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Université Claude Bernard (Lyon 1)

Activity Report 2017

Project-Team BEAGLE

Artificial Evolution and Computational Biology

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

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Computational Biology

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Project-Team BEAGLE

Creation of the Team: 2011 June 17, updated into Project-Team: 2013 January 01

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1. Personnel

Research Scientists

Hugues Berry [Inria, Senior Researcher, HDR]
Eric Tannier [Inria, Researcher, HDR]

Faculty Members

Guillaume Beslon [Team leader, INSA Lyon, Full Professor, HDR]
Carole Knibbe [INSA Lyon, Associate Professor]
Christophe Rigotti [INSA Lyon, Associate Professor, HDR]
Jonathan Rouzaud-Cornabas [INSA Lyon, Associate Professor]
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Post-Doctoral Fellows

Maurizio de Pitta [Inria, until Jun 2017]
Priscila Do Nascimento Biller [Inria]

PhD Students

Audrey Denizot [INSA Lyon]
Wandrille Duchemin [Univ Claude Bernard, until Dec 2017]
Marie Fernandez [Inria]
Alexandre Foncelle [Inria]

Vincent Liard [INSA Lyon]
Alvaro Mateos Gonzalez [Ecole Normale Supérieure Lyon, until Aug 2017]
Sergio Peignier [Inria, until Aug 2017]
Charles Rocabert [Inria, until Apr 2017]

Technical staff
Nicolas Comte [Inria]

Interns
Juliette Geoffray [Inria, from Apr 2017 until May 2017]
Thomas Labrux [ENS Lyon, from March 2017 until June 2017]
Mikita Mauvisseau [Inria, from May 2017 until Aug 2017]
Charles Mercier de Lacombe [Inria, from Feb 2017 until Jun 2017]
Lukas Schmidt [FIL, from November 2017 until Mars 2018]
Laurent Turpin [Inria, from Jun 2017 until Aug 2017]
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Administrative Assistants
Caroline Lothe [Inria]
Gaelle Tworkowski [Inria]

2. Overall Objectives

2.1. Overall Objectives

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, UCBL, 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.

[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.

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. Hence, the team research is organized in four 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 last two ones are more biologically oriented: they focus on specific questions in cell biology and evolutionary biology that mobilize a general effort of the team. These two axes are the "NeuroCell" axis (research axis 3), in which biochemical models are specifically applied on brain cells (neurons and glia), and the "EvoEvo" axis (research axis 4) in which we tackle the question of the evolution of the evolutionary process in microorganisms. The next four sections describe these four axes in more details. Evidently the two specific biological questions that constitute axes 3 and 4 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.

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 where 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. 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 stochasticity 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).

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 uncovering general laws which explain the organization of the genomes we observe today, and leveraging this knowledge to reconstruct some aspects of the history of life. To do so, we construct computational and mathematical models and apply them either in a "forward" way, *i.e.* observing the course of evolution from known ancestors and parameters, either by simulation (*in silico experimental evolution*) or by 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.biodiversity.

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 *in vivo* 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. We also tackle the more functional question of neural encoding of acoustic perception.

Research axis 4: EvoEvo Variation and Selection are the two core processes of Darwinian Evolution. Yet, both are directly regulated by many processes that are themselves products of evolution

(*e.g.* DNA repair, mutator genes, transposable elements, horizontal transfer, stochasticity of gene expression, sex, network modularity, niche construction...). This results in the ability of evolution to self-modify its operators, hence its dynamics. This process has been called "Evolution of Evolution" or EvoEvo [59]. Different EvoEvo strategies have been proposed in the literature, including regulation of variability, robustness/evolvability strategies, bet-hedging... However, most of these strategies are poorly characterized and the conditions under which they evolve as well as their consequences are generally unknown. On the current evaluation period, BEAGLE has taken the lead of the European Project "EvoEvo" that specifically focused on Evolution of Evolution by studying its biological mechanisms, evolutionary consequences and possible applications to bioinspired computation (evolutionary-base subspace clustering). Indeed, the EvoEvo project has had a profound structuring effect on the team since it involved more than half of it and led to the hiring of two PhD students and two engineers during the evaluation period.

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* [56] 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 modelization and simulation of cellular processes. More specifically, we focus on two specific processes that govern cell dynamics and behavior: Evolution and Biophysics.

3.2. Research axis 1: Computational cellular biochemistry

3.2.1. Biochemical kinetics with unconventional diffusion.

The movement of many biomolecules such as proteins in living cells has been reported as spatially heterogeneous diffusion (position-dependent diffusion coefficient) or even as anomalous diffusion, whereby the mean-squared displacement scales sub-linearly with time, $\langle \mathbf{r}^2 \rangle \sim t^\alpha$ with $\alpha < 1$. The influences of such deviations from simple Brownian motion on the biochemical reactions that take place in these media are just starting to be explored. Part of our efforts was aimed at improving the modeling of sub-diffusion in an intracellular context by extending the existing models of obstacle-based sub-diffusion to mobile obstacles [37] or proposing age-structured PDEs to model sub-diffusion [38], [43]. We also explored the effects of locally slowed-down diffusion or local sub-diffusion on the dynamics of simple reactions such as the ligand-binding equilibrium or protein aggregation [44], [39], [77], [78], [47].

3.2.2. Spatial and temporal organization of gene expression.

Gene expression is highly organized in space and diffusing factors often have to reach and bind partners which positions are not well-mixed, but exhibit stationary spatial organization. We have studied how the spatial organization of genes can affect their interaction [64], [65]. Combining modeling and experiments, we have studied the stochasticity of gene expression in single metazoan cells (chicken cells) and provided its quantification via stochasticity measures [89], [33], [48].

3.2.3. Adipose tissue modeling

Most cellular pathway models and equations assume that the cell / medium is size / volume constant during the whole duration of the process. However there is an important variability in size and volume within tissue, within cell type and of course during the life of a single cell. We have studied the mechanism of lipid storage in adipocytes both at equilibrium and non-equilibrium [80], [79] and confirmed that the main model predictions are indeed present in rats [57], [58].

3.2.4. Current Objectives

We will intensify our collaborations with mathematicians and theoretical physicists in order to develop age-structured PDEs as models of subdiffusion and (sub)diffusion-reaction coupling in the perspectives of non-parametric inference for classification of intracellular trajectories or the modeling of subdiffusion-reaction coupling. Regarding experimental data, we are developping collaborations with experts of super-resolution microscopy in order to be able to combine our models with single-molecule trajectory data and spatial localization data at single-molecule resolution in living cells. Moreover, since September 2017, Carole Knibbe shares her research time (co-affiliation) between Beagle and the biomedical research laboratory CarMeN (http://carmen.univ-lyon1.fr). On this occasion, her research has joined Research axis 1. In collaboration with experimental biologists of the CarMeN laboratory (*e.g.* Marie-Caroline Michalski), she now works on mathematical and computational models of lipolysis kinetics, with the aim of reaching a quantitative understanding of how the spatial supramolecular organization of lipids influences their digestion. A variety of experimental data are available at CarMeN to calibrate the models at the various scales, from in vitro enzymatic data, to cultures of intestinal cells, to animal models, to clinical data in normal and obese patients.

3.3. Research axis 2: Models for Molecular Evolution

3.3.1. Backwards models. The example of dating with transfers.

Here the goal is to compare extant genomes in order to propose plausible scenarios for their evolution. We constructed a multi-scale model of evolution, at the levels of species, chromosomes, genes and nucleotides. Reconstruction algorithms proposed a catalog of putative ancient transfers in different domains of life, as cyanobacteria, fungi, archaea. As transfers can only occur between contemporaneous species, they contain an information on the timing of life diversification. This allowed us to exploit a completely novel and abundant information for the history of biodiversity [81], [83], [82], [84], [45].

3.3.2. Forward models I. In silico experimental evolution.

We have made several crucial advances in particular around the *Aevol* software that we have been developing for more than 10 years. This software consists in evolving *in silico* a population of digital genomes from an ancestral state and quantifying expected or unexpected systematic behaviors, in function of settled parameters (see Figure 1). We formalized the method [35] and implemented a tracking system that allows us to measure histories of genes [61]. We explored the potentiality of epigenetic inheritance through R-Aevol, an extension of Aevol implementing genetic regulation and epigenetic (cytoplasmic) inheritance [86], [87]. We also developed models with a new artificial chemistry in the context of the European project Evoevo (see below).

3.3.3. Forward models II. Theoretical investigations.

Simulations are made when models are too complicated to be handled analytically. However, it is sometimes worth simplifying the model in order to demonstrate a given property and have a proven behavior in function of perfectly identified parameters. We have obtained important results in this scope, mostly about the size of impact of selection on genome sizes [55]. Another set of theoretical results was obtained by the introduction of phenotypic noise in Fisher's Geometric Model (see below).

3.3.4. The Forward-Backward and the double blind procedure.

One objective of simulations or mathematical forward models is to explain the shape of some extant particular data. When one (or more) evolutionary mechanism is evoked to explain a given dataset, simulations can test if the invoked mechanism is indeed likely to produce the observed dataset. We investigated for example the causes of genome reduction in *Prochlorococcus* and compared them with genome reduction in endosymbiots [35], [36]. Another way we made the forward and backward models enrich each other is by using forward models to construct test instances for the backward methods. We have developed forward and backward models that are not scientifically linked, except by a common biological background [42], [41]. That led us to initiate the development of a new version of the Aevol software, "Aevol_ACGT", that will include a four nucleotides genome decoded through a realistic genetic code [46], [63].

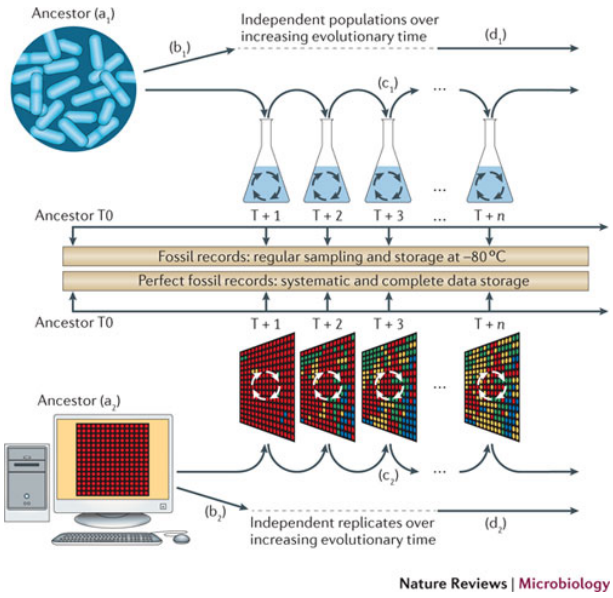

Figure 1. Parallel between experimental evolution and artificial evolution

3.3.5. Current Objectives

We are improving and publicizing the dating method using gene transfers. We are leaders on this subject, published already in very good journals or labels, so we still see this subject as highly promising. A second important goal is producing benchmarks for the validation of evolutionary studies. This can be very useful for the evolutionary biology community, which lacks good validation standards. We provided some proofs of concept during the last years and will work towards a completely usable platform in the following years. Moreover we are pushing our *in silico* experimental model towards standard models of theoretical biology to test the robustness of some hypotheses to complex models. Finally we want to explore the possibility to co-construct biological knowledge with the general public through participative platforms. We will propose a protocol usable by the public in order to solve unknown parts of the tree of life, which size now calls for a participative project like encyclopedias or maps. This will demand new skills in computer science, participative sciences, and also will depend on consequent funding applications.

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

3.4.1. Understanding neuronal plasticity

One of our main achievements concerns the study of synaptic plasticity in the the basal ganglia, the locus of procedural learning (the learning of skills and habits) and reinforcement learning. We have been carrying out joint experimental-modeling research to decipher the signaling pathways that underlay synaptic plasticity in this brain structure [49], [50]. This result is a significant advance for the understanding of synaptic plasticity because it shows that plasticity can be triggered even with low activity levels. In related threads of research, we have also studied the molecular basis of intrinsic plasticity [66] or the adult neurogenesis [66].

3.4.2. Biophysical models of astrocyte signaling

Neurons represent roughly half of the brain cells. The other part is made of glial cells, that include *e.g.* microglia, oligodendrocytes or astrocytes. The role of glial cells in cognition, learning or memory is a new field of research in neuroscience. We have developed reference mathematical models in the field, focusing on intra- and inter-cellular astrocyte calcium signals and astrocyte-to-neurons signaling via neuro- and gliotransmitters [67], [52], [62], [90]. We have initiated a modeling and theoretical study of the modulation of neuronal plasticity by astrocyte signaling [51].

3.4.3. Motor model for perceptive neural coding

In animal acoustic perception, the canonical representation of sound is through Fourier decomposition via a spectrographic representation. While generic, this approach does not take into account the (probable) tuning of neurons to familiar sound and therefore ad-hoc sound statistics. We have proposed an alternative view where sound representation is based on the motor representation needed to produce the acoustic output. In the context of songbirds, we proposed mechanical models that reproduce bird vocalization using muscles contractions dynamics. Part of auditory neural tuning is probably focused on decoding vocalization of endogenous individuals in the context of a social network. We have developed a series of analysis tools to identify acoustic social networks of Zebra Finches and applied them to the study of small bird groups in the lab [70], [71], [88], [53], [54].

3.4.4. Current Objectives

Research axis 3 will continue but with considerable modifications. We are carrying on work on synaptic plasticity in the basal ganglia focusing on the modulation of synaptic plasticity by neuromodulators like dopamine. In particular, understanding the impact of dopamine signaling in the basal ganglia could provide us with significant advances in dopamine-related pathologies (Parkinson's, addictions...). Regarding the work on astrocytes, we will concentrate our efforts on the deciphering of calcium signaling in the finest astrocyte branchlets that are expected to be the locus of interactions with the neurons. Our objective is to uncover how the spatial organization of the implied signaling molecules impacts the signaling between the synapse and the astrocyte. To obtain experimental data related to this spatial intracellular organization, we will initiate several new collaborations with experimental neuroscientists.

3.5. Research axis 4: EvoEvo

The EvoEvo project was a highly interdisciplinary project ranging from wet experiments (experimental evolution) to software application (evolving a musical personal companion).

3.5.1. Computational experiments

To help understand the results of the wet experiments conducted by our partners, we designed several computational experiments that used the models developed by the team (see Research axis 2 above).
Dynamics of innovation in viral strains. Viral strains show a surprising evolutionary dynamics in which long periods of stasis are interrupted by short evolutionary bursts. To understand this dynamics, we launched a very large scale *in silico* experiment in the Aevol software [40], [60].

Dynamics of mutator strains. The mutation rate of bacterial strains is known to adapt to the evolutionary conditions through the emergence of "mutator strains" that have a 10 to 100 fold raised mutation rate compared to the wild-type. Mutator strains are supposed to raise in specific conditions such as stress or environmental change. We studied this situation in the Aevol software and showed the importance of the reorganization of the genome structure in this phenomenon [76].
Diversification in seasonal environments. One of the targets of the EvoEvo project was the evolution of open-endedness. As a first step, we provided a careful definition of open-endedness [34], [85] and developed a new model, Evo2Sim (http://www.evoevo.eu/evo2sim/) [72], that contains all the ingredients to enable the emergence of structured populations. We then used it to simulate the evolution of populations in batch cultures and continuous conditions [73], [74], [75].

3.5.2. Bioinspired computation

Once EvoEvo strategies were identified *in vivo* an *in silico*, the final objective of the EvoEvo project was to transfer them into the ICT domain by developing new evolutionary metaheuristics and applying them to real problems.
Evolutionary-based subspace clustering. One on the main outcomes of the *in silico* models was the importance of chromosomal rearrangements (and of their consequences on the genome organization) for the evolutionary process. Hence, we proposed to use these properties to develop new evolutionary algorithms specifically dedicated to the subspace clustering task [69], [68]. We also developed the first evolutionary algorithm dedicated to the subspace clustering of datastreams.
EvoMove: A musical personal companion. To validate our evolutionary-based subspace clustering algorithm, we used it to develop EvoMove, a musical personal companion to be used by dancers and musicians [12], [24]. EvoMove has been tested by professional dancers (http://www.evoevo.eu/evomove-working-session/) and has been presented to the public in the context of the "Meute" ("Herd") performance that has been played eight times between February and July 2017.

3.5.3. Current Objectives

Research axis 4 is relatively new in the team since it started with the EvoEvo European project. Hence many of the activities of this research axis are still fully active. We will carry on the cooperation on the innovative dynamics of viral strains, with the objective to study whether the dynamics we observed in viruses is also observed in other kinds of genomes. We also will investigate further the role of large scale events (chromosomal rearrangements, recombination...) on the macro-evolutionary dynamics and on the interaction between micro- and macro-evolution. Finally, we will carry on our work on evolutionary-inspired subspace clustering algorithms and on the evolutionary metaphor applied to the development of new ICT technologies with a specific focus on the integration of temporal data.

4. Highlights of the Year

4.1. ECAL Conference

In September 2017 Beagle organized the 14th European Conference on Artificial Life in Lyon (https://project.inria.fr/ecal2017/). ECAL is a biannual scientific meeting supported by the International Society for Artificial Life (ISAL). Carole Knibbe was scientific chair of the conference and Guillaume Beslon was local chair. We welcomed 200 researchers from various disciplines (computer science, biology, physics, humanities...) for 5 days of conferences (including 7 keynotes) in the domain of modelling and simulation of life. The scientific program was completed by an amazing social program (vineyard visits, old city visit, wine&cheese, banquet dinner, sport activities...). The proceedings of the conference have been published by MIT Press (http://cognet.mit.edu/journal/ecal2017).

4.1.1. Awards

Guillaume Beslon was awarded the 3rd price at the international innovation academy of the International conference on prevention and infection control. Geneva, Juin 2017. Project presented: ISEE-Resistance, using in silico experimental evolution to sensitize providers on antibiotic resistance [13].

5. New Software and Platforms

5.1. aevol

Artificial 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.

RELEASE FUNCTIONAL DESCRIPTION: Fix compilation error on Mac (tr1 included in std). The new mac compiler includes the tr1 directly in std which caused a compilation error. This issue was specific to aevol-4.4.1

- Participants: Antoine Frénoy, Bérénice Batut, Carole Knibbe, David Parsons, Dusan Misevic, Guillaume Beslon, Jonathan Rouzaud-Cornabas and Vincent Liard
- Partners: UCBL Lyon 1 - INSERM - Université Paris-Descartes - Insa de Lyon
- Contact: Carole Knibbe
- URL: http://www.aevol.fr/

5.2. DeCoSTAR

KEYWORDS: Bioinformatics - Evolution
FUNCTIONAL DESCRIPTION: DeCoSTAR reconstructs ancestral genomes and improves the assembly of extant genomes. It takes as input a set of gene trees, a species tree and adjacency relations between extant genes. It outputs ancestral genes, adjacencies between extant and ancestral genes, and a statistical support associated to each inferred adjacency.
NEWS OF THE YEAR: Publication of the software with several test sets in Genome Biology and Evolution

- Participants: Eric Tannier and Wandrille Duchemin
- Contact: Eric Tannier
- Publication: DeCoSTAR: Reconstructing the ancestral organization of genes or genomes using reconciled phylogenies
- URL: http://pbil.univ-lyon1.fr/software/DeCoSTAR/

5.3. EvoEvo

Evolution of Evolution
KEYWORDS: Bioinformatics - Biology - Evolution

FUNCTIONAL DESCRIPTION: In the context of the EvoEvo european project we are developing an integrated model of microorganisms evolution. This model will extend the current evolutionary models developped in the team (Aevol and R-Aevol) by adding a metabolic level and an ecosystem level. In 2014, a first version has been developed and released that includes the genomic, genetic and metabolic levels.

- Participants: Carole Knibbe, Charles Rocabert and Guillaume Beslon
- Contact: Guillaume Beslon
- URL: http://www.evoevo.eu/

5.4. evowave

KEYWORDS: Data stream - Clustering - Evolution - Wireless network
FUNCTIONAL DESCRIPTION: This package is a toolbox to analyse signal strength in wifi activity logfiles. It includes three main modules. The first is a preprocessing module to agregate logfile contents. The second one is a subspace clustering module, based on an evolutionary algorithm, to identify similar wifi activity contexts. This similarity is defined on signal strength of wifi devices and the clusters can change over time. The third module is a visualisation tool to display the cluster modifications over time.

- Participants: Anthony Rossi, Christophe Rigotti, Guillaume Beslon, Jonas Abernot, Leo Lefebvre and Sergio Peignier
- Contact: Christophe Rigotti
- URL: http://evoevo.liris.cnrs.fr/download/4_-_deliverables/wp5/Deliverable_D5.1_software_archive.zip

5.5. FluoBacTracker

KEYWORDS: Bioinformatics - Biology - Biomedical imaging
SCIENTIFIC DESCRIPTION: FluoBacTracker is an ImageJ plugin allowing the segementation and tracking of growing bacterial cells from time-lapse microscopy movies. The segmentation and tracking algorithms used by FluoBacTracker have been developed by Lionel Moisan and colleagues at Université Paris Descartes.
FUNCTIONAL DESCRIPTION: FluoBacTracker has the following functionalities: 1) Select regions of interest in images of microcolonies 2) Denoise and renormalize the images 3) Identify each cells in each image (segmentation) 4) Follow cells through the whole movie (tracking), including the detection of cells washed out from a microfluidics channel 5) Detect divisions and construct cell lineage of the population
NEWS OF THE YEAR: Version 2 of FluoBacTracker also allows the analysis of microscopy of bacteria growing in a microfluidics device called "mother machine".

- Participants: Hugues Berry, Cyril Dutrieux, Hidde De Jong, Charles Kervrann, David Parsons and Magali Vangkeosay
- Partners: Université Descartes - UGA
- Contact: Hugues Berry
- URL: http://fluobactracker.inrialpes.fr

5.6. Tewep

Simulator of the dynamics of Transposable Elements Within Expanding Populations
KEYWORDS: Simulator - Transposable elements - Population genetics - Geographic expansion

FUNCTIONAL DESCRIPTION: Transposable elements, found in the genomes of most living organisms (including humans), are pieces of DNA able to replicate themselves and to proliferate. Their presence is a source of mutations which are, most of the time, detrimental to their host. As a consequence, natural selection usually limits their spread. There are, however, some conditions where natural selection cannot be efficient enough to remove them, for example when the population size is small. It is also hypothesized that when a population geographically expands, the efficiency of natural selection could be reduced at the expansion front. TEWEP is an individual-based simulator designed to test whether transposable elements could proliferate in large expanding populations. It combines several population genetics models to simulate the evolution of the number of transposable elements in each individual of an expanding population.

- Partner: Laboratoire de Biométrie et Biologie Evolutive (LBBE) - UMR CNRS 5558
- Contact: Carole Knibbe
- URL: https://gforge.inria.fr/projects/tewep/

6. New Results

6.1. The fossil record of microbes augmented by an order of magnitude

Participants: Eric Tannier
Biodiversity has always been predominantly microbial and the scarcity of fossils from bacteria, archaea and microbial eukaryotes has prevented a comprehensive dating of the tree of life. We have shown that patterns of lateral gene transfer deduced from the analysis of modern genomes encode a novel and abundant source of information about the temporal coexistence of lineages throughout the history of life. We constructed and used new phylogenetic methods to reconstruct the history of thousands of gene families and demonstrate that dates implied by gene transfers are consistent with estimates from relaxed molecular clocks in bacteria, archaea and eukaryotes. An inspection of discrepancies between transfers and clocks and a comparison with mammal fossils show that gene transfer in microbes is potentially as informative for dating the tree of life as the geological record in macroorganisms.
Main publications: [30]

6.2. Phylogenetics of dependence, and dependence of phylogenies

Participants: Wandrille Duchemin, Eric Tannier
Standard phylogenetics use DNA or protein sequences, along with probabilistic models of substitutions, which are Markov processes on trees. The big default of this methodology is to assume a common evolution of all sites inside a gene, and a total independence with other genes. This model does not capture the essence of living things, which is made of dependencies and interactions. We made several methodological developments to take into account these dependencies, by improving the gene tree species tree reconciliation methods and reconstructing phylogenies of relations between genes.
Publications: [16], [32], [19]

6.3. Beware batch culture: Seasonality and niche construction predicted to favor bacterial adaptive diversification

Participants: Charles Rocabert, Carole Knibbe, Guillaume Beslon
The evolution of stable bacterial cross-feeding interactions is often considered as the first step toward bacterial speciation in sympatry. It is thus important to study the conditions favoring the emergence and the stabilization of cross-feeding interactions in well-mixed environments. Experimental evolution in laboratory, where fast organisms are replicated for thousands of generations in controlled conditions, provides important insights on this question. Indeed cross-feeding is commonly observed in batch cultures or in chemostat. However, the reasons why cross-feeding interactions become stable and lead to monophyletic ecotypes remain unclear. Because laboratory experiments are a long and costly process, we explored this question by evolving digital organisms in artificial systems mimicking the conditions of wet experiments.

Models of digital evolution helped a lot to decipher the evolution of cross-feeding interactions. However, the evolution of real microorganisms implies the interaction of a wide range of biological structures and levels, while those models often include only two or three levels, limiting their ability to mimic real experiments. In this work, we developed a new multi-scale model of digital evolution, integrating a complex and realistic genotype-to-phenotype mapping (including a metabolic network) and a complex environment (that links the organism's metabolic networks together, opening the possibility for cross-feeding). This model has been developed under the European project EvoEvo, and has been inspired by previous models developed by the Beagle team, and in the Theoretical Biology and Bioinformatics group at Utrecht University. By mimicking laboratory experiment setups and running simulations for tens of thousands of generations, we were able to recover ecological dynamics similar to those found in real experiments.

In batch culture, like in the Long Term Evolution Experiment (LTEE), it is accepted that the seasonality generated by the serial transfers triggers the maintenance of cross-feeding interactions on the long-term by favoring niche construction and specialization. In chemostat, cross-feeding interactions are observed and seem stable for a few hundreds of generations but the reasons of their stability remain unclear. Thanks to our model, we were able to observe stable cross-feeding interactions reproducing the same properties as those observed in the LTEE. We then showed that seasonal conditions found in batch cultures are essential for the maintenance of stable ecotypes on the long-term, since it produces conditions for niche construction and stable cross-feeding. In chemostat conditions, the absence of seasonality and competitive exclusion precludes any stabilization of emerging cross-feeding interactions. Finally, we proposed to consider a cross-feeding interaction to be stable only if interacting ecotypes undergo independent periodic selection events on the long-term. Stable cross-feeding interactions could then be considered as premises to speciation in sympatry.

This work is the result of an enriching collaboration between the Beagle team (Charles Rocabert, Carole Knibbe, Guillaume Beslon), and microbiologists from the TIMC-IMAG in Grenoble (Jessika Consuegra, Dominique Schneider). It has been published in the renowned journal PLoS Computational Biology in January 2017. This work is of interest for the fields of evolutionary biology, microbiology but also for computer science. Indeed our findings also suggest that digital evolution is a useful tool to study bacterial evolution, and that the use of models integrating a complex genotype-to-phenotype mapping and complex interactions between digital organisms and their environment is important to accurately study real biological systems thus appealing for further fruitful transdisciplinary collaborations.
Publication: [21].

6.4. Evolution of phenotypic noise

Participants: Charles Rocabert, Guillaume Beslon, Carole Knibbe
The phenotype of an organism is a complex non-linear cascade of developmental, physiological and regulatory processes, formalized by the concept of genotype-to-phenotype map. An increasing number of experimental studies demonstrate the existence of phenotypic noise, which can be finely tuned by the genotype-to-phenotype map, and that phenotypic noise can be adaptive.

In stabilizing selection, when the population is at a fitness optimum, phenotypic noise is deleterious and minimized by evolution. Nevertheless, phenotypic noise can be positively selected when the population is exposed to stressful conditions. It was thus suggested that during an adaptation event, phenotypic noise would increase in directional evolution, and then be reduced when the selection becomes stabilizing. In 1930, R.A. Fisher suggested with its so-called Fisher's Geometric Model (FGM) that organisms adapting to a new environment experience a "cost of complexity", where beneficial mutations become increasingly harder to fix when the number of phenotypic characters increases. Predictions made on the evolution of phenotypic noise are mostly based on single trait observations. Is there also a cost of complexity on the phenotypic noise?

To address this question, we extended the FGM by adding an evolvable phenotypic noise. First, using a simple form of noise, affecting similarly every phenotypic character, we show that a cost of complexity indeed makes phenotypic noise deleterious in directional evolution. Second, we extended the FGM with a fully evolvable noise, allowing evolution on noise amplitudes on each character, as well as on noise correlations between characters. In directional evolution, we show that phenotypic noise evolves towards a flattened shape, with elevated noise in the direction of the optimum, and minimized noise in all other directions. In this case, the noise becomes advantageous again, even with many characters. Non-isotropic phenotypic noise thus facilitates evolution towards the fitness optimum, and significantly reduces the cost of complexity. Our results show that such non-isotropic phenotypic noise could be exploited by evolution, and suggest further experiments to assess the functional nature of phenotypic noise.

This result is currently under review for the Evolution journal. It is the result of an enriching collaboration between the Beagle team (Charles Rocabert, Guillaume Beslon, Carole Knibbe), and the Dracula team (Samuel Bernard). Although the results are grounded in theory and mathematical modeling, they provide stringent conditions for noise to be beneficial, which are experimentally testable. We believe the results to be of wide interest for researchers working on phenotypic evolution. By deciphering the conditions in which phenotypic noise evolves towards specific patterns, our work may also contribute to a better understanding of drug resistance and cancer cells proliferation, and also to the growing field of predictive biology.

6.5. Impact of group size and social composition on group vocal activity and acoustic network in a social songbird

Participants: Marie Fernandez, Hédi Soula
In social species individuals living in the same group may synchronize activities such as movements, foraging or antipredator vigilance. Vocalizations are behaviors that can be coordinated between individuals, but simultaneous vocalizations in groups have mostly been considered as noise that does not bear any information. Indeed, little is known about the structure and function of vocal communications involving a network of individuals. Zebra finches, Taeniopygia guttata, are social, monogamous songbirds that form lifelong pair bonds. In the wild, they are typically found in small groups and they gather in 'social' trees where they produce vocalizations. Here we investigated in the laboratory the influence of group size and composition on general vocal activity and synchrony, as well as the influence of pair bond and spatial location on the finer characteristics of dyads' vocal interactions. We used a set-up that locked the birds at fixed spatial positions of our choosing to control the proximity network and allowed us to match most of the vocalizations with specific individuals. We used an in-house software suite that automatically detects vocalizations from hours of passive recording. We found that zebra finch groups synchronized their general vocal activity with waves of collective vocalizations, which depended on both the size and the composition of the group. The acoustic network was shaped by pair bonds at different timescales.
Publication: [17].

6.6. Dopamine-endocannabinoid interactions mediate spike-timing dependent potentiation in the striatum

Participants: Hugues Berry, Alexandre Foncelle, Ilya Prokin
Synaptic long-term plasticity underlies multiple forms of learning and memory in the brain. In most systems, its bidirectionality - depression (LTD) and potentiation (LTP) allows adaptive adjustment of the synaptic weight depending on the activity. Endocannabinoids (eCBs), one of the most widespread neurotransmitter systems, are very well established as depressing neuronal communication but recent experimental evidence challenges this depression-only vision. Our previous work in collaboration with L. Venance's lab at CIRB, College de France, Paris (experimental neuroscience) has combined experimental and mathematical modeling approaches to identify in the basal ganglia the existence of an eCB-mediated spike-timing dependent LTP (eCB-tLTP) induced by a low number of paired stimulations [50], [49]. However, the regulation and control mechanisms of eCB-tLTP remained unknown. Using the same combination of experimental and modelling

approaches, we have now discovered that dopamine controls eCB-tLTP. The dopamine system is a key actor of associative learning in the basal ganglia and a pivotal system in several pathologies including Parkinson's disease. We identified that eCB-tLTP depends on dopamine and involves the activation of D2R dopamine receptors located presynaptically in corticostriatal glutamatergic afferents. We moreover show that dopamine control of eCB-tLTP is of pathological significance since it is impaired in a rodent model of Parkinson's disease and rescued by chronic L-DOPA treatment in those animals. Combining our experimental finding with a realistic mathematical model of the underlying signaling pathway, we could describe the mechanisms accounting for this endocannabinoid-dopamine regulation of eCB-tLTP.
This result is currently under review in the journal Nature Communications.

6.7. Subspace clustering based on medians using evolutionary algorithms

Participants: Sergio Peignier, Christophe Rigotti, Jonas Abernot, Guillaume Beslon
Subspace clustering is a data mining task that searches for objects sharing similar features, and at the same time looks for the subspaces where these similarities appear. For this reason subspace clustering is recognized as more general and complicated than standard clustering, since it needs to detect these relevant subspaces. Taking advantage of the expertise of the team in evolution in silico, we previously showed that evolutionary algorithms are promising approaches to address this problem. Another important clustering task is the K-medians one, where objects are grouped around medians, leading to cluster centers more robust to noise and outliers. In order to take advantage of these benefits within the subspace clustering process itself, we developed a new evolutionary algorithm, KymeroClust, that builds cluster centers that are medians in subspaces. This algorithm takes advantage of an evolvable representation of the genotypes to adapt the numbers of clusters produced and the subspace dimensionalities. It is based on new bio-inspired mutation operators to evolve the cluster centers as medians and is able to handle streaming data. KymeroClust has been compared to the main subspace clustering methods and turns out to be very competitive both in terms of cluster quality and runtime, while requiring an easier parameter setting.
Publications: [12], [24]

7. Partnerships and Cooperations

7.1. Regional Initiatives

IntraCellXevo (2016-2018). Participants: E. Tannier, in collaboration with T Henry, Insem Lyon. This projects mixes an experimental evolution of Franscicella tumarensis in the cytosol and a bioinformatics analysis of the adaptive mutations. It has been funded by the Labex Ecofect up to 120keuros.

Lipuscale (2017-2019). Participants: C. Knibbe, in collaboration with S. Bernard (Inria Dracula) and M.-C. Michalski (CarMeN laboratory, INSERM U1060/ INRA U1397/ Université Lyon1/ INSA de Lyon). This project aims at reaching a quantitative understanding of the lipolysis and adsorption of dietary triglycerides, by using and adapting SimuScale (a multi-scale simulator developed by the Inria Dracula team) to model and simulate the processes, and by using wet experiments on in vitro systems and cellular cultures to calibrate the models parameters. It is funded by the Rhône-Alpes Institute for Complex Systems (IXXI, 5k€ for two years).

PMSISEE (2017-2019): The goal of the PMSISEE (Performance, Maintainability and Scalability of In-Silico Experimental Evolution Simulation) project is to improve the collaboration between the Inria Avalon team of the LIP laboratory and the Inria Beagle team of the LIRIS laboratory through research activities on programming model and tools for High Performance Computing applied to in-silico experimental evolution. One of the outcome is to improve the scalability and performance of the Aevol software. Moreover, we are formalizing a mini-application (mini-Aevol) representative of the resources usage of Aevol. The goal of this mini-application is to propose a simplify version of Aevol that could be used by the parallel computing community as use case to test new improvements. It is founded by the Lyon Computer Science Federation (FIL FR2000).

7.2. National Initiatives

7.2.1. ANR

Ancestrome (2012-2017): phylogenetic reconstruction of ancestral "-omes", a five-year project, call "Bioinformatics" of the "Investissements d'avenir". Supervisor: V Daubin (CNRS, LBBE, Lyon) ; with Institut Pasteur, ENS Paris, ISEM (Univ Montpellier 2) Participant: E Tannier.

Aucomsi (2013-2016) (Models of the vocal tract to study auditory circuits): a 4-year project funded by a grant from the ANR-NSF-NIH Call for French-US Projects in Computational Neuroscience. With F. Theunissen, UC Berkeley, CA, USA. Supervisor: H. Soula (for France) and F. Theunissen (for US). Participants: H. Soula, M. Fernandez.

Dopaciumcity (2014-2017): Dopamine modulation of calcium influx underlying synaptic plasticity, a 4-year project funded by a grant from the ANR-NSF-NIH Call for French-US Projects in Computational Neuroscience. With L. Venance, College de France, CIRB, CNRS/UMR 7241 - INSERM U1050, Paris, France and K Blackwell, Krasnow Institute of Advanced Studies, George Mason University, Fairfax, VA, USA. Supervisor: L Venance (for France) and K.L. Blackwell (for US). Participants: H Berry, I Prokin, A Foncelle

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.

7.2.2. Inria

ADT Phylophile. Participants: E Tannier, in collaboration with D Parsons, Inria, V Daubin, B Boussau, CNRS, Université de Lyon 1. This project aims at producing an easy to use software integrating modern algorithmic methods to build gene trees. It has been funded by Inria by a 24 month software engineer.

ADT Aevol. Participants: C Kinbbe, G Beslon, V Liard, J Rouzaud-Cornabas, D Parsons. This project aims at speeding and scaling and maintaining the code for our most complex software, aevol. It has been funded by Inria by a 24 month software engineer.

7.3. European Initiatives

7.3.1. FP7 & H2020 Projects

7.3.1.1. EvoEvo

Although the EvoEvo project was officially closed in December 2016, we let it in the 2017 report because (*i*) the scientific actions and the cooperations started in the project were still very active in 2017, (*ii*) the remaining of the project grant has served to fund many actions of the team in 2017 (including of course the continuation of the EvoEvo researches themselves).

Title: Evolution of Evolution

Programm: FP7

Duration: November 2013 - October 2016

Coordinator: Inria

Partners:

Agencia Estatal Consejo Superior de Investigaciones Cientificas (Spain)

Institut National des Sciences Appliquees de Lyon (France)

Universite Lyon 1 Claude Bernard (France)

Universite Joseph Fourier Grenoble 1 (France)

Universiteit Utrecht (Netherlands)

University of York (United Kingdom)

Inria contact: Guillaume Beslon

Evolution is the major source of complexity on Earth, at the origin of all the species we can observe, interact with or breed. On a smaller scale, evolution is at the heart of the adaptation process for many species, in particular micro-organisms (*e.g.* bacteria, viruses...). Microbial evolution results in the emergence of the species itself, and it also contributes to the organisms' adaptation to perturbations or environmental changes. These organisms are not only organised by evolution, they are also organised to evolve. The EvoEvo project will develop new evolutionary approaches in information science and will produce algorithms based on the latest understanding of molecular and evolutionary biology. Our ultimate goal is to address open-ended problems, where the specifications are either unknown or too complicated to express, and to produce software able to operate in unpredictable, varying conditions.
We will start from experimental observations of micro-organism evolution, and abstract this to reproduce EvoEvo, in biological models, in computational models, and in application software. Our aim is to observe EvoEvo in action, to model EvoEvo, to understand EvoEvo and, ultimately, to implement and exploit EvoEvo in software and computational systems. The EvoEvo project will have impact in ICT, through the development of new technologies. It will also have impact in biology and public health, by providing a better understanding of micro-organism adaptation (such as the emergence of new pathogens or the development of antibiotic resistances).

7.4. International Initiatives

7.4.1. Participation in International Programs

Beagle is a member of the CNRS "Laboratoire International Associé" (LIA) EvoAct together with Dominique Schneider's team at TIMC-IMAG (Université Grenoble Alpes) and the Beacon center at Michigan State University (Richard Lenski and Charles Ofria). EvoAct aims at studying "Evolution in Action" by *in vivo*, *in vitro* and *in silico* experiments. More specifically the Beagle team is in charge of the *in silico* experiments.

8. Dissemination

8.1. Promoting Scientific Activities

8.1.1. Scientific Events Organisation

8.1.1.1. General Chair, Scientific Chair

Carole Knibbe and Guillaume Beslon: respectively scientific chair and local chair of the 14th European Conference on Artificial Life (ECAL), Lyon, September 2017 (https://project.inria.fr/ecal2017/).

Eric Tannier: main organizer (Organizing and Scientific chair) of the SMBE Regional meeting on interdisciplinary approaches for molecular evolution in Lyon in November 2017

8.1.1.2. Member of the Organizing Committees

Hugues Berry: Co-organizer of the workshop "Dynamiques des molecules et assemblages moleculaires", Montpellier, France (Dec 2017).

Guillaume Beslon:

- LyonSysBio conference, Lyon, November 2017
- AIEM2017 (Approches Interdisciplinaire de l'Evolution Moléculaire), Lyon, November 2017.
- ALPHY 2017 (Alignement et Phylogénie) workshop, Lyon, January 2017.

Carole Knibbe: member of the organizing committee of the Scientific Day on "Modelling living systems" of the Faculty of Sciences and Technologies of Université Lyon 1.

8.1.2. Scientific Events Selection

8.1.2.1. Member of the Conference Program Committees

Christophe Rigotti was a member of the program committee of the 33rd ACM Symposium On Applied Computing.

Jonathan Rouzaud-Cornabas was a member of the program comittee of ECAL 2017

Eric Tannier was a member of the program committee of RECOMB-Comparative Genomics 2017 and is a member of the program committee of ISMB 2018.

8.1.3. Journal

8.1.3.1. Member of the Editorial Boards

Hugues Berry: Guest Editor for PLoS Computational Biology (2 articles edited in 2017)

Eric Tannier is an editor of "Peer Community in Evolutionary biology", a peer-reviewing system alternative to publications in journals

8.1.3.2. Reviewer - Reviewing Activities

Hugues Berry: Scientific reports, eLife, Frontiers Cellular Neuroscience, PLoS Computational Biology, PLoS One, Journal Theoretical Biology, Biophysical Journal

Guillaume Beslon: Journals Proceedings of Royal Society B, Entropy and Neural Computing and Applications.

Christophe Rigotti: IEEE Access

Jonathan Rouzaud-Cornabas: IEEE Transactions on Cloud Computing

Eric Tannier: Information Processing Letters, PeerJ, Plos One, Discrete Mathematics and Theoretical Computer Science, BMC Genomics

8.1.4. Invited Talks

Hugues Berry gave invited talks at:

EJCIM (Ecole des Jeunes Chercheurs et Chercheuses en Informatique Mathematique) 2017, Jan. 2017, Lyon

Models of Life, College de France, Paris, Jan. 2017

Cosyne Workshop on Astrocyte-neuron interactions, Salt Lake City, UT, USA, Feb. 2017

Imaging the cell, Rennes, France, June 2017

Dynamiques des molecules et assemblages moleculaires, Montpellier, France, Dec. 2017

You Carreer Day, I2BC, Saclay France, Dec. 2017

and invited seminars at

Institut de Mathematiques de Marseille, Jan 2017

Institut du Fer a Moulin, Paris, March 2017

Guillaume Beslon gave invited seminars at:

Séminaire de Modélisation du Vivant (SeMoVi), Lyon, May 2017

Institut de Biologie Physico-Chimique (IBPC), Paris, June 2017

Journées scientifiques Inria, Nice, June 2017

Carole Knibbe was an invited speaker at the Systems Biology Meeting of Sorbonne Université on December 1st, 2017.

Christophe Rigotti gave an invited seminar at the Centre spatial universitaire de Grenoble (CSUG):"Recherche d'évolutions par fouille de données multi-temporelles satellitaires et photographiques", September 2017.

Eric Tannier gave an invited talk at the conference “Tour de sciences" Lyon, 2017 and an invited seminar at Trinity College, Dublin, Feb. 2017.

8.1.5. Scientific Expertise

Hugues Berry was a reviewer for the call for proposal CARREER of the NSF, USA and for the Research Projects call of the FNRS, Belgium

Guillaume Beslon

Member of a Comité d’Evaluation Scientifique (CES) at the ANR

Member of the HCERES evaluation committee for the Unité Mixte Internationale UMMISCO.

Christophe Rigotti was an expert/reviewer for the challenge "Univers" organized by Imaginove, Cluster Montagne and Indura.

Eric Tannier was an evaluator (committee bioinformatics) for the Fonds de recherche du Quebec, 2107.

8.1.6. Research Administration

Hugues Berry:

Vice-Chair of Inria’s Evaluation committee (2016-2018)

Vice-Chair of the Search Committee for “Inria Senior Research Scientists” (Jury d’admissibilité DR2 2017).

Member of the “Commission des thèses” of the Doctoral School “Info-Maths” (ED 512), Lyon.

Member of the Steering Commitee of GdR IMaBIO (Imagerie et Microscopie pour la BIOlogie)

Representative for Inria on the Administrative Board of the RNSC (“Réseau National des Systèmes Complexes”)

Facilitator (with R. Guillemaud, CEA/Leti) of the “Groupe de Travail CEA/Leti-Inria on Numerical Health”.

Guillaume Beslon is a member of the Commission Scientifique Sectorielle (CSS) 5 (Science des Données et des Modèles) at IRD

Carole Knibbe:

Member of the Laboratory Council, LIRIS, UMR 5205 CNRS (until August 2017)

Member of the Technological Grants Committee (CDT) of Inria Grenoble-Rhone Alpes

Member of the Doctoral Studies Committee of Inria Grenoble-Rhone Alpes.

Christophe Rigotti is an elected member of Insa Scientific board (Conseil scientifique)

Eric Tannier:

elected member of the administration council of Inria (2015-2018)

member of the scientific committee of the ethics platform of University of Lyon (2017-)

scientific referent for the conference committee of Inria (2014-)

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

Four team members are faculty (Guillaume Beslon, Carole Knibbe, Christophe Rigotti and Jonathan Rouzaud-Cornabas). They teach 192h/year each in INSA-Lyon and University Claude Bernard Lyon 1 in the computer science departments and bioinformatics departments.

All our PhD students who wish it benefit from "teaching contracts". They teach 64h/year at INSA-Lyon, mainly in the undergraduate school and in the bioinformatics department.

Eric Tannier teaches approximately 60h/year in Master programs at INSA-Lyon and University Claude Bernard Lyon 1.

Licence:

C. Knibbe, Fundamentals of algorithmics and programming, 56 heqTD, L3, Bioinformatics and Modelling program of INSA-Lyon

C. Knibbe, Fundamentals of databases, 27 heqTD, L3, Bioinformatics and Modelling program of INSA-Lyon

C. Knibbe, Architecture of computer systems, 10 heqTD, L3, Bioinformatics and Modelling program of INSA-Lyon

C. Knibbe, Software development, 24 heqTD, L3, Bioinformatics and Modelling program of INSA-Lyon

J. Rouzaud-Cornabas, Object-Oriented Programming, 57h, L3, Computer Science Dept, INSA Lyon, France

Master :

A. Denizot, Enzymology, Cell biology, Neuroscience, 64h, M1 and M2, INSA Lyon, France

M. Fernandez, Biostatistiques, 20h, M1, Universite´ Jean Monnet, Saint-Etienne, France; Méthode en informatique appliqué à la biologie, 17h, M2, Universite´ Jean Monnet, Saint-Etienne, France

C. Knibbe, Careers in bioinformatics and modelling, 35 heqTD, M1, Bioinformatics and Modelling program of INSA-Lyon

J. Rouzaud-Cornabas, Human Machine Interface, 42h, M1, Computer Science Dept, INSA Lyon, France

J. Rouzaud-Cornabas, Systems, 14h, M1, Computer Science Dept, INSA Lyon, France

J. Rouzaud-Cornabas, Parallel Computing, 93h, M2, Computer Science Dept, INSA Lyon

J. Rouzaud-Cornabas, Computational Sciences, 10h, M2, Computer Science Dept, INSA Lyon

J. Rouzaud-Cornabas, Parallel Computing, 8h, M2, BioSciences Dept, INSA Lyon

E. Tannier, Computational Biology, 24h, M1, Insa Lyon and Université de Lyon, France

Doctorat : E. Tannier, BMIC, 2h Université de Lyon, France

E-learning

Eric Tannier produced a 14mn MOOC on Ethics in science, for the Doctoral school of University of Lyon, France.

Faculty functions

Since Sept 2017, Carole Knibbe is the Head of the Bioinformatics and Modeling master program of INSA-Lyon

8.2.2. Supervision

PhD :

Yoann Anselmetti, co-supervised by E. Tannier, Univ Montpellier, defense November 29, 2017

Wandrille Duchemin,co-supervised by E. Tannier, Univ Lyon 1, defense December 4, 2017

Damic Hasic, co-supervised by E. Tannier, Univ Sarajevo, defense Juy 13, 2017

Alvaro Mateos Gonzalez, Asymptotic analysis of partial differential equations arising in biological processes of anomalous diffusion, co-supervised by H. Berry, T. Lepoutre (Inria Dracula) and V. Calvez (Inria Numed), defense 22 September 2017

Charles Rocabert, Étude de l'évolution des micro-organismes bactériens par des approches de modélisation et de simulation informatique, co-supervised by G. Beslon and C. Knibbe, defense 17 November 2017

Sergio Peignier, Subspace Clustering on Static Datasets and Dynamic Data Streams Using Bio-Inspired Algorithms, co-supervised by C. Rigotti and G. Beslon, defense 27 July 2017

PhD in progress :

Audrey Denizot, Simulation of calcium signaling in fine astrocytic processes, started Sept 2016, supervised by H. Berry

Marie Fernandez, Extraction and analysis of the acoustic network of social birds: tools for population tracking, started Sept 2016, co-supervised by H. Berry, H. Soula (UPMC, Paris) and C. Vignal (UPMC, Paris)

Alexandre Foncelle, Modeling the signaling pathway implicated in STDP: the role of endocannabinoid and dopamine signaling, started Sept 2014, supervised by H. Berry

Vincent Liard, Towards a quantitative digital genetics platform, INSA-Lyon, started Oct 2016, co-supervision: G Beslon, J Rouzaud-Cornabas, C Ofria (Michigan State University, BEACON Center)

8.2.3. Juries

8.2.3.1. HDR juries

H. Berry: Dominique Martinez, Univ. de Lorraine, Nancy, March 2017 (reviewer)

C. Rigotti: François Rioult, Univ. Caen Normandie, Caen, December 2017 (examiner).

8.2.3.2. PhD juries

H. Berry :

Alexandre Mendes, Univ. P & M Curie, Paris, Sep 2017 (examiner)

llyas Djafer-Cherif, Univ. Paris-Saclay, Paris, July 2017 (reviewer)

Martin Potier, Univ. Paris-Est, Creteil, July 2017 (examiner)

G. Beslon :

Roman Goulard, Univ. Aix-Marseille, Marseille, November 2017 (reviewer)

Andrei Kucharavy, Univ. P & M Curie, Paris, December 2017 (examiner)

8.2.3.3. Search committees

H. Berry served in the following search pannels: assistant professor (INSA Lyon, France), full professor (UPMC, Paris, France), junior researcher (CR2 Inria, Rennes), senior researcher (DR2 Inria, Paris).

8.3. Popularization

The subspace clustering algorithms developed by the team in the context of the EvoEvo project have been included in a software package (EvoMove) enabling real-time monitoring and clustering of a dancer movements. In interaction with the "Desoblique" dance company (Lyon, France), we used this system to interact with the dancers by triggering sounds following the moves of he dancers. This system has been used in the context of the dance performance "Meute" in which three dancers were equipped with inertial measurement units connected to EvoMove (see 2). Meute has been played in public 8 times in the Auvergne-Rhône-Alpes region beween January and July 2017

Figure 2. The EvoMove system has been used in the public performance"Meute" (here in "La Rotonde", INSA Lyon in February 2017). Dancers: Claire Lurin, Jean Boulvert, Maxence D'Hauthuille. Sound: Jonas Abernot. Lights: Laurent Turpin. The EvoMove inertial measurement units are tied to the wrists of the dancers.

G. Beslon, together with Dominique Schneider (UGA, France) published an article entitled "Darwin, bit à bit . . . " in the blog "Binaire" on le-monde.fr (http://binaire.blog.lemonde.fr/2017/11/24/darwin-bit-a-bit/). This article describes the interdisciplinary view of evolution that the two authors are developing.

A. Denizot is member of association Demesures (demesures.jimdo.com). She organized and participation to scientific events: Geek Touch 2017, Pop Sciences 2017, Fete de la Science 2017 and interviewed researchers (https://www.youtube.com/watch?v=qoKAwRYI48Q).

E. Tannier gave a series of lectures (8h) on genetically modified organisms for Universite Populaire de Lyon, for a large audience and gave a talk for the "Tour de science" 2017, in Lyon, a popularization event, for a public of interdisciplinary students.

9. Bibliography

Major publications by the team in recent years

[1] P. BILLER, L. GUÉGUEN, C. KNIBBE, E. TANNIER. *Breaking Good: Accounting for Fragility of Genomic Regions in Rearrangement Distance Estimation*, in "Genome Biology and Evolution", 2016, vol. 8, n^{o} 5, pp. 1427-1439 [*DOI :* 10.1093/GBE/EVW083], https://hal.archives-ouvertes.fr/hal-01334923

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