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SIgnals and SYstems in PHysiology and Engineering

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THEME BIO

Activity Report

2008

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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 created in July 2007 is a follow-up of SOSSO2 Research-Team.

SISYPHE (SIgnals and Systems in PHysiology and Engineering) deals with questions raised by some complex dynamical systems issued from Physiology and Engineering: modeling; identification and observation from signals ; real-time health monitoring or control. We consider networked or multi-scale dynamical systems involving exchanges of energy or control information among scales and subsystems or quantum & quantum-like systems. Most studies are motivated by health monitoring of the cardiovascular and reproductive systems or of some critical engineering systems. In monitoring of hemodynamic or electrical networks, a natural quantization is leading to quantum-like systems. This leads us to consider more generally some prospective questions of system theory arising from the emerging domain of "quantum engineering".

The research on the cardiovascular system is done, in part, in the framework of CardioSense3D (3D-electro-mechanical modeling of the heart and estimation of patient specific parameters for clinical applications), an Inria Large-scale Initiative Action. The research on the reproductive system is done in the framework of REGATE (REgulation of the GonAdoTropE axis), an Inria Large-scale Initiative Action in preparation.

Research topics leading to long-term projects and collaborations:
Signals & Systems:

- Dynamical systems modeled by ordinary differential equations: modeling, observation and control.
- Networks of dynamical systems: observation and control of synchrony and other coherent structures.
- Quantum & quantum-like systems: estimation and control.
- Multiscale dynamical systems: analysis of multiscale properties of signals and relations with the underlying dynamical systems.

Applications to Physiology & Engineering:

- Model-based observation and control of the cardiovascular system: (multiscale-) model-based signal processing (ECG, pressure, heart-rate). Monitoring and control of cardiac prosthesis.
- Quantization of waves propagation in transmission-line networks & Inverse scattering. Application to health monitoring of cabled electrical networks and to the arterial pressure waveform analysis.
- Health monitoring and control of energy conversion systems: glycemic control in critically ill patients ; fuel-cell systems monitoring.
- Identification and control of some quantum systems. Towards "quantum engineering".
- Multiscale modeling of the controlled follicle selection process & Control of the reproductive axis.

2.2. Highlights of the year

- In 2008, our researches on observation and control of the cardiovascular system have found a promising application: we start a collaboration with the newly created CARMAT SAS (Suresnes, France) medtech start-up, on the control of the Total Artificial Heart developed by this company with the help of Professor Alain Carpentier.

- Our results on health monitoring of transmission-line networks & Inverse scattering have a strong impact in several industrial research projects:
  - They are used in the ANR project SEEDS (Smart Embedded Electronic system for DiagnosiS), coordinated by CEA LIST that aims at developping a device to assist the diagnosis of failures in electric wire connections for automotive applications. In 2008, SEEDS received the "Information and Communication Systems Integration" PREDIT Prize.
  - They provide the methodological basis of two new ANR projects accepted in 2008: 0-DEFECT with CEA, PSA and Freescale, which aims to study and implement new methods suited to an onboard system for monitoring complex networks and INSCAN (INfrastructure Safety Cables ANalysis) with CEA and SNCF on the health monitoring of transmission lines for railway signaling.

3. Scientific Foundations

3.1. System theory for systems modeled by ordinary differential equations

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 using models is common to many research fields. For dynamical systems encountered in the domains of engineering and physiology, this is of practical importance for monitoring, prediction, and control. For such purposes, we consider the following model of dynamical systems:

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

where $x(t)$, $u(t)$ and $y(t)$ represent respectively the state, input and output of the system, f and g characterize the state and output equations, parameterized by θ and subject to modeling and measurement uncertainties $w(t)$ and $v(t)$. Modeling (i.e. the derivation of such equations) 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 [129], whereas algorithms for tracking the state trajectory $x(t)$ are called observers [111]. 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 [19], [82]. 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 raise new challenging problems.

3.1.2. Examples of reduced order models: cardiac cells, fuel cells & GnRH neurons

Reduced order modeling of cardiac ventricular cells for signal & image processing applications.
Models of the electro-mechanical activity of the cardiac muscle are useful at the scale of the cardiovascular system as well as at the organ scale. They are used in CardioSense3D for computing stress, strain and action potential fields from 3D image processing. We have obtained a 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 [145].

We have revisited the ionic-currents models of cells representing membrane phenomena and calcium dynamics in order to reduce them for signal or image processing applications [104], [105], [106]. 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. In the case of excitation-contraction coupling without mechano-electrical feedback considered in CardioSense3D, the model has the following structure:

$$\begin{aligned} \frac{dv}{dt} &= f_V(v,u,w,u_{ext},\theta_e,w_e) && \text{Membrane dynamics and excitation mechanism (CICR)} \\ \frac{du}{dt} &= f_U(v,u,w,\theta_e,w_e) && \text{Intracellular calcium dynamics} \\ \frac{dw}{dt} &= f_W(w,x,p_{O2},\theta_w,w_o) && \text{Chemical energy conversion (cell metabolism)} \\ \frac{dx}{dt} &= f_M(x,u,w,\theta_m,w_m) && \text{Energy production (contractility and motion dynamics)} \\ y &= g(x,v,w,\theta_e,\theta_m,v(t)) && \text{Measured output (e.g. membrane potential, stress)} \end{aligned} \tag{2}$$

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. Bifurcation analysis is used to study the various behaviors of this model: it can be 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). It can also behave like a controlled pacemaker [105], [103]. This type of model may help to better understand the control of the heart by the SNA or cardiac arrhythmias caused by abnormal automaticity.
The mechanical state variables x are typically (see our model [6]) a controlled stiffness and an internal variable of deformation (constitutive law) and a deformation and a deformation velocity (equation of motion).
The w-equation, added in a "fueled cardiac cell" model under development for CardioSense3D, takes into account oxygen supply and the main demands in energy (motors, pumps and exchangers). New state variables and input are necessary (vector w and p_{O2}). The output may now contain information on the V_{O2} drop.

Reduced order modeling of fuel cells for control and diagnosis applications.
A PEM Fuel Cell model has been developed in collaboration with Renault (RESPIRE project) [12]. 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). Its structure is similar to (2) when CO poisoning and membrane humidity are modeled.

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.
The GnRH neuron and interneuron networks can be modeled 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 [9].

3.1.3. Observation and control of networks of dynamical systems (NODS)

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

Networks of dynamical systems (NODS).
The real-life systems we consider, can be modeled (at least for some of their sub-systems) as networks of (almost identical) dynamical systems (NODS for short). Often, the available sensors provide information only at the macroscopic scale of the network. 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 sensor limitation implies challenging problems for the observation and control of such systems. The control objective may be formulated in terms of some kind of average behavior of the components and of bounds on some deviations from the average. To this end, appropriate modeling techniques must be developed.

The NODS are intensively studied in physics and mathematics (see, e.g. [146] or [93] 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. New control issues are also of particular interest as, here, the problem of control of synchronization. We illustrate this with an example of NODS where each dynamical system i exchanges with the others, $j = 1...N$, in an additive way, a frequent situation in our applications. A example of network based on dynamical systems (1) is [93]:

$$\begin{aligned} \frac{dx_i}{dt} &= f_i(x_i, u_i, \theta_i, w_i) - \Sigma_{j=1}^{N} \mathcal{C}_{i,j} g_j(x_j, u_j, \theta_j, v_j) \\ y &= g(x_1, ...x_N, u_1, ...u_N, \theta_1, ...\theta_N, v_1, ...v_N) \end{aligned} \tag{3}$$

The connectivity matrix $\mathcal{C}$ represents the structure of the network.

NODS and Partial Differential Equations.
Semi-discretization in space of a PDE of evolution leads to NODS and in some situations, working with the PDE may be more efficient. Consider for example the NODS version of the first two equations of (2):

$$\begin{aligned} \frac{dv_i}{dt} &= f_V(v_i, u_i, u_{ext,i}, \theta_{e,i}, w_{e,i}) - \Sigma_{j=1}^{N} \mathcal{C}_{i,j} g(x_j, u_j, \theta_j, v_j) \\ \frac{du_i}{dt} &= f_U(v_i, u_i, \theta_{e,i}, w_{e,i}) \end{aligned} \tag{4}$$

A particular case is the semi-discretization in space of a reaction-diffusion equation with no diffusion term for the intracellular state variables, the prototype being is the FitzHugh-Nagumo equation. For 3D computations as is the case in CardioSense3D, the PDE approach allows using well adapted discretization schemes.

$$\frac{\partial v}{\partial t} = \sigma \Delta v + g_V(v, u, u_{ext}, \theta_e, w), \quad \frac{\partial u}{\partial t} = f_U(v, u, \theta_e, w_e) \tag{5}$$

For a fuel-cell stack with less than 50 cells, the NODS approach is interesting.

Consider now the dynamical population of cells mentioned in section 3.4.2. The coupling between cells is due to the control and the NODS model, with $\mathcal{C} = 0$ and N variable (depending upon the set of trajectories of the cells in the age-maturity plane) corresponds to a particle approximation of a controlled conservation law [14], [13] where, for each follicle f, the cell population is represented in each cellular phase by a density ϕ_f and u_f and U are respectively a local control of follicle f and a global control of all follicles:

$$\frac{\partial \phi_f}{\partial t} + \frac{\partial g_f(u_f)\phi_f}{\partial a} + \frac{\partial h_f(\gamma, u_f)\phi_f}{\partial \gamma} = -\lambda(\gamma, U)\phi_f \tag{6}$$

3.1.4. Examples of NODS behaviors of interest: synchrony and other coherent structures

Our studies on fuel cells and cardiac tissues motivates 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, the electrocardiogram and arterial pressure provide some indication about their synchrony e.g. the width of the QRS in ECG is a index of dyssynchrony). Methods for more efficient dyssynchrony observation using these measurements, possibly completed by other measurements, would have important clinical applications. Understanding the natural synchrony control may be helpful for the design of devices for cardiac resynchronization.

For these questions, a possibility is to use NODS models like (2). 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 (3) 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 "average system" and it is natural to represent the system (3) 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 be redefined.

Coherent modes are collective behaviors of the dynamical systems in the ensemble 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. The following examples will be of particular interest for us: traveling waves of action potentials in cardiac electrophysiology ; 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 [96], bifurcations [147] ...

3.2. System theory for quantum and quantum-like systems

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

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

$$\frac{\partial V(z,k)}{\partial z} = -\left(R(z) + jkL(z)\right) I(z,k), \quad \frac{\partial I(z,k)}{\partial z} = -(G(z) + jkC(z))V(z,k) \tag{7}$$

Since the work of Noordergraaf [148], this model is also used for hemodynamic networks with V and I respectively the blood pressure and flow in vessels considered as 1D media, and with $R = \frac{8\pi\eta}{S^2}$, $L = \frac{\rho}{S}$, $C = \frac{3S(r+h)}{E(2r+h)}$ where ρ and η are the density and viscosity of the blood ; r, h and E are the inner radius, thickness and Young modulus of the vessel. $S = \pi r^2$. The conductivity G is a small constant for blood flow.

Monitoring such networks is leading us to consider the following inverse problem: *get information on the functions R, L, C, G from the reflection coefficient* $\mathcal{R}(k)$ (ratio of reflected over direct waves) measured in some location by Time or Frequency Domain Reflectometry (see section 5.2.3). To study this problem it is convenient to use a Liouville transform, setting $x(z) = \int_0^z \sqrt{L(z')C(z')}dz'$, to introduce auxiliary functions $q^{\pm}(x) = \frac{1}{4}\frac{d}{x}\left(\ln\frac{L(x)}{C(x)}\right) \pm \frac{1}{2}\left(\frac{R(x)}{L(x)} - \frac{G(x)}{C(x)}\right)$ and $q_p(x) = \frac{1}{2}\left(\frac{R(x)}{L(x)} + \frac{G(x)}{C(x)}\right)$, so that (7) becomes a Zakharov-Shabat system [119] that reduces to a Schrödinger equation in the lossless case ($R = G = 0$):

$$\frac{\partial v_1}{\partial x} = (q_p - jk)\, v_1 + q^+ v_2, \quad \frac{\partial v_2}{\partial x} = -\,(q_p - jk)\, v_2 + q^- v_1 \tag{8}$$

and $I(x,k) = \frac{1}{\sqrt{2}}\left[\frac{C(x)}{L(x)}\right]^{\frac{1}{4}}(v_1(x,k) + v_2(x,k))$, $V(x,k) = -\frac{1}{\sqrt{2}}\left[\frac{L(x)}{C(x)}\right]^{\frac{1}{4}}(v_1(x,k) - v_2(x,k))$. Our inverse problem becomes now an inverse scattering problem for a Zakharov-Shabat (or Schrödinger) equation: *find the potentials $q^{\pm}$ and q_p corresponding to* $\mathcal{R}$. This classical problem of mathematical physics can be solved using e.g. the Gelfand-Levitan-Marchenko method. See sections 3.4.1 (hemodynamics), 5.2 (general results), 5.2.4 (where Schrödinger on a graph is considered), 6.3.1 (electrical networks).

Nonlinear traveling waves. In some recent publications [124], [123], we use scattering theory to analyze a measured Arterial Blood Pressure (ABP) signal. Following a suggestion made in [149], a Korteweg-de Vries equation (KdV) is used as a physical model of the arterial flow during the pulse transit time. The signal analysis is based on the use of the Lax formalism: the iso-spectral property of the KdV flow allows to associate a constant spectrum to the non stationary signal. Let the non-dimensionalized KdV equation be

$$\frac{\partial y}{\partial t} - 6y\frac{\partial y}{\partial x} + \frac{\partial^3 y}{\partial x^3} = 0 \tag{9}$$

In the Lax formalism, y is associated to a Lax pair: a Schrödinger operator, $L(y) = -\frac{\partial^2}{\partial x^2} + y$ and an anti-Hermitian operator $M(y) = -4\frac{\partial^3}{\partial x^3} + 3y\frac{\partial}{\partial x} + 3\frac{\partial}{\partial x}y$. The signal y is playing here the role of the potential of $L(y)$ and is given by an operator equation equivalent to (9):

$$\frac{\partial L(y)}{\partial t} = [M(y), L(y)] \tag{10}$$

Scattering and inverse scattering transforms can be used to analyze y in term of the spectrum of $L(y)$ and conversely. The “bound states” of $L(y)$ are of particular interest: if $L(y)$ is solution of (10) and $L(y(t))$ has only bound states (no continuous spectrum), then this property is true at each time and y is a soliton of KdV. For example the arterial pulse pressure is close to a soliton [11].

Inverse scattering as a generalized Fourier transform. For “pulse-shaped” signals y, meaning that $y \in L^1(\mathbb{R}; (1 + |x|^2)dx)$, the squared eigenfunctions of $L(y)$ and their space derivatives are a basis in $L^1(\mathbb{R}; dx)$ (see e.g. [144]) and we use this property to analyze signals. Remark that the Fourier transform corresponds to using the basis associated with $L(0)$. The expression of a signal y in its associated basis is of particular interest. For a positive signal (as e.g. the arterial pressure), it is convenient to use $L(-y)$ as $-y$ is like a multi-well potential, and the Inverse scattering transform formula becomes:

$$y(x) = 4\sum_{n=1}^{n=N} \kappa_n \psi_n^2(x) - \frac{2i}{\pi}\int_{-\infty}^{-\infty} k\mathcal{R}(k) f^2(k,x)dk \tag{11}$$

where ψ_n and $f(k,.)$ are solutions of $L(-y)f = k^2 f$ with $k = i\kappa_n$, $\kappa_n > 0$, for ψ_n (bound states) and $k > 0$ for $f(k,.)$ (Jost solutions). The discrete part of this expression is easy to compute and provides useful informations on y in applications. The case $\mathcal{R} = 0$ ($-y$ is a reflectionless potential) is then of particular interest as $2N$ parameters are sufficient to represent the signal. We investigate in particular approximation of pulse-shaped signals by such potentials corresponding to N-solitons. See sections 5.2.2, 5.2.1.

3.2.2. Identification & control of quantum systems

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

Interesting applications for quantum control have motivated seminal studies in such wide-ranging fields as chemistry, metrology, optical networking and computer science. In chemistry, the ability of coherent light to manipulate molecular systems at the quantum scale has been demonstrated both theoretically and experimentally [142]. In computer science, first generations of quantum logical gates (restrictive in fidelity) has been constructed using trapped ions controlled by laser fields (see e.g. the "Quantum Optics and Spectroscopy Group, Univ. Innsbruck"). All these advances and demands for more faithful algorithms for manipulating the quantum particles are driving the theoretical and experimental research towards the development of new control techniques adapted to these particular systems. A very restrictive property, particular to the quantum systems, is due to the destructive behavior of the measurement concept. One can not measure a quantum system without interfering and perturbing the system in a non-negligible manner.

Quantum decoherence (environmentally induced dissipations) is the main obstacle for improving the existing algorithms [113]. Two approaches can be considered for this aim: first, to consider more resistant systems with respect to this quantum decoherence and developing faithful methods to manipulate the system in the time constants where the decoherence can not show up (in particular one can not consider the back-action of the measurement tool on the system); second, to consider dissipative models where the decoherence is also included and to develop control designs that best confronts the dissipative effects.

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

$$i\frac{d}{dt}\Psi(t,x) = (H_0 + u(t)H_1)\Psi(t,x) = (-\frac{1}{2}\Delta + V(x) + u(t)\mu(x))\Psi(t,x), \quad \Psi|_{t=0} = \Psi_0, \tag{12}$$

While the finite dimensional approximations ($\Psi(t) \in \mathbb{C}^N$) have been very well studied (see e.g. the works by H. Rabitz, G. Turinici, ...), the infinite dimensional case ($\Psi(t,.) \in L^2(\mathbb{R}^N;\mathbb{C})$) remains fairly open. Some partial results on the controllability and the control strategies for such kind of systems in particular test cases have already been provided [86], [87], [135]. As a first direction, in collaboration with K. Beauchard (CNRS, ENS Cachan) et J-M Coron (Paris-sud), we aim to extend the existing ideas to more general and interesting cases. We will consider in particular, the extension of the Lyapunov-based techniques developed in [136], [88], [135]. Some technical problems, like the pre-compactness of the trajectories in relevant functional spaces, seem to be the main obstacles in this direction.

In the second direction, one needs to consider dissipative models taking the decoherence phenomena into account. Such models can be presented in the density operator language. In fact, to the Schrödinger equation (12), one can associate an equation in the density operator language where $\rho = \Psi\Psi^*$ represents the projection operator on the wavefunction Ψ ($[A,B] = AB - BA$ is the commutator of the operators A and B):

$$\frac{d}{dt}\rho = -i[H_0 + u(t)H_1, \rho], \tag{13}$$

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

$$\begin{aligned} d\rho_t = -i[H_0 + u(t)H_1, \rho_t]dt + (L\rho_t L^* - \frac{1}{2}L^* L\rho_t - \frac{1}{2}\rho_t L^* L)dt \\ +\sqrt{\eta}(L\rho_t + \rho_t L^* - \mathrm{Tr}\left[(L+L^*)\rho_t\right]\rho_t)dW_t, \end{aligned} \tag{14}$$

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 [89], 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 [137].

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 [127]. Moreover, a first observer-based identification algorithm is under study.

3.3. Multiscale system theory: analysis of transfers of energy and information among scales

In the networks or other ensembles of cells that we consider, even if it is natural to use a small number of base models, corresponding to the various types of cells, it may be of interest to consider the case of non identical cells: the parameters θ_i in (3) are in general all different, even if close to an average value. Strictly speaking, in this case the solution of (3) can never live in the synchronization manifold and it is of theoretical and practical interest to study the deviations $x_i - x_S$ above mentioned.

We are specially interested by large networks with a particular structure, like e.g. possibly infinite binary trees as it is the case for hemodynamic networks (e.g. the coronary tree). When using thermodynamically consistent reduced order models for the cells (e.g. cardiac cells and coronary vessels for the heart or fuel cells) to model the multiscale systems we want to study, a natural question arises: what is the relation between the multiscale structure of the θ_i and the structure of energy $\mathcal{E}(x)$ and information u, y among scales?
The inverse problem is the principal motivation: gaining information on the θ_i from multiscale analysis of y.

3.3.1. Large deviations and singularity spectra ; scaling invariant models

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 ([110], [112], [94], [141], [117]).

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 [110] as well as in the heart-beat variability [134], [116] and in financial time series [131]. 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 (fractal) 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 ([130], [120], [143], [114], [118], [83], [108], [2], [5], [4]) 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.

3.3.2. 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. 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. An ANR project, DMASC, will start in 2009 on these questions.

3.4. Physiological & Clinical research topics

3.4.1. 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 [92]. 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.

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 [84], [145]. 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) [16]).

$0D$ 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 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.

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 [15]. 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 [15]. 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 [115].

Nonlinear spectral analysis of arterial blood pressure waveforms and application to clinical indexes

We have proposed [101] 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 [11]. 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 Schrödinger 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 [125], handgrip isometric exercise and orthostatic tilt test. [126]. 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.

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

Our objective 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. It will be also useful for the control of Artificial heart.

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 cardiorespiratory system dynamics in chronic heart failure [133], [132], [140] ; the autonomic control of the cardiovascular system during sleep [138] ; the effects of exercise intensity and repetition on heart rate variability during training [99], [100], [98]. 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 3.4.1.

3.4.2. 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 [14], [13]. The model results from the double structuration of the granulosa cell population according to the cell age (position within the cell cycle) and to the cell maturity (level of sensitivity towards hormonal control). In each ovarian follicle, the granulosa cell population is described by a density function whose changes are ruled by conservation laws. The multiscale structure arises from the formulation of a hierarchical control operating on the aging and maturation velocities as well on the source terms of the conservation law. The control is expressed from different momentums of the density leading to integro-differential expressions.
Future work will take place in the REGATE project and will consist in:
- predicting the selection outcome (mono-, poly-ovulation or anovulation / ovulation chronology) resulting from given combinations of parameters and corresponding to the subtle interplay between the different organs of the gonadotropic axis (hypothalamus, pituitary gland and ovaries). The systematic exploration of the situations engendered by the model calls for the improvement of the current implementation performances. The work will consist in improving the precision of the numerical scheme, in the framework of the finite volume method and to implement the improved scheme, 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 [9]. 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 [139]. 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. Convergence Study in Consensus Problems

Participant: Pierre-Alexandre Bliman.

We developed this year other aspects of the study of stability for a class of linear discrete-time systems made up of subsystems seeking consensus, a special type of synchronization. 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).

Based on bounds on agents' intercommunication interval, on intercommunication delay and on the weight of the active communications, we have proposed an estimate of the rate of convergence to consesus which sensibly improves those already existing. This work was conducted together with A. Nedić (University of Illinois at Urbana-Champaign, USA) and A. Ozdaglar (Massachusetts Institute of Technology, USA).

5.1.2. 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 a representation of the parameters more fitted to the computational techniques. In particular, we have introduced the use of cartesian products of simplexes ("multi-simplexes") and shown that this choice leads to substantial numerical simplifications.

5.1.3. Robust fault diagnosis based on parameter bounds estimated with an adaptive observer

Participant: Qinghua Zhang.

In model based approaches to fault diagnosis, it is often necessary to explicitly take into account modeling uncertainties in order to achieve robust diagnosis decisions. The robustness issue has been dealt with in the literature of fault diagnosis in different ways, such as statistical rejection and fuzzy logic reasoning. The assumed form of modeling uncertainties has strong impacts on the design of fault diagnosis methods. When bounded uncertainties are assumed, it is in principle possible to make decisions free of any false alarm. However, such approaches usually lead to conservative decisions and may result in an unacceptable rate of misdetections. In order to reduce the conservativeness in such approaches, a method associating adaptive estimation and set-membership computation has been developed in collaboration with Christophe Combastel of ECS-ENSEA [97]. This result is further developed this year in order to enlarge its practical applicability. Faults are modeled as parametric changes in this approach. It was previously assumed that model parameters are constant except at fault occurrences. In the new result, it is assumed that model parameters can vary slowly even in the fault-free case. The bounds of all the assumed modeling uncertainties are propagated to the residual designed for fault diagnosis by set-membership computation in order to ensure the robustness of diagnosis decisions. This new result has been presented at IFAC World Congress 2008 [58].

5.2. System theory for quantum and quantum-like systems

Keywords: *Control of PDEs*, *Extremum-seeking*, *Fault-detection /diagnostics of electrical cabling networks*, *Feedback synchronization*, *Hamiltonian identification*, *Inverse scattering*, *Korteweg-de Vries equation*, *Lindblad-Kossakowski master equation*, *Lyapunov stabilization*, *Singular perturbation*, *Symmetry-preserving asymptotic observers*, *bilinear Schrödinger equation*, *quantum feedback control*, *telegrapher equation*.

5.2.1. Scattering based analysis of pulse-shaped signals interpreted as quantum wells

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 [124], [123]. This inverse scattering technique consists on solving the spectral problem associated to an 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 terms of traveling waves (the N-solitons), low and high frequency components of the standard Fourier analysis, are replaced by low and high velocity components [62], [24]. Applications of the method to physiological signals are currently studied (see 3.4.1).

5.2.2. Parsimonious representation of signals based on scattering transforms

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

Representing numerical signals with mathematical models is a frequently encountered task in signal processing applications. Within a certain chosen model structure, such a model is usually characterized by a set of parameters fitted to the processed signal. Classical models of this nature are well known, for instance, interpolating polynomials, splines and Fourier series. Though computationally simple, these models are usually not parsimonious, i.e., they are not designed to characterize the processed signal with a small number of parameters. The parsimonious property is useful for the purposes of analysis, filtering, feature extraction, and data compression. This work aims at developing a general method for parsimonious modeling of signals based on scattering and inverse scattering transforms. The main idea is to treat a localized signal (a function with finite support or with sufficiently fast decay) as the potential function of a linear Schrödinger operator. After some suitable scaling, the signal is close to a reflectionless potential and thus can be characterized by the eigenfunctions associated to the discrete spectrum of this operator. It turns out that these eigenfunctions, also known as solitons in interaction, can be efficiently parametrized by a small number of parameters. A parsimonious model of the processed signal can thus be built with these solitons in interaction. Though the numerical computation of the eigenvalues and eigenfunctions of linear Schrdinger operators has been well studied in the literature, it is not the case for the computation of the normalizing coefficients which are also necessary for this parsimonious model. The method currently developed in our team can efficiently model signals of moderate complexity. The study is being pursued to deal with more complex signals. This work has been presented at IFAC World Congress 2008 [66].

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

Participants: Mehdi Admane, Michel Sorine, Qinghua Zhang.

Reflectometry is a technology currently developed by several research groups for the diagnosis of conduction failures in electric transmission lines. It consists in sending electric signals at one end of a line or at one nod of a network and in analyzing the reflected electric waves. In the framework of the ANR SEEDS project (see Section 6.3.1), we study the application of the scattering and inverse scattering transforms to the reflectometry technology in order to make advanced analysis of reflectometry measurements. The pioneer work made by Jaulent [119] has shown that the classical telegrapher's equations for transmission line modeling can be transformed into Schrödinger or Zakharov-Shabat equations, establishing the link between electric transmission lines and scattering transforms. Following this result, it possible to compute some spatially distributed characteristics of a transmission line from the reflectometry measurements made at one end of the line. While currently the reflectometry technology can only detect and locate discontinuities in homogeneous transmission lines, the power of this method resides in the ability to infer about continuous inhomogeneities of transmission lines. The application of this theory to real transmission lines remains a difficult task. Inspired by the numerical methods developed by Frangos and Jaggard [109] for inverse scattering, we have simulated reflectometry measurements for inhomogeneous transmission lines and successfully implemented the inverse scattering transform for simulated lossless transmission lines.

5.2.4. On the inverse scattering of star-shape LC-networks

Participants: Filippo Visco Comandini, Mazyar Mirrahimi, Michel Sorine.

The study of the scattering data for a star-shape network of LC-transmission lines is transformed into the scattering analysis of a Schrödinger operator on the same graph. The boundary conditions coming from the Kirchhoff rules ensure the existence of a unique self-adjoint extension of the mentioned Schrödinger operator. While the graph consists of infinite or finite branches, all joining at a central node, we provide a construction of the scattering solutions. Under non-degenerate circumstances (different wave travelling times for finite branches), we show that the study of the reflection coefficient in the high-frequency regime must provide us with the number of the infinite branches as well as the the wave travelling times for finite ones. This work will be published as [67].

5.2.5. Lyapunov control of a quantum particle in a decaying potential

Participant: Mazyar Mirrahimi.

A Lyapunov-based approach for the trajectory generation of an N-dimensional Schrödinger equation in whole $\mathbb{R}^N$ is proposed. For the case of a quantum particle in an N-dimensional decaying potential the convergence is precisely analyzed. The free system admitting a mixed spectrum, the dispersion through the absolutely continuous part is the main obstacle to ensure such a stabilization result. Whenever, the system is completely initialized in the discrete part of the spectrum, a Lyapunov strategy encoding both the distance with respect to the target state and the penalization of the passage through the continuous part of the spectrum, ensures the approximate stabilization. This work has been accepted for publication as [40].

5.2.6. Observer-based Hamiltonian identification for quantum systems

Participants: Mazyar Mirrahimi, Zaki Leghtas.

This work is done in collaboration with Silvère Bonnabel (Liège University) and Pierre Rouchon (Ecole des Mines de Paris).

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 atom-laser frequency detuning and coupling constant, we prove an exponential convergence result. The analysis is inspired by the Lyapunov and 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 and a continuous measurement of all of the populations of the free Hamiltonian eigenstates are provided. 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. This work has been accepted for publication as [36].

In an extension of this work and in order to get closer to real experimental situations, we have also considered the case where only one population is measured continuously in time. Through the summer internship of Zaki Leghtas at INRIA, we have been able to come up with a closed-loop identification algorithm where a more subtle modulation of the laser amplitudes, as the controls, allows us to retrieve the non-trivial information on the coupling constants even between those energy levels whose populations are not measured. A preliminary version of this work has been submitted as a report [79] and we are working on a more complete version of the paper for submission as a journal article.

5.2.7. Singular perturbations and Lindblad-Kossakowski differential equations

Participant: Mazyar Mirrahimi.

This work is done in collaboration with Pierre Rouchon (Ecole des Mines de Paris).
We consider an ensemble of quantum systems whose average evolution is described by a density matrix, solution of a Lindblad-Kossakowski differential equation. We focus on the special case where the decoherence is only due to a highly unstable excited state and where the spontaneously emitted photons are measured by a photo-detector. We propose a systematic method to eliminate the fast and asymptotically stable dynamics associated to the excited state in order to obtain another differential equation for the slow part. We show that this slow differential equation is still of Lindblad-Kossakowski type, that the decoherence terms and the measured output depend explicitly on the amplitudes of quasi-resonant applied field, i.e., the control. Beside a rigorous proof of the slow/fast (adiabatic) reduction based on singular perturbation theory, we also provide a physical interpretation of the result in the context of coherence population trapping via dark states and decoherence-free subspaces. Numerical simulations illustrate the accuracy of the proposed approximation for a 5-level systems. This work has been provisionally accepted for publication as [41]

5.2.8. Real-time synchronization feedbacks for single-atom frequency standards

Participant: Mazyar Mirrahimi.

This work is done in collaboration with Pierre Rouchon (Ecole des Mines de Paris).
Simple feedback loops, inspired from extremum-seeking, are proposed to lock a probe-frequency to the transition frequency of a single quantum system following quantum Monte-Carlo trajectories. Two specific quantum systems are addressed, a 2-level one and a 3-level one that appears in coherence population trapping and optical pumping. For both systems, the feedback algorithm is shown to be convergent in the following sense: the probe frequency converges in average towards the system-transition one and its standard deviation can be made arbitrarily small. Closed-loop simulations illustrate robustness versus jump-detection efficiency and modeling errors. This work has been submitted for publication as [80].

5.3. Probability Theory, Multifractal analysis and Geometric measure theory

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

5.3.1. Fractional multiplicative processes

Participant: Julien Barral.

This work is done in cooperation with Benoît Mandelbrot (Yale University).
Ê *Probability Theory.* Statistically self-similar measures on $[0,1]$ are limit of multiplicative cascades of random weights distributed on the b-adic subintervals of $[0,1]$. These weights are i.i.d, positive, and of expectation $1/b$. We extend these cascades naturally by allowing the random weights to take negative values. This yields martingales taking values in the space of continuous functions on $[0,1]$. Specifically, we consider for each $H \in (0,1)$ the martingale $(B_n)_{n\geq 1}$ obtained when the weights take the values $-b^{-H}$ and b^{-H}, in order to get B_n converging almost surely uniformly to a statistically self-similar function B whose Hölder regularity and fractal properties are comparable with that of the fractional Brownian motion of exponent H. This indeed holds when $H \in (1/2,1)$. Also the construction introduces a new kind of law, one that it is stable under random weighted averaging and satisfies the same functional equation as the standard symmetric stable law of index $1/H$. When $H \in (0,1/2]$, to the contrary, B_n diverges almost surely. However, a natural normalization factor a_n makes the normalized correlated random walk B_n/a_n converge in law, as n tends to ∞, to the restriction to $[0,1]$ of the standard Brownian motion. Limit theorems are also associated with the case $H > 1/2$.

5.3.2. Signed multiplicative cascades

Participants: Julien Barral, Xiong Jin.

This work is done in cooperation with Benoît Mandelbrot (Yale University).
Ê *Probability Theory.* The theory of positive T-martingales was developed in order to set up a general framework including the positive measure-valued martingales initially considered for intermittent turbulence modelling. We consider the natural extension consisting in allowing the martingale to take complex values. We focus on martingales constructed on the line: T is the interval $[0,1]$. Then, random measures are replaced by random functions. We specify a large class of such martingales, which contains the complex extension of b-adic independent cascades, compound Poisson cascades, and more generally infinitely divisible cascades. For the elements of this class, we find a sufficient condition for their almost sure uniform convergence to a non-trivial limit. Such limit provide new examples of multifractals. For the subclass consisting of b-adic canonical cascades, we have additional results. At first, we find conditions under which the limit function can be represented almost surely as a monofractal function in multifractal time. Also, when the sufficient condition of convergence does not hold, in most of the cases we show that either the limit is 0 or the martingale diverges almost surely. In the later case, under some condition we obtain a functional central limit theorem claiming that there is a natural normalization of the martingale, which converges in law to a Brownian motion in multifractal time.

5.3.3. How projections affect the validity of the multifractal formalism

Participant: Julien Barral.

This work is done in cooperation with Imen Bhouri (Monastir University).
Ê *Multifractal analysis.* Let $n > m \geq 1$ be two integers. We obtain general results for the multifractal analysis of the orthogonal projections on m-dimensional linear subspaces of singular measures on $\mathbb{R}^n$ satisfying the multifractal formalism. Specifically, the result holds for $\gamma_{n,m}$-almost every such subspace, where $\gamma_{n,m}$ is the uniform measure on the Grassmannian manifold. Suppose that the dimension of the measure μ is less than m (otherwise, for $\gamma_{n,m}$-almost every V, a positive piece of the orthogonal projection μ_V of μ is absolutely continuous with respect to the Lebesgue measure). If I stands for the interval over which the singularity spectrum of μ is increasing, and if the multifractal formalism holds over I, then there exists a non-trivial subinterval $\widetilde{I}$ of I such that for every $\alpha \in \widetilde{I}$, for $\gamma_{n,m}$-almost every m-dimensional subspace V, the multifractal formalism holds for μ_V at $\alpha \in I$. Moreover, the result is optimal in the sense that in general the interval $\widetilde{I}$ is maximal in I. Also the function $\tau_{\mu_V}(q)$ is determined on the minimal interval J necessary to recover the singularity spectrum of μ_V over $\widetilde{I}$ as the Legendre transform of τ_{μ_V}. Neither the function $\tau_{\mu_V}(q)$ nor the interval J depend on V, and $\tau_{\mu_V}(q)$ can differ from τ_μ on a non-trivial inverval.

For Gibbs measures and their discrete counterparts, we can improve substantially the above claim by showing the stronger uniform result: For $\gamma_{n,m}$-almost every m-dimensional subspace V, the multifractal formalism holds for μ_V over the whole interval $\widetilde{I}$. For discrete measures, this stronger property is based on results concerning heterogeneous ubiquity through projections.

5.3.4. The singularity spectrum for statistically self-similar functions

Participants: Julien Barral, Xiong Jin.

Multifractal analysis. We achieve the multifractal analysis of a class of statistically self-similar functions which are a natural exension of the non-decreasing funcions whose derivatives are the so-called Mandelbrot measures. This consists in computing the Hausdorff dimension of the iso-Hölder sets of these functions. In the non-decreasing case, our result is a non-trivial improvement of the known results. Indeed, while usually for a measure one only considers the Hölder exponent associated with the oscillation over centred intervals, we deal with exponents associated with oscillations of all orders as well as the exponent defined via the best local polynomial approximation. Also, we completely solve the delicate issue consisting in describing the endpoints of these spectra. The functions we deal with are shown to obey a multifractal formalism which extends to functions the notion of L^q-spectrum usually used for measures.

5.3.5. A localized Jarnik-Besicovich theorem on Diophantine approximation

Participants: Julien Barral, Stéphane Seuret.

Geometric measure theory. Classical questions in Diophantine approximation concern the Hausdorff dimension of sets of the form $\{x \in \mathbf{R} : \delta_x = \delta\}$, where δ_x is the Diophantine approximation rate of an element $x \in [0,1]$ by the rational numbers and $\delta \geq 1$. In this article we refine the classical results by computing the Hausdorff dimension of the sets $\{x \in \mathbf{R}^d : \delta_x = f(x)\}$, where f is a continuous function. Our result further applies to the study of the approximation rates by various systems of points, including Poisson point processes and dyadic numbers.

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

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

5.4.1. Robust detection of QRS onset and offset in ECG signals

Participants: Alfredo Illanes Manriquez, Qinghua Zhang.

The detection of QRS onset and offset in ECG signals is useful for the computation of QRS duration, as well as for the computation of QT and ST intervals. Though algorithms for automatic detection of waveforms in ECG signals have been intensively studied, the robustness of these algorithms is still an important issue in clinical applications. In this work, a new algorithm is developed to improve the robustness of QRS onset and offset detection. This algorithm mainly consists of two steps. In the first step, the envelope of the QRS complex is computed based on the Hilbert transform of the processed ECG signal. This envelope signal has the particularity of being a bell-shaped concave wave, with its two boundaries corresponding to the QRS onset and offset. In the second step, an indicator related to the area covered by the envelope signal is computed. This indicator was initially designed for T wave detection, whose robustness and efficiency for that purpose have been reported in [20]. Its application to the QRS envelope signal has encountered a new difficulty: the width of the QRS envelope, which affects the tuning of the algorithm, can vary considerably. To overcome this difficulty, a two-stage method has been developed. This new algorithm has been presented at Computers in Cardiology 2008 [61].

5.4.2. Scaling Invariance of Cardiac Signals, Dynamical Systems and Multifractal Analysis

Participants: Julien Barral, Claire Médigue, Michel Sorine.

Collaboration with Denis Chemla (Kremlin-Bicêtre Hospital), Paulo Gonçalves (INRIA Rhnes-Alpes) and Stéphane Seuret (Paris 12 University).
Numerical studies using ideas from statistical physics, large deviations theory and functions analysis have exhibited striking scaling invariance properties for human long-term R-R interval signals extracted from ECG (intervals between two consecutive heartbeats). These scaling invariance are reminiscent of geometric fractal properties verified theoretically by certain mathematical objects (measures or functions) called (self-similar) multifractals. These numerical studies also reveal that the scaling invariance may have different forms depending upon the states of the patients in particular for certain cardiac diseases. These observations suggest that a good understanding of multifractal properties of cardiac signals might lead to new pertinent tools for diagnosis and surveillance. However, until now, neither satisfactory physiological interpretations of these properties nor mathematical models have been proposed for these signals. For medical applications we need to go beyond the previously mentioned works and achieve a deepened study of the scaling invariance structure of cardiac signals. This requires new robust algorithms for the multifractal signals processing ; specifically, it seems relevant to complete the usual statistical approach with a geometric study of the scaling invariance. In addition, it is necessary to apply these tools to a number of data arising from distinct pathologies, in order to start a classification of the different features of the observed scaling invariance, and to relate them to physiology. This should contribute to develop a new flexible multifractal mathematical model whose parameters could be adjusted according to the observed pathology. This multifractal analysis can be applied to another fundamental signal, the arterial blood pressure, as well as to the couple (R-R, Blood Pressure).

We have proposed an ANR project, DMASC, that aims at achieving such a program. DMASC has been accepted for funding in July 2008.

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

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

5.5.1. Numerical simulation of the multiscale model of follicular development

Participants: Frédérique Clément, Chloé Hombourger, Pierre Malassene.

The numerical scheme used to solve equation (6) is based on high-resolution, wave-propagation algorithms developed by RJ LeVeque for multi-dimensional hyperbolic systems [128] in the framework of finite volume methods. In a first approach [107], we had considered the non conservative form of this equation, so that it amounts to a 2D color equation. The source term is then handled by a fractional step (Godunov splitting) method which formally limits the resolution to the first order. We have tested an alternative choice that consists in using the source term to modify the flux difference before performing the wave decomposition, as described in [85]. We have adapted a 2D version of this algorithm to our own problem and checked the (second order) resolution [77]. Specific care has been taken to detect sign changes in the velocities. The different numerical schemes have been implemented within the academic software environment bearclaw[1], where they are coupled to a dedicated adaptative mesh refinement (AMR) algorithm [91]. User-defined routines have been improved to gain computing time and generalised to handle any predefinite size of the follicular cohort. From a practical ground, the results are quite comparable between the different schemes.

To investigate the sensitivity of the model behavior towards the time constants of the aging and maturation velocities, we have conducted numerical experiments based on uniform designs (for the distribution of the parameter values within the parameter space) and kriging (gaussian) models to approximate the model responses. Our preliminary studies confirm our previous results enhancing the management of proliferating resources as a main control lever on the ability of an ovarian follicle to pursue its development up to ovulation.

5.5.2. Bifurcation-based parameter tuning in a model of the GnRH pulse and surge generator

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

We have deeply investigated the behavior of our model of the GnRH pulse and surge generator [9], with the definite aim of constraining the model GnRH output with respect to a physiologically relevant list of specifications [76], [70]. The alternating pulse and surge pattern of secretion results from the interaction between a GnRH secreting system and a regulating system exhibiting fast-slow dynamics. The mechanisms underlying the behavior of the model are reminded from the study of the Boundary-Layer System according to the "dissection method" principle. Using singular perturbation theory, we describe the sequence of bifurcations undergone by the regulating (FitzHugh-Nagumo) system, encompassing the rarely investigated case of homoclinic connexion. Basing on pure dynamical considerations, we restrict the space of parameter search for the regulating system and describe a foliation of this restricted space, whose leaves define constant duration ratios between the surge and the pulsatility phase in the whole system. We propose an algorithm to fix the parameter values to also meet the other prescribed ratios dealing with amplitude and frequency features of the secretion signal. We finally apply these results to illustrate the dynamics of GnRH secretion in the ovine species and the rhesus monkey.

5.5.3. Endogenous circannual rhythm in LH secretion: insight from signal analysis coupled to mathematical modelling

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

[1] http://www.amath.unc.edu/Faculty/mitran/bearclaw.html

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 is translated into circadian levels of melatonin. After multiple neuronal relays (within the hypothalamus), melatonin impacts GnRH (gonadotrophin releasing hormone) secretion that in turn controls ovarian cyclicity. The pattern of GnRH secretion is mirrored into that of LH (luteinising hormone) secretion, whose plasmatic level can be easily measured. We addressed the question of whether there exists an endogenous circannual rhythm in a tropical sheep (Black-belly) strain that exhibits clear seasonal ovarian activity when ewes are subject to temperate latitudes. We based on long-term (several years) time series of LH collected from ewes subject to constant photoperiodic regime. Due to intra- and inter-animal variability and unequal sampling times, the existence of an endogenous rhythm is not straightforward. We have thus used time-frequency signal processing methods, and especially the Smooth Pseudo-Wigner-Ville Distribution, to extract possible hidden rhythms from the data. To further investigate the LF (low frequency) and HF (high frequency) components of the signals, we have designed a simple mathematical model accounting for the effect of experimental sampling times on LH series. The model enables us (i) to confirm the existence of an endogenous circannual rhythm as detected by the BF signal component, (ii) to investigate the action mechanism of photoperiod on the pulsatile pattern of LH secretion (control of the interpulse interval) and (iii) to conclude that the HF component is mainly due to the experimental sampling protocol.

5.5.4. Modelling of FSHR-induced Signalling Network

Participant: Frédérique Clément.

Collaboration with François Fages (CONTRAINTES), Domitille Heitzler and Eric Reiter (UMR CNRS-INRA 6175). The FSHR-mediated signalling network comprises multiple parallel transduction mechanisms, amongst which, G protein- and beta-arrestin dependent pathways converging to MAP Kinase ERK activation are the best characterised. The information circulating in this network is likely to be tightly regulated by cross-talks, feed-back or feed-forward mechanisms. In order to gain a better understanding of these complex but very important processes, we wanted to set up a computational modelling approach integrating both G protein and beta-arrestin transduction mechanisms and how they translate into ERK activation [60].
Methodology: Using HEK293 cells transfected with the FSHR as a model, we generated phospho-ERK kinetics in response to FSH exposure. We compared a range of perturbed conditions including inhibition of PKA, beta-arrestin siRNA, GRK2 siRNA and GRK5 or 6 siRNA to control kinetics. In parallel, we collected the available knowledge on ERK activation by G protein-coupled receptors in general and by the FSHR in particular. These information were used to establish a detailed interaction map. Since too many parameters were unknown, this initial map has been reduced into an abstracted model. The reduced model consisted of a set of ordinary differential equations (ODE) representing each component kinetics and about 20 reaction rate constants (either molecule-molecule interaction, enzymatic, transport, synthesis or degradation reactions). Then, we have used Biocham (http://contraintes.inria.fr/BIOCHAM/) and Scilab (http://www.scilab.org/), two open source platforms from INRIA for numerical computation, in order to estimate parameters from the data. Different data-fitting algorithms have been compared. We have jointly fitted the simulation outputs of the model to experimental data in both control and perturbed conditions.
Results and discussion: Running the model with an optimised parameter set led to in silico simulations that were tightly fitting the experimental data in both control and perturbed conditions. Moreover, the model verified several additional biological hypotheses and provided kinetics values for experimentally unreachable variables.
Conclusions: This model's simplicity currently limits its predictive value. Hence, we now plan to improve this initial approach by generating larger amount of biological data using high throughput methodologies. This will lead to integration of additional (i.e.: other than ERK) FSH-regulated signalling pathways to the initial core of the model. Our ultimate goal is to gain a systemic understanding of the FSH-induced signalling network.

5.6. Clinical and physiological applications

Keywords: *Cardiovcascular system*, *Health*, *Heart rate variability*.

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

5.6.1. *Effect of heavy exercise on spectral baroreflex sensitivity, heart rate, and blood pressure variability in well-trained humans.*

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

The aim of the study was to assess the instantaneous spectral components of heart rate variability (HRV) and systolic blood pressure variability (SBPV) and determine the low-frequency (LF) and high-frequency baroreflex sensitivity (HF-BRS) during a graded maximal exercise test. The first hypothesis was that the hyperpnea elicited by heavy exercise could entail a significant increase in HF-SBPV by mechanical effect once the first and second ventilatory thresholds (VTs) were exceeded. It was secondly hypothesized that vagal tone progressively withdrawing with increasing load, HF-BRS could decrease during the exercise test. Fifteen well-trained subjects participated in this study. Electrocardiogram (ECG), blood pressure, and gas exchanges were recorded during a cycloergometer test. Ventilatory equivalents were computed from gas exchange parameters to assess VTs. Spectral analysis was applied on cardiovascular series to compute RR and systolic blood pressure power spectral densities, cross-spectral coherence, gain, and alpha index of BRS. Three exercise intensity stages were compared: below (A1), between (A2), and above (A3) VTs. From A1 to A3, both HF-SBPV (A1: 45 +/- 6, A2: 65 +/- 10, and A3: 120 +/- 23 mm2Hg, P < 0.001) and HF-HRV increased (A1: 20 +/- 5, A2: 23 +/- 8, and A3:40 +/- 11 ms2, P < 0.02), maintaining HF-BRS (gain, A1: 0.68 +/- 0.12, A2: 0.63 +/- 0.08, and A3: 0.57 +/- 0.09; alpha index, A1: 0.58 +/- 0.08, A2: 0.48 +/- 0.06, and A3: 0.50 +/- 0.09 ms/mmHg, not significant). However, LF-BRS decreased (gain, A1: 0.39 +/- 0.06, A2: 0.17 +/- 0.02, and A3: 0.11 +/- 0.01, P < 0.001; alpha index, A1: 0.46 +/- 0.07, A2: 0.20 +/- 0.02, and A3: 0.14 +/- 0.01 ms/mmHg, P < 0.001). As expected, once VTs were exceeded, hyperpnea induced a marked increase in both HF-HRV and HF-SBPV. However, this concomitant increase allowed the maintenance of HF-BRS, presumably by a mechanoelectric feedback mechanism.

5.6.2. *Breathing cardiovascular variability and baroreflex in mechanically ventilated patients.*

Collaboration with the Unité de Biologie Intégrative des Adaptations à l'Exercice, INSERM 902, Génopôle, Evry, and with the "Service de Réanimation Polyvalente, Centre Hospitalier Sud-Francilien, Evry.

Heart rate and blood pressure variations during spontaneous ventilation are related to the negative airway pressure during inspiration. Inspiratory airway pressure is positive during mechanical ventilation, suggesting that reversal of the normal baroreflex-mediated pattern of variability may occur. We investigated heart rate and blood pressure variability and baroreflex sensitivity in 17 mechanically ventilated patients. ECG (RR intervals), invasive systolic blood pressure (SBP), and respiratory flow signals were recorded. High-frequency (HF) amplitude of RR and SBP time series and HF phase differences between RR, SBP, and ventilatory signals were continuously computed by Complex DeModulation (CDM). Cross-spectral analysis was used to assess the coherence and the gain functions between RR and SBP, yielding baroreflex sensitivity indices. The HF phase difference between SBP and ventilatory signals was nearly constant in all patients with inversion of SBP variability during the ventilator cycle compared with cycling with negative inspiratory pressure to replicate spontaneous breathing. In 12 patients (group 1), the phase difference between RR and ventilatory signals changed over time and the HF-RR amplitude varied. In the remaining five patients (group 2), RR-ventilatory signal phase and HF-RR amplitude showed little change; however, only one of these patients exhibited a RR-ventilatory signal phase difference mimicking the normal pattern of respiratory sinus arrhythmia. Spectral coherence between RR and SBP was lower in the group with phase difference changes. Positive pressure ventilation exerts mainly a mechanical effect on SBP, whereas its influence on HR variability seems more complex, suggesting a role for neural influences.

This study is assessed in the context of the PH.D 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".

5.6.3. Anti-Mullerian Hormone Is an Endocrine Marker of Ovarian Gonadotropin-Responsive Follicles and Can Help to Predict Superovulatory Responses in the Cow

Participants: Frédérique Clément, Claire Médigue.

Collaboration with Danielle Monniaux (UMR CNRS-INRA 6175). The major limitation to development of embryo production in cattle is the strong between-animal variability in ovulatory response to FSH-induced superovulation, mainly due to differences in ovarian activity at the time of treatment. This study [44] aimed to establish whether anti-Mullerian hormone (AMH) was an endocrine marker of follicular populations in the cow, as in human, and a possible predictor of the ovarian response to superovulation. AMH concentrations in plasma varied 10-fold between cows before treatment and were found to be highly correlated with the numbers of 3 to 7 mm antral follicles detected by ovarian ultrasonography before treatment ($r=0.79$, $P<0.001$) and the numbers of ovulations after treatment ($r=0.64$, $P<0.01$). Between-animal differences in AMH concentrations were found to be unchanged after a 3-month delay ($r=0.87$, $P<0.01$), indicating that AMH endocrine levels were characteristic of each animal on a long-term period. The population of healthy 3 to 7 mm follicles was the main target of superovulatory treatments, contained the highest AMH concentrations and AMH mRNA levels compared to larger follicles, and contributed importantly to AMH endocrine levels. In conclusion, AMH was found to be a reliable endocrine marker of the population of small antral gonadotropin responsive follicles in the cow. Moreover, AMH concentrations in plasma of individuals were indicative of their ability to respond to superovulatory treatments.

6. Contracts and Grants with Industry

6.1. Mathematical modeling, monitoring and control of physiological systems

Keywords: *artificial heart*, *bioenergetics*, *control*, *glycemic control*, *modeling*, *monitoring*, *process bioengineering*.

6.1.1. TIght glycemic control enhanced by continuous monitoring (LK2 contract)

Participants: Alexandre Guerrini, Pierre Kalfon, Claire Médigue, Michel Sorine, Qinghua Zhang.

Collaboration with the Intensive Care Unit (ICU) of Chartres Hospital headed by Dr Pierre Kalfon. This work on tight glycaemic control (TGC) for ICU started in Septembrer. It is done in the framework of the CIFRE contract of Alexandre Guerrini with the small medtech company LK2 (Tours, France). For the medical context of this study, see [121]. Blood glucose has become a key biological parameter in critical care since publication of the study conducted by van den Berghe and colleagues [150], who demonstrated decreased mortality in surgical intensive care patients in association with TGC, based on intensive insulin therapy. However, two negative studies were recently reported, which were interrupted early because of high rates of severe hypoglycaemia, namely the VISEP study [95] and the as yet unpublished Glucontrol trial.

In this study, we aim at developing efficient monitoring and control tools that will help clinicians and nursing staff to control blood glucose levels in ICU patients, in particular to avoid hyperglycaemia superior to 10 mmol/l and hypoglycaemia episodes. A first controller has been designed and will be assessed. The controller determines the insulin infusion rate on the basis of the standard available glycaemia measurements despite their irregular sampling rate.

6.1.2. Modeling and control of a Total Artificial Heart (CARMAT SAS contract)

Participants: Karima Djabella, Claire Médigue, Yves Papelier, Michel Sorine, Qinghua Zhang.

This project is the beginning of our cooperation with the newly created CARMAT SAS (Suresnes, France) start-up that will continue the development of the prototype of the Total Artificial Heart designed by EADS (European Aeronautics Defense & Space) under the direction of Professor Alain Carpentier (who won the 2007 Lasker Award for his earlier work with artificial heart valves).

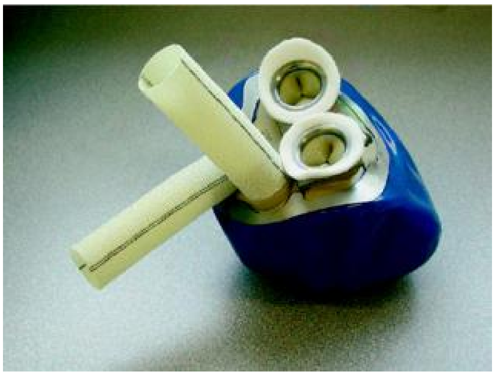

Figure 1. The CARMAT heart (courtesy of M. Grimmé, CARMAT SAS)

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

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

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

6.2. Mathematical modeling, monitoring and control of fuel cell systems

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

6.2.1. Modeling and control of energy conversion systems for automotive powertrains (Renault contract)

Participants: Fehd Benaïcha, Karim Bencherif, Michel Sorine.

This work is done in cooperation with Jean-Claude Vivalda (CONGE team-project). In this CIFRE contract of Fehd Benaïcha with Renault, we have studied two technological solutions of energy, environmental and economic problems related with automotive powertrains. The first solution is based on a new concept of powertrain with on board Fuel Cell and on board fuel reformer. The second solution is based on an evolution of the classic thermal engine with a controlled gas after-treatment system. We have proposed control laws and diagnosis methods in order to optimize and monitor the efficiency of the powertrains under autonomy, pollution and cost constraints. This has led us to develop reduced models of physical and chemical phenomena involved in powertrain components. When studying the two systems, we found several structural similarities which have allowed to formalize a common control problem and to propose a general almost optimal control law under the above mentioned constraints. The different models have been experimentally validated. Algorithms of control and diagnosis are validated in simulation and by using prototyping tools [90], [56], [55], [21].

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

Participants: Pierre-Alexandre Bliman, Mohamad Safa, Michel Sorine, Qinghua Zhang.

This work is conducted within the framework of the project Diapason (ANR, Program PAN-H 2006), which is dedicated to the diagnosis of PEM fuel cell systems for stationary and automotive applications. It is aimed at developing supervision and 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 defaults to detect and diagnose are CO poisoning, membrane dehydration and membrane flooding.

Based on 0D models, we have initialized the analysis of the Nyquist locus describing the equivalent impedance of a fuel cell, based on the harmonic balance method. Our main effort this year has been more on methodological issue, dedicated to reduced modeling of impedance networks. Roughly speaking, the problem may be described as follows: Given the impedance function of elementary cells or sub-cells (representing for example the totality or part of a single cell in a complete fuel cell system), which is supposed to depend upon some parameters (describing locally the electrochemical characteristics), how can one approximate the global impedance of the network constituted by series and parallel coupling of such cells, having possibly different parameter values? The superposition of currents and potentials is governed by Kirchoff laws, so the difficulty is not there, but rather in the network aspects. To answer the question, we have applied an expansion idea which allows to approximate the behavior of the network by the behavior of a simplified network, resulting from the superposition of a *mean cell* (characterized by the impedance function for the mean parameter value) and of two additional terms accounting respectively for series and parallel corrections, and involving some *second-order momentums* characteristic of the parameter dispersion in the network. These three quantities are then used as a basis for detecting and diagnosing loss of efficiency resulting from a desynchronization of the fuel cell system in damaged operating conditions.

6.3. Diagnosis of cable networks for automotive applications

Participants: Mehdi Admane, Mazyar Mirrahimi, Michel Sorine, Filippo Visco Commandini, Qinghua Zhang.

6.3.1. Smart Embedded Electronic system for DiagnosiS" (ANR project SEEDS)

The project 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 CEA LIST, Renault Trucks, Serma Ingénierie, Delphi, Sherpa, 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 focused on the application of the scattering transforms to the reflectometry technology. An algorithm based on the inverse scattering transform has been implemented for the diagnosis of progressive faults. See also Section 5.2.3.

Joined by PSA and Freescale, the main partners of SEEDS have submitted a new project in response to the PREDIT2008 call for proposals: the 0-DEFECT project, which aims to study and implement new methods suited to an onboard system. This project has been accepted for funding and will start in 2009.

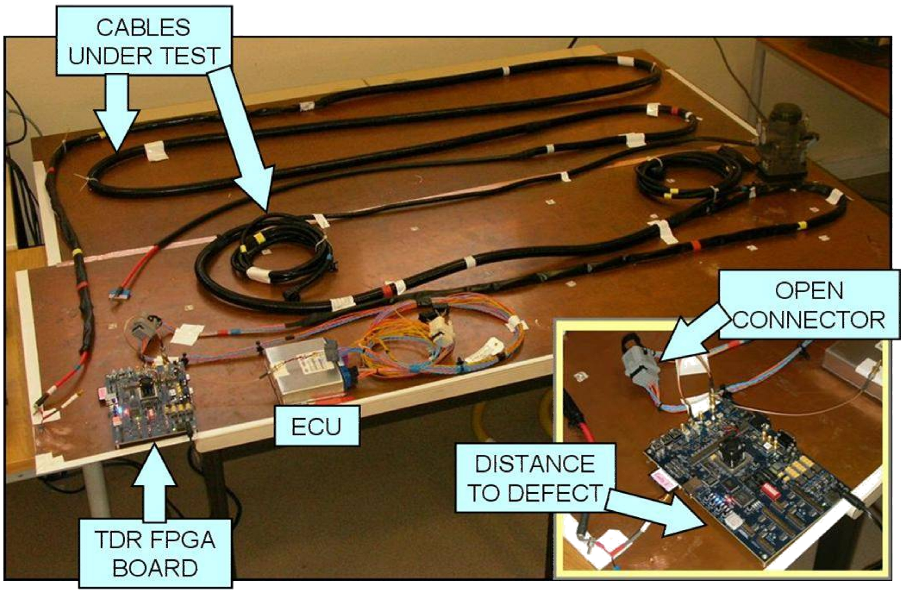

Figure 2. Diagnosis system prototype for automotive networks (courtesy of M. Olivas, CEA-LIST)

6.3.2. The DIGITEO project DIAGS

This project funded by DIGITEO aims at developing a platform for the development and validation of diagnostic systems embedded in vehicles. It comes in complement of SEEDS and will allow advanced experiments in an open environment. The involved partners are CEA LIST, Supelec LGEP and INRIA.

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 since 2007 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 CardioSense3D . See also [102].

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. See AgroBI and INSIGHT.

7.2. European grants

7.2.1. NoE HYCON

Participant: Michel Sorine.

We participate 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 (duration: 4 years). We ar involved in the WP4c (Automotive applications) in Hybrid Modeling of HCCI engine.

8. Dissemination

8.1. Scientific activity and coordination

J. Barral: - Member of the "Jury de l'Agrégation externe de Mathématiques", since january 2005 ;
- Coordination and redaction of the project proposal "DMASC " in the call for projects "SYSCOMM". This project has been selected.

P.A. Bliman: - Member of the Program Committee 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, 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).
- "Chargé de mission scientifique" at SUPCOR, INRIA support service for ANR research programs.
- Associate Editor of Systems & Control Letters.
- Member of the "Commission de spécialistes" (61st Section) Université Henri Poincaré (Nancy).
- Elected at INRIA Commission d'évaluation.

F. Clément: - Member of the scientific board of the PHASE (Animal Physiology and Breeding Systems) department of INRA (National Institute for Agronomic Research).
- Member of the scientific board of the INRA Research Centre of Jouy-en-Josas.
- Sisyphe team correspondent for the GdR MABEM (Mathematics for Biology and Medicine).

M. Sorine: - Member of the International Program Committees for the FIMH'09, JDMACS 2009 (Journées Doctorales d'Automatique) and FES 2009 (System Theory: Modelling, Analysis and Control) conferences.
- Member of several PhD committees.

Q. Zhang: - Member of IFAC Technical Committee on Fault Detection, Supervision and Safety of Technical Processes (SAFEPROCESS).
- Member of the International Program Committee of the 15th IFAC Symposium on System Identification.

8.2. Teaching activity

- 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” until September 2008. Full service since October 2008).
- M. Mirrahimi: “Introduction to Control Theory”. Course given at the “Irano European Master in Mathematics”, Tehran University, from 23 Oct 2008 to 09 Nov 2008.

8.3. Seminars

8.3.1. PhD defences

This year, five PhD thesis have been defended:
- F. Benaicha, “Modélisation et commande de systèmes de conversion d’énergie pour l’automobile”, Metz University, November, 24, 2008.
- K. Djabella, “Modélisation de l’activité électrique du coeur et de sa régulation par le systeme nerveux autonome”, Paris 11 University, June, 30, 2008.
- A. Illanes Manriquez, “Segmentation de l’électrocardiogramme pour la modélisation de la dynamique du QT lors de l’exercice du handgrip”, Université de Rennes 1, January, 15, 2008.
- M. Laleg-Kirati, “Analyse de signaux par quantification semi-classique. Application à l’analyse des signaux de pression artérielle”, Versailles-Saint-Quentin University, October, 15, 2008.
- P. L. Pommier, “Modélisation de l’interaction chimie-turbulence. Application à la combustion homogène diesel”, October, 22, 2008.

8.3.2. Seminars

J. Barral: - Presentation in “séminaire d’Analyse Multifractale de Paris 12”: “Dynamique des cascades de Mandelbrot”.
- Presentation in “séminaire de Probabilités de l’Institut Fourier”, Grenoble: “Dynamique des cascades de Mandelbrot”.
- Presentation in “Journées Techniques fractales”, Orléans: “Analyse multifractale de l’inverse d’une mesure de Gibbs sur un ensemble de Cantor non linéaire”.
- Presentation at the conférence “Fractal geometry and stochastics IV”, Greifswald: “The singularity spectrum of Gibbs measures on cookie-cutters and their inverse”.

P.A. Bliman: - Lecture at LAAS (Toulouse), July 2008; at Unicamp (Campinas, Brazil), October 2008; at Universities of Palermo and Padova (Italy), November 2008.
- Presentation in the meeting of the project Diapason (ANR PAN-H), March 2008.

F. Clément: - Invited speaker to the CANUM 2008 [52].
- Invited speaker to COST GEMINI [51].

M. Mirrahimi: - Invited speaker to the workshop “Optimal control theory in space and quantum dynamics”, June 24-25, 2008, Math. Institute, Bourgogne Univ.
- Invitation at Liège University by Prof. R. Sepulchre, February 2008.
- Visits of Prof. H. Rabitz (Princeton) and Prof. H. Mabuchi (Stanford) from 19 Jan 2008 to 30 Jan 2008.
- Visit of Prof. Shinji Hara, Tokyo University from 14 Nov 2008 to 22 Nov 2008.
- Participation to the “projet blanc, ANR C-QUID, contrôle et identification de systèmes quantiques”.

M. Sorine: Systèmes dynamiques en réseaux. L’exemple du coeur. Colloquium Jacques Morgenstern. Polytech’Nice-Sophia Antipolis, 3 avril 2008.

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[21] F. BENAICHA. *Modélisation et commande de systèmes de conversion d'énergie pour l'automobile*, Ph. D. Thesis, Metz University, November, 24 2008.

[22] K. DJABELLA. *Modélisation de l'activité électrique du coeur et de sa régulation par le systeme nerveux autonome*, Ph. D. Thesis, Paris 11 University, June, 30 2008.

[23] A. ILLANES MANRIQUEZ. *Segmentation de l'électrocardiogramme pour la modélisation de la dynamique du QT lors de l'exercice du handgrip*, Ph. D. Thesis, Université de Rennes 1, January, 15 2008.

[24] T.-M. LALEG. *Analyse de signaux par quantification semi-classique. Application à l'analyse des signaux de pression artérielle*, Ph. D. Thesis, Versailles-Saint-Quentin University, October, 15 2008.

[25] P.-L. POMMIER. *Modélisation de l'interaction chimie-turbulence. Application à la combustion homogène diesel*, Ph. D. Thesis, Paris 6 University, October, 22 2008.

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[26] D. ANGELI, P.-A. BLIMAN. *Convergence speed of unsteady distributed consensus: decay estimate along the settling spanning-trees*, in "SIAM Journal on Control and Optimization", to appear, 2008.

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