RESEARCH CENTRE
Grenoble - Rhône-Alpes

IN PARTNERSHIP WITH:

Institut national des sciences appliquées de Lyon, Université Claude Bernard (Lyon 1), CNRS

2021
ACTIVITY REPORT

Project-Team

BEAGLE

Artificial Evolution and Computational Biology

IN COLLABORATION WITH: Laboratoire d'InfoRmatique en Image et Systèmes d'information (LIRIS)

DOMAIN

Digital Health, Biology and Earth

THEME

Computational Biology

Contents

Project-Team BEAGLE

Creation of the Project-Team: 2013 January 01

Keywords

Computer sciences and digital sciences

A3.3.2. – Data mining

A6.1.1. – Continuous Modeling (PDE, ODE)

A6.1.3. – Discrete Modeling (multi-agent, people centered)

A6.1.4. – Multiscale modeling

A6.2.7. – High performance computing

A8.1. – Discrete mathematics, combinatorics

Other research topics and application domains

B1. – Life sciences

B1.1.2. – Molecular and cellular biology

B1.1.6. – Evolutionnary biology

B1.1.7. – Bioinformatics

B1.1.10. – Systems and synthetic biology

B1.1.11. – Plant Biology

B1.2.1. – Understanding and simulation of the brain and the nervous system

B3.5. – Agronomy

B3.6. – Ecology

B9.2.1. – Music, sound

B9.2.4. – Theater

B9.9. – Ethics

1   Team members, visitors, external collaborators

Research Scientists

- Hugues Berry [Inria, Senior Researcher, HDR]

- Antonius Crombach [Inria, Researcher]

- Thomas Guyet [Inria, Researcher, from Sep 2021, HDR]

- Eric Tannier [Inria, Senior Researcher, HDR]

- Leonardo Trujillo Lugo [Inria, Advanced Research Position]

Faculty Members

- Guillaume Beslon [Team leader, INSA Lyon, Professor, HDR]

- Carole Knibbe [INSA Lyon, Associate Professor, HDR]

- Catherine Pothier [INSA Lyon, Associate Professor, from Sep 2021, INSA Lyon]

- Christophe Rigotti [INSA Lyon, Associate Professor, HDR]

- Jonathan Rouzaud-Cornabas [INSA Lyon, Associate Professor]

Post-Doctoral Fellow

- Vincent Liard [Univ Lumière, until Aug 2021, ATER]

PhD Students

- Aquilina Al Khoury [Inria, Until October 2021]

- Paul Banse [INSA Lyon]

- Lisa Blum Moyse [INSA Lyon]

- Lisa Chabrier [Inria, from Oct 2021]

- Julie Etienne [INSERM]

- Marco Foley [Inria]

- Theotime Grohens [INSA Lyon]

- Nathan Quiblier [Inria, from Oct 2021]

- Laurent Turpin [Inria]

Technical Staff

- David Parsons [Inria, Engineer]

- Arnaud Tilbian [Inria, Engineer]

Interns and Apprentices

- Cedric Amiel [Inria, from Jun 2021 until Aug 2021]

- Lisa Chabrier [Inria, from Mar 2021 until Aug 2021]

- Cyril Elisei-Pothier [Inria, from Nov 2021]

- Clement Galan [Inria, from Mar 2021 until Jun 2021]

- Romain Galle [Inria, from Jun 2021 until Aug 2021]

- Juliette Luiselli [École Normale Supérieure de Paris]

- Nathan Quiblier [Inria, from Apr 2021 until Sep 2021]

Administrative Assistant

- Laetitia Gauthe [Inria]

2   Overall objectives

2.1   An interface between biology and computer science

The expanded name for the BEAGLE research group is "Artificial Evolution and Computational Biology". Our aim is to position our research at the interface between biology and computer science and to contribute new results in biology by modeling biological systems. In other words we are making artifacts – from the Latin *artis factum* (an entity made by human art rather than by Nature) – and we explore them in order to understand Nature. The team is an INRIA Project-Team since January, 2014. It gathers researchers from INRIA, INSA, who are members of three different labs, the LIRIS [1], the LBBE [2], and CARMEN [3]. It is led by Prof. Guillaume Beslon (INSA-Lyon, LIRIS, Computer Science Dept.).

Our research program requires the team members to have skills in computer science but also in life sciences: they must have or develop a strong knowledge in biosciences to interact efficiently with biologists or, ideally, to directly interpret the results given by the models they develop. A direct consequence of this claim is that it is mandatory to restrict the domain of expertise in life sciences. This is why we focus on a specific scale, central in biology: the cellular scale. Indeed, we restrict our investigations on the cell, viewed as a dynamical system made of molecular elements. This specific scale is rich in open questions that deserve modeling and simulation approaches. We also focus on two different kinds of constraints that structure the cellular level: biophysical constraints and historical constraints. The cell is a system composed of molecules that physically interact and the spatio-temporal nature of these interactions is likely to strongly influence its dynamics. But the cell is also the result of an evolutionary process that imposes its own limits on what can evolve (or is the most likely to evolve) and what cannot (or is the less likely to evolve). A better understanding of what kind of systems evolution is the most likely to lead to in a given context could give us important clues for the analysis of extant biological systems.

2.2   An organization into two tools and four main axes

To study these two kinds of constraints we mainly rely on two specific tools: computational cellular biochemistry and evolution models. We use these tools to develop our "artifacts" and we compare their output with real data, either direct measurements collected by experimentalists or ancestral properties computationally inferred from their extant descendants. The team research is currently organized in four main research axes. The first two ones are methodologically-oriented: we develop general formalisms

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[1]Laboratoire d'Informatique en Image et Systèmes d'Information: UMR 5205 CNRS, INSA-Lyon, Univ. Claude Bernard Lyon 1, Univ. Louis Lumière Lyon 2, École Centrale de Lyon

[2]Laboratoire de Biometrie et Biologie Evolutive: UMR CNRS 5558, Univ. Claude Bernard Lyon 1.

[3]Laboratoire de Recherche en Cardiovasculaire, Métabolisme, Diabétologie et Nutrition: UMR U1060 INSERM, INSA-Lyon, INRA 1235, Univ. Claude Bernard Lyon 1.

and tools for computational cellular biochemistry (research axis 1) and families of models to study the evolutionary process (research axis 2). The third "NeuroCell" axis (research axis 3) is the one in which biochemical models are specifically applied on brain cells (neurons and glia). Eventually the last axis aims at integrating the two tools, computational biochemistry and evolution, in what we call "Evolutionary Systems Biology" (research axis 4). The next four sections describe these four axes in more details. The biological questions described are not the sole topics tackled by the team. They are the ones that mobilize a substantial fraction of the researchers on the long run. Many other questions are tackled by individual researchers or even small groups. In the following these ones will be briefly described in their methodological context, *i.e.* in the two sections devoted to research axes 1 and 2.

2.3   A strategy

The scientific objective of the BEAGLE team is to develop a consistent set of concepts and tools – mainly based on computational science – to *in fine* contribute to knowledge discovery in systems biology. Our strategy is to develop strong interactions with life science researchers to become active partners of the biological discovery process. Thus, our aim as a team is not to be a computer science team interacting with biologists, nor to be a team of biologists using computer science tools, but rather to stay in the middle and to become a *trading zone* [31] between biology and computer science. Our very scientific identity is thus fuzzy, melting components from both sciences. Indeed, one of the central claims of the team is that interdisciplinarity involves permanent exchanges between the disciplines. Such exchanges can hardly be maintained between distant teams. That's why the BEAGLE team tries to develop local collaborations with local scientists. That's also why BEAGLE also tries to organize itself as an intrinsically interdisciplinary group, gathering different sensitivities between biology and computer science inside the group. Our ultimate objective is to develop interdisciplinarity at the individual level, all members of the team being able to interact efficiently with specialists from both fields.

3   Research program

3.1   Introduction

As stated above, the research topics of the BEAGLE Team are centered on the modeling and simulation of cellular processes. More specifically, we focus on two specific processes that govern cell dynamics and behavior: Biophysics and Evolution. We are strongly engaged into the integration of these level of biological understanding.

3.2   Research axis 1: Computational cellular biochemistry

Biochemical kinetics developed as an extension of chemical kinetics in the early 20th century and inherited the main hypotheses underlying Van't Hoff's law of mass action : a perfectly-stirred homogeneous medium with deterministic kinetics. This classical view is however challenged by recent experimental results regarding both the movement and the metabolic fate of biomolecules. First, it is now known that the diffusive motion of many proteins in cellular media exhibits deviations from the ideal case of Brownian motion, in the form of position-dependent diffusion or anomalous diffusion, a hallmark of poorly mixing media. Second, several lines of evidence indicate that the metabolic fate of molecules in the organism not only depends on their chemical nature, but also on their spatial organisation – for example, the fate of dietary lipids depends on whether they are organized into many small or a few large droplets (see e.g. [32]). In this modern-day framework, cellular media appear as heterogeneous collections of contiguous spatial domains with different characteristics, thus providing spatial organization of the reactants. Moreover, the number of implicated reactants is often small enough that fluctuations cannot be ignored. To improve our understanding of intracellular biochemistry, we study spatiotemporal biochemical kinetics using computer simulations (particle-based spatially explicit stochastic simulations) and mathematical models (age-structured PDEs).

3.3   Research axis 2: Models for Molecular Evolution

We study the processes of genome evolution, with a focus on large-scale genomic events (rearrangements, duplications, transfers). We are interested in deciphering general laws which explain the organization of the genomes we observe today, as well as using the knowledge of these processes to reconstruct some aspects of the history of life. To do so, we construct mathematical models and apply them either in a "forward" way, *i.e.* observing the course of evolution from known ancestors and parameters, by simulation (*in silico experimental evolution*) or mathematical analysis (*theoretical biology*), or in a "backward" way, *i.e.* reconstructing ancestral states and parameters from known extant states (*phylogeny, comparative genomics*). Moreover we often mix the two approaches either by validating backwards reconstruction methods on forward simulations, or by using the forward method to test evolutionary hypotheses on biological data.

3.4   Research axis 3: Computational systems biology of neurons and astrocytes

Brain cells are rarely considered by computational systems biologists, though they are especially well suited for the field: their major signaling pathways are well characterized, the cellular properties they support are well identified (e.g. synaptic plasticity) and eventually give rise to well known functions at the organ scale (learning, memory). Moreover, electro-physiology measurements provide us with an experimental monitoring of signaling at the single cell level (sometimes at the sub-cellular scale) with unrivaled temporal resolution (milliseconds) over durations up to an hour. In this research axis, we develop modeling approaches for systems biology of both neuronal cells and glial cells, in particular astrocytes. We are mostly interested in understanding how the pathways implicated in the signaling between neurons, astrocytes and neurons-astrocytes interactions implement and regulate synaptic plasticity.

3.5   Research axis 4: Evolutionary Systems Biology

This axis, consisting in integrating the two main biological levels we study, is a long-standing and long-term objective in the team. We have started to see significant advances in this direction, mainly due to the evolution of the team staff and team projects. These novel developments allow us to give this axis back its central place. We have several short and middle term projects that integrate biochemical data and evolution. First results were reported in 2019 with respect to an evolutionary perspective on chromatin-associated proteins. Other, ongoing projects include reverse engineering the regulatory networks of 'old' and 'young' brain regions (i.e. neuro-evo-devo) and finding new therapeutic targets for lung tumours that evolve treatment resistance.

4   Application domains

4.1   Functional and Evolutionary Biology

We do not distinguish our research and its application domains. Our shared idea is that the research is oriented by a scientific question, which is a multidisciplinary one, most often of biological nature. We do not develop methodologies independently from this question and then look for applications. Instead we collectively work with other disciplines to solve a question, with our competencies.

In consequence the application domains are already listed in the description of our projects and goals. They concern functional and evolutionary biology, related to critical social questions as human or global health.

4.2   Implication domains

We still advocate for the "application domains" section of the activity report to be called "implication domains" to broaden its scope. Implication contains applications, but not conversely.

This could allow us and others to report on orientation activities of our research programs guided by a social demand rather than by an intrinsic dynamic of scientific evolution, a simple claim for "progress", or a social demand coming only from industry.

This could allow a better awareness of social and environmental issues, and integrate them in this section.

5 Social and environmental responsibility

5.1 Footprint of research activities

The website we constructed two years ago ferme.yeswiki.net/Empreinte can still be used for simple carbon footprint calculations of a team, but is or will be supplanted by future internal tools from Inria or the released ones of Labo1p5.

5.2 Impact of research results

We organised in 2021 the "Sciences-Environnements-Sociétés" workshop in Inria Grenoble and Inria Lyon, in collaboration with Sophie Quinton. Seven one day workshops have been organised, and at least one participant from every team in the two centers have participated, so that every team can organise a workshop on its own if wished by the members. Several teams have already done it. We have other requests to organise it in the centers of Rennes, Sophia and Paris in 2022.

Besides this, Eric Tannier regularly teaches reserch ethics at university of Lyon, at Inria and University of Lyon 1, is a member of the ethics platform of university of Lyon and of the scientific committee of the science shop. He participated to the foundation of la fabrique des questions simples, a multidisciplinary institute for research in the Anthropocene in Lyon.

We also lead an "action exploratoire" related to environmental issues, on the development of agro-ecology, as it is recommended by the IPCC (GIEC) on climate change and IPBES on biodiversity.

6 Highlights of the year

Anton Crombach edited a book on evolutionary systems biology (Springer, June 2021) [20]. Two chapters of this book have been written by members of the team [21, 22].

7 New software and platforms

7.1 New software

7.1.1 aevol

Name: Artificial Evolution

Keywords: Bioinformatics, Genomics, Evolution

Functional Description: Aevol is a digital genetics model: populations of digital organisms are subjected to a process of selection and variation, which creates a Darwinian dynamics. By modifying the characteristics of selection (e.g. population size, type of environment, environmental variations) or variation (e.g. mutation rates, chromosomal rearrangement rates, types of rearrangements, horizontal transfer), one can study experimentally the impact of these parameters on the structure of the evolved organisms. In particular, since Aevol integrates a precise and realistic model of the genome, it allows for the study of structural variations of the genome (e.g. number of genes, synteny, proportion of coding sequences).

The simulation platform comes along with a set of tools for analysing phylogenies and measuring many characteristics of the organisms and populations along evolution.

An extension of the model (R-Aevol), integrates an explicit model of the regulation of gene expression, thus allowing for the study of the evolution of gene regulation networks.

News of the Year: In the context of the Evoluthon and NeGA ANR Projects, we developed two prototypes based on the main aevol software. The first one, "4Evol", extends the binary genetic code used in aevol into a 4-bases genetic code that respects the universal genetic code. The second one is a eukaryotic version of the model. While aevol genetic and genomic structure is inspired from the molecular structure of prokaryotes (haploid circular genome), this new version introduces diploidy and recombination. Both prototypes are currently tested by the team members and shall be released soon.

Futhermore, to keep Aevol computationally tractable, we have work a lot on improving its performance. A new version has been released that improved the sequential execution of Aevol through large code rewrite and low level optimization (such as vectorization). Moreover, the OpenMP implementation (parallel shared memory) has been improved and a MPI implementation (parallel distributed memory) has been released. Both of them can be combined to scale on large modern parallel cluster. Last, we are working on a GPU implementation. By doing so, we can keep complexifying the model and increasing the population size and still remain in acceptable execution time.

URL: http://www.aevol.fr/

Contact: Guillaume Beslon

Participants: Paul Banse, Guillaume Beslon, Marco Foley, Theotime Grohens, Juliette Luiselli, Jonathan Rouzaud-Cornabas, Laurent Turpin, Leonardo Trujillo Lugo

Partners: UCBL Lyon 1, INSERM, Université Paris-Descartes, Insa de Lyon

7.1.2 Treerecs

Name: Treerecs

Keywords: Bioinformatics, Biology, Computational biology

Scientific Description: The reconciliation between gene trees and species trees is a modern method of molecular phylogeny, which does not yet have its standard software, as for example phylogeny from DNA or amino acid sequences. Treerecs has this ambition, incorporating the classic functionalities of reconciliation: annotating the vertices of a gene tree with the tops of a species tree, rooting and correcting the gene tree. Rooting and correction are calculated to minimize the number of duplications and losses in reconciliation. Medium-sized solutions are randomly sampled according to a uniform law. A likelihood can then be calculated using probabilistic methods. In addition, Treerecs is integrated into a standard software ecosystem of phylogeny, bio ++, ALE, Seaview, and has a graphical interface. Some original features are implemented, such as the possibility of combining two types of likelihoods, the one calculated from the sequences and the one calculated from the reconciliations, the possibility of estimating the costs of the evolutionary events, the possibility of exploring the space of trees according to a joined likelihood.

Functional Description: Treerecs takes as minimum input a gene tree and a species tree. It "reconciles" them, that is, it annotates gene tree nodes with events and assign them to species tree nodes. Biologically, it is a reconstruction of the gene history, given the species history, in terms of duplications, speciations, losses.

With the appropriate options Treerecs can root and correct the gene tree.

News of the Year: Publication in 2021 of a book chapter from "Multiple Sequence Alignment" of version 5.0 of Seaview, a platform that now integrates Treerecs as one of the standard phylogeny software.

Contact: Eric Tannier

Participants: Nicolas Comte, David Parsons, Eric Tannier, Benoît Morel

Partner: Laboratoire de Biométrie et Biologie Evolutive (LBBE) - UMR CNRS 5558

7.2 New platforms

Participants: Eric Tannier, Arnaud Tilbian, David Parsons.

A new platform bioindication.com, issued from the Action Exploratoire Community Garden Book, has been released in 2021, but not integrated in the databases yet. Its goal is to provide an environmental evaluation from the observation of weeds.

8 New results

8.1 A model of on/off transitions in neurons of the deep cerebellar nuclei: deciphering the underlying ionic mechanisms.

Participant: H. Berry.

The neurons of the deep cerebellar nuclei (DCNn) represent the main functional link between the cerebellar cortex and the rest of the central nervous system. Therefore, understanding the electrophysiological properties of DCNn is of fundamental importance to understand the overall functioning of the cerebellum. Experimental data suggest that DCNn can reversibly switch between two states: the firing of spikes (F state) and a stable depolarized state (SD state). We have introduced a new biophysical model of the DCNn membrane electro-responsiveness to investigate how the interplay between the documented conductances identified in DCNn give rise to these states [6]. In the model, the F state emerges as an isola of limit cycles, i.e. a closed loop of periodic solutions disconnected from the branch of SD fixed points. This bifurcation structure endows the model with the ability to reproduce the F to SD transition triggered by hyperpolarizing current pulses. The model also reproduces the F to SD transition induced by blocking Ca currents and ascribes this transition to the blocking of the high-threshold Ca current. The model suggests that intracellular current injections can trigger fully reversible F to-and-from SD transitions. Investigation of low-dimension reduced models suggests that the voltage-dependent Na current is prominent for these dynamical features. Finally, simulations of the model suggest that physiological synaptic inputs may trigger F to-and-from SD transitions. These transitions could explain the puzzling observation of positively correlated activities of connected Purkinje cells and DCNn despite the former inhibit the latter.

8.2 Simulation of Astrocytic Calcium Dynamics in Lattice Light Sheet Microscopy Images

Participant: H. Berry.

Astrocytes regulate neuronal information processing through a variety of spatio-temporal calcium signals. Recent advances in calcium imaging have started to shine light on astrocytic activity, but the complexity and size of the recorded data strongly call for more advanced computational analysis tools. Their development is currently hindered by the lack of reliable, labeled annotations that are essential for the evaluation of algorithms and the training of learning-based methods. To solve this labeling problem, we have designed a generator of 2D/3D lattice light sheet microscopy (LLSM) sequences which realistically depict the calcium dynamics of astrocytes [10]. By closely modeling calcium kinetics in real astrocytic ramifications, the generated datasets open the door for the deployment of convolutional neural networks in LLSM.

8.3 Molecular characterization of projection neuron subtypes in the mouse olfactory bulb

Participant: A. Crombach.

Projection neurons (PNs) in the mammalian olfactory bulb (OB) receive input from the nose and project to diverse cortical and subcortical areas. Morphological and physiological studies have highlighted functional heterogeneity, yet no molecular markers have been described that delineate PN subtypes. Here, we used viral injections into olfactory cortex and fluorescent nucleus sorting to enrich PNs for high-throughput single nucleus and bulk RNA deep sequencing. Transcriptome analysis and RNA in situ hybridization identified distinct mitral and tufted cell populations with characteristic transcription factor network topology, cell adhesion, and excitability-related gene expression. Finally, we describe a new computational approach for integrating bulk and snRNA-seq data and provide evidence that different mitral cell populations preferentially project to different target regions. Together, we have identified potential molecular and gene regulatory mechanisms underlying PN diversity and provide new molecular entry points into studying the diverse functional roles of mitral and tufted cell subtypes.

8.4 Effect of inversions on the topology of the fitness landscape and on the long-term evolutionary dynamics

Participants: P. Banse, L. Trujillo, G. Beslon.

Evolution is classically viewed as a succession of point mutations filtered by selection. Yet, point mutations are not the sole mechanism of sequence variation. In particular, genomes can be altered by structural variations where large DNA segments can be moved, duplicated, deleted or inverted. However, integrating these structural variation mechanisms in theoretical models is very difficult and events like inversions, duplications or deletions are thus often neglected in models.

Using the well known family of NK fitness landscapes, we simulate random adaptive walks, i.e. successive mutational events constrained to incremental fitness selection, for which variation can be due to both point mutations and segmental inversions. We report the emergence of different time scales: a short-term dynamics mainly driven by point mutations, followed by a long-term (stasis-like) waiting period until a new mutation arises. This new mutation is an inversion which can trigger a burst of successive point mutations, and then drives the system to new short-term increasing-fitness period. We analyse the effect of genes epistatic interactions on the evolutionary time scales. We suggest that the present model mimics the process of evolutionary innovation and open-endedness.

This minimal model hence combines point and inversions-like mutations and simulates long waiting times followed by evolutionary bursts on rugged landscapes. It has been published in the 2021 conference on Artificial Life [13] and in the 2021 Conference on Complex Systems [30]. Further results include a theoretical analysis of the inversion-generated fitness landscape, showing that inversion-driven regimes are likely to reach higher fitness peaks that point-mutation-driven regimes (publication in prep.), and simulation of the effect of rearrangement on the innovation dynamics in viral genomes (publication in prep.).

8.5 Genome-wide simulation of the Transcription-Supercoiling Coupling (TSC)

Participants: Théotime Grohens, Guillaume Beslon.

DNA supercoiling (SC), the level of under- or overwinding of the DNA polymer around itself, is widely recognized as an ancestral regulation mechanism of gene expression in bacteria. Higher negative SC levels

facilitate the opening of the DNA double helix at gene promoters, and increase the associated expression levels. Different levels of SC have been measured in bacteria exposed to different environments, leading to the hypothesis that SC variation can be an environmental response. Moreover, DNA transcription has been shown to generate local variations in the SC level, and therefore to impact the transcription of neighboring genes.

We studied the coupled dynamics of DNA supercoiling and transcription at the genome scale by implementing a genome-wide model of gene expression based on the transcription-supercoiling coupling (TSC). We show that, in this model, a simple change in global DNA SC is sufficient to trigger differentiated responses in gene expression levels via the TSC. Then, studying our model in the light of evolution, we demonstrate that this SC-mediated non-linear response to environmental change can serve as the basis for the evolution of specialized phenotypes. Preliminary results have been presented at the 2021 International Conference on Artificial Life [12]. An extended version has been submitted to the Artificial Life Journal in December 2021. Latest results show that evolution under TSC constraints leads to the selection of a specific genomic architecture. A paper is in preparation.

8.6 The Danaïde genome

Participants: M. Foley, P. Panse, V. Lezaud, J. Rouzaud-Cornabas, G. Beslon.

Using the Aevol simulator we experimentally studied the dynamic of genome size in prokaryote-like organisms. To this aim we evolve five "Wild-Type" organisms with the simulator until the size of their genomes stabilizes (which occurs after 10 million generations). We then propagated 50 clones of each wild-type for 2 million generations and monitor the dispersal of their genome size and, more specifically of the size of non-coding compartment of their genome. Given that the non-coding compartment is not submitted to selection, its size should follow a random dispersal with a lower bound in zero. However, our experiments revealed that its dispersal is limited by two boundaries, a lower boundary that is much larger than zero and an upper boundary. To understand the origin of these boundaries, we developed a new analysis tool called "Neutral Mutation Accumulation". Neutral Mutation Accumulation revealed that the non-coding compartment size is driven by two forces. (*i.*) a neutral force due to a fixation bias between duplications and deletion. Indeed, neutral duplications appear to be more numerous (and longer) than neutral deletions. This neutral force create a permanent flux of genomic material from the coding to the non-coding compartment, hence explaining why the non-coding compartment never reaches the zero bound. (*ii.*) a selective force due to robustness constraints (the longer the genome, the less robust it is). This selective force limits the expansion of the genome, hence explaining its upper boundary. Both forces explain the observed dynamics of the genome in Aevol. Moreover, since only one of them is selective, we conjectured that the balance between these two forces is driven by the intensity of the selection, hence by the population size. Indeed, by changing the population size in our simulation, we observed that larger population sizes lead to shorter genomes and that, on the opposite, smaller population sizes lead to larger genomes. An empirical law that is well known in microbiology. A publication is now in preparation.

8.7 X-Aevol: A massive parallelism model to support GPU and accelerators

Participant: J. Rouzaud-Cornabas, L. Turpin.

X-Aevol is a response to the need of more computational power. It was designed to leverage the massive parallelization capabilities of GPU. As Aevol exposes an irregular and dynamic computational pattern, it was not a straightforward process to adapt it for massively parallel architectures. We present in [GECCO 2021] how we have adapted the Aevol underlying algorithms to GPU architectures. We implement our new algorithms with CUDA programming language and test them on a representative benchmark of Aevol workloads. We show that, by using the power of a GPU, we managed to massively accelerate the evaluation process of Aevol. We do performance evaluation on NVIDIA Tesla V100 and

A100. We show how we reach a speed-up of 1,000 over a sequential execution on a CPU and the speed-up gain up to 50% from using the newer Ampere micro-architecture in comparison with Volta one. However we have shown that this is not an easy task and that algorithms have to be re-designed to match this massive parallelism. Our work is then a successful GPU port of a program conveying irregular structures of data with variable size thanks to different parallel algorithms and their implementation using advanced hardware operations. Our experimental setup relies on populations built to control the heterogeneity of the genomes. The main interest is to let possible to generate worst and best scenarios to measure performance of X-Aevol.

Future work is to make real simulation in order to simulate the full evolution of an artificial organism. Another point of interest is the ability to execute our GPU port on other vendor GPUs than the ones from NVIDIA. As CUDA is a proprietary parallel computing platform, it cannot be used for AMD's or Intel's GPUs. Frameworks and languages have emerged recently to unify the development of parallel computing to use different kinds of accelerators with the same base code while maintaining a high performance portability. Last but not least, studies show the impact of the size of populations on the genome size and structures. Accordingly, Aevol can be required to simulate very large population exceeding million individuals. To do so, the computing power of a single GPU will not be enough. We would have to work on multi-GPUs implementation using partitioning algorithms that will take into account the micro architectural properties of GPU and our inner knowledge of the biological model of Aevol to cut the overall population into smaller ones assigned to different GPUs.

8.8 Obesity and hyperinsulinemia drive adipocytes to activate a cell cycle program and senesce

Participant: C. Knibbe.

Obesity is considered an important factor for many chronic diseases, including diabetes, cardio-vascular disease and cancer. The expansion of adipose tissue in obesity is due to an increase in both adipocyte progenitor differentiation and mature adipocyte cell size. Adipocytes, however, are thought to be unable to divide or enter the cell cycle. Our colleagues of the Karolinska Institute (Stockholm, Sweden) showed that mature human adipocytes unexpectedly display a gene and protein signature indicative of an active cell cycle program. By designing a statistical model of adipocyte cell cycle and adipocyte senescence as a function of obesity and hyperinsulinemia, we helped demonstrate that adipocyte cell cycle progression associates with obesity and hyperinsulinemia, with a concomitant increase in cell size, nuclear size and nuclear DNA content [7]. Chronic hyperinsulinemia in vitro or in humans, however, is associated with subsequent cell cycle exit, leading to a premature senescent transcriptomic and secretory profile in adipocytes. Premature senescence is rapidly becoming recognized as an important mediator of stress-induced tissue dysfunction. By demonstrating that adipocytes can activate a cell cycle program, we define a mechanism whereby mature human adipocytes senesce.

8.9 Intestinal uptake of fatty acids: quantitative modeling validates intracellular metabolism as a major driving force

Participant: C. Knibbe, J. Etienne.

The absorption of dietary triglycerides has recently been revealed as a key step in cardio-metabolic health, but the underlying molecular mechanisms in the enterocyte remain incompletely understood and are still debated. While many studies focused primarily on the roles of membrane proteins, other have suggested that a critical force governing fatty acid uptake could be the intracellular metabolic demand for fatty acids, which would drive entry by passive diffusion. Here, we test the compatibility of these hypotheses with experimental uptake data by expressing each of them into a quantitative mathematical model and by fitting it to seven experimental datasets. Our results show that passive diffusion alone is

generally not sufficient to reach experimental uptake data and fails to capture their saturation behavior. However, adding an enzymatic transformation of long-chain fatty acids inside the cell enables models to better fit the experimental data and is much more efficient than adding membrane active transport to obtain high uptake responses. This mechanistic modeling thus confirms that for identical kinetic parameters and protein concentration, fatty acid uptake is best improved with an intracellular enzyme than with an active membrane transport.

9   Bilateral contracts and grants with industry

9.1   Bilateral contracts with industry

Participants: Eric Tannier, David Parsons, Arnaud Tilbian.

A contract is signed with the company "Ovega" to exploit the results of the action exploratoire "Community Garden Book".

10   Partnerships and cooperations

10.1   International initiatives

10.1.1   Participation in other International Programs

Participant: Guillaume Beslon.

The Beagle team is part of the CNRS International Associated Laboratory "PredEvo". The two other members of the project are the Beacon Center (Michigan State University, East-Lansing, US) and the TIMC-IMAG (CNRS, Université Grenoble-Alpes, France).

10.2   National initiatives

10.2.1   ANR

- ABC4M, 2020-, Approximate Bayesian computation-driven multimodal microscopy to explore the nuclear mobility of transcription factors, a project funded by the French National Agency for Research (ANR), Call "AAP génériques 2020". We combine computer simulations and Approximate Bayesian computation with simultaneous multiple microscopy methods (FCS and spt-PALM) to quantify the way transcription factors explore the nucleus to find their binding sites. The project is supervised by H. Berry. Other participants are Institut Langevin, ESPCI, Paris (I. Izeddin), Phlam laboratory, Lille (L. Héliot) and Univ. Berlkeley, CA, USA (X. Darzacq). Total amount funded: 565 keuro.

- EngFlea (Engram of fast learning in the striatum), 2021-, Call AAPG ANR 2021. Our goal is to study the link between endocannabinoid-dependent plasticity and fast learning of rodents thanks to a multidisciplinary approach combining in vitro and in vivo experimental neurophysiology with detailed subcellular biophysical models and large-scale neural network models. Supervisor: L. Venance (CIRB, Collège de France, Paris). Participant: H. Berry.

- Evoluthon (2019-2022): Artificial Life as a benchmark for evolutionary studies, a 4-year project leaded by E Tannier with 2 partners, Beagle Inria and Le Cocon, LBBE.

- Storiz (2018-2021): Horizontal transfers as documents from extinct or unknown species. Call ANR JCJC 2018. Leaded by Damien de Vienne (LBBE, Lyon) Participant: Eric Tannier

- LncEvoSys (2018-2021): An evolutionary systems approach to understand long non-coding RNA functionality, Call ANR JCJC 2017. Leaded by Anamaria Necsulea (LBBE, Lyon). Participant: Eric Tannier

- ANR Equipex+ grant "Spatial Cell Id" (2021-) coordinated by Yad Ghavi-Helm (IGFL), Olivier Hamant (RDP), and Jonathan Enriquez (IGFL) - 4,2M€. Anton Crombach and Christophe Godin are contact persons between Inria teams (Beagle, Dracula, Mosaic) and Yad, Olivier, Jonathan.

- NeGA 2021-, Ne effect on Genetic Architecture. By studying several eukaryotic species as well as evolution models like Aevol, NeGA aims at a better understanding of the influence of the effective population size (Ne) on the Genetic Architecture of these species. The project is supervised by Tristan Lefebure (LEHNA, Lyon). Other participants are the Beagle team, the LBBE (Lyon) and the ISEM (Montpellier).

10.2.2 Inria

- Naviscope (Inria Project Lab, 2018-2022): image-guided Navigation and VIsualization of large data sets in live cell imaging and microSCOPy. Nowadays, the detection and visualization of important localized events and process in multidimensional and multi-valued images, especially in cell and tissue imaging, is tedious and inefficient. Specialized scientists can miss key events due to complexity of the data and the lack of computer guidance. In Naviscope we develop original and cutting-edge visualization and navigation methods to assist scientists, enabling semi-automatic analysis, manipulation, and investigation of temporal series of multi-valued volumetric images, with a strong focus on live cell imaging and microscopy application domains. We build Naviscope upon the strength of scientific visualization and machine learning methods in order to provide systems capable to assist the scientist to obtain a better understanding of massive amounts of information. Such systems will be able to recognize and highlight the most informative regions of the dataset by reducing the amount of information displayed and guiding the observer attention. Head: C. Kervrann (Serpico), other EPIs: Aviz, Beagle, Hybrid, Morpheme, Mosaic, Parietal, and MaIage (INRA unit).

- Action Exploratoire "Community Garden Book": IPBES's recent report on declining biodiversity calls for generalization of agroecological, productive, biodiversity and environmental friendly methods, oriented towards participatory action research. This exploratory action is a proposal to develop tools from open science, evolution science and algorithmics for the co-construction and use of an agroecological network of interactions between groups, species, varieties found in fields and gardens.

- Action Exploratoire ExODE: In biology, the vast majority of systems can be modeled as ordinary differential equations (ODEs). Modeling more finely biological objects leads to increase the number of equations. Simulating ever larger systems also leads to increasing the number of equations. Therefore, we observe a large increase in the size of the ODE systems to be solved. A major lock is the limitation of ODE numerical resolution so ware (ODE solver) to a few thousand equations due to prohibitive calculation time. The AEx ExODE tackles this lock via 1) the introduction of new numerical methods that will take advantage of the mixed precision that mixes several floating number precisions within numerical methods, 2) the adaptation of these new methods for next generation highly hierarchical and heterogeneous computers composed of a large number of CPUs and GPUs. For the past year, a new approach to Deep Learning has been proposed to replace the Recurrent Neural Network (RNN) with ODE systems. The numerical and parallel methods of ExODE will be evaluated and adapted in this framework in order to improve the performance and accuracy of these new approaches.

  In [24], we propose and validate the great behavior of the induced error of our mixed precision scheme DP-SP (double and simple floating point precision) while preserving the double precision. This method is justified by a mathematical reasoning which affirms its convergence with an average error of the order of $e/\sqrt{N}$ but also verified by various numerical tests which show the compensation of the error with the increase of the system size.

As we have already seen, this method is characterized by its simplicity, its efficiency and above all its vast field of application, especially in biology with large and complicated systems. By the way, following all these mentioned advantages we note that through this article the study of the precision was done by considering the rounding error, whereas we know well that this is not the only error involved in optimizing accuracy.

This encourages us to deal with approximation errors, in order to obtain a solver and a numerical scheme compatible with our mixed precision method, so we can be able to offer an optimal precision for large scale systems in future works. In order to do so, we will use existing tools (PROMISE [16] and VerifTracer [6]) to evaluate the numerical quality of our code and quantify the magnitude of floating point related errors. Nonetheless, one of our goal is to improve performance (execution time) of ODE solver. Thus we will do a thorough performance evaluation of our method on the different proposed biologicalsystems. To conclude, we will assess how our method can benefit from next generation computing platform. Especially, we will work on porting our method to take into account silicon based mixed precision implementations that were tailored for IA/ML.

10.2.3   Other National Initiatives

Participants: Anton Crombach.

- Fondation ARC funds the project CEDRiC, a collaboration of Anton Crombach with Sandra Ortiz-Cuaran (head), Pierre Martinez, Karene Mahtouk, and Janice Kielbassa from the Cancer Research Center of Lyon (CRCL) / Centre Léon Bérard (CLB). This is a two year grant of 50k€ for experiments (2021-2023).

:   All members involved .

11   Dissemination

11.1   Promoting scientific activities

11.1.1   Scientific events: organisation

Member of the organizing committees

- Guillaume Beslon was a member of the Artificial Life program committee (Prague, July 2021)

- Guillaume Beslon was a member of the Conference on Complex System committee (lyon, October 2021)

- Anton Crombach was a member of the organizing committee of the Advanced Winterschool in Computational Systems Biology, held in Aussois (November 2021).

- Guillaume Beslon and Anton Crombach were members of the local organizing committee of the GdR Bioinformatique Moleculaire yearly meeting, held in Lyon (November 2021).

- Eric Tannier was a member of the organizaing committee of the scientific days of Inria.

11.1.2   Scientific events: selection

Member of the conference program committees

- Christophe Rigotti was a member of the program committee of the 37th ACM Symposium On Applied Computing (SAC).

- Eric Tannier was a member of the program committee of ISMB 2021 (online conference this year).

11.1.3 Journal

Member of editorial boards. Hugues Berry is a member of the editorial board of

- PLoS Computational Biology (Associate Editor)

- Frontiers in Synaptic Neuroscience (Associate Editor)

Eric Tannier is a member of the editorial board of Peer Community in Evolutionary Biology, and a founding member of Peer Community in Mathematical and Computational Biology

Guillaume Beslon is associate editor for the journal Frontiers in Ecology and Evolution

Reviewer - reviewing activities (selection). Systematic Biology, Algorithms, Frontiers in Ecology and Evolution, ELife, Nature Communication,...

11.1.4 Invited talks

- Carole Knibbe, November 2021."Journe'e enjeu Sante' Globale et Bio-Inge'nierie", Insa Lyon.

- Guillaume Beslon gave a plenary talk at the GdR BIM annual Meeting (November 2021)

- Anton Crombach: May 2021, SingleStatOmics.

- Hugues Berry, November 2021. "Journée scientifique 2021" of the EDISS Doctoral School, Lyon, fully on-line.

- Hugues Berry, November 2021. "Journée enjeu Santé Globale et Bio-Ingénierie", Insa Lyon.

- Hugues Berry, March 2021. INSERM Workshop "Spatio-temporal encoding and decoding in cell signaling ", Paris, fully on-line.

- Hugues Berry, February 2021. The bi-academic workgroup on AI and Health (French Academy of Sciences and Academy of Medicine), fully on-line.

- Hugues Berry, January 2021. Interview with the French Comite National Pilote d'Ethique du Numerique, fully on-line.

- Eric Tannier, September 2021. Les ateliers Sciences Environnements Sociétés, colloque "Univer-shifté" de l'Insa Lyon (Shift project-Insa).

11.1.5 Leadership within the scientific community

Hugues Berry, Co-elaboration of the national research program "PEPR Digital Health" with INSERM

11.1.6 Scientific expertise

- Covid-19 Studies [Participants H. Berry, D. Parsons and C. Rigotti]

  In 2021, several members of the team have contributed, as experts in modelling and simulation, within two groups formed to design and implement studies related to the Covid-19 epidemic [25, 27, 8]. This work was made in collaboration with several teams, including members of HCL (Hospices Civils de Lyon). The first group focused on building a model to try and predict the evolution of the occupancy of intensive care units (ICU) by covid-19+ patients over the next few days. Substantial effort was put in the characterization of care pathway for covid-19+ patients. The results of the resulting model are sent weekly to the board of the HCL (who provide the input data). This was developed as part of a project of the Inria Covid-19 task force (Siwam). The second group studied the main compartmental EDO-based models proposed to account for the spread of the epidemic in France and assessed the ability of these models to capture the dynamic of the propagation during lockdown periods and in pre-post lockdown stages. The group extended one of this compartmental model to handle various individual states within an agent based model that was designed and implemented. The efficacy of several vaccination strategies (age-based priority, campaign durations, etc.) in the presence of variants were compared.

- Guillaume Beslon served as "president du comité de visite" for the HCERES Evaluation of the LITIS Laboratory.

- Hugues Berry, Comité d'Expertise et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé (CESREES), member

- Hugues Berry, ITMO Neurosciences Sciences Cognitives Neurologie Psychiatrie (itneuro.aviesan.fr), Conseiller Scientifique

- Hugues Berry, ITMO Technologies pour la santé (its.aviesan.fr), Conseiller Scientifique

- Hugues Berry, DFG (German central research funding organisation), Scientific project review board

- Hugues Berry, Wellcome Trust grants (UK charitable foundation for health research), Proposal Review

- Hugues Berry, Emergence Call for Proposals 2021, Proposal review, Sorbonne Université

- Hugues Berry, AUF (Agence Universitaire de la Francophonie), programme mobilités doctorales

- Eric Tannier served as a reviewer of the Israel Science Foundation

- Eric Tannier served as a reveiwer for the Belgian FNRS

- Eric Tannier is a member of the scientific board of the ethics platform of University of Lyon

- Eric Tannier is a member of the scientific board of the Boutique des sciences of University of Lyon

11.1.7   Research administration

- Carole Knibbe is the director of the Biosciences department at INSA Lyon

- Christophe Rigotti, elected member of Insa Scientific board (Conseil Scientifique).

- Guillaume Beslon is a member of the "commission des moyens incitatifs" of the Centre INRIA de Lyon

- Hugues Berry is Deputy scientific director of Inria for digital biology and health

- Hugues Berry is member of Coordination and Steering committees of the Daniel Bernoulli Lab, the joint laboratory between Inria and APHP

- Hugues Berry is member of Comité Stratégique de Pilotage for the INRAE "DigitBio" metaprogram (www.inrae.fr/nous-connaitre/metaprogrammes)

- Hugues Berry is member of Comité de la Recherche en Matiere Biomedicale et de Sante Publique (CRMBSP) of the "Hospices Civils de Lyon", HCL

- Hugues Berry is member of Comité de la Recherche en Matiere Biomedicale et de Sante Publique (CRMBSP) of the APHP

- Eric Tannier is a member of the administration council of Inria.

- Eric Tannier is the referent scientist for the conference committee of Inria Grenoble.

11.2 Teaching - Supervision - Juries

11.2.1 Teaching

- Licence: C. Knibbe, Fundamentals of algorithmics and programming, 48 heqTD, L3, Bioinformatics and Modelling program of INSA-Lyon

- Licence: C.Knibbe, Introduction to automatic data processing, 16h eqTD, L3, Biosciences program of INSA-Lyon

- Licence: C. Knibbe, HTML/CSS, 4 heqTD, L3, Bisociences program of INSA-Lyon

- Master: C. Knibbe, Careers in bioinformatics and modelling, 20 heqTD, M1, Bioinformatics and Modelling program of INSA-Lyon

- Licence: Christophe Rigotti, Object-Oriented Programming and Graphical User Interfaces, 86h, L2, Department 1er cycle of INSA-Lyon.

- Licence: Christophe Rigotti, Simulation of Chemical Reactions, 26h, L2, Department 1er cycle of INSA-Lyon.

- Licence: Christophe Rigotti, Numerical Modelling for Engineering, 60h, L2, Department 1er cycle of INSA-Lyon.

- Master: Christophe Rigotti, Data Mining, 25h, M1, Bioinformatics and Modeling Department of INSA-Lyon.

- Master: Eric Tannier, String algorithmics, 12h, M1, Bioinformatics UCBL.

- Master: Eric Tannier, Research Ethics, 6h, M2, Bioinformatics UCBL

- Doctorat: Eric Tannier, Research Ethics, 12h, all specialities, Université de Lyon

- Doctorat: Eric Tannier, Research Ethics, 8h, Inria.

- Licence: Guillaume Beslon, Computer Architecture, 100h, L3, Computer Science Department, INSA-Lyon

- Master: Guillaume Beslon, Computational Science, 25h, M2, Computer Science Department, INSA-Lyon

- Licence: Guillaume Beslon, Stage Lighting, 25h, L2, Humanities Department, INSA-Lyon

- **E-learning**

  - MOOC: Eric Tannier, member of the pedagogical team of the Research Ethics MOOC, FUN, released 2018, still online, Ph-D candidates, 3000 registered participants at each session.
  - MOOC: Eric Tannier, contributor for the "Impact of Digital Industries" MOOC, released 2021.
  - Online ethic courses: Eric Tannier, 2 videos on research ethics on vimeo, uploaded in 2020 to diversify distant courses.

11.2.2 Supervision

- PhD in progress (Inria-Inserm grant): Julie Etienne, Mode'lisation et simulation du flux de triglyce'rides alimentaires, de l'absorption entérocytaire à la sécrétion des chylomicrons, supervised by Carole Knibbe and Marie-Caroline Michalski (CarMeN laboratory, Inserm U1060, UMR INRA U1397)

- PhD in progress (Inria CPER LECO++ grant): Laurent Turpin, Vers une maîtrise des variations de code et des évolutions des architectures pour des applications en HPC, supervised by Jonathan Rouzaud-Cornabas and Thierry Gauthier (LIP / Inria Avalon)

- PhD in progress (Inria ANR Evoluthon grant): Marco Foley, Evoluthon : Artificial life as a benchmark for molecular evolutionary studies, supervised by Guillaume Beslon and Jonathan Rouzaud-Cornabas

- PhD (Inria AEx ExODE grant): Aquilina Al Khoury, Solving ODE systems from Computational Biology on HPC platform, supervised by Jonathan Rouzaud-Cornabas and Samuel Bernard (ICJ / Inria Dracula), End in October 2021

- PhD in progress (CORDI-S PhD grant): Lisa Chabrier, "Differential analysis of regulatory networks in multi-omics data", supervised by Anton Crombach, Christophe Rigotti and Sergio Peignier (BF2I UMR203 - Biologie Fonctionnelle Insectes et Interactions), started October 2021.

- PhD in progress: Alexandre Laverré, "The mammalian regulatory landscape from PC-HiC data" E2M2, supervised by Anouk Necsulea and Eric Tannier

- PhD in progress: Theo Tricou, "Horizontal gene flow in the context of a mainly unknown biodiversity" E2M2, supervised by Damien de Vienne and Eric Tannier

- PhD in progress: Hugo Menet, "Phylogenetics of the holobiont" E2M2, supervised by Vincent Daubin and Eric Tannier

- M2: Lisa Chabrier (M2 Bioinformatics Sorbonne Université,Paris) March-August 2021, "Data preprocessing strategies for network inference", supervised by Anton Crombach, Christophe Rigotti and Sergio Peignier (BF2I UMR203 - Biologie Fonctionnelle Insectes et Interactions).

- M2: Baptiste Maucourt, M2 from "Maths in actions" master, on the modelization of biological control in agro-ecology. (co-supervision of Leo Girardin and Bastien Boussau and Eric Tannier).

- M2: Syrine Ben Ali, M2 from Tunis, on the role of ghost lineages in phylogeny. (co-supervision of Damien de Vienne and Theo Tricou and Eric Tannier).

- M2: Maël Thomas, M2 from "Stratégies et Design pour l'Anthropocène", Lyon, on the use of the intellectual property as a tool for research policy.

- M2: Eric Tannier has supervised a group of 4 students of Isara (school of agronomy) for their professional study project.

- M1: Clement Galan (M1, CRI Paris), "An atlas of gene regulatory networks for neuronal lineage specification in mouse cortex", March-June 2021, supervised by Anton Crombach

11.2.3 Juries

- PhD: Stella Zevio, Sorbonne University, February 2021 (Christophe Rigotti, Reviewer).

- Guillaume Beslon was Reviewer and Member of the defence committee of the Habilitation à Diriger des Recherches of M. Edi Prifti (Sorbonne University, June 2021)

- Hugues Berry: R. Vuillaume, Univ. Bourgogne-Franche-Comté, December 2021 (reviewer)

11.3 Popularization

11.3.1 Education

Juliette Luiselli participated to a science education program in primary school. She proposed an introduction to evolutionary biology using the "GreenMice" educational game developed by the Beagle team.

11.3.2 Interventions

- Eric Tannier organizes a series of multidisciplinary seminars on research and planetary boundaries. In 2021 two seminars: Leo Coutellec, philosopher, on the responsibility of researchers, and Melody Faury, philosopher, on the implication of young researchers. All seminars are available online.

- Eric Tannier co-constructed the "Ateliers Sciences Environnements Sociétés", and animated four of them. A ressource is available online to all participants, which can be used for further animations by participants.

12 Scientific production

12.1 Major publications

[1] F. Berthoud, P. Guitton, L. Lefèvre, S. Quinton, A. Rousseau, J. Sainte-Marie, C. Serrano, J.-B. Stefani, P. Sturm and E. Tannier. *Sciences, Environnements et Sociétés*. Other. Inria, Oct. 2019. URL: https://hal.inria.fr/hal-02340948.

[2] J. Lehman, J. Clune, D. Misevic, C. Adami, J. Beaulieu, P. J. Bentley, S. Bernard, G. Beslon, D. M. Bryson, N. Cheney, A. Cully, S. Doncieux, F. C. Dyer, K. O. Ellefsen, R. Feldt, S. Fischer, S. Forrest, A. Frenoy, C. Gagneé, L. Le Goff, L. M. Grabowski, B. Hodjat, L. Keller, C. Knibbe, P. Krcah, R. E. Lenski, H. Lipson, R. MacCurdy, C. Maestre, R. Miikkulainen, S. Mitri, D. E. Moriarty, J.-B. Mouret, A. D. Nguyen, C. Ofria, M. Parizeau, D. Parsons, R. T. Pennock, W. F. Punch, T. S. Ray, M. Schoenauer, E. Shulte, K. Sims, K. O. Stanley, F. Taddei, D. Tarapore, S. Thibault, W. Weimer, R. Watson and J. Yosinksi. 'The Surprising Creativity of Digital Evolution: A Collection of Anecdotes from the Evolutionary Computation and Artificial Life Research Communities'. In: *Artificial Life* 26.2 (June 2020), pp. 274–306. DOI: 10.1162/artl_a_00319. URL: https://hal.inria.fr/hal-0173547 3.

[3] J. Marin, G. Achaz, A. Crombach and A. Lambert. 'The genomic view of diversification'. In: *Journal of Evolutionary Biology* 33.10 (Oct. 2020), pp. 1387–1404. DOI: 10.1111/jeb.13677. URL: https://hal.archives-ouvertes.fr/hal-03137815.

[4] C. Rocabert, G. Beslon, C. Knibbe and S. Bernard. 'Phenotypic noise and the cost of complexity'. In: *Evolution - International Journal of Organic Evolution* (Aug. 2020). DOI: 10.1111/evo.14083. URL: https://hal.archives-ouvertes.fr/hal-02920356.

[5] M. Woringer, I. Izeddin, C. Favard and H. Berry. 'Anomalous Subdiffusion in Living Cells: Bridging the Gap Between Experiments and Realistic Models Through Collaborative Challenges'. In: *Frontiers in Physics* 8 (2020), p. 134. DOI: 10.3389/fphy.2020.00134. URL: https://hal.sorbonne-uni versite.fr/hal-02871984.

12.2 Publications of the year

International journals

[6] H. Berry and S. Genet. 'A model of on/off transitions in neurons of the deep cerebellar nuclei: deciphering the underlying ionic mechanisms'. In: *Journal of Mathematical Neuroscience* 11.1 (1st Apr. 2021), pp. 1–34. DOI: 10.1186/s13408-021-00105-3. URL: https://hal.sorbonne-u niversite.fr/hal-03190183.

[7] Q. Li, C. Hagberg, H. Silva Cascales, S. Lang, M. Hyvönen, F. Salehzadeh, P. Chen, I. Alexandersson, E. Terezaki, M. Harms, M. Kutschke, N. Arifen, N. Krämer, M. Aouadi, C. Knibbe, J. Boucher, A. Thorell and K. Spalding. 'Obesity and hyperinsulinemia drive adipocytes to activate a cell cycle program and senesce'. In: *Nature Medicine* 27.11 (Nov. 2021), pp. 1941–1953. DOI: 10.1038/s4159 1-021-01501-8. URL: https://hal.inria.fr/hal-03479060.

[8] S. Pageaud, C. Pothier, C. Rigotti, A. Eyraud-Loisel, J.-P. Bertoglio, A. Bienvenüe, N. Leboisne, N. Ponthus, R. Gauchon, F. Gueyffier, P. Vanhems, J. Iwaz, S. Loisel and P. Roy. 'Expected Evolution of COVID-19 Epidemic in France for Several Combinations of Vaccination Strategies and Barrier Measures'. In: *Vaccines* 9.12 (Dec. 2021), p. 1462. DOI: `10.3390/vaccines9121462`. URL: `https://hal.archives-ouvertes.fr/hal-03482342`.

[9] S. Zeppilli, T. Ackels, R. Attey, N. Klimpert, K. Ritola, S. Boeing, A. Crombach, A. Schaefer and A. Fleischmann. 'Molecular characterization of projection neuron subtypes in the mouse olfactory bulb'. In: *eLife* 10 (22nd July 2021). DOI: `10.7554/eLife.65445`. URL: `https://hal.archives-ouvertes.fr/hal-03473445`.

International peer-reviewed conferences

[10] A. Badoual, M. Arizono, A. Denizot, M. Ducros, H. Berry, U. Valentin Nägerl and C. Kervrann. 'Simulation of Astrocytic Calcium Dynamics in Lattice Light Sheet Microscopy Images'. In: ISBI 2021 - IEEE International Symposium on Biomedical Imaging. Nice, France: IEEE, 13th Apr. 2021, pp. 1–5. DOI: `10.1109/ISBI48211.2021.9433984`. URL: `https://hal.inria.fr/hal-03106797`.

[11] J. Etienne, A. Penhoat, M.-C. Michalski and C. Knibbe. 'Uptake of fatty acids by the enterocyte: New insights gained from mathematical modeling'. In: GERLI 16th LIPIDOMICS MEETING (2021). Bordeaux, France, 26th Sept. 2021. URL: `https://hal.inria.fr/hal-03485562`.

[12] T. Grohens, S. Meyer and G. Beslon. 'A Genome-Wide Evolutionary Simulation of the Transcription-Supercoiling Coupling'. In: *ALIFE 2021: The 2021 Conference on Artificial Life*. ALIFE 2021: The 2021 Conference on Artificial Life. Prague, Czech Republic, 19th July 2021. URL: `https://hal.archives-ouvertes.fr/hal-03242696`.

[13] L. Trujillo, P. Banse and G. Beslon. 'Simulating short-and long-term evolutionary dynamics on rugged landscapes'. In: ALIFE 2021 - Conference on Artificial Life. Prague, Czech Republic, 19th July 2021, pp. 1–9. URL: `https://hal.inria.fr/hal-03426019`.

[14] L. Turpin, T. Gautier and J. Rouzaud-Cornabas. 'X-Aevol: GPU implementation of an evolutionary experimentation simulator'. In: GECCO 2021 - Genetic and Evolutionary Computation Conference. Lille France, France: ACM, 7th July 2021, pp. 1–9. DOI: `10.1145/3449726.3463195`. URL: `https://hal.inria.fr/hal-03290799`.

National peer-reviewed Conferences

[15] N. Bennani, S. Cazalens, V. Cheutet, C. Leschi, O. Merveille, C. Moriot, D. Muller, T. Pecatte, C. Pothier, C. Rigotti, H. Rivano and N. Stouls. 'Apprivoiser l'hétérogénéité en informatique 1ère année'. In: 7e Colloque pédagogie et formation 2021. Valenciennes, France, 20th May 2021, pp. 1–6. URL: `https://hal.inria.fr/hal-03230531`.

[16] N. Debs, S. Peignier, C. Douarre, T. Jourdan, C. Rigotti and C. Frindel. 'Apprendre l'apprentissage automatique : un retour d'expérience'. In: *Actes à paraître dans numéro spécial du Journal de l'Enseignement des Sciences et Technologies de l'Information et des Systèmes*. CETSIS 2021 - Colloque de l'Enseignement des Technologies et des Sciences de l'Information et des Systèmes. Valenciennes, France, 8th June 2021, pp. 1–5. URL: `https://hal.archives-ouvertes.fr/hal-03341954`.

[17] J. Etienne, A. Penhoat, M.-C. Michalski and C. Knibbe. 'A mathematical model for the uptake of fatty acids by the enterocyte'. In: EDISS 205 2021 - Journée de l'Ecole Doctorale Interdisciplinaire Sciences-Santé. Online, France, 18th Nov. 2021. URL: `https://hal.inria.fr/hal-03485600`.

Conferences without proceedings

[18] G. Beslon, V. F. Liard and J. Rouzaud-Cornabas. 'The Complexity Ratchet'. In: CCS 2021 - International Conference on Complex Systems. Lyon, France, 25th Oct. 2021. URL: `https://hal.archives-ouvertes.fr/hal-03511442`.

[19]   J. Etienne, A. Penhoat, M.-C. Michalski and C. Knibbe. 'Uptake of fatty acids by the enterocyte: New insights gained from mathematical modeling'. In: 2021 AOCS Annual Meeting & Expo. online, United States, 3rd May 2021. URL: https://hal.inrae.fr/hal-03252034.

Scientific books

[20]   A. Crombach. *Evolutionary Systems Biology: Advances, Questions, and Opportunities*. 2. Springer International Publishing, 2021, pp. 1–294. DOI: 10.1007/978-3-030-71737-7. URL: https://hal.archives-ouvertes.fr/hal-03473679.

Scientific book chapters

[21]   G. Beslon, V. F. Liard, D. P. Parsons and J. Rouzaud-Cornabas. 'Of Evolution, Systems and Complexity'. In: *Evolutionary Systems Biology II*. June 2021. URL: https://hal.archives-ouvertes.fr/hal-03136122.

[22]   A. Crombach and J. Jaeger. 'Life's Attractors Continued: Progress in Understanding Developmental Systems Through Reverse Engineering and In Silico Evolution'. In: *Evolutionary Systems Biology: Advances, Questions, and Opportunities*. 2021. URL: https://hal.archives-ouvertes.fr/hal-03128711.

[23]   M. Gouy, E. Tannier, N. Comte and D. Parsons. 'Seaview Version 5: A Multiplatform Software for Multiple Sequence Alignment, Molecular Phylogenetic Analyses, and Tree Reconciliation'. In: *Multiple Sequence Alignment*. Vol. 2231. Methods in Molecular Biology. Humana, 2021, pp. 241–260. DOI: 10.1007/978-1-0716-1036-7_15. URL: https://hal.archives-ouvertes.fr/hal-03065564.

Reports & preprints

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