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Review

COMPLEX NETWORKS FUTURING CHEMICAL MEDICINE

***Corina Seiman, Bianca Bîlc, and Mihai V. Putz* (♣)**
West University of Timișoara, Faculty of Chemistry, Biology, Geography, Biology-Chemistry Department

ABSTRACT

Networks can be interconnected via different types of links between a set of nodes, forming multiplex networks. The main challenge for these networks is represented by the mechanisms of control. Control can be applied in a rigid manner, a mathematical one, considering the input data and the output. Complex networks can be confronted with errors of function, but many of them show a certain degree of tolerance against errors. Theory of networks helps us understand a large variety of aspects, e.g. the most complex biological processes which allow to understand the mechanisms of diseases and to elaborate novel therapy strategies, up to the supreme concept of personalized medicine.

Keywords: multiplex networks, nodes, metabolic networks

1. INTRODUCTION

Scientific community is challenged in recent years with an increasing amount of research data in all domains. In certain situations, essential information is difficult to be quantified and, sometimes, to be controlled. Thus, a new concept has emerged, respectively that off topic networks that could explain conceptual relationships [1].

Networks can be interconnected via different types of links between a set of nodes, forming multiplex networks which comprise a very high number of complex social, biological and transportation networks [2,3].

The main challenge for these networks is represented by the mechanisms of control. Control can be applied in a rigid manner, a mathematical one, considering the input data and the output, measuring the feedback as an expression of the obtained and the desired output

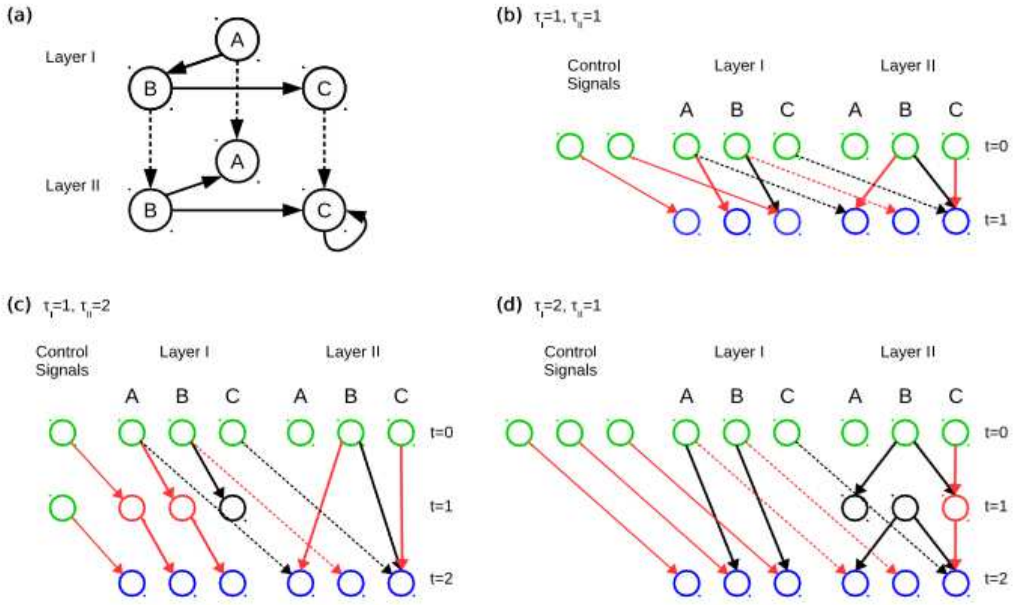
♣ Correspondent author: Tel: 0256-592-638, Fax: 0256-592-620, E-mail: mihai.putz@e-uvt.ro

[4]. A complex network is comprised of series of subsystems, but, interestingly, each subsystem has its own dynamics, but in most often situations, in between subsystems, their dynamics operate among a comparable time scale. The third essential feature regarding complex networks is that an external controller describes only a single direct interaction with only one subsystem [4]. In their work, Posfai et al. (2016), studied the controllability of coupled complex dynamical systems [5].

MULTIPLEX NETWORKS

For multiplex and multi-time-scale networks, there is necessary to find the minimum number of inputs N_i and to extend the definition of the dynamic graph. The authors established that it is possible to obtain full control in the case of one-to-one coupling between layer I and II with at most N independent inputs, normalizing N_i by N (e.g., $n_i = N_i/N$). The process of studying multiplex networks revealed that there is always the possibility not to consider nontrivial phenomena, conducting to the idea that without understanding and describing every effect, it will be quite impossible to describe a system in its entire features. Same authors established that dense networks characterized by homogeneous degree of distribution require less input data [5].

Figure 1: Mechanisms of control in case of a two-layer multiplex network (adapted from Posfai et al. 2016 [5])



In Fig. 1 (adapted from Posfai et al. 2016) we describe the function of control in the case of multiplex networks. (a) shows the representation of a two-layer network. (b) – (d) illustrates the evolution of the system from t_0= 0 to t_1 = max(τ_I, τ_{II}). There is an efficient control of the system if all nodes at t_1 (blue) are connected to nodes at t_0 or to nodes that are considered control signals (green) going through disjoint paths (red). (c) analyses the possibility in which layer I is faster than layer II(τ_I =1, τ_{II} =2), the number of inputs is reduced N_i = 1. (d) layer II is faster than layer I, requiring longer control pathways, N_i = 3 [5].

To have a successful controlling process, knowing its position in the state space is necessary. This can be accomplished if the state of each component is assessed separately. "A system is said to be observable if it is possible to recover the state of the whole system from the measured inputs and outputs" [4].

Following factors and their inter-relations compose de observability problem: the outputs $\mathbf{y}(t)$, the state vector $\mathbf{x}(t)$, the inputs $\mathbf{u}(t)$. They determine the initial state of the system $\mathbf{x}(0)$. If one of these factors cannot be determined, than the controller has not the possibility to play its role interfering in the feedback response. To establish if a variable provides full observability of small dynamical systems, a graphical approach (GA) can be used. This tool is essential in the case of large network systems because it translates observability to a characteristic of the static graph of the inference diagram with large applicability in chemistry, biology, biochemistry, ecology. To notice that for linear systems, full observability is not accomplished using the minimum sensor set predicted by the graphical approach [6].

Real networks are characterized by growth and preferential attachment. In a network, the elements of the system are vertices, and the edges are represented by the interactions between the vertices. Large networks (e.g., human body, the World Wide Web, etc.) consist of a complex topology. They can be assessed using the random graph theory of Erdös and Rényi (ER), a method that is not always feasible in real world because of lack of data in extremely large networks. These kinds of networks can organize themselves into a scale-free state because they fail to incorporate growth and preferential attachment. But, when these two are present, they are responsible for the power-law scaling met in networks in real life. The scale-invariant state represents a general feature of a large variety of complex networks, with large applicability in science [6,7].

2. MODELING INTERMEZZO

In the random graph ER model [8], one starts with N vertices, connecting each pair of nodes with the probability p. In this model, the probability that a vertex has k edges is described by Poisson's distribution equation $P(k)=e^{-\lambda}\lambda^{k}/k!$ [7].

$$\lambda = N\binom{N-1}{k}p^{k}(1-p)^{N-1-k}$$

Complex networks, in actual terms, can be classified as follows [9]:

- **Small worlds**: despite of the large size of a specific network, there are quite short pathways between two specific vertices (e.g., chemicals in a cell are commonly separated by three reactions);
- **Clustering**: in a community, there are circles of friends, where everyone knows everyone; the clustering coefficient quantifies the tendency of clustering;
- **Degree distribution**: expresses the fact that in a network, not all nodes have the same number of edges.

The Watts and Strogatz model [10] uses N vertices placed on a one-dimensional lattice. Connections are as follows: each vertex is connected to the two nearest vertices and next-nearest neighbors. Each edge is connected with a p probability to a randomly chosen vertex.

In this way, distances between vertices suffer a reduction process, being an example of small-world network. [11,12].

3. APPLICATIONS

One of the most important application of small-world type of networks is the human brain, because of following reasons [13]:

- Complexity of brain is translated into space and temporal connections;
- Brain can be drawn as a typical small-world topology: it is composed by both high-clustering modular processes, and short path length integrated processes;
- Brain has a typical behavior: it is cost-effective.

In their study, Felleman and Van Essen [14] have put together a connectivity matrix at the level of visual cortex of macaque monkey, comprising 305 axonal connections between 32 areas in the visual cortex. Experimental data have appeared after studying the visual cortex network in macaque monkeys and cortical networks in cats, after injecting each separately with uncorrelated noise in a computational model. This model proved to be dynamic and unweighted and undirected graphs were elaborated. The results demonstrated that brain, generally, acts as a small-world network with following characteristics: high complexity, dense local clusters of connections, sparse interconnections between clusters, abundance of reciprocal connections and cycles, minimal wiring, and global and local efficiency [15-17].

Efficiency of informational transfer in regular and complex networks [15]. Immediat applicability of these principles would be in understanding the behavior of neurodegenerative cognitive diseases, such as Alzheimer's. In this particular condition, analyzing the cortical network using electroencephalography, it was established that the cognitive decline is associated with an increased path length and/or reduced global effectiveness [18].

A KEY ROLE IN BIO-MEDICAL SCIENCES

The hierarchically organized networks of the brain are in their majority developed in early period of intrauterine life, but its definitive organization takes place in childhood and adolescence. Further research has to clarify the proportion in which genetic factors and environmental ones determine functional connectivity of the brain throughout adolescence. Resting-state networks showed a decrease with age of the degree of functional connections between them, while it increases within them with age. In the usual, default state of brain network, functional connectivity is stronger in girls. The study of Teeuw et al. (2019) showed that up to 53% heritability explains the variation in functional connectivity within and between resting-state networks, and environmental factors explained up to 33% of this variation [19].

Complex networks can be confronted with errors of function, but many of them show a certain degree of tolerance against errors, namely inhomogeneously wired networks identified as scale-free networks (e.g., the Internet, the World-Wide Web, social networks, cells). Their nodes communicate despite a high rate of failures [20].

The main disadvantage of this kind of networks is that they are in a quite increased rate vulnerable to attacks when one or more nodes can be removed leading to loss of connectivity.

Complex networks can be classified in two types, according to their connectivity distribution $P(k)$, determining the probability that a certain node of the network is connected

to other *k* nodes: i) quite homogenous networks, where each node has approximately the same number of links, $k = \langle k \rangle$; the most known are the random graph model of Erdös and Rényi, as well as the small-world model of Watts and Strogatz; ii) inhomogeneous networks (scale-free), where $P(k)$ ranks as power-law, free of a characteristic scale.

In their work, Albert et al. (2000), the authors conclude that scale-free networks are highly tolerant to random failures, explaining why large complex networks won't completely shut down when some connections don't work properly or at all [20].

Network theories have large applicability in real-life systems. Proteins play key-roles in *in vivo* systems: catalysts, signaling molecules, or structural molecules. Random mutations in microorganisms doesn't lead to a total change of the topology of the proteins' network. But, when most of the connected proteins are erased using different computational techniques, a rapid increase of the network diameter is observed. Proteins that express a large number of connections playing a central role in the construction of the network are essential in contrast to proteins that have only few connections to other proteins in the network. This fact allows to conclude that proteins, beyond their biochemical role, express various degrees of robustness against mutations based on the topology of the network, on the interactions between the components [21].

Yeast proteins express the tendency to high degree networks [22]. In humans, in tissues affected by cancer, up-regulated genes are highly connected and central, being essential for chaotic and increased cell proliferation, and expressing topological features of essential genes [23,24].

In another work, a study upon 346 genes with cancer development determinism in humans showed that comprising proteins were implied in interactions with at list double of protein partners than non-cancer proteins [25].

Also, it was established that mutated genes that determine certain diseases are coexpressed in specific tisuues, their proteins of synthesis interact among them, and express functions according to the Gene Ontology hierarchy [26].

The aspect of interoperability between networks plays a key role in bio-medical sciences. Intracellular networks are translated in graph models for better integration of genomics, structural biology and imaging. In this manner, especially qualitative data of cellular regulation is considered, but established models are reliable and can predict outcomes in terms of disease development and therapy and also can identify new disease biomarkers and novel drug targets [27,28]. Such a multi-layer network is shown in Fig. 2.

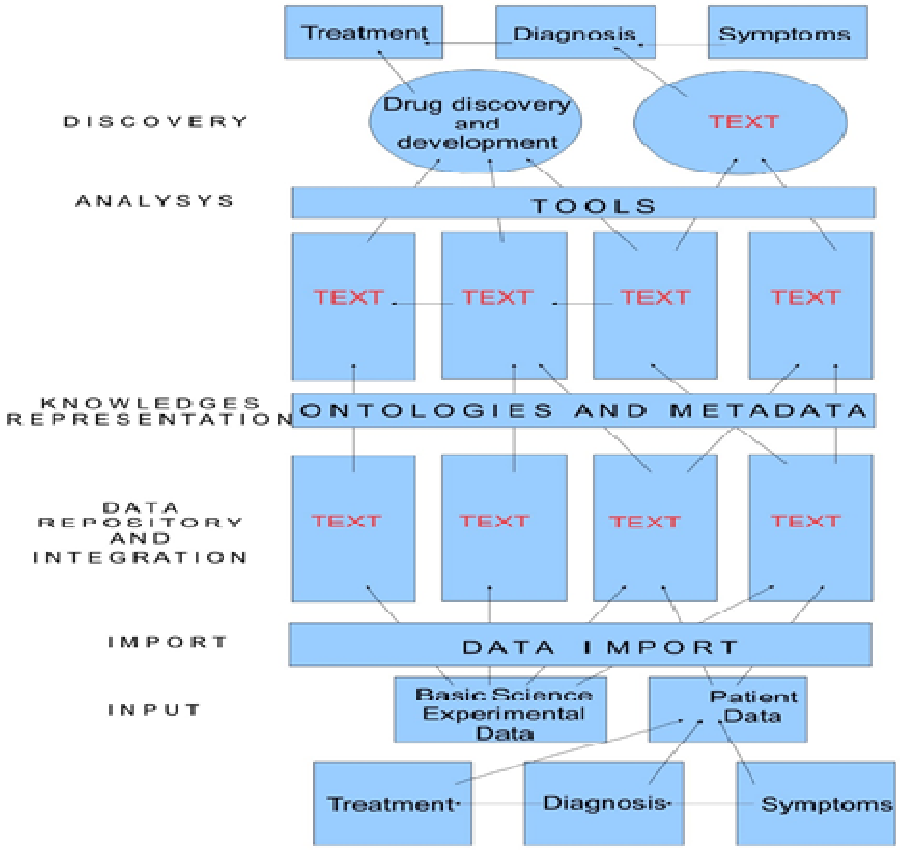
It is clear that living systems are complex networks and there is a huge amount of information deriving from cellular activity. The approach to understand this big small world has to provide comprehensive abstractions, algorithms and analytical techniques. The main problems to be answered are [29]:

- Rebuilding and inference of cellular complex networks;
- Identifying of common patterns in cellular networks and building blocks of cellular pathways;
- Identifying metabolic pathways which define cellular pathways, both in healthy cells and in diseased cells.

Further, protein-protein interactions define a number of physical combinations of them, but only a subset of proteins interacts in a particular cell or tissue [30]. After examining 31 human tissues quantifying the whole genome expression, there were identified a number of 2374 genes that are ubiquitously expressed being named "housekeeping" genes. An important

role in cellular metabolism and life cycle is given by tissue-specific proteins, with fewer physical interactions [31,32].

Figure 2. Schematic representation of the multi-layer aspect of networks



Tissue-specific proteins form sub-networks reported to "housekeeping" genes, being more 2 fragmented, but of much more importance for biological processes [33]. In Table 1 is summarized the quantification of tissue-specific proteins in human tissues [34].

Table 1. Tissue-specific proteins organized as networks in human tissue [34]

Tissue/Cell	Number of proteins	Percent of proteins(%)	Number of interactions	Percent of interactions(%)
Fetal Heart	12,368	91.55	101,864	58.93
Fetal Liver	12,055	89.24	92,323	53.41
Fetal Gut	12,522	92.69	108,548	62.80
Fetal Ovary	12,096	89.54	93,672	54.19
Fetal Testis	12,365	91.53	104,401	60.40

Table 1. Tissue-specific proteins organized as networks in human tissue [34]

Tissue/Cell	Number of proteins	Percent of proteins(%)	Number of interactions	Percent of interactions(%)
Fetal Brain	11,972	88.62	86,524	50.06
Adult Frontal Cortex	12,374	91.60	101,715	58.85
Adult Spinal Cord	12,081	89.43	92,704	53.63
Adult Retina	12,506	92.58	108,809	62.95
Adult Heart	12,151	89.95	93,794	54.26
Adult Liver	12,391	91.72	104,517	60.47
Adult Ovary	11,962	88.55	86,563	50.08
Adult Testis	12,376	91.61	101,865	58.93
Adult Lung	12,106	89.61	92,324	53.41
Adult Adrenal	12,506	92.58	108,549	62.80
Adult Gallbladder	12,157	89.99	93,673	54.19
Adult Pancreas	12,389	91.71	104,402	60.40
Adult Kidney	11,965	88.57	86,525	50.06
Adult Esophagus	12,361	91.50	101,716	58.85
Adult Colon	12,112	89.66	92,705	53.63
Adult Rectum	12,551	92.91	108,810	62.95
Adult Urinary Bladder	12,138	89.85	93,795	54.26
Adult Prostate	12,381	91.65	104,518	60.47
Placenta	11,894	88.05	86,564	50.08
B Cells	12,396	91.76	101,865	58.93
CD4 Cells	12,109	89.64	92,325	53.41
CD8 Cells	12,534	92.78	108,550	62.80
NK Cells	12,162	90.03	93,674	54.19
Monocytes	12,379	91.64	104,403	60.40
Platelets	11,931	88.32	86,525	50.06
Static network	13,509	100	172,848	100

PREDICTION MODELS

The World-Wide Web still remains a complex network with a low rate of control. Growth is irregular and non-linear. Documents and links are dynamic. This is why in this particular case it is impossible to catalogue all the nodes and edges. The World-Wide Web is subjected to the principle of power-law, documents with increased number of links and connections have a very significant high probability to be found, in relation with extremely well connected pages. Distribution of links is of scale-free nature. So, the understanding of development of web implies other models than the random graph models [35]. World-Wide Web (W^3) as a complex network can be defined through its "obvious" characteristics: ubiquity, interactivity, it is a hyperlinked but decentralized structure, with a multimedia format [36].

In vivo cells can be imagined as a complex network similarly to the web. Modern research has to be focused on understanding the intercellular interactions which determine the structure and function of a living tissue. This is the key for further development of drug design techniques and for personalized therapies in the large panel of diseases. Main interactions are protein-protein interactions, metabolic, signaling and transcription-regulatory interactions and networks [37]. Directed networks are those where the interaction between any two nodes has a very well established direction, while in undirected networks there is no established direction of the links.

In a recent paper, the authors had a new approach to build a directed network, starting from multivariate time series, on the principle of information theoretic reduction of linear auto-regressive models. The method comprises three distinctive steps: 1) each time series is a basic and distinct node; 2) models of multivariate reduced auto-regressive type are built; 3) direct links connect the nodes. Using this model, it is possible to analyze and to predict meteorological data, and, in medicine, it reconstructs and explains the electroencephalographic data, obtaining less links than traditional methods, excluding thus the redundant links [38].

To predict links means to consider those missing links, but also to assess new links in a complex network. There are three major link prediction metrics: 1) neighbor based; 2) path based; 3) pattern based [39].

These previous algorithms generally address to undirected networks. Table 2 shows acknowledged link prediction models.

Table 2. Acknowledged link prediction models [39]

Adamic -Adar (AA)	$AA(u,v) = \frac{\sum \omega \in \Gamma(u) \cap \Gamma(v)\mathbf{1}}{\log(k_w)}$
Common Neighbors	$CN(u,v) = \lvert \Gamma(u) \cap \Gamma(v) \rvert$
Hup Depresed Index (HD)	$HD(u,v) = (\square \lvert \Gamma(u) \cap \frac{\Gamma(v) \lvert \square)}{\max(k_u, k_v)}$
Hup Promoted Index	$HP(u,v) = (\square \lvert \Gamma(u) \cap \frac{\Gamma(v) \lvert \square)}{\min(k_u, k_v)}$
Jaccard's Coefficient (JC)	$JC(u,v) = (\square \lvert \Gamma(u) \cap \frac{\Gamma(v) \lvert \square)}{(\square \lvert \Gamma(u)} \cup \Gamma(v) \lvert \square)$

Table 2. Acknowledged link prediction models [39]

Leicht – Holme – Newman Index (LHN)	$LHN(u,v) = (\square \mid \Gamma(u) \cap \frac{\Gamma(v) \square}{k_u \times k_v}$
Resource Allocation Index (RA)	$RA(u,v) = \frac{\sum \omega \in \Gamma(u) \cap \Gamma(v) 1}{k_w}$
Salton Index (SA)	$SA(u,v) = (\square \mid \Gamma(u) \cap \frac{\Gamma(v) \square}{\sqrt{k_u \times k_v}}$
Sørensen Index (SO)	$SO\ (u,v) = (2 \mid \Gamma(u) \cap \frac{\Gamma(v) \square}{k_u + k_v}$

Starting from the Triadic Closeness (TC) (a metric based on frequency of sub-graphs in the network), a new extended metric based network was created and called TCX. The evaluation of TCX metric effectiveness was measured comparing it to TC metrics, TCX metrics obtaining the highest link prediction performance [39].

The well known *h* index used to measure academic performance of scientists has found its applicability in optimizing networks' functionality because it raises no difficulties in its calculation, it is not based on the global network information and it is difficult to be manipulated. So, in a network, "the *n*-order *h*-index of a node is defined to be the maximum value *h* such that there exists at least h neighbors whose (n−1)-order *h*-index is no less than *h*, where $n \geq 1$" [40,41].

METABOLIC NETWORKS

Scale-free networks are common in living cells, such as genetic regulatory networks, where the nodes are the genes themselves, and links are represented by the expression correlations or by the protein domain interactions. It is interesting that transcription regulatory networks may be also mixed scale-free and exponential. So, most transcription factors regulate only a few genes, and a few general transcription factors show interactions with a lot of genes. Despite the fact that the scale-free networks have a power law distribution degree, all cellular networks present hubs (nodes with the largest number of links) as a general characteristic. These features can be reduced to two basic mechanisms: growth and preferential attachment. A complete characterization of cellular networks implies to specify the intensity or strength of an interaction, as well as the time frame interactions evolve. Modules are groups of molecules with common features, like physical and/or functional properties. Protein-protein or protein-RNA are complex physical modules that determine specific biological functions, like nucleic acid synthesis or protein degradation. Motifs are elementary units of cellular networks [37,42].

Metabolic networks are of free-scale type, with some highly connected nodes that are implied in a large number of metabolic reactions. These hubs have a large number of links and they have the ability to join all the substrates into a single web where no fully separated modules can be found. There is an apparent non-concordance within metabolic networks. Calculations have demonstrated a high size-independent clustering coefficient (pleading for modularity), while the power law degree distribution of metabolic networks is in favor of the scale-free model, consistently excluding a modular topology. The problem can be solved

creating a hierarchical network, reconciling within a single framework all the characteristics of a metabolic network [43,44].

As mentioned above, random networks have been characterized using the Erdös and Rényi (ER) model, where the network is reduced to a set of nodes connected pairwise with equal probability. Watts and Strogatz stated that an important issue to define a network is to describe the local clustering aspect. In both models, the probability $P(k)$ for a node to be connected to other k nodes is bounded, decaying exponentially for high values of k. Free-scale networks are based on two mechanisms that are determinant for the final topology: i) new nodes are added in order to develop a network, in order to connect to pre-existent nodes; ii) a new node will link with high probability to a node with a large number of connections. An extended network model presumes the addition of new nodes, new links, and the rewiring of links. Universality is a concept that declares that in a complex network exponents are in no relation to microscopic aspects of the model. In scale-free networks, universality does not exist because scaling exponents are in a continuous dependence to the networks' parameters [45].

At a first look, functional networks are needed in real life. But, there are situations when one would prefer a broken, not functional network. This would be the case of pathogen agents, where effective treatment of the infection means to interfere and to break the molecular network of the causing microorganism. This process is based on identifying in the network sets of nodes defined as influencers. One would prefer to remove hubs, more easier to be located. To identify those sets of nodes that, through their deletion would produce the most destruction is a problem of non-deterministic polynomial-time hard type. For this, it is necessary to identify the sets of nodes with lowest energy. Further, it is necessary to define the collective influence, which is the product of the node's reduced degree (the number of its links minus one) and the sum of the reduced degrees of the nodes. The algorithm derived from the collective influence principle removes successively those nodes with the highest collective influence, at each cycle being calculated for the remaining nodes those sets with the highest collective influence. This method is feasible because a well defined and constant part of the network is removed at each step of the computation [46, 47]. Considering the Internet, it is not expected and it didn't happen to break down completely when random failures of routers or links appear. But, in a very-well targeted attack, a significant dysfunction of the network could appear because certain hubs of the network undergo the specific attack. Those networks where all the nodes are connected to a central node (the hub-and-spoke network) are more flexible in case of random failures. Only when the central hub is removed, such networks shut down completely [48].

Computers are seen as complex networks where viruses are aggressors. Viruses' penetrability isn't always a matter of intensity of infectiousness. Even those so-called weak viruses can spread and persist within the network. Hubs are highly connected and at least one might be infected by a single corrupted node. Further, the infection is spread to a large number of nodes implying also other hubs that "help" the virus to be wide-spread along the network [48]. Human viruses have a model of spreading respecting scale-free social networks. Immunization against viral diseases should target the hubs (the most connected individuals) in order to be effective [48]. The dynamics of such networks considers the temporal aspect, the range of time interactions take place.

NETWORK MEDICINE

Nowadays, science and research has reached the borders of inter- and multidisciplinarity. So, physics is connected to biology, chemistry, biochemistry, medicine, IT, etc., determining a large complex network. Complexity and networks go hand in hand, complexity being anchored both in the architecture of a system, and in the dynamical nature of the processes that emerge in a system [49]. The collaboration among scientists and researchers in various disciplines was examined: it was found that the obtained network has a scale-free pattern. It is worth mentioning that Paul Erdös represents one of the most large hubs in mathematics community: he wrote more than 1400 papers with at least 500 co-authors [50].

DNA is the expression of biological complexity. At cellular level there is a complex network with extremely well defined levels of organization: the cell's genome, transcriptome, proteome, metabolome. All these groups interact within large networks, but each level organizes itself as a network (e.g., the proteome is a protein interaction network) [51].

Obesity has clear genetic determinism. It is extremely interesting that there are proofs that support the idea that communities have also an important influence on obesity onset. In the Framingham Heart Study, investigators built social networks focused on the study participants, comprising their closest friends, neighbors, family members. In a group of two friends, if one was or became obese, the other one had a chance to become obese of 171% [52].

To understand diseases, it is necessary to develop cellular maps with implied pathophysiological interactions, identifying disrupted pathways. Modern diagnosis comprises the description of the chain of changes, from identifying the primary disease-causing gene (with the afferent mutation(s)), to clinical expression. In this way, therapy can be targeted and personalized. The mutated gene determines synthesis of modified proteins and facilitates the appearance of an intermediate subclinical and clinical response: inflammation, thrombosis or hemorrhage, aberrant cell proliferation, necrosis, apoptosis. Beyond genetic factors, environmental factors can intervene on the determinism of a disease, modulating gene expression. So, it is important to integrate the interactions between genome, proteome, environment, pathophenome, that take place on a cellular network basis. The main goals of this are to understand the development of a disease, to predict outcomes and to elaborate proper therapy strategies [53].

Novel therapy strategies are based on the previous concept of understanding a disease. So, modern therapies should not be focused on treating symptoms, but they should interfere the disorders of implied gene or group of genes. Studies have revealed that those genes associated with a certain disease show the tendency to cluster in the same network neighborhood (disease module), forming a connected subnetwork inside the interactome which contains a large amount of the disease proteins. New biological active molecules have to be targeted towards proteins inside or in immediate proximity to the corresponding disease module. For this, it is necessary to integrate protein-protein interaction, drug-disease association and drug-target association in order to assess the topological properties of drug targets taking into account the disease proteins [54].

There is the possibility that two disease modules overlap: local changes that cause one disease may interfere and disrupt other disease module, with mixed clinical and pathobiological characteristics. In this particular case, overlapping disease modules show important and significant molecular similarity, increased co-expression of the associated genes, and similar clinical expression and comorbidities [55].

Considering that human diseases/disorders are consequence of disturbances in highly interlinked cellular networks, they might be in a quite increased manner interconnected. This led to development of global disease network maps which associate disease phenotypes if there is found a degree of similarity between them at molecular or phenotypic level. Using the OMIM (Online Mendelian Inheritance in Man) database, such a map was developed: nodes are diseases and two diseases are linked by an edge only if there is at least one common gene where mutations associated to them are described. So, it was established that more than 500 human genetic disorders are connected to a single main giant component, suggesting that between human disorders can be described significant connections [56].

4. CONCLUSION

Networks are a modern concept with large applicability in real life. Theory of networks helps us understand a large variety of aspects, from social relations, "virtual" social networks, Internet, World-Wide Web, to the most complex biological processes which allow to understand the mechanisms of diseases and to elaborate novel therapy strategies, up to the supreme concept of personalized medicine. In our days where mobility of people is a defining, also business is often extended at global scale, thus, internationalizing firms can be handled as networks, being more effective in their strategies as new-entries, but also improving their evolution and development [57].

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