Supplemental Material

I: Proof of Theorem 3

There are some notation changes as follows for the convenience of the derivation: we use $b_{Y_1} = \beta_{1,l+1}$, $b_{Y_2} = \beta_{2,l+1}$, …, $b_{Y_n} = \beta_{l,l+1}$, $b_{Z_1} = \beta_{l+3,l+2}$, $b_{Z_2} = \beta_{l+4,l+2}$, …, $b_{Z_{\widetilde{m}}} = \beta_{l+m,l+2}$, $b_{21} = \beta_{l+1,l+2}$, $Y_1 = X_1$, $Y_2 = X_2$, … , $Y_n = X_l$, $Z_1 = X_{l+3}$, $Z_2 = X_{l+4}$, … , $Z_{\widetilde{m}} = X_{l+m}$, $X_1 = X_{l+1}$, $X_2 = X_{l+2}$. Finally, we use m instead of $\widetilde{m}$.

Based on Wright's second decomposition rule [56], the covariance matrix of all the variables, $T_{n,m}$, can be represented as a function of the parameters of the BN, i.e.,

$$T_{n,m} = Cov(Y_1, Y_2, ..., Y_n, X_1, X_2, Z_1, Z_2, ..., Z_m) = \begin{pmatrix} 1 & 0 & 0 & ... & 0 & b_{Y_1} & b_{21}b_{Y_1} & 0 & 0 & ... & 0 \\ 0 & 1 & 0 & ... & 0 & b_{Y_2} & b_{21}b_{Y_2} & 0 & 0 & ... & 0 \\ 0 & 0 & 1 & ... & 0 & b_{Y_3} & b_{21}b_{Y_3} & 0 & 0 & ... & 0 \\ ... & ... & ... & ... & ... & ... & ... & ... & ... & ... & ... \\ 0 & 0 & 0 & ... & 1 & b_{Y_n} & b_{21}b_{Y_n} & 0 & 0 & ... & 0 \\ b_{Y_1} & b_{Y_2} & b_{Y_3} & ... & b_{Y_n} & 1 & b_{21} & 0 & 0 & ... & 0 \\ b_{21}b_{Y_1} & b_{21}b_{Y_2} & b_{21}b_{Y_3} & ... & b_{21}b_{Y_n} & b_{21} & 1 & b_{Z_1} & b_{Z_2} & ... & b_{Z_m} \\ 0 & 0 & 0 & ... & 0 & 0 & b_{Z_1} & 1 & 0 & ... & 0 \\ 0 & 0 & 0 & ... & 0 & 0 & b_{Z_2} & 0 & 1 & ... & 0 \\ ... & ... & ... & ... & ... & ... & ... & ... & ... & ... & ... \\ 0 & 0 & 0 & ... & 0 & 0 & b_{Z_m} & 0 & 0 & ... & 1 \end{pmatrix} \quad \text{(A-1).}$$

Now, consider the regression of X_1 on all other variables, i.e., $X_1 = b_{Y_1}^{MB} Y_1 + b_{Y_2}^{MB} Y_2 + \cdots + b_{Y_n}^{MB} Y_n + b_{Z_1}^{MB} Z_1 + b_{Z_2}^{MB} Z_2 + \cdots + b_{Z_m}^{MB} Z_m + b_{21}^{MB} X_2 + e_{X_1}^{MB}$. According to the Least Square criterion, the regression coefficients are equal to

$$\begin{pmatrix} b_{Y_1}^{MB} \\ b_{Y_2}^{MB} \\ \ldots \\ b_{Y_n}^{MB} \\ b_{21}^{MB} \\ b_{Z_1}^{MB} \\ b_{Z_2}^{MB} \\ \ldots \\ b_{Z_m}^{MB} \end{pmatrix} = \begin{pmatrix} 1 & 0 & \ldots & 0 & b_{21}b_{Y_1} & 0 & 0 & \ldots & 0 \\ 0 & 1 & \ldots & 0 & b_{21}b_{Y_2} & 0 & 0 & \ldots & 0 \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ 0 & 0 & \ldots & 1 & b_{21}b_{Y_n} & 0 & 0 & \ldots & 0 \\ b_{21}b_{Y_1} & b_{21}b_{Y_2} & \ldots & b_{21}b_{Y_n} & 1 & b_{Z_1} & b_{Z_2} & \ldots & b_{Z_m} \\ 0 & 0 & \ldots & 0 & b_{Z_1} & 1 & 0 & \ldots & 0 \\ 0 & 0 & \ldots & 0 & b_{Z_2} & 0 & 1 & \ldots & 0 \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ 0 & 0 & \ldots & 0 & b_{Z_m} & 0 & 0 & \ldots & 1 \end{pmatrix}^{-1} \begin{pmatrix} b_{Y_1} \\ b_{Y_2} \\ \ldots \\ b_{Y_n} \\ b_{21} \\ 0 \\ 0 \\ \ldots \\ 0 \end{pmatrix}$$

(A-2)

Denote the first matrix in the right hand side of the equation as $A_{n,m}$, and its inverse matrix as $C_{n,m}$, with $A_{n,m} = (a_{i,j})_{i=1,2,\ldots,n;\, j=1,2,\ldots,m}$, $C_{n,m} = (c_{i,j})_{i=1,2,\ldots,n;\, j=1,2,\ldots,m}$. We first investigate the formula for $b_{y_1}^{MB}$. Based on (A-2), we have

$$b_{y_1}^{MB} = a_{11}b_{y_1} + a_{12}b_{y_2} + a_{13}b_{y_3} + \ldots + a_{1n}b_{y_n} + a_{1n+1}b_{21} . \tag{A-3}$$

Our final objective is to express $b_{y_1}^{MB}$ by the parameters of the BN. This can be achieved if we can express $a_{11}, a_{12}, a_{13}, \cdots, a_{1\,n+1}$ by the parameters of the BN, which is the goal of the following derivation.

It is known that

$$a_{i,j,n,m} = (-1)^{i+j} \frac{\det(\mathbf{C}_{j,i,n,m})}{\det(\mathbf{C}_{n,m})}, \tag{A-4}$$

where $\mathbf{C}_{j,i,n,m}$ is a matrix by deleting the i[st] row and the j^{th} column from $\mathbf{C}_{n,m}$. So, the problem becomes calculation of $\det(\mathbf{C}_{j,i,n,m})$ and $\det(\mathbf{C}_{n,m})$.

(i) Calculation of $\det(\mathbf{C}_{n,m})$ *:*

We first show the result:

$$\det(\mathbf{C}_{n,m}) = 1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=1}^{n} b_{Y_i}^2 \quad . \tag{A-5}$$

Next, we will use the induction method in 1)-3) below to prove (A-5):

1) When $n = 1$, for any fixed m, it is easy to see that (A-5) holds.

2) Assume that (A-5) holds for $n-1$, i.e., $\det(\mathbf{C}_{n-1,m}) = 1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=1}^{n-1} b_{Y_i}^2$ for any fixed m. Then we need prove that (A-5) holds for n. We apply the Lebiniz formula on the first row of $\det(\mathbf{C}_{n,m})$:

$$\det(\mathbf{C}_{\mathbf{n,m}}) = 1 \times \det\begin{pmatrix} 1 & 0 & ... & 0 & b_{21}b_{Y_2} & 0 & 0 & ... & 0 \\ 0 & 1 & ... & 0 & b_{21}b_{Y_3} & 0 & 0 & ... & 0 \\ ... & ... & ... & ... & ... & ... & ... & ... & ... \\ 0 & 0 & ... & 1 & b_{21}b_{Y_n} & 0 & 0 & ... & 0 \\ b_{21}b_{Y_2} & b_{21}b_{Y_3} & ... & b_{21}b_{Y_n} & 1 & b_{Z_1} & b_{Z_2} & ... & b_{Z_m} \\ 0 & 0 & ... & 0 & b_{Z_1} & 1 & 0 & ... & 0 \\ 0 & 0 & ... & 0 & b_{Z_2} & 0 & 1 & ... & 0 \\ ... & ... & ... & ... & ... & ... & ... & ... & ... \\ 0 & 0 & ... & 0 & b_{Z_m} & 0 & 0 & ... & 1 \end{pmatrix} + (-1)^{n+2} \times b_{21}b_{Y_1} \times \begin{pmatrix} 0 & 1 & 0 & ... & 0 & 0 & 0 & ... & 0 \\ 0 & 0 & 1 & ... & 0 & 0 & 0 & ... & 0 \\ ... & ... & ... & ... & ... & ... & ... & ... & ... \\ 0 & 0 & 0 & ... & 1 & 0 & 0 & ... & 0 \\ b_{21}b_{Y_1} & b_{21}b_{Y_2} & b_{21}b_{Y_3} & ... & b_{21}b_{Y_n} & b_{Z_1} & b_{Z_2} & ... & b_{Z_m} \\ 0 & 0 & 0 & ... & 0 & 1 & 0 & ... & 0 \\ 0 & 0 & 0 & ... & 0 & 0 & 1 & ... & 0 \\ ... & ... & ... & ... & ... & ... & ... & ... & ... \\ 0 & 0 & 0 & ... & 0 & 0 & 0 & ... & 1 \end{pmatrix}$$

It is easy to see

$$\det\begin{pmatrix} 0 & 1 & 0 & ... & 0 & 0 & 0 & ... & 0 \\ 0 & 0 & 1 & ... & 0 & 0 & 0 & ... & 0 \\ ... & ... & ... & ... & ... & ... & ... & ... & ... \\ 0 & 0 & 0 & ... & 1 & 0 & 0 & ... & 0 \\ b_{21}b_{Y_1} & b_{21}b_{Y_2} & b_{21}b_{Y_3} & ... & b_{21}b_{Y_n} & b_{Z_1} & b_{Z_2} & ... & b_{Z_m} \\ 0 & 0 & 0 & ... & 0 & 1 & 0 & ... & 0 \\ 0 & 0 & 0 & ... & 0 & 0 & 1 & ... & 0 \\ ... & ... & ... & ... & ... & ... & ... & ... & ... \\ 0 & 0 & 0 & ... & 0 & 0 & 0 & ... & 1 \end{pmatrix} = (-1)^{n+1} \times b_{21}b_{Y_1}$$

Thus, we get

$$\det(\mathbf{C}_{n,m}) = 1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=2}^{n} b_{Y_i}^2 + (-1)^{n+2} \times b_{21}b_{Y_1} \times (-1)^{n+1} \times b_{21}b_{Y_1} = 1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=1}^{n} b_{Y_i}^2 \ .$$

3) We show that the same induction method above can be applied to prove that (A-5) also holds for m, for any fixed n. This can be validated by the observation that

$$\det(\mathbf{C}_{n,m}) = \det\begin{pmatrix} 1 & 0 & \dots & 0 & b_{21}b_{Y_1} & 0 & 0 & \dots & 0 \\ 0 & 1 & \dots & 0 & b_{21}b_{Y_2} & 0 & 0 & \dots & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & 1 & b_{21}b_{Y_n} & 0 & 0 & \dots & 0 \\ b_{21}b_{Y_1} & b_{21}b_{Y_2} & \dots & b_{21}b_{Y_n} & 1 & b_{21}\frac{b_{Z_1}}{b_{21}} & b_{21}\frac{b_{Z_2}}{b_{21}} & \dots & b_{21}\frac{b_{Z_m}}{b_{21}} \\ 0 & 0 & \dots & 0 & b_{21}\frac{b_{Z_1}}{b_{21}} & 1 & 0 & \dots & 0 \\ 0 & 0 & \dots & 0 & b_{21}\frac{b_{Z_2}}{b_{21}} & 0 & 1 & \dots & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & 0 & b_{21}\frac{b_{Z_m}}{b_{21}} & 0 & 0 & \dots & 1 \end{pmatrix}$$

where $\left\{b_{Y_1}, b_{Y_2}, \dots, b_{Y_n}\right\}$ and $\left\{\frac{b_{Z_1}}{b_{21}}, \frac{b_{Z_2}}{b_{21}}, \dots, \frac{b_{Z_n}}{b_{21}}\right\}$ is symmetrical.

(ii) Calculation of $\det(\mathbf{C}_{1,j,n,m})$ *for* $j = 1,2,\dots,n$*:*

Using the Lebiniz formula again, on the j-1st row of $\mathbf{C}_{1,j,n,m}$, we get

$$\det(\mathbf{C}_{1,j,n,m}) = \det\begin{pmatrix} 0 & 1 & \dots & 0 & 0 & \dots & 0 & b_{21}b_{Y_2} & 0 & 0 & \dots & 0 \\ 0 & 0 & \dots & 0 & 0 & \dots & 0 & b_{21}b_{Y_3} & 0 & 0 & \dots & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & 1 & 0 & \dots & 0 & b_{21}b_{Y_{j-1}} & 0 & 0 & \dots & 0 \\ 0 & 0 & \dots & 0 & 0 & \dots & 0 & b_{21}b_{Y_j} & 0 & 0 & \dots & 0 \\ 0 & 0 & \dots & 0 & 1 & \dots & 0 & b_{21}b_{Y_{j+1}} & 0 & 0 & \dots & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & 0 & 0 & \dots & 1 & b_{21}b_{Y_n} & 0 & 0 & \dots & 0 \\ b_{21}b_{Y_1} & b_{21}b_{Y_2} & \dots & b_{21}b_{Y_{j-1}} & b_{21}b_{Y_{j+1}} & \dots & b_{21}b_{Y_n} & 1 & b_{Z_1} & b_{Z_2} & \dots & b_{Z_m} \\ 0 & 0 & \dots & 0 & 0 & \dots & 0 & b_{Z_1} & 1 & 0 & \dots & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & 0 & 0 & \dots & 0 & b_{Z_m} & 0 & 0 & \dots & 1 \end{pmatrix}$$

After some permutations, we get

$$\det(\mathbf{C}_{1,j,n,m}) = (-1)^{j-1} \times b_{21}^2 b_{Y_j} b_{Y_1} \qquad \text{(A-6)}$$

(iii) Calculation of $\det(\mathbf{C}_{1,j,n,m})$ *for* $j = n + 1$*:* through some permutation of the matrix, it is straightforward to get

$$\det(\mathbf{C}_{1,n+1,n,m}) = (-1)^{n-1} b_{21} b_{Y_1}\ , \qquad \text{(A-7)}$$

Inserting (A-5), (A-6), and (A-7) into (A-4), we get:

$$a_{11} = \frac{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=2}^{n} b_{Y_i}^2}{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=1}^{n} b_{Y_i}^2}$$

$$a_{1j} = \frac{b_{21}^2 b_{Y_1} b_{Y_j}}{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=1}^{n} b_{Y_i}^2},\ j = 2, 3, \ldots, n; \qquad \text{(A-8)}$$

$$a_{1,n+1} = \frac{-b_{21} b_{Y_1}}{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=1}^{n} b_{Y_i}^2}$$

Inserting (A-8) into (A-3), we get

$$b_{y_1}^{MB} = b_{y_1} \frac{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2}{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=1}^{n} b_{Y_i}^2}.$$

Due to the symmetry between $\left\{ b_{Y_1}, b_{Y_2}, \ldots, b_{Y_n} \right\}$, we get

$$b_{Y_i}^{MB} = b_{Y_i} \frac{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2}{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=1}^{n} b_{Y_i}^2}\ , \qquad \text{(A-9)}$$

Obviously, the faction at the right-hand side is between 0 and 1. Therefore, $\left| b_{Y_i}^{MB} \right| < \left| b_{Y_i} \right|$.

Next we derive the formula for $b_{Y_i}^{MB} \Big/ se\left(b_{Y_i}^{MB}\right)$. It is known that $se^2\left(b_{Y_i}^{MB}\right) = a_{11} \Big/ \left((n-1)\left(T_{n,m}^{-1}\right)_{11}\right)$. Since $\left(T_{n,m}^{-1}\right)_{11} = \det\left(T_{1,1,n,m}\right) \Big/ \det\left(T_{n,m}\right)$, the problem becomes the calculation of $\det\left(T_{1,1,n,m}\right)$ and $\det\left(T_{n,m}\right)$. Using the similar method for the calculation of $\det(\mathbf{C}_{j,i,n,m})$ and $\det(\mathbf{C}_{n,m})$, we can get

$$\det(T_{n,m}) = 1 - \sum_{i=1}^{n}\left[b_{Y_i}^2 \left(1 - b_{21}^2 - \sum_{j=1}^{m} b_{Z_j}^2\right)\right] \quad \text{and} \quad \det(T_{1,1,n,m}) = 1 - \sum_{i=2}^{n}\left[b_{Y_i}^2 \left(1 - b_{21}^2 - \sum_{j=1}^{m} b_{Z_j}^2\right)\right].$$

Hence, we get

$$se_n^2\left(b_{Y_i}^{MB}\right) = \frac{1}{n-1}\frac{\det(T_{1,1,\mathbf{n},\mathbf{m}})}{\det(T_{\mathbf{n},\mathbf{m}})} a_{11} = \frac{1}{n-1}\frac{1 - \sum_{i=2}^{n}\left[b_{Y_i}^2 \left(1 - b_{21}^2 - \sum_{j=1}^{m} b_{Z_j}^2\right)\right]}{1 - \sum_{i=1}^{n}\left[b_{Y_i}^2 \left(1 - b_{21}^2 - \sum_{j=1}^{m} b_{Z_j}^2\right)\right]} \frac{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=2}^{n} b_{Y_i}^2}{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=1}^{n} b_{Y_i}^2}.$$

Together with $se_n^2\left(b_{Y_i}\right) = \dfrac{1 - \sum_{i=1}^{n} b_{Y_i}^2}{n-1}$, we now have

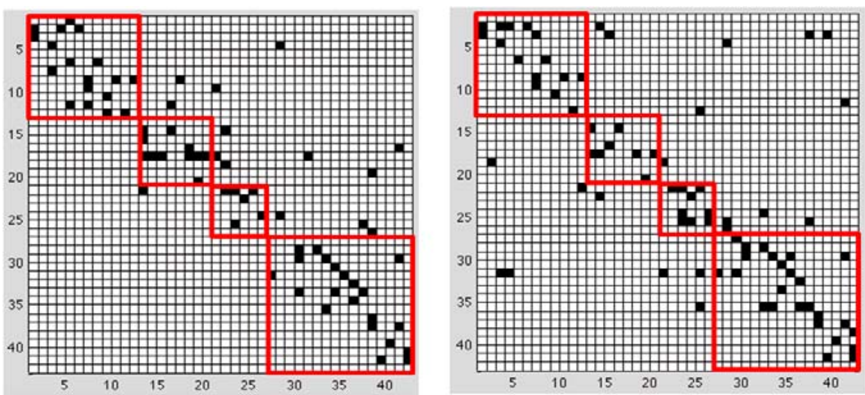
$$\frac{b_{Y_i}^{MB}}{se_n\left(b_{Y_i}^{MB}\right)} = \frac{b_{Y_i}}{se_n\left(b_{Y_i}\right)} \frac{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2}{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=1}^{n} b_{Y_i}^2} \sqrt{1 - \sum_{i=1}^{n} b_{Y_i}^2} \Bigg/ \sqrt{\frac{1 - \sum_{i=2}^{n}\left[b_{Y_i}^2 \left(1 - b_{21}^2 - \sum_{j=1}^{m} b_{Z_j}^2\right)\right]}{1 - \sum_{i=1}^{n}\left[b_{Y_i}^2 \left(1 - b_{21}^2 - \sum_{j=1}^{m} b_{Z_j}^2\right)\right]} \frac{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=2}^{n} b_{Y_i}^2}{1 - \sum_{i=1}^{m} b_{Z_i}^2 - b_{21}^2 \sum_{i=1}^{n} b_{Y_i}^2}}$$

.

Since $\sqrt{\frac{1-\sum_{i=2}^{n}\left[b_{Y_i}^2\left(1-b_{21}^2-\sum_{j=1}^{m}b_{Z_j}^2\right)\right]}{1-\sum_{i=1}^{n}\left[b_{Y_i}^2\left(1-b_{21}^2-\sum_{j=1}^{m}b_{Z_j}^2\right)\right]}\frac{1-\sum_{i=1}^{m}b_{Z_i}^2-b_{21}^2\sum_{i=2}^{n}b_{Y_i}^2}{1-\sum_{i=1}^{m}b_{Z_i}^2-b_{21}^2\sum_{i=1}^{n}b_{Y_i}^2}}>1$, $\sqrt{1-\sum_{i=1}^{n}b_{Y_i}^2}<1$ and

$\frac{1-\sum_{i=1}^{m}b_{Z_i}^2-b_{21}^2}{1-\sum_{i=1}^{m}b_{Z_i}^2-b_{21}^2\sum_{i=1}^{n}b_{Y_i}^2}<1$, we get $\frac{b_{Y_i}^{MB}}{se_n\left(b_{Y_i}^{MB}\right)}<\frac{b_{Y_i}}{se_n\left(b_{Y_i}\right)}$.

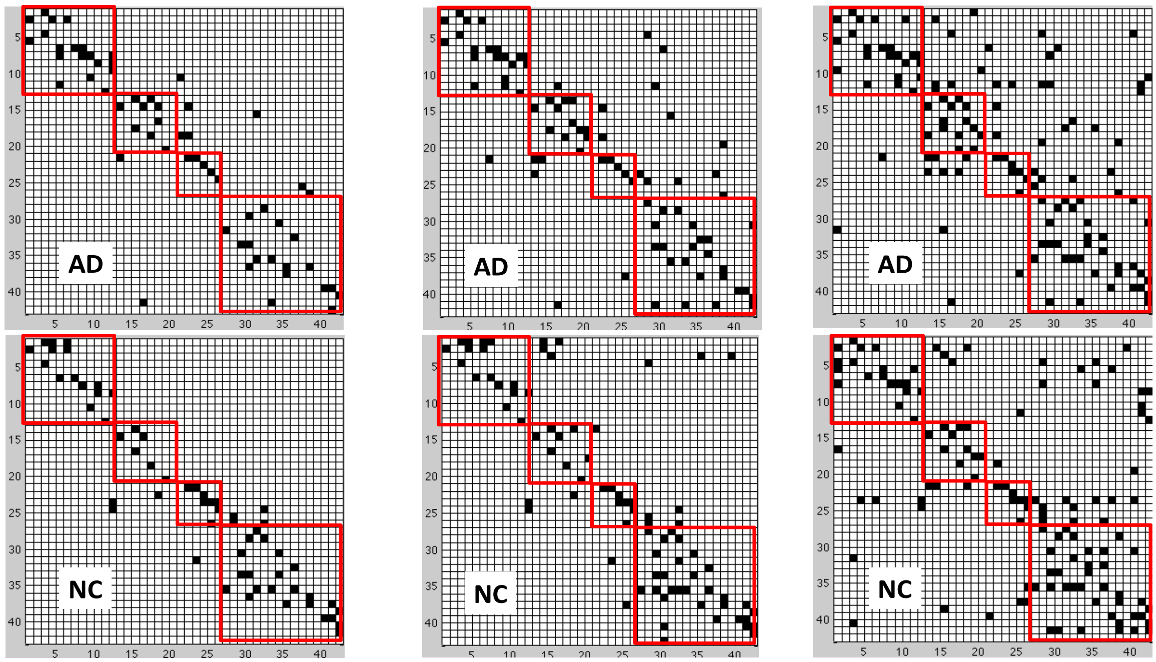
II: Effective connectivity models of AD and NC using BIC for selecting λ_1



(a) AD (b) NC

Fig. S-1: Effective connectivity models learned by SBN, with λ_1 selected to minimize BIC

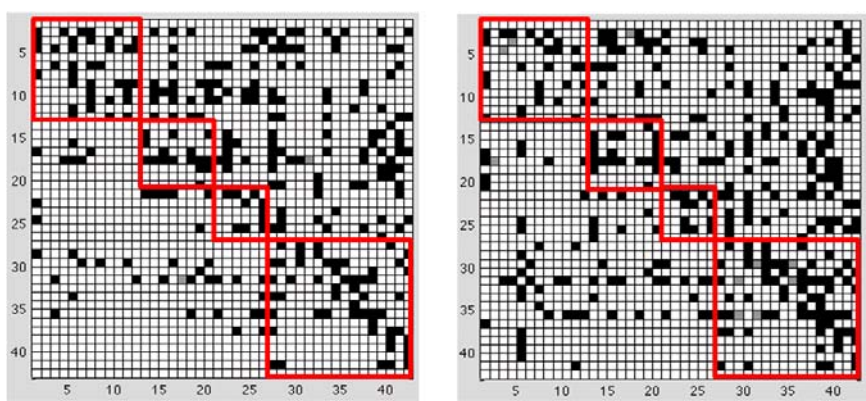
III: Effective connectivity models of AD and NC by controlling the total numbers of arcs to be the same



(a) (b) (c)

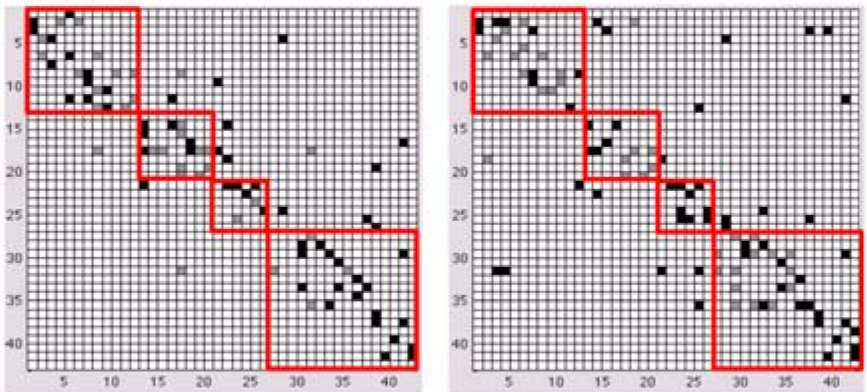
Fig. S-2: (a)-(c): Effective connectivity models with the total number of arcs = 60, 80, 120.

IV: PDAGs of AD and NC



(a) AD (b) NC

Fig S-3: PDAGs learned by SBN, with λ_1 selected to minimize the prediction error (a black cell represents a directed arc; a gray cell represents an undirected arc)



(a) AD (b) NC

Fig. S-4: PDAGs learned by SBN, with λ_1 selected to minimize BIC