Causal Inference Methods for Infectious Disease Prevention Trials

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Outline

- **Project 1**: Addressing Confounding and Continuous Exposure Measurement Error Using Corrected Score Functions

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- **Project 2**: Social Distancing to Reduce Transmission of Influenza-Like-Illness on College Campuses: the eX-FLU Trial

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- **Project 2**: Social Distancing to Reduce Transmission of Influenza-Like-Illness on College Campuses: the eX-FLU Trial
- **Project 3**: Causal Inference from Cluster Randomized Trials with Differential Nonresponse

Project 1 : Addressing Confounding and Continuous Exposure Measurement Error Using Corrected Score Functions

Brian Richardson, Brian Blette, Peter Gilbert, Michael Hudgens (2025)

Motivation: HVTN 505 trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 28, 2013 VOL. 369 NO. 22

Efficacy Trial of a DNA/rAd5 HIV-1 Preventive Vaccine

Scott M. Hammer, M.D., Magdalena E. Sobieszczyk, M.D., M.P.H., Holly Janes, Ph.D., Shelly T. Karuna, M.D., Mark J. Mulligan, M.D., Doug Grove, M.S., Beryl A. Koblin, Ph.D., Susan P. Buchbinder, M.D., Michael C. Keefer, M.D., Georgia D. Tomaras, Ph.D., Nicole Frahm, Ph.D., John Hural, Ph.D., Chuka Anude, M.D., Ph.D., Barney S. Graham, M.D., Ph.D., Mary E. Enama, M.A., P.A.-C., Elizabeth Adams, M.D., Edwin DeJesus, M.D., Richard M. Novak, M.D., Ian Frank, M.D., Carter Bentley, Ph.D., Shelly Ramirez, M.A., Rong Fu, M.S., Richard A. Koup, M.D., John R. Mascola, M.D., Gary J. Nabel, M.D., Ph.D., David C. Montefiori, Ph.D., James Kublin, M.D., M.P.H., M. Juliana McElrath, M.D., Ph.D., Lawrence Corey, M.D., and Peter B. Gilbert, Ph.D., for the HVTN 505 Study Team*

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- **HVTN 505 trial**: trial of a preventive HIV vaccine
- Stopped early after reaching predetermined cutoffs for efficacy futility (Hammer et al., 2013)

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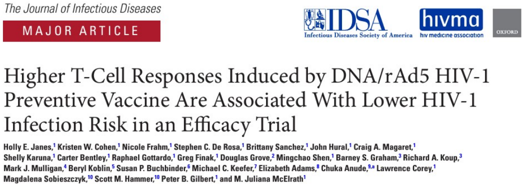
The Journal of Infectious Diseases
MAJOR ARTICLE

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- Is there a **causal** relationship between these biomarkers and HIV?
- Biomarker-HIV relationship is **confounded**
- Biomarkers are **measured with error**

Goal

To estimate the **causal effect** of a continuous exposure on an outcome when

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What Do We Mean by Causal Effect?

"What would be the risk of HIV if, possibly counter to fact, somebody were to have biomarker level $\mathbf{a}$?" (Neyman et al., 1935; Rubin, 1974; Holland, 1986; Hernan and Robins, 2024)

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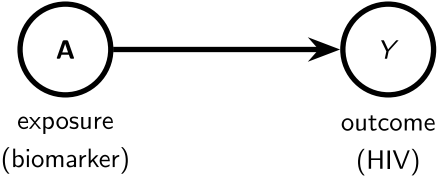
Estimand (**dose-response surface**): $\eta(\mathbf{a}) \equiv \mathrm{E}\{Y(\mathbf{a})\}$ for $\mathbf{a} \in \mathcal{A}$

Confounding



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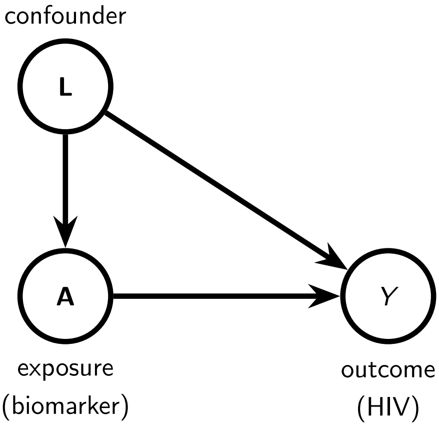

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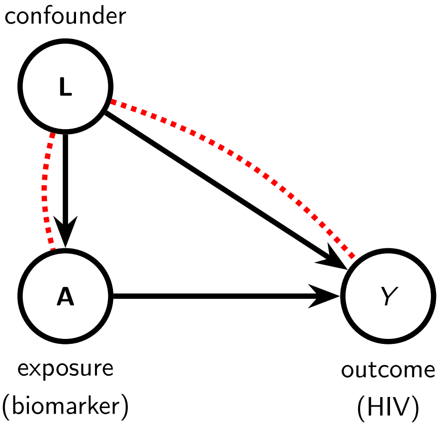
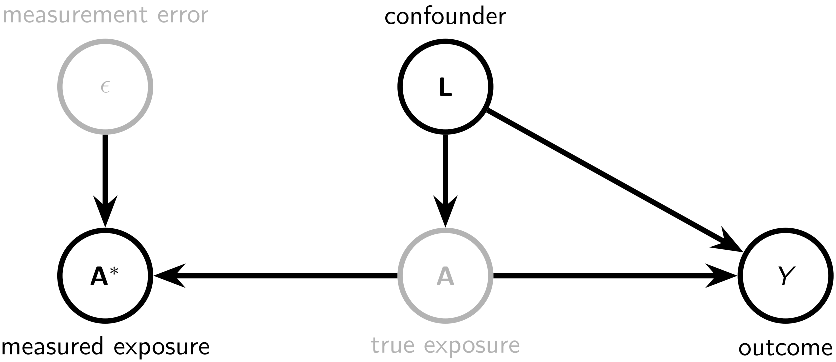
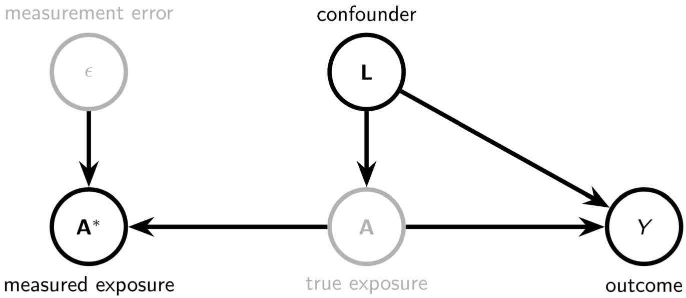


Measurement Error

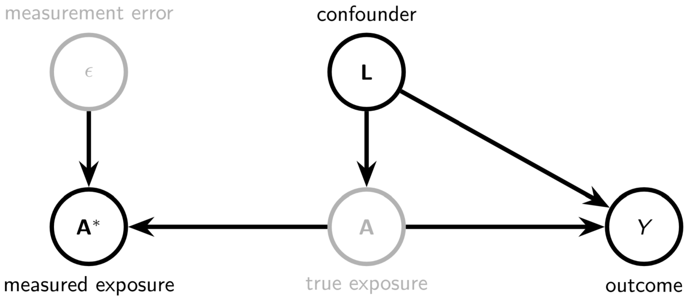


Notation



measurement error
confounder
ϵ
L
A^*
A
Y
measured exposure
true exposure
outcome

Notation



- True exposure: $\mathbf{A} = (A_1, \ldots, A_m)$

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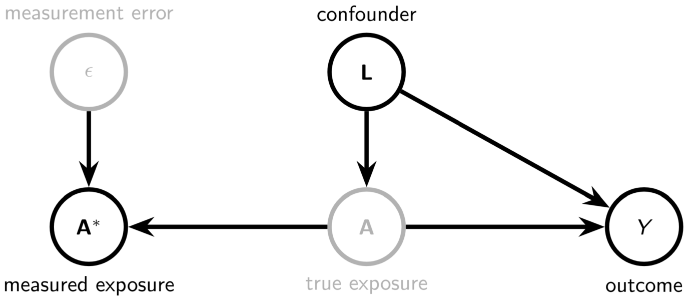

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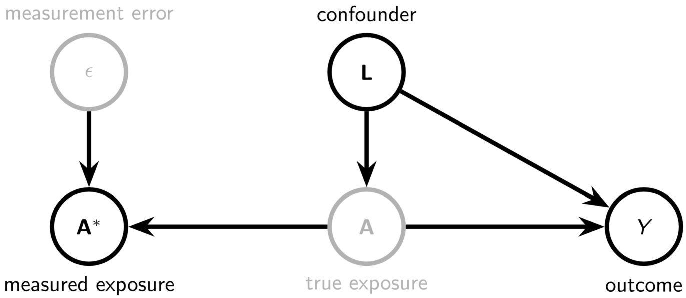

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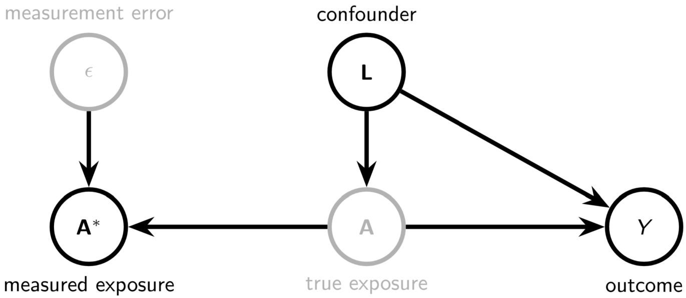

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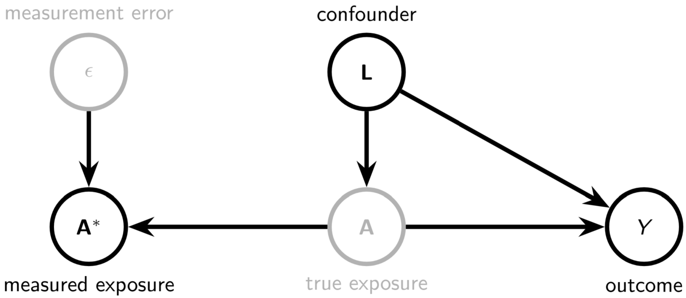

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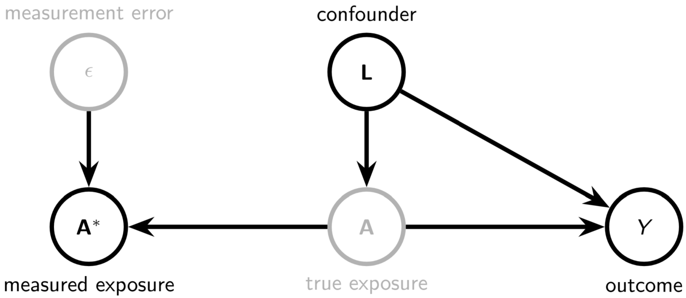

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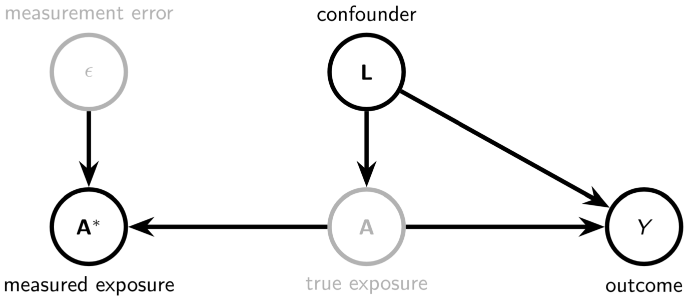

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(ii) **Conditional exchangeability**: $Y(\mathbf{a}) \perp\!\!\!\perp \mathbf{A}|\mathbf{L}$ for all $\mathbf{a} \in \mathcal{A}$

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(v) **Known or estimable measurement error variance $\mathbf{\Sigma}_{me}$**

Addressing Confounding Alone

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- These can all be framed as **M-estimators** (Stefanski and Boos, 2002)

Crash Course on M-Estimation

Score Function: a function of the observed data and the parameter of interest

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$\widehat{\theta}$ is consistent and asymptotically normal and has a simple variance estimator

G-Formula

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$$\mu(\mathbf{L}, \mathbf{A}; \beta) \equiv \mathrm{E}(Y|\mathbf{L}, \mathbf{A})$$

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This can be expressed as an M-estimator with score function

$$\boldsymbol{\Psi}_{0-GF}(Y, \mathbf{L}, \mathbf{A}; \theta_{GF}) = \begin{bmatrix} \{Y - \mu(\mathbf{L}, \mathbf{A}; \beta)\} \, \partial_\beta \mu(\mathbf{L}, \mathbf{A}; \beta) \\ \eta(\mathbf{a}) - \mu(\mathbf{L}, \mathbf{a}; \beta) \end{bmatrix}$$

Inverse Probability Weighting (IPW)

1. Obtain/estimate **standardized propensity score weights**

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This can be expressed as an M-estimator with score function

$$\boldsymbol{\Psi}_{0-IPW}(Y, \mathbf{L}, \mathbf{A}; \theta_{IPW}) = \begin{bmatrix} \boldsymbol{\Psi}_{PS}(\mathbf{L}, \mathbf{A}) \\ SW(\mathbf{L}, \mathbf{A}) \left\{ Y - \eta(\mathbf{A}; \gamma) \right\} \partial_\gamma \eta(\mathbf{A}; \gamma) \end{bmatrix}$$

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Doubly robust* to models for $\mu(\mathbf{L}, \mathbf{A}; \beta)$ and $f_{\mathbf{A}|\mathbf{L}}(\mathbf{A}|\mathbf{L})$

Addressing Confounding and Measurement Error

Can we just substitute $\mathbf{A}^*$ for $\mathbf{A}$ and find the solution to

$$\sum_{i=1}^{n} \mathbf{\Psi}_0(Y_i, \mathbf{L}_i, \underbrace{\mathbf{A}_i^*}_{\text{mismeasured}}; \theta) = \mathbf{0}?$$

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No! This leads to bias in $\widehat{\theta}$ because

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We need a new score function $\mathbf{\Psi}_{CS}$ such that

$$\mathrm{E}\{\underbrace{\mathbf{\Psi}_{CS}}_{\text{new score fun.}}(Y, \mathbf{L}, \underbrace{\mathbf{A}^*}_{\text{mismeasured}}; \theta_0)\} = \mathbf{0}.$$

Corrected Score Functions

Given the "oracle" score function $\mathbf{\Psi}_0$, the "corrected score" function $\mathbf{\Psi}_{CS}$ can be created following Novick and Stefanski (2002) (Novick and Stefanski, 2002):

$$\mathbf{\Psi}_0(Y, \mathbf{L}, \mathbf{A}^*; \theta)$$

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1. Add additional **imaginary** measurement error $i\widetilde{\epsilon}$ to the mismeasured exposure

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Corrected Score Functions (contd)

If the oracle score function is **conditionally unbiased**:

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The G-Formula, IPW, and DR score functions all satisfy these conditions, and so can be "corrected:"

$$\boldsymbol{\Psi}_{0-GF} \longrightarrow \boldsymbol{\Psi}_{CS-GF}$$
$$\boldsymbol{\Psi}_{0-IPW} \longrightarrow \boldsymbol{\Psi}_{CS-IPW}$$
$$\boldsymbol{\Psi}_{0-DR} \longrightarrow \boldsymbol{\Psi}_{CS-DR}$$

Monte Carlo Corrected Score Functions

- Sometimes we can find a closed-form algebraic expression for

$$\boldsymbol{\Psi}_{CS}(Y, \mathbf{L}, \mathbf{A}^*; \theta) = \underbrace{\mathrm{E}\left[\mathrm{Re}\left\{\boldsymbol{\Psi}_0(Y, \mathbf{L}, \mathbf{A}^* + i\widetilde{\epsilon}; \theta)\right\} \middle| Y, \mathbf{L}, \mathbf{A}^*\right]}_{\mathrm{E}\{f(\widetilde{\epsilon})\}}.$$

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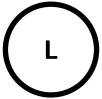
$$\implies \boldsymbol{\Psi}_{MCCS}^{B}(Y, \mathbf{L}, \mathbf{A}^*; \theta) = B^{-1} \textstyle\sum_{b=1}^{B} \mathrm{Re}\left\{\boldsymbol{\Psi}_0(Y, \mathbf{L}, \mathbf{A}^* + i\widetilde{\epsilon}_b; \theta)\right\}$$

Simulation Setting

$$L \sim \mathcal{N}(0, 0.36)$$



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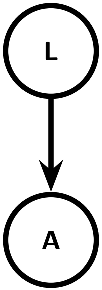

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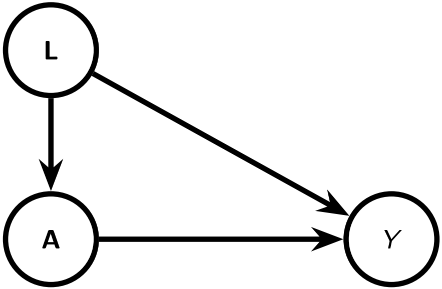

$\mathbf{A} | L \sim \mathcal{N}_2(\mathbf{0}, \boldsymbol{I})$

$Y | L, \mathbf{A} \sim \mathcal{N}(A_1 + A_2 + L, 1)$

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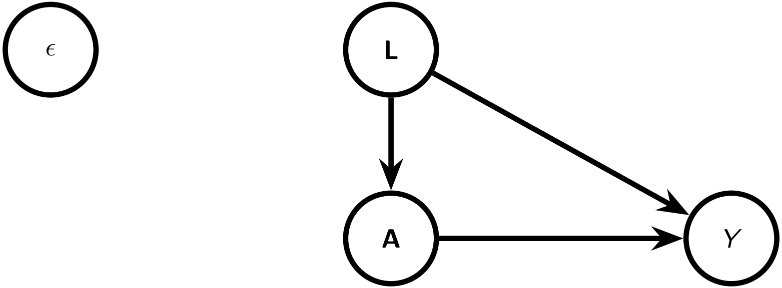

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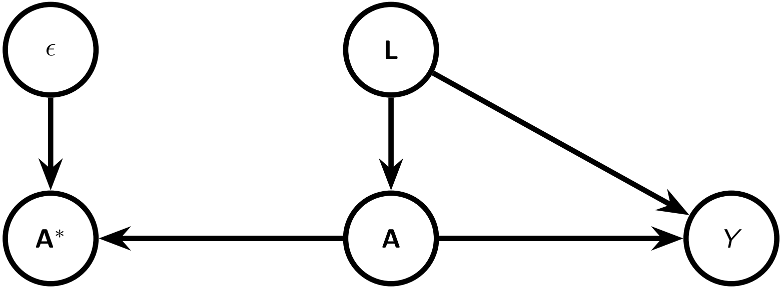

$\mathbf{A}^* = \mathbf{A} + \epsilon$

$\mathbf{A}|L \sim \mathcal{N}_2(\mathbf{0}, \boldsymbol{I})$

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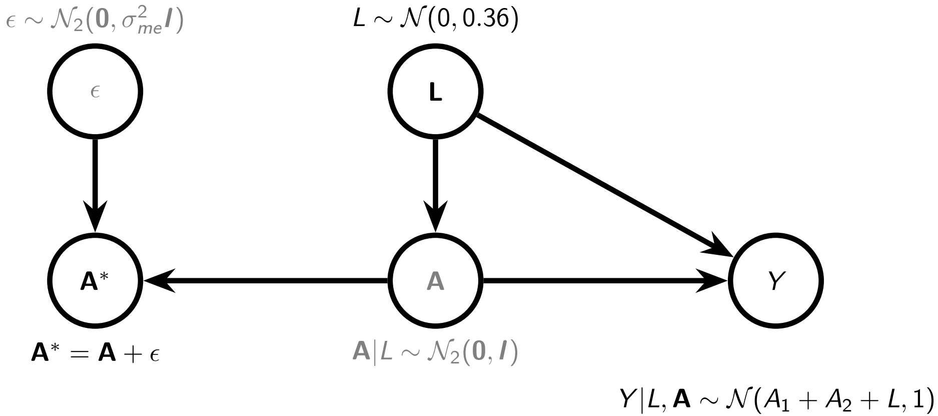

Simulation Setting

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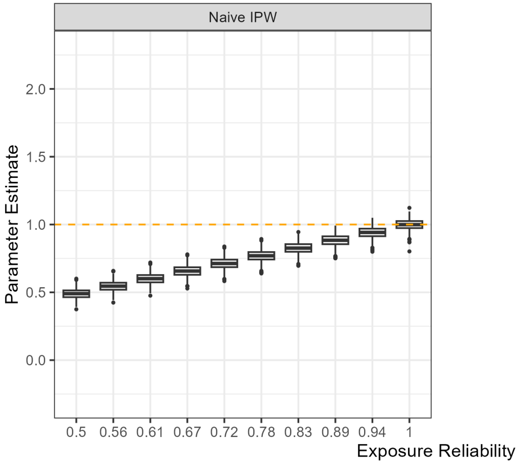
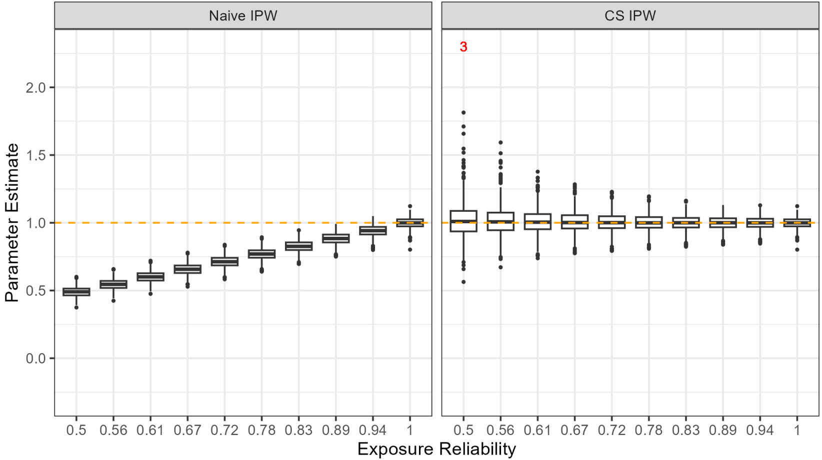
  2. Corrected Score IPW

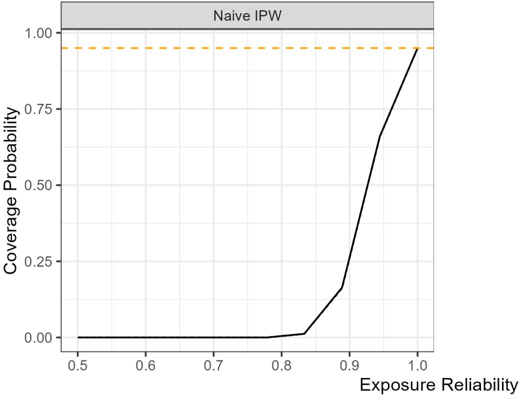
Simulation Results: Estimator



Simulation Results: Estimator



Simulation Results: Confidence Interval



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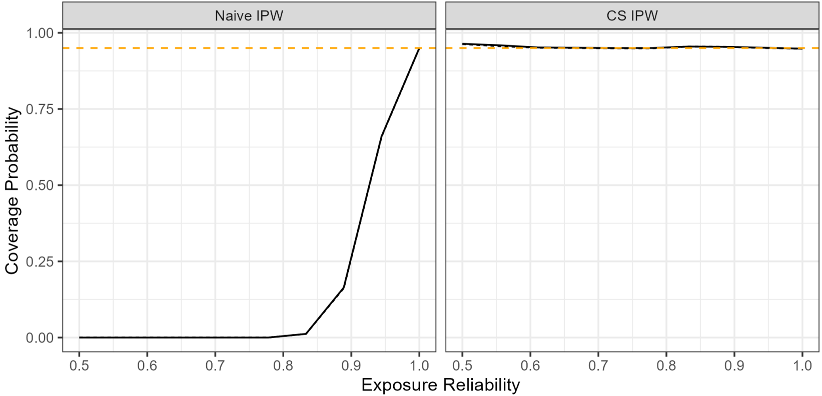

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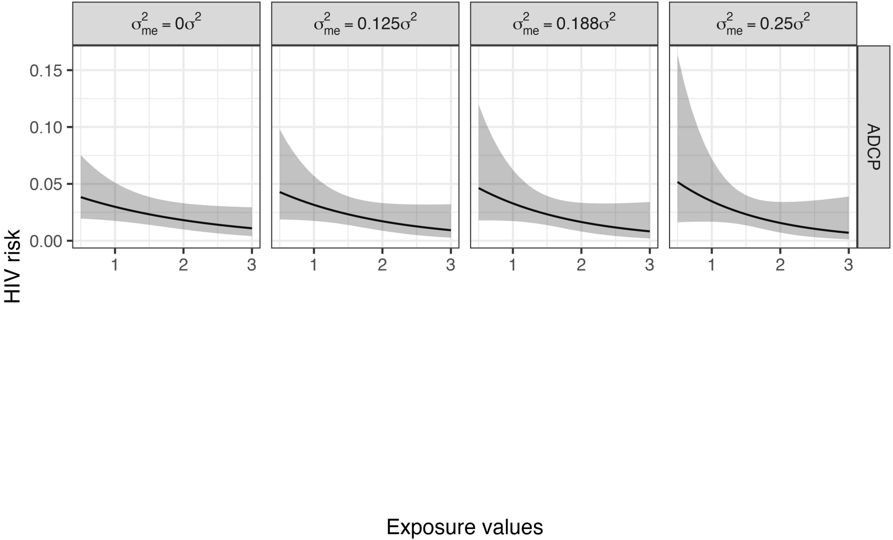
- **Analysis**: Corrected score DR estimator with a log-linear outcome model

Application: HVTN 505 Trial



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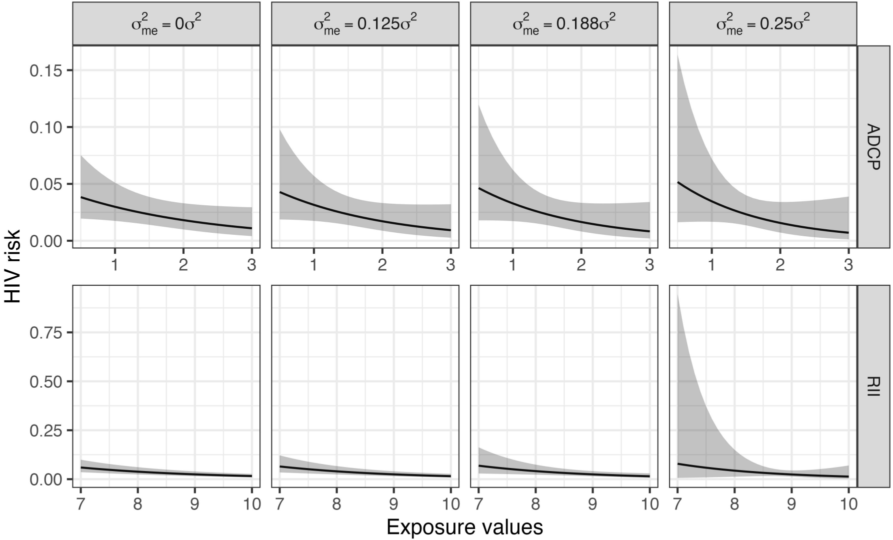

Summary of Project 1

Paper in *Biometrics* (2025)

GitHub R package

Mismex: Causal Inference for **Mism**easured **Ex**posures

Project 2: Social Distancing to Reduce Transmission of Influenza-Like-Illness on College Campuses: the eX-FLU Trial

Brian Richardson, Allison Aiello, Michael Hudgens

eX-FLU Trial

- **eX-FLU**: trial to evaluate a social distancing intervention on a college campus during flu season (Aiello et al., 2016; Zivich et al., 2020)

Design and methods of a social network isolation study for reducing respiratory infection transmission: The eX-FLU cluster randomized trial

Allison E. Aiello[a,*], Amanda M. Simanek[b,1], Marisa C. Eisenberg[c], Alison R. Walsh[c], Brian Davis[c], Erik Volz[d,1], Caroline Cheng[c], Jeanette J. Rainey[e], Amra Uzicanin[e], Hongjiang Gao[e], Nathaniel Osgood[f], Dylan Knowles[f], Kevin Stanley[f], Kara Tarter[c], Arnold S. Monto[c]

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- **Intervention**: encouragement to isolate in dorm for three days upon developing symptoms of **influenza-like illness** (ILI)
- **Central question**: does the encouragement-to-isolate intervention reduce transmission of ILI?

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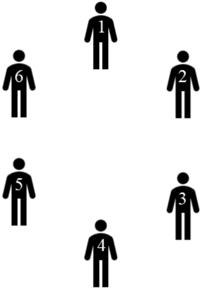
Transmission of Influenza-Like-Illness



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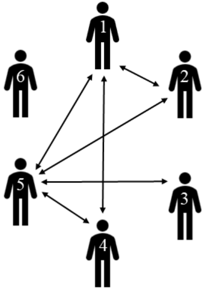

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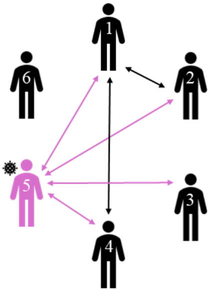

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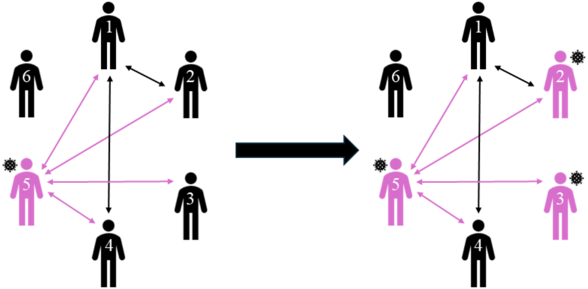
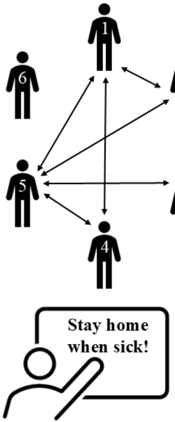


Example I: Intervention Affects Network and Transmission



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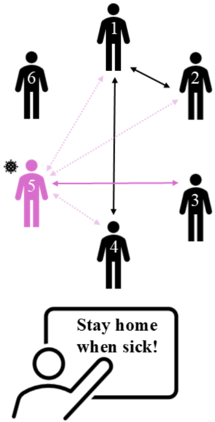

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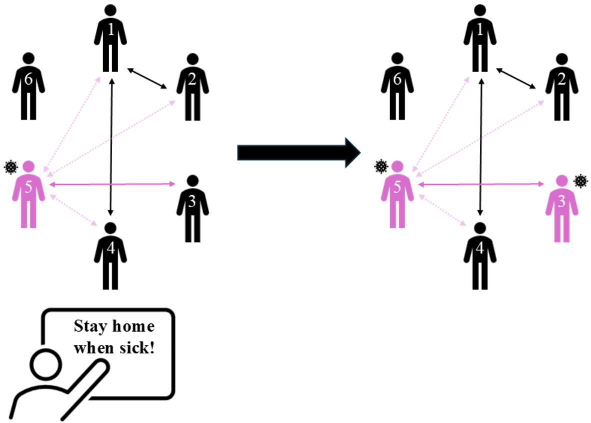
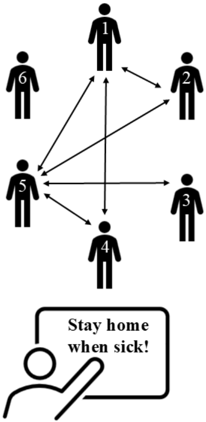


Example II: Intervention Affects Network, Not Transmission



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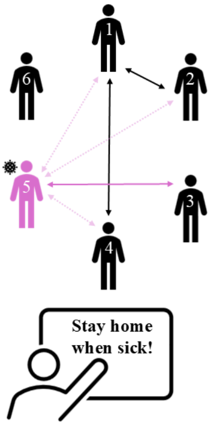

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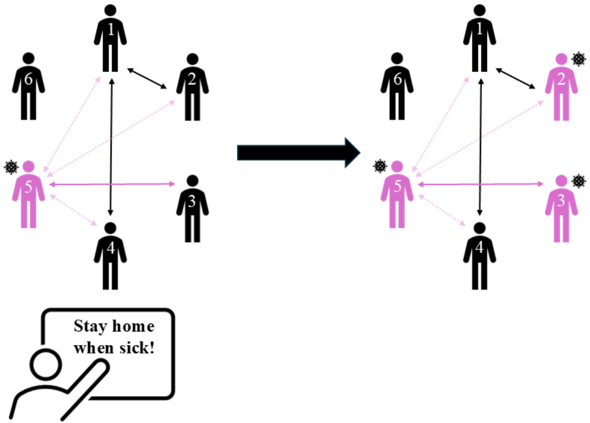
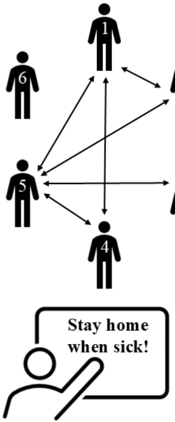


Example III: Intervention Affects Transmission, Not Network



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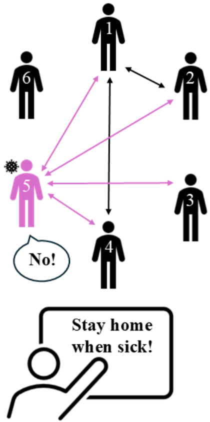
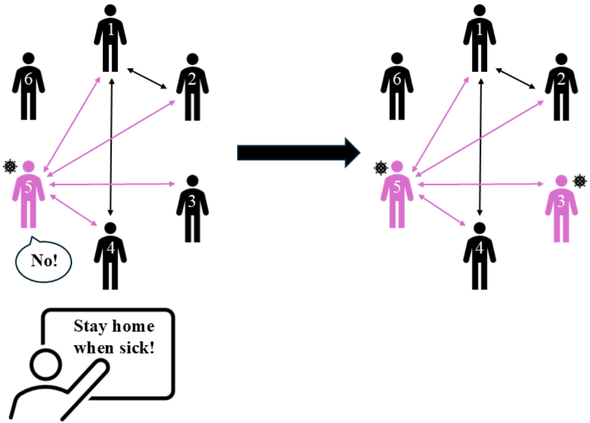
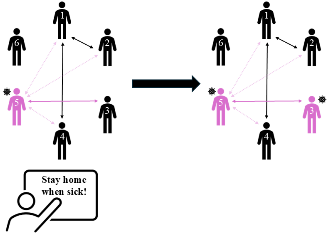


Example III: Intervention Affects Transmission, Not Network

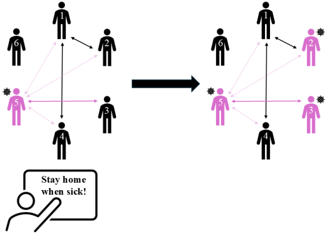


Central Question: Does the Intervention Affect Transmission of ILI?

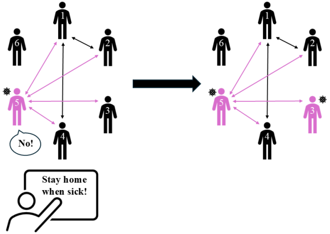
Example I:



Example II:



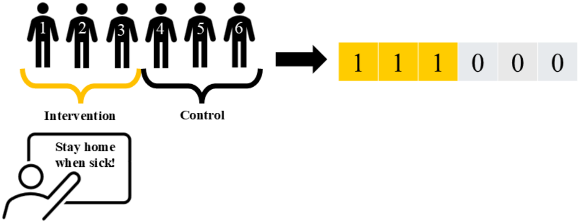
Example III:



In Examples I and III, the answer is yes

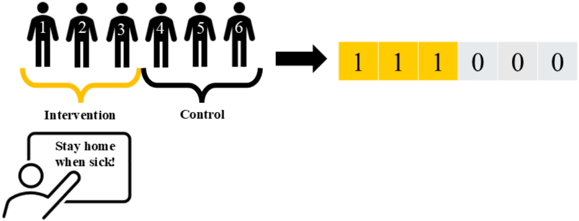
eX-FLU Observed Data

- Baseline randomization assignments
  $\mathbf{Z} = (Z_1, \ldots, Z_n) \in \mathcal{Z}$, for
  $Z_i = \mathbb{1}(\text{student } i \text{ gets intervention})$



eX-FLU Observed Data

- Baseline randomization assignments $\mathbf{Z} = (Z_1, \ldots, Z_n) \in \mathcal{Z}$, for $Z_i = \mathbb{1}(\text{student } i \text{ gets intervention})$
    - known randomization distribution $r(\mathbf{z})$



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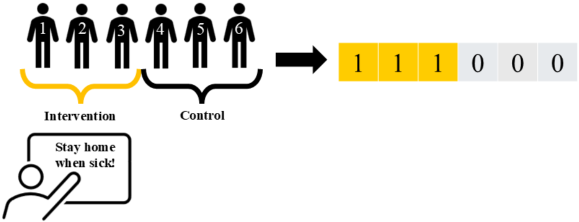
- At weeks $k = 1, \ldots, \tau$, we observe:



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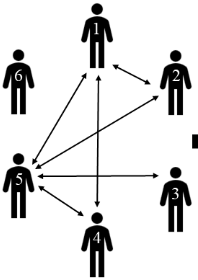

	1	2	3	4	5	6
1	0	1	0	1	1	0
2	1	0	0	0	1	0
3	0	0	0	0	1	0
4	1	0	0	0	1	0
5	1	1	1	1	0	0
6	0	0	0	0	0	0

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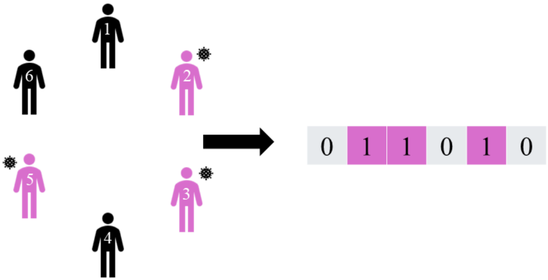
  - infections $\mathbf{Y}^k = (Y^k_1, \ldots, Y^k_n)$, for $Y^k_i = \mathbb{1}(\text{student } i \text{ is infected at week } k)$



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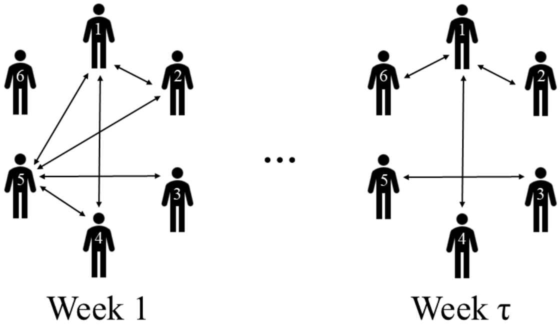
- network history: $\overline{\mathbf{A}} = \{\mathbf{A}^k\}_{k=1}^{\tau}$



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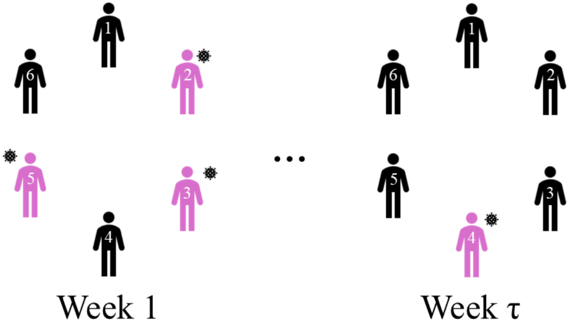

eX-FLU Potential Outcomes

Potential outcomes are defined for both the networks, and ILI infections:

$$\overline{\mathbf{A}}(\mathbf{z}), \quad \overline{\mathbf{Y}}(\mathbf{z}) \quad \text{for } \mathbf{z} \in \mathcal{Z}$$

- $\overline{\mathbf{A}}(\mathbf{z})$: sequence of networks that **would** occur if students **were** encouraged to isolate according to $\mathbf{z}$
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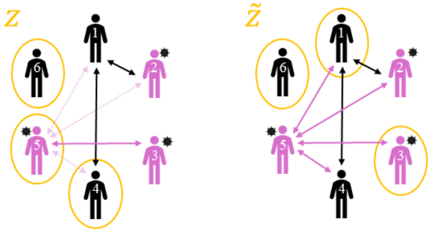
- Both of these depend on the entire vector $\mathbf{z}$
  - potential outcomes for one student depend on intervention assignment of other students (**interference**) (Rubin, 1980; Sobel, 2006; Rosenbaum, 2007; Hudgens and Halloran, 2008)
- Assume **causal consistency**:

$$\overline{\mathbf{A}} = \overline{\mathbf{A}}(\mathbf{Z}) \text{ and } \overline{\mathbf{Y}} = \overline{\mathbf{Y}}(\mathbf{Z})$$

eX-FLU Null Hypotheses

$$H_0^Y : \overline{\mathbf{Y}}(\mathbf{z}) = \overline{\mathbf{Y}}(\widetilde{\mathbf{z}}) \text{ for all } \mathbf{z}, \widetilde{\mathbf{z}} \in \mathcal{Z}$$

(“the intervention has no effect on the infections”)



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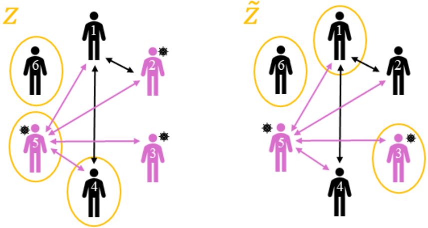

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$$H_0^\sharp = H_0^Y \cap H_0^A : \overline{\mathbf{Y}}(\mathbf{z}) = \overline{\mathbf{Y}}(\tilde{\mathbf{z}}) \text{ and } \overline{\mathbf{A}}(\mathbf{z}) = \overline{\mathbf{A}}(\tilde{\mathbf{z}}) \text{ for all } \mathbf{z}, \tilde{\mathbf{z}} \in \mathcal{Z}$$

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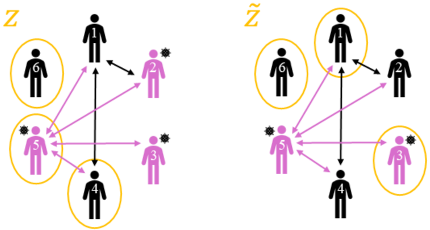

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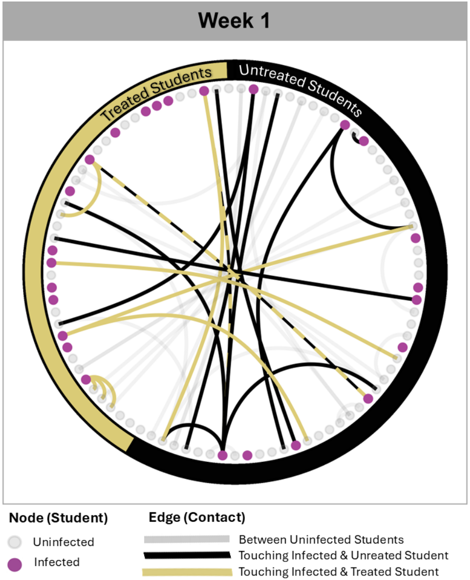
Previous analyses of the eX-FLU trial (Alexandria et al., 2023) tested $H_0^\sharp$, but no analyses have tested H_0^Y

eX-FLU: Descriptive Results

- 93 (out of 579) students with at least one infection



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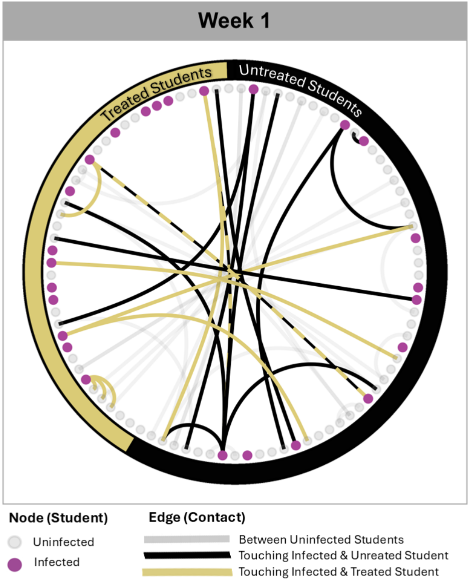

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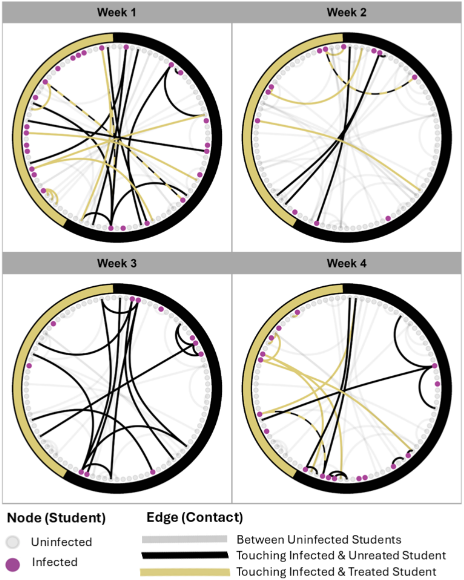
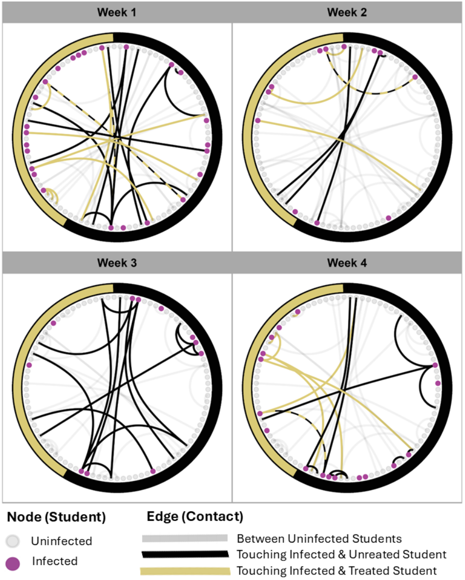


eX-FLU: Descriptive Results

- 93 (out of 579) students with at least one infection
- Bold edges represent possible transmission events
  - Proportion of possible transmission events attributable to students in the intervention group:

$$
\begin{aligned}
T &= \frac{\text{number of yellow edges}}{\text{total number of edges}} = \\
&= \frac{\sum_{k=2}^{\tau}\sum_{i=1}^{n}\sum_{j>i} Z_i Y_i^{k-1} A_{ij}^{k-1}}{\sum_{k=2}^{\tau}\sum_{i=1}^{n}\sum_{j>i} Y_i^{k-1} A_{ij}^{k-1}} \\
&= 0.359
\end{aligned}
$$



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Randomization	Networks	Infections	Test Statistic
$\mathbf{z}_1$			
$\mathbf{z}_2$			
$\ldots$			
$\mathbf{z}_{\lvert\mathcal{Z}\rvert}$			

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Randomization	Networks	Infections	Test Statistic
$\mathbf{z}_1$	$\overline{\mathbf{A}}(\mathbf{z}_1) = ?$	$\overline{\mathbf{Y}}(\mathbf{z}_1) = ?$	$T(\mathbf{z}_1, ?, ?)$
$\mathbf{z}_2$	$\overline{\mathbf{A}}(\mathbf{z}_2) = ?$	$\overline{\mathbf{Y}}(\mathbf{z}_1) = ?$	$T(\mathbf{z}_1, ?, ?)$
...	...	...	...
$\mathbf{z}_{\lvert\mathcal{Z}\rvert}$	$\overline{\mathbf{A}}(\mathbf{z}_{\lvert\mathcal{Z}\rvert}) = ?$	$\overline{\mathbf{Y}}(\mathbf{z}_{\lvert\mathcal{Z}\rvert}) = ?$	$T(\mathbf{z}_{\lvert\mathcal{Z}\rvert}, ?, ?)$

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$\mathbf{z}_1$	$\overline{\mathbf{A}}(\mathbf{z}_1) = \overline{\mathbf{A}}$	$\overline{\mathbf{Y}}(\mathbf{z}_1) = \overline{\mathbf{Y}}$	$T(\mathbf{z}_1, \overline{\mathbf{A}}, \overline{\mathbf{Y}})$
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...	...	...	...
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  - This is possible since $\overline{\mathbf{A}}(\mathbf{z}), \overline{\mathbf{Y}}(\mathbf{z})$ are **imputable** under $H_0^\sharp$

Randomization	Networks	Infections	Test Statistic
$\mathbf{z}_1$	$\overline{\mathbf{A}}(\mathbf{z}_1) = \overline{\mathbf{A}}$	$\overline{\mathbf{Y}}(\mathbf{z}_1) = \overline{\mathbf{Y}}$	$T(\mathbf{z}_1, \overline{\mathbf{A}}, \overline{\mathbf{Y}})$
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$\dots$	$\dots$	$\dots$	$\dots$
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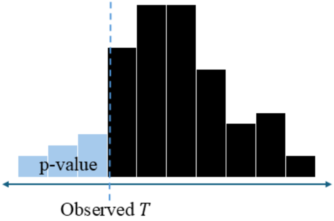
$$F_T(t|H_0^\sharp) = \sum_{\mathbf{z} \in \mathcal{Z}} r(\mathbf{z}) \mathbb{1}\{T(\mathbf{z}, \overline{\mathbf{A}}, \overline{\mathbf{Y}}) \leq t\}$$



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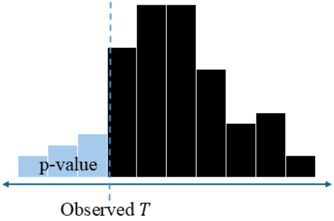
- Reject $H_0^\sharp$ if $\rho^\sharp \leq 0.05$



Testing $H_0^\sharp$

- This test of $H_0^\sharp$ controls the **type I error rate** exactly:

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$$\Pr\left(\rho^\sharp \leq \alpha | H_1\right)$$

  depends on the choice of test statistic
  - In general, T should be chosen such that small values indicate departures from $H_0^\sharp$

Testing H_0^Y

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$\mathbf{z}_2$			
$\cdots$			
$\mathbf{z}_{\|\mathcal{Z}\|}$			

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$\mathbf{z}_2$	$\overline{\mathbf{A}}(\mathbf{z}_2) =?$	$\overline{\mathbf{Y}}(\mathbf{z}_1) =?$	$T(\mathbf{z}_1, ?, ?)$
$\ldots$	$\ldots$	$\ldots$	$\ldots$
$\mathbf{z}_{\lvert\mathcal{Z}\rvert}$	$\overline{\mathbf{A}}(\mathbf{z}_{\lvert\mathcal{Z}\rvert}) =?$	$\overline{\mathbf{Y}}(\mathbf{z}_{\lvert\mathcal{Z}\rvert}) =?$	$T(\mathbf{z}_{\lvert\mathcal{Z}\rvert}, ?, ?)$

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  - If/when q is unknown, estimate it
    - E.g., using a **Separable Temporal Exponential Random Graph Model**
    - Use estimated q to obtain $\widehat{\rho}^Y$

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1. Estimate the unknown parameter θ in the PMF $q(\overline{\mathbf{a}}, \mathbf{z}; \theta)$ of $\overline{\mathbf{A}}(\mathbf{z})$

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Proposition: This procedure will **asymptotically** control the type I error rate

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- $\tau \in \{5, 10\}$ weeks
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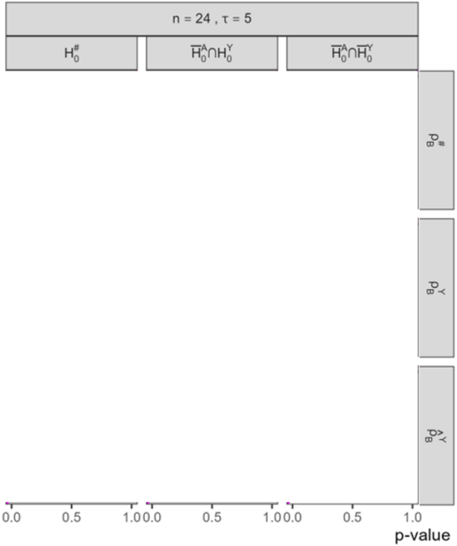
- Three testing procedures:
  1. $\rho_B^\sharp$: testing $H_0^\sharp$
  2. ρ_B^Y: testing H_0^Y using known q
  3. $\widehat{\rho}_B^Y$: testing H_0^Y using estimated q

Simulation Results



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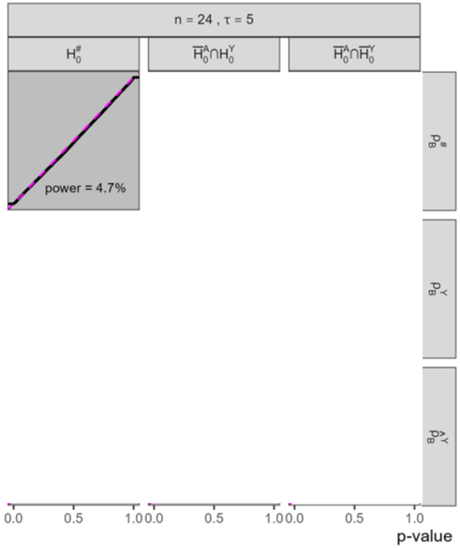

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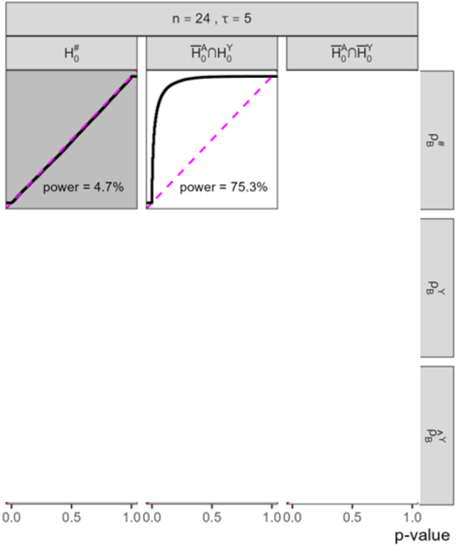

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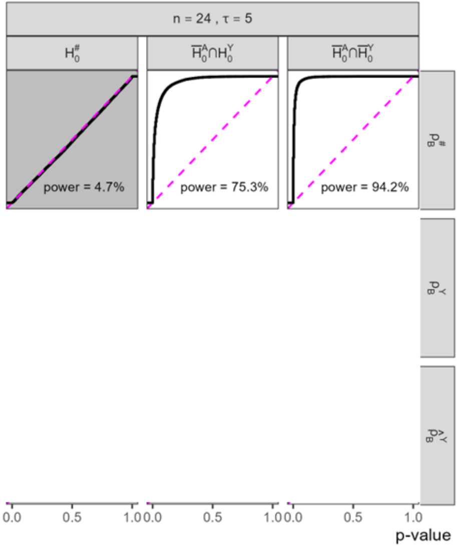

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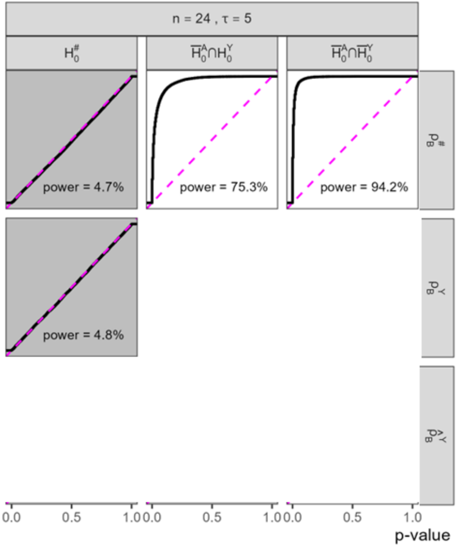

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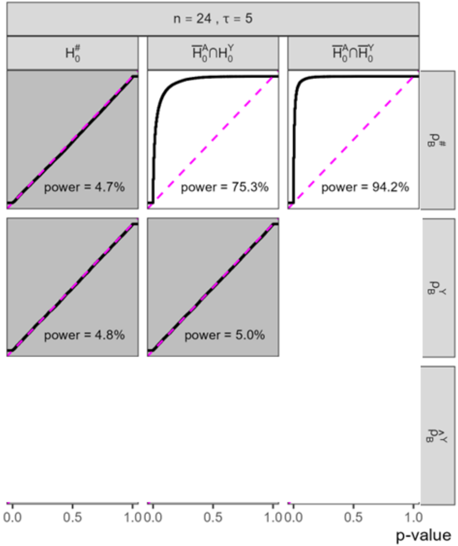

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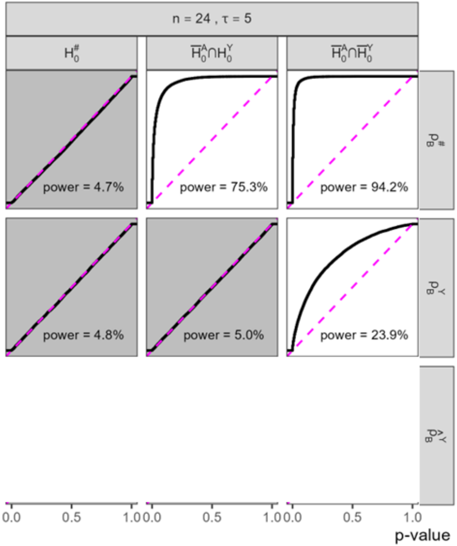

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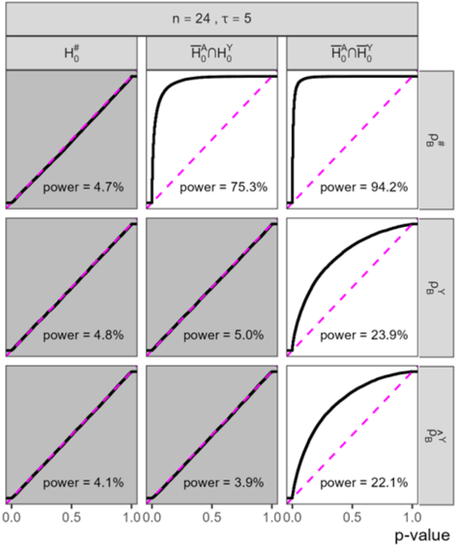

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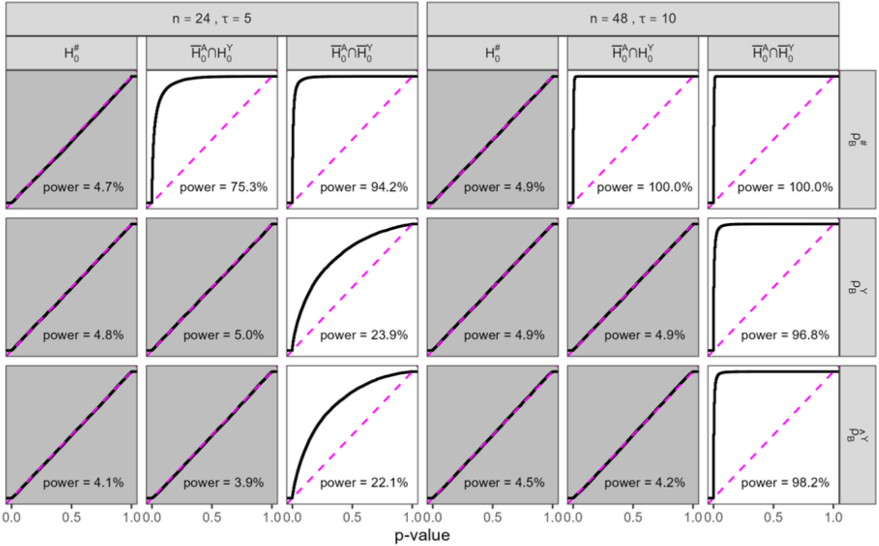

eX-FLU: Hypothesis Test Results

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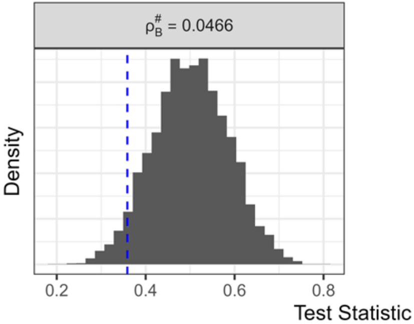

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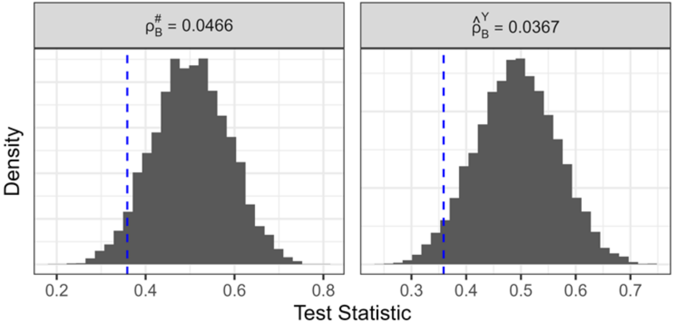

- Encouragement to isolate affects the social network and/or influenze-like illness ($\rho_B^\sharp = 0.0466$)
- Encouragement to isolate specifically affects influenze-like illness ($\widehat{\rho}_B^Y = 0.0367$)

Summary of Project 2

- Developed a new randomization-based inference procedure
  - Established theoretical properties (asymptotic control of Type I error)
  - Demonstrated empirical performance through simulations
- Applied the method to the **eX-FLU trial** to find a protective effect of an encouragement-to-isolate intervention on a college campus
- **Status**: preparing submission to *PNAS* (target: December)

Project 3 : Causal Inference from Cluster Randomized Trials with Differential Nonresponse

Brian Richardson, Bonnie Shook-Sa, Michael Hudgens

PopART Trial

- **PopART**: large **cluster randomized trial** designed to evaluate a combination **HIV prevention intervention** in Zambia and South Africa (Hayes et al., 2014)

Hayes *et al. Trials* 2014, **15**:57
http://www.trialsjournal.com/content/15/1/57

TRIALS

STUDY PROTOCOL **Open Access**

HPTN 071 (PopART): Rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment – a study protocol for a cluster randomised trial

Richard Hayes[1], Helen Ayles[2,3], Nulda Beyers[4], Kalpana Sabapathy[1*], Sian Floyd[1], Kwame Shanaube[3], Peter Bock[4], Sam Griffith[5], Ayana Moore[5], Deborah Watson-Jones[2], Christophe Fraser[6], Sten H Vermund[7], Sarah Fidler[8] and The HPTN 071 (PopART) Study Team

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  - Arm A: annual home-based HIV testing, promotion of medical male circumcision for HIV-negative men, and offer of immediate ART for those testing HIV-positive
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STUDY PROTOCOL Open Access

HPTN 071 (PopART): Rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment – a study protocol for a cluster randomised trial

Richard Hayes[1], Helen Ayles[2,3], Nulda Beyers[4], Kalpana Sabapathy[1*], Sian Floyd[1], Kwame Shanaube[3], Peter Bock[4], Sam Griffith[5], Ayana Moore[5], Deborah Watson-Jones[2], Christophe Fraser[6], Sten H Vermund[7], Sarah Fidler[8] and The HPTN 071 (PopART) Study Team

PopART Trial

- **Initial Findings**: no protective effect of the Arm A intervention (Hayes et al., 2019)
  - "unanticipated and not consistent with the data on viral suppression"

The NEW ENGLAND JOURNAL of MEDICINE

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PopART Trial

- **Initial Findings**: no protective effect of the Arm A intervention (Hayes et al., 2019)
  - "unanticipated and not consistent with the data on viral suppression"
- **Later Analyses**: identified possibly differential nonresponse that could bias trial results (Shook-Sa et al., 2025+)
  - Men were less likely to respond (i.e., have data collected)
  - The intervention appeared more effective among men

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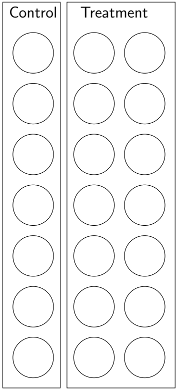

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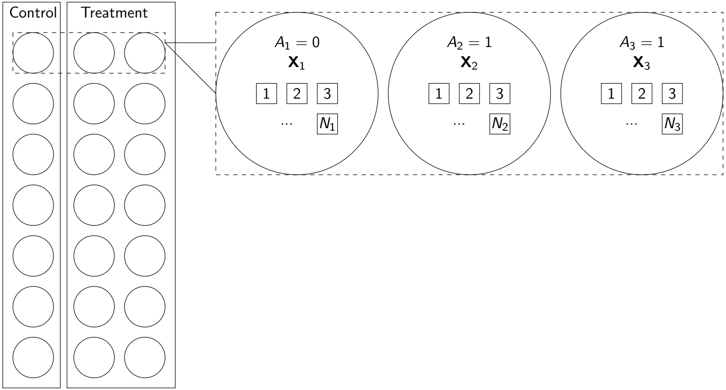

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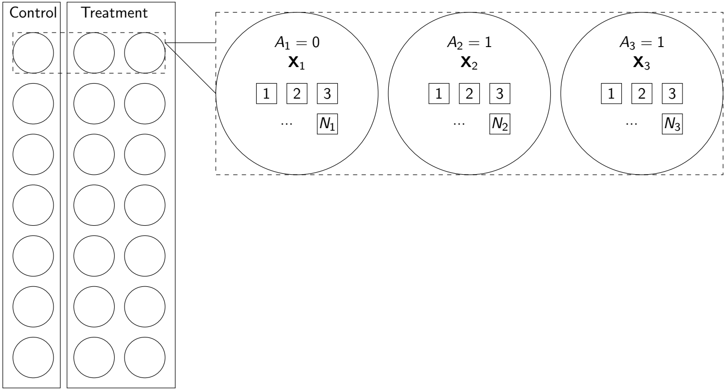

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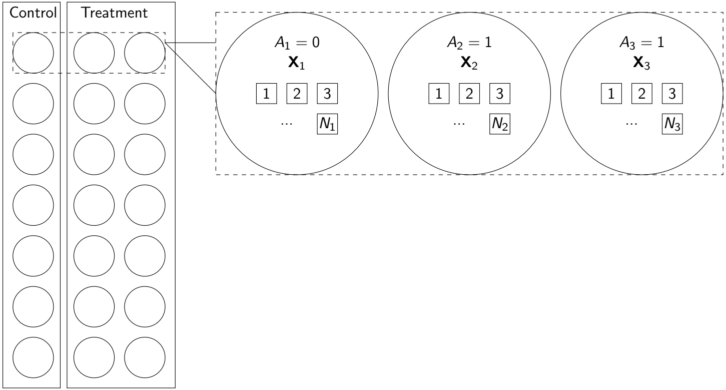

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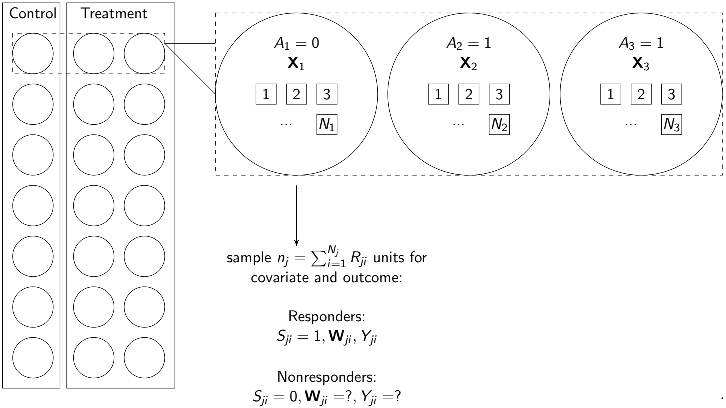

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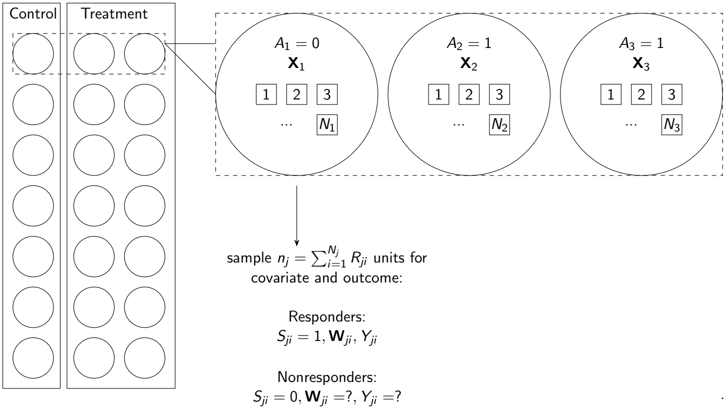

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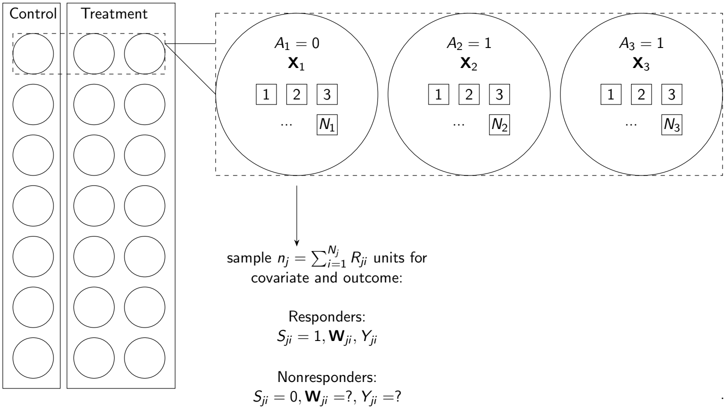

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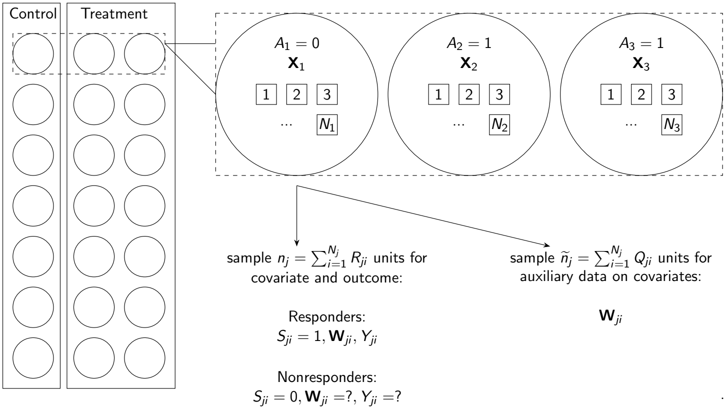

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- Auxiliary data available for $\widetilde{n}_j$ of N_j individuals
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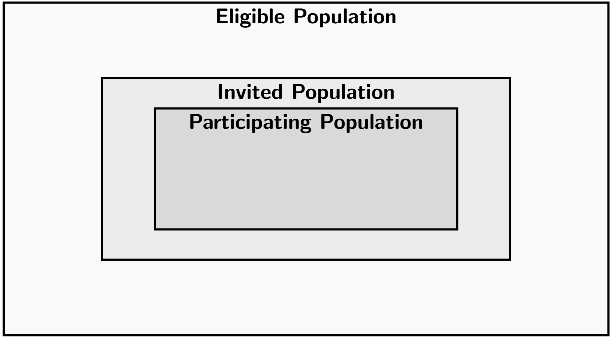
Extending Inference from Randomized Controlled Trials



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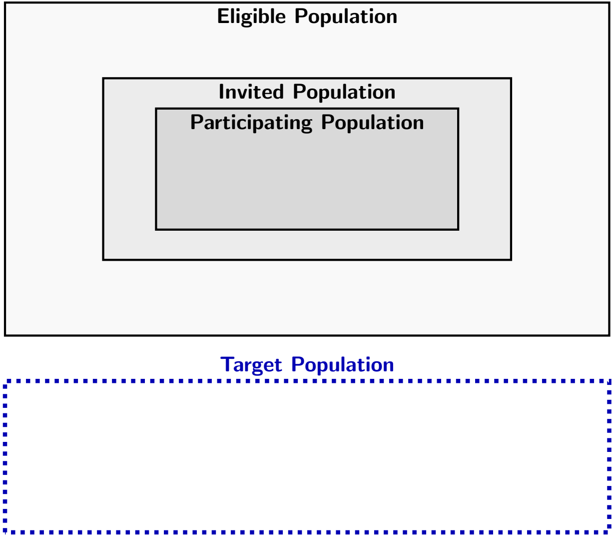

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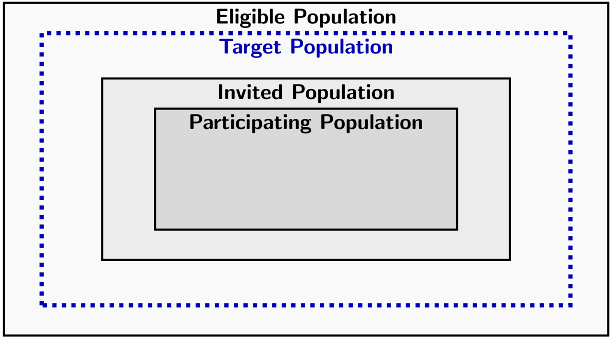

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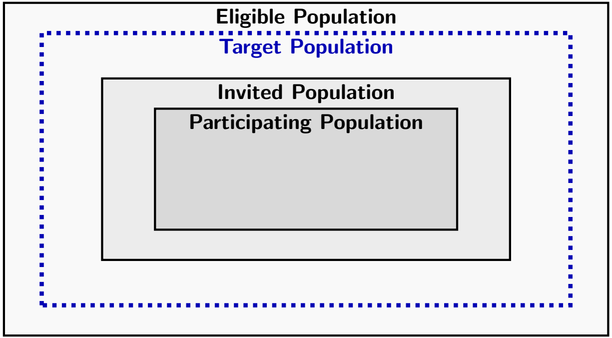

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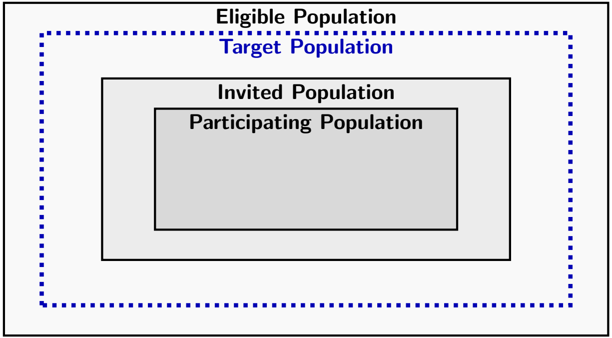

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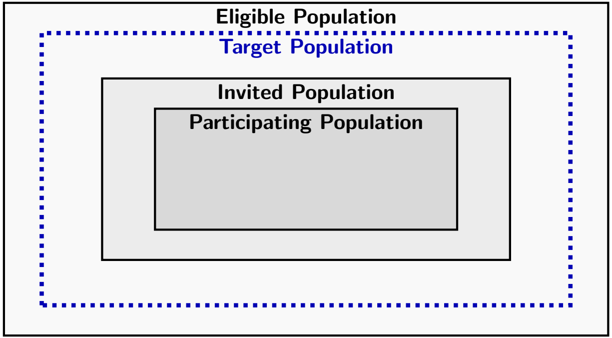

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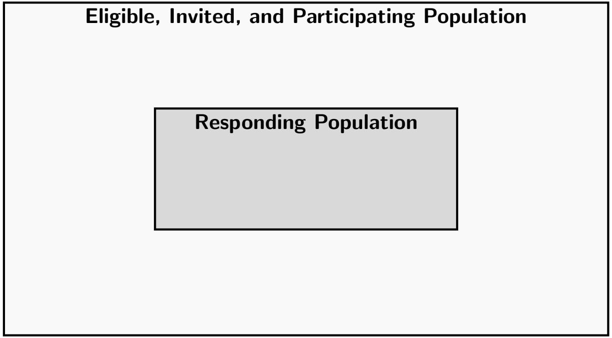
  - Dahabreh et al. (2020): generalizing results from participating clusters in a **cluster** RCT to eligible clusters

Participation vs Response

Eligible, Invited, and Participating Population

- PopART intervention was delivered at the cluster level $\implies$ all individuals **participated**

Participation vs Response



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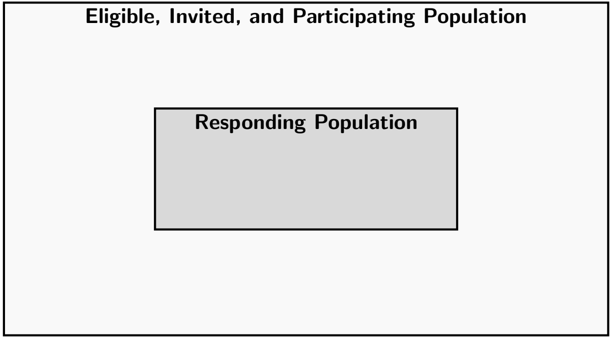

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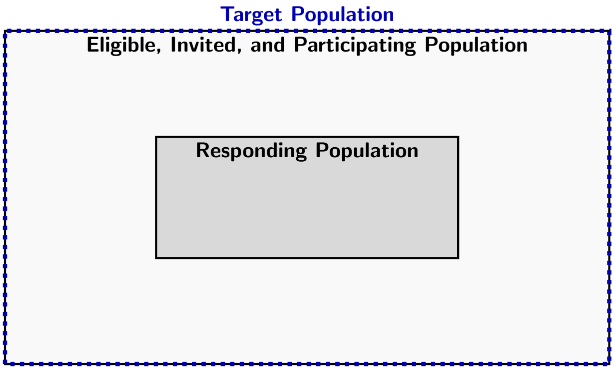

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- **Goal**: generalize results to trial-eligible population using data from responders

Proposal for Project 3

- Develop estimators of the causal effect of the PopART intervention in the trial eligible population

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  3. Augmented inverse probability weighting (AIPW)
     - ★ Both weighting and outcome regression
     - ★ Semiparametric efficient (?)
     - ★ (Doubly) Robust (?)

Thank you! Questions?

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Supplement to Project 1 : Addressing Confounding and Continuous Exposure Measurement Error Using Corrected Score Functions

Brian Richardson, Brian Blette, Peter Gilbert, Michael Hudgens

Corrected Score Functions: What?

- Suppose the oracle score function is **conditionally unbiased**, meaning

$$\mathrm{E}\{\boldsymbol{\Psi}_0(Y, \mathbf{L}, \mathbf{A}; \theta) | \mathbf{A}\} = \mathbf{0}.$$

- Define the corrected score function as

$$\boldsymbol{\Psi}_{CS}\left(Y, \mathbf{L}, \mathbf{A}^*; \theta\right) = \mathrm{E}\left[\mathrm{Re}\left\{\boldsymbol{\Psi}_0(Y, \mathbf{L}, \widetilde{\mathbf{A}}; \theta)\right\} | Y, \mathbf{L}, \mathbf{A}^*\right],$$

where $\widetilde{\mathbf{A}} = \mathbf{A}^* + i\widetilde{\epsilon}$, $i = \sqrt{-1}$, $\mathrm{Re}(\cdot)$ denotes the real component of a complex number, and $\widetilde{\epsilon} \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma}_{me})$.

- Then

$$\begin{aligned}
& \mathrm{E}\left\{\boldsymbol{\Psi}_{CS}\left(Y, \mathbf{L}, \mathbf{A}^*; \theta\right) | Y, \mathbf{L}, \mathbf{A}\right\} = \boldsymbol{\Psi}_0\left(Y, \mathbf{L}, \mathbf{A}; \theta\right) \\
\Longrightarrow\ & \mathrm{E}\left[\mathrm{E}\left\{\boldsymbol{\Psi}_{CS}\left(Y, \mathbf{L}, \mathbf{A}^*; \theta\right) | Y, \mathbf{L}, \mathbf{A}\right\}\right] = \mathrm{E}\left\{\boldsymbol{\Psi}_0\left(Y, \mathbf{L}, \mathbf{A}; \theta\right)\right\} \\
\Longrightarrow\ & \mathrm{E}\left\{\boldsymbol{\Psi}_{CS}\left(Y, \mathbf{L}, \mathbf{A}^*; \theta\right)\right\} = \mathbf{0}
\end{aligned}$$

Corrected Score Functions: Why?

The key result (Novick and Stefanski, 2002) for corrected score functions is that, for a smooth enough function $\mathbf{f}$, the function $\widetilde{\mathbf{f}}$ defined by

$$\widetilde{\mathbf{f}}(\mathbf{A}^*) \equiv \mathrm{E}[\mathrm{Re}\{\mathbf{f}(\mathbf{A}^* + i\widetilde{\epsilon})\}|\mathbf{A}, \mathbf{A}^*]$$

does not depend on $\mathbf{A}$ and satisfies

$$\mathrm{E}\{\widetilde{\mathbf{f}}(\mathbf{A}^*)|\mathbf{A}\} = \mathbf{f}(\mathbf{A}).$$

The proof of this for the special case $f(\mathbf{A}) = \exp\left(\mathbf{c}\mathbf{A}^T\right)$ is illustrative.

Corrected Score Functions: Why?

CLAIM: $\mathrm{E}\{\widetilde{f}(\mathbf{A}^*)|\mathbf{A}\} = f(\mathbf{A})$ for $f(\mathbf{A}) = \exp\left(\mathbf{cA}^T\right)$.

Corrected Score Functions: Why?

CLAIM: $\mathrm{E}\{\widetilde{f}(\mathbf{A}^*)|\mathbf{A}\} = f(\mathbf{A})$ for $f(\mathbf{A}) = \exp\left(\mathbf{c}\mathbf{A}^T\right)$.

$$\widetilde{f}(\mathbf{A}^*) \equiv \mathrm{E}(\mathrm{Re}[\exp\{\mathbf{c}(\mathbf{A}^* + i\widetilde{\epsilon})^T\}]|\mathbf{A}, \mathbf{A}^*)$$
$$= \exp\left(\mathbf{c}\mathbf{A}^{*T}\right)\mathrm{Re}[\underbrace{\mathrm{E}\{\exp\left(i\mathbf{c}\widetilde{\epsilon}^T\right)\}]}_{\text{normal c.f.}} = \exp\left(\mathbf{c}\mathbf{A}^{*T}\right)\exp\left(-\frac{1}{2}\mathbf{c}\mathbf{\Sigma}_{me}\mathbf{c}^T\right)$$

Corrected Score Functions: Why?

CLAIM: $\mathrm{E}\{\widetilde{f}(\mathbf{A}^*)|\mathbf{A}\} = f(\mathbf{A})$ for $f(\mathbf{A}) = \exp\left(\mathbf{c}\mathbf{A}^T\right)$.

$$
\begin{aligned}
\widetilde{f}(\mathbf{A}^*) &\equiv \mathrm{E}(\mathrm{Re}[\exp\{\mathbf{c}(\mathbf{A}^* + i\widetilde{\epsilon})^T\}]|\mathbf{A}, \mathbf{A}^*) \\
&= \exp\left(\mathbf{c}\mathbf{A}^{*T}\right)\mathrm{Re}[\underbrace{\mathrm{E}\{\exp\left(i\mathbf{c}\widetilde{\epsilon}^T\right)\}]}_{\text{normal c.f.}} = \exp\left(\mathbf{c}\mathbf{A}^{*T}\right)\exp\left(-\frac{1}{2}\mathbf{c}\mathbf{\Sigma}_{me}\mathbf{c}^T\right) \\
\Longrightarrow \quad \mathrm{E}\{\widetilde{f}(\mathbf{A}^*)|\mathbf{A}\} &= \mathrm{E}\{\exp\left(\mathbf{c}\mathbf{A}^{*T}\right)|\mathbf{A}\}\exp\left(-\frac{1}{2}\mathbf{c}\mathbf{\Sigma}_{me}\mathbf{c}^T\right) \\
&= \mathrm{E}\{\exp\{\mathbf{c}(\mathbf{A}^T + \epsilon^T)\}|\mathbf{A}\}\exp\left(-\frac{1}{2}\mathbf{c}\mathbf{\Sigma}_{me}\mathbf{c}^T\right) \\
&= \exp\left(\mathbf{c}\mathbf{A}^T\right)\underbrace{\mathrm{E}\{\exp\left(\mathbf{c}\epsilon^T\right)\}}_{\text{normal m.g.f.}}\exp\left(-\frac{1}{2}\mathbf{c}\mathbf{\Sigma}_{me}\mathbf{c}^T\right) \\
&= \exp\left(\mathbf{c}\mathbf{A}^T\right)\exp\left(\frac{1}{2}\mathbf{c}\mathbf{\Sigma}_{me}\mathbf{c}^T\right)\exp\left(-\frac{1}{2}\mathbf{c}\mathbf{\Sigma}_{me}\mathbf{c}^T\right) \\
&= \exp\left(\mathbf{c}\mathbf{A}^T\right) = f(\mathbf{A})
\end{aligned}
$$

Additional Simulation Results: G-Formula

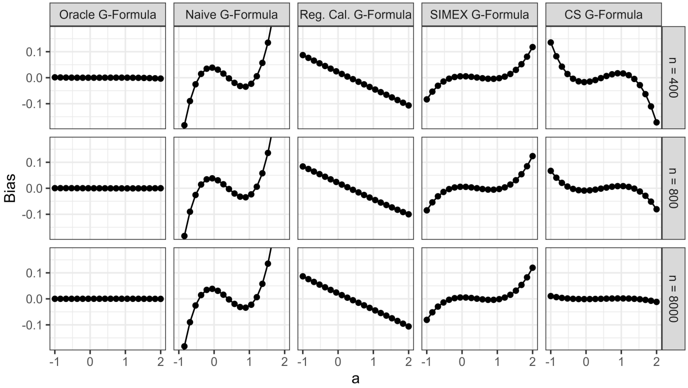


Figure: Estimated dose-response curve bias for the oracle, naive, regression calibration, SIMEX, and CS g-formula estimators. Bias refers to the average bias across 1000 simulated data sets for each method evaluated at each point on the horizontal axis, corresponding to setting the true exposure to $a \in [-1, 2]$. For the naive estimator, biases outside of $[-0.18, 0.18]$ are excluded from the plot.

Additional Simulation Results: IPW

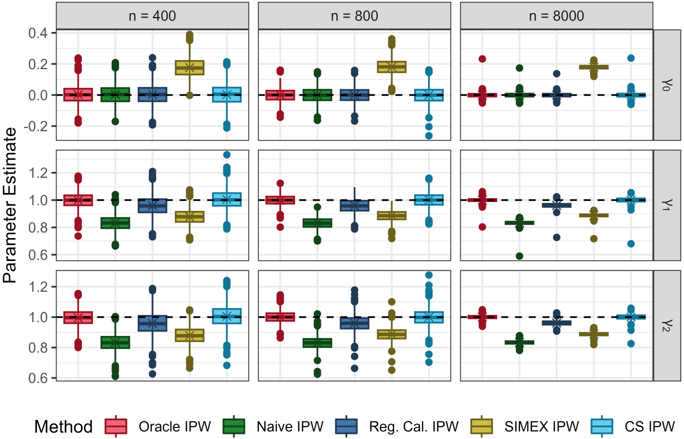


Figure: Empirical distribution of MSM parameter estimates from the simulation study of IPW estimators, using the oracle, naive, regression calibration (reg. cal.), simulation-extrapolation (SIMEX), and corrected score (CS) IPW estimators.

Additional Simulation Results: Doubly Robust Estimator

Table: Results from the simulation study of DR estimators. UC: uncorrected empirical sandwich variance estimator, BC: bias-corrected empirical sandwich variance estimator. PS indicates the propensity score model is correctly specified; OR indicates the outcome regression is correctly specified.

					UC		BC	
n	**Correct Specifications**	**Method**	**Bias**	**ESE**	**ASE**	**Cov**	**ASE**	**Cov**
2000	PS and OR	CS DR	0.2	8.5	7.9	92.6	7.9	92.9
		CS G-Formula	0.0	6.8	6.6	94.2	6.6	94.3
		CS IPW	0.1	8.9	8.3	93.5	8.4	94.0
	PS Only	CS DR	-0.1	8.6	8.0	93.3	8.1	93.4
		CS G-Formula	-14.9	6.7	6.6	39.7	6.6	40.0
		CS IPW	0.1	8.9	8.3	93.5	8.4	94.0
	OR Only	CS DR	0.1	7.7	7.2	93.0	7.2	93.0
		CS G-Formula	0.0	6.8	6.6	94.2	6.6	94.3
		CS IPW	-14.7	7.6	7.3	47.9	7.3	47.9
	Neither	CS DR	-14.7	7.5	7.1	47.0	7.2	47.3
		CS G-Formula	-14.9	6.7	6.6	39.7	6.6	40.0
		CS IPW	-14.7	7.6	7.3	47.9	7.3	47.9

Additional Simulation Results: Estimated Measurement Error Variance

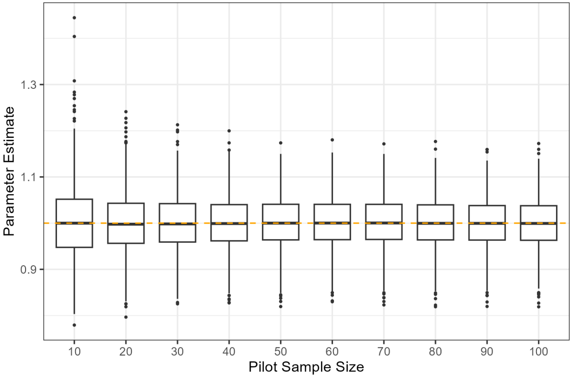


Figure: Empirical distribution of estimated γ_1 versus pilot study sample size n_p, using the corrected score (CS) IPW estimator with estimated measurement error covariance.

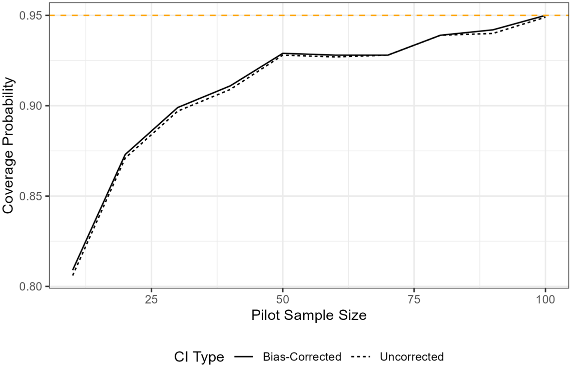


Figure: Empirical coverage probabilities of 95% confidence intervals for γ_1 versus pilot study sample size n_p, using the corrected score (CS) IPW estimator with estimated measurement error covariance.

Additional Simulation Results: Near-Positivity Violation

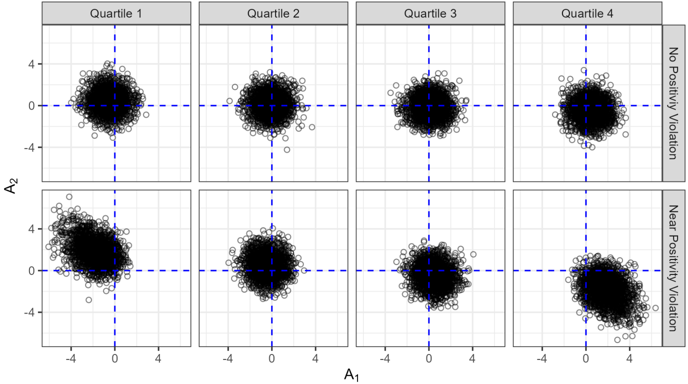


Figure: True exposure values (A_1, A_2) by quartile of L from one simulated data set of sample size $n = 8000$, with and without a near positivity violation.

Additional Simulation Results: Near-Positivity Violation

Table: Results from the simulation study with a near positivity violation. UC: uncorrected empirical sandwich variance estimator, BC: bias-corrected empirical sandwich variance estimator, n: sample size; Bias: 100 times the average bias across simulated data sets for each method; ESE: 100 times the standard deviation of parameter estimates; ASE: 100 times the average of estimated standard errors; Cov: Empirical percent coverage of 95% confidence intervals for each method.

					UC		BC	
n	**Method**	**Parameter**	**Bias**	**ESE**	**ASE**	**Cov**	**ASE**	**Cov**
8000	Oracle IPW	γ_0	-0.8	10.8	6.4	90.4	6.6	91.0
		γ_1	4.2	8.2	4.5	65.6	5.2	69.9
		γ_2	-3.6	8.2	4.7	64.3	5.4	68.7
	Naive IPW	γ_0	-0.4	10.7	6.8	89.1	7.0	89.5
		γ_1	-13.0	7.9	4.6	17.9	5.1	21.6
		γ_2	-19.9	8.0	4.6	10.2	5.1	12.2
	CS IPW	γ_0	-2.3	46.0	44.9	89.9	74.3	90.1
		γ_1	4.4	66.4	61.9	68.0	106.0	71.5
		γ_2	-4.3	33.0	31.0	76.6	49.8	78.8

Additional Simulation Results: Multiplicative Measurement Error

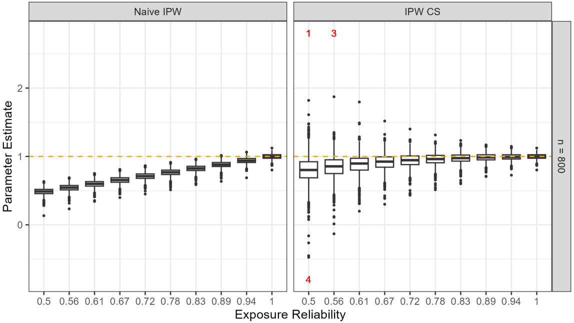


Figure: Empirical distribution of estimated γ_1 versus exposure reliability $\mathrm{Var}(A_1)/\mathrm{Var}(A_1^*) = \mathrm{Var}(A_2)/\mathrm{Var}(A_2^*)$, using naive and corrected score (CS) IPW estimators and for a multiplicative measurement error data generating process. For the CS IPW estimator, the number values beyond the ranges of the plot are shown in red on the tails of the boxplots.

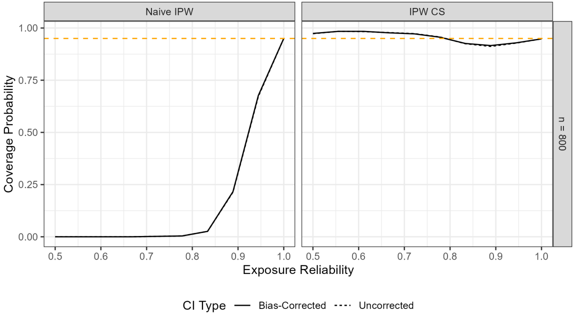


Figure: Empirical coverage probabilities of 95% confidence intervals for γ_1 versus exposure reliability $\mathrm{Var}(A_1)/\mathrm{Var}(A_1^*) = \mathrm{Var}(A_2)/\mathrm{Var}(A_2^*)$, using naive and corrected score (CS) IPW estimators for a multiplicative measurement error data generating process.

Supplement to Project 2: Social Distancing to Reduce Transmission of Influenza-Like-Illness on College Campuses: the eX-FLU Trial

Brian Richardson, Allison Aiello, Michael Hudgens

Choice of Test Statistic

Test statistics: "proportion of possible transmission events attributable to students in the intervention group:"

$$T^{**}(\mathbf{Z}, \overline{\mathbf{A}}, \overline{\mathbf{Y}}) = \frac{\sum_{k=2}^{\tau} \sum_{i=1}^{n} \sum_{j>i} Z_i E_{ijk}^{**}}{\sum_{k=2}^{\tau} \sum_{i=1}^{n} \sum_{j>i} E_{ijk}^{**}}.$$

	From Infected to Infected	**From Infected**
Contact at $k-1$	$E_{ijk}^{11} = Y_i^{k-1} A_{ij}^{k-1} Y_j^k$	$E_{ijk}^{12} = Y_i^{k-1} A_{ij}^{k-1}$
Contact at k	$E_{ijk}^{21} = Y_i^{k-1} A_{ij}^{k} Y_j^k$	$E_{ijk}^{22} = Y_i^{k-1} A_{ij}^{k}$
Contact at $k-1$ **or** k	$E_{ijk}^{31} = Y_i^{k-1} (A_{ij}^{k-1} \vee A_{ij}^{k}) Y_j^k$	$E_{ijk}^{32} = Y_i^{k-1} (A_{ij}^{k-1} \vee A_{ij}^{k})$
Contact at $k-1$ **and** k	$E_{ijk}^{41} = Y_i^{k-1} (A_{ij}^{k-1} * A_{ij}^{k}) Y_j^k$	$E_{ijk}^{42} = Y_i^{k-1} (A_{ij}^{k-1} * A_{ij}^{k})$

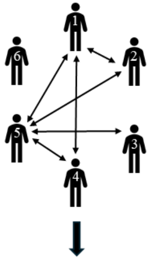
Table: Definitions of a possible transmission event E_{ijk} from student i to student j at time k. Y_i^k is an indicator for student i being infected at week k, A_{ij}^k is an indicator for students i and j being in contact at week k, and $a \vee b$ denotes the maximum of a and b.

Exponential Family Random Graph Models

Goal: model a network ($\mathbf{A}$) given covariates ($\mathbf{X}$)

Exponential Family Random Graph Models

Goal: model a network (**A**) given covariates (**X**)



	1	2	3	4	5	6
1	0	1	0	1	1	0
2	1	0	0	0	1	0
3	0	0	0	0	1	0
4	1	0	0	0	1	0
5	1	1	1	1	0	0
6	0	0	0	0	0	0

Exponential Family Random Graph Models

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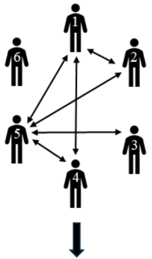
An **ERGM** assumes:

$$\Pr_{\theta}(\mathbf{A} = \mathbf{a} | \mathbf{X} = \mathbf{x}) = \frac{\exp\{\theta \cdot \mathbf{g}(\mathbf{a}, \mathbf{x})\}}{\kappa(\theta, \mathcal{A}, \mathbf{x})}$$



	1	2	3	4	5	6
1	0	1	0	1	1	0
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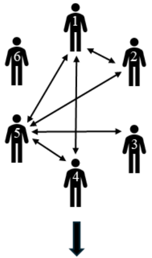
- normalizing constant:
  $\kappa(\theta, \mathcal{A}, \mathbf{x}) = \sum_{\mathbf{a} \in \mathcal{A}} \exp\{\theta \cdot \mathbf{g}(\mathbf{a}, \mathbf{x})\}$



	1	2	3	4	5	6
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2	1	0	0	0	1	0
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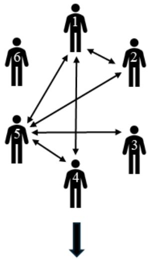
- $\mathcal{A}$: space of possible networks



	1	2	3	4	5	6
1	0	1	0	1	1	0
2	1	0	0	0	1	0
3	0	0	0	0	1	0
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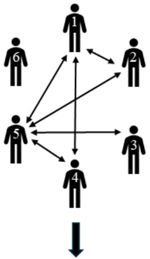
- $\mathcal{A}$: space of possible networks
- θ: model coefficients



	1	2	3	4	5	6
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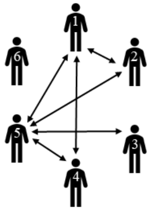
- $\mathcal{A}$: space of possible networks
- θ: model coefficients
- $\mathbf{g}(\mathbf{a}, \mathbf{x})$: sufficient statistics



	1	2	3	4	5	6
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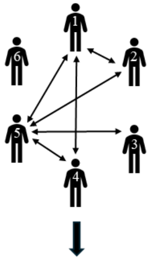
- θ: model coefficients
- $\mathbf{g}(\mathbf{a}, \mathbf{x})$: sufficient statistics
  - number of edges



	1	2	3	4	5	6
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2	1	0	0	0	1	0
3	0	0	0	0	1	0
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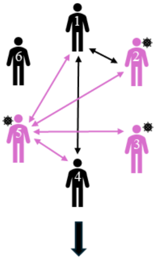
- $\mathcal{A}$: space of possible networks
- θ: model coefficients
- $\mathbf{g}(\mathbf{a}, \mathbf{x})$: sufficient statistics
  - number of edges
  - number of edges touching treated students



	1	2	3	4	5	6
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2	1	0	0	0	1	0
3	0	0	0	0	1	0
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Exponential Family Random Graph Models

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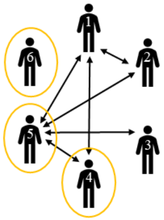
- $\mathcal{A}$: space of possible networks
- θ: model coefficients
- $\mathbf{g}(\mathbf{a}, \mathbf{x})$: sufficient statistics
  - number of edges
  - number of edges touching treated students
  - number of edges touching infected students



	1	2	3	4	5	6
1	0	1	0	1	1	0
2	1	0	0	0	1	0
3	0	0	0	0	1	0
4	1	0	0	0	1	0
5	1	1	1	1	0	0
6	0	0	0	0	0	0

Exponential Family Random Graph Models

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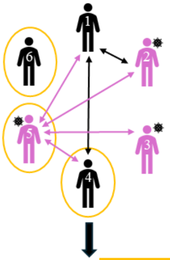
- normalizing constant:
  $\kappa(\theta, \mathcal{A}, \mathbf{x}) = \sum_{\mathbf{a} \in \mathcal{A}} \exp\{\theta \cdot \mathbf{g}(\mathbf{a}, \mathbf{x})\}$
- $\mathcal{A}$: space of possible networks
- θ: model coefficients
- $\mathbf{g}(\mathbf{a}, \mathbf{x})$: sufficient statistics
  - number of edges
  - number of edges touching treated students
  - number of edges touching infected students
  - number of edges touching treated $\times$ infected students



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ERGM Model Formulation

$$\Pr_{\theta}(\mathbf{A} = \mathbf{a} | \mathbf{X} = \mathbf{x}) = \frac{\exp\{\theta \cdot \mathbf{g}(\mathbf{a}, \mathbf{x})\}}{\kappa(\theta, \mathcal{A}, \mathbf{x})},$$

$$\kappa(\theta, \mathcal{A}, \mathbf{x}) = \sum_{\mathbf{a} \in \mathcal{A}} \exp\{\theta \cdot \mathbf{g}(\mathbf{a}, \mathbf{x})\}$$

For example, in the simulation study and eX-FLU application,

$$\mathbf{g}(\mathbf{a}, \mathbf{x}) = \begin{bmatrix} \text{\# edges} \\ \text{\# edges touching a treated node} \\ \text{\# edges touching an infected node} \\ \text{\# edges touching a treated and infected node} \\ \text{\# edges between roommate pairs} \end{bmatrix} = \begin{bmatrix} \sum_{i,j} a_{ij} \\ \sum_{i,j} a_{ij}(z_i + z_j) \\ \sum_{i,j} a_{ij}(y_i + y_j) \\ \sum_{i,j} a_{ij}(z_i y_i + z_j y_j) \\ \sum_{i,j} a_{ij} \mathbb{1}(i, j \text{ roomates}) \end{bmatrix}$$

ERGM Change Statistic Model Formulation

- **Change statistic**: $\delta_{\mathbf{g}}(\mathbf{a}, \mathbf{x})_{ij} = \mathbf{g}(\mathbf{a}_{ij}^{+}, \mathbf{x}) - \mathbf{g}(\mathbf{a}_{ij}^{-}, \mathbf{x})$ is the change in network statistic that would occur if a_{ij} were changed from 0 to 1
  - where $\mathbf{a}_{ij}^{+}$ and $\mathbf{a}_{ij}^{-}$ represent the network $\mathbf{a}$ with dyad a_{ij} set to 1 or 0, respectively
- Then the equivalent ERGM specification is

$$\text{logit}\{\Pr_{\theta}(A_{ij} = 1 | \mathbf{A}_{ij}^{C} = \mathbf{a}_{ij}^{C}, \mathbf{X} = \mathbf{x})\} = \theta^{k} \delta_{\mathbf{g}}(\mathbf{a}, \mathbf{x})_{ij}$$

  - where $\mathbf{A}_{ij}^{C}$ represents all dyads in $\mathbf{A}$ except A_{ij}
- **Interpretation of θ**: the change in conditional log-odds of the network associated with a one-unit increase in the corresponding component of $\mathbf{g}(\mathbf{a}, \mathbf{x})$ resulting from switching a particular dyad A_{ij} from 0 to 1 and leaving the rest of the network fixed at $\mathbf{A}_{ij}^{C}$

Dyadic Independence EGRMs

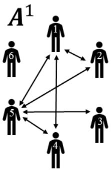
- **Dyadic independence term**: a component g of $\mathbf{g}$ in an ERGM for which the corresponding change statistic $\delta_g(\mathbf{a}, \mathbf{x})_{ij}$ can be calculated for any i, j without knowing $\mathbf{a}$
  - For example, if $g(\mathbf{a}, \mathbf{x}) = \sum_{i,j} a_{ij}(Z_i + Z_j)$ counts the number of edges touching treated nodes, then $\delta_g(\mathbf{a}, \mathbf{x})_{ij} = z_i + z_j$ doesn't depend on $\mathbf{a}$
- **Dyadic independence ERGM**: an ERGM with only dyadic independence terms
  - replace $\delta_g(\mathbf{a}, \mathbf{x})_{ij}$ with $\delta_g(\mathbf{x})_{ij}$ and write the model as

$$\text{logit}\{\Pr\big(A_{ij} = 1 | \mathbf{X} = \mathbf{x}\big)\} = \theta \cdot \delta_g(\mathbf{x})_{ij}$$

- **Interpretation of θ**: the change in log-odds of the network associated with a one-unit increase in the corresponding component of $\mathbf{g}(\mathbf{a}, \mathbf{x})$ resulting from switching a particular dyad A_{ij} from 0 to 1

Separable Temporal Exponential Family Random Graph Models

A **STERGM** assumes that, at each time step $k = 1, \ldots, \tau - 1$:

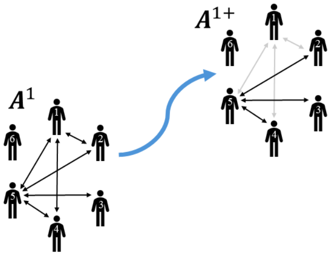


Separable Temporal Exponential Family Random Graph Models

A **STERGM** assumes that, at each time step $k = 1, \ldots, \tau - 1$:

- New edges form according to a **formation** ERGM

$$\Pr_{\theta^+}(\mathbf{A}^{k+} = \mathbf{a}^{k+} | \mathbf{A}^k = \mathbf{a}^k, \mathbf{X} = \mathbf{x}) = \frac{\exp\{\theta^+ \cdot \mathbf{g}^+(\mathbf{a}^{k+}, \mathbf{x})\}}{\kappa\{\theta^+, \mathcal{A}^+(\mathbf{a}^k), \mathbf{x}\}}$$

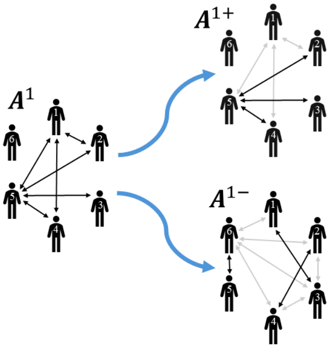


Separable Temporal Exponential Family Random Graph Models

A **STERGM** assumes that, at each time step $k = 1, \dots, \tau - 1$:

- New edges form according to a **formation** ERGM
- Old edges persist according to a **persistence** ERGM

$$\Pr_{\theta^-}(\mathbf{A}^{k-} = \mathbf{a}^{k-} | \mathbf{A}^k = \mathbf{a}^k, \mathbf{X} = \mathbf{x}) = \frac{\exp\{\theta^- \cdot \mathbf{g}^-(\mathbf{a}^{k-}, \mathbf{x})\}}{\kappa\{\theta^-, \mathcal{A}^-(\mathbf{a}^k), \mathbf{x}\}}.$$

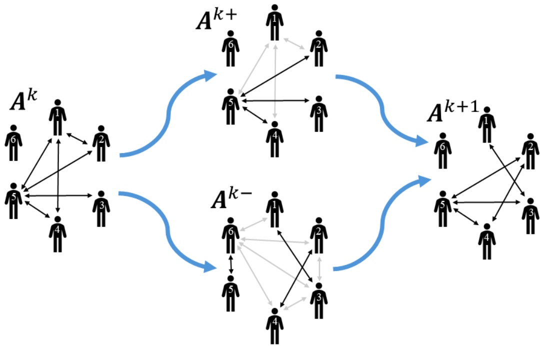


Separable Temporal Exponential Family Random Graph Models

A **STERGM** assumes that, at each time step $k = 1, \ldots, \tau - 1$:

- New edges form according to a **formation** ERGM
- Old edges persist according to a **persistence** ERGM
- The network at time step $k + 1$ is the result of formation and persistence

$$\mathbf{A}^{k+1} = \underbrace{\mathbf{A}^{k}}_{\text{previous network}} \cup \underbrace{(\mathbf{A}^{k+} - \mathbf{A}^{k})}_{\text{new edges formed}} - \underbrace{(\mathbf{A}^{k} - \mathbf{A}^{k-})}_{\text{old edges not persisting}}$$



STERGM Model Formulation

- **Formation model** is an ERGM conditional on only adding edges:

$$\Pr_{\theta^+}(\mathbf{A}^{k+} = \mathbf{a}^{k+} | \mathbf{A}^k = \mathbf{a}^k, \mathbf{X} = \mathbf{x}) = \frac{\exp\{\theta^+ \cdot \mathbf{g}^+(\mathbf{a}^{k+}, \mathbf{x})\}}{\kappa\{\theta^+, \mathcal{A}^+(\mathbf{a}^k), \mathbf{x}\}}$$

  - $\mathcal{A}^+(\mathbf{a})$: space of possible networks that can be formed by adding edges to $\mathbf{a}$

- **Persistence model** is an ERGM conditional on only removing edges:

$$\Pr_{\theta^-}(\mathbf{A}^{k-} = \mathbf{a}^{k-} | \mathbf{A}^k = \mathbf{a}^k, \mathbf{X} = \mathbf{x}) = \frac{\exp\{\theta^- \cdot \mathbf{g}^-(\mathbf{a}^{k-}, \mathbf{x})\}}{\kappa\{\theta^-, \mathcal{A}^-(\mathbf{a}^k), \mathbf{x}\}}$$

  - $\mathcal{A}^-(\mathbf{a})$: space of possible networks that can be formed by removing edges to $\mathbf{a}$

- A **STERGM** assumes the network at time $k+1$ is then the result of applying the changes in $\mathbf{A}^{k+}$ and $\mathbf{A}^{k-}$ to $\mathbf{A}^k$:

$$\mathbf{A}^{k+1} = \underbrace{\mathbf{A}^k}_{\text{previous network}} \cup \underbrace{(\mathbf{A}^{k+} - \mathbf{A}^k)}_{\text{new edges formed}} - \underbrace{(\mathbf{A}^k - \mathbf{A}^{k-})}_{\text{old edges not persisting}}$$

Separability of STERGMs

1. $\mathbf{A}^{k+} \perp\!\!\!\perp \mathbf{A}^{k-} | \mathbf{A}^{k}$, i.e., the formation and persistence processes are conditionally independent give the network at time k

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$$\begin{tikzcd}
& \mathbf{A}^{1+} \arrow[dr] & & \mathbf{A}^{2+} \arrow[dr] & & \mathbf{A}^{3+} \arrow[dr] & \\
\mathbf{A}^1 \arrow[ur] \arrow[rr] \arrow[dr] & & \mathbf{A}^2 \arrow[ur] \arrow[rr] \arrow[dr] & & \mathbf{A}^3 \arrow[ur] \arrow[rr] \arrow[dr] & & \mathbf{A}^4 \\
& \mathbf{A}^{1-} \arrow[ur] & & \mathbf{A}^{2-} \arrow[ur] & & \mathbf{A}^{3-} \arrow[ur] &
\end{tikzcd}$$

Separability of STERGMs

1. $\mathbf{A}^{k+} \perp\!\!\!\perp \mathbf{A}^{k-} | \mathbf{A}^k$, i.e., the formation and persistence processes are conditionally independent give the network at time k
2. the parameter space for $\theta = (\theta^+, \theta^-)$ is the product of the parameter spaces for θ^+ and θ^-

$$
\begin{tikzcd}
 & \mathbf{A}^{1+} \arrow[dr] & & \mathbf{A}^{2+} \arrow[dr] & & \mathbf{A}^{3+} \arrow[dr] & \\
\mathbf{A}^1 \arrow[ur] \arrow[rr] \arrow[dr] & & \mathbf{A}^2 \arrow[ur] \arrow[rr] \arrow[dr] & & \mathbf{A}^3 \arrow[ur] \arrow[rr] \arrow[dr] & & \mathbf{A}^4 \\
 & \mathbf{A}^{1-} \arrow[ur] & & \mathbf{A}^{2-} \arrow[ur] & & \mathbf{A}^{3-} \arrow[ur] &
\end{tikzcd}
$$

Simulation Setup

- $n \in \{24, 48\}$ students were equally divided into two residence halls, each with six clusters of equal size
- Within each residence hall group, the clusters were randomized using a 50:50 allocation to either the intervention group or the control group
- Five pairs of students were randomly selected to be roommates, meaning they had contact with each other each week
- Baseline $(k = 1)$ social contacts were simulated between each pair of students with probability 0.5
- Baseline infection statuses were simulated for each student with probability 0.5
- Social networks were simulated over the remaining $\tau \in \{5, 10\}$ weeks according to a STERGM with both formation and persistence models including edge count, intervention assignment Z, infection status Y, $Z \times Y$ interaction, and an offset to force constant edges between roommates
- Infection statuses were simulated for each student i at each week $k \in \{2, \ldots, \tau\}$ with probability $\Pr\left(Y_i^k = 1 | \overline{\mathbf{A}}^{k-1}, \overline{\mathbf{Y}}^{k-1}\right) = g(\sum_{j=1}^n A_{ij}^{k-1} Y_j^{k-1})$, where $\sum_{j=1}^n A_{ij}^{k-1} Y_j^{k-1}$ is the number of infected contacts at the previous week, and $g : [0, \infty) \to [0, 1]$ is a non-decreasing function

Simulation Setup

Three scenarios:

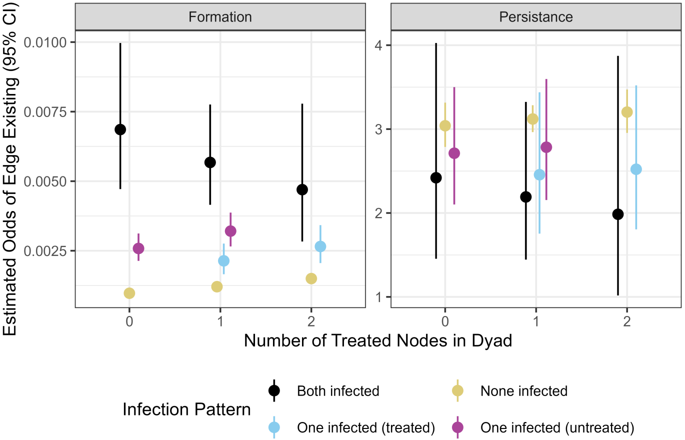
Null Hypothesis	Formation Model Parameters θ^+	Persistence Model Parameters θ^-	Infection Probability Function g
$H_0^\sharp$	$(-0.5, 0, 0, 0)$	$(-0.5, 0, 0, 0)$	$g(s) = 0.5$
$\overline{H}_0^A \cap H_0^Y$	$(-0.2, 0, 0, -1)$	$(-0.2, 0, 0, -1)$	$g(s) = 0.5$
$\overline{H}_0^A \cap \overline{H}_0^Y$	$(-0.2, 0, 0, -1)$	$(-0.2, 0, 0, -1)$	$g(s)$ increasing in s

Table: Data generating process for the simulation study. The null hypothesis refers to the null hypothesis that is true under the data generating process, formation model parameters are $\theta^+ = (\theta^+_{\text{edges}}, \theta^+_Z, \theta^+_Y, \theta^+_{ZY})$, persistence model parameters are $\theta^- = (\theta^-_{\text{edges}}, \theta^-_Z, \theta^-_Y, \theta^-_{ZY})$, and the infection probability function g provides a unit's probability of being infected at week k given their number of infected neighbors at week $k-1$.

Three p-values:

- $\rho_B^\sharp$: testing the sharp null
- ρ_B^Y: testing H_0^Y using known q
- $\widehat{\rho}_B^Y$: testing H_0^Y using estimated q

eX-FLU: STERGM Results



Type I Error Control

- **Proposition 2.1**: Let T_N be a test statistic with CDF F_N under H_0.
  1. Under H_0, $F_N(T_N)$ stochastically dominates a Uniform$(0,1)$ distribution for any N.
  2. If the test statistic T_N has a continuous limiting distribution, then $F_N(T_N) \to^d$ Uniform$(0,1)$.
- **Corollary 2.2**:
  1. Under $H_0^\sharp$, the sharp null p-value $\rho_N^\sharp$ stochastically dominates a Uniform$(0,1)$ distribution for any N.
  2. Under H_0^Y, the oracle p-value ρ_N^Y stochastically dominates a Uniform$(0,1)$ distribution for any N.
  3. If the test statistic T_N has a continuous limiting distribution, then $\rho_N^\sharp \to^d$ Uniform$(0,1)$ under $H_0^\sharp$ and $\rho_N^Y \to^d$ Uniform$(0,1)$ under H_0^Y.

Type I Error Control

- **Proposition 2.3**: Let $q(\mathbf{a}, \mathbf{z}, \theta) \equiv \Pr\{\mathbf{A}(\mathbf{z}) = \mathbf{a}; \theta\}$ denote the PMF of the distribution of stochastic potential networks $\mathbf{A}(\mathbf{z})$ at parameter value θ, let $\widehat{\theta}_N$ denote the estimator of θ, and let $F_N(\cdot; \theta)$ denote the CDF of the test statistic T_N at θ, with limiting CDF $F(\cdot; \theta)$. Let θ_0 denote the true value of θ. Assume the following:

  (A1) $\widehat{\theta}_N \to^p \theta_0$

  (A2) $F(t; \theta_0)$ is continuous in t on $\mathbb{R}$

  (A3) there exists a $\delta_0 > 0$ such that

  $$\sup_{\theta \in B_{\delta_0}(\theta_0)} \sup_{t \in \mathbb{R}} |F_N(t; \theta) - F(t; \theta)| \to 0$$

  (A4) $F(t; \theta)$ is continuous in θ at θ_0 uniformly in t, i.e.,

  $$\lim_{\theta \to \theta_0} \sup_{t \in \mathbb{R}} |F(t; \theta) - F(t; \theta_0)| = 0$$

  Then the plug-in p-value $\widehat{\rho}_N^Y$ converges in distribution to Uniform$(0, 1)$.

Type I Error Control

- **Proposition 2.4**: Let $\rho_N = F_N(T_N)$ for test statistic T_N and CDF F_N (not necessarily the true CDF of T_N). Let $T_N^* = h_N(T_N)$ for a sequence of deterministic, strictly increasing functions h_N. Define $F_N^*(t) = F_N\{h_N^{-1}(t)\}$, the (not necessarily true) CDF of the transformed test statistic, and let $\rho_N^* = F_N^*(T_N^*)$. Then $\rho_N^* = \rho_N$.
- **Corollary 2.5**: Let h_N be a sequence of deterministic, strictly increasing functions.
  1. If the hypotheses of Proposition 2.1 are met for a test statistic T_N, then the results also hold for $T_N^* = h_N(T_N)$.
  2. If the hypotheses of Proposition 2.3 are met for $T_N, F_N(\cdot;\theta)$, then the results also hold for $T_N^* = h_N(T_N), F_N^*(\cdot;\theta) = F_N\{h_N^{-1}(\cdot);\theta\}$.

Supplement to Project 3 : Causal Inference from Cluster Randomized Trials with Differential Nonresponse

Brian Richardson, Bonnie Shook-Sa, Michael Hudgens

Causal Estimand

- **individual-level potential outcomes**:

$$\mathbf{Y}_j(a) = [Y_{j1}(a), \ldots, Y_{jN_j}(a)]$$

Causal Estimand

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- **cluster-level mean potential outcome**:

$$\overline{Y}_j(a) = \frac{1}{N_j} \sum_{i=1}^{N_j} Y_{ji}(a)$$

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- Two ways to aggregate over the population:

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  1. Equal weight to each cluster:

$$\eta(a) = \frac{1}{m} \sum_{j=1}^{m} \mathrm{E}\{\overline{Y}_j(a)\},$$

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- Two ways to aggregate over the population:
  1. Equal weight to each cluster:

$$\eta(a) = \frac{1}{m} \sum_{j=1}^{m} \mathrm{E}\{\overline{Y}_j(a)\},$$

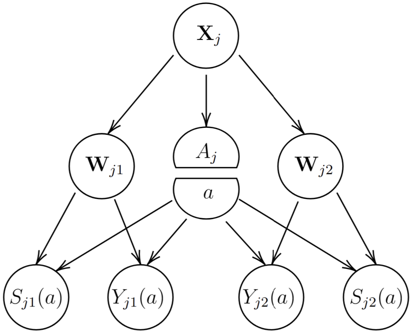
  2. Equal weight to each individual:

$$\eta'(a) = \frac{\sum_{j=1}^{m} N_j \mathrm{E}\{\overline{Y}_j(a)\}}{\sum_{j=1}^{m} N_j}.$$

Working Assumptions for Identifiability

For all clusters j, j', individuals i and treatment a:

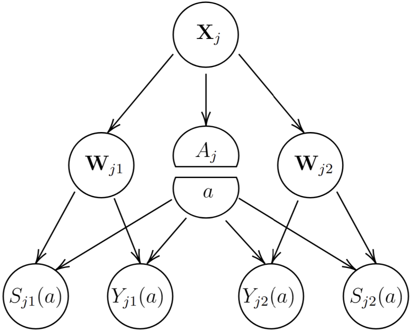
- causal consistency: $Y_{ji} = Y_{ji}(a)$ and $S_{ji} = S_{ji}(a)$ when $A_j = a$
- positivity of treatment assignment:
  $\Pr(A_j = a | \mathbf{X}_j = \mathbf{x}) > 0$ for all $\mathbf{x}$ with $\Pr(\mathbf{X}_j = \mathbf{x}) > 0$
- positivity of response: $\Pr(S_{ji} = 1 | A_j = a, \mathbf{X}_j = \mathbf{x}, \mathbf{W}_{ji} = \mathbf{w}) > 0$
  for all $\mathbf{x}, \mathbf{w}$ with
  $\Pr(\mathbf{X}_j = \mathbf{x}, \mathbf{W}_{ji} = \mathbf{w}) > 0$
- independent clusters:
  $$\left[A_j, \mathbf{X}_j, \{R_{ji}, S_{ji}(a)\}_{i=1}^{N_j}, \mathbf{Y}_j(a), Q_{ji}\right] \perp\!\!\!\perp \left[A_{j'}, \mathbf{X}_{j'}, \{R_{j'i}, S_{j'i}(a)\}_{i=1}^{N_{j'}}, \mathbf{Y}_{j'}(a), Q_{j'i}\right]$$



Working Assumptions for Identifiability

For all clusters j, j', individuals i and treatment a:

- conditional exchangeability: $Y_{ji}(a) \perp\!\!\!\perp A_j | \mathbf{X}_j, \mathbf{W}_{j,i}$
- conditional independence of potential outcome and responses: $Y_{ji}(a) \perp\!\!\!\perp S_{j,i}(a) | A_j, \mathbf{X}_j, \mathbf{W}_{j,i}$
- cluster-level randomization: $A_j \perp\!\!\!\perp (\mathbf{W}_{ji}, \ldots, \mathbf{W}_{jN_j}) | \mathbf{X}_j$
- independent random sampling: $R_{ji} \perp\!\!\!\perp \left[A_j, \mathbf{X}_j, \{S_{ji}(a)\}_{i=1}^{N_j}, \mathbf{Y}_j(a), Q_{ji}\right]$
- independent random sampling of auxiliary data: $Q_{ji} \perp\!\!\!\perp, \left[A_j, \mathbf{X}_j, \{R_{ji}, S_{ji}(a)\}_{i=1}^{N_j}, \mathbf{Y}_j(a)\right]$



Estimators: G-Formula

Define the conditional mean outcome among trial responders with cluster-level covariates $\mathbf{x}$ and individual-level covariates $\mathbf{w}$, and under treatment assignment a by

$$\mu_a(\mathbf{x}, \mathbf{w}) = \mathrm{E}\left(Y_{ji} | A_j = a, R_{ji} = 1, S_{ji} = 1, \mathbf{X}_j = \mathbf{x}, \mathbf{W}_{ji} = \mathbf{w}\right),$$

The g-formula estimator averages $\mu_a(\mathbf{x}, \mathbf{w})$ over the empirical distribution of $(\mathbf{X}_j, \mathbf{W}_{ji})$ in the auxiliary data:

$$\widehat{\eta}^{GF}(a) = \frac{1}{m} \sum_{j=1}^{m} \frac{1}{\widetilde{n}_j} \sum_{i=1}^{N_j} Q_{ji} \mu_a(\mathbf{X}_j, \mathbf{W}_{ji}).$$

Estimators: Inverse Probability Weighting

Define the conditional probability of responding and having treatment assignment to a given covariates.

$$\pi_a(\mathbf{x}, \mathbf{w}) = \Pr(S_{ji} = 1, A_j = a | \mathbf{X}_j = \mathbf{x}, \mathbf{W}_{ji} = \mathbf{w})$$

The IPW estimator weights the observed outcomes of responders using the inverse of $\pi_a(\mathbf{x}, \mathbf{w})$ to create a pseudopopulation that is free of both bias from nonresponse and confounding induced by the conditional randomization design:

$$\widehat{\eta}^{IPW}(a) = \frac{1}{m} \sum_{j=1}^{m} \frac{1}{n_j} \sum_{i=1}^{N_j} \frac{\mathbb{1}(A_j = a) R_{ji} S_{ji} Y_{ji}}{\pi_a(\mathbf{X}_j, \mathbf{W}_{ji})}.$$