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Constant specific growth rate in fed-batch cultivation of *Bordetella pertussis* using adaptive control

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Abstract

Monitoring and control of production processes for biopharmaceuticals have become standard requirements to support consistency and quality. In this paper, a constant specific growth rate in fed-batch cultivation of *Bordetella pertussis* is achieved by a newly designed specific growth rate controller.

The performance of standard control methods is limited because of the time-varying characteristics due to the exponentially increasing biomass and volume. To cope with the changing dynamics, a stable model reference adaptive controller is designed which adapts the controller settings as volume and biomass increase. An important asset of the design is that dissolved oxygen is the only required online measurement.

An original design without considering the dissolved oxygen dynamics resulted experimentally in oscillatory behaviour. Hence, in contrast to common believes, it is essential to include dissolved oxygen dynamics. The robustness of this novel design was tested in simulation.

The validity of the design was confirmed by laboratory experiments for small-scale production of *B. pertussis.* The controller was able to regulate the specific growth rate at the desired set point, even during a long fed-batch cultivation time with exponentially increasing demands for substrates and oxygen.

Keywords: Model-reference adaptive control; Biopharmaceuticals; Fed-batch cultivation; Specific growth rate; Dissolved oxygen; *Bordetella pertussis*

1. Introduction

Monitoring and control of production processes for biopharmaceuticals have become standard requirements to support consistency and quality. Recently, FDA encourages with its view on process analytical

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Nomenclature

a, b, c, d	constants for dual substrate model of *Bordetella pertussis*
C	nominal value of controller (mmol l^{-1})
C_G	glutamate concentration (mmol l^{-1})
C_{G0}	initial glutamate concentration (mmol l^{-1})
C_L	lactate concentration (mmol l^{-1})
C_{L0}	initial lactate concentration (mmol l^{-1})
C_X	biomass concentration (OD)
C_{X0}	initial biomass concentration (OD)
$\hat{C}_X$	software sensor biomass concentration (OD)
C_G^{in}	glutamate concentration in the feed (mmol l^{-1})
C_L^{in}	lactate concentration in the feed (mmol l^{-1})
DO	dissolved oxygen, oxygen concentration in the medium (mmol l^{-1})
DO_{set}	set point for oxygen concentration in the medium (mmol l^{-1})
DO_{sensor}	oxygen concentration measured by the sensor (mmol l^{-1})
E	objective function
E_{DO}	relative variation of DO
E_μ	relative variation of μ
f_G	Monod kinetics for glutamate
f_L	Monod kinetics for lactate
F_{O_2}	(enriched) airflow through the headspace (l h^{-1})
F_1	"proportional" correction substrate feed rate (l h^{-1})
F_2	feed rate by prior calculation (l h^{-1})
F_3	integral correction substrate feed rate (l h^{-1})
F_{G+L}^{in} F_{tot}	total substrate feed rate (glutamate + lactate) (l h^{-1})
ISE	integral squared error (h^{-1})
k_La	oxygen transfer coefficient (h^{-1})
K_C	gain for dissolved oxygen control
K_G	Monod constant on glutamate (mmol l^{-1})
K_L	Monod constant on lactate (mmol l^{-1})
K_1, K_2	gains for specific growth rate control
K_C^h	gain for headspace control
LPS	lipopolysaccharide
m_G	maintenance coefficient on glutamate (mmol OD^{-1} h^{-1})
m_L	maintenance coefficient on lactate (mmol OD^{-1} h^{-1})
m_O	maintenance coefficient on oxygen (mmol OD^{-1} h^{-1})
O_2^a	auxiliary oxygen concentration (mmol l^{-1})
O_2^h	oygen concentration in the headspace (mmol l^{-1})
O_2^{in}	oygen concentration in the incoming air (mmol l^{-1})
OD	optical density at 590 nm (OD_{590} ml^{-1})
OTR	oxygen transfer rate (mmol l^{-1} h^{-1})
OUR	oxygen uptake rate (mmol l^{-1} h^{-1})
OUR_{noise}	noise on the oxygen uptake rate (mmol l^{-1} h^{-1})
PRN	Pertactin
rpm	rounds per minute
t	cultivation time (h)
v, w	constants for normalised Monod equations
V	liquid volume (l)
$\hat{V}$	software sensor liquid volume (l)
V_h	volume of the headspace (l)
Y_{G1}	yield on glutamate over pathway 1 (OD mmol^{-1})
Y_{G2}	yield on glutamate over pathway 2 (OD mmol^{-1})
Y_L	yield on lactate (OD mmol^{-1})
Y_O	yield on oxygen (OD mmol^{-1})

Greek letters

β	ratio between normalised Monod equations
β_1, β_2	convergence speed of reference model
γ_1, γ_2	tuning parameters for MRAC
μ	specific growth rate (h^{-1})
$\hat{\mu}$	software sensor specific growth rate (h^{-1})
μ_{enh}	enhanced specific growth rate (h^{-1})
μ_{max}	maximum specific growth rate (h^{-1})
μ_{set}	set point specific growth rate (h^{-1})
$\hat{\mu}_0$	initial software sensor specific growth rate (h^{-1})