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Activity Report 2011

Team Beagle

Artificial Evolution and Computational Biology

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Computational Biology and Bioinformatics

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Team Beagle

Keywords: Computational Biology, Artificial Evolution, Modeling, Simulation, Evolution, Cell Biology

This team is a common project with INSA-Lyon and Claude Bernard University (Lyon 1). It has been created in June 2011 and is on its way to become a project team in 2012.

1. Members

Research Scientists

Hugues Berry [Junior Researcher Inria, HdR]
Eric Tannier [Junior Researcher Inria, since December 1st 2011 (since E. Tannier joins us in December, his work in 2011 is not integrated to the annual report)., HdR]

Faculty Members

Guillaume Beslon [Team leader, Professor INSA-Lyon]
Carole Knibbe [Associate Professor Univ. Claude Bernard Lyon 1]
Christophe Rigotti [Associate Professor, INSA-Lyon, HdR]
Hédi A. Soula [Associate Professor, INSA-Lyon]

PhD Students

Bérénice Batut [INSA Lyon, started September 2011, co-supervised by G. Beslon and G. Marais]
Bertrand Caré [Started October 2009, Funded by an ADR Région Rhône-Alpes grant, co-supervised by H. Soula and C. Rigotti]
Anne-Sophie Coquel [Funded by AE ColAge, started September 2010, co-supervised by H. Berry and A. Lindner]
Stephan Fischer [INSA Lyon, started September 2010, supervised by G. Beslon and C. Knibbe]
Jules Lallouette [INSA Lyon, started September 2011, supervised by H. Berry]
Gaël Kaneko [Started April 2008, Funded by an ADR Région Rhône-Alpes grant, co-supervised by G. Beslon and O. Gandrillon]
Pierre-Nicolas Mougel [INSA Lyon, started September 2009, supervised by C. Rigotti]
David P. Parsons [INSA Lyon, started September 2008, defended December 2011, co-supervised by G. Beslon and C. Knibbe]

Post-Doctoral Fellow

Pierre Gabriel [Funded by ANR project PagDeg]

Administrative Assistant

Caroline Suter

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). It has been created as an "Équipe Centre" by INRIA Rhône-Alpes in June 2011[3] 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 living sciences. Thanks to 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:

Computational Cell Biology We are developing models of the spatio-temporal dynamic 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.

In silico Models of 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 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...). The comparison with real data requires the reconstruction of the evolutionary events that have shaped the extant real genomes. To this aim, integrative models, including small substitutions as well as large reorganizations of a genome, are needed. The confrontation of what we can know of historical events and the laws we can infer from artificial experiments allow to explain some patterns of today's organisms and biodiversity.

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.

The scientific objectives 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 biologists and 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* [37] 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

[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] 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.

interdisciplinarity at the individual level, all members of the team being able to interact efficiently with specialists from both fields.

3. Scientific Foundations

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: *in silico* evolution and computational cell biology

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. We more specifically 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 [30]. 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 [29]. 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 [14]. 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 [36]. 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 [34]. 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. in silico 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 [40]). As a consequence, this model can be used to study how evolutionary pressures like the ones for robustness or evolvability can shape genome structure [41], [38], [39], [42].

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 [41], [38], [42]. 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 [35]. 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 [32], [31], [33]. 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 [31].

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 reflexion. 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 [38], and no difference in lifestyles and environment was needed to explain the complexity of the gene regulatory network [31].

Based on this experience, the Beagle team contributes individual-based computer models and *in silico* experiments to shed light on the evolutionary origin of the complex properties of cells.

4. Software

4.1. aevol (artificial evolution)

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

- Contact: Carole Knibbe (carole.knibbe@inrialpes.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://gforge.liris.cnrs.fr/projects/aevol/

4.2. DMT4SP (Data Mining Tool For Sequential Patterns)

Participant: Christophe Rigotti.

- Contact: Christophe.Rigotti@insa-lyon.fr.
- Summary: The dmt4sp prototype is a command line tool to extract episodes and episode rules, supporting various constraints, over a single sequence or several sequences of events. 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 the serial episodes with respect to the time gap between events).
- Url: http://liris.cnrs.fr/~crigotti/dmt4sp.html

5. New Results

5.1. Astrocyte Regulation of Synaptic Depression and Facilitation

Participants: Hugues Berry, Maurizio De Pitta, Vladislav Volman, Eshel Ben-Jacob.

Synaptic plasticity is the capacity of a preexisting connection between two neurons to change in strength as a function of neuronal activity. Because it admittedly underlies learning and memory, the elucidation of its constituting mechanisms is of crucial importance in many aspects of normal and pathological brain function. Short-term presynaptic plasticity refers to changes occurring over short time scales (milliseconds to seconds) that are mediated by frequency-dependent modifications of the amount of neurotransmitter released by presynaptic stimulation. Recent experiments have reported that glial cells, especially hippocampal astrocytes, can modulate short-term plasticity, but the mechanism of such modulation is poorly understood. Here, we explore a plausible form of modulation of short-term plasticity by astrocytes using a biophysically realistic computational model. Our analysis indicates that astrocytes could simultaneously affect synaptic release in two ways. First, they either decrease or increase the overall synaptic release of neurotransmitter. Second, for stimuli that are delivered as pairs within short intervals, they systematically increase or decrease the synaptic response to the second one. Hence, our model suggests that astrocytes could transiently trigger switches between paired-pulse depression and facilitation. This property explains several challenging experimental observations and has a deep impact on our understanding of synaptic information transfer [16].

5.2. A theory of rate coding control by intrinsic plasticity effects

Participants: J Naudé, J Paz, Hugues Berry, Bruno Delord.

Intrinsic plasticity (IP) is a ubiquitous activity-dependent process regulating neuronal excitability and a cellular correlate of behavioral learning and neuronal homeostasis. Because IP is induced rapidly and maintained long-term, it likely represents a major determinant of adaptive collective neuronal dynamics. However, assessing the exact impact of IP has remained elusive. Indeed, it is extremely difficult to disentangle the complex non-linear interaction between IP effects, by which conductance changes alter neuronal activity, and IP rules, whereby activity modifies conductance via signaling pathways. Moreover, the two major IP effects on firing rate, threshold and gain modulation, remain unknown in their very mechanisms. Here, using extensive simulations and sensitivity analysis of Hodgkin-Huxley models, we show that threshold and gain modulation are accounted for by maximal conductance plasticity of conductance in two separate domains of the parameter space corresponding to sub- and supra-threshold conductance (i.e. activating below or above the spike onset threshold potential). Analyzing equivalent integrate-and-fire models, we provide formal expressions of sensitivities relating to conductance parameters, unraveling unprecedented mechanisms governing IP effects. Our results generalize to the IP of other conductance parameters and allow inference of calcium-gated conductance, yielding a general picture that accounts for a large repertoire of experimental observations. The expressions we provide can be combined with IP rules in rate or spiking models, offering a general framework to systematically assess the computational consequences of IP of pharmacologically identified conductance with both fine grain description and mathematical tractability. We provide an example of such IP loop model addressing the important issue of the homeostatic regulation of spontaneous discharge. Because we do not formulate any assumptions on modification rules, the present theory is also relevant to other neural processes involving excitability changes, such as neuromodulation, development, aging and neural disorders [20].

5.3. Impact of receptor clustering on ligand binding

Participants: Hédi A. Soula, Bertrand Caré.

Cellular response to changes in the concentration of different chemical species in the extracellular medium is induced by ligand binding to dedicated transmembrane receptors. Receptor density, distribution, and clustering may be key spatial features that influence effective and proper physical and biochemical cellular responses to many regulatory signals. Classical equations describing this kind of binding kinetics assume the distributions of interacting species to be homogeneous, neglecting by doing so the impact of clustering. As there is experimental evidence that receptors tend to group in clusters inside membrane domains, we investigated the effects of receptor clustering on cellular receptor ligand binding. We implemented a model of receptor binding using a Monte-Carlo algorithm to simulate ligand diffusion and binding. In some simple cases, analytic solutions for binding equilibrium of ligand on clusters of receptors are provided, and supported by simulation results. Our simulations show that the so-called “apparent” affinity of the ligand for the receptor decreases with clustering although the microscopic affinity remains constant. Changing membrane receptors clustering could be a simple mechanism that allows cells to change and adapt their affinity/sensitivity toward a given stimulus [14].

5.4. Illegitimate and Homologous Rearrangements, an intricate relationship?

Participants: David P. Parsons, Guillaume Beslon, Carole Knibbe.

We have introduced homologous horizontal transfer in the aevol model. First results show that this process interacts in a complex way with both non-homologous transfer (that creates homologous sequences) and mutation rate (that destroys homologous sequences). We have shown that homologous transfer is useful only in strict conditions (small mutation rate and small - but non-null - non-homologous rate) [27]. This result confirms the genericity of the indirect selection mechanism we previously shown to be at the origin of scaling laws in genomes and transcriptomes [25].

5.5. An error threshold due to chromosomic rearrangements

Participants: Stephan Fischer, Guillaume Beslon, Carole Knibbe, Samuel Bernard.

Error threshold is a well known theory in evolutionary biology. However, the theory of error threshold only takes into account point mutation rate and states that this rate generates a maximum level of coding sequences in a given genome. Using aevol and mathematical formulations, we have shown other types of mutations are also likely to create error thresholds. In particular we have shown the chromosomic rearrangement (duplications and deletions) generate a very strong threshold.

5.6. Enhanced Stimulus Encoding Capabilities with Spectral Selectivity in Inhibitory Circuits by STDP

Participants: Guillaume Beslon, Hédi A. Soula, Antoine Coulon.

The ability to encode and transmit a signal is an essential property that must demonstrate many neuronal circuits in sensory areas in addition to any processing they may provide. It is known that an appropriate level of lateral inhibition, as observed in these areas, can significantly improve the encoding ability of a population of neurons. We have shown that a homeostatic mechanism by which a spike-timing-dependent plasticity (STDP) rule with a symmetric timing window (swSTDP) spontaneously drives the inhibitory coupling to a level that ensures accurate encoding in response to input signals within a certain frequency range. Interpreting these results mathematically, we find that this coupling level depends on the overlap of spectral information between stimulus and STDP window function. Generalization to arbitrary swSTDP and arbitrary stimuli reveals that the signals for which this improvement of encoding takes place can be finely selected on spectral criteria. We finally show that this spectral overlap principle holds for a variety of neuron types and network characteristics. The highly tunable frequency-power domain of efficiency of this mechanism, together with its ability to operate in very various neuronal contexts, suggest that it may be at work in most sensory areas [15].

6. Partnerships and Cooperations

6.1. Regional Initiatives

6.1.1. Evolution of endosymbiont genomes

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

Endosymbiotic organisms alway own shorter genomes than free living ones. This particularly the case in the prokaryotic kingdom. Many hypothesis have been proposed in the literature to explain this observation but it is very difficult to disentangle the effect of the proposed mechanisms and to asses whether they lead – or not – to genome reduction. We have received a BQR grant from INSA-Lyon to investigate this question by a joint work with aevol (to test *in silico* the different hypothesis) and with comparative genomic approaches (to better characterize the structural difference between short and long genomes). Total amount funded : 15,000 euros.

6.2. National Initiative

6.2.1. Evolution of bacterial genomes

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

Our work on the Aevol software has received two interdisciplinary grants from the CNRS: an inter-institute grant (PEPII) and a grant from the INS2I institute (PEPS). In both cases, the objective is to trigger collaborations with other computer science teams, life science teams or mathematicians. In the case of the PEPS project, our collaborators are the LIP (Lyon) and LAPM (Grenoble). In the case of the PEPII project, we collaborate with the LIP (Lyon), LAPM (Grenoble), LBBE (Lyon) and ICJ (Lyon).

6.2.2. ColAge

Participants: Hugues Berry, Anne-Sophie Coquel.

ColAge is a 4-year research project launched in early 2009 as a Large-Scale Initiative Action co-funded by the French national research institutes INRIA (computer science) and Inserm (medicine and health). We search for natural and engineering solutions to the control of bacterial growth and aging using both systems biology and synthetic biology approaches. Our main strategy is to leverage synergies resulting from day-to-day collaborations between computer scientists and cell biologists. The research topics on aging in bacteria above is one of the ColAge workpackages. Supervisor: H. Berry, EPI Beagle. Total amount funded (for 2009-2010): 330,000 euros. Further information available at http://colage.saclay.inria.fr/.

In 2010, ColAge fostered the emergence of two other grants/funding by the French national agency for research, ANR: Pagdeg (leaded by A. Lindner, see below) and GeMCo (leaded by M. Chaves, http://www-sop.inria.fr/members/Madalena.Chaves/).

6.2.3. PAGDEG

Participants: Hugues Berry, Anne-Sophie Coquel, Ariel Lindner, Y. Chen, L. Moisan.

A three-year project (2010-2012) funded by the French National Agency for Research (ANR), Call "PIRIBIO 2009" (Programme interdisciplinaire de recherche sur les systèmes moléculaires et cellulaires et d'innovation biomédicale). We study the causes and consequences of protein aggregation in cellular degeneration in bacteria combining innovative experimental (microfluidics, quantitative biology) and computer simulation (individual based-modeling, ODEs) approaches. Supervisor: A. Lindner (INSERM, Paris). Total amount funded: 450,000 euros.

6.2.4. Stochagene

Participants: Hugues Berry, Guillaume Beslon, Gaël Kaneko.

Stochagene is four-year project (2011-2015) funded by the French National Agency for Research (ANR), Call "Blanc 2011". The objective of the project is to identify the molecular causes of stochasticity in gene expression by experimental and modeling approaches. Supervisor: O. Gandrillon (CNRS, Lyon). Total amount funded: 466,000 euros.

6.2.5. NéoBG (pour une théorie biologiquement réaliste de l'apprentissage par renforcement)

Participants: Hugues Berry, Jules Lallouette.

NéoBG in an interdisciplinary project funded by the CNRS (Appel Projets exploratoires pluridisciplinaires inter-instituts – PEPII – 2011-2012). Total amount funded for Beagle: 6 000€

6.2.6. Partnership with F. Taddei's group, INSERM U1001, Cochin hospital Paris

Participants: Guillaume Beslon, Carole Knibbe, David P. Parsons, Hugues Berry, Anne-Sophie Coquel.

Strong collaboration links exist between Beagle and F. Taddei's and A. Lindner's group, in Paris: First, A. Lindner and H. Berry collaborate on the study of aging in bacteria. Both co-supervise A.S. Coquel's PhD within grants ColAge and Pagdeg (see above). Moreover, Aevol, a software developed by our team (see above), is used by the INSERM experimentalist group in Paris: with our help, D. Misevic and F. Taddei use it to study the evolution of cooperation in bacteria: Under which conditions can cooperation emerge? What kind of genetic architecture evolves when cooperation arises?

6.2.7. Partnership with D. Schneider's group, LAPM, Univ. Joseph Fourier, Grenoble

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

The team of Dominique Schneider is composed of life scientists developing experimental evolution strategies with micro-organisms. We are engaged in a close collaboration with this team since the methodology they use is very similar to the one we develop with aevol (though they are studying *real* organisms). Several projects have been submitted this year (ANR, Labex, Investissement d'avenir en bioinformatique) and we are waiting for the results.

6.2.8. Astrocytic regulation of neuronal network activity

Participants: Hugues Berry, Jules Lallouette.

Research Networks Program in Computational Neurosciences and Computational Cognitive Sciences of the High Council for Scientific and Technological Cooperation between France-Israel. Total amount funded for Beagle: 80 000 €.

Healthy functionality of the central nervous system (CNS) relies on intricate neuron-glia networks. Recent data suggest that glial cells, including astrocytes, play a crucial role in the way information is processed and stored by the brain. In particular, synapses should not be considered bipartite, but rather tripartite structures, comprised of the pre-synaptic terminal, the post-synaptic one and the surrounding astrocyte. Moreover, glial cells, like neurons, also form intricate networks of cells and are linked by gap junctions to 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 the neuron-glia interaction is essential to fully understand how the brain functions, and will serve as a stepping stone for deciphering disorders of the CNS. Our long-term goal is to reveal the underlying mechanism that controls 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 calcium wave propagation and (2) to reveal how astrocyte signals dynamically affect synaptic information transfer, thus regulating neuronal network activity. To achieve these objectives we will employ a methodology that combines corresponding theoretical and experimental investigations of small neuron-glial networks. We will use unique cortical cultures made of several hundred well-identified cells, thus facilitating very systematic investigation in a manner that is fully compatible with our analytical tools. 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 ataxia-telangiectasia (A-T), a progressive neurodegenerative disorder induced by mutations in the ATM gene encoding the protein kinase ATM, a key player in the DNA damage response. Leveraging the possibilities offered by our joint experimental and theoretical approach, we will be able to investigate heterogeneous neuron-glial networks where one element comes from a diseased mouse model and the other from healthy (WT) animals. This novel approach will provide us with a unique opportunity to uncover the cellular origin of these pathologies.

7. Dissemination

7.1. Animation of the scientific community

7.1.1. Invited seminar and lectures

- Hugues Berry – "Modeling disordered and crowded intracellular spaces with individual-based and hybrid models", Summer Solstice Conference 2011: Discrete Models of Complex Systems, Turku, Finland, June 6-10 2011.
- Hugues Berry – "Biochemistry and signaling in disordered and crowded cells: a new space odyssey" XXXIème Séminaire de la Société Francophone de Biologie Théorique, Autrans, France, May 15-18, 2011.
- Hugues Berry – "The many faces of spike-timing dependent plasticity in basal ganglia" Journée "The neurophysiology of cognition", IXXI, Lyon, February 28, 2011 (with Laurent Venance).
- Hugues Berry – "Biochemistry and signaling in disordered and crowded cells: a new space odyssey", Séminaire du laboratoire MAP5 (Mathématiques appliquées de Paris 5), Paris, France, 23 Sept 2011.
- Hugues Berry – "Unconventional forms of plasticity: beyond the synaptic Hebbian paradigm" Devleann workshop (Development and Learning in Artificial Neural Networks), Paris, Oct. 27-28, 2011.

- David P. Parsons – "Parcimonious modeling of scaling laws in prokaryotic genomes", séminaire invité à l'université de Clermond-Ferrand, Nov. 2011.
- Guillaume Beslon – "Modélisation et découverte de connaissances en biologie", séminaire invité par le laboratoire de la société LVMH, Paris, April 2011.

7.1.2. Scientific Popularization

- Guillaume Beslon gave two conferences during the 2011 "Fête de la Science" in Lyon.
- Guillaume Beslon gave a conference in the context of the "Défi Rap" (trophées lycéens de robotique), Lyon, May 2011.

7.1.3. Jurys and committees

In 2011, members of Beagle have served into various committees:

- Hugues Berry is member of the committee for the Spécif / Gilles Kahn award (2011-2014).
- Christophe Rigotti is member of the Scientific Council (C.S.) of INSA Lyon.
- Guillaume Beslon is director of the Rhône-Alpes Complex Systems Institute (IXXI).
- Carole Knibbe is president of the steering committee of the Rhône-Alpes Complex Systems Institute (IXXI).

Of course, members of Beagle also regularly participate to scientific evaluation (reviews, selection committees, projects evaluation...). In 2011 we have been involved in project reviewing for ANR (appels Blancs), for French Ile-de-France région (calls "DIM" and "LSC"), for the COFECUB (Coopération Universitaire et Scientifique avec le Brésil) evaluation committee, for selection committees in the university of Cergy-Pontoise, of the University of Lyon, for the University of Nice and for the INRIA.
We also regularly participate to PhD and HDR ("Habilitation à Diriger des Recherches") defense committees, either as reviewers or as committee members. In 2011, members of the BEAGLE team participated to the following committees (committees of our own students not included):

- Angélique Stephanou – H. Berry participated to defense committee for the HDR of Ms. Angélique Stéphanou (Univ. Grenoble).
- Régis Martinez – H. Berry participated to defense committee for the PhD of M. Regis Martinez (Univ. Lyon 2).
- Luician Alecu – H. Berry participated to defense committee for the PhD of M. Luician Alecu (Univ. Nancy).
- Hervé Le Nagard – G. Beslon reviewed and participated to defense committee for the PhD of M. Hervé Le Nagard (Univ. Paris 12, faculté de médecine Bichat).
- Guillaume Hutzler – G. Beslon reviewed and participated to defense committee for the HDR of M. Guillaume Hutzler (Univ. Evry Val d'Essonne).
- Geoffrey Portelli – G. Beslon reviewed and participated to defense committee for the PhD of M. Geoffrey Portelli (Univ. Paul Sabatier, Toulouse).
- Edi Prifti – G. Beslon reviewed and participated to defense committee for the PhD of M. Edi Prifti (Univ. Paris 6 Pierre et Marie Curie).
- Alice Demarez – H. Berry reviewed and participated to defense committee for the PhD of Ms. Alice Demarez (Univ. Paris Descartes).

7.1.4. Participation to INRIA's Life

- Hugues Berry is member (elected) of INRIA Commission d'Evaluation (CE).
- Hugues Berry is member (elected) of INRIA Commission Administrative Paritaire (CAP).

7.2. Teaching

7.2.1. Teaching at Universities

Most of us teach Computer Science at INSA Lyon or University Lyon 1:

- Guillaume Beslon teaches at the computer science department of INSA-Lyon (computer architecture, bioinspired intelligence), 196h.
- Carole Knibbe teaches at the computer science department of Université Claude Bernard Lyon 1 (programming, algorithmics), 196h.
- Christophe Rigotti teaches at the 1er cycle department of INSA-Lyon (bases of computer science), 196h.
- David Parsons teaches at the computer science department of INSA-Lyon (programming, C++, Prolog, Java), 196h.
- Bérénice Batut, Jules Lallouette and Stephan Fischer are "monitors" at the dept. 1er cycle of INSA-Lyon (bases of computer science, mathematics), 96h each.

Three of us (G. Beslon, C. Knibbe and C. Rigotti) teach in the "Master d'informatique de Lyon" (Univ. Claude Bernard Lyon 1) and two of us (G. Beslon and C. Knibbe) teach in the "Modélisation des Systèmes Complexes" Master program of ENS Lyon. In 2011, we also taught in specific programs such as the Systems Biology minor of the Bioscience Master of ENS Lyon.

7.2.2. PhD supervision

- Bérénice Batut – Period: September 2011-September 2014. Research topic: evolutionary origin of genome reduction in bacteria. Supervisors: Guillaume Beslon and Gabriel Marais (LBBE UMR CNRS 5558).
- Bertrand Caré – Period: September 2009-September 2012. Research topic: impact of receptor clustering on cell's signaling. Supervisors: Christophe Rigotti and Hédi Soula.
- Anne-Sophie Coquel – Period: September 2009-September 2012. Research topic: deciphering the molecular mechanisms underlying the role of protein aggregation in aging of *E. coli*. Supervisors: Hugues Berry and Ariel Lindner (INSERM U1001).
- Stephan Fischer – Period: September 2010-September 2013. Research topic: mathematical re-modeling of the *aevol* framework. Supervisors: Guillaume Beslon and Carole Knibbe.
- Jules Lallouette – Period: September 2011-September 2014. Research topic: Transport in complex networks: the case of mixed neuron/glial cell networks. Supervisor: Hugues Berry.
- Gael Kaneko – Period: April 2009-April 2012. Research topic: modeling of the effect of chromatin dynamic on the stochasticity of gene expression. Supervisors: Guillaume Beslon and Olivier Gandrillon (CGPhyMC, UMR CNRS 5534).
- Pierre-Nicolas Mougel – Period: September 2009-September 2012. Research topic: cross-mining of Boolean relations and graphs. Supervisor: Christophe Rigotti.
- David P. Parsons – Period: September 2008-December 2011 (PhD defended on Dec. 8th 2011). PhD title: Sélection Indirecte en Évolution Darwinienne: Mécanismes et Implications. Supervisors: Guillaume Beslon and Carole Knibbe.

7.2.3. Internships

- Bérénice Batut – *In silico experimental evolution study of reductive evolution in bacteria*. Département Bioinformatique (INSA-Lyon) and Master 2 "Modélisation des Systèmes Complexes" (ENS-Lyon). Advisor: C. Knibbe.
- Yoram Vadée le Brun – *Study of the R-aevol model*. Master 2 "Modélisation des Systèmes Complexes" (ENS-Lyon). Advisor: G. Beslon.
- Jules Lallouette – *Simulation of calcium waves in astrocytes*. Département Informatique (INSA-Lyon) and Master 2 "Connaissance et Raisonnement" (UCBL). Advisor: H. Berry.
- Florian Thöni – *Parallel experimental and computational evolution of L. pneumophila*. Département Bioinformatique (INSA-Lyon). Advisor: G. Beslon.
- Mathilde Dumond – *In silico experimental evolution study of reductive evolution in bacteria*. Département BioSciences (ENS-Lyon). Advisor: C. Knibbe.
- Jean-Marie Gomes – *The bidirectional response of cortico-striatal synapses to 2-arachidonyl-glycerol*. Master 2 "Modélisation des Systèmes Complexes" (ENS-Lyon). Advisor: H. Berry.

8. Bibliography

Major publications by the team in recent years

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[2] E. BERTIN, G. BESLON, O. GANDRILLON, S. GRAUWIN, P. JENSEN, N. SCHABANEL. *Les complexités : point de vue d'un institut des systèmes complexes*, in "Hermès", June 2011, n° 60, p. 145–150, http://liris.cnrs.fr/publis/?id=5283.

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[6] T. HINDRE, C. KNIBBE, G. BESLON, D. SCHNEIDER. *New insights into bacterial adaptive abilities by in vivo and in silico experimental evolution*, in "Nature Reviews Microbiology", 2011, to appear.

[7] A. JULEA, N. MEGER, C. RIGOTTI, E. TROUVE, R. JOLIVET, P. BOLON. *Efficient Spatiotemporal Mining of Satellite Image Time Series for Agricultural Monitoring*, in "Transactions on Machine Learning and Data Mining", 2011, vol. 4, n° 2, p. 75–97.

[8] C. KNIBBE, D. P. PARSONS, G. BESLON. *Parsimonious modeling of scaling laws in genomes and transcriptomes*, in "European Conference on Artificial Life (ECAL)", MIT Press, 2011, p. 414–415.

[9] J. NAUDÉ, J. PAZ, H. BERRY, B. DELORD. *A theory of rate coding control by intrinsic plasticity effects*, in "PloS Computational Biology", 2011, to appear.

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Publications of the year

Doctoral Dissertations and Habilitation Theses

[11] D. P. PARSONS. *Selection indirecte en Évolution Darwinienne : Mécanismes et Implications*, PhD Thesis, Institut National des Sciences Appliquées de Lyon, 2011.

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[12] H. BERRY, N. FATÈS. *Robustness of the critical behavior in the stochastic Greenberg-Hastings cellular automaton model*, in "Int. J. Unconv. Comput.", 2011, vol. 7, n^{o} 1–2, p. 65-85.

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