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Connecting the dots: Computational network analysis for disease insight and drug repurposing

Nicoleta Siminea[1,2], Eugen Czeizler[3,2], Victor-Bogdan Popescu[4], Ion Petre[5,2] and Andrei Păun[1,2]

Network biology is a powerful framework for studying the structure, function, and dynamics of biological systems, offering insights into the balance between health and disease states. The field is seeing rapid progress in all of its aspects: data availability, network synthesis, network analytics, and impactful applications in medicine and drug development. We review the most recent and significant results in network biomedicine, with a focus on the latest data, analytics, software resources, and applications in medicine. We also discuss what in our view are the likely directions of impactful development over the next few years.

Addresses
[1] Faculty of Mathematics and Computer Science, University of Bucharest, Romania
[2] National Institute of Research and Development for Biological Sciences, Romania
[3] Faculty of Medicine, University of Helsinki, Finland
[4] Revvity, Inc., Finland
[5] Department of Mathematics and Statistics, University of Turku, Finland

Corresponding authors: Petre, Ion (ion.petre@utu.fi); Păun, Andrei (apaun@fmi.unibuc.ro)

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Introduction

Networks have been successfully applied in biology and medicine for several decades now [1]. Placed at the intersection of computational and life sciences, they offer concepts and techniques from computational systems biology, bioinformatics, network science, graph theory, and medicine to analyse complex interactions within biological systems and their perturbations in disease states. The advent of advanced technologies like genomics, proteomics, big data analytics, network analysis, and machine learning has enabled this growth, allowing for a deeper understanding of diseases at a molecular level. Network methods play a key role in personalized and precision medicine, exploring the possibility of tailoring medical decisions to individuals based on their unique genetic makeup [2] (Figure 1).

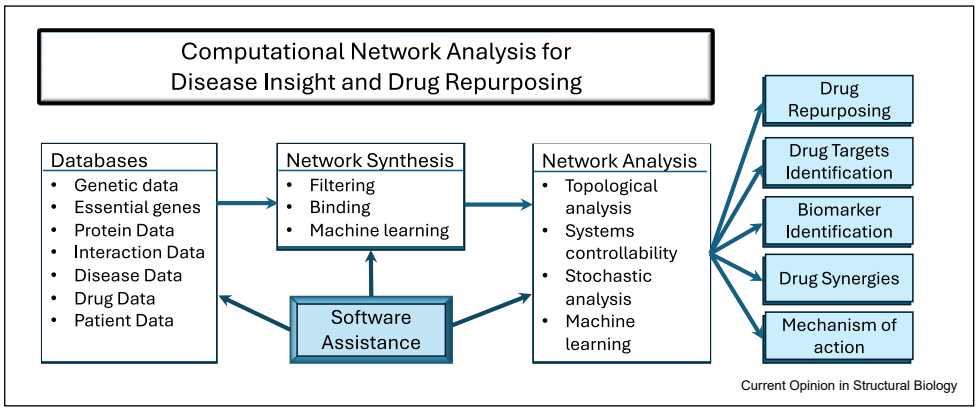
Network biomedicine is evolving fast, both on its computational side, as well as on its experimental and applicative side. This is made possible by the wider availability of more diverse and ever bigger datasets (Table 1) and by the fast development of computational tools (Table 2), especially related to artificial intelligence. We review some of the most significant recent developments in data integration, network synthesis, network analysis, software, and applications in medicine. We selected the studies in this review to reflect on the current state of the art on network analytics and its medical and pharmacological applications. Even with our focus being just on the literature of the last couple of years, the amount of new reported research is staggering, showing the high interest in this research field, and making this review unavoidably selective. To keep the review focused, we had to leave out many significant developments that are related but not right in the intersection of network science and bio/pharma applications, including AI-based protein folding and complex structure identification, drug target and drug synergy prediction, disease and patient stratification, and many others. Our goal is to offer practical indications to the types of datasets that can be used in network studies, methods of generating a network, types of analyzes that can be done, and some recent applications.

Data resources

The first step in a network project is to clarify the availability of data and identify the relevant datasets. There is a variety of datasets that can be used (Table 1).

- Protein data (**DPro**), which may include identifiers, synonyms, gene data, variants, organism details, and links to corresponding entries in external databases.
- Interaction data (**DInt**), which may include specific identifiers, type, pathways, identification method, and degree of confidence.

Figure 1



The flow of a typical network study. Multiple data resources get integrated into a network, either in a top-down fashion by filtering a comprehensive, standard network, or in a bottom-up fashion, by binding together interactions, pathways, and modules. The network can also be augmented through machine learning techniques. A multitude of network analysis methods can be applied (topological analysis, systems controllability, network dynamics, stochastic analysis) to investigate questions around drug repurposing, drug target identification, biomarker identification, drug synergies, mechanisms of action.

- Disease data (**DDis**), which may include essential genes, disease drivers, and common disease-specific expression abnormalities or mutations.
- Drug data (**DDru**), which may include drug-targets, pharmacokinetics, and diseases where a drug might be used as either main, secondary, or experimental line of treatment.
- Patient data (**DPat**), which may include patient-specific expression abnormalities or mutations, and previous responses to lines of treatment.

Table 1 lists some of the widely used, freely available resources that offer open APIs and/or web-based data browsers, or that allow to download their datasets in standard formats (e.g., JSON, XML, Microsoft Excel, or text-based comma- or tab-separated values).

The typical challenges that the modeler must handle concern the integration of data from multiple sources, the incompleteness of data, and the integration into the networks of drug targets and of possible disease targets (such as disease-specific essential proteins).

Data integration, incompleteness

The integration between different data resources is an important challenge [3], requiring the cross-referencing of different resource-specific identifiers, with an additional challenge caused by the lack of standardisation in identifier types. For example, the oncogene "YES1" is known, in different databases, as ENSG00000176105 (Ensembl), 7525 (NCBI), 12841 (HGNC), P07946 (UniProt), and IDBG-363.6 (InnateDB). Furthermore, the data is often incomplete [4], predicted through homology [5], or obtained through computational, predictive methods of suboptimal accuracy [6], which represents an additional challenge for validation [7].

Essential proteins

The integration of disease-specific, survivability-essential proteins [8] into the disease networks is of significant interest. Most often obtained through CRISPR-based knockout, synthetic lethality experiments, essential genes offer the possibility of targeted therapies [9]. Their integration into larger interaction networks and connecting them to available drugs offers the chance to investigate repurposing available drugs to target them indirectly through network-induced cascaded influences [2]. Recent results from the study by Hasibi et al. [10] expand this line of research by showing how metabolic fluxes can be used to predict their essentiality based on graph neural networks.

Drug targets

The integration of drug targets [11,12] into the networks allows tracing the effects of drugs through the network, making it possible to investigate questions about drug repurposing, drug synergies, optimal drug combination design, and identifying the action mechanism of drugs in a customised, stratified setup [13]. Several comprehensive drug target datasets with recent updates are listed in Table 1.

Network synthesis

Different types of networks can reveal different insights into disease [35]: metabolic networks, regulatory networks, protein–protein interaction networks, co-

Table 1

An annotated collection of data resources: protein data (DPro), interaction data (DInt), disease data (DDis), drug data (DDru), and patient data (DPat).

Data Resource	DPro	DInt	DDis	DDru	DPat
BioGRID [14]: protein and genetic interactions. **Advantages:** various species, interactions manually annotated, posttranslational modifications sites.		✓			
ChEMBL: bioactive molecules with drug-like properties [15]. **Advantages:** curated data, compounds nomenclature, bioactivity, chemical information.	✓			✓	
CORUM [16]: manually annotated data on protein complexes. **Advantages:** manually annotated protein complexes. **Limitations:** last release one year and a half ago; data can only be downloaded directly, no specific API available.	✓				
CTD [17]: interactions between genes or proteins and chemicals or diseases. **Advantages:** contains analysis tools, toxicogenomics data. **Limitations:** free noncommercial use, commercially licensed.	✓		✓	✓	
DisGeNET [18]: drugs, drug-targets, and related pharmaceuticals. **Advantages:** it integrates data from various sources, has a separate section for curated data. **Limitations:** only for noncommercial use; for commercial use, DISGENET Plus is offered; last update two and a half years ago.			✓		
DrugBank [11]: drugs, drug-targets, and related pharmaceuticals. **Advantages:** contains spectral data. **Limitations:** free for academic purpose, fee-based for commercial use.	✓		✓	✓	
Ensembl [19]: genome browser, gene and protein data. **Advantages:** automatically annotated genome. **Limitations:** only small amounts of data can be directly downloaded, while large amounts can be accessed via API.	✓				
Genomic Data Commons [20]: cancer progression and therapy response. **Advantages:** very large dataset, genetic data obtained by various methods, tumor images, patient clinical data. **Limitations:** not all data are public because there can be sensitive information.	✓				✓
HGNC [21]: human genes and related nomenclature. **Advantages:** comprehensive resource showing multiple names for a gene, links to orthologs, clinical resources.	✓				
Human Interactome Atlas [22]: binary protein interactions. **Advantages:** human protein interactions identified by high throughput yeast two-hybrid screens. **Limitations:** provided by only direct download; last data update 4 years ago.		✓			
InnateDB [23]: interactions involved in the innate immune response. **Advantages:** has a separate section for interactions validated experimentally; bovine data in addition to human and mouse data. **Limitations:** not clear when last updated.	✓	✓			
IntAct [24]: curated and user-submitted data on interactions. **Advantages:** experimental data from articles published or submitted for publication in a peer reviewed journal; interactions are grouped by diseases.		✓			
KEGG [25]: high-level functions and utilities of biological systems. **Advantages:** visual diagrams with pathways. **Limitations:** user licence required for commercial purposes.	✓	✓	✓	✓	
MINT [26]: experimentally verified data on interactions. **Advantages:** open source; interactions verified experimentally; identified by expert curators; it provides links to other resources; data for different species: *Homo sapiens*, *Mus musculus*, Drosophila Melanogaster, Saccharomyces Cerevisiae. **Limitations:** last update 5 years ago.	✓	✓			
NCBI Gene [27]: gene nomenclature and related information from multiple sources. **Advantages:** genes from different species can be searched; links to orthologs, to BLAST, and to Genome Data Viewer; information about lineage, official full name, a comprehensive description among others.	✓				
NetControl4BioMed [28]: aggregated data on proteins and interactions. **Advantages:** data from different sources can be combined; the possibility of creating and analyzing the control over a network.	✓	✓	✓		
OGEE [8]: gene essentiality and cancer cell-lines.	✓		✓		

(*continued on next page*)

Table 1 (*continued*)

Data Resource	DPro	DInt	DDis	DDru	DPat
Advantages: genes are categorized according to tissue, cell line, detection method. **Limitations:** last updated 3 years ago.					
Open Targets [29]: drugs and drug-targets. **Advantages:** integrates data from various sources; can view the targets associated with each disease, association score or a prioritization score.			✓	✓	
PharmGKB [30]: genetic drug responses. **Advantages:** data manually curated, but also extracted with an automated natural language processing tool.				✓	
Reactome [31]: curated data on interactions and pathways. **Advantages:** visual interface; can be zoomed in; own genes can be uploaded for analysis.	✓	✓	✓	✓	
SIGNOR [32]: annotated data on interactions and pathways. **Advantages:** causal interactions data on humans, mouses and rats; relevance score for each interaction; disease browser; pathway browser; advanced browser.		✓			
STRING [5]: aggregated data on physical interactions and functional associations. **Advantages:** search by protein id, by amino acid sequence, or even by disease; you can analyze data within the platform and you can export the results.	✓	✓			
UniProt [33]: annotated data on proteins and protein sequences. **Advantages:** detailed information and links to relevant databases.	✓				
WikiPathways [34]: biological pathways. **Advantages:** different applications to import the data, visualize and analyze it.		✓	✓	✓	

expression networks, signaling networks, or combinations thereof. There are two approaches to constructing a network [35].

- bottom-up, de-novo building the network around some key nodes of interest, or
- top-down, trimming a comprehensive interaction network (e.g., the Human Interactome [22]) to focus it on an area of interest, such as a certain pathway or tissue.

Either way, the modeler has some key decisions to make on how to acquire or to filter the data, and how to augment the data through predictions for missing links.

Data acquisition/filtering

The interaction data can be acquired from general repositories (Table 1), from disease-specific resources, from cell-line-specific resources, or even from the sample itself (if applicable). A major challenge here is that the sources of the interaction data are heterogeneous and occasionally even unspecified [5], bringing different levels of validation and trust in their validity: experimentally validated data (from the specific sample being studied or, less suitable, from related assays), data from in-vitro experiments (including those done on other organisms or on cell lines), or data inferred from in-silico studies. Another challenge is the selection and the integration of the relevant types of interactions [31]: co-localization, physical association, co-expression, activation, inhibition, post-translational modification, and many others. Additionally, some of these functions are compartment- and tissue-specific [22]. Some of these are relevant in dynamical, quantitative studies on systems behaviour, while others are useful in binding associations and regulatory studies. Such details are typically more difficult to clarify in the top-down approach, where they are already integrated in a ready-made comprehensive network.

Link prediction

There is a flurry of recent results on link predictions, many of them based on machine learning. Graph neural networks are a popular method to predict missing interactions between different node types, such as a drug and its targets [36], or to learn the structural patterns of the protein−protein interactions [37]. Graph convolutional networks and graph attention networks were used in the study by Sun et al. [38] to identify metabolite−disease associations, and in the study by Wang et al. [39] to identify interactions between long noncoding RNA (lncRNA) and microRNA (miRNA). An attention-based link prediction model that uses gene ontology (GO) terms together with network topology to predict protein function was developed in the study by Zhang et al. [40]. A protein−protein interaction network was extended in the study by Gysi et al. [41] with noncoding interactions, increasing the number of interactions by a staggering 107% and its ability to detect disease−disease relationships that could not be seen before. An example of a unusual network was in the study by Guthrie et al.. [42], where the authors integrated a set of innate immune errors into the network with the aim of identifying the peculiarities of rare diseases.

Table 2

A collection of recent software tools: network generation software (NGen), network visualization software (NVis), network analysis software (NAna).

Software Tool	NGen	NVis	NAna
CytoscapeJS [78] is an open-source JavaScript library for the analysis and visualization of complex networks, supporting modern web browsers and Node.js. **Advantages:** widespread usage; can run both in-browser and on-server; allows extensions; includes multiple graph theory algorithms; **Disadvantages:** JavaScript is out-performed by many other languages; performance depends on device when used in-browser; does not scale well with large networks; uses only JSON file format;	✓	✓	
Graphia [79] is an open-source desktop application for the visualisation, analysis, and interpretation of large and complex datasets. **Advantages:** does not require coding; accepts multiple standard file formats; fast and fluid rendering for large networks after the initial layout; can build tables and charts for analysing network data; **Disadvantages:** larger initial layout time; performance depends on device; no graph theory analysis algorithms;		✓	✓
iGraph [80] is an open-source C/C++/Mathematica/Python/R library for the analysis of networks, designed for efficiency and ease of use. **Advantages:** is highly configurable; allows for random graph generation; includes multiple graph theory algorithms; is very suitable for analysing alread-built networks; integrates with external plotting libraries; **Disadvantages:** different release schedules for the different languages that it supports; can layout a graph, but requires an external library to plot it; can handle multiple data formats, but some standard ones are missing (e.g., JSON or Cytoscape CX); has performance issues when dealing with dynamic networks;		✓	✓
NDEx IQuery [81] is a web application for the generation of networks, integrating with multiple external bioinformatics databases. **Advantages:** is focused on bioinformatics; contains extensive data to be used in network generation; integrates closely with Cytoscape; server-based, does not depend on device performance; **Disadvantages:** provides only basic subnetwork building algorithms; does not allow for direct network analysis; no support for additional file formats; offers accounts with limited, albeit generous, storage space;	✓		
NetControl4BioMed [28] is an open-source web application for the generation and controllability analysis of networks, integrating with multiple external bioinformatics databases. **Advantages:** contains extensive data to be used in network generation; provides several algorithms for network generation and analysis; server-based, does not depend on device performance; accepts multiple standard file formats; **Disadvantages:** limited in-app visualisation and interactivity; data is automatically deleted after three months of inactivity; only allows for controllability network analysis;	✓		✓
Retina [82] is an open-source web application for the online sharing of graph or network visualisations, without a server requirement. **Advantages:** no download, no installation, no coding required; server-based, performance does not depend on device; allows direct importing of online-available networks; **Disadvantages:** accepts only GEXF and GraphML file formats; allows only for network visualisation, no network interactivity; limited configuration options, without any layout configuration;		✓	

Network analysis

The diversity of network analysis methods is staggering and the field has developed tremendously in the last couple of years. There are three main categories of methods: topological analysis, with the main topic being to identify key nodes, modules, communities and structural patterns in the network; systems analysis and control, concerned with questions around the network dynamics, emerging behaviour and influencing/controlling the functioning of the network; machine learning and deep learning, exploiting the paradigm of data acquisition/generation/augmentation and automatic learning of patterns to answer a variety of questions such as target and link prediction. We discuss recent progress in each of these categories.

Topological analysis

Much of the recent network analysis research is focused on identifying important/driver/essential nodes or modules within the studied networks. One category of methods is based on probabilistic analysis; we discuss here two such studies. The first, proposed in the study by Meng et al. [43], uses a two-stage random walk was to discover driver genes: identify subnetworks with a high correlation with the seed nodes and then rank possible driver nodes. The second [44], identifies influential nodes based on a local propagation probability model, which ranks nodes based on total comprehensive scores of neighbor nodes within their three level neighborhood. Another category of methods is based on scoring and ranking proteins to predict their essentiality; a new such study is in Ref. [45], based on a modified Jaccard coefficient. Yet another category of methods is on system-level approaches that associate essentiality to the concept of graph domination; a new such study is in Ref. [46], based on a new heuristic for the group centrality problem, a well-known variant of the graph dominating problem.

Systems control

This topic, well studied over several decades, has also seen significant progress in the last two years. The most common approaches are based on the minimum dominating set (MDS) problem. A recent new study [47] proposes a new approach to identify the unavoidable nodes in the many solutions that the MDS problem may have. Another interesting proposal is in the study by Wong et al. [48], offering a solution to the MDS problem based on a biomolecular and quantum algorithm that was run on both IBM Quantum's QASM simulator and the Brooklyn superconducting quantum device. Another method that answers the same question in Boolean networks was presented in the study by Parmer et al. [49]. One other concept to address this problem is the intermittent nodes, with a new criticality metric for them proposed in the study by Someya et al. [50]. The related topic of network controllability has also received new results based on the probabilistic adaptive attack model [51], or on Boolean network models [52].

Machine learning for network analysis

This is one of the fastest growing research direction for network analysis. Graph neural networks and graph convolutional networks are the most common architecture in use, combining the power of deep learning with the idea of customising the network connections based on interaction data. One way to combine them is demonstrated in the study by Wang et al. [53] that introduces a graph neural network to infer gene regulatory networks from RNA-seq data, and then applies network control theory to identify key nodes. The study in the study by Peng et al. [54] does the combination in the other order: it first constructs a gene–sample association matrix and then it applies graph convolutional networks to eventually predict personalised driver genes for individual samples. Similarly, in the study by Duan et al. [55] the authors start from a set of protein–protein interaction (PPI) networks in order to identify low-dimensional node representations, and use them to generate de-novo driver gene prioritizations for new gene embedding. Another approach is introduced in the study by Wu et al. [56], that uses graph neural networks to learn drug–protein association networks. An attention-based deep learning model was developed in the study by Theodoris et al. [57] for predicting key gene regulators or therapeutic targets. Generative AI has also been tested for network analysis, a recent example being that of [58], that uses generative adversarial networks (GAN) to identify protein complexes from within PPI networks. Machine learning has been successfully applied to identify biomarkers, for example in papillary thyroid carcinoma [59], in DNA methylation in Graves' orbitopathy/thyroid associated orbitopathy [60], in colon cancer [61], in stomach adenocarcinoma [62], or in osteoarthritis starting from mRNA osteoarthritis datasets [63].

Applications in medicine

Precision medicine is one of the fields in which network science has been influential and holds promises for further impactful results, in disease network analysis, drug target identification and drug repurposing, precision oncology, biomarker discovery, bacterial resistance, clinical decision support systems, patient stratification and risk prediction. Integrating disease-specific data with patient-specific information into comprehensive interaction networks makes it possible to ask questions about personalised optimal therapies and drug repurposing.

Drug repurposing

On drug repurposing there are several recent network studies. In the study by Bai et al. [64] *bortezomib* was identified as a potential drug in nonsmall cell lung cancer, using a novel network analysis method, based on difference analysis, Spearman correlation, biological function analysis and Bayesian causality analysis. In the study by Chirom et al. [65] the authors found that 4 drugs (*uprosertib*, *progesterone*, *solitomab* and *regorafenib*) have strong interactions with key regulators in ovarian cancer. The study was based on the human interactome network and the roles of hubs in it in the disease states. While *uprosetib* is still under investigation for different types of cancer, *regorafenib* was already approved for metastatic colorectal cancer, advanced gastrointestinal tumors and hepatocellular carcinoma. Selecting drugs and drug combinations with optimal effect was investigated in the study by Ahmed et al. [66] by integrating an HPV-induced cervical cancer network with drug target interaction data, followed by a drug target network proximity analysis.

Drug target identification

On drug target identification recent progress includes [67] where a network was created to find out how far the targets of various traditional Chinese herbs are from the module of symptoms they relieve. In the study by Dwivedi et al. [68] the authors use the DisGeNET database to map breast cancer targets to those of *sinapic acid* using a diverse combination of methods: KEGG to view disease pathways, and Cytoscape to visualize them, then apply molecular docking, molecular dynamics simulations, molecular mechanics Poisson-Boltzmann surface area analysis, together with cluster analysis and GO analysis.

Network hub identification

Identifying hubs is one of the central topics of research in network science in biomedicine, as hubs tend to be associated with key regulators and disease drivers. This line of research continues to be very active. In the study by Zhai et al. [69] a study into network hubs was used to identify *dequalinium*, a drug that may decrease the impact of *Escherichia coli* on mutagenesis after *fluoroquinolone* administration. *E3 ligase UBR5* was pinpointed in the study by Mark et al. [70] as a signaling hub that helps degrade unpaired subunits. Metabolic drivers and signature clusters in Alzheimer's disease were identified in the study by Chang et al. [71] and *RE1*-silencing transcription factor was found in the study by Cheng et al. [72] as an upstream suppressor involved in axon regeneration.

Module identification

Modularity and community structure was successfully applied in the study by Shah et al. [73] to identify 5 modules associated with heart failure risk based on protein co-regulation networks, in the study by Humphrey et al. [74] where gene co-expression networks were exploited to identify activated microglia modules in amyotrophic lateral sclerosis, and in the study by van Oostrum et al. [75] where shared synaptic protein modules were identified to pinpoint the proteomic areas involved in synapse specialization. One step further was taken in the study by Berry et al. [76] where the subtypes of Sjogren's syndrome were mapped onto the identified modules, and different therapeutic targets for each subtype were identified. In the study by Kong et al. [77] the authors predicted the response of patients with melanoma, gastric cancer, or bladder cancer at immune checkpoint inhibitors through a network-based machine learning model.

Software

There are many software tools available for aspects related to the synthesis, analysis, and visualization of protein–protein interaction network. An overview of software developed or updated in the last two of years, and of particularly significant older software can be found in Table 2. We focused on freely available and open-source resources that accept, parse, and output data in standard formats (e.g., Cytoscape, JSON, XML, Microsoft Excel, or text-based comma- or tab-separated values for network generation, or PDF, PNG, or SVG for network visualization). The availability of import/export in standard formats makes it versatile to combine these tools for more complex analyses. We categorise the software based on the following three classes.

- Network generation software (**NGen**), which allows for the generation of PPI networks, starting from custom lists of proteins, using different generation algorithms, and integrating multiple data resources.
- Network visualization software (**NVis**), which allows for the visualization of PPI networks, using different layout algorithms, and offering static or dynamic on-screen graphic rendering.
- Network analysis software (**NAna**), which allows for the analysis of PPI networks, using different analysis measures and algorithms (e.g., topographical or controllability analysis).

We discuss now in more details the most significant recent tools for network inference and visualisation.

LEVELNET [83] is a recent, versatile tool for integrating and exploring protein–protein interaction networks synthesized from multiple data sources. LEVELNET represents networks as multilayered graphs, offering the possibility to zoom in and compare their subnetworks. Starting from a set of proteins with known structures, this tool builds a grid of networks for each data source, offering different views on the interactions. Interactions supported by multiple evidence are represented as multiedges in the aggregate graph. Also, each edge is tagged with a weight to reflect the reliability of the evidence supporting that edge. LEVELNET facilitates the identification of potential inconsistencies between different data sources.

The Cytoscape *stringApp* has been improved with analysis and visualisation for heterogeneous networks [84]. A visualisation program is also GraphBio [85], which provides visualisation options for a large palette of analyses, such as text group analysis, principal component analysis, correlation analysis among others. An R package built for cell–cell signaling network analysis and visualisation is presented in the study by Raredon et al. [86]. Obviously, neural network models have also materialized for the visualisation of networks, one of them being NeuroDAVIS [87], which is a neural network model that can be used for the visualisation of large data sets as well. Another novelty is the use of the Unity engine for the visualisation of the front-end network simulation exemplified by NetVision [88]. OpenPIP is an open source platform for the analysis and visualisation of

protein−protein interactions that is based on Cytoscape. js for network visualisation [89]. Another built platform for analysing and visualising omni data is presented in the study by Koh et al. [90], where the authors also provide the code so that users can change it if they need something else similar.

PathwayNexus [91] helps to observe relationships between metabolites and compounds as matrices, but also to group, sort, visualise pathways. DeepMAPS [92] is a tool for biological network inference from single-cell multiomics data. The networks are represented as heterogeneous graphs and analysed with a multihead graph transformer. The tool can be used through the DeepMAPS webserver.

Perspectives

Network biology, although a relatively young scientific field, has already offered many impactful applications in medicine and drug development [1,93,94]. The field is actively evolving and we reviewed some of the most significant results published in the last two years. Based on these recent results, we foresee several research directions that are likely to receive attention in the next few years and we anticipate that they will offer significant new developments in this field. We discuss them shortly here.

Machine learning has found deep applications in a myriad of fields in science and outside of it. This includes many exciting applications in biology and medicine, including network biomedicine [36,57]. Still, we believe that even more breakthroughs will be made when machine learning becomes integrated in a deeper way in network-based studies. The current applications in network studies are mostly focused on graph representation learning [55], that facilitates an easier identification of nodes, communities, and patterns. To a large extent, this does not yet take fully into account the global structure of the network as a model for how signals and information are distributed and influence each other. The combination of the *explainability* brought forward by the structural insights and mechanisms encoded into networks, and of the *de-novo, data-driven* ability of machine learning to discover hidden patterns with complex sources remains yet to be convincingly demonstrated. For example, the incomplete nature of the data [4], the noise in it, the uncertainty in its validity [7], the search for system controls [50] and other global patterns are all topics that can be addressed with machine learning. To some extent, difficult computational problems that have hindered network science (for example, graph matching), may start to be addressed with machine learning. Generative graph models have started to be investigated, but they are still in their infancy, and have not yet seen convincing proofs of concepts in network synthesis. Deep neural networks already brought forward several exciting new approaches: node classification using few-shot learning [95]; protein−protein interaction prediction using a multigraph neural network [96], a learning hierarchical graph [97], or a graph neural network [98]; drug-target prediction using a heterogeneous biological network [99], or a metapath-aggregated heterogeneous graph neural network [100]; drug−disease association prediction using graph neural networks on multiple biological relationships [101]; protein−ligand affinity identification using graph neural networks based on 3D structures and physical interactions [102]; drug repurposing with graph neural networks [103]; drug discovery with graph attention mechanisms [104].

Breakthroughs in protein structure identification using AlphaFold [105] have also brought significant new results in network studies. Significant recent results include predicting protein−ligand binding affinity [106]; designing protein sequences that can fit into a specific desired structure [107]; protein dynamics based on residue flexibility [108]; predicting multimeric protein complex structures; predicting protein−protein interactions [109], visualising the quality of predicted protein complexes [110]; drug repurposing based on the structural similarity of protein interfaces [111].

A research direction that we believe to be on the brink of breakthroughs is that of personalised medicine [30,54]. It has been clear for some time now that networks allow for the personalised integration of data and networks to include aging, medical background, genetic data, lifestyle, and environmental conditions. Adding these to disease-, biological- and drug-data offers an insightful, patient- and disease-specific insight into the personalised mechanisms of disease, that may be analysed to extract suggestions for optimal drug combinations and treatment planning.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data were used for the research described in the article.

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Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

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