CADLIVE System: Map-Based Dynamic Simulation of Biochemical Networks

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1 Introduction

Gene regulatory and metabolic networks within a cell seem too complicated and heterogeneous to convert them into mathematical models automatically. Some simulators have primitive converters for chemical reaction equations into conventional mass action (CMA) or general mass action (GMA), but such converters cannot necessarily support the complicated biochemical networks. Most simulators edit the mathematical models manually based on their expertise and experiences, which requires laborious and time-consuming operations involved in formulating and debugging. In order to convert such complicated biochemical reactions into a mathematical model accurately and efficiently, we propose the CADLIVE (Computer-Aided Design of LIVing systEms) System (Fig. 1), a software tool for converting biochemical reaction maps into mathematical models, and analyzing them, with tight integrated development environment of simulation tools and databases.

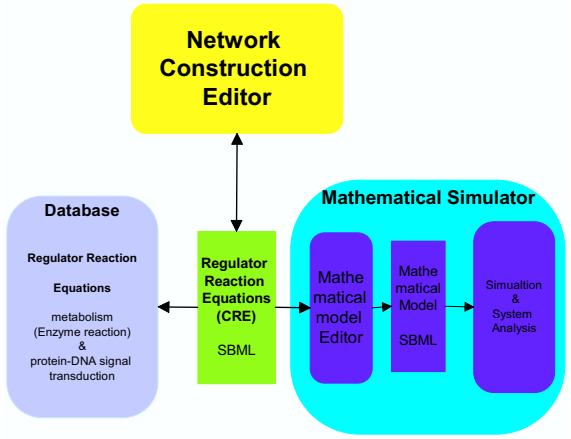

Figure 1: CADLIVE System.

2 CADLIVE System

2.1 Network Construction Editor

We developed the sophisticated notation to clearly represent the signal transduction pathways in a form that can be readily processed by both computers and humans. The regulator-reaction equations are combined with detailed attributes including the associated cellular component, molecular function, and biological process using a conventional XML-based representation. The data representation has been extended based on SBML level 2. We have developed the software suite, CADLIVE Editor [1], which features a graphical user interface (GUI), for editing large-scale maps of complicated signal transduction pathways based on a modification of Kohn's notation.

2.2 Database

The database stores the entire information regarding the molecular interaction networks using the regulator-reaction equations with necessary tags such as cellular component, molecular function, biological process, material, and types of reaction. Users easily obtain such equations by specifying the genes or biological processes that they analyze, and reconstruct molecular interaction maps by GUI.

2.3 Dynamic Simulator

The CADLIVE Simulator divides reactions into three layers, gene, protein, and metabolic layers, whereby the regulator-reaction equations are automatically converted into various mathematical models, *e.g.*, Conventional Mass Action (CMA), General Mass Action (GMA), the Michaelis-Menten type equations (MM), and ordinary transcription-translation equations. The generated differential equations are further converted into S-system and DAEs. The coefficients of S-system are calculated at the steady state, and DAEs are created by the two-phase partition method [2]. The two-phase partition method accurately simulates a complex biological system at an extremely high speed, which divides the regulator-reaction equations into the binding and reaction phases. The accuracy of the conversion is guaranteed by the rules that are defined in the XML format. The Simulator optimizes a large number of kinetic parameters so that the mathematical model expresses the required dynamic features, and analyses the robustness of the biological system.

3 Results and Discussion

In order to demonstrate the feasibility of CADLIVE, we simulated the *E. coli* heat shock response, circadian clock (Fig. 2), glycolysis, TCA cycles, and nitrogen fixation system. The heat shock response is a gene regulatory network that s^{32} shows a sharp transient response to the abrupt increase in temperature. The circadian clock shows the oscillatory behaviors of expressed genes, requiring the Simulator to consider the localization or transport of components. The glycolysis and TCA cycle are examples of metabolic networks whose sensitivity and stability S-system analyzes. The *E. coli* nitrogen fixation system is a great model that shows how the Simulator combines metabolic and gene regulatory networks. First, the GUI editor of CADLIVE constructed the biochemical networks that include various reactions such as gene regulations, signal transduction, transport, and metabolic pathways. Second, the Simulator parsed and converted the reaction network into a mathematical model. The employed technology of GAs optimized many unknown parameters of a biological system to fit the system with experimental data efficiently. Using parallel computing achieved high-speed calculation. To elucidate the dynamic behavior of molecular processes, the Simulator carried out the standard method of sensitivity and stability analysis.

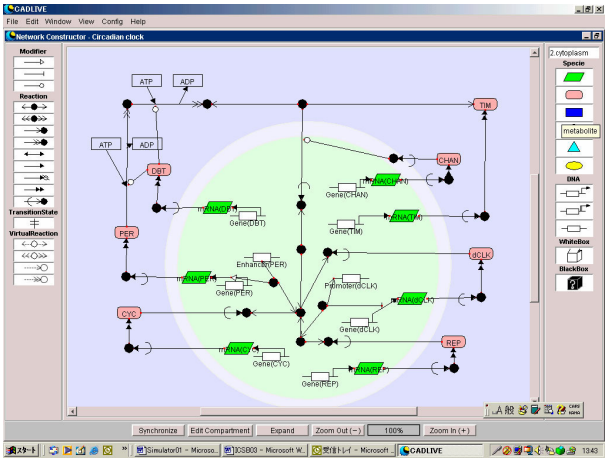

Figure 2: CADLIVE Editor for Circadian rhythm.

Acknowledgments

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References

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