

Sequential Regressions for Efficient Continuous-Time Causal Inference

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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 $[0, \tau_{\text{end}}]$

$$\mathcal{F}_t = \sigma\left(\left(A(s), L(s), N^a(s), N^\ell(s), N^y(s)\right) : s \leq t\right) \vee \sigma\left(\left(A(0), L(0)\right)\right)$$

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$$\mathcal{F}_t^{\text{full}} = \sigma\left(\left(A(s), L(s), N^a(s), N^\ell(s), N^y(s), N^c(s)\right) : s \leq t\right) \vee \sigma\left(\left(A(0), L(0)\right)\right)$$

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- Data format (uncensored)

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

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

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- **Intervention**

- ▶ Modify compensator: $\Lambda_t^{a*}(\cdot) = \pi_t(\cdot) \Lambda^a(t)$
- ▶ Replace treatment mechanism
 - $\pi_t(\{x\}) = P(A(t) = x \mid \mathcal{F}_{t-})$
 - Under new law P^{G^*} , compensator of N^a is $\pi_t^*(\cdot) \Lambda^a(t)$ with respect to \mathcal{F}_t

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- **Special case**

- ▶ $\pi_t^*(\{x\}) \equiv \mathbb{1}\{x = 1\}$ (stay on treatment)

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- **Target parameter**

- ▶ $\Psi_\tau(P) = \mathbb{E}_P \left[\frac{dP^{G^*}}{dP}(\tau) N^y(\tau) \right] = \mathbb{E}_{P^{G^*}} [N^y(\tau)], \tau < \tau_{\text{end}}$

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

$$\begin{aligned}
\varphi_\tau^*(P) &= \mathbb{E}_{P^{G^*}} [N_y(\tau) \mid \mathcal{F}_0] - \Psi_\tau(P) \\
&+ \int_0^\tau \frac{dP^{G^*}}{dP}(t-) (\mathbb{E}_{P^{G^*}} [N_y(\tau) \mid L(t), N^\ell(t), \mathcal{F}_{t-}] - \mathbb{E}_{P^{G^*}} [N_y(\tau) \mid N^\ell(t), \mathcal{F}_{t-}]) \tilde{N}^\ell(dt) \\
&+ \int_0^\tau \frac{dP^{G^*}}{dP}(t-) (\mathbb{E}_{P^{G^*}} [N_y(\tau) \mid \Delta N^\ell(t) = 1, \mathcal{F}_{t-}] - \mathbb{E}_{P^{G^*}} [N_y(\tau) \mid \Delta N^\ell(t) = 0, \mathcal{F}_{t-}]) \tilde{M}^\ell(dt) \\
&+ \int_0^\tau \frac{dP^{G^*}}{dP}(t-) (\mathbb{E}_{P^{G^*}} [N_y(\tau) \mid \Delta N^a(t) = 1, \mathcal{F}_{t-}] - \mathbb{E}_{P^{G^*}} [N_y(\tau) \mid \Delta N^a(t) = 0, \mathcal{F}_{t-}]) \tilde{M}^a(dt) \\
&+ \int_0^\tau \frac{dP^{G^*}}{dP}(t-) (1 - \mathbb{E}_{P^{G^*}} [N_y(\tau) \mid \Delta N^y(t) = 0, \mathcal{F}_{t-}]) \tilde{M}^y(dt).
\end{aligned}$$

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

5.1. Efficient influence function (continued) 5. Efficient influence function (Rytgaard et al. (2022))

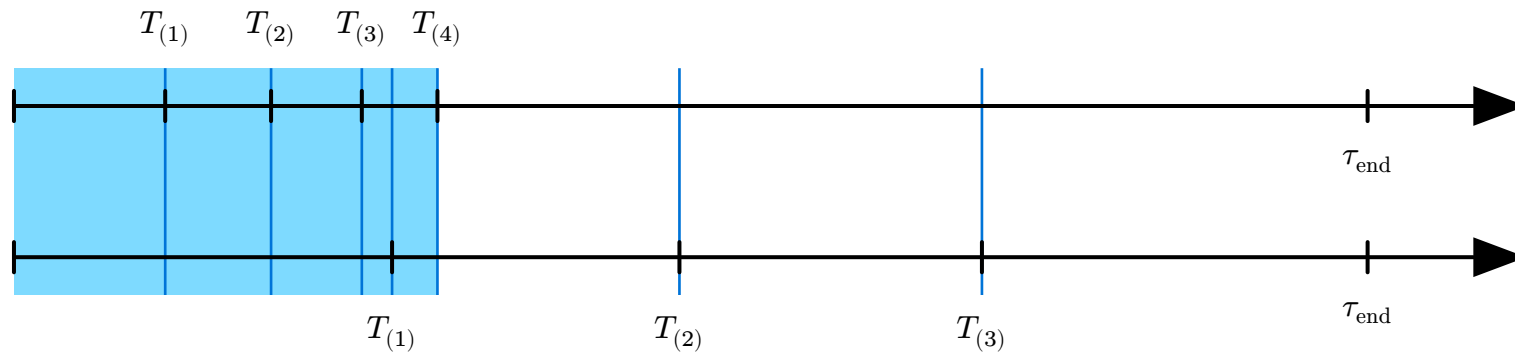
- To work within the targeted learning framework, we need the efficient influence function.
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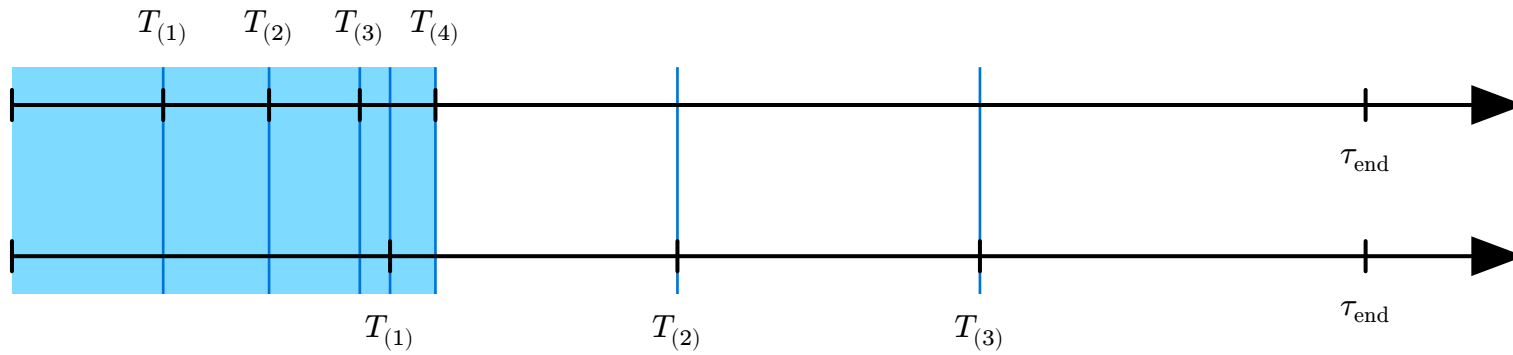
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- Rytgaard et al. (2022) propose sequential regressions for estimating terms in $\varphi_{\tau}^*(P)$.
- Implementation is unclear and may require thousands of iterations (iterate through all unique event times in the sample).
- **Idea:** Replace \mathcal{F}_{t-}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

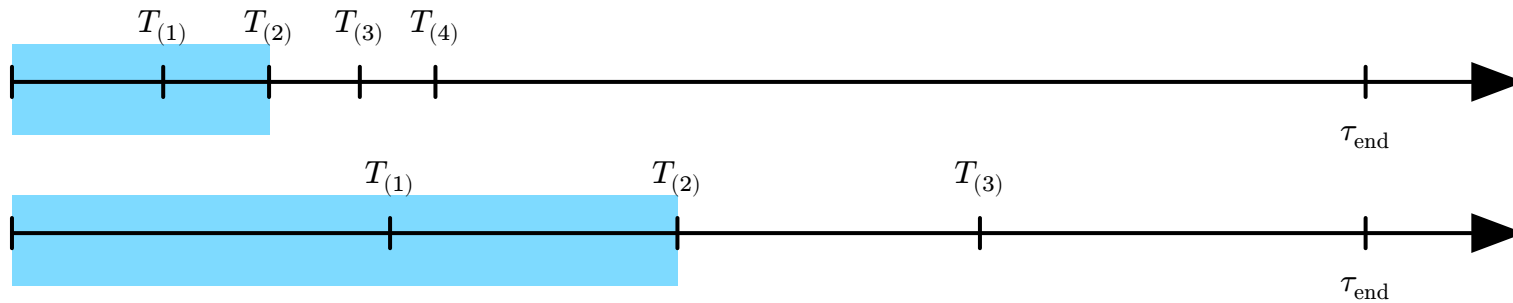
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ICE-IPCW (Ohlendorff et al. (2025)):



- **Propensity score:**

- $\pi_k(t, L(T_{(k)}), \mathcal{F}_{T_{(k-1)}}): P(A(T_{(k)}) = 1 \mid L(T_{(k)}), T_{(k)} = t, \Delta_{(k)} = a, \mathcal{F}_{T_{(k-1)}}).$

- **Hazard measures:**

- $\tilde{\Lambda}_k^c(t \mid \mathcal{F}_{\bar{T}_{(k-1)}}):$ hazard measure for $(\bar{T}_{(k)}, \mathbb{1}\{\bar{\Delta}_{(k)} = c\})$ given $\mathcal{F}_{\bar{T}_{(k-1)}}.$
 - $\Lambda_k^x(t, \mathcal{F}_{T_{(k-1)}}):$ hazard measure of $(T_{(k)}, \mathbb{1}\{\Delta_{(k)} = x\})$ given $\mathcal{F}_{T_{(k-1)}}$ for $x \in \{a, \ell, y, d\}.$

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- **Survival functions:**

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

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- **Random measure:**
 - $N = \sum_k \delta_{(T_{(k)}, \Delta_{(k)}, A(T_{(k)}), L(T_{(k)}))}.$
 - Turns out that natural filtration of N is $\mathcal{F}_t^{\text{full}}.$

7.1. Independent censoring conditions

- Let $\bar{Q}_{K,\tau}^g : (a_k, h_k) \mapsto 0$

7. Consistency of ICE-IPCW procedure under right-censoring

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- Let $\bar{Q}_{K,\tau}^g : (a_k, h_k) \mapsto 0$
- Define recursively, for $k = K, \dots, 0$,

$$\begin{aligned} \bar{Z}_{k,\tau}^a(u) = \frac{1}{\tilde{S}^c(\bar{T}_{(k)} - | A(\bar{T}_{k-1}), \bar{H}_{k-1})} & \left(\mathbb{1}\{\bar{T}_{(k)} \leq u, \bar{T}_{(k)} < \tau, \bar{\Delta}_{(k)} = a\} \bar{Q}_{k,\tau}^g(1, \bar{H}_k) \right. \\ & + \mathbb{1}\{\bar{T}_{(k)} \leq u, \bar{T}_{(k)} < \tau, \bar{\Delta}_{(k)} = \ell\} \bar{Q}_{k,\tau}^g(A(\bar{T}_k), \bar{H}_k) \\ & \left. + \mathbb{1}\{\bar{T}_{(k)} \leq u, \bar{\Delta}_{(k)} = y\} \right). \end{aligned}$$

and

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

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

7. Consistency of ICE-IPCW procedure under right-censoring

7.2. ICE-IPCW procedure: Consistency

7. Consistency of ICE-IPCW procedure under right-

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If

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

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It holds that

$$\Psi_\tau^g(P) = \mathbb{E}_P[\bar{Q}_{0,\tau}^g(\tau, 1, L(0))].$$

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It holds that

$$\Psi_{\tau}^g(P) = \mathbb{E}_P [\bar{Q}_{0,\tau}^g(\tau, 1, L(0))].$$

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

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

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

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- **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.

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- **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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