***Drug-ADR Associations Network***

In our method, a bipartite network was employed to represent drug-ADR associations, in which vertex are drugs/ADRs and edges are their associations. In such a network, drugs were connected with ADRs only, vice versa. So it could be divided into two disjoint subsets: drugs and ADRs. Here, a bipartite network G could therefore be defined as $G = (\perp, T, E)$, in which $\perp$ represents nodes of drugs, while T represents nodes of ADRs, and $E \subseteq \perp \times T$ represents the links between drugs and ADRs associations. Then, two kinds of homogeneous nodes' projection could be defined: $\perp - projection$ (drug projection) and $T - projection$ (ADR projection). In the $\perp - projection$, nodes were drugs and edges are connected for those sharing one or more common ADRs in the bipartite network. It is the same in the case of the $T - projection$. Depending on those two projections, external links prediction method was then proposed.

***External Link Prediction Method***

In our method, two kinds of *external links* could be defined depending on those two projections. Take the *external li*nk definition on basis of drug-projection ($\perp - projection$), for instance. Edge $(\mu,\nu)$, $\mu$ and $\nu$ represent a drug and an ADR respectively, is a newly added link in the bipartite network of drug-ADR associations. The link $(\mu, \nu)$ was external only if the number of the intersection of $\nu$'s neighbours in G and $\mu$'s neighbours in the $\perp - projection$ is equal to or larger than $n$, $n \in \{1,2,3,...\}$. An *external link* could also be similarly defined based on ADRs projection ($T - projection$).

Then, each new link $(\mu, \nu)$ was scored as the following scoring function:

$$P(\mu,\nu) = \max(P_{drug}(\mu,\nu), P_{ADR}(\mu,\nu)) \quad \text{(1)}$$

Where $P(\mu,\nu)$ is the scoring function which take the maximum score of $P_{\text{drug}}(\mu,\nu)$ and $P_{ADR}(\mu,\nu)$.

$P_{\text{drug}}(\mu,\nu)$ is a scoring function of link $(\mu, \nu)$ while we define the *external links* based on the drug-projection ($\perp - projection$). If the link $(\mu, \nu)$ is an *external link*,

$$P_{\text{drug}}(\mu,\nu) = \max(\{w(\mu,a_i), a_i \in N(\nu) \cap N_{\perp}(\mu)\}) \quad \text{(2)}$$

Otherwise, $P_{\text{drug}}(\mu,\nu) = 0$.

$P_{ADR}(\mu,\nu)$ is a scoring function of link $(\mu, \nu)$ while we define the *external links* based on the ADRs projection ($T - projection$). If the link $(\mu, \nu)$ is an *external link*,

$$P_{ADR}(\mu,\nu) = \max(\{w(b_j,\nu), b_j \in N(\mu) \cap N_{T}(\nu)\}) \quad \text{(3)}$$

Otherwise, $P_{\text{ADR}}(\mu,\nu) = 0$.

Where $a_i$ is the intersection node of $\nu$'s neighbours in G and $\mu$'s neighbours in the $\perp - projection$, $i = 1,...,|N(\nu) \cap N_{\perp}(\mu)|$; and $b_j$ is the intersection node of $\mu$'s neighbours in G and $\nu$'s neighbours in the $T - projection$, $j = 1,...,|N(\mu) \cap N_{T}(\nu)|$.

The weight of links $(\mu, a_i)$ and $(b_j, \mu)$ were calculated by a Jaccard coefficient[33]:

$$w(x,y) = \frac{|N(x) \cap N(y)|}{|N(x) \cup N(y)|} \quad \text{(4)}$$

N(x) and N(y) is the neighbour of node x and y.

Finally, given a weight threshold $\tau$ , the link $(\mu,\nu)$ could be predicted only if $P(\mu,\nu)$ equal to or larger than $\tau$ .