Update Slides

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Recap

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- Motivated by effects of drug-switching after TNFi drugs in RA patients, interested in Causal PheWAS type analysis of secondary outcomes
- Previously discussed/presented Hawkes estimation, elided formal problem statements and causal assumptions

Goals Today

- Articulate our problem more concretely in the LMTP/DTR and Off-Policy Evaluation formulations
  - Focus on novelties/nuances of $\mathbf{Y} \in \mathbb{R}^d$

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Summary

- Using the LMTP framework with extensions for simultaneous inference from Kennedy (2024)
  - **Pros:** Nicely characterized univariate problem
  - **Weaknesses:** Final inference still likely underutilizing shared information within $\mathbf{Y}$
- In OPE, remains unclear to me how to use multivariate reward space $R \in \mathbb{R}^d$

Outline

Motivation

Problem

- Persons with RA most often receive TNFi drugs as a first course of treatment
- Observe switching other drug classes based on non-response and/or adverse event or clinical history
- The goal is to understand:
  - For which patients will switching be effective? (ATE/CATE problem)
  - **How to optimize timing of switching? (DTR/OTR problem)**

Considerations:

- Certain events (e.g. cardiac arrest) prohibit certain treatment paths
  - Possible positivity violation (pending identifiability assumptions)

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Set-Up and Observables

- For times $t = 1, \dots, \tau$, observe $Z = (L_1, A_1, \cdots L_\tau, A_\tau, Y) \sim \mathbb{P}$
  - Covariates L_t, Binary treatment A_t; Outcome $Y_t \in \mathbb{R}^d$
  - Write history $h_t = (A_1, L_1, \cdots, L_t)$
- Implicitly, assume that observed treatments/actions $A_{1:\tau}$ follow some current behavior/policy
- Propose a policy, $\mathbf{d} : (a_t, h_t) \mapsto A^d_{t+1}$ with which we generate the counterfactual paths
- Estimand: $\mathbb{E}(Y(\overline{A}^{\mathbf{d}}))$

Example Switching Policy

$$\mathbf{d}(a_t, [h_{1t}, h_{2t}], \varepsilon_t) = \begin{cases} TNFi & if \;\; h_{1t} = 0 \;\&\; h_{2t} = 0 \\ CDA & h_{1t} = 0 \;\&\; h_{2t} = 1 \;\&\; \epsilon_t < 0.5 \\ IL-6R & h_{1t} = 1 \;\&\; h_{2t} = 1 \;\;\&\; \epsilon_t < 0.5 \end{cases}$$

$$(A_t, H_t)_{t \in T} \perp \varepsilon_t \sim U(0, 1)$$

- Requires us to formulate **d** policy shared across observations
- If $(a_t, h_t) \in \mathrm{supp}(A_t, H_t)$ then $\mathbf{d}(a_t, h_t) \in \mathrm{supp}(A_t, H_t)$
  - i.e. the positivity assumption is flexible to our proposed policy

Extensions to Multiple Outcomes

- Diaz 2021 derive the EIF, propose estimation for univariate Y (well-characterized)
- Using results from Kennedy (2024), can construct outcome specific IF's, preform controlled hypothesis testing
  - Requires extensions of Kennedy Lemma's for IF's of the form in Diaz

Outline

Kennedy (2024) Problem

- Observe $(X, A, Y)_i$, $Y \in \mathbb{R}^d$
- Goal is to estimate $\tau_k = \mathbb{E}(Y_k(1) - Y_k(0)$, $k = 1, \cdots, d$
- Construct outcome-specific IF's, φ_k
- Control FWER of testing via a Gaussian multiplier bootstrap procedure (tailored towards semiparametric inference problem)

Strength: Natural extension for problems whose individual IF-based estimation properties are well characterized

Weakness: Using little/no covariance/shared information among outcomes $Y_{1:k}$

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- Next Steps:
  - Continue review of OPE methods/literature
  - Review/implement simple LMTP analysis

Appendix

Lemma 11 (Gaussian approximation for nested hypotheses). (Kennedy 2024)

For $\tau_j = \tau_j^{\mathrm{TTE}}$ and $\vartheta = \vartheta^{\mathrm{STE}}$. For all $\mathcal{S} \subseteq \mathcal{A}^* \subseteq [p]$, define $M_s = \max_{j \in \mathcal{S}} \left| \sqrt{n} \left(\hat{\nu}_j - \tau_j \right) / \hat{\partial}_j \right|, \hat{\varphi}_i = \left(\hat{\varphi}_{ij} \right)_{j \in \delta'}, \hat{\mathbf{E}}_s = n^{-1} \sum_{i=1}^{n} \hat{\phi}_i \hat{\varphi}_i^{\top}$, and $\hat{\boldsymbol{D}}_s = \operatorname{diag}\left(\hat{\partial}_j \right)_{j \in \delta}$. Consider null hypotheses H_0^s indexed by $\mathcal{S}$ that $\forall j \in \mathcal{S}, \tau_j = \tau_j^*$. As $m, n, p \to \infty$, it holds that

$$\sup_{H_0^{\delta} : s \subseteq \mathcal{A}^*} \sup_{x \in \mathbb{R}} \left| \mathbb{P}\left(\mathbb{M}_s > x \right) - \mathbb{P}\left(\| \boldsymbol{g}_{\delta} \|_{\infty} > x \mid \{ \mathbb{Z}_i \}_{i=1}^{n} \right) \right| \xrightarrow{\mathrm{p}} 0,$$

where $\boldsymbol{g}_s \sim \mathcal{N}\left(\mathbf{0}, \hat{\mathbf{D}}_S^{-1} \hat{\mathrm{E}}_S \hat{\boldsymbol{D}}_s^{-1} \right)$. The conclusion also holds for $\tau_j = \tau_j^{\mathrm{QTE}}$ and $\vartheta = \vartheta^{\mathrm{QTE}}$ under conditions in Proposition 10 and Assumption 4.