An introduction to Longitudinal Modified Treatment Policies

A framework for defining, identifying, and estimating complex, continuous, and/or time-varying exposures

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TGIF
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An introduction to LMTPs

References and Caveats

- This talk will be based on,

  Hoffman K.L., Salazar D., Williams, N., Rudolph, K., Díaz, I. Studying continuous, time-varying, and/or complex exposures using longitudinal modified treatment policies. *Epidemiology (2024)*

- …which is itself based on,

  Díaz, I., Williams, N., Hoffman, K. L., & Schenck, E. J. Nonparametric Causal Effects Based on Longitudinal Modified Treatment Policies. *Journal of the American Statistical Association (2021)*

- *TGIF caveat:* my contributions to LMTP to date are practical, not theoretical.

An introduction to LMTPs

Today's talk

1. **Motivation**
2. **Setup**
3. **Defining an LMTP intervention**
4. **Identification assumptions**
5. **Estimation procedures**
6. **Extensions and applications**

Motivation

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    - **Difficult to interpret under model misspecification** *(Neugebauer and van der Laan, 2007)*

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- Summarizing the infinite-dimensional dose-response curve, e.g. through a Marginal Structural Model, typically requires restrictive and arbitrary **parametric assumptions**
  - **Difficult to interpret under model misspecification** *(Neugebauer and van der Laan, 2007)*
- Non-parametric estimation approaches of the dose-response cannot achieve $n^{1/2}$-consistency, because it is not a pathwise-differentiable parameter

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  - Multiple time points make a positivity violation more likely to occur

- Ignoring a time-varying exposure mechanism for practical purposes can cause serious time-alignment biases

  - Frequently done in practice, e.g. treat all units receiving exposure within a certain time interval from baseline as “treated,” otherwise “untreated”

LMTP's Methodological contribution

Extending MTPs to the time-varying setting

- Formally defining LMTP **estimands**
- **Identification** assumptions
- **Estimators** — two are efficient and one is *sequentially doubly robust*
- Open source **R package {lmtp}**
  - Author/maintainer: Nick Williams

Setup

Setup

Notation

- $Z_1, \ldots, Z_t$: a sample of i.i.d observations,
  $Z = (L_1, A_1, L_2, A_2, \ldots, L_\tau, A_\tau, Y) \sim \mathrm{P}$

- A_t : intervention variables, e.g. treatment and/or censoring status

- L_t : time-varying covariates

- $Y = L_{\tau+1}$: outcome at the end of follow-up

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- History of one variable, $\bar{X}_t = (X_1, \ldots, X_t)$
- Future of one variable, $\underline{X}_t = (X_t, \ldots, X_\tau)$
- $H_t = (\bar{A}_{t-1}, \bar{L}_t)$ — history of all variables up until just before A_t
- Parentheses denote counterfactual variables

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Non-parametric structural equation model

(Pearl, 2009)

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- Assume the existence of deterministic functions f_{L_t}, f_{A_t}, f_Y s.t.
  - $L_t = f_{L_t}(A_{t-1}, H_{t-1}, U_{L,t})$
  - $A_t = f_{A_t}(H_t, U_{A,t})$
  - $Y = f_Y(A_\tau, H_\tau, U_Y)$
  - where $U = (U_{L,t}, U_{A,t}, U_Y : t \in \{1, \ldots, \tau\})$ are a vector of exogenous variables with unrestricted joint distribution

Setup

Directed Acyclic Graph (Pearl, 2009)

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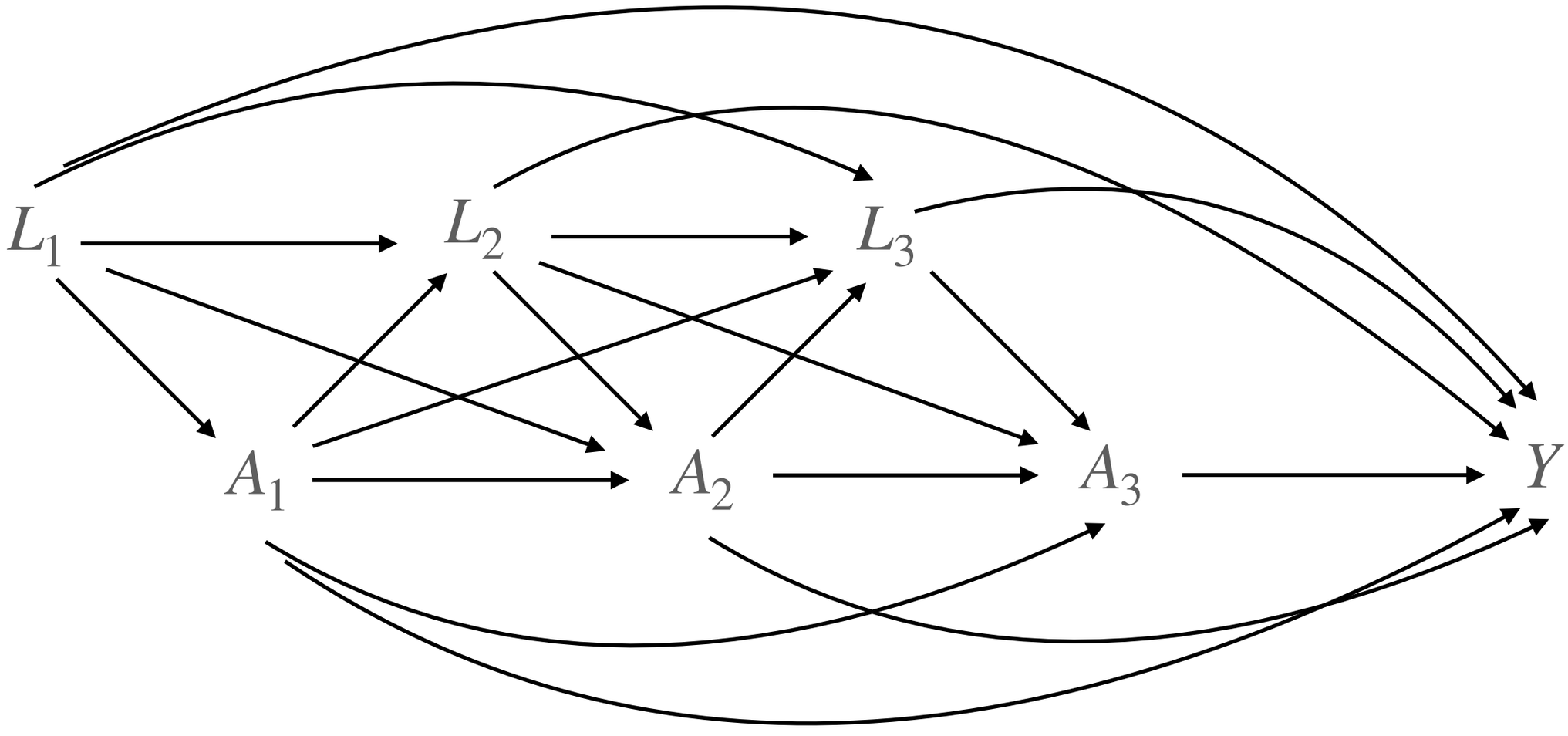

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Defining an LMTP intervention

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- Consider a user-defined intervention d
- **LMTP effects** defined as **hypothetical interventions** where we **replace**

$$A_t = f_{A_t}(H_t, U_{A,t})$$

in the SEM with a **new random variable**,

$$A_t^{\mathsf{d}}$$

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Intuition based on SWIGS

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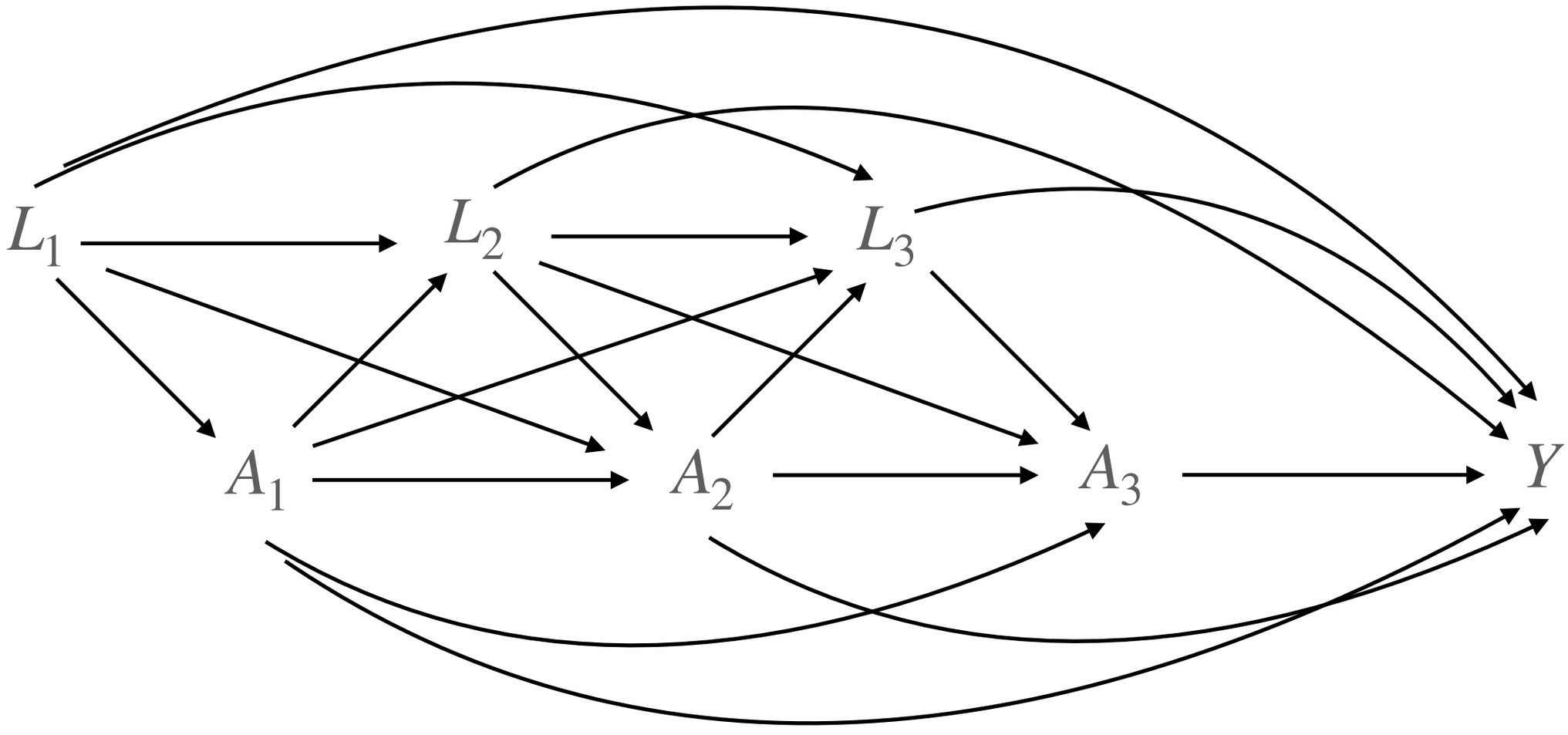

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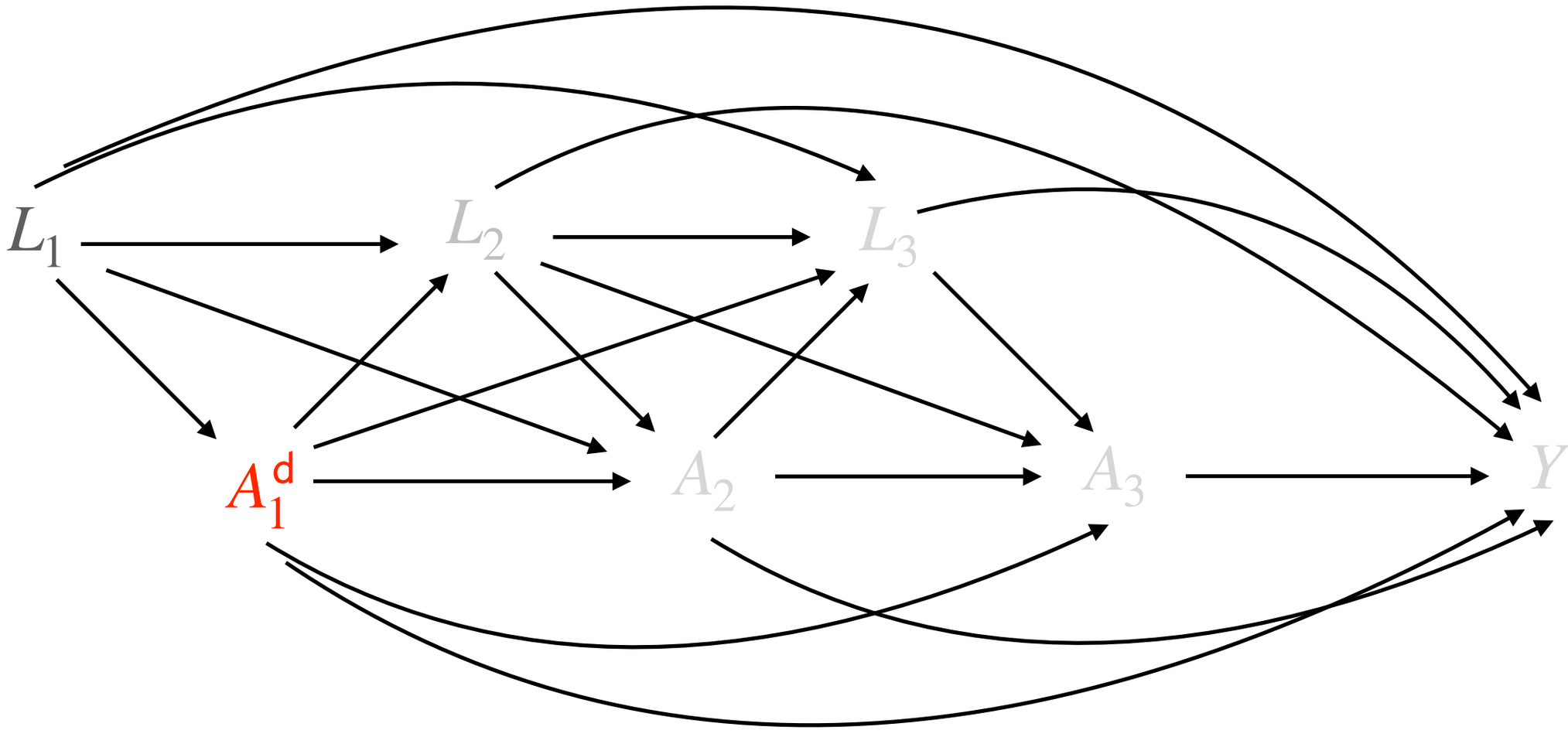

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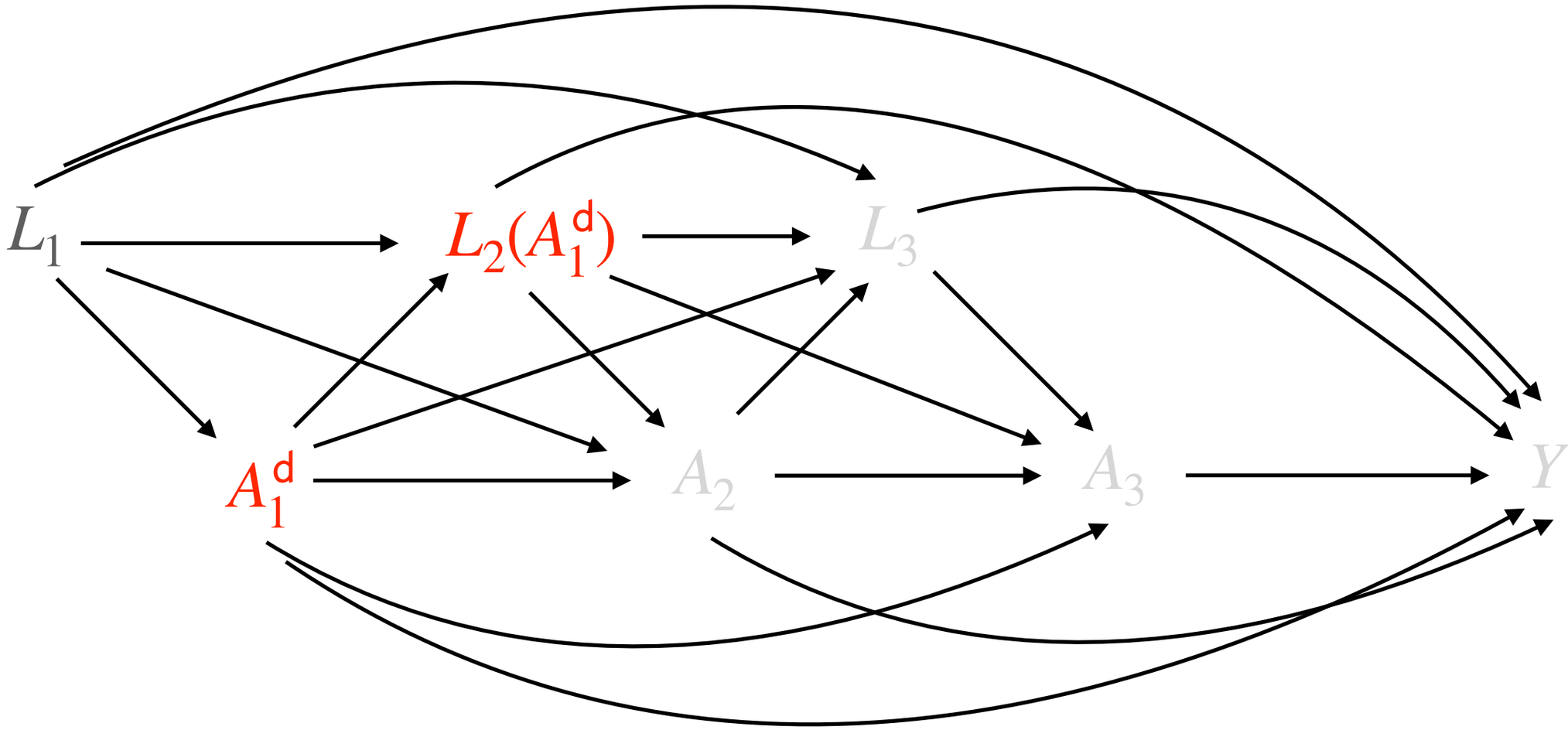

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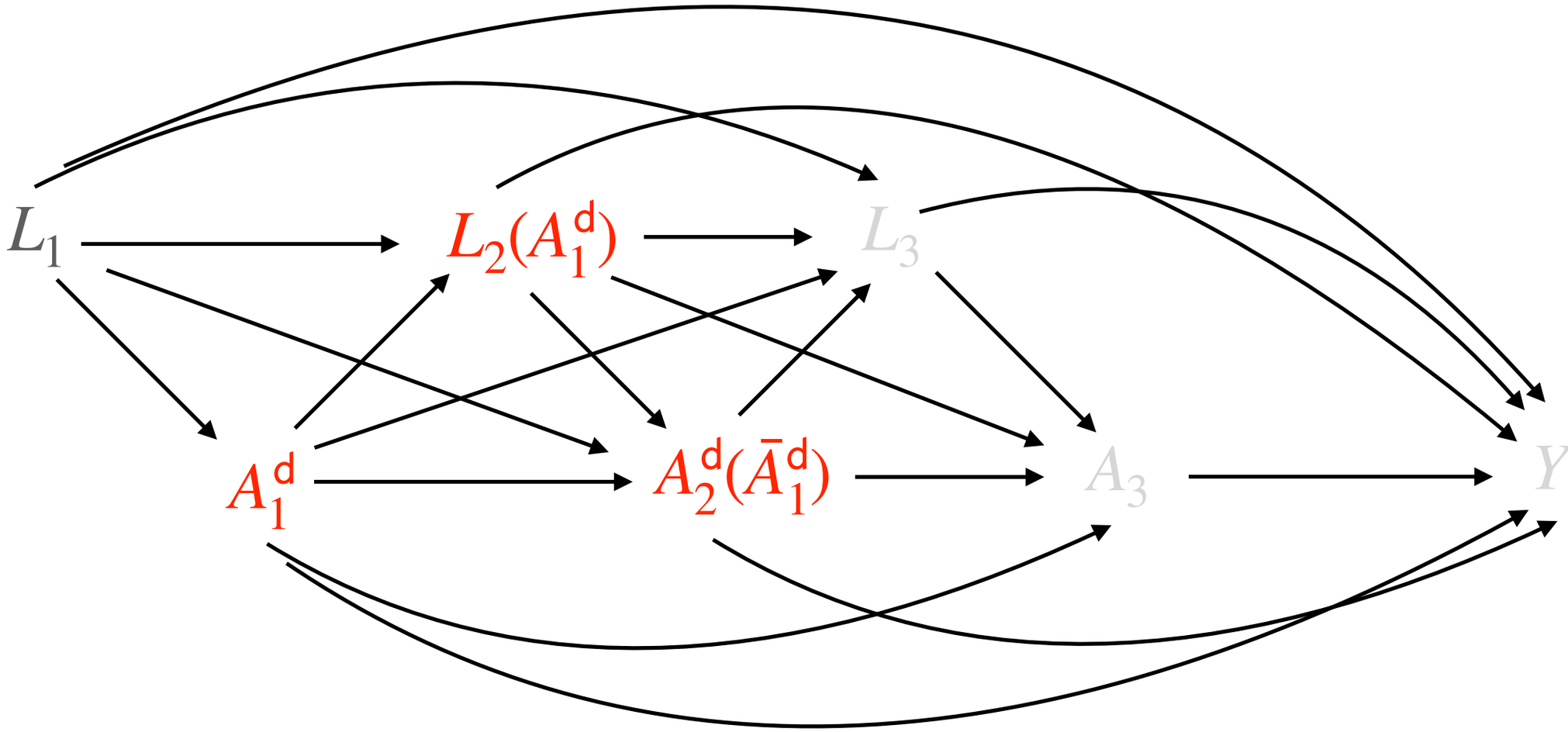

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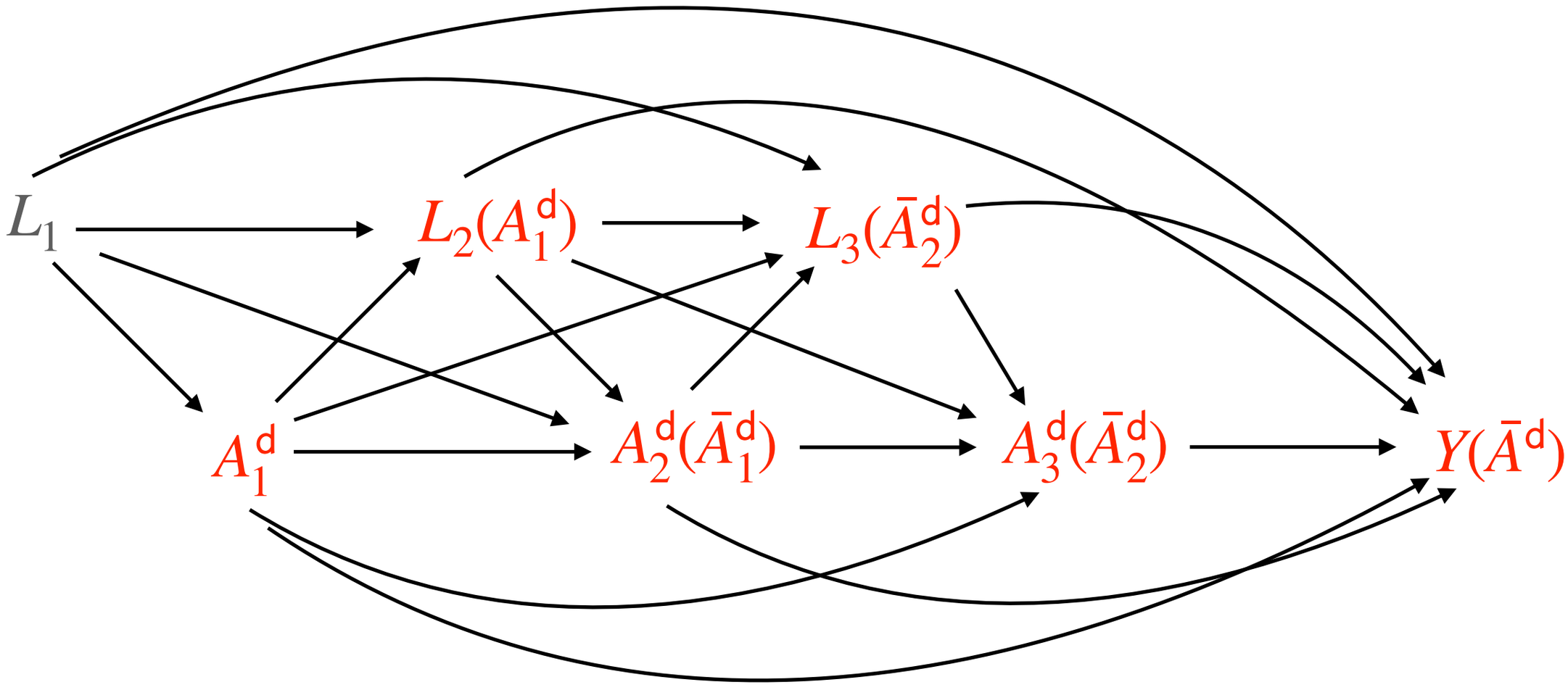

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- Natural value of treatment:
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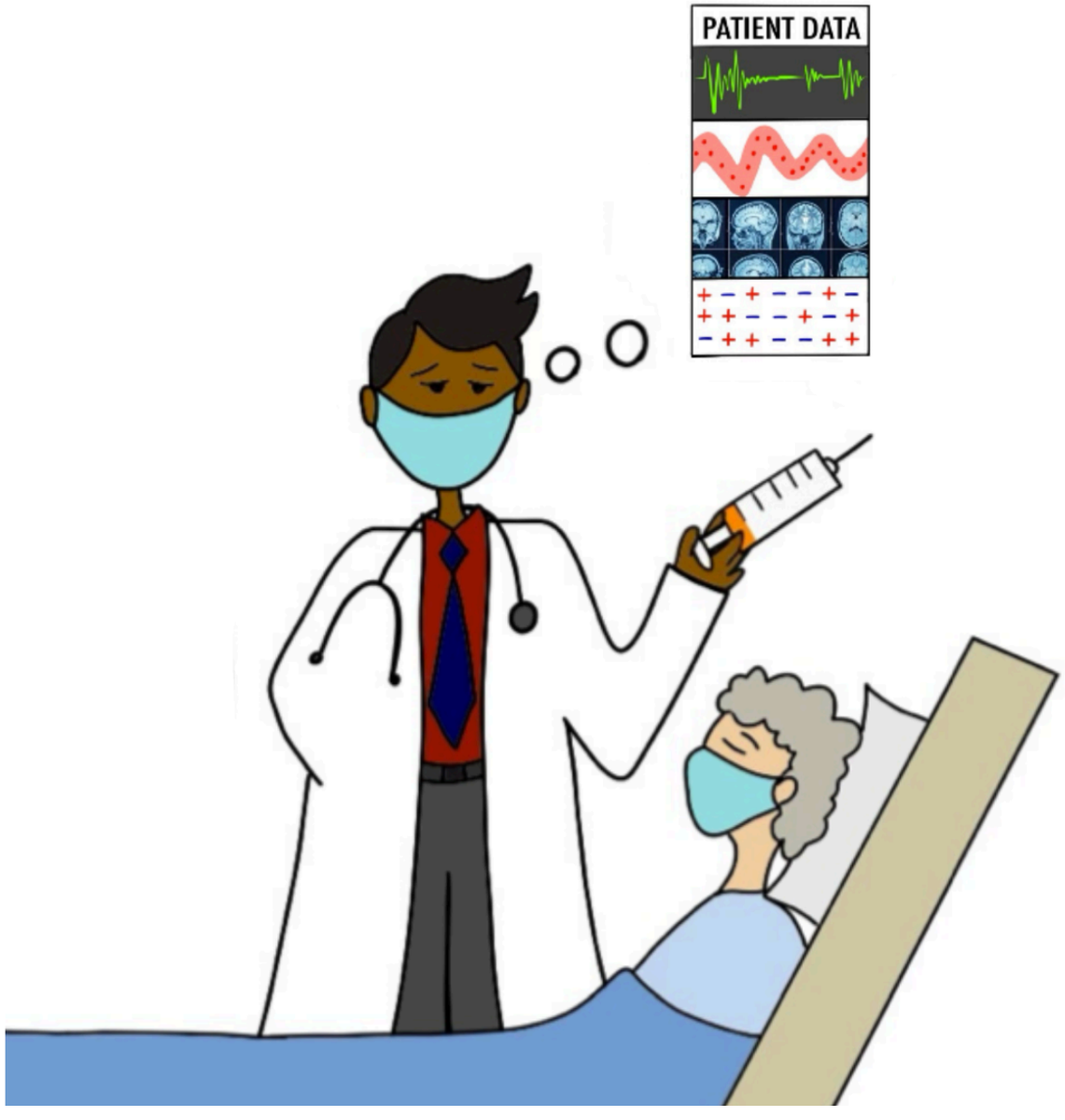
  - Value of treatment that would have been observed at time t under an intervention carried out up until time $t-1$ and then discontinued *(Richardson and Robins, 2013; Young et al., 2014)*



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- At time point 1, the observed treatment and natural value of treatment are equivalent

Types of interventions

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Brief review of static and dynamic

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  - Example: initiate corticosteroids for COVID-19 patients for 6 days if a patient's oxygen levels drop *(Hoffman et al., 2022)*

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  - "Treat everyone at all time points of the study"

$$\mathsf{d}_t = 1 \text{ for all } t \in 1,\ldots\tau$$

- **Dynamic intervention:** d is a function of a unit's covariate history h_t
  - Example: initiate corticosteroids for COVID-19 patients for 6 days if a patient's oxygen levels drop *(Hoffman et al., 2022)*

$$\mathsf{d}_t(h_t) = \begin{cases} 1 & \textit{if } l_s^* = 1 \textit{ for any } s \in \{t-5,\ldots,t\} \\ 0 & \textit{otherwise} \end{cases}$$

Types of interventions

Brief review of static and dynamic

- $Z_1, \ldots, Z_t$ i.i.d observations
  $Z = (L_1, A_1, L_2, A_2, \ldots, L_\tau, A_\tau, Y) \sim \mathsf{P}$
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where L_t^* is a variable in H_s denoting first instance of low oxygen

Types of interventions

Modified Treatment Policies

(Díaz and van der Laan, 2012; Haneuse and Rotnitzky, 2013)

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$$\mathsf{d}(a_t, h_t)$$

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In modified treatment policies (MTPs), the intervention d is a function of the **natural value of treatment**

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$$\mathsf{d}_t(a_t) = \begin{cases} a_t & \text{if } a_t < 4 \\ 3 & \text{otherwise} \end{cases}$$

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- *Example:* Smoking cessation policy *(Robins et al. 2004).*
  Consider an intervention in which half of all current smokers quit smoking forever. Define A_t a random variable denoting smoking status, and ϵ a random draw from a Uniform(0,1).

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$$\mathsf{d}_t(a_t, \epsilon_t) = \begin{cases} 0 & \text{if } \epsilon < 0.5 \text{ and } a_t = 1 \\ a_t & \text{otherwise} \end{cases}$$

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$$\mathsf{d}_t(a_t) = \begin{cases} a_t * 0.9 & \text{if } a_t > 5 \\ a_t & \text{otherwise} \end{cases}$$

Setup

Causal effects

- $Z_1, \ldots, Z_t$ i.i.d observations
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- Once an intervention d is specified, causal effects will be defined in terms of the **distribution of the counterfactual outcome**

$$Y(\bar{A}^{\mathsf{d}}) = f_Y(A_\tau^{\mathsf{d}}, H_\tau(\bar{A}_{\tau-1}^{\mathsf{d}}), U_Y)$$

  - Specifically, our causal parameter of interest is $\theta = \mathsf{E}[Y(\bar{A}_\tau^{\mathsf{d}})]$

- In *Epidemiology* tutorial, we focus on distributions of the contrast $\mathsf{E}[Y(\bar{A}_\tau{}^{\mathsf{d}}) - Y(\bar{A}_\tau^{\mathsf{d}'})]$, where d and d' are two different interventions

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Needed for static, dynamic, and (interestingly!) stochastic LMTPs*

**See LMTP-SI discussion in Diaz et al.*

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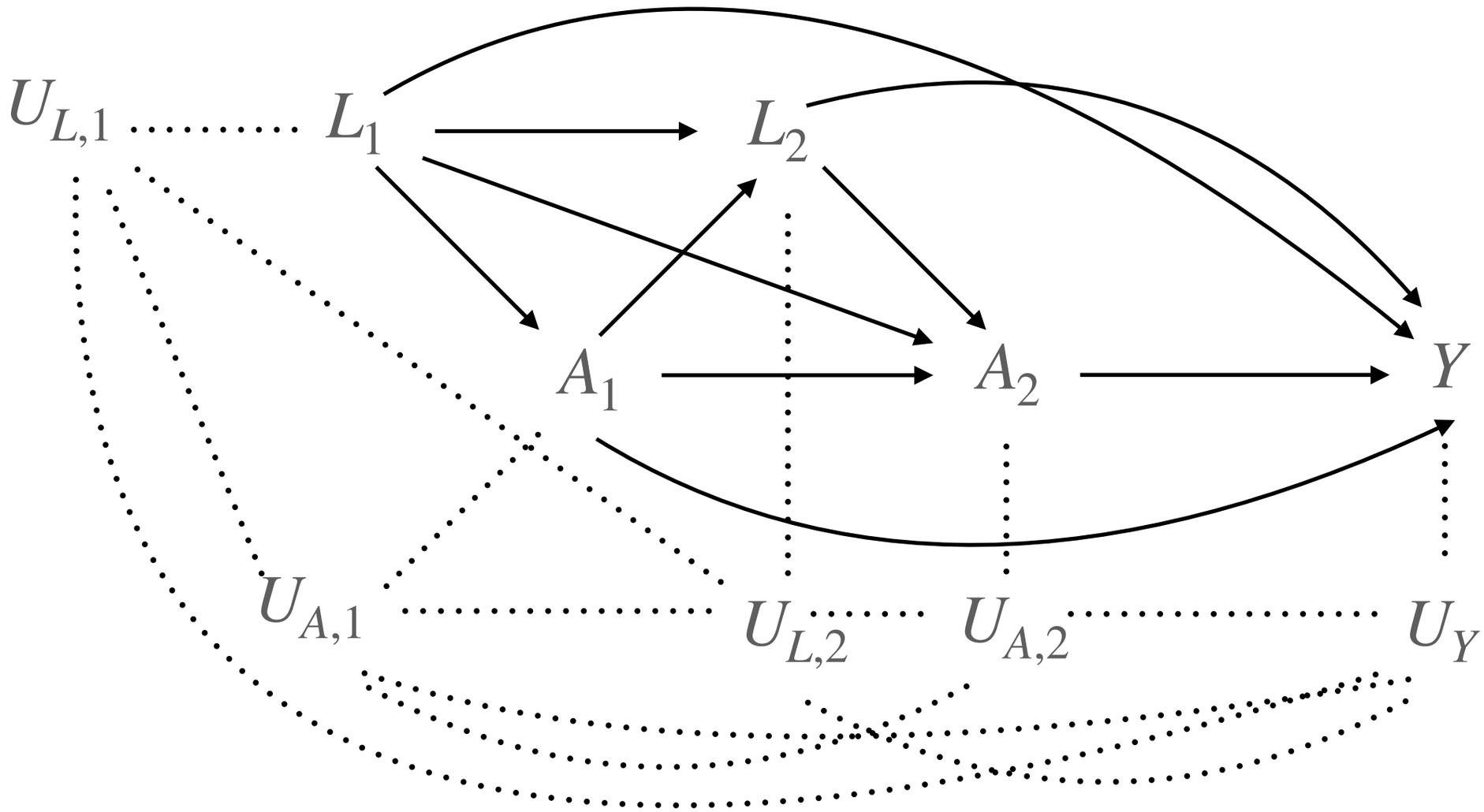
A DAG for two time points



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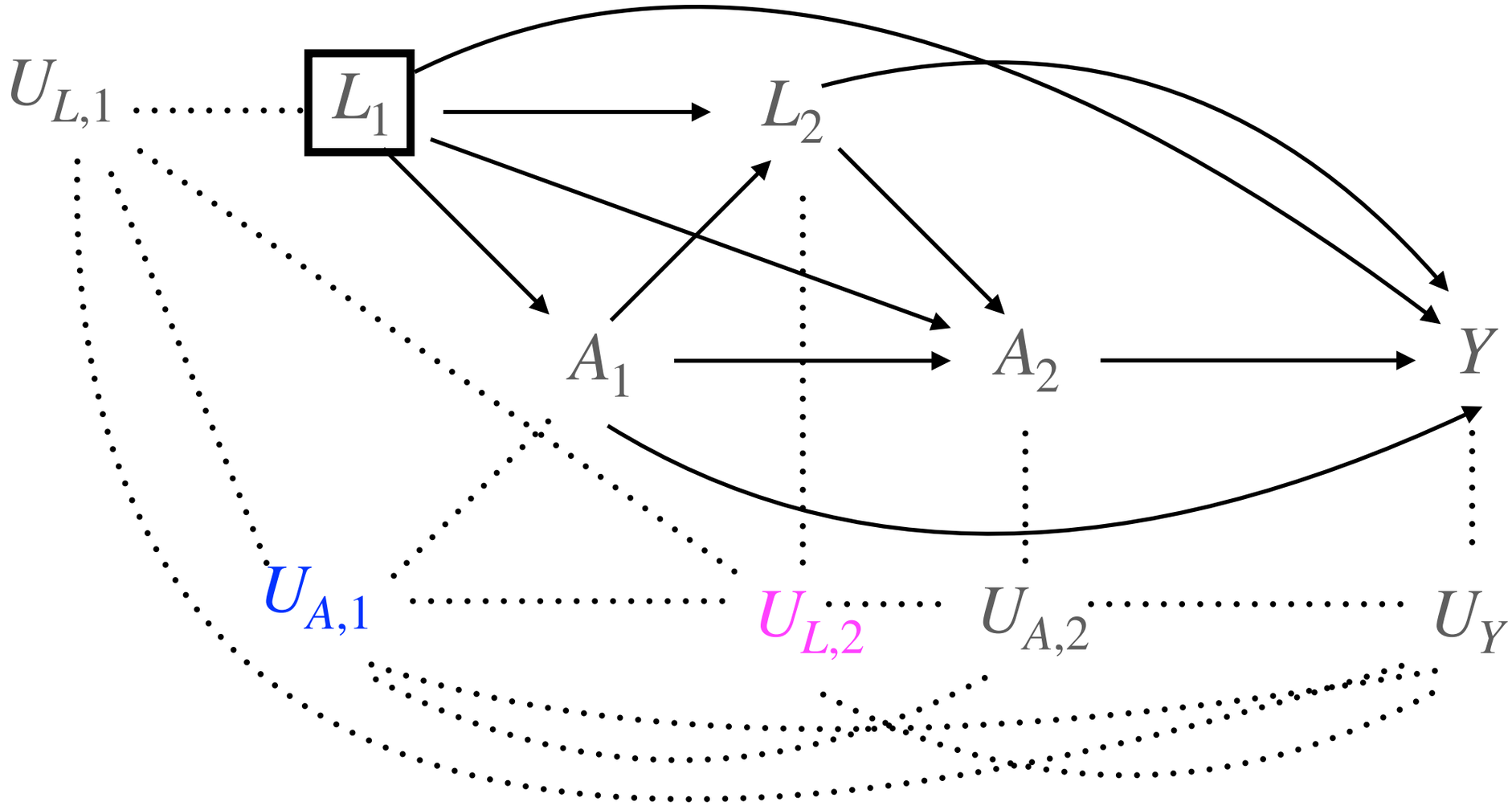

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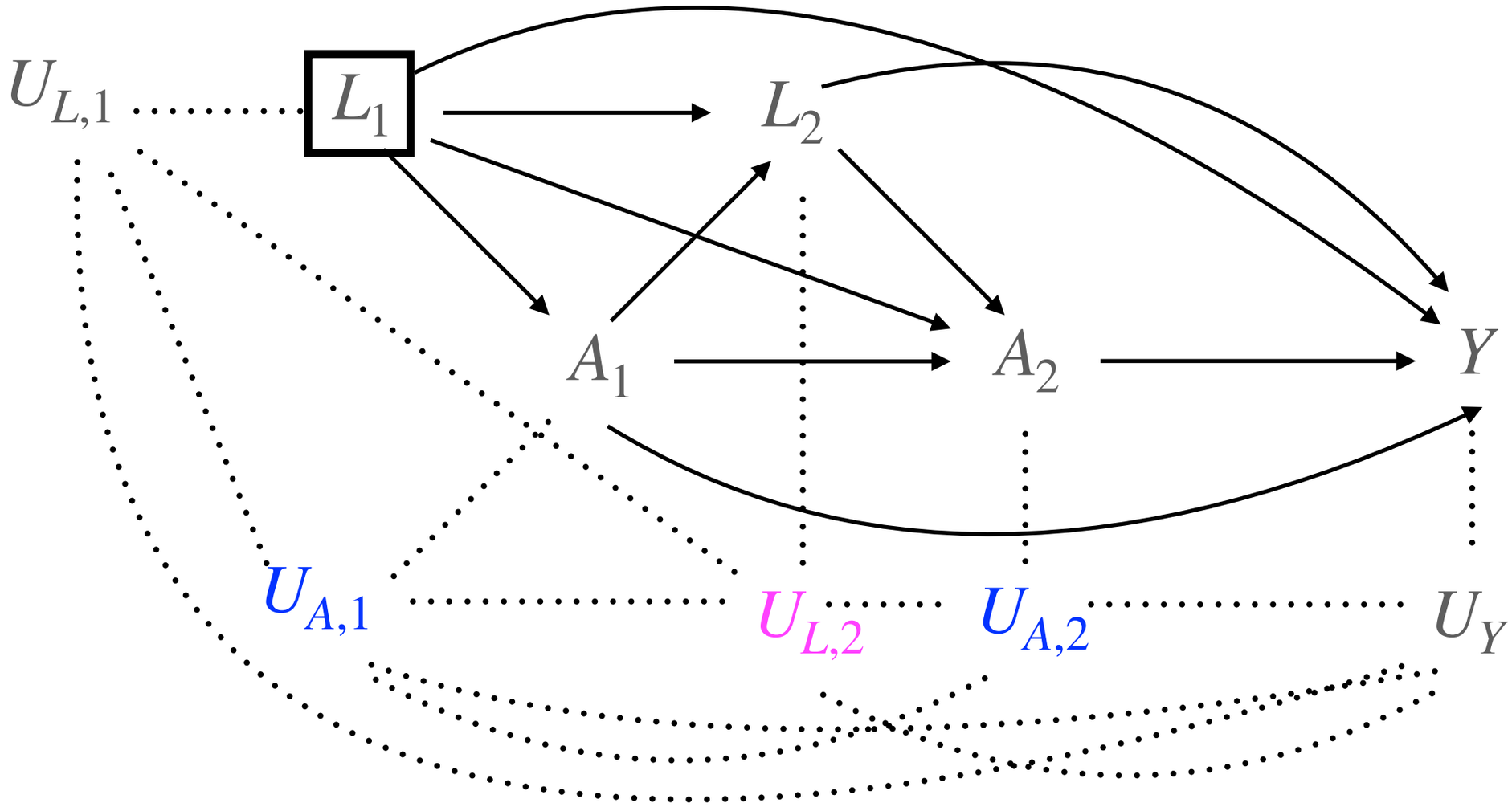

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- The distribution of interest is supported in the data *(Young et al. 2014)*

- If it is possible to find a unit with history h_t and exposure a_t at time t, then it is also possible to find a unit with history h_t and exposure $\mathsf{d}(a_t, h_t)$

- If exposure is multivariate (e.g. includes a loss-to-follow-up indicator), we also require a positive probability of observing a patient who is not lost to follow up

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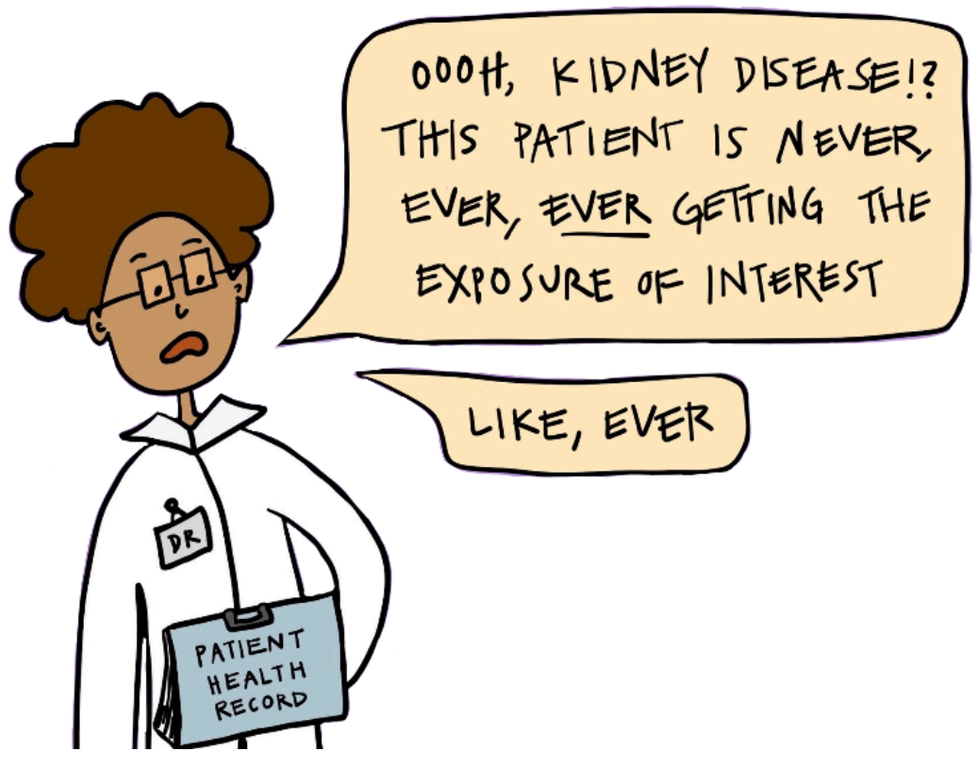
Violations to positivity can be

- **Structural:** certain characteristics of an individual or unit which will never yield receipt of the treatment assignment under the intervention

- **Practical:** due to random chance or small datasets, certain covariate combinations have zero or near zero predicted probabilities of treatment



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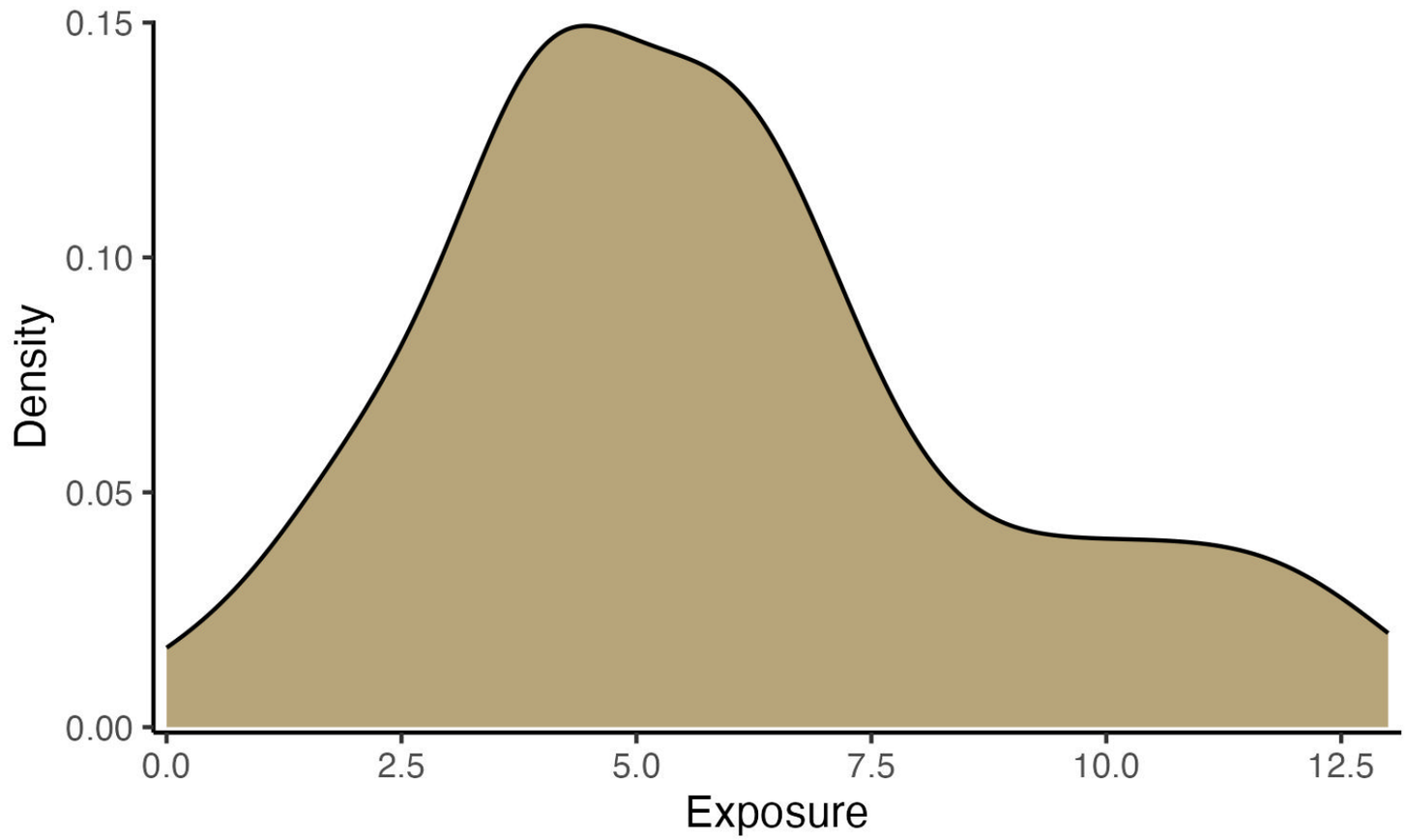
- By design, non-static interventions may help define estimands with plausible positivity



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- Under Positivity and Strong Sequential Randomization, an LMTP estimand is identified by an alternative expression of the extended g-formula *(Robins et al. 2004, Richardson and Robins, 2013)*

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Identification

General formula

- $Z_1, \ldots, Z_t$ i.i.d observations
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  - Define $\theta = \mathsf{E}[m_1(A_1^{\mathsf{d}}, L_1)]$.
  - Under the previously discussed assumptions, $\theta = \mathsf{E}[Y(\bar{A}_1^{\mathsf{d}})]$ is identified by $\theta = \mathsf{E}[m_1(A_1^{\mathsf{d}}, L_1)]$.

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5. Under identifying assumptions, $\mathsf{E}[Y(\bar{A}_\tau^{\mathsf{d}})] = \mathsf{E}[\tilde{Y}_1]$

Estimation

Estimation

Substitution estimator

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- The simplest form of estimation is to use a plug-in estimator

$$\hat{\theta}_{sub} = \frac{1}{n} \sum_{i=1}^{n} \hat{\mathsf{m}}_1(A_{1,i}^{\mathsf{d}}, L_{1,i})$$

Pseudo-R Algorithm:

```
1. fit_y <- glm(Y ~ A2 + L2
   + A1 + L1)

2. Y_tilde_2 <-
   predict(fit_y, A2 = A2d)

3. fit_ytilde_2 <-
   glm(Y_tilde_2 ~ A1 + L1)

4. Y_tilde_1 <-
   predict(fit_ytilde_2, A1
   = A1d)

5. mean(Y_tilde_1)
```

Estimation

Inverse Probability Weighting

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- Or, use an alternative expression of the parameter of interest with the density ratio, $\mathsf{r}_t(a_t, h_t) = \dfrac{g_t^{\mathsf{d}}(a_t \mid h_t)}{g_t(a_t \mid h_t)}$

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- And estimate with an inverse probability weighted estimator *(Young et al., 2014)*

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- And estimate with an inverse probability weighted estimator *(Young et al., 2014)*

$$\hat{\theta}_{IPW} = \frac{1}{n} \sum_{i=1}^{n} \left(\prod_{t=1}^{\tau} \hat{\mathsf{r}}_t(A_{t,i}, H_{t,i})\right) Y_i$$

Estimation

Motivation for non-parametric estimators

Estimation

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- If m_t and r_t are estimated with **pre-specified parametric models**, then by Delta method, $\hat{\theta}_{sub}$ and $\hat{\theta}_{IPW}$ are asymptotically linear

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Estimation

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  - If the models are correctly specified, $\hat{\theta}_{sub}$ and $\hat{\theta}_{IPW}$ will be $n^{1/2}$-consistent
- Use bootstrap or influence function-based estimator to construct asymptotically correct confidence intervals

Estimation

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  - Could use data-adaptive regressions, but $n^{1/2}$-consistency of $\hat{\theta}_{sub}$ and $\hat{\theta}_{IPW}$ requires $\hat{m}_t$ and $\hat{r}_t$ to be consistent in $L_2(P)$-norm at parametric rate, which is generally not possible with data-adaptive estimation of high-dimensional regressions

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- **Solution:** use the efficient influence function to propose estimators that are $n^{1/2}$-consistent and efficient under weaker assumptions

Estimation

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    - Enjoy multiple robustness properties of our estimator

Estimation

EIF Motivation

- The **efficient influence function** will allow us to
    - Construct locally efficient estimators
    - Enjoy multiple robustness properties of our estimator
    - Use flexible regression techniques in estimating nuisance quantities, since the EIF yields second-order bias terms with slow convergence rates for the nuisance parameters

Estimation

EIF Conditions

Technical requirements:

Assume d does not depend on P, and <u>one</u> of:

1. A_t is a **discrete** random variable for all t
2. A_t is a **continuous** random variable and the modified treatment policy d satisfies **piecewise smooth invertibility**

Then, the efficient influence function for estimation of $\theta = \mathsf{E}[\mathsf{m}_1(A^{\mathsf{d}}, L_1)]$ in the non-parametric model is given by

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$$\phi_1(Z) - \theta$$

Estimation

EIF Formula

Efficient influence function: $\phi_1(Z) - \theta$

Where,

$$\phi_t : z \mapsto \sum_{s=t}^{\tau} \Big(\prod_{k=t}^{s} \mathsf{r}_k(a_k, h_k) \Big) \{ \mathsf{m}_{s+1}(a_{s+1}^{\mathsf{d}}, h_{s+1}) - \mathsf{m}_s(a_s, h_s) \} + m_t(a_t^{\mathsf{d}}, h_t)$$

Recall $\mathsf{r}_t(a_t, h_t)$ is the density ratio,

$$\mathsf{r}_t(a_t, h_t) = \frac{g_t^{\mathsf{d}}(a_t \mid h_t)}{g_t(a_t \mid h_t)}$$

Estimation

Non-parametric estimators

- Two estimators for LMTP proposed in Díaz et al. and implemented in {lmtp} using m_t, r_t, and the derived EIF:

1. Targeted Minimum Loss-Based Estimation (TMLE)

2. Sequentially doubly robust (SDR) estimation

- Utilize sample splitting and cross-fitting *(Klassen, 1987; Zheng and van der Laan, 2011; Chernozhukov et al., 2018)*

- Algorithms formally proposed in *Díaz et al. (2021)*; pseudo-R code given in Appendix of *Hoffman et al. (2024)*

Estimation

TMLE

- A generalization of estimators proposed for MTPs in a single time point setting in (*Díaz and van der Laan, 2018; van der Laan and Gruber, 2012)*

- A substitution estimator that uses an estimate $\tilde{\mathsf{m}}_1$ (within cross-fitting folds) carefully constructed to solve a cross-validated efficient influence function estimating equation

- Motivated by the decomposition of the EIF as a sum of terms of the form,

$$\Big(\prod_{k=1}^{t} \mathsf{r}_k(a_k, h_k)\Big)\{\mathsf{m}_{t+1}(a_{t+1}^{\mathsf{d}}, h_{t+1}) - \mathsf{m}_t(a_t, h_t)\}$$

Estimation

SDR Estimator

- SDR is an extension of estimators for dynamic treatment regimes proposed by *Luedtke et al. (2017)* and *Rotnitzky et al. (2017)*

- Sequentially regress a multiply robust unbiased data transformation related to ϕ_{t+1} to construct pseudo-outcomes, and eventually, $\hat{\theta}_{SDR}$

- Not a substitution estimator, so SDR can yield estimates that are outside the bounds of Y, but it has better consistency properties than TMLE in the event of model misspecification

Estimation

Comparing statistical properties of proposed estimators

Statistical property	Sub.	IPW	TMLE	SDR	iTMLE
Doubly robust			X	X	X
Sequentially doubly robust				X	X
Valid inference using parametric regressions	X	X	X	X	X
Valid inference using data-adaptive regressions			X	X	X
Guaranteed to stay within outcome range	X		X		X

Extensions and Applications

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LMTP extension papers

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  Williams, N.T. & Díaz, I. lmtp: An R Package for Estimating the Causal Effects of Modified Treatment Policies. *Observational Studies (2023)*

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- Effect of **increasing numbers of tooth retention** and social participation among older adults in Japan *(Cooray et al.)*

Extensions and Applications

Concluding thoughts

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- LMTP allows researchers to define, identify, and estimate **novel and scientifically relevant estimands**

Extensions and Applications

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    - Formulating alternative estimands to satisfy the positivity assumption must be done with scientific reason, and practical positivity violations may still occur
        - Solutions to practical violations (e.g. truncation of density ratios) are arbitrary and may lead to biases

Thank you!

Questions, comments, suggestions?