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Review Article

Overview of Network Analysis in Systems Medicine

Ioanna Chouvarda[1]

[1]*Laboratory of Computing, Medical Informatics and Biomedical Imaging Technologies, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki*

Abstract

Systems Medicine (SM) is an interdisciplinary research paradigm, that heavily relies on complex systems theory, and emphasizes on the studies the human body in terms of systems and the interactions among them, incorporating biochemical, physiological, and environment interactions. The article presents developments in SM research, focusing specifically on the network analysis approaches. Network analysis is fundamental for the study of interactions among systems at different levels within the human body. The background knowledge is established: the basic concepts of nodes and edges, and network metrics as well as existing computational tools are described. Different applications in health research are discussed, including descriptive and predictive approaches. The use of network analysis in temporal data and data coming from digital health technologies is further highlighted. Finally, the current challenges are discussed and the foreseen developments.

Keywords: Network Analysis, Complex Systems, Systems Medicine, Graph

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Corresponding author:
Ioanna Chouvarda, Laboratory of Computing, Medical Informatics and Biomedical Imaging Technologies, School of Medicine, Aristotle University of Thessaloniki Greece. Thessaloniki 541 24, Greece, Tel.: 2310-999.247, E-mail: ioannach@auth.gr

Introduction

Systems medicine (SM) is an interdisciplinary field that considers the human organism as a system, composed of subsystems and their complex interactions, and also integrated and interacting with an external environment (Kamada;1992). It requires the synergy of medicine, systems biology, statistics, modelling and simulation, and data science. The SM is regarded as an approach complementary to the reductionist approach in medicine (Federoff and Gostin; 2009), as it embraces the complexity of human organism and the complex relationships on multiple levels, from genomics to behavior and environment, towards identification of critical systemic elements in patient's medical condition and achievement of tangible benefits for the patients. The diagnostic and therapeutic targets are not defined towards single molecules, but rather perturbed networks. The classic symptom-based disease definitions are consequently revisited (Berlin et al; 2018). Computational models that describe disease progression and the effect of therapeutic interventions are highly relevant (Tang and Aittokallio; 2014).

On the background of systems medicine, one could recognise the **Complex systems** theory, describing systems composed of a large number of elements, interacting in a non-linear way between them (Kaplan et al;1991). The interactions are central to understanding the behaviour of these systems. The complex systems often have nonlinear behaviour, which makes prediction quite challenging (Yan et al;2019). Emergent behaviors may unexpectedly emerge, leading to order or disorder, not to be explained by the system's units. Complex systems have often been analysed via networks, mathematical objects composed by entities (nodes), pairwise connected by links (edges), directed or undirected. This simple network formalism can be applied to represent for instance, people and their social connections (Grunspan et al; 2014), or o genes and their co-regulation. In all cases, the network structures can easily be mathematically studied and visualised, which offers an adequate level of abstraction for qualitative and quantitative analysis,

Network medicine (NM) is a complementary concept aiming to apply the complex networks theory to medicine, and hence to the identification, prevention and treatment of diseases. It is based on the idea of interdependence of elements constituting our bodies at all scales (e.g. from genes, to cells and organs), as a central concept in understanding one disease. A recent survey by (Sonawane et al, 2019) explores ways in which the NM approach can be applied, with a focus on biologically driven paradigms, like gene expression-based networks. In another case, network physiology is examined in sleep, considering sleep as a multi-organ phenomenon and examining the interactions within the brain and between brain and eye, chin, leg, heart and respiratory system (Bartsch et al; 2015) (Bashan et al; 2012).

Understanding the level of interdisciplinarity that a systems medicine and network medicine approach may require, this paper aims to provide an overview of network analysis in the systems medicine domain, along with example applications within this wide area. Technological methods are presented, and challenges are discussed towards the future of SM.

Background Concepts on systems networks

A network is defined as a set of nodes (entities, or actors) and the relations between them (represented by edges). Both nodes and edges can have attributes (Hevey;2018). Graphs, or networks provide a level of abstraction in concepts and relationships. These concepts and relations can be quantified and mathematically characterized, while in parallel, they can be intuitively visualized. A series of examples of intuitive and successful Network Analysis can be found in the social sciences. Network analysis offers computational efficiency as a data analysis method, and can also set the basis for neural network frameworks (Scarselli et al; 2008).

Within a domain, typically networks are constructed by mapping directly the domain elements to nodes (e.g. each symptom is a node), and by expressing their relationships as edges between pairs of nodes. In the example of symptoms, an edge would express the co-occurrence of symptoms. In a biological example, a gene co-regulation network, each gene would be represented by a node, and an edge between a pair of them would be present if one of them regulates the other. In this sense, the edges can be directed, to express a direction of relationship, indicating influence or causality, as in the case of partial correlations. Edges can also be undirected, expressing correlation, co-occurrence, or similarity.

The edges can have a weight and a sign, expressing a strong or weak, positive or negative relationship, respectively. Also, the nodes can have a binary value, e.g. 0 or 1 for the absence or presence of a symptom, or a continuous value corresponding to some other physiological measurement. Nodes are not necessarily connected by a single type of relationships, as in multi-layer or multi-level networks.

The network edges may be distributed in a non-uniform but rather selective manner. In this case, the network may comprise communities, i.e. node clusters that are highly interconnected, and rather isolated from nodes outside their cluster.

Network structures are often formulated from cross-sectional studies, corresponding to a snapshot. It has to be noted that in a real setup, links are not necessarily constant through time, and network dynamics are needed to study how the relationships between concepts/ nodes change across time. In order to describe time-evolving phenomena, temporal networks have been proposed, including the multivariate vector autoregression model (MLVAR) as described in (Epskamp et al;2017) and (Epskamp et al;2018), the temporal exponential random graph models (TERGMs) by (Leifeld et al;2017), or r stochastic actor-oriented models (SAOMs) (Snijders et al, 2010) and (Ruth et al, 2018). In the case of temporal sequences, granger causality between nodes can be investigated, and driver factors can be identified (Mainali et al;2019).

As series of metrics have been defined to mathematically characterise the network structure, in specific nodes and as a whole, enabling also the comparison among networks. Some known measures are described below. Network-wise, one may consider:

- **Average Path Length**. The average of the shortest path lengths for all possible node pairs. Gives a measure of ‘tightness’ of the Graph and can be used to understand how quickly/easily something flows in this Network.
- **Network Density**. A measure of how many edges a Graph has. A complete undirected Graph has Density=1, and an empty Graph has Density=0.

Regarding the nodes, the main characteristics are:

- **Degree**: the number of connections incident to the node of interest.
- **Node strength**: the sum of the weighted number and strength of all connections of a specific node relative to all other nodes, expressing the importance of that node. Note that a node with many weak connections may have a high degree, but is not as central to the network as one with fewer but stronger connections.
- **Closeness**: quantifies the node's relationship to all other nodes in the network. A high closeness index indicates a short average distance of a specific node to all other nodes. This means the node's change can affect the network and can be affected by changes in any part of the network.
- **Betweenness**: this index provides information on how important a node is in the average pathway between other pairs of nodes, for example, it is important to know if a node belongs to the shortest path between two other nodes.
- **Clustering**: The local clustering coefficient C is the proportion of edges that exist between the neighbours of a particular node relative to the total number of possible edges between neighbours, estimating the extent to which a node is part of a cluster of nodes. An overall global clustering coefficient for the entire network can be estimated.

Existing Tools and Approaches

A series of open R packages have been developed for network analysis. The most essential are mentioned below.

- IsingFit (https://cran.r-project.org/web/packages/IsingFit/index.html) is used for generation of binary networks
- ppcor (https://cran.r-project.org/web/packages/ppcor/index.html) performs partial correlation analysis, used for the network adjacency matrix
- qgraph (https://cran.r-project.org/web/packages/qgraph/index.html) is used for network visualization and analysis, as well as Gaussian graphical model computation.
- bootnet (https://cran.r-project.org/web/packages/bootnet/index.html) is used to assess accuracy and stability of estimated network structures and centrality indices.
- pcalg (https://cran.r-project.org/web/packages/pcalg/index.html) provides methods for causal structure learning and causal inference using graphical models.
- The packages graphicalvar (https://cran.r-project.org/web/packages/graphicalVAR/index.html), mlvar (https://cran.r-project.org/web/packages/mlVAR/index.html), GIMME (https://cran.r-project.org/web/packages/gimme/index.html), RSiena (https://cran.r-project.org/web/packages/RSiena/index.html) and btergm (https://cran.r-project.org/web/packages/btergm/index.html) provide different approaches for temporal network analysis.

In python, it is worth mentioning the general network analysis tools

- igraph (https://igraph.org/python/)

for the creation and manipulation of graphs

- Networkx (https://networkx.github.io/) for the study of complex networks
- Pyunicorn (https://github.com/pik-copan/pyunicorn) Unified Complex Network and RecurreNce analysis toolbox), for functional network and nonlinear time series analysis

Several free applications targeting network analysis are available to the scientific community:

- Cytoscape (https://cytoscape.org/) is a bioinformatics platform for visualizing biological interaction networks, including gene expression profiles and other relevant data.
- Gephi is an interactive visualization and exploration platform for all kinds of networks and complex systems, dynamic and hierarchical graphs. https://github.com/gephi/gephi/wiki
- Pajek enables analyses of large networks http://mrvar.fdv.uni-lj.si/pajek/
- Visone (https://visone.info/) is a software for the analysis & visualization of social networks
- graphml http://graphml.graphdrawing.org/
- MuxViz is a framework for the multilayer analysis and visualization of networks. http://muxviz.net
- Radatools is a software for communities detection in complex networks http://deim.urv.cat/~sergio.gomez/radatools.php
- KNIME modules https://www.knime.com https://www.knime.com/book/network-examples/socialNetworkAnalysis

Applications in the Health and Systems Medicine Domain

A series of representative examples are presented below, that follow the network medicine principles, in a descriptive manner leading to a better understanding of diseases, and in a for enabling predictions and decisions.

Descriptive Approaches

Network approach to psychopathology: the mental symptoms network

The network theory of mental disorders, as proposed by Cramer (2016) and Borsboom (2017), is based on the network medicine principle, complexity and interaction between components, as well as causal relations. This approach states that 'mental disorders arise from direct interactions between symptoms. Symptoms of psychopathology are causally connected through myriads of biological, psychological and societal mechanisms. If these causal relations are sufficiently strong, symptoms can generate a level of feedback that renders them self sustaining'. This suggests a network, in which symptoms are represented as nodes and relations, or causal interactions between symptoms are the edges between nodes.

In the same vein, in (Boschloo et al , 2015) a broad symptom network is suggested, where symptoms within the same diagnosis show differential associations, rendering rather insufficient the strategy of simple summing symptoms, as in current classification systems. Furthermore, some symptoms show strong connections with symptoms of other diagnoses, potentially explaining the comorbidity across diagnoses.

One interesting implication of this symptom network conceptualisation is the idea of resilience and vulnerability formed with the network structure and dynamics. Strong symptom connectivity and thus the possibility of positive propagation induces vulnerability, which, when coupled with a strong external stressor, leads to disorder.

While fundamentally descriptive, this approach opens decision making perspectives. Specifically, it can suggest, a) symptom interventions, targeting symptoms that have outward influence in the network towards changing the state of one or more symptoms, rather than symptoms that have many incoming connections, and b) network interventions, which change the network structure itself by modifying (desensitizing) symptom-symptom connections.

Cancer symptoms network

In the work of (Papachristou et al;2019) a standard symptom assessment scale was used to evaluate the occurrence, severity, and distress of more than 38 symptoms commonly associated with cancer and its treatment, generating a multidimensional experience of symptoms. Patients were asked to indicate whether or not they had experienced each symptom in the past week (i.e., symptom occurrence). If they had experienced the symptom, they were asked to rate its severity and distress. The symptoms were used to generate networks, and clusters were recognised. A psychological symptom cluster across all three dimensions, confirming its s that this is important in oncology patients, while hormonal, respiratory, nutrition, and medication-related clusters were also identified across all three symptom dimensions.

Network analysis in aging data

In (Valenzuela et al;2017), network analysis was performed on the Singapore Longitudinal Aging Study dataset (Niti et al;2008). Clusters of variables were obtained, which were mixed-domain, corresponding to a broad-scope structuring of the data. The clusters could be generally classified as central and non-central clusters, according to their betweenness centrality. In a cluster network where the nodes denote clusters, edges denote the presence of association between clusters, and the edge weights denote the “distance” (inversely-proportional to the strength of association) between connected clusters. Central clusters included Lipid Metabolism, Nutrition, Cardio-Renal and Cardio-Pulmonary Dysfunction, Frailty and Exhaustion, Physical Strength, and Cognitive Impairment.

This network analysis suggested that the phenotype of health and disease in old age can be regarded as a hierarchical network, a backbone of central nodes, and relations with other peripheral nodes, which includes inter-relationships between physiological and psychological functions, disease, disability, quality of life, and lifestyle and behavioural risk factors. This large scale analysis proposes an integrated view of human health, with interconnected diseases.

In the work of (Zierer et al; 2016) wider scope was adopted, including omics markers and phenotypes, and assessing conditional dependencies between them, by use of MGM networks (Haslbeck et al;2015). The produced model consists of seven modules that represent distinct aspects of aging. The modules are connected by hubs that potentially trigger comorbidities of age-related diseases, for example, body composition variables are associated with inflammatory IgG markers, mediated by the expression of the hormone oxytocin. This network modelling approach demonstrates the interconnectivity of age-related diseases and points at potential drivers of comorbidities.

Network neuroscience and functional networks

A comprehensive overview of network neuroscience is presented in the work of (Bassett and Sporns ;2017), conceived as a conceptual and practical framework. The review of (Farahani et al;2019) presents studies utilizing graph-based methods to analyze connectivity patterns in the human brain network using fMRI data, and discusses the topological architecture of human brain networks, such as small-worldness, modular organization, and presence of hubs.

Bartsch et al (2015) explore the coupling between systems in terms of presence of constant time delay (TDS) between activations of two systems. They construct physiologic networks based on the percentage of the time with TDS among physiological signals representing the function of different organs or systems. They use sleep data to demonstrate this principle of functional connectivity.

In (Chang and Yu;2019) the pathologic alterations of functional connectivity are under investigation. Specifically, alterations of resting-state effective connectivity (information flows) from and to hippocampal subregions after an acute social stressor, finding alterations in the thalamus-hippocampus-insula/midbrain circuit, that predicted the stress or control conditions. These connectivity alterations may be associated with the encoding of threatening stimuli under stress.

Predictive Approaches

The network analysis of symptoms with longitudinal data can lead to predictive models.

In the work of (Hoffart et al;2018) the temporal dynamics of symptom networks were explored, along with the predictive value of specific symptoms. Patients completed a measure of DSM-IV PTSD symptoms weekly. The multilevel vector autoregressive (mlVAR) model was used to analyse the data, producing a temporal (dynamic), contemporaneous, and between-person network. This approach illustrated how certain symptoms predicted the future appearance of other symptoms, for example, hypervigilance one week predicted external avoidance the subsequent week.

With respect to predictability, the work of (Haslbeck and Waldorp;2018) focuses on how well the structure of network models may predict observations. After recognizing the methodological gap, they introduce nodewise predictability, which quantifies how well a given node can be predicted by all other nodes it is connected to in the network, and provide examples with cross-sectional and temporal data.

Disease onset and epidemics outburst

The change of state from stable to disease onset was predicted via a new concept of dynamical network biomarker, the temporal differential networks, at the molecular network level (Chen et al;2017). The computational approach was based on an unsupervised hidden Markov model (HMM) that represented the network change, to automatically identify the critical point during disease progression. A similar approach was proposed by the same authors (Chen et al;2017) using clinical data for the prediction of influenza outbreak. In the work of Masuda and Holme (2013) an overview of network epidemiology models is presented, giving insights on the prediction and prevention opportunities offered by temporal networks, also sharing concepts with social network analysis. This is a direction that can be leveraged in the big data and large network technologies. An overview demonstrating the value of network analysis in epidemiology is provided in the work of (Silk et al; 2017).

Networks in Bioinformatics

In (Bhuva et al;2019), differential co-expression analysis is explored, i.e., an approach that attempts to identify how network structure, in this case, gene-gene associations, changes across conditions, with application specifically in cancer diagnosis.

When gene expressions, genetic polymorphisms, and DNA methylation are taken into account, multilevel approaches are required. In (Pineda et al;2015) an effort is paid to identify three-way trans-association 'hotspots'. Such integrative approaches would greatly benefit from multilevel network models.

An overview of integrated omics network analysis across multiple omics layers, and exploration of the flow of information that underlies disease, is presented in the work of (Hasin et al; 2017). Furthermore, temporal microbiome networks and Granger Causality are explored in (Mainali et al, 2019).

Personalised and temporal networks in Digital Health

Moving beyond population-based models, the idea of personalized temporal network modeling is discussed in (Epskamp et al;2018). Two networks are computed here: a temporal network, in which nodes predict one another over time, and a contemporaneous network, in which one investigates if nodes predict one another in the same window of measurement.

In the work of (Liu et al;2018) temporal data of social network and Fitbit-based activity are considered, in order to explore changes in time, their co-evolution and eventually to recognise traits. Networks were analysed at different time snapshots, and the change of network characteristics over time allowed to distinguish different profiles among them, which could be useful in the future to predict and to guide individuals’ health-related behaviors.

In (Zhao et al;2016) four subnetworks are constructed, representing different aspects of social behavior. Different topological, ‘centrality measures’ are employed to cluster subjects, and the predictive value of clustering in smoking cessation is examined.

These examples are of great interest towards a synthesis of systems medicine and connected health approaches, that allow not only the understanding of health and disease, or health-related behaviors, but also support in better decisions and interventions.

Discussion: Technical and Methodological Challenges

Having already two decades of SM research, it is essential to recognize the methodological frameworks already made available and discuss the opportunities to leverage SM interdisciplinary research, towards participatory, personalized, predictive, and preventive (P4) systems medicine, as envisioned by Charles Auffray (2018).

In order to scale up the use of systems networks, it is crucial to provide mature methods and pipelines that are usable with personal longitudinal data, and have descriptive and predictive value.

In the work by (Forbes et al;2017) very important concerns have been raised regarding the replicability of network methods. It is suggested to improve the credibility of network medicine approaches in different directions.

As conditional independence networks are unstable and lack replicability, likely due at least in part to the predominance of measurement error at the node level, it is important to improve the data measurement error before analysis. More abstract analysis, in terms of clusters rather than nodes, can also improve robustness. Statistical methods to test network stability are of value.

In addition, it has to be noted that networks are typically generated with population data, and networks derived from between-subjects variation do not necessarily represent individuals. Recently discussed 'ideographic' approaches (Beltz et a;2016) propose the generation of personal networks.

Causal networks are of great importance; however one should interpret with cautiousness directed networks based on cross-sectional observational symptom-level data. Multiple measurements and longitudinal data are more appropriate for making causal inferences. Methods for analysis of temporal networks are advancing in the last decade. For example, in (Büttner et al, 2016), a new method is proposed for temporal correlation coefficient for directed networks, which examines metrics quantifying the possibility for an edge to persist between two consecutive snapshots, extended in directed graphs, with outgoing and incoming connections/temporal correlations. It is important to proceed with a mature temporal network analysis framework, that incorporates such measures and encompasses for mixed data (continuous and categorical), and for different time resolutions with respect to the scale of events under examination. Such an approach should be designed, in view of personalized predictions.

Finally, incorporating clustering approaches, in system networks (including longitudinal and multilevel networks) need to be further elaborated, towards network structure segmentation, such as spectral clustering (Emmons et al;2016), as well as clustering of subjects.

Conclusion

Patient data, both clinical and daily life, belong to categories. For example, in lifestyle, data may belong to nutrition, sleep, activity, mood and cognition, medical intervention, while groups of symptoms characterize disease diagnosis to a large extent. Assumptions of independence facilitate more straightforward representations, and analysis, as well as decision making. A simple summation of the number of present symptoms may be a simple index characterizing diagnosis or progression. However, sometimes these data may be intertwined, which is especially true for symptoms and lifestyle features. Within the big-data era, extended data availability allows questioning these independence assumptions towards more data-intensive approaches. This would allow us to move beyond the reductionist approach of 'divide and conquer', embracing systems complexity. The variety and heterogeneity of diseases and comorbidities can be tackled by network analysis, showing different paths expressed in different patients.

The systems networks can be built with population data, or personal data, and explore causal relations, multiscale and time-evolving phenomena. Networks can start from existing knowledge, as in the case of the ontology built from existing literature (Livitckaia et al;2019) and evolve towards edge weights and directions via further data acquisition.

Finally, it has to be noted that, the systems networks approaches can significantly benefit from the evolution of new data-driven mehods, like the graph neural networks (Scarselli et al; 2009), and graph convolutional networks (Kipf and Welling;2017).

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