Mediation analysis with multiple non-ordered mediators

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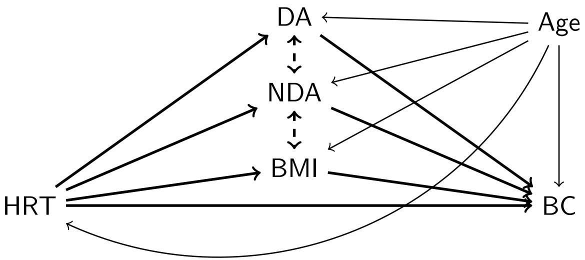
Motivation



- HRT: hormone replacement therapy
- BC: breast cancer
- DA: breast dense area; NDA: breast non-dense Area; BC: breast cancer

Questions:

- What is the indirect effect of HRT on BC through DA (NDA, BMI)?
- What is the direct effect of HRT on BC through other pathways?

Contents

The counterfactual framework

- T_i binary treatment, Y_i outcome
- for each individual i, two potential outcomes:
  - $Y_i(0)$ = outcome if we do not apply the intervention (i.e. $T_i = 0$)
  - $Y_i(1)$ = outcome if we apply the intervention (i.e. $T_i = 1$)
- only one of the two is observed: $Y_i(t) = Y_i$ conditionally to $T_i = t$ (consistency relation):

T_i	Y_i	$Y_i(0)$	$Y_i(1)$
0	0	0	NA
0	0	0	NA
0	1	1	NA
1	1	NA	1
1	1	NA	1
1	0	NA	0

Average causal effect

- The average causal effect of T on Y is

$$\tau := E[Y(1)] - E[Y(0)]$$

- If T is independent from $Y(1)$ and $Y(0)$, then τ is identifiable:

$$\tau = E[Y|T=0] - E[Y|T=1].$$

$\Rightarrow$ Randomized Controlled Trials are the gold standard to estimate τ

- If T is independent from $Y(1)$ and $Y(0)$ conditionally on X, then τ is identifiable:

$$\tau = \int \left(E[Y|X=x, T=1] - E[Y|X=x, T=0]\right) dF_X(x).$$

We say that X *deconfounds* the relationship between T and Y (conditionally ignorability)
$\Rightarrow$ in observational studies, τ can be estimated if all confounders of the relation between T and Y are observed

Simple mediation analysis

Goal is to explain the causal effect of T on Y by decomposing it in two parts:

- direct effect
- indirect effect through an intermediate variable M (e.g. education)

$$\begin{tikzcd} & M \arrow[dr] & \\ T \arrow[ur] \arrow[rr] & & Y \end{tikzcd}$$

Two types of counterfactuals:

- Potential mediators: $M(0)$, $M(1)$
- Potential outcomes:
  - $Y(0, M(0)) = Y(0)$, $Y(1, M(1)) = Y(1)$
  - $Y(0, M(1))$, $Y(1, M(0))$ (nested counterfactuals)

How to define the direct (and indirect) effects? (I)

Example: employment discrimination

- Does applicants' gender have a direct influence on hiring, regardless the indirect effect it might have through their qualification?
- It is not clear how these effects should be defined
- According to case law:

> "The central question in any employment-discrimination case is whether the employer would have taken the same action had the employee been of a different race (age, sex, religion, national origin etc.) and everything else had been the same." (Carson versus Bethlehem Steel Corp., 70 FEP Cases 921, 7th Cir. (1996), Quoted in Gastwirth 1997.)

- The idea is to hold Qualification steady and measure the remaining relationship between Gender and Hiring, but how?

How to define the direct (and indirect) effects? (II)

Example: employment discrimination

$$\begin{tikzcd}
 & M = \text{Qualification} \arrow[dr] & \\
T = \text{Gender} \arrow[ur] \arrow[rr] & & Y = \text{Hiring}
\end{tikzcd}$$

- we might think to condition on M to block the indirect path

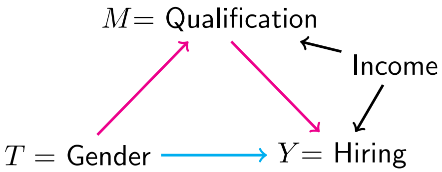
$$\text{Gender} \to \text{Qualification} \to \text{Hiring}$$

- … but in general this not right!
- in presence of a common cause between M and Y, say Income, conditioning on M is conditioning on a collider
- this will open the spurious path

$$\text{Gender} \to \text{Qualification} \leftarrow \text{Income} \to \text{Hiring}$$

How to define the direct (and indirect) effects? (II)

Example: employment discrimination



- we might think to condition on M to block the indirect path

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- ... but in general this not right!
- in presence of a common cause between M and Y, say Income, conditioning on M is conditioning on a collider
- this will open the spurious path

$$\text{Gender} \rightarrow \text{Qualification} \leftarrow \text{Income} \rightarrow \text{Hiring}$$

Controlled direct effect

Instead of *conditioning* we *intervene* so to remove the edge $T \to M$. The direct effect is then measured by comparing the two outcomes of Y

- obtained after setting T to its reference and alternative level *(had the employee been of a different sex)*
- while intervening on M to set it to a given value *(and everything else had been the same)*.

This leads to the definition of controlled direct effect:

$$CDE(m) := E[Y(1,m)] - E[Y(0,m)]$$

Natural direct and indirect effects

- In order to define the indirect effect of X on Y through M we cannot intervene on M as above. Instead, we make personalised interventions and *set M_i at the value that it would have under the intervention $T_i = 0$, ie $M_i(0)$*
- This leads to the definition of natural direct effect (NDE) (Pearl 2001):

$$\zeta(0) := E[Y(1, M(0))] - E[Y(0, M(0))]$$

- We can also define the natural indirect effect (NIE):

$$\delta(1) := E[Y(1, M(1))] - E[Y(1, M(0))]$$

- We have the decomposition:

$$\tau = \zeta(0) + \delta(1)$$

- Similar definitions hold for $\zeta(1)$ and $\delta(0)$. We say that there is no interaction between T and M on Y if $\zeta(0) = \zeta(1) = \zeta$ and $\delta(0) = \delta(1) = \delta$

SI assumptions (Imai el al 2010)

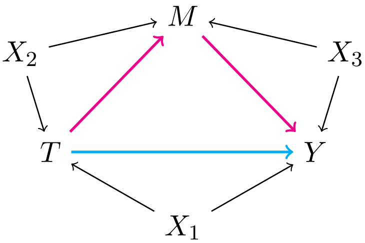
For all t, t', m:

$$T \perp\!\!\!\perp \{M(t), Y(t', m)\} | X = x \quad (1)$$

$$M(t) \perp\!\!\!\perp Y(t', m) | T = t, X = x \quad (2)$$

Interpretation:

- (1) $\Rightarrow$ X deconfounds the relationships $T - M$ and $T - Y$
- (2) $\Rightarrow$ T and X deconfound the relationship $M - Y$
- (1) and (2) $\Rightarrow$ No element in X is causally affected by T



Sequential Ignorability (II)

- (1) holds true if the treatment is randomized
- (2) may not hold even in randomized experiments
- SI cannot be directly tested on the observed data: how do we know that all pre-treatment confounders are measured and that there are no pos-treatment confounders?
- $\Rightarrow$ sensitivity analysis methods

Non-parametric identification

Theorem (Imai et al 2010, Pearl 2001)

Under sequential ignorability, NDE and NIE are identified by

$$\zeta(t) = \int\int \{E[Y|M=m, T=1, X=x] - E[Y|M=m, T=0, X=x]\} \, dF_{M|T=t,X=x}(m) dF_X(x)$$

$$\delta(t) = \int\int E[Y|M=m, T=t, X=x] \left\{dF_{M|T=1,X=x}(m) - dF_{M|T=0,X=x}(m)\right\} dF_X(x)$$

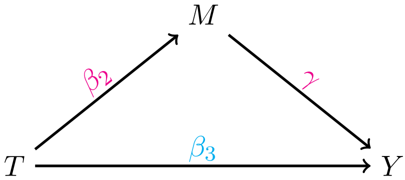
Linear Structural Equation Models

Consider the LSEM :

$$
\begin{aligned}
M &= \alpha_2 + \beta_2 T + \xi_2^\Gamma X + \epsilon_2 \\
Y &= \alpha_3 + \beta_3 T + \gamma M + \xi_3^\Gamma X + \epsilon_3
\end{aligned}
$$

One can show that under SI

$$
\begin{aligned}
\zeta(0) = \zeta(1) &= \beta_3 \\
\delta(0) = \delta(1) &= \beta_2 \gamma
\end{aligned}
$$



$\Rightarrow$ we obtain the classic LSEM definition of indirect effect as a product of coefficients (Baron and Kenny 1986).

Inference

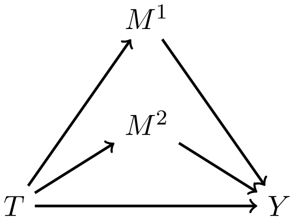
- In principle, the previous theorem allows non-parametric identification of NDE and NIE. In practice, calculating all the empirical means is not always feasible.
- Generalising the proof of the previous theorem, (Imai et al 2010) shows that

$$f(Y(t, M(t'))|X = x) = \int f(Y|M = m, T = t, X = x) dF_{M|T=t',X=x}(m)$$

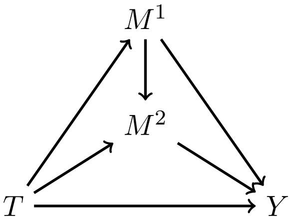
- We can obtain MC estimates of NDE and NIE by simulating the counterfactuals:
    - sample $M(t')$ from a model `M~T+X`
    - given this draw, sample $Y(t, M(t'))$ from a model `Y~T+M+X`
    - compute the empirical means of the appropriate counterfactuals
- Estimators' variance can be obtained by bootstrap or by simulating the model parameters from their sampling distributions (quasi-Bayesian MC approximation)
- Both approaches implemented in the `mediation` package (Tingley et al 2014)

Multiple mediation

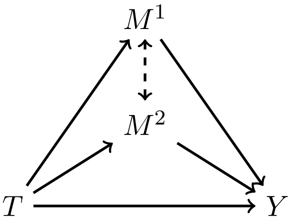
Three possible situations with multiple mediators, conditionally on treatment and measured covariates:



(a) Independent



(b) Causally related

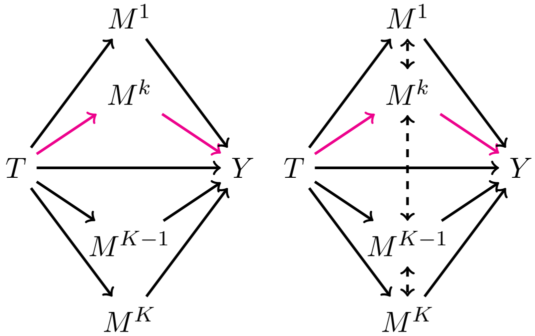


(c) Correlated

We focus on situations (a) and (c)

Natural indirect effect through individual mediators

NIE through M^k :

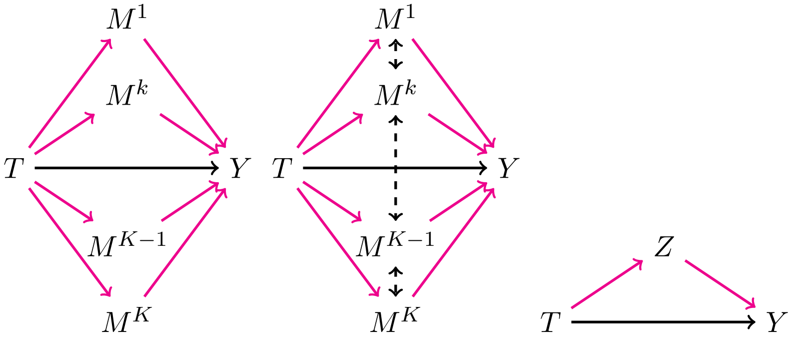


$$\delta^k(t) = \mathbb{E}[Y(t, M^k(1), W^k(t))] - \mathbb{E}[Y(t, M^k(0), W^k(t))],$$

where W^k is the vector of all mediators but M^k

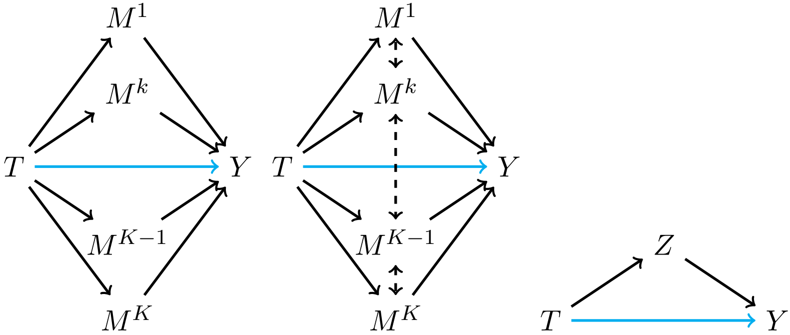
Joint natural indirect effect

NIE through all mediators taken jointly:



$$\delta^Z(t) \quad = \quad \mathbb{E}[Y(t, Z(1))] - \mathbb{E}[Y(t, Z(0))]$$

Natural direct effect



$$\zeta(t) = \mathbb{E}[Y(1, Z(t))] - \mathbb{E}[Y(0, Z(t))]$$

Total effect

$$
\begin{tikzcd}
 & Z \arrow[dr] & \\
T \arrow[ur] \arrow[rr] & & Y
\end{tikzcd}
$$

$$\tau = \mathbb{E}[Y(1, Z(1))] - \mathbb{E}[Y(0, Z(0))]$$

$$\tau = \delta^Z(t) + \zeta(1 - t)$$

Multiple independent mediators

NIE and NDE are non-parametrically identified under the assumption

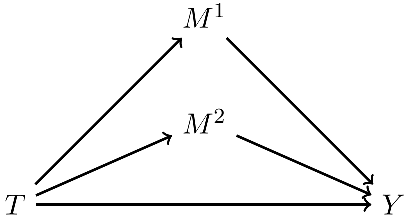
SI (Imai et al 2013)

For all t, t', m^1, m^2

$$\{Y(t, m^1, m^2), M^1(t'), M^2(t'')\} \perp\!\!\!\perp T | X = x \quad (3)$$

$$Y(t', m^1, M^2(t')) \perp\!\!\!\perp M^1(t) | T = t, X = x \quad (4)$$

$$Y(t', M^1(t'), m^2) \perp\!\!\!\perp M^2(t) | T = t, X = x \quad (5)$$



Multiple independent mediators

NIE and NDE are non-parametrically identified under the assumption

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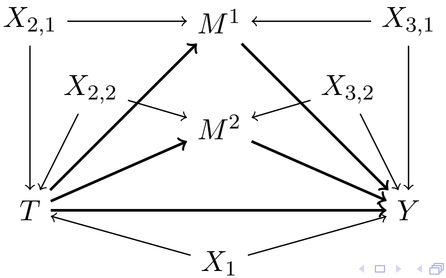
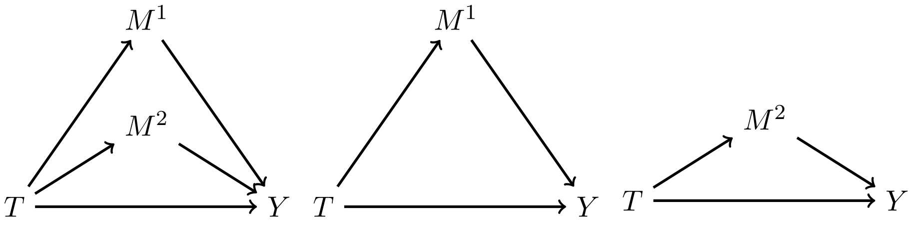
For all t, t', m^1, m^2

$$\{Y(t, m^1, m^2), M^1(t'), M^2(t'')\} \perp\!\!\!\perp T | X = x \tag{3}$$
$$Y(t', m^1, M^2(t')) \perp\!\!\!\perp M^1(t) | T = t, X = x \tag{4}$$
$$Y(t', M^1(t'), m^2) \perp\!\!\!\perp M^2(t) | T = t, X = x \tag{5}$$



Simple mediation analysis in parallel

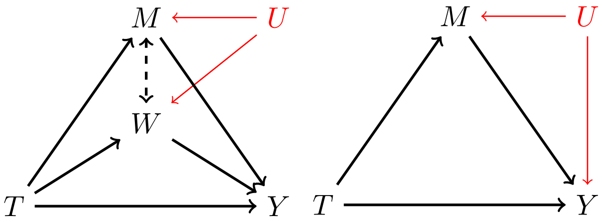
When mediators are idependent, a simple approach is to process one simple mediation analysis per mediator



- Approach implemented in the `mediation` package
- This will lead to biased estimates of the direct effect
- Moreover this approach is not valid if mediators show spurious correlation after adjustment on T and X

The problem with correlated mediators

- Mediators can be correlated because of an unmeasured common cause U
- In this case U is an unmeasured confounder between M and Y



- SI is violated $\Rightarrow$ standard analysis leads to biased estimates of the direct and indirect effects

- Treatment:

$$T \sim \mathcal{B}(0.3)$$

- Mediators:

$$\begin{pmatrix} M^1(t) \\ M^2(t') \end{pmatrix} \sim \mathcal{N}\left(\mu = \begin{pmatrix} \frac{1}{2} + \frac{3}{2} \times t \\ 2 + 6 \times t' \end{pmatrix}, \Sigma = \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}\right)$$

  where $\rho \in]-1, 1[$

- Outcome:

$$Y\left(t, M^1(t'), M^2(t'')\right) = 4 + 35 \times t + 2M^1(t') + 3M^2(t'') + \epsilon$$

where $\epsilon \sim \mathcal{N}(0, 1)$

Empirical illustration

Results of the `mediation` package

Effects	$\delta^1 = 3$	$\delta^2 = 24$	$\delta^Z = 27$	$\zeta = 35$
$\rho = 0$				
S.A. M^1	2.68[1.98;3.52]	-	-	59.22[58.05;60.34]
S.A. M^2	-	23.69[21.81;25.52]	-	38.2 [36.64;39.84]
$\rho = 0.9$				
S.A. M^1	8.30 [6.95;9.72]	-	-	53.6 [53.04;54.24]
S.A. M^2	-	34.83 [33.21;36.5]	-	27.06 [26.16;27.99]

Effects	$\tau = 62$
$\rho = 0$	
Simple M^1	61.9[60.82;63.00]
S.A M^2	61.89 [60.86;62.98]
$\rho = 0.9$	
S.A M^1	61.9 [60.39;63.36]
S.A M^2	61.9 [60.45;63.32]

S.A. : simple analysis

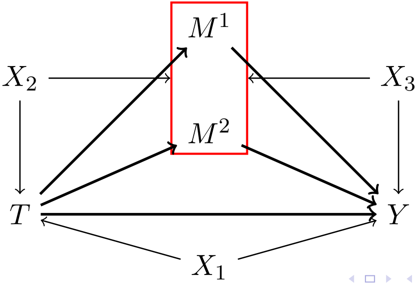
We replace the previous SI assumption with

Sequential Ignorability for Multiple Mediators Assumption (Jérolon et al 2018):

For all t, t', t'', m, w:

$$\{Y(t,m,w), M(t'), W(t'')\} \perp\!\!\!\perp T | X = x \quad (6)$$

$$Y(t,m,w) \perp\!\!\!\perp \left(M(t'), W(t'')\right) | T, X = x \quad (7)$$



Principal theoretical result

Theorem (Jérolon et al 2018)

The joint NIE and NDE are identified non-parametrically by:

$$\begin{aligned}\delta^Z(t) &= \int_{\mathbb{R}^K} \mathbb{E}\left[Y|Z=z, T=t\right]\{\mathrm{d}F_{Z|T=1}(z) - \mathrm{d}F_{Z|T=0}(z)\} \\ \zeta(t) &= \int_{\mathbb{R}^K} \mathbb{E}(Y|Z=z, T=1) - \mathbb{E}(Y|Z=z, T=0)\mathrm{d}F_{Z|T=t}(z)\end{aligned}$$

The NIE of the k-th mediator is given by

$$\begin{aligned}\delta^k(t) &= \int_{\mathbb{R}^K} \mathbb{E}\left[Y|M^k=m, W^k=w, T=t\right] \\ &\quad \{\mathrm{d}F_{(M^k(1), W^k(t))}(m,w) - \mathrm{d}F_{(M^k(0), W^k(t))}(m,w)\}\end{aligned}$$

N.B. Conditioning on X omitted for sake of simplicity

Corollary: LSEM

Consider the LSEM:

$$
\begin{aligned}
Z &= \alpha_2 + \beta_2^\Gamma T + \Upsilon_2, \text{ where } \Upsilon_2 \sim \mathcal{N}(0, \Sigma) \\
Y &= \alpha_3 + \beta_3 T + \gamma^\Gamma Z + \epsilon_3
\end{aligned}
$$

Under SIMMA the NIE of the k-th mediator is identified by

$$\delta^k(0) = \delta^k(1) = \gamma_k \beta_2^k$$

Moreover the joint NIE is given by

$$\delta^Z(t) = \sum_{k=1}^{K} \delta^k(t)$$

and the NDE is

$$\zeta(0) = \zeta(1) = \beta_3$$

Corollary: binary outcome (I)

Consider the following model, where Y is binary:

$$\begin{aligned} Z &= \alpha_2 + \beta_2^\Gamma T + \Upsilon_2, \text{ where } \Upsilon_2 \sim \mathcal{N}(0, \Sigma) \\ Y^* &= \alpha_3 + \beta_3 T + \gamma^\Gamma Z + \epsilon_3, \text{ where } \epsilon_3 \sim \mathcal{N}(0, \sigma_3^2) \text{ ou } \mathcal{L}(0,1) \\ Y &= \mathbb{1}_{\{Y^*>0\}} \end{aligned}$$

Under SIMMA the NIE of the 1st mediator is given by:

$$\begin{aligned} \delta^1(t) &= F_U\left((\alpha_3 + \sum_{k=1}^K \gamma_k \alpha_2^k) + (\beta_3 + \sum_{k=2}^K \gamma_k \beta_2^k)t + \gamma_1 \beta_2^1 \times 1\right) \\ &\quad - F_U\left((\alpha_3 + \sum_{k=1}^K \gamma_k \alpha_2^k) + (\beta_3 + \sum_{k=2}^K \gamma_k \beta_2^k)t + \gamma_1 \beta_2^1 \times 0\right) \end{aligned}$$

Corollary: Binary Outcome (II)

... where, for a probit regression of Y:

$$F_U(z) = \Phi\left(\frac{z}{\sqrt{\sigma_3^2 + \sum_{k=1}^K \sum_{j=1}^K \gamma_k \gamma_j cov(\epsilon_2^k, \epsilon_2^j)}}\right)$$

and for a logit regression of Y:

$$F_U(z) = \int_{\mathbb{R}} \Phi\left(\frac{z - e_3}{\sqrt{\sum_{k=1}^K \sum_{j=1}^K \gamma_k \gamma_j cov(\epsilon_2^k, \epsilon_2^j)}}\right) \frac{e^{e_3}}{(1+e^{e_3})^2} \, \mathrm{d}e_3$$

Similar formulas for the joint NIE and NDE

Algorithm for parametric inference (quasi-Bayesian MC)

Instead of the previous corollaries one can apply the following algorithm:

- Step 1. Fit models `Z~T+X` and `Y~T+Z+X`
- Step 2. Sample many times the model parameters from their sampling distribution
- Step 3. For each draw, repeat the following steps:
  a. Simulate the potential values of the mediators
  b. Simulate the the potential outcome
  c. Compute the effect of interest as mean of the appropriate potential outcomes
- Step 4. Compute summary statistics from the empirical distribution of the effect of interest obtained as above

Simulations: simple analysis vs our multiple analysis

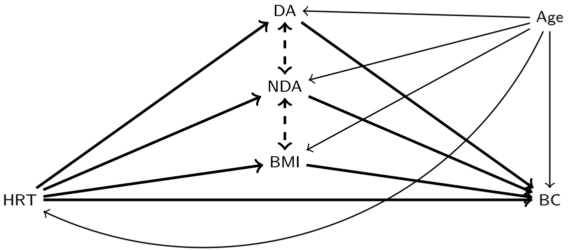
Effects	$\delta^1 = 3$	$\delta^2 = 24$	$\delta^Z = 27$	$\zeta = 35$
$\rho = 0$				
S.A. M^1	2.68[1.98;3.52]	-	-	59.22[58.05;60.34]
S.A. M^2	-	23.69[21.81;25.52]	-	38.2 [36.64;39.84]
M.A.	2.78 [2.26;3.27]	23.85 [22.7;24.97]	26.63 [25.35 ; 27.85]	35.27 [34.53;36.02]
$\rho = 0.9$				
S.A. M^1	8.30 [6.95;9.72]	-	-	53.6 [53.04;54.24]
S.A. M^2	-	34.83 [33.21;36.5]	-	27.06 [26.16;27.99]
M.A.	2.94 [2.35;3.58]	24.13 [22.33;25.95]	27.07 [25.36 ; 28.75]	34.83 [33.61;36.2]

Effects	$\tau = 62$
$\rho = 0$	
S.A. M^1	61.9[60.82;63.00]
S.A. M^2	61.89 [60.86;62.98]
M.A.	61.89 [60.71;62.95]
$\rho = 0.9$	
S.A. M^1	61.9 [60.39;63.36]
S.A. M^2	61.9 [60.45;63.32]
M.A.	61.9 [60.75;63.07]

S.A. : simple analysis in parallel, `mediation` package

M.A.: our approach

Application: hormone replacement therapy and breast cancer



HRT:	Hormone replacement therapy
DA:	Dense Area
NDA:	Non Dense Area
BMI:	Body Mass Index
BC:	Breast Cancer

Effect	Estimate and 95%CI
Indirect through DA	0.0251 [0.0121 ; 0.0414]
Indirect through NDA	0.0122 [0.0019 ; 0.0255]
Indirect through BMI	-0.0149 [-0.0305 ; -0.0038]
Direct	0.0800 [0.0160 ; 0.1471]
ATE	0.1024 [0.0358 ; 0.1660]

Data from the E3N cohort

Conclusions

- We propose to extend the existing method for multiple mediation to the situation of non-causally correlated mediators
- Preprint available
- R package `multimediate` under development:
  - Current implementation works for continuous or binary outcomes and continuous mediators
  - Coming very soon: ordered categorical mediators (needs to be validated)
- In progress:
  - Mediation "en bloc" of clusters of correlated mediators
  - Applications to different types of data, e.g. effect of smoking on cancer risk mediated by CpGs in candidate methylation regions
- In perspective:
  - High-dimensional mediation?

Some references

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