

Nonparametric Inference on Dose-Response Curves Without the Positivity Condition

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Introduction



Central Problem in Causal Inference:

Study the causal effect of a treatment $T \in \mathcal{T}$ on a outcome $Y \in \mathcal{Y}$.

¹Note that $Y(t)$ is the potential outcome that would have been observed under treatment level $T = t$.

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- $\mathbb{E}[Y(t)] = \text{mean counterfactual outcome}^1$ when we set $T = t$.
- $\mathbb{E}[Y(1)] - \mathbb{E}[Y(0)] = \text{average treatment effect}$.

► **Question:** What are the counterparts of the above estimands under *continuous* treatment (i.e., $\mathcal{T} \subset \mathbb{R}$)?

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- $t \mapsto m(t) := \mathbb{E}[Y(t)] = \text{(causal) dose-response curve}$.
- $t \mapsto \theta(t) := m'(t) = \frac{d}{dt}\mathbb{E}[Y(t)] = \text{(causal) derivative effect}$.

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Identification of a Causal Dose-Response Curve

Without confounding, $m(t) = \mathbb{E}[Y(t)] = \mathbb{E}(Y|T = t)$.

- Fitting $m(t)$ is to regress $\{Y_i\}_{i=1}^n$ with respect to $\{T_i\}_{i=1}^n$.
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However, confounding variables often exist in practice. Specifically, $\{(Y_i, T_i, S_i)\}_{i=1}^n$ would be generated from

$$Y = \mu(T, S) + \epsilon \quad \text{and} \quad T = f(S) + E \quad \text{with} \quad S \in \mathcal{S} \subset \mathbb{R}^d,$$

- E is an independent treatment variation with $\mathbb{E}(E) = 0$,
- ϵ is an exogenous noise with $\mathbb{E}(\epsilon) = 0$, $\text{Var}(\epsilon) = \sigma^2 > 0$, and $\mathbb{E}(\epsilon^4) < \infty$.

Some identification assumptions are required to estimate $m(t) = \mathbb{E}[Y(t)]$ and $\theta(t) = m'(t)$ from $\{(Y_i, T_i, S_i)\}_{i=1}^n$.

Assumption

- ① (Consistency) $Y(t) = Y$ for any $t \in \mathcal{T}$.
- ② (Ignorability or Unconfoundingness) $Y(t) \perp\!\!\!\perp T \mid \mathbf{S}$ for all $t \in \mathcal{T}$.
- ③ (Treatment Variation) E has nonzero variance, i.e., $\text{Var}(E) > 0$.

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$\implies m(t)$ and $\theta(t)$ can be identified through

$$m(t) = \mathbb{E}[Y(t)] = \mathbb{E}[\mu(t, \mathbf{S})] \quad \text{and} \quad \theta(t) = \frac{d}{dt} \mathbb{E}[Y(t)] = \frac{d}{dt} \mathbb{E}[\mu(t, \mathbf{S})],$$

where $\mu(t, \mathbf{s}) = \mathbb{E}(Y|T = t, \mathbf{S} = \mathbf{s})$.

► **Question:** Why is it necessary for $\text{Var}(E) > 0$?

Identification of a Causal Dose-Response Curve

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► **Question:** Why is it necessary for $\text{Var}(E) > 0$?

- Suppose that $\text{Var}(E) = 0$ and $T = f(\mathbf{S}) + E = S_1$ (a.s.) with $\mathbb{E}(S_1) = 0$.
- Let $\mu_1(T, \mathbf{S}) = T + 2S_1 \stackrel{\text{a.s.}}{=} 3S_1$ and $\mu_2(T, \mathbf{S}) = 2T + S_1 \stackrel{\text{a.s.}}{=} 3S_1$.
- However, μ_1, μ_2 lead to two distinct treatment effects:

$$m_1(t) = \mathbb{E}[\mu_1(t, \mathbf{S})] = t \quad \text{and} \quad m_2(t) = \mathbb{E}[\mu_2(t, \mathbf{S})] = 2t.$$

Estimation of Dose-Response Curves Under Positivity

To estimate

$$m(t) = \mathbb{E}[Y(t)] = \mathbb{E}[\mu(t, \mathbf{S})],$$

we only need to recover $\mu(t, \mathbf{s}) = \mathbb{E}(Y|T = t, \mathbf{S} = \mathbf{s})$ from $\{(Y_i, T_i, \mathbf{S}_i)\}_{i=1}^n$.

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- ① **Regression Adjustment:** $\hat{m}_{RA}(t) = \frac{1}{n} \sum_{i=1}^n \hat{\mu}(t, \mathbf{S}_i)$, where $\hat{\mu}$ is any consistent estimator of μ (Robins, 1986; Gill and Robins, 2001).
- ② **Inverse Probability Weighting (IPW):** Hirano and Imbens (2004); Imai and van Dyk (2004).
- ③ **Doubly Robust:** Kennedy et al. (2017); Westling et al. (2020); Colangelo and Lee (2020); Semenova and Chernozhukov (2021); Bonvini and Kennedy (2022); Takatsu and Westling (2022).

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Assumption (Positivity)

The conditional density $p(t|\mathbf{s})$ is bounded above and away from zero almost surely for all $t \in \mathcal{T}$ and $\mathbf{s} \in \mathcal{S}$.

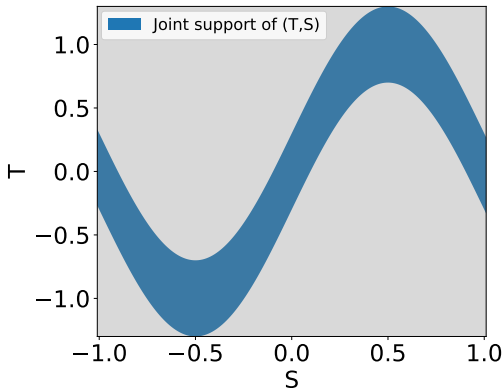
► **Issue:** Positivity is a particularly strong condition with continuous treatments!

Violation of the Positivity Condition

Consider a single confounder model:

$$Y = T^2 + T + 1 + 10S + \epsilon, \quad T = \sin(\pi S) + E, \quad \text{and} \quad S \sim \text{Uniform}[-1, 1].$$

- $E \sim \text{Uniform}[-0.3, 0.3]$ is an independent treatment variation,
- $\epsilon \sim \mathcal{N}(0, 1)$ is an exogenous normal noise.



► **Note:** $p(t|s) = 0$ in the gray regions, and the positivity condition fails.

Effect of $PM_{2.5}$ on the Cardiovascular Mortality Rate (CMR)

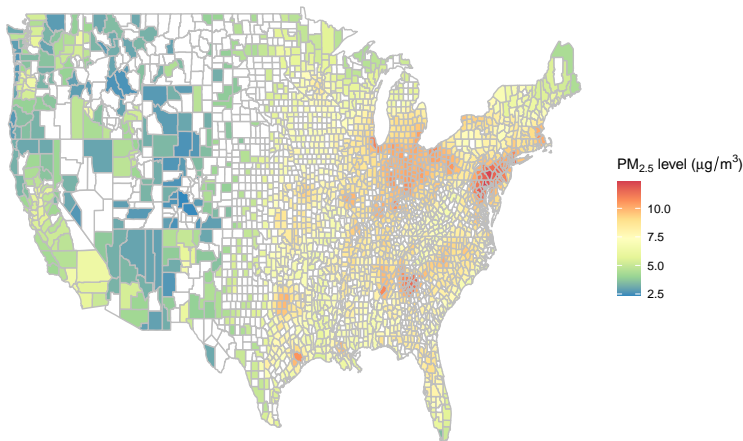


Figure: Average $PM_{2.5}$ levels over the years 1990-2010 within $n = 2132$ counties.

► **Problem:** Only one $PM_{2.5}$ level is available per county, but causal effects of different $PM_{2.5}$ levels on county-level CMRs are of interest.

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- ① The positivity condition may fail to hold in some regions of $\mathcal{T} \times \mathcal{S}$.
- ② We propose a novel integral estimator $\hat{m}_\theta(t)$ of $m(t)$ for all $t \in \mathcal{T}$.

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- ② We propose a novel integral estimator $\hat{m}_\theta(t)$ of $m(t)$ for all $t \in \mathcal{T}$.
 - Construct a localized derivative estimator $\hat{\theta}_C(t)$ of $\theta(t)$ around the observations $T_i, i = 1, \dots, n$.
 - Extrapolate $\hat{\theta}_C(t)$ to any treatment level of interest via the fundamental theorem of calculus.
 - Compute the integration via an efficient Riemann sum approximation.
 - $\hat{m}_\theta(t)$ is consistent within any compact set of \mathcal{T} even when the positivity condition fails in some regions of $\mathcal{T} \times \mathcal{S}$.

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 - Compute the integration via an efficient Riemann sum approximation.
 - $\hat{m}_\theta(t)$ is consistent within any compact set of \mathcal{T} even when the positivity condition fails in some regions of $\mathcal{T} \times \mathcal{S}$.
- ③ Nonparametric bootstrap inferences with our estimators on $m(t)$ and $\theta(t)$ are asymptotically valid.

Methodology



Interchangeability Assumption

Recall our model setup

$$Y = \mu(T, S) + \epsilon \quad \text{and} \quad T = f(S) + E \quad \text{with} \quad S \perp\!\!\!\perp E \quad \text{and} \quad \mathbb{E}(E) = 0.$$

Assumption (Interchangeability)

$\mu(t, s)$ is continuously differentiable with respect to t for any $(t, s) \in \mathcal{T} \times \mathcal{S}$, and the following two equalities hold true:

$$\underbrace{\mathbb{E} \left[\frac{\partial}{\partial t} \mu(t, S) \right]}_{:= \theta_M(t)} = \underbrace{\mathbb{E} \left[\frac{\partial}{\partial t} \mu(t, S) \middle| T = t \right]}_{:= \theta_C(t)} \quad \text{and} \quad \mathbb{E} [\mu(T, S)] = \mathbb{E} [m(T)].$$

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► **Note:** Estimating $\theta(t)$ by the form $\theta_C(t) = \mathbb{E} \left[\frac{\partial}{\partial t} \mu(t, S) \middle| T = t \right]$ is one key technique to bypass the positivity condition.

- It only requires an accurate estimator of $\frac{\partial}{\partial t} \mu(t, s)$ at the covariate s when $p(s|t)$ is high.

Additive Confounding Model

Consider the following additive confounding model

$$Y = \bar{m}(T) + \eta(\mathbf{S}) + \epsilon, \quad T = f(\mathbf{S}) + E \quad \text{with} \quad \mathbb{E}[\eta(\mathbf{S})] = 0 \quad \text{and} \quad \mathbb{E}(E) = 0.$$

- This additive form is a common working model in spatial confounding problems (Paciorek, 2010; Schnell and Papadogeorgou, 2020).
- It is also known as the geoaddivitive structural equation model (Kammann and Wand, 2003; Thaden and Kneib, 2018; Wiecha and Reich, 2024).

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Proposition (Proposition 1 in Zhang et al. 2024)

- 1 $\bar{m}(t) = m(t)$.
- 2 $\theta(t) = \theta_M(t) = \theta_C(t)$.
- 3 $\mathbb{E}[\mu(T, S)] = \mathbb{E}[m(T)]$ even when $\mathbb{E}[\eta(S)] \neq 0$.

Three Critical Insights

- ① $\mu(t, \mathbf{s})$ and $\frac{\partial}{\partial t}\mu(t, \mathbf{s})$ can be consistently estimated at each observed data point (T_i, \mathbf{S}_i) .
 - The positivity condition holds at (T_i, \mathbf{S}_i) for $i = 1, \dots, n$.

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- ② $\theta(t) = m'(t)$ can be consistently estimated by the localized form $\theta_C(t) = \mathbb{E} \left[\frac{\partial}{\partial t}\mu(t, \mathbf{S}) \mid T = t \right]$.
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- ③ By the fundamental theorem of calculus,

$$m(t) = m(T) + \int_{\tilde{t}=T}^{\tilde{t}=t} m'(\tilde{t}) d\tilde{t} = m(T) + \int_{\tilde{t}=T}^{\tilde{t}=t} \theta(\tilde{t}) d\tilde{t}.$$

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\Rightarrow Under our interchangeability assumption,

$$\begin{aligned} m(t) &= \mathbb{E} \left[m(T) + \int_{\tilde{t}=T}^{\tilde{t}=t} \theta(\tilde{t}) d\tilde{t} \right] = \mathbb{E} [\mu(T, \mathbf{S})] + \mathbb{E} \left[\int_{\tilde{t}=T}^{\tilde{t}=t} \theta_C(\tilde{t}) d\tilde{t} \right] \\ &= \mathbb{E}(Y) + \mathbb{E} \left[\int_{\tilde{t}=T}^{\tilde{t}=t} \theta_C(\tilde{t}) d\tilde{t} \right]. \end{aligned}$$

The form $m(t) = \mathbb{E}(Y) + \mathbb{E} \left[\int_T^t \theta_C(\tilde{t}) d\tilde{t} \right]$ leads to our proposed *integral estimator* of $m(t)$ as:

$$\hat{m}_\theta(t) = \frac{1}{n} \sum_{i=1}^n \left[Y_i + \int_{\tilde{t}=T_i}^{\tilde{t}=t} \hat{\theta}_C(\tilde{t}) d\tilde{t} \right],$$

where $\hat{\theta}_C(t)$ is a consistent estimator of

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- Estimate $\beta_2(t, \mathbf{s}) := \frac{\partial}{\partial t} \mu(t, \mathbf{s})$ by (partial) local polynomial regression (Fan and Gijbels, 1996).
- Estimate $P(\mathbf{s}|t)$ by Nadaraya-Watson conditional cumulative distribution function (CDF) estimator (Hall et al., 1999).

(Partial) Local Polynomial Regression

- ① Let $K_T : \mathbb{R} \rightarrow [0, \infty)$, $K_S : \mathbb{R}^d \rightarrow [0, \infty)$ be two symmetric kernel functions and $h, b > 0$ be their smoothing bandwidth parameters.
- Epanechnikov kernel $K(u) = \frac{3}{4} (1 - u^2) \cdot \mathbb{1}_{\{|u| \leq 1\}}$ and Gaussian kernel $K(u) = \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{u^2}{2}\right)$.
 - Product kernel technique $K_S(\mathbf{u}) = \prod_{i=1}^d K(u_i)$ for $\mathbf{u} \in \mathbb{R}^d$.
- ② Let $\mathbf{X}_i(t, \mathbf{s}) = (1, (T_i - t), \dots, (T_i - t)^q, (S_{i,1} - s_1), \dots, (S_{i,d} - s_d)) \in \mathbb{R}^{q+1+d}$,

$$\mathbf{X}(t, \mathbf{s}) = \begin{pmatrix} \mathbf{X}_1(t, \mathbf{s}) \\ \vdots \\ \mathbf{X}_n(t, \mathbf{s}) \end{pmatrix} \text{ and } \mathbf{W}(t, \mathbf{s}) = \begin{pmatrix} K_T\left(\frac{T_1 - t}{h}\right) K_S\left(\frac{\mathbf{S}_1 - \mathbf{s}}{b}\right) & & \\ & \ddots & \\ & & K_T\left(\frac{T_n - t}{h}\right) K_S\left(\frac{\mathbf{S}_n - \mathbf{s}}{b}\right) \end{pmatrix}.$$

- ③ Solve a weighted least-square problem

$$\begin{aligned} \left(\hat{\beta}(t, \mathbf{s}), \hat{\alpha}(t, \mathbf{s}) \right)^T &= \arg \min_{(\beta, \alpha)^T \in \mathbb{R}^{q+1+d}} \left[\mathbf{Y} - \mathbf{X}(t, \mathbf{s}) \begin{pmatrix} \beta \\ \alpha \end{pmatrix} \right]^T \mathbf{W}(t, \mathbf{s}) \left[\mathbf{Y} - \mathbf{X}(t, \mathbf{s}) \begin{pmatrix} \beta \\ \alpha \end{pmatrix} \right] \\ &= \arg \min_{(\beta, \alpha)^T \in \mathbb{R}^{q+1+d}} \sum_{i=1}^n \left[Y_i - \sum_{j=0}^q \beta_j (T_i - t)^j - \sum_{\ell=1}^d \alpha_\ell (S_{i,\ell} - s_\ell) \right]^2 K_T\left(\frac{T_i - t}{h}\right) K_S\left(\frac{\mathbf{S}_i - \mathbf{s}}{b}\right). \end{aligned}$$

Proposed Localized Derivative Estimator of $\theta(t)$

With $\mathbf{Y} = (Y_1, \dots, Y_n)^T \in \mathbb{R}^n$,

$$\left(\hat{\beta}(t, \mathbf{s}), \hat{\alpha}(t, \mathbf{s}) \right)^T = \left[\mathbf{X}^T(t, \mathbf{s}) \mathbf{W}(t, \mathbf{s}) \mathbf{X}(t, \mathbf{s}) \right]^{-1} \mathbf{X}(t, \mathbf{s})^T \mathbf{W}(t, \mathbf{s}) \mathbf{Y}.$$

- The second component $\hat{\beta}_2(t, \mathbf{s})$ of $\hat{\beta}(t, \mathbf{s}) \in \mathbb{R}^{q+1}$ provides a natural estimator of $\beta_2(t, \mathbf{s}) := \frac{\partial}{\partial t} \mu(t, \mathbf{s})$, and we recommend choosing $q = 2$.

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We estimate $P(\mathbf{s}|t)$ by Nadaraya-Watson conditional CDF estimator

$$\hat{P}_{\bar{h}}(\mathbf{s}|t) = \frac{\sum_{i=1}^n \mathbb{1}_{\{S_i \leq \mathbf{s}\}} \cdot \bar{K}_T\left(\frac{T_i - t}{\bar{h}}\right)}{\sum_{j=1}^n \bar{K}_T\left(\frac{T_j - t}{\bar{h}}\right)}.$$

- $\bar{K}_T : \mathbb{R} \rightarrow [0, \infty)$ is a kernel function and $\bar{h} > 0$ is the smoothing bandwidth parameter.

Proposed Localized Derivative Estimator of $\theta(t)$

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- $\bar{K}_T : \mathbb{R} \rightarrow [0, \infty)$ is a kernel function and $\bar{h} > 0$ is the smoothing bandwidth parameter.

► Proposed Localized Derivative Estimator:

$$\hat{\theta}_C(t) = \int \hat{\beta}_2(t, \mathbf{s}) d\hat{P}_{\bar{h}}(\mathbf{s}|t) = \frac{\sum_{i=1}^n \hat{\beta}_2(t, \mathbf{S}_i) \cdot \bar{K}_T\left(\frac{T_i - t}{\bar{h}}\right)}{\sum_{j=1}^n \bar{K}_T\left(\frac{T_j - t}{\bar{h}}\right)}.$$

Our *integral estimator* takes the form

$$\hat{m}_{\theta}(t) = \frac{1}{n} \sum_{i=1}^n \left[Y_i + \int_{\tilde{t}=T_i}^{\tilde{t}=t} \hat{\theta}_C(\tilde{t}) d\tilde{t} \right].$$

► **Issue:** The integral could be analytically difficult to compute.

Fast Computing Algorithm for Proposed Integral Estimator

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• Approximate $\hat{m}_\theta(T_{(j)})$ for each $j = 1, \dots, n$ as:

$$\hat{m}_\theta(T_{(j)}) \approx \frac{1}{n} \sum_{i=1}^n Y_i + \frac{1}{n} \sum_{i=1}^{n-1} \Delta_i \left[i \cdot \hat{\theta}_C(T_{(i)}) \mathbb{1}_{\{i < j\}} - (n-i) \cdot \hat{\theta}_C(T_{(i+1)}) \mathbb{1}_{\{i \geq j\}} \right].$$

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• Evaluate $\hat{m}_{\theta}(t)$ at any $t \in [T_{(j)}, T_{(j+1)}]$ by a linear interpolation between $\hat{m}_{\theta}(T_{(j)})$ and $\hat{m}_{\theta}(T_{(j+1)})$.

• The approximation error is at most $O_P\left(\frac{1}{n}\right)$.

Nonparametric Bootstrap Inference

- ① Compute $\hat{m}_\theta(t)$ on the original data $\{(Y_i, T_i, \mathbf{S}_i)\}_{i=1}^n$.
- ② Generate B bootstrap samples $\left\{ \left(Y_i^{*(b)}, T_i^{*(b)}, \mathbf{S}_i^{*(b)} \right) \right\}_{i=1}^n$ by sampling with replacement and compute $\hat{m}_\theta^{*(b)}(t)$ for each $b = 1, \dots, B$.
- ③ Let $\alpha \in (0, 1)$ be a pre-specified significance level.
 - For pointwise inference at $t_0 \in \mathcal{T}$, calculate the $1 - \alpha$ quantile $\zeta_{1-\alpha}^*(t_0)$ of $\{D_1(t_0), \dots, D_B(t_0)\}$, where $D_b(t_0) = \left| \hat{m}_\theta^{*(b)}(t_0) - \hat{m}_\theta(t_0) \right|$ for $b = 1, \dots, B$.
 - For uniform inference on $m(t)$, compute the $1 - \alpha$ quantile $\xi_{1-\alpha}^*$ of $\{D_{\text{sup},1}, \dots, D_{\text{sup},B}\}$, where $D_{\text{sup},b} = \sup_{t \in \mathcal{T}} \left| \hat{m}_\theta^{*(b)}(t) - \hat{m}_\theta(t) \right|$ for $b = 1, \dots, B$.
- ④ Define the $1 - \alpha$ confidence interval for $m(t_0)$ as:

$$\left[\hat{m}_\theta(t_0) - \zeta_{1-\alpha}^*(t_0), \hat{m}_\theta(t_0) + \zeta_{1-\alpha}^*(t_0) \right]$$

and the simultaneous $1 - \alpha$ confidence band for every $t \in \mathcal{T}$ as:

$$\left[\hat{m}_\theta(t) - \xi_{1-\alpha}^*, \hat{m}_\theta(t) + \xi_{1-\alpha}^* \right].$$

Asymptotic Theory



(Uniform) Consistencies of Proposed Estimators

Let $\mathcal{T}' \subset \mathcal{T}$ be a compact set so that $p_T(t) \geq p_{T,\min} > 0$ for all $t \in \mathcal{T}'$.

Assume

- smoothness conditions on $p(t, \mathbf{s})$ and $\mu(t, \mathbf{s})$,
- boundary conditions on $\mathcal{E} \subset \mathcal{T} \times \mathcal{S}$, which is the support of $p(t, \mathbf{s})$,
- regular and VC-type conditions on the kernel functions K_T, K_S, \bar{K}_T .

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Then, as $h, b, \hbar, \frac{\max\{h, b\}^4}{h} \rightarrow 0$ and $\frac{nh^3b^d}{|\log(hb^d)|}, \frac{|\log(hb^d)|}{\log \log n}, \frac{n\hbar}{|\log \hbar|}, \frac{|\log \hbar|}{\log \log n} \rightarrow \infty$,

$$\sup_{t \in \mathcal{T}'} |\hat{\theta}_C(t) - \theta_C(t)| = \underbrace{O\left(h^q + b^2 + \frac{\max\{h, b\}^4}{h}\right)}_{\text{Bias term}} + \underbrace{O_P\left(\sqrt{\frac{|\log(hb^d)|}{nh^3b^d}} + \hbar^2 + \sqrt{\frac{|\log \hbar|}{n\hbar}}\right)}_{\text{Stochastic variation}}$$

and

$$\begin{aligned} \sup_{t \in \mathcal{T}'} |\hat{m}_\theta(t) - m(t)| &= O_P\left(\frac{1}{\sqrt{n}}\right) + O\left(h^q + b^2 + \frac{\max\{h, b\}^4}{h}\right) \\ &\quad + O_P\left(\sqrt{\frac{|\log(hb^d)|}{nh^3b^d}} + \hbar^2 + \sqrt{\frac{|\log \hbar|}{n\hbar}}\right). \end{aligned}$$

Asymptotic Linearity of Proposed Estimators

Under the same regularity conditions, if $h \asymp b \asymp n^{-\frac{1}{\gamma}}$ and $\hbar \asymp n^{-\frac{1}{\varpi}}$ for some $\gamma \geq \varpi > 0$ such that $\frac{nh^{d+5}}{\log n} \rightarrow c_1$ and $\frac{n\hbar^5}{\log n} \rightarrow c_2$ for some $c_1, c_2 \geq 0$ and $\frac{\log n}{n\hbar^2}, \frac{h^{d+3} \log n}{\hbar}, \frac{h^{d+3}}{\hbar^2} \rightarrow 0$ as $n \rightarrow \infty$, then for any $t \in \mathcal{T}'$,

$$\sqrt{nh^3b^d} \left[\widehat{\theta}_C(t) - \theta_C(t) \right] = \mathbb{G}_n \bar{\varphi}_t + o_P(1),$$

$$\sqrt{nh^3b^d} \left[\widehat{m}_\theta(t) - m(t) \right] = \mathbb{G}_n \varphi_t + o_P(1),$$

where

$$\bar{\varphi}_t(Y, T, \mathbf{S}) = \mathbb{E}_{(T_{i_3}, \mathbf{S}_{i_3})} \left[\frac{\mathbf{e}_2^T \mathbf{M}_q^{-1} \boldsymbol{\Psi}_{t, \mathbf{S}_{i_3}}(Y, T, \mathbf{S})}{\sqrt{hb^d} \cdot p(t, \mathbf{S}_{i_3}) \cdot p_T(t)} \cdot \frac{1}{\hbar} \bar{K}_T \left(\frac{t - T_{i_3}}{\hbar} \right) \right]$$

$$\text{and } \varphi_t(Y, T, \mathbf{S}) = \mathbb{E}_{T_{i_2}} \left[\int_{T_{i_2}}^t \bar{\varphi}_{\tilde{t}}(Y, T, \mathbf{S}) d\tilde{t} \right].$$

- Note that $\bar{\varphi}_t$ and φ_t may not be efficient influence functions.

High-Level Proof of Asymptotic Linearity

Define

$$\mathbf{M}_q = \begin{pmatrix} \left(\kappa_{i+j-2}^{(T)} \right)_{1 \leq i, j \leq q+1} & \mathbf{0} \\ \mathbf{0} & \left(\kappa_{2, i-q-1}^{(S)} \mathbb{1}_{\{i=j\}} \right)_{q+1 < i, j \leq q+1+d} \end{pmatrix} \in \mathbb{R}^{(q+1+d) \times (q+1+d)}$$

and the function $\Psi_{t,s}, \psi_{t,s} : \mathbb{R} \times \mathbb{R} \times \mathbb{R}^d \rightarrow \mathbb{R}^{q+1+d}$ as:

$$\Psi_{t,s}(y, z, v) = \begin{bmatrix} \left(y \cdot \left(\frac{z-t}{h} \right)^{j-1} K_T \left(\frac{z-t}{h} \right) K_S \left(\frac{v-s}{b} \right) \right)_{1 \leq j \leq q+1} \\ \left(y \cdot \left(\frac{v_{j-q-1}-s_{j-q-1}}{b} \right) K_T \left(\frac{z-t}{h} \right) K_S \left(\frac{v-s}{b} \right) \right)_{q+1 < j \leq q+1+d} \end{bmatrix}.$$

► **Key Argument:** Write $\hat{m}_\theta(t) - m(t)$ into a V-statistic ([Shieh, 2014](#))

$$\begin{aligned} & \hat{m}_\theta(t) - m(t) \\ &= \frac{1}{n^3} \sum_{i_1=1}^n \sum_{i_2=1}^n \sum_{i_3=1}^n \int_{T_{i_1}} \frac{e_2^T \mathbf{M}_q^{-1} \Psi_{\tilde{t}, s_{i_2}}(Y_{i_3}, T_{i_3}, \mathbf{S}_{i_3})}{h^2 b^d \cdot p(\tilde{t}, \mathbf{S}_{i_2}) \cdot p_T(\tilde{t})} \cdot \frac{1}{h} \bar{K}_T \left(\frac{\tilde{t} - T_{i_2}}{h} \right) d\tilde{t} - \mathbb{E} \left[\int_T \theta_C(\tilde{t}) d\tilde{t} \right] \\ &+ O_P \left(\frac{1}{\sqrt{n}} + h^2 + \sqrt{\frac{\log n}{nh}} \right). \end{aligned}$$

Bootstrap Consistency

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$$\textcircled{1} \left| \sqrt{nh^3 b^d} \sup_{t \in \mathcal{T}'} |\hat{m}_\theta(t) - m(t)| - \sup_{t \in \mathcal{T}'} |\mathbb{G}_n \varphi_t| \right| = O_p \left(\sqrt{nh^{d+7}} + \sqrt{\frac{\log n}{n\hbar^2}} + \sqrt{\frac{\hbar^{d+3} \log n}{\hbar}} + \sqrt{\frac{\hbar^{d+3}}{\hbar^2}} \right).$$

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$\textcircled{2}$ there exists a mean-zero Gaussian process \mathbb{B} such that

$$\sup_{u \geq 0} \left| \mathbb{P} \left(\sqrt{nh^3 b^d} \sup_{t \in \mathcal{T}'} |\hat{m}_\theta(t) - m(t)| \leq u \right) - \mathbb{P} \left(\sup_{f \in \mathcal{F}} |\mathbb{B}(f)| \leq u \right) \right| = O \left(\left(\frac{\log^5 n}{nh^{d+3}} \right)^{\frac{1}{8}} \right).$$

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$$\textcircled{3} \sup_{u \geq 0} \left| \mathbb{P} \left(\sqrt{nh^3 b^d} \cdot \sup_{t \in \mathcal{T}'} |\hat{m}_\theta^*(t) - \hat{m}_\theta(t)| \leq u \mid \mathbb{U}_n \right) - \mathbb{P} \left(\sup_{f \in \mathcal{F}} |\mathbb{B}(f)| \leq u \right) \right| = O_p \left(\left(\frac{\log^5 n}{nh^{d+3}} \right)^{\frac{1}{8}} \right), \text{ where}$$

$$\mathcal{F} = \{(v, x, z) \mapsto \varphi_t(v, x, z) : t \in \mathcal{T}'\}.$$

Remarks on Our Asymptotic Results

- ① \mathcal{F} is not Donsker because φ_t is not uniformly bounded as $h \rightarrow 0$.
 - However, $\tilde{\mathcal{F}} = \left\{ (v, x, z) \mapsto \sqrt{h^3 b^d} \cdot \varphi_t(v, x, z) : t \in \mathcal{T}' \right\}$ is of VC-type.
 - Gaussian approximation in [Chernozhukov et al. \(2014\)](#) can be applied to bound the difference between $\sup_{f \in \mathcal{F}} |\mathbb{G}_n(f)|$ and $\sup_{f \in \mathcal{F}} |\mathbb{B}(f)|$.

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 - Pointwise bootstrap confidence intervals are asymptotically valid; see Lemma 23.3 in [van der Vaart \(1998\)](#).
- ③ For the validity of uniform bootstrap confidence band, one can choose the bandwidths $h \asymp b = O\left(n^{-\frac{1}{d+5}}\right)$ and $\tilde{h} = O\left(n^{-\frac{1}{5}}\right)$.
 - They match the outputs by the usual bandwidth selection methods ([Bashtannyk and Hyndman, 2001](#); [Li and Racine, 2004](#)).
 - No explicit undersmoothing is required!!

Simulations and Case Study



- Use the Epanechnikov kernel for K_T and K_S (with the product kernel technique) and Gaussian kernel for \bar{K}_T .
- Select the bandwidth parameters $h, b > 0$ by modifying the rule-of-thumb method in [Yang and Tschernig \(1999\)](#).
- Set the bandwidth parameter $\bar{h} > 0$ to the normal reference rule in [Chacón et al. \(2011\)](#); [Chen et al. \(2016\)](#).
- Set the bootstrap resampling time $B = 1000$ and the significance level $\alpha = 0.05$.
- Compare our proposed estimators with the regression adjustment estimators under the same choices of bandwidth parameters:

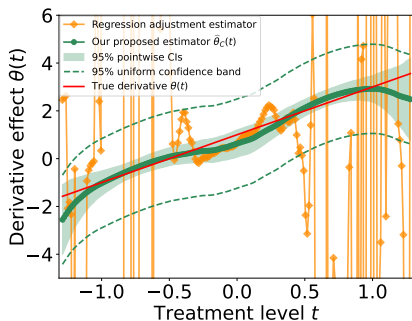
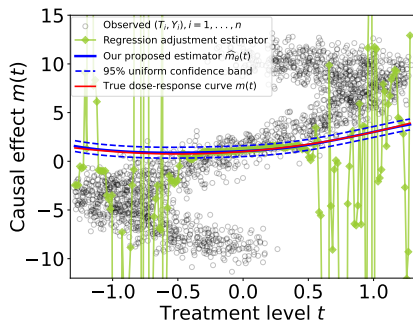
$$\hat{m}_{RA}(t) = \frac{1}{n} \sum_{i=1}^n \hat{\mu}(t, S_i) \quad \text{and} \quad \hat{\theta}_{RA}(t) = \frac{1}{n} \sum_{i=1}^n \hat{\beta}_2(t, S_i).$$

Single Confounder Model

Generate i.i.d. observations $\{(Y_i, T_i, S_i)\}_{i=1}^{2000}$ from

$$Y = T^2 + T + 1 + 10S + \epsilon, \quad T = \sin(\pi S) + E, \quad \text{and} \quad S \sim \text{Uniform}[-1, 1].$$

- $E \sim \text{Uniform}[-0.3, 0.3]$ is an independent treatment variation,
- $\epsilon \sim \mathcal{N}(0, 1)$ is an exogenous normal noise.

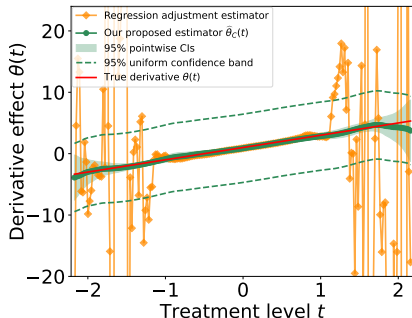
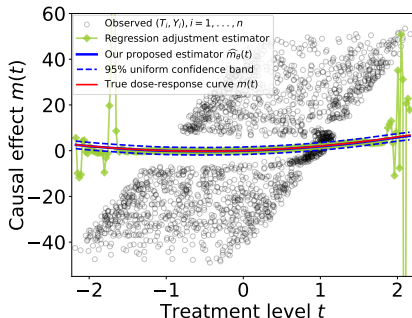


Nonlinear Confounding Model

Generate i.i.d. observations $\{(Y_i, T_i, S_i)\}_{i=1}^{2000}$ from

$$Y = T^2 + T + 10Z + \epsilon, \quad T = \cos(\pi Z^3) + \frac{Z}{4} + E, \quad \text{and} \quad Z = 4S_1 + S_2,$$

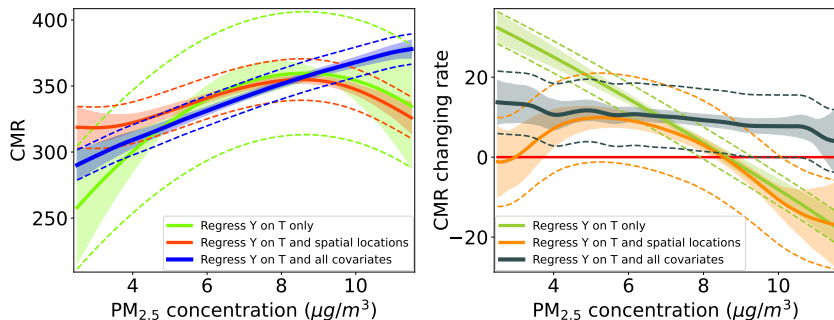
- $(S_1, S_2) \sim \text{Uniform}[-1, 1]^2$, $E \sim \text{Uniform}[-0.1, 0.1]$, and $\epsilon \sim \mathcal{N}(0, 1)$.
- Methods based on pseudo-outcomes ([Kennedy et al., 2017](#); [Takatsu and Westling, 2022](#)) does not work in this example.



Effect of $\text{PM}_{2.5}$ on the Cardiovascular Mortality Rate (CMR)

- ① Recent studies identify a positive association between $\text{PM}_{2.5}$ level ($\mu\text{g}/\text{m}^3$) and county-level CMR (deaths/100,000 person-years) in the U.S. after controlling for socioeconomic factors (Wyatt et al., 2020a).
- ② Obtain the average annual CMR as Y and $\text{PM}_{2.5}$ concentration as T over years 1990-2010 within $n = 2132$ U.S. counties from Wyatt et al. (2020b).
- ③ Our covariate vector $S \in \mathbb{R}^{10}$ consists of two parts:
 - Two spatial confounding variables, *i.e.*, latitude and longitude of each county.
 - Eight county-level socioeconomic factors acquired from the US census.
- ④ Focus on the values of $\text{PM}_{2.5}$ between $2.5 \mu\text{g}/\text{m}^3$ and $11.5 \mu\text{g}/\text{m}^3$ to avoid boundary effects (Takatsu and Westling, 2022).

Effect of $PM_{2.5}$ on the Cardiovascular Mortality Rate (CMR)



After adjusting for all the available confounding variables,

- the estimated relationship between $PM_{2.5}$ and CMR becomes monotonically increasing;
- the 95% confidence band of the estimated changing rate of CMR is unanimously above 0 when the $PM_{2.5}$ level is below $9 \mu g/m^3$.

Discussion



Summary and Future Works

We study nonparametric inference on dose-response curves and their derivative functions.

- Propose an integral estimator of $m(t)$ and a localized derivative estimator of $\theta(t)$.
- Both estimators are consistent without the positivity condition.

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► Future Directions:

- 1 Better estimates of the nuisance functions $\frac{\partial}{\partial t}\mu(t, s)$ and $P(s|t)$:
 - Bandwidth selection via the plug-in rule (Ruppert et al., 1995) or cross-validation (Li and Racine, 2004).
 - Regression splines for $\frac{\partial}{\partial t}\mu(t, s)$ (Friedman, 1991; Zhou and Wolfe, 2000) and local logistic approaches for $P(s|t)$ (Hall et al., 1999).

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 - Regression splines for $\frac{\partial}{\partial t}\mu(t, s)$ (Friedman, 1991; Zhou and Wolfe, 2000) and local logistic approaches for $P(s|t)$ (Hall et al., 1999).
- 2 Generalize our proposed estimators to their IPW and doubly robust variants.
- 3 Sensitivity analysis on unmeasured confounding (Chernozhukov et al., 2022) and the additive model assumption.

- ④ Study the semi-parametric efficiency of the influence functions from our proposed estimators.

$$\bar{\varphi}_t(Y, T, S) = \mathbb{E}_{(T_{i_3}, S_{i_3})} \left[\frac{\mathbf{e}_2^T \mathbf{M}_q^{-1} \Psi_{t, S_{i_3}}(Y, T, S)}{\sqrt{h b^d} \cdot p(t, S_{i_3}) \cdot p_T(t)} \cdot \frac{1}{h} \bar{K}_T \left(\frac{t - T_{i_3}}{h} \right) \right]$$

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and $\varphi_t(Y, T, S) = \mathbb{E}_{T_{i_2}} \left[\int_{T_{i_2}}^t \bar{\varphi}_t(Y, T, S) d\tilde{t} \right]$.

- ⑤ Our proposed nonparametric estimators suffer from the curse of dimensionality.
- Impose a semi-parametric model

$$\mathbb{E}(Y|T=t, S=s, \mathbf{Z}=\mathbf{z}) = m(t) + \eta(s) + \vartheta^T \mathbf{z},$$

where $\mathbf{Z} \in \mathbb{R}^{d'}$ is a high-dimensional covariate vector.

Thank you!

More details can be found in

- [1] Y. Zhang, Y.-C. Chen, and A. Giessing. Nonparametric Inference on Dose-Response Curves Without the Positivity Condition. *arXiv preprint*, 2024.
<https://arxiv.org/abs/2405.09003>.

Python Package: [npDoseResponse](https://npdoseresponse.readthedocs.io) with documentation
(<https://npdoseresponse.readthedocs.io>).
R Package: [npDoseResponse](#).

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Regularity Assumptions (Smoothness Conditions)

Let $\mathcal{E} \subset \mathcal{T} \times \mathcal{S}$ be the support of $p(t, s)$, \mathcal{E}° be the interior of \mathcal{E} , and $\partial\mathcal{E}$ be the boundary of \mathcal{E} .

- ① For any $(t, s) \in \mathcal{T} \times \mathcal{S}$, $\mu(t, s)$ is at least $(q + 1)$ times continuously differentiable with respect to t and at least four times continuously differentiable with respect to s . Furthermore, $\mu(t, s)$ and all of its partial derivatives are uniformly bounded on $\mathcal{T} \times \mathcal{S}$.
- ② $p(t, s)$ is bounded and at least twice continuously differentiable with bounded partial derivatives up to the second order on \mathcal{E}° . All these partial derivatives of $p(t, s)$ are continuous up to the boundary $\partial\mathcal{E}$. Furthermore, \mathcal{E} is compact and $p(t, s)$ is uniformly bounded away from 0 on \mathcal{E} . Finally, the marginal density $p_T(t)$ is non-degenerate.

Regularity Assumptions (Boundary Conditions)

- 3 There exists some constants $r_1, r_2 \in (0, 1)$ such that for any $(t, \mathbf{s}) \in \mathcal{E}$ and all $\delta \in (0, r_1]$, there is a point $(t', \mathbf{s}') \in \mathcal{E}$ satisfying

$$\mathcal{B}((t', \mathbf{s}'), r_2 \delta) \subset \mathcal{B}((t, \mathbf{s}), \delta) \cap \mathcal{E},$$

where

$$\mathcal{B}((t, \mathbf{s}), r) = \left\{ (t_1, \mathbf{s}_1) \in \mathbb{R}^{d+1} : \|(t_1 - t, \mathbf{s}_1 - \mathbf{s})\|_2 \leq r \right\}$$

with $\|\cdot\|_2$ being the standard Euclidean norm.

- 4 For any $(t, \mathbf{s}) \in \partial\mathcal{E}$, the boundary of \mathcal{E} , it satisfies that $\frac{\partial}{\partial t}p(t, \mathbf{s}) = \frac{\partial}{\partial s_j}p(t, \mathbf{s}) = 0$ and $\frac{\partial^2}{\partial s_j^2}\mu(t, \mathbf{s}) = 0$ for all $j = 1, \dots, d$.
- 5 For any $\delta > 0$, the Lebesgue measure of the set $\partial\mathcal{E} \oplus \delta$ satisfies $|\partial\mathcal{E} \oplus \delta| \leq A_1 \cdot \delta$ for some absolute constant $A_1 > 0$, where

$$\partial\mathcal{E} \oplus \delta = \left\{ \mathbf{z} \in \mathbb{R}^{d+1} : \inf_{\mathbf{x} \in \partial\mathcal{E}} \|\mathbf{z} - \mathbf{x}\|_2 \leq \delta \right\}.$$

Regularity Assumptions (Kernel Conditions)

- 6 $K_T : \mathbb{R} \rightarrow [0, \infty)$ and $K_S : \mathbb{R}^d \rightarrow [0, \infty)$ are compactly supported and Lipschitz continuous kernels such that $\int_{\mathbb{R}} K_T(t) dt = \int_{\mathbb{R}^d} K_S(s) ds = 1$, $K_T(t) = K_T(-t)$, and K_S is radially symmetric with $\int s \cdot K_S(s) ds = \mathbf{0}$. In addition, for all $j = 1, 2, \dots$, and $\ell = 1, \dots, d$,

$$\begin{aligned} \kappa_j^{(T)} &:= \int_{\mathbb{R}} u^j K_T(u) du < \infty, & \nu_j^{(T)} &:= \int_{\mathbb{R}} u^j K_T^2(u) du < \infty, \\ \kappa_{j,\ell}^{(S)} &:= \int_{\mathbb{R}^d} u_\ell^j K_S(u) du < \infty, & \text{and} & \quad \nu_{j,k}^{(S)} := \int_{\mathbb{R}^d} u_\ell^j K_S^2(u) du < \infty. \end{aligned}$$

Finally, both K_T and K_S are second-order kernels, *i.e.*, $\kappa_2^{(T)} > 0$ and $\kappa_{2,\ell}^{(S)} > 0$ for all $\ell = 1, \dots, d$.

- 7 Let $\mathcal{K}_{q,d} = \left\{ (y, z) \mapsto \left(\frac{y-t}{h} \right)^\ell \left(\frac{z_i-s_i}{b} \right)^{k_1} \left(\frac{z_j-s_j}{b} \right)^{k_2} K_T \left(\frac{y-t}{h} \right) K_S \left(\frac{z-s}{b} \right) : (t, s) \in \mathcal{T} \times \mathcal{S}; i, j = 1, \dots, d; \ell = 0, \dots, 2q; k_1, k_2 = 0, 1; h, b > 0 \right\}$. It holds that $\mathcal{K}_{q,d}$ is a bounded VC-type class of measurable functions on \mathbb{R}^{d+1} .

Regularity Assumptions (Kernel Conditions)

- 8 The function $\bar{K}_T : \mathbb{R} \rightarrow [0, \infty)$ is a second-order, Lipschitz continuous, and symmetric kernel with a compact support, i.e., $\int_{\mathbb{R}} \bar{K}_T(t) dt = 1$, $\bar{K}_T(t) = \bar{K}_T(-t)$, and $\int_{\mathbb{R}} t^2 \bar{K}_T(t) dt \in (0, \infty)$.
- 9 Let $\bar{\mathcal{K}} = \left\{ y \mapsto \bar{K}_T\left(\frac{y-t}{h}\right) : t \in \mathcal{T}, h > 0 \right\}$. It holds that $\bar{\mathcal{K}}$ is a bounded VC-type class of measurable functions on \mathbb{R} .

Recall that the class \mathcal{G} of measurable functions on \mathbb{R}^{d+1} is VC-type if there exist constants $A_2, v_2 > 0$ such that for any $0 < \epsilon < 1$,

$$\sup_Q N\left(\mathcal{G}, L_2(Q), \epsilon \|G\|_{L_2(Q)}\right) \leq \left(\frac{A_2}{\epsilon}\right)^{v_2},$$

where $N\left(\mathcal{G}, L_2(Q), \epsilon \|G\|_{L_2(Q)}\right)$ is the $\epsilon \|G\|_{L_2(Q)}$ -covering number of the (semi-)metric space $(\mathcal{G}, \|\cdot\|_{L_2(Q)})$, Q is any probability measure on \mathbb{R}^{d+1} , G is an envelope function of \mathcal{G} , and $\|G\|_{L_2(Q)}$ is defined as

$$\left[\int_{\mathbb{R}^{d+1}} [G(x)]^2 dQ(x) \right]^{\frac{1}{2}}.$$

Linear Confounding Model

Generate i.i.d. observations $\{(Y_i, T_i, S_i)\}_{i=1}^{2000}$ from

$$Y = T + 6S_1 + 6S_2 + \epsilon, \quad T = 2S_1 + S_2 + E, \quad \text{and} \quad (S_1, S_2) \sim \text{Uniform}[-1, 1]^2,$$

- $E \sim \text{Uniform}[-0.5, 0.5]$ and $\epsilon \sim \mathcal{N}(0, 1)$.

