nlmixr^2: past, present and future

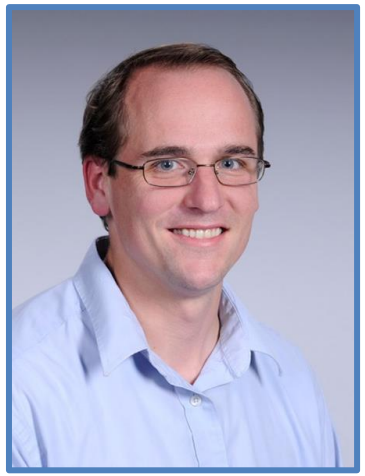
Matthew Fidler

On behalf of the nlmixr2 team:

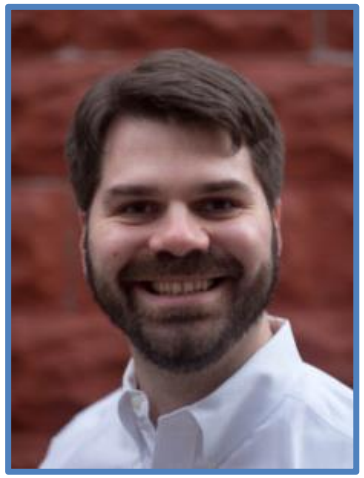
Matt Fidler, Bill Denney, John Harrold, Richard Hooijmaijers, Rik Schoemaker, Max Taubert, Mirjam Trame, Theodoros Papathanasiou, Justin Wilkins

nlmixr^2: who we are and our vision

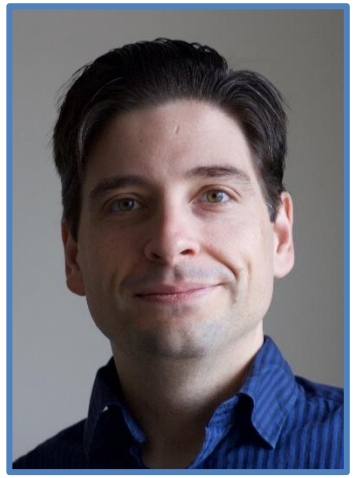
Active nlmixr^2 team



Matthew Fidler, PhD



Bill Denney, PhD



John Harrold, PhD

Richard Hooijmaijers, BSc

Theo Papathanasiou, PhD

Rik Schoemaker, PhD

Mirjam Trame, PhD

Justin Wilkins, PhD

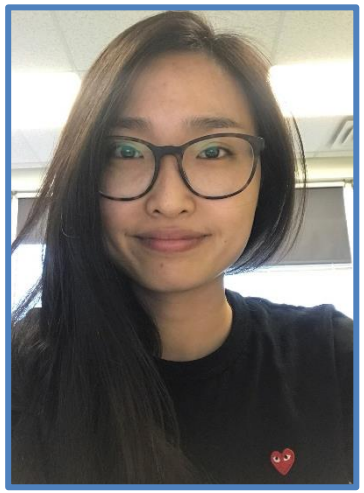
Max Taubert, PhD

Emeritus nlmixr and nlmixr^2 members

Founder, Emeritus

Wenping Wang, PhD

Teun Post, PharmD, PhD



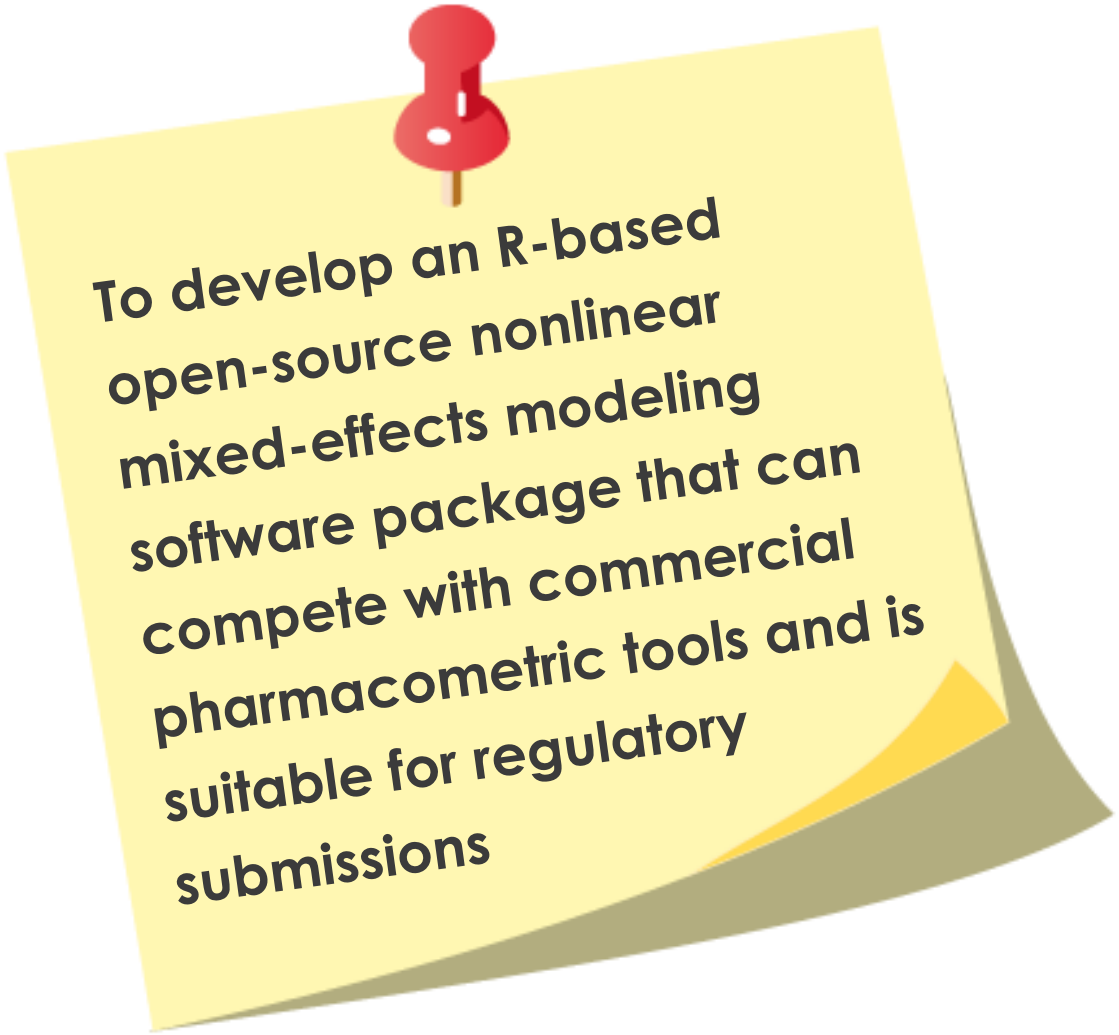
Huijuan Xu, PhD

Yuan Xiong , PhD

Advisory committee Members (no pictures yet)

- Paolo Denti
- Stephen Duffull
- Marc Gastonguay
- Lisa Hendricks
- Manuel Ibarra
- Mats Karlsson
- Joseph Standing

Vision of nlmixr



nlmixr^2: a short history

Nlmixr2 a brief history (1/2)

2005
- Inspiring Monolix Course

2005
- First C saem

2011
- Nmutil simulator

2015
- First RxODE

2016
- First nlmixr nlme

2017
- First CRAN

2017
- Saem & nlmixr2 fn

2018
- fo/focei(python)

2018
- ShinyMixR

2018
- Multiple Endpoint

2019
- First tutorial

2019
- Comparison paper

2019
- Lag/rate/dur/f

2019
- NONMEM EVIDs

2019
- Legible Parsing err

2021
- Drop python

Nlmixr2 a brief history (2/2)

- 2021
  - Parallel random
- 2021
  - Unbranched
- 2021
  - Censoring
- 2022
  - Nlmixr2 &rxode2
- 2022
  - Nlmixr2=rxode2 fn
- 2022
  - ETA Std. Errors
- 2022
  - babelmixr2
- 2023
  - +9 Pop Est Methods
- 2023
  - User Functons
- 2023
  - ODE EVID expansion
- 2023
  - Merge $fitMerge
- 2024
  - monolix2rx
- 2024
  - Poped

nlmixr2: where we are and looking forward

Features Already Implemented in nlmix2/rxode2

- Time varying covariates
- Parallel ODE solving in rxode2 and saem (still needs to be worked out for other methods)
- Generalized likelihood for certain population/mixed effects model
- Censored data (M3/M4) via LIMIT, CENS columns
- User Defined functions interfacing R and possibly converting to C (with derivatives)

Estimation methods – Naive Pooled

Method	Bounded	Gradient Free	Gradient	Hessian	Likelihood
bobyqa	☑	☑	☐	☐	☑
Uobyqa	☐	☑	☐	☐	☑
optim	☐	☑	☐	☐	☑
	method="Nelder-Mead“, "SANN“ or method="Brent"				
nls	☐	☐	☑	☑	☐
nlminb	☑	☐	☑	☑	☑
nlm	☐	☐	☑	☑	☑
lbfgsb3c	☑	☐	☑	☐	☑
n1qn1	☐	☐	☑	☐	☑
optim	☑(L-BFGS-B) ☐	☐	☑	☐	☑
	method="L-BFGS-B“, "BFGS“ or "CG"				
focei	☑	☑ or ☐ (outerOpt)	☑	☐	☑

Estimation Methods – mixed effects

Method	Bounded	Gradient Free	Gradient Inner	Mu-ref linear	Parallelized	Likelihood
fo	☑	☑	☐	☐	☐	☑
foi	☐	☑	☐	☐	☐	☑
foce	☐	☑	☐	☐	☐	☑
focei	☑	☑ or ☐ (outerOpt)	☑	☐	☐	☑
Saem	☐	☑	☐	☑	☑	☐

Future estimation methods?

- adfocei – instead of using forward sensitivity for inner gradients, use automatic-differentiation
- mufocei – replace etas with phi and determine population/covariate effects by linear models
- ffocei – calculate outer gradient of problem (can possibly be mixed with mufocei)
- fsaem – Implement f-SAEM (2020)
- Gc – Gausian Quadrature

Interaction with other tools with babelmixr2

Method	Import	Notes
nonmem	nonmem2rx	Creates NONMEM control stream, runs and imports into nlmixr2 • Can help diagnose NONMEM focei issues • Validates translation (also in the import)
monolix	monolix2rx	Creates Monolix project, runs and imports into nlmixr2 • Can add CWRES to monolix model • Validates translation (also in the import, work in progress)
poped	--	
pknca	--	

Other integration future features?

- Other ODE integrators, DEsolve, PKPDsim, mrgsolve
- Other modeling frameworks (dMod, torstan, stanette)

Features on the roadmap

- Linear-compartment model update
- Between Occasion variability (and other levels of variability; can be worked around)
- Easy way to code/simulate survival models (and perhaps survival specific regression techniques)
- Neural Network-based ODEs (Implemented in PAGE poser)
- Mixture models
- Adding prior parameters to do Bayesian analysis with adjusted likelihoods (likely needed before torstan/stanette integration)
- Proper different distributions of between subject variabilities (?)
- Delay Differential Equations (?)
- Matrix Exponential / Inductive Linearization
- Other ODE methods (we have lsoda and dop853)
- Different methods of covariance (eg SIR) and likelihood calculation (for SAEM)

Missing features not currently on the roadmap

- Autocorrelation
- Non-parametric estimation

Fit integration into other tools

- Goodness of fit plots
  - xpose (via xpose.nlmixr2)
  - ggPMX
  - pmPlot (through accessing merged dataset)
- VPC
  - Vpc package (regular, pred-corrected, and censoring VPCs)
  - Other VPC packages by simulating the vpc data
- Reporting
  - Nlmixr2rpt – word reports
  - Nlmixr2 models to LaTeX equations
- Tools
  - Some covariate selection methods (like SCM, Lasso, Horseshoe-prior)
  - Automatic model selection by nlmixr2auto (UCL)
  - Bootstrapping, preconditioning
- Shiny
  - shinyMixR for run management
- Pharmpy
  - Import/export nlmixr2 models

nlmixr^2 acknowledgements

- Nlmixr team past & present
- Advisory Committee
- Novartis support & internal advocates
  - Lisa Hendricks
  - Mick Looby
  - Kai Grosh
  - Farkad Ezzet
  - Andy Stein
  - Maja Skataric
- External Advocates

Thank you