INRIA

Project-Team SISYPHE

SIgnals and SYstems in PHysiology and Engineering

Paris - Rocquencourt

Theme : Observation, Modeling, and Control for Life Sciences

Activity Report

2010

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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 about some complex dynamical systems issued from Physiology and Engineering: modeling ; identification and observation from signals ; real-time health monitoring or control ; questions of system theory arising from the emerging domain of "quantum engineering". We consider networked or multi-scale dynamical systems and quantum & quantum-like systems. Most studies are motivated by the cardiovascular and reproductive systems or some critical engineering systems like electrical networks. In our approach of monitoring hemodynamic or electrical networks, a natural quantization of physical models is leading to quantum-like systems. The research on the reproductive system is done in the framework of REGATE (REgulation of the GonAdoTropE axis), an Inria Large-Scale Initiative Action (LSIA) coordinated by F. Clément.

Research topics:
Signals & Systems

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

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

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

Applications to Physiology & Engineering

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

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

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

- Identification and control of some quantum systems. Towards "quantum engineering".

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

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 [129], 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 [15]. Concerning control, robustness is an important issue, in particular to ensure various properties to all dynamical systems in some sets defined by uncertainties [76], [77]. 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. [126] or [78] 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 [78]:

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

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 [10], [9] 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 [128], 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 [101] 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 [106], [105], we use scattering theory to analyze a measured Arterial Blood Pressure (ABP) signal. Following a suggestion made in [130], 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 [6].

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. [124]) 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

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 [122]. 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 [94]. Two approaches can be considered for this aim: first, to consider more resistant systems with respect to this quantum decoherence and developing faithful methods to manipulate the system in the time constants where the decoherence can not show up (in particular one can not consider the back-action of the measurement tool on the system); second, to consider dissipative models where the decoherence is also included and to develop control designs that best confronts the dissipative effects.

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

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

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 [70], [71], [115]. 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 [116], [72], [115]. 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):

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

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:

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

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 $dW_t = dY_t - \text{Tr}\,[(L + L^*)\rho_t]\,dt$. This filter equation, initially introduced by Belavkin [73], 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 [117].

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 [109]. 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 ([91], [93], [79], [121], [99]).

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 [91] as well as in the heart-beat variability [114], [98] and in financial time series [111]. 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 ([110], [102], [123], [95], [100], [64], [90], [67], [69], [68]) 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 [104] 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 [74]. This law results from a model of the collective behavior of actin-myosin molecular motors converting chemical into mechanical energy [75]. It is thermodynamically consistent and the resulting dynamics of sarcomeres is consistent with the "sliding filament hypothesis" of A. F. Huxley.

The model in [74] 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 [65], [125]. 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 [12]).

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 [87], [88], [89]. 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 [11]. 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 [16]. In our previous work, the QT interval was obtained by adding a constant to the RT interval which is easier to delimit [11]. 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 [96], [97].

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

We have proposed [86] 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 [6]. 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 [107], handgrip isometric exercise and orthostatic tilt test. [108]. 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 cardio-respiratory system dynamics in chronic heart failure [113], [112], [120] ; the autonomic control of the cardiovascular system during sleep [118] ; the effects of exercise intensity and repetition on heart rate variability during training [84], [85], [83]. 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 [10], [9]. 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 $G\alpha_s$ and βarrestin-dependent pathways in response to FSH signal, determine how each pathway controls downstream cascades and which mechanisms are involved in the transition between different cellular states (quiescence, proliferation, differentiation and apoptosis). On the experimental ground, we propose to develop an antibody microarray approach in order to simultaneously measure the phosphorylation levels of a large number of signaling intermediates in a single experiment. On the modeling ground, we will use the BIOCHAM (biochemical abstract machine) environment first at the boolean level, to formalize the network of interactions corresponding to the FSH-induced signaling events on the cellular scale. This network will then be enriched with kinetic information coming from experimental data, which will allow the use of the ordinary differential equation level of BIOCHAM. In order to find and fine-tune the structure of the network and the values of the kinetic parameters, model-checking techniques will permit a systematic comparison between the model behavior and the results of experiments. In the end, the cell-level model should be abstracted to a much simpler model that can be embedded into a multiscale one without losing its main characteristics.

Bifurcations in coupled neuronal oscillators.

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

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

4. Software

4.1. 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. ISTL: Inverse Scattering for Transmission Lines

Participant: Qinghua Zhang.

ISTL is a software implementing a numerical algorithm of the inverse scattering transform for transmission lines. In addition to the inverse scattering transform, it includes a numerical simulator of transmission lines generating the reflection coefficients of user-specified transmission lines. With the aid of a graphical interface, the user can interactively define the distributed characteristics of a transmission line. This software is mainly for the purpose of demonstrating the inverse problem of non uniform transmission lines.

Its current version (V1.0) is limited to the case of lossless transmission lines. It is registered at Agence pour la Protection des Programmes (APP) under the number IDDN.FR.001.120003.000.S.P.2010.000.30705 in March 2010.

4.3. CGAO: Contrôle Glycémique Assisté par Ordinateur

Participants: Alexandre Guerrini, Michel Sorine.

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

At the end of 2010, 1835 patients have been included in CGAO-REA.

4.4. 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 [119]. 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. *Nonlinear system identification*
Participant: Qinghua Zhang.

Currently our researches on nonlinear system identification are mainly made in collaboration with the Laboratory of Industrial Process Monitoring and Optimization of Peking University (China). Two topics have been studied this year: subspace method for Hammerstein system identification, and system identification with quantized data.

A Hammerstein system is composed of a static nonlinearity block followed by a dynamic linear block. Typically, the nonlinearity of such a system is caused by actuator distortions. Subspace methods applied to Hammerstein system identification have already been investigated in the literature [92], [66]. These methods first relax a rank constraint that is essential in the Hammerstein system structure, before a model reduction step taking into account the rank constraint. Such an approach leads to the loss of optimality of the identification methods in terms of the variance of the estimated model parameters. We studied the effects of the rank constraint in such contexts and elaborated improvements to existing identification methods. The results have been partly published in [33].

In most applications, system identification is based on sampled and quantized data. When the quantized data is coded with a sufficiently large number of bits, the effect of quantization is often ignored in the design of system identification methods. However, when the data is quantized to a few bits, sometimes to the extreme of a single bit leading to binary data, then the effect of quantization must be explicitly taken into account. Data quantization can be modeled as a non differentiable hard nonlinearity, hence the widely used gradient-based optimization method cannot be used for the identification of such nonlinear systems. We have developed a quadratic-programming-based method for system identification from quantized data. Compared to existing methods [127], [81], the new method has the advantage of being valid for general input excitations.

These studies will be further pursued in the joint Franco-Chinese ANR-NSFC project EBONSI (See Section 6.5).

5.1.2. *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 minimize the quadratic function $\Phi(x) = \|Ax - b\|^2$ through well-known iterative gradient methods. In an attempt to achieve faster solution of this problem, we have introduced a new paradigm, called cooperative computation. The simplest version of the algorithm consists of two agents achieving one of the classical methods. Furthermore infrequent unidirectional communications have been introduced, allowing each local optimizer to use also the other estimate, in order to gain in speed of convergence. Deterministic and probabilistic implementations of this idea have been introduced and shown to be efficient, specifically in relation to the well known and much used Barzilai and Borwein algorithm, particularly for ill-conditioned matrices.

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

5.2.1. *Inverse scattering for soft fault diagnosis in electric transmission lines*
Participants: Michel Sorine, Huaibin Tang, Qinghua Zhang.

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 [101], but no real application of such methods was reported, to our knowledge. In this work, we clarified 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 the application of the inverse scattering transform to soft fault diagnosis is studied in [34] for lossless lines, and in [46], [62] for lossy lines. A demonstration software has been developed and registered at Agence pour la Protection des Programmes (APP). See Section 4.2.

5.2.2. *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 6.6 and 6.7 for more details about these two projects.

In order to study the extensions of the inverse scattering transform (see also Section 5.2.1) to the cases of transmission networks and multiconductor lines, reduced modeling of such systems in terms of distributed RLCG parameters has been studied. In the case of networks, a numerical simulator has been developed [43]. In the case of multiconductor lines, the similarity between parallel channels is explored to analyze the effect of faults affecting the insulation between conductors.

5.2.3. *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 paper to appear in the Journal of Mathematical Analysis and Applications [32].

5.2.4. *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 conference publication [39] and a submitted journal paper [56].

5.3. System theory approach of some quantum systems

5.3.1. *Observer-based state tomography for quantum systems*
Participants: Zaki Leghtas, Mazyar Mirrahimi, Pierre Rouchon.

Through the two months stay of Ashley Donovan (PhD student with H. Rabitz at Princeton) in 2009, 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. Thus, we are interested in inversion algorithms applying the measurement output over a short time interval. We propose an estimation algorithm based on the back- and-forth nudging method consisting in iterative application of Luenberger observers for the time-forward and time-backward dynamics. A clever change of variables unveils the needed symmetry in the observer design leading to the decrease of a certain distance (in an appropriate metric) between the estimator and the main system, both in forward and backward directions. This result has been published as a conference paper [40].

More recently, we have proposed a simpler version of a Back and Forth estimator ensuring the identification of the initial state as soon as the system is observable. This estimator admits as an advantage a natural extension to the case of multi-dimensional quantum systems. Even though it does not ensure the decrease of a Lyapunov function through the estimation process, the natural distance between the estimator and the real state decreases after each back and forth iteration. A detailed analysis of the proposed algorithm and the proof for the case of 2-level systems can be found in [59] and has been submitted as a conference publication.

5.3.2. *Stabilization of a delayed quantum system: the Photon-Box case-study*
Participants: Hadis Amini, Mazyar Mirrahimi, Pierre Rouchon.

We study a feedback scheme to stabilize an arbitrary photon number state in a microwave cavity. The quantum non-demolition measurement of the cavity state allows a non-deterministic preparation of Fock states. Here, by the mean of a controlled field injection, we desire to make this preparation process deterministic. The system evolves through a discrete-time Markov process and we design the feedback law applying Lyapunov techniques. Also, in our feedback design we take into account an unavoidable pure delay and we compensate it by a stochastic version of a Smith predictor. After illustrating the efficiency of the proposed feedback law through simulations, we provide a rigorous proof of the global stability of the closed-loop system based on tools from stochastic stability analysis. A brief study of the Lyapunov exponents of the linearized system around the target state gives a strong indication of the robustness of the method. These result have led to a submitted journal publication [52].

5.4. System theory approach of some multiscale systems

5.4.1. *Time-Frequency Analysis of Seismic Signals and Control of Transient Behaviors*
Participants: Pierre-Alexandre Bliman, Michel Sorine, Stefan Teodorescu.

This work is done in cooperation with the CEA. Active or semi-active control of structures under seismic solicitations is an important issue of civil engineering. Concerning the control problem itself, the problem is quite original, as the "perturbation" exerted on the buildings (the seism) is by nature a transient signal. This makes the presuppositions of the classical control and optimal control methods rather unsuitable. To go past this shortcoming, we initiated an analysis of the seismic signals in a time-frequency framework, allowing to describe better their properties.

5.4.2. *Multifractal analysis: multiplicative cascades*
Participants: Julien Barral, Xiong Jin.

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

The results obtained concern the following topics: Multifractal analysis of complex random cascades [18], Uniform convergence of $[0, 1]$-martingales [20], Convergence of signed multiplicative cascades [19] and has led to the PhD of X. Jin [17].

An application of multifractal analysis to the cardiovascular system can be found 6.3.

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

5.5.1. *A dynamical model for the control of the GnRH neurosecretory system*
Participants: Frédérique Clément, Alexandre Vidal.

The GnRH neurosecretory system involves both endocrine neurones and associated brain cells responsible for the control of GnRH release into the pituitary portal blood. Alternation between a pulsatile regime and the pre-ovulatory surge is the hallmark of GnRH secretion in ovarian cycles of female mammals. In previous papers, we have introduced a mathematical model of the pulse and surge GnRH generator and derived appropriate dynamics-based constraints on the model parameters both to reproduce the right sequence of secretion events and to fulfil quantitative specifications on GnRH release. Here, we explain how these constraints amount to embedding time- and dose-dependent steroid control within the model. We further examine under which conditions the oestradiol-driven surge may be withdrawn by pre-surge progesterone administration and simulate both oestradiol and progesterone challenges in the pulsatile regime [31].

5.5.2. *Analysis and control of a scalar conservation law modeling a highly re-entrant manufacturing system*
Participants: Frédérique Clément, Peipei Shang.

Collaboration with Jean-Michel Coron and Zhiqiang Wang.

In this paper, we study a scalar conservation law that models a highly re-entrant manufacturing system as encountered in semi-conductor production. As a generalization of Coron et al. (2010) [82], the velocity function possesses both the local and nonlocal character. We prove the existence and uniqueness of the weak solution to the Cauchy problem with initial and boundary data in L^∞. We also obtain the stability (continuous dependence) of both the solution and the out-flux with respect to the initial and boundary data. Finally, we prove the existence of an optimal control that minimizes, in the L^p-sense with $1 \le p \le = \infty$:, the difference between the actual out-flux and a forecast demand over a fixed time period [28].

5.5.3. *Cauchy problem for multiscale conservation laws: Application to structured cell populations*

Participants: Frédérique Clément, Peipei Shang.

Collaboration with Jean-Michel Coron.

In this paper, we study a vector conservation law that models the growth and selection of ovarian follicles. During each ovarian cycle, only a definite number of follicles ovulate, while the others undergo a degeneration process called atresia. This work is motivated by a multiscale mathematical model starting on the cellular scale, where ovulation or atresia result from a hormonally controlled selection process. A two-dimensional conservation law describes the age and maturity structuration of the follicular cell populations. The densities intersect through a coupled hyperbolic system between different follicles and cell phases, which results in a vector conservation law and coupling boundary conditions. The maturity velocity functions possess both a local and nonlocal character. We prove the existence and uniqueness of the weak solution to the Cauchy problem with bounded initial and boundary data [61].

5.6. Clinical and physiological applications - Cardiovascular system

5.6.1. *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 [29]. 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 [30] 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.

5.6.2. *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 [23].

5.7. Clinical and physiological applications - Reproductive system

5.7.1. *Regulation of Anti-Mullerian Hormone Production in the Cow: a Multi-scale Study at Endocrine, Ovarian, Follicular and Granulosa Cell Levels*

Participants: Frédérique Clément, Claire Médigue.

Collaboration with Danielle Monniaux (UMR CNRS-INRA 6175).

Anti-Mullerian hormone (AMH) is an endocrine marker which can help predict superovulatory responses to treatments administered to cows for embryo production. However, the optimal time of the estrous cycle at which a blood test should be performed for a highly reliable prognosis has not been established yet. Moreover, little is known about the regulation of AMH production. To answer these questions, a study was designed to investigate the regulation of AMH production in cows selected for their high or low ovulatory responses to superovulation. At the granulosa cell level, AMH production was inhibited by FSH but enhanced by bone morphogenetic proteins. At the follicular level, the expression of AMH within the follicle was dependent on the stage of follicular development. At the ovarian level, the size of the pool of small antral growing follicles determined ovarian AMH production. At the endocrine level, AMH followed a specific dynamic profile during the estrous cycle, which occurred independently of the follicular waves of terminal follicular development. Cows selected for their high or low responses to superovulation did not differ in the regulation of AMH production but cows with higher responses had higher AMH concentrations in plasma throughout the cycle.

The optimal period of the estrous cycle to measure AMH concentrations with the aim of selecting the best cows for embryo production was found to be at estrus and after day twelve of the cycle. From this multiscale study, we propose a model that integrates the different regulatory levels of AMH production [27].

5.7.2. *Anti-Mullerian hormone, an endocrine predictor of the response to ovarian stimulation in the bovine species*

Participants: Frédérique Clément, Claire Médigue.

Collaboration with Danielle Monniaux (UMR CNRS-INRA 6175).

The strong between-animal variability in the number of ovulations and embryos produced after ovarian stimulation by gonadotropins is a major limit to the development of embryo biotechnologies in cattle. In reproductive medicine, anti-mullerian hormone (AMH) is now widely used as an endocrine marker of the ovarian follicular reserve. In the cow, as in the woman, AMH is secreted by the granulosa cells of growing follicles. We have shown recently that in the cow, AMH is a very good endocrine marker of the population of small antral follicles that constitute the direct target of ovarian stimulatory treatments. AMH concentration measured in plasma before treatment varies between animals and is positively correlated to the number of ovulations and transferable embryos produced after an ovarian stimulatory treatment. Interestingly, AMH concentrations can remain stable over several months for each animal. Moreover, the number of embryos produced after ovarian stimulation is highly repeatable and has a relatively good heritability. From these observations, we propose the determination of AMH concentration in the plasma of a potential donor cow as a simple predictive method to evaluate both its level of ovarian activity and its capacity to produce high or low numbers of embryos. Optimal conditions for implementing this diagnostic test in cattle remain to be defined considering the age, the breed, the physiological status and the environmental factors related to breeding conditions for each animal [25].

6. Contracts and Grants with Industry

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

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 [103]. Blood glucose has become a key biological parameter in critical care since publication of the study conducted by van den Berghe and colleagues [131], 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 [80] and the Glucontrol trial.

After having studied a possible origin of the failure of the recent study NICE-SUGAR, we have worked on more robust control algorithms based on a database of representative "virtual patients" [41].

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 is assessed in the study CGAO-REA (see 4.3). The controller determines the insulin infusion rate on the basis of the standard available glycaemia measurements despite their irregular sampling rate.

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

Participants: Michel Sorine, Frédéric Vallais.

This project is the beginning of our cooperation with 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. ANR project DMASC: Scaling Invariance of Cardiac Signals, Dynamical Systems and Multifractal Analysis

Participants: Julien Barral, Patrick Loiseau, Claire Médigue, Michel Sorine.

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

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

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

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

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

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

This work is conducted within the framework of the project Diapason (ANR, Program PAN-H 2006), which is dedicated to the diagnosis of 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. Efforts have continued in view of precise modeling of the individual fuel cell.

6.5. ANR project EBONSI: Extended Block-Oriented Nonlinear System Identification

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

The main idea of block-oriented nonlinear system identification is to model a complex system with interconnected simple blocks. Such models can cover a large number of industrial applications, and are yet simple enough for theoretic studies. The objectives of the EBONSI project are to extend block-oriented nonlinear models with hysteresis blocks and bilinear blocks, and to relax some traditional restrictions on nonlinearity structures and on experimental conditions. The two extensions with hysteresis blocks and bilinear blocks have been motivated by their importance in process control. Through these extensions, it is expected to considerably increase the applicability of block-oriented nonlinear system identification to industrial systems. This is an international project jointly funded by the French Agence Nationale de la Recherche (ANR) and the Chinese National Natural Science Foundation (NSFC). Its duration is 3 years starting from 2010. The partners of the project are the SISYPHE project-team of INRIA and the Laboratory of Industrial Process Monitoring and Optimization of Peking University (China).

6.6. ANR project 0-DEFECT: On-board fault diagnosis for wired networks in automotive systems

Participants: 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 developing tools for on-bord diagnosis of failures in electric wire connections in automotive systems. This project is funded by Agence Nationale de la Recherche (ANR) for three years from 2009. The involved partners are CEA LIST, Renault Trucks, Freescale, PSA, Delphi, Supelec LGEP and INRIA. See also Section 5.2.2.

6.7. ANR project INSCAN: Fault diagnosis for security critical long distance electric transmission lines

Participants: Leila Djaziri, Michel Sorine, Qinghua Zhang.

The wired electric networks of the French railway system cover more than 50000 km. The electric insulation of the 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 5.2.2.

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

Participants: Hadis Amini, Zaki Leghtas, Ram Somaraju, Mazyar Mirrahimi, Pierre Rouchon, Michel Sorine, Filippo Visco Comandini.

The project EPOQ2 is an ANR "Young researcher" project led by Mazyar Mirrahimi (Sisyphe). It has for goal to address a class of inverse problems rising from either the emerging application domain of "quantum engineering" or from some classical applications where a natural quantization lead to quantum-like systems, as it is the case in particular for inverse scattering for transmission lines. 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). See EPOQ2.

6.9. The Mathworks contract: System Identification ToolBox (SITB)

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.

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

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

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

7. Other Grants and Activities

7.1. REGATE (Inria Large Scale Initiative Action)

Participants: Frédérique Clément, Claire Médigue, Peipei Shang.

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 2 INRIA research teams, Contraintes and Sisyphe. There are also participants from INRA, Université Libre de Bruxelles (Unité de Chronobiologie théorique) and Université Paris 6 (Laboratoire Jacques-Louis Lions).

StochToDet is a project selected after the RNSC 2009 call to ideas.

8. Dissemination

8.1. Scientific animation and responsibilities

P.A. Bliman:

- 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 2nd IFAC Workshop on Estimation and Control of Networked Systems, NecSys'10 (24-26 September, 2010, Annecy, France).
- 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.
- Member of the Scientific Committee of the collaboration program MATH AmSud.
- 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, Grenoble, 2010).
- Member of the Board for recruitment of Maître de conférence (Université Nancy I).
- Member of the PhD Board of A. Esna Ashari.
- Member of the Board for attribution of INRIA Postdoc internships.

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

M. Mirrahimi:
- Associate Editor of Systems & Control Letters.
- Member of the Board for attribution of INRIA Postdoc internships.
- Member of the PhD Student Fellowship Committee.
- Co-organiser of the INRIA Paris-Rocquencourt seminar, "Le Modèle et l'Algorithme".

M. Sorine:
- Member of the Program Committee for the conferences CIFA 2010 and SFIMAR 2011 (workshop of the Société Francophone d'Informatique et de Monitorage en Anesthésie - Réanimation).
- Member of the scientific board of the ITMO Circulation, Metabolism and Nutrition (Multi Organization Thematic Institute of the French National Alliance for Life and Health Sciences).
- Member of the steering committee of the clinical study CGAO-REA.
- 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 Program Committee of the 3èmes Journées Identification et Modélisation Expérimentale.
- Member of the International Program Committee of the 30th Chinese Control Conference.

8.2. Teaching activity

- P.-A. Bliman: Automatic control, 3rd year lectures at Ecole Nationale Supérieures des Mines de Paris.
- F. Clément: "Modelling and control of biological systems" course, part of the Master's Degree in BioInformatics and BioStatistics (Paris-Sud 11 University, in collaboration with Béatrice Laroche)
- M. Mirrahiml: Master (M2) courses on Modelisation and control of quantum systems (with P. Rouchon), in Control of Partial and Differential Equations and Applications Trimester. IHP, October 1st – December 18th 2010 ; Lectures in Mathematics, Ecole Nationale Supérieures des Mines de Paris.
- Z. Leghtas: associate professor for the course PA101 : Quantum and statistical physics. ENSTA Paristech, Year : 1A.

- A. Guerrini (with P. Kalfon): "Journées d'Enseignement Post Universitaire d'Anesthésie Réanimation 2010".
12 et 13 mars 2010. CNIT - Paris la Défense.

8.3. Participation in conferences, seminars ; PhD defenses

P.A. Bliman:
- Presentation in the meeting of the project Diapason (ANR PAN-H), May 2010 ;
- Invited speaker at the Multi-agent coordination and estimation semester (February 2010, Lund Center for Control of Complex Engineering Systems, Sweden).

F. Clément:
- Invited participant to the MBI (Mathematical Bioscience Institute) CWT (Current Workshop Topic) on Mathematical Neuroendocrinology http://mbi.osu.edu/2010/mndescription.html
- Invited speaker to the thematic school MifoBio (functional microscopy in biology)

M. Mirrahimi:
 - Feedback preparation of quantum entangled states, Groupe de Travail contrôle EDP, Laboratoire JLL, Paris VI, Mai 2010.
- Stabilization of a delayed quantum system: the Photon Box case-study, Workshop on quantum control, Cambridge, Nov 2010.
- Feedback preparation of quantum entangled states, Workshop on quantum control, IHP, Dec 2010.

M. Sorine:
 - Invited presentation to the "Rencontres INRIA-industries - Les industries du numérique pour la santé", april, 15, 2010, Bordeaux: "Le Contrôle Glycémique Assisté par Ordinateur testé dans 62 services de réanimation, un exemple d'application de l'automatique dans le cadre d'un partenariat INRIA/PME/Hôpital".
- Presentations in the meetings of the projects 0-DEFECT, INSCAN, EPOQ2.

Q. Zhang:
- Presentation at the Workshop of the European Research Network for System Identification (ERNSI), September 2010, Cambridge.
- Presentation in the working group Sûûreté-Surveillance-Supervision (S3), November 2010, Paris.

PhD theses: Xiong Jin has defended his PhD (on January, 14 th 2010).

8.4. Foreign Visitors

Alfredo Illanes Manriquez (Universidad Austral de Chile, 1 month) visited us during October for a collaboration on electrocardiogram signal processing and cardiovascular system modeling.

Martin Krupa (Nijmegen, Department of Mathematics) has been visiting the project-team since December to set up a collaboration in the field of Mathematical Neuroendocrinology.

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