Activity Report 2012

Exploratory Action POPIX

Modélisation en pharmacologie de population

RESEARCH CENTER
Saclay - Île-de-France

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Exploratory Action POPIX

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

Popix is located at Paris-Sud University (Mathematics, Building 440). All the researchers of POPIX are also members of the "Probability and Statistics" team of the Laboratory of Mathematics at Paris-Sud University.

Creation of the Exploratory Action: January 01, 2011 , *Updated into Team:* January 01, 2013 .

1. Members

Research Scientists

Marc Lavielle [Team Leader, Senior Researcher Inria, Habilite]
Kevin Bleakley [Researcher Inria, Habilite]

Faculty Member

Marie-Anne Poursat [Associate Professor, Paris-Sud University, Habilite]

Engineers

Hector Mesa
Elodie Maillot
Elena Carvajal
Laura Brocco

PhD Students

Maud Delattre [Inria and Paris-Sud University, defended her PhD in July, 2012]
Cyprien Mbogning [Inria, Paris-Sud University and ENSP Cameroon, defended his PhD in December, 2012]
Célia Barthelemy [Inria]

Administrative Assistant

Katia Evrat

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 a 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.

Futhermore, an important aim of POPIX is to transfer developed methods into software packages so that these methods can be used in practice.

3. Scientific Foundations

3.1. Scientific Foundations

Mathematical models that characterize comple 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 characterizeing 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

4. Application Domains

4.1. Pharmacometrics

Participants: Marc Lavielle, Kevin Bleakley, Maud Delattre, Cyprien Mbogning, Célia Barthelemy, Hector Mesa, Elodie Maillot, Elena Carvajal, 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 (see the Software section for more details)
- protocol optimization tools
- diagnostic tools
- model selection tools
- estimation techniques for complex models (eg, stochastic differential equations, partial differential equations)

4.2. Pharmacogenetics

Participants: Marc Lavielle, Kevin Bleakley.

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, and requires powerful classification and statistical learning tools.

4.3. Oncology

Participants: Marc Lavielle, Célia Barthelemy.

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 pluridiciplinary project 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 already underway, in particular with the aim of extending the statistical methods developed by POPIX to partial differential equations based models. NUMED works on models of tumor growth and has already implemented an extension of MONOLIX to KPP-type reaction-diffusion models.

4.4. Change-point detection in signals

Participants: Marc Lavielle, Kevin Bleakley.

Change-point detection is historically a signal processing problem whereby we search for points at which a 1-dimensional noisy signal has an abrupt change in some way, eg. change in mean or variance. It turns out that similar methods can be developed for finding the genomic locations at which the DNA copy number changes in a cancer-stricken (or other) patient. Normally, we have two copies of DNA along the whole genome, so specific changes (gains or losses) in copy number can be associated with the specific cancer, hopefully leading to treatment possibilites. Kevin Bleakley collaborates with researchers at the Curie Institute in change-point detection in one or many DNA copy number profiles. Related to this, Marc Lavielle and Kevin Bleakley have developed methods to find change-points in histogram probability density functions using data sampled from the (unknown) density.

5. Software

5.1. MONOLIX

Participant: Marc Lavielle.

MONOLIX is an easy, fast and powerful tool for parameter estimation in non-linear 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 spin-off 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, eg. 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.

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 2 of the CTS is available since June 2012. 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 distributions 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

6. New Results

6.1. Mixture of mixed effects models

Participants: Cyprien Mbogning, Marc Lavielle.

We have proposed a new methodology for maximum likelihood estimation in mixtures of non linear mixed effects models (NLMEM). The article *Inference in mixtures of non-linear mixed effects models* was submitted in 2012. 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 propose 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. Several criteria for classification of subjects and estimation of individual parameters were also proposed. 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 regard to initialization. An application to pharmacokinetic (PK) data demonstrates the potential of the method for practical applications.

6.2. Between-subject and within-subject model mixtures for classifying HIV treatment response

Participants: Cyprien Mbogning, Kevin Bleakley, Marc Lavielle.

We have proposed a method for classifying individuals into clinically-relevant population subgroups [5]. This is achieved by treating "subgroup" as a categorical covariate whose value is unknown for each individual, and predicting its value using mixtures of models that represent "typical" longitudinal data from each subgroup. Under a nonlinear mixed effects model framework, two types of model mixtures were developed:

- *Between-Subject Model Mixtures* (BSMM) assume that each individual's longitudinal data follows one of M "base" models, but we do not necessarily know *a priori* which one. Individual i thus has a label $z_i = m \in \{1, ..., M\}$ referring to the model that is supposed to have generated it. We have shown how to extract *a posteriori* estimates of the probability that each individual was generated by each of the base models; this can be used to predict which type of patient we have: non-responder, responder or rebounder.
- *Within-Subject Model Mixtures* (WSMM) make the hypothesis that the model mixture occurs *within each individual*. In the HIV example, this means that we consider that each patient is partially a non-responder, partially a responder and partially a rebounder. This is perhaps more biologically plausible than BSMMs in the sense that each individual's response may be due to their own particular combination of virus strains, cell populations, etc. Within the NLMEM framework, this means including individual "model proportion" parameters into the model and having to estimate them along with the other parameters of the NLMEM. It turns out that this does not require any mathematical extensions to a typical NLMEM. But we can use the estimated proportions to help categorize patients, especially those who do not naturally fall into one of the three "typical" categories.

An application to longitudinal viral load data for HIV-positive patients were used to predict whether they are responding – completely, partially or not at all – to a new drug treatment.

6.3. Joint modeling of longitudinal and repeated time-to-event data

Participants: Cyprien Mbogning, Kevin Bleakley, Marc Lavielle.

We have proposed a nonlinear mixed-effects framework to jointly model longitudinal and repeated time-to-event data. The article *Joint modeling of longitudinal and repeated time-to-event data with maximum likelihood estimation via the SAEM algorithm* was submitted in 2012. 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.

We have illustrated the use of these modeling methods in two real data examples: patient survival in primary biliary cirrhosis, and repeated epileptic seizure count data from a clinical trial.

This workflow for joint models is now implemented in the MONOLIX software

6.4. A new Bayesian Information Criteria for mixed-effects models

Participants: Maud Delattre, Marie-Anne Poursat, Marc Lavielle.

The Bayesian Information Criterion (BIC) is widely used for variable selection in mixed effects models. However, its expression is unclear in typical situations of mixed effects models, where simple definition of the sample size is not meaningful. Yet, in the mixed effects model literature, the BIC penalty usually involves the total number of observations $\log n_{\text{tot}}$. From a practical point of view, the $\log n_{\text{tot}}$ penalty is implemented in the R package nlme and in the SPSS procedure MIXED while the $\log N$ penalty, where N is the number of subjects, is used in MONOLIX, saemix or in the SAS proc NLMIXED.

We have derived an appropriate BIC expression that is consistent with the random effect structure of the mixed effects model [7]. We have illustrated the behavior of the proposed criterion through a simulation study. The use of this new version of BIC is recommended as an alternative to various existing BIC versions that are implemented in available software.

6.5. Inference in mixed hidden Markov models

Participants: Maud Delattre, Marc Lavielle.

Mixed hidden Markov models have been recently defined in the literature as an extension of hidden Markov models for dealing with population studies. The notion of mixed hidden Markov models is particularly relevant for modeling longitudinal data collected during clinical trials, especially when distinct disease stages can be considered. However, parameter estimation in such models is complex, especially due to their highly nonlinear structure and the presence of unobserved states. Moreover, existing inference algorithms are extremely time consuming when the model includes several random effects.

We have proposed new inference procedures for estimating population parameters, individual parameters and sequences of hidden states in mixed hidden Markov models [1]. The main contribution consists of a specific version of the stochastic approximation EM algorithm coupled with the Baum-Welch algorithm for estimating population parameters. The properties of this algorithm were investigated via a Monte-Carlo simulation study.

An application of mixed hidden Markov models to the description of daily seizure counts in epileptic patients was then considered. We proposed to describe exposure-response relationship of gabapentin in epileptic patients using MHMM approach. Longitudinal seizure frequency data from six clinical studies were available for the analysis. The model describes daily seizure frequencies to be governed by an unobserved, yet present, underlying disease dynamics, defined by states of high or low epileptic activity. Individual day-to-day states are dependent exhibiting their own dynamics with patients transitioning between disease states, according to a set of transition probabilities. MHMM estimates both unobserved disease dynamics and daily seizure frequencies in all disease states. Novel drug action modes are achievable: drug may influence both seizure frequencies and transition probabilities. The model showed that gabapentin significantly reduced seizure frequencies in both disease states, without altering disease dynamics. Novel methodology offers additional insights into understanding epilepsy time course, gabapentin mode of action and provides a tool for realistic clinical trial simulations.

6.6. Inference in mixed-effects diffusion models

Participants: Maud Delattre, Marc Lavielle.

The structure of mixed effects models allows a suitable consideration of the whole variability characterizing such data, which is usually split into some intra-individual variability - i.e., the variability occurring within the dynamics of each individual - and some between-subjects variability. In a mixed-effects model, the same structural model is used for describing each individual sequence of observations, but the parameters of this model vary randomly among the individuals, which allows a correct account of the differences between subjects. In a mixed-effects diffusion model, the description of each individual series of observations is based on stochastic differential equations (SDEs). Diffusion is known to be a relevant tool for describing random variability in dynamical systems, and is widely used in applications in many domains.

Although many methods are available for the inference in classical fixed-effects diffusion models, there is still a need for a general, fast and easy to implement method for the inference in mixed-effects diffusion models. Indeed, except in very specific classes of mixed-effects diffusion models, the likelihood of the observations does not have any closed-form expression, making maximum likelihood estimation of the model parameters an intricate issue. The difficulty is twofold for computing the observed likelihood since it involves the transition densities of the underlying individual diffusion processes and integrals over the unobserved individual parameters that can rarely be computed in a closed form. Specific versions of the SAEM algorithm have already been proposed for estimating the population parameters in mixed-effects diffusion models (using for instance an Euler-Maruyama approximation of the individual processes or some particle Markov Chain Monte-Carlo methods). In these two versions of SAEM however, simulation of both the random individual parameters and the individual latent processes is required at simulation step, which is computationally cumbersome.

We have proposed a new inference methodology for mixed-effects diffusion models which consists in coupling the SAEM algorithm with the extended Kalman filter for estimating the population parameters. The relevant article has been submitted in 2012. In this new version of the SAEM algorithm, we only need to simulate the individual parameters at each iteration. We also provide tools for estimating the individual parameters and the individual diffusion trajectories.

6.7. Random threshold for linear model selection

Participant: Marc Lavielle.

We have in a previous work introduced a random thresholding method to select the significant, or non-null, mean terms from a collection of independent random variables, and applied it to the problem of recovering the significant coefficients in nonordered model selection.

We have improved this method by introducing a simple modification which removes the dependency of the proposed estimator on a window parameter while maintaining its asymptotic properties [4]. A simulation study suggests that both procedures compare favorably to standard thresholding approaches, such as multiple testing or model-based clustering, in terms of the binary classification risk. An application to the problem of activation detection on functional magnetic resonance imaging (fMRI) data was used to illustrate the performance of the proposed method.

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

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

POPIX has a contract with LIXOFT (June 2011 - June 2013)

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.

Marc Lavielle reviewed articles for the journals *Computational Statistics and Data analysis*, *Biometrics*, *Statistics in Medecine*, *Journal of Pharmacokinetics and Pharmacodynamics*.

Kevin Bleakley reviewed articles for the journals *Human Genetics* and *Analytica Chimica Acta*.

Maud Delattre reviewed articles for the journal *Journal of Statistical Computation and Simulation*.

Conference Participation.

Marc Lavielle presented his work in the following conferences and workshops:

- CLAPEM, Viña del Mar, Chile, March 2012.
- Analysis of longitudinal data in oncology, Grenoble, June 2012.
- Population Approach Group in Europe, Venice, Italy, June 2012.
- Word Conference on Pharmacometrics, Seoul, Korea, September 2012.
- Analyse de données longitudinales de Cancer, Toulouse, October 2012.

Kevin Bleakley presented his work at:

- Spring Research Conference, Cambridge, USA, June 2012.

Maud Delattre presented her work at:

- GDR Stat et Santé, Rennes, September 2012.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

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

Masters: Marc Lavielle, Computational Biostatistiques, 12 hours, Paris-Sud University

PhD/Postdoc: Marc Lavielle, Population approach and Mixed effects models, 12 hours, University at Buffalo, USA

Miscellaneous: Marc Lavielle, Population approach and Mixed effects models, 12 hours, PAGE meeting 2012, Italy

Miscellaneous: Marc Lavielle, Population approach and Mixed effects models, 12 hours, WCOP meeting 2012, Korea

9.2.2. Supervision

- PhD: Maud Delattre, *Inférence statistique dans les modèles mixtes à dynamique Markovienne*, 4 July 2012 at Paris-Sud University, Marc Lavielle.
- PhD: Cyprien Mbogning, *Inference dans les modèles conjoints et de melange non-linéaires à effets mixtes*, 17 December 2012 at Paris-Sud University, Marc Lavielle.
- PhD in progress: Célia Barthelemy, *Modèles à effets mixtes pour l'assimilation de données en oncologie*, debut: October 2012, Marc Lavielle.
- 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.

9.3. Popularization

Marc Lavielle gave a tutorial called *Santé: quelles méthodes d'analyse des risques?* for the *Association des journalistes Scientifiques de la Presse d'Information* (AJSPI) on November 27, 2012, Paris: http://www.ajspi.com/activites/invitations/sante-quelles-methodes-danalyse-des-risques

Kevin Bleakley gave a talk entitled *United Stats of Obama* at Inria Saclay, describing the use of statistical and machine learning methods in the 2012 USA presidential campaign.

10. Bibliography

Publications of the year

Articles in International Peer-Reviewed Journals

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Research Reports

[7] M. DELATTRE, M. LAVIELLE, M.-A. POURSAT. *BIC selection procedures in mixed effects models*, Inria, May 2012, n^{o} RR-7948, http://hal.inria.fr/hal-00696435.