Population solvers in Torsten

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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);
```
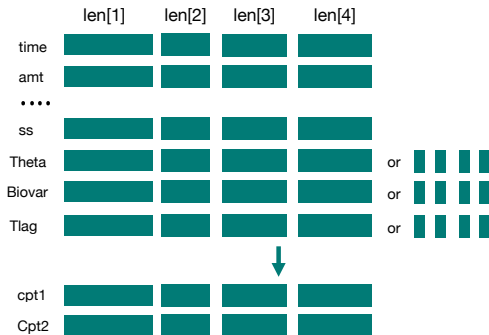

Figure: arguments and output of `pmx_solve_group_xxx`

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 [1].

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

Model scheme
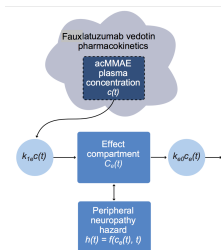
Note

- 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 PK.

Exercise

Likelihood for time to first PN ≥ 2 event in the ith 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.

Exercise

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

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

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 args for `pmx_solve_group_rk45` function and apply it. Use input data file `ttp2n.data2.R` as hint.

hard mode

- ▶ Code ODE
- ▶ Code args for `pmx_solve_group_rk45` function and apply it. Use input data file `ttp2n.data2.R` as hint.
- ▶ Code likelihood for harzard and censor event. Use `model` block as hint.

"why bother" mode

- ▶ Code the model ... input data file `ttp2n.data2.R` and ...

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.