Activity Report 2014

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

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

1. Members

Research Scientists

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Kevin Bleakley [Inria, Researcher, until Sep 2014]

Faculty Members

Astrid Decoene [Univ. Paris XI, Researcher, until Sep 2014]
Bertrand Maury [Univ. Paris XI, Professor, until Sep 2014]
Marie-Anne Poursat [Univ. Paris XI, Associate Professor, until Sep 2014]

Engineers

Fazia Bellal [Inria, until Sep 2014, granted by FP7 DDMoRE project]
Benoît Casseau [Inria]
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Post-Doctoral Fellow

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Administrative Assistant

Katia Evrat [Inria]

Other

Célia Barthélémy [Inria, until Sep 2014]

2. Overall Objectives

2.1. Overall Objectives

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.

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.

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
- models defined by partial 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.

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. Gene expression

Participant: Marc Lavielle.

Mixed effects models can also be successfully used in quantitative biology for modeling the dynamics of biological networks in cell populations. Indeed, the population approach is relevant for building predictive computational models of intracellular processes. POPIX was interested with the experiments performed by the CONTRAINTES Inria team looking at the high-osmolarity glycerol (HOG) pathway in budding yeast. Yeast cells are exposed to osmotic shocks, i.e., sudden changes in the solute concentration of their surroundings. Signal transduction pathways, most notably the HOG pathway, provide information to the cell about the osmolarity of its environment and activate responses to deal with these stress conditions. In particular, a large set of genes is turned on and corresponding stress-responsive proteins are produced. This protein production process can be quantified by replacing one target protein, for example STL1, by a fluorescent protein such as yECitrine. This can be done by genetically modifying the yeast genome.

Thanks to time-lapse microscopy and cell tracking algorithms, single cell responses can be measured over time. Significant inter-cell variability is often observed.

The related Hog1-induced gene expression model is given by a parametric reaction network. MONOLIX can then be used to estimate the model parameters.

A collaboration with LIFEWARE (formerly CONTRAINTES) is starting on this subject.

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. New Software and Platforms

5.1. Monolix

Participants: Marc Lavielle, 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, 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). A new version of the CTS is available as a R package since December 2014. 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)
- Inter individual and intra individual variability models
- Graphics and statistical tests

5.4. MLXplore

Participant: Marc Lavielle.

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 but POPIX collaborates closely with Lixoft on on the definition of the specifications of MLXplore.

6. New Results

6.1. Highlights of the Year

Marc Lavielle published the book, *Mixed Effects Models for the Population Approach: Models, Tasks, Methods and Tools* (Chapman & Hall/CRC), which presents a rigorous framework for describing, implementing, and using mixed effects models. With these models, readers can perform parameter estimation and modeling across a whole population of individuals at the same time.

6.2. New result 1

We have proposed a nonlinear mixed-effects framework to jointly model longitudinal and repeated time-to-event data. A parametric nonlinear mixed-effects model is used for the longitudinal observations and a parametric mixed-effects hazard model for repeated event times. We have shown the importance for parameter estimation of properly calculating the conditional density of the observations (given the individual parameters) in the presence of interval and/or right censoring. Parameters are estimated by maximizing the exact joint likelihood with the Stochastic Approximation Expectation-Maximization algorithm. This workflow for joint models is now implemented in the Monolix software, and illustrated on several simulated and real data examples.

6.3. New result 2

We have succesfully extended the methodologies previously developed for ordinary differential equations (ODE) to delay differential equations (DDE). A C++ solver for DDE, and based on an explicit Runge-Kutta scheme, has been developed. This solver can now be used with Monolix, a platform for population modeling of longitudinal data, MlxPlore, a tool for the exploration of complex models and Simulx a R and Matlab function for the simulation of longitudinal data. We use.

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

POPIX had a contract with Astrazeneca (November 2011 - November 2014)

POPIX has a contract with Lixoft (June 2011 - June 2015)

8. Partnerships and Cooperations

8.1. European Initiatives

8.1.1. FP7 & H2020 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; Takeda, 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.

8.2. International Initiatives

8.2.1. Inria International Partners

8.2.1.1. Informal International Partners

POPIX has a collaboration with the Faculty of Pharmacy of Manchester University (UK). Marc Lavielle is invited every year to give a one day course about mixed effects models and the MONOLIX software.

POPIX has a collaboration with the Faculty of Pharmacy of Buffalo university (USA). Marc Lavielle is invited every year to give a 2 days course about mixed effects models and the MONOLIX software.

8.2.2. Participation In other International Programs

Indo French Centre for the promotion of advanced research (CEFIPRA): Marc Lavielle was invited to participate to the the IFCAM Workshop in Statistics and Mathematical Biology, in Bangalore (August 2014).

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Journal

9.1.1.1. Member of the editorial board

Bertrand Maury is Associate Editor of *M2AN*

9.1.1.2. Reviewer

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*.

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 2014 (Alicante, Spain); University of Manchester (UK); University of Buffalo (USA).

9.2.2. Supervision

- Célia Barthélémy, was a PhD student working under the supervision of Marc Lavielle. She decided to stop her PhD in September 2014.
- 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.

9.2.3. Juries

- Marc Lavielle was referee for the HDR of Nicolas Savy (Toulouse 3) and the PhD of Charlotte Baey (ECP)
- Marc Lavielle was member of the jury for the HdR of Rémi Choquet (Montpellier 2) and for the PhD of Claire Christophe (Toulouse 3) and Nicklas Hartung (Marseille).

9.3. Popularization

- Marc Lavielle was invited to give a talk for the "Olympiades des Mathématiques" in Cachan
- Marc Lavielle was invited to participate to the "Nuit des Sciences" at ENS and give a talk about statistics and GMO.

10. Bibliography

Publications of the year

Articles in International Peer-Reviewed Journals

[1] M. DELATTRE, M. LAVIELLE, M.-A. POURSAT. *A note on BIC in mixed-effects models*, in "Electronic Journal of Statistics", 2014, vol. 8, pp. 456–475 [*DOI :* 10.1214/14-EJS890], https://hal.archives-ouvertes.fr/hal-00991708

[2] M. LAVIELLE, C. MBOGNING. *An improved SAEM algorithm for maximum likelihood estimation in mixtures of non linear mixed effects models*, in "Statistics and Computing", 2014, vol. 24, n^{o} 5, pp. 693–707 [*DOI :* 10.1007/s11222-013-9396-2], https://hal.archives-ouvertes.fr/hal-00916817

[3] C. MBOGNING, K. BLEAKLEY, M. LAVIELLE. *Joint modeling of longitudinal and repeated time-to-event data using nonlinear mixed-effects models and the SAEM algorithm*, in "Journal of Statistical Computation and Simulation", 2015, vol. 85, n° 8, pp. 1512–1528 [*DOI :* 10.1080/00949655.2013.878938], https://hal.archives-ouvertes.fr/hal-01122140

Scientific Books (or Scientific Book chapters)

[4] M. LAVIELLE. *Mixed Effects Models for the Population Approach: Models, Tasks, Methods and Tools*, Chapman and Hall/CRC, 2014, https://hal.archives-ouvertes.fr/hal-01122873

Research Reports

[5] R. KUATE, M. LAVIELLE, E. BLAUDEZ, K. CHATEL, J. MARQUET, J.-F. SI ABDALLAH. *A delay differential equation solver for MONOLIX & MLXPLORE*, February 2014, n° RR-8489, 19 p. , https://hal.inria.fr/hal-00952874