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Glucose concentration control of a fed-batch mammalian cell bioprocess using a nonlinear model predictive controller

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ABSTRACT

A non-linear model predictive controller (NMPC) was investigated as a route to delivering improved product quality, batch to batch reproducibility and significant cost reductions by providing a means for better controlling the bioreactor environment in a Chinese hamster ovary (CHO) mammalian cell fed-batch process.

A nonlinear fundamental bioprocess model was developed to represent the CHO mammalian cell fed-batch bioprocess under study. This developed nonlinear model aided in the configuration and tuning of a NMPC through off-line simulation. The tuned NMPC was applied to a 15 L pilot-plant bioreactor for glucose concentration fixed set-point control. Traditionally, bioprocesses are characterized by long critical process parameter (CPP) measurement intervals (24 h). However, advances in PAT have helped increase CPP measurement frequency. An in situ Kaiser RXN2 Raman spectroscopy instrument was used to monitor the glucose concentration at 6 min intervals.

Glucose concentration control of a bioreactor is not a trivial task due to high process variability, measurement noise and long measurement intervals. Nevertheless, NMPC proved successful in achieving closed loop fixed set-point control in the presence of these common bioprocess operation attributes.

1. Introduction

The biopharmaceutical sector represents a significant and growing division of the general pharmaceutical industry. The number of biopharmaceuticals currently on the market is just in excess of 200 and in 2009, they generated $99 billion in sales. The market is predicted to grow between 7 and 15% annually over the next several years and by 2013, four of the five top-selling drugs will be protein-based products [1].

The control of bioprocesses is in its infancy in comparison to the chemical and traditional pharmaceutical sectors. This is due in part to the challenges associated with bioreactor control: poor process understanding, the lack of measurement of relevant process parameters and difficulties inherent in controlling bioprocesses which are dynamic, complex and non-linear. Process control of bioreactors seeks to influence the complex intracellular reactions of billions of cells by controlling their extracellular environment [2].

Historically it has been observed that mammalian cell numbers and total protein productivity can be dramatically increased with lowered process concentrations of the byproducts associated with mammalian cell metabolism. The main byproducts of mammalian cell metabolism are lactate and ammonia which result from glucose and glutamine consumption, respectively. Controlling the glucose and glutamine concentrations in a bioreactor to reduced levels forces a metabolic shift, which results in cells becoming much more efficient in their use of the available nutrients [3,4].

Current industrial control of nutrient levels is predominately manual. Bolus feeds are generally introduced at 24 h intervals based on off-line analysis of daily process samples and *a priori* process knowledge [5,6]. However, these feeding strategies are labor intensive involving sampling, recalculation, and manual adjustments.

To reduce batch variation and improve process economics, many biopharmaceutical manufacturers aim to move beyond today's "quality-by-inspection" methodology and adopting quality by design (QbD) methods under the FDA's process analytical technologies (PAT) initiative. These methods center on measuring critical quality attributes and critical process parameters during processing. Application of the latest sensor technologies such as mass and Raman spectroscopy enables cell characteristics as well as substrate and metabolic byproduct concentrations to be measured online or at-line in a bioreactor [7]. Timely availability of such data helps improve the operators' knowledge of the bioprocess and thus enhances model development and the creation of

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Nomenclature

A	ammonia concentration (mM)
C_i	inhibitor concentration (mM)
C_{i^*}	inhibitor saturation concentration (mM)
d	magnitude of process-model mismatch (mM)
e	error between process variable and set-point (mM)
F	feed-rate ($L\,h^{-1}$)
G	glucose concentration (mM)
k	sample interval (h)
$k_{d,Q}$	degree of degradation of glutamine (h^{-1})
K_L	lactate saturation constant (mM)
K_A	ammonia saturation constant (mM)
K_G	glucose saturation constant (mM)
K_Q	glutamine saturation constant (mM)
k_d	death rate (h^{-1})
$k_{d,\max}$	maximum death rate (h^{-1})
k_μ	intrinsic death rate (h^{-1})
K_{LYSIS}	rate of cell lysis (h^{-1})
L	lactate concentration (mM)
m_G	glucose maintenance coefficient ($mmol\,cell^{-1}\,h^{-1}$)
m_Q	glutamine maintenance coefficient ($mmol\,cell^{-1}\,h^{-1}$)
M	control horizon
P	prediction horizon
Q	glutamine concentration (mM)
q_i	specific inhibitor production rate (h^{-1})
S_G	glucose concentration in the feed (mM)
S_Q	glutamine concentration in the feed (mM)
u	control action ($L\,h^{-1}$)
V	volume (L)
X_T	total cell density ($cells\,L^{-1}$)
X_D	dead cell density ($cells\,L^{-1}$)
X_V	viable cell density ($cells\,L^{-1}$)
y	process variable (mM)
y_{sp}	set-point (mM)
$\hat{y}$	model predictions (mM)
$Y_{A,Q}$	yield of ammonia from glutamine
$Y_{L,G}$	yield of lactate from glucose
$Y_{X,G}$	yield of cells from glucose ($cells\,mmol^{-1}$)
$Y_{X,Q}$	yield of cells from glutamine ($cells\,mmol^{-1}$)

Greek symbols

Γ	diagonal elements of output weight matrix
Λ	diagonal elements of input weight matrix
μ	growth rate (h^{-1})
$\mu_{\max}$	maximum growth rate (h^{-1})

more sophisticated automation and control systems used in such processes.

There are many academic projects focusing on following this trend through the application of automated open and closed loop nutrient concentration control strategies using predefined feeds and feeds determined using on-line or at-line sensors to measure the process variable (PV), respectively [8]. On-line models have also been used to estimate the nutrient concentration with an at-line sensor used to periodically update the model [6]. Lu et al. [8] demonstrated two different automated cell culture control strategies. The first method was based upon on-line capacitance measurements where cultures were fed based on an on-line calculation involving growth and nutrient consumption rates. The second method was based upon automated glucose measurements obtained from the Nova Bioprofile FLEX autosampler (Nova Biomedical, UK) where cultures were fed to maintain a target glucose level by using an on-line feedback calculation.

Lee et al. [9] used a low-glutamine fed-batch feedback control-loop process in attempting to control ammonia and lactate for a 293-HEK mammalian cell bioprocess for adenovirus production .The control algorithm consisted of a simple on-line calculation. Controlling glutamine levels at 0.1 mM, with no other modifications improved cell density and gave a 10-fold improvement in virus titer. Li et al. [10] controlled glucose at 0.3 mM and glutamine at 0.5 mM via an online closed loop feeding calculation, which related to ammonia and lactate levels decreasing by 74% and 63%, respectively. Their cultures extended from eight to 14 days, with a 1.7-fold increase in monoclonal antibody (MAb) titers.

Bioprocesses are inherently nonlinear and are traditionally associated with long nutrient concentration measurement intervals. Furthermore in a PAT environment, where the nutrient concentration is determined online via a spectroscopic technique, measurement noise is prevalent. The aforementioned closed-loop control strategies, based on simple online calculations of the controller output may not be advantageous or optimal for the nutrient concentration control of bioprocesses portraying such attributes.

In this study, nutrient concentration control was accomplished through the application of a model predictive controller (MPC). Model predictive control, also referred to as receding horizon control and moving horizon optimal control, has been widely adopted in industry [11–15] and is currently the most widely used of all model-based advanced control methodologies for industrial applications. Qin and Badgwell [16] presented a survey of industrial model predictive control technology. Originally developed to meet the needs of power plants and petroleum refineries, MPC technology can now be found in a wide range of application areas, including chemicals, food processing, automotive, and aerospace applications [16]. Bioprocess applications of MPC have appeared in a number of academic projects recently. Aehle et al. [17] experimentally applied a MPC to indirectly control the oxygen mass consumed by mammalian cells in a bioreactor by manipulating the glutamine feed-rate. Ashoori et al. [18] simulated the use of MPC based on a detailed model for penicillin production in a fed-batch bioreactor. The main control goal was to get a pure product with a high concentration, by regulating temperature and pH at certain levels.

The name MPC stems from the idea of employing a model of the process to be controlled which is used to predict the future behavior. This prediction capability allows optimal control problems to be solved on-line, where tracking error, namely the difference between the predicted output and the desired reference, is minimized over a future horizon, possibly subject to constraints on the manipulated inputs and outputs. While linear model predictive control (LMPC) has been popular since the 1970s, the 1990s witnessed an increased interest from control theoretists as well as control practitioners in the area of nonlinear model predictive control (NMPC) [19,20] due to the need to operate processes under tighter performance specifications. At the same time, more constraints, stemming, for example, from environmental and safety considerations need to be satisfied. Often these demands can only be met when process nonlinearities and constraints are explicitly considered in the controller. In addition, if the system is highly nonlinear, such as bioprocesses, control based on the prediction from a linear model may result in unacceptable response [21]. In some cases, remarkable static errors exist, and in other cases, oscillation or even instability may occur [22]. Therefore, non-linear models should be used to describe the behavior of a highly non-linear bioprocess system. Nagy [23] applied NMPC to adequately control the nonlinear nature of a bioreactor process.

There are a number of difficulties associated with implementing a NMPC [24–28]. One of the major difficulties is the