Assessing in/direct effects: from SEMs to causal mediation analysis

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Recap – motivating example

[Brader et al., 2008]

What Triggers Public Opposition to Immigration? Anxiety, Group Cues, and Immigration Threat

Ted Brader University of Michigan
Nicholas A. Valentino The University of Texas at Austin
Elizabeth Suhay University of Michigan

We examine whether and how elite discourse shapes mass opinion and action on immigration policy. One popular but untested suspicion is that reactions to news about the costs of immigration depend upon who the immigrants are. *We confirm this suspicion in a nationally representative experiment: news about the costs of immigration boosts white opposition far more when Latino immigrants, rather than European immigrants, are featured. We find these group cues influence opinion and political action by triggering emotions—in particular, anxiety—not simply by changing beliefs about the severity of the immigration problem. A second experiment replicates these findings but also confirms their sensitivity to the stereotypic consistency of group cues and their context. While these results echo recent insights about the power of anxiety, they also suggest the public is susceptible to error and manipulation when group cues trigger anxiety independently of the actual threat posed by the group.*

American Journal of Political Science, Vol. 52, No. 4, October 2008, Pp. 959–978

Recap – motivating example

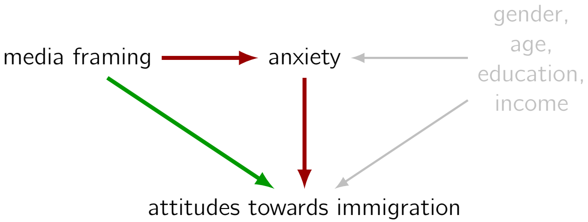
[Brader et al., 2008]

The web-based platform allows us to deliver stimuli matching those in actual news coverage. The study employed a 2 × 2 design with a control group. We manipulated the ethnic cue by altering the picture and name of an immigrant (white European versus Latino) featured in a mock *New York Times* report about a governors' conference on immigration.[3] We also manipulated the tone of the story, focusing either on the positive consequences of immigration for the nation (e.g., strengthening the economy, increasing tax revenues, enriching American culture) or the negative consequences (e.g., driving down wages, consuming public resources, undermining American values). Tone was also manipulated by portrayal of governors as either glad or concerned about immigration and citizens who had had either positive or negative interactions with immigrants.[4] Every story stated that immigration to the United States is increasing and will continue to do so.[5]

EMOTIONS. "Now, moving on, we would like to know how **you feel** about **increased immigration**. The following questions will ask you how you feel when you think about the high levels of immigration to this country. How [**anxious** (that is, uneasy)/**proud/angry/hopeful/worried/excited**] does it make you feel?" (Very, somewhat, a little, or not at all?)

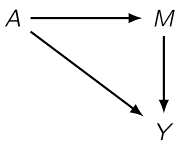
OPINIONS. *Immigration*: "Do you think the number of immigrants from foreign countries who are permitted to come to the United States to live should be increased a lot, increased a little, left the same as it is now, decreased a little, or decreased a lot?" *English Only*: "Do you favor a law

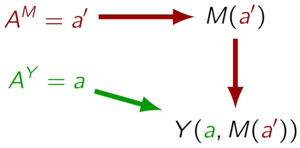
Recap – causal DAG of a stripped-down example



Recap – nested counterfactual outcomes $Y(a, M(a'))$

[Pearl, 2001, Robins and Greenland, 1992]





- conceptualize the intuitive notion of **changing treatment assignment along specific pathways** but not others, i.e. so-called 'edge interventions' [Shpitser and Tchetgen Tchetgen, 2016]
- provide a framework that allows for **model-free effect decomposition** into **natural direct and indirect effects**

$$\underbrace{E\{Y(1) - Y(0)\}}_{\text{total effect}}$$

$$= \underbrace{E\{Y(\mathbf{1}, M(0)) - Y(\mathbf{0}, M(0))\}}_{\text{pure direct effect} = \text{NDE}(0)} + \underbrace{E\{Y(1, M(\mathbf{1})) - Y(1, M(\mathbf{0}))\}}_{\text{total indirect effect} = \text{NIE}(1)}$$

$$= \underbrace{E\{Y(\mathbf{1}, M(1)) - Y(\mathbf{0}, M(1))\}}_{\text{total direct effect} = \text{NDE}(1)} + \underbrace{E\{Y(0, M(\mathbf{1})) - Y(0, M(\mathbf{0}))\}}_{\text{pure indirect effect} = \text{NIE}(0)}$$

Natural effect models

Parameterization using natural effect models

[Lange et al., 2012, Loeys et al., 2013, Vansteelandt et al., 2012]

Extension of marginal structural models for mean nested counterfactuals that allow for decomposition of a causal effect along multiple pathways

Linear natural effect model, e.g.,

$$E\{Y(a, M(a'))\} = \eta_0 + \eta_1 a + \eta_2 a' + \eta_3 a a'$$

$$\begin{aligned}
\underbrace{E\{Y(1) - Y(0)\}}_{\text{total effect}} &= \underbrace{E\{Y(\mathbf{1}, M(0)) - Y(\mathbf{0}, M(0))\}}_{\text{pure direct effect = NDE(0)}} && \eta_1 \\
&\quad + \underbrace{E\{Y(1, M(\mathbf{1})) - Y(1, M(\mathbf{0}))\}}_{\text{total indirect effect = NIE(1)}} && \eta_2 + \eta_3 \\
&= \underbrace{E\{Y(\mathbf{1}, M(1)) - Y(\mathbf{0}, M(1))\}}_{\text{total direct effect = NDE(1)}} && \eta_1 + \eta_3 \\
&\quad + \underbrace{E\{Y(0, M(\mathbf{1})) - Y(0, M(\mathbf{0}))\}}_{\text{pure indirect effect = NIE(0)}} && \eta_2
\end{aligned}$$

Parameterization using natural effect models

[Lange et al., 2012, Loeys et al., 2013, Vansteelandt et al., 2012]

Allowing for different link functions, effects can be expressed on desired scale

Logistic natural effect model, e.g.,

$$\text{logit}\,\Pr\{Y(a, M(a')) = 1\} = \eta_0 + \eta_1 a + \eta_2 a' + \eta_3 a a'$$

$$\underbrace{\frac{\text{odds}\{Y(1)=1\}}{\text{odds}\{Y(0)=1\}}}_{\text{total effect OR}} = \underbrace{\frac{\text{odds}\{Y(\mathbf{1}, M(0))=1\}}{\text{odds}\{Y(\mathbf{0}, M(0))=1\}}}_{\text{pure direct effect OR = NDE(0)}} \qquad \text{expit}(\eta_1)$$

$$\times \underbrace{\frac{\text{odds}\{Y(1, M(\mathbf{1}))=1\}}{\text{odds}\{Y(1, M(\mathbf{0}))=1\}}}_{\text{total indirect effect OR = NIE(1)}} \qquad \text{expit}(\eta_2 + \eta_3)$$

$$= \underbrace{\frac{\text{odds}\{Y(\mathbf{1}, M(1))=1\}}{\text{odds}\{Y(\mathbf{0}, M(1))=1\}}}_{\text{total direct effect OR = NDE(1)}} \qquad \text{expit}(\eta_1 + \eta_3)$$

$$\times \underbrace{\frac{\text{odds}\{Y(0, M(\mathbf{1}))=1\}}{\text{odds}\{Y(0, M(\mathbf{0}))=1\}}}_{\text{pure indirect effect OR = NIE(0)}} \qquad \text{expit}(\eta_2)$$

Wait, hang on a second...

Q: How can we fit this kind of model when most of the outcomes are missing?

	A	$M(1)$	$M(0)$	$Y(1, M(1))$	$Y(0, M(1))$	$Y(1, M(0))$	$Y(0, M(0))$
1	1	M_1		Y_1			
2	1	M_2		Y_2			
$\vdots$	$\vdots$	$\vdots$		$\vdots$			
	$\vdots$		$\vdots$				$\vdots$
n	0		M_n				Y_n

A: **By resorting to established missing data techniques!**

Weighting-based approach

[Hong, 2010, Lange et al., 2012]

	A	$M(1)$	$M(0)$	$Y(1, M(1))$	$Y(0, M(1))$	$Y(1, M(0))$	$Y(0, M(0))$
1	1	M_1		Y_1		$w_1 Y_1$	
2	1	M_2		Y_2		$w_2 Y_2$	
$\vdots$	$\vdots$	$\vdots$		$\vdots$		$\vdots$	
	$\vdots$		$\vdots$		$\vdots$		$\vdots$
n	0		M_n		$w_n Y_n$		Y_n

Key idea Up- (or down)-weigh individuals whose observed mediator level is more (less) typical for the other treatment group

such that, for each treatment group, we can construct a pseudo-population of individuals with mediator levels that would have been observed if each individual had been assigned to the other treatment arm. This can be achieved by weighing each observation (in an extended data set) by

$$\frac{\Pr(M = M_i | A = a', C_i)}{\Pr(M = M_i | A = a, C_i)} = \frac{\Pr(M = M_i | A = a', C_i)}{\Pr(M = M_i | A_i, C_i)}.$$

Imputation-based approach

[Loeys et al., 2013, Vansteelandt et al., 2012]

	A	$M(1)$	$M(0)$	$Y(1, M(1))$	$Y(0, M(1))$	$Y(1, M(0))$	$Y(0, M(0))$
1	1	M_1		Y_1	$\hat{Y}_1(0, M_1(1))$		
2	1	M_2		Y_2	$\hat{Y}_2(0, M_2(1))$		
$\vdots$	$\vdots$	$\vdots$		$\vdots$	$\vdots$		
	$\vdots$		$\vdots$			$\vdots$	$\vdots$
n	0		M_n			$\hat{Y}_n(1, M_n(0))$	Y_n

Key idea The consistency assumption that $M_i(a') = M_i$ for individuals assigned to treatment $A = a'$ implies $Y_i(a, M_i(a')) = Y_i(a, M_i)$

$Y_i(a, M_i(a'))$ can then (under sufficient causal assumptions) be imputed by fitted values from any appropriate model for $E(Y_i|A = a, M_i, C_i)$, that is, by the expected outcome one would have observed if individual i had been assigned to treatment $A = a$ instead of $A = a'$, but her mediator level would have remained unaltered.

Fitting natural effect models made easy in R

[Steen et al., 2017b]

medflex: an R package that...

- offers pain-free routes to mediation analysis and natural effect model fitting for applied researchers
- by casting mediation analysis in a GLM framework that closely mimicks established functionalities in R
- and thereby simplifies reporting and hypothesis testing

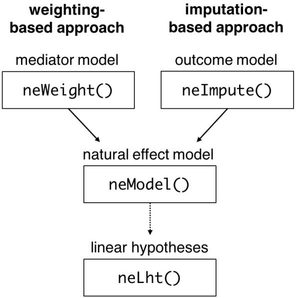


Figure: The medflex workflow

Fitting natural effect models made easy in R

[Steen et al., 2017b]

- medflex 0.6-6 freely available from the Comprehensive R Archive Network:
  https://cran.r-project.org/web/packages/medflex/index.html

  ```
  install.packages('medflex')
  ```

- development release 0.6-7 available from github:
  https://github.com/jmpsteen/medflex

  ```
  devtools::install_github('jmpsteen/medflex')
  ```

- companion paper in Journal of Statistical Software:
  https://www.jstatsoft.org/article/view/v076i11

  ```
  vignette('medflex')
  ```

Weighing in practice

First 'replicate' the data along unobserved (a, a') combinations (with $A = a$)

	A	a	a'	$M(a')$	$Y(a, M(a'))$
1	1	1	1	M_1	Y_1
2	1	1	1	M_2	Y_2
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
n	0	0	0	M_n	Y_n

Weighing in practice

First 'replicate' the data along unobserved (a, a') combinations (with $A = a$)

	A	a	a'	$M(a')$	$Y(a, M(a'))$
1	1	1	1	M_1	Y_1
1	1	1	**0**	M_1	.
2	1	1	1	M_2	Y_2
2	1	1	**0**	M_2	.
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
n	0	0	0	M_n	Y_n
n	0	0	**1**	M_n	.

Then regress the observed outcomes Y on a and a' (and possibly an adjustment set C), weighed by

$$\frac{\Pr(M = M_i | A = a', C)}{\Pr(M = M_i | A = a, C)}.$$

Weighing in medflex

`neWeight`:
wrapper of `glm` function that

1. **fits** a model for the mediator density $\Pr(M|A, C)$
2. **replicates** data along unobserved (a, a') combinations (with $A = a$)
3. **calculates** weights $\dfrac{\hat{\Pr}(M|A = a', C)}{\hat{\Pr}(M|A = a, C)}$ for these combinations

```r
library(medflex)
weightData <- neWeight(anxiety ~ factor(treat) + ..., data = framing)
head(data.frame(weightData, weights = weights(weightData)))
```

```
##   id treat0 treat1 anxiety immigr   weights
## 1  1      0      0       2      4 1.0000000
## 2  1      0      1       2      4 1.1897101
## 3  2      0      0       3      3 1.0000000
## 4  2      0      1       3      3 0.9799741
## 5  3      0      0       2      3 1.0000000
## 6  3      0      1       2      3 1.1476039
```

Imputing in practice

Again 'replicate' the data along unobserved (a, a') combinations (with $A = a'$)

	A	a	a'	$M(a')$	$Y(a, M(a'))$
1	1	1	1	M_1	Y_1
2	1	1	1	M_2	Y_2
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
n	0	0	0	M_n	Y_n

Imputing in practice

Again 'replicate' the data along unobserved (a, a') combinations (with $A = a'$)

	A	a	a'	$M(a')$	$Y(a, M(a'))$
1	1	1	1	M_1	Y_1
1	1	**0**	1	M_1	$\hat{Y}_1(\mathbf{0}, M_1(1))$
2	1	1	1	M_2	Y_2
2	1	**0**	1	M_2	$\hat{Y}_2(\mathbf{0}, M_2(1))$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
n	0	0	0	M_n	Y_n
n	0	**1**	0	M_n	$\hat{Y}_n(\mathbf{1}, M_n(0))$

Then regress imputed counterfactual outcomes $\hat{Y}(a, M(a'))$ on a and a' (and possibly an adjustment set C)

Imputing in medflex

`neImpute`:
wrapper of `glm` function that

1. **fits** a model for the outcome mean $E(Y|A, M, C)$
2. **replicates** data along unobserved (a, a') combinations (with $A = a'$)
3. **imputes** counterfactuals by $\hat{E}(Y|A = a, M, C)$ for these combinations

```
impData <- neImpute(immigr ~ factor(treat) * anxiety + ...,
                    data = framing)
head(impData)
```

```
##   id treat0 treat1 anxiety   immigr
## 1  1      0      0       2 3.640475
## 2  1      1      0       2 3.879241
## 3  2      0      0       3 2.854414
## 4  2      1      0       3 3.126197
## 5  3      0      0       2 2.754097
## 6  3      1      0       2 2.992863
```

Fitting natural effect models in medflex

`neModel`:
Both `neWeight` and `neImpute` return an extended data set that readily enables estimation of natural effects by **fitting a natural effect model**, e.g.,

$$E\{Y(a, M(a'))\} = \eta_0 + \eta_1 a + \eta_2 a' + \eta_3 a a'$$

either by

1. **weighted** regression of observed outcomes Y

$$E\left[Y \frac{\Pr(M|A = a', C)}{\Pr(M|A = a, C)} \middle| A = a \right]$$

```
neModW <- neModel(immigr ~ treat0 * treat1,
                  expData = weightData, se = "robust")
```

2. regression of **imputed** outcomes $\hat{E}(Y|A = a, M, C)$

$$E\left[E(Y|A = a, M, C) | A = a' \right]$$

```
neModI <- neModel(immigr ~ treat0 * treat1,
                  expData = impData, se = "robust")
```

Connection with the mediational g-formula

[Vansteelandt, 2012]

Both weighting- and imputation-based approaches build on semi-parametric formulations of the **mediation formula** [Pearl, 2001, Pearl, 2012]

$$E\{Y(a, M(a'))|C\}$$
$$= \sum_m E(Y|A = a, M = m, C)\Pr(M = m|A = a', C)$$

Pearl's main identification result for mean nested counterfactuals (a special case of the 'edge g-formula' [Shpitser and Tchetgen Tchetgen, 2016])

$$= E\left[Y\frac{\Pr(M|A = a', C)}{\Pr(M|A = a, C)}\middle|A = a, C\right] = E\left[E(Y|A = a, M, C)|A = a', C\right]$$

Reducing modeling demands

$$
\begin{aligned}
&E\{Y(a, M(a'))|C\} \\
&= \sum_m E(Y|A=a, M=m, C)\Pr(M=m|A=a', C) \\
&= E\left[Y\frac{\Pr(M|A=a', C)}{\Pr(M|A=a, C)}\middle|A=a, C\right] = E\left[E(Y|A=a, M, C)|A=a', C\right]
\end{aligned}
$$

Summation or standardization over the mediator density (evaluated at a possibly counterfactual treatment level $A=a'$) is either obtained

1. by re-weighting observed outcomes according to the counterfactual mediator density [Hong, 2010]
2. by summing over the empirical mediator density [Albert, 2012]

Unlike direct application of the mediation formula, which requires correct specification of both a mediator density model (i) and a model for the outcome mean (ii), the weighting- and imputation-based formulations require only a single correctly specified working model (either (i) or (ii), respectively), at the expense of correct specification of a natural effect model.

Weighting or imputing?

[Vansteelandt, 2012]

Consistent estimates can be obtained for both approaches upon adequate specification of the natural effect model and either (i) or (ii)

1. **Weighting-based approach**
   - (-) requires **adequate specification of mediator density** (rather than just its expectation)
   - (-) tends to yield less stable results due to **weight instability** (especially for continuous M)
   - (+) standard errors more honestly **reflect extrapolation uncertainty** due to strong $C - M$ or $A - M$ associations
2. **Imputation-based approach**
   - (-) potential **incompatibility** between imputation model and natural effect model may lead to misspecification bias $\longrightarrow$ aim for sufficiently rich imputation model (e.g. by using ensemble learner)
   - (-) risk for **extrapolation bias** due to strong $C - M$ or $A - M$ associations
   - (+) does not require any distributional assumptions on the mediator
   - (+) yields **more precise estimates** (given adequate model specification)

Recap – equivalence under strict linearity

Closed-form expressions for natural direct and indirect effects in terms of parameters of strictly linear working models (i) and (ii)

$$E(M|A, C) = \beta_0 + \beta_1 A + \beta_2 C \qquad \text{(i)}$$
$$E(Y|A, M, C) = \theta_0 + \theta_1 A + \theta_2 M + \theta_3 C \qquad \text{(ii)}$$

can be obtained by plugging (i) and (ii) in the mediation formula

$$\begin{aligned}
E\{Y(a, M(a'))|C\} &= \sum_m E(Y|A = a, M = m, C)\,\Pr(M = m|A = a', C) \\
&= \sum_m (\theta_0 + \theta_1 a + \theta_2 m + \theta_3 C)\,\Pr(M = m|A = a', C) \\
&= \theta_0 + \theta_1 a + \theta_2 E(M|A = a', C) + \theta_3 C \\
&= \theta_0 + \theta_1 a + \theta_2(\beta_0 + \beta_1 a' + \beta_2 C) + \theta_3 C \\
&= (\theta_0 + \theta_2\beta_0) + \theta_1 a + \theta_2\beta_1 a' + (\theta_3 + \theta_2\beta_2) C
\end{aligned}$$

Recap – equivalence under strict linearity

$$E\{Y(a, M(a'))|C\} = (\theta_0 + \theta_2\beta_0) + \theta_1 a + \theta_2\beta_1 a' + (\theta_3 + \theta_2\beta_2)C$$

This corresponds with natural effect model parameterization

$$E\{Y(a, M(a'))|C\} = \delta_0 + \delta_1 a + \delta_2 a' + \delta_3 C,$$

where $\delta_1 = \theta_1$ and $\delta_2 = \theta_2\beta_1$.

Note that under strict linearity, we obtain the well-known LSEM plug-in estimators for the direct and indirect effects (i.e. product-of-coefficients).
[Baron and Kenny, 1986]

However, linearity rarely applies in practice...

Complication 1: non-linearities

Beyond linear settings: example 1

[VanderWeele and Vansteelandt, 2009]

Suppose that we allow A and M to interact in their effect on the outcome (in order to allow for mediated interaction), i.e. we specify working model (ii) as

$$E(Y|A, M, C) = \theta_0 + \theta_1 A + \theta_2 M + \theta_3 AM + \theta_4 C.$$

Combined with (i), this yields

$$\begin{aligned}
E\{Y(a, M(a'))|C\} &= \sum_m (\theta_0 + \theta_1 a + (\theta_2 + \theta_3 a)m + \theta_4 C) \Pr(M = m|A = a', C) \\
&= \theta_0 + \theta_1 a + (\theta_2 + \theta_3 a) E(M|A = a', C) + \theta_4 C \\
&= \theta_0 + \theta_1 a + (\theta_2 + \theta_3 a)(\beta_0 + \beta_1 a' + \beta_2 C) + \theta_4 C \\
&= (\theta_0 + \theta_2\beta_0) + (\theta_1 + \theta_3\beta_0)a + \theta_2\beta_1 a' + (\theta_3\beta_1)aa' \\
&\quad + (\theta_4 + \theta_2\beta_2)C + (\theta_3\beta_2)aC,
\end{aligned}$$

which involves effect modification by C, even though such 'moderation' was not postulated in (i) nor (ii).

Beyond linear settings: example 2

[Vansteelandt et al., 2012]

For binary M and Y, combining respective logistic working models

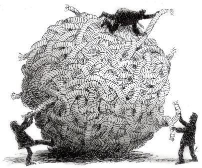
$$\text{logit}\,\Pr(M = 1|A, C) = \beta_0 + \beta_1 A + \beta_2 C$$
$$\text{logit}\,\Pr(Y = 1|A, M, C) = \theta_0 + \theta_1 A + \theta_2 M + \theta_3 C$$

yields

$$\begin{aligned} E\left\{Y(a, M(a'))|C\right\} = &\ \text{expit}\,(\theta_0 + \theta_1 a + \theta_2 + \theta_3 C)\,\text{expit}\left(\beta_0 + \beta_1 a' + \beta_2 C\right) \\ &+ \text{expit}\,(\theta_0 + \theta_1 a + \theta_3 C)\left\{1 - \text{expit}\left(\beta_0 + \beta_1 a' + \beta_2 C\right)\right\}, \end{aligned}$$

a result that does not translate into a simple (logistic) natural effect model parameterization and that leads to risk difference and odds ratio effect expressions of natural direct and indirect effects that again carry an intricate dependence on covariates C (and possibly continuous treatment A).

Beyond linear settings...



These examples illustrate that, as soon as non-linearities enter the picture, things get much more involved as (even simple) working models (i) and (ii) don't usually combine into a simple natural effect model structure, i.e. they tend to produce complex expressions of natural direct and indirect effects.

As a result, a fully parametric approach to the mediation formula that demands adequate model specification of both (i) and (ii) can make

1. results difficult to report
2. interesting hypotheses essentially impossible to test[1]

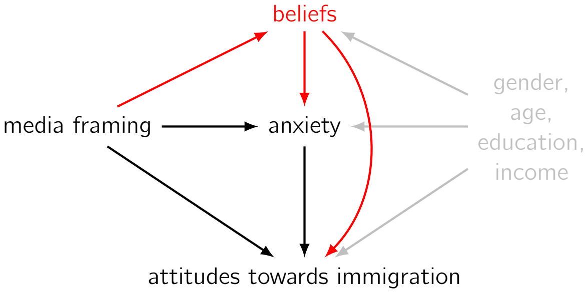
[1] as it turns out difficult (or even impossible) to come up with combinations of (i) and (ii) that yield effect expressions that are constant at all covariate levels of C (or continuous A), such that corresponding null hypotheses are guaranteed to be rejected in sufficiently large samples (g-null paradox [Robins and Wasserman, 1997])

Complication 2: multiple mediators

Dealing with treatment-induced confounding

or causally ordered mediators

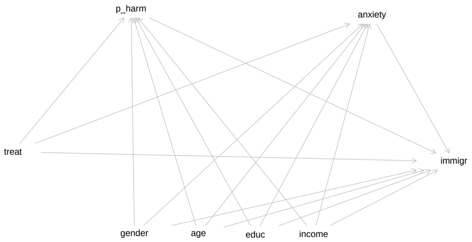
In the previous analysis, we assumed that no un/measured confounders of the mediator-outcome relation are affected by treatment. This allowed for model-free identification and sensible interpretation of the natural in/direct effect (without imposing parametric assumptions). However, any mediator L that is known or assumed to preceed the mediator-of-interest M, can be suspected to be such a treatment-induced confounder.

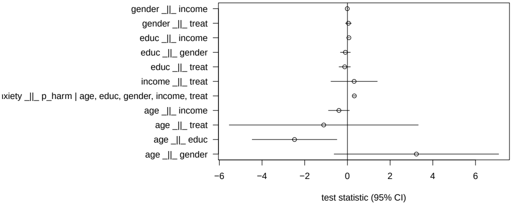


Dealing with treatment-induced confounding

or causally ordered mediators

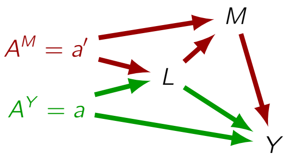
Testing conditional independence of mediators using DAGITTY





Dealing with treatment-induced confounding

or causally ordered mediators



$$E\{Y(a, M(a'))\}$$
$$= E\{Y(a, L(a), M(a', L(a')))\}$$

is not generally identifiable because of **conflicting edge intervention** wrt L (i.e. conflicting hypothetical treatment assignments that feed into L)

$\longrightarrow$ L acts as a so-called **recanting witness**[2] [Avin et al., 2005]

Essentially, the difficulty is that L fulfills a double role, i.e. it acts as both a mediator and a confounder: two roles that require irreconcilable treatments.

---

[2] Identification of the natural indirect effect wrt M would require L to retract an earlier statement, which allows treatment to transmit its entire effect on the mediator in order not to block the path from A to M via L, in favour of a new statement that keeps treatment from transmitting its effect on the outcome other than through the mediator, so as to block the path from A to Y via L.

Dealing with treatment-induced confounding

or causally ordered mediators

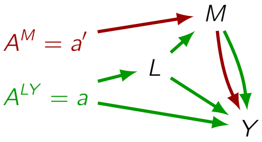
Possible solutions

1. calculate non-parametric **bounds** for natural direct and indirect effects in the presence of treatment-induced confounding (only applies to some settings that mainly involve binary variables) [Miles et al., 2017a, Tchetgen Tchetgen and Phiri, 2014]
2. adopt a **sensitivity analysis** approach (mostly relies on a parametric framework) [Daniel et al., 2015, Imai and Yamamoto, 2013]

However, these solutions aim to recover a target of inference (the natural in/direct effect) that may not be meaningful / of practical relevance (in terms of a hypothetical target trial)

Dealing with treatment-induced confounding
or causally ordered mediators

3. shift focus to **identifiable path-specific effects** such as the **partial indirect effect**, which expresses the effect that is solely mediated by M (i.e. over and above M's mediated effect via L)
   [Huber, 2014, Miles et al., 2017b, VanderWeele and Vansteelandt, 2013, VanderWeele et al., 2014]



$$E\{Y(a, L(a), M(a', L(a)))\}$$

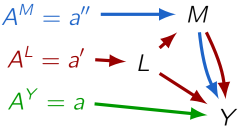
does not involve a conflicting edge intervention wrt L and is hence possibly identifiable.

In addition, this target of inference is again compatible with a hypothetical target trial that separates aspect of treatment to which only M is directly responsive to ($A^M = a'$) from the other aspects of treatment to which only L and Y are directly responsive to ($A^Y = a$).

The ‘partial’ indirect effect

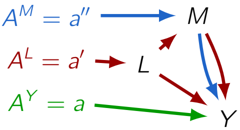
Different estimation approaches may target different instances of this target of inference. A natural effect model parameterization helps to shed light on these subtle differences.

Given two disjoint sets of mediators $\{L\}$ and $\{M\}$, consider the following natural effect model that enables three-way decomposition of the total effect:



$$
\begin{aligned}
&E\{Y(a, L(a'), M(a'', L(a')))\} \\
&= \eta_0 + \eta_1 a + \eta_2 a' + \eta_3 a'' \\
&\quad + \eta_4 aa' + \eta_5 aa'' + \eta_6 a'a'' + \eta_7 aa'a''
\end{aligned}
$$

The 'partial' indirect effect

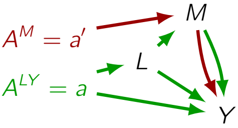


$$E\{Y(a, L(a'), M(a'', L(a')))\}$$
$$= \eta_0 + \eta_1 a + \eta_2 a' + \eta_3 a''$$
$$+ \eta_4 aa' + \eta_5 aa'' + \eta_6 a'a'' + \eta_7 aa'a''$$

This parameterization leads to 4 distinct instances of the partial indirect effect, i.e.

$$E\{Y(0, L(0), M(1, L(0))) - Y(0, L(0), M(0, L(0)))\} = \eta_3$$
$$E\{Y(1, L(0), M(1, L(0))) - Y(1, L(0), M(0, L(0)))\} = \eta_3 + \eta_5$$
$$E\{Y(0, L(1), M(1, L(1))) - Y(0, L(1), M(0, L(1)))\} = \eta_3 + \eta_6$$
$$E\{Y(1, L(1), M(1, L(1))) - Y(1, L(1), M(0, L(1)))\} = \eta_3 + \eta_5 + \eta_6 + \eta_7$$

The ‘partial’ indirect effect



$$
\begin{aligned}
&E\{Y(a, L(a), M(a', L(a)))\}\\
&= \gamma_0 + \gamma_1 a + \gamma_2 a' + \gamma_3 a a'\\
&= \eta_0 + (\eta_1 + \eta_2 + \eta_4) a + \eta_3 a'\\
&\quad + (\eta_5 + \eta_6 + \eta_7) a a'
\end{aligned}
$$

This parameterization leads to 4 distinct instances of the partial indirect effect, i.e.

$$
\begin{aligned}
E\{Y(0, L(0), M(1, L(0))) - Y(0, L(0), M(0, L(0)))\} &= \eta_3\\
&= \textit{pure} \text{ partial indirect effect} = \gamma_2\\
E\{Y(1, L(1), M(1, L(1))) - Y(1, L(1), M(0, L(1)))\} &= \eta_3 + \eta_5 + \eta_6 + \eta_7\\
&= \textit{total} \text{ partial indirect effect} = \gamma_2 + \gamma_3
\end{aligned}
$$

only 2 of which can be recovered from a simpler natural effect model that separates the pathway corresponding to the partial indirect effect from its complement.

The ‘partial’ indirect effect

Note that, as compared to the other two instances, the pure and total partial indirect effect can be recovered from a more simple hypothetical target trial, i.e. one in which only 2 (rather than 3) separable aspects of treatment are manipulated (because two aspects are collapsed into one).

Three estimation approaches for partial indirect effects

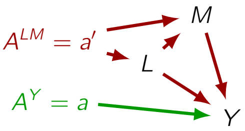
[Steen et al., 2017a, VanderWeele and Vansteelandt, 2013]

1. **Sequential approach** [VanderWeele and Vansteelandt, 2013]
    - fit a NEM for $E\{Y(a, L(a'), M(a', L(a')))\}$, treating $\{L, M\}$ as joint mediator
    - fit a NEM for $E\{Y(a, L(a'))\} = E\{Y(a, L(a'), M(a, L(a')))\}$, treating L as single mediator
    - partial indirect effect corresponds to the difference of respective total (pure) indirect effects or pure (total) direct effects
    - yields 2 out of 4 instances of the partial indirect effect, neither of which corresponds to a pure or total partial indirect effect $\longrightarrow$ complicates interpretation

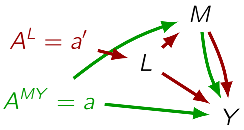
Sequential approach (decomposition 1)

[VanderWeele and Vansteelandt, 2013]

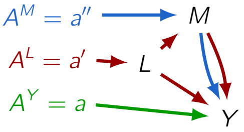
$\eta_3 + \eta_5$ = difference of total indirect effects = difference of pure direct effects



$$E\{Y(a, L(a'), M(a', L(a')))\}$$
$$= \eta_0 + \eta_1 a + \eta_2 a' + \eta_3 a' + \eta_4 aa' + \eta_5 aa' + \eta_6 a'a' + \eta_7 aa'a'$$



$$E\{Y(a, L(a'), M(a, L(a')))\}$$
$$= \eta_0 + \eta_1 a + \eta_2 a' + \eta_3 a + \eta_4 aa' + \eta_5 aa + \eta_6 a'a + \eta_7 aa'a$$

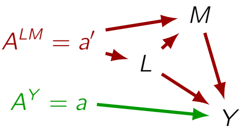


$$E\{Y(a, L(a'), M(a'', L(a')))\}$$
$$= \eta_0 + \eta_1 a + \eta_2 a' + \eta_3 a'' + \eta_4 aa' + \eta_5 aa'' + \eta_6 a'a'' + \eta_7 aa'a''$$

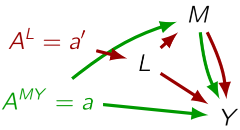
Sequential approach (decomposition 2)

[VanderWeele and Vansteelandt, 2013]

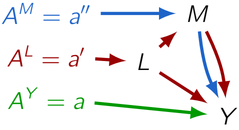
$\eta_3 + \eta_6$ = difference of pure indirect effects = difference of total direct effects



$$E\{Y(a, L(a'), M(a', L(a')))\}$$
$$= \eta_0 + \eta_1 a + \eta_2 a' + \eta_3 a' + \eta_4 aa' + \eta_5 aa' + \eta_6 a'a' + \eta_7 aa'a'$$



$$E\{Y(a, L(a'), M(a, L(a')))\}$$
$$= \eta_0 + \eta_1 a + \eta_2 a' + \eta_3 a + \eta_4 aa' + \eta_5 aa + \eta_6 a'a + \eta_7 aa'a$$



$$E\{Y(a, L(a'), M(a'', L(a')))\}$$
$$= \eta_0 + \eta_1 a + \eta_2 a' + \eta_3 a'' + \eta_4 aa' + \eta_5 aa'' + \eta_6 a'a'' + \eta_7 aa'a''$$

Three estimation approaches for partial indirect effects

[Steen et al., 2017a, VanderWeele and Vansteelandt, 2013]

❷ Direct approach based on weighted regression of imputed outcomes

[Steen et al., 2017a]

- fit a NEM for $E\{Y(a, L(a'), M(a'', L(a')))\}$

$$= E\left[E(Y|A = a, L, M, C)\frac{\Pr(L|A = a', C)}{\Pr(L|A = a'', C)}\middle|A = a''\right]$$

$$= E\left[E(Y|A = a, L, M, C)\frac{\Pr(M|A = a'', L, C)}{\Pr(M|A = a', L, C)}\middle|A = a'\right]$$

- aims for three-way decomposition of the total effect
- requires an imputation model and a model for either of the mediator densities
- partial indirect effect is directly captured by model parameter(s)
- yields all 4 instances of the partial indirect effect
- not implemented in `medflex`! (requires manual coding)

Direct approach via weighed imputation (option 1)

[Steen et al., 2017a]

First replicate the data along unobserved (a, a', a'') combinations

	A	a	a'	a''	$M(a'')$	$Y(a, L(a'), M(a'', L(a')))$
1	1	1	1	1	M_1	Y_1
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
n	0	0	0	0	M_n	Y_n

Direct approach via weighed imputation (option 1)

[Steen et al., 2017a]

First replicate the data along unobserved (a, a', a'') combinations

	A	a	a'	a''	$M(a'')$	$Y(a, L(a'), M(a'', L(a')))$
1	1	1	1	1	M_1	Y_1
1	1	0	1	1	M_1	$\hat{Y}_1(0, L_1(1), M_1(1, L_1(1)))$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
n	0	0	0	0	M_n	Y_n
n	0	1	0	0	M_n	$\hat{Y}_n(1, L_n(0), M_n(0, L_n(0)))$

Direct approach via weighed imputation (option 1)

[Steen et al., 2017a]

First replicate the data along unobserved (a, a', a'') combinations

	A	a	a'	a''	$M(a'')$	$Y(a, L(a'), M(a'', L(a')))$
1	1	1	1	1	M_1	Y_1
1	1	0	1	1	M_1	$\hat{Y}_1(0, L_1(1), M_1(1, L_1(1)))$
1	1	1	0	1	M_1	$\hat{Y}_1(1, L_1(1), M_1(1, L_1(1)))$
1	1	0	0	1	M_1	$\hat{Y}_1(0, L_1(1), M_1(1, L_1(1)))$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
n	0	0	0	0	M_n	Y_n
n	0	1	0	0	M_n	$\hat{Y}_n(1, L_n(0), M_n(0, L_n(0)))$
n	0	0	1	0	M_n	$\hat{Y}_n(0, L_n(0), M_n(0, L_n(0)))$
n	0	1	1	0	M_n	$\hat{Y}_n(1, L_n(0), M_n(0, L_n(0)))$

Then regress imputed counterfactual outcomes $\hat{Y}(a, L(a'), M(a', L(a')))$ on a, a' and a'' (and possibly an adjustment set C) weighed by

$$\frac{\Pr(L = L_i | A = a', C)}{\Pr(L = L_i | A = a'', C)}$$

Direct approach via weighed imputation (option 2)

[Steen et al., 2017a]

First replicate the data along unobserved (a, a', a'') combinations

	A	a	a'	a''	$M(a'')$	$Y(a, L(a'), M(a'', L(a')))$
1	1	1	1	1	M_1	Y_1
1	1	0	1	1	M_1	$\hat{Y}_1(0, L_1(1), M_1(1, L_1(1)))$
1	1	1	1	0	M_1	$\hat{Y}_1(1, L_1(1), M_1(1, L_1(1)))$
1	1	0	1	0	M_1	$\hat{Y}_1(0, L_1(1), M_1(1, L_1(1)))$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
n	0	0	0	0	M_n	Y_n
n	0	1	0	0	M_n	$\hat{Y}_n(1, L_n(0), M_n(0, L_n(0)))$
n	0	0	0	1	M_n	$\hat{Y}_n(0, L_n(0), M_n(0, L_n(0)))$
n	0	1	0	1	M_n	$\hat{Y}_n(1, L_n(0), M_n(0, L_n(0)))$

Then regress imputed counterfactual outcomes $\hat{Y}(a, L(a'), M(a', L(a')))$ on a, a' and a'' (and possibly an adjustment set C) weighed by

$$\frac{\Pr(M = M_i | A = a'', L, C)}{\Pr(M = M_i | A = a', L, C)}$$

Three estimation approaches for partial indirect effects

[Steen et al., 2017a, VanderWeele and Vansteelandt, 2013]

❸ Direct approach based on weighted regression of observed outcomes

- fit a NEM for $E\{Y(a, L(a), M(a', L(a)))\}$

$$= E\left[Y \frac{\Pr(M|A = a', L, C)}{\Pr(M|A = a, L, C)} \middle| A = a\right]$$

- aims for two-way decomposition of the total effect
- requires a model for the density of M
- partial indirect effect is directly captured by model parameter(s)
- yields 2 out of 4 instances of the partial indirect effect, corresponding to the pure and total partial indirect effect
- technically not implemented in `medflex`, but `medflex` can be tricked! I.e. corresponds to weighting-based estimator for single mediator setting upon conditioning on previous mediator L in model for density of M

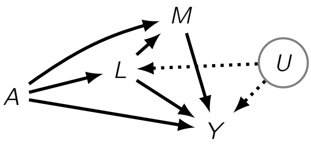
Preferred approach?

If the main target of interest is the partial indirect effect, fitting a NEM for

$$E\{Y(a, L(a), M(a', L(a)))\} = \gamma_0 + \gamma_1 a + \gamma_2 a' + \gamma_3 aa'$$

based on weighted regression of observed outcomes can be considered the preferred approach, because it

1. aligns best with a realistic (or at least: imaginable) hypothetical trial
2. aims for a decomposition that can be obtained under weaker structural assumptions (allowing for unmeasured $L - Y$ confounding)
   [Miles et al., 2017b, Steen and Vansteelandt, 2018]
3. reduces modeling demands
4. can easily be estimated with available (weighting-based) machinery in `medflex`



The appeal of natural effect modeling
as compared to alternative counterfactual-based approaches

Direct parameterization and estimation of path-specific of interest via natural effect models may be attractive because of various reasons:

- no more need to derive closed-form expressions for each specific combination of (i) and (ii)

  SPSS and SAS macros [Valeri and VanderWeele, 2013]
  Stata module PARAMED [Emsley and Liu, 2013]

- offers an **alternative to computer-intensive Monte Carlo integration** which has been suggested to deal with intractable effect expressions [Imai et al., 2010] (whenever sandwich variance estimator is available for inference)

  R package mediation [Tingley et al., 2014]
  Stata module GFORMULA [Daniel et al., 2011]

The appeal of natural effect modeling

as compared to alternative counterfactual-based approaches

- **alleviates modeling demands** (as only (i) or (ii) needs to be (correctly) specified, at the expense of a correctly specified natural effect model in observational studies) and may thus reduce risk of modeling bias and help to avoid the g-null paradox
- offers an **elegant framework for hypothesis testing**, i.e. hypotheses of interest can be captured by (a linear combination of) targeted model parameters
- imposing **parsimonious model structures** may be helpful in more complex settings, especially for extensions to multiple (causally ordered) mediators
- fits elegantly with **separable effects interpretation**, also in settings with multiple mediators, e.g. $E(Y|\text{do}(A^Y = a, A^L = a', A^M = a''))$

For those anxious to apply these methods...

Further guidance and detailed R code demonstrating

- features in `medflex`
- how to apply the estimation approaches for the partial indirect effect
- using the same illustrating example

available at `https://github.com/jmpsteen/medflex-workshopUKCIM2017`

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Opening new horizons

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