcher

Institution of origin: Utrecht University

Country: The Netherlands

Dates: July 10-16, 2025

Context of the visit: Scientific cooperation

Mobility program/type of mobility: Research stay

9.1.3 Visits to international teams

Sofia Pacheco-Garcia

Visited institution: Brown University

Country: USA

Dates: June 2025

Context of the visit: Visit of experimental lab of Alexander Fleischmann in the context of the PaleoCortex project.

Mobility program/type of mobility: Research stay

9.2 National initiatives

AEx ExODE: We lead an Inria Exploratory Research Actions (AEx) to foster collaborations between MUSICS, AVALON and BIO TIC. ExODE aims to study how mixed precision arithmetic could be used in computational biology software and especially ODE solver. Two journal articles have been published in 2025 [3, 4], and Arsène Marzorati doctoral thesis has been defended in December 2025. Our prototypes will be deployed in production within computational biology software and the results of this project will be further developed through an ANR grant application.

Participants: Jonathan Rouzaud-Cornabas, Arsène Marzorati, Ali al Sayed.

ANR NeGA NeGA (Influence de la taille efficace des populations sur l'architecture des génomes animaux) is a French ANR-funded project that investigates the hypothesis — initially proposed by population geneticist Michael Lynch — that many features of genome architecture (GA) result not from adaptation, but from non-adaptive processes shaped by the effective population size. To test this, NeGA compares the genomes of closely related species across five different animal groups and one *in silico* specie (Aevol) that have very different effective population sizes.

Participants: Guillaume Beslon, Jonathan Rouzaud-Cornabas, Juliette Luiselli.

Partners: BIO TIC, Laboratoire d'Écologie des Hydrosystèmes Naturels et Anthropisés (LEHNA, UMR CNRS 5023, Lyon), Laboratoire de Biométrie et Biologie Évolutive (LBBE, UMR CNRS 5558, Lyon), Institut des Sciences de l'Évolution de Montpellier (ISEM, UMR CNRS 5554, Montpellier).

Funding: 571,719 euros

Duration: 48 months (starting february 2021)

ANR JCJC ECOCURL C. Moulin-Frier obtained an ANR JCJC grant in 2020, with funding up to January 2026. The project is entitled "ECOCURL: Emergent communication through curiosity-driven multi-agent reinforcement learning". The project aims at integrating multi-agent reinforcement learning with curiosity-driven reinforcement learning to study emergent cooperation and communication in ecologically plausible simulated environments.

Participants: Clément Moulin-Frier.

Funding: 248,000 euros

Duration: 60 months

PEPR NumPEX Following our involvement in the French Exascale Project, our simulation platform Aevol has been selected as one of the target software in the Exa-DI ³ project. Due to the multiple versions of biological (2/4 base, prokaryote/eukaryote, regulatory networks, ...) and execution (sequential, OpenMP, GPU...) models, we are particularly involved in the extension ⁴ of the COMET component-based model.

Partners: CEA, CNRS, Inria, ...⁵

Funding: 40,8 million euros

Duration: 6 years (2023-2030)

³numpex.org/fr/exascale-developpement-et-integration/

⁴Jerry Lacmou Zeutouo, Christian Perez, Thierry Gautier and Jonathan Rouzaud-Cornabas. Extending the COMET component model to support hierarchical composite data: Aevol case study, ComPAS 2023

⁵numpex.org/fr/nos-partenaires/

PEPR Santé Numérique, project AI4scMed This project, led by Franck Picard (LBMC, CNRS), gathers approximately 40 researchers from different institutions on AI developments for single-cell (sc) biology applied to precision medicine. The consortium tackles methodological challenges to bridge the gap between sc data and personalized treatments, resolving cell type differences and integrating sc-multi-omics with imaging for spatial insights. Anton Crombach leads work package WP1.2.

Participants: Anton Crombach.

Partners: CNRS, INRIA, INSERM (PACA, Nouv. Aquit), Ecole Centrale de Nantes, Univ. Bordeaux, Sorbonne Univ., PSL.

Funding: 1,8 million euros

Duration: 4 years (2023-2027), plus extension of 2 years

Institut du Cancer, PLBIO project CLAIRE This project, led by Sandra Ortiz-Cuaran (CRCL), aims to provide novel insights into the molecular mechanisms of cancer cell adaptation to targeted therapies, aka drug-tolerance. The BioTiC team is involved to assess the pre-existence and the dynamics of the transcriptional states and gene regulatory networks associated with the emergence of drug-tolerance.

Participants: Anton Crombach.

Partners: Inria, INSERM

Funding: 525 591 euros

Duration: 3 years (2022-2025), plus a half year extension

9.3 Regional initiatives

Fédération Informatique de Lyon (FIL) Guillaume Beslon participates to a collaborative project granted by the FIL. EvoluNet aims at fostering a collaboration with Emmanuel Roux (CREATIS) to develop algorithms allowing to evolve simultaneously the weights and the architecture of deep neural networks. Funding 10 000 euros.

Institut Rhône-Alpin des Systèmes Complexes (IXXI) Guillaume Beslon participates to a collaborative project granted by IXXI. This project aims at fostering a collaboration with Nicolas Lartillot (CREATIS) to study the evolution of genome architecture. Funding 5000 euros.

10 Dissemination

10.1 Promoting scientific activities

10.1.1 Scientific events: organisation

We are strong advocates of interdisciplinarity in science and are committed to organizing interdisciplinary events at both the national and regional levels. However, the frequency of such events has been greatly reduced since INSA Lyon decided to charge rental fees for conference rooms (even for its own researchers) at a level that makes the organization of scientific events prohibitively expensive.

- Guillaume Beslon co-organized the ALPHY 2025 conference in Lyon (Alignment and Phylogeny, Lyon, February 2025).
- Guillaume Beslon co-organized the EvoLyon 2025 conference (Evolution in Lyon, Lyon, November 2025).
- Anton Crombach was member of the scientific and organization committees of CompSysBio 2025 (Aussois, October 2025).

Reviewer - reviewing activities

- Guillaume Beslon and Jonathan Rouzaud-Cornabas were reviewers for the international conference ALife 2025.
- Guillaume Beslon reviewed for *Royal Society Open Science Journal*.
- Anton Crombach reviewed for *Review Commons*.
- Clément Moulin-Frier reviewed for *Philosophical Transactions of the Royal Society B: Biological Sciences*.
- Clément Moulin-Frier reviewed for *Topics in Cognitive Science (topiCS)*.
- Clément Moulin-Frier was reviewer for the international conference GECCO 2025.

10.1.2 Invited talks

- Guillaume Beslon gave an invited conference to the group of bioinformatics of the TIMC-IMAG (Grenoble, September 2025).
- Guillaume Beslon gave an invited conference at CCS2025 (French Chapter of the Conference on Complex Systems, Paris, June 2025).
- Guillaume Beslon gave an opening keynote at the French national conference on theoretical biology (J-BIOT 2025, Grenoble, November 2025).
- Clément Moulin-Frier gave an invited talk at “Detection and Emergence of Complexity” (EPFL Lausanne, Switzerland, May 2025 — www.dem.eco).

10.1.3 Research administration

- David P. Parsons is a member of the national Comité Social d’Administration of Inria and of the local Formation Spécialisée de Site.
- Guillaume Beslon is a member of the Conseil Scientifique (CoS) and of the COMité des Moyens Incitatifs (COMI) of the Lyon Inria center.
- Guillaume Beslon is “Réfèrent Intégrité” for the Lyon Inria center.
- Jonathan Rouzaud-Cornabas is the head of the local Comité des Utilisateurs des Moyens Informatiques (CUMI which does the link between the DSI and the research teams and services of Inria), a member of the office for computing platform at Inria, the representative for biology in the user committee of the SLICES infrastructure, and a reviewer for computational biology applications wanting to use GENCI resources (eDARI).
- Anton Crombach served as a member of the 2025 hiring committee for the Inria junior researchers positions (CRCN and ISFP) for the Lyon Inria center.
- Guillaume Beslon served as an external evaluator on the selection committees for professor positions at the University of Montpellier, EPFL and INSA Lyon.

10.1.4 Supervision

Three PhDs have been defended in the team in 2025:

Lisa Chabrier *Approximation efficace pour l’explication locale des modèles d’apprentissage, appliquée à l’inférence d’activité locale des réseaux de régulation génique*, defended April 9th 2025.

Juliette Luiselli *How chromosomal rearrangements shape genomes: a computational and mathematical study*, defended June 25th 2025.

Arsène Marsorati *Insertion de précision mixte pour le passage à l'échelle de la résolution de systèmes d'équations différentielles ordinaires en grande dimension pour la biologie computationnelle*, defended December 16th 2025.

Note that Anton Crombach's "Habilitation à Diriger des Recherches" was prepared in 2025 but, due to scheduling issues, it has been defended early in 2026 (6th of January).

10.1.5 Juries and PhD advising committees

- Anton Crombach is a member of the PhD advising committee of Erwan Cruché (ED314 E2M2, Lyon), supervised by Sergio Peignier, Clement Marteau, and Federica Calevro.
- Guillaume Beslon is a member of the PhD advising committee of Bastien Saillant (ED512 Infomath, Lyon), supervised by Fabrice Jaillet, Florence Zara and Guillaume Damiand.
- Guillaume Beslon is a member of the PhD advising committee of Quentin Fernandez de Grado (ED216 ISCE, Grenoble), supervised by Antoine Frénoy.
- Guillaume Beslon is a member of the PhD advising committee of Marko Cvjetko (ED39 EDMI, Bordeaux), supervised by Pierre-Yves Oudeyer.
- Guillaume Beslon was a jury member for the defense of Etienne Rajon's Habilitation à Diriger des Recherches (Univ. Lyon 1), June 2025.

10.1.6 Educational and pedagogical outreach

Among the permanent members of the team, half are professor or associate professors. In France, this means that their teaching duty cannot be lower (but can be higher!) than 192 hours/year (approximately 6 hours/week). Moreover, all PhD students are encouraged to teach 64 hours/year and most of the PhD students of the BioTiC team actually do so as it is an important addition to their academic experience. Although this can change from one year to the other, we estimate that the members of the team together teach more than 1000 hours/year. Thus, it is impossible to list all the courses here. We will therefore limit ourselves to outlining the pedagogical commitment of the team members.

- Carole Knibbe (Professor, INSA-Lyon) is director of the Biosciences department at INSA-Lyon engineering school since 2020. In this department she teaches computer science (data-analysis, Python programming) at Licence and Master levels.
- Christophe Rigotti (Associate Professor, INSA-Lyon) is a member of the INSA-Lyon engineering school, in the FIMI ("Formation Initiale aux Métiers de l'Ingénieur", Licence level) department where he teaches the basis of computer science. He is also a regular speaker in the INSA-Lyon Biosciences department where he teaches data-mining at master-level.
- Jonathan Rouzaud-Cornabas (Associate Professor, INSA-Lyon) is a member of the Computer Sciences department at INSA-Lyon. He teaches High-Performance Computing (HPC), parallelism and scientific computing at Master Level. He also regularly intervenes in the Bioscience department where he teaches HPC at Master level in the "Bioinformatics and Modelling" option. Together with Guillaume Beslon he created the "P-SAT project", a STEAM⁶ project at master level in the computer science department. Since then both serve as supervisors of the P-SAT module.
- Guillaume Beslon (Professor, INSA-Lyon) is a member of the Computer Science department at INSA-Lyon where he teaches Computer Architecture at Licence level and Computational Sciences at Master level. Together with Jonathan Rouzaud Cornabas he created the "P-SAT project" and supervises it since 2020 (see above). Guillaume Beslon is also a member of the INSA-Lyon Humanities department where he supervises the artistic option "Backstage Light and Sound design" and teaches lighting design for theater, dance and movies. He also participates to the series of seminars to sensitize students to the anthropogenic crisis. In this context, he gives one seminar at licence level ("Numérique et Biodiversité") and one seminar at master level ("Numérique et Santé").

⁶Scientific, Technical, Engineering, Art and Mathematics

- David P. Parsons teaches C++ programming at INSA Lyon in the Biosciences department (Bioinformatics and Modelling track) at the Master 1 level. He also regularly gives tutorials on advanced Git usage as part of Inria’s continuing education program.
- Depending on their initial training discipline, BioTIC’s PhD students either teach in the INSA-Lyon Computer Science department (Computer Architecture, Programming, HPC. . .) or in the INSA-Lyon Biosciences department (physiology, data-analysis, Python programming. . .).

10.2 Popularization

Several permanent and non-permanent members of the team are regularly involved in science outreach activities (participation in the Inria and LIRIS science outreach activities, involvement in the “Fête de la Science”, in the “Nuit des chercheurs”, in the “Réseau Femmes&Sciences”, in the Université Ouverte de Lyon, etc.). Some of our initiatives are more specific and deserve to be mentioned here:

- Computer models can often be used for teaching purposes (for example, in courses at the Université Ouverte de Lyon). We have developed models specifically for this purpose. In particular, we have developed GreenMice, an educational game designed to teach children about evolutionary mechanisms. GreenMice has been presented during “La nuit des chercheurs” (October 2025), together with a dedicated version of the Aevol software – ISEE-Resistance – tailored to teach antibioresistance.
- Guillaume Beslon gave two conferences for the “Université Ouverte de Lyon”:
 - “Que peut-on apprendre d’une épidémie en 25 lignes de code” (April 2025)
 - “L’évolution, Hasard ou Nécessité ?” (May 2025)
- Jonathan Rouzaud-Cornabas published an article in “The Conversation” to present the “GPU revolution” to the general public (doi.org/10.64628/AAK.vtfhas9x9). Following this article, he was interviewed by a journalist of “Alternative économique”⁷ and another one with “We Demain” (To appear).
- Following the publication of our work on mammalian olfactory cortex as a “missing” evolutionary link, Anton Crombach and co-authors popularized their study through the communication departments of Inria and Brown University, respectively. An interview was published on Inria’s website (inria.fr/fr/cortex-olfactif-traces-passe-millions-annees) and another one on Brown University’s website (carney.brown.edu/news/2025-04-08/reptile-brain).
- Guillaume Beslon participated to the organization of “Hormones en Folies”, a theatrical performance that mixes biology with music and storytelling (Lyon, November 2025).

11 Scientific production

11.1 Major publications

- [1] J. Luiselli, P. Banse, O. Mazet, N. Lartillot and G. Beslon. ‘Structural mutations set an equilibrium non-coding genome fraction’. In: *Molecular Biology and Evolution* 42.12 (5th Feb. 2025). DOI: [10.1101/2025.02.03.636187](https://doi.org/10.1101/2025.02.03.636187). URL: <https://hal.science/hal-05382436>.
- [2] S. Zeppilli, A. Gurrola, P. Demetci, D. Brann, T. Pham, R. Attey, N. Zilkha, T. Kimchi, S. Datta, R. Singh, M. Tosches, A. Crombach and A. Fleischmann. ‘Single-cell genomics of the mouse olfactory cortex reveals contrasts with neocortex and ancestral signatures of cell type evolution’. In: *Nature Neuroscience* 28.5 (8th Apr. 2025), pp. 937–948. DOI: [10.1038/s41593-025-01924-3](https://doi.org/10.1038/s41593-025-01924-3). URL: <https://hal.science/hal-05349503>.

⁷www.alternatives-economiques.fr/nvidia-sest-hissee-sommet-de-tech-mondiale/00116697

11.2 Publications of the year

International journals

- [3] M. Al Sayed Ali, S. Bernard, A. Marzorati and J. Rouzaud-Cornabas. ‘Mixed precision implicit numerical schemes for systems of ordinary differential equations’. In: *Numerical Algorithms* (27th Nov. 2025). DOI: [10.1007/s11075-025-02256-w](https://doi.org/10.1007/s11075-025-02256-w). URL: <https://inria.hal.science/hal-05385014> (cit. on pp. 12, 14).
- [4] M. A. S. Ali and M. Sadkane. ‘Acceleration of implicit schemes for large systems of delay differential equations’. In: *Journal of Computational and Applied Mathematics* 473 (Feb. 2026). DOI: [10.1016/j.cam.2025.116863](https://doi.org/10.1016/j.cam.2025.116863). URL: <https://hal.science/hal-05386989> (cit. on pp. 12, 14).
- [5] T. Grohens, S. Meyer and G. Beslon. ‘Emergence of supercoiling-mediated regulatory networks through the evolution of bacterial chromosome organization’. In: *PLoS Computational Biology* 21 (29th Sept. 2025). DOI: [10.1371/journal.pcbi.1013482](https://doi.org/10.1371/journal.pcbi.1013482). URL: <https://hal.science/hal-05357653> (cit. on p. 11).
- [6] J. Luiselli, P. Banse, O. Mazet, N. Lartillot and G. Beslon. ‘Structural mutations set an equilibrium non-coding genome fraction’. In: *Molecular Biology and Evolution* 42.12 (5th Feb. 2025). DOI: [10.1101/2025.02.03.636187](https://doi.org/10.1101/2025.02.03.636187). URL: <https://hal.science/hal-05382436> (cit. on p. 10).
- [7] R. Pensa, A. Crombach, S. Peignier and C. Rigotti. ‘Explaining Random Forest and XGBoost with Shallow Decision Trees by Co-clustering Feature Importance’. In: *Machine Learning* 114.12 (20th Nov. 2025). DOI: [10.1007/s10994-025-06932-9](https://doi.org/10.1007/s10994-025-06932-9). URL: <https://hal.science/hal-05379633>.
- [8] S. Zeppilli, A. Gurrola, P. Demetci, D. Brann, T. Pham, R. Attey, N. Zilkha, T. Kimchi, S. Datta, R. Singh, M. Tosches, A. Crombach and A. Fleischmann. ‘Single-cell genomics of the mouse olfactory cortex reveals contrasts with neocortex and ancestral signatures of cell type evolution’. In: *Nature Neuroscience* 28.5 (8th Apr. 2025), pp. 937–948. DOI: [10.1038/s41593-025-01924-3](https://doi.org/10.1038/s41593-025-01924-3). URL: <https://hal.science/hal-05349503> (cit. on p. 12).

Invited conferences

- [9] C. Rigotti, R. G. Pensa, S. Peignier and A. Crombach. ‘Bridging local and global explanations of tree ensemble predictions using co-clustering of SHAP values’. In: NuTS-AI 2025 workshop on Artificial Intelligence and Application to Solid Earth. Paris, France, 7th July 2025. URL: <https://hal.science/hal-05165103>.

International peer-reviewed conferences

- [10] J. Luiselli and M. Lafond. ‘Eukaryotic Ancestry in a Finite World’. In: *Lecture Notes in Computer Science ((LNBI, volume 15959))*. International Conference on Computational Methods in Systems Biology. Vol. 15959. Lecture Notes in Computer Science. Lyon, France: Springer Nature Switzerland, 19th Aug. 2026, pp. 337–355. DOI: [10.1007/978-3-032-01436-8_18](https://doi.org/10.1007/978-3-032-01436-8_18). URL: <https://hal.science/hal-05376481>.
- [11] B. Morel, C. Moulin-Frier and P. Barla. ‘Complex System Exploration with Interactive Human Guidance’. In: WIVACE 2025 - XIX International Workshop on Artificial Life and Evolutionary Computation. Siena, Italy, 2025. URL: <https://inria.hal.science/hal-05295843>.
- [12] 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 pp. 6, 10).

National peer-reviewed Conferences

- [13] L. Chabrier, A. Crombach, S. Peignier and C. Rigotti. ‘Re_actShap : détection de rebranchements des réseaux de régulation d’expression génique à l’aide des valeurs SHAP’. In: *Actes EGC’25. 25ième conférence sur l’Extraction et Gestion des Connaissances (EGC)*, session demonstrations. Strasbourg, France, 2025, p. 8. URL: <https://inria.hal.science/hal-04877547> (cit. on p. 11).

Reports & preprints

- [14] A. P. Fernandes, R. M. A. Vroomans and E. S. Colizzi. *Evolution of multicellular reproduction through co-option of ecological interactions*. 8th Oct. 2025. DOI: [10.1101/2025.10.08.681199](https://doi.org/10.1101/2025.10.08.681199). URL: <https://hal.science/hal-05451399> (cit. on p. 10).
- [15] P. F. Hagolani, M. Sémon, G. Beslon and S. Pantalacci. *Pleiotropy accelerates tooth phenotypic and genomic evolution - An in silico study under the lens of development*. 13th Apr. 2025. DOI: [10.1101/2025.04.11.648404](https://doi.org/10.1101/2025.04.11.648404). URL: <https://hal.science/hal-05390919>.
- [16] J. Luiselli, D. Parsons, R. Gallé, P. Banse, J. Rouzaud-Cornabas and G. Beslon. *Aevol-9: A simulation platform to decipher the evolution of genome architecture*. 10th Apr. 2025. DOI: [10.1101/2025.04.10.648095](https://doi.org/10.1101/2025.04.10.648095). URL: <https://hal.science/hal-05357667> (cit. on p. 9).