

Robust and efficient estimation in the presence of a randomly censored covariate

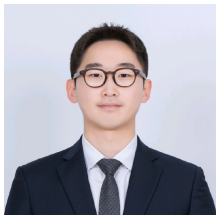
Brian Richardson

November 12, 2024



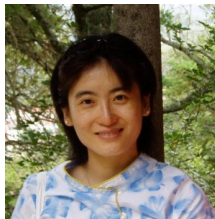
Acknowledgements

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Medical Center

Tanya Garcia, PhD



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Huntington's Disease



Huntington's Disease

Cause

Mutation: extra C-A-G repeats



10-26



27-35



36-39



40+



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Symptoms



Cognitive

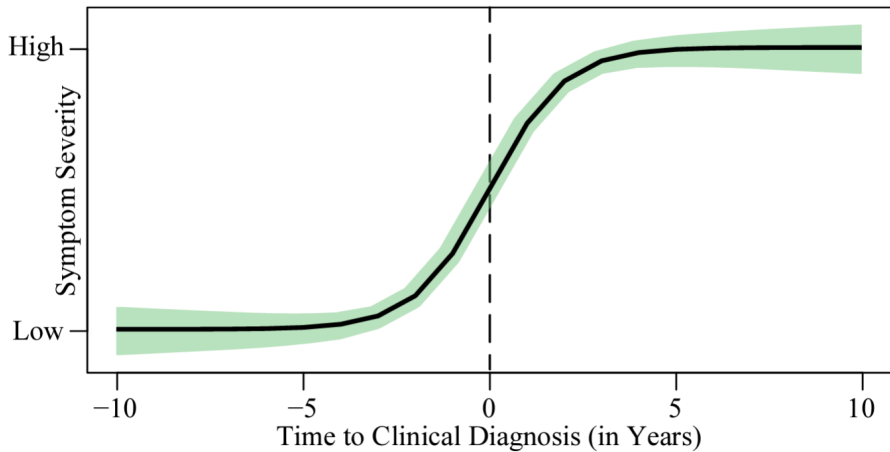


Motor



Functional

Huntington's Disease



(Lotspeich et. al., 2024)

Censoring in Huntington's Disease Studies

- **model:** $E(Y|X) = m(X, \beta)$

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“Humans are precious”

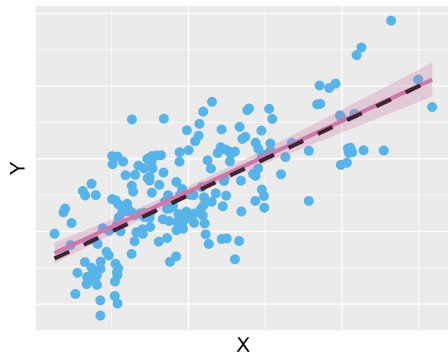
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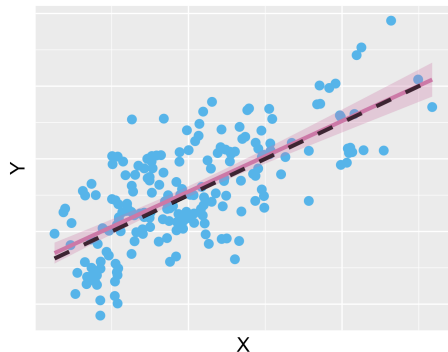
Want methods that are **robust** and **efficient**

Censored Covariates: a Simple Example



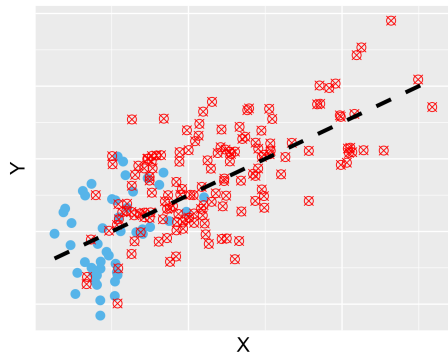
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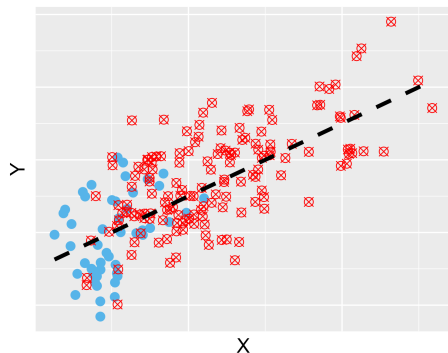
- Regression model: $E(Y|X) = \beta_0 + \beta_1 X$
- Estimate $\beta = (\beta_0, \beta_1)^T$ with least squares/maximum likelihood
- Solve estimating equation
$$\sum_{i=1}^n (Y_i - \beta_0 - \beta_1 X_i)(1, X_i)^T = \mathbf{0}$$

Censored Covariates: a Simple Example



Problem: X is censored by a **random censoring time C**

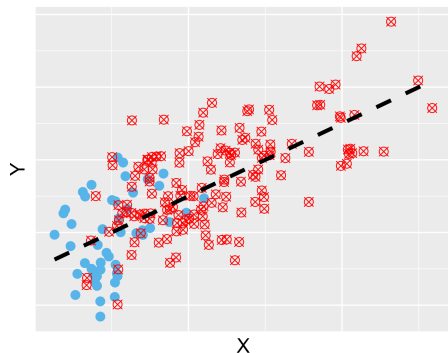
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Problem: X is censored by a **random censoring time** C

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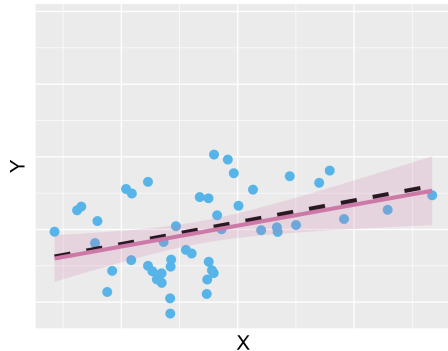
Censored Covariates: a Simple Example



Problem: X is censored by a **random censoring time** C

- $W = \min(X, C)$
- $\Delta = I(X \leq C)$
- assume: $C \perp\!\!\!\perp (X, Y)$

Complete Case Analysis

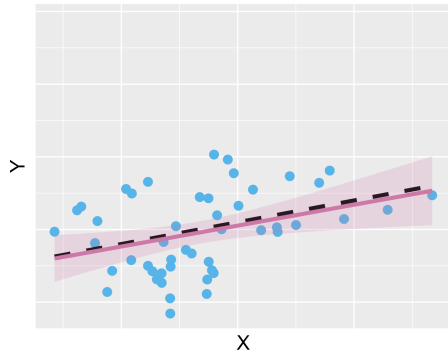


Only use *uncensored* observations

Solve estimating equation

$$\sum_{i=1}^n \Delta_i (Y_i - \beta_0 - \beta_1 W_i) (1, W_i)^T = \mathbf{0}$$

Complete Case Analysis



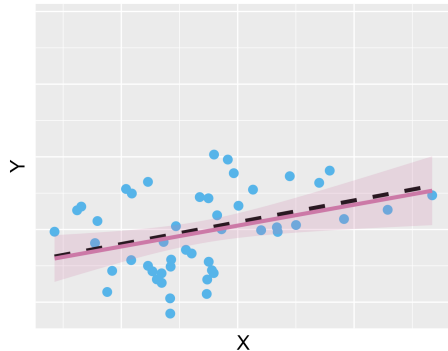
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Solve estimating equation

$$\sum_{i=1}^n \Delta_i (Y_i - \beta_0 - \beta_1 W_i) (1, W_i)^T = \mathbf{0}$$

✓ Consistent

Complete Case Analysis



Only use *uncensored* observations

Solve estimating equation

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✓ Consistent

✗ Inefficient

Maximum Likelihood Estimation (MLE)

$$f_{Y,W,\Delta}(y, w, \delta, \beta, \alpha) \propto \underbrace{\{f_{Y|X}(y, w, \beta)\}^\delta}_{\text{uncensored}} \underbrace{\left\{ \int_w^\infty f_{Y|X}(y, x, \beta) f_X(x, \alpha) dx \right\}^{1-\delta}}_{\text{censored}}$$

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$$\mathbf{S}_{\text{ML}}(y, w, \delta, \beta) \equiv \frac{\partial}{\partial \beta} \log f_{Y,W,\Delta}(y, w, \delta, \beta, \alpha), \quad \sum_{i=1}^n \mathbf{S}_{\text{ML}}(Y_i, W_i, \Delta_i, \beta) = \mathbf{0}$$

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- ✓ consistent
- ✓ fully efficient

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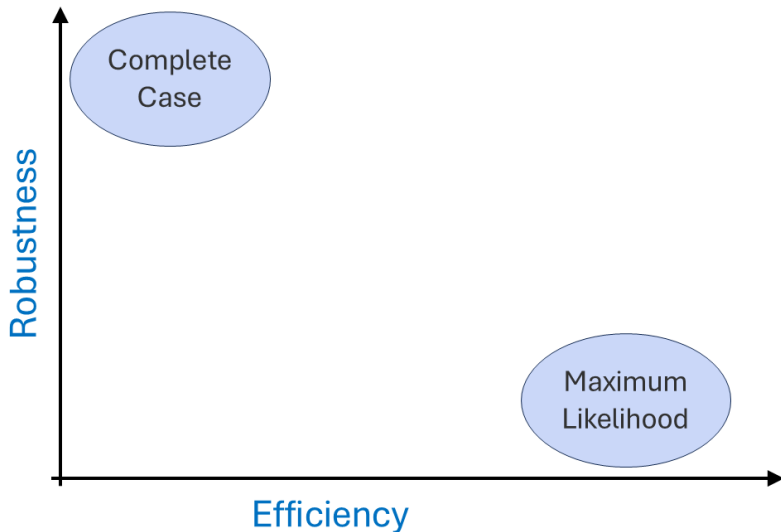
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✓ consistent

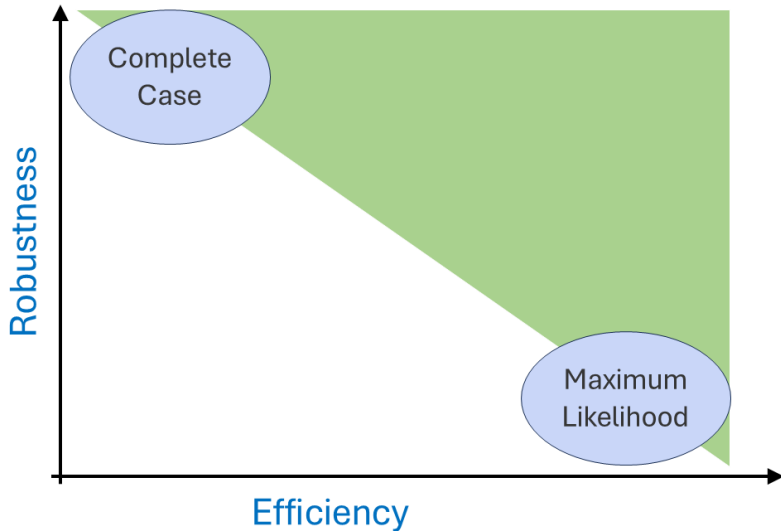
✓ fully efficient

✗ inconsistent when model for f_X is incorrect

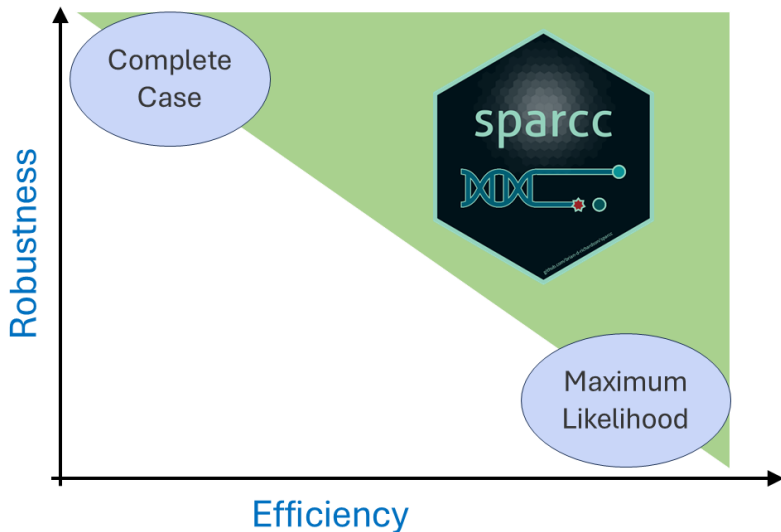
Existing Opportunity



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The Semiparametric Recipe

- **model:** $E(Y|X) = \beta_0 + \beta_1 X$

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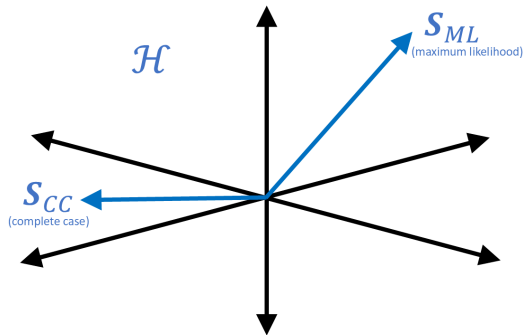
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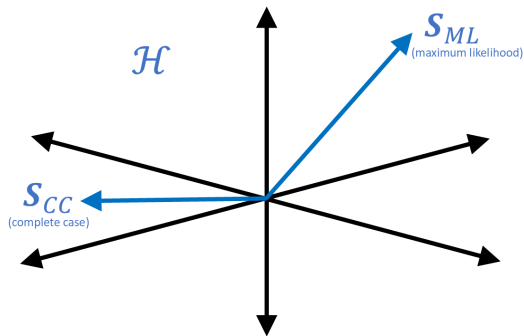
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- **goal:** derive the SPARCC estimator

The Semiparametric Recipe



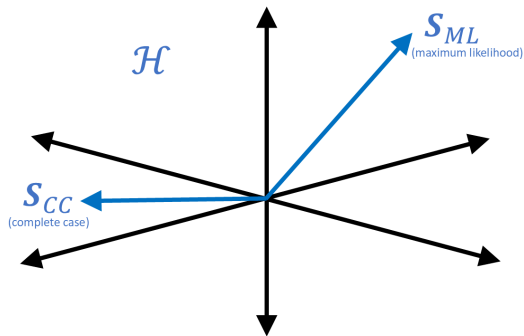
- **Hilbert space** of estimating functions

The Semiparametric Recipe



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- **covariance inner product**
 $\langle \mathbf{h}, \mathbf{g} \rangle \equiv \mathbb{E}(\mathbf{h}^T \mathbf{g})$

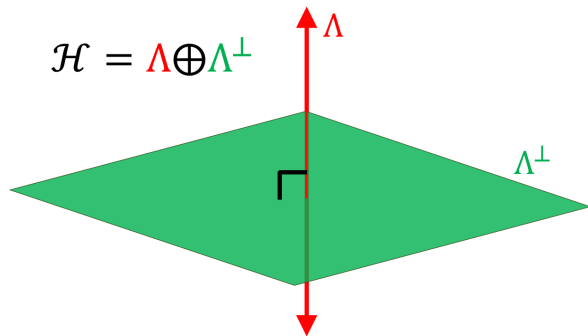
The Semiparametric Recipe



- **Hilbert space** of estimating functions
- **covariance inner product**
 $\langle h, g \rangle \equiv E(h^T g)$
- **orthogonal** \Leftrightarrow **uncorrelated**

$$h \perp g \iff \langle h, g \rangle = 0$$

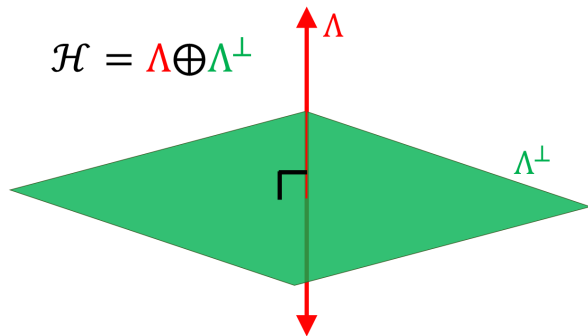
The Semiparametric Recipe



- construct Λ using **nuisance scores**

$$\partial \log f_{Y,W,\Delta}(y, w, \delta, \beta, \eta) / \partial \eta$$

The Semiparametric Recipe

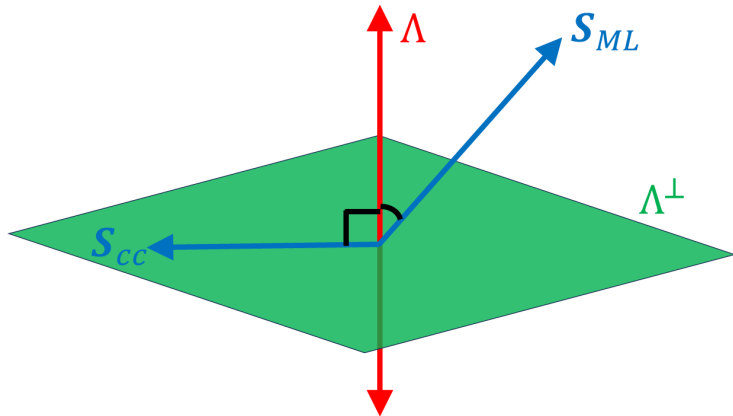


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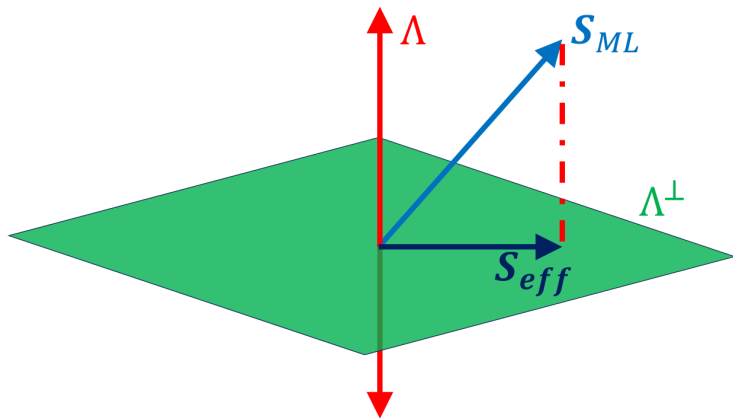
$$\partial \log f_{Y,W,\Delta}(y, w, \delta, \beta, \eta) / \partial \eta$$

- orthogonal complement Λ^\perp

The Semiparametric Recipe



The Semiparametric Recipe



Implementing the SPARCC Estimator

The **SPARCC Estimator** $\hat{\beta}$ is the solution to

$$\sum_{i=1}^n \mathbf{s}_{\text{eff}}(Y_i, W_i, \Delta_i, \beta) = \mathbf{0}$$

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Can be modeled either **parametrically** or **nonparametrically**

Properties of the SPARCC Estimator

With **parametric** $f_X, f_C, \hat{\beta}$ is:

- ✓ **doubly robust**: consistent if one of f_X, f_C is correctly specified

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With **nonparametric** $f_X, f_C, \hat{\beta}$ is:

- ✓ **consistent**
- ✓ **semiparametric efficient**

Simulation Setup

$$\underbrace{Y}_{\text{outcome}} \mid X, Z \sim N(\beta_0 + \beta_1 X + \beta_2 Z, \sigma^2)$$

Simulation Setup

$$Y \mid \underbrace{X}_{\text{censored}}, Z \sim N(\beta_0 + \beta_1 X + \beta_2 Z, \sigma^2)$$

Simulation Setup

$$Y|X, \underbrace{Z}_{\text{uncensored}} \sim N(\beta_0 + \beta_1 X + \beta_2 Z, \sigma^2)$$

Simulation Setup

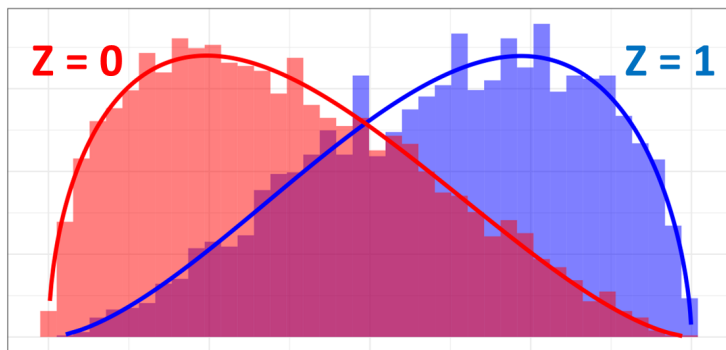
$$Y|X, Z \sim N(\underbrace{\beta_0 + \beta_1 X + \beta_2 Z}_{\text{parameter of interest: } (\beta_0, \beta_1, \beta_2, \sigma^2)}, \sigma^2)$$

Simulation Setup: Nuisance Distributions

$$\boldsymbol{\eta} = (f_{X|Z}, f_{C|Z})$$

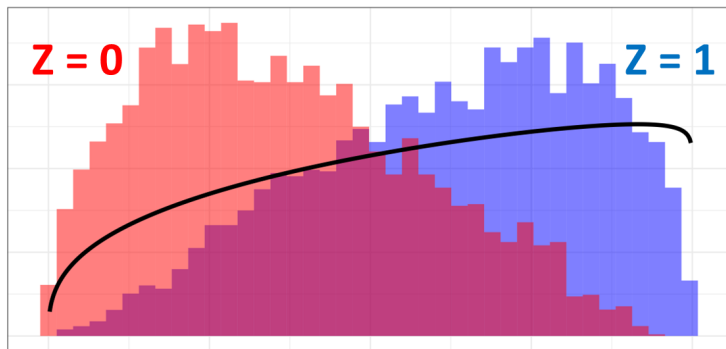
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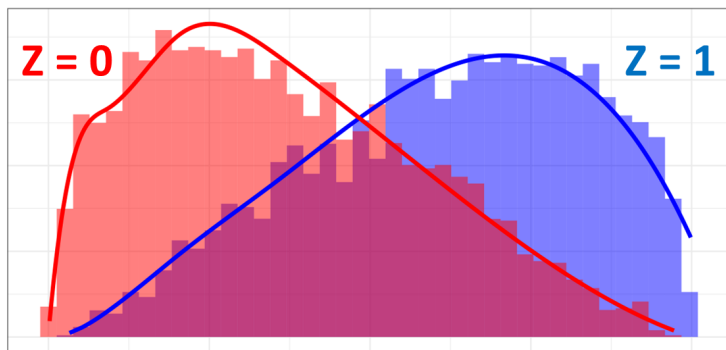
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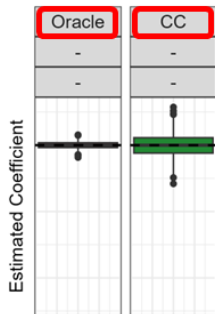


Simulation Setup: Nuisance Distributions

$f_{X|Z}$ nonparametric:

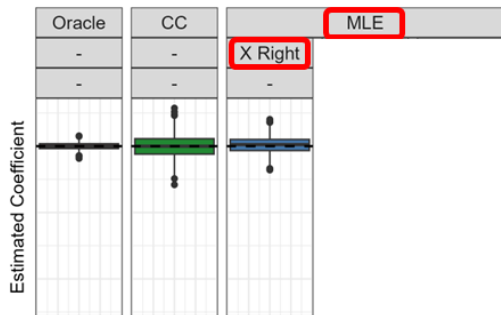


Simulation Results: Robustness



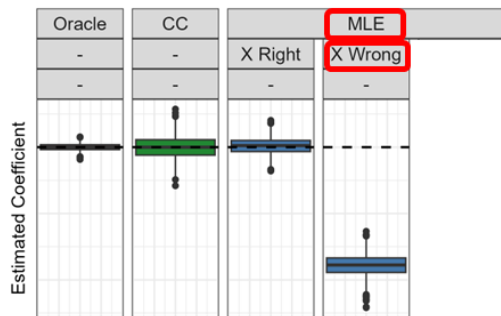
(censoring proportion $q = 0.8$)

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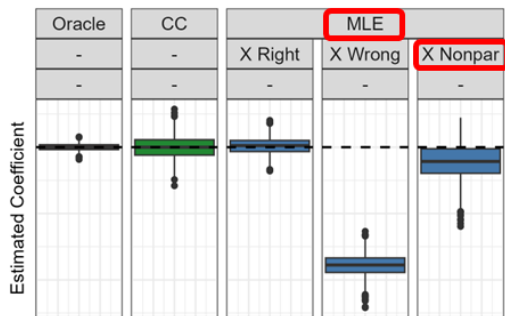
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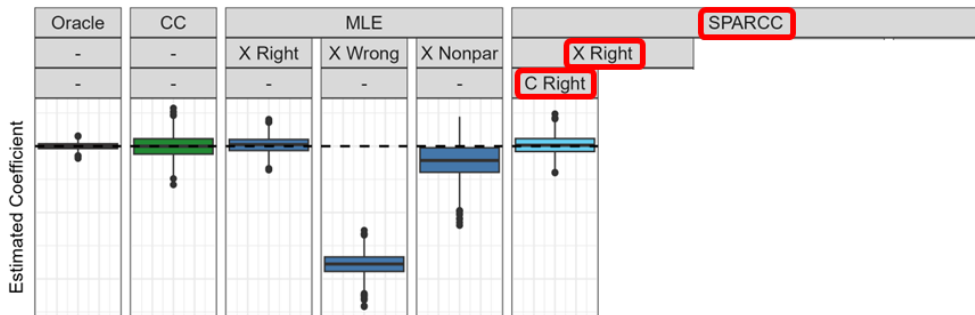
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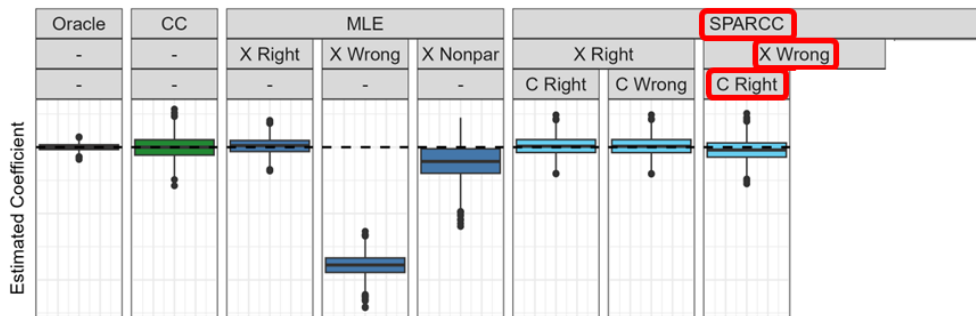
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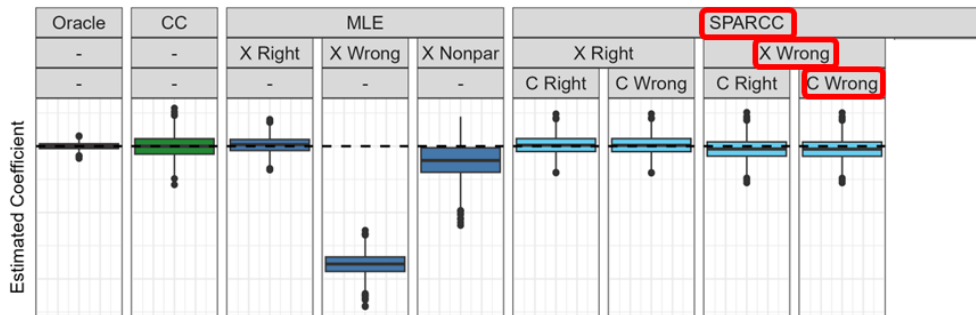
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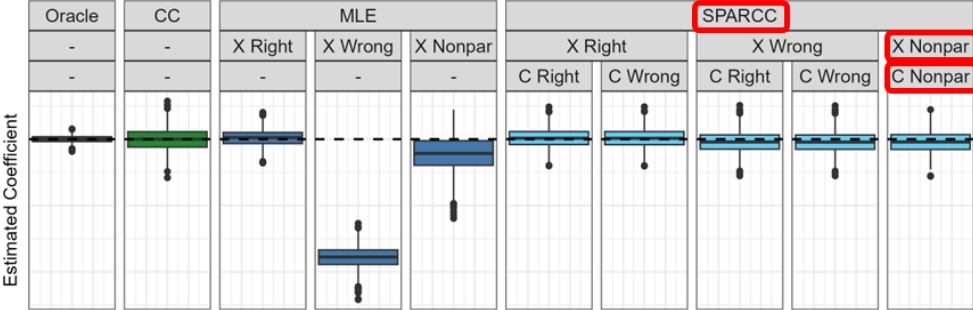
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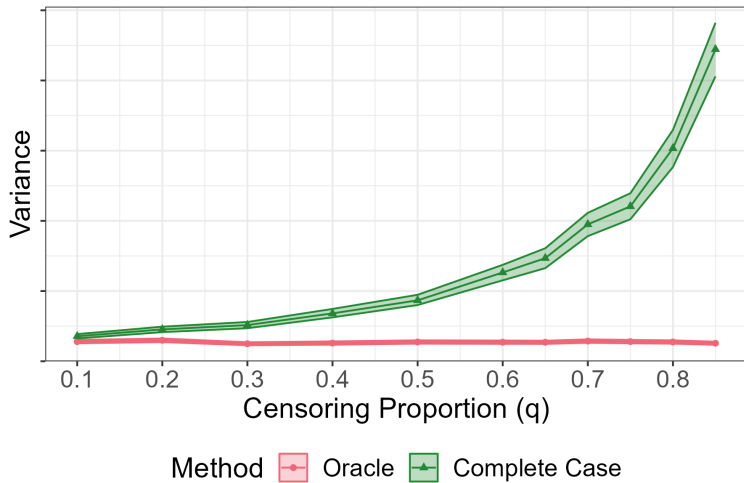
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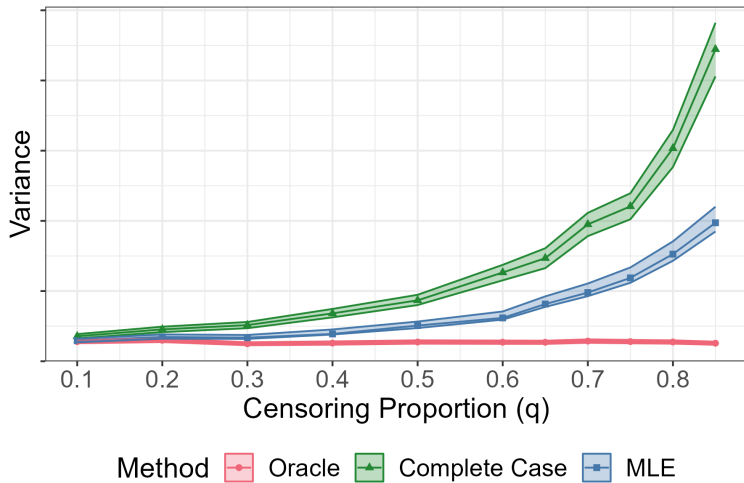


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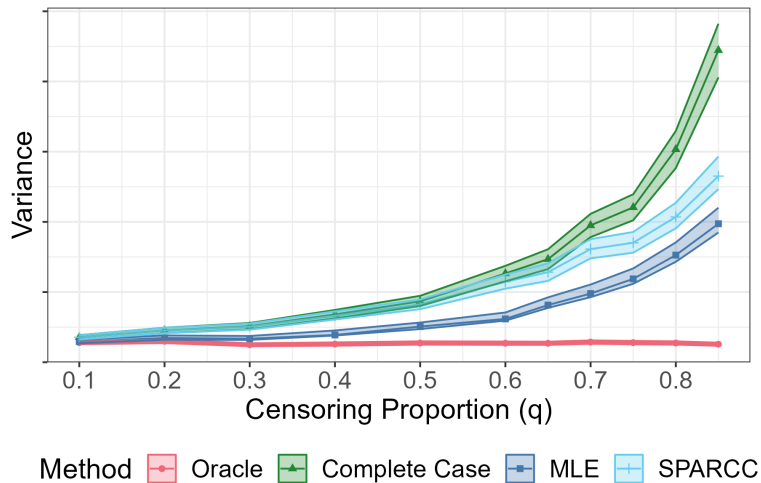
Simulation Results: Efficiency



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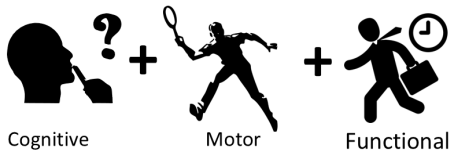


ENROLL-HD Study

- large, observational study of people with Huntington's disease or mutation

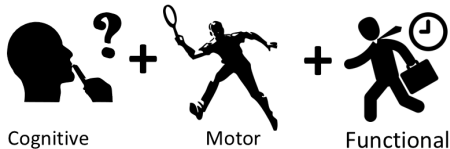
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- **composite Unified Huntington Disease Rating Scale (cUHDRS) score**



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- **CAP** Score: product of age and mutation severity

Huntington's Disease Application

$$\underbrace{Y}_{\text{cUHRS}} \mid X, Z \sim N(\beta_0 + \beta_1 X + \beta_2 Z, \sigma^2)$$

Huntington's Disease Application

$$Y | \underbrace{X}_{\text{time to diagnosis}}, Z \sim N(\beta_0 + \beta_1 X + \beta_2 Z, \sigma^2)$$

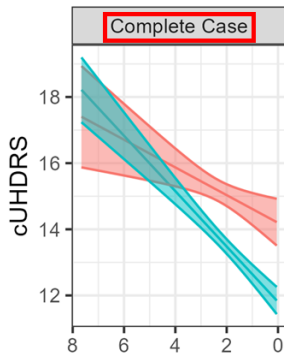
Huntington's Disease Application

$$Y|X, \underbrace{Z}_{\text{CAP group}} \sim N(\beta_0 + \beta_1 X + \beta_2 Z, \sigma^2)$$

- **sample size:** $n = 4530$
- **censoring rate:** $q = 81.9\%$

Huntington's Disease Results

Estimated Mean cUHDRS (and 95% Confidence Intervals)

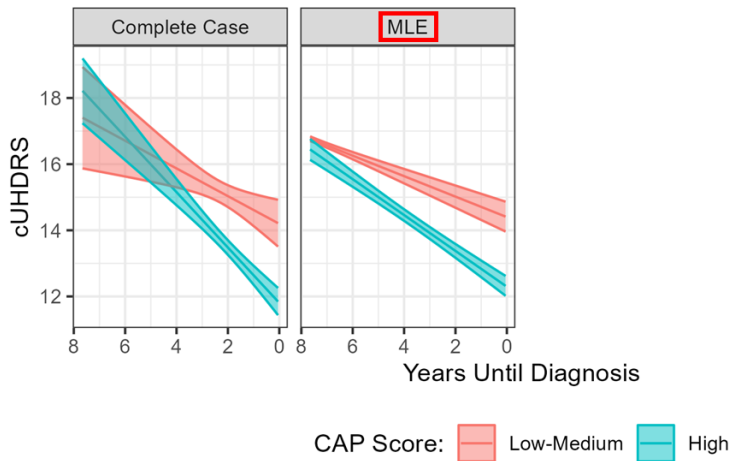


Years Until Diagnosis

CAP Score: ■ Low-Medium ■ High

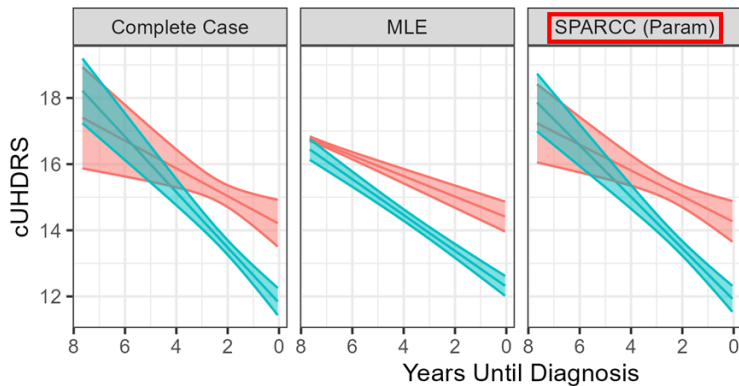
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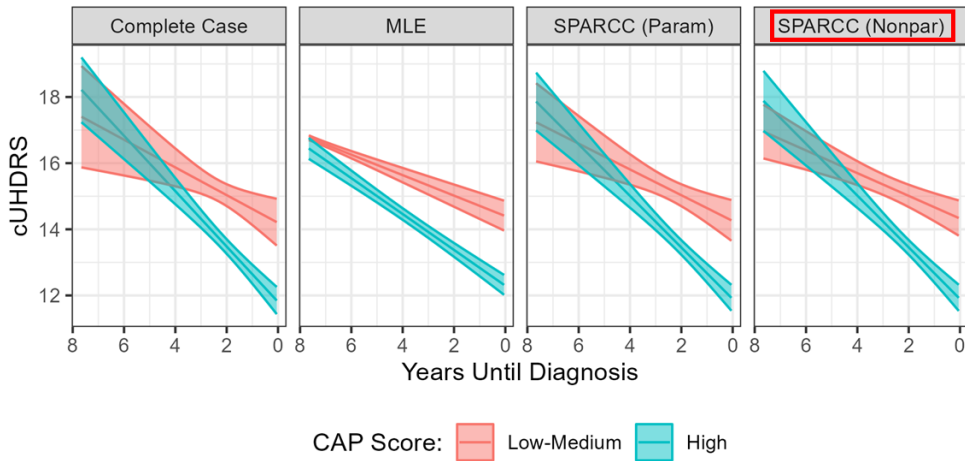
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Discussion

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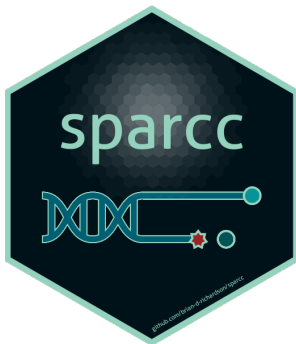
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- longitudinal extension

SPARCC: Semiparametric Censored Covariate Estimation



Paper on arXiv



GitHub R package