nlmixr: pharmacometric modelling for the people

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On behalf of the nlmixr development team:

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History

- **2015:** Melissa Hallow's PAGE 2015 poster on RxODE[1] mentions parameter estimation with nlme
- **2015:** Wenping Wang implements parameter estimation using nlme (R-package) and SAEM from scratch
- **2016:** Yuan Xiong writes PMXStan[2] linking RxODE and stan
- **October 2016:** first public release of nlmixr
- **December 2016:** nlmixr presentation in Uppsala where Mats Karlsson mentions Almquist et al[3] implementing FOCEi
- **January 2017:** Matt Fidler joins the team and implements FOCEi
- **June 2017:** unified user interface
- **October 2017:** first pre-release nlmixr on CRAN
- **August 2018:** nlmixr 1.0 on CRAN
- **September 2019:** nlmixr tutorial in CPT:PSP[4]
- **November 2019:** paper in CPT:PSP comparing nlmixr FOCEi to NONMEM, nlmixr SAEM to Monolix[5]
- **April 2021:** nlmixr version 2.0 on CRAN no longer needs Python, hugely simplifying life!
- **June 2022:** nlmixr2 and rxode2 on CRAN

[1]https://www.page-meeting.org/default.asp?abstract=3542
[2]https://discuss.go-isop.org/t/introduction-to-pmxstan-an-r-library-to-facilitate-pkpd-modeling-with-stan/554
[3]https://pubmed.ncbi.nlm.nih.gov/25801663/
[4]https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/psp4.12445
[5]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6930853/

The nlmixr team

Founder, Emeritus

Wenping Wang, PhD

nlmixr Team Lead

Matthew Fidler, PhD

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Rik Schoemaker, PhD

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Justin Wilkins, PhD

Yuan Xiong, PhD

Motivation

- ~~Commercial gain~~
  - Commercial gain is not a motivation for this project. Pharmacometrics is a small community and therefore to make a commercial software product is very risky, and when you succeed will need to be very expensive to recoup investments
  - By starting out not wanting to make money but have motivation from other sources, the project becomes attractive to members with other mentalities, and allows setting up a team you would never get for a commercial project

Motivation

- **Curiosity:** can we actually pull this off?
  - The attraction of inventing something new, to venture where no-one has succeeded (in R that is)

Motivation

- **Curiosity:** can we actually pull this off?
- **Consolidation:** testing, checking, documenting
  - Not very sexy, but an essential task to support the inventor
  - Attractive to those team members that like to be sure everything works properly!

Motivation

- **Curiosity:** can we actually pull this off?
- **Consolidation:** testing, checking, documenting
- **Convenience:** parameter estimation in R
  - To have both input, analysis and output in a single package is super-attractive and makes workflows potentially very efficient

Motivation

- **Curiosity:** can we actually pull this off?
- **Consolidation:** testing, checking, documenting
- **Convenience:** parameter estimation in R
- **Collaboration:** open-source encourages other to contribute
  - Where open-science allows you to ‘stand on the shoulder of giants’, open-source allows everyone to take the software and run with it, creating applications you would never think of before

Collaboration: projects so far

- **ShinyMixR:** shiny app for interactively running nlmixr (Richard Hooijmaijers)
- **xpose.nlmixr:** diagnostics using xpose (Justin Wilkins)
- **ggPMX:** diagnostics and reporting (Irina Baltcheva and Bruno Bieth)

Under development:

- **nlmixr2rpt:** automatic and scripted reporting (John Harrold)
- **babelmixr:** nlmixr as front-end to NONMEM and Monolix (Bill Denney and Matt Fidler)
  - PKNCA provides initial estimates
  - Unit conversion and implementation in code
  - Advanced diagnostics when NONMEM fails to run correctly

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- **Collaboration:** open-source encourages other to contribute
- **Concern:** continuity of existing software
  - What will happen to NONMEM when Bob Bauer retires? Having a backup solution is very reassuring

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- **Concern:** continuity of existing software
- **Cost:** modelling software is expensive and limits use when funds are restricted
  - Free software makes modelling accessible in lower to middle income countries
  - Not needing a license makes giving courses much easier, and many pharmacometrics courses are already using nlmixr
  - Academic licenses appear to solve the issue of cost, but usually cannot be applied for commercial work making drug development in a low income environment difficult

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- **Collaboration:** open-source encourages other to contribute
- **Concern:** continuity of existing software
- **Cost:** modelling software is expensive and limits use when funds are restricted
- **Community:** non-linear mixed effect modelling available for everyone
  - Truly pharmacometric modelling for the people
  - Highly motivating to be able to help others
  - Many nlmixr courses have already been taught, and many publications are out there
  - Multiple teams are already using nlmixr for all their work (e.g. Joe Standing's group at UCL)

Community

- **nlmixr courses:**
  - PAGE (Montreux, Stockholm, Ljubljana)
  - ACoP (San Diego, Denver)
  - WCoP (Cape Town)
  - PAGANZ (Queenstown)
  - RedIF (Mexico, Uruguay)
  - Cuba (3 courses)

- **publications:**
  - 3 nlmixr publications from the nlmixr team
  - 45 publications and counting using nlmixr

Future

- Further nlmixr development:
  - Log-likelihood based parameter estimation (odd-type data)
  - Inter-occasion variability
  - Mixture models
  - Parallelisation FOCEi

- Setting up an advisory board
  - Keeps the nlmixr development team grounded in practice
  - Guides us on the direction forward
  - Helps consolidate the support base