Preface

Population models describe biological and physical phenomena observed in each of a set of individuals, and also the variability between individuals. This approach finds its place in domains like pharmacometrics when we need to quantitatively describe interactions between diseases, drugs and patients. This means developing models that take into account that different patients react differently to the same disease and the same drug.

The adoption of the population approach in pharmacometrics is largely due to the creation of the NONMEM software in the late 1970s which enabled the use of nonlinear mixed effects models for pharmacometric data analysis. Indeed, the population approach can be formulated in statistical terms using mixed effects models. While linear mixed effects models have been around and widely used since the 1950s, nonlinear mixed effects models remain rarely used even in areas where they are particularly well-suited such as biology, agronomy, econometrics, environmental and human sciences.

Even though each of these domains has its own models and particularities, a rigorous framework for describing and representing any given model turns out to be possible. This leads to a streamlined and precise way to implement methods of interest as readily available software. The main goal of this book is to give a coherent overview of the different components that make up this framework.

First, we will see how the framework allows us to represent models for many different data types including continuous, categorical, count and time-to-event data. This opens the way for the use of quite generic methods for modeling these diverse data types. In particular, the SAEM (Stochastic Approximation of EM) algorithm is extremely efficient for maximum likelihood estimation of population parameters, and has been proven to converge in quite general settings.

Though these practical and theoretical properties are satisfying and extremely useful, the implementation of the methods themselves is rather intricate, requiring considerable knowledge of stochastic algorithms, Monte Carlo Markov chain (MCMC) methods, importance sampling techniques and so on.

To bring these methods to a much wider audience, they have therefore been implemented in the Monolix software and are ready-to-use for a

vast array of real-world data modeling situations. One can also visually explore models in detail using MLXPLORE, or simulate using Simulx. These publicly available tools all use the same model coding language MLXTRAN and will be used throughout the book to illustrate the various tasks a modeler must perform.

All of this leads to a coherency in the overall process from models to methods, methods to tools, and tools to results. It also means that statisticians and mathematicians can be satisfied with the rigorous representation of the models and theoretical properties of the methods, and modelers with the practical capabilities of the tools.

It is not, however, the goal of the book to exhaustively cover the whole range of models and methods available for the population approach. We will limit ourselves to parametric approaches, without ignoring the fact that nonparametric approaches can perhaps be imagined in certain situations. In our treatment, Bayesian methods are not looked at as a specific approach competing with frequentist ones, but integrated into the general statistical framework. In effect, we will construct models using available information, then use these models to perform various tasks. The tasks might include maximum likelihood estimation if we only have data, posterior distribution estimation if we also have prior information, or a mixture of both if we have partial prior information.

The underlying goal of this book is to provide a rigorous approach for model description, implementation and practical use, not "recipes" for modeling or "tricks" for using software. It is intended for mathematicians and statisticians interested in modeling, and for modelers aware of the role of mathematics and statistics in models. It will be useful for training and teaching in any field where population modeling occurs. Furthermore, all the tools presented and used here (MONOLIX, MLXPLORE, Simulx, R) are free for academic and teaching purposes.

All code and data used in the text are available from the supporting website:

`http://www.math.u-psud.fr/~lavielle/book.html`

Acknowledgments

Now that the book is completed, I can see more clearly that it is the final result of several years of intensive work, but also the result of many crossed paths and collaborations.

Above all, I have to emphasize the luck I have had to be a part of the Orsay Mathematics Laboratory for many years now. It is a fantastic environment in which to do mathematics and also create collaborations

with scientists from different disciplines. I would also like to gratefully thank Inria, which has always supported and encouraged me and my projects.

Developing new methods and algorithms constitutes undeniably the heart of my activities. But it was my collaboration with Eric Moulines followed by Bernard Delyon on the SAEM algorithm that definitively convinced me that if an algorithm could work so well in practice, its properties must be provable mathematically (the converse of which is often far from being true ...).

SAEM quickly asserted itself as an incredible estimation tool for (nonlinear) mixed effets models. In 2003, I along with France Mentré (Inserm) and Jean-Louis Foulley (Inra) formed the MONOLIX (MOdèles NOn LInéaires à effets miXtes) working group, active for around six years, with the aim of popularizing new statistical methods for mixed effects models. I would like to personally thank all the participants of this group and especially France with whom I collaborated over several years, and who introduced me to the world of pharmacometrics and the PAGE (Population Approach Group in Europe) community.

Here, I found a fascinating and rich environment where numerous disciplines such as statistics, pharmacology and biology co-exist. I appreciated meeting several modelers from this community who were understanding of the need to develop new and innovative modeling methods and tools while also being conscious of the need for rigorous mathematics to support them.

I very quickly came to the conclusion of the necessity of implementing as software the new methods we were developing in order to make them accessible to the wider community. I give heartfelt thanks to Inria and various modeling and simulation groups (Johnson & Johnson, Novartis, Roche, Sanofi-Aventis, Astrazeneca) for having actively supported development of the MONOLIX software.

I have been lucky to be able to count on the development team of Hector Mesa, Kaelig Chatel and later Eric Blaudez, a group of exceptional engineers who have carried this project further than my highest hopes. I thank them greatly as well as the rest of the current Lixoft team that continues to develop MONOLIX as well as other new modeling tools.

Much of this book has benefited from joint research with a number of colleagues, including Gregory Batt (Inria), Kevin Bleakley (Inria), Emmanuelle Comets (Inserm), Anne Dubois (Inserm), Mats Karlsson (Uppsala University), France Mentré (Inserm), Eric Moulines (Télécom ParisTech), Rada Savic (UCSF), Eric Snoeck (Exprimo) and Benjamin Ribba (Inria). I thank you all.

Several chapters are also based on collaborations with current and past doctoral students: Estelle Kuhn, Adeline Samson, Sophie Donnet,

Maud Delattre, Cyprien Mbogning, Cristian Meza and Célia Barthélémy, with whom I have had great pleasure in working.

I gratefully acknowledge support from the French national research agency, project ANR-05-blan-0274 "MONOLIX", and the Innovative Medicines Initiative Joint Undertaking under grant agreement n. 115156, "Drug and Disease Modeling Resources" (DDMoRe).

A big thanks to Kevin Bleakley for his work in translating my *frenglish* into something readable, as well as his ruthless proofreading of the manuscript.

Lastly, I would like to thank John Kimmel at Chapman & Hall for his interest in this project from the beginning and his continuous support throughout.

Marc Lavielle,
Orsay, May 2014