INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Team Sosso2

Applications and tools for automatic control

Rocquencourt

THEME BIO

Activity Report

2006

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2. Overall Objectives

2.1. Overall Objectives

Keywords: *bioenergetics*, *biology*, *cardiovcascular system*, *combustion engine*, *control*, *energetics*, *fuel cell*, *health*, *modelling*, *multi-scale systems*, *observation*, *ovulation control*, *process engineering*.

The SOSSO2 team is involved in modelling, observation and control of natural or engineered feedback-controlled systems. A particular emphasis is on applications to some controlled multi-scale systems in physiology or engineering. Two such multi-scale systems concern energy conversion: the Human Heart, a naturally controlled pump, and the controlled combustion in some new engines for automobiles. A third multi-scale system is considered for modelling the development of ovarian follicles. In the case of physiological systems some applications to diagnosis and therapy are also considered.
The main part of the research on the cardiovascular system is done in the framework of the Inria Large-scale Initiative Action, Cardiosense3D. See http://www-sop.inria.fr/CardioSense3D. The present topics of the team are:

- Multi-scale modelling of the controlled chemomechanical conversion in the heart (cell, tissue and organ scales) ;
- Model-based non-invasive assessment of the function of the cardiac pump on the cardiovascular system scale ;
- Multi-scale modelling of the selection of ovulatory follicles.

Control of energy conversion is also considered in low-emission vehicles:

- Multi-scale reduced-order modelling and control of auto-ignition in internal combustion engines ;
- Multi-scale modelling, monitoring and control of fuel-cell systems.

3. Software

3.1. 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, developed in the SCILAB_SCICOS scientific environment [80]. 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.

3.2. The System Identification ToolBox (SITB)

Participant: Qinghua Zhang.

Contract with The Mathworks, from July 2005 to July 2010.

The System Identification ToolBox (SITB) is one of the main Matlab toolboxes commercialized by The Mathworks. The current version of the toolbox is limited to the identification of linear systems. In collaboration with Lennart Ljung (Sweden), the author of the current version of the SITB, and also with Anatoli Juditsky (Grenoble University) and Peter Lindskog (Sweden), an extension of the SITB for nonlinear system identification is under development. Future versions of the toolbox will include algorithms for black box and grey box identification of nonlinear dynamic systems. INRIA is mainly responsible for the development of black box identification.

4. New Results

4.1. System control and observation

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

4.1.1. Robustness Properties of Linear Systems

Participant: Pierre-Alexandre Bliman.

We developed with P.L.D. Peres, V.F. Montagner and R.C.L.F. Oliveira (Unicamp, Campinas, Brazil) some tools for the robust analysis of some uncertain linear systems with parametric uncertainties, namely the class of *polytopic systems*. We established a general regularity result, stating that the solution to a system of linear matrix inequalities (LMIs) depending continuously upon a parameter located anywhere in a polytope can be assumed with no loss of generality to be a *homogeneous polynomial* in this parameter — provided that a solution exists everywhere on the polytope.

This leads to fast numerical methods to solve the LMIs involved in the solution of several problems of importance for control of polytopic systems, namely robust stability and robust performance analysis, and gain scheduling.

4.1.2. Stability Analysis of Systems Defined on Interaction Graph

Participant: Pierre-Alexandre Bliman.

We previously studied in a general framework the stability for a class of linear discrete-time systems made up of sub-systems seeking consensus via communications defined by time-varying, directed, interaction graph. These systems are also known in the literature as *multi-agent systems*. Continuing our collaboration with D. Angeli (Università degli Studi di Firenze, Italy), we initiated this year a work on the *quantitative aspects of convergence* towards a consensus.

While the classical results use in general some connectedness assumption, plus a lower bound on the non-zero weights to estimate the decay rate, we introduced more sophisticated tools, based on some alternate weights related to the expansion of the trees which dynamically span the interaction graph. First results indicated that this new method provides surprisingly tight estimates.

4.1.3. Robust control of some fractional delay systems of neutral type

Participants: Catherine Bonnet, Jonathan Partington, Matthew Peet.

We have continued this year the study of H_∞-stability (stabilization) of neutral delay systems. In particular we have progressed in the characterization of delay systems of the type $G(s) = \dfrac{r(s)}{p(s) + q(s)e^{-sh}}$ (with $h > 0$, p, q, r real polynomials such that $\deg p = \deg q \geq \deg r$) which are H_∞-stabilizable by rational controllers. The case of multiple delays has also been investigated as well as the case of some MIMO neutral delay systems.

4.1.4. Adaptive observers for fault diagnosis

Participants: Stefano Perabò, Qinghua Zhang.

For model-based fault diagnosis, faults are typically modeled either as unknown disturbances or parametric changes. The approach of unknown disturbances has the advantage of flexibility for the description of quite general faults, but has a strong requirement on the number of available sensors. The approach of parametric changes does not have any hard requirement on the number of sensors, but it is more restrictive to the nature of modeled faults and requires some excitation condition. Though fault diagnosis has been largely studied with one or the other type of modeled faults, there has not been a systematic study with both types of modeled faults co-existing in a same system. In this work the diagnosis of both types of faults is studied for general linear time varying systems. The basic idea is to study the behavior of the innovation of the Kalman filter applied to the monitored system under the fault-free assumption. The original fault diagnosis problem for a dynamic system is then transformed to a linear regression problem. Based on this idea, the diagnosis of faults of both types can be achieved in the same framework through the implementation of adaptive observers.

4.1.5. Identification of Wiener system with monotonous nonlinearity

Participant: Qinghua Zhang.

A Wiener system is composed of a linear dynamic subsystem followed by a static nonlinearity. In general, the estimation of the linear and nonlinear parts needs to be jointly performed through a non convex optimization problem, because the estimation of one needs the knowledge of the other. One exception is when the input of the system is a Gaussian distributed random signal: it is well known that, in this case, the identification of the linear subsystem can be separated from that of the output nonlinearity. However, Gaussian distribution is a quite restrictive condition in practice. In this work, a new method is developed for direct identification of the linear subsystem, regardless of any parametrization of the output nonlinearity. No particular distribution of the input signal is assumed. Instead it is assumed that the output nonlinearity is strictly monotonous. In practice the output nonlinearity is usually caused by sensor distortion, it is thus reasonable to assume that the nonlinear distortion is monotonous. The new method is not based on the inversion of the output nonlinearity. It is essentially based on the fact that the monotonous nonlinear function conserves relative signs: for a strictly monotonously increasing nonlinear function $f(x)$, the equality

$$\text{sign}[f(x_1) - f(x_2)] = \text{sign}(x_1 - x_2)$$

always holds. Two algorithms have been developed following this idea.

This work has been carried out in collaboration with Anatoli Iouditski of Grenoble University (France) and Lennart Ljung of Linköping University (Sweden), and has been presented at the 14th IFAC Symposium on System Identification (SYSID 2006) [66].

4.1.6. Robust fault diagnosis based on adaptive estimation and set-membership computation

Participant: Qinghua Zhang.

Robustness to modeling and measurement uncertainties are an important issue for model-based fault diagnosis. Such uncertainties are typically modeled as random noises or as bounded errors. In the approach of bounded errors, thresholds used in diagnosis decisions can be estimated from error bounds to prevent false alarms. These thresholds, adaptive or not, are usually estimated by propagating inequalities through the equations of the dynamic system model. The propagation of inequalities requires approximations to make the problem tractable. These approximations are made by preventing false alarms, however, they are often so conservative that the resulting thresholds do not allow to detect the faults of reasonable magnitude. In this work the technique of set-membership computation is used to compute adaptive thresholds. This method aims to reduce the conservativeness of the thresholds estimation while keeping the computations within a reasonable complexity. Its efficiency has been demonstrated by numerical simulations.

This work has been jointly made with Christophe Combastel of Ecole Nationale Supérieure de l'Electronique et de ses Applications, and has been presented at the 6th IFAC Symposium on Fault Detection, Supervision and Safety of Technical Processes (SAFEPROCESS 2006) [49].

4.2. Multifractal analysis and signal processing

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

4.2.1. The singularity spectrum of Gibbs measures on self-affine Sierpinski carpets

Participants: Julien Barral, Mounir Mensi.

We consider a class of Gibbs measures on self-affine Sierpinski carpets and perform the multifractal analysis of its elements. These deterministic measures are Gibbs measures associated with bundle random dynamical systems defined on probability spaces whose geometrical structure plays a central rôle.

A special subclass of these measures is the class of multinomial measures on Sierpinski carpets. Our result improves the already known result concerning the multifractal nature of the elements of this subclass by considerably weakening and even eliminating in some cases a strong separation condition of geometrical nature.

4.2.2. Renewal of Singularity sets of statistically self-similar measures

Participants: Julien Barral, Stéphane Seuret.

This work investigates new properties concerning the multifractal structure of a class of random self-similar measures. These measures include the well-known Mandelbrot multiplicative cascades, sometimes called independent random cascades. We evaluate the scale at which the multifractal structure of these measures becomes discernible. The value of this scale is obtained through what we call the growth speed in Hölder singularity sets of a Borel measure. This growth speed yields new information on the multifractal behavior of the rescaled copies involved in the structure of statistically self-similar measures. Our results are useful to understand the multifractal nature of various heterogeneous jump processes.

4.2.3. The multifractal nature of heterogeneous sums of Dirac masses

Participants: Julien Barral, Stéphane Seuret.

This work deals with the natural problem of performing the multifractal analysis of heterogeneous sums of Dirac masses

$$\nu = \sum_{n\geq 0} w_n \, \delta_{x_n},$$

where $(x_n)_{n\geq 0}$ is a sequence of points in $[0,1]^d$ and $(w_n)_{n\geq 0}$ is a positive sequence of weights such that $\sum_{n\geq 0} w_n < \infty$. We consider the case when the points x_n are roughly uniformly distributed in $[0,1]^d$, and the weights w_n depend on a random self-similar measure μ, a parameter $\rho \in (0,1]$, and a sequence of positive radii $(\lambda_n)_{n\geq 1}$ converging to 0 in the following way

$$w_n = \lambda_n^{d(1-\rho)} \mu\left(B(x_n, \lambda_n^{\rho})\right) |\log \lambda_n|^{-2}.$$

The measure ν has a rich multiscale structure exhibiting a kind of phase transition due to the presence of atoms. The computation of the singularity spectrum is related to heterogeneous ubiquity properties of the system $\{(x_n, \lambda_n)\}_n$ with respect to μ.

4.2.4. Information parameters and large deviation spectrum of discontinuous measures

Participants: Julien Barral, Stéphane Seuret.

Let ν be a finite Borel measure on $[0,1]^d$. Consider the L^q-spectrum of ν:

$$\tau_\nu(q) = \liminf_{n\to\infty} -n^{-1} \log_b \sum_{Q\in\mathcal{G}_n} \nu(Q)^q, \quad (q \geq 0),$$

where $\mathcal{G}_n$ is the set of b-adic cubes of generation n (b integer ≥ 2). Let $q_\tau = \inf\{q: \ \tau_\nu(q) = 0\}$ and$H_\tau = \tau_\nu'(q_\tau^-)$. When ν is a mono-dimensional continuous measure of information dimension D, $(q_\tau, H_\tau) = (1, D)$. When ν is purely discontinuous, its information dimension is $D = 0$, but the pair (q_τ, H_τ) may be non-trivial and contain relevant information on the distribution of ν. Intrinsic characterizations of (q_τ, H_τ) are found, as well as sharp estimates for the large deviations spectrum of ν on $[0,H_\tau]$. We exhibit the differences between the cases $q_\tau = 1$ and $q_\tau \in (0,1)$. We conclude that the properties observed for special classes of measures are generally true.

4.2.5. Threshold and Hausdorff spectrum of discontinous measures

Participants: Julien Barral, Stéphane Seuret.

Let χ be a finite Borel measure on $[0,1]^d$. Consider the L^q-spectrum of χ:

$$\tau_\chi(q) = \liminf_{n\to\infty} -n^{-1}\log_b \sum_{Q\in\mathcal{G}_n,\ \chi(Q)\neq 0} \chi(Q)^q,$$

where $\mathcal{G}_n$ is the set of b-adic cubes of generation n. Let $q_\tau = \inf\{q :\ \ \tau_\chi(q)=0\}$ and $H_\tau = \tau'_\chi(q_\tau^-)$. When χ is a mono-dimensional continuous measure of information dimension D, $(q_\tau, H_\tau) = (1, D)$. When χ is purely discontinuous, its information dimension is $D = 0$, but the non-trivial pair (q_τ, H_τ) may contain relevant information on the distribution of χ. The connection between (q_τ, H_τ) and the large deviations spectrum of χ is studied in a companion paper. This paper shows that when a discontinuous measure χ possesses self-similarity properties, the pair (q_τ, H_τ) may store the main multifractal properties of χ, in particular the Hausdorff spectrum. This is observed thanks to a threshold performed on χ.

4.3. Modelling, observation and control in biosciences: the controlled cardiovascular system

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

4.3.1. *The cardiovascular system: a multi-scale controlled system*

From the cardiovascular system scale to the cell scale, the function of the circulation is to supply cells with oxygen, nutrients and to remove carbon dioxide and other catabolits. On each of these scales, variables involved in cardiovascular regulation, such as blood flow, blood pressure, oxygen blood concentration, ATP concentration, are kept around their reference points by different feedback control mechanisms having different dynamics depending upon the considered scale.
We are interested in the mechano-energetics of the heart with its short term (some few minutes) intrinsic control mechanisms, from the cell scale to the cardiovascular system scale:

- On the cell and tissue scales, models of the mechano-energetics of the heart provide us with constitutive laws for the cardiac tissue, used in $3D$ models for computing stress, strain and action potential fields in the heart from three-dimensional image processing, as in our CardioSense3D project where, the chemically-controlled constitutive law of cardiac myofibre that we have obtained [4] is currently used [2]. This law ensues from the modelling of the collective behaviour of actin-myosin molecular motors converting chemical energy into mechanical energy. It is thermodynamically consistent and the resulting dynamics of sarcomeres is consistent with the “sliding filament hypothesis” of A. F. Huxley.
Intrinsic heart control mechanisms we consider, range from the Starling and Treppe effects on the cell scale to the excitability of the cardiac tissue. They all contribute to the function of the heart in a coordinated manner that we want to analyse and assess.
This year we have continued the mathematical analysis of the models used in CardioSense3D, see 4.3.2 and studied a reduced order model of the intracellular calcium dynamics that will be useful to represent the rate-dependent inotropic effects like Treppe effect (also called positive staircase effect). See 4.3.3.

- On the cardiovascular system and heart scales, we use $0D$ models of the electro-mechanical activity of the cardiac muscle for control analysis and signal processing applications. Here the heart is seen as a small number of “averaged cells” representing the walls of the atrial and ventricular chambers. The short term control of blood flow and pressure on the cardiovascular system scale (the heart and the vascular compartments) is performed by the autonomic nervous system through baroreceptor control loops. We don’t consider longer horizons where slower control mechanisms operate such as hormonal regulation. A good autonomic function is of crucial importance for life and is of great prognostic value in many diseases.
Our objective here, is to relate discrete-time 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 pratical interest.

This year we have studied an intrinsic control effect, represented by the restitution curve associated to a very simple cardiac cell model, see 4.3.6 and we have continued our researches on arterial pressure analysis, see 4.3.4 and ECG analysis, see 4.3.5.

4.3.2. Multi-scale modelling of the controlled contraction of cardiac muscle

Participant: Michel Sorine.

This work takes place in the framework of CardioSense3D.
We have used ideas originating from the kinetic equation theory to model, on the molecular scale, the controlled collective behaviour of actin-myosin nanomotors at the root of muscle contraction. The classical Huxley's model is recovered on the sarcomere scale by using moment equations. A controlled constitutive law on the tissue scale is obtained using the same type of scaling techniques. This multi-scale description of controlled muscle contraction may be useful in studying modelling and control problems associated to the heart considered as a multi-scaled system. The control viewpoint is useful in accounting for macroscopic properties (such as the Starling law or the Hill force-velocity relation) on lower scales and defining performance indexes of the electro-mechanical coupling on each scale.
This year, in a joint work with Pavel Krejčí (Weierstrass Institute for Applied Analysis and Stochastics, Berlin), J. Sainte-Marie (MACS project) and J.M. Urquiza (CRM, Montreal), we have considered the mathematical analysis of the fibre model used in CardioSense3D in the more simple case of a one dimensional geometry ($1D$ problem). We have proved the well-posedness of that model and some asymptotic behaviour results [19] and we continue to study a more complete system with valves and vascular compartments.

4.3.3. Differential models of cardiac cells

Participants: Karima Djabella, Michel Sorine.

We have presented [79] a differential model of excitation - contraction coupling in a cardiac cell intended to be used in simulations of one or many heart cycles on the cell or the heart scales. It takes into account the dynamics of the main ionic currents flowing through the membrane channels (fast sodium, L-type calcium and outward potassium) and Na+/Ca2+ exchangers and Na+/K+ pumps. The model includes also a description of the dynamics of the main calcium buffers in the bulk cytosol and in the sarcoplasmic reticulum. With thirteen state variables, its complexity is between that of FitzHugh-Nagumo type models of the action potential (two state variables) and that of the more complex ionic channels models (up to sixty state variables for some of them). It allows realistic modelling of action potential, total ionic current, current gating, intracellular calcium transients, in particular for calcium bound on troponin C, and multicycle effects, like restitution curves for the action potential duration, CICR dependence on intracellular calcium concentration, positive staircase effect for the heart rate. Due to its sound asymptotic behavior without drifts of the state and its medium complexity, this model can be used in multi-beat simulations from the cell to the heart scales. This year, the model has been reduced and extended to represent pacemaker or Purkinje cells [53], [54].

4.3.4. Reduced model of pulsatile flow and application to arterial pressure analysis

Participants: Emmanuelle Crépeau-Jaisson, Taous-Meriem Laleg, Claire Médigue, Yves Papelier, Michel Sorine.

We have proposed [78] a reduced model of the input-output behaviour of an arterial compartment, including the short systolic phase where wave phenomena are predominant. A more detailed analysis is now available [14]. The objective is to provide basis for model-based signal processing methods for the estimation from non-invasive measurements and the interpretation of the characteristics of these waves. Standard space discretizations of distributed models of the flow lead to high order models for the pressure wave transfer function, and low order rational transfer functions approximations give poor results. The main idea developed here to circumvent these problems is to explicitly use a propagation delay in the reduced model. Due to phenomena such that peaking and steepening, the considered pressure pulse waves behave more like solitons generated by a Korteweg de Vries (KdV) equation than like linear waves. So we start with a quasi-1D Navier-Stokes equation that takes into account a radial acceleration of the wall, in order to be able to recover, during the reduction process, the dispersive term of KdV equation which, combined with the nonlinear transport

term gives rise to solitons. The radial and axial acceleration terms being supposed small, a multiscale singular perturbation technique is used to separate the fast wave propagation phenomena taking place in a boundary layer in time and space described by a KdV equation from the slow phenomena represented by a parabolic equation leading to two-elements windkessel models. Some particular solutions of the KdV equation, the 2 soliton solutions, seem to be good candidates to match the observed pressure pulse waves. They are given by close form formulae involving propagation delays that are proposed to represent input and output wave shapes. Some very promising preliminary comparisons of numerical results obtained along this line with real pressure data are shown.
This work will be continued within the preparation of the PhD of M. Laleg and it will lead to clinical studies. Some first results have been published [60], [58] [59].

4.3.5. ECG analysis: T-wave end location

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

For the purpose of developping methods associating mathematical modeling of the cardio-vascular system and the processing of non invasive measurements, studies on new methods for electrocardiogram (ECG) processing have been carried out [81]. The results of these studies can also have direct applications to computer-aided cardiac disease diagnosis. One important result of these studies is a new algorithm for ECG T-wave end location. It mainly consists of the computation of an indicator related to the area covered by the T-wave curve and delimited in a special manner. Based on simple assumptions, essentially on the concavity of the T-wave form, it is formally proved that the maximum of the computed indicator inside each cardiac cycle coincides with the T-wave end. The resulting algorithm is computationally very simple: the main computation can be implemented as a simple finite impulse response (FIR) filter. The most remarkable property of the algorithm is its robustness to measurement noise, to wave form morphological variations and to baseline wander. This robustness has been demonstrated in the processing of ECG signals recorded during handgrip exercise and also in the processing of the PhysioNet QT database. This new algorithm is playing an important role in our current studies on cardio-vascular modeling related to the restitution curve. A detailed analysis has been published [26]. This year, we have also considered a first approach towards multi-lead T wave end detection based on statistical hypothesis testing [57].

4.3.6. Electrocardiogram-based restitution curve

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

For isolated cardiac cells, the relationship between each action potential duration (APD) and the preceding diastolic interval (DI) is well known under the term of *restitution curve*. Though the electrocardiogram (ECG) reflects the cardiac electric activity, it was not possible to observe a relationship between events in ECG signals similar the restitution curve. In principle, the QT interval is related to the global ventricular electric activity. However, the QT interval observed at the body surface corresponds to the APDs of a large number of cells which vary from site to site in the ventricle. In this study, under special conditions for ECG recording, a relationship between the QT interval and the preceding TQ interval has been revealed. This relationship, we refer to as *ECG-based restitution curve*, has a form similar to the cellular restitution curve. Moreover, an analytical model originally used to describe cellular restitution curves has been successfully fitted to the experimental ECG-based restitution curves. Two factors have been essential for the observation of the ECG-based restitution curves. First, the ECG signals are recorded under the handgrip isometric exercise which triggers in a short term strictly autonomic responses. Second, in order to measure the QT and TQ intervals, the T-wave ends must be located with a sufficient accuracy. The algorithm for T-wave end location recently developed by the SOSSO2 team [45] has been successfully applied for this purpose.

The results of this study have been presented at Computers in Cardiology 2006 [56].

4.4. Modelling, observation and control in biosciences: ovulation control

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

4.4.1. Multi-scale modelling of the selection of ovulatory follicles

Participants: Frédérique Clément, Nki Echenim, Michel Sorine.

This work is the matter of a PhD thesis (University Paris 11, Sciences and Technologies for Information, Telecommunications and Systems).

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

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

$$\frac{\partial \varphi_f}{\partial t} + \frac{\partial (h_f \varphi_f)}{\partial \gamma} + \frac{\partial (g_f \varphi_f)}{\partial a} = G - L \qquad (1)$$

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

The model is associated with two nested accessibility problems, respectively on the ovarian scale (reachability of the conditions for ovulatory surge triggering) and on the follicular scale (reachability of the conditions for ovulation). Due to the complexity of the model formulation (hybrid features, feedback in the velocity and loss terms), such problems cannot be tackled head-on. Defining similar accessibility problems from a characteristics-like formulation of the conservation law is the subject of current research, see [55], [73] and [27].

4.4.2. Modelling of the GnRH pulse and surge generator

Participants: Frédérique Clément, Jean-Pierre Françoise.

Biological background. The reproductive axis is under the control of the GnRH (Gonadotropin Releasing Hormone), which is secreted from specific hypothalamic areas in a pulsatile manner. This pulsatility (between 1 pulse per hour and 1 pulse every 6 hours) has a fundamental role in the differential control of the secretion of both gonadotropins: LH (Luteinizing Hormone)–enhanced by higher frequency– and FSH (Follicle Stimulating Hormone) –enhanced by lower frequency–. The pulsatile pattern is tremendously altered once per ovarian cycle into a surge which triggers ovulation in response to increasing levels of estradiol. The estradiol signal is conveyed to GnRH neurons through a network of interneurons. The balance between stimulatory and inhibitory signals emanating from interneurons controls the behaviour of the GnRH network.
Modelling approach. We propose a mathematical model allowing for the alternating pulse and surge pattern of GnRH (Gonadotropin Releasing Hormone) secretion. The model is based on the coupling between two FitzHugh-Nagumo 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. Specifications on the model parameter values are derived from physiological knowledge in terms of amplitude, frequency and plateau length of oscillations. The behavior of the model is finally illustrated by numerical simulations, see [72].

4.4.3. Signal processing of GnRH neuron-derived data

Participants: Frédérique Clément, Claire Médigue, Anne Duittoz.

Biological background. The pulsatility pattern of GnRH secretion ensues from the synchronisation of the secretory activity of several GnRH neurons. Such secretory rhythms result from calcium rhythms which in turn are determined by electrical rhythms. The direct investigation of the synchronisation mechanims is difficult, since GnRH neurons are both scarce (at most 3000 in the sheep) and scattered in different areas of the hypothalamus. We can yet dispose of data collected separately on the neuron network scale: time series of GnRH concentration measured within the hypothalamo-hypophyseal portal blood in the sheep, or on the individual neuron scale: calcium dynamics in primary cultures of sheep olfactory placode explants (GnRH neurons originate from the olfactory bulb from where they migrate into the hypothalamus in the course of embryonic life).
Signal processing. In both cases, we apply signal processing methods (mainly Fast Fourier Transform and Smoothed Pseudo-Wigner-Ville Distribution) to extract dynamical features from the data. From GnRH secretion pattern, we aim at detecting subtle changes occuring at the transition between the pulse and surge secretion pattern. The main question is whether an underlying pulsatile pattern may remain during the surge. From the calcium data, we aim at studying the maturation of calcium oscillations in embryonic neurons and characterising the effect of pharmacological drugs on calcium dynamics. This will help to identify the ionic channels involved in calcium signalling within GnRH neurons, and ultimately to understand the coupling between calcium dynamics and secretory events.

4.5. Clinical and physiological applications

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

Participants: François Cottin, Claire Médigue, Yves Papelier, Michel Sorine.

4.5.1. Assessment of the ventilatory thresholds from heart rate variability in well-trained subjects during cycling.

Collaboration with the LEPHE (Laboratoire d'Etude de la PHysiologie de l'Exercice, Université d'Evry).

The purpose of this study was to implement a new method for assessing the ventilatory thresholds from heart rate variability (HRV) analysis. ECG, VO2, VCO2, and VE were collected from eleven well-trained subjects during an incremental exhaustive test performed on a cycle ergometer. The "Short- Term Fourier Transform" analysis was applied to RR time series to compute the high frequency HRV energy (HF, frequency range: 0.15-2 Hz) and HF frequency peak (fHF) vs. power stages. For all subjects, visual examination of ventilatory equivalents, fHF and instantaneous HF energy multiplied by fHF (HF.fHF) showed two non linear increases. The first non linear increase corresponded to the first ventilatory threshold (VT1) and was associated with the first HF threshold (TRSA1 from fHF and HFT1 from HF.fHF detection). The second non linear increase represented the second ventilatory threshold (VT2) and was associated with the second HF threshold (TRSA2 from fHF and HFT2 from HF.fHF detection). HFT1, TRSA1, HFT2 and TRSA2 were, respectively, not significantly different from VT1 (VT1 = 219 $\pm$ 45 vs. HFT1 = 220 $\pm$ 48 W, p=0.975; VT1 vs. TRSA1 = 213 $\pm$ 56 W, p=0.662) and VT2 (VT2 = 293 $\pm$ 45 vs. HFT2 = 294 $\pm$-48 W, p=0.956; vs. TRSA2 = 300 $\pm$ 58 W, p=0.445). In addition, when expressed as a function of power, HFT1, TRSA1, HFT2 and TRSA2 were respectively correlated with VT1 (with HFT1 R $\leq$ 0.94, p<0.001; with TRSA1 R $\leq$ 0.48, p<0.05) and VT2 (with HFT2 R $\leq$ 0.97, p<0.001; with TRSA2 R $\leq$ 0.79, p<0.001). This study confirms that ventilatory thresholds can be determined from RR time series using HRV time- frequency analysis in healthy well-trained subjects. In addition it shows that HF.fHF provides a more reliable and accurate index than fHF alone for this assessment.

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

Collaboration with the LEPHE.

The present study examined whether the ventilatory thresholds during an incremental exhaustive running test could be determined using heart rate variability (HRV) analysis. Beat-to-beat RR interval, VO_2, VCO_2 and V_E of twelve professional soccer players were collected during an incremental test performed on track until exhaustion. The “Smoothed Pseudo Wigner-Ville Distribution” (SPWVD) time-frequency analysis method was applied to the RR time series to compute the usual HRV components vs. running speed stages. The ventilatory equivalent method was used to assess the ventilatory thresholds (VT1 and VT2) from respiratory components. In addition, ventilatory thresholds were assessed from the instantaneous components of respiratory sinus arrhythmia (RSA) by two different methods: 1) from the high frequency peak of HRV (fHF). 2) From the product of the spectral power contained within the high frequency band (0.15 Hz to $f$max) by fHF (HF.fHF) giving two thresholds: HFT1 and HFT2. Since the relationship between fHF and running speed was linear for all subjects, the VTs could not be determined from fHF. No significant differences were found between respective running speeds at VT1 vs. HFT1 (9.83$\pm$1.12 vs. 10.08$\pm$1.29 km.h^{-1}, NS) nor between the respective running speeds at VT2 vs. HFT2 (12.55$\pm$1.31 vs. 12.58$\pm$1.33 km.h^{-1}, NS). Linear regression analysis showed a strong correlation between VT1 vs. HFT1 (R^2=0.94, p$<$0.001) and VT2 vs. HFT2 (R^2=0.96, p$<$0.001). The Bland-Altman plot analysis reveals that the assessment from RSA gives an accurate estimation of the VTs, HF.fHF providing a reliable index for the ventilatory thresholds detection. This study has shown that VTs could be assessed during an incremental running test performed on track using a simple beat to beat heart rate monitor, less expensive and complex than the classical respiratory measurement devices.

4.5.3. *Can O2-pulse and pO2-over-pCO2 ratio kinetics provide novel indicators for phase time delays of the VO2 kinetics during heavy square-wave dynamic exercise?*

VO2 kinetics has been found to exhibit a complex tri-exponential appearance (with switch points and delays) during heavy square-wave exercise. HR kinetics appears roughly comparable to that of VO2. The purpose of this study was to compare and cross-analyse the O2-pulse (VO2/HR ratio) and pO2/pCO2 ratio kinetics to have a novel insight into the mechanisms underlying these different kinetics. Eight healthy men performed a cycle ergometer exercise at the work rate corresponding to midway between the work rate at VAT and at VO2peak (P@delta50). Gas exchange was measured breath by breath and HR series were computed from ECG and A/D recorder. VO2 kinetics was comparatively modelled by a ten parameters tri-exponential regression equation and by a simplified eight parameters bi-exponential equation. Moreover O2-pulse and pO2/pCO2 ratio kinetics were cross-analysed. The eight parameters model appears more robust than the ten parameters model with a greater significance of the computed parameters. A mono-exponential model with delay fit at best the kinetics of O2-pulse expressed vs. HR: the exponential component begins at 132±10.7 min(-1) (delay RD), matching the onset of the VO2 fast component (TD2), and reaches a steady state at 156±9.4 min(-1) (HR95). pO2/pCO2 ratio shows an early switch point at 131±11.8 min(-1) that matches RD and TD2 and a later switch point at 149±8.3 min(-1) that matches HR95. This study shows that cross-analysis of O2-pulse and pO2/pCO2 ratio kinetics expressed in relation to HR can provide novel indicators for phase time delays and underlying mechanisms of the VO2 kinetics at exercise.

5. Contracts and Grants with Industry

5.1. Modelling of HCCI engines for control applications

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

5.1.1. Reduced order models of HCCI engines (Renault contract)

Participants: Mehdi Gati, Fadila Maroteaux, Jean-Baptiste Millet, Michel Sorine.

Renault contrat 1 04 D0004 00 21102 012. The HCCI engine tuning requires a large number of engine tests which are time-consuming and very expensive. To reduce the number of tests, a model with a very short computational time to simulate the engines in the whole operating range is needed. Therefore, the objective of this study is to present a new type of zero-dimensional thermodynamic model without chemical kinetics to analyze the HCCI combustion process. A model based on mathematical bifurcation is proposed, where stabilities of the system describe the cool flame and the main ignition. The system of equations governing the model is reduced to three state variables: the temperature and two mass fractions. The model has been compared to the detailed mechanism developed by Lawrence Livermore National laboratory (LLNL) and to Renault engine experimental data. This comparison shows that the model gives reasonable accuracy [62].
M. Gati and J.B. Millet have defended their PhD-thesis [28], [29] prepared in the framework of CIFRE contracts with Renault.

5.1.2. Modelling of HCCI combustion: effects of chemical kinetics and turbulent mixing (Renault contract)

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

Renault contract 104 D1151 00 21102. P.-L. Pommier is preparing his PhD in the framework of this contract. The numerical modelling of complex turbulent flow is an important issue in engines applications. In order to investigate the effects of both the chemical kinetics and turbulent mixing, a stochastic model is used. At first a simple partially stirred plug flow (PaSPFR) is considered, where spatial homogeneity is assumed and were only two physical processes remain: chemical reaction and mixing. In the combustion chamber, local quantities are chemical species mass fractions and temperature and are assumed to be random variables (with their joint random vector). The time evolution of the mass density function (MDF) transport equation takes into account the terms representing the mixing properties and the reaction mechanism of the system. The two terms are approached by a stochastic process, the 26 reactions mechanism developed above is used to model the reaction term [41]. This work is under progress with the PhD of Pierre-Lin Pommier, where the first step was centred on the general modelling of reacting system.

5.2. Mathematical modelling monitoring and control of a fuel cell system with a fuel processor

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

Participants: Fehd Benaïcha, Damiano Di Penta, Karim Bencherif, Masoud Najafi, Stefano Perabò, Michel Sorine, Qinghua Zhang.

During the last 4 years we have considered modelling and control of polymer electrolyte fuel cells (PEMFC) [77]. PEMFC have a high energy conversion efficiency and zero pollutant emission when fueled with hydrogen. They are one of the most promising candidates for fuel cell powered vehicles. Hydrogen can be stored or produced onboard the vehicle by reforming methanol or hydrocarbon fuels in a so called "fuel processor" (or reformer). In our present researches, we consider modelling, monitoring and control problems for a complete system with four stacks of 100 PEMFC each and a gasoline processor. The framework for this work is the cooperative research project RESPIRE, which is partly supported by a public agency, ADEME, and two CIFRE contracts with Renault for Fehd Benaïcha and Damiano Di Penta.

5.2.1. RESPIRE project (ADEME contract)

For the purpose of developing new generation automotive vehicles with reduced exhaust emission, a research project on fuel cells and fuel reformer system, entitled "Réduction des Emissions par Système PIle et Reformeur Essence (RESPIRE)", has been started since September 2004 with industrial partners (Renault, Snecma, Total) and academic partners (INRIA, Supelec, Armine).

The technology of fuel cells is used to generate electric power for electric engines. When hydrogen is used as fuel, this technology allows to design vehicles with almost total absence of pollution at exhaust emission. However, in addition to the difficulty of on board hydrogen storage, it is not realistic to quickly develop a large number of hydrogen service stations when the first cars equipped with fuel cells are available on the market. The particularity of the RESPIRE project is a combination of fuel cells with a fuel reformer. Conventional petrol fuel stored on board is used by the reformer to produce hydrogen fuel which is then fed to the fuel cells. This solution has the advantage of using normal petrol stations. Though petrol fuel is still used as energy source, with this new technology, the pollution emission can be considerably reduced, and the energy efficiency is better than the classical thermal engines.

This year, the SOSSO2 team has worked on several aspects in this project. On the one side, the modeling, control and diagnosis of a stack of fuel cells were studied by treating the stack as if it was a single cell. On the other hand, the diversity in the behaviors of the individual cells in a stack was also investigated. These efforts are for the purpose of monitoring at different scales of the fuel cell system.

5.2.2. Modelling and monitoring of a single PEMFC (Renault contract)

In this CIFRE contract with Renault, Damiano Di Penta will study modelling and monitoring of a single PEMFC or of a stack of PEMFC (a series of 100 PEMFC), considered as an averaged PEMFC. The problem of CO poisoning has been studied and a reduced fuel cell stack model for control and fault diagnosis has been proposed [15]. The estimation and control problem has also been studied [52].

5.2.3. Modelling and control of a single PEMFC (Renault contract)

In this CIFRE contract with Renault, Fehd Benaïcha will study control strategies optimising the system efficiency. This work is done in cooperation with Jean-Claude Vivalda (CONGE team-project).

5.3. The SEEDS project

Participants: Mehdi Admane, Michel Sorine, Qinghua Zhang.

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

The number of electronic equipments is increasing rapidly in automotive vehicles. Consequently, the reliability of electric connections is becoming more and more important. The first goal of this project is to develop a compact and easy to use device for the diagnosis of electric connection failures in garage or at the end of the production chain. It should be capable of detecting and locating failures in cables and in connectors. The second goal is on-board diagnosis: the diagnosis device will be integrated to the vehicle, and failure then should be detected under normal working conditions of the vehicle. The work of the SOSSO2 team during this year has been concentrated to the modeling of electric transmission in cables.

5.4. Nonlinear system identification (The Mathworks contract)

Participant: Qinghua Zhang.

Contract with The Mathworks, from July 2005 to July 2010. See also the software section 3.2. The System Identification ToolBox (SITB) is one of the main Matlab toolboxes commercialized by The Mathworks. The current version of the toolbox is limited to the identification of linear systems. In collaboration with Lennart Ljung (Sweden), the author of the current version of the SITB, and also with Anatoli Juditsky (Université de Grenoble) and Peter Lindskog (Sweden), an extension of the SITB for nonlinear system identification is under development. Future versions of the toolbox will include algorithms for black box and grey box identification of nonlinear dynamic systems. INRIA is mainly responsible for the development of black box identification.

6. Other Grants and Activities

6.1. National grants

6.1.1. CardioSense3D (Inria Large Initiative Action)

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

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

6.1.2. AgroBI (Inra federative program)

Participant: Frédérique Clément.

This new project on the Biology of the signaling system induced by FSH (Follicle-Stimulating Hormone) has been accepted for funding by INRA. It is coordinated by Eric Reiter (INRA) and the research will be done in cooperation with the INRIA team Contraintes.
http://www.inra.fr/internet/Projets/agroBI/pageagroBI.html

6.2. European grants

6.2.1. NoE HYCON

Participant: Michel Sorine.

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

7. Dissemination

7.1. Scientific activity and coordination

7.1.1. Coordination activity

J. Barral:

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

P.A. Bliman:
- Member of International Program Committee of *6th IFAC workshop on Time-Delay Systems TDS06*, L'Aquila (Italie), 2006, and of *5th IFAC Symposium on Robust Control Design* (Rocond 2006), Toulouse, 2006.
- Responsible for INRIA, Rocquencourt Research center, of the activities of the Multi-partner Marie Curie Training Site entitled Control Training Site (beginning in 2002).
- Officially charged by the board of INRIA of the relations with Agence nationale pour la Recherche ("chargé de mission pour l'ANR").
- Member of the "Commission de spécialistes" (61st Section) in Université Paris Sud-Orsay and Université Henri Poincaré (Nancy).

C. Bonnet:
- Member of the IFAC technical committee on Robust Control (2005-2008).
- Member of the board of directors of the GDR MACS (Research group on modelisation analysis and tracking of systems of the CNRS).
- Member of CCRRESTI (Conseil Consultatif Regional de la Recherche, de l'Enseignement Superieur, de la Technologie et de l'Innovation).
- Member of the board of the association *Femmes et mathématiques* (Women and Mathematics).
- Member of the french piloting committee of the Helsinki group on Women and Science of the European Commission.
- Member of the piloting committee of the convention "INRIA-Académie de Versailles".
- Member of the International Program Committee of JDMACS 2007.
- Member of the PhD committe of Michaël Di Loreto, Nov 17th 2006 at Ecole Centrale de Nantes.
- Co-organizer of the 8ème Forum des jeunes mathématiciennes, Oct 6-7 2006, IHP, Paris. - Member of a Research Engineer recruiting committee at INRIA.

F. Clément:
- Member of several evaluation boards and recruiting committees.

M. Sorine:
- Member of the International Program Committees for the JDMACS 2007, CIFA 2006 and IFAC MCBMS'06 conferences.
- Member of the program committee of the Cnrs-Inria-Inserm program "Health: information and technology".
- Member of the program committe of the 13th INRIA-Industry Meeting on Information and Communication Science and Technology for Medicine.
- Member of the evaluation committees of the LAAS-CNRS and of the Applied Math division of IFP. - Member of five PhD committees.

Q. Zhang:
- Member of IFAC Technical Committee on Fault Detection, Supervision and Safety of Technical Processes (SAFEPROCESS).
- Co-chair of the Workshop of the European Research Network on System Identification (ERNSI 2006).

7.2. Teaching activity

- F. Clément: "Modelling and control of biological systems" course, part of the "Master's Degree in BioInformatics and BioStatistics" (Paris 11 University).
- E. Crépeau and F. Maroteaux: associate professors (full time service) at Paris 6 and UVSQ respectively.

7.3. Seminars

- J. Barral: “Une classe de processus multifractals incluant naturellement processus de Lévy et cascades de Mandelbrot”, séminaire de Probabilités de l’Université Paris 6, January 2006. "Eléments d’analyse multifractale", Rencontres ALEA, CIRM, March 2006. "Lévy processes in multifractal time", in Stochastic processes and random fractals, University of Lille1, March 2006. "Théorèmes d’ubiquité", séminaire de l’équipe du professeur Ben Nasr, Faculté des Sciences de Monastir, November 2006.

- P.A. Bliman: 1 lecture at Università degli Studi di Firenze (Italy), April 2006 ;
1 lecture at Congress of Mathematics and its Applications, Foz do Iguaçu (Brazil), August 2006 ; 3 lectures at Universidade Federal de Santa Catarina (UFSC, Florianópolis, Brazil), August 2006 ; 2 lectures at Unicamp (Campinas, Brazil), August 2006 ; 1 lecture at Instituto Militar de Engenharia (IME, Rio de Janeiro, Brazil), August 2006

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