

# Doubly Robust Estimation under Covariate-induced Dependent Left Truncation

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## Left truncation and selection bias

- Quantity of interest: time to event ( $T$ )
- $T$  is **left truncated** by the enrollment time ( $Q$ ) if only subjects with  $T > Q$  are included in the data.
  - ▶ e.g., prevalent cohort studies, aging studies.

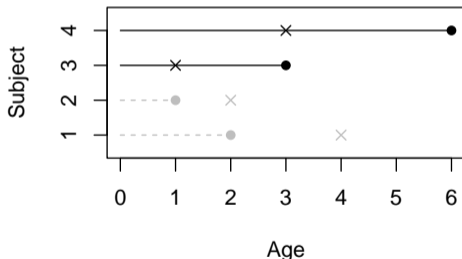
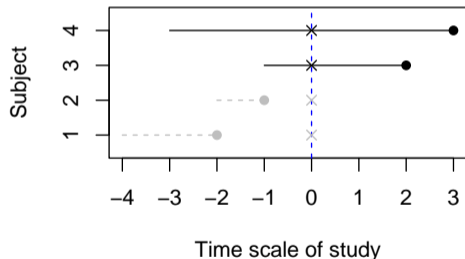
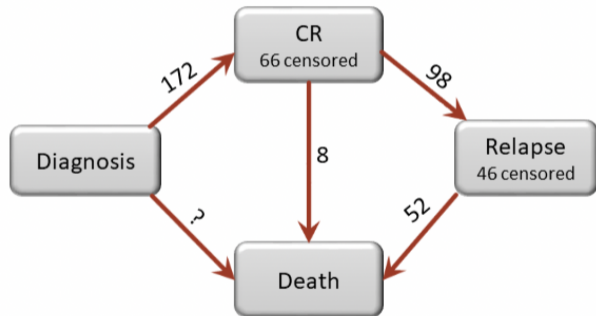


Figure: A toy example for aging study; 'x' - enrollment times; dots - times to events.

## Example: CNS lymphoma data

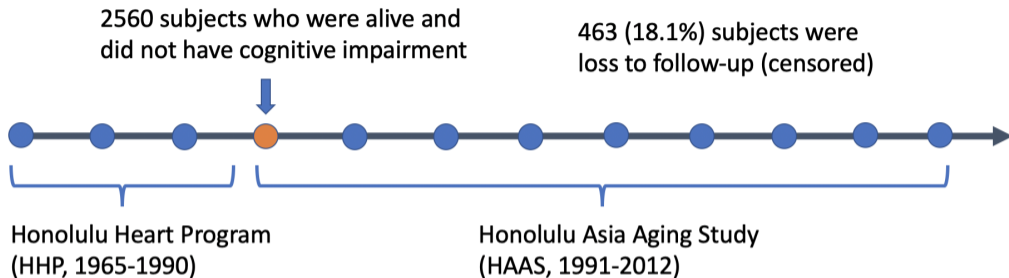
- Data from a study on central nervous system (CNS) lymphoma (Wang et al., 2015)  
*[Publicly available in the supplement of Vakulenko-Lagun et al. (2022)]*



- Quantity of interest: overall survival
  - ▶  $T$  - time to death
- Original data with 172 patients
  - ▶  $Q$  - time to CR
- Restricted data with 98 patients
  - ▶  $Q$  - time to relapse

CR: complete response. *[Figure from Vakulenko-Lagun et al., (2022)]*

## Example: HAAS data



- Quantity of interest: Cognitive impairment-free survival on the age scale.
- $T$  - age to moderate cognitive impairment or death
- $Q$  - age at entry of HAAS

→ **Selection bias**

# Literature

## Under the random left truncation assumption

- Likelihood-based approaches

(Woodroffe, 1985; Wang et al., 1986; Wang, 1989, 1991; Qin et al. 2011)

- Random truncation assumption can be weakened to quasi-independence assumption

(Tsai, 1990)

! The quasi-independence assumption may be violated.

- CNS lymphoma data:

- ▶ It is plausible that time to death and time to relapse are dependent (Vakulenko-Lagun et al., 2022).

- HAAS data:

- ▶ Violation of quasi-independence is detected by conditional Kendall's tau test (Tsai, 1990);
- ▶  $\tau = 0.0426$  with p-value 0.0014.

# Literature

When the left truncation time and the event time are dependent:

- Copula models (Chaieb et al., 2006; Emura et al., 2011; Emura & Wang, 2012)
  - Structural transformation models (Efron & Petrosian, 1994; Chiou et al., 2019)
- ! Depend on strong model assumptions

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  - Structural transformation models (Efron & Petrosian, 1994; Chiou et al., 2019)
- ! Depend on strong model assumptions
- Incorporate left truncation time as a covariate in the event time model (Gail et al., 2009; Mackenzie, 2012; Cheng & Wang 2015).
    - ▶ e.g., Entry-age adjusted age-scale model (Gail et al., 2009)
- ! Biologically unjustified; depend on model assumptions.

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  - ▶ e.g., Entry-age adjusted age-scale model (Gail et al., 2009)
- ! Biologically unjustified; depend on model assumptions.
  
- ! Do not use covariate information.



# Literature

When the dependence is captured by measured covariates:

In regression settings:

- Cox model with risk set adjustment

For marginal survival probabilities:

- Inverse probability weighting (IPW) estimators (Vakulenko-Lagun et al., 2022).

! Sensitive to misspecification of the truncation model; inefficient.

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When the dependence is captured by measured covariates:

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**Motivate us to seek estimators that**

- Have more protection against model misspecification;
- More efficient;
- Allow us to incorporate nonparametric methods (which are known to have slower than root- $n$  convergence) to obtain root- $n$  consistent estimators.

## Our contributions

- Derive the efficient influence curve (EIC) for the expectation of an arbitrarily transformed survival time.
- Construct EIC-based estimators that are shown to have favorable properties:
  - ▶ Model double robustness
  - ▶ Rate double robustness
  - ▶ Semiparametric efficiency
- Provide technical conditions for the asymptotic properties that appear to not have been carefully examined in the literature for time-to-event data.
- Our work represents the **first attempt** to construct doubly robust estimators in the presence of left truncation.
  - ▶ Does NOT fall under the established framework of coarsened data where doubly robust approaches are developed.

## Notation and estimand

- $Q$  - left truncation time;  $T$  - event time;  $Z$  - covariates
- Full data - if there were no left truncation
- We observe  $O = (Q, T, Z)$  only if  $Q < T$
  
- $F, G, H$ : the full data CDF's of  $T|Z, Q|Z$  and  $Z$ , respectively.
- superscript  $*$ : quantities related to the full data distribution, e.g.,  $\mathbb{P}^*, \mathbb{E}^*, p^*, P^*$
- without  $*$ : quantities related to the observed data distribution, e.g.,  $\mathbb{P}, \mathbb{E}, p, P$

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- Estimand:  $\theta := \mathbb{E}^* \{ \nu(T) \}$ , where  $\nu$  is a given function.
  - ▶ e.g., when  $\nu(t) = \mathbb{1}(t > t_0)$ ,  $\theta = \mathbb{P}^*(T > t_0)$  (survival probability).
  - ▶ e.g., when  $\nu(t) = \min(t, t_0)$ ,  $\theta = \mathbb{E}^* \{ \min(T, t_0) \}$  (RMST).

# Assumptions

① **Conditional quasi-independence:**

$Q$  and  $T$  are conditionally “independent” given  $Z$  on the observed region  $\{t > q\}$ .

② **Positivity:**  $G(T|Z) > 0$  a.s.

③ **Overlap:** There exist  $\delta_1, \delta_2 > 0$  such that  $1 - F(Q|Z) \geq \delta_1$  a.s. and  $G(T|Z) \geq \delta_2$  a.s..

- Consider the semiparametric model under Assumptions 1 and 2.
- Assume the true distribution also satisfies Assumption 3.

## Deriving the Efficient Influence Curve (EIC)

- Inverse probability weighting (IPW) identification:

$$\theta = \mathbb{E} \left\{ \frac{\nu(T)}{G(T|Z)} \right\} / \mathbb{E} \left\{ \frac{1}{G(T|Z)} \right\},$$

$$G(q|z) = e^{-\int_q^\infty \alpha(t|z) dt}, \quad \alpha(t|z) = \frac{p_{Q|Z}(t|z)}{\mathbb{P}(Q \leq t < T | Z = z)}$$

- Derive an influence curve (IC):  $\varphi(O)$  s.t.  $\mathbb{E}\{\varphi(O)\} = 0$  and

$$\left. \frac{\partial}{\partial \epsilon} \theta(P_\epsilon) \right|_{\epsilon=0} = \mathbb{E} \{ \varphi(O) S(O) \}, \quad S(O) = \left. \frac{\partial}{\partial \epsilon} \log p_\epsilon(O) \right|_{\epsilon=0}.$$

- Tangent space:  $L_2^0(P_{T,Z}) + L_2^0(P_{Q,Z})$ .
- Project the IC onto the tangent space  $\rightarrow$  EIC

## Efficient influence curve and double robustness

- Efficient influence curve:

$$\varphi(O; \theta, F, G, H) = \beta \cdot U(\theta; F, G),$$

where  $\beta = \mathbb{P}^*(Q < T)$  and

$$U(\theta; F, G) = \frac{\nu(T) - \theta}{G(T|Z)} - \int_0^\infty \mathbb{E}^* \{ \nu(T) - \theta \mid T < t, Z \} \cdot \frac{F(t|Z)}{1 - F(t|Z)} \cdot \frac{d\bar{M}_Q(t; G)}{G(t|Z)}.$$

- The semiparametric efficiency bound :  $\mathbb{E}(\varphi^2)$ .



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### Double robustness:

$$\mathbb{E}\{U(\theta_0; F, G)\} = 0 \text{ if either } F = F_0 \text{ or } G = G_0.$$

## Estimation

Let  $\{O_i\}_{i=1}^n$  be an observed random sample of size  $n$ ;  $O_i = (Q_i, T_i, Z_i)$ .

- First estimate  $F$  and  $G$
- Then solve the following equation for  $\theta$ :

$$\sum_{i=1}^n U_i(\theta; \hat{F}, \hat{G}) = 0$$

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- Closed-form solution:

$$\hat{\theta}_{dr} = \left( \sum_{i=1}^n \left[ \frac{1}{\hat{G}(T_i|Z_i)} - \int_0^\infty \frac{\hat{F}(v|Z_i)}{\hat{G}(v|Z_i)\{1 - \hat{F}(v|Z_i)\}} d\bar{M}_{Q,i}(v; \hat{G}) \right] \right)^{-1} \\ \times \left( \sum_{i=1}^n \left[ \frac{\nu(T_i)}{\hat{G}(T_i|Z_i)} - \int_0^\infty \frac{\int_0^v \nu(t) d\hat{F}(t|Z_i)}{\hat{G}(v|Z_i)\{1 - \hat{F}(v|Z_i)\}} d\bar{M}_{Q,i}(v; \hat{G}) \right] \right)$$

## Model double robustness under asymptotic linearity

Suppose

- $\hat{F}$  and  $\hat{G}$  uniformly converge to  $F^*$  and  $G^*$ , respectively;
- $\hat{F}$  and  $\hat{G}$  are asymptotically linear.

If either  $F^* = F_0$  or  $G^* = G_0$ , then

$$\sqrt{n}(\hat{\theta}_{dr} - \theta_0) \xrightarrow{d} N(0, \sigma^2).$$

Furthermore, when both  $F^* = F_0$  and  $G^* = G_0$ ,

- $\hat{\theta}_{dr}$  achieves the semiparametric efficiency bound;
- $\sigma^2$  can be consistently estimated by  $\hat{\sigma}^2$ , where

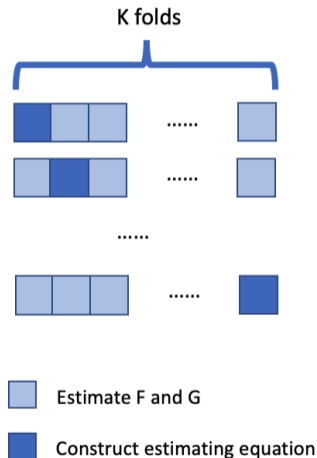
$$\hat{\sigma}^2 = \hat{\beta}^2 \cdot \frac{1}{n} \sum_{i=1}^n U_i^2(\hat{\theta}_{dr}, \hat{F}, \hat{G}), \quad \hat{\beta} = \left\{ n^{-1} \sum_{i=1}^n 1/\hat{G}(T_i|Z_i) \right\}^{-1}.$$

# Rate double robustness with cross-fitting

## $K$ -fold cross-fitting

- 1: Split the data into  $K$  folds of (almost) equal size with the index sets  $\mathcal{I}_1, \dots, \mathcal{I}_K$ .
- 2: **for**  $k = 1$  to  $K$  **do**
- 3:     Estimate  $F$  and  $G$  with the out-of- $k$ -fold data  
       $\implies \hat{F}^{(-k)}$  and  $\hat{G}^{(-k)}$
- 4: **end for**
- 5: Obtain  $\hat{\theta}_{cf}$  by solving

$$\sum_{k=1}^K \sum_{i \in \mathcal{I}_k} U_i \{ \theta, \hat{F}^{(-k)}, \hat{G}^{(-k)} \} = 0.$$



## Rate double robustness with cross-fitting

**Out-of-sample cross integral product:**

$$\mathcal{D}_{\dagger}(\hat{F}, \hat{G}; F_0, G_0) := \mathbb{E} \left( \mathbb{E}_{\dagger} \left[ \left[ \int_{\tau_1}^{\tau_2} \left\{ a(t, \mathbf{Z}_{\dagger}; \hat{F}) - a(t, \mathbf{Z}_{\dagger}; F_0) \right\} \cdot Y_{\dagger}(t) d \left\{ \frac{1}{\hat{G}(t|\mathbf{Z}_{\dagger})} - \frac{1}{G_0(t|\mathbf{Z}_{\dagger})} \right\} \right] \right] \right),$$

where

$$a(t, Z; F) = \frac{\int_0^t \{\nu(u) - \theta\} dF(u|Z)}{1 - F(t|Z)},$$
$$Y_{\dagger}(t) = \mathbb{1}(Q_{\dagger} \leq t < T_{\dagger}).$$

## Rate double robustness

Suppose

- $\hat{F}$  and  $\hat{G}$  are uniformly consistent;
- $\mathcal{D}_\dagger(\hat{F}, \hat{G}; F_0, G_0) = o(n^{-1/2})$ .

We have

- $\sqrt{n}(\hat{\theta}_{cf} - \theta_0) \xrightarrow{d} N(0, \sigma^2)$ , where  $\sigma^2 = \mathbb{E}(\varphi^2)$ ;
- $\hat{\theta}_{cf}$  achieves the semiparametric efficiency bound;
- $\sigma^2$  can be consistently estimated by  $\hat{\sigma}_{cf}^2$ , where

$$\hat{\sigma}_{cf}^2 = \hat{\beta}_{cf}^2 \cdot \frac{1}{n} \sum_{k=1}^K \sum_{i \in \mathcal{I}_k} U_i^2 \{ \hat{\theta}_{cf}, \hat{F}^{(-k)}, \hat{G}^{(-k)} \},$$

$$\hat{\beta}_{cf} = \left\{ \frac{1}{n} \sum_{k=1}^K \sum_{i \in \mathcal{I}_k} \frac{1}{\hat{G}^{(-k)}(T_i | Z_i)} \right\}^{-1}.$$

**Nonparametric methods can be used to estimate  $F$  and  $G$ !**

## Extensions to handle right censoring

$C$ : censoring time;  $X := \min(T, C)$ ;  $\Delta := \mathbb{1}(T < C)$

$S_c(t) := \mathbb{P}(C > t)$ ,  $S_D(t) := \mathbb{P}(D > t)$ , where  $D = C - Q$

Assume noninformative censoring.

### Two scenarios:

- Censoring can happen before truncation

▶  $\mathbb{P}^*(C < Q) > 0$ ; subjects with  $Q < X$  are included;  $C \perp\!\!\!\perp (Q, T, Z)$  in the full data.

$$U_{c1}(\theta; F_x, G, S_c) = \frac{\Delta\{\nu(X) - \theta\}}{S_c(X)G(X|Z)} - \int_0^\infty \frac{\int_0^t \Delta\{\nu(x) - \theta\}/S_c(x) dF_x(x|Z)}{1 - F(t|Z)} \cdot \frac{d\tilde{M}_Q(t; G)}{G(t|Z)}.$$

- Censoring always after truncation

▶  $\mathbb{P}^*(Q < C) = 1$ ; subjects with  $Q < T$  are included;  $D \perp\!\!\!\perp (Q, T, Z)$  in the observed data.

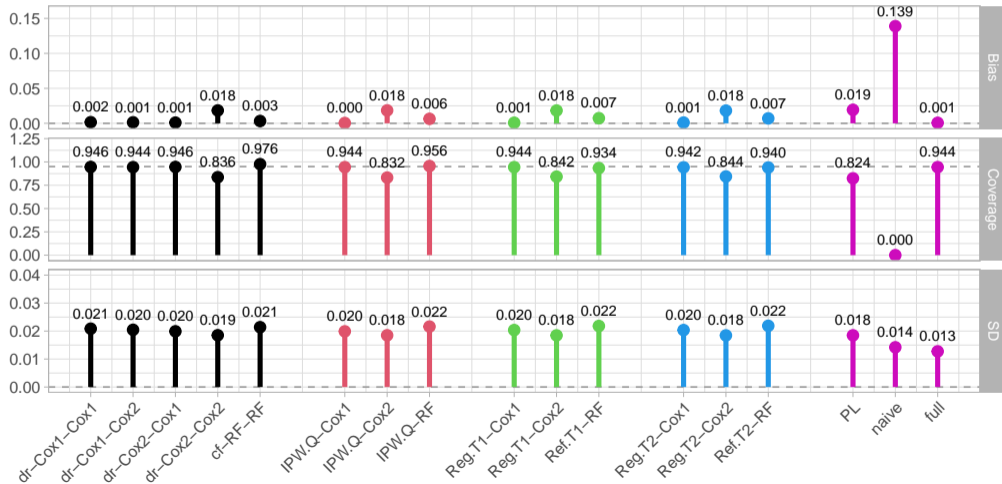
$$U_{c2}(\theta; F, G, S_D) = \frac{\Delta}{S_D(X - Q)} \left[ \frac{\nu(X) - \theta}{G(X|Z)} - \int_0^\infty \frac{\int_0^t \{\nu(u) - \theta\} dF(u|z)}{1 - F(t|Z)} \cdot \frac{d\tilde{M}_Q(t; G)}{G(t|Z)} \right].$$



# Simulation

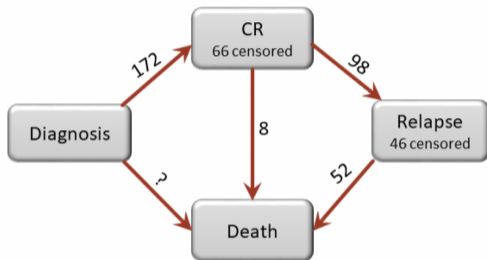
500 simulated data sets each with sample size 1000.

Truncation rate: 29.5%;  $\theta_0 = P^*(T > 3) = 0.576$ .



## Application: CNS lymphoma data

- Data from a study on central nervous system (CNS) lymphoma (Wang et al., 2015)  
*[Publicly available in the supplement of Vakulenko-Lagun et al. (2022)]*



- Quantity of interest: overall survival.
  - ▶  $T$  - time to death
  - ▶  $Q$  - time to relapse
- Include two binary treatment variables:
  - ▶ Chemotherapy
  - ▶ Radiation therapy

CR: complete response. *[Figure from Vakulenko-Lagun et al., (2022)]*

→ Restrict to the 98 patients that were relapsed, for which the time is recorded.

## Application: CNS lymphoma data

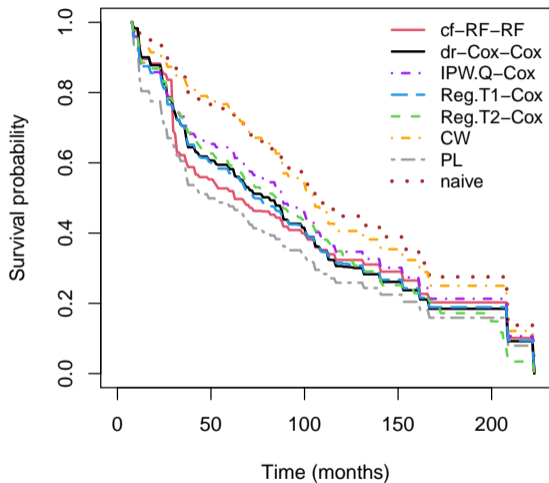
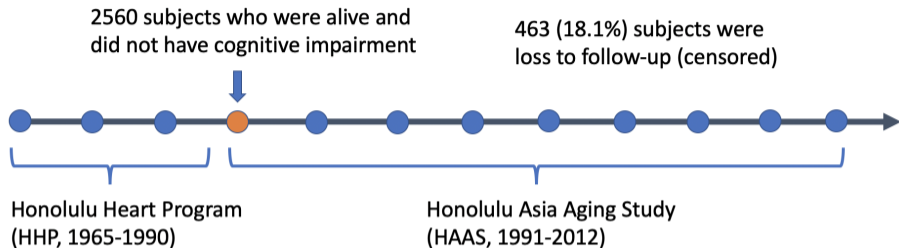


Figure: Estimates of the overall survival for the CNS lymphoma data.

## Application: HAAS data



- Quantity of interest: Cognitive impairment-free survival on the age scale.
- Covariates:
  - ▶ Education (years)
  - ▶ APOE positive (yes/no)
  - ▶ Mid-life alcohol consumption (light/heavy)
  - ▶ Mid-life cigarette consumption (yes/no)

## Application: HAAS data

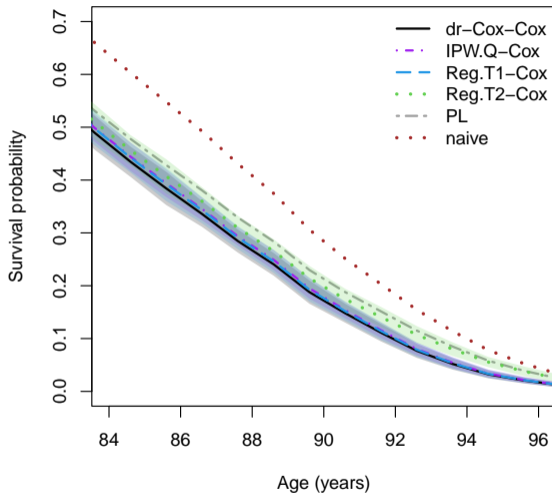


Figure: Estimated cognitive impairment-free survival and their 95% bootstrap confidence intervals (shaded, except for PL and naive) for the HAAS data.

## Discussion

- We derived the efficient influence curve for the mean of an arbitrarily transformed survival time and construct doubly robust estimators.
- Extension: for parameter  $\theta$  that can be identified from an unbiased full data estimating function  $u^*(T, Z; \theta)$ . We consider the following AIPW estimating function for left truncation:

$$V(\theta; F, G) = \frac{u^*(T, Z; \theta)}{G(T|Z)} - \int_0^\infty \mathbb{E}^* \{u^*(T, Z; \theta) \mid T < t, Z\} \cdot \frac{F(t|Z)}{1 - F(t|Z)} \cdot \frac{d\bar{M}_Q(t; G)}{G(t|Z)}.$$

- ArXiv preprint: [arXiv:2208.06836](https://arxiv.org/abs/2208.06836)
- R package: `truncAIPW`
- Code: [https://github.com/wangyuyao98/left\\_trunc\\_DR](https://github.com/wangyuyao98/left_trunc_DR)

# Appendix

## Assumptions

$f, g, h$ : the densities of  $T|Z, Q|Z$  and  $Z$ , respectively.

### Assumption 1 (Conditional quasi-independence)

The observed data density for  $(Q, T, Z)$  satisfies

$$p_{Q,T,Z}(q, t, z) = \begin{cases} f(t|z)g(q|z)h(z)/\beta, & \text{if } t > q, \\ 0, & \text{otherwise,} \end{cases}$$

where  $\beta = \mathbb{P}^*(Q < T) = \int \mathbb{1}(q < t)f(t|z)g(q|z)h(z) dt dq dz$ .

### Assumption 2 (Positivity)

$G(T|Z) > 0$  a.s.

### Assumption 3 (Overlap)

There exists  $0 < \tau_1 < \tau_2 < \infty$  such that  $T \geq \tau_1$  a.s.,  $Q \leq \tau_2$  a.s.; also  $G(\tau_1|Z) \geq \delta_1$  a.s. and  $F(\tau_2|Z) \leq 1 - \delta_2$  a.s. for some constants  $\delta_1 > 0$  and  $\delta_2 > 0$ .



## Inverse probability weighting (IPW) identification

- Under Assumptions 1 and 2,

$$\theta = \mathbb{E} \left\{ \frac{\nu(T)}{G(T|Z)} \right\} / \mathbb{E} \left\{ \frac{1}{G(T|Z)} \right\}.$$

- Let  $\alpha$  be the *reverse time hazard function* of  $Q$  given  $Z$  in the full data:

$$\begin{aligned} \alpha(q|z) &:= \lim_{h \rightarrow 0^+} \frac{\mathbb{P}^*(q-h < Q \leq q | Q \leq q, Z = z)}{h} \\ &= \lim_{h \rightarrow 0^+} \frac{\mathbb{P}^*(q-h < Q \leq q | Z = z)}{h \mathbb{P}^*(Q \leq q | Z = z)} = \frac{\partial G(q|z) / \partial q}{G(q|z)}. \end{aligned}$$

$$\implies G(q|z) = \exp\left\{-\int_q^\infty \alpha(t|z) dt\right\}.$$

- $\alpha$  can be identified:

$$\alpha(q|z) = \frac{p_{Q|Z}(q|z)}{\mathbb{P}(Q \leq q < T | Z = z)}.$$

$$\implies G \text{ can be identified from the observed data distribution.}$$

## Reverse time counting process and backwards martingale

For  $t \geq 0$ , let

$$\begin{aligned}\bar{N}_Q(t) &= \mathbb{1}(t \leq Q < T), \\ \bar{\mathcal{F}}_t &= \sigma\{Z, \mathbb{1}(Q < T), \mathbb{1}(s \leq Q < T), \mathbb{1}(s \leq T) : s \geq t\}.\end{aligned}$$

Define

$$\bar{A}_Q(t; G) = \int_t^\infty \mathbb{1}(Q \leq s < T) \alpha(s|Z) ds = \int_t^\infty \mathbb{1}(Q \leq s < T) \frac{dG(s|Z)}{G(s|Z)}.$$

Then

$$\bar{M}_Q(t; G) := \bar{N}_Q(t) - \bar{A}_Q(t; G)$$

is a backwards martingale with respect to  $\{\bar{\mathcal{F}}_t\}_{t \geq 0}$  in the observed data.

## Two special cases

- By setting  $\hat{F} \equiv 0 \rightarrow$  IPW estimator

$$\hat{\theta}_{\text{IPW.Q}} = \left\{ \sum_{i=1}^n \frac{\nu(T_i)}{\hat{G}(T_i|Z_i)} \right\} / \left\{ \sum_{i=1}^n \frac{1}{\hat{G}(T_i|Z_i)} \right\},$$

- By setting  $\hat{G} \equiv 1 \rightarrow$  Regression-based estimator

$$\hat{\theta}_{\text{Reg.T1}} = \left\{ \sum_{i=1}^n \frac{1}{1 - \hat{F}(Q_i|Z_i)} \right\}^{-1} \left[ \sum_{i=1}^n \frac{\nu(T_i)\{1 - \hat{F}(Q_i|Z_i)\} + \int_0^{Q_i} \nu(t)d\hat{F}(t|Z_i)}{1 - \hat{F}(Q_i|Z_i)} \right].$$

- ▶  $[\nu(T)\{1 - F(Q|Z)\} + \int_0^Q \nu(t)dF(t|Z)]$  identifies  $\mathbb{E}^* \{\nu(T)|Q, Z\}$ .

- Another regression based estimator is

$$\hat{\theta}_{\text{Reg.T2}} = \left[ \sum_{i=1}^n \frac{\hat{\mathbb{E}}^* \{\nu(T_i)|Z_i\}}{1 - \hat{F}(Q_i|Z_i)} \right] / \left\{ \sum_{i=1}^n \frac{1}{1 - \hat{F}(Q_i|Z_i)} \right\},$$

## Some norm notation

For a random function  $X(t, z)$  with  $t \in [\tau_1, \tau_2]$  and  $z \in \mathcal{Z}$ , define

$$\|X(\cdot, Z)\|_{\text{sup},2}^2 = \mathbb{E} \left\{ \sup_{t \in [\tau_1, \tau_2]} |X(t, Z)|^2 \right\},$$

$$\|X(\cdot, Z)\|_{\text{TV},2}^2 = \mathbb{E} [\text{TV}\{X(\cdot, Z)\}^2],$$

- $\text{TV}\{X(\cdot, z)\} = \sup_{\mathcal{P}} \sum_{j=1}^J |X(x_j, z) - X(x_{j-1}, z)|$  is the total variation of  $X(\cdot, z)$  on the interval  $[\tau_1, \tau_2]$
- $\mathcal{P}$  is the set of all possible partitions  $\tau_1 = x_0 < x_1 < \dots < x_J = \tau_2$  of  $[\tau_1, \tau_2]$

## Assumptions for $\hat{F}$ and $\hat{G}$ for $\hat{\theta}_{dr}$

- **Uniform convergence:** There exist  $F^*$  and  $G^*$  such that

$$\left\| \hat{F}(\cdot|Z) - F^*(\cdot|Z) \right\|_{\text{sup},2} = o(1), \quad \left\| \hat{G}(\cdot|Z) - G^*(\cdot|Z) \right\|_{\text{sup},2} = o(1).$$

- **Asymptotic linearity:**

$$\hat{F}(t|z) - F^*(t|z) = \frac{1}{n} \sum_{i=1}^n \xi_1(t, z, O_i) + R_1(t, z),$$

$$\hat{G}(t|z) - G^*(t|z) = \frac{1}{n} \sum_{i=1}^n \xi_2(t, z, O_i) + R_2(t, z).$$

where  $\|R_1(\cdot, Z)\|_{\text{sup},2} = o(n^{-1/2})$ ,  $\|R_2(\cdot, Z)\|_{\text{sup},2} = o(n^{-1/2})$ ,  
and either  $\|R_1(\cdot, Z)\|_{\text{TV},2} = o(1)$  or  $\|R_2(\cdot, Z)\|_{\text{TV},2} = o(1)$ .

- e.g., it is satisfied when Cox model is used to estimate  $F$  and  $G$ .

## Norm notation

Let  $\mathcal{O} = \{(Q_i, T_i, Z_i) : i = 1, \dots, m\}$  denote the data used to obtain  $\hat{F}$  and  $\hat{G}$ , and let  $\mathcal{O}_\dagger = (Q_\dagger, T_\dagger, Z_\dagger)$  be an copy of the data that is independent of, but from the same distribution as  $\mathcal{O}$ .

$$\|\hat{F} - F_0\|_{\dagger, \text{sup}, 2}^2 := \mathbb{E} \left( \mathbb{E}_{\dagger} \left[ \left\{ \sup_{t \in [\tau_1, \tau_2]} |\hat{F}(t|Z_\dagger) - F_0(t|Z_\dagger)| \right\}^2 \right] \right),$$
$$\|\hat{G} - G_0\|_{\dagger, \text{sup}, 2}^2 := \mathbb{E} \left( \mathbb{E}_{\dagger} \left[ \left\{ \sup_{t \in [\tau_1, \tau_2]} |\hat{G}(t|Z_\dagger) - G_0(t|Z_\dagger)| \right\}^2 \right] \right).$$

## Assumptions on $\hat{F}$ and $\hat{G}$ for $\hat{\theta}_{cf}$

- **Uniform Consistency:**

$$\|\hat{F} - F_0\|_{\dagger, \text{sup}, 2} = o(1), \quad \|\hat{G} - G_0\|_{\dagger, \text{sup}, 2} = o(1)$$

- **Product rate condition:**  $\mathcal{D}_{\dagger}(\hat{F}, \hat{G}; F_0, G_0) = o(n^{-1/2})$ .

## Simulation

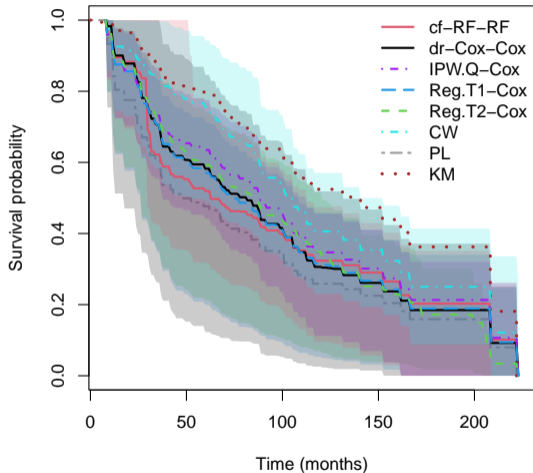
The models in red are misspecified.

SD: standard deviation, SE: standard error, CP: coverage probability.

Estimator	bias	SD	SE/boot SE	CP/boot CP
dr-Cox1-Cox1	-0.0016	0.021	0.020/0.020	0.948/0.946
dr-Cox1-Cox2	-0.0014	0.020	0.019/0.020	0.930/0.944
dr-Cox2-Cox1	-0.0010	0.020	0.019/0.020	0.938/0.946
dr-Cox2-Cox2	0.0184	0.019	0.018/0.019	0.838/0.836
cf-RF-RF	0.0032	0.021	0.023/0.025	0.966/0.976
IPW.Q-Cox1	-0.0004	0.020	0.018/0.020	0.924/0.944
IPW.Q-Cox2	0.0184	0.018	0.017/0.019	0.814/0.832
IPW.Q-RF	-0.0064	0.022	0.019/0.022	0.886/0.956
Reg.T1-Cox1	-0.0008	0.020	- /0.020	- /0.944
Reg.T1-Cox2	0.0183	0.018	- /0.019	- /0.842
Reg.T1-RF	-0.0073	0.022	- /0.022	- /0.934
Reg.T2-Cox1	-0.0010	0.020	- /0.020	- /0.942
Reg.T2-Cox2	0.0181	0.018	- /0.019	- /0.844
Reg.T2-RF	-0.0070	0.022	- /0.022	- /0.940
PL	0.0193	0.018	- /0.018	- /0.824
naive	0.1389	0.014	0.014/0.014	0.000/0.000
full data	-0.0007	0.013	0.013/0.013	0.956/0.944



## CNS lymphoma data



**Figure:** Estimates of the overall survival for the CNS lymphoma data with their 95% bootstrap confidence intervals.