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INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team SISYPHE

SIgnals and SYstems in PHysiology and Engineering

Paris - Rocquencourt

Theme : Observation, Modeling, and Control for Life Sciences

Activity Report

2009

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2. Overall Objectives

2.1. Overall Objectives

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

SISYPHE (SIgnals and Systems in PHysiology and Engineering) is studying 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 (LSIA). The research on the reproductive system is done in the framework of REGATE (REgulation of the GonAdoTropE axis), a new Inria LSIA coordinated by F. Clément.

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

- **REGATE.** During the past years, some results have been obtained in modeling of the reproductive function and some fruitful collaborations have been established with experts of different domains all interested by this function. This has led INRIA to launch the LSIA REGATE (REgulation of the GonAdoTropE axis) in 2009. This action is coordinated by F. Clément.
- **CGAO transfered in ICUs.** The concepts of "tight glycemic control" and its drawback, the "glycemic variability" invoked by physicians in Intensive Care Units (ICU), are linked to the concepts of "precision" and "stability" of automatic control. The software CGAO (Contrôle Glycémique Assisté par Ordinateur) has been developed with LK2 to help physicians to deal with this version of the classical Stability/Precision dilemma. It has been tested in the ICU of Chartres and is now used in a large scale study launched by the SFAR (French Society of Anesthesia and Intensive Care) involving 62 ICUs and including 6422 patients.

3. Scientific Foundations

3.1. System theory for systems modeled by ordinary differential equations

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

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

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

where $x(t)$, $u(t)$ and $y(t)$ represent respectively the state, input and output of the system, f and g characterize the state and output equations, parameterized by θ and subject to modeling and measurement uncertainties $w(t)$ and $v(t)$. Modeling is usually based on physical knowledge or on empirical experiences, strongly depending on the nature of the system. Typically only the input $u(t)$ and output $y(t)$ are directly observed by sensors. Inferring the parameters θ from available observations is known as system identification and may be useful for system monitoring [18], whereas algorithms for tracking the state trajectory $x(t)$ are called observers. The members of SISYPHE have gained important experiences in the modeling of some engineering systems and biomedical systems. The identification and observation of such systems often remain challenging because of strong nonlinearities [17]. Concerning control, robustness is an important issue, in particular to ensure various properties to all dynamical systems in some sets defined by uncertainties [5], [89]. The particularities of ensembles of connected dynamical systems raise new challenging problems.

Examples of reduced order models:
- Reduced order modeling of the cardiovascular system for signal & image processing or control applications. See section 3.4.1.
- Excitable neuronal networks & control of the reproductive axis by the GnRH. See section 3.4.2.
- Reduced order modeling of fuel cells for control and diagnosis applications. See section 6.4.

3.1.2. Observation and control of networks of dynamical systems

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. [135] or [90] 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 [90]:

$$\begin{aligned} \frac{dx_i}{dt} &= f_i(x_i, u_i, \theta_i, w_i) - \Sigma_{j=1}^{N} \mathcal{C}_{i,j} g_j(x_j, u_j, \theta_j, v_j) \\ y &= g(x_1, ...x_N, u_1, ...u_N, \theta_1, ...\theta_N, v_1, ...v_N) \end{aligned} \tag{2}$$

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 a cardiac cell model:

$$\begin{aligned}\frac{dv_i}{dt} &= f_V(v_i, u_i, u_{ext,i}, \theta_{e,i}, w_{e,i}) - \Sigma_{j=1}^{N} \mathcal{C}_{i,j} g(x_j, u_j, \theta_j, v_j) \\ \frac{du_i}{dt} &= f_U(v_i, u_i, \theta_{e,i}, w_{e,i})\end{aligned} \tag{3}$$

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.

$$\frac{\partial v}{\partial t} = \sigma \Delta v + g_V(v, u, u_{ext}, \theta_e, w), \quad \frac{\partial u}{\partial t} = f_U(v, u, \theta_e, w_e) \tag{4}$$

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 [12], [11] 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:

$$\frac{\partial \phi_f}{\partial t} + \frac{\partial g_f(u_f)\phi_f}{\partial a} + \frac{\partial h_f(\gamma, u_f)\phi_f}{\partial \gamma} = -\lambda(\gamma, U)\phi_f \tag{5}$$

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:

$$\frac{\partial V(z,k)}{\partial z} = -\left(R(z) + jkL(z)\right) I(z,k), \quad \frac{\partial I(z,k)}{\partial z} = -(G(z) + jkC(z))V(z,k) \tag{6}$$

Since the work of Noordergraaf [136], this model is also used for hemodynamic networks with V and I respectively the blood pressure and flow in vessels considered as 1D media, and with $R = \frac{8\pi\eta}{S^2}$, $L = \frac{\rho}{S}$, $C = \frac{3S(r+h)}{E(2r+h)}$ where ρ and η are the density and viscosity of the blood ; r, h and E are the inner radius, thickness and Young modulus of the vessel. $S = \pi r^2$. The conductivity G is a small constant for blood flow.
Monitoring such networks is leading us to consider the following inverse problem: *get information on the functions R, L, C, G from the reflection coefficient* $\mathcal{R}(k)$ (ratio of reflected over direct waves) measured in some location by Time or Frequency Domain Reflectometry. To study this problem it is convenient to use a Liouville transform, setting $x(z) = \int_0^z \sqrt{L(z')C(z')}dz'$, to introduce auxiliary functions $q^{\pm}(x) = \frac{1}{4}\frac{d}{x}\left(\ln \frac{L(x)}{C(x)}\right) \pm \frac{1}{2}\left(\frac{R(x)}{L(x)} - \frac{G(x)}{C(x)}\right)$ and $q_p(x) = \frac{1}{2}\left(\frac{R(x)}{L(x)} + \frac{G(x)}{C(x)}\right)$, so that (6) becomes a Zakharov-Shabat system [110] that reduces to a Schrödinger equation in the lossless case ($R = G = 0$):

$$\frac{\partial v_1}{\partial x} = (q_p - jk)\, v_1 + q^+ v_2, \quad \frac{\partial v_2}{\partial x} = -\,(q_p - jk)\, v_2 + q^- v_1 \tag{7}$$

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

Nonlinear traveling waves. In some recent publications [115], [114], we use scattering theory to analyze a measured Arterial Blood Pressure (ABP) signal. Following a suggestion made in [137], 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

$$\frac{\partial y}{\partial t} - 6y\frac{\partial y}{\partial x} + \frac{\partial^3 y}{\partial x^3} = 0 \tag{8}$$

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 (8):

$$\frac{\partial L(y)}{\partial t} = [M(y), L(y)] \tag{9}$$

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 (9) 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 [8].

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. [133]) 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:

$$y(x) = 4\sum_{n=1}^{n=N} \kappa_n \psi_n^2(x) - \frac{2i}{\pi}\int_{-\infty}^{-\infty} k\mathcal{R}(k) f^2(k,x)dk \tag{10}$$

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

3.2.2. Identification & control of quantum systems

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 [131]. 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 [103]. 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):

$$i\frac{d}{dt}\Psi(t,x) = (H_0 + u(t)H_1)\Psi(t,x) = (-\frac{1}{2}\Delta + V(x) + u(t)\mu(x))\Psi(t,x), \quad \Psi|_{t=0} = \Psi_0, \tag{11}$$

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 [84], [85], [124]. 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 [125], [86], [124]. 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 (11), 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):

$$\frac{d}{dt}\rho = -i[H_0 + u(t)H_1, \rho], \tag{12}$$

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:

$$d\rho_t = -i[H_0 + u(t)H_1, \rho_t]dt + (L\rho_t L^* - \frac{1}{2}L^*L\rho_t - \frac{1}{2}\rho_t L^*L)dt \\ + \sqrt{\eta}(L\rho_t + \rho_t L^* - \mathrm{Tr}\left[(L+L^*)\rho_t\right]\rho_t)dW_t, \tag{13}$$

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 [87], 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 [126].

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

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

We consider networks or ensembles of cells of the same type modeled by (2) with a single base model and different parameters θ_i. In this case the solution of (2) may never live in the synchronization manifold and it is of theoretical and practical interest to study the deviations from this manifold.

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 cell systems) 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 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 ([101], [102], [91], [130], [108]).

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 [101] as well as in the heart-beat variability [123], [107] and in financial time series [120]. 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 ([119], [111], [132], [104], [109], [78], [100], [81], [83], [82]) 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 [113] 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. The ANR project DMASC has started in 2009 on these questions.

3.4. Physiological & Clinical research topics

3.4.1. The cardiovascular system: a multiscale controlled system

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

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

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

Modeling the controlled contraction/relaxation from molecular to tissue and organ scales.

We have obtained a controlled constitutive law of cardiac myofibre mechanics aimed at being embedded into 0D or 3D models [4]. This law results from a model of the collective behavior of actin-myosin molecular motors converting chemical into mechanical energy [88]. It is thermodynamically consistent and the resulting dynamics of sarcomeres is consistent with the “sliding filament hypothesis” of A. F. Huxley.

The model in [4] is currently used as the constitutive law for the cardiac tissue in the $3D$ model of the heart developed in the CardioSense3D project. It is useful for computing stress, strain and the action potential fields when coupled with an electrical model [79], [134]. 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 3D image processing). In order to check the mathematical consistency of our models, we have considered, in the more simple case of a 1D geometry, the mathematical analysis of the fibre model used in CardioSense3D based on the previous constitutive law [14]).

Direct and inverse modeling the electro-mechanical activity of the heart on the cell scale.

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 [97], [98], [99]. An objective here, is to obtain invertible (depending upon available measurements) thermodynamically consistent models (the various ATP consumption have to be taken into account). This will allow in particular a better connection with the perfusion models developed in CardioSense3D.

We 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 [13]. 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. For that purpose, we use the algorithm for T wave detection, whose robustness and efficiency have been reported in [19]. In our previous work, the QT interval was obtained by adding a constant to the RT interval which is easier to delimit [13]. 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 [105], [106].

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

We have proposed [96] 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 [8]. 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 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 [116], handgrip isometric exercise and orthostatic tilt test. [117]. 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 [122], [121], [129] ; the autonomic control of the cardiovascular system during sleep [127] ; the effects of exercise intensity and repetition on heart rate variability during training [94], [95], [93]. 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.

This approach is applied to the control of a Total Artificial Heart.

3.4.2. Reproductive system: follicular development & ovulation control

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

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

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

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

Simulation and control of a multiscale conservation law for follicular cells

In the past years, we have designed a multiscale model of the selection process of ovulatory follicles, including the cellular, follicular and ovarian levels [12], [11]. 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 [6]. 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. SITB: The Matlab System Identification ToolBox

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. CGAO: Controle Glycémique Assisté par Ordinateur

Participants: Alexandre Guerrini, Michel Sorine.

This development is made in collaboration with Pierre Kalfon (Chartres Hospital) and Gaëtan Roudillon (LK2).

This software developed with LK2 and Hospital Louis Pasteur (Chartres) provides efficient monitoring and control tools that will help physicians and nursing staff to avoid hyperglycaemia and hypoglycaemia episodes in Intensive Care Units. It is used in a large clinical study, CGAO-REA. Commercialization will be done by LK2.

The software is designed to assist physicians to deal with a variant of the classical Stability/Precision dilemma of control theory met during blood-glucose control. It has been tested in the ICU of Chartres and, since November 2009, it is used in a large scale study launched by the SFAR (French Society of Anesthesia and Intensive Care) involving 62 ICUs and including 6422 patients.

4.3. 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 [128]. 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

5.1.1. Control ideas for optimization

Participant: Pierre-Alexandre Bliman.

This subject has been worked on with A. Bhaya and F. Pazos (UFRJ, Rio de Janeiro, Brazil). For large size problems, solving the equation $Ax = b$ for x, where A is a symmetric positive definite matrix and b a vector, cannot be done simply by inversion of A. Rather, one can try to search recursively for the minimum of the quadratic function $\Phi(x) = \|Ax - b\|^2$. The various gradient methods search at each step along the current gradient $\nabla\Phi(x_k) = Ax_k - b$, where x_k is the current estimate. Among them, the steepest descent amounts to choose the step length which minimizes the residue norm $\|A^{-1/2}(Ax_k - b)\|$ at step k. The latest, equal to $\frac{\|Ax_k-b\|^2}{\|A^{1/2}(Ax_k-b)\|}$ (Rayleigh coefficient), ensures a monotone decrease to zero of the residue norm, but is not especially fast. Quite surprisingly, the choice made by Barzilai and Borwein in a renowned paper of the delayed expression $\frac{\|Ax_{k-1}-b\|^2}{\|A^{1/2}(Ax_{k-1}-b)\|}$ works remarkably better.

Our work has been to try to find better choices, considering the problem as a control issue. Deadbeat control ideas yield interesting results, while some preliminary cooperative control ideas seem to lead to quite sensible speed up. Further studies are presently under consideration.

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.

Previous efforts had been concentrated on a representation of the parameters more fitted to the computational techniques. In particular, cartesian products of simplexes ("multi-simplexes") had been introduced. This formalism has been used now for gain-scheduling purposes.

5.1.3. The two-stage algorithm for Hammerstein system identification

Participant: Qinghua Zhang.

A Hammerstein system is composed of a static nonlinearity block followed by a linear dynamic block. Typically, the nonlinearity of such a system is caused by actuator distortions. The Two-Stage Algorithm (TSA) has been widely used and adapted for the identification of Hammerstein systems. It is essentially based on a particular formulation of Hammerstein systems in the form of bilinearly parameterized linear regressions. In collaboration with Jiandong Wang (Peking University, China) and Lennart Ljung (Linköping University, Sweden), we have studied various aspects of the TSA. We first elaborated a constructive method for deriving the TSA, whereas it was initially proposed as a heuristic method in the literature. We then studied the parametrization of the weighting matrix used in the TSA. These results are reported in [59]. We also studied a somewhat contradictory fact about the TSA: though the optimality of the TSA has been established by Bai in 1998 [80] only in the case of some special weighting matrices, the unweighted TSA is usually used in practice. Our investigation shows that the unweighted TSA indeed gives the optimal solution of the weighted nonlinear least-squares problem formulated with a particular weighting matrix. This provides a theoretical justification of the unweighted TSA, and also leads to a generalization of the result to the case of colored noise with noise whitening. These results are reported in [58], [43].

5.2. System theory for quantum and quantum-like systems

5.2.1. Distributed source identification for wave equations: an observer-based approach

Participants: Marianne Chapouly, Mazyar Mirrahimi.

We consider the problem of identifying an unknown distributed source term for the wave equation inside a bounded domain. Assuming Dirichlet boundary conditions for the system, the output is given by the Neumann condition on a part of the boundary. It is a well-known result (applying observability inequality) that as soon as the observed part of the boundary satisfies the geometric control condition, the source term is identifiable. Furthermore, the minimal identifiability time corresponds to the minimal observability time. Here, we are rather interested in the practical problem of proposing an efficient inversion algorithm allowing us to identify the source in the case of minimal observation time. We propose, once again, to apply back-and-forth observer techniques to do this. However, as we are dealing with an infinite dimensional system, we have to deal with some additive problems such as the precomactness of the trajectories (in appropriate functional spaces) to ensure the convergence of the estimator. This work has led to a submitted conference publication [68] and a journal paper in preparation.

5.2.2. Inverse scattering for soft fault diagnosis in electric transmission lines

Participants: Michel Sorine, Qinghua Zhang.

Reflectometry is a technology studied in various domains to gather information about properties of media where waves are propagated and reflected. In electric engineering, today's advanced reflectometry methods provide an efficient solution for the diagnosis of electric transmission line hard faults (open and short circuits), but they are much less efficient for soft faults (spatially smooth variations of characteristic impedance). Studies on the relationship between the inverse scattering transform and the reflectometry technology for soft fault diagnosis have been started more than a quarter of a century ago [110], but no real application of such methods has been reported, to our knowledge. In this work, we attempt to fill an important gap between inverse scattering transform and the practical reflectometry technology: it clarifies the relationship between the reflection coefficient measured with reflectometry instruments and the mathematical object of the same name defined in the inverse scattering theory, by reconciling *finite length* transmission lines with the inverse scattering transform defined on the *infinite interval*. The feasibility of applications of the inverse scattering transform to soft fault diagnosis is then studied by numerical simulation of lossless transmission lines affected by soft faults, and by the solution of the inverse scattering problem effectively retrieving smoothly varying characteristic impedance profiles from reflection coefficients. These results have been reported in [77].

5.2.3. Modeling of electric transmission networks and multiconductor lines

Participants: Leila Djaziri, Mohamed Oumri, Michel Sorine, Qinghua Zhang.

The increasing number of electric transmission lines in modern engineering systems is amplifying the importance of the reliability of electric connections. In this context, two ANR projects, 0-DEFECT and INSCAN, have been started in 2009, both aiming at developing fault diagnosis techniques for transmission lines, with the former focusing on transmission networks, and the latter on multiconductor lines. See Sections 6.5 and 6.6 for more details about these two projects.

In order to prepare the studies on extensions of the inverse scattering transform (see also Section 5.2.2) to the cases of transmission networks and multiconductor lines, reduced modeling of such systems in terms of distributed RLCG parameters has been studied in two master training projects. The purpose has been to generalize the well known telegrapher's equations for a single transmission line to the considered more complex cases, and also to derive the corresponding Zakharov-Shabat equations, which are directly related to the inverse scattering transform. Numerical simulation of transmission networks has also been studied.

5.2.4. Some inverse scattering problems on star-shaped graphs

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

We consider some inverse scattering problems for Schrödinger operators over star-shaped graphs motivated by applications to the fault location of lossless electrical networks. We restrict ourselves to the case of minimal experimental setup consisting in measuring, at most, two reflection coefficients when an infinite homogeneous (potential-less) branch is added to the central node. First, by studying the asymptotic behavior of only one reflection coefficient in the high-frequency limit, we prove the identifiablity of the geometry of this star-shaped graph: the number of edges and their lengths. Next, we study the potential identification problem by inverse scattering, noting that the potentials represent the inhomogeneities due to the soft faults in the network wirings (potentials with bounded H^1-norms). The main result states that, under some assumptions on the geometry of the graph, The measurement of two reflection coefficients, associated to two different sets of boundary conditions at the extremities of the tree, determines uniquely the potentials; it can be seen as a generalization of the theorem of the two boundary spectra on an interval. This work has led to a conference publication [57] and a submitted journal paper [76].

5.2.5. Observer-based parameter estimation for quantum systems

Participants: Ashley Donovan, Zaki Leghtas, Mazyar Mirrahimi, Pierre Rouchon.

We had recently proposed an observer-based Hamiltonian identification algorithm for quantum systems [28]. The later paper provided a method to estimate the dipole moment matrix of a quantum system requiring the measurement of the populations on all states, which could be experimentally difficult to achieve. We propose here an extension to a 3-level quantum system, having access to the population of the ground state only. By a more adapted choice of the control field, we will show that a continuous measurement of this observable, alone, is enough to identify the field coupling parameters (dipole moment). This work has led to a conference publication [50].

Also, through the two months stay of Ashley Donovan, we have considered the problem of the initial state reconstruction for quantum systems via continuous weak measurement. The decoherence due to the measurement induces a lost of information after a certain time-horizon; i.e. after a certain time interval the state of the system gets very near to a completely mixed state and therefore the measurement output is completely invaded by noise. This, we are interested in inversion algorithms applying the measurement output over a short time interval. Here, our approach consists in applying a recently developed back-and-forth nudging algorithm (developed by J. Blum and D. Auroux). This algorithm is based on the iterative application of two observers, one for the main system (over the time interval $[0, T]$) and one for the same system in the time-reversed direction. As soon as the observer gains are well-defined so that the whole back-and-forth iteration leads to a contraction for the error dynamics, this iterative algorithm will provide a reliable estimator for the initial state of the system. This is a work in progress and must lead to publications in near future.

5.2.6. Quantum feedback by discrete quantum non-demolition measurements: towards on-demand generation of photon-number states

Participants: Hadis Amini, Mazyar Mirrahimi, Pierre Rouchon.

This work is done in collaboration with Michel Brune, Igor Dotsenko, Serge Haroche, Jean-Michel Raimond (Laboratoire Kastler-Brossel, ENS Paris).

We propose a quantum feedback scheme for the preparation and protection of photon number states of light trapped in a high-Q microwave cavity. A quantum non-demolition measurement of the cavity field provides information on the photon number distribution. The feedback loop is closed by injecting into the cavity a coherent pulse adjusted to increase the probability of the target photon number. In the ideal case (perfect cavity and measures), we present the feedback scheme and its detailed convergence proof through stochastic Lyapunov techniques based on super-martingales and other probabilistic arguments. The efficiency and reliability of the closed-loop state stabilization is assessed by quantum Monte-Carlo simulations. In realistic situations, we provide a quantum filter taking into account the cavity decay and the imperfections in the measurement process. Quantum Monte-Carlo simulations performed with experimental parameters illustrate convergence and protection of the photon number states. This work has led to one conference publication [52] and a journal publication [10]. This feedback algorithm is currently being integrated into the cavity QED experimental setup at Laboratoire Kastler-Brossel (ENS Paris).

5.3. Multifractal analysis

Participants: Julien Barral, Xiong Jin, Yan-Hui Qu.

5.3.1. Multiplicative cascades

Part of this work is done in cooperation with Benoît Mandelbrot (Yale University).

The results obtained concern the following topics: Multifractal analysis of complex random cascades [21], Fractional multiplicative processes [24], Uniform convergence of $[0,1]$-martingales [23], Convergence of signed multiplicative cascades [22], Dynamics of Mandelbrot cascades [25].

5.3.2. Multifractal analysis and Geometric measure theory

The results obtained concern the following topics:

Multifractal analysis for projections of Gibbs and related measures. This is done in cooperation with Imen Bhouri (Monastir University) [65].

In cooperation with IStéphane Seuret: Multifractal analysis, large deviations, and localized asymptotic behavior for almost additive potentials [67], A pure jump Markov process with a random singularity spectrum [66], The singularity spectrum of the inverse of Cookie-Cutters [26].

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

5.4.1. Foliation-based parameter tuning in a model of the GnRH pulse and surge generator

Participants: Frédérique Clément, Alexandre Vidal.

We investigate a model of the GnRH pulse and surge generator [6], with the definite aim of constraining the model GnRH output with respect to a physiologically relevant list of specifications [30]. The alternating pulse and surge pattern of secretion results from the interaction between a GnRH secreting system and a regulating system exhibiting slow-fast dynamics. The mechanisms underlying the behavior of the model are reviewed 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 connection. 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.

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

Participants: Frédérique Clément, Claire Médigue, Alexandre Vidal.

In sheep, as in many vertebrates, the seasonal pattern of reproduction is timed by the annual photoperiodic cycle, characterized by seasonal changes in the day length. The photoperiodic information is translated into a circadian profile of melatonin secretion. After multiple neuronal relays (within the hypothalamus), melatonin affects gonadotrophin-releasing hormone (GnRH) secretion, which in turn controls ovarian cyclicity. The pattern of GnRH secretion is mirrored by that of luteinizing hormone (LH) secretion, whose plasmatic level can be easily measured. We addressed the question of whether there exists an endogenous circannual rhythm in a tropical sheep (Blackbelly) population that exhibits clear seasonal ovarian activity when ewes are subject to temperate latitudes [42]. We based our analysis on LH time series collected in the course of 3 years from ewes subject to a constant photoperiodic regime. Owing to intra- and interanimal variability and unequal sampling times, the existence of an endogenous rhythm is not straightforward. We have used time–frequency signal processing methods, and especially the smooth pseudo-Wigner–Ville distribution, to extract possible hidden rhythms from the data. To further investigate the low-frequency (LF) and high-frequency (HF) components of the signals, we have designed a simple mathematical model of the LH plasmatic level accounting for the effect of experimental sampling times. The model enables us to (i) confirm the existence of an endogenous circannual rhythm as detected by the LF signal component, (ii) investigate the action mechanism of the photoperiod on the pulsatile pattern of LH secretion (control of the interpulse interval), and (iii) conclude that the HF component is mainly due to the experimental sampling protocol.

5.4.3. Towards a systems biology approach of G protein-coupled receptors' signalling: challenges and expectations

Participant: Frédérique Clément.

Collaboration with François Fages (CONTRAINTES), Domitille Heitzler and Eric Reiter (UMR CNRS-INRA 6175)
G protein-coupled receptors (GPCRs) control all the main physiological functions and are targeted by more than 50% of therapeutics. Our perception of GPCRs signalling has grown increasingly complex since it is now accepted that they activate large signalling networks which are integrating the information fluxes into appropriate biological responses. These concepts lead the way to the development of pathway-selective agonists (or antagonists) with fewer side effects. Systems biology approaches focused on GPCR-mediated signalling would help dealing with the huge complexity of these mechanisms therefore speeding-up the discovery of new drug classes. In this review [34], we present the various technical and conceptual possibilities allowing a systems approach of GPCR-mediated signalling. The main remaining limitations are also discussed.

5.5. Clinical and physiological applications - Cardiovascular system

5.5.1. Analysis of cardiovascular and respiratory interactions in mechanically ventilated patients in intensive care ,

Participant: Claire Médigue.

Collaboration with François Cottin (Unité de Biologie Intégrative des Adaptations à l'Exercice, INSERM 902, Génopôle, Evry), Andry Van de Louw (Service de Réanimation Polyvalente, Centre Hospitalier Sud-Francilien, Evry) and Yves Papelier.

Positive End Expiratory Pressure may alter breathing cardiovascular variability and baroreflex gain in mechanically ventilated patients. [74] During mechanical ventilation, some patients have stable cardiorespiratory phase difference and stable high frequency (HF) amplitude of heart rate high-frequency (HF) heart rate variability over time and others do not. We hypothesized that a steady pattern could reflect a blunted autonomic nervous system and that positive end-expiratory pressure (PEEP) could further alter the autonomic nervous function. We tested the effect of increasing PEEP from 5 to 10 cm H2O on the breathing variability of arterial pressure and RR intervals, and on the baroreflex. Invasive arterial pressure, ECG and ventilatory flow were recorded in 23 mechanically ventilated patients during 15 minutes for both PEEP levels. HF amplitude of RR and systolic blood pressure time series and HF phase differences between RR, SBP and ventilatory signals were continuously computed by complex demodulation. Cross-spectral analysis was used to assess the coherence and gain functions between RR and SBP, yielding baroreflex-sensitivity indices. At PEEP 10, the 12 patients with a stable pattern had lower baroreflex gain and HF RR amplitude than the 11 other patients. Increasing PEEP was globally associated with a decreased baroreflex gain and a greater stability of HF RR amplitude and cardiorespiratory phase difference over all the patients. Anyway, four of them who exhibited a variable pattern at PEEP 5 became stable at PEEP 10. At PEEP 10, a stable pattern was associated with higher organ failure score and catecholamine dosage. Thus, stable HF RR amplitude and cardiorespiratory phase difference over time reflect a blunted autonomic nervous function which might worsen as PEEP increases with a prognostic value.

Cardiorespiratory phase difference in mechanically ventilated patients: evidence for the role of central nervous mechanisms [75] Under mechanical ventilation, large inter-patient and intra-patient RR variations of the phase of respiratory sinus arrhythmia (RSA) have been described. We sought to determine whether these variations were of central nervous origin or related to the mechanical effect of positive pressure ventilation. Therefore, we compared the RSA phase between: 1) 12 control subjects enforced to breath at the same breathing frequency than the mechanically ventilated patients, 2) 23 mechanically ventilated patients without brain injury (MV group) and 3) 12 brain dead, mechanically ventilated patients, whose central nervous functions were abolished (BD group). ECG, arterial pressure and ventilatory flow were recorded during 15 minutes. High-Frequency phase difference between RR, arterial pressure and ventilatory signals was continuously computed by complex demodulation. About RR intervals, control group exhibited RSA phases between 180° and 250° whereas an opposite pattern, between 0° and 90°, was observed in the BD group. For the two groups, the phase was stable over time. By contrast, in the MV group, the RSA phases were distributed between 0° and 260°, with a greater variability over time than the two other groups. Concerning arterial pressure, the phase difference with ventilatory signal was very close to 0° in all MV and BD patients, with minimal fluctuations over time. Therefore, during mechanical ventilation, breathing arterial pressure variability is mainly mechanically mediated, whereas functional nervous centers may sometimes induce large variations of the RSA phase, not synchronous with the mechanical effect of ventilation.

5.5.2. *Validation of a New Method for Stroke Volume Variation Assessment: a comparison with the PiCCO Technique*

Participants: Claire Médigue, Michel Sorine.

Collaboration with François Cottin (Unité de Biologie Intégrative des Adaptations à l'Exercice, INSERM 902, Génopôle, Evry), Andry Van de Louw (Service de Réanimation Polyvalente, Centre Hospitalier Sud-Francilien, Evry), Taous-Meriem Laleg (INRIA project-team Magique-3D) and Yves Papelier.

This new method is based on scattering transform for a one dimension Schrödinger equation and provides new parameters, related to the systolic and diastolic parts of the pressure. We aimed at assessing the first systolic invariant $INVS_1$, linearly correlated to the stroke volume, by comparison with a reference method, the Picco technique, using the pulse contour method. To validate this approach, a statistical comparison between $INVS_1$ and the stroke volume measured with the PiCCO technique was performed during a 15-mn recording in 21 mechanically ventilated patients in intensive care.

5.6. Clinical and physiological applications - Reproductive system

5.6.1. *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 the 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 [40] aimed to establish whether anti-Müllerian 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. Anti-Müllerian hormone 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-mo 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 with 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 the plasma of individuals were indicative of their ability to respond to superovulatory treatments.

5.6.2. *In vivo imaging of in situ motility of fresh and liquid stored ram spermatozoa in the ewe genital tract*

Participant: Frédérique Clément.

Collaboration with Xavier Druart (UMR CNRS-INRA 6175)

The fertility of ram semen after cervical insemination is substantially reduced by 24 h of storage in liquid form. The effects of liquid storage on the transit of ram spermatozoa in the ewe genital tract was investigated using a new procedure allowing direct observation of the spermatozoa in the genital tract [32]. Ejaculated ram spermatozoa were double labeled with R18 and MitoTracker Green FM, and used to inseminate ewes in estrus either cervically through the vagina or laparoscopically into the base of the uterine horns. Four hours after insemination, the spermatozoa were directly observed in situ using fibered confocal fluorescence microscopy in the base, middle and tip of the uterine horns, the utero-tubal junction (UTJ) and the oviduct. The high resolution video images obtained with this technique allowed determination of the distribution of spermatozoa and individual motility in the lumen of the ewe's genital tract. The results showed a gradient of increasing concentration of spermatozoa from the base of the uterus to the UTJ 4 h after intra-uterine insemination into the base of the horns. The UTJ was shown to be a storage region for spermatozoa before their transfer to the oviduct. The in vitro storage of spermatozoa in liquid form decreased their migration through the cervix and reduced the proportion of motile spermatozoa and their straight line velocity at the UTJ and their transit into the oviduct.

6. Contracts and Grants with Industry

6.1. TIght glycemic control for Intensive Care Units (LK2)

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 2008. 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 [112]. Blood glucose has become a key biological parameter in critical care since publication of the study conducted by van den Berghe and colleagues [138], 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 [92] and the Glucontrol trial.

We have studied a possible origin of the failure of the recent study NICE-SUGAR [33].

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.

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

Participants: Karima Djabella, Michel Sorine, Frédéric Vallais.

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).

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.

This year we have studied the filling of the prosthesis during special conditions (e.g. Valsalva maneuver).

6.3. DMASC: Scaling Invariance of Cardiac Signals, Dynamical Systems and Multifractal Analysis (ANR)

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).

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

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

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

6.4. DIAPASON: Reduced Modeling and Diagnosis of Fuel Cell Systems (ANR)

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

This work is conducted within the framework of the ANR project Diapason (Program PAN-H 2006), which is dedicated to the diagnosis of 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 failures which have to be detected and diagnosed are CO poisoning, membrane dehydration and membrane flooding.

Our main efforts this year have been devoted to precise modeling of the individual fuel cell. In order to take into account the critical phenomena, it has been necessary to analyze and model the following phenomena:

Diffusion. The impedance essays obtained by our partners in the project clearly show the characteristic finite slope in high frequency behavior usually considered as a consequence of diffusion, here in the Gas Diffusion Layers. This aspect is usually introduced as a $1/\sqrt{s}$ term in the frequency domain. however, in order to respect the consistency of the approach, including nonlinear terms, we prefer to use a Partial Differential Equation, subsequently discretized via collocation method.
Temporal scales of the chemical reactions. To simplify the models while keeping a good precision of the actual phenomena involved, we have taken into account the discrepancy between the several temporal scales involved in the the different reactions. More precisely, we have considered that the concentration balance equations are much more rapid than the adsorption/desorption reactions, and the former ones have been simplified by singular perturbations.
Water balance. A compartmental model of water exchanges inspired by work by J.B. Benziger *al.* has been used. Simplified dynamics have been introduced here too, taking advantage of the time scale separations.
Double layer capacity. This important phenomenon is typically rendered in electrochemistry by a capacitance put in parallel or in series to the other models. In order to have the subsequent ability to get a full model aging of the reactive zones of the cell, we have worked on a physically based model. The latter is inspired especially from a multiscale analysis due to A.A. Franco, detailing electronic and protonic flows in the compact layer, as well as water adsorption and dipolar effects to explain the capacitance effect.

6.5. 0-DEFECT: On-board fault diagnosis for wired networks in automotive systems (ANR)

Participants: Mazyar Mirrahimi, Mohamed Oumri, Michel Sorine, Qinghua Zhang.

The number of electronic equipments is increasing rapidly in automotive vehicles. Consequently, the reliability of electric connections is becoming more and more important. The project entitled “Outil de diagnostic embarqué de faisseaux automobiles" (0-DEFECT) aims at developping tools for on-bord diagnosis of failures in electric wire connections in automotive systems. This project is funded by Agence Nationale de la Recherche (ANR) for three years from 2009. The involved partners are CEA LIST, Renault Trucks, Freescale, PSA, Delphi, Supelec LGEP and INRIA. See also Section 5.2.3.

6.6. INSCAN: Fault diagnosis for security critical long distance electric transmission lines (ANR)

Participants: Leila Djaziri, Michel Sorine, Qinghua Zhang.

The wired electric networks of the French railway system cover more than 50000 km. The electric insulation of the railway signaling lines is particularly monitored by regular inspections. Today these inspections are based on an expensive procedure realized by human operators located at both ends of each transmission line. The service of signaling devices has to be interrupted during this procedure, and so does the railway traffic. The in situ monitoring of the transmission lines, without interruption of service, is thus an important economic issue. For this purpose, the project entitled “Diagnostic de câbles électriques sécuritaires pour grandes infrastructures" is funded by ANR for three years in order to study the feasibility of in situ monitoring tools for these transmission lines. The involved partners are SNCF, CEA LIST and INRIA. See also Section 5.2.3.

6.7. DIAGS: Platform for the development and validation of diagnostic systems (DIGITEO)

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

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.

6.8. EPOQ2: Estimation PrOblems for Quantum & Quantumlike systems (ANR)

Participants: Mazyar Mirrahimi, Emmanuelle Crépeau-Jaisson, Pierre Rouchon, Michel Sorine, Filippo Visco Comandini.

This project is an ANR "Young researcher" project led by Mazyar Mirrahimi (Sisyphe). It has for goal to address a class of inverse problems rising from either the emerging application domain of "quantum engineering" or from some classical applications where a natural quantization lead to quantum-like systems, as it is the case in particular for inverse scattering for transmission lines. The partners of INRIA are Emmanuelle Crépeau-Jaisson (University of Versailles - Saint Quentin), Hideo Mabuchi (Stanford University), Herschel Rabitz and Ramon Van Handel (Princeton University), Pierre Rouchon (Mines de Paris).

6.9. SITB: System Identification ToolBox (The Mathworks)

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. REGATE (Inria Large Scale Initiative Action)

Participants: Benjamin Ambrosio, Frédérique Clément, Jean-Pierre Françoise, Claire Médigue, Peipei Shang, Alexandre Vidal.

REGATE (REgulation of the GonAdoTropE axis) is a 4-year LSIA funded by INRIA in May 2009 dedicated to the modeling, simulation and control of the gonadotrope axis. The INRIA participants to this action are researchers of 3 INRIA research teams, Asclepios, Contraintes and Sisyphe. There are also participants from INRA, Université Libre de Bruxelles (Unité de Chronobiologie théorique) and Université Paris 6 (Laboratoire Jacques-Louis Lions).

7.2. CardioSense3D (Inria Large Scale Initiative Action)

Participants: Julien Barral, Denis Chemla, 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. The INRIA participants to this action are researchers of 4 INRIA research teams, Asclepios, Contraintes Reo and Sisyphe. There are also several clinical, industrial and academic partners.

8. Dissemination

8.1. Scientific animation and responsibilities

P.A. Bliman: - Member of the Program Committee of the 2009 IEEE Conference on Decision and Control (Shanghai, China, December 2009). Member of the CDC Best Student Paper Award Committee.

- Member of the International Program Committee of the 2010 IEEE Multi-conference on Systems and Control MSC2010 (Yokohama, Japan, September 8-10 2010).
- Member of the Technical Program Committee of the 1st IFAC Workshop on Estimation and Control of Networked Systems, NecSys'09 (24-26 September, 2009, Venice, Italy).
- Member of the Technical Program Committee of Colibri, Colloque dÕInformatique: Brésil / INRIA, Coopérations, Avancées et Défis (22-23 September, 2009, Bento Gonalves, Rio Grande do Sul, Brazil).
- 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).
- Scientist in charge of latin America at Department of International Affairs, INRIA.
- Associate Editor of Systems & Control Letters.
- Elected at INRIA Commission d'évaluation.
- Member of the board for recruitment of Chargés de recherche (Centre de recherche INRIA, Saclay, 2009).

F. Clément: - INRA (National Institute for Agronomic Research) examination board for junior research scientist recruitment.
- AERES evaluation committee of UMR 791 INRA-AgroParisTech (Physiologie de la Nutrition et Alimentation).
- Appointed member of the scientific board of the PHASE (Animal Physiology and Breeding Systems) department of INRA
- Appointed member of the scientific board of the INRA Research Centre of Jouy-en-Josas.
- Co-organisation (with Alexandre Vidal and Jean-Pierre Françoise) of the international workshop "Dynamical systems and Neuroendocrinology" (http://alx.vidal.googlepages.com/ANAR-REGATE.htm), Paris, October 16th.
- Scientific head of the Large Scale Initiative Action REGATE (REgulation of the GonAdoTropE axis) (http://www-roc.inria.fr/who/Frederique.Clement/regate.html).
- PhD Thesis examination board (Benjamin Ambrosio, Propagation d'ondes dans un milieu excitable: simulations numériques et approche analytique, Univ. Paris 6).

M. Sorine: - Member of the International Program Committees for the FIMH'09, JDMACS 2009 (Journées Doctorales d'Automatique), FES 2009 (System Theory: Modelling, Analysis and Control) conferences, CIFA 2010.
- 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 SYSID 2009.

8.2. Teaching activity

- F. Clément: "Dynamical models in Biology : analysis/estimation". Master 2 recherche BIBS (BioInformatique et BioStatistiques), Université Paris-Sud 11 BIBS
- M. Sorine: "Modélisation de systèmes complexes : l'exemple du coeur", ENPC, 2nd year lectures "Supply Chain et Systèmes Complexes".

8.3. Participation in conferences, seminars ; PhD defenses

J. Barral has given presentations at Tsinghua University (Wen Zhi-Ying team seminar) and at Paris 11-Sud (workshop in honor to Jacques Peyrière).
P.A. Bliman: - Plenary speaker at Nescoc, Symposium on Recent Trends in Networked Systems and Cooperative Control (September 28, 2009, Institute for Systems Theory and Automatic Control, Stuttgart, Germany).
- Presentation in the meeting of the project Diapason (ANR PAN-H), November 2009.

F. Clément: - Invited speaker to the Spring School on Modelling Complex Biological Systems in the Context of Genomics [48].
- Invited speaker to SISC'09 : Vers une science et ingénierie des systèmes complexes (3ième colloque national RNSC/iXXi/iSC-PiF) [61].
- Cemracs'09 seminars: Mathematical modelling and control of neuroendocrine systems, July 28th. Supervision (with Philippe Michel, Centrale Lyon) of a Cemracs'09 young researcher project (Hormonal control of coupled structured populations).

M. Sorine: Presentations in the frameworks of the projects 0-DEFECT, INSCAN, EPOQ2.

PhD theses: After the five PhD thesis defended in 2008, this year has seen the arrival of six new PhD students. Xiong Jin will be the next one to defend his PhD (on January, 14 th 2010).

8.4. Foreign Visitors

Richard Bertram (Florida State University, Department of Mathematics) has visited the project-team in October 2009 to set up a collaboration in the field of Mathematical Neuroendocrinology.
Ashley Donovan visited the project-team in June in the framework of a collaboration with Herschel Rabitz, head of the Department of Chemistry, Princeton University. Zaki Leghtas visited this Department during October 2009.
Pavel Krejci (Institute of Mathematics, Academy of Sciences of the Czech Republic) visited the project-team in November 2009.

9. Bibliography

Major publications by the team in recent years

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