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INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team SISYPHE

SIgnals and SYstems in PHysiology and Engineering

Paris - Rocquencourt

THEME BIO

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2. Overall Objectives

2.1. Overall Objectives

Keywords: *biology*, *cardiovascular system*, *combustion engine*, *complex dynamical systems*, *control*, *energy conversion systems*, *fuel cell*, *health*, *modeling*, *multiscale systems*, *observation*, *ovulation control*, *physiological systems*, *physiology*, *process engineering*.

This Research-Team is a follow-up of SOSSO2 Research-Team.

SISYPHE is dealing with questions raised by some complex dynamical systems issued from Physiology and Engineering: modeling; identification and observation from signals; control. We consider multiscale or networked dynamical systems involving exchanges of energy or control information among scales and subsystems. Most studies are motivated by the cardiovascular and reproductive systems or by some energy conversion systems for low-emission vehicles. We consider systems and associated signals together, as coupling models and measured data is necessary for monitoring or real-time control. Some clinical or engineering applications are studied within academic or industrial collaborations. The research on the cardiovascular system is done, in part, in the framework of Cardiosense3D (an Inria Large Initiative Action focusing on clinical applications of electro-mechanical models of the heart, and involving academic, clinical and industrial partners. See http://www-sop.inria.fr/CardioSense3D).

The research topics are:
Signals & Systems. We study some modeling, observation, identification and control techniques in collaboration with colleagues from various places in the World:

- Reduced order modeling, observation and control of isolated cells or multi-cell systems (ovarian follicles, cardiac cells, fuel-cell stacks ...). Cells are represented by differential models. [Collaborations with Paris 6 University, Georgia Tech (Dynamics and control systems laboratory), Linkoping University (Sweden)].
- Analysis of some phenomena in networks of dynamical systems: excitability and traveling waves; scattering of waves & inverse scattering, synchronization of sub-systems. [Collaborations with University of Firenze, Unicamp (Campinas, Brazil), UVSQ].
- Modeling, identification and control of some systems modeled by partial differential equations (quantum systems, reaction-diffusion systems). [Collaborations with Paris 6 University, UVSQ, Ecole des Mines de Paris (Systems and Control Centre), CNRS-LAAS (Toulouse), Caltech (MURI Center for Quantum Networks), Weierstrass Institute for Applied Analysis and Stochastics].
- Analysis of multiscale properties of signals and relations with the underlying dynamical systems. [Collaborations with Tsinghua University (Beijing), Monastir University (Tunisia)].

Physiology and Engineering. The above techniques are developed and applied within long-term projects and collaborations:

- Model-based observation of the cardiovascular system and its short-term control & signal processing of the arterial pressure and ECG. [Collaborations with A. Béclère Hospital (Clamart), Kremlin-Bicêtre Hospital, Inserm unit 902, CardioSense3D].
- Multiscale modeling of the controlled follicle selection process (ovulation control) & Control of the reproductive axis. [Collaborations with INRA (Tours)].
- Analysis of traveling pulses in networks (cabled electrical transmission networks) and application to diagnosis. [Collaborations with CEA-LIST (Saclay), Supelec-LGEP (Gif-sur-Yvette)].
- Multiscale modeling, monitoring and control of fuel-cell systems. [Collaborations with EDF, CEA-LIST, Fuel Cell Lab (Belfort), Helion].
- Multiscale reduced-order modeling and control of auto-ignition in internal combustion engines. [Collaboration with Renault].

3. Scientific Foundations

3.1. Modeling, observation and control of nonlinear systems & Isolated cells

Keywords: *GnRH neurons*, *Modeling*, *cardiac cell*, *control*, *nonlinear systems*, *observation*, *pacemaker cell*.

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 are common aspects of many research fields. For dynamical systems encountered in the domains of engineering, such investigations are often of practical importance for prediction, control and decision making. For such purposes, a dynamical system can be generally formulated in the form of

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

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 $v(t)$. The derivation of such equations, referred to as 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 [124], whereas algorithms for tracking the state trajectory $x(t)$ are called observers [114]. 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 still remain challenging because of strong nonlinearities, despite recent progress on nonlinear systems [29], [96]. Though linear systems have been extensively studied for these purposes, it is not the case for nonlinear systems. Concerning control, robustness is an important issue, in particular to ensure various properties to all dynamical systems in some sets defined by uncertainties. We intend to achieve some works attached to parametric uncertainties [7], [8]. The particularities of ensembles of connected dynamical systems, as introduced in Section 2.1, raise new challenging problems. Our studies on these topics have been motivated by applications related to control and fault diagnosis of engineering and biomedical systems.

3.1.2. Reduced order modeling of controlled energy-conversion cells

We look for thermodynamically consistent reduced order models for the cardiac cells, fuel cells and combustion cells in order to model the multiscale systems we want to study. These cells are controlled by smooth controls of their “basal metabolism” (set points) or by excitations provoking bifurcations in the excitable cardiac cells (and then oscillations or traveling waves) or faults in the case of fuel cells.

Reduced order modeling of cardiac ventricular cells for signal & image processing applications.
Models of the electro-mechanical activity of the cardiac muscle are very useful at the scale of the cardiovascular system as well as at the organ scale. In this later case, they are used for computing stress, strain and action potential fields from 3D image processing. We have obtained a chemically-controlled constitutive law of cardiac myofibre mechanics aimed at being embedded into 0D or 3D models [6]. This law results from a model of the collective behavior of actin-myosin molecular motors converting chemical into mechanical energy. It is thermodynamically consistent and the resulting dynamics of sarcomeres is consistent with the “sliding filament hypothesis” of A. F. Huxley. This model is now currently used [137].
A next step will be to continue revisiting the ionic-currents models of cells representing membrane phenomena and calcium dynamics in order to reduce them for signal or image processing applications [109], [110], [111]. An objective here, is to obtain invertible (depending upon available measurements) thermodynamically consistent models (the various ATP consumption have to be taken into account). This will allow in particular a better connection with the perfusion models developed in CardioSense3D.

We will first consider the standard hypothesis of an excitation-contraction coupling without mechano-electrical feedback (it is an hypothesis of many studies and in particular today, of CardioSense3D): the electrical phenomena are driving the mechanical behavior. The model has the particular structure of an unidirectional coupling (or drive - response coupling):

$$\begin{aligned}
\frac{dv}{dt} &= f_V(v, u, u_{ext}, \theta_e, w_e) && \text{Membrane dynamics and excitation mechanism (CICR)}\\
\frac{du}{dt} &= f_U(v, u, \theta_e, w_e) && \text{Intracellular calcium dynamics}\\
\frac{dx}{dt} &= f_M(x, u, \theta_m, w_m) && \text{Contractility and motion dynamics}\\
y &= g(x, v, \theta_e, \theta_m, v(t)) && \text{Measured output (e.g. membrane potential, stress)}
\end{aligned} \tag{2}$$

The two first ODE (2) are the electrical model of the cell, where v is the vector of “membrane variables” (membrane potential, calcium, sodium, potassium concentrations, gate variables), u is the vector of intracellular calcium concentrations and u_{ext} is an external stimulation input. This is a structurally unstable model: it is excitable, meaning that it may undergo bifurcations under the effect of the external input u_{ext} (master-slave mode at the origin of the propagation of the action potential for ventricular cells) or of values of the parameter θ_e (making a limit cycle to appear or disappear for pacemaker cells). The mechanical state variables x are typically (at least in our model [6]) - for the constitutive law: a controlled stiffness and an internal variable of deformation - for the equation of motion: a deformation and a deformation velocity. Even for this seemingly simple model, it is already interesting to study how to observe or control the many possible behaviors of this system.

We will then consider a “fueled cardiac cell” model taking into account oxygen supply and the main demand in energy of the motors, pumps and exchangers. Some new state variables and input are necessary (vector w and p_{O2}) . In that case the output may contain information on the V_{O2} drop. This kind of model will be useful for CardioSense3D. In that case there is a bidirectional coupling that may render the previous analysis more complex.

$$\begin{aligned}
\frac{dw}{dt} &= f_W(w, x, p_{O2}, \theta_w, w_o) && \text{Chemical energy conversion (cell metabolism)}\\
\frac{dv}{dt} &= f_V(v, u, w, u_{ext}, \theta_e, w_e) && \text{Membrane dynamics and excitation mechanism (CICR)}\\
\frac{du}{dt} &= f_U(v, u, w, \theta_e, w_e) && \text{Intracellular calcium dynamics}\\
\frac{dx}{dt} &= f_M(x, u, w, \theta_m, w_m) && \text{End energy production (contractility and motion dynamics)}\\
y &= g(x, v, w, \theta_e, \theta_m, v(t)) && \text{Measured output (e.g. membrane potential, stress)}
\end{aligned} \tag{3}$$

Reduced order modeling of PEMFC for control and diagnosis applications.
A PEMFC model has been developed in collaboration with Renault (RESPIRE project) [15]. The model will be extended to take into account the damages caused by dryness of the membrane. It will serve as a basis for the diagnosis studies in the framework of the DIAPASON project (see section 6.2.2). Its structure is similar to (2) when only CO poisoning is considered and to (3) when considering both CO poisoning and membrane humidity are modeled.

3.1.3. Reduced order modeling of “controller” cells: cardiac pacemaker cells & GnRH neurons

These two situations are very similar from the mathematical viewpoint. Perturbation techniques and bifurcation analysis are combined to study models like (2).

Cardiac pacemaker cells and their control.
Bifurcation analysis is used to compare the structures of pacemaker models and validate some reduced order models. Such a pacemaker model has been proposed [110] and is studied to obtain insights into the mechanisms of control of the sinoatrial node pacemaker activity [66]. This will improve the present 0D model of the control of the heart by the SNA. The objective is to improve the understanding of cardiac arrhythmias caused by abnormal automaticity.

Excitable neuronal networks & control of the reproductive axis by the GnRH.
The reproductive axis is under the control of the GnRH (Gonadotropin Releasing Hormone), which is secreted from specific hypothalamic areas in a pulsatile manner. This pulsatility has a fundamental role in the differential control of the secretion of both gonadotropins: LH (Luteinizing Hormone) and FSH (Follicle Stimulating Hormone). In females, the pulsatile pattern is tremendously altered once per ovarian cycle into a surge which triggers ovulation in response to increasing levels of estradiol. The estradiol signal is conveyed to GnRH neurons through a network of interneurons. The balance between stimulatory and inhibitory signals emanating from interneurons controls the behavior of the GnRH network.
Formally, the GnRH neuron and interneuron networks can be considered as coupled excitable ODE systems with different time scales. 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 [44].

3.2. Observation and control of networks of dynamical systems & Multi-cell systems

Keywords: *Networks of dynamical systems*, *Partial Differential Equations*, *synchrony*, *traveling waves*.

The real-life systems considered have some structural similarity leading to model some of their sub-systems as networks of dynamical systems. They also all share a common practical constraint: in typical applications, the available sensors collecting information are limited to the macroscopic scale. For example, usually in a fuel cell system, sensors measuring voltage and temperature are only available for the entire stack, not for individual cells. This limitation in sensors implies challenging problems for the observation and control of such systems. As a matter of fact, the details of such a system may be neither observable, nor controllable in the classical sense. New multiscale concepts of observation and control need to be developed in this framework.

The following aspects are of particular interest for the above-mentioned applications: on the one hand, the characterization of the average behavior of the similar components in a large system ; on the other hand, the characterization, to some extent, of the deviations of individual components from the average behavior. The control objective may be formulated in terms of the average behavior of components and an assessment of their deviations. To this end, appropriate modeling techniques must be developed, probably in a multiscale form. These are exciting topics, not only because of their theoretic difficulty, but also because of their potentially important applications in various fields, such as health, energy and transportation.

Networks of dynamical systems.
The networks of dynamical systems are intensively studied in physics and mathematics (see, e.g. [139] or [103] for a survey). This complex structure gives rise to new dynamical behaviors — ranging from de-correlation to coherent behaviors, such as synchronization or emergence of traveling waves —, and to new control issues too. The problem of synchronization has in particular, deserved a considerable interest and some approaches may be useful here too.

We illustrate this with an example of network where each dynamical system i exchanges with the others, $j = 1...N$, in an additive way, a frequent situation for systems of conservation laws as are often the physical models we consider. In this situation, the Network variant of the ODE (NODE for short) (1) is [103]:

$$\begin{aligned} \frac{dx_i}{dt} &= f_i(x_i, u_i, \theta_i, w_i) - \Sigma_{j=1}^{N} \mathcal{C}_{i,j} g_j(x_j, u_j, \theta_j, v_j) \\ y &= g(x_1, ...x_N, u_1, ...u_N, \theta_1, ...\theta_N, v_1, ...v_N) \end{aligned} \tag{4}$$

where $\mathcal{C}$ is the connectivity matrix depending upon the structure of the network. Synchronizing the system means that, at least asymptotically, $x_1 = ... = x_N$. In some particular cases, this problem has been solved. For example when $\mathcal{C} = \mathcal{C}^T$ and $\mathcal{C}_{i,i} > 0$, $\Sigma_{j=1}^{N} \mathcal{C}_{i,j} = 0$ and all the dynamics are identical ($f_1 = ... = f_N$, $u_1 = ... = u_N$, ...), projecting (4) on the vector $v_0 = 1/\sqrt{N}(1, ..., 1)^T$ of the kernel of $\mathcal{C}$ defines a synchronization manifold $\mathcal{S}$ (i.e. if $x_1(t) = ... = x_N(t) = x_{\mathcal{S}}(t)$ then $x_1(t') = ... = x_N(t') = x_{\mathcal{S}}(t)$ for $t' \geq t$) and it is possible to give conditions for the stability of $\mathcal{S}$ depending upon f and $\mathcal{C}$. The system $x_{\mathcal{S}}$ on $\mathcal{S}$ is the natural "averaged system" and it is also natural to represent the system (4) under the hypothesis of identical dynamics, by its "deviations" $x_i - x_{\mathcal{S}}, i = 1, ..., N$.

This approach is difficult to extend in the general case of non identical controlled systems. We will be mainly interested by the controlled case with $f_1 = ... = f_N$ but the u_i, θ_i, w_i being possibly different. Remark that in this case, complete synchronization may not be expected because, in general, the invariant manifold $\mathcal{S}$ no more exists. The properties to detect (partial synchronization, desynchronization), the objectives of the control (resynchronization), have then to redefined.

Partial Differential Equations models of particular networks.
Consider for example the NODE version of first two equations of (2):

$$\begin{aligned} \frac{dv_i}{dt} &= f_V(v_i, u_i, u_{ext,i}, \theta_{e,i}, w_{e,i}) - \Sigma_{j=1}^{N} \mathcal{C}_{i,j} g(x_j, u_j, \theta_j, v_j) \\ \frac{du_i}{dt} &= f_U(v_i, u_i, \theta_{e,i}, w_{e,i}) \end{aligned} \tag{5}$$

It is the semi-discretization in space of a reaction-diffusion equation. In some situation, working with this PDE may be very useful. It is of course the case for the heart, but even for the fuel-cell stack, above, say 50 cells, it may give insight on the system. The typical form for such PDE will be:

$$\begin{aligned} \frac{\partial v}{\partial t} &= \sigma \Delta v + g_V(v, u, u_{ext}, \theta_e, w) \\ \frac{\partial u}{\partial t} &= f_U(v, u, \theta_e, w_e) \end{aligned} \tag{6}$$

with no diffusion term for the intracellular state variables. The prototype for such PDE is the FitzHugh-Nagumo equation.

Consider now the dynamical population of cells mentioned in section 3.5.2. For each follicle f, the cell population is represented in each cellular phase by a density ϕ_f solution of a controlled conservation law of the form [16], [49]:

$$\frac{\partial \phi_f}{\partial t} + \frac{\partial g_f(u_f)\phi_f}{\partial a} + \frac{\partial h_f(\gamma, u_f)\phi_f}{\partial \gamma} = -\lambda(\gamma, U)\phi_f \tag{7}$$

where u_f and U are respectively a local control of follicle f and a global control of all follicles.
Using a particle approximation of this equation leads to a model similar to (4), but with $\mathcal{C} = 0$ (the coupling is due to control) and N is now variable, depending upon the set of trajectories of the cells in the age-maturity plane.

3.2.1. Observation and control of synchrony in networks of dynamical systems

Our studies on fuel cells and cardiac tissues have motivated general investigation of observation and control of synchrony in lattice dynamical systems. In such a system, a large number of subsystems are regularly organized in space, and the global performance of the whole system strongly depends on the synchrony of the subsystems. In the case of a fuel cell system, the lack of synchronization of the electrochemical reactions in individual cells may transform some cells to consumers of the electrical energy produced by other cells, reducing the overall performance of the system. The synchrony is also important for cardiac cells, because their contractions must be coordinated for a good efficiency of the cardiac pump. An important question is how to monitor the synchrony with limited observations. For the example of cardiac cells, it is known that electrocardiogram and arterial pressure provide some indication about their synchrony. Methods for more efficient synchrony observation using these measurements, possibly completed by other measurements, will have important clinical applications. The understanding of natural synchrony control may be helpful for the design of artificial devices for cardiac resynchronization.

For these questions, a possibility is to study network versions, in the form (4), of the models (2) or (3), along the lines presented in the example (considering the average behavior and the associated deviations).

3.2.2. Observation and control of other coherent structures (traveling waves...)

Coherent modes are not simply collective behaviors of all the dynamical systems in the ensemble, but as well, coherent structures emerging from evolutions far from equilibrium when the system is excited. They can result from combined non-linearities and dissipation or dispersion of waves in some wave representation of the system states. Such coherent responses to excitations are signs that the system is “alive” and their analysis is often useful in monitoring or control applications. Among the many examples, the following will be of particular interest: traveling waves of action potentials in cardiac electro-physiology ; solitons in various dispersive propagation media (the arterial tree as well as electric or optic transmission lines). Several related questions have been investigated in the literature, in particular: traveling waves in Lattice Dynamical Systems and links with synchronization [107], bifurcations [140] ...

3.3. Estimation and control of quantization of energy in systems & signals

3.3.1. Identification & control of quantum systems

Keywords: *Lindblad equation*, *Quantum systems*, *Schrödinger equation*, *quantum decoherence*, *quantum filter*.

Interesting applications for quantum control have been noted and 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 [134]. 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 web page of 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 [116]. Two different 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

$$\begin{aligned} i\frac{d}{dt}\Psi(t,x) = (H_0 + u(t)H_1)\Psi(t,x) = (-\frac{1}{2}\triangle + V(x) + u(t)\mu(x))\Psi(t,x), \\ \Psi|_{t=0} = \Psi_0, \end{aligned} \tag{8}$$

where $\Psi(t,x)$, $-\frac{1}{2}\triangle$, 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). While the finite dimensional approximations ($\Psi(t) \in \mathbb{C}^N$) have been very well studied and explored (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 [98], [99], [130]. 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. Particularly, we would like to consider the extension of the Lyapunov-based techniques developed in [23], [100], [130]. 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 where the decoherence phenomena is taken into account. Such models can be presented in the density operator language. In fact, to the Schrödinger equation (8), one can associate an equation in the density operator language:

$$\frac{d}{dt}\rho = -i[H_0 + u(t)H_1, \rho], \tag{9}$$

where $\rho = \Psi\Psi^*$ represents the projection operator on the wavefunction Ψ. Here $[A,B] = AB - BA$ is the commutator of the operators A and B. Whenever, we consider a quantum system in its environment with the quantum jumps induced by the vacuum fluctuations, we needs 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:

$$\begin{aligned} d\rho_t = -i[H_0 + u(t)H_1, \rho_t]dt + (L\rho_t L^* - \frac{1}{2}L^*L\rho_t - \frac{1}{2}\rho_t L^*L)dt \\ + \sqrt{\eta}(L\rho_t + \rho_t L^* - \mathrm{Tr}\left[(L + L^*)\rho_t\right]\rho_t)dW_t, \end{aligned} \tag{10}$$

where L is the so-called Lindblad operator associated to the measurement, $0 < \eta \leq 1$ is the detector's efficiency and where the Wiener process W_t corresponds to the system output Y_t via the relation $dW_t = dY_t - \mathrm{Tr}\left[(L + L^*)\rho_t\right]dt$. This filter equation, initially introduced by Belavkin [101], 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 [52].

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 [51]. Moreover, a first observer-based identification algorithm is under study and will lead to publications in near future.

3.3.2. Scattering theory, solitons & quantization of energy in signals

Spectral analysis of some traveling waves. In some recent publications [71], [70], we use the scattering theory to analyze a measured Arterial Blood Pressure (ABP) signal. Following a suggestion made in [141], a Korteweg-de Vries equation (KdV) is used as a physical model of the arterial flow. The signal analysis method is then 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. In the Lax formalism, the non-dimensionalized KdV equation

$$\frac{\partial y}{\partial t} - 6y\frac{\partial y}{\partial x} + \frac{\partial^3 y}{\partial x^3} = 0, \tag{11}$$

is associated to a Lax pair, $L(y)$, $M(y)$, where $L(y)$ is a Schrödinger operator:

$$L(y) = -\frac{\partial^2}{\partial x^2} + y, \qquad M(y) = -4\frac{\partial^3}{\partial x^3} + 3y\frac{\partial}{\partial x} + 3\frac{\partial}{\partial x}y. \tag{12}$$

The KdV equation (11) is therefore equivalent to the operator equation:

$$\frac{\partial L(y)}{\partial t} = [M(y), L(y)], \tag{13}$$

where $M(y)$ is an anti-Hermitian operator. Finally, the output of the system would be the signal y playing here the role of the potential of $L(y)$. The scattering and inverse scattering theory can be used to analyze y in term of the spectrum of $L(y)$ and conversely. The “bound states” of $L(y)$ seem of particular interest: if $L(y)$ is solution of (13) and $L(y(t))$ has only bound states (no continuous spectrum), then the property is true at each time and y is a soliton of KdV. For example the arterial pulse pressure is close to a soliton [46].

Inverse scattering as a generalized Fourier transform. We consider here “pulse-shaped” functions y, meaning that $y \in L^1(\mathbb{R}; (1 + |x|^2)dx)$. The squared eigenfunctions of $L(y)$ and their space derivatives are then a basis in $L^1(\mathbb{R}; dx)$ (see e.g. [136]) 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 us. 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:

$$y(x) = 4\sum_{n=1}^{n=N} \kappa_n \psi_n^2(x) - \frac{2i}{\pi}\int_{-\infty}^{-\infty} kR(k)f^2(k,x)dk \tag{14}$$

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). R is the reflection coefficient. The discrete part of this expression is easy to compute and provides useful informations on y in applications. The case $R = 0$ is of particular interest: $-y$ is a reflectionless potential. We investigate in particular approximation of pulse-shaped signals by such potentials corresponding to N-solitons in the non stationary case.

Some extensions to signals with a complex structure. The deterministic approach just described can be generalized by considering the vessels as random media, whose random components are known up to a certain noise. This yields a more realistic description of the system. Then, the solution y becomes random, as well as the coefficients invoked in the KdV equation and the Lax pair. We will use the spectral theory of random Schrödinger operators [106], [104] and the inverse Schrödinger scattering theory for random potentials [123].

Remark that the idea to use solitons in signal processing is not new: Oppenheim, Singer and Wornell [138] were using solitons in a form of “multiplexed soliton communication” and considered the questions of detection and estimation of soliton signals. But the interactions they consider were linear (a N-soliton seen as the linear superposition of N 1-solitons, with N less than 4 in their case). This corresponds to the weak interactions taking place after the different two by two crossings. Here we consider the fully nonlinear situation.

This method based on scattering theory, associates a discrete spectrum to a possibly non stationary signal through an iso-spectral flow approximation using N-solitons. The examples studied are particular travelling pulses (solutions of dispersive equations) and for this particular cases, the analysis can be interpreted as a kind of “time - velocity” analysis [71]. It will be interesting to test the method on other signals related to travelling waves. The systems considered offer several opportunities of this kind.

3.4. Analysis of transfers of energy and control among scales in multiscale signals & systems

3.4.1. Large deviations and singularity spectra ; scaling invariant models and heart-beat variability

Two possible approaches for describing the transfer of energy among scales are the following: Looking at the way a given positive measure μ is distributed at the successive scales of regular nested grids (denoted G_n at resolution n), or looking at the manner the wavelet coefficients of a square integrable function g decay to 0 along the scales. This can be done by using ideas initially used by physicists in order to describe the geometry of turbulence and then formalized by mathematicians in the so-called multifractal formalism ([113], [115], [105], [133], [119]).

On the one hand one uses tools coming from *statistical physics* and *large deviations theory* in order to describe asymptotically for each singularity value α the logarithmic proportion of cubes C in G_n (the dyadic grid of level n) such that the mass distributed in C is approximately equal to the power α of the diameter of C, i.e. $\mu(C) \approx 2^{-n\alpha}$. This yields a sequence of functions f_n of α called large deviation spectrum, which describes statistically the heterogeneity of the distribution of the measure at small scales. Another tool associated with this spectrum consists in the partitions functions

$$\tau_n(q) = \frac{1}{n} \log_2 \sum_{C \in G_n} \mu(C)^q.$$

They are Laplace transforms closely related to the functions f_n.

The same quantities can be associated with the L^2 function g by replacing the masses $\mu(C)$ by the wavelet coefficients $|d_C(g)|$.

In practice, the functions f_n and τ_n can be computed and are used to exhibit a scaling invariance structure in a given signal as soon as they remain quasi constant when n ranges in some non trivial interval. This approach proves to be efficient in detecting scaling invariance in energy dissipation and velocity variability in fully developed turbulence [113], in the measure counting the accumulation (in time) of packets at a router in internet traffic variability [125], as well as in the heart-beat variability [129], [118] and in financial time series [127]. Scaling invariance in heart-beat variability is one of our research directions (see Section 3.2). It should reflect the heterogeneous spatiotemporal distribution of the energy in the cardiac cells and should be related to models of this phenomenon.

On the other hand one uses tools from *geometric measure theory* such as Hausdorff measures and dimensions in order to have a geometrical description of the (fractals) sets of singularities S_α obtained as the sets of those points x at which the sequences $\mu(C_n(x))$ or $|d_{C_n(x)}(g)|$ behaves asymptotically like $2^{-n\alpha}$, where $(C_n(x))$ is the sequence of nested cubes in the grids G_n that contain the point x. The singularity spectrum obtained by computing the Hausdorff dimension of the sets S_α yields a finer description of the heterogeneity in the energy distribution than the statistical one provided by large deviations spectra. But this object is purely theoretical since it necessitates the resolution to go until ∞.

Since the tools described above are efficient in physical and social phenomena, it is important to investigate models of measures and functions having such properties and develop associated statistical tools of identification. Such models do exist and have been studied for a long time ([126], [121], [135], [117], [120], [97], [112], [2], [4], [3]) but few satisfactory associated statistical tools have been developed. We shall study new models of scaling invariant measures, signed multiplicative cascades, and wavelet series. In particular we will be inspired by the model proposed in [122] of cascading mechanisms for the evolution of wavelet coefficients of the solution of the Euler equation. It could be used to construct a model for the multiscale control of cardiac cellular energetics and, as we already said above, a model for the heart-beat variability.

These works will contribute to one of the theoretical aspects developed in the team, which consists in studying and classifying statistically self-affine and multifractal mathematical objects.

3.4.2. Multiscale signals analysis & dynamical systems. Example of the cardiovascular system

Analysis of Heart Rate Variability (HRV), the beat-to-beat fluctuations in heart rate, has many clinical applications, from prediction of the consequences of a heart attack to the detection of obstructive sleep apnea [26].

The observation of the $1/f$ shape of the HRV spectrum has been strengthened recently by using techniques of multifractal signals processing. These techniques quantify a signal temporal irregularity for instance by constructing an histogram of the “coarse-grained” Hölder exponents computed on finer and finer nested grids. This leads to the so-called large deviations spectrum, which describes the frequency at which each Hölder exponent occurs. This is a way to estimate variability. One can say that some scale invariance holds when the large deviation spectrum weakly depends on the scale in the nested grid. Such a scale invariance has been observed on RR signals, and one concluded that the largest the range of the exponents, the better the patient’s health. In particular the multifractal large deviation spectrum is shown to be a useful tool to study the long-term fluctuations for the diagnosis of some pathologies like congestive heart failure.

HRV analysis can be completed considering Blood Pressure Variability (BPV). For example joint analysis of short-term HRV and BPV leads to the baroreflex sensitivity (BRS), the gain of the parasympathetic feedback loop, a useful index of parasympathetic activity that has a prognostic value in several situations (myocardial infarction, heart failure of diabetic patients): low BRS is correlated with mortality in patients with heart failure. In the case of BPV, $1/f$ shaped spectra have also been observed and it has been found that sympathetic nerve traffic and BPV follow comparable self-similar scaling relationships.

In both case, HRV or BPV, the physiological origins of these long-term fluctuations remain mysterious. The goal of this study is to provide methods and tools to improve variability analysis for a better understanding of these fluctuations.

Our method will be to associate multiscale signal analysis and mathematical models whenever it will be possible. We will proceed through three main steps in order to test new approaches to cardiac variability (CV) analysis based on some apparently new ideas:
- Better localization of HR and BP variability. The RR interval estimated from the ECG, as well as the arterial pressure, measured at the finger (FBP), will be decomposed into components: RR subintervals, intra-beat invariants of the pressure computed with the Inverse Scattering Technique developed in the team. The beat-to-beat variability of these components will be analyzed by using a multiscale signal analysis, especially the notion of large deviation spectrum.

- Assessment of the arterial vascular compartment as a proximal-to-distal transmission channel of cardiac variability. We will use FBP, then a question is: to what extent, FBP variability is the image of CV? Theoretical as well as experimental approaches will be used here.
- Cardiac variability and models of the cardiac electromechanical activity. The variability of some of the components such as short term energy of the Pulse Pressure Wave (2nd invariant resulting from the soliton analysis), is expected to be at the image of CV. It will be then possible to consider a model-based approach to CV.

3.5. Physiological & Clinical research topics

3.5.1. The cardiovascular system: a multiscale controlled system

Applicative & scientific challenges.

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. Clinicians in both the pharmaceutical industry and the hospitals are concerned, even if there is a gap between molecular and cell biology and clinical practice. Our objective will be to contribute to reduce this gap by developing low-order models imbedding knowledge on the controlled cell mechano-energetics, together with being identifiable from cardiovascular signals or images. We will study in particular the possibility to gain insight on the cell scale by using model-based multiscale signal processing techniques of long records of cardiovascular signals (pressure, ecg...).

Cardiovascular modeling: the multiscale controlled-system approach.

From the cardiovascular system scale to the cell scale, the function of the circulation is to supply cells with oxygen, nutrients and to remove carbon dioxide and other catabolits. On each of these scales, variables involved in cardiovascular regulation, such as blood flow, blood pressure, oxygen blood concentration, ATP concentration, are kept around their reference points by different feedback control mechanisms having different dynamics depending upon the considered scale. We are interested in the mechano-energetics of the heart with its short term (some few minutes) intrinsic control mechanisms, from the cell scale to the cardiovascular system scale. The control viewpoint is useful in accounting for macroscopic properties on different scales (such as the Starling law or the Hill force-velocity relation) and to define performance indexes of the electro-mechanical coupling on each scale.

Modeling of the controlled contraction / relaxation of cardiac muscle: from molecular to tissue scales.

We have used ideas originating from the kinetic equation theory to model, on the molecular scale, the controlled collective behaviour of actin-myosin nanomotors at the root of muscle contraction. The conversion of chemical energy into mechanical energy by these molecular motors has been described and the classical Huxley's model has been recovered on the sarcomere / cell scale by using moment equations [102]. This model has been extended using the same type of scaling techniques to a thermodynamically consistent constitutive law on the tissue scale that is also consistent with the "sliding filament hypothesis" of A. F. Huxley [6].
This multiscale description of controlled muscle contraction may be useful in studying modeling and control problems associated to the heart considered as a multiscaled system.

Modeling of the electro-mechanical activity of the heart on the cell scale.

We consider intrinsic heart control mechanisms, ranging from the Starling and Treppe effects (also called positive staircase effect) on the cell scale to the excitability of the cardiac tissue. They all contribute to the function of the heart in a coordinated manner that we want to analyse and assess.

For this purpose, we also study reduced-order models of the electrical activity of cardiac cells designed to be coupled with measures available on the organ scale (e.g. ECG signals) and with the natural input of the contraction / relaxation model mentioned above on a sub-cellular scale. Two output variables are then of major importance in these applications: the membrane potential and the concentration of Calcium bound on the Troponin-C. Some other state variables must therefore be considered, even for a reduced order model. It is in particular necessary to take into account the intracellular calcium dynamics that is the link between these two main variables. This dynamics is also useful to represent the rate-dependent inotropic effects like Treppe effect. See equation (2) for the structure of these models and 5.5.1 for the results of this year.

Modeling of the controlled contraction of cardiac muscle on the organ scale.

$3D$ modeling. The model of [6] is currently used as the constitutive law for the cardiac tissue in the $3D$ model of the heart developed in the CardioSense3D project (see 7.1.1). It is useful for computing stress, strain and, coupled with an electrical model, action potential fields [1], [137]. Depending upon a small number of parameters having a clear physical meaning, it is well suited for the study of inverse problems as considered in the CardioSense3D project (model-based processing of three-dimensional images).

We are currently studying the coupling of this fibre model with a coronary flow model developed by the project-team REO in order to take into account the mechano-energetics of the contraction - relaxation process in a reduced order model.

$1D$ modeling. In order to check the mathematical consistency of our models, we have considered, in the more simple case of a one dimensional geometry ($1D$ problem), the mathematical analysis of the fibre model used in CardioSense3D based on the previous constitutive law (joint work with Pavel Krejčí (Weierstrass Institute for Applied Analysis and Stochastics, Berlin), J. Sainte-Marie (MACS project) and J.M. Urquiza (CRM, Montreal) [20]).

$0D$ modeling. On the heart and cardiovascular system scales, we study $0D$ models of the electro-mechanical activity of the cardiac muscle for control analysis and signal processing applications. Here the heart is seen as a small number of "averaged cells" representing the walls of the atrial and ventricular chambers. These models are of particular interest to study intrinsic control mechanisms of the heart. For example, this year we have studied an intrinsic control effect, represented by the restitution curve associated to a very simple cardiac cell model and estimated by ECG analysis, see 5.5.2.

Modeling short-term and long-term control dynamics on the cardiovascular-system scale.

Our objective here, is to relate discrete-time (beat-to-beat) cardiovascular signal analysis to models of the cardiovascular and control systems taking into account its multiple feedback loop organisation. This will lead to a model-based signal processing approach for the estimation of the classical arterial-pressure/heart-rate baroreflex sensitivity and of several other discrete-time feedback loop sensitivities of practical interest.

In the past we have used time-frequency techniques for these studies (Fourier Transform, spectral gain between the cardiac and blood pressure series, Smooth Pseudo Wigner_Ville Distribution, Complex DeModulation, temporal method of the cardiovascular Sequences). Different situations have been studied: the cardio-respiratory system dynamics in chronic heart failure [22], [21], [27] ; the autonomic control of the cardiovascular system during sleep [26] ; the effects of exercise intensity and repetition on heart rate variability during training [12], [13], [11].

We will combine these techniques with our new inverse scattering approach. In particular the scattering-based description of cadiovascular signals leads to the definition of new indexes we want to investigate, see paragraph 5.7.1 our recent results along this line.

3.5.2. Reproductive system: follicular development & ovulation control

Applicative & scientific challenges.

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 [16], [49]. 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 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, basing by instance on the current routines designed within the Bearclaw (http://www.amath.unc.edu/Faculty/mitran/bearclaw.html) academic environment,

- 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 particular 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 Gα_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 [44]. 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.

Quantification of the follicular vascularization and cell number.

There is a crucial need for both quantitative and dynamical data on follicular development. Such data may be retrieved from different modalities of ovarian imaging. Within the framework of the REGLO cooperative research initiative, http://www-rocq.inria.fr/who/Frederique.Clement/reglo.html the Asclepios members have been reconstructing a 3-D image of the ovary from a series of 2-D stained histologic images. From this reconstruction, we expect to get statistical (i.e. from a given population of growing follicles) information on the cell number (which corresponds to a follicular level output of the multiscale model), derived from the volume of the granulosa tissue, as well as on the degree of follicular vascularization (which corresponds to a follicular level input in the multiscale model).

In the middle-long term, we intend to design a morphological model of follicular growth. We will base on the analogy of follicle growth with solid tumor growth and on the image-derived data to design the model. In turn, such a model would be very useful in analyzing low signal-to-noise ratio imaging modalities such as ultrasonography.

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

Participant: Claire Médigue.

LARY_CR is a software package dedicated to the study of cardiovascular and respiratory rhythms [132]. 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 only internally, in the framework of our clinical collaborations.

5. New Results

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

Keywords: *ECG*, *LMI*, *biology*, *diagnosis*, *health*, *heart*, *identification*, *observation*, *ovulation control*, *pressure*, *robust control*, *stability*, *systems of agents*.

5.1.1. Stability Analysis of Systems Defined on Interaction Graph

Participants: David Angeli, Pierre-Alexandre Bliman.

We carried on this year the study of stability for a class of linear discrete-time systems made up of subsystems seeking consensus, a special type of synchronization [57], [85]. For this class of systems, the communications between the subsystems are defined by time-varying directed interaction graph (such systems are also named multi-agent systems).

We have been interested by the quantitative aspects of convergence towards consensus. Based on a priori knowledge of certain weights related to the expansion of trees spanning the interaction graph, tight estimates have been given. The latter are easily computable, being the spectral radius of some square matrices of size the depth of the trees. This work is connected to properties of the products of stochastic matrices and to mixing rates of heterogeneous Markov chains.

5.1.2. *Converse Lyapunov Results*

Participants: Pierre-Alexandre Bliman, Matthew Peet.

The use of Semi-Definite Programming to construct polynomial Lyapunov functions for delayed and nonlinear systems of differential equations motivates the study of the necessity of such functions. We have devoted ourselves to two directions [77].

First, for linear stationary systems with pointwise delays, asymptotic stability was known to be equivalent to the existence of some Lyapunov functional depending quadratically, via integral terms, upon the (infinite-dimensional) state value. We studied the approximation of the corresponding kernel by polynomials in the time variable.

Second, we proved that for nonlinear (delay-free) systems, exponential stability implies existence of a Lyapunov function polynomial in the state variable.

Both results constitute attempts at exploring and extending the applicability of sum-of-squares optimization techniques

5.1.3. *Robustness Properties of Linear Systems*

Participant: Pierre-Alexandre Bliman.

We went on developing with P.L.D. Peres and R.C.L.F. Oliveira (Unicamp, Campinas, Brazil), M.C. de Oliveira (University of California San Diego, USA) and V.F. Montagner (University of Santa Maria, Brazil) tools for robust analysis, robust synthesis and gain-scheduling dedicated to uncertain linear systems subject to parametric uncertainties.

Our efforts have been concentrated on control design with guaranteed performance for LPV systems with constant, slow-varying or fast-varying parameters. Tight results have been obtained and tested, based on linear matrix inequalities [76].

5.1.4. *Adaptive estimation of unknown parameters and disturbances for fault diagnosis*

Participants: Stefano Perabò, Qinghua Zhang.

The study on joint estimation of states, parameters and disturbances in dynamic systems is closely related to model-based fault diagnosis. Faults are typically modeled either as unknown disturbances or as parametric changes. The approach of unknown disturbances has the advantage of flexibility for the description of quite general faults, but has a strong requirement on the number of available sensors. The approach of parametric changes has a weaker requirement on sensors, but it is more restrictive to the nature of modeled faults and requires some excitation condition. Though fault diagnosis has been largely studied for one or the other type of modeled faults, there was no systematic study for both types of modeled faults co-existing in a same system. The results of this study allow to estimate both types of faults in general linear time varying systems, under appropriate structural and excitation conditions. The basic idea is to study the behavior of the innovation of the Kalman filter applied to the monitored system under the fault-free assumption. Among the new results of this year, the possibility of delayed estimation is studied in order to weaken the structural requirement on the monitored system, and a recursive algorithm is developed. These results have been presented at International Conference on Informatics in Control, Automation and Robotics [79] and European Control Conference [78].

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

Keywords: *Korteweg-de Vries equation*, *Schrödinger equation*, *electrical networks*, *excitable media*, *inverse scattering*, *quantum systems*.

5.2.1. *Scattering based analysis of pulse-shaped signals*

Participants: Emmanuelle Crépeau-Jaisson, Taous-Meriem Laleg, Michel Sorine, Qinghua Zhang.

In this work we develop a new signal processing technique based on scattering theory [71], [70]. This inverse scattering technique consists on solving the spectral problem associated to a one-dimensional Schrödinger operator perturbed by a potential depending upon the signal to analyze, and optimized in order to approximate this signal. Some functions associated with the Schrödinger equation (the squared Jost solutions) play an analogous role to sinus and cosinus in the Fourier analysis of signals. In the proposed analysis, by using an interpretation in term of traveling waves (the N-solitons), low and high frequency components of the standard Fourier analysis, are replaced by low and high velocity components.
Applications of the method to physiological signals are currently studied (see 5.7.1).

5.2.2. Scattering based analysis of electric transmission lines for fault diagnosis

Participants: Mehdi Admane, Michel Sorine, Qinghua Zhang.

In order to develop methods for the diagnosis of conduction failures in electric transmission lines with the technology of reflectometry, mathematical models of transmission lines have been studied, as part of the SEEDS project (see Section 6.3). Our first modeling study has been on a reduced order differential model optimized to simulate electric transmission lines with skin effect. It corresponds to a simple equivalent electric circuit in the form of a ladder, consisting of frequency independent electric elements. This model is efficient for numerical simulation and is suitable for the study of conduction failure detection with time domain reflectometry. This work has been presented at Reliability in Electromagnetic Systems 2007 [56]. More recently, the modeling of transmission lines with the inverse scattering theory (IST) is studied. By transforming the classical model of transmission lines (known as telegrapher's equations) to the Schrödinger equation or to the Zakharov-Shabat equation, it is possible to deduce functions of the distributed parameters of a pair of transmission lines which can be estimated from measurements made at one end of the transmission lines. The advantage of this method is the possibility of working with non homogeneous lines without full knowledge about their distributed parameters.

5.2.3. Control and stabilization of Korteweg-de Vries equation

Participants: Emmanuelle Crépeau, Eduardo Cerpa.

It is known that the linear Korteweg-de Vries (KdV) equation with homogeneous Dirichlet boundary conditions and Neumann boundary control is not controllable for some critical spatial domains. In this work, we have proved, in these critical cases, that the nonlinear KdV equation is locally controllable around the origin provided that the time of control is large enough. It is done by performing a power series expansion of the solution and studying the cascade system resulting of this expansion.

We have also considered a control system for a Korteweg-de Vries equation with homogeneous Dirichlet boundary conditions and Neumann boundary control. We addressed the rapid exponential stabilization problem. More precisely, we built some feedback laws forcing the solutions of the closed-loop system to decay exponentially to zero with arbitrarily prescribed decay rates. We also performed some numerical computations in order to illustrate this theoretical result [43].

5.2.4. Approximate controllability of a reaction-diffusion system

Participants: Emmanuelle Crépeau, Christophe Prieur.

We have studied an open loop control for a system coupling a reaction-diffusion system and an ordinary differential equation. We used a flatness-like property, indeed, the solutions of the system can be expressed in terms of an infinite series depending on a flat output its derivatives and its integrals. This series is shown to be convergent if the flat output is Gevrey of order $1 < a \leq 2$. Approximate controllability of the system is then proved [82].

5.3. Dynamics, control and identification of quantum systems

Keywords: *Asymptotic observers*, *Control of PDEs*, *Hamiltonian identification*, *Lyapunov stabilization*, *Symmetries*, *bilinear Schrödinger equation*, *identifiability*, *quantum feedback control*, *quantum filtering equations*, *stochastic stabilization*.

Participant: Mazyar Mirrahimi.

5.3.1. Hamiltonian identification for quantum systems: well-posedness and numerical approaches

This work is done in collaboration with Claude Le Bris, Herschel Rabitz and Gabriel Turinici.

We consider the inversion problem related to the manipulation of quantum systems using laser-matter interactions. The focus is on the identification of the field free Hamiltonian and/or the dipole moment of a quantum system. The evolution of the system is given by the Schrödinger equation. The available data are the observations of different populations as a function of time corresponding to dynamics generated by electric fields. The well-posedness of the problem is proved, mainly focusing on the uniqueness of the inversion solution. A numerical approach is also introduced with an illustration of its efficiency on a test problem. This work has been published as [51].

5.3.2. Observer-based Hamiltonian identification for quantum systems

This work is done in collaboration with Silvère Bonnabel and Pierre Rouchon.

A symmetry-preserving observer-based parameter identification algorithm for quantum systems is proposed. Starting with a Qubit (2-level quantum system) and where the unknown parameters consist of the de-tuning and the atom-laser coupling constants, we prove an exponential convergence result [93]. The analysis is inspired by the adaptive control techniques and is mainly based on the averaging arguments and some relevant transformations. The observer is then extended to the multi-level case where eventually all the atom-laser coupling constants are unknown. The extension of the convergence analysis is discussed through some heuristic arguments. The relevance and the robustness with respect to various noises are tested through numerical simulations. A complete version of the results has been submitted as a journal paper [92].

5.3.3. Implicit Lyapunov control of finite dimensional Schrödinger equations

This work is done in collaboration with Karine Beauchard, Jean-Michel Coron, Pierre Rouchon.

An implicit Lyapunov based approach is proposed for generating trajectories of a finite dimensional controlled quantum system. In a previous work [131], we had proposed a Lyapunov technique to stabilize an arbitrary equilibrium state of a finite dimensional Schrödinger equation. The asymptotic convergence of the closed-loop system was proved whenever some non-degeneracy assumptions, equivalent to the controllability of the linearized system, were satisfied. The main contribution of this new work is to relax these assumptions and to show that applying some implicit Lyapunov theory we may have the same asymptotic stabilization results under much weaker assumptions.

As mentioned, the controlled Lyapunov function is defined by an implicit equation and its existence is shown by a fix point theorem. The convergence analysis is done using LaSalle invariance principle. Closed-loop simulations illustrate the interest of such feedback laws for the open-loop control of a test case considered by chemists. This work has been published as a journal paper [40].

5.3.4. Approximate stabilization of a quantum particle in a 1D infinite square potential well

This work is done in collaboration with Karine Beauchard.

We consider a non relativistic charged particle in a 1D infinite square potential well. This quantum system is subjected to a control, which is a uniform (in space) time depending electric field. It is represented by a complex probability amplitude solution of a Schrödinger equation on a 1D bounded domain, with Dirichlet boundary conditions. The system admitting non-degenerate discrete spectrum, We prove the almost global approximate stabilization of any arbitrary eigenstate by explicit feedback laws.

Dealing here with the stabilization of a partial differential equation, the main difficulty is due to the lack of the pre-compactness of the trajectories in the desired functional space. In fact, a deep study of the problem showed us that such lack of pre-compactness actually is due to phenomena's such as L^2-mass lost at high energy levels of the quantum well. In order to overpass such problems, and in the same direction as a previous work [130], we consider a Lyapunov function which encodes two tasks at the same times: 1- by an appropriate truncation does not allow the population to pass through the higher energy levels; 2- privileges slightly the increase in the population of the desired eigenstate. After proving the appropriate existence and uniqueness results for the closed-loop system, we prove the approximate stability of the system around the desired eigenstate. A short version of this result has been submitted as a conference paper [90] and a long version has been submitted as a journal paper [91].

5.3.5. *Stabilizing feedback controls for quantum systems*

This work is done in collaboration with Ramon Van Handel.

No quantum measurement can give full information on the state of a quantum system; hence any quantum feedback control problem is necessarily one with partial observations, and can generally be converted into a completely observed control problem for an appropriate quantum filter as in classical stochastic control theory. Here we study the properties of controlled quantum filtering equations as classical stochastic differential equations. We then develop methods, using a combination of geometric control and classical probabilistic techniques, for global feedback stabilization of a class of quantum filters around a particular eigenstate of the measurement operator. This work has been published as a journal paper [52].

5.3.6. *Robustness of stabilized quantum filter equations.*

This work is done in collaboration with Ramon Van Handel.

During a long stay of about 3 months at the Theoretical Physics Department of California Institute of Technology, I was able to continue my collaborations with the Hideo Mabuchi's team.

In particular, following the previous work with Ramon Van Handel [52], we were able to prove the robustness of the stabilized filter equation with respect to the initial state uncertainties. As it was remarked in the previous paper [52], the statistics of the observation depend both on the controls and on the initial state. It was, however, assumed that the filter initial state matches the state in which the system is initially prepared (i.e. the "wrongly initialized" filters was not considered). Quantum filtering theory then guaranteed that the considered innovation W_t is a Wiener process. This work had for goal to go further and to show that the proposed stabilization technique is actually robust with respect to the filter's initial state errors. We were able to show this fact, through the application of a generic filter stability result, some extensions of stochastic Lyapunov theory and some probabilistic arguments.

Observing in simulations, similar robustness with respect to the uncertainties in other parameters of the filter, our next goal is to extend the previous techniques to prove such strong robustness results.

5.3.7. *Feedback control designs for preparation of multi-qubit quantum states.*

This work is done in collaboration with Hideo Mabuchi, Anthony E. Miller, Ramon Van Handel.

During the same stay at Caltech, we considered the difficult problem of the preparation of general entangled states for multi-qubit systems.

In a first part of the work, we considered the case of a two-qubit system. We showed that under some appropriate assumptions, it is possible to prepare (in an approximate way) any entangled state of the form $(\alpha_1 |\uparrow\downarrow\rangle + \alpha_2 |\downarrow\uparrow\rangle)$. The proof of the approximate stabilization result is mainly based on the techniques from the perturbation theory of linear operators and the Strook-Varadhan support theorem. The efficiency of the method is tested through numerical simulations. Finally an extension to the $2N$-qubit cases is discussed and a method to prepare a large class of entangled states has been provided.

5.4. Multifractal analysis and signal processing

Keywords: *Gibbs measures*, *Hausdorff spectrum*, *Multifractal analysis*, *Sierpinski carpets*, *large deviation spectrum*.

5.4.1. Multifractal analysis of Birkhoff averages on “self-affine” symbolic spaces

Participants: Julien Barral, Mounir Mensi.

We perform the multifractal analysis of the Birkhoff averages of a potential satisfying a Dini condition on a self-affine Sierpinski carpet. The Hausdorff spectrum that we find cannot be deduced from that of the associated Gibbs measure by a simple transformation. Indeed, these spectra are respectively obtained as the Legendre transform of two distinct concave differentiable functions that cannot be deduced from one another by a dilation and a translation. This situation is in contrast with what happens in the familiar self-similar case. Our results are presented in the frame of almost-multiplicative functions on the product of two distinct symbolic spaces and their projection onto self-affine carpets [87].

5.4.2. Bilateral Canonical Cascades: Multiplicative Refinement Paths to Wiener’s and Variant Fractional Brownian Limits

Participants: Julien Barral, Benoît Mandelbrot.

Statistically self-similar measures on $[0,1]$ are obtained as limit of multiplicative cascades of independent positive random weights W distributed on the b-adic subintervals of $[0,1]$. We extend these cascades naturally by allowing the random weights to take negative values. This yields martingales taking values in the space of real valued continuous functions on $[0,1]$. We focus on a family $\{(B_n^H)_{n\geq 1}\}_{H\in(-\infty,1)}$ of such martingales for which the random weights are $\pm b^{-H}$ with the probabilities $\frac{1+b^{H-1}}{2}$ and $\frac{1-b^{H-1}}{2}$. Their study leads to the following alternative: When $H\in(1/2,1)$, as expected, B_n^H converges almost surely uniformly to a function B^H whose Hölder regularity and fractal properties are comparable to those of the sample paths of the fractional Brownian motion of exponent H. Hence H plays the role of a Hurst exponent for B_n^H. When $H\in(-\infty,1/2]$, to the contrary, the martingale B_n^H diverges, but there exists a normalization factor a_n^H tending to ∞ as n tends to ∞ such that B_n^H/a_n^H converges in law to the restriction of a Brownian motion to $[0,1]$. This property has the following counterpart for $H\in(1/2,1)$: There exists a sequence a_n^H tending to 0 when n tends to ∞ such that $(B^H-B_n^H)/a_n^H$ converges in law to the restriction of a Brownian motion to $[0,1]$ [86].

5.4.3. Dynamics of Mandelbrot cascades

Participants: Julien Barral, Jacques Peyrière, Zhi-Ying Wen.

Mandelbrot multiplicative cascades provide a construction of a dynamical system on a set of probability measures defined by inequalities on moments. To be more specific, beyond the first iteration, the trajectories take values in the set of fixed points of smoothing transformations (i.e., some generalized stable laws).

Studying this system leads to a central limit theorem and to its functional version. The limit Gaussian process can also be obtained as limit of an “additive cascade” of independent normal variables [88].

5.4.4. Ubiquity and large intersections properties under digit frequencies constraints

Participants: Julien Barral, Stéphane Seuret.

We are interested in two properties of real numbers: the first one is the property of being well-approximated by some dense family of real numbers $\{x_n\}_{n\geq 1}$, such as rational numbers and more generally algebraic numbers, and the second one is the property of having given digit frequencies in some b-adic expansion.

We combine these two ways of classifying the real numbers, in order to provide a finer classification. We exhibit sets S of points x which are approximated at a given rate by some of the $\{x_n\}_n$, those x_n being selected according to their digit frequencies. We compute the Hausdorff dimension of any countable intersection of such sets S, and prove that these sets enjoy the so-called large intersection property [39].

5.5. Modeling, observation and control in biosciences: the controlled cardiovascular system

Keywords: *bioenergetics*, *biology*, *cardiovcascular system*, *health*, *heart*, *modeling*.

5.5.1. *Differential models of cardiac cells*

Participants: Karima Djabella, Mayer Landau, Michel Sorine.

A two-variable model of cardiac action potential with controlled pacemaker activity and ionic current interpretation. [65]

Since the introduction of the historical Fitzhugh-Nagumo model (1961) with its two state-variables used to describe the excitability phenomena of cell membranes and action potential generation, more complex models have been proposed to better capture the physiology of cardiac cells. However in some model-based signal or image processing applications, two-state-variable models are still useful and there is a need to improve both their qualitative behaviors (shape of action potential, pacemaker activity, ...) and the interpretation of their parameters. Several models have then been derived from the Fitzhugh-Nagumo model, e.g. the van Capelle-Durrer (1980) or Aliev-Panfilov (1996) models, or from simplifications of more complex ionic models, like the Mitchell-Schaeffer model (2003). In this paper, we introduce a two state-variable model of cardiac action potentials from which the above mentioned models can be derived for particular values of its parameters. Like the Mitchell-Schaeffer model, it has an ionic current interpretation relevant for inverse problems and it improves that model, being capable of pacemaker activity as we show using the phase plane representation and a bifurcation analysis.

Reduction of a cardiac pacemaker cell Model using singular perturbation theory. [68]

Cardiac-cell models are now frequently used on the heart scale in model-based signal or image processing applications for understanding cardiac diseases. For these applications, it is necessary to design models representing a good trade-off between detailed description of the complex physiological phenomena on the cardiac-cell scale and available data on the heart scale. In order to contribute to this issue, a detailed cardiac cell model has been developed and is briefly presented. However, the computational burden associated with such a detailed model, the number of parameters and state variables used to describe the behavior of the cardiac electrical activity may render its practical application very difficult. To overcome this problem, singular perturbation theory has been applied to reduce the order of the detailed cardiac pacemaker cell model, while retaining the relevant dynamics with respect to the real system. The model exhibits three time scales (Tikhonov generalized form). Validation results show the ability of the reduced order model to match some of the behavioral features of the detailed model, such as the excitability, but fails to reproduce other features, such as the shape of pacemaker action potential. This drawback is the consequence that our cardiac pacemaker cell model has a non-Tikhonov asymptotic structure.

5.5.2. *Electrocardiogram QT interval detection and restitution curve*

Participants: Alfredo Illanes Manriquez, Claire Médigue, Yves Papelier, Michel Sorine, Qinghua Zhang.

For isolated and electrically excited cardiac cells, there is a well known relationship between each action potential duration (APD) and the preceding diastolic interval (DI) under the name of *restitution curve*. A similar relationship has been recently revealed between the QT interval and the preceding TQ interval computed from electrocardiogram (ECG) signals measured at the body surface [18]. By analogy to the cellular restitution curve, we call this relationship *ECG-based restitution curve*. To successfully build this curve, the ECG signals must be recorded under some particular conditions. The isometric Handgrip test has proved to be a good choice for this purpose. It is also important to delimit the QT interval with a sufficient accuracy. In our previous work, the QT interval was obtained by adding a constant to the RT interval which is easier to delimit [18]. More recently, in order to improve the delimitation of the QT interval, an algorithm for QRS onset detection has been developed. It is based on the computation of the envelop signal of the QRS defined with the Hilbert transform, and also on the application of a statistical detection algorithm. This new algorithm is now used for building ECG-based restitution curves and has been presented at the Annual International Conference of the IEEE Engineering in Medicine and Biology Society [69].

5.6. Modeling, observation and control in biosciences: ovulation control

Keywords: *conservation laws*, *coupled oscillators*, *dynamical systems*, *neuro-endocrinology*, *physiology*.

5.6.1. Multiscale modeling of the selection of ovulatory follicles

Participants: Frédérique Clément, Nki Echenim, Mazyar Mirrahimi, Michel Sorine.

Biological background. Ovarian follicles are spheroidal structures sheltering the maturating oocytes. Follicular development is the process of growth and functional maturation undergone by ovarian follicles, from the time they leave the pool of primordial follicles until ovulation, at which point they release a fertilizable oocyte. Actually, very few terminally developing follicles reach ovulatory size; most of them undergo a degeneration process, known as atresia. The species-specific ovulation rate (number of ovulatory follicles) results from an FSH-dependent follicle selection process. FSH acts on the somatic cells surrounding the oocyte, making-up the granulosa cell layer, and controls their commitment toward either proliferation, differentiation or apoptosis. The cellular composition of the granulosa ultimately determines the follicular fate: a shift from a proliferative state to a differentiated one characterizes an ovulatory trajectory, while a trend toward apoptosis leads to atresia. FSH release by the pituitary gland is in turn modulated by granulosa cell products such as estradiol and inhibin. This feedback is responsible for reducing FSH release, leading to the degeneration of all but those follicles selected for ovulation.

Modeling approach. Up to now, the mathematical models interested in follicular development could be cast into two approaches. One focuses on the mechanims underlying follicular development, on the molecular and cellular scales, and considers separately either ovulatory or atretic (degenerating) paths. The other focuses on the selection process by itself which is investigated in the sense of population dynamics. We aim at merging the molecular and cellular mechanistic description introduced by the former approach with the competition process dealt with in the latter, using both multiscale modeling and control theory concepts [16]. Each ovarian follicle is described through a 2D density function, $\phi_f\,(a,\gamma,t)$, giving an age and maturity-structured description of its cell population. The conservation law for ϕ_f reads :

$$\frac{\partial \phi_f}{\partial t} + \frac{\partial (h_f \phi_f)}{\partial \gamma} + \frac{\partial (g_f \phi_f)}{\partial a} = G - L \qquad (15)$$

where a represents the cytological age and γ the cellular maturity. A control term representing FSH signal intervenes in the aging (g_f) and maturation (h_f) velocities, gain (G) and loss (L) terms of this conservation law. The multiscale feature of the model operates through the zero and first-order moments of the density, corresponding respectively to the total number of cells and global maturity in a follicle. Summing those moments on the whole population of follicles gives further information on the ovarian scale. The model accounts for the changes in the total cell number, growth fraction (proportion of proliferating cells in the whole population) and global maturity of both ovulatory and degenerating follicles for various intensities of the selection rate. The different selection process outputs (mono- or poly-ovulation, anovulation) predicted by the model are consistent with physiological knowledge regarding vascularisation, pituitary sensitivity to ovarian feedback and treatment with exogenous FSH.

Control approach. The model is associated with two nested accessibility problems, respectively on the ovarian scale (reachability of the conditions for ovulatory surge triggering) and on the follicular scale (reachability of the conditions for ovulation). Due to the complexity of the model formulation (hybrid features, feedback in the velocity and loss terms), such problems cannot be tackled head-on. Defining similar accessibility problems from a characteristics-like formulation of the conservation law has been the subject of recent research. We have in particular described the set of microscopic initial conditions leading to the macroscopic phenomenon of either ovulation or atresia, in the framework of backwards reachable sets theory [49].

5.6.2. Modeling of the GnRH pulse and surge generator

Participants: Frédérique Clément, Jean-Pierre Françoise, Claire Médigue, Alexandre Vidal.

Biological background. The reproductive axis is under the control of the GnRH (Gonadotropin Releasing Hormone), which is secreted from specific hypothalamic areas in a pulsatile manner. This pulsatility (between 1 pulse per hour and 1 pulse every 6 hours) has a fundamental role in the differential control of the secretion of both gonadotropins: LH (Luteinizing Hormone)–enhanced by higher frequency– and FSH (Follicle Stimulating Hormone) –enhanced by lower frequency–. The pulsatile pattern is tremendously altered once per ovarian cycle into a surge which triggers ovulation in response to increasing levels of estradiol. The estradiol signal is conveyed to GnRH neurons through a network of interneurons. The balance between stimulatory and inhibitory signals emanating from interneurons controls the behaviour of the GnRH network.

Modeling approach. We have proposed a mathematical model allowing for the alternating pulse and surge pattern of GnRH (Gonadotropin Releasing Hormone) secretion. 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 explaining the sequence of different secretion patterns (slow oscillations, fast oscillations and periodical surge) of GnRH secretion as an hysteresis loop. Specifications on the model parameter values are derived from physiological knowledge in terms of amplitude, frequency and plateau length of oscillations. The behaviour of the model can be illustrated by numerical simulations reproducing natural ovarian cycles and either direct or indirect actions of ovarian steroids on GnRH secretion [44].

5.6.3. Circannual rhythmicity in ovulation control

Participants: Frédérique Clément, Claire Médigue.

This work is done in collaboration with Benoît Malpaux (UMR CNRS-INRA 6175).

In sheep as in many vertebrates, the seasonal pattern of reproduction is timed by the annual photoperiodic cycle, characterised by seasonal changes in the daylength. The photoperiodic information, conveyed by optic nerves from the retina to the pineal gland, is translated into circadian levels of melatonin. This hormone acts in an endocrine way upon GnRH secretion to control ovarian cyclicity. The main question to address is whether there exists an endogenous circannual rhythm and in which extent it is entrained and/or synchronised by the photoperiodic cycle. We dispose of long-term time series (several years) of LH (Luteinizing Hormone) collected from ewes subject to different photoperiodic regimes. Due to intra- and inter- animal variability and unequal sampling times, the existence of an endogenous rhythm is not straightforward. We have used time-frequency signal processing methods, and especially the Pseudo-Wigner-Ville Distribution, to extract possible hidden rhythms from the data and to characterise their frequency, amplitude, synchronisation and correlation with the synthetic photoperiodic environment.

5.6.4. Connectivity and dynamics of the FSH signalling network in granulosa cells

Participants: Frédérique Clément, Claire Médigue.

This work is done in collaboration with François Fages (CONTRAINTES), Domitille Heitzler and Eric Reiter (UMR CNRS-INRA 6175).

Our current work consists in analysing the connectivity and dynamics of the FSH signalling network in its target cells, and embedding the network within a multiscale representation, from the molecular up to the organic level [60]. We are examining the relative contributions of different pathways to the cell response to FSH signal, in order to determine how each pathway controls downstream cascades and which mechanisms are involved in the transitions between different cellular states. We have used the BIOCHAM (BIOCHemical Abstract Machine) environment, first at the boolean level, to formalise the network of interactions corresponding to the FSH-induced signalling events on the cellular scale. This network has then be enriched with kinetic information coming from experimental data, which allows us to use 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 are applied to undertake a systematic comparison between the model behaviour and the results of experiments.

5.7. Clinical and physiological applications

Keywords: *Heart rate variability*, *cardiovcascular system*, *health*.

Participants: François Cottin, Taous-Meriem Laleg, Claire Médigue, Yves Papelier, Michel Sorine.

5.7.1. A nonlinear spectral analysis of arterial blood pressure waveforms: application to physiological and clinical conditions

We have proposed [108] a reduced model of the input-output behaviour of an arterial compartment, including the short systolic phase where wave phenomena are predominant. A more detailed analysis is now available [14]. The objective is to provide basis for model-based signal processing methods for the estimation from non-invasive measurements and the interpretation of the characteristics of these waves. We develop now the corresponding signal processing method (see 5.2.1) and some applications.

This method, based on scattering transform for a one dimensional SchrËdinger equation, provides new parameters, related to the systolic and diastolic parts of the pressure. They are compared to the classical blood pressure indexes in four conditions: moderate chronic heart failure, exercise before and after training in high fit triathlets [73], handgrip isometric exercise and orthostatic tilt test. [84]. In each case these parameters are more significant than the classical ones. Moreover, they bring up new indexes, difficult to measure routinely: we think that the two first invariants might give information about the variation of the stroke volume and the ventricular contractility. At last, the first eigenvalue seems to reflect the baroreflex sensitivity in a certain way. We are now working on the validation of these hypotheses.

5.7.2. Ventilatory Thresholds Assessment from Heart Rate Variability during an Incremental Exhaustive Running Test

Collaboration with the “Unité de Biologie Intégrative des Adaptations à l’Exercice”, INSERM 902/EA 3872, Génopôle, Evry.

The present study examined whether the ventilatory thresholds during an incremental exhaustive running test could be determined using heart rate variability (HRV) analysis. Beat-to-beat RR interval, V(.-)O (2), V(.-)CO (2) and V(.-) (E) of twelve professional soccer players were collected during an incremental test performed on a track until exhaustion. The “smoothed pseudo Wigner-Ville distribution” (SPWVD) time-frequency analysis method was applied to the RR time series to compute the usual HRV components vs. running speed stages. The ventilatory equivalent method was used to assess the ventilatory thresholds (VT1 and VT2) from respiratory components. In addition, ventilatory thresholds were assessed from the instantaneous components of respiratory sinus arrhythmia (RSA) by two different methods: 1) from the high frequency peak of HRV (FHF), and 2) from the product of the spectral power contained within the high frequency band (0.15 Hz to fmax) by FHF (HF x FHF) giving two thresholds: HFT1 and HFT2. Since the relationship between FHF and running speed was linear for all subjects, the VTs could not be determined from FHF. No significant differences were found between respective running speeds at VT1 vs. HFT1 (9.83 +/- 1.12 vs. 10.08 +/- 1.29 km x h (-1), n.s.) nor between the respective running speeds at VT2 vs. HFT2 (12.55 +/- 1.31 vs. 12.58 +/- 1.33 km x h (-1), n.s.). Linear regression analysis showed a strong correlation between VT1 vs. HFT1 (R (2) = 0.94, p < 0.001) and VT2 vs. HFT2 (R (2) = 0.96, p < 0.001). The Bland-Altman plot analysis reveals that the assessment from RSA gives an accurate estimation of the VTs, with HF x FHF providing a reliable index for the ventilatory thresholds detection. This study has shown that VTs could be assessed during an incremental running test performed on a track using a simple beat-to-beat heart rate monitor, which is less expensive and complex than the classical respiratory measurement devices [45].

5.7.3. Effect of ventilatory thresholds overstepping on blood pressure variability in well-conditioned humans.

Collaboration with the Unité de Biologie Intégrative des Adaptations à l’Exercice, INSERM 902/EA 3872, Génopôle, Evry.

The present study hypothesized that both SBPV and instantaneous baroreflex sensitivity (BRS) should be different just below (A1), between (A2) and above VTs (A3). Sixteen well-conditioned subjects participated to this study. ECG, blood pressure and gas exchanges were recorded during an exhaustive incremental exercise test on a cycle ergometer. To assess VTs, ventilatory equivalents were computed from gas exchange parameters. A spectral analysis provided RR and SBP smoothed power spectral densities, and spectral baroreflex sensitivity. A cross-spectral analysis was performed to assess the coherence function between RR and SBP smoothed power spectral densities (SPSD). The coherence function, ranging from 0 to 1, provides an estimate of the linearity between two spectra. A coherence greater than 0.5 is required for the assessment of spectral baroreflex sensitivity, and the values between 0.5 and 1 measure the degree of linear correlation between the spectra. Baroreflex sensitivity is estimated by two parameters: the modulus of the transfer function between RR-SPSD and SBP-SPSD (so called spectral gain) and the square of the RR-SPSD/SBP-SPSD ratio (so called alpha index).

5.7.4. Cardiovascular and respiratory interactions in patients with acute lung injury under mechanical ventilation

Collaboration with the Unité de Biologie Intégrative des Adaptations à l'Exercice, INSERM 902/EA 3872, Génopôle, Evry.

This study is assessed in the context of the PhD of the Dr. Andry Van de Louw, École doctorale "des génomes aux organismes". The title is: "Etude des interactions cardiorespiratoires chez le patient en réanimation : contribution respective des effets mécaniques et nerveux dans la genèse de la variabilité à court terme des paramètres cardiovasculaires". 17 subjects were recorded in the 14-bed medicosurgical intensive care unit (ICU) of the Centre Hospitalier Sud-Francilien (Evry, France). The assessment of the phase between cardiovascular and respiratory signals is made using the Complex DeModulation (CDM), whereas the spectral baroreflex sensitivity is estimated using the transfer function between RR and SBP smoothed power spectral densities (SPSD).

6. Contracts and Grants with Industry

6.1. Modeling of Diesel & HCCI engines for control applications

Keywords: *HCCI*, *combustion engine*, *control*, *diesel*, *energetics*, *modeling*, *monitoring*, *process engineering*.

6.1.1. Modeling of HCCI combustion: effects of chemical kinetics and turbulent mixing (Renault contract)

Participants: Fadila Maroteaux, Pierre-Lin Pommier, Michel Sorine.

Renault contract 104 D1151 00 21102. P.-L. Pommier is preparing his PhD in the framework of this contract. The numerical modeling of complex turbulent flow is an important issue in engines applications. In order to investigate the effects of both the chemical kinetics and turbulent mixing, a stochastic model is used. At first a simple partially stirred plug flow (PaSPFR) is considered, where spatial homogeneity is assumed and were only two physical processes remain: chemical reaction and mixing. In the combustion chamber, local quantities are chemical species mass fractions and temperature and are assumed to be random variables (with their joint random vector). The time evolution of the mass density function (MDF) transport equation takes into account the terms representing the mixing properties and the reaction mechanism of the system. The two terms are approached by a stochastic process, the 26 reactions mechanism developed above is used to model the reaction term [128]. This work is under progress with the PhD of Pierre-Lin Pommier, where the first step was centred on the general modeling of reacting system.

6.1.2. Monitoring of NOx trap regeneration (Renault contract)

Participants: Damiano Di Penta, Michel Sorine, Qinghua Zhang.

CIFRE Contract with Renault, from October 2004 to October 2007.

A NOx trap is a post-combustion catalytic device designed to reduce oxides of nitrogen (NOx) emitted in the exhaust gas of diesel engines. Because of the combustion with a relatively high level of oxygen, the resulting NOx components in the exhaust gas is a major issue of pollution for vehicles equipped with such engines. A NOx trap treats the NOx through a mechanism of storage and regeneration. The catalytic reactions in the NOx trap allow to store NOx molecules. When the trap is full, it can be regenerated by excess of fuel or by injection of other reducing agents. The control of the regeneration activation is difficult, because no sensor is available for direct measurement of the level of NOx storage. This study has been part of the PhD project of Damiano Di-Penta [31]. Based on a reduced mathematical model of NOx trap and on available sensors, two approaches to evaluating the level of NOx storage and the efficiency of regeneration procedures have been studied. The results have been validated through experimentations on a test bed.

6.2. Mathematical modeling monitoring and control of a fuel cell system

Keywords: *control*, *energetics*, *fuel cell*, *fuel processor*, *modeling*, *monitoring*, *process engineering*.

6.2.1. Water and heat conservation modelling for a reformate supplied fuel cell system (Renault contract)

Participants: Fehd Benaïcha, Karim Bencherif, Michel Sorine.

In this CIFRE contract with Renault, Fehd Benaïcha has studied control strategies optimising the fuel-cell system efficiency [58]. This work is done in cooperation with Jean-Claude Vivalda (CONGE team-project).

6.2.2. Modeling and Diagnosis of PEM Fuel Cell Systems (ANR project DIAPASON)

Participants: Pierre-Alexandre Bliman, Stefano Perabò, Michel Sorine, Hassen Taidirt, Qinghua Zhang.

This work is conducted within the framework of the project Diapason (ANR, Program PAN-H 2006), dedicated to the diagnosis of fuel cell systems for stationary and automotive applications. This project is aimed at developing diagnosis methods using the fuel cell stack itself as a sensor, with limited instrumentation. These methods are thought up for real-time use, coupled with the stack control system, or during planned maintenance operations, in order to improve the system reliability and its energetic and environmental performances, and to extend its life.

Our diagnosis strategy is based on impedance spectroscopy measurements and physical modeling. The main failures which have to be detected and diagnosed are CO poisoning, membrane dehydration and membrane flooding.

We have worked in two directions. First, based on 0D models, we have studied the existing models and started the analysis of the Nyquist locus describing the equivalent impedance of a fuel cell, based on the harmonic balance method. Complementarily, a 1D model of intermediary complexity describing the main electrical and chemical phenomena along the cathode-anode axis has been elaborated and implemented to provide more detailed description of the behavior during impedance measurements. This more complex model is intended to evaluate the ability of the coarser one to reproduce nominal and damaged operating conditions.

6.3. Diagnosis of cable networks for automotive applications (ANR project SEEDS)

Participants: Mehdi Admane, Michel Sorine, Qinghua Zhang.

The project entitled “Smart Embedded Electronic system for DiagnosiS" (SEEDS) aims at developping a device to assist the diagnosis of failures in electric wire connections for automotive applications. This project is funded by Agence Nationale de la Recherche (ANR) for three years from January 2006. The involved partners are Renault Trucks, Serma Ingénierie, Delphi, Monditech, Supelec-LGEP and INRIA.

The number of electronic equipments is increasing rapidly in automotive vehicles. Consequently, the reliability of electric connections is becoming more and more important. The first goal of this project is to develop a compact and easy to use device for the diagnosis of electric connection failures in garage or at the end of the production chain. It should be capable of detecting and locating failures in cables and in connectors. The second goal is on-board diagnosis: the diagnosis device will be integrated to the vehicle in order to detect failures under normal working conditions of the vehicle. The work of our team during this year has been on a reduced order differential model and on the application of the inverse scattering theory. See also Section 5.2.2.

6.4. Nonlinear system identification (The Mathworks contract)

Participant: Qinghua Zhang.

Contract with The Mathworks, from July 2005 to July 2010. See also the software section 4.1.

The System Identification ToolBox (SITB) is one of the main Matlab toolboxes commercialized by The Mathworks. Initially, the toolbox authored by Lennart Ljung (Sweden) was limited to the identification of linear systems. After years of research and development with several partners, the extension of the toolbox to nonlinear system identification has been released this year by The Mathworks. As an important upgrade of the toolbox, it includes algorithms for both black box and grey box identification of nonlinear dynamic systems. Under this contract, INRIA continues to maintain the product and to develop future versions.

7. Other Grants and Activities

7.1. National grants

7.1.1. CardioSense3D (Inria Large Initiative Action)

Participants: Karima Djabella, Alfredo Illanes Manriquez, Taous-Meriem Laleg, Yves Papelier, Michel Sorine, Qinghua Zhang.

CardioSense3D is a 4-year Large Initiative Action launched in 2005 and funded by INRIA, which focuses on the electro-mechanical modeling of the heart. This action follows the 4-year ICEMA project and is described in great details in http://www-sop.inria.fr/CardioSense3D. See also [63].

7.1.2. AgroBI (Inra federative program)

Participant: Frédérique Clément.

This project deals with the integrative biology of the signalling system induced by FSH (Follicle-Stimulating Hormone). It is funded and coordinated by INRA (Eric Reiter). The research is undergone in cooperation with the INRIA project team Contraintes.
http://www.inra.fr/internet/Projets/agroBI/pageagroBI.html
http://contraintes.inria.fr/~heitzler/INSIGHT/Home.html

7.2. European grants

7.2.1. NoE HYCON

Participant: Michel Sorine.

M. Sorine participates to the Network of Excellence HYCON (“Taming Heterogeneity and Complexity of Networked Embedded Systems”) started on 15/09/04 in the context of the Sixth Framework Programme. He is involved in the WP4c (Automotive applications) in Hybrid Modeling of HCCI engine.

8. Dissemination

8.1. Scientific activity and coordination

8.1.1. Coordination activity

J. Barral:
- Co-head, with F. Ben Nasr, of the franco-tunisian CMCU Project “Fractales, Images et Ondelettes” (2005-2007).
- Member of the “Jury de l’Agrégation externe de Mathématiques”, since january 2005.
- Member of the scientific and organizing committees of the conference "Fractals and Related Fields", September 8-13 2007, Monastir (Tunisia).

P.A. Bliman:
- Member of the Program Committee of the 2007 IEEE Conference on Decision and Control (New Orleans, LA, USA, December 2007) and of the 2008 IEEE Conference on Decision and Control (Cancun, Mexico, December 2008).
- French coordinator of the INRIA-FAPESP Cooperation Program ‘Parameter-dependent semidefinite programming in robust control. Application to analysis of dynamical system interaction networks.’ (February 2007–January 2009). Partner: Unicamp (Campinas, Brazil).
- Responsible for INRIA of the STIC-AmSud International Research Program ‘Analysis and synthesis for dynamical systems submitted to nonlinearities, uncertainties and delays’ (January 2008–December 2009). Apart from INRIA, partners are: LAAS (Toulouse), Universidade Federal do Rio Grande do Sul (Porto-Alegre, Brazil), Unicamp (Campinas, Brazil), Universidad de Concéption (Chile).
- Responsible for INRIA, Paris-Rocquencourt Research center, of the activities of the Multi-partner Marie Curie Training Site entitled Control Training Site (beginning in 2002).
- Responsible for INRIA of the ANR contract DIAPASON (Diagnostic methods for fuel cell power generator for automotive applications and stationary applications without instrumentation) & Webmaster of the website of the research project Diapason (ANR PAN-H).
- Officially charged by the board of INRIA of reporting on the relations with Agence nationale pour la Recherche (“chargé de mission pour l’ANR").
- Member of the “Commission de spécialistes" (61st Section) Université Henri Poincaré (Nancy).
- Referee and member of the board for PhD Vincent Bompart (Université Paul Sabatier, Toulouse III).

F. Clément:
- Member of the scientific board of the PHASE (Animal Physiology and Breeding Systems) department of INRA (National Institute for Agronomic Research).
- Sisyphe team correspondent for the GdR MABEM (Mathematics for Biology and Medicine).
- Expert for the BBSRC (Biotechnology and Biological Sciences Research Council).
- Coordinator of the REGATE (REgulation of the GonAdoTropE axis) working group.
- Expert for the *American Journal of Physiology*.
- Member of a CR2 recruiting committee.

M. Sorine:
- Member of the International Program Committees for the JDMACS / JNMACS 2007 (Journées Doctorales & Nationales d’Automatique) and Reliability in electromagnetic systems 2007, conferences.
- Member of several PhD and HDR committees.

Q. Zhang:

- Member of IFAC Technical Committee on Fault Detection, Supervision and Safety of Technical Processes (SAFEPROCESS).

8.2. Teaching activity

- P.A. Bliman: “Tools for system analysis and design by Linear Matrix Inequalities techniques” (16 hours, course MP302, Instituto Tecnológico de Aeronáutica, São José dos Campos, Brazil).
- F. Clément: “Modeling and control of biological systems” course, part of the "Master’s Degree in BioInformatics and BioStatistics” (Paris-Sud 11 University).
- E. Crépeau is Associate professor at UVSQ (“en détachement” in 2007).
- F. Maroteaux is Professor at UVSQ (full time service).

8.3. Seminars

J. Barral:
- “Eléments d’analyse multifractale” and “Spectre de singularité des mesures de Gibbs auto-affines”, séminaire d’analyse et probabilité et groupe de travail d’analyse et systèmes dynamiques de l’Université d’Orléans, January 2007.
- “Multifractal analysis of sums of Dirac masses”, Fractal Geometry seminar of Tsinghua University, April 2007.
- “Dynamique des cascades multiplicatives de Mandelbrot”, sÃ©minaire de ProbabilitÃ©s de l’UniversitÃ© Paris 6, September 2007.
- “Mandelbrot Martingales and related questions I, II, III”, lectures given in the Mathematics Department of the Chinese University of Hong-Kong, October-November 2007.
- “Dynamique des cascades multiplicatives de Mandelbrot”, sÃ©minaire de ProbabilitÃ©s de l’UniversitÃ© de Versailles, November 2007.

P.A. Bliman:
- 1 lecture at Unicamp (Campinas, Brazil), July 2007.
- 1 lecture at Instituto Tecnológico de Aeronáutica (ITA, São José dos Campos, Brazil), July 2007.
- 1 lecture at Instituto Militar de Engenharia (IME, Rio de Janeiro, Brazil), July 2007.
- 1 lecture at Universidade Federal de Rio de Janeiro (Coppe, UFRJ, Rio de Janeiro, Brazil), July 2007.
- 1 lecture at Universidade de São Paulo (Escola PolitÃ©cnica, USP, São Paulo, Brazil), July 2007.
- Presentations in the meetings of the project Diapason (ANR PAN-H), April and October 2007.

F. Clément:
- Talk “Integrative signalling of the FSH receptor, 28 novembre 2007. Open seminar of the Bang project team”.

M. Mirrahimi:
- Invitation at Caltech by Prof. Daniel (Lidar’s group at the Univerity of South California). Talk on the “Feedback stabilization of quantum states”.
- In the framework of the collaborations with Prof. Herschel Rabitz’s team at the chemistry department of the Princeton university, discussions with different members of his team and on different subjects: the quantum landscape control, quantum parameter identification and open quantum system’s control. Talk on the “Observer-based Hamiltonian identification for quantum systems”.
- Invited speaker to the physics workshop, “*The Principles and Applications of Control in Quantum Systems, 9-13 July 2007 Sydney, Australia*”. Talk on “*Some results on the feedback control of multi-qubit systems*”.
- Invitation at the Griffith University at Brisbane, Australia by Prof. Howard Wiseman to visit his theoretical physics group. Talk on the “Observer-based Hamiltonian identification for quantum systems”.
- Participation to the “projet blanc, ANR C-QUID, contrôle et identification de systèmes quantiques”.

Q. Zhang
- Lecture "Adaptive observer for linear and nonlinear systems" at Zhejian University, Advanced Control Institute, August 2007, Hangzhou, China.
- Lecture "Data line change detection with application to Mud Logging data processing" at Zhejian University, Advanced Control Institute, August 2007, Hangzhou, China.
- Talk "Parsimonious Representation of Signals Based on Scattering Transform". Workshop of European Research Network System Identification, October 2007, Venice, Italy.

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