MODELING
WITHOUT BORDERS
ACoP10

Tutorial 3: Pharmacometrics Goes Open-Source

Chairs:
Mirjam Trame (Novartis)
Nahor Haddish-Berhane (Janssen)

A completely open-source pharmacometrics tool set: Moving from vision to reality with R, mrgsolve and Stan/Torsten

Marc Gastonguay (MetrumRG), Bill Gillespie (MetrumRG)

Orlando, FL

October 20 – 23, 2019

Free Software?

“***Free software*** is a matter of liberty, not price. To understand the concept, you should think of ***free*** as in ***free speech***, not as in ***free beer***.”

- Richard M. Stallman

Free Software, Free Society:
Selected Essays of Richard M. Stallman

1983 - GNU (GNU’s Not UNIX) project
1989 - GPL (General Public License), copyleft

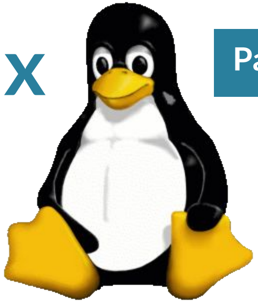
Introduction by Lawrence Lessig

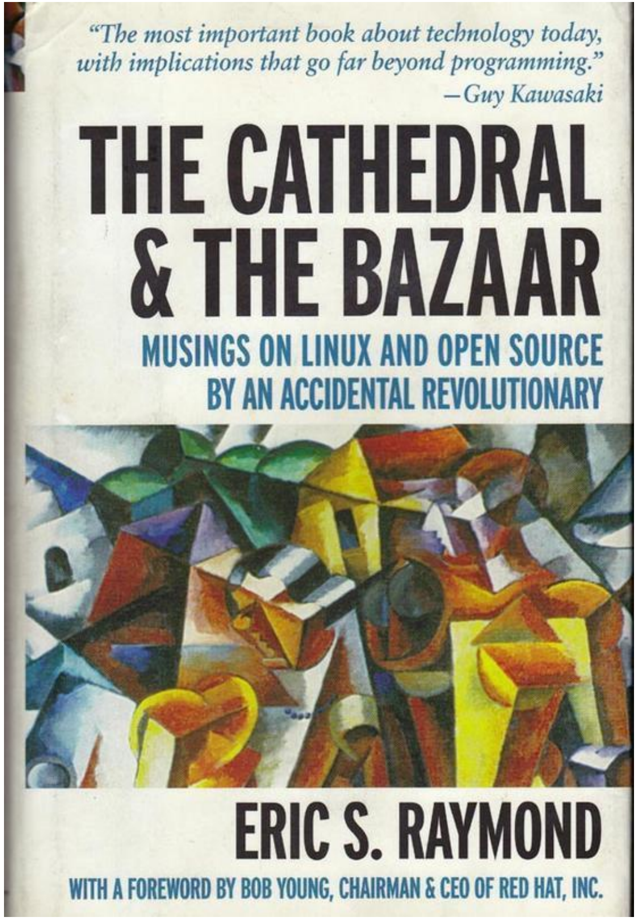
Edited by Joshua Gay

GNU Press
www.gnupress.org
Free Software Foundation
Boston, MA USA

2002, Free Software Foundation, Inc.

Linux





"The most important book about technology today, with implications that go far beyond programming."
—Guy Kawasaki

THE CATHEDRAL & THE BAZAAR

MUSINGS ON LINUX AND OPEN SOURCE BY AN ACCIDENTAL REVOLUTIONARY

ERIC S. RAYMOND

WITH A FOREWORD BY BOB YOUNG, CHAIRMAN & CEO OF RED HAT, INC.

The Cathedral

- Source code is available at each software release, but between-release code is restricted to an exclusive group of software developers (e.g. GNU Emacs and GCC).

The Bazaar

- Source code is developed over the internet in view of the public. Linus Torvalds, leader of the Linux kernel project, considered the inventor of this process.

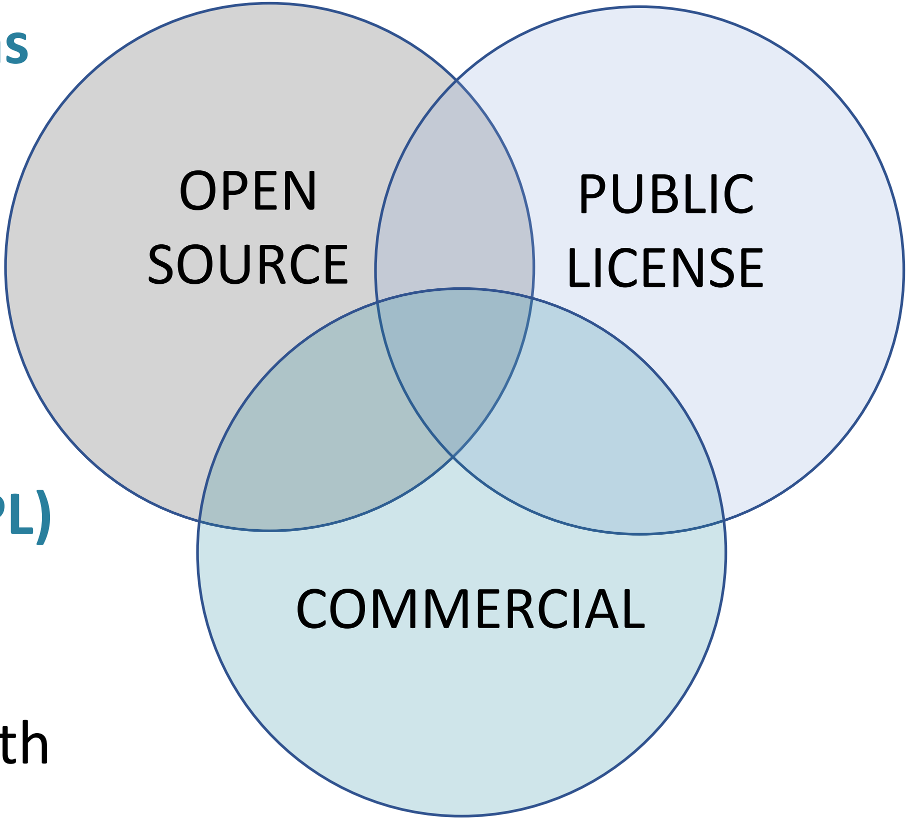
Source Code and Licensing Matter

Commercial software distributed as Open Source code

- Intellectual and practical value for end users
- Limited liberty

Open Source & Public License (OSPL)

- Extends the value across entire community and future tools
- Fosters liberty, creativity, growth



Factors Driving OSPL Software

- Community needs (features, urgency, direction) not met by commercial developers

- Commercial license limits freedom:

“Freedom to use, study, distribute, and modify software” – RMS

- Full transparency and community involvement leads to more useful software

- OSPL fosters growth of science & technology

Open Source Software Quality

- Professional and Regulatory Standards
  - Software Development Life Cycle (SDLC)
  - Quality documentation

- Full transparency to community (e.g. the Bazaar)

“Given enough eyeballs, all bugs are shallow.” - E.S. Raymond

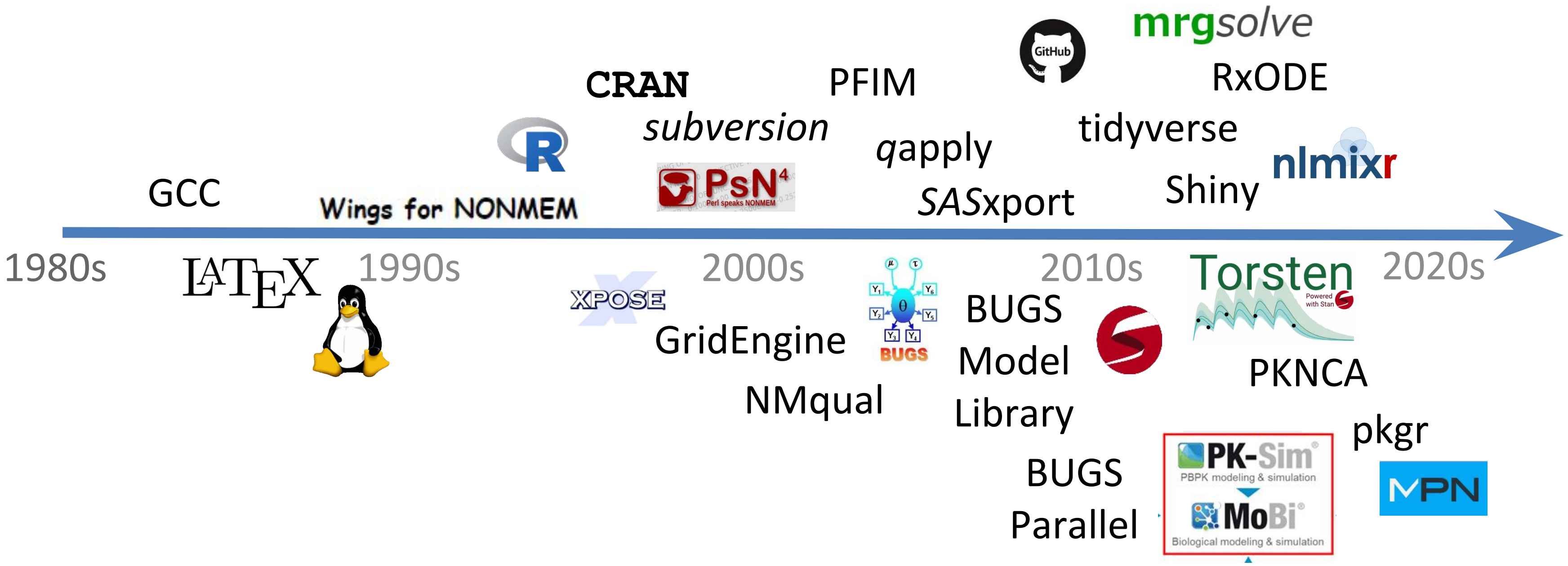
“In the open-source software world, bug reports are welcome.” – A. Gelman

Software Development Life Cycle

https://www.digite.com/blog/waterfall-to-agile-with-kanban/

Open SDLC - https://github.com/metrumresearchgroup/open-sdlc

OSPL Software in Pharmacometrics



1980s

GCC

LATEX

1990s

Wings for NONMEM

R

CRAN

XPOSE

subversion

PsN4
Perl speaks NONMEM

2000s

GridEngine

NMqual

PFIM

BUGS

qapply

SASxport

BUGS Model Library

BUGS Parallel

GitHub

2010s

tidyverse

Shiny

mrgsolve

RxODE

nlmixr

Torsten
Powered with Stan

PKNCA

PK-Sim
PBPK modeling & simulation

MoBi
Biological modeling & simulation

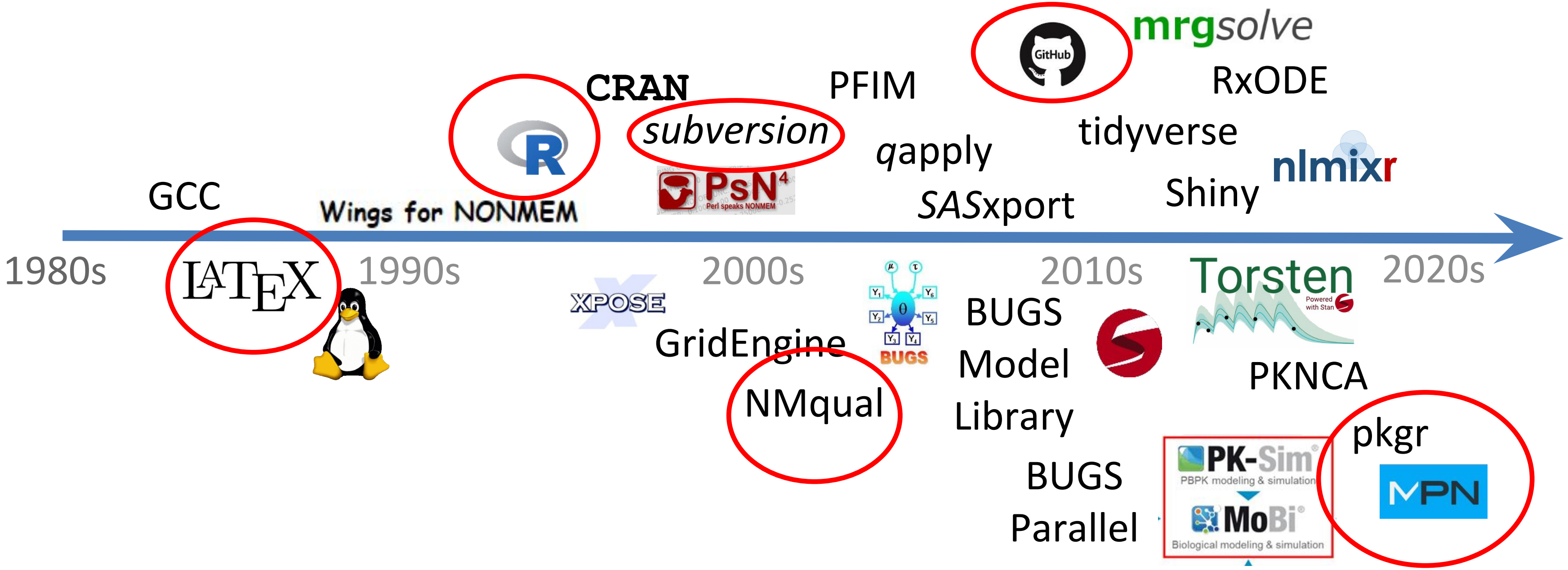
pkgr

MPN

2020s

Adapted from: Brian Corrigan, ACoP 2016.
Display may not be inclusive of all open source, public license software used in pharmacometrics.
Suggestions for additions welcome. Send software name, url, and license type to marcg@metrumrg.com.

OSPL Software: Reproducible Research



1980s

GCC

LaTeX

1990s

Wings for NONMEM

R

CRAN

subversion

PsN4 Perl speaks NONMEM

XPOSE

2000s

GridEngine

NMqual

PFIM

qapply

*SAS*xport

BUGS

BUGS Model Library

BUGS Parallel

GitHub

2010s

mrgsolve

RxODE

tidyverse

Shiny

nlmixr

Torsten Powered with Stan

PKNCA

PK-Sim PBPK modeling & simulation

MoBi Biological modeling & simulation

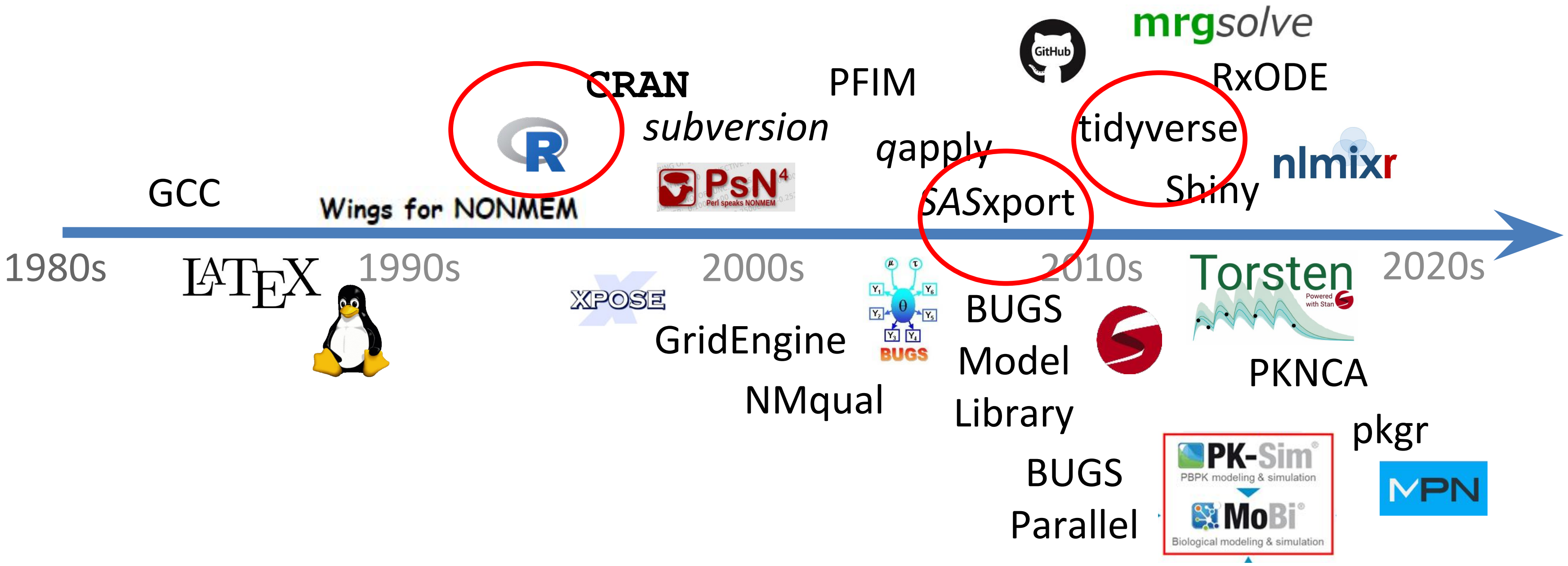
2020s

pkgr

MPN

Adapted from: Brian Corrigan, ACoP 2016.
Display may not be inclusive of all open source, public license software used in pharmacometrics.
Suggestions for additions welcome. Send software name, url, and license type to marcg@metrumrg.com.

OSPL Software: Data Assembly



1980s

GCC

LaTeX

Wings for NONMEM

1990s

R

CRAN

XPOSE

subversion

PsN4 Perl speaks NONMEM

2000s

PFIM

GridEngine

NMqual

qapply

SASxport

BUGS

BUGS Model Library

BUGS Parallel

GitHub

tidyverse

Shiny

2010s

mrgsolve

RxODE

nlmixr

Torsten Powered with Stan

PKNCA

PK-Sim PBPK modeling & simulation

MoBi Biological modeling & simulation

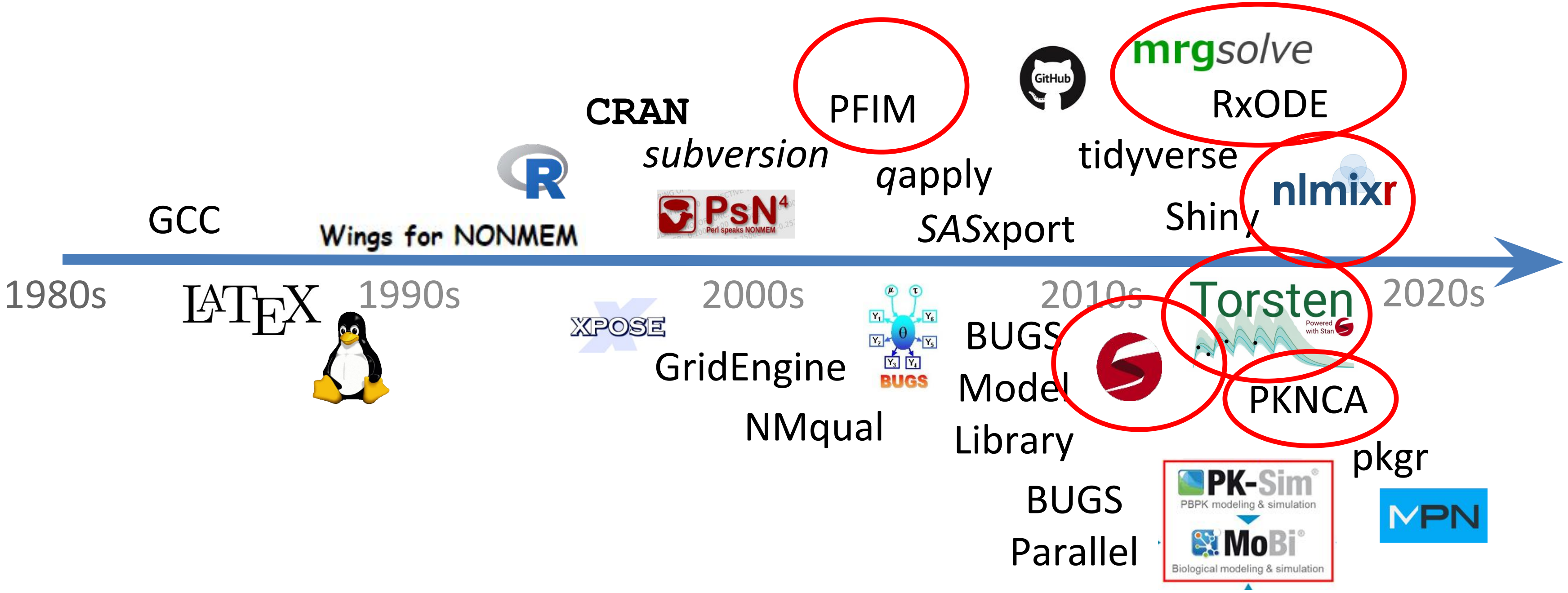
pkgr

MPN

2020s

Adapted from: Brian Corrigan, ACoP 2016.
Display may not be inclusive of all open source, public license software used in pharmacometrics.
Suggestions for additions welcome. Send software name, url, and license type to marcg@metrumrg.com.

OSPL Software: Analysis, Modeling, Simulation



1980s

GCC

LATEX

Wings for NONMEM

1990s

R

XPOSE

CRAN

subversion

PsN4 Perl speaks NONMEM

2000s

GridEngine

NMqual

PFIM

qapply

BUGS

SASxport

BUGS Model Library

BUGS Parallel

GitHub

2010s

tidyverse

Shiny

mrgsolve

RxODE

nlmixr

Torsten Powered with Stan

PKNCA

PK-Sim PBPK modeling & simulation

MoBi Biological modeling & simulation

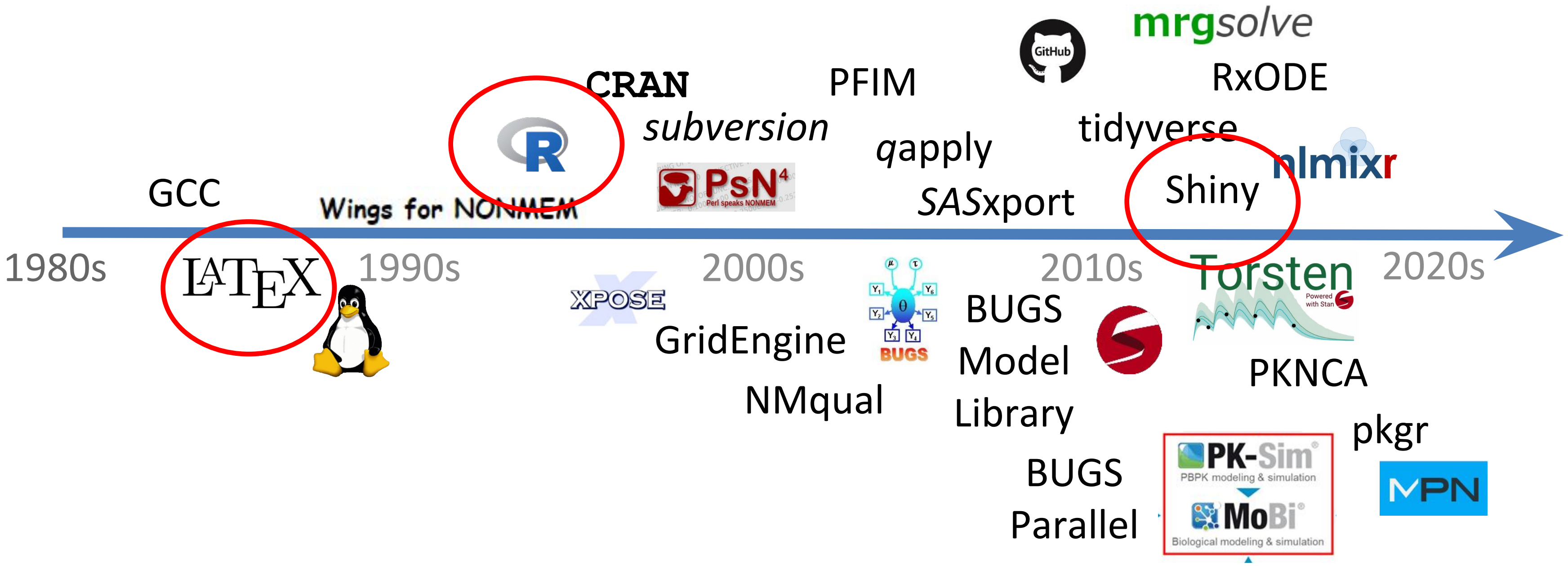
2020s

pkgr

MPN

Adapted from: Brian Corrigan, ACoP 2016.
Display may not be inclusive of all open source, public license software used in pharmacometrics.
Suggestions for additions welcome. Send software name, url, and license type to marcg@metrumrg.com.

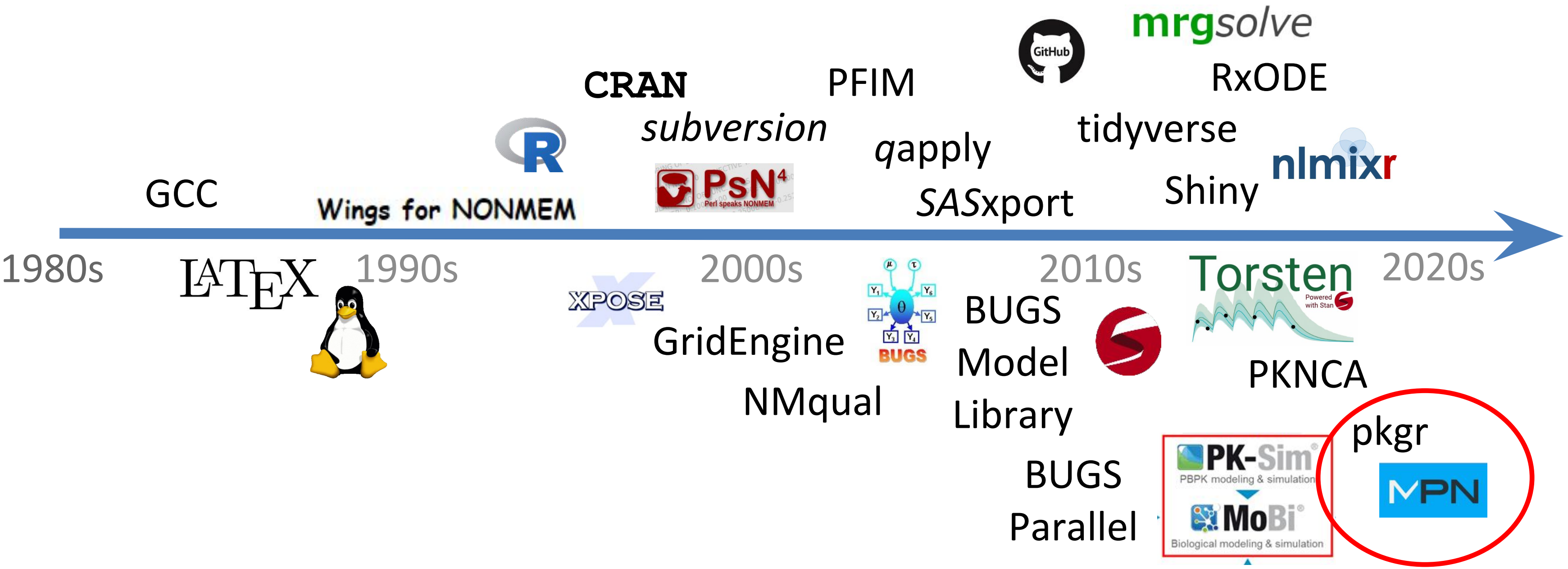
OSPL Software: Sharing Results and Reporting



1980s
GCC
LaTeX
1990s
Wings for NONMEM
R
CRAN
subversion
PsN4 Perl speaks NONMEM
XPOSE
2000s
GridEngine
NMqual
PFIM
qapply
SASxport
BUGS
BUGS Model Library
BUGS Parallel
GitHub
tidyverse
Shiny
2010s
mrgsolve
RxODE
nlmixr
Torsten Powered with Stan
PKNCA
PK-Sim PBPK modeling & simulation
MoBi Biological modeling & simulation
pkgr
MPN
2020s

Adapted from: Brian Corrigan, ACoP 2016.
Display may not be inclusive of all open source, public license software used in pharmacometrics.
Suggestions for additions welcome. Send software name, url, and license type to marcg@metrumrg.com.

OSPL Software: Package Management



1980s

GCC

LaTeX

1990s

Wings for NONMEM

R

CRAN

subversion

PsN4
Perl speaks NONMEM

XPOSE

2000s

GridEngine

NMqual

PFIM

qapply

SASxport

BUGS

BUGS
Model
Library

BUGS
Parallel

GitHub

tidyverse

Shiny

mrgsolve

RxODE

nlmixr

2010s

Torsten
Powered with Stan

PKNCA

PK-Sim
PBPK modeling & simulation

MoBi
Biological modeling & simulation

2020s

pkgr

MPN

Adapted from: Brian Corrigan, ACoP 2016.
Display may not be inclusive of all open source, public license software used in pharmacometrics.
Suggestions for additions welcome. Send software name, url, and license type to marcg@metrumrg.com.

Holistic Package Management for Individuals and Enterprise

metworx
an innovation by METRUM RESEARCH GROUP

pkgr

- Fast, auditable, consistent package installation across all platforms
- Compatible with MPN, Rstudio package manager, CRAN, and others.

https://github.com/metrumresearchgroup/pkgr

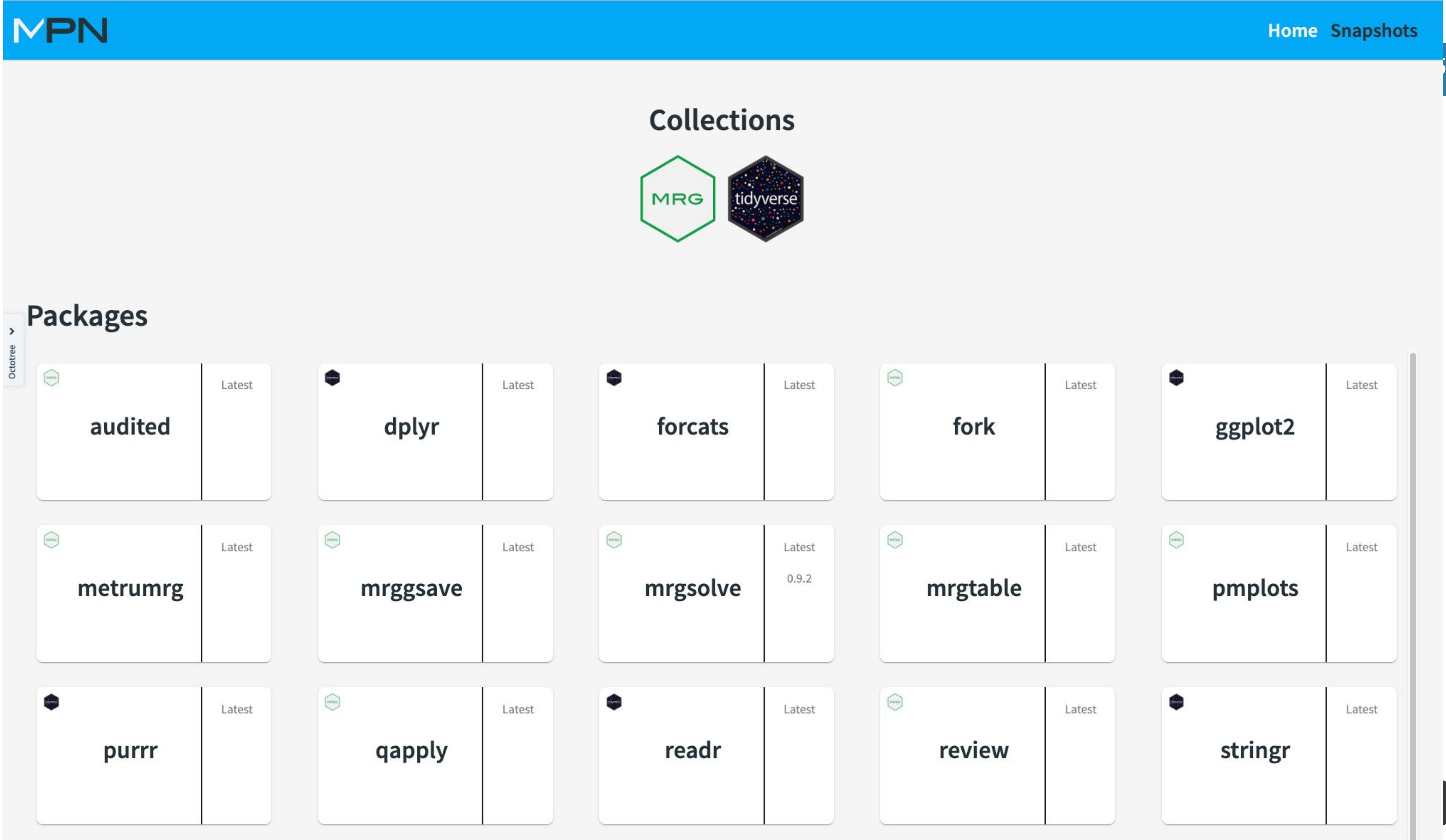
https://metrumrg.com/wp-content/uploads/Pubs/Moving-Fast-without-Breaking-Things.pdf

https://metrumrg.com/wp-content/uploads/2019/08/R-in-pharma-2019-shared.pdf

MPN

(metrum package network)

- Open repository of ~750 packages specific to PMX from CRAN/github/MetrumRG
- Compatibility and stability tested
- Binaries for Windows and MacOS across multiple versions of R
- Immutable repository
- Custom documentation
- Freely available and accessible to all.
- IQ/OQ/PQ documentation, support, and additional package requests available to subscribers



Collections

Packages

audited — Latest
dplyr — Latest
forcats — Latest
fork — Latest
ggplot2 — Latest
metrumrg — Latest
mrggsave — Latest
mrgsolve — Latest 0.9.2
mrgtable — Latest
pmplots — Latest
purrr — Latest
qapply — Latest
readr — Latest
review — Latest
stringr — Latest

Development Plans: pkgr & MPN

pkgr

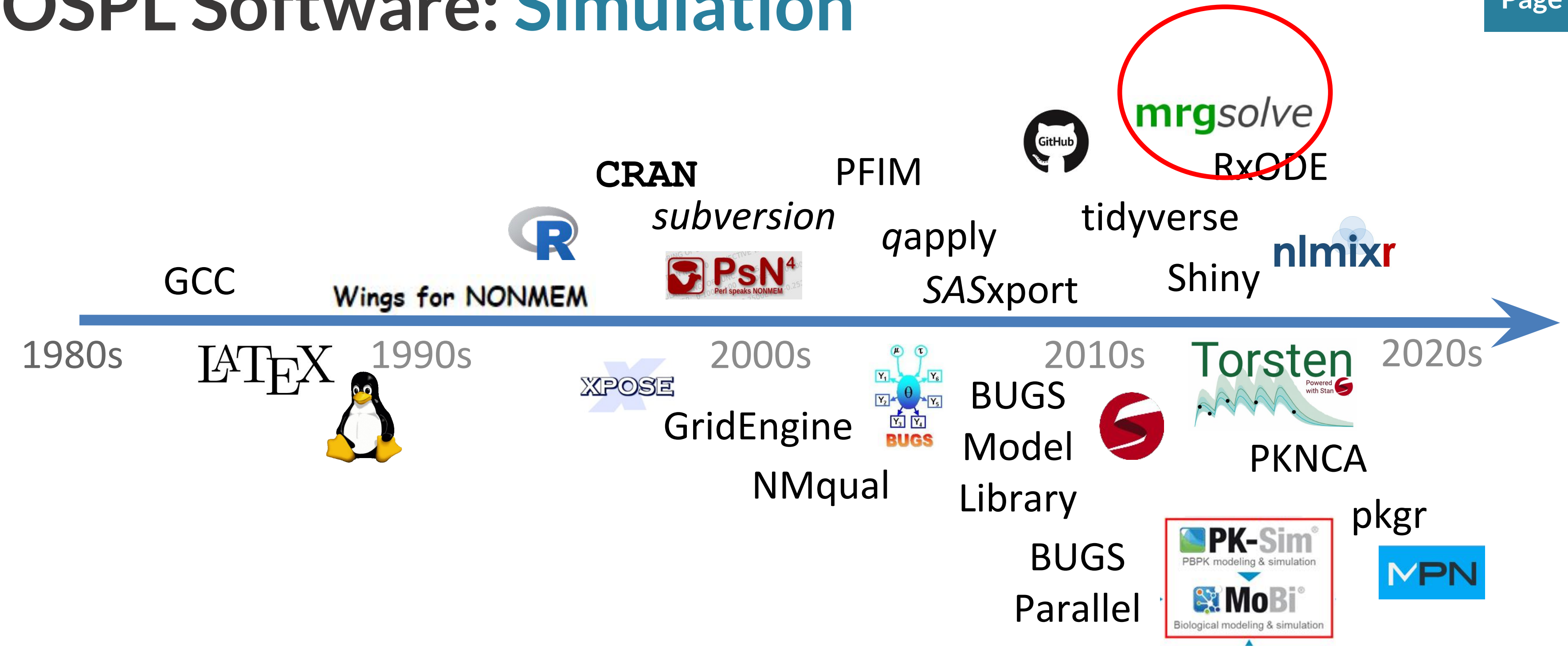
- Ongoing development
- Documentation, vignettes
- Try it, track issues.

MPN

(metrum package network)

- Public release by end Oct. 2019
- Continued organic addition of new packages from a variety of sources
- Driven by community requests
- Enterprise solution also available

OSPL Software: Simulation



1980s

GCC

LaTeX

1990s

Wings for NONMEM

R

CRAN

subversion

PsN^4 Perl speaks NONMEM

XPOSE

2000s

GridEngine

NMqual

PFIM

qapply

*SAS*xport

BUGS

BUGS Model Library

BUGS Parallel

GitHub

tidyverse

Shiny

2010s

mrgsolve

RxODE

nlmixr

Torsten Powered with Stan

PKNCA

pkgr

PK-Sim PBPK modeling & simulation

MoBi Biological modeling & simulation

MPN

2020s

Adapted from: Brian Corrigan, ACoP 2016.
Display may not be inclusive of all open source, public license software used in pharmacometrics.
Suggestions for additions welcome. Send software name, url, and license type to marcg@metrumrg.com.

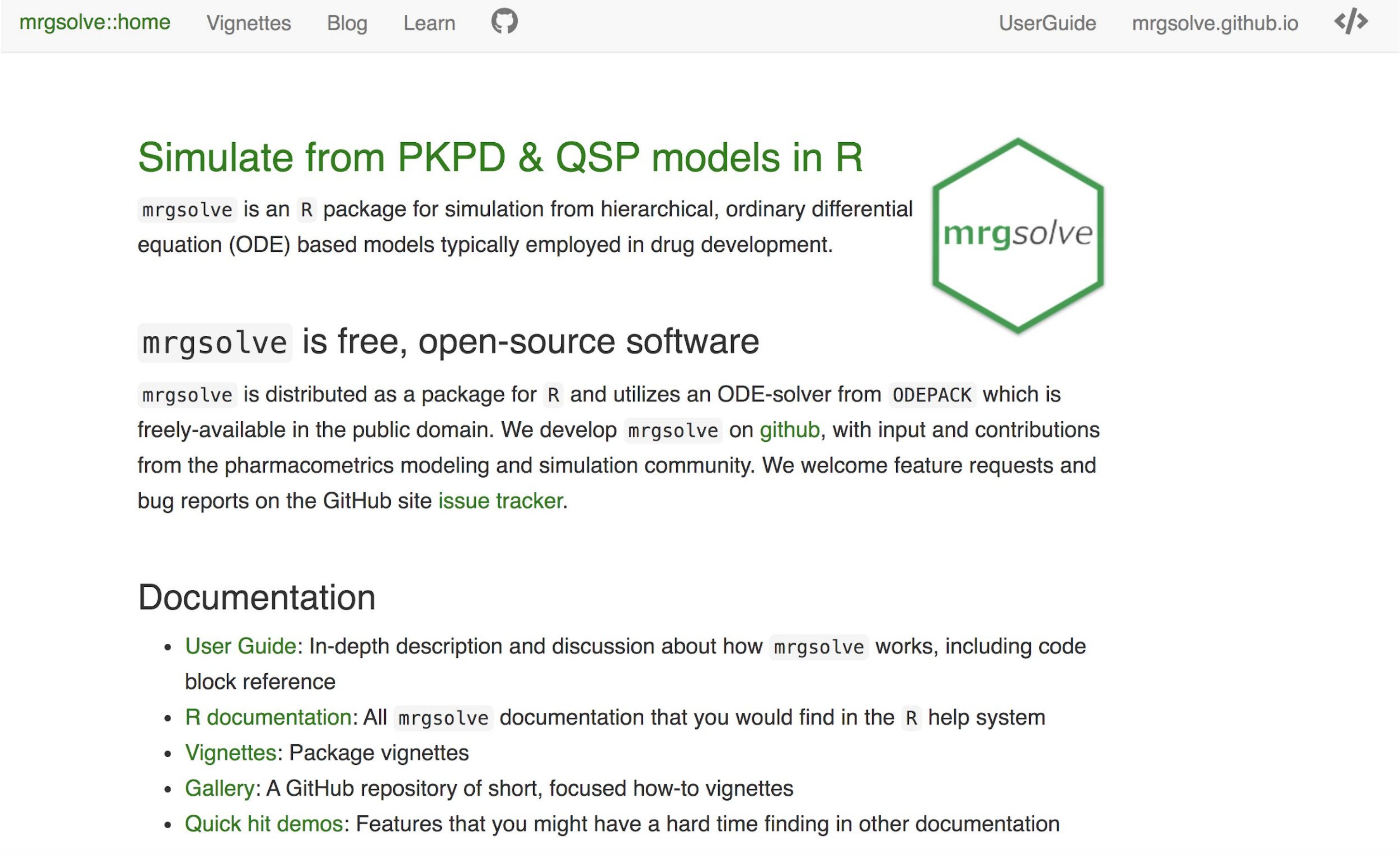
About mrgsolve

- R package for simulation from ODE-based models
  - Free, OpenSource, Public License
  - GitHub, CRAN
- Language
  - Model written in C++ inside model specification format
  - General purpose solver: C++ translation of ODEPACK DLSODA
  - Simulation workflow and post-processing with R
- Hierarchical (population) simulation
  - ID, ETA, EPS
- Integrated PK functionality
  - Bolus, infusion, F, ALAG, SS etc handled under the hood
  - 1- and 2-compartment models in closed form
- Extensible using R, C++, Rcpp, boost, RcppArmadillo
- R in its natural habitat

mrgsolve started as QSP modeling tool

- Motivation: large bone/mineral homeostasis model (CaBone)
- History using
  - Berleley Madonna
  - WinBUGS
  - NONMEM (attempted)
- 2010: write R front end to deSolve
- 2012: write C++ interface to ODEPACK DLSODA
- Develop dosing / event capability
- More recently, expose functionality provided by
  - Rcpp - vectors, matrices, functions, environments, random numbers
  - boost - numerical tools called by model C++ code
  - users' own C++ code (classes, functions, other data structures)
- Translator from SBML to mrgsolve using R bindings to libSBML

mrgsolve.github.io



Simulate from PKPD & QSP models in R

`mrgsolve` is an `R` package for simulation from hierarchical, ordinary differential equation (ODE) based models typically employed in drug development.

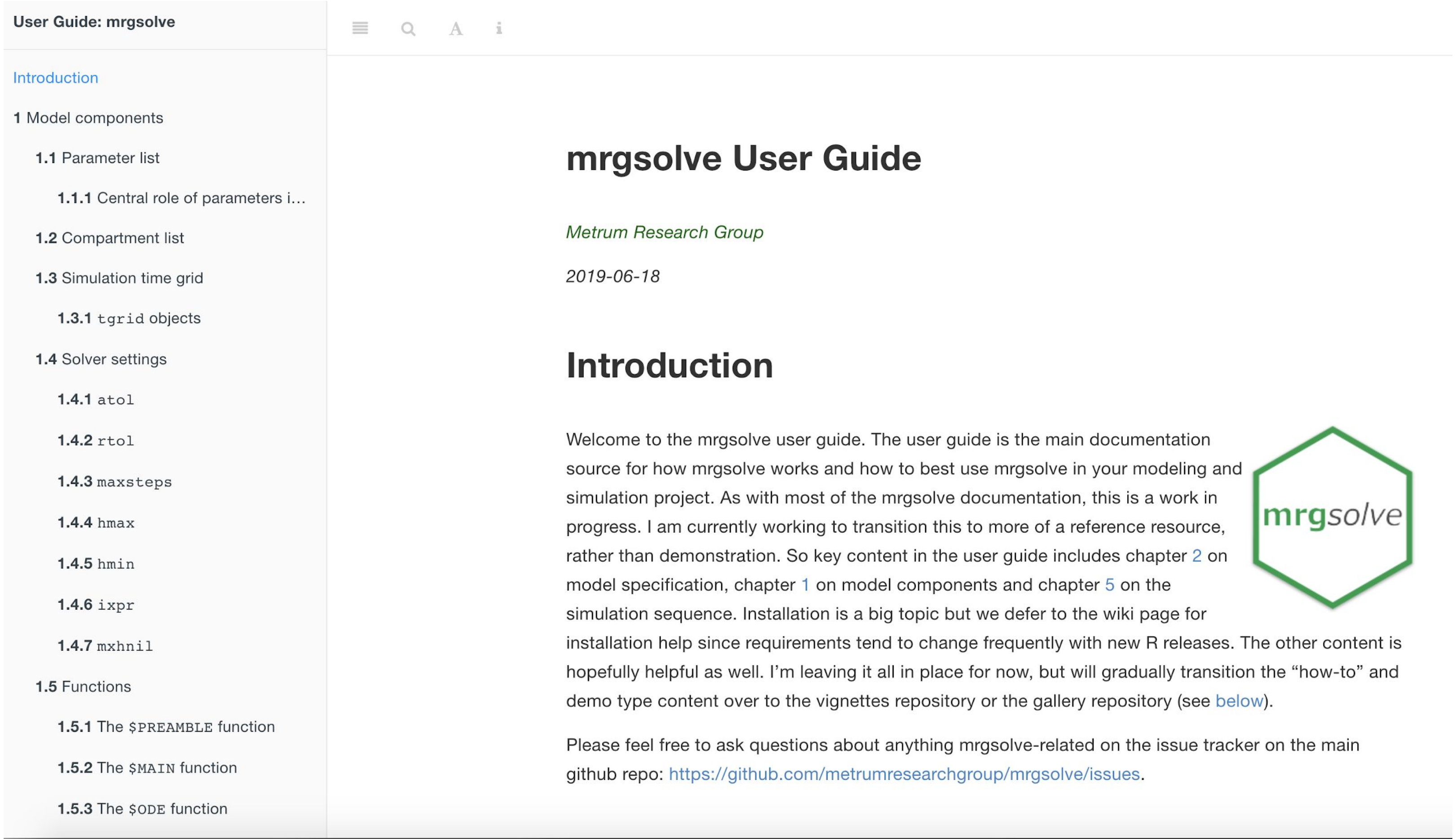
`mrgsolve` is free, open-source software

`mrgsolve` is distributed as a package for `R` and utilizes an ODE-solver from `ODEPACK` which is freely-available in the public domain. We develop `mrgsolve` on github, with input and contributions from the pharmacometrics modeling and simulation community. We welcome feature requests and bug reports on the GitHub site issue tracker.

Documentation

- User Guide: In-depth description and discussion about how `mrgsolve` works, including code block reference
- R documentation: All `mrgsolve` documentation that you would find in the `R` help system
- Vignettes: Package vignettes
- Gallery: A GitHub repository of short, focused how-to vignettes
- Quick hit demos: Features that you might have a hard time finding in other documentation

mrgsolve.github.io/user_guide



User Guide: mrgsolve

mrgsolve User Guide

Metrum Research Group

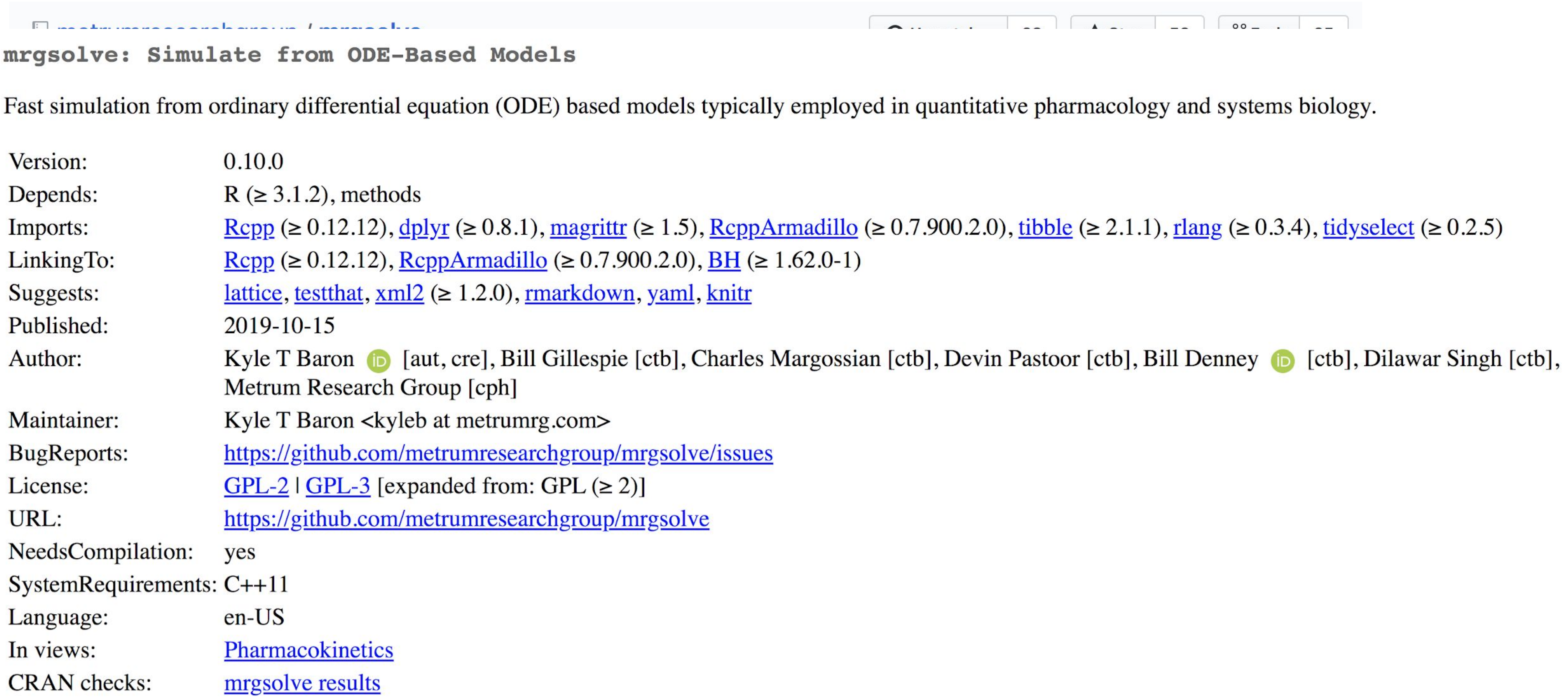
2019-06-18

Introduction

Welcome to the mrgsolve user guide. The user guide is the main documentation source for how mrgsolve works and how to best use mrgsolve in your modeling and simulation project. As with most of the mrgsolve documentation, this is a work in progress. I am currently working to transition this to more of a reference resource, rather than demonstration. So key content in the user guide includes chapter 2 on model specification, chapter 1 on model components and chapter 5 on the simulation sequence. Installation is a big topic but we defer to the wiki page for installation help since requirements tend to change frequently with new R releases. The other content is hopefully helpful as well. I'm leaving it all in place for now, but will gradually transition the "how-to" and demo type content over to the vignettes repository or the gallery repository (see below).

Please feel free to ask questions about anything mrgsolve-related on the issue tracker on the main github repo: https://github.com/metrumresearchgroup/mrgsolve/issues.

mrgsolve on GitHub and CRAN



mrgsolve: Simulate from ODE-Based Models

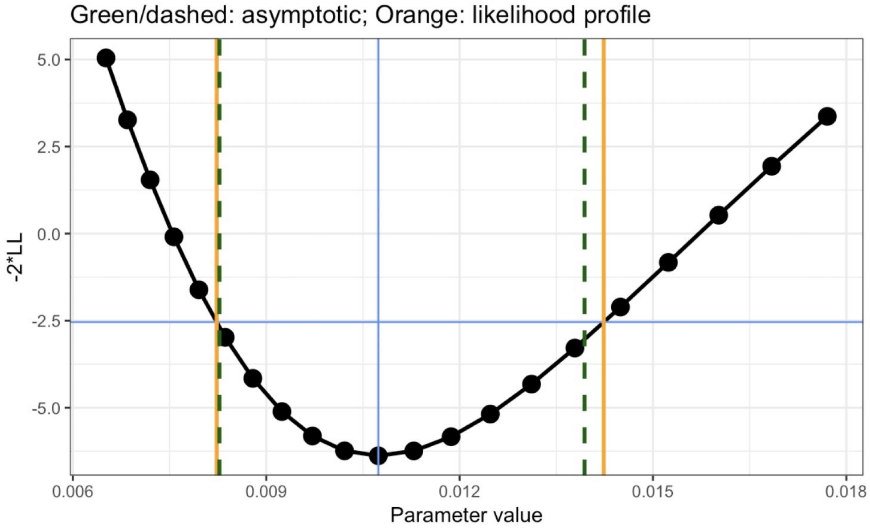
Fast simulation from ordinary differential equation (ODE) based models typically employed in quantitative pharmacology and systems biology.

Version:	0.10.0
Depends:	R (≥ 3.1.2), methods
Imports:	Rcpp (≥ 0.12.12), dplyr (≥ 0.8.1), magrittr (≥ 1.5), RcppArmadillo (≥ 0.7.900.2.0), tibble (≥ 2.1.1), rlang (≥ 0.3.4), tidyselect (≥ 0.2.5)
LinkingTo:	Rcpp (≥ 0.12.12), RcppArmadillo (≥ 0.7.900.2.0), BH (≥ 1.62.0-1)
Suggests:	lattice, testthat, xml2 (≥ 1.2.0), rmarkdown, yaml, knitr
Published:	2019-10-15
Author:	Kyle T Baron [aut, cre], Bill Gillespie [ctb], Charles Margossian [ctb], Devin Pastoor [ctb], Bill Denney [ctb], Dilawar Singh [ctb], Metrum Research Group [cph]
Maintainer:	Kyle T Baron <kyleb at metrumrg.com>
BugReports:	https://github.com/metrumresearchgroup/mrgsolve/issues
License:	GPL-2 | GPL-3 [expanded from: GPL (≥ 2)]
URL:	https://github.com/metrumresearchgroup/mrgsolve
NeedsCompilation:	yes
SystemRequirements:	C++11
Language:	en-US
In views:	Pharmacokinetics
CRAN checks:	mrgsolve results

Integrating the R Package mrgsolve With Available Optimization Routines for Parameter Estimation With PK, PK-PD and QSP Models

Where / when

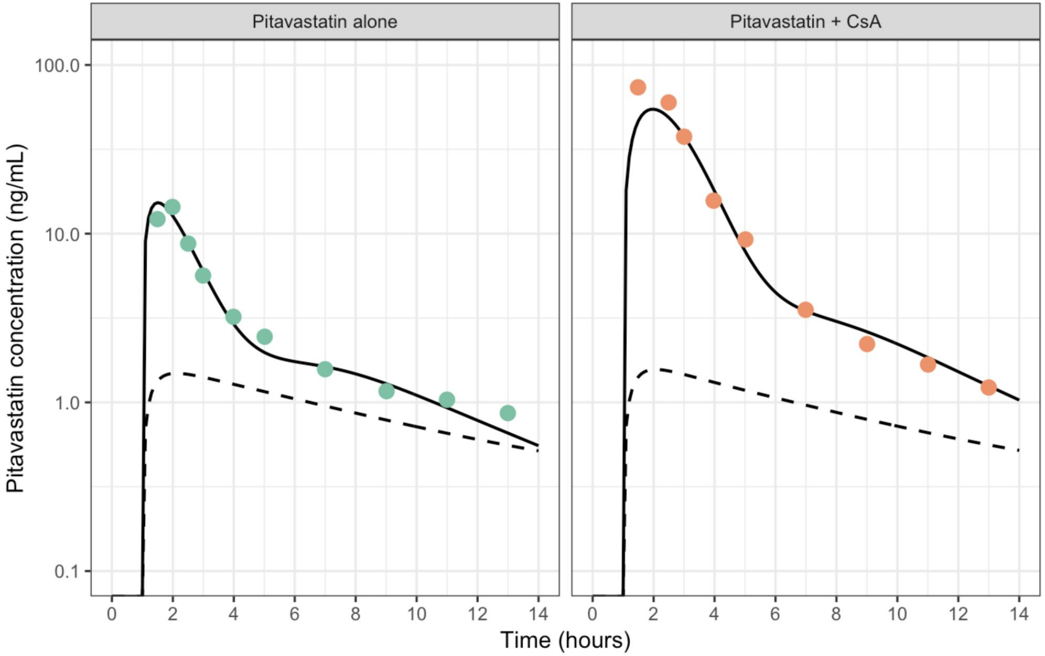
- University at Buffalo
    - 2019 CDSE Days (Buffalo, NY)
    - Wednesday, 10 April 2019 09:00 to 12:00



https://github.com/metrumresearchgroup/ub-cdse-2019

Parameter optimization in PBPK model

Yoshikado T et al. Quantitative Analyses of Hepatic OATP-Mediated Interactions Between Statins and Inhibitors Using PBPK Modeling With a Parameter Optimization Method. Clin Pharmacol Ther. 2016



Nelder-Mead
`stats::optim`

Unconstrained optimization with quadratic approximation
`nloptr::newuoa`

Simulated annealing (SA)
`GenSA`

Differential evolution (DE)
`DEoptim`

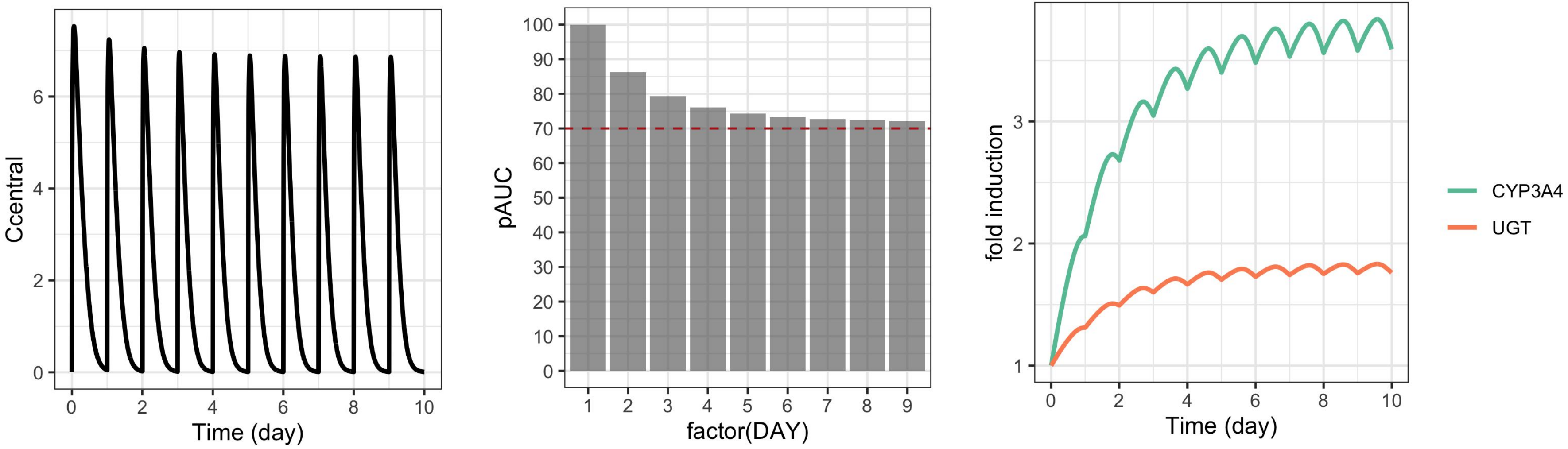
Particle swarm (PSO)
`hydroPSO`

Controlled random search (CRS)
`nloptr::crs2lm`

https://github.com/metrumresearchgroup/pbpk-qsp-mrgsolve

Simulating Rifampin Auto-induction - PBPK

Comprehensive PBPK Model of Rifampicin for Quantitative Prediction of Complex Drug-Drug Interactions: CYP3A/2C9 Induction and OATP Inhibition Effects Asaumi R et al. CPT Pharmacometrics Syst Pharmacol. 2018



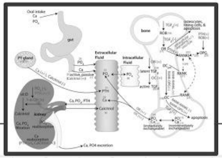
Linzagolix Doses to Control BMD Loss at 6 months

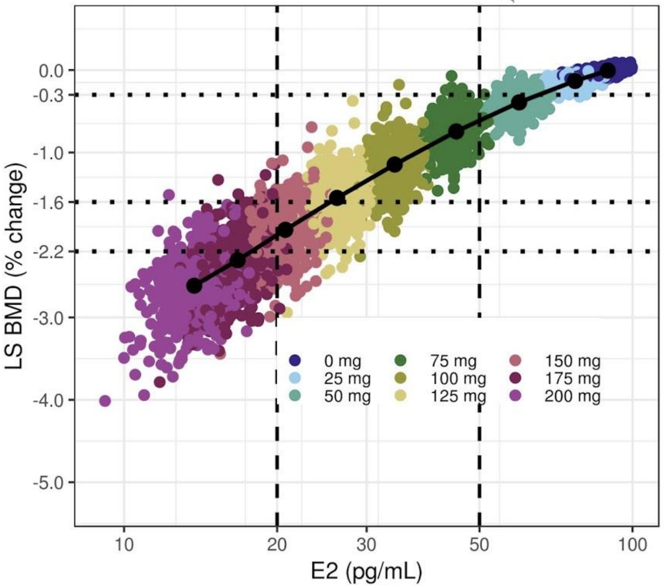
linzagolix dose

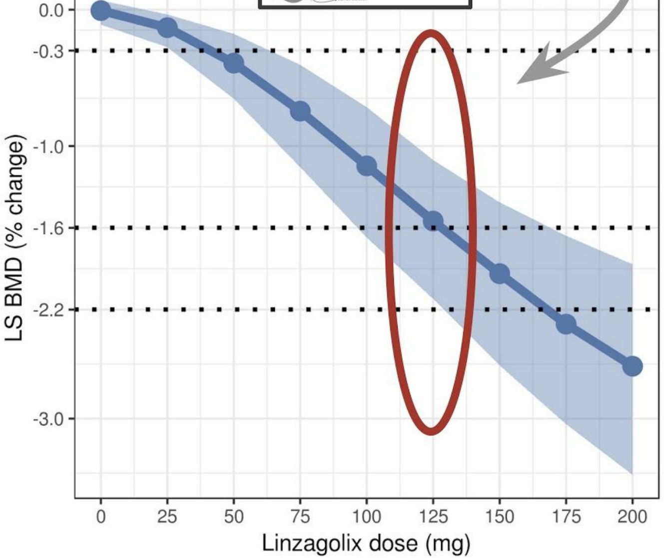
decrease estradiol

possible BMD losses

controlled BMD loss







METRUM RESEARCH GROUP

OBSEVA obstetrics & beyond

Riggs MM, et al. CPT PSP (2012)
PMID: 23887363

npj Systems Biology
and Applications

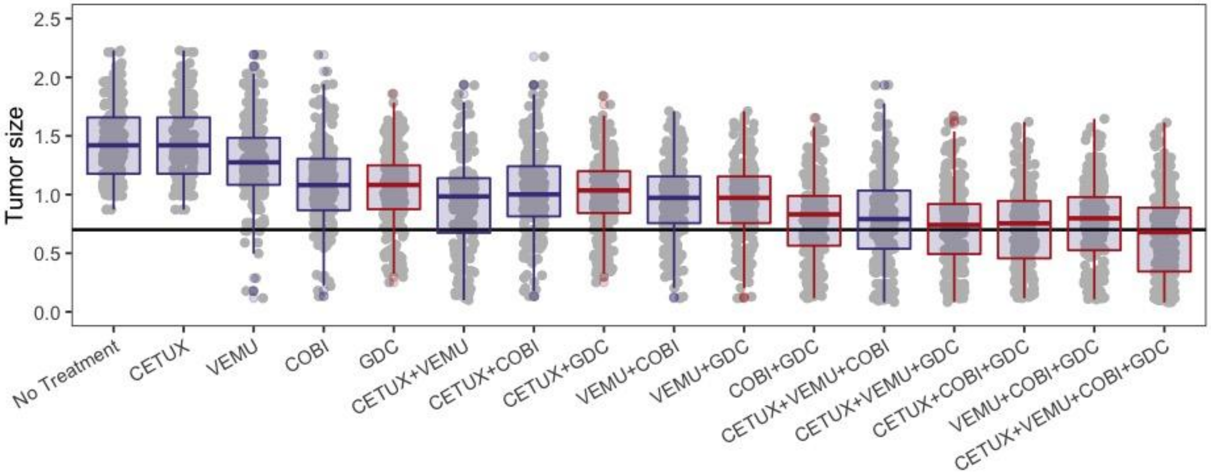
www.nature.com/npjsba

ARTICLE **OPEN**

Clinical responses to ERK inhibition in *BRAF*^{V600E}-mutant colorectal cancer predicted using a computational model

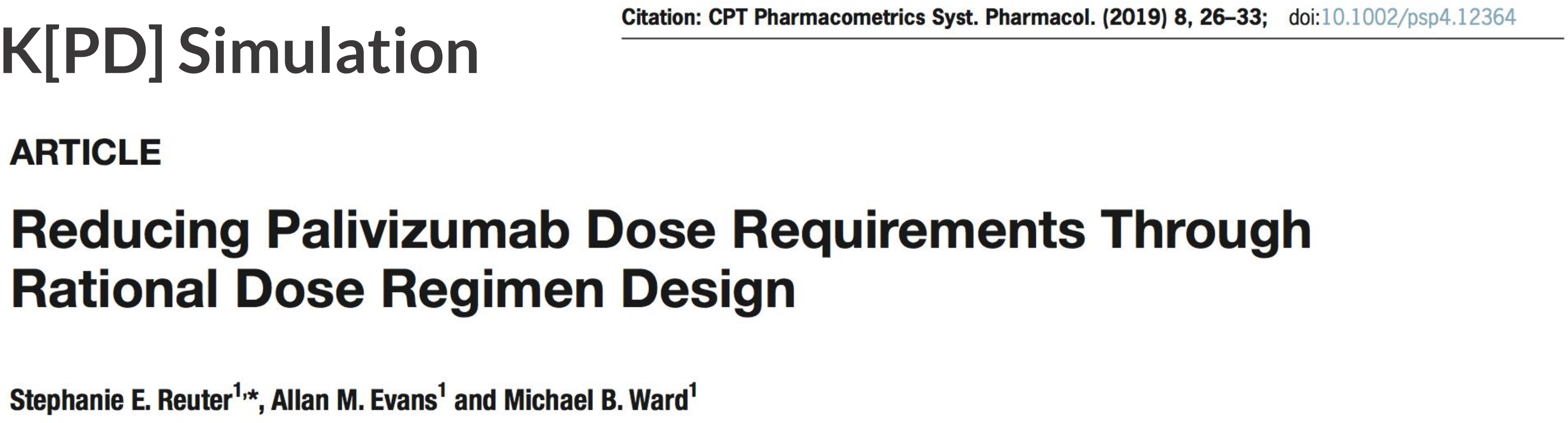
Daniel C. Kirouac[1], Gabriele Schaefer[1], Jocelyn Chan[1], Mark Merchant[1], Christine Orr[1], Shih-Min A. Huang[1], John Moffat[1], Lichuan Liu[1], Kapil Gadkar[1] and Saroja Ramanujan[1]

Note: GDC-0944 +/- cobimetinib



- Translate from SBML
- Simulate from virtual population
- All combinations of 4 different therapeutics

PK[PD] Simulation

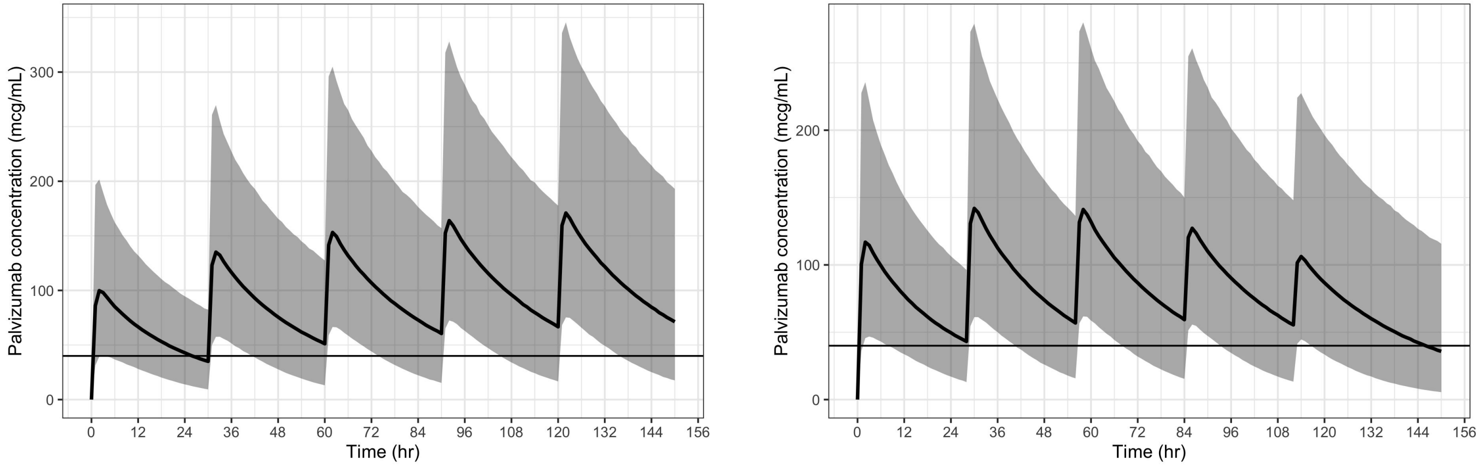


Citation: CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 26–33; doi:10.1002/psp4.12364

ARTICLE

Reducing Palivizumab Dose Requirements Through Rational Dose Regimen Design

Stephanie E. Reuter[1,*], Allan M. Evans[1] and Michael B. Ward[1]

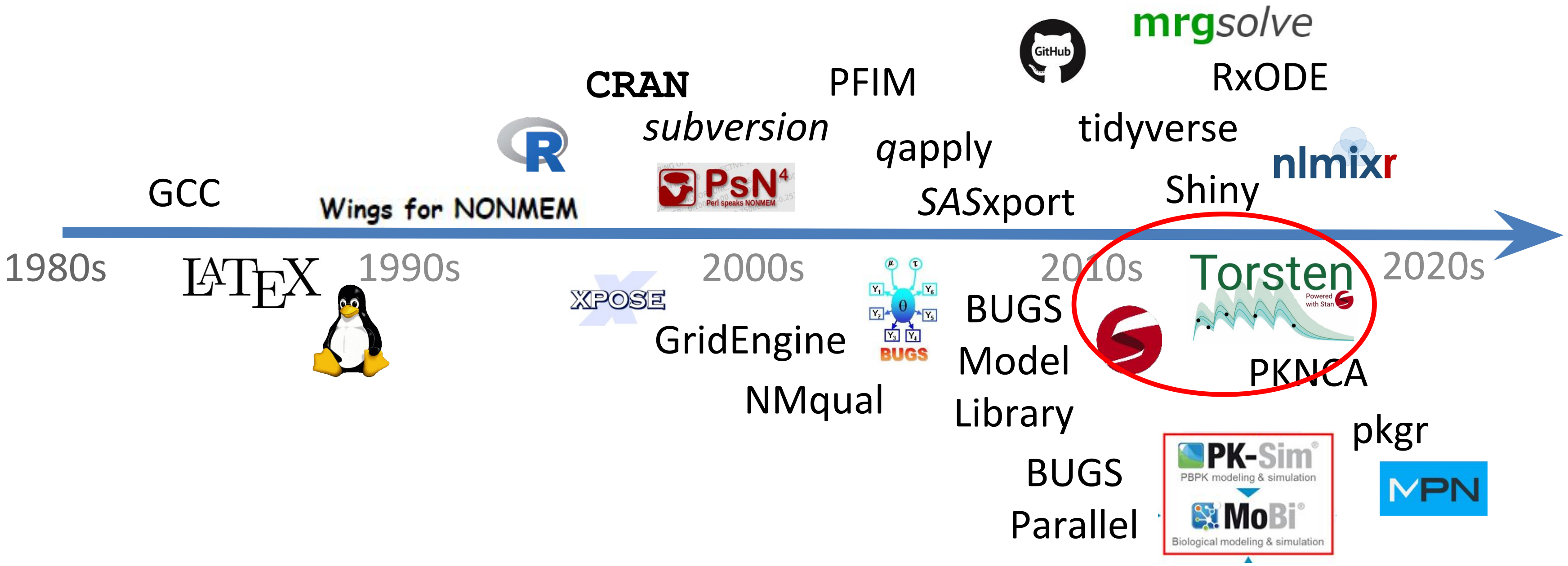


Additional Training Resources: mrgsolve

- Introduction to mrgsolve https://metrumrg.com/course/introduction-mrgsolve-page-workshop-2018/

- PBPK and QSP model implementation and utilization in R https://metrumrg.com/course/pbpk-qsp-model-implementation-utilization-r/

OSPL Software: Bayesian M&S



1980s

GCC

LATEX

1990s

Wings for NONMEM

R

CRAN

subversion

PsN4
Perl speaks NONMEM

XPOSE

2000s

GridEngine

NMqual

PFIM

qapply

*SAS*xport

BUGS

BUGS
Model
Library

GitHub

tidyverse

2010s

BUGS
Parallel

mrgsolve

RxODE

Shiny

nlmixr

Torsten
Powered with Stan

PKNCA

PK-Sim
PBPK modeling & simulation

MoBi
Biological modeling & simulation

pkgr

MPN

2020s

Adapted from: Brian Corrigan, ACoP 2016.
Display may not be inclusive of all open source, public license software used in pharmacometrics.
Suggestions for additions welcome. Send software name, url, and license type to marcg@metrumrg.com.

Why Bayesian?

- Pharmacometricians are often called on to leverage prior knowledge in order to interpret new data and facilitate decision-making in drug development.
  - Qualitative prior knowledge is captured in the mathematical form of a model, i.e., the **likelihood function**.
  - Quantitative prior knowledge may be captured in the form of probability distributions of model parameter values, i.e., **prior distributions.**
- Add **data** and you have all the ingredients of Bayesian data analysis.
- With Bayes Rule and suitable computation tools those components are combined to yield **posterior distributions** of model parameters and predictions.
- Those distributions permit probabilistic inferences directly relevant to decision-making.

Why Bayesian analysis for pharmacometrics applications?

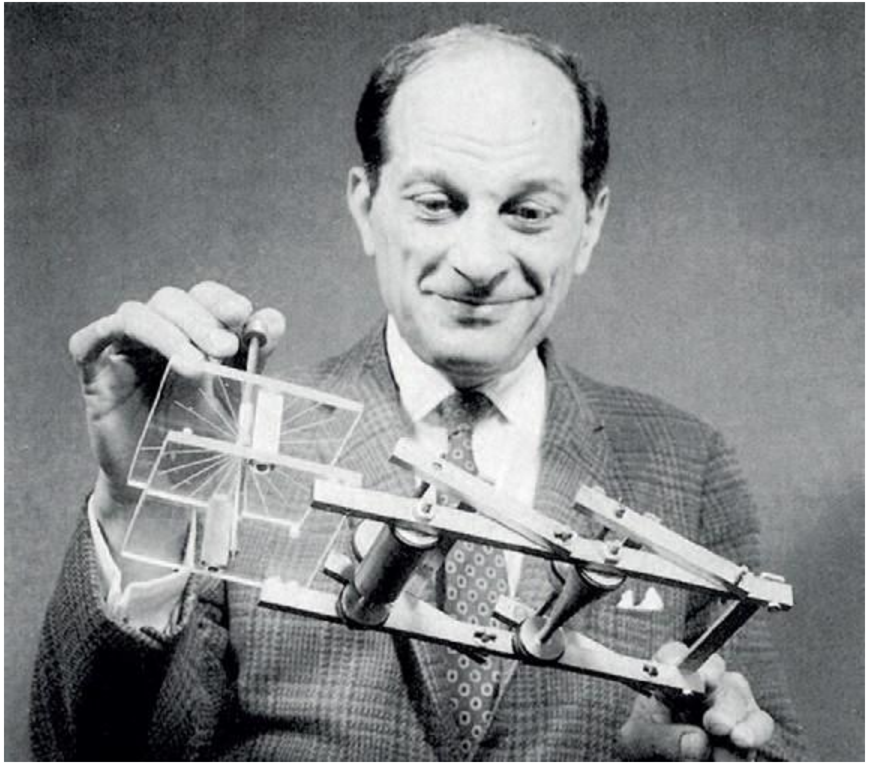
- Decision-making supported by quantitative synthesis of prior knowledge and heterogenous data.
- Calibration (and recalibration) of complex QSP models as new data accumulates.
- Bayesian framework more easily accommodates
    - model complexity, particularly in the stochastic structure of a model,
    - analysis of data from heterogeneous sources.

Stan: What is it?

Stan (http://mc-stan.org/) is a general purpose Bayesian modeling package

- General model specification language
- Primarily uses a Hamiltonian Monte Carlo (HMC) sampler (standard HMC or NUTS (no U-turn sampler)). Other methods include:
  - Optimization for estimation of posterior modes.
  - Variational inference for approximate Bayesian inference.
- Developed by a team headed by Andrew Gelman of Columbia University
- Freely distributed, open source C++ program available with several interfaces: rstan, PyStan, CmdStan, MatlabStan, Stan.jl, StataStan

Stan: Why is it called that?



Stanislaw Ulam, co-inventor of Monte Carlo methods, holding an analog computer known as the FERMIAC that performed a mechanical simulation of random diffusion of neutrons (http://fas.org/sgp/othergov/doe/lanl/pubs/00326866.pdf).

Stan model specification language

Very flexible model specification language

- Imperative language: statements executed in the order in which they are written.
- Computational control structures, e.g., if-then-else, for and while loops
- Large collection of:
    - Operators
    - Built-in functions including ODE solvers
    - Probability distributions
- User-defined functions and distributions

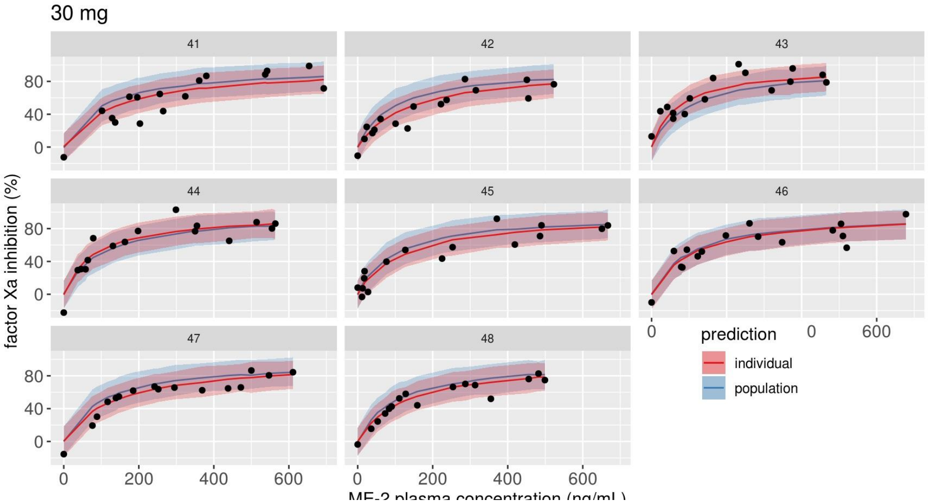
Population E-R models are easy to implement in Stan

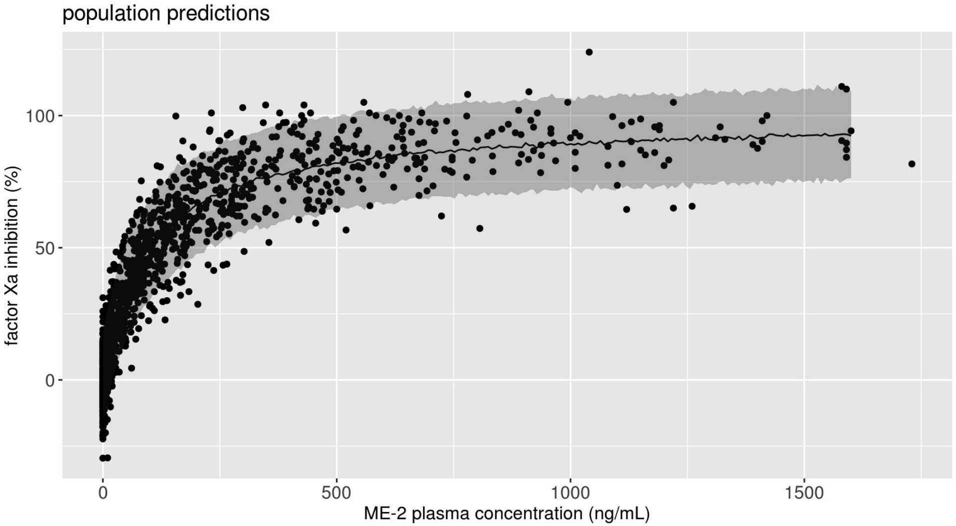
Sigmoid Emax model relating % inhibition of factor Xa activity to ME-2 plasma concentration on the i^{th} occasion in the j^{th} subject:

$$
\begin{aligned}
E_{ij} &\sim N\left(\hat{E}_{ij}, \sigma\right) \\
\hat{E}_{ij} &= \frac{E_{max} c_{ij}^{\gamma}}{EC_{50,j}^{\gamma} + c_{ij}^{\gamma}} \\
\log\left(EC_{50,j}\right) &\sim N\left(\log\left(\widehat{EC_{50}}\right), \omega_{EC_{50}}\right)
\end{aligned}
$$

Some possible weakly informative prior distributions:

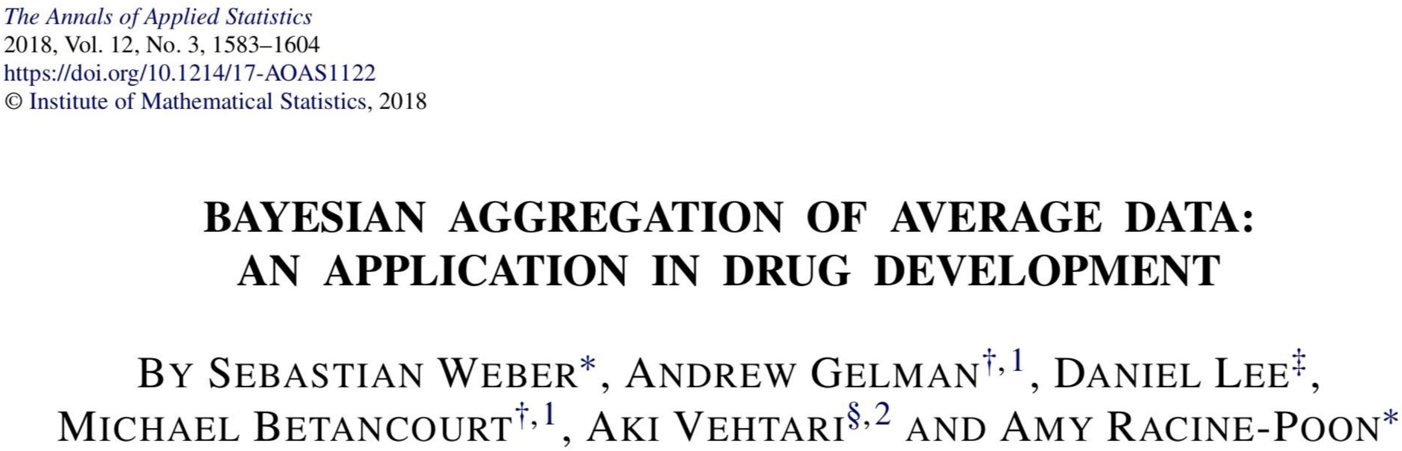
$$
\begin{aligned}
E_{max} &\sim U(0, 100) \quad \widehat{EC_{50}} \sim \text{half-}N(0, 250) \\
\gamma &\sim \text{half-}N(0, 5) \\
\omega_{EC_{50}} &\sim \text{half-Cauchy}(0, 1) \quad \sigma \sim \text{half-Cauchy}(0, 10)
\end{aligned}
$$





Rigorous meta-analysis of combined individual & aggregate data is challenging

- But you can do it in Stan.
- Does not use a linear approximation of the likelihood.
- Example of an approach that cannot be done with our usual PMX platforms.



The Annals of Applied Statistics
2018, Vol. 12, No. 3, 1583–1604
https://doi.org/10.1214/17-AOAS1122

BAYESIAN AGGREGATION OF AVERAGE DATA: AN APPLICATION IN DRUG DEVELOPMENT

BY SEBASTIAN WEBER[*], ANDREW GELMAN[†,1], DANIEL LEE[‡],
MICHAEL BETANCOURT[†,1], AKI VEHTARI[§,2] AND AMY RACINE-POON[*]

Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 635–641; doi:10.1002/

ORIGINAL ARTICLE

A Longitudinal Item Response Theory Model to Characterize Cognition Over Time in Elderly Subjects

Marc Vandemeulebroecke[1]*, Björn Bornkamp[1], Tillmann Krahnke[2], Johanna Mielke[1], Andreas Monsch[3] and Peter Qua

- Implemented in Stan, JAGS, BUGS

> “Run times were similar for Stan and JAGS, but Stan produced more efficient chains: The mean effective sample size across the non subject-specific parameters was 506 for JAGS and 3791 for Stan, based on the 5000 inference samples each.”

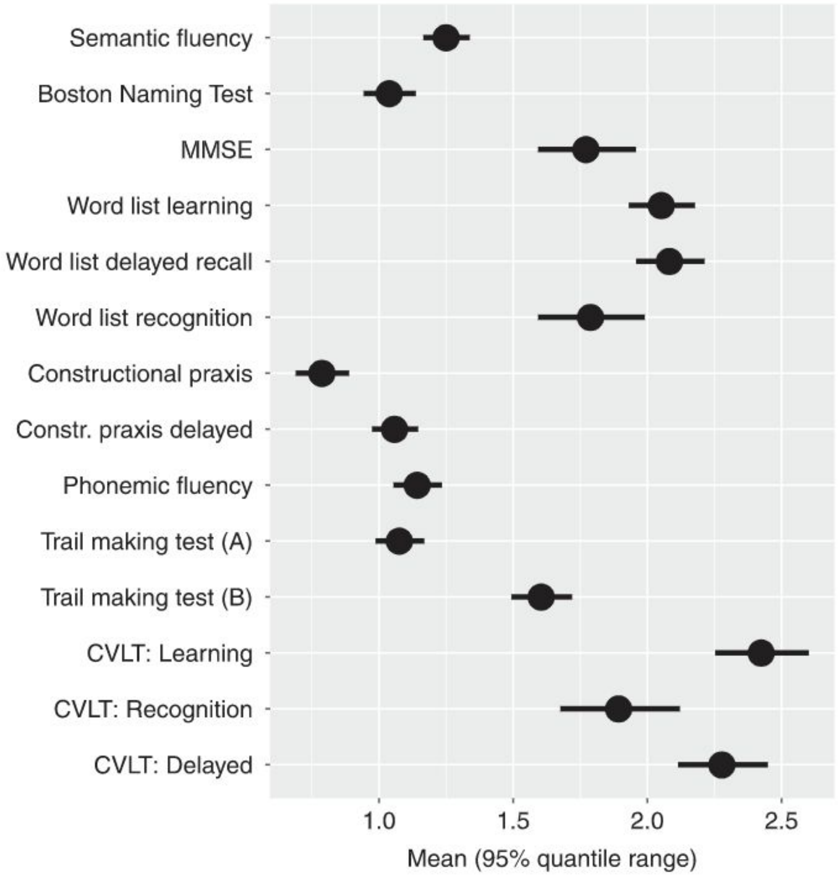
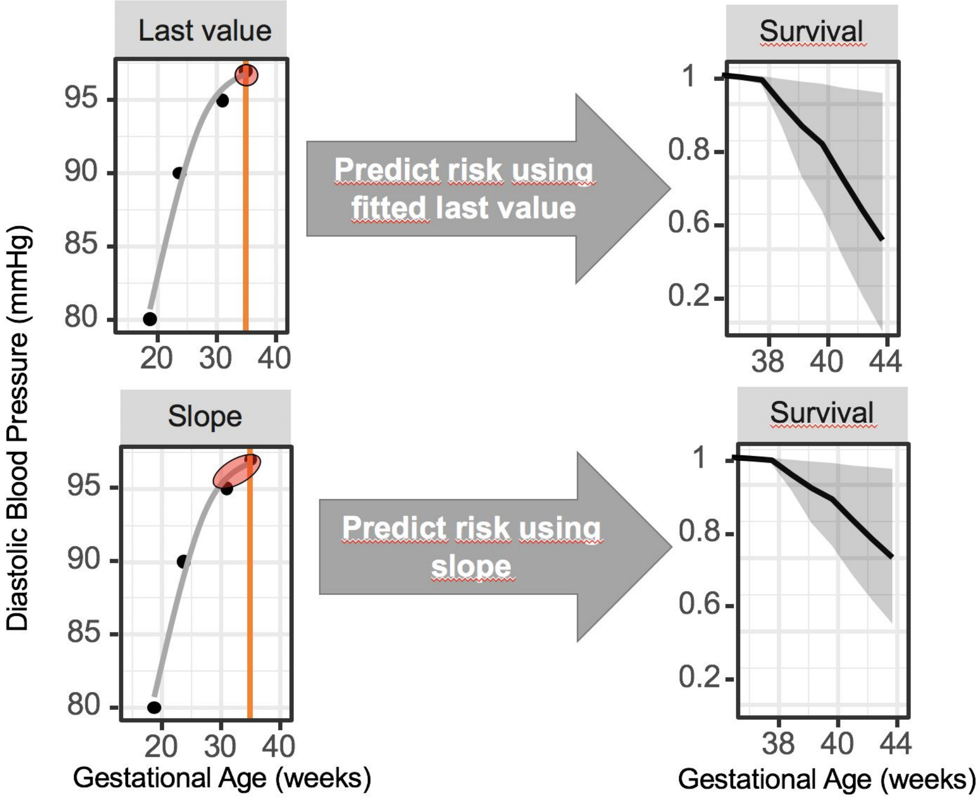


Figure 1 Posterior means and 95% quantile ranges of the discrimination parameters.

Joint Model for pre-eclampsia risk

- Probability of ”surviving” pregnancy without pre-eclampsia (right) incorporates the mother’s history of pre-eclampsia as well as parameters related to diastolic blood pressure (e.g. last predicted value or slope).

- The risk prediction is dynamic and changes depending on which parameter.



Samer Mouksassi. Joint longitudinal and time-to-event model for estimating risk of preeclampsia during pregnancy. ACoP 2019. (*implemented in Stan*)

Torsten: What is it?

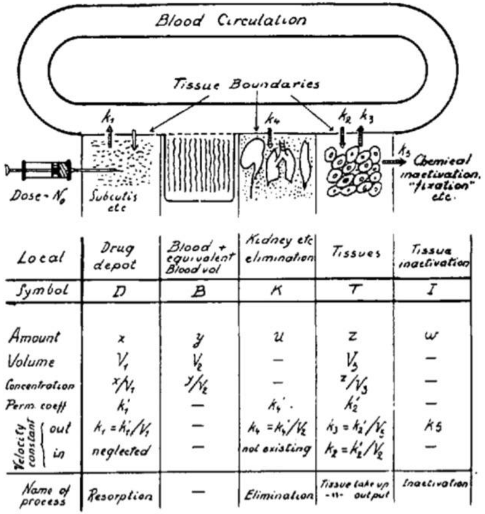
Torsten is a library of PKPD functions for Stan that provides functionality similar to NONMEM's PREDPP library

Core functions in the current version include:

- One & two compartment PK models with 1st order absorption
  - Analytical solutions
- Linear compartment model specified as a rate constant matrix
  - Semi-analytical solution based on matrix exponential
- General compartmental model specified as a system of 1st order ODEs
- Numerical solutions
  - Non-stiff solvers:
    - Runge Kutta Dopri 4th/5th order algorithm from Boost library
    - Adams-Moulton method from the SUNDIALS library (CVODES)
  - Stiff solver: Backward differentiation formula (BDF) method from the SUNDIALS library (CVODES)

Torsten: Why did we call it that?

Torsten Teorell



Local	Drug depot	Blood + equivalent Blood vol	Kidney etc elimination	Tissues	Tissue inactivation
Symbol	D	B	K	T	I
Amount	x	y	u	z	w
Volume	V_1	V_2	—	V_3	—
Concentration	x/V_1	y/V_2	—	z/V_3	—
Perm. coeff	k_1'	—	k_4'	k_2'	—
Velocity constant out	$k_1 = k_1'/V_1$	—	$k_4 = k_4'/V_2$	$k_3 = k_2'/V_3$	k_5
Velocity constant in	neglected	—	not existing	$k_2 = k_2'/V_2$	—
Name of process	Resorption	—	Elimination	Tissue take up -"- output	Inactivation

FIG. 1

Scheme of the Concept of Drug Distribution used in this paper.
Instead the *injection* pictured in the figure, the administration of the drug depot can be made *per os*, *per rectum*, *by inhalation*, etc.

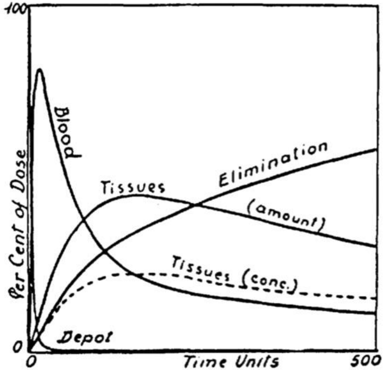


FIG. 3

Typical Case of Extravascular Administration in the absence of tissue inactivation.
($k_1 = 0.2$; $k_2 = 0.01$; $k_3 = 0.005$; i.e. " blood " volume/" tissue " volume is 1 : 2; $k_4 = 0.005$; $k_5 = 0$).

T. Teorell. Kinetics of distribution of substances administered to the body. I. The extravascular modes of administration. Arch Int Pharmacodyn et Ther 57: 205-225, 1937.

Torsten PMX functions

- Uses NONMEM/PREDPP conventions for data specification and event handling
- Data format: Time-ordered event records for each individual à la NONMEM
- Implemented NONMEM data types: TIME, CMT, AMT, RATE, EVID, II, ADDL, SS
- Recursive calculation: For each event time calculate the amount in each compartment given the compartment amounts plus doses at the previous event time.
  - Allows for time-varying (piece-wise constant) parameter values.

An Adaptive Bayesian Method for the Development of Individualized Anemia Management Protocols in End-Stage Renal Disease Patients

Ly Minh Nguyen[1], Calvin Meaney[2], Gauri Rao[3], Mandip Panesar[4], and Wojciech Krzyzanski[1]
[1]Department of Pharmaceutical Sciences, [2]Department of Pharmacy Practice, The State University of New York, Buffalo, NY, USA.
[3]Division of Pharmacotherapy and Experimental Therapeutics, University of North Carolina, Chapel Hill, NC, USA.
[4]Erie County Medical Center, Buffalo, NY, USA.

$$\frac{dA_1}{dt} = \begin{cases} \frac{Dose\ fr\ F}{D_1} - k_a A_1, & if\ t \le D_1, \quad A_1(0) = 0 \\ -k_a A_1, & if\ t > D_1 \end{cases}$$

$$\frac{dA_c}{dt} = \begin{cases} \frac{Dose\ (1-fr)F}{D_2} + k_a A_1 + \frac{Q\ A_p}{V_p} - \frac{(CL+Q)A_c}{V_c} - \frac{\frac{V_{max}\ A_c}{V_c}}{K_m + \frac{A_c}{V_c}}, & if\ T_{lag2} \le t \le D_2, \\ k_a A_1 + \frac{Q\ A_p}{V_p} - \frac{(CL+Q)A_c}{V_c} - \frac{\frac{V_{max}\ A_c}{V_c}}{K_m + \frac{A_c}{V_c}}, & if\ 0 < t < T_{lag2}\ or\ t > D_2, \\ A_c(0) = C_0 V_c, & where\ C_0\ is\ the\ baseline\ endogenous\ EPO \end{cases}$$

$$\frac{dA_p}{dt} = \frac{Q\ A_c}{V_c} - \frac{Q\ A_p}{V_p}, \qquad A_p(0) = C_0 V_p$$

$$\frac{dHGB_1}{dt} = \frac{S_{max}\ C}{SC_{50} + C} - k_{tr} HGB_1, \qquad k_{tr} = \frac{5}{T_{RBC}}, \qquad HGB_1(0) = HGB_{1\_IN}$$

$$\frac{dHGB_i}{dt} = k_{tr}(HGB_{i-1} - HGB_i), \qquad for\ i = 2\ to\ 5, \quad HGB_i(0) = HGB_{i\_IN}$$

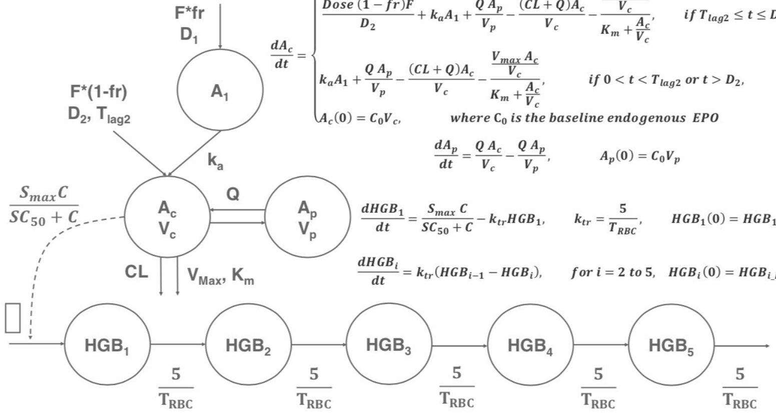


Figure 1: Diagram of the PKPD model of epoetin alfa in ESRD patients.

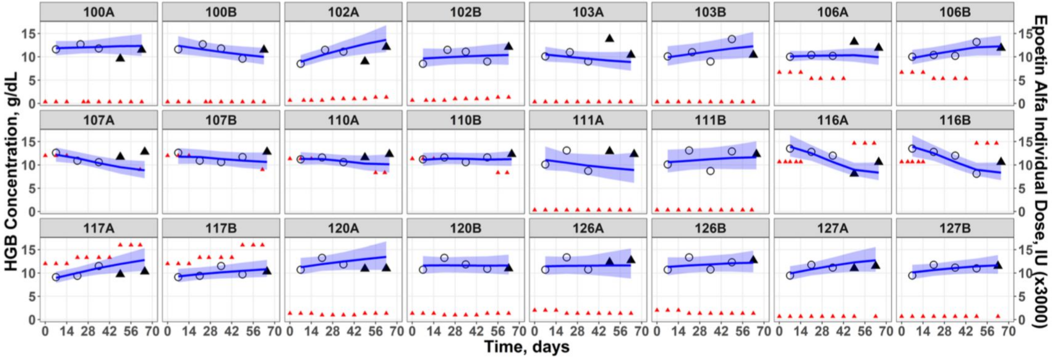
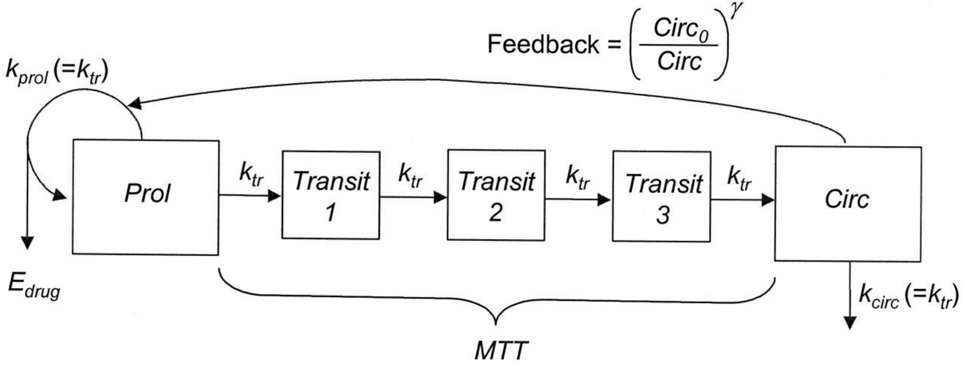


Figure 4: Predictions of new HGB concentrations in ESRD patients given SC epoetin alfa doses. At step 1 **(A)**, HGB concentrations were well predicted within 95% prediction intervals (PIs) in 15/24 and 16/24 subjects for the 4th and 5th observations, respectively. At step 2 **(B)**, the 5th observations in 16/24 subjects were predicted within 95% PIs. Compared with step 1, the 5th observations in 14/24 were predicted more accurately after the model was adaptively updated. Red triangles are individual epoetin alfa doses. Results of 12/24 subjects are shown.

Clinical Pharmacometrics SIG Trainee Award winner: poster M-027

Friberg-Karlsson semi-mechanistic model for drug-induced myelosuppression



$$\frac{dProl}{dt} = k_{prol} Prol \left(1 - E_{drug}\right) \left(\frac{Circ_0}{Circ}\right)^{\gamma} - k_{tr} Prol$$

$$\frac{dTransit1}{dt} = k_{tr} Prol - k_{tr} Transit1$$

$$\frac{dTransit2}{dt} = k_{tr} Transit1 - k_{tr} Transit2$$

$$\frac{dTransit3}{dt} = k_{tr} Transit2 - k_{tr} Transit3$$

$$\frac{dCirc}{dt} = k_{tr} Transit3 - k_{circ} Circ$$

$\widehat{c} \equiv$ plasma drug concentration

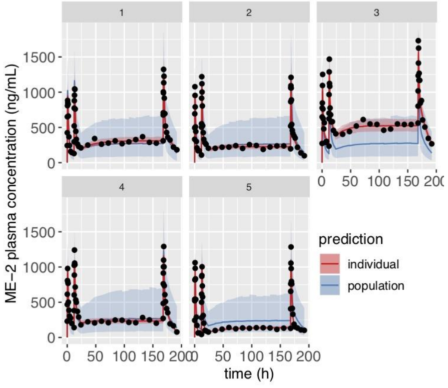
$Circ \equiv$ absolute neutrophil count (ANC)

Parameters in red are *system* parameters, i.e., drug-independent.

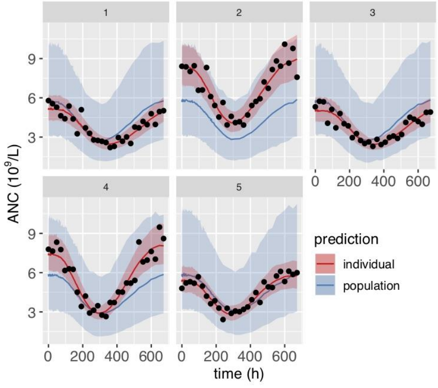
$$E_{drug} = \alpha \widehat{c}$$

$$k_{prol} = k_{circ} = k_{tr}$$

$$MTT = \frac{n+1}{k_{tr}}$$



Source code: neutropenia2.Rmd
Source graphic: /data/advancedStan/deliv/figure/neutropenia2/neutropenia2−PPC001.pdf



Source code: neutropenia2.Rmd
Source graphic: /data/advancedStan/deliv/figure/neutropenia2/neutropenia2−PPC002.pdf

So we can borrow information from previous studies to construct informative priors for those system parameters.

Why Stan/Torsten?

Flexibility

- Flexible w.r.t. stochastic structure
  - Any number of levels variability
  - Large selection of built-in probability distributions
  - Permits sub-models with very different stochastic hierarchies
- Flexible w.r.t. deterministic structure
  - Control structures: if-then-else, for and while loops
  - Large collection of built-in functions
  - Operators and functions for vector and matrix calculations

Computational efficiency

- Typically faster than Gibbs or Metropolis-Hastings
  - Measured in terms of $\frac{\text{time}}{\text{effective sample size}}$
- Also includes optimization and variational inference methods for rapid approximate Bayesian analysis

Current role of Stan/Torsten for PMX applications

- Very flexible platform for fully Bayesian analyses that cannot be implemented in standard PMX platforms, e.g., NONMEM or Monolix.
- You can do more routine popPK and popPKPD analyses with Stan, particularly with the Torsten extensions, but
  - Computation times make it non-optimal for such applications
- Bottom line: For the moment save it for problems where
  - Fully Bayesian methods are particularly valuable, e.g., use of informative priors.
  - A more flexible model specification language is needed.

Stan & Torsten development plans

Our ambition is to make Stan/Torsten a viable open-source tool for a wide range of PMX data analyses:

- Bayesian calibration of complex QSP models,
- Analysis of data from heterogeneous sources, e.g.,
  - combine non-clinical and clinical data and
  - combine individual and aggregate data,
- As well as more routine popPK and popPKPD analyses.

Stan & Torsten development plans

Near-term development plans include:

- Better fast approximate Bayesian methods
- Additional parallel computation capabilities
- Additional DE support (PDE, DAE, DDE, SDE)
- R package(s) to simplify implementation of pharmacometrics models
- R package(s) for specialized visualization and reporting of PKPD model analyses

Assertion

Addition of those features will make Stan/Torsten a superior open source alternative to (your favorite PMX platform here).

Stan & Torsten development sites

Your participation is welcome whether it be contributing code, compliments or complaints at the following sites:

- Stan development repositories
  - Stan: https://github.com/stan-dev/stan
  - Stan math: https://github.com/stan-dev/math
  - CmdStan: https://github.com/stan-dev/cmdstan
  - RStan: https://github.com/stan-dev/rstan
- Torsten development repository
  - https://github.com/metrumresearchgroup/Torsten

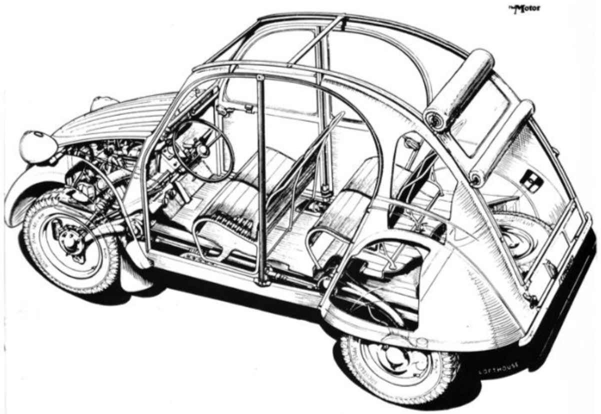
Stan & Torsten online training

- A Brief Introduction to Bayesian Modeling Using Stan https://metrumrg.com/course/brief-introduction-bayesian-modeling-using-stan/

- Advanced Use of Stan, RStan and Torsten for Pharmacometric Applications https://metrumrg.com/course/advanced-use-stan-rstan-torsten-pharmacometric-applications/

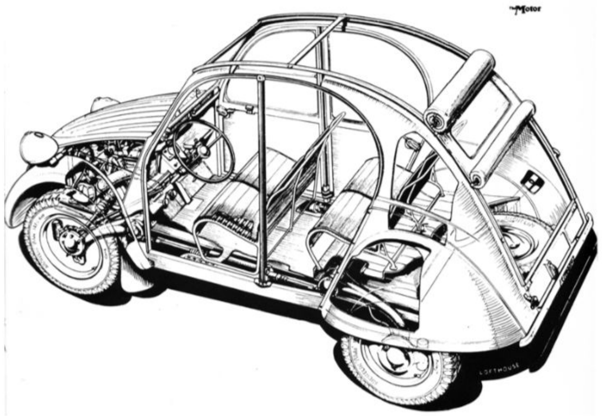
If you're interested...

All of the tools described here are free and open source.



If you're interested...

All of the tools described here are free and open source.



Kick the tires.

If you're interested...

Take them for a spin.

If you’re interested...

Take them for a spin.

Comment, recommend features, complain, etc.

If you're interested...

Contribute code.
Make them better.

Why OSPL Software in Pharmacometrics?

FREEDOM

SHARED LEARNING & INNOVATION

SUSTAINABILITY

INCLUSIVENESS & ACCESSIBILITY

TRANSPARENCY & REPRODUCIBILITY

COMMUNITY BASED COLLABORATION

QUALITY SOFTWARE

A Call to Action

Support open-source, public license software projects…

- in-kind effort
- use & feedback
- funding
- advocacy

Thank You

Presentation available at https://metrumrg.com/publications/