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On the use of Networks in Biomedicine

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Abstract

The concept of "neural network" emerges by electronic models inspired to the neural structure of human brain. Neural networks aim to solve problems currently out of computer's calculation capacity, trying to mimic the role of human brain. Recently, the number of biological based applications using neural networks is growing up. Biological networks represent correlations, extracted from sets of clinical data, diseases, mutations, and patients, and many other types of clinical or biological features. Biological networks are used to model both the state of a range of functionalities in a particular moment, and the space-time distribution of biological and clinical events.

The study of biological networks, their analysis and modeling are important tasks in life sciences. Most biological networks are still far from being complete and they are often difficult to interpret due to the complexity of relationships and the peculiarities of the data. Starting from preliminary notions about neural networks, we focus on biological networks and discuss some well-known applications, like protein-protein interaction networks, gene regulatory networks (DNA-protein interaction networks), metabolic networks, signaling networks, neuronal network, phylogenetic trees and special networks. Finally, we consider the use of biological network inside a proposed model to map health related data.

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Keywords: Biological Networks; Protein-Protein Interaction Networks (PPIn); Gene Regulatory Networks (GRN); Metabolic Networks; Signaling Networks; Neuronal Networks; Food Webs; Phylogenetic Trees, Special Networks and Hierarchies; Health Care Model.

1. Introduction

The human brain has the capacity of processing information and making decisions instantaneously. Many researchers have shown that human brain performs calculations in a different way than computers, hence the aspiration to solve problems whose complexity is beyond the current computing power, has prompted the scientific community to the neural networks. For biological network is meant any network applied to a biological systems.

A network, in a broad sense, identifies a system, which is characterized by interconnected sub-units. Biological networks are types of important applicable model in various contexts; complex biological systems can be represented and analyzed by computable networks. Like the computer networks, the high complexity degree of biological networks is generated by a simple mechanism. Bioinformatics really shifted its focus from individual genes, proteins, structures and search algorithms for large networks; even more biologists are discovering the links between Internet and metabolic pathways, interactions of proteins through a network topology or a scale-free network.

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A neural network is composed of a set of parallel and distributed processing units, referred as nodes or neurons; they are arranged in layers, and are interconnected by unidirectional or bidirectional connections (see Fig. 1). Typically, a neural network has a set of N input nodes, whose generic element is related with, and each node is interconnected to others through weighted arcs. The products of input and weight are simply summed and feed through (Activation Function) to generate the output (see Fig. 2).

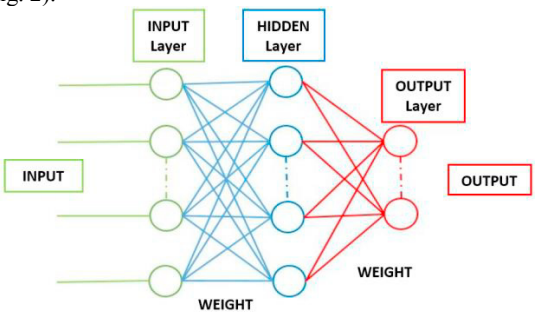

Fig. 1. Typical Structure of Neural Network

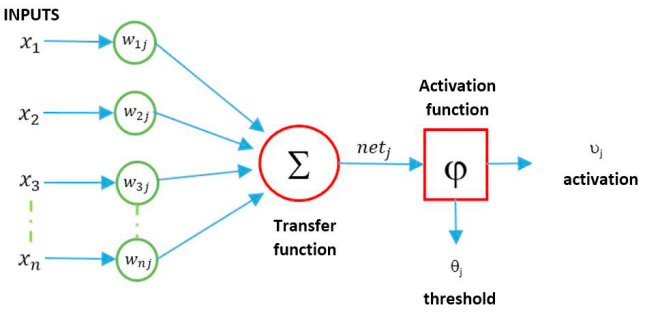

Fig. 2. Activation Functions

Neural network design typically consists of Topology, Transfer Function and Learning Algorithm. The neural network topologies are actually classified by the directions of interconnection in the layer; so the most referred topologies are, *Feed Forward Topology* and *Recurrent Topology*.

In *feed forward topology (FFT)* network, the nodes are "*hierarchically arranged*" in layers starting with the input layers and ending with output layers. The number of hidden layers provides most of the network computational power. In literature typical application of this topology are the *multilayer perception network* and *radial basic function network*. The nodes in each layers are connected to next layer through *unidirection* paths starting from one layer (source) and ending at the subsequently layer (sink). The output of a given layer feeds the nodes of the following layer in a forward direction and does not allow feedback flow of information[12].

Unlike the FFT, in the *recurring topology* (RNT) the flow of information between connected nodes is bidirectional. Typical applications of RNT, for example, are Hopfield Network[1] and time delay neural network (TDNN)[2]. A recurrent network structure has a sort of memory, which helps storing information in output nodes through dynamic states. Biological networks shapes both the state of a range of functionalities in a particular moment, and the space-time distribution of biological and clinical events[14].

In neural networks, the basic unit are the neurons that work like simple processors. Any neuron takes the weighted sum of its input nodes and thanks to the mapping function (activation function) delivers the output to the next neuron. In computational networks, the *activation function* of a node defines the output of that node given as an input or set of inputs. However *nonlinear* activation function allows such networks to compute nontrivial problems using only a small number of nodes. In artificial neural networks, this function is also called transfer function.

In training processes of the network, learning algorithm are used for updating the weight parameter of the input connections level of the neurons. Specifically, there are three types of algorithms: *Supervised*, *Unsupervised* and *Reinforcement*.

Supervised learning is the machine-learning task of inferring a function from *labeled training data*. The training data consist of a set of *training examples*. In supervised learning, each example is a *pair* consisting of an input object (typically a vector) and a desired output value (referred as *supervisory signal*). A supervised learning algorithm analyzes the training data and produces an inferred function that can be used for mapping new examples. Thus the learning algorithm is designed to generalize from the training data to unseen situations in a "reasonable" way. In *supervised learning* mechanism, the external source provides the network with a set of input stimuli for which the output is just known and during the running process the output results are continuously compared with the desired data. The gradient descent rule uses the error between the actual output and the target data for setting the connections weights to the closest match between the target output and the actual output. These types of learning algorithms are used in applications with feed forward networks[3].

Unsupervised machine learning is the machine-learning task of inferring a function to describe hidden structure from "unlabeled" data. In *unsupervised learning* algorithm, a classification or categorization is not included in the observations. The training data and input pattern are presented to the system that organizes data into clusters or categories. A set of training data is provided to the system at the input layer level; the network connection weights are then adjusted through a competition among the nodes of the output layer where the successful candidate will be the node with the highest value.

Reinforcement learning regards software agents ought to take *actions* in an *environment* so as to maximize some notion of cumulative *reward*. The problem, due to its generality, is studied in many disciplines, such as game theory, control theory, information theory, simulation-based optimization, statistics, and genetic algorithms. The *reinforcement learning* algorithm, is also called as graded learning. In this way the network connections are modified according to feedback information provided to the network by its environment. In case of correct response the corresponding connections leading to that output are strengthened otherwise they are weakened.

2. Biological Network

For solving the complexity of biological molecule into a neat code, in a linear sequence, or in an information protocol, the bases are thrown; biology and cybernetics can be fused in one discipline. For example, a protein can be modeled as a network of nodes and edges with amino acids. Since 1980, many researchers have already started viewing DNA or genomes as a means of dynamic storage with precise computable finite represented by a finite state machine. A finite state machine (FSM) is a mathematical calculation model conceived as an abstract machine that can be in one or in a finite number of states. The machine is in only one state at a time; this state is referred as current status.

An event or condition, in literature referred as *transition*, can activate the change from one state to another. A particular FSM is defined by a list of its states, and by the trigger condition for each transition[4]. In biology the state machines typically have been used to describe the neurological systems. Considered as an abstract model of computation, the finite state machine is weak; it depends by a limited number of states[5]. Even more many important biological networks are defined on molecules such as DNA, RNA, proteins and metabolites, and the networks describe interactions between these molecules[6].

Gene regulatory, signal transduction, protein-protein interaction (PPI) and metabolic networks interact with each other and build a complex biological network[7]. Similarly, these networks are not universal but are organism-specific and environment-specific, for example, the same network differs between different organisms and environments in which these organisms live.

3. Types of Biological Networks

In this section we give an overview about some well-known types of biological networks. *Protein-Protein Interaction (PPI)* networks is a model used to represent interactions between proteins, for example, in a process to build complexes protein where the activation of one protein is due to another protein.

Gene regulatory networks (DNA-protein interaction networks) are constructed studying couple of genes with similar expression patterns in determinate conditions. *Signal transduction and gene regulatory networks* are models used to describe the way with genes can be activated or repressed, containing information about which proteins are produced in a cell at a particular time. Yet *Metabolic networks* show the transformation of metabolites for the production of energy or for the synthetization of specific substances. Other types of biological networks include *phylogenetic trees*, *special networks and hierarchies*, which are typically based on information from molecular biology such as DNA and protein sequences. Phylogenetic trees can be used for the representation of relationships between different organisms, their origins, also giving prediction about the probability for their survival or their extinction. However, there are many more networks in biology: ecological networks such as food-webs, biological data analysis networks such as correlation networks, neuronal networks, similarity networks, residue interaction networks (contact maps), drug and drug-target networks and co-expression networks to name just a few.

3.1. Protein-Protein Interaction networks (PPI): Protein–protein interactions, also referred PPI, occur when two or more proteins bind together, often to carry out their biological function. Their visualization aids biologists in pinpointing the role of proteins and in evaluation of new insights about the processes within and across cellular processes and compartments, in testing specific hypotheses about gene function.

In PPI networks nodes represent proteins and edges represent interactions. Two proteins are connected if they interact with each other. A protein can interact with another protein for building a protein complex or to activate it. A PPI network is an undirected graph; often only the existence of an interaction between two proteins is known, but the interaction type or their effects remains unknown. The events of *activation* and/or *deactivation* are usually related to signaling cascades that to PPIs.

For the understanding of biological processes, information about the interaction type is crucial, although up to now databases contain little information about that. PPI networks can be derived from databases such as BioGRID[8] and STRING[9].

Many protein-protein interactions (PPIs) in a cell form Protein Interaction Networks (PINs) where proteins are nodes and their interactions are edges. PINs are the most intensively analyzed networks in biology.

There are many PPI detection methods to identify such interactions. The yeast two-hybrid system is a commonly used experimental technique for the study of binary interactions[10]. Important molecular processes in the cell like DNA replication are analyzed with large molecular machines built from a large number of protein components organized by their PPI.

PPI mechanism regulates best part of biological activities. One of the most important PPI bio-function is the signal transduction, involving the signal transmission in a cell, where certain molecules interact and communicate through proteins. This signal transduction, takes a decisive part in biological processes of the living cells and, consequently, in pathologies and illness (e.g., cancer). We can find out several types of protein-protein interaction processes with different resulting output, like the creation of a multiprotein complex, or the modify of a protein by a briefly interaction of the protein to another one.
Thus, mapping and analyzing these interactions is crucial, in order to get relevant biological and medical data, to be used to support diagnostics and treatment, as well as new health care methods[10].

3.2. Gene regulatory networks (DNA-protein interaction networks): Typically, a cell reacts coordinately to changes in its environment through a communication process, called signal transduction. The signal transduction network of a cell is the complete network of all signal transduction pathways. Biological networks are used to represent a signal transduction path. Within a cell, there exists a directed network of chemical reactions: by a trigger, such as the stimulus of an external molecule connecting to a receptor on the membrane of the cell, to the response, such as the change of the genetic behavior due to the connection of an external molecule. All signal transduction pathways of the cell determinate its complete transduction network. Signal transduction does not necessarily ends with a change in gene expression regulation; it could also activate an enzyme.

In this regulation process, a gene controls another one via the corresponding protein (a transcription factor); so the whole process is managed through a gene regulatory directed network: nodes correspond to genes, edges to regulatory relations.

Directed edges connecting two nodes will exist only if there is a direct relation between them and there is not any node (or subset of nodes) intermediating the connection. As mentioned above, proteins (usually related to DNA) rule, as transcription factors, the genetic activity. A genome has several binding sites, combined and coordinated by transcription factors. It follows, every single cell is characterized by complex gene regulatory networks. Referring to the human genome, we find out encodes on the order of 1.400 DNA-binding transcription factors, regulating the activity of more than 20.000 genes. There are different methods and technologies to analyze gene regulatory networks, as, for instance, Chip-chip, Chip-seq, Clip-seq and others[11].

The acronym GRN (Gene Regulatory Network) is referred to a set of DNA segments in a cell. These DNA segments interact in different ways: each-other indirectly, that is through their RNA and protein expression outputs; moreover, there is interaction with different elements in the cell, thus managing the level of genes transcription into mRNA.

Typically, every single mRNA molecule corresponds to a specific protein. These proteins can be structural, giving particular structural features and properties to the cell; they will amass at the cell membrane or within the same cell[17].

GRN can also include transcriptional networks; sRNAs and other ncRNAs are also mechanisms of gene expression although at transcriptional level. Modi, Camacho[23] studies on functional characterization of bacterial sRNAs using a network biology approach. They show that a network-based approach can be used to identify the cellular function of sRNAs and characterize the relationship between sRNAs and transcription factors.

The function of living cells is controlled by complex regulatory networks that are built of a wide diversity of interacting molecular components. Kim Sneppen, Sandeep Krishna et al[24] discusses the achievements and promise of a bottom-up approach that uses well-characterized subnetworks as model systems for understanding larger networks.

3.3. Metabolic networks: Like the other networks, we are aware also, the structure of metabolic networks is composed of nodes and edges. Nodes represent the compounds of a cell (i.e. molecule), while edges represent the reactions between chemical substances, that produces other substances. Thus, all compounds in a cell are parts of an intricate biochemical network of reactions called *metabolic network*. Metabolic networks represent the complete life of a cell: its initial composition, its interactions and processes that can involve the cell. Therefore, the metabolic networks may represent also a long and complex chain of metabolic reactions of an organism. Metabolic networks can also be composed by some subnetworks representing specific processes, called *metabolic pathway*: a sort of hyper-graph that represents an entire process (from reactants to products), in which nodes and the chemical reactions represent substances by hyper-edges. This way, it is possible to create a graphic representation of the metabolic and physical processes of each organism, from the smallest and simplest to the most complex one[13].

3.4. Signaling networks: Signaling networks are complex graphs representing the various signals communicated between or within the cells of an organism. Signaling networks typically integrate protein-protein interaction networks, gene regulatory networks, and metabolic networks. The graphic representation of this communication system is important, because it rules all the cellular and intercellular activities and produces the ability (or the inability) of cells to respond to a trauma or to a pathological situation: when cells do not give or do not receive the information properly, the body will be involved in diseases. Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity, and diabetes. Diseases can be treated more effectively understanding cell signaling, and, theoretically, artificial tissues may be created.

Signaling networks can help, in a future research perspective, to find new experimental solution to diseases. Analysis of cell signaling networks requires a combination of experimental and theoretical approaches including the development and analysis of simulations and modeling. Long-range allostery is a significant component of cell signaling events[15]. This kind of network helps the graphic analysis of these complex cellular information system, in a strictly connection with biology research.

3.5. Neuronal network: Typically, in neuroscience, a neural network refers at a series of interconnected neurons, whose activation identifies a recognizable linear pathway. The interface through which neurons interact with their neighbors usually consists of many axon terminals connected through synapses to dendrites on neurons.

If the resultant of the input signals, i.e. the sum of the input signals in a given neuron, exceeds a threshold value, the neuron forwards an action potential (AP) at the axon hillock transmitting this same electric signal along an the axon[16]. In contrast, a neural circuit is a functional entity of interconnected neurons that is able to regulate its own activity using a feedback loop (similar to a control loop in cybernetics). Applications of neural networks it is also adopted for chemical neurotransmission that occurs at chemical synapses. The presynaptic neuron and the postsynaptic neuron are physically separated by the fluid-filled synaptic cleft. The arrival of an action potential in the presynaptic neuron causes it to release neurotransmitter. Neurotransmitter diffuses across the cleft and binds to receptors on ion channels. This causes the activation of the ion channels. The influx of ions causes a synaptic potential in the postsynaptic neuron.

Chemical neurotransmission requires neurotransmitters to act as chemical messengers linking an action potential in one neuron with a synaptic potential in another[25].

3.6. Food webs: In the Food Chain, all the organisms are related to each other because the one eats the other. There is a complex food network made of bait and prey. Ecologists divide all the basic forms of life by the trophic levels in *autotrophic* and *heterotrophic*. Autotrophic produce organic substances from inorganic substances, including minerals and carbon dioxide gases.

A gradient exists between trophic levels running from complete autotrophs that obtain their sole source of carbon from the atmosphere, to mixotrophs (such as carnivorous plants) that are autotrophic organisms that partially obtain organic matter from sources other than the atmosphere, and complete heterotrophs that must feed to obtain organic matter.

Ecologists collect data on trophic levels and food webs to perform statistical modeling and to calculate the parameters, performing real network analysis; so they are able to study emerging schemes and shared property between ecosystems. With the use of neural network, the ecologists can mapped different ecological dimensions, creating food networks more complicated. New ecological dimensions that it is possible to analyze are for example: type and the richness of species[26], the biomass (dry weight of plants and animals), the productivity calculated related to energy conversion rates and nutrient Growth and Stability food networks over time.

3.7. Phylogenetic Trees, Special Networks and Hierarchies: Hierarchical organization of organisms in an evolutionary context is one of the fundamental principles in biology. Reconstruction of ancestral relationships between different species, genes, or DNA sequences, is a very important issue even more analyzed in its relationship with a phylogenetic tree.

The leaf nodes represent species, sequences or similar entity. Internal nodes represent the potential ancestors, generated using phylogenetic analysis. An appropriate application is the gene-phenotype, for example[18,19,20]. A gene-phenotype network is a network bipartite with two sets of nodes. One is the phenotypes, for example, the diseases, of a particular organism and the other is the body's genes. A phenotype gene is linked if the gene is affected by disease. A very important example of biological data hierarchies are *The Gene Ontology (http://geneontology.org)*[21]. The Gene Ontology is a prominent bioinformatics project which provides dynamic structured model of gene properties and their connections with biological activities. In the Gene Ontology modeling, genetic features and properties are represented as terms. These terms are distinguished in three categories (cellular components, molecular functions and biological processes), and are encoded in specific hierarchical vocabularies. Cellular components' domain concerns the internal structure of a cell and its interaction with external environment. Molecular functions' domain concerns the elementary molecular activities of a gene product.

Finally, biological processes' domain concerns operations or complexes of time defined molecular actions, related to living units (e.g. cells, tissues, organs and organisms). The whole hierarchical organization of The Gene Ontology is represented as a directed acyclic graph, where terms are linked to each other, according to the existing relationships and interactions. Each gene is flagged by Gene Ontology terms (i.e. gene annotation), in order to support data mapping and analysis[22].

4. Biological Networks and health care model

We now consider the use of biological networks inside a new health related model. Interaction of huge quantity of data, like patients' data, clinical data process and data generated by medical devices, represents an important knowledge source. From here, the idea of an health care model based also on the information extracted from biological networks, in order to improve the quality of life in a population and for the process optimization in socio-economical and health care area.

Thus, our purpose is to consider biological networks, in order to feed a new health care model, improving and extending traditional ones, providing more features and services, involving and driven by patient, supporting decision and responsibility processes, considering predictive and preventive aspects[27].

Our model proposes to map clinical data from heterogeneous sources, trying to link clinical and biological data. Such information can feed a platform of business intelligence, able to define a personalized medicine, targeting also to define wellbeing indicators. Similarly environmental factors may be related to the onset of biological indicators (e.g. hardness of the water, the presence of minerals in the drinking water related to the onset of pathologies identifiable with analysis values from biological analyzes extracts). In Fig.3, we represent the idea of using networks to relate clinical, biological, environmental as well as personal data. Experts of domain can use the output data from network models, analyzing such information and extracting knowledge, feeding an evolved model of health care that makes the proposed objectives (Fig.4).

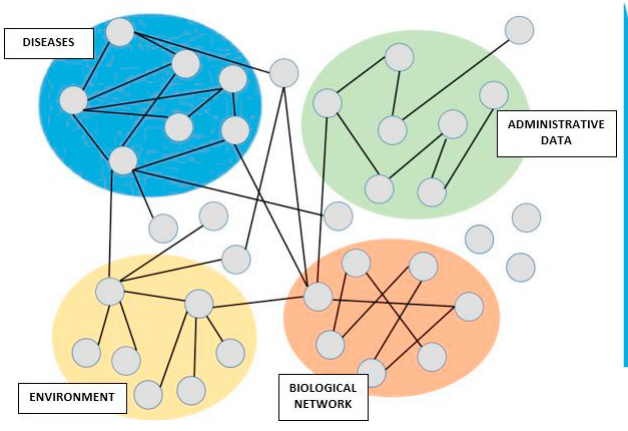

Fig. 3. Use of network to relate data

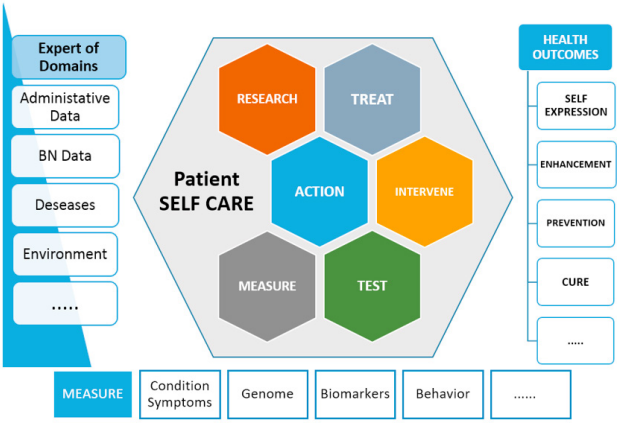

Fig.4. An idea of a new model of health care

The scheme in figure 4 outlines the logic we intend to use in modeling new health care model. We will refer ourselves to a widened concept of health and health care (right column in the figure 4), including not only the traditional data of pathologies, illness and cure, but also considering the patients, involved as active actors in prevention to reach a better health condition, both physical and psychological: health care as an individual way of life, to express oneself.

Health measurement data (bottom side in figure 4), are considered analyzing both traditional and new medical indicators (e.g. genome and biomarker screening). Moreover, according to our vision, other factors to be processed will be about patients' daily life, mapping individual habits in the health and social environment (e.g. diet, work place, free time activities and so on). The core of our health care model includes several prescriptions of medical discipline, and their relevance level referred to the single patient (central block of the scheme in figure 4). The idea of patient-driven health care system is pointed out by the central, active role played by single persons, becoming information sharers.

Nowadays people, supported by professionals and experts, provide on their own various medical data, such as measuring, self tracking and experimenting results. Thus, single patients, through this informative flow, become active part of decision and action-taking processes, supporting the professionals in diagnostics, treatments and research too.

5. Conclusion

In this paper, we surveyed several types of biological networks, closely related to molecular biology. In the near future new models have to be developed, since the existing approaches can scale better to large networks.

Our focus in this work is to raise awareness of the relevance of the types of biological networks for the area of health related data. We introduce an idea of a model hosting clinical, biological, health related information thus to extract knowledge and to improve wellbeing; experts of domain can use data coming from applications of biological networks to feed an experimental health care model.

6. Future Work

Our purpose is to introduce new concepts in health system modeling, extending the traditional vision of medical data analysis. Patients play active role, providing and sharing information, thus feeding action-making and decision shells, to be used by physician in diagnostics and treatments. This collaborative approach in health care model is actually in early stage, but has great development opportunities for the future, especially thanks to the expected health outcomes of genomic medicine, and to the diffusion of fast web connectivity, allowing rapid data acquisition, sharing and interchange between the different figures involved.

References

1. MacKay DJ. *42. Hopfield Networks. Information Theory, Inference and Learning Algorithms*. Cambridge University Press ISBN 0521642981, 2003.
2. Waibel A. *Phoneme Recognition Using Time-Delay Neural Networks* IEEE Transactions on Acoustics, Speech and Signal Processing, Vol 37, No. 3/3/1989.
3. Mohri M, Rostamizadeh A, Talwalkar A. *Foundations of Machine Learning*, The MIT Press ISBN 9780262018258, 2012.
4. Arbib MA. *Theories of Abstract Automata* (1st Ed.). Englewood Cliffs, N.J.: Prentice-Hall, Inc. ISBN 0-13-913368-2, 1969.
5. Belzer J, Holzman AG, Kent A. *Encyclopedia of Computer Science and Technology,* Vol. 25. USA: CRC Press. pp. 73. ISBN 0824722752, 1975.
6. Sharan R, Ulitsky I, Shamir R. *Network-based prediction of protein function*, *Mol Syst Biol*. Available: http://dx.doi.org/10.1038/msb4100129 vol. 3, 03/2007.
7. Davidson EH and Erwin DH. *Gene regulatory networks and the evolution of animal body plans*. Science, vol. 311, no. 5762, pp. 796–800 February 2006.
8. Chatr-Aryamontri A, Breitkreutz BJ, Oughtred R, Boucher L, Heinicke S, Chen D, Stark C, Breitkreutz A, Kolas N, O'Donnell L, et al. *The BioGRID interaction database: 2015 update. Nucleic Acids Research*, 43(D1):D470-D478, 2015.
9. Szklarczyk D, Franceschini A, Wyder S, Heller D, Huerta-Cepas J, Simonovic M, Roth A, Santos A, Tsafou KP, et al. *STRING v10: protein-protein interaction networks, integrated over the tree of life. Nucleic Acids Research*, page gku1003, 2014.
10. Kohn KW. *Molecular Interaction Map of the Mammalian Cell Cycle Control and DNA Repair Systems*. Molecular Biology of the Cell 10 (8): 2703–2734. PMC 25504. PMID 10436023, August 1, 1999.
11. Vaquerizas JM et al. *A census of human transcription factors: function, expression and evolution*. Nat Rev Genet. 10 (4): 252-263. PMID 19274049, 2009.
12. Wang Z, Di Massimo C, Tham MT, Morris AJ. *A procedure for determining the topology of multilayer feedforward neural networks* Volume 7, Issue 2, 1994, Pages 291–300 University of Newcastle, Available online Neural Networks, 19 March 2003.
13. Franke C, Siezen RJ, Teusink B. *Reconstructing the metabolic network of a bacterium from its genome. Trends in Microbiology*. 13 (11): 550–558. doi:10.1016/j.tim.2005.09.001. PMID 16169729, 2005.
14. Milo R, Shen-Orr S, Itzkovitz S, Chklovskii D, Alon U. *Network Motifs: Simple Building Blocks of Complex Networks* VOL 298 SCIENCE 25/10/2002.
15. Bu Z, Callaway DJ. *Proteins MOVE! Protein dynamics and long-range allostery in cell signaling*. Advances in Protein Chemistry and Structural Biology 83: 163–221. doi:10.1016/B978-0-12-381262-9.00005-7. ISBN 978-0-12-381262-9. PMID 21570668, 2011.
16. Graves A, Schmidhuber J. *Offline Handwriting Recognition with Multidimensional Recurrent Neural Networks*, in Bengio, Yoshua; Schuurmans D, Lafferty J, Williams CKI, Culotta A. *Advances in Neural Information Processing Systems 22 (NIPS'22)2009, Vancouver, BC*, (NIPS) Foundation, pp. 545–552, 2009.
17. Guzzi PH, Di Martino MT, Tradigo G, Veltri P, Tassone P, Tagliaferri P, Cannataro M. *Automatic summarisation and annotation of microarray data*, Soft Computing vol. 15 n° 8 1505-1512 issn 1433-7479, 2011.
18. Amberger J, Bocchini CA, Scott AF et al. *McKusick's online Mendelian inheritance in man (OMIM).* Nucleic Acids Research, 37(suppl 1):D793-D796, 2009.
19. Davis AP, King BL, Mockus S, Murphy CG, Saraceni-Richards C, Rosenstein M, Wiegers T, Mattingly CJ. *The comparative toxicogenomics database: update 2011*. Nucleic Acids Research, 39(suppl 1): D1067-D1072, 2011.
20. Pinero J, Queralt-Rosinach N, Bravo A, Deu-Pons J, Bauer-Mehren A, Baron M, Sanz F, Furlong LI. *DisGeNET: a discovery platform for the dynamical exploration of human diseases and their genes.* Database, 2015: bav028, 2015.
21. Gene Ontology Consortium et al. *The Gene Ontology (GO) database and informatics resource*. Nucleic Acids Research, 32(suppl 1): D258-D261, 2004.
22. Radivojac P, Clark WT, Oron TR, Schnoes AM, WittkopT, Sokolov A, Graim K, Funk C, Verspoor K, Ben-Hur A, et al. *A large-scale evaluation of computational protein function prediction*. Nature Methods, 10(3):221-227, 2013.
23. Modi SR, Camacho DM, Kohanski MA, Walker GC. *Functional characterization of bacterial sRNAs using a network biology approach*. PNAS 2011 108 (37) 15522-15527; published ahead of print August 29, 2011, doi:10.1073/pnas.1104318108
24. Sneppen K, Krishna S, Semsey S. *Simplified Models of Biological Networks*. Article's doi: 10.1146/annurev.biophys.093008.131241 Copyright c 2010 by Annual Reviews, 2010.
25. Stufflebeam R. *Neurons, Synapses, Action Potentials, and Neurotramission National Science Foundation Grants* #9981217 and #0127561, 2008.
26. *Dunne JA, Williams RJ, Martinez ND. Food-web structure and network theory: The role of connectance and size.* Proceedings of the National Academy of Sciences*. 99: 12917–12922.* doi*:*10.1073/pnas.192407699. PMC 130560 . PMID 12235364*,* 2009.
27. Vocaturo E, Confluenze, Rivista Culturale Quadrimestrale - Anno V n.1 *Informatica Clinica in Italia* 59:64 Comet Editor Press ISSN 2282-5177, April 2017.