INRIA

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Team BAMBOO

An algorithmic view on genomes, cells, and environments

Grenoble - Rhône-Alpes

Theme : Computational Biology and Bioinformatics

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1. Team

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Visiting Scientists

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Mike Charleston [Professor, University of Sydney, Australia, visit of 2 weeks]
Pierluigi Crescenzi [Professor, University of Florence, Italy, various visits of 1-2 weeks]
Zanoni Dias [Professor, University of Campinas, Brazil, visit of 4 weeks]

Paulo Gustavo Fonseca [Junior Researcher, INESC-ID, IST Lisbon, Portugal, visit of 1 week]
Ana Teresa Freitas [Professor, INESC-ID, IST Lisbon, Portugal, visit of 1 week]
Roberto Grossi [Professor, University of Pisa, Italy, visit of 1 week]
Alberto Marchetti-Spaccamela [Professor, University La Sapienza, Rome, Italy, visit of 1 week]
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Leen Stougie [Free University Amsterdam and CWI, Amsterdam, the Netherlands, visit of 1 week]
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Other

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2. Overall Objectives

2.1. Highlights

The obtention of an ERC Advanced Grant in 2010 (that started on April 1st, acronym SISYPHE for "Species Identity and SYmbiosis Formally and Experimentally explored") implies that a greater focus of the topics developed in the Team will be put on the main biological question of SISYPHE, namely symbiosis. This can be informally defined as a close relationship between different biological species. It is a pervasive phenomenon, often of a long term nature that appears essential to understand some of the most fundamental evolutionary and functional questions related to living organisms. Although symbiotic relationships have been studied by biologists since the early 19th century, they however remain little explored by computational biologists.

By a pluri-disciplinary approach that blends mathematics, algorithmics and wet-lab experiments, we propose to do an intensive, large-scale exploration of the huge variety of genomic and biochemical landscapes observed in the symbiont world, at the interface between symbionts and hosts, and of both with their environment. Our objective, towards which we started working this year, is to arrive at a clear view of the importance of symbiosis.

The symbiotic relation extends the more general study of interactions which has been our concern for over six years now. This earlier study included metabolism, but also the spatial arrangement formed by genetic elements that may stand far apart along a chromosome or even on different chromosomes, but are in close proximity inside a cell. This earlier work is also continued.

3. Scientific Foundations

3.1. Formal methods

The study of symbiosis and of biological interactions more in general is the motivation for the work conducted within BAMBOO, but runs in parallel with another important objective. This concerns to (re)visit classical combinatorial (mainly counting / enumerating) and algorithmic problems on strings and (hyper)graphs, and to explore the new variants / original combinatorial and algorithmic problems that are raised by the main areas of application of this project. As the objectives of these formal methods are motivated by biological questions, they are briefly described together with those questions in the next section.

3.2. Symbiosis

The study we propose to do on symbiosis decomposes into four main parts - (1) genetic dialog, (2) metabolic dialog, (3) symbiotic dialog and genome evolution, and (4) symbiotic dynamics - that are however strongly interrelated, and the study of such interrelations will represent an important part of our work. Another biological objective, larger and which we hope within the ERC project SISYPHE just to sketch for a longer term investigation, will aim at getting at a better grasp of species identity and of a number of identity-related concepts. We now briefly indicate the main points that have started been investigated or should be investigated in the next five years.

Genetic dialog

We plan to study the genetic dialog at the regulation level between symbiont and host by addressing the following mathematical and algorithmic issues:

1. model and identify all small RNAs from the bacterium and the host which may be involved in the genetic dialog between the two, and model/identify the targets of such small RNAs;
2. infer selected parts of the regulatory network of both symbiont and host (this will enable to treat the next point) using all available information;
3. explore at both the computational and experimental levels the complementarity of the two networks, and revisit at a network level the question of a regulatory response of the symbiont to its host's demand;
4. compare the complementarities observed between pairs of networks (the host's and the symbiont's); such complementarities will presumably vary with the different types of host-symbiont relationships considered, and of course with the information the networks model (structural or dynamic); Along the way, it may become important at some point to address also the issue of transposable elements (abbreviated into TEs, that are genes which can jump spontaneously from one site to another in a genome following or not a duplication event). It is increasingly believed that TEs play a role in the regulation of the expression of the genes in eukaryotic genomes. The same role in symbionts, and in the host-symbiont dialog has been less or not explored. This requires to address the following additional task:
5. accurately and systematically detect all transposable elements (*i.e.* genes which can jump spontaneously from one site to another in a genome following or not a duplication event) and assess their implication in their own regulation and that of their host genome (the new sequencing technologies should facilitate this task as well as other data expression analyses, if we are able to master the computational problem of analysing the flow of data they generate: fragment indexing, mapping and assembly);
6. where possible, obtain data enabling to infer the PPI (Protein-Protein Interaction) for hosts and symbionts, and at the host-symbiont interface and analyse the PPI networks obtained and how they interact.

Initial algorithmic and statistical approaches for the first two items above are under way and are sustained by a well-established expertise of the team on sequence and microarray bioinformatic analysis. Both problems are however notoriously hard because of the high level of missing data and noise, and of our relative lack of knowledge of what could be the key elements of genetic regulation, such as small and micro RNAs.

We also plan to establish the complete repertoire of transcription factors of the interacting partners (with possible exchanges between them) at both the computational and experimental levels. Comparative biology (search by sequence homology of known regulators), 3D-structural modelling of putative domains interacting with the DNA molecule, regulatory domains conserved in the upstream region of coding DNA are among classical and routinely used methods to search for putative regulatory proteins and elements in the genomes. Experimentaly, the BiaCore (using the surface plasmon resonance principle) and ChIP-Seq (using chromatin precipitation coupled with high-throughput sequencing from Solexa) techniques offer powerful tools to capture all the protein-DNA interactions corresponding to a specific putative regulator. However, these techniques have not been evaluated in the context of interacting partners making this task an interesting challenge.

Metabolic dialog
Our main plan for this part, where we have already many results, some obtained this last year, is to:

1. continue with and improve our work on reconstructing the metabolic networks of organisms with sequenced genomes, taking in particular care to cover as much as possible the different types of hosts and symbionts in interaction;
2. refine the network reconstructions by using flux balance analysis which will in turn require addressing the next item;
3. improve our capacity to efficiently compute fluxes and do flux balance analysis; current algorithms can handle only relatively small networks;
4. analyse and compare the networks in terms of their general structural, quantitative and dynamic characteristics;
5. develop models and algorithms to compare different types of metabolic interfaces which will imply being able, by a joint computational and experimental approach, to determine what is transported across interacting metabolisms;
6. define what would be a good null hypothesis to test the statistical significance, and therefore possible biological relevance of the characteristics observed when analysing or comparing (random network problem, a mostly open issue despite the various models available);
7. use the results from item 5, that is indications on the precursors of a bacterial metabolism that are key players in the dialog with the metabolism of the host, to revisit the genetic regulation dialog between symbiont and host.

Computational results from the last item will be complemented with experiments to help understand what is transported from the host to the symbiont and how what is transported may be related with the genetic dialog between the two organisms (items 5 and 6).

Great care will also be taken in all cases (metabolism- or regulation-only, or both together) to consider the situations, rather common, where more than two partners are involved in a symbiosis, that is when there are secondary symbionts of a same host.

The first five items above have started being computationally explored by our team, as has the last item including experimentally. Some algorithmic proofs-of-concept, notably as concerns structural, flux, precursor and chemical organisation studies (see some of the publications of the last year and this one), have been established but much more work is necessary. The main difficulties with items 3 and 4 are of two sorts. The first one is a modelling issue: what are the best models for analysing and comparing two or more networks? This will greatly depend on the biological question put, whether evolutionary or functional, structural or physiologic, besides being a choice that should be motivated by the extent and quality of the data available. The second sort of difficulty ,which also applies to other items notably (item 2), is computational. Most of the problems related with analysing and specially comparing are known to be hard but many issues remain open. The question of a good random model (item 6) is also largely open.

Symbiotic dialog and genome evolution
Genomes are not static. Genes may get duplicated, sometimes the duplication affects the whole genome, or genes can transpose, while whole genomic segments can be reversed or deleted. Deletions are indeed one of the most common events observed for some symbionts. Genetic material may also be transferred across sub-species or species (lateral transfer), thus leading to the insertion of new elements in a genome. Finally, parts of a genome may be amplified through, for instance, slippage during DNA replication resulting in the multiplication of the copies of a repeat that appear tandemly arrayed along a genome. Tandem repeats, and other types of short or long repetitions are also believed to play a role in the generation of new genomic rearrangements although whether they are always the cause or consequence of the genome break and gene order change remains a disputed issue.

Work on this part will involve the following items:

1. extend the theoretical work done in the past years (rearrangement distance, rearrangement scenarios enumeration) to deal with different types of rearrangements and explore various types of biological constraints;
2. develop good random models (a largely open question despite some initial work in the area) for rearrangement distances and scenarios under a certain model, i.e. type of rearrangement operation(s) and of constraint(s), to assess whether the distances / scenarios observed have statistically notable characteristics;
3. extensively use the method(s) developed to investigate the rearrangement histories for the families of symbionts whose genomes have been sequenced and sufficiently annotated;
4. investigate the correlation of such histories with the repeats content and distribution along the genomes;
5. use the results of the above analyses together with a natural selection criterion to revisit the optimality model of rearrangement dynamics;
6. extend such model to deal with eukaryotic (multi-chromosomal) genomes;
7. at the interface host-symbiont, investigate the relation between the rearrangement histories in hosts and symbionts and the various types of symbiotic relationships observed in nature;
8. map such histories and their relation with the genetic and metabolic networks of hosts and symbionts, separately and at the interface;
9. develop methods to identify and quantify rearrangement events from NGS data.

Symbiotic dynamics
In order to understand the evolutionary consequences of symbiotic relations and their long term trajectories, one should be able to assess how tight is the association between symbionts and their hosts.

The main questions we would like to address are:

1. how often are symbionts horizontally transferred among branches of the host phylogenetic tree?
2. how long do parasites persist inside their host following the invasion of a new lineage?
3. what processes underlie this dynamic gain/loss equilibrium?

Mathematically, these questions have been traditionally addressed by co-phylogenetic methods, that is by comparing the evolutionary histories of hosts and parasites as represented in phylogenetic trees.

Currently available co-phylogenetic algorithms present various types of limitations as suggested in recent surveys. This may seriously compromise their interpretation with a view to understanding the evolutionary dynamics of parasites in communities. A few examples of limitations are the (often wrong) assumption made that the same rates of loss and gain of parasite infection apply for every host taxonomic group, and the fact that the possibility of multi-infections is not considered. In the latter case, exchange of genetic material between different parasites of a same host could further scramble the co-evolutionary signal. We therefore plan to:

1. better formalise the problem and the different simplifications that could be made, or inversely, should be avoided in the co-phylogeny studies; examples of the latter are the possibility of multi-infections, differential rate of loss and gain of infection depending on the host taxonomic group and geographic distance between hosts, etc., and propose better co-phylogenetic algorithms;
2. elaborate series of simulated data that will enable to (i) get a better grasp of the effect of the different parameters of the problem and, more pratically, (ii) evaluate the performance of the method(s) that exist or are proposed (see next item);
3. apply the new methods to address the three questions above.

3.3. Intracellular interactions

The interactions of a symbiont with others sharing a same host, or with a symbiont and the cell of its host in the case of endosymbionts (organism that lives within the body or cells of another) are special, perhaps more complex cases of intracellular interactions that may concern different types of genetic elements, from organelles to whole chromosomes. The spatial arrangement of those genetic elements inside the nucleus of a cell is believed to be important both for gene expression and exchanges of genetic material between chromosomes. This question goes beyond the symbiosis one and has been investigated in the team in the last few years. Work on this will continue in future and concern developing algorithmic and statistical methods to analyse the interaction data that is starting to become available, in particular using NGS methods, in order to arrive at a better understanding of transcription, regulation both classical and epigenetic (inherited changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence), alternative splicing and trans-splicing phenomena, as well as study the possible interactions between an eukaryotic cell and its organelles or other cytoplasmic structures.

4. Application Domains

4.1. Biology with a focus on symbiosis

The main area of application of BAMBOO is biology, with a special focus on symbiosis (ERC project) and on intracellular interactions.

5. Software

5.1. AcypiCyc

Participants: Hubert Charles [EPI], Patrice Baa Puyoule [Contact, Patrice.Baa-Puyoulet@lyon.inra.fr], Stefano Colella [Contact, stefano.colella@lyon.inra.fr], Ludovic Cottret, Marie-France Sagot [EPI], Augusto Vellozo [Contact, augusto@cycadsys.org], Amélie Véron.

Database of the metabolic network of *Acyrthosiphon pisum*.
http://acypicyc.cycadsys.org/

5.2. Alfacinha

Participants: Laurent Guéguen [EPI], Leonor Palmeira [Contact, mlpalmeira@ulg.ac.be].

Simulation of sequence evolution with neighbouring-site dependencies.
http://pbil.univ-lyon1.fr/software/alfacinha

5.3. BaobabLuna

Participants: Marília Braga [Contact, mdvbraga@gmail.com], Marie-France Sagot [EPI], Eric Tannier [EPI].

Manipulation of signed permutations in the context of genomic evolution.
http://pbil.univ-lyon1.fr/software/luna/

5.4. Cassis

Participants: Christian Baudet [EPI, Contact, christian.baudet@univ-lyon1.fr], Christian Gautier [EPI], Claire Lemaitre [Contact, claire.lemaitre@inria.fr], Marie-France Sagot [EPI], Eric Tannier [EPI].

Algorithm for precisely detecting genomic rearrangement breakpoints.
http://pbil.univ-lyon1.fr/software/Cassis/

5.5. Cravela

Participants: Ana Teresa Freitas, Nuno Mendes [EPI, Contact, ndm@kdbio.inesc-id.pt], Marie-France Sagot [EPI, Contact, marie-france.sagot@inria.fr].

Framework for the identification and evaluation of miRNA precursors (finished), targets (in development) and regulatory modules(in development).
http://www.cravela.org/

5.6. C3P

Participants: Frédéric Boyer, Anne Morgat [EPI, ext. member], Alain Viari [EPI, Contact, alain.viari@inria.fr].

Merging two or more graphs representing biological data (e.g. pathways, ...).
http://www.inrialpes.fr/helix/people/viari/cccpart

5.7. DCJ2HP

Participants: István Miklós [Contact, miklosi@ramet.elte.hu], Eric Tannier [EPI].

Bayesian sampling of genomic rearrangement scenarios via Double Cut and Join.
http://www.renyi.hu/~miklosi/DCJ2HP/

5.8. Ed'Nimbus

Participants: Pierre Peterlongo [Contact, pierre.peterlongo@inria.fr], Marie-France Sagot [EPI].

Algorithm for detecting and filtering repeats in sequences prior to multiple alignments.
htp://mobyle.genouest.org/cgi-bin/Mobyle/portal.py?form=tuiuiu

5.9. GeM

Participants: Gisèle Bronner, Christian Gautier [EPI, Contact, christian.gautier@univ-lyon1.fr], Bruno Spataro.

noindent Database for comparative genomic analysis of complete vertebrate genomes.
http://pbil.univ-lyon1.fr/gem/gem_home.php

5.10. Hogenom

Participants: Laurent Duret, Manolo Gouy [EPI], Simon Penel, Guy Perrière [Contact, guy.perriere@univ-lyon1.fr], Dominique Mouchiroud.

Database of homologous genes between fully-sequenced genomes.
http://pbil.univ-lyon1.fr/databases/hogenom.html

5.11. HoSeqI

Participants: Anne-Muriel Arigon, Manolo Gouy [EPI], Guy Perrière [Contact, guy.perriere@univ-lyon1.fr].

Automatic identification of large collections of protein-coding or rRNA sequences.
http://pbil.univ-lyon1.fr/software/HoSeqI/

5.12. kisSnp

Participants: Vincent Lacroix [EPI], Pierre Peterlongo [Contact, pierre.peterlongo@inria.fr], Nadia Pisanti, Marie-France Sagot [EPI], Nicolas Schnel.

Algorithm for identifying SNPs without a reference genome by comparing raw reads.
http://alcovna.genouest.org/kissnp/

5.13. MetExplore

Participants: Michael Barrett, Hubert Charles [EPI], Ludovic Cottret [Contact, Ludovic.Cottret@toulouse.inra.fr], Fabien Jourdan, Marie-France Sagot [EPI], Florence Vinson, David Wildridge.

Web server to link metabolomic experiments and genome-scale metabolic networks.
http://metexplore.toulouse.inra.fr/metexplore/

5.14. Migal

Participants: Julien Allali [Contact, julien.allali@labri.fr], Marie-France Sagot [EPI].

Algorithm for comparing RNA structures.
http://www-igm.univ-mlv.fr/~allali/logiciels/index.en.php

5.15. MotusWEB

Participants: Ludovic Cottret, Fabien Jourdan, Vincent Lacroix [EPI, Contact, vincent.lacroix@univ-lyon1.fr], Odile Rogier, Marie-France Sagot [EPI].

Algorithm for searching and inferring coloured motifs in metabolic networks (web-based version - offers different functionalities from the downloadable version).
http://pbil.univ-lyon1.fr/software/motus_web/

5.16. Motus

Participants: Ludovic Cottret, Fabien Jourdan, Vincent Lacroix [EPI, Contact, vincent.lacroix@univ-lyon1.fr], Odile Rogier, Marie-France Sagot [EPI].

Algorithm for searching and inferring coloured motifs in undirected graphs (downloable version - offers different functionalities from the web-based version).
http://pbil.univ-lyon1.fr/software/motus/

5.17. Njplot

Participant: Manolo Gouy [EPI, Contact, manolo.gouy@univ-lyon1.fr].

Algorithm for drawing phylogenetic trees.
http://pbil.univ-lyon1.fr/software/njplot.html

5.18. OBIWarehouse

Participants: Eric Coissac [Contact, eric.coissac@inrialpes.fr], Anne Morgat [EPI, ext. member], Alain Viari [EPI].

Integrated and synchronised heterogeneous public data on micro-organisms.
http://www.grenoble.prabi.fr/obiwarehouse

5.19. PhEVER

Participants: Christian Gautier [EPI], Vincent Lotteau, Leonor Palmeira [Contact, mlpalmeira@ulg.ac.be], Chantal Rabourdin-Combe, Simon Penel.

Database of homologous gene families built from the complete genomes of all available viruses, prokaryotes and eukaryotes and aimed at the detection of virus/virus and virus/host lateral gene transfers.
http://pbil.univ-lyon1.fr/databases/phever/

5.20. PepLine

Participants: Jérôme Garin, Alain Viari [EPI, Contact, alain.viari@inria.fr].

Pipeline for the high-throughput analysis of proteomic data.
http://www.grenoble.prabi.fr/protehome/software/pepline

5.21. PhyloJava

Participants: Laurent Duret, Manolo Gouy [EPI, Contact, manolo.gouy@univ-lyon1.fr], Simon Penel, Timothée Sylvestre.

Server for grid-powered phylogenetic reconstruction.
http://pbil.univ-lyon1.fr/software/phylojava/phylojava.html

5.22. Pitufo

Participants: Vicente Acuña [EPI], Ludovic Cottret [Contact, Ludovic.Cottret@toulouse.inra.fr], Alberto Marchetti-Spaccamela [EPI, ext. member], Paulo Vieira Milreu [EPI, Contact, pvmilreu@gmail.com], Marie-France Sagot [EPI], Leen Stougie [EPI, ext. member], Fabio Viduani-Martinez.

Algorithm to enumerate all minimal sets of precursors of target compounds in a metabolic network.
http://sites.google.com/site/pitufosoftware/

5.23. Prunier

Participants: Sophie Abby [Contact, Sophie.Abby@univ-lyon1.fr>], Vincent Daubin, Manolo Gouy [EPI], Eric Tannier [EPI].

Algorithm for detecting lateral gene transfers in a gene tree given a species tree.
http://pbil.univ-lyon1.fr/software/prunier/

5.24. PSbR

Participants: Yoan Diekmann, Marie-France Sagot [EPI, Contact, marie-france.sagot@inria.fr], Eric Tannier [EPI].

Algorithm for testing the evolution and conservation of common clusters of genes.
http://pbil.univ-lyon1.fr/members/sagot/htdocs/team/software/PSbR/

5.25. Repseek

Participants: Guillaume Achaz [Contact, achaz@abi.snv.jussieu.fr], Eric Coissac, Alain Viari [EPI].

Finding approximate repeats in large DNA sequences.
http://wwwabi.snv.jussieu.fr/~public/RepSeek/

5.26. Sarment

Participant: Laurent Guéguen [EPI, Contact, laurent.gueguen@univ-lyon1.fr].

HMM sequence partitioning and Maximal Predictive Partitioning.
http://pbil.univ-lyon1.fr/software/sarment/

5.27. SeaView

Participant: Manolo Gouy [EPI, Contact, manolo.gouy@univ-lyon1.fr].

Sequence Alignment and Phylogenetic Tree Building.
http://pbil.univ-lyon1.fr/software/seaview.html

5.28. Smile

Participants: Laurent Marsan, Marie-France Sagot [EPI, Contact, marie-france.sagot@inria.fr].

Motif inference algorithm taking as input a set of biological sequences.

5.29. SymBioCyc

Participants: Hubert Charles [EPI], Ludovic Cottret [Contact, Ludovic.Cottret@toulouse.inra.fr], Marie-France Sagot [EPI].

Database of metabolic data dedicated to endosymbiotic organisms.
http://pbil.univ-lyon1.fr/software/symbiocyc

5.30. Tuiuiu

Participants: Alair Pereira do Lago, Pierre Peterlongo [Contact, pierre.peterlongo@inria.fr], Nadia Pisanti, Gustavo Sacomoto [EPI from Feb 2011], Marie-France Sagot [EPI].

Multiple repeat search filter with edit distance.
http://mobyle.genouest.org/cgi-bin/Mobyle/portal.py?form=tuiuiu

5.31. UniPathway

Participants: Eric Coissac, Anne Morgat [EPI, Contact, anne.morgat@inria.fr], Alain Viari [EPI].

Database of manually curated pathways developed with the Swiss-Prot group.
http://www.grenoble.prabi.fr/obiwarehouse/unipathway

6. New Results

6.1. SNP identification from non assembled short sequenced reads

An algorithm for identifying SNPs (Single Nucleotide Polymorphisms) from non assembled short sequence reads was developed in collaboration with P. Peterlongo (INRIA EPI Symbiose) and N. Pisanti (University of Pisa, Italy). The method enables to work with non model species, for which no reference genome is available. The algorithm was applied on data simulated using MetaSim, where it was shown under which sets of parameters the method works best. The method was also applied to real data for *Escherichia coli* for which experimentally validated SNPs are available (Barrick *et al.*, *Nature*, 461:1243-1247, 2009). The method successfully identifies the previously known SNPs and predicts new SNPs missed by the conservative method used in the original publication of Barrick *et al.* See reference [42].

6.2. Buchnera aphidicola genetic network exploration

The genetic network of *Buchnera aphidicola* was explored using bottom-up and top-down systemic analyses. The first approach includes the characterisation of all the putative protein regulators and their binding sites, the identification of all the transcription units, as well as a global analysis of the DNA topological properties of the bacterium. The second approach is dedicated to the inference of genetic networks from a matrix of gene expression data using the 0-1 mutual information as an estimator of the gene correlation in a genetic network. See references [2], [12].

6.3. Elaboration of a combination of measures distinguishes pre-miRNAs from other stem-loops

We proposed a scoring scheme for microRNA precursor candidates which combines four robustness measures. This was used to show that there is a strong bias amongst annotated pre-miRNAs towards robust stem-loops in the genomes of *Drosophila melanogaster* and *Anopheles gambiae*. Additionally, we identified several known pre-miRNA homologs in the newly-sequenced *Anopheles darlingi* and showed that most are found amongst the top-scoring precursor candidates. Furthermore, a comparison of the performance of our approach was made against two single-genome pre-miRNA classification methods. See reference [25] and the software framework CRAVELA (Software section).

6.4. Chemical organisations in metabolic networks

Chemical organisations have been defined as sets of molecules which are closed and self-maintaining (Dittrich and di Fenizio, *Bull. Math. Biol.*, 69(4):1199-1231, 2007). The complexity of enumerating all chemical organisations in a consistent metabolic network was characterised. An algorithm that is theoretically better than previous ones (by the group of P. Dittrich) was also developed to deterministically enumerate all reactive connected chemical organisations. This work was done in collaboration with the INRIA Associated Team SIMBIOSI (A. Marchetti-Spaccamela, L. Stougie), with P. Crescenzi (University of Florence, Italy), and with E. Birmelé (University of Évry, France). See reference [40]. The corresponding software is in development.

6.5. Graph-based analysis of the metabolic exchanges between a host and its endosymbionts

In a collaboration with L. Cottret (INSA Toulouse) and using the algorithm PITUFO developed in the team (see Software), we studied the metabolic exchanges between two co-resident intracellular symbionts (endosymbionts), *Baumannia cicadellinicola* and *Sulcia muelleri*, with their insect host, *Homalodisca coagulata*. The results show the complementarity of the two metabolisms is not only manifested in the metabolic capabilities of each bacterium, but also by their different use of the same environment. The results show also that each intracellular symbiont may be only dependent on the metabolites obtained from the insect, not its co-resident endosymbiont, to produce the carbon backbone of the metabolites provided to the symbiotic system. Indeed, the metabolites *B. cicadellinicola* obtains from *B. S. muelleri* are only exploited by the latter to produce its proteins. See reference [14].

6.6. Development of a web server for the exploration of metabolic networks

In a collaboration with L. Cottret (INSA Toulouse) and F. Jourdan (INRA Toulouse), we participated in the development of METEXPLORE, a web server that offers the possibility to link metabolites identified in untargeted metabolomics experiments within the context of genome-scale reconstructed metabolic networks. The analysis pipeline comprises mapping metabolomics data onto the specific metabolic network of an organism, then applying graph-based methods and advanced visualisation tools to enhance data analysis. METEXPLORE is a greatly enhanced and extended web server in relation to SYMBIOCYC, also developed with L. Cottret. See reference [15] and the web server METEXPLORE in the Software section.

6.7. Metabolic network comparison

The lifestyle of an organism can be considered as the sum of the effects of the environment and of the relations that the organism maintains with other organisms. For intracellular bacteria, both factors are closely linked because the environment is the host cell. Some characteristics, such as network reduction, are common to all intracellular bacteria but others depend on the type of interaction established with the host, i.e. parasitic or mutualistic. Using 48 carefully selected organisms, we tried to establish what links exist between the lifestyle of bacteria, and the composition and organisation of their metabolic networks. We obtained some surprising results that are currently been written and that will be submitted before the end of 2010. This work is done in a collaboration with L. Cottret (INSA Toulouse).

6.8. Pea aphid genome and metabolism annotation

The pea aphid genome sequence was published in *PLoS Biology* and is a major step in enhancing our understanding of insect ecology and evolution with important implications for controlling these significant plant pests. Our group contributed to the genome sequence annotation especially for the insect metabolism. We also developed dedicated databases for storage, visualisation and comparison of metabolic networks that includes insects and their symbiotic bacteria. See reference [22], software CYCADS, and database ACYPICYC in the Software section. The paper on CYCADS is submitted.

6.9. Sinorhizobium meliloti and genomic scale modelling of nodulating species

The work presented here is on-going and is the result of a collaboration that involves the Groups of Prof. Marco Bazzicalupo and Dr. Alessio Mengoni (University of Florence, Dept. of Evolutionary Biology); Emanuele Biondi (Laboratory of Biochemistry and Integrated Structural Biology, Institut de Recherche Interdisciplinaire, Lille), Stefano Mocali (Center for Agronomic Research (CRA), Rome). The genome sequences were obtained in collaboration with the Joint Genome Institute of the Department of Energy (USA). *Sinorhizobium meliloti* is an alpha-proteobacterium able to establish a symbiosis with agriculturally important crops. Its ability to fix atmospheric nitrogen is exploited by the plant to boost growth, and the bacterium is fed with sugars within organs called nodules. The well recognised agricultural/economical importance of this association asks for a detailed knowledge of *Sinorhizobium* physiology in the environment and within its host. Comparative genomics will be used to facilitate genome scale modelling which could help understanding of this bacterium. Once having obtained a workable mathematical model, it could be used to identify genetic changes that optimise the symbiosis in different hosts and/or environments and of novel genes that are important for symbiosis. Moreover, it allows to define the minimum complement of genes that are conserved in all nodulating species, and thus the set of genes to be considered in the genome-scale model.

6.10. Close 3D proximity of evolutionary breakpoints arguing for the notion of spatial synteny

Folding and intermingling of chromosomes has the potential of bringing close to each other loci that are very distant genomically or even on different chromosomes. On the other hand, genomic rearrangements also play a major role in the reorganisation of loci proximities. Whether the same loci are involved in both mechanisms has been studied in the case of somatic rearrangements, but never from an evolutionary standpoint. Surprisingly, we found that frequently interacting loci are enriched in evolutionary breakpoints. More precisely, we found that genes which are detected as frequently interacting in Hi-C experiments in human cells tend to have orthologs in mouse that are close to each other genomically. We show that this result is true even for loci that are over 100Mb away from each other on the human genome. Proximity, whether genomic or spatial, may thus be preserved over very large evolutionary distances. This provides an indirect evidence that spatial proximity has a functional role. This analysis was performed using 3D data available from the literature, and an algorithm for fine breakpoint region detection we developed, CASSIS (see [9] and the Software section). This work is currently submitted to an international journal. It was accepted for a presentation at the conference Integrative Post-Genomics (IPG). See reference [43].

6.11. Bayesian sampling of genomic rearrangement scenarios via Double Cut and Join

A statistical method to sample among genome rearrangement scenarios was developed in collaboration with I. Miklós (Rényi Institute, Budapest, Hungary). It allowed to study the modes of structural evolution of eukaryote genomes, estimating the rates of different rearrangements in several lineages. In particular, the ratio of inversions/translocations is very different in the human and mouse lineages since their divergence. See reference [26] and the software DCJ2HP.

6.12. Reconstruction of ancestral genomes

A survey that examines both models and algorithms and attempts to measure the reliability of several kinds of methods for the mapping of genes in ancestral genomes was done in collaboration with C. Chauve (Simon Fraser University, Vancouver, Canada). An application to yeast was performed by the same in collaboration with H. Gavranovic (University of Sarajevo, Bosnia and Herzegovinia). Finally, the ancestral genome of grasses was reconstructed by E. Tannier in collaboration with J. Salse (INRA Clermont-Ferrand). This used several comparative genomic common principles, as well as new methodologies to account for genome duplication and massive losses of genes. New mechanisms of grass genome evolution were identified. See references [6], [13], [39], [28].

6.13. Detection of lateral gene transfers by statistical reconciliation of phylogenetic forests

The systematic reconstruction of molecular phylogenies based on the diversity of genes found in complete genomes reveals an unforeseen degree of incongruence among phylogenetic trees based on genes. In unicellular organisms, and particularly Bacteria and Archaea, most of the real phylogenetic conflict is likely the result of lateral gene transfer, process in which an organism incorporates genetic material from another. Accurate methods are needed to identify transferred genes and infer their timing of acquisition. We developed one that is based on the search for a maximum statistical agreement forest (MSAF) between a gene tree and a reference tree. See reference [5].

6.14. The location of transposable element in the human genome is dependent on the function of genes

Transposable elements (TEs) are major components of mammalian genomes, and their impact on genome evolution is now well established. In recent years several findings have shown that they are associated with the expression level and function of genes. By analising the relationships between human genes and full-length TE copies in terms of three factors (gene function, expression level, and selective pressure), we classified human genes according to their TE density, and found that TE-free genes are involved in important functions such as development, transcription, and the regulation of transcription, whereas TE-rich genes are involved in functions such as transport and metabolism. This trend is conserved through evolution. See reference [27].

6.15. Mod/Resc Parsimony Inference

We addressed a problem that aims at understanding a mechanism that could potentially be used to genetically manipulate natural insect populations infected by inherited, intra-cellular parasitic bacteria. In this problem, that we denote by Mod/Resc Parsimony Inference, we are given a boolean matrix and the goal is to find two other boolean matrices with a minimum number of columns such that an appropriately defined operation on these matrices gives back the input. We show that this is formally equivalent to the Bipartite Biclique Edge Cover problem and derive some complexity results for our problem using this equivalence. We provide a new, fixed-parameter tractability approach for solving both that slightly improves upon a previously published algorithm for the Bipartite Biclique Edge Cover. This work, together with a continuation that takes into account further characteristics of the biological problem being studied, is being currently used to analyse a classical and much discussed dataset from the literature in collaboration with a biologist from the LBBE. A biological paper is in preparation describing this analysis. See reference [41].

6.16. Bemisia tabaci species complex

Bemici tabaci is becoming a model system for studying communities of vertically-transmitted symbionts. We demonstrated that the symbiotic communities are specific to particular biotypes. This result shows that symbiotic communities are highly stable within biotypes, but highly variable between biotypes. See reference [21]. The next step is to understand the dynamics of the symbiont communities. One way to address this question is to study the genome of these symbionts and look for metabolic complementations among symbionts and mechanisms for interactions. This work will be done in the context of Genoscope program "Metagenomics of bacterial symbionts of *Bemisia tabaci*".

6.17. Polymorphism of the dependence phenotype in the Asobara tabida-Wolbachia association

We established that the evolution of host dependence to bacterial symbionts may involve the evolution of tolerance mechanisms. More precisely, the presence of the symbiont may generate modification in the regulation of oxidative stress, leading the host to adapt the expression of genes related to oxidative stress. See reference [23].

7. Other Grants and Activities

7.1. Regional Initiatives

7.1.1. PuceAphid

- Title: Développement et validation d'une première puce à ADN à oligonucléotides et à haute-densité pour l'analyse du transcriptome du puceron du pois (*Acyrthosiphon pisum*)
- Coordinator: S. Collela (BF2I, INSA Lyon)
- BAMBOO participant(s): H. Charles, Y. Rahbé
- Type: Bonus Qualité Recherche (BQR) INSA (2009-2010)
- Web page: Not available

7.1.2. TransSeq

- Title: Dévelopement d'une architecture Bioinformatique Orientée Service pour l'exploitation de données de transcriptome par séquençage)
- Coordinator: H. Charles
- BAMBOO participant(s): H. Charles
- Type: CATI BIOS (INRA SPE) (2009-2010)
- Web page: Not available

7.2. National Initiatives

7.2.1. ADAPTHANTROPH

- Title: Adaptation des insectes aux anthroposystèmes
- Coordinator: M. Harry
- BAMBOO participant(s): C. Vieira
- Type: ANR Génoplante (2009-2012)
- Web page: Not available

7.2.2. Alcovna

- Title: ALgorithms for COmparing and Visulazing Non Assembled data
- Coordinator: Pierre peterlomgo
- BAMBOO participant(s): V. Lacroix and M.-F. Sagot
- Type: ARC INRIA (2010-2011)
- Web page: http://alcovna.genouest.org/

7.2.3. AphiCible

- Title: Impact de la recombinaison et de la conversion génique biaisée sur l'évolution de génomes
- Coordinator: Y. Rahbé
- BAMBOO participant(s): Y. Rahbé and H. Charles
- Type: ANR Génoplante (2008-2011)
- Web page: Not available

7.2.4. Cogebi

- Title: Symbiosis, digestion and reproduction as aphid physiological processes to identify new targets for insecticides
- Coordinator: L. Duret (LBBE)
- BAMBOO participant(s): C. Gautier, E. Tannier
- Type: ANR Génomique Animale (2008-2011)
- Web page: Not available

7.2.5. EcoGenome

- Title: From a genomic species definition toward an Ecological Species Concept for bacteria
- Coordinator: X. Nesme
- BAMBOO participant(s): L. Guéguen
- Type: ANR Blanc (2009-2011)
- Web page: Not available

7.2.6. ImmunSymbArt

- Title: Immunity and Symbiosis in Arthropods
- Coordinator: D. Bouchon
- BAMBOO participant(s): F. Vavre
- Type: ANR Blanc (2010-2014)
- Web page: Not available

7.2.7. LivingDeep

- Title: Bases génomiques et moléculaires de la piézophilie chez *Pyrococcus yayanosii* CH1, un piézophile obligatoire
- Coordinator: M. Jebbar
- BAMBOO participant(s): L. Guéguen
- Type: ANR Blanc SHS (2010-2013)
- Web page: Not available

7.2.8. NeMo

- Title: Network Motifs
- Coordinator: S. Robin (AgroParisTech, Paris)
- BAMBOO participant(s): V. Lacroix, M.-F. Sagot
- Type: ANR Blanc (2008-2011)
- Web page: http://nemo.ssbgroup.fr/

7.2.9. MIRI

- Title: Mathematical Investigation of "Relations Intimes"
- Coordinator: M.-F. Sagot
- BAMBOO participant(s): V. Acuña, C. Baudet, C. Gautier, V. Lacroix, P. Milreu, C. Klein, I. Nor, M.-F. Sagot, P. Simões

- Type: ANR Blanc (2009-2012)
- Web page: http://pbil.univ-lyon1.fr/members/sagot/htdocs/team/projects/miri/miri.html

7.2.10. Phylariane

- Title: Integrated algorithms and visualisations for analysing the evolution of life dates
- Coordinator: V. Berry (LIRMM, Montpellier)
- BAMBOO participant(s): E. Tannier
- Type: ANR Domaines Émergents (2009-2011)
- Web page: http://www.lirmm.fr/phylariane/index.php

7.2.11. RMAPC

- Title: Reconstruction par modélisation de l'ancêtre des plantes cultivées
- Coordinator: J. Salse (INRA Clermont-Ferrand)
- BAMBOO participant(s): E. Tannier
- Type: INRA (2010-2011)
- Web page: Not available

7.3. European Initiatives

7.3.1. METNET4SysBio

- Title: System level analysis of animal metabolism by multicompartment graph- and constraint-based modelling
- Coordinator: H. Charles (INSA Lyon, France)
- BAMBOO participant(s): V. Acuña, H. Charles, C. Gautier, V. Lacroix, Y. Rahbé, M.-F. Sagot
- European Partner: Angela Douglas, York University, UK
- Type: ANR-BBSRC BioSys (2007-2011)
- Web page: http://www.metnet4sysbio.org/

7.3.2. SysTryp

- Title: Metabolomic systems biology analysis of differentiation in trypanomosomes
- Coordinator: Fabien Jourdan (INRA Toulouse, France)
- BAMBOO participant(s): M.-F. Sagot (did not ask for funds)
- European Partner: Michael P. Barrett, Glasgow Biomedical Research Centre, University of Glasgow, UK
- Type: ANR-BBSRC BioSys (2007-2010)
- Web page: http://www.systryp.org/

7.3.3. SIMBIOSI

- Title: Mathematical and algorithmic investigation of symbiosis
- Coordinators: M.-F. Sagot (France), A. Marchetti-Spaccamela (Italy), L. Stougie (the Netherlands)
- BAMBOO participant(s): Whole BAMBOO Team
- Type: Associated Team INRIA-USP (2005-2008)
- Web page: http://pbil.univ-lyon1.fr/members/sagot/htdocs/team/projects/simbiosi/simbiosi.html

7.3.4. SISYPHE

- Title: Species Identity and SYmbiosis Formally and Experimentally explored
- Coordinator: M.-F. Sagot
- BAMBOO participant(s): Whole BAMBOO team
- Type: ERC Advanced Grant (2010-2015)
- Web page: http://pbil.univ-lyon1.fr/members/sagot/htdocs/team/projects/sisyphe/sisyphe.html

7.4. Exterior research visitors

- Visits in the context of the INRIA Associated Team SIMBIOSI: all details may be found on the web page of the team, with meetings indicated at the url http://pbil.univ-lyon1.fr/members/sagot/htdocs/team/projects/simbiosi/meetings.html.
- Prof. Rolf Backofen, University of Freiburg, Germany, http://www.bioinf.uni-freiburg.de/~backofen/ , 4 days
- Prof. Mike Charleston, University of Sidney, Australia, http://www.it.usyd.edu.au/~mcharles/, 2 weeks
- Prof. Pierluigi Crescenzi, University of Florence, Italy, http://piluc.algoritmica.org/, repeated visits of 1-2 weeks
- Prof. Zanoni Dias, University of Campinas, Brazil, http://www.ic.unicamp.br/~zanoni/, 4 weeks
- Dr. Paulo Gustavo Soares da Fonseca, INESC-ID, IST, Lisbon, Portugal, 1 week
- Prof. Ana Teresa Freitas, INESC-ID, IST, Lisbon, Portugal, http://kdbio.inesc-id.pt/~atf/, 1 week
- Prof. Roberto Grossi, University of Pisa, Italy, http://www.di.unipi.it/~grossi/, three days
- Ass. Prof. Nadia Pisanti, University of Pisa, Italy, http://www.di.unipi.it/~pisanti/, repeated visits of a few days
- Dr. Ana Tereza Vasconcelos, Lab. Nacional de Computação Científica, Petrópolis, Brazil, http://www.lncc.br/~atrv/, 1 month early in 2010, and then 1 year starting from Sept. 2010

8. Dissemination

8.1. Organisational activities

Manolo Gouy was co-chair and co-organiser of the Annual Meeting of the Society for Molecular Biology and Evolution (SMBE) at Lyon, France, July 4-8, 2010 (http://smbe2010.univ-lyon1.fr/en).

Vincent Lacroix co-organised one of the Symposia - on "Evolution of molecular networks" - at SMBE at Lyon, July 4-8, 2010.

Marie-France Sagot was co-chair of JOBIM, the French National Conference on Bioinformatics, at Montpellier, France, September 7-9 (http://www.jobim2010.fr/). She co-organised one of the Symposia - on "Evolution of molecular networks" - at SMBE at Lyon, July 4-8, 2010.

Eric Tannier was program chair for the RECOMB Satellite Workshop on Comparative Genomics at the University of Ottawa, Canada, October 9-11, 2010 (http://recombcg.uottawa.ca/recombcg2010/).

8.2. Editorial activities

Manolo Gouy is Associate Editor of *Molecular Biology and Evolution*.

Marie-France Sagot is Editor-in-Chief of *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, and Associate Editor of *BMC Bioinformatics*, *Algorithms for Molecular Biology*, *Journal of Discrete Algorithms*, and *Lecture Notes in BioInformatics*. She is member of the Steering Committee for the European Conference on Computational Biology (ECCB), for the International Symposium on Bioinformatics Research and Applications (ISBRA), and since 2010, for the Latin American Theoretical Informatics Symposium (LATIN). She was member of the Program Committee for APBC, CPM, ECCB, ISMB, PSC, RECOMB.

Eric Tannier was Editor of the *Proceedings of the RECOMB Satellite Workshop on Comparative Genomics* that took place at the University of Ottawa, Canada, October 9-11, 2010.

8.3. Other administrative activities

Christian Gautier is Director of the PRABI. He is member of the "Conseil d'administration" of the University of Lyon 1, and of the selecting committee for biology at the École Polytechnique, Paris. He is deputy director of the IFR 41 "Bio-environnement et santé" of the University of Lyon 1.

Manolo Gouy was until this year member of the CNU Section 67 (Evolution). He is member of the selection committee of the CNRS ATIP Biodiversity, and of the Scientific Advisory Board of the Swiss Institute of Bioinformatics.

Marie-France Sagot was until this year member of the "Comité National" Section 01 (Maths) and of the "Commission Interdisciplinaire" 43 (Modelling and Bioinformatics). She participated in the reviewing process of applications to the Wellcome Trust PhD programme in the UK and in the selection of candidates for an Associate Professor position at the University Ludwig-Maximilians, Munich, Germany.

Fabrice Vavre is director of the GDR 2153(CNRS) "Interactions multipartenaires dans les populations et les communautés d'insectes". He is also member of the management committee and responsible of a working group in the COST Action FA0701 "Arthropod Symbiosis: from fundamental studies to pest and disease management".

Alain Viari is a member of the "Commission de spécialistes" Section 65 at the University of Paris 6 and of the scientific advisory board of the MIA (Mathematics and Applied Mathematics) at the INRA. Since February 2007, he is the scientific delegate of the INRIA Grenoble Rhône-Alpes Research Center.

Cristina Vieira est responsable du GDRE "Comparative genomics" since the GDRE was renewed in 2010.

8.4. Seminars, talks and posters

Vicente Acuña

- Seminar AGCO, Aug. 18, Departamento Ingeniería Matemática, Universidad de Chile. "On the computational complexity of enumerating all the solutions of some biological problems in metabolic networks".
- Seminar Computational Biology Lab, Aug. 19, CMM Universidad de Chile. "On the computational complexity of enumerating all the solutions of some biological problems in metabolic networks".
- Talk at Workshop in Bioinformatics and Algorithms, http://www.ime.usp.br/~yw/workshop/biocomp.html, Jul. 28, USP, São Paulo, Brazil. "On the computational complexity of enumerating all the solutions of some biological problems in metabolic networks".

Christian Baudet

- Talk at Workshop in Bioinformatics and Algorithms, http://www.ime.usp.br/~yw/workshop/biocomp.html, Jul. 28, USP, São Paulo, Brazil. "Enumerating traces of solutions of the problem of sorting by signed reversals".

Hubert Charles

- Talk at the Séminaire Rhônalpin de Modélisation du Vivant (SEMOVI) http://www.cgmc.univ-lyon1.fr/Semovi/, Jun. 9, 2010, Lyon, France. "Exploring the regulatory network of *Buchnera aphidicola*: a case-study of genome evolution in a symbiotic context".

Paulo Vieira Milreu

- Talk at Workshop in Bioinformatics and Algorithms, http://www.ime.usp.br/~yw/workshop/biocomp.html, Jul. 28, USP, São Paulo, Brazil. "Enumerating Chemical Organisations in Consistent Networks".

Marie-France Sagot

- Talk at Workshop in Bioinformatics and Algorithms, http://www.ime.usp.br/~yw/workshop/biocomp.html, Jul. 28, USP, São Paulo, Brazil. "Introducing BAMBOO-BAOBAB, SIMBIOSI, and SISYPHE".
- Talk at the "Arthropod Symbiont Genomics and Metagenomics" Meeting of the EU COST Action FA0701 "Arthropod Symbioses: from fundamental studies to pest and disease management", Jan. 20-23, Funchal, Madeira, Portugal. "Computational exploration of the metabolic exchanges in symbiotic systems".

Fabrice Vavre

- Talk at the "Arthropod Symbiont Genomics and Metagenomics" Meeting of the EU COST Action FA0701 "Arthropod Symbioses: from fundamental studies to pest and disease management", Jan. 20-23, Funchal, Madeira, Portugal. "Are there common host functions involved in insect symbioses? A comparative transcriptomic approach".
- Talk at the "6th International Wolbachia Conference", Jun. 9-14, Asilomar, California, USA. "Host-Wolbachia interactions: beyond reproductive manipulation".
- Talk at the "Arthropod Symbiont Genomics and Metagenomics" Meeting of the EU COST Action FA0701 "Arthropod Symbioses: from fundamental studies to pest and disease management", Jun. 30-Jul. 3, BadBenvensen, Germany. "Evolution of multiple infection with vertically transmitted symbionts".
- Talk at the "Beneficial Microbes" Conference, Oct. 25-29, Miami, Florida, USA. "Repeated interactions and the evolution of dependence."

Cristina Vieira

- Talk at the NATO Advanced Research Workshop, Radiobiological issues pertaining to environmental security and ecoterrorism, Alushta, Ukraine, Oct. 9-13 2010, "Transposable elements and genomes evolution".

Oral communications (plus poster in some cases) of work involving EPI members

- Charles H., Brinza L., Calevro F. Chromosome organization and gene expression regulation in *Buchnera aphidicola*, the obligate intracellular bacteria of the pea aphid *Acyrthosiphon pisum*. 2010 ESA Annual Meeting, San Diego (California, USA), Dec. 2010.
- Gallot A., Guernec G., Colella S., Charles H., Jaubert-Possamai S., Tagu D. Genes regulated in early embryogenesis during the switch from parthenogenetic to sexual reproduction in the pea aphid (*Acyrthosiphon pisum*). 4th Annual Arthropod Genomics Symposium "Arthropod Genomics: New Approaches and Outcomes", Kansas City (USA), Jun. 2010.
- Mendes N., Freitas A.T., Vasconcelos A.T., Sagot M.-F. CRAVELA: a framework to identify and evaluate miRNA regulatory modules. RECOMB 2010 - Lisbon, Portugal - Aug. 2010.

- Palmeira L., Penel S., Lotteau V., Rabourdin-Combe C. and Gautier C. PhEVER: a database for the global exploration of virus-host evolutionary relationships. Belgian Society for Microbiology - Annual Symposium 2010, Brussels, Belgium, Nov. 2010.
- Parisot N., Gaget K., Colella S., Rabatel A., Calevro F., Duport G., Febvay G., Gabaldon T., Charles H., Rahbé Y., 2010. Annotation et évolution des familles de transporteurs chez le puceron du pois (*Acyrthosiphon pisum*). Réseau Français de Biologie Adaptative des Pucerons, Lyon (France), Oct. 2010.
- Rabatel A., Febvay G., Gaget K., Duport G., Rahbé Y., Charles H., Calevro F., Colella S., 2010. Caractérisation transcriptomique du développement embryonnaire et larvaire du puceron du pois *Acyrthosiphon pisum*. 16ème Colloque de Biologie de l'Insecte - CBI-2010, Lyon (France), Oct. 2010.
- Sapountzis P., Duport G., Gaget K., Balmand S., Febvay G., Jaubert-Possamai S., Charles H., RahbÂ Y., Colella S., Calevro F., 2010. Individual and compartment specific response to RNAi in aphids: each individual matters. Réseau Français de Biologie Adaptative des Pucerons, Lyon (France), Oct. 2010.
- Vellozo A.F., Baa-Puyoulet P., Huerta-Cepas J., Febvay G., Calevro F., Rahbé Y., Gabaldon T., Sagot M-.F., Charles H., Colella S., 2010. Using the "CycADS" annotation management system to develop a BioCyc metabolic network database for sequenced arthropods genomes: first steps towards "ArthropodsCyc". 4th Annual Arthropod Genomics Symposium ÒArthropod Genomics: New Approaches and OutcomesÓ, Kansas City (USA), Jun. 2010.

Posters involving various EPI members

- Brinza L., Calevro F., Duport G., Rahbé Y., Da Silva P., Gauthier J.P., Charles H. Evolution of the regulatory network in *Buchnera aphidicola*, the obligate intracellular symbiotic bacteria of aphids. Annual Meeting of the Society for Molecular Biology and Evolution (SMBE 2010), Lyon (France), Jul. 2010.
- Baudet C. Partial enumeration of traces of solutions for the problem of sorting by signed reversals. RECOMB 2010 - Lisbon, Portugal - Aug. 2010.
- Cottret L., Wildridge D., Vinson F., Barrett M.P., Sagot M.-F., Charles H., Jourdan F. MetExplore: a web server to link metabolomic experiments and genome-scale metabolic networks. Journées Ouvertes Biologie Informatique MathÂmatiques (JOBIM), Montpellier (France), Sept. 2010.
- Guéguen L., Dutheil J., Gaillard S., Boussau B., Dugas G., Belkhir K. The BIO ++ Libraries V 2.0: Object-oriented libraries for sequence analysis, population genetics, phylogenetics and molecular evolution. SMBE, Lyon, Jul. 2010.
- Lassalle F., Muller D., Costechareyre D., Chapulliot D., Lavire C., Campillo T., Baude J., Ortega E., Oger C., Hommais F., GuÂguen L., Daubin D., Nesme X. Identification of species specific functions involved in the ecological speciation of *Agrobaterium tumefaciens* genomovar G8. SMBE, Lyon, Jul. 2010.
- Legeai F., Colella S., Huerta-Cepas J., Gauthier J.P., Vellozo A., Baa-Puyoulet P., Sagot M.-F., Gabaldon T., Collin O., Charles H., Tagu D. A tale of genome, annotations, metabolism and phylogenomics: the pea aphid genome resources. 10th Cold Spring Harbor Laboratory / Wellcome Trust conference "Genome Informatics", Hinxton (UK), Sept. 2010.
- Palmeira L., Penel S., Lotteau V., Gautier C. and Rabourdin-Combe C. PhEVER: a database for the global exploration of virus-host evolutionary relationships. RECOMB 2010 - Lisbon, Portugal - Aug. 2010.
- Parisot N., Gaget K., Colella S., Rabatel A., Calevro F., Duport G., Febvay G., Gabaldon T., Charles H., Rahbé Y. Analyse génomique de la fonction de transport dans le système symbiotique du puceron du pois *Acyrthosiphon pisum*. 16Âme Colloque de Biologie de lÕInsecte - CBI-2010, Lyon (France), Oct. 2010.

- Rabatel A., Febvay G., Gaget K., Duport G., Rahbé Y., Charles H., Calevro F., Colella S. Transcriptome analysis of embryo development in a parthenogenetic and symbiotic insect model, the pea aphid. Integrative Post-Genomics - IPG'10, Lyon (France), Nov. 2010.
- Rabatel A., Febvay G., Masselot P., Gaget K., Duport G., RahbÂ Y., Charles H., Calevro F., Colella S. Characterization of parthenogenetic embryo development in the context of symbiosis using transcriptome analysis in the pea aphid model. EMBO Workshop "Systems Biology of Development", Ascona (Suisse), Aug. 2010.
- Sapountzis P., Duport G., Gaget K., Balmand S., Jaubert-Possamai S., Febvay G., Charles H., Rahbé Y., Colella S., Calevro F. Réponse tissu-spécifique au traitement par RNAi chez le puceron du pois : une étude cinétique à l'échelle de l'individu. 16ème Colloque de Biologie de l'Insecte - CBI-2010, Lyon (France), Oct. 2010.
- Sapountzis P., Duport G., Gaget K., Horn T., Boutros M., Febvay G., Jaubert-Possamai S., Charles H., Rahbé Y., Colella S., Calevro F. Single insect and tissue compartment specific response to RNAi microinjection in aphids: each individual matters. 4th Annual Arthropod Genomics Symposium "Arthropod Genomics: New Approaches and Outcomes", Kansas City (USA), Jun. 2010.

8.5. Participation to PhD committees

Manolo Gouy was member of the following PhD and HDR committees:

- Des séquences moléculaire à l'arbre de la vie: résultats théoriques, algorithmiques et outils pour la phylogénomique, Vincent Ranwez, HDR, reviewer, Université Montpellier II, Dec. 6, 2010
- Sur deux problèmes mathématiques de reconstruction phylogénétique, Mikael Falconnet, PhD, reviewer, Université Joseph Fourier (Grenoble), Jul. 9, 2010
- Intérêt des transferts horizontaux de gènes pour comprendre l'histoire évolutive des procaryotes, Sophie Abby, PhD, co-supervisor with Vincent Daubin, Université Lyon 1, Jun. 11, 2010

Yvan Rahbé was member of the following PhD committees:

- Rôle des modifications post-traductionnelles des particules virales du CABYV dans la transmission par puceron, Sébastien Revollon, PhD, examiner, ULP Strasbourg, Feb. 23, 2010
- Évolution comparée des génomes d'insectes ; évolution des familles multigéniques et adaptation chez les pucerons, Morganne Ollivier, PhD, examiner, Agrocampus Rennes, Oct. 6, 2010
- Comportement de *Scaphoideus titanus*, conséquences spatiales et démographique, Julien Chuche PhD, reviewer, UVS Bordeaux, Dec. 12, 2010

Marie-France Sagot was member of the following PhD committee:

- Algorithmes de comparaison de génomes appliqués aux génomes bactériens, Raluca Uricaru, PhD, reviewer, Université Montpellier II, Dec. 14, 2010

Eric Tannier was member of the following PhD committees:

- Méthodes combinatoires de reconstruction de réseaux phylogénétiques, Philippe Gambette, PhD, examiner, Université Montpellier 2, Nov. 30, 2010.
- Ancestral genome reconstruction in vertebrates, Matthieu Muffato, PhD, examiner, ENS Paris, Dec. 15th, 2010.

Cristina Vieira was member of the following PhD and HDR committees:

- Assemblage de la chromatine et formation du zygote chez la drosophile, Benjamin Loppin, HDR, examiner, Université de Lyon, Jun. 11, 2010.
- Les effets de l'(a)sexualité sur la dynamique des éléments transposables, Thibault Boutin, PhD, reviewer, Université d'Orsay, Sept.15, 2010.

- Étude comparative des rétrotransposons DIRS1 dans les génomes de crustacés décapodes et autres eucaryotes, Mathieu Piednoël, PhD, examiner, Paris 6, Nov. 25, 2010.
- Dynamique des éléments transposables, Eric Bonnivard, HDR, reviewer, Paris 6, Nov. 9, 2010.
- Dynamique évolutive et impact génomique des éléments transposables, Richard Cordaux, HDR, reviewer, Université de Poitiers, Dec. 1st, 2010.
- Organisation et expression de la région responsable de la distortion de la ségrégation méiotique sex-ratio chez *Drosophila simulans*, Lucy Fouvry, PhD, reviewer, Université d'Orsay, Dec. 14, 2010.

8.6. Teaching

General comments
Five members of the BAMBOO project are professors or associate professors at the University Claude Bernard in Lyon and at the INSA Lyon: Hubert Charles, Christian Gautier, Laurent Guéguen, Vincent Lacroix, Cristina Vieira. They therefore have a full teaching service (at least 192 hours) except for Cristina Vieira who became since this year a Junior Member of the Institut Universitaire de France.

Various members of the EPI have developed over the years courses in biometry, bioinformatics and evolutionary biology at all levels of the University as well as at the "École Normale Supérieure" (ENS) of Lyon and the INSA ("Institut National de Sciences Appliquées"). Two members of the EPI have also in the past participated in, or sometimes organised courses or teaching modules at the international level: creation and support of a Master's course in Ho-Chi-Minh, Vietnam, and creation and direction of a PhD Program in Computational Biology in Lisbon, Portugal (http://bc.igc.gulbenkian.pt/pdbc/). Besides the full time professors in BAMBOO, the following non professor members have contributed with lectures during the year. These are described below.

Manolo Gouy

- University Lyon 1 and INSA, M2, 10 h of lectures about methods for molecular phylogeny
- École Normale Supérieure de Lyon, L3, 6 h of lectures about molecular phylogeny
- École Normale Supérieure de Lyon, M1, 3 h of lectures about comparative genomics
- Pôle Rhône-Alpin de Bio-Informatique, Formation continue, 3-day session of introduction to molecular phylogeny taught together with Vincent Daubin and Gabriel Marais

Yvan Rahbé

- INSA, M2, 8h of lectures on "Insects, organisation principles, biodiversity and ecosystemic functions, interactions with human societies, pest control and long-term development".

Eric Tannier

- Université Populaire de Lyon, 8h of lectures on genetics and genomics
- INSA Lyon, M1 Bioinformatics and Modelling cursus, 16h of lectures on math and computer science for genomics
- INSA Lyon, M1 Bioinformatics and Modelling cursus, 8h of lectures on discrete maths

9. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] V. ACUÑA. *Models and algorithms for metabolic networks: elementary modes and precursor sets*, Université Lyon 1, 2010, Supervisors: M.-F. Sagot and C. Gautier.

[2] L. BRINZA. *Exploration et inférence du réseau de régulation de la transcription de la bactérie symbiotique intracellulaire à génome réduit Buchnera aphidicola*, INSA Lyon, 2010, Supervisors: H. Charles and C. Gautier.

[3] Y.-P. DENIÉLOU. *Alignement multiple de données génomiques et post-génomiques : approches algorithmiques*, Université Joseph Fourier, 2010, Supervisors: A. Viari and M.-F. Sagot.

[4] E. PRESTAT. *Les réseaux bayésiens : classification et recherche de réseaux locaux en cancérologie*, Université Lyon 1, 2010, Supervisor: C. Gautier, President of Committee: M.-F. Sagot.

Articles in International Peer-Reviewed Journal

[5] S. ABBY, E. TANNIER, M. GOUY, V. DAUBIN. *Detecting lateral gene transfers by statistical reconciliation of phylogenetic forests*, in "BMC Bioinformatics", 2010, vol. 11, n^{o} 324, p. 1-13.

[6] M. ABROUK, F. MURAT, C. PONT, J. MESSING, S. JACKSON, T. FARAUT, E. TANNIER, C. PLOMION, R. COOKE, C. FEUILLET, J. SALSE. *Palaeogenomics of plants: syntenybased modelling of extinct ancestors*, in "Trends in Plant Science", 2010, vol. 15, n^{o} 9, p. 479-487.

[7] S. ADI, M. BRAGA, C. FERNANDES, C. FERREIRA, F. MARTINEZ, M.-F. SAGOT, M. STEFANES, C. TJANDRAATMADJA, Y. WAKABAYASHI. *Repetition-free longest common subsequence*, in "Discrete Applied Mathematics", 2010, vol. 158, n^{o} 12, p. 1315-1324.

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[9] C. BAUDET, C. LEMAITRE, Z. DIAS, C. GAUTIER, E. TANNIER, M.-F. SAGOT. *Cassis: detection of genomic rearrangement breakpoints*, in "Bioinformatics", 2010, vol. 26, n^{o} 15, p. 1897-1898.

[10] M. BONDI, G. BACCI, M. BRILLI, M. PAPALEO, A. MENGONI, M. VANEECHOUTTE, L. DIJKSHOORN, R. FANI. *Exploring the evolutionary dynamics of plasmids: the Acinetobacter pan-plasmidome*, in "BMC Evolutionary Biology", 2010, vol. 10, 59.

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[13] C. CHAUVE, H. GAVRANOVIC, A. OUANGRAOUA, E. TANNIER. *Yeast Ancestral Genome Reconstructions: The Possibilities of Computational Methods II*, in "Journal of Computational Biology", 2010, vol. 17, n^{o} 9, p. 1097-1112.

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[15] L. COTTRET, D. WILDRIDGE, F. VINSON, M. BARRETT, H. CHARLES, M.-F. SAGOT, F. JOURDAN. *MetExplore: a web server to link metabolomic experiments and genome-scale metabolic networks*, in "Nucleic Acids Research", 2010, vol. 38, p. 132-137.

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[36] E. TANNIER. *Le génome aux ordres des mathématiciens*, in "La Recherche", 2010, vol. 439, p. 54-56.

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