

Population and ODE-based models using Stan and Torsten

Charles Margossian, Yi Zhang

StanCon 2019, Cambridge UK
August 2019

Outline

1. Course information
2. Introduction and modeling framework | Charles Margossian
3. Models in pharmacometrics | Charles Margossian
4. ODEs in Stan and Torsten | Charles Margossian
5. Numerical ODE integrators | Yi Zhang
6. Population models | Charles Margossian
7. ODE group integrators | Yi Zhang
8. PMX population solvers | Yi Zhang
9. Additional nonlinear ODE example | Charles Margossian

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Instructors

- ▶ Charles Margossian
 - ▶ Columbia University, Department of Statistics
- ▶ Yi Zhang
 - ▶ Metrum Research Group

TA

- ▶ Steve Bronder
 - ▶ Capital One

Outline

Day 1

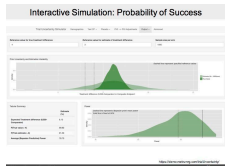
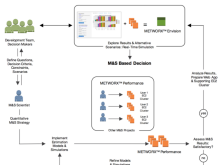
- ▶ Introduction and modeling framework
- ▶ Pharmacometrics models
- ▶ Ordinary differential equation(ODE) based models
- ▶ Numerical ODE integrators

Day 2

- ▶ Population models
- ▶ Group/Population ODE integrators and MPI parallelisation
- ▶ Group/Population solvers and MPI parallelisation

Logistics

METWORX™, cloud-based modeling & simulation platform by Metrum Research Group.



Logistics

Workshop package

- ▶ R scripts and Stan files to do the exercises
- ▶ These slides
- ▶ Outline of the course
- ▶ Additional documentation

We will be using:

- ▶ Torsten v0.87
- ▶ RStan v2.19.2
- ▶ ggplot, plyr, tidyr, dplyr

Outline

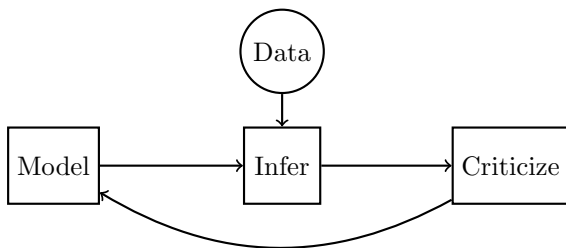
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Preliminary question

- ▶ Why Bayesian in a field such as pharmacometrics?
- ▶ Example - *Bayesian aggregation of average data: an application in drug development* [Weber et al., 2018]

Modeling framework

Box's loop



Inference

- ▶ find the set of parameters consistent with our model and our data
- ▶ approximate this set with draws from the posterior distribution

Sampling algorithm

- ▶ Use the NUTS to sample $\pi(\theta|y)$
- ▶ Requires users the specify $\log \pi(\theta, y) = \log \pi(y|\theta) + \log \pi(\theta)$

The "criticism" step

This step can be broken up in two parts:

1. did we sample from the correct distribution?
2. does our model capture the characteristics of the data we care about?

Diagnosing the inference algorithm

- ▶ look at the trace and the density plots
- ▶ look at \hat{R} and effective number of samples
- ▶ have any warning messages been issued, i.e. divergent transitions ?

Example: fitting a linear model

Likelihood:

$$Y \sim \text{Normal}(\mathbf{x}\beta, \sigma^2)$$

Prior:

$$\beta \sim \text{Normal}(2, 1)$$

$$\sigma^2 \sim \text{Normal}(1, 1)$$

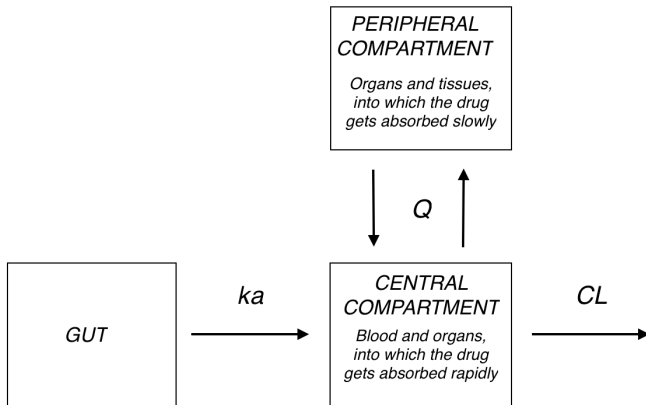
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What is the effect of a treatment on a patient?

- ▶ *pharmacokinetics (PK)*: how is the drug absorbed in the body?
- ▶ *pharmacodynamics (PD)*: once it is absorbed, what are its effects?

Example: Two compartment model



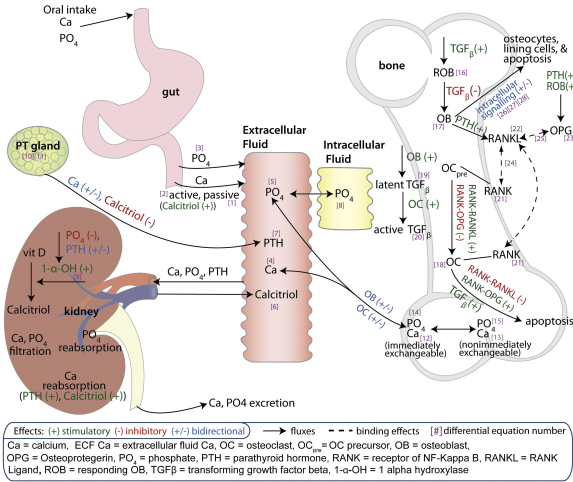
Two compartment model

$$y'_{\text{gut}} = -k_a y_{\text{gut}}$$

$$y'_{\text{cent}} = k_a y_{\text{gut}} - \left(\frac{CL}{V_{\text{cent}}} + \frac{Q}{V_{\text{cent}}} \right) y_{\text{cent}} + \frac{Q}{V_{\text{peri}}} y_{\text{peri}}$$

$$y'_{\text{peri}} = \frac{Q}{V_{\text{cent}}} y_{\text{cent}} - \frac{Q}{V_{\text{peri}}} y_{\text{peri}}$$

Example 2: Bone mineral density model from [Peterson and Riggs, 2012]



Two compartment model

Denote $\theta = \{CL, Q, VC, VP, K_a\}$, the ODE coefficients. Then

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

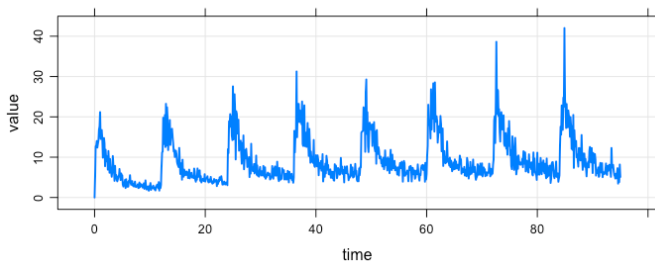
Given an initial condition $y_0 = y(t_0)$, solving the above ODE gives us the *{natural evolution}* of the system at any given time point.

The event schedule

An event can be:

- ▶ **State changer**: an (exterior) intervention that alters the state of the system; for example a bolus dosing or the beginning of an infusion.
- ▶ **Observation**: a measurement of a quantity of interest at a certain time.

Drug concentration in a patient's blood

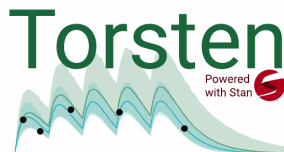


The event schedule

- ▶ There is no general theory for the event schedule :(
- ▶ The modeling software NONMEM® proposes a convention for pharmacometrics, which we adopt in Torsten.

Torsten functions

Torsten functions offers additional built-in functions to simulate data from a compartment model.



Each Torsten function requires users to specify:

- ▶ a system of ODEs and a method to solve it.
- ▶ An event schedule.

Torsten functions

```
matrix = pmx_solve_onecpt(real[] time, real[] amt, real[] rate,  
                           real[] ii, int[] evid, int[] cmt,  
                           real[] addl, int[] ss, real[]  
                               ↪ theta,  
                           real[] biovar, real[] tlag);
```

```
matrix = pmx_solve_twocpt(real[] time, real[] amt, real[] rate,  
                           real[] ii, int[] evid, int[] cmt,  
                           real[] addl, int[] ss, real[]  
                               ↪ theta,  
                           real[] biovar, real[] tlag);
```

- ▶ Analytically solutions for the one/two cpt models.
- ▶ Event schedule
- ▶ ODE coefficients, e.g. $\theta = \{CL, Q, VC, VP, ka\}$ for two-cpt model.
- ▶ bio-availability fraction and lag times.

Example

Clinical trial

- ▶ Single patient
- ▶ Bolus doses with 1200 mg, administered every 12 hours, for a total of 15 doses.
- ▶ Many observations for the first, second, and last doses.
- ▶ Additional observation every 12 hours.

Note: the observation are plasma drug concentration measurement.

See `data/twoCpt.data.r`.

Example

Model

- ▶ two compartment model with first-order absorption
- ▶ prior information based on clinical trial conducted on a large population
- ▶ normal error for the plasma drug concentration measurement.

Example

Prior

```
CL ~ lognormal(log(10), 0.25);  
Q ~ lognormal(log(15), 0.5);  
VC ~ lognormal(log(35), 0.25);  
VP ~ lognormal(log(105), 0.5);  
ka ~ lognormal(log(2.5), 1);  
sigma ~ cauchy(0, 1);
```

Likelihood

$$\log(cObs) \sim \text{Normal} \left(\log \left(\frac{y_2}{VC} \right), \sigma^2 \right)$$

Exercise 1: write and fit this model, using `twoCptModel.r` and `model/twoCptModel.stan`. *Exercise 2:* Write a generated quantities block and do posterior predictive checks.

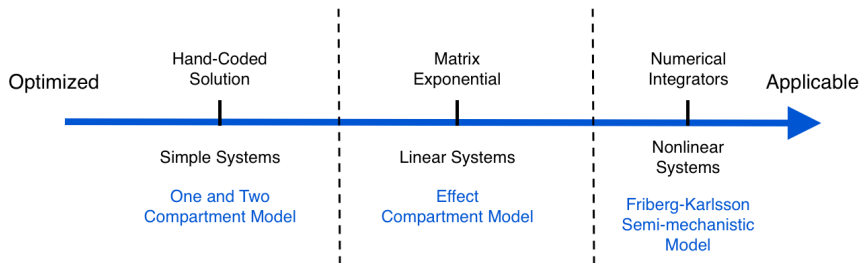
Resources

- ▶ Torsten repository:
`https://github.com/metrumresearchgroup/Torsten`
- ▶ Torsten User manual (on GitHub and in the workshop folder).

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Arsenal of tools



For some examples, see [Margossian and Gillespie, 2017a].

- ▶ the "optimized - applicable" spectrum is a heuristic; counter-examples can be built.
- ▶ coding effort may also be a criterion

Matrix exponential

Consider a system of linear ODEs:

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

where K is a constant matrix.

Then

$$y(t) = e^{tK}y_0$$

Matrix Exponential

$$e^{tK} = \sum_{n=0}^{\infty} \frac{(tK)^n}{n!} = I + tK + \frac{(tK)^2}{2} + \frac{(tK)^3}{3!} + \dots$$

Matrix Exponential

For example, the two compartment model generates the following matrix:

$$K = \begin{bmatrix} -ka & 0 & 0 \\ ka & -(CL + Q)/V_c & Q/V_p \\ 0 & Q/V_c & -Q/V_p \end{bmatrix}$$

Linear ODE solver in Torsten

```
matrix = pmx_solve_linode(real[] time, real[] amt, real[] rate,  
                           real[] ii, int[] evid, int[] cmt,  
                           real[] addl, int[] ss,  
                           matrix K, real[] biovar, real[] tlag)
```

Numerical integrator

```
real[ , ] pmx_integrate_ode_rk45(ODE_RHS, real[] y0, real t0,  
  ↪ real[] ts, real[] theta, real[] x_r, int[] x_i, real rtol =  
  ↪ 1.e-6, real atol = 1.e-6, int max_step = 1e6);
```

- ▶ ODE_RHS: ODE right-hand-side f in $y' = f(y, t, \theta, x_r, x_i)$.
- ▶ y0: initial condition at time t0.
- ▶ t0: initial time.
- ▶ ts: times at which we require a solution.
- ▶ theta: parameters to be passed to f .
- ▶ x_r: real data to be passed to f .
- ▶ x_i: integer data to be passed to f .
- ▶ rtol, atol, and max_step are optional control parameters for *relative tolerance*, *absolute tolerance*, and *max number of time steps*, respectively. Their default values have no theoretical justification.

System function

```
functions {  
  real[] system(real time, real[] y,  
                real[] theta, real[] x_r, int[] x_i) {  
    real dydt[3];  
    real CL = theta[1];  
    real Q = theta[2];  
  
    /* .... */  
  
    return dydt;  
  }  
}
```

Torsten function

```
matrix pmx_solve_rk45(ODE_system, int nCmt, real[] time, real[]  
  ↪ amt, real[] rate, real[] ii, int[] evid, int[] cmt, real[]  
  ↪ addl, int[] ss, real[] theta, real[] biovar, real[] tlag,  
  ↪ real rel_tol, real abs_tol, int max_step);
```

Exercise 3: Write, fit, and diagnose the two compartment model using the `pmx_solve_rk45` function.

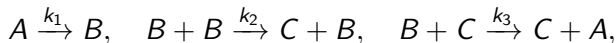
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Nonlinear ODEs without analytical solution

kinetics of an autocatalytic reaction [Robertson, 1966]

The structure of the reactions is



where k_1 , k_2 , k_3 are the rate constants and A , B and C are the chemical species involved. The corresponding ODEs are

$$x_1' = -k_1 x_1 + k_3 x_2 x_3$$

$$x_2' = k_1 x_1 - k_2 x_2^2 - k_3 x_2 x_3$$

$$x_3' = k_2 x_2^2$$

Given $k_1 = 0.04$, $k_2 = 3.0e7$, $k_3 = 1.0e4$, we make inference regarding the initial condition for $x_1(t = 0)$.

Nonlinear ODEs without analytical solution

$$x_1' = -k_1 x_1 + k_3 x_2 x_3$$

$$x_2' = k_1 x_1 - k_2 x_2^2 - k_3 x_2 x_3$$

$$x_3' = k_2 x_2^2$$

Given $k_1 = 0.04$, $k_2 = 3.0\text{e}7$, $k_3 = 1.0\text{e}4$, we make inference regarding the initial condition for $x_1(t = 0)$.

Exercise

Write Stan function for the above ODE's RHS.

Stan function for autocatalytic kinetics

$$x_1' = -k_1x_1 + k_3x_2x_3$$

$$x_2' = k_1x_1 - k_2x_2^2 - k_3x_2x_3$$

$$x_3' = k_2x_2^2$$

```
functions{  
  real[] reaction(real t, real[] x, real[] theta, real[] r,  
    ↪ int[] i){  
    real dxdt[3];  
    real k1 = theta[1];  
    real k2 = theta[2];  
    real k3 = theta[3];  
    dxdt[1] = -k1*x[1] + k3*x[2]*x[3];  
    dxdt[2] = k1*x[1] - k3*x[2]*x[3] - k2*(x[2])^2;  
    dxdt[3] = k2*(x[2])^2;  
    return dxdt;  
  }  
}
```

- What's the initial conditions for x_2 and x_3 ?

Numerical integrators

- ▶ Runge-Kutta 4th/5th (rk45)
 - ▶ non-stiff equations
 - ▶ Most popular, try this if you don't know the nature of the ODE, or what you're doing, or both.
- ▶ Backward differentiation formula (bdf)
 - ▶ stiff equations
 - ▶ More expensive to use
- ▶ Adams-Moulton
 - ▶ non-stiff equations
 - ▶ higher-order of accuracy(do you really need it?)
 - ▶ scales better with number of steps

Numerical integrators

Integrators	Stan	Torsten
rk45	integrate_ode_rk45	pmx_integrate_ode_rk45
BDF	integrate_ode_bdf	pmx_integrate_ode_bdf
Adams	integrate_ode_adams	pmx_integrate_ode_adams

```
real[ , ] pmx_integrate_ode_rk45(ODE_RHS, real[] y0, real t0,  
  ↪ real[] ts, real[] theta, real[] x_r, int[] x_i, real rtol =  
  ↪ 1.e-6, real atol = 1.e-6, int max_step = 1e6);
```

- ▶ ODE_RHS: ODE right-hand-side f in $y' = f(y, t, \theta, x_r, x_i)$.
- ▶ y0: initial condition at time t0.
- ▶ t0: initial time.
- ▶ ts: times at which we require a solution.
- ▶ theta: parameters to be passed to f .
- ▶ x_r: real data to be passed to f .
- ▶ x_i: integer data to be passed to f .

Exercise

- ▶ In each of 8 experiments performed x_3 is observed.
- ▶ Hierarchical model for $x_0[1]$

```
model {  
  y0_mu ~ lognormal(log(2.0), 0.5);  
  for (i in 1:nsub) {  
    y0_1[i] ~ lognormal(y0_mu, 0.5);  
  }  
  sigma ~ cauchy(0, 0.5);  
  obs ~ lognormal(log(x3), sigma);  
}
```

Exercise

Data available for the inference

```
data {  
  int<lower=1> nsub;      /* nb. of subjects */  
  int<lower=1> len[nsub]; /* nb. of results-extraction time  
    ↪ points for each subject */  
  int<lower=1> ntot;      /* total nb. of results-extraction  
    ↪ time points */  
  real ts[ntot];          /* concatenated array for  
    ↪ results-extraction time points */  
  real obs[ntot];         /* concatenated array for observed  
    ↪ x3 */  
}
```

Exercise

Given above data and model, write the rest of Stan code.

- ▶ Hint: use `chem.stan` as template, also see `chem.data.R` and `chem.init.R`.
- ▶ Reaction begins with A (on which is also what we'd like to make inference), the other two species are non-existent at the beginning of the reaction.
- ▶ Which numerical integrator are you using? Why?

Exercise

How to build & run?

Edit/Add cmdstan/make/local

```
TORSTEN_MPI = 1  # flag on torsten's MPI solvers  
CXXFLAGS += -isystem /usr/local/include    # path to MPI  
↪      library's headers
```

Build in cmdstan

```
make path_to_workshop/RScript/model/chemical_reactions/chem
```

Run

```
./chem sample adapt delta=0.95 random seed=1104508041 data  
↪   file=chem.data.R init=chem.init.R
```

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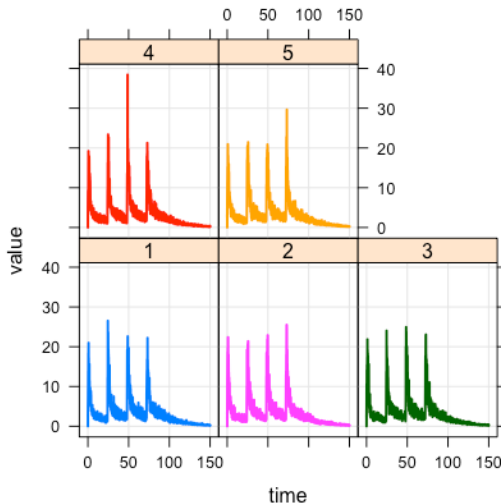
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Data pooled into groups

- ▶ sport measurements are grouped by players
- ▶ people's voting intention can be grouped by states, social status, etc.
- ▶ medical measurements are grouped by patients

Data pooled into groups

- ▶ medical measurements are grouped by patients
 - ▶ Simulated with mrgsolve <https://mrgsolve.github.io/>



Hierarchical model

With a hierarchical model, we can

- ▶ do partial pooling.
- ▶ estimate how similar the groups are to one another.
- ▶ estimate individual parameters.

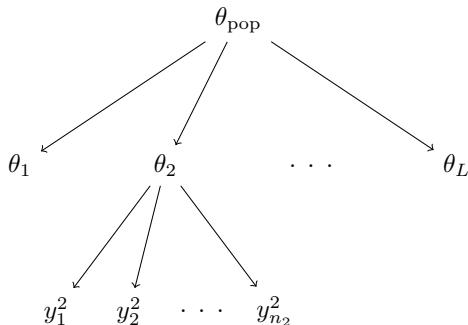
$$\theta = (\theta_1, \dots, \theta_L) \sim p(\theta | \theta_{\text{pop}})$$

$$y = (y_1, \dots, y_N) \sim p(y | \theta, x)$$

Hierarchical model

$$\theta = (\theta_1, \dots, \theta_L) \sim p(\theta | \theta_{\text{pop}})$$

$$y = (y_1, \dots, y_N) \sim p(y | \theta, x)$$



Example 3: Hierarchical two compartment model

Likelihood function:

$$\log \theta \sim \text{Normal}(\log \theta_{\text{pop}}, \Omega)$$

$$\Omega = \begin{pmatrix} \omega_1 & 0 & 0 & 0 & 0 \\ 0 & \omega_2 & 0 & 0 & 0 \\ 0 & 0 & \omega_3 & 0 & 0 \\ 0 & 0 & 0 & \omega_4 & 0 \\ 0 & 0 & 0 & 0 & \omega_5 \end{pmatrix}$$

$$\log(cObs) \sim \text{Normal} \left(\log \left(\frac{y_2}{VC} \right), \sigma^2 \right)$$

Exercise 6: Write, fit, and diagnose a hierarchical two

compartment model for a population of 10 patients. Use
`data/twoCptPop.data.r` and `twoCptPop.r` }

- ▶ *Start by running 3 chains with 30 iterations.*
- ▶ *Do you get any warning messages?*

Divergent transitions

- ▶ *Do you get any warning messages?*

There were 29 divergent transitions after warmup.

- ▶ A divergent transition occurs when we fail to accurately compute a Hamiltonian trajectory.
- ▶ This is because we *approximate* trajectories.
- ▶ Our sampler may not be refined enough to explore the entire typical set.

Divergent transitions

Consider the following hierarchical model:

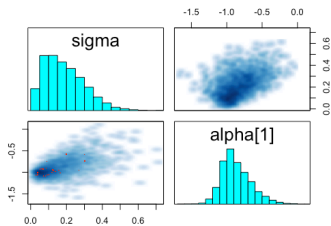
$$\alpha_i \sim \text{Normal}(\mu, \sigma)$$

$$y_i \sim p(y|\alpha_i)$$

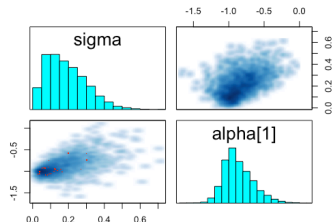
Divergent transitions

$$\alpha_i \sim \text{Normal}(\mu, \sigma)$$

Fitting this model yields the following pairs plot:



Divergent transitions



- ▶ This geometric shape is known as Neil's funnel [Neil, 2003].
- ▶ Its interactions with HMC is described in [Betancourt and Girolmi, 2015].
- ▶ It occurs in hierarchical models when we have sparse data and a centered prior.

Reparameterization

Proposition

Reparameterize the model to avoid the funnel shape. We will do so by standardizing α .

$$\alpha_{\text{std},i} := \frac{\alpha_i - \mu}{\sigma}$$

Then

$$\alpha_{\text{std}} \sim \text{Normal}(0, 1)$$

Reparameterization

Then

$$\alpha_i = \mu + \sigma \alpha_{\text{std},i}$$

Hence

$$y_i \sim p(\mu + \sigma \alpha_{\text{std},i})$$

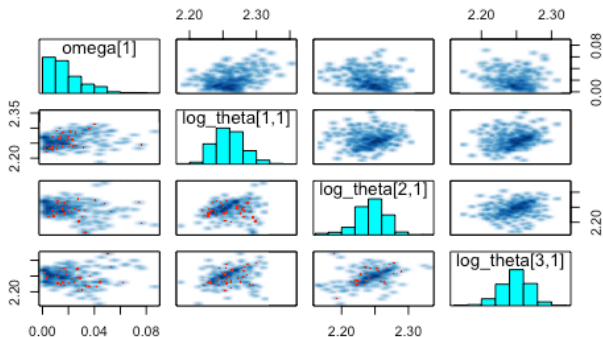
- ▶ Same data generating process; but how does this affect the geometry of the posterior?

Reparameterization

Our model is a little more complicated than the above example:

- ▶ a lot of parameters (100 +)!
- ▶ multiple population parameters and hierarchical structures.
- ▶ these parameters follow a log normal distribution (so we need a pairs plot with $\log \theta$).

Reparameterization



Reparameterization

Exercise 6: Reparametrize the two compartment population model and fit it.}

- ▶ First, work out the appropriate parametrization. You should start with $\log \theta_i \sim \text{Normal}(\theta_{\text{pop},i}, \omega)$
- ▶ Write, fit, and check the inference (run 100 chains).
- ▶ What kind of predictive checks can we do?

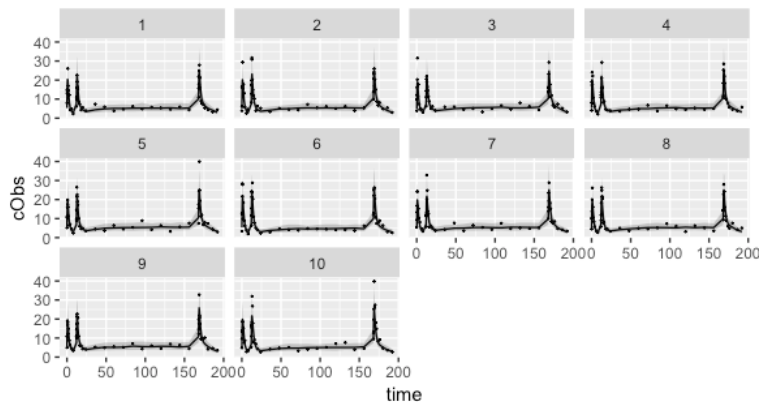
Reparameterization

Need:

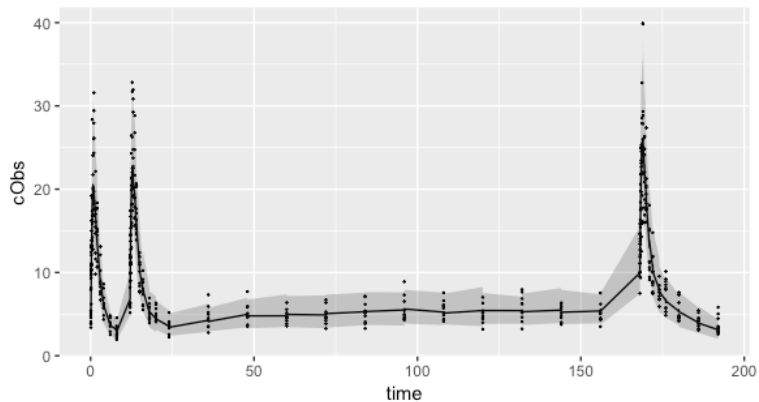
- ▶ predictions at an individual level
- ▶ predictions at a population level

As always, this comes down to properly writing the data generating process in the generated quantities block.

Individual predictions



Population predictions



Further reading

For a very good case study on hierarchical models, see, Bob Carpenter's *Pooling with Hierarchical Models for Repeated Binary Trials*

<https://mc-stan.org/users/documentation/case-studies/pool-binary-trials.html>

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ODE group integrators

Single ODE system

```
pmx_integrate_ode_rk45  
pmx_integrate_ode_bdf  
pmx_integrate_ode_adams
```

ODE group

```
pmx_integrate_ode_group_rk45  
pmx_integrate_ode_group_bdf  
pmx_integrate_ode_group_adams
```

Single ODE system

```
real[,]  
pmx_integrate_ode_xxx(  
    f,  
    real[] y0, real t0,  
    real[] ts,  
    real[] theta,  
    real[] x_r, int[] x_i,  
    ...);
```

ODE group

```
matrix  
pmx_integrate_ode_group_xxx(  
    f,  
    real[ , ] y0, real t0,  
    int[] len, real[] ts,  
    real[ , ] theta,  
    real[ , ] x_r, int[ , ] x_i,  
    ...);
```

ODE group integrators

Single ODE system

```
real[ , ]  
pmx_integrate_ode_xxx(  
    f,  
    real[] y0, real t0,  
    real[] ts,  
    real[] theta,  
    real[] x_r, int[] x_i,  
    ...);
```

ODE group

```
matrix  
pmx_integrate_ode_group_xxx(  
    f,  
    real[ , ] y0, real t0,  
    int[] len, real[] ts,  
    real[ , ] theta,  
    real[ , ] x_r, int[ , ] x_i,  
    ...);
```

- ▶ `len` specifies the length of data for each subject within the above ragged arrays, and the size of `len` is the size of the population.
- ▶ The group integrators return a single matrix ragged column-wise. The number of rows equals to the size of ODE system.

Exercise

autocatalytic reaction model: ODE group version

- ▶ Change the loop with the numerical integrator to use group integrator.
- ▶ Remember the return of the group integrator is a matrix
 - ▶ nb. of rows: nb. of states
 - ▶ nb. of cols: nb. of *total* results-extraction time points.

Exercise

Build and run

- ▶ Edit/Add cmdstan/make/local

```
TORSTEN_MPI = 1  # flag on torsten's MPI solvers  
CXXFLAGS += -isystem /usr/local/include    # path to MPI  
↪      library's headers
```

- ▶ Build in cmdstan

```
make ../example-models/chemical_reactions/chem_group
```

- ▶ Run

```
mpiexec -n 2 -l ./chem_group sample adapt delta=0.95 random  
↪      seed=1104508041 data file=chem.data.R init=chem.init.R
```

Exercise

- ▶ What does output say?
- ▶ How many cores can you use until performance saturates? Why?
- ▶ (optional) Can you do it using Stan's `map_rect`? Is there a difference in style, output, and performance?

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1. Course information
2. Introduction and modeling framework | Charles Margossian
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7. ODE group integrators | Yi Zhang
8. PMX population solvers | Yi Zhang

PMX population solvers

Single ODE system	ODE group
<code>pmx_solve_rk45</code>	<code>pmx_solve_group_rk45</code>
<code>pmx_solve_bdf</code>	<code>pmx_solve_group_bdf</code>
<code>pmx_solve_adams</code>	<code>pmx_solve_group_adams</code>

Individual solvers

matrix

```
pmx_solve_bdf(f, int nCmt,  
  real[] time, real[] amt,  
  real[] rate, real[] ii,  
  int[] evid, int[] cmt,  
  real[] addl, int[] ss,  
  real[] theta, real[]  
    ↪ biovar,  
  real[] tlag, real rel_tol,  
  real abs_tol, int  
    ↪ max_step);
```

Population solvers

matrix

```
pmx_solve_group_bdf(f, int nCmt,  
  int[] len, real[] time,  
  real[] amt, real[] rate,  
  real[] ii, int[] evid,  
  int[] cmt, real[] addl,  
  int[] ss, real[ , ] theta,  
  real[ , ] biovar, real[ , ] tlag,  
  real rel_tol, real abs_tol,  
  int max_step);
```

PMX population solvers

matrix

```
pmx_solve_group_bdf(f, int nCmt, int[] len, real[] time, real[]  
  ↪ amt, real[] rate, real[] ii, int[] evid, int[] cmt, real[]  
  ↪ addl, int[] ss, real[,] theta, real[,] biovar, real[,]  
  ↪ tlag, real rel_tol, real abs_tol, int max_step);
```

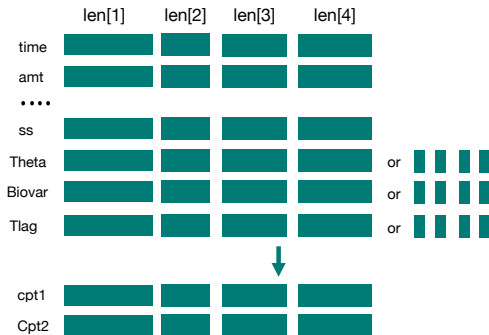


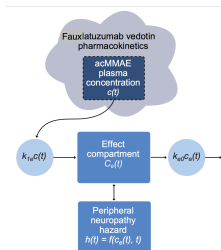
Figure: arguments and output of `pmx_solve_group_xxx`

Exercise

We analyze the time to the first grade 2+ peripheral neuropathy (PN) event in patients treated with an antibody-drug conjugate (ADC) delivering monomethyl auristatin E (MMAE). We will simulate and analyze data using a simplified version of the model reported in [Lu et al., 2017].

- ▶ Fauxlatuzumab vedotin 1.2 mg/kg IV boluses q3w \times 6 does.
- ▶ 19 patients with 6 right-censored (simulated data).

Model scheme



Note

- ▶ To keep things simpler, we use the simulated individual CL and V values, and only model PD part of the problem.
- ▶ PN hazard is substantially delayed relative to PK exposure.
- ▶ Hazard increases over time to an extent not completely described by P

Exercise

Likelihood for time to first $\text{PN} \geq 2$ event in the i^{th} patient:

$$L(\theta | t_{\text{PN},i}, \text{censor}_i, X_i) \\ = \begin{cases} h_i(t_{\text{PN},i} | \theta, X_i) e^{-\int_0^{t_{\text{PN},i}} h_i(u | \theta, X_i) du}, & \text{censor}_i = 0 \\ e^{-\int_0^{t_{\text{PN},i}} h_i(u | \theta, X_i) du}, & \text{censor}_i = 1 \end{cases}$$

where

$t_{\text{PN}} \equiv$ time to first $\text{PN} \geq 2$ or right censoring event

$\theta \equiv$ model parameters

$X \equiv$ independent variables / covariates

$\text{censor} \equiv \begin{cases} 1, & \text{PN} \geq 2 \text{ event is right censored} \\ 0, & \text{PN} \geq 2 \text{ event is observed} \end{cases}$

One can see the expression

$$e^{-\int_0^{t_{\text{PN},i}} h_i(u | \theta, X_i) du}$$

as the survival function at time t .

Exercise

Hazard of PN grade 2+ based on the Weibull distribution, with drug effect proportional to effect site concentration of MMAE:

$$h_j(t) = \beta E_{\text{drug}j}(t)^{\beta} t^{(\beta-1)}$$

$$E_{\text{drug}j}(t) = \alpha c_{ej}(t)$$

$$c'_{ej}(t) = k_{e0} (c_j(t) - c_{ej}(t)).$$

Overall ODE system including integration of the hazard function:

$$x'_1 = -\frac{CL}{V} x_1 \tag{1}$$

$$x'_2 = k_{e0} \left(\frac{x_1}{V} - x_2 \right) \tag{2}$$

$$x'_3 = h(t) \tag{3}$$

where $x_2(t) = c_e(t)$ and $x_3(t) = \int_0^t h(u) du$ aka cumulative hazard.

Exercise

"just walk in a minute ago, literally" mode

Apply `pmx_solve_group_rk45` function

Intermediate mode

Code `pmx_solve_group_rk45` function and its args. Use input data file `ttp2n.data2.R` as hint.

hard mode

Code ODE, `pmx_solve_group_rk45` function and its args, and the likelihood for harzard and censor event. Use input data file `ttp2n.data2.R` and `model` block as hint.

"why bother" mode

Exercise

Edit/Add cmdstan/make/local

```
TORSTEN_MPI = 1           # flag on torsten's MPI solvers  
CXXFLAGS += -isystem /usr/local/include # path to MPI library's  
↳ headers
```

Build in cmdstan

```
make ../example-models/ttpn2/ttpn2_group
```

Run

```
mpiexec -n 4 -l ttpn2_group sample num_warmup=500  
↳ num_samples=500 data file=ttpn2.data2.R init=ttpn2.init.R
```

Exercise

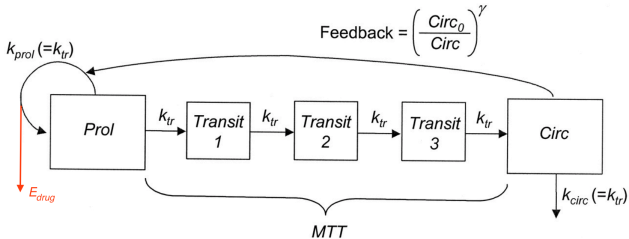
- ▶ The parallel performance is not optimal, why?
- ▶ Can you do it using Stan's `map_rect`?

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Friberg-Karlsson semi-mechanistic model

[Friberg et al., 2002]



ODE system of F-K model

$$y'_{\text{prol}} = k_{\text{tr}} y_{\text{prol}} (1 - E_{\text{drug}}) \left(\frac{Circ_0}{y_{\text{circ}}} \right)^{\gamma} - k_{\text{tr}} y_{\text{prol}}$$

$$y'_{\text{tr1}} = k_{\text{tr}} y_{\text{prol}} - k_{\text{tr}} y_{\text{tr1}}$$

$$y'_{\text{tr2}} = k_{\text{tr}} y_{\text{tr1}} - k_{\text{tr}} y_{\text{tr2}}$$

$$y'_{\text{tr3}} = k_{\text{tr}} y_{\text{tr2}} - k_{\text{tr}} y_{\text{tr3}}$$

$$y'_{\text{circ}} = k_{\text{tr}} y_{\text{tr3}} - k_{\text{tr}} y_{\text{circ}}$$

where $E_{\text{drug}} = \alpha \frac{y_{\text{cent}}}{V_{\text{cent}}}$, $k_{\text{tr}} = 4/MTT$, and $\alpha \approx 3e - 4$.

- ▶ y_{cent} is obtained from a two compartment model.
- ▶ Our PK/PD model therefore has a total of 8 equations.
- ▶ This problem can be solved using `pmx_solve_*`.

Coupled PK-PD system

Alternatively, we may elect to solve the PK ODEs **analytically** and the PD ODEs **numerically**.

- ▶ This can yield some speedup, in particular for problems that require ODE solutions and sensitivities (e.g [Margossian and Gillespie, 2017b]).

```
real[] pmx_solve_twocpt_rk45(reduced_ODE_system, int nOde,  
  ↪ real[] time, real[] amt, real[] rate, real[] ii, int[]  
  ↪ evid, int[] cmt, real[] addl, int[] ss, real[] theta,  
  ↪ real[] biovar, real[] tlag, real rel_tol, real abs_tol,  
  ↪ real max_step)
```


Coupled PK-PD system

```
real[] pmx_solve_twocpt_rk45(reduced_ODE_system, int nOde,  
  ↪ real[] time, real[] amt, real[] rate, real[] ii, int[]  
  ↪ evid, int[] cmt, real[] addl, int[] ss, real[] theta,  
  ↪ real[] biovar, real[] tlag, real rel_tol, real abs_tol,  
  ↪ real max_step)
```

- ▶ we now pass a "reduced system".
- ▶ we specify the number of ODEs to be solved numerically, not the number of compartments.
- ▶ theta now contains the parameters for the two cpt model, followed by the parameters that get passed to the numerical solver:

```
theta = {CL, Q, VC, VP, ka, /* ... */};
```

Reduced system

```
real[] reduced_system(real time, real[] y, real[] yPK, real[]  
  ↪ theta, real[] x_r, int[] x_i) {  
  real[3] dydt;  
  /* .... */  
  return dydt;  
}
```

Exercise 4 (optional): Write, fit, and diagnose a Friberg-Karlsson model with a two compartment with first order absorption PK. Use `FKModel.r` and `data/FKModel.data.r`.

Exercise

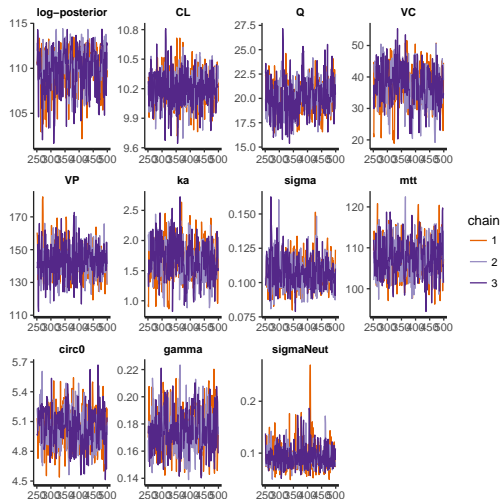
Write, fit, and diagnose a Friberg-Karlsson model with a two compartment with first order absorption PK. Use `FKModel.r` and `data/FKModel.data.r`.

- ▶ You may either use `pmx_solve_*` or `pmx_solve_twocpt_*`.
- ▶ Use $\alpha = 3e - 4$ and estimate all other 8 ODE coefficients, i.e. $\theta = \{CL, Q, VC, VP, ka, MTT, circ0, \gamma\}$.
- ▶ The initial state for the neutrophil count is $Circ_0$. Either edit the event schedule to reflect this at time 0, or write the solution to your ODEs as a deviation from the baseline.

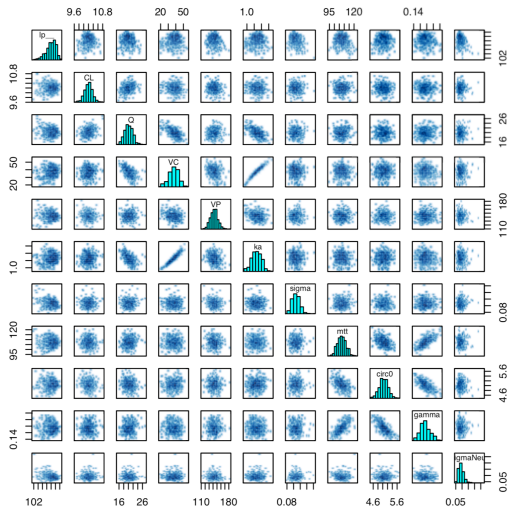
Exercise

- ▶ This exercise entails a few subtleties; in the interest of time we won't go through it in class.
- ▶ Here are however results I get from 3 chains with 500 iterations you can use as a benchmark.

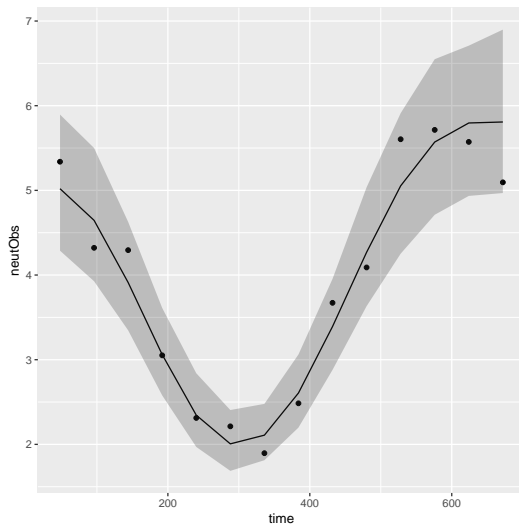
Exercise



Exercise



Exercise



Reference I



Betancourt, M. and Girolmi, M. (2015).

Hamiltonian monte carlo for hierarchical models.

Current trends in Bayesian methodology with applications, 79.



Friberg, L. E., Henningsson, A., Maas, H., Nguyen, L., and Karlsson, M. O. (2002).

Model of chemotherapy-induced myelosuppression with parameter consistency across drugs.

J Clin Oncol, 20(24):4713–21.



Lu, D., Gillespie, W. R., Girish, S., Agarwal, P., Li, C., Hirata, J., Chu, Y.-W., Kagedal, M., Leon, L., Maiya, V., and Jin, J. Y. (2017).

Time-to-Event Analysis of Polatuzumab Vedotin-Induced Peripheral Neuropathy to Assist in the Comparison of Clinical Dosing Regimens.

CPT: pharmacometrics & systems pharmacology, 6(6):401–408.



Margossian, C. C. and Gillespie, W. R. (2017a).

Differential equations based models in stan.

In *Stan Conference*, <http://mc-stan.org/events/stancon2017-notebooks/stancon2017-margossian-gillespie-ode.html>.

Reference II



Margossian, C. C. and Gillespie, W. R. (2017b).

Gaining efficiency by combining analytical and numerical methods to solve odes: Implementation in stan and application to bayesian pk/pd.

In Journal of Pharmacokinetics and Pharmacodynamics, volume 44.



Neil, R. M. (2003).

Slice sampling.

Annals of Statistics, 31.



Peterson, M. and Riggs, M. (2012).

Predicting nonlinear changes in bone mineral density over time using a multi scale systems pharmacology model.

CCPT Pharmacometrics, Systems pharmacology.



Robertson, H. H. (1966).

Numerical analysis, an introduction, chapitre The solution of a set of reaction rate equations.

Academic Press.

Reference III



Weber, S., Gelman, A., Lee, D., Betancourt, M., Vehtari, A., and Racine-Poon, A. (2018).

Bayesian aggregation of average data: an application in drug development.

The Annals of applied statistics, 12.