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Hybrid simulation-optimization based approach for the optimal design of single-product biotechnological processes

Robert Brunet[a], Gonzalo Guillén-Gosálbez[a,*], J. Ricardo Pérez-Correa[b], José Antonio Caballero[c], Laureano Jiménez[a]

[a] Departament d'Enginyeria Quimica, Escola Tecnica Superior d'Enginyeria Quimica, Universitat Rovira i Virgili, Campus Sescelades, Avinguda Paisos Catalans 26, 43007 Tarragona, Spain
[b] Departamento de Ingenieria Quimica y Bioprocesos, Pontificia Universidad Catolica de Chile, Casilla 306, Correo 22, Santiago de Chile, Chile
[c] Departmento de Ingenieria Quimica, Universidad de Alicante, Aparatado de Correos 99. 03080 Alicante, Spain

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ABSTRACT

In this work, we present a systematic method for the optimal development of bioprocesses that relies on the combined use of simulation packages and optimization tools. One of the main advantages of our method is that it allows for the simultaneous optimization of all the individual components of a bioprocess, including the main upstream and downstream units. The design task is mathematically formulated as a mixed-integer dynamic optimization (MIDO) problem, which is solved by a decomposition method that iterates between primal and master sub-problems. The primal dynamic optimization problem optimizes the operating conditions, bioreactor kinetics and equipment sizes, whereas the master levels entails the solution of a tailored mixed-integer linear programming (MILP) model that decides on the values of the integer variables (i.e., number of equipments in parallel and topological decisions). The dynamic optimization primal sub-problems are solved via a sequential approach that integrates the process simulator SuperPro Designer® with an external NLP solver implemented in Matlab®. The capabilities of the proposed methodology are illustrated through its application to a typical fermentation process and to the production of the amino acid L-lysine.

1. Introduction

Because of their potential to produce high-value products in human health and care, bioprocesses have recently gained wider interest. The recent boost in competitiveness for customers and new products experienced in this sector has created a clear need for modeling and optimization tools to assist decision-makers in the early stages of the process development.

A bioprocess is a special type of chemical process that produces biochemical products (e.g. antibiotics, proteins, amino acids, etc.) from microorganisms or enzymes. Bioprocesses share some common features with general chemical processes, but differ in their kinetics of product formation, process structure (unit operations and procedures) and operating constraints (Heinzle, Biwer, & Cooney, 2006a).

Optimization approaches devised so far in biotechnology have primarily focused on the bioreactor step. Cuthrell and Biegler (1989) optimized a fed-batch reactor for penicillin production with a solution strategy based on successive quadratic programming (SQP) and orthogonal collocation on finite elements. Carrasco and Banga (1997) addressed the dynamic optimization of batch and fed-batch reactors using stochastic optimization algorithms. More recently, Banga, Moles, Balsa-Canto, and Alonso (2005) introduced a new solution method for this problem based on control parameterization, whereas Sarkar and Modak (2005) proposed the use of genetic algorithms in this context. For an extensive review of dynamic optimization of bioreactors, the reader is referred to Banga, Moles, Balsa-Canto, and Alonso (2003).

Another area related with the bioreactor step that has received attention in the literature is the optimization of metabolic networks. Raghunathan, Pérez-Correa, and Biegler (2003) addressed the data reconciliation and parameter estimation problems in metabolic networks, whereas Guillen-Gosálbez and Sorribas (2009) and Pozo et al. (2010) have proposed deterministic global optimization techniques for kinetic models of metabolic networks that assist in biotechnological and evolutive studies.

In contrast to these approaches, the optimization of complete bioprocesses considering all their individual steps has received very little attention to date. This can be attributed to the fact that these problems lead to complex formulations that integrate structural and operating decisions, some of which change over time. To the

* Corresponding author. Tel.: +34 977558618.
E-mail address: gonzalo.guillen@urv.cat (G. Guillén-Gosálbez).

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Nomenclature

Abbreviations

CF	centrifuge
COM	component object module
DAEs	differential-algebraic equations
MF	microfilter
MIDO	mixed-integer dynamic optimization
MILP	mixed-integer linear programming
MINLP	mixed-integer non-linear programming
NLP	non-linear programming
ODE	ordinary differential equation
RVF	rotary vacuum filter
SQP	successive quadratic programming
STY	space time yield (g/L h)
Y_{oa}	overall yield (g/g)

Indices

a	algebraic
d	differential
f	final
i	intermedium
m	unit type selected
n	units in parallel
k	iterations
p	equality
q	inequality

Variables

K_M	substrate concentration at half max. rate (g/L)
NPV	net present value ($)
S	substrate concentration (g/L)
STY	space-time yield (g/L h)
VVM	volume of air per volume of liquid per min
Y_{oa}	overall-yield (g/g)
μ	specific growth rate (g/L h)
μ_{max}	maximum specific growth rate (g/L h)

Bioreaction parameters

c_L	oxygen concentration (g/L)
c_P	product concentration (g/L)
c_S	substrate concentration (g/L)
c_{SF}	substrate concentration in the feed (g/L)
c_{slN}	initial substrate concentration (g/L)
c_{Thr}	threonine concentration (g/L)
c_x	biomass concentration (g/L)
F	feed rate (L/h) or (m^3/h)
K_La	specific mass transfer coefficient (1/h)
K_{IP}	product inhibition constant (g/L)
K_{IThr}	threonine inhibition constant (g/L)
K_O	substrate oxygen affinity constant (g/L)
K_{PS}	product affinity constant (g/L)
K_s	substrate carbon source affinity constant (g/L)
K_{Thr}	substrate threonine affinity constant (g/L)
L_{O_2}	oxygen solubility (mol/L/bar)
mo	specific oxygen consumption for maintenance (g/L)
ms	specific substrate consumption for maintenance (g/L)
OTR	oxygen transfer rate (mol/L h)
P_R	reactor pressure (bar)
r_p	rate of lysine production (g/L h)
STY	space time yield (g/L h)
t	time (h)
V	fermentor filling volume (m^3)
y_l	mole fraction of oxygen in the liquid phase (mol/mol)
y_{o_2}	mole fraction of oxygen in the gas phase (mol/mol)
Y_{oa}	overall yield (g/g)
$Y_{P/O}$	product yield per amount of oxygen (g/g)
$Y_{P/S}$	product yield per amount of substrate (g/g)
$Y_{x/s}$	biomass yield per amount of substrate (g/g)
$Y_{x/o}$	biomass yield per amount of oxygen (g/g)
$Y_{x/Thr}$	biomass yield per amount of threonine (g/g)
a_p	growth-associated coefficient for product synthesis (g/g)
b_p	non-growth-associated coefficient for product synthesis (g/g h)
μ	specific growth rate (1/h)
μ_{max}	maximum specific growth rate (1/h)

best of our knowledge, the work by Groep, Gregory, Kershenbaum, and Bogle (2000), is the only one that addressed the optimization of a entire bioprocess (i.e., production of an intracellular enzyme alcohol dehydrogenase). This pioneering work has two main limitations: (i) it assumed a fixed plant topology; and (ii) it applied a simple sensitivity analysis to optimize the operating variables of the process that is not guaranteed to converge to a local (or global) optimum.

Hence, it seems clear that the rich theory available for synthesizing standard chemical process flowsheets has not been applied to the same extent to their biochemical counterparts. In fact, the design of bioprocess flowsheets is nowadays typically accomplished by empirical and/or intuitive methods such as rules of thumb or simple heuristics (Koulouris, Calandranis, & Petrides 2000; Petrides, Calandris, & Cooney, 1996; Petrides, Papavasileiou, Kolouris, & Siletti, 2006; Wong, Oh, & Kuek, 2004) that are likely to lead to sub-optimal process alternatives.

With this observation in mind, the aim of this paper is to present a systematic tool for the design of bioprocesses that relies on the combined use of simulation and optimization techniques. More precisely, the design task is formulated as a mixed-integer dynamic optimization (MIDO) problem, which is solved by a hybrid simulation-optimization decomposition method that exploits the complementary strengths of optimization tools (i.e., nonlinear programming, NLP, and mixed-integer linear programming, MILP) and commercial bioprocess simulators (i.e., SuperPro Designer®). Our methodology has been tested using two different examples: a typical fermentation process and the production of the amino acid L-lysine.

2. Problem statement

The problem addressed in this article can be formally stated as follows. Given are the demand and prices of final products, cost parameters, including capital investment and operating cost data (i.e., raw materials and utilities cost), time horizon, thermodynamic properties and performance models of the equipment units embedded in the flowsheet, including the bioreactor kinetics. The goal of the analysis is to determine the optimal process design, including type and size of process units (e.g., centrifuge, decanter, filtration, etc.), number of equipment units in parallel and operating conditions (concentrations, flow rates, temperatures, etc.) that maximize a given economic performance indicator over a specified time horizon.

In this work, we consider single-product batch plants that can operate with more than one equipment unit (in parallel) per stage.