METRUM
RESEARCH GROUP

Bayesian pharmacometric modeling with BUGS, NONMEM and Stan

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BAYES2015 BASEL

Bayesian pharmacometric modeling with BUGS, NONMEM and Stan

- Adapting available software for typical pharmacometric modeling tasks
  - Necessary components
  - PKPD modeling software
    - NONMEM: METHOD = BAYES
  - Adapting general purpose Bayesian software
    - WinBUGS + BUGSModelLibrary
    - Stan
- Pros & cons of studied platforms
- Wish list

Adapting available software for typical pharmacometric modeling tasks

Common elements of pharmacometric model-based analyses

- PK and/or PD models described in terms of first order ODEs
  - Some have analytic solutions, e.g., linear 1, 2 and 3 compartment PK models,
  - But many require numerical solutions.
- Model calculations that depend on a sequence of events
  - Doses
  - Changes in covariate values
  - “Reset” events, e.g., zeroing out the amount in the compartment representing cumulative renal excretion when urine is collected

PKPD modeling software
NONMEM: METHOD = BAYES

NONMEM is a program primarily for estimation of the parameters of nonlinear mixed effects models via maximum likelihood.

- Venerable history reaching back to 1980.
- Includes a model specification language, a variety of built-in PK models and numerical ODE solvers that permit specification of more complex PK and PD models.
- Most recent versions (7.*) also includes an MCMC method (Gibbs/Metropolis-Hastings) that allows fully Bayesian analysis (See presentation by Thierry Wendling.).

NONMEM: METHOD = BAYES

NONMEM is primarily designed for nonlinear mixed effects models of the form

$$
\begin{aligned}
y_{ij} &\sim p\left(\widehat{y}_{ij}|\theta_j, X_{ij}\right) \\
\widehat{y}_{ij} &= f\left(X_{ij}, \theta_j\right) \\
\theta_i &\sim N\left(\widehat{\theta}, \Omega\right)
\end{aligned}
$$

where y_{ij} is observed data for the i^{th} occasion in the j^{th} individual, p is either a normal or user-specified conditional likelihood, and X_{ij} are independent variables, e.g., time.

- Though version 7.* provides methods for more levels of nested random effects (normally distributed).
- Prior distributions are limited to normal for $\widehat{\theta}$ and inverse Wishart for Ω.

NONMEM: METHOD = BAYES

Features include:

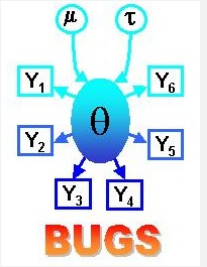
- PREDPP component provides several built-in PK models and ODE solvers
  - Linear 1, 2 and 3 compartment models using analytic solutions
  - General linear compartmental models using numerical calculation of matrix exponential
  - General nonlinear compartmental models using numeral solution of ODEs via DVERK (5th/6th order Runge Kutta), DGEAR (Gear's method for stiff ODEs) or LSODA (automatic switching between methods for stiff and non-stiff problems)
- Flexible FORTRAN-like language for specifying the conditional likelihood

NONMEM: METHOD = BAYES

Features include:

- Event-oriented data sets
  - Each individual's data is a set of time-ordered records containing dependent variables, independent variables and event information, e.g., doses
  - Accommodates complicated event schedules without requiring custom programming by the user
- Parallel computation that takes advantage of the hierarchical model structure
  - Allows within chain parallelization

Adapting general purpose Bayesian software
WinBUGS + BUGSModelLibrary



BUGSModelLibrary (`https://bitbucket.org/metrumrg/bugsmodellibrary/`) is a PKPD model library for use with WinBUGS 1.4.3. 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 matrix exponential
- General compartmental model described by a system of first order ODEs

BUGSModelLibrary

The models and data format are based on NONMEM/NMTRAN/PREDPP conventions including:

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

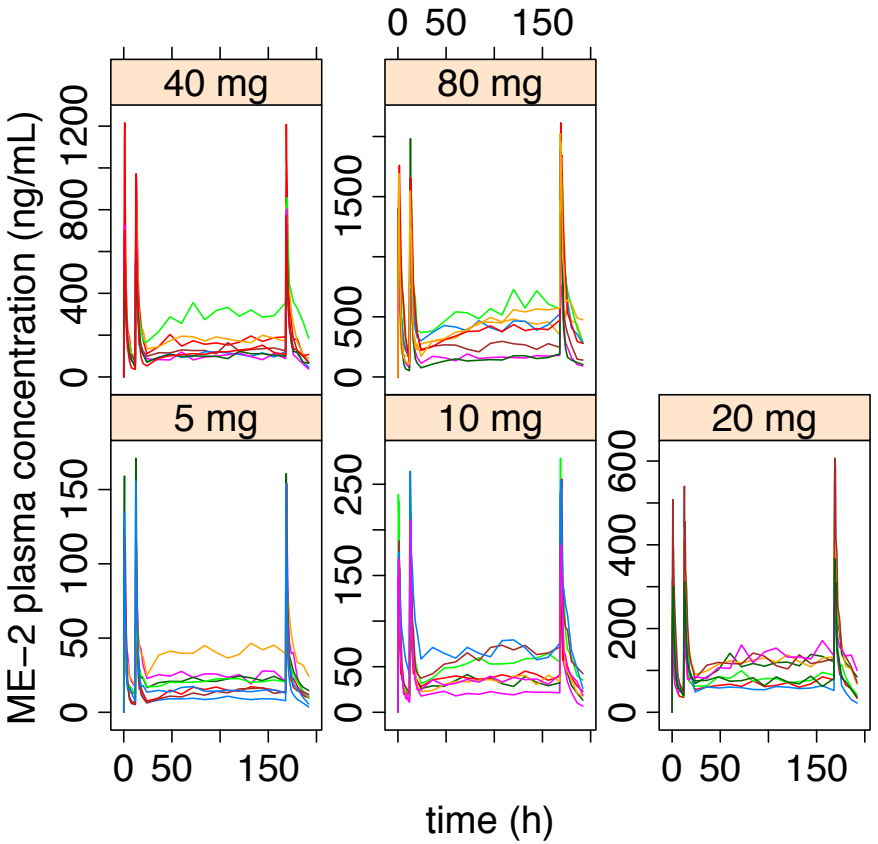
BUGSModelLibrary
User-programmed models

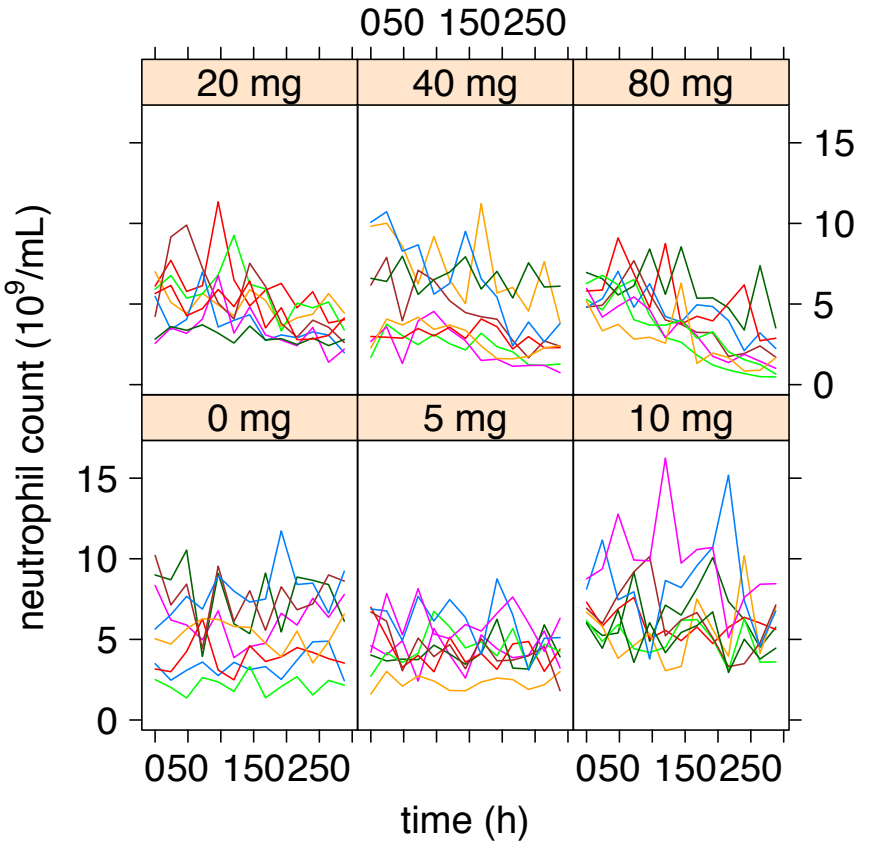
- Linear compartmental models
  - User specifies the non-zero elements of the rate constant matrix.
  - Linear ODE's are solved using matrix exponential methods.
- General compartmental models
  - User specifies the ODE's.
  - The ODE's are solved using either a Runge-Kutta 4th/5th order method or LSODA, the Livermore Solver for Ordinary Differential equations with Automatic method switching for stiff and nonstiff problems.
- Both cases require user specification of a rate constant matrix or ODE's in a template Component Pascal procedure that must be compiled using the BlackBox Component Builder 1.5.

Fictional example using LSODA
Population PK/PD modeling of ME-2 induced neutropenia

- Neutropenia was observed in some subjects receiving higher ME-2 doses in Phase I.
- Objective: Model the relationship between neutrophil counts and drug exposure to support dose-optimization
- Phase 1 multiple dose study in healthy volunteers
  - Parallel dose-escalation design
  - 8 subjects per dose arm
  - Placebo or ME-2 5, 10, 20, 40 or 80 mg bid (q12h) x 7 days
  - PK: plasma concentrations of parent drug
    - PK measured at 0, 0.083, 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 12.1, 12.2, 12.2, 12.5, 12.8, 13, 13.5, 14, 15, 16, 18, 20, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 168, 168, 168, 168, 169, 169, 170, 170, 171, 172, 174, 176, 180, 186 and 192 hours after the first dose.
    - LOQ = 10 ng/mL
  - PD: Absolute neutrophil count (ANC) measured daily for 12 days

Simulated ME-2 PK/PD data from Phase I MD trial





Proposed model

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

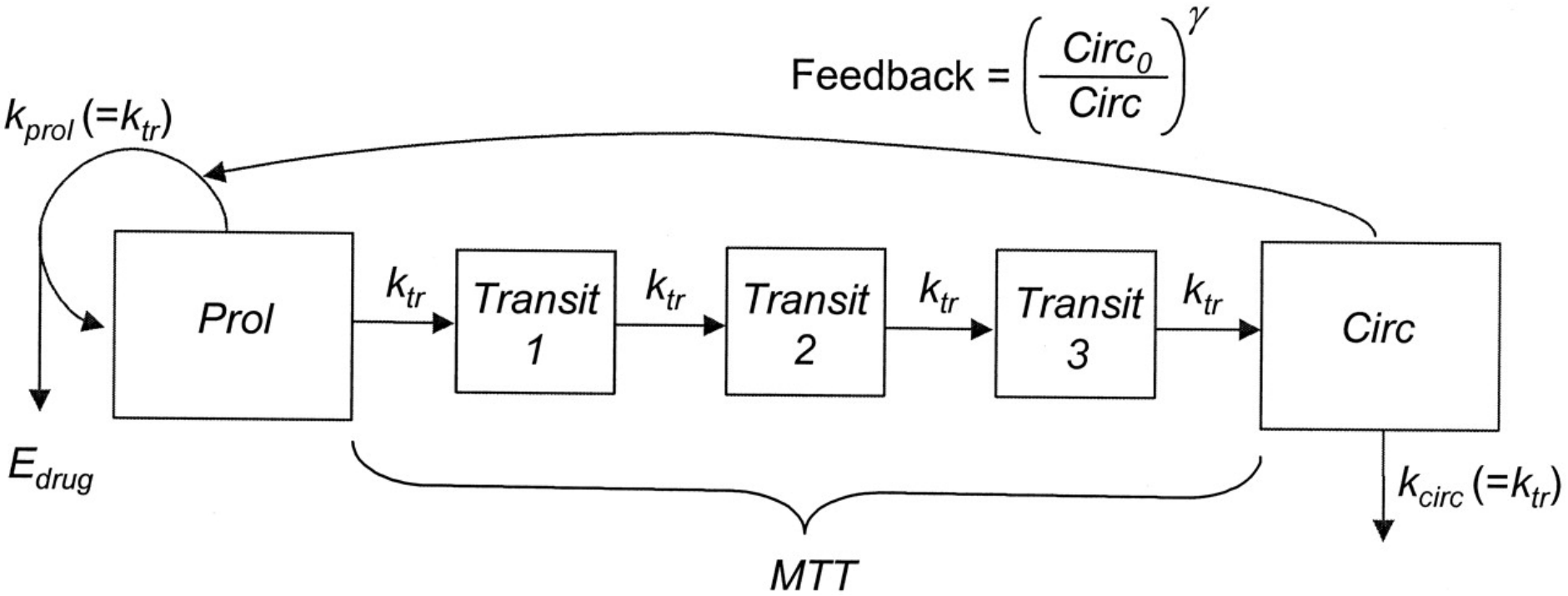


Figure 2 of reference [1]

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.

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

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

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

PK 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:

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

- Informative prior distributions based on Phase I single dose trial:

$$\log\left(\widehat{CL}\right) \sim N\left(\log(10), 0.10\right) \quad \log\left(\widehat{Q}\right) \sim N\left(\log(15), 0.18\right) \quad \log\left(\widehat{V}_1\right) \sim N\left(\log(35), 0.14\right)$$

$$\log\left(\widehat{V}_2\right) \sim N\left(\log(106), 0.17\right) \quad \log\left(\widehat{k}_a - \lambda_1\right) \sim N\left(\log(1.2), 0.16\right) \quad \sigma \sim \Gamma^{-1}\left(0.001, 0.001\right)$$

$$\Omega^{-1} \sim \text{Wishart}\left(\frac{1}{20}\begin{pmatrix} 0.25^2 & 0 & 0 & 0 & 0 \\ 0 & 0.4^2 & 0 & 0 & 0 \\ 0 & 0 & 0.25^2 & 0 & 0 \\ 0 & 0 & 0 & 0.4^2 & 0 \\ 0 & 0 & 0 & 0 & 0.25^2 \end{pmatrix}^{-1}, 20\right)$$

Additional stochastic model components

- Inter-individual variation in PD parameters:

$$\begin{aligned}
\log\left(MTT_j\right) &\sim N\left(\log\left(\widehat{MTT}\right), \omega^2_{MTT}\right) \\
\log\left(Circ_{0j}\right) &\sim N\left(\log\left(\widehat{Circ_0}\right), \omega^2_{Circ_0}\right) \\
\log\left(\alpha_j\right) &\sim N\left(\log\left(\widehat{\alpha}\right), \omega^2_{\alpha}\right)
\end{aligned}$$

- Log-normal residual variation in ANC:

$$\log\left(ANC_{ij}\right) \sim N\left(Circ_{ij}, \sigma^2_{ANC}\right)$$

PD model prior distributions

- Informative priors for PD system parameters constructed using values reported in [1, 2, 3, 4, 5, 6]
  - Prior mean = mean of published values
  - Prior sd = 2 $\times$ sd of published values.
  - Normal priors for $\log\left(\widehat{Circ_0}\right)$, $\log\left(\widehat{MTT}\right)$ and $\log(\gamma)$
  - Gamma priors for $1/\omega^2_{Circ_0}$ and $1/\omega^2_{MTT}$

	mean	standard deviation
$\log\left(\widehat{Circ_0}\right)$	$\log(5.4)$	0.20
$\log\left(\widehat{MTT}\right)$	$\log(110)$	0.16
$\log(\gamma)$	$\log(0.16)$	0.16
$1/\omega^2_{Circ_0}$	11	21
$1/\omega^2_{MTT}$	37	61

- Weakly informative priors for the rest...

$$\widehat{\alpha} \sim U(0,1) \qquad \omega_\alpha \sim U(0,5)$$

Component Pascal code

```
PROCEDURE UserDerivatives(IN theta: ARRAY OF REAL; VAR x: ARRAY [untagged] OF REAL
    ;
  numEq: INTEGER; t: REAL; OUT dxdt: ARRAY [untagged] OF REAL) ;
  VAR
    CL, Q, V2, V3, ka, mtt, ktr, circ0, gamma, alpha, k10, k12, k21, conc,
    EDrug, prol, transit1, transit2, transit3, circ: REAL;
  BEGIN
    CL := theta[0];
    Q := theta[1];
    V2 := theta[2];
    V3 := theta[3];
    ka := theta[4];
    mtt := theta[5];
    circ0 := theta[6];
    gamma := theta[7];
    alpha := theta[8];
    k10 := CL/V2;
    k12 := Q/V2;
    k21 := Q/V3;
    ktr := 4 / mtt;
```

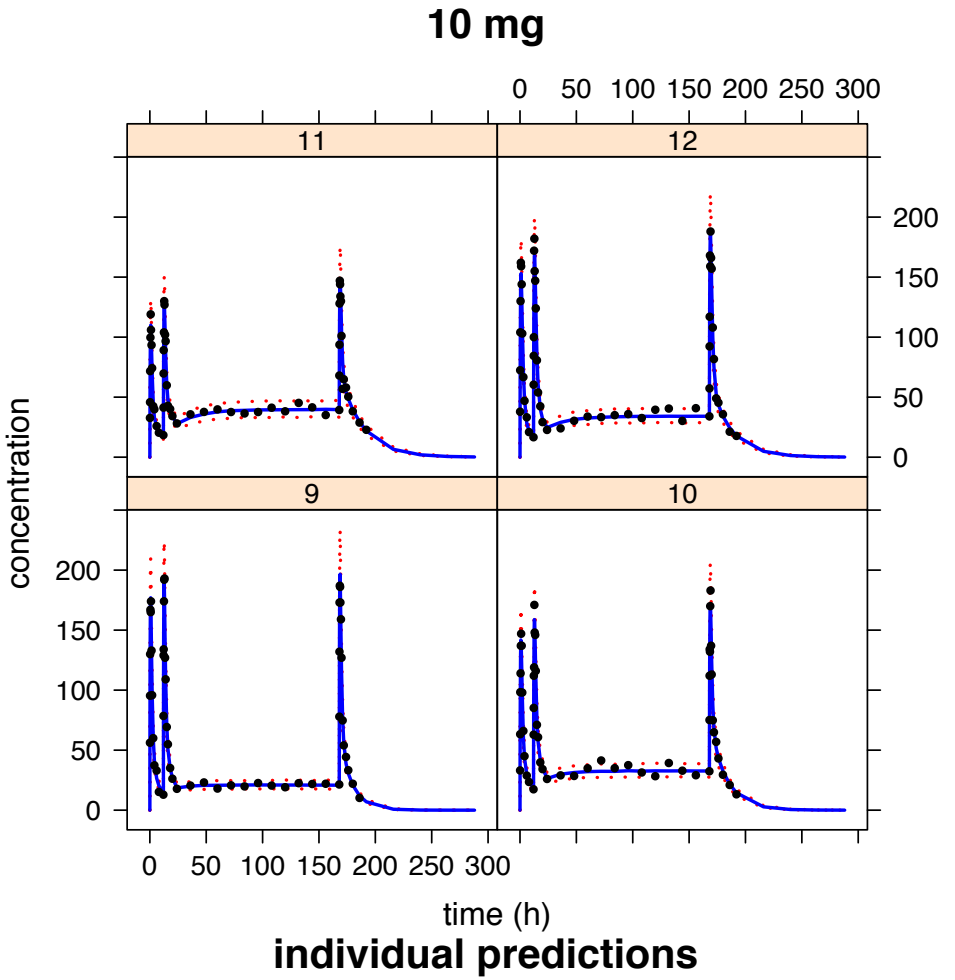
Component Pascal code

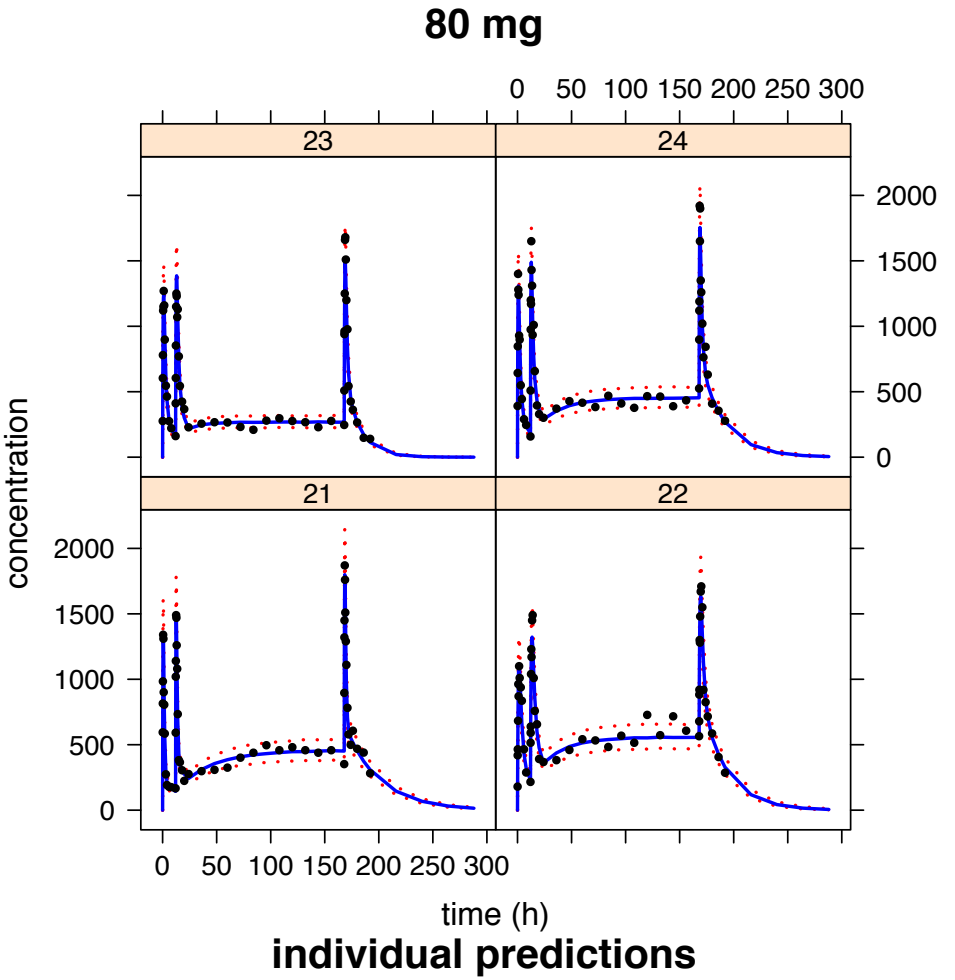
```
(* Differential equations for the model excluding piecewise *)
(* constant input rates provided in the data set *)

dxdt[0] := -ka * x[0];
dxdt[1] := ka * x[0] - (k10 + k12) * x[1] + k21 * x[2];
dxdt[2] := k12 * x[1] - k21 * x[2];
conc := 1000 * x[1]/V2;
EDrug := alpha * conc;
(* x[3], x[4], x[5], x[6] and x[7] are differences from circ0. *)
prol := x[3] + circ0;
transit1 := x[4] + circ0;
transit2 := x[5] + circ0;
transit3 := x[6] + circ0;
circ := x[7] + circ0;
dxdt[3] := ktr * prol * ((1 - EDrug) * Math.Power(circ0 / circ, gamma) - 1);
dxdt[4] := ktr * (prol - transit1);
dxdt[5] := ktr * (transit1 - transit2);
dxdt[6] := ktr * (transit2 - transit3);
dxdt[7] := ktr * (transit3 - circ);

END UserDerivatives;
```

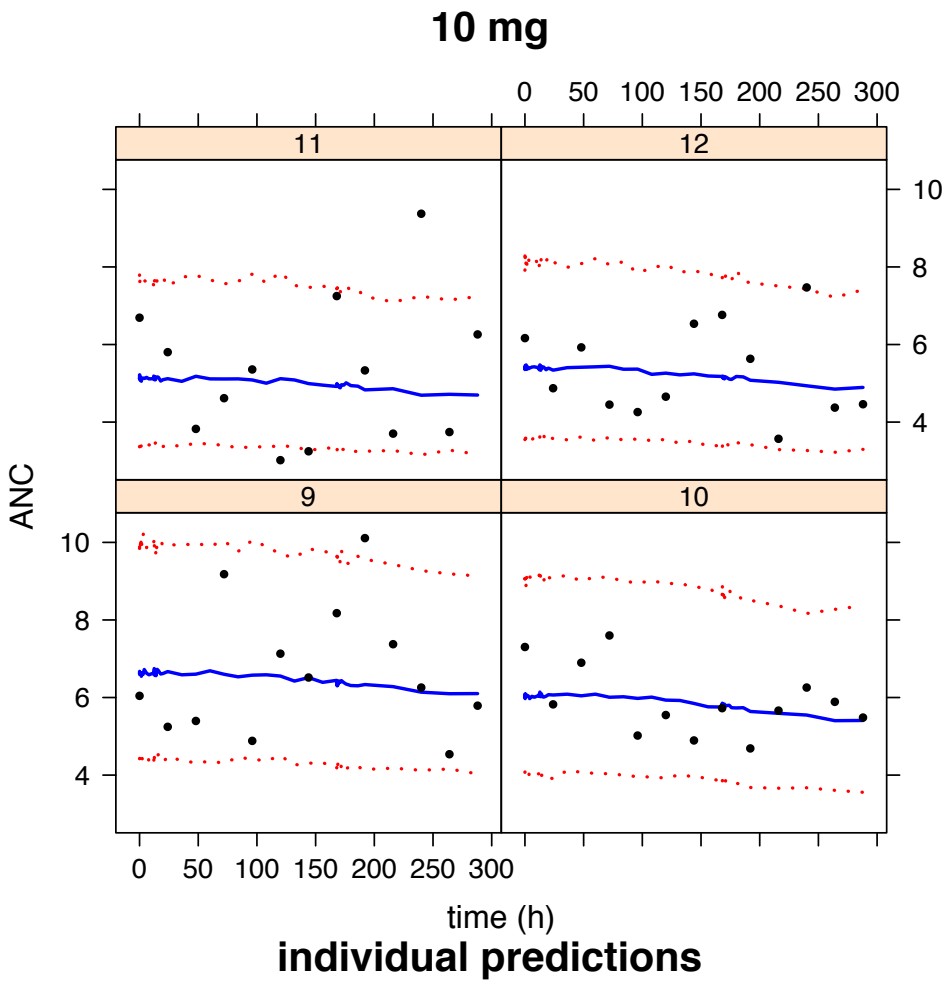
Typical individual fits: PK data

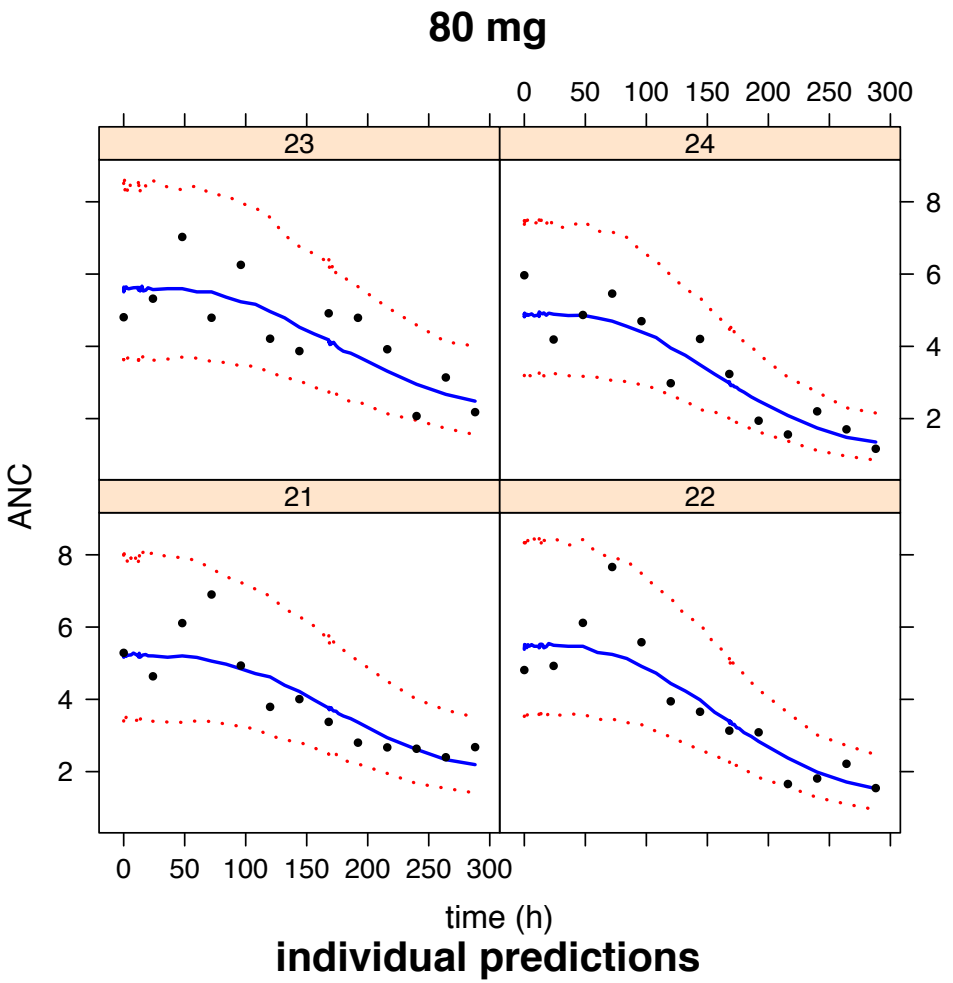




Posterior medians & 90% prediction intervals compared to observed data

Typical individual fits: PD data





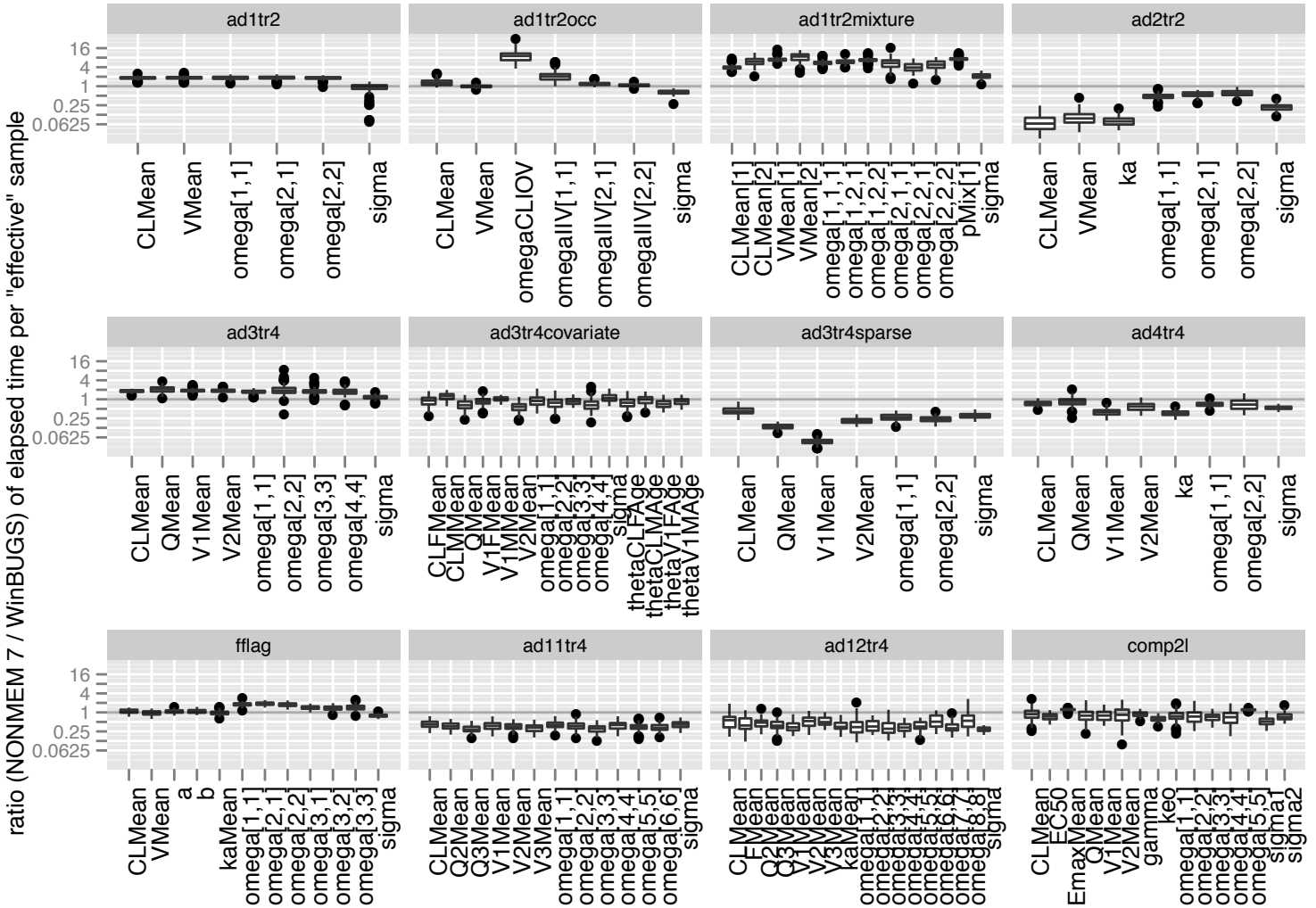
Posterior medians & 90% prediction intervals compared to observed data

Comparison of NONMEM 7 and WinBUGS + BUGSModelLibrary [7]

For each of the following test cases, 100 simulated data sets analyzed with NONMEM 7 BAYES method and WinBUGS + BUGSModelLibrary

label	**model**
ad1tr2	1 compartment IV
ad1tr2mixture	1 compartment IV model, mixture model with two sub-populations
ad1tr2occ	1 compartment IV model, inter-occasion variability over 3 occasions
ad2tr2	1 compartment with 1^{st} order absorption
ad3tr4	2 compartment IV
ad3tr4covariate	2 compartment IV, CL & V1 are functions of age & gender
ad3tr4sparse	2 compartment IV
ad4tr4	2 compartment with 1^{st} order absorption
ad11tr4	3 compartment IV
ad12tr4	3 compartment with 1^{st} order absorption
comp2l	2 compartment IV PK + effect compartment & sigmoid Emax PD
fflag	1 compartment with 1^{st} order absorption PK + binary PD

Distributions of the NONMEM/WinBUGS ratio of computation time per “effective” sample



Observations/conclusions

For the classes of models studied:

- MCMC simulations using NONMEM 7 and WinBUGS produced results with comparable accuracy.
- WinBUGS required much less computation time to produce comparable MCMC results for a mixture model (ad1tr2mixture), and about half the computation time for the ad1tr2, ad3tr4, ad3tr4covariate and fflag examples.
- WinBUGS required more time to produce less precise results for the ad2tr2, at4tr4, ad11tr4 and ad12tr4 examples.

Recommendations

- NONMEM 7 is a recommended platform for Bayesian modeling when suitable models can be implemented within the limits imposed by NONMEM, e.g., 2 levels of random variation (3 including priors), normally-distributed IIV and priors for fixed effects, and inverse Wishart prior for the IIV variance matrix.]
- WinBUGS is a recommended platform when greater flexibility is required w.r.t. stochastic aspects of models, e.g., when other distributions or more levels of variability are desired.
- Based on the limited testing presented here, WinBUGS appears to perform better with mixture models and models with inter-occasion variability and is the preferred platform for those cases.

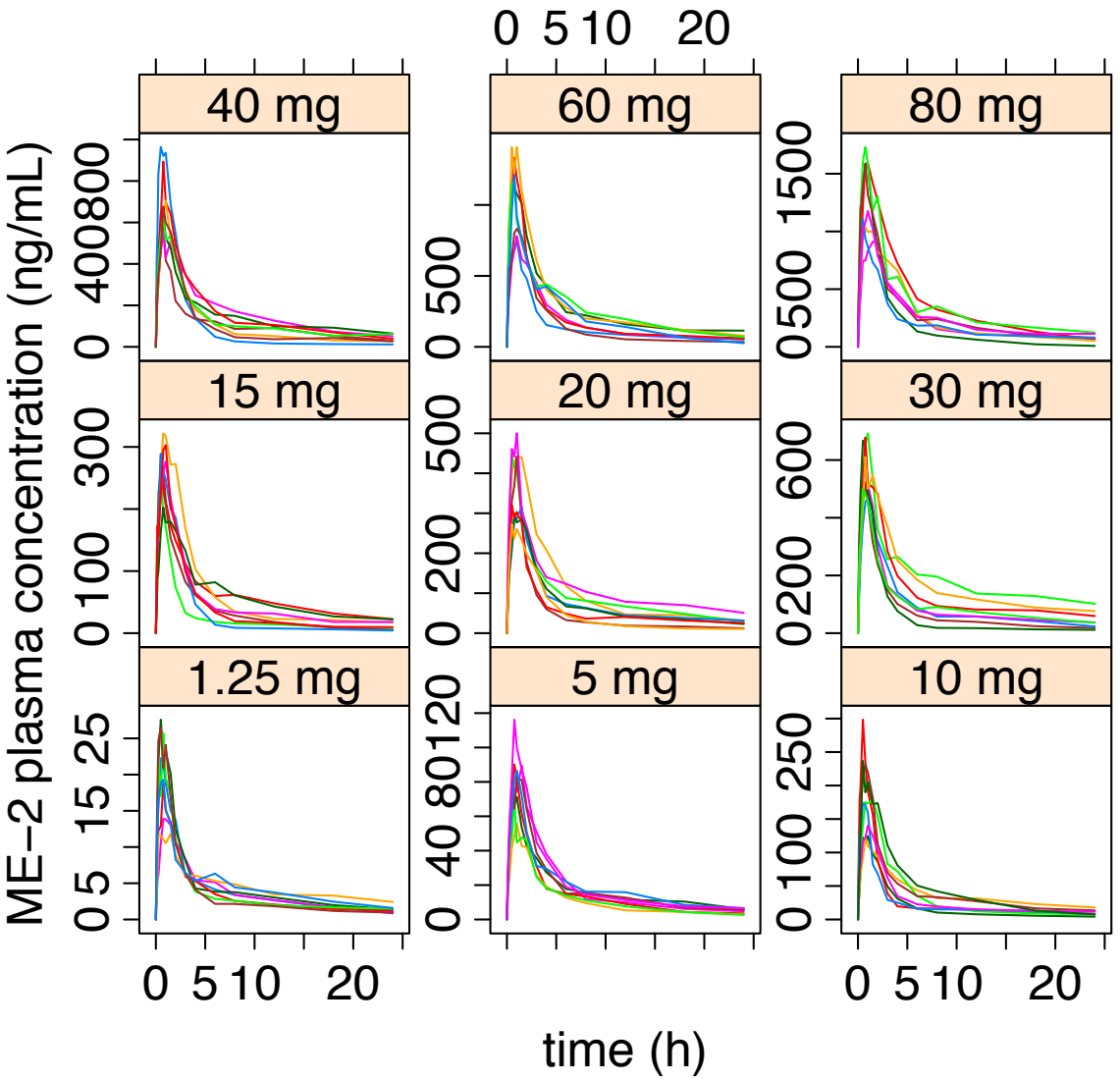
Adapting general purpose Bayesian software
Stan

- Stan versions 2.5.0 and above include a function for numerical solution of ODEs using a Runge-Kutta 4th/5th order method.
- No explicit support for dosing or other events is provided, though it is relatively easy to implement such schedules in Stan's flexible model specification language.

Stan population PK modeling example

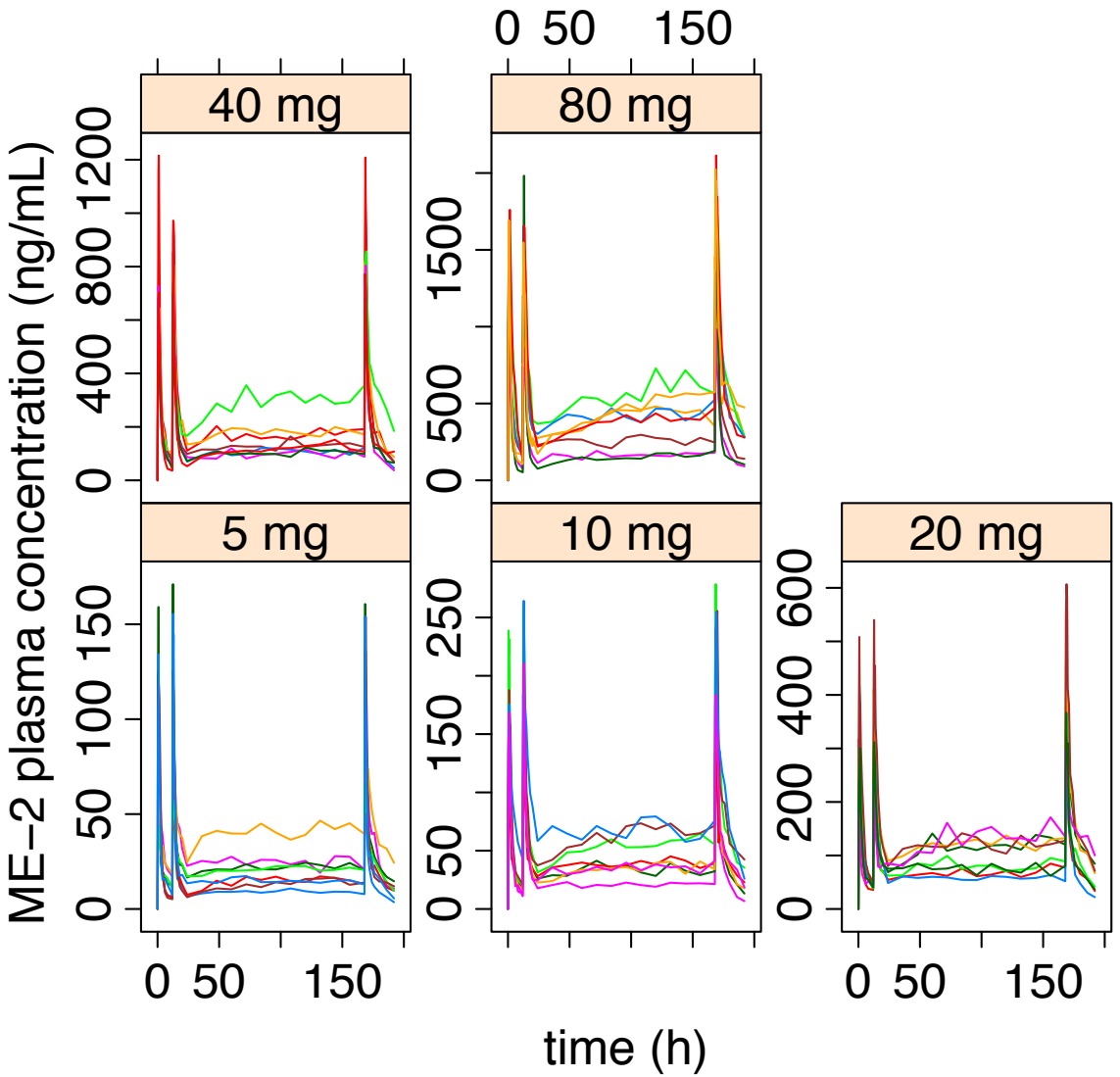
- Linear two compartment model with first order absorption (analytic solution)
- Multiple dosing allowing for irregular intervals
- User-defined Stan function to calculate matrix of amounts in each compartment at all observation times for an individual
- Event-oriented data structure like that for NONMEM and BUGSModelLibrary

Population PK of simulated ME-2 data



ME-2 PK data from Phase I SD trial
n = 80

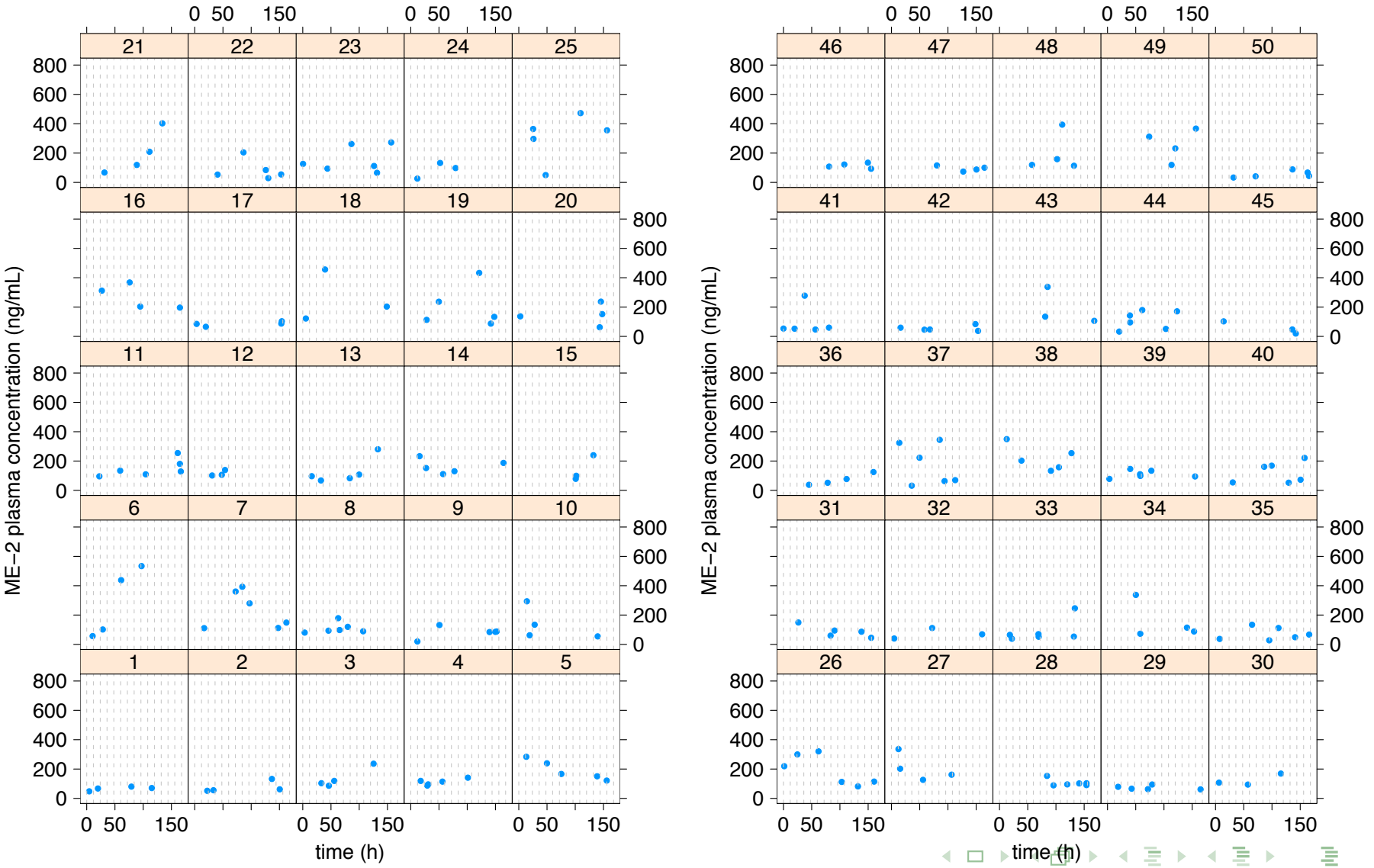
Population PK of simulated ME-2 data



ME-2 PK data from Phase I MD trial
n = 48

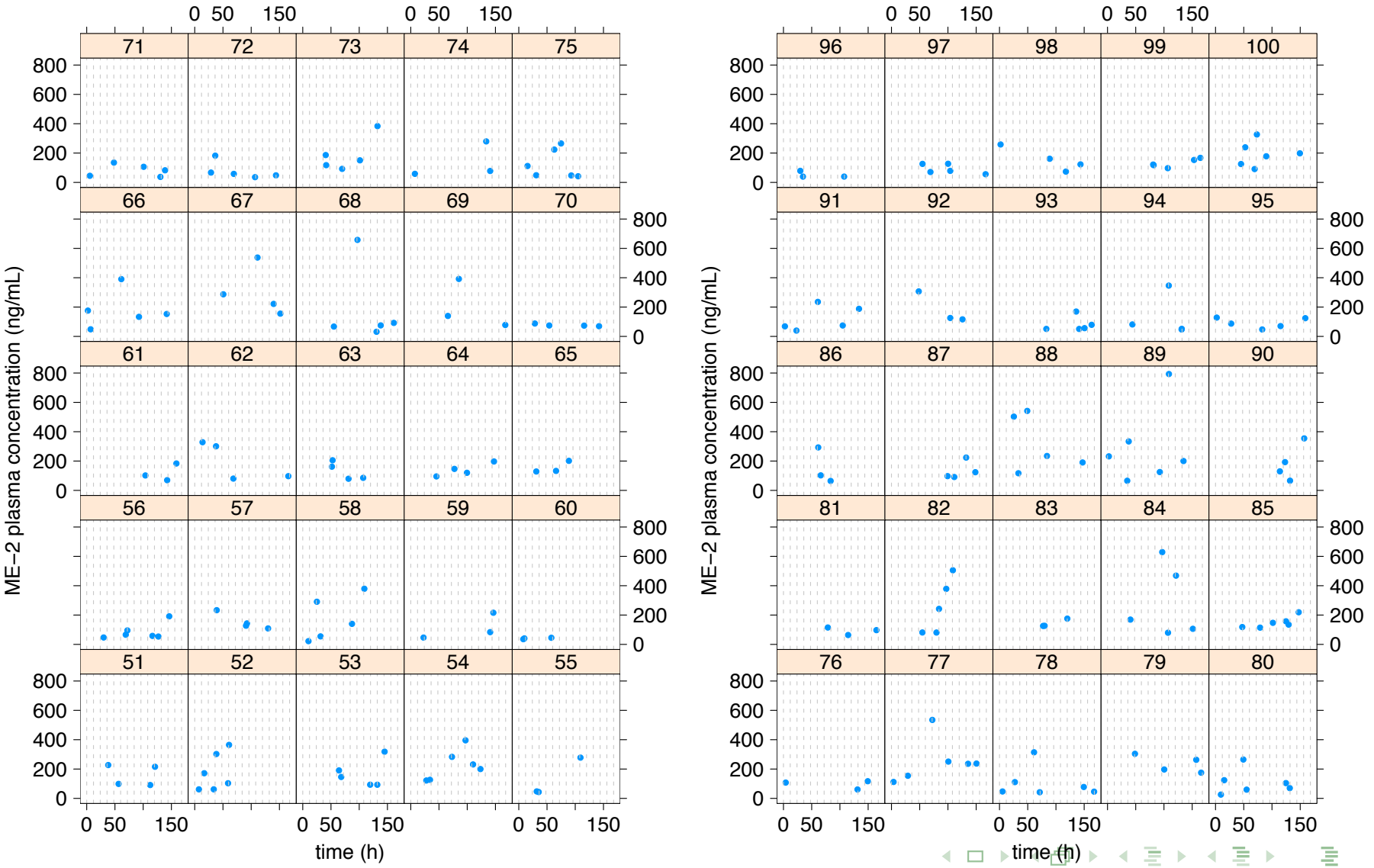
Population PK of simulated ME-2 data

ME-2 PK data from Phase IIa trial (n = 100)



Population PK of simulated ME-2 data

ME-2 PK data from Phase IIa trial

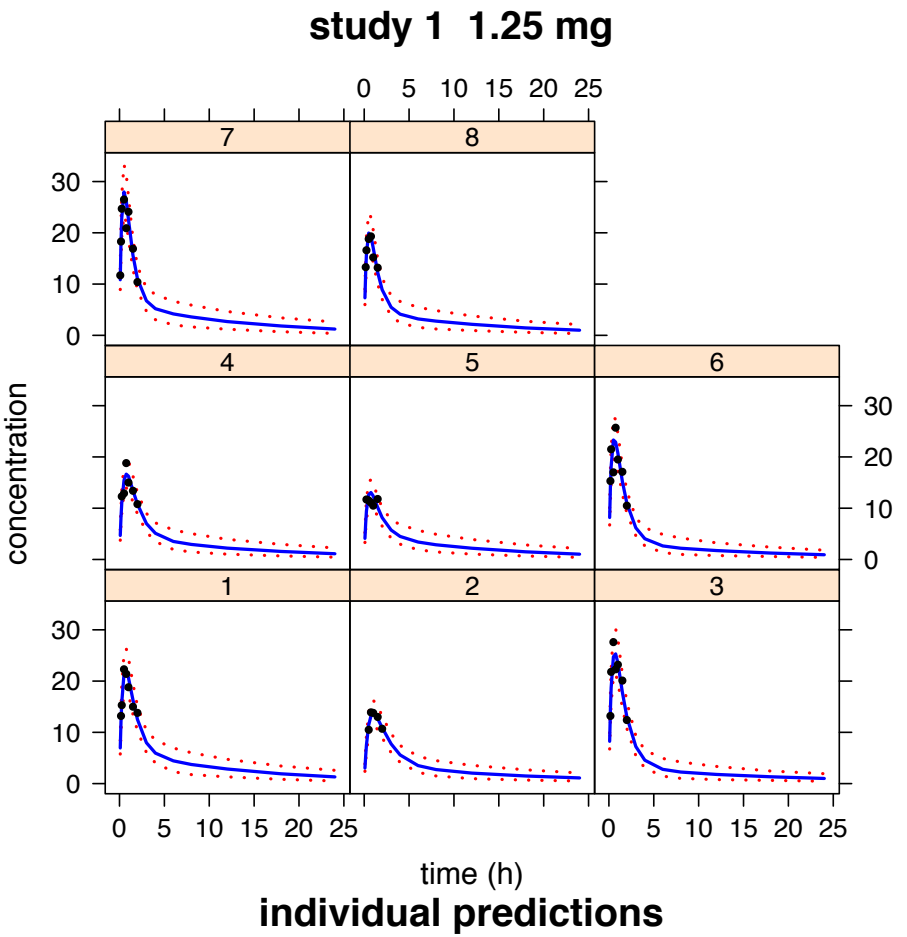


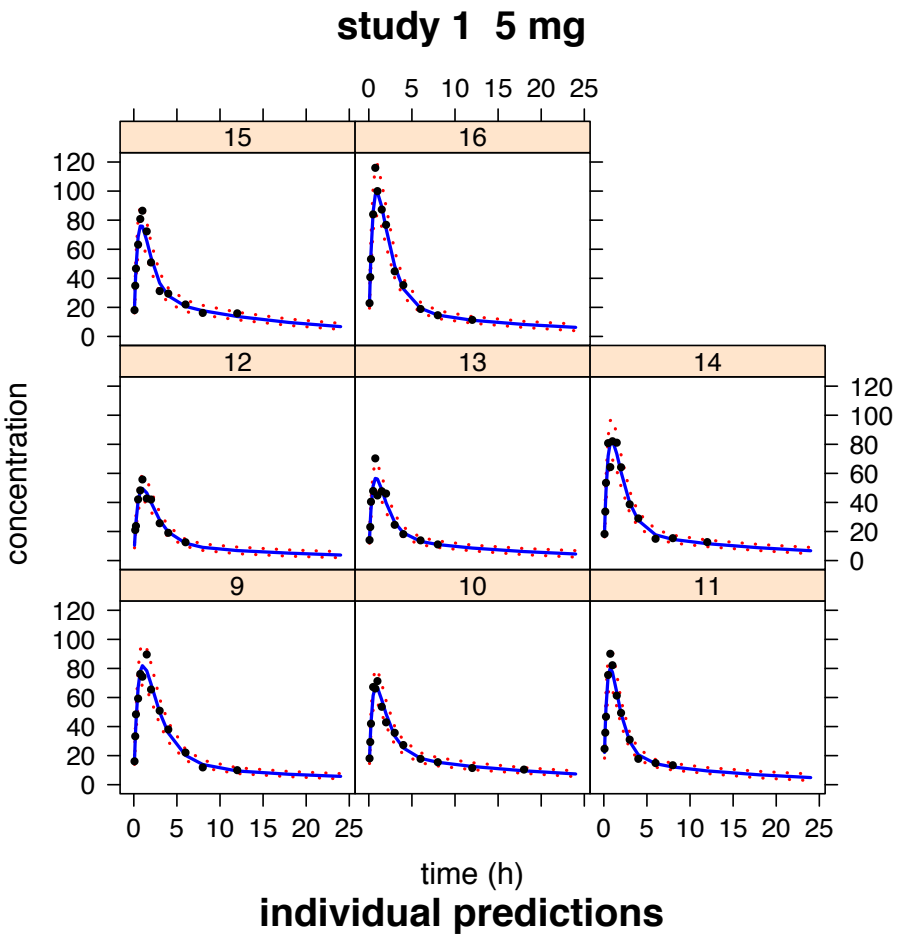
- Two compartment model with first order absorption describing ME-2 plasma concentration on the i^{th} occasion in the j^{th} subject as a function of time, dose and body weight:

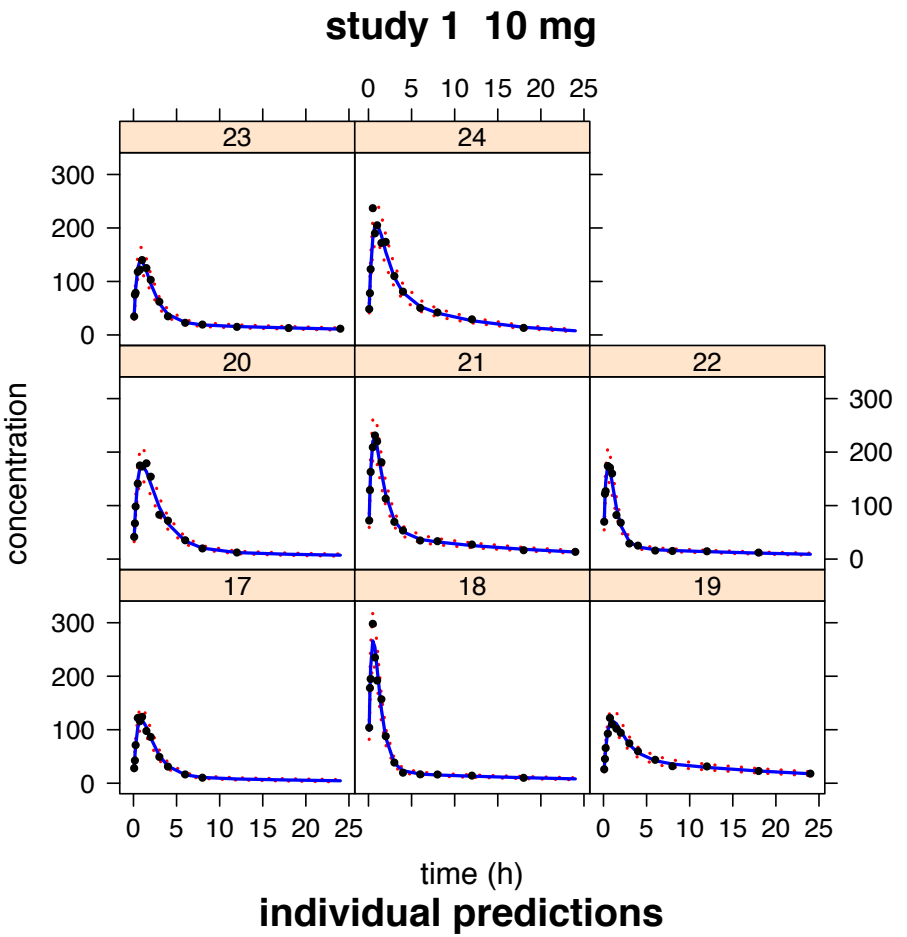
$$\begin{aligned}
\log\left(c_{ij}\right) &\sim N\left(\log\left(\hat{c}_{ij}\right), \sigma^2\right) \\
\hat{c}_{ij} &= f_{2cpt}\left(t_{ij}, D_j, \tau_j, CL_j, Q_j, V_{1j}, V_{2j}, k_{aj}\right) \\
\log\left(CL_j, Q_j, V_{1j}, V_{2j}, k_{aj}\right) & \\
&\sim N\left(\log\left(\widehat{CL}\left(\frac{bw_j}{70}\right)^{0.75},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

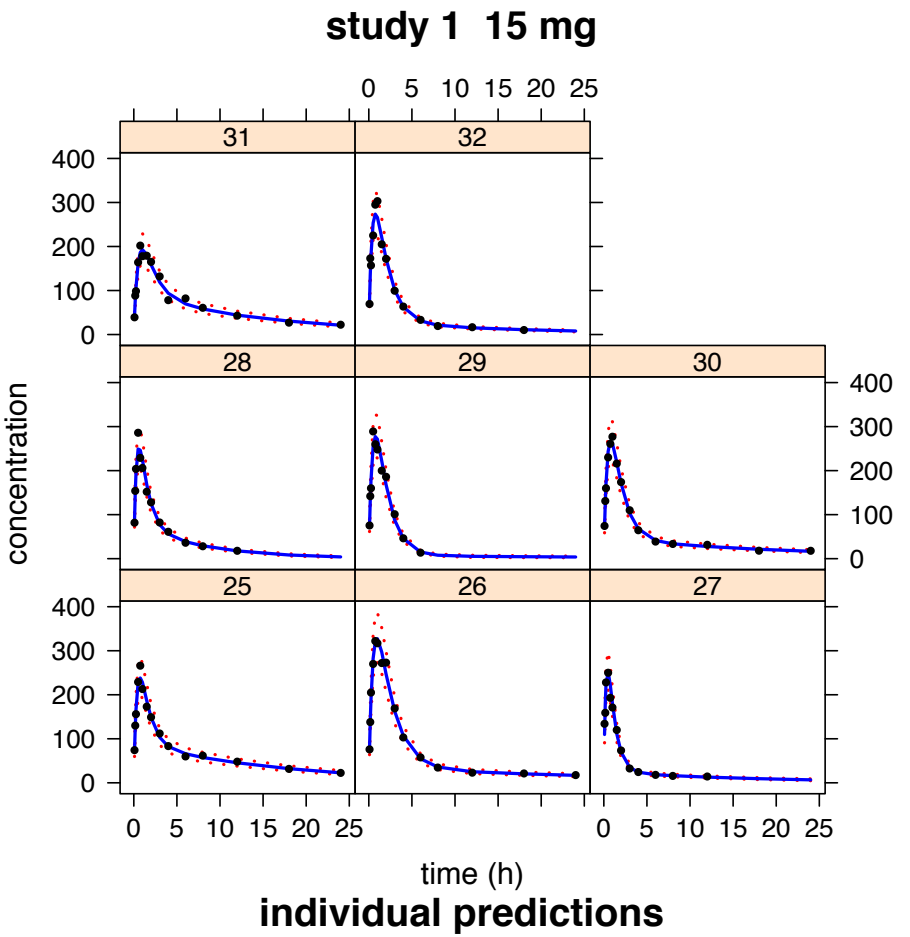
- Weakly informative prior distributions:

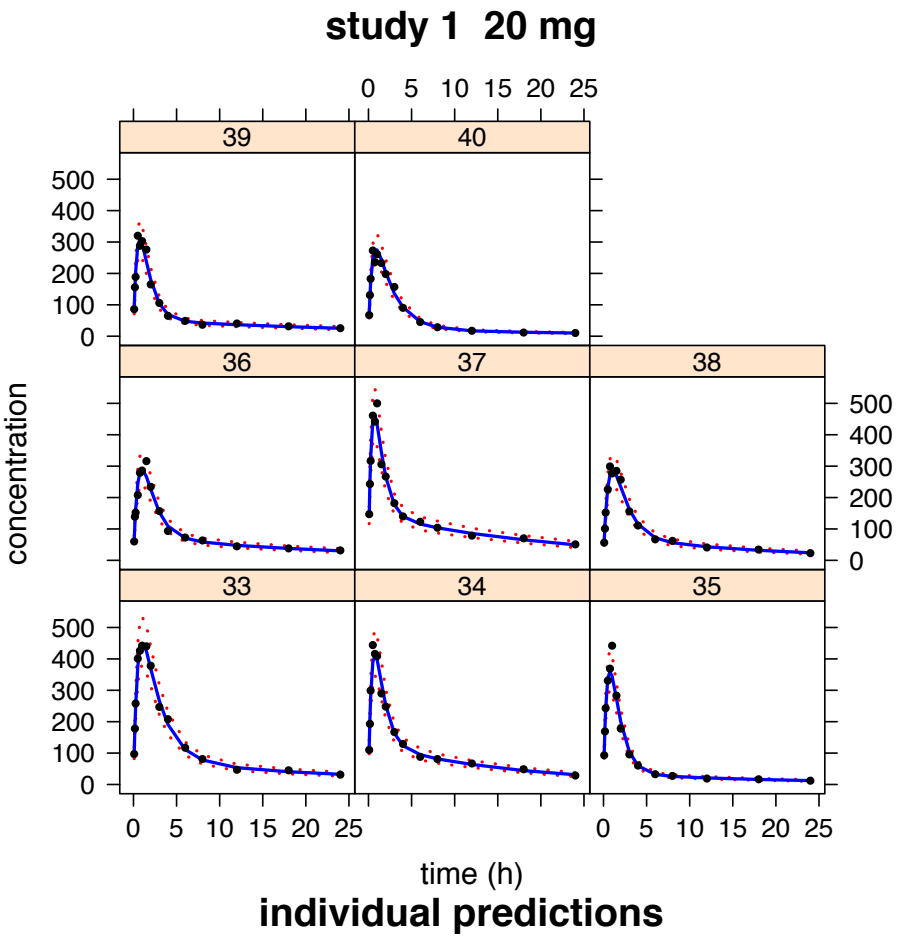
$$\begin{aligned}
\log\left(\widehat{CL}\right) &\sim N\left(0, 10^6\right) \quad \log\left(\widehat{Q}\right) \sim N\left(0, 10^6\right) \quad \log\left(\widehat{V}_1\right) \sim N\left(0, 10^6\right) \\
\log\left(\widehat{V}_2\right) &\sim N\left(0, 10^6\right) \quad \log\left(\widehat{k}_a - \lambda_1\right) \sim N\left(0, 10^6\right) \quad \sigma \sim \text{half Cauchy}\left(0, 5^2\right) \\
\Omega &= \text{diag_matrix}(\omega) P \, \text{diag_matrix}(\omega) \\
\omega_k &\sim \text{half Cauchy}\left(0, 5^2\right) \quad P \sim LKJ\left(1\right)
\end{aligned}$$

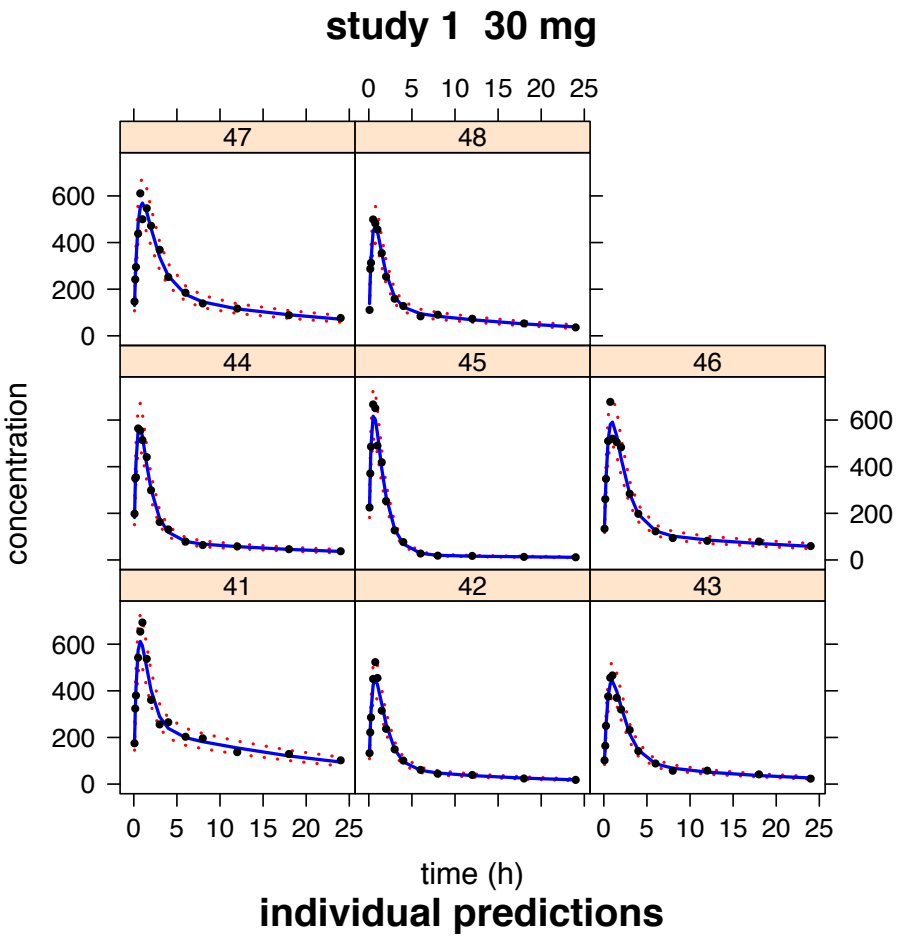

study 1 1.25 mg
concentration
time (h)
individual predictions

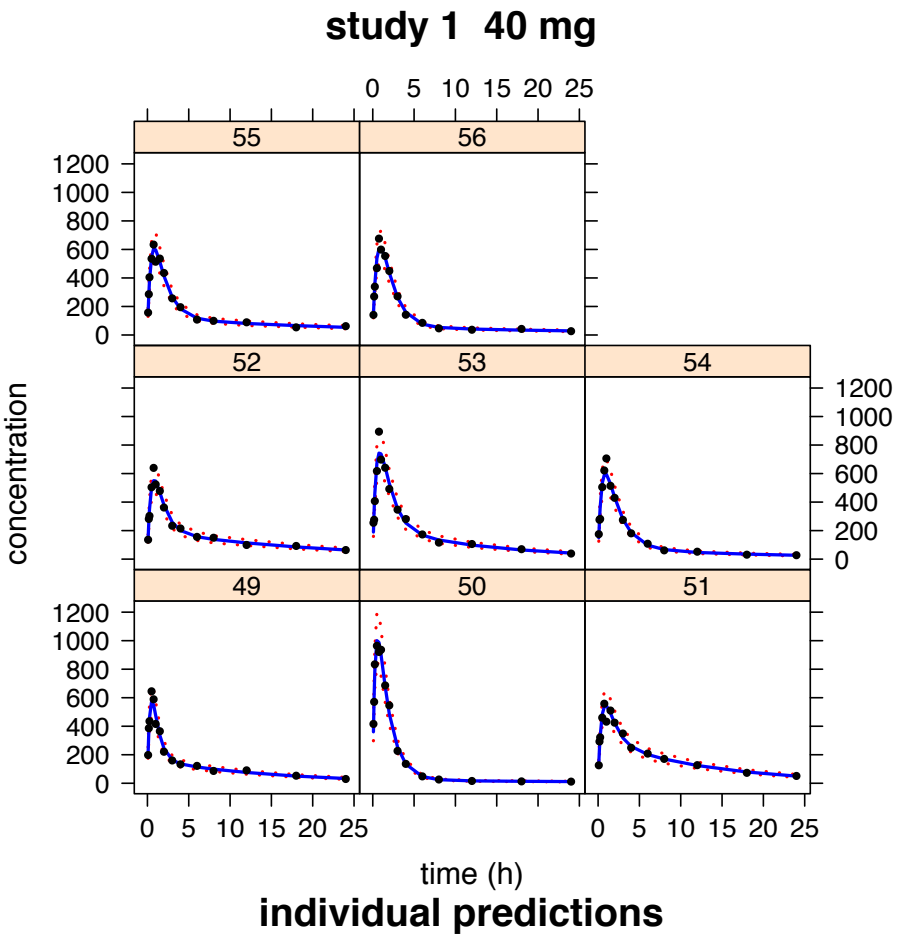

study 1 5 mg
concentration
time (h)
individual predictions

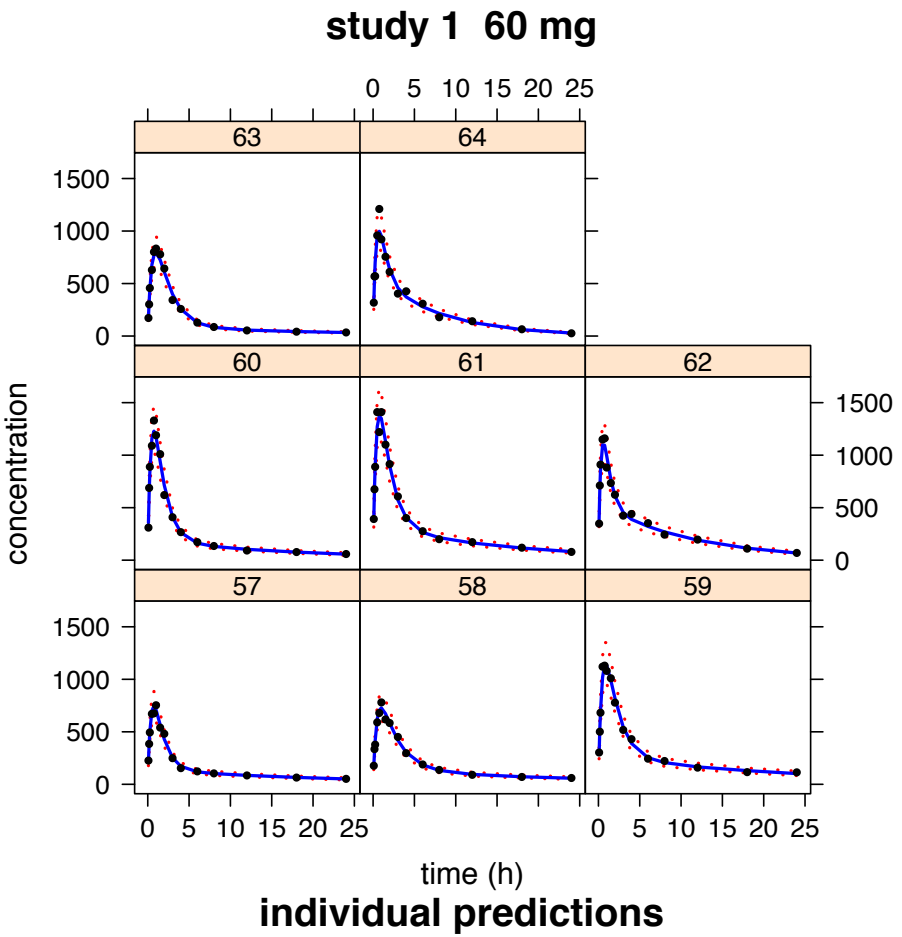

study 1 10 mg
23
24
20
21
22
17
18
19
concentration
time (h)
individual predictions

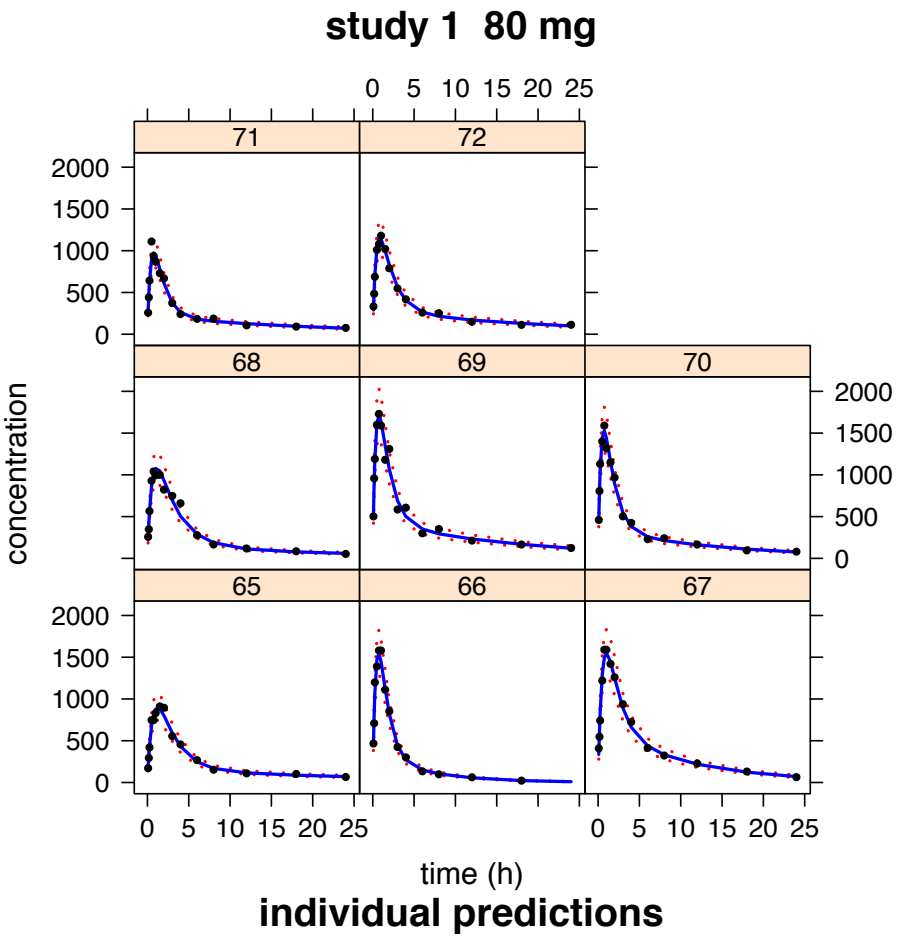

study 1 15 mg
31
32
28
29
30
25
26
27
concentration
time (h)
individual predictions

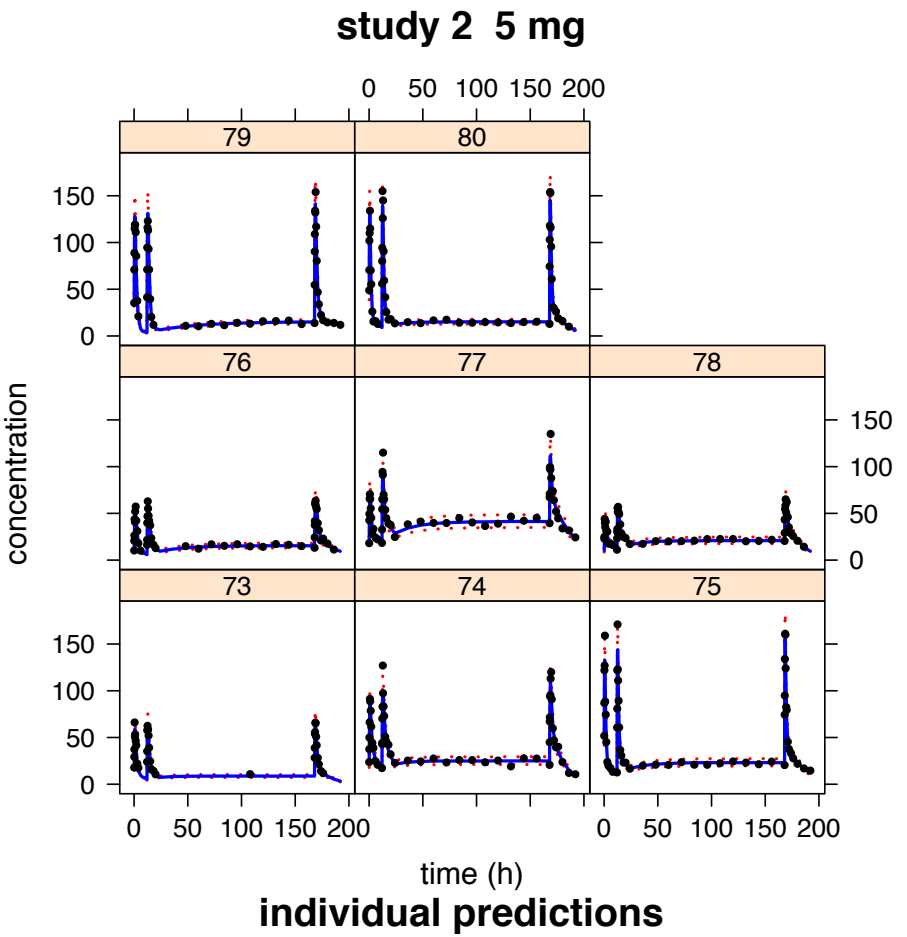

study 1 20 mg
39
40
36
37
38
33
34
35
concentration
time (h)
individual predictions


study 1 30 mg
47
48
44
45
46
41
42
43
concentration
time (h)
individual predictions


study 1 40 mg
55
56
52
53
54
49
50
51
concentration
time (h)
individual predictions


study 1 60 mg
63
64
60
61
62
57
58
59
concentration
time (h)
individual predictions


study 1 80 mg
71
72
68
69
70
65
66
67
concentration
time (h)
individual predictions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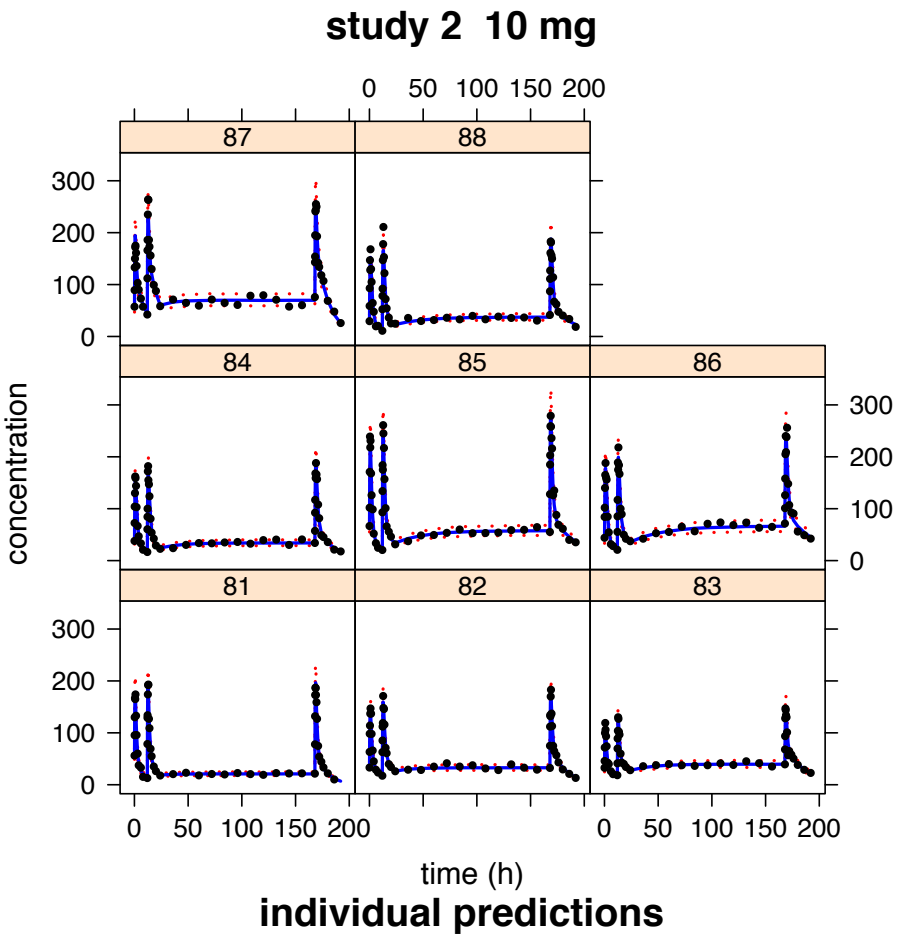
80
76
77
78
73
74
75
concentration
time (h)
individual predictions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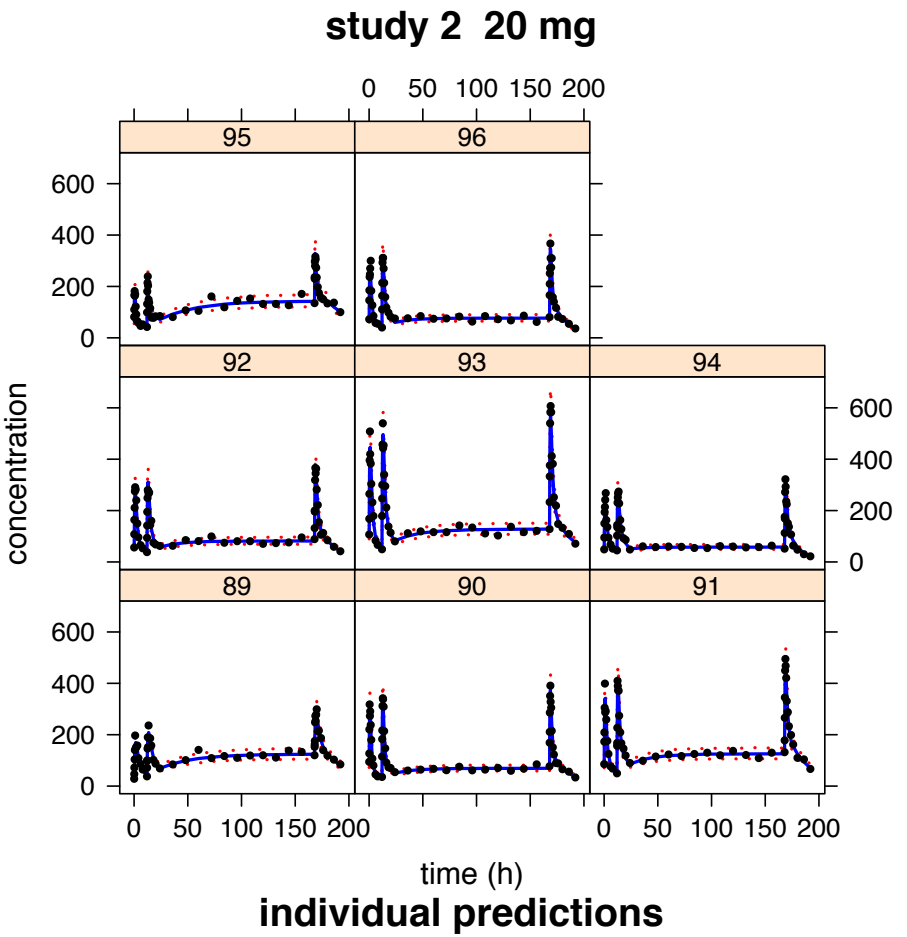
88
84
85
86
81
82
83
concentration
time (h)
individual predictions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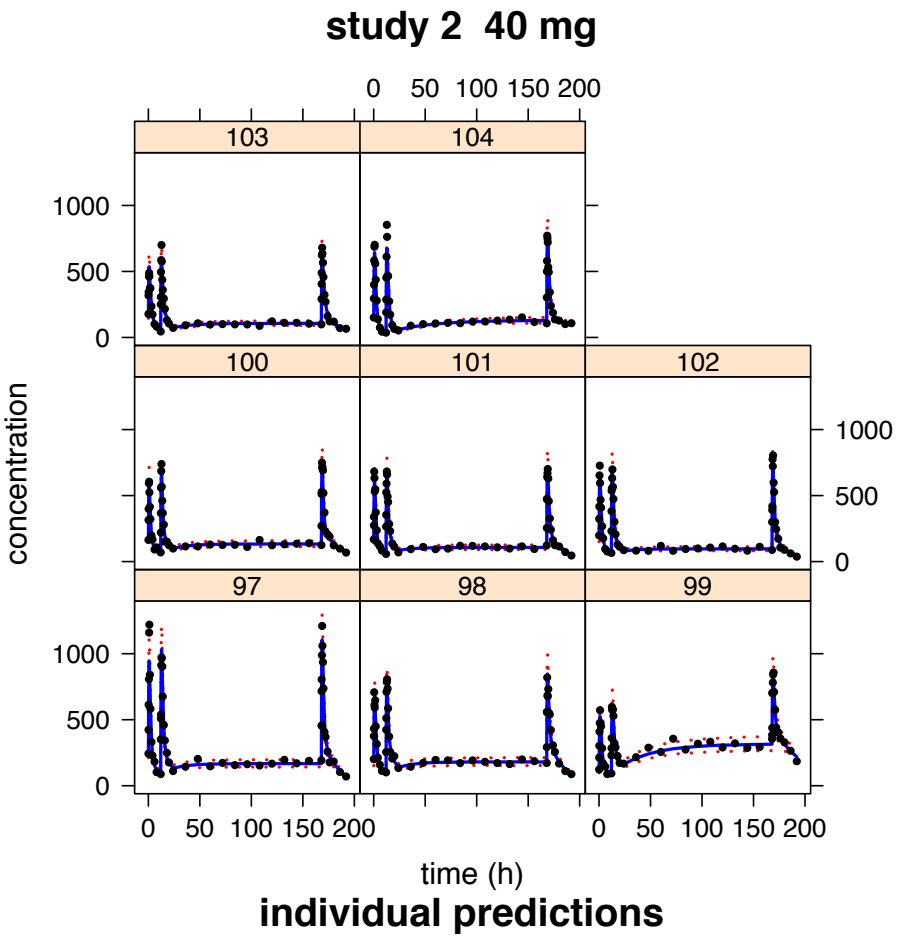
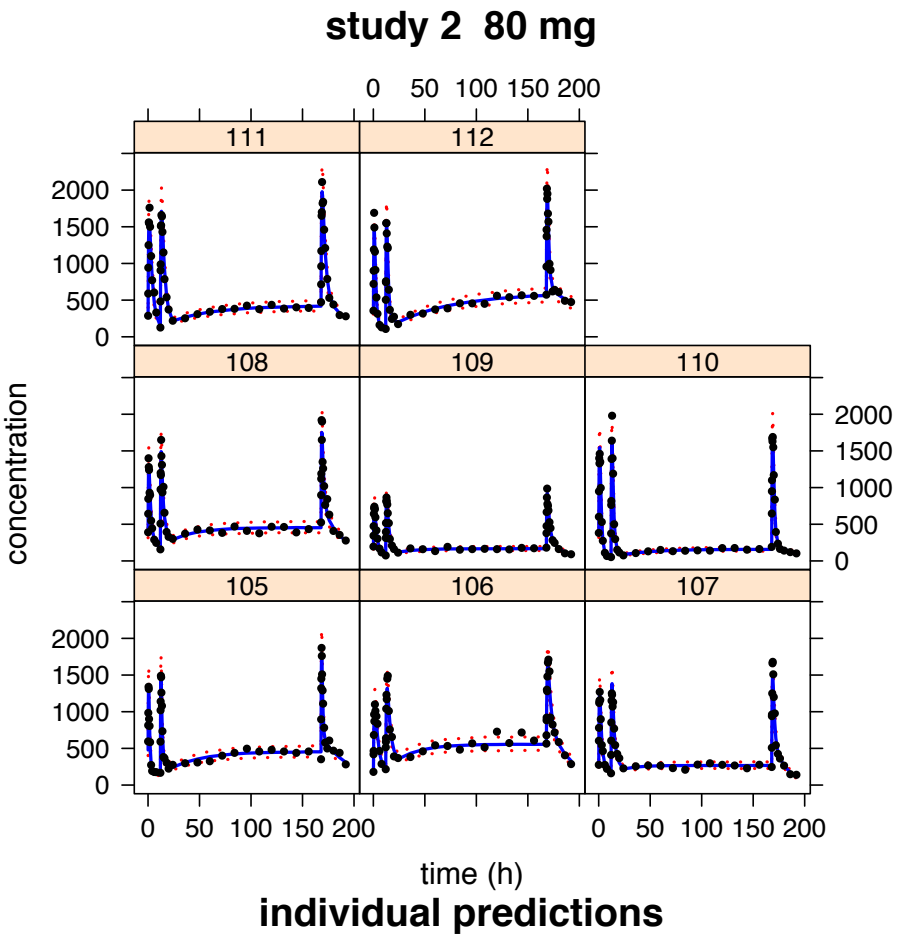
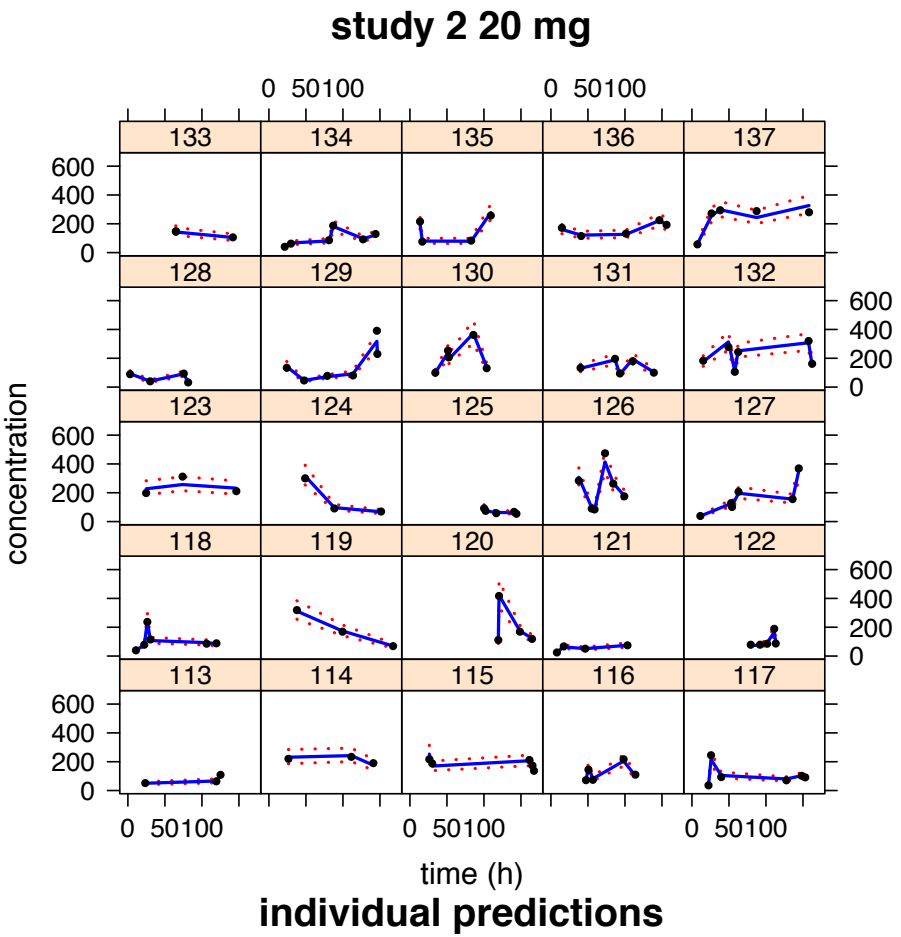
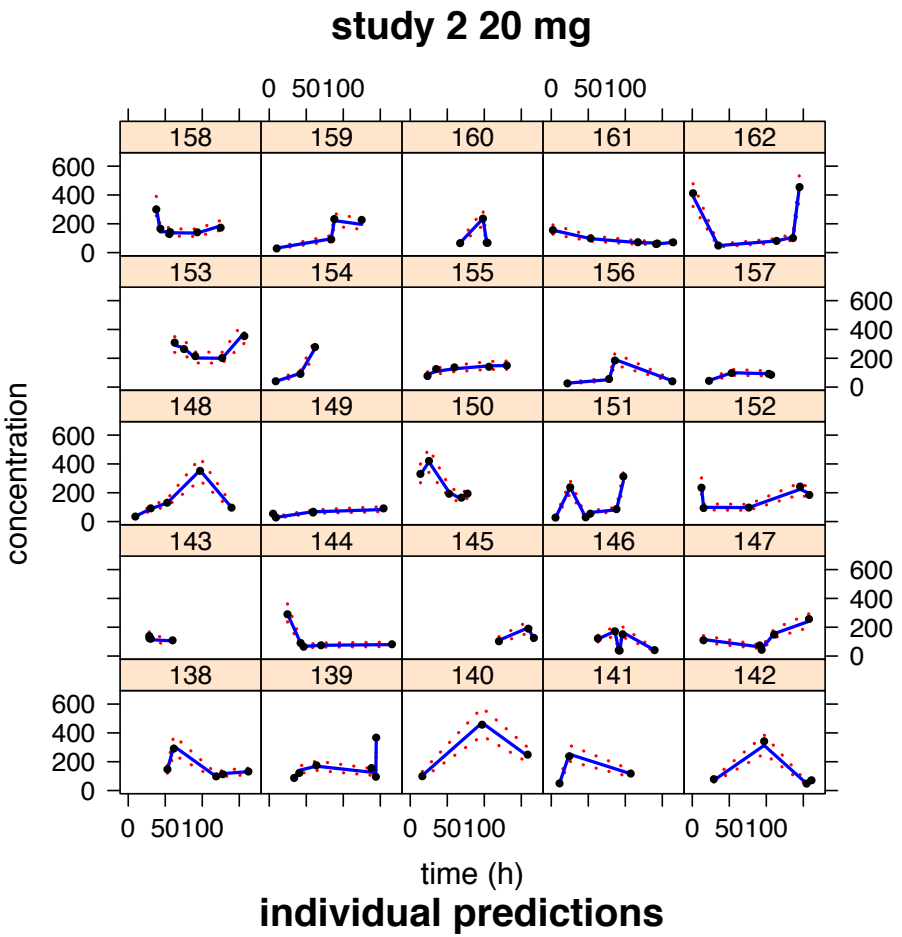
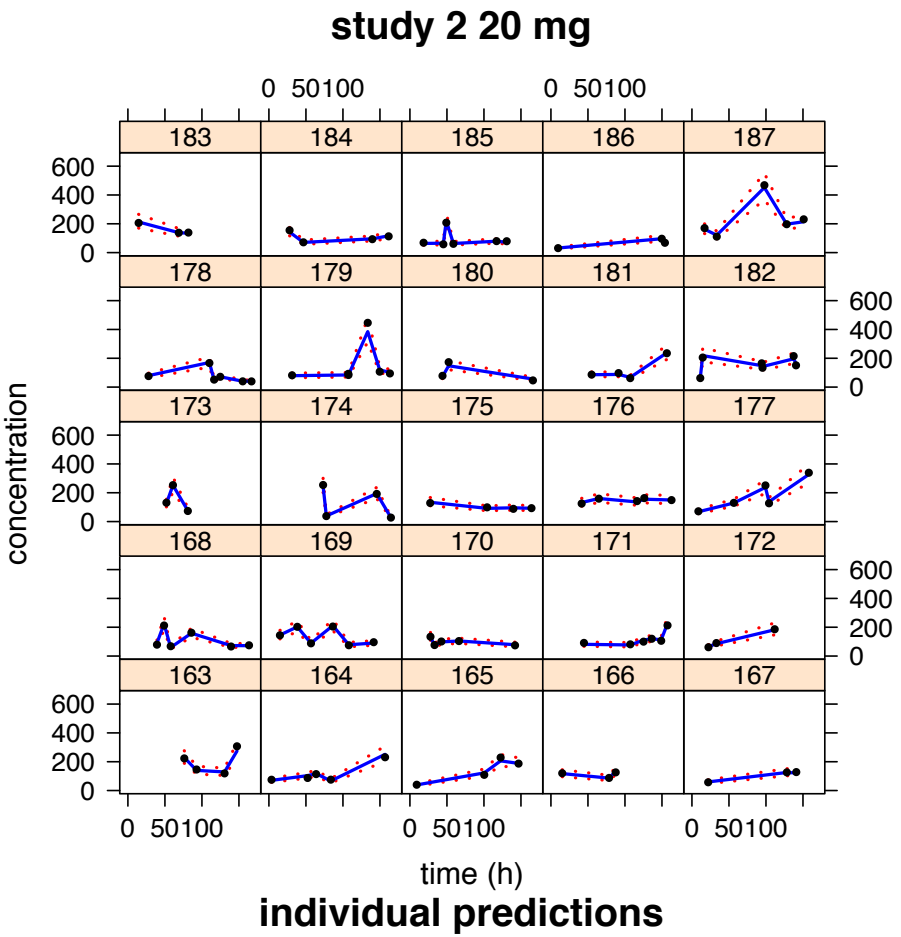
96
92
93
94
89
90
91
concentration
time (h)
individual predictions

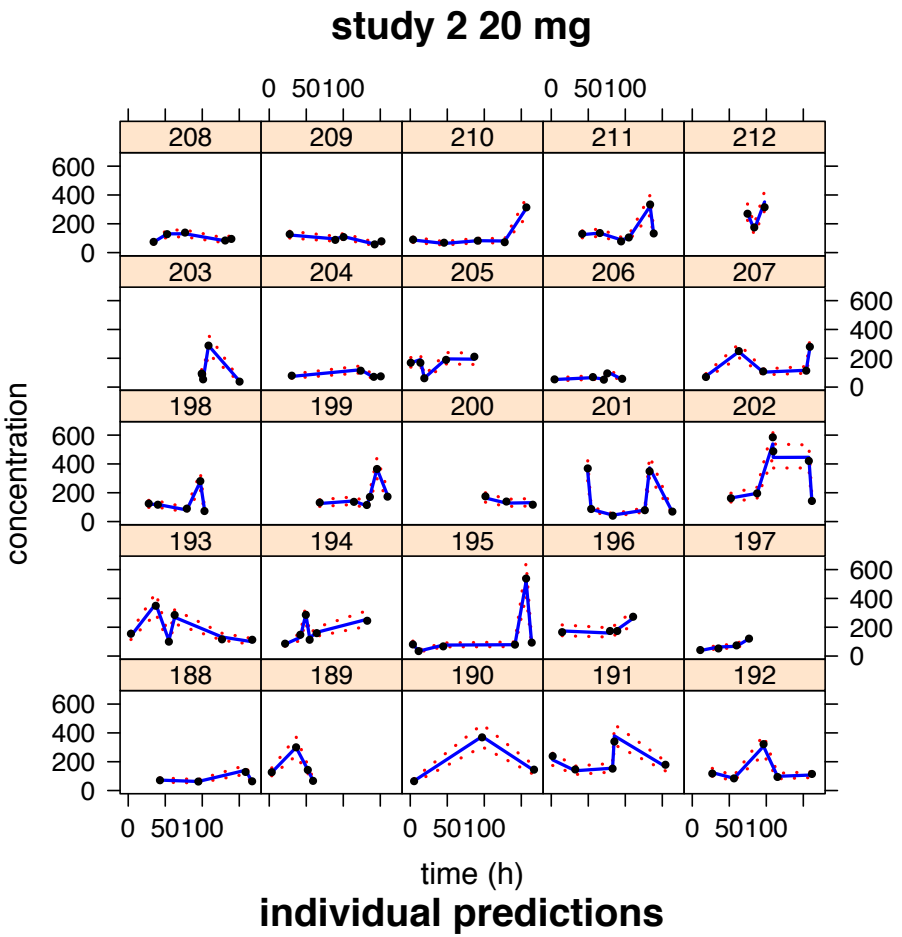

study 2 40 mg
103
104
100
101
102
97
98
99
concentration
time (h)
individual predictions


study 2 80 mg
111
112
108
109
110
105
106
107
concentration
time (h)
individual predictions


study 2 20 mg
concentration
time (h)
individual predictions


study 2 20 mg
concentration
time (h)
individual predictions


study 2 20 mg
concentration
time (h)
individual predictions


study 2 20 mg
concentration
time (h)
individual predictions

Selected parameter estimates with Stan 2.6.0 and WinBUGS 1.4.3

		iterations/chain			
	chains	burn-in	post-burn-in	thin	net
Stan	4	200	500	1	2000
WinBUGS	4	5000	5000	10	2000

	Stan			WinBUGS/BUGSModelLibrary		
parameter	mean	95% CI	effective N	mean	95% CI	effective N
$\widehat{CL}$	9.91	(9.56, 10.3)	89	9.93	(9.57, 10.3)	2000
$\widehat{Q}$	14.6	(13.7, 15.8)	271	14.6	(13.6, 15.7)	1954
$\widehat{V_1}$	35.5	(33.4, 37.4)	664	35.4	(33.3, 37.4)	21
$\widehat{V_2}$	105	(98.5, 113)	406	105	(98.4, 113)	1907
$\widehat{k_a}$	2.06	(1.92, 2.19)	997	2.06	(1.92, 2.18)	26

Stan for ODE-based models?

My attempts to use Stan's numerical ODE solver with problems like the myelosuppression example have not been very successful.

- Grinds to a halt with stiff ODEs
  - Even if the problem is non-stiff over most of the posterior distribution, MCMC simulation is likely to visit regions of the parameter space that lead to stiffness if they exist.
- Users cannot adjust ODE solver specs like tolerances or limits on step size or number of steps.
- Conclusion: Not well-suited to PKPD models that require numerical solution of ODEs.
- Recommend addition of ODE solver suitable for stiff equations, e.g., LSODA or CVODE (see presentation by Jan Serroyen).

Pros & cons: NONMEM

- Pros
  - Flexible model specification language for the conditional likelihood of an observation
  - Built-in handlers for event schedules encountered in PKPD data
  - Good numerical ODE solvers: LSODA and matrix exponential solver
  - Support for parallel computations within chain
  - Steady-state calculations even for ODE-based models (via numerical solution of boundary value problem)
  - Optimization for estimation of posterior modes
- Cons
  - Restricted stochastic model structure
  - Very restricted choice of prior distributions
  - Relatively expensive and not open source

Pros & cons: WinBUGS + BUGSModelLibrary

- Pros
  - Flexible model specification language
  - Many built-in functions and distributions
  - Built-in handlers for event schedules encountered in PKPD data
  - Good numerical ODE solvers: LSODA, Runge-Kutta and matrix exponential solver
  - Steady-state calculations even for ODE-based models (via numerical solution of boundary value problem)
  - Freely available
- Cons
  - Windows app. Requires Wine or similar to run on *nix platforms.
  - ODE models require writing/compiling a Component Pascal model
  - Lack of control structures like true loops and if-then-else in BUGS language
  - BUGSModelLibrary has not (yet?) been ported to OpenBUGS
  - WinBUGS 1.4.3 is not open source
  - Little or no continued development of BUGS and the BlackBox Component Builder

Pros & cons: Stan

- Pros
  - HMC/NUTS sampler often performs better than the Gibbs/Metropolis samplers in NONMEM and BUGS
  - Very flexible imperative model specification language (vs BUGS declarative language)
    - Many built-in functions and distributions
    - Easy to create user-defined functions
    - Control structures like for loops, while loops, if-then-else
    - Vector and matrix operators and functions
    - Can directly specify likelihood without resorting to tricks
  - Optimization for estimation of posterior modes
  - Active development program
  - Freely available and open source
- Cons
  - No built-in handlers for PKPD event schedules
  - Numerical ODE solver in current version (2.6.*) is a Runge Kutta method that fails (rather ungracefully) with stiff ODEs
  - Steady-state calculations for ODE models not readily implemented

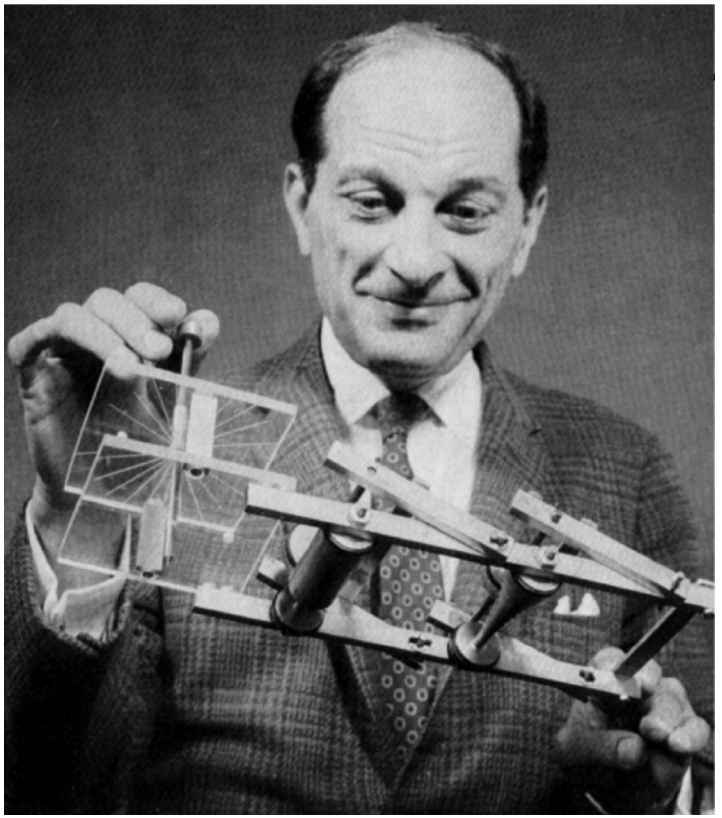
Wish list

Stan extensions

- Better, more flexible ODE solvers
  - Support for stiff ODEs, e.g., LSODA or CVODE
  - Matrix exponential solver for linear ODEs
- Numerical root solver that may be used for steady-state calculations
- Support for event schedules ala NONMEM
- Parallel computation support for some classes of hierarchical models

BUGSModelLibrary equivalent for OpenBUGS and/or JAGS?

Stan Ulam



“The first sign of senility is that a man forgets his theorems, the second sign is that he forgets to zip up, the third sign is that he forgets to zip down.”

A few more of my favorite Stans

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