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Presentation of the funded projects in 2009 for the « ERA-Net ERASysBio+ » Programme

ACRONYME et titre du projet	Page
BioModUE_PTL Biophysical Modelling of the Uterine Electromyogram for understanding and preventing PreTerm Labor	2
C5Sys Circadian and cell cycle clock systems in cancer	3
FRIM FRuit Integrative Modelling	4
GRAPPLE Iterative modelling of gene regulatory interactions underlying stress, disease and ageing in *C. elegans*	5
iSAM Integrative Systems Analysis of the Shoot Apical Meristem	7
ModHeart Modelling the genetic network controlling heart development using the model organism Drosophila melanogaster	8
SHIPREC Living with uninvited guests comparing plant and animal responses to endocytic invasions	9
TB-HOST-NET Integration of computational modelling with transcription and gene essentiality profiling of both MTB bacillus and infected human dendritic cells and macrophages to understand molecular interaction networks involved in the host-pathogen cross-talk	11
Zebrain Understanding decision-making from the dynamics of large neural populations in behaving zebrafish	12

« ERA-Net ERASysBio+» programme

YEAR 2009

Project title	**BioMod UE_PTL**– Biophysical Modelling of the Uterine Electromygram for understanding and preventing Pre term Labor

Abstract

The aim of the BioMod UE_PTL project is to better understand the links existing between the microscopic phenomenon involved in uterine contractility leading to labour and the macroscopic electrical activity observed on the abdomen of pregnant women, the electrohysterogram (EHG). The ultimate goal is to provide the knowledge to create a clinical tool that can detect the presence of pathological uterine contractility leading to preterm labour.

The uterus is a very complex and dynamic system, which is controlled by hormonal environment as well as by electric and mechanical feedbacks. Many open questions remain regarding the actual mechanisms leading to onset of labour. The only way to address these questions is through multiscale modeling starting at the biological phenomenon involved in individual uterine cell contractility, leading to the generation of EHG on the abdomen. The model will work as a tool to increase our understanding of the uterine contractile system, to validate or invalidate previously raised hypothesis, and finally to permit the development of tools specific for the prediction of preterm labour. It will integrate the generation of contractile activity at the cell level, communication in bundles of cells, and propagation to the whole organ and to the abdomen, through the complex conduction volume.

The data, acquired from animal and human experiments, will be used to create a model of the behaviour of the uterus.

The results obtained from the models will then be used to guide experimentation and to model the effects of pharmacological agents on the uterus. Apart from disseminating results in the classical manner for scientific and technical research, a separate aim of the project is to develop means to share data and results, both between the partners and with the larger scientific community. As far as we know, there are no data standards for smooth muscle EMG and EHG digital recordings and preterm delivery models. These standards will be developed and set as best practice by the project consortium.

Partners	CEA/INSERM MIRCen (FR) Technological University Eindhoven (NL) Máxima Medical Centre (NL) University of Ljubljana (SI) Reykjavik University (IS) TMS International (NL)
Coordinator	Catherine Marque – Université de Technologie de Compiègne (FR)
ANR funding	357 k€ (partenaires français)
Starting date and duration	Juin 2010 - 36 mois
Reference	ANR-09-SYSB-001
Cluster label	

Project title	**C5Sys** – Circadian and cell cycle clock systems in cancer
Abstract	Mammalian cells are endowed with biological oscillators which time their activities. The circadian clock (circa, about; dies, day) generates a 24-hour rhythm which controls both cellular metabolism and cell division. The cell division cycle is an oscillator which times DNA synthesis, mitosis, and related apoptosis and DNA repair. Our understanding of the molecular mechanisms at work in both oscillators has greatly improved. In sharp contrast, little is known about how these two crucial oscillators interact, and how these interactions affect cellular proliferation in normal or cancer cells. On the one hand, the disruption of circadian clocks impairs cell physiology and quality of life. On the other hand, disruption of cell cycle, DNA repair or apoptosis impacts on cell and organism survival. Experimental and clinical data show that circadian disruption accelerates malignant proliferation, and that DNA damage can reset the circadian clock. The central question addressed is how interactions between the circadian clock and cell cycle affect cellular proliferation and genotoxic sensitivity in normal and cancer cells, and how this knowledge translates into new prevention or therapeutic applications. Seven teams in France, Netherlands and United Kingdom integrate experimental, mathematical and bioinformatic approaches, so as to develop novel cell lines, biomarker monitoring methods and mathematical tools. C5Sys triggers innovative chronotherapeutic research for human cancers and advances systems medicine for improving patient care.

Partners	Erasmus University Medical Center (ERM) (NL) University College London (UK) University of Nice, CNRS (NL) University Paris Sud 11, CNRS (FR) INRIA (FR) Warwick Systems Biology (WSB) (FR)
Coordinator	Francis Levi – INSERM and University Paris Sud 11 (FR)
ANR funding	788 k€ (partenaires français)
Starting date and duration	Juin 2010 - 36 mois
Reference	ANR-09-SYSB-002
Cluster label	

Project title	**FRIM** – Fruit Integrative Modelling
Abstract	Commercial fruit production is under significant pressure from environmental stresses, but also by changes in the consumer's demand for taste and nutritional value. One key goal of fruit biology is therefore to understand the factors that influence metabolite levels. Both genetic and environmental factors have a strong and multifaceted influence on fruit quality. They act and interact in such a complex way that it is extremely difficult to study their effects experimentally. To circumvent such difficulty, we will build a virtual tomato fruit that enables the prediction of metabolite levels given genetic and environmental inputs, by an iterative process between laboratories which combine expertise in fruit biology, ecophysiology, theoretical and experimental biochemistry, and biotechnology. There are three major aims: (1) To build a kinetic model encompassing the routes carbon takes, once imported into the fruit cells from the source organs of the mother plant. The model will include subcellular compartmentation. To parameterize the model, data for enzyme and transporter properties and metabolite levels will be measured in fruits harvested at different developmental stages and grown under contrasted environments. (2) To integrate the kinetic model with a phenomenological model predicting sugar and organic acid contents as functions of time, light intensity, temperature and water availability. Sub-models describing carbon and water transfer within the plant, fruit growth, sugar and organic acid accumulation will be implemented and integrated with the kinetic model. This

	"multi-scale" integration will then be used to run virtual experiments. (3) To obtain large-scale experimental measures of the consequences of altered environmental conditions. Such studies will allow validation and iterative optimization of the model. As a first application of the combined model, environmental scenarios leading to metabolic phenotypes will be searched in silico for existing transgenic plants with altered enzyme activities, and validated.
Partners	Bordeaux University (FR) INRA-Avignon (FR) Oxford University (UK) Oxford Brookes University (UK) MPIMP-Golm (DE) Stellenbosch University (ZA)
Coordinator	Yves Gibon– INRA-Bordeaux (FR)
ANR funding	385 k€ (partenaires français)
Starting date and duration	Mai 2010 - 36 mois
Reference	ANR-09-SYSB-003
Cluster label	

Project title	**GRAPPLE** – Iterative modeling of gene regulatory interactions underlying stress, disease and ageing in *C. elegans*
Abstract	The genetic predispositions of many complex human diseases, stress responses and ageing are proving difficult to uncover due to involvement of many different genes and because these gene groups interact with the environment. Our approach to resolving this problem is to identify gene networks by mapping the properties of genetic stress-responses onto graphical representations of the underlying network. This approach will be powered by taking advantage of natural genetic variation among individuals in respect of disease susceptibility and ageing. Compared to other network approaches, this focuses attention more specifically on functionally important gene-gene interactions and the gene regulatory networks. For this we shall take advantage of a powerful model genetic system presented by the nematode worm, Caenorhabditis elegans. Approximately 200 genetic mosaic lines have been created by crossing genetically-divergent parental strains. These present a wide spectrum of

responses to stress exposure, disease susceptibility and longevity. The gene regulatory properties of each line will be determined in response to stress treatment using DNA microarrays, thereby providing a detailed response profile for all lines across the 17,000 known genes. Detailed genetic mapping of these gene expression traits allows the identification of the regulatory genetic locus and ultimately the gene regulating the trait and associated genes. The gene regulatory interactions that affect the relevant biomedical phenotypes will be mapped onto existing depictions of gene interactions. New network models will be developed which will suggest an additional set of gene perturbation tests, the outcome of which will further refine the network model. This iterative loop of directed gene perturbation experiments, network refinement and model prediction is a key means of leveraging our understanding of such complex systems. This functional, genetic approach contrasts with previous protein-protein interaction or gene co-expression interaction maps used to date. In particular, we seek to identify large-scale connectivity patterns between genes that re-occur at multiple sites across the network.

Partners	EMBL/CRG Barcelona (ES) Wageningen University (NL) Oxford University (UK) MRC Laboratory Cambridge (UK) Universite Paris Sud (FR)
Coordinator	Andrew R. Cossins– University of Liverpool (UK)
ANR funding	130 k€ (partenaires français)
Starting date and duration	Juin 2010 - 36 mois
Reference	ANR-09-SYSB-004
Cluster label	

Project title	**iSAM** – Integrative Systems Analysis of the Shoot Apical Meristem
Abstract	The aim of the project iSAM is to understand how complex structures and patterns are produced at the growing tip of the plant shoot using combined modelling and experimentation. The shoot tip contains the shoot apical meristem (SAM), a population of dividing, undifferentiated cells that generates leaves and other organs in highly ordered patterns at shoot tips throughout the life of the plant. The SAM therefore has two functions. First it houses at its centre a stem cell population that is stable throughout the life cycle of the plant, which may be hundreds of years in the case of long-lived trees. It also initiates organs, and, since plant growth arises from the repeated production of new organs as the plant grows, the SAM is responsible for specifying all aboveground plant tissues. It therefore determines plant architecture and, indirectly, many aspects of agricultural productivity. The SAM has been extensively studied and we know many of its molecular and cellular components, but we do not understand how these components assemble into the multicellular structure with specific shape and growth dynamics. It is these questions this project will address using an iterative process of analysis, model building, biological testing and refinement. The individual cells within the SAM interact by exchanging signals and the interaction network that feeds back on the 'machineries' of individual cells, controlling local growth through the modulation of division rates. Added up, the local cell proliferation rates, patterned by the signalling networks, lead to specific shape changes. To understand the SAM, we will use a complex systems modelling approach, focusing on the interaction networks provided by the key plant hormones auxin and cytokinin. This proposal links four leading research teams in UK, France and Finland, bringing synergistic expertise and technologies in imaging, modelling, plant hormones and cell cycle to address this important systems problem
Partners	ENS Lyon (FR) INRIA Montpellier (FR) University of Helsinki (FI)
Coordinator	James A.H. Murray - Cardiff University (UK)
ANR funding	456 k€ (partenaires français)
Starting date	Avril 2010 - 36 mois

and duration	
Reference	ANR-09-SYSB-006
Cluster label	

Project title	**ModHeart** – Modelling the genetic network controlling heart development using the model organism *Drosophila melanogaster*
Abstract	Developmental geneticists have unraveled the transcription factors and signaling pathways that control the formation of the cardiovascular system. These investigations have demonstrated a clear conservation of genetic control, from Drosophila to mammals. However, what these pathways control in terms of downstream gene networks and how they dynamically interact to control the diversification and the differentiation of cardiomyocytes remains largely unknown. A detailed understanding of these processes will provide essential insights into both normal and pathological heart development. Drosophila is an excellent model system to study gene regulatory networks involved in cardiac organogenesis: in addition to the wealth of genetic and genomic tools available, this 'simple' genetic model organism possesses a fluid pumping heart. Our objectives are to generate and integrate genome-wide qualitative and quantitative data to dissect the Gene Regulatory Network that dynamically controls the diversification and progressive differentiation of the cardiovascular system in Drosophila. More precisely, we will: • Generate large scale data sets by ChIP-seq and transcriptomics to describe the direct transcriptional target genes and their enhancers (cis-regulatory control elements). • Use computational tools to integrate and analyse the newly generated datasets with pre-existing public data (coming from large scale transcriptome, proteome, and interactome screens, as well as low-throughput data documented in scientific articles and public databases). • Establish predictive, qualitative and quantitative dynamical models of the regulatory network controlling cardioblast cell specification and differentiation. • Exploit the genetic tools (reporter gene essays, in situ hybridization, targeted overexpression mediated gain of function, dsRNA mediated gene function knockdown...) available in Drosophila to validate and refine theses models. • Use computational tools to evaluate the conservation of the underlying regulatory circuits from insects to mammals. Overall, this project will contribute to building a systems-level view of Drosophila heart development and will benefit from

	the balanced expertise of its members.
Partners	TAGC (FR) GReD - UMR6247 (FR) EMBL Heidelberg (DE) EMBL/CRG Barcelona (ES)
Coordinator	Laurent Perrin - Developmental Biology Institute of Marseille-Luminy (FR)
ANR funding	536 k€ (partenaire français)
Starting date and duration	Avril 2010 - 36 mois
Reference	ANR-09-SYSB-008
Cluster label	

Project title	**SHIPREC** – Living with uninvited guests - comparing plant and animal responses to endocytic invasions
Abstract	Salmonella are Gram-negative bacterial facultative endopathogens capable of infecting an unusually wide range of organisms and the causative agent of various human diseases, from enteritis to typhoid fever. Salmonellosis is the most frequent food-borne disease with ~ 1,5 billion infections world-wide yearly and has been linked to contamination of vegetables and fruits. Salmonella communicate with their hosts at every stage of their life cycles. However, unlike for other pathogens, such as HIV-1, for which more than 2500 interactions with its human host have been reported, taking a system-wide view for Salmonella is in its infancy but is critical to fully grasp the mechanisms of host-pathogen responses. In this project, we address the basic biological question how divergent hosts, such as plants and animals, respond to invasion by Salmonella. This can help us elucidate the way the interaction between the hosts and the pathogen works. Analyzing the responses of different hosts to invasion, and integrating these results using a systems biology approach will expose the weaknesses and strengths in the responses: Are there host 'weak points' that Salmonella exploits in animals and plant host cells alike? By comparison of the reactions of evolutionarily diverse hosts, fundamentally conserved communication mechanisms may be discovered, and can potentially be exploited for drug discovery and biomarker development. An interdisciplinary consortium of

	experimental and computational scientists will develop dynamic models of Salmonella infecting diverse host cells. Project partners are located at 8 institutions (universities, companies and government laboratories) in four countries. Project coordinator is Judith Klein-Seetharaman, Univ. of Pittsburgh, USA and Research Center Jülich, Germany. Experimental partners are the Veterinary Laboratory Agency, England, Heribert Hirt, URGV, France, Gary Coulton, St George's, England, Harald Mischak, mosaiques diagnostics Inc., Germany, and Mikhail Soloviev, RHUL, England. High-throughput transcriptomic and proteomic data will be generated. Machine learning, mathematical modelling, statistics and network analysis will be carried out by Vincent Jansen and Alex Gammerman at RHUL, England, Baldo Oliva, Pompeu Fabra, Spain and Infociencia Inc., Spain.
Partners	URGV Plant Genomics (FR) Royal Holloway University of London (UK) St George's University of London (UK) Mosaiques diagnostics GmbH (DE) Barcelona Research Park of Biomedicine (PRBB) (ES) INFOCIENCIA (ES)
Coordinator	Judith Klein-Seetharaman - Research Centre Jülich GmbH (DE)
ANR funding	318 k€ (partenaire français)
Starting date and duration	Juillet 2010 - 36 mois
Reference	ANR-09-SYSB-007
Cluster label	

Project title	**TB-HOST-NET** – Integration of computational modelling with transcription and gene essentiality profiling of both MTB bacillus and infected human dendritic cells and macrophages to understand molecular interaction networks involved in the host pathogen cross-talk
Abstract	*Mycobacterium tuberculosis* is a major pathogen of man. Drug treatment is available for human disease but it takes six months, which is impractical in developing world settings where TB is most common. Consequent non-compliance with treatment regimes leads to the emergence of drug resistance. This is now a major world-wide problem with practically incurable "extreme drug-resistant" strains appearing in many countries. In this project we will study the molecular mechanisms of the interaction between *Mycobacterium tuberculosis* and human immune system. The knowledge about these mechanisms is necessary for the development of new therapeutic approaches and vaccines which are needed to shorten TB treatment and combat drug resistant strains. We will focus on the interaction of the pathogen with dendritic cells and macrophages, which are cell types active during the immune system response to the infection. The *M. tuberculosis* is capable of infecting macrophages, but not dendritic cells. Therefore, comparison of the responses of these two cell types to *M. tuberculosis* will highlight the mechanisms participating in host pathogen interaction. To understand the complex phenomenon of host-pathogen interaction the Systems Biology approach has to be employed, where molecular biology methods are integrated with computational modelling approaches to study cells at the whole genome scale level. We will use state of the art functional genomics techniques to compare interaction of the pathogen with dendritic cells and macrophages and identify human and bacterial genes, which are involved in host-pathogen interaction. The voluminous experimental data sets will be analyzed in the context of the literature knowledge about the vast networks of interacting molecules in the living cells. The computer simulation approaches developed in the physical sciences and engineering fields will be used. The computer models will generate hypotheses, which will be subjected to experimental verification. At the end of the project we expect to deliver a set of models of the molecular interaction networks involved in the interaction of *M. tuberculosis* with immune system. These models can be used to design therapeutic, diagnostic and vaccination strategies.
Partners	CNRS Toulouse (FR)

	Institut Pasteur (FR) MPI for Dynamics of Complex Technical Systems (DE) University of Milan-Bicocca (IT)
Coordinator	Andrzej M. Kierzek - University of Surrey (UK)
ANR funding	622 k€ (partenaires français)
Starting date and duration	Avril 2010 - 36 mois
Reference	ANR-09-SYSB-005
Cluster label	

Project title	**Zebrain** – Understanding decision-making from the dynamics of large neural populations in behaving zebrafish
Abstract	One of the central goals in brain research is the elucidation of the dynamic interactions among neurons and circuits underlying cognitive processes. In this project we focus on decision making as an essential element of cognition. We propose a multidisciplinary systems biology approach towards the understanding of the neuronal network mechanisms underlying decision making in behaving zebrafish. To study how simple decisions are represented and processed in the nervous system, we shall present to naïve zebrafish larva ambiguous visual stimuli (stimuli that induce two possible behaviours with similar probabilities). This type of stimulus always evokes similar patterns among sensory circuits, but depending on the behavioural choice, very distinctive ones among networks involved in decision making. To that end, the activity of large neuronal networks and behaviour will be simultaneously monitored, using a two-photon Ca2+ imaging custom-built system. Both behaviour and circuit activities will be analysed using decision-making theory, information-theory tools, and biophysical circuit models. Using these tools, we shall identify 'network functional states' and 'cell-specific states'. We shall also examine the role of spontaneous activity in the brain. Ongoing activity, once interpreted as irrelevant random noise, has been found to exhibit highly coherent spatiotemporal patterns suggesting a possible role in cognition. To examine the role of ongoing spontaneous activity on the decision, we shall test the idea that decisions

result from the interaction between the internal state of the brain and the activity evoked by external sensory stimulation.

Finally, we will perform experiments in zebrafish modelling neurological disorders and addiction (e.g. Parkinson and amphetamine addiction) and then, expecting to provide a quantitative understanding of the impact of these diseases on decision making at both behavioural and neuronal circuit levels.

Partners	Ecole Normale Supérieure (FR) Karlsruhe Institute of Technology (KIT) (DE) Weizmann Institute of Science (IL)
Coordinator	Gonzalo G. de Polavieja- Instituto Cajal, CSIC (ES)
ANR funding	301 k€ (partenaire français)
Starting date and duration	Juin 2010 - 36 mois
Reference	ANR-09-SYSB-009
Cluster label	