Sequential Regressions for Efficient Continuous-Time Causal Inference

Johan Sebastian Ohlendorff

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- We follow the setting in Rytgaard et al. (2022) and are interested in the mean interventional absolute risk under a specified treatment regime in continuous time.
- **Problem**: Rytgaard et al. (2022) do not provide a feasibly implementable procedure for estimation.

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- **Bounded events**
  - Each individual has at most K events in $[0, \tau_{\text{end}}]$

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

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- Data format (uncensored)

$$\left(T_{(K)}, \Delta_{(K)}, A\big(T_{(K-1)}\big), L\big(T_{(K-1)}\big), \underbrace{T_{(K-1)}}_{\text{ordered event time}}, \underbrace{\Delta_{(K-1)}}_{\substack{\in\{a,y,\ell\} \\ \text{status indicator}}}, \ldots, A(0), L(0)\right)$$

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- **Random measure** N_t^{a*}: random measure linked to N_a and A given by

$$N_t^{a*} = \sum_{k:\Delta_{(k)}=a} \delta_{\left(T_{(k)}, A\left(T_{(k)}\right)\right)}$$

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- **Intervention**
  - Modify compensator: $\Lambda_t^{a*}(\cdot) = \pi_t(\cdot)\Lambda^a(t)$
  - Replace treatment mechanism
    - $\pi_t(\{x\}) = P(A(t) = x \mid \mathcal{F}_{t-})$
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- **Special case**
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- **Target parameter**
  - $\Psi_\tau(P) = \mathbb{E}_P\left[\frac{\mathrm{d}P^{G^*}}{\mathrm{d}P}(\tau)N^y(\tau)\right] = \mathbb{E}_{P^{G^*}}[N^y(\tau)], \tau < \tau_{\text{end}}$

- **Efficient influence function (EIF)** for $\Psi_\tau(P)$ in the nonparametric model is given by (Rytgaard et al. (2022))

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

- $\widetilde{M}^x(t) = \widetilde{N}^x(t) - \Lambda^x(t)$ is the P-$\bar{\mathcal{F}}_t$ martingale for $\widetilde{N}^x(t) = N^x(t \wedge C)$.

5.1. Efficient influence function (continued)

- To work within the targeted learning framework, we need the efficient influence function.
- Rytgaard et al. (2022) propose sequential regressions for estimating terms in $\varphi_\tau^*(P)$.

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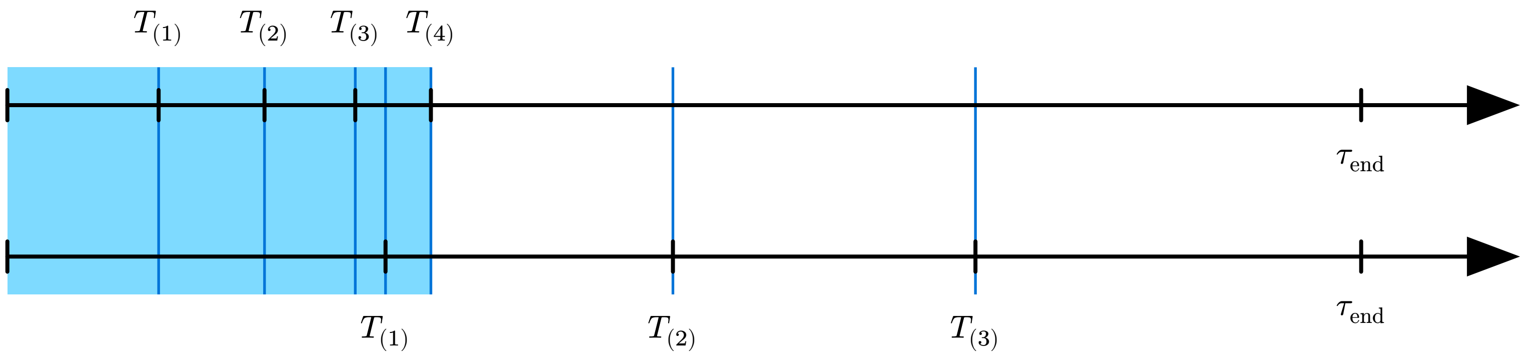
5.1. Efficient influence function (continued)

- To work within the targeted learning framework, we need the efficient influence function.
- Rytgaard et al. (2022) propose sequential regressions for estimating terms in $\varphi^*_\tau(P)$.
- Implementation is unclear and may require thousands of iterations (iterate through all unique event times in the sample).
- **Idea**: Replace $\mathcal{F}_{t-}$ with simpler histories:
  - $\mathcal{F}_{T_{(k)}} = \sigma\left(A\left(T_{(j)}\right), L\left(T_{(j)}\right), T_{(j)}, \Delta_{(j)} : j \leq k\right) \vee \sigma((A(0), L(0)))$
  - Censored versions: $\bar{\mathcal{F}}_{\bar{T}_{(k)}} = \sigma\left(A\left(\bar{T}_j\right), L\left(\bar{T}_j\right), \bar{T}_{(j)}, \bar{\Delta}_{(j)} : j \leq k\right) \vee \sigma((A(0), L(0)))$

Rytgaard et al. (2022):



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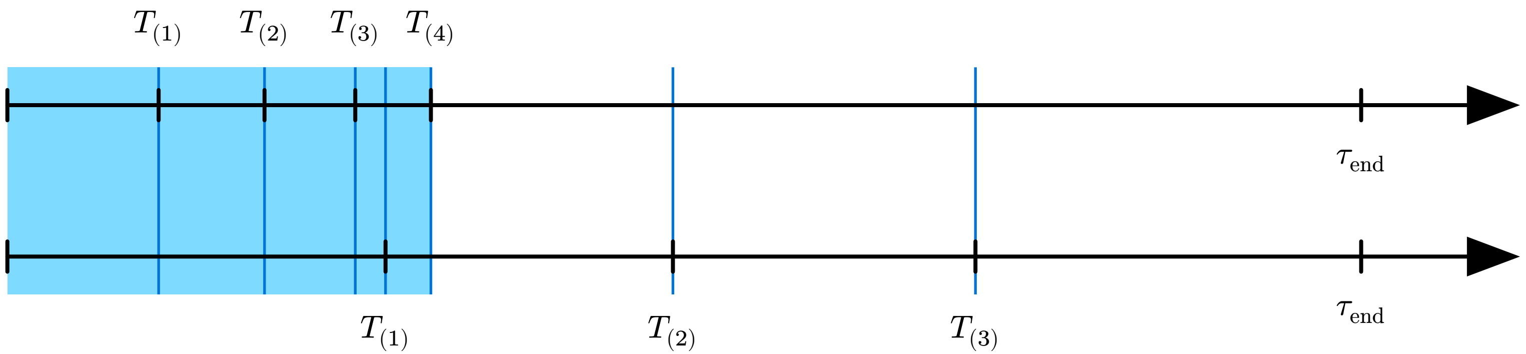

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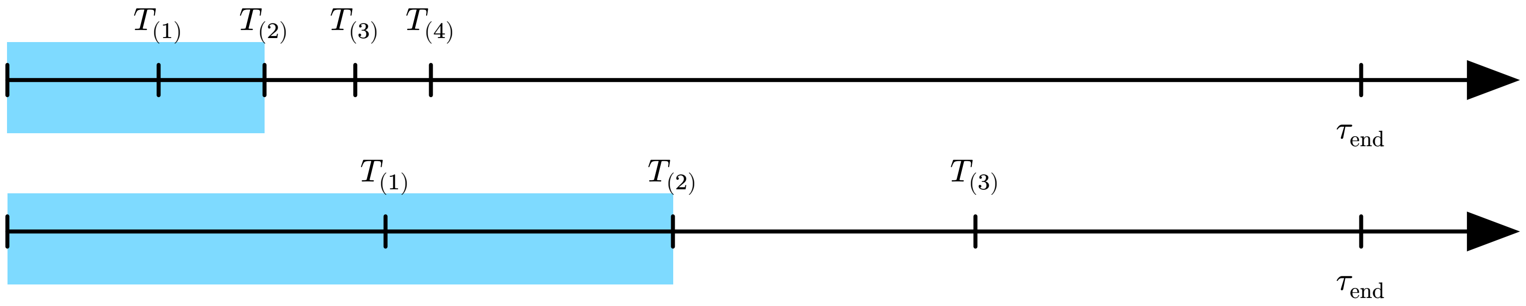

- **Propensity score**:
  - $\pi_k\left(t, L\left(T_{(k)}\right), \mathcal{F}_{T_{(k-1)}}\right)$: $P\left(A\left(T_{(k)}\right) = 1 \mid L\left(T_{(k)}\right), T_{(k)} = t, \Delta_{(k)} = a, \mathcal{F}_{T_{(k-1)}}\right)$.
- **Hazard measures**:
  - $\tilde{\Lambda}_k^c\left(t \mid \bar{\mathcal{F}}_{\bar{T}_{(k-1)}}\right)$: hazard measure for $\left(\bar{T}_{(k)}, \mathbb{1}\left\{\bar{\Delta}_{(k)} = c\right\}\right)$ given $\bar{\mathcal{F}}_{\bar{T}_{(k-1)}}$.
  - $\Lambda_k^x\left(t, \mathcal{F}_{T_{(k-1)}}\right)$: 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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- $\prod$: product integral (Gill & Johansen (1990)).
- **Survival functions**:
  - $\tilde{S}^c\left(t \mid \bar{\mathcal{F}}_{\bar{T}_{(k-1)}}\right) = \prod_{s \in \left(\bar{T}_{(k-1)}, t\right]}\left(1 - d\tilde{\Lambda}_k^c\left(s \mid \bar{\mathcal{F}}_{\bar{T}_{(k-1)}}\right)\right)$.
  - $S\left(t \mid \mathcal{F}_{T_{(k-1)}}\right) = \prod_{s \in \left(T_{(k-1)}, t\right]}\left(1 - \sum_{x=a,\ell,y,d} d\Lambda_k^x\left(s \mid \mathcal{F}_{T_{(k-1)}}\right)\right)$.

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- Define recursively, for $k = K, ..., 0,$

$$\bar{Z}^a_{k,\tau}(u) = \frac{1}{\tilde{S}^c\left(\bar{T}_{(k)} - \mid A\left(\bar{T}_{k-1}\right), \bar{H}_{k-1}\right)}\Big(\mathbb{1}\left\{\bar{T}_{(k)} \le u, \bar{T}_{(k)} < \tau, \bar{\Delta}_{(k)} = a\right\}\bar{Q}^g_{k,\tau}\left(1, \bar{H}_k\right)$$
$$+\mathbb{1}\left\{\bar{T}_{(k)} \le u, \bar{T}_{(k)} < \tau, \bar{\Delta}_{(k)} = \ell\right\}\bar{Q}^g_{k,\tau}\left(A\left(\bar{T}_k\right), \bar{H}_k\right)$$
$$+\mathbb{1}\left\{\bar{T}_{(k)} \le u, \bar{\Delta}_{(k)} = y\right\}\Big).$$

and

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

where $h_k = (a_k, l_k, t_k, d_k, ..., a_0, l_0)$ for $u \le \tau$.

7.2. ICE-IPCW procedure: Consistency

Theorem 7.2.1 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 $\mathcal{F}_t$.

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1. $\Delta\tilde{\Lambda}_k^c\left(\cdot, \bar{\mathcal{F}}_{\bar{T}_{(k-1)}}\right)\Delta\Lambda_k^x\left(\cdot, \mathcal{F}_{T_{(k-1)}}\right) \equiv 0$ for $x \in \{a, \ell, y, d\}$ and $k \in \{1, \ldots, K\}$.
2. $\tilde{S}^c\left(t \mid \bar{\mathcal{F}}_{\bar{T}_{(k-1)}}\right) > \eta$ for all $t \in (0, \tau]$ and $k \in \{1, \ldots, K\}$ P-a.s. for some $\eta > 0$.

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- We make *explicit* use of the fact that the compensator can be explicitly written in terms of the regular conditional distributions of the variables $\left(\bar{T}_{(k)}, \bar{\Delta}_{(k)}, A\left(\bar{T}_k\right), L\left(\bar{T}_k\right)\right)$, $k = 1, ..., K$ and $(A(0), L(0))$.

Theorem 8.1 Under suitable regularity conditions, $\varphi^*_\tau(P)$ can be rewritten as

$$\varphi^*_\tau(P) = \frac{\mathbb{1}\{A(0)=1\}}{\pi_0(L(0))} \sum_{k=1}^{K} \prod_{j=1}^{k-1} \left(\frac{\mathbb{1}\{A(\bar{T}_j)=1\}}{\pi_j\left(\bar{T}_{(j)}, L(\bar{T}_j), \bar{\mathcal{F}}_{\bar{T}_{(j-1)}}\right)} \right)^{\mathbb{1}\{\bar{\Delta}_{(j)}=a\}} \frac{1}{\prod_{j=1}^{k-1} \tilde{S}^c\left(\bar{T}_{(j)} - \mid \bar{\mathcal{F}}_{\bar{T}_{(j-1)}}\right)}$$

$$\times \mathbb{1}\left\{\bar{\Delta}_{(k-1)} \in \{\ell, a\}, \bar{T}_{(k-1)} < \tau\right\} \Bigg(\left(\bar{Z}^a_{k,\tau}(\tau) - \bar{Q}^g_{k-1,\tau}(\tau)\right)$$

$$+ \int_{\bar{T}_{(k-1)}}^{\tau \wedge \bar{T}_{(k)}} \left(\bar{Q}^g_{k-1,\tau}(\tau) - \bar{Q}^g_{k-1,\tau}(u)\right) \frac{1}{\tilde{S}^c\left(u \mid \bar{\mathcal{F}}_{\bar{T}_{(k-1)}}\right) S\left(u - \mid \bar{\mathcal{F}}_{\bar{T}_{(k-1)}}\right)} \widetilde{M}^c(\mathrm{d}u) \Bigg)$$

$$+ \bar{Q}^g_{0,\tau}(\tau) - \Psi^g_\tau(P).$$

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- **Application**: Apply to real-world data with Danish registry data:
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- **Challenges**
  - Variance estimation is difficult (censoring martingale term)
  - Possible approaches:
    - Undersmooth estimation of censoring compensator
    - Machine learning (e.g., neural networks) methods for multivariate outcomes (to $\bar{Q}^g_{k,\tau}(u)$)

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- **Application**: Apply to real-world data with Danish registry data:
  - EIF provides confidence intervals comparable to bootstrap CIs.
- **Challenges**
  - Variance estimation is difficult (censoring martingale term)
  - Possible approaches:
    - Undersmooth estimation of censoring compensator
    - Machine learning (e.g., neural networks) methods for multivariate outcomes (to $\bar{Q}^g_{k,\tau}(u)$)
- **Simplifications**
  - Empirical process & remainder term conditions not yet addressed (ongoing work)

- **Estimator**
  - One-step estimator based on the efficient influence function
- **Simulations**
  - Lower bias than LTMLE (van der Laan & Gruber (2012)) and good CI coverage.
  - Mean squared errors are however close to being the same.
- **Application**: Apply to real-world data with Danish registry data:
  - EIF provides confidence intervals comparable to bootstrap CIs.
- **Challenges**
  - Variance estimation is difficult (censoring martingale term)
  - Possible approaches:
    - Undersmooth estimation of censoring compensator
    - Machine learning (e.g., neural networks) methods for multivariate outcomes (to $\bar{Q}^g_{k,\tau}(u)$)
- **Simplifications**
  - Empirical process & remainder term conditions not yet addressed (ongoing work)
- **Next steps**
  - Consider TMLE instead of one-step $\Rightarrow$ ensures estimates in $[0, 1]$
  - Apply flexible, data-adaptive estimators for nuisance parameters

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