Journal of Process Control 53 (2017) 95–105

Contents lists available at ScienceDirect

Journal of Process Control

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

Operation of a mechanically agitated semi-continuous multi-enzymatic reactor by using the Pareto-optimal multiple front method

Gheorghe Maria*, Mara Crişan

University Politehnica of Bucharest, Department of Chemical & Biochemical Engineering, Polizu Str. 1, 011061 Bucharest, P.O. 35-107, Romania

ARTICLE INFO

Article history:
Received 18 August 2016
Received in revised form 6 December 2016
Accepted 7 February 2017
Available online 11 March 2017

Keywords:
Mechanically agitated semi-continuous enzymatic reactor optimization
D-glucose oxidation
Pyranose oxidase
Catalase
Pareto-optimal fronts
Optimal operating policies

ABSTRACT

One essential engineering problem when developing an industrial enzymatic process concerns the choice of the reactor operating alternative based on à-priori knowledge of the process kinetics and enzyme inactivation characteristics. For a multi-enzymatic system, involving complex interactions among enzymes that exhibit optimal activity on different parametric domains, and a high-order deactivation, this problem requires an extended analysis. The optimization and control engineering problems become very challenging due to the process high nonlinearity and the presence of a large number of complex constraints. All these will translate into a multi-objective optimization problem to be solved for each case. An elegant option developed in this paper is to obtain sets of Pareto optimal solutions, also called Pareto-optimal fronts, successively generated for pairs of adverse objectives. Then, the final choice of the enzymatic reactor operating policy results from the comparative analysis of these Pareto-fronts. Exemplification is made for the complex case of the oxidation of D-glucose (DG) to 2-keto-D-glucose (kDG) in the presence of P2Ox (Pyranose oxidase, EC 1.1.3.10) and catalase, continuously operated in a three-phase mechanically agitated semibatch reactor (MASCR) with co-immobilized enzymes on alginate beads. Optimal operating policy choice is based on the minimum amount of required P2Ox that ensures an imposed reaction conversion and maximum reactor productivity under various technological constraints, and for catalase/P2Ox ratios of 200–300 U/U.

1. Introduction

Over the last decades it was a continuous trend to replace complex chemical syntheses, energetically intensive and generating toxic wastes, with biosynthesis processes to produce fine-chemicals or organic compounds in food, pharmaceutical, or detergent industry, by using enzymatic or cell culture in batch, semi-batch (fed-batch), fixed-bed or fluidized-bed reactors [1,2]. Among these, it is worth mentioning, the production of monosaccharide derivatives, organic acids, alcohols, amino-acids, etc., by using single- or multi-enzymatic reactors, or the production of baker's yeast, food products and additives, recombinant proteins (enzymes, vaccines), or biopolimers by using bioreactors with cell cultures [3–5].

When developing a new complex enzymatic process, of known characteristics, several essential difficult engineering problems have to be solved related to biocatalyst design, process integration, and cost minimization [6]. The first problem concerns the optimal choice of the reactor type based on a satisfactory cost/reactor productivity trade-off, that is continuous mixing tank reactor vs. plug-flow operation mode, batch/semi-batch vs. continuous reactors, and enzyme utilization (free/suspended vs. immobilized enzyme in gel/solid porous beads). This analysis can be better performed in a systematic way based on the process and reactor models, by comparing the optimal operation policies determined in respect to several formulated objectives [2,7,8].

For a given reactor type the next crucial problem is to determine the optimal operating and control policy on a cost/productivity basis. Solving such an optimization problem is not an easy task, depending on the process complexity and characteristics (kinetics), enzyme activity and stability domains, the presence of a large number of nonlinear constraints, and contrary objectives. For instance, in the bioreactor case, these objectives (reviewed by Scoban, and Maria [10]) are mainly related to the bioreactor productivity, maximum usage of biomass, and minimum fluctuations in the output variables (related to the reactor productivity).

* Corresponding author.
E-mail address: gmaria99m@hotmail.com (G. Maria).

http://dx.doi.org/10.1016/j.jprocont.2017.02.004
0959-1524/

Nomenclature

a_s	L-S specific interfacial area
c_j	Species j concentration
$D_{j,e}$	Effective diffusivity of species j in the solid particle
D_L,D_m	Diffusion coefficients in liquid
d_p	Particle diameter
d_r	Reactor diameter
f	P2Ox enzyme solution feed flow rate
g	Constraint function vector, or gravitational acceleration
H,H	Model function vector, or reactor length
k_j, k_c, k_d, K_j	Rate constants
$k_{oxl}a$	Overall gas-liquid mass transfer coefficient
k_s	L-S mass transfer coefficient (on liquid side)
M	Molecular weight
m	Mass
n	Yano-Koya exponent
N_{div}	Number of equal divisions of the running time t_f
$Re_L = (\Sigma_L d_p^4 \rho_L^3)/\mu_L^3$	Reynolds number (liquid)
r_j	Species j reaction rate
$Sc_L = \mu_L/(\rho_L D_{S,L})$	Schmidt number (liquid)
$Sh = (k_s d_p)/D_{S,L}$	Sherwood number
t	Time
t_f	Final running time
u	Control variable vector
$u_{s,L}$	Liquid superficial velocity
V	Liquid volume
V_r	Reactor volume
v_m	Maximum reaction rate
x, x	Conversion, or state variable vector
Y	Stoichiometric coefficient

Greek symbols

α,β,Ψ	Model constants used in evaluation of the particle effectiveness
Δ	Finite difference
ε_L	Volume fraction of the liquid in the bed
ε_p	Particle porosity
ε_s	Volume fraction of particles in the bed
Φ	Optimisation objective function
φ	Operating parameter vector, or thiele modulus
ϕ_C	Carman shape factor (Trambouze et al. [31])
η	Effectiveness factor
μ_L	Dynamic viscosity of the liquid
μ_m	Turnover number of the main reaction
ρ	Density
ξ	Time for batch/semi-batch operation, and residence time for continuous operation
Σ_L	Power dissipated per unit mass of liquid
$\tau = V/f_o$	Contact/residence time in the continuous reactor
τ_p	Particle tortuosity

Index

app	Apparent
f	Final
in	Inlet
L	Liquid
min	Minimum
max	Maximum
o	Initial
out	Outlet
p	Particle
s	at liquid (L) – solid (S) interface, or on the solid particle (enzyme support)
S	Substrate
w	Water

Superscripts

^	Estimated
*	Saturation

Abbreviations

ABTS	2.2′-azinobis(3-ethylbenzthiazoline-6-sulfonic acid
DG	D-glucose
DO	Dissolved oxygen
kDG	2-keto-D-glucose
E	P2Ox enzyme
L-S	Liquid-solid
M	Molar
MASCR	Mechanically agitated solid-liquid continuous reactor
NAD(P)H	Nicotinamide adenine dinucleotide (phosphate)
P2Ox	Pyranose oxidase
PF	Pareto optimal front
S	Substrate
SP	Setpoint
W	Water

For the multi-enzymatic reactors, solving this multi-objective optimization problem is even more difficult due to complex interactions among reactions and enzymes that exhibit optimal activity on different parametric domains, and a high-order deactivation. Determination of the optimal operation mode (enzyme feeding policy, and their ratio) leading to reactor performance maximization, along with enzyme consumption minimization usually turn into a difficult multi-objective optimization problem to be solved for every particular system, due to the presence of a large number of specific constraints [9]. Multi-objective performance criteria, including economic benefits, investment, operating and materials costs, quality and control aspects, are currently used to derive feasible optimal solutions for a wide range of enzymatic reactors [14–16], using specific numerical algorithms [17]. Finally, enzyme selection has to be based on economic aspects related to enzyme (immobilization) cost and stability (half-life), carrier loading capacity, enzyme activity and recovery possibilities [13].

In spite of their difficult operation, multi-enzymatic reactors are more and more employed in the biosynthesis industry. In general, employment of a bi-enzymatic system follows one of the following patterns [20]: I) Binding two (or more) enzymes to the same support so that the substrate for the second enzyme is generated *in-situ* as the first reaction step occurs (e.g. the H_2O_2 removal by catalase as it is formed in oxidative processes; this is also the approached case here) [9]; ii) The second reaction regenerates the co-factor of the first enzymatic reaction (e.g. regeneration of NADPH [44]); iii) The second reaction shifts equilibrium to remove the intermediate or by-product from the system (e.g. removal of pyruvic acid as lactate by lactate dehydrogenase in the presence of NADH [20]); iv) The second enzyme removes the biomass excess by hydrolysis, or prolongs the life of the first one by a certain mechanism (e.g. catalase prolongs the life of P2Ox used in the present study for D-glucose oxidation by decomposing the H_2O_2 by-product; [21]).

To assist such a reactor design/control step, Maria [2]. developed a computational modular platform that is capable, for a given enzymatic process of known kinetics, to evaluate and compare the optimal performances of various reactors, or performances of vari-