RESEARCH CENTRE

Grenoble - Rhône-Alpes

IN PARTNERSHIP WITH:

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

2020 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

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Project-Team BEAGLE

Creation of the Team: 2011 June 17, updated into 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]
- 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]
- Christophe Rigotti [INSA Lyon, Associate Professor, HDR]
- Jonathan Rouzaud-Cornabas [INSA Lyon, Associate Professor]

Post-Doctoral Fellows

- Vincent Liard [Univ Lumière, from Oct 2020]
- Charles Rocabert [Inria, until Aug 2020]

PhD Students

- Aquilina Al Khoury [Inria, from Apr 2020]
- Paul Banse [INSA Lyon, from Sep 2020]
- Lisa Blum Moyse [INSA Lyon, from Sep 2020]
- Julie Etienne [INSERM]
- Marco Foley [Inria]
- Theotime Grohens [INSA Lyon]
- Vincent Liard [Inria, until Oct 2020]
- Laurent Turpin [Inria]

Technical Staff

- David P Parsons [Inria, Engineer]
- Arnaud Tilbian [Inria, Engineer, from Aug 2020]

Interns and Apprentices

- Paul Banse [École normale supérieure de Rennes, until Jan 2020]
- Lisa Blum Moyse [École Normale Supérieure de Lyon, from Mar 2020 until Aug 2020]
- Geoffroy Boussard [Inria, from Jun 2020 until Aug 2020]
- Solal Flechelles [École Normale Supérieure de Lyon, until May 2020]
- Catalina Gonzalez Gomez [Inria, from Apr 2020 until Jul 2020]
- Eglantine Karlé [Inria, from Apr 2020 until Oct 2020]
- Victor Lezaud [Inria, from Feb 2020 until Jul 2020]
- Thibaut Peyric [Inria, from Jun 2020 until Aug 2020]

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

[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.

main research axes. The first two ones are methodologically-oriented: we develop general formalisms 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* [30] 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. [31]). 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 last year (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

Part of our team has a wish to consider the relations between science and societies, not only in terms of applications and explaining, but in terms of implication. That is why we would also like to 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.

For example, we participated to several citizen science programs. One of them is "Fabrique des questions simples" https://simple-question.org/. Another was conducted with the Théâtre Nouvelles Générations with wich we gathered a group of citizens to discuss the orientations of modern science.

5 Social and environmental responsibility

5.1 Footprint of research activities

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

Last year we began to estimate the carbon footprint of our activities, and noticed that the main item of carbon emissions was plane travels, either by members of the team, or invited researchers.

2020 was very special because plane travels were almost absent.

This year we tried to estimate the carbon footprint of our home-work trips. Home-work trips are not part of the upcoming Inria or Labo1p5 tools, so it is still an interesting calculation. We asked to all members of the team the distance they travel per day, and the transportation mean, in a non covid period. We took unit costs from the cabon base of Ademe for the use of machines and from the report "CyCle more often 2Cool down the planet !" for the physical effort footprint.

Results : out of 19.97 members of the team in 2020(considering the arrival and departure dates of some people in 2020), 11.55 answered. Most of them walk or bike to work.The average carbon footprint per person in 2020 is 586kg CO2. For comparison, it is half of the estimation of the mean footprint of professors at EPFL, which is our only point of comparison available.

Beyond footprint calculations, we should soon engage in the discussion of what would be an acceptable footprint for a research team. Indeed, a simple reduction objective is not fully satisfactory: we would like to know where we are going, beyond the reduction. We have two propositions, one egalitarian and one non egalitarian.

The egaliarian one consists in assuming that the whole human population has a carbon budget, which is an estimated maximum CO2 amount that we can emit to stop global warming in 2050. Then divide this number by the population size, and allow to the team this ratio, times the team size, corrected by the proportion of time we spend at work.

The non egalitarian one consist in making sure that our emissions divided by our budget does not excess the global carbon budget divided by the global richness.

The two ways fit the Kantian responsibility: if all people act the same way, then humanity engages in a sustainable scenario.

Given the 2016-2018 footprint that we calculated last year, we are far above the two measures. We then encourage the institute to engage into a reduction by allowing a carbon budget, or better, an environmental budget, to each team, as well as there is a financial budget negociated each year.

Of course these propositions ignore the indirect impacts of our activities. The budget should be calculated based on these as well, but they are almost impossible to quantify.

5.2 Impact of research results

We have not yet seriously evaluated the impact of our research results. This requires a deep discussion and reflexion on the economy of our disciplines. We organise in april and may 2021 the "Sciences-Environnements-Sociétés" workshop in Inria Grenoble and Inria Lyon to be able, in all teams which will implement this workshop, to report something interesting in this section next year.

These discussions were planned for 2020 but it has been impossible to conduct them efficiently in the context of the COVID pandemy.

Besides this, Eric Tannier regularly teaches reserch ethics at university of Lyon, organized a workshop on the environmental responsibility of research institutions in january 2020, co-authored part of the Shift

Project report on the transformation of economy, 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

- We were deeply engaged in the research efforts related to the covid pandemics. Several members of the team helped research consortia in this line, and were up to 100% engaged. See section "Scientific expertize" for more details.

- We participated to the founding of a new journal "PCI Mathematical and Computational Biology", launched in march 2020.

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: Version of the genetic code close to the universal code. Significant improvement in calculation speeds. Exploration of programming on GPUs.

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

Authors: Guillaume Beslon, Vincent Liard, Jonathan Rouzaud-Cornabas, Carole Knibbe, David P. Parsons, Antoine Frénoy, Bérénice Batut, Dusan Misevic, Virginie Mathivet, Yolanda Sanchez-Dehesa

Contacts: Jonathan Rouzaud-Cornabas, Guillaume Beslon

Participants: Antoine Frénoy, Bérénice Batut, Carole Knibbe, David P. Parsons, Dusan Misevic, Guillaume Beslon, Jonathan Rouzaud-Cornabas, Vincent Liard

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: Release of version 1.0 software in 2020 and release of version 5.0 of Seaview, a platform that now integrates Treerecs as one of the standard phylogeny software.

Authors: Nicolas Comte, Eric Tannier, David P. Parsons

Contact: Eric Tannier

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

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

8 New results

8.1 The genomic view of diversification

Participant: A Crombach

The process of species diversification is traditionally summarized by a single tree, the species tree, whose reconstruction from molecular data is hindered by frequent conflicts between gene genealogies. We argue that instead of seeing these conflicts as nuisances, we can exploit them to inform the diversification process itself. We adopt a gene-based view of diversification to model the ubiquitous presence of gene flow between diverging lineages, one of the most important processes explaining disagreements among gene trees. We propose a new framework for modelling the joint evolution of gene and species lineages relaxing the hierarchy between the species tree and gene trees inherent to the standard view, as embodied in a popular model known as the multispecies coalescent (MSC). We implement this framework in two alternative models called the gene-based diversification models (GBD): (a) GBD-forward following all evolving genomes through time and (b) GBD-backward based on coalescent theory. They feature four parameters tuning colonization, gene flow, genetic drift and genetic differentiation. We propose an inference method based on differences between gene trees. Applied to two empirical data sets prone to gene flow, we find better support for the GBD-backward model than for the MSC model. Along with the increasing awareness of the extent of gene flow, this work shows the importance of considering the richer signal contained in genomic histories, rather than in the mere species tree, to better apprehend the complex evolutionary history of species.

8.2 Modelling the modulation of cortical on-off state switching by astrocytes

Participants: L. Blum Moyse and H. Berry

In some cortical brain areas, neural networks are known to exhibit Up-Down bistability, or switches, under sleep or anaesthesia. This phenomenon is an alternation between long lasting periods of high activity (Up state) and periods of relative silence (Down state). Neuroscience research has focused for long on neurons in general, and so did it to explain such kind of collective behaviour. Nevertheless some recent experimental studies highlighted the key role played by astrocytes in this phenomenon. This raises the issue of how astrocyte cells can modulate the switches between Up and Down neural states. In order to answer that question we used mathematical modelling and implemented models of neural and astrocyte networks that emulates the Up-Down bistability regime, rate (mean-field) and spiking (discrete) models. In parallel we carried out an analysis of fixed points of our systems, and their stabilities. Our model suggests how astrocytes can contribute to neuronal bistability. For instance we observed that transitions from a Down state to a bistable Up-Down state can be triggered by astrocyte activity, which is coherent with experimental observations. Depending on initial conditions a transition from a Down to an Up stable state can also happen, and then return to the Down state in a case of a short and isolated astrocytic stimulation, which is coherent with other experimental research. Our model also suggests that the duration of Up states should be longer than Down states when both excitatory and inhibitory neurons trigger astrocyte calcium transients as compared to the case where only excitatory neurons do. This could be used as a criterion in experiments to determine the astrocyte connectivity involved in Up-Down phenomenon.

8.3 Ancestral Genome Organization as a Diagnosis Tool for Phylogenomics

Participants: E Tannier

The reconstruction of the chromosomal organization of ancient genomes has many applicationsin comparative and evolutionary genomics. Here we propose a novel, methodological, use forthese predicted ancestral syntenies, directly focused on phylogenomics. It is a way to assess theaccuracy of gene trees and species trees. We use a method that reconstructs, from gene treesand extant gene orders, ancestral adjacencies, i.e. the immediate neighborhood between pairsof genes, independently for each pair. This independence allows to split the computations intomany independent problems that can each be solved exactly using efficient algorithms, but mightresult in sets of ancestral adjacencies that are incompatible with the expected linear or circularstructure of chromosomes. We show here that this drawback can actually be turned into a useful feature. We show on simulated data that the degree of linearity of the reconstructed ancestralgene orders is well correlated to the accuracy of the input gene trees. Moreover, a localized errorin the species trees results in a burst of non linearity of ancestral genomes at the wrong node. Weeventually show that integrated phylogenomic methods expectedly lead to better linearity scoresthan methods based on gene alignments only. Allowing a method to output an unrealistic result,but proving that the expected output is closer to realistic when the input is closer to correct, wethus provide an original validation protocol for standard evolutionary studies.

8.4 The complexity ratchet of evolution

Participants : V Liard, G Beslon, J Rouzaud Cornabas

Using the in silico experimental evolution platform Aevol, we have tested the existence of a "complexity ratchet" by evolving populations of digital organisms under environmental conditions in which simple organisms can very well thrive and reproduce. We observed that in most simulations, organisms become complex although such organisms are a lot less fit than simple ones and have no robustness or evolvability advantage. This excludes selection from the set of possible explanations for the evolution of complexity. However, complementary experiments showed that selection is nevertheless necessary for complexity to evolve, also excluding non-selective effects. Analyzing the long-term fate of complex organisms, we showed that complex organisms almost never switch back to simplicity despite the potential fitness benefit. On the contrary, they consistently accumulate complexity on the long term, meanwhile slowly increasing their fitness but never overtaking that of simple organisms. This suggests the existence of a complexity ratchet powered by negative epistasis: mutations leading to simple solutions, that are

favourable at the beginning of the simulation, become deleterious after other mutations-leading to complex solutionshave been fixed. This also suggests that this complexity ratchet cannot be beaten by selection, but that it can be overthrown by robustness because of the constraints it imposes on the coding capacity of the genome.

8.5 The Danaïde genome

Participants : M. Foley, P. Banse, 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.

9 Bilateral contracts and grants with industry

9.1 Bilateral contracts with industry

- A contract has been 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 Inria International Labs

- JLESC — Joint Laboratory on Extreme Scale Computing

  The University of Illinois at Urbana-Champaign, Inria, the French national computer science institute, Argonne National Laboratory, Barcelona Supercomputing Center, Jülich Supercomputing Centre and the Riken Advanced Institute for Computational Science formed the Joint Laboratory on Extreme Scale Computing, a follow-up of the Inria-Illinois Joint Laboratory for Petascale Computing. The Joint Laboratory is based at Illinois and includes researchers from Inria, and the National Center for Supercomputing Applications, ANL, BSC and JSC. It focuses on software challenges found in extreme scale high-performance computers.

  Research areas include

  Scientific applications (big compute and big data) that are the drivers of the research in the other topics of the joint-laboratory.

Modeling and optimizing numerical libraries, which are at the heart of many scientific applications.

Novel programming models and runtime systems, which allow scientific applications to be updated or reimagined to take full advantage of extreme-scale supercomputers.

Resilience and Fault-tolerance research, which reduces the negative impact when processors, disk drives, or memory fail in supercomputers that have tens or hundreds of thousands of those components

I/O and visualization, which are important part of parallel execution for numerical silulations and data analytics

HPC Clouds, that may execute a portion of the HPC workload in the near future.

Jonathan Rouzaud-Cornabas and Laurent Turpin are involved through their research on runtime systems, programming models and numerical libraries for HPC Computational Biology. Laurent Turpin did a presentation at the last JLESC meeting.

10.1.2 Inria international partners

- Beagle is a member of the CNRS International Research Projects (IRP) PredEvo (Prediction in Evolution). Other members of PredEvo are the TIMC-IMAG (Grenoble) and the Beacon Center (Michigan State University, USA).

10.2 International research visitors

10.2.1 Visits of international scientists

- Leonardo Trujillo (Venezuela), who was a visiting professor from January 2019 to July 2019, was awarded an advanced research position from Inria. Leonardo Trujillo worked on the innovation dynamics in evolution using NK Fitness-Landscapes.

10.3 National initiatives

10.3.1 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.

- 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.

- Dallish (2016-2020): Data Assimilation and Lattice LIght SHeet imaging for endocytosis/exocytosis pathway modeling in the whole cell, Call AAPG ANR 2016. With C. Kervrann (INRIA Rennes), J. Salamero (Institute Curie, Paris), B. Laroche (INRA, Jouy-en-Josas). Participants: H. Berry.

- 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).

10.3.2 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.

10.3.3 Other National Initiatives

- 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).

11 Dissemination

11.1 Promoting scientific activities

11.1.1 Scientific events: organisation

General chair, scientific chair

- Eric Tannier co-organized with Vincent Daubin and Bastien Boussau (LBBE) an interdisciplinary workshop (with philosophers, artists, scientists, activists) on environmental responsibility of researchers in january 2020 "La recherche a-t-elle les pieds sur Terre?", Ecole de l'anthropocène, école urbaine de Lyon.

11.1.2 Scientific events: selection

Member of the conference program committees

- Christophe Rigotti was a member of the program committee of the IEEE International Conference on Data Mining (ICDM 2020).
- Eric Tannier was a member of the program committee of ISMB 2020.
- Eric Tannier was a member of the program committee of Jobim 2020.
- Guillaume Beslon and Jonathan Rouzaud-Cornabas were members of the program committee of Alife 2020.

Reviewer

- RECOMB 2020, CIAC 2021, ALife 2020...

11.1.3 Journal

Member of the editorial boards

- Hugues Berry is Associate Editor for PLoS Computational Biology
- Eric Tannier is an editor of "Peer Community in Evolutionary Biology"
- Eric Tannier is a founding editor of "Peer Community in Mathematical and Computational Biology" which has been launched in 2020
- Eric Tannier is a guest editor for the epijournal DMTCS, and edited a special issue, which last article was published in 2020.

Reviewer - reviewing activities

- Bioinformatics, ...

11.1.4 Invited talks

- Hugues Berry: November 2020. 2nd Japan-France-Germany trilateral symposium on AI. fully on-line.
- Hugues Berry: November 2020. 9th annual conference of the Groupement de Recherche "GPCR-PhysioMed". fully on-line
- Guillaume Beslon : September 2020. Symposium "Generic patterns of evolution and its (non)predictability", Utrecht. Fully on-line."
- Guillaume Beslon : February 2020. Omic's days, Montpellier.

11.1.5 Scientific expertise

- Covid-19 Studies [Participants T. Grohens, D. Parsons and C. Rigotti]

  Since spring 2020, several members of the team have contributed, as experts in modelling and simulation, within groups formed to design and implement studies related to the Covid-19 epidemic [7] and [26]. This work was made in collaboration with several teams, including members of AP-HP (Assistance Publique - Hôpitaux de Paris) and HCL (Hospices Civils de Lyon). It corresponds to two main tasks. The first one was the study of medical emergency calls received by the emergency medical system of the four central departments of the Paris area. It revealed strong dissimilarities between these departments and also the possibility to detect epidemic resurgences using the emergency call stream. The second task focused on the main compartmental EDO-based models proposed to account for the spread of the epidemic in France. Its objective was to assess the ability of these models to capture the dynamic of the propagation during lockdown periods and in pre-post lockdown stages. It showed the need for repeated prevalence studies on representative population samples to refine the calibration.

- Hugues Berry: AUF (Agence Universitaire de la Francophonie), programme mobilités doctorales 2020

- Hugues Berry: BBSRC (UK non-medical bioscience public funding), Grants 2020

- Hugues Berry: Conseiller Scientifique, ITMO Neurosciences Sciences Cognitives Neurologie Psychiatrie (https: //itneuro.aviesan.fr), 2020-

- Hugues Berry: Conseiller Scientifique, ITMO Technologies pour la santé (https://its.aviesan.fr), 2018-

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

- Eric Tannier participated to the "Shift project" report on transforming economy, section "Research and Education".

11.1.6 Research administration

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

- Eric Tannier, elected member of the Inria Administration Council

- Eric Tannier, member of the ethics platform of the university of Lyon

- Eric Tannier, scientific responsible of the "cours colloques" committee of Inria

- Eric Tannier, member of the scientific committee of the science shop, univ Lyon

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

- Hugues Berry, Chargé de mission and co-head of Inria's "Mission Covid-19"

- Guillaume Beslon, member of the IRD CSS5 committee (Science des données et des modèles)

11.2 Teaching - Supervision - Juries

11.2.1 Teaching administration

- Carole Knibbe has been nominated in 2020 at the head of the biosciences department at Insa Lyon.

11.2.2 Teaching

- Licence: C. Knibbe, Fundamentals of algorithmics and programming, 80 heqTD, L3, Bioinformatics and Modelling program of INSA-Lyon
- Licence: C. Knibbe, Architecture of computer systems, 19 heqTD, L3, Bioinformatics and Modelling program of INSA-Lyon
- Licence: C. Knibbe, Software development, 32 heqTD, L3, Bioinformatics and Modelling program of INSA-Lyon
- Licence: C. Knibbe, HTML/CSS, 4 heqTD, L3, Bioinformatics and Modelling 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
- 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, Research Ethics, FUN, Ph-D candidates, 3000 registered participants
  - Online ethic courses: Eric Tannier, 2 videos on research ethics on vimeo, uploaded in 2020 to diversify distant courses.

11.2.3 Supervision

- HDR: Carole Knibbe has defended her habilitation to supervise researches in 2020.
- PhD in progress: Paul Banse “La fabrique de l’innovation évolutive”, supervised by Guillaume Beslon, started september 2020
- PhD in progress: Marco Foley “Vers une plate-forme de benchmarking pour la phylogénie”, supervised by Guillaume Beslon and Jonathan Rouzaud-Cornabas, started september 2019
- PhD in progress: Théotime Grohens “modélisation de la superhélicité dans aevol”, supervised by Guillaume Beslon, started september 2019
- PhD: Vincent Liard defended his PhD in november 2020.

- M2: Victor Lezaud (INSA-Lyon, M2 computer science) February-July 2020, The Danaïde Genome, supervised by Guillaume Beslon
- PhD in progress: Julie Etienne, "Modélisation et simulation du flux de triglycérides alimentaires, de l'absorption entérocytaire à la sécrétion des chylomicrons", INSA-Lyon, co-supervised by Carole Knibbe and Marie-Caroline michalski (CarMeN laboratory), started in October 2019.
- Hugues Berry and Christophe Rigotti where co-supervisors of the M1 internship of Catalina Gonzalez Gomez (co-supervision with Olivier Pascual of team SynatAc INSERM/CNRS) from 14/04/2020 to 29/07/2020. Title: "Classification and clustering of in vivo cellular data from microglial cells activity during sleep-wake cycles".
- PhD: Eric Tannier participated to the PhD Advisory Committee of Raphael Forquet (UCBLyon)
- PhD in progress: Alexandre Laverré, "influence croisée de l'organisation spatiale et des mutations structurales dans les génomes", supervised by Anamaria Necsulea et Eric Tannier, starting september 2018
- PhD in progress: Théo Tricou, "Détection d'espèces éteintes avec les transferts horizontaux", supervised by Damien de Vienne et Eric Tannier, started september 2018
- PhD in progress: Hugo Menet, "Phylogénie multi-échelles des holobiontes", supervised by Eric Tannier et Vincent Daubin, started in september 2019
- PhD in progress : Laurent Turpin "Vers une maîtrise des variations de code et des évolutions des architectures pour des applications en HPC" supervised by Thierry Gauthier (Avalon – LIP), Christian Perez (Avalon – LIP) and Jonathan Rouzaud-Cornabas, started September 2019
- PhD in progress: Aquilina Al Khoury "Equations Différentielles Ordinaires appliquées à la biologie computationnelle et calcul haute performance" supervised by Samuel Bernard (Dracula – ICJ) and Jonathan Rouzaud-cornabas, started April 2020
- PhD: Lisa Blum-Moyse, 2020-, Modelling the integration of synaptic activity by astrocytes, ED Info-Maths Lyon, "Contrat Doctoral Normaliens" ENS Lyon, supervised by Hugues Berry
- M2: Lisa Blum-Moyse (ENS Lyon, M2 Physics) February-June 2020, Modelling the modulation of cortical on-off state switching by astrocytes, supervised by Hugues Berry.
- M2: Eglantine Karlé (M2 Maths in Action) April-October 2020, "Évolution du développement des dents : Étude de données transcriptomiques issues de rongeurs" supervised by Anton Crombach
- Summer stage: Thibaut Peyric (Lyon 1, L2 Informatique) June-August 2020 "Analysis of fresh mouse cortex" supervised by Anton Crombach

11.2.4 Juries

- PhD: A. Douilet, Univ. Bretagne Ouest, September 2020 (president Hugues Berry)
- PhD: Bram van Dijk, Utrecht University, September 2020 (Guillaume Beslon, Reviewer)
- PhD: David Bernard, Univ. Toulouse 1, July 2020 (Guillaume Beslon, Reviewer)

11.3 Popularization

11.3.1 Articles and contents

- Eric Tannier wrote two popularization articles, one on the blog "binaire" hosted by lemonde.fr on environmental responsibilities of researchers [29] and one in Interstices on computational agro-ecology [28]. He also participated in a collective text in Liberation by 13 authors : Donner un nouveau sens à la recherche scientifique face aux défis de l'Anthropocène https://www.liberation.fr/debats/2020/06/13/donner-un-nouveau-sens-a-la-recherche-scientifique-face-aux-defis-de-l-anthropocene_1790877/

11.3.2 Interventions

- Eric Tannier co-organized a series of seminars on research in the anthropocene (1 seminar in 2019, 3 seminars in 2020).

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-01735473.

[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-universite.fr/hal-02871984.

12.2 Publications of the year

International journals

[6] N. Comte, B. Morel, D. Hasic, L. Guéguen, B. Boussau, V. Daubin, S. Penel, C. Scornavacca, M. Gouy, A. Stamatakis, E. Tannier and D. P. Parsons. 'Treerecs: an integrated phylogenetic tool, from sequences to reconciliations.' In: *Bioinformatics* 36.18 (15th Sept. 2020), pp. 4822–4824. DOI: 10.1093/bioinformatics/btaa615. URL: https://hal.inria.fr/hal-02883386.

[7] S. Gaubert, M. Akian, X. Allamigeon, M. Boyet, B. Colin, T. Grohens, L. Massoulié, D. P. Parsons, F. Adnet, É. Chanzy, L. Goix, F. Lapostolle, É. Lecarpentier, C. Leroy, T. Loeb, J.-S. Marx, C. Télion, L. Treluyer and P. Carli. 'Understanding and monitoring the evolution of the Covid-19 epidemic from medical emergency calls: the example of the Paris area'. In: *Comptes Rendus Mathématique* 358.7 (16th Nov. 2020), pp. 843–875. DOI: 10.5802/crmath.99. URL: https://hal.inria.fr/hal-02648075.

[8] R. Kusters, D. Misevic, H. Berry, A. Cully, Y. Le Cunff, L. Dandoy, N. Díaz-Rodríguez, M. Ficher, J. Grizou, A. Othmani, T. Palpanas, M. Komorowski, P. Loiseau, C. Moulin-Frier, S. Nanini, D. Quercia, M. Sebag, F. Soulié Fogelman, S. Taleb, L. Tupikina, V. Sahu, J.-J. Vie and F. Wehbi. 'Interdisciplinary Research in Artificial Intelligence: Challenges and Opportunities'. In: *Frontiers in Big Data* 3 (23rd Nov. 2020). DOI: 10.3389/fdata.2020.577974. URL: https://hal.inria.fr/hal-03111148.

[9] F. Laugerette, C. Vors, M. Alligier, G. Pineau, J. Drai, C. Knibbe, B. Morio, S. Lambert-Porcheron, M. Laville, H. Vidal and M.-C. Michalski. 'Postprandial Endotoxin Transporters LBP and sCD14 Differ in Obese vs. Overweight and Normal Weight Men during Fat-Rich Meal Digestion'. In: *Nutrients* 12.6 (June 2020), p. 1820. DOI: 10.3390/nu12061820. URL: https://hal.inrae.fr/hal-02959609.

[10] 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 (3rd June 2020), pp. 274–306. DOI: 10.1162/artl_a_00319. URL: https://hal.inria.fr/hal-01735473.

[11] K. Lenk, E. Satuvuori, J. Lallouette, A. Ladrón-De-Guevara, H. Berry and J. A. K. Hyttinen. 'A Computational Model of Interactions Between Neuronal and Astrocytic Networks: The Role of Astrocytes in the Stability of the Neuronal Firing Rate'. In: *Frontiers in Computational Neuroscience* 13 (22nd Jan. 2020), pp. 1–19. DOI: 10.3389/fncom.2019.00092. URL: https://hal.archives-ouvertes.fr/hal-02453587.

[12] V. F. Liard, D. P. Parsons, J. Rouzaud-Cornabas and G. Beslon. 'The complexity ratchet: Stronger than selection, stronger than evolvability, weaker than robustness'. In: *Artificial Life* (Apr. 2020). URL: https://hal.archives-ouvertes.fr/hal-03136077.

[13] J. Marin, G. Achaz, A. Crombach and A. Lambert. 'The genomic view of diversification'. In: *Journal of Evolutionary Biology* 33.10 (12th Oct. 2020), pp. 1387–1404. DOI: 10.1111/jeb.13677. URL: https://hal.archives-ouvertes.fr/hal-03137815.

[14] S. Peignier, C. Rigotti and G. Beslon. 'Evolutionary Subspace Clustering Using Variable Genome Length'. In: *Computational Intelligence* 36.2 (2020), pp. 574–612. DOI: 10.1111/coin.12254. URL: https://hal.archives-ouvertes.fr/hal-02405598.

[15] C. Robert, L. Couëdelo, C. Knibbe, L. Fonseca, C. Buisson, E. Errazuriz-Cerda, E. Meugnier, E. Loizon, C. Vaysse and M.-C. Michalski. 'Rapeseed Lecithin Increases Lymphatic Lipid Output and α-Linolenic Acid Bioavailability in Rats'. In: *Journal of Nutrition* 150.11 (19th Nov. 2020), pp. 2900–2911. DOI: 10.1093/jn/nxaa244. URL: https://hal.archives-ouvertes.fr/hal-03149749.

[16] C. Rocabert, G. Beslon, C. Knibbe and S. Bernard. 'Phenotypic noise and the cost of complexity'. In: *Evolution - International Journal of Organic Evolution* (21st Aug. 2020). DOI: 10.1111/evo.14083. URL: https://hal.archives-ouvertes.fr/hal-02920356.

[17] M. Vincent, O. Ménard, J. Etienne, J. Ossemond, A. Durand, R. Buffin, E. Loizon, E. Meugnier, A. Deglaire, D. Dupont, J.-C. Picaud, C. Knibbe, M.-C. Michalski and A. Penhoat. 'Human milk pasteurisation reduces pre-lipolysis but not digestive lipolysis and moderately decreases intestinal lipid uptake in a combination of preterm infant in vitro models'. In: *Food Chemistry* 329 (26th Apr. 2020), p. 126927. DOI: 10.1016/j.foodchem.2020.126927. URL: https://hal.inrae.fr/hal-02862386.

[18] R. Waterhouse, S. Aganezov, Y. Anselmetti, J. Lee, L. Ruzzante, M. Reijnders, R. Feron, S. Bérard, P. George, M. Hahn, P. Howell, M. Kamali, S. Koren, D. Lawson, G. Maslen, A. Peery, A. Phillippy, M. Sharakhova, E. Tannier, M. Unger, S. Zhang, M. Alekseyev, N. J. Besansky, C. Chauve, S. Emrich and I. Sharakhov. 'Evolutionary superscaffolding and chromosome anchoring to improve Anopheles genome assemblies'. In: *BMC Biology* 18.1 (Dec. 2020), pp. 1–20. DOI: 10.1186/s12915-019-0728-3. URL: https://hal.archives-ouvertes.fr/hal-02455139.

[19] 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-universite.fr/hal-02871984.

International peer-reviewed conferences

[20] 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: IEEE International Symposium on Biomedical Imaging. Nice, France, 13th Apr. 2021. URL: https://hal.inria.fr/hal-03106797.

[21] L. Turpin, J. Rouzaud-Cornabas, T. Gautier and C. Pérez. 'P-Aevol: an OpenMP Parallelization of a Biological Evolution Simulator, Through Decomposition in Multiple Loops'. In: *OpenMP: Portable Multi-Level Parallelism on Modern Systems*. 16th International Workshop on OpenMP. OpenMP: Portable Multi-Level Parallelism on Modern Systems. Austin, United States, 1st Sept. 2020, pp. 52–66. DOI: 10.1007/978-3-030-58144-2_4. URL: https://hal.inria.fr/hal-02962838.

Scientific book chapters

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

[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. 9th Dec. 2020, pp. 241–260. DOI: 10.1007/978-1-0716-1036-7_15. URL: https://hal.archives-ouvertes.fr/hal-03065564.

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