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Modeling Biological Networks: Computational Approaches to Network Dynamics

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Abstract Biological networks are important tools for understanding the complexity and functionality of biological systems, and their dynamic analysis can reveal the dynamic behavior of biological processes. However, the high complexity and diversity of biological networks pose urgent challenges for research, requiring the development and application of advanced computational methods. This study reviews the different types of biological networks and their functional roles in biology, and explores in detail network dynamics calculation methods including graph theory, agent-based modeling, differential equations, etc. In addition, we also focus on dynamic modeling of gene regulatory networks, protein-protein interaction networks, and metabolic networks, analyzing the applications and limitations of these methods in practical biological systems. In order to provide a comprehensive reference for researchers in the field of biological network dynamics.

Keywords Biological networks; Network dynamics; Computational methods; Gene regulatory networks; Protein-protein interaction networks

1 Introduction

Biological networks, encompassing gene regulatory networks (GRNs), protein-protein interaction networks, and metabolic pathways, are fundamental to understanding the complex interactions that govern cellular processes. These networks are integral to various biological functions, including cell differentiation, metabolism, and signal transduction (Karlebach and Shamir, 2008; Wang and Gao, 2010). The advent of high-throughput technologies and computational methods has enabled the detailed mapping and analysis of these networks, providing insights into their structure and function (Covert et al., 2004; Glass et al., 2013). The integration of experimental data with computational models has become essential for elucidating the intricate dynamics of biological systems (Mangan et al., 2016; Manipur et al., 2020).

Understanding the dynamics of biological networks is crucial for several reasons. Firstly, it allows researchers to predict the behavior of these networks under different conditions, which is vital for identifying the mechanisms underlying diseases caused by dysregulated cellular processes (Liu et al., 2020; Jolly and Roy, 2022). Secondly, dynamic models can facilitate the development of biotechnological applications by providing faster and more cost-effective alternatives to experimental approaches (Liu et al., 2020). Moreover, the study of network dynamics can reveal emergent properties and interactions that are not apparent from static network analyses, thereby offering a more comprehensive understanding of biological systems (Boccaletti et al., 2006; Paulevé et al., 2020). The application of control theory and other mathematical frameworks to these networks has further enhanced our ability to analyze and manipulate their behavior (Jolly and Roy, 2022).

This study attempts to emphasize the methods used, the challenges encountered, and the progress made in this field. Specifically studying various modeling techniques, including Boolean modeling, differential equations, and data-driven methods, as well as their applications in understanding gene regulatory networks, metabolic pathways, and other biological systems. We will discuss the integration of high-throughput data and computational models, as well as the impact of these methods on future research and biotechnology innovation. We hope to provide valuable resources for researchers and practitioners interested in dynamic modeling of biological networks.

2 Overview of Biological Networks

Biological networks are intricate systems that represent the interactions among various biological entities, such as genes, proteins, and metabolites. These networks are essential for understanding the complex relationships and dynamics within biological systems. Advances in network science and high-throughput biomedical technologies have significantly enhanced our ability to study these networks, providing deeper insights into their structure and function (Bocci et al., 2023).

2.1 Types of biological networks

Biological networks can be categorized into several types based on the nature of the interactions they represent. Common types include genetic regulatory networks, protein-protein interaction networks, metabolic networks, and signaling networks. Genetic regulatory networks depict the interactions between genes and their regulatory elements, while protein-protein interaction networks illustrate the physical interactions between proteins. Metabolic networks map the biochemical reactions within a cell, and signaling networks represent the pathways through which cells respond to external stimuli (Koutrouli et al., 2020; Jolly and Roy, 2022). Each type of network provides a unique perspective on the biological processes and helps in understanding the underlying mechanisms of cellular functions.

2.2 Structural properties of networks

The structural properties of biological networks are crucial for understanding their behavior and functionality. Key properties include network topology, degree distribution, clustering coefficient, and path length. Network topology refers to the overall arrangement of nodes and edges, which can be characterized by patterns such as scale-free or small-world structures. Degree distribution describes the number of connections each node has, often following a power-law distribution in biological networks. The clustering coefficient measures the tendency of nodes to form tightly knit groups, while path length indicates the average number of steps required to traverse the network (Koutrouli et al., 2020; Paulevé et al., 2020). These properties help in identifying critical nodes and understanding the robustness and efficiency of biological networks.

2.3 Functional roles of networks in biology

Biological networks play vital roles in various biological processes and functions. They are involved in cellular communication, metabolic regulation, and the coordination of complex biological responses. For instance, genetic regulatory networks control gene expression patterns, which are essential for cellular differentiation and development. Protein-protein interaction networks facilitate the formation of protein complexes that carry out specific cellular functions. Metabolic networks ensure the efficient flow of metabolites through biochemical pathways, supporting cellular energy production and biosynthesis. Signaling networks enable cells to perceive and respond to environmental changes, maintaining homeostasis and facilitating adaptation (Mangan et al., 2017). Understanding these functional roles is critical for deciphering the complexities of biological systems and developing therapeutic strategies for diseases.

3 Computational Approaches to Network Dynamics

3.1 Graph-theoretical methods

Graph-theoretical methods are pivotal in analyzing biological networks due to their ability to represent complex systems as interconnected nodes and edges. These methods facilitate the understanding of the structural properties and functional dynamics of biological systems. For instance, graph theory can be used to analyze molecular structures in microbiology, where cells, genes, or proteins are represented as vertices, and their interactions as edges. This approach allows for the computation of topological indices, which can reveal significant biological activities and properties (Pavlopoulos et al., 2011; Gao et al., 2017). Additionally, graph-based methods can characterize global and local structural properties of cellular networks, detect motifs or clusters involved in common biological functions, and integrate large-scale experimental data for comprehensive network inference (Aittokallio and Schwikowski, 2006).

3.2 Agent-based modeling

3.2.1 Principles and applications

Agent-based modeling (ABM) is a flexible computational approach used to simulate the interactions of individual agents within a system, capturing the emergent behavior of complex biological networks. ABMs are particularly useful in fields ranging from molecular biology to ecology, where they can model phenomena such as cell migration, molecular dynamics, and disease spread (Hinkelmann et al., 2010; Nardini et al., 2020). These models are typically specified through protocols like the ODD protocol, which standardizes model descriptions and facilitates their analysis (Grob et al., 2019).

3.2.2 Strengths and limitations

The strengths of ABM include its ability to model heterogeneous agents and capture stochastic behaviors, making it suitable for simulating real-world biological systems. However, ABMs often require extensive computational resources due to their complexity and the need for numerous simulations to explore parameter spaces. This computational demand can be mitigated by using neural networks to emulate ABMs, significantly improving efficiency while maintaining accuracy (Wang et al., 2019). Despite these advancements, challenges remain in accurately predicting model dynamics in certain parameter regimes, which can sometimes be addressed by integrating differential equation models learned from ABM simulations (Nardini et al., 2020).

3.2.3 Case studies in biological systems

Several case studies highlight the application of ABM in biological systems. For example, ABMs have been used to model cell biology experiments, such as birth-death-migration processes, and epidemiological models like the susceptible-infected-recovered (SIR) model. These studies demonstrate the utility of ABM in predicting system dynamics and exploring biological phenomena. Additionally, the integration of ABM with other computational frameworks, such as equation learning, has shown promise in enhancing the predictive power and applicability of these models in various biological contexts.

3.3 Differential equation-based approaches

Differential equation-based approaches are fundamental in modeling the dynamic behavior of biological networks. These methods use mathematical equations to describe the rate of change of system variables over time, providing insights into the underlying mechanisms of biological processes. For instance, control-theoretic approaches using differential equations have been applied to drug delivery systems, while other methods have been used to infer biochemical network dynamics and predict system behavior under different conditions (Mochizuki, 2016). Additionally, multi-scale probabilistic models, such as ProbRules, combine differential equations with logical rules to represent network dynamics across different scales, offering robust predictions of gene expression and molecular interactions (Grob et al., 2019). These approaches are crucial for understanding the complex interactions within biological networks and developing effective interventions.

4 Dynamic Modeling of Gene Regulatory Networks

4.1 Boolean networks

4.1.1 Basic concepts and applications

Boolean networks are a fundamental approach to modeling gene regulatory networks (GRNs) due to their simplicity and intuitive nature. They represent genes as nodes and regulatory interactions as edges, with each gene being in one of two states: active or inactive. This binary representation allows for the construction of dynamic models that can predict the behavior of genetic networks under various conditions. Boolean networks are particularly useful for understanding the overall structure and dynamics of GRNs, making them a popular choice for initial modeling efforts (Saadat and Albert, 2013; Tyson et al., 2019).

4.1.2 Modeling gene regulation

The process of modeling gene regulation using Boolean networks involves several key steps. First, experimental data is used to infer the network structure, identifying which genes regulate which others. This is followed by the application of graph-theoretical measures to analyze the network's properties. The network is then converted into a

dynamic model that can simulate the behavior of the system over time. This approach allows researchers to make predictions about gene expression patterns and identify potential targets for therapeutic intervention (Murrugarra and Aguilar, 2019).

4.1.3 Examples in genetic networks

Boolean networks have been successfully applied to various genetic networks, providing insights into complex biological processes. For instance, the segment polarity gene network in Drosophila melanogaster has been modeled using Boolean networks to understand the regulatory mechanisms involved in embryonic development (Saadat and Albert, 2013). Additionally, Boolean networks have been used to study cell differentiation and functional states, highlighting their utility in capturing the dynamic behavior of GRNs. These models have also been extended to incorporate stochastic elements, allowing for the simulation of gene expression variability observed in biological systems (Murrugarra and Aguilar, 2019).

4.2 Bayesian networks

Bayesian networks offer a probabilistic approach to modeling gene regulatory networks, capturing the inherent uncertainty and variability in gene expression. These models use conditional probabilities to represent the relationships between genes, allowing for the integration of diverse data types and the inference of regulatory interactions. Bayesian networks are particularly useful for identifying causal relationships and predicting the effects of perturbations in the network (Grob et al., 2019).

4.3 Stochastic models

Stochastic models are essential for capturing the random nature of gene regulatory processes, which arise from the small number of molecules involved and the stochasticity of their interactions. These models use mathematical frameworks such as the chemical master equation and the stochastic simulation algorithm (SSA) to simulate the behavior of GRNs under different conditions. Stochastic models provide a more accurate representation of gene expression dynamics, accounting for the noise and variability observed in experimental data (Liang and Han, 2012; Murrugarra and Aguilar, 2019). They are particularly useful for studying systems with significant molecular noise and for developing therapeutic strategies that target specific regulatory pathways.

5 Modeling Protein-Protein Interaction Networks

5.1 Structural and functional analysis

Protein-protein interaction (PPI) networks are fundamental to understanding cellular processes and biological functions. Structural and functional analysis of these networks involves deciphering the atomic details of protein binding interfaces and their dynamic interactions within the cellular environment. Computational models, such as the multiscale framework integrating high-resolution structural information and simplified representations for long-time-scale dynamics, have proven effective in simulating these interactions and unraveling their complexities (Wang et al., 2018). Additionally, network-based modeling and coevolutionary analysis have enriched our understanding of protein dynamics and allosteric regulation, providing insights into the molecular mechanisms underlying protein functions and interactions (Liang et al., 2020).

5.2 Dynamic simulations

Dynamic simulations, particularly molecular dynamics (MD) simulations, play a crucial role in studying the behavior of proteins and their interactions over time. These simulations capture the full atomic detail and temporal resolution of biomolecular processes, offering valuable insights into protein dynamics, structure-function relationships, and interaction mechanisms (Hollingsworth and Dror, 2018). Enhanced sampling MD approaches, combined with regular MD methods, assist in steering structure-based drug discovery by elucidating drug-protein interactions and binding mechanisms (Kalyaanamoorthy and Chen, 2014). Tools like SenseNet further analyze protein structure networks from MD simulations, predicting allosteric residues and their roles in signal transduction (Schneider and Antes, 2021).

5.3 Applications in drug discovery

The application of computational approaches to PPI networks has significant implications for drug discovery. MD

simulations have been widely used to investigate pathogenic mechanisms, virtual screening, and drug resistance mechanisms, providing essential information that guides the drug discovery and design process (Liu et al., 2018). Deep learning methods, such as graph neural networks (GNNs), have also emerged as powerful tools for predicting protein functions and interactions (Figure 1), facilitating in silico drug discovery and development (Muzio et al., 2020). These computational methods enable the identification of candidate disease genes or drug targets, which can be further validated experimentally, thus accelerating the drug discovery pipeline (Liang and Kelemen, 2018).

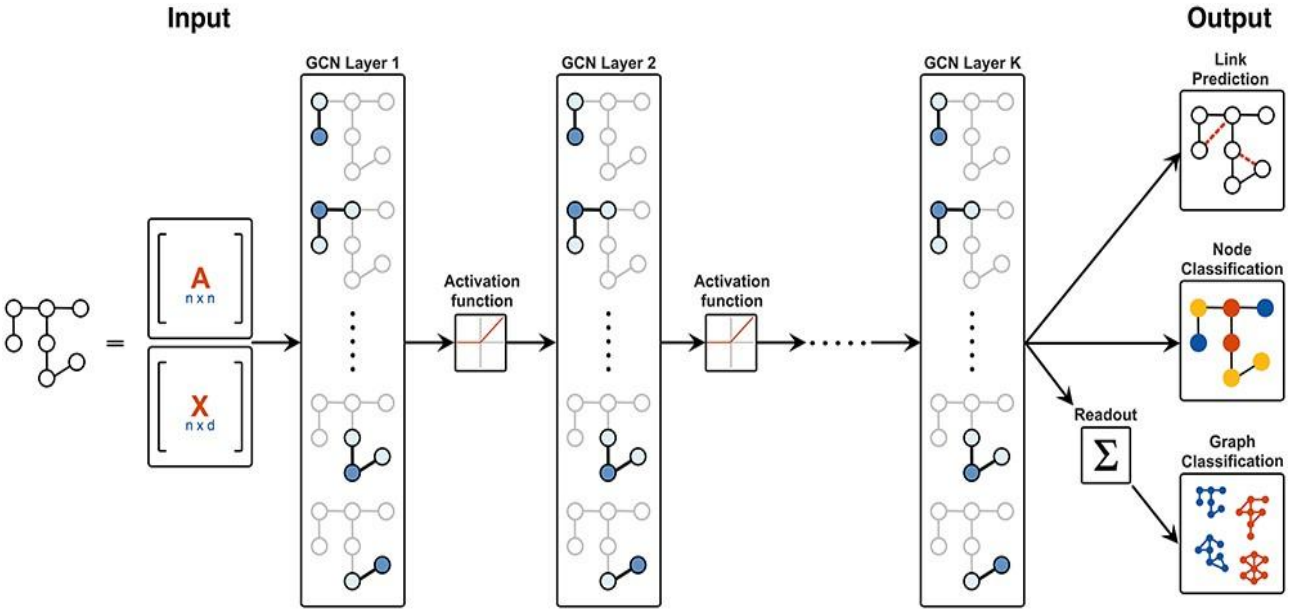

Figure 1 On the GCN layer of the k-layer GCN (Aodpted from Muzio et al., 2020)

Image caption: Each layer of the GCN is aggregated on each node's neighborhood using the node representation of the previous layer in the network. The aggregates in each layer then pass through an activation function (in this case, ReLU) before moving on to the next layer. The network can be used to generate a variety of different outputs: to predict new edges in the input network (link prediction), to classify individual nodes in the input graph (node classification), or to classify the entire input graph (graph classification) (Aodpted from Muzio et al., 2020)

6 Metabolic Network Modeling

6.1 Flux balance analysis

Flux Balance Analysis (FBA) is a widely used computational method for predicting the flow of metabolites through a metabolic network. It relies on the principle of mass conservation and uses a stoichiometric matrix along with a biologically relevant objective function, such as biomass production or ATP generation, to identify optimal reaction flux distributions (Vidal-Limon et al., 2022). FBA has been instrumental in analyzing genome-scale reconstructions of various organisms and has applications in metabolic engineering and drug target identification (Sen, 2022). However, FBA has limitations, such as its inability to predict intracellular fluxes under all environmental conditions, necessitating the development of alternative strategies (Megchelenbrink et al., 2015).

6.2 Constraint-based optimization

Constraint-based optimization methods extend the capabilities of FBA by incorporating additional constraints, such as kinetic, thermodynamic, and regulatory constraints, to improve the accuracy of metabolic flux predictions (Pandey et al., 2018; Sen et al., 2022). These methods allow for a more detailed and realistic representation of metabolic networks, enabling the analysis of complex cellular behaviors and the identification of key metabolic bottlenecks. For instance, the Maximum Metabolic Flexibility (MMF) method utilizes the observation that microorganisms often favor a suboptimal growth rate to maintain metabolic flexibility, thereby improving the quantitative predictions made by FBA.

6.3 Integration with omics data

The integration of omics data, such as transcriptomics, proteomics, and metabolomics, into metabolic network models has significantly enhanced their predictive capabilities. High-throughput technologies have generated vast amounts of omics data, which can be used to refine and constrain metabolic models, leading to more accurate predictions of cellular phenotypes (Blazier and Papin, 2012; Wang et al., 2021). Several methods have been developed to incorporate omics data into FBA, such as the Relative Expression and Metabolomic Integrations (REMI) method, which integrates gene expression and metabolomic data with thermodynamic constraints to provide more robust and biologically relevant results (Figure 2) (Pandey et al., 2018). These integrated models are valuable for understanding the dynamic adaptation of biochemical reaction fluxes and for exploring the interplay between metabolism and regulation in various physiological states (Wang et al., 2021).

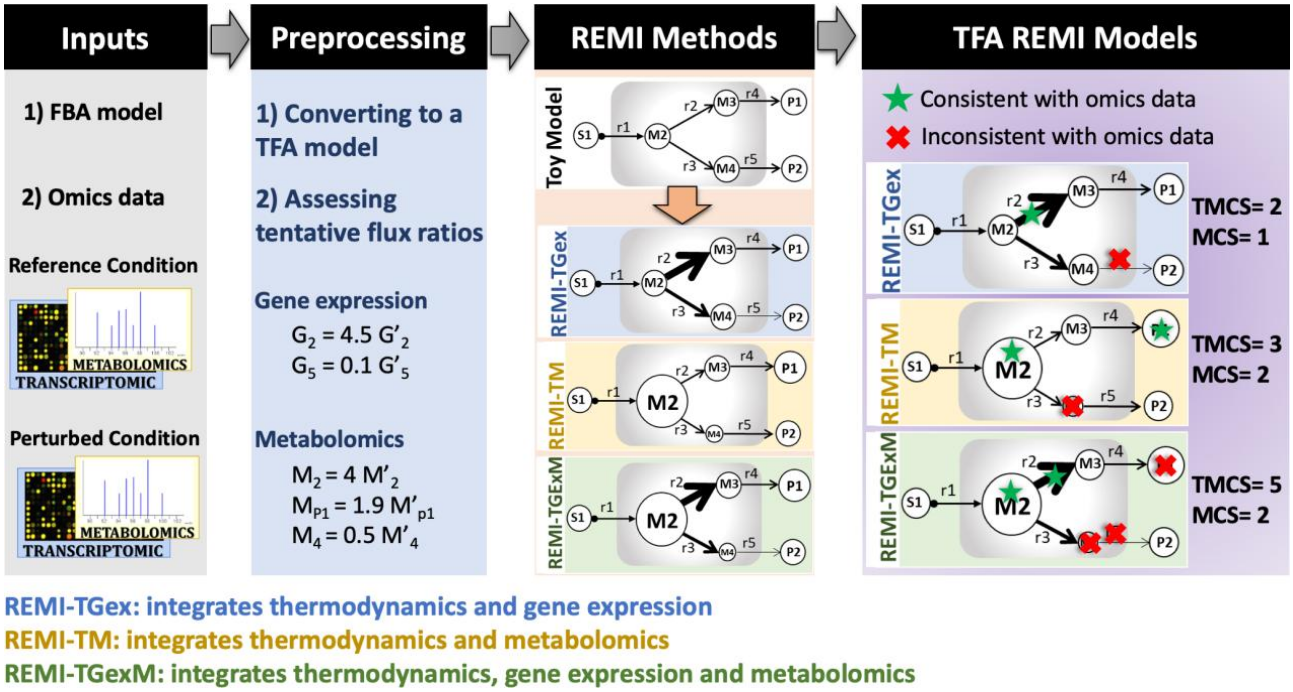

Figure 2 A genome-scale flux balance analysis (FBA) model and sets of gene-expression and or metabolomic data (Adopted from Pandey et al., 2018)

In the pre-processing step, the FBA model is converted into a thermodynamic-based flux analysis (TFA) formulation, and the relative flux ratios are further assessed based on the omics data. Also based on the omics data provided, REMI translates to the REMI-TGex, REMI-TM, and REMI-TGexM methods (third block). Examples of gene-expression and metabolomic data (second block) together with a toy mode (third block) are used to illustrate the applicability of the REMI methods. The theoretical maximum consistency score (TMCS) is the number of available omics data (for metabolites, genes (reactions), or both) and the maximum consistency score (MCS) is the number of those constraints that are consistent with fluxes and could be integrated into REMI models. The MCS is always equal to or smaller than the TMCS.

7 Challenges and Future Directions

7.1 Scalability and complexity

One of the primary challenges in modeling biological networks is managing the scalability and complexity of these systems. Biological networks often involve numerous components and interactions, making it difficult to create models that are both comprehensive and computationally feasible. For instance, the integration of various omics data (proteomics, genomics, lipidomics, and metabolomics) has led to large inventories of biological entities, but understanding how these entities interact remains a significant challenge (Kholodenko et al., 2012). Additionally, traditional methods such as Boolean networks and differential equations face limitations when applied to complex signal transduction networks due to their inability to handle the spatial and temporal dynamics

effectively (Lee et al., 2020). New approaches like Most Permissive Boolean Networks (MPBNs) have been proposed to reduce the complexity of dynamical analysis, enabling the modeling of genome-scale networks (Paulevé et al., 2020).

7.2 Data integration and interoperability

The integration of heterogeneous data types is another major challenge. Advances in high-throughput techniques have generated vast amounts of diverse omics data, which need to be integrated to provide a holistic view of biological systems. However, the complexity, heterogeneity, and high-dimensionality of these data pose significant challenges for data integration and interoperability (Lee et al., 2020). Methods for collective mining of various types of networked biological data have been proposed, but they still face limitations in dealing with heterogeneous networked data (Gligorijević and Przulj, 2015). The development of heterogeneous multi-layered networks (HMLNs) has shown promise in integrating diverse biological data, but new computational challenges arise in establishing causal genotype-phenotype associations and understanding environmental impacts on organisms (Wang et al., 2021).

7.3 Advances in computational techniques

To address the challenges of scalability, complexity, and data integration, advances in computational techniques are essential. Probabilistic models like ProbRules, which combine probabilities and logical rules, have been developed to represent the dynamics of biological systems across multiple scales (Grob et al., 2019). These models have shown robustness in predicting gene expression readouts and clarifying molecular mechanisms. Additionally, non-negative matrix factorization-based approaches have been highlighted for their potential in dealing with heterogeneous data and providing accurate integrative analyses (Pham et al., 2008). The application of machine learning methods to network biology has also been emphasized, offering new biological insights and aiding in the development of more accurate in silico representations of biological systems (Liu et al., 2020).

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Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Aittokallio T., and Schwikowski B., 2006, Graph-based methods for analysing networks in cell biology, Briefings in Bioinformatics, 7(3): 243-255. https://doi.org/10.1093/BIB/BBL022

Blazier A.S., and Papin J.A., 2012, Integration of expression data in genome-scale metabolic network reconstructions, Frontiers in Physiology, 3: 299. https://doi.org/10.3389/fphys.2012.00299

Boccaletti S., Latora V., Moreno Y., Chavez M., and Hwang D., 2006, Complex networks: structure and dynamics, Physics Reports, 424: 175-308. https://doi.org/10.1016/J.PHYSREP.2005.10.009

Bocci F., Jia D., Nie Q., Jolly M.K., and Onuchic J., 2023, Theoretical and computational tools to model multistable gene regulatory networks, Reports on, Progress in Physics, 2023: 86. https://doi.org/10.1088/1361-6633/acec88

Covert M., Knight E., Reed J., Herrgård M., and Palsson B., 2004, Integrating high-throughput and computational data elucidates bacterial networks, Nature, 429: 92-96. https://doi.org/10.1038/nature02456

Gao W., Wu H., Siddiqui M., and Baig A., 2017, Study of biological networks using graph theory, Saudi Journal of Biological Sciences, 25: 1212-1219. https://doi.org/10.1016/j.sjbs.2017.11.022

Glass K., Huttenhower C., Quackenbush J., and Yuan G., 2013, Passing messages between biological networks to refine predicted interactions, PLoS ONE, 8(5): e64832. https://doi.org/10.1371/journal.pone.0064832

Gligorijević V., and Przulj N., 2015, Methods for biological data integration: perspectives and challenges, Journal of The Royal Society Interface, 12(112): 20150571. https://doi.org/10.1098/rsif.2015.0571

Grob A., Kracher B., Kraus J.M., Kühlwein S.D., Pfister A.S., Wiese S., Luckert K., Pötz O., Joos T., Daele D., Raedt L., Kühl M., and Kestler H., 2019, Representing dynamic biological networks with multi-scale probabilistic models, Communications Biology, 2(1): 21.
https://doi.org/10.1038/s42003-018-0268-3

Hinkelmann F., Murrugarra D., Jarrah A., and Laubenbacher R., 2010, A mathematical framework for agent based models of complex biological networks, Bulletin of Mathematical Biology, 73: 1583-1602.
https://doi.org/10.1007/S11538-010-9582-8.

Hollingsworth S., and Dror R., 2018, Molecular dynamics simulation for all, Neuron, 99: 1129-1143.
https://doi.org/10.1016/j.neuron.2018.08.011

Jolly M.K., and Roy S., 2022, Editorial: topical collection on emergent dynamics of biological networks, Journal of Biosciences, 47(4): 82.

Kalyaanamoorthy S., and Chen Y., 2014, Modelling and enhanced molecular dynamics to steer structure-based drug discovery, Progress in Biophysics and Molecular Biology, 114(3): 123-136.
https://doi.org/10.1016/j.pbiomolbio.2013.06.004

Karlebach G., and Shamir R., 2008, Modelling and analysis of gene regulatory networks, Nature Reviews Molecular Cell Biology, 9: 770-780.
https://doi.org/10.1038/nrm2503

Kholodenko B., Yaffe M.B., and Kolch W., 2012, Computational approaches for analyzing information flow in biological networks, Science Signaling, 5(220): re1.
https://doi.org/10.1126/scisignal.2002961

Koutrouli M., Karatzas E., Páez-Espino D., and Pavlopoulos G.A., 2020, A guide to conquer the biological network era using graph theory, Frontiers in Bioengineering and Biotechnology, 8: 34.
https://doi.org/10.3389/fbioe.2020.00034

Lee B., Zhang S., Poleksic A., and Xie L., 2020, Heterogeneous multi-layered network model for omics data integration and analysis, Frontiers in Genetics, 10.
https://doi.org/10.3389/fgene.2019.01381

Liang J., and Han J., 2012, Stochastic boolean networks: an efficient approach to modeling gene regulatory networks, BMC Systems Biology, 6: 1-21.
https://doi.org/10.1186/1752-0509-6-113

Liang Y., and Kelemen A., 2018, Dynamic modeling and network approaches for omics time course data: overview of computational approaches and applications, Briefings in Bioinformatics, 19(5): 1051-1068.
https://doi.org/10.1093/bib/bbx036

Liang Z., Verkhivker G., and Hu G., 2020, Integration of network models and evolutionary analysis into high-throughput modeling of protein dynamics and allosteric regulation: theory tools and applications, Briefings in Bioinformatics, 21(3): 815-835.
https://doi.org/10.1093/bib/bbz029

Liu C., Ma Y., Zhao J., Nussinov R., Zhang Y., Cheng F., and Zhang Z., 2020, Computational network biology: data models and applications, Physics Reports, 846: 1-66.
https://doi.org/10.1016/j.physrep.2019.12.004

Liu X.W., Shi D.F., Zhou S.Y., Liu H.L., Liu H.X., and Yao X.J., 2018, Molecular dynamics simulations and novel drug discovery, Expert Opinion on Drug Discovery, 13(1): 23-37.
https://doi.org/10.1080/17460441.2018.1403419

Mangan N., Brunton S., Proctor J., and Kutz J., 2016, Inferring biological networks by sparse identification of nonlinear dynamics, IEEE Transactions on Molecular Biological and Multi-Scale Communications, 2: 52-63.
https://doi.org/10.1109/TMBMC.2016.2633265

Manipur I., Granata I., Maddalena L., and Guarracino M.R., 2020, Clustering analysis of tumor metabolic networks, BMC Bioinformatics, 21: 1-14.
https://doi.org/10.1186/s12859-020-03564-9

Megchelenbrink W., Rossell S., Huynen M.A., Notebaart R.A., and Marchiori E., 2015, Estimating metabolic fluxes using a maximum network flexibility paradigm, PLoS ONE, 10(10): e0139665.
https://doi.org/10.1371/journal.pone.0139665

Mochizuki A., 2016, Theoretical approaches for the dynamics of complex biological systems from information of networks, Proceedings of the Japan Academy, Series B Physical and Biological Sciences, 92: 255-264.
https://doi.org/10.2183/pjab.92.255

Murrugarra D., and Aguilar B., 2019, Modeling the stochastic nature of gene regulation with boolean networks, Algebraic and Combinatorial Computational Biology, 2019: 147-173.
https://doi.org/10.1016/B978-0-12-814066-6.00005-2

Muzio G., O'Bray L., and Borgwardt K., 2020, Biological network analysis with deep learning, Briefings in Bioinformatics, 22: 1515-1530.
https://doi.org/10.1093/bib/bbaa257

Nardini J.T., Baker R.E., Simpson M.E., and Flores K.B., 2020, Learning differential equation models from stochastic agent-based model simulations, Journal of the Royal Society Interface, 18(176): 20200987.
https://doi.org/10.1098/rsif.2020.0987

Pandey V., Hadadi N., and Hatzimanikatis V., 2018, Enhanced flux prediction by integrating relative expression and relative metabolite abundance into thermodynamically consistent metabolic models, PLoS Computational Biology, 15(5): e1007036.
https://doi.org/10.1371/journal.pcbi.1007036

Paulevé L., Kolcák J., Chatain T., and Haar S., 2020, Reconciling qualitative abstract and scalable modeling of biological networks, Nature Communications, 11(1): 4256.
https://doi.org/10.1038/s41467-020-18112-5

Pavlopoulos G.A., Secrier M., Moschopoulos C.N., Soldatos T., Kossida S., Aerts J., Schneider R., and Bagos P., 2011, Using graph theory to analyze biological networks, BioData Mining, 4: 1-27.
https://doi.org/10.1186/1756-0381-4-10

Pham E., Li I., and Truong K., 2008, Computational modeling approaches for studying of synthetic biological networks, Current Bioinformatics, 3: 130-141.
https://doi.org/10.2174/157489308784340667

Saadat pour A., and Albert R., 2013, Boolean modeling of biological regulatory networks: a methodology tutorial, Methods, 62(1): 3-12.
https://doi.org/10.1016/j.ymeth.2012.10.012

Schneider M., and Antes I., 2021, SenseNet a tool for analysis of protein structure networks obtained from molecular dynamics simulations, PLoS ONE, 17(3): e0265194.
https://doi.org/10.1371/journal.pone.0265194

Sen P., 2022, Flux balance analysis of metabolic networks for efficient engineering of microbial cell factories, Biotechnology and Genetic Engineering Reviews, 2022: 1-34.
https://doi.org/10.1080/02648725.2022.2152631

Tyson J., Laomettachit T., and Kraikivski P., 2019, Modeling the dynamic behavior of biochemical regulatory networks, Journal of Theoretical Biology, 462: 514-527.
https://doi.org/10.1016/j.jtbi.2018.11.034

Vidal-Limon A., Aguilar-Toalá J., and Liceaga A., 2022, Integration of molecular docking analysis and molecular dynamics simulations for studying food proteins and bioactive peptides, Journal of Agricultural and Food Chemistry, 70(4): 934-943.
https://doi.org/10.1021/acs.jafc.1c06110

Wang Y.X.R., Li L., Li J.J., 2021, Network modeling in biology: statistical methods for gene and brain networks, Statistical Science: A Review Journal of the Institute of Mathematical Statistics, 36(1): 89.
https://doi.org/10.1214/20-sts792

Wang B., Xie Z., Chen J., and Wu Y., 2018, Integrating structural information to study the dynamics of protein-protein interactions in cells, Structure, 26(10):1414-1424.
https://doi.org/10.1016/j.str.2018.07.010

Wang S., Fan K., Luo N., Cao Y., Wu F., Zhang C., Heller K., and You L., 2019, Massive computational acceleration by using neural networks to emulate mechanism-based biological models, Nature Communications, 10(1): 4354.
https://doi.org/10.1038/s41467-019-12342-y

Wang X., Zhang Y., and Wen T., 2021, Progress on genome-scale metabolic models integrated with multi-omics data, Chinese Science Bulletin, 13(7): 855.
https://doi.org/10.1360/tb-2020-1468

Wang Z., and Gao H., 2010, Dynamics analysis of gene regulatory networks, International Journal of Systems Science, 41: 1-4.
https://doi.org/10.1080/00207720903477952