Causal inference for infectious disease intervention in inter-connected clusters

Xiaoxuan Cai

joint work with Eben Kenah, Forrest W. Crawford

Department of Biostatistics, Yale School of Public Health

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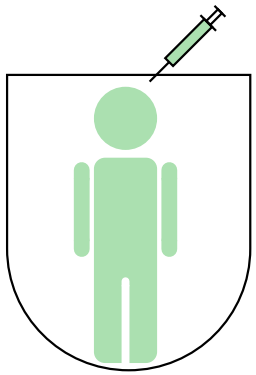
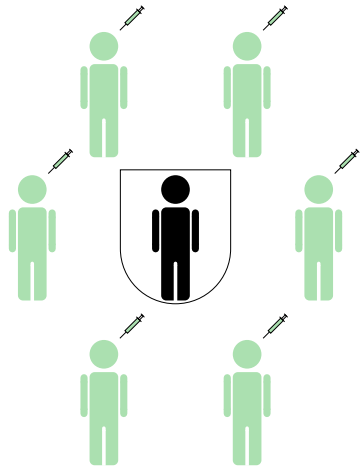
Infectious disease and vaccination

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?

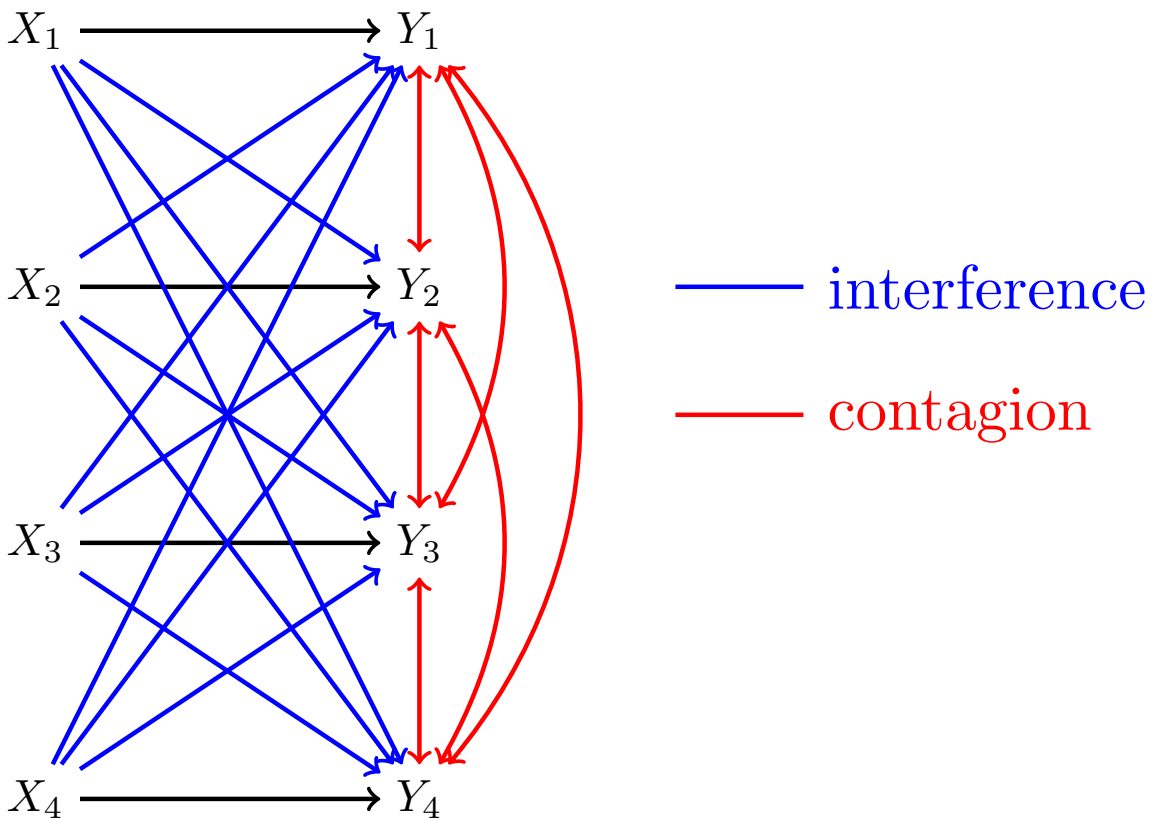
Research on transmission of infectious disease has some unique features and challenges.

- 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
- Individuals' interaction along the transmission process reveals essential information about transmission mechanism.

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

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).

How to solve the problem?

Can randomization solve the problem?

- Even under randomization, direct comparisons of treated and untreated individuals may not be valid due to differential "exposure to infection".
- For example, if vaccinated individuals get infected later in general, then later infected, vaccinated subjects face higher exposure to infection, comparing to unvaccinated, earlier infected individuals.
  $\rightarrow$ not a fair comparison !

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, $i = 1, \ldots, n$

- Treatment assignment: $\mathrm{X} = (X_1, \ldots, X_n)$
- Infection time: $\mathrm{T} = (T_1, \ldots, T_n)$
- Infection outcome: $\mathrm{Y}(t) = (Y_1(t), \ldots, Y_n(t))$
  ,where $Y_i(t) = \mathbb{1}\{T_i < t\}$
- Others' treatments: $\mathrm{X}_{(i)} = (X_1, \ldots, X_{i-1}, X_{i+1}, \ldots, X_n)$
- Others' infection times: $\mathrm{T}_{(i)} = (T_1, \ldots, T_{i-1}, T_{i+1}, \ldots, T_n)$
- Others' infection history: $\boldsymbol{\mathcal{H}}_{(i)} = \{Y_j(s) : s \geq 0, j \neq i\}$
  , or $\boldsymbol{\mathcal{H}}_{(i)} = \mathrm{T}_{(i)}$

Notation

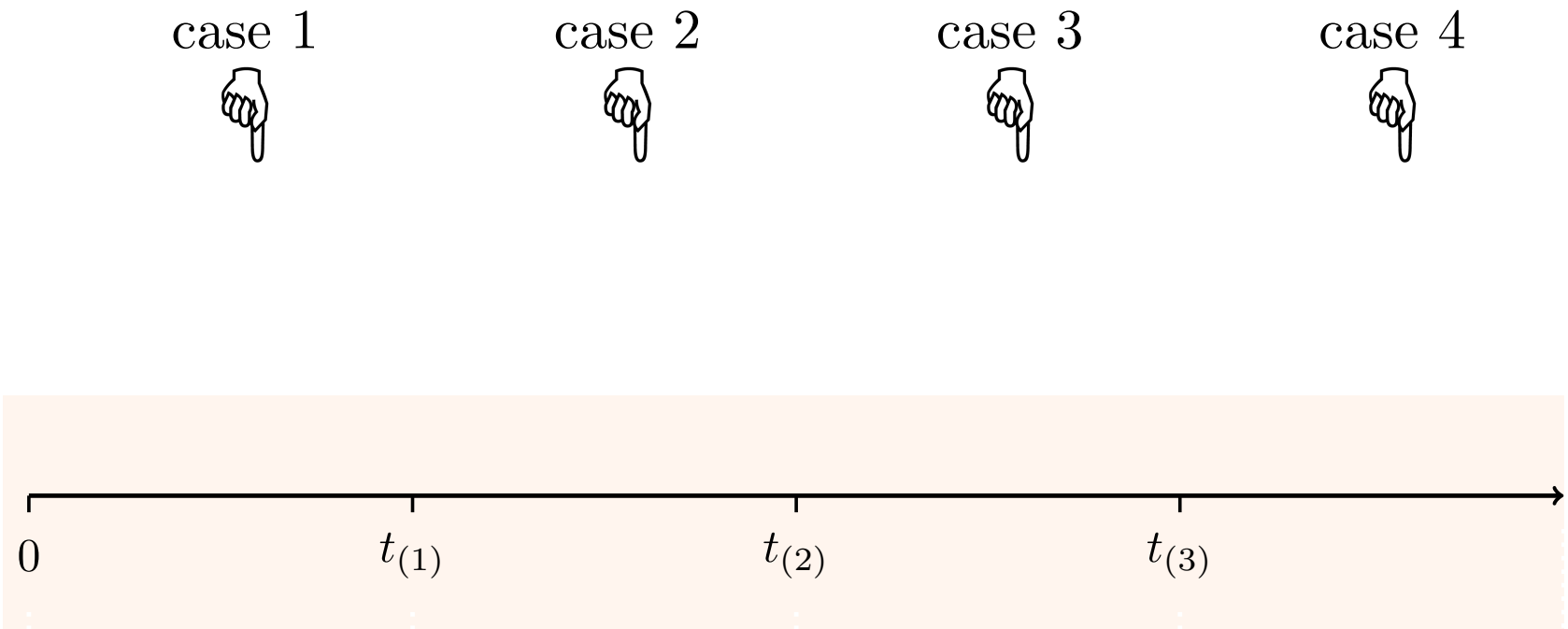
Define $T_i(\mathrm{X} = \mathrm{x}, \boldsymbol{\mathcal{H}}_{(i)} = \mathrm{h}_{(i)})$ and $Y_i(t; \mathrm{X} = \mathrm{x}, \boldsymbol{\mathcal{H}}_{(i)} = \mathrm{h}_{(i)})$ as the counterfactual infection time and outcome of i under a joint treatment x and a deterministic infection history $\mathrm{h}_{(i)}$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

Goal 1

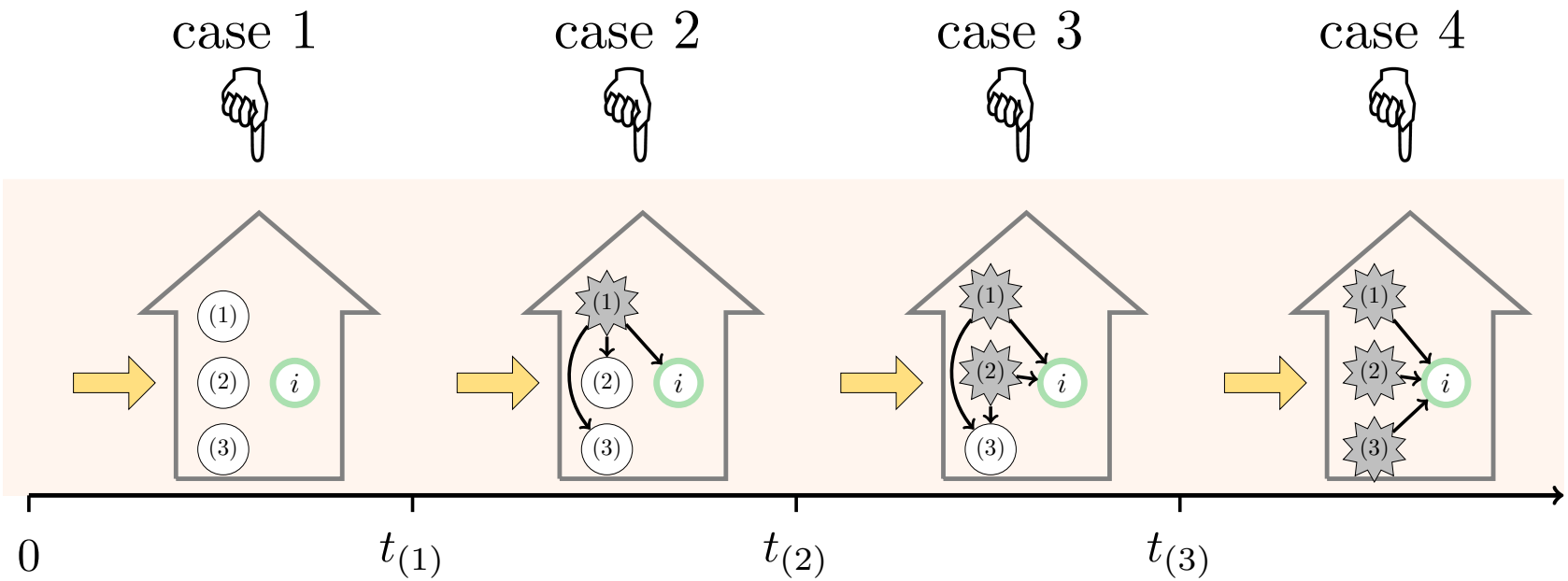
Identify $T_i(\mathrm{h}_{(i)}, \mathrm{x})$ or $Y_i(t; \mathrm{h}_{(i)}, \mathrm{x})$ under joint intervention $(\mathrm{h}_{(i)}, \mathrm{x})$.

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

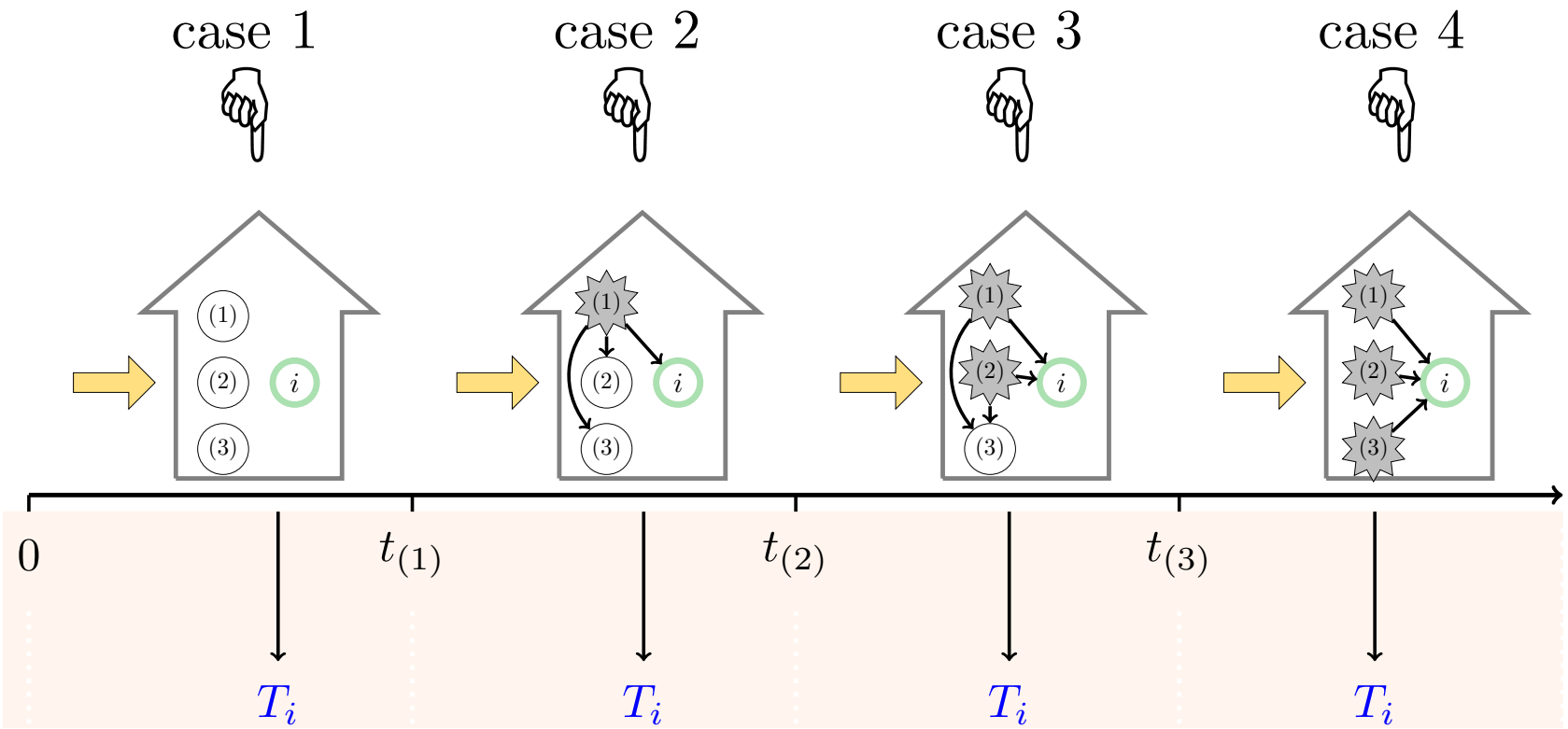
Clusters of 4 individuals



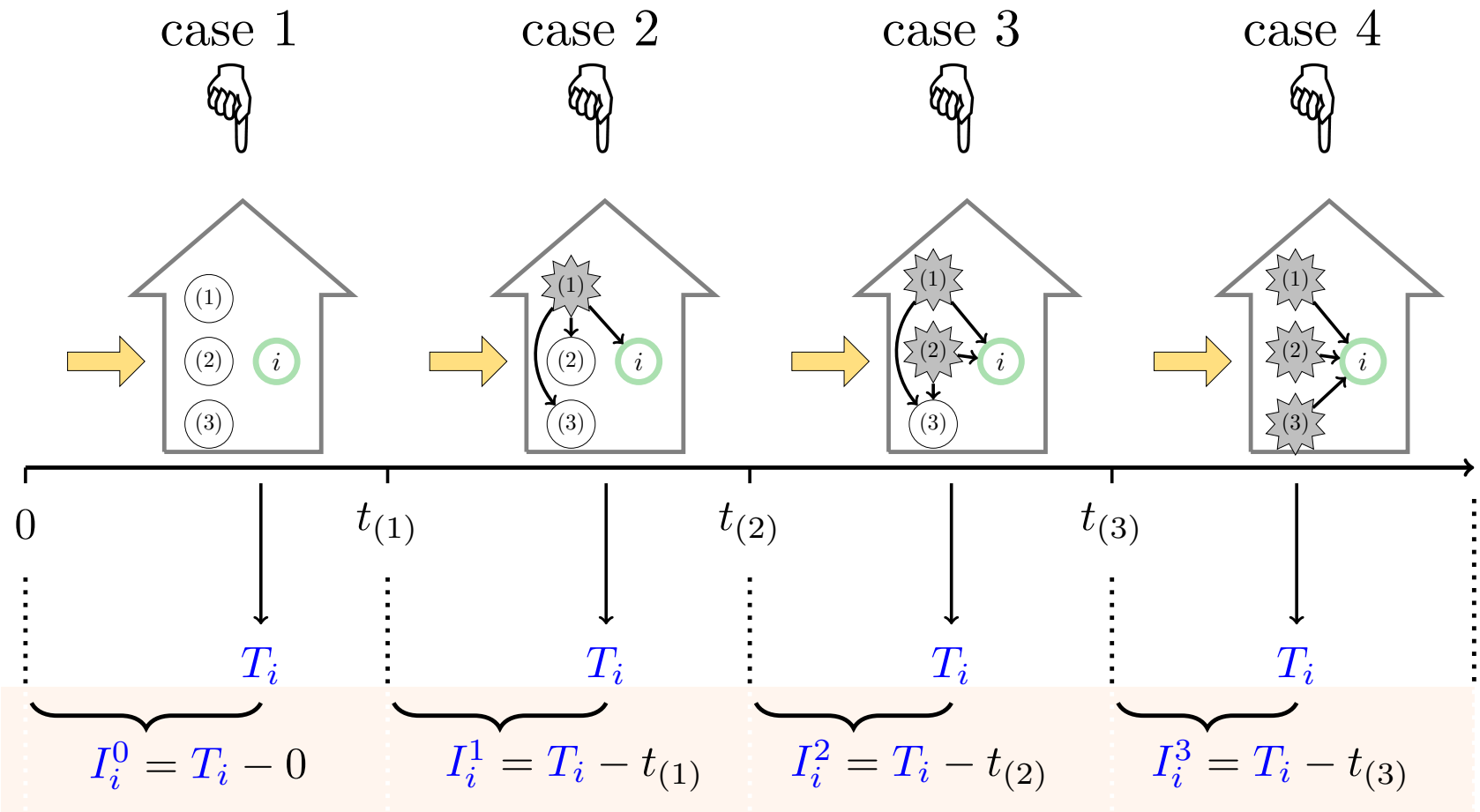
Clusters of 4 individuals



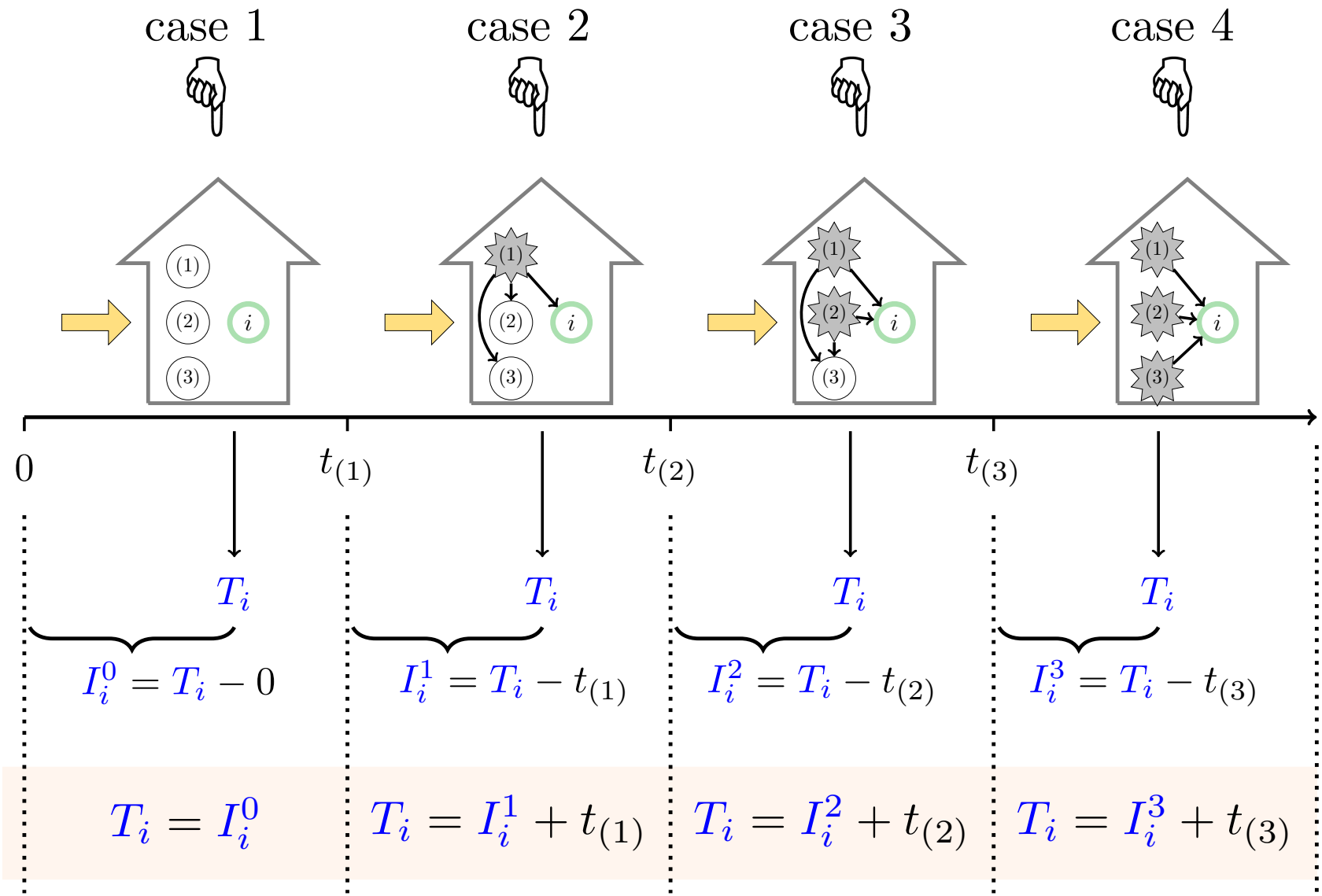
Clusters of 4 individuals



Clusters of 4 individuals



Clusters of 4 individuals



Decomposition of $T_i(\mathrm{x}, \mathrm{h}_{(i)})$

For a deterministic $\mathrm{h}_{(i)}$ with $\mathrm{t}_{(i)}$, reorder infection times as $\mathrm{t}_{(i)} = (t^1_{(i)}, t^2_{(i)}, \ldots, t^{n-1}_{(i)})$, then we rewrite

$$
\begin{aligned}
&T_i(\mathrm{x}, \mathrm{h}_{(i)}) \\
&= \begin{cases}
I_i^0(\mathrm{x}, \mathrm{h}_{(i)}) & \text{if } I_i^0(\mathrm{x}, \mathrm{h}_{(i)}) < t^1_{(i)} \\
t^1_{(i)} + I_i^1(\mathrm{x}, \mathrm{h}_{(i)}) & \text{if } I_i^0(\mathrm{x}, \mathrm{h}_{(i)}) \geq t^1_{(i)}, I_i^1(\mathrm{x}, \mathrm{h}_{(i)}) < t^2_{(i)} - t^1_{(i)} \\
\vdots & \vdots \\
t^{n-1}_{(i)} + I_i^{n-1}(\mathrm{x}, \mathrm{h}_{(i)}) & \text{if } I_i^0(\mathrm{x}, \mathrm{h}_{(i)}) \geq t^1_{(i)}, \ldots, I_i^{n-2}(\mathrm{x}, \mathrm{h}_{(i)}) \geq t^{n-1}_{(i)} - t^{n-2}_{(i)}
\end{cases}
\end{aligned}
$$

where $I_i^k(\mathrm{x}, \mathrm{h}_{(i)})$ is the potential additional time to infection after the k^{th} infection at $t^k_{(i)}$.

Main Result: Exposure-controlled potential outcome

Theorem: Identification of exposure-controlled potential outcomes

Under conventional assumptions in causal inference,

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

where $F_{I_i^j}(s \,|\, \mathsf{x}, \mathsf{h}_{(i)}, \mathsf{l})$ is the distribution of the latent waiting times to infection $I_i^k(\mathsf{x}, \mathsf{h}_{(i)})$ and is identified by

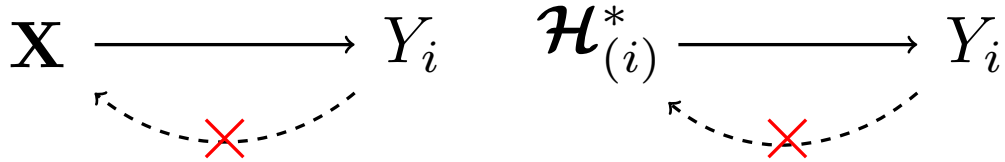
$$F_{I_i^j}(s|\mathsf{x}, \mathsf{h}_{(i)}, \mathsf{l}) = 1 - \exp\left[- \int_{t_{(i)}^j}^{t_{(i)}^j + s} \frac{f_i^j(u|\mathsf{x}, \mathsf{h}_{(i)}, \mathsf{l})}{S_i^j(u|\mathsf{x}, \mathsf{h}_{(i)}, \mathsf{l})} du \right] \text{ for } j = 0, \ldots, n-1$$

where $f_i^j(u|\mathsf{x}, \mathsf{h}_{(i)}, \mathsf{l})$ and $S_i^j(u|\mathsf{x}, \mathsf{h}_{(i)}, \mathsf{l})$ are identifiable by standard results from competing risks.

The natural distribution of the deterministic $h_{(i)}$

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

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



Define $Y_i(t; x, \mathcal{H}^*_{(i)}(x_{(i)}))$ as the counterfactual infection outcome i under a joint treatment x and the natural distribution of $h_{(i)}$ under $x_{(i)}$.

Goal 2

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

Main Result: Exposure-marginalized (Natural) potential outcomes

Theorem: Identification of exposure-marginalized potential outcomes

Under conventional assumptions in causal inference,

$$\mathbb{E}\left[Y_i\left(t; x_i, \mathsf{x}_{(i)}, \boldsymbol{\mathcal{H}}^*_{(i)}(\mathsf{x}_{(i)})\right)|\mathsf{L}=\mathsf{l}\right] = \int \mathbb{E}[Y_i(t; x_i, \mathsf{x}_{(i)}, \mathsf{h}_{(i)})|\mathsf{L}=\mathsf{l}]\,\mathrm{d}G^*_{(i)}(\mathsf{h}_{(i)}|\mathsf{x}_{(i)}, \mathsf{l}_{(i)})$$

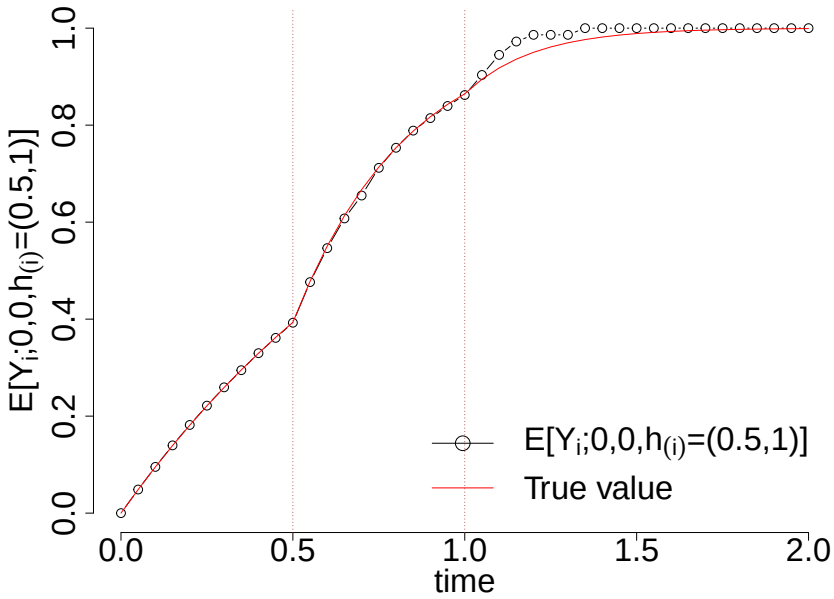
where $G^*_{(i)}(\mathsf{h}_{(i)}|\mathsf{x}_{(i)}, \mathsf{l}_{(i)})$ is the distribution of the potential infection history $\boldsymbol{\mathcal{H}}^*_{(i)}(\mathsf{x}_{(i)})$ given $\mathsf{L}_{(i)} = \mathsf{l}_{(i)}$ and can be identified by

$$\mathrm{d}G^*_{(i)}(\mathsf{h}_{(i)}|\mathsf{x}_{(i)}, \mathsf{l}_{(i)}) = \prod_{j=1}^{n-1}\left[f_{I^{j-1}_{\varphi^j_i}}\left(t^j_{(i)} - t^{j-1}_{(i)}|\mathsf{x}, \mathsf{h}^i_{(\varphi^j_i)}, \mathsf{l}\right)\prod_{k=j+1}^{n-1} S_{I^{j-1}_{\varphi^k_i}}\left(t^j_{(i)} - t^{j-1}_{(i)}|\mathsf{x}, \mathsf{h}^j_{(\varphi^k_i)}, \mathsf{l}\right)\right]$$

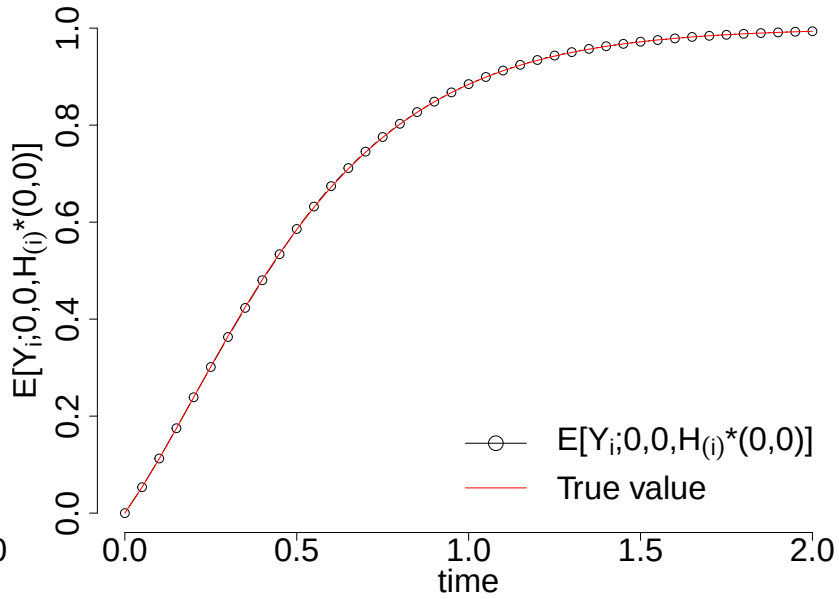
where $f^j_i(u|\mathsf{x}, \mathsf{h}_{(i)}, \mathsf{l})$ and $S^j_i(u|\mathsf{x}, \mathsf{h}_{(i)}, \mathsf{l})$ are identifiable by standard results from competing risks.

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-controlled causal estimands

Exposure-controlled causal estimands

- Susceptibility effect

$$SE_i(t, \mathrm{x}_{(i)}, \mathrm{h}_{(i)}) = \mathbb{E}[Y_i(t; x_i = 1, \mathrm{x}_{(i)}, \mathrm{h}_{(i)}) - Y_i(t; x_i = 0, \mathrm{x}_{(i)}, \mathrm{h}_{(i)})]$$

- Infectiousness effect

$$IE_i(t, x_i, \mathrm{h}_{(i)}) = \mathbb{E}[Y_i(t; x_i, \mathrm{x}_{(i)} = 1, \mathrm{h}_{(i)}) - Y_i(t; x_i, \mathrm{x}_{(i)} = 0, \mathrm{h}_{(i)})]$$

- Contagion effect

$$CE_i(t, \mathrm{x}, \mathrm{h}_{(i)}, \mathrm{h}'_{(i)}) = \mathbb{E}[Y_i(t; \mathrm{x}, \mathrm{h}_{(i)}) - Y_i(t; \mathrm{x}, \mathrm{h}'_{(i)})]$$

- 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

Causal estimands: Exposure-marginalized causal estimands

Exposure-marginalized (natural) causal estimands

- Susceptibility effect

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

- Infectiousness effect

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

- Contagion effect

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

Other commonly used estimators:

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

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

Simulation: Estimations of causal estimands

Cluster	Treatment	Probability estimands				
		$\hat{CE}(t,0,0,1)$	$\hat{SE}(t,0)$	$\hat{IE}(t,0,0)$	$DE(t)$	$IDE(t)$
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	0.004	-0.013	-0.036	0.025	-
	Cluster	0.004	-0.013	-0.035	-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	0.026	-0.015	-0.082	0.016	-
	Cluster	0.025	-0.014	-0.083	-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	0.069	-0.014	-0.132	0.010	-
	Cluster	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.

Cox-type hazard model for pairwise infection times

Assume previously infected individuals, along with a exogenous source of infection, impose **indepdendent** 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 the pairwise infection times:

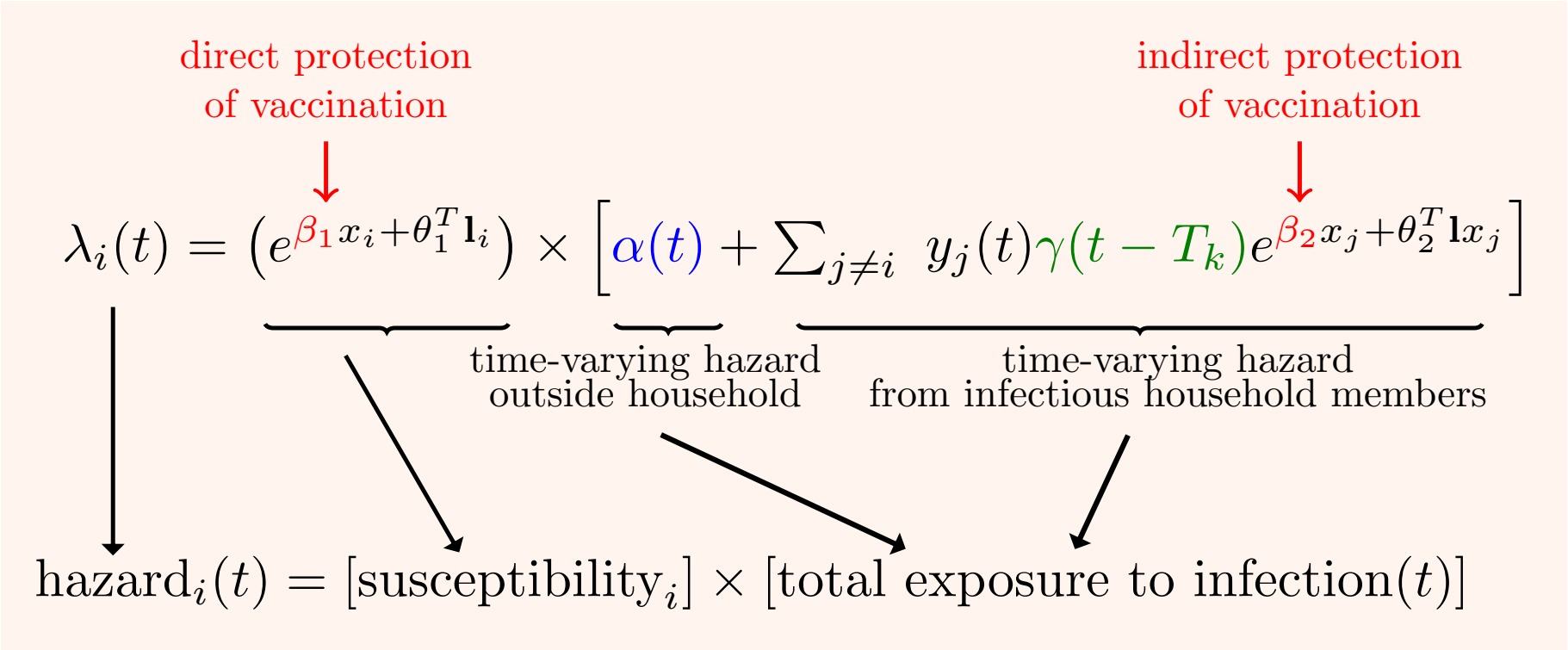
- **External** source of infection:

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

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

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

Stochastic model for disease transmission



- $\alpha(t)$ is exogenous hazard of infection, $\gamma(t)$ is endogenous hazard of transmission between individuals
- β_1 is for susceptibility effect, β_2 is for infectiousness effect
- θ_1 and θ_2 are covariate effects of susceptibility and infectiousness

New vaccine estimands based on hazards

Controlled hazard ratio vaccine effects

- Susceptibility hazard ratio:

$$HSE^C(t, \mathrm{x}_{(i)}, \mathrm{h}_{(i)}, \mathrm{l}) = \frac{\lambda_i(t \mid 1, \mathrm{x}_{(i)}, \mathrm{h}_{(i)}, \mathrm{l})}{\lambda_i(t \mid 0, \mathrm{x}_{(i)}, \mathrm{h}_{(i)}, \mathrm{l})} = e^{\beta_1}$$

- Infectiousness hazard ratio:

$$HIE^C(t, h_j, h_j', \mathrm{x}_{(j)}, \mathrm{h}_{(i,j)}, \mathrm{l}) = \frac{\lambda_i(t|1,\mathrm{x}_{(j)},h_j',\mathrm{h}_{(i,j)},\mathrm{l}) - \lambda_i(t|1,\mathrm{x}_{(j)},h_j,\mathrm{h}_{(i,j)},\mathrm{l})}{\lambda_i(t|0,\mathrm{x}_{(j)},h_j',\mathrm{h}_{(i,j)},\mathrm{l}) - \lambda_i(t|0,\mathrm{x}_{(j)},h_j,\mathrm{h}_{(i,j)},\mathrm{l})} = e^{\beta_2}$$

  where $y_j(t) = 1$ as specified in h_j', and $y_j(t) = 0$ as specified in h_j.

- Contagion cumulative hazard ratio:

$$HCE^C(t; h_j'', h_j', \mathrm{h}_{(i,j)}, \mathrm{l}) = \frac{\int_0^t \left[\lambda_i(u;0,h_j'(t),\mathrm{h}_{(i,j)},\mathrm{l}) - \lambda_i(u;0,h_j(t),\mathrm{h}_{(i,j)},\mathrm{l})\right] du}{\int_0^t \left[\lambda_i(u;0,h_j''(t),\mathrm{h}_{(i,j)},\mathrm{l}) - \lambda_i(u;0,h_j(t),\mathrm{h}_{(i,j)},\mathrm{l})\right] du} = \frac{\int_{t_j'}^t \gamma(u) du}{\int_{t_j''}^t \gamma(u) du}$$

  where $y_j(t) = 1$ as specified in h_j', and $y_j(t) = 0$ as specified in h_j.

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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xiaoxuan.cai@yale.edu
https://xiaoxuan-cai.github.io/