IN PARTNERSHIP WITH:
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Université Claude Bernard (Lyon 1)

Activity Report 2014

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 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 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* [47] 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

[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 Biométrie 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.

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 [35]. 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 [39]. 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 [45]. 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 [41]. 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 [52]).

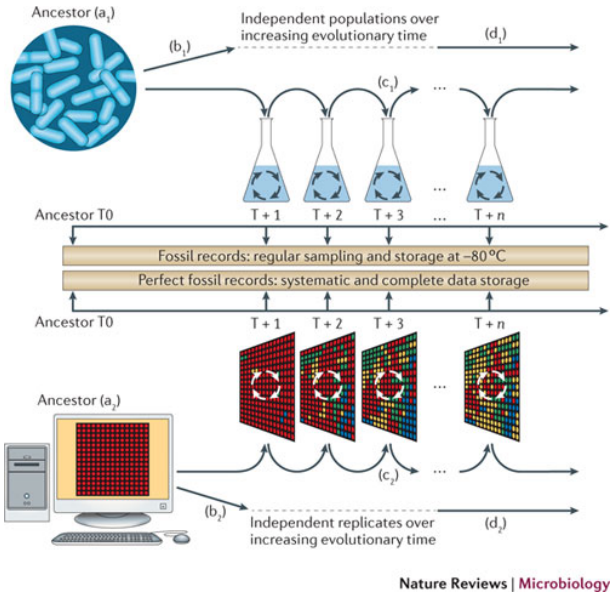

Figure 1. Parallel between experimental evolution and artificial evolution

As a consequence, this model can be used to study how evolutionary pressures like the ones for robustness or evolvability can shape genome structure [53], [50], [51], [60]. 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 [53], [50], [61]. 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 [44]. 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 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 [37], [36], [38]. 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 [36]. 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 [53], and no difference in lifestyles and environment was needed to explain the complexity of the gene regulatory network [36]. 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 Raevol, 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, we have started to study how to improve the performance of (R-)Aevol. Thanks to the ADT Aevol, one and a half full time engineers will work to improve 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 Telsa). 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, RUNTIME, MESCAL). 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.

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 [54], [48], 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 [46], which enable the reconstruction of small parts of ancestral sequences, individual genes for example [55]. But models of whole genome evolution, taking into account large scale events like duplications, insertions, deletions, lateral transfer, rearrangements are just being developped [63], [42]. 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 [43], on the rearrangements due to duplications [33], [62], on the reasons of variation of genome size [49], [56]. 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 [57], methods for reconstructing the organization of ancestral genomes [58], [40], [59], or for detecting lateral gene transfer events [32], [8]. 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. New Software and Platforms

4.1. Aevol (artificial evolution)

Participants: Guillaume Beslon, Jonathan Rouzaud-Cornabas, Carole Knibbe, Priscila Biller, 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. Thanks to a two-year grant from Inria's Technological Development Department (ADT « aevol »), the development of an improved and parallel version of the software has started in October.
- URL: http://www.aevol.fr

4.2. EvoEvo modelization tool

Participants: Charles Rocabert, Guillaume Beslon, Carole Knibbe.

- Contact: Guillaume Beslon
- In the context of the EvoEvo european project (http://www.evoevo.eu/) 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.

4.3. 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) has been supported by 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).

4.4. 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/

4.5. 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).

5. New Results

5.1. Highlights of the Year

We organized two satellite workshops of international conferences:

- The Aevol tutorial during ALife 2014 (July 30 - August 2, New York) http://www.aevol.fr/alifeTutorial
- The "Computational Methods and Modeling of Astrocyte Physiology and Neuron-Glia Interactions" workshop during the Computational NeuroScience 2014 conference (July 26 - 31, Quebec City, Canada)

These highlight our active presence in the scientific life of our two sub-domains in major conferences.

5.2. Sparse short-distance connections enhance calcium wave propagation in a 3D model of astrocyte networks

Participants: H. Berry, J. Lallouette, M. De Pittá

Traditionally, astrocytes have been considered to couple via gap-junctions into a syncytium with only rudimentary spatial organization. However, this view is challenged by growing experimental evidence that astrocytes organize as a proper gap-junction mediated network with more complex region-dependent properties. On the other hand, the propagation range of intercellular calcium waves (ICW) within astrocyte populations is as well highly variable, depending on the brain region considered. This suggests that the variability of the topology of gap-junction couplings could play a role in the variability of the ICW propagation range. Since this hypothesis is very difficult to investigate with current experimental approaches, we explored it using a biophysically realistic model of three-dimensional astrocyte networks in which we varied the topology of the astrocyte network, while keeping intracellular properties and spatial cell distribution and density constant. Computer simulations of the model suggest that changing the topology of the network is indeed sufficient to reproduce the distinct ranges of ICW propagation reported experimentally. Unexpectedly, our simulations also predict that sparse connectivity and restriction of gap-junction couplings to short distances should favor propagation while long–distance or dense connectivity should impair it. Altogether, those results provide support to recent experimental findings that point towards a significant functional role of the organization of gap-junction couplings into proper astroglial networks. Dynamic control of this topology by neurons and signaling molecules could thus constitute a new type of regulation of neuron-glia and glia-glia interactions.

This result has been published in [18] and as conference talks. It is based on J. Lallouette's PhD thesis work in collaboration with M. De Pittà (postdoc in the team) and E Ben-Jacob, Tel Aviv University, Israel.

5.3. Glutamate Mediated Astrocytic Filtering of Neuronal Activity

Participants: H. Berry, J. Lallouette, M. De Pittá

Neuron-astrocyte communication is an important regulatory mechanism in various brain functions but its complexity and role are yet to be fully understood. In particular, the temporal pattern of astrocyte response to neuronal firing has not been fully characterized. Here, we used neuron-astrocyte cultures on multi-electrode arrays coupled to Ca2+ imaging and explored the range of neuronal stimulation frequencies while keeping constant the amount of stimulation. Our results reveal that astrocytes specifically respond to the frequency of neuronal stimulation by intracellular Ca2+ transients, with a clear onset of astrocytic activation at neuron firing rates around 3-5 Hz. The cell-to-cell heterogeneity of the astrocyte Ca2+ response was however large and increasing with stimulation frequency. Astrocytic activation by neurons was abolished with antagonists of type I metabotropic glutamate receptor, validating the glutamate-dependence of this neuron-to-astrocyte pathway. Using a realistic biophysical model of glutamate-based intracellular calcium signaling in astrocytes, we suggest that the stepwise response is due to the supralinear dynamics of intracellular IP3 and that the heterogeneity of the responses may be due to the heterogeneity of the astrocyte-to-astrocyte couplings via gap junction channels. Therefore our results present astrocyte intracellular Ca2+ activity as a nonlinear integrator of glutamate-dependent neuronal activity.

This result has been published in a paper currently in press, [26] and is a direct result from J. Lallouette's PhD thesis in collaboration with Y. Hanein's group, in Tel Aviv University (for the experimental measurements), M. De Pittà (postdoc in the team), and E Ben-Jacob, Tel Aviv University, Israel.

5.4. Space-induced bifurcation in repression-based transcriptional circuits

Participants: H. Berry, A. Lo Van

Experimental measurements of the mobility of macromolecules, especially proteins, in cells and their membranes consistently report transient subdiffusion with possibly position-dependent —non-homogeneous— properties. However, the spatiotemporal dynamics of protein mobility when transient subdiffusion is restricted to a subregion of space is still unclear. We have investigated the spatial distribution at equilibrium of proteins undergoing transient subdiffusion due to continuous-time random walks (CTRW) in a restricted subregion of a two-dimensional space. Our Monte-Carlo simulations suggest that this process leads to a non-homogeneous spatial distribution of the proteins at equilibrium, where proteins increasingly accumulate in the CTRW subregion as its anomalous properties are increasingly marked. These results suggest that, even though they exhibit the same time-dependence of the mean-squared displacement, the different scenarios proposed to account for subdiffusion in the cell lead to different protein distribution in space, even at equilibrium and without coupling with reaction. We also we assessed the influence of the spatial distribution of the genes on the dynamics of 3-gene transcriptional ring networks regulated by repression, i.e. repressilator circuits. Our simulations suggest that variations of spatial parameters – namely the degree of demixing of the positions of the gene or the spatial range of the mRNA and proteins (i.e. the typical distance they travel before degradation) – have dramatic effects by switching the dynamical regime from spontaneous oscillations to a stationary state where each species fluctuates around a constant value. By analogy with the bifurcations arising from the variation of kinetic parameters, we referred to those transitions as space-induced bifurcations. Therefore, our results strongly support the idea that the spatial organization of the molecular actors of transcriptional networks is crucial for the dynamics of gene expression and suggest that the spatial localization of the synthetic genes in the cell could be used as an additional toggle to control the dynamics of the inserted construct in synthetic biology experiments.

This group of results has been published in [20], [13], [12] and [23]. It consists in the PhD and Master works of B. Caré and A. Lo Van, respectively, and a collaboration with H Chaté, CEA, Saclay.

5.5. Modeling interaction of transcription processes in neighbour genes

Participants: G. Beslon, S. Meyer

During the transcription process, the genetic sequence encoded in the DNA molecule is expressed by an enzymatic complex. This process is often considered as independent for each gene, despite numerous reported cases of one transcribed gene perturbing a neighbour gene's expression, which is then regarded as a side-effect. Here, we suggest in the contrary that such interactions are a widespread feature, resulting from the propagation along the DNA molecule of mechanical stress generated during gene transcription. This torsional stress modifies the facility with which the transcription machinery separates the two strands of the double-helix in order to access the bases, and thus the expression level of any gene located nearby. We develop a quantitative model of this effect, showing that it depends strongly on the orientation of the genes, which is confirmed by the analysis of in vivo expression levels in the drosophila genome. This observation suggests that torsional coupling may play an important role in genetic regulation, and might favor the orientation-dependent co-localization of genes involved in similar functions, which need to be expressed together.

Publication: [21]

5.6. A model of genome size evolution

Participants: G. Beslon, C. Knibbe, S. Fisher

Even though numerous genomic 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.

In collaboration with Samuel Bernard (Inria Dracula Team and Institut Camille Jordan, UMR CNRS 5208, Lyon), we have developed a model for genome size evolution that takes into account both local mutations such as small insertions and small deletions, and large chromosomal rearrangements such as duplications and large deletions. We introduced the possibility of undergoing several mutations within one generation. The model, albeit minimalist, revealed a non-trivial spontaneous dynamics of genome size: in the absence of selection, an arbitrary large part of genomes remains beneath a finite size, even for a duplication rate 2.6-fold higher than the rate of large deletions, and even if there is also a systematic bias toward small insertions compared to small deletions. Specifically, we showed that the condition of existence of an asymptotic stationary distribution for genome size non-trivially depends on the rates and mean sizes of the different mutation types. We also gave upper bounds for the median and other quantiles of the genome size distribution, and argue that these bounds cannot be overcome by selection. Taken together, these results show that the spontaneous dynamics of genome size naturally prevents it from growing infinitely, even in cases where intuition would suggest an infinite growth. This work was part of Stephan Fischer's PhD thesis, which was defended in December 2013.

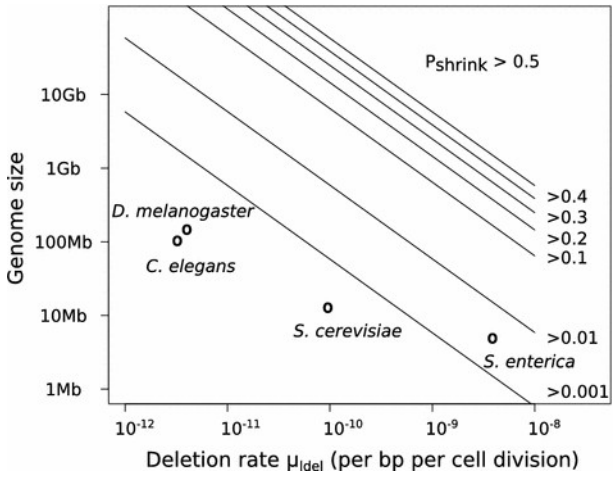

Figure 2. Comparison of the bounds on genome size with the genome size for four organisms. Spontaneous deletion rates were computed per base pair and per cell division from experimental data on mutation accumulations for the bacterium Salmonella enterica, the budding yeast Saccharomyces cerevisiae, the worm Caenorhabditis elegans and the fruit fly Drosophila melanogaster. The value next to each line is the lower bound for the probability that a genome located along this line will shrink at the next step in our model for equal duplication and deletion rates.

This year, using quantitative numerical examples with parameters taken from biological data, we showed that, in practice, a shrinkage bias appears very quickly in genomes undergoing mutation accumulation, even though DNA gains and losses appear to be perfectly symmetrical at first sight. This spontaneous dynamics provides the genome with a stability-related size limit below which it can be influenced by other evolutionary forces (selection, drift, biases, ...).

All this work has been published this year [15], and is already mentioned as "most read article" by Springer.

5.7. A novel view on reductive evolution

Participants: G. Beslon, C. Knibbe, B. Batut

Bacterial genomes show substantial variations in size. The smallest bacterial genomes are those of endocellular symbionts of eukaryotic hosts, which have undergone massive genome reduction and show patterns that are consistent with the degenerative processes that are predicted to occur in species with small effective

population sizes. However, similar genome reduction is found in some free-living marine cyanobacteria that are characterized by extremely large populations. Using a combination of bioinformatics approaches and of in silico experimental evolution (with the aevol model), we have been able to propose a scenario that explains the reductive evolution of marine bacteria.

This work was part of Bérénice Batut's PhD thesis [10], which was defended in November 2014. Bérénice was co-supervised by Guillaume Beslon and Carole Knibbe (Inria BEAGLE team) for the simulations and by Gabriel Marais and Vincent Daubin (Laboratoire de Biométrie et Biologie Evolutive, UMR CNRS 5558) for the genomic analyses. This work had already yielded a publication in 2013 [34]. This year, we published a review in the high-level journal [11]. The scenario proposed in the PhD manuscript, as well as the simulations and analyses done this year to support it, should be published in 2015.

5.8. Genome evolution aware gene trees

Participant: E. Tannier

Traditionally the inference of a gene tree is made from a multiple alignment of homologous sequences according to a model of molecular evolution. Trees for several gene families are thus constructed one by one, independently from each other. Constructed this way trees often carry unresolutions or bad resolutions. Information for their full resolution may lie in the poorly exploited dependency between gene families, each bringing information for the resolution of the others. We used several kinds of such dependencies in the construction of gene trees: information from a species tree through a model of gene content evolution, information from extant synteny through ortholog predictions, and information from ancestral synteny through a model of gene neighborhood evolution. We developed, improved, implemented and gave a user interface to several "correction" techniques, yielding a series of correction modules called "RefineTree". We tested its parts on simulated data and apply it on the full set of gene families from the Ensembl Compara database. We showed that according to several measures including the tree likelihood computed from sequence evolution, the stability of genome content and the linearity of ancestral chromosomes, trees corrected by refineTree are arguably more plausible than the ones stored by Ensembl.

This work has been achieved by Magali Semeria, Laurent Gueguen (LBBE) and Eric Tannier in Lyon, in collaboration with Nadia El-Mabrouk's group from the computer science department of the university of Montreal. This collaboration started when Nadia El-Mabrouk was an Inria visiting professor in our team in 2012 and 2013. An article has been submitted.

5.9. Variable food availability increases weight: a mathematical prediction

Participant: H. Soula

Due to the conservation of energy, the energy storage in adipose tissue reflect the difference of energy expenditure and energy intake. Without change in physical activity, the main paradigm has always been that this storage does not depend on the timing of intake but on its whole temporal integration: the overall food intake. However, mammal and especially rats can compensate energy expenditure to save energy in case of starving. This adaptation should provoke variation in energy expenditure when food availability varies in time. Using animal experiments and mathematical modelling, we showed that indeed food availability variation - while conserving the same amount of energy - can disrupt and perturb energy balance. Submitted to variation in availability with a period above 4 weeks, rats where bigger with higher fat mass than control. Even so these rats had eaten the same amount of food as the control group during the same period. Our mathematical model uses delay equations and can predict both the food intake and the body weight variations. We showed that delay in energy saving adaptation cause this variation and estimate the lag at 1 week. This result could very well apply to humans in the so called 'yoyo regime'. Regime that are stopped are a typical case of food intake variation and could cause greater fat accretion instead of body weight reduction. We show that this should happen if the regime lasts longer than one week.

This result has been the subject of an article in the weekly journal of Inserm Rhônes-Alpes with an interview of author H. Soula.

5.10. Insights on gene family dynamics from digital genetics experiments

Participants: C. Knibbe

Gene families are sets of homologous genes formed by duplications of a single original gene. Inferring their history in terms of gene duplications, gene losses and gene mutations yields fundamental insights into the molecular basis of evolution. However, the traditional approach, the phylogenetic inference of gene family evolution, faces two difficulties: (i) the delimitation of gene families based on sequence similarity, and (ii) the fact that the models of evolution used for reconstruction are tested against simulated data that are produced by the model itself. This year, we showed that digital genetics, or in silico experimental evolution, can provide thought-provoking synthetic gene family data, robust to rearrangements in gene sequences and, most importantly, not biased by where and how we think natural selection should act. Using Aevol, we analyzed the evolution of 3,512 synthetic gene families under directional selection. The turnover of gene families in evolutionary runs was such that only 21% of those families would be accessible for classical phylogenetic inference. Extinct families showed patterns different from the final, observable ones, both in terms of dynamics of gene gains and losses and in terms of gene sequence evolution. This study also reveals that gene sequence evolution, and thus evolutionary innovation, occurred not only through local mutations, but also through chromosomal rearrangements that re-assembled parts of existing genes.

This work was published in the international conference ALIFE 2014 [28].

6. Partnerships and Cooperations

6.1. Regional Initiatives

6.1.1. Labex Ecofect Call

- IntraCell-X-Evo (2014-2015): Experimental evolution of an intracellular bacterium within its host cell. Supervisor: Thomas Henry, INSERM Lyon. Participants: Eric Tannier.

6.2. National Initiatives

6.2.1. ANR

- Stochagene (2011-2014). Objective: identify the molecular basis of the stochasticity of gene expression in eukaryotic cells. Partners: CGPhyMC (O Gandrillon, Lyon, Leader), Genethon (A Paldi, Evry). Participants: G Beslon, H Berry, G Kaneko
- Ancestrome: phylogenetic reconstruction of ancestral "-omes", a five-year project (2012-2017), 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.
- Foster: Spatiotemporal data mining: application to the understanding and monitoring of soil erosion (2011-2014). Supervisor: N Selmaoui and F Flouvat (PPME Univ. Nouvelle Caledonie); with LISTIC Univ. Savoie, ICube Univ. Strasbourg, BlueCham Company. Participant: C Rigotti.
- Dopaciumcity (2014-2017) (Dopamine modulation of calcium influx underlying synaptic plasticity): a 4-year project (2014-2017) 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

6.3. European Initiatives

6.3.1. FP7 & H2020 Projects

6.3.1.1. EvoEvo

Type: FP7

Defi: Future and Emerging Technologies

Instrument: Specific Targeted Research Project

Objectif: FET Proactive: Evolving Living Technologies

Duration: September 2013 - August 2016

Coordinator: Guillaume Beslon

Partner: Université Joseph Fourier (France, D. Schneider), Utrecht University (Netherland, 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 study this process of "evolution of evolution" and use this knowledge to develop new evolutionary approaches in information science. 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.

6.3.1.2. Neuron-Astro-Nets

Type: FP7

Defi: NC

Instrument: Marie Curie International Outgoing Fellowships for Career Development

Objectif: NC

Duration: (2013-2017)

Coordinator: H. Berry, M. De Pittà (Inria)

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

Inria contact: Maurizio DE PITTA

Abstract: 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.

6.4. International Initiatives

6.4.1. Inria International Partners

6.4.1.1. Declared Inria International Partners

- Nadia El-Mabrouk, from the University of Montreal in Canada, came as an Inria invited researcher in 2012 and 2013. Since then we have several co-authored papers, including one submitted this year, and a co-edited book.
- Cedric Chauve from Simon Fraser University in Vancouver, Canada, is a very regular collaborator of Eric Tannier. We still have a publication in preparation. Cedric was visiting the LBBE lab in june 2014. We obtained a PIMS (Pacific Institute of Mathematics Studies) grant for a visit in 2015.
- Istvan Miklos, from the Renyi Institute in Budapest, is a regular collaborator of Eric Tannier, and we have a co-publication in 2014 [22].

- Joao Meidanis, from the University of Campinas in Brazil, is a collaborator of Eric Tannier. Priscila Biller, supervised by J. Meidanis, is spending 12 months in the BEAGLE team.

6.4.1.2. Informal International Partners

- Wolfgang Banzhaf (New Foundland Memorial University, Canada). Together with Wolfgang Banzhaf, we initiated a theoretical work on the concept of "open-endedness". We are currently writing a collective position paper to precisely define this currently informal concept and to design minimal conditions to simulate it in silico.

6.4.2. Participation In other International Programs

- Dopaciumcity (2014-2016): Dopamine modulation of calcium influx underlying synaptic plasticity. Partners: George Mason University, Fairfax, VA, USA (Kim L. Blackwell, US project leader) Collège de France, Paris, France (Laurent Venance, French project leader) Inria Rhône-Alpes, France, (H. Berry) from the ANR-NSF-NIH Call for French-US Projects in Computational Neuroscience.
- User-friendly Phylogenomics (2014): Bayesian simultaneous reconstruction of gene trees and species trees. France Berkeley Fund. Inria Participants: Eric Tannier. 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.
- 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 Computtional 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.

6.5. International Research Visitors

6.5.1. Visits of International Scientists

- Sergei Fedotov (Department of Mathematics, University of Manchester, UK) was a visiting professor in BEAGLE from June 5 to June 17, 2014. Collaboration with H. Berry and A. Mateos-Gonzalez

6.5.1.1. Internships

- Priscilla Biller spends a year in the BEAGLE team, during her Ph-D preparation in University of Campinas, Brazil

6.5.2. Visits to International Teams

- G Beslon spent a week in New Foundland Memorial University (July 2014) to attend a workshop on the concept of "open-endedness".
- C Rocabert spent 10 days in Utrecht University to collaborate with the bioinformatics and theoretical biology group. The objective was to exchange ideas to develop and integrated evolutionary model.
- H. Berry was invited to the BioMedTech Institute of Tampere University of Technology for one week (8-12 Dec. 2014)

7. Dissemination

7.1. Promoting Scientific Activities

7.1.1. Scientific events organisation

7.1.1.1. general chair, scientific chair

- Guillaume Beslon is a member of the Comité National de la Recherche Scientifique (CoNRS), section 6 (computer science) and CID 51 (interdisciplinary commission, Bioinformatics, Biophysics, Biomathematics)
- Guillaume Beslon is a member of the direction committee of the Rhône-Alpes Institute of Complex Systems (IXXI)
- Hugues Berry is the President of the hiring committee for "young researchers" (CR2), Inria Grenoble Research Center, 2014.
- Hugues Berry is a Member of Inria's Evaluation Committee (Commission d'Evaluation)
- Hugues Berry is a Member of the Inria's Administrative Committee (Commission Administrative Paritaire)
- Eric Tannier is an elected member of the administration council of Inria.
- Hugues Berry is a Member of the Science Steering Committee of the Rhône-Alpes Complex Systems Institute (IXXI)
- Hugues Berry is Co-organizer (with M. De Pittà, BEAGLE) of the workshop "Computational Methods and Modeling of Astrocyte Physiology and Neuron-Glia Interactions", held as part of the conference OCNS (Organization for Computational Neuroscience) 2014 in Quebec, Canada, July 26-31, 2014.

7.1.2. Scientific events selection

7.1.2.1. member of the conference program committee

- Eric Tannier: Recomb Comparative Genomics 2014
- Christophe Rigotti: International Conference on Data Mining
- Christophe Rigotti: Workshop on Spatial Data Mining at the national conference EGC 2014
- Guillaume Beslon and Carole Knibbe: scientific committee of Alife'14 (New-York, July 2014)
- Carole Knibbe: ECCB 2014 (European Conference on Computational Biology)

7.1.2.2. reviewer

- Eric Tannier: LATIN 2014

7.1.3. Journal

7.1.3.1. member of the editorial board

- Hugues Berry: AIMS Biophysics (http://aimspress.com/aimsbpoa/ch/index.aspx/)
- Hugues Berry: the Journal of Complex Systems (www.hindawi.com/journals/jcs/)

7.1.3.2. reviewer

- Eric Tannier: BMC Bioinformatics, BMC Genomics, Theoretical Computer Science, Journal of Bioinformatics and Computational Biology.
- H. Soula: Biophysical Journal, Biosystems, Journal of theoretical Biology
- Carole Knibbe: Journal of Theoretical Biology

7.2. Teaching - Supervision - Juries

7.2.1. Teaching

Master : Eric Tannier, Computational Molecular Biology, 30heqTD, M2 ENS Lyon (responsabilité du module)

Master : Eric Tannier, Mathématiques et Informatique pour le Génome, 24heqTD, M1 INSA Lyon

Master : Eric Tannier, Mathématiques Discrètes, 8heqTD, M1 INSA Lyon

Doctorat : Eric Tannier, Comparative Genomics, 4heqTD, Ecole de Printemps d'Informatique Théorique, Oléron

Licence: Jonathan Rouzaud-Cornabas, Programmation Orienté Objet - C++, 48.5h, L3, INSA de Lyon, France

Master: Jonathan Rouzaud-Cornabas, Interface Homme-Machine, 42.75h, M1, INSA de Lyon, France

Master: Jonathan Rouzaud-Cornabas, Systèmes d'Exploitation Avancés, 59.87h, M1, INSA de Lyon, France

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

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

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

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

Licence : Guillaume Beslon, architecture des ordinateurs, 150heqTD, INSA-Lyon

Master : Guillaume Beslon, informatique bioinspirée, 30heqTD, M2 INSA Lyon et M2 Lyon 1

Master : Guillaume Beslon, biologie computationnelle, 9heqTD, M2 INSA Lyon

Licence H. Soula Software Development L3 90h INSA LYON

Licence H. Soula Linear Algebra L3 45h INSA LYON

Licence H. Soula Biology Modelling L3 45h INSA LYON

Master H. Soula Numerical Optimization M1 12h

Master H. Soula Computational Biology M2 30h

7.2.2. Supervision

PhD: Jules Lallouette, Modélisation des réponses calciques de réseaux d'astrocytes: relation entre topologie et dynamiques, INSA Lyon, dec 4th 2014, H. Berry

PhD in progress: Alexandre Foncelle, Modeling the signaling pathway implicated in STDP: the role of endocannabinoid and dopamine signaling, 2014, H. Berry

PhD in progress: Sergio Peignier, Conception d'algorithmes de fouille de données exploitant des mécanismes inspirés de l'évolution, INSA de Lyon, started in September 2014, Christophe Rigotti and Guillaume Beslon.

PhD in progress: Alvaro Mateos Gonzalez, Anomalous subdiffusion equations as diffusion limits to integro PDEs with age structure. 2014. co-supervised by H. Berry (30%) with Vincent Calvez (EPI Numed) and Thomas Lepoutre (EPI Dracula).

PhD in progress: Ilya Prokin, Modeling and simulation of signal transduction in living cells: synaptic plasticity of basal ganglia neurons, 2013, H. Berry

PhD in progress : Magali Semeria, Modèles d'évolution de relations entre les gènes, 2012, Eric Tannier, Laurent Gueguen

PhD in progress : Wandrille Duchemin, Phylogénie des dépendances, dépendances des phylogénies, 2014, Eric Tannier, Vincent Daubin

PhD in progress : Yoann Anselmetti, Evolution de la structure des génomes même mal assemblés, 2014, Eric Tannier, Sèverine Bérard

PhD in progress : Priscila Biller, Phylogenies of artificial lineages, 2012, Joao Meidanis (1 year internship supervised by Eric Tannier)

PhD in progress: Arnaud Lefray, Information Flow Protection on Cloud Infrastructure, 2012, INSA CVL et ENS Lyon, Eddy Caron, Jonathan Rouzaud-Cornabas, Christian Toinard

PhD in progress : Charles Rocabert, modélisation de l'évolution de l'évolution, 2013, Guillaume Beslon, Carole Knibbe

PhD in progress : Yoram Vadée-le-Brun, évolution des réseaux de régulation, 2013, Guillaume Beslon, Jonathan Rouzaud-Cornabas

PhD : Bérénice Batut, Étude de l'évolution réductive des génomes bactériens par expériences d'évolution in silico et analyses bioinformatiques, soutenue le 21 novembre 2014, Guillaume Beslon, Carole Knibbe, Gabriel Marais, Vincent Daubin.

HdR : Hédi Soula, Signalisation en biologie computationnelle : de la membrane à l'individu, soutenue le 26 mai 2014.

PhD in progress M. Jacquier 'mathematical model of food intake and leptin resistance' 2012-2015 H. Soula and F. Crauste (Dracula)

7.2.3. Juries

- Guillaume Beslon reviewed the manuscript and participated to the defence committee of the HdR of Philippe Lopez, UPMC.
- Guillaume Beslon reviewed the manuscript and participated to the defence committee of the PhD of Colin Raeside, Université de Grenoble
- Eric Tannier reviewed the manuscript and participated to the defense committee of the Ph-D of Antoine Thomas, Inria Lille.
- H. Berry served in the PhD examination committee of Z. Chaker, "Rôle de la signalisation IGF dans la régulation de l'homéostasie tissulaire durant le vieillissement ", Univ. Paris Descartes, December 2014 (examiner)
- H. Soula was in the examination committee of J. Lalouette Modélisation des réponses calciques de réseaux d'astrocytes: relation entre topologie et dynamiques, INSA Lyon, dec 4th 2014
- Cacole Knibbe was a member of the recruiting committee of an assistant professor at INSA.

7.3. Popularization

- Guillaume Beslon published an interview on modeling in "la revue du progres".

8. Bibliography

Major publications by the team in recent years

[1] 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

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Publications of the year

Doctoral Dissertations and Habilitation Theses

[10] B. BATUT. *Study of reductive genome evolution in bacterial genomes with in silico evolution experiments and bioinformatics analyses*, INSA de Lyon, November 2014, https://hal.inria.fr/tel-01092571

Articles in International Peer-Reviewed Journals

[11] B. BATUT, C. KNIBBE, G. MARAIS, V. DAUBIN. *Reductive genome evolution at both ends of bacterial population size spectrum*, in "Nature Reviews Microbiology", December 2014, vol. 12, n° 12, pp. 841-850 [*DOI :* 10.1038/NRMICRO3331], https://hal.archives-ouvertes.fr/hal-01092392

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