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Activity Report 2018

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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A5.1.5. - Body-based interfaces
A5.7.2. - Music
A5.11.1. - Human activity analysis and recognition
A6.1.1. - Continuous Modeling (PDE, ODE)
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Other Research Topics and Application Domains:

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1. Team, Visitors, External Collaborators

Research Scientists

Hugues Berry [Inria, Senior Researcher, HDR]
Anton Crombach [Inria, Researcher, from Mar 2018]
Eric Tannier [Inria, Researcher, HDR]

Faculty Members

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

Post-Doctoral Fellow

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PhD Students

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Marie Fernandez [Inria, until Jun 2018]
Alexandre Foncelle [Inria, until Mar 2018]
Vincent Liard [INSA Lyon]

Technical staff

Nicolas Comte [Inria, until Sep 2018]

David Parsons [Inria, from Apr 2018]

Interns

Camille Camporelli [Inria, from May 2018 until Jun 2018]
Yvan Cluet [Inria, from May 2018 until Aug 2018]
Kerstin Eisenkolb [Inria, from May 2018 until Aug 2018]
Adrien Stadler [Inria, from Jun 2018 until Aug 2018]
Grégoire Bailly [INSA, from June 2018 to July 2018]

Administrative Assistants

Florence Maillard [Inria, from Feb 2018]
Gaelle Tworkowski [Inria, until Feb 2018]

External Collaborator

Hedi Soula [Univ Pierre et Marie Curie]

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, 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.

2.2. An organization into two tools and four main axes

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

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[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.

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* [34] 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: 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. [36]). 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).

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. These last years we did not make significant advances in this direction and we even removed this objective from last year's report. However the evolution of the team staff and projects allows us to give it back its central place. We now have the forces and ideas to progress. We have several short and middle term projects to integrate biochemical data and evolution. In particular we are analysing with an evolutionary perspective the 3D conformation of chromosomes, the regulatory landscape of genomes, the chromatin-associated proteins.

4. Application Domains

4.1. Domain 1

Applications concern Functional and Evolutionary Biology, plant, animal and human health. They are not detailed here because the project itself is oriented by its applications, so the description of applications is described along the project in the previous sections.

5. Highlights of the Year

5.1. Highlights of the Year

We had several remarkable publications in 2018, including 3 in the highest standard journals and 2 best paper awards.

Cui Y, Yang Y, Ni Z, Dong Y, Cai G, Foncelle A, Ma S, Sang K, Tang S, Li Y, Shen Y, Berry H, Wu S and Hu H (2018). Astroglial-Kir4.1 in Lateral Habenula Drives Neuronal Bursts to Mediate Depression. *Nature* 554:323-327 [15]

Davin AA, Tannier E, Williams TA, Boussau B, Daubin V, Szollosi GJ (2018) Gene transfers can date the tree of life, *Nature ecology and evolution*, vol. 2 pp.904-909. [16]

Berta Verd, Erik Clark, Karl R Wotton, Hilde Janssens, Eva Jiménez-Guri, Anton Crombach, Johannes Jaeger (2018) A damped oscillator imposes temporal order on posterior gap gene expression in Drosophila *PLoS biology* 16 (2), e2003174 [35]

5.1.1. Awards

BEST PAPERS AWARDS:

[28]
V. F. LIARD, D. P. PARSONS, J. ROUZAUD-CORNABAS, G. BESLON. *The Complexity Ratchet: Stronger than selection, weaker than robustness*, in "ALIFE 2018 - the 2018 conference on artificial Life", Tokyo, Japan, July 2018, pp. 1-8 [*DOI :* 10.1162/ISAL_A_00051], https://hal.archives-ouvertes.fr/hal-01882628

[26]
S. PEIGNIER, C. RIGOTTI, A. ROSSI, G. BESLON. *Weight-based search to find clusters around medians in subspaces*, in "SAC 2018 - ACM Symposium On Applied Computing", Pau, France, Proceedings of the 33rd ACM Symposium On Applied Computing, April 2018, pp. 1-10, https://hal.archives-ouvertes.fr/hal-01869974

6. New Software and Platforms

6.1. aevol

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.

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: Guillaume Beslon
- URL: http://www.aevol.fr/

6.2. 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: hal-01503766
- URL: http://pbil.univ-lyon1.fr/software/DeCoSTAR/

6.3. Evo2Sim

Evolution of Evolution Simulator
KEYWORDS: Bioinformatics - Biology - Evolution
FUNCTIONAL DESCRIPTION: In the context of the EvoEvo european project we developed an integrated model of microorganisms evolution. This model extends the evolutionary models developped in the team (Aevol and R-Aevol) by adding a metabolic level and an ecosystem level. It includes the genomic, genetic and metabolic levels.

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

6.4. 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

6.5. 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

6.6. 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/

6.7. 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 a 0.1 stable version

- Participants: Nicolas Comte, David Parsons, Eric Tannier and Benoît Morel
- Partner: Laboratoire de Biométrie et Biologie Evolutive (LBBE) - UMR CNRS 5558
- Contact: Eric Tannier

6.8. EvoMove

KEYWORDS: Music - Improvisation - Clustering - Evolution - Evolutionary Algorithms
FUNCTIONAL DESCRIPTION: EvoMove uses data from Inertial Measurement Units carried by dancers. It classifies these data in a non-supervised way to recognise "moves" and from these triggers music samples that accompany the dancers.

- Contact: Guillaume Beslon

7. New Results

7.1. Dopamine interacts with endocannabinoids to regulate spike timing dependent plasticity

participants: H. Berry, I. Prokin
Dopamine modulates striatal synaptic plasticity, a key substrate for action selection and procedural learning. Thus, characterizing the repertoire of activity-dependent plasticity in striatum and its dependence on dopamine is of crucial importance. In collaboration with L. Venance Lab (CIRB, Collège de France) we recently unraveled a striatal spike-timing-dependent long-term potentiation (tLTP) mediated by endocannabinoids (eCBs) and induced with few spikes (5-15). Whether this eCB-tLTP interacts with the dopaminergic system remains to be investigated. We found that eCB-tLTP is impaired in a rodent model of Parkinson's disease and rescued by L-DOPA. Dopamine controls eCB-tLTP via dopamine type-2 receptors (D2R) located presynaptically in cortical terminals. Dopamine-endocannabinoid interactions via D2R are required for the emergence of tLTP in response to few coincident pre-and post-synaptic spikes and control eCB-plasticity by modulating the long-term potentiation (LTP)/depression (LTD) thresholds. While usually considered as a depressing synaptic function, our results show that eCBs in the presence of dopamine constitute a versatile system underlying bidirectional plasticity implicated in basal ganglia pathophysiology. These results have been published in Nature Communications [23]

7.2. Estimating the robustness of spike timing dependent plasticity to timing jitter

participants: H. Berry, I. Prokin
In Hebbian plasticity, neural circuits adjust their synaptic weights depending on patterned firing. Spike-timing-dependent plasticity (STDP), a synaptic Hebbian learning rule, relies on the order and timing of the paired activities in pre- and postsynaptic neurons. Classically, in ex vivo experiments, STDP is assessed with deterministic (constant) spike timings and time intervals between successive pairings, thus exhibiting a regularity that differs from biological variability. Hence, STDP emergence from noisy inputs as occurring in in vivo-like firing remains unresolved. In collaboration with the laboratories of L. Venance (CIRB, Collège de France) and A. De Kerchove d'Exaerde (Univ. Libre Bruxelles), we used noisy STDP pairings where the spike timing and/or interval between pairings were jittered. We explored with electrophysiology and mathematical modeling, the impact of jitter on three forms of STDP at corticostriatal synapses: NMDAR-LTP, endocannabinoid-LTD and endocannabinoid-LTP. We found that NMDAR-LTP was highly fragile to jitter, whereas endocannabinoid-plasticity appeared more resistant. When the frequency or number of pairings was increased, NMDAR-LTP became more robust and could be expressed despite strong jittering. Our results identify endocannabinoid-plasticity as a robust form of STDP, whereas the sensitivity to jitter of NMDAR-LTP varies with activity frequency. This provides new insights into the mechanisms at play during the different phases of learning and memory and the emergence of Hebbian plasticity in in vivo-like activity. These results have been published in Scientific Reports [14]

7.3. A new method to monitor gap junctional comunication in astrocytes

participants: H. Berry
Intercellular communication through gap junction channels plays a key role in cellular homeostasis and in synchronizing physiological functions, a feature that is modified in number of pathological situations. In the brain, astrocytes are the cell population that expresses the highest amount of gap junction proteins, named connexins. Several techniques have been used to assess the level of gap junctional communication in astrocytes, but so far they remain very difficult to apply in adult brain tissue. Using specific loading of astrocytes with sulforhodamine 101, we adapted in collaboration with C. Giaume's laboratory (CIRB, Collège de France) the gap-FRAP (Fluorescence Recovery After Photobleaching) to acute hippocampal slices from 9 month-old adult mice. We show that gap junctional communication monitored in astrocytes with this technique was inhibited either by pharmacological treatment with a gap junctional blocker or in mice lacking the two main astroglial connexins, while a partial inhibition was measured when only one connexin was knocked-out. We validate this approach using a mathematical model of sulforhodamine 101 diffusion in an elementary astroglial network and a quantitative analysis of the exponential fits to the fluorescence recovery curves. Consequently, we consider that the adaptation of the gap-FRAP technique to acute brain slices from adult mice provides an easy going and valuable approach that allows overpassing this age-dependent obstacle and will facilitate the investigation of gap junctional communication in adult healthy or pathological brain. These results have been published in J. Neuroscience Methods [24].

7.4. Kir4.1 upregulation in astrocytes of the lateral habenula is involved in depression

participants: H. Berry, A. Foncelle
Enhanced bursting activity of neurons in the lateral habenula (LHb) is essential in driving depression-like behaviours, but the cause of this increase has been unknown. In collaboration with H. Hu's laboratory (Zhejiang University, China), using a high-throughput quantitative proteomic screen, we show that an astroglial potassium channel (Kir4.1) is upregulated in the LHb in rat models of depression. Kir4.1 in the LHb shows a distinct pattern of expression on astrocytic membrane processes that wrap tightly around the neuronal soma. Electrophysiology and modelling data show that the level of Kir4.1 on astrocytes tightly regulates the degree of membrane hyperpolarization and the amount of bursting activity of LHb neurons. Astrocyte-specific gain and loss of Kir4.1 in the LHb bidirectionally regulates neuronal bursting and depression-like symptoms. Together, these results show that a glia–neuron interaction at the perisomatic space of LHb is involved in setting the neuronal firing mode in models of a major psychiatric disease. Kir4.1 in the LHb might have potential as a target for treating clinical depression. These results have been published in Nature [15] and were commented in the "News and views" section of the journal: Howe WM and Kenny PJ (2018). Burst firing sets the stage for depression.

7.5. The evolutionary complexity ratchet

participants: G Beslon, V Liard, D Parsons, Jonathan Rouzaud-Cornabas
Using the *in silico* experimental evolution platform Aevol, we evolved populations of digital organisms in conditions where a simple functional structure is best.

Strikingly, we observed that in a large fraction of the simulations, organisms evolved a complex functional structure and that their complexity increased during evolution despite being a lot less fit than simple organisms in other populations. However, when submitted to a harsh mutational pressure, we observed that a significant proportion of complex individuals ended up with a simple functional structure.

Our results suggest the existence of a complexity ratchet that is powered by epistasis and that cannot be beaten by selection. They also show that this ratchet can be overthrown by robustness because of the strong constraints it imposes on the coding capacity of the genome.

This result has been published in the International conference ALife in Tokyo (July 2018) where it received the best paper award [28]

7.6. Weight-based search to find clusters around medians in subspaces

participants: C Rigotti, G Beslon
There exist several clustering paradigms, leading to different techniques that are complementary in the analyst toolbox, each having its own merits and interests. Among these techniques, the K-medians approach is recognized as being robust to noise and outliers, and is an important optimization task with many different applications (e.g., facility location). In the context of subspace clustering, several paradigms have been investigated (e.g., centroid-based, cell-based), while the median-based approach has received less attention. Moreover, using standard subspace clustering outputs (e.g., centroids, medoids) there is no straightforward procedure to compute the cluster membership that optimizes the dispersion around medians. We advocated for the use of median-based subspace clustering as a complementary tool. Indeed, we showed that such an approach exhibits satisfactory quality clusters when compared to well-established paradigms, while medians have still their own interests depending on the user application (robustness to noise/outliers and location optimality). We showed that a weight-based hill climbing algorithm using a stochastic local exploration step can be sufficient to produce the clusters.

This research has been published in the proceedings of the ACM-SAC conference (Pau, March 2018) where it received the best paper award [26].

7.7. The surprising creativity of digital evolution

participants: C Knibbe, G Beslon
Natural evolution is a creative fount of complex adaptations that often surprise the scientists who discover them. However, the creativity of evolution is not limited to the natural world; artificial organisms evolving in computational environments are also able to elicit a similar degree of surprise and wonder from the researchers studying them. The process of evolution has proven to be an algorithmic process that transcends the substrate to which it is applied. Indeed, most digital evolution researchers can relate anecdotes highlighting how common it is for their algorithms to creatively subvert their expectations or intentions, expose unrecognized bugs in their code, produce unexpectedly potent adaptations, or engage in behaviors and outcomes uncannily convergent with ones found in nature. Such stories routinely reveal surprise and creativity by evolution in these digital worlds, but they rarely fit into the standard scientific narrative and are thus often treated as obstacles to be overcome rather than results that warrant publication in their own right. Bugs are fixed, experiments are refocused, one-off surprises are collapsed 1into a single data point. The stories themselves are traded among researchers through oral tradition, but that mode of information transmission is lossy, inefficient and error-prone. Moreover, the very fact that these stories tend to be confined to practitioners means that many natural scientists do not recognize how lifelike digital organisms are and how natural their evolution can be. We actively participated to a crowd-sourced research in which evolutionary computation researchers providing first-hand reports of such cases, and thus functions as a written, fact-checked collection of entertaining and important stories.

7.8. HPC support for Aevol

participants: Jonathan Rouzaud-Cornabas, David Parsons, Guillaume Beslon
During the year, we had three internships that focus around HPC. The three of them were founded through the Federation Informatique de Lyon (FIL FR2000) and were common between the Inria Beagle team (LIRIS) and the Inria Avalon team (LIP).

The first one (Lukas Schmidt - M2) was working on component-based software engineering and HPC with Aevol as use-case. The goal was to see if and how the COMET [1] task-based parallel component model (and its implementation Halley) can fit the parallelization requirement of Aevol. An extension of the model was proposed to support hierarchical data structure and a prototype implementation has been done. In the future, we will work on the formalization of the extension and an efficient implementation on it. The goal is to ease the development and replacement of core components of the Aevol software (e.g. be able to easily replace the 2-base DNA code by a 4-base one).

The second internship (Valentin Huguet - M2) was evolving around Aevol and how to ease the distribution of the computation. To do so, an extension of the DIET software [2] was proposed and a fully functional webboard was implemented. We have a first prototype that support the execution of a large set of distributed computing resources and the control of its execution through a webboard. Moreover, basic visualization of the simulation results can be done through the same webboard. A following internship (starting Feb. 2019) will continue the work. The goal is to support workflow composed of multiple execution of Aevol and its pre/post treatments to automate the execution of large campaign that are done manually at the moment.

The goal of the third internship (Nathan Payre - L3) was to propose a prototype of a bitset for Aevol and its efficient implementation on modern hardware (Intel Skylake and Intel Xeon Phi). Indeed, the current implementation of Aevol DNA (2 base) uses a char type (8bit) to store a bit value (0 or 1). Accordingly, working at the bitset level could save up to 8 time memory space and speed up the computation (as Aevol is memory bound, reducing the memory transfer by 8 could dramatically speed up the global execution). Moreover, modern processors have vectorization extension that are perfectly fitting our requirements (we could process 512bit per cycle with AVX512 extension). During the internship, the bitset and the different operation we use in Aevol model (e.g. Hamming distance) were formalized and implemented. The preliminary results show a speed up of 140x on these operations. A full evaluation on the impact of the performance of Aevol and how different modern processor react to such implementation will be done in the future.

Last, a part of the Beagle team (Guillaume Beslon, David Parsons, Jonathan Rouzaud-Cornabas) were selected and participate to the EuroHack 2018 GPU Programming Hackathon in Lugano (Switzerland) organized by CSCS (Swiss National Supercomputing Centre) and NVidia. The goal was to port Aevol to modern GPU and thus to the CUDA programming language. In order to be able to do so in a week, we propose a mini-application (mini-Aevol) of Aevol [3] that is representative of the computation and memory pattern of the full Aevol. This prototype will be reuse in our collaboration with team focusing on HPC research. At the end of the week, we had a full implementation of mini-Aevol on GPU. New core algorithms of Aevol have been proposed to support massively parallel processors such as GPU. The prototype will be transfer to the full Aevol code in the future to be able to support GPU. It is worth noting that this mini-apps is also used in teaching context (INSA Lyon - Computer Science M2) to learn how to parallelize and optimize code with OpenMP and CUDA.

[1] Olivier Aumage, Julien Bigot, Hélène Coullon, Christian Pérez, Jérôme Richard. Combining Both a Component Model and a Task-based Model for HPC Applications: a Feasibility Study on GYSELA. 17th IEEE/ACM International Symposium on Cluster, Cloud and Grid Computing (CCGrid)., May 2017, Madrid, Spain.

[2] https://graal.ens-lyon.fr/diet/

[3] https://gitlab.inria.fr/rouzaudc/mini-aevol

[4] https://github.com/fomics/EuroHack18/blob/master/final/beagle_aevol.pdf

7.9. Exploring the evolution of chromatin-associated proteins

participants: A Crombach

Eukaryotic gene regulation depends strongly on chromatin state. High-throughput studies in the fruit fly Drosophila melanogaster have shown that instead of the canonical two types of chromatin, hetero- and euchromatin, one can subdivide chromatin into five states. These states are each characterized by a unique combination of chromatin-associated proteins (CAPs). We were interested in the evolution of CAPs and studied them by means of phylogenomic methods. We found three evolutionary trends. One type of heterochomatin,

called GREEN, is specific to centromeres and some of its proteins are found to be under a Red Queen type evolution, where they rapidly accumulate amino acid changes. The second type of heterochromatin, BLUE, is tightly linked to Polycomb Group proteins. These proteins are important regulators in developmental processes and our findings confirm their origin in multicellular organisms. Finally, the two euchromatic types, YELLOW and RED, have strong lineage-specific characteristics. Their origins seem to date back to the start of eukaryotic life.

7.10. Evolutionary interplay of genome content and 3D spatial structure

participants: A Crombach
Genomes are hierarchically folded, which involves transposable elements (TEs). The most prominently observed folding domains are conserved between cell types and across species, yet their building blocks, TEs, are powerful mutagens. This paradox raises the question why we observe evolutionary stable folding domains. Using in silico evolution of polymer genomes, the aim is to elucidate the interplay between mutations and folding structure. We have built the software and are in the process of generating data. First results indicate that due to accessibility in 3D (some parts of the genome are more tightly compacted than others), a positive feedback is created between (1) where mutations happen, (2) how genome content is changed, and (3) how genomes fold in 3D.

7.11. Network inference for mammalian cortex development

participants: A Crombach
The mammalian cortex divides into two major regions, neocortex (NCx) and the structurally simpler allocortex. Whereas NCx is well-characterized, the allocortex is much less studied. Its best known region is the olfactory (piriform, PCx) cortex. The regions have a laminar structure, with distinct neuronal cell types in each of the layers: NCx has 6 layers, PCx has 3. The differentiation of precursor cells into various neuronal cell types determines to which layer these cells will migrate. This process is mostly studied in NCx and depends on the activity of 10–20 developmental genes. In PCx the same genes are used, yet they appear in other combinations and may indicate diverse target layers, sometimes violating rules-of-thumb derived from NCx. Current understanding is rather incomplete with respect to how cortical neurons are specified. We propose that, despite apparent contradictions, a single gene network can explain the development of distinct cortical regions.

In collaboration with Dr. A. Fleischmann at Brown University (USA), we are measuring the expression of genes involved in neurodevelopment at cellular resolution using light-sheet microscopy. These data will form the basis for the inference of a regulatory network describing neuronal differentiation in NCx and PCx. Inference is done by fitting mathematical models of gene regulation to the data using global optimization methods. Currently, we are processing the image data. Moreover, single cell RNA sequencing will allow the study of the temporal dynamics of the expression of these genes and many others. We are completing an in-depth statistical analysis of the resulting genome-wide expression data.

7.12. Gene transfers can date the tree of life

participants: E 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. Here, we show that patterns of lateral gene transfer deduced from an analysis of modern genomes encode a novel and abundant source of information about the temporal coexistence of lineages throughout the history of life. We use state-of-the-art species tree-aware 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 Eukarya. We present the order of speciations according to lateral gene transfer data calibrated to geological time for three datasets comprising 40 genomes for Cyanobacteria, 60 genomes for Archaea and 60 genomes for Fungi. An inspection of discrepancies between transfers and clocks and a comparison with mammalian fossils show that gene transfer in microbes is potentially as informative for dating the tree of life as the geological record in macroorganisms. [16]

7.13. The devil in the details of evolvability

Participants: E Tannier, P Biller, V Liard, G Beslon

The theory of Evolvability consists in studying the evolution of living organisms as a computational learning process. It defines the possibilities of a population under Darwinian selection, to evolve in a certain direction, in a reasonable amount of time. While its robustness to certain parameters has been theoretically assessed, this theory has not been experimentally tested. We use a standard *in silico* experimental evolution tool to compare some predictions of the theory and the behavior of digital populations designed to resemble biological organisms. We obtain that the evolvability of monotone conjunctions under the uniform distribution of environmental conditions, presented as a major result of the theory, is not reproduced by the experiments. We show that this is due to different mutation algorithms, by a proof of exponential expectation time to target under theoretical conditions closer to the experiments. We examine into detail the choices of mutation algorithms. In the Evolvability theory it is any Turing machine, while much more restricted in the experimental design. This definition allows a wider range of conditions and in a certain way is conform to biological reality, where mutators evolve and can be selected. However it also allows, if it is misused, for the inclusion of oracles that are incompatible with the principles of a Darwinian evolution. Unfortunately these oracles are extensively used in the current evolvability proofs.

8. Partnerships and Cooperations

8.1. Regional Initiatives

- Lipuscale (2018-2019): Hybrid simulation of lipid digestion and absorption, a two-year project funded by the Rhône-Alpes Institute for Complex Systems (IXXI). With Marie-Caroline Michalski (CarMeN, INSERM U1060, INRA U1397) and Samuel Bernard (Institut Camille Jordan and Inria Dracula team). Participant: Carole Knibbe.

8.2. National Initiatives

8.2.1. ANR

Dopaciumcity (2014-2018): 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.

Storiz (2018-2020): Horizontal transfers as documents from extinct or unknown species. Call ANR JCJC 2018. Leaded by Damien de Vienne (LBBE, Lyon) Participant: Eric Tannier

LncEvoSys (2017-2019): An evolutionary systems approach to understand long non-coding RNA functionality, Call ANR JCJC 2017. Leaded by Anamaria Necsulea (LBBE, Lyon). Participant: Eric Tannier

8.2.2. Inria

ADT Phylophile (2016-2018). 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.

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).

8.3. International Initiatives

8.3.1. Inria International Partners

8.3.1.1. Informal International Partners

- Anton Crombach collaborates with Dr. Alexander Fleischmann, who moved this year from CIRB, College de France (Paris), to Brown University, USA.
- Carole Knibbe collaborates with Kirsty Spalding and Peter Arner from Karolinska University Hospital in Stockholm, Sweden.
- Eric Tannier collaborates with Gergerly Szollosi, Eotvos University, Budapest, Cedric Chauve, SFU, Vancouver, Igor Sharakov, from Virginia Tech, Rob Waterhous, Univ Lausanne, Tom Williams, Univ Bristol, ...
- Eric Tannier has leaded the publication of a collaborative paper on a phylogenetic format co-signed by 27 researchers from 10 nationalities.

8.3.2. Participation in Other International Programs

Program: CNRS-Royal society

Project title: Modeling lateral gene transfer on a new bacterial tree

Duration: 2018

Coordinator: Bastien Boussau

Other partners: Eric Tannier (Beagle), LBBE (Lyon), Eotvos University (Budapest), University of Bristol (UK)

Abstract: Bacteria play a major role in human health and in the functioning of all ecosystems. Most of the genomes available in public databases come from Bacteria. However, we understand little of their evolution: both their phylogeny and their timeline of diversification are highly uncertain. This is due in great part to the difficulty of reconstructing events that happened billions of years ago, and also to the fact that individual genes are often transferred across species and therefore have a history that differs from that of the species that contain them. Recently we have proposed novel methods for dealing with the very problems that make reconstructing the bacterial phylogeny challenging. This proposal aims to support a joint project that will reconstruct and date the bacterial phylogeny by combining novel methods (Boussau, Lyon) with existing skills in microbial phylogenetics, genomics and evolution (Williams, Bristol).

8.4. International Research Visitors

8.4.1. Visits to International Teams

Audrey Denizot stayed 4 months in Okinawa, OIST University, Erik de Schutter's team, from june to october 2018

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific Events Organisation

9.1.1.1. General Chair, Scientific Chair

- Guillaume Beslon co-organized a symposium on “in vivo, in vitro, in silico experimental evolution” during the World Evolution conference. Montpellier, August 2018.

9.1.1.2. Member of the Organizing Committees

- Hugues Berry was a member of the Local Organizing committee of MedInfo2019 (https://medinfo-lyon.org/)
- Eric Tannier was a member of the local Organizing committee of ICGT 2018 (https://projet.liris.cnrs.fr/~icgt2018/)
- Eric Tannier was a member of the local Organizing committee of RECOMB 2018 (http://recomb2018.fr/)
- Anton Crombach is a member of the organizing and scientific committee of the "Advanced Lecture Course on Computational Systems Biology", in Aussois, March 2019. Also,
- Anton Crombach is a member of the organizing committee of "Mathematical Models in Ecology and Evolution", that will take place in Lyon, July 2019.
- Guillaume Beslon served as a member of the Organizing Committee of ICSB (International Conference on Systems Biology), Lyon, October 2018.

9.1.2. Scientific Events Selection

9.1.2.1. Member of the Conference Program Committees

- Christophe Rigotti was a member of the program committee of the 34rd ACM Symposium On Applied Computing.
- Eric Tannier was a member of the program committee of RECOMB Comparative Genomics
- Eric Tannier was a member of the program committee of ISMB

9.1.2.2. Reviewer

- Eric Tannier reviewed 3 conference articles for Recomb-CG, 3 conference articles for ISMB

9.1.3. Journal

9.1.3.1. Member of the Editorial Boards

- H. Berry: Associate Editor for PLoS Computational Biology
- Eric Tannier : Recommender for Peer Community in Evolutionary Biology
- Eric Tannier : guest editor for a special issue of Discrete Mathematics and Theoretical Computer Science
- Carole Knibbe and Guillaume Beslon are guest editors for a special issue of the Artificial Life journal, in preparation.

9.1.3.2. Reviewer - Reviewing Activities

- Anton Crombach has reviewed two articles for Nature Communications and a book proposal for Springer-Verlag.
- Eric Tannier has reviewed articles fo Bioinformatics, Bulletin of mathematical biology, PeerJ, Genome biology and evolution, a book chapter for a book on genome evolution,

9.1.4. Invited Talks

- H. Berry - May 2018: Stochastic simulations of calcium signaling in fine astrocytic processes: spatial properties, invited talk at the workshop "Modelisation Stochastique en Biologie", Tours
- H. Berry - Nov 2018: "Modelling the signaling pathways of neuronal plasticity", invited talk at the 10ème journée ITMO Technologies pour la Santé, Strasbourg.
- E Tannier, December 2018: "Gene transfers can date the tree of life" Lille
- Eric Tannier, August 2018: "Treerecs: a fast and easy to use phylogenetic reconciliation software", for the "Software in phylogenomics" workshop, satellite of Evolution 2018, in Montpellier.
- Eric Tannier, February 2018: "Comparative Genomics on artificial life", ALPHY 2018, Montpellier
- Guillaume Beslon gave an invited Keynote at the 10th Symposium on Seach-Based Software Engineering (Montpellier, September 2018)
- Guillaume Beslon gave an invited Keynote at the First International TRANSIT workshop on Cross-disciplinary Research (TWCR 2018). York (UK), April 2018.
- Guillaume Beslon gave an invited conference for the Systems Biology research group, Université Pierre et Marie Curie, Paris, May 2018.

9.1.5. Scientific Expertise

- Guillaume Beslon was a member of the ANR CES45 panel (Mathématique, informatique, automatique, traitement du signal pour répondre aux défis de la biologie et de la santé)

9.1.6. Research and Teaching Administration

- Hugues Berry is Inria's Deputy Scientific Director for the field "Digital Health, Biology and Earth" and has been:
  - Inria's representative on the board of Aviesan
  - Conseiller Scientifique, ITMO Technologies pour la sante
  - Member of the Working Group for the prefiguration of the French Health Data Hub
  - Member of the Comité d'Orientation Scientifique et Stratégique, Institut Français de Bioinformatique (IFB)
  - Memnber of the Comité Directeur of GIS IBISA
  - Member of the Comité des Tutelles for INBS France Life Imaging, FranceBioImaging
  - Member of the steering committee for the Action de Recherche Prospective "Biologie Predictive" of INRA
  - Member of the "Commission des thèses" of the Doctoral School "Info-Maths" (ED 512)
  - Member of the Steering Commitee of GdR IMaBIO (Imagerie et Microscopie pour la BIOlogie, http://imabio-cnrs.fr)
- Eric Tannier is
  - Member of the committee for Open Science, Ministry of Research
  - Member of the Administration Council of Inria
  - Member of the scientific Committee of the Ethics Platform of Université de Lyon
  - Member and founder of the scientific committee of the GTGC (National Working group on Comparative Genomics)
- Guillaume Beslon is a member of the IRD Commission Scientifique Sectorielle 5 (CSS5, Science des données et des modèles). He served as a president of the hiring committee for a position of Chargé de Recherche number 12.
- Christophe Rigotti is an elected member of Insa Scientific board (Conseil Scientifique)
- Carole Knibbe is
  - Member of the Doctoral Studies Committee of Inria Grenoble-Rhone Alpes

– Head of the Bioinformatics and Modeling master program of INSA-Lyon Since Sept 2017

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Master : Audrey Denizot, enzymology and cellular biology, 64h, 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, Bioinformatics, 12h INSA Lyon

Master: Eric Tannier, Bioinformatics, 12h M2 UCBL Lyon

Master: Eric Tannier, Ethique de la recherche, 2h, Lille

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

License: Jonathan Rouzaud-Cornabas, Object-Oriented Programming, 64h, L3, Computer Science Department, INSA de Lyon

Master: Jonathan Rouzaud-Cornabas, Advanced Operating System Programming, 64h, M1, Computer Science Department, INSA de Lyon

Master: Jonathan Rouzaud-Cornabas, Graphical User Interfaces, 64h, M1, Computer Science Department, INSA de Lyon

Master: Jonathan Rouzaud-Cornabas, High Performance Computing, 84h, M2, Computer Science Department, INSA de Lyon

Master: Jonathan Rouzaud-Cornabas, High Performance Computing, 84h, M2, Bioinformatics and Modeling Department, INSA de Lyon

CNRS GDR Calcul: Jonathan Rouzaud-Cornabas, High Performance Computing, 6h, CNRS

E-learning

Eric Tannier was in the pedagogical team of a Mooc "Ethique de la Recherche", for Ph-D students in France. 4000 participants. He participated to 2 introductory videos (7min).

9.2.2. Supervision

PhD in progress : 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

PhD : Tuan Nguyen, Handling data quality in extraction and selection of evolutions from displacement field time series obtained by satellite imagery, at LISTIC laboratory of University Grenoble Alpes co-supervised by C. Rigotti, defended 10 October 2018.

PhD in progress : Audrey Denizot Simulating calcium signaling in fine astrocytic processes, september 2016, Hugues Berry

PhD in progress : Theo Tricou, Lateral Gene Transfer as a document from extinct and unknown species, 2018-2020 Eric Tannier (50%)

PhD in progress : Alexandre Laverré, cross-influcence between gene regulatory landscape and 1D-3D genome organization 2018-2020, Eric Tannier (40%)

M2 student Alexandre Laverré (Eric Tannier)

M1 student Adrien Stadler (Hugues Berry)

M2 student Elisa Denier (Eric Tannier)

M1 student Yvan Cluet (Anton Crombach)

M1 student Damien Agopian (Carole Knibbe)

9.2.3. Juries

- Hugues Berry- HDR: Samuel Bottani, Univ Denis Diderot, Paris, Nov 2018 (reviewer)
- Hugues Berry- PhD: Yi Cui, Univ Descartes, Paris, Dec 2018 (reviewer)
- Hugues Berry- PhD: Franziska Oschmann, TU Berlin, Oct 2018 (reviewer)
- Hugues Berry- search pannel: two assistant professor positions (Univ. Pierre et Marie Curie, INSA Lyon)
- Anton Crombach - tutor on the thesis committee of Elise Parey, IBENS, ENS Paris.
- Guillaume Beslon served as a member of the defence committee for the HDR of Alexandre Muzy. Nice, October 2018.
- Jonathan Rouzaud-Cornabas - Associate Professor Recruitment - Université de Toulouse

9.3. Popularization

9.3.1. Interventions

- Eric Tannier gave a series of four lectures at the Université Populaire de Lyon, on "science and democracy".
- Eric Tannier participated to a round table on scientific communication for the BMIC days, november 2018.
- Audrey Denizot has participated in the organization and animation of activities for children about research during the event "Dans la blouse d'un chercheur" in ENS de Lyon. More specifically, she worked on a project aiming at explaining to children what microbes are, where they are and if/when you should worry about them and what is immunodeficiency. She made a small movie about it.
- Audrey Denizot is a member of a public outreach association : DéMesures. She is in charge of collaborations with external entities, including laboratories, museums and artists collectives. Website: https://demesures.jimdo.com/ Facebook: https://www.facebook.com/DMesures/ Twitter: https://twitter.com/DMesures Radio podcasts: https://demesures.jimdo.com/radio-1/radio-brume/ Interviews are available on our YouTube channel: https://www.youtube.com/channel/UCIn3CucWk1mLgbzE0noO2Iw
- National events: Audrey Denizot organized several events including Fête de la Science 2017 and 2018 and A Nous de Voir 2018, as well as conducted projects such as radio podcasts on science/society topics, interviews of researchers, projects mixing Science and Art.

9.3.2. Creation of media or tools for science outreach

- In collaboration with Sylvain Charlat (LBBE, Lyon), we developed game to present the effect of random mutations on evolution to young children. The “GreenMice” game has been presented to the general public in the “Maison des Mathématiques et de l’Informatique” during the exhibition “Comme par hasard”.

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Major publications by the team in recent years

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