Chapter 17
Modeling and Optimization of Molecular Biosystems to Generate Predictive Models

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17.1 Introduction

A system can be defined as a complex structure in which different components have a specific role, and when they work together, they accomplish tasks in much efficient manner compared to each component separately (Kitano 2002). The system is a collection of elements or components that are organized for a common purpose. The biological system analysis provides us tools and techniques that help in

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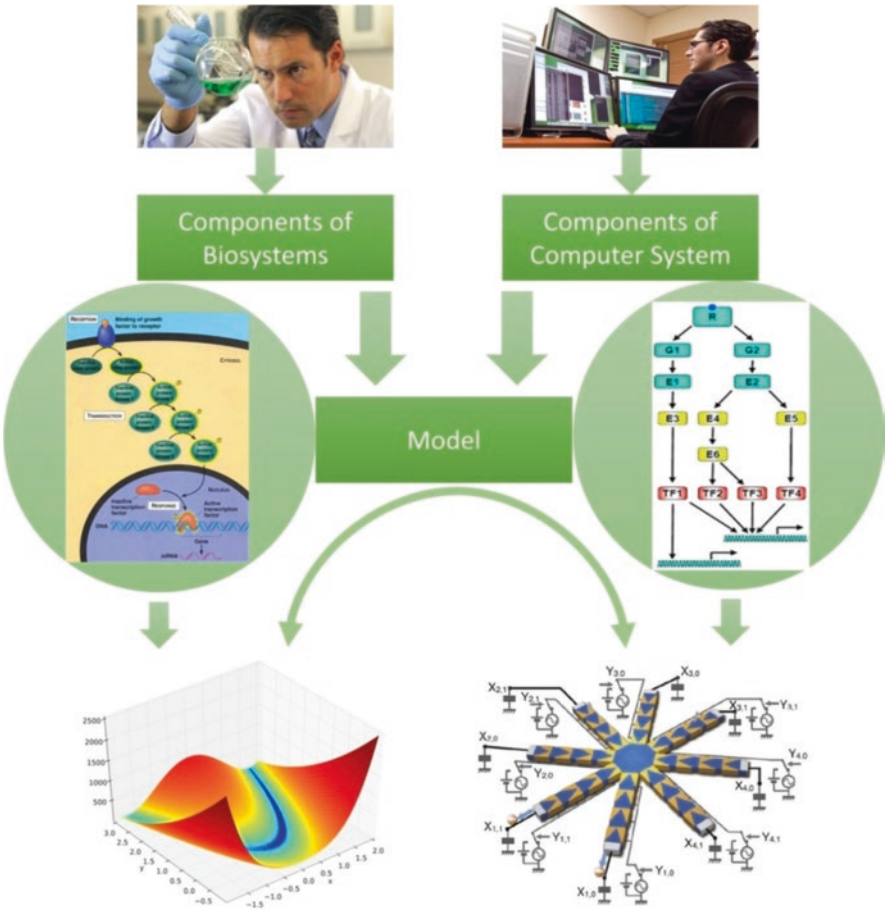

Fig. 17.1 System level understanding of bio-models

organizing the diverse piece of information and data gathered from traditional biological experiments. Development, integration, and experimental testing of hypothesis help us to analyze these systems, as depicted in Fig. 17.1.

Modeling means converting our hypothesis or assumptions into computational programs which further can be used for prediction. Some suitable assumptions are essential for model construction which includes modeling of the system into mathematical form. The mathematical model includes all kind of variables, real numbers, integers, Boolean flags, matrices, and other data structure. Each interaction represents a state in the model, and the final step involves converting the mathematical model into a computer program which is done by suitable genetic algorithms and other differential equation analysis-based algorithm. Once the computational model is built, it requires testing and verification in terms of validation. Models are

helpful as they help us to test the different hypothesis, refine and interpret experiment, and integrate knowledge, leading to new approaches by investigating coupling and feedback. The model helps us to unlock biological systems as they offer different perspectives compared to the perspective provided by experiments and theory. Though models cannot replace lab experiments and cannot prove mechanism, still they serve as a standard feature for scientific investigations.

The illustrative models are precise representation of real situations. Here, we specifically focus on the controlling element from the real world which can be used as a deterministic factor to control our modeled system. Mathematics plays a dominant role in defining system using variables which precisely define real-world scenario. Using mathematical equations we can simply find the solution of various common problems. There are various network level studies exist in literature to perform modeling for individual nodes or high throughput data (Bansal and Ramana 2015; Bansal and Srivastava 2018; Davis et al. 2017; Giraud et al. 2017; Griffen et al. 2017; Jindal and Bansal 2016; Jo et al. 2017; Kim et al. 2017; Nordholt et al. 2017; Romero & López 2017; Vreven et al. 2017; Xie et al. 2017).

Once the model has been generated, it should be optimized. Optimization means to find the best solution that helps in better decision making. The key elements in optimization problems are decision variables and objective function (Zheng et al. 2017). Decision variables are the variables that can be varied during the search of the best solution. An objective function helps us to quantify the quality of a solution, and constraints are the conditions that should be fulfilled in order to achieve the desired results. Different optimization techniques such as linear programming, nonlinear programming, parameter estimation, dynamic optimization, etc. are used for different problems.

Modeling is of no use until it is optimized as per the real situation. Thus, it is a key process for any kind of real model establishment. Optimization mainly controlled the principles of machine learning. We are considering one dataset for analysis and splitting it into two datasets, commonly known as training and test dataset. Various modelers use machine learning-based approaches in their algorithms for better efficiency. Henceforth, we can say that model is typically dependent on optimization using set of variables or parameters which can be used to regulate or control the models as per the need of optimizer. Mathematical modeling is compiled with various machine learning approaches in applicable manner which came into market in the form of various development tools and software.

With the increase of computer power and advanced mathematical techniques, mathematics is now playing the prominent role of integrating information and generating predictions, through the generation of the computationally inspired hypothesis. Therefore, mathematical models can be used to understand the complex biological problems to unbind various diseases and drug effects to benefit the society in utmost sophisticated manner. Mathematical model allows a systematic approach for investigating system perturbations and is not limited to experimental constraints (Fan et al. 2017). These models are able to determine the systematic behavior of any real-world disease scenario.

17.2 Development of Concept Map Models

Biological experiments deal with understanding of hidden processes in the layers of various unannotated datasets. The major goal of such analysis is to provide new insight about regulation mechanisms so that the system can be controlled in an efficient manner. A variety of homogeneous and heterogeneous data are generated through various big data approaches using high-throughput methods. Generation of data is not sufficient to perform analysis to reveal the function of the system. There is a great need of concept map modeling to understand the systematic way to deal with such big data (Kumar et al. 2017).

Concept map modeling focuses on understanding and developing concept for development of methods for mathematical analysis. This approach is time-consuming as it involves the development of a model for the process and response for each level. Therefore it is important to derive such models that allow the incorporation of simple as well as complex methods for complete as well as incomplete datasets at defined instance (Sun et al. 2017). The main objective of this approach is to get acquainted with the quantitative formalization of the biological phenomenon by developing mathematical model for the hypothesis.

The initial step of this approach consists of converting or transforming a stable or static map to dynamic biological map. The next step consists of interpretation of local dynamic response under a set of conditions. By following these two steps, one can determine a parameterized model which is further analyzed and refined. A flow diagram of this approach is shown in Fig. 17.2.

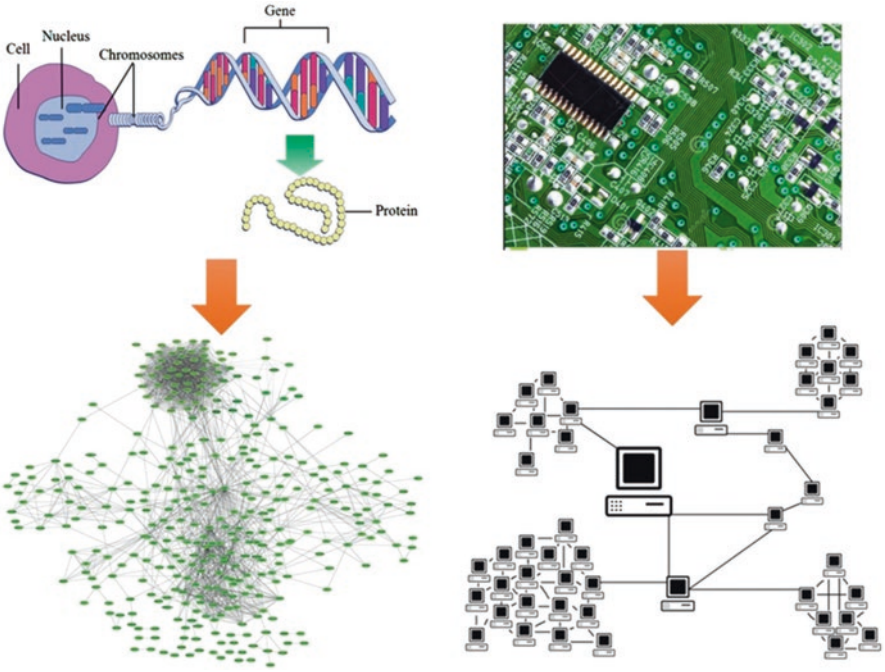

Fig. 17.2 Molecular classification of system to modeling and optimization

One needs to examine how the components and process in a concept map relate to each other and contribute to the overall functioning. Conversion of the map into mathematically testable structures is an essential part of maps as such system cannot provide quantitative analysis themselves. Considering a modeling method, regulatory interactions can be inferred using mathematical variables or symbolic representations (Fig. 17.3).

The static maps can be converted into Boolean or semiquantitative dynamics (SOD) map if a biologist has some prior knowledge about the information contained in the static map such as the type of reaction or time required to convert gene expression (Kumar and Singh 2017; Teku and Vihinen 2017). The Boolean case determines the close relationship of having direct control on the components within the global system. For instance, gene X is essential for process Y to occur. It helps us to determine the accurate function which is applied in inverse methods.

In the real case, the concept of the model represents control about dynamics of each node available rather than the detailed time series. An initial model can be constructed with the help of this minimum information. Once the model is substituted by actual time series, a simple function can be determined that captures the dynamics at each node (Sehgal et al. 2015). The overall mathematical formulation and understanding to develop models are not always a critical task as generalized

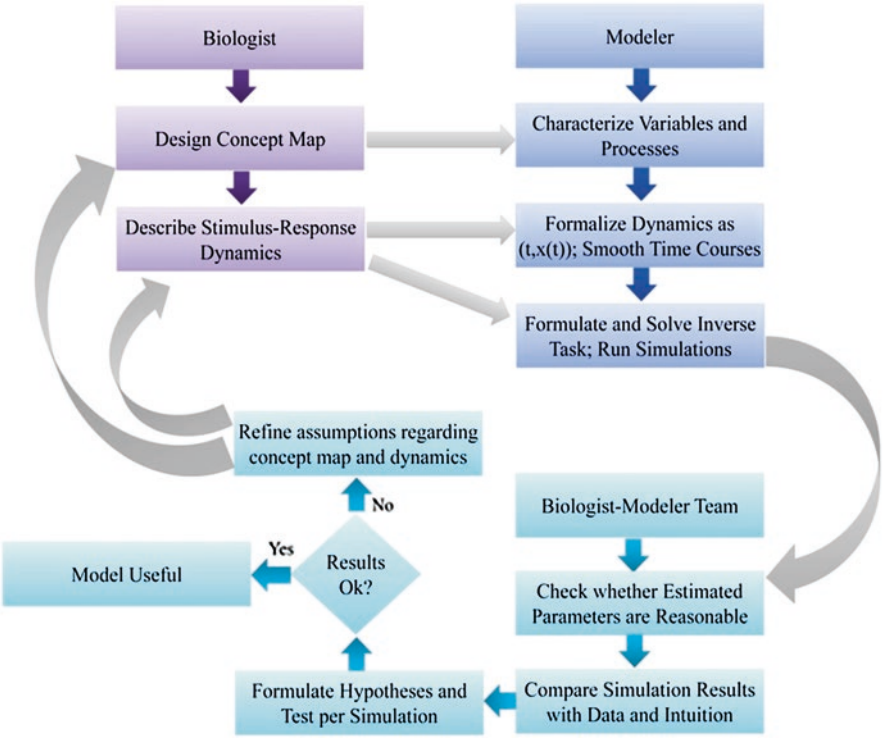

Fig. 17.3 Flow diagram of the proposed approach to formalizing biological concept maps

models can be used for depictions of user-specific data. This data can be further customized in the forms of graphs or curves. For instance, dynamicity of the system can be represented in the form of various distributional curves or sigmoid curves. Once we have constructed these model-derived curves, we can switch on or off the functions and change the curves as per the need in the presence or absence of defined variables or parameters. Condition-based approximation and differential analysis on the basis of conditions can be applied on these generated models.

17.3 Network of Networks

A network helps in understanding and combining scattered data at various dimensions. One of the key features of systems biology is focusing on "network of networks." In the human body, *n* number of networks is integrated in such a fashion so that efficient communication can happen at molecular and cellular levels. Generating understandable biosystems may help us to get insights about biological functions and variations and trace out changes at cellular to phenotypic levels. Figure 17.4 represents the structure of "network of networks" which gives an idea about various system biology approaches which differs from traditional biological approaches.

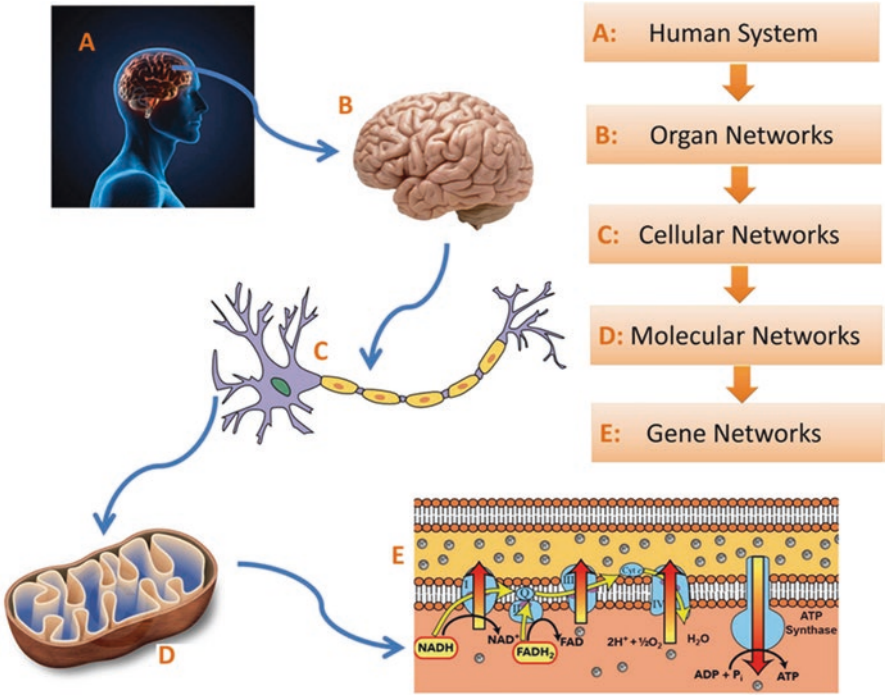

Fig. 17.4 Systems Dissection in terms of networks of networks

17.4 System Dissection into Components

Biological systems can be implemented in various ways; precisely it can be dissected using four components.

1. High-throughput methods for data generation which includes identifying unknown information from the depth of biological aura.
2. Developing concept, logic, and computational methods to combine various biological datasets to infer meaningful information.
3. Hypothesis generation and testing on newly generated data and comparison of the same existing data in various online portals and literature.
4. Understanding global scenario as big data and solving the phenotypic effects related to problems in differential data analysis for new information discovery.

17.5 Types of Modeling

Mathematical modeling is composed of various standard parameters, conceptual framing of tools, and interpretation of any kind of real system in mathematical form to decipher the control mechanics of the system. Mathematical representation of biological systems not only constructs the models but also optimizes and predicts in much efficient way compared to various traditional approaches. Thus, mathematical models can be implemented in terms of stochastic process, continuous process, or any other black box representation which doesn't have well-known information of composition.

For all the cases, the modeling process consists of the following same steps. First, using physical laws from first principles, a symbolic model is constructed which serves as an extension to the already known existing model (Athanasiou et al. 2017). This model consists of variables and parameters. The analysis requires comprehension of all parameter values obtained from biological knowledge. Variables in mathematical modeling can represent anything, whether it is a plant, animal, metabolite, pathway, or gene expression. Approximation and estimation of any parameter in biological terms is quite difficult as biological phenomenon doesn't reveal complete information in one go as other modeled systems do. The analysis of the model is done with the techniques and tricks of mathematics and computer science once the parameters are estimated. Due to the complexity of biological systems, optimization and analysis of differential conditions and large datasets are performed using computational approaches. Interpretation in terms of graphs and matrix provides an edge to scientific community to accurately depict the behavior of the aligned system.

The identification of unknown parameters in terms of biological entities is the genuine deterrent in the progress of biomathematical modeling. A non-specific approach called *biochemical systems theory* is used for biological systems modeling and analysis which is used for the improvements, developments, and applications of

thousands of research papers. BST was initially used to study the control systems and biochemical pathways.

The fundamental precepts of BST are very basic and transparent. Every variable that progresses after some time is given a name X and is represented in the form of the different orders of differential equation and depicts the variation in such a way so that it can affect other variables or parameters in positive or negative regulatory ways. BST also addresses the problem where the modeler has some broad data about the procedures but does not know their mathematical representation to develop a structure to solve the complexity of biological systems. Sometimes it is very difficult for a developer to develop a system which doesn't contain absolute values, or sometimes a developer is not having an idea of unknown things in the systems, but logically if we speak about linear regression, we are not sure about what kind of data points are there which need to be included or excluded at initial point. Both approaches are somehow similar while dealing with unknown information and positively providing an edge to mathematical modeling to structure the unstructured data. As biological networks don't follow the Poisson distribution and converge toward scale-free networks which comprises the properties of power law. So, it will not be wrong to say that such approaches can result in successful analysis toward validation of real dataset.

17.5.1 Forward Modeling

Identification of a parameter in a system is based on local information which subsequently deals with small component integration and formation of complete network. For instance, for metabolic pathway construction, there is a need to understand the enzymes involved in pathway, transporters involved, co-factors playing the role in regulation, and ultimately metabolite formation through secondary metabolisms. All these terms need to be integrated to form mathematical equations and depict the understanding of biological phenomenon. Biological modeling is generally dealt with Michaelis-Menten or power law function. Dynamicity of the system is controlled by various rate law and parameter approximations like Km and Vmax, and forward rate of reactions can be controlled on the basis of concentration assigned to each entity defined in the model (Apostolopoulos et al. 2017). In such modeling methods, there is a need to study the direct rate law to control the local parameters and test various hypotheses on the basis of developed models.

The main utilization of this method is the use of kinetic equations, using enzyme concentration for tracing the rate of reaction. Variation in the rate of reaction subsequently leads to variation at phenotypic levels. Construction of such models and their refinements always has been a crucial task for scientists in biological community.

17.5.2 Inverse Modeling

Variables are observed from high end to low end which means reduction approach. The most important advantage of this technique is that data is originated from the same organism, acquired in a similar trial condition, and represented in all the procedures within the organism that could affect the factors of the framework (Kallhovd et al. 2017). Computational time complexity is a major issue with such kind of analysis. Moreover, various biological entities are ignored in case of modeling. The inverse modeling also use time-dependent analysis where pathways information is not absolute.

17.5.3 Partial Modeling

A specific issue with any model building approaches emerges due to the presence of the "omnipresent" metabolites like energy molecules (ATP) which cannot be modeled as they are additionally required in different reactions. As a result, a mathematical buffer is constructed that absorbs the excess material, thus adjusting the dynamic changes in concentration at an already determined rate (Yalçın et al. 2017). Better-characterized statements are defined as differential conditions in BST, and their progression includes energy molecules as factors.

17.6 Inference from Qualitative Data to Computational Simulation

Biological system usually deals with enormous methods and tools whether they are qualitative or quantitative. Sometimes, there are exact implications of a system that are missing, and semiquantitative methods are prioritized over other measures of data segmentation or integration for network model construction. For instance, graphical methods represent directional flow of the information by connecting components of a system in a systematic fashion. Moreover, network construction and hypothesis testing on the basis of available information and predicting the information of missing links in the networks provide more insights about qualitative measurement from raw unstructured data. Various probabilistic measures like Markov chains which are used to represent Hidden Markov models and Bayesian model-based networks deal with graphical presentation of unknown entities in a network through random measure.

Sometimes, these graphical methods do not represent the dynamicity of the network and do not express much detailed information as per real-time scenario;

therefore mechanistic models come to existence where data can be analyzed in an automated manner.

Computer-based models and simulations provide an easy tool to understand biological systems in terms of complex nonlinear dynamics. The first is that "instinctive thinking about MAP kinase pathways led to the long-held view that the obligatory cascade of three sequential kinases serves to provide signal intensification. In contrast, computational studies have suggested that the purpose of such a network is to achieve extreme positive cooperativity so that the pathway behaves in a switch-like, rather than a graded, fashion."

Simulations present an understanding of biological phenomenon over differential time. Using differential equations on the same biological dataset can reveal hidden properties of the systems. But it will be unfair to expect accurate prediction through computational methods as these methods are developed to get insight about candidate entity selection. More data leads to more simulation time and subsequently increases the rate of precise selection of prediction attribute. Optimization can be performed on the basis of simulation measures of selected parameter. Simulation results in certain biological behavior analysis especially can be used in case of complex disease like cancer, diabetes, and neurodegenerative diseases. Simulations are modern and nontraditional techniques. In earlier days, people used conferences, abstract, and poster presentations to grab the idea of one's understanding. With the advancement in the internet world, these techniques can be integrated to form network to get holistic view of understanding of different people across the world (Huang et al. 2017). With the advancement in computational resources, the time and space complexity has not been an issue in the present world. So, mathematical simulations remain as the best alternative to reduce the time, effort, and resources of any wet lab experiments.

17.7 Protein Class Identification

The helix-turn-helix structural motif has an important and crucial role in various cellular pathways that are involved in transcription, DNA recombination and repair, and DNA replication. At present, methods that are used for motif identification are dependent on the amino acid sequence. The major drawback of these methods is that motif members belong to different sequence families that do not share common ancestry or homology, and hence these methods are incapable to identify all motif members (Qing and Gerson 2017).

So to overcome this drawback, a new method based on three-dimensional structure was created that involved the following steps:

1. Selecting a conserved component of the motif.
2. Computing structural features relative to that component.

3. Generating categorization models by comparing the relevant measurements of structures that contain motifs and those structures that do not contain motifs.

With the establishment of classification model, the entire Protein Data Bank of experimentally measured structures was searched, and new examples of motifs were identified that do not show any sequence homology with previously known examples. Two such examples are Esa1 histone acetyltransferase and flavone 4-O-methyltransferase. This result shows the importance of classification-based method that is proven helpful for the two abovementioned examples. The sequence-based methods are used to recognize a functional class of protein which can be improved by using the classification model that is based on three-dimensional structure information.

17.8 Computational Structure and Function Prediction

With the help of X-ray, NMR, and computational method techniques, structural genomics is now showing great enhancement in producing the three-dimensional structures of proteins. The important and crucial step after this is to understand how protein structure and functions are related. Studying protein structure individually impairs the overall understanding of the protein as various missing links will exist while studying a part of the protein. The availability of the expected surfeit protein structures has resulted in the development of computational methods that examines multiple protein structures at once and returns the important biophysical and biochemical features. Apart from this, these methods can also recognize important features in new protein structures (Winter et al. 2015) (Fig. 17.5).

FEATURE is an automated system developed by Wei and Altman. This system applies statistical parameters to study vital functional and structural sites in protein structures such as active sites, binding sites, disulfide bonding sites, and so forth. By collecting all known examples of a type of site and non-site, FEATURE computes the spatial distributions of defined biophysical and biochemical properties. It applies various statistical measures to calculate accurate, active, and binding sites. The use of parametric and nonparametric test provides this tool a high-level sensitivity and specificity.

SBML, Gepasi, and CellML are specialized systems for biological and biochemical modeling (Webb and White 2005). Madonna is a general-purpose system for solving a variety of equations (differential equations, integral equations, and so on). This has been represented in Fig. 17.6.

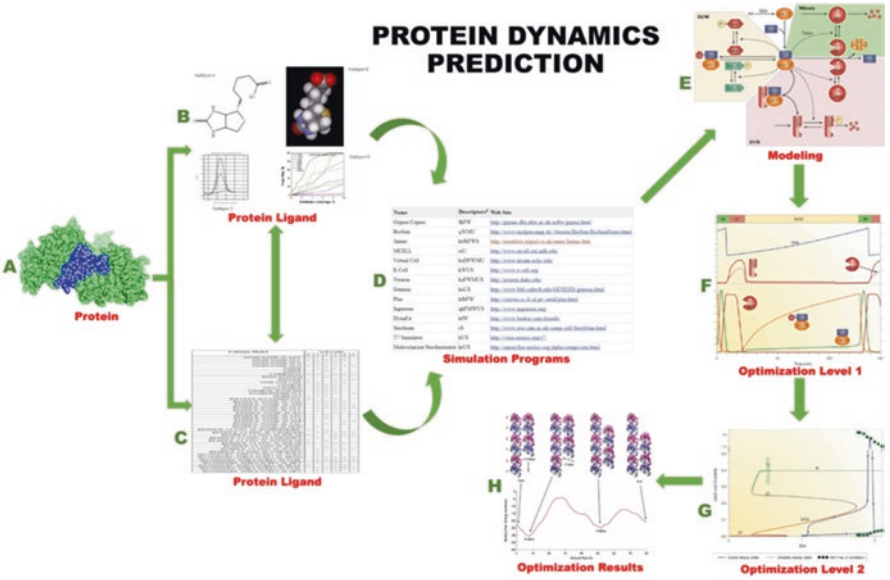

Fig. 17.5 Protein structure, docking and dynamics study

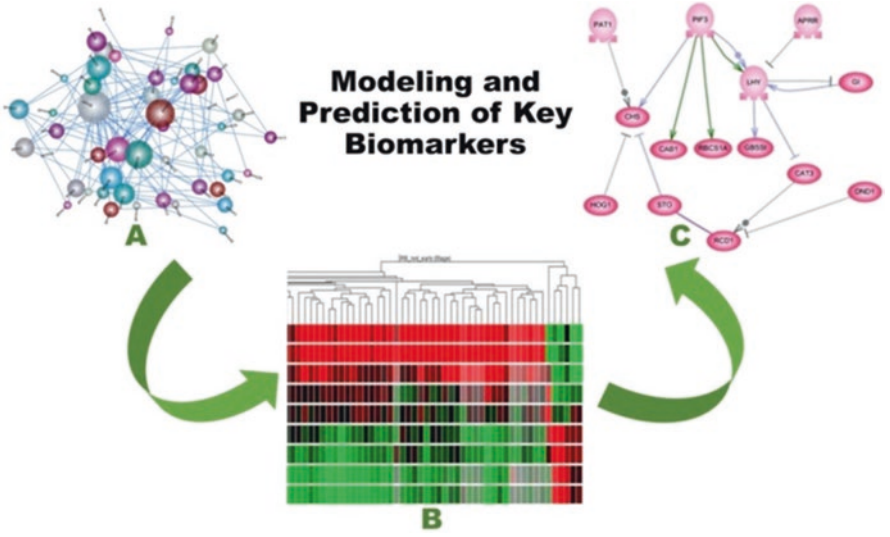

Fig. 17.6 Modeling system and screening key biomarkers

17.9 Forest Dynamics

SORTIE is a stochastic and mechanistic model that has been developed to simulate the growth of northeastern forests. This model mimics the fate of individual tree and its offspring. The model is based on the species-specific information regarding the growth rates, fecundity, mortality, and seed dispersal distances as well as some information regarding local regimes. SORTIE generates dynamic map by following tens of thousands of trees. This dynamic map depicts the distribution of nine dominant or subdominant species of trees that look like real forests. The model also predicts the realistic forest responses to certain minor and major disturbances like destruction of tress within small circle of forest boundary and improved tree mortality.

17.10 Cell Designer: A Computational Tool for Modeling

CellDesigner is a software developed by Systems Biology Institute using Systems Biology Markup Language and graphical notation. Different kinds of boxes were used to represent different kinds of biological entities. And different kinds of flux box reactions are present in the model to define kinetic equations. Interaction between one entity (i.e., node) to another is represented by edges. The graphical design of the software is supported by Jarnac, Plot, and Gibson, while associated databases are BioModels, PubMed, IHOP, KEGG, and SABIO. With the help of all these integrated modules, a user can model biochemical and gene regulatory networks. Using cell designer the user can create graphical notation for gene, RNA, and protein and also make a complex of protein. There are options to import and control the models developed by other people in systems biology field. The major parameter in this software is to perform simulation at molecular level using genes, proteins, or metabolite concentration at different time periods. Ordinary differential equations are used to create the simulation profiles. Simulation profiles can be analyzed and compared within a model, same organism model or other model. Another important feature of this modeling tool is to study the small pathway by considering a system as a whole which implies that the user need not to study complete information at one instance. The user can split their pathway of interests into different modules and later integrate them to reduce the time complexity for the simulation. Apart from this, there are various plugins which can be integrated with this software.

Cytoscape is a similar tool for model development on the basis of topological analysis. This tool lacks the use of simulation to study differential conditions, but statistical analysis and beautiful graphical layouts for representing networks provide an edge for this tool over other modeling softwares.

17.11 Conclusion

Major purpose of modeling and optimization in research is to systematically assemble and simulate all the molecules and their interactions that are occurring inside the living cell. There is a need to understand how these molecular interactions take place and how to determine the function of this complex machinery that cannot be solved only by biotechnology lab experiments. The advancement in the modeling techniques indicates that cellular networks are governed by diverse universal properties and offer a new conceptual structure that could potentially renovate our view of biology and drug therapies.

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