HDMA-EM: High-Dimensional Mediation Analysis with Effect Modifications

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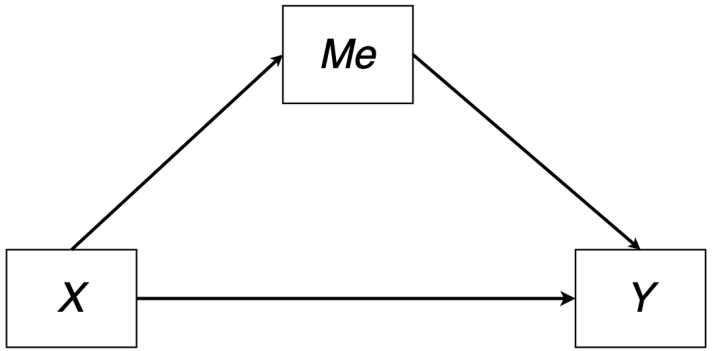
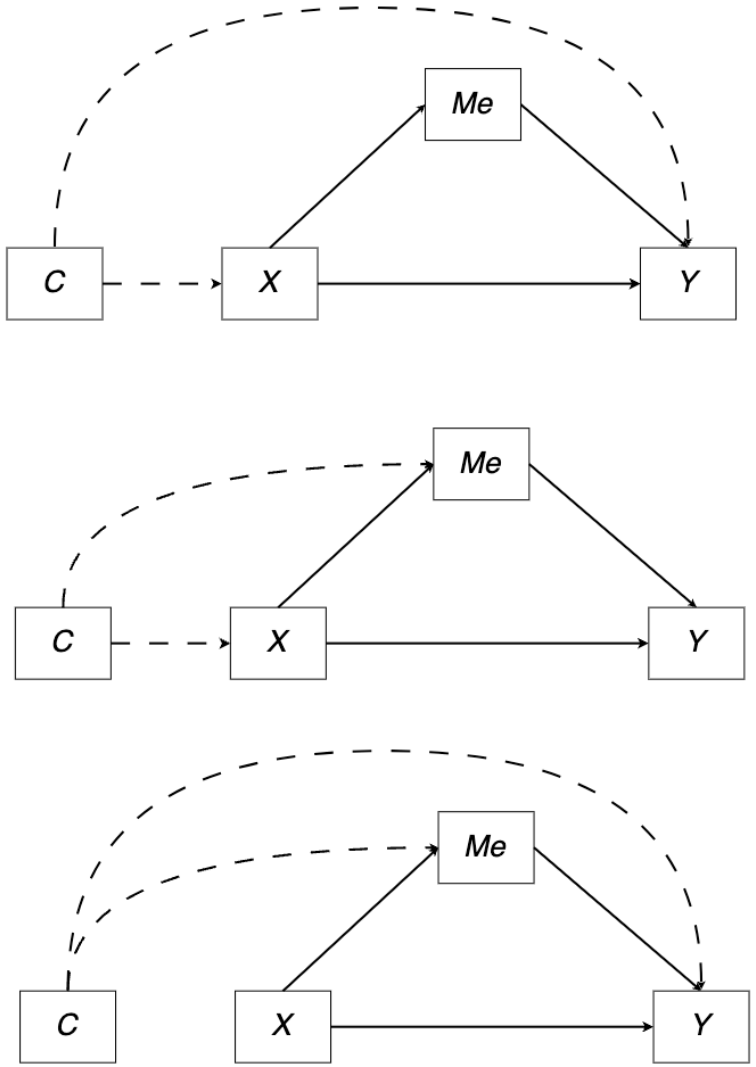
Lin Yu

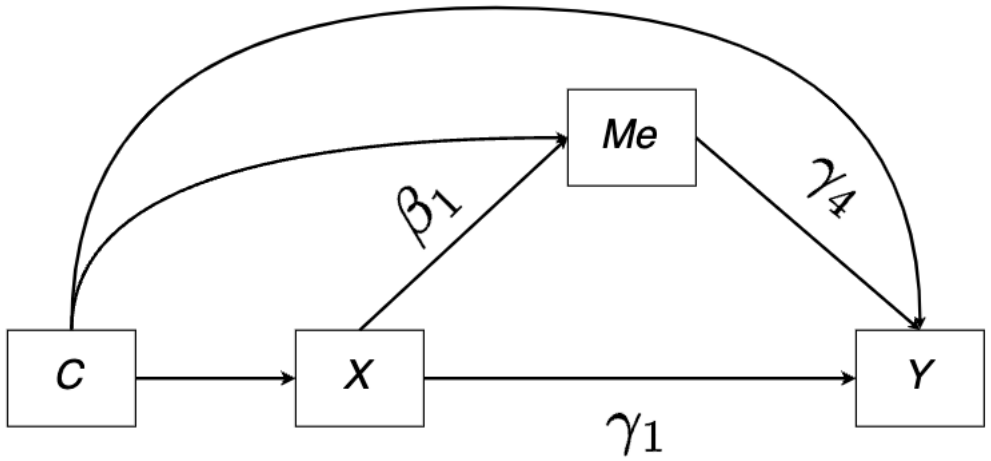
Mediation Analysis (one mediator)



Mediation Analysis (one mediator)



Mediation Analysis (one mediator)



Under sequential ignorability assumptions, for subject *i*,

(i) Overall treatment effect on the outcome Y_i:

$$E(Y_i|X_i, C_i) = \alpha_0 + \alpha_1 X_i + \alpha_4 C_i \quad (1)$$

(ii) Treatment effect on the mediator Me_i:

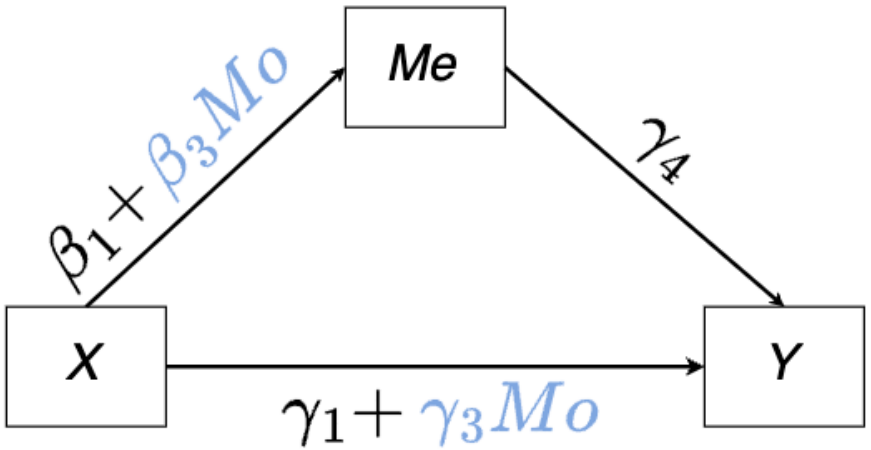
$$E(Me_i|X_i, C_i) = \beta_0 + \beta_1 X_i + \beta_4 C_i \quad (2)$$

(iii) Treatment and mediator effects on the outcome Y_i:

$$E(Y_i|X_i, Me_i, C_i) = \gamma_0 + \gamma_1 X_i + \gamma_4 Me_i + \gamma_7 C_i. \quad (3)$$

Mediation Analysis (with effect modifications)

Type I: mediated moderation



(i) Moderated treatment effect on the mediator Me_i:

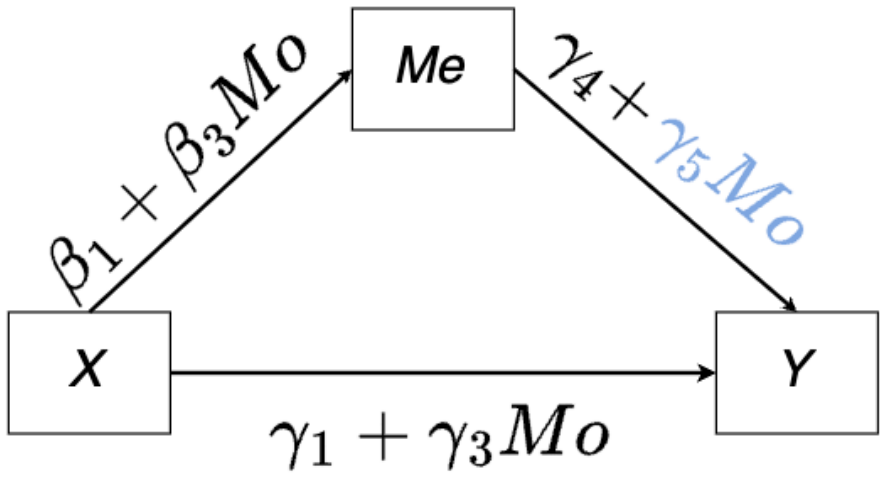
$$E(Me_i|X_i, Mo_i, C_i) = \beta_0 + \beta_1 X_i + \beta_2 Mo_i + \beta_3 X_i Mo_i + \beta_4 C_i \quad (4)$$

(ii) Moderated treatment effect, and mediation effects on the outcome Y_i:

$$E(Y_i|X_i, Me_i, Mo_i, C_i) = \gamma_0 + \gamma_1 X_i + \gamma_2 Mo_i + \gamma_3 X_i Mo_i$$
$$+\gamma_4 Me_i + \gamma_7 C_i \quad (5)$$

Mediation Analysis (with effect modifications)

Type II: moderated mediation



(i) Moderated treatment effect on the mediator Me_i:

$$E(Me_i|X_i, Mo_i, C_i) = \beta_0 + \beta_1 X_i + \beta_2 Mo_i + \beta_3 X_i Mo_i + \beta_4 C_i \quad (4)$$

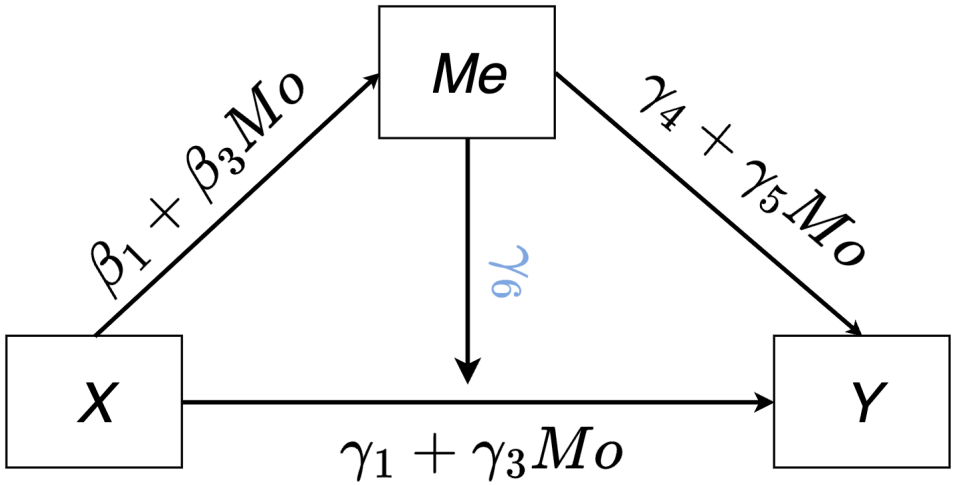
(ii) Moderated treatment effect, and mediation effects on the outcome Y_i:

$$E(Y_i|X_i, Me_i, Mo_i, C_i) = \gamma_0 + \gamma_1 X_i + \gamma_2 Mo_i + \gamma_3 X_i Mo_i$$

$$+\gamma_4 Me_i + \gamma_5 Me_i Mo_i + \gamma_7 C_i \quad (6)$$

Mediation Analysis (with effect modifications)

Type III: exposure-mediator interactive effect



(i) Moderated treatment effect on the mediator Me_i:

$$E(Me_i|X_i, Mo_i, C_i) = \beta_0 + \beta_1 X_i + \beta_2 Mo_i + \beta_3 X_i Mo_i + \beta_4 C_i \quad (4)$$

(ii) Moderated treatment effect, and mediation effects on the outcome Y_i:

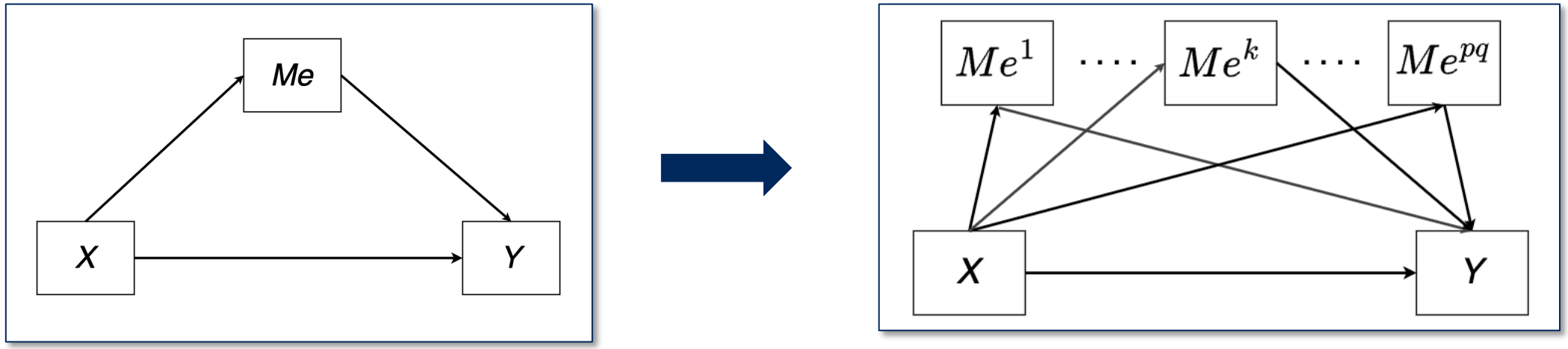
$$E(Y_i|X_i, Me_i, Mo_i, C_i) = \gamma_0 + \gamma_1 X_i + \gamma_2 Mo_i + \gamma_3 X_i Mo_i + \gamma_4 Me_i + \gamma_5 Me_i Mo_i + \gamma_6 X_i Me_i + \gamma_7 C_i \quad (7)$$

Mediation Analysis (high-dimensional mediators)

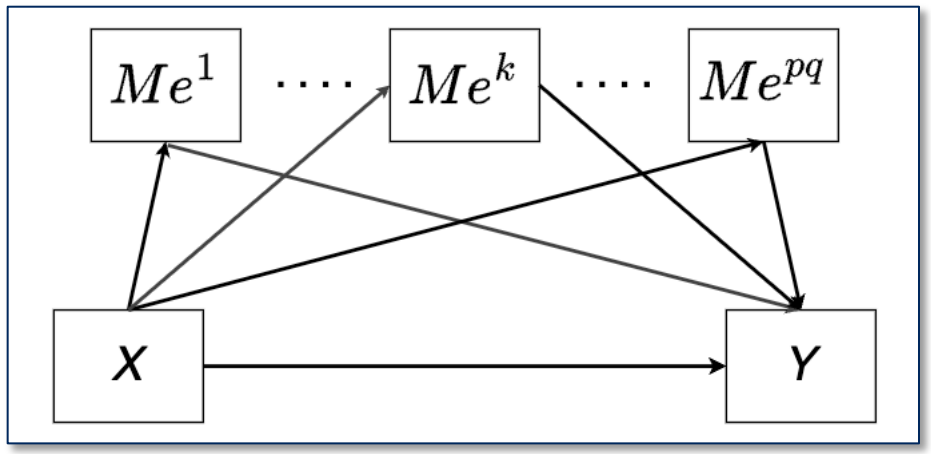
Liu Z et. al. : A Bayesian joint model for mediation analysis with matrix-valued mediators

Motivating study:

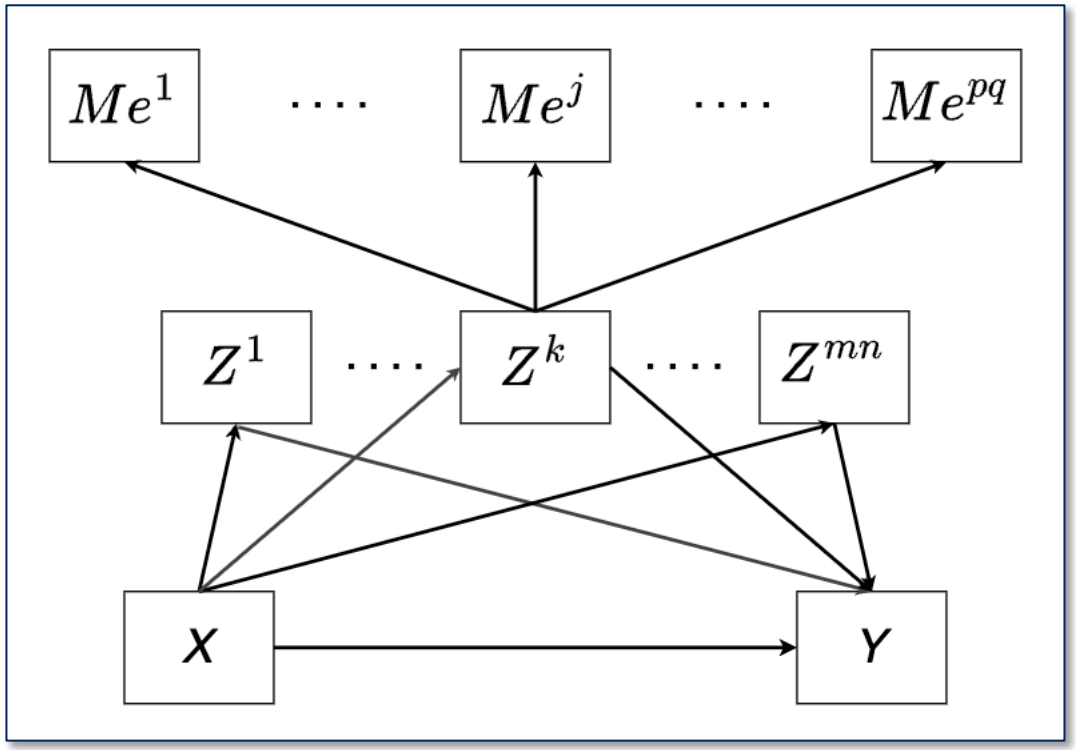
- X: radiation exposure → Me: radiation exposure to organs-at-risk → Y: treatment interruption due to complications
- Me: summarized by Dose Volume Histogram (DVH), A $p \times q$ matrix.



Latent-variable Mediation Analysis (high-dimensional mediators)

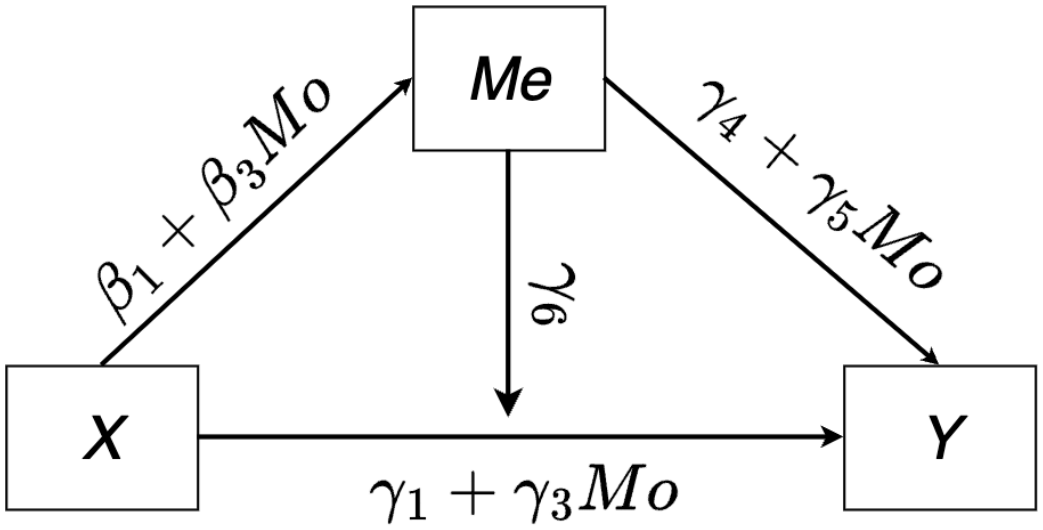


Dimension Reduction

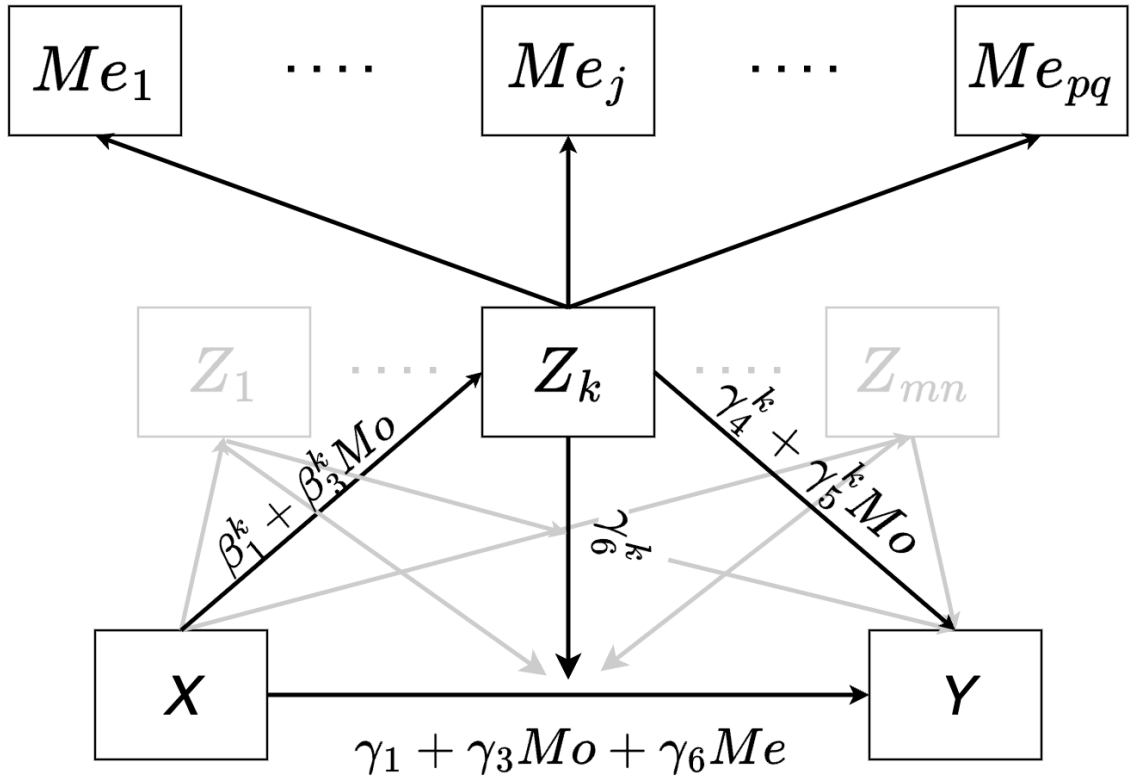


Mediation Analysis (high-dimensional mediators+ effect modifications)

Research question: incorporating effect modifications in the high-dimensional mediators setting?

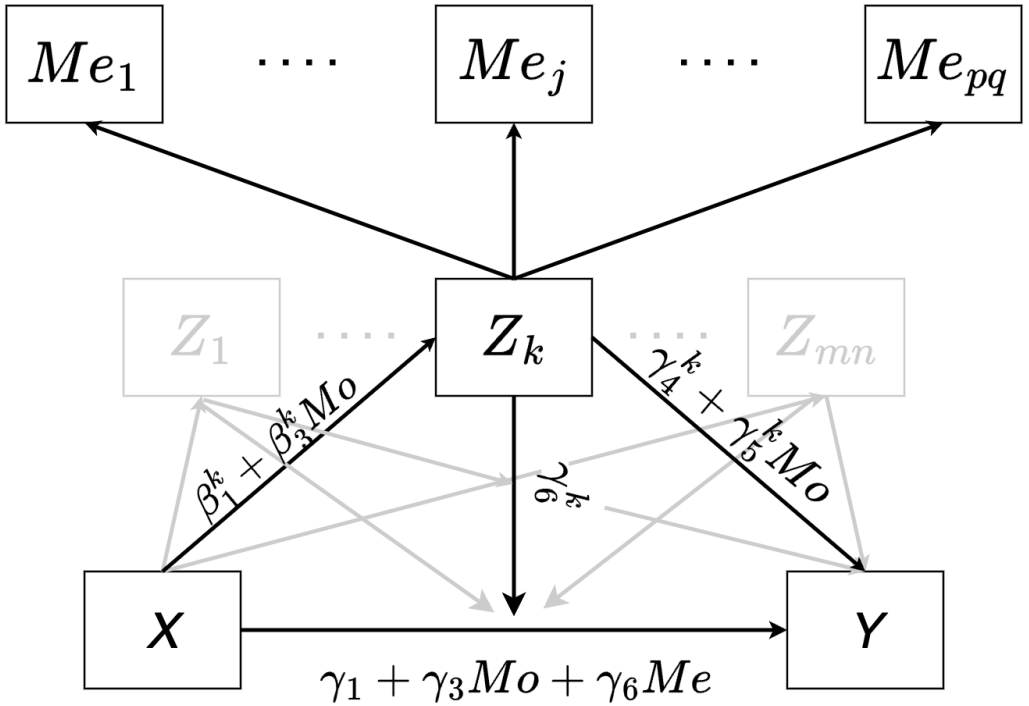


One mediator



High-dimensional mediators

Proposed HDMA-EM Algorithm



Step 1: Dimension Reduction

Non-negative Matrix Factorization(NMF)

$$Me_i \approx Z_i H_i \quad (8)$$

$$where\ Me_i \in \mathbb{R}_+^{p\times q}, Z_i \in \mathbb{R}_+^{p\times k}, H_i \in \mathbb{R}_+^{k\times q}.$$

Step 2: Mediation Analysis

(i) Moderated treatment effect on the mediator Me_i:

- $E(Z_i|X_i, Mo_i, C_i) = \beta_0 + \beta_1 X_i + \beta_2 Mo_i + \beta_3 X_i Mo_i + \beta_4 C_i$ (9)

(ii) Moderated treatment and mediation effects on the outcome Y_i:

- $E(Y_i|X_i, Z_i, Mo_i, C_i) = \gamma_0 + \gamma_1 X_i + \gamma_2 Mo_i + \gamma_3 X_i Mo_i + \gamma_4 Z_i + \gamma_5 Z_i Mo_i + \gamma_6 X_i Z_i + \gamma_7 C_i$ (10)

Proposed HDMA-EM Algorithm

Effect Decomposition: For exposure X change from level a to a^* , the total effect (TE) can be partitioned into the natural direct effect (NDE) and the natural indirect effect (NIE).

- $NDE\ (a^*-a) = E[Y_i(X_i = a^*, Z_i(a))] - E[Y_i(X_i = a, Z_i(a))] = (\gamma_1 + \gamma_3 Mo_i + \gamma_6 Z_i)(a^*-a)$
- $NIE^k\ (a^*-a) = E[Y_i(X_i = a^*, Z_i^1(a), .., Z_i^k(a^*), Z_i^{mn}(a))] - E[Y_i(X_i = a^*, Z_i^1(a), \ldots, Z_i^k(a), Z_i^{mn}(a))] = (\beta_1^k + \beta_3^k Mo_i)[\gamma_4^k + \gamma_5^k Mo_i + \gamma_6^k a^*](a^*-a)$
- $NIE\ (a^*-a) = NIE^1\ (a^*-a) + NIE^2\ (a^*-a) + \ldots NIE^k\ (a^*-a) + \ldots NIE^{mn}\ (a^*-a)$
- $TE = NDE + NIE$

The likelihood (EM algorithm for computing parameter estimates):

$$L_n(\theta, \lambda | Y, X, Mo, C, Z) = \Pi_{i=1}^N P(Y_i | X_i, Mo_i, C_i, Z_i, \theta) P(Z_i | X_i, Mo_i, C_i, \lambda)$$

$$= \Pi_{i=1}^N [P(y_i = \delta_i | X_i, Mo_i, C_i, Z_i, \theta)]^{\delta_i} [P(y_i = 1 - \delta_i | X_i, Mo_i, C_i, Z_i, \theta)]^{1-\delta_i} P(Z_i | X_i, Mo_i, C_i, \lambda)$$

$$= \Pi_{i=1}^N \int_z [P_{y_i = \delta_i}(X_i, Mo_i, C_i, Z_i, \theta)]^{\delta_i} [P_{y_i = 1-\delta_i}(X_i, Mo_i, Z_i, C_i | \theta)]^{\delta_i} P(Z_i | X_i, Mo_i, C_i, \lambda) dz$$

References

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Thank You