Sequential Regressions for Efficient Continuous-Time Causal Inference

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- Work on continuous-time longitudinal causal inference using
  - Targeted learning (e.g., TMLE Rytgaard et al. (2022) or one-step estimation).
  - Efficiency theory.

- We observe a càdlàg, jump process for the treatment $(A(t))_{t \in [0, \tau_{\text{end}}]} \in \{0, 1\}$ and a covariate process $(L(t))_{t \in [0, \tau_{\text{end}}]}$, such that $L(t)$ almost surely takes values some finite subset of $\mathbb{R}^d$.

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- Assume that we are observe the counting processes N^x, $x = a, \ell, y$ (treatment, covariate, death, censoring) up to a right-censoring time C which is distinct from all event times with probability 1. Terminal event time is denoted by T^e.

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- Assume that $\Delta A(t) \neq 0$ only if $\Delta N^a(t) \neq 0$ and $\Delta L(t) \neq 0$ only if $\Delta N^\ell(t) \neq 0$ or $\Delta N^a(t) \neq 0$.

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- The doctor may decide treatment based at times at which $\Delta N^a(t) \neq 0$. The intervention in which we are interested attempts to specify what this decision should be (or the probability of being treated), but does not naturally intervene on when the doctor decides to do so.
- Each individual has at most K events in $[0, \tau_{\text{end}}]$, i.e., $\sum_{x=a,y,c,\ell} N^x(\tau_{\text{end}}) \leq K$ almost surely.

$$\mathcal{F}_t = \sigma\Big(\big(A(s), L(s), N^a(s), N^\ell(s), N^y(s)\big) : s \leq t\Big)$$

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$$\begin{aligned}\mathcal{F}_t^{\tilde{\beta}} = \sigma\big(\big(&A(s \wedge C), L(s \wedge C), N^a(s \wedge C), N^\ell(s \wedge C), \\ &N^y(s \wedge C), N^c(s \wedge T^e)\big) : s \leq t\big)\end{aligned}$$

- $\mathcal{F}_t$ is the natural filtration for the processes without censoring.
- $\mathcal{F}_t^\beta$ is the natural filtration for the processes including censoring.
- $\mathcal{F}_t^{\tilde{\beta}}$ is the observed filtration, i.e., the natural filtration stopped by death and censoring.

- Data format:

$$O = \left(T_{(K)}, \Delta_{(K)}, A\left(T_{(K-1)}\right), L\left(T_{(K-1)}\right), T_{(K-1)}, \Delta_{(K-1)}, ..., A(0), L(0)\right)$$

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- Let $N^a_t(\cdot)$ denote the random measure associated with N^a and $A(\cdot)$,

$$N^a_t(A) = \sum_{k:\Delta_{(k)}=a} \delta_{\left(T_{(k)}, A\left(T_{(k)}\right)\right)}(A).$$

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- The intervention defines a probability measure P^{G^*}, where $N^a(\cdot)$ has compensator $\pi_t^*(A)\Lambda^a(t)$ for specified $\pi_t^*(A)$.
- Focus on the case $\pi_t^*(\{x\}) \equiv \mathbb{1}\{x = 1\}$.

4.1 Target parameter (continued)

- We are then interested (are we?) in

$$\Psi_\tau(P) = \mathbb{E}_P\left[\frac{dP^{G^*}}{dP}(\tau) N^y(\tau)\right] = \mathbb{E}_{P^{G^*}}[N^y(\tau)]$$

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- With $W^g(t) = \frac{dP^{G^*}}{dP}(t)$, Rytgaard et al. (2022) claims that the following is the EIF:

$$\begin{aligned}
\varphi^*_\tau(P) &= \mathbb{E}_{P^{G^*}}\left[N_y(\tau) \mid \mathcal{F}_0\right] - \Psi_\tau(P) \\
&\quad + \int_0^\tau W^g(t-)\left(\mathbb{E}_{P^{G^*}}\left[N_y(\tau) \mid L(t), N^\ell(t), \mathcal{F}_{t-}\right] - \mathbb{E}_{P^{G^*}}\left[N_y(\tau) \mid N^\ell(t), \mathcal{F}_{t-}\right]\right)\widetilde{N}^\ell(\mathrm{d}t) \\
&\quad + \int_0^\tau W^g(t-)\left(\mathbb{E}_{P^{G^*}}\left[N_y(\tau) \mid \Delta N^\ell(t) = 1, \mathcal{F}_{t-}\right] - \mathbb{E}_{P^{G^*}}\left[N_y(\tau) \mid \Delta N^\ell(t) = 0, \mathcal{F}_{t-}\right]\right)\widetilde{M}^\ell(\mathrm{d}t) \\
&\quad + \int_0^\tau W^g(t-)\left(\mathbb{E}_{P^{G^*}}\left[N_y(\tau) \mid \Delta N^a(t) = 1, \mathcal{F}_{t-}\right] - \mathbb{E}_{P^{G^*}}\left[N_y(\tau) \mid \Delta N^a(t) = 0, \mathcal{F}_{t-}\right]\right)\widetilde{M}^a(\mathrm{d}t) \\
&\quad + \int_0^\tau W^g(t-)\left(1 - \mathbb{E}_{P^{G^*}}\left[N_y(\tau) \mid \Delta N^y(t) = 0, \mathcal{F}_{t-}\right]\right)\widetilde{M}^y(\mathrm{d}t).
\end{aligned}$$

4.2 Sequential regressions

- Here $\widetilde{M}^x(t) = \widetilde{N}^x(t) - \Lambda^x(t)$ is the martingale for $\widetilde{N}^x(t) = N^x(t \wedge C)$.
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- It is unclear how to estimate $\mathbb{E}_{P^{G^*}}\left[N_y(\tau) \mid \Delta N^x(t), \mathcal{F}_{t-}\right]$.
- Sequential regression not clear how to implement.
- Rytgaard et al. (2022) iterative procedure requires 1000s of iterative steps.
  - Assume that $n = 1000$; if all registrations in the sample are unique and each person has 10 events on average, then we need to fit 10,000 regressions.
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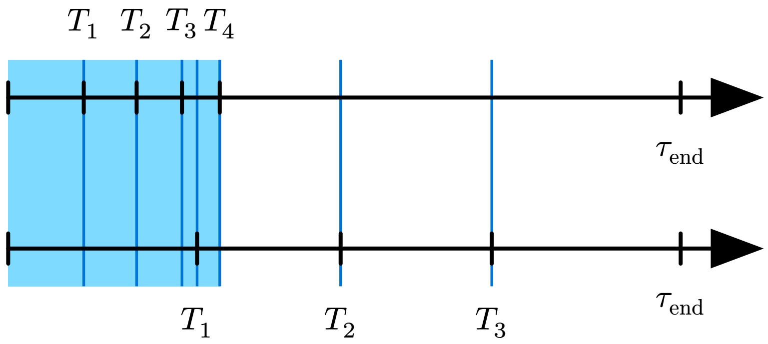
- It is unclear how to estimate $\mathbb{E}_{PG^*}\left[N_y(\tau) \mid \Delta N^x(t), \mathcal{F}_{t-}\right]$.
- Sequential regression not clear how to implement.
- Rytgaard et al. (2022) iterative procedure requires 1000s of iterative steps.
  - Assume that $n = 1000$; if all registrations in the sample are unique and each person has 10 events on average, then we need to fit 10,000 regressions.
- Hard to work with $\mathcal{F}_{t-}$.
- My idea: Can we work with $\mathcal{F}_{T_{(k)}} = \sigma\left(A\left(T_{(j)}\right), L\left(T_{(j)}\right), T_{(j)}, \Delta_{(j)} : j \leq k\right) \vee \sigma((A(0), L(0)))$ instead and more generally $\mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k)}} = \sigma\left(A\left(\bar{T}_j\right), L\left(\bar{T}_j\right), \bar{T}_{(j)}, \bar{\Delta}_{(j)} : j \leq k\right) \vee \sigma((A(0), L(0)))$ and regress back on that information instead of $\mathcal{F}_{t-}$?

4.3 Illustration



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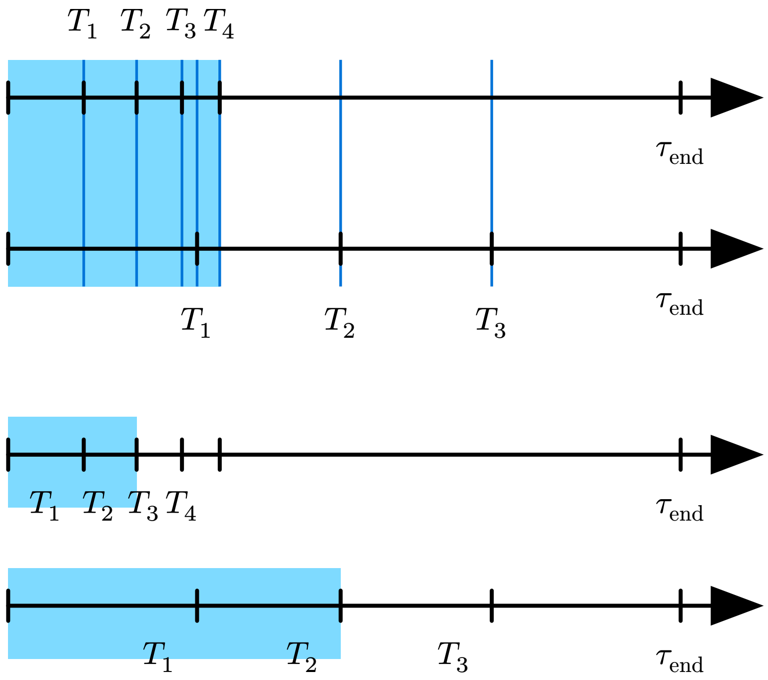

Theorem 5.1

Let $H_k = \left(L\left(T_{(k)}\right), T_{(k)}, \Delta_{(k)}, A\left(T_{(k-1)}\right), L\left(T_{(k-1)}\right), T_{(k-1)}, \Delta_{(k-1)}, \dots, A(0), L(0)\right)$ be the history up to and including the k'th event, but excluding the k'th treatment values for $k > 0$. For $k = 0$, let $H_0 = L(0)$. Let $\bar{Q}^g_{K,\tau} : (a_k, h_k) \mapsto 0$ and recursively define for $k = K - 1, \dots, 1$,

$$\begin{aligned} Z^a_{k+1,\tau}(u) = \mathbb{1}\Big\{T_{(k+1)} \leq u, T_{(k+1)} < \tau, \Delta_{(k+1)} = \ell\Big)\bar{Q}^g_{k+1,\tau}\left(\tau, A\left(T_{(k)}\right), H_{k+1}\right) \\ + \mathbb{1}\Big\{T_{(k+1)} \leq u, T_{(k+1)} < \tau, \Delta_{(k+1)} = a\Big)\bar{Q}^g_{k+1,\tau}\left(\tau, 1, H_{k+1}\right) \\ + \mathbb{1}\Big\{T_{(k+1)} \leq u, \Delta_{(k+1)} = y\Big), \end{aligned}$$

and

$$\bar{Q}^g_{k,\tau} : (u, a_k, h_k) \mapsto \mathbb{E}_P\left[Z^a_{k+1,\tau}(u) \mid A\left(T_{(k)}\right) = a_k, H_k = h_k\right],$$

for $u \leq \tau$. Then,

$$\Psi^g_\tau(P) = \mathbb{E}_P\left[\bar{Q}^g_{0,\tau}(\tau, 1, L(0))\right].$$

Let

$$\bar{Z}^a_{k,\tau}(u) = \frac{1}{\tilde{S}^c\left(\bar{T}_{(k)} - \mid A\left(\bar{T}_{k-1}\right), \bar{H}_{k-1}\right)}\Big(\mathbb{1}\left\{\bar{T}_{(k)} \leq u, \bar{T}_{(k)} < \tau, \bar{\Delta}_{(k)} = a\right\}\bar{Q}^g_{k,\tau}\left(1, \bar{H}_k\right)$$
$$+\mathbb{1}\left\{\bar{T}_{(k)} \leq u, \bar{T}_{(k)} < \tau, \bar{\Delta}_{(k)} = \ell\right\}\bar{Q}^g_{k,\tau}\left(A\left(\bar{T}_k\right), \bar{H}_k\right)$$
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- $\tilde{S}^c\left(t \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right) = \prod_{s \in \left(\bar{T}_{(k-1)}, t\right]}\left(1 - d\tilde{\Lambda}^c_k\left(s \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right)\right).$

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$$+ \mathbb{1}\left\{\bar{T}_{(k)} \leq u, \bar{T}_{(k)} < \tau, \bar{\Delta}_{(k)} = \ell\right\} \bar{Q}^g_{k,\tau}(A(\bar{T}_k), \bar{H}_k)$$
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- $\tilde{S}^c\left(t \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right) = \prod_{s \in (\bar{T}_{(k-1)}, t]} \left(1 - d\tilde{\Lambda}^c_k\left(s \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right)\right)$.
- $\tilde{\Lambda}^c_k\left(t \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right)$ denotes the hazard measure of $\left(\bar{T}_{(k)}, \mathbb{1}\left\{\bar{\Delta}_{(k)} = c\right\}\right)$ given $\mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}$ and $\Lambda^x_k\left(t, \mathcal{F}_{T_{(k-1)}}\right)$ denotes the hazard measure of $\left(T_{(k)}, \mathbb{1}\left\{\Delta_{(k)} = x\right\}\right)$ given $\mathcal{F}_{T_{(k-1)}}$ for $x \in \{a, \ell, y, d\}$.

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1. $\Delta\tilde{\Lambda}_k^c\left(t \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right) + \sum_x \Delta\Lambda_k^x\left(t, \mathcal{F}_{T_{(k-1)}}\right) = 1 \quad P-\text{a.s.} \Rightarrow \Delta\tilde{\Lambda}_{k+1}^c\left(t \mid \mathcal{F}_{T_{(k-1)}}\right) = 1 \quad P-\text{a.s.} \vee \sum_x \Delta\Lambda_k^x\left(t, \mathcal{F}_{T_{(k-1)}}\right) = 1 \quad P-\text{a.s.}$.
2. $\tilde{S}^c\left(t \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right) > \eta$ for all $t \in (0, \tau]$ and $k \in \{1, ..., K\}$ P-a.s. for some $\eta > 0$.

Assume that the compensator Λ^α of N^α with respect to the filtration $\mathcal{F}_t^\beta$ is also the compensator with respect to the filtration $\mathcal{F}_t$. If

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2. $\tilde{S}^c\left(t \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right) > \eta$ for all $t \in (0, \tau]$ and $k \in \{1, \dots, K\}$ P-a.s. for some $\eta > 0$.

Then with $h_k = (a_k, l_k, t_k, d_k, \dots, a_0, l_0)$,

$$\mathbb{1}\{d_1 \in \{a, \ell\}, \dots, d_k \in \{a, \ell\}\}\bar{Q}^g_{k,\tau}(u, a_k, h_k) = \mathbb{E}_P\left[\bar{Z}^a_{k+1,\tau}(u) \mid A\left(\bar{T}_k\right) = a_k, \bar{H}_k = h_k\right].$$

Hence $\Psi^g_\tau(P)$ is identifiable from the observed data.

7.1 Rewriting the efficient influence function

- $\widetilde{M}^c(t) = \widetilde{N}^c(t) - \tilde{\Lambda}^c(t)$. Here $\widetilde{N}^c(t) = \mathbb{1}\{C \leq t, T^e > t\} = \sum_{k=1}^{K} \mathbb{1}\left\{\bar{T}_{(k)} \leq t, \bar{\Delta}_{(k)} = c\right\}$ is the censoring counting process.

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- $S\left(t \mid \mathcal{F}_{T_{(k-1)}}\right) = \prod_{s \in (0,t]} \left(1 - \sum_{x=a,\ell,y,d} \Lambda_k^x\left(\mathrm{d}s \mid \mathcal{F}_{T_{(k-1)}}\right)\right)$.

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- Suppose that there is a universal constant $C^* > 0$ such that $\tilde{\Lambda}_k^c\left(\tau_{\text{end}} \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}; P\right) \leq C^*$ for all $k = 1, \ldots, K$ and every $P \in \mathcal{M}$.

7.2 Rewriting the efficient influence function

The Gateaux derivative is then given by

$$
\begin{aligned}
\varphi_\tau^*(P) = {} & \frac{\mathbb{1}\{A(0)=1\}}{\pi_0(L(0))} \sum_{k=1}^{K} \prod_{j=1}^{k-1} \left(\frac{\mathbb{1}\{A(\bar{T}_j)=1\}}{\pi_j\left(\bar{T}_{(j)}, L(\bar{T}_j), \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(j-1)}}\right)} \right)^{\mathbb{1}\{\bar{\Delta}_{(j)}=a\}} \frac{1}{\prod_{j=1}^{k-1} \tilde{S}^c\left(\bar{T}_{(j)} - \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(j-1)}}\right)} \\
& \times \mathbb{1}\left\{\bar{\Delta}_{(k-1)} \in \{\ell, a\}, \bar{T}_{(k-1)} < \tau\right\} \left(\left(\bar{Z}^a_{k,\tau}(\tau) - \bar{Q}^g_{k-1,\tau}(\tau)\right) \right. \\
& \left. + \int_{\bar{T}_{(k-1)}}^{\tau \wedge \bar{T}_{(k)}} \left(\bar{Q}^g_{k-1,\tau}(\tau) - \bar{Q}^g_{k-1,\tau}(u)\right) \frac{1}{\tilde{S}^c\left(u \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right) S\left(u - \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right)} \widetilde{M}^c(\mathrm{d}u) \right) \\
& + \bar{Q}^g_{0,\tau}(\tau) - \Psi^g_\tau(P),
\end{aligned}
$$

7.3 Practical considerations

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- Simulation studies demonstrate favorable performance of the proposed procedure – lower bias than discrete-time procedures and good coverage of confidence intervals.
- However, variance estimation is challenging due to the censoring martingale term.

7.4 Perspectives

- Estimating the martingale term
  - Undersmoothing of the estimation of the censoring compensator to avoid estimation altogether.
  - Using a machine learning methods that can handle multivariate outcomes.

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- Identifiability, i.e., does the target parameter have a causal interpretation?
- Similar ideas for other target parameters, e.g., recurrent events, restricted mean survival time, etc.

Bibliography

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