Available online at www.sciencedirect.com
SCIENCE DIRECT®
Mathematical Biosciences 196 (2005) 99–123
Mathematical Biosciences
www.elsevier.com/locate/mbs

Controllability of non-linear biochemical systems

Anandhi Ervadi-Radhakrishnan [a], Eberhard O. Voit [a,b,*]

[a] *Department of Biostatistics, Bioinformatics and Epidemiology, Medical University of South Carolina, Charleston, SC 29425, USA*
[b] *The Wallace H. Coulter Department of Biomedical Engineering at Georgia Institute of Technology, Emory University, 313 Ferst Drive, Atlanta, GA 30332-0535, USA*

Received 31 December 2004; received in revised form 22 March 2005; accepted 23 March 2005
Available online 27 June 2005

Abstract

Mathematical methods of biochemical pathway analysis are rapidly maturing to a point where it is possible to provide objective rationale for the natural design of metabolic systems and where it is becoming feasible to manipulate these systems based on model predictions, for instance, with the goal of optimizing the yield of a desired microbial product. So far, theory-based metabolic optimization techniques have mostly been applied to steady-state conditions or the minimization of transition time, using either linear stoichiometric models or fully kinetic models within biochemical systems theory (BST). This article addresses the related problem of controllability, where the task is to steer a non-linear biochemical system, within a given time period, from an initial state to some target state, which may or may not be a steady state. For this purpose, BST models in S-system form are transformed into affine non-linear control systems, which are subjected to an exact feedback linearization that permits controllability through independent variables. The method is exemplified with a small glycolytic–glycogenolytic pathway that had been analyzed previously by several other authors in different contexts.

Keywords: Controllability; Non-linear control systems; Feedback linearization; Biochemical systems theory; S-system; Metabolic engineering

* Corresponding author. Address: The Wallace H. Coulter Department of Biomedical Engineering at Georgia Institute of Technology, Emory University, 313 Ferst Drive, Atlanta, GA 30332-0535, USA. Tel.: +1 404 385 5057; fax: +1 404 894 4243.
E-mail address: eberhard.voit@bme.gatech.edu (E.O. Voit).

0025-5564/$ - see front matter
doi:10.1016/j.mbs.2005.03.012

1. Introduction

Cells are regularly exposed to environmental fluctuations that require coordinated physiological responses, which in turn involve transitions from one metabolic state to another. The transitions are achieved through changes in control variables, such as the differential up-regulation of appropriate genes, which adapt dynamically to the environmental demands (e.g., [17,62]). It is important to investigate these control mechanisms, not only to understand the biological aspects of natural stress responses, but also for targeted manipulations of microorganisms that are of biotechnological interest. Indeed, the time is ripe for control-theoretical studies in biochemical and metabolic systems, because experimental techniques are already available and because the mathematical representation and analysis of these systems has matured to a point where it is becoming feasible not only to diagnose and explain the normal functioning of networks of pathways but also to manipulate and optimize them, based on mathematical models, in a predictable and desired fashion, for instance, with the goal of improving the yield of some desired metabolite.

In the past, this type of theory-based metabolic engineering has primarily focused on stoichiometric systems that describe the balancing of metabolic fluxes at steady state and therefore permit the use of the rich repertoire of linear methods [32,42,48,53]. Optimization strategies based on mathematical theory have also been proposed for some non-linear systems (e.g., [1,12,15, 25,29,9,10]). However, because of the complexity of fully regulated, kinetic models, these analyses have in most cases addressed small algebraic systems or they were limited to systems at steady state, where convenient mathematical representations permitted the application of well-understood methods of linear programming [14,33,51,57].

While it is of great importance to investigate means of optimizing biochemical systems under steady-state conditions, it is of equal interest to study to what degree it is possible to move systems through external controls to new states, including steady states as well as transient states. Directly associated with this goal are dynamic issues, such as the minimum time required to reach the new state or the characteristics of the transients between the initial and target states. The challenge with this type of control task is that regulatory kinetic systems are non-linear and that, in contrast to systems of linear equations, the control of non-linear differential systems is complicated and not solved in general. The purpose of this article is thus to begin filling this gap by demonstrating some basic methods for steering non-linear metabolic systems through feedback control mechanisms to desired target states.

1.1. S-systems

The infinite possibilities for defining non-linear systems complicate any generalized analytical approaches. In the context of biological systems, experience over the past 35 years has demonstrated that the power-law representation, as proposed in biochemical systems theory (BST; [36,38,54,61]), effectively combines biological and mathematical validity with accuracy and mathematical and computational tractability.

The power-law representation can be viewed as a canonical non-linear description of biological systems from four different perspectives [40,41]. First, it is a direct generalization of mass-action kinetics, and in this fundamental form also contains functions like the Michaelis–Menten rate law as special cases [45]. Second, it has been shown to be a recast representation that is globally equiv-