ORIGINAL ARTICLE

Multi-agent-based bio-network for systems biology: protein–protein interaction network as an example

Li-Hong Ren · Yong-Sheng Ding · Yi-Zhen Shen · Xiang-Feng Zhang

Abstract Recently, a collective effort from multiple research areas has been made to understand biological systems at the system level. This research requires the ability to simulate particular biological systems as cells, organs, organisms, and communities. In this paper, a novel bio-network simulation platform is proposed for system biology studies by combining agent approaches. We consider a biological system as a set of active computational components interacting with each other and with an external environment. Then, we propose a bio-network platform for simulating the behaviors of biological systems and modelling them in terms of bio-entities and society-entities. As a demonstration, we discuss how a protein–protein interaction (PPI) network can be seen as a society of autonomous interactive components. From interactions among small PPI networks, a large PPI network can emerge that has a remarkable ability to accomplish a complex function or task. We also simulate the evolution of the PPI networks by using the bio-operators of the bio-entities. Based on the proposed approach, various simulators with different functions can be embedded in the simulation platform, and further research can be done from design to development, including complexity validation of the biological system.

Introduction

Systems biology attempts to integrate the huge and multi-form amount of biological data in order to understand the behaviors of biological systems, and to study the relationships and interactions among the various components of a biological system. A biological system is an assembly of interrelated biological components. Besides describing a system's components in detail, in order to promote system-level understanding of biological systems, it is also necessary to describe the behavior of any component at the molecular level, and to comprehend what happens when certain stimuli or malfunctions occur (Cardelli 2005; Finkelstein et al. 2004; Jeong et al. 2000; Kitano 2002; González-Díaz et al. 2008). Some work addresses various system-biology-related problems from different angles (Qi et al. 2007; Shikata et al. 2007; Xu and Chang 2008).

Biological systems are complex systems characterized by nonlinearity, i.e., emergence, which also means "the whole is not equal to the sum of its parts." The whole behavior of the biological system is an emergent behavior of many local components' interactions (such as DNA, proteins, and cells). The molecular foundation of this nonlinearity is the generic and intricate interactions among all sorts of biomacromolecules, such as genes and proteins. Moreover, these biomacromolecules never behave or

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perform their biological functions alone, but have many direct or indirect relations among each other that yield various biological networks, such as metabolic networks, gene regulation networks, and signal transduction networks (Maslov and Sneppen 2002; Milo et al. 2002; Stelling et al. 2002). Various components provide different services and perform different functions in the biological system. Every component has its simple behavior rules, while a group of components can display complex emergent behavior (i.e., adaptability, evolution, security, self-maintenance). The interactions among various components adjust the biological system to be in a stable state through diversity and natural selection. The biological system is inherently distributed with no central "element" controlling it.

In biological systems, the whole is more than the sum of the system's parts because of the interactions among the parts, as is true for emergent behaviors in other complex systems (Bhalla and Lyengar 1999; Harada and Kinoshita 2003; Read 2003). In order to investigate complex biological behavior, it is necessary to develop nonlinear mathematical models and software to provide powerful numerical analysis methods. The development of software platforms for systems biology research is ongoing, such as systems biology modelling language (SBML, http://www.sbml.org; Hucka et al. 2003) and CELLML (http://www.cellml.org; Tomita et al. 1999).

Biological systems are composed of dispersive, autonomous, and mobile biological individuals that express self-regulation, adaptability, evolution, and survivability. Due to the resemblance between biological systems and multi-agent systems, an agent-based approach is regarded as a suitable approach to simulate the behaviors of the biological systems. For example, the Cellulat model was a combination of the behavioral-based paradigm and the blackboard architecture for intracellular signaling modelling (Gonzalez et al. 2003). d'Inverno and Saunders (2005) adopted a multi-agent system to model and simulate the behavior of stem cells. Walker et al. (2004) proposed an agent-based modelling approach for the social behavior of cells. Pogson et al. (2004) built an agent-based model for the NFkB signaling pathways.

And, inspired by the resemblance between biological systems and multi-agent systems, we have abstracted an integrated computation framework from the biological neuroendocrine-immune system (NEIS) and developed the NEIS-based bio-network architecture (Ding 2007; Ding and Ren 2003). The agent-based simulation platform for the bio-network architecture has also been presented. We use it as network middleware for complex services and applications on the Internet and distributed networks (Ding et al. 2007b; Gao et al. 2004, 2006).

In this paper, we propose a multi-agent-based bio-network simulation platform to support the modelling and analysis of biological systems. We consider a biological system as a set of active computational components interacting in a dynamic and often unpredictable environment. Then, the behavior of biological systems can be modelled in terms of bio-entities and society entities. The bio-network platform will make it possible for the complexity of the biological systems to emerge from the interactions of bio-entities. As an example, we implement protein–protein interaction (PPI) networks on the bio-network platform by regarding a PPI network as a society of autonomous interactive components.

Virtually all cellular processes depend on precisely orchestrated interactions between proteins. This is because specific and normal PPIs are involved in almost all physiological processes (see, e.g., Chou 2005). Therefore, characterization of PPI (Chou and Cai 2006) or understanding of the protein network is important for problems ranging from rational drug design (see e.g., Chou 2004; Chou et al. 1999; Zhang et al. 2002) to analysis of metabolic and signal transduction networks (see e.g., Chou et al. 2006; Kanehisa et al. 2004; Yan et al. 2004).

The large amount of biological data available from high-throughput experiments has been used to identify thousands of pairwise PPI in yeast cells and in other biological models. The integration of this type of data in PPI networks or graphs can be used to predict different cellular behaviors under specific physiological conditions. It is good to introduce the graphical approach to study PPI networks because it makes the physical picture more intuitive and helps people to catch the essence of a very complicated biological system. A similar graphical approach was also used to study the enzyme-catalyzed system and protein-folding system (Chou 1989, 1990; Zhou and Deng 1984). The graphical approach in Chou (1989, 1990) and Zhou and Deng (1984) is quantitative, i.e., one can use the graph to directly derive the enzyme-catalyzed rates according to some graphical rules. In this paper, the graphical model can not only directly derive the relationship of PPI, but can also demonstrate the dynamic and evolutionary process of PPI networks. Because most of the PPI networks are characterized by a power-law degree distribution, most of the nodes or vertices have only a few links, whereas a few nodes show a very large number of links. These scalefree networks can be applied to the analysis of PPI in various biological models.

The paper is organized as follows: the section "Systems and methods" discusses how the bio-network and its components are designed. Section "Protein–protein interaction network simulator on bio-network platform" presents a simulator of PPI for emergent behaviors on the bio-network platform. Section "Conclusion" concludes the paper by discussing the trends of the bio-network simulation platform.

Systems and methods

Design of the bio-network

In order to study complex biological behaviors, particularly emergent behaviors, we design a bio-network based on multi-agent systems, as shown in Fig. 1. We consider a biological system as a set of active computational components interacting in a dynamic and often unpredictable environment. Then, the behavior of the biological systems can be modelled in terms of bio-entities and society entities. Bio-entities in the bio-network are regarded as autonomous agents and possess characteristics such as interaction, no central control, diversity, mobility, and evolution. The bio-network platform will make it possible for the complexity of the biological systems to emerge from the interactions of bio-entities. We only need to design simple behaviors of bio-entities; complex biological behaviors emerge from bio-entity behaviors. The platform should be a helpful tool to support life scientists in building models and verifying experimental hypotheses by simulation. And it can be used to design new models from known ones by the integration of different models and tools.

The layered infrastructure of the bio-network consists of bio-entities, bio-entity survivable environment, bio-network core services, bio-network low-level functional modules, and bio-network simulators, as shown in Fig. 1.
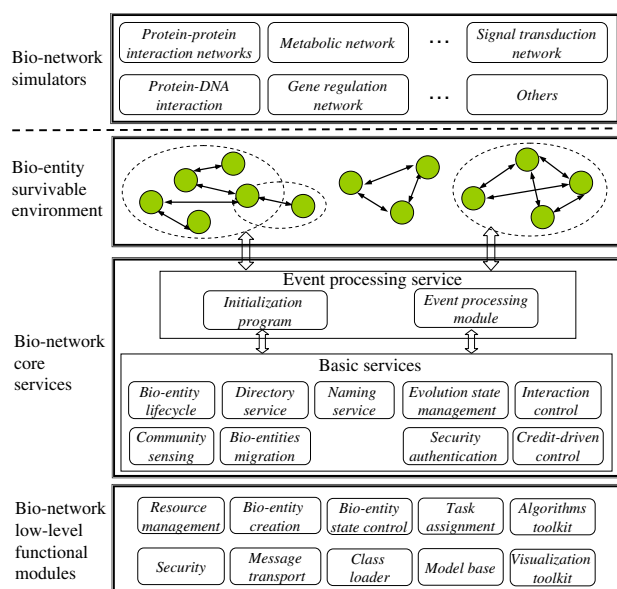

Fig. 1 The bio-network

The components of the bio-network

Bio-entity

Bio-entities are the basic and important components. A bio-entity is designed to be an autonomous agent; it can be a unit of DNA, a protein, or a cell. It can be implemented as an object in software development. A bio-entity consists of attributes, behaviors, function information, and communication mechanisms.

Attributes Attributes describe the characteristics of a bio-entity itself. Attributes include unique identity (UID), service type, credit, state, and relationship, as shown in Table 1. All these attribute values are stored in a bio-entity table. There are many different bio-entities, such as network bio-entity, response bio-entity, and collaborative bio-entity. In the platform, bio-entities interact with each other to form a society bio-entity and then to form a bio-sub-network (for example, protein–protein interaction forms a protein network) to provide some functions.

Behaviors A bio-entity's behaviors make it run freely in the platform. The behaviors mainly include credit exchange, migration, replication, reproduction, interaction, and announcement, based on the type of bio-entity. All these behaviors are implemented as methods of bio-entity class. Credit exchange is an important behavior because it controls and manages other behaviors. A bio-entity must store and consume credit for its existence in the bio-network. In addition, changes in bio-entity actions and the transitions of bio-entity evolution states are driven by the credit mechanism. Migration behavior decides where and when the entity will migrate by considering the cost of migrating towards a neighbor node. A bio-entity can provide more services to the requesters from other nodes through migration. Replication behaviors allow an excellent bio-entity to replicate in order to perform the services more effectively. A newly replicated bio-entity acquires credit from its parent and derives its behaviors from its parent's. Reproduction behaviors are similar to replication behaviors and can produce a child bio-entity from two parent bio-entities. The two parent bio-entities create a new

Table 1 Attributes of a bio-entity in the bio-network

Attribute	Meaning
UID	A global unique identifier
Service type	Provided service type
Credit	Evaluating a bio-entity's ability to provide a task
State	The state of a bio-entity: active, suspended, or inactive
Relationship	The relationship among the bio-entities, denoted by relationship strength

offspring bio-entity with a new identifier and an initial amount of stored credit from both of its parents. Mutation and crossover behaviors may happen during the process of reproduction. New bio-entities are able to complete tasks more effectively through evolution. Interaction behavior means that each bio-entity autonomously interacts with appropriate bio-entities in the environment to perform component functions. A bio-entity with announcement behavior can announce its information to the platform, which will be helpful for these bio-entities to establish their relationships. Some other behaviors can be designed according to the requirements of the biological networks. The above behaviors of the bio-entities can be selectively used to generate complex biological behaviors.

Function information Function information contains the information relevant to the functions that a bio-entity provides. It also describes how to use these functions.

Communication mechanisms In order for bio-entities to collaborate and for complex functions or behaviors to emerge, a set of communication mechanisms is needed. We adopt a message-based communication mechanism to realize complex collaboration policies. The bio-network reuses agent communication language (ACL) defined by the Foundation for Intelligent Physical Agents (FIPA) as a communication language among the bio-entities (Ding et al. 2007a). We call it the bio-network communication language (BNCL). It includes not only some common actions used by ACL, but also some special actions defined by the bio-network. All bio-entities can communicate through these actions. Also, we use XML as the primary code language of BNCL because of its strong capability for data description and metadata.

Society-entity

Community structure is a common property of many biological networks. The ability to find and analyze such groups can provide invaluable help in understanding and visualizing the structure of biological networks (Girvan and Newman 2002). In the bio-network, a group of bio-entities establishes relationships and interacts to form a society-entity. A society-entity is an emergent behavior based on interactions and relationships established among the bio-entities. The society-entity can be used to simulate the evolution features of biological networks through diversity and natural selection functions on the platform. Diverse functions emerge by dynamically creating and modifying society-entity relationships. Diverse behaviors of bio-entities promote successful evolution through a large domain of behaviors. Diversity coupled with variable environmental conditions will lead bio-entities to evolve their behaviors to be suitable for the local environment. Natural selection makes a bio-entity's behaviors and

relationships more effective. The construction of a society-entity is simple because only the relatively simple bio-entity behaviors need to be designed. The complex features naturally emerge from the simple behaviors of bio-entities.

Bio-entity survivable environment

The bio-entity survivable environment provides bio-entities with a uniform view of their working environments. Also it is a runtime environment for deploying and executing bio-entities. In bio-entity survivable environment, different bio-entities may be available to the bio-network and may contribute to different functions. Information carried by the bio-entities may or may not be accessible to other bio-entities at different levels. So the availability of a bio-entity depends on its relationship to the survivable environment, with very relevant bio-entities providing functions quickly and irrelevant bio-entities interacting loosely or not at all. In this way, the survivable environment determines the interaction behaviors among bio-entities.

Bio-network core services

The bio-network core services provide a set of general-purpose runtime services that are frequently used by bio-entities. They include event processing services and some basic services such as lifecycle service, directory service, naming service, community-sensing service, bio-entity migration service, evolution state management service, interaction control service, credit-driven control service, security authentication service, and application service.

Bio-network low-level functional modules

Bio-network low-level functional modules are a bridge to maintain access to various resources. They include resource management, bio-entity creation, bio-entity state control, security, message transport, class loader, task assignment, model base, algorithms toolkit, and visualization toolkit.

Bio-network simulators

Based on the bio-network, we can build various simulators to study complex biological networks, such as protein-DNA interaction networks, protein–protein interaction networks, metabolic networks, gene regulation networks, signal transduction networks, and others. We only need to design simple behaviors of bio-entities, complex biological behaviors emerge from the bio-entity behaviors. Also, we can seek the mapped relationships among bio-entity behaviors and emergent behaviors. The various simulators should be helpful to describe complex biological systems

of interacting bio-entities and can be used to explore the bio-network's possible applications in the system biology domain.

Protein-protein interaction network simulator on the bio-network platform

The bio-network simulation platform

Based on the bio-network, we can develop its simulation platform by utilizing multi-agent systems. In biological system simulations, agents can be suitably adopted for modelling at the appropriate level of abstractions of the biological activities (tasks) and the biological components that are responsible for them. The heterogeneity of the available agent models makes it possible to describe the behavior of biological components. A different kind of interaction within the biological environment can be suitably modelled in terms of actions and perceptions (including communication).

In addition to individual bio-components, we can also model the environment the bio-components are immersed in, and the biological systems overall. Agent interaction can be modelled both as direct communication among agents and as mediated interaction with their environment. If an agent represents an individual component of the systems, the bio-network captures the overall set of the biological components and their environment and the structures involved in their interactions.

In the context of the multi-agent systems paradigm, high-level organizational models are used to characterize the structure as well as the structure relationships among the components. The agent society (society-entity) can be used to define an ensemble of agents and their environment and can be suitably adopted for scaling with complexity, identifying different levels of descriptions of the same system. These modelling features can be then exploited for the simulation of biological systems involving different description levels, each one characterized by different sorts of emerging phenomena.

The bio-network simulation platform is a software framework fully implemented in Java language. The main components and the main interface of the bio-network simulation platform are shown in Fig. 2. The platform includes simulators, configuration file, database, figure display, algorithms toolkit, visualization toolkit, and main modules such as the basic services module, event processing module, and bio-entity object module. The basic services module implements the services designed in the bio-network platform. The event processing module is intended to connect basic services and collaborative components to provide more services. The bio-entity object
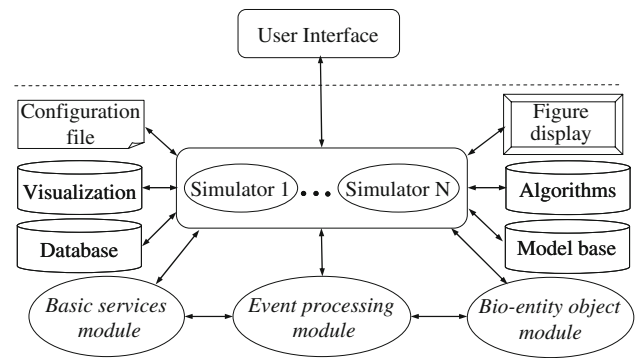

Fig. 2 The main components of the bio-network simulation platform

module implements the construction of a bio-entity, including the bio-entity's attributes and behaviors. It also implements simple services (tasks) that can be recalled by the simulator module. The algorithms toolkit includes various traditional or intelligent algorithms and can be loaded by the bio-network platform. The visualization toolkit includes various visual methods to demonstrate the results in the bio-network platform.

On the platform, we can develop various biological network simulators. Critical points of biological systems, including structures, activities, and interactions, can be captured directly by the simulators. The simulators can be framed as on-line experiments, where the scientist can observe and interact dynamically with the system and its environment. The dynamics of system interactions is fundamental for supporting the analysis of system behaviors. By introducing new agents representing biological components or removing existing ones to change the structure, or by acting on the mediating/coordination artifacts to the global biological processes, we can promote system behavior analysis and control.

Protein–protein interaction network simulator

The simulation of a complex biological system first of all requires the construction of the system model. In order to demonstrate how a bio-network simulator is built on the bio-network platform, we provide an example of the emergent behaviors generated from the PPI network. We discuss how a PPI network can be seen as a society of autonomous interactive components. From interactions among the small PPI networks, a large PPI network can emerge with a remarkable ability to accomplish a complex function or task.

PPI networks are complex entities generally containing thousands of interactions. In PPI networks, the nodes represent proteins and the edges represent specific interactions, such as recorded evidence of co-immunoprecipitation or a two-hybrid interaction. Prediction tools as

well as experimental techniques aim at assigning quantitative metrics to the interaction edges within such networks (Bader and Hogue 2002; Bader and Hogue 2003; Ferracuti et al. 2002; von Mering et al. 2002; Tong et al. 2002). A number of specialized and publicly accessible databases are available that contain data about the nodes and the interactions, so it is not difficult to construct a PPI network from these data. However, static PPI network topology is not sufficient to define protein function, incorporating time-dependent expression data is also important for understanding pathway function. The dynamic and evolutionary features of the PPI networks should be obtained. As such, some PPI links that have not been verified by experimental data may be mined and could be a direction to design the experiments. In the following, we discuss how the emergent behaviors can be generated by constructing the PPI networks on the bio-network simulation platform.

In a PPI network model, we regard a protein as a bio-entity. First, some bio-entities on the platform will interact with each other to form a small PPI network (i.e., society-entity) based on the experimental data. Further, the small PPI networks (society-entities) will mutually communicate and cooperate to form a large PPI network (society-entity network). The large PPI network has its remarkable ability to accomplish a complex task. Interactions among the large PPI networks can be further conducted to form a larger PPI network with a remarkable ability to accomplish even more complex tasks, and so on. We demonstrate the above process of how the PPI join to form a larger PPI network in Fig. 3.

In the platform, we simulate two kinds of environments with and without evolutionary operations. The simulated network topology is set to 50, 100, 200, 500, 1,000, and 2,000 nodes, with 100, 300, 1,000, 2,000, and 5,000 links. There are two kinds of bio-entities in the simulation: bio-entities without biological behaviors, which are arbitrary
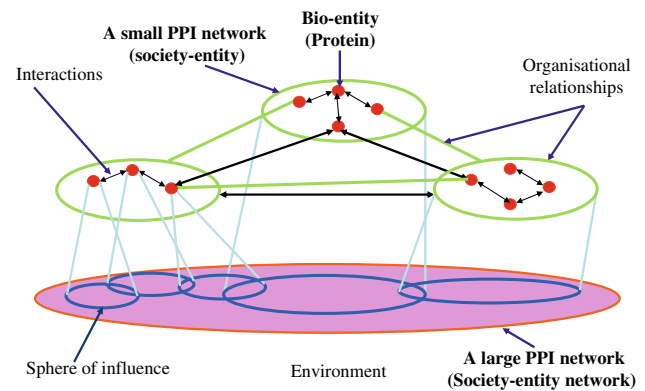

Fig. 3 The emergent PPI network model

on the platform, and bio-entities with biological behaviors. The bio-entities with biological behaviors can migrate and replicate according to their link degrees. Figure 4 shows two examples of PPI networks with and without evolutionary operations. The two PPI networks are generated by randomly reassigning node and edge labels for the networks of interest. In Fig. 4b, the link degrees between the nodes in the PPI networks belong to [0, 1]. The bigger the link degrees, the darker is the link line.

From the results, we can know that, if we need to study deeply the possible evolutionary behaviors, we can use the bio-operators of the bio-entities to evolve the PPI networks. In this way, the society-entities dynamically make the superior bio-entities live and remove the inferior bio-entities from the PPI network. Given multiple observed protein interaction networks, we can investigate gene duplication, deletion, and "re-wiring" processes by considering their evolution to their contemporary forms.

PPI network simulator is a bioinformatics application designed for simultaneous analysis and visualization of multiple structures and sequences of proteins. We are

Fig. 4 The simulated PPI network topology is set to 100 nodes and 300 links

(a) Bio-entities without biological behaviors   **(b)** Bio-entities with biological behaviors
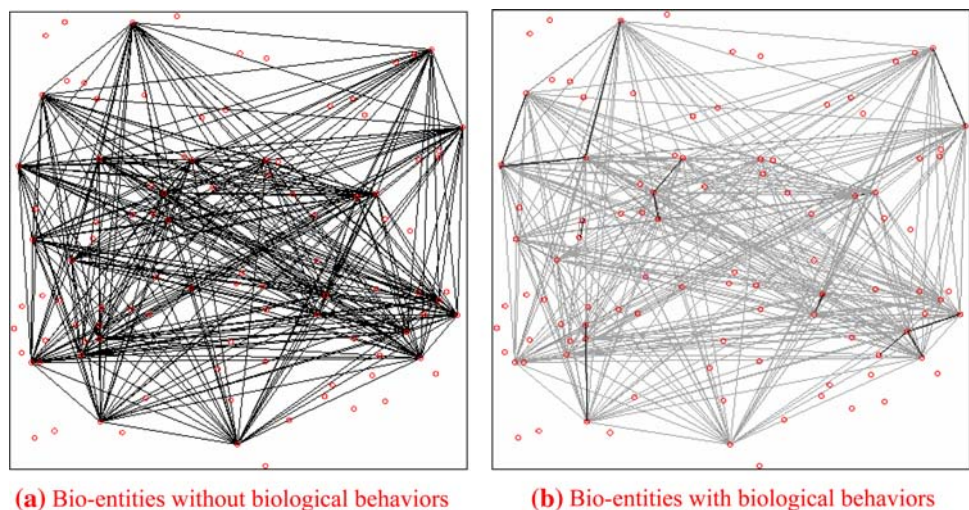
further developing the simulator by providing more functionalities, such as structure visualization, performing more complex analyses of sequence structure relationships, including structural alignment of proteins, investigation of specific interaction motifs, studies of protein–protein interactions, protein–DNA interactions and protein superfamilies, and discovery of hub proteins and protein complexes.

Conclusion

In this paper, a novel bio-network and its simulation platform are proposed for system biology studies by combining multi-agent-based approaches. The bio-network platform provides a good engineering simulation environment of biological systems. We discuss how a PPI network can be seen as a society of autonomous interactive components. From interactions among the small PPI networks, a larger PPI network can emerge with a remarkable ability to accomplish a complex task. As the platform provides a remarkable tool to describe complex biological systems of interacting bio-entities, this study explores its possible application in the system biology domain. Based on the proposed approach, further research can be done from design to development, including complexity validation of the biological systems.

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