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MetaFluxNet: the management of metabolic reaction information and quantitative metabolic flux analysis

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ABSTRACT

Summary: MetaFluxNet is a program package for managing information on the metabolic reaction network and for quantitatively analyzing metabolic fluxes in an interactive and customized way. It allows users to interpret and examine metabolic behavior in response to genetic and/or environmental modifications. As a result, quantitative *in silico* simulations of metabolic pathways can be carried out to understand the metabolic status and to design the metabolic engineering strategies. The main features of the program include a well-developed model construction environment, user-friendly interface for metabolic flux analysis (MFA), comparative MFA of strains having different genotypes under various environmental conditions, and automated pathway layout creation.

Availability: http://mbel.kaist.ac.kr/

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Supplementary information: A manual for MetaFluxNet is available as PDF file.

INTRODUCTION

Analysis and modeling of the metabolic network are essential in understanding complex biological functions. Several available approaches for such analysis and modeling include structural pathway analysis, metabolic flux analysis (MFA), metabolic control analysis and dynamic simulation (Stephanopoulos *et al*., 1998). Among them, MFA is most widely adopted for rational design and *in silico* engineering of metabolic pathways based on the stoichiometry of metabolic reactions and mass balances around the metabolites under steady-state assumption (Lee and Papoutsakis, 1999).

Several computer programs have been developed to assist users in implementing MFA easily: FBA (http://gcrg.ucsd.edu/downloads/index.html), FluxAnalyzer (Klamt *et al*., 2003), and Fluxmap (http://www.biotecnol.com/Paginas/Fluxmap.htm). However, most of the programs available have focused on the limited part of MFA. Moreover, to our knowledge there is no MFA tool supporting dynamic visualization of calculated fluxes mapped on metabolic pathways. Here, we have developed an integrated program package MetaFluxNet satisfying various computational demands in the flux analysis.

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PROGRAM OVERVIEW

MetaFluxNet (version 1.6) provides with an easy and customized environment for constructing a metabolic reaction network and for performing MFA and dynamic visualization of the MFA results. The package was mainly written in Microsoft's programming language C# under the .NET platform, where several Java libraries for the graph layout in dynamic visualization and computational algorithms in MFA are all integrated: JAMA package (http://math.nist.gov/javanumerics/jama/) for various matrix operations; lp_solve (http://www.cs.wustl.edu/~javagrp/help/LinearProgramming.html) for simplex algorithm of linear programming (LP); VGJ (ftp://ftp.eng.auburn.edu/pub/larrybar/VGJ.zip) for the graph layout. The main features of the MetaFluxNet are as follows.

Construction of a metabolic reaction model

MetaFluxNet provides users with a well-developed model construction environment. It allows users to set up their own metabolic reaction network models by registering information on two object classes, *Metabolites* and *Reactions*, which are interactively linked in a metabolic system. Each class consists of several fields describing biological information. For example, the entries of the Reactions class contain Enzyme Commission (EC) number, gene name, and substrates and

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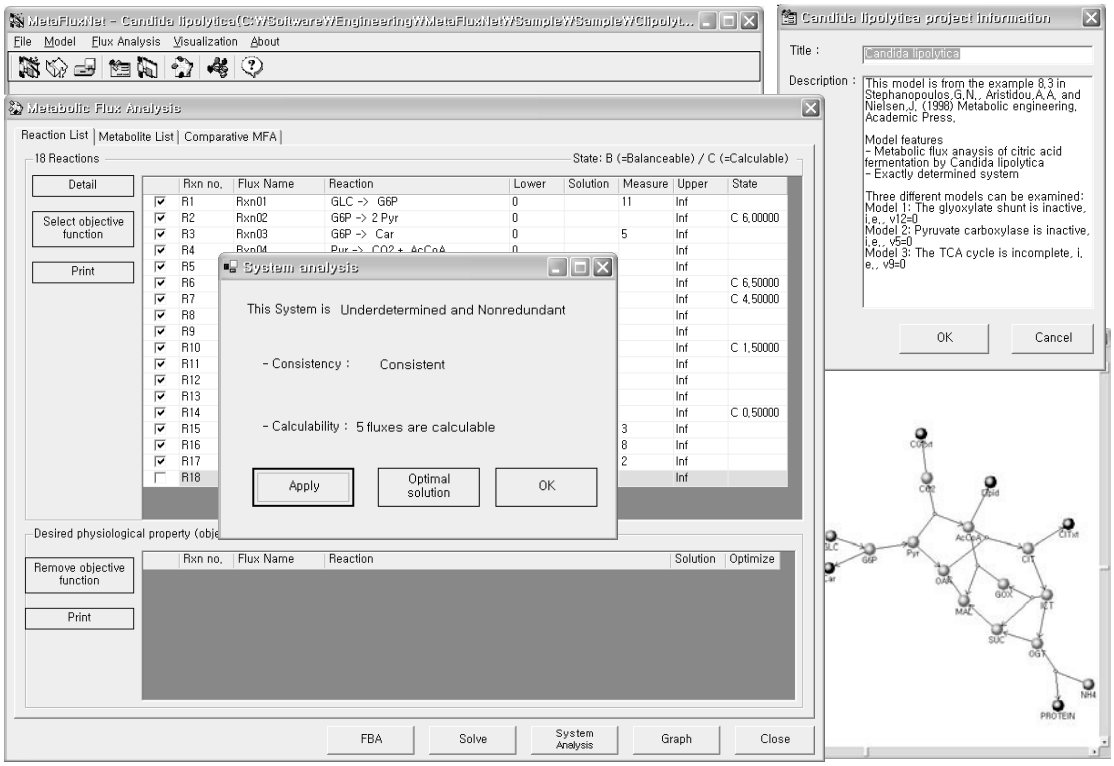

Fig. 1. Screen shot of the flux analysis part of MetaFluxNet. Flux distributions can be interactively determined and dynamically visualized via user-friendly interface.

products participating in the reaction. Data contents in the fields can be edited, stored and modified individually by the users.

Metabolic flux analysis

MetaFluxNet provides a user-friendly interface for MFA as shown in Figure 1. Once the metabolic reaction model is constructed, a stoichiometric model is defined under the steady-state assumption on the basis of measured reaction rates or fluxes. Then, the defined system is classified by one of four possible cases according to *Determinacy* and *Redundancy* (Klamt *et al*., 2002). In the case of the determined system, a unique solution or a least-squares solution is obtained by matrix operations if the system is observable. Otherwise, measured fluxes are reconciled to remove the inconsistency in the case of the redundant system, followed by inspecting calculable fluxes which can be uniquely determined by the least-squares solution using the pseudo-inverse (see Klamt *et al*., 2002). LP approach can be exploited to quantify optimal flux distribution by optimizing a desired physiological property (objective function) such as growth rate, substrate uptake rate and product formation rate (Stephanopoulos *et al*., 1998).

Comparative flux analysis

MetaFluxNet also allows the users to investigate the influences of gene addition or deletion, and of varying cultivation conditions on the optimal metabolic flux distribution. This makes it possible to understand the metabolic and physiological changes of cell under different conditions, and consequently to design new metabolic engineering strategies to achieve desired goals. Furthermore, the results of comparative MFA are displayed in one window, where specified measurements and gene modification (addition or deletion) can be represented by ‘measured’ and ‘added or deleted’, respectively, in the state field of fluxes, while the states of non-measured metabolic fluxes are categorized by ‘calculated’ and ‘bound’. Using this feature of MetaFluxNet, one can design and evaluate various metabolically engineered *in silico* strains by relaxing the capacity range of bound fluxes and/or by changing the genotypes.

Visualization of reaction pathways and flux distribution

MetaFluxNet provides an interactive and dynamic graphical user interface to display metabolic reaction pathways with flux distribution results as shown in Figure 1. The pathways

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are automatically and dynamically visualized by the spring embedder layout algorithm supported in the program.

In the near future, this program will be upgraded to integrate the database management system, structural pathway analysis, and dynamic simulation for comprehensive metabolic network modeling and simulation.

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