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Network modeling helps to tackle the complexity of drug–disease systems

Maurizio Recanatini | **Luca Menestrina**

Department of Pharmacy and Biotechnology, Alma Mater Studiorum—University of Bologna, Via Belmeloro 6, Bologna 40126, Italy

Correspondence
Maurizio Recanatini, Department of Pharmacy and Biotechnology, Alma Mater Studiorum—University of Bologna, Via Belmeloro 6, Bologna, 40126, Italy.
Email: maurizio.recanatini@unibo.it

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Abstract

From the (patho)physiological point of view, diseases can be considered as emergent properties of living systems stemming from the complexity of these systems. Complex systems display some typical features, including the presence of emergent behavior and the organization in successive hierarchic levels. Drug treatments increase this complexity scenario, and from some years the use of network models has been introduced to describe drug–disease systems and to make predictions about them with regard to several aspects related to drug discovery. Here, we review some recent examples thereof with the aim to illustrate how network science tools can be very effective in addressing both tasks. We will examine the use of bipartite networks that lead to the important concept of "disease module", as well as the introduction of more articulated models, like multi-scale and multiplex networks, able to describe disease systems at increasing levels of organization. Examples of predictive models will then be discussed, considering both those that exploit approaches purely based on graph theory and those that integrate machine learning methods. A short account of both kinds of methodological applications will be provided. Finally, the point will be made on the present situation of modeling complex drug–disease systems highlighting some open issues.

This article is categorized under:

Neurological Diseases > Computational Models
Infectious Diseases > Computational Models
Cardiovascular Diseases > Computational Models

KEYWORDS

computational modeling, drug discovery, network medicine

1 | INTRODUCTION

The purpose of this article is to illustrate and discuss some recent developments of drug discovery-related network-based models in the light of the complexity of drug–disease systems. It stems from the realization that this kind of implementations are appearing in the literature at an increasing pace, but also from the need of casting some light on

how the scientific community working on drugs and diseases is confronting with the inherent complexity of the field. Complexity (Gentili, 2018) is an intrinsic feature of living matter, and it is characterized by several aspects, like, for example, the spontaneous appearance of emergent phenomena (Artime & De Domenico, 2022). These are events or behaviors unpredictable on the basis of the knowledge of the system's single elements. Life as we know it, from single cells to humans, is considered an emergent property (Goldenfeld & Woese, 2011), as are other self-organized events at both microscopic and macroscopic scales. Among the latter, diseases are typical examples of emergent behaviors. If we conceptualize a disease as a human (patho)phenotype, then we can consider it as the reflection of interacting pathobiological processes (both deterministic and stochastic) giving rise to a spontaneous unpredictable process, that is, an emergent property. This concept is masterfully presented by Loscalzo et al. (2007) and Loscalzo and Barabási (2011), who show how systems biology and network science can provide the basis for a redefinition of human diseases under this perspective.

Moreover, there is another aspect of complexity that cannot be disregarded in any attempt to describe the living matter, namely its organization in successive, higher-order, integrated levels (Novikoff, 1945). Moving from atoms to molecules, macromolecules, subcellular structures, cells, tissues, organs, and so on till to the whole individual, we all know these levels of organization, and we cannot fail to recognize that living systems along this scale show new and unique properties emerging through the combination of the lower-level layers. Again, the nature of diseases can be investigated at any level, but it is the combination and integration of them that should provide us with a comprehensive description.

If we are to enter the new era of drug discovery, we must consider the complexity of the state of illness and make it the basis from which to start in order to make the right decisions about effective new treatments. As regards the theoretical methods to be employed for building a representation of such complex system, since long time, physics provided us with the framework of network science (Barabási, 2016). A network is a list of the components of the real system and of the interactions between them, and it can be represented by a graph usually visualized as an ensemble of dots connected by lines. Visually, networks often appear as interwoven diagrams describing the interactions between the entities that make up a complex system. Since the early 2000s, several research groups started to explore the application of network-based approaches in drug discovery settings (Recanatini & Cabrelle, 2020), and here we briefly examine some recent contributions to, (1) the construction of descriptive conceptual models able to point out and analyze the complexity characteristics of diseases, and (2) the setting up of computational models allowing to tackle predictive tasks on drug–disease systems, particularly aimed at the identification of drugs and drug targets. With regard to this last point, a further aspect will be considered, namely, the methods by which the predictions are obtained.

2 | NETWORK MODELS OF THE DRUG–DISEASE SYSTEM

The theoretical modelization of the drugs' actions on diseases is a long-sought goal that can be traced back to the introduction of the "magic bullet" concept developed by Ehrlich at the dawn of the XXth century (Winau et al., 2004). On this basis, the "one disease-one target-one drug" paradigm arose that accompanied us in the discovery of most of the medicines presently used in pharmacological therapies. Despite its extremely reductionist character, the target-centered approach to drug discovery has had the undisputable merit of forcing the drug discoverers to think in terms of molecules and molecular interactions. With the advent of both systems biology and the "omics" technologies, the drug discovery paradigm evolved toward systems pharmacology (Hopkins, 2008), a strategy that can be comprised within the framework of network medicine (Loscalzo et al., 2017). The latter is an established discipline largely based on the use of networks for the analysis and study of diseases, from molecular etiology to clinical treatments (Silverman et al., 2020). In this context, a key concept is that, to understand the drugs' actions and to design new pharmacological treatments, one must consider not only one or some protein targets directly related to the disease but take into account the subnetwork of proteins connected to the specific target(s) involved in the disease: the "disease module" (Figure 1). At the basis of this hypothesis, there is the observation that quite often the proteins involved in a disease tend to interact with each other in an identifiable local neighborhood of the human protein–protein interaction network (since now on, interactome; Barabási et al., 2011).

Starting from the last decade, mainly inspired by the work of Barabási and coworkers, a consistent number of articles have contributed to pave the way toward this new mode of modeling the complex scenario of drugs and diseases. One of the first examples of this approach describes the whole landscape of genetic diseases by building and analyzing

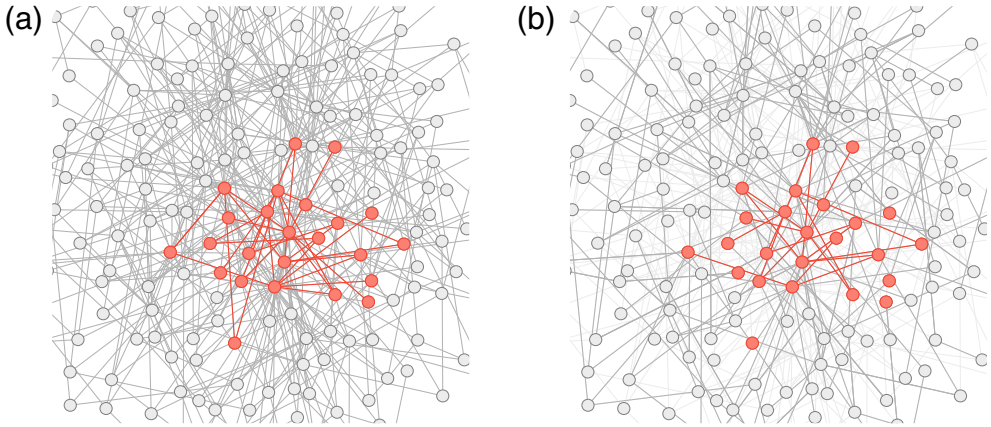

FIGURE 1 (a) A disease module (red nodes) is constituted by a set of connected nodes within the whole human protein–protein interactome. It represents a subnetwork including the proteins involved in the disease, that is, those proteins whose modifications are at the basis of the pathogenetic process (Barabási et al., 2011). (b) However, due to the incomplete knowledge of both the interactome and the disease associated genes, the observable disease module shows missing nodes and missing links that can leave some disease proteins disconnected from the subnetwork (Menche et al., 2015).

the "diseasome" (Goh et al., 2007), that is, a bipartite network (Pavlopoulos et al., 2018) showing the relations among diseases and the genes responsible for them. This kind of networks are made by two disjoint sets of nodes (here, diseases and genes), and the connections occur only between nodes belonging to different sets. The Goh's diseasome, where nodes can be both genes and diseases connected if the genes are involved in the pathobiology of the disease, provided a wealth of systematic information contained in the comprehensive map resulting from the data available in the OMIM database (version 2005). From the bipartite network, two projections were generated, that is the two monopartite networks containing only one type of nodes: genes (linked if they share at least one disease) or diseases (linked if they share at least one gene). From the disease network projection, it was possible to visualize that 867 (out of 1284) genetic diseases shared at least one gene with another disorder, and that 516 out of the 867 ones belonged to a single connected cluster, an observation that pointed out the interconnectedness of a relevant number of genetic diseases with regard to their genetic, that is, molecular, bases. On the other hand, the analysis of the gene network projection brought to the light the fact that genes that contribute to the same disease have the tendency to group into modules that reflect their common tissue expression patterns, as well as participation in biological processes and molecular functions, not to mention the tendency of their products to physically interact through protein–protein interactions (Goh et al., 2007). Notably, these observations contributed to the formulation of the disease module hypothesis mentioned above and to the subsequent refinement of the concept (Barabási et al., 2011; Menche et al., 2015).

Considering the gene products (i.e., proteins) and the activities performed by them inside the cell, it is easy to understand how soon molecular networks like gene regulatory networks, metabolic networks, and, mostly, protein–protein interaction networks (interactomes) became the favorite knowledge bases on which to rely to build models representing diseases even in the drug research context (Vidal et al., 2011). However, this molecular level of description is just the "basic" one and does not completely meet the need of a comprehensive modelization of diseases, say from genotype to phenotype. In fact, only the integrated consideration of intermediate levels of organization of the living matter could place us in a genuine complex system perspective. From here, the idea, that has already led to some interesting applications, of including multiple sources of information within the network models, mainly through the construction of multiplex networks (De Domenico et al., 2013). Multiplex networks, that belong to the more general class of multilayer network (Hammoud & Kramer, 2020), are made by one set of nodes connected by more than one type of relations represented in the respective layers, such that each layer contains one different type of link between the same set of nodes (Figure 2).

De Domenico's group is among the most active ones in proposing the use of multiplex networks to study diseases, and a first representative example was presented in a 2019 article (Halu et al., 2019). In this work, the authors reported the construction and analysis of a multiplex network of human diseases, containing both a genotype-based and a phenotype-based layer. The two layers represent the same set of diseases (nodes), but account for different kinds of

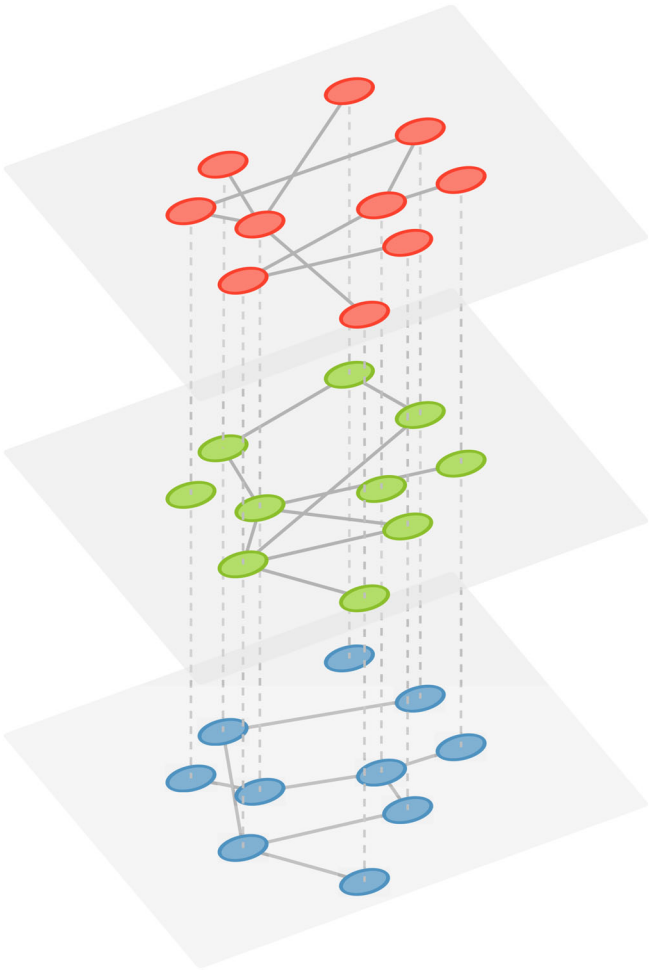

FIGURE 2 Multiplex network. Nodes represent the same entity (e.g., diseases), intra-layer links represent different relations among nodes (e.g., common gene[s], common phenotype[s], and common drug[s]), inter-layer links outline the connectivity across layers.

relations among them (links): in the genotype-based layer, two disorders are linked if they share at least one common gene, whereas in the phenotype-based layer, two diseases are connected if they share a common symptom. The resulting multiplex network consists of 779 diseases connected by 1115 genotypic and 5005 phenotypic relations. One of the important results claimed by the authors in terms of disease classification was the identification of disease communities on the basis of the simultaneous consideration of both genotypic (molecular) and phenotypic (symptoms) features made possible by the multilayer structure of the network. It is interesting to note that, in this case, a second level of description was added to the disease projection of the diseasome of Goh et al. (2007) mentioned above taking a top (the diseases) down perspective. The multilayer approach was further developed in an article published by Menche's group (Buphamalai et al., 2021) that, in the context of rare diseases, built a multiplex network accounting for six levels of biological organization and consisting of 46 layers describing the relations (over 20 million links) among 20,354 genes. Here, the nodes are genes (bottom-up perspective), and the first layer accounted for genetic interactions derived from analysis of many cell lines. Then, in a sequence of increasing organizational levels, layers were added to include co-expression data, as well as interactions between gene products, pathway co-membership, co-annotations in biological processes and molecular functions (derived from GO [The Gene Ontology Consortium, 2021]), and in phenotypes (derived from Mammalian phenotype ontology (MP) [Smith & Eppig, 2012] and Human phenotype ontology (HPO) [Köhler et al., 2021]). The resulting overall picture is impressive and contains a lot of information useful for carrying out the systematic investigation of rare disease in a real holistic perspective. But what is important from the standpoint of the present discussion is that the possibility of building disease descriptions taking into consideration several levels of complexity seems definitely acquired. The road opened by the Goh's diseasome model can now be traveled (either bottom-up or top-down) toward an ever deeper knowledge and description of diseases.

3 | PREDICTIVE NETWORK MODELS

The above-mentioned articles show the power of network tools in allowing the construction of comprehensive models capable of including and highlighting the features of the human diseasome (here understood as all the human diseases as a whole). The next step is to use this kind of models in a predictive setting within the drug discovery scenario, that is, to advance hypotheses regarding such typical issues of the field, as, for example, the identification of drug candidates, the elucidation of mechanisms of action, the prediction of adverse effects.

One of the first attempts to quantitatively relate drugs and diseases purely on the basis of network tools is presented in a landmark article of Guney et al. (2016). These authors developed a procedure to account for the relationships among drugs and disease-related proteins in the context of the human interactome, previously defined as "a comprehensive map of all biologically relevant molecular interactions" (Menche et al., 2015). In this work, the authors, based on the disease module hypothesis, postulated that for a drug to treat effectively a disease, its targets should be within or in the close vicinity of the disease module, and proposed to use the distance of drug targets to proteins of the disease module (the "drug–disease proximity") as a metrics to assess the effect of a drug on that disease, in essence, to predict the association between the drug and the disease. As shown in Figure 3, for a given drug, the distance d on the protein–protein interactome between all drug's targets and the nearest disease protein is calculated as the average shortest path length between them, where the shortest path between two nodes is the path with the minimum number of edges. Then, d is normalized into a proximity value (z-score) by comparing the measured distance to that of a dummy reference distribution.

Using this computational framework able to quantify the relationship between disease modules and drug targets, Guney et al. (2016) showed the reliability of the drug–disease proximity concept to analyze several features of the therapeutic action of 238 drugs on 78 diseases. In fact, even though the main focus was on predicting drug–disease associations in view of both pinpointing the treatments prescribed for a disease and identifying repurposable drug candidates, the analysis of the relationships between drug targets and disease modules made it possible to help the understanding of drugs' mechanism of action and to evaluate drug–drug similarity. This approach was further extended and experimentally validated by Cheng et al. (2018) in the field of cardiovascular (CV) diseases. Using a human interactome consisting of 16,677 proteins connected by 243,603 interactions, these authors identified 431 non-CV FDA-approved drugs (out of 807) as significantly associated to 22 CV diseases on the basis of the proximity (z-score) of drug targets to disease modules. To validate the results, analyses of patient-level data as well as in vitro experiments in human aortic endothelial cells were carried out for some of the predicted treatments.

Following the approach proposed and validated in the two just mentioned articles, the concept of drug–disease proximity has been widely applied to prioritize potentially repurposable drugs in several therapeutic areas, like, for example, cancers (Cheng et al., 2019), COVID-19 (Gysi et al., 2021; Patten et al., 2022; Zhou, Hou, Shen, Huang, et al., 2020; Zhou, Hou, Shen, Mehra, et al., 2020), and neurological diseases (Fang et al., 2021; Menestrina & Recanatini, 2022; Peng et al., 2020), as it allows to quantitatively rank drugs on the basis of the distance of their known targets from the disease module on the human protein–protein interactome.

In the attempt to overcome the limitations of methods based on a description of the drug–disease system that takes into consideration "only" proteins, several authors have started to add further levels of knowledge to the network models in a multi-scalar perspective. For example, a recent article by Ruiz et al. (2021) extends the protein–protein interactome-centered view and describes the construction of a more articulated network-based model of how drugs act on diseases. The article illustrates a multiscale approach to the modelization of disease treatments, where the molecular level of proteins (both drug- and disease-related) and drugs is combined with a superior biological level of description, namely, GO (The Gene Ontology Consortium, 2021) biological processes, to allow for the analysis of nearly 6000 approved drug treatments. To give an idea of the knowledge base used in the construction of the model, it is worth noting the list of nodes and links considered:

1661 drugs connect to the proteins they target (8568 edges);
840 diseases connect to the proteins they disrupt (25,212 edges);
17,660 proteins connect to other proteins through physical interactions (387,626 edges);
proteins connect to the 9798 biological functions they affect (34,777 edges);
biological functions connect to each other in a hierarchy (22,545 edges).

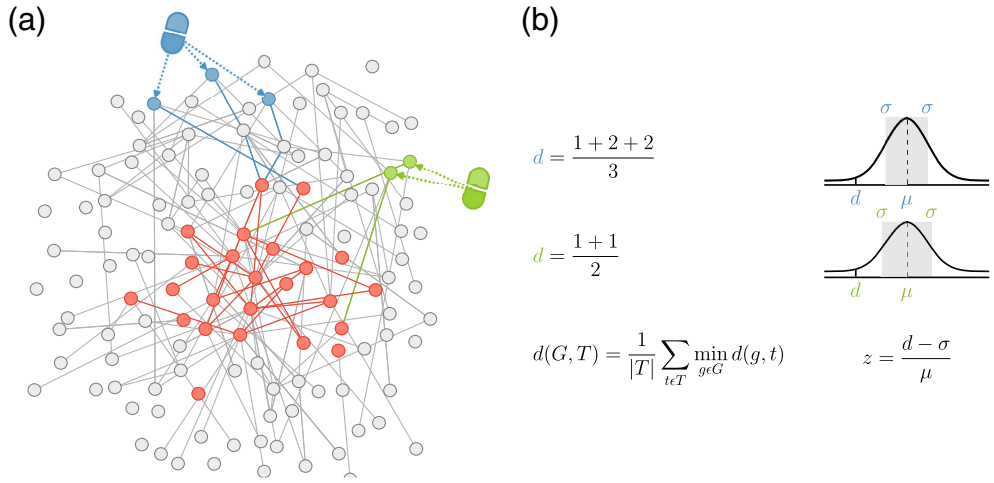

FIGURE 3 (a) The drug–disease proximity for two drugs (blue and green) on the human interactome. The shortest paths on the interactome between the drugs' targets (blue and green nodes) and the respective nearest disease proteins (red nodes) are highlighted by blue and green colored edges. (b) The calculation of d for the two exemplary drugs and the generalized formulas for the calculation of d and its normalization into a z-score. Mean (μ) and standard deviation (σ) refer to the distribution of distances calculated for a reference set of nodes that has the same number and degree values as the real one (drug targets plus disease module). G is the set of disease-related genes, T is the set of drug targets, and $d(g,t)$ is the shortest path length between nodes g ($g \in G$) and t ($t \in T$); $d(G,T)$ is the distance between the drug and the disease. μ and σ are the mean and standard deviation, respectively, of the distance distributions calculated for the reference sets of nodes used to calculate the z-score.

This integrated model appears to give better results in the prediction of drug treatments for diseases than the approach based only on protein–protein interactions. Moreover, it allows one to tackle such important pharmacological issues as, (i) the identification of proteins and biological functions relevant to treatments, and (ii) the identification of genes possibly interfering in the action of drugs. The method adopted by the authors to predict drug treatments is based on the calculation of the network diffusion profiles of both drugs and diseases, that are then compared to infer the drugs most suitable to treat a given disease. The diffusion profiles are vectors that encode the propagation of drugs and diseases effects across the multiscale network: they are calculated based on the probability that a "random walker" visits the network nodes (proteins and biological functions) starting from each drug and disease node.

The article by Ruiz et al. (2021) is just one example of how network science-based mathematical tools can be applied to network models to draw predictions about drug treatments considering the multi-level global landscape of human diseases. The important contribution provided by this work is that it integrates the molecular interactome with a further level of description of the drug–disease system, still maintaining the structure of a heterogeneous graph with four types of nodes and undirected edges of only one type. Following a similar approach, in recent times, other groups investigated the treatments-disease scenario of different pathologies with the aim of repurposing known drugs to tackle them (see, e.g., Fiscon et al., 2021; Paci et al., 2022).

As a further example of the predictive capability of network-based models accounting for the complexity of the drug–disease systems, we can consider the work by Zeng et al. (2020), who proposed a method to infer drug–target interactions (DTIs) allowing for the prediction of both targets and repurposable drugs. These authors aimed at incorporating several types of data into a heterogeneous drug–target–disease network by taking advantage of a deep neural network algorithm to embed all information on each node into low-dimensional feature vectors. The prediction of DTIs is then obtained on the basis of a score that estimates the likelihood of the pairwise interaction between each drug–target pair. The data used in this work, that resulted in the proposal of a new pharmacological treatment for multiple sclerosis validated by in vivo experiments, are the following:

5680 drug–target interactions connecting 732 FDA-approved drugs and 1178 unique human targets;
16,133 protein–protein interactions connecting 1915 unique drug targets;
132,768 clinically reported drug–drug interactions connecting 732 unique FDA-approved drugs;
1208 drug–disease pairs connecting 732 drugs and 440 diseases;
263,805 drug–adverse drug effects (ADEs) associations connecting 732 approved drugs and 12,904 ADEs;

23,080 disease–gene pairs connecting 440 diseases and 1915 drug target-coding genes.

Based on the cases presented above, it can be observed that the complexity of the drug–disease system is increasingly considered as a central issue in the drug–disease modelization studies, not only in view of the rationalization of acquired knowledge, but also in the perspective of prediction. This is clear evidence of the new paradigm of drug discovery, that increasingly takes advantage of the new opportunities provided by theoretical modeling, better algorithms, and data accumulation and availability.

3.1 | Computational approaches for predictions

As seen above, when it comes to making predictions in network models applied to drug discovery (actually, in any kind of drug discovery-related models since the early times of QSAR (Hansch & Silipo, 1974)), the goal is to associate one or more compound(s) to one or more target(s)—the latter being protein(s) or disease(s)—producing a ranked list of molecule-target pairs. The computational methods used in this context cover an extremely wide range, but those applied to network models can be roughly divided into purely network-based techniques and applications of machine learning (ML). The above discussed work of Guney et al. (2016) is a typical example of the former approach, where the algorithm to compute the drug–disease proximity is based on calculation and averaging of the shortest path lengths between nodes on the human protein–protein interactome. However, initially, and still nowadays, the most popular class of network-based methods applied to the prediction of DTIs is that of similarity-based algorithms, built on the guilt-by-association principle. These are link prediction methods on which we briefly accounted for previously (Recanatini & Cabrelle, 2020), that include both recommendation techniques, like the network-based inference (NBI) method developed by Cheng et al. (2012) and enhanced by Alaimo et al. (2013), and network propagation methods (Cowen et al., 2017). As regards the latter, random walk with restart (RWR) in various versions has been frequently employed in the field of drug discovery (see below for references). A detailed illustration of the algorithm is out of the scope of this article, but a short description of the approach with regard to DTI prediction is due. RWR is a stochastic method that usually runs on a heterogeneous network composed of drugs and targets and aims to calculate the probabilities associated to each compound-protein pair. The drug–target integrated network is constructed as a combination of the drug–drug and target–target similarity networks with the known drug–target associations network. The algorithm simulates a walker that randomly moves from source (seed) nodes (e.g., drugs, if one is interested in predicting their targets) to neighbors. Eventually, with a probability r, the walker restarts from the source node, and, after several iterations, the diffusion process reaches a steady state where the probabilities of all the drug–target associations are defined and finally ranked. In Figure 4, a simplified schematic illustration of RWR is provided.

RWR appears to be an efficient method to rank associations like, drug–target, drug–disease, gene–disease, and in the last decade it has been applied to heterogeneous networks for both target prediction and drug repurposing (see, e.g., Cheng et al., 2012; Liu et al., 2016; Luo et al., 2017; Seal et al., 2015). Actually, the above discussed article by Ruiz et al. (2021) takes advantage of a biased RWR algorithm to calculate the diffusion profiles of drugs and diseases on a multiscale model in order to compare them and to predict drug–disease associations, that is, pharmacological treatments. Recently, Valdeolivas et al. (2019) extended the RWR algorithm to multiplex and multiplex-heterogeneous networks, in this way broadening the field of applicability of the method to models capable of taking into consideration multiple levels of information. This approach was employed by Yao et al. (2021) to successfully predict associations between diseases and long noncoding RNAs.

ML-based methods have become very popular in drug discovery nowadays, and their use in pursuing predictive goals in network models is also increasing. Under the broad definition of ML a plethora of algorithms are comprised, basically aimed at learning from a set of known input and output data (features, X, and labels or targets, Y, respectively) a function able to mapping X to Y, such that unknown Y labels or targets are correctly predicted from new X features. Deep learning (DL) techniques are a group of ML algorithms based on the architecture of artificial neural networks (ANN) made up of a pool of interconnected artificial neurons organized in layers. Model training consists of fitting the weights of a (nonlinear) function so that the input data is correctly mapped to the output. DL algorithms are characterized by the presence of multiple hidden layers. Quite a few reviews can lead the interested reader into the field of ML. For general applications in drug discovery and more focused ones on DTIs prediction, see Vamathevan et al. (2019) and Bagherian et al. (2021), respectively. A thorough review of the current literature of ML applications to drug–disease network models is out of scope here, but it is worth mentioning a couple of examples where this kind of

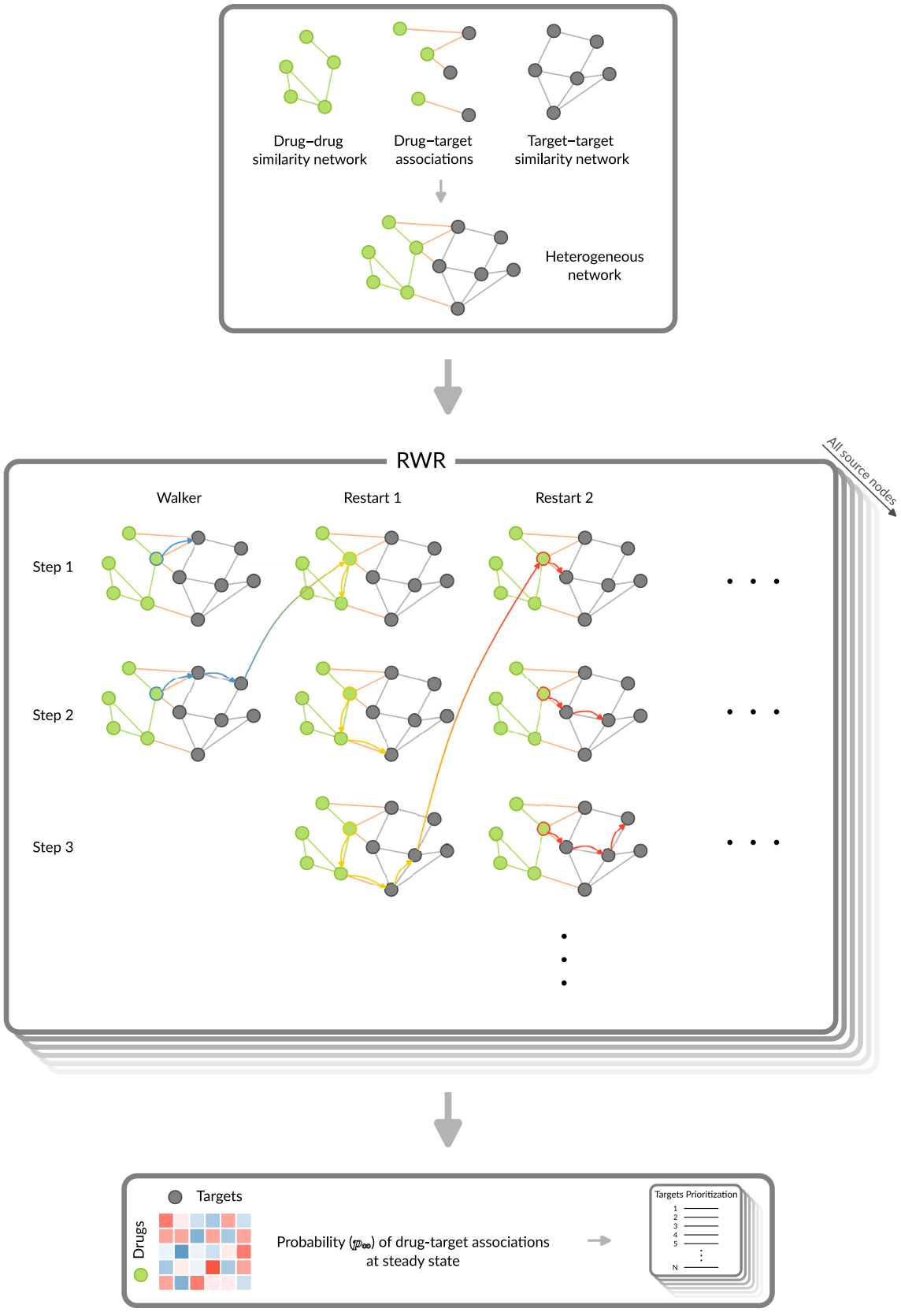

FIGURE 4 Legend on next page.

methods have shown their usefulness. The first is reported in an article of Yamanishi et al. (2008), who as early as in 2008 published one of the first network-based models for DTI prediction. The same way as in the examples above, a heterogeneous drug–target network was built (here called "pharmacological space") by integrating drug–drug and target–target similarity data with known drug–target association information. This network is represented by a matrix whose row vectors are the feature vectors of known drugs and targets. Based on a "gold standard" set of known DTIs, two ML models (kernel regression) were trained, one for the correlation between drug feature space and pharmacological feature space and one for the correlation between the target feature space and the pharmacological feature space. In this way, the authors could then map new drugs and new targets to the heterogeneous network and obtain the feature vectors of new drugs and targets. Finally, by combining the feature vectors, it was possible to obtain feature-based similarity scores for the drug–target pairs used as a measure of the association of drugs and targets. Twelve years after the pioneering work of Yamanishi et al. (2008), the power of DL algorithms applied to heterogeneous networks to analyze the drug–disease system was displayed in the article by Zeng et al. (2020) illustrated above. Note that, also in this case, the key result of the procedure was the achievement of vectors encoding the features of nodes that could then be compared to infer the predictions on drug–target associations.

Finally, it is worth noting that network-based approaches like RWR and ML-based methods can be combined. For example, Liu et al. (2019) predicted effective drug combinations using a heterogeneous drug–target network and running an adapted version of RWR using two or more drug nodes as source nodes. The probability distributions of the drug combinations at the steady state encoded in the $\boldsymbol{p}_\infty$ vectors were then used as feature vectors to train a classifier (gradient tree boosting) able to predict effective drug combinations.

4 | DISCUSSION

Fifty years ago, P. W. Anderson in his article entitled "More is different" (Anderson, 1972) strongly criticized the reductionist view of science and proposed a hierarchic organization of the knowledge, whereby each level, besides being connected with the upper and lower ones, displays his own unique properties requiring research to be carried out and eventually new concepts or laws to be formulated. These ideas set a landmark in the development of complexity science, and nowadays they are being applied to as different fields as societal organization, economics and life sciences, particularly with regard to the study of emergent phenomena (Strogatz et al., 2022). Since several years, these complexity concepts broke into the field of medicine giving rise to the now established discipline of network medicine (Loscalzo et al., 2017) that combines systems biology and network science to provide a theoretical and methodological framework, on which to rely to achieve understanding of the ultimate nature of human illnesses and to provide effective treatments. The cases illustrated above are examples of how these concepts are put into practice. Network models of different architecture describe the disease systems either at a single level, for example, genes or proteins, or at multiple levels, for example, multiplex or multi-scalar cases, allowing us to investigate on the nature of the illnesses, ideally, from genotype to phenotype (see the above presented articles [Buphamalai et al., 2021; Goh et al., 2007; Halu et al., 2019]). Furthermore, if the network models are coupled with suitable computational algorithms, they become the basis of powerful predictive tools, useful among others to identify treatment candidates, like, for example, repurposable drugs, as shown in the articles (Guney et al., 2016; Ruiz et al., 2021; Zeng et al., 2020), as well as in the early work by Yamanishi et al.

FIGURE 4 The RWR algorithm illustrated for a drug–target system. RWR runs on the heterogeneous network that integrates similarity drug–drug and target–target connections, as well as known relationships between drugs and targets (upper panel). The algorithm simulates a walker that, starting from a seed node (here a blue circled green node) randomly moves to neighbor nodes. Occasionally, it can return back to the initial node and then start walking again (middle panel). This procedure is carried out for all source nodes, and the main equation implemented in the algorithm allows to calculate for each of them the probability matrix $\boldsymbol{p}$, whose elements contain the probabilities of finding the walker at different target nodes at subsequent steps starting from the initial probability matrix $\boldsymbol{p}_0$:

$$\boldsymbol{p}_{t+1} = (1-r)\boldsymbol{W}^T\boldsymbol{p}_t + r\boldsymbol{p}_0$$

where $\boldsymbol{W}^T$ is the transition matrix of the integrated network. After several iterations, a steady probability $\boldsymbol{p}_\infty$ is obtained (when the change between $\boldsymbol{p}_t$ and $\boldsymbol{p}_{t+1}$ is less than a threshold value), and for each drug source node, the target nodes with the highest probability values are considered as the predicted targets of that drug (lower panel).

(2008). In all cases, network models provided the essential opportunity to take into consideration the complexity of the biological system, and when they were combined with predictive algorithms, either purely network-based or ML, proved to be fully suitable for drug discovery tasks.

Now, being ascertained that networks represent an effective operational trade-off between the old reductionist vision and the impossible fully detailed description of drug–disease systems (Csermely et al., 2013), the question is: what's next? That is, what are the still open issues requiring further research efforts in order to strengthen the theoretical basis of the approach and improve both descriptions and predictions?

The first one has to do with data. The quality of data on which models aimed at modeling complexity are built is vital. This must be interpreted not only and simply in terms of "technical" accuracy, but it represents an issue that is pervading the network-based modelization of complex biological systems. Indeed, the problem of literature bias in the construction of the protein–protein interactome is well known (Rolland et al., 2014), and the inherent incompleteness of the network (Menche et al., 2015) is just another face of the same problem. Indeed, DTI prediction models based on the guilt-by-association principle particularly suffer from it and even though methods to tackle this problem begin to appear (Zietz et al., 2023), the challenge is still wide open. In addition, when it comes to modeling drug–disease systems, deeper and more insidious questions might arise, like, for example, the physiological relevance of experimental data toward the illness. In an illuminating article (Gintant & George, 2018), Gintant and George have clearly pointed out how experiment outputs should ideally reflect the physiological complexity of the system (e.g., with regard to the dynamic nature of pathological processes) and comply with the operable range of parameters related to biological processes (temperature, pH, ion concentration, etc.). In the absence of these conditions, the risk exists of getting results that "may not be all that believable or physiologically relevant" (Gintant & George, 2018). A similar concern was already raised by Ideker and Krogan (2012), who argued that network models might be poorly able to faithfully capture the physical reality of protein interactions in a living system. This is because proteins are modified, transported, and have different concentrations in the cell (or in a tissue), thus being exposed to a plethora of possible interactions that vary in many aspects, including time, affinity, specificity, and stoichiometry. The very concept of simple binary connection between two protein nodes might be questioned if one considers post-translational modifications (Aebersold et al., 2018), and eventually the possibility of nonindependent binding due to allosteric modifications.

A further issue partly related to the previous one arises from the fact that for the system that we aim to model by building the network we neglect such quantitative parameters as intracellular protein concentrations, and equilibrium and kinetic constants, which determine the dynamic response to perturbations. In other words, it must be remarked that the network models discussed in this article do not take into consideration the intrinsic dynamic character of biological systems. Actually, they provide a static framework within which the determinants of diseases can be identified by analyzing the network topology (Loscalzo, 2019). Notably, besides taking a deterministic approach based on the knowledge of kinetic parameters and on the solution of systems of ordinary differential equations, the construction and analysis of Boolean network models might offer a valuable alternative when the time evolution of the network must be considered (Hemedan et al., 2022).

Finally, a more basic question to be investigated regards, in our opinion, the assessment of the complexity of the drug–disease system. An attempt in this sense has been done by López-Rodríguez et al. (2021), who explored a comprehensive drug–disease network by means of two measures of complexity, that is, Shannon entropy and algorithmic complexity. This work provides an initial look at the complex drug–disease system, even though it has some limitations, particularly regarding the completeness of the database on which the analysis is based. However, this kind of studies are needed to investigate in depth the nature and the origin of the behaviors that render a drug–disease system complex, and they are practically useful to set the most proper modeling environment to allow one to make the right decisions. Complexity science provides theory and methods to do that (Siegenfeld & Bar-Yam, 2020), and further applications are certainly desirable.

5 | CONCLUSION

In conclusion, graph theory and network science provide us with powerful methods to tackle the description of complex drug–disease systems. Moreover, when coupled with such effective computational tools as ML or its fast-growing branch DL, drug–disease network models can make available predictive tools able to guide us to the right selection of target entities (e.g., drugs, molecular drug targets, diseases) to be prioritized from vast collections of data. Challenging issues remain to be solved, but time is set for a full integration of complexity science into drug discovery.

AUTHOR CONTRIBUTIONS

Maurizio Recanatini: Conceptualization (lead); writing – original draft (equal); writing – review and editing (equal). **Luca Menestrina:** Writing – original draft (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Maurizio Recanatini https://orcid.org/0000-0002-0039-0518
Luca Menestrina https://orcid.org/0000-0002-3397-7737

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REFERENCES

Aebersold, R., Agar, J. N., Amster, I. J., Baker, M. S., Bertozzi, C. R., Boja, E. S., Costello, C. E., Cravatt, B. F., Fenselau, C., Garcia, B. A., Ge, Y., Gunawardena, J., Hendrickson, R. C., Hergenrother, P. J., Huber, C. G., Ivanov, A. R., Jensen, O. N., Jewett, M. C., Kelleher, N. L., ... Zhang, B. (2018). How many human proteoforms are there? *Nature Chemical Biology*, *14*(3), 206–214. https://doi.org/10.1038/NCHEMBIO.2576

Alaimo, S., Pulvirenti, A., Giugno, R., & Ferro, A. (2013). Drug-target interaction prediction through domain-tuned network-based inference. *Bioinformatics*, *29*(16), 2004–2008. https://doi.org/10.1093/bioinformatics/btt307

Anderson, P. W. (1972). More is different. *Science*, *177*(4047), 393–396. https://doi.org/10.1126/science.177.4047.393

Artime, O., & De Domenico, M. (2022). From the origin of life to pandemics: Emergent phenomena in complex systems. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, *380*(2227), 20200410. https://doi.org/10.1098/rsta.2020.0410

Bagherian, M., Sabeti, E., Wang, K., Sartor, M. A., Nikolovska-Coleska, Z., & Najarian, K. (2021). Machine learning approaches and databases for prediction of drug-target interaction: A survey paper. *Briefings in Bioinformatics*, *22*(1), 247–269. https://doi.org/10.1093/bib/bbz157

Barabási, A. L. (2016). *Network science*. Cambridge University Press.

Barabási, A. L., Gulbahce, N., & Loscalzo, J. (2011). Network medicine: A network-based approach to human disease. *Nature Reviews Genetics*, *12*(1), 56–68. https://doi.org/10.1038/nrg2918

Buphamalai, P., Kokotovic, T., Nagy, V., & Menche, J. (2021). Network analysis reveals rare disease signatures across multiple levels of biological organization. *Nature Communications*, *12*(1), 6306. https://doi.org/10.1038/s41467-021-26674-1

Cheng, F., Desai, R. J., Handy, D. E., Wang, R., Schneeweiss, S., Barabási, A. L., & Loscalzo, J. (2018). Network-based approach to prediction and population-based validation of in silico drug repurposing. *Nature Communications*, *9*(1), 2691. https://doi.org/10.1038/s41467-018-05116-5

Cheng, F., Liu, C., Jiang, J., Lu, W., Li, W., Liu, G., Zhou, W., Huang, J., & Tang, Y. (2012). Prediction of drug-target interactions and drug repositioning via network-based inference. *PLoS Computational Biology*, *8*(5), e1002503. https://doi.org/10.1371/journal.pcbi.1002503

Cheng, F., Lu, W., Liu, C., Fang, J., Hou, Y., Handy, D. E., Wang, R., Zhao, Y., Yang, Y., Huang, J., Hill, D. E., Vidal, M., Eng, C., & Loscalzo, J. (2019). A genome-wide positioning systems network algorithm for in silico drug repurposing. *Nature Communications*, *10*(1), 3476. https://doi.org/10.1038/s41467-019-10744-6

Cowen, L., Ideker, T., Raphael, B. J., & Sharan, R. (2017). Network propagation: A universal amplifier of genetic associations. *Nature Reviews Genetics*, *18*(9), 551–562. https://doi.org/10.1038/nrg.2017.38

Csermely, P., Korcsmáros, T., Kiss, H. J. M., London, G., & Nussinov, R. (2013). Structure and dynamics of molecular networks: A novel paradigm of drug discovery: A comprehensive review. *Pharmacology and Therapeutics*, *138*(3), 333–408. https://doi.org/10.1016/j.pharmthera.2013.01.016

De Domenico, M., Solé-Ribalta, A., Cozzo, E., Kivelä, M., Moreno, Y., Porter, M. A., Gómez, S., & Arenas, A. (2013). Mathematical formulation of multilayer networks. *Physical Review X*, *3*(4), 041022. https://doi.org/10.1103/PhysRevX.3.041022

Fang, J., Zhang, P., Zhou, Y., Chiang, C.-W., Tan, J., Hou, Y., Stauffer, S., Li, L., Pieper, A. A., Cummings, J., & Cheng, F. (2021). End-ophenotype-based in silico network medicine discovery combined with insurance record data mining identifies sildenafil as a candidate drug for Alzheimer's disease. *Nature Aging*, *1*(12), 1175–1188. https://doi.org/10.1038/s43587-021-00138-z

Fiscon, G., Conte, F., Farina, L., & Paci, P. (2021). SAveRUNNER: A network-based algorithm for drug repurposing and its application to COVID-19. *PLoS Computational Biology*, *17*(2), e1008686. https://doi.org/10.1371/journal.pcbi.1008686

Gentili, P. L. (2018). *Untangling complex systems*. CRC Press.

Gintant, G. A., & George, C. H. (2018). Introduction to biological complexity as a missing link in drug discovery. *Expert Opinion on Drug Discovery*, *13*(8), 753–763. https://doi.org/10.1080/17460441.2018.1480608

Goh, K. I., Cusick, M. E., Valle, D., Childs, B., Vidal, M., & Barabási, A. L. (2007). The human disease network. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(21), 8685–8690. https://doi.org/10.1073/pnas.0701361104

Goldenfeld, N., & Woese, C. (2011). Life is physics: Evolution as a collective phenomenon far from equilibrium. *Annual Review of Condensed Matter Physics*, *2*(1), 375–399. https://doi.org/10.1146/annurev-conmatphys-062910-140509

Guney, E., Menche, J., Vidal, M., & Barabási, A. L. (2016). Network-based in silico drug efficacy screening. *Nature Communications*, *7*, 10331. https://doi.org/10.1038/ncomms10331

Gysi, D. M., Do Valle, Í., Zitnik, M., Ameli, A., Gan, X., Varol, O., Ghiassian, S. D., Patten, J. J., Davey, R. A., Loscalzo, J., & Barabási, A. L. (2021). Network medicine framework for identifying drug-repurposing opportunities for COVID-19. *Proceedings of the National Academy of Sciences of the United States of America*, *118*(19), e2025581118. https://doi.org/10.1073/pnas.2025581118

Halu, A., De Domenico, M., Arenas, A., & Sharma, A. (2019). The multiplex network of human diseases. *Npj Systems Biology and Applications*, *5*(1), 15. https://doi.org/10.1038/s41540-019-0092-5

Hammoud, Z., & Kramer, F. (2020). Multilayer networks: Aspects, implementations, and application in biomedicine. *Big Data Analytics*, *5*(1), 2. https://doi.org/10.1186/s41044-020-00046-0

Hansch, C., & Silipo, C. (1974). Quantitative structure-activity relationship of reversible dihydrofolate reductase inhibitors diaminotriazines. *Journal of Medicinal Chemistry*, *17*(7), 661–667. https://doi.org/10.1021/jm00253a001

Hemedan, A. A., Niarakis, A., Schneider, R., & Ostaszewski, M. (2022). Boolean modelling as a logic-based dynamic approach in systems medicine. *Computational and Structural Biotechnology Journal*, *20*, 3161–3172. https://doi.org/10.1016/j.csbj.2022.06.035

Hopkins, A. L. (2008). Network pharmacology: The next paradigm in drug discovery. *Nature Chemical Biology*, *4*(11), 682–690. https://doi.org/10.1038/nchembio.118

Ideker, T., & Krogan, N. J. (2012). Differential network biology. *Molecular Systems Biology*, *8*(1), 565. https://doi.org/10.1038/msb.2011.99

Köhler, S., Gargano, M., Matentzoglu, N., Carmody, L. C., Lewis-Smith, D., Vasilevsky, N. A., Danis, D., Balagura, G., Baynam, G., Brower, A. M., Callahan, T. J., Chute, C. G., Est, J. L., Galer, P. D., Ganesan, S., Griese, M., Haimel, M., Pazmandi, J., Hanauer, M., … Robinson, P. N. (2021). The human phenotype ontology in 2021. *Nucleic Acids Research*, *49*(D1), D1207–D1217. https://doi.org/10.1093/nar/gkaa1043

Liu, H., Song, Y., Guan, J., Luo, L., & Zhuang, Z. (2016). Inferring new indications for approved drugs via random walk on drug-disease heterogenous networks. *BMC Bioinformatics*, *17*(Suppl 17), 539. https://doi.org/10.1186/s12859-016-1336-7

Liu, H., Zhang, W., Nie, L., Ding, X., Luo, J., & Zou, L. (2019). Predicting effective drug combinations using gradient tree boosting based on features extracted from drug-protein heterogeneous network. *BMC Bioinformatics*, *20*(1), 645. https://doi.org/10.1186/s12859-019-3288-1

López-Rodríguez, I., Reyes-Manzano, C. F., Guzmán-Vargas, A., & Guzmán-Vargas, L. (2021). The complex structure of the pharmacological drug-disease network. *Entropy*, *23*(9), 1139. https://doi.org/10.3390/e23091139

Loscalzo, J. (2019). A new paradigm for defining human disease and therapy. In J. Loscalzo, A. L. Barabási, & E. K. Silverman (Eds.), *Network medicine* (pp. 137–152). Harvard University Press. https://doi.org/10.4159/9780674545533-007

Loscalzo, J., & Barabási, A. L. (2011). Systems biology and the future of medicine. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*, *3*(6), 619–627. https://doi.org/10.1002/wsbm.144

Loscalzo, J., Barabási, A. L., & Silverman, E. K. (2017). In J. Loscalzo, A. L. Barabási, & E. K. Silverman (Eds.), *Network medicine: Complex systems in human disease and therapeutics*. Harvard University Press.

Loscalzo, J., Kohane, I., & Barabási, A. L. (2007). Human disease classification in the postgenomic era: A complex systems approach to human pathobiology. *Molecular Systems Biology*, *3*, 124. https://doi.org/10.1038/msb4100163

Luo, Y., Zhao, X., Zhou, J., Yang, J., Zhang, Y., Kuang, W., Peng, J., Chen, L., & Zeng, J. (2017). A network integration approach for drug-target interaction prediction and computational drug repositioning from heterogeneous information. *Nature Communications*, *8*(1), 573. https://doi.org/10.1038/s41467-017-00680-8

Menche, J., Sharma, A., Kitsak, M., Ghiassian, S. D., Vidal, M., Loscalzo, J., & Barabási, A. L. (2015). Uncovering disease-disease relationships through the incomplete interactome. *Science*, *347*(6224), 841. https://doi.org/10.1126/science.1257601

Menestrina, L., & Recanatini, M. (2022). An unsupervised computational pipeline identifies potential repurposable drugs to treat Huntington's disease and multiple sclerosis. *Artificial Intelligence in the Life Sciences*, *2*, 100042. https://doi.org/10.1016/J.AILSCI.2022.100042

Novikoff, A. B. (1945). The concept of integrative levels. *Science*, *101*(2618), 209–215.

Paci, P., Fiscon, G., Conte, F., Wang, R. S., Handy, D. E., Farina, L., & Loscalzo, J. (2022). Comprehensive network medicine-based drug repositioning via integration of therapeutic efficacy and side effects. *npj Systems Biology and Applications*, *8*(1), 12. https://doi.org/10.1038/s41540-022-00221-0

Patten, J. J., Keiser, P. T., Morselli-Gysi, D., Menichetti, G., Mori, H., Donahue, C. J., Gan, X., Valle, I. d., Geoghegan-Barek, K., Anantpadma, M., Boytz, R. M., Berrigan, J. L., Stubbs, S. H., Ayazika, T., O'Leary, C., Jalloh, S., Wagner, F., Ayehunie, S., Elledge, S. J., ... Davey, R. A. (2022). Identification of potent inhibitors of SARS-CoV-2 infection by combined pharmacological evaluation and cellular network prioritization. *iScience*, *25*(9), 104925. https://doi.org/10.1016/j.isci.2022.104925

Pavlopoulos, G. A., Kontou, P. I., Pavlopoulou, A., Bouyioukos, C., Markou, E., & Bagos, P. G. (2018). Bipartite graphs in systems biology and medicine: A survey of methods and applications. *Gigascience*, *7*(4), 1–31. https://doi.org/10.1093/gigascience/giy014

Peng, Y., Yuan, M., Xin, J., Liu, X., & Wang, J. (2020). Screening novel drug candidates for Alzheimer's disease by an integrated network and transcriptome analysis. *Bioinformatics*, *36*(17), 4626–4632. https://doi.org/10.1093/bioinformatics/btaa563

Recanatini, M., & Cabrelle, C. (2020). Drug research meets network science: Where are we? *Journal of Medicinal Chemistry*, *63*(16), 8653–8666. https://doi.org/10.1021/acs.jmedchem.9b01989

Rolland, T., Taşan, M., Charloteaux, B., Pevzner, S. J., Zhong, Q., Sahni, N., Yi, S., Lemmens, I., Fontanillo, C., Mosca, R., Kamburov, A., Ghiassian, S. D., Yang, X., Ghamsari, L., Balcha, D., Begg, B. E., Braun, P., Brehme, M., Broly, M. P., ... Vidal, M. (2014). A proteome-scale map of the human interactome network. *Cell*, *159*(5), 1212–1226. https://doi.org/10.1016/j.cell.2014.10.050

Ruiz, C., Zitnik, M., & Leskovec, J. (2021). Identification of disease treatment mechanisms through the multiscale interactome. *Nature Communications*, *12*(1), 1796. https://doi.org/10.1038/s41467-021-21770-8

Seal, A., Ahn, Y. Y., & Wild, D. J. (2015). Optimizing drug-target interaction prediction based on random walk on heterogeneous networks. *Journal of Cheminformatics*, *7*(1), 40. https://doi.org/10.1186/s13321-015-0089-z

Siegenfeld, A. F., & Bar-Yam, Y. (2020). An introduction to complex systems science and its applications. *Complexity*, *2020*, 6105872. https://doi.org/10.1155/2020/6105872

Silverman, E. K., Schmidt, H. H. H. W., Anastasiadou, E., Altucci, L., Angelini, M., Badimon, L., Balligand, J., Benincasa, G., Capasso, G., Conte, F., Di Costanzo, A., Farina, L., Fiscon, G., Gatto, L., Gentili, M., Loscalzo, J., Marchese, C., Napoli, C., Paci, P., ... Baumbach, J. (2020). Molecular networks in network medicine: Development and applications. *WIREs Systems Biology and Medicine*, *12*(6), e1489. https://doi.org/10.1002/wsbm.1489

Smith, C. L., & Eppig, J. T. (2012). The mammalian phenotype ontology as a unifying standard for experimental and high-throughput phenotyping data. *Mammalian Genome*, *23*(9), 653–668. https://doi.org/10.1007/s00335-012-9421-3

Strogatz, S., Walker, S., Yeomans, J. M., Tarnita, C., Arcaute, E., De Domenico, M., Artime, O., & Goh, K.-I. (2022). Fifty years of 'More is different'. *Nature Reviews Physics*, *4*, 508–510. https://doi.org/10.1038/s42254-022-00483-x

The Gene Ontology Consortium. (2021). The gene ontology resource: Enriching a GOld mine. *Nucleic Acids Research*, *49*(D1), D325–D334. https://doi.org/10.1093/nar/gkaa1113

Valdeolivas, A., Tichit, L., Navarro, C., Perrin, S., Odelin, G., Levy, N., Cau, P., Remy, E., & Baudot, A. (2019). Random walk with restart on multiplex and heterogeneous biological networks. *Bioinformatics*, *35*(3), 497–505. https://doi.org/10.1093/bioinformatics/bty637

Vamathevan, J., Clark, D., Czodrowski, P., Dunham, I., Ferran, E., Lee, G., Li, B., Madabhushi, A., Shah, P., Spitzer, M., & Zhao, S. (2019). Applications of machine learning in drug discovery and development. *Nature Reviews Drug Discovery*, *18*(6), 463–477. https://doi.org/10.1038/s41573-019-0024-5

Vidal, M., Cusick, M. E., & Barabási, A. L. (2011). Interactome networks and human disease. *Cell*, *144*(6), 986–998. https://doi.org/10.1016/j.cell.2011.02.016

Winau, F., Westphal, O., & Winau, R. (2004). Paul Ehrlich—In search of the magic bullet. *Microbes and Infection*, *6*(8), 786–789. https://doi.org/10.1016/j.micinf.2004.04.003

Yamanishi, Y., Araki, M., Gutteridge, A., Honda, W., & Kanehisa, M. (2008). Prediction of drug-target interaction networks from the integration of chemical and genomic spaces. *Bioinformatics*, *24*(13), 232–240. https://doi.org/10.1093/bioinformatics/btn162

Yao, Y., Ji, B., Lv, Y., Li, L., Xiang, J., Liao, B., & Gao, W. (2021). Predicting LncRNA–disease association by a random walk with restart on multiplex and heterogeneous networks. *Frontiers in Genetics*, *12*, 712170. https://doi.org/10.3389/fgene.2021.712170

Zeng, X., Zhu, S., Lu, W., Liu, Z., Huang, J., Zhou, Y., Fang, J., Huang, Y., Guo, H., Li, L., Trapp, B. D., Nussinov, R., Eng, C., Loscalzo, J., & Cheng, F. (2020). Target identification among known drugs by deep learning from heterogeneous networks. *Chemical Science*, *11*(7), 1775–1797. https://doi.org/10.1039/c9sc04336e

Zhou, Y., Hou, Y., Shen, J., Huang, Y., Martin, W., & Cheng, F. (2020). Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discovery*, *6*(1), 14. https://doi.org/10.1038/s41421-020-0153-3

Zhou, Y., Hou, Y., Shen, J., Mehra, R., Kallianpur, A., Culver, D. A., Gack, M. U., Farha, S., Zein, J., Comhair, S., Fiocchi, C., Stappenbeck, T., Chan, T., Eng, C., Jung, J. U., Jehi, L., Erzurum, S., & Cheng, F. (2020). A network medicine approach to investigation and population-based validation of disease manifestations and drug repurposing for COVID-19. *PLoS Biology*, *18*(11), e3000970. https://doi.org/10.1371/journal.pbio.3000970

Zietz, M., Himmelstein, D. S., Kloster, K., Williams, C., Nagle, M. W., & Greene, C. S. (2023). The probability of edge existence due to node degree: A baseline for network-based predictions. *bioRxiv*, 2023.01.05.522939. https://doi.org/10.1101/2023.01.05.522939

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