IN PARTNERSHIP WITH:
CNRS

Institut national des sciences appliquées de Lyon

Université Claude Bernard (Lyon 1)

Activity Report 2016

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

Table of contents

Project-Team BEAGLE

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

Keywords:

Computer Science and Digital Science:

3.3.2. - Data mining
5.1.5. - Body-based interfaces
5.7.2. - Music
5.11.1. - Human activity analysis and recognition
6.1.1. - Continuous Modeling (PDE, ODE)
6.1.3. - Discrete Modeling (multi-agent, people centered)
6.1.4. - Multiscale modeling
6.2.7. - High performance computing
7.2. - Discrete mathematics, combinatorics

Other Research Topics and Application Domains:

1. - Life sciences
1.1.2. - Molecular biology
1.1.3. - Cellular biology
1.1.8. - Evolutionnary biology
1.1.9. - Bioinformatics
1.1.11. - Systems biology
1.3.1. - Understanding and simulation of the brain and the nervous system
9.2.1. - Music, sound
9.2.4. - Theater

1. Members

Research Scientists

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

Faculty Members

Guillaume Beslon [Team leader, INSA Lyon, Professor, HDR]
Carole Knibbe [Univ. Lyon I, Associate professor]
Christophe Rigotti [INSA Lyon, Associate professor, HDR]
Jonathan Rouzaud-Cornabas [INSA Lyon, Associate professor]
Hedi Soula [INSA Lyon, Associate professor, HDR]

Engineers

Jonas Abernot [Inria, from Feb 2016]
Nicolas Comte [Inria, from Oct 2016]
Vincent Liard [Inria, Until Sept 2016]

PhD Students

Audrey Denizot [INSA Lyon, from Oct 2016]
Wandrille Duchemin [Univ. Lyon I]
Marie Fernandez [Région Auvergne Rhône-Alpes]

Alexandre Foncelle [Inria]
Vincent Liard [INSA Lyon, from Oct 2016]
Alvaro Mateos Gonzalez [ENS Lyon]
Sergio Peignier [Inria]
Ilya Prokin [Inria]
Charles Rocabert [Inria, granted by FP7 EVOEVO project]
Yoram Vadée Le Brun [Min. de l'Education Nationale]

Post-Doctoral Fellows

Maurizio de Pittà [FP7 MC IOF Post-doctoral fellow]
Priscila Do Nascimento Biller [Inria, from Nov 2016]

Administrative Assistant

Caroline Lothe [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 is based on an interdisciplinary scientific strategy: we are developing computer science formalisms and software for complex system modeling in synergy with multidisciplinary cooperations in the area of life sciences. Using computational approaches we study abstractions of biological systems and processes in order to unravel the organizational principles of cellular systems. More precisely, the scientific activity of the BEAGLE group focuses on two different topics. Both topics are strongly complementary. Indeed, on the short time scales, biological systems are constrained by the physical nature of their substrate but, on long time scales, they are also constrained by their evolutionary history. Thus, studying both time scales and both constraints – including their interactions – gives us a global viewpoint on the roots of biological organization.

Computational Cell Biology We develop models of the spatio-temporal dynamics of cells and their molecular components. More precisely, we study the complex interplay between the reaction and the diffusion processes when the medium is not homogeneous or when the number of molecules is too low to account for a perfect mixing hypothesis. We particularly focus on the consequences on the signaling networks and on the stochasticity of transcription. In this domain, we always try to mix up modeling and "wet" experimental approaches by developing close collaborations with experimental biologists.

Models of Genome Evolution To better understand the cellular structures (genome organization, transcription networks or signaling cascades) we propose to study their historical – evolutionary – origin. Individual-based evolutionary models (*in silico experimental evolution*) allow us to study how evolution leads to some specific structures shaped by the needs of robustness, variability or evolvability, depending on some specific conditions (e.g., large vs. small efficient population sizes, high vs. low

[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.

mutation rates, stable vs. unstable environments). Models can also be used for predictive purposes on real data: we reconstruct the evolutionary events that have shaped the extant real genomes, including small substitutions as well as large genome reorganizations. By comparing the reconstructed historical events and the laws inferred from artificial experiments, we can explain some patterns of today's organisms and biodiversity.

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* [57] 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 sensibilities 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 modelisation and simulation of cellular processes. More specifically, we focus on two specific processes that govern cell dynamics and behavior: Evolution and Biophysics. This leads to two main topics: computational cell biology and models for genome evolution.

3.2. Computational Cell Biology

BEAGLE contributes computational models and simulations to the study of cell signaling in prokaryotic and eukaryotic cells, with a special focus on the dynamics of cell signaling both in time and in space. Importantly, our objective here is not so much to produce innovative computer methodologies, but rather to improve our knowledge of the field of cell biology by means of computer methodologies.

This objective is not accessible without a thorough immersion in experimental cell biology. Hence, one specificity of BEAGLE is to be closely associated inside each research project with experimental biology groups. For instance, all the current PhD students implicated in the research projects below have strong interactions with experimenters, most of them conducting experiments themselves in our collaborators' labs. In such a case, the supervision of their PhD is systematically shared between an experimentalist and a theoretician (modeler/computer scientist).

Standard modeling works in cell biochemistry are usually based on mean-field equations, most often referred to as "laws of mass-action". Yet, the derivation of these laws is based on strict assumptions. In particular, the reaction medium must be dilute, perfectly-mixed, three-dimensional and spatially homogeneous and the resulting kinetics are purely deterministic. Many of these assumptions are obviously violated in cells. As already stressed out before, the external membrane or the interior of eukaryotic as well as prokaryotic cells evidence spatial organization at several length scales, so that they must be considered as non-homogeneous media. Moreover, in many case, the small number of molecule copies present in the cell violates the condition for perfect mixing, and more generally, the "law of large numbers" supporting mean-field equations.

When the laws-of-mass-action are invalidated, individual-based models (IBM) appear as the best modeling alternative to evaluate the impact of these specific cellular conditions on the spatial and temporal dynamics of the signaling networks. We develop Individual-Based Models to evaluate the fundamental impact of non-homogeneous space conditions on biochemical diffusion and reaction. More specifically, we focus on the effects of two major sources of non-homogeneity within cells: macromolecular crowding and non-homogeneous diffusion. Macromolecular crowding provides obstacles to the diffusive movement of the signaling molecules, which may in turn have a strong impact on biochemical reactions [45]. In this perspective, we use IBM to renew the interpretation of the experimental literature on this aspect, in particular in the light of the available evidence for anomalous subdiffusion in living cells. Another pertinent source of non-homogeneity is the presence of lipid rafts and/or caveolae in eukaryotic cell membranes that locally alter diffusion. We showed several properties of these diffusion gradients on cells membranes. In addition, combining IBMs and cell biology experiments, we investigate the spatial organization of membrane receptors in plasmic membranes and the impact of these spatial features on the initiation of the signaling networks [49]. More recently, we started to develop IBMs to propose experimentally-verifiable tests able to distinguish between hindered diffusion due to obstacles (macromolecular crowding) and non-homogeneous diffusion (lipid rafts) in experimental data.

The last aspect we tackle concerns the stochasticity of gene expression. Indeed, the stochastic nature of gene expression at the single cell level is now a well established fact [55]. Most modeling works try to explain this stochasticity through the small number of copies of the implicated molecules (transcription factors, in particular). In collaboration with the experimental cell biology group led by Olivier Gandrillon at the Centre de Génétique et de Physiologie Moléculaire et Cellulaire (CGPhyMC, UMR CNRS 5534), Lyon, we study how stochastic gene expression in eukaryotic cells is linked to the physical properties of the cellular medium (e.g., nature of diffusion in the nucleoplasm, promoter accessibility to various molecules, crowding). We have already developed a computer model whose analysis suggests that factors such as chromatin remodeling dynamics have to be accounted for [51]. Other works introduce spatial dimensions in the model, in particular to estimate the role of space in complex (protein+ DNA) formation. Such models should yield useful insights into the sources of stochasticity that are currently not explained by obvious causes (e.g. small copy numbers).

3.3. Models of genome evolution

Classical artificial evolution frameworks lack the basic structure of biological genome (i.e. a double-strand sequence supporting variable size genes separated by variable size intergenic sequences). Yet, if one wants to study how a mutation-selection process is likely (or not) to result in particular biological structures, it is mandatory that the effect of mutation modifies this structure in a realistic way. We have developed an artificial chemistry based on a mathematical formulation of proteins and of the phenotypic traits. In our framework, the digital genome has a structure similar to prokaryotic genomes and a non-trivial genotype-phenotype map. It is a double-stranded genome on which genes are identified using promoter-terminator- like and start-stop-like signal sequences. Each gene is transcribed and translated into an elementary mathematical element (a "protein") and these elements - whatever their number - are combined to compute the phenotype of the organism. The Aevol (Artificial EVOLution) model is based on this framework and is thus able to represent genomes with variable length, gene number and order, and with a variable amount of non-coding sequences (for a complete description of the model, see [63]).

As a consequence, this model can be used to study how evolutionary pressures like the ones for robustness or evolvability can shape genome structure [64], [61], [62], [71]. Indeed, using this model, we have shown that genome compactness is strongly influenced by indirect selective pressures for robustness and evolvability. By genome compactness, we mean several structural features of genome structure, like gene number, amount of non functional DNA, presence or absence of overlapping genes, presence or absence of operons [64], [61], [72]. More precisely, we have shown that the genome evolves towards a compact structure if the rate of spontaneous mutations and rearrangements is high. As far as gene number is concerned, this effect was known as an error-threshold effect [54]. However, the effect we observed on the amount of non functional DNA was unexpected. We have shown that it can only be understood if rearrangements are taken into account: by promoting large duplications or deletions, non functional DNA can be mutagenic for the genes it surrounds.

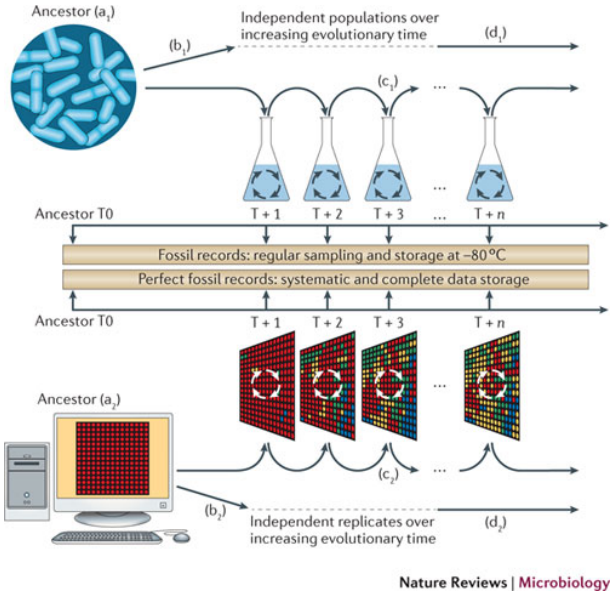

Figure 1. Parallel between experimental evolution and artificial evolution

We have extended this framework to include genetic regulation (R-Aevol variant of the model). We are now able to study how these pressures also shape the structure and size of the genetic network in our virtual organisms [47], [46], [48],[29]. Using R-Aevol we have been able to show that (i) the model qualitatively reproduces known scaling properties in the gene content of prokaryotic genomes and that (ii) these laws are not due to differences in lifestyles but to differences in the spontaneous rates of mutations and rearrangements [46]. Our approach consists in addressing unsolved questions on Darwinian evolution by designing controlled and repeated evolutionary experiments, either to test the various evolutionary scenarios found in the literature or to propose new ones. Our experience is that "thought experiments" are often misleading: because evolution is a complex process involving long-term and indirect effects (like the indirect selection of robustness and evolvability), it is hard to correctly predict the effect of a factor by mere thinking. The type of models we develop are particularly well suited to provide control experiments or test of null hypotheses for specific evolutionary scenarios. We often find that the scenarios commonly found in the literature may not be necessary, after all, to explain the evolutionary origin of a specific biological feature. No selective cost to genome size was needed to explain the evolution of genome compactness [64], and no difference in lifestyles and environment was needed to explain the complexity of the gene regulatory network [46]. When we unravel such phenomena in the individual-based simulations, we try to build "simpler" mathematical models (using for instance population genetics-like frameworks) to determine the minimal set of ingredients required to produce the effect. Both approaches are complementary: the individual-based model is a more natural tool to interact with biologists, while the mathematical models contain fewer parameters and fewer ad-hoc hypotheses about the cellular chemistry.

At this time, simulating the evolution of large genomes during hundreds of thousands of generation with the Aevol software can take several weeks or even months. It is worse with R-aevol, where we not only simulate mutations and selection at the evolutionary timescale, but also simulate the lifetime of the individuals, allowing them to respond to environmental signals. Previous efforts to parallelize and distribute Aevol had yielded limited results due to the lack of dedicated staff on these problems. Since September 2014, we have been improving the performance of (R-)Aevol. Thanks to the ADT Aevol, one and a half full time

engineers work on improving Aevol and especially to parallelize it. Moreover, we are working to formalize the numerical computation problems with (R-)Aevol to use state-of-the-art optimization techniques from the HPC community. It ranges from dense and sparse matrix multiplication and their optimizations (such as Tridiagonal matrix algorithm) to using new generation accelerator (Intel Xeon Phi and NVidia GPU). However, our goal is not to become a HPC nor a numerical computation team but to work with well-established teams in these fields, such as through the Joint Laboratory for Extreme-Scale Computing, but also with Inria teams in these fields (e.g. ROMA, Avalon, Corse, Storm, DataMove). By doing so, (R-)Aevol simulations will be faster, allowing us to study more parameters in a shorter time. Furthermore, we will also be able to simulate more realistic population sizes, that currently do not fit into the memory of a single computer.

In 2016 we have improved both the quality and the performance of the code. We are currently investigating advance usage of OpenMP to be able to offload part of our execution to accelerator. In particular, we are currently evaluating the performance of the OpenMP version of Aevol on Xeon Phi KNL and on NVidia GPU. In collaboration with the Avalon team and with the help of a shared internship (Mehdi Ghesh), we have build a benchmark for ordinary differential equation (ODE). This benchmark is based on a representative sample of the ODEs (formalizing the genetic network) found within the R-Aevol model. Thanks to this benchmark, we can compare different ODE solvers and methods. Furthermore, researchers working on ODE solvers and methods could use it to evaluate the quality of their approach. We are now working with Avalon team on an algorithm that will automatically choose at runtime the best fitting solver and method (from a performance and a quality of results point of view). Through this collaboration, we have also extended the execo experimental engine [59] to support Aevol and R-Aevol. By doing so, we have now a complete automatic workflow to conduct large scale campaign experiments with thousands of different parameters of our model and use the resources of distributed platform (Grid'5000, CC-IN2P3 and a dedicated cluster).

Since 2014, we are also working on a second model of genome evolution.This new model, developed by the team within the Evoevo european Project, encompasses not only the gene regulation network (as R-aevol does) but also the metabolic level [8]. It allows us to have a real notion of resources and thus to have more complex ecological interactions between the individuals. To speed up computations, the genomic level is simplified compared to aevol, as a chromosome is modelled as a sequence of genes and regulatory elements and not as a sequence of nucleotides. Both models are thus complementary.

Little has been achieved concerning the validation of these models, and the relevance of the observed evolutionary tendencies for living organisms. Some comparisons have been made between Avida and experimental evolution [65], [58], but the comparison with what happened in a long timescale to life on earth is still missing. It is partly because the reconstruction of ancient genomes from the similarities and differences between extant ones is a difficult computational problem which still misses good solutions for every type of mutations, in particular the ones concerning changes in the genome structure.

There exist good phylogenic models of punctual mutations on sequences [56], which enable the reconstruction of small parts of ancestral sequences, individual genes for example [66]. But models of whole genome evolution, taking into account large scale events like duplications, insertions, deletions, lateral transfer, rearrangements are just being developped [74], [52]. Integrative phylogenetic models, considering both nucleotide subsitutions and genome architectures, like Aevol does, are still missing.

Partial models lead to evolutionary hypotheses on the birth and death of genes [53], on the rearrangements due to duplications [44], [73], on the reasons of variation of genome size [60], [67]. Most of these hypotheses are difficult to test due to the difficulty of *in vivo* evolutionary experiments.

To this aim, we develop evolutionary models to reconstruct the history of organisms from the comparison of their genome, at every scale, from nucleotide substitutions to genome organisation rearrangements. These models include large-scale duplications as well as loss of DNA material, and lateral gene transfers from distant species. In particular we have developed models of evolution by rearrangements [68], methods for reconstructing the organization of ancestral genomes [69], [50], [70], or for detecting lateral gene transfer events [43], [10]. It is complementary with the Aevol development because both the model of artificial evolution and the phylogenetic models we develop emphasize on the architecture of genomes. So we are in a good position to compare artificial and biological data on this point.

We improve the phylogenetic models to reconstruct ancestral genomes, jointly seen as gene contents, orders, organizations, sequences. It requires integrative models of genome evolution, which is desirable not only because they will provide a unifying view on molecular evolution, but also because they will shed light onto the relations between different kinds of mutations, and enable the comparison with artificial experiments from models like Aevol.

Based on this experience, the BEAGLE team contributes individual-based and mathematical models of genome evolution, in silico experiments as well as historical reconstruction on real genomes, to shed light on the evolutionary origin of the complex properties of cells.

4. Highlights of the Year

4.1. Highlights of the Year

EvoMove

We completed the implementation of the EvoMove system, an evolving music generation system based on performer moves. The moves are not predefined, they are identified by an evolutionary subspace clustering algorithm that builds on-the-fly move categories. Such a category is created when similar moves are repeated, but it remains flexible in the sense that it can adapt to gradual changes of the moves. A category can also be forgotten when the corresponding moves do not occur any longer. We run working sessions with dancers and record parts of these performances on videos. The first prototype of EvoMove has been tested with the Anou Skan company (https://www.youtube.com/channel/UCoyfXJx_izpQZi6hD8w5M3A). The system immediately convinced the dancers of its interest and we are now working on the creation of a short play with Claire Lurin, an INSA-Lyon student who is also a semi-professional dancer.

ECAL

The Beagle team was chosen by the board of the ISAL (International Society For Artificial Life) to organize ECAL 2017, the 14th European Conference on Artificial Life. ECAL is the offical conference of the ISAL on odd years. Organizing ECAL 2017 will confirm the Beagle team as a major player in the international artificial life community and as the domain leader in France.

5. New Software and Platforms

5.1. DeCoSTAR

KEYWORDS: Bioinformatics - Evolution

FUNCTIONAL DESCRIPTION Given a set of gene trees, a species tree and adjacency relations between extant genes, DeCoSTAR reconstructs adjacencies between ancestral genes

- Contact: Eric Tannier
- URL: http://pbil.univ-lyon1.fr/software/DeCoSTAR/

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

5.3. FluoBacTracker

KEYWORDS: Bioinformatics - Biology - Biomedical imaging

FUNCTIONAL DESCRIPTION FluoBacTracker is an ImageJ plugin designed to segment and track growing E. Coli cells from microscopy images and movies. FluoBacTracker is a software tool to : 1) Select regions of interest in each image (detect the colony) 2) Denoise and renormalize the images 3) Identify each cells in each image (segmentation) 4) Follow cells through the whole movie (tracking) 5) Detect divisions and construct cell lineage in the population FluoBacTracker is an open-source software (under a tailored license agremment), downloadable free of charge for academics.

- Participants: Magali Vangkeosay, David Parsons and Hugues Berry
- Partner: Université Descartes
- Contact: Hugues Berry
- URL: http://fluobactracker.inrialpes.fr

5.4. 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/

5.5. 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.

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

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

6. New Results

6.1. Open-Ended Novelty: Requirements, Guidelines, and Challenges

Participants: G. Beslon

We started in 2014 a collective reflexion on the concept of "Open-Endedness". This reflexion led to a collective paper published this year in "Theory in Biosciences" [12]. The open-endedness of a system is often defined as a continual production of novelty. In this paper we pin down this concept more fully by defining several types of novelty that a system may exhibit, classified as variation, innovation, and emergence. We then provide a meta-model for including levels of structure in a system's model. From there, we define an architecture suitable for building simulations of open-ended novelty-generating systems and discuss how previously proposed systems fit into this framework. We discuss the design principles applicable to those systems and close with some challenges for the community.

6.2. Endocannabinoid dynamics gate spike timing dependent depression and potentiation

Participants: I. Prokin and H. Berry, in collaboration with L. Venance lab, CIRB, Collège de France, Paris.

Learning and memory depend on processes that alter the connections – or synapses – between neurons in the brain. For example, molecules called endocannabinoids can alter synapses to decrease the influence that one neuron has on another neuron's activity. This "synaptic depression" is an important mechanism through which the brain can adapt to an experience. However, recent research also suggests that endocannabinoids might also increase the influence one neuron has on another neuron's activity by strengthening the synaptic connection between neurons. This opposite process is known as synaptic potentiation, and is also important for learning from experience. But how do endocannabinoids manage to produce opposing effects? Using a combination of electrophysiological recording experiments from our experimental collaborator lab and mathematical modeling, we have deciphered the molecular mechanisms that govern the action of endocannabinoids at key synapses in rat brain slices. This revealed that both the levels and timing of endocannabinoid release control changes in the strength of the synaptic connections. Electrical stimulations that produced moderate amounts of endocannabinoids over a prolonged period led to synaptic depression. However, stimulation that produced short but large endocannabinoid peaks caused synaptic potentiation. The enzymes that control endocannabinoid levels thus play a crucial role in determining whether a given stimulation leads to the strengthening or weakening of a synaptic connection. In the type of synapses studied, changes to synaptic strength also depend on another chemical called dopamine. Abnormal dopamine production is implicated in a number of disorders, including Parkinson's disease and addiction. These results have been published in eLife [16].

6.3. Quantitative convergence towards a self similar profile in an age-structured renewal equation for subdiffusion

Participants: A. Mateos Gonzalez and H. Berry, in collaboration with T. Lepoutre, EPI Dracula, Inria.

Continuous-time random walks are generalisations of random walks frequently used to account for the consistent observations that many molecules in living cells undergo anomalous diffusion, i.e. subdiffusion. We described the subdiffusive continuous-time random walk using age-structured partial differential equations with age renewal upon each walker jump, where the age of a walker is the time elapsed since its last jump. In the spatially-homogeneous (zero-dimensional) case, we followed the evolution in time of the age distribution. An approach inspired by relative entropy techniques allows us to obtain quantitative explicit rates for the convergence of the age distribution to a self-similar profile, which corresponds to convergence to a stationnary profile for the rescaled variables. An important difficulty arises from the fact that the equation in self-similar variables is not autonomous and we do not have a specific analyitcal solution. Therefore, in order to quantify the latter convergence, we estimate attraction to a time-dependent "pseudo-equilibrium", which in turn converges to the stationnary profile. These results have been published in Acta Applicandae Mathematicae [13].

6.4. Modulation of Synaptic Plasticity by Glutamatergic Gliotransmission

Participants: M. De Pittà in collaboration with N. Brunel, Dept of Neuroscience and Statistics, University of Chicago, USA.

Glutamatergic gliotransmission, that is the release of glutamate from perisynaptic astrocyte processes in an activity-dependent manner, has emerged as a potentially crucial signal-ing pathway for regulation of synaptic plasticity, yet its modes of expression and function in vivo remain unclear. We focused on two experimentally well-identified gliotransmitter patwhays: (i) modulations of synaptic release and (ii) postynaptic slow inward currents mediated by glutamate released from astrocytes, and investigate their possible functional relevance on synaptic plasticity in a biophysical model of an astrocyte-regulated synapse. Our model predicts that both pathways could profoundly affect both short-and long-term plasticity. In particular, activity-dependent glutamate release from astrocytes, could dramatically change spike-timing–dependent plasticity, turning potentiation into depression (and vice versa) for the same protocol. These results have been published in Neural plasticity [17] and in a review targetting a biologist audience in the journal Neuroscience [18].

6.5. Comparative Genomics and artificial life

Participants: P Biller, C Knibbe, G Beslon, E Tannier

Molecular evolutionary methods and tools are difficult to validate as we have almost no direct access to ancient molecules. Inference methods may be tested with simulated data, producing full scenarios they can be compared with. But often simulations design is concomitant with the design of a particular method, developed by a same team, based on the same assumptions, when both should be blind to each other. In silico experimental evolution consists in evolving digital organisms with the aim of testing or discovering complex evolutionary processes. Models were not designed with a particular inference method in mind, only with basic biological principles. As such they provide a unique opportunity to blind test the behavior of inference methods. We give a proof of this concept on a comparative genomics problem: inferring the number of inversions separating two genomes. We use Aevol, an in silico experimental evolution platform, to produce benchmarks, and show that most combinatorial or statistical estimators of the number of inversions fail on this dataset while they were behaving perfectly on ad-hoc simulations. We argue that biological data is probably closer to the difficult situation.

This work has been published in the article [23] and presented at the Jobim conference [25] and provided the inspiration for a new estimator of the evolutionary distance between two genomes (see below).

6.6. Breaking good

Participants: P Biller, C Knibbe, E Tannier, in collaboration with L Guéguen, University of Lyon 1.

Models of evolution by genome rearrangements are prone to two types of flaws: one is to ignore the diversity of susceptibility to breakage across genomic regions, the other is to suppose that susceptibility values are given. Without necessarily supposing their precise localization, we call "solid" the regions that are improbably broken by rearrangements and "fragile" the regions outside solid ones. We propose a model of evolution by inversions where breakage probabilities vary across fragile regions and over time. It contains as a particular case the uniform breakage model on the nucleotidic sequence, where breakage probabilities are proportional to fragile region lengths. This is very different from the frequently used pseudo-uniform model where all fragile regions have the same probability to break. Estimations of rearrangement distances based on the pseudo-uniform model completely fail on simulations with the truly uniform model. On pairs of amniote genomes, we show that identifying coding genes with solid regions yields incoherent distance estimations, especially with the pseudo-uniform model, and to a lesser extent with the truly uniform model. This incoherence is solved when we co-estimate the number of fragile regions with the rearrangement distance. The estimated number of fragile regions is surprisingly small, suggesting that a minority of regions are recurrently used by rearrangements. Estimations for several pairs of genomes at different divergence times are in agreement with a slowly evolvable co-localization of active genomic regions in the cell.

This work has been published in an article for a reference biology journal [14].

6.7. Subspace clustering

Participants: S Peignier, C Rigotti

We developed an algorithm to tackle the subspace clustering problem over a data stream containing clusters than change over time. Very few subspace clustering algorithms can handle such streams. Our starting point was the work made in the team on evolution of evolution mechanisms and on a preliminary bio-inspired algorithm that we have proposed last year. This previous algorithm included many bio-like features like variable genome length and organization, functional and non-functional elements, and variation operators including chromosomal rearrangements. It achieved satisfying results on standard benchmark data sets but was not designed to process dynamic streams. The new algorithm finds and adapts changing clusters over such streams, while preserving high cluster quality. It has been successfully used to build the evolving music generation system EvoMove.

7. Partnerships and Cooperations

7.1. Regional Initiatives

- Labex Ecofect IntraCellXevo. 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. There is one publication associated with this project [19]. It has been funded by ANR and Investissements d'Avenir up to 120keuros.

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

Title: Evolution of Evolution

Programm: FP7

Duration: November 2013 - October 2016

Coordinator: Inria

Partners:

Instituto de Biología Molecular y Celular de Plantas, Agencia Estatal Consejo Superior de Investigaciones Cientificas (Spain)

LIRIS, Institut National des Sciences Appliquees de Lyon (France)

LIRIS, Universite Lyon 1 Claude Bernard (France)

LAPM, Universite Joseph Fourier Grenoble 1 (France)

Bioinformatics and Theoretical Biology, Universiteit Utrecht (Netherlands)

Computer science department, 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).

7.3.1.2. Neuron-Astro-Nets

Title: Neuron-Astro-Nets

Programm: FP7 Marie-Curie International Outgoing Fellowship (IOF)

Duration: 2013-2017

Partners: Inria Grenoble-Rhone-Alpes; Dept Statistics and Neurobiology, University of Chicago, USA (N. Brunel)

Inria contact: H. Berry

This project aims at developing a new model of synaptic plasticity that takes into account astrocyte signaling, its extension to astrocytes-synapse biochemical interactions in ensembles of synapses enwrapped by the same astrocyte and, eventually, to the firing of a single neuron or networks. The project funds Maurizio De Pittá's postdoc for 4 years (June 2013- May 2017). M. De Pittá´ spent two years in N. Brunel's group in Chicago (06/2014-05/2016) then one year back in Beagle in Lyon (06/2016-05/2017).

7.4. International Initiatives

- The Beagle team is part of the LIA (Laboratoire International Associé) EvoAct (Evolution in action with living and artificial organisms). EvoAct is a joint laboratory gathering researchers from Dominique Schneider's team (UJF, LAPM, UMR CNRS 5163, France), Richard Lenski's team (Michigan State University, Beacon center, US) and the Beagle team.

8. Dissemination

8.1. Promoting Scientific Activities

8.1.1. Scientific Events Organisation

8.1.1.1. General Chair, Scientific Chair

- The team has been accepted as the main organizer of ECAL 2017
- Organization and chair of the second EvoEvo workshop (satellite workshop of CSS 2016), Amsterdam, September 20th 2016

8.1.1.2. Member of the Organizing Committees

- Co-organization of the minisymposium "Modeling Spatiotemporal Calcium Dynamics" at ECMTB 2016 (10th European Conference on Mathematical and Theoretical Biology), The University of Nottingham, UK, 11-15 July 2016 (H. Berry and R. Thüll, U Nottingham)
- Co-organization the thematic school "EIEFB 2016: Ecole interdisciplinaire d'échanges et de formation en biologie", Paris, 13-15 June 2016 (H. Berry and B. Abou, Univ. Paris Diderot).
- Co-organization of the module "Molecular assembling and dynamics: from experimentation to modeling" at the thematic school "Functional Microscopy in Biology" (MiFoBio 2016), Seignosse, France, 30 Sep-07 Oct 2016 (H. Berry, C. Favard, CNRS Montpellier and L. Héliot, CNRS Lille).
- E Tannier is a member of the organizing committee of ICGT 2018 (International Conference on Graph Theory)

8.1.2. Scientific Events Selection

8.1.2.1. Member of the Conference Program Committees

- C Knibbe is a member of the Program committee of Alife XV, Cancun, Mexico, July 2016
- C Rigotti is a member of the Program committee of ACM International Conference on Knowledge Discovery and Data Mining (KDD)
- E Tannier is a member of Recomb Comparative Genomics 2016 program Committee
- E Tannier is a member of ECCB 2016 program Committee
- E Tannier is a member of SEMOVI (séminaire de modélisation du vivant) program Committee
- G Beslon is a member of the Program committee of ALife 2016 (Cancun, Mexico)
- G Beslon is a member of the Program committee of Jobim 2016 (Lyon, France)
- G Beslon is a member of the Program Committee of MUME 2016 (Paris, France)

8.1.2.2. Reviewer

- CPM 2016, RECOMB 2016 (E Tannier)
- ECCB 2016 (C Knibbe)
- EuroPar 2016 (J Rouzaud-Cornabas)

8.1.3. Journal

8.1.3.1. Member of the Editorial Boards

- E Tannier is a member of the editorial committee of *Peer Community in Evolutionary Biology*, an open archive labeling system alternative to publications.
- H Berry is a member of the editorial committee of AIMS Biophysics

8.1.3.2. Reviewer - Reviewing Activities

- PLoS One, Systematic Biology, Bioinformatics, Discrete Applied Mathematics, PLoS Computational Biology, BMC evolutionary Biology, Genome Biology and Evolution, Bulletin of Mathematical Biology (E Tannier)
- Scientific Reports, Physical Biology, Frontiers Synaptic Neuroscience, PLoS Computational Biology, Journal Mathematical Neuroscience, New Journal of Physics (H Berry)
- Entropy, PLoS Computational Biology (G Beslon)
- IEEE Geoscience, Remote Sensing Letters (C Rigotti)
- IEEE Transaction on Cloud Computing (J Rouzaud-Cornabas)

8.1.4. Invited Talks

- J Rouzaud-Cornabas, "Performance Optimization for Computational Biolog", Perfomance Analysis Day, Lyon, December 2016
- C Knibbe, "Insights on genome dynamics from in silico experimental evolution and mathematical modelling", Séminaire de Modélisation du Vivant (SeMoVi), 28th of September 2016, Lyon, France.
- C Knibbe, "Genome size evolution: Putting intuition to the test with modeling and simulation", Jacques Monod Conference on "Evolutionary genomics and systems biology: bringing together theoretical and experimental approaches", 10-14th of October 2016, Roscoff, France.
- G Beslon, Hybrid Systems Biology workshop (Grenoble, France) at the Semideev meeting (Saclay, France), at the FET technical seminar (Brussels, Belgium)
- H Berry, “Estimating the impact of anomalous diffusion on intracellular biochemical kinetics", workshop "Stochastic Modelling of Transport Processes In Biology", 30th-31st March 2016, Manchester, UK
- H Berry, “Estimating the effects of spatial non-homogeneities in intracellular diffusion-reactions”, meeting of the BIOSS Working-Group, July 1st 2016, Lyon
- H Berry, “Calcium signals in astrocytes: from intercellular to subcellular models”, workshop “In vitro and in silico modelling of neuron-astrocyte communication” of the 2016 Bernstein Conference, September 20-21 2016, Berlin, Germany
- H Berry, “The many dimensions of cortico-striatal STDP”, meeting of the GDR BioComp, 10-12 Oct 2016, Lyon
- H Berry, “Anomalous diffusion in cells: experimental data and modelling”, CIMPA School "Mathematical models in biology and medicine", December 05-16 2016, Moka, Mauritius.
- E Tannier, "The second root of molecular evolution" Genetic depatment of the Trinity College, Dublin, Feruary 2017
- E Tannier, "Molecules as documents of evolutionary history: 50 years before", Jacques Monod Conference *Molecules as Documents of Evolutionary History*, Roscoff, May 2016
- E Tannier, "Breaking bad", workshop *Pattern Avoidance and Genome Sorting*, Dagstuhl, February 2016

8.1.5. Leadership within the Scientific Community

- H Berry is a Member of the Scientific Board (comité scientifique) of GdR MIV (Microscopie et Imagerie du Vivant, GdR 2588)
- H Berry is a Member of the Steering Commitee (comité de pilotage) of GdR IMaBIO (Imagerie et Microscopie pour la BIOlogie, submitted)

8.1.6. Scientific Expertise

- H Berry is a Reviewer for the US National Science Foundation (NSF), call “Early-career Program”
- H Berry is a Member of the evaluation committee for research program ROSIRIS of the IRSN (Institut de Radioprotection et de Sûreté Nucléaire)
- E Tannier is a Member of the evaluation committee for the FRNQT, Research program in Quebec.

8.1.7. Research Administration

- C Knibbe is a member of Inria Grenoble-Rhône Alpes Comité de Développement Technologique (CDT)
- C Knibbe is a member of the Selection committee in CNU section 67/64 at Université Paris Diderot
- C Knibbe is a member of the Conseil de Laboratoire LIRIS (UMR 5205 CNRS)
- C Rigotti is an elected member of Insa Scientific board (Conseil scientifique)

- G Beslon member of the CoNRS (Section 6 and CID 51)
- G Beslon member of the scientific commission 5 (CSS5) of the IRD (Institut de Recherche pour le Developpement)
- H Berry is Vice-Chair of Inria's "Evaluation Committee" (Commission d'Evaluation)
- H Berry is Chair of the Search Committee for "Junior Research Scientists" (Président Jury d'admissibilité CR2) of Inria Grenoble Research Center
- H Berry is Elected member of Inria's "Scientific Board" (Conseil Scientifique)
- H Berry is Member of Inria's "Parity-Equality" Committee
- H Berry is Member of the Science Steering Committee of the Rhône-Alpes Complex Systems Institute (IXXI)
- E Tannier is an elected member of Inria Administration Council
- E Tannier is the scientific referent of the Inria symposium committee

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

License: J Rouzaud-Cornabas, Programmation orientée objets, 20heqTD, L3, INSA-Lyon, France

Master: J Rouzaud-Cornabas, Systèmes, 10heqTD, M1, INSA-Lyon, France

Master: J Rouzaud-Cornabas, Interface Homme Machine, 50heqTD, M1, INSA-Lyon, France

Master: J Rouzaud-Cornabas, Évaluation de performance et reproducibilité, 6heqTD, M2, INSA-Lyon, France

Master: J Rouzaud-Cornabas, Computational Science and High Performance Computing, 6heqTD, M2, INSA-Lyon, France

Master: J Rouzaud-Cornabas, Parallel Computing, 80heqTD, M2, INSA-Lyon, France

Master: J Rouzaud-Cornabas, Parallel Computing for Bio-informatics, 10heqTD, M2, INSA-Lyon, France

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

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

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

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

Master: E Tannier, Algorithmics for Bioinformatics, 18h, M1, Bioinformatics and Modeling Department of INSA-Lyon.

Master: E Tannier, Algorithmics for Bioinformatics, 12h, M1, University of Lyon 1.

Licence: C Knibbe, Algorithmique et programmation procédurale, 123h eqTD, L2 Informatique, Université Lyon 1, France

Master: C Knibbe, Programmation web, 40h eqTD, M1 Informatique, Université Lyon 1, France

Master: C Knibbe, Connaissance métier pour la recherche, 24h eqTD, M2 Informatique, Université Lyon 1, France

Master: C Knibbe, Intelligence artificielle bio-inspirée, 22h eqTD, M2 Informatique, Université Lyon 1, France

Licence: C Knibbe, Applications en mathématiques et informatique, 39h eqTD, L1 Informatique, Université Lyon 1, France

Licence: C Knibbe, Programmation fonctionnelle pour le web, 20h eqTD, L2 Informatique, Université Lyon 1, France

Master: C Knibbe, Programmation orientée objets pour la bioinformatique, 52h eqTD, M1 Bioinformatique, Université Lyon 1, France

Master: C Knibbe, Projet en bioinformatique, 25h eqTD, M1 Bioinformatique, Université Lyon 1, France

8.2.2. Supervision

PhD : Ilya Prokin, “Modeling and simulation of signal transduction in living cells: synaptic plasticity of basal ganglia neurons”, INSA Lyon, Ph.D. defended: December 02, 2016, Supervisor: H. Berry

PhD in progress : Marie Fernandez, “Extraction and analysis of the acoustic network of social birds: tools for population tracking”, Starting date Oct 2016, co-supervision: H. Berry, H. Soula (CRC, Univ. P&M Curie, Paris) and C. Vignal (Univ. J. Monnet, Saint-Etienne)

PhD in progress : Audrey Denizot, “Simulation of calcium signaling in fine astrocytic processes”, Starting date Oct 2016, co-supervision: H. Berry and H. Soula (CRC, Univ. P&M Curie, Paris)

PhD in progress : Alexandre Foncelle, ‘Modeling the signaling pathway implicated in STDP: the role of endocannabinoid and dopamine signaling”, Starting date Oct 2014, supervision: H. Berry

PhD in progress : Alvaro Mateos Gonzalez; “Anomalous subdiffusion equations as diffusion limits to integro PDEs with age structure”, Starting date Sep 2014, co-supervision: H. Berry, Vincent Calvez (EPI Numed) and Thomas Lepoutre (EPI Dracula).

PhD in progress : Wandrille Duchemin; "Phylogénie des dépendences, dépendances des phylogénies", Starting date 2015, co-supervision: E Tannier and V Daubin (CNRS, Univ Lyon 1)

PhD in progress : Yoann Anselmetti; "Evolution de l’organisation des génomes en présence de génomes non assemblés", Starting date 2015, co-supervision: E Tannier and S Bérard (Univ Montpellier)

PhD in progress : Damir Hasic; "Gene tree Species tree reconciliation in the presence of gene conversion", Starting date 2016, co-supervision: E Tannier (Univ Sarajevo)

PhD in progress: Sergio Peignier, Subspace clustering algorithms based on biological evolution mechanisms, INSA de Lyon, started in September 2014, C Rigotti and G Beslon.

PhD in progress : Charles Rocabert, Studying Evolution of Evolution of Bacterial Microorganisms by Computer Simulation Approaches, started in October 2013, supervised by G Beslon and C Knibbe

PhD in progress: Yoram Vadee Le Brun, "Evolution expérimentale in silico de réseaux de régulation génétique", INSA-Lyon (now Min. Enseignement National), Starting date Sep 2013, co-supervision: G Beslon, J Rouzaud-Cornabas

PhD in progress: Vincent Liar, "Towards a quantitative digital genetics platform", INSA-Lyon, Starting date Oct 2016, co-supervision: G Beslon, J Rouzaud-Cornabas, C Ofria (Michigan State University, BEACON Center)

8.2.3. Juries

- C Knibbe is a reviewer of the PhD thesis Gaël Jalowicki, University College Dublin, October 2016
- H Berry is a Member (reviewer) of the PhD jury for Guillaume Rodriguez, “Modélisation des bases neuronales de la mémoire de travail paramétrique dans le cortex préfrontal” Univ. P & M Curie, Paris, Oct 20, 2016.
- H Berry is a Member (reviewer) of the HdR jury for Dominique Martinez, “Modélisation biologique, biocapteurs et inspiration pour la robotique autonome”, Univ. Nancy-Lorraine, Nancy, 2017
- H Berry is a Member of the Search committee for two tenured Full Professor positions in Systems Biology at University P & M Curie, Paris, 2016 (64PR0596 and 65PR3266)

- G Beslon is a member of the Jury of Ilya Prokins (INSA-Lyon, Lyon, France)
- G Beslon is a reviewer of the PhD thesis of Arthur Bertrand (UPMC, Paris, France)
- G Beslon is a reviewer of the PhD thesis of Sandro Colizzi (Utrecht University, Utrecht, NL)

8.3. Popularization

- E Tannier gave a series of lectures for a large public at "Université Populaire de Lyon", on "anarchy in biology".

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° 5, pp. 1427-1439 [*DOI :* 10.1093/GBE/EVW083], https://hal.archives-ouvertes.fr/hal-01334923

[2] A.-S. COQUEL, J.-P. JACOB, M. PRIMET, A. DEMAREZ, M. DIMICCOLI, T. JULOU, L. MOISAN, A. B. LINDNER, H. BERRY. *Localization of protein aggregation in Escherichia coli is governed by diffusion and nucleoid macromolecular crowding effect*, in "PLoS Computational Biology", 2013, vol. 9, n° 4 [*DOI :* 10.1371/JOURNAL.PCBI.100303], http://hal.inria.fr/hal-00798053

[3] Y. CUI, V. PAILLE, H. XU, S. GENET, B. DELORD, E. FINO, H. BERRY, L. VENANCE. *Endocannabinoids mediate bidirectional striatal spike-timing dependent plasticity*, in "Journal of Physiology", 2015, vol. 593, n° 13, pp. 2833-2849 [*DOI :* 10.1113/JP270324], https://hal.inria.fr/hal-01141205

[4] W. DUCHEMIN, V. DAUBIN, E. TANNIER. *Reconstruction of an ancestral Yersinia pestis genome and comparison with an ancient sequence*, in "BMC Genomics", 2015, vol. 16, n° Suppl 10, S9 p. [*DOI :* 10.1007/978-3-319-19048-8_16], https://hal.inria.fr/hal-01179197

[5] S. FISCHER, S. BERNARD, G. BESLON, C. KNIBBE. *A model for genome size evolution*, in "Bulletin of Mathematical Biology", September 2014, vol. 76, n° 9, pp. 2249-2291 [*DOI :* 10.1007/S11538-014-9997-8], https://hal.archives-ouvertes.fr/hal-01090964

[6] T. HINDRÉ, C. KNIBBE, G. BESLON, D. SCHNEIDER. *New insights into bacterial adaptation through in vivo and in silico experimental evolution*, in "Nature Reviews Microbiology", 2012, vol. 10, pp. 352-365, http://hal.inria.fr/hal-00696231

[7] P.-N. MOUGEL, C. RIGOTTI, M. PLANTEVIT, O. GANDRILLON. *Finding maximal homogeneous clique sets*, in "Knowledge and Information Systems", March 2013, vol. 35, n° 1, pp. 1-30 [*DOI :* 10.1007/S10115-013-0625-Y], http://hal.inria.fr/hal-00827164

[8] C. ROCABERT, C. KNIBBE, G. BESLON. *Towards a Integrated Evolutionary Model to Study Evolution of Evolution*, in "EvoEvo Workshop (Satellite workshop of ECAL 2015)", York, United Kingdom, July 2015, https://hal.inria.fr/hal-01252796

[9] H. SOULA, B. CARÉ, G. BESLON, H. BERRY. *Anomalous versus slowed-down Brownian diffusion in the ligand-binding equilibrium*, in "Biophysical Journal", 2013, vol. 105, n° 9, pp. 2064-2073 [*DOI :* 10.1016/J.BPJ.2013.07.023], http://hal.inria.fr/hal-00720515

[10] G. J. SZÖLLOSI, B. BOUSSAU, S. S. ABBY, E. TANNIER, V. DAUBIN. *Phylogenetic modeling of lateral gene transfer reconstructs the pattern and relative timing of speciations*, in "Proceedings- National Academy of Sciences Usa", October 2012, vol. 109, n^{o} 43, pp. 17513-17518 [*DOI :* 10.1073/PNAS.1202997109], http://hal.inria.fr/hal-00740292

[11] J. VIÑUELAS, G. KANEKO, A. COULON, E. VALLIN, V. MORIN, C. MEJIA-POUS, J.-J. KUPIEC, G. BESLON, O. GANDRILLON. *Quantifying the contribution of chromatin dynamics to stochastic gene expression reveals long, locus-dependent periods between transcriptional bursts*, in "BMC Biology", February 2013, vol. 11, n^{o} 1, 15 p. [*DOI :* 10.1186/1741-7007-11-15], http://hal.inria.fr/inserm-00817963

Publications of the year

Articles in International Peer-Reviewed Journals

[12] W. BANZHAF, B. BAUMGAERTNER, G. BESLON, R. DOURSAT, J. A. FOSTER, B. MCMULLIN, V. V. DE MELO, T. MICONI, L. SPECTOR, S. STEPNEY, R. WHITE. *Defining and simulating open-ended novelty: requirements, guidelines, and challenges.*, in "Theory in biosciences = Theorie in den Biowissenschaften", May 2016 [*DOI :* 10.1007/S12064-016-0229-7], https://hal.archives-ouvertes.fr/hal-01323108

[13] H. BERRY, T. LEPOUTRE, Á. MATEOS GONZÁLEZ. *Quantitative convergence towards a self similar profile in an age-structured renewal equation for subdiffusion*, in "Acta Applicandae Mathematicae", 2016, n^{o} 145, pp. 15-45, in press, https://hal.inria.fr/hal-01136667

[14] 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

[15] L. BULTEAU, G. FERTIN, E. TANNIER. *Genome rearrangements with indels in intergenes restrict the scenario space*, in "BMC Bioinformatics", 2016, vol. 17, n^{o} Suppl 14, 426 p. [*DOI :* 10.1186/S12859-016-1264-6], https://hal.archives-ouvertes.fr/hal-01396842

[16] Y. CUI, I. PROKIN, H. XU, B. DELORD, S. GENET, L. VENANCE, H. BERRY. *Endocannabinoid dynamics gate spike-timing dependent depression and potentiation*, in "eLife", February 2016, vol. 5, e13185 p. [*DOI :* 10.7554/ELIFE.13185], https://hal.inria.fr/hal-01279901

[17] M. DE PITTÀ, N. BRUNEL. *Modulation of Synaptic Plasticity by Glutamatergic Gliotransmission: A Modeling Study*, in "Neural plasticity", 2016 [*DOI :* 10.1155/2016/7607924], https://hal.archives-ouvertes.fr/hal-01353306

[18] M. DE PITTÀ, N. BRUNEL, A. VOLTERRA. *Astrocytes: Orchestrating Synaptic Plasticity?*, in "Neuroscience", 2016, vol. 323, pp. 43-61 [*DOI :* 10.1016/J.NEUROSCIENCE.2015.04.001], https://hal.archives-ouvertes.fr/hal-01353308

[19] C. LAYS, E. TANNIER, T. HENRY. *Francisella IglG protein and the DUF4280 proteins: PAAR-like proteins in non-canonical Type VI secretion systems?*, in "Microbial Cell ", 2016 [*DOI :* 10.15698/MIC2016.11.543], https://hal.archives-ouvertes.fr/hal-01394403

[20] E. NOUTAHI, M. SEMERIA, M. LAFOND, J. SEGUIN, B. BOUSSAU, L. GUÉGUEN, N. EL-MABROUK, E. TANNIER. *Efficient gene tree correction guided by genome evolution*, in "PLoS ONE", 2016, vol. 11, n^{o} 8, e0159559 p. [*DOI :* 10.1371/JOURNAL.PONE.0159559], https://hal.archives-ouvertes.fr/hal-01162963

[21] T. TAYLOR, M. BEDAU, A. CHANNON, D. ACKLEY, W. BANZHAF, G. BESLON, E. DOLSON, T. FROESE, S. HICKINBOTHAM, T. IKEGAMI, B. MCMULLIN, N. PACKARD, S. RASMUSSEN, V. NATHANIEL, E. AGMON, C. EDWARD, S. MCGREGOR, C. OFRIA, G. ROPELLA, L. SPECTOR, K. O. STANLEY, A. STANTON, C. TIMPERLEY, A. VOSTINAR, M. WISER. *Open-Ended Evolution: Perspectives from the OEE Workshop in York*, in "Artificial Life", 2016, vol. 22, n^{o} 3, pp. 408-423 [*DOI :* 10.1162/ARTL_A_00210], https://hal.archives-ouvertes.fr/hal-01371116

[22] A. VILLAIN, M. S. FERNANDEZ, C. BOUCHUT, H. SOULA, C. VIGNAL. *Songbird mates change their call structure and intrapair communication at the nest in response to environmental noise*, in "Animal Behaviour", June 2016, vol. 116, pp. 113-129 [*DOI :* 10.1016/J.ANBEHAV.2016.03.009], https://hal.archives-ouvertes.fr/hal-01404754

Invited Conferences

[23] P. BILLER, C. KNIBBE, G. BESLON, E. TANNIER. *Comparative Genomics on Artificial Life*, in "Computability in Europe", Paris, France, Pursuit of the Universal, 2016, https://hal.archives-ouvertes.fr/hal-01334930

International Conferences with Proceedings

[24] J. ABERNOT, G. BESLON, S. HICKINBOTHAM, S. PEIGNIER, C. RIGOTTI. *A Commensal Architecture for Evolving Living Instruments*, in "Conference on Computer Simulation of Musical Creativity", Huddersfield, United Kingdom, June 2016, https://hal.archives-ouvertes.fr/hal-01368034

[25] P. BILLER, E. TANNIER, G. BESLON, C. KNIBBE. *In silico experimental evolution provides independent and challenging benchmarks for comparative genomics*, in "Journées ouvertes Biologie Informatique Mathématiques", Lyon, France, June 2016, pp. 79-82, https://hal.archives-ouvertes.fr/hal-01375657

[26] G. FERTIN, G. JEAN, E. TANNIER. *Genome Rearrangements on both Gene Order and Intergenic Regions*, in "WABI 2016", Aarhus, Denmark, Algorithms for Bioinformatics, 2016, https://hal.archives-ouvertes.fr/hal-01334942

[27] J. GIPPET, S. FENET, A. DUMET, B. KAUFMANN, C. ROCABERT. *MoRIS: Model of Routes of Invasive Spread. Human-mediated dispersal, road network and invasion parameters*, in "5th International Conference on Ecology and Transportation: Integrating Transport Infrastructures with Living Landscapes", Lyon, France, Proceedings of the IENE 2016 conference, August 2016, https://hal.inria.fr/hal-01412280

[28] T. NGUYEN, N. MÉGER, C. RIGOTTI, C. POTHIER, R. ANDRÉOLI. *SITS-P2miner: Pattern-Based Mining of Satellite Image Time Series*, in "European Conference on Machine Learning and Principles and Practice of Knowledge Discovery in Databases (ECML-PKDD) Demo", Riva del Garda, Italy, September 2016, pp. 63-66 [*DOI :* 10.1007/978-3-319-46131-1_14], https://hal.archives-ouvertes.fr/hal-01367996

[29] Y. VADÉE-LE-BRUN, J. ROUZAUD-CORNABAS, G. BESLON. *In Silico Experimental Evolution suggests a complex intertwining of selection, robustness and drift in the evolution of genetic networks complexity*, in "Artificial Life", Cancun, Mexico, Proceedings of the Artificial Life Conference 2016, MIT Press, July 2016, https://hal.archives-ouvertes.fr/hal-01375645

National Conferences with Proceedings

[30] Y. ANSELMETTI, V. BERRY, C. CHAUVE, A. CHÂTEAU, E. TANNIER, S. BÉRARD. *Comment la reconstruction de génomes ancestraux peut aider à l'assemblage de génomes actuels*, in "Journées Ouvertes Biologie Informatique Mathématiques", Lyon, France, 2016, https://hal.archives-ouvertes.fr/hal-01394409

[31] A. DAVÍN, G. J. SZÖLLOSI, E. TANNIER, B. BOUSSAU, V. DAUBIN. *Dating with transfers*, in "Journées Ouvertes Biologie Informatique Mathématiques", Lyon, France, 2016, https://hal.archives-ouvertes.fr/hal-01394410

[32] W. DUCHEMIN, V. DAUBIN, E. TANNIER. *Nucleotide, gene and genome evolution : a score to bind them all*, in "Journées Ouvertes Biologie Informatique Mathématiques", Lyon, France, 2016, https://hal.archives-ouvertes.fr/hal-01394417

[33] C. POTHIER, R. ANDRÉOLI, N. MÉGER, C. RIGOTTI. *Erosion monitoring by satellite image analysis and spatiotemporal data mining*, in "Journées Nationales de Géotechnique et de Géologie de l'Ingénieur", Nancy, France, July 2016, https://hal.archives-ouvertes.fr/hal-01367992

Conferences without Proceedings

[34] G. BESLON, V. F. LIARD, S. F. ELENA. *Evolvability drives innovation in viral genomes*, in "2nd Evo-Evo Workshop, satellite workshop of CCS2016", Amsterdam, France, September 2016, https://hal.archives-ouvertes.fr/hal-01375665

[35] Y. PERICAULT, C. POTHIER, N. MÉGER, E. TROUVÉ, F. VERNIER, C. RIGOTTI, J.-P. MALET. *Grouped frequent sequential patterns derived from terrestrial image time series tomonitor landslide behaviour – Application to the dynamics of the Sanières/Roche Plombée rockslide.*, in "Geophysical Research Abstracts - EGU General Assembly 2016", Vienna, Austria, April 2016, https://hal.archives-ouvertes.fr/hal-01306556

[36] C. ROCABERT, C. KNIBBE, J. CONSUEGRA, D. SCHNEIDER, G. BESLON. *In Silico Experimental Evolution Highlights the Influence of Environmental Seasonality on Bacterial Diversification*, in "2nd EvoEvo Workshop, satellite workshop of CCS2016", Amsterdam, Netherlands, September 2016, https://hal.archives-ouvertes.fr/hal-01375677

[37] J. P. RUTTEN, P. HOGEWEG, G. BESLON. *Evolution of mutator populations in constant environments*, in "2nd EvoEvo Workshop, satellite workshop of CCS2016", Amsterdam, Netherlands, September 2016, https://hal.archives-ouvertes.fr/hal-01375669

[38] S. STEPNEY, G. BESLON. *Open-Endedness: Definitions and Shortcuts*, in "2nd EvoEvo Workshop, satellite workshop of CCS2016", Amsterdam, Netherlands, September 2016, https://hal.archives-ouvertes.fr/hal-01375671

Scientific Books (or Scientific Book chapters)

[39] M. GROUSSIN, M. GOUY, V. DAUBIN, E. TANNIER. *Ancestral Reconstruction: Theory and Practice*, in "Encyclopedia of Evolutionary Biology", R. M. KLIMAN (editor), Elsevier, 2016, https://hal.archives-ouvertes.fr/hal-01334934

[40] E. TANNIER. *Sorting Signed Permutations by Reversal (Reversal Sequence)*, in "Encyclopedia of Algorithms", M.-Y. KAO (editor), Springer, 2016, https://hal.archives-ouvertes.fr/hal-01334936

Other Publications

[41] B. BATUT, G. BESLON, C. KNIBBE. *Unexpected genome inflation and streamlining in variable environments*, June 2016, pp. 320-322, Journées ouvertes de Biologie Informatique & Mathématiques 2016, Poster, https://hal.archives-ouvertes.fr/hal-01375653

[42] V. CALVEZ, P. GABRIEL, Á. MATEOS GONZÁLEZ. *Limiting Hamilton-Jacobi equation for the large scale asymptotics of a subdiffusion jump-renewal equation.*, September 2016, working paper or preprint, https://hal.archives-ouvertes.fr/hal-01372949

References in notes

[43] S. S. ABBY, E. TANNIER, M. GOUY, V. DAUBIN. *Detecting lateral gene transfers by statistical reconciliation of phylogenetic forests*, in "BMC Bioinformatics", 2010, vol. 11, 13 p. , http://dx.doi.org/10.1186/1471-2105-11-324

[44] J. A. BAILEY, R. BAERTSCH, W. J. KENT, D. HAUSSLER, E. E. EICHLER. *Hotspots of mammalian chromosomal evolution*, in "Genome Biol", 2004, vol. 5, n^{o} 4, 7 p. , http://dx.doi.org/10.1186/gb-2004-5-4-r23

[45] H. BERRY. *Monte Carlo simulations of enzyme reactions in two dimensions: fractal kinetics and spatial segregation*, in "Biophys J", 2002, vol. 83, n^{o} 4, pp. 1891–1901

[46] G. BESLON, D. P. PARSONS, Y. SANCHEZ-DEHESA, J.-M. PEÑA, C. KNIBBE. *Scaling Laws in Bacterial Genomes: A Side-Effect of Selection of Mutational Robustness*, in "BioSystems", 2010, vol. 102, n^{o} 1, pp. 32-40

[47] G. BESLON, Y. SANCHEZ-DEHESA, D. P. PARSONS, J.-M. PEÑA, C. KNIBBE. *Scaling Laws in Digital Organisms*, in "Proceedings of Information Processing in Cells and Tissues (IPCAT'09)", 2009, pp. 111-114

[48] G. BESLON, Y. SANCHEZ-DEHESA, D. P. PARSONS, C. RIGOTTI, J.-M. PEÑA. *From Digital Genetics to Knowledge Discovery: Perspectives in Genetic Network Understanding*, in "Intelligent Data Analysis journal (IDAj)", 2010, vol. 14, n^{o} 2, pp. 173-191

[49] B. CARÉ, H. A. SOULA. *Impact of receptor clustering on ligand binding*, in "BMC Systems Biology", March 2011, vol. 5, n^{o} 1, 48 p. , PMID: 21453460 [*DOI :* 10.1186/1752-0509-5-48], http://www.ncbi.nlm.nih.gov/pubmed/21453460

[50] C. CHAUVE, H. GAVRANOVIC, A. OUANGRAOUA, E. TANNIER. *Yeast ancestral genome reconstructions: the possibilities of computational methods II*, in "J Comput Biol", Sep 2010, vol. 17, n^{o} 9, pp. 1097–1112, http://dx.doi.org/10.1089/cmb.2010.0092

[51] A. COULON, O. GANDRILLON, G. BESLON. *On the spontaneous stochastic dynamics of a single gene: complexity of the molecular interplay at the promoter*, in "BMC Systems Biology", 2010, vol. 4, n^{o} 1, 2 p.

[52] A. E. DARLING, I. MIKLÓS, M. A. RAGAN. *Dynamics of genome rearrangement in bacterial populations*, in "PLoS Genet", 2008, vol. 4, n^{o} 7, e1000128, http://dx.doi.org/10.1371/journal.pgen.1000128

[53] L. A. DAVID, E. J. ALM. *Rapid evolutionary innovation during an Archaean genetic expansion*, in "Nature", Jan 2011, vol. 469, n^{o} 7328, pp. 93–96 [*DOI :* 10.1038/NATURE09649]

[54] M. EIGEN. *Selforganization of matter and the evolution of biological macromolecules*, in "Naturwissenschaften", 1971, vol. 58, n^{o} 10, pp. 465-523

[55] M. ELOWITZ, A. LEVINE, E. SIGGIA, P. SWAIN. *Stochastic gene expression in a single cell*, in "Science", 2002, vol. 297, n^{o} 5584, pp. 1183–1186

[56] J. FELSENSTEIN. *Inferring phylogenies*, Sinauer Associates, 2004

[57] P. GALISON. *Image and Logic: A Material Culture of Microphysics*, University Of Chicago Press, 1997

[58] T. HINDRÉ, C. KNIBBE, G. BESLON, D. SCHNEIDER. *New insights into bacterial adaptation through in vivo and in silico experimental evolution*, in "Nature Reviews Microbiology", 2012, vol. 10, pp. 352-365, http://hal.inria.fr/hal-00696231

[59] M. IMBERT, L. POUILLOUX, J. ROUZAUD-CORNABAS, A. LÈBRE, T. HIROFUCHI. *Using the EXECO toolbox to perform automatic and reproducible cloud experiments*, in "1st International Workshop on UsiNg and building ClOud Testbeds (UNICO, collocated with IEEE CloudCom 2013", Bristol, United Kingdom, December 2013, https://hal.inria.fr/hal-00861886

[60] INTERNATIONAL APHID GENOMICS CONSORTIUM. *Genome sequence of the pea aphid Acyrthosiphon pisum*, in "PLoS Biol", Feb 2010, vol. 8, n^{o} 2, e1000313, http://dx.doi.org/10.1371/journal.pbio.1000313

[61] C. KNIBBE, A. COULON, J.-M. FAYARD, G. BESLON. *A long term evolutionary pressure on the amount of noncoding DNA*, in "Molecular Biology and Evolution", 2007, vol. 24, n^{o} 10, pp. 2344-2353

[62] C. KNIBBE, J.-M. FAYARD, G. BESLON. *The topology of the protein network influences the dynamics of gene order : From systems biology to a systemic understanding of evolution*, in "Artificial Life", 2008, vol. 14, n^{o} 1, pp. 149-156

[63] C. KNIBBE. *Structuration de génomes par sélection indirecte de la variabilité mutationnelle, une approche par modélisation et simulation*, PhD Thesis, Institut National des Sciences Appliquées de Lyon, 2006, 174 p.

[64] C. KNIBBE, O. MAZET, F. CHAUDIER, J.-M. FAYARD, G. BESLON. *Evolutionary coupling between the deleteriousness of gene mutations and the amount of non-coding sequences*, in "Journal of Theoretical Biology", 2007, vol. 244, n^{o} 4, pp. 621–630

[65] R. E. LENSKI, C. OFRIA, R. T. PENNOCK, C. ADAMI. *The evolutionary origin of complex features*, in "Nature", 2003, vol. 423, pp. 139–144

[66] D. A. LIBERLES. *Ancestral Sequence Reconstruction*, Oxford University Press, 2007

[67] G. A. B. MARAIS, A. FORREST, E. KAMAU, J. KÄFER, V. DAUBIN, D. CHARLESWORTH. *Multiple nuclear gene phylogenetic analysis of the evolution of dioecy and sex chromosomes in the genus Silene*, in "PLoS One", 2011, vol. 6, n^{o} 8, e21915, http://dx.doi.org/10.1371/journal.pone.0021915

[68] I. MIKLÓS, E. TANNIER. *Bayesian sampling of genomic rearrangement scenarios via double cut and join*, in "Bioinformatics", Dec 2010, vol. 26, n^{o} 24, pp. 3012–3019, http://dx.doi.org/10.1093/bioinformatics/btq574

[69] F. MURAT, J.-H. XU, E. TANNIER, M. ABROUK, N. GUILHOT, C. PONT, J. MESSING, J. SALSE. *Ancestral grass karyotype reconstruction unravels new mechanisms of genome shuffling as a source of plant evolution*, in "Genome Res", Nov 2010, vol. 20, n^{o} 11, pp. 1545–1557 [*DOI :* 10.1101/GR.109744.110]

[70] A. OUANGRAOUA, E. TANNIER, C. CHAUVE. *Reconstructing the architecture of the ancestral amniote genome*, in "Bioinformatics", Oct 2011, vol. 27, n^{o} 19, pp. 2664–2671, http://dx.doi.org/10.1093/bioinformatics/btr461

[71] D. P. PARSONS, C. KNIBBE, G. BESLON. *Importance of the rearrangement rates on the organization of transcription*, in "Proceedings of Artificial Life 12", MIT Press, 2010, pp. 479-486

[72] D. P. PARSONS, C. KNIBBE, G. BESLON. *Homologous and nonhomologous rearrangements: Interactions and effects on evolvability*, in "European Conference on Artificial Life (ECAL)", MIT Press, 2011, pp. 622–629

[73] M. SÉMON, K. H. WOLFE. *Consequences of genome duplication*, in "Curr Opin Genet Dev", Dec 2007, vol. 17, n^{o} 6, pp. 505–512, http://dx.doi.org/10.1016/j.gde.2007.09.007

[74] A. TOFIGH, M. HALLETT, J. LAGERGREN. *Simultaneous identification of duplications and lateral gene transfers*, in "IEEE/ACM Trans Comput Biol Bioinform", 2011, vol. 8, n^{o} 2, pp. 517–535, http://dx.doi.org/10.1109/TCBB.2010.14