FunPred 3.0: Improved Protein function prediction using protein interaction network: Supplementary Document

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DEFINITIONS AND NOTATIONS

Before proceeding into the main section of our work, it is important to discuss the graphical properties as well as other relevant terms associated with our work.

Protein-protein interaction network: Protein-protein interactions occur when two or more proteins bind together, often to carry out their biological function. These protein interactions form a network like structure which is known as a protein interaction network. Protein interaction network is generally represented as a graph consisting of a set of nodes connected by edges or links. Proteins are represented as nodes in the graph and the edges signify interactions between two proteins. Here protein interaction network is represented as a graph $G_p$which consists of a set of vertex V (nodes) connected by edges E (links). Thus $G = (V, E)$.

Protein complex/cluster: It can be defined as group of proteins (usually in close proximity to one another) interconnected through a network to work as one centralized data processing resource. Here it is defined by C_i where i represent cluster number.

Sub graph: A graph G'_p is a sub graph of G_p if the vertex set of G'_p is a subset of the vertex set of G_p and if the edge set of G'_p is a subset of the edge set of G_p. That is, if $G'_p = (V', E')$ and $G_p = (V, E)$, then G'_p is called as sub graph of G_p if $V' \subseteq V$ and $E' \subseteq E$. G'_p may be defined as a set of $\{P_U | P_A\}$ where P_U represents the set of un-annotated proteins while P_A represents the set of annotated protein.

Level − 1 Neighbors: For any vertex v in G'_p, all those vertices in G'_pthat are connected with v through an edge are deemed Level − 1 neighbors of v.

Edge weight (W_{uv}): The weight W_{uv} of edge (u, v) (Wang & Wu 2013) is defined as the similarity between u and v. It is obvious that two nodes with an edge between them belong to the same cluster if they have high similarity. The similarity between u and v is measured by Jaccard's coefficient. Jaccard's coefficient adopts the proportion of common neighbors of two nodes in all distinct neighbors of these nodes to measure node similarity in complex networks. Obviously, the more common neighbors two nodes share, the higher similarity these nodes have. Therefore, the edge weight W_{uv} is represented by

$$W_{uv} = (\Gamma(u) \cap \Gamma(v)) / (\Gamma(u) \cup \Gamma(v)) \quad (1)$$

where, Γ(u) and Γ(v) are neighbors of u and v respectively. Γ(u) ∩ Γ(v) represents all common neighbors of u and v, and Γ(u) ∪ Γ(v) represents all distinct neighbors of u and v. In our algorithm, edge weight is used to guarantee that in the same

cluster every pair of nodes with an edge between them should have relatively high similarity.

Neighborhood graph (G_v): The neighborhood graph of v ∈ V consists of v, all its neighbors and the edges among them. It is defined as $G_v = (V', E')$, in which $V' = \{v\} \cup \{u | u \in V, (u, v) \in E\}$, and $E' = \{(u_i, u_j) | (u_i, u_j) \in E, u_i, u_j \in V'\}$.

Node weight ($\mathbf{W_v}$): In G_v, there are some nodes with degree 1 that only have connections with v and the connections among these nodes are often false positive according to topological reliability measures (Wang & Wu 2013).So nodes with degree 1 and corresponding edges are removed from G_v. The remaining sub graph of G_v is marked as G'_v.The node weight wv of node v ∈ V in PPI networks is the average degree of all nodes in G'_v. It is represented by

$$w_v = \sum_{u \in V''} deg(u)/|V''| \quad (2)$$

where, V'' is the set of nodes in G'_v.$|V''|$ is the number of nodes in G'_v. And deg(u) is the degree of a node u∈ V'' in W_v. In our algorithm, the weight W_v of a node v ∈ V is used in the step of seed chosen. Higher value of W_v of a graph indicates a collection of nodes with maximum interactions among them and hence the graph is densely connected region.

Physico-Chemical Properties (PCP): Physico-Chemical Properties (Saha & Chatterjee 2014; Singh et al. 2008) of amino acids are the various features of protein which are used to predict protein class. These properties are very important in protein class prediction. The various Physico-Chemical Properties used in this work are as given below:

1.**Extinction Coefficient ($\mathbf{E_{protein}}$):** Extinction Coefficient (Singh et al. 2008) is a protein parameter that is commonly used in the laboratory for determining the protein concentration in a solution by spectrophotometry. It describes to what extent light is absorbed by the protein and depends upon the protein size and composition as well as the wavelength of the light. For proteins measured in water at wavelength of 280nm, the value of the Extinction coefficient can be determined from the composition of Tyrosine, Tryptophan and Cystine.

Mathematically it can be defined as:

$$E_{protein} = (N_{tyr} \times E_{tyr}) + (N_{trp} \times E_{trp}) + (N_{cys} \times E_{cys}) \quad (3)$$

where E_{tyr} =1490, E_{trp} =5500, E_{cys} =125 are the Extinction coefficients of the individual amino acid residues.

2.**Absorbance (Optical Density):** For proteins measured in water at wavelength of 280nm the absorbance can be determined by the ratio of Extinction coefficient and the molecular weight of the protein. It is a representation of a material's light blocking ability (Singh et al. 2008).

Mathematically absorbance is defined as:

$$\text{Absorbance} = E_{protein}/\text{Molecular Weight} \quad (4)$$

3.**Number of Negatively Charged Residues (N_{neg}):** This can be calculated from the composition of Aspartic acid and Glutamic acid (Singh et al. 2008).

4.**Number of Positively Charged Residues (N_{pos}):** This can be calculated from the composition of Arginine and Lysine (Singh et al. 2008).

5.**Aliphatic Index (AI):** The aliphatic index of a protein is defined as the relative volume occupied by aliphatic side chains (alanine, valine, isoleucine, and leucine). It may be regarded as a positive factor for the increase of thermo stability of globular (Singh et al. 2008).

Mathematically aliphatic index is defined as:

$$AI = X_{ala} + a \times X_{val} + b \times (X_{ile} + X_{leu}) \quad (5)$$

where X_{ala} , X_{val} , X_{ile} and X_{leu} are the mole percentages of alanine, valine, isoleucine and leucine respectively. Coefficients a and b are the relative volume of valine side chain and side chains to the side chain of alanine i.e. a = 2.9 and b = 3.9.

6.**Compute IP/Mol weight:** It calculates the isoelectric point by molecular weight (Singh et al. 2008) of the input amino acid sequence. IP stands for isoelectric point of the input amino acid sequence. Mol weight stands for molecular weight of the input amino acid sequence.

7.**Grand average of hydropathicity (GRAVY):** The GRAVY value for a protein or a peptide (Kyte & Doolittle 1982) is calculated by adding the hydropathy values of each amino acid residues and dividing by the number of residues in the sequence or length of the sequence. Increasing positive score indicates a greater hydrophobicity.

8.**Instability index:** The instability index (Guruprasad et al. 1990) provides an estimate of the stability of your protein in a test tube. A protein whose instability index is smaller than 40 is predicted as stable, a value above 40 predicts that the protein may be unstable.

9.**Aromaticity:** Aromaticity (Lobry & Gautier 1994) is simply the relative frequency of phenylalanine (Phe), tryptophan (Trp), tyrosine (Tyr).

10. **Isoelectric point:** The isoelectric point (Bjellqvist et al. 1994) is the pH at which a molecule or surface carries no net electrical charge.

11. **PCP_{score} :** PCP_{score} is defined as scaling of the mean value obtained from top-ranked physico-chemical properties among the properties mentioned above which are obtained by the execution of four classifiers: XGBoost classifier, Random Forest classifier, Extra Tree classifier and Recursive feature elimination classifier.

XGBoost Classifier: XGBoost is a scalable end to end tree boosting system which proves to be highly effective and widely used machine learning method for feature selection .

Random forest Classifier: A random forest is defined to be a meta-estimator that fits a number of decision tree classifiers on various sub-samples of the dataset and use averaging to improve the predictive accuracy and control over-fitting (Breiman 2001).

Extra Tree Classifier: Extra Tree classifier is a new tree-based ensemble method for supervised classification of feature selection (Geurts et al. 2006; Pedregosa et al. 2011).

Recursive feature elimination (RFE) Classifier: RFE is used to select features by recursively considering smaller and smaller sets of features (Pedregosa et al. 2011). First, the estimator is trained on the initial set of features and the importance of each feature is obtained either through a *coef_* attribute or through a *feature_importances_* attribute. Then, the least important features are pruned from current set of features.

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