Nonlinear mixed-effects modelling with nlmixr2

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Welcome

This is the website for the work-in-progress **"Nonlinear mixed-effects modelling with nlmixr2"**.

Our book will describe the installation of `nlmixr2`, and walk the reader through its use in pharmacological modelling and simulation using pharmacokinetic and pharmacodynamic data. We intend to start with simple examples and work towards more complex and useful applications. As well as the use of `nlmixr2` as a routine tool in academic and industrial drug research and development, the book will elaborate on the structure of the tool so that readers interested in contributing to the project or developing extensions have a good starting point for doing so.

Readers will need some familiarity with pharmacology and biostatistics to get the most out of the book.

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1 Introduction

1.1 Pharmacometrics

Wikipedia defines pharmacometrics (PMx) as a field of study of the methodology and application of mathematical models for disease and pharmacological measurement. It applies mathematical models of biology, pharmacology, disease, and physiology to describe and quantify interactions between xenobiotics (drugs) and patients (human and non-human), including both beneficial and adverse effects. It is normally applied to combine data from drugs, diseases and clinical trials to aid efficient drug development, regulatory decisions and rational drug treatment in patients.

Pharmacometrics rolls up modeling and simulation for pharmacokinetics, pharmacodynamics, and #DiseaseProgression, with a focus on populations and variability. A major focus is to understand variability in drug response, which can be predictable (e.g. due to differences in body weight or kidney function) or unpredictable (differences between subjects seem random, but likely reflect a lack of knowledge or data).

Quantitative systems pharmacology (QSP) is also considered to be a part of the PMx ecosystem, but applies a more theoretical and less data-driven approach to building models. QSP models are often much more complex than PK/PD models, with less of a populations focus.

What this boils down to is using mathematical/statistical models to help explain and predict what the body does to the drug (pharmacokinetics, PK) and what the drug does to the body (pharmacodynamics, PD) - these are often combined to produce PKPD or exposure-response (ER) models. We build these using data collected from clinical trials (e.g. blood samples, clinical observations, scores, X-rays and suchlike - multiple samples, over time, from many subjects), which we use to build compartmental models which approximate what is happening over time using ordinary differential equations (ODEs).

This sounds complicated - and it can be - but it's based on the well-stirred compartmental model for PK, a well-established set of principles for how systems like these can be approximated.

I promised you beer! It's actually a pretty good example. PK describes what happens to the alcohol (ethanol) you consume between the glass and the bathroom, and PD describes what it does while it's circulating in your blood (quite a few things, including making you tipsy). Ethanol is a pretty interesting case, because it's eye-wateringly complex. The "DrinkMe"

simulation on Nick Holford's website is a fun interactive example of how it fits together! You can find it at http://holford.fmhs.auckland.ac.nz/research/ethanol.

So pharmacometrics can help us understand how drugs behave in different people. The "DrinkMe" model includes body weight - the bigger you are, the bigger your organs are (usually) and the more machinery you have for metabolizing substances like ethanol, so the slower you get drunk, and if you've eaten something, the alcohol will take longer to get into your system (although these are just two aspects of a very complex system).

These principles apply to every drug we take, from aspirin to metformin (which is commonly used for treating diabetes). We use these models to figure out what an appropriate dose is, and what might affect it.

We can use pharmacometric models like these to simulate clinical trials, dose regimens and so on, *in silico*, so that we can predict what will happen when we actually give a drug to a human, and whether the design we have proposed for our clinical trial will actually work when we run it.

Later on in drug development, as we get close to registration, we can use these models to identify covariates whcih might inform differences in exposure and effect between patients (like age, weight, and sex), and to quantify the relationships between dose, exposure, and response for efficacy (e.g. how well the drug does at reducing or eliminating a tumour) and safety (e.g. how many unwanted side effects the drug generates at a useful dose).

It's not just about the drugs themselves. Drug-disease and disease progression models are also an area in which pharmacometrics continues to have an impact - FDA maintains a list the ones they've developed internally (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/division-pharmacometrics), including examples for Alzheimer's disease and diabetes, although there are many, many more.

So far we've mostly talked about empirical, data-driven models, but pharmacometrics goes further, especially now that the computers are getting so fast (models take time to fit to data, and the more complex they are, and the more patients you have, the longer they take).

Physiologically-based PK (PBPK) models, for example, find the middle ground between PK and QSP, having a more mechanistic bent by taking into account anatomical, physiological, physical, and chemical descriptions of the phenomena involved in complex absorption, distribution, metabolic and elimination (ADME) processes, while remaining fundamentally driven by observed data.

1.2 `nlmixr2`

`nlmixr2` is a set of packages - let's call it the "mixrverse" - for R that provides an open source alternative for nonlinear mixed-effects (NLME) model development, which are the core of most pharmacometrics workflows (amongst others).

Modeling tools in our area are largely closed-source and massively expensive, and are a gigantic entry barrier for new people, especially in low and middle-income countries (and borderline unaffordable even for CROs like mine). `nlmixr2` is intended to be a solution to this problem.

1.3 What you will learn

This book is intended to be a guide to using `nlmixr2` and its constellation of supporting and allied packages in R to develop and use nonlinear mixed-effect pharmacometric models. It is not going to teach you pharmacology, or the core tenets of pharmacometrics. You can learn about those elsewhere.

You will, however, learn to construct datasets for analysis, to write models in `rxode2` and `nlmixr2`, to fit them using `nlmixr2`, to use `shinyMixR` for tracking model development steps, to use `xpose.nlmixr2` for model evaluation, to use `babelmixr` to cross-convert models from different tools, and to use `PKNCA` for figuring out initial estimates. You'll also learn how the "mixrverse" ecosystem has been constructed and how to work with it efficiently.

Throughout the book, we'll point you to resources where you can learn more.

1.4 How this book is organised

We start off with a summary of `nlmixr2` and all its dependencies, and how they're built and work together. This is essential for understanding why things have been set up in the way they have, and how to drill down into the source code to figure out what is actually happening under the hood. It is not, however, essential if you want to dive straight into modeling.

We then get into datasets - how they should be structured, how events like doses are handled, visualization, and what variables should be.

Next up, we look at a simple PK model, to illustrate how models can be written - both with closed-form solutions and ODEs - as well as how `nlmixr2` objects are constructed, and how to extract information from them. We'll use this example to explore the various minimization algorithms that are available and how to tune them.

We'll then move on to a more complex PK example, to illustrate some of `nlmixr2`'s niftier features, like transit absorption models, and how to use the various diagnostics that are available, as well as `shinyMixR`. We'll then segue into simulation (using `rxode2`) to see how pharmacometric models can be used to predict clinical trial outcomes, for example.

PK/PD models will be demonstrated using a version of the legendary haematological toxicity ("hemtox") model, along with a practical demonstration of how it can be used to predict neutropenia rates.

Finally, we'll wrap up with a demonstration of using `babelmixr` to import models from NONMEM, and `PKNCA` for providing credible initial estimates, and some guidelines on how you can contribute to the project if you so wish. `nlmixr2` is, after all, an open-source project and relies entirely on volunteers for its development and maintenance.

Within each chapter, we try and adhere to a similar pattern: start with some motivating examples so you can see the bigger picture, and then dive into the details. Each section of the book is paired with exercises to help you practice what you've learned.

Although it can be tempting to skip the exercises, there's no better way to learn than practicing on real problems.

1.5 What you won't learn

There are some topics that this book doesn't cover, simply because there isn't space.

1.5.1 Pharmacology

This is quite a big one. You can't be an effective pharmacometrician unless you're up to speed with basic pharmacology, which you can't pick up in an afternoon. We'll be touching on pharmacology concepts throughout, but we're assuming you already know the theory. There are quite a few good books that can serve as an introduction to the topic - we particularly like Rowland & Tozer (1).

1.5.2 Pharmacometrics

Even bigger. Although you'll be able to infer a lot of things as we go, it would help if you already know what compartmental nonlinear mixed-effects models are and how they can be used to model the behaviour of drugs. Mould & Upton published a nice overview of the field a decade or so ago (2–4), and there are good textbooks as well (5,6).

1.5.3 Big data

This book assumes you're working with relatively small in-memory datasets. The kinds of models we talk about here don't work well with bigger ones.

1.5.4 Data science

We are dealing with specifically pharmacometric data analysis round these parts. If it's pure data science you're interested in, we heartily recommend R for Data Science, which provides a comprehensive grounding. (We also swiped its structure for our book, which is a compliment of a sort, we guess.)

1.5.5 Python/Julia/Matlab/SAS/Ruby on Rails/etc

In this book, you won't learn anything about Python, Julia, JavaScript or any other language outside of R. This is because `nlmixr2` is written in R.

R is an environment designed from the ground up to support quantitative science, being not just a programming language, but also an interactive environment. It is - in our opinion - a much more flexible language than many of its peers.

1.6 Prerequisites

There's some things we assume you know to get the most out of this book. We expect you to know your way around numbers and math, and to have at least basic experience with programming in R. If you're new to R programming, Hands on Programming with R is a highly-recommended place to start.

You need a computer running a recent version of Windows, macOS or Linux with a decent amount of RAM, and some software.

1.6.1 R

R is free and open source, and can be freely downloaded from CRAN, the **c**omprehensive **R** **a**rchive **n**etwork. CRAN is composed of a vast collection of mirrored servers located around the world and is used to distribute R and R packages. Rather than trying to pick the nearest server, use the cloud mirror, https://cloud.r-project.org, which automatically does the heavy lifting for you. New major releases come once a year, interspersed with 2-3 minor releases. It's a good idea to keep current, but we know that people in the pharma industry aren't necessarily able to do this. That being said, you need version 4.2.2 or better for this book.

1.6.2 RStudio

RStudio is an integrated development environment, or IDE, for R and Python. You can get it from https://posit.co/download/rstudio-desktop/. You'll need at least version 2022.07.2+576.

1.6.3 `nlmixr2` and friends

It goes without saying that you'll need to install some additional R packages. An R package is, essentially, a bundle of functions, data, and documentation that can be added to base R to extend its capabilities. As of today, there are tens of thousands of them.

Install `nlmixr2` and its many dependencies from CRAN by entering the following code into R (or RStudio):

```
install.packages("nlmixr2","sessioninfo","pmxTools","PKNCA","babelmixr2","xpose.nlmixr2")
```

Once installed, it can be loaded as follows. Note that you can't use it until it's been loaded.

```
library(nlmixr2)
```

```
Loading required package: nlmixr2data
```

1.7 Acknowledgements

`nlmixr2` is the product of countless hours of hard work by many, many contributors. In particular the authors wish to acknowledge Wenping Wang, who started this project, and is in no small part responsible for its continuing success.

We would also like to highlight the contributions of our employers, whose generous donation of our time to this project have enabled it to grow into what it is today. So heartfelt thanks to Novartis (in particular, Lisa Hendricks and Mick Looby), Occams, LAP&P, Certara, Seattle Genetics, and Johnson & Johnson for letting us play in this wonderful sandbox.

1.8 Colophon

This book is powered by Quarto which makes it easy to write books that combine text and executable code.

This book was built with:

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sessioninfo::session_info(c("nlmixr2"))
```

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   withr           2.5.0       2022-03-03 [1] CRAN (R 4.2.2)
P  xfun            0.34        2022-10-18 [?] CRAN (R 4.2.2)
   xgxr            1.1.1       2021-04-22 [1] CRAN (R 4.2.2)
   xml2            1.3.3       2021-11-30 [1] CRAN (R 4.2.2)
P  yaml            2.3.6       2022-10-18 [?] CRAN (R 4.2.1)

[1] C:/Occams/Local/GitHub/nlmixr2_book/renv/library/R-4.2/x86_64-w64-mingw32
[2] C:/Users/justin/AppData/Local/Temp/RtmpqMvULP/renv-system-library

P -- Loaded and on-disk path mismatch.
```

```
 D -- DLL MD5 mismatch, broken installation.

--------------------------------------------------------------------------------
```

2 History

This book has been a long time in coming.

2.1 In the beginning, there was `RxODE`

Our story begins with `RxODE`. `RxODE` was developed by Melissa Hallow and Wenping Wang as an R package for facilitating quick and efficient simulations of ODE models (7), and when it was presented by Melissa Hallow at the PAGE meeting in Crete in 2015 (8), the idea was floated to use its machinery for parameter estimation using `nlme`, the R implementation of nonlinear mixed-effects models by Pinheiro and Bates (9). As it turned out, work was already pretty advanced by that time, and parameter estimation with both `nlme` and stochastic annealing expectation maximization (SAEM) (10) was implemented by Wenping by the end of that year.

2.2 Stan and deliver

The next milestone came at ACoP6 the same year, when Yuan Xiong first presented `PMXstan` (11). Applying fully Bayesian approaches to pharmacometric modeling has always been a challenging task, and `PMXstan` was proposed as a way to bridge the gap. Stan implements gradient-based Markov chain Monte Carlo (MCMC) algorithms for Bayesian inference, stochastic, gradient-based variational Bayesian methods for approximate Bayesian inference, and gradient-based optimization for penalized maximum likelihood estimation, and can easily be run from R. However, before `PMXstan`, pharmacometricians had to write their own Stan code to describe PKPD models, and preparing data files was arduous and counter-intuitive for those used to event-based data files like those used in NONMEM. Also, there were no efficient ODE solvers that could handle stiff systems that would work with its No-U-Turn Sampler (NUTS). `PMXstan` solved this by providing wrappers for the more unfriendly parts of the process, closed-form solutions for common PK systems written in Stan code, and a NUTS-compatible template LSODA solver to deal with stiff ODE systems. Significantly, these were components that would become quite important for a more general nonlinear mixed-effects (NLME) model fitting tool.

2.3 GitHub

The first `nlmixr` commit to GitHub was on 19 October 2016, and by then a small team had sprung up around the project, with Wenping Wang and Yuan Xiong at its core within Novartis, and a small group of interested parties including Teun Post and Richard Hooijmaaijers at LAP&P and Rik Schoemaker and Justin Wilkins at Occams.

In December 2016, `nlmixr` was presented to the modeling group at Uppsala University, where the implementation of the first-order conditional estimation method with interaction (FOCEI) by Almquist and colleagues (12) was first discussed.

2.4 CRAN

Matt Fidler joined the team at Novartis in January 2017, and implemented the FOCEI method, bringing the number of available algorithms to three. June 2017 saw the introduction of a unified user interface across all three algorithms, a major milestone, and our first CRAN release was `nlmixr` 0.9.0-1 on 9 November 2017. An official 1.0 would follow in August 2018. By now the team had widened to include Mirjam Trame, who, together with Wenping, was using `nlmixr` as the core of a series of pharmacometric training courses in Cuba and elsewhere in Central and South America.

2.5 First peer-reviewed publications

Although `nlmixr` had been a regular fixture at PAGE and ACoP in the intervening years, our first major publication would arrive in 2019, in the form of a tutorial introducing `nlmixr` to the wider pharmacometric world (13), and two months later, a comparison of algorithms between `nlmixr` and its gold standard commercial alternatives (FOCEI in NONMEM and SAEM in Monolix) followed (14).

2.6 Streamlining and modularization

Installing `nlmixr` was, at this time, a complicated and daunting undertaking, and although many in the pharmacometrics community had taken to `nlmixr` with enthusiasm, this was a large disadvantage that, to be frank, was turning people off. It had long been necessary to use Python for handling some aspects of FOCEI fitting, and getting it to work properly together with R was *hard*. This was further complicated by CRAN's effective but very rigid package review and approval system, which was leading to endless problems with keeping the various dependencies `nlmixr` had in sync with one another. In April 2021, `nlmixr` 2.0 was unleashed

upon the world, and Python was left behind forever. To say this was a relief to the development team was to understate the emotional catharsis that occurred.

Although this solved one problem, another had been brewing. `nlmixr` had become a large package by R standards, and compile times at CRAN had begun to irk its administrators, leading to significant delays in approval. This eventually led to the decision to reimplement `nlmixr` as a series of closely linked, modular packages as opposed to a single monolithic unit. Rather than reverse-engineer the original `nlmixr`, the decision was taken to fork the project, and `nlmixr2` was born in February 2022. `nlmixr` would remain on GitHub, but would no longer be developed actively, while new features and ongoing improvements would be applied to `nlmixr2`. The first CRAN release of `nlmixr2` took place in June 2022.

Up to 26 March 2022, the date on which the last commit was made to the original version of `nlmixr`, there were 2,403 commits to the nlmixr repository and 17 more CRAN releases. `RxODE` had 4,860 commits and 33 CRAN releases (some before `nlmixr`'s time, but we're just going to go ahead and count them anyway).

2.7 Community enthusiasm

Over the years, we've hosted numerous tutorials at the major pharmacometrics meetings (PAGE, ACoP, PAGANZ and WCoP), and used nlmixr as the centrepoint for a series of well-received pharmacometrics courses in Cuba and elsewhere. We've also managed to publish a bit (15), as have others (we get into this a little later on). Our tutorial in *Clinical Pharmacology & Therapeutics: Pharmacometrics & Systems Pharmacology* (13) was one of that journal's top ten most-read articles in 2021, with over 4,000 downloads. Our article had been one of the top 10% most-downloaded papers in 2018-2019, and having such interest for the second time in a row is tremendously encouraging for all of us! We hope it's a reflection of the enthusiasm the community is building for our tool, and hope that it will continue.

This book is the next step in our journey; we hope you'll take it with us.

References

1. Derendorf H, Schmidt S. Rowland and Tozer's Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications. Wolters Kluwer; 2019.
2. Mould DR, Upton RN. Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development. CPT: Pharmacometrics & Systems Pharmacology. 2012;1(9):e6.
3. Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development - Part 2: Introduction to pharmacokinetic modeling methods. CPT: Pharmacometrics and Systems Pharmacology. 2013 Apr;2(4).
4. Upton RN, Mould DR. Basic concepts in population modeling, simulation, and model-based drug development: Part 3-introduction to pharmacodynamic modeling methods. CPT: Pharmacometrics and Systems Pharmacology. 2014 Jan;3(1).
5. Ette EI, Williams PJ. Pharmacometrics: The science of quantitative pharmacology. Wiley; 2007.
6. Gabrielsson J, Weiner D. Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications, Fourth Edition. Taylor & Francis; 2007.
7. Wang W, Hallow KM, James DA. A tutorial on RxODE: Simulating differential equation pharmacometric models in R. CPT: Pharmacometrics and Systems Pharmacology. 2016;5(1):3–10.
8. Hallow KM, James DA, Wang W. Interactive evaluation of dosing regimens for a novel anti-diabetic agent: a case-study in the application of RxODE. In: PAGE 24 [Internet]. 2015. p. Abstr 3542. Available from: https://www.page-meeting.org/?abstract=3542
9. Pinheiro JC, Bates DM. Mixed-effects models in s and s-PLUS. New York: Springer; 2000.
10. Delyon BYB, Lavielle M, Moulines E. Convergence of a stochastic approximation version of the EM algorithm. Annals of Statistics [Internet]. 1999;27(1):94–128. Available from: https://arxiv.org/abs/arXiv:1011.1669v3
11. Xiong Y, James D, He F, Wang W. PMXstan: An R Library to Facilitate PKPD Modeling with Stan (M-01). Journal of Pharmacokinetics and Pharmacodynamics. 2015 Oct;42(S1):S11.
12. Almquist J, Leander J, Jirstrand M. Using sensitivity equations for computing gradients of the FOCE and FOCEI approximations to the population likelihood. Journal of Pharmacokinetics and Pharmacodynamics. 2015;42(3):191–209.

13. Fidler M, Wilkins JJ, Hooijmaijers R, Post TM, Schoemaker R, Trame MN, et al. Nonlinear Mixed-Effects Model Development and Simulation Using nlmixr and Related R Open-Source Packages. CPT: Pharmacometrics and Systems Pharmacology. 2019 Sep;8(9):621–33.

14. Schoemaker R, Fidler M, Laveille C, Wilkins JJ, Hooijmaijers R, Post TM, et al. Performance of the SAEM and FOCEI Algorithms in the Open-Source, Nonlinear Mixed Effect Modeling Tool nlmixr. CPT: Pharmacometrics and Systems Pharmacology. 2019;8(12):923–30.

15. Fidler M, Hooijmaijers R, Schoemaker R, Wilkins JJ, Xiong Y, Wang W. R and nlmixr as a gateway between statistics and pharmacometrics. CPT: Pharmacometrics and Systems Pharmacology. 2021 Apr;10(4):283–5.