Discrete Applied Mathematics 157 (2009) 2483–2493

Contents lists available at ScienceDirect

Discrete Applied Mathematics

journal homepage: www.elsevier.com/locate/dam

Modeling and simulation of metabolic networks for estimation of biomass accumulation parameters

U. Kaplan [a], M. Türkay [a,*], L. Biegler [b], B. Karasözen [c]

[a] Department of Industrial Engineering, Koç University, 34450 Istanbul, Turkey
[b] Department of Chemical Engineering, Carnegie Mellon University, Pittsburgh, PA 15213, USA
[c] Department of Mathematics and Institute of Applied Mathematics, Middle East Technical University, 06531 Ankara, Turkey

ARTICLE INFO

Article history:
Received 25 December 2006
Received in revised form 4 April 2007
Accepted 11 June 2008
Available online 9 September 2008

Keywords:
Metabolic networks
Hybrid systems
Parameter estimation
Optimization
Dynamic optimization

ABSTRACT

Metabolic networks are defined as the collection of biochemical reactions within a cell that define the functions of that cell. Due to the growing need to understand the functions of biological organisms for industrial and medical purposes, modeling and simulation of metabolic networks has attracted a lot of attention recently. Traditionally, metabolic networks are modeled such as flux-balance analysis that considers the steady state nature of the cell. However, it is important to consider the dynamic behavior of a cell since the environmental conditions change continuously. Sometimes due to the critical changes in the environment some of the reactions exhibit completely different behavior leading to discrete changes in the metabolic network. Therefore, a cell exhibits discrete-continuous behavior in continuous time. Since hybrid systems exhibit the same characteristics modeling a cell as a hybrid system gives an accurate representation. The aim of this paper is to develop a simulation framework to model the evolving structure of the cell metabolism under changes in the environment. The metabolic responses that cell gives, against multiple changes in the environment are not fully understood. Therefore, in this study, a cell is modeled as a hybrid system that is composed of a system of differential and algebraic equations. The changes in the concentration of metabolites in the environment are represented by Ordinary Differential Equations and the intracellular cell metabolism is represented by a set of algebraic equations. To understand the feedback relationship between intracellular and extracellular changes, the system is solved considering the effects of extracellular stresses on the metabolic responses.

1. Introduction

Recent years have witnessed dramatic changes in cellular biology. One of the main problems in cellular biology was the lack of enough dependable information. However, the sequencing of the first bacterial genome changed this biology from a data-poor science to a data-rich science [3,6]. In this data-rich environment, an entire metabolic map representing all metabolic reactions that take place in the cell are determined [9]. The cellular organism can be modeled using this information to understand its behavior in certain environmental conditions. The prediction of the behavior of the cellular organism gives valuable opportunities for using these organisms for industrial and medical purposes. In this work, we use the fermentation of wine as a case study. Because of highly variable environmental conditions during fermentation, determination of the behavior of yeast and the content of wine during fermentation is a very challenging task. Due to that unpredictability, many fermentations can be problematic. In some cases, the fermentation process takes too long and in

* Corresponding author. Fax: +90 2123381548.
E-mail address: mturkay@ku.edu.tr (M. Türkay).

0166-218X/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.dam.2008.06.048

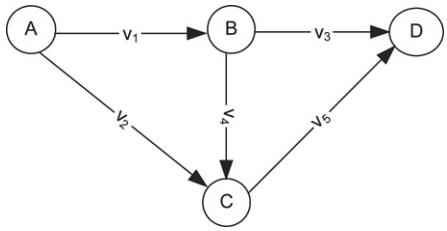

Fig. 1. Sample metabolic network.

Table 1
Stoichiometric matrix representation of metabolic network in Fig. 1

S_{ij}	v_1	v_2	v_3	v_4	v_5
A	−2	−2	0	0	0
B	1	0	−1	−1	0
C	0	1	0	1	−1
D	0	0	2	0	2

some cases the process finishes very quickly without consuming all of the sugar. In these cases, the main problem is the inhibition of some pathways in the metabolism of the yeast rather than cell death [7]. The main reason for the inhibition of certain pathways are the changing environmental conditions such as excessive temperature or lack of nitrogen. Therefore, if the behavior of the cell is known under different environmental conditions, the problems during the fermentation process can be handled and huge economic loss can be prevented in the wine making industry.

There are a number of approaches to modeling metabolic networks. One of the most used modeling techniques is Flux Balance Analysis (FBA) [16–18]. In FBA, models are built with respect to the stoichiometry of the reactions that take place in the cellular organism and predictions are made using linear programming (LP) with the objective of maximizing certain products or minimizing the consumption of certain metabolites. Burgard and Maranas [2] proposed a bi-level optimization model to determine the objective function in FBA. Sainz et al. [14] proposed a two stage model to simulate yeast metabolism and its interaction with the environment. The internal metabolism of the yeast is modeled as a linear programming problem and variations in the environment are modeled with a set of Ordinary Differential Equations (ODE). In the LP part, the biomass is maximized with respect to flow bounds that depend on the environmental conditions. Raghunathan et al. [13] describe the dynamics of the fermentation process using Differential Variational Inequalities (DVIs). The solution of the problem is accomplished by discretization of the differential equations.

In this paper, the internal metabolism of yeast is modeled as an LP problem and variations in environmental metabolic concentration are modeled by a set of Ordinary Differential Equations (ODE). In the LP part, the biomass accumulation is maximized with respect to flow bounds that depend on the environmental conditions. The relationship between environmental conditions and flow constraints are obtained based on experimental data that are represented with piecewise smooth functions of environmental metabolite concentrations. Instead of using two separate models, an LP that represents intracellular activities and a set of ODEs that represents extracellular metabolite concentration; we apply an integrated approach. This model leads to a Differential Algebraic Equation (DAE) system to predict the important parameters in the fermentation process. The rest of the paper is organized as follows. We describe the theoretical background in Section 2. Section 3 is devoted to explanation of the model. In Section 4, a solution procedure and result of the model will be discussed. Conclusions are presented in Section 5.

2. Theoretical background

The complete genomes of cellular organisms can be sequenced in a short time with currently available experimental methods [4]. However, the real challenge begins after sequencing. Because the abundance of biological data requires a new and revolutionary understanding of biology focusing on how the chemical and biological functions of organism are realized, a new and interdisciplinary field appeared: systems biology [9,15]. In systems biology, the main concern is the determination of the emergent properties of interconnected nodes of the data rather than determination of the properties of a single object or node of data. In this paper, the emergent property that we are looking for is the fermentation dynamics of the yeast during wine formation [5].

Intracellular representation: With today's technology the metabolic network and the set of reactions that take place in the cell can easily be determined [10,9]. We can acquire knowledge of components that comprise cells and how they interact using metabolic networks. A sample metabolic network is illustrated in Fig. 1. In Fig. 1 only the reactants and products of each reaction are shown without explicitly showing the stoichiometry of the network.

In this simple metabolic network, there are 5 reactions (v_1 to v_5) and 4 metabolites (A, B, C, D). In the reaction set, the network converts 2 moles of A to 1 mole of B and the remaining reactions have similar effect in the network. The stoichiometry of the network in Fig. 1 is represented in Table 1. In this representation each row corresponds to a metabolite