Centralities in Simplicial Complexes. Applications to Protein Interaction Networks

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Abstract

Complex networks can be used to represent complex systems which originate in the real world. Here we study a transformation of these complex networks into simplicial complexes, where cliques represent the simplices of the complex. We extend the concept of node centrality to that of simplicial centrality and study several mathematical properties of degree, closeness, betweenness, eigenvector, Katz, and subgraph centrality for simplicial complexes. We study the degree distributions of these centralities at the different levels. We also compare and describe the differences between the centralities at the different levels. Using these centralities we study a method for detecting essential proteins in PPI networks of cells and explain the varying abilities of the centrality measures at the different levels in identifying these essential proteins.

1 Introduction

There is little doubt that the use of graphs and networks to represent the skeleton of complex systems has been a successful paradigm. This simple representation in which nodes of the graph accounts for the entities of a complex system and the edges describe the interactions between these entities captures many of the complex structural and dynamical properties of the represented systems. However, such representation is far from complete. One of its main drawbacks is its concentration of binary relations only. That is, in a network the interaction between entities occurs in a pairwise way. This excludes other higher-order interactions involving groups of entities. Let us provide some examples. Networks have been widely used to represent protein-protein interactions (PPIs) where the nodes represent proteins and pairs of interacting proteins are connected by edges of the network. These PPI networks contain many triangles in which triples of proteins are considered to be interacting to each other. Now, let us consider that there are three proteins A, B and C that form a heterotrimer, that is an ABC complex in which the three

proteins interact with each other at the same time. The network-theoretic representation is not able to differentiate this situation from the case where there are three proteins A, B and C and they interact in a pairwise manner, e.g. AB, AC, BC. The existence of heterotrimers in well-documented, an example is the heterotrimeric G protein formed by the three proteins G_α, G_β and G_γ. An attempt to amend this problem has been made by using hypergraphs, also known as hypernetworks. In this case, the triple of proteins form an hyper-edge which accounts for the simultaneous interaction of the proteins in the complex. However, hypergraphs have a main drawback when trying to capture all the subtleties of these complexes. For instance, in the heterotrimeric G protein, the proteins G_β and G_γ form a subcomplex known as $G_{\beta\gamma}$ which is part of the trimeric form. This situation is not necessarily captured by the hypergraph representation where hyperedges are not necessarily closed under the subset operation. Examples of real-world systems where this closure under the subset operation is required abound and a very nice example provided by Maletić and Rajković [Maletić and Rajković, 2012] according to them provided by Spivak—, where four people have a chat in which everybody can listen to each other. Obviously, the conversation is not pairwise as represented by the graph, and is not only in the form of the hyper-edge represented by the hypergraph, but a combination of the quadruple, triangles and edges. The best way to represent such situations is by means of the so-called *simplicial complexes*.

Informally, a simplicial complex is a mathematical object, which originated in algebraic topology and is a generalization of a network. Starting with a set of nodes, instead of being limited to sets of size two, the simplices can contain any number of nodes. A characteristic feature of a simplex S of a certain size is that all subsets of S must also be simplices. In this way simplicial complexes differ from hypergraphs. For instance, if there is a simplex $\{1,3,4,6\}$ in a simplicial complex then $\{1,3,4\},\{1,3,6\},\{1,4,6\},\{3,4,6\}$ are also simplices in the simplicial complex. All subsets of those four simplices must also be simplices in the complex. There is a recent interest in these mathematical objects for representing complex systems and we should mention here their applications to study brain networks [Giusti et al., 2016; Courtney and Bianconi, 2016; Lee et al., 2012; Petri et al., 2014; Pirino et al., 2015], social systems [Maletić and Rajković, 2009] [Maletić and Rajković, 2014; Kee et al., 2016], biological networks [Xia and Wei, 2014] [Xia and Wei, 2015; Cang et al., 2015], and infrastructural systems [Muhammad and Egerstedt, 2006] [Tahbaz-Salehi and Jadbabaie, 2010; De Silva and Ghrist, 2007; De Silva et al., 2005; Ghrist and Muhammad, 2005].

Centrality indices have been among the most successful tools used for discovering structural and dynamical properties of networks. A centrality index is a numeric quantification of the 'importance' of a node in terms of its position, structural and/or dynamical, in the network. Here, we extend this concept to simplicial complexes to capture the relevance of a simplex of a given order in a simplicial complex. In particular, we apply this extended concept to the study of properties of protein-protein interaction (PPI) networks.

2 Preliminaries

Simplicial complexes have been much studied in the literature [Horak et al., 2009; Sizemore et al., 2016] and definitions similar to those which appear in the preliminaries section can be found elsewhere [Muhammad and Egerstedt, 2006; Tahbaz-Salehi and Jadbabaie, 2010; Muhammad and Jadbabaie, 2007; Maletić and Rajković, 2012; Goldberg, 2002]. However, we repeat them here to make this paper self-contained.

Let V be a set of nodes or vertices. Then a k-simplex is a set $\{v_0, v_1, \ldots, v_k\}$ such that $v_i \in V$ and $v_i \neq v_j$ for all $i \neq j$. A face of a k-simplex is a $(k-1)$-simplex of the form $\{v_0, \ldots, v_{i-1}, v_{i+1}, \ldots, v_k\}$ for $0 \leq i \leq k$. A simplicial complex C is a collection of simplices such that if a simplex S is a member of C then all faces of S are also members of C. Less formally, a simplicial complex is a collection of simplices such that if $\{v_0, v_1, \ldots, v_k\}$ is a simplex then all of its faces $\{v_0, \ldots, v_{i-1}, v_{i+1}, \ldots, v_k\}$ are also simplices, and all of the faces of its faces $\{v_0, \ldots, v_{i-1}, v_{i+1}, \ldots, v_{j-1}, v_{j+1}, \ldots, v_k\}$ are also simplices, and so on down to the 0-simplices, which are formed just by the nodes. As mentioned previously, networks can be realized as simplicial complexes. The nodes are the 0-simplices which are specified by the set V, while the edges are the 1-simplices and there are no higher order simplices. It is also possible to create simplicial complexes from networks. In this work we will be interested only in the kind of simplicial complexes defined below, which are known as *clique complexes*. A clique complex is a simplicial complex formed from a network as follows. The nodes of the network become the nodes of the simplicial complex. Let X be a clique of k nodes in the network. Then, X is a $(k-1)$-simplex in the clique complex. As an example in Figure 1 we illustrate a simplicial complex which has one 3-simplex $\{1,2,3,4\}$, seven 2-simplices $\{1,2,3\}$,$\{1,2,4\}$,$\{1,3,4\}$,$\{2,3,4\}$,$\{3,4,5\}$,$\{4,5,6\}$ and$\{6,7,8\}$. It also has fourteen 1-simplices represented by the edges and nine 0-simplices which are usually known as the nodes.

In network theory it is fairly clear when two nodes are adjacent. However, adjacency is less easy to define in simplicial complexes. There are two ways in which two k-simplices σ_j and σ_i can be considered to be adjacent. We call them *lower* and *upper adjacency*. Let σ_j and σ_i be two k-simplices. Then, the two k-simplices are lower adjacent if they share a common face. That is, for two distinct k-simplices $\sigma_j = \{v_0, v_1, \ldots, v_k\}$ and $\sigma_i = \{w_0, w_1, \ldots, w_k\}$ then σ_j and σ_i are lower adjacent if and only if there is a $(k-1)$-simplex $\tau = \{x_0, x_1, \ldots, x_{k-1}\}$ such that $\tau \subset \sigma_j$ and $\tau \subset \sigma_i$. We denote lower adjacency by $\sigma_j \smile \sigma_i$. For instance, in the simplicial complex in Figure 1, the 1-simplices $\{6,7\}$ and $\{6,9\}$ are lower adjacent because the 0-simplex $\{6\}$ is a common face of them and we can write $\{6,7\} \smile \{6,9\}$. Similarly, $\{1,3,4\} \smile \{3,4,5\}$ are lower adjacent as they share the common face $\{3,4\}$. However, $\{4,5,6\}$ and $\{6,7,8\}$ are not lower adjacent because although they have the common 0-simplex $\{6\}$ they would need to share a common 1-simplex to be considered lower adjacent. Note that two 0-simplices can never be lower adjacent as we do not allow $\varnothing$ to be a -1-simplex. Let σ_j and σ_i be two k-simplices. Then,the two k-simplices

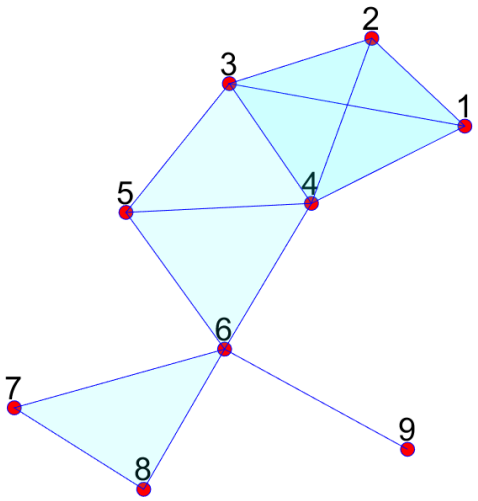
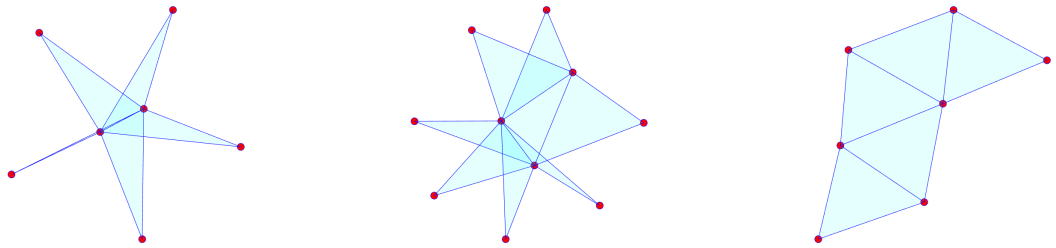


Figure 1: A simplicial complex with labeled nodes.

are upper adjacent if they are both faces of the same common $(k+1)$-simplex. That is, for $\sigma_j = \{v_0, v_1, \ldots, v_k\}$ and $\sigma_i = \{w_0, w_1, \ldots, w_k\}$ then σ_j and σ_i are upper adjacent if and only if there is a $(k+1)$-simplex $\tau = \{x_0, x_1, \ldots, x_{k+1}\}$ such that $\sigma_j \subset \tau$ and $\sigma_i \subset \tau$. We denote the upper adjacency by $\sigma_j \frown \sigma_i$. In the simplicial complex in Figure 1, the 1-simplices $\{5,6\}$ and $\{4,6\}$ are upper adjacent because they are both faces of the 2-simplex $\{4,5,6\}$which is a common face of them. So we can write $\{5,6\} \frown \{4,6\}$. Similarly, $\{1,3,4\} \frown \{2,3,4\}$ are upper adjacent as they are both faces of the 3-simplex $\{1,2,3,4\}$. However, $\{4,5,6\}$ is not upper adjacent to any other simplex as it is not part of any 3-simplices. Also note that $\{6\} \frown \{7\}$ are upper adjacent because they are both being faces of $\{6,7\}$. So two 0-simplices are upper adjacent if they are both faces of a 1-simplex which is identical to saying that two nodes are adjacent if they are connected by an edge in the network theoretic sense. Hence upper adjacency of 0-simplices is the same as network theoretic adjacency.

We shall now introduce some families of simplicial complexes which shall be important later in the paper. Firstly, we introduce the family denoted S_l^k. The simplicial complex S_l^k consists of a central $(k-1)$-simplex which is a face of every one of the l k-simplices. In addition, there are no other simplices except those necessary by the closure axiom. For instance, S_l^2 would consist of an edge $\{1,2\}$ and l triangles of the form $1,2,i$ in addition to all subsimplices necessary by the closure axiom. While, S_l^1 consists of a central node with l pendant nodes connected to it, which corresponds to the star graph in graph theory. The simplicial complex S_5^2 is shown in Figure 2(left).

Next we introduce a family of simplicial complexes labeled $t^k(x_1, x_2, \ldots, x_{k+1})$ which consists of a central k-simplex with x_1 k-simplices lower adjacent through one face, x_2 k-simplices lower adjacent through another, and so on. A k-simplex which is lower adjacent



(a) (b) (c)

Figure 2: Illustration of the simplicial complexes S_5^2 (a), $t^2(1,2,4)$ (b) and P_5^2 (c). See text for definitions and notation.

to the central k-simplex can only be lower adjacent to other k-simplices which are lower adjacent to the central k-simplex through the same face as itself. There are no other simplices except those necessary by the closure axiom. One member of this family of simplices, $t^2(1,2,4)$ is shown in Figure 2(center).

The final family of simplicial complexes which we shall introduce are denoted P_l^k, consisting of a k-simplex at one end which is only adjacent to one other k-simplex. This one is only lower adjacent to the first k-simplex and another k-simplex, and so on until arriving at another end k-simplex. In addition, there are l k-simplices in the simplicial complex and no other simplices except those necessary by the closure axiom. Note that a simplicial complex P_l^1 is the same as a path graph in the traditional network theory. The simplicial complexP_5^2 is illustrated in Figure 2(right).

3 Adjacency Matrices in Simplicial Complexes

The goal of this section is to define a general adjacency matrix for a simplicial complex that allows us to define general centrality indices for these mathematical objects. Based on the previous definitions of lower and upper adjacency relations we define the corresponding adjacency matrices here.

Definition 1. Let i and j be two k-simplices in a simplicial complex. Then, the *lower adjacency matrix* A_l^k at the k-level in the simplicial complex has entries defined by

$$(A_l^k)_{ij} = \begin{cases} 1 & \text{if } \sigma_i \smile \sigma_j \\ 0 & \text{if } \sigma_i \nsim \sigma_j \text{ or } i = j \end{cases},$$

where the subindex l indicates lower adjacency.

In a similar way we have the following.

Definition 2. Let i and j be two k-simplices in a simplicial complex. Then, the *upper adjacency matrix* A_u^k at the k-level in the simplicial complex has entries defined by

$$(A_u^k)_{ij} = \begin{cases} 1 & \text{if } \sigma_i \frown \sigma_j \\ 0 & \text{if } \sigma_i \not\frown \sigma_j \text{ or } i = j \end{cases},$$

where the subindex u indicates upper adjacency.

If two distinct k-simplices σ_i and σ_j are upper adjacent then there exists some $(k+1)$-simplex $\tau = \{v_0, v_1, \dots v_{k+1}\}$ such that $\sigma_i \subset \tau$ and $\sigma_j \subset \tau$. Without loss of generality we have $\sigma_i = \{v_1, v_2, \dots v_{k+1}\}$ and $\sigma_j = \{v_0, v_2, v_3, \dots v_{k+1}\}$ then $\|\sigma_i \cap \sigma_j\| = \|\{v_1, v_2, \dots v_{k+1}\} \cap \{v_0, v_2, v_3, \dots v_{k+1}\}\| = k - 1$. This means that σ_i and σ_j are also lower adjacent. An alternative proof of this can be found in [Goldberg, 2002].

The above two definitions for two k-simplices to be adjacent leads us to the problem that there are now four possible notions we can use to define a general adjacency matrix for simplicial complexes. The four possibilities are $A_l^k, A_u^k, A_l^k - A_u^k, A_l^k + A_u^k$. Each of these possible definitions of adjacency have pros and cons as we explain in the next paragraph.

Simply using the lower adjacency matrix A_l^k does not isolate the effects of k-simplices from higher order simplices. In particular, for 1-simplices the lower adjacency matrix A_l^1 simply describes the line graph of the network. The line graph is a transformation of the graph in which the nodes of the line graph are the edges of the graph, and two nodes of the line graph are connected if the corresponding edges in the graph are incident to a common node. On the other hand, using the upper adjacency matrix A_u^k would ignore the effects of any k-simplices which are not faces of higher simplices, meaning that there is potential for a lot of information to be missed. For instance, there could be many 2-simplices (triangles) in a network but not necessarily so many 3-simplices, then the upper adjacency matrix does not identify any of them as adjacent to each other. It is worth noting that the traditional adjacency matrix of a network corresponds to A_u^0 although two 0-simplices cannot be lower adjacent. Using the sum of the two adjacency matrices, would emphasize the effects of the higher simplices over the lower ones. However, it would lead to an adjacency matrix which features 2's where two simplices are upper adjacent. What we want is an adjacency matrix which indicates when two simplices are adjacent or not. Thus this would not be appropriate. This leaves us with the difference of the two adjacency matrices $A_l^k - A_u^k$ as our notion of general adjacency.

Definition 3. For $k \geq 1$ we have that two k-simplices are considered adjacent if they are both lower adjacent and not upper adjacent. For $k = 0$ two simplices shall be adjacent if they are upper adjacent. We shall denote two k-simplices, t_i, t_j to be adjacent in the way defined here by $t_i \backsim t_j$.

This definition allows us to remove most of the effects of higher simplices being adjacent in the adjacency matrix at the lower simplex levels. A consequence of this is that it allows us to analyze the relationships between the centralities of simplices and their faces which we are particularly interested in at the node level. Secondly, this notion of adjacency lines up nicely with the extensively studied higher order Laplacians of simplicial complexes

[Muhammad and Egerstedt, 2006]. An off-diagonal entry of the higher order Laplacian matrix is non zero if and only if the corresponding off-diagonal entry of $A_l^k - A_u^k$ is non-zero. This is the definition that shall be used in the rest of this work. Further information on the Hodge Laplacian matrices can be found in [Muhammad and Egerstedt, 2006; Tahbaz-Salehi and Jadbabaie, 2010; Muhammad and Jadbabaie, 2007; Maletić and Rajković, 2012; Goldberg, 2002]. Then we have the following important definition of adjacency matrix of the simplicial complex.

Definition 4. Let i and j be two k-simplices in a simplicial complex. Then, for $k \geq 1$ the *adjacency matrix* A^k at the k-level in the simplicial complex has entries defined by

$$(A^k)_{ij} = \begin{cases} 1 & \text{if } \sigma_i \smile \sigma_j \text{ and } \sigma_i \pitchfork \sigma_j \\ 0 & \text{if } i = j \text{ or } \sigma_i \barwedge \sigma_j \text{ or } \sigma_i \frown \sigma_j \end{cases},$$

for $k = 0$ the adjacency matrix shall be given by the upper adjacency matrix.

4 Simplicial Shortest Path Distance

In this section we will extend the concept of shortest path distance to the different levels of a simplicial complex. We start by extending the concept of walks to simplicial complexes.

Definition 5. Let $k \geq 1$. Then, a s^k-walk is a sequence of alternating k-simplices and $(k-1)$-simplices $s_1, e_1, s_2, e_2, \ldots, e_{r-1}, s_r$ such that for each $i \in \{1, \ldots, r-1\}$ e_i is a face of both s_i and s_{i+1}, and s_i and s_{i+1} are not both faces of the same $(k+1)$-simplex. For $k = 0$ a walk on the 0-simplices is just a walk in the normal graph-theoretic sense.

On the simplicial complex from Figure 1, we have that $\{1,3,4\}, \{3,4\}, \{3,4,5\}, \{4,5\}, \{4,5,6\}, \{4,5\}, \{3,4,5\}, \{3,4\}, \{2,3,4\}$ is an s^2-walk. Meanwhile, $\{6,9\}, \{6\}, \{6,7\}, \{6\}, \{5,6\}, \{5\}, \{3,5\}, \{3\}, \{2,3\}$ is an s^1-walk.

Definition 6. A s^k-shortest path between two k-simplices s_a, s_b is a s^k-walk, $s_a, e_1, s_2, e_2, \ldots, s_n, e_n, s_b$, such that n is minimized. The value n is the s^k-shortest path length between the two k-simplices s_a, s_b. We denote this $d(s_a, s_b) = n$.

It can be easily seen that the simplicial shortest path length between two k-simplices is a proper distance. By definition $d(s_a, s_b) \geq 0$ for all $s_a, s_b \in R_k$where R_k is the set of k-simplices. Clearly $d(s_a, s_b) = 0 \iff s_a = s_b$. To prove $d(s_a, s_b) = d(s_b, s_a)$ then assume $d(s_a, s_b) = n$ then the s^k-shortest path from s_a to s_b is of the form $s_a, e_1, s_2, e_2, \ldots, s_{n-1}, e_{n-1}, s_n, e_n, s_b$. This means that there is a s^k-walk from $s_b$to s_a of the form $s_b, e_n, s_n, e_{n-1}, s_{n-1}, \ldots, e_2, s_2, e_1, s_a$. We can then relabel $e_1 \to e_n, s_2 \to s_n, e_2 \to e_{n-1}, s_3 \to s_{n-1}, \ldots, e_n \to e_1$ and so on to give a s^k-walk from $s_b$to s_a of the form $s_b, e_1, s_2, e_2, \ldots, s_{n-1}, e_{n-1}, s_n, e_n, s_a$ thus $d(s_b, s_a) \leq n$. If there was a s^k-walk shorter than this then there would also be a s^k-walk from s_a to s_b which was shorter than the original walk by symmetric arguments thus $d(s_b, s_a) = n$ and $d(s_a, s_b) = d(s_b, s_a)$. To prove $d(s_a, s_c) \leq$

$d(s_a, s_b) + d(s_b, s_c)$ let $d(s_a, s_b) = n$ and $d(s_b, s_c) = m$ then there is a s^k-walk from s_a to s_b of the form $s_a, e_1, s_2, e_2, \ldots, s_{n-1}, e_{n-1}, s_n, e_n, s_b$ and s^k-walk from s_b to s_c of the form $s_b, e_1, s_2, e_2, \ldots, s_{m-1}, e_{m-1}, s_m, e_m, s_c$ we can combine these and relabel the simplices in the second walk by the rules $s_b \to s_{n+1}, e_i \to e_{n+i}, s_i \to s_{n+i}$ to form a s^k-walk from s_a to s_c of the form $s_a, e_1, s_2, e_2, \ldots, s_{n-1}, e_{n-1}, s_n, e_n, s_{n+1}\ e_{n+1}, s_{n+2}, e_{n+2}, \ldots, s_{n+m-1}, e_{n+m-1}, s_{n+m}, e_{n+m}, s_c$. This implies that $d(s_a, s_c) \leq n+m = d(s_a, s_b)+d(s_b, s_c)$. For instance, on the simplicial complex from Figure 1, we have that $\{1,3,4\}, \{3,4\}, \{3,4,5\}, \{3,4\}, \{2,3,4\}$ is a s^2-shortest path from $\{1,3,4\}$ to $\{2,3,4\}$ and we have $d(\{1, 3,4\}, \{2,3,4\}) = 2$. Meanwhile, $\{2,4\}, \{4\}, \{4,6\}, \{6\}, \{6,7\}$ is a s^1-shortest path between $\{2,4\}$ and $\{6,7\}$ and we have $d(\{2,4\}, \{6,7\}) = 2$.

Definition 7. A simplicial complex is s^k-connected if and only if there does not exist a pair of k-simplices $s_a, s_b \in R_k$, where R_k is the set of k-simplices, such that $d(s_a, s_b) = \infty$.

Note that a simplicial complex being s^k-connected does not mean that it is s^{k+1}-connected or s^{k-1}-connected. The simplicial complex in Figure 1 is s^0-connected but not s^1-connected because $\{1,2\}$ and $\{7,8\}$ are not adjacent to any of the other 1-simplices. Many of the real world networks we will introduce in a later section are s^1-connected but not s^2-connected. In addition, a simplicial complex from the family S_l^k is s^k-connected but it is not s^{k-1}-connected. The central $(k-1)$-simplex is upper adjacent to every other $(k-1)$-simplex and hence is not adjacent to any of them.

Definition 8. An s^k-connected component of a simplicial complex is a subset S_k of the k-simplices R_k such that for any two k-simplices $s_a, s_b \in S_k$ we have $d(s_a, s_b) < \infty$ and for any $s \in S_k$ and $r \in R_k \setminus S_k$ we have that $d(s, r) = \infty$.

The s^k-eccentricity $\epsilon(t)$ of a k-simplex s is the largest s^k-shortest path distance between s and any other k-simplex. The s^k-diameter D of a simplicial complex is the maximum s^k-eccentricity of any simplex in the network $D = \max_{s \in R} \epsilon(s)$ where R_k is the set of k-simplices. As an example, in the simplicial complex $t^2(1,2,4)$, depicted in Figure 2, the central 2-simplex has s^2-eccentricity 1 because it is adjacent to all the other 2-simplices in the complex. However all the peripheral 2-simplices have a s^2-eccentricity of 2 because the shortest path form a peripheral 2-simplex on one arm to a peripheral 2-simplex on another is through the central 2-simplex for a shortest path of length 2. This means that $t^2(1,2,4)$ has s^k-diameter 2.

Given a notion of shortest path distance we are now equipped to define the average simplicial shortest path distance. The s^k-average simplicial shortest path length is the average s^k-shortest path distance for all possible k-simplices in the network

$$l_k = \frac{2 \sum_{i<j} d_k(s_i, s_j)}{\|R_k\|(\|R_k\| - 1)}, \tag{1}$$

where R_k is the set of k-simplices in the network and $d_k(s_i, s_j)$ is the s^k-shortest path distance between s_i and s_j. Note for this measure to make any sense the simplicial

complex needs to be s^k-connected. If the simplicial complex is not s^k-connected then we can analyze each s^k-connected component separately. We will now prove bounds on the s^k-average path length. If we assume that there are at least two k-simplices in the simplicial complex. For l_k to be less than 1 there would need to be two k-simplices, s_i, s_j such that $d(s_i, s_j) < 1$ this would imply $d(s_i, s_j) = 0$ and hence $s_i = s_j$ by the properties of a metric. The lower bound $l_k = 1$ is achieved by a simplicial complex of the form S^k_r. This is easy to check. A simplicial complex of the form S^k_r consists of a $(k-1)$-simplex $\{1, 2, \ldots, k\}$ and some k-simplices of the form $\{1, 2, \ldots, k, i\}$, where $i > k$, in addition to all subsimplices necessary by the closure axiom. Hence, all k-simplices are lower adjacent to each other by the $(k-1)$-simplex $\{1, 2, \ldots, k\}$ and they are not upper adjacent to each other because there are no $(k+1)$-simplices. Thus, every k-simplex is adjacent to every other k-simplex and the s^k-shortest path distance between any two k-simplices is 1. Hence, the s^k-average path length is 1, which implies that the lower bound of l_k is 1.

A general upper bound of l_k is hard to establish due to of the dependence on the number of simplices, $\|R_k\|$. However, if we fix both k and $\|R_k\|$ then we can prove the following result.

Lemma 9. *Let $\|R_k\|$ be the number of k-simplices. Then, the upper bound of l_k is*

$$\frac{\frac{(\|R_k\|-1)\|R_k\|(\|R_k\|+1)}{3}}{\|R_k\|(\|R_k\|-1)} = \frac{\|R_k\|+1}{3}. \tag{2}$$

Proof. Assume that the simplicial complex is s^k-connected and that $\|R_k\| \geq 2$. If $\|R_k\| = 2$ then $\sum_{i<j} d_k(s_i, s_j) = 1$, the simplicial complex is s^k-connected and there are only 2 k-simplices hence they must be adjacent. Thus $l_k = \frac{2\sum_{i<j} d_k(s_i,s_j)}{\|R_k\|(\|R_k\|-1)} = 1$. In addition $\frac{\|R_k\|+1}{3} = 1$. Hence the lemma holds for $\|R_k\| = 2$. Assume that the Lemma holds for $\|R_k\| \leq n$. Let $\|R_k\| = n+1$ then to maximize l_k we need to maximize $\sum_{i<j} d_k(s_i, s_j)$. Pick a k-simplex s_1. First, we will maximize $\sum_j d_k(s_1, s_j)$. For $d_k(s_1, s_j) = y$ for some $s_j \in R_k$, first it must be the case that $d_k(s_1, s_m) = y - 1$ for some $s_m \in R_k$ such that $s_m \backsim s_j$. This means that the largest possible value of $d_k(s_1, s_j)$ for some $s_j \in R_k$ is $\|R_k\| - 1 = n$. This gives $\max \sum_j d_k(s_1, s_j) = (\|R_k\| - 1) + (\|R_k\| - 2) + \cdots + 1 = T_{\|R_k\|-1} = T_n$ where T_z represents the zth triangle number. Now this implies that there is only one k-simplex, $s_a \in R_k$ such that $d_k(s_a, s_1) = 1$. This means that s_1 is adjacent to precisely one other k-simplex, namely s_a. Because s_1 is adjacent to only one other simplex, s_1 can be removed without affecting the s^k-shortest path distances between any other k-simplices. We now have a simplicial complex such that $\|R_k\| = n$. We know that the upper bound of the s^k-average path distance for this smaller simplicial complex is $\frac{\|R_k\|+1}{3} = \frac{n+1}{3}$ by assumption where $\frac{(n-1)n(n+1)}{6}$ is the contribution given by $\sum_{i<j} d_k(s_i, s_j)$. We also know that the largest number we can add to the sum $\sum_{i<j} d_k(s_i, s_j)$ by the addition of a k-simplex is given by $T_n = \frac{n(n+1)}{2}$. Thus $\max(\sum_{i<j} d_k(t_i, t_j)) = \frac{(n-1)n(n+1)}{6} + \frac{n(n+1)}{2} = \frac{n(n+1)(n+2)}{6}$. This means that the upper bound of l_k is $\frac{\frac{(\|R_k\|-1)\|R_k\|(\|R_k\|+1)}{3}}{(\|R_k\|-1)\|R_k\|} = \frac{\|R_k\|+1}{3}$. Clearly as $\|R_k\| \to \infty$, $l_k \to \infty$

and so there is no upper bound for l_k. It should be fairly clear that a simplicial complex of the form P_r^k will achieve this bound. □

5 Simplicial Centralities

5.1 Centralities based on simplicial shortest-path

We are now in a position to generalize some centrality notions for simplices which are based on the simplicial shortest path distance. The simplest of all centrality measures is the degree. In the case of the simplicial complexes we have three levels of degrees, which we will designate as $\delta_k(i)$, where $k = 0, 1, 2$ is the level of the simplex, i.e., nodes, edges and triangles, respectively, and i is the corresponding simplex. The degree of a k-simplex s is the number of other k-simplices to which s is adjacent. If $p(\delta_k)$ is the probability of finding a k-simplex of degree δ_k in a simplicial complex and $P(\delta_k)$ is the probability of finding a k-simplex of degree larger or equal than δ_k in the simplicial complex, then the degree distribution of the k-simplices is the probability distribution of the degrees of the k-simplices across the whole of the simplicial complex.

Closeness centrality is a concept first introduced by Bavelas [Bavelas, 1950] to capture the idea of how close—in terms of shortest path distance—two nodes are in a network. Here we will generalize this concept to simplicial complexes. The simplicial farness of a k-simplex F is the sum of its s^k-shortest path distances to all other k-simplices, $\sum_{Y \neq F} d(Y, F)$. The simplicial closeness is the reciprocal of simplicial farness. That is

$$C(F) = \frac{1}{\sum_{Y \neq F} d(Y, F)} \tag{3}$$

Note that if the simplicial complex is not s^k-connected then $\sum_{Y \neq F} d(Y, F)$ could be considered undefined or ∞ for all k-simplices in the simplicial complex. In this case we can calculate simplicial harmonic closeness instead. This is a generalization of a definition that can be found in [Rochat, 2009]. The simplicial harmonic closeness of a k-simplex F is defined as follows

$$H(F) = \sum_{Y \neq F} \frac{1}{d(Y, F)}, \tag{4}$$

where we treat $\frac{1}{\infty} = 0$.

We would now like to establish some bounds on the simplicial closeness centrality. However, there is an issue that needs to be considered before bounds can be established. The issue is that the sum, $\sum_{Y \neq F} d(Y, F)$ depends on the number of simplices in the complex. If for all $Y \in R_k$ and $Y \neq F$, where R_k is the set of k-simplices, $d(Y, F) = 1$ then $C(F) = \frac{1}{\|R_k\| - 1}$. Clearly this is the largest $C(F)$ can be for $\|R\|$ k-simplices. We can normalize this by multiplying $C(F)$ by $(\|R\| - 1)$ to give an upper bound of $C(F) = 1$.

Lemma 10. *The upper bound of the normalized simplicial closeness centrality can be attained by all simplices in a simplicial complex of the form S_l^k.*

Proof. In a simplicial complex of the form S_l^k we have $l = \|R_k\|$ k-simplices which are all adjacent to each other. Thus if we select a particular k-simplex $s_i \in R_k$ we have that $d(s_i, s_j) = 1$ for all $s_j \in R_k$ such that $s_i \neq s_j$. This gives $\sum_{s_i \neq s_j} d(s_i, s_j) = \|R_k\| - 1$. Hence $C(s_i) = \frac{\|R_k\|-1}{\|R_k\|-1} = 1$. □

We now prove a lower bound for the normalized simplicial closeness centrality

Lemma 11. *Let us consider a s^k-connected simplicial complex with $\|R\|$ k-simplices. Then, the lower bound for the normalized simplicial closeness centrality of a k-simplex is 0, and this is attained asymptotically when $\|R\| \to \infty$.*

Proof. Assume the simplicial complex is s^k-connected. We are trying to minimize $\frac{1}{\sum_{Y \neq F} d(Y,F)}$ and hence trying to maximize $\sum_{Y \neq F} d(Y, F)$. Take a k-simplex F in a simplicial complex X which has $\|R\|$ k-simplices. Firstly, because X is s^k-connected there exists a s^k-walk between F and every other k-simplex in the simplicial complex. The farthest distance possible between F and another simplex $s_{\|R\|}$ is $\|R\| - 1$. This means that the s^k-shortest path between these two simplices looks like $F, e_1, s_2, e_2, s_3, \ldots, s_{\|R\|-1}, e_{\|R\|-1}, s_{\|R\|}$. The shortest path between F and any other k-simplex t_n must be the path $F, e_1, s_2, e_2, s_3, \ldots, e_{n-1}, s_n$, i.e. the shortest path from F to $s_{\|R\|}$ but cut off at simplex s_n. If there was a shorter path from F to s_n then you could replace this part of the path from F to $s_{\|R\|}$ with said shorter path from F to s_n and have a shorter path from F to $s_{\|R\|}$. Hence, the s^k-shortest path distance from F to any other k-simplex, s_n is $n - 1$. Note that for F to be at distance r from a k-simplex s_r, F must first be at distance $r - 1$ from a simplex adjacent to s_r. Hence, the maximum value for $\sum_{Y \neq F} d(Y, F) = 1 + 2 + 3 + \cdots + (\|R\| - 1) = \frac{(\|R\|-1)\|R\|}{2}$. This gives a lower bound on $C(F)$ of $\frac{2}{(\|R\|-1)\|R\|}$ which after normalization by multiplication by $(\|R\| - 1)$ gives a lower bound on $C(F)$ of $\frac{2}{\|R\|}$. This clearly tends to 0 as $\|R\| \to \infty$. □

The bound of $\frac{2}{\|R\|}$ for a given number of k-simplices is achieved by the end simplex in a t^k-path.

If a simplicial complex is not s^k-connected then $C(F) = 0$ or it is considered undefined for all k-simplices $F \in R$. Thus, the peripheral 2-simplex which is only adjacent to the central 2-simplex in the complex $t^2(1, 2, 4)$ has simplicial closeness given by $\frac{7}{13}$. We have $\sum_{Y \neq F} d(Y, F) = 1 + 2 + 2 + 2 + 2 + 2 + 2 = 13$ where Y is the given simplex and F is a run through of the other simplices. The 1 is contributed by the shortest path from Y to the central simplex while the 2s are given by the shortest path distances from Y to the other peripheral simplices on the other branches. While $\|R\| - 1 = 7$ for the normalization.

To give an example from the simplicial complex in Figure 1 we need to use the definition of simplicial closeness given in Definition 14. So to calculate the Simplicial closeness of $\{2, 3, 4\}$ we have $H(\{2, 3, 4\}) = \frac{1}{1} + \frac{1}{2} + \frac{1}{2} + \frac{1}{\infty} + \frac{1}{\infty} + \frac{1}{\infty} = 2$. This is because it is adjacent to

$\{3,4,5\}$ and has shortest path distance 2 to both $\{1,3,4\}$ and $\{4,5,6\}$. There is no s-path from $\{2,3,4\}$ to any of the other simplices.

The second centrality notion which is based on shortest paths that we can generalize is the betweenness centrality. Betweenness centrality was introduced by Freeman in 1977 in order to capture the notion of how central a node in a network is in passing information through other nodes. The following is a direct generalization of this definition [Freeman, 1977]. The simplicial betweenness of a k-simplex F is defined as follows

$$g(F) = \sum_{S \neq F \neq T} \frac{\sigma_{ST}(F)}{\sigma_{ST}} \tag{5}$$

where σ_{ST} is the total number of shortest paths from S to T and $\sigma_{ST}(F)$ is the number of such paths that pass through F, where $F, S, T \in R_k$.

The betweenness centrality of a k-simplex increases as the number of pairs of other simplices increases. It is therefore sensible to divide $g(F)$ by $\frac{(\|R\|-1)(\|R\|-2)}{2}$, the number of pairs of k-simplices which are not the simplex F. This gives a value for simplicial betweenness in the range $[0,1]$. The lower bound of 0 is attained by every k-simplex in a simplicial complex of the form S^k_l. It is also attained by any simplex which is adjacent to only one other simplex. The upper bound of 1 can be attained by the central k-simplex of a $t^k(x_1, x_2, \ldots, x_{k+1})$ simplicial complex where $x_i \in \{0,1\} \forall i \in \{1,2,\ldots,k+1\}$.

5.2 Spectral simplicial centralities

We now move to the concepts of centrality based on spectral properties of the simplicial complexes. Historically, for networks the first of these centralities was developed by Katz [Katz, 1953]. The Katz centrality index tries to capture the notion that a node in a network is not only influenced by its nearest neighbors but in a lower extension by any other node separated at a given distance from it, in a way in which such influence decays with the separation between the nodes. In this section we generalize these ideas to simplicial complexes largely following the example of [Estrada et al., 2015].

To make this task easier we define an underlying network of simplices at every level of a simplicial complex. For all k the adjacency matrix of the k-simplices of a simplicial complex also gives rise to a network where each node corresponds to a simplicial complex and there is an edge between two nodes if and only if their corresponding k-simplices are adjacent in the simplicial complex. We call this network the underlying network of simplices. This immediately gives us some results from network theory.

Lemma 12. *Let A_k be the adjacency matrix between k-simplices in a simplicial complex. Then, $(A_k)^m_{ij}$ gives the number of s^k-walks of length m between k-simplex, i and k-simplex, j.*

Proof. Every walk on the underlying network of simplices for a given simplex of size k, has a corresponding s^k-walk over the k-simplices. We have that A_k is also the adjacency matrix

for the nodes in the underlying network of simplices. Thus, powers of the adjacency matrix can be used to give the numbers of walks of a given length on the underlying network of simplices. In particular, $(A_k)^m_{ij} = b$ means that there are b walks of length m between node i and node j in the underlying network of simplices at the k-simplex level. This precisely corresponds to s^k-walks of length m between simplex i and simplex j. Simplex i and simplex j are the simplices represented by node i and node j respectively in the underlying network of simplices. □

Let A_k be the adjacency matrix representing the adjacency between k-simplices in a simplicial complex. The simplicial Katz centrality index is given by

$$K_{k,i} = [(\alpha^0 A_k^0 + \alpha A_k + \alpha^2 A_k^2 + \cdots + \alpha^m A_k^m + \dots)(e)]_i = \Big[\sum_{m=0}^{\infty} (\alpha^m A_k^m)\mathbf{e}\Big]_i, \tag{6}$$

where $0 < \alpha < \frac{1}{\lambda_1(A_k)}$. The simplicial Katz centrality is essentially the network-theoretic Katz centrality applied to the underlying network of simplices. This means that as proved in [Estrada et al., 2015] the series, $(\alpha^0 A_k^0 + \alpha A_k + \alpha^2 A_k^2 + \cdots + \alpha^m A_k^m + \dots)$ converges when $\alpha \leq \rho(A_k)$, where $\rho(A_k)$ is the spectral radius of A_k. This means that $K_i = [(I - \alpha A_k)^{-1}\mathbf{e}]_i$. We also have from [Estrada et al., 2015] the representation of the Katz centrality in terms the eigenvalues and eigenvectors of A_k. This representation gives $K_i = \sum_l \sum_j \psi_{k,j}(i)\psi_{k,j}(l)\frac{1}{1-\alpha\lambda_{k,j}}$. Where $\psi_{k,j}(i)$ and $\psi_{k,j}(l)$ are the ith and lth entries of the jth eigenvector of A_k, respectively and $\lambda_{k,j}$ is the jth eigenvalue of A_k.

We can now use the simplicial Katz centrality to define the simplicial eigenvector centrality. The following adjustment of the Katz centrality appears in [Estrada et al., 2015] and can also be applied to the simplicial Katz centrality.

$$\begin{aligned}\vec{v}_k &= \Big(\sum_{m=1}^{\infty} \alpha^{m-1} A_k^m\Big)\mathbf{e} = \Big(\sum_{m=1}^{\infty} \alpha^{m-1} \sum_{j=1}^{n} \vec{\psi}_{k,j}\vec{\psi}_{k,j}^T \lambda_{k,j}^m\Big)\mathbf{e} \\ &= \Big(\frac{1}{\alpha}\sum_{j=1}^{n}\sum_{m=1}^{\infty} (\alpha\lambda_{k,j})^m \vec{\psi}_{k,j}\vec{\psi}_{k,j}^T\Big)\mathbf{e} = \Big(\frac{1}{\alpha}\sum_{j=1}^{n} \frac{1}{1-\alpha\lambda_{k,j}}\vec{\psi}_{k,j}\vec{\psi}_{k,j}^T\Big)\mathbf{e}.\end{aligned} \tag{7}$$

Again following the example of [Estrada et al., 2015] allows α to approach the inverse of the largest eigenvalue of A_k from below ($\alpha \to \frac{1}{\lambda_1}^-$). This gives

$$\begin{aligned}\lim_{\alpha\to\frac{1}{\lambda_{k,1}}^-}(1-\alpha\lambda_{k,1})\vec{v}_k &= \lim_{\alpha\to\frac{1}{\lambda_{k,1}}^-}\Big(\frac{1}{\alpha}\sum_{j=1}^{n}\frac{(1-\alpha\lambda_{k,1})(v)}{1-\alpha\lambda_{k,j}}\vec{\psi}_{k,j}\vec{\psi}_{k,j}^T\Big)\mathbf{e} \\ &= \Big(\lambda_{k,1}\sum_{i=1}^{n}\psi_{k,1}(i)\Big)\vec{\psi}_{k,1} = \gamma\vec{\psi}_{1,j}\end{aligned} \tag{8}$$

Therefore the eigenvector associated with the largest eigenvalue of A_k could also be said to be a centrality measure. This leads us to the following definition. The simplicial eigenvector centrality of the ith k-simplex in a simplicial complex is given by the ith component of the principal eigenvector of A_k, $\psi_{k,1}(i)$.

In a similar way as in the previous section we make a generalization of the exponential of the adjacency matrix of k-simplices which relies on results from the paper [Estrada and Rodriguez-Velazquez, 2005] The following power series of the adjacency matrix of k-simplices A_k in a simplicial complex converges to the corresponding matrix exponential

$$\sum_{l=0}^{\infty} \frac{A_k^l}{l!} = \exp\left(A_k\right). \tag{9}$$

Obviously,

$$\exp\left(A_k\right) = \sum_{l=0}^{\infty} \frac{A_k^{2l}}{(2l)!} + \sum_{l=0}^{\infty} \frac{A_k^{2l+1}}{(2l+1)!} = \cosh\left(A_k\right) + \sinh\left(A_k\right), \tag{10}$$

where the first term accounts for the weighted sum of even-length walks and the second one accounts for odd-length walks in the simplicial complex.

We can now define a centrality measure analogous to subgraph centrality for simplicial complexes. Subgraph centrality was introduced for networks by Estrada and RodrÃguez-VelÃ¡zquez [Estrada and Rodriguez-Velazquez, 2005] to capture the participation of a node in a network in all subgraphs in the network, giving more weight to the smaller than to the larger ones. This is a direct generalization made possible by the adjacency matrices at the different levels of the simplicial complex. Then, the simplicial subgraph centrality of a k-simplex, i, is given by $(\exp^{A_k})_{ii}$. For the simplicial complex in Figure 1 we have that the simplicial subgraph centrality of the 1-simplex $\{1,4\}$ is 2.714 while the simplicial communicability between $\{1,4\}$ and $\{6,9\}$ is 2.0363. Note that any bounds on subgraph centrality or simplicial communicability for networks still hold due to the underlying network of simplices.

Lemma 13. *Let $k \geq 1$ and let us consider an s^k-connected simplicial complexes which contain a fixed number b of k-simplices. The upper bound of the simplicial subgraph centrality is attained by every simplex in a simplicial complex S_b^k and the lower bound is attained by the two end simplices in a simplicial complex of the form P_b^k.*

Proof. Fix a number of k-simplices to b. It is known that for b nodes the upper bound of subgraph centrality in networks is attained by every node in the complete graph K_b [Estrada and Rodriguez-Velazquez, 2005]. The subgraph centrality for the underlying network of simplices at the k-simplex level is the same as the simplicial subgraph centrality for k-simplices. Thus, to find the upper bound of the simplicial subgraph centrality we need to find a simplicial complex whose underlying network of simplices is a complete graph. The simplicial complex S_b^k satisfies this criterion. Similarly, the lower bound of subgraph centrality in networks is attained by the two end simplices in a path graph of length b. Thus to find the lower bound of the simplicial subgraph centrality you need to find a simplicial complex whose underlying network of simplices is a path graph. The simplicial complex P_b^k satisfies this criterion. □

	nodes		edges	triangles	
species	simplices	interact.	interact.	simplices	interact.
A. fulgidus	32	37	101	1	0
KSHV	50	114	606	34	82
VZV	53	148	1156	104	343
B.subtilus	84	98	463	4	1
P. falsiparum	229	604	4599	201	401
E. coli	230	695	7803	478	2425
H. pylory	710	1396	14736	76	79
S. cereviciae	2224	6609	99882	3530	15004
human	2783	6007	85617	1047	2170
D. melanogaster	3039	3687	11369	163	113

Table 1: Number of simplices and their interactions at the nodes, edges and triangles levels for the 10 PPI networks studied. Notice that the number of simplices at the edge level is the same as the number of interactions at the node level.

6 Analysis of Protein Interaction Networks

Here we study 10 protein-protein interaction (PPI) networks. In these networks nodes represent proteins and undirected links represent the interaction between two proteins determined experimentally. The networks studied correspond to the following organisms: *D. melanogaster* (fruit fly) Giot et al. [2003], Kaposi sarcoma herpes virus (KSHV) Uetz et al. [2006], *P. falsiparum* (malaria parasite) LaCount et al. [2005], varicella zoster virus (VZV) Uetz et al. [2006], human Rual et al. [2005], *S. cereviciae* (yeast) Bu et al. [2003], *A. fulgidus* Motz et al. [2002], *H. pylori* (Lin et al. [2004]; Rain et al. [2001]), *E. coli Butland et al. [2005]* and *B.subtilus* Noirot and Noirot-Gros [2004]. We study only the largest (main) connected component of each of these networks, which range from 50 to 3039 proteins. We then transformed these networks into their clique simplicial complexes consisting of edges and of triangles, respectively. The number of simplices and interactions at the nodes, edges and triangle level are given in Table 1. Notice that the number of simplices at the edges level is the same as the number of interactions at the nodes level.

6.1 Degree distributions

The study of node degree distribution has become one of the standard tests considered for the structural analysis of networks. A network with a broad degree distribution–also know as fat-tailed distribution–is characterized by the presence of a few hubs–high degree node–which keep the network together. These hubs are important from the structural and functional point of view in these networks. In the case of PPI networks hubs are

expected to play fundamental role in the cell and their knockout is expected to produce a large cellular damage. This is the main hypothesis of the centrality-lethality paradigm. A particular kind of fat-tailed distribution, the power-law one, received a large deal of attention in the literature. A power-law degree distribution is also know as a scale-free distribution and it is indicative of some self-similarities properties in the network. At the beginning of the XXI century a deluge of papers finding scale-free distributions in almost every network were published. Many of the existing PPI networks were characterized as scale-free ones based on these findings. Later, more order has being in place and some authors have found that almost none of the PPI networks previously claimed to have scale-free structures were so [Stumpf and Ingram, 2005]. The main message of these experiences is that most of PPI networks indeed display some kind of heavy-tailed degree distributions, such as power-law, lognormal, Burr, logGamma, Pareto, etc. However, as we will see here this is not necessarily true when a large number of statistical distributions and goodness of fit parameters are tested for the 10 PPI networks considered in this work.

Here we consider the probability degree functions (PDF), $p(\delta_k)$ vs. δ_k, for 10 PPI networks at the three different levels studied in this work, i.e., nodes, edges, and triangles. For each of the PDFs we fit the data to every of the following distributions: Beta, Binomial, Birnbaum-Saunders, Burr, Exponential, Extreme Value, Gamma, Generalized Extreme Value (GEV), Generalized Pareto (gen-Pareto), Half-normal, Inverse Gaussian, Kernel, Logistic, Loglogistic, Lognormal, Nakagami, Negative Binomial, Normal, Poisson, Rayleigh, Rician, Stable, t Location-Scale, and Weibull. The best fit was determined on the basis of the following statistical parameters: Akaike information criterion (AIC) [Konishi and Kitagawa, 2008; Symonds and Moussalli, 2011] and the Bayesian information criterion (BIC) [Konishi and Kitagawa, 2008]. These indices are defined as follow:

$$AIC = 2k - 2\ln\left(\hat{L}\right), \tag{11}$$

$$BIC = k\ln(n) - 2\ln\left(\hat{L}\right), \tag{12}$$

where n is the number of data points, k is the number of parameters to be estimated and $\hat{L} = p\left(x|\hat{\theta}, M\right)$ is the maximized value of the likelihood function of the model M, where $\hat{\theta}$ are the parameter values that maximize the likelihood function and x are the data points. For a series of models trying to describe the same dataset, the smallest values of these three parameters gives the best fit for the data. However, it is important to consider the differences between the values of these parameters for the corresponding models as we describe below.

We then first fit the dataset corresponding to the degrees of the corresponding simplices in a PPI to all the studied distributions. Then, we rank all the distributions in increasing order of their AIC. We then compare the values of the first few distributions in the ranking using $\Delta AIC_i = \exp\left(\left(AIC_{min} - AIC_i\right)/2\right)$, where AIC_{min} is the AIC for the

species	nodes	edges	triangles
A. fulgidus	NA	gen-Pareto	NA
KSHV	NA	gen-Pareto	gen-Pareto*
VZV	gen-Pareto*	gen-Pareto/gamma**	NA
B. subtilus	gen-Pareto	NA	NA
P. falsiparum	NA	gamma	gen-Pareto
E. coli	gen-Pareto	GEV*	gen-Pareto
H. pylory	gen-Pareto	gamma	NA
S. cereviciae	gen-Pareto	GEV	gen-Pareto
human	gen-Pareto	NA	NA
D. melanogaster	gen-Pareto	GEV	gen-Pareto

Table 2: Degree distributions of the nodes, edges and triangles in the simplicial complexes representing 10 PPI networks studied here (see text for selection criteria). Not available (NA) distributions are reported when the data was scarce for a statistically significant fit of the distributions or the statistical criteria used were unable to decide between two or more distributions. *BIC criterion indicates only a strong differentiation with the second best distribution. **BIC criterion indicates only a positive differentiation with the second best distribution (see Appendix).

top distribution in the ranking. If $\Delta AIC_i < 0.01$ we consider that the first distribution in the ranking is significantly different from the second (and consequently the rest) as to accept it as the most significant one. In those cases where the differences in the AIC is not significant we also consider the difference in the BIC values. In this case we apply the Kass-Raftery criterion as follows:

ΔBIC_i	meaning
0-2	not significant
2-6	positive
6-10	strong
>10	very strong

This means, for instance, that if the difference in the values of BIC is not bigger than 2, this criterion is not able to distinguish between the two distributions. If, however, it is between 6-10 there is a strong criterion to consider the distribution with the smallest BIC as the most significant one [Kass and Raftery, 1995]. In Table 2 we show the best distribution fitted for each of the datasets studied.

The most interesting observation from the results shown in Table 2 is that all distributions obtained for the three levels of the simplicial complexes of the 10 PPI networks studied are heavy-tailed distributions. At the node level, the 7 distributions that were

statistical significant–for the other three the statistical criteria used were not able to distinguish between the first few distributions—correspond to a generalized Pareto distribution, where the probability of finding nodes of a given degree decays as a power-law of the corresponding degree (see Appendix). At the edge level, the PPI networks display GEV, generalized Pareto, and gamma distributions, all of which are heavy-tailed (see Appendix). Finally, at the triangles level 5 PPI networks display generalized Pareto distributions and for the others it was not possible to determine the best distribution. These results indicate that at the three levels studied here, nodes, edges and triangles, there are simplicial-hubs which concentrate most of the connectivity of the simplicial complexes at the corresponding level. The damage of these hubs is expected to produce catastrophic consequences for the functionality of the cell. On the other side of the coin, the existence of heavy-tailed distributions guarantees that the corresponding simplicial complexes are more robust at these levels to the random failure of simplices. These results also point out to the necessity of using other types of characterization of the degree heterogeneity for simplicial complexes by considering not-statistical indices, which can be applied even for small datasets and/or datasets with small variability in their degrees [Estrada, 2010]. This is an ongoing project in our group which will be considered in a separate work.

6.2 Comparison of centralities at different levels

Simplicial centrality measures are all designed to identify the "most important" simplices in a simplicial complex at different levels and according to certain topological feature of the complex, such as nearest-neighbor connectivity (degrees), proximity of other simplices (closeness) and participation of a simplex in small sub-complexes with other simplices (subgraph centralities). Then, it is expected that there is some correlation between the centralities inside each level of analysis. That is, it is expected that node degree is somehow correlated to node closeness or node subgraph centrality for a given PPI. For instance, in the yeast PPI the node centralities (degree, closeness and subgraph centrality) have an average rank correlation coefficient $\langle r_{n,n} \rangle \approx 0.828$, with the hugest rank correlation coefficient r being between the closeness and the subgraph centralities ($r \approx 0.924$). At the edges level this average rank correlation is of $\langle r_{e,e} \rangle \approx 0.827$ and at the triangle level it raises up to $\langle r_{t,t} \rangle \approx 0.970$.

In contrast with what we expect, and observe, at the individual levels of the simplicial complex, is what we should expect on the relations between two different levels of the simplicial complex. That is, we do not have any theoretical insight indicating whether the information provided by the centralities at the node level is or is not correlated to that provided at the edges or triangles ones. In this case, however, it should be desirable that not so high rank correlation is observed as a way to increase the amount of different structural information encoded by the simplicial centralities. This is indeed what is observed for the PPI simplicial complex of yeast. The average rank correlation coefficient between the nodes and edges centralities is just $\langle r_{n,e} \rangle \approx 0.609$, and that between nodes

	nodes		edges			triangles		
	SC	CC	DC	SC	CC	DC	SC	CC
Node Degree	0.7602	0.7984	0.3292	0.3856	0.3020	0.6586	0.6951	0.6812
Node Subgraph		0.9245	0.7376	0.6981	0.7471	0.5562	0.5780	0.5990
Node Closeness			0.7347	0.7710	0.7805	0.4795	0.5103	0.5260
Edge Degree				0.7617	0.9025	0.2744	0.2794	0.2928
Edge Subgraph					0.8180	0.2042	0.2207	0.2456
Edge Closeness						0.1558	0.1691	0.2076
Triangle Degree							0.9725	0.9772
Triangle Subgraph								0.9589

Table 3: Spearman's rank correlation coefficients between the rankings of three centralities of the 0,1 and 2-simplices in the yeast PPI.

and triangles centralities is $\langle r_{n,t} \rangle \approx 0.587$. Finally, the average rank correlation between the edges and triangles levels is barely $\langle r_{e,t} \rangle \approx 0.228$. These lack of correlations between the inter-level centralities (see Table 3) clearly indicate that the top nodes in the ranking at one simplicial level does not necessarily coincide with that produced by the centralities at a different level.

It is also important to consider that none of the correlations are negative. This implies that none of the centralities fundamentally disagree with each other. It is not the case that a centrality at one level is telling us that one set of nodes is not important and another set of nodes is, while a centrality at a different level is telling us the exact opposite. It is more likely that a centrality at one level is telling us that one set of nodes is important while a centrality at a different level is telling us the same thing but the order of importance is shuffled between the two centralities. This hypothesis is backed up when we consider the triangle and node degrees. Of the 100 most central nodes according to these centralities 24 coincide. When we consider the top 300 this rises to 111 proteins (37%) and looking at the top 500 the two centralities identify 268 (53.6%). This may explain the difference between the centralities capabilities in the detection of essential proteins in the next section when a small percentage of the top proteins are considered compared to the similarity when a larger percentage is considered.

We then study the average rank correlation coefficient for all the PPI networks considered in this work. In Table (4) we give the average Spearman rank correlation coefficients for all the PPI networks studied. As can be seen the inter-level correlations between the centralities considered is relatively high following our expectations of different centralities identifying essentially the same groups of proteins at each corresponding level. The highest correlations are observed for the triangle level, which is mainly due to the high correlation between the triangle degree and closeness centralities. This high correlation could be a consequence of the fact that most of the high degree triangles are clumped together form-

	$\langle r_{n,n}\rangle$	$\langle r_{e,e}\rangle$	$\langle r_{t,t}\rangle$	$\langle r_{n,e}\rangle$	$\langle r_{n,t}\rangle$	$\langle r_{e,t}\rangle$
A. fulgidus	0.822	0.844	NA	0.399	NA	NA
KSHV	0.912	0.778	0.993	0.632	0.666	0.493
VZV	0.873	0.783	0.899	0.176	0.751	0.186
B. subtilus	0.749	0.865	0.792	0.407	0.294	-0.030
P. falsiparum	0.842	0.826	0.957	0.608	0.655	0.403
E. coli	0.842	0.915	0.959	0.714	0.699	0.483
H. pylory	0.847	0.740	0.932	0.608	0.458	0.254
S. cereviciae	0.828	0.827	0.970	0.609	0.587	0.228
human	0.732	0.818	0.929	0.641	0.505	0.235
D. melanogaster	0.661	0.703	0.795	0.568	0.303	0.188

Table 4: Intra- ($\langle r_{n,n}\rangle$, $\langle r_{e,e}\rangle$ and $\langle r_{t,t}\rangle$) and inter-level ($\langle r_{n,e}\rangle$, $\langle r_{n,t}\rangle$ and $\langle r_{e,t}\rangle$) average Spearman's rank correlation coefficients between the rankings of three centralities of the 0, 1 and 2-simplices in the 10 PPI networks studied. See text for notation and explanations.

ing complexes of many other triangles (see next section for the case of yeast). Then, these high-degree triangles are close to each other, giving also a high triangle closeness. Finally, we also observe poor rank correlation between the different pairs of levels considered for the 10 PPI networks analyzed. The slightly negative average obtained for $\langle r_{e,t}\rangle$ in *B. subtilus* can be considered more like a lack of correlation than as a negative correlation between the indices because in no case the Spearman correlation coefficient is larger, in modular terms, than 0.1.

6.3 Identification of essential proteins

6.3.1 Methodology

An essential protein is the one that if knocked out the cell dies. Then, the identification of such proteins has become one of the main paradigms of the study of centrality measures in PPIs [Seringhaus et al., 2006; Yu et al., 2007; Wang et al., 2012; Gustafson et al., 2006]. The reasons for such interest are twofold. On the one hand, it is important to have theoretical tools that allow the identification of proteins that can be drug targets, think for instance in the identification of essential proteins in a pathogenic microorganism. On the other hand, it is one of the scarce examples in which centrality measures can be validated against some experimental data. The methodology for essential protein identification that we consider here is adapted from the one developed by Estrada in 2006, and consists of the following steps [Estrada, 2006]. First, we transform the PPI network into a clique simplicial complex to consider node, edge and triangle centralities. Then, we calculate the corresponding centralities at the three levels for each of the simplicies. We transform edge and triangle centrality into information based on the nodes forming such fragments

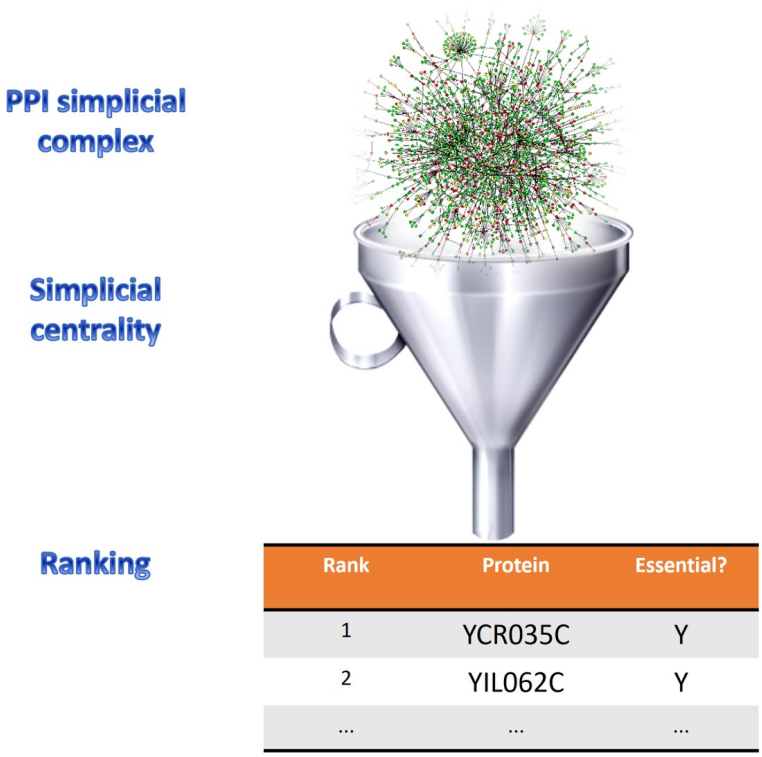


Figure 3: Schematic representation of the process of identification of essential proteins using simplicial centralities in a PPI.

by calculating the average centrality of all the edges and triangles in which a given node is involved in, respectively. Using these centralities we rank all the proteins in the PPI in decreasing order of their centralities. We then count how many essential proteins are in the top $x\%$ of the ranking and report this number as the percentage of essential proteins identified by the corresponding centrality (see Fig. 3). An ideal index for essential protein identification will be the one which rank all essential proteins at the top of the ranking, such as if we want to select 100 essential proteins we simply pick the top 100 proteins in that ranking. We always compare the results of this process with the random selection of proteins. That is, we rank randomly the proteins in the PPI and count the number of essential ones in the top $x\%$ of the ranking.

6.3.2 Application to yeast PPI

We now apply the methodology previously described to identify essential proteins in the yeast PPI. There are several datasets of the interactions of proteins in yeast. Here we use the data compiled by Bu et al. [Bu et al., 2003]. The original data was obtained by von Mering et al. [Von Mering et al., 2002] by assessing a total of 80,000 interactions among 5400 proteins reported previously and assigning each interaction a confidence level. Bu et al. [Bu et al., 2003] focused on 11,855 interactions between 2617 proteins with high

and medium confidence in order to reduce the interference of false positives, from which they reported a network consisting on 2361 nodes and 6646 links (http://vlado.fmf.uni-lj.si/pub/networks/data/bio/Yeast/Yeast.htm). This interaction map is considered here as a network in which proteins are represented as the nodes and two nodes are linked by an edge if the corresponding two proteins can be expected with high or medium confidence of interacting. In this section we consider the node, edge and triangle degree, closeness, and subgraph centralities as examples of nearest-neighbor, shortest-path and spectral centralities.

The first interesting observation obtained from this analysis is that the centralities based on the edge level of the simplicial complex perform very badly in identifying the essential proteins. For instance, for the top 1% of proteins in the ranking, the node and triangle centralities identify more than 45% of essential protein (see detailed analysis below), but the edge centralities do not identify more than 10% of them (edge degree identifies 27%). In general, neither of the edge centrality is able to identify more than 35% of essential proteins at any percentage of top proteins selected. This result contrast very much with the ones obtained by using node and triangle centralities. For instance, for the closeness centrality at both node and triangle level, the number of essential proteins identified is always larger than 37%. As can be seen in Fig. (4(a)) the triangle closeness centrality significantly outperforms the node one for all the percentages of proteins considered. Triangle closeness can identify up to 10% more essential proteins than the same centrality based on nodes, e.g., for 10% and 15% of top proteins. These differences represent up to 40 essential proteins more identified by the triangle centrality than the ones identified by the node one.

The largest percentages of essential proteins identified are obtained by means of the subgraph centralities. In particular, for 1% and 3%, the triangle subgraph centrality outperforms the node one in significant proportions. For 1% of top proteins the triangle subgraph centrality identifies 20% more of essential proteins than its node analogous, and for the 3% it outperforms the node centrality in 14%. However, for top percentages of rankings over 5%, the node and triangle subgraph centrality do not show very significant differences in the identification of essential proteins and they both identify around 50% of the essential proteins existing.

The first observation which merits to be explained from a theoretical point of view is the fact that edge centralities do not describe correctly the essentiality of proteins in the yeast PPI simplicial complex. This observation clearly indicates that increasing the complexity of the representation of a complex system, i.e., the PPI of yeast, does not necessarily implies increasing the amount of information which is extracted from that system. Here we explain these facts based on the degree of the edges for the sake of simplicity but the explanation provided is also valid for all the other centralities studied here. Let us recall that two edges are considered to be adjacent if and only if they share a node and do not form part of the same triangle. Thus, the edge degree is given by $k_p + k_q - (2 + 2t)$, where

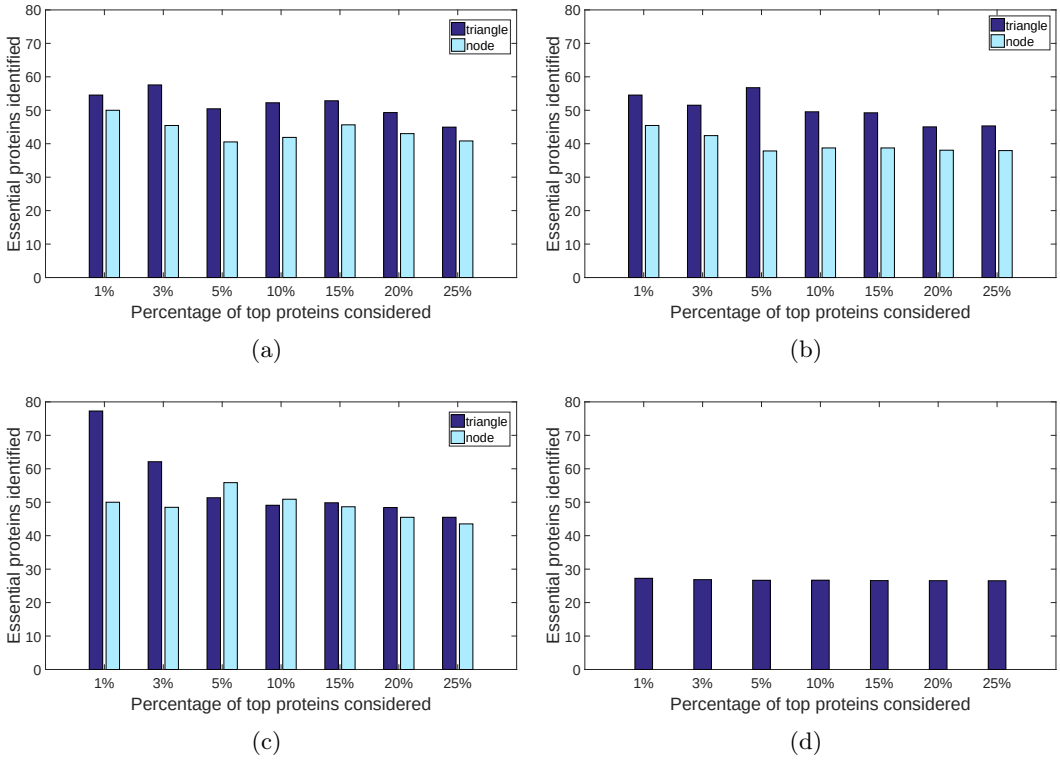
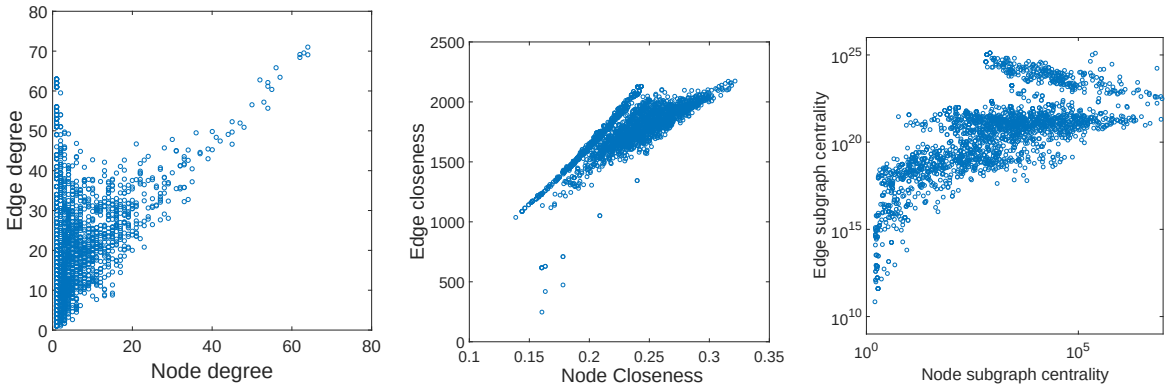


Figure 4: Percentage of essential proteins identified using simplicial degree (a), closeness (b), simplicial subgraph centrality (c) and random selection (d) based on nodes and of triangles of the simplicial complex for yeast PPI. For the case of the random selection, as the edges and triangle information is reduced to values for the nodes, it is only needed the selection of essential proteins based on random ranking of the nodes.

p and q are the nodes forming the edge and t is the number of triangles that the edge is a face of. Notice that in the graph the edge degree is simply defined as $k_p + k_q - 2$. Now, the important thing here is that the edge degree in the simplicial complex depends on the degree of the nodes forming such edge. In Fig. (5) we show the scatterplots of the edge centrality indices versus their node analogues. As can be seen in all cases the correlation is positive and for the cases of the degree and closeness the correlation between the two centralities is relatively good. We now analyze the causes of the differences between the node and edge centralities and how they influence the lack of ability of edge centrality to identify essential proteins in the yeast PPI.

Suppose that the number of triangles that the edge is a face of is relatively small, such that the degree of the edge is mainly dependent on the degree of the nodes forming that edge. Then, it is possible to have two different edges with exactly the same edge degree which differ significantly in the degree of the nodes forming the edges. That is, we can have an edge formed by two nodes of mid-degree, e.g., MD-MD, and another formed by a high-degree (HD) and a low-degree (LD) node. It is not difficult to find many of these

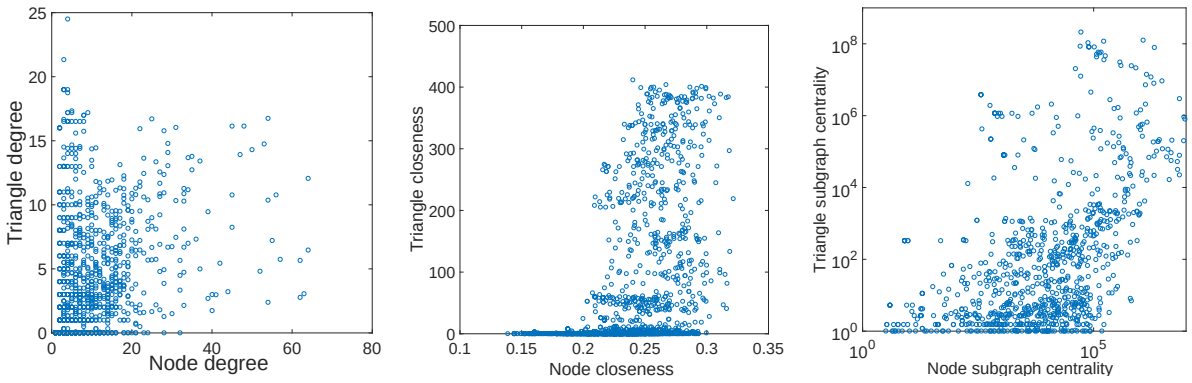


(a) (b) (c)

Figure 5: Scatter plots of the edge centralities, degree (a), closeness (b) and subgraph centrality (c), versus the node analogues of the same centralities. Notice that the subgraph centrality plot is in log-log scale.

examples in the yeast PPI. For instance, the edges YMR125C-YOL139C and YDR386W-YOL139C are formed by nodes of degrees 39-36 and 31-36, respectively. That is, these two edges are of the MD-MD type. On the other hand, the edges YPR110C-YLR086W and YPR110C-YGL016W are formed both by nodes of degrees 64-3, which clearly means that they are of the HD-LD type. It is well-know that high-degree nodes are more probable to represent essential proteins. Thus, it is more probable that the edges HD-HD contains an essential protein than the edges MD-MD. Indeed, neither of the proteins in the previous example in MD-MD are essential, but the protein YPR110C in the HD-LD edges is an essential one. Now, the situation is even worse when the nodes involved in a given edge participate in a large number of triangles. In this case, twice the number of triangles is subtracted from the edge degree as we have seen before. Then, if the HD node involved in an edge is also involved in a large number of triangles, its edge degree will be relatively small due to the fact that it is penalized for such participation in triangles. Thus edges which were HD-HD would be unlikely to have a high edge centrality. The existence of nodes having low degree but displaying either very low or very high edge degree is easy to understand. In edges of the HD-LD type, there is always a node with low degree which displays very large edge degree due to the influence of the HD node. In those edges where a LD node is connected to another LD node, both the node and the edge degree are low. These factors explain very well the failure of all edge centrality in accounting for the number of essential proteins in the yeast PPI in a similar way as the node and triangle centralities.

Now we move to the analysis of the triangle centrality indices. The first thing to be noted is the lack of correlation between the node and triangle centralities (see Fig. 6) even for the degree centralities. This lack of correlation clearly indicates that the information contained in one of the indices is not duplicated by the other. This is confirmed by the

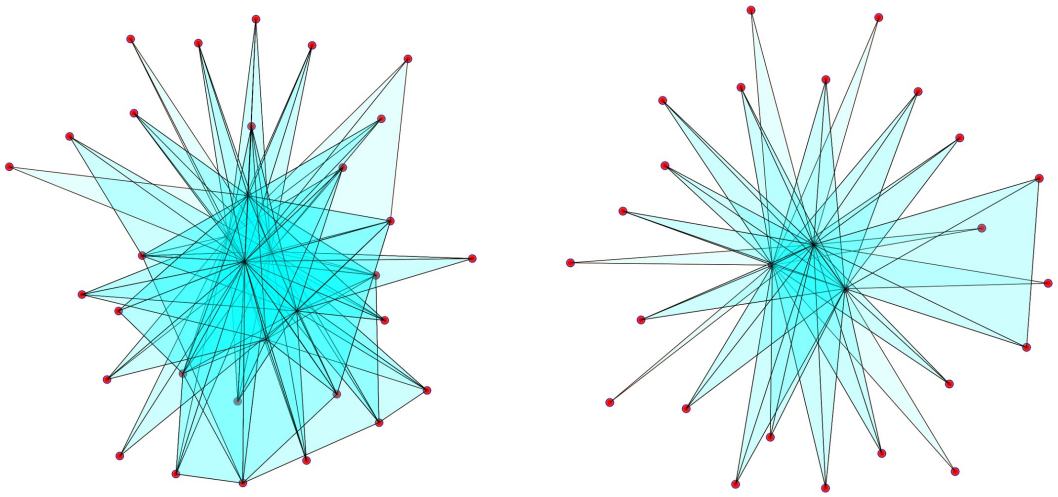


(a) (b) (c)

Figure 6: Scatter plots of the triangle centralities, degree (a), closeness (b) and subgraph centrality (c), versus the node analogues of the same centralities. Notice that the subgraph centrality plot is in log-log scale.

fact that the ranking based on node degree and triangle degree only identify 24 common proteins in the top 100 nodes ranked according to them.

Because the triangle centralities outperform the node ones in identifying essential protein, our main goal here is to identify some structural pattern which contributes to the triangle centralities and do not contribute to the node ones. In order to perform our analysis we again consider the degree centralities for the sake of simplicity. We are only interested in the structural information which is useful for the identification of essential proteins. The structural pattern that we identify here consists of a node A which is the vertex of a relatively small number of triangles, such that its node degree is small. Suppose for instance that A is connected to the nodes B, C, and D forming the triangles ABC and ACD. Obviously the node degree of A is only 3. Now, let us consider that BC is the edge of a large number of triangles, and in a similar way the edge CD. This makes that the triangles ABC and ACD have large triangle degree and consequently the node A is very central according to this index. This means that a node is triangle-central not only if it takes part in a large number of triangles, but also if the edges of the triangles it forms participate in a large number of triangles. As a matter of example we provide two complexes displaying exactly this kind of structural pattern. The first is formed by the protein YDL148C, which is connected to other proteins, namely YGR090W, YBR247C, YCL059C and YCR057C. These proteins form 5 triangles in which YDL148C is a vertex. Then, obviously, the protein YDL148C is not very central according to this nearest-neighbor structure, i.e., its node degree is only 4 and it participates in only 5 triangles. However, the edges of these 5 triangles participate in a total of 88 other triangles. That is, the edge YGR090W–YBR247C takes place in 11 other triangles, YGR090W–YCR057C in 22, YBR247C–YCL059C in 14, YCL059C–YCR057C in 25, and YBR247C–YCR057C in 16. The protein YDL148C is then very central according to the triangle centrality. This



(a) (b)

Figure 7: Illustration of the two simplicial complexes in formed by the proteins YDL148C (a) and YMR112C (b).

protein is indeed an essential one. Another example is provided by the protein YMR112C, which is also essential and is connected only to YDL005C, YOL135C, YBR253W and YJR068W. It forms only 4 triangles, but the edges of these triangles form 14, 15, 17 and 19 other triangles, respectively. Thus, the protein YMR112C which is not central according to node centrality is one of the most central ones according to the triangle centrality indices.

It should also be noted that there is structural information contained in the node centralities which is not accounted for by the triangle ones. As we have seen before there are proteins with high node centrality and low triangle centrality. However, the number of structural patterns contributing to this situation is wider and range from the simplest case when a protein interacts with a large number of other proteins which do not interact among each other, to the cases in which a central protein forms a wheel-like structure. In the first case obviously the protein has a high degree but its triangle degree is zero. In the second case—where a central node is connected to every node of a cycle having $n-1$ nodes, the central node has degree $n-1$ but every triangle has degree only two. In closing, the important message of this section is the the triangle centrality include some structural information which is relevant for understanding biological processes such as the essentiality of proteins in the yeast PPI.

7 Conclusion

We have developed here the mathematical framework for the analysis of centralities in simplicial complexes representing the topological structure of complex systems. We also

provide sufficient examples on the use of these centrality indices for the analysis of the structure of simplicial complexes emerging from PPI networks. The main conclusion of this work is that the understanding of the centrality of simplices at one level of the simplicial complex, e.g., node centralities, does not necessarily implies the understanding of the same centrality at another level, e.g., edges or triangles. This conclusion can have important consequence for the analysis not only of the structure of simplicial complexes but also for understanding dynamical processes taking place on them. We have provided here evidence that has shown that (i) the ranking of nodes, edges and triangles according to a given centrality measure can differ significantly for certain simplicial complexes, (ii) the node, edge, and triangle degrees can display very significant distributions in some simplicial complexes.We hope that this work opens these new research avenues for a better understanding of complex systems.

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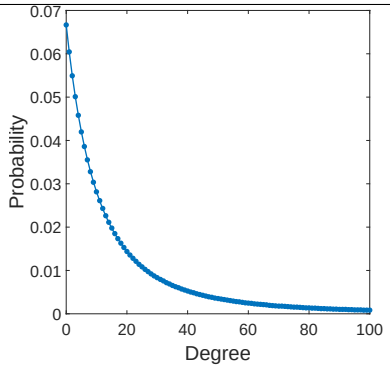
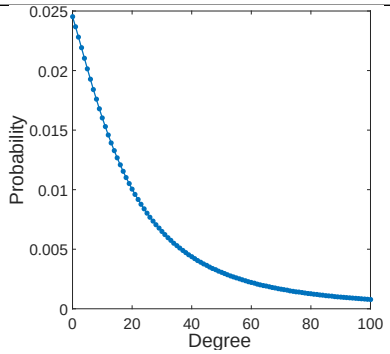
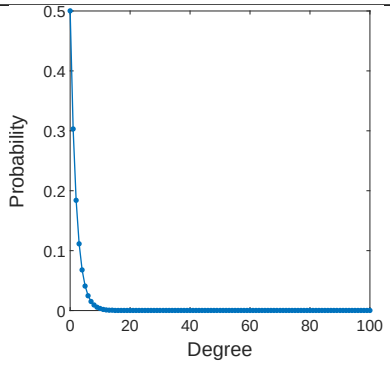
Appendix. Degree distributions

Distribution	PDF	Plot
gen-Pareto	$y = \left(\frac{1}{\sigma}\right)\left(1 + k\frac{(x-\theta)}{\sigma}\right)^{-1-1/k}$ k: tail index (shape) parameter σ: scale parameter μ: threshold (location) parameter	 $k = 0.5,\ \sigma = 15,\ \mu = 0$
GVE	$y = \left(\frac{1}{\sigma}\right)\exp\left(-\left(1 + k\frac{(x-\mu)}{\sigma}\right)^{-1/k}\right)\left(1 + k\frac{(x-\mu)}{\sigma}\right)^{-1-1/k}$ k: shape parameter σ: scale parameter μ: location parameter	 $k = 0.5,\ \sigma = 15,\ \mu = 0$
gamma	$y = \frac{x^{a-1}}{b^a \Gamma(a)}\exp\left(-\frac{x}{b}\right),$ a: shape parameter b: scale parameter	 $a = 1,\ b = 2$