Nonparametric Inference on Dose-Response Curves Without the Positivity Condition

Yikun Zhang[1]

Joint work with *Yen-Chi Chen*[1] and *Alexander Giessing*[2]

[1]Department of Statistics, University of Washington
[2]Department of Statistics and Data Science, National University of Singapore

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Department of
STATISTICS

UNIVERSITY of WASHINGTON

Introduction

A Central Problem in Causal Inference:

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

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

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

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Identification of Dose-Response Curves

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 $\{T_i\}_{i=1}^n$.
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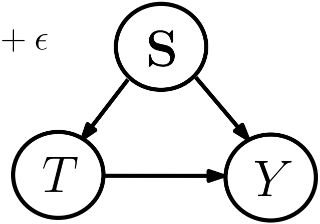
$$Y = \mu(T, \mathbf{S}) + \epsilon$$
$$T = f(\mathbf{S}, E)$$



- 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 $\mathbb{E}(\epsilon^4) < \infty$.

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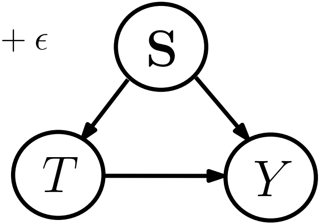

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► **Solution:** Some identification assumptions are required to estimate $m(t) = \mathbb{E}\left[Y(t)\right]$ and $\theta(t) = m'(t)$ from $\{(Y_i, T_i, S_i)\}_{i=1}^n$.

Identification of Dose-Response Curves

Assumption

1. *(Consistency)* $Y = Y(t)$ *whenever* $T = t \in \mathcal{T}$.
2. *(Ignorability or Unconfoundedness)* $Y(t) \perp\!\!\!\perp T \,\big|\, \boldsymbol{S}$ *for all* $t \in \mathcal{T}$.
3. *(Treatment Variation) The conditional variance of* T *given any* $\boldsymbol{S} = \boldsymbol{s} \in \mathcal{S}$ *is strictly positive, i.e.,* $\mathrm{Var}(T|\boldsymbol{S} = \boldsymbol{s}) > 0$.

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- **Question:** Why is it necessary for $\mathrm{Var}(T|\boldsymbol{S} = \boldsymbol{s}) > 0$ for all $\boldsymbol{s} \in \mathcal{S}$?

- Consider the following example with $\mathrm{Var}(T|\boldsymbol{S}) = 0$ as:

$$T = f(\boldsymbol{S}, E) = S_1 \quad \text{and} \quad \mathbb{E}(S_1) = 0.$$

- Let $Y = T + 2S_1 + \epsilon = 3S_1 + \epsilon$ and $\widetilde{Y} = 2T + S_1 + \widetilde{\epsilon} = 3S_1 + \widetilde{\epsilon}$. Then,

$$\mathbb{E}\left(Y|T = t, \boldsymbol{S} = \boldsymbol{s}\right) = 3s_1 = \mathbb{E}\left(\widetilde{Y}\middle|T = t, \boldsymbol{S} = \boldsymbol{s}\right).$$

- However,

$$m(t) = \mathbb{E}\left[Y(t)\right] = t \quad \text{and} \quad \widetilde{m}(t) = \mathbb{E}\left[\widetilde{Y}(t)\right] = 2t.$$

Identification of Dose-Response Curves Under Positivity

Assumption

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3. *(Treatment Variation) The conditional variance of* T *given* $\boldsymbol{S}$ *is strictly positive, i.e.,* $\mathrm{Var}(T|\boldsymbol{S}) > 0$.

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m(t) = \mathbb{E}\left[Y(t)\right] &\overset{(*)}{=} \mathbb{E}\left\{\mathbb{E}\left[Y(t)|\boldsymbol{S}\right]\right\} && \text{(*) Law of total expectation} \\
&\overset{(**)}{=} \mathbb{E}\left\{\mathbb{E}\left[Y(t)|T = t, \boldsymbol{S}\right]\right\} && \text{(**) Ignorability} \\
&\overset{(***)}{=} \mathbb{E}\left[\mathbb{E}\left(Y|T = t, \boldsymbol{S}\right)\right] && \text{(***) Consistency}
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However, in order for $\mu(t, \boldsymbol{s}) = \mathbb{E}\left(Y|T = t, \boldsymbol{S} = \boldsymbol{s}\right)$ to be well-defined on $\mathcal{T} \times \mathcal{S}$, we need the positivity condition.

Assumption (Positivity or Overlap Condition)

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

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3. *(Treatment Variation) The conditional variance of* T *given* $\boldsymbol{S}$ *is strictly positive, i.e.,* $\mathrm{Var}(T|\boldsymbol{S}) > 0$.
4. *(Positivity) The conditional density* $p(t|\boldsymbol{s})$ *is bounded away from zero almost surely for all* $t \in \mathcal{T}$ *and* $\boldsymbol{s} \in \mathcal{S}$.

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

$$\begin{cases} m(t) = \mathbb{E}\left[Y(t)\right] = \mathbb{E}\left[\mu(t,\boldsymbol{S})\right], \\ \theta(t) = \frac{d}{dt}\mathbb{E}\left[Y(t)\right] = \frac{d}{dt}\mathbb{E}\left[\mu(t,\boldsymbol{S})\right] \overset{(\star)^2}{=} \mathbb{E}\left[\frac{\partial}{\partial t}\mu(t,\boldsymbol{S})\right], \end{cases}$$

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

[2] For $(\star)$, we only need some mild assumption; see Theorem 1.1 in Shao (2003).

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 $\{(Y_i, T_i, \boldsymbol{S}_i)\}_{i=1}^n$.

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1. **Regression Adjustment:** $\widehat{m}_{\mathrm{RA}}(t) = \frac{1}{n}\sum_{i=1}^n \widehat{\mu}(t, \boldsymbol{S}_i)$, where $\widehat{\mu}$ is any consistent estimator of μ (Robins, 1986; Gill and Robins, 2001).

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2. **Inverse Probability Weighting (IPW):** $\widehat{m}_{\mathrm{IPW}}(t) = \frac{1}{nh}\sum_{i=1}^n \frac{K\left(\frac{T_i - t}{h}\right)}{\widehat{p}_{T|S}(T_i|\boldsymbol{S}_i)} \cdot Y_i$ (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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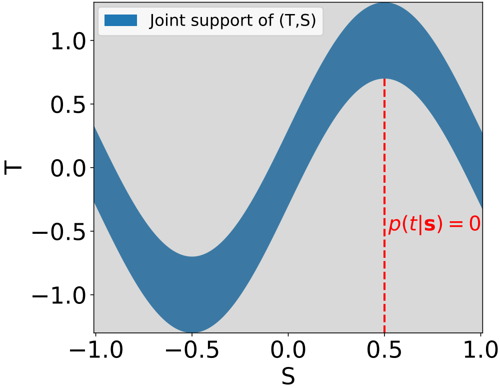
► **Issue:** Positivity is a very strong assumption with continuous treatments!

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)

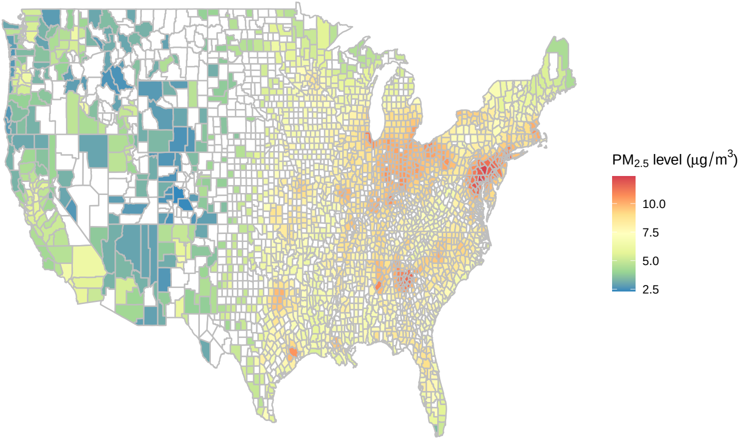


Figure: Average $PM_{2.5}$ levels from 1990 to 2010 in $n = 2132$ counties. T is $PM_{2.5}$ level, while S consists of the county location and some socioeconomic factors.

▶ **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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   - Identify $m(t)$ through an identification assumption on $\theta(t) = m'(t)$.

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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

Identification Condition for $\theta(t)$

Assumption (Interchangeability)

$\mathbb{E}[Y(t)|\boldsymbol{S}=\boldsymbol{s}]$ is continuously differentiable with respect to t for any $(t, \boldsymbol{s})$ such that $p(\boldsymbol{s}|t) > 0$, and the following two equalities hold true:

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

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

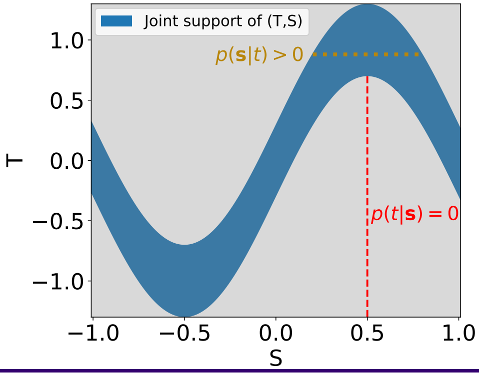
Identification Condition for $\theta(t)$

$$\theta(t) = \theta_C(t) = \mathbb{E}\left[\frac{\partial}{\partial t}\mathbb{E}(Y|T=t,\boldsymbol{S})\Big|T=t\right].$$

- Different from the identification via $\theta(t) = \frac{d}{dt}\mathbb{E}\left[\mu(t,\boldsymbol{S})\right] = \mathbb{E}\left[\frac{\partial}{\partial t}\mu(t,\boldsymbol{S})\right]$ under the positivity condition, we only need

$$\frac{\partial}{\partial t}\mu(t,\boldsymbol{s}) = \frac{\partial}{\partial t}\mathbb{E}(Y|T=t,\boldsymbol{s})$$

to be well-defined when $p(\boldsymbol{s}|t) > 0$.



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)

Under the additive confounding model,

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. $\theta(t)$ can be consistently estimated via $\theta_C(t) = \mathbb{E}\left[\frac{\partial}{\partial t}\mu(t, \boldsymbol{S}) \middle| T = t\right]$.
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   - Only require an accurate estimator of $\frac{\partial}{\partial t}\mu(t, \boldsymbol{s})$ at the covariate $\boldsymbol{s}$ when the conditional density $p(\boldsymbol{s}|t)$ is high.
3. By the fundamental theorem of calculus,

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

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 $i = 1, ..., n$.

2. $\theta(t)$ can be consistently estimated via $\theta_C(t) = \mathbb{E}\left[\frac{\partial}{\partial t}\mu(t, \boldsymbol{S}) \middle| T = t\right]$.
   - Only require an accurate estimator of $\frac{\partial}{\partial t}\mu(t, \boldsymbol{s})$ at the covariate $\boldsymbol{s}$ when the conditional density $p(\boldsymbol{s}|t)$ is high.

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$\Longrightarrow$ Under our identification assumption for $\theta(t)$,

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

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:

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

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

$$\theta_C(t) = \mathbb{E}\left[\frac{\partial}{\partial t}\mu(t, \boldsymbol{S})\middle| T = t\right] = \int \frac{\partial}{\partial t}\mu(t, \boldsymbol{s})\, d\mathrm{P}(\boldsymbol{s}|t).$$

Proposed Integral Estimator of Dose-Response Curve

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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 $K(u) = \frac{3}{4}\left(1 - u^2\right) \cdot \mathbb{1}_{\{|u| \leq 1\}}$.
   - 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

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

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

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 $\widehat{\boldsymbol{\beta}}(t, \boldsymbol{s}) \in \mathbb{R}^{q+1}$.

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

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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.

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- **Proposed Localized Derivative Estimator of $\theta(t)$:**

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

Fast Computing Algorithm for Our 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:

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

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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 $O_P\left(\frac{1}{n}\right)$.

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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 $p(t, \boldsymbol{s})$,
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Then, when $q = 2$, as $h, b, \hbar, \frac{\max\{h,b\}^4}{h} \to 0$ and $\frac{n\max\{h,\hbar\}b^d}{\log n}, \frac{n\hbar}{\log n} \to \infty$,

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

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

[3] We thank Alex Luedtke for pointing out an unexpected dimension dependence of our previous rate $o_P\left(\sqrt{\frac{\log n}{nh^3b^d}} + \hbar^2 + \sqrt{\frac{\log n}{n\hbar}}\right)$. Our new proof is inspired by Fan et al. (1998).

Under the same regularity conditions, if $h \asymp n^{-\frac{1}{\gamma}}$ and $\hbar \asymp n^{-\frac{1}{\varpi}}$ for some $\gamma \geq \varpi > 0$ such that $\frac{nh^5}{\log n} \to c_1$ and $\frac{n\hbar^5}{\log n} \to c_2$ for some $c_1, c_2 \geq 0$ and $\frac{n \max\{h,\hbar\} b^d}{\log n}, \frac{n\hbar}{\log n}, \frac{h^3 \log n}{\hbar}, \frac{nh^3\hbar^4}{\log n} \to \infty$ as $n \to \infty$, then for any $t \in \mathcal{T}'$,

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

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

where[4]

$$\bar{\varphi}_t(Y,T,\boldsymbol{S}) = \frac{C_{K_T}\left[Y - \mu(T,\boldsymbol{S})\right]}{\sqrt{h} \cdot p_T(t)} \left(\frac{T-t}{h}\right) K_T\left(\frac{T-t}{h}\right)$$

and $\varphi_t\left(Y,T,\boldsymbol{S}\right) = \mathbb{E}_{T_1}\left[\int_{T_1}^{t} \bar{\varphi}_{\tilde{t}}(Y,T,\boldsymbol{S})\, d\tilde{t}\right]$ with $\mathbb{G}_n = \sqrt{n}\left(\mathbb{P}_n - \mathrm{P}\right)$.

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

[4] The key of our previous proof is to write $\widehat{m}_\theta(t) - m(t)$ into a V-statistic (Shieh, 2014).

Bootstrap Consistency

Under the same regularity conditions, if $h \asymp n^{-\frac{1}{\gamma}}$ and $b \lesssim \hbar \asymp n^{-\frac{1}{\varpi}}$ 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 $\frac{\hbar}{h^3 \log n}, \hbar n^{\frac{1}{3}} \log n, \frac{\sqrt{n\hbar}}{\log n}, \frac{n \max\{h,\hbar\} b^d}{\log n} \to \infty$ as $n \to \infty$,

1.
$$\left| \sqrt{nh^3} \sup_{t \in \mathcal{T}'} |\widehat{m}_\theta(t) - m(t)| - \sup_{t \in \mathcal{T}'} |\mathbb{G}_n \varphi_t| \right| = O_P\left(\sqrt{nh^3 \max\{h, \hbar\}^4} + \sqrt{\frac{h^3 \log n}{\hbar}} + \frac{\log n}{\sqrt{n\hbar}} + \sqrt{\frac{\log n}{nb^d \hbar}} \right).$$

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

$$\sup_{u \geq 0} \left| \mathrm{P}\left(\sqrt{nh^3} \sup_{t \in \mathcal{T}'} \left|\widehat{m}_\theta(t) - m(t)\right| \leq u \right) - \mathrm{P}\left(\sup_{f \in \mathcal{F}} \left|\mathbb{B}(f)\right| \leq u \right) \right| = O\left(\left(\frac{\log^5 n}{nh^3} \right)^{\frac{1}{8}} + \left(\frac{\log^2 n}{nb^d \hbar} \right)^{\frac{3}{8}} \right).$$

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3. $$\sup_{u \geq 0} \left| \mathrm{P}\left(\sqrt{nh^3} \sup_{t \in \mathcal{T}'} |\widehat{m}^*_\theta(t) - \widehat{m}_\theta(t)| \leq u \middle| \mathbb{U}_n \right) - \mathrm{P}\left(\sup_{f \in \mathcal{F}} |\mathbb{B}(f)| \leq u \right) \right| = O_P\left(\left(\frac{\log^5 n}{nh^3} \right)^{\frac{1}{8}} + \left(\frac{\log^2 n}{nb^d \hbar} \right)^{\frac{3}{8}} \right)$$
   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, $\widetilde{\mathcal{F}} = \left\{(v, x, z) \mapsto \sqrt{h^3} \cdot \varphi_t(v, x, z) : t \in \mathcal{T}'\right\}$ 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 $\text{Var}(\epsilon) = \sigma^2 > 0$, $\text{Var}\left[\varphi_t(Y, T, \boldsymbol{S})\right]$ is a positive finite number.
   - The asymptotic linearity (or V-statistic) is non-degenerate.
   - Pointwise bootstrap confidence intervals are asymptotically valid.

Remarks on Our Asymptotic Results

1. $\mathcal{F}$ is not Donsker because φ_t is not uniformly bounded as $h \to 0$.
   - However, $\widetilde{\mathcal{F}} = \left\{(v, x, z) \mapsto \sqrt{h^3} \cdot \varphi_t(v, x, z) : t \in \mathcal{T}'\right\}$ 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 $\sup_{f \in \mathcal{F}} |\mathbb{B}(f)|$.
2. As long as $\mathrm{Var}(\epsilon) = \sigma^2 > 0$, $\mathrm{Var}\left[\varphi_t(Y, T, S)\right]$ is a positive finite number.
   - 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 $h \asymp \hbar = O\left(n^{-\frac{1}{5}}\right)$ and $\left(\frac{\log n}{n}\right)^{\frac{4}{5d}} \lesssim b \lesssim n^{-\frac{1}{5}}$.
   - They match up with 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

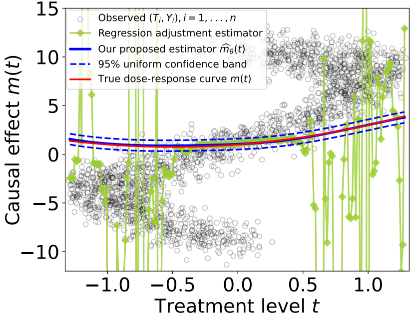
- Use the Epanechnikov kernel for K_T and K_S (with the product kernel technique) and Gaussian kernel for $\bar{K}_T$.
- Select the bandwidth parameters $h, b > 0$ by modifying the rule-of-thumb method in Yang and Tschernig (1999).
- Set the bandwidth parameter $\hbar > 0$ to the normal reference rule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

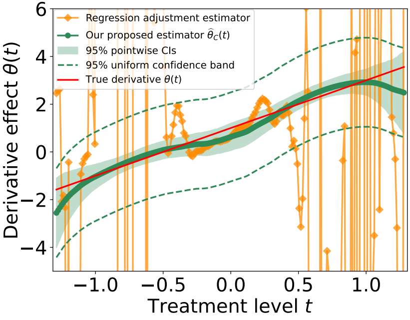
$$\widehat{m}_{\mathrm{RA}}(t) = \frac{1}{n}\sum_{i=1}^{n} \widehat{\mu}(t, \boldsymbol{S}_i) \quad \text{and} \quad \widehat{\theta}_{\mathrm{RA}}(t) = \frac{1}{n}\sum_{i=1}^{n} \widehat{\beta}_2(t, \boldsymbol{S}_i).$$

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.



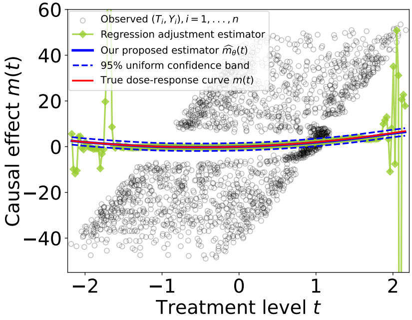


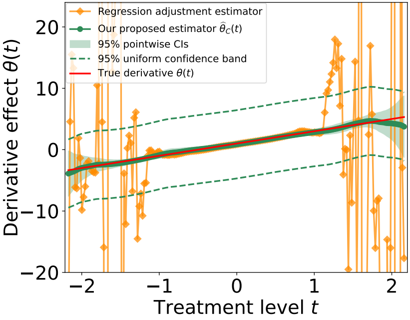
Nonlinear Confounding Model

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 ($\mu g/m^3$) 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).

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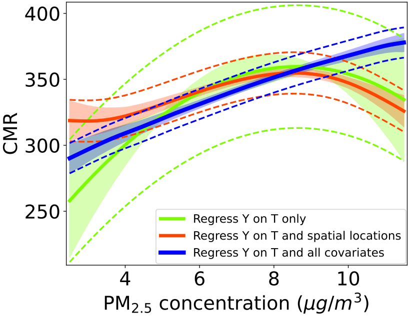
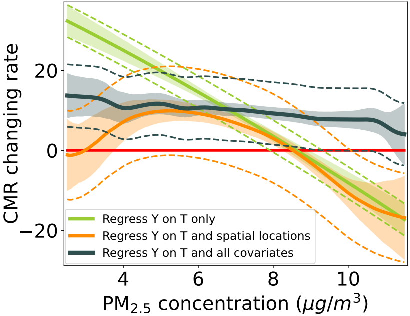
2. Obtain the average annual CMR as Y and $PM_{2.5}$ concentration as T over years 1990-2010 within $n = 2132$ U.S. counties from Wyatt et al. (2020b).
3. The covariate vector $\boldsymbol{S} \in \mathbb{R}^{10}$ consists of two parts:
   - Two spatial confounding variables, *i.e.*, latitude and longitude 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).

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.

- We identify $m(t)$ through the identification of $\theta(t)$ when the positivity condition fails to hold.
- We 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 integral estimators to the IPW and doubly robust variants.

Semi-parametric Inference With High-Dimensional Covariates

3. Sensitivity analysis on unmeasured confounding (Chernozhukov et al., 2022) and the interchangeability assumption.

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4. Study the semi-parametric efficiency (Kennedy, 2016) of the influence functions from our proposed estimators:

$$\bar{\varphi}_t(Y, T, \boldsymbol{S}) = \frac{C_{K_T}\left[Y - \mu(T, \boldsymbol{S})\right]}{\sqrt{h} \cdot p_T(t)} \left(\frac{T-t}{h}\right) K_T\left(\frac{T-t}{h}\right)$$

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

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

5. Our proposed nonparametric estimators suffer from the curse of dimensionality.

   - $\left(\frac{\log n}{n}\right)^{\frac{4}{5d}} \lesssim b \lesssim n^{-\frac{1}{5}}$ only works when $d<5$.
   - Impose a semi-parametric additive model (Guo et al., 2019) as:

$$\mathbb{E}\left(Y|T=t,\boldsymbol{S}=\boldsymbol{s},\boldsymbol{Z}=\boldsymbol{z}\right) = m(t)+\eta(\boldsymbol{s})+\sum_{j=1}^{d'} g_j(\boldsymbol{z}_j),$$

   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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Reference

D. M. Bashtannyk and R. J. Hyndman. Bandwidth selection for kernel conditional density estimation. *Computational Statistics & Data Analysis*, 36(3):279–298, 2001.

M. Bonvini and E. H. Kennedy. Fast convergence rates for dose-response estimation. *arXiv preprint arXiv:2207.11825*, 2022.

J. E. Chacón, T. Duong, and M. Wand. Asymptotics for general multivariate kernel density derivative estimators. *Statistica Sinica*, pages 807–840, 2011.

Y.-C. Chen, C. R. Genovese, and L. Wasserman. A comprehensive approach to mode clustering. *Electronic Journal of Statistics*, 10(1):210 – 241, 2016.

V. Chernozhukov, D. Chetverikov, and K. Kato. Gaussian approximation of suprema of empirical processes. *The Annals of Statistics*, 42(4):1564–1597, 2014.

V. Chernozhukov, C. Cinelli, W. Newey, A. Sharma, and V. Syrgkanis. Long story short: Omitted variable bias in causal machine learning. Technical report, National Bureau of Economic Research, 2022.

K. Colangelo and Y.-Y. Lee. Double debiased machine learning nonparametric inference with continuous treatments. *arXiv preprint arXiv:2004.03036*, 2020.

J. Fan and I. Gijbels. *Local polynomial modelling and its applications*, volume 66. Chapman & Hall/CRC, 1996.

J. Fan, W. Härdle, and E. Mammen. Direct estimation of low-dimensional components in additive models. *The Annals of Statistics*, 26(3):943–971, 1998.

J. H. Friedman. Multivariate adaptive regression splines. *The Annals of Statistics*, 19(1):1–67, 1991.

T. Gasser and H.-G. Müller. Estimating regression functions and their derivatives by the kernel method. *Scandinavian Journal of Statistics*, pages 171–185, 1984.

R. D. Gill and J. M. Robins. Causal inference for complex longitudinal data: the continuous case. *Annals of Statistics*, 29(6):1785–1811, 2001.

Reference

Z. Guo, W. Yuan, and C.-H. Zhang. Decorrelated local linear estimator: Inference for non-linear effects in high-dimensional additive models. *arXiv preprint arXiv:1907.12732*, 2019.

P. Hall, R. C. Wolff, and Q. Yao. Methods for estimating a conditional distribution function. *Journal of the American Statistical Association*, 94(445):154–163, 1999.

K. Hirano and G. W. Imbens. *The Propensity Score with Continuous Treatments*, chapter 7, pages 73–84. John Wiley & Sons, Ltd, 2004.

K. Imai and D. A. van Dyk. Causal inference with general treatment regimes: Generalizing the propensity score. *Journal of the American Statistical Association*, 99(467):854–866, 2004.

E. Kammann and M. P. Wand. Geoadditive models. *Journal of the Royal Statistical Society Series C: Applied Statistics*, 52(1):1–18, 2003.

E. H. Kennedy. Semiparametric theory and empirical processes in causal inference. *Statistical causal inferences and their applications in public health research*, pages 141–167, 2016.

E. H. Kennedy, Z. Ma, M. D. McHugh, and D. S. Small. Nonparametric methods for doubly robust estimation of continuous treatment effects. *Journal of the Royal Statistical Society Series B: Statistical Methodology*, 79(4):1229–1245, 2017.

Q. Li and J. Racine. Cross-validated local linear nonparametric regression. *Statistica Sinica*, pages 485–512, 2004.

C. J. Paciorek. The importance of scale for spatial-confounding bias and precision of spatial regression estimators. *Statistical Science*, 25(1):107–125, 2010.

J. Robins. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. *Mathematical modelling*, 7(9-12): 1393–1512, 1986.

Reference

D. Ruppert, S. J. Sheather, and M. P. Wand. An effective bandwidth selector for local least squares regression. *Journal of the American Statistical Association*, 90(432):1257–1270, 1995.

P. Schnell and G. Papadogeorgou. Mitigating unobserved spatial confounding when estimating the effect of supermarket access on cardiovascular disease deaths. *Annals of Applied Statistics*, 14: 2069–2095, 12 2020.

V. Semenova and V. Chernozhukov. Debiased machine learning of conditional average treatment effects and other causal functions. *The Econometrics Journal*, 24(2):264–289, 2021.

J. Shao. *Mathematical Statistics*. Springer Science & Business Media, 2003.

G. S. Shieh. U-and V-statistics. *Wiley StatsRef: Statistics Reference Online*, 2014.

K. Takatsu and T. Westling. Debiased inference for a covariate-adjusted regression function. *arXiv preprint arXiv:2210.06448*, 2022.

H. Thaden and T. Kneib. Structural equation models for dealing with spatial confounding. *The American Statistician*, 72(3):239–252, 2018.

T. Westling, P. Gilbert, and M. Carone. Causal isotonic regression. *Journal of the Royal Statistical Society Series B: Statistical Methodology*, 82(3):719–747, 2020.

N. Wiecha and B. J. Reich. Two-stage spatial regression models for spatial confounding. *arXiv preprint arXiv:2404.09358*, 2024.

L. H. Wyatt, G. C. Peterson, T. J. Wade, L. M. Neas, and A. G. Rappold. The contribution of improved air quality to reduced cardiovascular mortality: Declines in socioeconomic differences over time. *Environment international*, 136:105430, 2020a.

L. H. Wyatt, G. C. L. Peterson, T. J. Wade, L. M. Neas, and A. G. Rappold. Annual pm2.5 and cardiovascular mortality rate data: Trends modified by county socioeconomic status in 2,132 us counties. *Data in Brief*, 30:105318, 2020b.

Reference

L. Yang and R. Tschernig. Multivariate bandwidth selection for local linear regression. *Journal of the Royal Statistical Society Series B: Statistical Methodology*, 61(4):793–815, 1999.

Y. Zhang, Y.-C. Chen, and A. Giessing. Nonparametric inference on dose-response curves without the positivity condition. *arXiv preprint arXiv:2405.09003*, 2024.

S. Zhou and D. A. Wolfe. On derivative estimation in spline regression. *Statistica Sinica*, 10(1):93–108, 2000.

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

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 $0 < \epsilon < 1$,

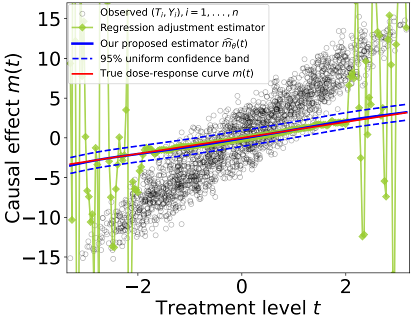
$$\sup_Q N\left(\mathcal{G}, L_2(Q), \epsilon \,||G||_{L_2(Q)}\right) \leq \left(\frac{A_2}{\epsilon}\right)^{\upsilon_2},$$

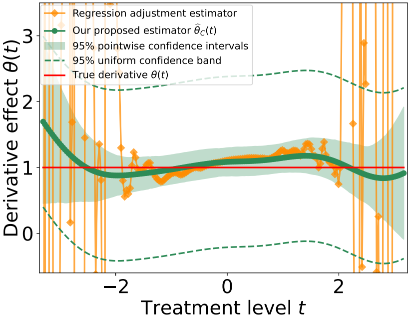
where $N\left(\mathcal{G}, L_2(Q), \epsilon \,||G||_{L_2(Q)}\right)$ is the $\epsilon \,||G||_{L_2(Q)}$-covering number of the (semi-)metric space $\left(\mathcal{G}, ||\cdot||_{L_2(Q)}\right)$, Q is any probability measure on $\mathbb{R}^{d+1}$, G is an envelope function of $\mathcal{G}$, and $||G||_{L_2(Q)}$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

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 $\epsilon \sim \mathcal{N}(0, 1)$.





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

$$\mu\left(f(\boldsymbol{s}), \boldsymbol{s}\right) = \bar{m}\left(f(\boldsymbol{s})\right) + \eta(\boldsymbol{s}) = m\left(f(\boldsymbol{s})\right) + \eta(\boldsymbol{s}). \tag{1}$$

- 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 $\mathrm{Var}(E) = 0$

By (1) 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 $\mathrm{Var}(E) = 0$.

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