Flexible models for causal mediation analysis: an introduction to the R package medflex

pre-meeting workshop B, April 4, UK-CIM 2017
University of Essex, Colchester

Johan Steen

Universitair Ziekenhuis Gent
UNIVERSITEIT GENT

Illustrating example

[Brader et al., 2008]

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

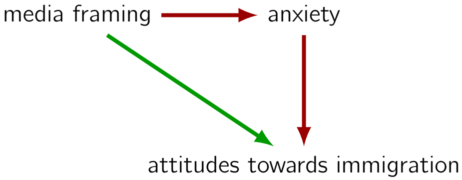
Ted Brader University of Michigan
Nicholas A. Valentino The University of Texas at Austin
Elizabeth Suhay University of Michigan

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

Mediational hypothesis

[Brader et al., 2008]



total effect = direct effect + indirect/mediated effect

Illustrating 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

It's all about assumptions!

To strengthen causal claims, one needs to aim at making minimal **assumptions** for identifying causal effects of interest

1. **Causal assumptions:** do **sufficient** identifying assumptions match a realistic reflection of underlying causal structure? [Pearl, 2001, VanderWeele and Vansteelandt, 2009]
   - => no omitted confounders and no treatment-induced confounding (under NPSEMs[1])
   - => **common practice:** adjustment for a common set of baseline covariates
   - => overly restrictive? (weaker [Pearl, 2014] or even complete identifying assumptions [Shpitser, 2013])
   - => some key assumptions encoded in NPSEMs are not empirically verifiable (cross-world assumptions)

[1] non-parametric structural equation models with independent error terms

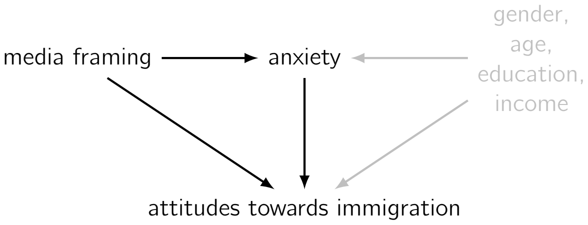
It's all about assumptions!

Focus of this workshop:

2. **Modeling assumptions**: adequate modeling of relations via nuisance working models
   - => correct specification of functional form (and possibly distributional assumptions)
   - => increased modeling demands (and hence risk for bias) as more confounders and/or mediators enter the picture

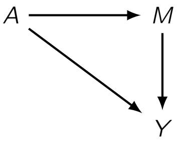
Interdependence between two types of assumptions:
Common (and often implicit) parametric assumptions imposed in (parametric) SEMs have long obscured the difficulties related to identification in the presence of treatment-induced confounding since traditional SEM estimands for direct and indirect effects are typically defined in terms of model parameters, i.e. their definitions are not model-free.

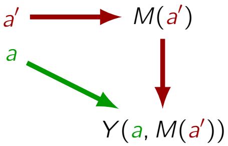
Causal DAG of a stripped-down example



Introducing nested counterfactuals $Y(a, M(a'))$

[Pearl, 2001, Robins and Greenland, 1992]



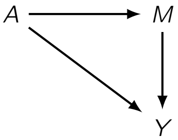


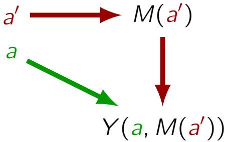
$M(a')$	mediator level that would have been observed had A (possibly contrary to the fact) been set to a'
$Y(a, M(a'))$	outcome that would have been observed had A been set to a and M to $M(a')$

=> 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]

Introducing nested counterfactuals $Y(a, M(a'))$

[Pearl, 2001, Robins and Greenland, 1992]





=> provide a framework that allows for **model-free effect decomposition** into **natural direct and indirect effects**

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

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

Natural effect model, e.g.,

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

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

Wait, hang on a second...

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

=> 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

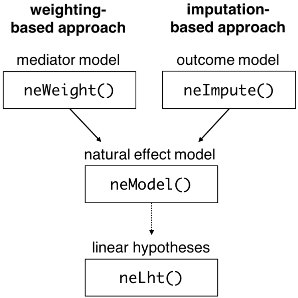


Figure: The medflex workflow

Fitting natural effect models made easy in R

[Steen et al., 2017b]

=> medflex 0.6-1 freely available from the Comprehensive R Archive Network:
`https://cran.r-project.org/web/packages/medflex/index.html`

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

=> development release 0.6-2 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')
```

Weighting 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

Weighting 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

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

Weighting 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

```
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 3.633748
## 2  1      1      0       2 3.884263
## 3  2      0      0       3 2.853889
## 4  2      1      0       3 3.104404
## 5  3      0      0       2 2.749488
## 6  3      1      0       2 3.000004
```

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.,

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

either by

=> **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")
```

=> 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 mediation formula

[Vansteelandt, 2012]

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

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

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

=> by re-weighting observed outcomes according to the counterfactual mediator density [Hong, 2010]

=> 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).

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

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

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...

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

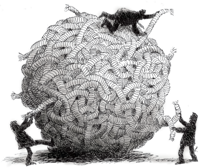
$$\text{logit}\,\Pr(M = 1|A, C) = \beta_0 + \beta_1 A + \beta_2 C$$
$$\text{logit}\,\Pr(Y = 1|A, M, C) = \theta_0 + \theta_1 A + \theta_2 M + \theta_3 C$$

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[2]

[2] 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 (cf 'g-null paradox' [Robins and Wasserman, 1997])

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

It may therefore be more attractive to **prioritize parameterization** of the natural effects of interest and, if necessary, refine the corresponding natural effect model until it yields a good model fit.

=> 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]

=> may offer 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) and may thus reduce risk of modeling bias
- => 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

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) whenever Y is not linear in M
   - 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
     => aim for sufficiently rich imputation model
   - risk for **extrapolation bias** due to strong $C - M$ or $A - M$ associations
   - \+ does not require any distributional assumptions
   - \+ yields **more precise estimates** (given adequate model specification)

Some practical considerations

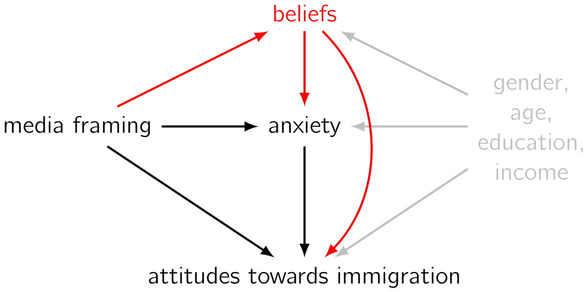
1. Use `residualPlots` function (from the car package) to **assess goodness-of-fit** for both (i) or (ii) and final natural effect model
2. Parsimonious natural effect model may still provide **summary result** tailored to answer the practitioner's main research questions (despite slight misspecification of natural effect model but given adequate model for (i) or (ii))
3. For randomized studies with continuous M and high risk of model extrapolation: consider **inverse-odds weighting** by[3]
[Huber, 2014, Tchetgen Tchetgen, 2013]

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

=> currently not implemented in medflex!

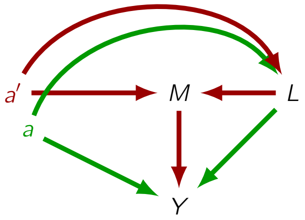
[3] Using Bayes' rule, we can simply re-write $\frac{\Pr(M_i|A=a',C_i)}{\Pr(M_i|A_i,C_i)}$ as $\frac{\Pr(A=a'|M_i,C_i)\Pr(M_i|C_i)\Pr(A_i|C_i)}{\Pr(A_i|M_i,C_i)\Pr(M_i|C_i)\Pr(A=a'|C_i)}$, which reduces to (iow) if A is randomized.

Dealing with treatment-induced confounding
or causally ordered mediators



Dealing with treatment-induced confounding

or causally ordered mediators



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

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

L acts as a so-called **recanting witness**[4] [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.

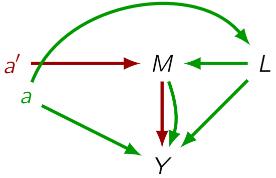
---

[4] 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]
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.

Two estimation approaches for partial indirect effects

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

1. **Sequential approach** [VanderWeele and Vansteelandt, 2013]

   => requires fitting **two** natural effect models (each with a corresponding working model):

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

   => partial indirect effect corresponds to difference of total indirect effects (or pure direct effects) as parameterized by the respective models

2. **Direct approach** [Steen et al., 2017a]

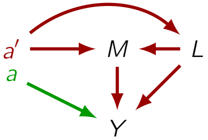
   => requires fitting **only one** natural effect model (with two corresponding working models):
   for $E\{Y(a, L(a'), M(a'', L(a')))\}$

   => partial indirect effect is directly captured by model parameter(s)

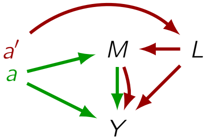
   => enables recovering all possible three-way decompositions that involve the partial indirect effect (<=> sequential approach)

Sequential approach

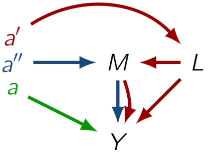
[VanderWeele and Vansteelandt, 2013]



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



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



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

Direct approach via weighed imputation

[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

[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

[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

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

Future prospects for medflex

In the future, we hope to implement functionalities for

1. **inverse odds weighting**
2. **sensitivity analysis**

as well as extensions of natural effect models

3. for **time-to-event outcomes**
4. that enable decompositions into predefined natural **path-specific effects** (in the presence of causally ordered mediators)

Special thanks

medflex authors

Beatrijs Moerkerke
Tom Loeys
Stijn Vansteelandt

medflex contributors

Theis Lange
Joris Meys
Joscha Legewie

the UK-CIM organisers for inviting me

funded by

Fonds Wetenschappelijk Onderzoek Vlaanderen
Opening new horizons

Bibliography I

Albert, J. M. (2012).

Distribution-Free Mediation Analysis for Nonlinear Models with Confounding.

Epidemiology, 23(6):879–88.

Avin, C., Shpitser, I., and Pearl, J. (2005).

Identifiability of Path-Specific Effects.

In *Proceedings of the 19th International Joint Conference on Artificial Intelligence*, IJCAI'05, pages 357–363, San Francisco, CA, USA. Morgan Kaufmann Publishers Inc.

Baron, R. M. and Kenny, D. A. (1986).

The ModeratorâĂŞMediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical Considerations.

Journal of Personality and Social Psychology, 51(6):1173–1182.

Brader, T., Valentino, N. a., and Suhay, E. (2008).

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

American Journal of Political Science, 52(4):959–978.

Bibliography II

Daniel, R. M., De Stavola, B. L., and Cousens, S. N. (2011).

gformula: Estimating Causal Effects in the Presence of Time-Varying Confounding or Mediation Using the G-computation Formula.

Stata Journal, 11(4):479–517.

Daniel, R. M., De Stavola, B. L., Cousens, S. N., and Vansteelandt, S. (2015).

Causal Mediation Analysis with Multiple Mediators.

Biometrics, 71(1):1–14.

Emsley, R. and Liu, H. (2013).

PARAMED: Stata Module to Perform Causal Mediation Analysis Using Parametric Regression Models.

Hong, G. (2010).

Ratio of Mediator Probability Weighting for Estimating Natural Direct and Indirect Effects.

In *Proceedings of the American Statistical Association, Biometrics Section*, pages 2401–2415, Alexandria, VA. American Statistical Association.

Huber, M. (2014).

Identifying Causal Mechanisms (Primarily) Based on Inverse Probability Weighting.

Journal of Applied Econometrics, 29(6):920–943.

Bibliography III

Imai, K., Keele, L., and Tingley, D. (2010).
A General Approach to Causal Mediation Analysis.
Psychological Methods, 15(4):309–334.

Imai, K. and Yamamoto, T. (2013).
Identification and Sensitivity Analysis for Multiple Causal Mechanisms: Revisiting Evidence from Framing Experiments.
Political Analysis, 21(2):141–171.

Lange, T., Vansteelandt, S., and Bekaert, M. (2012).
A Simple Unified Approach for Estimating Natural Direct and Indirect Effects.
American Journal of Epidemiology, 176(3):190–195.

Loeys, T., Moerkerke, B., De Smet, O., Buysse, A., Steen, J., and Vansteelandt, S. (2013).
Flexible Mediation Analysis in the Presence of Nonlinear Relations: Beyond the Mediation Formula.
Multivariate Behavioral Research, 48(6):871–894.

Bibliography IV

Miles, C., Kanki, P., Meloni, S., and Tchetgen Tchetgen, E. (2017a).
On Partial Identification of the Natural Indirect Effect.
Journal of Causal Inference.

Miles, C. H., Shpitser, I., Kanki, P., Meloni, S., and Tchetgen Tchetgen, E. J. (2017b).
Quantifying an Adherence Path-Specific Effect of Antiretroviral Therapy in the Nigeria PEPFAR Program.
Journal of the American Statistical Association.

Pearl, J. (2001).
Direct and Indirect Effects.
In Breese, J. and Koller, D., editors, *Proceedings of the Seventeenth Conference on Uncertainty in Artificial Intelligence (UAI-01)*, UAI-01, pages 411–420, San Francisco, CA. Morgan Kaufmann.

Pearl, J. (2012).
The Mediation Formula: A Guide to the Assessment of Causal Pathways in Nonlinear Models.
In C. Berzuini, Dawid, P., and Bernardinelli, L., editors, *Causality: Statistical Perspectives and Applications*, number October 2011, pages 151–179. John Wiley & Sons, Chichester, UK.

Bibliography V

Pearl, J. (2014).
Interpretation and Identification of Causal Mediation.
Psychological Methods, 19(4):459–481.

Robins, J. M. and Greenland, S. (1992).
Identifiability and Exchangeability for Direct and Indirect Effects.
Epidemiology, 3(2):143–155.

Robins, J. M. and Wasserman, L. (1997).
Estimation of Effects of Sequential Treatments by Reparameterizing Directed Acyclic Graphs.
Proceedings of the Thirteenth Conference on Uncertainty in Artificial Intelligence, pages 409–420.

Shpitser, I. (2013).
Counterfactual graphical models for longitudinal mediation analysis with unobserved confounding.
Cognitive Science, 37(6):1011–35.

Bibliography VI

Shpitser, I. and Tchetgen Tchetgen, E. J. (2016).
Causal inference with a graphical hierarchy of interventions.
The Annals of Statistics, 44(6):2433–2466.

Steen, J., Loeys, T., Moerkerke, B., and Vansteelandt, S. (2017a).
Flexible mediation analysis with multiple mediators.
American Journal of Epidemiology, in press.

Steen, J., Loeys, T., Moerkerke, B., and Vansteelandt, S. (2017b).
medflex: An R Package for Flexible Mediation Analysis using Natural Effect Models.
Journal of Statistical Software, 76(11).

Tchetgen Tchetgen, E. J. (2013).
Inverse Odds Ratio-Weighted Estimation for Causal Mediation Analysis.
Statistics in Medicine, 32(26):4567–80.

Tchetgen Tchetgen, E. J. and Phiri, K. (2014).
Bounds for pure direct effect.
Epidemiology, 25(5):775–6.

Bibliography VII

Tingley, D., Yamamoto, T., Hirose, K., Keele, L., and Imai, K. (2014).
mediation: R Package for Causal Mediation Analysis.
Journal of Statistical Software, 59(5).

Valeri, L. and VanderWeele, T. J. (2013).
Mediation Analysis Allowing for Exposure-Mediator Interactions and Causal Interpretation: Theoretical Assumptions and Implementation with SAS and SPSS Macros.
Psychological Methods, 18(2):137–50.

VanderWeele, T. J. and Vansteelandt, S. (2009).
Conceptual Issues Concerning Mediation, Interventions and Composition.
Statistics and Its Interface, 2(4):457–468.

VanderWeele, T. J. and Vansteelandt, S. (2013).
Mediation Analysis with Multiple Mediators.
Epidemiologic Methods, 2(1):95–115.

VanderWeele, T. J., Vansteelandt, S., and Robins, J. M. (2014).
Effect Decomposition in the Presence of an Exposure-Induced Mediator-Outcome Confounder.
Epidemiology, 25(2):300–306.

Bibliography VIII

Vansteelandt, S. (2012).

Understanding Counterfactual-Based Mediation Analysis Approaches and Their Differences.

Epidemiology, 23(6):889–91.

Vansteelandt, S., Bekaert, M., and Lange, T. (2012).

Imputation Strategies for the Estimation of Natural Direct and Indirect Effects.

Epidemiologic Methods, 1(1):Article 7.