Activity Report 2015

Team POPIX

Modélisation en pharmacologie de population

Inria teams are typically groups of researchers working on the definition of a common project, and objectives, with the goal to arrive at the creation of a project-team. Such project-teams may include other partners (universities or research institutions).

RESEARCH CENTER
Saclay - Île-de-France

THEME
Computational Neuroscience and Medecine

Table of contents

Team POPIX

Creation of the Team: 2013 January 01, end of the Team: 2015 December 31

Keywords:

Computer Science and Digital Science:

3.3. - Data and knowledge analysis
3.4. - Machine learning and statistics
6.1. - Mathematical Modeling

Other Research Topics and Application Domains:

2.2.3. - Cancer
2.4.1. - Pharmaco kinetics and dynamics

Popix stopped on December 31st, 2015.

1. Members

Research Scientist

Marc Lavielle [Team leader, Inria, Senior Researcher]

Engineers

Benoit Casseau [Inria, until November 2015]
Francois-Marie Floch [Inria, since November 2015]
Raphael Kuate [Inria, until Sep 2015, granted by FP7 DDMoRE project]

Administrative Assistant

Katia Evrat [Inria]

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, Raphael Kuate.

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 majorally 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)

5. Highlights of the Year

5.1. Highlights of the Year

5.1.1. Awards

Marc Lavielle received the 2015 ISoP (International Society of Pharmacometrics) Innovation award

Marc Lavielle received the 2015 Inria – French Académie des Sciences – Dassault Systèmes Innovation Award

6. New Software and Platforms

6.1. Clinical Trial Simulator

KEYWORDS: Statistics - Bioinformatics - Drug development
FUNCTIONAL DESCRIPTION

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 developing the mlxR R package for the model based simulation of clinical trials.

- Participants: Marc Lavielle
- URL: http://simulx.webpopix.org

6.2. Monolix

KEYWORDS: Statistics - Bioinformatics - Health - Drug development
FUNCTIONAL DESCRIPTION

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.

A first extension of MONOLIX for partial differential equations (PDEs) based models was developed by POPIX in 2015.

- Participants: Marc Lavielle, Raphael Kuate

6.3. MLXtran

KEYWORDS: Statistics - Bioinformatics - Health - Drug development
FUNCTIONAL DESCRIPTION

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.

- Participants: Marc Lavielle

7. New Results

7.1. Model identifiability

We have discussed the question of model identifiability within the context of nonlinear mixed effects models. Although there has been extensive research in the area of fixed effects models, much less attention has been paid to random effects models. In this context we distinguish between theoretical identifiability, in which different parameter values lead to non-identical probability distributions, structural identifiability which concerns the algebraic properties of the structural model, and practical identifiability, whereby the model may be theoretically identifiable but the design of the experiment may make parameter estimation difficult and imprecise. We have explored a number of pharmacokinetic models which are known to be non-identifiable at an individual level but can become identifiable at the population level if a number of specific assumptions on the probabilistic model hold. Essentially if the probabilistic models are different, even though the structural models are non-identifiable, then they will lead to different likelihoods.

7.2. Model of tumor growth

Both molecular profiling of tumors and longitudinal tumor size data modeling are relevant strategies to predict cancer patients' response to treatment. Herein we have proposed a model of tumor growth inhibition integrating a tumor's genetic characteristics that successfully describes the time course of tumor size in patients with low-grade gliomas treated with first-line temozolomide chemotherapy. The model captures potential tumor progression under chemotherapy by accounting for the emergence of tissue resistance to treatment following prolonged exposure to temozolomide. Using information on individual tumors' genetic characteristics, in addition to early tumor size measurements, the model was able to predict the duration and magnitude of response, especially in those patients in whom repeated assessment of tumor response was obtained during the first 3 months of treatment. Combining longitudinal tumor size quantitative modeling with a tumor"s genetic characterization appears as a promising strategy to personalize treatments in patients with low-grade gliomas

7.3. Methods for PDEs based model

We have extended the methodologies previously developed for ordinary differential equations (ODE) to partial differential equations (PDE). A finite element method solver for a given family of PDEs has been developed. This solver can now be used with a prototype version of Monolix, a platform for population modeling of longitudinal data. We have implemented the well-known Lagrange finite element method in one, two and three dimensions of the space.

8. Bilateral Contracts and Grants with Industry

8.1. Bilateral Contracts with Industry

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

9. Partnerships and Cooperations

9.1. European Initiatives

9.1.1. 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 - 2016

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.

9.2. International Initiatives

9.2.1. Inria International Partners

9.2.1.1. Informal International Partners

POPIX has a collaboration with the Faculty of Pharmacy of Manchester University (UK).

POPIX is Adjunct Professor at the Faculty of Pharmacy of Florida University (USA).

POPIX is Adjunct Professor at the Faculty of Pharmacy of Buffalo University (USA).

9.2.2. 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 in Bangalore (July 2015).

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Invited talks

Marc Lavielle was invited speaker at Bayes 2015 (Basel).

10.1.2. Scientific expertise

Marc Lavielle is member of the Scientific Committee of the High Council for Biotechnologies

10.1.3. Research administration

Marc Lavielle is member of

- the Scientific Programming Committee (CPS) of the Institute Henri Poincaré (IHP),
- the Executive Board (CA) of SMAI.

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

Miscellaneous: Marc Lavielle, Population approach and Mixed effects models: PAGE meeting 2015 (Crete);

Miscellaneous: Marc Lavielle, SFdS Workshop about mixed effects models, Paris 2015.

10.2.2. Juries

- Marc Lavielle was referee for PhD of Artemis Llamosi (Paris Diderot)

11. Bibliography

Publications of the year

Articles in International Peer-Reviewed Journals

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[2] C. JELEAZCOV, M. LAVIELLE, J. SCHÜTTLER, H. IHMSEN. *Pharmacodynamic response modelling of arterial blood pressure in adult volunteers during propofol anaesthesia*, in "British Journal of Anaesthesia", January 2015 [*DOI :* 10.1093/BJA/AEU553], https://hal.archives-ouvertes.fr/hal-01252009

[3] M. LAVIELLE, L. AARONS. *What do we mean by identifiability in mixed effects models?*, in "Journal of Pharmacokinetics and Pharmacodynamics", 2015 [*DOI :* 10.1007/s10928-015-9459-4], https://hal.archives-ouvertes.fr/hal-01251986

[4] P. MAZZOCCO, C. BARTHÉLÉMY, G. KALOSHI, M. LAVIELLE, D. RICARD, A. IDBAIH, D. PSIMARAS, M.-A. RENARD, A. ALENTORN, J. HONNORAT, J.-Y. DELATTRE, F. DUCRAY, B. RIBBA. *Prediction of Response to Temozolomide in Low-Grade Glioma Patients Based on Tumor Size Dynamics and Genetic Characteristics*, in "CPT Pharmacometrics Syst Pharmacol", 2015 [*DOI :* 10.1002/PSP4.54], https://hal.archives-ouvertes.fr/hal-01252076

[5] 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

Research Reports

[6] R. KUATE, M. LAVIELLE, E. BLAUDEZ, K. CHATEL, J.-F. SI ABDALLAH. *A finite element solver for PDEs in MONOLIX*, Inria, March 2015, n° RR-8717, https://hal.inria.fr/hal-01144679

Other Publications

[7] P. BARBILLON, C. BARTHÉLÉMY, A. SAMSON. *Parametric estimation of complex mixed models based on meta-model approach*, June 2015, working paper or preprint, https://hal.archives-ouvertes.fr/hal-01162351