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 $Y \in \mathcal{Y}$.

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For *binary* treatment (*i.e.*, $\mathcal{T} \in \{0, 1\}$), common causal estimands are

- $\mathbb{E}\left[Y(t)\right] =$ mean counterfactual outcome[1] when we set $T = t$.
- $\mathbb{E}\left[Y(1)\right] - \mathbb{E}\left[Y(0)\right]$ = 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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Causal Inference For Continuous Treatments

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

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

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

Identification of a Causal Dose-Response Curve

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

- Fitting $m(t)$ is to regress $\{Y_i\}_{i=1}^n$ with respect to $\{T_i\}_{i=1}^n$.
- Recovering $\theta(t)$ is a classical derivative estimation problem (Gasser and Müller, 1984).

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However, confounding variables often exist in practice. Specifically, $\{(Y_i, T_i, \boldsymbol{S}_i)\}_{i=1}^n$ would be generated from

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

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

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

Identification of a Causal Dose-Response Curve

Assumption

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

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

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

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

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- **Question:** Why is it necessary for $\mathrm{Var}(E) > 0$?
  - Suppose that $\mathrm{Var}(E) = 0$ and $T = f(\boldsymbol{S}) + E = S_1$ (a.s.) with $\mathbb{E}(S_1) = 0$.
  - Let $\mu_1(T, \boldsymbol{S}) = T + 2S_1 \overset{\text{a.s.}}{=} 3S_1$ and $\mu_2(T, \boldsymbol{S}) = 2T + S_1 \overset{\text{a.s.}}{=} 3S_1$.
  - However, μ_1, μ_2 lead to two distinct treatment effects:

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

Estimation of Dose-Response Curves Under Positivity

To estimate

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

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

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1. **Regression Adjustment:** $\widehat{m}_{RA}(t) = \frac{1}{n}\sum_{i=1}^n \widehat{\mu}(t, \boldsymbol{S}_i)$, where $\widehat{\mu}$ 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 $p(t|\boldsymbol{s})$ is bounded above and away from zero almost surely for all $t \in \mathcal{T}$ and $\boldsymbol{s} \in \mathcal{S}$.

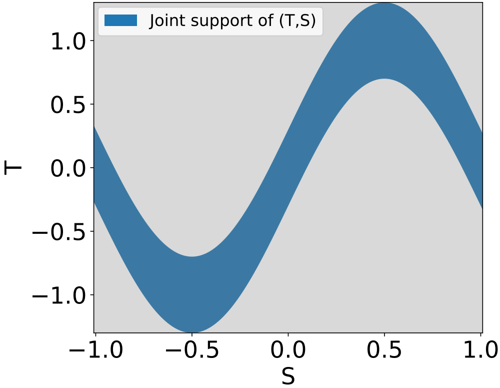
▶ **Issue:** Positivity is a particularly strong condition with continuous treatments!

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)

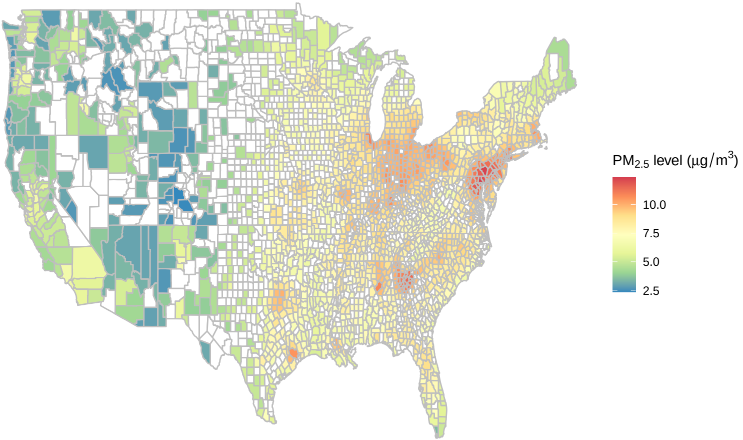


Figure: Average $PM_{2.5}$ levels over the years 1990-2010 within $n = 2132$ counties.

- **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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2. We propose a novel integral estimator $\widehat{m}_\theta(t)$ of $m(t)$ for all $t \in \mathcal{T}$.

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2. We propose a novel integral estimator $\widehat{m}_\theta(t)$ of $m(t)$ for all $t \in \mathcal{T}$.

   - Construct a localized derivative estimator $\widehat{\theta}_C(t)$ of $\theta(t)$ around the observations $T_i, i = 1, ..., n$.
   - Extrapolate $\widehat{\theta}_C(t)$ to any treatment level of interest via the fundamental theorem of calculus.
   - Compute the integration via an efficient Riemann sum approximation.
   - $\widehat{m}_\theta(t)$ 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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   - $\widehat{m}_\theta(t)$ 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

Recall our model setup

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

Assumption (Interchangeability)

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

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

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

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

Additive Confounding Model

Consider the following additive confounding model

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

- This additive form is a common working model in spatial confounding problems (Paciorek, 2010; Schnell and Papadogeorgou, 2020).
- It is also known as the geoadditive 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. $\mathbb{E}\left[\mu(T, \boldsymbol{S})\right] = \mathbb{E}\left[m(T)\right]$ *even when* $\mathbb{E}\left[\eta(\boldsymbol{S})\right] \neq 0$.

Three Critical Insights

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

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

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

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$\Longrightarrow$ Under our interchangeability assumption,

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

Proposed Integral Estimator of Dose-Response Curve

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:

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

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

(Partial) Local Polynomial Regression

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

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

3. Solve a weighted least-square problem

$$\left(\widehat{\boldsymbol{\beta}}(t, \boldsymbol{s}), \widehat{\boldsymbol{\alpha}}(t, \boldsymbol{s})\right)^T = \mathop{\arg\min}_{(\boldsymbol{\beta}, \boldsymbol{\alpha})^T \in \mathbb{R}^{q+1+d}} \left[\boldsymbol{Y} - \boldsymbol{X}(t, \boldsymbol{s}) \begin{pmatrix} \boldsymbol{\beta} \\ \boldsymbol{\alpha} \end{pmatrix}\right]^T \boldsymbol{W}(t, \boldsymbol{s}) \left[\boldsymbol{Y} - \boldsymbol{X}(t, \boldsymbol{s}) \begin{pmatrix} \boldsymbol{\beta} \\ \boldsymbol{\alpha} \end{pmatrix}\right]$$

$$= \mathop{\arg\min}_{(\boldsymbol{\beta}, \boldsymbol{\alpha})^T \in \mathbb{R}^{q+1+d}} \sum_{i=1}^{n} \left[Y_i - \sum_{j=0}^{q} \beta_j (T_i - t)^q - \sum_{\ell=1}^{d} \alpha_\ell (S_{i,\ell} - s_\ell)\right]^2 K_T\left(\frac{T_i - t}{h}\right) K_S\left(\frac{\boldsymbol{S}_i - \boldsymbol{s}}{b}\right).$$

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

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

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

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

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

$$\widehat{P}_{\hbar}(\boldsymbol{s}|t) = \frac{\sum_{i=1}^n \mathbb{1}_{\{\boldsymbol{S}_i \leq \boldsymbol{s}\}} \cdot \bar{K}_T\left(\frac{T_i - t}{\hbar}\right)}{\sum_{j=1}^n \bar{K}_T\left(\frac{T_j - t}{\hbar}\right)}.$$

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

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

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

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

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

$$\widehat{P}_\hbar(\boldsymbol{s}|t) = \frac{\sum_{i=1}^n \mathbb{1}_{\{\boldsymbol{S}_i \leq \boldsymbol{s}\}} \cdot \bar{K}_T\left(\frac{T_i - t}{\hbar}\right)}{\sum_{j=1}^n \bar{K}_T\left(\frac{T_j - t}{\hbar}\right)}.$$

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

▶ **Proposed Localized Derivative Estimator:**

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

Our *integral estimator* takes the form

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

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- Approximate $\widehat{m}_\theta(T_{(j)})$ for each $j = 1, ..., n$ as:

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

Fast Computing Algorithm for Proposed Integral Estimator

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- Evaluate $\widehat{m}_\theta(t)$ at any $t \in \left[T_{(j)}, T_{(j+1)}\right]$ by a linear interpolation between $\widehat{m}_\theta(T_{(j)})$ and $\widehat{m}_\theta(T_{(j+1)})$.
- The approximation error is at most $O_P\left(\frac{1}{n}\right)$.

Nonparametric Bootstrap Inference

1. Compute $\widehat{m}_\theta(t)$ on the original data $\{(Y_i, T_i, \boldsymbol{S}_i)\}_{i=1}^n$.
2. Generate B bootstrap samples $\left\{\left(Y_i^{*(b)}, T_i^{*(b)}, \boldsymbol{S}_i^{*(b)}\right)\right\}_{i=1}^n$ by sampling with replacement and compute $\widehat{m}_\theta^{*(b)}(t)$ for each $b = 1, ..., B$.
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 $\{D_1(t_0), ..., D_B(t_0)\}$, where $D_b(t_0) = \left|\widehat{m}_\theta^{*(b)}(t_0) - \widehat{m}_\theta(t_0)\right|$ for $b = 1, ..., B$.
   - For uniform inference on $m(t)$, compute the $1-\alpha$ quantile $\xi_{1-\alpha}^*$ of $\{D_{\mathrm{sup},1}, ..., D_{\mathrm{sup},B}\}$, where $D_{\mathrm{sup},b} = \sup_{t\in\mathcal{T}} \left|\widehat{m}_\theta^{*(b)}(t) - \widehat{m}_\theta(t)\right|$ for $b = 1, ..., B$.
4. Define the $1-\alpha$ confidence interval for $m(t_0)$ as:

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

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

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

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

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

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

and

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

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 $\frac{nh^{d+5}}{\log n} \to c_1$ and $\frac{n\hbar^5}{\log n} \to c_2$ for some $c_1, c_2 \geq 0$ and $\frac{\log n}{n\hbar^2}, \frac{h^{d+3}\log n}{\hbar}, \frac{h^{d+3}}{\hbar^2} \to 0$ as $n \to \infty$, 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

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

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

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

Define

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

and the function $\boldsymbol{\Psi}_{t,\boldsymbol{s}}, \boldsymbol{\psi}_{t,\boldsymbol{s}} : \mathbb{R}\times\mathbb{R}\times\mathbb{R}^d \to \mathbb{R}^{q+1+d}$ as:

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

- **Key Argument:** Write $\widehat{m}_\theta(t) - m(t)$ into a V-statistic (Shieh, 2014)

$$\widehat{m}_\theta(t) - m(t)$$

$$= \frac{1}{n^3}\sum_{i_1=1}^n\sum_{i_2=1}^n\sum_{i_3=1}^n \int_{T_{i_1}}^t \frac{\boldsymbol{e}_2^T\boldsymbol{M}_q^{-1}\boldsymbol{\Psi}_{\widetilde{t},\boldsymbol{S}_{i_2}}\left(Y_{i_3},T_{i_3},\boldsymbol{S}_{i_3}\right)}{h^2b^d\cdot p(\widetilde{t},\boldsymbol{S}_{i_2})\cdot p_T(\widetilde{t})}\cdot\frac{1}{\hbar}\bar{K}_T\left(\frac{\widetilde{t}-T_{i_2}}{\hbar}\right)d\widetilde{t} - \mathbb{E}\left[\int_T^t \theta_C(\widetilde{t})\,d\widetilde{t}\right]$$

$$+ O_P\left(\frac{1}{\sqrt{n}} + \hbar^2 + \sqrt{\frac{\log n}{n\hbar}}\right).$$

Bootstrap Consistency

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 $\frac{nh^{d+5}}{\log n} \to c_1$ and $\frac{n\hbar^5}{\log n} \to c_2$ for some $c_1, c_2 \geq 0$ and $\frac{n\hbar^2}{\log n}, \frac{\hbar}{h^{d+3}\log n}, \hbar n^{\frac{1}{4}}, \frac{\hbar^2}{h^{d+3}} \to \infty$ as $n \to \infty$,

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

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

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

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

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

Remarks on Our Asymptotic Results

1. $\mathcal{F}$ is not Donsker because φ_t is not uniformly bounded as $h \to 0$.
   - However, $\widetilde{\mathcal{F}} = \left\{(v, x, z) \mapsto \sqrt{h^3 b^d} \cdot \varphi_t(v, x, z) : t \in \mathcal{T}'\right\}$ 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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2. As long as $\mathrm{Var}(\epsilon) = \sigma^2 > 0$, $\mathrm{Var}\left[\varphi_t(Y, T, \boldsymbol{S})\right]$ is a positive finite number.
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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 $\hbar = O\left(n^{-\frac{1}{5}}\right)$.
   - 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

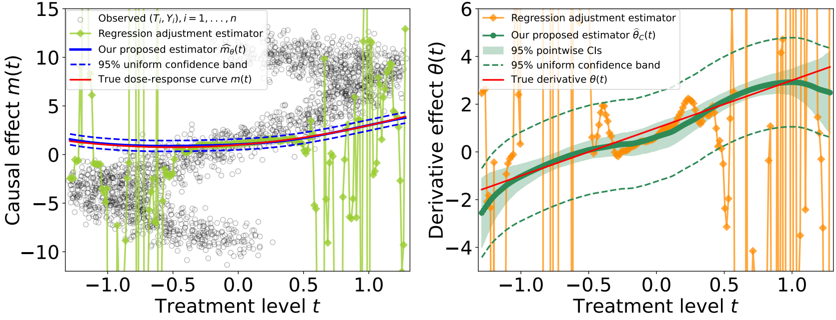
- Use the Epanechnikov kernel for K_T and K_S (with the product kernel technique) and Gaussian kernel for $\bar{K}_T$.
- Select the bandwidth parameters $h, b > 0$ by modifying the rule-of-thumb method in Yang and Tschernig (1999).
- Set the bandwidth parameter $\hbar > 0$ to the normal reference rule 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:

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

Generate i.i.d. observations $\{(Y_i, T_i, \boldsymbol{S}_i)\}_{i=1}^{2000}$ 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.

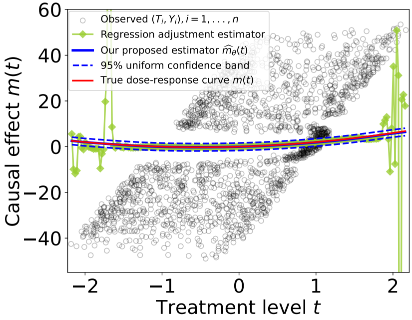


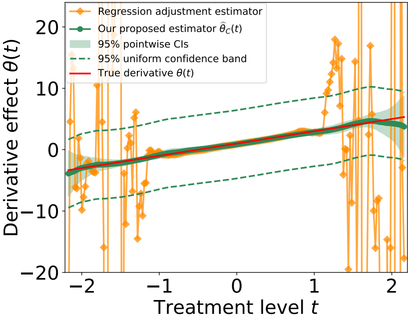
Nonlinear Confounding Model

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

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

- $(S_1, S_2) \sim \text{Uniform}[-1,1]^2$, $E \sim \text{Uniform}[-0.1, 0.1]$, 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 $PM_{2.5}$ on the Cardiovascular Mortality Rate (CMR)

1. Recent studies identify a positive association between $PM_{2.5}$ level (μg/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 $PM_{2.5}$ concentration as T over years 1990-2010 within $n = 2132$ U.S. counties from Wyatt et al. (2020b).
3. Our covariate vector $\boldsymbol{S} \in \mathbb{R}^{10}$ 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 $PM_{2.5}$ between 2.5 μg/m^3 and 11.5 μg/m^3 to avoid boundary effects (Takatsu and Westling, 2022).

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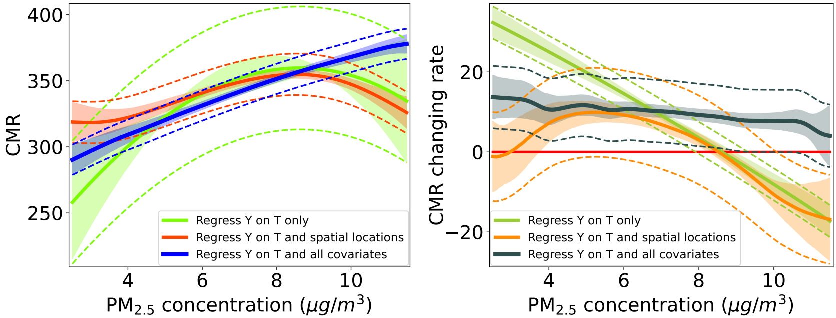

After adjusting for all the available confounding variables,

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

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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.

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

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

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

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

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

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

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

   where $\boldsymbol{Z}\in\mathbb{R}^{d'}$ 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` 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 $p(t, \boldsymbol{s})$, $\mathcal{E}^\circ$ be the interior of $\mathcal{E}$, and $\partial\mathcal{E}$ be the boundary of $\mathcal{E}$.

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

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

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

where

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

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

4. For any $(t, \boldsymbol{s}) \in \partial\mathcal{E}$, the boundary of $\mathcal{E}$, it satisfies that $\frac{\partial}{\partial t} p(t, \boldsymbol{s}) = \frac{\partial}{\partial s_j} p(t, \boldsymbol{s}) = 0$ and $\frac{\partial^2}{\partial s_j^2} \mu(t, \boldsymbol{s}) = 0$ for all $j = 1, ..., d$.

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

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

Regularity Assumptions (Kernel Conditions)

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

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

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 $\ell = 1, ..., d$.

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

8. The function $\bar{K}_T : \mathbb{R} \to [0, \infty)$ 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 $\bar{\mathcal{K}} = \left\{ y \mapsto \bar{K}_T\left(\frac{y-t}{\hbar}\right) : t \in \mathcal{T}, \hbar > 0 \right\}$. 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 $A_2, \upsilon_2 > 0$ such that for any $0 < \epsilon < 1$,

$$\sup_Q N\left(\mathcal{G}, L_2(Q), \epsilon\, ||G||_{L_2(Q)}\right) \leq \left(\frac{A_2}{\epsilon}\right)^{\upsilon_2},$$

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 $\left(\mathcal{G}, ||\cdot||_{L_2(Q)}\right)$, 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 $\{(Y_i, T_i, \boldsymbol{S}_i)\}_{i=1}^{2000}$ 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 $\epsilon \sim \mathcal{N}(0,1)$.