Causal Mediation Analysis with Non-linear Models, Multiple Mediators, and DAGs

James Long
Department of Biostatistics
MD Anderson Cancer Center

SMU Statistics Seminar
November 13, 2020

Outline

Causation and Mediation

Causal Inference with Causal Directed Acyclic Graphs

Mediation Analysis with Causal DAGs

Our Framework

Example: TCGA Kidney Cancer

Discussion

Outline

Causation and Mediation

Causal Inference with Causal Directed Acyclic Graphs

Mediation Analysis with Causal DAGs

Our Framework

Example: TCGA Kidney Cancer

Discussion

Causation and Mediation

Causation in science and medicine:

- Statins reduce incidence of heart attack

- SNP increases protein expression

- BRCA mutations cause breast cancer

Causation and Mediation

Causation in science and medicine:

- Statins reduce incidence of heart attack

  by lowering cholesterol.

- SNP increases protein expression

  by increasing mRNA expression.

- BRCA mutations cause breast cancer

  by inhibiting DNA repair.

Causation and Mediation

Causation in science and medicine:

- Statins reduce incidence of heart attack

  by lowering cholesterol.

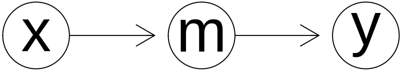
- SNP increases protein expression

  by increasing mRNA expression.

- BRCA mutations cause breast cancer

  by inhibiting DNA repair.

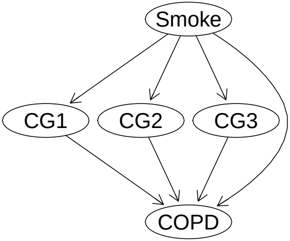
Causal mediators: variables that facilitate a causal relation.



x changes *y* by altering *m*.

Smoking → Methylation → COPD

- Chronic obstructive pulmonary disease (COPD): chronic inflammation of lungs, obstructs airflow
- Smoking is leading risk factor.
- Hypothesis: Smoking causes COPD by **methlyating** genes. Gaynor et al. [2018], Wan et al. [2012]



Data:

- Smoke = 1 for smoker, 0 no
- CG1,CG2,CG3 = methylation at 3 sites
- COPD = 1 or 0 disease status

Scientific Questions:

- Does methylation mediate smoking-COPD causal relation?
- Which sites?
- How much of the total effect is mediated by methylation?

Overview of Talk

- Causal Modeling with DAGs
  - Is m a mediator?
  - What percentage of total effect of x on y is mediated by m? Are there other causal pathways?
  - Control for confounders
- Our Framework: `mediateR` package
  - Estimation with non–linear models
  - Multiple mediators (e.g. many gene expressions)
  - Effect Scales
- Example: TCGA Kidney Renal Cell Carcinoma Data
- Discussion

Outline

Causation and Mediation

Causal Inference with Causal Directed Acyclic Graphs

Mediation Analysis with Causal DAGs

Our Framework

Example: TCGA Kidney Cancer

Discussion

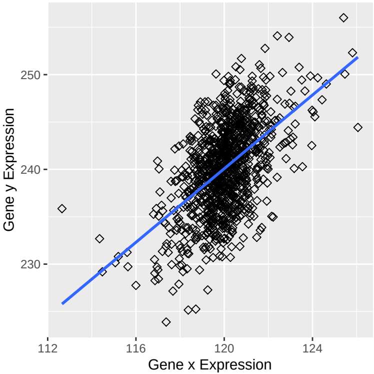
Statistical and Causal Models

- x = Gene x Expression
- y = Gene y Expression
- Fit linear model:

$$y \approx 1.94x + 6.88$$

- How do we interpret model predictions at x=124?

$$y \approx 1.94 \times 124 + 6.88 \approx 248$$



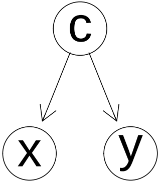
Association: If I **see** x=124, y ≈ 248. Passive observers of nature.
Causation: If I set (or **do**) x=124, y ≈ 248. Intervene in nature.

The statistical model (i.e. set of assumptions) does not permit the causal conclusion. Need a causal model for data.

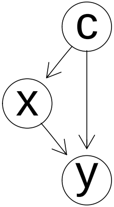
DAG Definition

A **directed acyclic graph** (DAG) is a set of edges (directed arrows) between vertices (variables) such that there are no loops (acyclic).

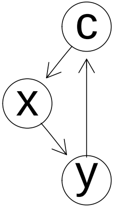
Example: Vertices = variables = (c, x, y)



DAG



DAG



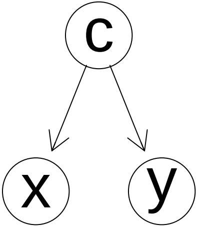
Not a DAG (loop)

Causal DAG

Causal DAGs encode causal assumptions by specifying the process by which variables are generated.

Example

(c,x,y) are three gene expression levels



$$
\begin{aligned}
c &\leftarrow f_c(\epsilon_c) \\
x &\leftarrow f_x(c, \epsilon_x) \\
y &\leftarrow f_y(c, \epsilon_y)
\end{aligned}
$$

for some functions f_c, f_x, f_y and independent[a] random variables $(\epsilon_c, \epsilon_x, \epsilon_y)$.

Not true: $y \leftarrow f_y(x, c, \epsilon_y)$ because no x to y arrow.

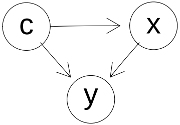
[a] This is the Markovian assumption. More discussion later in talk.

External Interventions with Causal DAGs

Definition: $y^{x=0}$ (counterfactual) is the value of y if x is set to 0

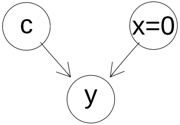
Example of Computing $y^{x=0}$ using Causal DAG:

Original Causal DAG:



$$c \leftarrow f_c(\epsilon_c)$$
$$x \leftarrow f_x(c, \epsilon_x)$$
$$y \leftarrow f_y(x, c, \epsilon_y)$$

Mutilated DAG (intervention on x):



$$c \leftarrow f_c(\epsilon_c)$$
$$x \leftarrow 0$$
$$y \leftarrow f_y(x = 0, c, \epsilon_y)$$

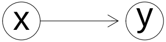
Summarizing the Causal Effect: (Pearl [2009])

- $p(y^{x=0} = y) \equiv p(y|do(x = 0))$
- $\mathbb{E}[y^{x=0}] \equiv \mathbb{E}[y|do(x = 0)] = \int yp(y|do(x = 0))dy$

$y^{x=2}$ and $x^{y=2}$ in Simple Model

Assumptions:

(x, y) is jointly normal

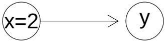


$$x \leftarrow \mu + \epsilon_x$$

$$y \leftarrow \beta_0 + \beta_x x + \epsilon_y$$

where $\epsilon_x \sim N(0, \sigma_x^2)$ and $\epsilon_y \sim N(0, \sigma_y^2)$, *independent*

$y^{x=2}$ (value of y when x set to 2):

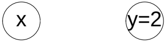


$$x \leftarrow 2$$

$$y \leftarrow \beta_0 + 2\beta_x + \epsilon_y$$

$$\mathbb{E}[y|do(x=2)] = \mathbb{E}[y|x=2] = \beta_0 + 2\beta_x$$

$x^{y=2}$ (value of x when y set to 2):



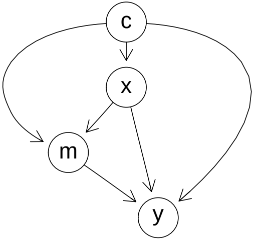
$$x \leftarrow \mu + \epsilon_x$$

$$y \leftarrow 2$$

$$\mathbb{E}[x|do(y=2)] = \mathbb{E}[x] = \mu$$

More Complex Causal Model

- c = SNP
- x = gene expression (binarized to high / low)
- m = protein expression (continuous)
- y = phenotype (continuous)



$$c \leftarrow f_c(\epsilon_c)$$

$$x \leftarrow f_x(c, \epsilon_x)$$

$$m \leftarrow f_m(x, c, \epsilon_m) = \alpha_x x + \alpha_c c + \epsilon_m$$

$$y \leftarrow f_y(x, c, m, \epsilon_y) = \beta_x x + \beta_c c + \beta_m m + \epsilon_y$$

orange: causal assumptions from DAG

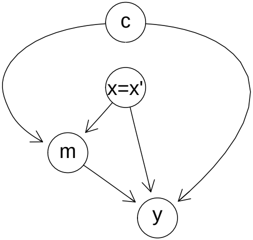
blue: statistical assumptions

Goal: Compute expected change in phenotype when changing gene expression from low ($x = 0$) to high ($x = 1$)

$$TE(0, 1) \equiv \mathbb{E}[y^{x=1}] - \mathbb{E}[y^{x=0}] = \mathbb{E}[y|do(x = 1)] - \mathbb{E}[y|do(x = 0)]$$

Computation of Total Effect

For $x' = 0$ or 1, mutilated graph is:



$$
\begin{aligned}
c &\leftarrow f_c(\epsilon_c) \\
x &\leftarrow x' \\
m &\leftarrow f_m(x = x', c, \epsilon_m) = \alpha_x x' + \alpha_c c + \epsilon_m \\
y &\leftarrow f_y(x = x', c, m, \epsilon_y) = \beta_x x' + \beta_c c + \beta_m m + \epsilon_y
\end{aligned}
$$

After some algebra

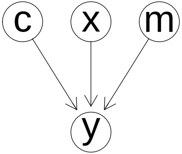
$$\mathbb{E}[y|do(x = x')] = (\beta_x + \alpha_x \beta_m)x' + z$$

where z does not depend on x'. So

$$
\begin{aligned}
TE(0,1) &= \mathbb{E}[y|do(x = 1)] - \mathbb{E}[y|do(x = 0)] \\
&= \underbrace{\beta_x}_{\text{direct effect}} + \underbrace{\alpha_x \beta_m}_{\substack{\text{indirect effect} \\ \text{passing through m}}}
\end{aligned}
$$

Variables to Control For

- "Controlling for everything" gives **wrong** result:
  - regress y on (x, m, c)
  - coefficient on x is β_x
  - β_x ignores $x \to m \to y$ effect
  - gives correct TE for:



- "Controlling for nothing" gives **wrong** result:
  - $TE \neq \mathbb{E}[y|x=1] - \mathbb{E}[y|x=0]$
- "Controlling for c" gives **correct** result:
  - regress y on (x, c)
  - coefficient on x is $\beta_x + \beta_m \alpha_x$

Message: Determining variables to control for requires assumptions on the causal structure of data. DAG can express these assumptions formally.

Summary of Causal DAGs

- DAGs encode causal assumptions
- Enable computation of effects of interventions
- Judea Pearl pioneered this approach, see Pearl [2009]

Outline

Causation and Mediation

Causal Inference with Causal Directed Acyclic Graphs

Mediation Analysis with Causal DAGs

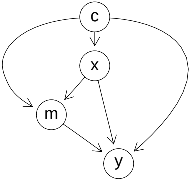
Our Framework

Example: TCGA Kidney Cancer

Discussion

Mediation in Linear Models

Developed by Baron and Kenny [1986], Sobel [1982], others.



- Direct Effect $\equiv \beta_x$
- Indirect Effect $\equiv \alpha_x \beta_m$
- Total Effect $\equiv \beta_x + \alpha_x \beta_m$

$\equiv$ is "by definition"

<u>Statistical Inference:</u> Fit two least squares models:

1. m | x,c
2. y | x,m,c

- Point estimators, confidence intervals, tests, based on parameter estimates e.g.

$$H_0 : \alpha_x \beta_m = 0 \text{ i.e. m is not a mediator}$$

$$H_a : \alpha_x \beta_m \neq 0 \text{ i.e. m is a mediator}$$

Limitation: Only applies to linear models, single mediator.

Direct Effect: General Model Definition

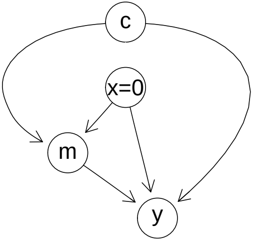
The direct effect* of changing x from 0 to 1 is

$$y^{x=1,m^{x=0}} - y^{x=0}$$

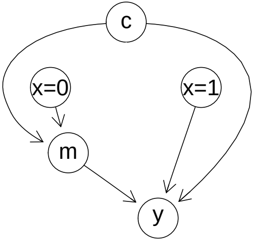
where

$$\begin{aligned} y^{x=1,m^{x=0}} &= \text{the value of } y \text{ when setting } x = 1 \text{ for the direct path} \\ & \text{from } x \rightarrow y \text{ while generating } m \text{ as if } x = 0 \\ y^{x=0} &= \text{the value of } y \text{ when setting } x = 0 \end{aligned}$$

$y^{x=0}$



$y^{x=1,m^{x=0}}$



* Based on Pearl [2001] and VanderWeele and Vansteelandt [2010] definitions.

Natural Direct Effect Interpretation

- $x = 1$ if smoker, 0 no
- $m =$ gene methylation
- $y = 1$ if COPD, 0 if no

The direct effect

$$y^{x=1,m^{x=0}} - y^{x=0}$$

is the change in COPD if someone smokes but takes a methylation prevention drug which blocks any potential change in COPD induced via methylation.

Natural Direct Effect

The **natural direct effect** is:

$$DE(0,1) = \mathbb{E}[y^{x=1,m^{x=0}}] - \mathbb{E}[y^{x=0}]$$

where assuming causal DAG structure*:

$$\mathbb{E}[y^{x=1,m^{x=0}}] = \int_{m,c} \mathbb{E}[y|x=1,m,c]p(m|x=0,c)p(c)dmdc$$

$$\mathbb{E}[y^{x=0}] = \int_{m,c} \mathbb{E}[y|x=0,m,c]p(m|x=0,c)p(c)dmdc$$

* See Pearl [2001].

Indirect Effect: General Model Definition

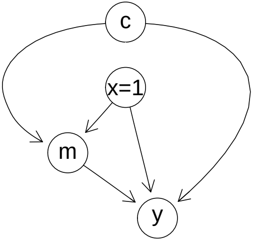
The indirect effect* of changing x from 0 to 1 is

$$y^{x=1} - y^{x=1,m^{x=0}}$$

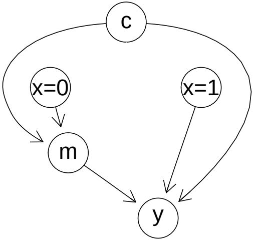
where

$$\begin{aligned} y^{x=1,m^{x=0}} &= \text{ the value of } y \text{ when setting } x = 1 \text{ for the direct path} \\ &\quad\ \text{from } x \to y \text{ while generating } m \text{ as if } x = 0 \\ y^{x=1} &= \text{ the value of } y \text{ when setting } x = 1 \end{aligned}$$

$y^{x=1}$



$y^{x=1,m^{x=0}}$



*Based on VanderWeele and Vansteelandt [2010] and others. See Pearl [2001] for alternative definition.

Natural Indirect Effect

The **natural indirect effect** is:

$$IE(0,1) = \mathbb{E}[y^{x=1}] - \mathbb{E}[y^{x=1,m^{x=0}}]$$

where assuming causal DAG structure:

$$\mathbb{E}[y^{x=1,m^{x=0}}] = \int_{m,c} \mathbb{E}[y|x=1,m,c]p(m|x=0,c)p(c)dmdc$$
$$\mathbb{E}[y^{x=1}] = \int_{m,c} \mathbb{E}[y|x=1,m,c]p(m|x=1,c)p(c)dmdc$$

Mediation Formula

Mediation formula:

$$
\begin{aligned}
TE(x', x'') &= \mathbb{E}[y|do(x = x'')] - \mathbb{E}[y|do(x = x')] \\
&= DE(x', x'') + IE(x', x'')
\end{aligned}
$$

- Previously x'=0 and x"=1.
- For linear models, effects only depend on $(x'' - x')$:
  - $DE(x', x'') = \beta_x(x'' - x')$
  - $IE(x', x'') = \alpha_x \beta_m (x'' - x')$

Outline

Causation and Mediation

Causal Inference with Causal Directed Acyclic Graphs

Mediation Analysis with Causal DAGs

Our Framework

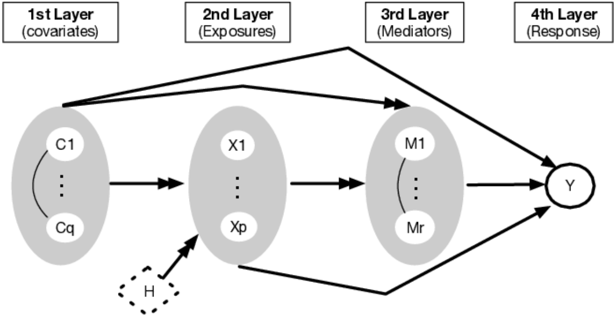
Example: TCGA Kidney Cancer

Discussion

Causal Mediation for Genomic Data Sets

- Many exposures and potential mediators
  - mRNA expression of many genes
  - Protein expression of many genes
- Non–linear response models
  - Logistic model for disease status
  - Cox PH model for survival time

Summary of Our Framework



- Numerical approximation of DE and IE integrals
- Multiple exposures x, Multivariate mediators m, Non–linear response models y
- Various Effect Scales: Mean, Odds, Restricted Mean

`mediateR` https://github.com/longjp/mediateR

Estimation

Require estimate of:

$$\mathbb{E}[y^{x=1,m^{x=0}}] = \int_{m,c} \mathbb{E}[y|x=1,m,c]p(m|x=0,c)p(c)dmdc$$

Approaches to estimating effects:

- Rare disease assumption with logistic response model
    - Assume rare disease ($P(y=1)$ small)
    - Effects are approximately linear combinations of path coefficients [VanderWeele and Vansteelandt, 2010, Huang et al., 2014]
- Common disease assumption with logistic response model
    - Use probit approximation to logistic [Gaynor et al., 2018]
- **Numerically approximate integral: Discuss now**
    - Use empirical distribution of c to approximate $p(c)$
    - Draw $\widehat{m}$ from plug–in estimate of $p(m|x=0,c)$
    - Use plug–in estimate of $\mathbb{E}[y|x=1,m,c]$

Numerical Integration in Logistic Model

Statistical Model: (c_i, x_i, m_i, y_i) i.i.d. from

- $m = \alpha^{(x)}x + \alpha^{(c)}c + \alpha^{(0)} + \epsilon$
- $y \sim Bern((1 + e^{-(x^T\beta^{(x)} + m^T\beta^{(m)} + c^T\beta^{(c)} + \beta^{(0)})})^{-1})$

$\alpha^{(x)} \in \mathbb{R}^r$, $\alpha^{(c)} \in \mathbb{R}^{r\times q}$, $\alpha^{(0)} \in \mathbb{R}^r$, $\epsilon \sim N(0, \Sigma_\epsilon)$, $\Sigma_\epsilon \in \mathbb{R}^{r\times r}$, $\beta^{(x)} \in \mathbb{R}^1$, $\beta^{(c)} \in \mathbb{R}^q$, $\beta^{(m)} \in \mathbb{R}^r$, and $\beta^{(0)} \in \mathbb{R}^1$.

Then:

$$\begin{aligned}\mathbb{E}[y^{x=1,m^{x=0}}] &= \int_{m,c} \mathbb{E}[y|x=1,m,c]p(m|x=0,c)p(c)dmdc \\ &\approx \frac{1}{n}\sum_{i=1}^{n} \widehat{\mathbb{E}}[y|x=1,\widehat{m}_i,c_i]\end{aligned}$$

where

$$\widehat{m}_i \sim N(m; \widehat{\alpha}^{(x)}0 + \widehat{\alpha}^{(c)}c_i + \widehat{\alpha}^{(0)}, \widehat{\Sigma_\epsilon})$$

$$\widehat{\mathbb{E}}[y|x=1,\widehat{m}_i,c_i] = \frac{1}{1 + e^{-\widehat{\beta}^{(x)}(1) - \widehat{m}_i^T\widehat{\beta}^{(m)} - c_i^T\widehat{\beta}^{(c)} - \widehat{\beta}^{(0)}}}$$

Notes on Numerical Integration

- Calculations for $\mathbb{E}[y^{x=1}]$ and $\mathbb{E}[y^{x=0}]$ similar
- More generally, $x = 0$ and $x = 1$ can be replaced by any $x = x'$ and $x = x''$
- Similar strategy employed for y with Cox proportional hazards model
- Bootstrap sample (c_i, x_i, m_i, y_i) to obtain sampling distributions of DE, IE, TE
    - CI and hypothesis tests based on bootstrap quantiles

Effect Scale for Logistic Response Model

- Odds ratios useful for summarizing effects with binary responses
- For logistic model, effects may be defined on odds scale:

$$DE^o(0,1) \equiv \frac{\frac{\mathbb{E}[y^{x=1,m^{x=0}}]}{1-\mathbb{E}[y^{x=1,m^{x=0}}]}}{\frac{\mathbb{E}[y^{x=0}]}{1-\mathbb{E}[y^{x=0}]}} \quad IE^o(0,1) \equiv \frac{\frac{\mathbb{E}[y^{x=1}]}{1-\mathbb{E}[y^{x=1}]}}{\frac{\mathbb{E}[y^{x=1,m^{x=0}}]}{1-\mathbb{E}[y^{x=1,m^{x=0}}]}}$$

- Mediation Formula on the Odds Scale:

$$TE^o(0,1) \equiv \frac{\frac{\mathbb{E}[y^{x=1}]}{1-\mathbb{E}[y^{x=1}]}}{\frac{\mathbb{E}[y^{x=0}]}{1-\mathbb{E}[y^{x=0}]}} = DE^o(0,1) \times IE^o(0,1)$$

Proposed by VanderWeele and Vansteelandt [2010]

Effect Scale for Survival Response

The mean of y restricted to L is

$$\mathbb{E}[\min(y, L)]$$

where L is some constant

- Restricted mean scale popular in survival applications because mean estimate has high variance
- Direct and Indirect Effects on restricted mean scale

$$DE^R(0,1) \equiv \mathbb{E}[\min(y^{x=1,m^{x=0}}, L)] - \mathbb{E}[\min(y^{x=0}, L)]$$
$$IE^R(0,1) \equiv \mathbb{E}[\min(y^{x=1}, L)] - \mathbb{E}[\min(y^{x=1,m^{x=0}}, L)]$$

- Mediation Formula on Restricted Mean Scale:

$$\begin{aligned} TE^R(0,1) &\equiv \mathbb{E}[\min(y^{x=1}, L)] - \mathbb{E}[\min(y^{x=0}, L)] \\ &= DE^R(0,1) + IE^R(0,1) \end{aligned}$$

Outline

Causation and Mediation

Causal Inference with Causal Directed Acyclic Graphs

Mediation Analysis with Causal DAGs

Our Framework

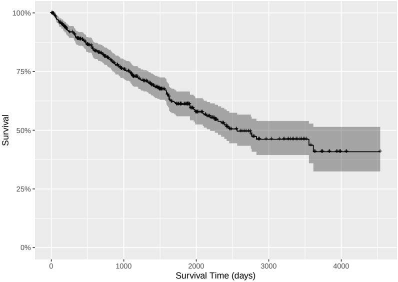
Example: TCGA Kidney Cancer

Discussion

TCGA Kidney Renal Cell Carcinoma

$n = 470$ patients with:

- Clinical features, e.g. survival time
- RPPA Protein Expression
- mRNA Expression



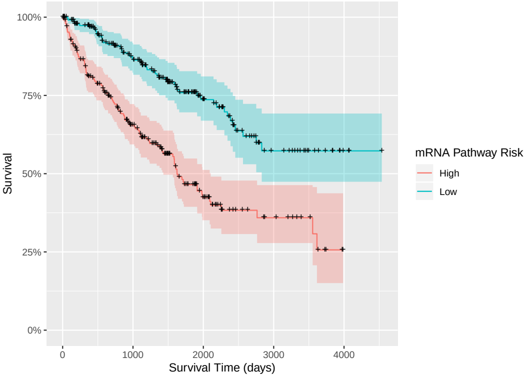
Questions:

1. What gene expressions are associated with / causing changes in survival?
2. Are these changes being mediated at the protein level?

Data available: https://portal.gdc.cancer.gov/

Gene Expression–Survival Correlations

- Network et al. [2013] identified 5 core metabolic pathways: PTEN, TCA cycle, Fatty acid synthesis, AMPK, Pentose phosphate
- Summarize each pathway at mRNA level with 1st principal component
- Fit Cox model on survival given pathway scores
- Survival curves by pathway score risk:



Mediation Model

- mRNA expression can alter protein expression (via increased translation by ribosomes)
- Treat 5 proteins as mediators
  AMPKA alpha, AMPK pT172, ACC pS79, ACC, and PTEN
- For each mRNA pathway
  - Compute DE^R, IE^R, TE^R with $L = 2000$ at
    - $x' =$ 5th percentile of pathway score
    - $x'' =$ 95th percentile of pathway score
- Interpretation of DE^R for Pentose Phosphate
  - 1) $y^{x=x'', m^{x=x'}}$ = generate the mediators from Pentose phosphate at 5th percentile and then survival with Pentose phosphate at 95th percentile.
  - 2) $y^{x=x'}$ = Generate both mediators and response with Pentose phosphate at 5th percentile.
  - Take expected difference (lifelime restricted to 2000) of 1 - 2

Results

Pathway	Indirect		Direct		Total	
PTEN	-29	[-146,77]	203	[-49,409]	174	[-74,384]
TCA cycle	40	[-23,120]	289	[42,494]	329	[117,525]
Fatty acid synthesis	-156	[-339,20]	-290	[-537,-91]	-446	[-654,-268]
AMPK	23	[-74,126]	8	[-292,316]	30	[-245,328]
Pentose phosphate	-94	[-247,79]	-181	[-511,91]	-274	[-574,-29]

Table 1: Indirect, Direct, and Total effects and 95% confidence intervals (in days) of metabolomic mRNA expression as mediated by protein expression.

Under model assumptions:

- TCA cycle, Fatty Acid Synthesis, Pentose phosphate have significant total effects (at $\alpha = 0.05$)
- Fatty acid synthesis largest indirect effect estimate, but not significant (at $\alpha = 0.05$)

Outline

Causation and Mediation

Causal Inference with Causal Directed Acyclic Graphs

Mediation Analysis with Causal DAGs

Our Framework

Example: TCGA Kidney Cancer

Discussion

Summary

- Causal DAGs graphically represent a set of assumptions about the causal structure of the data.
- Causal DAG + Statistical model → predict interventions
- Assumptions implied by causal DAGs may be implausible, especially for observational genetic data.
- Manuscript describing work: https://arxiv.org/abs/2011.06061
- Software Resources
  - `mediateR` (https://github.com/longjp/mediateR): package I codeveloped for implementing models. Joint work with Kim-Anh Do, Min Jin Ha, Ehsan Irajizad (MDACC Biostatistics), and James Doecke (CSIRO).
  - `mediation` (https://cran.r-project.org/web/packages/mediation/index.html): package with partially overlapping functionality (Imai et al. [2010])

Inferring Causal Network from Data

Causal Discovery: Inferring causal structure (e.g. DAG) from data.

- PC algorithm: Estimates skeleton of DAG

  (Kalisch and Bühlmann [2007], Spirtes et al. [2000], Ha et al. [2016])

- Invariant Causal Prediction: Use mix of observational / experimental data to determine entire causal structure

  Peters et al. [2016]

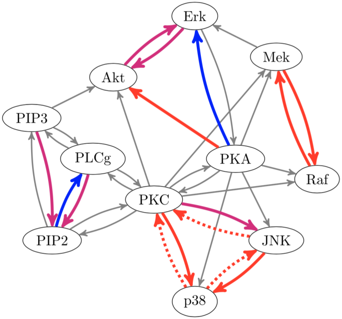


Figure source Meinshausen et al. [2016]

Potential Outcomes Framework

- **DAG Framework**:
  - Graph specifies causal assumptions.
  - $y^{x=0}$ and $y^{x=1}$ (counterfactuals) distributions inferred from graph.
  - Developed / advocated by: Pearl [2009], Spirtes et al. [2000], Wright [1934]
- **Potential Outcomes Framework:**
  - $y^{x=0}$ and $y^{x=1}$ (potential outcomes) are primitive notions.
  - Causal knowledge conveyed via conditional independence assumptions, e.g.

$$y^{x=x'} \perp\!\!\!\perp x | c \;\; \forall \;\; x'$$

  - Developed / advocated by: Rubin [2005], Splawa-Neyman et al. [1990]
  - "Direct and indirect causal effects via potential outcomes" Rubin [2004]

Thank you. Questions?

Bibliography I

R. M. Baron and D. A. Kenny. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of personality and social psychology*, 51(6):1173, 1986.

S. M. Gaynor, J. Schwartz, and X. Lin. Mediation analysis for common binary outcomes. *Statistics in medicine*, 2018.

M. J. Ha, W. Sun, and J. Xie. Penpc: A two-step approach to estimate the skeletons of high-dimensional directed acyclic graphs. *Biometrics*, 72(1):146–155, 2016.

Y.-T. Huang, T. J. VanderWeele, and X. Lin. Joint analysis of snp and gene expression data in genetic association studies of complex diseases. *The annals of applied statistics*, 8(1):352, 2014.

K. Imai, L. Keele, and T. Yamamoto. Identification, inference and sensitivity analysis for causal mediation effects. *Statistical science*, pages 51–71, 2010.

M. Kalisch and P. Bühlmann. Estimating high-dimensional directed acyclic graphs with the pc-algorithm. *Journal of Machine Learning Research*, 8(Mar):613–636, 2007.

N. Meinshausen, A. Hauser, J. M. Mooij, J. Peters, P. Versteeg, and P. Bühlmann. Methods for causal inference from gene perturbation experiments and validation. *Proceedings of the National Academy of Sciences*, 113 (27):7361–7368, 2016.

C. G. A. R. Network et al. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature*, 499 (7456):43, 2013.

J. Pearl. Direct and indirect effects. In *Proceedings of the seventeenth conference on uncertainty in artificial intelligence*, pages 411–420. Morgan Kaufmann Publishers Inc., 2001.

J. Pearl. *Causality*. Cambridge university press, 2009.

J. Peters, P. Bühlmann, and N. Meinshausen. Causal inference by using invariant prediction: identification and confidence intervals. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 78(5): 947–1012, 2016.

D. B. Rubin. Direct and indirect causal effects via potential outcomes. *Scandinavian Journal of Statistics*, 31(2): 161–170, 2004.

Bibliography II

D. B. Rubin. Causal inference using potential outcomes: Design, modeling, decisions. *Journal of the American Statistical Association*, 100(469):322–331, 2005.

M. E. Sobel. Asymptotic confidence intervals for indirect effects in structural equation models. *Sociological methodology*, 13:290–312, 1982.

P. Spirtes, C. N. Glymour, R. Scheines, D. Heckerman, C. Meek, G. Cooper, and T. Richardson. *Causation, prediction, and search*. MIT press, 2000.

J. Splawa-Neyman, D. M. Dabrowska, and T. Speed. On the application of probability theory to agricultural experiments. essay on principles. section 9. *Statistical Science*, pages 465–472, 1990.

T. J. VanderWeele and S. Vansteelandt. Odds ratios for mediation analysis for a dichotomous outcome. *American journal of epidemiology*, 172(12):1339–1348, 2010.

E. S. Wan, W. Qiu, A. Baccarelli, V. J. Carey, H. Bacherman, S. I. Rennard, A. Agusti, W. Anderson, D. A. Lomas, and D. L. DeMeo. Cigarette smoking behaviors and time since quitting are associated with differential dna methylation across the human genome. *Human molecular genetics*, 21(13):3073–3082, 2012.

S. Wright. The method of path coefficients. *The annals of mathematical statistics*, 5(3):161–215, 1934.