MR-PATH: A Latent Mixture Model for Heterogeneous Causal Mechanisms in Mendelian Randomization

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Background

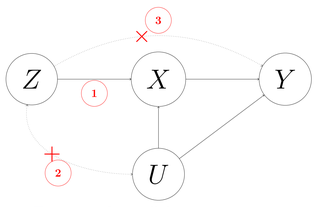

Figure: Core IV assumptions

- **Mendelian Randomization (MR)**: an instrumental variables (IV) method that uses genetic variants (Z) as instruments to estimate the causal effect of a modifiable risk exposure (X) on a disease outcome (Y) in the presence of confounders (U).
- Most robust MR methods rely on the **"effect homogeneity" assumption**: the risk exposure has the same causal effect for every individual. This assumption may be unrealistic when we use MR to study complex biological systems involving multiple mechanisms.

Our contributions

- **"Mechanistic heterogeneity"**: A novel concept we formalized to describe effect heterogeneity in MR due to multiple causal mechanisms.
- **MR-PATH**: A mixture model for mechanistic heterogeneity in MR.
- **Statistical inference for MR-PATH**: Monte-Carlo EM algorithm, approximate confidence intervals, modified BIC criterion

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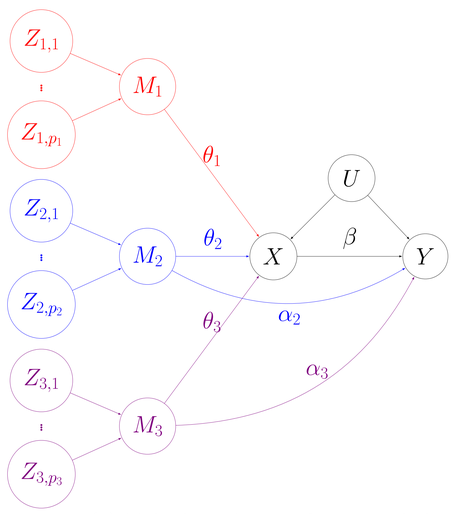
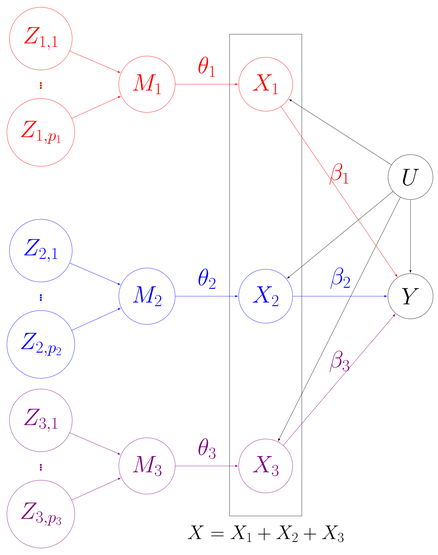
Mechanistic Heterogeneity in MR



(a) Multiple pathways of horizontal pleiotropy.



(b) Multiple mechanisms for the exposure X.

Model

$$\begin{pmatrix}\hat{\theta}_{X_i}\\ \hat{\theta}_{Y_i}\end{pmatrix} \overset{\text{indep.}}{\sim} N\left(\begin{pmatrix}\theta_{X_i}\\ \beta_i\theta_{X_i}\end{pmatrix}, \begin{pmatrix}\sigma^2_{X_i} & 0\\ 0 & \sigma^2_{Y_i}\end{pmatrix}\right) \quad i = 1, \ldots, p.$$

$$Z_i \sim \text{Categorical}\ (\pi_1, \ldots, \pi_K)$$
$$\beta_i | Z_i = k \sim N(\mu_k, \sigma_k^2), \quad k = 1, \ldots, K.$$

Observed Data

- $\hat{\theta}_{X_i}$,$\hat{\theta}_{Y_i}$: Observed SNP-exposure/SNP-outcome effects
- σ_{X_i}, σ_{Y_i}: Corresponding standard errors

Latent variables

- θ_{X_i}: True SNP-exposure effects
- β_i: SNP-specific causal effects

Parameters

- π_k: Proportion of SNPs in cluster K
- μ_k: Average causal effect of cluster K
- σ_k^2: Variance of cluster K

Statistical Inference

EM algorithm

- E-step is not tractable ⇒ approximate with importance sampling ⇒ **Monte-Carlo EM (MC-EM)**

Approximate Confidence Intervals

- Compute observed information matrix using Louis (1982) ⇒ invert to get standard errors.

Model Selection

- Modified BIC criterion from Ibrahim et al. (2008).

Software

The **MRPATH** R package is available at
`https://github.com/danieliong/MRPATH`

Preprint

A preprint of this work is available at
`https://arxiv.org/abs/2007.06476`

Application: Is HDL the good cholesterol?

- Observational studies have found a consistent **inverse association** between HDL cholesterol (HDL-C) and coronary heart disease (CHD)

  ⇒ **HDL hypothesis**: HDL protects from atherosclerosis. (*HDL is the "good" cholesterol.*)

- However, the HDL hypothesis has received scrutiny after
  - Several clinical trials raising HDL cholesterol showed, at best, modest cardiovascular benefit.
  - MR studies reached conflicting conclusions.
- **Our hypothesis**: There are multiple causal mechanisms between HDL-C and CHD.