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Activity Report 2013

Project-Team BEAGLE

Artificial Evolution and Computational Biology

IN COLLABORATION WITH: Laboratoire de Biométrie et Biologie Evolutive (LBBE), Laboratoire d'InfoRmatique en Image et Systèmes d'information, Laboratoire de Recherche en Cardiovasculaire, Métabolisme, Diabétologie et Nutrition

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Computational Biology

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Project-Team BEAGLE

Keywords: Computational Biology, Modeling, Cell Biology, Evolution, Systems Biology

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

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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 BEAGLE Team results from the merging of three researchers of the "COMBINING" Team led by Jean-François Boulicaut in the LIRIS [1] (Computer Science), one researcher of the CARMEN institute[2] (Biology) and two Inria researchers (Computational Biology), one of them being a member of the BBE institute[3]. It has been created as an "Équipe Centre" by Inria Rhône-Alpes in June 2011[4] and is on the way to be created as "Équipe-Projet". The BEAGLE Team 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 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.

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

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

[4] BEAGLE follows from the COMBINING team with a more focused topic: COMBINING is composed of 8 researchers and includes a data-mining research topic. To clarify the respective research areas of the Inria Team and of the LIRIS COMBINING team, Inria suggested to focus the BEAGLE research topic on computational biology. The members of COMBINING – including the data-mining part – collectively consented to this proposal.

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* [62] 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.

2.2. Highlights of the Year

- The Beagle Team has been granted an FP7 project (FET Proactive "Evolving Living Technologies" call). The EvoEvo ("Evolution of Evolution") project connects five european teams working in evolutionary biology (D. Schneider, UJF, France; S. Elena, CSIC, Spain; Beagle, Inria, France), computational biology (P. Hogeweg, Utrecht University, Nederland; Beagle, Inria, France) and unconventional computing (S. Stepney, University of York, UK; Beagle, Inria, France). EvoEvo has been launched at the initiative of the Beagle Team who leads the project. Total amount funded: 2.6 Million euros. Amount funded for Inria : 800.000 euros.
- We organized the international conference "RECOMB Comparative Genomics" in October 2013, in Lyon and the international conference "Models and Algorithms for Genome Evolution" in August 2013 in Montreal, Canada. Following the latter conference, we co-edited a book published in the "Computational biology" series of Springer [37].
- Our long-lasting collaboration with the BM2A team of the CGphyMC (Centre de Génétique et de Physiologie Moléculaire et Cellulaire) is based on co-development of experimental work in the "wet lab" of the CGphyMC and computational experiments in the "dry lab" of Beagle. By using this approach to investigate the molecular basis of the stochasticity of gene expression in higher eukaryotic cells, we have been able to show that this stochasticity is due to intermittent transcription events with very long periods of quiet states. These results have been published in a high impact biological journal in February 2013 [12].
- Our work on the signalling pathways implicated in synaptic plasticity, initiated in 2012 [34] and carried out in collaboration with the experimental neurobiology lab led by L. Venance at Collège de France, Paris, became a major project for Beagle in 2013, with the recruitment of I. Prokin (PhD, Inria grant) and the extension of the collaboration to the group of A. Blackwell (Georges Mason University, USA). Respective publications and funded projects are expected for 2014.
- The project related to the study of intracellular reaction-diffusion dynamics of signalling pathways started to develop in 2013 a more mathematical direction. This is carried out with Beagle and S. Fedotov (School Mathematics, Univ. Manchester, UK), V. Calvez (Inria Numed, Lyon), T. Lepoutre (Inria Dracula, Lyon) and Master student A. Mateos-Gonzalez (ENS Lyon, Mathematics).

3. Research Program

3.1. Introduction

As stated above, the research topics of the Beagle Team are centered on the 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 will be 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 [49]. 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 [53]. 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 [60]. 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 [55]. 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. To overcome this difficulty, 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 [68]). As a consequence, this model can be used to study how evolutionary pressures like the ones for robustness or evolvability can shape genome structure [69], [66], [67], [78]. 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 [69], [66], [79]. 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 [59]. 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. We have recently 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 [51], [50], [52]. 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 [50]. 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 [69], and no difference in lifestyles and environment was needed to explain the complexity of the gene regulatory network [50]. 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.

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 Adiva and experimental evolution [70], [63], 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.

There exist good phylogenic models of punctual mutations on sequences [61], which enable the reconstruction of small parts of ancestral sequences, individual genes for example [71]. But models of whole genome evolution, taking into account large scale events like duplications, insertions, deletions, lateral transfer, rearrangements are just being developped: [81] model punctual mutations as well as duplication and losses of genes, while [56] can reconstruct the evolution of the structure of genomes by inversions. This allows a more comprehensive view of the history of the molecules and the genes, which sometimes have their own historical pattern. But integrative models, considering both nucleotide subsitutions and genome architectures, are still missing.

It is possible to partially reconstruct ancestral genomes for limited cases, by treating separately different types of mutations. It has been done for example for gene content [57], gene order [72], [75], the fate of gene copies after a duplication [65], [47]. All these lead to evolutionary hypotheses on the birth and death of genes [58], on the rearrangements due to duplications [48], [80], on the reasons of variation of genome size [64], [73]. Most of these hypotheses are difficult to test due to the difficulty of *in vivo* evolutionary experiments.

To this aim, we develop evolutionary models for reconstructing 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 [74], methods for reconstructing the organization of ancestral genomes [76], [54], [77], or for detecting lateral gene transfer events [46], [11]. 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 will necessitate 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 put into light the relations between different kinds of mutations, and enable the comparison with artificial experiments from 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. Application Domains

4.1. Cellular Biology

The straightforward application domain for our spatio-temporal models of cellular processes is Cellular Biology.

4.2. Evolutionary Biology

The straightforward application domain for our models of genome evolution and for our algorithms of phylogenetic inference is Evolutionary Biology.

5. Software and Platforms

5.1. aevol (artificial evolution)

Participants: Guillaume Beslon, Stephan Fischer, Carole Knibbe, David P Parsons, Bérénice Batut.

- Contact: Carole Knibbe (carole.knibbe@inria.fr).
- Aevol is a simulation software dedicated to the study of genome evolution. It allows to carry out *in silico* experimental evolution. Populations of digital organisms reproduce and mutate randomly, with both small mutations and large chromosomic rearrangements, in a steady or varying environment. A curve-fitting task is used to determine the fitness of the organisms and thus their rate of reproduction. The number of genes, their order, their sequences, their intergenic distances are all free to evolve.
- URL: http://www.aevol.fr

5.2. FluoBacTracker

Participants: Hugues Berry, David P Parsons, Magali Vangkeosay.

- Contact: Hugues Berry (hugues.berry@inria.fr)
- FluoBacTracker is a software for automated quantification of bacterial cells in microscopy movies, developed in collaboration with INSERM U1001 and Paris 5 MAP (Applied Mathematics) Labs. The development (started october 2012) is supported by is a 2-year grant (ADT) funded by Inria's Technological Development Department (Sept 2012- July 2014, project name: "MultiPop"). We hope this software will be useful to all the experimental biology labs that tries to derive single-cell data from bacteria growth microscopy movies. Co-developers include Magali Vangkeosay (Beagle), David P Parsons (SED, Inria Grenoble) and Xiaohu Song (INSERM U1001).

5.3. Ancestral Genome Reconstructions

Participant: Eric Tannier.

- Contact: Eric Tannier (eric.tannier@inria.fr).
- We participated in the development of a series of softwares for genome organization analysis:
  - ANGES, for ANcestral GEnomeS maps, is a toolkit for ordering ancestral genomic markers in chromosomes. An application note has been published in *Bioinformatics* in 2012 to advertise its first release. It is hosted at SFU in Vancouver, URL: http://paleogenomics.irmacs.sfu.ca/ANGES/, under a GNU license, 2012.
  - DeCo and DeCoLT, for Detection of Co-evolution (with Lateral gene Transfer), reconstruct neighborhood relationships between genes of ancient genomes, in the presence of gene duplications, transfer and losses. Both are hosted at the PRABI, the bioinformatics platform in Lyon, under a Cecill license, 2012 and 2013. URL: http://pbil.univ-lyon1.fr/software/DeCo/ and http://pbil.univ-lyon1.fr/software/DeCoLT/.
  - DCJ2HP provides bayesian samples of rearrangements scenarios between two genomes. It is hosted at the Renyi Institute in Budapest. URL: http://www.renyi.hu/~miklosi/DCJ2HP/

5.4. DMT4SP mining tool

Participant: Christophe Rigotti.

- Contact: Christophe Rigotti (christophe.rigotti@insa-lyon.fr).
- DMT4SP (Data-Mining Tool For Sequential Patterns) – DMT4SP is command-line tool to extract episodes and episode rules over a single sequence or several sequences of events. It allows to specify constraints on the episodes or on the rules. Three kinds of patterns can be extracted: (1) serial episodes, (2) serial episode rules having a single event type in the consequent, and (3) quantitative episodes (aka grouping of "homogeneous" occurrences of serial episodes with respect to the time gap between events). DMT4SP is a prototype that is freely distributed (http://liris.cnrs.fr/~crigotti/dmt4sp.html).

6. New Results

6.1. Stochastic dynamics of gene expression

A number of studies have established that stochasticity in gene expression may play an important role in many biological phenomena but the molecular mechanisms at stake are still poorly understood. By joint experimental and computational approaches, we explored the role played by chromatin dynamics in the regulation of stochastic gene expression in higher eukaryotic cells [31]. For this purpose, our biological partner generated isogenic chicken-cell populations expressing a fluorescent reporter integrated in one copy per clone.

Although the clones differed only in the genetic locus at which the reporter was inserted, they showed markedly different fluorescence distributions, revealing different levels of stochastic gene expression. Use of chromatin-modifying agents then showed that direct manipulation of chromatin dynamics had a marked effect on the extent of stochastic gene expression. We then fitted the experimental data to a two-state model describing the opening/closing process of the chromatin. The model showed that the differences between clones seemed to be due mainly to the duration of the closed state, and that the agents we used mainly seem to act on the opening probability. These results highlight the importance of chromatin dynamics in stochastic gene expression. They shed a new light on the mechanisms of gene expression in higher eukaryotic cells, and argues in favor of relatively slow dynamics with long (hours to days) periods of quiet state.

This work was part of Gaël Kaneko's PhD and results from our long-lasting collaboration with Olivier Grandrillon and his BM2A team in the CGphyMC (Centre de Génétique et de Physiologie Moléculaire et Cellulaire, Lyon).

6.2. The impact of anomalous diffusion on cell signaling

This year, we published two papers describing the impact of diffusion and clustering in membrane domains for ubiquitous biological pathways. In the first paper [18], we showed that clustering of receptors in membrane domains affect severely the activation of 'hit and run' type of pathways (eg. IRS1, G proteins). This is a pure diffusion result and it is obtained without modifying molecular affinity. This impairment is dramatically important when receptors are highly clustered such are the cases for insulin and adrenergic receptors. In the same direction, we studied the impact of modified diffusion on the other ubiquitous pathway: enzyme/substrate equilibrium [10]. In that case diffusion was modified either using subdiffusion - obstacles and Continuous Time Random Walk - or using space-based inhomogeneous diffusion. We showed that while impairing diffusion all three mechanisms behave differently in the stationary regime. Therefore it it not possible to assume simple space-dependent diffusion for subdiffusion at the equilibrium limit (as it is always assumed). Furthermore, we showed that in the case of space-dependent diffusion - the shape of the diffusion profile can drastically affect the equilibrium and modify the pathway. Since these three phenomenons are thought to occur either in the membrane or the cytosplasm, our results show they can have non trivial effect of all chemical reaction occurring within these medium.

This research will be carried on in the group in 2014 and expanded by the more mathematical approaches initiated in 2013 by collaborations with V Calvez (Numed Inria Lyon), T Lepoutre (Dracula, INIA Lyon) and S. Fedotov (Univ Manchester, UK).

6.3. Localization of protein aggregates in E. coli

Aggregates of misfolded proteins are a hallmark of many age-related diseases. Recently, they have been linked to aging of *Escherichia coli* (*E. coli*) where protein aggregates accumulate at the old pole region of the aging bacterium. Because of the potential of *E. coli* as a model organism, elucidating aging and protein aggregation in this bacterium may pave the way to significant advances in our global understanding of aging. A first obstacle along this path is to decipher the mechanisms by which protein aggregates are targeted to specific intercellular locations. Here, using an integrated approach based on individual-based modeling, time-lapse fluorescence microscopy and automated image analysis, we show that the movement of aging-related protein aggregates in *E. coli* is purely diffusive (Brownian). Using single-particle tracking of protein aggregates in live *E. coli* cells, we estimated the average size and diffusion constant of the aggregates. Our results provide evidence that the aggregates passively diffuse within the cell, with diffusion constants that depend on their size in agreement with the Stokes-Einstein law. However, the aggregate displacements along the cell long axis are confined to a region that roughly corresponds to the nucleoid-free space in the cell pole, thus confirming the importance of increased macromolecular crowding in the nucleoids. We thus used 3D individual-based modeling to show that these three ingredients (diffusion, aggregation and diffusion hindrance in the nucleoids) are sufficient and necessary to reproduce the available experimental data on aggregate localization in the cells. Taken together, our results strongly support the hypothesis that the localization of aging-related protein aggregates in the poles of *E. coli* results from the coupling of passive diffusion-aggregation with spatially non-homogeneous

macromolecular crowding. They further support the importance of "soft" intracellular structuring (based on macromolecular crowding) in diffusion-based protein localization in *E. coli*.

This work is a collaboration with the microbiology group led by A. Lindner (INSERM U1001, Cochin Med School, Paris). It has been published in [3] as part of A.S. Coquel's PhD (defended Nov 2012, co-supervision H. Berry-A. Lindner).

6.4. The molecular signaling basis of neuronal plasticity

Many of the cell-level properties of the neurons vary as a function of the signals from other neurons or past activity. These modifications are often maintained in the long term, giving rise to cell memory. We have developed models of how the implicated signaling networks self-organize to support a memory and how this leads to cell-level responses such as changes of the firing threshold [24] or the spike-timing dependence [34]. The latter, for instance, corresponds to the observation that the probability of transfer of an electrical signal (spike) between two connected neurons (the synaptic weight) adapts depending on the timing between previous consecutive presynaptic and postsynaptic spikes. Combining a model of the implicated signaling networks with experimental measurements, we have uncovered the molecular mechanisms supporting this memory.

This work is developed in collaboration with both with applied mathematicians (B. Cessac, Inria Neuromathcomp, Sophia-Antipolis) and experimental neurobiologists (L. Venance, Collège de France, Paris).

6.5. A model for adipocyte size based on size-dependent lipid fluxes

We proposed in a paper published this year [28] a novel model that explains some of the peculiarities in the fat tissue storage cells. Indeed, adipocytes, as they are called, come in various size – with up to one order of magnitude in amplitude – but do not possess any characteristic size. The cellularity, the cell size distribution, is bimodal. We showed that a simple model of size-dependent lipid fluxes (using data from Carmen Lab) can explain this bimodality and allow us to retrieve any target cell distribution. Our result also provides an elegant and testable hypothesis for the triggering of adipocytes proliferation. The amount of unstored free fatty acid is actually a marker that the population has reached its maximal volume. This amount could serve as an index to start the proliferation.

This was a joint work with experimentalists from the CARMEN Institute (INSERM UMR1060, Lyon), namely C. Soulage and A. Géloën, and was part of H. Julienne master's thesis.

6.6. Evolution of antibiotic resistance

The emergence of antibiotic resistant bacteria is a major threat to public health and there is a constant need for education to limit dangerous practices. Here, we propose to use alife software to develop training media for the public and the physicians. On the basis of the Aevol model we have been developing for more than six years, we built a game in which players fight bacterial infections using antibiotics. In this game the bacteria can evolve resistance traits, making the infection more and more difficult to cure. The game has been tested with automatic treatment procedures, showing that it behaves correctly. It was demonstrated during the French "Nuit des Chercheurs" in October 2012 and was published in 2013 in the ECAL conference [2].

This is a joint work with Dominique Schneider from the Laboratoire Adaptation et Pathogénie des Microorganismes (LAPM, UMR CNRS 5163, Grenoble).

6.7. Spontaneous dynamics of genome size

Even though numerous genome sequences are now available, evolutionary mechanisms that determine genome size, notably their fraction of non-coding DNA, are still debated. In particular, although several mechanisms responsible for genome growth (proliferation of transposable elements, gene duplication and divergence, etc.) were clearly identified, mechanisms limiting the overall genome size remain unclear. By using a matrix population model, we showed that genome size can be simply limited by the spontaneous dynamics of duplications and large deletions, which tends to make genomes shrink even if the two types of rearrangements

occur at the same rate. In the absence of Darwinian selection, we proved the existence of a stationary distribution of genome size even if duplications are twice as frequent as large deletions. To test whether selection can overcome this spontaneous dynamics, we also simulated our model numerically and chose a fitness function that directly favors genomes containing more genes, while keeping duplications twice as frequent as large deletions. In this scenario where, at first sight, everything seems to favor infinite genome growth, we showed that genome size remains nonetheless bounded. As a result, our study reveals a new pressure that could help limiting genome growth.

This work was part of Stephan Fischer's PhD thesis, which was defended in December 2013. A manuscript is currently under review. Stephan's PhD was co-supervised by Samuel Bernard (Inria Dracula team and Institut Camille Jordan, UMR CNRS 5208, Lyon).

6.8. Inference of evolutionary molecular events at different scales

We have progressed in the integration of several evolutionary events at different scales of genomes in a single model used for inference of ancient events from the observation of extant genomes. We handle nucleotide substitutions, gene duplications, losses, lateral transfers and rearrangements. We have tested the framework on 36 cyanobacteria species, reconstructing up to 80% of ancestral chromosomes in some clades [8]. The inference algorithm is still mainly sequencial, in the sense that it first accounts for nucleotide substitutions, gene duplications, losses, lateral transfers [29], and then for rearrangements. But we also developed a way to provide a feedback of the result on rearrangements to the inference of substitutions by correcting gene trees [22], [38]. We have used these methods to reconstruct a nucleotide-scale sequence of the genome of the medieval black death agent [9],[44]. It includes a chromosome and three plasmids, and is different in structure from any extant strain. We follow the first ancient bacterial genome sequencing in 2011 and complete and order the genome with computational predictions. We then dispose of a complete view of the molecular evolution in the *Yersinia pestis* clade.

This work was part of Murray Patterson's post-doctoral fellowship. It also involved collaborations with L. Gueguen and V. Daubin from the Laboratoire de Biométrie et Biologie Evolutive (UMR CNRS 5558, Lyon), with Nadia El-Mabrouk from the Département d'Informatique et de Recherche Opérationnelle in Montréal (Canada), with Cédric Chauve from the Department of Mathematics of Simon Fraser University (Burnaby, Canada), and with G. Szollosi from the Biophysics Research Group in Budapest (Hungary).

7. Partnerships and Cooperations

7.1. National Initiatives

7.1.1. ANR

- Stochagene (2011-2014). Objective: identify the molecular basis of the stochasticity of gene expression in eukaryotic cells. Partners: CGPhyMC (Olivier Gandrillon, Lyon, Leader), Genethon (Andras Paldi, Evry). Participants: G Beslon, H Berry, Gael Kaneko
- Ancestrome: phylogenetic reconstruction of ancestral "-omes", a five-year project (2012-2016), call "Bioinformatics" of the "Investissements d'avenir". Supervisor: V. Daubin (CNRS, LBBE, Lyon) ; with Institut Pasteur, ENS Paris, ISEM (Univ Montpellier 2) Participant: Eric Tannier.
- Foster: Spatiotemporal data mining: application to the understanding and monitoring of soil erosion (2011-2014). Supervisor: Nazha Selmaoui and Frédéric Flouvat (PPME Univ. Nouvelle Caledonie); with LISTIC Univ. Savoie, ICube Univ. Strasbourg, BlueCham Company. Participant: Christophe Rigotti.

7.1.2. CNRS

- E Tannier participates to a PEPS (Projet exploratoire premier soutien) called C1P: algorithmics of 1D structures, 2012-2013. Supervisor: M. Raffinot (CNRS, LIAFA, Paris), involved teams from Marne-la-Vallée, Nantes, Marseille, Bordeaux, Lyon.

7.2. European Initiatives

7.2.1. FP7 Projects

7.2.1.1. EvoEvo

Type: COOPERATION

Defi:

Instrument: Specific Targeted Research Project

Objectif: NC

Duration: November 2013 - October 2016

Coordinator: Guillaume Beslon (Inria)

Partners: Université Joseph Fourier (France, D. Schneider), Utrecht University (Nederland, P. Hogeweg), University of York (UK, S. Stepney) and CSIC (Spain, S. Elena)

Inria contact: Guillaume Beslon

Abstract: 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).

7.2.1.2. Neuron-Astro-Nets

Type: PEOPLE

Defi:

Instrument: ERCIM and Marie Curie International Outgoing Fellowships for Career Development

Objectif: NC

Duration: Juin 2013-Mai 2017 (ERCIM Juin 2013-mai 2014 puis IOF Marie Curie Juin 2014-mai 2017)

Coordinator: Hugues Berry

Partner: N. Brunel, Statistics Dept, University of Chicago (USA)

Inria contact: Maurizio DE PITTA

Abstract: Healthy functionality in the brain relies on intricate neuron-glia networks. Recent data suggest that glial, including astrocytes, play a crucial role in the processing and storing on by the brain. In particular, synapses might not be bipartite, but rather tripartite structures, comprised of the pre- and the postsynaptic terminals and the surrounding astrocyte. Moreover, astrocytes, like neurons, form intricate interconnected networks that afford long-range communication via the propagation of calcium waves. Therefore, neurons and astrocytes form intertwined neuron-glial networks supporting active partnership between the two cell populations. Hence, understanding the nature of neuron-glia interactions is essential to understand how the brain functions, and will serve as a stepping stone for deciphering brain disorders. Our long-term goal is to reveal the mechanisms that control and regulates the activity of combined neuron-glia networks. The specific objectives of this application, which are fundamental in the pursuit of that goal, are (1) to determine the properties of astrocytic modulation of synaptic transmission; and (2) to characterize how such modulation shapes neuronal activity in neuron-glia networks of the brain. To pursue these aims we will employ a comprehensive theoretical investigation to develop mathematical and biophysical models in support to experiments, at the many levels and scales of action of neuron-astrocyte signaling. The significance of understanding glia-neuron interactions is several-fold as it pertains to a very wide range of applications, from basic understanding of neuronal activity, to developing therapeutic strategies toward the treatment of neurological disorders. Here, we will focus on how modulations of synaptic transmission by astrocytes could favor the emergence of synchronized neuronal, leveraging the predictions of our theoretical approach in the perspective of brain disorders, and epilepsy in particular.

7.2.2. Collaborations with Major European Organizations

European PRACE 7th regular call.

Allocation of 34 million hours computing on the Curie super-computer for the project "Thousands of trees for 4 billon years of life evolution on Earth" led by Bastien Boussau (LBBE, UMR CNRS 5558, Lyon) and involving Eric Tannier from the Beagle team.

7.3. International Initiatives

7.3.1. Inria International Partners

7.3.1.1. Informal International Partners

- Ecole Polytechnique Fédérale de Lausanne (EPFL). We collaborate with Marion Leleu and Jacques Rougemont of the Bioinformatics and Biostatistics Core Facility of the EPFL. The general objective of this exploratory work is to investigate the relationships between epigenetic profiles and 3D structure of the genome. More precisely, we currently compare the clustering of DNA intervals based on descriptors computed from epigenetic profiles in two cases: with and without making use of information about the 3D structure of the genome. We have co-supervised a Master student (Duc Thanh Phan) in 2012-2013 on this topic.

7.3.2. Participation In other International Programs

7.3.2.1. Research Networks Program of the High Council for Scientific and Technological Cooperation between France-Israel: Astrocytic regulation of neuronal network activity (2012-2013)

The specific objectives of this joint project with groups from Tel Aviv University are to determine the properties of astrocytic calcium wave propagation and to reveal how astrocyte signals dynamically affect synaptic information transfer, thus regulating neuronal network activity. To this aim, we combine theoretical and experimental investigations of small neuron-glial networks.

Beagle (H. Berry) is coordinator of the project for the French side and supervises the modeling aspects. The coordinator for the Israeli group is Pr. Y. Hanein (Tel Aviv University Institute for Nanoscience and Nanotechnology, http://nano.tau.ac.il/hanein), who is responsible for the experimental parts. The other partner is Pr. E. Ben-Jacob (School of Physics and Astronomy, Tel Aviv University, http://tamar.tau.ac.il/~eshel/EBJG/). The project also gathers 4 PhD or Master students in Tel Aviv and Lyon.

Total amount funded : 160 k€.

7.3.2.2. ANR/NSF Bilateral programme for Collaborative Research in Computational Neuroscience (CRCNS): Modelling the vocal apparatus of birds (2013-2016)

This joint project with F. Theunissen (UC Berkeley, USA) aims at modelling the vocal apparatus of birds (Zebra Finches) to recreate vocal range of this bird using a sparser representation than the spectrum. This new representation can be used as a new parameter space to test acoustic neural coding.

This collaboration has been granted by ANR/NSF Bilateral program for Collaborative Research in Computational Neuroscience (CRCNS)(CRCNS 2012), which promotes collaborations between French and American teams. Beagle (H. Soula) is coordinator of the project for the French side and supervises the modeling aspects.

7.3.2.3. France Berkeley Fund: User-friendly phylogenomics: Bayesian simultaneous reconstruction of gene trees and species trees

We obtained a grant for a common project with J. Huelsenbeck's lab (UC Berkeley, USA) on the development of probabilistic models of genome and sequence evolution to simultaneously reconstruct gene trees and species trees, and thus study how species and their genomes have changed through time.

7.4. International Research Visitors

7.4.1. Visits of International Scientists

7.4.1.1. Visiting Professors

Participant: Sergei Fedotov.

Dates: 3 weeks in March 2013 and 3 weeks in September 2013

Institution: Mathematical School, University of Manchester (UK)

Funded by the "Lyon Mathematics Labex MiLyon, and by Inria's visiting professor's program.

Participant: Nadia El-Mabrouk.

Dates: April 2013

Institution: Département d'Informatique et de Recherche Opérationnelle in Montréal (Canada)

Funded by Inria's visiting professor's program.

7.4.1.2. Internships

Osama Khalil

Subject: Computational systems biology of signal transduction in living cells: synaptic plasticity of striatum neurons

Date: from Feb 2013 until May 2013

Institution: American University in Cairo (Egypt)

7.4.2. Visits to International Teams

During the whole 2012-2013 academic year, Hédi Soula was an Invited Professor at UC Berkeley (USA) in F. Theunissen's lab.

8. Dissemination

8.1. Scientific Animation

- Guillaume Beslon is a member of the “Comité National de la Recherche Scientifique” (CoNRS), in 6th section (Computer Science) and in the 51st section (interdisciplinary section in bioinformatics, biomathematics and biophysics).
- Guillaume Beslon is co-director of the Institut Rhône-Alpin des Systèmes Complexes (IXXI) since 2007 (the institute is directed by two persons from different disciplines – G. Beslon and P. Jensen – who exchange their roles between director and vice-director every two years. G. Beslon was vice-director for the 2011-2013 period. He was director for the previous period).
- Guillaume Beslon served as an expert for the AERES evaluation of a laboratory and a master program
- Guillaume Beslon served as an expert for the University of Windsor (Canada)
- Guillaume Beslon is a member of the Institut de Génomique Fonctionnelle de Lyon Scientific Advisory Board since 2011.
- Guillaume Beslon is member of the “Conseil de Laboratoire” of the UMR CNRS 5205 LIRIS.
- Guillaume Beslon is a member of the scientific committee of the 2014 EMBO conference “Experimental Approaches in Ecology and Evolution using Yeast and Other Species”.
- Guillaume Beslon was chairman of the 2013 edition of Evolyon.
- Carole Knibbe and Guillaume Beslon are members of the program committee of the “Alife’14” Conference.
- Hugues Berry is a member of Inria’s Evaluation Committee (CE).
- Hugues Berry was a member of hiring committees for Inria researcher positions, 2013 (Inria Centers of Lille and Sophia-Antipolis).
- Hugues Berry is a member of the steering committee of IXXI, the Rhône-Alpes Institute for Complex Systems.
- Hugues Berry co-organized, with V. Calvez, (EPI Numed) the conference “Mathematical modeling in cell biology” in Lyon, March 25-29, 2013 (http://mathbio2013.sciencesconf.org/resource/page?id=3), mainly funded by the “laboratoire d’excellence” MILYON (“Mathématique et Informatique Fondamentale de Lyon”).
- Hugues Berry was a member of the Evaluation committee for the INSERM call for funding on Cancer (“Plan Cancer”), subfield: Systems Biology.
- Hugues Berry was a member of the organization committee of the annual CNRS-INRA thematic school “EIEFB: Ecole interdisciplinaire d’échanges et de formation en biologie”, Berder Island (Morbihan, France), since 2008 (http://biophysique.mnhn.fr/berder2013/).
- Hugues Berry is editor for the "Journal of Complex Systems" (http://www.hindawi.com/journals/jcs/).
- Hugues Berry was reviewer for the conferences ISBI (IEEE International Symposium on Biomedical Imaging) 2014, UCNC (Unconventional Computation and Natural Computation) 2013 and HPCS (International Conference on High Performance Computing and Simulation) 2013.
- Hugues Berry was a member of the SPECIF committee, that awards each year the Gilles Kahn award, for the best French PhD in Computer Science, 2013.
- Christophe Rigotti is member of the Scientific Council (C.S.) of INSA Lyon.
- Christophe Rigotti co-chaired and co-organized the EGC satellite workshop FOSTA on spatiotemporal data mining, January 2012, Toulouse.

- Christophe Rigotti was a member of the Program Committee of the EGC satellite workshop FST/CERGEO on spatial and temporal data, January 2014, Rennes.
- Eric Tannier co-organized the international conference “RECOMB Comparative Genomics” in October 2013, in Lyon.
- Eric Tannier co-organized the international conference “Models and Algorithms for Genome Evolution” in August 2013 in Montreal, Canada and co-edited a book published in the "Computational biology" series of Springer [37].
- Eric Tannier and Guillaume Beslon are members of the committee of the Semovi Rhône-Alpes regular seminars.
- Eric Tannier was a member of the Program Committee of Recomb satellite workshop on comparative genomics, Lyon 2013.
- Eric Tannier was a member of the Program Committee of SeqBio-13, Paris 2013.
- Eric Tannier was a member of the Program Committee of WABI 2013.
- Eric Tannier was reviewer for the conferences BSB 2013, ICCT 2013 and LATIN 2014.
- In 2013, the members of the team were reviewers for several journals including *Theoretical Computer Science, SIAM Journal on Discrete Mathematics, Bull Math Biol, J Theor Biol, Mol Syst Biol, BMC Syst Biol, Communications in Nonlinear Science and Numerical Simulation, ISRN Computational Biology, Journal of Bioinformatics and Computational Biology, BioSystems, Journal of Biodiversity and Conservation, Frontiers in Synaptic Neuroscience, Data Mining and Knowledge Discovery, Knowledge and Information Systems, Data and Knowledge Engineering.*

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

Note that due to his sabbatical stay in Berkeley, Hédi Soula had no teaching assignment in 2012-2013.

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

Licence: Guillaume Beslon, Project Management, 20h, L3 and M1, Computer Science Department of INSA-Lyon.

Licence: Guillaume Beslon, Backstage management and organization, 20h, L3, Humanities Department of INSA-Lyon.

Licence: Carole Knibbe [5], Procedural Programming, 133h, L2

Licence: Christophe Rigotti, Imperative Programming, 39h L1 and 47h L2, Département 1er cycle of INSA-Lyon.

Licence: Christophe Rigotti, Object-Oriented Programming, 47h, L2, Département 1er cycle of INSA-Lyon.

Licence: Christophe Rigotti, Computer Simulation, 24h, L2, Département 1er cycle of INSA-Lyon.

Master: Guillaume Beslon, Bio-inspired computing, 30h, M2, Computer Science Department of INSA-Lyon and Artificial Intelligence master program of Université Lyon 1.

Master: Guillaume Beslon, Computational Biology, 10h, M2, Bioinformatics and Modeling Department of INSA-Lyon.

Master: Guillaume Beslon, Digital genetics, 2h, M2, Interface Physics-Biology master program at Ecole Normale Supérieure de Lyon (ENS-Lyon).

Master: Guillaume Beslon, Introduction to Modeling, 20h, M2, Master of Complex Systems at Ecole Normale Supérieure de Lyon (ENS-Lyon).

[5] Carole Knibbe has a “délégation Inria” for the 2013-2014 period. The teaching indicated here is for the 2012-2013 period.

Master: Carole Knibbe, Scientific methodology, 24h, M2, Artificial Intelligence master program of Université Lyon 1.

Master: Carole Knibbe, Bio-inspired computing, 14h, M2, Artificial Intelligence master program of Université Lyon 1.

Master: Carole Knibbe, Modeling and simulation in Biology and Medicine, 12h, M2, Complex Systems master program of Ecole Normale Supérieure de Lyon.

Master: Eric Tannier, Computational Biology, 24h, M2, Ecole Normale Supérieure de Lyon.

Master: Eric Tannier, Discrete Mathematics, 8h, M1, Bioinformatics and Modeling Department of INSA-Lyon.

Master: Eric Tannier, Mathématiques et Informatique pour le génome, 26h, M1, Bioinformatics and Modeling Department of INSA-Lyon.

Master: Eric Tannier, Bioinformatique, 24h, M1, ISBM Monastir, Tunisie.

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

8.2.2. Supervision

PhD: Gaël Kaneko, Analyse et modélisation de la stochasticité de l'expression génique dans des cellules eucaryotes, INSA de Lyon, defended on September 26th, 2013, co-supervised by G. Beslon and O. Gandrillon (CGPhiMC, UMR CNRS 5534, Lyon).

PhD: Stephan Fischer, Modélisation de l'évolution de la taille des génomes et de leur densite´ en gènes par mutations locales et grands réarrangements chromosomiques, INSA de Lyon, defended on December 2nd, 2013, co-supervised by C. Knibbe, G. Beslon and S. Bernard (Inria Dracula team and Institut Camille Jordan, UMR CNRS 5208, Lyon).

PhD in progress: Bérénice Batut, Study of reductive evolution of bacterial genomes using bioinformatic analyses and in silico evolutionary experiments, INSA de Lyon, started in October 2011, co-supervised by C. Knibbe, G. Beslon and G. Marais (LBBE, UMR CNRS 5558, Lyon).

PhD in progress: Charles Rocabert, Modélisation de l'évolution des microorganismes bactériens par des approches de simulation informatique, INSA de Lyon, started in Novembre 2013, co-supervised by G. Beslon and C. Knibbe.

PhD in progress: Yoram Vadee Le Brun, Evolution expérimentale in silico de réseaux de régulation génétique, INSA de Lyon, started in September 2013, superviser by G. Beslon.

PhD in progress: Magali Semeria, Biologie évolutive des systèmes, Université Lyon 1, started in September 2012, co-supervised by E. Tannier and L. Gueguen (LBBE, UMR CNRS 5558)

PhD in progress: Jules Lallouette, Transport dans les reseaux complexes : le cas des réseaux mixtes neurones-cellules gliales, INSA de Lyon, started in October 2011, supervised by H. Berry.

PhD in progress: Ilia Prokin, Computational Systems Biology of Signal Transduction in Living Cells: Synaptic Plasticity of Basal Ganglia Neurons, INSA de Lyon, started in October 2013, supervised by H. Berry.

Master internship: Ewy Yang, Détection phylogénétique de co-évolution de gènes, March-August 2013, supervised by E. Tannier

Master internship: Charles Rocabert, Evolution de la stochasticité de l'expression génique, from February 2013 to June 2013, supervised by G. Beslon

Master internship: Sylvain Devaux, Development of a computer game to teach evolution of antibiotic resistance, from October 2013 to February 2014, supervised by G. Beslon

Master internship: Maxence Dolle, Simulation of biochemical reactions in non-homogeneous media, from May 2013 until Aug 2013, co-supervised by G. Beslon and H. Berry

Master internship: Osama Khalil, Computational systems biology of signal transduction in living cells, from Feb 2013 until May 2013, supervised by H. Berry

Master internship: Amanda Lo Van, Modélisation basée sur l'individu de circuits génétiques simples, from Feb 2013 until Jun 2013, supervised by H. Berry

Master internship: Alvaro Mateos Gonzalez, Analysis of a Jump-Renewal Equation for Intracellular Subdiffusion, from Apr 2013 until Aug 2013, supervised by V. Calvez (Inria Numed) 66% and H. Berry 33%

Master internship: Duc Thanh Phan, Clustering of DNA intervals based on descriptors computed from epigenetic profiles, from Feb 2013 until Jul 2013, co-supervised by C. Rigotti and Marion Leleu (Ecole Polytechnique Fédérale de Lausanne).

8.2.3. Juries

- Guillaume Beslon reviewed the HDR manuscript and participated to the HDR defense committee of Philippe Lopez, Univ. Paris 6 Pierre et Marie Curie, December 2013.
- Guillaume Beslon participated to the PhD defense committee of Guenola Drillon, Univ. Paris 6 Pierre et Marie Curie, March 2013.
- Guillaume Beslon reviewed the PhD manuscript and participated to the PhD defense committee of Guillaume Chérel, Univ. Paris 6 Pierre et Marie Curie, 2013.
- Guillaume Beslon reviewed the PhD manuscript and participated to the PhD defense committee of Thomas Garcia, Ecole Normale Supérieure de la rue d'Ulm, Paris, December 2013.
- Guillaume Beslon reviewed the PhD manuscript and participated to the PhD defense committee of Jean-Marc Montanier, Univ. Paris Sud, 2013.
- Hugues Berry reviewed the PhD manuscript and participated to the PhD defense committee of G. Detorakis, "Cortical Plasticity, Dynamic neural fields and self-organisation", Nancy, October 2013.
- Hugues Berry reviewed the PhD manuscript and participated to the PhD defense committee of Visou ADY, "Développement et plasticité des connexions des cellules de Purkinje", Paris Descartes University, November 2013.
- Eric Tannier reviewed the PhD manuscript and participated to the PhD defense committee of Thi Hau NGuyen from the University of Montpellier 2, on October 3, 2013.
- Eric Tannier reviewed the PhD manuscript and participated to the PhD defense committee of Guenola Drillon from the University of Paris 6, on March 25, 2013.
- Eric Tannier participated to the HDR defense committee of Nicolas Thierry-Mieg, from University of Grenoble 1, January 25, 2013.
- Christophe Rigotti reviewed the PhD manuscript and participated to the defense committee of Winn Voravuthikunchai, PhD, Univ. Caen Basse Normandie, 2013.
- Christophe Rigotti participated to the HDR defense committee of Nicolas Méger, HDR, Univ. de Savoie, Annecy, 2013.

8.2.4. Invited talks

- Guillaume Beslon was an invited speaker at the workshop "Games in evolution", Ecole Normale de la rue d'Ulm, Paris, December 2013.
- Guillaume Beslon was an invited speaker of the Dyliss/Genscales groups, May 2013, Rennes, France.
- Hugues Berry was an invited speaker at the workshop "Complex Network Dynamics", March 25-26, 2013, Montpellier, France.
- Hugues Berry was an invited speaker at the workshop " Control of Self-Organizing Nonlinear Systems", August 28-30, Wittenberg (Berlin), Germany.

- Hugues Berry was an invited speaker at the workshop "BioImage Informatics", 8-9 July 2013, Curie Institute, Paris, France.
- Carole Knibbe was an invited speaker at the Evolyon workshop, November 21st 2013, Lyon.
- Carole Knibbe was an invited speaker at a FINOVI mini-symposium, June 20th 2013, Lyon.
- Christophe Rigotti gave an invited talk on "Spatiotemporal data mining" during "The Meetings of Digital Technologies" organized by ANR at the Cit ´e des Sciences et de l'Industrie, April 2013, Paris. Work in collaboration with N. Meger, C. Pothier, R. Andreoli, F. Lodge, M.-P. Doin, C. Lasserre and R. Jolivet.
- Christophe Rigotti gave an invited talk on "GFS-pattern extraction in satellite image time series: application to the monitoring of Mount Etna", Atelier Mesure de Déformations par Imagerie Spatiale, October 2013, Autrans. Work in collaboration with F. Lodge, N. Meger, L. Gueguen, C. Pothier, R. Andreoli, M.-P. Doin and M. Datcu.
- Hédi Soula was invited an invited speaker in the Seminar Sessions of ETHOS Rennes in December 2013.
- Eric Tannier was a keynote speaker at the IBC (Computational Biology Institute) in Montpellier in 2013.
- Eric Tannier was invited by the "Laboratoire d'Informatique Fondamentale" in Marseille for a talk in March 2013.

8.3. Popularization

- E. Tannier participated to large audience conferences at the Université Populaire de Lyon in Febuary 2013, giving three lectures on scientific revolutions.
- E. Tannier is a co-author of an article to the large audience journal "Pour la science" [32].

9. Bibliography

Major publications by the team in recent years

[1] B. BATUT, D. PARSONS, S. FISCHER, G. BESLON, C. KNIBBE. *In silico experimental evolution: a tool to test evolutionary scenarios*, in "BMC Bioinformatics", October 2013, vol. 14, n^{o} Suppl 15, S11 p. , http://hal.inria.fr/hal-00856813

[2] G. BESLON, B. BATUT, D. P. PARSONS, D. SCHNEIDER, C. KNIBBE. *An alife game to teach evolution of antibiotic resistance*, in "ECAL - 12th European Conference on Artificial Life - 2013", Taormina, Italy, MIT Press, 2013, http://hal.inria.fr/hal-00849345

[3] A.-S. COQUEL, J.-P. JACOB, M. PRIMET, A. DEMAREZ, M. DIMICCOLI, T. JULOU, L. MOISAN, A. 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^{o} 4 [*DOI :* 10.1371/JOURNAL.PCBI.100303], http://hal.inria.fr/hal-00798053

[4] M. DE PITTÀ, V. VOLMAN, H. BERRY, E. BEN-JACOB. *A tale of two stories: astrocyte regulation of synaptic depression and facilitation*, in "PLoS Computational Biology", 2011, vol. 7, n^{o} 12

[5] 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

[6] 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

[7] J. NAUDÉ, J. T. PAZ, H. BERRY, B. DELORD. *A theory of rate coding control by intrinsic plasticity effects*, in "PLoS Computational Biology", 2012, vol. 8, n° 1 [*DOI :* 10.1371/ JOURNAL.PCBI.1002349], http://hal.inria.fr/hal-00645336

[8] M. PATTERSON, G. SZÖLLŐSI, V. DAUBIN, E. TANNIER. *Lateral gene transfer, rearrangement, reconciliation*, in "BMC Bioinformatics", 2013, vol. 14, n° Suppl 15, S4 p. , http://hal.inria.fr/hal-00873233

[9] A. RAJARAMAN, E. TANNIER, C. CHAUVE. *FPSAC: Fast Phylogenetic Scaffolding of Ancient Contigs*, in "Bioinformatics", December 2013, vol. 29, n° 23, pp. 2987-2994, http://hal.inria.fr/hal-00859185

[10] 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

[11] 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° 43, pp. 17513-17518 [*DOI :* 10.1073/pnas.1202997109], http://hal.inria.fr/hal-00740292

[12] 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° 1, 15 p. [*DOI :* 10.1186/1741-7007-11-15], http://hal.inria.fr/inserm-00817963

Publications of the year

Doctoral Dissertations and Habilitation Theses

[13] S. FISCHER. , *Modélisation de l'évolution de la taille des génomes et de leur densité en gènes par mutations locales et grands réarrangements chromosomiques*, INSA de Lyon, December 2013, http://hal.inria.fr/tel-00924831

[14] G. KANEKO. , *Analyse et modélisation de la stochasticité de l'expression génique dans des cellules eucaryotes*, INSA de Lyon, September 2013, http://hal.inria.fr/tel-00926607

Articles in International Peer-Reviewed Journals

[15] B. BATUT, D. PARSONS, S. FISCHER, G. BESLON, C. KNIBBE. *In silico experimental evolution: a tool to test evolutionary scenarios*, in "BMC Bioinformatics", October 2013, vol. 14, n° Suppl 15, S11 p. , http://hal.inria.fr/hal-00856813

[16] H. BERRY, H. CHATÉ. *Anomalous diffusion due to hindering by mobile obstacles undergoing Brownian motion or Orstein-Ulhenbeck processes*, in "Physical Review E", 2014, http://hal.inria.fr/inria-00575651

[17] B. BOUSSAU, G. J. SZÖLLOSI, L. DURET, M. GOUY, E. TANNIER, V. DAUBIN. *Genome-scale coestimation of species and gene trees*, in "Genome Research", February 2013, vol. 23, pp. 323-330 [*DOI :* 10.1101/GR.141978.112], http://hal.inria.fr/hal-00750148

[18] B. R. CARÉ, H. A. SOULA. *Receptor clustering affects signal transduction at the membrane level in the reaction-limited regime*, in "Physical Review E", January 2013, vol. 87, n° 1 [*DOI :* 10.1103/PHYSREVE.87.012720], http://hal.inria.fr/hal-00858439

[19] A.-S. COQUEL, J.-P. JACOB, M. PRIMET, A. DEMAREZ, M. DIMICCOLI, T. JULOU, L. MOISAN, A. 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

[20] M. L. CROZE, R. E. VELLA, N. J. PILLON, H. A. SOULA, L. HADJI, M. GUICHARDANT, C. O. SOULAGE. *Chronic treatment with myo-inositol reduces white adipose tissue accretion and improves insulin sensitivity in female mice*, in "The Journal of Nutritional Biochemistry", February 2013, vol. 24, n° 2, pp. 457-66 [*DOI :* 10.1016/J.JNUTBIO.2012.01.008], http://hal.inria.fr/hal-00759518

[21] L. KOPPE, N. J. PILLON, R. E. VELLA, M. L. CROZE, C. C. PELLETIER, S. CHAMBERT, Z. MASSY, G. GLORIEUX, R. VANHOLDER, Y. DUGENET, H. A. SOULA, D. FOUQUE, C. O. SOULAGE. *p-Cresyl sulfate promotes insulin resistance associated with CKD*, in "Journal of the American Society of Nephrology", January 2013, vol. 24, n° 1, pp. 88-99 [*DOI :* 10.1681/ASN.2012050503], http://hal.inria.fr/hal-00850482

[22] M. LAFOND, M. SEMERIA, K. SWENSON, E. TANNIER, N. EL-MABROUK. *Gene tree correction guided by orthology*, in "BMC Bioinformatics", 2013, vol. 14, n° Suppl 15, S5 p. , http://hal.inria.fr/hal-00873235

[23] 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

[24] J. NAUDÉ, B. CESSAC, H. BERRY, B. DELORD. *Effects of Cellular Homeostatic Intrinsic Plasticity on Dynamical and Computational Properties of Biological Recurrent Neural Networks*, in "Journal of Neuroscience", 2013, vol. 33, n° 38, pp. 15032-15043 [*DOI :* 10.1523/JNEUROSCI.0870-13.2013], http://hal.inria.fr/hal-00844218

[25] M. PATTERSON, G. SZÖLLŐSI, V. DAUBIN, E. TANNIER. *Lateral gene transfer, rearrangement, reconciliation*, in "BMC Bioinformatics", 2013, vol. 14, n° Suppl 15, S4 p. , http://hal.inria.fr/hal-00873233

[26] A. RAJARAMAN, E. TANNIER, C. CHAUVE. *FPSAC: Fast Phylogenetic Scaffolding of Ancient Contigs*, in "Bioinformatics", September 2013, vol. 29, n° 23, pp. 2987-2994 [*DOI :* 10.1093/BIOINFORMATICS/BTT527], http://hal.inria.fr/hal-00859185

[27] 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

[28] H. A. SOULA, H. JULIENNE, C. O. SOULAGE, A. GÉLOËN. *Modelling adipocytes size distribution*, in "J Theor Biol, Journal-Full = Journal of theoretical biology", September 2013, vol. 332, pp. 89-95 [*DOI :* 10.1016/J.JTBI.2013.04.025], http://hal.inria.fr/hal-00850474

[29] G. J. SZÖLLOSI, W. ROSIKIEWICZ, B. BOUSSAU, E. TANNIER, V. DAUBIN. *Efficient Exploration of the Space of Reconciled Gene Trees*, in "Systematic Biology", August 2013, epub ahead of print [*DOI :* 10.1093/SYSBIO/SYT054], http://hal.inria.fr/hal-00856826

[30] G. J. SZÖLLOSI, E. TANNIER, N. LARTILLOT, V. DAUBIN. *Lateral Gene Transfer from the Dead*, in "Systematic Biology", January 2013, epub ahead of print [*DOI :* 10.1093/SYSBIO/SYT003], http://hal.inria.fr/hal-00784662

[31] 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

Articles in Non Peer-Reviewed Journals

[32] V. DAUBIN, S. PENEL, E. TANNIER. *L'ADN, mémoire numérique du vivant*, in "Pour la Science", October 2013, pp. 102-108, http://hal.inria.fr/hal-00878875

International Conferences with Proceedings

[33] G. BESLON, B. BATUT, D. P. PARSONS, D. SCHNEIDER, C. KNIBBE. *An alife game to teach evolution of antibiotic resistance*, in "ECAL - 12th European Conference on Artificial Life - 2013", Taormina, Italy, MIT Press, 2013, http://hal.inria.fr/hal-00849345

[34] Y. CUI, V. PAILLE, B. DELORD, S. GENET, E. FINO, L. VENANCE, H. BERRY. *Endocannabinoids mediate spike-timing dependent potentiation and depression: a model-based experimental approach*, in "the Twenty Second Annual Computational Neuroscience Meeting: CNS*2013", Paris, France, G. S. CYMBALYUK, A. A. PRINZ (editors), Biomed Central, 2013, vol. 14, O1 p. [*DOI :* 10.1186/1471-2202-14-S1-O1], http://hal.inria.fr/inserm-00842298

Scientific Books (or Scientific Book chapters)

[35] H. BERRY. *Modélisation de la diffusion-réaction dans les milieux intracellulaires encombrés*, in "Le vivant discret et continu", N. GLADE, A. STÉPHANOU (editors), Editions Matériologiques, September 2013, pp. 241-266, http://hal.inria.fr/hal-00858738

[36] H. BERRY, G. BESLON. *De la modélisation comme poésie. La modélisation de systèmes biologiques complexes vue par deux modélisateurs*, in "Modéliser & simuler. Epistémologies et pratiques de la modélisation et de la simulation", F. VARENNE, M. SILBERSTEIN (editors), Editions Matériologiques, Paris, April 2013, vol. 1, http://hal.inria.fr/hal-00815550

[37] C. CHAUVE, N. EL-MABROUK, E. TANNIER. , *Models and Algorithms for Genome Evolution*, Springer, 2013, 318 p. , http://hal.inria.fr/hal-00847154

[38] C. CHAUVE, N. EL-MABROUK, L. GUEGUEN, M. SEMERIA, E. TANNIER. *Duplication, Rearrangement and Reconciliation*, in "Models and Algorithms for Genome Evolution", Springer, 2013, http://hal.inria.fr/hal-00847155

[39] J.-G. DUMAS, J.-L. ROCH, E. TANNIER, S. VARETTE. , *Foundations of Coding: Compression, Encryption, Error-Correction*, –, 2014, A paraître, http://hal.inria.fr/hal-00765802

[40] J.-G. DUMAS, J.-L. ROCH, E. TANNIER, S. VARRETTE. , *Théorie des Codes : compression, cryptage, correction, 2e edition*, Sciences Sup, Dunod, August 2013, 384 p. , http://hal.inria.fr/hal-00932851

[41] C. KNIBBE. *L'évolution expérimentale in silico*, in "Modéliser et simuler - Epistémologies et pratiques de la modélisation et de la simulation - Tome 1", F. VARENNE, M. SILBERSTEIN (editors), Editions Matériologiques, April 2013, pp. 581-610, http://hal.inria.fr/hal-00850175

Other Publications

[42] C. CHAUVE, M. PATTERSON, A. RAJARAMAN. , *Hypergraph covering problems motivated by genome assembly questions*, 2013, 13 pages+3 page appendix A short version will appear in the proceedings of IWOCA 2013, http://hal.inria.fr/hal-00849753

[43] Y. CUI, V. PAILLE, B. DELORD, S. GENET, E. FINO, L. VENANCE, H. BERRY. *Endocannabinoids mediate spike-timing dependent potentiation and depression: a model-based experimental approach*, in "Twenty Second Annual Computational Neuroscience Meeting : CNS 2013", Paris, France, July 2013, 01 p. [*DOI :* 10.1186/1471-2202-14-S1-O1], http://hal.inria.fr/hal-00842299

[44] A. RAJARAMAN, E. TANNIER, C. CHAUVE. , *The genome of the medieval Black Death agent (extended abstract)*, 2013, Extended abstract of a talk presented at the conference JOBIM 2013. Full paper submitted, https://colloque.inra.fr/jobim2013_eng/, http://hal.inria.fr/hal-00849754

[45] G. SZÖLLŐSI, E. TANNIER, V. DAUBIN, B. BOUSSAU. , *The inference of gene trees with species trees*, 2013, arXiv:1311.0651, http://hal.inria.fr/hal-00915301

References in notes

[46] 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, 324 p. , http://dx.doi.org/10.1186/1471-2105-11-324

[47] J.-M. AURY, O. JAILLON, L. DURET, B. NOEL, C. JUBIN, B. M. PORCEL, B. SÉGURENS, V. DAUBIN, V. ANTHOUARD, N. AIACH, O. ARNAIZ, A. BILLAUT, J. BEISSON, I. BLANC, K. BOUHOUCHE, F. CÂMARA, S. DUHARCOURT, R. GUIGÓ, D. GOGENDEAU, M. KATINKA, A.-M. KELLER, R. KISSMEHL, C. KLOTZ, F. KOLL, A. LE MOUËL, G. LEPÈRE, S. MALINSKY, M. NOWACKI, J. K. NOWAK, H. PLATTNER, J. POULAIN, F. RUIZ, V. SERRANO, M. ZAGULSKI, P. DESSEN, M. BÉTERMIER, J. WEISSENBACH, C. SCARPELLI, V. SCHÄCHTER, L. SPERLING, E. MEYER, J. COHEN, P. WINCKER. *Global trends of whole-genome duplications revealed by the ciliate Paramecium tetraurelia*, in "Nature", Nov 2006, vol. 444, n^{o} 7116, pp. 171–178, http://dx.doi.org/10.1038/nature05230

[48] 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, R23 p. , http://dx.doi.org/10.1186/gb-2004-5-4-r23

[49] 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

[50] 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

[51] 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

[52] 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

[53] B. R. 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

[54] 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

[55] 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.

[56] 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

[57] V. DAUBIN, N. A. MORAN, H. OCHMAN. *Phylogenetics and the cohesion of bacterial genomes*, in "Science", Aug 2003, vol. 301, n^{o} 5634, pp. 829–832, http://dx.doi.org/10.1126/science.1086568

[58] 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]

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

[60] 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

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

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

[63] 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

[64] 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

[65] O. JAILLON, J.-M. AURY, F. BRUNET, J.-L. PETIT, N. STANGE-THOMANN, E. MAUCELI, L. BOUNEAU, C. FISCHER, C. OZOUF-COSTAZ, A. BERNOT, S. NICAUD, D. JAFFE, S. FISHER, G. LUTFALLA, C. DOSSAT, B. SÉGURENS, C. DASILVA, M. SALANOUBAT, M. LEVY, N. BOUDET, S. CASTELLANO, V.

ANTHOUARD, C. JUBIN, V. CASTELLI, M. KATINKA, B. VACHERIE, C. BIÉMONT, Z. SKALLI, L. CATTOLICO, J. POULAIN, V. DE BERARDINIS, C. CRUAUD, S. DUPRAT, P. BROTTIER, J.-P. COUTANCEAU, J. GOUZY, G. PARRA, G. LARDIER, C. CHAPPLE, K. J. MCKERNAN, P. MCEWAN, S. BOSAK, M. KELLIS, J.-N. VOLFF, R. GUIGÓ, M. C. ZODY, J. MESIROV, K. LINDBLAD-TOH, B. BIRREN, C. NUSBAUM, D. KAHN, M. ROBINSON-RECHAVI, V. LAUDET, V. SCHÄCHTER, F. QUÉTIER, W. SAURIN, C. SCARPELLI, P. WINCKER, E. S. LANDER, J. WEISSENBACH, H. R. CROLLIUS. *Genome duplication in the teleost fish Tetraodon nigroviridis reveals the early vertebrate proto-karyotype.*, in "Nature", Oct 2004, vol. 431, n° 7011, pp. 946–957, http://dx.doi.org/10.1038/nature03025

[66] 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° 10, pp. 2344-2353

[67] 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° 1, pp. 149-156c

[68] 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.

[69] 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° 4, pp. 621–630

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

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

[72] J. MA, L. ZHANG, B. B. SUH, B. J. RANEY, R. C. BURHANS, W. J. KENT, M. BLANCHETTE, D. HAUSSLER, W. MILLER. *Reconstructing contiguous regions of an ancestral genome*, in "Genome Res", Dec 2006, vol. 16, n° 12, pp. 1557–1565, http://dx.doi.org/10.1101/gr.5383506

[73] 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° 8, e21915, http://dx.doi.org/10.1371/journal.pone.0021915

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

[75] M. MUFFATO, A. LOUIS, C.-E. POISNEL, H. R. CROLLIUS. *Genomicus: a database and a browser to study gene synteny in modern and ancestral genomes.*, in "Bioinformatics", Apr 2010, vol. 26, n° 8, pp. 1119–1121, http://dx.doi.org/10.1093/bioinformatics/btq079

[76] 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° 11, pp. 1545–1557 [*DOI :* 10.1101/GR.109744.110]

[77] 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

[78] 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

[79] 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

[80] 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

[81] 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