Activity Report 2012

Project-Team SISYPHE

SIgnals and SYstems in PHysiology &
Engineering

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Project-Team SISYPHE

Keywords: Models, Control Theory, Multiscale Models, Integrative Physiology, System Analysis And Control

Creation of the Project-Team: July 01, 2007 .

1. Members

Research Scientists

Pierre-Alexandre Bliman [Senior Researcher Inria (DR), HdR]
Frédérique Clément [Senior Researcher Inria (DR), HdR]
Mathieu Desroches [Junior Researcher Inria (CR)]
Jacques Henry [Senior Researcher Inria (DR Emeritus), HdR]
Maciej Krupa [Advanced Research Position]
Claire Médigue [Research Engineer (IR), Inria]
Mazyar Mirrahimi [Senior Researcher Inria (DR), HdR]
Michel Sorine [Senior Researcher Inria (DR), Team Leader, HdR]
Serge Steer [Senior Researcher Inria (DR)]
Qinghua Zhang [Senior Researcher Inria (DR), HdR]

External Collaborators

Julien Barral [Professor, Paris 13 University (LAGA), HdR]
Jean-Pierre Françoise [Professor, Paris 6 University, HdR]
Pierre Rouchon [Professor, Ecole des Mines de Paris, Systems and Control Centre, HdR]
Alexandre Vidal [Associate Professor, Université Évry-Val-d'Essonne, on half-time delegation since September 2012]

Engineers

Arnaud Ferré [Associate Engineer, Inria, January-August 2012]
Habib Jreige [Senior Engineer, Inria, from November 2012]
Vincent Ladevèze [Senior Engineer seconded from the Experimentation and Development Department (SED)]
Abdouramane Moussa Ali [Associate Engineer, Inria, from June 2011]
Mouhamadoul-Bachir Syll [Associate Engineer, Inria, from August 2012]

PhD Students

Hadis Amini [Ecole polytechnique fellowship, École des Mines de Paris, until September 2012]
Benjamin Aymard [UPMC fellowship, UPMC University (Paris), from October 2011]
Najmeddine Attia [Inria fellowship, Paris 13 University, until October 2012]
Julien Bernard [Cifre CARMAT SAS, Paris 11 University, from October 2010]
Leila Djaziri [Inria fellowship, Paris 11 University (Orsay), from October 2009]
Alexandre Guerrini [Cifre LK2, Paris 11 University (Orsay), part-time since October 2008]
Zaki Leghtas [Inria fellowship, École des Mines de Paris, until September 2012]
David Marie-Luce [Cifre Renault, Paris 11 University (Orsay), from November 2009]
Mohamed Oumri [Inria fellowship, Paris 11 University (Orsay), from October 2009]
Mohamad Safa [Paris 11 University (Orsay), until October 2012]
Peipei Shang [Inria fellowship, UPMC University (Paris), until August 2012]
Quang Ahn Tran [Inria fellowship, UVSQ University (Versailles), from january 2012]

Post-Doctoral Fellows

Alberto Granados Corsellas [from November 2012]
Boyi Ni [from August 2012]

Administrative Assistant

Martine Verneuille [Secretary (AI), Inria]

2. Overall Objectives

2.1. Overall Objectives

SISYPHE (SIgnals and Systems in PHysiology and Engineering) is studying questions about some complex dynamical systems issued from Physiology and Engineering: modeling ; identification and observation from signals ; real-time health monitoring or control ; questions of system theory arising from the emerging domain of "quantum engineering".

Most studies are motivated, in Physiology, by the reproductive and the cardiovascular systems and in Engineering, by control of some new engineered quantum systems and by monitoring of some critical engineering systems like electrical networks.

The research on the reproductive system, after an important development in the framework of REGATE (REgulation of the GonAdoTropE axis), an Inria Large-Scale Initiative Action (LSIA), will lead to a new team proposed by Frédérique Clément in October 2012.

Research topics:
Signals & Systems

- Dynamical systems modeled by ordinary differential equations: modeling, observation and control.

- Quantum & quantum-like systems: estimation and control.

- Multiscale dynamical systems: analysis of multiscale properties of signals and relations with the underlying dynamical systems.

Applications to Physiology & Engineering

- Multiscale modeling of the controlled follicle selection process & Control of the reproductive axis.

- Model-based observation and control of the cardiovascular system: (multiscale-) model-based signal processing (ECG, pressure, heart-rate). Monitoring and control of cardiac prosthesis.

- Identification and control of some quantum systems: towards "quantum engineering".

- Waves propagation in transmission-line networks & Inverse scattering. Application to health monitoring of cabled electrical networks and to the arterial pressure waveform analysis.

- Health monitoring and control of energy conversion systems: glycemic control in critically ill patients ; monitoring of exhaust gas aftertreatment systems.

2.2. Highlights of the Year

The feedback scheme for quantum systems proposed by Mazyar Mirrahimi and his co-authors have been very successful in some important physical experiments. After the preparation and stabilization of a small number of photons in a cavity in 2011 with the group of Serge Haroche, Nobel Prize for Physics (2012) at ENS Paris ([9], [8], [17], some new results have been obtained by Mazyar and his PhD student, Zaki Leghtas with the groups of Robert Schoelkopf and Michel Devoret at Yale University [74], [75], [77], [78]. In particular, they have proposed a new method to autonomously correct for errors of a logical qubit induced by energy relaxation. This proposal directly addresses the task of building a hardware-efficient and technically realizable quantum memory.

3. Scientific Foundations

3.1. System theory for systems modeled by ordinary differential equations

3.1.1. *Identification, observation, control and diagnosis of linear and nonlinear systems*

Characterizing and inferring properties and behaviors of objects or phenomena from observations using models is common to many research fields. For dynamical systems encountered in the domains of engineering and physiology, this is of practical importance for monitoring, prediction, and control. For such purposes, we consider most frequently, the following model of dynamical systems:

$$\begin{aligned}
\frac{dx(t)}{dt} &= f(x(t), u(t), \theta, w(t)) \\
y(t) &= g(x(t), u(t), \theta, v(t))
\end{aligned} \tag{1}$$

where $x(t)$, $u(t)$ and $y(t)$ represent respectively the state, input and output of the system, f and g characterize the state and output equations, parameterized by θ and subject to modeling and measurement uncertainties $w(t)$ and $v(t)$. Modeling is usually based on physical knowledge or on empirical experiences, strongly depending on the nature of the system. Typically only the input $u(t)$ and output $y(t)$ are directly observed by sensors. Inferring the parameters θ from available observations is known as system identification and may be useful for system monitoring [102], whereas algorithms for tracking the state trajectory $x(t)$ are called observers. The members of SISYPHE have gained important experiences in the modeling of some engineering systems and biomedical systems. The identification and observation of such systems often remain challenging because of strong nonlinearities [21]. Concerning control, robustness is an important issue, in particular to ensure various properties to all dynamical systems in some sets defined by uncertainties [83], [84]. The particularities of ensembles of connected dynamical systems raise new challenging problems.

Examples of reduced order models:
- Reduced order modeling of the cardiovascular system for signal & image processing or control applications. See section 3.3.1.
- Excitable neuronal networks & control of the reproductive axis by the GnRH. See section 3.3.2.
- Modeling, Control, Monitoring and Diagnosis of Depollution Systems. See section 6.1.

3.2. System theory for quantum and quantum-like systems

3.2.1. *Quantization of waves propagation in transmission-line networks & Inverse scattering*

Linear stationary waves. Our main example of classical system that is interesting to see as a quantum-like system is the Telegrapher Equation, a model of transmission lines, possibly connected into a network. This is the standard model for electrical networks, where V and I are the voltage and intensity functions of z and k, the position and frequency and $R(z)$, $L(z)$, $C(z)$, $G(z)$ are the characteristics of the line:

$$\frac{\partial V(z, k)}{\partial z} = -(R(z) + jkL(z))I(z, k), \quad \frac{\partial I(z, k)}{\partial z} = -(G(z) + jkC(z))V(z, k) \tag{2}$$

Since the work of Noordergraaf [101], this model is also used for hemodynamic networks with V and I respectively the blood pressure and flow in vessels considered as 1D media, and with $R = \frac{8\pi\eta}{S^2}$, $L = \frac{\rho}{S}$, $C = \frac{3S(r+h)}{E(2r+h)}$ where ρ and η are the density and viscosity of the blood ; r, h and E are the inner radius, thickness and Young modulus of the vessel. $S = \pi r^2$. The conductivity G is a small constant for blood flow. Monitoring such networks is leading us to consider the following inverse problem: *get information on the functions R, L, C, G from the reflection coefficient $\mathcal{R}(k)$ (ratio of reflected over direct waves) measured in some location by Time or Frequency Domain Reflectometry.*

To study this problem it is convenient to use a Liouville transform, setting $x(z) = \int_0^z \sqrt{L(z')C(z')}dz'$, to introduce auxiliary functions $q^{\pm}(x) = \frac{1}{4}\frac{d}{x}\left(\ln\frac{L(x)}{C(x)}\right) \pm \frac{1}{2}\left(\frac{R(x)}{L(x)} - \frac{G(x)}{C(x)}\right)$ and $q_p(x) = \frac{1}{2}\left(\frac{R(x)}{L(x)} + \frac{G(x)}{C(x)}\right)$, so that (2) becomes a Zakharov-Shabat system [89] that reduces to a Schrödinger equation in the lossless case ($R = G = 0$):

$$\frac{\partial v_1}{\partial x} = (q_p - jk)\,v_1 + q^+ v_2, \quad \frac{\partial v_2}{\partial x} = -(q_p - jk)\,v_2 + q^- v_1 \tag{3}$$

and $I(x,k) = \frac{1}{\sqrt{2}}\left[\frac{C(x)}{L(x)}\right]^{\frac{1}{4}}(v_1(x,k) + v_2(x,k))$, $V(x,k) = -\frac{1}{\sqrt{2}}\left[\frac{L(x)}{C(x)}\right]^{\frac{1}{4}}(v_1(x,k) - v_2(x,k))$.

Our inverse problem becomes now an inverse scattering problem for a Zakharov-Shabat (or Schrödinger) equation: *find the potentials $q^{\pm}$ and q_p corresponding to $\mathcal{R}$.* This classical problem of mathematical physics can be solved using e.g. the Gelfand-Levitan-Marchenko method.

Nonlinear traveling waves. In some recent publications [92], [91], we use scattering theory to analyze a measured Arterial Blood Pressure (ABP) signal. Following a suggestion made in [103], a Korteweg-de Vries equation (KdV) is used as a physical model of the arterial flow during the pulse transit time. The signal analysis is based on the use of the Lax formalism: the iso-spectral property of the KdV flow allows to associate a constant spectrum to the non stationary signal. Let the non-dimensionalized KdV equation be

$$\frac{\partial y}{\partial t} - 6y\frac{\partial y}{\partial x} + \frac{\partial^3 y}{\partial x^3} = 0 \tag{4}$$

In the Lax formalism, y is associated to a Lax pair: a Schrödinger operator, $L(y) = -\frac{\partial^2}{\partial x^2} + y$ and an anti-Hermitian operator $M(y) = -4\frac{\partial^3}{\partial x^3} + 3y\frac{\partial}{\partial x} + 3\frac{\partial}{\partial x}y$. The signal y is playing here the role of the potential of $L(y)$ and is given by an operator equation equivalent to (4):

$$\frac{\partial L(y)}{\partial t} = [M(y), L(y)] \tag{5}$$

Scattering and inverse scattering transforms can be used to analyze y in term of the spectrum of $L(y)$ and conversely. The "bound states" of $L(y)$ are of particular interest: if $L(y)$ is solution of (5) and $L(y(t))$ has only bound states (no continuous spectrum), then this property is true at each time and y is a soliton of KdV. For example the arterial pulse pressure is close to a soliton [86], [14].

Inverse scattering as a generalized Fourier transform. For "pulse-shaped" signals y, meaning that $y \in L^1(\mathbb{R}; (1 + |x|^2)dx)$, the squared eigenfunctions of $L(y)$ and their space derivatives are a basis in $L^1(\mathbb{R}; dx)$ (see e.g. [99]) and we use this property to analyze signals. Remark that the Fourier transform corresponds to using the basis associated with $L(0)$. The expression of a signal y in its associated basis is of particular interest. For a positive signal (as e.g. the arterial pressure), it is convenient to use $L(-y)$ as $-y$ is like a multi-well potential, and the Inverse scattering transform formula becomes:

$$y(x) = 4\sum_{n=1}^{n=N} \kappa_n \psi_n^2(x) - \frac{2i}{\pi}\int_{-\infty}^{-\infty} k\mathcal{R}(k)f^2(k,x)dk \tag{6}$$

where ψ_n and $f(k,.)$ are solutions of $L(-y)f = k^2 f$ with $k = i\kappa_n$, $\kappa_n > 0$, for ψ_n (bound states) and $k > 0$ for $f(k,.)$ (Jost solutions). The discrete part of this expression is easy to compute and provides useful informations on y in applications. The case $\mathcal{R} = 0$ ($-y$ is a reflectionless potential) is then of particular interest as $2N$ parameters are sufficient to represent the signal. We investigate in particular approximation of pulse-shaped signals by such potentials corresponding to N-solitons.

3.2.2. *Identification & control of quantum systems*

Interesting applications for quantum control have motivated seminal studies in such wide-ranging fields as chemistry, metrology, optical networking and computer science. In chemistry, the ability of coherent light to manipulate molecular systems at the quantum scale has been demonstrated both theoretically and experimentally [98]. In computer science, first generations of quantum logical gates (restrictive in fidelity) has been constructed using trapped ions controlled by laser fields (see e.g. the "Quantum Optics and Spectroscopy Group, Univ. Innsbruck"). All these advances and demands for more faithful algorithms for manipulating the quantum particles are driving the theoretical and experimental research towards the development of new control techniques adapted to these particular systems. A very restrictive property, particular to the quantum systems, is due to the destructive behavior of the measurement concept. One can not measure a quantum system without interfering and perturbing the system in a non-negligible manner.

Quantum decoherence (environmentally induced dissipations) is the main obstacle for improving the existing algorithms [88]. Two approaches can be considered for this aim: first, to consider more resistant systems with respect to this quantum decoherence and developing faithful methods to manipulate the system in the time constants where the decoherence can not show up (in particular one can not consider the back-action of the measurement tool on the system); second, to consider dissipative models where the decoherence is also included and to develop control designs that best confronts the dissipative effects.

In the first direction, we consider the Schrödinger equation where $\Psi(t,x)$, $-\frac{1}{2}\Delta$, V, μ and $u(t)$ respectively represent the wavefunction, the kinetic energy operator, the internal potential, the dipole moment and the laser amplitude (control field):

$$i\frac{d}{dt}\Psi(t,x) = (H_0 + u(t)H_1)\Psi(t,x) = (-\frac{1}{2}\Delta + V(x) + u(t)\mu(x))\Psi(t,x), \quad \Psi|_{t=0} = \Psi_0, \qquad (7)$$

While the finite dimensional approximations ($\Psi(t) \in \mathbb{C}^N$) have been very well studied (see e.g. the works by H. Rabitz, G. Turinici, ...), the infinite dimensional case ($\Psi(t,.) \in L^2(\mathbb{R}^N; \mathbb{C})$) remains fairly open. Some partial results on the controllability and the control strategies for such kind of systems in particular test cases have already been provided [79], [80], [94]. As a first direction, in collaboration with K. Beauchard (CNRS, ENS Cachan) et J-M Coron (Paris-sud), we aim to extend the existing ideas to more general and interesting cases. We will consider in particular, the extension of the Lyapunov-based techniques developed in [95], [81], [94]. Some technical problems, like the pre-compactness of the trajectories in relevant functional spaces, seem to be the main obstacles in this direction.

In the second direction, one needs to consider dissipative models taking the decoherence phenomena into account. Such models can be presented in the density operator language. In fact, to the Schrödinger equation (7), one can associate an equation in the density operator language where $\rho = \Psi\Psi^*$ represents the projection operator on the wavefunction Ψ ($[A, B] = AB - BA$ is the commutator of the operators A and B):

$$\frac{d}{dt}\rho = -i[H_0 + u(t)H_1, \rho], \qquad (8)$$

Whenever, we consider a quantum system in its environment with the quantum jumps induced by the vacuum fluctuations, we need to add the dissipative effect due to these stochastic jumps. Note that at this level, one also can consider a measurement tool as a part of the environment. The outputs being partial and not giving complete information about the state of the system (Heisenberg uncertainty principle), we consider a so-called quantum filtering equation in order to model the conditional evolution of the system. Whenever the measurement tool composes the only (or the only non-negligible) source of decoherence, this filter equation admits the following form:

$$dρ_t = -i[H_0 + u(t)H_1, ρ_t]dt + (Lρ_tL^* - \frac{1}{2}L^*Lρ_t - \frac{1}{2}ρ_tL^*L)dt$$
$$+\sqrt{η}(Lρ_t + ρ_tL^* - \text{Tr}\left[(L + L^*)ρ_t\right]ρ_t)dW_t,$$

$$(9)$$

where L is the so-called Lindblad operator associated to the measurement, $0 < η \leq 1$ is the detector's efficiency and where the Wiener process W_t corresponds to the system output Y_t via the relation $dW_t = dY_t - \text{Tr}\left[(L + L^*)ρ_t\right]dt$. This filter equation, initially introduced by Belavkin [82], is the quantum analogous of a Kushner-Stratonovic equation. In collaboration with H. Mabuchi and his co-workers (Physics department, Caltech), we would like to investigate the derivation and the stochastic control of such filtering equations for different settings coming from different experiments [96].

Finally, as a dual to the control problem, physicists and chemists are also interested in the parameter identification for these quantum systems. Observing different physical observables for different choices of the input $u(t)$, they hope to derive more precise information about the unknown parameters of the system being parts of the internal Hamiltonian or the dipole moment. In collaboration with C. Le Bris (Ecole des ponts and Inria), G. Turinici (Paris Dauphine and Inria), P. Rouchon (Ecole des Mines) and H. Rabitz (Chemistry department, Princeton), we would like to propose new methods coming from the systems theory and well-adapted to this particular context. A first theoretical identifiability result has been proposed [93]. Moreover, a first observer-based identification algorithm is under study.

3.3. Physiological & Clinical research topics

3.3.1. *The cardiovascular system: a multiscale controlled system*

Understanding the complex mechanisms involved in the cardiac pathological processes requires fundamental researches in molecular and cell biology, together with rigorous clinical evaluation protocols on the whole organ or system scales. Our objective is to contribute to to these researches by developing low-order models of the cardiac mechano-energetics and control mechanisms, for applications in model-based cardiovascular signal or image processing.

We consider intrinsic heart control mechanisms, ranging from the Starling and Treppe effects on the cell scale to the excitability of the cardiac tissue and to the control by the autonomous nervous system. They all contribute to the function of the heart in a coordinated manner that we want to analyze and assess. For this purpose, we study reduced-order models of the electro-mechanical activity of cardiac cells designed to be coupled with measures available on the organ scale (e.g. ECG and pressure signals). We study also the possibility to gain insight on the cell scale by using model-based multiscale signal processing techniques of long records of cardiovascular signals.

Here are some questions of this kind, we are considering:
- Modeling the controlled contraction/relaxation from molecular to tissue and organ scales.
- Direct and inverse modeling the electro-mechanical activity of the heart on the cell scale.
- Nonlinear spectral analysis of arterial blood pressure waveforms and application to clinical indexes.
- Modeling short-term and long-term control dynamics on the cardiovascular-system scale. Application to a Total Artificial Heart.

3.3.2. Reproductive system: follicular development & ovulation control

The ovulatory success is the main limiting factor of the whole reproductive process, so that a better understanding of ovulation control is needed both for clinical and zootechnical applications. It is necessary to improve the treatment of anovulatory infertility in women, as it can be by instance encountered in the PolyCystic Ovarian Syndrome (PCOS), whose prevalence among reproductive-age women has been estimated at up to 10%. In farm domestic species, embryo production following FSH stimulation (and subsequent insemination) enables to amplify the lineage of chosen females (via embryo transfer) and to preserve the genetic diversity (via embryo storage in cryobanks). The large variability in the individual responses to ovarian stimulation treatment hampers both their therapeutic and farming applications. Improving the knowledge upon the mechanisms underlying FSH control will help to improve the success of assisted reproductive technologies, hence to prevent ovarian failure or hyperstimulation syndrome in women and to manage ovulation rate and ovarian cycle chronology in farm species.

To control ovarian cycle and ovulation, we have to deeply understand the selection process of ovulatory follicles, the determinism of the species-specific ovulation rate and of its intra- and between-species variability, as well as the triggering of the ovulatory GnRH surge from hypothalamic neurons.
Beyond the strict scope of Reproductive Physiology, this understanding raises biological questions of general interest, especially in the fields of

Molecular and Cellular Biology. The granulosa cell, which is the primary target of FSH in ovarian follicles, is a remarkable cellular model to study the dynamical control of the transitions between the cellular states of quiescence, proliferation, differentiation, and apoptosis, as well as the adaptability of the response to the same extra-cellular signal according to the maturity level of the target cell. Moreover, the FSH receptor belongs to the seven transmembrane spanning receptor family, which represent the most frequent target (over 50%) amongst the therapeutic agents currently available. The study of FSH receptor-mediated signaling is thus not only susceptible to allow the identification of relaying controls to the control exerted by FSH, but it is also interesting from a more generic pharmacological viewpoint.

Neuroendocrinology and Chronobiology. The mechanisms underlying the GnRH ovulatory surge involve plasticity phenomena of both neuronal cell bodies and synaptic endings comparable to those occurring in cognitive processes. Many time scales are interlinked in ovulation control from the fastest time constants of neuronal activation (millisecond) to the circannual variations in ovarian cyclicity. The influence of daylength on ovarian activity is an interesting instance of a circannual rhythm driven by a circadian rhythm (melatonin secretion from the pineal gland).

Simulation and control of a multiscale conservation law for follicular cells

In the past years, we have designed a multiscale model of the selection process of ovulatory follicles, including the cellular, follicular and ovarian levels [11], [10]. The model results from the double structuration of the granulosa cell population according to the cell age (position within the cell cycle) and to the cell maturity (level of sensitivity towards hormonal control). In each ovarian follicle, the granulosa cell population is described by a density function whose changes are ruled by conservation laws. The multiscale structure arises from the formulation of a hierarchical control operating on the aging and maturation velocities as well on the source terms of the conservation law. The control is expressed from different momentums of the density leading to integro-differential expressions.
Future work will take place in the REGATE project and will consist in:
- predicting the selection outcome (mono-, poly-ovulation or anovulation / ovulation chronology) resulting from given combinations of parameters and corresponding to the subtle interplay between the different organs of the gonadotropic axis (hypothalamus, pituitary gland and ovaries). The systematic exploration of the situations engendered by the model calls for the improvement of the current implementation performances. The work will consist in improving the precision of the numerical scheme, in the framework of the finite volume method and to implement the improved scheme,

- solving the control problems associated with the model. Indeed, the physiological conditions for the triggering of ovulation, as well as the counting of ovulatory follicles amongst all follicles, define two nested and coupled reachability control problems. Such particularly awkward problems will first be tackled from a particle approximation of the density, in order to design appropriate control laws operating on the particles and allowing them to reach the target state sets.

Connectivity and dynamics of the FSH signaling network in granulosa cells

The project consists in analyzing the connectivity and dynamics of the FSH signaling network in the granulosa cells of ovarian follicles and embedding the network within the multiscale representation described above, from the molecular up to the organic level. We will examine the relative contributions of the $G\alpha_s$ and βarrestin-dependent pathways in response to FSH signal, determine how each pathway controls downstream cascades and which mechanisms are involved in the transition between different cellular states (quiescence, proliferation, differentiation and apoptosis). On the experimental ground, we propose to develop an antibody microarray approach in order to simultaneously measure the phosphorylation levels of a large number of signaling intermediates in a single experiment. On the modeling ground, we will use the BIOCHAM (biochemical abstract machine) environment first at the boolean level, to formalize the network of interactions corresponding to the FSH-induced signaling events on the cellular scale. This network will then be enriched with kinetic information coming from experimental data, which will allow the use of the ordinary differential equation level of BIOCHAM. In order to find and fine-tune the structure of the network and the values of the kinetic parameters, model-checking techniques will permit a systematic comparison between the model behavior and the results of experiments. In the end, the cell-level model should be abstracted to a much simpler model that can be embedded into a multiscale one without losing its main characteristics.

Bifurcations in coupled neuronal oscillators.
We have proposed a mathematical model allowing for the alternating pulse and surge pattern of GnRH (Gonadotropin Releasing Hormone) secretion [5]. The model is based on the coupling between two systems running on different time scales. The faster system corresponds to the average activity of GnRH neurons, while the slower one corresponds to the average activity of regulatory neurons. The analysis of the slow/fast dynamics exhibited within and between both systems allows to explain the different patterns (slow oscillations, fast oscillations and periodical surge) of GnRH secretion.

This model will be used as a basis to understand the control exerted by ovarian steroids on GnRH secretion, in terms of amplitude, frequency and plateau length of oscillations and to discriminate a direct action (on the GnrH network) from an indirect action (on the regulatory network) of steroids. From a mathematical viewpoint, we have to fully understand the sequences of bifurcations corresponding to the different phases of GnRH secretion. This study will be derived from a 3D reduction of the original model.

4. Software

4.1. The Matlab System Identification ToolBox (SITB)

Participant: Qinghua Zhang.

This development is made in collaboration with Lennart Ljung (Linköping University, Sweden), Anatoli Juditsky (Joseph Fourier University, France) and Peter Lindskog (NIRA Dynamics, Sweden).

The System Identification ToolBox (SITB) is one of the main Matlab toolboxes commercialized by The Mathworks. Inria participates in the development of its extension to the identification of nonlinear systems which is released since 2007. It includes algorithms for both black box and grey box identification of nonlinear dynamic systems. Inria is mainly responsible for the development of black box identification, with nonlinear autoregressive (NLARX) models and block-oriented (Hammerstein-Wiener) models.

4.2. Inverse Scattering for Transmission Lines (ISTL)

Participants: Michel Sorine, Qinghua Zhang.

ISTL is a software for numerical computation of the inverse scattering transform for electrical transmission lines. In addition to the inverse scattering transform, it includes a numerical simulator generating the reflection coefficients of user-specified transmission lines. With the aid of a graphical interface, the user can interactively define the distributed characteristics of a transmission line. This software is mainly for the purpose of demonstrating a numerical solution to the inverse problem of non uniform transmission lines. Its current version is limited to the case of lossless transmission lines. It is registered at Agence pour la Protection des Programmes (APP) under the number IDDN.FR.001.120003.000.S.P.2010.000.30705.

4.3. CGAO: Contrôle Glycémique Assisté par Ordinateur

Participants: Alexandre Guerrini, Michel Sorine.

This development is made in collaboration with Pierre Kalfon (Chartres Hospital) and the small business enterprise LK2.

This software CGAO developed with LK2 and Hospital Louis Pasteur (Chartres) provides efficient monitoring and control tools that will help physicians and nursing staff to avoid hyperglycaemia and hypoglycaemia episodes in Intensive Care Units. It has been used in a large clinical study, CGAO-REA. More than 3500 patients have been included in CGAO-REA. Commercialization is done by LK2. CGAO has been sold to the company Fresenius Kabi.

4.4. DYNPEAK: a user-friendly interface for the analysis of LH (Luteinizing Hormone) secretion rhythms

Participants: Frédérique Clément, Arnaud Ferré, Vincent Ladevèze, Claire Médigue, Serge Steer, Mouhamadoul-Bachir Syll, Alexandre Vidal, Qinghua Zhang.

DYNPEAK is a Webresource interface dedicated to the analysis of the pulsatile rhythm of secretion of the pituitary hormone LH, that aims at providing the final users (experimentalists and clinicians) with a simple-to-use version of the algorithm developed in [54]. DYNPEAK is developed within the PALOMA project devoted to the development of a prototype for a collaborative platform in Biomathematics.

4.5. LARY_CR: Software package for the Analysis of Cardio Vascular and Respiratory Rhythms

Participants: Claire Médigue, Serge Steer.

LARY_CR is a software package dedicated to the study of cardiovascular and respiratory rhythms [97]. It presents signal processing methods, from events detection on raw signals to the variability analysis of the resulting time series. The events detection concerns the heart beat recognition on the electrocardiogram, defining the RR time series, the maxima and minima on the arterial blood pressure defining the systolic and diastolic time series. These detections are followed by the resampling of the time series then their analyse. This analyse uses temporal and time frequency methods: Fourier Transform, spectral gain between the cardiac and blood pressure series, Smooth Pseudo Wigner_Ville Distribution, Complex DeModulation, temporal method of the cardiovascular Sequences. The objective of this software is to provide some tools for studying the autonomic nervous system, acting in particular in the baroreflex loop; its functionning is reflected by the cardiovascular variabilities and their relationships with the other physiological signals, especially the respiratory activity. Today LARY_CR is used internally, in the framework of our clinical collaborations, and the functions devoted to the rhythms analysis are now freely available through the Scilab Cardiovascular toolbox, as an atom module.

5. New Results

5.1. Modeling, observation and control: systems modeled by ordinary differential equations

5.1.1. *Nonlinear system identification*

Participants: Pierre-Alexandre Bliman, Boyi Ni, Michel Sorine, Qinghua Zhang.

In the framework of the joint Franco-Chinese ANR-NSFC EBONSI project, in collaboration with the Laboratory of Industrial Process Monitoring and Optimization of Peking University, and with Centre de Recherche en Automatique de Nancy (CRAN), the topics studied this year on nonlinear system identification are mainly on extended Hammerstein system identification with hysteresis nonlinearity and on continuous time block-oriented nonlinear system identification.

Motivated by the modeling of control valves with significant stiction, we have studied extended Hammerstein systems composed of a hysteresis nonlinearity followed by a linear dynamic subsystem. The joint characterization of the control valve and of the controlled process is formulated as the identification of an extended Hammerstein system. A point-slope based hysteresis model is used to describe the input hysteresis nonlinearity of the control valve. An iterative algorithm is proposed to solve the identification problem. The basic idea is to separate the ascent and descent paths of the input hysteresis nonlinearity subject to oscillatory excitations. Industrial examples are tested to verify the effectiveness of the proposed identification algorithm for characterizing complex behavior of control valve stiction in practice. This work has been presented at the 16th IFAC Symposium on System Identification [66].

A Hammerstein-Wiener system is composed of a dynamic linear subsystem preceded and followed by two static nonlinearities. Typically, the nonlinearities of such a system are caused by actuator and sensor distortions. The identification of such systems with a continuous time model has been studied this year in collaboration with colleagues of CRAN. Based on previously developed simplified refined instrumental variable method, and by making use of an adaptive observer for data filtering, a combined approach, referred to as Kalman pre-filtered instrumental variable based method, is developed. By taking advantages of the two aforementioned methods, the new method is faster and has a naturally stabilizing Kalman filter that does not color white noises. This work has been presented at the 16th IFAC Symposium on System Identification [62].

5.1.2. *Model-based fault diagnosis*

Participants: Abdouramane Moussa Ali, Qinghua Zhang.

The increasing requirements for higher performance, efficiency, reliability and safety of modern engineering systems call for continuous research investigations in the field of fault detection and isolation. This year we have studied algebro-differential systems through an adaptive observer based approach, and linear time varying systems through a Kalman filter based statistical testing approach.

In the framework of the MODIPRO project funded by Paris Region ASTech, the monitoring of the air conditioning system of an aircraft has been studied this year. Part of this system is modeled by nonlinear algebro-differential equations. A method for fault diagnosis of such systems has been developed in our study. Through a particular discretization method and under realistic assumptions, the considered continuous time DAE model is transformed to an explicit state space model in discrete time. An adaptive observer is then applied to the discretized system for monitoring faults possibly affecting the system and represented by changes in model parameters. This work will be presented at the 5th IFAC Symposium on System Structure and Control [61].

While the theory of fault diagnosis has been mostly developed for linear time invariant (LTI) systems, in many industrial applications it is important to take into account the nonlinear behavior of the monitored systems. One possible approach is to linearize a nonlinear system all along its state trajectory, resulting in linear time varying (LTV) or linear parameter varying (LPV) models. In collaboration with Michèle Basseville of IRISA (Institut de Recherche en Informatique et Systèmes Aléatoires), fault diagnosis for stochastic LTV systems has been studied this year. By applying the Kalman filter in a particular manner avoiding the difficulty related to unknown faults possibly affecting the system, the problem of fault diagnosis in a dynamic LTV system is transformed into a hypothesis testing problem in a simple linear regression model. Generalized likelihood ratio (GLR) tests are then applied to the resulting hypothesis testing problem. This work has been presented at the 16th IFAC Symposium on System Identification [67].

5.2. Observation, control and traveling waves in systems modeled by partial differential equations

5.2.1. *Modeling of electric transmission networks*
Participants: Mohamed Oumri, Michel Sorine, Qinghua Zhang.

The increasing number and complexity of wired electric networks in modern engineering systems is amplifying the importance of the reliability of electric connections. In the framework of the ANR 0-DEFECT project, we have studied mathematical models of complex electric networks with the aim of designing algorithms for fault diagnosis. The well known Baum-Liu-Tesche (BLT) equation is a powerful model for describing quite general networks and allows to compute the current and voltage waves at the nodes of a network from the specifications of its nodes and connecting cables [63]. This year we have studied the inverse problem: what can we know about the properties of the cables connecting the nodes of a network from experiments made at the nodes of the network? A convenient model for this purpose is formulated with admittance matrices. It is essentially equivalent to the BLT equation, hence can describe quite general networks. The inverse problem is then solved through a decomposition of the admittance matrix of the entire network.

5.2.2. *Diagnosis of insulator degradation in long electric cables*
Participants: Leila Djaziri, Michel Sorine, Qinghua Zhang.

For the diagnosis of insulator degradation in long electric cables, the estimation of the shunt conductance of such cables have been studied, in the framework of the ANR INSCAN project. The shunt conductance of a healthy electric cable is usually very weak. Even when the insulator in the cable is significantly degraded, the shunt conductance can still remain at a quite low level. The main difficulty in this study is due to the fact that the measurements made at the ends of a cable are hardly sensitive to the variations of the shunt conductance. To overcome this difficulty, two methods have been studied. One of them is based on the analysis of the sensitivity of the wave phase shift to the shunt conductance. The efficiency of this method has been demonstrated through extensive tests on cables of SNCF (Société Nationale des Chemins de Fer français). Another method is based on the processing of long time data records. It is designed for the estimation of distributed shunt conductance, in order to detect and to locate inhomogeneous degradation of the insulator. The main idea of this method is to compensate the weak sensitivity of the measurement by long time data records. The results of this method evaluated by numerical simulations have been reported at the 16th IFAC Symposium on System Identification [68].

5.3. System theory approach of some quantum systems
Participants: Hadis Amini, Zaki Leghtas, Mazyar Mirrahimi, Pierre Rouchon.

Most of this work is done in close collaboration with the Pierre Aigrain laboratory (LPA) at ENS Paris and the Quantronics Laboratory (Qlab) of Michel Devoret and the Rob Schoelkopf Lab at Yale University.

Modern scientific and technologic requirements have led the theoretical and experimental research toward an engineering of quantum systems. The technologies that are proposed or developed include nano-scale electromechanical devices, tools for implementing quantum computation and quantum communication, NMR applications, quantum chemistry synthesis, high-resolution sensors, etc. The recent theoretical and experimental researches have shown that the quantum dynamics can be studied in the framework of the theory of estimation and control of systems, but give place to models that are not completely explored yet.

Our activities lie in the theoretical and experimental interface of this progressing field of research with an accent on the applications in quantum information and computation as well as high-precision metrology. By focusing on two different but similar types of experimental setups, consisting of cavity quantum electro-dynamical systems and quantum Josephson circuits, we aim in preparing highly non-classical states of a microwave field and protect these states against decoherence. Two different approaches are considered: 1- real-time measurement, quantum filtering and feedback ; 2- dissipation engineering also called reservoir engineering. Through the first methodology, we try to propose new experimental feedback protocols based on a fast real-time processing of measurement signal, followed by a state estimation applying the filtered signal and finally designing simple feedback laws based on the estimated state. The second methodology consists of designing new quantum circuit schemes that allow to orient the system's coupling to its environment in such a way that evacuates the undesired entropy induced by un-controlled noise sources.

5.3.1. *Measurement based feedback*

We have developed the mathematical methods underlying a recent quantum feedback experiment stabilizing photon-number states [17], [30], [29], [24]. We consider a controlled system whose quantum state, a finite dimensional density operator, is governed by a discrete-time nonlinear Markov process. In open-loop, the measurements are assumed to be quantum non-demolition (QND) measurements. This Markov process admits a set of stationary pure states associated to an orthonormal basis. These stationary states provide martingales crucial to prove the open-loop stability: under simple assumptions, almost all trajectories converge to one of these stationary states; the probability to converge to a stationary state is given by its overlap with the initial quantum state. From these open-loop martingales, we construct a supermartingale whose parameters are given by inverting a Metzler matrix characterizing the impact of the control input on the Kraus operators defining the Markov process. This supermartingale measures the "distance" between the current quantum state and the goal state chosen from one of the open-loop stationary pure states. At each step, the control input minimizes the conditional expectation of this distance. It is proven that the resulting feedback scheme stabilizes almost surely towards the goal state whatever the initial quantum state. This state feedback takes into account a known constant delay of arbitrary length in the control loop. This control strategy is proved to remain also convergent when the state is replaced by its estimate based on a quantum filter. It relies on measurements that can be corrupted by random errors with conditional probabilities described by a known left stochastic matrix. Closed-loop simulations corroborated by experimental data illustrate the interest of such nonlinear feedback scheme for the photon box [29].

We have also investigated the stabilization of the dynamical state of a superconducting qubit. In a series of papers, A. Korotkov and his co-workers suggested that continuous weak measurement of the state of a qubit and applying an appropriate feedback on the amplitude of a Rabi drive, should maintain the coherence of the Rabi oscillations for arbitrary time. Here, in the aim of addressing a metrological application of these persistent Rabi oscillations, we explore a new variant of such strategies. This variant is based on performing strong measurements in a discrete manner and using the measurement record to correct the phase of the Rabi oscillations. Noting that such persistent Rabi oscillations can be viewed as an amplitude- to-frequency convertor (converting the amplitude of the Rabi microwave drive to a precise frequency), we propose another feedback layer consisting of a simple analog phase locked loop to compensate the low frequency deviations in the amplitude of the Rabi drive [60].

5.3.2. *Dissipation engineering*

We have introduced a new quantum gate that transfers an arbitrary state of a qubit into a superposition of two quasi-orthogonal coherent states of a cavity mode, with opposite phases. This qcMAP gate is based on

conditional qubit and cavity operations exploiting the energy level dispersive shifts, in the regime where they are much stronger than the cavity and qubit linewidths [77], [26]. The generation of multi-component superpositions of quasi-orthogonal coherent states, non-local entangled states of two resonators and multi-qubit GHZ states can be efficiently achieved by this gate. We also propose a new method, based on the application of this gate, to autonomously correct for errors of a logical qubit induced by energy relaxation. This scheme encodes the logical qubit as a multi-component superposition of coherent states in a harmonic oscillator. The error correction is performed by transferring the entropy to an ancila qubit and resetting the qubit. We layout in detail how to implement these operations in a practical system [78]. This proposal directly addresses the task of building a hardware-efficient and technically realizable quantum memory [78].

We have also studied the application of dissipation engineering techniques to perform a high-performance and fast qubit reset. Qubit rest is crucial at the start of and during quantum information algorithms. Our protocol, nicknamed DDROP (Double Drive Reset of Population) is experimentally tested on a superconducting transmon qubit and achieves a ground state preparation of at least 99.5% in times less than $3\mu s$; faster and higher fidelity are predicted upon parameter optimization [74]. We are currently working on extending our protocol to prepare and protect two-qubit entangled states and to perform autonomous quantum error correction.

5.4. Modeling, observation and control in biosciences - Reproductive system

5.4.1. *Numerical simulation of the selection process of the ovarian follicles*
Participants: Benjamin Aymard, Frédérique Clément.

Collaboration with Frédéric Coquel and Marie Postel.
Implementation of a parallelized numerical scheme based on finite volumes. We have designed and implemented a numerical method to simulate a multiscale model describing the selection process in ovarian follicles [11], [10]. The PDE model consists in a quasi-linear hyperbolic system of large size, namely $N_f \times N_f$, ruling the time evolution of the cell density functions of N_f follicles (in practice N_f is of the order of a few to twenty). These equations are weakly coupled through the sum of the first order moments of the density functions. The time-dependent equations make use of two structuring variables, age and maturity, which play the roles of space variables. The problem is naturally set over a compact domain of $\mathbf{R}^2$. The formulation of the time-dependent controlled transport coefficients accounts for available biological knowledge on follicular cell kinetics. We introduce a dedicated numerical scheme that is amenable to parallelization, by taking advantage of the weak coupling. Numerical illustrations assess the relevance of the proposed method both in term of accuracy and HPC achievements [32].
A numerical method for cell dynamics: kinetic equations with discontinuous coefficients. The motivation of this work is the numerical treatment of the mitosis in biological models involving cell dynamics. More generally we study hyperbolic PDEs with flux transmission conditions at interfaces between subdomains where coefficients are discontinuous. A dedicated finite volume scheme with a limited high order enhancement is adapted to treat the discontinuities arising at interfaces. The validation of the method is done on 1D and 2D toy problems for which exact solutions are available, allowing us to do a thorough convergence study. A simulation on the original biological model illustrates the full potentialities of the scheme [72].

5.4.2. *Optimal control of cell mass and maturity in a model of follicular ovulation*
Participants: Frédérique Clément, Peipei Shang.

Collaboration with Jean-Michel Coron
We have studied some optimal control problems associated with a scalar hyperbolic conservation law modeling the development of ovarian follicles. Changes in the age and maturity of follicular cells are described by a 2D conservation law, where the control terms act on the velocities. The control problem consists in optimizing the follicular cell resources so that the follicular maturity reaches a maximal value in fixed time. Formulating the optimal control problem within a hybrid framework, we have proved necessary optimality conditions in the form of Hybrid Maximum Principle [36]. We have then derived the optimal strategy and shown that there exists at least one optimal bang-bang control with one single switching time.

5.4.3. *Multiscale analysis of mixed-mode oscillations in a phantom bursting model*

Participants: Frédérique Clément, Mathieu Desroches, Maciej Krupa, Alexandre Vidal.

We have studied mixed mode oscillations in a model of secretion of GnRH (gonadotropin releasing hormone). The model is a phantom burster consisting of two feedforward coupled FitzHugh-Nagumo systems, with three time scales. The forcing system (Regulator) evolves on the slowest scale and acts by moving the slow null-cline of the forced system (Secretor). There are three modes of dynamics: pulsatility (transient relaxation oscillation), surge (quasi steady state) and small oscillations related to the passage of the slow null-cline through a fold point of the fast null-cline. We have derived a variety of reductions, taking advantage of the mentioned features of the system. We have obtained two results; one on the local dynamics near the fold in the parameter regime corresponding to the presence of small oscillations and the other on the global dynamics, more specifically on the existence of an attracting limit cycle. Our local result is a rigorous characterization of small canards and sectors of rotation in the case of folded node with an additional time scale, a feature allowing for a clear geometric argument. The global result gives the existence of an attracting unique limit cycle, which, in some parameter regimes, remains attracting and unique even during passages through a canard explosion [43].

5.4.4. *A network model of the periodic synchronization process in the dynamics of calcium concentration in GnRH neurons*

Participants: Frédérique Clément, Maciej Krupa, Alexandre Vidal.

Mathematical neuroendocrinology is a branch of mathematical neurosciences that is specifically interested in endocrine neurons, which have the uncommon ability of secreting neurohormones into the blood. One of the most striking features of neuroendocrine networks is their ability to exhibit very slow rhythms of neurosecretion, on the order of one or several hours. A prototypical instance is that of the pulsatile secretion pattern of GnRH (gonadotropin releasing hormone), the master hormone controlling the reproductive function, whose origin remains a puzzle issue since its discovery in the seventies. We have investigated the question of GnRH neuron synchronization on a mesoscopic scale and study how synchronized events in calcium dynamics can arise from the average electric activity of individual neurons. We have used as reference seminal experiments performed on embryonic GnRH neurons from rhesus monkeys, where calcium imaging series were recorded simultaneously in tens of neurons, and which have clearly shown the occurrence of synchronized calcium peaks associated with GnRH pulses, superposed on asynchronous, yet oscillatory individual background dynamics [100]. We have designed a network model by coupling 3D individual dynamics of FitzHugh-Nagumo type. Using phase-plane analysis, we have constrained the model behavior so that it meets qualitative and quantitative specifications derived from the experiments, including the precise control of the frequency of the synchronization episodes. In particular, we have shown how the time scales of the model can be tuned to fit the individual and synchronized time scales of the experiments. Finally, we have illustrated the ability of the model to reproduce additional experimental observations, such as partial recruitment of cells within the synchronization process or the occurrence of doublets of synchronization [76].

5.5. Clinical and physiological applications

5.5.1. *DynPeak: An algorithm for pulse detection and frequency analysis in hormonal time series*

Participants: Frédérique Clément, Claire Médigue, Alexandre Vidal, Qinghua Zhang.

Collaboration with Stéphane Fabre (UMR CNRS-INRA 6175).

The endocrine control of the reproductive function is often studied from the analysis of luteinizing hormone (LH) pulsatile secretion by the pituitary gland. Whereas measurements in the cavernous sinus cumulate anatomical and technical difficulties, LH levels can be easily assessed from jugular blood. However, plasma levels result from a convolution process due to clearance effects when LH enters the general circulation. Simultaneous measurements comparing LH levels in the cavernous sinus and jugular blood have revealed clear differences in the pulse shape, the amplitude and the baseline. Besides, experimental sampling occurs at a relatively low frequency (typically every 10 min) with respect to LH highest frequency release (one pulse per hour) and the resulting LH measurements are noised by both experimental and assay errors. As a result, the pattern of plasma LH may be not so clearly pulsatile. Yet, reliable information on the InterPulse Intervals (IPI) is a prerequisite to study precisely the steroid feedback exerted on the pituitary level. Hence, there is a real need for robust IPI detection algorithms. We have designed an algorithm for the monitoring of LH pulse frequency, basing ourselves both on the available endocrinological knowledge on LH pulse (shape and duration with respect to the frequency regime) and synthetic LH data generated by a simple model [54]. We make use of synthetic data to make clear some basic notions underlying our algorithmic choices. We focus on explaining how the process of sampling affects drastically the original pattern of secretion, and especially the amplitude of the detectable pulses. We then describe the algorithm in details and perform it on different sets of both synthetic and experimental LH time series. We further comment on how to diagnose possible outliers from the series of IPIs which is the main output of the algorithm.

6. Bilateral Contracts and Grants with Industry

6.1. Renault contract: Modeling, Control, Monitoring and Diagnosis of Depollution Systems

Participants: Pierre-Alexandre Bliman, David Marie-Luce, Michel Sorine.

This work is done in cooperation with Renault in the framework of a CIFRE contract. The issue of depollution has become a central preoccupation for the automotive industry, and the increased severity of the emission norms necessitates tight modeling and control solutions. We have worked on simple models for two devices, namely the NOx-trap and the SCR (Selective catalytic reduction). Observers have been obtained and tested against real-world data. See [16].

Based on the later, a control law has been obtained this year, for the control of the NOx-trap. This control law is defined by setting thresholds for the estimated NOx coverage fraction, to switch between storage mode and purge mode. These thresholds are optimal in stationary conditions, in the sense that they minimize the gas consumption under given pollutant emission constraint. Adequate moving window is fitted to define the switching values in non-stationary conditions. The algorithm has led to successful numerical tests.

6.2. CARMAT SAS contract: Modeling and control of a Total Artificial Heart

Participants: Julien Bernard, Michel Sorine.

This is a cooperation with CARMAT SAS (Suresnes, France) on the development of a Total Artificial Heart.

This fully implantable artificial heart is designed to replace the two ventricles, possibly as an alternative to heart transplant from donors. In a first time, it will be used as a end-of-life treatment for patients waiting for a transplant. The first patients may receive this artificial organ in less than three years.

Compared with the mechanical hearts used up today, that are mainly LVAD (left ventricular assist devices) or with its main concurrent, the Abiocor implantable replacement heart system (Abiomed), the present artificial heart is designed to be highly reliable and with a low thromboembolism rate. It will allow longer waiting periods for heart transplants and even, in a next future, may be an alternative to these transplants.

The prosthesis uses two controlled pumps that are not in direct contact with the blood, eliminating hemolysis risk and is equipped with miniature sensors in order to have a full control of the heart rate and arterial blood pressure. Our objective is to improve the control strategies by mimicking the physiological feedback loops (Starling effect, baroreflex loop, ...) to allowing patients to live as normally as possible. In a first step, this year we have modeled the prosthesis with its present controller and its testbed, a "mock circulation system" (MCS). This year we have tried some control algorithms with the MCS.

6.3. LK2 contract: TIght glycemic control for Intensive Care Units

Participants: Alexandre Guerrini, Michel Sorine.

This work on tight glycaemic control (TGC) for ICU started in Septembrer 2008 in the framework of the CIFRE contract of Alexandre Guerrini with the small medtech company LK2 (Tours, France). It is in collaboration with the Intensive Care Unit (ICU) of Chartres Hospital headed by Dr Pierre Kalfon. For the medical context of this study, see [90].

Blood glucose has become a key biological parameter in critical care since publication of the study conducted by van den Berghe and colleagues [104], who demonstrated decreased mortality in surgical intensive care patients in association with TGC, based on intensive insulin therapy. However, two negative studies were recently reported, which were interrupted early because of high rates of severe hypoglycaemia, namely the VISEP study [85] and the Glucontrol trial.

After having studied a possible origin of the failure of the recent study NICE-SUGAR, we have worked on more robust control algorithms based on a database of representative "virtual patients" [87].

In this study, we have developed efficient monitoring and control tools, now marketed by LK2 that will help clinicians and nursing staff to control blood glucose levels in ICU patients, in particular to avoid hyperglycaemia superior to 10 mmol/l and hypoglycaemia episodes. Our first controller has been assessed in the study CGAO-REA (see 4.3) with more than 3500 included patients. The controller determines the insulin infusion rate on the basis of the standard available glycaemia measurements despite their irregular sampling rate.

7. Partnerships and Cooperations

7.1. Regional Initiatives

7.1.1. *Paris Region ASTech project MODIPRO: Modeling for diagnosis and prognosis*
Participants: Abdouramane Moussa Ali, Qinghua Zhang.

In order to improve the safety and reliability of airplanes, the MODIPRO project (Modélisation pour le Diagnostic et le Pronostic) funded by the Pôle de Compétitivité Aérospatial ASTech of Paris Region from 2009 to 2012 aims at developing a software for deriving airplane functional models for the purpose of fault diagnosis and prognosis, by analyzing the flight data of a fleet of airplanes. The involved partners are Dassault Aviation (project leader), Snecma, IT4Control, Bayesia, KBS, UPMC, Supelec and Inria.

7.2. National Initiatives

7.2.1. *ANR project DMASC: Scaling Invariance of Cardiac Signals, Dynamical Systems and Multifractal Analysis*
Participants: Julien Barral, Claire Médigue, Michel Sorine.

Collaboration with Denis Chemla (Kremlin-Bicêtre Hospital), Paulo Gonçalves (Inria Rhônes-Alpes) and Stéphane Seuret (Paris 12 University).

The ANR project DMASC (Program SYSCOMM 2008) started in January 2009 under the coordination of J. Barral.

Numerical studies using ideas from statistical physics, large deviations theory and functions analysis have exhibited striking scaling invariance properties for human long-term R-R interval signals extracted from ECG (intervals between two consecutive heartbeats). These numerical studies reveal that the scaling invariance may have different forms depending upon the states of the patients in particular for certain cardiac diseases. These observations suggest that a good understanding of multifractal properties of cardiac signals might lead to new pertinent tools for diagnosis and surveillance. However, until now, neither satisfactory physiological interpretations of these properties nor mathematical models have been proposed for these signals. For medical applications we need to go beyond the previously mentioned works and achieve a deepened study of the scaling invariance structure of cardiac signals. This is the aim of DMASC.

New robust algorithms for the multifractal signals processing are required ; specifically, it seems relevant to complete the usual statistical approach with a geometric study of the scaling invariance. In addition, it is necessary to apply these tools to a number of data arising from distinct pathologies, in order to start a classification of the different features of the observed scaling invariance, and to relate them to physiology. This should contribute to develop a new flexible multifractal mathematical model whose parameters could be adjusted according to the observed pathology. This multifractal analysis can be applied to another fundamental signal, the arterial blood pressure, as well as to the couple (R-R, Blood Pressure). The main results of this project can be found in [15].

7.2.2. *ANR project EBONSI: Extended Block-Oriented Nonlinear System Identification*
Participants: Pierre-Alexandre Bliman, Michel Sorine, Qinghua Zhang.

The main idea of block-oriented nonlinear system identification is to model a complex system with interconnected simple blocks. Such models can cover a large number of industrial applications, and are yet simple enough for theoretic studies. The objectives of the EBONSI project are to extend classical block-oriented nonlinear models to new model structures motivated by industrial applications, and to relax some traditional restrictions on experimental conditions. This is an international project jointly funded by the French Agence Nationale de la Recherche (ANR) and the Chinese National Natural Science Foundation (NSFC) from 2011 to 2014. The project partners are the SISYPHE project-team of Inria (project leader), the Centre de Recherche en Automatique de Nancy (CRAN), and the Laboratory of Industrial Process Monitoring and Optimization of Peking University.

7.2.3. *ANR project 0-DEFECT: On-board fault diagnosis for wired networks in automotive systems*
Participants: Mohamed Oumri, Michel Sorine, Qinghua Zhang.

The number of electric and electronic equipments is increasing rapidly in automotive vehicles. Consequently, the reliability of electric connections is becoming more and more important. The project entitled "Outil de diagnostic embarqué de faisseaux automobiles" (0-DEFECT) aims at developing tools for on-bord diagnosis of failures in electric wire connections in automotive systems. This project is funded by Agence Nationale de la Recherche (ANR) from 2009 to 2012. The involved partners are CEA LIST (project leader), Renault Trucks, Freescale, PSA, Delphi, Supelec LGEP and Inria.

7.2.4. *ANR project INSCAN: Fault diagnosis for security critical long distance electric transmission lines*
Participants: Leila Djaziri, Michel Sorine, Qinghua Zhang.

The wired electric networks of the French railway system cover more than 50000 km. The electric insulation of the signaling lines along the railways is monitored by regular inspections. Today these inspections are based on an expensive procedure realized by human operators located at both ends of each section of a transmission line. The service of signaling devices has to be interrupted during this procedure, and so does the railway traffic. The in situ monitoring of the transmission lines, without interruption of service, is thus an important economic issue. For this purpose, the project entitled "Diagnostic de câbles électriques sécuritaires pour grandes infrastructures" is funded by ANR from 2009 to 2012 in order to study the feasibility of in situ monitoring tools for these transmission lines. The involved partners are SNCF (project leader), CEA LIST and Inria.

7.2.5. *ANR project SODDA: Soft Defects Diagnosis in wired networks*

The need for detection, localization and characterization of defects in a cables network has led to several projects, funded by the ANR: SEEDS followed by 0-DEFECT in the automotive domain, INSCAN for cables along railways. These co-operative works made it possible to provide the foundations of diagnosis methods for cables – with a proof of feasibility in the case of hard defects (short-circuit, open circuit) - and some theoretical results on the associated inverse problems in the case of soft faults. They also made it possible to identify their limits. One of the principal limits of these methods, based on the principles of reflectometry, is the difficulty of detecting soft defects. If it was possible to detect and locate precisely these defects, that would help for preventive maintenance or prognosis. The objective of the SODDA project is to study the signatures of the soft defects, by combining theory and experiment, and to design and test innovative methods adapted to these signatures which are very difficult to detect. The project will be run by an academic consortium, in close connection with an industrial board, responsible for keeping the work in realistic and relevant use cases. The Inria teams involved are POEMS and Sisyphe.

7.2.6. *ANR project EPOQ2: Estimation PrOblems for Quantum & Quantumlike systems*

Participants: Hadis Amini, Zaki Leghtas, Mazyar Mirrahimi, Pierre Rouchon, Michel Sorine.

The project EPOQ2 is an ANR "Young researcher" project led by Mazyar Mirrahimi (Sisyphe). It has for goal to address a class of inverse problems rising from either the emerging application domain of "quantum engineering" or from some classical applications where a natural quantization lead to quantum-like systems, as it is the case in particular for inverse scattering for transmission lines. This research is in collaboration with the Pierre Aigrain laboratory (LPA) at ENS Paris and the Quantronics Laboratory (Qlab) of Michel Devoret and the Rob Schoelkopf Lab at Yale University and Pierre Rouchon from Ecole Nationale Supérieure des Mines de Paris.

7.2.7. *Inria Large Scale Initiative Action REGATE*

REGATE (REgulation of the GonAdoTropE axis) is a 4-year Large Scale Initiative Action funded by Inria in May 2009 dedicated to the modeling, simulation and control of the gonadotrope axis.

The action is coordinated by Frédérique Clément. The Inria participants to this action are researchers of 2 Inria research teams, Contraintes and Sisyphe. There are also participants from INRA, Université Libre de Bruxelles (Unité de Chronobiologie théorique) and Université Paris 6 (Laboratoire Jacques-Louis Lions).

7.3. European Initiatives

7.3.1. *Collaborations in European Programs, except FP7*

7.3.1.1. *ERNSI*

The SISYPHE project-team is involved in the activities of the European Research Network on System Identification (ERNSI) federating major European research teams on system identification.

- Program: Funded as a SCIENCE project (1992 - 1995), HCM Project (1993-1996), TMR Project (1998 - 2003).
- Project acronym: ERNSI

- Project title: European Research Network System Identification
- Duration: 1992 —
- Coordinator: The network ERNSI is currently coordinated by Bo Wahlberg, Automatic Control, KTH SE 100 44 Stockholm, Sweden.
- Other partners: KTH (Sweden), Inria (France), TUD (Technische Universität Darmstadt), TUW (Vienna University of Technology), UCAM-DENG (University of Cambridge), ELEC (Vrije Universiteit Brussel), ULIN (Sweden), UNIPD (Italy).
- Abstract: Modeling of dynamical systems is fundamental in almost all disciplines of science and engineering, ranging from life science to process control. Engineering uses models for the design and analysis of complex technical systems. System identification concerns the construction, estimation and validation of mathematical models of dynamical physical or engineering phenomena from experimental data.

7.3.1.2. MODRIO

Participants: Abdouramane Moussa Ali, Qinghua Zhang.

The SISYPHE project-team, with two other Inria project-teams (PARKAS, S4) participates in the MODRIO project regrouping partners from 7 european countries.

- Program: ITEA 2.
- Project acronym: MODRIO.
- Project title: Model Driven Physical Systems Operation.
- Duration: 2012 – 2015
- Coordinator: Daniel Bouskela, EDF, France.
- Other partners: ABB (Sweden AB), ABB AG (Germany), AIT Austrian Institute Of Technology (Austria), Ampère Laboratory-CNRS-University of Lyon (France), Bielefeld University of Applied Sciences (Germany), Dassault Aviation (France), Deutsches Zentrum für Luft- und Raumfahrt (DLR) (Germany), Digital Product Simulation (DPS) (France), DS AB (Sweden), EADS (France), Enicon Eco-Energy-Consulting GmbH (Austria), Equa Simulation AB (Sweden), IFP Energies nouvelles (France), Ilmenau University of Technology (Germany), Inria (France), ITI (Germany), Katholieke Universiteit Leuven (Belgium), Knorr-Bremse (Germany), Linkping University (Sweden), LMS Imagine (France), LMS International (Belgium), MathCore Engineering AB (Sweden), Modelon AB (Sweden), Pöyry Finland Oy (Finland), Qtronic (Germany), Scania (Sweden), Semantum Oy (Finland), Sherpa Engineering (France), Siemens AG (Germany), Siemens Industrial Turbomachinery AB Industrial Turbomachinery A.B. (Sweden), Simpack AG (Germany), Supmeca (France), Triphase (Belgium), University of Calabria (Italy), Vattenfall (Sweden), VTT Technical Research Centre of Finland Tec (Finland), Wapice Ltd (Finland).
- Abstract: To meet the evermore stringent safety and environmental regulations for power plants and transportation vehicles, system operators need new techniques to improve system diagnosis and operation. Open standards are necessary for different teams to cooperate by sharing compatible information and data. The objective of the MODRIO project is to extend modeling and simulation tools based on open standards from system design to system diagnosis and operation. This project joined by partners from Austria, Belgium, Finland, France, Germany, Italy and Sweden has been selected by the board of Information Technology for European Advancement (ITEA 2). The involved Inria project-teams are PARKAS, S4 and SISYPHE.

7.4. International Initiatives

7.4.1. Inria International Partners

Mazyar Mirrahimi closely collaborates with the Quantronics Laboratory (Qlab) of Michel Devoret and the Rob Schoelkopf Lab at Yale University.

7.5. International Research Visitors

7.5.1. Visits of International Scientists

7.5.1.1. Internships

Patrick FLETCHER (two months: February and July 2012)

Subject: Regulation of hormone production by the frequency of a periodic stimulating signal

Institution: Florida State University (United States)

7.5.2. Visits to International Teams

Mazyar Mirrahimi spent one year in the Quantronics Laboratory (Qlab) of Michel Devoret and the Rob Schoelkopf Lab at Yale University.

Qingua Zhang visited the Laboratory of Industrial Process Monitoring and Optimization of Peking University, in the framework of the ANR EBONSI project.

8. Dissemination

8.1. Scientific Animation

P.A. Bliman:

- Scientist in charge of latin America at Department of International Affairs, Inria.
- Associate Editor of Systems & Control Letters.
- Chargé de mission in the Ministry of research.

F. Clément:

- Scientific head of the Large Scale Initiative Action REGATE (REgulation of the GonAdoTropE axis).
- Appointed member of the scientific board of the BCDE (Cell Biology, Development and Evolution) ITMO (Multi OrganizationThematic Institute) of the French National Alliance for Life and Health Sciences http://www.aviesan.fr/en.

Participations in examination boards:

- INRA Experienced Research Scientist open competitions for non-assigned positions (admissibility phase).
- INRA Research Director open competitions (admissibility and admission phases).
- Inria Research Director open competitions (admission).

M. Desroches:

- Section Chief Editor of the Media Gallery of the dynamical systems website http://www.dynamicalsystems.org (hosted by the Society for Applied and Industrial Mathematics (SIAM)).
- Co-organizer, together with Martin Krupa and Alexandre Vidal, of a special session titled "Multiple Time Scale Dynamics With a View Towards Biological Applications" at the 9th AIMS Conference on Dynamical Systems, Differential Equations and Applications, 1-5 July 2012, Orlando, USA.

M. Mirrahimi:

- Associate Editor of Systems & Control Letters.
- Member of IFAC Technical Committee on Distributed Parameter Systems.
- Co-organizer together with Matt R. James, Australian National University, of two invited sessions on Quantum Control at the 48th IEEE Conference on Decision and Control.

M. Sorine:

- Member of IFAC Technical Committee on the Biological and Medical Systems (IFAC TC 8.2).
- Member of the Program Committee of FHIES 2012, the "Second International Symposium on Foundations of Health Information Engineering and Systems".
- Member of the Program Committee of the 8th IFAC Symposium on Biological and Medical Systems, Budapest, Hungary / 29–31 August, 2012.

- Member of the scientific board of the ITMO Circulation, Metabolism and Nutrition (Multi Organization Thematic Institute of the French National Alliance for Life and Health Sciences).
- Member of the steering committee of the clinical study CGAO-REA.

Q. Zhang:
- Member of IFAC Technical Committee on Fault Detection, Supervision and Safety of Technical Processes.
- Member of IFAC Technical Committee on Modelling, Identification and Signal Processing.
- Member of the International Program Committee of the 16th IFAC Symposium on System Identification.

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

Master: F. Clément, "Modelling and control of biological systems" course, 2,5 ECTS, part of the "Master's Degree in BioInformatics and BioStatistics" (Paris-Sud 11 University, in collaboration with Béatrice Laroche) http://www.bibs.u-psud.fr/

Master : M. Desroches, "Introduction to ODEs and PDEs, 20 heures, M1, University of Bristol, UK.

Master: M. Desroches, mini-course on "Numerical simulation of ODEs and numerical bifurcations analysis", 6 hours, Université Pierre et Marie Curie, Station Biologique de Roscoff, July 2012.

Master: M. Sorine, "The cardiovascular system and its short-term control - Modelling and signal analysis", 3 ECTS. BioMedical Engineering - Master's Degree Program, Paris-Descartes University and the Paris Institute of Technology (ParisTech) http://www.bme-paris.com/en/article/46.

8.2.2. Supervision

PhD : Najmeddine Attia, "Comportement asymptotique de marches aléatoires de branchement dans $\mathbb{R}^d$ et dimension de Hausdorff", Paris 13 University, December, 20. Advisor: J. Barral.

PhD: Hadis Amini, "Stabilisation des systèmes quantiques à temps discrets et stabilité des filtres quantiques à temps continus", Ecole Nationale Superieure Des Mines de Paris, September, 27. Advisors: M. Mirrahimi, P. Rouchon.

PhD: Zaki Leghtas, "Préparation et stabilisation de systèmes quantiques", Ecole Nationale Superieure Des Mines de Paris, September, 27. Advisors: M. Mirrahimi, P. Rouchon.

PhD : Mohamad Safa, "Modélisation réduite de la pile à combustible en vue de la surveillance et du diagnostic par spectroscopie d'impédance", Paris-Sud 11 University, October 24. Advisors: P.-A. Bliman, M. Sorine.

PhD : Peipei Shang, "Analyse mathématique et contrôle optimal de lois de conservation multi-échelles: application à des populations cellulaires structurées", UPMC (Université Pierre et Marie Curie), July, 5. Advisors: F. Clément, J.-M. Coron.

8.2.3. Juries

P.-A. Bliman: member of the PhD committee of Samuel Martin, Grenoble University, Novembre 28.
M. Desroches: member of a PhD committee at the University of Sevilla (Spain) on the 19 December 2012.
M. Sorine: member of the following committees:
- PhD committee of Delphine Bresch-Pietri, Ecole Nationale Supérieure des Mines de Paris, December 17.
- HdR committee of Denis Efimov, Lille 1 University, November 28.
- PhD committee of Mohamad Safa, Paris-Sud 11 University, October 24.

9. Bibliography

Major publications by the team in recent years

[1] H. AMINI, M. MIRRAHIMI, P. ROUCHON. *Stabilization of a Delayed Quantum System: The Photon Box Case-Study*, in "IEEE Transactions on Automatic Control", 2012, vol. 57, n° 8, p. 1918 - 1930 [*DOI :* 10.1109/TAC.2012.2195853], http://hal.inria.fr/hal-00755188.

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[3] D. CHAPELLE, P. LE TALLEC, P. MOIREAU, M. SORINE. *Energy-preserving muscle tissue model: formulation and compatible discretizations*, in "International Journal for Multiscale Computational Engineering", 2012, vol. 10, n° 2, p. 189–211, http://hal.inria.fr/hal-00678772.

[4] F. CLÉMENT, A. VIDAL. *Foliation-based parameter tuning in a model of the GnRH pulse and surge generator*, in "SIAM Journal on Applied Dynamical Systems", 2009, vol. 8, n° 4, p. 1591–1631, http://hal.archives-ouvertes.fr/inria-00319866.

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Publications of the year

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[25] N. ATTIA. *Comportement asymptotique de marches aléatoires de branchement dans $\mathbb{R}^d$ et dimension de Hausdorff*, Paris 13 University, December, 20 2012.

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