Nonparametric Inference on Dose-Response Curves Without the Positivity Condition

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Introduction

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

$$Y = \mu(T, \boldsymbol{S}) + \epsilon \quad \text{and} \quad T = f(\boldsymbol{S}) + E \quad \text{with} \quad \boldsymbol{S} \in \mathcal{S} \subset \mathbb{R}^d. \tag{1}$$

- 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 $\theta(t) = m'(t)$ based on $\{(Y_i, T_i, \boldsymbol{S}_i)\}_{i=1}^n$ from (1).

Identification of a Causal Dose-Response Curve

Assumption

1. *(Consistency)* $Y = Y(t)$ *whenever* $T = t \in \mathcal{T}$.
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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$\implies$ $m(t)$ and $\theta(t)$ can be identified through

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

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

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

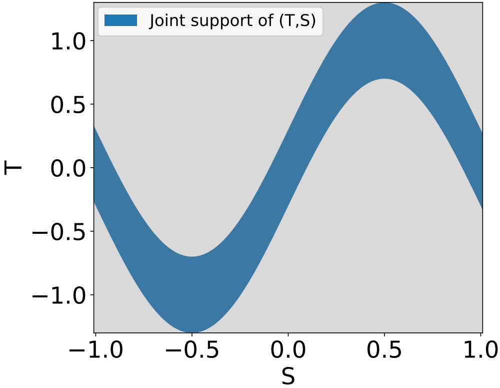
▶ **Issue:** Positivity is a particularly strong condition with continuous treatments!

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)

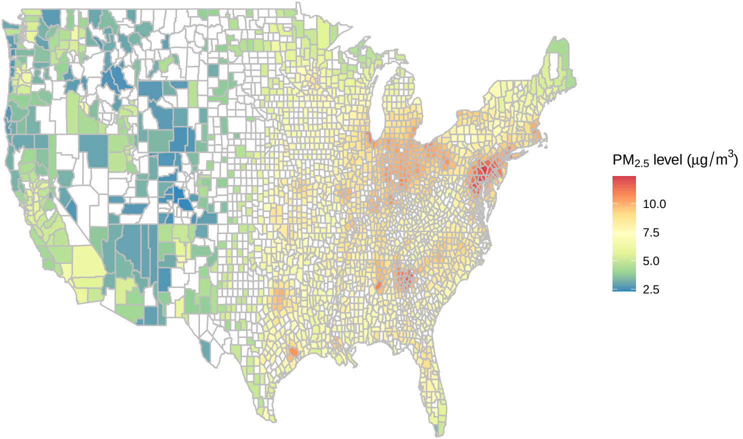


Figure: Average $PM_{2.5}$ levels over the years 1990-2010 in $n = 2132$ counties. T is $PM_{2.5}$ level, while S consists of county location and demographic features.

► **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 $t \in \mathcal{T}$.
   - 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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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:

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

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

Example: 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 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* $\mathbb{E}\left[\eta(\boldsymbol{S})\right] \neq 0$.

► **Note:** The additive confounding model satisfies the Interchangeability Assumption.

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 $(T_i, \boldsymbol{S}_i)$.
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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,

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

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).
- Fit $\mathrm{P}(\boldsymbol{s}|t)$ by Nadaraya-Watson conditional cumulative distribution function (CDF) estimator (Hall et al., 1999).

(Partial) Order q 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

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

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

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

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

We estimate $\beta_2(t, \boldsymbol{s}) := \frac{\partial}{\partial t}\mu(t, \boldsymbol{s})$ by the second component $\widehat{\beta}_2(t, \boldsymbol{s})$ of $\widehat{\boldsymbol{\beta}}(t, \boldsymbol{s}) \in \mathbb{R}^{q+1}$, where $q = 2$ is recommended.

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

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

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We fit $\mathrm{P}(\boldsymbol{s}|t)$ 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 of $\theta(t)$

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

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

We estimate $\beta_2(t, \boldsymbol{s}) := \frac{\partial}{\partial t}\mu(t, \boldsymbol{s})$ by the second component $\widehat{\beta}_2(t, \boldsymbol{s})$ of $\widehat{\boldsymbol{\beta}}(t, \boldsymbol{s}) \in \mathbb{R}^{q+1}$, where $q = 2$ is recommended.

We fit $\mathrm{P}(\boldsymbol{s}|t)$ 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:**

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

A Fast Computing Algorithm for Proposed Integral Estimator

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:

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

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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

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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 $b = 1, ..., B$.

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

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

Define

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

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

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

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

$$\begin{aligned}
&\widehat{m}_\theta(t) - m(t) \\
&= \frac{1}{n^3}\sum_{i_1=1}^n \sum_{i_2=1}^n \sum_{i_3=1}^n \int_{T_{i_1}}^t \frac{\boldsymbol{e}_2^T \boldsymbol{M}_q^{-1} \boldsymbol{\Psi}_{\tilde{t},\boldsymbol{S}_{i_2}}(Y_{i_3}, T_{i_3}, \boldsymbol{S}_{i_3})}{h^2 b^d \cdot p(\tilde{t}, \boldsymbol{S}_{i_2}) \cdot p_T(\tilde{t})} \cdot \frac{1}{\hbar}\bar{K}_T\left(\frac{\tilde{t} - T_{i_2}}{\hbar}\right) d\tilde{t} - \mathbb{E}\left[\int_T^t \theta_C(\tilde{t})\, d\tilde{t}\right] \\
&\quad + O_P\left(\frac{1}{\sqrt{n}} + \hbar^2 + \sqrt{\frac{\log n}{n\hbar}}\right).
\end{aligned}$$

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

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

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

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

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

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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   - The asymptotic linearity (or V-statistic) is non-degenerate.
   - Pointwise bootstrap confidence intervals are asymptotically valid.
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

Simulation Setup

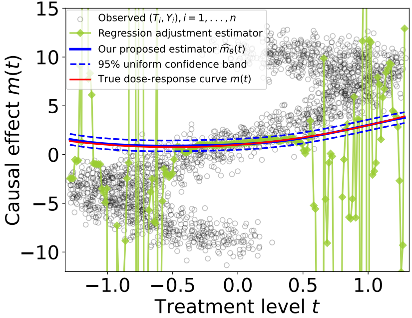
- Use the Epanechnikov kernel for K_T and K_S (with the product kernel technique) and Gaussian kernel for $\bar{K}_T$.
- Select the bandwidth parameters $h, b > 0$ by modifying the rule-of-thumb method in Yang and Tschernig (1999).
- Set the bandwidth parameter $\hbar > 0$ to the normal reference rule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

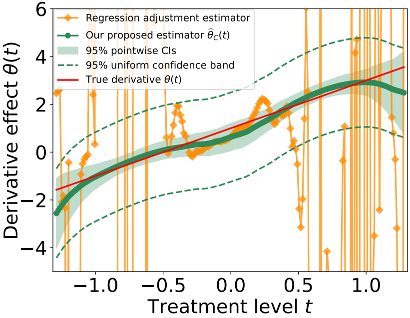
$$\widehat{m}_{RA}(t) = \frac{1}{n}\sum_{i=1}^{n} \widehat{\mu}(t, \boldsymbol{S}_i) \quad \text{and} \quad \widehat{\theta}_{RA}(t) = \frac{1}{n}\sum_{i=1}^{n} \widehat{\beta}_2(t, \boldsymbol{S}_i).$$

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.

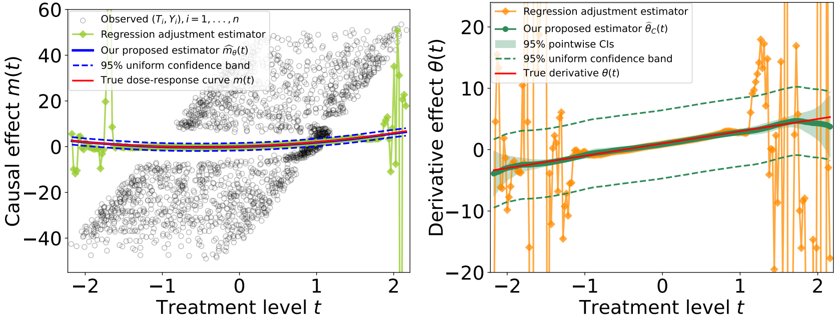




Generate i.i.d. observations $\{(Y_i, T_i, \boldsymbol{S}_i)\}_{i=1}^{2000}$ from

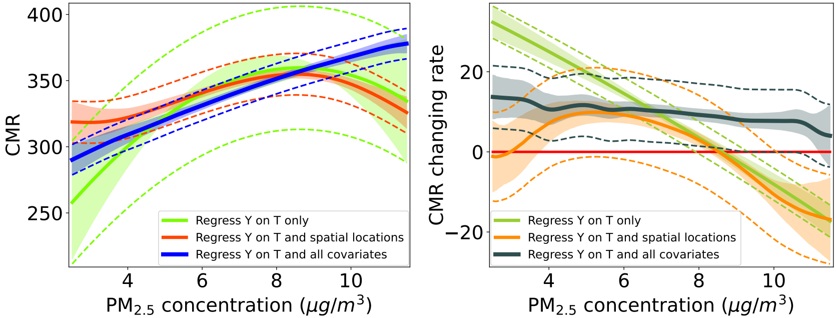
$$Y = T^2 + T + 10Z + \epsilon, \quad T = \cos\left(\pi Z^3\right) + \frac{Z}{4} + E, \quad \text{and} \quad Z = 4S_1 + S_2,$$

- $(S_1, S_2) \sim \text{Uniform}[-1,1]^2$, $E \sim \text{Uniform}[-0.1, 0.1]$, 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 ($\mu g/m^3$) 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. The 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 $\mu g/m^3$ and 11.5 $\mu g/m^3$ to avoid boundary effects (Takatsu and Westling, 2022).



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).

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.

▶ **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).
2. Generalize our proposed integral estimators to the 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 $\varphi_t(Y,T,\boldsymbol{S}) = \mathbb{E}_{T_{i_2}}\left[\int_{T_{i_2}}^t \bar{\varphi}_{\tilde{t}}(Y,T,\boldsymbol{S})\, d\tilde{t}\right]$.

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 and 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.

Regularity Assumptions (Boundary Conditions)

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 $\mathbb{R}^{d+1}$.

Regularity Assumptions (Kernel Conditions)

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 $0 < \epsilon < 1$,

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

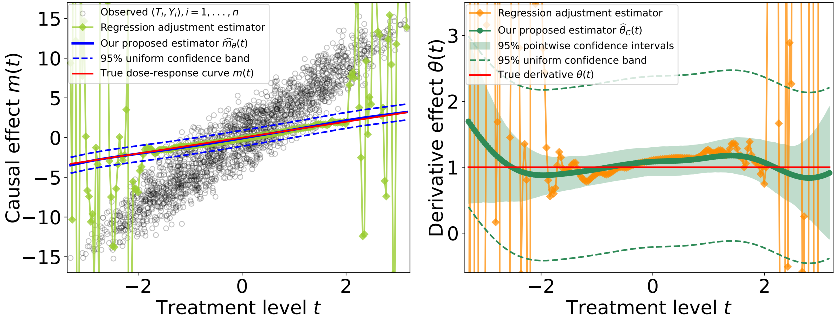
where $N\left(\mathcal{G}, L_2(Q), \epsilon \left|\left|G\right|\right|_{L_2(Q)}\right)$ is the $\epsilon \left|\left|G\right|\right|_{L_2(Q)}$-covering number of the (semi-)metric space $\left(\mathcal{G}, \left|\left|\cdot\right|\right|_{L_2(Q)}\right)$, Q is any probability measure on $\mathbb{R}^{d+1}$, G is an envelope function of $\mathcal{G}$, and $\left|\left|G\right|\right|_{L_2(Q)}$ is defined as $\left[\int_{\mathbb{R}^{d+1}} \left[G(x)\right]^2\, dQ(x)\right]^{\frac{1}{2}}$.

Linear Confounding Model

Generate i.i.d. observations $\{(Y_i, T_i, \mathbf{S}_i)\}_{i=1}^{2000}$ 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 $\epsilon \sim \mathcal{N}(0, 1)$.



Nonparametric Bound on $m(t)$ When $\mathrm{Var}(E) = 0$

For simplicity, we assume the additive confounding model

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

When $\mathrm{Var}(E) = 0$,

- $\mu(t, \boldsymbol{s}) = \mathbb{E}\left(Y | T = t, \boldsymbol{S} = \boldsymbol{s}\right)$ can only be identified on a lower dimensional surface $\{(t, \boldsymbol{s}) \in \mathcal{T} \times \mathcal{S} : t = f(\boldsymbol{s})\}$ so that

$$\mu\left(f(\boldsymbol{s}), \boldsymbol{s}\right) = \bar{m}\left(f(\boldsymbol{s})\right) + \eta(\boldsymbol{s}) = m\left(f(\boldsymbol{s})\right) + \eta(\boldsymbol{s}). \tag{2}$$

- the relation $T = f(\boldsymbol{S})$ can be recovered from the data $\{(T_i, \boldsymbol{S}_i)\}_{i=1}^n$.

Assumption (Bounded random effect)

Let $L_f(t) = \{\boldsymbol{s} \in \mathcal{S} : f(\boldsymbol{s}) = t\}$ be a level set of the function $f : \mathcal{S} \to \mathbb{R}$ at $t \in \mathcal{T}$. There exists a constant $\rho_1 > 0$ such that

$$\rho_1 \geq \max\left\{\sup_{t \in \mathcal{T}} \sup_{\boldsymbol{s} \in L_f(t)} |\eta(\boldsymbol{s})|, \; \frac{\sup_{t \in \mathcal{T}} \sup_{\boldsymbol{s} \in L_f(t)} \mu(f(\boldsymbol{s}), \boldsymbol{s}) - \inf_{t \in \mathcal{T}} \inf_{\boldsymbol{s} \in L_f(t)} \mu(f(\boldsymbol{s}), \boldsymbol{s})}{2}\right\}.$$

Nonparametric Bound on $m(t)$ When $\text{Var}(E) = 0$

By (2) and the first lower bound on $\rho_1 \geq \sup_{t\in\mathcal{T}} \sup_{\boldsymbol{s}\in L_f(t)} |\eta(\boldsymbol{s})|$ in the previous assumption, we know that

$$|\mu(f(\boldsymbol{s}), \boldsymbol{s}) - m(t)| = |\eta(\boldsymbol{s})| \leq \rho_1$$

for any $\boldsymbol{s} \in L_f(t)$. It also implies that

$$\begin{aligned} m(t) &\in \bigcap_{\boldsymbol{s}\in L_f(t)} \left[\mu(f(\boldsymbol{s}), \boldsymbol{s}) - \rho_1,\ \mu(f(\boldsymbol{s}), \boldsymbol{s}) + \rho_1\right] \\ &= \left[\sup_{\boldsymbol{s}\in L_f(t)} \mu(f(\boldsymbol{s}), \boldsymbol{s}) - \rho_1,\ \inf_{\boldsymbol{s}\in L_f(t)} \mu(f(\boldsymbol{s}), \boldsymbol{s}) + \rho_1\right], \end{aligned}$$

which is the nonparametric bound on $m(t)$ that contains all the possible values of $m(t)$ for any fixed $t \in \mathcal{T}$ when $\text{Var}(E) = 0$.

- This bound is well-defined and nonempty under the second lower bound on ρ_1 in the previous assumption.