

Property-driven statistics of biological networks

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Abstract. An analysis of biological networks based on property-preserving randomizations is presented. Unlike any other method proposed yet, ours assumes no preliminary notion of random network and is not limited to the detection of local properties.

The feasibility and relevance of the method are demonstrated in the yeast protein-protein interaction and transcriptional regulation interaction network. A measure of modularity is proposed revealing a significant deviation between the real network and the randomized versions.

1 Introduction

The availability of genome-scale metabolic, protein-protein interaction and regulatory networks [23,8,4,6,19]—following closely the availability of large graphs derived from the Internet hardware and software network structure, from social or collaborative relationships—has spurred considerable interest in the empirical study of the statistical properties of these ‘real-world’ networks. As part of a wider effort to reverse-engineer biological networks, recent studies have focused on identifying *salient* graph properties that can be interpreted as ‘traces’ of underlying biological mechanisms, shedding light either on their dynamics [21,11,7,26] (*i.e.*, how the connectivity structure of the biological process reflects its dynamics), on their evolution [10,28,25] (*i.e.*, likely scenarios for the evolution of a network exhibiting the observed property or properties), or both [9,13,14]. The statistical graph properties that have been studied in this context include the distribution of vertex degrees [10,9], the distribution of the clustering coefficient and other notions of density [15,16,17,20,5], the distribution of vertex-vertex distances [20], and more recently the distribution of network motifs occurrences [14].

Identification of a salient property in an empirical graph—for example the fact that the graph exhibits a unexpectedly skewed vertex degree distribution—requires a prior notion of the distribution of that property in a class of graphs relatively to which saliency is determined. The approach chosen by most authors so far has been to use a *random graph model*, typically given by a probabilistic graph generation algorithm that constructs graphs by local addition of vertices and edges [18,1,22]. For the simplest random graph models, such as the classical Erdős-Rényi model (where each pair of vertices is connected with constant probability p , [3]), analytical derivations of the simplest of the above graph properties are known [18,1].

In the general case, however, analytical derivation is beyond the reach of current mathematical knowledge and one has to resort to numerical simulation. The random graph model is used to generate a sample of the corresponding class of graphs and the distribution of the graph property of interest is evaluated on that sample, providing a standard against which the bias of the studied graph can be measured [21,13,27]. Some of these random graph models are not only designed to emulate one or more network properties —such as the small-world property (the average distance between nodes is logarithmic in the total number of nodes), or the power-law nature of vertex degree distribution (the probability of having n immediate neighbours varies as $1/n^\gamma$ with $2 < \gamma \leq 3$)— but also understood as *constructive explanations* for the evolution of the class of biological networks under scrutiny [10,9,25,20]. Again, perhaps because of the local nature of the random graph generation process, it is mostly simple *local* network properties that have been successfully reproduced in that fashion.

Our general approach, in essence, is to reverse the process. Rather than contrast the network of interest against an independent random graph model, one generates the model from the original graph itself. Specifically, one selects a property of the graph and generates a sample of randomized graphs within the class of graphs sharing this property. This sample is then compared with the original graph. Whichever property is lost in the shuffling process can then be construed as a system property that has to be understood and can serve as a means of statistically validating and classifying other networks, perhaps by homology considerations. That said, there are obvious constraints bearing on the choice of properties both for shuffling the original graph and for comparing it with the obtained sample. First, the associated randomization has to be feasible. Second, new properties, one could not obtain in the traditional bottom-up approach have to be made accessible by the new method, else why bother with a new method ?

The specific contribution of this article is to rigorously define a category of global properties where the shuffling procedure is easily implemented and does lead to something new, in that properties may describe at some level of detail how a biological attribute of vertices or edges unfolds on the graph structure, and may include detailed topological structures of subgraphs. Clearly such investigations are not within reach of the usual methods. To be a bit more concrete, suppose a heterogeneous network, *i.e.*, with several types of edges (relationships) on the same set of vertices (biological entities, *e.g.*, proteins), is given. One can then demand that the shuffling preserve homogeneous component subnetworks —each corresponding to one type of edge— and allow them to be glued back randomly. Various criteria can be used to measure the relative strength of the chunk cooperativity in the true graph compared to a randomized one.

To illustrate the method, we investigated the network obtained by combining protein-protein interactions (PPI) and direct transcriptional influences (protein-DNA interactions, thereafter abbreviated as TRI) in yeast, using the protein-protein distance distribution as a means of measuring cooperativity. One would expect, and the authors did, to observe a significant statistical deviation, showing

more cooperation between the PPI and the TRI chunks in the true graph. One would think that the way both subnetworks are glued in the true network makes it an even smaller or more compact world than the randomized variants. It turns out it is the exact opposite. Distances in the real network are larger in average. A reasonable guess is that the network seen as an information processor has more definite functions (in other words is more expressive) if it is modular, and being modular means probably losing on the side of having short paths. However, we don't have at the moment any solid explanation for this phenomenon but it is certainly a good point for the method itself to generate new observations from data that demand a biological explanation, and most likely one of an unusual kind.

The rest of this article is organized as follows. Section 2 defines more precisely what we mean by graph property, invariants and shuffles. Section 3 describes the application to the combined PPI—TRI network in yeast. Finally, we list several directions for future research on the identification of relevant properties in biological networks.

2 Properties, invariants and shuffles

The notion of graph property can be used within a variety of contexts and thrives without the umbrella of an overarching definition. Existing work on the analysis of biological networks and other types of large networks modeling 'real-world' phenomena, however, is actually very focused on a small set of graph properties, such as the distribution of vertices degrees, the clustering coefficient, or more recently the distribution of small 'network motifs' within the graph. One common point of these properties is that they describe a statistical distribution of *local* characteristics of the graph structure.

In the case of biological networks, another layer of information is often associated with the graph: attributes of vertices and edges bearing biological information. These are also local characteristics of the graph in the sense that they are associated with individual graph elements, and their distribution on the graph can also be studied.

Here, we will take the view that an attribute of graph elements (vertices or edges) is a mapping from these elements to a discrete set of values. While this view extends to continuous sets of values, for instance via discretization, the discrete nature of a property is precisely what allows its study in the present context.

An attribute of vertices or edges may represent a biological piece of information (*e.g.*, the functional class associated to a protein), but it may also reflect some local property of the graph structure (*e.g.*, the degree of a vertex, or inclusion of a vertex within a cluster, where the clustering was performed by using some distance on the graph). The point is that we do not focus here on how the property is obtained. Rather, we focus on how the *distribution of the attribute values on the graph structure* can be imposed as an *invariant* on a class

of graphs, in order to study how it influences the distribution of other observable properties.

Several types of such invariants can be envisioned, based either on vertices or edges attributes:

1. the complete graph structure of one or more subgraphs of the initial graph, subgraphs which may be defined on the basis of edge or vertices attributes.
2. the partition of vertices (or edges) into a set of equivalence classes defined on the basis of a given attribute. This can also be seen as the distribution of vertices (or edges) into clusters, and described formally as a map from the initial graph into an abstract graph of clusters, with no edges; the invariant to be preserved is then the morphism onto that specific abstract graph.
3. the structure of the partition into equivalence classes along with constraints on the edges between these classes. This corresponds to a morphism into an abstract graph of *interconnected* clusters.

A *shuffle* relative to an invariant is then defined as a special case of permutation on the graph that preserves that invariant.

For the rest of this paper, we will focus on the first type of invariant: preservation of the complete connectivity structure of subgraphs defined on the basis of an edge attribute. In order to give a rigorous definition of this type of invariant, let us define a notion of heterogeneous graph as a graph obtained by combining several graphs by ‘glueing them together’ on the same set of vertices.

2.1 Graphs and morphisms

Graphs can be defined in many ways depending on whether loops, multi edges and directed edges are allowed or not; we take here the view that a graph is directed, include loops and multi-edges (two vertices may be connected more than once).

Definition 1 A graph *consists of*:

- two finite sets E, V of edges and vertices (or nodes),
- and two maps t, s , called target and source, mapping E to V .

Equally important here, is the notion of a *morphism* between two graphs.

Definition 2 Suppose two graphs (V, E, t, s) and (V', E', t', s') given, then a map f from V to V' and E to E' is said to be a *morphism* if for all $e \in E$:

$$f(s(e)) = s'(f(e)) \text{ and } f(t(e)) = t'(f(e))$$

Morphisms compose, that is given $f_1 : G_1 \rightarrow G_2$ and $f_2 : G_2 \rightarrow G_3$, one can form their composite $f_2 \circ f_1 : G_1 \rightarrow G_3$. This composition endows the set of graphs with the structure of a *category* [2].

An invertible morphism $f : G \rightarrow H$ is called an *isomorphism*, and an *automorphism* if $G = H$. Two graphs related by an isomorphism share all the same graph-theoretical properties, average degree, number of cycles, etc. Let us remember this for later use.

2.2 Glueing

Definition 3 Given a set V , a tuple of graphs $G_1 = (V_1, E_1, t_1, s_1), \dots, G_n = (V_n, E_n, t_n, s_n)$, and a tuple of maps $p_1 : V_1 \rightarrow V, \dots, p_n : V_n \rightarrow V$, one may define a new graph $G = (V, E, t, s)$ as follows:

- $E = \sum_{1 \leq i \leq n} E_i$ (disjoint sum);
- for all i and $e_i \in E_i$, $t(e_i) = p_i(t_i(e_i))$ and $s(e_i) = p_i(s_i(e_i))$.

This graph G is said to be obtained by *glueing* the G_i along the maps p_i , and is denoted by $[(G_1, p_1), \dots, (G_n, p_n)]$. The G_i s will be referred to as the *components* of the glueing and the maps p_i as the *glueing maps*.

The glueing maps represent instructions explaining how the vertices in $\sum_i V_i$ should be glued together. By construction, they extend to graph morphisms from G_i to G by setting $p_i(e_i) = e_i$ (indeed a morphism, since for each e_i , $p_i(t_i(e_i)) = t(e_i) = t(p_i(e_i))$). Those morphisms are injective on edges, and in the application will also be injective on vertices.

An example of glueing For instance, the following component graphs:

$$G_1 = v \xrightarrow{a} u \quad G_2 = v \xleftarrow{b} u \quad G_3 = u \begin{array}{c} \circlearrowright \\ c \end{array}$$

together with the glueing maps defined by $p_1(u) = p_2(u) = p_3(u) = u$ and $p_1(v) = p_2(v) = v$, obtain the glueing:

$$G = \begin{array}{c} \begin{array}{c} \circlearrowright \\ c \end{array} \quad u \begin{array}{c} \xrightarrow{a} \\ \xleftarrow{b} \end{array} v \end{array}$$

Incidentally, one sees that glueing may result in multiple edges connecting the same two vertices, even though no components has multi edges.

2.3 Shuffling

When a graph is obtained as a glueing, one can define transformations that preserve each of the components.

Definition 4 Given a graph $G = [(G_1, p_1), \dots, (G_n, p_n)]$ and a tuple of bijections $\alpha_1 : V_1 \rightarrow V_1, \dots, \alpha_n : V_n \rightarrow V_n$, one defines the shuffle of G as:

$$G^{\alpha_1, \dots, \alpha_n} = [(G_1, p_1 \circ \alpha_1), \dots, (G_n, p_n \circ \alpha_n)] \quad (1)$$

In words, $G^{\alpha_1, \dots, \alpha_n}$ is obtained by glueing back together the component graphs after applying to each an automorphism. Of course, the result depends both on the glueing and the choice made of the automorphisms.

Although a shuffle preserves the component graphs, by modifying the way in which these are interconnected, it may result in an overall graph which is not isomorphic to the original one.

An example of shuffling We can see this by going back to the example and choosing the shuffle defined by $\alpha_1(u) = v$, $\alpha_1(v) = u$, and both α_2 and α_3 are the identity, then:

$$G^{\alpha_1, \alpha_2, \alpha_3} = c \begin{array}{c} \circlearrowleft \\ u \end{array} \begin{array}{c} \xrightarrow{a} \\ \circlearrowright \\ v \\ \xrightarrow{b} \end{array}$$

which indeed is not isomorphic to G .

Glueing and shuffling can be presented in a more abstract and algebraic way by using *amalgamated sums* (also known as *pushouts*) in the category of graphs. While not directly relevant for our development, this more abstract view may prove useful with richer notion of graphs. It is a warrant of the robustness of the approach and will be developed in future work.

3 Application to the combined PPI TRI network in yeast

With our definitions in place, we can now illustrate the approach on a biologically meaningful example using a graph obtained by glueing two components.

It is known that regulatory influences, including those inferred from expression data analysis or genetic experiments, are implemented by the cell through a combination of direct regulatory interactions and protein-protein interactions, which propagate signals and modulate the activity level of transcription factors. The detailed principles underlying that implementation are not well understood, but one guiding property is the fact that protein interaction and transcriptional regulation events take place in the regulatory network at different time-scales.

In order to clarify the interplay between these two types of interactions, we have combined protein-protein (PPI) and protein-DNA (TRI, for ‘transcriptional regulation interaction’) interaction data coming from various sources into a heterogeneous network by glueing together these two networks on the underlying set of yeast proteins.

The data from which the composite network was built includes: 1440 protein complexes identified from the literature, through HMS-PCI or TAP [4,6], 8531 physical interactions generated using high-throughput Y2H assays [24], and 7455 direct regulatory interactions compiled from literature and from ChIP-Chip experiments [5,12], connecting a total of 6541 yeast proteins. A subnetwork of high-reliability interactions was defined, using a reliability scale founded on assay type, and quality indicators provided by the authors, if any. The PPI network is built by connecting two proteins, in both directions, whenever there is a protein-protein or a complex interaction between the two corresponding proteins. In the case of the TRI network, an edge connects a regulator protein with its regulatee.

To assess the role of PPI in the TRI network, one needs a measure of the cooperativity between the two associated subgraphs. The property we choose to observe in the combined network, and its randomized variants, is the distribution of the distance between proteins, *i.e.*, the length of the shortest directed path connecting any given pair of proteins. As explained in the preceding section, randomized variants are obtained by shuffling the TRI network (in this case it

is enough to shuffle one of the two subgraphs to get all possible results up to isomorphism). We then estimate the distance distribution both for the actual and the shuffled networks.

At this point we have to compromise in two ways to make the computation feasible. First, we only consider a small sample of shuffled variants (10). This is a necessary evil, since a complete statistics performed over the population of all shuffled variants is clearly unfeasible. However, the empirical standard deviation observed suggests we obtain a statistically significant estimate (see below the comments on Figure 1). Second, the distance distributions are only evaluated on a subset of the protein pairs (10000 out of roughly $25 \cdot 10^6$). One needs here to further examine the confidence one can have on such a small sample to predict the full distribution. Note that although we deal here with a subset of the complete set of protein pairs, distances are evaluated in the full graph.

As said at the end of the introduction, Figure 1 reveals that the cumulative distribution of such distances in the combined network (plain line) is well below that of the average of the shuffled variants (dashed line). In addition, the two curves have very distinct asymptotes, namely 45% of all protein pairs are joined in the real network by paths, against 53% in the shuffled network. Standard deviation on the sample of shuffled graphs, indicated with vertical bars, seems to suggest our sample of 10 shuffled graphs is statistically significant.

To examine whether this difference might be related to a greater modularity of the real network, we counted its number of connected components and compared it with the number of connected components in 100 shuffled networks. As shown in Figure 2, the number of connected components in the real network is 37 versus 15 ± 4 in the shuffled networks. It seems that when shuffled, TRIs link together many connected components that were previously isolated, increasing the number of proteins that can be reached from a given protein. In contrast, TRIs in the real network appear to be localised within the most connected parts of the PPI network.

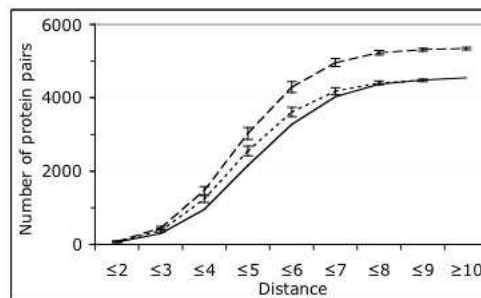


Fig. 1. Cumulative distance distribution between protein pairs (10000), in the real network (plain line), averaged over shuffled networks (dashed line), and normalized to make the asymptote fit the one of the real network (dotted line). Standard deviations are represented by vertical lines.

To study a second effect of the shuffling operation, we normalised the shuffle networks distribution (dotted line) to fit the asymptote of the real network distribution. The real network curve (plain line) remains below, at twice the standard deviation from the normalised shuffled networks distribution (dotted line). This confirms that TRIs are statistically mostly localised between proteins pairs that are already linked by a PPI path in the network.

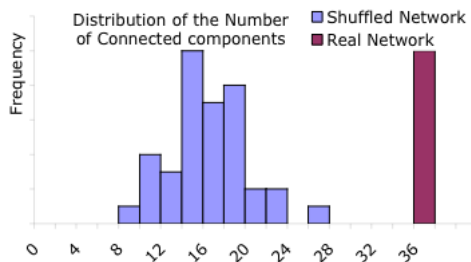


Fig. 2. Distribution of the number of connected components

While these results are preliminary and should be confirmed by more systematic sampling of the class of shuffled networks and of the distance distribution, they suggest that the precise way in which the two networks are interconnected—the set of interconnecting proteins, along with their associated interactions in both networks—is a key cause of the shortening of distances between protein pairs under shuffling.

4 Conclusion and future work

We have introduced a methodology for the identification of potentially meaningful properties in biological networks, based on randomizations that preserve other classes of properties. We have also provided the definition of a specific category of such invariants, reflecting the decomposition of a network into several subnetworks corresponding to different types of edges, and a procedure to generate the corresponding class of networks with uniform probability. Finally, we have given an illustration of the method on a network composed of PPI and TRI interactions, where we show that the actual network exhibits a biased distribution of protein-protein distances relatively to the class of networks obtained by shuffling the TRI network in all possible ways.

The extant ‘bottom-up’ approaches typically proceed by first selecting a statistical property thought to be characteristic of the class of networks against which the network of interest is to be contrasted. That class of networks is then obtained through a random generation procedure that provides no guarantee of capturing precisely that property (*i.e.*, there may be ‘false positive’ or ‘false neg-

ative’ networks), and little control over the probability of occurrence of networks in that class.

In contrast, our ‘top-down’ approach allows for both a rigorous definition of the invariant property and of the class of networks which obey it. This methodology can be driven by any biological property of interest that one may attribute to interactions (edges) or species (nodes). As we have shown in the preceding section, interactions can be partitioned in the PPI and TRI class. Different kinds of biological information could also be put to use. For instance, species could be sorted according to either clustering information, localisation within the various cell organelles and membranes, biochemical specificities (*e.g.*, length of the amino-acid sequence, hydrophoby), or combinations thereof. Then, other categories of top-down invariants, such as the projection of a network onto a given network of abstract clusters could be explored. In addition, there is also room for using other observable properties. In fact, we believe that the approach sketched in this paper is quite general.

Another line of investigation, perhaps more theoretical but potentially very fruitful in terms of applied insights, is the design of a solid unified theoretical framework for the definition of top-down invariant properties of networks, using category theory. The ‘glueing’ invariant presented enjoys a natural definition in this framework, and it seems likely that other properties that are related to the preservation of (partial) connectivity structures will, too.

Finally, a longer-term promise of the above extensions is to provide the foundations of an iterative search process for relevant properties in biological networks: at stage n , a class of networks is given by a set of invariants (biological constraints/hypotheses), and one searches for a property that discriminates the network of interest against the current class. Such a property is then considered as a candidate for ‘biologically meaningful’ status, and subjected to finer scrutiny, theoretical and perhaps experimental. If that status is confirmed, then the property is added to the set of invariants, thus defining a more restrictive class of biological networks, against which the same or another network can be pitted at the next iteration. In other words, the principle would be to search for properties that are *not yet explained* by the existing store of invariants — a form of conditional probability assessment— and to elevate some of them to explanation/invariant status.

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