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### Title

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# Transitive Closure and Metric Inequality of Weighted Graphs – Detecting Protein Interaction Modules Using Cliques

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## Abstract

We study transitivity properties of edge weights in complex networks. We show that enforcing transitivity leads to a transitivity inequality which is equivalent to ultra-metric inequality. This can be used to define transitive closure on weighted undirected graphs, which can be computed using a modified Floyd-Warshall algorithm. We outline several applications and present results of detecting protein functional modules in a protein interaction network.

Keywords: transitive closure, ultrametric, triangle inequality, weighted graph, protein interaction

## 1 Introduction

Complex network studies[8] include the internet and the Web, social networks, biological networks, etc. Much progress has been made in degree distribution, network topology, growth models, small-world effect, etc.

In this paper, we study transitivity properties of edge weights, reflecting affinity between two proteins, relatedness between two persons or similarity between two webpages. Generally speaking, these complex networks exhibit some level of transitivity[8]. For example, for 3 persons  $A, B, C$ . If  $A$  is related to (a friend of)  $B$  and  $B$  is related to  $C$ ,  $A$  is likely to be related to  $C$ , at least in comparison with two randomly selected persons. In the protein interaction network, if protein  $p_i$  interacts with protein  $p_j$  and protein  $p_j$  interacts with protein  $p_k$ , it is likely that protein  $p_i$  also interacts with protein  $p_k$ . Another way to characterize the same feature is to say that the average clustering coefficient of the network is large (in the language of small world[13]).

Beyond this general understanding, not many studies on network transitivity exist so far. In the social network field, there are some studies focusing on statistical evidence of this being true [12]. We wish to push this further and in a somewhat different direction. We ask: Over a large number of different networks, what kind of transitivity we should expect? What are the consequence of transitivity of network affinity (edge weights)?

At present, most network models use unweighted graphs (edge weights are either 1 or 0). This is a simplification convenient for understanding large scale properties. A detailed study of transitivity requires a “quantitative” analysis, i.e., the edge weights in the network are more realistically assigned on a gradual scale. For example, in a protein interaction network, the weight (the interaction strength) should be the

probability that two proteins have a synergistic interaction. In a social network data (Freeman’s electronic information exchange system data[12]), the relationship between two persons has 5 scales: (1) don’t know each other; (2) have heard of the other, but never met; (3) have met ; (4) are friends; (5) are close friends. Therefore, we focus on weighted graphs.

We approach the transitivity problem by seeking maximum mathematical consistency, and relate it to the well-known properties of metric distances, such as the triangle inequality and the ultra-metric inequality. Note that we are not “asserting” that complex networks “must” follow mathematical consistency. Our goal is to see how far we can go by assuming mathematical consistency.

In §2 we introduce a new concept of transitive affinity and discuss its properties. We show that transitive affinity satisfies an inequality which is shown to be equivalent to the ultra-metric inequality of a distance metric. Through this, we introduce the concept of transitive closure of a weighted graph. An efficient algorithm is also presented. In §3- §4, the transitive closure on affinity graphs is extended to dissimilarity graphs and to situations where triangle inequalities hold.

In §5, we outline several applications. In §6 - §8, we present results of detecting protein functional modules from protein interaction networks.

## 2 Transitive affinity of a weighted affinity graph

### 2.1 Transitivity and associativity

We study transitive properties of affinity graphs where the edge weights measure pairwise affinities between nodes. We use the protein interaction as example.

Suppose protein  $p_1$  strongly interacts with  $p_2$ , say  $w_{12} = 0.7$ . Suppose protein  $p_2$  strongly interacts with  $p_3$ , say  $w_{23} = 0.9$ . Given these, there is a reasonable probability that protein  $p_1$  also interacts with  $p_3$ , i.e., there is a nonzero *transitive* affinity between  $p_1$  and  $p_3$ . There are three probable quantitative ways to characterize the transitivity:

$$\mathbb{T}_{max}(w_{12}, w_{23}) = \max(w_{12}, w_{23}) = 0.9, \tag{1}$$

$$\mathbb{T}_{avg}(w_{12}, w_{23}) = (w_{12} + w_{23})/2 = 0.8, \tag{2}$$

$$\mathbb{T}_{min}(w_{12}, w_{23}) = \min(w_{12}, w_{23}) = 0.7. \tag{3}$$

Let  $P_{13} = (1, 2, 3)$  be the path connecting  $p_1$  to  $p_3$ . We say that  $\mathbb{T}(w_{12}, w_{23}) = \mathbb{T}(P_{13}) = \mathbb{T}(1, 2, 3)$  is the transitive affinity along path  $P_{13}$ , which is a 2-hop path (passing through 2 edges). The question is: among the three possible choices, which one best captures the transitivity and satisfies many other consistency principles?

Suppose protein  $p_3$  interacts with another protein  $p_4$ . Thus a nonzero transitive affinity  $\mathbb{T}(P_{14}) = \mathbb{T}(1, 2, 3, 4)$  exists between  $p_1$  and  $p_4$ . For the transitive affinity to be consistent along a path of  $(1, 2, 3, 4)$ , we require it have the associativity:

$$\mathbb{T}(\mathbb{T}(w_{12}, w_{23}), w_{34}) = \mathbb{T}(w_{12}, \mathbb{T}(w_{23}, w_{34})) \tag{4}$$

With this associativity,  $\mathbb{T}(w_{12}, w_{23}, w_{34})$  is uniquely defined and is denoted as  $\mathbb{T}(P_{14})$ . One can easily extend this to longer paths. It is clear that  $\mathbb{T}_{avg}$  does not satisfy associativity; this rules out  $\mathbb{T}_{avg}$ . Both

$\mathbb{T}_{max}$  and  $\mathbb{T}_{min}$  satisfy associativity. In general, transitivity is regulated by the weakest link on the path. Thus we choose  $\mathbb{T} = \mathbb{T}_{min}$ . In the rest of this paper, we study the transitivity associated with  $\mathbb{T}_{min}$ . The transitive affinity on the path  $P_{ij} = (i, k_1, \dots, k_m, j)$  is therefore

$$\mathbb{T}(P_{ij}) = \min(W(P_{ij})), \quad W(P_{ij}) \equiv \{w_{i,k_1}, w_{k_1,k_2}, \dots, w_{k_{m-1},k_m}, w_{k_m,j}\}. \quad (5)$$

## 2.2 Maximal transitive affinity

Transitive affinity is defined on a specific path. In general, fixing nodes  $i, j$ , transitive affinities on different paths connecting  $i, j$  are different. For this reason, we define maximal transitive affinity between  $i, j$  as

$$h_{ij} = \max_{P_{ij}} \mathbb{T}(P_{ij}), \quad (6)$$

where  $P_{ij}$  is any possible path between  $i, j$ . Given a graph, the maximal transitive affinity between any pair of vertices is uniquely defined. We can show that  $h_{ij} \geq w_{ij}, \forall i, j$ . Furthermore, we can prove that

**Theorem 1.** For any weighted graph, the maximal transitive affinity between any pair of vertices satisfies the following transitive affinity inequality relationship

$$h_{ij} \geq \min(h_{ik}, h_{kj}) \quad \forall i, j, k. \quad (7)$$

Proof. Let  $(P_{ik}, P_{kj})$  be a path starting at  $i$ , going through  $k$ , and ending at  $j$ .  $P_{ij}$  is a path starting at  $i$  and ending at  $j$ . Clearly  $\{(P_{ik}, P_{kj})\}$  is a subset of  $\{P_{ij}\}$ . Thus,

$$h_{ij} = \max_{P_{ij}} \min [W(P_{ij})] \quad (8)$$

$$\geq \max_{(P_{ik}, P_{kj})} \min [W(P_{ik}, P_{kj})] \quad (9)$$

$$= \max_{(P_{ik}, P_{kj})} \min [\min [W(P_{ik})], \min [W(P_{kj})]] \quad (10)$$

$$= \min \left[ \max_{P_{ik}} (\min [W(P_{ik})]), \max_{P_{kj}} (\min [W(P_{kj})]) \right] \quad (11)$$

$$= \min(h_{ik}, h_{kj}). \quad (12)$$

□

## 2.3 Metric inequality

Here we show that the transitive affinity inequality is identical to the ultra-metric of a distance metric, and therefore, a general principle.

Recall the definition of the metric space. A function  $d(x_i, x_j) = d_{ij}$  on all pairs of objects in the space, i.e., pairwise dissimilarities, is a metric, if (m1) nonnegativity:  $d_{ij} \geq 0 \forall i, j$ . (m2) identity:  $d_{ij} = 0$  if  $x_i = x_j$ . (m3) symmetry:  $d_{ij} = d_{ji}$ . (m4) triangle inequality

$$d_{ij} \leq d_{ik} + d_{kj}. \quad (13)$$

A metric function preserves the important notion of *distance*. Metric space has a large number of properties and is useful for many problems. A special case of metric space is ultra-metric space, where the triangle

inequality is replaced by a stronger ultra-metric inequality

$$d_{ij} \leq \max(d_{ik}, d_{kj}). \quad (14)$$

A dissimilarity function satisfying the ultra-metric inequality also satisfies the triangle inequality; however, not all metric functions satisfy ultra-metric inequality.

First, we note that *similarity* is a decreasing function of *distance*: the more similar two objects are, the smaller their distance is. Thus  $s_{ij} = f(d_{ij})$ , where  $f(\cdot)$  is a monotonic decreasing function (more precisely, a nonincreasing function).

**Theorem 2.** The distance-based ultra-metric inequality is identical to the similarity-based transitive affinity inequality, assuming that  $s_{ij} = f(d_{ij})$  is a nonincreasing function.

Proof. By construction,  $s_{ij} = f(d_{ij}) \geq f(\max(d_{ik}, d_{kj})) = \min(f(d_{ik}), f(d_{kj}))$  □

The ultra-metric inequality Eq.(14)] can be viewed as a general principle (or a highly desirable property for distance functions) from the axiomatic point of view, similar to the triangular inequality. Therefore, we may consider the transitive affinity inequality of Eq.(7) as a general principle that affinity functions should obey.

## 2.4 Transitive closure of a weighted graph

If we repeat the same line of discussions of transitive affinity in §2.1 - §2.2 on an unweighted graph, it is clear that the maximal transitive affinity  $h_{ij}$  will be 1 between any two nodes in a connected component. This process is very similar to the concept of transitive closure of a directed unweighted graph. Thus the transitive closure of an undirected unweighted graph is the complete graph on the nodes of any connected component.

Now we further extend this concept to an undirected weighted graph with weight  $\{w_{ij}\}$ . We replace the original weight  $w_{ij}$  by the maximal transitive affinity  $h_{ij}$ . The new graph weights are thus consistent with the idea of transitivity of affinity relationship, because it satisfies the transitive affinity inequality. We therefore have

**Definition 1.** The transitive closure of weighted graph  $G$  is formed by their maximal transitive affinity  $h_{ij}$ .

**Remark.** This definition can be extended to the transitive closure of a weighted directed graph, by generalizing the maximal transitive affinity  $h_{ij}$  to directed graphs in a straightforward manner. For unweighted graphs, this definition reduces to the standard definition of transitive closure.

## 2.5 Computing transitive closure of a weighted graph

Computing maximal transitive affinity  $h_{ij}$  by its original definition Eq.(6) is fairly complicated. However, since  $h_{ij}$  satisfy the transitive affinity inequality, this property can be used to compute  $h_{ij}$  in a much more efficient way:

**Theorem 3.** The transitive closure of weighted graph  $G$  can be equivalently computed by increasing edge weights such that the transitive affinity inequality are satisfied.

The basis for this theorem is the following:

**Theorem 4.** Suppose the edge weights of given graph satisfy the transitive affinity inequality. The transitive affinities as defined in Eq.(6) are equal to edge weights:  $h_{ij} = w_{ij}$ .

**Proof.** We first show that for 2-hop paths, maximal transitive weight is equal to the edge weight. Fixing  $i, j$ , we consider a 2-hop path  $i - k - j$ . Since weights satisfy transitive affinity inequality,  $w_{ij}$  must be larger or equal to 2-hop transitive weight  $t(P_{ikj})$  for any  $k$ . Thus  $w_{ij}$  must be the 2-hop maximal transitive weight between  $i, j$ . This is valid for all  $i, j$  pairs.

Now consider 3-hop paths between  $i, j$ . Consider a 3-hop path  $i - k - l - j$ . Since for 2-hop paths, maximal transitive weight is equal to the edge weight, we can replace  $i - k - l$  by  $i - l$ , or replace  $k - l - j$  by  $k - j$  when computing maximal transitive weight. Thus we need consider only 2-hop paths  $i - l - j$  and  $i - k - j$ . Apply the 2-hop path equivalence property, these two paths have the same maximal transitive weight as path  $i - j$ . Thus the maximal transitive weight for the path  $i - k - l - j$  is  $w_{ij}$ . This is valid for all possible  $i, k, l, j$ .

The proof for 4-hop paths, 5-hop paths, etc. are the same. □

## 2.6 Modified Floyd-Warshall algorithm

Using Theorems 3 and 4, we see that for computation of maximal transitive affinities on multi-hop paths, it is sufficient to computing for 2-hop paths only and simultaneously updating  $w_{ij}$  such that eventually  $h_{ij} = w_{ij}$ . This 2-hop path (or triangle) only property is crucial to for an efficient algorithm implementation. Since to verify whether a given graph weights satisfy transitive closure, we need to go through all possible triangles  $\binom{n}{3} = n(n-1)(n-2)/3! = O(n^3)$  to check the transitive affinity inequality. This is the minimal computational cost.

We can show that the transitive closure can be computed by a slight modification of the Floyd-Warshall algorithm for all-pair shortest paths in  $O(n^3)$ . Since  $O(n^3)$  is the the minimal computational cost. to check the correctness of the triangle inequality, the Floyd-Warshall algorithm is optimally efficient.

Given input  $W$ , the weight matrix of a network. The algorithm computes the maximal transitive affinity as the following:

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Floyd-Warshall to compute transitive closure of graph with weights  $W$ .

```

1   $H = W$ 
2  for  $k = 1$  to  $N$ 
3      do for  $i = 1$  to  $N$ 
4          do for  $j = 1$  to  $N$ 
5               $h_{ij} = \max(h_{ij}, \min(h_{ik}, h_{kj}))$ 
6  return  $H$ 

```

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The modification is on Line 5, updating  $h_{ij}$ , which uses Eq.(7) for satisfying the transitive affinity inequality.

### 3 Transitive closure of dissimilarity graphs

The concepts and results in §2 for affinity graphs can be extended to dissimilarity graphs where the edge weights  $D = (d_{ij})$  measure the “dis-similarity” or “distance”. The “transitive dissimilarity” on path  $P_{ij}$  is defined as

$$f(P_{ij}) = \min(D(P_{ij})), \quad D(P_{ij}) \equiv \{d_{i,k_1}, d_{k_1,k_2}, \dots, d_{k_{m-1},k_m}, d_{k_m,j}\}. \quad (15)$$

Fixing  $i, j$ , transitive dissimilarity depends on the particular path. Thus we define minimal transitive dissimilarity (analog of shortest path) between  $i, j$  as

$$g_{ij} = \min_{P_{ij}} f(P_{ij}). \quad (16)$$

**Theorem 5.** For any weighted dissimilarity graph, minimal transitive dissimilarity between any pair of vertices satisfies the ultra-metric inequality

$$g_{ij} \leq \max(g_{ik}, g_{kj}). \quad (17)$$

Therefore,  $\{g_{ij}\}$  is consistent with the transitivity of dissimilarity relationship. We therefore define

**Definition 2.** The transitive closure of weighted dissimilarity  $G$  is formed by the minimal transitive dissimilarity  $\{g_{ij}\}$ .

Computing  $g_{ij}$  by its original definition, Eq.(16), is fairly complicated. Instead we can efficiently compute them using the ultra-metric inequality:

**Theorem 6.** The transitive closure of a dissimilarity graph can be equivalently computed by reducing edge dissimilarities such that the ultra-metric inequality is satisfied.

The transitive closure of a dissimilarity graph can be computed using the same Floyd-Warshall algorithm in §2.6, with Line 1 replaced by  $G = D$ , and Line 5 replaced by  $g_{ij} = \min(g_{ij}, \max(g_{ik}, g_{kj}))$ .

## 4 Transitive closure based on the triangle inequality

### 4.1 Transitive closure of dissimilarity graphs w.r.t. the triangle inequality

Theorem 6 indicates the transitive closure of a dissimilarity graph can be viewed as reducing the edge dissimilarities such that the ultra-metric inequality Eq.(14) is satisfied. Since ultra-metric inequality is a special case of the triangle inequality Eq.(13), we can generalize this and define

**Definition 3.** The transitive closure of a dissimilarity graph w.r.t. the triangle inequality is defined by reducing edge dissimilarities such that the triangle inequality is satisfied.

In this case, the edge weight on the transitive closure no longer has the meaning of transitive dissimilarity as discussed in §3. The benefit of transitive closure w.r.t. the triangle inequality is that the edge weights are reduced relatively small (in comparison to the transitive closure w.r.t. ultra-metric inequality). The transitive closure can be computed using the same Floyd-Warshall algorithm in §2.6, with Line 5 replaced by  $g_{ij} = \min(g_{ij}, g_{ik} + g_{kj})$ .

## 4.2 Transitive closure of affinity graphs w.r.t. the triangle inequality

The concept of transitive closure of a dissimilarity graph w.r.t. to triangle inequality can be extended to affinity graphs.

Although the ultra-metric inequality of distance metric has a natural counterpart in affinity measures as shown in Theorem 2 in §2.3, the triangle inequality of distance metric has no clear counterpart in affinity measures.

The simplest and perhaps most natural counterpart is obtained by assuming that affinity is inversely proportional to distance:  $s_{ij} = \text{const}/d_{ij}$ . From this, we obtain

$$\frac{1}{s_{ij}} \leq \frac{1}{s_{ik}} + \frac{1}{s_{kj}}.$$

We call this the “harmonic triangle inequality” since it resembles the harmonic average:  $\frac{1}{\langle x \rangle} = \frac{1}{2}(\frac{1}{x_1} + \frac{1}{x_2})$ . With this, we can define

**Definition 4.** The transitive closure of an affinity graph w.r.t. the triangle inequality is defined by increasing edge weights such that the above harmonic triangle inequality is satisfied.

The benefit of this transitive closure is that edge weights are increased relatively small (in comparison to the transitive closure w.r.t. ultra-metric inequality in §2.4). The transitive closure can be computed using the same Floyd-Warshall algorithm in §2.6, with Line 5 replaced by  $h_{ij} = \max[h_{ij}, h_{ik}h_{kj}/(h_{ik} + h_{kj})]$ .

## 5 Applications of transitive closure

Here we discuss practical applications of transitive closure of weighted graphs.

First, in transitive closure, the originally not-so-densely connected subgraph structures become more dense, therefore this facilitates the discovery of these dense subgraph structures, i.e., communities in the network. In this direction, we will discuss an application to protein interaction in §7-8.

Second, in standard web link structure analysis, the web is represented by an unweighted directed graph. Since our approach emphasizes weighted graphs, we can incorporate webpage content into the link structure by weighting the link with the cosine similarity between the two webpage word contents. In this way, the transitive affinity along a path decreases with the number of edges because its strength is the weakest link between  $i, j$ . This is more natural than unweighted link analysis approaches.

Third, transitive closure provides a way to update affinity weights in a changing environment. Suppose we are given a social network. After a while two person get married. This marriage will lead to series of changes in the social network. Transitive closure provides a quantitative way to update the network weights. First the edge weight between the two persons in the graph is suddenly increased to maximum. Second, the affinity weights between their in-laws are increased such that the transitive inequality holds for every node triple, etc.

## 6 Cliques on a weighted graph

A clique is the tightest structure or the densest subgraph in a unweighted graph, because every nodes in a clique connect to every other nodes. We generalize the concept of clique to weighted graphs and introduce



an algorithm to compute them. The generalization is based on the theorem due to Motzkin and Straus [7] which relates maximal cliques of an unweighted undirected graph to the optimization of a quadratic function.

Let  $G = (V, E)$  be an unweighted undirected graph of  $n = |V|$  vertices and  $|E|$  edges with adjacency matrix  $A$ . Define a vector  $\mathbf{x} = (x_1, \dots, x_n)^T$  on the vertices, i.e.,  $\mathbf{x} \in \mathbb{R}^n$ . Consider the optimization problem:

$$\max_{\mathbf{x} \in S_n} J(\mathbf{x}) = \mathbf{x}^T A \mathbf{x} \quad (18)$$

where  $\mathbf{x}$  is restricted to the unit simplex  $S_n$  defined as

$$S_n : x_1 + \dots + x_n = 1, x_i \geq 0, \forall i. \quad (19)$$

The nonzero elements in the solution vector  $\mathbf{x}$  play an important role. In particular, we define a characteristic vector of a subset  $C$  of vertices as  $\mathbf{x}^C = (x_1^c, \dots, x_n^c)^T$ , where  $x_i^c = 1/|C|$  if  $i \in C$ ,  $x_i^c = 0$  otherwise. The following theorem make the connection between vertices corresponding to nonzero elements to maximal cliques.

**Theorem 7**[Motzkin and Straus]. (1) Subset  $C$  is the largest maximal clique if and only if its characteristic vector is a global optimal solution of the optimization problem; (2) Subset  $C$  is a maximal clique if and only if its characteristic vector is a local optimal solution of the above optimization problem.

The Motzkin-Straus Theorem provides a convenient formalism for generalize the concept of cliques to weighted graphs.

**Definition 5.** *Generalized cliques* in a weighted graph with adjacency matrix  $A$ . The subset of vertices corresponding to the nonzero elements in the optimal solution  $\mathbf{x}^*$  form a clique in  $A$ .

The key to this generalization is the recognition of the  $L_1$ -type constraint of Eq.(19) in the quadratic programming problem of Eq.(18) (The  $L_p$ -norm of a vector  $\mathbf{x}$  in  $n$ -dimensional space is defined as  $\|\mathbf{x}\|_p = (\sum_{j=1}^n |x_j|^p)^{1/p}$ ,  $1 \leq p \leq \infty$ .) It is well-known [10, 4] that this  $L_1$ -type constraint leads to sparse solutions, i.e., many if not most of entries in the final optimal solution  $\mathbf{x}^*$  are zero. This sparsity property of the solution is the theoretical basis for our generalization of the Motzkin-Straus formalism to define cliques in weighted graphs.

The quadratic programming problem of Eq.(18) can be solved by a simple method developed in the biological evolution field [9]. The method is an iterative algorithm updating a current solution vector using:

$$x_i \leftarrow x_i \frac{(A\mathbf{x})_i}{\mathbf{x}^T A \mathbf{x}}, \forall i. \quad (20)$$

One can easily see the feasibility of the solution: if the initial  $\mathbf{x} \in S_n$  [defined in Eq.(19)], it will remain in  $S_n$ , since  $\sum_i x_i = \sum_i x_i (A\mathbf{x})_i / (\mathbf{x}^T A \mathbf{x}) = 1$ . We can also prove the convergence of the algorithm, by showing that the objective function  $J$  is monotonically increasing (or non-decreasing) under the above update rule. Since  $L(\mathbf{x})$  is bounded above, the updating algorithm converges.

If adjacency matrix  $A$  is positive definite, the objective  $J$  is a convex function and the optimal maxima is also the global maxima. Unfortunately, for many applications,  $A$  is in generally indefinite. There are a large number of local maximas, each representing a densely connected subgraph.

We use the above updating algorithm to solve for cliques. After one local optimal solution is obtained,

the clique corresponding to non-zero entries in the solution vector is extracted; these nodes are eliminated from the graph. We solve for another local optimal solution and its corresponding clique, etc.

## 7 Application to the protein interaction network

In §7 - §8, we present application of transitive affinity and transitive closure to protein interaction networks.

Proteins carry out cellular functions and processes in a modular fashion, involving multiple interacting proteins. Identification of protein functional modules thus becomes an urgent research topic. There is a large body of genome-wide comprehensive experiments on protein interaction networks. The two-hybrid genetic screen [6, 11] yields binary interaction data. High throughput mass spectrometry methods [3, 5] combine tagged “bait” proteins and protein-complex purification schemes with mass spectrometric measurements to yield physiologically relevant data on intact multi-protein complexes.

However, these high-throughput experiments are often associated with large false-positives. Protein interaction data obtained in two independent experiments [6] and [11] overlap by less than 4%. Therefore, using computational methods to predict protein interaction modules from these data is an important way to extract additional information.

An effective approach for predicting protein modules is to detect the densely connected subgraphs in protein interaction networks. The most intuitive definition of a densely connected subgraph is clique. One difficulty with this approach is that protein interactions are typically very sparse. Thus the cliques detected are very small. One way to overcome this problem is to use  $k$ -core [5, 1], where each protein only interacts with a fraction of other proteins in the subgraph. This relaxes the strict definition of clique, but it introduces the issue of how to choose the parameter  $k$ .

We resolve the sparsity issue by using the transitive closure of §2. The idea is that on transitive closure, missing connection/interactions will be added and the graph become dense; therefore the detected cliques will be larger, thus more close to the true protein interaction modules.

Note that the simplest protein interaction network is unweighted, i.e., the interaction strength is either 1 or 0. This is a crude approximation. More refined descriptions use a weighted graph, assigning a probability or level of certainty that two proteins interact. Thus, the definition of cliques needs to be generalized to weighted graphs. This has been done in §6.

## 8 Experiments on Yeast multi-protein complex data

Two datasets of high-throughput mass spectrometry analysis of multi-protein complexes are available for the yeast *S. Cerevisiae*[3, 5]. Studies have shown that the tandem affinity purification using mass spectrometry (TAP-MS) dataset by Gavin, *et al.* [3] has the highest accuracy for predicting protein functions. Hence we use this data.

A protein complex is an assembly of a small number of proteins in permanent contact and usually perform a clear and specific biological function. A multi-protein complex can be represented as a bipartite graph which in turn gives several important quantities[2]. The bipartite graph has two type of nodes: p-nodes denote proteins and are represented by a row in the bipartite graph adjacency matrix  $B$ . The

c-nodes denote protein complexes, and are represented by columns in  $B$ . From the bipartite graph, we can naturally obtain the following two weighted interaction networks:

**Protein - Protein Interactions.** The interaction strength between two proteins  $p_i, p_j$  is given by  $(BB^T)_{ij}$  which is the number of protein complexes containing both proteins  $p_i, p_j$ .  $(BB^T)_{ii}$  = the number of protein complexes that protein  $p_i$  is involved.

**Complex - Complex Cross Talk Associations.** The interaction strength between two protein complexes  $c_i, c_j$  is given by  $(B^TB)_{ij}$ , which is the number of proteins shared by protein complexes  $c_i, c_j$ . Note  $(B^TB)_{jj}$  = the number of proteins contained in the protein complex  $c_j$ .

To see clearly the net effects of transitive closure, we run the clique finding algorithm on two network weights: the original network  $W = BB^T$  and its transitive closure  $W_{TC}$ , which is obtained using the modified Floyd-Warshall algorithm of §2. The graph has 1,440 distinct proteins. We obtain two sets of cliques  $C$  and  $C_{TC}$  as the results, corresponding to  $W$  and  $W_{TC}$  respectively. The obtained cliques are summarized below:

	# of cliques	Average-Size	Internal-Weight	External-Weight
$C$	296	4	0.59	0.014
$C_{TC}$	82	15	0.68	0.010

On the original network, the resulting  $C$  contains 296 cliques. On the transitive closure, the resulting  $C_{TC}$  contains 82 cliques. The original network is very sparse, thus we get a larger number of cliques with rather small sizes. The transitive closure is much more densely connected, thus we get a smaller number of cliques with larger sizes. These cliques also have higher average edge weight within the clique (measured in the original weight  $W$ ) and lower average strength between different cliques. (Note that weights are normalized to  $0 \leq w_{ij} \leq 1$ .) These indicate that proteins in the cliques detected based on the transitive closure are more densely connected with each other, meanwhile the average connectivities between different cliques are sparser. Both of these features are desirable for protein module discovery from protein interaction networks.

We list the 10 largest cliques in Table 1. They also have large average weights in the original interaction strength  $W$ , thus representing dense regions in the interaction network. Their biological significances have been verified by Gene Ontology analysis, similar to Figure 1.

In Fig. 1, we show an example of the usefulness of transitive closure. Two smaller cliques [shown in Fig. 1 (b) and (c)] in the original interaction network  $W$  are merged into one big clique in the transitive closure  $W_{TC}$ . GO annotations show that cliques (b) and (c) have the same function as the merged clique: *structural constituent of ribosome*. This example shows why we obtain fewer cliques on the transitive closure  $W_{TC}$ , but the sizes of these cliques are much larger. Since the larger cliques have the same function as the smaller merged ones, the cliques on the transitive closure are biologically more relevant (complete) protein modules.

Note that there are a number of uncharacterized proteins in GO (boldface protein names in Table 1). Since the GO annotation gives a clear biological function for most other proteins in the clique, we infer that these uncharacterized proteins should have similar functions. Thus our approach has the additional benefit of protein annotation.

Clique	GO Annotation
Emg1 Imp3 Imp4 Kre31 <b>Mpp10</b> Nop14 Sof1 YMR093W YPR144C	sRNA transcript processing
Cus1 Msl1 Prp3 Prp9 Sme1 Smx2 Smx3 Yhc1 <b>YJR084W</b>	nuclear mRNA splicing
<b>Fyv4</b> Mrp1 Mrp10 Mrp13 Mrp17 Mrp21 Mrp4 Mrp51 Mrps9 Nam9 Pet123 Rsm10 Rsm19 Rsm22 Rsm23 Rsm24 Rsm25 Rsm26 Rsm27 Trf4 Ubp10 YDR036C <b>YGR150C</b> YMR158W YMR188C YNL306W <b>YOR205C</b> YPL013C	protein biosynthesis & metabolism
<b>Atp11 Caf130 Caf40</b> Ccr4 Cdc36 Cdc39 Fas2 Not3 Not5 Pop2 Sig1 YDR214W	regulation of transcription from RNA polymerase II promoter
Apc1 Apc2 Cdc16 Cdc23 Cdc27 Doc1	cyclin catabolism & ubiquitin-dependent catabolism protein
Sec65 Srp14 Srp21 Srp54 Srp68 Srp72	signal recognition complex
Csl4 Mtr3 Rrp42 Rrp43 Rrp45 Rrp6 Ski6 Ski7	mRNA catabolism
Cft2 Fip1 Pap1 Pfs2 <b>Pta1</b> Ref2 Rna14 YGR156W Ysh1	mRNA cleavage and polyadenylation
Lsm1 Lsm2 Lsm5 Lsm6 Lsm7 Pat1 Prp24 Prp38 Snu23	mRNA metabolism
Apl1 Apl3 Apl5 Apl6 Apm3 Apm4 Aps2 Aps3	vesicle-mediated transport

Table 1: Ten cliques identified by our algorithm. Boldfaced proteins are uncharacterized in GO.

## 9 Summary

We study transitive properties of affinity graphs. We show that maximal transitive affinity satisfies the transitive inequality which in turn is proved to be equivalent to the ultra-metric inequality of a distance metric. The maximal transitive affinity defines the transitive closure of the weighted affinity graphs. These concepts can be equivalently extended to dissimilarity graphs. We prove that a modified Floyd-Warshall algorithm is optimally efficient to compute transitive closures. Furthermore, transitive closure of weighted affinity and dissimilarity graphs are generalized to transitive closure w.r.t. triangle inequalities. They change the edge weights relatively little and thus can apply to wider applications. These new metrics/concepts are parameterless, revealing intrinsic properties of the networks.

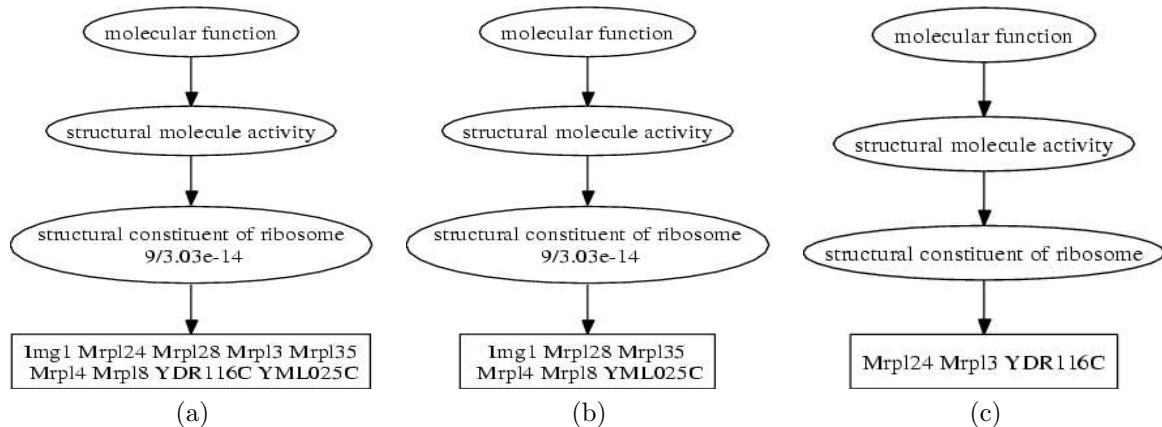


Figure 1: Gene ontology annotations of 3 cliques. (a) The clique obtained from the transitive closure, which is formed by merging the smaller cliques shown in (b) and (c) obtained on the original network.

We apply transitive closure to protein interaction networks to overcome the sparsity problem. The Motzkin-Straus formalism for identifying cliques is generalized to weighted interaction networks; densely connected protein modules are detected as cliques on the weighted graph and their biological significance are verified by Gene Ontology analysis.

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