NONPARAMETRIC INFERENCE ON DOSE-RESPONSE CURVES WITHOUT THE POSITIVITY CONDITION

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Introduction

Prelude: causal inference

• In a typical causal problem, our data consists of IID random vectors

$$(Y_1, T_1, S_1), \cdots, (Y_n, T_n, S_n).$$

- $Y \in \mathbb{R}$: outcome of interest.
- $T \in \mathbb{R}$: treatment.
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- We want to investigate the causal effect of *T* on the outcome of interest *Y*.
- Many well-established work when the treatment *T* is binary, i.e., $T \in \{0, 1\}$.

Continuous treatment: PM2.5 Example

	fips	name	lng	lat	PM2.5	CMR
1	1059	Franklin	-87.84328	34.44238	8.045251	452.8492
3	19109	Kossuth	-94.20690	43.20414	6.857354	294.3387
4	40115	Ottawa	-94.81059	36.83588	8.073921	424.5076
5	42115	Susquehanna	-75.80090	41.82128	7.955338	383.5730
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Figure: An example of PM2.5 data on cardiovascular mortality rate (CMR) at county-level.

- We want to investigate the effect of PM2.5 on the CMR¹.
- The treatment variable *T* is the amount of PM2.5 at a county, which is *not binary but a continuous number*!

¹Data from US National Center for Health Statistics and Community Multiscale Air Quality modeling system

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- We want to investigate the effect of PM2.5 on the CMR¹.
- The treatment variable *T* is the amount of PM2.5 at a county, which is *not binary but a continuous number*!
- We then encounter the problem of *continuous* treatment.

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PM2.5 Distribution



Figure: The average PM2.5 value of each county.

Continuous treatment: do-calculus

- To deal with continuous treatment problem, we use the graphical model framework with the *do-calculus* technique to define a causal effect.
- The causal effect of *T* on *Y* is defined to be

 $m(t) \equiv \mathbb{E}(Y|\text{do}(T=t)) = \mathbb{E}[\mathbb{E}(Y|T=t,S)].$

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• The above implies a simple estimation procedure. We first estimate $\mu(t, s) = \mathbb{E}(Y|T = t, S = s)$ with $\widehat{\mu}(t, s)$. Then we estimate m(t) via a naive estimator

$$\widetilde{m}(t) = \frac{1}{n} \sum_{i=1}^{n} \widehat{\mu}(t, S_i).$$

Continuous treatment: the positivity condition

• The naive estimator requires the positivity condition, i.e.,

 $(PS) \qquad p(t|s) > 0 \qquad \forall s \in \mathbb{S},$

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where S is the support of *S*.

• To see why (PS) is needed, recall the naive estimator is

$$\widetilde{m}(t) = \frac{1}{n} \sum_{i=1}^{n} \widehat{\mu}(t, S_i).$$

• Without (PS), we cannot have a consistent estimator of $\hat{\mu}(t, s)$ evaluating on $s = S_i$!

Reality: the support of (T,S)



A very common scenario is that the noise *E* is bounded, leading to a violation of the positivity condition.

Identification

Additive confounding model

- In this work, we will focus on additive confounding model.
- Recall that we have a triplet of observations (Y, T, S), where $Y \in \mathbb{R}$ is the outcome, $T \in \mathbb{R}$ is the treatment, and $S \in \mathbb{R}^d$ is the confounder.

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- We assume that

$$Y = m(T) + \eta(S) + \epsilon,$$

$$T = f(S) + E,$$
(1)

where (ϵ, E) are independent mean 0 noises and $\mathbb{E}(\eta(S)) = 0$.

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 In spatial confounding problem (such as PM2.5 studies), the above model is often assumed and is known as *spatial additive confounding model* [KW2003, WD2024].

Theorem (ZCG2024)

Assume the additive confounding model and $\mathbb{E}(\eta(S)) = 0$. Then

- 1. $\mathbb{E}(Y|T = t) = m(t) + \mathbb{E}(\eta(S)|T = t) \neq m(t).$
- **2.** Let $\theta(t) = \frac{\partial}{\partial t}m(t)$. Then

$$\theta(t) = \theta_C(t)$$

$$\theta_C(t) = \mathbb{E}\left(\frac{\partial}{\partial t}\mu(t,S)|T=t\right)$$

The first result shows that naively using conditional mean suffers from a spatial confounding bias. The second result is a key to our identification.

The support of S given T



Identification of $\theta_C(t)$ only require derivatives on the support of *S* given *T*.

Properties of the derivative

- Without positivity, p(t|s) can be 0 so we do not have a consistent estimator of $\mu(t, s)$.
- Our integral estimator is based on the following fact:

$$\Theta(t) = m'(t) = \Theta_C(t) = \mathbb{E}\left(\frac{\partial}{\partial t}\mu(t,S)|T=t\right).$$

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- The quantity $\theta_C(t)$ can be estimated consistently because it is conditioned on T = t.
- We then use the relation

$$m(t) - m(\tau) = \int_{s=\tau}^{s=t} m'(s) ds = \int_{s=\tau}^{s=t} \theta_C(s) ds$$

to estimate m(t).

The integral estimator

The integral estimator - 1

• Recall that we have

$$m(t) - m(\tau) = \int_{s=\tau}^{s=t} m'(s) ds = \int_{s=\tau}^{s=t} \theta_{\mathcal{C}}(s) ds$$

for any τ .

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for any τ .

• Thus, $m(t) = m(T) + \int_{s=T}^{s=t} \theta_C(s) ds$, which implies

$$m(t) = \mathbb{E}\left(m(T) + \int_{s=T}^{s=t} \Theta_C(s)ds\right)$$
$$= \mathbb{E}\left(m(T) + \eta(S) + \epsilon + \int_{s=T}^{s=t} \Theta_C(s)ds\right)$$
$$= \mathbb{E}\left(Y + \int_{s=T}^{s=t} \Theta_C(s)ds\right).$$

- Let $\widehat{\theta}_C(t)$ be an estimator of $\theta_C(t)$.
- The **integral estimator** is

$$\widehat{m}(t) = \frac{1}{n} \sum_{i=1}^{n} Y_i + \int_{s=T_i}^{s=t} \widehat{\theta}_C(s) ds.$$

• Thus, the key is to construct a good estimator of $\theta_C(t) = \mathbb{E}\left(\frac{\partial}{\partial t}\mu(t, S)|T = t\right).$

• We recommend to use the local polynomial regression to estimate $\frac{\partial}{\partial t}\mu(t,s).$

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- Let $\widehat{\beta}(t,s) \in \mathbb{R}^3$, $\widehat{\alpha}(t,s) \in \mathbb{R}^d$ be the minimizer of

$$\sum_{i=1}^{n} \left[Y_i - \sum_{j=1}^{3} \beta_j (T_i - t)^{j-1} - \sum_{\ell=1}^{d} \alpha_\ell (S_{i,\ell} - s_\ell) \right]^2 K_T \left(\frac{T_i - t}{h} \right) K_S \left(\frac{\|S_i - s\|}{b} \right),$$

where K_T and K_S are smoothing kernel and h, b > 0 are smoothing bandwidth.

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where K_T and K_S are smoothing kernel and h, b > 0 are smoothing bandwidth.

• It is known that the second component $\widehat{\beta}_2(t, s)$ is a consistent estimator of $\frac{\partial}{\partial t} \mu(t, s)$; see, e.g., [F2018].

• Note that

$$\theta_C(t) = \mathbb{E}\left(\frac{\partial}{\partial t}\mu(t,S)|T=t\right) = \int \frac{\partial}{\partial t}\mu(t,s)dP(s|t).$$

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• Thus, we also need an estimator of *P*(*s*|*t*). Here we simply use a kernel CDF estimator

$$\widehat{P}(s|t) = \frac{\sum_{i=1}^{n} I(S_i \le s) \overline{K}_T\left(\frac{T_i - t}{\hbar}\right)}{\sum_{j=1}^{n} \overline{K}_T\left(\frac{T_j - t}{\hbar}\right)}$$

• Note: other estimators are applicable–kernel CDF is just a simple and reliable estimator.

• Combining the above two estimators, our estimator $\theta_C(t)$ can be written as

$$\widehat{\theta}_{C}(t) = \frac{\sum_{i=1}^{n} \widehat{\beta}_{2}(t, S_{i}) \overline{K}_{T}\left(\frac{T_{i}-t}{\hbar}\right)}{\sum_{j=1}^{n} \overline{K}_{T}\left(\frac{T_{j}-t}{\hbar}\right)}.$$

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• Thus, the integral estimator is

$$\widehat{m}(t) = \frac{1}{n} \sum_{i=1}^{n} Y_i + \int_{s=T_i}^{s=t} \widehat{\theta}_C(s) ds.$$

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- Note: the above integral estimator is also a *linear smoother*.
- We can use the bootstrap to construct a simultaneous confidence band.

Asymptotic theory

The support of (T,S) revisited



- Let \mathscr{C} be the support of (T, S).
- In the above figure, the support is the blue area, which shows a clear violation of (PS).

- $\theta_C(t) = \int \frac{\partial}{\partial t} \mu(t, s) dP(s|t)$ only require $\hat{\beta}_2(t, s)$ to be consistent on $\mathscr{C}!$
- Feature of the local polynomial estimator: β₂(t, s) is consistent estimator in %.

Uniform convergence of derivative estimator

Lemma (ZCG2024)

Under regularity conditions (A3-A5, A6-1, A6-2),

$$\sup_{t,s)\in\mathscr{C}} \left| \widehat{\beta}_2(t,s) - \frac{\partial}{\partial t} \mu(t,s) \right|$$
$$= O\left(h^2 + b^2 + \frac{\max\{b,h\}^4}{h} \right) + O_P\left(\sqrt{\frac{|\log(h)|}{nh^3}}\right)$$

This shows that the local polynomial estimator is uniformly consistent in \mathcal{C} . Note that the convergence rate differs a little on the boundary of \mathcal{C} versus its interior.

Uniform convergence of integral estimator - 1

Combining with the convergence of kernel CDF, we immediately have the following result:

Theorem (ZCG2024)

Let $\mathcal{T}' \subset \mathcal{T} \equiv \text{supp}(T)$ be a compact set. Under regularity conditions (A1-A6),

$$\begin{split} \sup_{t \in \mathcal{T}'} |\widehat{\theta}_{C}(t) - \theta_{C}(t)| \\ &= O\left(h^{2} + b^{2} + \frac{\max\{b, h\}^{4}}{h}\right) + O_{P}\left(\sqrt{\frac{|\log(h)|}{nh^{3}}} + \hbar^{2} + \sqrt{\frac{|\log\hbar|}{n\hbar}}\right), \\ \sup_{t \in \mathcal{T}'} |\widehat{m}(t) - m(t)| \\ &= \left(1 - \frac{\sqrt{|\log\hbar|}}{n\hbar} + h^{2}\right) = \left(1 - \frac{\sqrt{|\log\hbar|}}{n\hbar}\right), \end{split}$$

$$= O\left(h^2 + b^2 + \frac{\max\{b, h\}^*}{h}\right) + O_P\left(\frac{1}{\sqrt{n}} + \sqrt{\frac{|\log(h)|}{nh^3}} + \hbar^2 + \sqrt{\frac{|\log n|}{n\hbar}}\right).$$

23/31

Uniform convergence of integral estimator - 2

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

- Blue term: the bias in local polynomial estimator.
- Red term: additional bias from boundary of *C*.
- Orange term: rate from \bar{Y}_n .
- Brown term: stochastic variation of local polynomial estimator.
- Cyan term: rate from kernel CDF.

Case study: PM2.5 effect

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Figure: An example of PM2.5 data on cardiovascular mortality rate (CMR) at county-level.

- The above data table shows the average PM2.5 and CMR over 1990-2010 of each county.
- We also have other 8 county-level informations such as population, unemployment rates, household income, ...etc.
- We want to investigate how PM2.5 would impact the CMR.

PM2.5 data



- We consider three model: naive method, adjusting for spatial confounding, adjusting for all covariates.
- The confidence bands are pointwise.
- A clear increasing effect after adjusting for all covariates.

Discussion

- Our integral estimator allows us to bypass the positivity condition.
- We have a fast algorithm, nice asymptotic theory, and methods for making inferences.
- This idea opens a new direction for investigating continuous treatments because the violation of positivity is very common!

Open problems and future work

- **Inverse probability weighting.** Our method is essentially a regression adjustment (g-computation) method. Can we generalize it to the inverse probability weighting approach?
- **Doubly-robustness.** Following the previous result, are we able to construct a doubly-robust estimator? We may need to use a cross-fitting (double machine learning) approach in this case.
- **High-dimensional confounders.** In addition to 2D spatial confounders, we may have high-dimensional confounders with a sparse linear effect. Will our method work?
- **Unmeasured confounders.** We assume all confounders are observed. Can we handle unmeasured confounders? Perhaps with some known instruments?

Thank You!

All codes and data are available: https://github.com/zhangyk8/npDoseResponse/tree/main Paper reference: https://arxiv.org/abs/2405.09003.

References

- [CCK2014] Chernozhukov, V., Chetverikov, D., & Kato, K. (2014). Gaussian approximation of suprema of empirical processes.
- [CL2020] Colangelo, K., & Lee, Y. Y. (2020). Double debiased machine learning nonparametric inference with continuous treatments. arXiv preprint arXiv:2004.03036.
- [F2018] Fan, J. (2018). Local polynomial modelling and its applications: monographs on statistics and applied probability 66. Routledge.
- [G2023] Giessing, A. (2023). Gaussian and Bootstrap Approximations for Suprema of Empirical Processes. arXiv preprint arXiv:2309.01307.
- [HHLL2020] Huber, M., Hsu, Y. C., Lee, Y. Y., & Lettry, L. (2020). Direct and indirect effects of continuous treatments based on generalized propensity score weighting. Journal of Applied Econometrics, 35(7), 814-840.
- 6. [KW2003] Kammann, E. E., & Wand, M. P. (2003). Geoadditive models. Journal of the Royal Statistical Society Series C: Applied Statistics, 52(1), 1-18.
- [KMMS2017] Kennedy, E. H., Ma, Z., McHugh, M. D., & Small, D. S. (2017). Non-parametric methods for doubly robust estimation of continuous treatment effects. Journal of the Royal Statistical Society Series B: Statistical Methodology, 79(4), 1229-1245.
- 8. [RHB2000] Robins, J. M., Hernan, M. A., & Brumback, B. (2000). Marginal structural models and causal inference in epidemiology. Epidemiology, 11(5), 550-560.
- 9. [WR2024] Wiecha, N., & Reich, B. J. (2024). Two-stage Spatial Regression Models for Spatial Confounding. arXiv preprint arXiv:2404.09358.
- [ZCG2024] Zhang, Y., Chen, Y. C., & Giessing, A. (2024). Nonparametric Inference on Dose-Response Curves Without the Positivity Condition. arXiv preprint arXiv:2405.09003.

• We may use an inverse probability weighting (IPW; [CL2020, HHLL2020]) estimator for this problem:

$$\widetilde{m}_{IPW}(t) = \frac{1}{nh} \sum_{i=1}^{n} K\left(\frac{T_i - t}{h}\right) \frac{Y_i}{\widehat{p}(t|S_i)},$$

where $\hat{p}(t|s)$ is an estimator of the conditional PDF p(t|s) and $K(\cdot)$ is a smoothing kernel such as a Gaussian.

• There is also a doubly-robust version of this idea via pseudo-outcome [KMMS2017].

• The integral estimator

$$\widehat{m}(t) = \frac{1}{n} \sum_{i=1}^{n} Y_i + \int_{s=T_i}^{s=t} \widehat{\theta}_C(s) ds$$

require the evaluation of integration $\int_{s=T_i}^{s=t}$, which could be computationally expansive.

• Here we propose a simple numerical method for approximating this.

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- Here we propose a simple numerical method for approximating this.
- Let $T_{(1)} \leq T_{(2)} \leq \cdots \leq T_{(n)}$ be the ordered values of the observed treatment.
- We then have

$$\frac{1}{n}\sum_{i=1}^n\int_{s=T_i}^{s=t}\widehat{\theta}_C(s)ds=\frac{1}{n}\sum_{i=1}^n\int_{s=T_{(i)}}^{s=t}\widehat{\theta}_C(s)ds.$$

• The above result implies

$$\widehat{m}(T_{(j)}) = \overline{Y}_n + \frac{1}{n} \sum_{i=1}^n \int_{s=T_{(i)}}^{s=T_{(j)}} \widehat{\theta}_C(s) ds.$$

• Let $\Delta_j = T_{(j+1)} - T_{(j)}$.

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• When i < j, we use Riemann sum,

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• When i > j, we use Riemann sum,

$$\int_{s=T_{(i)}}^{s=T_{(j)}} \widehat{\theta}_{C}(s) ds \approx -\sum_{\ell=j}^{\ell=i-1} \widehat{\theta}_{C}(T_{(\ell+1)}) \Delta_{\ell}.$$

• When we include $\sum_{i=1}^{n}$, some $\hat{\theta}_{C}(T_{(\ell)})$ will be used multiple times, which eventually leads to the following result:

$$\frac{1}{n} \sum_{i=1}^{n} \int_{s=T_{(i)}}^{s=T_{(j)}} \widehat{\theta}_{C}(s) ds$$
$$\approx \frac{1}{n} \sum_{i=1}^{n-1} \Delta_{i} \left[i \cdot \widehat{\theta}_{C}(T_{(i)}) I(i < j) - (n-i) \cdot \widehat{\theta}_{C}(T_{(i+1)}) I(i \ge j) \right].$$

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- The above result only requires evaluating $\hat{\theta}_C(t)$ at the observed T_1, \dots, T_n once!
- As a result, we can quickly approximate

$$\widehat{m}(T_{(j)}) \approx \overline{Y}_n + \frac{1}{n} \sum_{i=1}^{n-1} \Delta_i \left[i \cdot \widehat{\theta}_C(T_{(i)}) I(i < j) - (n-i) \cdot \widehat{\theta}_C(T_{(i+1)}) I(i \ge j) \right]$$

• Finally, to approximate $\widehat{m}(t)$, we first find the interval $[T_{(j^*)}, T_{(j^*+1)}]$ such that

$$t \in [T_{(j^*)}, T_{(j^*+1)}].$$

• We then use a linear interpolation between $\widehat{m}(T_{(j^*)})$ and $\widehat{m}(T_{(j^*+1)})$ to approximate $\widehat{m}(t)$.

Confidence bands via the bootstrap

- We may construct a simultaneous confidence band of *m*(*t*) via the bootstrap.
- Let $(Y_1^*, T_1^*, S_1^*), \dots, (Y_n^*, T_n^*, S_n^*)$ be a bootstrap sample (sampling with replacement of the original data).
- We compute the bootstrap estimator $\widehat{m}^*(t)$.
- Let $\widehat{\xi}_{1-\alpha}^*$ be the 1α quantile of

$$\sup_t |\widehat{m}^*(t) - \widehat{m}(t)|.$$

• A $1 - \alpha$ simultaneous confidence band is

$$[\widehat{m}(t) - \widehat{\xi}^*_{1-\alpha}, \quad \widehat{m}(t) + \widehat{\xi}^*_{1-\alpha}]$$

Bootstrap Validity - 1

- To show the bootstrap validity, we first need to derive an asymptotic linear form of $\widehat{m}(t)$.
- For simplicity, we assume that $h \asymp b$, so the convergence rate becomes

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

• We let $\hbar \approx \left(\frac{\log n}{n}\right)^{-1/5}$ be the optimal choice so the kernel CDF converges faster. Thus, we only need to focus on the primary term

$$O(h^2) + O_P\left(\sqrt{\frac{|\log(h^{d+1})}{nh^{d+3}}}\right)$$

• We consider an undersmoothing *h* so that $nh^{d+7} \rightarrow 0$. Under this choice, the bias converges faster than the variance, and the rate is

$$\sup_{t\in\mathcal{T}'}|\widehat{m}(t)-m(t)|=O_P\left(\sqrt{\frac{|\log(h^{d+1})}{nh^{d+3}}}\right).$$

Lemma (Asymptotic linearity)

Under regularity conditions (A1-A6), $h \approx b$, $\hbar \approx \left(\frac{\log n}{n}\right)^{-1/5}$, and $nh^{d+7} \rightarrow 0$. There exists a function $\psi_t : \mathbb{Y} \times \mathbb{T} \times \mathbb{S} \rightarrow \mathbb{R}$ such that

$$\begin{split} |\sqrt{nh^{d+3}(\widehat{m}(t) - m(t))} - \mathbb{G}_n \psi_t| \\ &= O_P \left(\sqrt{nh^{d+7}} + \sqrt{\frac{\log n}{n\hbar^2}} + \sqrt{\frac{h^{d+3}\log n}{\hbar}} + \sqrt{\frac{h^{d+3}}{\hbar^2}} \right), \end{split}$$

where $\mathbb{G}_n f = \frac{1}{\sqrt{n}} \sum_{i=1}^n [f(Y_i, T_i, S_i) - \mathbb{E}(f(Y, T, S))]$.

Note that \mathbb{Y} , \mathbb{T} , \mathbb{S} are the support of *Y*, *T*, *S*, respectively.

- With the above asymptotic linearity, we are able to approximate the distribution of $\sup_t |\widehat{m}(t) m(t)|$ by a maximum of a Gaussian process, leading to the validity of the bootstrap.
- Namely, we have

$$\sqrt{nh^{d+3}}\sup_{t\in\mathcal{T}'}|\widehat{m}(t)-m(t)|\approx\sup_{t\in\mathcal{T}'}|\mathbb{G}_n\psi_t|\approx\sup_{t\in\mathcal{T}'}|\mathbb{B}_n\psi_t|,$$

where $\mathbb{B}_n f_t$ is a Gaussian process on the function class f_t indexed by t.

 The bootstrap maximum approximates the above maximum, leading to the consistency of the bootstrap confidence band [CCK2014, G2023].

Corollary (Bootstrap validity)

Under regularity conditions (A1-A6), $h \approx b$, $\hbar \approx \left(\frac{\log n}{n}\right)^{-1/5}$, and $nh^{d+7} \rightarrow 0$. Let $\xi_{1-\alpha}^*$ be the bootstrap quantile. Then

$$P\left(m(t) \in \left[\widehat{m}(t) - \widehat{\xi}_{1-\alpha}^*, \widehat{m}(t) + \widehat{\xi}_{1-\alpha}^*\right] \quad \forall t \in \mathcal{T}'\right) = 1 - \alpha + O_P\left(\left(\frac{\log^5 n}{nh^{d+3}}\right)^{1/8}\right)$$

- **A1-1:** Consistency. Given T = t, Y = Y(t).
- A1-2: Ignorability. $\{Y(t) : t \in \mathbb{T}\} \perp T | S$.
- **A1-3: Treatment variation.** The variance Var(E) > 0 in the equation T = f(S) + E.
- **A2:** Derivative identification. $\theta(t) = \theta_C(t) = \mathbb{E}\left[\frac{\partial}{\partial t}\mu(t, S)|T = t\right]$ and $\mathbb{E}(\mu(T, S)) = \mathbb{E}(m(T))$.

- A3: Conditional mean. μ(t, s) is at least 3-times continuously differentiable with respect to t and at least 4-times continuously differentiable with respect to s.
- A4: Joint density. p(t, s) is at least twice continuously differentiable with bounded partial derivatives up to 2nd order in the interior of *C*. All partial derivative are continuous up to, ∂*C*, the boundary of *C*. *C* is compact and sup_{(t,s)∈C} p(t,s) > 0.

• **A5-1:** Smooth boundary. There are constants $r_1, r_2 \in (0, 1)$ such that for any $(t, s) \in \mathcal{C}$ and all $\delta \in (0, r_1]$, there is another point $(t', s') \in \mathcal{C}$ such that

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

- **A5-2:** Boundary derivative. For any $(t, s) \in \mathcal{C}$, $\frac{\partial}{\partial t}p(t, s) = \frac{\partial}{\partial s_j}p(t, s) = 0$ and $\frac{\partial^2}{\partial s_i^2}\mu(t, s) = 0$ for all $j = 1, \dots, d$.
- **A5-3: Stable volume.** The Lebesgue measure of the set $\partial \mathscr{C} \oplus \delta$ satisfies

$$\mathsf{Leb}(\partial \mathscr{C} \oplus \delta) \le A_1 \cdot \delta$$

for some constant A_1 , where $\mathbb{A} \oplus \delta = \{z : \inf_{x \in \mathbb{A}} ||x - z|| \le \delta\}.$

- **A6-1: Regular.** *K*_{*T*}, *K*_{*S*} are compactly supported and Lipchitz kernel with *K*_{*T*} being symmetric and *K*_{*S*} is radially symmetric and are second-order kernels.
- A6-2: VC-type kernels. Let

$$\begin{aligned} \mathcal{K}_{3,d} &= \left\{ (y,z) \mapsto \left(\frac{y-t}{h}\right)^{\ell} \left(\frac{z_i - s_i}{b}\right)^{k_1} \left(\frac{z_j - s_j}{b}\right)^{k_2} \\ &\times K_T \left(\frac{y-t}{h}\right) K_S \left(\frac{z-s}{b}\right) : (t,s) \in \mathcal{C}; \\ &i, j = 1, \cdots, d; \ell = 0, \cdots, 6; k_1, k_2 = 0, 1; h, b > 0 \right\} \end{aligned}$$

The class $\mathcal{K}_{3,d}$ is VC-type class.

- **A6-3: Regular of kernel CDF.** \bar{K}_T is a compactly supported, Lipchitz, symmetric, and second-order kernel.
- A6-4: VC-type kernel CDF. Let

$$\bar{\mathcal{K}} = \left\{ y \mapsto \bar{K}_T \left(\frac{y-t}{\hbar} \right) : t \in \mathbb{T}, \hbar > 0 \right\}$$

The class $\bar{\mathcal{K}}$ is VC-type class.

Asymptotic linearity - 1

• In the asymptotic linearity, we have

$$\sqrt{nh^{d+3}}(\widehat{m}(t)-m(t))\approx \mathbb{G}_n\psi_t.$$

• ψ_t is the following function

$$\psi_t(Y,T,S) = \mathbb{E}_{T_2}\left[\int_{\tilde{t}=T_2}^t \widetilde{\psi}_{\tilde{t}}(Y,T,S)d\tilde{t}\right]$$

with

$$\widetilde{\psi}_{\widetilde{t}}(Y,T,S) = \mathbb{E}_{T_3,S_3}\left[\frac{e_2^T M_3^{-1} \Psi_{\widetilde{t},S_3}(Y,T,S)}{\sqrt{hb^d} p(\widetilde{t},S_3) p_T(\widetilde{t})} \cdot \frac{1}{\hbar} \bar{K}_T\left(\frac{\widetilde{t}-T_3}{\hbar}\right)\right],$$

where $e_2 = (0, 1, 0, \dots, 0) \in \mathbb{R}^{3+d}$ and $M_2 \in \mathbb{R}^{(3+d) \times (3+d)}$ is a block diagonal matrix of constants.

•
$$\Psi_{t,s}(y, z, v) \in \mathbb{R}^{3+d}$$
 is the following function

$$\Psi_{t,s}(y,z,v) = y \cdot \begin{bmatrix} \left(\frac{z-t}{h}\right)^{j-1} K_T\left(\frac{z-t}{h}\right) K_S\left(\frac{v-s}{b}\right)_{1 \le j \le 3} \\ \left(\frac{v_{j-3}-s_{j-3}}{b}\right) K_T\left(\frac{z-t}{h}\right) K_S\left(\frac{v-s}{b}\right)_{4 \le j \le 3+d} \end{bmatrix}$$