Estimation of ATE (average treatment effect) in Causal Survival Analysis : Practical recommendations

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Introduction

- Causal survival inferences: mixed between causal inference vs survival analysis. It assesses the **causal effect** of a **treatment** on an outcome which is a **time until an event** occurs in the presence of **censoring**
- HR mainly used in survival analysis but not a causal measure and assumes proportional hazard.

Objectives:

- Comprehensive overview of the different estimators & Implementations
- Practical recommandation for users

Causal estimand

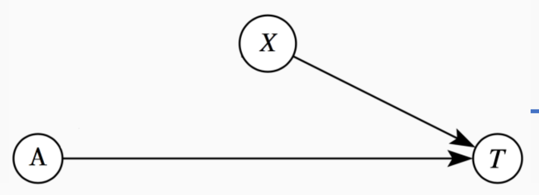
In grey, the observed data $(X_i, A_i, \Delta_i, \widetilde{T}_i)$ with $\widetilde{T}_i = \min(T_i, C_i)$

Covariates		Treatment	Censoring	Status	Outcomes		
X_1	X_2	A	C	Δ	T(0)	T(1)	$\widetilde{T}$
1	24	1	?	1	?	200	200
2	52	0	?	1	100	?	100
1	33	1	200	0	?	?	200

Difference in RMST: Average treatment effect in survival analysis

$$\theta_{RMST}(\tau) = E[\min(T(1),\tau) - \min(T(0),\tau)] = \int_0^\tau S_1(t) - S_0(t)\, dt$$

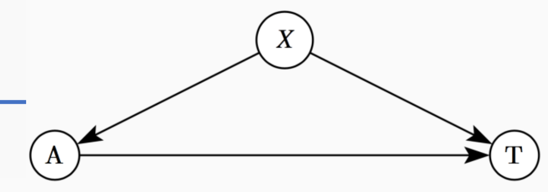
Identifiability assumptions & Estimators



RCT

S.T.U.V.A. $T = AT(1) + (1-A)T(0)$

Observational study



RCT & Independent censoring

- **Random treatment assignment** $A \perp\!\!\!\perp (T(0), T(1), C, X)$
- **Independent censoring** $C \perp\!\!\!\perp T(0), T(1), X, A$

Non-adjusted Kaplan-Meier estimator [1]

$$\hat{S}_{KM}(t|a) = \prod_{j=1, t_j \le t} 1 - \frac{\sum_i I\{\widetilde{T}_i = t_j, \Delta_i = 1, A_i = a\}}{\sum_k I\{\widetilde{T}_k \ge t_j, A_i = a\}}$$

RCT & Dependent censoring

- **Random treatment assignment** $A \perp\!\!\!\perp (T(0), T(1), C, X)$
- **Conditionally independent censoring** $C \perp\!\!\!\perp T(0), T(1) | X, A$
- **Positivity for censoring** $0 < P(C > t \mid X = x, A = a) < 1$

IPCW Kaplan-Meier estimator [2]

$$\hat{S}_{IPCW}(t|a) = \prod_{j=1, t_j \le t} 1 - \frac{\sum_i \widehat{w_i}(t_j, X_i).I\{\widetilde{T}_i = t_j, \Delta_i = 1, A_i = a\}}{\sum_k \widehat{w_k}(t_j, X_k).I\{\widetilde{T}_k \ge t_j, A_i = a\}}$$

with $\widehat{w}_i(t, X_i) = \frac{\Delta^{\tau}{}_i}{\widehat{S_c}(t|X_i, A_i)}$

- $\widehat{S_c}(t|X_i, A_i)$ is the survival function of remain uncensored given the covariate X in the treatment arm A=a.
- $\Delta^\tau = I\{T \wedge \tau < C | A = 1\}$ is the status of the individual truncated at τ.

Every uncensored observation is weighted by the inverse of the probability of remain uncensored given the covariates.

Observational & Independent censoring

- **Unconfoundedness** $A \perp\!\!\!\perp (T(0), T(1)) | X$
- **Positivity for treatment** $1 > P(A = a \mid X = x) > 0$
- **Independent censoring** $C \perp\!\!\!\perp T(0), T(1), X, A$

IPTW Kaplan-Meier estimator [3]

$$\hat{S}_{IPCW}(t|a) = \prod_{j=1, t_j \le t} 1 - \frac{\sum_i \widehat{w_i}(t_j, X_i).I\{\widetilde{T}_i = t_j, \Delta_i = 1, A_i = a\}}{\sum_k \widehat{w_k}(t_j, X_k).I\{\widetilde{T}_k \ge t_j, A_i = a\}}$$

with $\widehat{w}_i(t, X_i) = \frac{A_i}{\hat{e}(X_i)} + \frac{1-A_i}{1-\hat{e}(X_i)}$

Observational & Dependent censoring

- **Unconfoundedness** $A \perp\!\!\!\perp (T(0), T(1)) | X$
- **Positivity for treatment** $1 > P(A = a \mid X = x) > 0$
- **Conditionally independent censoring** $C \perp\!\!\!\perp T(0), T(1) | X, A$
- **Positivity for censoring** $0 < P(C > t \mid X = x, A = a) < 1$

IPTW-IPCW Kaplan-Meier estimator [4]

$\hat{S}_{IPTW-IPCW}$ corresponds to a weighted KM with $\widehat{w}_i(t, X_i) = \frac{\Delta^{\tau}{}_i}{\widehat{S_c}(t|X_i, A_i)}\left(\frac{A_i}{\hat{e}(X_i)} + \frac{1-A_i}{1-\hat{e}(X_i)}\right)$

G-formula plug-in estimator [5]

$$\hat{\theta}_{g-formula}(\tau) = \frac{1}{n}\sum_{1}^{n}[\hat{F}(X_i, A = 1) - \hat{F}(X_i, A = 0)]$$

with $\hat{F}(x, a) = E[T \wedge \tau | X = x, A = a]$

AIPTW-AIPCW estimator [6][7]

$\hat{\theta}_{AIPTW-AIPCW}$ is an **augmented** estimator of $\hat{\theta}_{IPTW-IPCW}$:

- 3 **nuisance models** to compute
- Consistent if at least one of nuisance parameter is consistent (**Double robust**)
- Parametric **convergence** rate

Methodology

Simulations of various scenario:

- Type of study: RCT or Observational study.
- Type of censoring: Independent or Dependent censoring.
- DGP: Parametric (well estimated by cox) and Non-parametric (well estimated by forest).

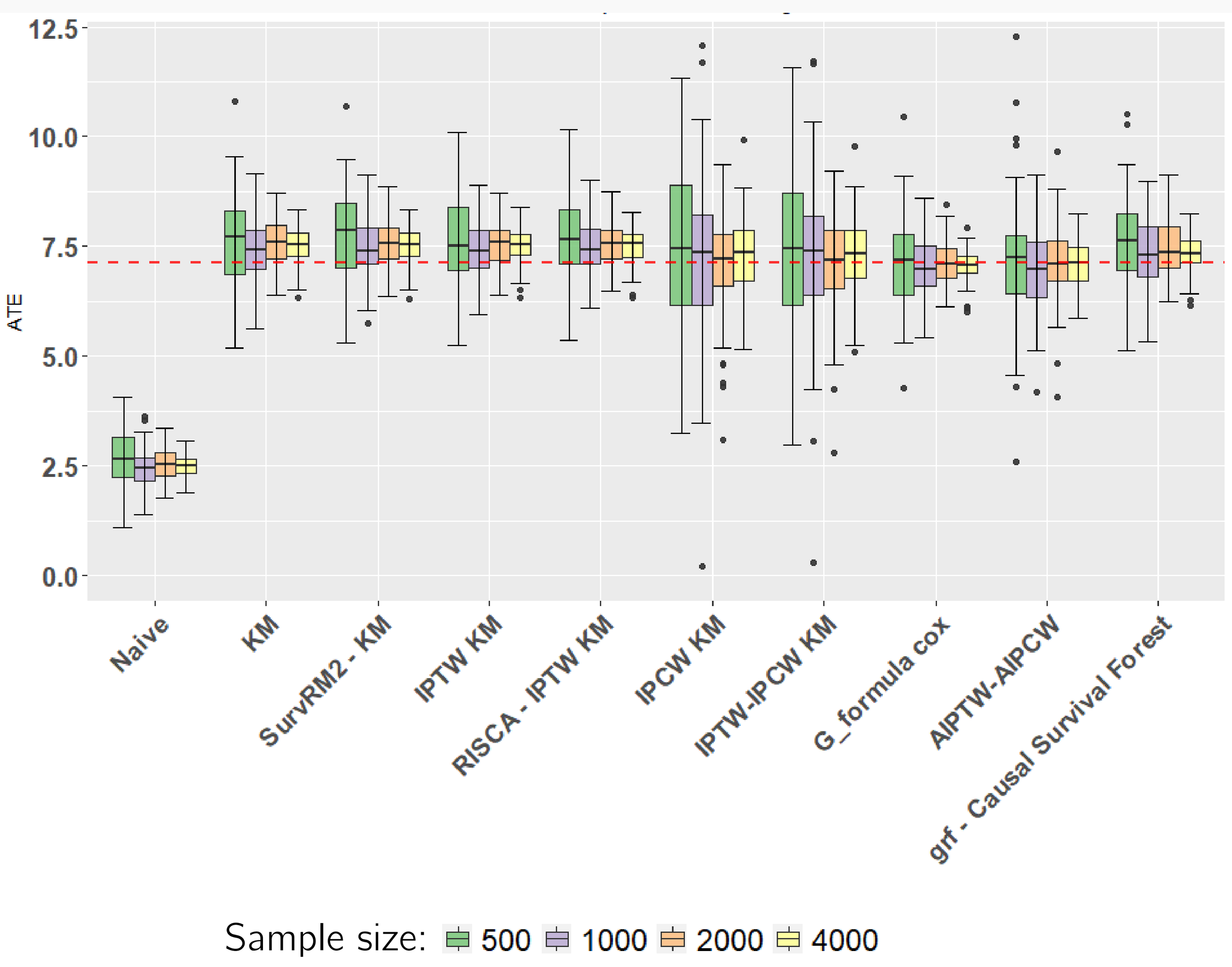
Evaluate and compare efficiency of:

- Self-implemented RMST estimators & Naive estimator $(E(\min(\widetilde{T}(1),\tau) - \min(\widetilde{T}(0),\tau))$.
- RMST Estimators from R-Packages:
  - IPTW Kaplan-Meier from RISCA.
  - Unadjusted Kaplan-Meier from SurvRM2.
  - Causal survival forest from grf.

Simulations results

Boxplot of RMST results from different estimators under well specified nuisance models (nuisance for propensity = « glm », conditional survival & conditional censoring =« cox », number of simulations = 150 and τ=25)

RCT & Dependent censoring: Parametric simulation



- **Biased:**

Naive,
Kaplan Meier (KM),
Rmst2() from SurvRM2,
IPTW Kaplan Meier,
ipw.survival() from RISCA,
Causal survival forest.

- **Unbiased:**

IPCW Kaplan Meier,
IPTW-IPCW Kaplan Meier,
🏆 G-formula,
AIPTW-AIPCW.

Boxplot of RMST results from different estimators under well specified nuisance models (nuisance for propensity = « probability forest », conditional survival & conditional censoring =« survival forest », number of simulations = 150, n.folds = 5, and τ=50)

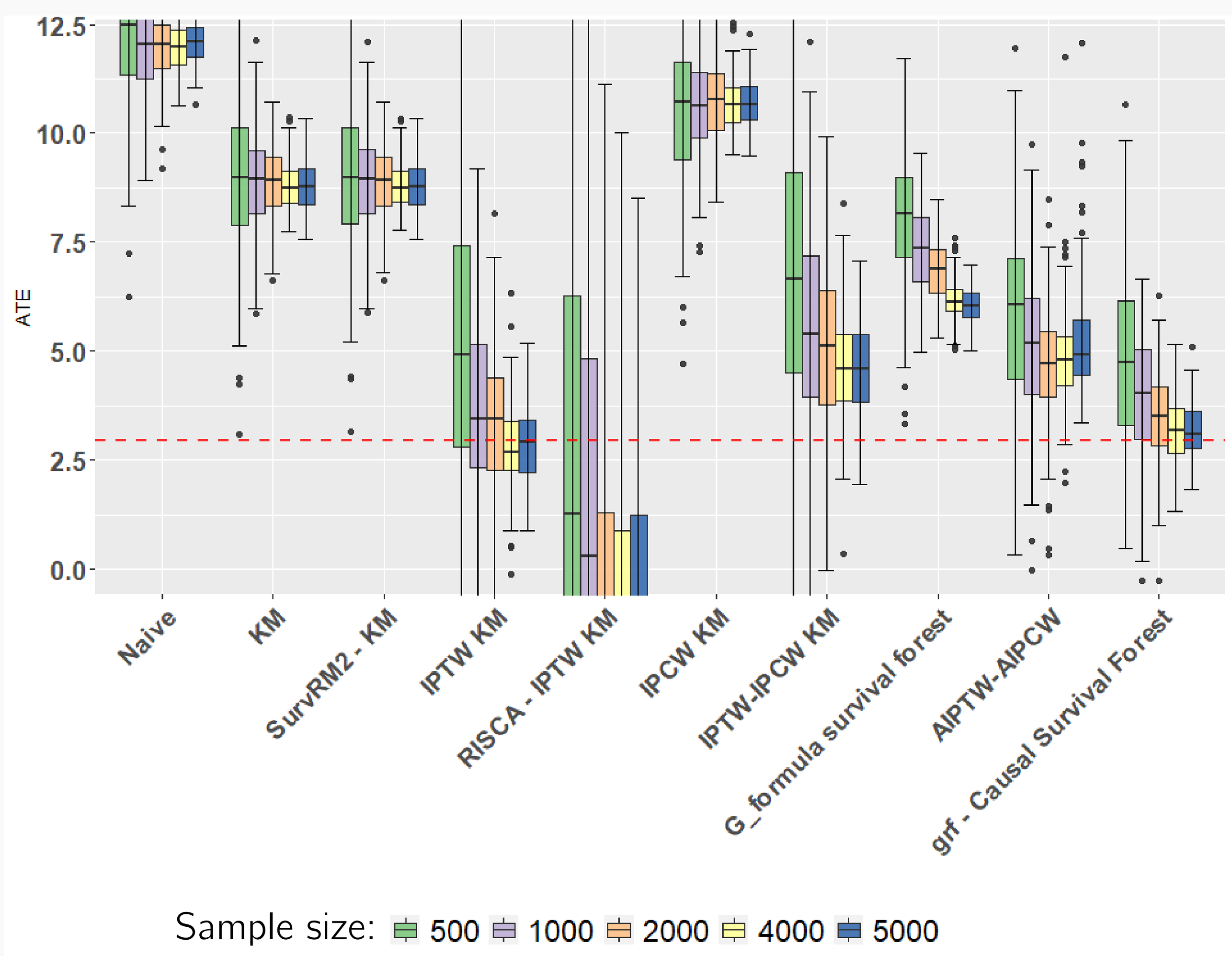
Observational & Dependent censoring: Non-parametric simulation

- **Biased:**

Naive,
Kaplan Meier (KM),
Rmst2() from SurvRM2,
ipw.survival() from RISCA,
IPCW Kaplan Meier,
IPTW-IPCW Kaplan Meier,
G-formula,
AIPTW-AIPCW.

- **Unbiased:**

IPTW Kaplan Meier
🏆 Causal survival forest.



Conclusions & Perspectives

- Few packages available (RISCA, SurvRM2, grf).
- **G-formula** has the **lowest variance** when conditional survival model is **well specified** in parametric simulation. In complex simulation, it converges slowly with survival forest (need a lot of observations).
- **Causal survival forest** is **accurate** for **complex** setting and large sample size and have nice theoretical properties.

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