METRUM
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Prototype Stan Functions for Bayesian Pharmacometric Modeling

Bill Gillespie & Charles Margossian

Metrum Research Group

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What Stan already brings to the PMX party

- More flexible model specification language than the usual suspects.
- Numerical ODE solvers
  - Non-stiff solver: Runge-Kutta 4th/5th order
  - Stiff solver: Backward differentiation formula (CVODES BDF method)

On the drawing board

- Additional ODE solvers
  - Adams-Mouton
  - Matrix exponential
- Root solver(s)
  - Needed for steady-state calculations
- More flexible and generalizable approach to discrete event handling
  - Dose events
  - Reset events
  - Other ODE discontinuities, e.g., changes in parameter values

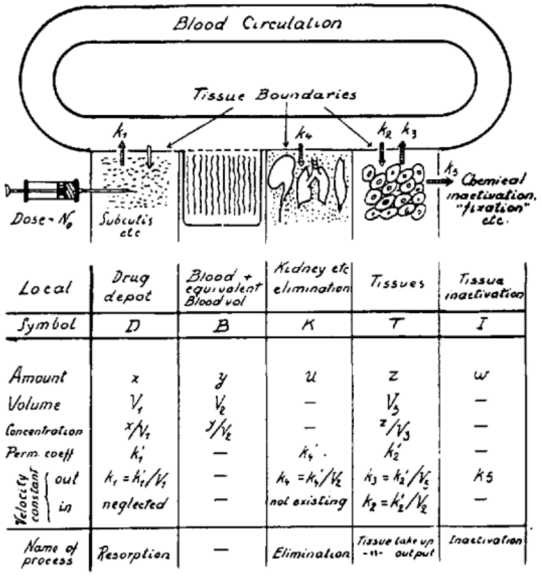
A little something we put together: Torsten: Prototype PKPD functions

Objective: A set of Stan functions that replicates the functionality of NONMEM's PREDPP library

Current status:

- Functions in current prototype:
  - One & two compartment PK models with 1st order absorption
    - PKModelOneCpt(theta, time, amt, rate, ii, evid, cmt, addl, ss)
    - PKModelTwoCpt(theta, time, amt, rate, ii, evid, cmt, addl, ss)
  - General compartmental model specified as a system of 1st order ODEs
    - GeneralCptModel_rk45(odeFunction, nCmt, theta, time, amt, rate, ii, evid, cmt, addl, ss, rel_tol, abs_tol, max_num_steps)
    - GeneralCptModel_bdf(odeFunction, nCmt, theta, time, amt, rate, ii, evid, cmt, addl, ss, rel_tol, abs_tol, max_num_steps)

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_3'	k_2'	–
Velocity constant out	$k_1 = k_1'/V_1$	–	$k_3 = k_3'/V_2$	$k_3 = k_2'/V_2$	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.

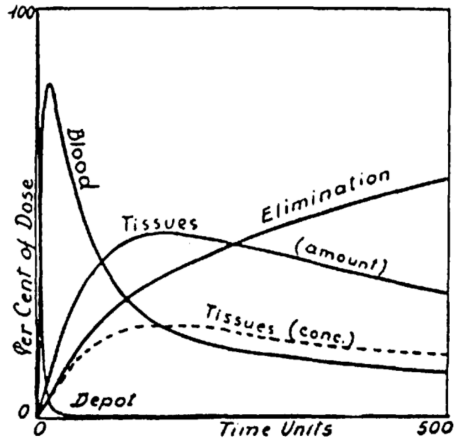


FIG. 3

Typical Case of Extravascular Administration in the absence of tissue inactivation.

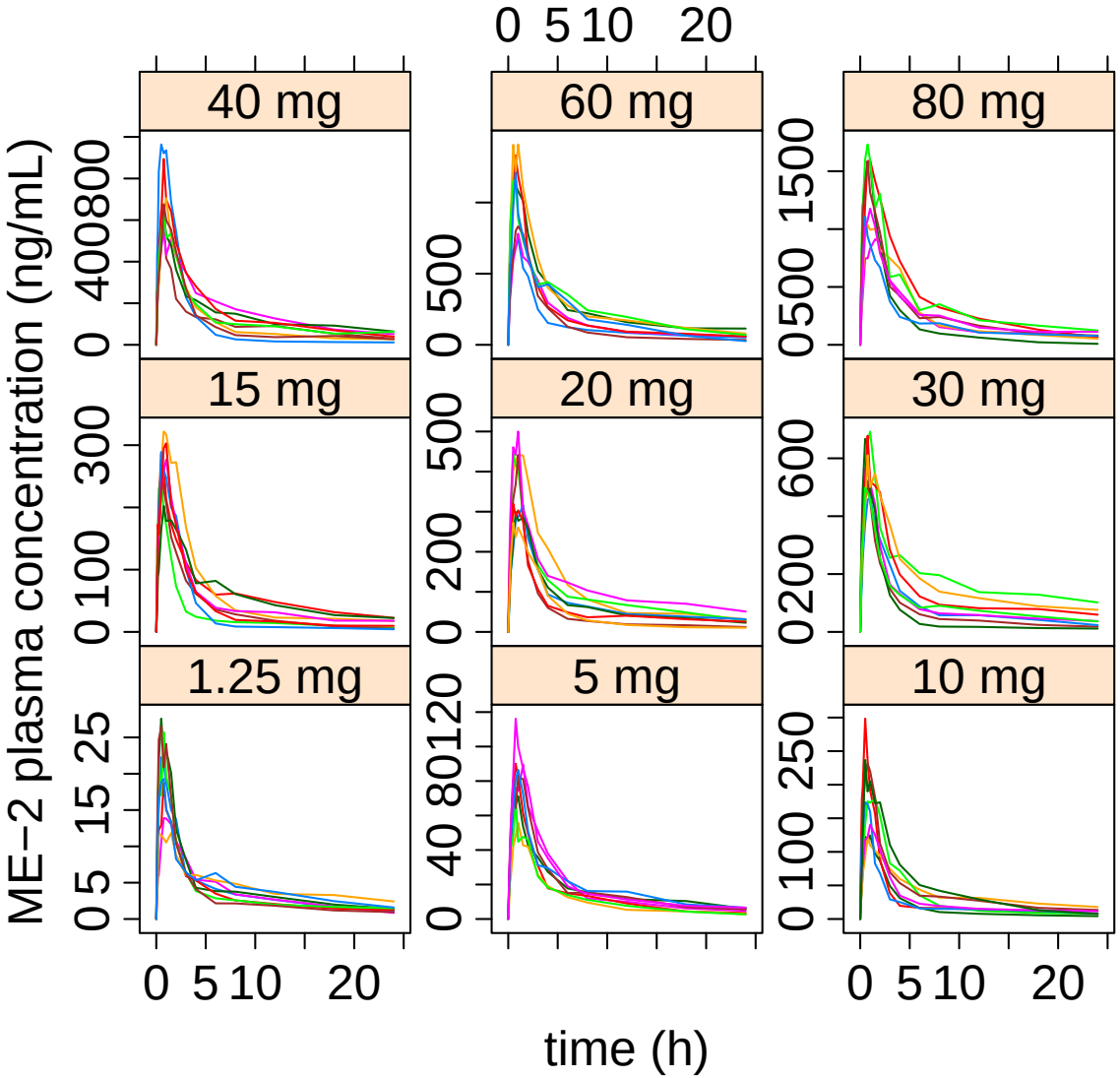
($k_1 = 0.2$; $k_2 = 0.01$; $k_3 = 0.005$; i.e. "blood" volume/"tissue" volume is 1 : 2; $k_4 = 0.005$; $k_5 = 0$).

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.

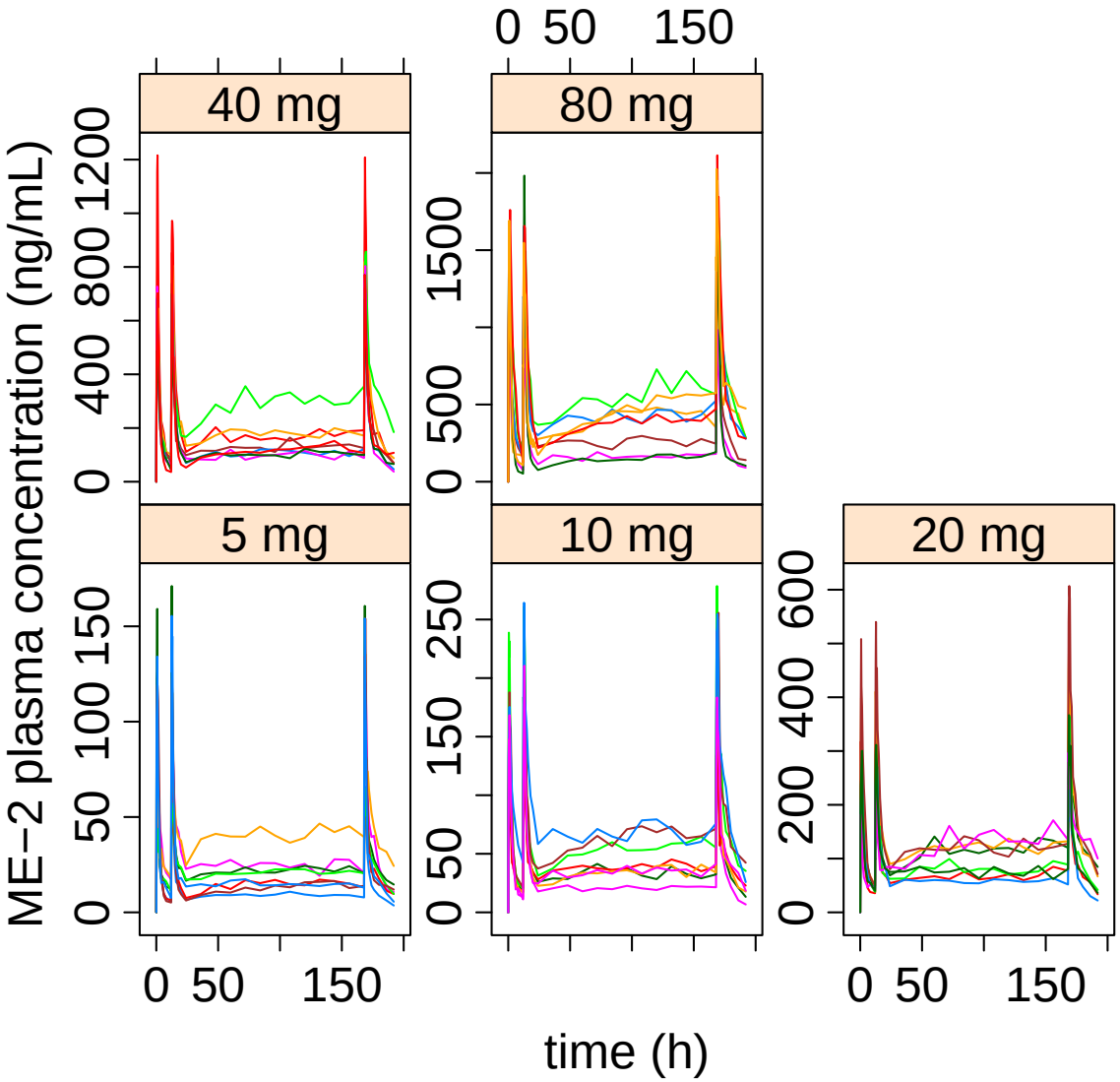
Torsten PMX functions

- 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.
- Steady-state (SS) currently implemented only for PKModelOneCpt and PKModelTwoCpt

Population PK modeling of accumulated ME-2 plasma concentration data from 3 trials: Phase I SD, Phase I MD and Phase IIa

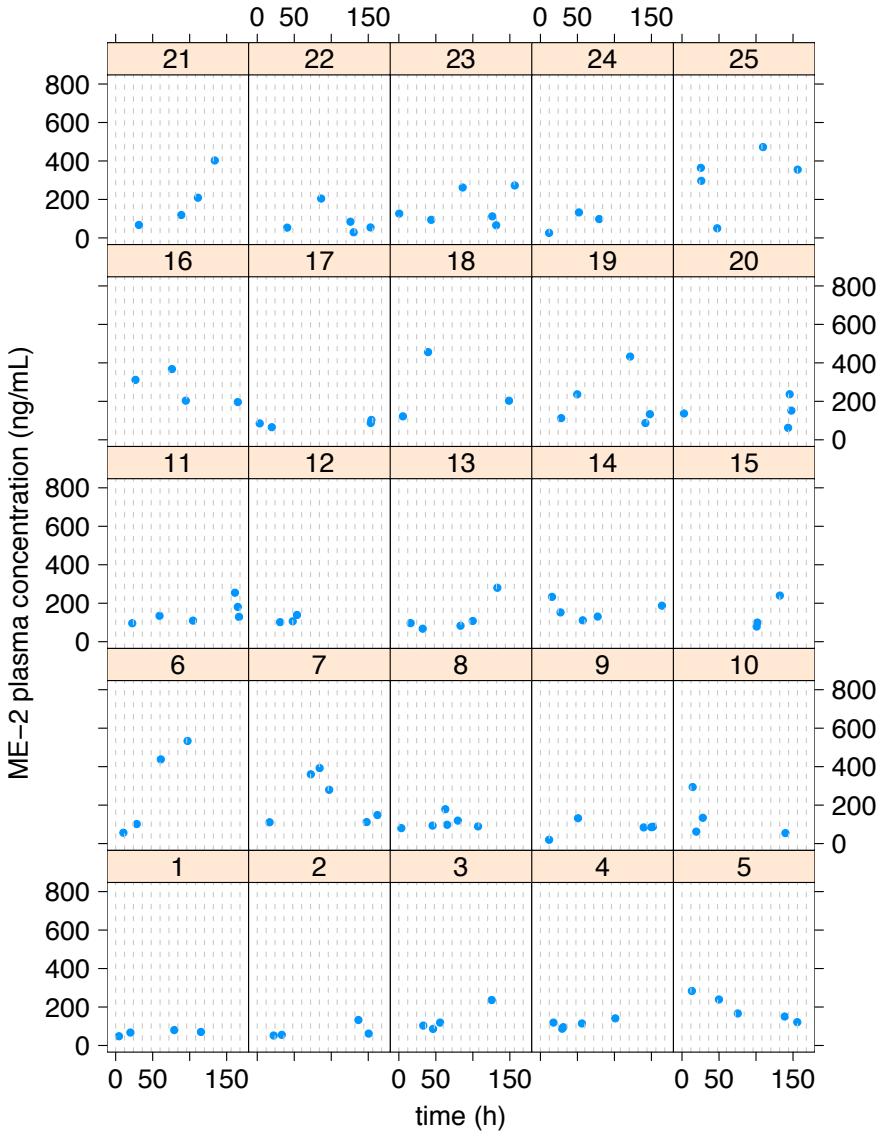


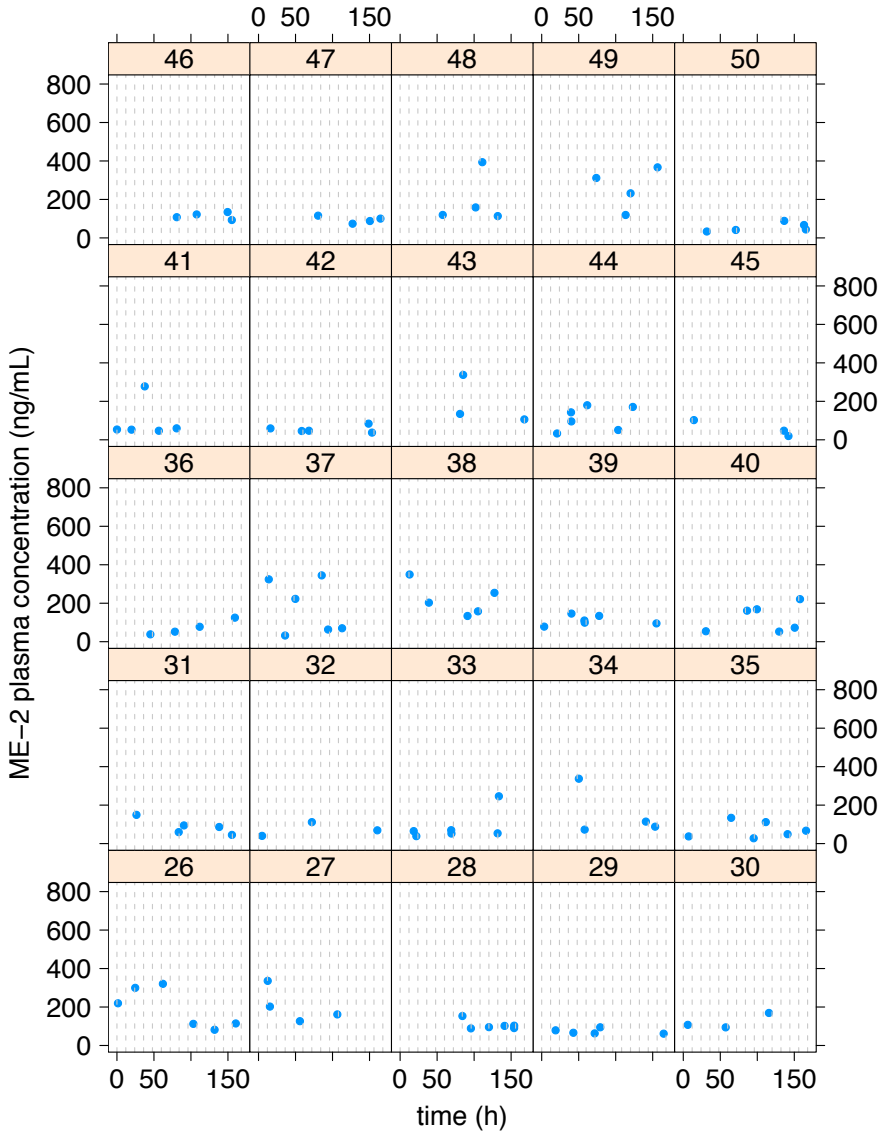
ME-2 PK data from Phase I SD trial



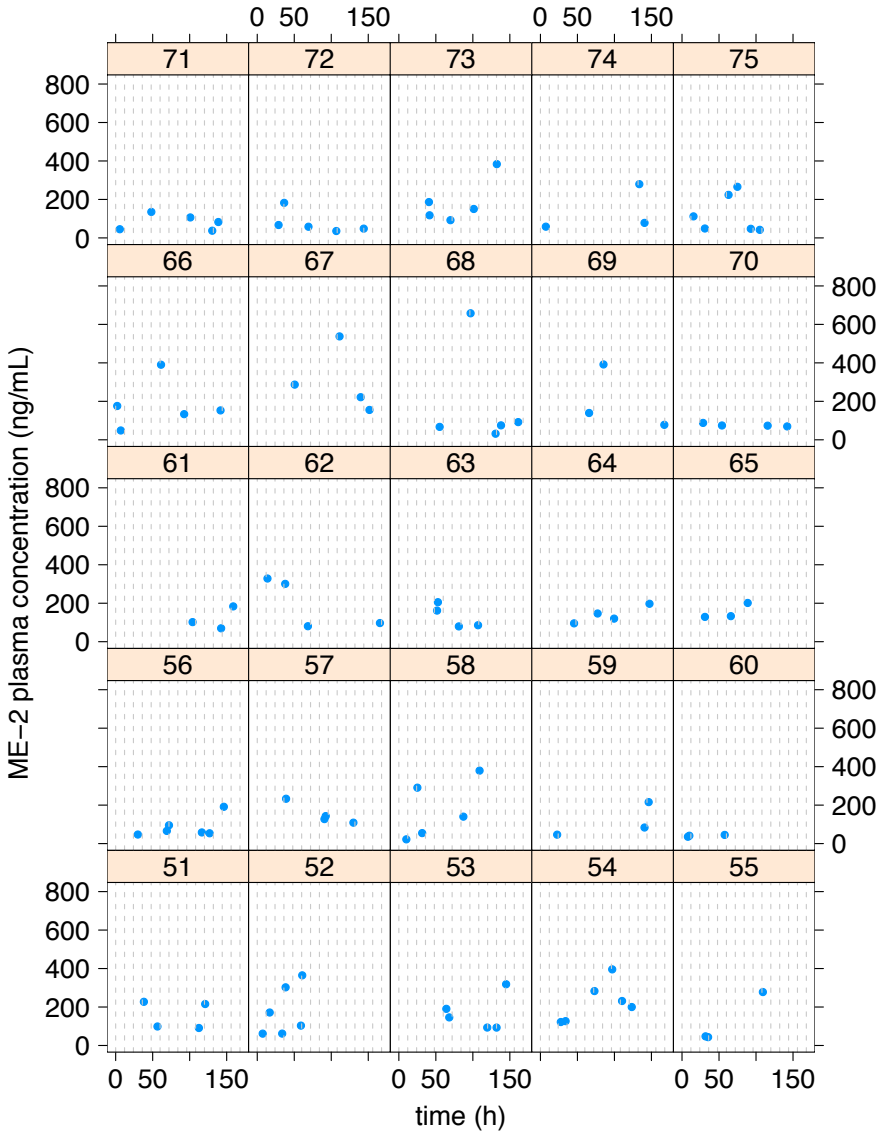
ME-2 PK data from Phase I MD trial

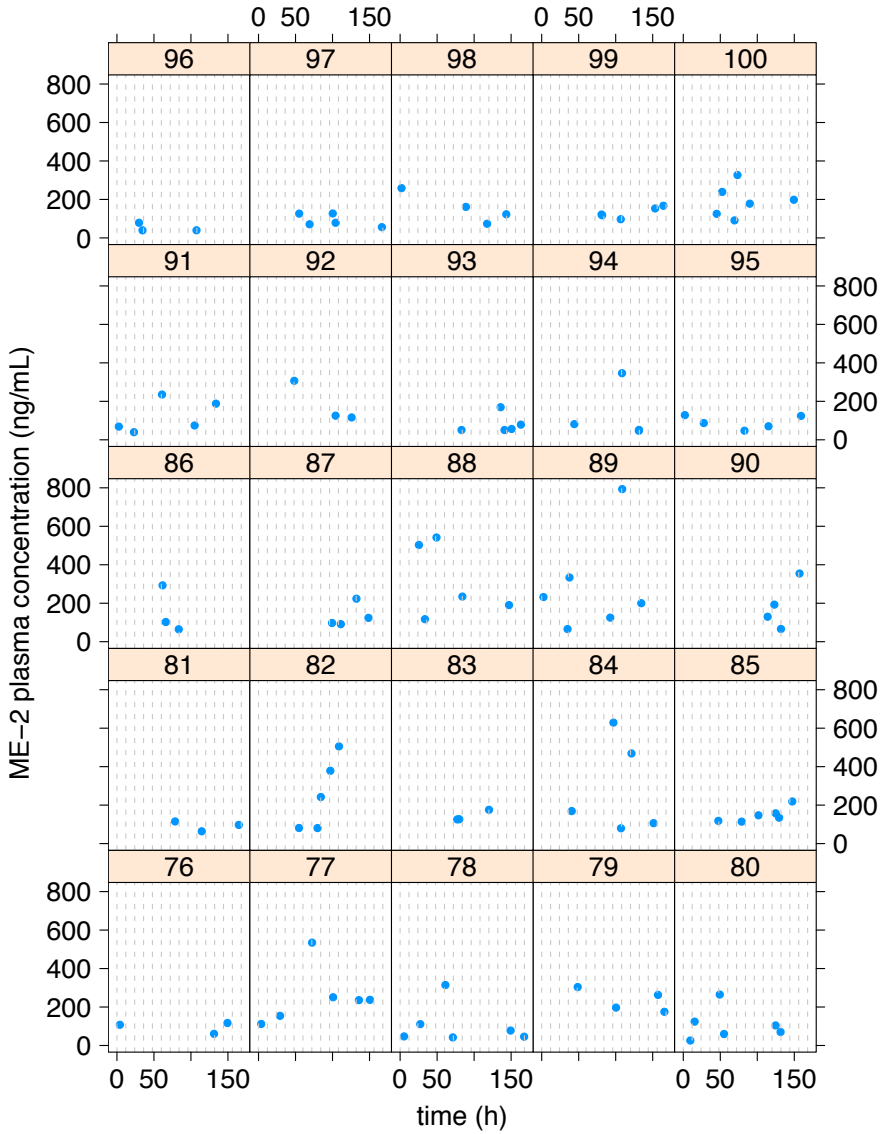
ME-2 PK data from Phase IIa trial





ME-2 PK data from Phase IIa trial





Proposed base model

- Two compartment model with first order absorption describing ME-2 plasma concentration on the i^{th} occasion in the j^{th} subject as a function of time, dose and body weight:

$$\begin{aligned}
\log\left(c_{ij}\right) &\sim N\left(\log\left(\hat{c}_{ij}\right), \sigma^2\right) \\
\hat{c}_{ij} &= f_{2cpt}\left(t_{ij}, D_j, \tau_j, CL_j, Q_j, V_{1j}, V_{2j}, k_{aj}\right) \\
\log\left(CL_j, Q_j, V_{1j}, V_{2j}, k_{aj}\right) & \\
&\sim N\left(\log\left(\widehat{CL}\left(\frac{bw_j}{70}\right)^{0.75}, \widehat{Q}\left(\frac{bw_j}{70}\right)^{0.75}, \widehat{V}_1\left(\frac{bw_j}{70}\right), \widehat{V}_2\left(\frac{bw_j}{70}\right), \widehat{k}_a\right), \Omega\right)
\end{aligned}$$

- Some possible weakly informative prior distributions:

$$\begin{aligned}
\widehat{CL} &\sim \text{half-}N\left(0, 20^2\right) \quad \widehat{Q} \sim \text{half-}N\left(0, 20^2\right) \quad \widehat{V}_1 \sim \text{half-}N\left(0, 100^2\right) \\
\widehat{V}_2 &\sim \text{half-}N\left(0, 1000^2\right) \quad \widehat{k}_a \sim \text{half-}N\left(0, 5^2\right) \quad \sigma \sim \text{half-Cauchy}\left(0, 5\right) \\
\Omega &= \text{diag}\left(\omega\right) P \,\text{diag}\left(\omega\right) \\
\omega_i &\sim \text{half-Cauchy}\left(0, 2\right), i \in \{1, 2, 3, 4, 5\} \quad P \sim \text{LKJCorr}\left(1\right)
\end{aligned}$$

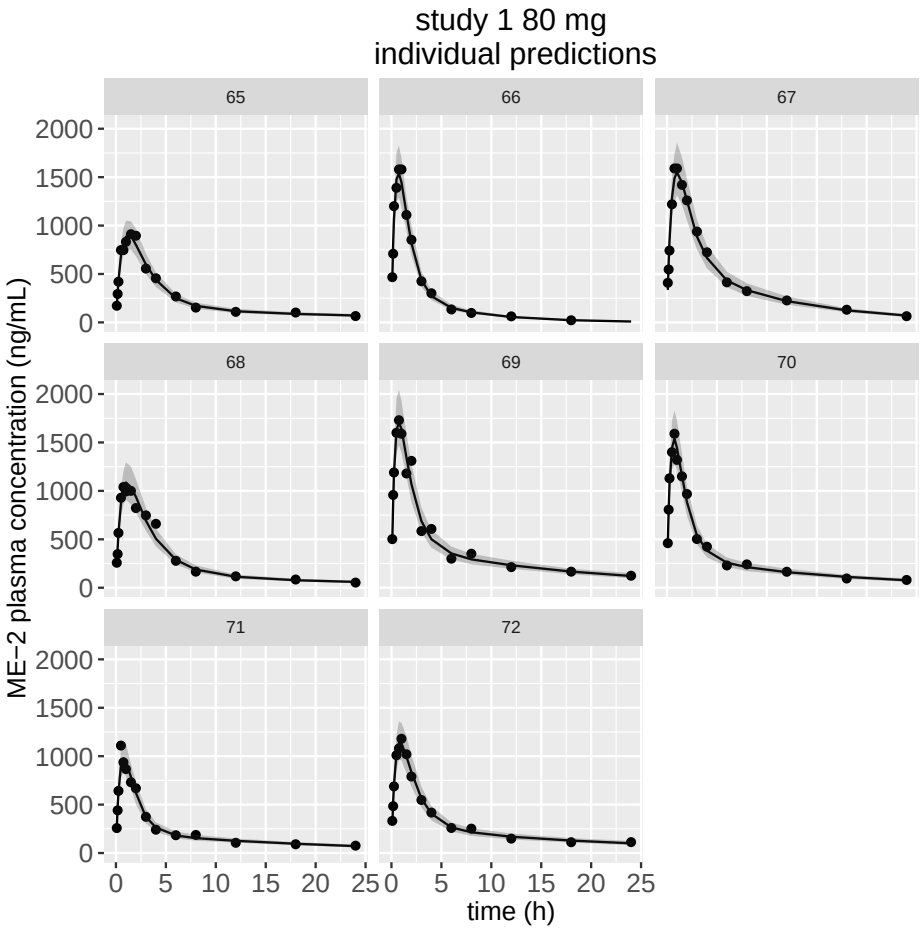
multiDoseME2PK2Torsten.stan excerpt

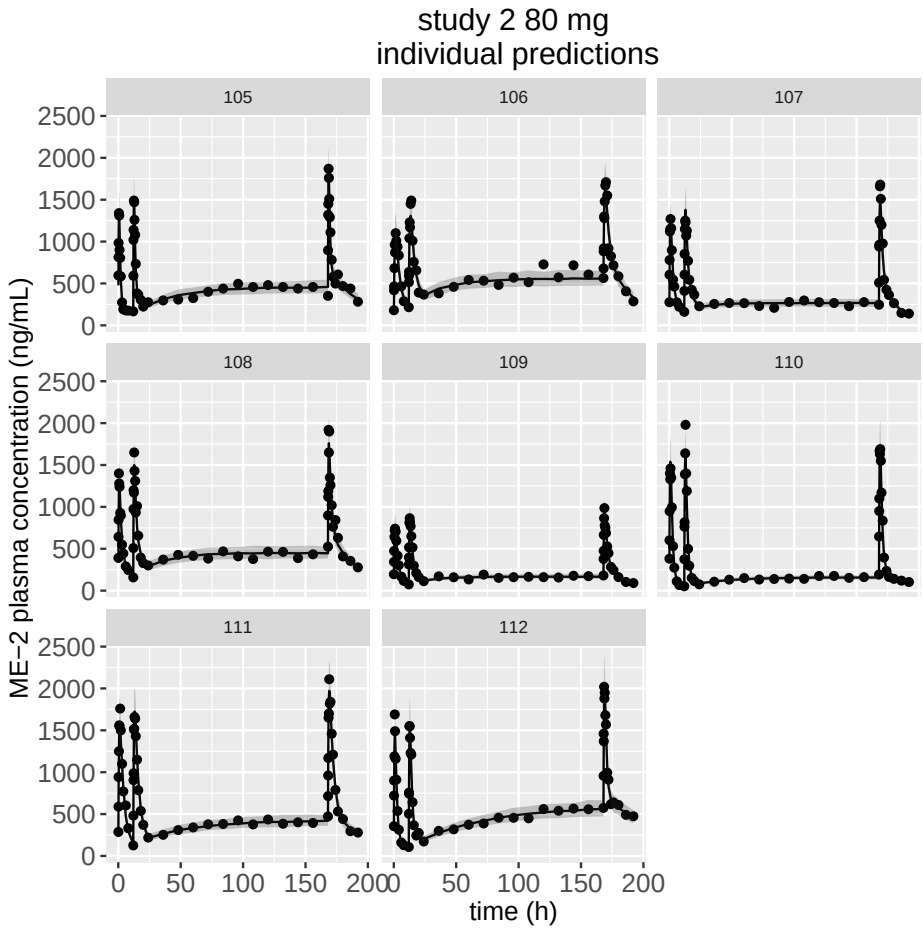
```
for(j in 1:nSubjects){
  CL[j] = exp(logtheta[j, 1]) * (weight[j] / 70)^0.75;
  Q[j] = exp(logtheta[j, 2]) * (weight[j] / 70)^0.75;
  V1[j] = exp(logtheta[j, 3]) * weight[j] / 70;
  V2[j] = exp(logtheta[j, 4]) * weight[j] / 70;
  ka[j] = exp(logtheta[j, 5]);

  parms[1][1] = CL[j];
  parms[1][2] = Q[j];
  parms[1][3] = V1[j];
  parms[1][4] = V2[j];
  parms[1][5] = ka[j];
  parms[1][6] = 1; # F1
  parms[1][7] = 1; # F2
  parms[1][8] = 1; # F3
  parms[1][9] = 0; # tlag1
  parms[1][10] = 0; # tlag2
  parms[1][11] = 0; # tlag3
          :
          :
```

multiDoseME2PK2Torsten.stan excerpt

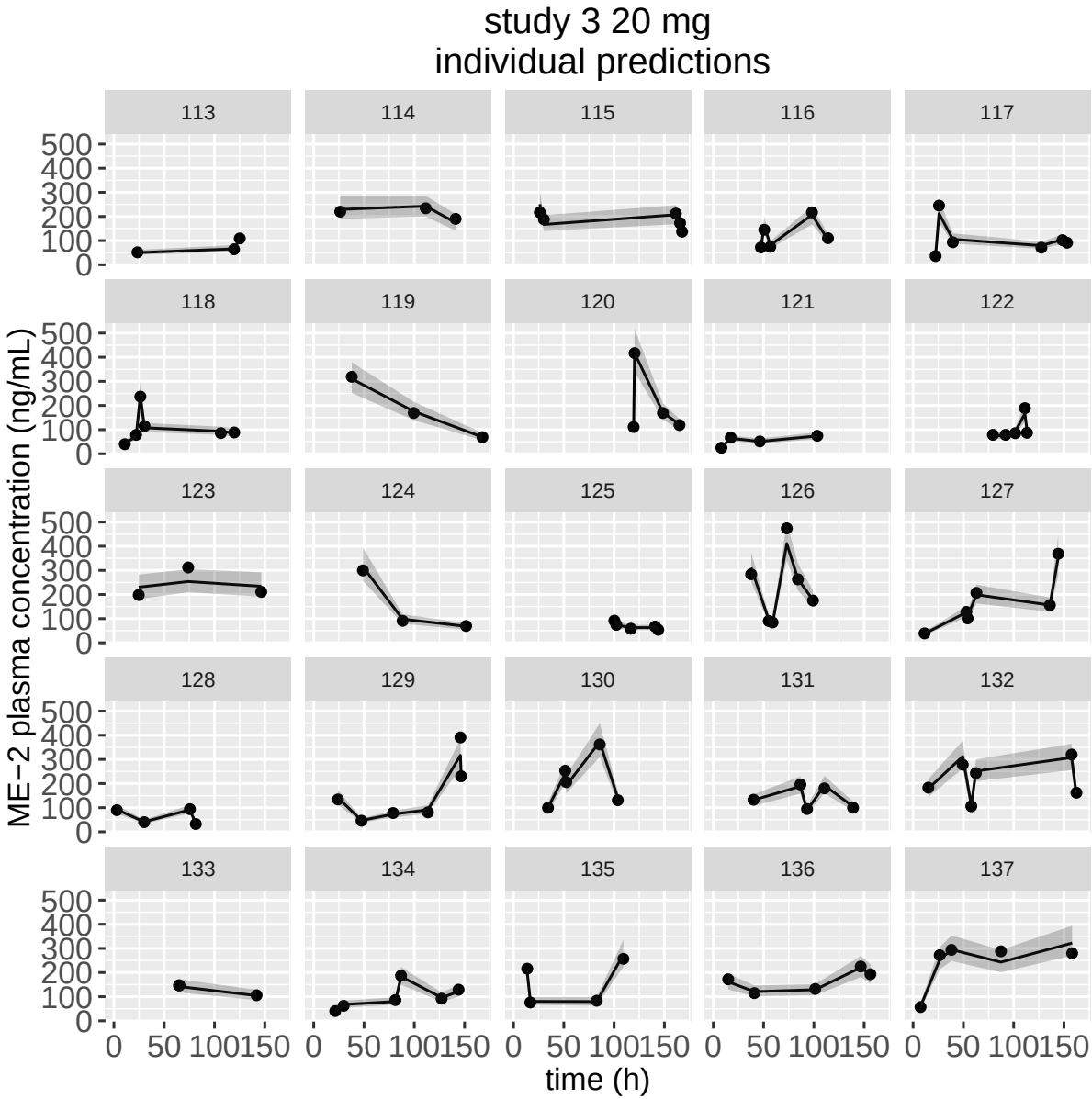
```
                :
  x[start[j]:end[j],]= PKModelTwoCpt(parms,
                                     time[start[j]:end[j]],
                                     amt[start[j]:end[j]],
                                     rate[start[j]:end[j]],
                                     ii[start[j]:end[j]],
                                     evid[start[j]:end[j]],
                                     cmt[start[j]:end[j]],
                                     addl[start[j]:end[j]],
                                     ss[start[j]:end[j]]);

  cHat[start[j]:end[j]] = x[start[j]:end[j], 2] ./ V1[j];
}
```

Typical fits: Studies 1 & 2



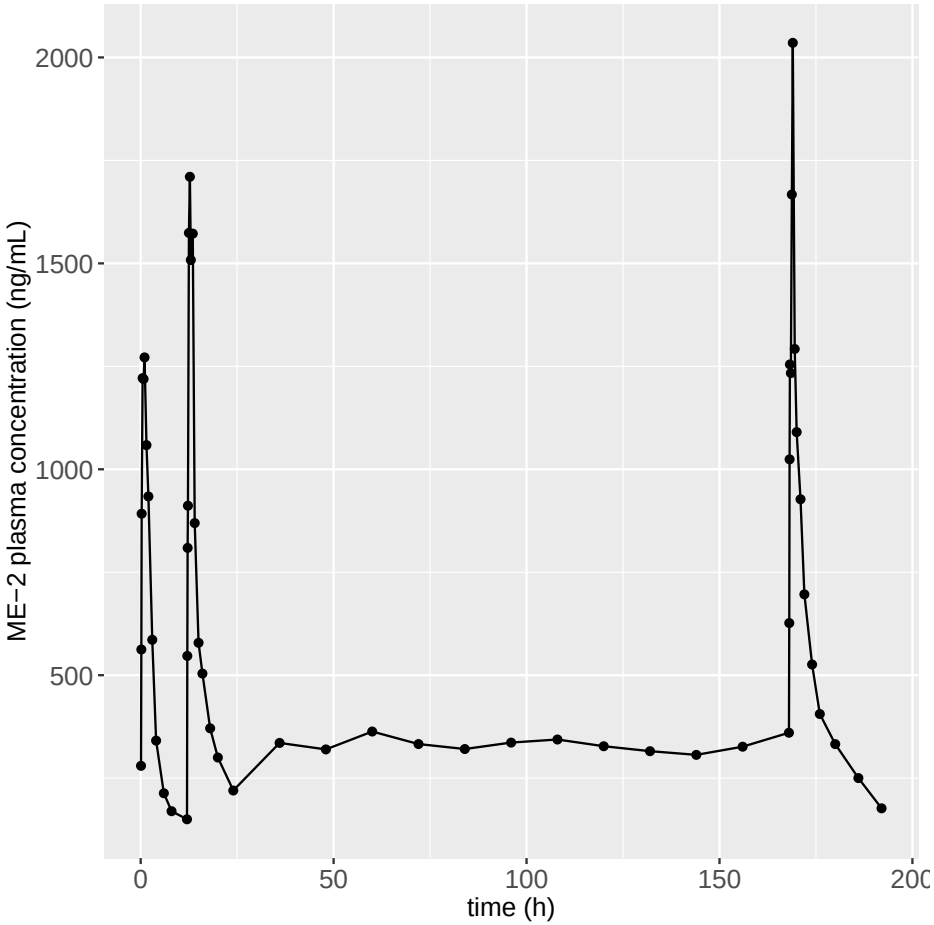


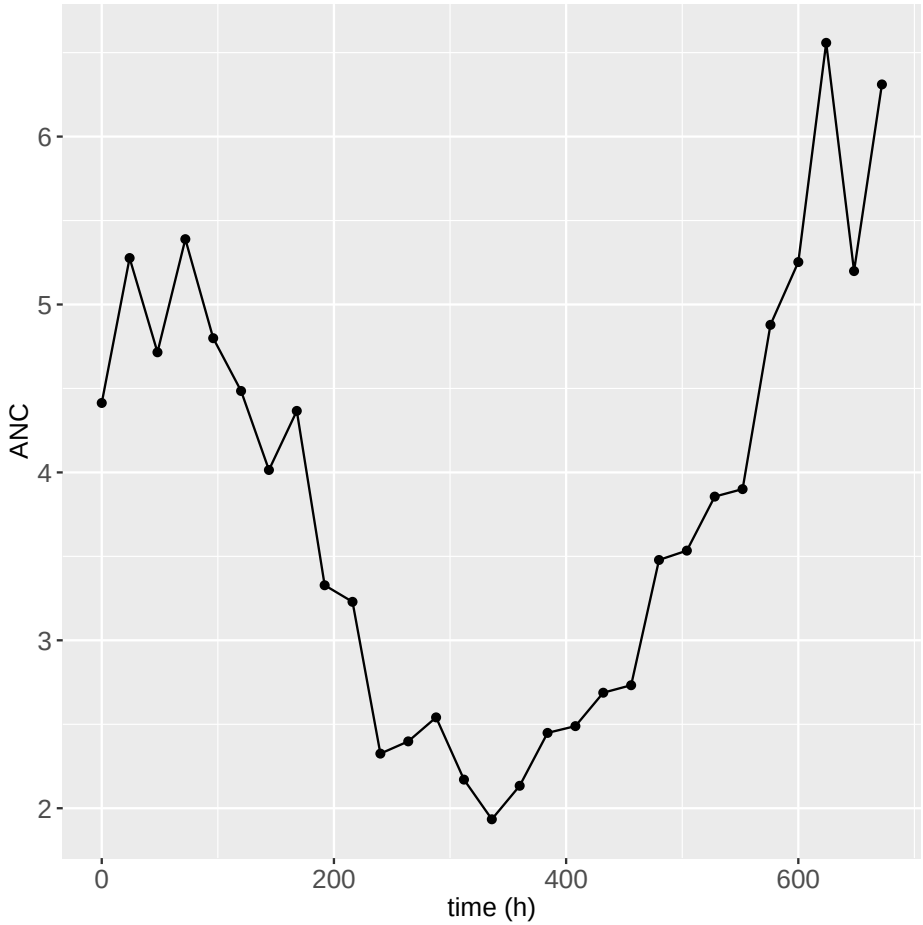
Typical fits: Study 3



PKPD model based on nonlinear ODEs

PKPD modeling of ME-2 induced neutropenia in a single patient





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

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

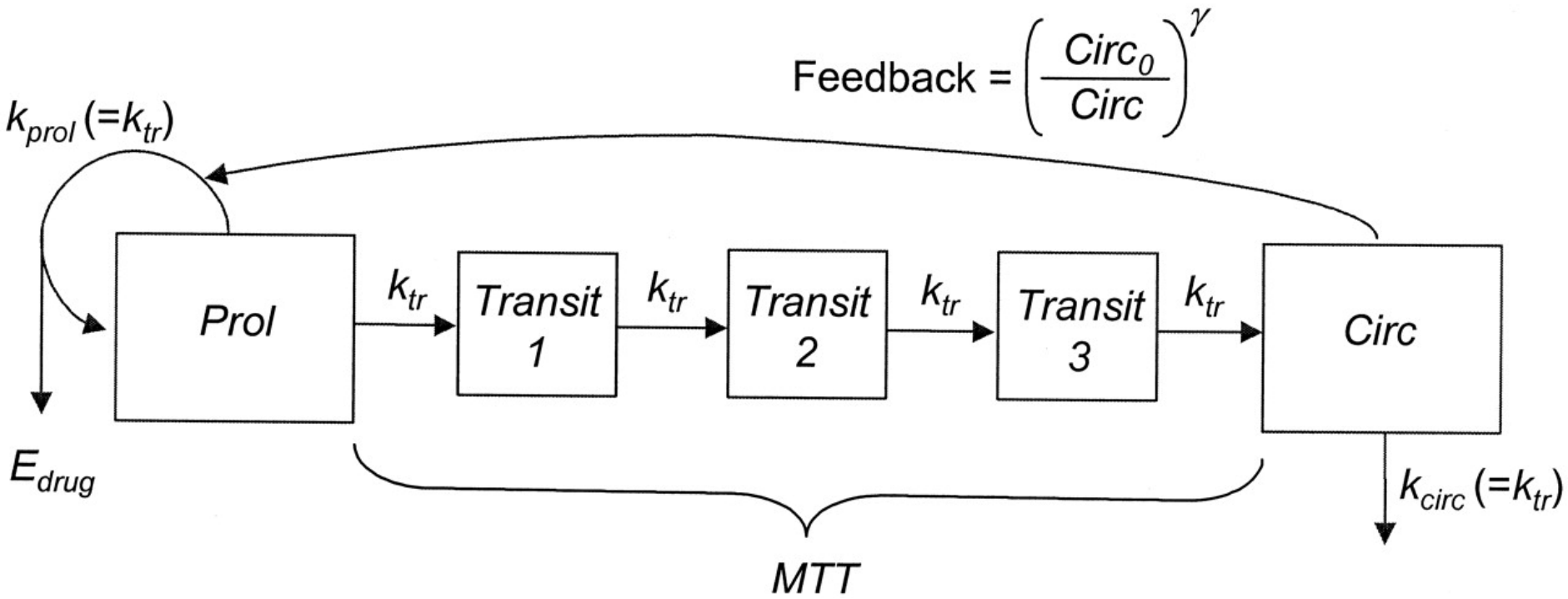


Figure 2 of reference [1]

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)

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

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

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

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

neutropenia1patient1Torsten.stan excerpt

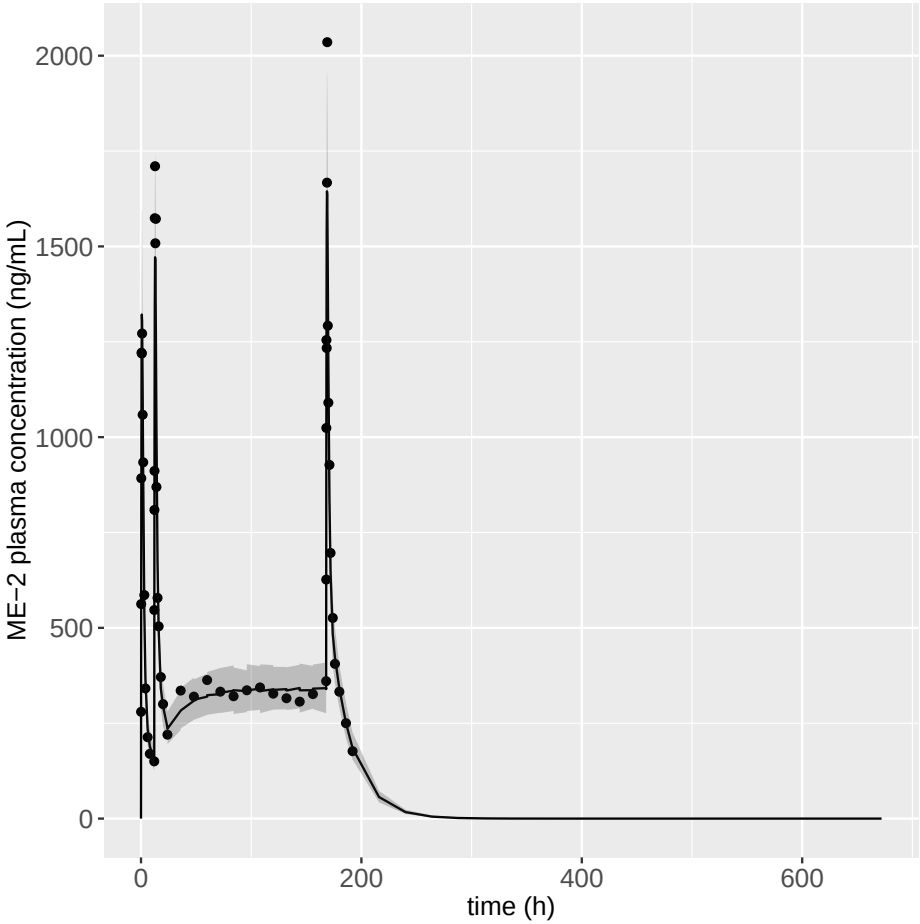
```
real[] twoCptNeutModelODE(real t, real[] x, real[] parms, real[]
    rdummy, int[] idummy){

          :

  CL = parms[1];
  Q = parms[2];
  V1 = parms[3];
  V2 = parms[4];
  ka = parms[5];
  mtt = parms[6];
  circ0 = parms[7];
  gamma = parms[8];
  alpha = parms[9];

  k10 = CL / V1;
  k12 = Q / V1;
  k21 = Q / V2;

  ktr = 4 / mtt;

          :
```

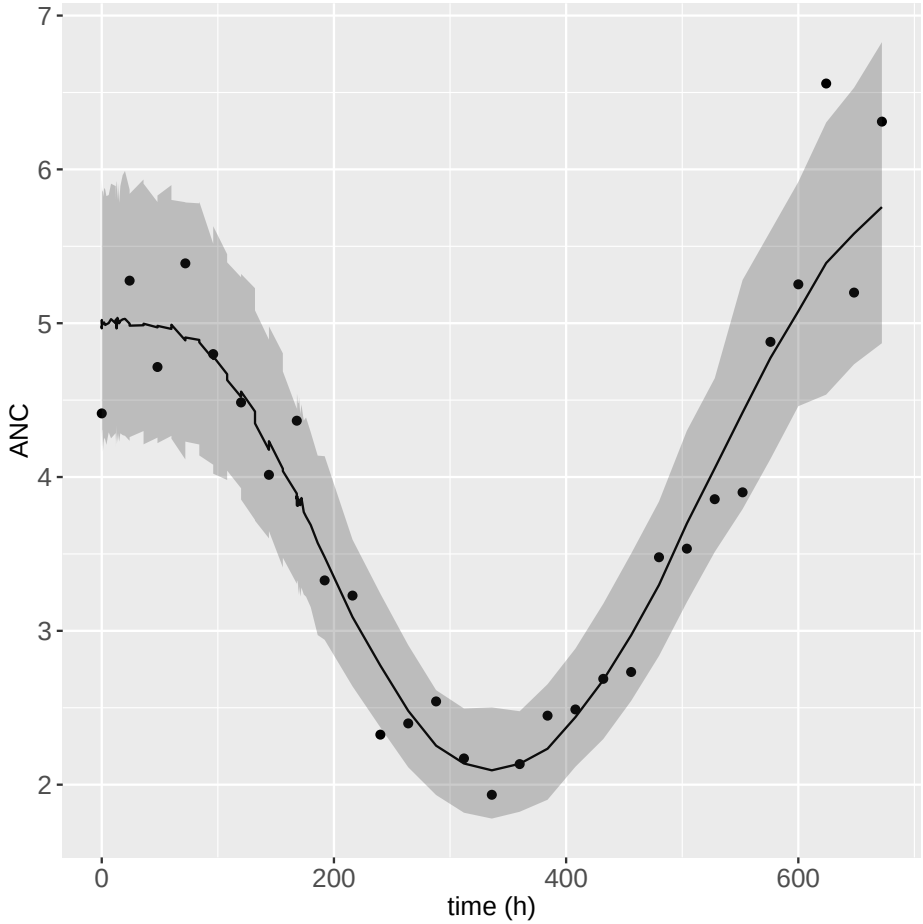
neutropenia1patient1Torsten.stan excerpt

```
                :
  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);
  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;
}
```

neutropenia1patient1Torsten.stan excerpt

```
parms[1][1]= CL;
parms[1][2] = Q;

          :
          :
parms[1][8] = gamma;
parms[1][9] = alpha;
parms[1][10] = 1; # F1
parms[1][11] = 1; # F2

          :
          :
parms[1][17] = 1; # F8
parms[1][18] = 0; # tlag1
parms[1][19] = 0; # tlag2

          :
          :
parms[1][25] = 0; # tlag8

x = generalCptModel_rk45(twoCptNeutModelODE, 8,
                         parms, time, amt, rate, ii, evid, cmt, addl, ss,
                         1e-6, 1e-6, 1e8);
cHat = x[, 2] / V1;
neutHat = x[, 8] + circ0;
```


ME−2 plasma concentration (ng/mL)
2000
1500
1000
500
0
0
200
400
600
time (h)


ANC
7
6
5
4
3
2
0
200
400
600
time (h)

A little something more: matrix exponential

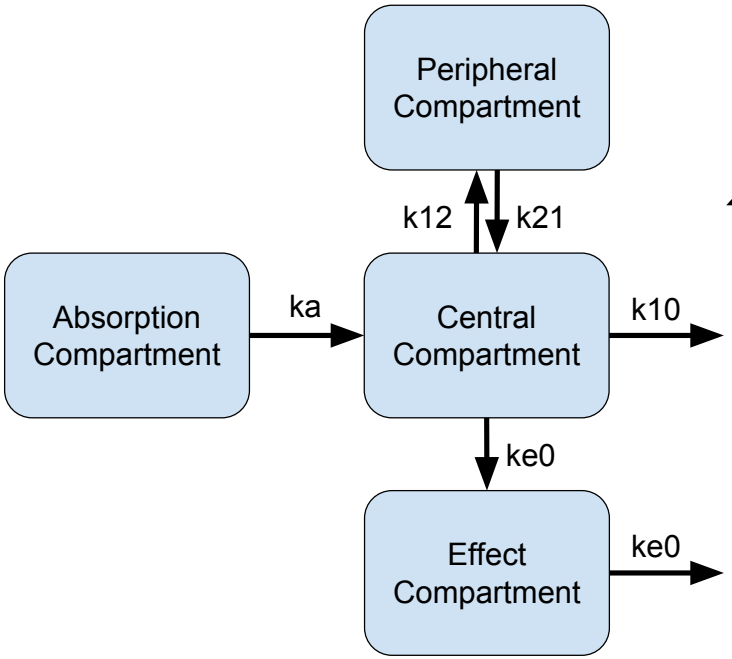
- matrix_exp(A)
  - Calculates a matrix exponential e^A where A is a square matrix.
  - Uses a Padé approximation with scaling and squaring [7].
  - Typical PMX use case is the solution of a linear system of ODEs with constant coefficients, e.g., an initial value problem that may be expressed:

$$x' = Kx$$
$$x(t_0) = x_0$$

where x is a vector and K is a square matrix. The solution may be expressed in terms of the matrix exponential:

$$x(t) = e^{(t-t_0)K} x_0$$

PKPD modeling example using the matrix exponential



$$x' = Kx$$

$$x(t_0) = x_0$$

$$K = \begin{bmatrix} -k_a & 0 & 0 & 0 \\ ka & -(k_{10} + k_{12}) & k_{21} & 0 \\ 0 & k_{12} & -k_{21} & 0 \\ 0 & k_{e0} & 0 & -k_{e0} \end{bmatrix}$$

$$c = \frac{x_2}{V_1}$$

$$c_e = \frac{x_4}{V_1}$$

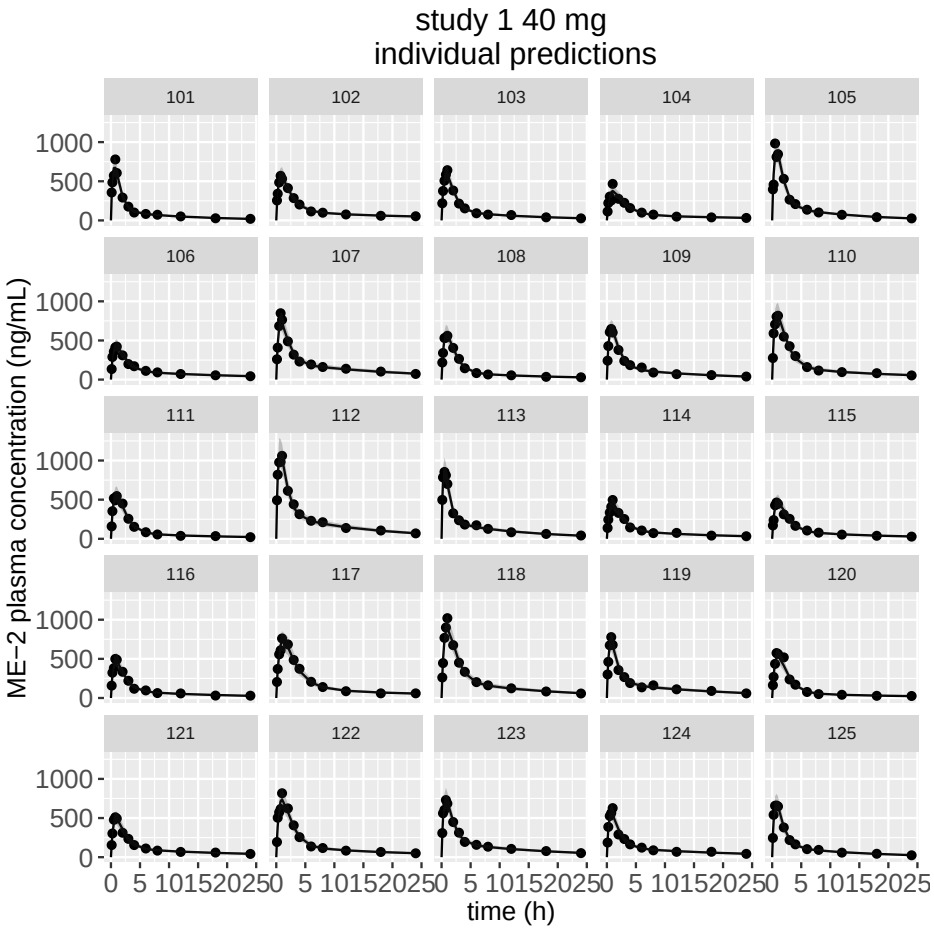
$$E = \frac{100 c_e}{EC_{50} + c_e}$$

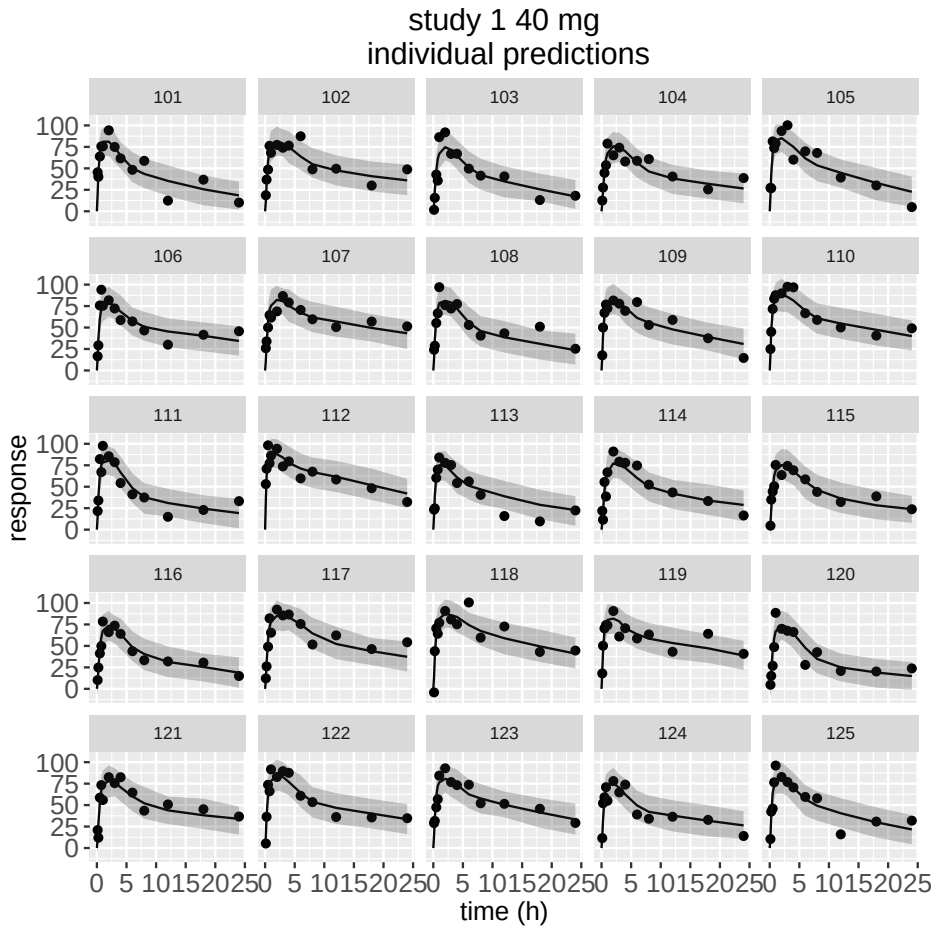
- PK: Two compartment model with 1st order absorption
- PD: Response described by an Emax function of "concentration" in an effect compartment.

effCptTorsten.stan excerpt

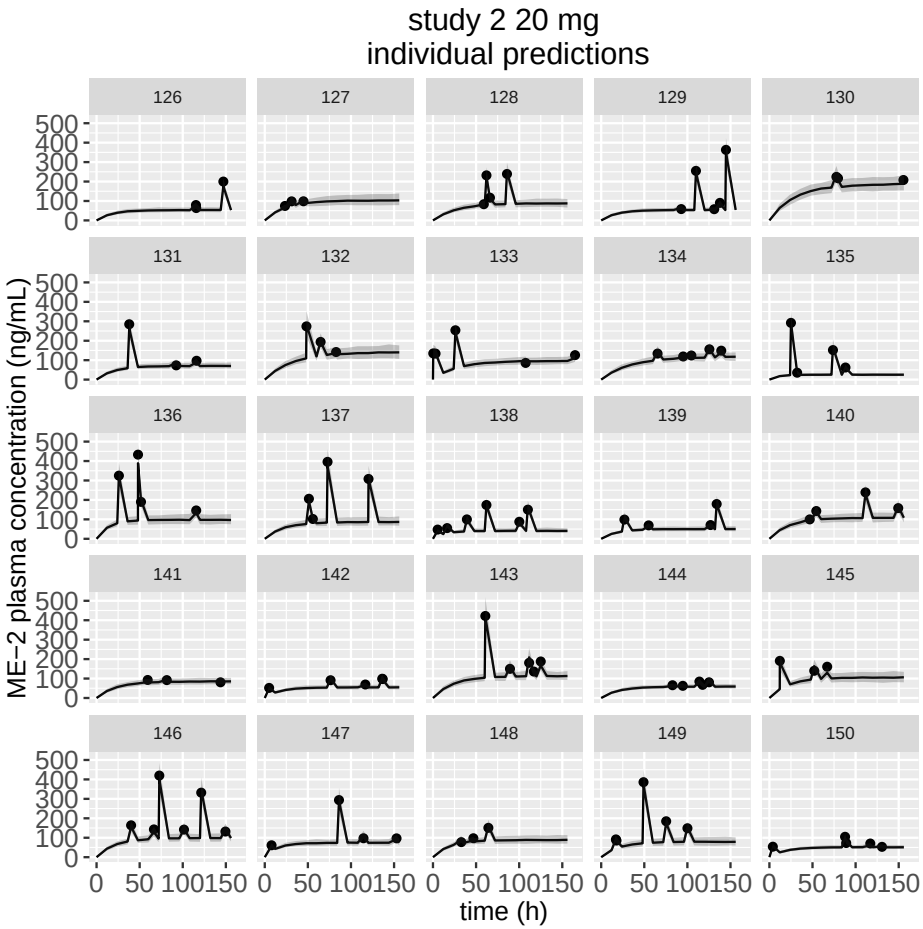
```
real[] effCptModel1(real t0, real t, real[] init, real amt, int cmt,
                    int evid, real CL, real Q, real V1, real V2,
                    real ka, real ke0){

            ⋮

  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;
  K[4, 2] = ke0;
  K[4, 4] = -ke0;

  x = to_array_1d(matrix_exp((t - t0) * K) * to_vector(init));

  if(evid == 1) x[cmt] = x[cmt] + amt;

  return x;
}
```

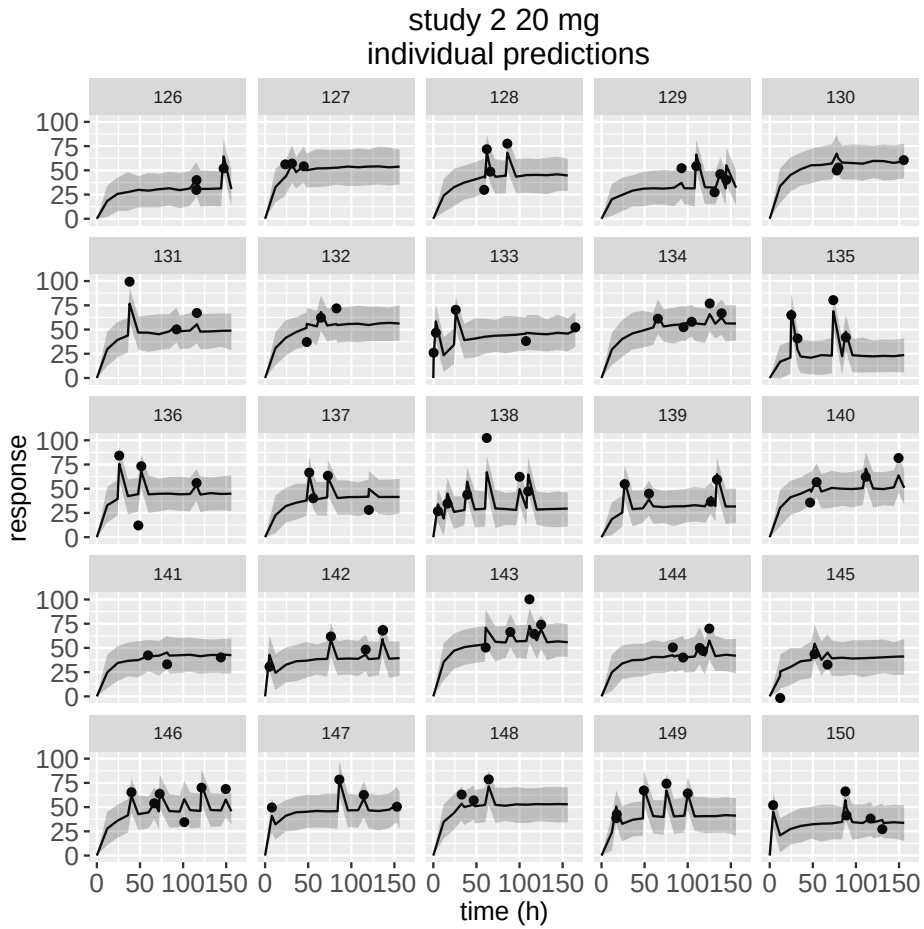
Typical fits: Study 1





Typical fits: Study 2





What next?

- PMX function for compartmental models described by user-specified linear ODEs
  - Solved semi-analytically using matrix exponentials
- Numerical solution of nonlinear algebraic equations (aka a root solver)
- Extend GeneralCptModel_rk45 and GeneralCptModel_bdf to handle steady-state

Issues

- Generalizability to other fields
- Data and event handling would be cleaner if we had a tuples data type in Stan and permitted vectors of tuples.
- Sharing packages of Stan functions (C++ or Stan language)
- I would really love to be able to pass Stan functions as arguments.

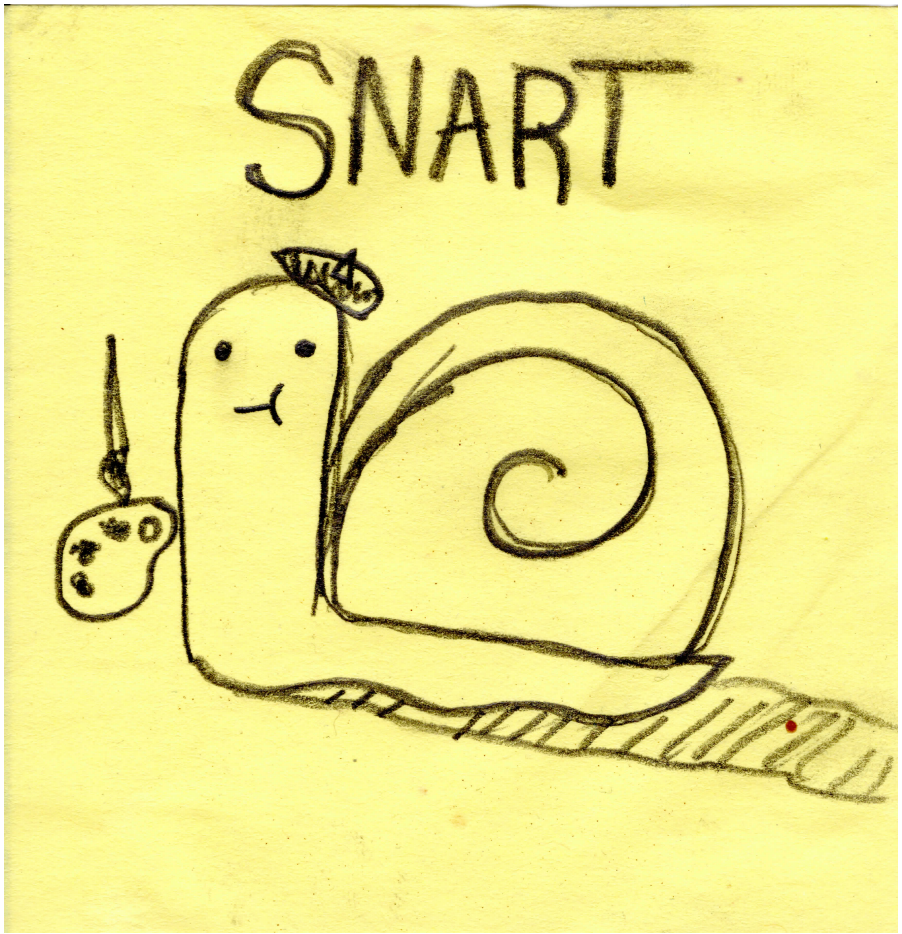
Credit where it is due

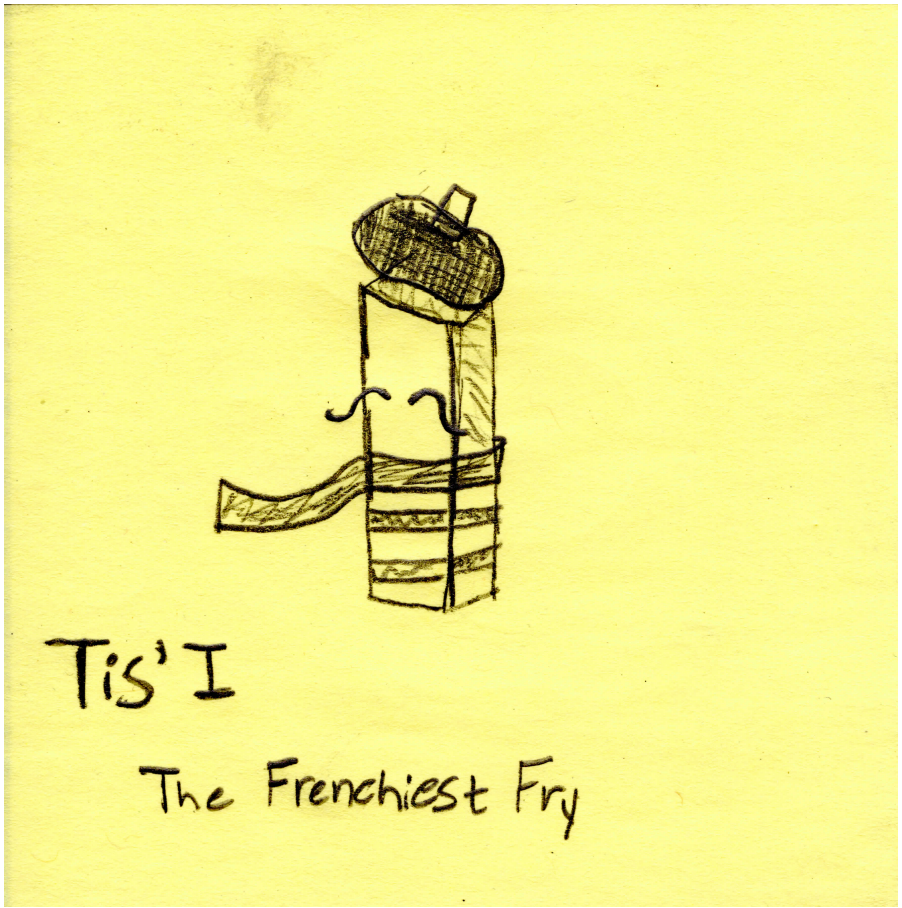
- Charles Margossian
  - Programming and testing of the presented Stan functions.
- Stan Team/Developers:
  - Providing constructive feedback,
  - Developing a powerful flexible platform for PMX and other applications.
- Sebastian Weber
  - Contributing the Stan implementation of the CVODES BDF solver,
  - Improving the Runge-Kutta solver in Stan.

Related links

- https://github.com/stan-dev/stan/wiki/Complex-ODE-Based-Models
- https://github.com/charlesm93/example-models/blob/feature/issue-70-PKPDexamples-torsten/PKPD/torsten/README.md

Un petit arte de Post-it par ma fille





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[3] J. E. Latz, M. O. Karlsson, J. J. Rusthoven, A. Ghosh, and R. D. Johnson.
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