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1 Brief description of the causal mediation analysis

The literature on the causal mediation is vast [VanderWeele, 2015] and is evolving, thus, only the pieces relevant for the current software are reviewed here.

1.1 Decomposition of total effect

Let Y be the outcome variable of interest, A be the treatment variable of interest, M be the mediator variable of interest, and \mathbf{C} be the potentially vector-valued pre-treatment baseline covariates necessary for exchangeability. The treatment contrast of interest is a_1 vs a_0 , the second being the reference level. The counterfactual $Y_{a,m}$ is the value of Y for an individual when, possibly contrary to the fact, the treatment level a and mediator level m are assigned.

Given these notations, the effects are defined as follows at the covariate level $\mathbf{C} = \mathbf{c}$ and the mediator level $M = m$ (only for CDE).

$$CDE(m) = E[Y_{a_1,m} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0,m} | \mathbf{C} = \mathbf{c}]$$

$$TNIE = E[Y_{a_1,M_{a_1}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_1,M_{a_0}} | \mathbf{C} = \mathbf{c}]$$

$$PNDE = E[Y_{a_1,M_{a_0}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0,M_{a_0}} | \mathbf{C} = \mathbf{c}]$$

$$TNDE = E[Y_{a_1,M_{a_1}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0,M_{a_1}} | \mathbf{C} = \mathbf{c}]$$

$$PNIE = E[Y_{a_0,M_{a_1}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0,M_{a_0}} | \mathbf{C} = \mathbf{c}]$$

$$TE = E[Y_{a_1} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0} | \mathbf{C} = \mathbf{c}]$$

The total effect (TE) can be decomposed into the direct (non-mediated) effect and indirect (mediated) effect in two different ways [Robins and Greenland, 1992, VanderWeele, 2013].

The decomposition of TE into the pure (natural) direct effect (PNDE) and the total (natural) indirect effect (TNIE) is the usual decomposition [Pearl, 2001].

$$PNDE = E[Y_{a_1,M_{a_0}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0,M_{a_0}} | \mathbf{C} = \mathbf{c}]$$

$$TNIE = E[Y_{a_1,M_{a_1}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_1,M_{a_0}} | \mathbf{C} = \mathbf{c}]$$

The other decomposition of TE is into the pure (natural) indirect effect (PNIE) and the total (natural) direct effect (TNDE) [Robins and Greenland, 1992].

$$TNDE = E[Y_{a_1,M_{a_1}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0,M_{a_1}} | \mathbf{C} = \mathbf{c}]$$

$$PNIE = E[Y_{a_0,M_{a_1}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0,M_{a_0}} | \mathbf{C} = \mathbf{c}]$$

These decomposition differs in the cross-world counterfactual state that is used as the partition. The PNDE+TNIE decomposition uses $Y_{a_1,M_{a_0}}$ (treatment exerting on the outcome changes first), whereas the PNIE+TNDE decomposition uses $Y_{a_0,M_{a_1}}$ (treatment exerting on the mediator changes first). In either case, the effect that has the reference counterfactual outcome $Y_{a_0} = Y_{a_0,M_0}$ is the "pure" effect and the effect that has $Y_{a_1} = Y_{a_1,M_1}$ is the total effect. See [VanderWeele, 2013] for the meaning of these two decompositions.

More in general, we can consider the effects on the link function scale as follows [Starkopf et al., 2017].

$$CDE(m) = g(E[Y_{a_1,m} | \mathbf{C} = \mathbf{c}]) - g(E[Y_{a_0,m} | \mathbf{C} = \mathbf{c}])$$

$$PNDE = g(E[Y_{a_1, M_{a_0}} | \mathbf{C} = \mathbf{c}]) - g(E[Y_{a_0, M_{a_0}} | \mathbf{C} = \mathbf{c}])$$

$$TNIE = g(E[Y_{a_1, M_{a_1}} | \mathbf{C} = \mathbf{c}]) - g(E[Y_{a_1, M_{a_0}} | \mathbf{C} = \mathbf{c}])$$

$$TNDE = g(E[Y_{a_1, M_{a_1}} | \mathbf{C} = \mathbf{c}]) - g(E[Y_{a_0, M_{a_1}} | \mathbf{C} = \mathbf{c}])$$

$$PNIE = g(E[Y_{a_0, M_{a_1}} | \mathbf{C} = \mathbf{c}]) - g(E[Y_{a_0, M_{a_0}} | \mathbf{C} = \mathbf{c}])$$

$$TE = g(E[Y_{a_1} | \mathbf{C} = \mathbf{c}]) - g(E[Y_{a_0} | \mathbf{C} = \mathbf{c}])$$

2 Understanding the approach

Here we describe the formulas implemented in `regmendint`, using the notational convention in [VanderWeele, 2015, Valeri and Vanderweele, 2013, Valeri and VanderWeele, 2015].

2.1 Parametrizing the mediation formulas

The method directly parametrizes the effects with the coefficients of the mediator model (β) and the outcome model (θ). The maximum likelihood estimates (MLE) of these effects are the ones with these parameters replaced with their respective MLEs. See XYZ for derivation of these formulas.

2.2 Obtaining standard errors via multivariate delta method

As seen above, each effects of interest is estimated as a scalar-valued, non-linear function of estimated coefficients for the mediator model and the outcome model. Thus, we can obtain the standard error of each effect estimate using the variance covariance matrix for the coefficients and multivariate delta method [Hoef, 2012].

Let the scalar quantity of interest be Q , a function of parameter vector $(\beta^T, \theta^T)^T$. Then, its gradient (vector of partial derivatives) with respect to the parameter vector $(\beta^T, \theta^T)^T$ is the following.

$$\begin{aligned} \nabla Q &= \frac{\partial Q}{\partial (\beta^T, \theta^T)^T} \\ &= \begin{bmatrix} \frac{\partial Q}{\partial \beta_0} \\ \frac{\partial Q}{\partial \beta_1} \\ \frac{\partial Q}{\partial \beta_2} \\ \frac{\partial Q}{\partial \theta_0} \\ \frac{\partial Q}{\partial \theta_1} \\ \frac{\partial Q}{\partial \theta_2} \\ \frac{\partial Q}{\partial \theta_3} \\ \frac{\partial Q}{\partial \theta_4} \end{bmatrix} \end{aligned}$$

In the case of a linear mediator model and a non-linear outcome model, there is an additional element $\frac{\partial Q}{\partial \sigma^2}$ at the bottom of the gradient vector.

By the large sample approximation using the multivariate delta method, the variance of the quantity of interest evaluated at the MLEs $(\hat{\beta}^T, \hat{\theta}^T)^T$ is the following.

$$\underbrace{Var \left[Q \left\{ (\hat{\beta}^T, \hat{\theta}^T)^T \right\} \right]}_{\text{scalar}} \approx \underbrace{\left[\nabla Q \left((\hat{\beta}^T, \hat{\theta}^T)^T \right) \right]^T}_{\text{row vector}} \underbrace{Var((\hat{\beta}^T, \hat{\theta}^T)^T)}_{\text{matrix}} \underbrace{\left[\nabla Q \left((\hat{\beta}^T, \hat{\theta}^T)^T \right) \right]}_{\text{column vector}}$$

This expression is abbreviated as $\Gamma\Sigma\Gamma'$ in [VanderWeele, 2015, Valeri and Vanderweele, 2013, Valeri and VanderWeele, 2015]. In these references, the treatment contrast $(a_1 - a_0)$ is factored out from $\nabla Q \left((\hat{\beta}^T, \hat{\theta}^T)^T \right)$ when possible.

2.3 Linear mediator model, linear outcome model

2.3.1 Effect formulas

The function `calc_myreg_mreg_linear_yreg_linear_est()` implements the effect formulas in [VanderWeele, 2015] (p466).

Models

$$\begin{aligned} E[Y|A = a, M = m, \mathbf{C} = \mathbf{c}] &= \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \boldsymbol{\theta}_4^T \mathbf{c} \\ E[M|A = a, \mathbf{C} = \mathbf{c}] &= \beta_0 + \beta_1 a + \boldsymbol{\beta}_2^T \mathbf{c} \end{aligned}$$

Effects

$$\begin{aligned} CDE(m) &= E[Y_{a_1, m} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0, m} | \mathbf{C} = \mathbf{c}] \\ &= (\theta_1 + \theta_3 m)(a_1 - a_0) \end{aligned}$$

$$\begin{aligned} PNDE &= E[Y_{a_1, \widetilde{M}_{a_0}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0, \widetilde{M}_{a_0}} | \mathbf{C} = \mathbf{c}] \\ &= \left\{ \theta_1 + \theta_3(\beta_0 + \beta_1 \widetilde{a_0} + \boldsymbol{\beta}_2^T \mathbf{c}) \right\} (a_1 - a_0) \\ TNIE &= E[Y_{\widetilde{a_1}, M_{a_1}} | \mathbf{C} = \mathbf{c}] - E[Y_{\widetilde{a_1}, M_{a_0}} | \mathbf{C} = \mathbf{c}] \\ &= \beta_1(\theta_2 + \theta_3 \widetilde{a_1})(a_1 - a_0) \end{aligned}$$

$$\begin{aligned} TNDE &= E[Y_{a_1, \widetilde{M}_{a_1}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0, \widetilde{M}_{a_1}} | \mathbf{C} = \mathbf{c}] \\ &= \left\{ \theta_1 + \theta_3(\beta_0 + \beta_1 \widetilde{a_1} + \boldsymbol{\beta}_2^T \mathbf{c}) \right\} (a_1 - a_0) \\ PNIE &= E[Y_{a_0, M_{a_1}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0, M_{a_0}} | \mathbf{C} = \mathbf{c}] \\ &= \beta_1(\theta_2 + \theta_3 \widetilde{a_0})(a_1 - a_0) \end{aligned}$$

$$TE = PNDE + TNIE$$

$$PM = \frac{TNIE}{PNDE + TNIE}$$

2.3.2 Variance formulas

The function `calc_myreg_mreg_linear_yreg_linear_se()` implements the standard error formulas in [VanderWeele, 2015] (p466).

$$(a_1 - a_0)\Gamma_{CDE(m)} = \frac{\partial CDE(m)}{\partial (\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T}$$

$$= (a_1 - a_0) \begin{bmatrix} 0 \\ 0 \\ \underline{0} \\ 0 \\ 1 \\ 0 \\ m \\ \underline{0} \end{bmatrix}$$

$$(a_1 - a_0)\Gamma_{PNDE} = \frac{\partial PNDE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T}$$

$$= (a_1 - a_0) \begin{bmatrix} \theta_3 \\ \theta_3 a_0 \\ \theta_3 \mathbf{c} \\ 0 \\ 1 \\ 0 \\ \beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c} \\ \underline{0} \end{bmatrix}$$

$$(a_1 - a_0)\Gamma_{TNIE} = \frac{\partial TNIE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T}$$

$$= (a_1 - a_0) \begin{bmatrix} 0 \\ \theta_2 + \theta_3 a_1 \\ \underline{0} \\ 0 \\ 0 \\ \beta_1 \\ \beta_1 a_1 \\ \underline{0} \end{bmatrix}$$

$$(a_1 - a_0)\Gamma_{TNDE} = \frac{\partial TNDE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T}$$

$$= (a_1 - a_0) \begin{bmatrix} \theta_3 \\ \theta_3 a_1 \\ \theta_3 \mathbf{c} \\ 0 \\ 1 \\ 0 \\ \beta_0 + \beta_1 a_1 + \boldsymbol{\beta}_2^T \mathbf{c} \\ \underline{0} \end{bmatrix}$$

$$(a_1 - a_0)\Gamma_{PNIE} = \frac{\partial PNIE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T}$$

$$= (a_1 - a_0) \begin{bmatrix} 0 \\ \theta_2 + \theta_3 a_0 \\ \underline{0} \\ 0 \\ 0 \\ \beta_1 \\ \beta_1 a_0 \\ \underline{0} \end{bmatrix}$$

$$\begin{aligned}
(a_1 - a_0)\Gamma_{TE} &= \frac{\partial TE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&= \frac{\partial(PNDE + TNIE)}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&= (a_1 - a_0)(\Gamma_{PNDE} + \Gamma_{TNIE})
\end{aligned}$$

$$\begin{aligned}
(a_1 - a_0)\Gamma_{PM} &= \frac{\partial PM}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&\text{By multivariate chain rule} \\
&= \frac{\partial PM}{\partial PNDE} \frac{\partial PNDE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} + \frac{\partial PM}{\partial TNIE} \frac{\partial TNIE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&= \frac{\partial PM}{\partial PNDE} (a_1 - a_0)\Gamma_{PNDE} + \frac{\partial PM}{\partial TNIE} (a_1 - a_0)\Gamma_{TNIE} \\
&= \frac{-TNIE}{(PNDE + TNIE)^2} (a_1 - a_0)\Gamma_{PNDE} + \frac{PNDE}{(PNDE + TNIE)^2} (a_1 - a_0)\Gamma_{TNIE} \\
&= (a_1 - a_0) \frac{-TNIE \Gamma_{PNDE} + PNDE \Gamma_{TNIE}}{(PNDE + TNIE)^2}
\end{aligned}$$

Variance-covariance matrix from two models

$$\begin{aligned}
\boldsymbol{\Sigma} &= \begin{bmatrix} \boldsymbol{\Sigma}_{\boldsymbol{\beta}} & 0 \\ 0 & \boldsymbol{\Sigma}_{\boldsymbol{\theta}} \end{bmatrix} \\
SE(\widehat{CDE}(m)) &= \sqrt{\Gamma_{CDE(m)}^T \boldsymbol{\Sigma} \Gamma_{CDE(m)}} |a_1 - a_0| \\
SE(\widehat{PNDE}) &= \sqrt{\Gamma_{PNDE}^T \boldsymbol{\Sigma} \Gamma_{PNDE}} |a_1 - a_0| \\
SE(\widehat{TNIE}) &= \sqrt{\Gamma_{TNIE}^T \boldsymbol{\Sigma} \Gamma_{TNIE}} |a_1 - a_0| \\
SE(\widehat{TNDE}) &= \sqrt{\Gamma_{TNDE}^T \boldsymbol{\Sigma} \Gamma_{TNDE}} |a_1 - a_0| \\
SE(\widehat{PNIE}) &= \sqrt{\Gamma_{PNIE}^T \boldsymbol{\Sigma} \Gamma_{PNIE}} |a_1 - a_0| \\
SE(\widehat{TE}) &= \sqrt{\Gamma_{TE}^T \boldsymbol{\Sigma} \Gamma_{TE}} |a_1 - a_0| \\
SE(\widehat{PM}) &= \sqrt{\Gamma_{PM}^T \boldsymbol{\Sigma} \Gamma_{PM}} |a_1 - a_0|
\end{aligned}$$

2.4 Linear mediator model, non-linear outcome model

2.4.1 Effect formulas

The function `calc_myreg_mreg_linear_yreg_logistic_est()` implements the effect formulas in [VanderWeele, 2015] (p468).

Models

$$\begin{aligned}
\text{logit}(E[Y|A = a, M = m, \mathbf{C} = \mathbf{c}]) &= \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \boldsymbol{\theta}_4^T \mathbf{c} \\
E[M|A = a, \mathbf{C} = \mathbf{c}] &= \beta_0 + \beta_1 a + \boldsymbol{\beta}_2^T \mathbf{c}
\end{aligned}$$

Effects on link function scale

$$\begin{aligned}
CDE(m) &= \text{logit}(E[Y_{a_1, m} | \mathbf{C} = \mathbf{c}]) - \text{logit}(E[Y_{a_0, m} | \mathbf{C} = \mathbf{c}]) \\
&= (\theta_1 + \theta_3 m)(a_1 - a_0)
\end{aligned}$$

$$\begin{aligned}
PNDE &= \text{logit}(E[Y_{a_1, \widetilde{M}_{a_0}} | \mathbf{C} = \mathbf{c}]) - \text{logit}(E[Y_{a_0, \widetilde{M}_{a_0}} | \mathbf{C} = \mathbf{c}]) \\
&\approx \left\{ \theta_1 + \theta_3(\beta_0 + \beta_1 \widetilde{a_0} + \beta_2^T \mathbf{c} + \theta_2 \sigma^2) \right\} (a_1 - a_0) + \frac{1}{2} \theta_3^2 \sigma^2 (a_1^2 - a_0^2) \\
TNIE &= \text{logit}(E[Y_{a_1, M_{a_1}} | \mathbf{C} = \mathbf{c}]) - \text{logit}(E[Y_{a_0, M_{a_1}} | \mathbf{C} = \mathbf{c}]) \\
&\approx \beta_1(\theta_2 + \theta_3 \widetilde{a_1})(a_1 - a_0) \\
TNDE &= \text{logit}(E[Y_{a_1, \widetilde{M}_{a_1}} | \mathbf{C} = \mathbf{c}]) - \text{logit}(E[Y_{a_0, \widetilde{M}_{a_1}} | \mathbf{C} = \mathbf{c}]) \\
&\approx \left\{ \theta_1 + \theta_3(\beta_0 + \beta_1 \widetilde{a_1} + \beta_2^T \mathbf{c} + \theta_2 \sigma^2) \right\} (a_1 - a_0) + \frac{1}{2} \theta_3^2 \sigma^2 (a_1^2 - a_0^2) \\
PNIE &= \text{logit}(E[Y_{a_0, M_{a_1}} | \mathbf{C} = \mathbf{c}]) - \text{logit}(E[Y_{a_0, M_{a_0}} | \mathbf{C} = \mathbf{c}]) \\
&\approx \beta_1(\theta_2 + \theta_3 \widetilde{a_0})(a_1 - a_0) \\
TE &= PNDE + TNIE \\
PM &= \frac{\exp(PNDE)(\exp(TNIE) - 1)}{\exp(PNDE)\exp(TNIE) - 1}
\end{aligned}$$

2.4.2 Variance formulas

The function `calc_myreg_mreg_linear_yreg_logistic_se()` implements the standard error formulas in [VanderWeele, 2015] (p468).

$$\begin{aligned}
(a_1 - a_0)\Gamma_{CDE(m)} &= \frac{\partial CDE(m)}{\partial(\beta^T, \theta^T, \sigma^2)^T} \\
&= (a_1 - a_0) \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ m \\ 0 \\ 0 \end{bmatrix} \\
(a_1 - a_0)\Gamma_{PNDE} &= \frac{\partial PNDE}{\partial(\beta^T, \theta^T, \sigma^2)^T} \\
&= (a_1 - a_0) \begin{bmatrix} \theta_3 \\ \theta_3 \widetilde{a_0} \\ \theta_3 \mathbf{c} \\ 0 \\ 1 \\ \theta_3 \sigma^2 \\ \beta_0 + \beta_1 \widetilde{a_0} + \beta_2^T \mathbf{c} + \theta_2 \sigma^2 + \theta_3 \sigma^2 (a_0 + a_1) \\ 0 \\ \theta_3 \theta_2 + \frac{1}{2} \theta_3^2 (a_1 + a_0) \end{bmatrix} \\
(a_1 - a_0)\Gamma_{TNIE} &= \frac{\partial TNIE}{\partial(\beta^T, \theta^T, \sigma^2)^T}
\end{aligned}$$

$$= (a_1 - a_0) \begin{bmatrix} 0 \\ \theta_2 + \theta_3 a_{1\sim} \\ 0 \\ 0 \\ 0 \\ \beta_1 \\ \beta_1 a_{1\sim} \\ 0 \\ 0 \end{bmatrix}$$

$$(a_1 - a_0) \Gamma_{TNDE} = \frac{\partial TNDE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T, \sigma^2)^T}$$

$$= (a_1 - a_0) \begin{bmatrix} \theta_3 \\ \theta_3 a_{1\sim} \\ \theta_3 \mathbf{c} \\ 0 \\ 1 \\ \theta_3 \sigma^2 \\ \beta_0 + \beta_1 a_{1\sim} + \boldsymbol{\beta}_2^T \mathbf{c} + \theta_2 \sigma^2 + \theta_3 \sigma^2 (a_0 + a_1) \\ 0 \\ \theta_3 \theta_2 + \frac{1}{2} \theta_3^2 (a_1 + a_0) \end{bmatrix}$$

$$(a_1 - a_0) \Gamma_{PNIE} = \frac{\partial PNIE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T, \sigma^2)^T}$$

$$= (a_1 - a_0) \begin{bmatrix} 0 \\ \theta_2 + \theta_3 a_{0\sim} \\ 0 \\ 0 \\ 0 \\ \beta_1 \\ \beta_1 a_{0\sim} \\ 0 \\ 0 \end{bmatrix}$$

$$(a_1 - a_0) \Gamma_{TE} = \frac{\partial TE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T, \sigma^2)^T}$$

$$= \frac{\partial(PNDE + TNIE)}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T, \sigma^2)^T}$$

$$= (a_1 - a_0)(\Gamma_{PNDE} + \Gamma_{TNIE})$$

$$(a_1 - a_0) \Gamma_{PM} = \frac{\partial PM}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T, \sigma^2)^T}$$

By multivariate chain rule

$$= \frac{\partial PM}{\partial PNDE} \frac{\partial PNDE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T, \sigma^2)^T} + \frac{\partial PM}{\partial TNIE} \frac{\partial TNIE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T, \sigma^2)^T}$$

$$= \frac{\partial PM}{\partial PNDE} (a_1 - a_0) \Gamma_{PNDE} + \frac{\partial PM}{\partial TNIE} (a_1 - a_0) \Gamma_{TNIE}$$

$$= - \frac{\exp(PNDE) \{ \exp(TNIE) - 1 \}}{\{ \exp(PNDE) \exp(TNIE) - 1 \}^2} (a_1 - a_0) \Gamma_{PNDE}$$

$$+ \frac{\exp(PNDE) \exp(TNIE) \{\exp(PNDE) - 1\}}{\{\exp(PNDE) \exp(TNIE) - 1\}^2} (a_1 - a_0) \Gamma_{TNIE}$$

Variance-covariance matrix from two models

$$\begin{aligned} \Sigma &= \begin{bmatrix} \Sigma_{\beta} & 0 & 0 \\ 0 & \Sigma_{\theta} & 0 \\ 0 & 0 & \Sigma_{\sigma^2} \end{bmatrix} \\ \Sigma_{\sigma^2} &= \frac{2(\sigma^2)^2}{n-p} \text{ where } p = \text{length}(\beta) \\ SE(\widehat{CDE}(m)) &= \sqrt{\Gamma_{CDE(m)}^T \Sigma \Gamma_{CDE(m)}} |a_1 - a_0| \\ SE(\widehat{PNDE}) &= \sqrt{\Gamma_{PNDE}^T \Sigma \Gamma_{PNDE}} |a_1 - a_0| \\ SE(\widehat{TNIE}) &= \sqrt{\Gamma_{TNIE}^T \Sigma \Gamma_{TNIE}} |a_1 - a_0| \\ SE(\widehat{TNDE}) &= \sqrt{\Gamma_{TNDE}^T \Sigma \Gamma_{TNDE}} |a_1 - a_0| \\ SE(\widehat{PNIE}) &= \sqrt{\Gamma_{PNIE}^T \Sigma \Gamma_{PNIE}} |a_1 - a_0| \\ SE(\widehat{TE}) &= \sqrt{\Gamma_{TE}^T \Sigma \Gamma_{TE}} |a_1 - a_0| \\ SE(\widehat{PM}) &= \sqrt{\Gamma_{PM}^T \Sigma \Gamma_{PM}} |a_1 - a_0| \end{aligned}$$

2.5 Logistic mediator model, linear outcome model

2.5.1 Effect formulas

The function `calc_myreg_mreg_logistic_yreg_linear_est()` implements the effect formulas in [VanderWeele, 2015] (p471).

Models

$$\begin{aligned} E[Y|A = a, M = m, \mathbf{C} = \mathbf{c}] &= \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4^T \mathbf{c} \\ \text{logit}(E[M|A = a, \mathbf{C} = \mathbf{c}]) &= \beta_0 + \beta_1 a + \beta_2^T \mathbf{c} \end{aligned}$$

Effects

$$\begin{aligned} CDE(m) &= E[Y_{a_1, m} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0, m} | \mathbf{C} = \mathbf{c}] \\ &= (\theta_1 + \theta_3 m)(a_1 - a_0) \end{aligned}$$

$$\begin{aligned} PNDE &= E[Y_{a_1, M_{a_0}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0, M_{a_0}} | \mathbf{C} = \mathbf{c}] \\ &= \{\theta_1(a_1 - a_0)\} + \{\theta_3(a_1 - a_0)\} \frac{\exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})} \\ TNIE &= E[Y_{a_1, M_{a_1}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_1, M_{a_0}} | \mathbf{C} = \mathbf{c}] \\ &= (\theta_2 + \theta_3 a_1) \left\{ \frac{\exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})} - \frac{\exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})} \right\} \\ TNDE &= E[Y_{a_1, M_{a_1}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0, M_{a_1}} | \mathbf{C} = \mathbf{c}] \\ &= \{\theta_1(a_1 - a_0)\} + \{\theta_3(a_1 - a_0)\} \frac{\exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})} \\ PNIE &= E[Y_{a_0, M_{a_1}} | \mathbf{C} = \mathbf{c}] - E[Y_{a_0, M_{a_0}} | \mathbf{C} = \mathbf{c}] \\ &= (\theta_2 + \theta_3 a_0) \left\{ \frac{\exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})} - \frac{\exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})} \right\} \end{aligned}$$

$$TE = PNDE + TNIE$$

$$PM = \frac{TNIE}{PNDE + TNIE}$$

2.5.2 Variance formulas

The function `calc_myreg_mreg_logistic_yreg_linear_se()` implements the standard error formulas in [VanderWeele, 2015] (p471).

$$(a_1 - a_0)\Gamma_{CDE(m)} = \frac{\partial CDE(m)}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T}$$

$$= (a_1 - a_0) \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ m \\ 0 \end{bmatrix}$$

$$d_{1,PNDE} = \theta_3 \frac{\exp(\beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})}$$

$$d_{2,PNDE} = a_0 \theta_3 \frac{\exp(\beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})}$$

$$d_{3,PNDE} = \mathbf{c} \theta_3 \frac{\exp(\beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})}$$

$$d_{4,PNDE} = 0$$

$$d_{5,PNDE} = 1$$

$$d_{6,PNDE} = 0$$

$$d_{7,PNDE} = \frac{\exp(\beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})}$$

$$d_{8,PNDE} = 0$$

$$(a_1 - a_0)\Gamma_{PNDE} = \frac{\partial PNDE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T}$$

$$= (a_1 - a_0) \begin{bmatrix} d_{1,PNDE} \\ d_{2,PNDE} \\ d_{3,PNDE} \\ d_{4,PNDE} \\ d_{5,PNDE} \\ d_{6,PNDE} \\ d_{7,PNDE} \\ d_{8,PNDE} \end{bmatrix}$$

$$Q_{TNIE} = \frac{\exp(\beta_0 + \beta_1 a_1 + \boldsymbol{\beta}_2^T \mathbf{c})}{\left\{1 + \exp(\beta_0 + \beta_1 a_1 + \boldsymbol{\beta}_2^T \mathbf{c})\right\}^2}$$

$$B_{TNIE} = \frac{\exp(\beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})}{\left\{1 + \exp(\beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})\right\}^2}$$

$$\begin{aligned}
K_{TNIE} &= \frac{\exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})} \\
D_{TNIE} &= \frac{\exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})} \\
d_{1,TNIE} &= (\theta_2 + \theta_3 a_1)(Q_{TNIE} - B_{TNIE}) \\
d_{2,TNIE} &= (\theta_2 + \theta_3 a_1)(a_1 Q_{TNIE} - a_0 B_{TNIE}) \\
d_{3,TNIE} &= (\theta_2 + \theta_3 a_1) \mathbf{c}(Q_{TNIE} - B_{TNIE}) \\
d_{4,TNIE} &= 0 \\
d_{5,TNIE} &= 0 \\
d_{6,TNIE} &= K_{TNIE} - D_{TNIE} \\
d_{7,TNIE} &= a_1(K_{TNIE} - D_{TNIE}) \\
d_{8,TNIE} &= 0
\end{aligned}$$

Note the lack of the common factor $(a_1 - a_0)$

$$\begin{aligned}
\Gamma_{TNIE} &= \frac{\partial TNIE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&= \begin{bmatrix} d_{1,TNIE} \\ d_{2,TNIE} \\ d_{3,TNIE} \\ d_{4,TNIE} \\ d_{5,TNIE} \\ d_{6,TNIE} \\ d_{7,TNIE} \\ d_{8,TNIE} \end{bmatrix}
\end{aligned}$$

$$\begin{aligned}
d_{1,TNDE} &= \theta_3 \frac{\exp(\beta_1 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_1 + \beta_1 a_1 + \beta_2^T \mathbf{c})} \\
d_{2,TNDE} &= a_1 \theta_3 \frac{\exp(\beta_1 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_1 + \beta_1 a_1 + \beta_2^T \mathbf{c})} \\
d_{3,TNDE} &= \mathbf{c} \theta_3 \frac{\exp(\beta_1 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_1 + \beta_1 a_1 + \beta_2^T \mathbf{c})} \\
d_{4,TNDE} &= 0 \\
d_{5,TNDE} &= 1 \\
d_{6,TNDE} &= 0 \\
d_{7,TNDE} &= \frac{\exp(\beta_1 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_1 + \beta_1 a_1 + \beta_2^T \mathbf{c})} \\
d_{8,TNDE} &= 0
\end{aligned}$$

$$\begin{aligned}
(a_1 - a_0) \Gamma_{TNDE} &= \frac{\partial TNDE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&= (a_1 - a_0) \begin{bmatrix} d_{1,TNDE} \\ d_{2,TNDE} \\ d_{3,TNDE} \\ d_{4,TNDE} \\ d_{5,TNDE} \\ d_{6,TNDE} \\ d_{7,TNDE} \\ d_{8,TNDE} \end{bmatrix}
\end{aligned}$$

$$\begin{aligned}
Q_{PNIE} &= \frac{\exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{\left\{1 + \exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})\right\}^2} \\
B_{PNIE} &= \frac{\exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}{\left\{1 + \exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})\right\}^2} \\
K_{PNIE} &= \frac{\exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})} \\
D_{PNIE} &= \theta_3 \frac{\exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})} \\
d_{1,PNIE} &= (\theta_2 + \theta_3 a_0)(Q_{PNIE} - B_{PNIE}) \\
d_{2,PNIE} &= (\theta_2 + \theta_3 a_0)(a_1 Q_{PNIE} - a_0 B_{PNIE}) \\
d_{3,PNIE} &= (\theta_2 + \theta_3 a_0) \mathbf{c}(Q_{PNIE} - B_{PNIE}) \\
d_{4,PNIE} &= 0 \\
d_{5,PNIE} &= 0 \\
d_{6,PNIE} &= K_{PNIE} - D_{PNIE} \\
d_{7,PNIE} &= a_0(K_{PNIE} - D_{PNIE}) \\
d_{8,PNIE} &= 0
\end{aligned}$$

Note the lack of the common factor $(a_1 - a_0)$

$$\begin{aligned}
\Gamma_{PNIE} &= \frac{\partial PNIE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&= \begin{bmatrix} d_{1,PNIE} \\ d_{2,PNIE} \\ d_{3,PNIE} \\ d_{4,PNIE} \\ d_{5,PNIE} \\ d_{6,PNIE} \\ d_{7,PNIE} \\ d_{8,PNIE} \end{bmatrix}
\end{aligned}$$

Note the lack of the common factor $(a_1 - a_0)$

$$\begin{aligned}
\Gamma_{TE} &= \frac{\partial TE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&= \frac{\partial(PNDE + TNIE)}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&= (a_1 - a_0)\Gamma_{PNDE} + \Gamma_{TNIE}
\end{aligned}$$

Note the lack of the common factor $(a_1 - a_0)$

$$\begin{aligned}
\Gamma_{PM} &= \frac{\partial PM}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&\text{By multivariate chain rule} \\
&= \frac{\partial PM}{\partial PNDE} \frac{\partial PNDE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} + \frac{\partial PM}{\partial TNIE} \frac{\partial TNIE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&= \frac{\partial PM}{\partial PNDE} (a_1 - a_0)\Gamma_{PNDE} + \frac{\partial PM}{\partial TNIE} \Gamma_{TNIE} \\
&= \frac{-TNIE}{(PNDE + TNIE)^2} (a_1 - a_0)\Gamma_{PNDE} + \frac{PNDE}{(PNDE + TNIE)^2} \Gamma_{TNIE} \\
&= \frac{-TNIE (a_1 - a_0)\Gamma_{PNDE} + PNDE \Gamma_{TNIE}}{(PNDE + TNIE)^2}
\end{aligned}$$

Variance-covariance matrix from two models

$$\begin{aligned}\boldsymbol{\Sigma} &= \begin{bmatrix} \boldsymbol{\Sigma}_{\beta} & 0 \\ 0 & \boldsymbol{\Sigma}_{\theta} \end{bmatrix} \\ SE(\widehat{CDE}(m)) &= \sqrt{\Gamma_{CDE(m)}^T \boldsymbol{\Sigma} \Gamma_{CDE(m)}} |a_1 - a_0| \\ SE(\widehat{PNDE}) &= \sqrt{\Gamma_{PNDE}^T \boldsymbol{\Sigma} \Gamma_{PNDE}} |a_1 - a_0| \\ SE(\widehat{TNIE}) &= \sqrt{\Gamma_{TNIE}^T \boldsymbol{\Sigma} \Gamma_{TNIE}} \\ SE(\widehat{TNDE}) &= \sqrt{\Gamma_{TNDE}^T \boldsymbol{\Sigma} \Gamma_{TNDE}} |a_1 - a_0| \\ SE(\widehat{PNIE}) &= \sqrt{\Gamma_{PNIE}^T \boldsymbol{\Sigma} \Gamma_{PNIE}} \\ SE(\widehat{TE}) &= \sqrt{\Gamma_{TE}^T \boldsymbol{\Sigma} \Gamma_{TE}} \\ SE(\widehat{PM}) &= \sqrt{\Gamma_{PM}^T \boldsymbol{\Sigma} \Gamma_{PM}}\end{aligned}$$

2.6 Logistic mediator model, non-linear outcome model

2.6.1 Effect formulas

The function `calc_myreg_mreg_logistic_yreg_logistic_est()` implements the effect formulas in [VanderWeele, 2015] (p473).

Models

$$\begin{aligned}\text{logit}(E[Y|A = a, M = m, \mathbf{C} = \mathbf{c}]) &= \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \boldsymbol{\theta}_4^T \mathbf{c} \\ \text{logit}(E[M|A = a, \mathbf{C} = \mathbf{c}]) &= \beta_0 + \beta_1 a + \boldsymbol{\beta}_2^T \mathbf{c}\end{aligned}$$

Effects on link function scale

$$\begin{aligned}CDE(m) &= \text{logit}(E[Y_{a_1, m} | \mathbf{C} = \mathbf{c}]) - \text{logit}(E[Y_{a_0, m} | \mathbf{C} = \mathbf{c}]) \\ &= (\theta_1 + \theta_3 m)(a_1 - a_0)\end{aligned}$$

$$\begin{aligned}PNDE &= \text{logit}(E[Y_{a_1, M_{a_0}} | \mathbf{C} = \mathbf{c}]) - \text{logit}(E[Y_{a_0, M_{a_0}} | \mathbf{C} = \mathbf{c}]) \\ &\approx \theta_1(a_1 - a_0) \\ &\quad + \log(1 + \exp(\theta_2 + \theta_3 a_1 + \beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})) \\ &\quad - \log(1 + \exp(\theta_2 + \theta_3 a_0 + \beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})) \\ TNIE &= \text{logit}(E[Y_{a_1, M_{a_1}} | \mathbf{C} = \mathbf{c}]) - \text{logit}(E[Y_{a_1, M_{a_0}} | \mathbf{C} = \mathbf{c}]) \\ &\approx \log(1 + \exp(\beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})) \\ &\quad - \log(1 + \exp(\beta_0 + \beta_1 a_1 + \boldsymbol{\beta}_2^T \mathbf{c})) \\ &\quad + \log(1 + \exp(\theta_2 + \theta_3 a_1 + \beta_0 + \beta_1 a_1 + \boldsymbol{\beta}_2^T \mathbf{c})) \\ &\quad - \log(1 + \exp(\theta_2 + \theta_3 a_1 + \beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c}))\end{aligned}$$

Note the $a_0 \rightarrow a_1$ changes associated with β_1 .

$$\begin{aligned}TNDE &= \text{logit}(E[Y_{a_1, M_{a_1}} | \mathbf{C} = \mathbf{c}]) - \text{logit}(E[Y_{a_0, M_{a_1}} | \mathbf{C} = \mathbf{c}]) \\ &\approx \theta_1(a_1 - a_0) \\ &\quad + \log(1 + \exp(\theta_2 + \theta_3 a_1 + \beta_0 + \beta_1 a_1 + \boldsymbol{\beta}_2^T \mathbf{c})) \\ &\quad - \log(1 + \exp(\theta_2 + \theta_3 a_0 + \beta_0 + \beta_1 a_1 + \boldsymbol{\beta}_2^T \mathbf{c}))\end{aligned}$$

Note the $a_1 \rightarrow a_0$ changes associated with θ_3 .

$$\begin{aligned}
 PNIE &= \text{logit}(E[Y_{a_0, M_{a_1}} | \mathbf{C} = \mathbf{c}]) - \text{logit}(E[Y_{a_0, M_{a_0}} | \mathbf{C} = \mathbf{c}]) \\
 &\approx \log(1 + \exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})) \\
 &\quad - \log(1 + \exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})) \\
 &\quad + \log(1 + \exp(\theta_2 + \theta_3 a_0 + \beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})) \\
 &\quad - \log(1 + \exp(\theta_2 + \theta_3 a_0 + \beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c}))
 \end{aligned}$$

$$TE = PNDE + TNIE$$

$$PM = \frac{\exp(PNDE)(\exp(TNIE) - 1)}{\exp(PNDE)\exp(TNIE) - 1}$$

2.6.2 Variance formulas

The function `calc_myreg_mreg_logistic_yreg_logistic_se()` implements the standard error formulas in [VanderWeele, 2015] (p473).

Note the lack of the common factor $(a_1 - a_0)$ throughout.

$$\begin{aligned}
 \Gamma_{CDE(m)} &= \frac{\partial CDE(m)}{\partial(\beta^T, \theta^T)^T} \\
 &= (a_1 - a_0) \begin{bmatrix} 0 \\ 0 \\ \underline{0} \\ 0 \\ (a_1 - a_0) \\ 0 \\ m(a_1 - a_0) \\ \underline{0} \end{bmatrix}
 \end{aligned}$$

$$Q_{PNDE} = \frac{\exp(\theta_2 + \theta_3 a_1 + \beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}{1 + \exp(\theta_2 + \theta_3 a_1 + \beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}$$

$$B_{PNDE} = \frac{\exp(\theta_2 + \theta_3 a_0 + \beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}{1 + \exp(\theta_2 + \theta_3 a_0 + \beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}$$

$$d_{1,PNDE} = Q_{PNDE} - B_{PNDE}$$

$$d_{2,PNDE} = a_0(Q_{PNDE} - B_{PNDE})$$

$$d_{3,PNDE} = \mathbf{c}(Q_{PNDE} - B_{PNDE})$$

$$d_{4,PNDE} = 0$$

$$d_{5,PNDE} = a_1 - a_0$$

$$d_{6,PNDE} = Q_{PNDE} - B_{PNDE}$$

$$d_{7,PNDE} = a_1 Q_{PNDE} - a_0 B_{PNDE}$$

$$d_{8,PNDE} = \underline{0}$$

$$\Gamma_{PNDE} = \frac{\partial PNDE}{\partial(\beta^T, \theta^T)^T}$$

$$= \begin{bmatrix} d_{1,PNDE} \\ d_{2,PNDE} \\ d_{3,PNDE} \\ d_{4,PNDE} \\ d_{5,PNDE} \\ d_{6,PNDE} \\ d_{7,PNDE} \\ d_{8,PNDE} \end{bmatrix}$$

$$Q_{TNIE} = \frac{\exp(\theta_2 + \theta_3 a_1 + \beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{1 + \exp(\theta_2 + \theta_3 a_1 + \beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}$$

$$B_{TNIE} = \frac{\exp(\theta_2 + \theta_3 a_1 + \beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}{1 + \exp(\theta_2 + \theta_3 a_1 + \beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}$$

$$K_{TNIE} = \frac{\exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}$$

$$D_{TNIE} = \theta_3 \frac{\exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_0 + \beta_2^T \mathbf{c})}$$

$$d_{1,TNIE} = (D_{TNIE} + Q_{TNIE}) - (K_{TNIE} + B_{TNIE})$$

$$d_{2,TNIE} = a_0(D_{TNIE} - B_{TNIE}) + a_1(Q_{TNIE} - K_{TNIE})$$

$$d_{3,TNIE} = \mathbf{c} \{ (D_{TNIE} + Q_{TNIE}) - (K_{TNIE} + B_{TNIE}) \}$$

$$d_{4,TNIE} = 0$$

$$d_{5,TNIE} = 0$$

$$d_{6,TNIE} = Q_{TNIE} - B_{TNIE}$$

$$d_{7,TNIE} = a_1(Q_{TNIE} - B_{TNIE})$$

$$d_{8,TNIE} = 0$$

$$\Gamma_{TNIE} = \frac{\partial TNIE}{\partial (\beta^T, \theta^T)^T}$$

$$= \begin{bmatrix} d_{1,TNIE} \\ d_{2,TNIE} \\ d_{3,TNIE} \\ d_{4,TNIE} \\ d_{5,TNIE} \\ d_{6,TNIE} \\ d_{7,TNIE} \\ d_{8,TNIE} \end{bmatrix}$$

$$Q_{TNDE} = \frac{\exp(\theta_2 + \theta_3 a_1 + \beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{1 + \exp(\theta_2 + \theta_3 a_1 + \beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}$$

$$B_{TNDE} = \frac{\exp(\theta_2 + \theta_3 a_0 + \beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}{1 + \exp(\theta_2 + \theta_3 a_0 + \beta_0 + \beta_1 a_1 + \beta_2^T \mathbf{c})}$$

$$d_{1,TNDE} = Q_{TNDE} - B_{TNDE}$$

$$d_{2,TNDE} = a_1(Q_{TNDE} - B_{TNDE})$$

$$d_{3,TNDE} = \mathbf{c}(Q_{TNDE} - B_{TNDE})$$

$$d_{4,TNDE} = 0$$

$$d_{5,TNDE} = a_1 - a_0$$

$$d_{6,TNDE} = Q_{TNDE} - B_{TNDE}$$

$$d_{7,TNDE} = a_1 Q_{TNDE} - a_0 B_{TNDE}$$

$$d_{8,TNDE} = 0$$

$$\begin{aligned}\Gamma_{TNDE} &= \frac{\partial TNDE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\ &= \begin{bmatrix} d_{1,TNDE} \\ d_{2,TNDE} \\ d_{3,TNDE} \\ d_{4,TNDE} \\ d_{5,TNDE} \\ d_{6,TNDE} \\ d_{7,TNDE} \\ d_{8,TNDE} \end{bmatrix}\end{aligned}$$

$$\begin{aligned}Q_{PNIE} &= \frac{\exp(\theta_2 + \theta_3 a_0 + \text{beta}_0 + \beta_1 a_1 + \boldsymbol{\beta}_2^T \mathbf{c})}{1 + \exp(\theta_2 + \theta_3 a_0 + \text{beta}_0 + \beta_1 a_1 + \boldsymbol{\beta}_2^T \mathbf{c})} \\ B_{PNIE} &= \frac{\exp(\theta_2 + \theta_3 a_0 + \text{beta}_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})}{1 + \exp(\theta_2 + \theta_3 a_0 + \text{beta}_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})} \\ K_{PNIE} &= \frac{\exp(\beta_0 + \beta_1 a_1 + \boldsymbol{\beta}_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_1 + \boldsymbol{\beta}_2^T \mathbf{c})} \\ D_{PNIE} &= \theta_3 \frac{\exp(\beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})}{1 + \exp(\beta_0 + \beta_1 a_0 + \boldsymbol{\beta}_2^T \mathbf{c})} \\ d_{1,PNIE} &= (D_{PNIE} + Q_{PNIE}) - (K_{PNIE} + B_{PNIE}) \\ d_{2,PNIE} &= a_0(D_{PNIE} - B_{PNIE}) + a_1(Q_{PNIE} - K_{PNIE}) \\ d_{3,PNIE} &= \mathbf{c} \{ (D_{PNIE} + Q_{PNIE}) - (K_{PNIE} + B_{PNIE}) \} \\ d_{4,PNIE} &= 0 \\ d_{5,PNIE} &= 0 \\ d_{6,PNIE} &= Q_{PNIE} - B_{PNIE} \\ d_{7,PNIE} &= a_0(Q_{PNIE} - B_{PNIE}) \\ d_{8,PNIE} &= 0\end{aligned}$$

$$\begin{aligned}\Gamma_{PNIE} &= \frac{\partial PNIE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\ &= \begin{bmatrix} d_{1,PNIE} \\ d_{2,PNIE} \\ d_{3,PNIE} \\ d_{4,PNIE} \\ d_{5,PNIE} \\ d_{6,PNIE} \\ d_{7,PNIE} \\ d_{8,PNIE} \end{bmatrix}\end{aligned}$$

$$\begin{aligned}\Gamma_{TE} &= \frac{\partial TE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\ &= \frac{\partial(PNDE + TNIE)}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\ &= \Gamma_{PNDE} + \Gamma_{TNIE}\end{aligned}$$

$$\Gamma_{PM} = \frac{\partial PM}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T}$$

By multivariate chain rule

$$\begin{aligned}
&= \frac{\partial PM}{\partial PNDE} \frac{\partial PNDE}{\partial(\beta^T, \theta^T)^T} + \frac{\partial PM}{\partial TNIE} \frac{\partial TNIE}{\partial(\beta^T, \theta^T)^T} \\
&= \frac{\partial PM}{\partial PNDE} \Gamma_{PNDE} + \frac{\partial PM}{\partial TNIE} \Gamma_{TNIE} \\
&= - \frac{\exp(PNDE) \{\exp(TNIE) - 1\}}{\{\exp(PNDE) \exp(TNIE) - 1\}^2} \Gamma_{PNDE} \\
&\quad + \frac{\exp(PNDE) \exp(TNIE) \{\exp(PNDE) - 1\}}{\{\exp(PNDE) \exp(TNIE) - 1\}^2} \Gamma_{TNIE}
\end{aligned}$$

Variance-covariance matrix from two models

$$\begin{aligned}
\Sigma &= \begin{bmatrix} \Sigma_\beta & 0 \\ 0 & \Sigma_\theta \end{bmatrix} \\
SE(\widehat{CDE}(m)) &= \sqrt{\Gamma_{CDE(m)}^T \Sigma \Gamma_{CDE(m)}} \\
SE(\widehat{PNDE}) &= \sqrt{\Gamma_{PNDE}^T \Sigma \Gamma_{PNDE}} \\
SE(\widehat{TNIE}) &= \sqrt{\Gamma_{TNIE}^T \Sigma \Gamma_{TNIE}} \\
SE(\widehat{TNDE}) &= \sqrt{\Gamma_{TNDE}^T \Sigma \Gamma_{TNDE}} \\
SE(\widehat{PNIE}) &= \sqrt{\Gamma_{PNIE}^T \Sigma \Gamma_{PNIE}} \\
SE(\widehat{TE}) &= \sqrt{\Gamma_{TE}^T \Sigma \Gamma_{TE}} \\
SE(\widehat{PM}) &= \sqrt{\Gamma_{PM}^T \Sigma \Gamma_{PM}}
\end{aligned}$$

3 Software

The detailed explanation of the software implementation is given on its website (<https://kaz-yos.github.io/regmedint/index.html>).

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