INRIA

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Team combining

COMputational BIology and data miNING

Grenoble - Rhône-Alpes

Theme : Computational Biology and Bioinformatics

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1. Team

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2. Scientific Foundations

2.1. Introduction

The expanded name for the Combining research group is "Computational Biology and Data-Mining". Our aim is to position our research at the interface between biology and computer science and to contribute to the production of new results in biology by modeling biological systems and developing tools and methods to analyze automatically or semi-automatically the huge amount of raw data produced by high-throughput experimental devices.

The COMBINING Team results from the merging of a part of the "Turing" Team in the LIRIS Laboratory (Computer Science), a researcher of the RMND laboratory (Biology) and an INRIA researcher (Computational Biology). It has been created as an "Équipe Centre" by the INRIA Rhône-Alpes in April 2010 and is on the way to be created as an "Équipe-Projet INRIA" (EPI). The COMBINING Team is led by Prof. Guillaume Beslon (INSA-Lyon, LIRIS, Computer Science Department).

Our research is based on an interdisciplinary scientific strategy: a strong contribution to core computer science (e.g., generic data mining algorithm design, formalisms and architectures for complex system modeling) in synergy with multidisciplinary cooperations in the area of living sciences. We study abstractions of biological systems and processes thanks to computational approaches. Our studies can be oriented "From Data to Knowledge" (say, a data mining approach) or "From Knowledge to Data" (say, a modeling approach). More precisely, the scientific activity of the Combining group is organized in three topics: Computational cell biology, *in silico* experimental evolution and data-mining.

2.2. Computational Cell Biology

We are developing models of the spatio-temporal dynamic of cells and their molecular components. More precisely, we focus on 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 experimental "wet" approaches by developing closed collaborations with experimental biologists.

2.3. In silico experimental evolution

To better understand the cellular structures (genome organization, transcription networks or signaling cascades) we propose to study their historical evolutionary origin. We propose individual based evolutionary models to study how evolution in various conditions (e.g., large vs. small efficient population sizes, high vs. low mutation rates, stable vs. unstable environments, ...) lead to some specific structures shaped by the needs of robustness, variability or evolvability.

2.4. Data-Mining

In vivo, *in vitro* or *in silico* experiments in biology produce huge amounts of data that deserve complex analysis techniques. We develop generic methods, tools and solvers in order to help practitioners to extract knowledge from such data. We particularly focus on inductive databases framework that is likely to lead to efficient tools for biological data and on specific data formats that are of a great interest, either for their universality or for their biological pertinence: boolean tensors (especially n-ary relations), spatiotemporal data and dynamic graphs. Our aim in this domain is to benefit from the interactions with the modeling approaches to experiments with our solvers and simultaneously test our approaches on the artificial datasets produced by the models and on the data produced by the related *in vitro* an *in vivo* experiments.

2.5. Conclusion: Toward interdisciplinarity

The scientific objectives of the COMBINING team is to develop a coherent set of concepts and tools – mainly based on computational science – to contribute to knowledge discovery in systems biology. Our strategy is to develop synergies inside the team (between modeling and data-mining approaches) and outside the team with our partners in biology and life science. Thus, our aim as a team is neither 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* between biology and computer science. Our very scientific identity is thus fuzzy, melting components from both sciences. Of course, this aim at the team level can be differently instanciated by the members of the project, some of us being more or less unbalanced in favor of one side or the other. This creates a complementarity between the members of the project. This complementarity is coupled with a global will to support biological discovery by the mean of computational tools which acts as a cohesive force.

One of the central claim 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 COMBINING team tries to develop local collaborations with local scientists. That's also why COMBINING also tries to organize itself as an instrinsically interdisciplinary group, gathering different sensibilities between biology and computer science inside the group. Our ultimate objective being to develop interdisciplinarity at the individual level, most members of the team being able to interact efficiently with specialists from both fields.

3. Application Domains

3.1. Application Domains

Our scientific domain is centered on the development of computational tools for scientific discovery in cellular biology. Our tools come from three different domains:

- Computational Biology: 2D and 3D simulation of cellular compartments, mathematical description of the same.
- Digital Genetics: Simulation of evolution, creation of artificial artifacts that evolve in the computer.
- Data-Mining: Knowledge Discovery in Data, especially in the context of multidimensional binary data-sets.

4. Software

4.1. aevol (artificial evolution)

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

- 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)

- 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
- Active contributor: Christophe Rigotti

5. New Results

5.1. Importance of the rearrangement rates on the organization of transcription

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

The organization of genomes shows striking differences among the different life forms. These differences come along with important variations in the way genomes are transcribed, operon structures being frequent in short genomes and the exception in large ones, while non-coding RNAs are frequent in large genomes but rare in short ones. We used the digital genetics model *aevol* to explore the influence of the mutation rates on these structures, showing that their diversity can be accurately reproduced when varying the rearrangement rate. This result points us to the mutational burden hypothesis as one of the main explanation. In this view, a specific level of mutational robustness indirectly leads to genome and transcriptome streamlining [42].

5.2. Scaling Laws in Bacterial Genomes: A Side-Effect of Selection of Mutational Robustness?

Participants: Guillaume Beslon, Yolanda Sanchez-Dehesa, David P. Parsons, Jose-Maria Pena, Carole Knibbe.

We carried out simulations of genome evolution with the RAevol model, which allows for regulatory interactions to take place between genes. We thus simulated the evolution of both the genome sequence and the gene regulatory network. Not only the weights of the interactions, but also the topology of the network were free to evolve, as genes were acquired or deleted. We have shown that the pressure for complexification of the network can be indirect, unrelated to the differences in the environment or the lifestyle: When facing identical environmental constraints, the organisms' structure can range from very simple life forms (with a reduced gene set and loose connectivity) to very complex ones, the main determinant of the structure being only the rate of mutations and rearrangements in our simulations [12].

5.3. Aging and Protein aggregation in bacteria

Participants: Hugues Berry, Anne-Sophie Coquel, Ariel Lindner, A. Demarez.

Aging in bacteria is related to asymmetric protein aggregation. In particular protein aggregates accumulate with age in one of the poles of E. coli [65]. To uncover the implicated molecular mechanisms, we developed a synergy between innovative experimental approaches and computer models. Spatial distribution and trajectories within single cells of aggregates of fluorescently tagged proteins were compared to 3D individual-based model of protein diffusion-aggregation in E. coli. Our preliminary results indicate that the experimentally-observed spatial distribution of the aggregates can be accounted for by the large macromolecular crowding in the nucleoids. They also explain reported differences of the experimental results obtained in native versus heat shock conditions. Preliminary results have been presented as a poster in a national workshop [49] and a full paper will be submitted shortly. The study is funded by grants AE ColAge and ANR Pagdeg (see below).

5.4. Systems biology of neuronal and glial cells

Participants: Hugues Berry, E. Ben Jacob, M. DePitta, V. Volman, M. Goldberg, Bruno Delord, S. Genet, E. Guigon.

Computer models of the intracellular biochemical reaction networks that are implicated in the chemical communications between neurons and glial cells in the brain were developped. More specifically, we study the influence of intracellular calcium dynamics on the capacities of neurons to encode durations [4], with a more recent focus on the cerebellum (collaboration with S. Genet in Paris) [15]. On the other hands, we have initiated a collaboration with E. Ben Jacob's group at Tel Aviv University, to model the communications between neurons and glial cells. On the basis of our previous modeling work on the calcium signaling networks in single astrocytes [63], we developed and studied calcium wave propagation in populations of connected glial cells on a 2d space [16], [52].

5.5. Impact of Receptor Clustering on Ligand-Receptor Binding

Participants: Bertrand Caré, Hédi Soula, Christophe Rigotti, Christophe Soulage, N. Pillon.

Computational models for ligand-receptor biological interaction. Cell receptors tend to form clusters at the cell surface. This leads to divergence with mean-field classical models for receptor occupation. This work proposes a computational study of receptor spatial distribution, and its effects on the cell response. Results show that cell membrane receptors specific spatial distributions influence the apparent affinity of receptors, and may be a feature allowing cell response adaptation. By modifying the probabilities of binding/rebinding events, the receptor occupation at equilibrium is decreased by receptor colocalization. Publication in revision to appear. This work was featured as a short talk [48] in the conference IPG Nov. 25-26, 2010.

5.6. Aggregating MYriads of Bio-Inspired Agents

Participants: Hugues Berry, N. Fates, B. Girau, V. Vlassopoulos.

Collaboration in the framework of the Amybia project (http://www.loria.fr/~fates/Amybia/project.html), a 2008 INRIA Collaborative Initiative (ARC). We look for new decentralized and locally expressed algorithms to control the emergent behavior of a myriad of locally interacting computing elements with defects or faults in their operations. To this aim we take inspiration from the slime mold Dictyostelium discoideum. We studied the global dynamical behavior of this stochastic cellular automata model, in particular the nonequilibrium phase transition it exhibits [38] and proposed a high-performance hardware design as an FPGA implementation [43].

5.7. Dissemination of aquatic plant species in shallow lakes and pond networks

Participants: Serge Fenet, F. Arthaud, G. Bornette, F. Piola, Christine Solnon.

This is a new collaboration with the 'Ecologie vegetale et zones humides' team of the 'Laboratoire d'ecologie des Hydrosystemes Fluviaux' (Univ. Lyon 1). We built a model of the process of dissemination of aquatic plant species in shallow lakes and pond networks by using tools coming from complex systems studies and data mining techniques (non linear time series analysis, individual-based models, mining of dynamical interaction graphs...). A computer simulation of this model will help identify key anthropogenical and ecological factors, and guide the building of decision making software that will help to optimise biodiversity conservation in considering both ecological and societal constraints. This project is derived in two main contexts that have contrasted but complementary stakes. Both of them aim at the comprehension of the impact on biodiversity of the increasing of connectivity between communities (blue and green wefts) :(i) biodiversity conservation in the aquatic metacommunities of the Dombes ; (ii) protection against invasive species (*Fallopia Japonica*) threatening endemic species. These first work resulted in 2 communications (one of them co-published) in workshops of the field [47], [50].

5.8. Co-clustering Numerical Data under User-defined Constraints

Participants: Ruggero Pensa, Jean-François Boulicaut, F. Cordero, M. Atzori.

Many constrained clustering algorithms have been proposed to exploit the domain knowledge and to improve partition relevancy in the mono-dimensional clustering case (e.g. using the must-link and cannot-link constraints on one of the two dimensions). Here, we consider constrained co-clustering not only for extended must-link and cannot-link constraints (i.e. both objects and attributes can be involved), but also for interval constraints that enforce properties of co-clusters when considering ordered domains. We describe an iterative co-clustering algorithm which exploits user-defined constraints while minimizing a given objective function. Thanks to a generic setting, we emphasize that different objective functions can be used. The added value of our approach is demonstrated on both synthetic and real data. Among others, several experiments illustrate the practical impact of this original co-clustering setting in the context of gene expression data analysis, and in an original application to a protein motif discovery problem [18].

5.9. Sequential Patterns to Discover and Characterize Biological Relations

Participants: Marc Plantevit, P. Cellier, T. Charnois.

We present a method to automatically detect and characterize interactions between genes in biomedical literature. Our approach is based on a combination of data mining techniques: frequent sequential patterns filtered by linguistic constraints and recursive mining. Unlike most Natural Language Processing (NLP) approaches, our approach does not use syntactic parsing to learn and apply linguistic rules. It does not require any resource except the training corpus to learn patterns. First, frequent sequential patterns are extracted from the training corpus. Second, after validation of those patterns, they are applied on the application corpus to detect and characterize new interactions. An advantage of our method is that interactions can be enhanced with modalities and biological information. We use two corpora containing only sentences with gene interactions as training corpus. Another corpus from PubMed abstracts is used as application corpus. [36].

5.10. Recursive Sequence Mining to Discover Named Entity Relations

Participants: M. Plantevit, P. Cellier, T. Charnois, B. Crémilleux.

Extraction of named entity relations in textual data is an important challenge in natural language processing. For that purpose, we propose a new data mining approach based on recursive sequence mining.First, we present a method based on a cross-fertilization of sequence mining under constraints and recursive pattern mining to produce a user-manageable set of linguistic information extraction rules. Moreover, unlike most works from the state-of-the-art in natural language processing, our approach does not need syntactic parsing of the sentences neither resource except the training data. Second, we show in practice how to apply the computed rules to detect new relations between named entities, highlighting the interest of hybridization of data mining and natural language processing techniques in the discovery of knowledge. We illustrate our approach with the detection of gene interactions in biomedical literature [37].

5.11. Constraint-Based Mining of Sets of Cliques Sharing Vertex Properties

Participants: Marc Plantevit, Pierre-Nicolas Mougel, Christophe Rigotti, Olivier Gandrillon, Jean-François Boulicaut.

We consider data mining methods on large graphs where a set of labels is associated to each vertex. We investigate the extraction of sets of dense subgraphs such that the vertices in all subgraphs of a set share a large enough set of labels. As a first step, we consider here the special case of dense subgraphs that are cliques. We propose a method to compute all maximal homogeneous clique sets that satisfy user-defined constraints on the number of separated cliques, on the size of the cliques, and on the number of labels shared by all the vertices. The empirical validation illustrates the scalability of our approach and it provides experimental feedback on two real datasets, more precisely an annotated social network derived from the DBLP database and an enriched biological network concerning protein-protein interactions [40].

5.12. A Data-Mining Approach to Highlight Relations Between Functional Modules

Participants: Pierre-Nicolas Mougel, Marc Plantevit, Christophe Rigotti, Olivier Gandrillon, Jean-François Boulicaut.

We propose a data-mining approach to work on large graphs with set of labels associated to vertices which fits well with biological datasets, for example, a protein/protein interaction graph where each protein is labeled with the biological situations in which the corresponding gene is over-expressed. Our main originality considering previous work on this type of dataset consists in finding collections of functional modules. It may also highlight relations between densely connected subgraphs, for example genes connecting different functional modules. It might also locate groups of non-interacting proteins but whose genes are over-expressed in the same biological situations. [45].

5.13. Local pattern mining in spatio-temporal context

Participants: Christophe Rigotti, A. Julea, Nicolas Meger, E. Trouve, P. Bolon, R. Fallourd, J.-M. Nicolas, G. Vasile, M. Gay, O. Harant, L. Ferro-Famil.

This work aims to develop a framework for local pattern mining in spatio-temporal context, and is applied to satellite image time series. The approach relies on pixel-based evolution and sub-evolution extraction. We look for sub-evolutions that cover a minimum surface and that affect pixels that are sufficiently connected. We called such patterns the Grouped Frequent Sequential patterns. The minimum surface coverage and the spatial connectivity constraints are actively used to speed-up extraction on large data volumes and to select evolutions that make sense to the users. Applications have been run on real data in collaboration with other partners: LTCI Lab. Telecom ParisTech, GIPSA Lab. Grenoble, IETR Lab. Rennes, Geology Lab. ENS Paris, LGIT Lab. Grenoble, Polytechnic University of Bucharest Romania [39].

5.14. Multi-purpose multi-loop accelerator hardware architectures

Participants: Hugues Berry, D. Auras, S. Girbal, Olivier Temam, S. Yehia.

Collaboration with EPI Alchemy (INRIA Saclay, O. Temam) and Thales R & T (D. Auras, S. Girbal and S. Yehia) concerning computer architecture. We are developing methods and tools for multi-purpose loop-based accelerators (as architectural alternatives to current Chip-Multiprocessors). Based on our recent proposal for compound circuits [66], we recently proposed dedicated memory hierarchy systems [51], [34] and hybrid architectures containing both cores and accelerators [33]. This work resulted into a french patent co-owned by INRIA and Thales R&T [61].

5.15. Characterizing the speed and paths of shared bicycle use in Lyon

Participants: Pablo Jensen, Jean-Baptiste Rouquier, Nicolas Ovtracht, Céline Robardet.

Data gathered relating to the Lyon's shared bicycling system, VÈlo'v, is used to analyze 11.6 millions bicycle trips in the city. The data show that bicycles now compete with the car in terms of speed in downtown Lyon. It also provides information on cycle flows that can be of use in the planning of dedicated bicycle lanes and other facilities. See the published article, Ref. [17].

5.16. Mining multidimensional and multilevel sequential patterns

Participants: Marc Plantevit, A. Laurent, D. Laurent, M. Teisseire, Y.W. Choong.

Multidimensional databases have been designed to provide decision makers with the necessary tools to help them understand their data. However, automatic tools are still missing to mine this type of data in order to discover regular specific patterns. In [20], we present a method for mining sequential patterns from multidimensional databases, at the same time taking advantage of the different dimensions and levels of granularity, which is original compared to existing work. The necessary definitions and algorithms are extended from regular sequential patterns to this particular case.

5.17. Fenêtres sur cube

Participants: Marc Plantevit, Y. Pitarch, A. Laurent, P. Poncelet.

We propose a compact architecture to perform on-line multi-level and multi-dimensional analytical processing of stream data. Since time and space are critical in the context of stream analysis, our architecture is based on two techniques. First, a tilted-time model is used to compress the temporal dimension: the more recent the data is, the finer it is registered. Secondly, recent data are mostly interrogated on fine level of precision. So, we extend the tilted-time model to other multi-level dimensions: precision levels, which are never interrogated, are not materialized. Based on this design methodology, stream cube can be constructed and maintained incrementally with a low amount of memory and a reasonable computation cost [23].

5.18. Sequential data mining for knowledge extraction

Participants: Marc Plantevit, T. Charnois, Christophe Rigotti, Bruno Crémilleux.

We show the benefit of using data mining methods for BioNLP. We propose a method for learning linguistic patterns with a method based on sequential patterns enhanced by a recursive mining of patterns. The method does not use sentence parsing for learning patterns and for application (extraction of relations between named entities) neither ressource except the training data set. For named entities recognition problem, we propose a method based on a new kind of patterns taking account the sequence and its context [22].

5.19. Discovering Inter-Dimensional Rules in Dynamic Graphs

Participants: Marc Plantevit, Thi Kim-Ngan Nguyen, Loïc Cerf, Jean-François Boulicaut.

We consider the dynamic oriented graphs that can be encoded as n-ary relations with n >= 3 such that we have a least 3 dimensions: the dimensions of departure (tail) and arrival (head) vertices plus the time dimension. In other terms, it encodes the sequence of adjacency matrices of the graph. In such datasets, we propose a new semantics for inter-dimensional rules in dynamic graphs. We define rules that may involve subsets of any dimensions in their antecedents and their consequents and we propose the new objective interestingness measure called the exclusive confidence. We introduce a first algorithm for computing such inter-dimensional rules and we illustrate the added-value of exclusive confidence for supporting the discovery of relevant rules from a real-life dynamic graph [41].

5.20. Stochastic Dynamic of Gene Expression

Participants: Guillaume Beslon, Serge Fenet, Antoine Coulon, Gaël Kaneko, Olivier Gandrillon, José Vinuelas.

Gene Expression is now recognized as an intrinsically stochastic process [64]. However the nature and origin of the stochasticity of gene expression still has to be discovered. In this project, we collaborate with the Centre de Génétique Moléculaire et Cellulaire (O. Gandrillon's Team) to develop a joint research (modeling and wet experiments) to decipher the origin, structure and role of expression noise in multicellular eukaryotic organisms. We particularly study the dynamic of gene's promoter [13] and the effect of chromatin characteristics on the stochasticity [53].

5.21. Semantics and computation of descriptive rules in an n-ary relation

Participants: Thi Kim-Ngan Nguyen, Loïc Cerf, Jean-François Boulicaut.

We study the generalization of association rule mining within arbitrary binary n-ary relation (n >= 2). A challenging problem is to provide a semantics to such generalized rules by means of objective interestingness measures that have to be carefully designed. Therefore, we discuss the need for different generalizations of the classical confidence measure (e.g., the notions of the exclusive confidence and the natural confidence). We also present the first algorithm that computes, in such a general framework, every rule that satisfies both a minimal frequency constraint and minimal confidence constraints. The approach is tested on a real ternary relation [46].

5.22. Comparing Intended and Real Usage in Web Portal: Temporal Logic and Data Mining

Participants: Jérémy Besson, Ieva Mitasiunaite, A. Lupeikiene, Jean-François Boulicaut.

Nowadays the software systems, including web portals, are developed from a priori assumptions about how the system will be used. However, frequently these assumptions hold only partly and are defined also partially. Therefore one must be capable to compare the a priori assumptions with the actual user behavior in order to decide how the system could be improved. To tackle this problem, we consider a promising approach to employ the same formalism to express the intended usage, the web portal model and the frequent real usage patterns, extracted from the experimental data by data mining algorithms. This allows to automate the verification whether the frequent real usage patterns satisfy the intended usage in the web portal model. We propose to use temporal logic and Kripke structure as such a common formalism [35].

6. Other Grants and Activities

6.1. Regional Initiatives

6.1.1. PEACE

Participants: Dominique Schneider, Elisabeth Kay, Guillaume Beslon, Stephan Fischer, Carole Knibbe, David P. Parsons, Frédéric Desprez, Yves Caniou.

We are involved in the PEACE project with Dominique Schneider and Elisabeth Kay, from the Laboratoire Adaptation et Pathogénie des Microorganismes (CNRS UMR5163) in Grenoble and Frédéric Desprez and Yves Caniou, from the EPI GRAAL in Lyon. PEACE means Parallel Experimental and Computational Evolution. This project is funded by the RTRA FINOVI (Fondation Innovations en infectiologie). It aims at carrying both wet experimental evolution experiments and computer simulations to better understand the evolution of the virulence of *Legionella pneumophila*, the causative agent of legionnaires' disease. Total amount funded: 50,000 euros.

6.1.2. Digital Evolution and Comparative Genomics

Participants: Guillaume Beslon, Carole Knibbe.

We have received a BQR grant from the INSA-Lyon. The aim is to compare the results obtained with our simulation software *aevol* with the content of prokaryotes sequence databases. Total amount funded: 15,000 euros and a Six monthes post-doc.

6.1.3. Modelling and optimizing the factors acting on spatio-temporal dissemination of vegetal communities

Participants: Serge Fenet, F. Arthaud, G. Bornette, F. Piola, Christine Solnon.

A research project based on our collaboration with the LEHF (see section 5.7). Funded by the 'Institut Rhône-alpin des Systèmes Complexes' (IXXI). Involves 5 persons of both LEHF and LIRIS laboratories. Total amount funded: 5,000 euros.

6.2. National Initiative

6.2.1. ColAge

Participants: Hugues Berry, Anne-Sophie Coquel, Ariel Lindner, François Taddei, Hans Geiselmann, Hidde de Jong, Delphine Ropers, Magdalena Chaves, Jean-Luc Gouzé, Grégory Batt, François Fages.

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 Combining. 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 (to A. Lindner, see below) and GeMCo (to M. Chaves, http://www-sop.inria.fr/members/Madalena.Chaves/).

6.2.2. PAGDEG

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

A three-year project (2010-20012) 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.

6.2.3. Spatio-temporal data mining: Application to soil erosion monitoring

Participants: Christophe Rigotti, Nazha Selmaoui, P. Gancarski, Nicolas Meger.

Three year (2010) research project funded by the ANR call "COSINUS'. Project leader : N. Selmaoui, University of New Caledonia.

6.2.4. RASMOT

Participants: Hugues Berry, E. Guigon.

One year (2010) research project funded by the call "Programme interdisciplinaire CNRS Neuro-IC : Neurosciences et neuroinformatique computationnelle". We explore the possibility to use recent bioinspired machine learning techniques to learn and represent in a neural network an optimal controller mimicking human brain-like motor control. Supervisor: E. Guigon (ISIR, CNRS, Univ. P&M Curie Paris). Total amount funded : 24,000 euros.

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

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

Strong collaboration links exist between Combining and F. Taddei's and A. Lindner's group, in Paris: Firts, 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, Dusan Misevic and Francois 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?

6.3. International Initiatives

6.3.1. Partnership with E. Ben Jacob's Group, Univ. Tel Aviv.

Participant: Hugues Berry.

Strong collaboration links between H. Berry and E. Ben Jacob's group in Israel (mainly M. De Pitta and E. Ben Jacob at the Maguy-Glass Chair in Physics of Complex Systems, School of Physics and Astronomy, Tel-Aviv University, Tel Aviv, Israel and V. Volman, Center for Theoretical Biological Physics, UC San Diego and Computational Neurobiology Lab, The Salk Institute, La Jolla, CA, USA). The topics of the collaboration are the modeling and simulation of the biochemical communications between neurons and glia cells and the modulation of synaptic plasticity due to neuron-glia biochemical interactions (see section 5.4). H. Berry visited V. Volman in San Diego at the occasion of the Neuroscience Conference 2010 (Nov. 13-17 2010) and two co-publications were recently published: [63], in 2010: [16].

7. Dissemination

7.1. Animation of the scientific community

7.1.1. Scientific Popularization

- Guillaume Beslon and Carole Knibbe contributed a chapter in the general-public book "Des mondes bricolés? Arts et sciences à l'épreuve de la notion de bricolage", edited by Francoise Odin and Christian Thuderoz [54]. This contribution is about the notion of tinkering, both in the process of Darwinian evolution and in the way scientists play with models to study it.
- Hugues Berry and Bruno Cessac from EPI Neuromathcomp, INRIA Sophia, wrote an article about the complex dynamics of the brain and the utilization of chaos theory to model them. The original article published on 2009 in the french journal "Pour La Science" [62] has been re-edited on)I(nterstice's web site [58].
- Guillaume Beslon has been interviewed by the)I(nterstice web site (April 2010) to present his view of models and modeling [59].
- Guillaume Beslon has been interviewed by France Inter (La tête au carré, December 10 2010) to present the activity of the IXXI (Institut Rhône-Alpin des Systèmes Complexes) [60].

- Guillaume Beslon gave a conference on evolutionary robotics in the context of the "Trophées de Robotique" (Centre Culture Charlie Chaplin, Vaulx-en-Velin, March 2010).
- Guillaume Beslon gave a conference on the notion of "adaptive landscape" to the students of the ENSAD (École Nationale Supérieure des Arts Déco, February 2010).

7.1.2. Editorial activities

- Jean-François Boulicaut was member of the following PCs : the 2010 Conférence francophone d'apprentissage automatique, CAp'10, Clermont-Ferrand, June 2010; Journées Francophones Extraction et Gestion de la Connaissance, EGC'10 (Hammamet, janvier 2010); Congrès AFRIF-AFIA Reconnaissance de Formes et Intelligence Artificielle RFIA'10 (Caen, janvier 2010); Dynamic Networks and Knowledge Discovery DYNAK'10 co-located with ECML/PKDD 2010 (Barcelona, September 2010); Integrative Post-Genomics IPG'10 (Lyon, November 2010); Workshop on Semantics Aspects for Data Mining SADM'10 co-located with IEEE ICDM'10 (Sydney, December 2010); Discovery Science DS'10 (Canberra, October 2010); European Conf. on Machine Learning & European Conf. on Principles and Practice Knowledge Discovery in Databases ECML/PKDD'10 (Barcelona, September 2010); IEEE Int. Conf. on Data Mining, ICDM'10 (Sydney, December 2010); Int. Conf. on Formal Concept Analysis ICFCA'10 (Agadir, March 2010); Int. Symp. on Intelligent Data Analysis IDA'10 (Tucson, May 2010); SIAM Int. Conf. on Data Mining SDM'10 (Colombus, April 2010); IDA'10 and DS'10. He was also member of the Editorial Board of the journals "Bioinformatics and Biology Insights" and "Data Mining and Knowledge Discovery".
- Marc Plantevit was member of the following PCs : the 2010 International Conference on Advances in Social Networks Analysis and Mining http://asonam2010.hau.gr/ and the European Conference on Machine Learning and Principles and Practice of Knowledge Discovery in Databases (ECML PKDD) http://www.ecmlpkdd2010.org/
- Christophe Rigotti was member of the PC for the 2010 International Conference on Data Mining (ICDM'10) and the 2010 Conference on Advanced Data Mining and Applications (ADMA'10).
- Céline Robardet was area chair for SDM11 (Eleventh SIAM International Conference on Data Mining, April 28-30, 2011, Mesa, Arizona, USA).
- Hugues Berry was review editor for the journal "Frontiers in Neurorobotics" (http://www.frontiersin.org/neurorobotics/editorialboard) and member of the organization committee of the 2010 CNRS-INRA thematic school "**EIEFB**: Ecole interdisciplinaire d'échanges et de formation en biologie", Berder Island (Morbihan, France). Main Organizer: Ch. Lavelle (CNRS, Lille).
- Guillaume Beslon was member of the program committee of Journées Ouvertes en Biologie, Informatique et Mathématiques JOBIM'10 (Montpellier, September 2010); Dynamic Networks and Knowledge Discovery DYNAK'10 co-located with ECML/PKDD 2010 (Barcelona, September 2010); Integrative Post-Genomics IPG'10 (Lyon, November 2010). He was reviewer for the journals "BMC Bioinformatics" and "BMC Evolutionary Biology".

7.1.3. Misc. given talks

- Hugues Berry gave talks at the IN2P3, Lyon in March and at Lyon Institute for Complex Systems, IXXI, in May.
- Anne-Sophie Coquel presented posters during a summer school on aging and cancer at Beijing University, China in July and during a workshop on aging a Newcastle, UK in June.
- Guillaume Beslon gave the following talks:
  - Talk at the LORIA (INRIA Lorraine, iPAC seminars) in February. Title: "Modélisation et Découverte de Connaissances en Biologie" [29].
  - Talk at the Berder Interdisciplinary Spring School in April 2010. Title: "Évolution et Mémoire Génétique; Quatre petites histoires de mémoire en évolution (digitale)" [26].

- Invited talk at the COMMISCO conference (Bondy, IRD, October 2010). Title: “Digital Genetics: a view on the origin of biological complexity” [28].
- Invited talk at the Theoretical Aspects of Genomes and Proteomes (Annecy, October 2010). Title: “Digital genetics with aevol: a view on the (evolutionary) origin of biological complexity” [27].
- Talk at the workshop “A l’interface des sciences du vivant, de l’informatique et des mathématiques” (Lyon, June 2010). Title: “Vers une complémentarité entre évolution expérimentale et évolution numérique : le projet PEACE”.
- Invited seminars at the LBBE (Lyon, January 2010) and at the Institut des Sciences de l’Evolution (Montpellier, April 2010). Title: “Lois d’echelles dans les genomes et les proteomes, une etude par genetique digitale”.
- 4 hours tutorial at the Spring School of Porquerolle (Porquerolle, June 2010). Title: “Modelisation individu-centree de systemes biologiques complexes. Application a la simulation de l’evolution de reseaux genétiques bacteriens”.
- 3 hours tutorial at the Spring School “Introduction aux Sciences Cognitives” (Lyon, May 2010). Title: “From Complex Systems to the Science of Complex Systems; An Introduction ”.
- 12 hours tutorial at the “Complex Systems Summer School” (Paris, August 2010). Title: “Introduction to Digital Genetics”.

7.2. PhDs defended

In 2010, two PhDs students in the team have defended their PhD

- Loic Cerf : “Constraint-based Mining of closed Patterns from Noisy Arbitrary n-ary Relations†” (supervised by J.F. Boulicault, July 09 2010) [9].
- Antoine Coulon: “Stochasticité de l’expression génique et régulation transcriptionnelle; Modélisation de la dynamique spatiale et temporelle des structures multiprotéiques” (supervised by G. Beslon and O. Gandrillon,) [10].

7.3. Teaching

7.3.1. Teaching at Universities

- Most of us teach Computer Science at INSA Lyon or University Lyon 1.
- We also taught in specific programs such as the Systems Biology minor of the Bioscience Master of ENS Lyon.
- Two of us (G. Beslon and C. Knibbe) teach in the “Modélisation des Systèmes Complexes” Master program of ENS Lyon

7.3.2. Internships

- Zayna Chaker. *Protein aggregation underlying bacterial aging : Computer simulations*. Master 2 AIV (Paris 5 Descartes). Advisor: H. Berry.
- Guillaume Debras. *Optimization of the R-aevol simulation software*. Département Informatique (INSA-Lyon). Advisor: G. Beslon.
- Sébastien Mériot. *Parallel implementation of the aevol simulation software*. Département Informatique (INSA-Lyon). Advisor: G. Beslon.

7.4. Jurys and committees

- In 2010, members of Combining have served into
  - 5 PhD committees (among which 1 as reviewers).
  - 1 HdR committees (as reviewer)
  - 3 AERES evaluation committees (UR protection radiologique de l'homme, IRSN, Fontenay-aux-Roses; LITIS, Rouen; LIMOS, Clermont-Ferrand).
  - 7 selection committees for the hiring of (associate or full) professors in external universities.
  - Expert committees for ANR Funding calls (Jeunes Chercheurs, appels Blancs), for foreign funding institutions (NWO, The Netherlands; CNRC, Canada; FWO, Belgium) and UE (COST actions).
- J.F. Boulicaut and C. Rigotti are members of the Scientific Council (C.S.) of INSA Lyon.
- J.F. Boulicaut is also member of the "comité de direction" of LIRIS laboratory (CNRS UMR 5205) and of the "conseil de department" of INSA Lyon Computer Science Department.
- G. Beslon is director of the Rhône-Alpes Complex Systems Institute (IXXI).
- C. Knibbe is president of the steering commitee of the Rhône-Alpes Complex Systems Institute (IXXI).

7.5. Participation to INRIA's Life

- H. Berry was member of the "comités de recrutements" INRIA ASS3 and AF5 in June.
- On behalf of G. Malandin (INRIA Sophia) for the Scientific Direction, H. Berry wrote the mid-term update of Jalon 17 ("Cellular Dynamics") in the 2008-2012 INRIA strategic plan.

8. Bibliography

Major publications by the team in recent years

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

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