

Population solvers in Torsten

Yi Zhang, William R. Gillespie

July 31, 2019

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);
```

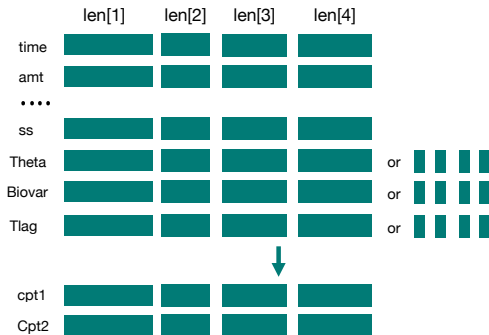


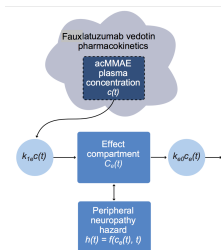
Figure: arguments and output of `pmx_solve_group_xxx`

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 [1].

- ▶ Fauxlatuzumab vedotin 1.2 mg/kg IV boluses q3w \times 6 doses.
- ▶ 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 PK.

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`?

Reference



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