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RESPONSE OF LYAPUNOV EXPONENTS TO DIFFUSION STATE OF BIOLOGICAL NETWORKS

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The topologies of protein-protein interaction networks are uncertain and noisy. The network topology determines the reliability of computational knowledge acquired from noisy networks and can impose the deterministic and non-deterministic character of the resulting data. In this study, we analyze the effect of the network topology on Lyapunov exponents and its relationship with network stability. We define the methodology to convert the network data into signal data and obtain the Lyapunov exponents for a variety of networks. We then compare the Lyapunov exponent response and the stability results. Our technique can be applied to all types of network topologies as demonstrated with our experiments, conducted on both synthetic and real networks from public databases. For the first time, this article presents findings where Lyapunov exponents are evaluated under topological mutations and used for network analysis. Experimental results show that Lyapunov exponents have a strong correlation with network stability and both are correlatively affected by the network model. Hence we develop a novel coefficient, termed LEC, to measure the robustness of biological networks. LEC can be applied to real or synthetic biological networks rapidly. Results are a striking indication that the Lyapunov exponent is a potential candidate measure for network analysis.

Keywords: synthetic networks, biological networks, diffusion, stability, Lyapunov exponents.

1. Introduction

Networks are used to describe the interactions between objects of interest in various areas. In molecular biology, network representations are useful to analyze important biological activities. These activities do not result from a single molecule but ensue from the effects of multiple molecules interacting with each other (Yu *et al*., 2013). Intermolecular interactions are modeled with networks so that edges represent interactions and nodes represent molecules (Gabr and Kahveci, 2015). Biological networks are abstract representations of biological systems. Networks capture many of the essential characteristics which cannot be obtained from an individual component of biological systems. Most biological networks are incomplete. They are difficult to interpret because of the complexity of relationships (Vocaturo and Veltri, 2017). Analyzing biological networks provides novel information in understanding basic mechanisms that control cellular processes. Essentially, we expect that networks will change how we think about biological systems in a fundamental way (Alm and Arkin, 2003).

Although the number of living species, the number of proteins, and the number of interactions are different in each protein-protein interaction database, there is a difference in the amount and content of information derived from the same source. Of the 14,899 publications shared by at least two databases, 5,782 (39%) were reported with different numbers of interactions in different databases (Altuntaş and Gök, 2020). Even the low rate differences found in the databases affect the results of

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the algorithms that use these data. Network stability is important as the effect of the difference in the predicted results using the network data is greater than the difference in the network data (Altuntas *et al*., 2018). There may be significant differences in the information received from databases from the same publication. According to the information obtained from different databases referring to the same publication, 42% of the interactions and 62% of the proteins were the same (Turinsky *et al*., 2010). In addition, it is emphasized that more than half of the total networks contain protein interaction networks with false positive and false negative data (Stumpf and Wiuf, 2010). The reason why the results are not the same may be that the parameters that provide a different interpretation of the experimental data, such as the use of a different confidence set or threshold, are not used in the same way.

The Lyapunov exponent is a parameter used to quantify the sensitivity of the system to the initial conditions and it is widely used as a distinctive feature in many areas (Nazarimehr *et al*., 2017). Also, due to the nature of biological events, Lyapunov exponents provide useful information to explain the biological activities that occur. It has been claimed that many biological systems have chaotic properties (Nazarimehr *et al*., 2017). Based on the successful results using Lyapunov exponents in the literature, this parameter can also be used on biological networks and we can understand the hidden properties of biological networks by the Lyapunov exponent.

In this paper, unlike the existing studies, we take into account that the existing mutations in the network topology can influence the Lyapunov exponent response to the network. Our contributions are the following. In order to test our hypothesis, we define the methodology to convert the network data into signal data and obtain Lyapunov exponents. To evaluate the relationship between Lyapunov exponents and the stability of the network, we define some measure based on the stability of the network. Our technique can be applied to all types of network topologies. This is the first time that the Lypunov exponents have been evaluated under topological mutations and have been used for network analysis. Calculating the stability of biological networks is a method that requires time and processing power. With the method we developed in this study, stability can be expressed with a rapidly calculated coefficient.

The rest of this paper is organized as follows. In the next section, we present the literature overview about network stability, diffusion state, and the Lyapunov exponent. We then discuss our methodology which measures the Lyapunov exponents of a given network topology and we describe the centrality measures that we use in our method. The last section includes details about the experimental setup and data sets, and presents our discussion of related findings.

2. Background

Network stability. Some studies aim to model and test the stability or robustness of biological systems under mutations that cause conditions of uncertainty (Stelling *et al*., 2004; Li *et al*., 2010; Altuntas *et al*., 2018). Biological systems have been shown to be highly resistant to a diverse set of perturbations, both through mathematical modeling and experimental observations.

Studies that consider topological perturbations mostly concentrate on random or selective node removals (Albert and Barabási, 2002; Holme *et al*., 2002; Altuntaş and Gök, 2017). These methods test the hypothesis that most complex systems contain noise for various reasons such as mutation and that the detected nodes may be incorrect. They accept that all interactions associated with a node are all true or all false. For several network characteristics such as the shortest path and clustering coefficient, they assess the effect of node removals. According to their findings, it is possible to say that there is a strong correlation between robustness and the network topology. Especially scale-free networks are less affected by random node removals than by selective node removals.

Furthermore, in several studies, the effect of noise on edges has been studied. Holme *et al*. (2002) investigated the effect of edge deletion on the geodesic length and the size of the target network. To test the performance of prediction algorithms that identify and prioritize disease genes and drug targets, some studies work with random edge removal models (Erten *et al*., 2011). Altuntas *et al*. (2018) defined an algorithm that generates the most influential mutation in the network and the concept of stability that measures the robustness of mutant networks. In the human protein-protein interaction (PPI) network, Zhang *et al*. (2016) define the concept of *indispensable nodes* with respect to the structural changes by using a selective edge removal with the confidence scores of the interactions.

In this paper, we consider the most influential mutations. Unlike the existing literature, we consider the influence of topological perturbations on the Lyapunov exponent response of the given network. To the best of our knowledge, this is the first study in which the Lyapunov exponents are used for network analysis and have been evaluated under topological mutations.

Diffusion state. Diffusion analysis is widely used in interaction networks. It provides successful results for many problems such as protein function prediction (Cao *et al*., 2013; Cho *et al*., 2015), conserved network module detection (Jeong *et al*., 2016), gene prioritization (Köhler *et al*., 2008; Erten *et al*., 2011), and sub-network detection (He *et al*., 2017). The random walk based diffusion state distance is used as a measure of the protein neighborhood distance for the protein function

prediction by Cao *et al*. (2013). Cho *et al*. (2015) reduced the number of variables for the network diffusion state. Jeong *et al*. (2016) detected conserved functional network modules with the use of the random walk model. Köhler *et al*. (2008) prioritized the candidate hereditary disorders genes, and Erten *et al*. (2011) prioritized the candidate disease genes with the random walk. For the detection of PPI subnetworks, He *et al*. (2017) used a limited K-walks algorithm.

Lyapunov exponent. The Lyapunov exponent (LE) of a system is a quantity that characterizes the rate of separation of infinitesimally close trajectories. Lyapunov exponents tell us the rate of divergence of nearby trajectories. The Lyapunov exponent is used as a feature extraction method in many studies. Liu *et al*. (2015) used the largest LE as a metric of the balance ability during human quiet standing. They proposed a metric of the human body's standing balance ability based on the multivariate largest LE. For the prediction of critical transitions in biological systems, Nazarimehr *et al*. (2017) proposed LE as an indicator of "critical slowing down". Gao (2012) used the LE for multiscale analysis of biological data. They analyzed heart-rate variability and electroencephalography data to detect a congestive heart failure and seizures consecutively. For the detection of irregular regions in proteins, Gök *et al*. (2016) developed a new feature coding technique that connects physicochemical properties using the LE. The LE was used for anomaly detection (Ruiz and Finke, 2019) and impulsive control (Li *et al*., 2019). Han and Wang (2007) analyzed the heart rate variability of healthy people versus those with arrhythmia.

3. Methods

We define a methodology to measure the Lyapunov exponents of network topologies. Given a network, our method finds the largest Lyapunov exponents to characterize the target network. We introduce the networks and mutations in Sections 3.1 and 3.2 respectively. We discuss our method in Section 3.5. We then describe the centrality measures that we use in our method in Section 3.6. In this section, we describe our method in detail.

3.1. Networks. Biological activities are not the result of a single molecule, but rather through coordinated interaction of multiple systems that interact with others. Molecular systems that jointly perform cellular tasks such as gene expression, information transfer, or regulation of metabolism are modeled by biological networks (Albert and Barabási, 2002). Synthetic networks are those produced by adhering to a particular mathematical model. Networks contain inter-node interaction information. A graph network G with n vertices can be represented by an $n \times n$ adjacency matrix. The rows and columns correspond to the vertices and a matrix-element $A_{ij} = 1$ if and only if there is an edge between the vertices v_i and v_j, and $A_{ij} = 0$ otherwise. When we use inter-node similarity criteria, A_{ij} represents the similarity ratio or distance by taking a value between 0 and 1. The line of the node in the matrix is a signal of the similarity/distance change of that node relative to all other nodes in the network. All nodes in the network have their unique signals, and a network contains as many signals as the number of nodes in the network.

3.2. Mutations and stability. Biological networks have uncertain topologies since biological processes governing interactions are inherently uncertain events (Gabr *et al*., 2015). We know that there are studies reporting that false positive and false negative rates in the data of protein interaction networks often exceed half the total network, particularly (Stumpf and Wiuf, 2010). In a network with n edges, to find the most influential set of r elements to produce synthetic mutations, we use the novel metaheuristic method on all target networks (Altuntas *et al*., 2018). For a given amount of perturbation ϵ, we compute the stability of G under the function q. After mutating the topology of G by a factor of ϵ stability is the largest amount of alteration in the diffusion quality function q. Stability is defined mathematically as (Altuntas *et al*., 2018)

$$\arg\max_{G^\epsilon}\{|q(G) - q(G^\epsilon)|\}. \tag{1}$$

The formulation above seeks the network topology among all possible ϵ perturbations of G with the highest change in the diffusion state. For a given ϵ, the smaller $|q(G) - q(G^\epsilon)|$, the more stable the network (Altuntas *et al*., 2018).

3.3. Random walk (RW). The random walk method is simulation of a random walk that starts from a given node in the target network. At walking each step, it chooses a random direction. For a given network $G = (V, E)$, write the walking distance from the source node n_i in terms of the number of steps as restriction parameter k, the adjacency matrix of network G as A_G, and set the diagonal matrix D of the same size as A_G with D_G, where each diagonal entry $D_G[i, i]$ has the value $1/\text{degree}(n_i)$, and $M = D_G \times A_G$. We denote by matrix RW_k the random walk after k steps. We compute it as $RW_1 = D_G$, and for $k > 1$, $RW_k = M^T RW_{k-1}$ (Can *et al*., 2005).

3.4. Diffusion state distance (DSD). For a given node pair (n_x, n_y) and the number of steps k we compute DSD using the previously calculated matrix RW_k. In detail, it

is the $L1$ norm of the difference between the n_x and n_y node columns of RW_k. The L1 norm is the sum of the magnitudes of vectors. Let us denote by $RW_k(n_i)$ the column of RW_k corresponding to a node n_i. The DSD formally defined as (Cao *et al*., 2013)

$$DSD_k(n_x, n_y) = \|RW_k(n_x) - RW_k(n_y)\|_1. \quad (2)$$

3.5. Lyapunov exponent. The Lyapunov exponent (LE) quantifies the sensitivity of the system to the initial conditions. Actually, it is a quantity that characterizes the rate of separation of close trajectories. Nearby trajectories is the path that a signal vector follows through the phase space. For different orientations of the phase space, the rate of divergence can be different. Thus, there is a whole spectrum of LEs in the phase space and the number of them is equal to the number of phase space dimensions. A positive exponent means divergence. The trajectories are initially close to each other and move apart over time. In the same way, a negative exponent means convergence. The trajectories move closer to each other (Kennel *et al*., 1992).

In this section, we describe our method in detail. Denote by V and E the set of nodes, and the set of interactions among those nodes, respectively; we also denote by $G = (V, E)$ the given network. In this paper, we focus on PPI networks. Therefore G is an undirected network. The input graph G has n nodes $V = (v_1, v_2, \ldots, v_n)$. For a specific node v_i there are n edges $E(v_i) = (e_1, e_2, \ldots, e_n)$ that represent distances of node v_i to all other nodes. The phase space matrix of node i, named s_i, is calculated from $E(v_i)$ and $s(k)_i = [E(v_i)(k), E(v_i)(k + T), \ldots, E(v_i)(k + (M - 1)T)]$. M and T are the embedding dimension and the delay, respectively. Denote by $s(n)_i$ the reference point and by $s(m)_i$ the nearest neighbor of $s(n)_i$ on a nearby trajectory. The LE is calculated for each dimension of the phase space as

$$\lambda = \frac{1}{N} \sum_{n=1}^{N} \ln \frac{d(s(n+1)_i, s(m+1)_i)}{d(s(n)_i, s(m)_i)}, \quad (3)$$

where $d(s(n)_i, s(m)_i)$ is the initial Euclidean distance between the nearest neighbors. Here $d(s(n+1)_i, s(m+1)_i)$ is the Euclidean distance between the next pair of neighbors on their trajectories (Abarbanel, 2012). When calculating the Lyapunov exponent from network data, the size of N is the size of network nodes. For the calculation of the LE we use the TISEAN package (Hegger *et al*., 1999). This program is based on the work of Sano and Sawada (1985), and it estimates the whole spectrum of the LE.

Our method takes an undirected graph $G = (V, E)$ as its input parameter and reports the LE frequency for input graph G. Algorithm 1 presents the pseudo-code of our method. The purpose of reconstructing the signal in the phase space is to provide a sufficiently large Euclidean space to see the structure of the system's attractor without any uncertainty. The space dimension, where all uncertainties are resolved, gives the embedded dimension (Abarbanel *et al*., 1993). The phase space dimension can be determined by increasing the embedded dimension until the value changes in the calculated quantities stops (Cao, 1997). Our experiments on synthetic and biological networks show that using 6 as the embedding dimension can be used to differentiate the different responses of the networks. The embedding dimension can be reduced to 4 to speed up the calculations. In the method we proposed, the embedding dimension was not reduced in order to avoid reducing the coverage of the networks with possible different characteristics.

Our algorithm first divides the input graph G into n lines that correspond to each node. Let us denote by $Le(v_i) = (ex_1, ex_2, ex_3, ex_4, ex_5, ex_6)$ the largest 6 LEs of node v_i. Starting from the first node v_1, the algorithm calculates the LE for each node of input graph G as $Le(G) = \{Le(v_1), Le(v_2), \ldots, Le(v_n)\}$. Having computed Lyapunov exponents, we find the positive exponent frequency of $Le(G)$ by counting positive exponents. Denote by $pf(G) = (f_0, f_1, f_2, f_3, f_4, f_5, f_6)$ the positive exponent frequency of graph G. Here $pf(G)$ has a value of 7 that represents no positive exponent and 1, 2, 3, 4, 5, 6 positive exponents frequencies of graph G, respectively. The frequency value is proportional to the number of nodes in the graph. We normalized the frequency values of G to percentage Lyapunov exponent values (ranging from 0 to 100) by dividing them by the number of nodes in the network and multiplying the result by 100. The resulting vector can be used as a 7-element feature vector showing the percentage of Lyapunov exponents for any given network. Each Lyapunov exponent attribute that represents LEs in 7-element feature vector is a cumulative value. Hence $f_1 \geq f_2 \geq f_3 \geq f_4 \geq f_5 \geq f_6$. The minimum value for these attributes is 0 and the maximum value is 100. In order to produce a single measurement representing the Lyapunov exponent response of the networks, we use the arithmetic mean of $f_1 \geq f_2 \geq f_3 \geq f_4 \geq f_5 \geq f_6$ as a coefficient. The Lyapunov exponent response for each network is a measurement between 0 and 100. We named the Lyapunov exponent based network coefficient measurement as LEC, which we described in this section.

Incorrect data or noise that do not belong to the systems can dramatically change the system dynamics and this may affect the Lyapunov exponent response of systems (Serletis *et al*., 2007). According to the hypothesis that we present in this study, incorrect detections in protein-protein interaction networks may affect the Lyapunov exponent of the network by changing

Algorithm 1. LEC calculation.

Require: G
for each $node$ in G **do**
  $E(v_i) \leftarrow (e_1, e_2, \ldots, e_n)$ {distance signal vector}
  $Le(v_i) \leftarrow (ex_1, ex_2, ex_3, ex_4, ex_5, ex_6)$ {estimate spectrum of Lyapunov exponents}
end for
$Le(G) \leftarrow \{Le(v_1), Le(v_2), \ldots, Le(v_n)\}$ {Lyapunov exponents of G}
for each $exponent$ in $Le(G)$ **do**
  if $exponent > zero$ **then**
    $increasef_1, f_2, f_3, f_4, f_5, f_6$ {update related frequency}
  else
    $increasef_0$ {update no positive exponent frequency}
  end if
end for
$pf(G) \leftarrow (f_0, f_1, f_2, f_3, f_4, f_5, f_6)$ {positive exponent frequency of G}
$pf_n(G) \leftarrow normalize_{0-1}(pf(G))x100$
$LEC \leftarrow mean(pf_n(G))$
return $LEC, pf_n(G)$

the topological dynamics of the networks and this effect may be related to the stability of the network. For the calculation of $d(s(n+1), s(m+1))$ the noise has the following effect (Koçal *et al*., 2008):

$$E[d(s(n+1), s(m+1))^2] = d(s(n+1), s(m+1))^2 + 2\sigma^2 D, \quad (4)$$

where D is the embedding dimensions and σ is the standard deviation of noise. Inaccurate data in the network can be considered as noise in the calculation of the Lyapunov exponent in phase space. The effect of noise in the phase space can be seen in the previous equation. As a result, inaccurate edges have an effect on the Lyapunov exponent calculation, as shown in this equation.

3.6. Node centrality. In graph theory and network analysis, node centrality indicators are used to identify important nodes in a graph. This is used to characterize the importance of each node relative to their position within the network, with network centrality indicators closely related to distance criteria. The concepts of centrality were first developed in social network analysis, and many of the terms used to measure centralization reflect their sociological origins (Newman, 2018). The centrality of nodes, or the identification of which nodes are more "central" than others, has been a key issue in network analysis (Freeman *et al*., 1991).

Nodes in real networks do not have a specific order. The node sequence may vary from database to database, or even within the database. The node order can affect the results because it changes the signal to be used in the Lyapunov exponent computation. We have established a sorting standard for networks through node centrality measurements and examined the effect of sorting on results.

Denote by $c(v_i)$ the centrality of node i in a given network $G = (V, E)$. The input of the sorting algorithm is a network G and the output is a new network G_s whose nodes are sorted according to the target measurement. The algorithm calculates the centrality value of all nodes $\{c(v_1), \ldots, c(v_n)\}$ in the given network G using the target measurement metric. Denote by o_1 and o_n the first node order number and the last node order number with, respectively. The algorithm determines node order with centrality values for each node in the network G from big to small and creates node order vector $no = (o_1, o_2, \ldots, o_n)$. Finally, the algorithm changes the node order of network G by using the centrality order vector no and creates a new sorted network G_s for the Lyapunov exponent calculation.

Degree centrality. The degree measures the node centrality by using the local structure around nodes only. In undirected graphs, the degree of a node can be calculated by using the number of adjacent nodes that directly connected to the node or simply the number of edges connected to that node (Borgatti, 2005). The degree is important because it provides an advantage or risk in terms of whether or not to generate an alternative path to the information flowing through the network. A node with a larger degree is likely to have higher influence than a node with smaller degree.

Betweenness centrality. The betweenness centrality allows one node to act as a bridge along the shortest path between the other two nodes. Nodes with a high probability of occurrence in the shortest randomly selected path between two randomly selected nodes have a high weight. Betweenness centrality measures how important a node is to the shortest paths through the network. It is calculated by taking the ratio of all the shortest distances in the network where the measured node is located to all the shortest distances in the network. To compute betweenness for a node n, select a pair of nodes and find all the shortest paths between those nodes. Then compute the fraction of those shortest paths that include node n (Freeman, 1977). For a given network $G = (V, E)$ denote by σ_{st} the total shortest path number from node s to node t and by $\sigma_{st}(n)$ the total shortest path number from node s to node t that pass through node n. Betweenness centrality for node n is calculated as

$$B(n) = \sum_{s \neq t \neq n \in V} \frac{\sigma_{st}(n)}{\sigma_{st}}. \quad (5)$$

Closeness centrality. In a connected graph, the proximity center of a node is the average length of the shortest path between the node and all other nodes in the graph. Thus, the more central node is, the closer it will be to all other nodes (Perez and Germon, 2016). The benefits of closeness centrality are that it indicates nodes as more central if they are closer to most nodes in the graph. This strongly corresponds to visual centrality; a node that would appear toward the center of a graph when we draw it, usually has a high closeness centrality. Denote by $d(y,x)$ the distance between vertices x and y. The closeness centrality for node x is calculated by the following formula:

$$C(x) = \frac{N-1}{\sum_y d(x,y)}. \tag{6}$$

Load centrality. Load centrality is the fraction of all shortest paths passing through that node. It is very close to the measurement of the betweenness centrality (Hagberg *et al.*, 2008). Load centrality is a betweenness-like measure defined through a hypothetical flow process. For a given network $G = (V,E)$ denote by $\sigma_{st}(n)$ the total shortest path number from node s to node t that pass through node n. Load centrality for node n is calculated as

$$L(n) = \sum \frac{1}{\sigma_{st}(n)}. \tag{7}$$

Clustering coefficient centrality. The clustering coefficient is a measure of the degree of clustering of nodes in a graph. In many real networks, the nodes tend to form tightly linked groups characterized by a relatively high link density. This centrality has an intuitive meaning. The clustering coefficient reflects the extent to which neighbors of the target node are also neighbors of each other, and thus the clustering coefficient measures the cliquishness of a typical connection circle (Watts and Strogatz, 1998). Denote by k_v the vertices count within the k neighbourhood of node v. There may exist vertices counts within the k neighbourhood of node v with $p_v = k \times (k-1)$. The clustering coefficient centrality for node v is calculated as

$$C(v) = \frac{k_v}{p_v}. \tag{8}$$

Random centrality. In this sorting criterion, the node priorities are determined by random numbers so that the nodes are in random order as in the databases. To create a random node order, we use a random number generator so that the numbers do not repeat and each number can be used once. Denote by $ro_n(o_1, o_2, \ldots, o_n)$ the generated random number vector for n nodes. For a given network $G = (V,E)$ we change the order of the nodes in G using the random order vector ro to generate G_s. Although G and G_s are the same networks, the node order of G_s is different from G.

4. Results

In this section, we examine experimentally the performance of our methods on target networks. On both synthetic and real datasets, we run experiments. Then using previously defined Lyapunov exponent measures, we measure the performances (cf. Section 3.5). In the following, we describe the datasets used in experiments and describe the implementation details.

4.1. Datasets. We performed comprehensive experiments on synthetically produced and real networks. The network type, the number of nodes, the number of edges, and average node degree are parameters to express the networks.

Synthetic datasets. In order to evaluate the response of the Lyapunov exponent under mutations on different artificial networks, we use synthetic networks with different topological properties. We use three well-known reference network models named Erdos–Renyi (ER), Watts–Strogats (WS) and Barabasi–Albert (BA) as target synthetic networks. To observe the effect of network parameters, we use varying network parameters such as node size: $500, 1000, 1500$ and 2000, average node degree: $2, 3, 4$ and 5. Each experiment was repeated 5 times. Therefore, for each specific network a total of 240 synthetic networks were studied. In this section we shortly describe the reference synthetic network models.

Denote by n and p the number of edges and the probability of possible edges, respectively. The ER model generates a random network $G = (n,p)$ that, with probability p, connects node pairs by an edge. This model has binomial degree distribution, it has a small clustering coefficient and small-world characteristic (the average path length is very small). In the resulting network, the number of edges is $C_2^n \times p$. The WS model is also called the small-world (SW) network. On a one-dimensional ring, this model first arranges each vertex. Then edges are assigned to vertices by connecting each vertices to its $k/2$ nearest neighbors. The WS network model has a high clustering coefficient. The average path length of network scales linearly with the network size. For n vertices the number of edges in the resulting network is $n \times k/2$. The BA network model has scale-free (SF) degree distribution and this distribution follows the power-law characteristic. The BA model starts with a network with m nodes and zero edges. What is required for the enlargement of a network are new nodes attached to existing edges with

m edges. High-grade nodes are preferentially selected for a new edge connection. In the resulting network, for n vertices, there are $(n - m) \times m$ edges. We create a network for a target node size and the average node degree for each network model. Thus the edge size is determined by these parameters. In order for a network to be sufficient, the created network must have a sufficient number of edges, otherwise the process is repeated until the desired number of edges is reached. Similarly, if the created network has more edges than desired, we discarded these edges. In this manner, we ensure the edge size criterion with these rules. For the creation and manipulation of complex synthetic networks, we use the NetworkX Python package (Hagberg *et al*., 2008).

Real datasets. We use eight protein-protein interaction networks of different organisms. Real networks have a variety of node sizes, edge sizes, and average node degrees. Networks were downloaded from the BioGRID (Chatr-Aryamontri *et al*., 2015) and STRING (Szklarczyk *et al*., 2014) databases. Before using the datasets, firstly we discard the redundant edges and then the largest connected component derived from the experimental PPI network, which is the result of a physical interaction of all microorganisms, is used. Table 1 displays topological properties of resulting real target networks.

Experimental setup. Our new Lyapunov exponent based analysis method LEC runs on an ordinary system with 8 processors and 16 GB RAM. Besides, stability analysis with the most influential edge set searching algorithm run on single instruction multiple data (MIMD) distributed architecture that has far too much computation power (421 processors and 212 GB RAM).

4.2. Results on synthetic data. We use synthetic networks to observe the response of the Lyapunov exponent on synthetic networks. This paper contains a wide variety of network parameters representing topological properties and experiments with various network mutation. We measure the relevant response using previously defined Lyapunov exponent measures on the original and the mutant networks (see Section 3.5).

4.2.1. Evaluation of network parameters. This study focuses on revealing the Lyapunov exponent response on the network topology and diffusion state. Therefore, we first investigated whether the response of the Lyapunov exponent depends on the topological properties of synthetic networks. The purpose of this experiment is to evaluate how the different parameters governing the network topology affect the Lyapunov exponent response of the target network. To observe the effect of topological changes, we use network models of ER, WS, BA and 500, 1000, 1500, 2000 as the number of total nodes and 2, 3, 4, 5 as the number of average node degrees with 5 repetitions. We use the $Le(G)$ measure to evaluate the response of the Lyapunov exponent on the target networks. Figure 1 illustrates the results.

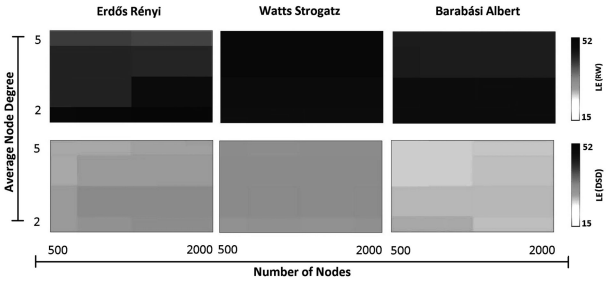

Fig. 1. Evaluation of network parameters on synthetic networks. Columns: ER, WS, BA, row 1: $Le(RW)$, row 2: $Le(DSD)$. For all heat maps, the left axis indicates the average node degree and the bottom axis indicates the number of nodes.

As displayed in Fig. 1, RW and DSD distributions of ER, WS and BA synthetic networks have different Lyapunov exponent responses. In all experiments, the RW distribution has a higher percentage of the Lyapunov exponent than the DSD distribution. For each network model and distribution, the average node degree and the number of node topological properties have almost no effect on the Lypunov exponent response and all results are almost the same. In all experiments, the WS synthetic networks have greater Lyapunov exponents than the ER and BA synthetic networks. Results for ER and BA synthetic networks are very similar.

Consequently, this study contributes to our understanding of the Lyapunov exponent response of networks highly dependent on the network topology. These observations show that the Lyapunov exponent response varies depending on the topological properties of synthetic networks, especially the network model and distribution. When the results are compared with the results of the network stability (cf. Altuntas *et al.*, 2018, Figs. 2 and 4), there are similarities between them. The comparisons show that Lyapunov exponent at a higher percentage in networks with high stability.

4.2.2. Evaluation of mutations. One of our motivations for this study is that protein interaction networks are noisy. They have false positive and false negative edges at varying rates. The next question is whether the Lyapunov exponents of networks change according to the topological mutations. In this experiment, we measure the effect of the mutations on Lyapunov exponents of the target network.

Table 1. Real network properties.

Organism	Number of nodes	Number of edges	Average node degree
Saccharomyces cerevisiae (7)	5,936	65,139	10.9
Homo sapiens (8)	6,122	14,426	2.3
Arabidopsis thaliana (6)	5,726	13,409	2.3
Caenorhabditis elegans (5)	2,937	5,333	1.8
Plasmodium falciparum (4)	1,262	2,598	2.0
Helicobacter pylori (1)	733	1,480	2.0
Mus musculus (2)	1,340	1,416	1.0
Rattus norvegicus (3)	631	704	1.1

To observe the effect of topological mutations, we use ER, WA, BA network models. As the numbers of total nodes, we use 500, 1000, 1500, 2000, and 2, 3, 4, 5 as the numbers of average node degrees. We fix the mutation ratio as 1% of edges. All experiments run with 5 repetitions. Then, for each network G we create maximum influential mutations by using the previously defined mutation algorithm (see Section 3.2) to create the mutant network G'. We use the $Le(G')$ measure to evaluate the response of the Lyapunov exponent on the target mutant networks. Figure 2 illustrates the comparison results of original and mutant networks.

The mutation operator ensures that the minimum number of edges is deleted, which ensures the most effective change in the network. The process continues until the change is ineffective. The resulting network is stable to mutation. In all experiments, the networks formed as a result of edge mutations have a higher rate of Lyapunov exponents. It is seen that for all type of networks RW distribution is more stable than DSD distribution to topological mutations (cf. Altuntas *et al.*, 2018, Figs. 2 and 4). For all types of networks, similar to the stability results, the less stable DSD distribution exhibits a higher rate of Lyapunov change after mutation and a lower rate of Lyapunov change in the RW distribution that is more resistant to mutations. In all experiments the WS networks are more resistant to mutations, more stable and have lower Lyapunov change.

Our findings prove that networks that become more stable with topological mutations have a higher rate of Lyapunov exponents. The RW distribution is more resistant to mutations, more stable, and has a lower Lyapunov exponent change after mutations. The DSD distribution is fragile to mutations, less stable, and has a higher Lyapunov exponent change after mutations. Lyapunov exponents have a correlation with network stability and both correlatively affected by the network model.

4.2.3. Evaluation of order. One of the questions is whether the response of Lyapunov exponents depends on the node order of synthetic networks. Also, we examine how different node orders affect the response of the Lyapunov exponents.

To observe the effect of node order, we use ER, WS, BA models as a network creation model. As the numbers of total nodes we use 500, 1000, 1500, 2000, and as the numbers of average node degrees we use 2, 3, 4, 5, respectively. All experiments run with 5 repetitions. Then, for each network G we change the node order by using the previously defined node centrality algorithms (see Section 3.6) to create a node reordered network G^r. We use the $Le(G^r)$ measure to evaluate the response of the Lyapunov exponent on the target reordered network. Figure 3 illustrates the comparison results of original and reordered networks.

According to the obtained results, it is clear that the RW and DSD distributions of ER, WS and BA synthetic networks to the Lyapunov exponent response are not affected by different node orders. In all experiments, the node order parameter has effect on the Lyapunov exponent response but this effect is not significant. For each network model, both RW and DSD distributions are affected by the node order. The Lyapunov exponent results obtained by order using OCC, OBC, OLC, OCLC and ORA are almost identical to the predefined order Lyapunov exponent results. The changes with these orders are near zero. The ODC order has insignificant influence on the Lyapunov exponent. With ODC order of all networks, the models produce similar results. A random node order ORA is produced in 10 replicates and there is no difference between the results.

In conclusion, our experimental results show that node order has an insignificant effect on the Lyapunov exponents of the target network. There is always a possibility that a different sorting type may distort the significance of the Lyapunov exponent results. The nodes can be randomly arranged to avoid the possibility that the target network has an order that will affect the Lyapunov exponent calculation.

The insensitivity of the signal generated from the network to the order results from the protein-protein

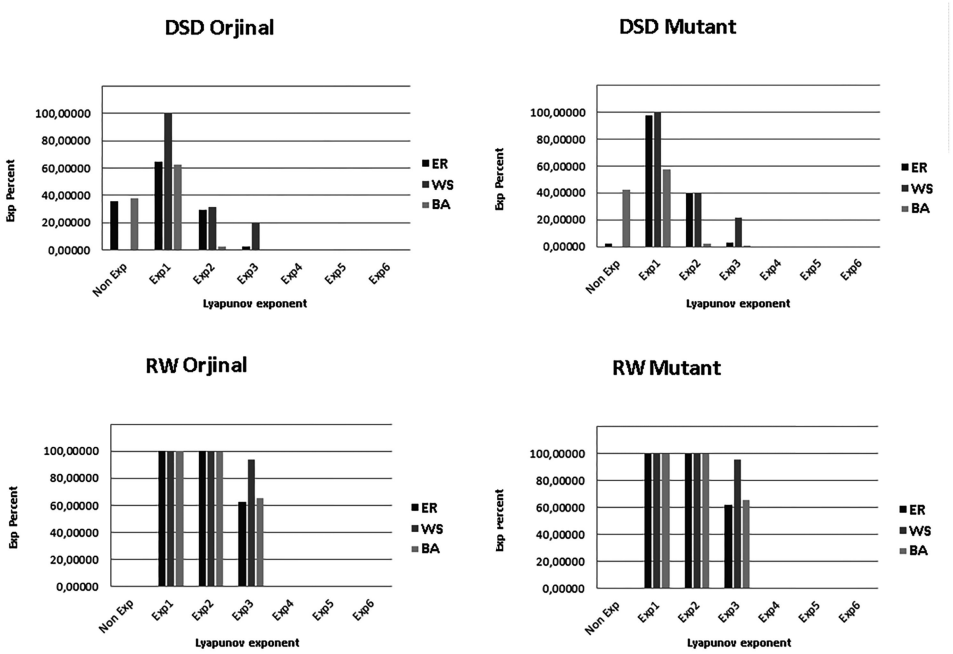

Fig. 2. Evaluation of mutations on synthetic networks.

interaction network data structure. The PPI network matrix is a repetitive matrix and mutual values are equal. With this feature, the network consists of similar series. For instance, a sample interaction network p with 3 protein nodes consisting of 6 interaction values is defined as $[(n_{1,2}, n_{1,3})(n_{2,1}, n_{2,3})(n_{3,1}, n_{3,2})]$. This is a matrix of 3 rows, 3 columns and 6 independent interaction results. Assuming that the interaction results such as $n_{1,2}$ and $n_{2,1}$ are the same, the network matrix becomes a similar series $[(n_{1,2}, n_{1,3})(n_{1,2}, n_{2,3})(n_{1,3}, n_{2,3})]$. Another factor is node similarity. The PPI networks contain topologically and biologically similar nodes (i.e., $n1 = n2$). This increases the sequence similarity and repetition. $[(n_{1,2}, n_{1,3})(n_{1,2}, n_{1,3})(n_{1,3}, n_{1,3})]$. Because of the series repetitions and similarity of the network matrices, when the node order changes, for many series, only the location in the network is changed. This ensures that the signal set generated from the network is order-independent.

4.3. Results on real data. So far, we have demonstrated the Lyapunov exponent response of synthetic networks with a variety of parameters, different node orders, and topological mutations. However, we foresee that there may be differences between the Lyapunov exponent responses of real and synthetic networks. For this purpose, we observe the response of the Lyapunov exponent on real networks, using eight protein-protein interaction networks of different organisms in this section. They have a variety of average node degrees, edge sizes, and node sizes. We measure the relevant response using the previously defined Lyapunov exponent measures (see Section 3.5).

4.3.1. Evaluation of organisms. Our next topic is to determine whether artificial and real networks are similar in terms of the Lyapunov exponent response. With this experiment, we succeed to reveal the Lyapunov exponent response of different real networks. We use the $L_e(G)$ measure to evaluate the response of Lyapunov exponent on the target real networks. Figure 4 illustrates the results. We present detailed results in Appendix (Table A1).

It is seen that the RW and DSD distributions of real networks have different Lyapunov exponent responses. Similarly to experimental results of synthetic networks, in all experiments, the RW distribution has a higher percentage of Lyapunov exponents than the DSD distribution. *Rattus norvegicus* (3) is the network with the least exponential rate of the Lyapunov exponent and *Helicobacter pylori* (1) is the network with the most exponential rate of the Lyapunov exponent.

Based on our experimental results, we found that RW and DSD distributions have similar Lyapunov exponent responses to synthetic networks. Observations show that the Lyapunov exponent response varies depending on the topological properties of real networks. When the results are compared with the results of the network stability (cf. Altuntas *et al.*, 2018, Fig. 5), there are similarities

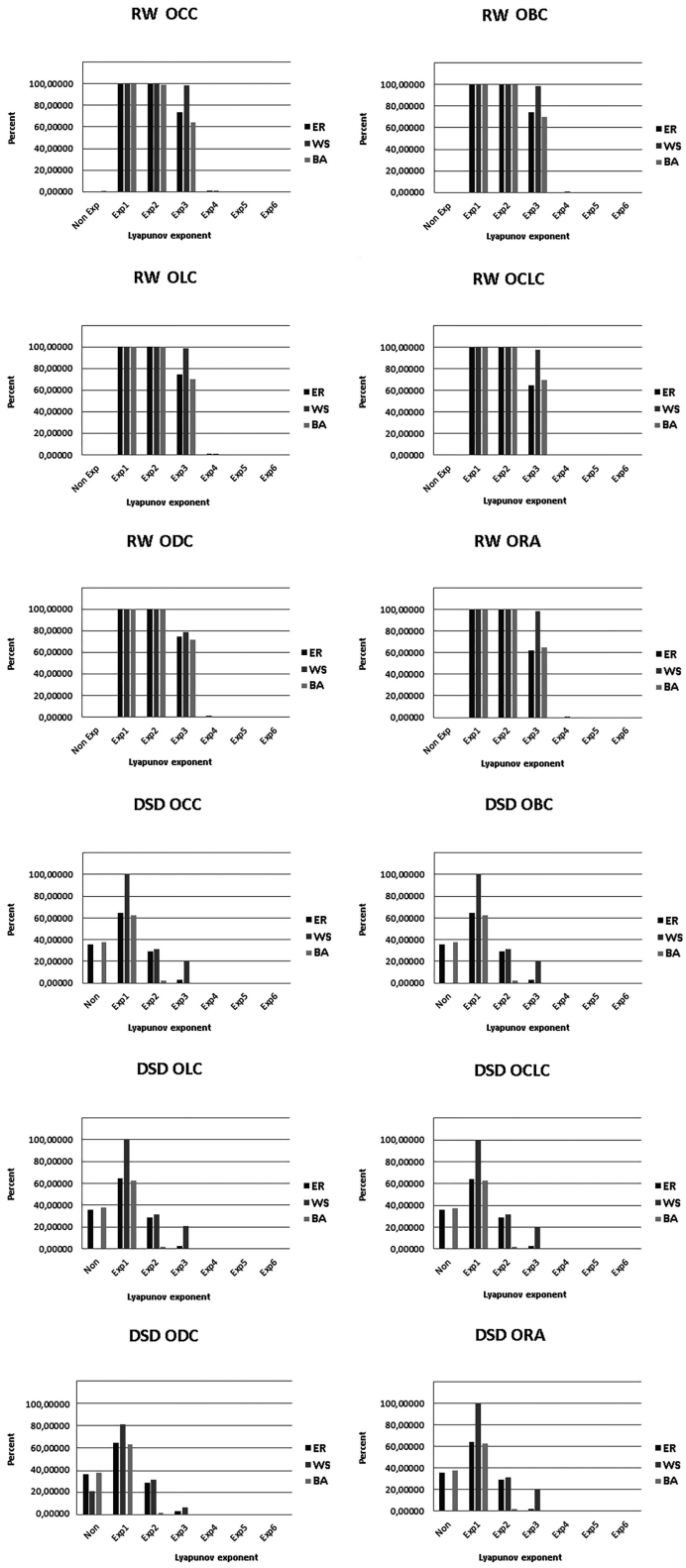

Fig. 3. Evaluation of node order on synthetic networks. OCC: Closeness Centrality, OBC: Betweenness Centrality, OLC: Load Centrality, OCLC: Clustering Coefficient Centrality, ODC: Degree Centrality, ORA: Random Centrality.

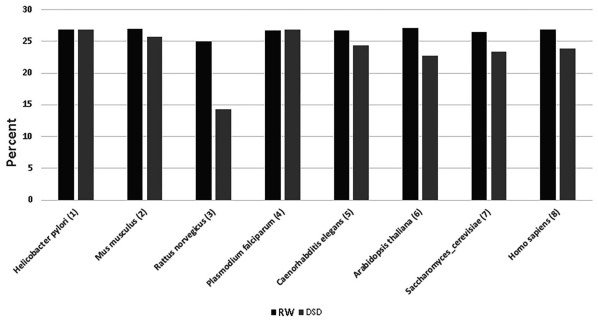

Fig. 4. Evaluation of organisms. The number in brackets represents the organism code, (x): x is the organism code.

between them. The comparisons show the Lyapunov exponent at a higher percentage in networks with high stability.

4.3.2. Evaluation of order. The interaction data of proteins are presented in different orders in each database. The next question is whether the response of Lyapunov exponents depends on the node order of real networks. We expect to answer this question and also to observe how different node orders affect the Lyapunov exponents' response to the real network's response.

We explore its effect using eight protein interaction networks from different organisms. Then, for each real network G, we change the node order by using the previously defined node centrality algorithms (see Section 3.6) to create a node reordered real network G^r. We use the $Le(G^r)$ measure to evaluate the response of Lyapunov exponent on the target reordered real network. Figure 5 illustrates the comparison results of original and reordered real networks. Appendix (Table A2) contains detailed results.

It is seen that the RW and DSD distributions of real networks yields similar Lyapunov exponent responses under different node orders. In all experiments, the node order parameter has effect on the Lyapunov exponent response but the effect is not significant. For each network model, both RW and DSD distributions are affected by the node order. The Lyapunov exponent results obtained by order using OCC, OBC, OLC, OCLC and ORA are almost identical to the predefined order Lyapunov exponent results. The changes with these orders are near zero. The ODC order has insignificant influence on the Lyapunov exponent. Unlike synthetic networks, the effect of ODC order is minor. The random node order ORA is produced in 10 replicates and there is no difference between the results.

In conclusion, our experimental results show that the node order has an insignificant effect on the Lyapunov exponents of target real network. There is always a possibility that a different sorting type may distort the significance of the Lyapunov exponent results. The nodes can be randomly arranged to avoid the possibility that the target network has an order that will affect the Lyapunov exponent calculation.

5. Conclusions

Inspired by the reported works that put theoretical and experimental evidence for the existence of the Lyapunov exponent success in nature data, we have investigated Lyapunov exponents for network analysis. In this study, we present the effect of network topology and mutations on Lyapunov exponents and its relationship with network stability. This is the first study in which the Lyapunov exponents are used for network analysis and have been evaluated under topological mutations. With the purpose of demonstrating the effect of topological mutations on both real and synthetic networks, first we define the methodology to convert the network data into signal data and obtain the Lyapunov exponents with our Lyapunov exponent based coefficient LEC for a variety of networks. Then, we evaluate the relationship between Lyapunov exponents and stability of the network by measuring the stability and Lyapunov exponent response of each network.

Our experiments demonstrated that our technique LEC can be applied to all types of network topologies. Network topologies and mutations have a significant influence on the Lyapunov exponents of the network. Lyapunov exponents have a correlation with network stability and both are correlatively affected by the network model. The stability of a network can be measured by Lyapunov exponents. Experimental results have shown the potential of Lyapunov exponents to be used for the detection of network stability. Thanks to the LEC method we developed, the stability of the networks can be determined more quickly by saving time and processing power. For the resource diversity and size of biological networks, the speed of network analysis is of high importance. Additionally, results are a striking indication that the Lyapunov exponent is a potential candidate measure for network analysis. These observations can initiate subsequent novel studies for future researches on network analysis.

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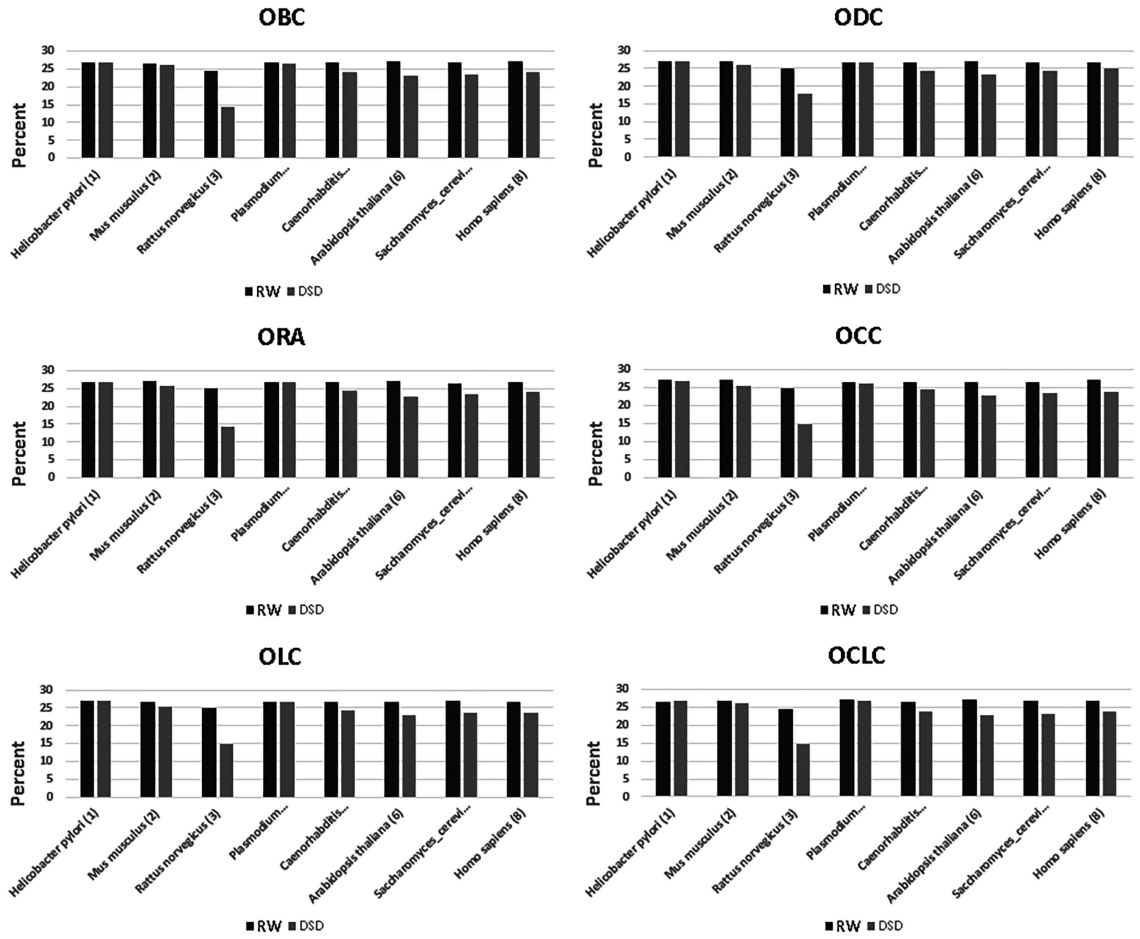

Fig. 5. Evaluation of node order on real networks. The number in brackets represents the organism code, (x): x is the organism code.

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Appendix

Table A1.

Organism	RW	DSD
Helicobacter pylori (1)	26,86	26,90
Mus musculus (2)	26,92	25,78
Rattus norvegicus (3)	24,94	14,35
Plasmodium falciparum (4)	26,77	26,84
Caenorhabditis elegans (5)	26,72	24,37
Arabidopsis thaliana (6)	27,11	22,73
Saccharomyces_cerevisiae (7)	26,51	23,38
Homo sapiens (8)	26,83	23,93

Table A2.

Organism	obc		odc		ora		occ		olc		oclc	
	RW	DSD	RW	DSD	RW	DSD	RW	DSD	RW	DSD	RW	DSD
Helicobacter pylori (1)	26,99	26,97	26,86	26,90	26,86	26,90	27,11	26,87	26,92	27,11	26,32	26,96
Mus musculus (2)	26,59	26,07	26,92	26,05	26,92	25,78	27,11	25,67	26,65	25,27	26,76	26,18
Rattus norvegicus (3)	24,63	14,21	24,94	17,87	24,94	14,35	24,79	14,88	24,93	14,73	24,62	14,62
Plasmodium falciparum (4)	26,80	26,56	26,77	26,84	26,77	26,84	26,59	26,37	26,78	26,65	27,11	26,78
Caenorhabditis elegans (5)	26,69	23,98	26,72	24,37	26,72	24,37	26,54	24,61	26,63	24,17	26,48	23,84
Arabidopsis thaliana (6)	27,28	23,09	27,11	23,28	27,11	22,73	26,57	22,97	26,79	22,96	27,11	22,64
Saccharomyces_cerevisiae (7)	26,77	23,59	26,51	24,19	26,51	23,38	26,61	23,65	26,92	23,68	26,77	23,28
Homo sapiens (8)	27,27	24,09	26,83	25,02	26,83	23,93	27,11	23,76	26,71	23,79	26,87	23,84

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