TMLE for continuous-time survival analysis

1 Simulation plan

We consider a setting in which we have observations on a bounded interval of time $[0, \tau]$ of the following:

- $L_0 \in \mathbb{R}$, is a uniformly distributed baseline covariate.
- $A \in \{0, 1\}$ is binary baseline treatment.
- $L(t) \in \mathbb{R}^p$ is a time-varying covariate $L(t) \in \mathbb{R}^p$ with corresponding univariate counting process $N^\ell(t)$. We denote the times where $N^\ell(t)$ jumps by $T_1^\ell, T_2^\ell, \dots$ (with $T_0^\ell = 0$).
- $C(t) \in \{0, 1\}$ is a censoring indicator: Represented as a binary variable that jumps only once and only at a jump time of the corresponding counting process $N^c(t)$. We denote by T^c the time where $C(t)$ jumps from 0 to 1.
- $Y(t) \in \{0, 1\}$ is the event indicator: Represented as a binary variable that jumps only once and only at a jump time of the corresponding counting process $N^y(t)$. Denote by T^y the time where $Y(t)$ jumps from 0 to 1.

Potentially the setting should also include:

- An indicator of death (or other competing risk), $D(t) \in \{0, 1\}$, represented as a binary variable that jumps only once and only at a jump time of a corresponding counting process $N^d(t)$. Then we also denote by T^d the time where $D(t)$ jumps from 0 to 1.

In Section 3 we describe the simulation scheme in detail.

2 Statistical estimation problem

3 Simulation scheme

We let $\Delta(T_k) = \mathbb{1}\{T_k = T_k^\ell\} + 2 \cdot \mathbb{1}\{T_k = T^c\}$, i.e., $\Delta(T_k)$ is an indicator, at time k, of what event happened at time T_k (a bit odd now, since $\Delta(T_k) = 0$ indicates event of interest, $\Delta(T_k) = 1$ indicates monitoring of covariates and $\Delta(T_k) = 2$ indicates censoring, but whatever, this can of course be changed). Table 1 gives an overview of how the simulations were done. We present more detail in the following. For the simulations we have used $\tau = 365.24$. Table 2 shows an example of simulated data for a subject. Figure 1 plots monitoring times (jumps of $N^\ell(t)$), censoring times (jumps of $N^c(t)$ or $\tau = 365.24$) and event times (jumps of $N^y(t)$).

3.1 Baseline variables

We draw the baseline covariate L_0 and the treatment as follows:

$$L_0 \sim \text{unif}(0, 1),$$
$$A \sim \text{Bern}(\text{expit}(\beta_0^A + \beta_1^A L_0)).$$

Draw:	$L_0 \sim \text{unif}(0,1)$
	$A \sim \text{Bern}(\text{expit}(\beta_0^A + \beta_1^A L_0)$
	$L_1(0) \sim \text{unif}(0,1)$
	$L_2(0) \sim \text{unif}(0,1)$
	$L_3(0) \sim \text{unif}(0,1)$
Initialize:	$T_0 = 0$, $\Delta = 1$
From k to $k+1$:	$V \sim \text{unif}(0,1)$
	$W_{k+1} \mid T_k = t \sim \tilde{\Lambda}_t^{-1}(-\log V, A, L_0, L_1(T_k), L_2(T_k), L_3(T_k))$
	$T_{k+1} = T_k + W_{k+1}$
	$p^y = \phi^y(A, L_0, L_1(T_k), L_2(T_k), L_3(T_k), k)$
	$p^\ell = \phi^\ell(A, L_0, L_1(T_k), L_2(T_k), L_3(T_k), k)$
	$p^c = \phi^c(A, L_0, L_1(T_k), L_2(T_k), L_3(T_k), k)$
	$p' = p^y + p^\ell + p^c$
	$\Delta \sim (\{0,1,2\}, p = (p^y/p', p^\ell/p', p^c/p'))$
if $\Delta = 1$:	$L_1(T_{k+1}) \sim N(\mu = 0.05L_0 + L_1(T_k), \sigma = 0.1)$
	$L_2(T_{k+1}) \sim N(\mu = 0.02A + 0.025L_0 + L_2(T_k), \sigma = 0.1)$
	$L_3(T_{k+1}) \sim N(\mu = 0.04A + 0.0167L_0 + L_3(T_k), \sigma = 0.1)$
if $\Delta \in \{0,2\}$:	Stop.
if $\Delta \in \{0,2\}$:	Stop.

Table 1: Simulation overview.

3.2 Weibull intensities

For $x = \ell, y, c$, we define,

$$\lambda_k^x(t \mid \mathcal{F}_{t-}) = \eta\nu t^{\nu-1}\phi^x(t \mid \mathcal{F}_{t-}), \tag{1}$$

where η is a scale parameter and ν is a shape parameter. For instance, the Weibull distribution allows the baseline to increase ($\nu > 1$) or decrease ($\nu < 1$).

For each subject, T_k denotes the time between the origin and the kth monitoring. We have that $T_0 = 0$. Now define $W_k = T_k - T_{k-1}$, the kth waiting time between two consecutive events. We simulate these waiting times.

Notably, we need the conditional intensity $\tilde{\lambda}_k$ for $W_k \mid T_{k-1} = t$. This is derived by,

$$\tilde{\lambda}_k(u \mid T_{k-1} = t)du = \lambda(u + t)du,$$

where λ is the intensity for the original times. The corresponding cumulative hazard is now,

$$\tilde{\Lambda}_k(u \mid T_{k-1} = t) = \int_0^u \tilde{\lambda}_k(s \mid T_{k-1} = t)ds = \int_0^u \lambda(s+t)ds = \Lambda(u+t) - \Lambda(t)$$

id	time	Δ	L_1	L_2	L_3	A	L_0
9	0	1	0.996	0.79	0.566	1	0.556
9	134	1	0.939	0.932	0.577	1	0.556
9	163	0	0.939	0.932	0.577	1	0.556

Table 2: Simulated data for id=9.

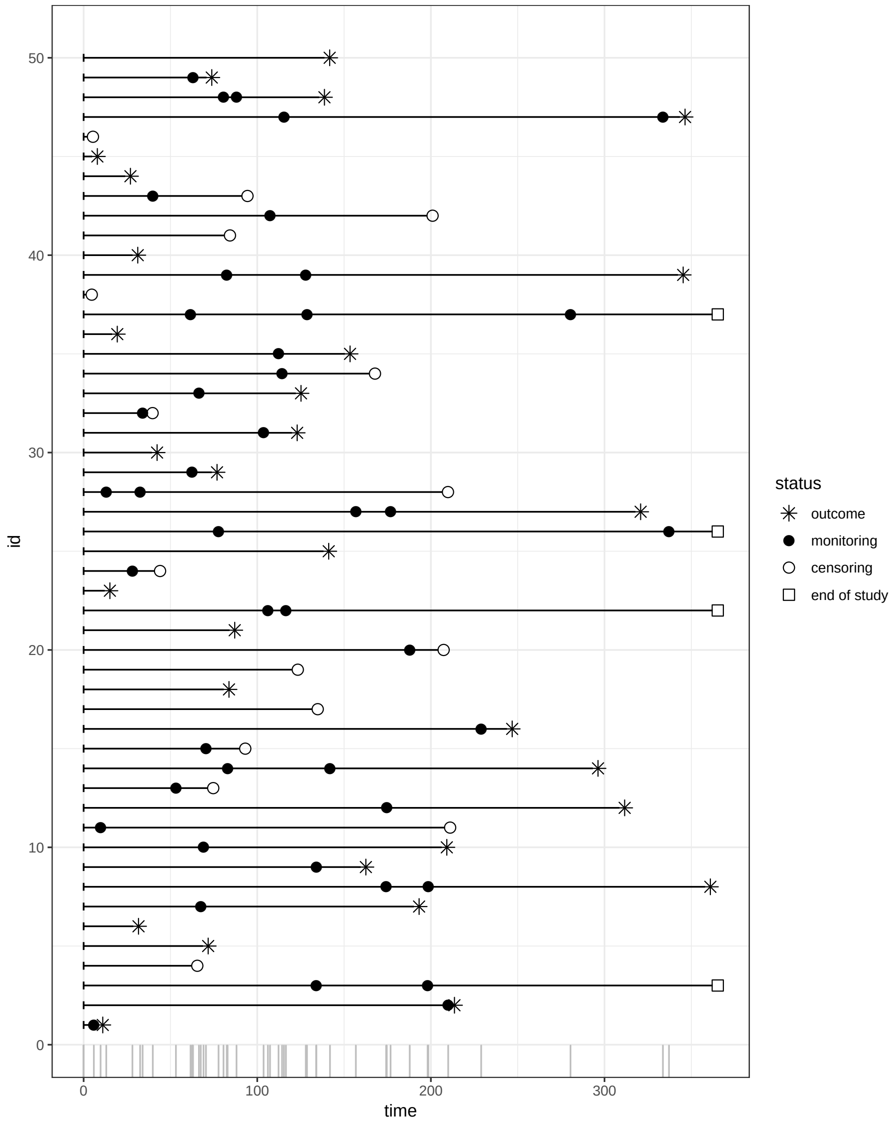

Figure 1: Plot showing simulated data (monitoring and event times).

And then we can use that,

$$W_k \,|\, T_{k-1} = t \,\sim\, \tilde{\Lambda}_t^{-1}(-\log V),$$

where $V \sim \text{unif}(0, 1)$.

The cumulative intensities of the waiting times corresponding to (1) are given as,

$$\tilde{\Lambda}_t^x(u) = \eta\, \phi^x(t \,|\, \mathcal{F}_{t-})\, ((t+u)^\nu - t^\nu), \tag{2}$$

so that the cumulative hazard of T is,

$$\tilde{\Lambda}_t(u) = \tilde{\Lambda}_t^\ell(u) + \tilde{\Lambda}_t^y(u) + \tilde{\Lambda}_t^c(u) = \left\{\phi^\ell(t \,|\, \mathcal{F}_{t-}) + \phi^y(t \,|\, \mathcal{F}_{t-}) + \phi^c(t \,|\, \mathcal{F}_{t-})\right\} \eta\, ((t+u)^\nu - t^\nu) \tag{3}$$

Note that for (2) we have that,

$$\begin{aligned}
\tilde{\Lambda}_t^x(u) &= \eta\, \phi^x(t \,|\, \mathcal{F}_{t-})\, ((t+u)^\nu - t^\nu), \\
\tilde{\Lambda}_t^{-1}(u) &= \left(\frac{u + \eta t^\nu}{\eta}\right)^{1/\nu} - t,
\end{aligned}$$

and similarly for (3) by substituting $\eta\left(\phi^\ell(t \,|\, \mathcal{F}_{t-}) + \phi^y(t \,|\, \mathcal{F}_{t-}) + \phi^c(t \,|\, \mathcal{F}_{t-})\right)$ for η.

We simulate the monitoring times $T_1, T_2, \ldots$. At each monitoring time we determine the type of event by drawing Δ from $\{0,1,2\}$ with probability $p = (p^y/p', p^\ell/p', p^c/p')$, where, at the kth time,

$$\begin{aligned}
p^x &= \lambda_k^x(t \,|\, \mathcal{F}_{t-}), \quad x = \ell, y, c, \\
p' &= p^\ell + p^y + p^c,
\end{aligned}$$

where, notably, the $(\eta\nu t^{\nu-1})$ factors out. In our simulations, we let,

$$\begin{aligned}
\phi^y(A, L_0, L_1(T_k), L_2(T_k), L_3(T_k), k) &= \eta_y \alpha_y^{\mathbb{1}\{k>3\}} \exp(\beta_{y,L_0} L_0 + \beta_{y,L}^\top L(T_{k-1}) + \beta_{y,A} A), \\
\phi^\ell(A, L_0, L_1(T_k), L_2(T_k), L_3(T_k), k) &= \eta_\ell \alpha_\ell^{\min(k, K_{\max})} \exp(\beta_{\ell,L_0} L_0 + \beta_{\ell,A} A), \\
\phi^c(A, L_0, L_1(T_k), L_2(T_k), L_3(T_k), k) &= \eta_c \alpha_c^{\mathbb{1}\{k>3\}} \exp(\beta_{c,L_0} L_0 + \beta_{c,A} A).
\end{aligned}$$

Note that we include α to adjust dependence on the number of previous events ($\alpha > 1$ ($\alpha < 1$) causes the rate to increase (decrease) with the number of previous events)

3.3 Time-varying covariates

At time $T_0 = T_0^\ell$ we draw:

$$\begin{aligned}
L_1(0) &\sim \text{unif}(0,1), \\
L_2(0) &\sim \text{unif}(0,1), \\
L_3(0) &\sim \text{unif}(0,1),
\end{aligned}$$

and at all following monitoring times T_k^ℓ, $k = 1, 2, \ldots$, we draw covariates $L_1(T_k), L_2(T_k), L_3(T_k)$ as follows:

$$\begin{aligned}
L_1(T_{k+1}) &\sim N(\mu = 0.05 L_0 + L_1(T_k), \\
L_2(T_{k+1}) &\sim N(\mu = 0.02 A + 0.025 L_0 + L_2(T_k), \sigma = 0.1), \\
L_3(T_{k+1}) &\sim N(\mu = 0.04 A + 0.0167 L_0 + L_3(T_k), \sigma = 0.1).
\end{aligned}$$