Sequential Regressions for Efficient Continuous-Time Causal Inference

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- Work on continuous-time longitudinal causal inference using
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  - Targeted learning (e.g., TMLE Rytgaard et al. (2022) or one-step estimation).
- Working on a continuous-time scale is motivated by:
  - Real-world data often recorded in continuous time (e.g., electronic health records).
  - Avoiding bias due to discretization (Adams et al. (2020); Ferreira Guerra et al. (2020); Kant & Krijthe (2025); Ryalen et al. (2019); Sofrygin et al. (2019); Sun & Crawford (2023))

- 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 specifies 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.

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

- $\mathcal{F}_t$ is the natural filtration for the processes without censoring.

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

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

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

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

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

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

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- Data format (uncensored)

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

- Data format (censored)

$$\left(\bar{T}_{(K)}, \bar{\Delta}_{(K)}, A\left(\bar{T}_{K-1}\right), L\left(\bar{T}_{K-1}\right), \bar{T}_{(K-1)}, \bar{\Delta}_{(K-1)}, \dots, A(0), L(0)\right)$$

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

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

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- Interested on "intervening" on the compensator of $N^a(\cdot)$, $\Lambda^a_t(A) = \pi_t(A)\Lambda^a(t)$, replacing the treatment mechanism $\pi_t(\{x\}) = P(A(t) = x \mid \mathcal{F}_{t-})$ with a specified treatment mechanism $\pi^*_t(A)$. We denote by P^{G^*} the probability measure in which the P^{G^*}-$\mathcal{F}_t$ compensator of $N^a(\cdot)$ is $\pi^*_t(A)\Lambda^a(t)$.

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- Focus on the case $\pi_t^*(\{x\}) \equiv \mathbb{1}\{x = 1\}$.

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- Focus on the case $\pi^*_t(\{x\}) \equiv \mathbb{1}\{x = 1\}$.
- We are then interested (are we?) in

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

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

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

- Here $\widetilde{M}^x(t) = \widetilde{N}^x(t) - \Lambda^x(t)$ is the martingale for $\widetilde{N}^x(t) = N^x(t \wedge C)$.

Efficient influence function (continued)

- It is unclear how to estimate $\mathbb{E}_{P^{G^*}}\left[N_y(\tau) \mid \Delta N^x(t), \mathcal{F}_{t-}\right]$.

Efficient influence function (continued)

- 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 $\mathcal{F}_{t-}$.

Efficient influence function (continued)

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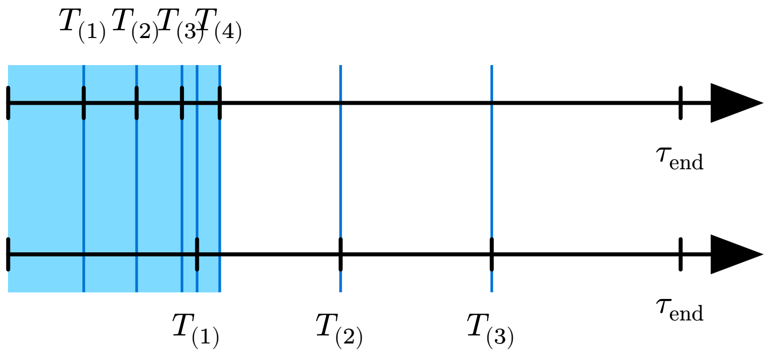
- Rytgaard et al. (2022) iterative procedure requires 1000s of iterative steps.
  - Assume that $n = 1000$; if all registrations in the sample are unique and each person has 10 events on average, then we need to fit 10,000 regressions.
- Hard to work with $\mathcal{F}_{t-}$.
- My idea: Can we work with $\mathcal{F}_{T_{(k)}} = \sigma\left(A\left(T_{(j)}\right), L\left(T_{(j)}\right), T_{(j)}, \Delta_{(j)} : j \leq k\right) \vee \sigma((A(0), L(0)))$ 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 $\mathcal{F}_{t-}$?

Illustration



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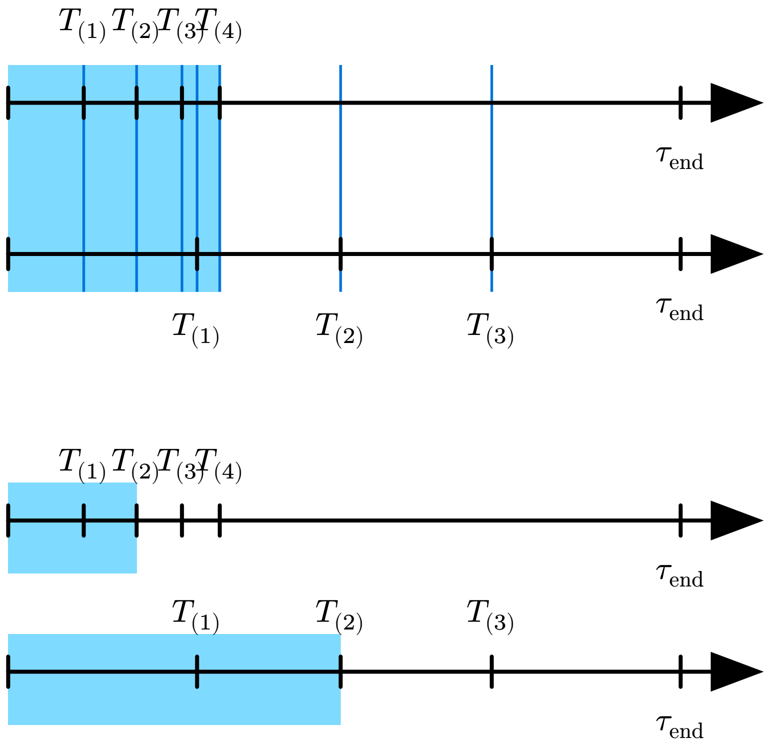

Let

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

- $\tilde{S}^c\left(t \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right) = \prod_{s\in\left(\bar{T}_{(k-1)},t\right]}\left(1 - d\tilde{\Lambda}^c_k\left(s \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right)\right).$

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

$$+\mathbb{1}\left\{\bar{T}_{(k)} \le u, \bar{T}_{(k)} < \tau, \bar{\Delta}_{(k)} = \ell\right\}\bar{Q}^g_{k,\tau}\left(A(\bar{T}_k), \bar{H}_k\right)$$

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- $\tilde{\Lambda}^c_k\left(t \mid \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right)$ 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 $x \in \{a, \ell, y, d\}$.

Theorem 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 $\mathcal{F}_t$. Let $\bar{Q}^g_{K,\tau} : (a_k, h_k) \mapsto 0$.

Theorem 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 $\mathcal{F}_t$. Let $\bar{Q}^g_{K,\tau} : (a_k, h_k) \mapsto 0$. If

1. $\Delta\tilde{\Lambda}^c_k\left(\cdot, \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right)\Delta\Lambda^x_k\left(\cdot, \mathcal{F}_{T_{(k-1)}}\right) \equiv 0$ for $x \in \{a, \ell, y, d\}$ and $k \in \{1, \dots, K\}$.
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 $\eta > 0$.

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1. $\Delta\tilde{\Lambda}^c_k\left(\cdot, \mathcal{F}^{\tilde{\beta}}_{\bar{T}_{(k-1)}}\right)\Delta\Lambda^x_k\left(\cdot, \mathcal{F}_{T_{(k-1)}}\right) \equiv 0$ for $x \in \{a, \ell, y, d\}$ and $k \in \{1, ..., K\}$.
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 $\eta > 0$.

With $h_k = (a_k, l_k, t_k, d_k, ..., a_0, l_0)$,

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

for $u \leq \tau$, it holds that

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

Rewriting the efficient influence function

Let $\widetilde{M}^c(t) = \widetilde{N}^c(t) - \tilde{\Lambda}^c(t)$ and $S\left(t \mid \mathcal{F}_{T_{(k-1)}}\right) = \prod_{s \in (0,t]}\left(1 - \sum_{x=a,\ell,y,d} \Lambda_k^x\left(\mathrm{d}s \mid \mathcal{F}_{T_{(k-1)}}\right)\right)$. Under suitable regularity conditions, the efficient influence function can be written as

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

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- However, variance estimation is challenging due to the censoring martingale term.
- Estimating the censoring 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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- Other target parameters (e.g., recurrent events, restricted mean survival time, etc.).

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