

# BIOCAD Project for Constructing a Biological System *in Silico*

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## 1 Introduction

In postgenomic era the entire image of a biological substance is expected to be elucidated based on genome. Biological systems are experimentally and theoretically analyzed at various levels such as transcriptome, proteome, metabolome, and systeome. Such systematic approaches will present lots of the functions of genes, and enable computers to reconstruct a biological network at a molecular interaction level.

To construct a biological system *in silico*, the map of molecular interactions such as metabolism and gene regulatory networks are required, which can be regarded as a blueprint of life. The molecular interaction maps with kinetic data will enable us to mathematically predict the dynamic behaviors of the biological system.

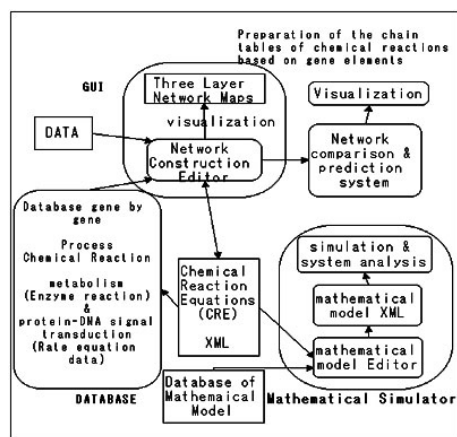


Figure 1: BIOCAD system.

The BIOCAD system consists of three subsystems, the network construction editor that helps users draw the molecular interaction maps, the database that stores the reaction equations showing the interaction maps, and the simulator that synthesizes and analyzes the dynamic system (Figure 1).

## 2 BIOCAD System

### 2.1 Network Construction Editor

To make a large-scale and complicated map of metabolic and gene regulatory networks, the sophisticated equations that describe elementary biochemical reactions are required. Of course,

The maps have been employed to draw the mechanism of molecular interaction networks. KEGG [2] is the database containing the maps of various metabolic circuits, and TRANSFAC [3] is the database regarding gene regulatory networks. On the other hand, various simulators such as E-Cell [4], Genomic Object Net [5], and Best-Kit [6] have been developed to predict the dynamic behaviors of the biological networks. In the near future, it will be possible to reconstruct and design the biological system *in silico* based on the molecular interaction maps and kinetic knowledge. Although the simulators and the database should work together to reconstruct biological systems, they have been separately developed so far. There have been few reports to develop an integrated system of the database and simulator. Our objective is to develop the BIOCAD (Computer-Aided Design of a Biological System) system that integrates the database of molecular interaction networks and the simulator that makes a dynamic system based on the interaction maps. The BIOCAD system consists of three subsystems, the network construction editor that helps users draw the molecular interaction maps, the database that stores the reaction equations showing the interaction maps, and the simulator that synthesizes and analyzes the dynamic system (Figure 1).

chemical reaction equations can describe all the biochemical reactions, but we found that the use of them was not the best way to describe a complicated biological system. Since biochemical reactions can be divided into regulators and the reactions that are controlled by the regulators, we defined the regulator-reaction equations. For example, an enzyme reaction is usually described as follows;  $E + S \rightleftharpoons E : S \longrightarrow E + P$ . The regulator-reaction equations describe the above as follows;  $E$ : activator,  $S \longrightarrow P$ , where the regulator  $E$  activates the reaction  $S \longrightarrow P$ . These equations are useful for classifying the reaction equations in a database. Besides the definition of the regulator-reaction equations, an editor system is necessary to describe the correct networks consisting of the regulator-reaction equations. We are developing the editor system with the graphical user interface (GUI) that helps users draw the networks (Figure 2). In addition, a visualization system is constructed to visualize the regulator-reaction equations into the molecular interaction maps, which enable users to make the regulator-reaction equations without any error.

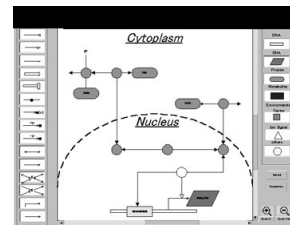


Figure 2: Network Construction Editor.

## 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, kinds of reaction, etc. Users easily obtain the equations by specifying the genes or biological processes that they like to analyze, and reconstruct molecular interaction maps by the visualization system. Since data are well classified with the various tags, it is easy to delete, add, and improve the equations.

## 2.3 Simulator

We developed the simulator that automatically converted the regulator-reaction equations into a mathematical model, and simulated them. The well-established S-system is employed to mathematically calculate a metabolic network. The two-phase partition method is applied for simulating a gene regulatory network [1]. The two-phase partition method divides a biological system, which can be described by the regulator-reaction equations, into two-phases: the binding and reaction phases. We demonstrated the capability of the two-phase partition method to accurately simulate a complex biological system at an extremely high speed. The simulator employed the solvers of MATLAB as the calculation engines solving differential equations and simultaneous algebraic equations in order to avoid any technical error regarding mathematical simulation.

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