Metabolic Engineering ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Metabolic Engineering

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

Minireview

Kinetic models in industrial biotechnology – Improving cell factory performance

Joachim Almquist [a,b,*], Marija Cvijovic [c,d], Vassily Hatzimanikatis [e], Jens Nielsen [b], Mats Jirstrand [a]

[a] Fraunhofer-Chalmers Centre, Chalmers Science Park, SE-412 88 Go teborg, Sweden
[b] Systems and Synthetic Biology, Department of Chemical and Biological Engineering, Chalmers University of Technology, SE-412 96 Go teborg, Sweden
[c] Mathematical Sciences, Chalmers University of Technology and University of Gothenburg, SE-412 96 Go teborg, Sweden
[d] Mathematical Sciences, University of Gothenburg, SE-412 96 Go teborg, Sweden
[e] Laboratory of Computational Systems Biotechnology, Ecole Polytechnique Federale de Lausanne, CH 1015 Lausanne, Switzerland

ARTICLE INFO

Article history:
Received 11 September 2013
Received in revised form
7 March 2014
Accepted 9 March 2014

Keywords:
Mathematical modeling
Kinetic models
Dynamic models
Parameter estimation
Cell factory
Industrial biotechnology

ABSTRACT

An increasing number of industrial bioprocesses capitalize on living cells by using them as cell factories that convert sugars into chemicals. These processes range from the production of bulk chemicals in yeasts and bacteria to the synthesis of therapeutic proteins in mammalian cell lines. One of the tools in the continuous search for improved performance of such production systems is the development and application of mathematical models. To be of value for industrial biotechnology, mathematical models should be able to assist in the rational design of cell factory properties or in the production processes in which they are utilized. Kinetic models are particularly suitable towards this end because they are capable of representing the complex biochemistry of cells in a more complete way compared to most other types of models. They can, at least in principle, be used to in detail understand, predict, and evaluate the effects of adding, removing, or modifying molecular components of a cell factory and for supporting the design of the bioreactor or fermentation process. However, several challenges still remain before kinetic modeling will reach the degree of maturity required for routine application in industry. Here we review the current status of kinetic cell factory modeling. Emphasis is on modeling methodology concepts, including model network structure, kinetic rate expressions, parameter estimation, optimization methods, identifiability analysis, model reduction, and model validation, but several applications of kinetic models for the improvement of cell factories are also discussed.
© 2014 The Authors Published by Elsevier Inc. On behalf of International Metabolic Engineering Society. This is an open access article under the CC BY-NC-SA license (http://creativecommons.org/licenses/by-nc-sa/3.0/).

UNCORRECTED PROOF

1. Introduction

Throughout the World there is a desire to move towards sustainable production of energy, fuels, materials and chemicals, and biobased production of transportation fuels and chemicals is expected to contribute significantly towards reaching this objective. This has resulted in the advancement of industrial biotechnology, where microbial fermentation is used for the conversion of bio-based feedstocks to fuels and chemicals (Nielsen and Jewett, 2008; Tang and Zhao, 2009; Otero and Nielsen, 2010; Du et al., 2011; Sauer and Mattanovich, 2012). Not only has this resulted in a significant expansion of traditional processes such as bioethanol production, which has increased from 10 billion liters produced in 2010 to 75 billion liters produced in 2012, but it has also resulted in the introduction of novel processes for the production of chemicals that can be used for the production of polymers, e.g. lactic acid that goes into poly-lactate and 1,3 propanediol that goes into Sorona®. With these successes the chemical industry is looking into the development of other processes for the production of platform chemicals that can find application in the manufacturing of solvents and polymers. Traditionally the fermentation industry used naturally producing microorganisms, but today there is a focus on using a few microorganisms, often referred to as platform cell factories, and then engineering their metabolism such that they efficiently can produce the chemical of interest. This engineering process is referred to as metabolic engineering, and it involves the introduction of directed genetic modifications. Due to the complexity of microbial metabolism, both due to the large number of interacting reactions and the complex regulation, there has been an increasing focus on the use of mathematical models for the identification of metabolic

* Corresponding author at: Fraunhofer-Chalmers Centre, Chalmers Science Park, SE-412 88 Go teborg, Sweden.
E-mail address: joachim.almquist@fcc.chalmers.se (J. Almquist).

http://dx.doi.org/10.1016/j.ymben.2014.03.007
1096-7176/© 2014 The Authors Published by Elsevier Inc. On behalf of International Metabolic Engineering Society. This is an open access article under the CC BY-NC-SA license (http://creativecommons.org/licenses/by-nc-sa/3.0/).

engineering targets (Patil et al., 2004; Cvijovic et al., 2011; Wiechert and Noack, 2011; Soh et al., 2012).

Industrial biotechnology can benefit from mathematical models by using them to understand, predict, and optimize the properties and behavior of cell factories (Tyo et al., 2010). With valid models, improvement strategies can be discovered and evaluated in silico, saving both time and resources. Popular application of models thus includes using them to suggest targets for metabolic engineering leading to increases in yield, titer, and productivity of a desired product. Since these quantities not only depend on the genetic constitution of cells but to a large extent also on how the cells are utilized, models can additionally play a critical role in the optimization and control of the bioreactor and fermentation processes. Other possible model focus includes expanding the range of cell factory substrates, minimizing the formation of undesired by-products, increasing product quality, and guidance in the choice of cell factory when introducing a novel product.

Many biological processes or systems of importance to biotechnology, such as the metabolism of a cell culture during a fed-batch process, cellular stress responses, or the decision making during the cell cycle, are non-stationary in their nature. These systems are characterized by their dependence on time and the fact that the effect of inputs to the systems depends on the systems history. The most common way of modeling such dynamic systems is to set up mathematical expressions for the rates at which biochemical reactions of the systems are taking place. The reaction kinetics are then used to form mass balance equations which in turn describe the temporal behavior of all biochemical species present in the modeled system. Mathematical models of this type are usually referred to as kinetic models but the literature sometimes tends to use the terms dynamic and kinetic models interchangeably due to their largely overlapping concepts as far as biological models are concerned. Reaction kinetics being the fundamental building block of kinetic models, they are clearly distinguished from the large body of so-called genome-scale metabolic models (GEMs) which mainly focus on the stoichiometry of reactions (Thiele et al., 2009; Sohn et al., 2010; Chung et al., 2010; Österlund et al., 2012). Although kinetic models are frequently being used to describe dynamic behaviors, they are equally important in the study of processes that may be stationary or close to stationary, such as cell metabolism during exponential phase, since they can relate the properties of a (quasi) steady-state to the kinetic properties of the model components.

This review looks at the work-flow and methods for setting up, analyzing, and using kinetic models, focusing on models and modeling methodology with relevance for industrial biotechnology. The paper is divided into three main parts. The first part discusses and describes different aspects of the model building procedure, including defining the model focus, how to set up a model structure, determine parameter values and validate the model. The second part looks at how kinetic models have been used once they are set up. Applications of kinetic cell factory models for improving production, substrate utilization, product quality, and process design are reviewed. In the last part, a number of advantages and challenges of kinetic modeling are listed and some future perspectives of kinetic modeling in biotechnology are discussed. A complete overview of the organization can be found in Table 1. To increase the readability, especially for readers who are not experienced modelers, parts of the material which are of technical or mathematical nature are displayed in special boxes. The models and methods on which this review has been based have been supplied by the partners of SYSINBIO (Systems Biology as a Driver for Industrial Biotechnology, a coordination and support action funded by the European commission within the seventh framework programme) and through a thorough literature review.

Table 1
Organization of this review.

Contents		
1	Introduction	2
2	Setting up kinetic models – Modeling framework	4
	2.1 Purpose	7
	2.2 Model structure	8
	2.2.1 Representation of network structure	12
	2.2.2 Kinetic rate expressions	13
	2.2.3 Approximate kinetic rate expressions	14
	2.2.4 Stochastic kinetics	15
	2.3 Parameter determination	16
	2.3.1 Computing the estimate	17
	2.3.2 Identifiability analysis and experimental design	18
	2.3.3 Model reduction	21
	2.4 Validation	22
3	Using kinetic models	23
	3.1 Improving production	23
	3.1.1 Local parameter sensitivity analysis	24
	3.1.2 Simulating larger changes	27
	3.1.3 Optimization problems	29
	3.2 Improving substrate utilization	30
	3.3 Improving product quality	31
	3.4 Improving process design	32
4	Advantages, challenges and perspectives	34
	4.1 Advantages	34
	4.2 Challenges	36
	4.3 Perspectives	39

2. Setting up kinetic models – Modeling framework

The kinetic modeling procedure can be divided into a number of steps which are illustrated in Fig. 1. Since the choices and decisions made at the different steps are dependent both on the objective of the modeling and on the previous steps, the exact details of how a model is set up will be different from case to case. Also, some steps will probably have to be iterated several times before a complete model can be presented (van Riel, 2006). For instance, the model structure will most certainly evolve during the model building process, having new elements added and other removed or changed. Parameter estimation may have to be performed again as new data sets are collected, and different types of analysis on the finished model may lead to new applications that was not initially foreseen. This type of iterative work-flow is not unique for kinetic models of cell factories, but apply for modeling efforts in general (Ljung, 1987). The steps of the kinetic modeling procedure are now described briefly, and then followed by elaboration and in-depth discussions on some of their aspects.

Purpose: The first step of modeling is to define the purpose of the model, an important step as it includes the very reason for setting up a model in the first place. Typical questions are: Why do we model? What do we want to use the model for? What type of behavior should the model be able to explain? The majority of the goals of modeling cell factories are related to understanding and predicting their behavior when perturbing them either internally through genetic modifications, or externally by changing various environmental factors. The model purpose defines the complexity of the modeling problem and will influence all subsequent steps of the modeling procedure.

Network structure: The model network structure is the wiring diagram of the model. It defines the network of interconnected elements that are assumed to be important for the modeling task in question. For instance, it will contain elements such as compartments, concentrations of metabolites, enzymes and transcripts, and reactions (including transport across membranes),

UNCORRECTED PROOF

Download English Version:

https://daneshyari.com/en/article/6494582

Download Persian Version:

https://daneshyari.com/article/6494582

Daneshyari.com