

# A New Iterated Conditional Expectations Estimator for Longitudinal Causal Effects in Continuous Time

Johan Sebastian Ohlendorff<sup>1</sup>, Anders Munch<sup>1</sup>, and Thomas Alexander Gerds<sup>1</sup>,

<sup>1</sup> Section of Biostatistics, University of Copenhagen

## Motivation

- In medical research, the estimation of causal effects of treatments over time is often of interest.
- Continuous-time inference allows for data that is more closely aligned with the data collection process (Table 1). Moreover, discrete time approaches usually require the discretization of time, leading to a loss of information.
- There is a scarcity of (applied) literature on the estimation of longitudinal causal effects in continuous time. Rytgaard et al. (2022) considered a targeted minimum-loss based estimator based on iterated conditional expectations (Figure 1) for estimating causal effects flexibly. However, this estimator quickly becomes intractable.
- We propose a new feasible iterated conditional expectations estimator (Figure 2) for the estimation of longitudinal causal effects in continuous time.

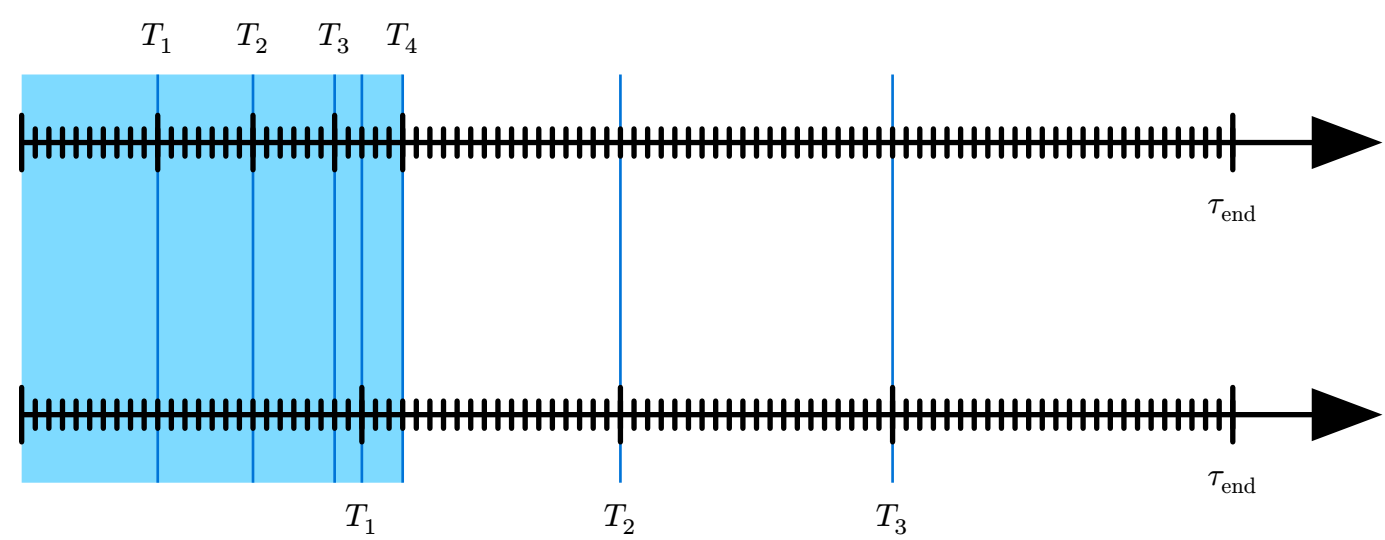


Figure 1: The figure illustrates the sequential regression approach given in Rytgaard et al. (2022) for two observations.

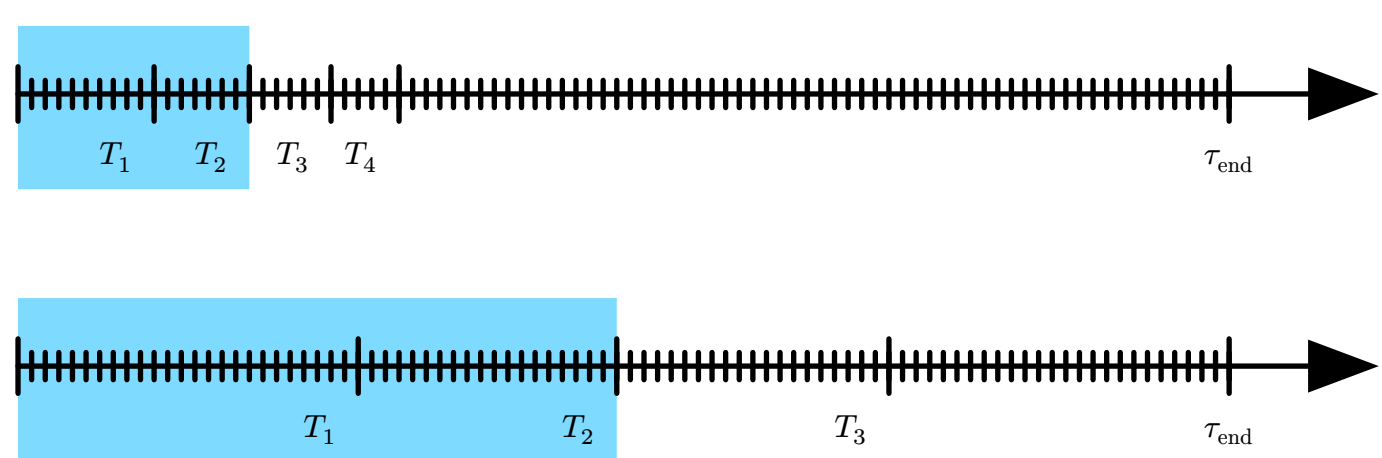


Figure 2: The figure illustrates the sequential regression approach proposed in this article.

id	time	event
1	3	side effect
1	8	primary event
2	10	primary event
3	2	side effect
3	5	treatment shift
3	7	censoring
...		

Table 1: An example of a longitudinal dataset from electronic health records or a clinical trial. Events are registered at irregular/subject-specific time points.

## Setting

Let  $(N^a(t), A(t), N^\ell(t), L(t), N^y(t), N^d(t), N^c(t))^1$  be a stochastic processes observed in  $[0, \tau_{\text{end}}]$ , consisting of a counting process for treatment visits, treatment values, a counting process for treatment covariate measurements, covariate values, and counting processes for the primary event, competing event, and censoring, respectively. Furthermore,  $A(t) \in \{0, 1\}$  and  $L(t) \in \mathcal{L}$ , where  $\mathcal{L} \subseteq \mathbb{R}^d$  is a finite set.

**Assumption 1:** In the time interval  $[0, \tau_{\text{end}}]$  there are at most  $K - 1 < \infty$  many changes of treatment and covariates in total for a single individual.

**Assumption 2:** The counting processes  $N^a$ ,  $N^\ell$ ,  $N^y$ ,  $N^d$ , and  $N^c$  have with probability 1 no jump times in common.

Under these assumptions, the observed data can be written in the form

$$O = \mathcal{F}_{T_{(K)}}$$

where

$$\mathcal{F}_{T_{(k)}} = (T_{(k)}, \Delta_k, A(T_{(k)}), L(T_{(k)})) \vee \mathcal{F}_{T_{(k-1)}} \text{ and } \mathcal{F}_0 = (L_0, A_0)$$

**Assumption 3:** For each  $k \in \{1, \dots, K\}$ ,  $T_{(k)} \mid \mathcal{F}_{T_{(k-1)}} \ll m^2$ ,  $A(T_{(k)}) \mid T_{(k)} = t, \Delta_k = a, \mathcal{F}_{T_{(k-1)}} \ll \nu_a$ , and  $L(T_{(k)}) \mid T_{(k)} = t, D_{(k)} = \ell, \mathcal{F}_{T_{(k-1)}} \ll \nu_\ell$ .

## Target parameter

Let  $\tilde{T}_k^1$  and  $\tilde{\Delta}_k^1$  be the counterfactual event time and indicator for the  $k$ 'th had the patient stayed on treatment and initially received treatment (and not been censored). Our target parameter  $\Psi_\tau^g : \mathcal{M} \rightarrow \mathbb{R}$  is the mean interventional potential outcome at time  $\tau$  given the intervention plan  $g$ .

$$\Psi_\tau^g(P) = \mathbb{E}_P \left[ \sum_{k=1}^K \mathbb{1} \{ \tilde{T}_k^1 \leq \tau, \tilde{\Delta}_k^1 = y \} \right].$$

## Identification

We consider identification conditions in Theorem 3 of Ryalen (2024). These are stated in our present uncensored setting. Let  $\tilde{Y}_t = (\mathbb{1} \{ \tilde{T}_1^1 \leq t, \tilde{\Delta}_1^1 = y \}, \dots, \mathbb{1} \{ \tilde{T}_K^1 \leq t, \tilde{\Delta}_K^1 = y \})$  and  $T^a = \inf \{ t > 0 : A(t) \neq 1 \}$ . For each  $k \in \{1, \dots, K\}$ , we need:

- Consistency:

$$\mathbb{1} \{ \tilde{T}_k^1 \leq t, \tilde{\Delta}_k^1 = y \} \mathbb{1} \{ T^a > t, A(0) = 1 \} = \mathbb{1} \{ T_k \leq t, \Delta_k = y \} \mathbb{1} \{ T^a > t, A(0) = 1 \}$$

for  $t \in [0, \tau_{\text{end}}]$ .

- Exchangeability:

$$A(T_{(k)}) \perp (\mathbb{1} \{ \tilde{T}_{k+1}^1 \leq t, \tilde{D}_{k+1}^1 = y \}, \dots, \mathbb{1} \{ \tilde{T}_K^1 \leq t, \tilde{D}_K^1 = y \}) \mid D_{(k)} = a, \mathcal{F}_{T_{(k-1)}}$$

(and

$$\lambda^a \left( t \mid \mathcal{F}_{T_{(k-1)}} \vee (\tilde{Y}_t)_{t \in [0, \tau_{\text{end}}]} \right) = \lim_{h \rightarrow 0} \frac{P \left( t \leq T_{(k)} < t + h, \Delta_k = a \mid T_{(k)} \geq t, \mathcal{F}_{T_{(k-1)}}, (\tilde{Y}_t)_{t \in [0, \tau_{\text{end}}]} \right)}{h}$$

does not depend on  $(\tilde{Y}_t)_{t \in [0, \tau_{\text{end}}]}$ ).

- Positivity: The weights

$$w_k(f_{k-1}, t_k) = \frac{\mathbb{1} \{ a_0 = 1 \}}{\pi_0(l_0)} \prod_{j=1}^{k-1} \left( \frac{\mathbb{1} \{ a_j = 1 \}}{\pi_j(f_{j-1})} \right)^{\mathbb{1} \{ \delta_j = a \}} \mathbb{1} \{ t_1 < \dots < t_k \}$$

fulfill  $\mathbb{E}_P \left[ w_k \left( \mathcal{F}_{T_{(k-1)}}, T_{(k)} \right) \right] = 1$ .

### Identification formula

Under the assumptions of consistency, exchangeability, and positivity, the target parameter is identified via

$$\Psi_\tau^g(P) = \mathbb{E}_P \left[ \sum_{k=1}^K w_k \left( \mathcal{F}_{T_{(k-1)}}, T_{(k)} \right) \mathbb{1} \{ T_k \leq \tau, \Delta_k = y \} \right].$$

## Iterated Conditional Expectation Estimator

The form of the efficient influence function (Bickel et al. (1993)) in this setting suggests the use of a iterated conditional expectations estimator. Let  $S^c(t \mid \mathcal{F}_{T_{(k)}})$  be the conditional survival function of the censoring time given the  $k$  previous events and  $\mathcal{F}_{T_{(k)}}^A$  denote the history without the treatment process.

### Proposed continuous-time ICE estimator

- For each event point  $k = K, K - 1, \dots, 1$  (starting with  $k = K$ ):

1. Obtain  $\hat{S}^c(t \mid \mathcal{F}_{T_{(k)}})$  by fitting a cause-specific hazard model for the censoring via the interevent time  $S_{(k)} = T_{(k)} - T_{(k-1)}$ , regressing on  $\mathcal{F}_{T_{(k-1)}}$  (among the people who are still at risk after  $k$  events).
2. Define the subject-specific weight:

$$\hat{\eta}_k = \frac{\mathbb{1} \{ T_{(k)} \leq \tau, \Delta_k \in \{a, \ell\}, k < K \} \hat{\nu}_k \left( \mathcal{F}_{T_{(k)}}^A, 1 \right)}{\hat{S}^c \left( T_{(k)} \mid \mathcal{F}_{T_{(k-1)}} \right)}$$

Then calculate the subject-specific pseudo-outcome

$$\hat{R}_k = \frac{\mathbb{1} \{ T_{(k)} \leq \tau, \Delta_k = y \}}{\hat{S}^c \left( T_{(k)} \mid \mathcal{F}_{T_{(k-1)}} \right)} + \hat{\eta}_k$$

Regress  $\hat{R}_k$  on  $\mathcal{F}_{T_{(k-1)}}$  on the data with  $T_{(k-1)} < \tau$  and  $\Delta_k \in \{a, \ell\}$  to obtain a prediction function  $\hat{\nu}_{k-1} : \mathcal{H}_{k-1} \rightarrow \mathbb{R}_+$ .

- At baseline, we obtain the estimate  $\hat{\Psi}_n = \frac{1}{n} \sum_{i=1}^n \hat{\nu}_0(L_i(0), 1)$ .

### Existing discrete-time ICE estimator

1. For each time point  $k = K, K - 1, \dots, 1$  (starting with  $\hat{R}_K = Y$ ): Regress  $\hat{R}_k$  on  $(\bar{L}_{k-1}, \bar{A}_{k-1})$  to obtain  $\hat{\nu}_{k-1}$ ; obtain predictions  $\hat{R}_{k-1} = \hat{\nu}_{k-1}(\bar{L}_{k-1}, 1)$ .
2. At baseline, we obtain the estimate  $\hat{\Psi}_n = \frac{1}{n} \sum_{i=1}^n \hat{\nu}_0(L_i(0), 1)$ .

- This approach can be extended to survival outcomes.

## References

- Bickel, P. J., Klaassen, C. A., Bickel, P. J., Ritov, Y., Klaassen, J., Wellner, J. A., & Ritov, Y. (1993). *Efficient and adaptive estimation for semiparametric models* (Vol. 4). Johns Hopkins University Press Baltimore.
- Ryalen, P. (2024). *On the role of martingales in continuous-time causal inference*.
- Rytgaard, H. C., Gerds, T. A., & Laan, M. J. van der. (2022). Continuous-Time Targeted Minimum Loss-Based Estimation of Intervention-Specific Mean Outcomes. *The Annals of Statistics*, 50(5), 2469–2491. <https://doi.org/10.1214/21-AOS2114>

<sup>1</sup>We associate to this process its natural filtration  $\mathcal{F}_t$  implicitly defined on a probability space  $(\Omega, \mathcal{F}, P)$ .

<sup>2</sup> $m$  is the Lebesgue measure on  $\mathbb{R}_+$ .