Population and ODE-based models using Stan and Torsten

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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

Outline

Instructors

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

Outline

Day 1

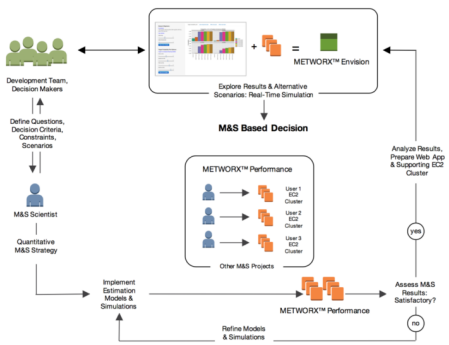
- Introduction and modeling framework
- Pharmacometrics models
- Ordinary differential equation(ODE) based models
- Numerical ODE integrators

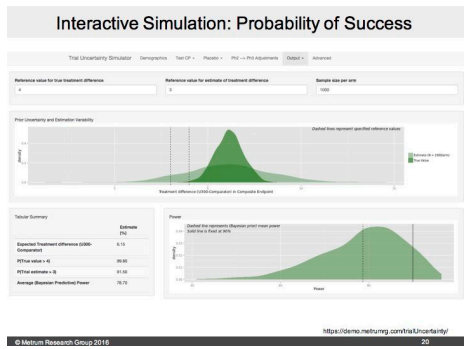
Day 2

- 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
- pAdditional documentation

We will be using:

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

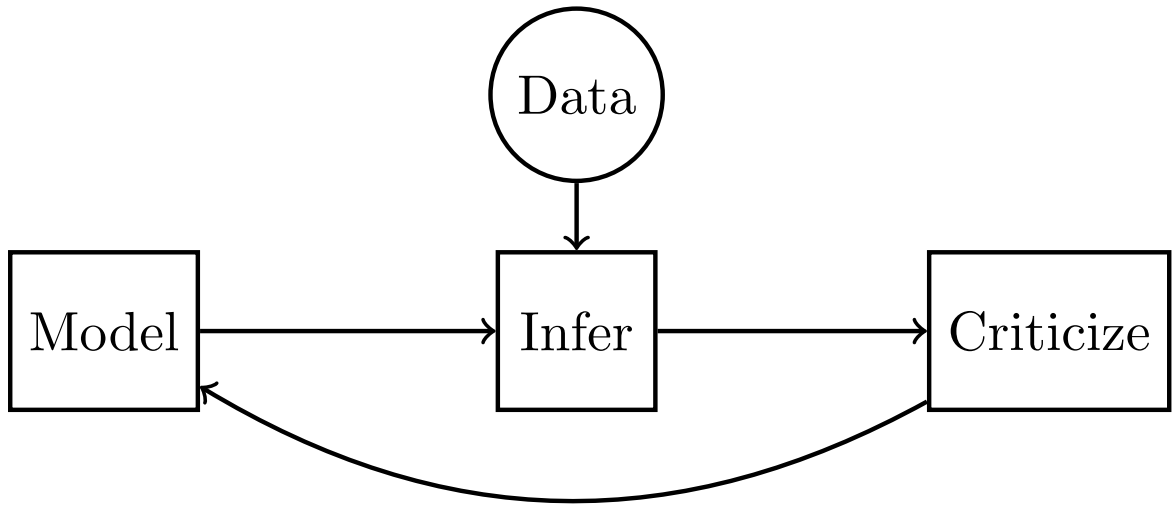
Outline

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

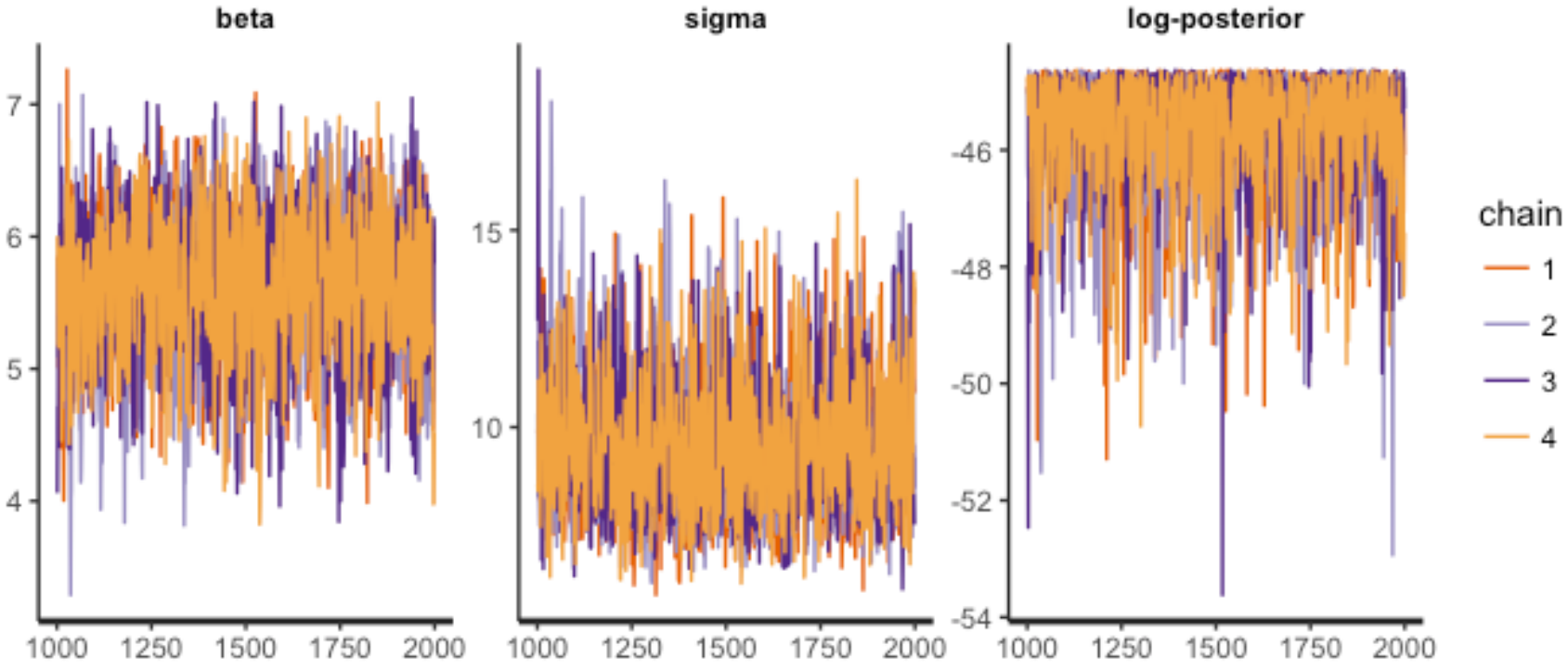
Likelihood:

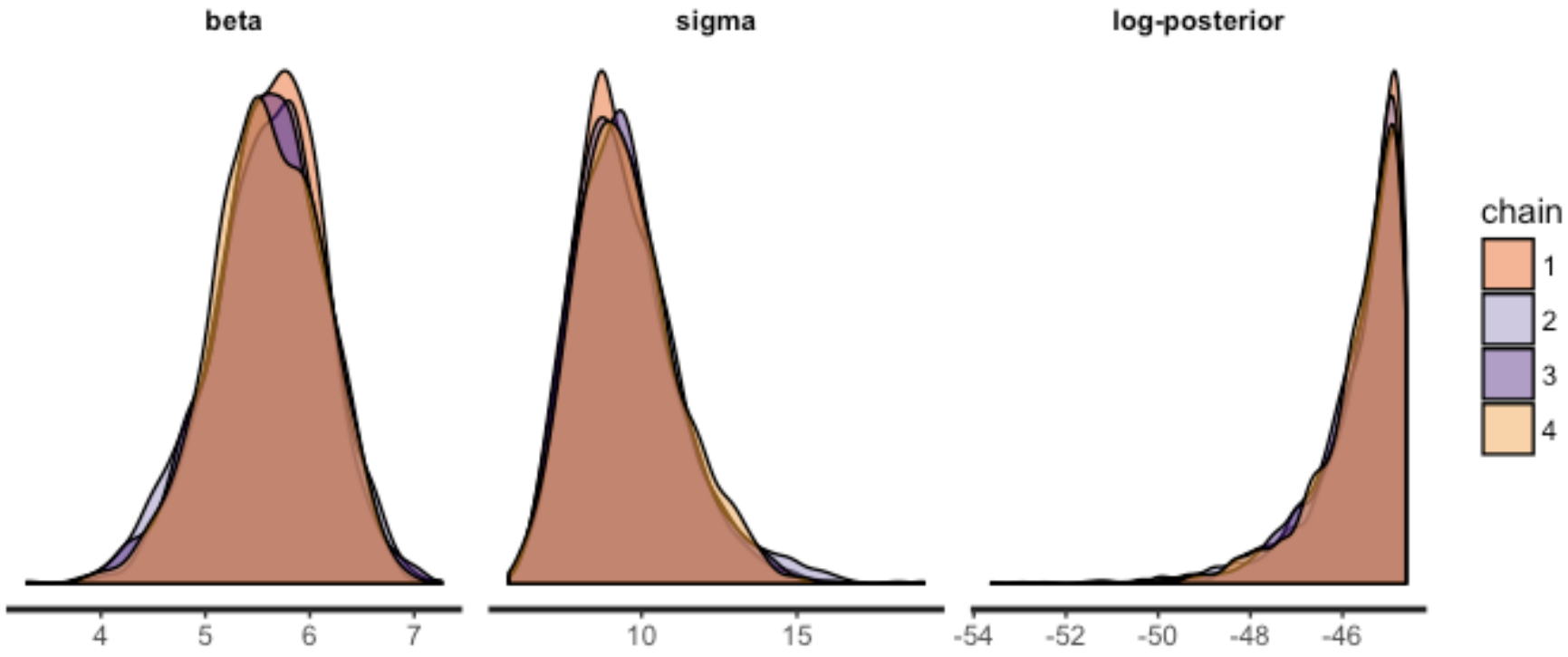
$$Y \sim \text{Normal}(x\beta, \sigma^2)$$

Prior:

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

```
$summary
              mean     se_mean         sd        2.5%         25%         50%         75%
beta     5.601258 0.01359227 0.5305772   4.479154   5.264460   5.614632   5.966383
sigma    9.502691 0.04383169 1.6813433   6.859379   8.320122   9.282212  10.454978
lp__   -45.636140 0.02492619 1.0048605 -48.314041 -46.014181 -45.318003 -44.916883
             97.5%    n_eff      Rhat
beta     6.570396 1523.749 0.9998578
sigma   13.457200 1471.419 1.0013391
lp__   -44.651010 1625.173 1.0002468
```


beta
sigma
log-posterior
7
6
5
4
15
10
-46
-48
-50
-52
-54
1000
1250
1500
1750
2000
chain
1
2
3
4


beta
sigma
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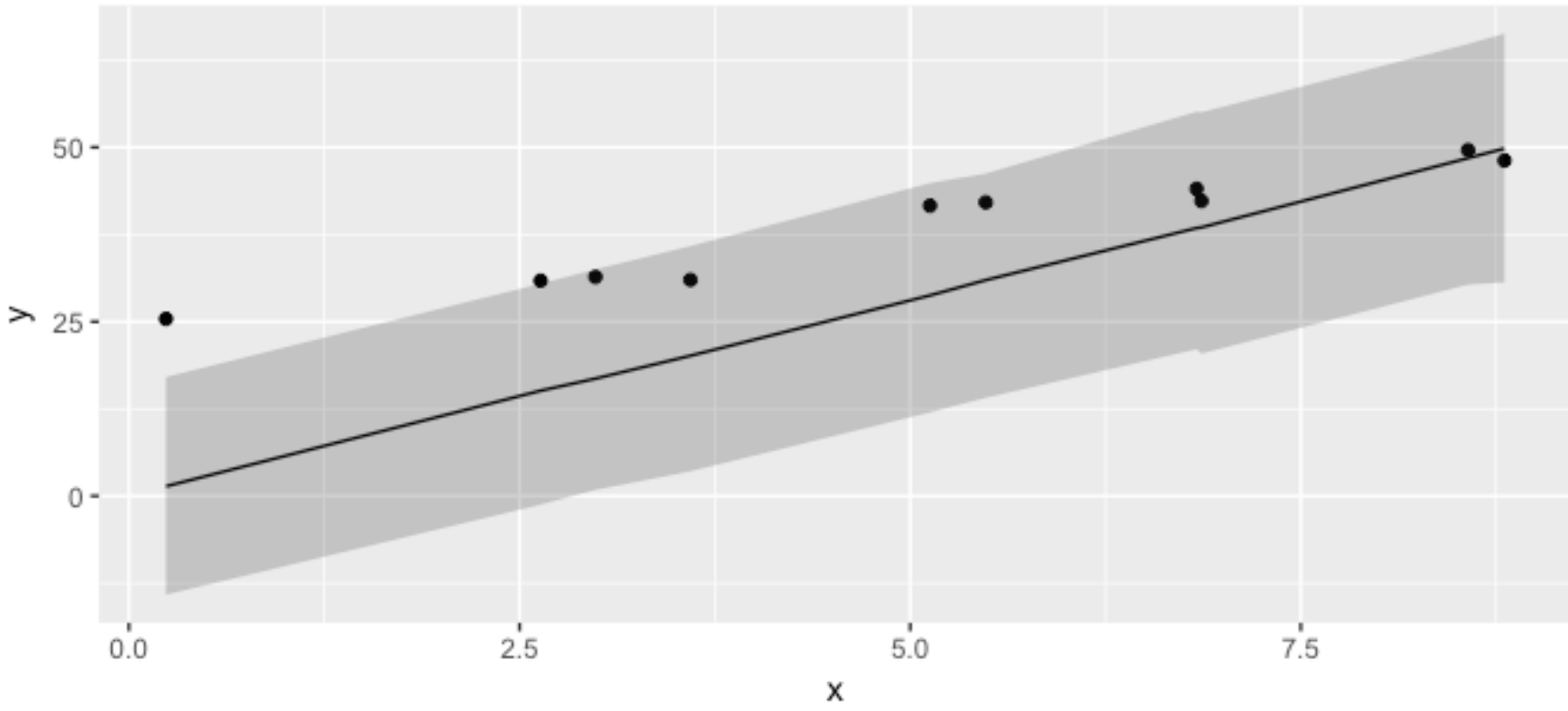

50
25
0
y
0.0
2.5
5.0
7.5
x

So, how can we improve the model?

Likelihood:

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

Prior:

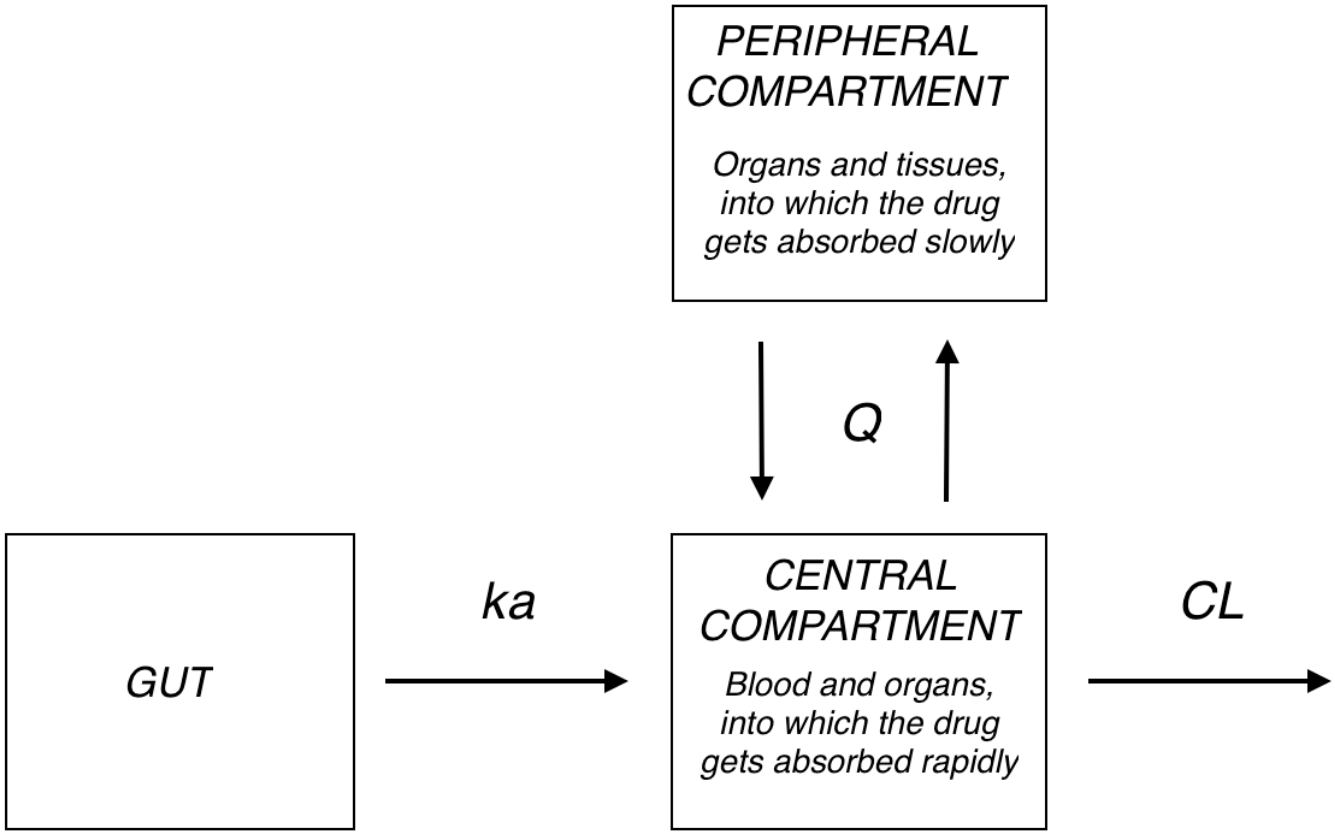
$$\beta \sim \text{Normal}(2, 1)$$
$$\sigma^2 \sim \text{Normal}(1, 1)$$

Outline

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?

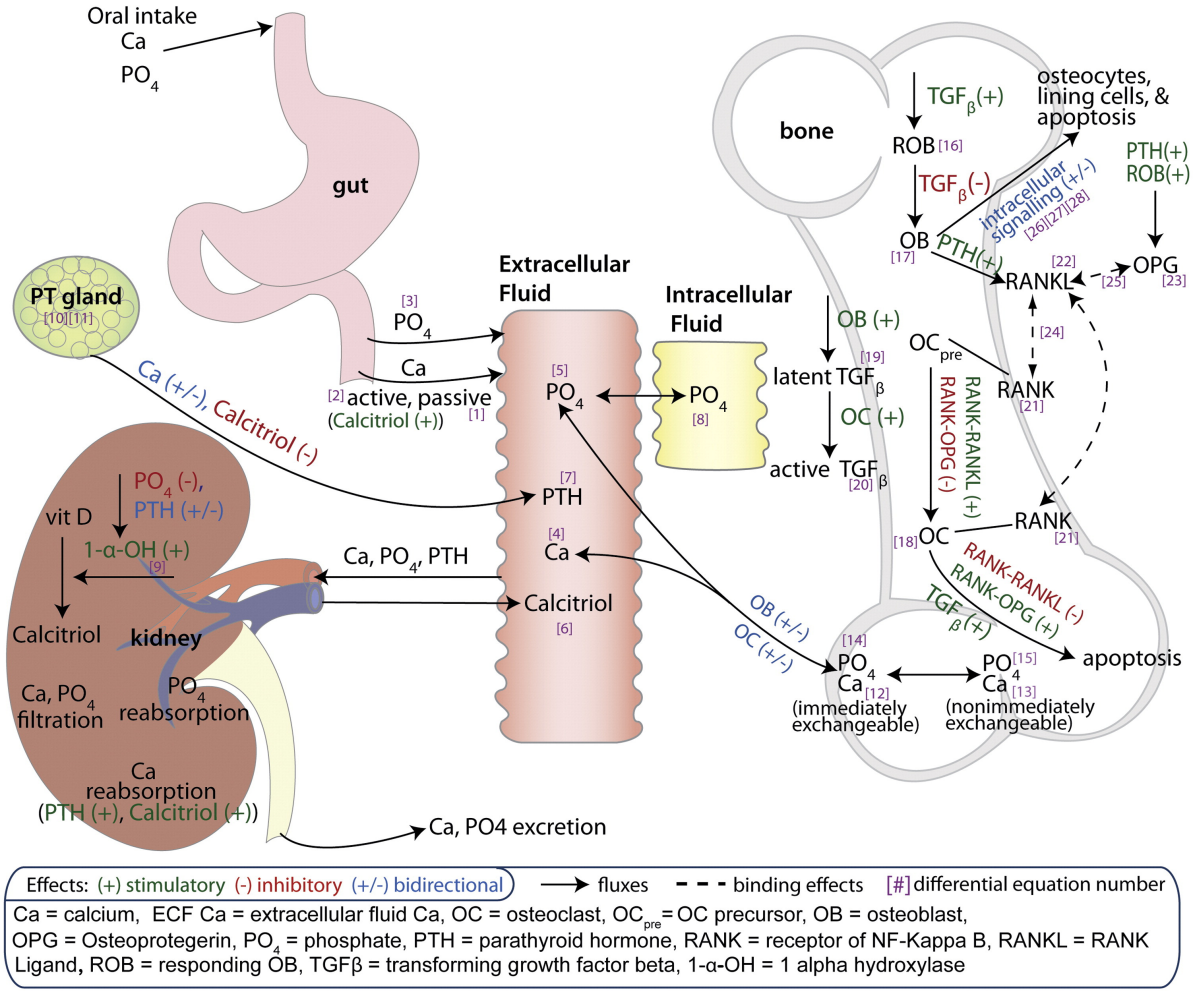
Example: Two compartment model



Two compartment model

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

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

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

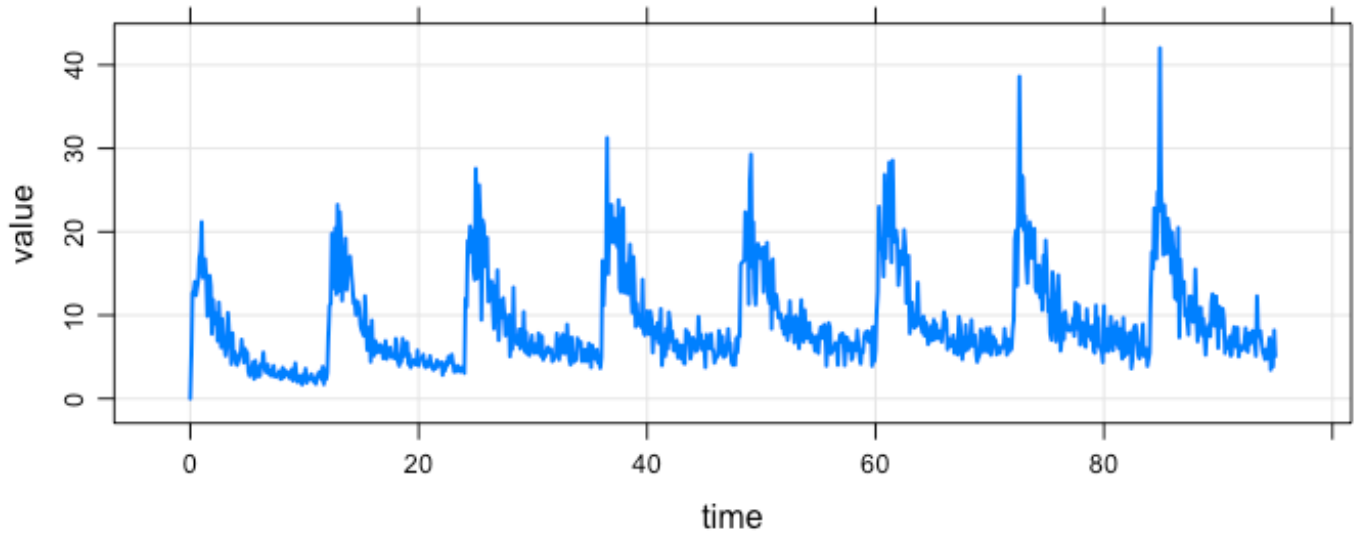
Given an initial condition $y_0 = y(t_0)$, solving the above ODE gives us the $\{$*natural evolution*$\}$ of the system at any given time point.

The event schedule

An event can be:

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

Drug concentration in a patient's blood

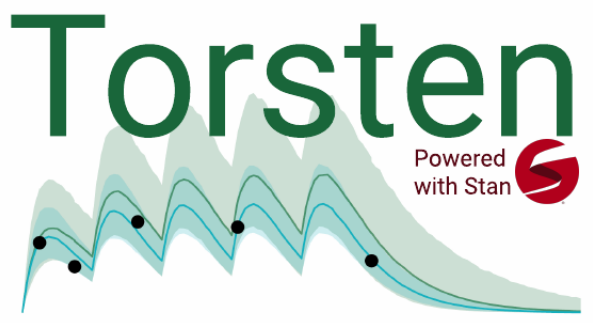


The event schedule

- 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-availibility 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

(a) write and fit this model, using `twoCptModel.r` and `model/twoCptModel.stan`.

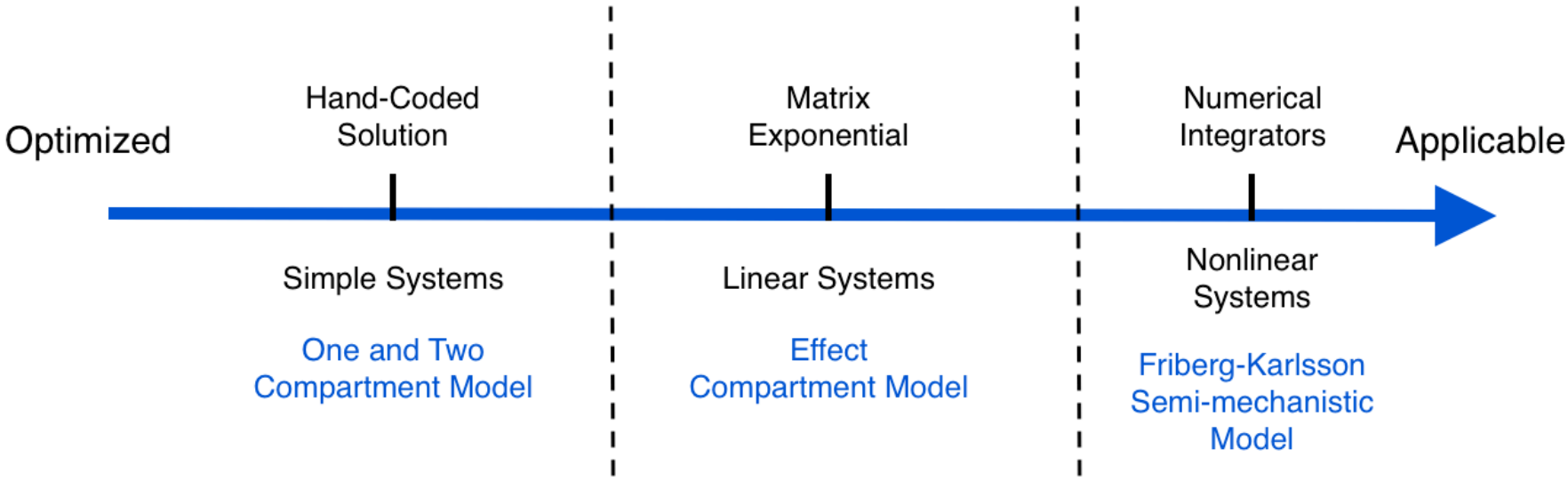
(b) write a generated quantities block and do posterior predictive checks.

Resources

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

Outline

Arsenal of tools



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

- 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

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

Matrix Exponential

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

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

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 2: Write, fit, and diagnose the two compartment model using (a) the `pmx_solve_rk45` function and (b) the `pmx_solve_linode` function.
Do the results agree? How does performance vary?

Outline

Nonlinear ODEs without analytical solution

kinetics of an autocatalytic reaction [Robertson, 1966]

The structure of the reactions is

$$A \xrightarrow{k_1} B, \quad B + B \xrightarrow{k_2} C + B, \quad B + C \xrightarrow{k_3} C + A,$$

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

$$\begin{aligned} x_1' &= -k_1 x_1 + k_3 x_2 x_3 \\ x_2' &= k_1 x_1 - k_2 x_2^2 - k_3 x_2 x_3 \\ x_3' &= k_2 x_2^2 \end{aligned}$$

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

$$
\begin{aligned}
x_1' &= -k_1 x_1 + k_3 x_2 x_3 \\
x_2' &= k_1 x_1 - k_2 x_2^2 - k_3 x_2 x_3 \\
x_3' &= k_2 x_2^2
\end{aligned}
$$

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

Exercise 3

Write Stan function for the above ODE's RHS.

Stan function for autocatalytic kinetics

$$
\begin{aligned}
x_1' &= -k_1 x_1 + k_3 x_2 x_3 \\
x_2' &= k_1 x_1 - k_2 x_2^2 - k_3 x_2 x_3 \\
x_3' &= k_2 x_2^2
\end{aligned}
$$

```
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.

Model

- In each of 8 experiments performed $x3$ is observed.
- Hierarchical model for $x0[1]$

```
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);
}
```

Data

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 4

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 spiecies are non-existent at the beginning of the reaction.
- Which numerical integrator are you using? Why?

Exercise 4

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
```

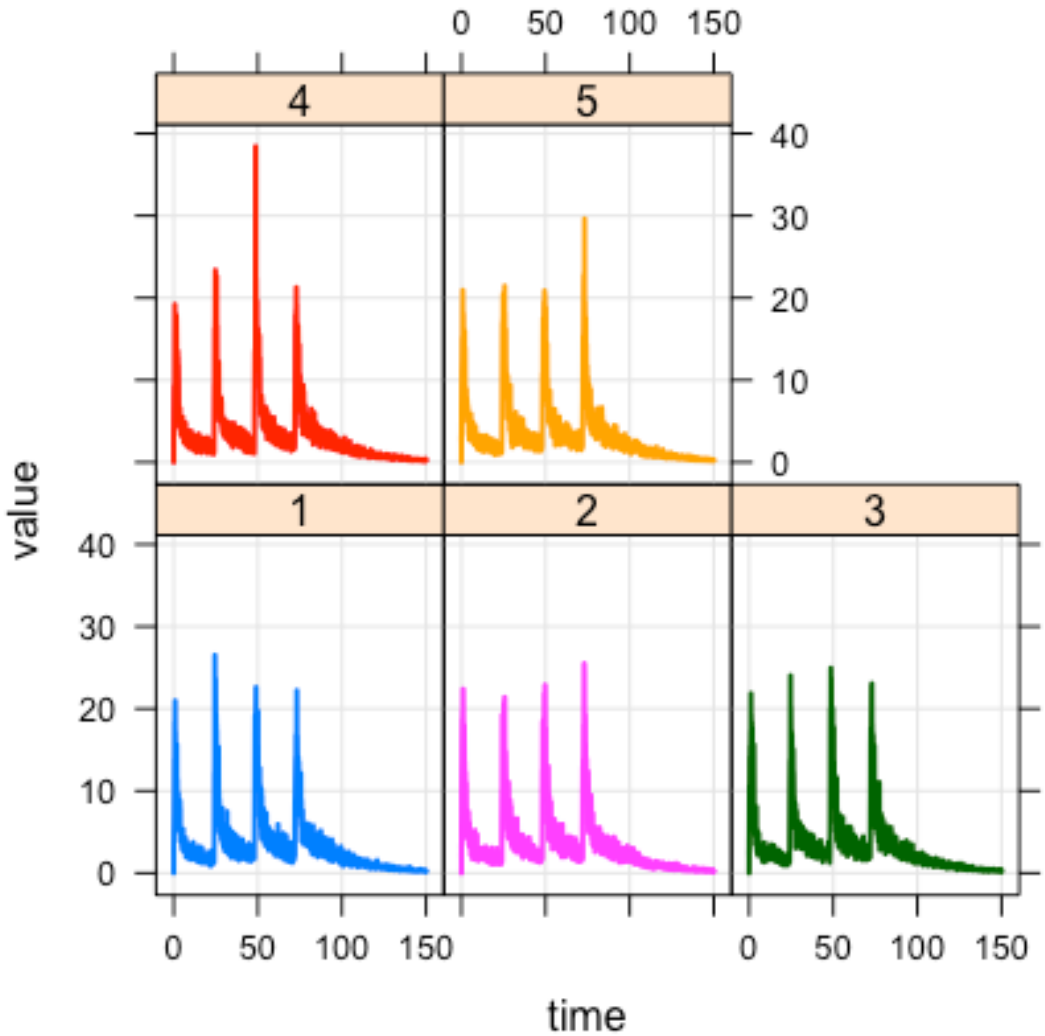
Outline

Data pooled into groups

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

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.

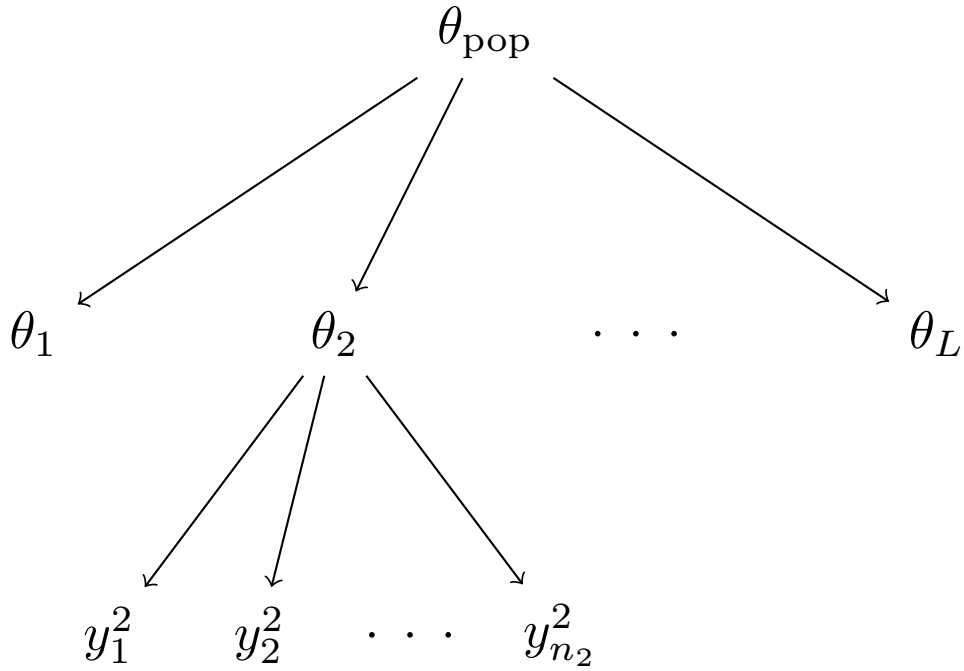
$$\theta = (\theta_1, ..., \theta_L) \sim p(\theta|\theta_{\text{pop}})$$

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

Hierarchical model

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

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



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 5: 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

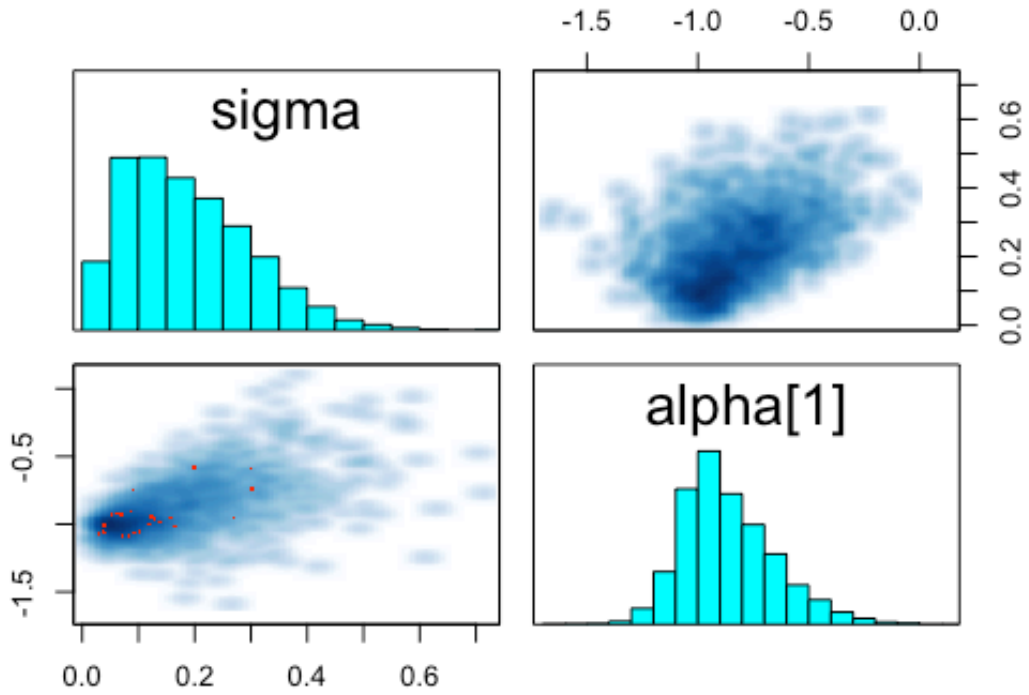
Consider the following hierarchical model:

$$\alpha_i \sim \text{Normal}(\mu, \sigma)$$
$$y_i \sim p(y|\alpha_i)$$

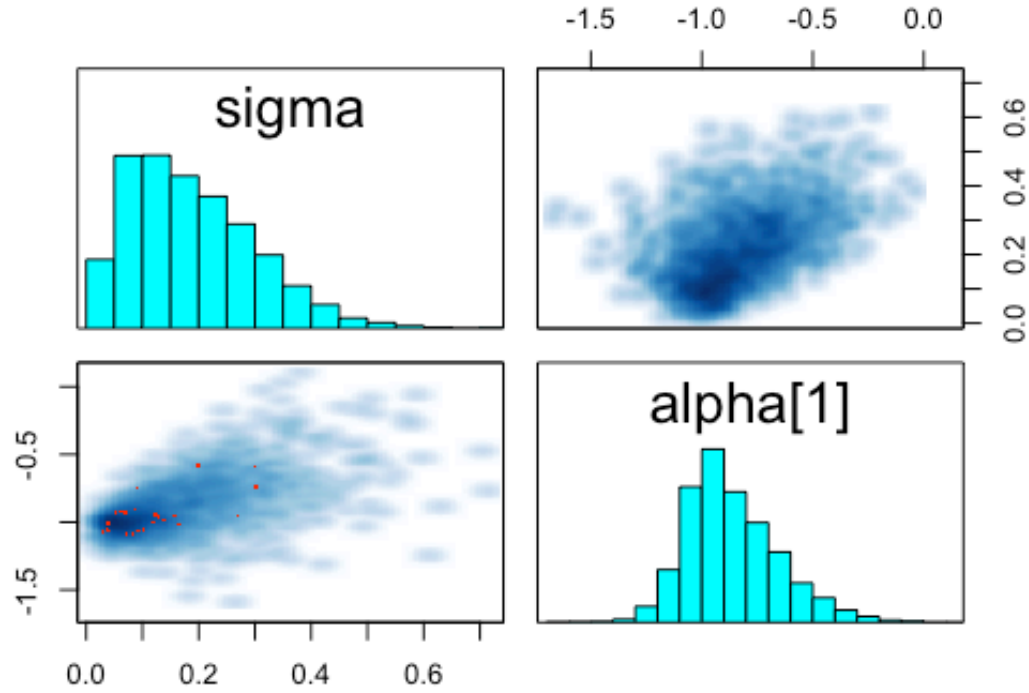
Divergent transitons

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

Fitting this model yields the following pairs plot:



Divergent transitons



- 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

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

Hence

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

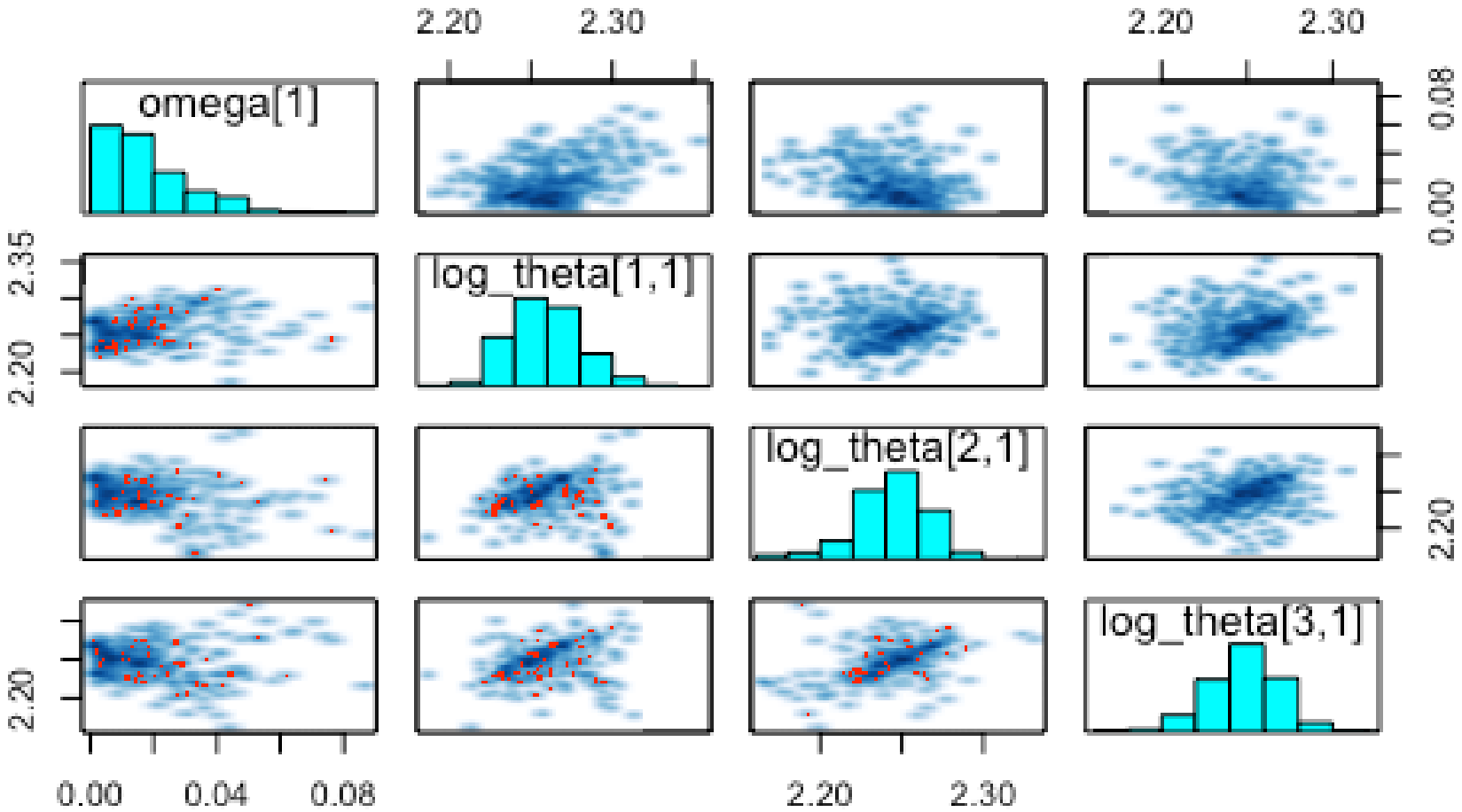
- Same data generating process; but how does this affect the geometry of the posterior?

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.

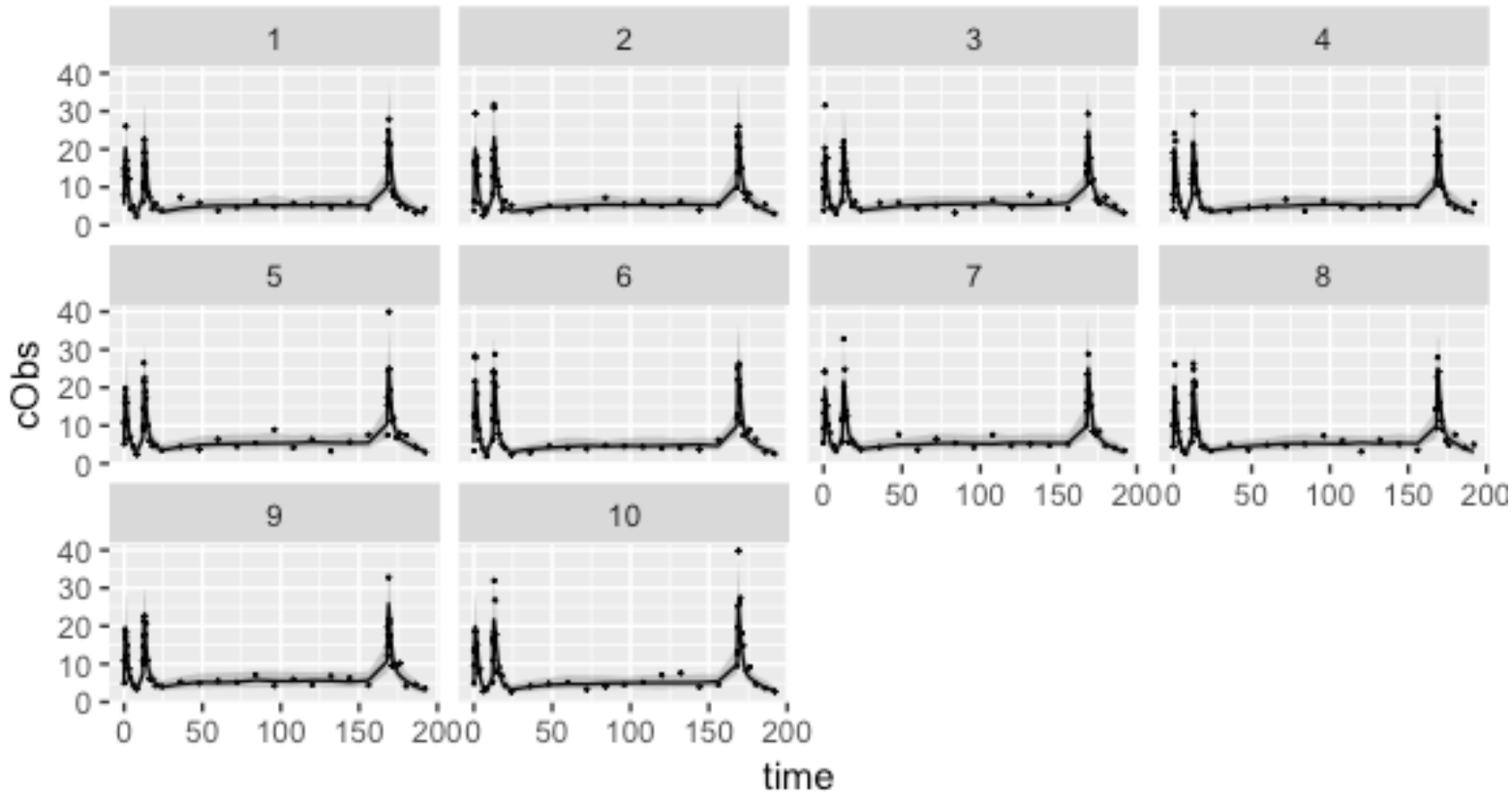
- First, work out the appropriate parametrization. You should start with $\log \theta_i \sim \mathrm{Normal}(\theta_{\mathrm{pop},i}, \omega)$
- Write, fit, and check the inference (run 100 chains).
- What kind of predictive checks can we do?

Reparameterization

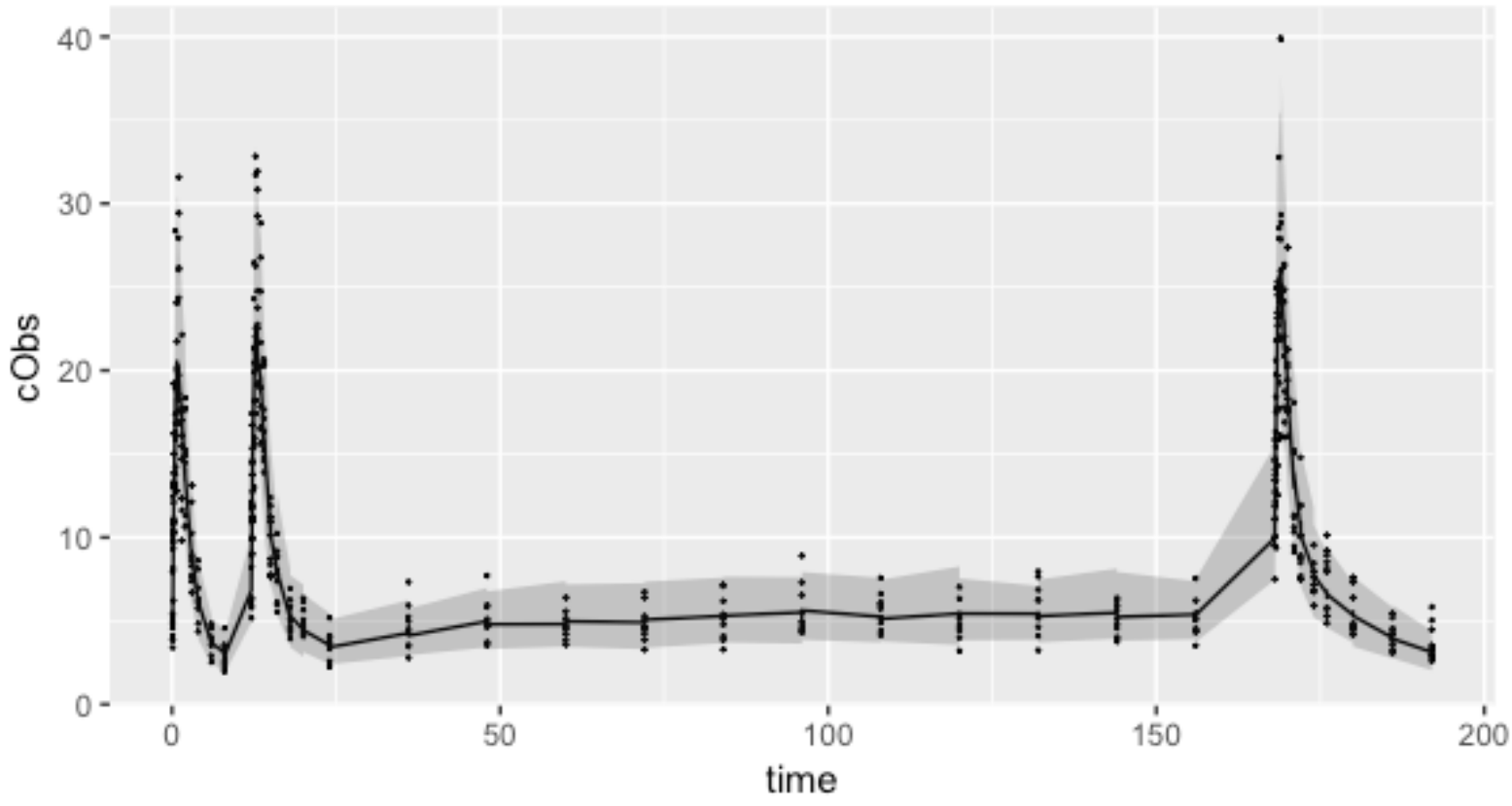
Need:

- 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`

Outline

ODE group integrators

Single ODE system	ODE group
`pmx_integrate_ode_rk45`	`pmx_integrate_ode_group_rk45`
`pmx_integrate_ode_bdf`	`pmx_integrate_ode_group_bdf`
`pmx_integrate_ode_adams`	`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 7

autocatalytic reaction model: ODE group version

- Change the loop with the numerical integrator to use group integrator.
- Remeber 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 7

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 7

- 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?

Outline

PMX population solvers

Single ODE system	ODE group
`pmx_solve_rk45`	`pmx_solve_group_rk45`
`pmx_solve_bdf`	`pmx_solve_group_bdf`
`pmx_solve_adams`	`pmx_solve_group_adams`

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);
```

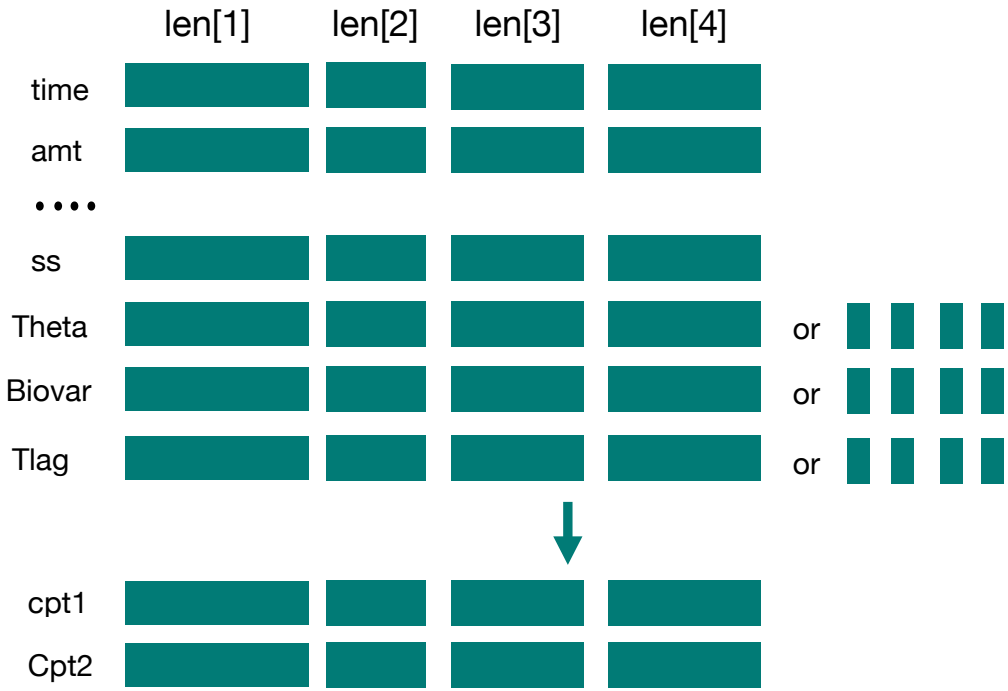


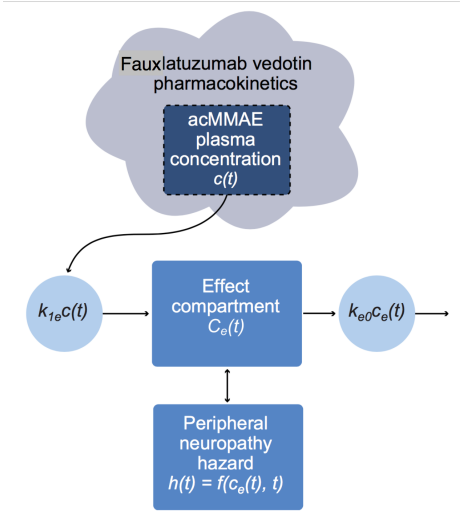
Figure: arguments and output of `pmx_solve_group_xxx`

Time-to-event model

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

Likelihood

Likelihood for time to first PN ≥ 2 event in the i^{th} patient:

$$L\left(\theta | t_{\text{PN},i}, \text{censor}_i, X_i\right)$$

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

where

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

$$\theta \equiv \text{model parameters}$$

$$X \equiv \text{independent variables / covariates}$$

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

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.

ODEs

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

$$\begin{aligned} h_j(t) &= \beta E_{\text{drug}j}(t)^{\beta} t^{(\beta-1)} \\ E_{\text{drug}j}(t) &= \alpha c_{ej}(t) \\ c'_{ej}(t) &= k_{e0}\left(c_j(t) - c_{ej}(t)\right). \end{aligned}$$

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 8: write the ODE system

```
functions{
    real[] oneCptPNODE(real t, real[] x, real[] parms, real[]
    ↪  x_r, int[] x_i){
    real dxdt[3];
    real CL = parms[1];
    real V = parms[2];
    real ke0 = parms[3];
    real alpha = parms[4];
    real beta = parms[5];
    real Edrug;
    real hazard;
    /* ... */
    return dxdt;
  }
}
```

Exercise 8: the ODE system

```
real[] oneCptPNODE(real t, real[] x, real[] parms, real[] x_r,
↪  int[] x_i){
  real dxdt[3];
  real CL = parms[1];
  real V = parms[2];
  real ke0 = parms[3];
  real alpha = parms[4];
  real beta = parms[5];
  real Edrug;
  real hazard;

  dxdt[1] = -(CL / V) * x[1];
  dxdt[2] = ke0 * (x[1] / V - x[2]);
  Edrug = alpha * x[2];
  if(t == 0){
    hazard = 0;
  }else{
    hazard = beta * Edrug^beta * t^(beta - 1);
  }
  dxdt[3] = hazard;
  return dxdt;
}
```

Parameters

parameters

```
parameters{
  real<lower = 0> ke0;
  real<lower = 0> alpha;
  real<lower = 0> beta;
}
transformed parameters{
  vector<lower = 0>[nPNObs] survObs;
  row_vector<lower = 0>[nPNObs] EdrugObs;
  vector<lower = 0>[nPNObs] hazardObs;
  vector<lower = 0>[nPNCens] survCens;
  matrix<lower = 0>[3, nt] x;
  real<lower = 0> parms[nId, 5];

  for(j in 1:nId) {
    parms[j, ] = {CL[j], V[j], ke0, alpha, beta};
  }
  /* ... */
}
```

Parameters

```
transformed parameters{
  vector<lower = 0>[nPNObs] survObs;
  row_vector<lower = 0>[nPNObs] EdrugObs;
  vector<lower = 0>[nPNObs] hazardObs;
  vector<lower = 0>[nPNCens] survCens;
  matrix<lower = 0>[3, nt] x;
  real<lower = 0> parms[nId, 5];

  for(j in 1:nId) {
    parms[j, ] = {CL[j], V[j], ke0, alpha, beta};
  }
  /* ... */
}
```

Exercise 9

- Use `pmx_solve_group_rk45` to solve for `x`.
- Write likelihood expressions for `survObs`, `EdrugObs`, `hazardObs`, and `survCens`.

Exercise 9

- Stan's `target` variable and user-defined likelihood.

```
model{
  ke0 ~ normal(0, 0.0005);
  alpha ~ normal(0, 0.000003);
  beta ~ normal(0, 1.5);

  target += log(hazardObs .* survObs); // observed PN event log
  ↪  likelihood
  target += log(survCens); // censored PN event log likelihood
}
```

Exercise 9

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 9

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

Concluding Remarks

Where does Stan fit in the pharmacometrician's toolkit?

Bayesian modeling can be implemented using an array of softwares:

- probabilistic programing languages: TensorFlow probability, PyMC3, Edward
- pharmacometrics softwares: NONMEM, Monolix, etc.

Where does Stan fit in the pharmacometrician's toolkit?

There is synergy between the research we do, and the development of other softwares:

- PyMC3, Edward, and NONMEM implement Stan's No-U Turn Sampler.
- Torsten borrows many of NONMEM's conventions

What do Stan and Torsten bring to the table?

Currently:

- a very flexible and expressive language
- algorithms that are efficient and fast for a full Bayesian inference, and that warn you when they fail.
- Diagnostic tools
- It's free and open-source

Our goals:

- More expressive features: PDEs and SDEs
- Algorithms for fast approximate Bayesian inference (variational inference, nested Laplace).
- High performance tools: GPU, within solver parallelization.

What we covered

- Writing and fitting compartment models with Torsten
- Defining ODEs and picking a numerical solver
- Building and parameterizing a population model
- Within-chain parallelization for population models

What we didn't cover

- Computing steady states with an algebraic solver.
- Combining multiple solvers, e.g. analytical and numerical methods
- More elaborate problems that combine all the moving parts we went through

Where can I learn more?

- The Stan book and the Torsten manual
- Bill Gillespie's workshop: *Advanced use of Stan, Rstan, and Torsten for pharmacometric applications*
- Contributions to the Stan Conference: `https://github.com/stan-dev/stancontalks`
- Online tutorials: `https://mc-stan.org/users/documentation/tutorials.html`
- Betancourt's case studies: `https://betanalpha.github.io/writing/`

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- Andrew Gelman
- Michael Betancourt
- Bob Carpenter

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Reference I

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

Hamiltonian monte carlo for hierarchical models.

Current trends in Bayesian methodology with applications, 79.

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. (2017).

Differential equations based models in stan.

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

Neil, R. M. (2003).

Slice sampling.

Annals of Statistics, 31.

Reference II

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.

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.