CADLIVE-Based Analysis for the Budding Yeast Cell Cycle

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Keywords: CAD, XML, yeast, cell cycle, network, simulation, integration

1 Introduction

The completion of the yeast genome sequence and the subsequent postgenomic studies regarding transcriptome and proteome (`http://www.yeastgenome.org/`, `http://mips.gsf.de/proj/yeast/CYGD/db/`) remind one how one understands the gene regulatory networks at the molecular level. With the increase in the postgenomic data, the further understanding of the mechanisms of the budding cell cycle networks requires comprehensive tools for the representation of large-scale signal transduction pathways, which have been provided by advanced molecular biology, and the integration of DNA microarray data and protein-protein interaction data into the network. Consequently, the well-designed map enables one to simulate the molecular process dynamically. In order to fulfill these requirements, the CADLIVE (Computer-Aided Design of LIVing systEms) System has been developed that allows to construct a large-scale map of complicated signal transduction pathways and to simulate it [1].

In this paper, the CADLIVE System designs a large-scale map of the budding yeast cell cycle and searches its signal transduction pathways computationally. The use of CADLIVE enables one to look at the whole view of the large-scale map, to integrate postgenomic data into the biochemical map. The inconsistency between the network map and the postgenomic data greatly facilitates predicting novel or unexpected biochemical interactions. Based on the well-designed map, the CADLIVE Simulator simulated the budding yeast cell cycle dynamically.

2 Methods

2.1 CADLIVE Application Program

CADLIVE is a software suite for building large-scale maps of complicated biochemical reactions, and for storing their regulator-reaction equations in a database. Its graphical user interface enables one to draw gene regulatory/metabolic maps in a simple manner, which eliminates the need for laborious, time-consuming, and annoying activities [1] (Appendix 1: `http://www.bse.kyutech.ac.jp/~kurata/NARwww/cadlive.html`).

2.2 Prediction of Gene Regulatory Networks

To infer a gene regulatory network of the cell cycle of *Saccharomyces cerevisiae*, we employed the VoyaGene system (Mitsui Knowledge Industry Co., Ltd.) that predicts the binary relationships of expressed mRNAs using a Bayesian network model. The Bayesian network model estimated the binary relation between mRNAs from the time course data for the mRNA expression, which were synchronized with respect to alpha, Cdc15, Cdc28, and eu [2] (`http://genome-www.stanford.edu/cellcycle/`). Detailed procedure is described elsewhere (Appendix 2: `http://www.bse.kyutech.ac.jp/~kurata/NARwww/cadlive.html`).

2.3 Dynamic Simulation with CADLIVE Simulator

To simulate the budding yeast cell cycle, the CADLIVE Simulator imported the XML file of regulator-reaction equations, which are described by the CADLIVE Text Editor, to convert them into the mathematical model automatically.

3 Results and Discussion

3.1 Design of a Yeast Cell Cycle Map

The use of CADLIVE drew the budding yeast cell cycle map that consisted of 184 species and 152 reactions, as shown in Figure 1. CADLIVE was able to describe not only reactions but also various events. This map is one of the most sophisticated images of the whole system of the yeast cell cycle. CADLIVE not only drew a large-scale biochemical map according to the well-defined rules, but also generated the regulator-reaction equations that were consistent with the signal transduction pathways of the map.

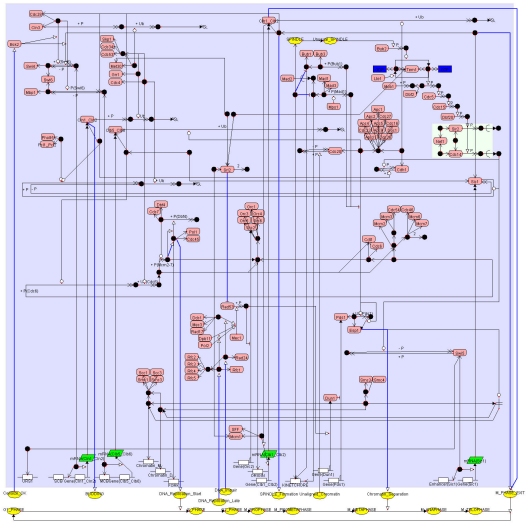

Figure 1: Cell cycle map of *Saccharomyces cerevisiae* constructed by CADLIVE.

3.2 Integration of DNA Microarray Data and Protein-Protein Interaction Data into the Map

To map the experimental data of DNA microarray on the budding yeast cell cycle map, Using VoyaGene, we inferred only 16 binary relationships between the mRNAs of Cln1, Clb5, Clb2, and Sic1 that appeared on the cell cycle map, because most of the detailed transcription regulations remain to be described on the map. Therefore, we searched the binary relationships between a protein and an mRNA, where the upstream of a protein regulates the downstream of an mRNA, and found 57 relationships on the map (Appendix 3: `http://www.bse.kyutech.ac.jp/~kurata/NARwww/cadlive.html`). The cell cycle map contained the same binary relationships as inferred by VoyaGene, but most of the inferred gene regulations were missed on the map.

The use of CADLIVE mapped the protein-protein interaction data on the cell cycle map. We detected hundreds interactions between the proteins that appeared on the cell cycle map from BIND database (`http://www.bind.ca/`). Consequently, the DNA checkpoint system and DNA replication system was suggested to exist as macromolecular complexes as had been expected. The use of protein interactions among different processes can predict novel signal transduction pathways that connect distant processes mutually.

3.3 Dynamic Simulation

Using the CADLIVE Simulator, we simulated the simple model of budding yeast cell cycle. The time courses of Cln2, Clb5, Clb2 and Sic1 are shown in Figure 2, which well correspond to the experimental data.

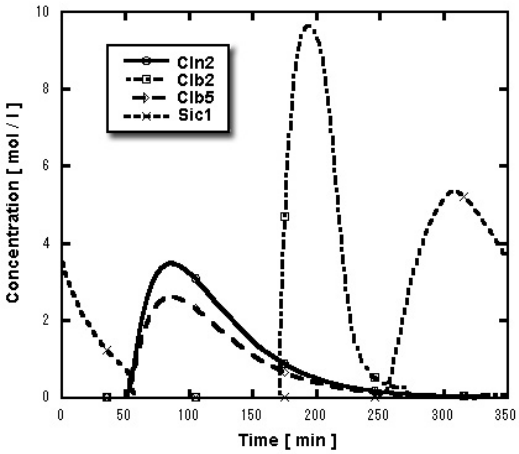

Figure 2: Simulation results of Cell cycle of *Saccharomyces cerevisiae*.

Acknowledgments

This study was carried out as a part of The Project for Development of a Technological Infrastructure for Industrial Bioprocesses on R&D of New Energy and Industrial Technology Development Organization (NEDO).

References

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