METRUM
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Torsten: Stan functions for pharmacometrics applications

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Stan for Pharmacometrics
Paris, France
24 July 2018

What is Torsten and what are we up to?

As Stan developers/collaborators we are developing Stan components for PMX applications.

- PMX-specific components are distributed as Torsten.
- More general components are contributed to Stan & Stan Math.

Like Stan, Torsten is open source (BSD-3-Clause).

Torsten Teorell

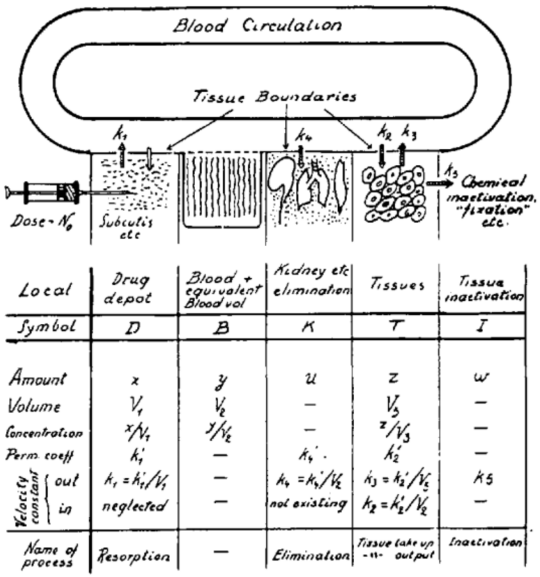

FIG. 1

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.

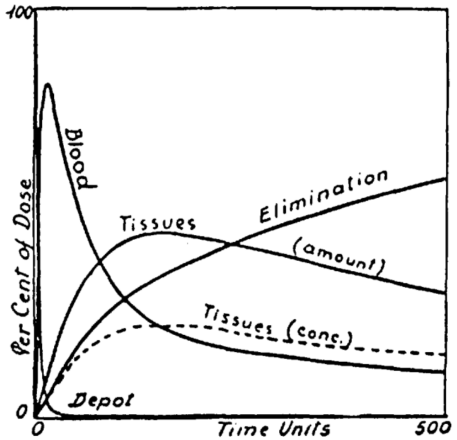

FIG. 3

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.

What we've got

PK & PKPD model functions that provide functionality similar to NONMEM's PREDPP library:

- Calculate state of each compartment at a sequence of event times.
- Event schedule specified similar to NONMEM.

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- Mixed models that couple analytically solved PK models with numerically solved ODE systems.

Torsten PMX functions

- Use 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.

Torsten PMX functions

- PKModelOneCpt(time, amt, rate, ii, evid, cmt, addl, ss, theta, F, tlag)
- PKModelTwoCpt(time, amt, rate, ii, evid, cmt, addl, ss, theta, F, tlag)
- linOdeModel(time, amt, rate, ii, evid, cmt, addl, ss, K, F, tlag)
- generalOdeModel_*(ODE_system, nOde, time, amt, rate, ii, evid, cmt, addl, ss, theta, F, tlag, rel_tol, abs_tol, max_step)
- mixOde1CptModel_*(reduced_ODE_system, nOde, time, amt, rate, ii, evid, cmt, addl, ss, theta, F, tlag, rel_tol, abs_tol, max_step)
- mixOde2CptModel_*(reduced_ODE_system, nOde, time, amt, rate, ii, evid, cmt, addl, ss, theta, F, tlag, rel_tol, abs_tol, max_step)

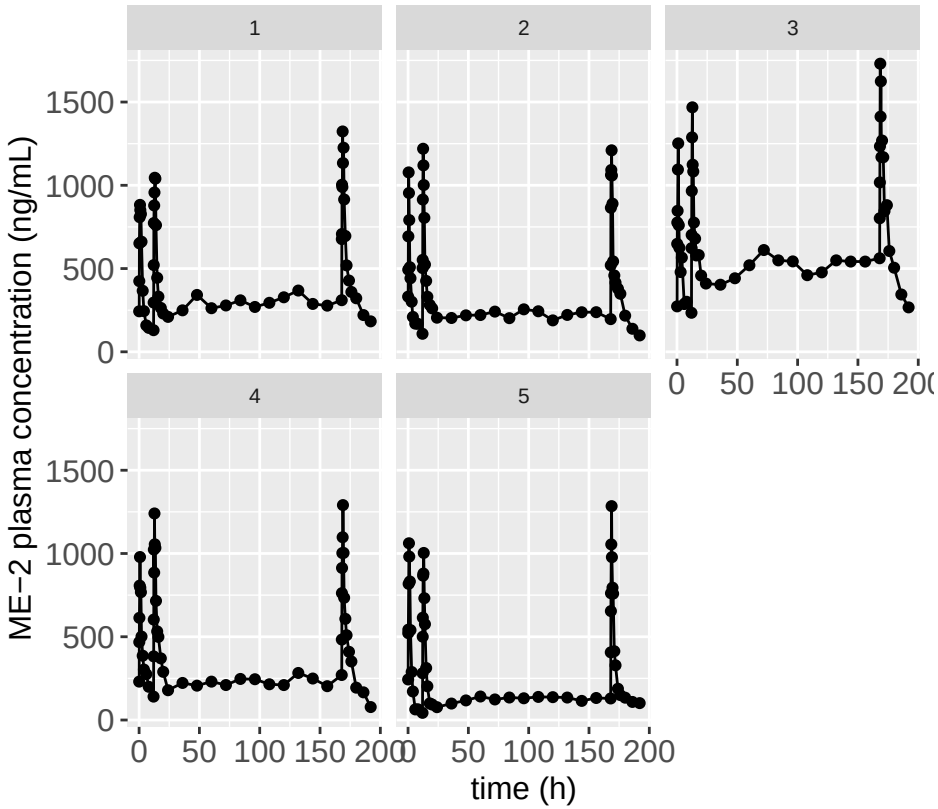
* = rk45 or bdf

Torsten: Where to get it...

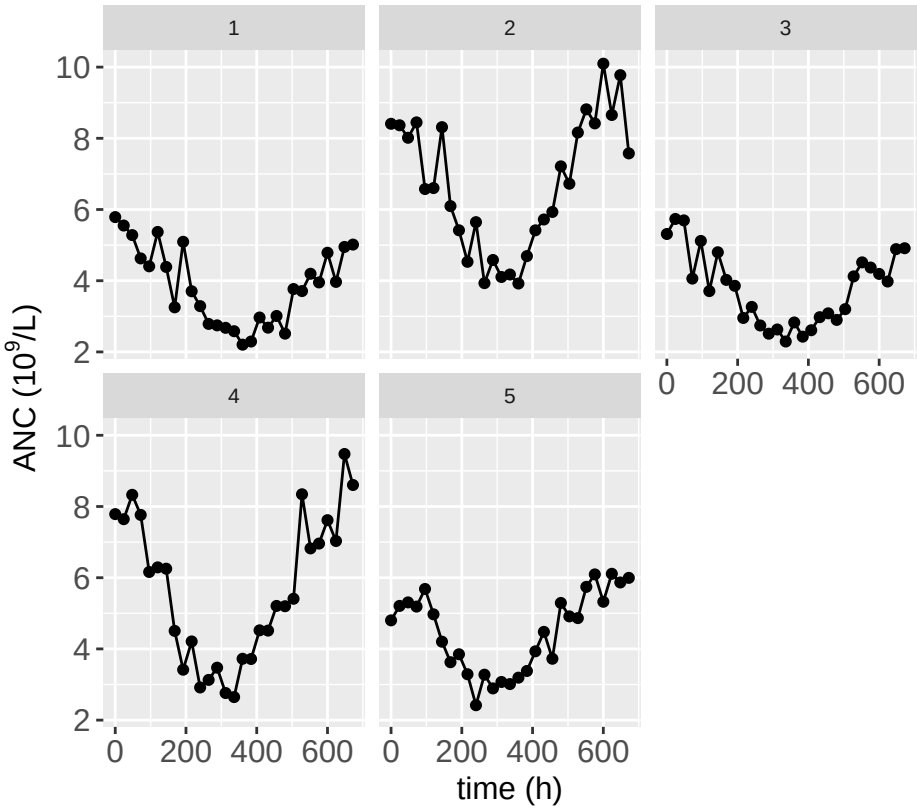
- Torsten is available at: https://github.com/metrumresearchgroup/Torsten
- Includes installation instructions for use with CmdStan and RStan.
- Documentation: https://github.com/metrumresearchgroup/Torsten/blob/master/docs/torsten_manual.pdf
- Current version (0.84) uses Stan 2.17.1. We will update to Stan 2.18 soon.

Torsten example: PKPD model of drug-induced neutropenia

ME-2 plasma concentrations and neutrophil counts resulting from 80 mg ME-2 q12h x 1 week



Source code: neutropenia2.Rmd
Source graphic: /data/advancedStan/deliv/figure/neutropenia2/neutropenia2−PKPDData001.pdf



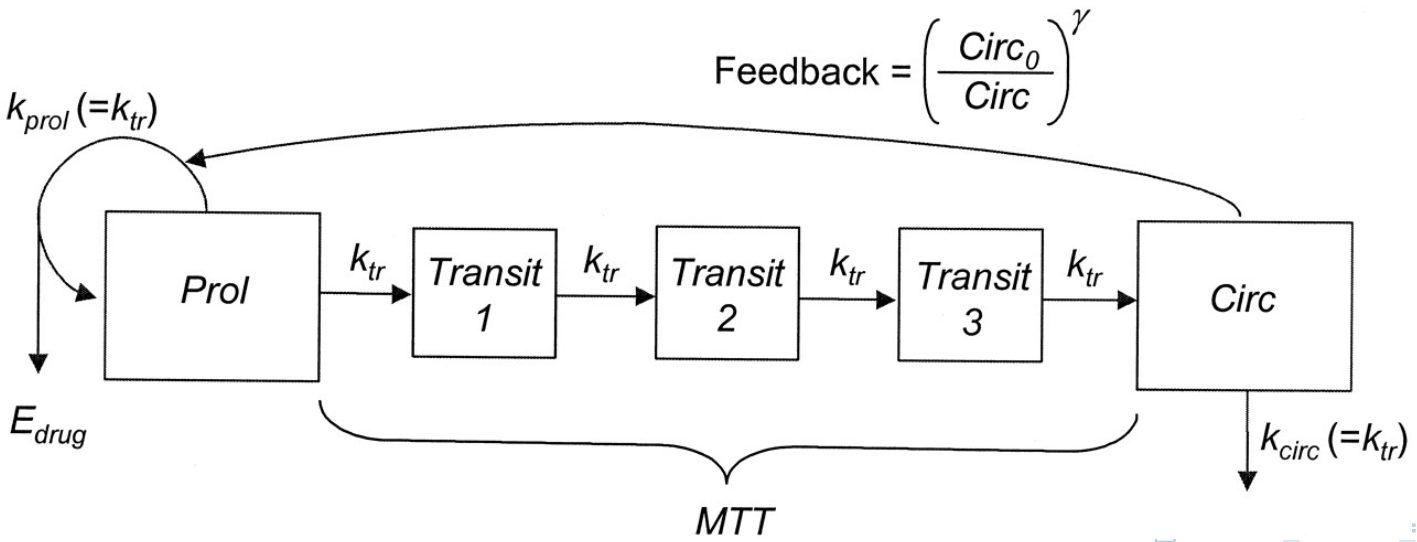
Source code: neutropenia2.Rmd
Source graphic: /data/advancedStan/deliv/figure/neutropenia2/neutropenia2−PKPDData002.pdf

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

- PK model: Two compartment model with first order absorption describing plasma drug concentration on the i^{th} occasion in the j^{th} subject as a function of time, dose and body weight:

$$\begin{aligned} \log\left(c_{ij}\right) &\sim N\left(\log\left(\hat{c}_{ij}\right), \sigma\right) \\ \hat{c}_{ij} &= f_{2cpt}\left(t_{ij}, D_j, \tau_j, CL_j, Q_j, V_{1j}, V_{2j}, k_{aj}\right) \end{aligned}$$

- Friberg-Karlsson semi-mechanistic model for drug-induced myelosuppression [1, 2, 3, 4, 5, 6]



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

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

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

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

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

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

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

$Circ$ $\equiv$ absolute neutrophil count (ANC)

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

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

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

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

IIV and prior distributions

- Inter-individual variation

$$\log\left(CL_j, Q_j, V_{1j}, V_{2j}, k_{aj}, MTT_j, Circ_{0j}, \alpha_j\right) \sim N\left(\log\left(\widehat{CL}\left(\frac{bw_j}{70}\right)^{0.75}, \widehat{Q}\left(\frac{bw_j}{70}\right)^{0.75}, \widehat{V}_1\left(\frac{bw_j}{70}\right), \widehat{V}_2\left(\frac{bw_j}{70}\right), \widehat{k}_a, \widehat{MTT}, \widehat{Circ_0}, \widehat{\alpha}\right), \Omega\right)$$

- Prior distributions: moderately informative for PK, strongly informative for system parameters, weakly informative for drug effect

$$\begin{aligned}
\widehat{CL} &\sim \log N(\log(10), 0.5) \quad \widehat{Q} \sim \log N(\log(15), 0.5) \quad \widehat{V}_1 \sim \log N(\log(35), 0.5) \\
\widehat{V}_2 &\sim \log N(\log(105), 0.5) \quad \widehat{k}_a \sim \log N(\log(2), 0.5) \\
\widehat{MTT} &\sim \log N(\log(125), 0.2) \quad \widehat{Circ_0} \sim \log N(\log(5), 0.2) \quad \gamma \sim \log N(\log(0.17), 0.2) \\
\widehat{\alpha} &\sim \log N\left(\log(3 \times 10^{-4}), 1\right) \quad \sigma \sim \text{half-Cauchy}(0, 1) \\
\Omega &= \text{diag}(\omega)\, P\, \text{diag}(\omega) \\
\omega_i &\sim \text{half-Cauchy}(0, 1), i \in \{1, 2, \ldots, 8\} \quad P \sim \text{LKJCorr}(1)
\end{aligned}$$

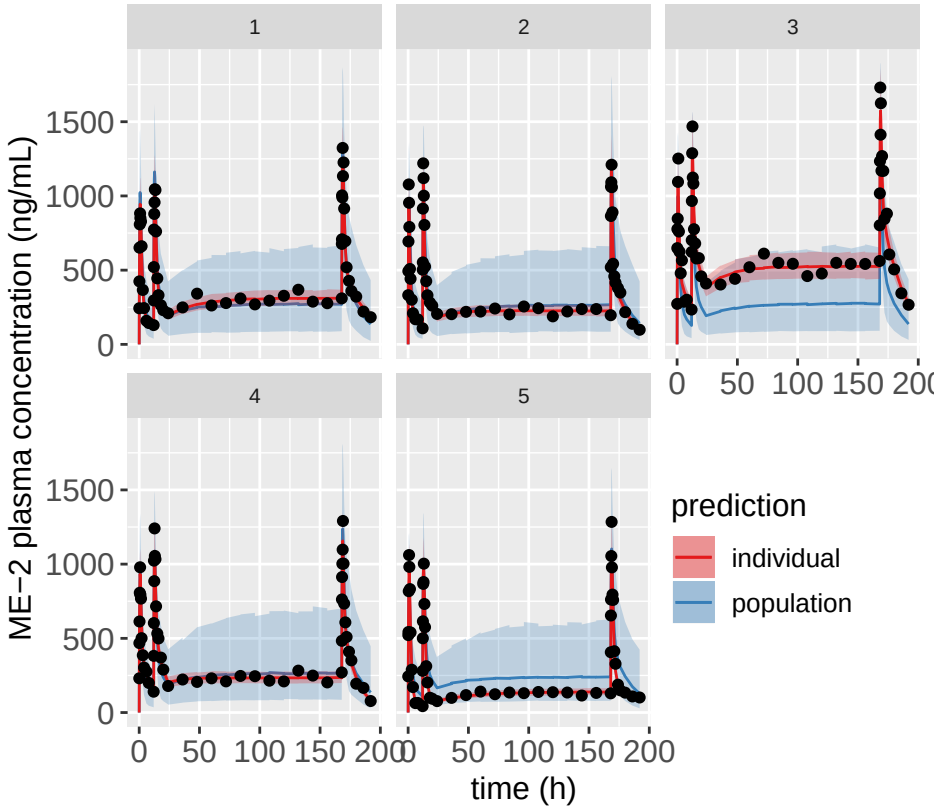
Stan model excerpt with Torsten function call

```
for(j in 1:nId){
  CL[j] = theta[j, 1] * (weight[j] / 70)^0.75;
        ⋮
  alpha[j] = theta[j, 8];

  parms = {CL[j], Q[j], V1[j], V2[j], ka[j], mtt[j], circ0[j],
           gamma, alpha[j]};

  x[start[j]:end[j],] = generalOdeModel_bdf(twoCptNeutModelODE, 8,
                        time[start[j]:end[j]], amt[start[j]:end[j]],
                        rate[start[j]:end[j]], ii[start[j]:end[j]],
                        evid[start[j]:end[j]], cmt[start[j]:end[j]],
                        addl[start[j]:end[j]], ss[start[j]:end[j]],
                        parms, F, tLag,
                        1e-6, 1e-6, 1e8);

  cHat[start[j]:end[j]] = x[start[j]:end[j], 2] / V1[j];
  neutHat[start[j]:end[j]] = x[start[j]:end[j], 8] + circ0[j];
}
```

Good convergence and mixing with 4 chains of 250 warmup and 250 post-warmup samples/chain

parameter	mean	SD	median	95% CI	Neff	Rhat
$\widehat{CL}$	11.2	1.6	11.2	(8.13, 14.7)	480	1.01
$\widehat{Q}$	22.7	4.3	22.4	(15.3, 32.7)	614	1
$\widehat{V1}$	30.9	4.58	31	(21.5, 40.4)	701	1
$\widehat{V2}$	117	24.5	114	(75.3, 173)	710	0.999
$\widehat{k_a}$	1.78	0.293	1.77	(1.23, 2.37)	779	1.01
σ	0.1	0.00489	0.1	(0.0919, 0.111)	1000	1
$\widehat{\alpha}$	0.000323	5.14e-05	0.000319	(0.000234, 0.000432)	792	0.998
$\widehat{MTT}$	117	10.1	116	(100, 141)	847	1
$\widehat{Circ_0}$	5.77	0.649	5.75	(4.44, 7.05)	829	1
γ	0.152	0.0128	0.151	(0.128, 0.178)	1000	0.997
σ_{ANC}	0.107	0.00683	0.106	(0.0951, 0.122)	1000	1

Model fits (posterior median & 90 % CI)



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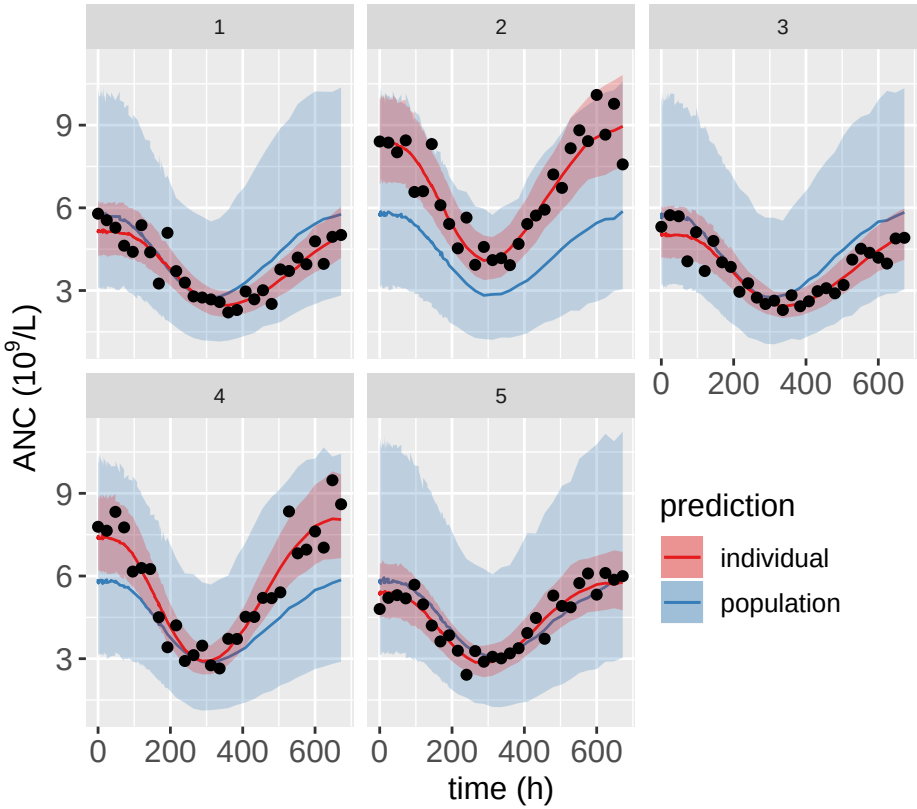

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For more details and instruction...

We provide some free online workshops at https://metrumrg.com/courses/.

- A Brief Introduction to Bayesian Modeling Using Stan
- Advanced Use of Stan, RStan and Torsten for Pharmacometric Applications

Course materials including complete code and data for many illustrative examples are provided.

We're not done

We want to reduce the barriers to routine use of Stan for PMX applications, e.g.,

- Computation time required for Bayesian data analysis.
- Programming time required to implement typical popPKPD models.

We want to expand the range of applications, e.g., models described in terms of other equation types that require numerical solution like DAEs, PDEs, SDEs, etc.

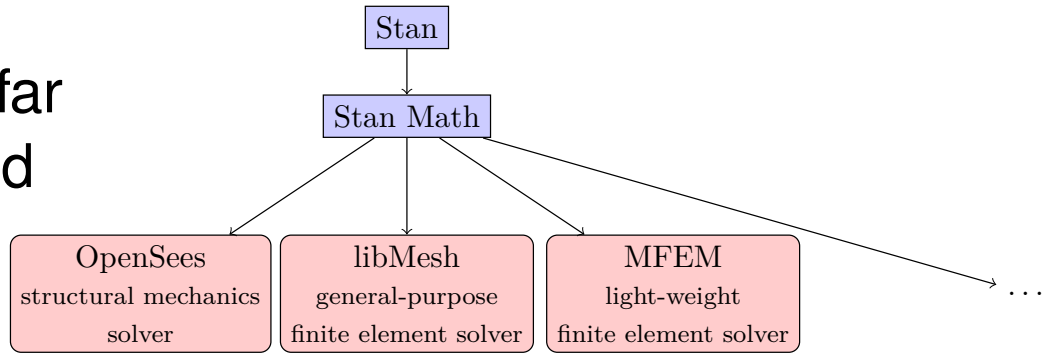

WHAT WILL THE NEXT HUNDRED YEARS BRING TO MANKIND?
H.G. WELLS' "THINGS TO COME"
An ALEXANDER KORDA production
with RAYMOND MASSEY · RALPH RICHARDSON
SIR CEDRIC HARDWICKE · PEARL ARGYLE
MARGARETTA SCOTT and a cast of 20,000
Directed by WILLIAM CAMERON MENZIES
A London Film · Released thru United Artists

What else are we working on?

- Additional ODE support
  - Adams-Moulton solver for non-stiff ODEs implemented as integrate_ode_adams in Stan 2.18
  - Action of the matrix exponential function to speed up linear ODE solving implemented as matrix_exp_multiply and scale_matrix_exp_multiply in Stan 2.18
- DAEs
  - Stan interface for IDAS from SUNDIALS
  - Pull request under review
- PDEs
  - Initial approach interfaces Stan with 3rd-party PDE libraries.
  - Pull request under review
- R packages
  - to simplify implementation of common classes of pharmacometrics models.
  - for specialized visualization and reporting of PKPD model analyses.

Stan interface with 3rd-party PDE libraries

- Interface with user-provided numerical PDE solvers. So far the interface has been tested on three external solvers. More can be added with similar fashion.



- Pros
  - Stan to a broader audience
  - Flexibility
  - Better modeling by field specialists
  - Better performance tuning by field specialists
  - ...
- Cons
  - Requires C++ coding and library management

Example: Darcy's flow

- Darcy's flow is a fundamental model describing fluid flow in many tissues. It is commonly used to model interstitial flow that plays important roles in tissue morphogenesis, function, and pathogenesis.
- Noisy data: $\|\boldsymbol{u}_{\text{obs}}\|_2$
- parameter: k(ratio between viscosity and permeability)
- Problem is setup and solved on an arbitrary domain in MFEM.

$$k\boldsymbol{u} + \nabla p = f$$
$$-\nabla \cdot \boldsymbol{u} = g$$

- $\boldsymbol{u}$: velocity
- p: pressure

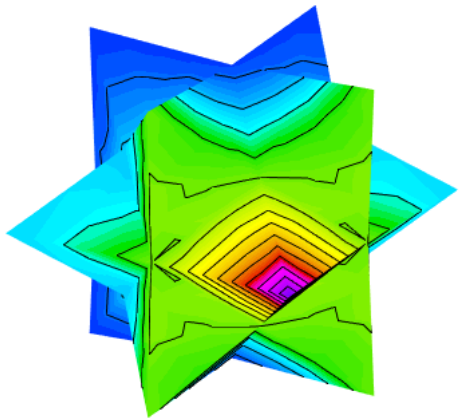


Figure: Contour of p in PDE solution

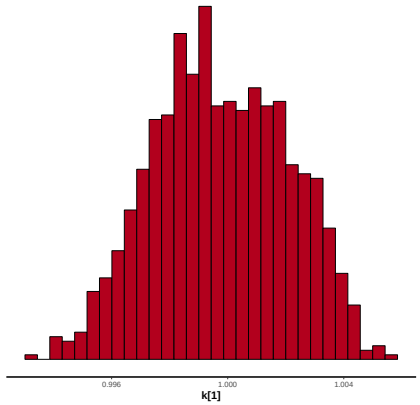


Figure: Sampling of k

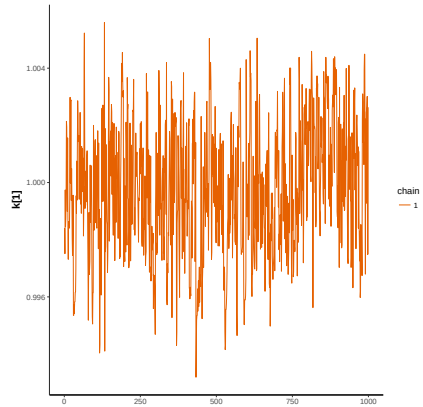


Figure: Trace of k

Related Stan development by other developers

- Within chain parallel computation
  - MPI or threading approaches available in Stan 2.18.
    - https://github.com/stan-dev/math/wiki/MPI-Parallelism
    - https://github.com/stan-dev/math/wiki/Threading-Support
- Fast approximate Bayesian engines
  - Improvements to existing ADVI engine
  - Gradient-based marginal optimization (GMO) for marginal maximum penalized likelihood estimation
  - Data-streaming variational Bayes via stochastic automatic differentiation variational inference (ADVI)
  - Data-parallel variational Bayes via expectation propagation (EP)

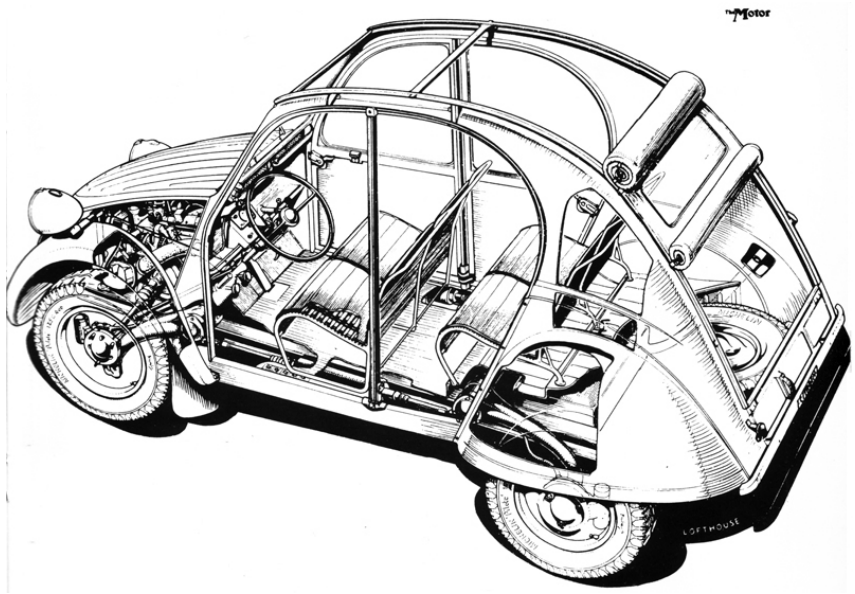
Our ambitions

Where we're heading

- Flexible open source platform that makes BDA a practical option for
  - routine popPK/popPKPD analyses.
  - larger scale models (e.g., QSP models) and/or data sets.

If you’re interested...

Torsten is free and open source.



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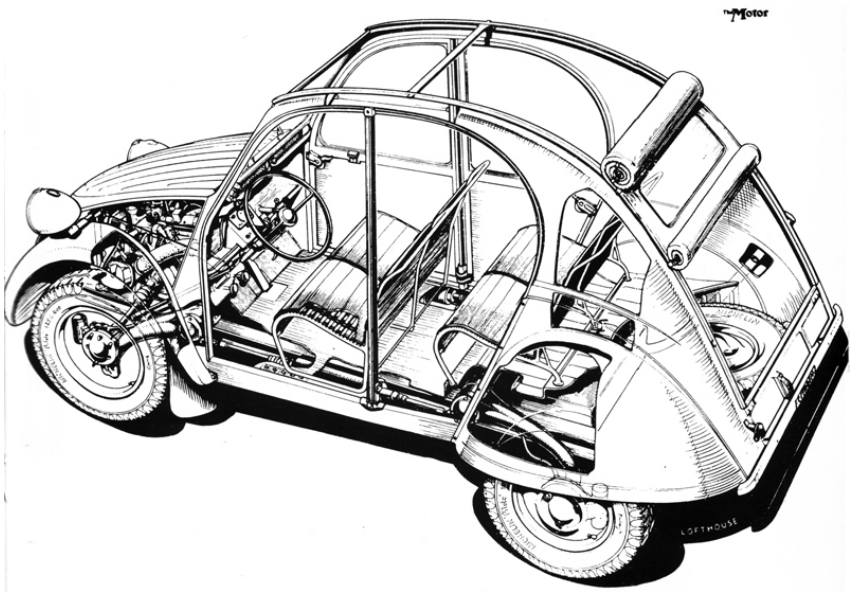

Kick the tires.

If you’re interested...

Take it for a spin.

If you're interested...

Take it for a spin.

Comment, recommend features, complain, etc.

If you're interested...

Contribute code.

Make it better.

https://github.com/metrumresearchgroup/Torsten

Credit where it is due...

Metrum Research Group

- Charles Margossian
- Yi Zhang
- Marc Gastonguay

Stan developers

- Andrew Gelman, Columbia Univ.
- Bob Carpenter, Columbia Univ.
- Sean Talts, Columbia Univ.
- Mike Betancourt, Columbia Univ.
- Daniel Lee, Columbia Univ.
- Sebastian Weber, Novartis
- + contributions from many more

Funding sources:

- Bill & Melinda Gates Foundation
- Office of Naval Research STTR Program
  - contract no. N00014-16-P-2039
  - contract no. N6833518C0110

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