**Supplementary\_File\_S1**

**1 Structural consistency**

The concept of structural consistency was first proposed by Lü et al., which can be used to quantify the link predictability of complex networks (Lü et al., 2015; Zeng et al., 2018). They define it as the consistency of network structure features before and after random removal of partial links. In this study, we applied this method to weighted bilayer networks; viz. weighted lncRNA–miRNA bilayer network .

We use graph  to represent the weighted lncRNA–miRNA bilayer network.  and  are the sets of nodes (include both lncRNA and miRNA nodes) and edges, respectively; and  is set of weights. We select a small part of the links to compose a perturbation set , while the rest of the links are defined as .  and  represent the corresponding weighted adjacency matrix, respectively; and . Obviously,  is a real symmetric matrix; therefore, it can be diagonalized as follows.

|  |  |
| --- | --- |
| , | (2) |

where  are the eigenvalues for  and  are the corresponding orthogonal and normalized eigenvectors.

Using  as the perturbation set, we obtain a perturbed matrix by first-order approximation. First-order approximation allows the eigenvalues to change but keeps the eigenvectors constant. Two cases are considered. First, consider the non-degenerated case without any repeated eigenvalues. After perturbation, the eigenvalue  is adjusted to , and the corresponding eigenvector is adjusted to . By multiplying the eigenfunction, we have

|  |  |
| --- | --- |
| . | (3) |

By  and neglecting the second-order terms  and , we obtain

|  |  |
| --- | --- |
| . | (4) |

Using the perturbed eigenvalues while keeping eigenvectors unchanged, the perturbed matrix can be obtained,

|  |  |
| --- | --- |
| , | (5) |

which can be considered a linear approximation of the given network  if the expansion is based on .

Next, considering the adjacency matrix contains repeated eigenvalues. If  is eigenvalues, the index  denotes  related eigenvectors of the same eigenvalues and the index  denotes different eigenvalues. It is given that any linear combination of eigenvectors belonging to the same eigenvalue is still an eigenvector. After adding a perturbation into the network, we choose the degenerate eigenvalues, which can be changed successively into the perturbed nondegenerate eigenvalues. If we define the chosen eigenvectors to be , the eigenfunction becomes

|  |  |
| --- | --- |
| , | (6) |

giving us

|  |  |
| --- | --- |
| , | (7) |

for any  , left multiplying Equation (7) by , we obtain

|  |  |
| --- | --- |
| . | (8) |

Written in matrix form, Equation (8) becomes

|  |  |
| --- | --- |
| , | (9) |

where , which is a  matrix, and  is the column vector of . Then, according to eigenfunction (9), we obtain  and ; the perturbed adjacency matrix  is obtained by simply replacing  and  in Equation (5) with  and .

Matrix eigenvectors can reflect the network structural features. If the eigenvectors of matrix  and matrix  are nearly the same, it indicates that the perturbation set does not significantly change the structural features. In other words, the network is of high structural consistency. All unobserved links (including perturbed links) are ranked in descending order according to their corresponding scores in perturbed matrix . Denote the set of top-*L* links as , where . Structural consistency  is defined as the ratio of shared links between  and  to , follow as

|  |  |
| --- | --- |
| . | (10) |

Figure S1 shows how to calculate the structural consistency  of a toy example. The left figure shows the adjacency matrix , where the number in each square is the corresponding value of the matrix element. The second figure represents the matrix , which is obtained by randomly removing a fraction of the observed links. The removed links, namely, , , , ,  and , constitute the perturbation set . Obviously, . The right figure is the perturbed matrix . By ranking the unobserved links in  according to their corresponding values in , we obtain the top-*L* links in  as , , , ,  and . Therefore, there are four shared links between  and , .

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|  |

**Figure S1.** Toy example of  calculation.

**2 Structural perturbation method** **for lncRNA–miRNA interaction prediction**

Generally, the link prediction problem of a network is how to estimate the probability of the existence of unobserved links according to known topological information. The network structure perturbation involved in the structure consistency calculation process can be used to predict the missing links (Lü et al., 2015).

For the lncRNA–miRNA bilayer network , taking 5-fold cross-validation as an example, the observed links in the original adjacency matrix () are randomly divided into 5 equal sized subsets. Of these 5 subsets, one is selected as the probe set, and the others, together with  and **, as the training set. Next, we randomly remove a fraction of links from training sets to constitute the perturbation set. The perturbation matrix can be calculated as , see the section 1 for details. The final prediction matrix  is obtained by averaging over ***t*** independent selections of the perturbation set. In this way, the elements in prediction matrix  can be regarded as a score between a pair of nodes of the bilayer network . The scores in  determine the extent of all unobserved lncRNA–miRNA interactions, and we assume that the higher the score, the more likely the potential interaction will be.

**3 References**

Lü, L., Pan, L., Zhou, T., Zhang, Y.C. and Stanley, H.E., 2015. Toward link predictability of complex networks. Proc Natl Acad Sci U S A 112, 2325-30.

Zeng, X., Liu, L., Lu, L. and Zou, Q., 2018. Prediction of potential disease-associated microRNAs using structural perturbation method. Bioinformatics 34, 2425-2432.