

monolix2rx / babelmixr2 automatically translates Monolix to a qualified rxode²/nlmixr²/NONMEM model/fit

A nlmixr² model can create reports (docx/pptx), VPCs and add CWRES to fits

nlmixr², rxode² and Monolix: interchangeable models using monolix2rx and babelmixr2

Introduction: *nlmixr2* (www.nlmixr2.org) is an open-source R package, freely available on CRAN[1] and GitHub[2]. It builds on rxode2[3], an R package for simulation of nonlinear mixed effect models using ordinary differential equations (ODEs), providing an efficient and versatile way to specify pharmacometric models and dosing scenarios, with rapid execution due to compilation in C. Monolix[4] is a commercial tool for non-linear mixed effects modeling built around the SAEM algorithm.

Since nlmixr², rxode² and Monolix perform similar tasks, tools to convert between these different model specification formats have the potential to greatly improve efficiency when implementing Monolix models in rxode², or converting an nlmixr² model to run in Monolix.

Objectives:

Create tools to allow bidirectional interoperability with nlmixr²/rxode² and Monolix:

- Create a tool to run nlmixr² models in Monolix, and automatically ensure the translation is accurate
- Create a tool to import Monolix models into rxode²/nlmixr², and automatically ensure the translation is accurate

Methods: The R package babelmixr2[5] accepts rxode²/nlmixr² models and uses the built-in R parser to navigate the create an internal representation of the model. With this information, babelmixr2 generates a Monolix Mlxtran file and Monolix text model file. The input data are also translated from rxode²/nlmixr² to Monolix-compatible format. Once the code and data are generated, Monolix is used to run the model (through the lixoftConnectors package). After Monolix has completed its run, the parameter estimates are read in (including random effects), and nlmixr² is used to calculate residuals and predictions. This allows the individual predictions and population predictions to be compared easily between Monolix and nlmixr² outputs and simultaneously generates a valid and validated nlmixr²/rxode² model suitable for performing simulations.

The R package monolix2rx[6] takes Monolix Mlxtran project and model files as input and creates an rxode² model representation of the model. It reads the final parameter estimates and uses C-based parsing in dparser[7] to create a nlmixr²-compatible model. Additionally, the parsing routine for Mlxtran model files is capable of converting a Monolix model to an R-readable object which can be used in other open source packages like ggPMX[8].

We will demonstrate the application and utility of these tools with model case studies. For tool validation, we successfully ran the nlmixr² example models in Monolix.

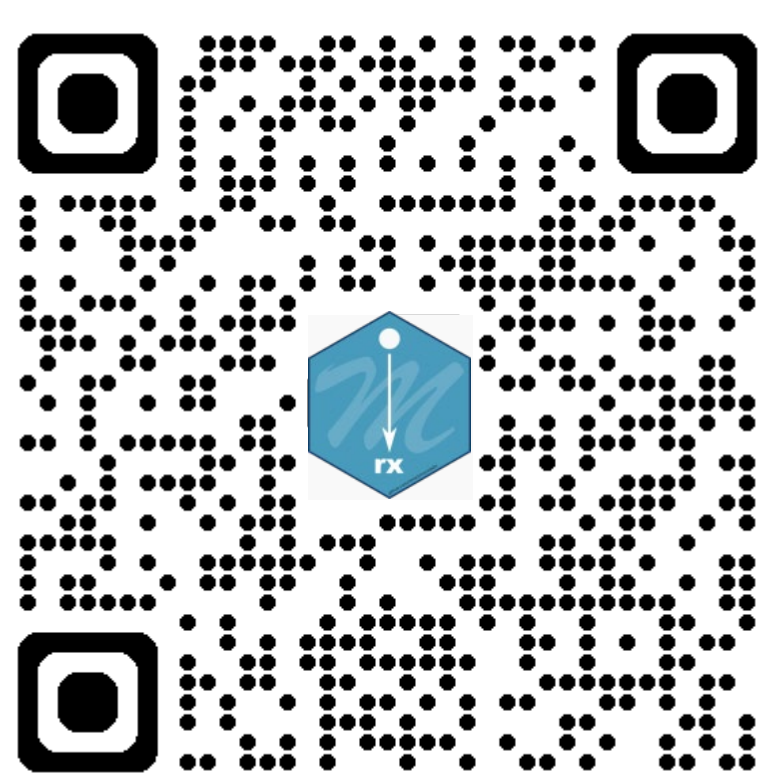
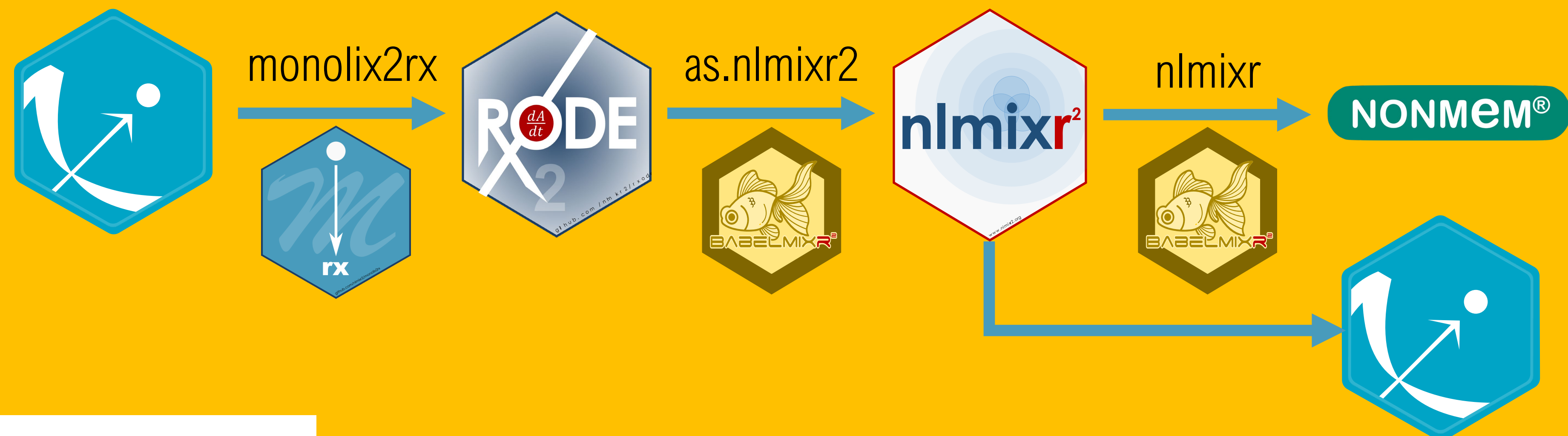
Results: All of the demonstration files in Monolix could be read by the monolix2rx Mlxtran parser. Continuous-endpoint models were converted to rxode²/nlmixr² format. Additionally, the models provided with the Monolix 2021R2_ library were successfully imported and converted.

One feature when using *nlmixr2* and Monolix translations is they allowed calculation of conditional weighted residuals which is not available in Monolix, but can use the nlmixr² methodology to calculate with the Monolix fits. This could add another option for diagnosing Monolix model fits in addition to the PDE plots that are often used.

Conclusion: The results of our testing illustrate how these tools can be used to speed up model development time and minimize error when cross-converting Monolix and nlmixr² models. For nlmixr² runs, we know instantaneously how well the translation tools are performing relative to one another. Additionally, the ability to use rxode² to generate visual predictive checks (VPCs) and clinical trial simulations without any intermediate steps, and knowing immediately whether a translation has worked correctly, represents a great convenience for pharmacometricians wishing to share their analyses with those without Monolix.

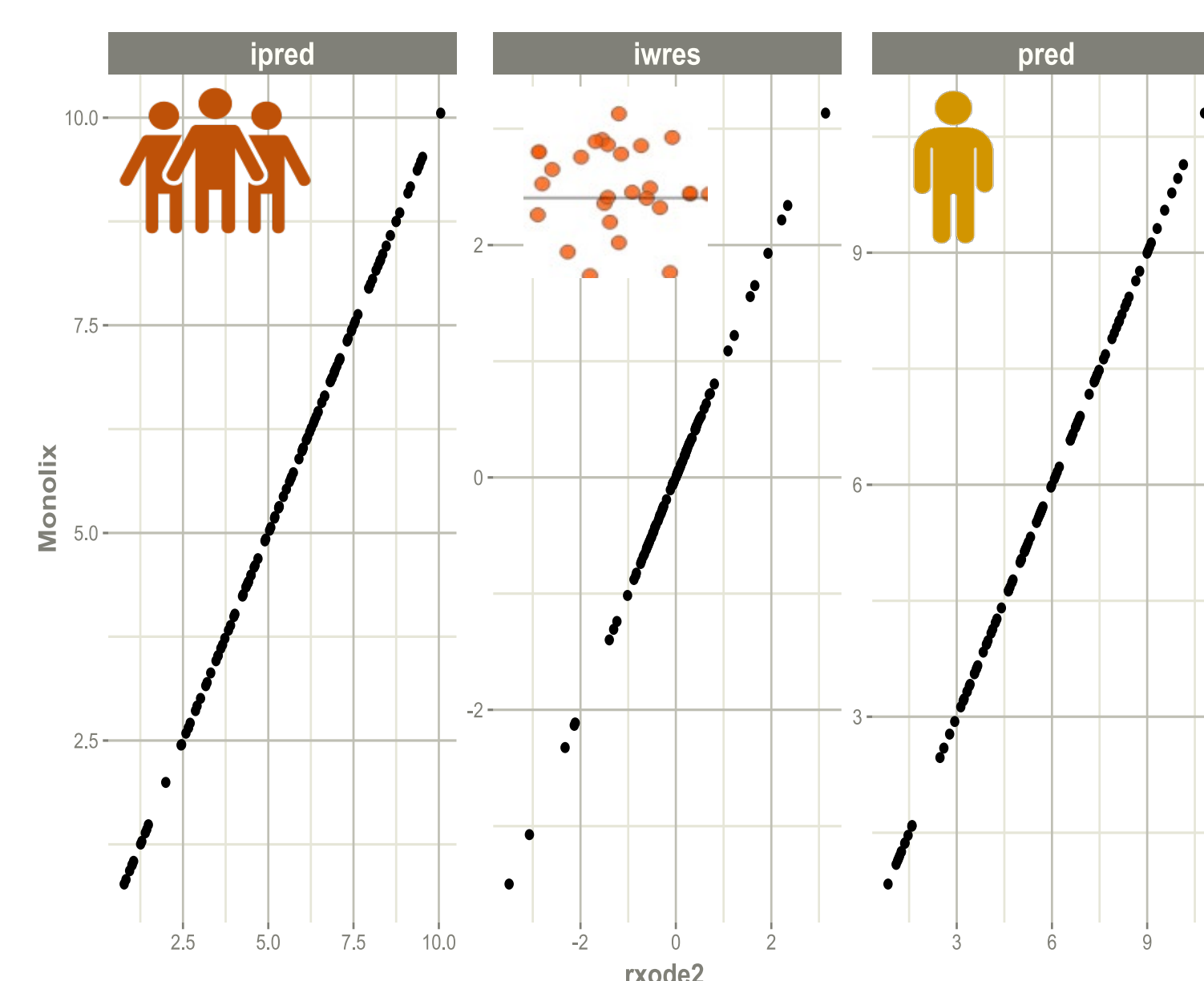
References:

- [1] <https://cran.r-project.org/package=nlmixr2>
- [2] <https://github.com/nlmixr2/nlmixr2>
- [3] <https://github.com/nlmixr2/rxode2>
- [4] <https://lixoft.com/products/monolix/>
- [5] <https://github.com/nlmixr2/babelmixr2>
- [6] <https://github.com/nlmixr2/monolix2rx/>
- [7] <https://github.com/nlmixr2/dparser-R>

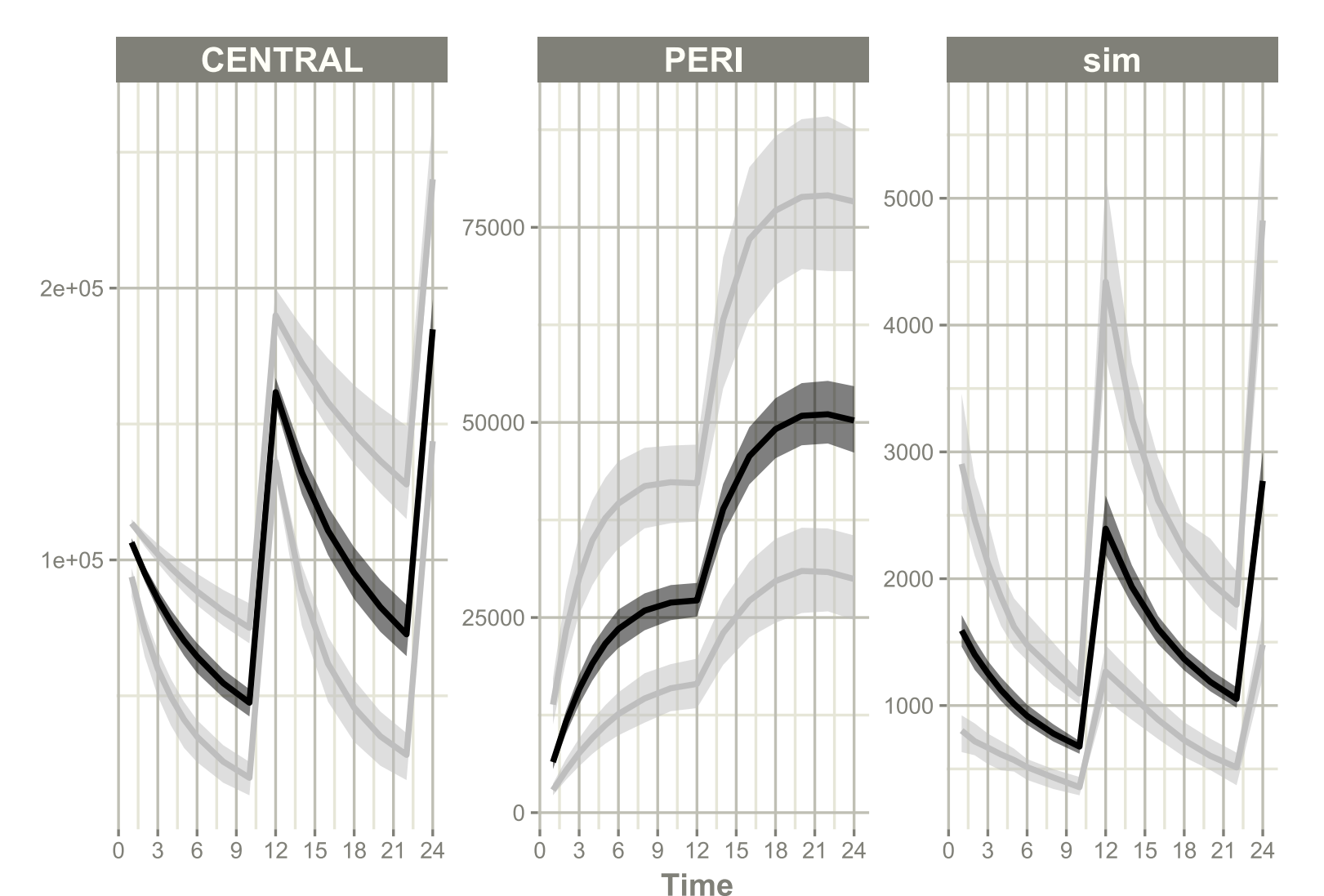


Monolix to rxode²/ nlmixr²/NONMEM uses four functions monolix2rx, qs.nlmixr2, nlmixr

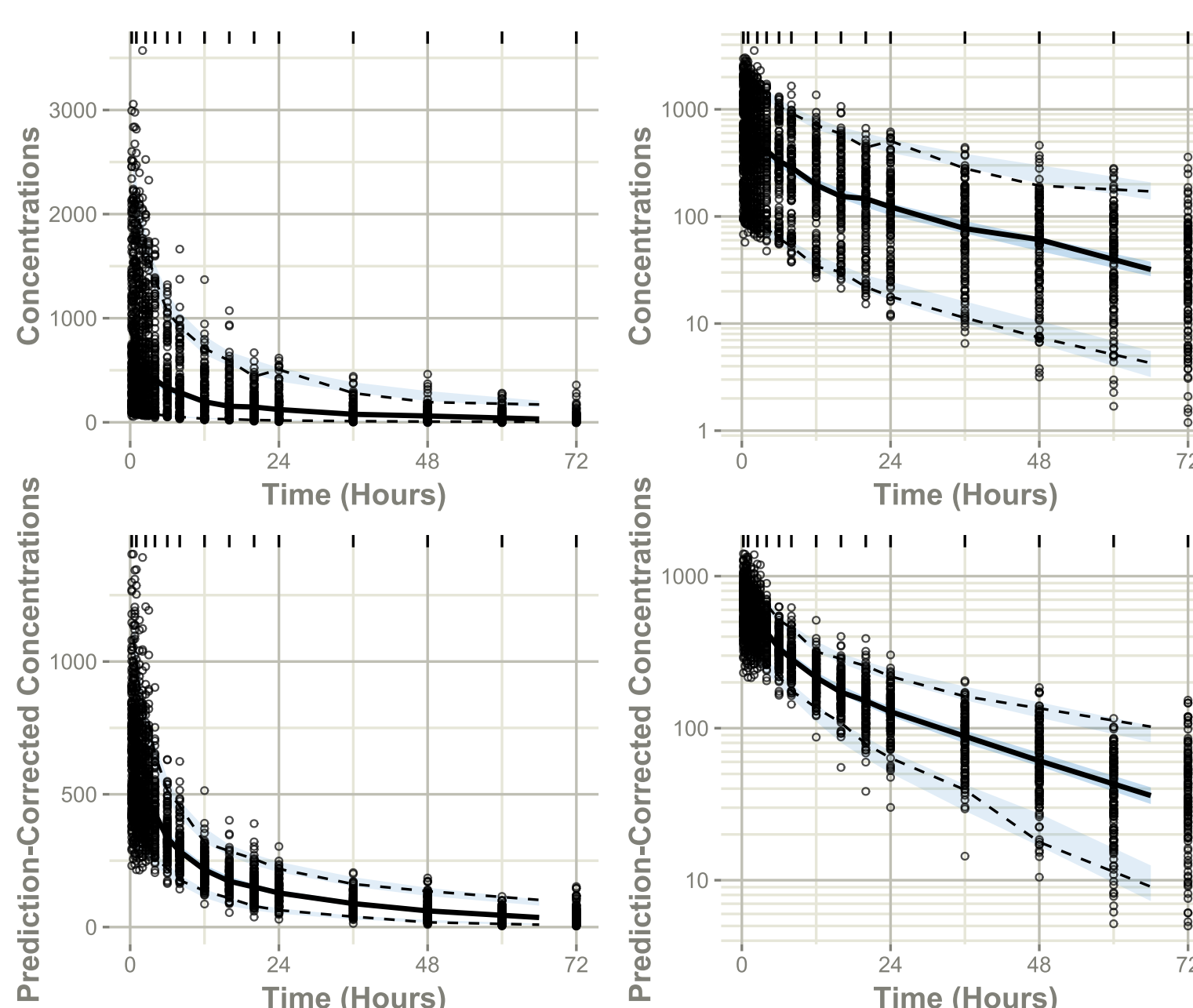
Qualified: population, individual and residual differences are small



Simulate Trials with Uncertainty & Derived Parameters

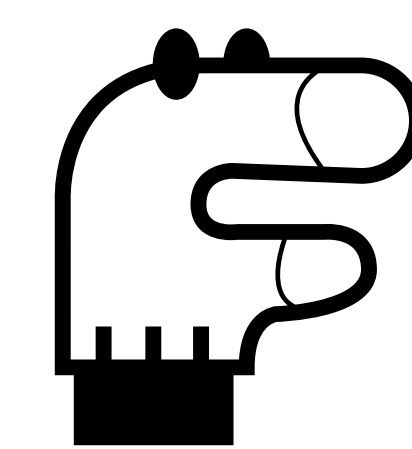


Create VPC with nlmixr2::vpcPlot() and docx/ppt with nlmixr2report::report_fit()

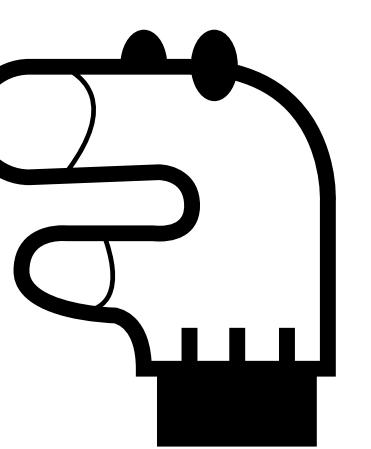


Convert to Monolix to NONMEM or add CWRES to Monolix fit

I have a model in Monolix I need to convert to NONMEM...



Try monolix2rx / babelmixr2. It calculates CWRES too!



Authors

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Sock Puppet from Myles McCoy from the Noun Project