On Biological And Non-Biological Networks

Biyolojik ve Biyolojik Olmayan Ağlar Üzerine

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Abstract: With a general classification, there are two types of networks in the world: Biological and non-biological networks. We are unable to change the structure of biological networks. However, for networks such as social networks, technological networks and transportation networks, the architectures of non-biological networks are designed and can be changed by people. Networks can be classified as random networks, small-world networks and scale-free networks. However, we have problems with small-world networks and scale free networks. As some authors ask, "how small is a small-world network and how does it compare to other models?" Even the issue of scale-free networks are whether abundant or rare is still debated. Our main goal in this study is to investigate whether biological and non-biological networks have basic defining features. Especially if we can determine the properties of biological networks in a detailed way, then we may have the chance to design more robust and efficient non-biological networks. However, this research results shows that discussions on the properties of biological networks are not yet complete.

Keywords: Biological Networks, Non-Biological Networks, Scale-Free Networks, Small-World Networks, Network Models

JEL Classification: D85, O31, C10

Öz: Genel bir sınıflandırmayla, dünyada iki tür ağ vardır: Biyolojik ve biyolojik olmayan ağlar. Biyolojik ağların yapısı değiştirilememektedir. Ancak sosyal ağlar, teknolojik ağlar ve ulaşım ağları gibi biyolojik olmayan ağların mimarileri tasarlanabilir ve bu ağlar insanlar tarafından değiştirilebilir. Ağlar; rassal ağlar, küçük dünya ağları ve ölçekten bağımsız ağlar olarak sınıflandırılabilir. Ancak küçük dünya ağları ve ölçekten bağımsız ağlar ile ilgili sorunlarımız vardır. Bazı yazarların sorduğu gibi, "Küçük dünya ağları ne kadar küçüktür ve diğer modeller ile karşılaştırıldığında nasıldır?". Ölçekten bağımsız ağların yaygın mı yoksa nadir mi olduğu konusu halen tartışılmaktadır. Bu çalışmadaki temel amaç biyolojik ve biyolojik olmayan ağların temel tanımlayıcı özelliklere sahip olup olmadığının araştırılmasıdır. Özellikle biyolojik ağların özelliklerini detaylı bir şekilde belirleyebilirsek, daha sağlam ve etkili biyolojik olmayan ağları tasarlama şansımız olabilir. Ancak bu araştırma sonuçları, biyolojik ağların özelliklerine ilişkin tartışmaların henüz tamamlanmadığını göstermektedir.

Anahtar Kelimeler: Biyolojik Ağlar, Biyolojik Olmayan Ağlar, Ölçekten Bağımsız Ağlar, Küçük Dünya Ağları, Ağ Modelleri

JEL Sınıflandırması: D85, O31, C10

1. Introduction

Roughly 20 years ago multidisciplinary network science was born. Paul Erdős and Alfréd Rényi, two Hungarian mathematicians introduced random networks in 1959. In those years, people

thought that all networks were random. Although this was very surprising, the thought that the networks were random lasted forty years. Then, two articles (Barabási and Albert 1999; Watts and Strogatz 1998) published a few years before the 2000s drastically changed this 40-year understanding and the network science community got acquainted with small world hypothesis and scale-free concepts. However, even as a result of all these developments, approximately 20 years later, discussions continue about both the concept of the small world and the concept of scale-free, and it is seen that a definite consensus on these concepts has not been achieved yet.

It is not even possible to compare biological and non-biological networks in terms of "time". We have to emphasize that biological networks are started long time ago and formed in very long periods of time. Protein-protein interaction (PPI) networks, genetic regulatory networks, food-web, neural networks are included in biological networks. We can easily distinguish whether a network is biological network or not. However, we do not have sufficient and detailed information about the differences between these two types. In fact, people did not know exactly how networks were formed until the 2000s. They designed and constructed their networks largely by trial and error.

Researchers interested in network science argue that networks continue to function within a certain set of rules. Therefore, network models (type) were established in order to determine these operating rules. If the models of networks are known, better information can be obtained about the behavior of networks, as well as making analyzes and experiments on real-life networks can be easily performed. There are three network models known so far. These are;

1. Random Networks   : Erdős-Rényi Model (ER)
2. Small-World Network   : Watts-Strogatz Model (WA)
3. Scale-Free Networks: : Barabási-Albert Model (BA)

With regard to these models, we should add that in a single real network, it is generally examined whether a single model is valid or not. However, Figure 1 tells us that a normal brain network can be thought of as a combination of different models in terms of hierarchy, order and degree diversity dimensions. In short, Figure 1 shows us that we need to be careful that reality can be more complex than we think. Stam (2014) focuses on exploiting the small-world and scale-free features of brain networks in order to get a comprehensive understanding of various brain disorders through a combination of three different models (Khaluf et al. 2017).
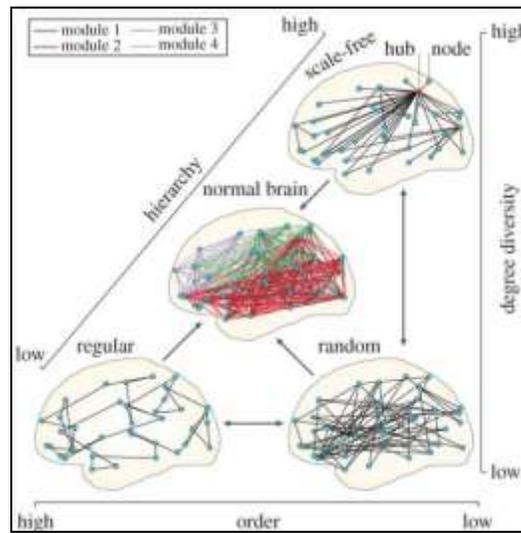
Figure 1. Combination of three different types of network models in brain networks
Source: (Khaluf et al. 2017)

This article tries to summarize the differences between biological and non-biological networks within the framework of the three models we have mentioned. Learning these differences in a detailed way, can enable us to take advantage of biological networks that are much better in robustness than non-biological networks. In addition, focusing on these differences can bring us new perspectives on the design of human-made networks. Our article tries to make a comparison within the same framework after mentioning some basic concepts and discussions within the framework of models. The study will end with a results section.

2. Robustness and Scale-Invariant Concepts

"Robust", which means oak tree in Latin, is the symbol of strength and longevity in the ancient world (A. Barabási 2016; p:4). In the world of complex, for both biological and non-biological networks, networks work with mutual interaction. Stable living systems, such as the brain and cellular networks are organized by interconnected networks. In such an environment, failure of nodes in one of the networks to function may cause disruption in other networks that this network interacts in the exchange of information. However, networks with robustness feature can avoid such effects. Even if some components of many natural and social systems fail, we can say that these systems are robust if they have an extraordinary ability to maintain their basic functions (A. Barabási 2016). We know that, a broader degree distribution increases the vulnerability of interdependent networks to random failure, and this fact should be taken into account when designing robust networks (Buldyrev et al. 2010).

One of the most important questions about the organization of natural systems is this; "How can these systems be so stable if they are interconnected to each other?" The answer to this question is as follows; "If the connections are established by hubs and the connections between the networks are moderately convergent, the system is stable and resistant to failure" (Reis et al. 2014). How can we achieve this aim? It may be achieved through implementation of scale-invariant features in our engineered systems. The issue here is how to achieve this through a decentralized and self-organized way. The challenge was resolved by many systems in the natural world; however, we, human beings, still have a long way to go (Khaluf et al. 2017).

If an object looks "roughly" the same on any scale it is said to be self-similar. Self-similarity and scale-invariant are nearly the same concepts. Scale-invariant systems appear with some stable features at different length or time scales. Scale-invariant features may be observed at molecular, cellular and organism levels in neuroscience and social networks. Natural systems obtain a scale-invariant collective behavior characterized by a system-level integration at a higher grade. Brambilla et al. (2013) reported that these systems are characterized by three features that engineers would benefit from replicating in decentralized designs including *scalability, robustness,* and *adaptivity.* Robustness and scalability directly appear from large-scale systems that achieve collective objectives that do not depend on global information. On the other hand, achieving flexibility in artificial self-organizing systems remains as a challenge (Khaluf et al. 2017).

3. Random Networks

Random network model has been introduced by Hungarian Mathematicians Paul Erdős and Alfréd Rényi and called ER model (Figure 2). If we have N nodes and if we connect every pair of nodes with probability p, we will have a random graph. One of the most basic features of random networks is that the nodes in these networks are not very different from each other in terms of connectivity. This model is the first model that explains us how networks form. When we ask the question to what extent this model explains real-life networks, other questions come to mind. Regardless, it took another 40 years before someone asked whether in Manhattan/New York City cable networks randomly go somewhere.
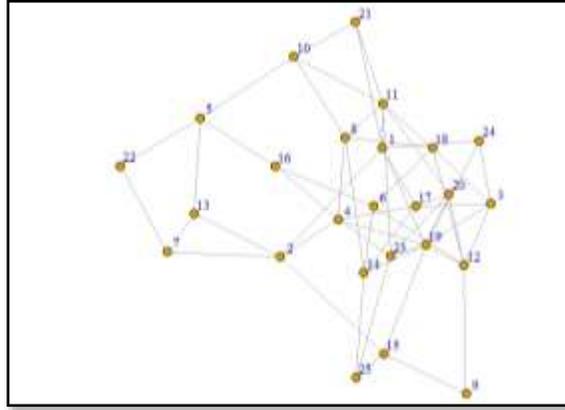
Figure 2. A random network (N=25, p= 0.3)

We can see in Figure 3 how Figure 1 changes the model only in terms of randomness. This dimension is named as "order" on the horizontal axis in Figure 1.
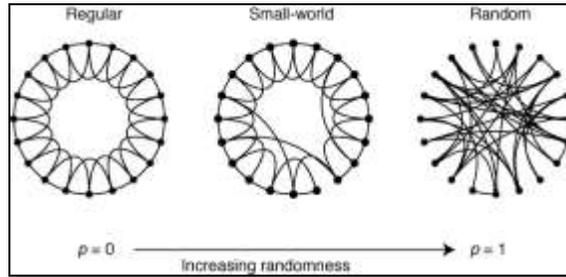

Figure 3. How increasing randomness changes the type of a model?
Source: (Watts and Strogatz 1998)

If we evaluate biological networks in terms of random network model; biological network patterns are more heterogeneous than simple models presented by random networks (Bansal, Khandelwal, and Meyers 2009). According to Proulx, Promislow, and Phillips (2005) heterogeneity, non-trivial clustering coefficient, community structure and assortative mixing are the most important features seen in biological networks. Although the ER model is simple and straightforward, it cannot bear the characteristics of the degree distribution and clustering coefficients observed in biological networks (Almaas, Vazquez, and Barabási 2013). It is obvious that biological networks are significantly different from random networks; and often present ubiquitous characteristics in terms of their structure and organization (Zhu, Gerstein, and Snyder 2007).

4. Small World Networks

In 1967, a sociologist named Steve Milgram introduced the concept of *six degrees of separation*. Milgram (1967) wrote and confirmed the words "the world is small" used in daily life with his experiments. It is determined by his study that there are six steps as a median between two people who do not know each other. Much later, in digital media such as Facebook, this distance shrinks towards four steps. Using a regular network and rewiring you can generate a small world network. Regular networks 'rewired' to reveal increasing amounts of disorder. It was detected that these systems may be highly clustered like regular lattices, and appear with small characteristic path lengths such as random graphs. They are called 'small-world' networks (Watts and Strogatz 1998). It was stressed out that the small-world is a relevant and popular phenomenon in many features of natural and man-made complex networks (Zamora-lópez and Brasselet 2019; Figure 4).

The main difference between random networks and small world networks is that in small word networks, two nodes are connected by a shorter path in small word networks than the same size random network. In small world networks, the distance between any pair of nodes, increases slowly (logarithmically) with the number of nodes in the network.

Small world networks can be seen in biological and non-biological networks. Collaboration among film actors network, the power grid network in the Western United States, the neural network of a worm species of Caenorhabditis elegance, are examples of small world networks (Watts and Strogatz 1998). Metabolic networks are small world networks and the network diameter does not appear to vary between different organisms. But on the contrary, we can also find sources stating that metabolic networks are scale-free because of their preferential attachment feature (Alm and Arkin 2003). And also, in the studies of Tanaka (2005) and Jeong et al. (2000) it is stated that metabolic networks have the characteristic of scale-free networks.

Small world network features have also been observed in brain networks (Bassett and Bullmore 2006), generally measured as high clustering and a short path length (Sporns 2013). As it has been seen in Figure 1, whether the brain really is a small world network remains unclear, although there is some evidence (Hilgetag and Goulas 2015). Another problem in small world networks is the size of small-world network, and comparison with others. We should also emphasize that a reliable and comparable quantification of the average path length of networks persists as an open challenge over the years.
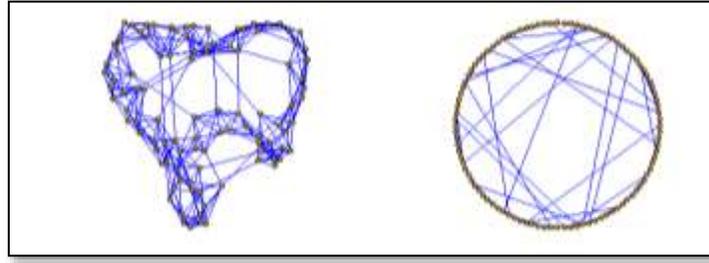
Figure 4. Small world network (N= 100, 4, p=0.03)

In a small world network, nodes tend to form triangles and this makes the network robust. But there is an inverse relationship between robustness and small world effect and vice versa (Peng et al. 2016).

5. Scale-Free Networks

In 1999, Barabási and Albert explained the principle of preferential attachment and how this principle works in scale-free networks (Barabási and Albert 1999). It is also shown on Figure 5. For instance, scale-freeness include the distributions of the sizes of cities, earthquakes, solar flares, moon craters, wars and people's personal fortunes, all appear to follow power laws (Newman 2005). As we know, most networks grow in time. The probability of a new node connecting to a node with k links is proportional to k, and in this case, a node with many connections will have mode connections over time and activates the phenomenon that *rich becomes richer.* The degree distribution of scale-free networks conforms to the power law;

$$P(k) \sim k^{-\lambda} \tag{1}$$

Exponent λ most of the times ranges between 2 and 3, this kind of network lacks a characteristic scale, hence such networks are called *scale-free* networks (Bullmore and Sporns 2009).
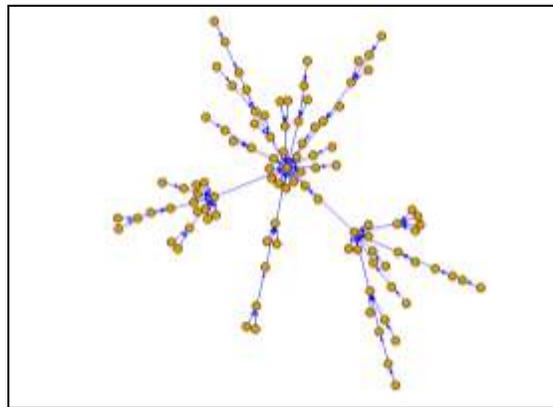

Figure 5. Scale-free network (N=100)

6. Are Scale-Free Networks So Abundant In Nature?

In biological networks the most characteristic feature is the presence of many hubs and many nodes have few connections which convenient for power-law. Another important feature of scale-free networks are also to be in the small world networks class (Amaral et al. 2000). Because they have clustering coefficients much larger than random networks (Watts and Wu 2002) and their diameter increases logarithmically with the number of vertices n. The small world feature of networks enables faster communication between different nodes. In addition, it is known that scale- free networks are robust to random attacks. All these properties are very important for biological networks (Khanin and Wit 2006).

However many biological networks exhibit the topological characteristics of scale-free networks with their preferential attachment feature, we want to deal with two questions. The first one is; "Are scale-free networks so abundant or rare?" and second one is "Even if scale-free networks are common, are there differences in these parameters of natural and man-made networks?". We should point out that there are no clear answers for these questions yet and all we do is to list these views one after another.

Some researchers ask that they focus on answering questions, which remain to be unanswered in this field of research including why scale-free networks are so abundant in nature (cosnet.bifi.es, 2013). Although software class diagrams, electronic circuits are detected as scale-free, some researchers have argued the opposite of this idea, claiming that scale-free networks are not ubiquitous phenomenon. In addition, they argue that they do not have a good basis empirically to analyze and model the structure of real networks (Broido and Clauset 2019).

Some authors have expressed that, in many cases hypothesized distributions are not tested rigorously against the data. This naturally leaves open the possibility that apparent power-law behavior is, in some cases at least, the result of wishful thinking (Clauset, Shalizi, and Newman 2009).

Some researches state that scale-free networks are abundant and their application to a representative collection of degree sequences in real-world networks confirms that they are not rare (Voitalov et al. 2019); however some say they are not. It is stated by Broido and Clauset (2019) that direct or indirect evidence is insufficient for the prevalence of scale-free structure in most of the biological networks. Broido and Clauset used five categories of scale-freeness from 'super-weak' to 'strongest'. They found that 57% the data sets belong to at least some kind of scale-free class; however, only 4% belong to the 'strongest' category. Broido and Clauset stated

that biological and technological networks may reach the "strongest" level whereas social networks may barely be "weakly" scale-free.

However, Khanin and Wit (2006) concluded that the number of connections in biological networks are quite different from the power law distribution, so they are not scale-free networks. The study conducted by Stumpf, Wiuf, and May (2005) also supports Khanin and Wit (2006). Apart from all these studies, let us emphasize that another aspect of the debate about whether biological networks are scale-free is about the α parameter. According to Broido and Clauset (2019) studies' the distribution of median α parameters significantly differs in five categories of evidence for scale-free formation

Another issue about scale-free structure is its rare or not. If strongly scale-free structure is empirically rare (Broido and Clauset 2019), how can they be "universal"? But again one point that confuses us in the Broido and Clauset's approach. In this approach, taxonomy of scale-free network definitions is used. How do we decide whether a data set is suitable for a particular distribution or not? By making classifications according to certain criteria (Broido and Clauset's approach use certain criteria) or by applying statistical hypothesis testing? For instance, we do not say as a result of hypothesis testing that if any dataset has a poor normal or a strong normal distribution. A dataset may or may not comply with a normal distribution. Only the level of significance may be altered in the merit of fit tests or if we should say that distributions of which tests passed at a significance level of 1% are strong, and the tests of which passed by 5% are poor. It is obviously the opposite. This classification problem may be resolved by neural networks. Xin, Zhang, and Shao (2020) report that Convolutional Neural Network (CNN) was used to find the differences between small-world and scale-free networks for network classification problem. Another study utilizing machine learning detected that Gaussian Naive Bayes and Random Forest classifiers may estimate the collections of real-world networks by accuracy rates of 92.8% and 92.3%, respectively (Canning et al. 2017).

7. Some Comparisons

Table 1 contains the evaluation of random, small world and scale independent networks with biological and non-biological networks. A summary of the features we touched on while introducing the models is available in this table. The table, which includes the *main features* of the models in terms of understanding the difference from each other, also includes the *degree distributions* that are very important for the models.

Table 1. Two-Way Table of Network Models For Biological and Non-Biological Networks

Network Models	Biological Networks	Non-Biological Networks	Main Feature	Degree distribution
Random Networks	It has been demonstrated that real world networks do not have the characteristics of ER networks. The probability of any two nodes connecting with each other may not be constant in real world networks (Khaluf et al. 2017). ER is not a good model for biological networks with respect to degree distribution.	It has been demonstrated that real world networks do not have the characteristics of ER networks. The probability of any two nodes connecting with each other may not be constant in real world networks (Khaluf et al. 2017)	Undirected, small clustering coefficient with high average path.	For small networks Binomial For large networks Poisson.
Small-World Networks	As a principle, a scale-free, small-world behavior may basically appear from the types of genetic evolutionary events that we are used to do including gene duplication, point mutation, and gene loss (Aloy and Russell 2004)	Small world networks are seen in non-biological networks. For example, Facebook from social networks shows the characteristics of small world networks with an average of 4.74 steps between two nodes.	High clustering coefficients with short average path lengths.	Small-world networks differs from other synthetic networks. The characteristics of the degree distribution change as the p value increases, which shows the degree of randomness, varying between 0 and 1. The common feature of various studies is that the distance between any two nodes increases logarithmically as the network expands (Huang, Sun, and Lin 2005)
Scale-free networks	"Scale-free nature of biological networks may have to be treated with some caution."(Khanin and Wit 2006). The examples obviously indicate that scale-free networks ranging between our brains and social networks have valuable consequences (Rajula, Mauri, and Fanos 2018). Some authors (see Chung et al. 2003) discuss that the estimated value of the exponent for the PPI networks meets $2 < \gamma < 3$. However, there are some significant oppositions to this claim; and it is stated on statistical grounds that the PPI graphs do correspond to power-law degree distribution category (Tanaka, Yi, and Doyle 2005; Khanin and Wit 2006; Sreedharan, Turowski, and Szpankowski 2020)	Most real networks have power-law consistent degree distributions labeling them as scale-free(Albert and Barabási 2002); (A.-L. Barabási and Albert 1999). However according to Broido and Clauset (2019) in their article, they found evidence that scale-free networks are rare. It is certain that it will be an open topic for discussion in the following years.	Preferential attachment.	Power law

Table 2 lists some of the features that can be considered as important differences in biological and non-biological networks. In networks, looping is the connection of a node to itself. A network loop occurs when moving information from the same source to the same destination in a network has more than one active path. There are loops in natural networks but looping is not a desired feature in Internet networks. In fact, retweets in tweet networks and emailing yourself, although not very common, are shown as loops in general. However, they are defined as loops,

we can say that there are no loops in the majority of non-biological networks since they cannot fulfill the loop function exactly in the networks. Although we mentioned that loops are not seen in biological networks, we have to emphasize that the same is not true for artificial neural networks. Because feedback loops are also used in artificial neural networks. If the output in artificial neural networks is not at the expected level, a technique called backpropagation allows the artificial neural networks to know this and adjust the neuron layers accordingly. So the error doesn't happen again.

Table 2. Comparison of Biological and Non-Biological Networks

	Biological networks	Non-biological networks
Loops	"Since feedback readily found in most biological networks, they have a significant importance" (Kwon and Cho 2007). Feed-forward-loops are common.	Loops are uncommon.
Community Structure	Community Structure is very important to determining the structural or functional relationships between objects and determining the identity of the network.	Community Structure is very important to determining the structural or functional relationships between objects and determining the identity of the network.
Assortativity	A dichotomy is seen	No dichotomy can be seen.
Hierarchy	Hierarchy is an important property of many natural and artificial networks (Mones and Vicsek 2012) The ontology specifically organizes biological knowledge about cell components and functions hierarchically (Bechtel 2020)	Hierarchy is an important property of many natural and artificial networks (Mones and Vicsek 2012)
Small-world phenomenon	It may be detected.	It may be detected.
Diameter	However, the diameter of the metabolic network is similar for all of 43 organisms (Jeong et al. 2000).	Mean connectivity of a node is fixed, for all non-biological networks analyzed; this implies that the diameter of a network increases logarithmically with addition of new nodes (Jeong et al. 2000).
The empirical ratio of the second to first moments $\langle k^2\rangle/\langle k\rangle^2$	According to Figure 1 it has been seen that in biological networks the empirical ratio of the second to first moments $\langle k2\rangle/\langle k\rangle2$ changes mostly between 10-1 and 101 range.	In social networks, the upper limit of this range is exceeded. In terms of the number of nodes, social networks cover a much wider range than biological networks in Figure 1.

The study of community structure in networks has a long history. The issue of finding communities in networks goes back to the 70's. This subject is referred to as *graph partitioning* in mathematic area, *community detection* and *hierarchical clustering* in social networks and sociology (Newman and Girvan 2004). This feature is also referred to as clustering in some places. In addition to the mathematical and statistical inferences of networks, hidden information in complex systems can be accessed by determining the community structures of networks. Community structure can be displayed in different ways in networks. Figure 6 is a graphical

representation of a network with a community structure. In this network, there appears to be less intensive inter-community linkages, although there are extensive links within communities.
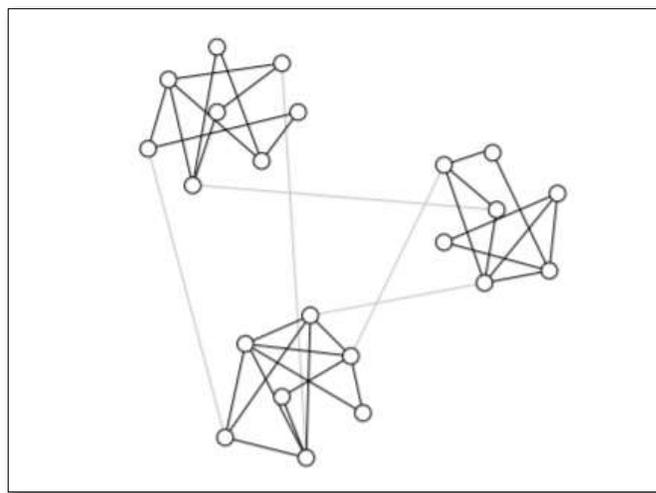

Figure 6. A graphical representation of a network with a community structure
Source: (Broido and Clauset 2019)

Many biological and non-biological networks exist divided into communities or we can say modules (Atay, 2018). Community structures generally refer to clusters of nodes obtained according to some topological properties such as the number of links in the network, their density, number of nodes, neighborhood relations. These sub-charts provide very important information in determining the structural or functional relationships between objects in real world networks and determining the identity of the network.

If the function of a group of molecules in biological networks is known, one can make predictions about the function of other assemblages of molecules that interact with this community but whose function is unknown (He et al. 2009). Figure 7 shows the community structure of the human brain. According to the figure, it refers to the regions where the human brain has five different modularity and each node plays an important role in the flow of information. It is observed that intra-community interactions are intense and inter-module connections are observed less frequently. He et al. (2009) and Olesen et al. (2007) express that modularity within a system increases the robustness of the system. It has been found that metabolic networks of organisms living in a variable environment are more modular. It is important to reveal modules that can be considered functionally meaningful from such biological interaction networks.
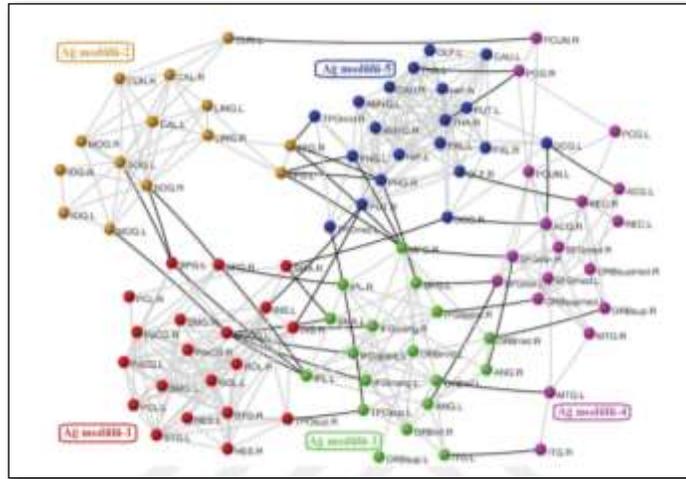
Figure 7. Modular Structure of Human Brain
Source: (He et al. 2009)

We know that rich nodes can or cannot have connections between them (Mondragón 2020). If nodes in a network establish random connections with other nodes regardless of their degree, these networks are "neutral networks". Conversely, if hub nodes attach to hub nodes, these networks are "assortative". The marriage of famous people with famous people is an example of assortative networks. Figure 8 shows that nodes in different biological networks show the same dichotomous in degree correlation. This dichotomous discern biological networks from real classifying networks such as the internet and social networks (Hao and Li 2011).
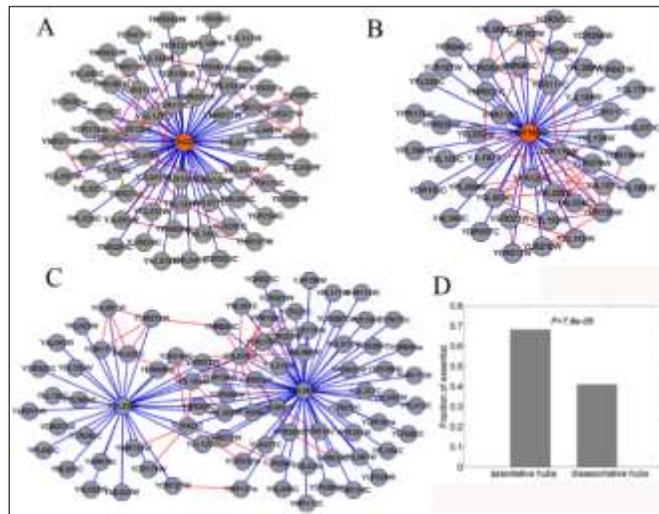

Figure 8. Dichotomous modules.
Source: (Hao and Li 2011)

A. Modules organized around YLR423C YBR160W. Classifying links are indicated in red whereas non-classifying links are shown in blue. **B**. Modules organized around YBR160W. **C**. Two modules organized around YDL239C and YML264C are connected to each other through classifying links. **D.** Classifying hubs are more essential than non-classifying hubs (chi-square test).

In Figure 9, we see moment ratio scaling for various degree sequences. As it can be seen on Figure 9, sometimes lognormal distribution enters the stage. De Silva and Stumpf (2005) find that for the yeast protein interaction networks (PIN) the lognormal distribution (blue) offers a better description of the data than the pure power-law or its heuristic finite-size versions.
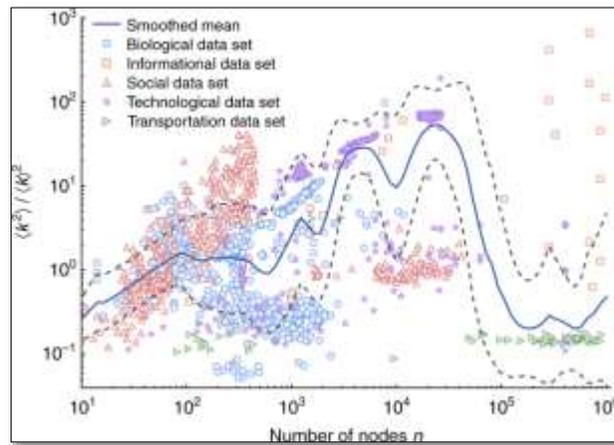

Figure 9. Moment ratio scaling. For 3662 degree sequences, the empirical ratio of the second to first moments $\langle k^2 \rangle / \langle k \rangle^2$ as a function of network size n,
Source: (Broido and Clauset 2019)

Graphical representation of a system actually means that interactions are also dyadic. However, many biological networks do not conform to this assumption. Therefore, we may need to wait before understanding the real differences in biological networks. It is not probable that any method or mode of thinking may complete an analysis; however, rather than combining tools from topology, statistics, and other fields may support our capability to derive biological understanding and pinpoint biological mechanisms (Blevins and Bassett 2020).

Barabási, Albert, and Jeong (1999), and Erdős and Rėnyi (1959) indicated that networks are created by random processes including homogeneous node sets in their mathematical evaluation. However, changes and variations exist in life. Proulx, Promislow, and Phillips (2005) state that three basic properties of biological networks should be considered to improve biological network models as follows; 1) Networks may lose nodes or new nodes may be added to networks; 2) Features of the nodes in the network may change; and 3) External factors may affect the structure

of the network. It should be remembered that characteristics of the entities (i.e. genes, species) forming biological networks may affect the dynamics of network formation.

8. Results

In this paper, we aimed to compare biological and non-biological networks based on the three models, which are random networks, small-world networks, scale-free networks. And also we compared some of the basic properties of biological and non-biological networks. Among these features, there were similarities and differences. We think it is important to highlight these features in order to better understand the structure of biologic and non-biologic networks and to shed light on future studies.

As a result of our work, we saw that there are very different and sometimes even opposite ideas about biological and non-biological networks are occurred on studies. We find particularly surprising and thought-provoking studies on whether scale-free networks are common or rare. The exact judgments that biological networks present a scale-free network model in the past are increasingly replaced doubt. Therefore, biological networks scale-free structure inferences should be require more examined.

We think that with the advancement of science and technology, this research makes a prediction that "unknowns" or "well-known mistakes" about the biological and non-biological networks may emerge over time. Depending on researches and the changing world order, perhaps different network models will be defined in the coming years.

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