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ORIGINAL ARTICLE

A study of the Immune Epitope Database for some fungi species using network topological indices

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Abstract In the last years, the encryption of system structure information with different network topological indices has been a very active field of research. In the present study, we assembled for the first time a complex network using data obtained from the Immune Epitope Database for fungi species, and we then considered the general topology, the node degree distribution, and the local structure of this network. We also calculated eight node centrality measures for the observed network and compared it with three theoretical models. In view of the results obtained, we may expect that the present approach can become a valuable tool to explore the complexity of this database, as well as for the storage, manipulation, comparison, and retrieval of information contained therein.

Keywords Network theory · Topological indices · B-cells epitopes

Introduction

Fungi are ubiquitous in the environment. There are approximate 1.5 million different species, but only about 300 are known to cause disease in humans. Infections caused by these organisms have increased dramatically during the past decades, mainly concomitant with other diseases (e.g., AIDS, diabetes) or caused by treatment with chemotherapeutics, corticosteroids, or tumor necrosis factor inhibitors [1].

On the other hand, as expressed by González-Díaz et al. [2], the number of systems that can be represented and studied with network theory in nature is so vast that many authors regard this theory as a science [3]. A network is a real system in which the vertices correspond to parts of the real entity that is intended to represent and the edges to the relationships of different nature that are established between them [4]. One can numerically describe a network by what are known as topological indices (TIs) [5–8]. These parameters have the advantage of having a straightforward theoretical base, which can be understood by scientists non-expert on computational techniques, and being not time-consuming in terms of computational resources [9]. Consequently, over time, the use of this type of indices has been extended to the encoding of information contained in complex networks of very diverse fields [10–15].

The body of the Immune Epitope Database (IEDB; www.iedb.org) has considerably increased in the last few years, providing a wealth of data potentially useful for basic and clinical applications [16]. Given the complexity of this database, a complex network approach may be applied to analyze the huge amount of information contained

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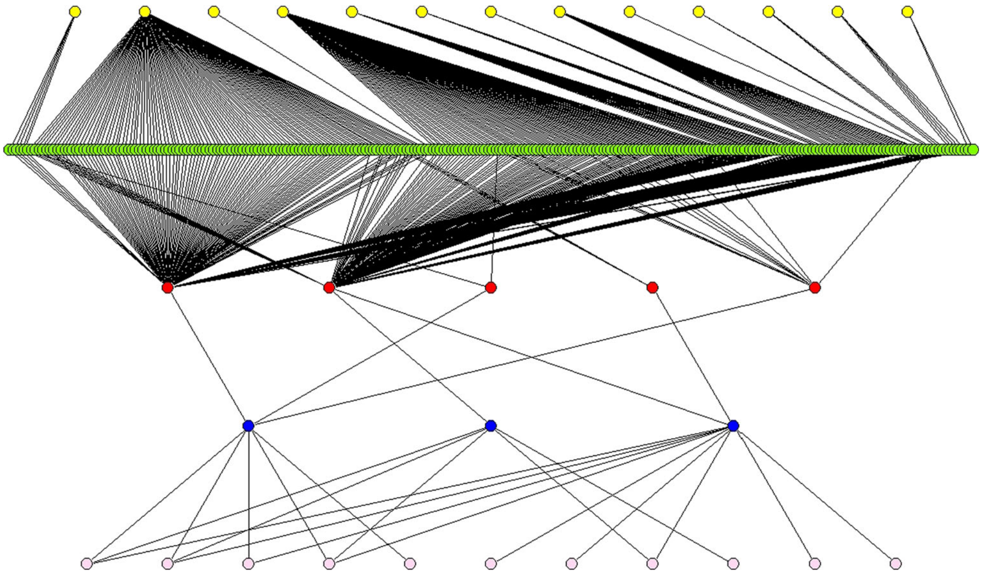


Fig. 1 Observed network for data obtained from the Immune Epitope Database for fungi species. Source organisms (*yellow*), peptide sequences (*green*), immunological processes (*red*), host organisms (*blue*), and experimental techniques (*pink*).The network is 5th-partite in such a way that nodes of a given class are connected with nodes of other classes, but nodes of the same class are never connected to each other. Thus, the information encoded by a link depends on the classes of the two nodes interconnected. For example, if one node belongs to the class host organism and the other to the class experimental technique, this link indicates the technique by which *i*th molecule was determined to be an immune epitope for the corresponding host organism. (Color figure online)

therein. Moreover, understanding the topology of a network may give direct insight into various network characteristics [17–20].

In the present study, we proposed the application of a topological network approach for the analysis of information obtained from the IEDB on fungi species. For it, we defined and built for the first time a complex network based on data obtained from the IEDB for some of such organisms, and we then considered the general topology, the node degree distribution and the local structure of this network. We also calculated eight node centrality measurements for the observed network and compared it with three theoretical models.

Results and discussion

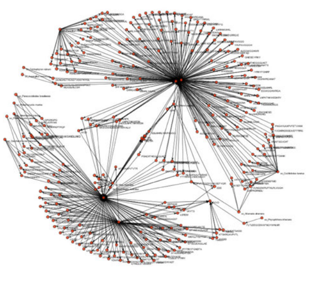
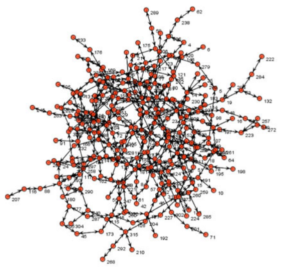
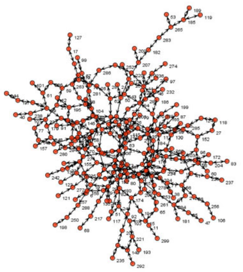
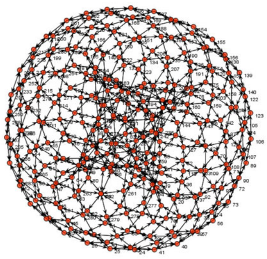
In the present study, we assembled for the first time a complex network using data obtained from the IEDB on fungi species. The observed network contained a total of 292 nodes (13 source organisms, 260 peptide sequences, 5 immunological processes, 3 host organisms, and 11 experimental techniques) interconnected by 559 directed edges (Fig. 1).

The names and codes for all nodes are listed in Table S1 of the Supplementary material. We provide the top 10 values for each of the node centrality measures calculated in this work in Table S2 of the Supplementary material. The node degree distributions, based on the Kolmogorov–Smirnov and the Chi-Square tests, did not fit any previously studied distribution (Table S3, Supplementary material). The three types of generated random networks showed some remarkable properties. For example, the Erdös–Rényi network (ERN) and Eppstein Power Law network (EPLN) presented a similar average degree (*Ad*), although relatively lower than that showed by 2D-lattice network (2D-L). The graphical representation and numerical comparison of the observed and random networks are shown in Table 1.

An interesting review on the applications of networks' TIs for the study of small molecules, macromolecules, and other networks may be read in González-Díaz et al. [7]. The general topologies of the corresponding ideal theoretical networks with respect to that of the real network in terms of the relative difference percentage (RD%) are given in Table 2.

The lower differences for different features were 2D-L and ERN for number of nodes (n) (RD% 1.0 and 1.4%, respectively), and EPLN for number of edges (m) (RD% = −4.5%). The absolute values means of RD%s for EPLN, ERN, and 2D-L were 56.4, 60.2, and 81.4%, respectively. Therefore, the observed network does not match with any of ideal behaviors studied here. We show the triadic census analysis results (local structure) for the complex network constructed in this work in Table 3. The most triads were null triads (type 1-003), which coincide with the behavior of complex social networks where this type of triads accounts for more than 50% of the total [21]. The 5-021U and 4-021D triads had values higher than the expected ones; however,

Table 1 Comparison of observed versus random networks

Observed network	Value	TIs[a]	Value	Erdös–Rényi network
	292	*n*	288	
	559	*m*	744	
	0.007	*d*	0.009	
	3.829	*Ad*	5.167	
	55568	*M1*	9680	
	115228	*M2*	30912	
	55.171	*Xr*	134.036	
	54450	*F*	8192	
Eppstein Power Law network	**Value**	**TIs**	**Value**	**2D-Lattice network**
	247	*n*	289	
	584	*m*	1156	
	0.01	*d*	0.014	
	4.729	*Ad*	8	
	7104	*M1*	18496	
	21072	*M2*	73984	
	114.22	*Xr*	144.5	
	5936	*F*	16184	

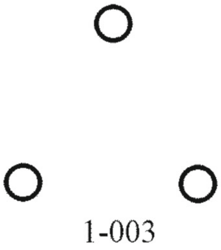
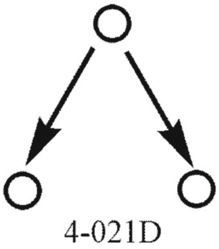
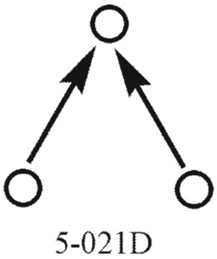
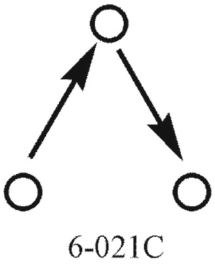
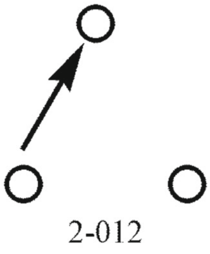
[a] The TIs used are number of nodes (*n*), the total adjacency index or the number of edges (*m*), the density (*d*), the average degree (*Ad*), the Zagreb group index 1 (*M1*), the Zagreb group index 2 (*M2*), the Randic connectivity index (*Xr*), and the Platt index (*F*)

Table 2 Summary of the comparative study of the observed versus random networks

Parameters[a]	ERN	EPLN	2D-L
n	1.4	15.4	1.0
m	−33.1	−4.5	−106.8
d	−28.6	−42.9	−100.0
Ad	−34.9	−23.5	−108.9
$M1$	82.6	87.2	66.7
$M2$	73.2	81.7	35.8
Xr	−142.9	−107.0	−161.9
F	85.0	89.1	70.3

[a] The TIs used are: number of nodes (*n*), the total adjacency index or the number of edges (*m*), the density (*d*), the average degree (*Ad*), the Zagreb group index 1 (*M1*), the Zagreb group index 2 (*M2*), the Randic connectivity index (*Xr*), and the Platt index (*F*). The results are expressed as relative difference percentage, defined as RD% = (TIreal − TIideal) * 100/TIreal. ERN, EPLN, and 2D-L means Erdös–Rényi network, Eppstein Power Law network, and 2D-lattice network, respectively

Table 3 Triadic census analysis of the real network

Triad representation	Triad type	Number of triads (ni)	Expected (ei)	(ni—ei)/ei	Triad details and examples [a]
	1 - 003	3972095	3947512.89	0.00	Null triad, e.g., isolated nodes of one source organism, one epitope, and one immunological process totally unrelated
	4 - 021D	9618	519.34	17.52	Divergent triad, e.g., one peptide that is epitope in two different immunological processes
	5 - 021U	16910	519.34	31.56	Convergent triad, e.g., two peptides that are epitopes in the same immunological process
	6 - 021C	697	1038.68	–0.33	Transitivity triad; e.g., one peptide isolate from one source organism that is epitope in one specific immunological process
	2 - 012	107660	156847.38	–0.31	Not transitive triad, e.g., the peptide isolated from the source organism is not epitope for this specific immunological process

[a] Please, take into consideration the existence of only the following hierarchy relationships (and not others) inside the network source organisms => peptide sequences => immunological processes => host organisms => experimental techniques (see Fig. 1) In consequence, all other triads do not appear due to the asymmetrical nature of the network

the 6-021C and 2-012 triads presented a number lower than the expected value (see Table 3 for triad details and examples).

Using graphical approaches, one can obtain easily an intuitive image that provides useful information about the complex biological system under study. Consequently, different approaches of this type have been fruitfully applied to a broad spectrum of biological topics, such as enzyme-catalyzed systems [22–25], protein folding kinetics [26], analysis of codon usage [27,28], HIV-1 reverse transcriptase inhibition mechanisms [29,30], base frequencies in the anti-sense strands [31], analysis of DNA sequence [32], and the parasite *Fasciola hepatica* [33]. In the field of mycology, a network approach can be used to identify drugs with similar mechanism of action [34] or predict the antifungal activity of drugs against different species [35,36]. On the other hand, the study of protein–protein interaction networks in this type of organisms may be a key tool in understanding the basic principles that govern their biological processes [37–40].

Conclusions

We have demonstrated that TIs are promising indices of general use at different structural organization levels. In particular, we have confirmed that it is possible to use these parameters in the study of data obtained from IEDB for fungi species. Consequently, we may expect that the present approach can become a valuable tool to explore the complexity of this database, as well as for the storage, manipulation, comparison, and retrieval of information contained therein. On the other hand, this relatively simple approach may be very useful for mycological research. For example, it could provide a fast way to carry out a preliminary evaluation that allow us to make a decision on the best experimental conditions to determine whether the molecules being studied are immune epitopes or not, by detecting groups of nodes highly connected among each other. Thus, this methodology could help us to somewhat rationalize this process and reducing costs in terms of material resources and time. In addition, the present study could be the seed for further development of new software programs, webs-serves, and/or theoretical methods for handling structure-function information and data mining in this field in the near future.

Experimental

Using Microsoft Excel, we constructed a network from data obtained from the database utilized by González-Díaz et al. [41] and Vázquez-Prieto et al. [42]. Once the network is constructed, the *.mat file was uploaded in CentiBin [43] and the program tools were used to prepare the network for the calculation of eight node centralities directed: in-Degree, out-Degree, Eigenvector, Hubbel Index, Bargaining, PageRank, HITS-Authority, and HITS-Hubs. We then generated random networks by using three different algorithms: the Erdös–Rényi network (ERN), the Eppstein Power Law network (EPLN), and the 2D-Lattice network (2D-L). The networks were generated with a number of nodes and edges as close as possible to the observed network. Pajek software [44] was used to calculate several global measures of network structure for both observed and random networks, including number of nodes (n) and edges (m), density (d), average degree (Ad), Zagreb group index 1 ($M1$), Zagreb group index 2 ($M2$), Randic connectivity index (Xr), and Platt index (F). We used these parameters to compare the topology of the observed network with random networks in terms of the relative difference percentage, defined as RD% = (TIreal-TIideal) * 100 / TIreal. We also performed a triadic census analysis using Pajek software. Finally, all node in- and out-degrees were used as input in STATISTICA 6.0 software package [45] in order to study the distribution of the observed network and compare it with other ideal network distributions, including Normal, Exponential, Poisson and Chi-Square.

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