Evaluating the Promise of a Hypothetical HIV Curative Treatment using Organic Indirect Effects with Mediator Values Below an Assay Limit

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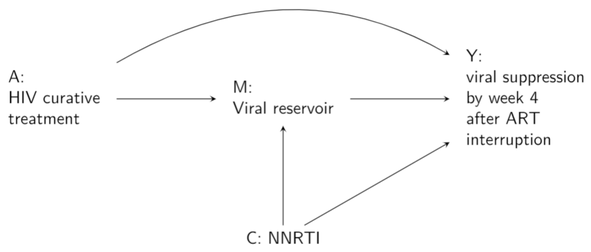
Research Question



- Methodological question: How do we estimate the indirect effect of a treatment A on an outcome Y through a mediator M when M has an assay limit?

Background

HIV Motivation

- Antiretroviral Therapy (ART)
  - Current standard of care but not a cure
  - Once initiated must be continued
  - Targets actively reproducing HIV infected cells
- Testing new curative drugs requires ART interruption
- Curing HIV is thought to require targeting the viral reservoir which has an assay limit

Causal Mediation[3]

Intervention I on a mediator M, is organic if:

1. $M_{0,I=1} \mid C = c \;\sim\; M_1 \mid C = c.$
2. $Y_{0,I=1} \mid M_{0,I=1} = m, C = c \;\sim\; Y_0 \mid M_0 = m, C = c,$

where C is a collection of pre-treatment M-Y common causes
Organic indirect effect: $E[Y_{0,I=1}] - E[Y_0]$.
Mediation formula:

$$E[Y_{0,I=1}] = \int_{m,c} E[Y \mid M = m, C = c, A = 0] f_{M|C=c,A=1}(m) f_C(c) dm dc.$$

*If observed data is $(C_i, A_i = 0, M_i, Y_i)$ for $i = 1, ..., N$ and the effect of A on M is known or hypothesized then the indirect effect can be estimated as a measure of treatment promise.
Example: If $M \mid C = c, A = 1 \sim M - \xi \mid C = c, A = 0$ then an estimate for the indirect effect is:

$$\hat{E}[Y_{0,I=1}] - \hat{E}[Y_0] = \frac{1}{N}\sum_{i=1}^{N} \hat{p}_i(m_i - \xi, c_i) - \frac{1}{N}\sum_{i=1}^{N} Y_i,$$

where $\hat{p}_i(m_i, c_i) = \hat{\mathbb{P}}(Y_i = 1 \mid C_i, A_i = 0, M_i)$ is estimated from a specified model for a binary outcome

Methods

Assumptions for $(C_i, A_i = 0, M_i, Y_i, \delta_i)$ $i = 1, ..., N$:

- Binary pre-treatment mediator outcome common cause C_i
- Continuous mediator $\tilde{M}_i$, with $\tilde{M}_i = \alpha_0 + \alpha_1 C_i + \epsilon_M$ where $\epsilon_M \sim N(0, \sigma^2_M)$
  - Assume: $\tilde{M}_i \mid C = c, A = 1 \sim \tilde{M}_i - \xi \mid C = c, A = 0$
  - $M_i = \begin{cases} \tilde{M}_i, & \text{if } \delta_i = 1 \\ \text{below assay limit}, & \text{if } \delta_i = 0 \end{cases}$
- Binary outcome Y_i, where

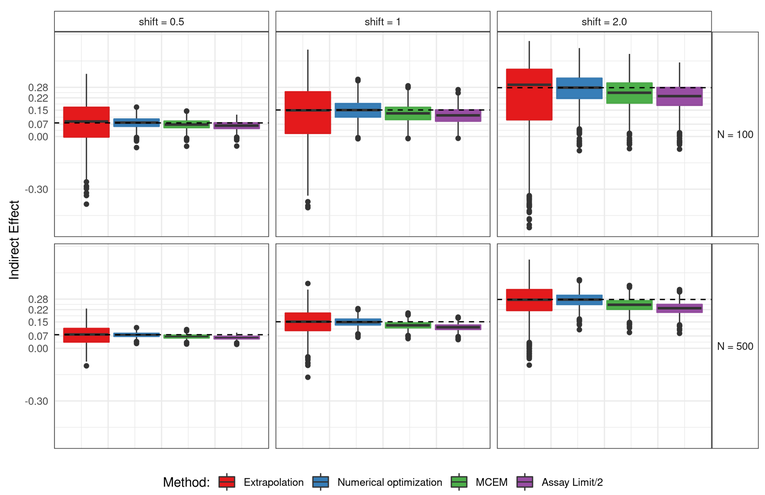
$$logit\Big(P(Y \mid \tilde{M} = m, A = 0, C = c)\Big) = \beta_0 + \beta_1 \tilde{M}_i + \beta_2 C_i.$$

Estimation of the indirect effect with an assay limit requires fitting a mediator and outcome model. Below are methods for estimation of the model parameters.

Method	Description
Extrapolation	Fit mediator model with iterative least squares, fit outcome model on subjects above the assay limit extrapolate values below assay limit to outcome model
Numerical Optimization [1]	Numerical integration and optimization of observed joint mediator-outcome log likelihood
Monte Carlo EM [4]	EM estimation of parameters of complete joint mediator-outcome log likelihood with Monte Carlo approximated E-step with grid sampling
Assay Limit / 2	Impute values below assay limit with assay limit / 2

Simulations

- Data generated to mimic HIV application
- Simulated N = 100 or N = 500 and treatment causing a mediator distribution shift of $\xi = 0.5, 1.0, 1.5, 2.0$



HIV Application

- Pooled analysis of AIDS Clinical Trial Group (ACTG) ART interruption studies (N = 124) [2]
- Y: viral suppression by week 4 after ART interruption
- M: log(CA-RNA) with assay limit 1.96
- C: NNRTI based (yes versus no)
- A: Hypothetical treatment with mediator shifts: 0.50, 1.00, 2.00

shift	method	indirect effect (95% CI)
0.50	Extrapolation	0.029 (-0.182, 0.213)
	Bumerical optimization	0.078 (0.026, 0.126)
	MCEM	0.094 (0.026, 0.158)
	AL / 2	0.064 (0.024, 0.101)
1.00	Extrapolation	0.087 (-0.231, 0.326)
	Numerical optimization	0.151 (0.05, 0.239)
	MCEM	0.181 (0.055, 0.291)
	AL / 2	0.126 (0.043, 0.197)
2.00	Extrapolation	0.195 (-0.296, 0.445)
	Numerical optimization	0.278 (0.102, 0.397)
	MCEM	0.321 (0.12, 0.445)
	AL / 2	0.237 (0.085, 0.345)

Conclusions

- The numerical optimization method performs best with respect to bias and variance
- The MCEM method is heavily effected by the sampling technique
- Require a large shift in viral reservoir for even a modest improvement in probability of viral suppression at week 4

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