Global Snapshot of Protein Interaction Network – A Percolation Based Approach

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(Dated: February 2, 2008)

Abstract

In this paper, we study the large-scale protein interaction network of yeast utilizing a stochastic method based upon percolation of random graphs. In order to find the global features of connectivities in the network, we introduce numerical measures that quantify (1) how strongly a protein ties with the other parts of the network and (2) how significantly an interaction contributes to the integrity of the network. Our study shows that the distribution of essential proteins is distinct from the background in terms of global connectivities. This observation highlights a fundamental difference between the essential and the non-essential proteins in the network. Furthermore, we find that the interaction data obtained from different experimental methods such as immunoprecipitation and two-hybrid techniques possess different characteristics. We discuss the biological implications of these observations.

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I. INTRODUCTION

Recent availability of a large amount of data from high-throughput experiments [1–5] has brought about a fundamental change in the way we study biological systems. Unlike the traditional methods which relied on probing a single or a few proteins to identify important pathways, it is now becoming possible to describe larger functional ‘modules’ [6] and even the global properties of the entire proteome [7–10]. Researchers are attempting to connect large-scale protein interaction data with information from phenotype studies [7, 8]. In one such analysis of data from yeast, Jeong et al. observed the connectivities of individual proteins in the network to closely follow a power-law distribution. Similar to other power-law networks, positive correlation existed between a protein’s inviability and its connectivity [7]. In another study, Maslov et al. observed interesting patterns in the distribution of the links between the nearest neighbors in the network and postulated that such patterns give rise to the specificity and the robustness of the network [8].

One of the shortcomings of the previous approaches is that they drew conclusions about the global nature of the network from its local connectivity properties. It is unclear whether such local studies based on individual nodes or nearest neighbors fully capture the global picture of the network. For example, some essential proteins, namely, those for which null mutants produce inviable strains [11], may have few numbers of direct links but still take important roles in the network through the proteins to which they are connected. Such proteins would not be correctly identified by just counting the number of links as in Ref. [7]. To properly recognize such cases, it is necessary to go beyond the nearest neighbor links. However, it is not clear that the techniques mentioned above can easily be extended to answer such questions.

In this paper, we introduce a stochastic method inspired by the percolation model in statistical mechanics[12] that overcomes the shortcomings of the previous approaches. This method allows us to define a quantity that measures the correlation between any two nodes in the network, taking the topology of the entire network into account. Biologically, such correlations describe the direct and indirect influences of one protein on another through the protein interaction network. If such correlations indeed carry biological significance, we expect the essential proteins to be highly correlated, in general, with the rest of the network. One of our main results is that most essential proteins do possess higher correlations...
between themselves and the rest of the network. This is consistent with previous results [7], because in the first order, the correlations computed by us are proportional to the connectivities of the proteins. However, we show that it is important to go beyond the first order. Identifying essential proteins by our method performs consistently better than just counting links. Additionally, we observe that the essential proteins interact more tightly with the other essential proteins, thus forming a ‘network core’. This directly agrees with large-scale experiments probing protein networks [4].

Based on our method, we can also quantify the relative significance of an interaction to the integrity of the network. We observe that the interaction data from different measurement techniques, such as immunoprecipitation (IP) and the two-hybrid test, give distinct distributions. This suggests that various experimental techniques for probing the protein interaction might explore different regions of the network.

II. METHOD AND MATERIALS

A. Bond-percolation on Graph

Given any two nodes in a network, the strength of their connectivity can be estimated in different ways. Some of these measures are local. For example, we can ask whether any two nodes are directed linked, how many common neighbors they share [13], etc. We can also ask how local properties of a node, such as the degree of links, associate with its function and its importance in the network [7]. Furthermore, information about the correlations between nodes involving nonlocal properties, such as the length of the shortest path and clustering structures, will enable us to uncover hidden features buried within the massive data. Here, we present a generic approach that extracts useful information about a node beyond its local connections.

Correlations between two nodes may come from other numerous short paths rather than just the shortest path. A reasonable estimate of correlation should take into account the number and lengths of different paths between two nodes. One possible way to estimate such correlation between two nodes is to repeatedly remove some fraction $q$ of the links in the network chosen randomly and check whether they still remain connected. Their probability remaining connected is proportional to the number of short paths between them.
and inversely proportional the length of those paths. This probability provides a good measurement of the correlation between two nodes that includes the information regarding the non-local topology of the network. The described process of finding the correlation between two nodes in a network is equivalent to the bond-percolation model in statistical mechanics[12].

Mathematically, a network is treated in the language of graph theory, where a node is denoted as a vertex and a link as an edge. Given a graph $G$ with vertices $V$ and edges $E$, a percolation configuration is realized as follows. Each edge $e_{ij}$ linking vertices $i$ and $j$ is assigned a random number $p_{ij}$ distributed uniformly from 0 to 1. If this random number is greater than $p = 1 - q$, a given percolation probability, then the edge is eliminated from the original graph. The final graph $G'$ consists of the edge set $E' = E - \bar{E}$, where $\bar{E}$ is the set of edges that $p_{ij} > p$ and $E'$ consists those edges with $p_{ij} < p$. Assuming that $G$ is connected, the reduced graph $G'$ may or may not remain a single connected component depending on $p$.

**B. Susceptibility**

The first step in applying the algorithm is to determine the appropriate value of the probability $p$. If $p$ is near one, then we only produce totally connected graphs. If $p$ is too close to zero, then the network is split into individual vertices and small clusters. An intermediate value of $p$ provides information about the non-local properties of the network.

The degree of fragmentation in the graph $G'$ can be quantified by the order parameter $m(p)$, the ratio of the largest connected component to the total graph size. It is defined as $m(p) = N_{\text{max}}/|V|$, where $N_{\text{max}}$ is the number of vertices of the largest connected component and $|V|$ is the total number of vertices. For a connected graph $G$, $m(p)$ varies from $1/|V|$ to 1 as $p$ changes from 0 to 1. Here, $m$ is a stochastic variable, whose fluctuation is defined by

$$\chi(p) = \langle (m - \langle m \rangle)^2 \rangle^{\frac{1}{2}}$$

(1)

The brackets denote the ensemble average, which is the average over many different realizations of $G'$. The curve of $\chi(p)$ reveals certain aspects of the graph topology. For example, if $G$ is a regular two dimensional square lattice, then $\chi$ diverges with a power law behavior as a function of $p - p_c$, for $p_c = 1/2$. For other types of regular lattices, like triangular
lattices or higher dimensional lattices, \( p_c \) and/or the power law exponent also change. A maximum in \( \chi(p) \) occurs at the transition point \( p_c \), indicating a phase transition and critical behavior[12]. At this critical point, the distribution of the sizes of the connected clusters decay as a power law. Chosing a value of \( p \) near this critical value, we get the most non-local information regarding the network.

C. Correlations and the definition of \( v_i \)

Whether two arbitrary vertices \( i \) and \( j \) remain connected in \( G' \) can provide more detailed information about \( G \). If two vertices retain their connection, it means that there exist paths in \( E' \) from vertex \( i \) to vertex \( j \). Define \( \delta_{ij} \) as function of a pair of vertices \( i \) and \( j \) such that \( \delta_{ij} = 1 \) if vertices \( i \) and \( j \) are connected, and \( \delta_{ij} = 0 \) otherwise. The percolation correlation \( c_{ij} \) is then defined as the ensemble average of \( \delta_{ij} \),

\[
c_{ij} = \langle \delta_{ij} \rangle.
\] (2)

With knowledge of the \( c_{ij} \), we are equipped to measure how strongly a vertex \( i \) links to the rest of the network counting both direct and indirect connections to vertex \( i \). We define the quantity \( v_i \) for vertex \( i \),

\[
v_i = \frac{1}{|V|} \sum_{j \in V} c_{ij}
\] (3)

This value is sensitive not only to the linking degree at each vertex but also to higher order connections between a vertex and the rest of the random graph. Thus, \( v_i \) effectively ranks the importance of a vertex in the graph. Intuitively, \( v_i \) may be interpreted as the fraction of other vertices to which vertex \( i \) remains linked, if each edge is broken with probability \( q = 1 - p \) in the graph \( G \). In Fig. 1, we show the descending ranking order of the \( v_i \)'s for a small graph.

D. The definition of \( \beta_{ij} \)

Using a similar idea, we can define a quantity that allows us to check the influence of an edge on the graph integrity. The elimination of some edges may fundamentally change the connectivity properties whereas the graph topology may be relatively unchanged against the deletion of others. For example, for a small fully connected subgraph, termed a clique,
removal of a certain number of edges between the vertices of the subgraph tends not to separate the graph into disconnected pieces. Individual links in the subgraph do not play crucial roles in supporting the integrity of the subgraph and the whole graph. We define the quantity $\beta_{ij}$ to monitor the importance of edge $e_{ij}$ to the integrity of the graph,

$$\beta_{ij} = \frac{1}{|V|^2} \sum_{l,m \in V} (c_{lm}(G' \cup \{e_{ij}\}) - c_{lm}(G' \setminus \{e_{ij}\})).$$

(4)

The first term in the summation is correlation $c_{lm}$ measured by adding $e_{ij}$ in $G'$ independent of $p_{ij}$ and $p$. The second term in $c_{lm}$ measured by removing $e_{ij}$ in $G'$. The difference in measurement of $c_{lm}$ under the presence or absence of edge $e_{ij}$ allows us to distinguish edges. For example, if $e_{ij}$ bridges two clusters, then $\beta_{ij}$ will be elevated (note the edges 1, 2 and 3 in Fig. 1). Suppose edge $e_{ij}$ connects two disjoint connected components $A$ and $B$ with sizes $n_A$ and $n_B$. Then, in a realization of $G'$, the contribution to $\beta_{ij}$ is the difference between $\sum_{l,m \in A \cup B} \delta_{lm} = |n_A + n_B|^2$ and $\sum_{l,m \in A} \delta_{lm} + \sum_{l,m \in B} \delta_{lm} = |n_A|^2 + |n_B|^2$. Namely, the contribution to $\beta_{ij}$ is proportional to $n_An_B$. However, if $e_{ij}$ is embedded within a connected component such that adding or removing $e_{ij}$ does not perturb the component’s connectivity, then $e_{ij}$ is redundant and does not contribute to $\beta_{ij}$. With this interpretation, $\beta_{ij}$ measures how well $e_{ij}$ succeeds in connecting differing big components or modules.

E. Protein interaction data

Here, we apply the described method on the yeast protein interaction data taken from the Database of Interacting Proteins (DIP) [14]. The dataset contains 14871 interactions between 4692 proteins [17] and includes interactions measured by different experimental methods. We treat the interaction network as an undirected graph, with the proteins as vertices. If two proteins are interaction partners in the dataset, the corresponding vertices are joined by an edge.
FIG. 1: We applied our algorithm with $p = 0.43$ on a small graph. The vertices are indexed in the descending order of $v$ and the parenthesized numbers indicate the degree of connection. Some vertices, like vertex 3, have few neighbors but are out-ranked in terms of $v_i$ to other vertices with more neighbors. Vertices with equivalent degree of connectivity might be ranked very differently because they have differing number of next nearest neighbors. The edges having largest eighteen $\beta_{ij}$ shown in gray and are ranked. If we remove these edges, the graph is severed into several compact subgraphs. The edges carrying largest $\beta_{ij}$ tend to link different large components. The edges within a clique, like vertices 5,4,9,13, and 14, have the smallest $\beta_{ij}$.

III. RESULTS AND DISCUSSIONS

A. Determination of $p$

As a first step in applying this stochastic method on the protein interaction network, we need to determine the appropriate value of $p$. If $p$ is near one, then we will only produce totally connected graphs. If $p$ is too close to zero, then we will only obtain information about small clusters. Some intermediate value of $p$ will give us global properties of the network.

In order to determine the proper value of $p$, we need to compute the curve $\chi(p)$. Such a curve for the DIP data is shown in Fig. 2. The curve peaks at about $p = 0.07$, where the size fluctuations of the largest cluster are maximal. Most realizations of the percolation graph $G'$ in the neighborhood of this peak yield sparse but still predominantly connected graphs. Accordingly, computing $v_i$ and $\beta_{ij}$ around this peak in $\chi(p)$ avoids the finite size effect at
smaller \( p \) and loss of resolutions at larger \( p \).

![Graph showing susceptibility curve of the parameter \( m \). The curve peaks at \( p = 0.07 \), where the fluctuations of \( m \) are greatest.](image)

**FIG. 2:** Susceptibility curve of the parameter \( m \). The curve peaks at \( p = 0.07 \), where the fluctuations of \( m \) are greatest.

### B. Distribution of \( v_i \)

We gathered our data from \( 10^5 \) realizations of the graph at \( p = 0.07 \). The distribution of \( \log(v_i) \) for the protein interaction network is shown in Fig. 3. We also report the distributions of a subset composing only the essential proteins[18]. The distribution of \( v_i \) for essential proteins significantly differs from the background distribution and is biased toward greater \( v_i \). A protein with a greater \( v_i \) ties to the network more strongly than a protein possessing a smaller \( v_i \). Therefore, we would predict that removing a protein from yeast with a greater \( v_i \) harms more biologically important pathways and would thereby be more likely to destroy viability. The percentage of proteins having a given \( v_i \) which are essential (\( \frac{\text{number of essential proteins of a given } v_i}{\text{number of proteins of the given } v_i} \)) is shown in Fig. 4. This percentage has strong positive correlation with \( v_i \), in agreement with the prediction.

What are the specific connectivity properties that produce a large \( v_i \) for a specific protein? To a first order approximation, \( v_i \) is proportional to the degree of connectivity of the \( i^{\text{th}} \) protein. Since a protein with \( k \) interactions is usually connected to at least \( p \cdot k \) proteins, in the first order \( v_i \) is proportional to \( k_i \). However, the protein interaction network displays small world properties[19], Therefore, the correction to \( v_i \) from higher order connections should be included. For example, if the number of next-nearest neighbors of a protein is
FIG. 3: Histogram of $\log(v_i)$. The distribution of $v_i$ for essential proteins is skewed toward larger $v$.

FIG. 4: The percentage of proteins which are essential as a function of $v_i$.

much greater than the number of nearest neighbors, then the contribution from the next-nearest neighbors is comparable to that of the nearest neighbors. In such a case, the proteins with the same $k_i$ have a broad distribution of $v_i$ as in our results. The value of $v_i$ gives more extensive information about the protein’s connectivity in the network beyond that of its nearest neighbors.

Our method is advantageous because we can identify important proteins that might otherwise not be considered significant because they have lower first-order interaction degree. Such proteins probably control other essential proteins through a few critical interactions. To illustrate the power of this approach compared to merely counting the nearest neighbor degree of interactions, we rank the proteins by $v_i$ and compare the result to the ranking by
$k_i$ (see Table I). For example, 61% of the proteins in the top 2% of $v_i$ are essential, whereas only 52% of the proteins in the top 2% of $k_i$ are required for viability. Such a result suggests the essential proteins with higher $v_i$ not only have more interactions but are also more likely to interact more frequently with other proteins, which also tend to be essential. A similar observation has been reported by Gavin, et al. [4], and our independent evidence supports their hypothesis.

| Percentile | by $v_i$ | by $k_i$ | by $v_i$ (randomize) |
|------------|----------|----------|----------------------|
| 2%(94)     | 61%      | 52%      | 53%                  |
| 5%(234)    | 53%      | 47%      | 50%                  |
| 10%(469)   | 48%      | 46%      | 48%                  |
| 25%(1173)  | 39%      | 38%      | 38%                  |

TABLE I: The percentage of essential proteins in selected percentiles ranked by $v_i$ and the degree of connection $k_i$. In the top 92 proteins ranked by $v_i$, 61% of them are essential while only 52% of essential proteins are captured when ranked by $k_i$. The third column is a control in which the $v_i$ are recalculated for a (quasi-)randomized graph in which edges have been swapped while retaining the degrees of connection of all vertices in the original graph. Identifying essential proteins by calculating $v_i$ performs consistently better than only computing $k_i$, demonstrating the significance of nonlocal structure beyond that of nearest neighbor relations. If we randomly perturb the global graph structure, the ability to identify essential proteins drops, even though the degree of connection at each vertex is unchanged.

The proteins with 10 highest $v_i$ are listed in Table II. The full list of proteins with their $v_i$ can be found in the supplemental web site[20]. A selection of a few essential proteins with high $v_i$ but low $k_i$ is also shown in Table III.

C. Distribution of $\beta_{ij}$

The interactions in the network can be grouped by the experimental methods used to detect them. We score each interaction within the network by $\beta_{ij}$. The distribution of $\log(\beta_{ij})$ (Fig. 5) provides a mechanism to detect differences amongst different subsets of
interactions obtained by varied experimental methods. In Fig. 5, we compare the distribution of $\log(\beta_{ij})$ from the whole network to distribution derived from several subsets of the network. First, we use the subset, as the core set, of the interactions that was derived by Deane et al. [14]. Interactions in the core set are statistically verified to reduce the false positive rate, yielding 1925 interactions (excluding self-interacting pairs). The distribution of $\log(\beta_{ij})$ for
the core set is similar to that obtained for the entire network. However, upon comparing the distribution of $\log(\beta_{ij})$ for subsets of those interactions obtained from different experimental procedures, differences emerge. For example, interactions measured by immunoprecipitation tends to have a larger $\beta_{ij}$, so that the distribution of $\log(\beta_{ij})$ of this subset shifts to the right. In contrast, the distribution for the subset of interactions measured with high-throughput two-hybrid tests display the opposite trend.

![Graph showing normalized distributions of $\log(\beta_{ij})$ for different subsets of interactions. The solid line represents the distribution for all interactions in the data. The dotted line corresponds to the core set extracted by Deane, et al[14]. The short dashed line refers to interactions obtained by immunoprecipitation, and the long dashed line represents the subset of interactions derived from high-throughput two-hybrid tests.](image)

**FIG. 5:** Normalized distributions of $\log(\beta_{ij})$ for different subsets of interactions. The solid line represents the distribution for all interactions in the data. The dotted line corresponds to the core set extracted by Deane, et al[14]. The short dashed line refers to interactions obtained by immunoprecipitation, and the long dashed line represents the subset of interactions derived from high-throughput two-hybrid tests.

If $e_{ij}$ is the only edge linking two clusters, the contribution of a particular realization of the percolation procedure to $\beta_{ij}$ is proportional to the product of the sizes of the two clusters. Hence, an edge with a greater $\beta_{ij}$ has a greater tendency to link two large modules or clusters in the network. With this notion in mind, an examination of Fig. 5 suggests that the IP method is possibly more sensitive to interactions between proteins in different large modules while the two-hybrid tests are better suited to detecting interactions which tend not to link larger modules.

The discrepancy between the IP method and the two-hybrid tests might reflect the underlying biochemical differences between the two methods. Unlike IP, the two-hybrid test is an *in vivo* technique, and thus it can detect transient and unstable interactions[9]. Our analysis of the distribution of $\log(\beta_{ij})$ for the two-hybrid data is a quantitative demonstration that
these transient and unstable interactions contribute less to the integrity of the interaction network.

IV. CONCLUSION

We presented a stochastic algorithm that explored the global connectivity properties of a protein interaction network. This percolation-based algorithm allowed us to assign weights to vertices and edges according to non-local topological properties. We applied the algorithm to the protein interaction network for yeast and found that the percentage of essential proteins correlated strongly with $v_i$. Importantly, the values of $v_i$, which incorporated the knowledge of connections beyond the nearest neighbors, could more successfully discriminate essential proteins than a method based solely on local connections. In addition, the essential proteins with greater $v_i$ not only possessed more interactions with any other proteins but also displayed more interactions with other essential proteins. This result suggested that essential proteins along with other proteins having greater $v_i$ might form a “core network” with a higher density of interactions within the “core network” than the background network. If this unverified hypothesis is confirmed, then we would gain significant insight into the evolution of a protein interaction network. Are the proteins in this “core network” in general more evolutionarily conserved than others? Hunter et al. claimed that there is significant negative correlation between each protein’s degree of connectivity and protein evolutionary rate, and that evolutionary change may occur largely by coevolution [15]. If this is indeed so, we expect a stronger correlation between $v_i$ and protein evolutionary rate, since $v_i$ provides a better resolution than the degree of connectivity for proteins’ positions in their interaction network.

The $\beta_{ij}$ scores for interaction could distinguish the differences between different experimental methods for measuring protein interactions. Such a quantitative measure of the distinction amongst the experimental approaches will aid the interpretation of the proteomic data.

In principle, $c_{ij}$ can be calculated exactly given a percolation probability $p$. However, this would require recursive iterations over all possible sub-graphs. Our stochastic approach efficiently obtains the approximations to the exact value of $c_{ij}$, $v_i$ and $\beta_{ij}$. In this work, we model the interaction network as a static graph with uniform weight on each edge. For a
biological system, dynamical aspects need to be incorporated. Various experimental methods for probing the physical interactions between proteins respond differently to the dynamics of biological systems. The two-hybrid test is more sensitive to transient interactions while the IP method is more sensitive to large and stable protein complexes. The differences might be addressed from different dynamics aspects in the interaction network.

With regard to future pursuits, we note that it is also possible to use $\beta_{ij}$ to cluster vertices within a random graph. The $\beta_{ij}$ score for a random graph is similar to the edge “betweenness”, defined as the number of shortest paths between all pairs of vertices passing through a given edge. An edge with a greater $\beta_{ij}$ is likely also an edge with a greater edge “betweenness”, because such an edge has great tendency to bridge two different clusters or modules. Clustering utilizing edge “betweenness” have been successfully applied to certain types of random networks[16]. We expect that results similar to those shown in Fig. 1 could be achieved with $\beta_{ij}$ not only for this small test graph but more significantly for larger graphs in which the computational cost of calculating edge “betweenness” is prohibitive. For the present, however, the idea of percolation on random networks provides a natural mechanism for revealing dominant cluster structure within a graph. We hope such natural cluster structure will provide further details about the protein interaction network.

Acknowledgments

We thank Hao Li and Shoudan Liang for fruitful discussion. C. S. Chin also likes to thank Yigal Nochomovitz for critical reading of the manuscript. C. S. Chin is supported by Sandler Opportunity Grant. M. P. Samanta is supported by NASA contract DTTS59-99-D-00437/A61812D to CSC.

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[19] The graph diameter (the maximum amongst all the shortest paths between all pairs of vertices) of the protein interaction network is 12. The average path length of the path between any two proteins is 4.23.

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