Discussion of Lok and Bosch (2020)

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Contributions

1. Reinterpretation of the mediation formula based on the *organic indirect and direct effects* (Lok 2016)
   - avoids cross-world counterfactuals
   - use of stochastic intervention on mediator

2. In linear models, the organic indirect and direct effects under the control condition equals the product method of Baron and Kenny
   - the assumption of no treatment-mediator interaction is not required
   - different from the organic indirect and direct effects under the treatment condition

3. Application to HIV-treatments

Natural Indirect and Direct Effects

- Natural indirect effects

$$\zeta(a) \;=\; \mathbb{E}\{Y_i(a, M_i(1)) - Y_i(a, M_i(0))\} \quad \text{for } a = 0, 1$$

- Natural direct effects

$$\xi(a) \;=\; \mathbb{E}\{Y_i(1, M_i(a)) - Y_i(0, M_i(a))\} \quad \text{for } a = 0, 1$$

- We must infer cross-world counterfactual $\mathbb{E}\{Y_i(a, M_i(a'))\}$ for $a \neq a'$
- Even in RCT, we need the cross-world independence assumption:

$$Y_i(a', m) \perp\!\!\!\perp M_i(a) \mid A_i = a, C_i \quad \text{for any } a, a' \text{ and } C_i$$

1. randomization of mediator does not satisfy this
2. no post-treatment confounder allowed

Organic Indirect and Direct Effects

- Organic indirect effect:

$$\zeta^*(1) \;=\; \mathbb{E}\{Y_i(1, M_i(1))\} - \sum_m \mathbb{E}\{Y_i(1, m)\} \cdot \Pr(M_i(0) = m)$$

- Organic direct effect:

$$\xi^*(0) \;=\; \sum_m \mathbb{E}\{Y_i(1, m)\} \cdot \Pr(M_i(0) = m) - \mathbb{E}\{Y_i(0, M_i(0))\}$$

- They do not require cross-world counterfactuals and assumptions
- Contrast this with the natural effects counterpart:

$$\mathbb{E}\{Y_i(1, M_i(0))\} \;=\; \sum_m \mathbb{E}\{Y_i(1, m) \mid M_i(0) = m\} \cdot \Pr(M_i(0) = m)$$

- Cross-world independence implies:

$$\mathbb{E}\{Y_i(1, m) \mid M_i(0) = m\} \;=\; \mathbb{E}\{Y_i(1, m)\}$$

Relation between Organic and Natural Effects

Organic indirect and direct effects generalize natural indirect and direct effects: provided that $M_{1,I=1} = M_0$ exists, the usual cross-worlds assumption implies that the intervention I that sets the mediator to M_0, $M_{1,I=1} = M_0$, is organic! (page 5)

- Questions:
  1. Natural effects become organic effects under cross-world independence $\rightsquigarrow$ organic effects are special cases of natural effects?
  2. What does it mean to say $M_{1,I=1} = M_0$ exists?
     - For natural effects, the intervention is about individual values whereas for organic effects, it is about their distribution
     - This seems only possible in the limiting case where the mediator is a deterministic function of A and C $\rightsquigarrow$ violation of positivity assumption

New Organic Indirect and Direct Effects

- Organic indirect effect:

$$\zeta^*(0) \;=\; \sum_m \mathbb{E}\{Y_i(0,m)\} \cdot \Pr(M_i(1)=m) - \mathbb{E}\{Y_i(0,M_i(0))\}$$

- Organic direct effect:

$$\xi^*(0) \;=\; \mathbb{E}\{Y_i(1,M_i(1))\} - \sum_m \mathbb{E}\{Y_i(0,m)\} \cdot \Pr(M_i(1)=m)$$

With the new definition, the product method works for linear models regardless of whether the outcome model has treatment-mediator interaction. (page 7)

- This is consistent with the standard result for the natural effects
- Product method for binary mediator is also applicable to natural effects

Concluding Remarks

- Organic indirect and direct effects:
  - avoid cross-world counterfactuals
  - yet the same mediation formula and all the standard results apply
  - different interpretation and same methods
  - appropriateness depends on applications

- Future research:
  - general stochastic intervention on mediators
  - potentially useful for high-dimensional mediators