Causal inference for infectious disease intervention in inter-connected clusters

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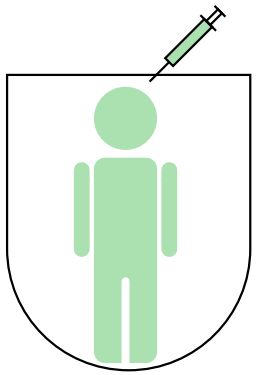
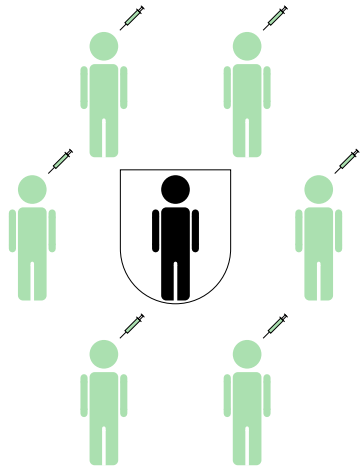
Infectious disease and vaccination

Distinct mechanisms of infectious disease interventions/vaccinations,

- Direct protection for the treated individuals:
  - direct effect, vaccine efficacy, susceptibility effect...
- Indirect protection for the surrounding individuals:
  - indirect effect, herd immunity, contagion effect, infectiousness effect...
- Vaccines for Polio, Influenza, HIV/AIDS, Malaria and etc.



Direct protection



Indirect protection

Why infectious disease is difficult to study?

Research on transmission of infectious disease has some unique features and challenges.

- The infection outcome of one individual also depends on others' treatments, conditional on other individuals being infected.
  – Interference
- The outcome of interest (infection) is transmissible, so outcomes are not independent from each other. – Contagion
- The infection times of others compose an important factor for the infection outcome – Exposure to infection
  Earlier exposure to infectious individual (higher "exposure to infection") increases the risk of infection.

One infection outcome depends on (i) its **own treatment**, (ii) **treatments of others**, and (iii) **infection times of others**.

Bias due to differential "exposure to infection"

Direct comparisons of treated and untreated individuals may not be valid due to differential "exposure to infection" [1,2,3].

$$E[Y_i|X_i = 1] - E[Y_i|X_i = 0]$$

- For example, if vaccinated individuals get infected later in general, then later infected and vaccinated subjects face higher exposure to infection, comparing to earlier infected and unvaccinated individuals. $\rightarrow$ not a fair comparison !

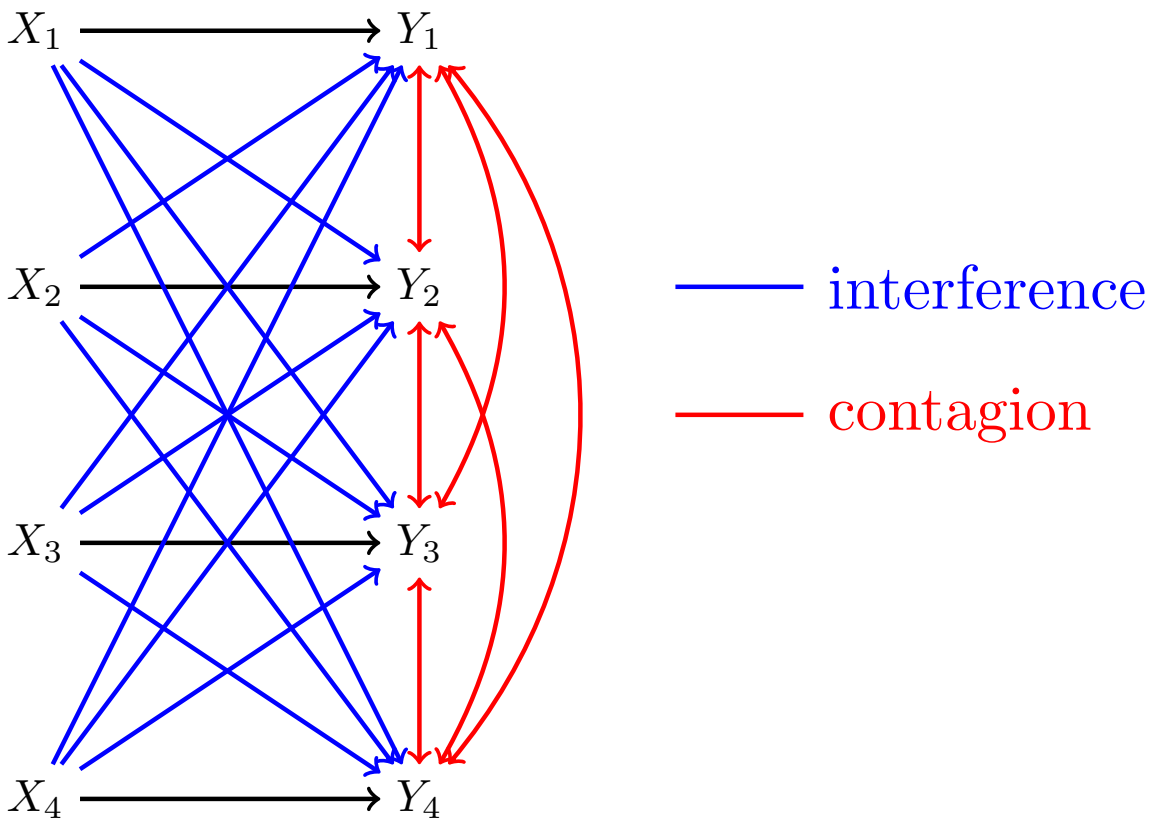
Can randomization solve the problem?

- No. Differential "exposure to infection" due to others' infection happens after randomization.

[1] Longini et al. Statistical inference for infectious diseases: risk-specific household and community transmission parameters. American Journal of Epidemiology, 128(4):845–859, 1988.
[2] Halloran et al. Direct and indirect effects in vaccine efficacy and effectiveness. American Journal of Epidemiology, 133(4):323–331, 1991.
[3] Halloran et al. Exposure efficacy and change in contact rates in evaluating prophylactic HIV vaccines in the field. Statistics in Medicine, 13(4):357–377, 1994.

Challenges for causal identification

Consider a interconnected four individuals with treatment (X_1, X_2, X_3, X_4) and infection outcome (Y_1, Y_2, Y_3, Y_4).



- The graph is not an acyclic directed graph (DAG).

Propose new methodology to evaluate interventions effects for contagious outcomes

We will provide new methods that

- Do not depend on certain study design or randomization strategy
- Apply to various transmission dynamics, cluster size and observational time
- Incorporate individual- and cluster-level covariates
- Yield biologically meaningful causal estimands for direct and indirect protection provided by interventions
- Allow flexible statistical inferential framework, ranging from parametric, semi-parametric to non-parametric estimation

Notation

Consider a cluster of n individuals, $i = 1, \ldots, n$, denote

- Treatment assignment: $\mathbf{X} = (X_1, \ldots, X_n)$
- Infection time: $\mathbf{T} = (T_1, \ldots, T_n)$
- Infection outcome: $\mathbf{Y}(t) = (Y_1(t), \ldots, Y_n(t))$,
  where $Y_i(t) = \mathbb{1}\{T_i < t\}$

For a focal subject i, denote

- Others' treatments: $\mathbf{X}_{(i)} = (X_1, \ldots, X_{i-1}, X_{i+1}, \ldots, X_n)$
- Others' infection times: $\mathbf{T}_{(i)} = (T_1, \ldots, T_{i-1}, T_{i+1}, \ldots, T_n)$
- Others' infection history: $\boldsymbol{\mathcal{H}}_{(i)}(t) = \{Y_j(s) : 0 \leq s < t, j \neq i\}$,
  or equivalently, $\boldsymbol{\mathcal{H}}_{(i)}(t) = \{T_j;\, T_j < t, j \neq i\}$

  Note: $\boldsymbol{\mathcal{H}}_{(i)} = \{Y_j(s) : s \geq 0, j \neq i\}$, or equivalently, $\boldsymbol{\mathcal{H}}_{(i)} = \mathbf{T}_{(i)}$

Notation

Define $T_i(\mathbf{X} = \mathbf{x}, \mathcal{H}_{(i)} = \mathbf{h}_{(i)})$ and $Y_i(t; \mathbf{X} = \mathbf{x}, \mathcal{H}_{(i)} = \mathbf{h}_{(i)})$ as the counterfactual infection time and outcome of i under a joint treatment $\mathbf{x}$ and a deterministic infection history $\mathbf{h}_{(i)}$ of other individuals, respectively.

Goal 1

Identify $T_i(\mathbf{x}, \mathbf{h}_{(i)})$ or $Y_i(t; \mathbf{x}, \mathbf{h}_{(i)})$ under joint intervention $(\mathbf{x}, \mathbf{h}_{(i)})$.

- (i) own treatment: $X_i = x_i$
- (ii) others' treatments: $\mathbf{X}_{(i)} = \mathbf{x}_{(i)}$
- (iii) others' infection times: $\mathbf{h}_{(i)}$

Main Result: Exposure-controlled potential outcome

Goal 1

Identify $T_i(\mathbf{x}, \mathbf{h}_{(i)})$ or $Y_i(t; \mathbf{x}, \mathbf{h}_{(i)})$ under joint intervention $(\mathbf{x}, \mathbf{h}_{(i)})$.

Theorem: Identification of exposure-controlled potential outcomes

Under conventional assumptions in causal inference,

$$\mathbb{E}\left[Y_i(t; \mathbf{h}_{(i)}, \mathbf{x}) \,\middle|\, \mathbf{L} = \mathbf{l}\right] = \sum_{j=0}^{n-1} \left[F_{I_i^j}(\min\{t, t_{(i)}^{j+1}\} - t_{(i)}^{j} \,|\, \mathbf{x}, \mathbf{h}_{(i)}, \mathbf{l}) \prod_{k=0}^{j-1} \left(1 - F_{I_i^k}(t_{(i)}^{k+1} - t_{(i)}^{k} \,|\, \mathbf{x}, \mathbf{h}_{(i)}, \mathbf{l})\right) \right]$$

where $F_{I_i^j}(s \,|\, \mathbf{x}, \mathbf{h}_{(i)}, \mathbf{l})$ –distribution of $I_i^k(\mathbf{x}, \mathbf{h}_{(i)})$ – is identifiable by standard results from competing risks.

Main Result: Exposure-marginalized potential outcomes

- $\mathcal{H}^*_{(i)}(\mathbf{x})$: the random history of infection times in individuals other than i under $\mathbf{X} = \mathbf{x}$, in an otherwise identical group of $n-1$ individuals in which i is absent, or cannot transmit infection.

Goal 2

Identify $Y_i\left(t; \mathbf{x}, \mathcal{H}^*_{(i)}(\mathbf{x}_{(i)})\right)$ under joint intervention $\mathbf{x}$ and $\mathcal{H}^*_{(i)}(\mathbf{x}_{(i)})$.

Theorem: Identification of exposure-marginalized potential outcomes

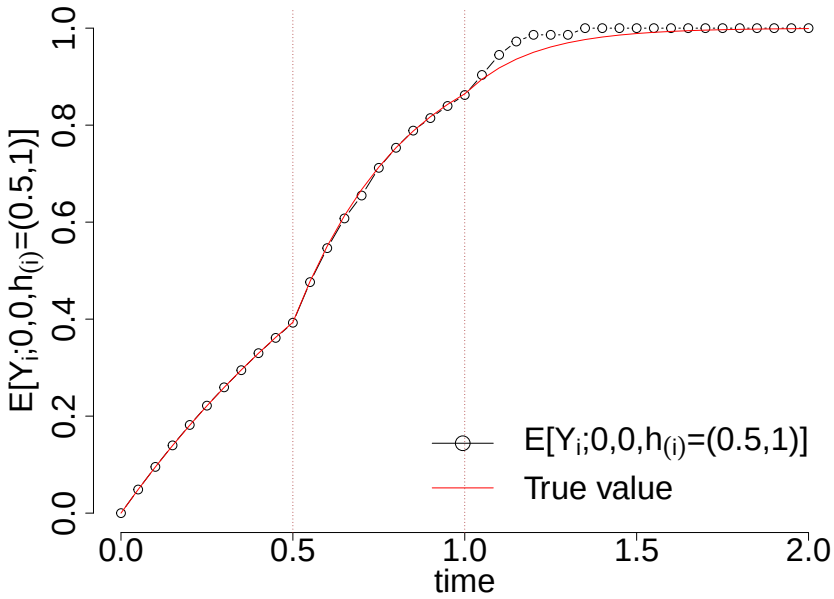
Under conventional assumptions in causal inference,

$$\mathbb{E}\left[Y_i\left(t; x_i, \mathbf{x}_{(i)}, \mathcal{H}^*_{(i)}(\mathbf{x}'_{(i)})\right)|\mathbf{L} = \mathbf{l}\right] = \int \mathbb{E}[Y_i(t; x_i, \mathbf{x}_{(i)}, \mathbf{h}_{(i)})|\mathbf{L} = \mathbf{l}]\, \mathrm{d}G^*_{(i)}(\mathbf{h}_{(i)}|\mathbf{x}'_{(i)}, \mathbf{l}_{(i)})$$

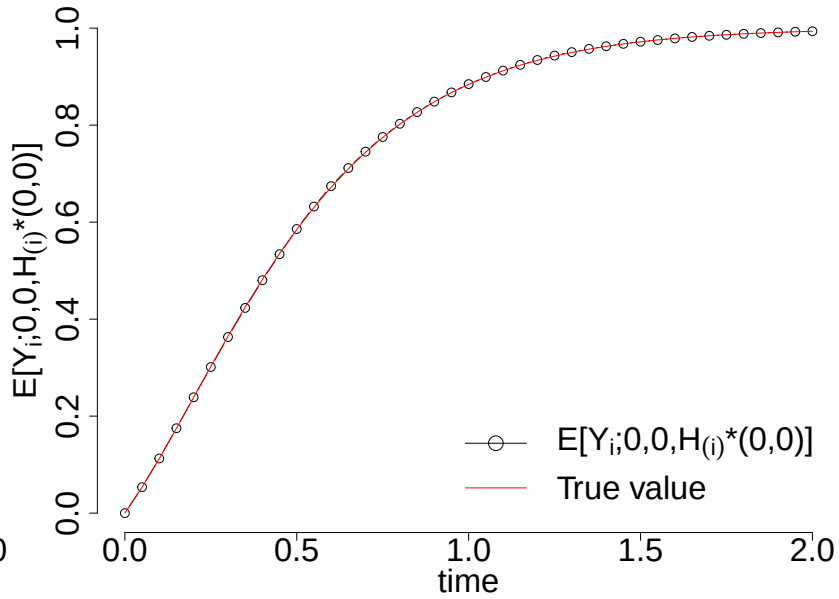
where $\mathbf{x}'_{(i)}$ may (not) equal to $\mathbf{x}_{(i)}$, and $G^*_{(i)}(\mathbf{h}_{(i)}|\mathbf{x}_{(i)}, \mathbf{l}_{(i)})$ – the distribution of $\mathcal{H}^*_{(i)}(\mathbf{x}_{(i)})$ – is identified by standard results from competing risks.

Simulation: causal identification for potential outcomes

We simulate N=100,000 clusters of **three** individuals with constant exogenous and internal infection hazards, without covariates.



Controlled-exposure outcome



Marginalized-exposure outcome

Causal estimands: Exposure-marginalized causal estimands

Exposure-marginalized (natural) causal estimands

- Susceptibility effect

$$SE_i(t, \mathbf{x}_{(i)}) = \mathbb{E}\big[Y_i\big(t; 1, \mathbf{x}_{(i)}, \mathcal{H}^*_{(i)}(\mathbf{x}_{(i)})\big) - Y_i\big(t; 0, \mathbf{x}_{(i)}, \mathcal{H}^*_{(i)}(\mathbf{x}_{(i)})\big)\big]$$

- Infectiousness effect

$$IE_i(t, x_i, \mathbf{x}_{(i)}) = \mathbb{E}\big[Y_i\big(t; x_i, 1, \mathcal{H}_{(i)}(\mathbf{x}_{(i)})\big) - Y_i\big(t; x_i, 0, \mathcal{H}_{(i)}(\mathbf{x}_{(i)})\big)\big]$$

- Contagion effect

$$CE_i(t, x_i, \mathbf{x}_{(i)}, \mathbf{x}'_{(i)}) = \mathbb{E}\big[Y_i\big(t; x_i, \mathbf{x}_{(i)}, \mathcal{H}^*_{(i)}(\mathbf{x}_{(i)})\big) - Y_i\big(t; x_i, \mathbf{x}_{(i)}, \mathcal{H}^*_{(i)}(\mathbf{x}'_{(i)})\big)\big]$$

- Susceptibility effect $\rightarrow$ shows if the vaccine protects treated individual
- Infectiousness effect $\rightarrow$ shows if the vaccine decreases transmission ability
- Contagion effect $\rightarrow$ shows if the disease is contagious

Traditional estimands on the cluster level

- Direct effect:

$$DE(t) = \mathbb{E}[Y_i(t)|X_i = 1] - \mathbb{E}[Y_i(t)|X_i = 0]$$

- Indirect effect:

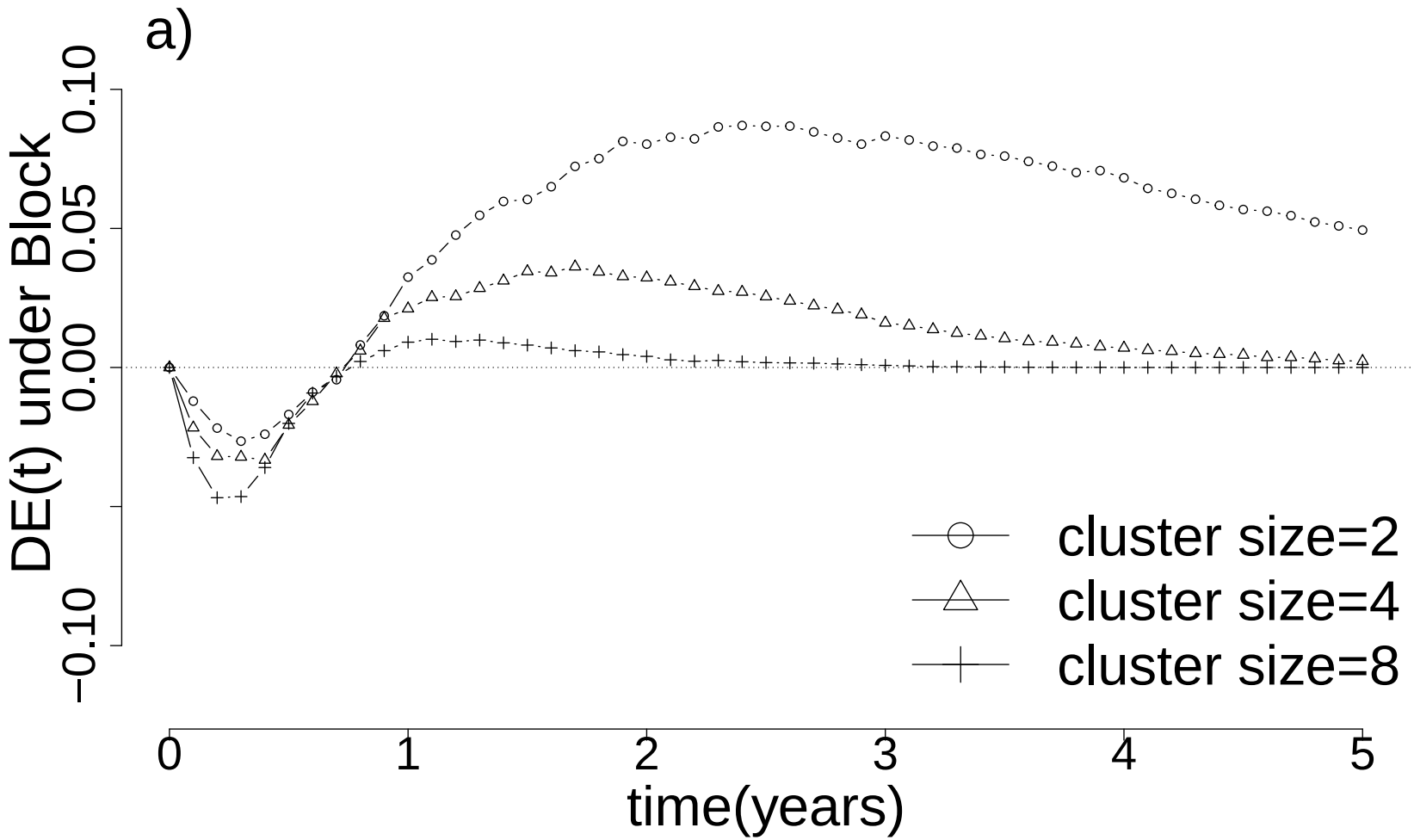
$$IDE(t) = \sum_{|\mathbf{x}_{(i)}|=\frac{n}{2}} \mathbb{E}[Y_i(t)|X_i = 0, \mathbf{X}_{(i)} = \mathbf{x}_{(i)}]p(\mathbf{x}_{(i)}) - \sum_{|\mathbf{x}_{(i)}|=0} \mathbb{E}[Y_i(t)|X_i = 0, \mathbf{X}_{(i)} = \mathbf{x}_{(i)}]p(\mathbf{x}_{(i)})$$

Simulation: Estimations of causal estimands

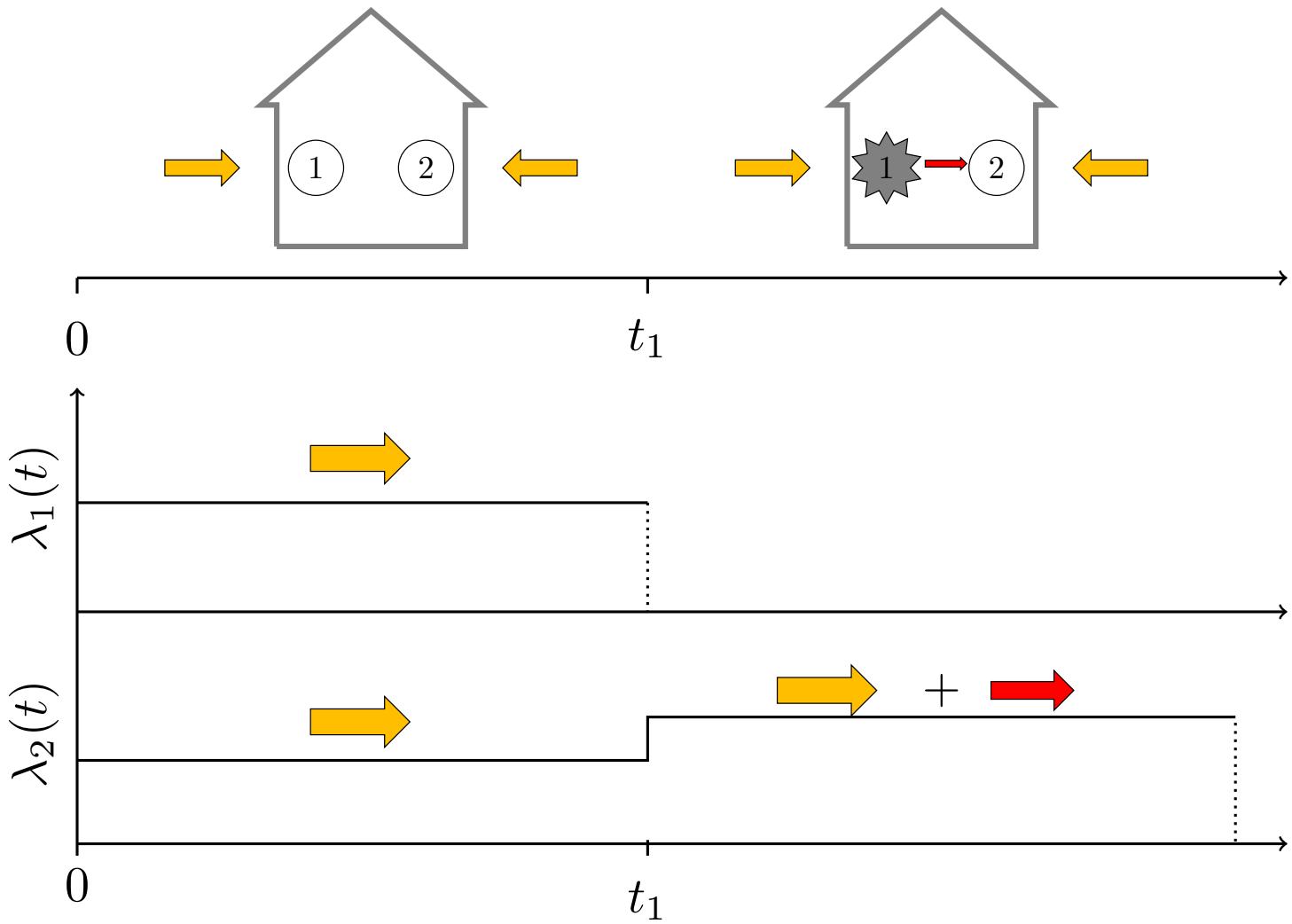
Cluster	Treatment	Probability estimands				
		$\hat{CE}(t,0,\mathbf{0},\mathbf{1})$	$\hat{SE}(t,\mathbf{0})$	$\hat{IE}(t,0,\mathbf{0})$	$DE(t)$	$IDE(t)$
Constant external and internal hazards						
2	Obs.	0.005	-0.015	-0.036	-0.013	-0.036
	Bernoulli	0.004	-0.015	-0.036	-0.014	-0.038
	Block	-	-	-	0.025	-
	Cluster	-	-	-	-0.048	-
4	Obs.	0.026	-0.014	-0.084	-0.012	-0.073
	Bernoulli	0.025	-0.013	-0.082	-0.012	-0.063
	Block	-	-	-	0.016	-
	Cluster	-	-	-	-0.099	-
8	Obs.	0.068	-0.013	-0.131	-0.010	-0.088
	Bernoulli	0.069	-0.014	-0.133	-0.010	-0.096
	Block	-	-	-	0.010	-
	Cluster	-	-	-	-0.154	-

Simulation under $e^{\beta_1} = 0.9$, $e^{\beta_2} = 0.1$, $\alpha(t) = 0.3$, $\gamma(t) = 3$ and $e^{\theta_1} = e^{\theta_2} = 0.9$. Clusters of 2, 4, and 8 are observed at 0.4, 0.3 and 0.2 year.

Biased $DE(t)$ over time under different cluster sizes



How do epidemiologists understand infectious disease transmission?



Cox-type hazard model for pairwise infection times

Assume previously infected individuals, along with a exogenous source of infection, impose **independent** and **competing** risks of disease transmission to the remaining uninfected individuals. For all i and all infected individual j, $j \neq i$, we consider a Cox-type hazard model for:

- **External** source of infection:

$$\lambda_{0i}(t \mid x_i, \mathbf{I}_i) = \alpha(t) \exp[\beta_1 x_i + \theta_1^T \mathbf{I}_i]$$

- **Internal** source of infection from infectious j to yet-uninfected i:

$$\lambda_{ji}(t \mid x_i, \mathbf{I}_i) = \gamma(t - t_j) \exp[\beta_1 x_i + \beta_2 x_j + \theta_1^T \mathbf{I}_i + \theta_2^T \mathbf{I}_j]$$

$\beta_1 < 0$ means a beneficial treatment effect on treated individuals.
$\beta_2 < 0$ means a decreased transmission risk due to vaccination.
$\gamma(t) > 0$ means an infectious disease.

Simulation: Estimations of causal estimands

Cluster	Treatment	Hazard estimands		Probability estimands				
		$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{CE}$	$\hat{SE}$	$\hat{IE}$	$DE(t)$	$IDE(t)$
Constant external and internal hazards								
2	Obs.	-0.119	-2.271	0.005	-0.015	-0.036	-0.013	-0.036
	Bernoulli	-0.115	-2.334	0.004	-0.015	-0.036	-0.014	-0.038
	Block	-0.102	-2.364	0.004	-0.013	-0.036	0.025	-
	Cluster	-0.103	-2.288	0.004	-0.013	-0.035	-0.048	-
4	Obs.	-0.105	-2.368	0.026	-0.014	-0.084	-0.012	-0.073
	Bernoulli	-0.105	-2.286	0.025	-0.013	-0.082	-0.012	-0.063
	Block	-0.116	-2.278	0.026	-0.015	-0.082	0.016	-
	Cluster.	-0.107	-2.323	0.025	-0.014	-0.083	-0.099	-
8	Obs.	-0.100	-2.287	0.068	-0.013	-0.131	-0.010	-0.088
	Bernoulli	-0.106	-2.331	0.069	-0.014	-0.133	-0.010	-0.096
	Block	-0.111	-2.311	0.069	-0.014	-0.132	0.010	-
	Cluster	-0.120	-2.299	0.070	-0.016	-0.132	-0.154	-

Simulation under $e^{\beta_1} = 0.9$, $e^{\beta_2} = 0.1$, $\alpha(t) = 0.3$, $\gamma(t) = 3$ and $e^{\theta_1} = e^{\theta_2} = 0.9$.
Clusters of 2, 4, and 8 are observed at 0.4, 0.3 and 0.2 year.

Summary

- We articulate the causal structure between individuals' treatments and outcomes in infectious disease, and illustrate the identification strategy for the potential outcomes under contagion, in the example of inter-connected clusters.
- A class of fundamental (controlled- and marginalized-) causal estimands for the susceptibility, infectiousness and contagion effect of vaccines are proposed, and comprehensively compared to popular estimands in contemporary epidemiology.
- We provide the identification of causal estimands non-parametrically, and further apply a generalized Cox-type transmission hazard model to facilitate the inference of causal estimands.
- We promote hazard ratio as alternative causal estimands for the susceptibility and infectiousness effect, and compared them to existing estimands for vaccine efficacy.

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