IN PARTNERSHIP WITH:
Institut national des sciences appliquées de Lyon

Université Claude Bernard (Lyon 1)

Activity Report 2012

Team BEAGLE

Artificial Evolution and Computational Biology

IN COLLABORATION WITH: Laboratoire de Biométrie et Bologie 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 and Bioinformatics

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Team BEAGLE

Keywords: Computational Biology, Modeling, Cell Biology, Evolution, Systems 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 2013. It is hosted in the Inria "Antenne La Doua".

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

1. Members

Research Scientists

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Engineer

Magali Vangkeosay [IJD, ADT MultiPop, October 2012 Setptember 2014, supervised by H. Berry]

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Bertrand Caré [Started October 2009, Funded by an ADR Région Rhône-Alpes grant, co-supervised by H. Soula and C. Rigotti, defense nov 26, 2012]
Anne-Sophie Coquel [Funded by AE ColAge, started September 2010, co-supervised by H. Berry and A. Lindner, defense nov 16, 2012]
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]
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Post-Doctoral Fellows

Murray Patterson [Ercim, February 2012 - January 2013, supervised by E. Tannier]
David P Parsons [September 2011 - August 2012, supervised by G. Beslon]
Pierre Gabriel [September 2011 - August 2012, supervised by H. Berry]

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), one of them being a member of the

[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

BBE institute[3]. It has been created as an "Équipe Centre" by Inria Rhône-Alpes in June 2011[4] and is on the way to be created as "Équipe-Projet". The BEAGLE Team is led by Prof. Guillaume Beslon (INSA-Lyon, LIRIS, Computer Science Dept.).

Our research is based on an interdisciplinary scientific strategy: we are developing computer science formalisms and software for complex system modeling in synergy with multidisciplinary cooperations in the area of living 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* [58] between biology and computer science. Our very scientific identity is thus fuzzy, melting components from both sciences. Indeed, one of the central claims of the team is that interdisciplinarity involves permanent exchanges between the disciplines. Such exchanges can hardly be maintained between distant teams. That's why the BEAGLE team tries to develop local collaborations with local scientists. That's also why BEAGLE also tries to organize itself as an intrinsically interdisciplinary group, gathering different sensibilities between biology and computer science inside the group. Our ultimate objective is to develop interdisciplinarity at the individual level, all members of the team being able to interact efficiently with specialists from both fields.

2.2. Highlights of the Year

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

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

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

- We published at least three papers in high impact journals [16], [31], [23]: two in *PNAS* about the use of horizontal transfer in reconstructing and dating the history of bacterial diversification, and one in *Nature reviews microbiology* about the comparison between experimental and artificial evolution.
- Guillaume Beslon was nominated as a member of the CoNRS, section 06.
- 2012 has been fructuous in terms of collaborations between permanent members of the team, sometimes coming from different teams and backgrounds, as it is shown by a submitted article [43], gathering the different projects in the Computational Cell Biology part.

BEST PAPER AWARD :
[39] **Effects of public good properties on the evolution of cooperation in Artificial Life XIII**. D. MISEVIC, A. FRÉNOY, D. P. PARSONS, F. TADDEI.

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: computational cell biology and models for genome evolution.

3.2. Computational Cell Biology

Beagle contributes computational models and simulations to the study of cell signaling in prokaryotic and eukaryotic cells, with a special focus on the dynamics of cell signaling both in time and in space. Importantly, our objective here is not so much to produce innovative computer methodologies, but rather to improve our knowledge of the field of cell biology by means of computer methodologies. This objective is not accessible without a thorough immersion in experimental cell biology. Hence, one specificity of BEAGLE will be to be closely associated inside each research project with experimental biology groups. For instance, all the current PhD students implicated in the research projects below have strong interactions with experimenters, most of them conducting experiments themselves in our collaborators' labs. In such a case, the supervision of their PhD is systematically shared between an experimentalist and a theoretician (modeler/computer scientist). Standard modeling works in cell biochemistry are usually based on mean-field equations, most often referred to as "laws of mass-action". Yet, the derivation of these laws is based on strict assumptions. In particular, the reaction medium must be dilute, perfectly-mixed, three-dimensional and spatially homogeneous and the resulting kinetics are purely deterministic. Many of these assumptions are obviously violated in cells. As already stressed out before, the external membrane or the interior of eukaryotic as well as prokaryotic cells evidence spatial organization at several length scales, so that they must be considered as non-homogeneous media. Moreover, in many case, the small number of molecule copies present in the cell violates the condition for perfect mixing, and more generally, the "law of large numbers" supporting mean-field equations. When the laws-of-mass-action are invalidated, individual-based models (IBM) appear as the best modeling alternative to evaluate the impact of these specific cellular conditions on the spatial and temporal dynamics of the signaling networks. We develop Individual-Based Models to evaluate the fundamental impact of non-homogeneous space conditions on biochemical diffusion and reaction.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 [47]. 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 [3]. 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 [56]. 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 [4]. Other works introduce spatial dimensions in the model, in particular to estimate the role of space in complex (protein+ DNA) formation. Such models should yield useful insights into the sources of stochasticity that are currently not explained by obvious causes (e.g. small copy numbers).

3.3. Models of genome evolution

Classical artificial evolution frameworks lack the basic structure of biological genome (i.e. a double-strand sequence supporting variable size genes separated by variable size intergenic sequences). Yet, if one wants to study how a mutation-selection process is likely (or not) to result in particular biological structures, it is mandatory that the effect of mutation modifies this structure in a realistic way. To overcome this difficulty, we have developed an artificial chemistry based on a mathematical formulation of proteins and of the phenotypic traits. In our framework, the digital genome has a structure similar to prokaryotic genomes and a non-trivial genotype-phenotype map. It is a double-stranded genome on which genes are identified using promoterterminator- 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 [64]). As a consequence, this model can be used to study how evolutionary pressures like the ones for robustness or evolvability can shape genome structure [65], [62], [63], [74]. 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 [65], [62], [75]. 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 [55]. 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 [49], [48], [50]. 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 [48]. 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 [65], and no difference in lifestyles and environment was needed to explain the complexity of the gene regulatory network [48]. When we unravel such phenomena in the individual-based simulations, we try to build ”simpler” mathematical models (using for instance population genetics-like frameworks) to

determine the minimal set of ingredients required to produce the effect. Both approaches are complementary: the individual-based model is a more natural tool to interact with biologists, while the mathematical models contain fewer parameters and fewer ad-hoc hypotheses about the cellular chemistry.

Little has been achieved concerning the validation of these models, and the relevance of the observed evolutionary tendencies for living organisms. Some comparisons have been made between Adiva and experimental evolution [66], [59], but the comparison with what happened in a long timescale to life on earth is still missing. It is partly because the reconstruction of ancient genomes from the similarities and differences between extant ones is a difficult computational problem which still misses good solutions for every type of mutations.

There exist good phylogenic models of punctual mutations on sequences [57], which enable the reconstruction of small parts of ancestral sequences, individual genes for example [67]. But models of whole genome evolution, taking into account large scale events like duplications, insertions, deletions, lateral transfer, rearrangements are just being developped: [77] model punctual mutations as well as duplication and losses of genes, while [52] can reconstruct the evolution of the structure of genomes by inversions. This allows a more comprehensive view of the history of the molecules and the genes, which sometimes have their own historical pattern. But integrative models, considering both nucleotide subsitutions and genome architectures, are still missing.

It is possible to partially reconstruct ancestral genomes for limited cases, by treating separately different types of mutations. It has been done for example for gene content [53], gene order [68], [71], the fate of gene copies after a duplication [61], [45]. All these lead to evolutionary hypotheses on the birth and death of genes [54], on the rearrangements due to duplications [46], [76], on the reasons of variation of genome size [60], [69]. 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 [70], methods for reconstructing the organization of ancestral genomes [72], [51], [73], or for detecting lateral gene transfer events [44], [12]. It is complementary with the aevol development because both the model of artificial evolution and the phylogenetic models we develop emphasize on the architecture of genomes. So we are in a good position to compare artificial and biological data on this point.

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

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

4. Application Domains

4.1. Application Domains

- Molecular and cellular biology
- Genome evolution

5. Software

5.1. aevol (artificial evolution)

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

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

5.2. FluoBacTracker

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

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

5.3. Ancestral Genome Reconstructions

Participant: Eric Tannier.

- Contact: Eric Tannier (eric.tannier@inria.fr).
- We participated in the development of a series of softwares for genome organization analysis:
  - ANGES, for ANcestral GEnomeS maps, is a toolkit for ordering ancestral genomic markers in chromosomes. An application note has been published in *Bioinformatics* in 2012 to advertise its first release. It is hosted at SFU in Vancouver, URL: http://paleogenomics.irmacs.sfu.ca/ANGES/, under a GNU license, 2012.
  - DeCo, for Detection of Co-evolution, reconstructs neighborhood relationships between genes of ancient genomes, in the presence of gene duplications and losses. It is hosted at the PRABI, the bioinformatics platform in Lyon, URL: http://pbil.univ-lyon1.fr/software/DeCo/, under a Cecill license, 2012.
  - DCJ2HP provides bayesian samples of rearrangements scenarios between 2 genomes. It is hosted at the Renyi Institute in Budapest, URL http://www.renyi.hu/~miklosi/DCJ2HP/

6. New Results

6.1. Model of genome reduction

To test whether the effect of the rearrangement rate on genome size holds independently of the artificial chemistry of the aevol (individual-based) model, we have written a simpler, mathematical model of genome size evolution including both genes and intergenic sequences, evolving through small insertions and deletions, large deletions and duplications and through selection based on gene number. The approach was presented this summer as a poster at the SMBE conference (Society for Molecular Biology and Evolution). We have shown analytically that without selective pressure, genomes spontaneously shrink and that large genomes are particularly unstable. When selection is included that favors the highest gene number, simulations show that genome sizes do not grow indefinitely as large genomes cannot be sustained. There is a trade-off between fitness and structural stability. A manuscript is being written and will be submitted in January.

6.2. The Paradoxical Effects of Allelic Recombination on Fitness

D.P. Parsons, C. Knibbe, G. Beslon. [42]

We introduced in the aevol model the possibility of DNA exchange by allelic recombination, in order to study the influence of recombination on the evolution of both fitness and genomic architecture. Surprisingly, despite the theoretical benefits it could confer, there seems to be very little (if any) differences in the fitness of the evolved organisms between the different groups of simulations.

6.3. Genome histories reconstructions

E. Tannier (Beagle), with B. Boussau, G. Szollosi, V. Daubin, L. Duret, M. Gouy, S. Abby (LBBE, Lyon), N. Lartillot (Univ Montreal), C. Chauve (SFU Vancouver)

Lateral gene transfer has been discovered in the 1940's and since has been seen by phylogeneticists as a noise one had to remove before analyses in molecular evolution. Thi noise was recently considered so important that it would blur the historical signal and leave no hope for reconstructing a phylogeny. In a series of papers [16], [31], [32], we model the lateral gene transfer and prove that it can be used as a signal to

- reinforce the support for the phylogeny of vertical descent [16]
- order in time some bacterial diversification events, and thus provide a unique source for dating the history of life (more than 3/4 of it is prokaryotic and the fossil record is not abundant) [31]
- have a trace of extinct species which did not leave any descendants, if they gave some genes to more successful lineages, which opens the way to include them in molecular phylogenies [32]

We devised methods to trace whole genome evolution, with multi-scale mutations: from nucleotide substitutions to large-scale rearrangements. We provided a mammalian phylogeny accounting fot the evolution of several thousand genes [17], and a method to sample among evolutionary scenarios [27].

Eventually we built a model of evolution of relations between pairs of genes, enable us to reconstruct ancestral genome structure or ancestral systems of interactions [18]. In the case of genome structure we also published a method to linearize a set of ancestral relations [26].

6.4. A Theory of Rate Coding Control by Intrinsic Plasticity Effects

H. Berry (Beagle), J. Naudé and B. Delord (ISIR, CNRS UMR 7222, Univ P&M Curie, Paris) and J.T. Paz (Stanford Univ Medical Center, CA, USA).

Over the past decades, experimental and theoretical studies of the cellular basis of learning and memory have mainly focused on synaptic plasticity, the experience-dependent modification of synapses. However, behavioral learning has also been correlated with experience-dependent changes of non-synaptic voltage-dependent ion channels. This intrinsic plasticity changes the neuron's propensity to fire action potentials in response to synaptic inputs. Thus a fundamental problem is to relate changes of the neuron input-output function with voltage-gated conductance modifications. Using a sensitivity analysis in biophysically realistic models, we depicted a generic dichotomy between two classes of voltage-dependent ion channels [28]. These two classes modify the threshold and the slope of the neuron input-output relation, allowing neurons to regulate the range of inputs they respond to and the gain of that response, respectively. We further provide analytical descriptions that enlighten the dynamical mechanisms underlying these effects and propose a concise and realistic framework for assessing the computational impact of intrinsic plasticity in neuron network models. Our results account for a large repertoire of empirical observations and may enlighten functional changes that characterize development, aging and several neural diseases, which also involve changes in voltage-dependent ion channels.

6.5. The influence of topology on calcium wave propagation in 3D astrocyte networks

H. Berry, Jules Lallouette (Beagle)

Glial cells are non-neuronal cells that constitute the majority of cells in the human brain and significantly modulate information processing via permanent cross-talk with the neurons. Astrocytes are also themselves inter-connected as networks and communicate via chemical wave propagation. How astrocyte wave propagation depends on the local properties of the astrocyte networks is however unknown. We have investigated the influence of the characteristics of the network topology on wave propagation [38]. Using a model of realistic astrocyte networks (> 1000 cells embedded in a 3D space), we show that the major classes of propagations reported experimentally can be emulated by a mere variation of the topology. Our study indicates that calcium wave propagation is favored when astrocyte connections are limited by the distance between the cells, which means that propagation is better when the mean-shortest path of the network is larger. This unusual property sheds new light on consistent reports that astrocytes in vivo tend to restrict their connections to their nearest neighbors.

6.6. Dynamics of protein aggregation in Escherichia coli

H. Berry, Anne-Sophie Coquel (Beagle) and Ariel Lindner (INSERM U1001, Cochin Medical School, Paris).

Protein aggregation plays a key role in cell decline and leads to several human disease linked to ageing like Alzheimer or Parkinson disease and prion disease. In Escherichia coli bacteria, accumulation of damaged proteins and their asymmetric segregation allowed to show ageing signs. This work [14] is focused on the in vivo spatial dynamics of protein aggregates in E. coli. Protein aggregates can be classified as inclusion bodies and they are amorphous or amyloid with a high order level due to β sheets. Combining a double theoretical and experimental approach, based on modeling and time-lapse and microfluidic microscopy, we studied the mechanism governing the motion of protein aggregates and the long-term vertical transmission of prionoid aggregates for about 10 generations. Our results show clearly that Brownian diffusion governs the motion of protein aggregates and the diffusion coefficient depends on the molecule size. The amyloid proteinopathy study shows the existence of lineages propagating two kind of aggregates : globular or comet-like. Lineages maintaining globular aggregates present an increase of the aggregate size until inhibition of the growth rate while comet-like aggregates are mildly detrimental to growth. We observed also at low frequency in some lineages the presence of both aggregates and a switch between them. Globular foci give born to comet-like aggregates.

6.7. Model of membrane domains emergence

HA Soula, A Coulon, G Beslon (Beagle)

In the classical view, cell membrane proteins undergo isotropic random motion, that is a 2D Brownian diffusion that should result in an homogeneous distribution of concentration. It is, however, far from the reality: Membrane proteins can assemble into so-called microdomains (sometimes called lipid rafts) which also display a specific lipid composition. The amount of this so-called overconcentration at equilibrium is simply related to the ratio of diffusion coefficients between zones of high and low diffusion. Expanding the model to include particle interaction, we show that inhomogeneous diffusion can impact particles clusterization as well. The clusters of particles were more numerous and appear for a lower value of interaction strength in the zones of low diffusion compared to zones of high diffusion. Provided we assume stable viscosity heterogeneity in the membrane, our model proposes a simple mechanism to explain particle concentration heterogeneity and hence domains.

6.8. Deleterious effect of receptor clustering on canonical signaling pathways

BR Caré, HA Soula (Beagle)

Classical framework for analyzing system biology pathways assumed that the cells are a well mixed and stirred medium. This hypothesis can dramatically fail in the case of membrane based stage of signaling. Due to microdomains membrane receptors are colocalized. Using individual based-model we show that this clustering seriously impairs the overall ligands binding as well as several pathways downstream. We contend that this unexpected effect is a very simple tool available for a cell to adjust its response.

6.9. Novel mathematical model of Adipose tissue cells size distribution

HA Soula (Beagle) C. Soulage, A Géloën (CARMEN)

We present a novel model to explain bimodality of size distribution of adipocytes: adipose tissue cells. These cells are dedicated to storing energy excess in form of fat and therefore can experience wide variations of sizes. Ubiquitous to all the species, we tested so far the size distributions are bimodal with no characteristic size. Using data from experiments, we provide a simple surface based model of circulating fats that cells can exchange. We show that in the physiological range for the parameters of the model, we obtain bimodal distribution. We also provide prediction of the size evolution during severe caloric restriction that we were able to verify experimentally as well.

7. Partnerships and Cooperations

7.1. National Initiatives

7.1.1. ANR

- PAGDEG: Causes and consequences of protein aggregation in cellular degeneration, a three-year project (2009-20012), Call “PIRIBIO”. Supervisor: A. Lindner (INSERM, Paris) ; Other participants: Y. Chen (ENS Paris), L. Moisan (Univ. Paris 5). Participants: Hugues Berry, Anne-Sophie Coquel
- Stochagene (2011-2014). Objective: identify the molecular basis of the stochasticity of gene expression in eukaryotic cells. Partners: CGPhyMC (Olivier Gandrillon, Lyon, Leader), Genethon (Andras Paldi, Evry). Participants: G Beslon, H Berry, Gael Kaneko
- Ancestrome: phylogenetic reconstruction of ancestral "-omes", a five-year project (2012-2016), call "Bioinformatics" of the "Investissements d’avenir". Supervisor: V. Daubin (CNRS, LBBE, Lyon) ; with Institut Pasteur, ENS Paris, ISEM (Univ Montpellier 2) Participant: E Tannier

7.1.2. CNRS

- H Berry participates to a PEPII (Projets exploratoires pluridisciplinaires inter-instituts) called NeoBG: towards a biologically realistic theory of reinforcement learning, 2011-2012, Supervisor : B. Delord (Univ. P & M Curie, Paris). With Ph. Faure and L. Venance (College de France, Paris)
- Carole Knibbe coordinated in 2011 and 2012 a PEPII (Projets exploratoires pluridisciplinaires inter-instituts) called "Analyser, simuler et expérimenter l’évolution des génomes bactériens". The aim of the project was to study the dynamics and the evolvability of bacterial genomes by combining "wet" evolution experiments, individual-based simulations, mathematical models and bioinfomatics of real genomes. The total budget was 50 k€. The involved teams were, beside Beagle, Dynamics and evolution of the bacterial genome / Laboratoire Adaptation et Pathogénie des Microorganismes (LAPM, CNRS UMR5163, Grenoble), Modélisation mathématique et calcul scientifique / Institut Camille Jordan (ICJ, CNRS UMR5208, Lyon), Algorithmique et ordonnancement pour plates-formes hétérogènes distribuées / Laboratoire de l’Informatique du Parallélisme (LIP, CNRS UMR5668, Lyon), and Bioinformatique et génomique évolutive / Laboratoire de Biométrie et Biologie Evolutive (LBBE, CNRS UMR5558, Lyon)
- E Tannier participates to a PEPS (Projet exploratoire premier soutien) called C1P: algorithmics of 1D structures, 2012-2013. Supervisor: M. Raffinot (CNRS, LIAFA, Paris), involved teams from Marne-la-Vallée, Nantes, Marseille, Bordeaux, Lyon.

7.2. International Initiatives

7.2.1. Inria International Partners

- “Astrocytic regulation of neuronal network activity” 2012-2103, A Research Networks Program in Computational Neurosciences and Computational Cognitive Sciences of the High Council for Scientific and Technological Cooperation between France-Israel, with E Ben-Jacob and Y Hanein (Tel Aviv Univ, Israel). Supervisors: H. Berry (French side) and Y. Hanein (Israeli side).

7.3. International Research Visitors

7.3.1. Visits of International Scientists

- Nadia El-Mabrouk, professeure à l’université de Montreal, "chercheur invité" of Inria, October 1-12, 2012
- Jacques Rougemont (team leader) and Marion Leleu (researcher) of the Bioinformatics and Biostatistics Core Facility of EPFL (Ecole Polytechnique Fédérale de Lausanne). November 23, 2012.
- Thomas Höfer (Heidelberg) in May
- Kirsten HWJ ten Tusscher (Theoretical Biology/Bioinformatics, Utrecht University, Netherlands) in September

7.3.2. Visits to International Teams

- H. Soula is visiting professor in the Theunissen Lab of Auditory and Neuroscience during the academic year 2012-2013. Grant: CRCT CNU.
- Visit of C Rigotti to the team Bioinformatics and Biostatistics Core Facility of EPFL (Ecole Polytechnique Fédérale de Lausanne). March 8 and 9, 2012.

8. Dissemination

8.1. Scientific Animation

- G Beslon is a nomiated member at the CoNRS, section 06
- G Beslon is chair of the Scientific Committee of the Rhône-Alpes Institute for Complex Systems (IXXI).
- C Knibbe was vice-chair of the Scientific Committee of the Rhône-Alpes Institute for Complex Systems (IXXI).
- C Knibbe was a member of the Program Committee of ECCB 2012 (11th European Conference on Computational Biology)
- C Knibbe was a member of the Program Committee of the annual workshop of the Faculté des Sciences et Technologies of Université Lyon 1.
- C Knibbe participated in the evaluation of project proposals of the Blanc SVSE 7 2012 ANR program (Biodiversité, évolution, écologie et agronomie).
- H Berry is a Member of the Inria Evaluation Committee (Commission d’Evaluation) (2011-2015).
- H Berry is a Member of the Inria hiring committee 2012 (selection for associate research professor positions, jury d’admissibilite et d’admission).
- H Berry is a Member of the SPECIF committee (best French PhD in Computer Science) (2011-2012)
- H Berry is a Member of the Evaluation committee for the 2012 “Systems Biology” call for funding of the “ITMO Cancer”.
- H Berry is a Reviewer for the 2012 Call for funding of the FNRS, Belgium.
- E Tannier is co-chairing the organizing committee of Recomb satellite workshop on comparative genomics, Lyon 2013

- E Tannier is co-chairing the organizing committee of "Models and Algorithms for Genome Evolution", Montreal 2013
- E Tannier was a member of the Program Committee of ECCB 2012 (11th European Conference on Computational Biology)
- E Tannier was a member of the Program Committee of Recomb satellite workshop on comparative genomics, Rio 2012
- E Tannier is a Reviewer for the 2012 Call for funding of the Fonds Québécois pour la recherche

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

Several of us are half time teachers, and all their teaching record is not necessarily reported here. Researchers, post-doc and students teaching modules are detailed.

Licence and Master: Guillaume Beslon, computer achitecture and bioinspired intellignece at the computer science department of INSA Lyon, 192h eq TD

Licence: Carole Knibbe, "Algorithmique et programmation procédurale", 67 h eqTD, niveau L2 (+ responsabilité de l'UE), Université C. Bernard Lyon 1, France.

Licence: Carole Knibbe, "Encadrement de stage en informatique ", 3 h eqTD, niveau L3, Université C. Bernard Lyon 1, France.

Master: Carole Knibbe, "Intelligence artificielle bio-inspirée ", 14 h eqTD, niveau M2R, Université C. Bernard Lyon 1, France.

Master: Carole Knibbe, "Méthodologie scientifique et préparation à la recherche ", 24 h eqTD (+ responsabilité de l'UE), niveau M2R, Université C. Bernard Lyon 1, France.

Master: Carole Knibbe, "Modélisation et simulation en biologie et médecine ", 9 h eqTD (+ responsabilité de l'UE), niveau M2R, Université C. Bernard Lyon 1, France.

Master: Christophe Rigotti, Data Mining, 25 H eqTD, M1, INSA Lyon

Licence: Christophe Rigotti, Imperative Programming, 44 H eqTD, L1, INSA Lyon

Licence: Christophe Rigotti, Object-Oriented Programming 42 H eqTD, L2, INSA Lyon

Licence: Christophe Rigotti, Computer Simulation 71 H eqTD, L2, INSA Lyon

Licence: Bérénice Batut, Computer Science, 64h eq TD, INSA Lyon

Licence: Jules Lalouette, Computer Science, 64h eq TD, INSA Lyon

Licence : Stephan Fischer, "Mathématiques", 74 h eqTD, prépa intégrée première année, INSA de Lyon, France.

Licence: David P. Parsons, Algorithmique, Programmation Oriente´e Objet - C++, 19HeqTD, niveau L3, INSA Lyon, France

Licence: David P. Parsons, Approche Logique de l'Intelligence Artificielle, 57HeqTD, niveau L3, INSA Lyon, France

Licence: David P. Parsons, De´veloppement d'Applications pour les Syste`mes d'Information, 66HeqTD, niveau L3, INSA Lyon, France

Licence: David P. Parsons, Syste`mes d'Exploitation, 38HeqTD, niveau L3, INSA Lyon, France

Master: Eric Tannier, Discrete Mathematics, 8h, M1 UCBL and M1, INSA Lyon

Master: Eric Tannier, Mathématiques et Informatique pour le génome, 26h, M1 INSA Lyon

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

Master: Eric Tannier, Evolution des systèmes, 2h, M2, Université de Montpellier 2

Licence: Eric Tannier, Histoire des théories de l'évolution, 2h, L3, ENS Lyon

8.2.2. Supervision

PhD & HdR :

PhD: Anne-Sophie Coquel, Dynamique de l'agrégation protéique chez la bactérie Escherichia coli, soutenue le 16 Novembre 2012, co-supervisée par H. Berry (Beagle) and A. Lindner (INSERM U1001, Cochin Medical School, Paris), INSA Lyon, ED 512 Informatique

PhD: Pierre-Nicolas Mougel. Title: Finding homogenous collections of dense subgraphs using constraint-based data mining approaches. Application to the analysis of scientific collaboration networks and protein interaction graphs. INSA Lyon, September 14, 2012. Supervised by C. Rigotti.

PhD: Bertrand Caré. Title: Modèles individu-centrés de l'impact fonctionnel des hétérogénéités de diffusion et de distribution spatiale des protéines de signalisation cellulaire. INSA Lyon, November 26, 2012. Co-supervised by H. Soula and C. Rigotti.

PhD : David P. Parsons, "Sélection Indirecte en Évolution Darwinienne, Mécanismes et Implications", INSA de Lyon, December 8, 2011, co-supervised by Guillaume Beslon and Carole Knibbe

PhD in progress : Stephan Fischer, "Modélisation mathématique des phénomènes de s sélection indirecte dans l'évolution darwinienne", started in sept. 2010, co-supervised by Guillaume Beslon and Carole Knibbe, with the help of Samuel Bernard (Inria Dracula team)

PhD in progress : Bérénice Batut, "Etude de l'évolution réductive des génomes bactériens par analyses bioinformatiques et expériences d'évolution in silico", co-supervised by Guillaume Beslon and Gabriel Marais (LBBE), with the help of Carole Knibbe

PhD in progress: Jules Lallouette, Transport dans les réseaux complexes : le cas des réseaux mixtes neurones/cellules gliales, September 2011, supervised by Hugues Berry

PhD in progress: Magali Semeria, Biologie évolutive des systèmes, encadrée par E. Tannier et L. Gueguen (LBBE)

PhD in progress: Gael Kaneko, "modeling of the effect of chromatin dynamic on the stochasticity of gene expression", April 2009. Supervisors: Guillaume Beslon and Olivier Gandrillon (CGPhyMC, UMR CNRS 5534).

8.2.3. Juries

- G Beslon participated to the PhD jury of Linda Dib (Université Pierre et Marie Curie), "Détection des mutations simultanées dans les séquences protéiques non-divergentes". March 26 2012.
- G Beslon participated to the PhD jury of Hervé Le Nagard (Université Pierre et Marie Curie), Etude de l'émergence et de l'impact de la complexité phénotypique au travers de modèles théoriques et computationnels. December 15 2011
- E Tannier is invited to the HDR jury of N Thierry-Mieg, "smart pooling and interactomes", Grenoble, 2013
- E Tannier is invited to the Ph-D jury of G. Drillon, 2013 (reviewer)
- E Tannier participated to the Ph-D jury of C. Berthelot, ENS Paris, 2012
- H Berry participated to the Ph-D jury of Mathieu Lefort, "Apprentissage spatial de correlations multimodales par des mecanismes d'inspiration corticale", Nancy, July 04, 2012 (reviewer)
- H Berry participated to the Ph-D jury of Guillaume Core, "Heterogeneite phenotypique dans les populations d'origine clonale: origine et consequences", Paris, June 27, 2012 (reviewer)
- H Berry participated to the Ph-D jury of Hana Belmabrouk, "Modelisation et simulation du complexe macroglomerulaire des papillons de nuit", Nancy, May 15, 2012 (reviewer)

8.2.4. International Invited talks

- H Berry, "The remarkable effect of topology on calcium wave propagation in astrocyte networks", Workshop on the organization of excitable dynamics in hierarchical neural networks, 23-25 mai 2012, Bremen, Germany

- G Beslon, "Experimental approaches in ecology and evolution within yeast", EMBL Heidelberg, nov 2012

8.3. Popularization

- G Beslon participated to the "nuit des chercheurs" event in Villeurbanne on September 28, 2012 for the animation of a stand named "biologie artificielle - biologie synthetique".
- E Tannier teaches at the Université Populaire de Lyon, on science and politics, March 2012
- E Tannier participated to a scientific event "Les fourneaux de l'invention" gathering physicists, sociologists, biologists in Lyon, April 2012

9. 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^{o} 60, p. 145–150, http://liris.cnrs.fr/publis/?id=5283.

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Doctoral Dissertations and Habilitation Theses

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[14] A.-S. COQUEL. *Dynamique de l'agrégation protéique chez la bactérie Escherichia coli*, INSA Lyon, ED 512 Informatique Mathématiques, Lyon, France, November 2012.

[15] P.-N. MOUGEL. *Finding homogenous collections of dense subgraphs using constraint-based data mining approaches. Application to the analysis of scientific collaboration networks and protein interaction graphs*, INSA Lyon, 2012.

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[16] S. S. ABBY, E. TANNIER, M. GOUY, V. DAUBIN. *Lateral gene transfer as a support for the tree of life.*, in "Proceedings of the National Academy of Sciences", March 2012, vol. 109, n° 13, p. 4962-4967 [*DOI :* 10.1073/PNAS.1116871109], http://hal.inria.fr/hal-00681090.

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D. MISEVIC, A. FRÉNOY, D. P. PARSONS, F. TADDEI. *Effects of public good properties on the evolution of cooperation*, in "Artificial Life XIII", 2012.

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