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Estimating the causal effects of longitudinal exposures

Novel statistical methods and software

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Joint work with

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Motivation

- A causal inference framework allows us to define many important questions in HIV
  - Effects of longitudinal exposures
  - Censoring dependent on time varying variables
  - Effects of "dynamic" treatment strategies
- Answering these questions requires moving beyond standard multivariable regression
  - Inverse Probability Weighted Estimators (IPTW)
  - Targeted Maximum Likelihood Estimators (TMLE)
- New R software implementing these estimators is now available

Outline

1. What types of questions can these methods help us answer?
2. Why are more complex statistical methods needed?
   - Challenge of time-varying confounders
3. Overview of available estimators
   - Inverse Probability of Treatment Weighted (IPTW)
   - Targeted Maximum Likelihood (TMLE)
4. Introduction to R software: Joshua Schwab
   - Sample data, code, and simulation results
5. Conclusion

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Overview: What types of questions these methods can let us answer?

- Effects of longitudinal treatments
  - Cumulative effect of multiple treatment decisions or exposures over time
    - Ex: Cumulative exposure to a specific ARV (Abacavir)
    - Ex: Time to starting ART after HIV diagnosis
- Effects of dynamic treatments
  - Strategies for assigning treatment in response to patient characteristics
    - Ex: Different CD4 thresholds for ART start
    - Ex: Different CD4, clinical or viral load-based strategies for defining 1st line failure and initiating switch

Overview: What types of questions these methods can let us answer?

- Exposure effects when censoring can depend on time-varying variables
  - Ex: Patients who get sicker over course of study more likely lost to follow up
- Effects on many types of outcomes
  - At a single time point
    - Ex: Survival at 12 months
  - Repeated measures
    - Ex: CD4 over time
  - Time to event
    - Ex: Survival time

Example: When to switch to second line ART following virological failure?

- HIV can develop resistance to 1st line NNRTI-based therapy quickly, resulting in HIV RNA rebound (virological failure)
- In Africa, delayed switch to second line ART following virological failure is common
  - Routine plasma viral load monitoring often unavailable
  - CD4 and clinical criteria detect rebound poorly
- Clinical effect of delayed switch in resource-limited settings not adequately quantified

Example 1: Point treatment

- Treatment: A
  - A single treatment decision or an exposure at a single time point
  - Ex: Indicator if switched immediately (first visit failure detected)
- Outcome: Y
  - Ex. Death within 1 quarter (3 months) after failure
- Counterfactual outcome: Outcome that would have been observed under a specific treatment
  - Ex: An individual's vital status had she switched immediately (in reality she may not have)

Example 1: Point treatment

- Example target quantity:
  - Proportion of patients that would have died within 1 quarter if all had been switched immediately
- Can use this to define various effects
  - Causal Risk Difference/Additive Treatment Effect
    - Ex: Difference in the proportion who would have died if all had been switched immediately versus if none had been switched immediately
  - Causal Relative Risk
  - Causal Odds Ratio
  - Etc…

Example 2: Longitudinal treatment

- Time point: t=1,…,K (end of study)
  - Ex: quarterly intervals at which patients seen and treatment decisions made
- Treatment: A(t), t=1,…,K
  - Treatment decisions at multiple time points
  - Ex: A(t)= Indicator if switched by time *t*
    - A(1)=0, A(2)=0, A(3)=1, A(4)=1 : switch at time 3
- Outcome: Y(t), t=1,…,K
  - Ex: Vital status at end of each interval

Example 2: Longitudinal treatment

- Example counterfactual outcome:
  - An individual's vital status at time *t* under a specific switch time
- Example target quantity:
  - The proportion of patients that would have died within *t* time points had none switched at any point
- Can again use this to define various effects
  - Ex: Difference in the proportion that would died within *t* time points had all switched immediately vs. had none switched at any point

Example 3: Marginal Structural Models

- Model how the expected counterfactual outcome varies as a function of treatment
  - Can model survival or hazard for a single or multiple time points
  - For point or longitudinal treatments
- Ex: How counterfactual probability of death within 3 time points varies as a function of switch time
  - Hypothetical randomized trial: Randomly assign subjects with virological failure a switch time and measure their survival
  - Ex MSM: $\text{logit}(E(Y(3)_{\text{switch}}))=\beta_0 + \beta_1 \text{switch time}$

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The methodological challenge

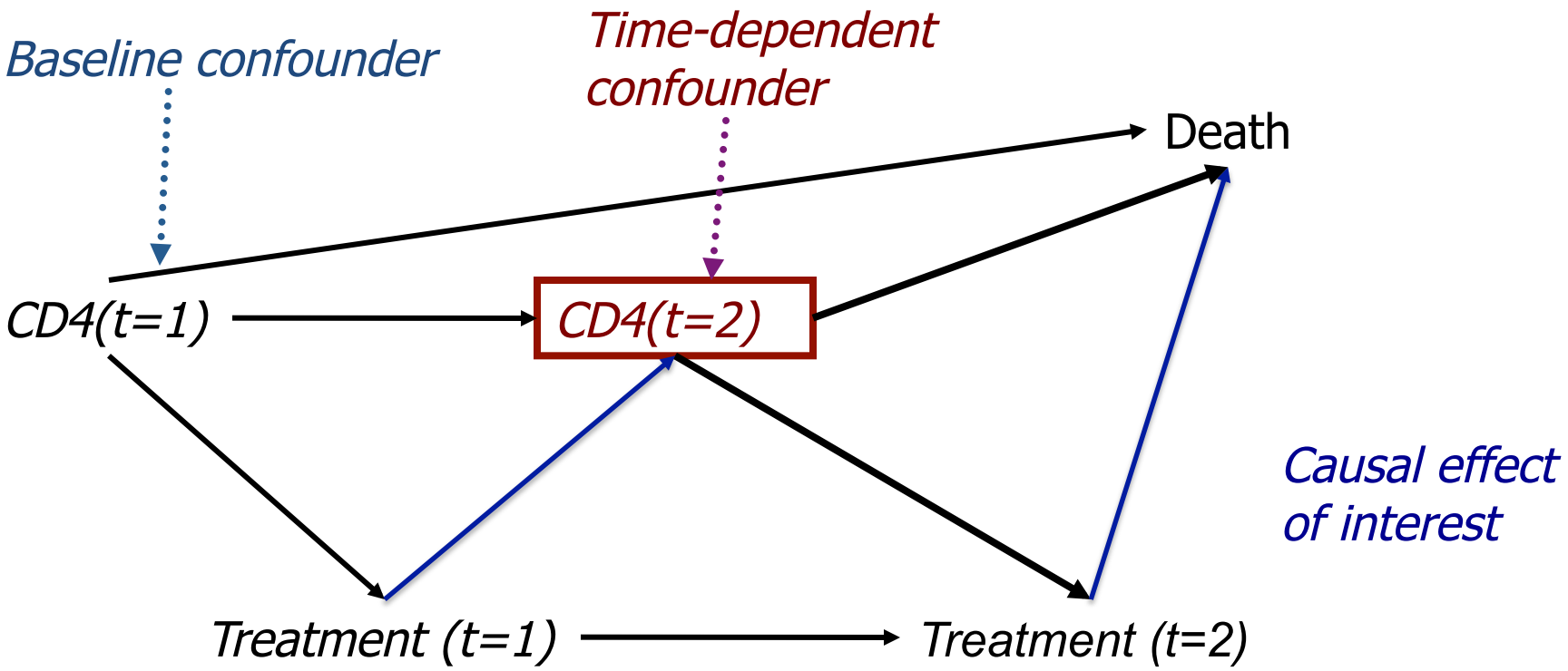
- For results to have causal interpretation, all methods (including these) rely on untestable assumptions
- We want

1. A clear understanding of those assumptions
   - Study designs to optimize their plausibility
2. Statistical methods that give the best possible answers given what we measure
   - Standard parametric regression not sufficient

Time-dependent confounding

- Time varying variables can
  1. Confound treatment-outcome relationships
  2. Be affected by prior treatment
     - Part of the causal pathway of interest
- How to analyze?
  - If we don't adjust -> Bias
  - If we adjust using stratification or standard multivariable regression -> Bias
- Similar issue when censoring depends on time varying variables

Ex: Time-dependent confounding



- Can't control for *CD4(t=2)* in standard analyses: on causal pathway!

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Overview: IPTW

- Likelihood of the Observed Data

P(Treatment & Censoring | Past) P(Other covariates | Past)

"Treatment Mechanism"

- IPTW

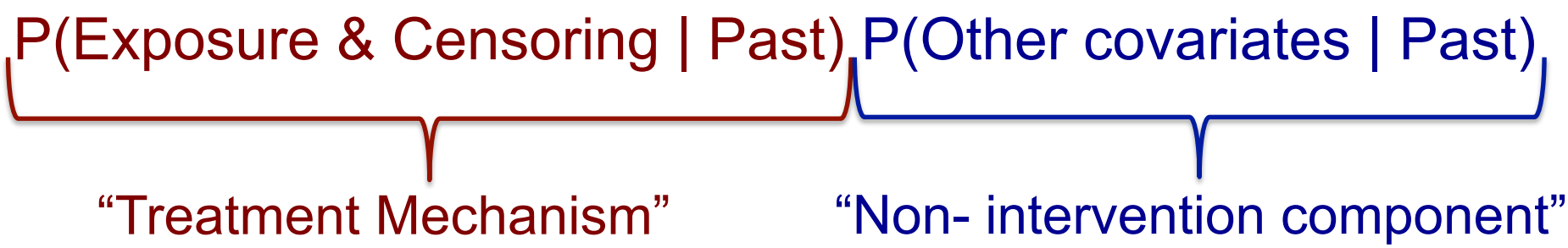
1. Estimate treatment mechanism
   - How treatment (and/or censoring) depend on the observed past
2. Use this estimate to reweight data

IPTW Properties

- Relies on doing a good job estimating the weights
  - If treatment mechanism estimated using a misspecified model -> Bias
- Subject to bias and high variance with moderate to strong confounding
  - When certain treatment or exposure levels of interest are rare/absent for some patient histories

Overview: TMLE

- Likelihood of the Observed Data



- TMLE

1. Estimate non-intervention component
2. Update this estimate to remove bias for quantity you care about
   - Update step uses estimate of treatment mechanism

TMLE Properties

- Minimize bias due to model misspecification
  - Double Robust - Two chances to get it "right"
    - Consistent if you estimate either component correctly
- Maximize precision of effect estimates
  - Efficient (minimal asymptotic variance in semi-parametric model) if you get both right
- In practice (finite samples)
  - May reduce bias and variance compared to IPTW

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Example 1: Point treatment

Simulated Data:

id	male	age	CD4_1	A1	Y1
1	1	27	345	0	0
2	1	33	78	1	1
3	0	25	264	0	0
4	0	18	212	1	0
5	0	34	363	0	0
6	1	31	414	0	0

…

CD4_1: CD4 count at first visit failed

A1: Indicator switched to second line ART at first visit failed

Y1: Death by the end of first quarter after failure

Example 1: Point treatment

What proportion of patients who failed would have died within one quarter if all had been switched immediately?

Call:

```
ltmle(data, Anodes="A1”, Ynodes="Y1", abar=1)
```

Output:

```
TMLE Estimate:  0.0294344
```

Example 1: Point treatment

- Additional outputs: IPTW and TMLE Estimates (95% CI) for proportion died under immediate switch ("est1") and proportion died under no immediate switch ("est0")

```
> est1 <- ltmle(data, Anodes="A1", Ynodes="Y1", abar=1)
> est0 <- ltmle(data, Anodes="A1", Ynodes="Y1", abar=0)

> summary(est1, estimator="tmle")
    Parameter Estimate:  0.029434
    Estimated Variance:  0.000170
    95% Conf Interval:  (0.003832, 0.055036)

> summary(est1, estimator="iptw")
    Parameter Estimate:  0.023879
    Estimated Variance:  0.000147
    95% Conf Interval:  (5.0134e-05, 0.047708)
```

Example 1: Point treatment

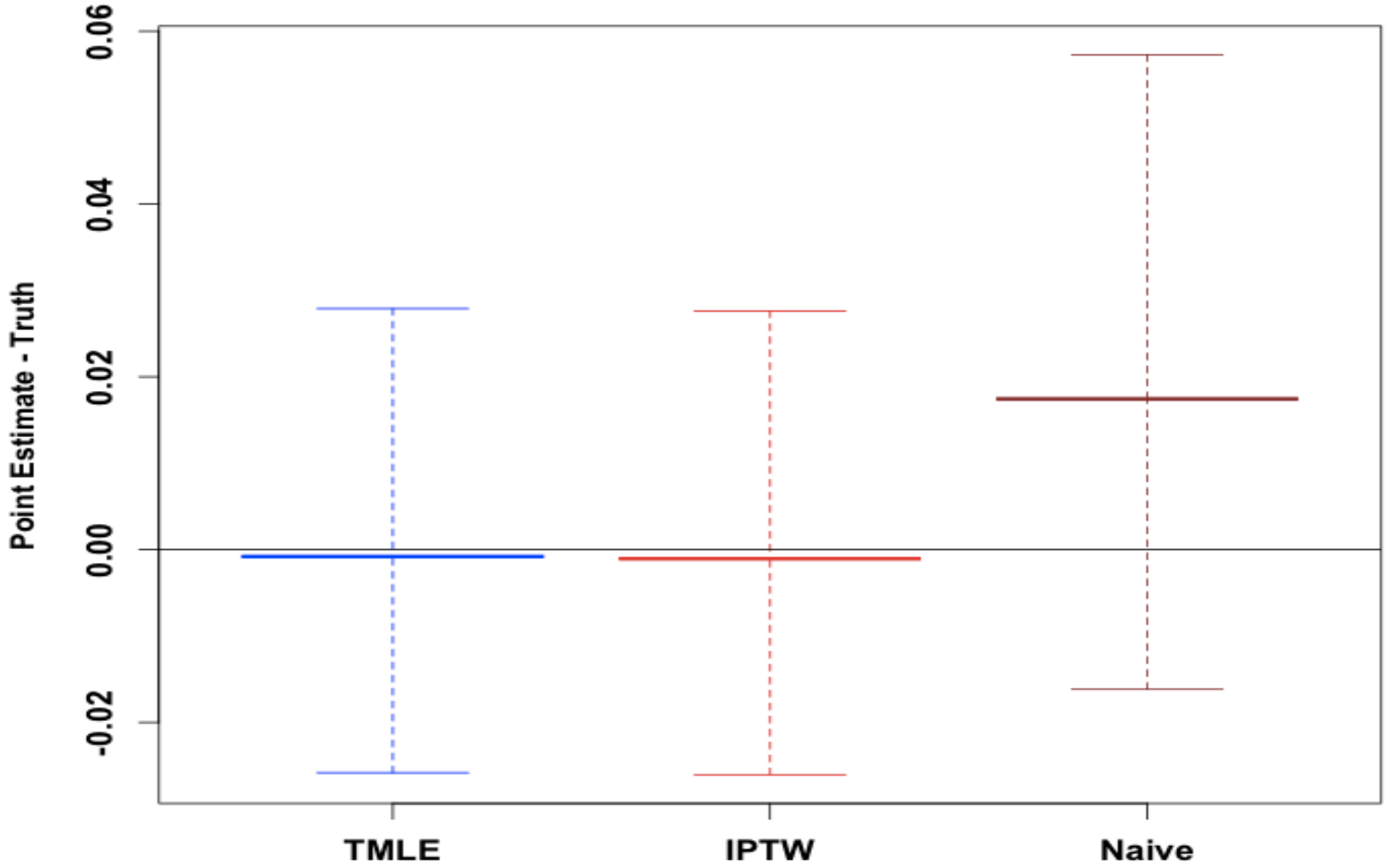
- Additional outputs: Estimates and 95% CI for risk difference (additive effect)
  - Difference in the proportion who would have died if all had been switched immediately versus if none had been switched immediately

```
> summary(est1, est0,  estimator="tmle")
   Additive Effect:
   Parameter Estimate:  -0.11425
   Estimated Variance:  0.0017416
               p-value:  0.0061865
    95% Conf Interval: (-0.19605, -0.032457)
```

- Also gives: relative risk, and odds ratio

Example 1: Point treatment

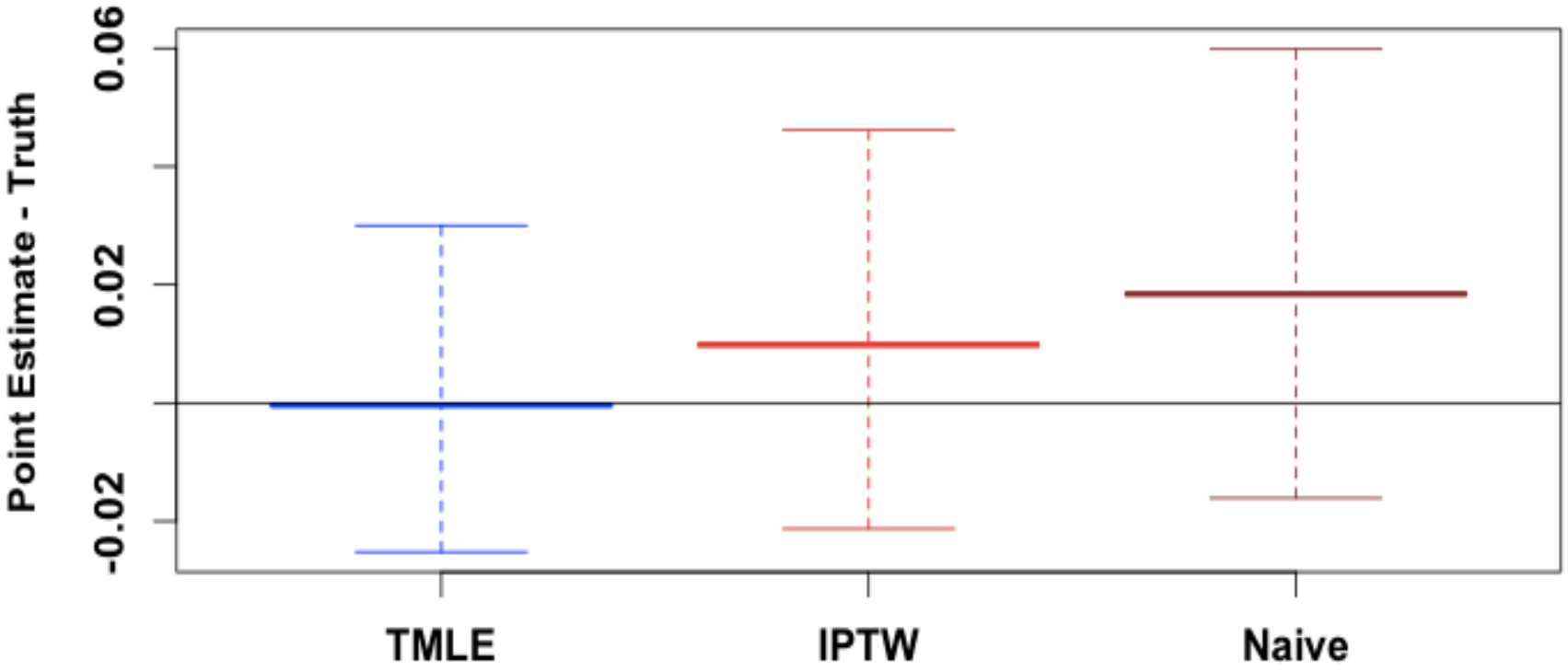
Results from simulated data:



Example 1: Point treatment

What if the treatment mechanism is estimated using a misspecified model?

```
ltmle(data, Anodes="A1", Ynodes="Y1", abar=1,
    gform="A1 ~ male + age")
```



Example 2: Longitudinal treatment

Simulated Data:

id	male	age	CD4_1	A1	Y1	CD4_2	A2	Y2	CD4_3	A3	Y3
1	0	37	101	1	0	152	1	0	228	1	0
2	0	31	301	0	0	297	0	0	302	0	0
3	1	31	323	0	0	351	1	0	395	1	0
4	0	26	29	1	0	81	1	0	124	1	1
5	0	23	280	0	0	315	0	0	321	0	0
6	1	43	237	1	1	NA	NA	1	NA	NA	1
...											

CD4_t: CD4 count at start of quarter *t*

At: switched to second line at or before start of quarter *t*

Yt: death by end of quarter *t*

Example 2: Longitudinal treatment

What proportion of patients would have died within 3 quarters had none switched?

Call:

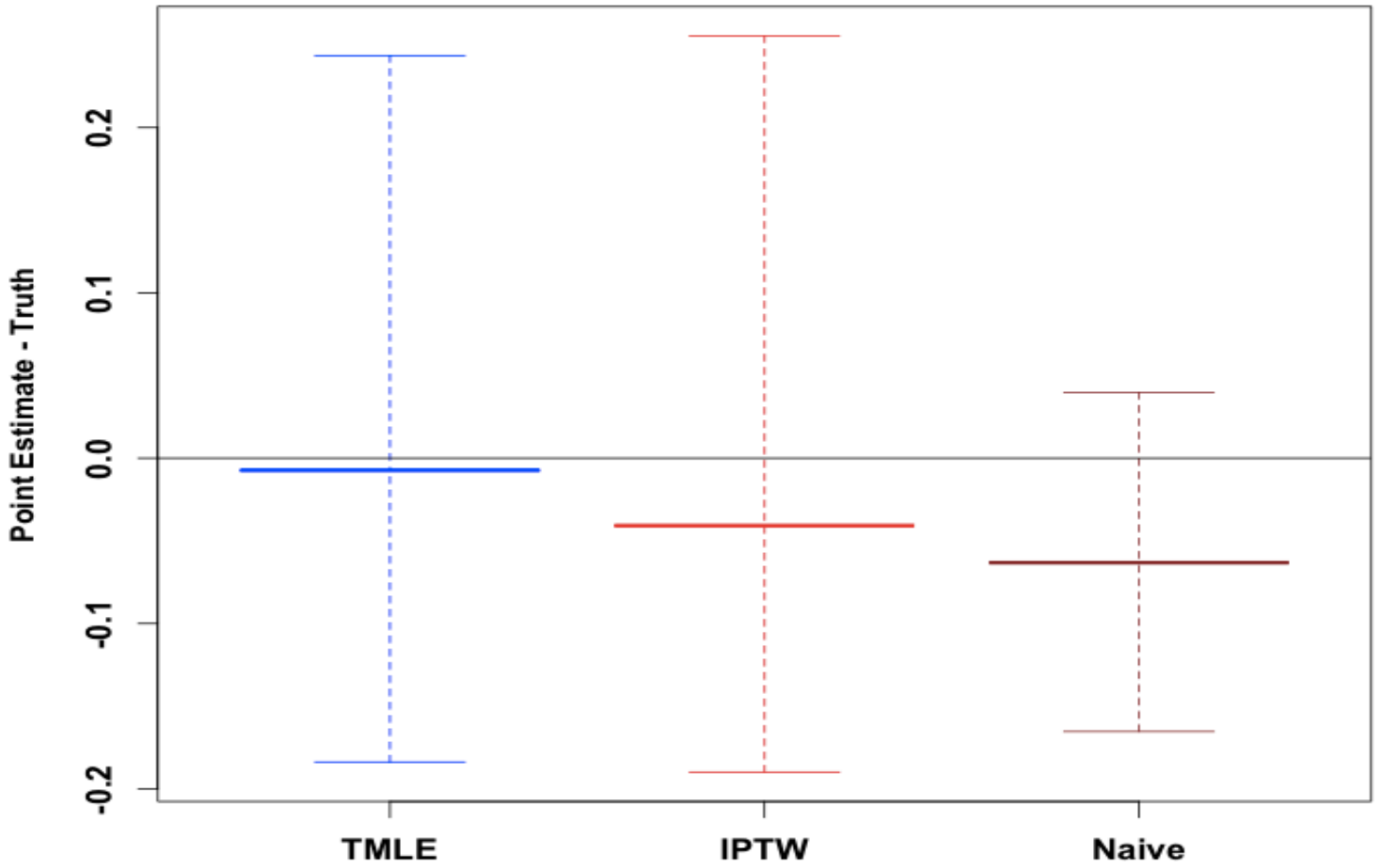
```
ltmle(data, Anodes=c("A1", "A2", "A3”),
   Ynodes=c("Y1", "Y2", "Y3"),
   abar=c(0, 0, 0))
```

Output:

```
TMLE Estimate:  0.1546657
```

Example 2: Longitudinal treatment

Results from simulated data:



Example 3: Marginal Structural Model

- How does counterfactual probability of dying within 3 quarters vary as function of switch time?
  - MSM: logit(E($Y3_{switch}$))=β_0 + $\beta_1$switch time

Call:

```
ltmleMSM(data, Anodes=c("A1", "A2","A3"),
   Ynodes=c("Y1", "Y2", "Y3"),
   working.msm="Y ~ switch.time",
   regimens=regimens,
   summary.measures=summary.measures)
```

Output:

```
(Intercept) switch.time
  -2.733044    0.418045
```

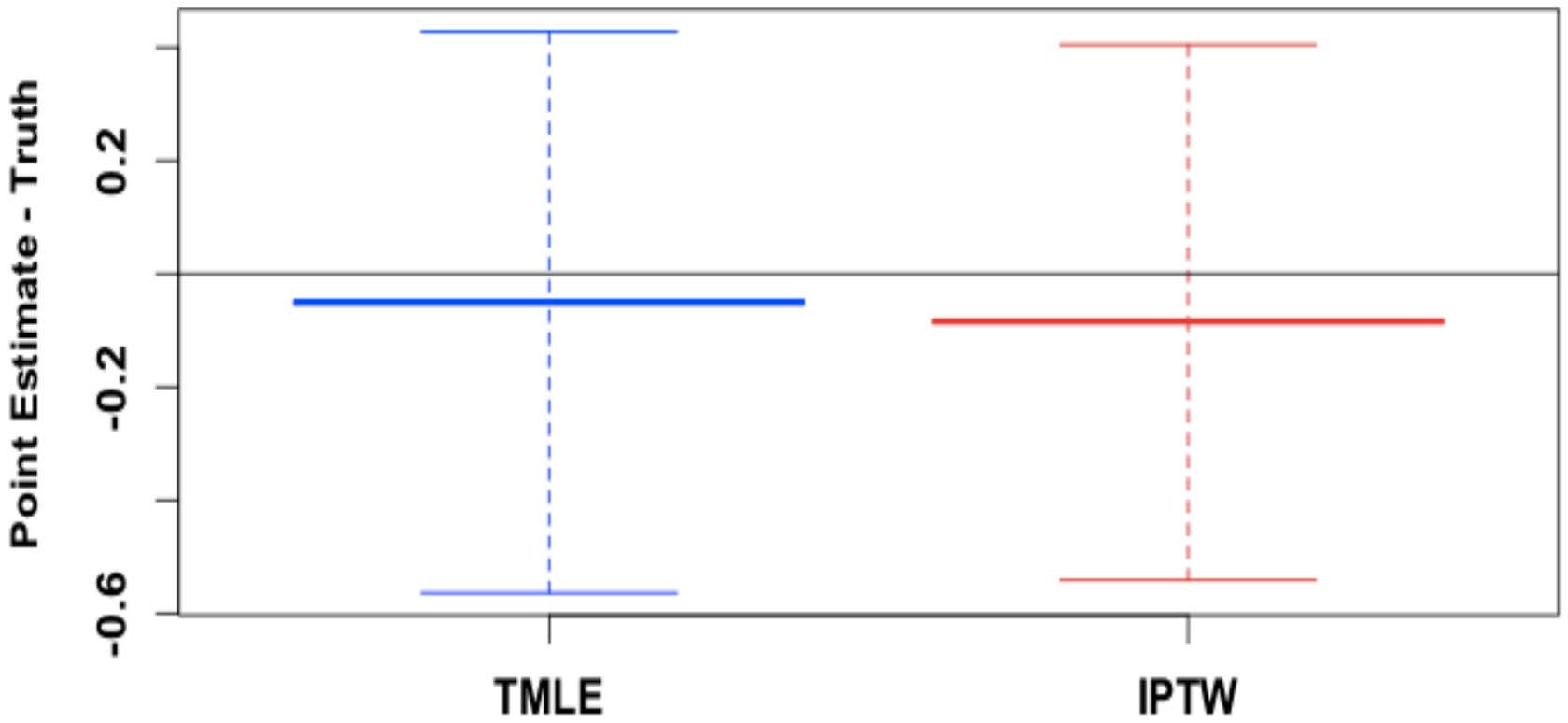
β_0 estimate

β_1 estimate:

OR per additional quarter until switch = exp(0.418) = 1.52

Example 3: Marginal Structural Model

Results from simulated data:



Take home points

- Applying these methods to answer real questions with real data

1. Can give you better answers
2. Is feasible
   - Software is available
3. Mastery not possible in 45 minutes
   - We are showing simple calls for simplified data
     - Using default for many options
   - Software has substantial additional functionality

- Look for upcoming training workshop!

Select References and Resources

- Marginal structural models, time dependent confounding, IPTW:
  - Robins, Hernan, Brumback. Marginal Structural Models and Causal Inference in Epidemiology. *Epidemiology* 2000; 11(5) 550-560
- Longitudinal TMLE
  - van der Laan, Gruber. Targeted Minimum Loss Based Estimation of Causal Effects of Multiple Time Point Interventions" *The International Journal of Biostatistics* 2012; 8.1
- Websites
  - Mark's: www.stat.berkeley.edu/~laan
    - R code at: www.stat.berkeley.edu/~laan/Software
  - Maya's: works.bepress.com/maya_petersen

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    - PI: van der Laan
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R package: ltmle

- Casual effect estimation with multiple intervention nodes
  - Intervention-specific mean under longitudinal static and dynamic interventions
  - Static and dynamic marginal structural models
- General longitudinal data structures
  - Repeated measures outcomes
  - Right censoring
- Estimators
  - IPTW
  - Non-targeted MLE
  - TMLE (two algorithms for MSM)
- Options include nuisance parameter estimation via glm regression formulas or calling SuperLearner()
- Available on CRAN April 2013