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From Data to Knowledge: A Mini-Review on Molecular Network Modeling and Analysis for Therapeutic Target Discovery

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Abstract

Successful drug development is a risky and lengthy process that can take over ten years and consume billions of dollars. Target discovery is a critical stage of drug development for the identification of key molecules and pathways that can be targeted by novel therapeutics to find more effective treatments. Due to the rapid development in artificial intelligence and machine learning techniques over the past decade, computational approaches have now emerged as powerful tools to unravel complex interactions within biological systems to identify novel therapeutic targets. In particular, modeling and analysis of intracellular molecular networks play a pivotal role in target discovery by enabling researchers to efficiently and simultaneously navigate massive amounts of biological data to identify potential therapeutic targets. Such technologies can significantly accelerate the prolonged process of development of innovative therapies for complex diseases. Besides highlighting the findings of the recently introduced extreme signaling failures in intracellular molecular networks, here we briefly review various methods for modeling and analysis of intracellular molecular networks and discuss how they can be utilized to predict potential drug targets within such complex signaling systems. Overall, this review emphasizes the significance of modeling and analysis of molecular networks for fast-tracking and rapid discovery of novel therapeutic targets; to pave the way for the development of more effective treatments.

Introduction

Molecular networks are comprised of complex and interconnected signaling pathways with hundreds of interactions between the molecules of the networks. They can be represented by a graph, in which nodes represent biomolecules such as genes, RNA, and proteins; plus edges that represent the physical or biochemical regulatory interactions between the molecules [1-8]. There are different types of molecular networks such as protein-protein interaction (PPI) networks, in which the nodes are proteins and edges are the interaction between them [9]; gene regulatory networks (GRNs), in which the nodes are transcription factors and target genes, and edges are the interactions regulating transcription and gene expression [10,11]; and cell signaling networks that are PPI networks in which signals are propagated within the cell via molecules and their interactions [12]. These networks have various functionalities and have been used for understanding complex physiological and pathological processes. Therefore, the need for the development of tools to construct, model, and analyze such molecular networks became a necessity to understand the function of such networks at a system level.

Due to the advancements in technology and artificial intelligence (AI)/machine learning (ML) techniques in recent years, high-resolution biological data is being generated at large scales within a short period of time. The availability of such a large volume of molecular data prompted scientists to develop techniques to convert biological data into mechanistic knowledge about complex processes [13-16]. Studying molecular networks became a key for understanding complex biological activities. More specifically, they play a crucial role in

drug discovery, understanding the role of different molecular components in the pathogenesis of diseases [8,17-19], cellular decision-making processes [20,21], and cell development and differentiation [22], by providing valuable insights into the complex interactions between biological molecules. These networks are typically constructed using data extracted from peer-reviewed molecular biology studies on PPIs, gene expression, and other regulatory mechanisms [23-25].

The availability of extensive molecular biology data and the construction of molecular networks is not sufficient to gain functional knowledge at the system level. One needs to convert the molecular network graphs into numerable models so that they can be analyzed further and derive novel biological hypotheses. Different modeling frameworks such as continuous (e.g., mass-action kinetics with ordinary differential equations (ODEs)) [14,26], discrete (e.g., logic models) [15,27,28], and hybrid (e.g., a model with logic-based ODEs) [16,29] models have been developed and used, according to the complexity of networks and data. Besides, to make reliable predictions from these models, one needs to tune the models into the data, and infer the model parameters for which several approaches and tools have been developed [30-33]. Once the model is calibrated using the prior knowledge, approaches such as network fluxes and signal executions [34,35], network communication capacities [36,37], signaling failures [38], and fault diagnosis techniques [39-41] are used to reveal novel mechanistic knowledge about the network-driven processes of interest.

Overall, analyses of molecular networks by integrating experimental data with computational approaches are critical for understanding complex biological processes, disease mechanisms, and the identification of novel drug candidates and their mechanisms of action. In this review, we provide insights into the commonly used computational frameworks to convert biological data into knowledge, and discuss their pros and cons in the following order: (i) we explain how the molecular networks are constructed, (ii) we discuss molecular network modeling and model calibration approaches, and (iii) we discuss how the calibrated models are analyzed using various approaches, specifically focusing on the recent findings from the approach of extreme signaling failure analysis and its potential use in target discovery.

Constructing Molecular Networks

In systems biology applications, many dynamic processes can be represented as networks of interconnected components, representing intracellular biochemical reactions that enable the study of their dynamics and signaling mechanisms. One way of building such networks is constructing them with expert knowledge from literature and repositories. The importance of biological network studies led to the creation of several databases so that one can build a network of interest and develop a theory on it. Some examples of such databases, and perhaps the most commonly used ones, can be listed as:: (i) STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database containing known and predicted protein interactions [42]; (ii) REACTOME database, which is an open-source relational database of signaling and metabolic molecules and their relations organized into biological pathways and processes [43]; and (iii) KEGG (Kyoto Encyclopedia of Genes and Genomes) database, which is a collection of manually drawn molecular interaction, reaction and relation networks [44]. These examples can be populated with MINT (Molecular INTeraction), which is built to collect experimentally verified protein-protein interactions [45]; TissueNet, which is a tissue-specific interaction database containing tissue-specific data of 40 human tissues [46]; and several other databases reviewed by Miryala et al. [47]. Using these databases, one can construct molecular networks to study diverse biological processes of interest. However, one potential downside of this way of constructing the networks is that, typically, models for literature-curated molecular networks do not adequately match experimental data. This could be due to the incompleteness of the network and the heterogeneity of resources, databases, and literature. Therefore, in general, the models built on these networks require training of the model parameters against the available experimental data to improve the quality and reliability of the model predictions, as discussed in detail in the next section.

Another way of constructing molecular networks is by inferring the network itself from the experimental data using reverse engineering and AI/ML techniques. Such methodologies guided by the data aim to identify molecules that are involved in the network, as well as the causal relationships between them. An earlier example of such methods was provided by Ideker et al. [30], where two methods called "predictor" and "chooser" work interactively to infer the genetic network from gene expression measurements. Later, Bayesian inference approaches were used to construct highly probable molecular network structures [48,49]. More recently, due to the developments in AI/ML approaches, several automatic network inference tools have been proposed [50-55]. Although directly inferring networks from the data seem the most reliable way for further analyses and hypotheses generation, it is still very challenging to computationally extract true causality due to the lack of data and multimodal approaches. To accurately infer causal relationships and generate such networks, there is a need for different sets of empirical data obtained from experimental setups designed for producing high-quality data with the lowest variability and highest reproducibility; for example, single-cell proteomics and single-cell RNA sequencing, as well as multimodal methodologies and tools that can integrate such large-scale biological data.

Modeling Molecular Networks and Training the Network Models

To study molecular networks, one needs to convert molecular

network graphs into computational models so that they can be analyzed to generate testable hypotheses. One way to model molecular networks is to convert them into a mathematical form, by building a system of differential equations that can capture temporal and spatial behaviors of molecules within a complex network, the so-called continuous models [14,56-58]. Such models describe the system dynamics over time using, for instance, mass-action kinetics for the rates of consumption and production of molecular species. Given well-characterized molecular networks, continuous models can provide detailed mechanistic information about the system of interest. Therefore, various tools have been developed to implement such models and perform in-silico analyses of complex processes [59,60]. However, such models require knowledge of biological mechanisms and kinetic parameters such as rate constants, which is usually very limited. Furthermore, the complexity of the mathematical system as well as the number of free parameters to be estimated, and hence, the need for prior information, i.e., experimental data, increases drastically if the network becomes larger.

Another way of modeling molecular networks is using discrete models such as logic models, e.g., Boolean [15,27,28] and ternary models [41,61], fuzzy logic models [62], and Petri nets [63] that do not require detailed kinetic information and can still sufficiently model the dynamics of the system. Because of the applicability of these models to networks of any size, and the flexibility of the model parameters, they became very popular and still being commonly used [20,28,29,33,39-41,64-66]. However, the downside of these models is that they do not provide as detailed information as the continuous models. For instance, the Boolean models can only provide predictions of ON/OFF behavior of the molecules. Similarly, multilevel models like fuzzy logic, can provide dynamics of molecules in discrete multiple levels at distinct time points. Moreover, the predictive capacity of these models also depends on the network structure. Therefore, similar to the need for parameter estimation in continuous models, discrete models may also require some calibration steps which would be the tuning of the network structure, or the model assumptions such as the logic rules.

Regardless of the type of modeling approach, calibrating the models is very critical for making reliable predictions. The implemented models should be able to reproduce the existing biological findings so that they can be used for further analyses. Therefore, the models need to be trained against the experimental data. For the continuous models, training usually means estimating the free model parameters such as the reaction rate constants, endogenous levels of molecules, and other hyperparameters (if used in the model). Various techniques and tools are available to estimate model parameters such as Bayesian inference approaches [32,67] that sample the posterior distribution of parameter space to maximize the likelihood of data; or optimization-based approaches [68] that aim to find the best parameter set by minimizing an error function such as minimum squared error between the model predictions and the experimental data. On the other hand, in discrete models, although there are not typically any kinetic parameters, one can consider the model assumptions, i.e., the rules, and the network structure as parameters to be estimated. Given a fixed network structure, one way of calibrating the discrete models is learning, for instance in Boolean models, proper combinations of logic rules representing how biological interactions occur [69,70]. Another approach is fixing the model rules and learning a network sub-structure - by removing interactions/nodes - on which the model provides maximum prediction accuracy [19,33]. Similarly, one can train the models by both learning model rules and the network structure simultaneously, which is a more complex and challenging problem [23].

Depending on the network and model complexity, and the interdependency between the model parameters, one common issue to deal with after the model calibration is that some model parameters are practically unidentifiable [71], which means that their values cannot be uniquely determined using the available data. Therefore, after model calibration, several combinations of parameter sets (or model rules, or network structures) might be inferred that provide equally-well data prediction accuracy. Then, the question is which set of parameters (or model rules, or network structures) should be used for further analyses. A common practice has emerged where one or a few parameter vectors are chosen at random to make predictions, with varying degrees of success [72,73]. This led to ongoing criticisms regarding the usefulness of large and complex mathematical models of cellular processes with multiple uncertain parameters. Hence, methods need to be developed that can infer biological information, perhaps probabilistically as proposed by Ortega et al. [35], because of the uncertainty of parameters or models.

Analyses of Models of Molecular Networks for Target Discovery

The main goal of constructing the underlying network of a biological process, building network models, and training them against limited experimental data is to eventually use them to test various hypotheses, discover novel insights into complex diseases, generate novel and testable hypotheses, and discover new drug targets to develop novel therapeutics with lower costs. For this purpose, regardless of the model type, a common analysis approach is to induce *in silico* mutations or molecular dysfunctionalities in the network and then compute the network response deviation from the normal response. Different forms of this approach are developed in different frameworks such as fault diagnosis or vulnerability analysis [39], and sensitivity analysis [74,75]. Fault diagnosis is a platform for finding selective targets by using computational and systems biology techniques that have been developed and optimized over the years [38-41]. The main purpose of this approach is to understand how vulnerable the entire

molecular network is to the dysfunction of each molecule or a group of molecules.

For fault diagnosis of molecular networks, studies usually focus on intracellular signaling networks which can be divided into three main components: (i) input molecules, (ii) intermediate signaling molecules, and (iii) output molecules. Input molecules of the network are typically ligands that bind to their receptors on the cell membrane. Upon ligand binding, a series of intracellular events such as activation or inhibition of secondary messengers, G proteins, kinases, phosphatases, and other intracellular signaling molecules can occur. Through a cascade of such signaling events, output molecules such as transcription factors are regulated, which ultimately alter cellular functions by changing the gene expression pattern. In the fault diagnosis analyses, in general, first, a molecule or a group of molecules is set to a dysfunctional state, e.g., very low (hypoactivity) or very high (hyperactivity) activity levels, i.e., a fault is introduced in the model. The effect of a dysfunctional state on the overall network function is then quantified by computing the vulnerability level of the molecule, or a group of molecules. In other words, a vulnerability value is computed for every molecule that reflects the sensitivity of the network to the dysfunction of that molecule, or a group of molecules. A high vulnerability level for a molecule (or a group of molecules) indicates that the dysfunction of that specific molecule (or a group of molecules) drastically alters the network function. Thus, in the context of target discovery, highly vulnerable molecules of a network that is known to be involved in a certain disease are potential targets due to their high probability of having causative involvement in the dysfunction of the network, and consequently to the development of the pathology.

Recently, using the abovementioned fault diagnosis analysis framework as well as our previous observations, we developed an algorithm [38] that performs extreme signaling failure analysis of molecular networks of any size in the context of the Boolean modeling approach. In this algorithm, hyper and hypoactivity of molecules are represented by always ON - molecule state is stuck-at-1 or always OFF - molecule state is stuck-at-0 - fault models [38]. We defined extreme signaling failure as a pathological phenomenon that results in the highest probability of network failure, where network failure is defined as the departure of the network response from its normal or expected response. The said pathological phenomenon is characterized to be emerged from the presence of one or more dysfunctional molecules in the network. Additionally, we defined the vulnerability level of a molecule (or group of molecules) as the probability of having incorrect network responses when that specific molecule (or group of molecules) is dysfunctional (see Methods section of Ozen et al. [38]). Given a molecular network with at least one input, one output, and some intermediate molecules, the algorithm outputs a graph of the maximum vulnerability level versus the number of simultaneously faulty molecules. This graph depicts how the worst-case functional failure of the network varies as the number of concurrently dysfunctional molecules changes.

Interestingly, when this algorithm is applied to some networks with different sizes and complexity - i.e., whether it includes feedback interactions or not - we observe that it is sufficient to have only a few dysfunctional molecules to reach the maximum possible vulnerability level of a network. While these findings should be verified by experiments, this may mean that it is likely that no matter how complex a network-driven biological process is, perhaps only a few simultaneously dysfunctional molecules may fully change the network function and markedly contribute to an unexpected event such as the development of a disease. From a target discovery point of view, this observation means that it perhaps suffices to identify and focus on only a few target molecules whose dysfunction causes the largest network response departure from the physiological response.

To elaborate and show how this type of analysis can be used for target discovery, here we present the results of analysis of three different networks: Caspase 3 network (**Figure 1A**) involved in cell death and survival regulated by various upstream pathways [41], ERBB signaling network (**Figure 1B**) that is a therapeutic target in breast cancer [76], and T cell network (**Figure 1C**) involved in a variety of immune system response [27]. These three networks are of different sizes and complexities, i.e., 17 intermediate molecules without feedback interactions, 18 intermediate molecules with feedback interactions, and 64 intermediate molecules with feedback interactions, respectively. When we perform the extreme signaling failure analysis by setting a single or a group of molecules to be simultaneously dysfunctional and then simulating each network, we observe that the maximum vulnerability levels of these networks are reached when there are only N=3 concurrently faulty molecules in the Caspase 3 network (**Figure 1D**), and N=2 concurrently faulty molecules in the ERBB and T cell networks (**Figures 1E and 1F**).

Another interesting observation is that a fully crashed network, i.e., the network whose all intermediate molecules are dysfunctional, may not necessarily function worse than the same network that has only a few faulty molecules. For instance, the maximum vulnerability level of the Caspase 3 network is 0.5 when there are three concurrently faulty molecules, N=3 in Figure 1D, whereas it is 0.465 when all the intermediate molecules are faulty, N=17 in **Figure 1D**. Similarly, the ERBB and T cell networks reach their maximum vulnerability levels of 0.885 and 0.75, respectively, when there are two concurrently faulty molecules (N=2, Figure 1E-F), whereas their maximum vulnerability levels become 0.625 when all of their intermediate molecules are dysfunctional (N=18 and N=64, **Figures 1E and 1F**, respectively). This further supports the idea that the identification of a few highly vulnerable faulty molecules, for example, three, can effectively assist with the target discovery process.

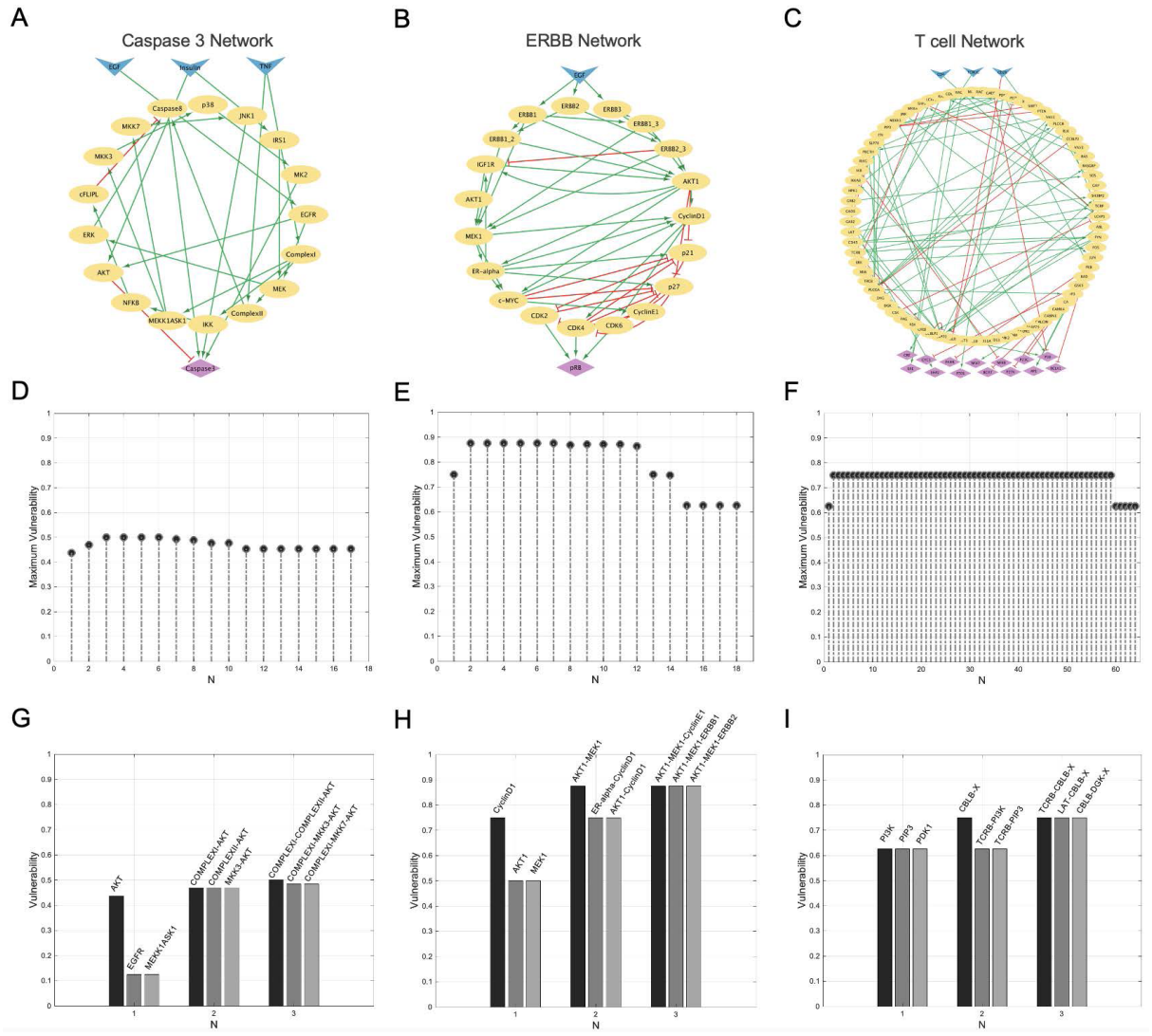

Figure 1. Extreme signaling failure analyses of three networks of different sizes and complexities. **(A)** The feedback-free Caspase 3 network. **(B)** The ERBB network with feedback interactions. **(C)** The T cell network with feedback interactions. **(D)** The Caspase 3 network maximum vulnerability levels when there are N concurrently dysfunctional molecules in the network, N = 1,…,17. **(E)** The ERBB network maximum vulnerability levels when there are N concurrently dysfunctional molecules in the network, N = 1,…,18. **(F)** The T cell signaling network maximum vulnerability levels for the network output BCAT, when there are N concurrently dysfunctional molecules in the network, N = 1,…,64. **(G, H, I)** Top three vulnerability levels in each network, when there are N concurrently dysfunctional molecules, N = 1, 2, and 3.

These types of analyses not only can help to understand the overall functional fidelity of the network but also can help with predicting the molecules or groups of molecules that cause the most divergence from its normal function, when they are dysfunctional. To exemplify, the fault diagnosis analysis of the Caspase 3 network predicts that the network loses most of its normal function when AKT is dysfunctional (**Figure 1G**, N=1), which is biologically relevant since the activity of AKT has a positive correlation with Caspase 3 activity [77]. We computationally predict that the dysfunctionality of AKT together with COMPLEX I or II or MKK3 causes some more damage (**Figure 1G**, N=2). Similarly, we predict that CyclinD1 alone has the highest vulnerability level in the ERBB network (Figure 1H, N=1), which is relevant as its role in breast cancer has been previously shown [78]. Unexpectedly, although CyclinD1 individually has the highest vulnerability level, the maximum damage to the function of the network is observed when AKT1 and MEK1 are concurrently faulty (**Figure 1H**, N=2). This means that maybe searching for a single target to mitigate the network dysfunction is less productive because the network malfunction can be a cumulative effect of multiple simultaneously dysfunctional molecules. This may suggest that drugs with multiple targets, such as multi-kinase inhibitor drugs, might be more effective. In the pharmaceutical industry, especially in oncology drug development, it is now well established that drugs that can target multiple molecules

are much more effective in treating cancer compared to those that have a single target. They also show significantly lower chances of drug resistance [79]. Lastly, some similar observations can be made for the T cell network. The top three highest vulnerability levels for one, two, or three concurrently faulty molecules are shown in **Figure 1I** for the T cell network.

Conclusion

In conclusion, computational approaches, specifically technologies for modeling and analyses of signaling networks, have revolutionized the field of target discovery, offering powerful tools and techniques that enable researchers to uncover new insights into complex biological systems. Several classes of molecular network modeling and analysis methods are briefly reviewed in this paper, and some findings of the recently introduced extreme signaling failures in intracellular molecular networks are highlighted as well. These approaches have demonstrated remarkable success in identifying potential drug targets, accelerating the prolonged process of drug discovery, and providing a deeper understanding of disease mechanisms. By integrating various computational methods, such as network modeling and analysis algorithms, together with AI and machine learning approaches [80], researchers can uncover hidden relationships, predict target-drug interactions, and prioritize targets for further experimental validation. Despite the challenges and limitations, computational modeling of molecular networks continues to evolve, opening new possibilities for the discovery of novel therapeutics. As we delve deeper into the new era of computational biology by the rapid development in artificial intelligence and machine learning techniques, the integration of diverse data sources and the development of more sophisticated algorithms will undoubtedly fuel further breakthroughs in understanding disease mechanisms and discovery of better targets for drug development, which eventually enables scientists to find more effective treatments for some of the most complex and incurable human diseases.

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