Activity Report 2013

Team Popix

Modélisation en pharmacologie de population

RESEARCH CENTER
Saclay - Île-de-France

THEME
Computational Neuroscience and Medecine

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Team Popix

Keywords: Population Modeling, Statistical Methods, Model-checking, Computational Biology

POPIX *is located at Paris-Sud University (Mathematics, Building 440). All the researchers of* POPIX *are also members of the Laboratory of Mathematics at Paris-Sud University ("Probability and Statistics" and "Numerical Analysis and Partial Differential Equations" teams).*

Creation of the Action exploratoire: 2011 January 01*, updated into Team:* 2013 January 01.

1. Members

Research Scientists

Marc Lavielle [Team leader, Inria, Senior Researcher]
Kevin Bleakley [Inria, Researcher]

Faculty Members

Astrid Decoene [Univ. Paris XI, Researcher]
Sébastien Martin [Univ. Paris XI, Associate Professor until Sept. 2013]
Marie-Anne Poursat [Univ. Paris XI, Researcher]
Bertrand Maury [Univ. Paris XI, Professor]

Engineers

Fazia Bellal [Inria, granted by FP7 DDMoRE project, from Sep 2013]
Laura Brocco [Inria, granted by Astrazeneca, until Sep 2013]
Raphael Kuate [Inria, granted by FP7 DDMoRE project, from Sep 2013]
Elodie Maillot [Inria, granted by FP7 DDMoRE project, until Aug 2013]
Hector Mesa [Inria, granted by Lixoft, until Jun 2013]

PhD Student

Célia Barthélémy [Inria, granted by Astrazeneca]

2. Overall Objectives

2.1. Introduction

POPIX is focused on models for explaining complex biological phenomena (pharmacokinetics, viral dynamics, glucose-insulin, tumor growth, human respiration). In the population approach, these models have to be capable of characterizing the biological phenomenon under consideration, but also variability that exists between individuals from the same population.

The main objective of POPIX is thus to develop new methods for population modeling. These tools for modeling include statistical methods of estimation, model diagnostics and model selection.

Confronted with complex modeling problems, one of the goals of POPIX is to show the importance of combining numerical, statistical and stochastic approaches. To emphasize this push, POPIX enlarged to include new researchers in 2013 at the interface of these domains. Bertrand Maury, Astrid Decoene and Jean-Baptiste Lagaert, researchers at Paris 11 University in the LMO (into which POPIX is also integrated) joined POPIX in 2013. Bertrand Maury is the leader of the Numerical Analysis and PDE team, and Astrid Decoene and Jean-Baptiste Lagaert are researchers in the same team. Their knowledge will extend the capabilities of POPIX into the domain of mathematical analysis of complex biological phenomena which include both time and spatial components, and which are described by systems of partial differential equations.

Lastly, an important aim of POPIX is to transfer developed methods into software packages so that these methods can be used in practice. It is this exact approach that has ensured the success of MONOLIX, a software package now widely used in population pharmacology. Indeed, pharmacometricians are satisfied with the tools provided and mathematicians by the methods used.

2.2. Highlights of the Year

The Inria Innovation Lab *Lollipox* was created. This i-Lab brings together POPIX and the start-up Lixoft. It aims to boost the transfer of new statistical methods developed by POPIX to new tools developed by Lixoft.

We have built a comprehensive online wiki (WikiPopix, https://wiki.inria.fr/popix) for the population approach with mixed-effects models. This wiki aims to be an invaluable resource for all pharmacometricians, statisticians, teachers, graduate and undergraduate students in academia, industry and regulatory agencies. It is freely available online for all these communities.

Bertrand Maury published the book, *The Respiratory System in Equations* (Springer), which gives an introduction to the mathematical modeling of the respiratory system. The book starts with detailed introduction to physiological aspects, and then different levels of description are proposed, from lumped models with a small number of parameters (ordinary differential equations), up to infinite dimensional models based on partial differential equations.

3. Research Program

3.1. Research Program

Mathematical models that characterize complex biological phenomena are complex numerical models which are defined by systems of ordinary differential equations when dealing with dynamical systems that evolve with respect to time, or by partial differential equations when there is a spatial component to the model. Also, it is sometimes useful to integrate a stochastic aspect into the dynamical systems in order to model stochastic intra-individual variability.

In order to use such methods, we are rapidly confronted with complex numerical difficulties, generally related to resolving the systems of differential equations. Furthermore, to be able to check the quality of a model, we require data. The statistical aspect of the model is thus critical in its way of taking into account different sources of variability and uncertainty, especially when data comes from several individuals and we are interested in characterizing the inter-subject variability. Here, the tool of reference is mixed-effects models.

Mixed-effects models are statistical models with both fixed effects and random effects, i.e., mixed effects. They are useful in many real-world situations, especially in the physical, biological and social sciences. In particular, they are well-adapted to situations where repeated measurements are made on the same individual/statistical unit.

POPIX develops new methods for estimation of complex mixed-effects models. Some of the extensions to these models that POPIX is actively researching include:

- models defined by a large system of differential equations
- models defined by a system of stochastic differential equations
- mixed hidden Markov models
- mixture models and model mixtures
- time-to-event models
- models including a large number of covariates

It is also important to clarify that POPIX is not meant to be a team of modelers; our main activity is not to develop models, but to develop tools for modelers. Indeed, we are of course led via our various collaborations to interact closely with modelers involved in model development, in particular in the case of our collaborations with modeling and simulation teams in the pharmaceutical industry. But POPIX is not in the business of building PKPD models per se.

Lastly, though pharmacometrics remains the main field of interest for the population approach, this approach is also appropriate to address other types of complex biological phenomena exhibiting inter-individual variability and necessitating therefore to be described by numerical and statistical models. We have already demonstrated the relevance of the developed approaches and tools in diverse other domains such as agronomy for characterizing corn production, and cellular biology for characterizing the cell cycle and the creation of free radicals in cells. Now we wish to push on to explore new areas of modeling such as for the respiratory system and blood flow. But again, it is not within the scope of the activities of POPIX to develop new models; instead, the goal is to demonstrate the relevance of the population approach in these areas.

4. Application Domains

4.1. Pharmacometrics

Participants: Marc Lavielle, Kevin Bleakley, Célia Barthélémy, Hector Mesa, Elodie Maillot, Laura Brocco.

POPIX is directly implicated in the domain of pharmacology. Historically, Marc Lavielle was the driving force behind the pharmacological modeling software MONOLIX, now an industry standard. Lixoft, an Inria start-up, now develops and supports MONOLIX and the commercial side of things. POPIX collaborates closely with Lixoft to transfer research results into software improvements and the development of new user tools in MONOLIX.

POPIX is also majorly implicated in the 5-year DDMoRe (Drug and Disease Model Resources) European project financed by the IMI (Innovative Medicines Initiative), a public-private partnership. In particular, POPIX has the task of developing new tools and methods for this project regrouping researchers in pharmacometrics, biostatistics and biology from both the public and private sectors. Specific tools and methods being developed by POPIX include:

- a clinical trial simulator
- protocol optimization tools
- diagnostic tools
- model selection tools
- data exploration tools
- estimation techniques for complex models (eg, stochastic differential equations, partial differential equations)

4.2. Pharmacogenetics

Participants: Marc Lavielle, Kevin Bleakley, Célia Barthélémy.

Medicine, even when prescribed following dosage rules, is an important cause of illness and death. In essence, people's reaction to a given drug depends on their physiological state and environmental factors, but also to their individual genetic make-up.

Pharmacogenetics, a subdomain of pharmacology, is the study of the the relationship between genetic variability and the therapeutic outcome. The future goal is "personal medicine" whereby the drug and dose are chosen with respect to the individual's genetic make-up.

Currently, in the population approach followed by POPIX, inter-individual variability in the reaction to drugs is modeled using covariates such as weight, age, sex, ethnic origin, etc. Genetic polymorphisms susceptible to modify pharmacokinetic or pharmacodynamic parameters are much more harder to include, especially as there are millions of possible polymorphisms (and thus covariates) per patient. The subsequent model selection problem is thus very complicated. POPIX is working to develop methods for simultaneous model selection and parameter estimation in the SAEM framework in such cases.

4.3. Oncology

Participants: Marc Lavielle, Célia Barthélémy.

Despite great advances in the treatment and diagnosis of cancer, many steps remain to further improve prognoses and quality of life of cancer patients. Numerical models can be used to help adapt treatment protocol to the characteristics of each patient, ie, improve treatment efficacy by:

- choosing the best treatment
- choosing the best dose
- choosing the best drug-delivery protocol
- optimizing the above parameters to minimize toxicity

POPIX is part of the Inria project Lab MoNICa (MOdèles Numériques et Imagerie pour le CAncer), including the NUMED, MC2 and ASCLEPIOS Inria teams, that aims to optimize the parameters listed above using numerical modeling.

Collaborations with NUMED and MC2 are ongoing, with the aim of extending the statistical methods developed by POPIX to partial differential equation-based models. NUMED works on models of tumor growth and has previously implemented an extension of MONOLIX to KPP-type reaction-diffusion models.

4.4. Respiratory system

Participants: Bertrand Maury, Astrid Decoene.

Comprehensive models to simulate the whole pulmonary system, i.e., the mechanical behavior of the lung and gas exchanges within the pulmonary system, are built upon ODE and PDE approaches. For instance, the mechanical behavior of a lung is often described by single or multi-compartment ODE models, whereas air flow may be determined by the coupling of a 3D PDE system in the proximal part of the bronchial tree with a 0D ODE system in the distal part of the bronchial tree. Gas exchange has so far been investigated using 0D or 1D models in which heterogeneity of gas exchange along the path length may be investigated.

In a mathematical representation of such physiological systems, model parameters can be associated with specific quantities in the real system, such as the resistance and compliance of the pulmonary system. These quantities are time-dependent and nonlinear and are measured by pneumologists in order to characterize chronic obstructive pulmonary diseases (COPD) such as asthma and emphysema. These parameters may be useful in assessing lung conditions.

Although most physiological studies have used averaged deterministic models of the tracheobronchial tree geometry, morphometric studies show that inter-subject and intra-subject variability in the structural components of the human lung is significant. In particular, the resistance of the respiratory tract may be significantly affected as it is directly related to the inner diameter of the bronchi. Feedback from such variability to resistance and, as a consequence efficiency of the gas exchange process, within the framework of a fully coupled model, is unclear. In this situation, the statistical and numerical approaches being developed by POPIX are clearly promising estimation methods for respiratory system analysis.

4.5. Blood flow modeling

Participants: Bertrand Maury, Astrid Decoene.

Modeling and numerical simulation of blood flow in arteries and veins may become an important tool for medical applications, as for instance in the prediction of cardiovascular disease. Analyzing the pressure waves and estimating the wall compliance of arteries is fundamental, as these exhibit strong inter- and intra-subject variability. Currently, non-invasive pressure measurements involve excessive errors; intensive direct estimation is thus not applicable in practice. Physiologists therefore hope to be able to predict the time and space evolution of the pressure in the arterial network from a small amount of flow data measured at a few points.

Several numerical models have been developed in order to simulate blood flow in arteries and veins. They mainly consist of one to three-dimensional systems of partial differential equations, depending on the level of complexity one desires to achieve. Coupling the various models is also an issue. These numerical models allow us to compute the transversal section area, as well as the velocity or flow at different points in space, leading to a rather complete description of the arterial flow (velocity, pressure, section). But for these models to be adapted to each patient, certain numerical and physical parameters must be fitted, such as the compliance of walls and the viscosity of the blood. These parameters are difficult to estimate experimentally and may be related to measurements which involve a non-negligible error. Furthermore, their optimal value is linked to the particular modeling framework and therefore can differ from the value given by their physical definition.

Mixed models appear to be an appropriate framework for taking into account the specific nature of each patient and quantifying uncertainty in the numerical model. Flow data are available as it is possible to non-invasively measure the mean velocity in and diameter of an artery.

We aim to introduce statistical mixed models to the framework for the classical one-dimensional blood flow model.

5. Software and Platforms

5.1. Monolix

Participants: Marc Lavielle, Hector Mesa, Célia Barthélémy.

MONOLIX is an easy, fast and powerful tool for parameter estimation in nonlinear mixed-effect models, model diagnosis and assessment, and advanced graphical representation. It is a platform of reference for model-based drug development. Pharmacometricians and biostatisticians can rely on MONOLIX for population analysis and to model PK/PD and other complex biochemical and physiological processes.

MONOLIX was developed by Inria until June 2011. The start-up Lixoft now develops and supports MONOLIX. POPIX collaborates closely with Lixoft to convert research results into new user features available in MONOLIX.

5.2. MLXtran

Participant: Marc Lavielle.

MONOLIX is associated with MLXtran, a powerful and immediately readable declarative language for describing complex pharmacometric and statistical models. MLXtran can be used and interfaced with various environments, e.g., R, Matlab, etc.

POPIX collaborates closely with Lixoft on the definition of the specifications and the syntax of MLXtran. Implementation is then ensured by Lixoft.

5.3. Clinical trial simulator

Participants: Marc Lavielle, Elodie Maillot, Laura Brocco, Fazia Bellal, Célia Barthélémy.

A clinical trial simulator (CTS) enables effective implementation of the learn-and-confirm paradigm in drug development. Through simulations the anticipated success rate of a future trial can be estimated. For various reasons industry has not embraced currently available software for trial simulation. A new tool is essential for Model Based Drug Development (MBDD).

POPIX is responsible for developing a new CTS within the DDMoRe project (see below). Version 3 of the CTS is available since June 2013. The capabilities of this new version comprise:

- Flexible study designs used in Phase 2 of clinical drug development: parallel group studies, crossover studies, complex treatments defined as a combination of different treatments
- Simulation of patients sampled from a joint distribution or using an external data file
- Simulation of exposure to the investigated drug and several types of drug effects related to drug exposure (continuous, categorical, count, time-to-event)
- Graphics and statistical tests
- Automatic reporting

5.4. MLXplore

Participants: Marc Lavielle, Laura Brocco.

MLXplore is a graphical and interactive software for the exploration and visualization of complex pharmacometric models. MLXplore also includes the ability to study the statistical variability of the models, and to model and study complex administration designs.

MLXplore does not require MONOLIX, although they make for a powerful combination, enabling to use the same, human-readable model description, to finely explore the properties of the model on the one hand, and on the other hand use the same model for advanced parameter estimation in the context of population analysis and mixed effect statistics.

MLXplore is an ideal tool to learn about pharmacometric models and population analysis, and is used extensively in the online wiki WikiPopix created by POPIX, found at: https://wiki.inria.fr/popix.

MLXplore is developed by Lixoft. POPIX collaborates closely with Lixoft on on the definition of the specifications of MLXplore.

6. New Results

6.1. Estimation in mixed-effects diffusion models

Participant: Marc Lavielle.

We have coupled the SAEM algorithm and the extended Kalman filter for maximum likelihood estimation in mixed-effects diffusion models: we have considered some general mixed-effects diffusion models, in which observations are made at discrete time points and include measurement errors. In these models, the observed likelihood is generally not explicit, making maximum likelihood estimation of the parameters particularly complex. We have proposed a specific inference methodology for these models. In particular, it combines the SAEM algorithm with the extended Kalman filter to estimate the population parameters. We have also provided some tools for estimating the individual parameters, for recovering the individual underlying diffusion trajectories and for evaluating the model. We evaluated the methods on simulations and applied them to a pharmacokinetics example.

6.2. Estimation in mixtures of models

Participant: Marc Lavielle.

We have proposed an improved SAEM algorithm for maximum likelihood estimation in mixtures of non linear mixed effects models. This involves a new methodology for maximum likelihood estimation in mixtures of non linear mixed effects models (NLMEM). Such mixtures of models include mixtures of distributions, mixtures of structural models and mixtures of residual error models. Since the individual parameters inside the NLMEM are not observed, we have proposed to combine the EM algorithm usually used for mixtures models when the mixture structure concerns an observed variable, with the Stochastic Approximation EM (SAEM) algorithm, which is known to be suitable for maximum likelihood estimation in NLMEM and also has nice theoretical properties. The main advantage of this hybrid procedure is to avoid a simulation step of unknown group labels required by a "full" version of SAEM. The resulting MSAEM (Mixture SAEM) algorithm is now implemented in the MONOLIX software. We have also proposed several criteria for classification of subjects and estimation of individual parameters. Our numerical experiments on simulated data have shown that MSAEM performs well in a general framework of mixtures of NLMEM. Indeed, MSAEM provides an estimator close to the maximum likelihood estimator in very few iterations and is robust with regards to initialization. Our application of the method to pharmacokinetic (PK) data demonstrated the potential of the method for practical applications.

6.3. Moving meshes with freefem++

Participants: Astrid Decoene, Bertrand Maury.

The Arbitrary Lagrangian-Eulerian framework allows to compute free surface flows with the Finite Element functions defined on a fittedmesh which follows the globalmotion of the fluid domain. We have described how freefem++ can be used to implement this method, and we have provided two and three dimensional illustrations in the context of water waves.

6.4. Modeling of the oxygen transfer in the respiratory process

Participant: Bertrand Maury.

We have proposed an integrated model for oxygen transfer into the blood, coupled with a lumped mechanical model for the ventilation process. We aim at investigating oxygen transfer into the blood at rest or exercise. The first task consists in describing nonlinear effects of the oxygen transfer under normal conditions. We also include the possible diffusion limitation in oxygen transfer observed in extreme regimes involving parameters such as alveolar and venous blood oxygen partial pressures, capillary volume, diffusing capacity of the membrane, oxygen binding by hemoglobin and transit time of the red blood cells in the capillaries. The second task consists in discussing the oxygen concentration heterogeneity along the path length in the acinus

6.5. Congestion-driven dendritic growth

Participant: Bertrand Maury.

In order to observe growth phenomena in biology where dendritic shapes appear, we have proposed a simple model where a given population evolves feeded by a diffusing nutriment, but is subject to a density constraint. The particles (e.g., cells) of the population spontaneously stay passive at rest, and only move in order to satisfy some constraint, by choosing the minimal correction velocity so as to prevent overcongestion. We treat this constraint by means of projections in the space of densities endowed with the Wasserstein distance, defined through optimal transport. This allows to provide an existence result and suggests some numerical computations, in the same spirit of what the authors did for crowd motion (but with extra difficulties, essentially due to the fact that the total mass may increase). The numerical simulations show, according to the values of the parameter and in particular of the diffusion coefficient of the nutriment, the formation of dendritic patterns in the space occupied by cells.

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

POPIX has a contract with Astrazeneca (November 2011 - November 2013)

POPIX has a contract with Lixoft (June 2011 - June 2014)

8. Partnerships and Cooperations

8.1. European Initiatives

8.1.1. FP7 Projects

The Drug Disease Model Resources (DDMoRe) consortium will build and maintain a universally applicable, open source, model-based framework, intended as the gold standard for future collaborative drug and disease modeling and simulation.

The DDMoRe project is supported by the Innovative Medicines Initiative (IMI), a large-scale public-private partnership between the European Union and the pharmaceutical industry association EFPIA.

Marc Lavielle is leader of WP6: "New tools for Model Based Drug Development".

DDMoRe website: http://www.ddmore.eu

Duration: 2010 - 2015

Project members: Uppsala Universitet, Sweden; University of Navarra, Spain; Universiteit Leiden, Netherlands; Université Paris Diderot, France; Universita degli Studi di Pavia, Italy; UCB Pharma , Belgium; Simcyp, UK; Pfizer, UK; Optimata , Israel; Novo Nordisk , Denmark; Novartis, Switzerland; Merck Serono, Switzerland; Mango Business Solutions , UK; Lixoft, France; Interface Europe, Belgium; Institut de Recherches Internationales Servier, France; Inria, France; GlaxoSmithKline Research and Development, UK; Freie Universitat Berlin, Germany; F. Hoffmann - La Roche , Switzerland; EMBL - European Bioinformatics Institute, UK; Eli Lilly , UK; Cyprotex Discovery, UK; Consiglio Nazionale delle Ricerche, Italy; AstraZeneca, Sweden.

9. Dissemination

9.1. Scientific Animation

Editorial Activity.

POPIX members reviewed articles for *Bioinformatics*, *Journal of Statistical Software*, *Computational Biology and Chemistry*, *European Journal of Clinical Pharmacology*, *Ecological Modelling*, *Scientia Iranica*, *Computers in Biology and Medicine*, *Communications in Mathematical Sciences*, *SIAM journal of Scientific Computing*, *Computational Statistics and Data Analysis*, *Statistical Sciences*.

Bertrand Maury is Associate Editor of *M2AN*.

Conference Participation

Marc Lavielle:

- PAGE Meeting, Glasgow UK, June 2013
- ACOP Meeting, Fort-Lauderdale USA, May 2013
- Rencontres de statistiques, Avignon, June 2013
- Combine 2013, Paris, September 2013
- GDR Metice, Paris, June 2013
- SMB 2013, Paris , September 2013

Bertrand Maury:

- MMCS 2013 (Ecole Centrale de Paris),
- CPDE 2013 (IHP),
- French Chilian Polish Conference 2013 (Poland),
- Conference NUMACH 2013 (Sevilla)
- Bertrand Maury is the leader of the GDR (Groupement de Recherche) Maths-Entreprise, a group of more than 300 researchers, dedicated to tighten the links between academic research in mathematics and private companies (http://www.maths-entreprises.fr).

Astrid Decoene:

- MOTIMO colloquium, Nice, September 2013.

Célia Barthélémy:

- PAGE Meeting, Glasgow UK, June 2013
- Journées de la SFdS, Toulouse, June 2013

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Masters: Astrid Decoene, Elements finis et optimisation sous contraintes, Master EDPCS, Paris-Sud University.

Licence: Astrid Decoene, Licence Sciences Technologie Santé, mention mathématiques, Paris-Sud University.

Masters: Marie-Anne Poursat, Coordinator of the Mathematical Engineering course, Paris-Sud University

Masters: Marc Lavielle, Modèles Mixtes et Approche de Population, 24 hours, Paris-Sud University.

Masters: Bertrand Maury, Finite element method and optimization, modeling of the respiratory system, Paris-Sud University.

Masters: Bertrand Maury, Computational Fluid Dynamics, Numerical Analysis and Optimization, Ecole Polytechnique.

Miscellaneous: Marc Lavielle, Population approach and Mixed effects models: PAGE meeting 2013 (Glasgow); ACOP meeting 2013 (Fort-Lauderdale); University of Manchester (UK); University of Buffalo (USA).

9.2.2. Supervision

- PhD in progress: Célia Barthélémy, *Modèles à effets mixtes pour l'assimilation de données en oncologie*, debut: October 2012, Marc Lavielle.
- Bertrand Maury co-supervises several PhD students: J. Fouchet-Incaux, A. Preux, G. Le Poultier, L. Lacouture, C. Etchegarai.
- Astrid Decoene co-supervises the PhD thesis of L. Lacouture.
- Other: Kevin Bleakley supervised two student projects in statistical learning in the *Marketing et gestion de la relation client* year 3 class at ENSAI, Rennes.

9.2.3. Juries

- Kevin Bleakley was in selection committees for Maître de Conférence positions in biostatistics at Paris 6 and Paris 11 Universities. He also participated in the Thesis Committee of Eltaf Alamyar, Montpellier 2 University.
- Marc Lavielle was referee for the HDR of Stéphanie Allassonière.

- Bertrand Maury was member of the jury for CR2 Inria. He was also member of the selection committees of Nice (PR) and Orsay (MCF).
- Marie-Anne Poursat was member of the selection committee of Orsay (MCF).

9.3. Popularization

We have built a comprehensive online wiki (WikiPopix, https://wiki.inria.fr/popix) for the population approach with mixed-effects models. This wiki aims to be an invaluable resource for all pharmacometricians, statisticians, teachers, graduate and undergraduate students in academia, industry and regulatory agencies. It is freely available online for all these communities.

Furthermore, the team developed an online animated film called *Introduction to PK modeling* for interested members of the public and for teaching and training purposes. It can be seen at https://team.inria.fr/popix/files/2013/02/PKmodelling.swf, and joins two previous animated films already developed by the team (see http://team.inria.fr/popix/files/2011/11/PopulationApproach.swf.

10. Bibliography

Publications of the year

Articles in International Peer-Reviewed Journals

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[2] M.-C. FAURE, J.-C. SULPICE, M. DELATTRE, M. LAVIELLE, M. PRIGENT, M.-H. CUIF, C. MELCHIORT, E. TSCHIRHART, O. NUSSE, S. DUPRE-CROCHET. *The recruitment of p47phox and Rac2G12V at the phagosome is transient and phosphatidylserine-dependent*, in "Biology of the Cell", 2013, vol. 105, pp. 1–18, http://hal.inria.fr/hal-00916837

[3] M. LAVIELLE. *Rôle et limites de la statistique dans l'évaluation des risques sanitaires liés aux OGM*, in "Statistique et Société", mai 2013, vol. 1, n^{o} 1, http://hal.inria.fr/hal-00916844

[4] M. LAVIELLE, C. MBOGNING. *An improved SAEM algorithm for maximum likelihood estimation in mixtures of non linear mixed effects models*, in "Statistics and Computing", 2013 [*DOI :* 10.1007/s11222-013-9396-2], http://hal.inria.fr/hal-00916817

Scientific Books (or Scientific Book chapters)

[5] B. MAURY. , *The Respiratory System in Equations*, Springer, 2013, 300 p. , http://hal.inria.fr/hal-00929739