



Activity Report 2014

## **Project-Team SISYPHE**

Signals and SYstems in PHysiology &  
Engineering

RESEARCH CENTER  
**Paris - Rocquencourt**

THEME  
**Modeling and Control for Life Sci-  
ences**



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## Project-Team SISYPHE

**Keywords:** Models, Control Theory, Multiscale Models, Physiology, System Analysis And Control

*Creation of the Project-Team:* 2007 July 01, end of the Project-Team: 2014 December 31.

### 1. Members

#### Research Scientists

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Pierre-Alexandre Bliman [Inria, Senior Researcher, on sabbatical leave since May 2014, HdR]  
James Leifer [Inria, Researcher]  
Claire Médigue [Inria, until Aug 2014]  
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#### Post-Doctoral Fellows

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#### Others

Leïla Djaziri [Univ. Paris-Sud, until July 2014]  
Habib Jreige [SciWorks Technologies]  
Mohamed Oumri [Univ. Picardie, until May 2014]

### 2. Overall Objectives

#### 2.1. Introduction

The project-team SISYPHE (SIGNALS and SYSTEMS in PHYSIOLOGY and ENGINEERING) has stopped its activity at the end of the year. Since 2007, it has studied questions about 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”. The great potential of two topics and the results obtained have led to the follow-up project-teams, **MYCENAE** and **QUANTIC**.

*Neuroscience & Neuroendocrinology: Regulation of the Gonadotrope axis.* Controlled conservation laws for structured cell populations; Dynamical systems and neuroendocrinology; Innovative computational and theoretical tools for slow-fast dynamics.

*This part of the research program has led to launch **MYCENAE** (Multiscale dYnamiCs in neuroENdocrine AxEs), a project-team led by Frédérique Clément, created in Jan. 2014.*

*Quantum engineering: controlled quantum systems.* Measurement based feedback; Dissipation engineering. *This part of the research program has led to launch the team **QUANTIC** (QUANTum Information Circuits), led by Mazyar Mirrahimi.*

## 2.2. Sisyphé research program in 2014

In 2014, we continued working on the third topic: *Monitoring and control of complex systems*. We have studied questions of modeling, identification, signal analysis and control with medical or engineering applications in the continuation of some of the themes presented in Sections 3.1, 3.2. Four issues were considered:

- *Identification of transmission line characteristics*. Our method based on inverse scattering techniques for fault detection and localization in networks of transmission lines has been tested and improved with Qinghua Zhang, Sisyphé member until end 2013, now working with the project-team I4S. See Section 5.1.

- *Cardiovascular signal processing and applications*. The numerical tools developed during a study of HFpEF (Heart Failure with preserved Ejection Fraction) have been gathered into a Scilab toolbox. See Section 4.1.

- *Glycemic control in ICUs*. This was the last step on this topic with the statistical analysis of the results of the large clinical trial CGAO-REA. See Section 5.3.

- *Modeling and optimizing patient pathways in hospital*. In this work, we consider the complex flows of patients along treatment pathways in hospital in order to understand the steps of medical care provided by man and machine, as well as the passage of information that governs these steps. Our goal is to *model* the qualitative and quantitative aspects of these pathways, *simulate* their flow, *identify* problematic areas, and collaborate with medical staff to *optimize* the pathways in order to reduce medical errors (and near misses), waiting times, and cost.

## 3. Application Domains

### 3.1. Medical applications of modeling, signal analysis and control

- *3D cardiac modeling for personalized medicine*. Our main contribution to Inria's collective efforts in this field (project-teams Asclepios, MACS, REO, Sisyphé) is the so-called "Bestel-Clément-Sorine" model of contraction of cardiac muscle [39], at the origin of the 3D electromechanical direct and inverse modeling of the heart at Inria. This model is based on ideas originating from the kinetic equation theory, used to model, on the molecular scale, the controlled collective behavior of actin-myosin nanomotors at the root of muscle contraction. The classical Huxley model was recovered on the sarcomere scale by using moment equations and a controlled constitutive law on the tissue scale was obtained using the same type of scaling techniques. The model, now embedded in heart simulators, is used in various studies [51], [3], [54], [53].

- *Semiclassical analysis of cardiovascular signals*. This work began with the article [41] and the PhD of M. Laleg-Kirati [47], [46], [49]. The theory and a validation of a new method of blood pressure analysis are now published [17], [48].

The main idea is to consider a signal  $x \rightarrow y(x)$  to analyze as the multiplication operator  $\phi \rightarrow y\phi$  on some function space, and to analyze it as a potential. The signal is represented by the spectrum of an associated Schrödinger operator, combined with a semi-classical quantification:  $-h^2 \frac{d^2}{dx^2} - y(x)$  with  $h > 0$  small. For signals looking as "superpositions of bumps" (e.g. the systolic pulse, the dichrotic notch for the arterial pulse pressure), this leads to some kind of nonlinear Fourier analysis [17]. The spectral parameters associated with the arterial pressure can be useful cardiovascular indices, e.g. for noninvasive blood flow estimation [48]. In the arterial pressure case, this is equivalent to approximate the traveling pressure pulse by a  $N$ -soliton solution of a Korteweg-de Vries (KdV) equation [41] and using ideas similar to the Lax pair representation of  $N$ -solitons and proof technique for the weak dispersion limit of KdV. A striking result is that an  $N$ -soliton is a very good representation of the arterial pressure waveform for values of  $N$  as small as  $N = 3$ . The representation of pulse-shaped signals is parsimonious, having only  $2N$  parameters [55].

- *Multiscale signal analysis of cardiovascular signals*: collaboration with Julien Barral (former member of Sisyphé) and partners of the ANR project DMASC. The starting point was the common idea that "A Healthy Heart Is a Fractal Heart". We have developed a method to test the existence of scale laws in signals and applied it to RR signals: the heart rate is not always fractal or even multifractal in an Healthy Heart [19].

- *Modeling and control of CARMAT Total Artificial Heart.* This TAH has been implanted for the first time in a patient in Dec 2013. We have contributed to this industrial project since 2008 on modeling and control questions during the post-doc of Karima Djabella (now engineer at CARMAT), Frédéric Vallais and the two-year contract for supervising Julien Bernard (CARMAT control engineer). It was an opportunity to exploit some results on the baroreflex control [42] or heart rate variability during exercise [40].

- *Glycemic control in Intensive Care Units (ICUs):* Blood glucose is a key biological parameter in ICU since the study of van den Berghe et al [60] who demonstrated decreased mortality in surgical intensive care patients in association with tight glyceic control (TGC), based on intensive insulin therapy. In their work, however, there was only one ICU and the protocol was not formalized. Trying to decrease mortality in standard ICUs by using computer aided glyceic control is still a challenge. Previous studies have failed because of high rates of severe hypoglycemia. The last one was NICE-SUGAR [57] with a 2% increase in mortality (death ratio from any cause within 90 days after randomization compared between control and TGC patients). In cooperation with Pierre Kalfon (Intensive Care, Hospital of Chartres) and in the framework of a CIFRE contract with a small medtech company LK2 (Tours, France), we have studied the origins of these failures and proposed more robust control algorithms tuned using a database of representative “virtual patients”. See [44] and the PhD of A. Guerrini, [43]. A first version of the controller has been tested in a large clinical study CGAO-REA [14].

### 3.2. Engineering applications of modeling, signal analysis and control

*Identification of nonlinear systems: from algorithms to a popular matlab toolbox:*

Block-oriented nonlinear system identification with Jiandong Wang (Associate Professor, Beijing University, China) [58]; Development of the Matlab System Identification ToolBox (SITB).

*Identification of transmission line characteristics: from algorithms to electronic experiments.* Collaboration with CEA LIST (Lab of applied research on software-intensive technologies) and LGEP (Laboratoire de génie électrique de Paris) with Florent Loete [50] (ANR projects SEEDS, 0-DEFECT, INSCAN, SODDA).

We have extended to some networks the seminal work of Jaulent [45] for the real line: all the information contained in a measured reflection coefficient can be obtained by solving an inverse scattering problem for a system of Schrödinger or Zakharov-Shabat equations on the graph of the network, which allows one to recover the geometry of the network and some electrical characteristics for nonuniform lossless electrical star-shaped networks [26]. An efficient method to solve the associated Guelfand-Levitan-Marchenko equations has been studied and is used in the software ISTL that has been developed in Sisyphé [59], [56]. This development will continue in the project-team I4S. An engineering methodology based on this approach has been described [29] and some first experimental results obtained [36], [50].

*Monitoring and control of automotive depollution systems:* with RENAULT (Karim Bencherif, Damiano Di Penta and PhD students): [52], [20], [38].

### 3.3. Modeling and optimizing patient pathways in hospital

This research theme was inspired by the observation that the practice of modern industrialized medical care proceeds by queueing and forwarding patients from one step of care to the next, with each step involving specialized personnel and machinery. Whereas the human competence and machine performance available in hospital are both highly evolved, the deployment of these resources for the patient’s benefit is problematic.

If we change our point of view and, rather than look in the traditional way at the hospital as a collection of “vertical” silos (emergency room, cardiac ward, respiratory ward, operating rooms, imagery services, blood services, logistics, etc.), we instead consider the patient’s “horizontal” trajectory crossing through many different silos, we can see significant problems. In between each step, whose value added part typically lasts at most a few minutes, there are long stretches of time (on the order of hours) during which the patient simply waits for the hospital to arrange the next step of care — with serious consequences:

- delayed treatment is directly correlated with increased rates of hospital acquired nosocomial infection for the immuno-compromised and to loss of autonomy for the elderly;

- the cost in terms of scarce resources (for example, bed-hours in hospital) is significant, but the root causes of these costs due to problems at the interfaces between silos are hard to observe since they do not fit neatly into the hospital's traditional hierarchy;
- the slow and error prone hand-offs of information between silos are dangerous for the patient who is vulnerable to medical errors. In the US, for example, it is estimated that there are 100,000 deaths per year attributable to hospital error (triple the number due to road traffic accidents by way of comparison).

## 4. New Software and Platforms

### 4.1. The Cardiovascular Waves Analysis toolbox for Scilab

**Participants:** Lisa Guigue, Claire Médigue, Michel Sorine, Serge Steer.

The work about Heart Failure with preserved Ejection Fraction required the development of a set of tools for ECG signal manipulation and analysis. These tools, developed by Serge Steer, have been included in a Scilab toolbox named Cardiovascular Waves Analysis toolbox that will be available soon as a Scilab module.

It extends the former Cardiovascular Toolbox and provides functions for:

- ECG reading multi channel ECG files in various formats (ISHNE, MIT, TMS32),
- Handling huge ECG files obtained through Holter devices,
- ECG pretreatment (filtering, subsampling, power line interference and base line wander removal),
- ECG events detection (P, Q, R, S, T) peaks, onset and end, based on former tools developed by Qinghua Zhang,
- Cardiovascular signals analysis using various approaches like frequency or time-frequency analysis, complex demodulation, non parametric, multilevel and multifractal methods,
- Specialized plotting facilities.

## 5. New Results

### 5.1. Fault detection and localization in networks of transmission lines

**Participants:** Mohamed Oumri, Michel Sorine.

Some results have been obtained in collaboration with Florent Loete (LGEP) and Qinghua Zhang (Inria, I4S):

- *Experimental validation of the inverse scattering method for distributed characteristic impedance estimation.* Our theoretic results and numerical simulations have shown the ability of inverse scattering-based methods to diagnose soft faults in electric cables, in particular, faults implying smooth spatial variations of cable characteristic parameters. We have obtained laboratory experiments confirming the ability of the inverse scattering method for retrieving spatially distributed characteristic impedance from reflectometry measurements. Various smooth or stepped spatial variations of characteristic impedance profiles have been tested. The tested electric cables are CAN unshielded twisted pairs used in trucks and coaxial cables [37].

- *Diagnosis of networks using tagged electric lines.* A new electromagnetic marking method of transmission lines has been proposed for diagnosis of electric networks when conditions of uniqueness of the solution are not fulfilled (e.g. in case of symmetries): small non-interfering characteristic defaults are added to the lines and used as tags. A patent application has been submitted [36].

A new application of our monitoring technique has been explored in collaboration with EDF and a first result has been obtained:



- *Monitoring of post-tensioned ducts or water content in concrete walls with embedded transmission lines.* We have presented an electromagnetic method of diagnosis based on frequency domain reflectometry (FDR) associated with our inversion algorithm, ISTL (Inverse Scattering for Transmission Lines). ISTL allows one to estimate the spatial profile of the electrical impedance of the line from the FDR measurements. Experimental results on two mockups of external post-tensioned ducts with filling defects show the feasibility of the method. We will try to show the similarities between auscultation external post-tensioned ducts and measurement of water content by TDR probes (Time Domain Reflectometry) [34].

- *Fault diagnosis of wired electric networks by reflectometry.* A first extension to Baum-Liu-Tesche equations has been proposed in [31].

## 5.2. Cardiovascular signal processing and applications

**Participants:** Lisa Guigue, Claire Médigue, Michel Sorine, Serge Steer.

See the Software section 4.1 for a description of tools developed for *Cardiovascular Waves Analysis*.

## 5.3. Glycemic control in ICUs

**Participant:** Michel Sorine.

The results of statistical analysis of the data gathered during the large clinical trial **CGAO-REA** have been published in [14]: “Tight computerized versus conventional glucose control in the ICU: a randomized controlled trial”. Despite the increase in the incidence of severe hypoglycemia in our experimental group, based on the absence of difference in mortality between patients on tight computerized glucose control and those on less stringent glucose control without computerized decision support systems (CDSS), this study could pave the way for future randomized controlled trials assessing new generation CDSSs allowing the safe implementation of blood glucose control in the ICU that take into account the complexity of glucose control throughout the ICU stay and the variability of individualized insulin needs. Some new objectives for computer aided glycemic control in ICUs have been proposed in [32]. An article proposing a more detailed statistical analysis of the severe hypoglycemic events has been submitted.

## 5.4. Modeling and optimizing patient pathways in hospital

**Participants:** James Leifer, Michel Sorine.

External scientific collaboration with:

- Niccolo Curatolo, Directeur des opérations, Hôpitaux universitaires Paris-Sud, Assistance publique-Hôpitaux de Paris (AP-HP);
- Dr Maurice Raphaël, Chef de service, Urgences adultes, Hôpital Bicêtre, AP-HP;
- Dr Christophe Vincent-Cassy, Responsable des systèmes informatiques des urgences, AP-HP;
- Lucie Gaillardot-Roussel, Ingénieur en organisation, AP-HP;
- Dr Paul Jarvis, Senior consultant doctor in emergency medicine, Calderdale and Huddersfield National Health Service Foundation Trust, UK.

In 2014, we began a case study of the emergency department (ED) at Bicêtre Hospital, a large ED handling 50,000 patient visits per year, which is amongst the top 10 by volume and by annual volume growth for EDs in the Paris region.

Rather than presume the appropriateness of a predetermined scientific formalism, our strategy was to allow the application to frame a series of questions in order to lead us to experiment with several potential scientific tools at the present “low risk, high uncertainty” phase of investigation:

- *Top-down modeling:* Can we capture the expert knowledge of doctors and nurses as to the pathways followed by their patients by transforming this knowledge into a series of “use case” rules borrowed from the techniques of software specification? Can these rules be transformed into an executable model using business process modeling languages and tools (Orc, YAWL, ...) for simulating the complex parallel composition of man-machine processes in a hospital setting?

- *Bottom-up modeling*: How can the hospital be instrumented for cheaply and accurately capturing its real activity (movement of people and machines, delays, errors, ...) and tuning the parameters of the model? Can we intercept HL7 messages (a standardized electronic message format for medical data) and/or access raw time-stamped database entries to use machine learning techniques (particularly process mining) to extract from the running hospital the graphs representing the actual sequence of care events in order to get rapid feedback about the most heavily used and most often delayed path segments?
- *Underlying cost semantics*: Can we formalize in process calculi (for example, a variation of pi calculus) the “micro internal economy” of costs exchanged inside the hospital to quantify the economic performance of each patient pathway?
- *Offline experimentation and optimization*: Can potential optimization to the model be explored offline in a sort of “serious game” to allow non-intrusive experimentation with different strategies for eliminating bottlenecks, increasing flow rates, decreasing costs, etc.?
- *Data visualization for medical personnel*: Given that the medical personnel themselves are best suited to fixing the daily frictional time losses that most are resigned to accept as “part of the job”, how can the model be presented in a visually lucid manner to render the previously “invisible” aspects of the hospital’s organization visible?
- *Online real-time control*: Can the feedback loop be completed and the model be used to directly provide real-time visual feedback to the hospital personnel to enable them to measure their systemic progress (or systemic unintended consequences) of their localized optimizations?

## 6. Bilateral Contracts and Grants with Industry

### 6.1. SciWorks Technologies contract: development of K-Assessor

**Participants:** Habib Jreige, Michel Sorine.

*Development of K-Assessor.* This contract ended in November 2014. The software K-Assessor has been developed with SciWorks Technologies for the monitoring and supervision of *master GC*, a prototype system of Fresenius-Kabi dedicated to glycemic control assistance based on the control algorithm CGAO\_v2, we have previously developed [43].

*Distribution of ISTL.* ISTL is a software that we developed for numerical computation of the inverse scattering transform for electrical transmission lines. In addition to the inverse scattering transform, it includes a numerical simulator 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. ISTL is now distributed by [SciWorks Technologies](#).

## 7. Partnerships and Cooperations

### 7.1. National Initiatives

#### 7.1.1. ANR project SODDA: *Soft Defects Diagnosis in wired networks*

**Participants:** Thomas Lepetit, Mohamed Oumri, Michel Sorine.

The need for detection, localization and characterization of defects in a cable network has led to the ANR projects SEEDS followed by 0-DEFECT in the automotive domain and INSCAN for cables along railways. These projects provide the foundations of diagnosis methods for cables – with a proof of feasibility in the case of hard defects (short-circuit, open circuit) – and some theoretical results on the associated inverse problems in the case of soft faults. They also made it possible to identify their limits. One of the principal limits of these methods, based on the principles of reflectometry, is the difficulty of detecting soft defects. If it was possible to detect and locate precisely these defects, that would help for preventive maintenance or prognosis. The objective of SODDA is to study the signatures of the soft defects, by combining theory and experiment, and to design and test innovative methods adapted to these signatures which are very difficult to detect. The project is run by an academic consortium, in close connection with an industrial board, responsible for keeping the work in realistic and relevant use cases. The Inria teams involved are I4S (Qinghua Zhang), POEMS and Sisyphe.

## 7.2. International Research Visitors

### 7.2.1. Visits to International Teams

#### 7.2.1.1. Sabbatical programme

Bliman Pierre-Alexandre

Date: May 2014 - Apr 2015

Institution: Fundação Getulio Vargas, Brazil [EMAp](#) (Brazil)

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