Population and ODE-based models using Stan and Torsten

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Outline

Course information

Introduction and modeling framework
Charles Margossian

Numerical ODE integrators
Yi Zhang

ODE group integrators
Yi Zhang

PMX population solvers
Yi Zhang

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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

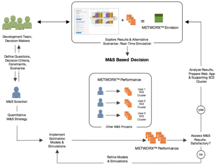
Day 2

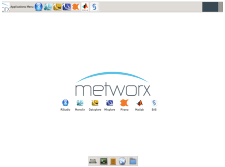
- Population models
- Group/Population ODE integrators and MPI parallelisation
- Group/Population solvers and MPI parallelisation

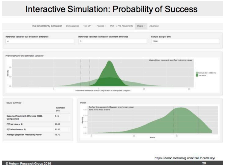
Logistics

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

metworx






Interactive Simulation: Probability of Success

Trial Uncertainty Simulator
Demographics
Test CP ▾
Placebo ▾
Ph2 --> Ph3 Adjustments
Output ▾
Advanced

Reference value for true treatment difference: 4

Reference value for estimate of treatment difference: 3

Sample size per arm: 1000

Prior Uncertainty and Estimation Variability

Dashed lines represent specified reference values
density
Treatment difference (U300-Comparator) in Composite Endpoint
Estimate (N = 1000/arm)
True Value

Tabular Summary

	Estimate (%)
Expected Treatment difference (U300-Comparator)	6.15
P(True value > 4)	99.80
P(Trial estimate > 3)	91.30
Average (Bayesian Predictive) Power	78.70

Power

Dashed line represents (Bayesian prior) mean power
Solid line is fixed at 90%
density
Power

https://demo.metrumrg.com/trialUncertainty/

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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

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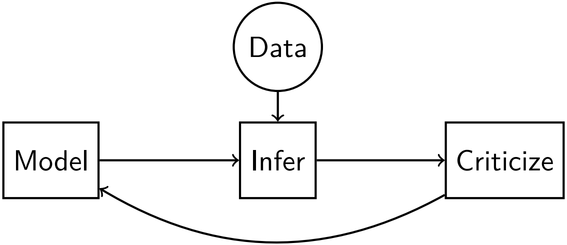
Preliminary question

- Why Bayesian in a field such as pharmacometrics?
- Example - *Bayesian aggregation of average data: an application in drug development* [**?**]

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:

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

Prior:

$$\begin{aligned} \beta \sim& \mathrm{Normal}(2, 1) \\ \sigma^2 \sim& \mathrm{Normal}(1, 1) \end{aligned}$$

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Nonlinear ODEs without analytical solution

kinetics of an autocatalytic reaction [?]

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 $x_1(t = 0)$.

Exercise

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[] p, real[] r, int[]
i){
    real dxdt[3];
    real k1 = p[1];
    real k2 = p[2];
    real k3 = p[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 $x3$ is observed.
- Hierarchical model for $x0[1]$

```
model {
  x0_mu ~ lognormal(log(2.0), 0.5);     /* hyperparam */
  for (i in 1:nsub) {
    x0_1[i] ~ lognormal(x0_mu, 0.5);    /* loop each subject,
     ↪   sample initial condition */
  }
  sigma ~ cauchy(0, 1);                 /* observation
   ↪   uncertainty */
  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 */
}
```

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

- Hint: see `chem.data.R` and `chem.init.R` .
- 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 ../example-models/examples/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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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

autocatalytic reaction model: ODE group version

- Change the loop with the numerical integrator to use group integrator.
- 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?
- Can you do it using Stan's `map_rect`? Is there a difference in style, output, and performance?

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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);
```

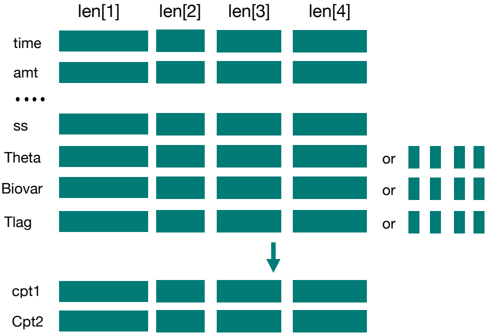


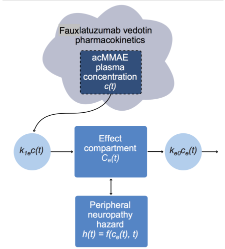
Figure: arguments and output of `pmx_solve_group_xxx`

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 [**?**].

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

Model scheme


Fauxlatuzumab vedotin pharmacokinetics
acMMAE plasma concentration $c(t)$
$k_{1e}c(t)$
Effect compartment $C_e(t)$
$k_{e0}c_e(t)$
Peripheral neuropathy hazard $h(t) = f(c_e(t), t)$

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 PK.

Exercise

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

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

where

$$
\begin{aligned}
t_{\mathrm{PN}} &\equiv \text{time to first PN} \geq 2 \text{ or right censoring event} \\
\theta &\equiv \text{model parameters} \\
X &\equiv \text{independent variables / covariates} \\
\text{censor} &\equiv \begin{cases} 1, & \text{PN} \geq 2 \text{ event is right censored} \\ 0, & \text{PN} \geq 2 \text{ event is observed} \end{cases}
\end{aligned}
$$

One can see the expression

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

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:

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

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

"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`?

Reference

Reference