A Single Index Model for Longitudinal Outcomes to Optimize Individual Treatment Decision Rules

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August 3, 2020

JSM 2020

Introduction

Precision Medicine: Identify the Treatment Decision Rule (TDR) with patient's baseline information.

- Baseline measures: $\boldsymbol{x} = (x_1, ..., x_p)'$
- A function D that assigns a treatment decision to a patient based on $\boldsymbol{x} = (x_1, ..., x_p)'$

$$D : \boldsymbol{x} \rightarrow T$$

- A treatment decision:
  - $T = 1$ for treatment 1
  - $T = 2$ for treatment 2

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Single index model

Generated Effect Modifier (GEM) model
Petkova et al (2016, *Biostatistics*)

$$GEM = w = \alpha' \boldsymbol{x} = \alpha_1 x_1 + \cdots + \alpha_p x_p$$

GEM model ($k = 2$):

$$\begin{cases} y_1 = \gamma_{01} + \gamma_{11} GEM + \epsilon_1 & \text{(Treatment 1)} \\ y_2 = \gamma_{02} + \gamma_{21} GEM + \epsilon_2 & \text{(Treatment 2)} \end{cases}$$

- Choose α that maximizes the statistical significance of modifying or interaction effect

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Single index model with multiple links (SIMML) model
Park et al (2019, *JSPI*)
Model:

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where g_k is a nonlinear link function for treatment k.

- Non linear link function
- Flexible methods for determining composite variables

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Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC)

- A multi-site, placebo-controlled randomized clinical trial (RCT)
- Two treatment arms: Anti-depression ("*drug*") and placebo
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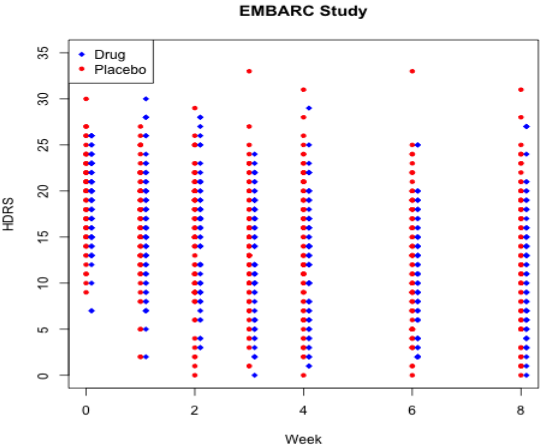

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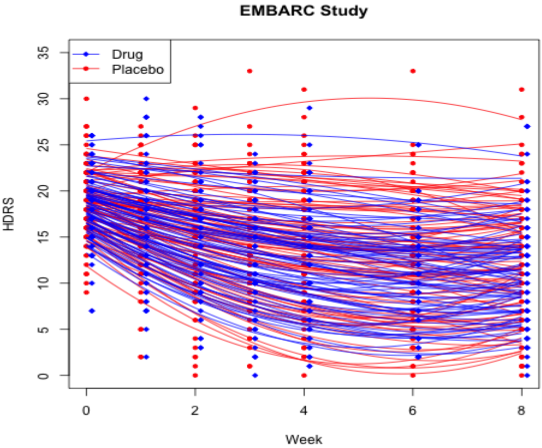

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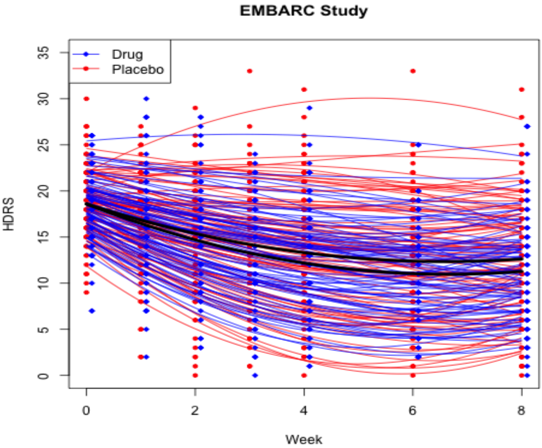

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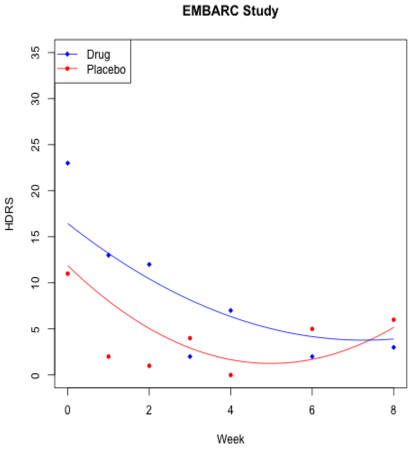

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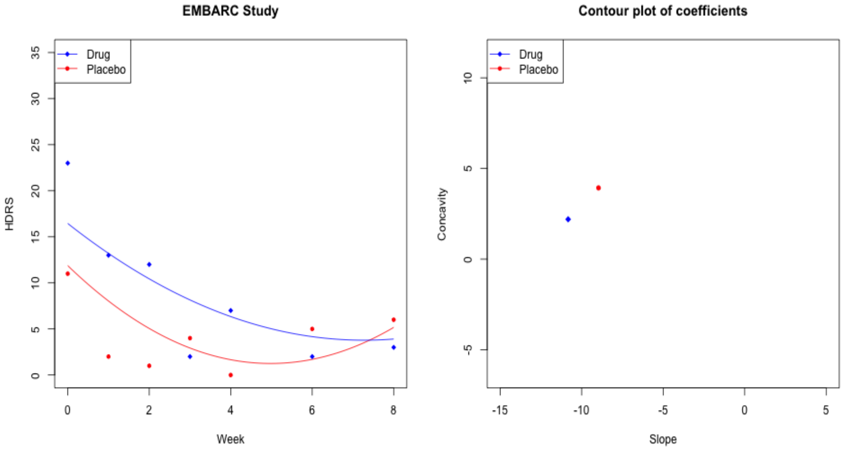

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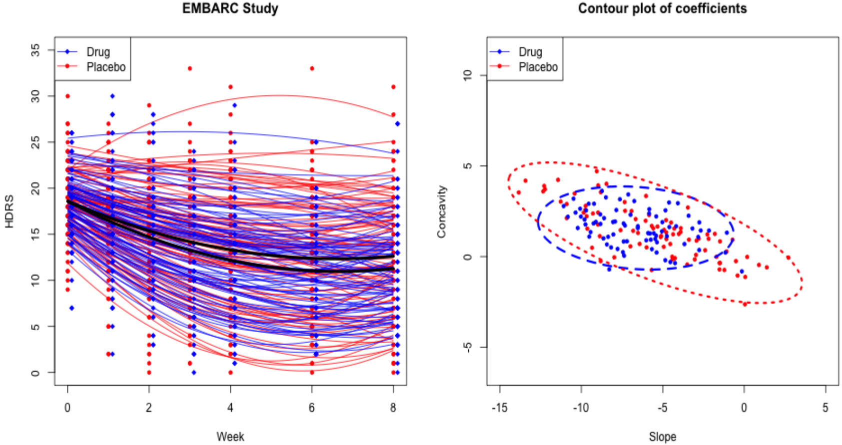

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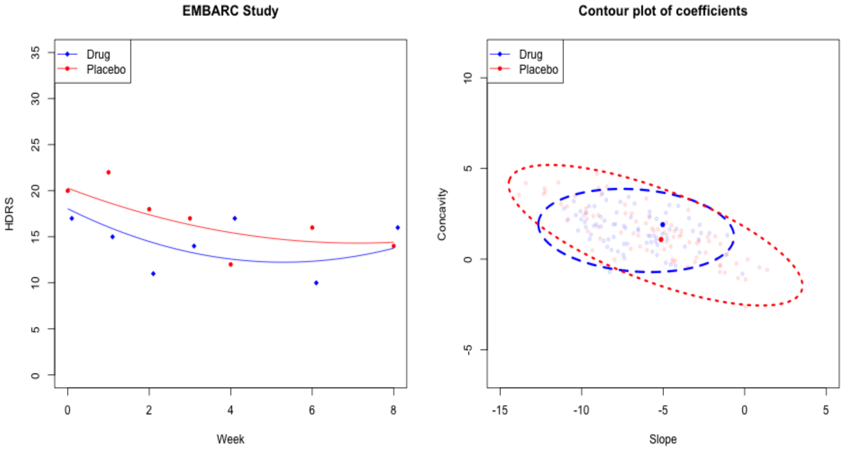

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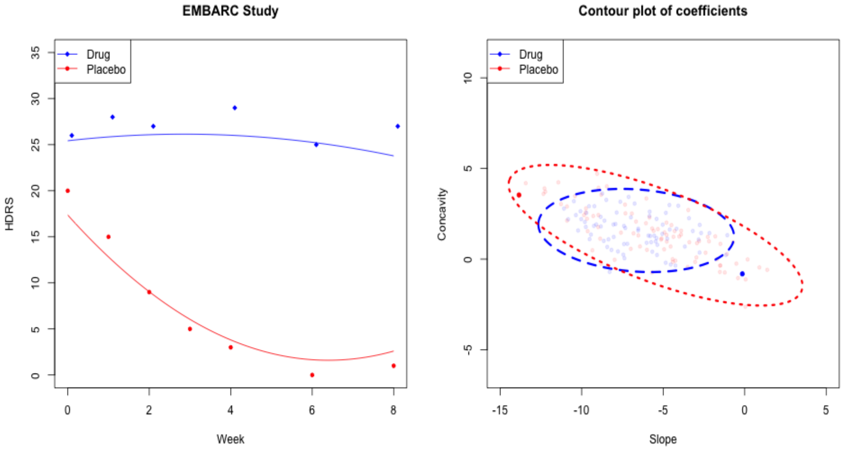
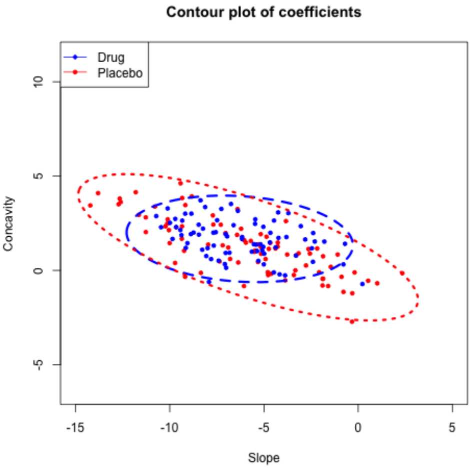


Purity


Contour plot of coefficients
Drug
Placebo
Concavity
Slope
10
5
0
-5
-15
-10
-5
0
5

Single Index Model for Longitudinal Outcomes

Linear mixed effect model for longitudinal data:

$$\boldsymbol{y_{ki}} = \boldsymbol{S_i}\boldsymbol{\beta_k} + \boldsymbol{S}_i\boldsymbol{b}_{ki} + \boldsymbol{\epsilon_{ki}} \tag{1}$$

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Single index model for longitudinal data:

$$\boldsymbol{y_{ki}} = \boldsymbol{S_i}(\beta_{\boldsymbol{k}} + \Gamma_{\boldsymbol{k}}(\alpha' \boldsymbol{x_i})) + \boldsymbol{S}_{ki}\boldsymbol{b}_{ki} + \epsilon_{\boldsymbol{ki}} \qquad (2)$$

- $\boldsymbol{S}_i$ is the design matrix, $S_{ki} = \begin{pmatrix} 1 & t_1 & t_1^2 \\ \vdots & \vdots & \vdots \\ 1 & t_{n_t} & t_{n_t}^2 \end{pmatrix}_{n_t \times t}$;
- β_k is the fixed effect coefficients
- Γ_k is the fixed effect coefficients
- Biosignature: $w_i = \alpha' \boldsymbol{x}_i$
- $\boldsymbol{b}_{ki} \sim MVN(0, \boldsymbol{D}_k)$
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Single Index Model for Longitudinal Outcomes

Goal: Estimate a linear biosignature using baseline measures that optimally separates outcomes from the two treatment groups

$$\boldsymbol{y}_{ki} = \boldsymbol{S}_i\left(\beta_k + \Gamma_k(\alpha'\boldsymbol{x}_i) + \boldsymbol{b}_{ki}\right) + \epsilon_{\boldsymbol{ki}}$$

Coefficients:

$$\boldsymbol{z}_{ki} = \beta_k + \Gamma_k(\alpha'\boldsymbol{x}_i) + \boldsymbol{b}_{ki}$$

Distributions of coefficients:

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Treatment 2:

$$\boldsymbol{z}_{2i} | \boldsymbol{x}_i \sim MVN(\beta_2 + \Gamma_2(\alpha' \boldsymbol{x}_i), \boldsymbol{D}_2)$$

The distributions can "move" apart in directions Γ_k as $\boldsymbol{w}_i = \alpha' x_i$ varies.

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Kullback-Leibler divergence

KL divergence

$$D_{KL}(F_1||F_2) = \int_{-\infty}^{+\infty} f_1(x)\log(\frac{f_1(x)}{f_2(x)})dx$$

where f_1 and f_2 denote the probability density of F_1 and F_2.

It has properties:

- The Non-negative;
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Purity

Individual Purity

$$g(\alpha'\boldsymbol{x}) = D_{KL}(F_1||F_2)(\alpha'\boldsymbol{x}) + D_{KL}(F_2||F_1)(\alpha'\boldsymbol{x}) \qquad (3)$$

Dataset Purity

$$G(\alpha) = E(g(\alpha'\boldsymbol{x})) = A_0 + A_1\mu_x'\alpha + A_2\alpha'(\Sigma_x + \mu_x\mu_x')\alpha \qquad (4)$$

where

- $A_0 = -q + \frac{1}{2}tr(\boldsymbol{D}_2^{-1}\boldsymbol{D}_1) + \frac{1}{2}tr(\boldsymbol{D}_1^{-1}\boldsymbol{D}_2) + \frac{1}{2}(\beta_1 - \beta_2)'(\boldsymbol{D}_1^{-1} + \boldsymbol{D}_2^{-1})(\beta_1 - \beta_2)$
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Algorithm

- 0: Initial an $\boldsymbol{\alpha}$
- 1: Fit the longitudinal single index models

$$\boldsymbol{Y}_{ki} = \boldsymbol{S}_i(\beta_k + \boldsymbol{b}_k + \Gamma_k(\boldsymbol{\alpha}'\boldsymbol{x}_i)) + \epsilon_{ki}, k = \{1, 2\}$$

- 2: Estimate $\hat{\beta}_1, \hat{\beta}_2, \hat{\Gamma}_1, \hat{\Gamma}_2, \hat{\boldsymbol{D}}_1, \hat{\boldsymbol{D}}_2$
- 3: Calculate purity based on the function

$$G(\boldsymbol{\alpha}) = \hat{A}_0 + \hat{A}_1\hat{\boldsymbol{\mu}}_x'\boldsymbol{\alpha} + \hat{A}_2\boldsymbol{\alpha}'(\hat{\boldsymbol{\Sigma}}_x + \hat{\boldsymbol{\mu}}_x\hat{\boldsymbol{\mu}}_x')\boldsymbol{\alpha}$$

- 4: Obtain $\hat{\boldsymbol{\alpha}}^*$ that maximizes the purity function

$$\hat{\boldsymbol{\alpha}}^* = \arg\max_{\boldsymbol{\alpha}} G(\boldsymbol{\alpha})$$

- 5: Fit LME and calculate $\hat{\beta}_1^*, \hat{\beta}_2^*, \hat{\Gamma}_1^*, \hat{\Gamma}_2^*, \hat{\boldsymbol{D}}_1^*, \hat{\boldsymbol{D}}_2^*$ for treatment decision rule calculation.

Simulation

Outcome generation function

$$\boldsymbol{y_{ki}} = \boldsymbol{S_i}(\beta_{\boldsymbol{k}} + \Gamma_{\boldsymbol{k}}(\alpha'\boldsymbol{x_i})) + \boldsymbol{S}_i\boldsymbol{b}_{ki} + \epsilon_{\boldsymbol{ki}}$$

- Treatment group: $k = 2$;
- Number of subjects in group k: $n_k = 100$; $N = \sum_k n_k$
- Design matrix: $S_i = \begin{bmatrix} \mathbf{1} & \boldsymbol{t} & \boldsymbol{t}^2 \end{bmatrix}, t = (0, 1, 2, 3, 4, 6, 8)'$
- Fixed effect: $\beta_1 = \begin{pmatrix} 0 & 1 & 0.1 \end{pmatrix}', \beta_2 = \begin{pmatrix} 0 & 0.9 & 0.1 \end{pmatrix}'$
- Random effect: $\boldsymbol{b}_{ki} \sim MVN(0, D_k)$
- $\boldsymbol{D}_1 = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 2 \end{pmatrix}, \boldsymbol{D}_2 = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0.5 \\ 0 & 0.5 & 1 \end{pmatrix}$

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- $\Gamma_1 = \begin{pmatrix} 0 & 1 & 0 \end{pmatrix}', \Gamma_2 = \begin{pmatrix} 0 & \cos(\theta) & \sin(\theta) \end{pmatrix}'$;
- $\theta : \{0°, 60°, 120°, 180°\}$
- Covariates: $\boldsymbol{x}_i \sim MVN(0, \Sigma_x)$
- Σ_x: equal correlation matrix, correlation $= 0.5$
- Dimension of predictors: $p = 2, 4, 8, 16$
- Random error: $\sigma_k = 1, 2, 10$
- Simulated 1000 data sets

Simulation

Outcome generation function

$$\boldsymbol{y_{ki}} = \boldsymbol{S_i}(\beta_{\boldsymbol{k}} + \Gamma_{\boldsymbol{k}}(\alpha' \boldsymbol{x_i})) + \boldsymbol{S}_i \boldsymbol{b}_{ki} + \epsilon_{\boldsymbol{ki}}$$

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Proportion of correct decision (PCD)

Average change scores:

$$U_{ki} = \frac{Y_{ki}(t=8) - Y_{ki}(t=0)}{8-0}$$

Treatment decision rule (TDR):

$$D(\alpha' x_i) = I(U_{1i} > U_{2i}) + 1 = \begin{cases} 1 & \text{Treatment 1} \\ 2 & \text{Treatment 2} \end{cases}$$

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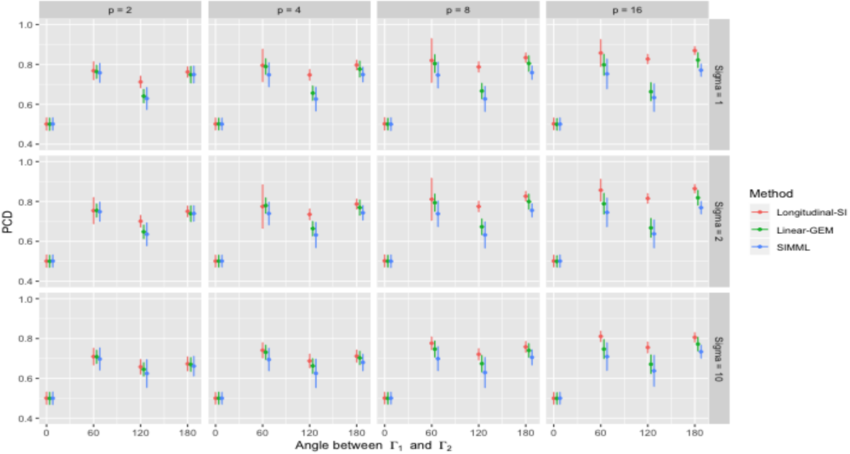
Simulation

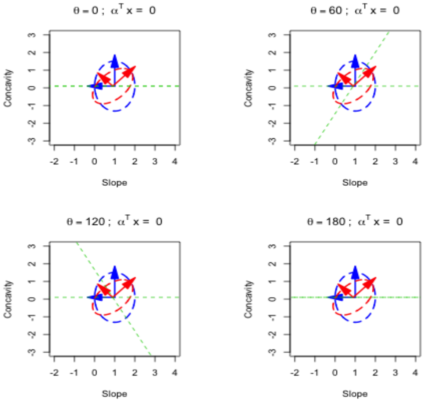
Approaches:

- Longitudinal single index model (Longitudinal-SI)
- Linear generated effect modifier model (Linear-GEM)
- Single index model with multiple links model (SIMML)

Simulation: Proportion of correct decision (PCD)



Simulation: Contour plots



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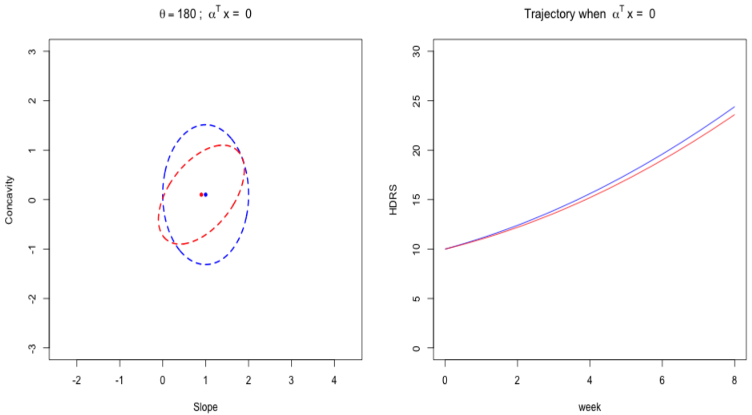

EMBARC

Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC)

- 58 subjects in placebo group, 45 subjects in treatment group
- Covariates: Demographics, Behavior measure, Cortical thickness
- 13 covariates were selected by stepwise selection.

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- Average change scores:

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- Performance measure: The "value" (V) of treatment decision rule D:

$$V(D) = E_{\mathbf{x}}(E_{U|\mathbf{x}}(U|\mathbf{x}, T = D(\alpha'\mathbf{x}))$$

- Estimation: Inverse Probability Weighted Estimator (IPWE)

$$\widehat{V(D)} = \sum_{i=1}^{n_1+n_2} U_i I(T_i = D(\widehat{\alpha}' x_i)) / \sum_{i=1}^{n_1+n_2} I(T_i = D(\widehat{\alpha}' x_i))$$

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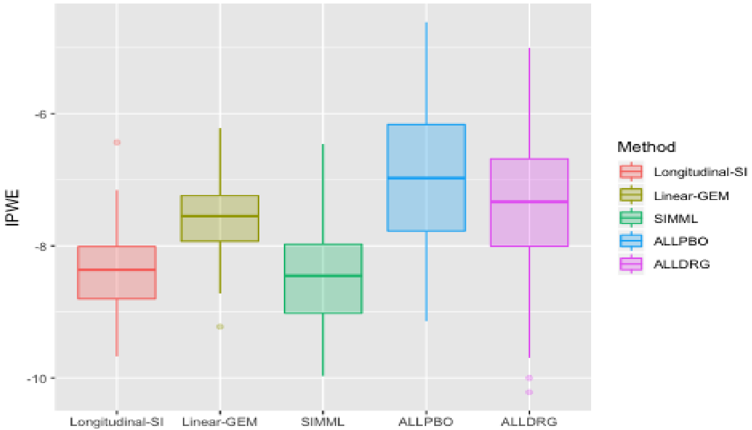
Estimated value of treatment decision rules



Discussion

- **Longitudinal Single Index model**: Combine baseline characteristics into a single index in the context of linear mixed effect model
- **Simulation**: Good estimation of Proportion of correction decision (PCD) in simulation study
- **EMBARC** Similar performance as SIMML, less variance.
- **Future work**: Variable selection, Hypothesis test,...

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Thank You!

Questions&Comments

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