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Torsten

A Prototype Library for Bayesian Pharmacometrics Modeling in Stan

User Manual

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Torsten Version 0.82
for Stan Version 2.14.0

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Contents

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1. Introduction

1.1. **Preface.**

Stan is an open source probabilistic language designed primarily to do Bayesian data analysis [**?**]. Several of its features make it a powerful tool to specify and fit complex models. Notably, its language is extremely flexible and its No U-Turn Sampler (NUTS), an adaptative Hamiltonian Monte Carlo algorithm, has proven more efficient than commonly used Monte Carlo Markov Chains (MCMC) samplers for complex high dimensional problems [**?**]. Our goal is to harness these innovative features and make Stan a better software for pharmacometrics modeling. Our efforts are twofold:

(1) We contribute to the development of new mathematical tools, such as functions that support differential equations based models, and implement them directly into Stan's core language.
(2) We develop Torsten, an extension with specialized pharmacometrics functions.

Throughout the process, we have been working very closely with Stan's development team. We have benefited immensely from their mentoring, advice, and feedback. Just like Stan, Torsten is an open source project that fosters collaborative work. Interested in contributing? Shoot us an e-mail and we will help you help us (`charlesm@metrumrg.com` and `billg@metrumrg.com`)!

WARNING: The current version of Torsten is a *prototype*. It is being released for review and comment, and to support limited research applications. It has not been rigorously tested and should not be used for critical applications without further testing or cross-checking by comparison with other methods.

We encourage interested users to try Torsten out and are happy to assist. Please report issues, bugs, and feature requests on our GitHub page: `https://github.com/charlesm93/stan`.

1.2. **Installing Torsten.**

Installation files are available on GitHub: `https://github.com/charlesm93/example-models/tree/torsten-0.82/PKPD/torsten`

There is currently no mechanism to install Torsten on top of your version of Stan. This is still a work in progress. In the meantime, we offer a version of Stan with Torsten built inside of it. Torsten 0.82 works with Stan 2.14.0. Torsten is built inside the Stan and Stan-math repositories and is agnostic to the interface. We offer support to install Torsten with RStan and CmdStan.

1.2.1. *Intalling Torsten with RStan.*

The easiest way to install the RStan interface with Stan and Torsten is to run the R script `R/setupRTorsten.R`. You'll need to make a few minor adjustments, notably by specifying the location at which you wish to install the libraries rstan (and its dependency StanHeaders). If you already have these packages installed, the script will not automatically overwrite them, which is why you should remove them prior to running `setupRTorsten.R`.

1.2.2. *Installing Torsten with CmdStan.*

Similarly, you can install the CmdStan interface with Stan and Torsten using the bash file `setupTorsten.sh`[1].

[1] To get the development version of Torsten use `setupTorsten-dev.sh`.

1.3. **Overview.**

Torsten is a prototype Pharmacokinetic/Pharmacodynamic (PKPD) model library for use in Stan 2.14.0. The current version includes:

- Specific linear compartmental models:
  - One compartment model with first order absorption
  - Two compartment model with elimination from and first order absorption into central compartment
- General linear compartmental model described by a system of first-order linear Ordinary Differential Equations (ODEs).
- General compartmental model described by a system of first order ODEs

The models and data format are based on NONMEM®[2]/NMTRAN/PREDPP conventions including:

- Recursive calculation of model predictions
  - This permits piecewise constant covariate values
- Bolus or constant rate inputs into any compartment
- Handles single dose and multiple dose histories
- Handles steady-state dosing histories for specific and general linear models
- Implemented NMTRAN data items include: TIME, EVID, CMT, AMT, RATE, ADDL, II, SS

This library provides Stan language functions that calculate amounts in each compartment, given an event schedule and an ODE system.

1.4. **Implementation details.**

- Stan version 2.14.0 (`http://mc-stan.org/`)
- All functions are programmed in C++ and are compatible with the Stan-math automatic differentiation library [**?**]
- All functions can be called directly in a Stan file in a manner identical to other built-in functions
- One and two compartment models: hand-coded analytical solutions
- General linear compartment models with semi-analytical solutions using a built-in Matrix Exponential function (Pade approximation coupled with scaling and squaring [**?**])
- General compartment models with numerical solutions to ODEs using built-in ODE integrators in Stan (Runge-Kutta 4th/5th and backward differentiation methods from CVODES library), with adjustable tuning parameters

1.5. **Development plans.**

Our current plans for future development of Torsten include the following:

- A system to easily share packages of Stan functions (written in C++ or in the Stan language)
- Steady state calculation for the General compartment model
  - This requires a solver for nonlinear algebraic equations (aka a root solver)
- Optimize Matrix exponential functions
  - Function for the action of Matrix Exponential on a vector
  - Hand-coded gradients

[2]NONMEM® is licensed and distributed by ICON Development Solutions.

  - Special algorithm for matrices with special properties
- Fix issue that arises when computing the adjoint of the lag time parameter (in a dosing compartment) evaluated at $t_{lag} = 0$.
- Make the following arguments optional
  - `biovar` and `tlag`, respectively used for the bioavailability fraction and the lag times in each compartment
  - Tuning parameters of the ODE integrators for the general compartmental function.
- Extend formal tests
  - We want more C++ Google unit tests to address cases users may encounter
  - Comparison with simulations from the R package *mrgsolve* and the software NONMEM®
  - Recruit non-developer users to conduct beta testing

1.6. **Updates since Torsten 0.81.**

- Torsten is now up to date with Stan version 2.14.0
- We fixed a bug that prevented the user from passing tuning parameters for the ODE integrators.
- We split the parameter argument into three arguments: `pMatrix` (parameters for the ODE system), `biovar` (parameters for the bioavailability), and `tlag` (parameters for lag times). This gives the users more control over which arguments get passed as data and as parameters. The model is most efficient when all fixed values are passed as data.
- We changed the order of the arguments: the user first passes the data arguments and then the parameter arguments. This is because in future versions we will want optional arguments to be passed last.
- The user can now pass parameter arguments as 1D or 2D arrays, depending on whether the parameters are constant or change from one event to the other.
- We have significantly increased the number of unit tests – but we still have more to do!
- The unit tests now check automatic differentiation against finite differentiation calculations.
- Fixed minor bugs and report issues.

2. Using Torsten

The reader should have a basic understanding of how Stan works before tackling this chapter. There are excellent resources online to get started with Stan (`http://mc-stan.org/documentation/`).

In this section we go through the different functions Torsten adds to Stan. It will be helpful to apply these functions to a simple example. We have uploaded code and data on `https://github.com/charlesm93/example-models/tree/torsten-0.82/PKPD/torsten`.

2.1. Example 1: Two Compartment Model.

We model drug absorption in a single patient and simulate plasma drug concentrations:

- Multiple Doses: 1250 mg, every 12 hours, for a total of 15 doses
- PK: plasma concentrations of parent drug (c)
- PK measured at 0.083, 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10 and 12 hours after 1st, 2nd, and 15th dose. In addition, the PK is measured every 12 hours throughout the trial.

The plasma concentration (c) are simulated according to the following equations:

$$\begin{aligned} \log(c) &\sim N\left(\log(\widehat{c}), \sigma^2\right) \\ \widehat{c} &= f_{2cpt}(t, CL, Q, V_2, V_3, k_a) \\ (CL, Q, V_2, V_3, ka) &= \left(5 \text{ L/h}, 8 \text{ L/h}, 20 \text{ L}, 70 \text{ L}, 1.2 \text{ h}^{-1}\right) \\ \sigma^2 &= 0.01 \end{aligned}$$

The data are generated using the R package *mrgsolve*[3], see `TwoCptModelSimulation.R`. We show the results obtained when using the function `PKModelTwoCpt`, which computes solutions to the ODEs analytically.

2.2. Linear One and Two Compartment Model Function.

The one and two compartment model functions have the form:

```
<model name>(time, amt, rate, ii, evid, cmt, addl, ss,
             theta, biovar, tlag)
```

There is no need to skip a line, but we do so to separate *event* arguments and *model* arguments.

The event arguments describe the event schedule of the clinical trial. time, amt, rate, and ii are arrays of real and evid, cmt, addl, and ss arrays of integers. All arrays have the same length, which corresponds to the number of events.

Next we have the model arguments: `theta` contains the ODE parameters, `biovar` the bioavailability fraction in each compartment (sometimes denoted as F), and `tlag` the lag times in each compartment. The model arguments may be either one or two dimensional arrays. If they are one dimensional arrays, the parameters are constant for all events. If they are two dimensional arrays then each row should contain the listed parameters, and the number of rows should equal the lengths of the time, amt, rate, ii, evid, cmt,

[3] https://github.com/metrumresearchgroup/mrgsolve

addl, and ss arrays. The values of the ith row should be the parameter values for the interval [`time[i-1]`, `time[i]`].

The options for *model name* are:

- PKModelOneCpt
- PKModelTwoCpt

which respectively correspond to the one and two compartment model with first order absorption (figure **??**). A vector in `theta` is expected to contain parameters CL, $V2$, and ka for the one compartment case, and CL, Q, $V2$, $V3$, and ka for the two compartments case, in this order. Setting ka to 0 eliminates the fist-order absoprtion. `biovar` contains the bioavailability fraction of each compartment (non-effective if set to 1) and `tlag` the lag time in each compartment (non-effective if set to 0).

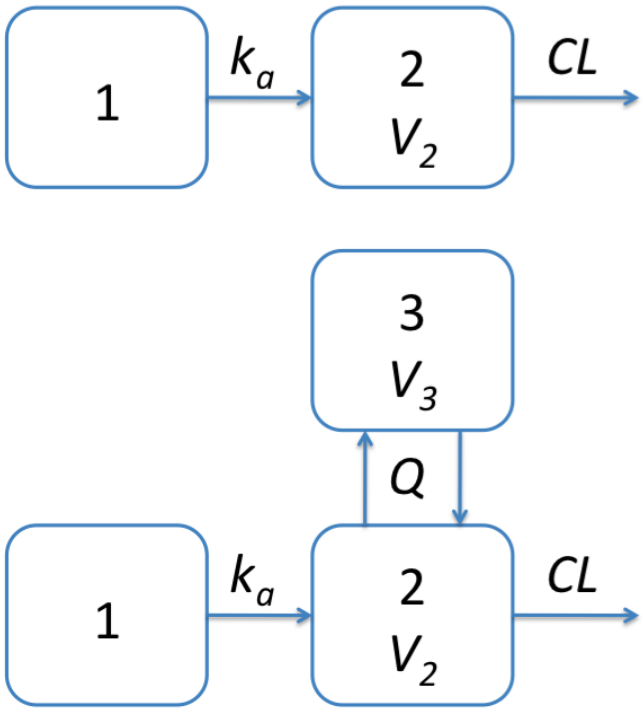

FIGURE 1. One and two compartment models with first order absorption implemented in Torsten.

`PKModelTwoCpt` can be used to fit example 1, see `TwoCptModel.stan`. We are interested in evaluating the ODE parameters, stored in `theta`. The bioavailability fraction and the lag times on the other hand are fixed, and we therefore declare `biovar` and `tlag` in the transformed data block. Three MCMC chains of 2000 iterations were simulated. The first 1000 iteration of each chain were discarded. Thus 1000 MCMC samples were used for the subsequent analyses.

Result. The MCMC history plots (figure **??**) suggest that the 3 chains have converged to common distributions for all of the key model parameters. The fit to the plasma concentration data (figure **??**) are in close agreement with the data, which is not surprising since the fitted model is identical to the one used to simulate the data. Similarly the parameter estimates summarized in Table 1 are consistent with the values used for simulation.

FIGURE 2. Stan language for fitting a two compartment model using the `PKModelTwoCpt` function (abstract)

```
data {
  int<lower = 1> nt; # number of events
  int<lower = 1> nObs; # number of observation
  int<lower = 1> iObs[nObs]; # index of observation
  int cmt[nt];
  int evid[nt];
  int addl[nt];
  int ss[nt];
  real amt[nt];
  real time[nt];
  real rate[nt];
  real ii[nt];

  vector<lower = 0>[nObs] cObs; # observed concentration (Dependent Variable)
}

transformed data {
                                ⋮
  biovar[1] = 1;
  biovar[2] = 1;
  biovar[3] = 1;

  tlag[1] = 0;
  tlag[2] = 0;
  tlag[3] = 0;


}
                                ⋮
parameters {
  real<lower = 0> CL;
  real<lower = 0> Q;
  real<lower = 0> V2;
  real<lower = 0> V3;
  real<lower = 0> ka;
  real<lower = 0> sigma;
}

transformed parameters {
                                ⋮
  theta[1] = CL;
  theta[2] = Q;
  theta[3] = V2;
  theta[4] = V3;
  theta[5] = ka;

  x = PKModelTwoCpt(time, amt, rate, ii, evid, cmt, addl, ss,
                    theta, biovar, tlag);

  cHat = col(x, 2) ./ V2; # get concentration in the central compartment

  cHatObs = cHat[iObs]; # predictions for observed data records

 }
                                ⋮
```

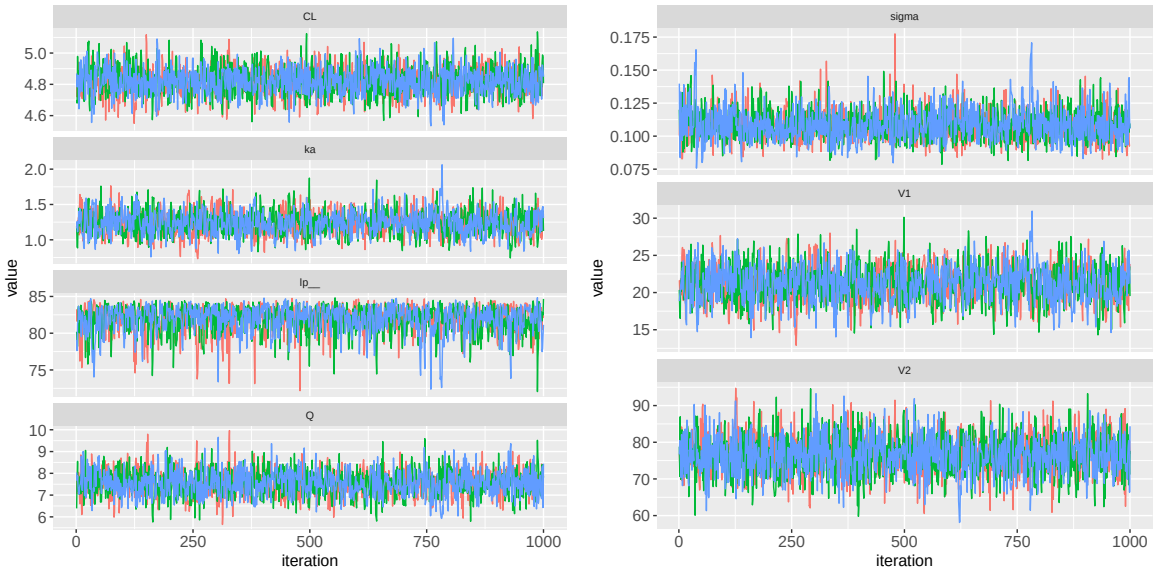

FIGURE 3. MCMC history plots for the parameters of a two compartment model with first order absorption (each color corresponds to a different chain)

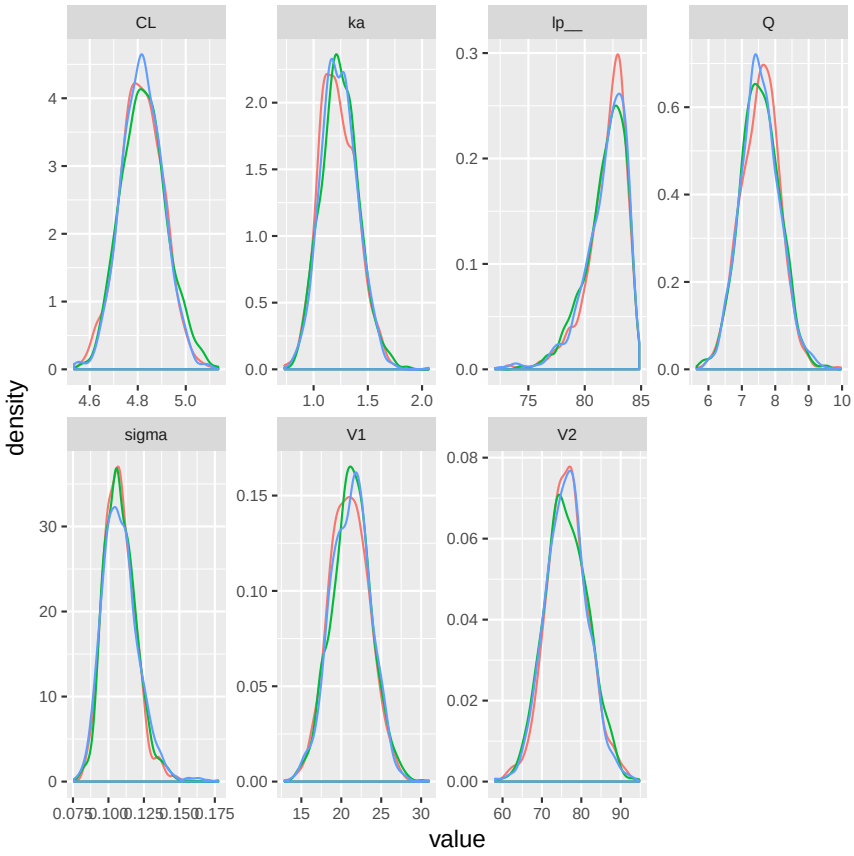

FIGURE 4. Posterior Marginal Densities of the Model Parameters of a two compartment model with first order absorption (each color corresponds to a different chain)

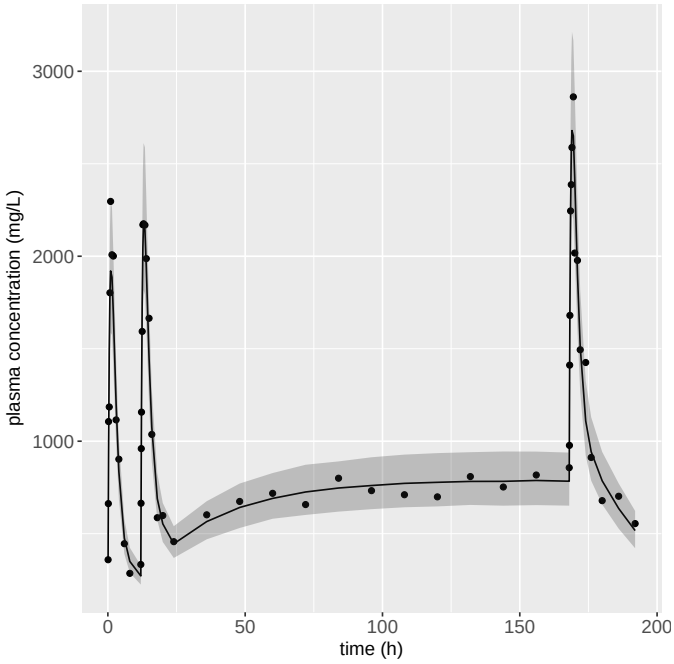

FIGURE 5. Predicted (posterior median and 90 % credible intervals) and observed plasma drug concentrations of a two compartment model with first order absorption

TABLE 1. Summary of the MCMC simulations of the marginal posterior distributions of the model parameters

	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
CL	4.82	0.002	0.0901	4.64	4.76	4.82	4.88	5.00	2464.73	1.00
Q	7.54	0.016	0.58	6.43	7.15	7.54	7.92	8.69	1385.75	1.00
V2	21.14	0.069	2.45	16.37	19.44	21.19	22.78	25.89	1245.64	1.00
V3	76.35	0.110	5.35	65.98	72.75	76.26	79.83	87.30	2379.15	1.00
ka	1.23	0.005	0.169	0.923	1.12	1.23	1.35	1.58	1295.01	1.00
sigma	0.108	0.000	0.012	0.0887	0.0999	0.107	0.115	0.135	1973.97	1.00

2.3. **General Linear ODE Model Function.**

A general linear ODE model refers to a model that may be described in terms of a system of first order linear differential equations with (piecewise) constant coefficients, i.e., a differential equation of the form:

$$y'(t) = Ky(t)$$

where K is a matrix. For example K for a two compartment model with first order absorption is:

$$K = \begin{bmatrix} -k_a & 0 & 0 \\ k_a & -(k_{10} + k_{12}) & k_{21} \\ 0 & k_{12} & -k_{21} \end{bmatrix}$$

where $k_{10} = CL/V2$, $k_{12} = Q/V2$, and $k_{21} = Q/V3$.

The linear ODE model function has the form:

```
linOdeModel(time, amt, rate, ii, evid, cmt, addl, ss,
            system, biovar, tlag)
```

`system` can be:

- the matrix `K`, if the constant rate matrix is the same for all events.
- an array of constant rate matrices. The length of the array is the number of events and each element corresponds to the matrix at the interval [`time[i-1], time[i]`].

`system` contains all the ODE parameters, so we no longer need `theta`.

FIGURE 6. Stan language for fitting a two compartment model using the `linOdeModel` function (abstract)

```
transformed parameters {
  matrix[3, 3] K;
  real k10 = CL / V2;
  real k12 = Q / V2;
  real k21 = Q / V3;
  vector<lower = 0>[nTheta] theta[1];
  vector<lower = 0>[nt] cHat;
  vector<lower = 0>[nObs] cHatObs;
  matrix<lower = 0>[nt, 3] x;

  K = rep_matrix(0, 3, 3);

  K[1, 1] = -ka;
  K[2, 1] = ka;
  K[2, 2] = -(k10 + k12);
  K[2, 3] = k21;
  K[3, 2] = k12;
  K[3, 3] = -k21;

  x = linOdeModel(time, amt, rate, ii, evid, cmt, addl, ss,
                  K, biovar, tlag);

  cHat = col(x, 2) ./ V1;

  cHatObs = cHat[iObs]; # predictions for observed data records

}

model{
  logCObs ~ normal(log(cHatObs), sigma);
}
```

2.4. **General ODE Model Function.**

Torsten may be used to fit models described by a system of first-order ODEs, i.e., differential equations of the form:

$$y'(t) = f(t, y(t))$$

where y and f are vector-valued functions.

The general ODE model functions have the form:

```
<model_name>(ODE_system, nCmt,
             time, amt, rate, ii, evid, cmt, addl, ss,
             theta, biovar, tlag,
             rel_tol, abs_tol, max_step)
```

where `ODE_system` is a system of first-order ODEs defined in the function block of Stan (see section 19.2 of the Stan reference manual) and `nCmt` is the number of compartments (or, equivalently, the number of ODEs) in the model. `rel_tol`, `abs_tol`, and `max_step` are the tuning parameters for the ODE integrator: respectively the relative tolerance, the absolute tolerance, and the maximum number of steps.

The options for `model_name` are:

- generalOdeModel_rk45
- generalOdeModel_bdf

They respectively call the built-in Runge-Kutta 4th/5th order (rk45) integrator, recommended for non-stiff ODEs, and the Backward Differentiation (BDF) integrator, recommended for stiff ODEs. Which value to use for the tuning parameters depends on the integrator and the specifics of the ODE system. Reducing the tolerance parameters and increasing the number of steps make for a more robust integrator but can significantly slow down the algorithm. The following can be used as a starting point: `rel_tol = 1e-6`, `abs_tol = 1e-6` and `max_step = 1e+6` for the rk45 integrator and `rel_tol = 1e-10`, `abs_tol = 1e-10` and `max_step = 1e+8` for the bdf integrator[4]. The user should be prepared to adjust these values. For additional information, see Stan's reference manual (section 19).

[4]These are the default tuning parameters for integrate_ode_rk45() and integrate_ode_bdf(). The Torsten functions do not have a default value. The user must explicitly pass the tuning parameters for generalOdeModel_*().

FIGURE 7. Stan language for fitting a two compartment model using the genOdeModel_rk45 function (abstract)

```
functions{
  # define ODE system for two compartment model
  real[] twoCptModelODE(real t,
                        real[] x,
                        real[] theta,
                        real[] dummy_real,
                        int[] dummy_int){
    real Q = theta[1];
    real CL = theta[2];
    real V2 = theta[3];
    real V3 = theta[4];
    real ka = theta[5];
    real k12 = Q / V2;
    real k21 = Q / V3;
    real k10 = CL / V2;
    real y[3];

    y[1] = -ka * x[1];
    y[2] = ka * x[1] - (k10 + k12)*x[2] + k21*x[3];
    y[3] = k12 * x[2] - k21 * x[3];

    return y;
  }
}
                              ⋮
transformed parameters {
                              ⋮
  theta[1] = CL;
  theta[2] = Q;
  theta[3] = V1;
  theta[4] = V2;
  theta[5] = ka;

  x = generalCptModel_rk45(twoCptModelODE, 3,
                           time, amt, rate, ii, evid, cmt, addl, ss,
                           theta, biovar, tlag,
                           1e-8, 1e-8, 1e8);
                            ⋮
```

TABLE 2. Summary: Arguments of Torsten functions.

model	function name	argument names	parameters in `theta`
one compartment model with first order absorption	`PKModelOneCpt`	`time`, `amt`, `rate`, `ii`, `evid`, `cmt`, `addl`, `ss`, `theta`, `biovar`, `tlag`	CL, V_2, k_a
two compartment model with first order absorption	`PKModelTwoCpt`	`time`, `amt`, `rate`, `ii`, `evid`, `cmt`, `addl`, `ss`, `theta`, `biovar`, `tlag`	CL, Q, V_2, V_3, k_a
general linear compartment model	`linOdeModel`	`time`, `amt`, `rate`, `ii`, `evid`, `cmt`, `addl`, `ss`, `system`, `biovar`, `tlag`	NA: pass in constant rate matrix instead of `theta`
general compartment models	`genOdeModel_*`	`ODE_system`, `nCmt`, `time`, `amt`, `rate`, `ii`, `evid`, `cmt`, `addl`, `ss`, `theta`, `biovar`, `tlag`, `rel_tol`, `abs_tol`, `max_num_steps`	Parameters that get passed to ODE system

3. Additional Examples

Code for examples can be found on GitHub: `https://github.com/charlesm93/example-models/tree/torsten-0.82/PKPD/torsten`.

All the files to run a model are stored under the directory that bears the model's name. There are four files per example:

- `<model name>.stan`
- `<model name>.data.R`
- `<model name>.init.R`
- `<model name>Simulation.R`

`data.R` contains the data we fit the model to and `init.R` the initial estimates of the parameters. These two files are generated using `Simulation.R`. The `R` folder contains R scripts to compile and run the models, as well as code to output diagnostic plots and statistics.

3.1. **Effect Compartment Model.**

Let us expand example 1 to a population model fitted to the combined data from phase I and phase IIa studies. The parameters exhibit inter-individual variations (IIV), due to both random effects and to the patients' body weight, treated as a covariate and denoted *bw*:

Population Model for Plasma Drug Concentration (c).

$$
\begin{aligned}
\log\left(c_{ij}\right) &\sim N\left(\log\left(\widehat{c}_{ij}\right), \sigma^2\right) \\
\widehat{c}_{ij} &= f_{2cpt}\left(t_{ij}, D_j, \tau_j, CL_j, Q_j, V_{1j}, V_{2j}, k_{aj}\right) \\
\log\left(CL_j, Q_j, V_{ssj}, k_{aj}\right) &\sim N\left(\log\left(\widehat{CL}\left(\frac{bw_j}{70}\right)^{0.75}, \widehat{Q}\left(\frac{bw_j}{70}\right)^{0.75}, \widehat{V}_{ss}\left(\frac{bw_j}{70}\right), \widehat{k}_a\right), \Omega\right) \\
V_{1j} &= f_{V_1} V_{ssj} \qquad V_{2j} = \left(1 - f_{V_1}\right) V_{ssj} \\
\left(\widehat{CL}, \widehat{Q}, \widehat{V}_{ss}, \widehat{k}_a, f_{V_1}\right) &= \left(10 \text{ L/h}, 15 \text{ L/h}, 140 \text{ L}, 2 \text{ h}^{-1}, 0.25\right) \\
\Omega &= \begin{pmatrix} 0.25^2 & 0 & 0 & 0 \\ 0 & 0.25^2 & 0 & 0 \\ 0 & 0 & 0.25^2 & 0 \\ 0 & 0 & 0 & 0.25^2 \end{pmatrix}, \quad \sigma = 0.1
\end{aligned}
$$

Furthermore we add a fourth compartment in which we measure a PD effect (figure **??**).

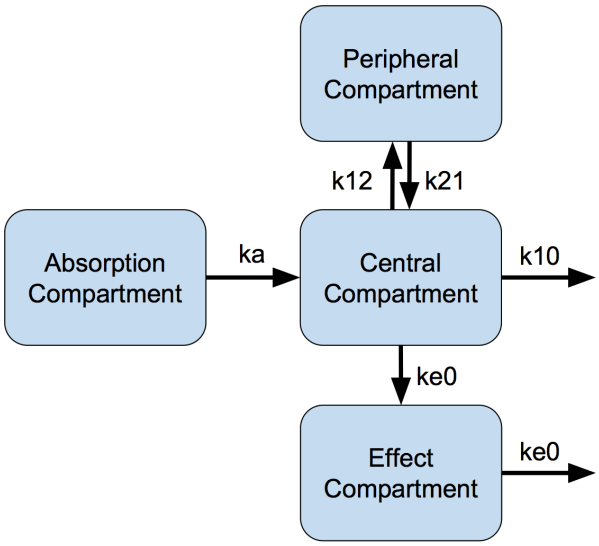

FIGURE 8. Effect Compartment Model

Effect Compartment Model for PD response (R).

$$
\begin{aligned}
R_{ij} &\sim N\left(\widehat{R}_{ij}, \sigma_R^2\right) \\
\widehat{R}_{ij} &= \frac{E_{max} c_{eij}}{EC_{50j} + c_{eij}} \\
c'_{e\cdot j} &= k_{e0j}\left(c_{\cdot j} - c_{e\cdot j}\right) \\
\log\left(EC_{50j}, k_{e0j}\right) &\sim N\left(\log\left(\widehat{EC}_{50}, \widehat{k}_{e0}\right), \Omega_R\right) \\
\left(E_{max}, \widehat{EC}_{50}, \widehat{k}_{e0}\right) &= (100, 100.7, 1) \\
\Omega_R &= \begin{pmatrix} 0.2^2 & 0 \\ 0 & 0.25^2 \end{pmatrix}, \quad \sigma_R = 10
\end{aligned}
$$

The PK and the PD data are simulated using the following treatment.

- Phase I study
  - Single dose and multiple doses
  - Parallel dose escalation design
  - 25 subjects per dose
  - Single doses: 1.25, 5, 10, 20, and 40 mg
  - PK: plasma concentration of parent drug (c)
  - PD response: Emax function of effect compartment concentration (R)
  - PK and PD measured at 0.083, 0.167, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours
- Phase IIa trial in patients
  - 100 subjects
  - Multiple doses: 20 mg
  - sparse PK and PD data (3-6 samples per patient)

FIGURE 9. Stan language for fitting an effect compartment model using `linOdeModel` (abstract)

```
transformed parameters {
  for(j in 1:nSubjects){
                        ⋮
  Omega = quad_form_diag(rho, omega);

  for(j in 1:nSubjects){
    CL[j] = exp(logtheta[j, 1]) * (weight[j] / 70)^0.75;
    Q[j] = exp(logtheta[j, 2]) * (weight[j] / 70)^0.75;
    V1[j] = exp(logtheta[j, 3]) * weight[j] / 70;
    V2[j] = exp(logtheta[j, 4]) * weight[j] / 70;
    ka[j] = exp(logtheta[j, 5]);
    ke0[j] = exp(logKe0[j]);
    EC50[j] = exp(logEC50[j]);

    k10 = CL[j] / V1[j];
    k12 = Q[j] / V1[j];
    k21 = Q[j] / V2[j];
    ke0[j] = exp(logKe0[j]);
    EC50[j] = exp(logEC50[j]);

    K = rep_matrix(0, 4, 4);

    K[1, 1] = -ka[j];
    K[2, 1] = ka[j];
    K[2, 2] = -(k10 + k12);
    K[2, 3] = k21;
    K[3, 2] = k12;
    K[3, 3] = -k21;
    K[4, 2] = ke0[j];
    K[4, 4] = -ke0[j];

    x[start[j]:end[j],] = linOdeModel(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]],
                                      K, biovar, tlag);

    cHat[start[j]:end[j]] = 1000 * x[start[j]:end[j], 2] ./ V1[j];
    ceHat[start[j]:end[j]] = 1000 * x[start[j]:end[j], 4] ./ V1[j];
    respHat[start[j]:end[j]] = 100 * ceHat[start[j]:end[j]] ./
       (EC50[j] + ceHat[start[j]:end[j]]);
  }

  cHatObs = cHat[iObs];
  respHatObs = respHat[iObs];
}
                        ⋮
}
```

The model is simultaneously fitted to the PK and the PD data. For this effect compartment model, we construct a constant rate matrix and use `linOdeModel`. Correct use of Torsten requires the user pass the entire event history (observation and dosing events) for an individual to the function. Thus the Stan model shows the call to `linOdeModel` within a loop over the individual subjects rather than over the individual observations.

Results. We use the same diagnosis tools as for the previous example. The MCMC history plots (figure **??**) suggest the 4 chains have converged to common distributions. We note some minor auto-correlations for $lp\_$ (the log posterior) and for IIV parameters: specifically Ω_{ke_0} and ρ. The correlation matrix ρ does not explicitly appear in the model, but it is used to construct Ω, which parametrizes the PK IIV. The fits to the plasma concentration (figure **??**) are in close agreement with the data, notably for the sparse data

case (phase IIa study). The fits to the PD data (figure **??**) look good, though the data is more noisy. The model reflects the noise by producing larger credible intervals. The estimated values of the parameters are consistent with the values used to simulate the data.

TABLE 3. Summary of the MCMC simulations of the marginal posterior distributions of the model parameters for example 2

	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
CLHat	10.523	0.003	0.201	9.712	9.958	10.096	10.231	10.483	4000.000	0.999
QHat	14.867	0.014	0.357	14.182	14.620	14.862	15.106	15.563	678.208	1.007
V1Hat	34.188	0.067	1.089	31.940	33.494	34.214	34.918	36.251	267.748	1.016
V2Hat	103.562	0.076	2.925	98.031	101.600	103.455	105.472	109.583	488.296	1.001
kaHat	1.930	0.004	0.077	1.771	1.880	1.933	1.982	2.076	334.888	1.014
ke0Hat	1.050	0.001	0.044	0.967	1.020	1.051	1.078	1.137	164.741	1.000
EC50Hat	104.337	0.040	2.100	100.169	102.909	104.345	105.768	108.351	744.041	1.000
sigma	0.099	0.000	0.002	0.095	0.097	0.099	0.100	0.103	906.342	1.002
sigmaResp	10.156	0.003	0.197	9.779	10.023	10.154	10.286	10.552	4000.000	1.000
omega[1]	0.270	0.000	0.016	0.241	0.259	0.269	0.280	0.302	4000.000	1.001
omega[2]	0.231	0.001	0.021	0.192	0.217	0.230	0.245	0.275	531.512	1.006
omega[3]	0.219	0.002	0.031	0.158	0.199	0.218	0.238	0.281	158.198	1.017
omega[4]	0.267	0.001	0.026	0.218	0.249	0.266	0.284	0.319	684.870	1.001
omega[5]	0.285	0.002	0.037	0.214	0.259	0.284	0.309	0.361	284.545	1.009
omegaKe0	0.271	0.003	0.047	0.183	0.239	0.271	0.303	0.363	217.350	1.007
omegaEC50	0.213	0.001	0.021	0.174	0.199	0.213	0.227	0.255	190.193	1.000

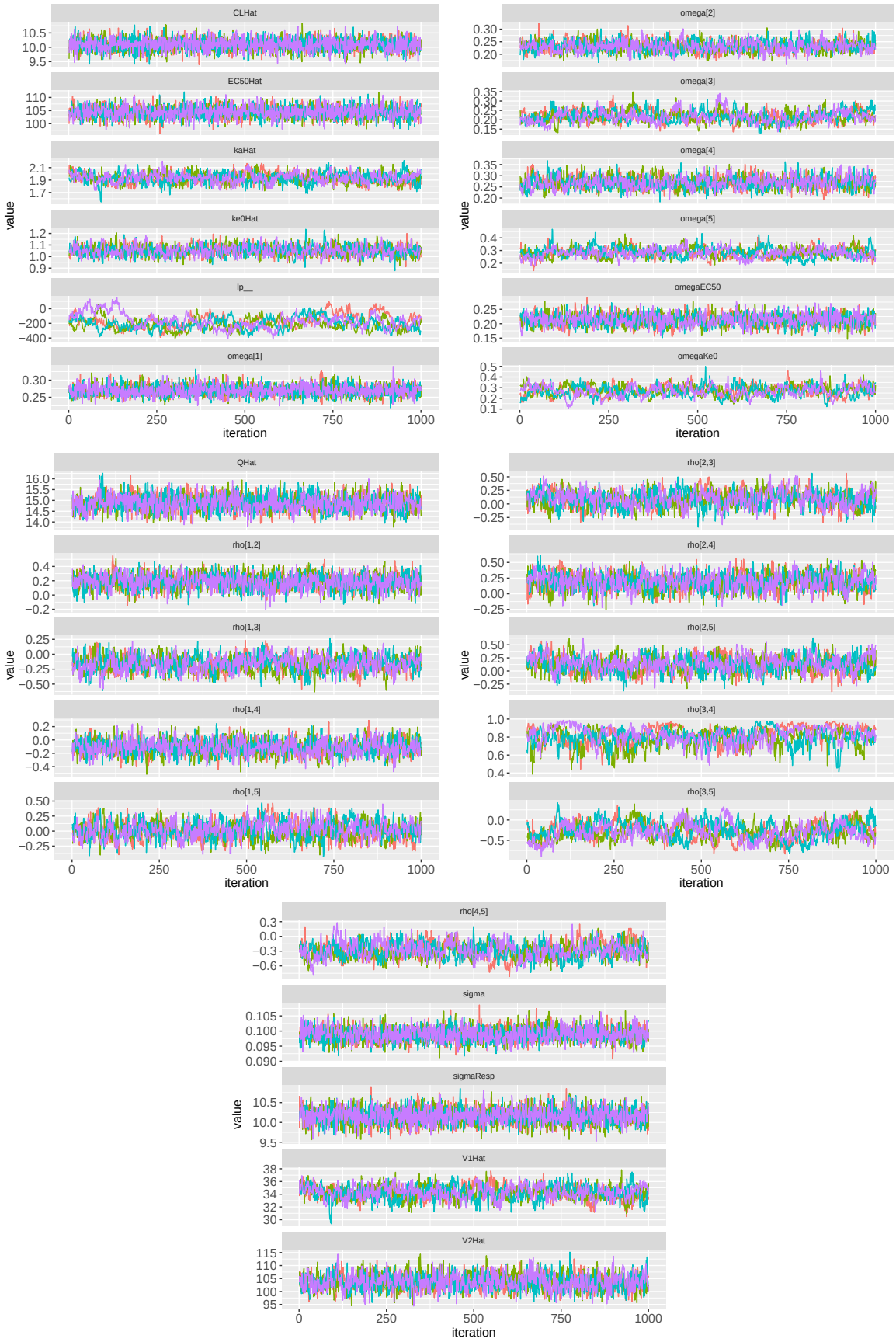

FIGURE 10. MCMC history plots for the parameters of an Effect Compartment Model (each color corresponds to a different chain) for example 2

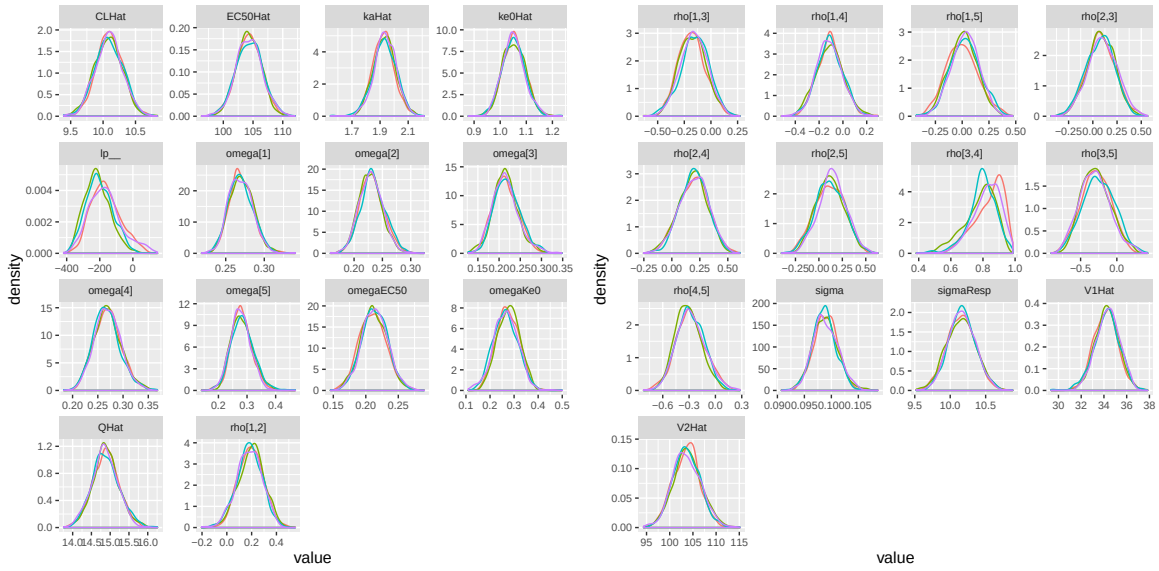

FIGURE 11. Posterior Marginal Densities of the Model Parameters of an Effect Compartment Model (each color corresponds to a different chain) for example 2

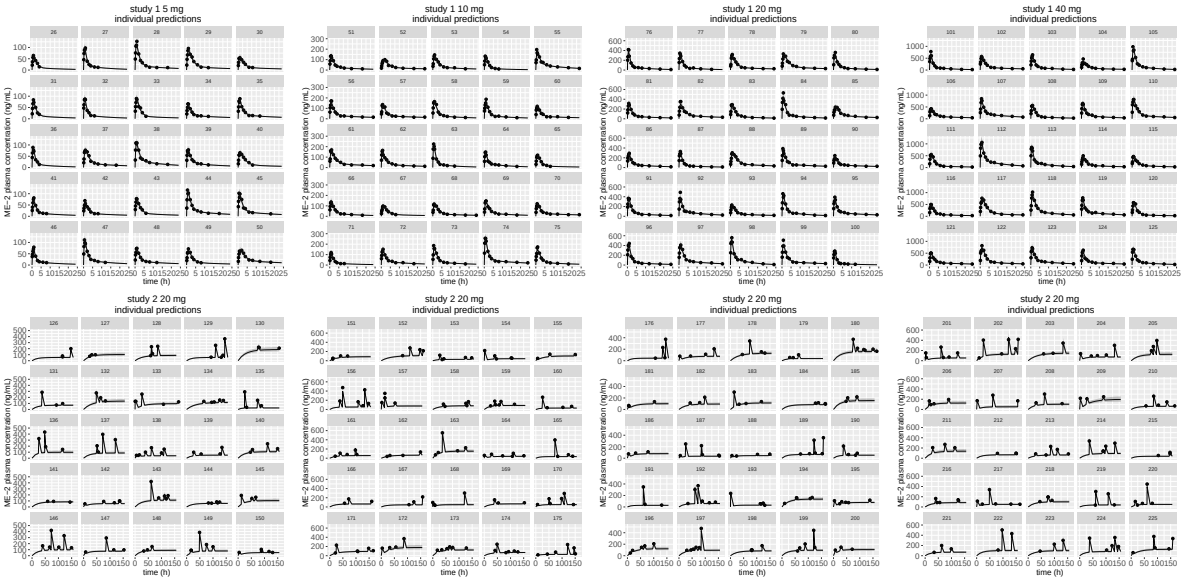

FIGURE 12. Predicted (posterior median and 90 % credible intervals) and observed plasma drug concentrations for example 2 for an Effect Compartment Model

FIGURE 13. Predicted (posterior median and 90 % credible intervals) and observed PD Response for example 2

3.2. **Friberg-Karlsson Semi-Mechanistic Model [?].**

In this third example, we deal with a more sophisticated PD effect, described by a system of nonlinear ODEs. The PK effects are still described by a two compartment model with a first-order absorption.

Neutropenia is observed in patients receiving an ME-2 drug. Our goal is to model the relation between neutrophil counts and drug exposure. Using a feedback mechanism, the body maintains the number of neutrophils at a baseline value (figure **??**). While in the patient's blood, the drug impedes the production of neutrophils. As a result, the neutrophil count goes down, and after the drug clears out, the feedback mechanism kicks in and brings the neutrophil count back to baseline.

Friberg-Karlsson Model for drug-induced myelosuppression (ANC)

$$
\begin{aligned}
\log(ANC_{ij}) &\sim N(Circ_{ij}, \sigma^2_{ANC}) \\
\log\left(MTT_j, Circ_{0j}, \alpha_j\right) &\sim N\left(\log\left(\widehat{MTT}, \widehat{Circ_0}, \widehat{\alpha}\right), \Omega_{ANC}\right) \\
\left(\widehat{MTT}, \widehat{Circ_0}, \widehat{\alpha}, \gamma\right) &= (125, 5, 2, 0.17) \\
\Omega_{ANC} &= \begin{pmatrix} 0.2^2 & 0 & 0 \\ 0 & 0.35^2 & 0 \\ 0 & 0 & 0.2^2 \end{pmatrix}, \quad \sigma_{ANC} = 0.1 \\
\Omega_{PK} &= \begin{pmatrix} 0.25^2 & 0 & a0 & 0 & 0 \\ 0 & 0.4^2 & 0 & 0 & 0 \\ 0 & 0 & 0.25^2 & 0 & 0 \\ 0 & 0 & 0 & 0.4^2 & 0 \\ 0 & 0 & 0 & 0 & 0.25^2 \end{pmatrix}
\end{aligned}
$$

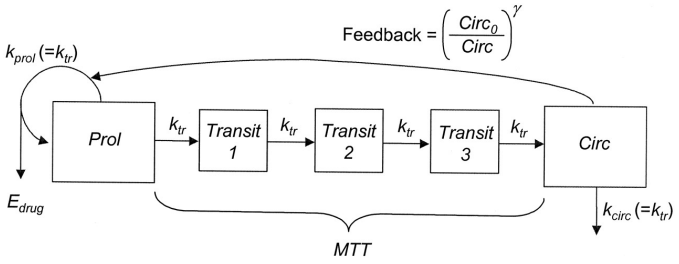

FIGURE 14. Friberg-Karlsson semi-mechanistic Model [**?**]

The PK and the PD data are simulated using the following treatment.

- Phase IIa trial in patients
  - Multiple doses: 80,000 mg
  - Parallel dose escalation design
  - 15 subjects
  - PK: plasma concentration of parent drug (c)
  - PD response: Neutrophil count (ANC)
  - PK measured at 0.083, 0.167, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours
  - PD measured once every two days for 28 days.

FIGURE 15. Stan language for coding an ODE system describing a Friberg-Karlsson Mechanism

```
real[] twoCptNeutModelODE(real t,
                real[] x,
                real[] parms,
                real[] rdummy,
                int[] idummy){
real CL = parms[1];
real Q = parms[2];
real V2 = parms[3];
real V3 = parms[4];
real ka = parms[5];
real mtt = parms[6];
real circ0 = parms[7];
real gamma = parms[8];
real alpha = parns[9];
real k10 = CL / V2;
real k12 = Q / V2;
real k21 = Q / V3;
real ktr = 4 / mtt;
real dxdt[8];
real conc;
real EDrug;
real transit1;
real transit2;
real transit3;
real circ;
real prol;

dxdt[1] = -ka * x[1];
dxdt[2] = ka * x[1] - (k10 + k12) * x[2] + k21 * x[3];
dxdt[3] = k12 * x[2] - k21 * x[3];
conc = x[2]/V1;
EDrug = alpha * conc;
// x[4], x[5], x[6], x[7] and x[8] are differences from circ0.
prol = x[4] + circ0;
transit1 = x[5] + circ0;
transit2 = x[6] + circ0;
transit3 = x[7] + circ0;
circ = fmax(machine_precision(), x[8] + circ0); // Device for implementing a modeled
                                                // initial condition
dxdt[4] = ktr * prol * ((1 - EDrug) * ((circ0 / circ)^gamma) - 1);
dxdt[5] = ktr * (prol - transit1);
dxdt[6] = ktr * (transit1 - transit2);
dxdt[7] = ktr * (transit2 - transit3);
dxdt[8] = ktr * (transit3 - circ);

return dxdt;
}
```

Once again, we simultaneously fit the model to the PK and the PD data. From a computational perspective, this is a much more difficult problem than the one we dealt with in previous examples. The nonlinear nature of the ODEs forces us to use a numerical solver, which is significantly slower than the linear methods we have employed so far. Because the ODE system of interest is non-stiff, we use the *rk45* version of `genOdeModel`.

It pays off to construct informative priors. For instance, we could fit the PK data first, as was done in example 1, and get informative priors on the PK parameters. The PD parameters are drug independent, so we can use information from the neutropenia literature. In this example, we choose to use weakly informative priors on the PK parameters and strongly informative priors on the PD parameters.

Since it takes a long time to run the model, we only use 100 iterations per chain, and study what we can learn from this less than optimal scenario. It is worth noting that Stan, because of its highly efficient MCMC sampler, still does a reasonable job estimating the posterior distribution.

FIGURE 16. Stan language for fitting a Friberg-Karlsson model using `genCptModel_rk45` (abstract)

```
transformed parameters {
                      :
                      :
  for(i in 1:nSubjects) {

    parms[1] = thetaM[i, 1] * (weight[i] / 70)^0.75; # CL
    parms[2] = thetaM[i, 2] * (weight[i] / 70)^0.75; # Q
    parms[3] = thetaM[i, 3] * (weight[i] / 70); # V1
    parms[4] = thetaM[i, 4] * (weight[i] / 70); # V2
    parms[5] = kaHat; # ka
    parms[6] = thetaM[i, 5]; # mtt
    parms[7] = thetaM[i, 6]; # circ0
    parms[8] = gamma;
    parms[9] = thetaM[i, 7]; # alpha

    x[start[i]:end[i]] = generalOdeModel_rk45(twoCptNeutModelODE, 8,
                                              time[start[i]:end[i]],
                                              amt[start[i]:end[i]],
                                              rate[start[i]:end[i]],
                                              ii[start[i]:end[i]],
                                              evid[start[i]:end[i]],
                                              cmt[start[i]:end[i]],
                                              addl[start[i]:end[i]],
                                              ss[start[i]:end[i]],
                                              parms, biovar, tlag,
                                              1e-6, 1e-6, 1e6);

    cHat[start[i]:end[i]] = x[start[i]:end[i], 2] / parms[1][3]; # divide by V1
    neutHat[start[i]:end[i]] = x[start[i]:end[i], 8] + parms[1][7]; # Add baseline

  }

  cHatObs = cHat[iObsPK];
  neutHatObs = neutHat[iObsPD];

                      :
                      :
```

Results. The MCMC history plots are not as convincing as in the previous examples, mostly because the number of iterations is small (100 versus 1000 in the previous example). It does however look as though the chains are converging to a common distribution, and we see little auto-correlation (in particular, we expect that if we had run the model for 1000 iterations, we would obtain the desired "fuzzy caterpillar" look). The plots of the marginal posterior distributions clearly show that the chains have not (yet) converged to a common distribution, but they do not disagree significantly. Still, the need for more iterations is evident. The model fits the data, and the credible interval reflect the noise in the data. The parameters estimation reflects the real value of the parameters.

TABLE 4. Summary of the MCMC simulations of the marginal posterior distributions of the model parameters for example 3

	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
CL	9.986	0.009	0.174	9.641	9.872	9.982	10.107	10.331	400.000	0.997
Q	14.633	0.055	1.106	12.505	13.992	14.623	15.296	16.948	400.000	0.996
V1	32.909	0.174	2.439	28.203	31.186	32.836	34.762	37.750	195.828	1.008
V2	106.631	0.311	6.226	95.234	102.269	106.403	111.000	118.533	400.000	0.999
ka	1.882	0.012	0.175	1.582	1.756	1.871	2.006	2.223	196.052	1.007
sigma	0.106	0.001	0.010	0.089	0.098	0.105	0.112	0.132	259.693	1.009
alpha	3.3E-04	1.4E-06	2.2E-05	2.9E-04	3.2E-04	3.3E-04	3.5E-04	3.8E-04	247	1.01
mtt	132.763	0.515	6.498	120.843	128.082	132.223	136.694	146.845	159.372	1.024
circ0	5.014	0.009	0.172	4.711	4.888	5.000	5.138	5.334	400.000	1.000
gamma	0.190	0.002	0.022	0.153	0.175	0.187	0.202	0.239	139.485	1.025
sigmaNeut	0.092	0.001	0.014	0.068	0.082	0.090	0.100	0.125	161.199	1.010

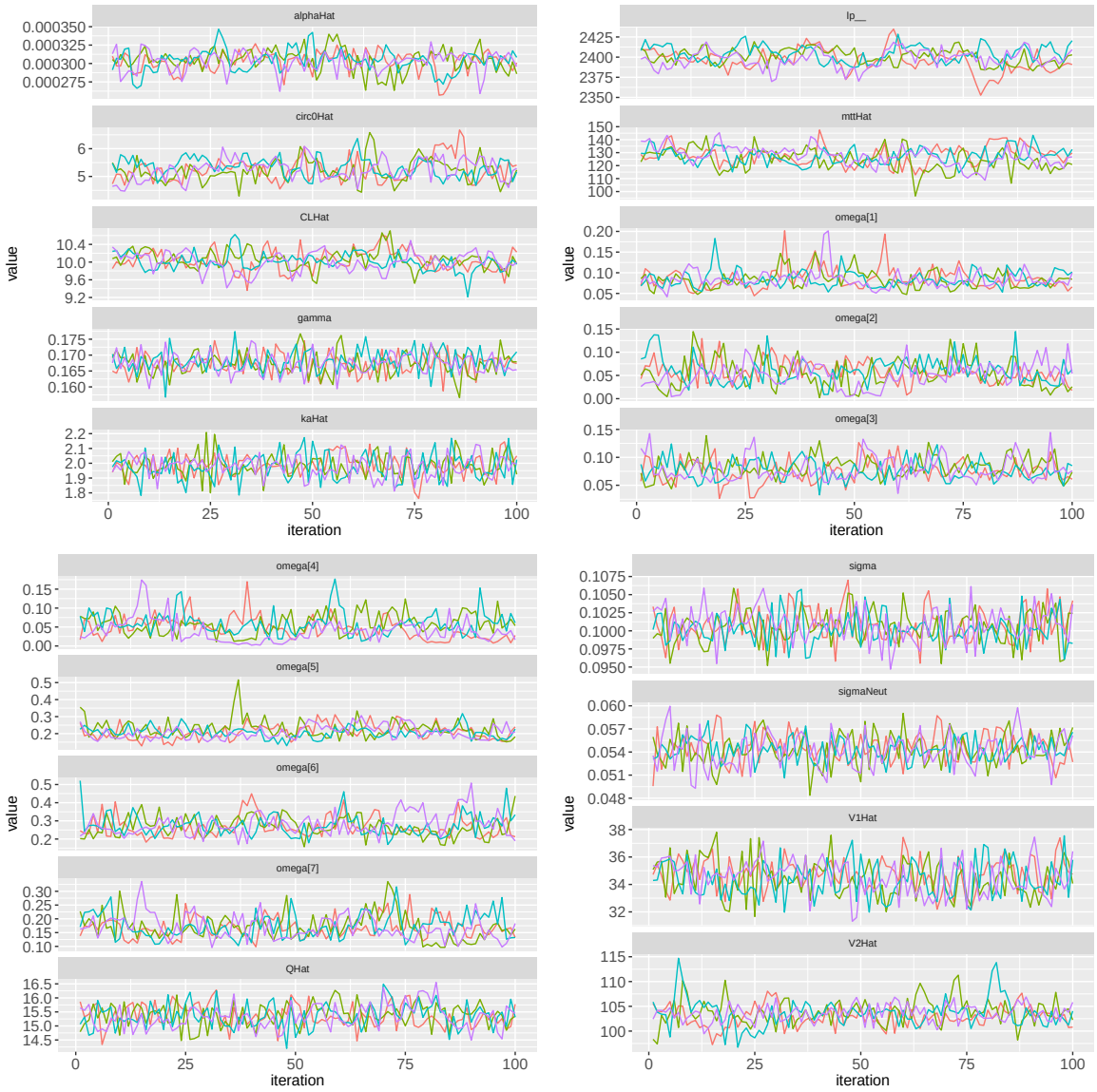

FIGURE 17. MCMC history plots for the parameters of a Friberg-Karlsson semi-mechanistic model (each color corresponds to a different chain) for example 3

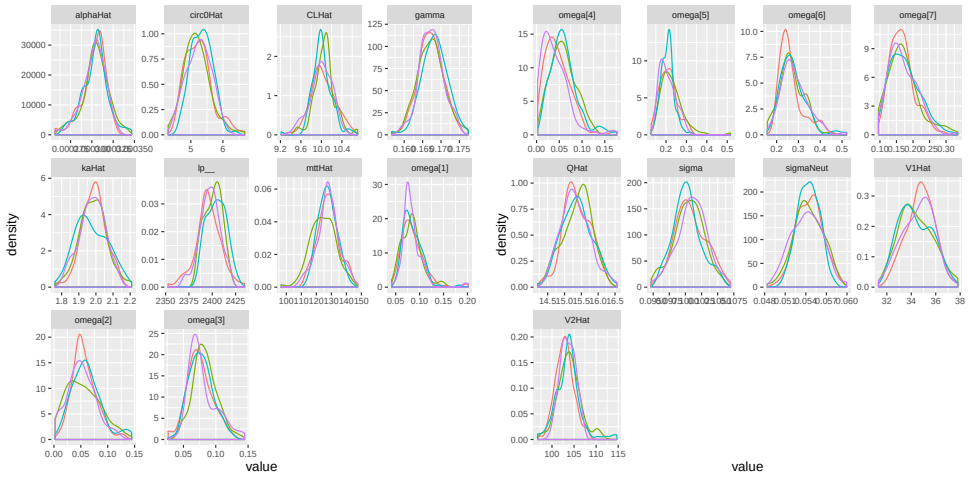

FIGURE 18. Posterior Marginal Densities of the Model Parameters of a Friberg-Karlsson semi-mechanistic model (each color corresponds to a different chain)

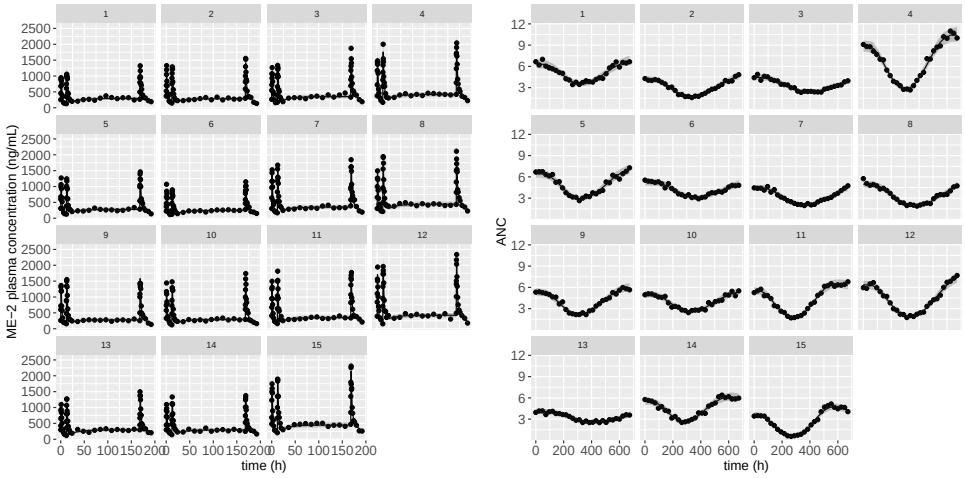

FIGURE 19. Predicted (posterior median and 90 % credible intervals) and observed plasma drug concentrations, and Neutrophil counts, for a Friberg-Karlsson semi-mechanistic model

4. Technical Appendix

The details we cover here are not required to use Torsten but may be of interest to developers and advanced users. Our goal is to motivate the development of Torsten by looking at common challenges in pharmacometrics. The problems we address are mostly mathematical in nature but scientifically motivated. We discuss why Stan strikes us as a powerful tool to analyse data; and which needs in pharmacometrics Torsten answers. We then go over the algorithms and programming techniques we deploy in Torsten.

4.1. **Differential Equations Based Models.**

The following section is in part based on a presentation we gave at the 2017 Stan Conference [**?**] and motivates the use of Ordinary Differential Equations (ODEs) in pharmacometrics.

4.1.1. *When do Ordinary Differential Equations Arise?*

We deal with an ODE when we want to determine a function $y(t)$ at a specific time but only know the derivative of that function, $\frac{dy}{dt}$. In other words, we know the rate at which a quantity of interest changes but not the quantity itself. In many scenarios, the rate depends on the quantity itself.

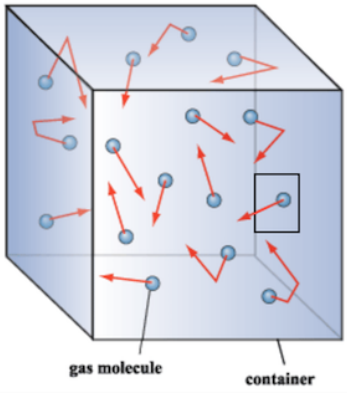

Figure 20. Gas container with a hole. The rate at which the gas leaks is proportional to the amount of gas in the container. We can describe this physical process using the differential equation $\frac{dy}{dt} = -ky(t)$, where y is the amount of gas in the container. **Will need to create our own figure**

To get a basic intuition, let us consider an example. Imagine a gas container with a hole in it (figure **??**). We can think of the gas as being made of molecules that move randomly in the container. Each molecule has a small chance of leaking through the hole. Thus the more molecules inside the container, the higher the number of escaping molecules per unit time. If there are a large number of molecules, and the gas behaves like a continuous fluid, we observe that the more gas in the container, the higher the leakage. This statement can be written as the differential equation:

$$\frac{dy}{dt} = -ky(t)$$

where k is a positive constant.

In a pharmacokinetic-pharmacodynamic (PKPD) compartment model, we treat physiological components, such as organs, tissues, and circulating blood, as compartments between which the drug flows and/or in which the drug has an effect. A compartment may refer to more than one physiological component. For example, the central compartment typically consists of the systemic circulation (the blood) plus tissues and organs into which the drug diffuses rapidly.

Just like our leaking gas in a container, the rate at which the quantity of drug changes depends on the drug amount in the various compartments. Things are slightly more complicated because instead of one box, we now deal with a network of containers. This results in a system of differential equations.

4.1.2. *An Example: ODE system for the Two Compartment Model.*

Consider the common scenario in which a patient orally takes a drug. The drug enters the body through the gut and is then absorbed into the blood. From there it diffuses into and circulates back and forth between various tissues and organs. Over time, the body clears the drug, i.e. the drug exits the body (for instance through urine) (figure **??**).

Our model divides the patient's body into three compartments:

- **The absorption compartment**: the gut
- **The central compartment**: the systemic circulation (blood) and tissues/organs into which the drug diffuses rapidly
- **The peripheral compartment**: other tissues/organs into which the drug distributes more slowly

We conventionally call this a *Two Compartment Model*, which may seem odd since the model has three compartments. The idea is that the "absorption compartment" doesn't really count. We adopt this convention mostly to agree with the community.

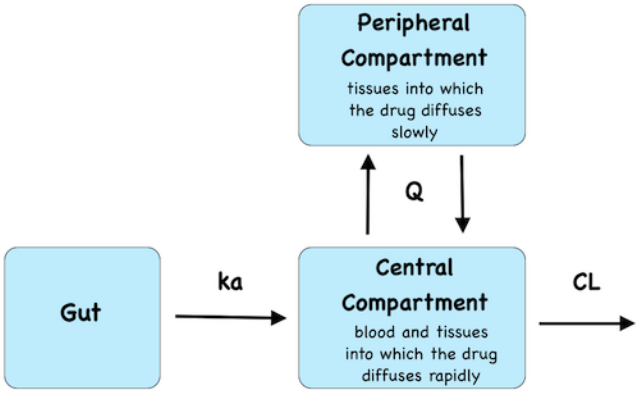

FIGURE 21. Two Compartment Model: Describes the absorption of a drug in a patient's body.

We describe the drug absorption using the following differential equations:

$$\begin{aligned}
\frac{dy_{\text{gut}}}{dt} &= -k_a y_{\text{gut}} \\
\frac{dy_{\text{central}}}{dt} &= k_a y_{\text{gut}} - (\frac{CL}{V_{\text{central}}} + \frac{Q}{V_{\text{central}}}) y_{\text{central}} + \frac{Q}{V_{\text{peripheral}}} y_{\text{peripheral}} \\
\frac{dy_{\text{peripheral}}}{dt} &= \frac{Q}{V_{\text{central}}} y_{\text{central}} - \frac{Q}{V_{\text{peripheral}}} y_{\text{peripheral}}
\end{aligned}$$

with
y_{gut} : the drug amount in the gut (mg)
y_{central} : the drug amount in the central compartment (mg)
$y_{\text{peripheral}}$: the drug amount in the peripheral compartment (mg)
k_a : the rate constant at which the drug flows from the gut to the central compartment (h^{-1})
Q : the clearance at which the drug flows back and forth between the central and the peripheral compartment (L/h)
CL : the clearance at which the drug is cleared from the central compartment (L/h)
V_{central} : the volume of the central compartment (L)
$V_{\text{peripheral}}$: the volume of the peripheral compartment (L)

The data we fit our model to is the drug concentration in the blood, which our model treats as the concentration in the central compartment, and is given by:

$$c = \frac{y_{\text{central}}}{V_{\text{central}}}$$

4.1.3. *Overview of Tools for Solving Differential Equations.*

Solving ODEs can be notoriously hard.

In the best case scenario, an ODE system has an analytical solution we can hand-code (as we have done for the one and two compartment model). The vast majority of times, we need to approximate the solution numerically. There exists a very nice technique, involving matrix exponentials, for solving linear ODEs. Nonlinear systems are significantly more difficult but fortunately we can tackle these problems with numerical integrators.

Specialized algorithms for solving ODEs tend be more efficient but have a narrower application; the reverse holds for more general tools. We provide both, thereby allowing users to tackle a broad range of problems and optimize their model when possible (figure **??**).

4.1.4. *The Event Schedule.*

The ODE system only describes the natural evolution of the patient's system, i.e, how does the drug behave once it is already in the body. It does not account for outside interventions, such as drug intake. To be accurate, our models must compute these exterior events and solve ODEs in the context of an event schedule.

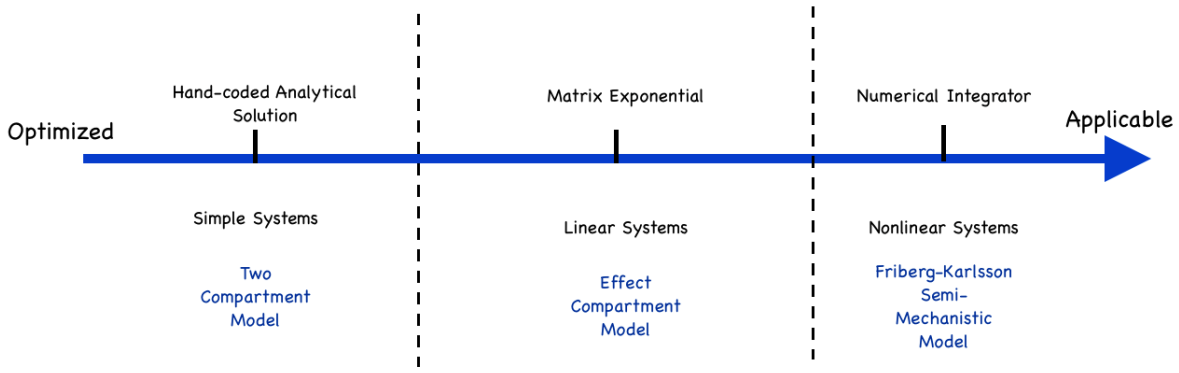

FIGURE 22. The "Optimized-Applicable Spectrum" of tools for solving differential equations: the top line gives the technique to solve differential equations, the next line the type of ODE system this method should be applied to, and the third line (in blue) an example from pharmacometrics. We discuss these examples in greater details in sections 2 and 3 of the manual.

We follow the convention set by NONMEM®[5], which is popular amongst pharmacometricians and which we find acceptable.

An event can either be a change in the state of the system or the observation of a certain quantity. We label these types:

(1) **State changer**: an (exterior) intervention that alters the state of the system, such as a bolus dosing
(2) **Observation**: usually specifies the time and the quantity of interest at which a measurement occurs

Between two subsequent events, the ODEs fully describe the PKPD system. Knowing the state y_0 at time t_0 fully defines the solution at finite times. Exploiting this property, Torsten calculates amounts in each compartment from one event to the other. The initial conditions of the ODEs are specified by the previous event and the ODEs integrated from t_{previous} to t_{current}.

If an event is a state changer, Torsten computes the changes in the state after integrating the ODEs.

The users passes the event schedule using a data table. NONMEM's convention allows one row to code for multiple events. For example, a single row can specify a patient receives multiple doses at a regular time interval. Consider:

```
TIME = 0, EVID = 1, CMT = 1, AMT = 1500, RATE = 0, ADDL = 4, II = 10, SS = 0
```

This row specifies that a time 0 (TIME = 0), a patient receives a 1500 mg (AMT = 1500) drug dose (EVID = 1) in the gut (CMT = 1), and will receive an additional dose every 10 hours (II = 10) until the patient has taken a total of 5 doses (ADDL = 4, being the number of additional doses, + 1, the original dose).

[5]NONMEM® is licensed and distributed by ICON Development Solutions.

Such an event really corresponds to 5 dosing events. Torsten augments the event schedule accordingly, before solving the ODEs recursively from one event to the other.

In summary, all Torsten functions:

(1) augment the event schedule to include all state changers
(2) calculate the amounts in each compartment at each event of the augmented schedule by
    (a) integrating the ODEs and computing the *natural* evolution of the system
    (b) computing the effects of state changers
(3) return the amounts at each event of the original schedule.

4.2. **Code Structure of Torsten Functions.**

The previous section lays out the problem from a pharmacometrics perspective. If we can solve differential equations and handle the event schedule, we can simulate data from a pharmacometrics model. Fitting the model to data is another challenge we need to address, and which we will cover in future sections.

We offer five functions in Torsten, which only differ in task (2)(a): solving the ODEs.

4.3. **Bayesian Data Analysis with Stan.**

4.4. **Tools for Solving Differential Equations.**

4.5. **Implementing Torsten.**

Stan's `math` library is written in C++, which offers a great deal of speed and flexibility. The Stan language provides a very handy interface that allows us to focus on statistical modeling and saves us the trouble of doing extensive coding in C++. At run time, a *make* file translates our Stan model into C++, which then gets compiled and executed. Accordingly, there are two steps to add a function to Stan: (1) write the procedure in C++, (2) expose the procedure to the language so users may use it in a Stan file.

The Stan code is open-source and available on GitHub. It is compartmentalized into several repos: `math` contains the mathematical functions, `stan` exposes these functions. Other repos provide code to interface Stan with higher level languages, such as R and Python. Torsten exists as a forked version of `math` and `stan`. Other repos remain unchanged.

Regularly, we merge Stan's latest release into Torsten.

Modifications in math. All Torsten files are located in the `Torsten` directory, under `stan/math`. The code can be found on GitHub: `https://github.com/charlesm93/math`

Modifications in Stan. We do further modifications in `stan` to expose Torsten's functions. We edit `function_signatures.h` to expose `PKModelOneCpt`, `PKModelTwoCpt`, and `linOdeModel`. The general ODE model functions are higher-order functions (i.e. they take another function as one of their arguments). They are exposed by directly modifying the grammar files, following closely the example of `integrate_ode_rk45` and `integrate_ode_bdf`.

The code can be found on GitHub: `https://github.com/charlesm93/stan`.

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