Pseudocode for MRPC Update

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1.1 - The Trio Specific Case:

In a network consisting of three nodes: $G(V_1, T_1, T_2)$ we can identify the 5 possible topologies laid out under MRPC using results of the coefficient tests from the pair of regressions on each non-instrumental variable (Please refer to the **Appendix** at the end for Tables, Figures, and mathematical definitions).

Step 1. Preform two regressions treating each non-instumental variable as the response once:

$$T_1 = \beta_0 + \beta_{11} V_1 + \beta_{21} T_2 + \mathbf{\Gamma U} + \epsilon \tag{1}$$

$$T_2 = \beta_0 + \beta_{12} V_1 + \beta_{22} T_1 + \mathbf{\Gamma U} + \epsilon \tag{2}$$

and retain the p-values $p_{\beta_{11}}, p_{\beta_{21}}, p_{\beta_{12}}, p_{\beta_{22}}$ for tests on the coefficients $\beta_{11}, \beta_{21}, \beta_{12}, \beta_{22}$

Step 2. Calculate the frequency of the minor allele of the variant/instrumental variable as f_{minor}.

> **Step 2.1** - If the minor variant frequency f_{minor} (allele frequency or copy number variation) from **Step 1.** is less than the predetermined threshold γ, preform the permuted regressions described in **Section 1.2** else proceed directly to **Step 3**

Step 3. following **Steps 1 - 2** obtain the vector of p-values for hypothesis tests on $\beta_{11}, \beta_{21}, \beta_{12}, \beta_{22}$ (in this order and using the nominal pvalues for β_{21}, β_{22} if the permuted regression was preformed) as the vector $\mathbf{p}$

> **Step 3.1** Convert the vector of p-values $\mathbf{p}$ into the indicator vector $\mathbf{x}_p$ where 1 denotes a significant p-value at threshold α and 0 denotes a nonsignificant p-value

Step 4. If $\mathbf{x}_p$ matches the expected result for the M3 topology given in **Tables 1 and 2** allocate the trio to M3, return the correct adjacency matrix for M3, and **Stop**.

Else, calculate the correlations between the instrumental variable and T_1 and T_2, and then preform hypothesis testing on r_{V_1,T_2} and r_{V_1,T_1} and proceed to **Step 4.2** (i.e infer the marginal relationships between V_1, T_2 and V_1, T_1)

> **Step 4.2** Convert the p-values for the marginal test **Step 4** into the indicator vector $\mathbf{r}_p$ where 1 denotes a significant p-value at threshold α and 0 denotes a nonsignificant p-value

Step 5. - Compare $\mathbf{x}_p$ and $\mathbf{r}_p$ with the expected results for the other four model topologies given in **Tables 1 and 2** in the **Appendix** and allocate the trio to model type for which it matches (note that models M0, M1, and M2 have two cases each depending on the directions of the edges). If no match is available allocate the trio the class "other".

Step 6. - Return the correct adjacency matrix from the inferred model type in **Step 5**

1.2 - Permuted Regression for Rare Variants

- We will apply the permuted regression described by Yang et al., 2017 whenever the instrumental variable contains a rare count at frequency $< \gamma$. The permuted regression is preformed to obtain a robust estimate of the mediation effect between the nodes T_i and T_j in $G(V_k, T_i, T_j)$ which may be masked in the standard regression when V_k contains few observations for the minor variant. The algorithm for preforming the permuted regression is as follows:

Step 1. - permute T_2 in (**1**) within the levels of V_1 denoted T_2^*. Similarly, permute T_1 in (**2**) within the levels of V_1 denoted T_1^*.

> **Step 1.1** - Next preform the regressions in **Section 1.1** using the permuted variables:
>
> $$T_1 = \beta_0 + \beta_{11}V_1 + \beta_{21}^* T_2^* + \mathbf{\Gamma U} + \epsilon \tag{3}$$
>
> $$T_2 = \beta_0 + \beta_{12}V_1 + \beta_{22}^* T_1^* + \mathbf{\Gamma U} + \epsilon \tag{4}$$
>
> **Step 1.2** - store the observed t-statistic for β_{21}^* in the vector $\mathbf{\Theta}_{21}$ and the t-statistic for β_{22}^* in the vector $\mathbf{\Theta}_{22}$

Step 2. repeat **Steps 1 - 1.2** m times to obtain the $m \times 1$ vectors of observed t-statistics $\mathbf{\Theta}_{21}$ and $\mathbf{\Theta}_{22}$.

> **Step 2.1** - Using $\mathbf{\Theta}_{21}$, $\mathbf{\Theta}_{22}$, $t_{\text{obs}_{21}}$, and $t_{\text{obs}_{21}}$, calculate the permutation nominal p-values for β_{21} and β_{22} (which we will denote respectively)

Step 3. - retain $p^*_{\beta_{21}}$ and $p^*_{\beta_{22}}$ and return to **Step 3** in **Section 1.1**

2. General Algorithm

Step 1. - Given a data matrix $\mathbf{X}$ of q instrumental variables, p non-instrumental variables, and g confounders. Calculate the partial correlation matrix $\mathbf{H}$ and extract the first $\lambda = \{1 : q + p\}$ rows and columns of $\mathbf{H}$ which represents the partial correlations between all nodes in the graph $G(V_1, V_2, ...V_q, T_1, T_2, ...T_p)$.

Step 1.1 - preform a partial correlation test on all non-diagonal entries in $\mathbf{H}[\lambda, \lambda]$ to obtain the $(q+p) \times (q+p)$ matrix of p-values $\mathbf{P}$ corresponding to the nodes in $G(V_1, V_2, ...V_q, T_1, T_2, ...T_p)$.

Step 1.2 -For each non-diagonal entry in $\mathbf{P}$ replace significant p-values at threshold α with 1 and nonsignificant p-values with 0 to obtain the $(q+p) \times (q+p)$ adjacency matrix $\mathbf{A}$ for the skeleton of $G(V_1, V_2, ...V_q, T_1, T_2, ...T_p)$.

Note that **Steps 1-1.2** are to infer the entire graph skeleton by filtering unnecessary edges and reduce computational time/complexity in later steps

Step 2. - For each instrumental variable V_i: Allocate all possible trios with V_i such that the row in $\mathbf{A}$ representing V_i has at least one edge between V_i and one of the non-instrumental variables in each trio. Let p_i be the number of non-instrumental variables that have an edge with V_i (e.g $p_i = \sum \mathbf{a}_{i\cdot}$) then there are $p_i \times (p - p_i) + \binom{p_i}{2}$ trios that will be formed with V_i

Step 2.1 - Preallocate all trios from **Step 2** for each V_i into a list where each entry in the list is the $n \times (3+g)$ data matrix $[V_i, T_j, T_k, \mathbf{U}]$

Step 3. - Determine the directed structure of all trios with an instrumental variable from the list in **Step 2.1** using the regressions and tests outlined in **Sections 1.1-1.2**.

Step 3.1 - For each trio: If the inference returned in **Step 3** is one of the 5 MRPC model structures, update/direct the appropriate entries in the overall adjacency matrix $\mathbf{A}$ with the inferred result. Else, if the inference returned is of the type "Other" ignore (this point may be redundant as "Other" types aren't likely to arise since we require only trios with at least one edge between the instrumental variable/variant)

Step 4. - Form all possible trios among strictly T-nodes i.e $G(T_i, T_j, T_k)$ such that the submatrix from $\mathbf{A}$ corresponding to each trio denoted $\mathbf{A}[ijk, ijk]$ has exactly two edges: e.g $\sum\sum \mathbf{A}$[ijk,ijk]= 2

Step 4.1 - Preallocate all trios formed in **Step 4** into a list where each entry in the list is the $n \times (3+g)$ data matrix $[T_i, T_j, T_k, \mathbf{U}]$

Step 5. - Determine the directed structure of all trios from **Step 4.1**:

Step 5.1 - If $\mathbf{A}[ijk, ijk]$ contains a single directed edge after it has been updated by **Step 3.1**, replace the instrumental variable in **Section 1.1, Step 1** with the parent node of the directed edge and infer the direction of the remaining edge using only a single regression from **Section 1.1, Step 1**.

Example: if we have the graph $G(T_1, T_2, T_3)$ and from $\mathbf{A}$ (after **Step 3.1**) we have $T_1 \rightarrow T_2$ and $T_2 - T_3$ then we preform only a single regression:

$$T_2 = \beta_0 + \beta_{12} T_1 + \beta_{22} T_3 + \mathbf{\Gamma U} + \epsilon$$

to determine the direction of $T_2 - T_3$

Step 5.2 - If $\mathbf{A}[ijk, ijk]$ has no directed edges after updating in **Step 3.1** replace V_1 in **Section 1.1, Step 1** with one of the T-nodes:

$$T_1 = \beta_0 + \beta_{11} T_3 + \beta^*_{21} T^*_2 + \mathbf{\Gamma U} + \epsilon \tag{5}$$

$$T_2 = \beta_0 + \beta_{12} T_3 + \beta^*_{22} T^*_1 + \mathbf{\Gamma U} + \epsilon \tag{6}$$

and determine if the network is M2 using the regressions and tests from **Section 1.1**

Step 6. - Use the results from **Step 5.1** and the trios inferred to be $M2$ in **Step 5.2** to update the appropriate entries in adjacency matrix $\mathbf{A}$ (i.e direct any additional edges in $\mathbf{A}$)

Step 7. - following **Steps 1 - 6**, return $\mathbf{A}$

3. Simulation Strategy to Validate Section 1.1

To verify that the indicator vectors $\mathbf{x}_p$ derived from the the hypothesis tests in **Section 1.1** are sufficient in identifying the proposed model structures from MRPC given in **Tables 1 and 2**, we propose the following simulation methodology:

(1.) - Using the linear models for the 5 basic topologies described by Badsha and Fu 2019, we propose to simulate each trio topology under varying signal strengths (and possibly sample size) using the simulation functions in the R package $MRPC$.

(2.) - we then apply the algorithm proposed in **Section 1.1** to determine if the expected results given in **Tables 1 and 2** are identified. we compare the indicator vector $\mathbf{x}_p$ to the expected indicator vectors for each topology and allocate the trio to one of the 5 topologies as laid out in **Section 1.1 Step 5**. Our goal is to determine if the inference for each trio is adequate for identifying the generating model or if unexpected indicator vectors arise.

(3.) - Investigate, if any, the indicator vectors allocated to the "Other" class.

Appendix

Definitions

V_i - The i^{th} instrumental variable when $q > 1$

T_i - a non-instrumental variable/node

p - the number of non-instrumental variables/nodes in a network

q - the number of instrumental variables

g - the number of confounding variables selected for a network

m - the number of permutations to preform in a permuted regression (mediation test)

n - the sample size of the data

$\mathbf{U}$ - the $(n \times g)$ matrix whose columns represent confounding variables

$\mathbf{X}$ - the $(n \times p+q+g)$ data matrix of all variables/nodes and all confounders

$\mathbf{H}$ - the $(p+q+g \times p+q+g)$ precision matrix

A - a $(p+q \times p+q)$ adjacency matrix for the network

$G(A, B, C)$ - a graph with nodes A, B, and C

$F(\cdot)$ - the Fisher transformation function

f_{minor} - The frequency of the minor variant of V_i (when V represents a type of genetic variation)

γ - the threshold frequency of the minor variant for which we determine if a permuted regression is needed

$\rho_{\mathbf{x_i},\mathbf{x_j}\cdot\mathbf{x}_{-(\mathbf{i},\mathbf{j})}}$ - the partial correlation between the i^{th} and j^{th} columns/variables of $\mathbf{X}$

Table 1: - Expected results for the tests on the regression coefficients under each model scenario (trios with variants only).

Model	$\beta_{\mathbf{11}}$	$\beta_{\mathbf{21}}$	$\beta_{\mathbf{12}}$	$\beta_{\mathbf{22}}$	$V_1 \perp\!\!\!\perp T_2$	$V_1 \perp\!\!\!\perp T_1$
M0	$\neq 0$	$= 0$	$= 0$	$= 0$	Yes	
	$= 0$	$= 0$	$\neq 0$	$= 0$		Yes
M1	$\neq 0$	$\neq 0$	$= 0$	$\neq 0$	No	
	$= 0$	$\neq 0$	$\neq 0$	$\neq 0$		No
M2	$\neq 0$	$\neq 0$	$\neq 0$	$\neq 0$	Yes	
	$\neq 0$	$\neq 0$	$\neq 0$	$\neq 0$		Yes
M3	$\neq 0$	$= 0$	$\neq 0$	$= 0$	–	–
M4	$\neq 0$	$\neq 0$	$\neq 0$	$\neq 0$	No	
Conditionally: $Y \sim$	$V_i \mid T_j, \mathbf{U}$	$T_j \mid V_i, \mathbf{U}$	$V_i \mid T_i, \mathbf{U}$	$T_j \mid V_i, \mathbf{U}$		

$$T_1 = \beta_0 + \beta_{11} V_1 + \beta_{21} T_2 + \mathbf{\Gamma U} + \epsilon \tag{7}$$

$$T_2 = \beta_0 + \beta_{12} V_1 + \beta_{22} T_1 + \mathbf{\Gamma U} + \epsilon \tag{8}$$

Table 2: - Expected indicator table for the tests on the regression coefficients under each model scenario (trios with variants only). Note that 1 indicates a a rejection of H_0 and 0 indicates a failure to reject

Model	$H_0 : \beta_{\mathbf{11}} = \mathbf{0}$	$H_0 : \beta_{\mathbf{21}} = \mathbf{0}$	$H_0 : \beta_{\mathbf{12}} = \mathbf{0}$	$H_0 : \beta_{\mathbf{22}} = \mathbf{0}$	$H_0 : V_1 \perp\!\!\!\perp T_2$	$H_0 : V_1 \perp\!\!\!\perp T_1$
M0	1	0	0	0	1	
	0	0	1	0		1
M1	1	1	0	1	1	
	0	1	1	1		1
M2	1	1	1	1	0	
	1	1	1	1		0
M3	1	0	1	0		
M4	1	1	1	1	1	

Table 3: - The set up for the adjacency matrix for each 3-node network denoted by the graph $G(T_i, T_j, T_k) \quad i, j, k \in \{1 : p\}; \forall i \neq j \neq k$ found using the regressions outlined in **Section 1.3**. Each entry in the table shows the null hypothesis used for testing the edge between the node in the row and node in the column. An entry with 1 means we keep the edge between the nodes (i.e we reject H_0) and a 0 means we remove the edge between the nodes (i.e we fail to reject H_0)

Response	T_i	T_j	T_k
T_i	0	$H_0 : T_i \perp\!\!\!\perp T_j \mid T_k, \mathbf{U}$	$T_i \perp\!\!\!\perp T_k \mid T_j, \mathbf{U}$
T_j	$H_0 : T_j \perp\!\!\!\perp T_i \mid T_k, \mathbf{U}$	0	$T_j \perp\!\!\!\perp T_k \mid T_i, \mathbf{U}$
T_k	$H_0 : T_k \perp\!\!\!\perp T_i \mid T_j, \mathbf{U}$	$H_0 : T_k \perp\!\!\!\perp T_j \mid T_i, \mathbf{U}$	0

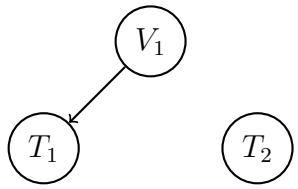


Figure 1: M0 - $V_1 \not\perp\!\!\!\perp T_1; V_1 \perp\!\!\!\perp T_2; T_1 \perp\!\!\!\perp T_2$

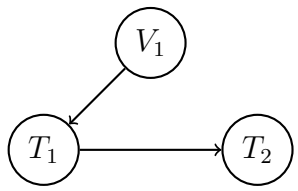


Figure 2: M1 - $V_1 \not\perp\!\!\!\perp T_1; V_1 \not\perp\!\!\!\perp T_2; T_1 \not\perp\!\!\!\perp T_2; V_1 \perp\!\!\!\perp T_2 | T_1$

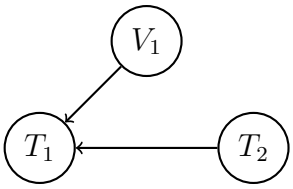


Figure 3: M2 - $V_1 \not\perp\!\!\!\perp T_1; V_1 \perp\!\!\!\perp T_2; T_1 \not\perp\!\!\!\perp T_2; V_1 \not\perp\!\!\!\perp T_2|T_1$

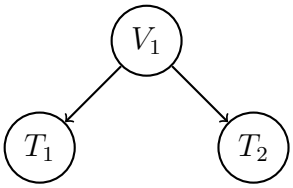


Figure 4: fig: M3 - $V_1 \not\perp\!\!\!\perp T_1; V_1 \not\perp\!\!\!\perp T_2; T_1 \not\perp\!\!\!\perp T_2; T_1 \perp\!\!\!\perp T_2|V_1$

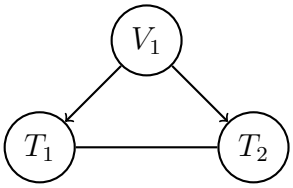


Figure 5: fig: M4 - $V_1 \not\perp\!\!\!\perp T_1; V_1 \not\perp\!\!\!\perp T_2; T_1 \not\perp\!\!\!\perp T_2; T_1 \not\perp\!\!\!\perp T_2|V_1$

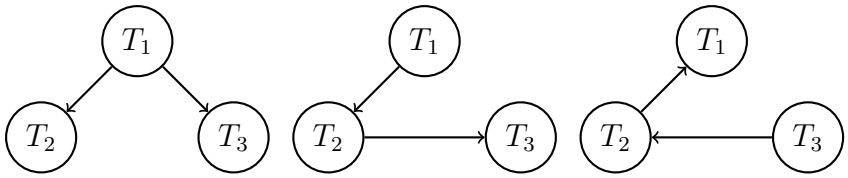


Figure 6: fig: The three graphs above are Markov equivalent meaning they share the same conditional and marginal independence relations Markove: $T_1 \perp\!\!\!\perp T_3|T_2$ Minimality: $T_1 \not\perp\!\!\!\perp T_2$; $T_2 \not\perp\!\!\!\perp T_3$ faithfulness: $T_1 \not\perp\!\!\!\perp T_3$ and are therefore indistinguishable from each other

Details On Statistical Methods

Calculating Precision

Given a data matrix $\mathbf{X}$ of q instrumental variables, p non-instrumental variables, and g confounders:
Assuming $\mathbf{X}$ is centered:

$$X \sim N_k(\mathbf{0}, \mathbf{\Sigma}) \quad \text{for } k = p + q + g$$

Then the precision matrix of $\mathbf{X}$ is defined as

$$\mathbf{H} = \mathbf{\Sigma}^{-1}$$

$\mathbf{H}$ can be scaled to the partial correlation matrix for the entries in $\mathbf{X}$. Given the entry in the i^{th} row and j^{th} column of $\mathbf{H}$:

$$\mathbf{x}_i, \mathbf{x}_j | \mathbf{x}_{-(i,j)} = -\frac{h_{ij}}{\sqrt{h_{ii}}\sqrt{h_{jj}}} = \hat{\rho}_{\mathbf{x_i}, \mathbf{x_j} \cdot \mathbf{x}_{-(\mathbf{i},\mathbf{j})}}$$

which is a measure of the association between the i^{th} and j^{th} columns/variables in $\mathbf{X}$ conditioned on all other variables.

The Fisher transformation can be used to formulate a test for each partial correlation coefficient of interest:

$$\frac{\sqrt{n - |\mathbf{x_{-i,j}}| - 3}}{2} \ln\left(\frac{1 + \hat{\rho}_{\mathbf{x_i}, \mathbf{x_j} \cdot \mathbf{x}_{-(\mathbf{i},\mathbf{j})}}}{1 - \hat{\rho}_{\mathbf{x_i}, \mathbf{x_j} \cdot \mathbf{x}_{-(\mathbf{i},\mathbf{j})}}}\right) \approx N(0, 1)$$

where null and alternative hypotheses are

$$H_0 : \hat{\rho}_{\mathbf{x_i}, \mathbf{x_j} \cdot \mathbf{x}_{-(\mathbf{i},\mathbf{j})}} = 0 \quad H_A : \hat{\rho}_{\mathbf{x_i}, \mathbf{x_j} \cdot \mathbf{x}_{-(\mathbf{i},\mathbf{j})}} \neq 0$$

$$\text{reject } H_0 \text{ if } \; |Z_{\text{obs}}| > Z_{1-\alpha/2}$$

by applying the cases:

$$a_{i,j} = \begin{cases} 1 & \text{if } \; 2 \times P(Z > |Z_{\text{obs}}|) < \alpha \\ 0 & \text{else} \end{cases} \quad \forall i, j \in \{1 : p + q\}$$

we can obtain the $(p + q \times p + q)$ adjacency matrix $\mathbf{A}$ for the network skeleton

Permutated Regression mediation test

repeat m times: permute T_j in (**1**) within the levels of V_i denoted T_j^*. Similarly, permute T_i in (**2**) within the levels of V_k denoted T_i^*. Next preform the regressions using the permuted variables:

$$T_i = \beta_0 + \beta_{1i} V_k + \beta_{2i}^* T_j^* + \mathbf{\Gamma U} + \epsilon \tag{9}$$

$$T_j = \beta_0 + \beta_{1j} V_k + \beta_{2j}^* T_i^* + \mathbf{\Gamma U} + \epsilon$$

Let $\mathbf{\Theta}_{2i}$ and $\mathbf{\Theta}_{2j}$ denote the $(m \times 1)$ vectors representing the collection of t statistics from the wald tests on β_{2i}^* and β_{2j}^* coefficients (respectively) from the permuted regressions in **Step 2.**. such that:

$$\mathbf{\Theta}_{2i} = \left[T_{2i}^{*(1)},\ T_{2i}^{*(2)},\ T_{2i}^{*(3)}, \cdots \right]$$

$$\mathbf{\Theta}_{2j} = \left[T_{2j}^{*(1)},\ T_{2j}^{*(2)},\ T_{2j}^{*(3)}, \cdots \right]$$

We next test the conditional association between T_i and T_j using the nominal test defined by Yang et. al., 2017. Let $T_{\text{obs}_{2i}}$ be the observed wald statistic from (**1**) and $T_{\text{obs}_{2j}}$ be the observed wald statistic from (**2**). We formulate the testable hypotheses:

$$H_0 : T_{\text{obs}_{2i}} = \mu_{2i}^*, \quad H_A : T_{\text{obs}_{2i}} \neq \mu_{2i}^*$$

and

$$H_0 : T_{\text{obs}_{2j}} = \mu_{2j}^*, \quad H_A : T_{\text{obs}_{2j}} \neq \mu_{2j}^*$$

where μ_{2i}^* and μ_{2j}^* denote the centers of the non-central t-distributions of $\mathbf{\Theta}_{2i}$ and $\mathbf{\Theta}_{2j}$ respectively. Therefore the mediation test statistic is:

$$Z_{\text{obs}_{ij}} = \frac{T_{\text{obs}_{ij}} - \frac{\sum \mathbf{\Theta}_{ij}}{m}}{SE(\mathbf{\Theta}_{ij})}$$

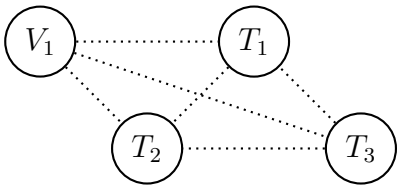
where we

$$\text{reject } H_0 \text{ if } \quad 2 \times P(Z > |Z_{\text{obs}_{ij}}|) < \alpha$$

Inferring the Network Among Non-Instrumental Variables

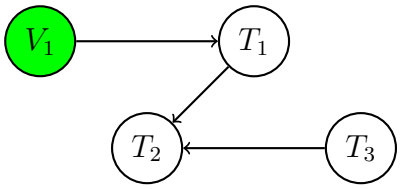
Because we infer the network among all 3-node networks involving an instrumental variable first, we have additional information for each 3-node network among T-nodes. When we lack an instrumental variable, we can only uniquely infer M2. As a result we cannot distinguish M1 and M3 due to Markov equivalence, but we are able to determine the undirected graphs of M0 and M4. (**Figure 6**). Exploiting the information provided by

the associations between the T-nodes and the instrumental variable(s) we obtain in **Step 3** of the **General Algorithm** we can actually view the problem as a partially inferred network among 4 nodes i.e the graph $G(V_1, T_1, T_2, T_3)$.



The above graph demonstrates how we may view the problem of classifying trios of T-nodes, by exploiting whatever relationships exist in the subnetwork of the graphs $G(V_1, T_1, T_2), G(V_1, T_1, T_3)$ and $G(V_1, T_2, T_3)$.

Example 1: v-structure in $G(T_1, T_2, T_3)$

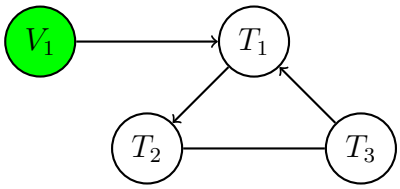


Take the example above as one such network that may exist among the nodes V_1, T_1, T_2, T_3 defined by the individual graph types:

$$G(V_1, T_1, T_2, T_3) = \begin{cases} G(V_1, T_1, T_2) : M1 \\ G(V_1, T_1, T_3) : M0 \\ G(V_1, T_2, T_3) : Other \\ G(T_1, T_2, T_3) : M2 \end{cases}$$

Therefore, we require the step of inferring $G(T_1, T_2, T_3)$ to identify v-structures in the non-instrumental variable network of T-nodes. If we did not preform a separate trio analysis for the nodes T_1, T_2, T_3 we could still infer all the edges in the above graph, however the edge between T_2 and T_3 would be left undirected. Therefore, by including this step in the algorithm we are able to direct an additional edge whenever the relationship between T_i, T_j, T_k is of type M2:

Example 2: No v-structure in $G(T_1, T_2, T_3)$



$$G(V_1, T_1, T_2, T_3) = \begin{cases} G(V_1, T_1, T_2) : M1 \\ G(V_1, T_1, T_3) : M2 \\ G(V_1, T_2, T_3) : Other \\ G(T_1, T_2, T_3) : M4 \end{cases}$$

This is a counter example where the inference for the subnetwork for T_1, T_2, T_3 would be returned as M4 which is undirectable in the absence of the PMR assumption. As a result the subnetworks for the combinations of nodes involving the variant fully specify the graph $G((V_1, T_1, T_2, T_3)$