Stan/Torsten tutorial example: Parametric time-to-event model

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July 29, 2019

1 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 [1].

- Fauxlatuzumab vedotin 1.2 mg/kg IV boluses q3w × 6 does.

- 19 patients with 6 right-censored (simulated data).

- To keep things simpler, we use the simulated individual CL and V values, and only model PD part of the problem.
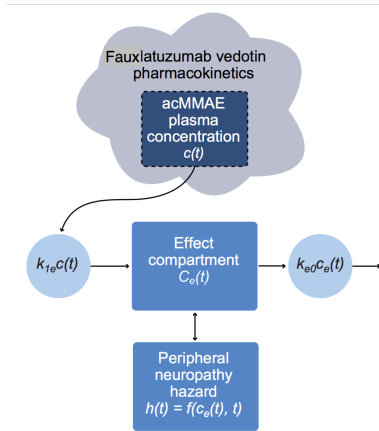

Figure 1: Model scheme

- PN hazard is substantially delayed relative to PK exposure.

- Hazard increases over time to an extent not completely described by PK.

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

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

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

where

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

One can see the expression

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

as the survival function at time t.

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

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

Overall ODE system including integration of the hazard function:

$$x'_1 = -\frac{CL}{V} x_1$$
$$x'_2 = k_{e0}\left(\frac{x_1}{V} - x_2\right)$$
$$x'_3 = h(t)$$

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

2

2 Build

2.1 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
```

2.2 Build in `cmdstan`

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

3 Run

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

References

[1] 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.