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Problem Solving Protocol

Network analysis of multivariate time series data in biological systems: methods and applications

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Abstract

Network analysis has become an essential tool in biological and biomedical research, providing insights into complex biological mechanisms. Since biological systems are inherently time-dependent, incorporating time-varying methods is crucial for capturing temporal changes, adaptive interactions, and evolving dependencies within networks. Our study explores key time-varying methodologies for network structure estimation and network inference based on observed structures. We begin by discussing approaches for estimating network structures from data, focusing on the time-varying Gaussian graphical model, dynamic Bayesian network, and vector autoregression-based causal analysis. Next, we examine analytical techniques that leverage pre-specified or observed networks, including other autoregression-based methods and latent variable models. Furthermore, we explore practical applications and computational tools designed for these methods. By synthesizing these approaches, our study provides a comprehensive evaluation of their strengths and limitations in the context of biological data analysis.

Keywords: network analysis; time-varying networks; biological systems; high-throughput data

Introduction

In recent years, biological data have expanded significantly in volume, diversity, and complexity. For example, high-throughput data, such as genomic, transcriptomic, and proteomic datasets, have emerged from advanced sequencing and omics technologies, enabling the exploration of biological processes at an unprecedented scale. These data present both immense opportunities and challenges in developing bioinformatic methodologies and advancing biomedical research. We refer to [1] for further details about relevant applications.

Extensive statistical methods have been developed for handling biological data, including marginal analysis focusing on individual variables (e.g. differential expression analysis [2] and genome-wide association studies [3]) and joint analysis focusing on a set of variables (e.g. regression-based methods). Besides, Bayesian and machine learning approaches are also available for both marginal and joint analysis. Recent advances in analytical methods have been comprehensively reviewed in [4–6]. Despite their success, these methods often fall short of uncovering intricate interactions among biological entities, a challenge that is particularly prevalent in complex biological data. To address this gap, network analysis has emerged as a powerful alternative. Network analysis in bioinformatics refers to the process of visualizing and analyzing the intricate relationships between biological entities through statistical tools derived from graph theory. In this context, biological entities such as genes, proteins,and metabolites are represented by nodes/vertices in a network, and the interactions between them are represented by edges/links. These edges can be either directed, indicating a one-way relationship (e.g. gene A regulates gene B but not vice versa), or undirected, representing a bidirectional or non-directional relationship (e.g. physical interactions between proteins). Additionally, edges may be weighted to quantify the strength of interactions (e.g. correlation coefficients in gene co-expression networks) or unweighted, simply indicating the presence or absence of interactions.

In the early 21st century, network analysis experienced a significant surge, enabling researchers to analyze large-scale, complex networks using various types of biological and biomedical data [7]. For example, protein interaction networks are constructed to predict protein functions and identify disease pathways [8]; gene networks capture different cellular processes, such as molecular-level interactomes and activity flows, providing insights into complex biological systems [9]; and epigenetic data, such as DNA methylation, can be used to build gene regulatory networks, which elucidate how gene expression is controlled [10]. When phenotype information is available, networks can be further enriched to create gene-phenotype networks [11]. Another example is the human disease network, which connects diseases based on their underlying molecular [12], phenotypic [13], or clinical [14] interactions. While high-dimensional data contain rich biological information, their large scale and inherent noise often complicate the extraction of meaningful patterns, calling for methodological advances.

Broadly, there are two categories of networks: static and time-varying [15]. Here, the term "static" refers to examining a network at a single point in time or within a pre-specified time window,

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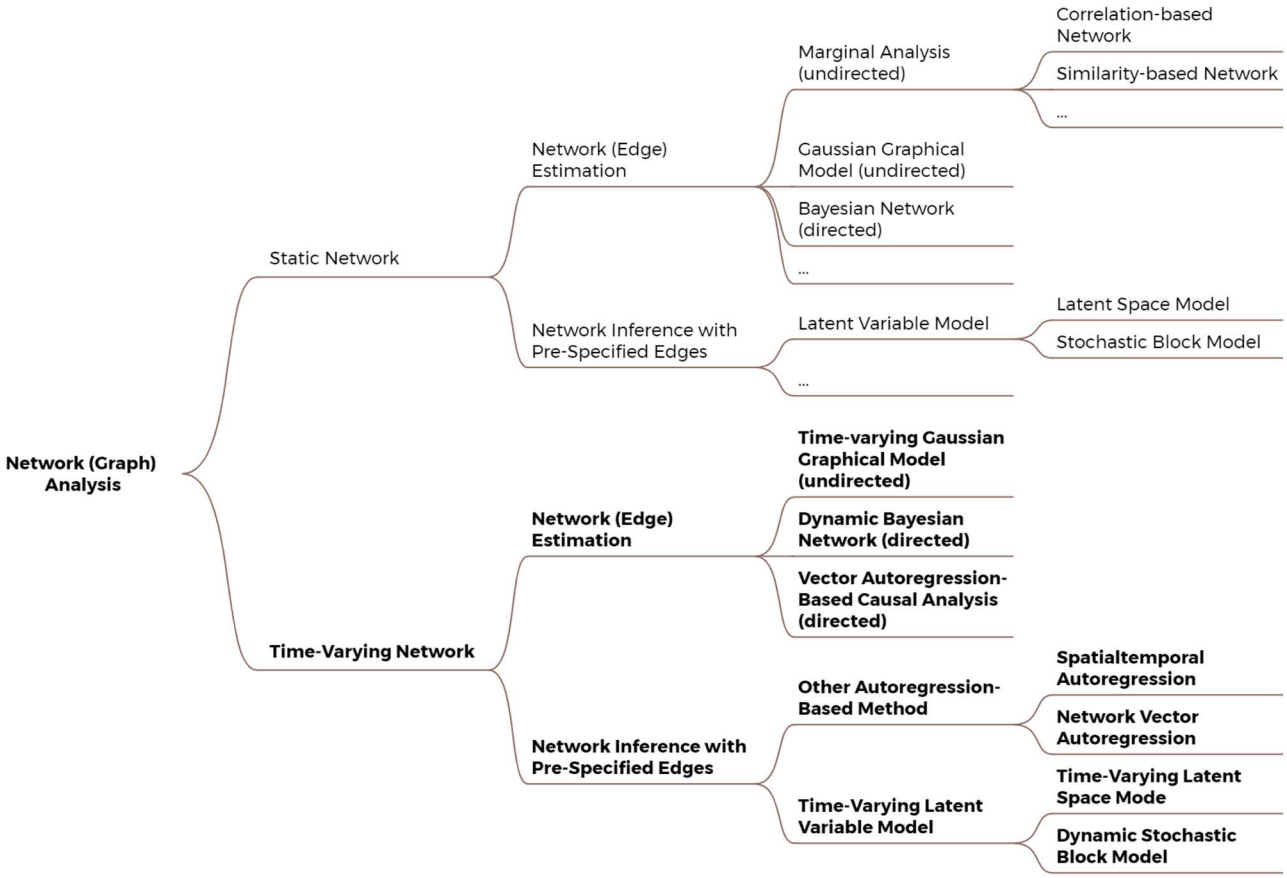

Figure 1. Structure diagram of network analysis methodologies.

where connections and relationships between nodes are considered fixed. In contrast, time-varying ones focus on how a network evolves over time, taking into account changes in connections and node properties. Essentially, static analysis provides a snapshot of a network, whereas time-varying analysis reveals its progression and changes over time. While there exists comprehensive literature on static network analysis [16, 17], our study provides a thorough examination of methodologies and applications in time-varying network analysis. Focusing on time-varying analysis, we summarize the categories of network analysis methods in Fig. 1. Specifically, we first focus on methods for estimating network structures, where the presence of edges is inferred based on node attributes. Then, we delve into methods tailored for networks that are either fully pre-specified or partially observed. Both sections are systematically organized according to major methodological frameworks. To offer a practical perspective, we also summarize key bioinformatics applications in Table 1 and list commonly used computational tools in Table 2. Extending the methods discussed in the study, Table 2 also includes relevant databases and integrated analysis platforms to provide a greater practical utility. Building on the methodologies, we analyze a time-course microarray dataset and present results. Finally, we conclude this article with a discussion of key challenges and future directions in network analysis.

Network structure estimation

Understanding the network structure and how it evolves over time is critical for capturing dynamic relationships in complex biological systems. To address this challenge, this section focuses on methods that estimate the topological structure of a network from observed multivariate time series data. These approaches aim to uncover the underlying connections between nodes through time-varying graphical models. We begin by formalizing the concept of time-varying graphical models, and then delve into three widely used frameworks in this domain.

Basic formulation of time-varying graphical models

The time-varying graphical model is a probabilistic model that describes relationships among entities in dynamic systems. In such a model, the presence of edges reflects conditional independence. Unlike static graphs, time-varying graphs consider how the graph structure evolves over time. This evolution can involve the establishment or dissolution of relationships or changes in the strength of connections. The goal of a time-varying graphical model is to infer the dynamic evolution of these relationships from time-series data to better understand the behavior of the system.

Consider a system with multiple entities, represented by $\mathbf{V} = \{1, 2, \ldots, d\}$. The length of the time series is denoted as T. For each time point $t = 1, 2, \ldots, T$, the time-varying graphical model defines a graph $\boldsymbol{G}_t = (\mathbf{V}, \boldsymbol{E}_t)$, where $\boldsymbol{E}_t \subseteq \mathbf{V} \times \mathbf{V}$ represents the set of edges present at time t. Each graph $\boldsymbol{G}_t$ can be represented by an adjacency matrix $\boldsymbol{A}_t$, where A_t^{ij} indicates whether there is an edge between node i and node j at time t. The goal of the time-varying graphical model is to infer the patterns of change in the adjacency

Table 1. Applications of time-varying network analysis in bioinformatics

Network (edge) estimation	Reference	Data type	Description	Software/Packages
Time-varying Gaussian graphical model	[11] Ou-Yang *et al.*	Gene expression data and protein–protein interaction data	The article proposes a method for detecting temporal protein complexes based on dynamic protein–protein interaction networks	http://mail.sysu.edu.cn/home/stsddq@mail.sysu.edu.cn/dai/others/TSOCD.zip
	[18] Yang and Peng	Gene expression data	The article introduces a log-determinant penalty-based estimation model for time-varying graphical models.	https://github.com/jlyang1990/loggle (R)
	[19] Keshavarz *et al.*	Gene expression data and protein–protein interaction data	The study focuses on sequential change point detection in high-dimensional Gaussian graphical models.	/
	[20] Wit and Abbruzzo	Gene expression data	The article introduces a new model for estimating slowly-changing dynamic gene-regulatory networks, which is suitable for high-dimensional data.	/
	[21] Hallac *et al.*	Gene expression data and protein-protein interaction data	The article presents a Time-Varying Graphical LASSO (TVGL) method for inferring dynamic networks from time series data. Utilizing alternating direction method of multipliers (ADMM), it also introduces an efficient message-passing algorithm scalable to large datasets. https://github.com/tpetaja1/tvgl (Python)	
	[22] Erkip and Erman	Protein structure and residue dynamics data	The article introduces the dynamically perturbed Gaussian network model (DP-GNM).	/
Dynamic Bayesian network	[23] Robinson *et al.*	Gene expression data	The paper introduces non-stationary dynamic Bayesian networks (nsDBNs). A Markov Chain Monte Carlo (MCMC) algorithm is developed to learn nsDBN structures, applicable to evolving networks like transcriptional regulatory or neural pathways	/
	[24] Thorne	Gene expression data	The article introduces a gene regulatory network inference method using dynamic Bayesian networks and negative binomial distribution, enhanced by sparse regression and variational inference to improve accuracy and efficiency.	/
	[25] Yu *et al.*	Gene expression data	The article proposes a hybrid method combining dynamic Bayesian networks (DBNs) with multivariate change-point processes to infer time-delayed gene regulatory networks, effectively addressing non-stationarity in gene expression data.	/
	[26] Yang *et al.*	Gene expression data, protein–protein interaction data and genetic interaction data	TV-DBN can reconstruct transcriptional networks from gene expression data and integrate protein–protein/genetic interactions via Bayesian models to identify biological pathways.	/
	[27] Zhang *et al.*	Gene expression data	The article proposes a method using nonhomogeneous dynamic Bayesian networks (nhDBN) combined with enhanced Markov Monte Carlo (MCMC) sampling to infer gene regulatory networks.	/
	[28] Song *et al.*	Gene expression data	The article applies Time-Varying Dynamic Bayesian Networks (TV-DBN) to yeast cell cycle gene expression data.	/

(continued)

Table 1. Continued

Network (edge) estimation	Reference	Data type	Description	Software/Packages
Vector autoregression-based causal analysis	[29] Fujita *et al.*	Gene expression data	The Sparse Vector Autoregressive (SVAR) model estimates gene regulatory networks from time-series data, even with fewer samples than genes.	The original paper is not open-source, but there are similar available packages as follows. 1. https://github.com/svazzole/sparsevar (R) 2. https://cran.r-project.org/web/packages/bigtime/index.html (R)
	[30] Yao *et al.*	Gene expression data	The article presents the Conditional Granger Causality with Two-Step Prior Ridge Regularization (CGC-2SPR) method.	https://bitbucket.org/dtyu/granger-causality/src/master/ (python)
Network inference with pre-specified edges	Reference	Data type	Description	Software/Packages
Time-varying latent variable model	[31] García-Jiménez *et al.*	Microbiological data	The article integrates deep learning with microbiome data, proposing a heterogeneous autoencoder-based neural network architecture. It also develops models to predict these latent representations.	https://github.com/jorgemf/DeepLatentMicrobiome (python)
	[32] Ding *et al.*	Protein sequence data	The article employs latent space models to analyze protein sequences, capturing evolutionary relationships in low-dimensional representations.	https://github.com/BrooksResearchGroup-UM/PEVAE_Paper (python)
	[33] Liang *et al.*	Histological data	The article introduces a restricted Boltzmann machine for multi-purpose early disease prediction (MMPDENB-RBM), a model that integrates personalized dynamic edge network biomarkers (PDENB), multimodal optimization, and latent space search.	/
	[34] Schaub *et al.*	Gene expression data and protein–protein interaction data	The study infers statistical network models from snapshots of dynamic node processes without directly observing edges. It applies to gene regulatory and protein-protein interaction network inference.	/
	[35] Airoldi *et al.*	Gene expression data	The paper introduces Mixed Membership Stochastic Blockmodels. A variational inference algorithm is also developed for efficient posterior inference.	https://github.com/aburnap/Mixed-Membership-Stochastic-Blockmodel (python)

matrix $\mathbf{A}_t$. A basic model can be expressed as:

$$\mathbf{A}_t \sim P(\mathbf{A}_t \mid \mathbf{A}_{t-1}, \ldots, \mathbf{A}_1, \boldsymbol{\Theta}),$$

$$\mathbf{Y}_t \sim P(\mathbf{Y}_t \mid \mathbf{A}_t, \boldsymbol{\phi}).$$

Here, $\mathbf{Y}_t \in \mathbb{R}^d$ denotes the observed data vector of d variables (nodes) at time t, and $\boldsymbol{\Theta}$ and $\boldsymbol{\phi}$ represent the static model hyper-parameters, which can also be time-varying if needed. The probability functions $P(\cdot)$ can be any appropriate model, such as methods based on probability distributions or machine learning techniques.

Common methods for estimating a graphical model include maximum likelihood estimation (MLE) and ordinary least squares (OLS). To avoid a complete graph where all nodes are connected to each other, sparsity assumptions are enforced by selecting edges based on specific criteria, including ℓ_0 regularization (e.g. AIC, BIC) [36], ℓ_1 regularization (e.g. graphical LASSO) [37], and neighborhood selection that infers edges node-by-node rather than globally [38]. Temporal assumptions in modeling often rely on nonparametric (kernel) methods or regularization. These include (i) continuous evolution, where the graph structure changes smoothly over time; (ii) edge-piecewise dynamics, which enforce smoothness by limiting the number of jumps or change-points in individual edges; and (iii) graph-piecewise dynamics, which count change-points globally across the entire graph or covariance/precision matrix, rather than edge-by-edge. We refer to [18] and [19] for further details.

Time-varying Gaussian graphical model

The time-varying Gaussian graphical model (TVGGM) is a special case of time-varying graphical models, in which the random

Table 2. Computational tools for time-varying network analysis

Type	Software/Platform	Link	Description
Database	STRING	https://string-db.org/	STRING is an online database specialized in constructing protein-protein interaction (PPI) networks by integrating experimental data, computational predictions, and text mining results.
	IntAct	https://www.ebi.ac.uk/intact/	IntAct is a molecular interaction database developed by the European Bioinformatics Institute (EBI), providing experimentally validated protein-protein interaction data for PPI network construction.
	BioGRID	https://thebiogrid.org/	BioGRID is a large-scale interaction database containing protein-protein, gene-gene, and chemical-gene interactions, supporting Cytoscape export for systems biology and gene regulatory network analysis.
	Reactome Pathway Database	https://reactome.org/	Reactome is a detailed human biological pathway database supporting interactive analysis of signaling and metabolic pathways, and can be directly imported into Cytoscape for network analysis.
	InnateDB	https://www.innatedb.com/	InnateDB is a database dedicated to immune system and innate immune response interaction networks, containing protein-protein and gene-gene regulatory network data, suitable for immunology research and inflammatory disease network analysis.
	NetPath	http://www.netpath.org/	NetPath is a database focusing on cancer and immune-related signaling pathway networks, with data derived from experimentally validated pathways such as Notch, Wnt, and TGF-beta, suitable for signaling transduction and cancer biology research.
	miRTarBase	https://mirtarbase.cuhk.edu.cn/	miRTarBase is a database specializing in miRNA-target gene interactions with experimentally validated data, suitable for miRNA regulatory network analysis and construction using Cytoscape or other tools.
Comprehensive Analysis Platform	Cytoscape	https://cytoscape.org/	Cytoscape is an open-source bio-network visualization and analysis tool that supports complex protein-protein interactions (PPI), metabolic pathways, gene regulation networks, and more.
	OmicsNet	https://www.omicsnet.ca/	OmicsNet provides network analysis tools integrating multi-omics data (genes, proteins, metabolites), enabling the visualization of protein-protein interactions, metabolic networks, and gene regulatory networks.
	NAViGaTOR	http://ophid.utoronto.ca/navigator/	NAViGaTOR is an efficient bio-network visualization software particularly suitable for analyzing large-scale PPI datasets, providing various interactive layouts and network analysis functions.
	HiView	https://www.hiview.org/	HiView is a network visualization and mining tool for large-scale omics data, offering various visualization modes such as hierarchical and force-directed graphs, suitable for exploring relationships in large-scale data and biological network mining.
	PCViz	https://www.pathwaycommons.org/pcviz/	PCViz is a visualization tool from Pathway Commons for interactive viewing and analysis of biological pathway networks, supporting graphical display and integration with Cytoscape for signaling pathway and regulatory network analysis.
	MetaboAnalyst	https://www.metaboanalyst.ca/	MetaboAnalyst is an online tool for constructing and analyzing metabolic networks, offering integrative analysis of metabolites, genes, and pathways, suitable for metabolomics, multi-omics integration, and disease metabolism studies.
	Hipathia	https://hipathia.babelomics.org/	Hipathia is a tool for analyzing signaling pathways and gene regulatory networks, suitable for cancer gene, drug target, and disease pathway research.
	CyTargetLinker	https://projects.bigcat.unimaas.nl/cytargetlinker/	CyTargetLinker is a Cytoscape plugin for analyzing drug-gene, miRNA-gene, and TF-gene interaction networks, suitable for drug target prediction and gene regulatory network studies.
	OmicsNet	https://www.omicsnet.ca/	OmicsNet is an online tool for multi-omics data integration and network analysis, visualizing associations among genes, proteins, and metabolites, suitable for multi-omics data analysis and network biology research.
	Pathway Studio	https://www.pathwaystudio.com/	Pathway Studio is a commercial software for biological network modeling, signaling pathway, and disease mechanism studies, suitable for drug target discovery, gene regulatory network, and biomarker research.
Database + Comprehensive Analysis Platform	GeneMANIA	https://genemania.org/	GeneMANIA is a tool for predicting gene functions and gene network relationships based on interaction data from multiple databases, allowing users to input gene lists and generate corresponding functional association networks.
	Pathway Commons	https://www.pathwaycommons.org/	Pathway Commons is a platform integrating multiple biological pathway databases (such as Reactome, BioGRID, and PID), offering access to pathway-related interactions for systems biology research.

(continued)

Table 2. Continued

Type	Software/Platform	Link	Description
	NDEx	http://www.ndexbio.org/	NDEx is an open-source platform dedicated to sharing and visualizing biological networks, providing various network analysis tools and integrating with Cytoscape for seamless data exchange.
	STITCH	http://stitch.embl.de/	STITCH is a database and network visualization tool for exploring chemical-protein interactions, integrating information on drugs, metabolites, and small molecule compounds.
	RegNetwork	http://www.regnetworkweb.org/	RegNetwork is a data integration platform focusing on transcription factor (TF) and miRNA regulatory networks, suitable for gene regulatory network analysis and miRNA-gene interaction studies.
	miRNet	https://www.mirnet.ca/	miRNet is a tool for analyzing miRNA-gene, protein, and metabolite interactions, integrating multiple databases (such as miRTarBase and TarBase), with a visualization interface for constructing miRNA-disease and miRNA-pathway association networks.
	DisGeNET	https://www.disgenet.org/	DisGeNET is a disease-gene association database with data from sources like ClinVar and GWAS Catalog, supporting visualization for constructing disease-related gene networks, suitable for biomedical research, disease biomarker discovery, and drug target identification.
	STRING-DB	https://string-db.org/	STRING-DB is a large-scale database for protein-protein interaction (PPI) analysis, integrating experimentally validated, computationally predicted, and literature-mined data, supporting network visualization for PPI research and functional module analysis.
	TRRUST	https://www.grnpedia.org/trrust/	TRRUST is a database focusing on transcription factor (TF)-target gene regulatory networks, with data from text mining and experimental validation, suitable for gene regulatory network analysis using Cytoscape or other network tools.
	KEGG Mapper	https://www.genome.jp/kegg/mapper.html	KEGG Mapper is a pathway mapping tool from KEGG for locating genes, proteins, and metabolites within pathways, suitable for metabolic network, signaling pathway, and gene regulatory network analysis, and can be integrated with tools like Cytoscape and Pathview.
	BioGRID ORCS	https://orcs.thebiogrid.org/	BioGRID ORCS is a sub-database of BioGRID for CRISPR gene screening data, suitable for gene function network analysis and predicting key regulatory factors, applicable to CRISPR functional screening and gene regulatory network analysis.
	PINA	https://omics.bjcancer.org/pina/	PINA is a platform integrating multiple PPI databases, offering tools for constructing and analyzing protein interaction networks, suitable for protein interaction studies, pathway analysis, and protein complex prediction.
	NGDC	https://ngdc.cncb.ac.cn/	NGDC is China's leading bioinformatics and genomics data management platform, providing open-access resources to support life and health sciences research, with tools like BioCode and GEN for biological network analysis.
	BioPAX & Paxtools	https://www.biopax.org/	BioPAX is a standardized format for biological pathway data integration from various sources, while Paxtools is a Java library based on BioPAX for parsing and analyzing biological networks, suitable for large-scale pathway data integration and standardization.
Python library	NetworkX	https://pypi.org/project/networkx/	A Python library for constructing and analyzing biological networks, such as gene regulatory and protein-protein interaction networks, supporting graph operations, path analysis, and visualization.
	igraph	https://pypi.org/project/igraph/	A high-performance Python library for large-scale biological network analysis, supporting gene co-expression networks and biological pathway modeling.
	dynetworkx	https://pypi.org/project/dynetworkx/	DyNetworkX is a Python package for the study of dynamic network analysis (DNA).
	pgmpy	https://pypi.org/project/pgmpy/	pgmpy is a Python package for working with Bayesian Networks and related models such as Directed Acyclic Graphs, Dynamic Bayesian Networks, and Structural Equation Models.
	PyBNesian	https://pypi.org/project/pybnesian/	PyBNesian is a Python package that implements Bayesian networks. Currently, it is mainly dedicated to learning Bayesian networks.
	PyTorch	https://pypi.org/project/torch/	PyTorch is a Python package that provides two high-level features:Tensor computation (like NumPy) with strong GPU acceleration and deep neural networks built on a tape-based autograd system
	Keras	https://pypi.org/project/keras/	SimpleRNN, LSTM, GRU). Provides a user-friendly interface for building and training RNN models with various RNN layers (e.g., SimpleRNN, LSTM, GRU).

(continued)

Table 2. Continued

Type	Software/Platform	Link	Description
	torch_geometric	https://github.com/pyg-team/pytorch_geometric	torch_geometric is a library based on PyTorch, which provides a set of tools and modules for building and training graph neural networks
	SimpleBool	https://github.com/lujunyan1118/SimpleBool	SimpleBool is a python package for simulation and analysis of dynamic Boolean network models.
	tvgl	https://github.com/tpetaja1/tvgl	The tvgl Python library is designed to solve the time - varying graphical lasso problem, enabling the estimation of time - varying covariance matrices and graph structures from data, with efficient optimization algorithms suitable for various time - series data applications such as finance, biomedicine, and social network analysis.
	scipy.integrate	https://pypi.org/project/scipy/	scipy.integrate is a module in the scipy library, which provides various functions for solving ordinary differential equations (ODEs), such as odeint and solve_ivp, being powerful and widely used.
	DynGEM	https://github.com/palash1992/DynamicGEM	DynGEM is a Python library specifically designed for dynamic network embedding. It can learn the low - dimensional representations of nodes in a dynamic network and capture the changes in network structure over time.
	Bioconductor (R-Package: igraph, graph, RBGL, etc.)	https://www.bioconductor.org/	Bioconductor is a collection of bioinformatics tools for R, including multiple network analysis-related R packages (such as igraph, graph, RBGL, and RedeR), enabling biological network visualization and analysis.
R package	deSolve	https://cran.r-project.org/web/packages/deSolve/index.html	deSolve is a standard R package for solving differential equations. It supports a variety of numerical solution methods and can handle various types of equations such as ordinary differential equations and partial differential equations.
	MARSS	https://cran.r-project.org/web/packages/MARSS/index.html	The MARSS package provides maximum-likelihood parameter estimation for constrained and unconstrained linear multivariate autoregressive state-space (MARSS) models, including partially deterministic models.
	vars	https://cran.r-project.org/web/packages/vars/index.html	The vars package provides the implementation of Vector Autoregression (VAR) models. You can build a Network Vector Autoregression model based on it by combining network structure information. It can fit and analyze multivariate time - series data.
	blockmodels	https://cran.r-project.org/web/packages/blockmodels/index.html	Dedicated to SBM, applied to functional module detection in biological networks. This package has certain limitations in dynamic network processing and needs to be combined with other packages for use.
	dynsbm	https://cran.r-project.org/src/contrib/Archive/dynsbm/	dynsbm is an R package that implements the dynamic stochastic block model, combining the static part of the stochastic block model with independent Markov chains for analyzing network data that changes over time.
	dbnR	https://www.rdocumentation.org/packages/dbnR/versions/0.7.8	This package offers an implementation of Gaussian dynamic Bayesian networks (GDBN) structure learning and inference based partially on Marco Scutari's package bnlearn
	DCM	https://cran.r-project.org/src/contrib/Archive/DCM/	DCM is an R package for Dynamic Causal Model analysis, which can be used to model and infer neuroscience data.
	kerasR	https://cran.r-project.org/src/contrib/Archive/kerasR/	Allows building and training RNN models in R using the Keras API with various RNN layers.
	rnn	https://cran.r-project.org/web/packages/rnn/index.html	Provides a simple interface for defining and training RNN models for tasks like time series prediction.
	BoolNet	https://cran.r-project.org/web/packages/BoolNet/index.html	BoolNet is a classic R package for Boolean network analysis, providing various methods for building, simulating, and analyzing Boolean networks.

variables at each node are assumed to follow a Gaussian distribution (i.e. the data are continuous and normally distributed). It is widely used in bioinformatics for modeling dynamic gene regulatory networks [20, 21], protein interactions [19, 39], and other biological systems with temporal dependencies [18, 22]. As a graph model tailored for Gaussian-distributed data, the primary goal of TVGGMs is to estimate the time-varying precision matrix (inverse covariance matrix), which captures the evolving conditional dependencies among variables over time.

In the literature, [40–42] are recognized as pioneering studies to formally introduce TVGGMs, their estimation methods, and the theoretical framework. Further extending these works, [21] introduces Time-Varying Graphical LASSO (TVGL), a framework combining LASSO-based sparsity and temporal smoothness to estimate undirected precision matrices that evolve smoothly over time. Based on convex optimization, TVGL efficiently infers large-scale time-varying network structures. Several extensions of Graphical LASSO, such as Local Groups Graphical LASSO, T-LASSO, and G-LASSO, have been integrated into TVGGMs to improve performance [18, 43]. The identifiability of TVGGMs can be challenged by limited sample sizes and high-dimensional settings, especially when smoothness penalties induce non-unique or overly similar network estimates across time; incorporating structural priors [44], selecting regularization parameters via cross-validation [21],

and using stability-based approaches like resampling [45] can help mitigate these issues.

Other extensional studies focus on specific characteristics of time-varying graphical models, with temporal trend detection being a major area of interest. Research on gene regulatory networks emphasizes detecting slow-evolving dependencies in time-series data [20]. In contrast, [46] introduces methods for estimating networks with abrupt changes, or "jumps," which are also common in biological systems. Change-point detection methods, such as those proposed by [47] and [19], address structural shifts in high-dimensional settings. Additionally, [48] quantifies interaction persistence, revealing long-term network evolution patterns, and [49] establishes the robustness of networks by optimizing network resilience.

Dynamic Bayesian network

Dynamic Bayesian networks (DBNs) are directed acyclic graphs that are particularly useful for inferring temporal dependencies and causal relationships within complex systems [50], and have been widely applied in bioinformatics [23–25]. DBNs are probabilistic graphical models that extend Bayesian networks (BNs) to model time series data by capturing both contemporaneous dependencies (within the same time step) and lagged dependencies (across different time steps). A basic DBN infers a time-invariant network structure that remains constant across all time steps, with the lagged dependencies are limited to a single time step (time $t-1$ to t), while it can be extended to estimate time-varying dependencies [26, 27] and more than one steps of lagged dependencies [51, 52]. For the basic model, the joint probability distribution over a sequence of time steps 1 to T is factorized as:

$$P(\mathbf{Y}_{1:T}) = P(\mathbf{Y}_1)\prod_{t=2}^{T} P(\mathbf{Y}_t|\mathbf{Y}_{t-1}),$$

where $P(\mathbf{Y}_1)$ is the initial state distribution, and $P(\mathbf{Y}_t|\mathbf{Y}_{t-1})$ is the transition model. The initial network is typically a static BN that captures contemporaneous dependencies at $t = 1$, while the transition network models one-step lagged dependencies by connecting variables across time steps.

For identifying network structure in DBNs, the goal is to estimate

$$P(Y_t^i|\mathrm{Pa}(Y_t^i))$$

for a specific node i, where $\mathrm{Pa}(Y_t^i)$ denotes the parents of Y_i including variables from the same or previous time steps, indicating the existence of directed edges. Network sparsity is induced through shrinkage priors (e.g. penalization-based methods or domain-knowledge-informed constraints) on edge parameters, enabling data-driven pruning of insignificant connections during posterior inference [53]. The identifiability of DBNs is often hindered by limited temporal observations and the presence of equivalent network structures, which can be mitigated through the use of informative priors, temporal constraints, and score-equivalence-breaking structure learning algorithms [50, 54].

In this section, we introduce two lines of research: (i) discrete DBNs (dDBNs), where the system's state takes values from a discrete state space, and (ii) continuous DBNs (cDBNs), which handle systems with continuous state variables. We demonstrate how these two different dynamic Bayesian network models have evolved in the dynamic network literature and summarize extensions and applications in both directions, respectively.

Discrete dynamic Bayesian network

dDBNs are a class of DBNs in which variables take on a finite set of states, making them particularly suitable for modeling systems with categorical or binary outcomes. The joint probability distribution takes the same form as in the standard DBNs. The transition model in a dDBN is typically represented using conditional probability tables (CPTs) for discrete variables. For a specific variable i, the transition probability is given by:

$$P(Y_t^i|\mathrm{Pa}(Y_t^i)) = CPT(Y_t^i|\mathrm{Pa}(Y_t^i)).$$

Extensional studies have been conducted on dDBNs, focusing on different aspects to enhance their modeling capabilities. [55] demonstrates the use of dDBNs for modeling neuroanatomical regions with multinomial distributions, capturing nonlinear relationships while highlighting limitations such as the need for improved structure search heuristics. [56] emphasizes the critical role of sample size, proposing a guideline for reliable model discovery in binary and ternary-valued networks. To address challenges in small-sample environments, [57] introduces a fuzzy KNN-based parameter learning method, which effectively handles missing data and improves inference accuracy. These advancements, along with hybrid modeling and scalable inference techniques [58], continue to expand the applicability of dDBNs in complex systems.

Continuous dynamic Bayesian network

cDBNs are another class of DBNs, where the variables are continuous, meaning they take on real-valued quantities. The joint probability distribution over a sequence of time steps also takes the form as in a standard DBN. For continuous variables, the transition model is often represented using Gaussian distributions:

$$P(Y_t^i|\mathrm{Pa}(Y_t^i)) = \mathcal{N}(Y_t^i; \mu_t^i, \sigma_t^i),$$

where μ_t^i and σ_t^i are the mean and variance, respectively, which depends on the parents $\mathrm{Pa}(Y_t^i)$. For linear Gaussian models, the transition can be expressed as:

$$\mathbf{Y}_t = \mathbf{A}\mathbf{Y}_{t-1} + \boldsymbol{\epsilon}_t, \quad \boldsymbol{\epsilon}_t \sim \mathcal{N}(\mathbf{0}, \mathbf{Q}),$$

where $\mathbf{A}$ is the transition matrix, and $\mathbf{Q}$ is the covariance matrix of the noise.

For cDBNs, inference and learning can be more computationally intensive due to the continuous nature of variables, often requiring approximations or specialized algorithms. For instance, variational inference methods provide efficient approximations for posterior distributions in high-dimensional continuous spaces [59]. Similarly, particle filtering techniques, as discussed in [60], offer scalable solutions for sequential inference in nonlinear and non-Gaussian systems. Additionally, Bayesian deep learning approaches combine cDBNs with neural networks to improve inference accuracy and scalability [61]. These advancements address the computational challenges of cDBNs, enabling their application to large-scale, real-world problems.

For time-varying networks, the state variables are usually continuous. Time-varying DBNs (TVDBNs) are a key extension to cDBN [28]. Unlike traditional Bayesian networks, which assume a static structure, TVDBNs model changing parameters and structures as random processes, ensuring the underlying network remains probabilistically identifiable. Expanding on this, [26] proposes a VAR-based TVDBN that captures both intra-slice

and inter-slice directed dependencies while preserving acyclicity, allowing the network structure to evolve segment-wise over time. To further enhance flexibility and address high-dimensional challenges, [62] develops a tensor-to-tensor regression model incorporating zero-inflated logistic regression for sparsity control and Markov-switching coefficients for structural adaptation, effectively balancing flexibility and robustness.

Vector autoregression-based causal analysis

Vector autoregression (VAR) models are designed to model linear dynamic relationships among multiple variables, with which Granger causality can be assessed to extend VAR models to graphical models, thereby inferring directed temporal dependencies and helping predict the future states of the system [63]. VAR models do not impose strict structural assumptions, providing flexibility in modeling various dynamic systems. The VAR model of order p, denoted as VAR(p), is defined as:

$$\mathbf{Y}_t = \mathbf{c} + \mathbf{A}_1\mathbf{Y}_{t-1} + \mathbf{A}_2\mathbf{Y}_{t-2} + \cdots + \mathbf{A}_p\mathbf{Y}_{t-p} + \boldsymbol{\epsilon}_t,$$

where:

- $\mathbf{c} \in \mathbb{R}^d$ is a vector of intercept terms,
- $\mathbf{A}_1, \ldots, \mathbf{A}_p$ are coefficient matrices capturing lagged dependencies,
- p is the number of lags,
- $\boldsymbol{\epsilon}_t \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma})$ is a vector of white noise error terms with covariance matrix $\boldsymbol{\Sigma}$.

The above regression-based model can be easily extended to incorporate the current values of all other variables to capture contemporaneous relationships within the same time step [64]. However, VAR models, as well as other autoregression-based methods explored in later sections, can suffer from identifiability issues due to multicollinearity and limited time series length, which can be alleviated by regularization techniques, dimensionality reduction, or incorporating sparsity constraints [29, 65].

While VAR explicitly models lagged dependencies between variables (via coefficient matrices $\mathbf{A}_s$), it does not inherently assume conditional independence, which is a core feature of graphical models [66]. To address this problem, Granger causality analysis can be employed to test whether past values of one variable significantly improve the prediction of another. This approach infers directed causal relationships (edges), thereby enabling the estimation of network structure. [30]. A traditional Granger causality analysis assumes stationarity, which means the inferred network structure is time-invariant. However, non-stationary signals, which imply time-varying causal relationships, are frequently observed in bioinformatics [67]. To solve this problem, a Granger statistic that is time-specific is desired, allowing the examination of how Granger causality evolves over time [68]. One of the simplest approaches is time-varying window analysis to achieve local stationarity [69], though selecting an appropriate sliding window size remains a challenge. More advanced methods include wavelet-transformed spectral decomposition [70], adaptive recursive least squares [71], Kalman filtering [72], and the Wavelet Dynamic VAR model [73]. These methods enhance the analysis of dynamic interactions and directional information flow in complex systems.

Another important extension of the standard VAR model is the Structural VAR (SVAR) framework, which can also be viewed as a time-varying graphical model. Unlike standard VAR models, SVAR incorporates economic theory and prior knowledge to impose testable restrictions on the relationships between variables, transforming statistical correlations into causally interpretable dynamics [74]. The structural form of the SVAR model is:

$$\mathbf{A}\mathbf{Y}_t = \mathbf{c} + \mathbf{B}_1\mathbf{Y}_{t-1} + \mathbf{B}_2\mathbf{Y}_{t-2} + \cdots + \mathbf{B}_p\mathbf{Y}_{t-p} + \mathbf{S}\boldsymbol{u}_t,$$

where:

- $\mathbf{A}$ is a matrix capturing contemporaneous relationships among variables,
- $\mathbf{c} \in \mathbb{R}^d$ is a vector of intercept terms,
- $\mathbf{B}_1, \ldots, \mathbf{B}_p$ are coefficient matrices for lagged variables,
- $\mathbf{S}$ is a matrix mapping structural shocks $\boldsymbol{u}_t$ to the system,
- $\boldsymbol{u}_t$ is a vector of structural shocks (assumed to be uncorrelated and with unit variance).

In this framework, matrices $\mathbf{A}$ and $\mathbf{B}$'s can be used to construct contemporaneous and time-varying lagged dependencies, respectively. This feature makes SVAR a highly effective tool for time-varying network analysis, particularly in studying the propagation and impact of structural shocks within dynamic systems.

Network inference with pre-specified structures

Building upon the time-varying network estimation methods presented in the previous section, we now focus inference on networks with pre-specified or partially observed topologies. In this section, we explore autoregression-based methods and latent variable models. The two approaches mainly differ in analysis goals. Specifically, autoregression-based methods estimate the effects of network interactions in predicting future node attributes, while latent variable models are useful for inferring latent network structures/properties with possible missingness or noisiness in observed edges. These methods can be integrated in a sequential manner, where network structures (from prior knowledge, observed edges, or previous estimates) serve as inputs for the inferential tasks discussed here.

Autoregression-based methods

Different from the VAR-based causal analysis presented in the previous section—which focuses on constructing time-lagged causal (directed) networks—the autoregression-based methods discussed here are designed to evaluate the effects of pre-specified network structures on the prediction of future observations. In this section, we discuss two primary approaches. The first approach leverages spatiotemporal autoregressive (STAR) models, where spatial correlations characterize relationships between nodes, while temporal correlations account for dynamics in the system. The second one extends the traditional VAR to incorporate network structure into the analysis of multivariate time series data.

Spatiotemporal autoregressive models

In static network analysis, the spatial autoregressive (SAR) model [75] has been widely utilized as an effective tool for capturing network effects. It assumes that the response at each node is influenced by a weighted linear combination of responses of connected neighbors. When analyzing time series network data, an extension known as the spatial autoregressive panel (SARP)

model has been introduced [76, 77], which has the form of:

$$\mathbf{Y}_t = \rho \mathbf{W}\mathbf{Y}_t + \mathbf{X}_t\boldsymbol{\beta} + \boldsymbol{\mu} + \boldsymbol{\lambda}_t + \boldsymbol{\epsilon}_t,$$

where:

- $\mathbf{W}$ is the $d \times d$ spatial weight matrix characterizing the pre-specified network, which can be either directed or undirected, and weighted or unweighted,
- $\mathbf{X}_t$ is the matrix of covariates (explanatory variables),
- ρ is the spatial autoregressive coefficient, measuring strength of the network effect,
- $\boldsymbol{\beta}$ is the vector of coefficients for the covariates,
- $\boldsymbol{\mu}$ is the vector of individual fixed effects,
- $\boldsymbol{\lambda}_t$ is the vector of fixed time effect for period t,
- $\boldsymbol{\epsilon}_t$ is the vector of error terms, assumed to be i.i.d. with zero mean and variance σ^2.

By incorporating temporal information, SARP enhances the precision of spatial effect estimation, allowing for the capture of spatial spillover effects that propagate across nodes between consecutive time points.

Despite its advantages, the SARP model has certain limitations. First, it assumes a homogeneous autocorrelation parameter across all nodes. To address this limitation, various studies have explored alternative formulations: some allow node-specific variations in network autocorrelation parameters [78–80], while others introduce heterogeneity across predefined or unknown groups [81, 82]. Second, the SARP model assumes a homogeneous autocorrelation parameter across all time steps. One notable extension is the time-varying STAR (TV-STAR) model, which allows the autoregressive parameters to evolve over time, improving the model's ability to capture dynamic changes in spatial dependencies [83]. Last, the STAR model often assumes a pre-defined and static network structure. To address this limitation, researchers have explored unknown and time-varying network structures [84, 85].

Network vector autoregression

With the same goal of estimating network effects in predicting future values using historical values, network vector autoregression (NAR) models extend SARP by incorporating temporal dependencies. These models assume that each node's response depends on both past observations of its connected neighbors and its own historical values. Unlike SARP, NAR incorporates one-step time-lagged network effects through $\mathbf{W}\mathbf{Y}_{t-1}$, instead of contemporaneous network effects through $\mathbf{W}\mathbf{Y}_t$ [86]. The standard NAR model is:

$$\mathbf{Y}_t = \alpha \mathbf{Y}_{t-1} + \rho \mathbf{W}\mathbf{Y}_{t-1} + \mathbf{X}_t\boldsymbol{\beta} + \boldsymbol{\epsilon}_t.$$

In this specification, the coefficient α represents the autoregressive parameter that quantifies the direct temporal dependence of each variable on its own past values. The error term $\boldsymbol{\epsilon}_t \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma})$, where the covariance matrix $\boldsymbol{\Sigma}$ captures contemporaneous dependencies among the error terms across nodes. All other notations and parameters retain the same definitions as in the SARP model.

While NAR models treat the network as pre-determined, [84] regards the network structure as unknown parameters. Additionally, to characterize the heterogeneity in relationships between individuals, [87] and [88] propose community-augmented network autoregression (CNAR) and grouped network vector autoregression (GNAR) models, respectively. In these works, network autocorrelation parameters are assumed to be distinct for different groups.

Dynamic latent variable model

A latent variable model is a statistical model that represents the relationship between unobservable or difficult-to-measure latent variables and observable variables [89]. It assumes that the observed variables are influenced by underlying latent factors. Estimating parameters in latent variable models involves statistical methods such as MLE or Bayesian methods to infer the relationships between latent and observed variables. These models often face identifiability challenges due to non-unique latent representations and weakly constrained temporal dependencies, which can be addressed through geometric constraints like Procrustes alignment [90], temporal smoothing methods [91], and identifiable prior specifications [92]. There are different types of dynamic latent variable models, among which two classes—dynamic latent space models (DLSMs) and dynamic stochastic block models (DSBMs)—are closely related to time-varying network analysis and have been widely applied in bioinformatics [31–33].

Dynamic latent space model

DLSMs are a class of statistical models used to analyze time-varying networks by embedding nodes in a latent (unobserved) space, where the time-varying probability of interactions between nodes depends on their positions in a low-dimensional latent space at different time steps [90]. DLSMs are designed to infer the latent structure of networks from observed edge data. Since they infer time-varying probability of interactions, edges are generally undirected and unweighted. By modeling the positions of nodes in a latent space as probabilistic models, DLSMs are robust to noise and incompleteness in the observed data, leveraging the smoothness of the latent space to correct for unreliable and missing observed edges. Furthermore, DLSMs capture the dynamic evolution of network structures by allowing node positions to vary over time. This flexibility enables DLSMs to provide a comprehensive understanding of both observed and unobserved network interactions, as well as their temporal dynamics.

The general formulation of a DLSM can be expressed as:

$$\text{Latent space model: } \sim \mathbf{Z}_t^i \sim \mathcal{N}(\boldsymbol{\mu}_i, \boldsymbol{\Sigma}),$$

$$\text{Temporal evolution: } \sim \mathbf{Z}_t^i = \mathbf{Z}_{t-1}^i + \mathbf{drift} + \boldsymbol{\epsilon}_t^i,$$

$$\text{Observational model: } \sim Y_t^i = f(\mathbf{Z}_t^i) + \eta_t^i,$$

where

- $\mathbf{Z}_t^i$ represents the latent position vector of node i at time t,
- $\boldsymbol{\mu}_i$ is the mean position of node i in the latent space,
- $\boldsymbol{\Sigma}$ is the covariance matrix of the latent space,
- The temporal evolution is modeled with a drift term and $\boldsymbol{\epsilon}_t^i$ representing the random error,
- Y_t^i is the observed data associated with the latent position $\mathbf{Z}_t^i$.
- $f(\cdot)$ is the observational model and η_t^i is the observational error.

In this model, the goal is to estimate the latent space parameters ($\boldsymbol{\mu}_i$ and $\boldsymbol{\Sigma}$), the temporal evolution parameter (drift), and the observational model parameters in $f(\cdot)$. These parameters are used to capture latent space network structures and their changes over time [90].

DLSMs have been widely developed to analyze evolving networks. [93] introduces a tractable approach using kernel functions and low-dimensional KD-trees, enabling efficient inference in social networks. To address high-dimensional settings, [94] proposes a convex framework combining dimension reduction and graphical modeling, consistently estimating latent components and conditional structures. For dynamic networks, [90] embeds longitudinal data into a latent Euclidean space, providing insights into network evolution and enabling edge prediction, while [95] extends this to weighted networks, modeling count and non-negative continuous dyadic data. Further advancing dynamic network inference, [96] develops a locally adaptive dynamic network model, leveraging stochastic differential equations and state-space representations for real-time updates and forecasting. These advancements collectively enhance the ability to model, visualize, and predict complex network dynamics.

Extensions of DLSMs have been developed to better model directed dynamic networks. [97] introduces an approximate filtering algorithm extending the CODE model to embed participants in a latent space for longitudinal count networks, though it struggles with directed edges in non-count data. Addressing this limitation, [90] proposes a longitudinal network model allowing nodes to follow time trajectories in latent Euclidean space, capturing both popularity and activity effects. They later refine it to support weighted edges and diverse data types [95].

Dynamic stochastic block model

A DSBM is another widely used model for time-varying network analysis, particularly when the community structure and node memberships change over time [98]. It assumes that nodes in a network belong to latent (unobserved) communities, and the probability of interactions between nodes depends on their community memberships. Unlike a static SBM, a DSBM allows community memberships and interaction probabilities to evolve over time. Like DLSMs, a DSBM requires at least partially observed edge data, which is generally considered undirected and unweighted.

At each time point, nodes are assigned to different blocks. Let m_t^i denote the block assignment of node i at time t, which can be encoded using one-hot encoding:

$$P(m_t^i = k) = \pi_{k,t},$$

where $\pi_{k,t}$ represents the probability that a node is assigned to block k at time t.

Define $\gamma_{k,l,t}$ as the probability of a connection between a node belonging to block k and a node belonging to block l at time t, we have:

$$P(a_t^{ij} = 1 | z_t^i = k, z_t^j = l) = \gamma_{k,l,t},$$

where $a_t^{ij} = 1$ means that there exists an edge between nodes i and j.

In DSBMs, estimating the model structure involves determining the parameters that govern the time-varying block assignments and connection probabilities between blocks. Block assignment probability $\pi_{k,t}$ represents the likelihood of nodes being assigned to different blocks at each time point. Connection probability $\gamma_{k,l,t}$ between nodes in different blocks at each time point captures the evolving relationships between communities. By estimating these parameters, the DSBM can effectively capture the dynamic evolution of communities within a network.

To estimate model properties in DSBMs, various approaches have been proposed. [99] defines a generative model where edge probabilities vary with seasonal processes, allowing the recovery of latent temporal patterns. [100] introduces a kernel-based spectral clustering method that adapts to the unknown smoothness of connection probabilities, membership transitions, and cluster count. Addressing blind identification, [34] develops spectral algorithms leveraging random matrix theory for accurate partition recovery and parameter estimation. Change point detection methods are explored by [101], proposing least-squares-based techniques, which are computationally intensive but robust to identifiability conditions.

Extensions of DSBMs have been developed to incorporate directed edges. [35] introduces the mixed membership stochastic block model (MMSBM) for directed networks, allowing nodes to belong to multiple groups. [102] further extends MMSBM to dynamic settings, modeling international militarized conflicts by linking conflict probabilities to evolving group memberships influenced by country-level factors. Further advancing the model, [103] incorporates simple time priors to handle dynamically weighted and labeled networks, demonstrating its effectiveness in applications with small datasets.

Applications of network analysis

To further illustrate the applicability of time-varying network analysis in bioinformatics, we apply the methods introduced in the preceding sections to a real-world time-course microarray dataset. The data consist of gene expression measurements from 209 mouse lung tissue samples collected at 14 time points following influenza infection (0, 3, 6, 9, 12, 18, 24, 30, 36, 48, 60, 72, 120, and 168 hours) [104]. This dataset, available in the R package `timecoursedata` as `shoemaker2015`, provides a valuable test case for our network estimation and inference approaches.

We apply TVGL, DBN, and VAR-based Granger analysis to estimate structures of the gene expression network. Building on the time-varying edges identified by TVGL, we further implement NAR, DLSM, and DSBM for network inferences. Complete details of our analytical procedures, including software implementations and algorithmic specifications, are provided in Supplementary Appendix A, while the corresponding analysis results are presented in Supplementary Appendix B.

Discussion

Extensive network analysis studies have been published in the literature to unveil time-varying patterns of complex biological data. In this paper, we have explored key methodologies for dynamic network analysis, focusing on both network structure estimation and subsequent inference based on pre-specified networks. From a practical perspective, we have also examined applications of bioinformatics and related computational tools.

While substantial progress has been made in developing dynamic network analysis methods, several key challenges remain. First, since biological systems are inherently stochastic with experimental noise that arises from technical variability in sequencing, imaging, or mass spectrometry, temporal resolution gaps in time-course data may obscure true network patterns. Temporal resolution gaps in time-course data further complicate the reconstruction of causal or time-dependent relationships, calling for methods tailored to the complexity and noise. Second, the high dimensionality of biological data introduces fundamental scalability challenges, requiring computationally

efficient approaches. For example, Bayesian network inference becomes intractable for large datasets due to the combinatorial complexity of structure learning and the associated computational demands. As such, developing methodologies tailored for complex and noisy data is crucial to promote more accurate and practically useful tools in network analysis. Third, the growing reliance on multi-omics data, imaging, and clinical metadata in modern bioinformatics introduces additional complexity. Effectively integrating these heterogeneous data types while preserving temporal and contextual relationships remains a significant challenge, whereas many existing frameworks fail to accommodate such multidimensional information.

Meanwhile, these challenges present emerging opportunities that can guide future methodological advancements. One promising direction is to enhance the interpretability of inferred network structures, particularly as many current models rely on simplifying assumptions that may not adequately reflect the true patterns of real-world biological systems. Additionally, the application of machine learning and deep learning techniques to time-varying network modeling holds considerable potential. This study is inevitably limited by the selection of methods discussed, given the rapid pace of new developments in the field. Moreover, the emphasis has been primarily on methodological advancements, while specific domain applications and comparative performance evaluations warrant further investigation. Despite these limitations, we provide this study as a useful resource for researchers seeking to advance time-varying network analysis in biological and biomedical contexts.

Key Points

- Network analysis is crucial in biological and biomedical research as it provides insights into complex biological mechanisms, enabling the understanding of interactions, dependencies, and dynamic changes within systems.
- Time-varying methodologies, such as the time-varying Gaussian graphical model, dynamic Bayesian network, and vector autoregression-based causal analysis, are essential for capturing temporal changes and evolving dependencies in biological networks.
- Our study evaluates the strengths and limitations of the time-varying approaches and their computational tools, providing comprehensive insights for biological network data analysis.

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Author contributions

Hao Mei: Conceptualization, Methodology; Zhiyuan Wang: Methodology, Formal analysis; Hang Yang: Formal analysis; Xiaoke Li: Methodology; Yaqing Xu: Conceptualization, Methodology. All authors contributed to Writing—Original Draft and Writing—Reviewing and Editing.

Supplementary data

Supplementary data is available at *Briefings in Bioinformatics* online.

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Data availability

The dataset used in this study is publicly available as `shoemaker2015` in the R package `timecoursedata`.

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Problem Solving Protocol