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A simple output-feedback strategy for the control of perfused mammalian cell cultures

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ABSTRACT

This paper presents a framework for the multivariable robust control of perfusion animal cell cultures. It consists of a cascade control structure and an estimation algorithm, which provides the unmeasurable variables needed in the design of the control law, and ensures the regulation of the cell and glucose concentrations at imposed levels by manipulating the bleed and the dilution rates. The cascade control structure uses a feedback linearizing controller in the inner loop and linear (PI) controllers in the outer loops, and requires the measurement of the cell concentration and the glucose concentration in the bioreactor. Two approaches are provided: the first one assumes the availability of an approximate model of the process kinetics and uses an extended Kalman filter (EKF) to estimate the system states; the second approach does not require the prior knowledge of the process kinetics. These are estimated from the available measurements using sliding mode observers (SMO). A receding horizon optimization algorithm is employed to (periodically) tune the gains of the outer loop controllers. The proposed framework is easy to implement and tune, and may be applied to a general class of perfusion cell culture systems. Its effectiveness and robustness are illustrated by means of simulation results.

1. Introduction

Many of the important active pharmaceutical ingredients are produced by the cultivation of either genetically modified micro-organisms or animal cells. These cells can grow in suspension in stirred tank reactors (Jain & Kumar, 2008), which may be operated in batch, fed-batch or perfusion mode. Among them, the operation in perfusion mode leads to higher cell density and higher productivity (Komolpis, Udomchokmongkol, Phutong, & Palaga, 2010). However, it also requires tight control to avoid nutrient limitation, accumulation of inhibitory metabolites, retardation in cell growth or even cell wash-out through the cell-containing flow (the bleed), which is necessary to maintain culture viability and to reach a steady state (Banik & Heath, 1995; Dalm, 2004; Ozturk, Thrift, Blackie, & Naveh, 1997).

Control of animal cell cultures in perfusion mode is a delicate task as it usually requires the availability of a process model and of several on-line probes (Gnoth, Jenzsch, Simutis, & Lübbert, 2008). The former requires experimental data collection and model identification, whereas the latter is limited by investment and operational constraints. It is therefore of interest to develop control structures that require a minimum amount of prior process knowledge, and a minimum number of measured signals, while providing robust performance in terms of process variability and measurement errors. Additionally, the perfusion operation of a bioreactor is naturally a multivariable process, whose performance depends on both inputs: the dilution/perfusion rate and the bleed rate. However, it has been controlled for a long time in a suboptimal way as a single input single output system (Dowd, Kwok, & Piret, 2001a, 2001b; Ozturk et al., 1997). Recently, the potential of using the bleed flow (see Fig. 1) in multivariable control structures has been investigated in several simulation studies in view of a prospective practical implementation: Deschênes, Desbiens, Perrier, and Kamen (2006a, 2006b) have developed an adaptive backstepping strategy for a simple model to simultaneously control the cell and metabolite concentrations, while Sbarciog, Saraiva, and Vande Wouwer (2013) have designed a multivariable nonlinear predictive control strategy based on a more realistic model, for accelerating the growth of cells and controlling the substrate concentration in the effluent.

A major issue in controlling cell cultures is the selection of the control criterion, which has to combine the knowledge about the process and the available on-line measurements. Several alternatives have been reported which can be mainly classified as (i) control of the growth rate, to increase system productivity; (ii) control of the metabolite concentrations, to avoid their negative effect such as growth inhibition or death enhancement; (iii) control of the

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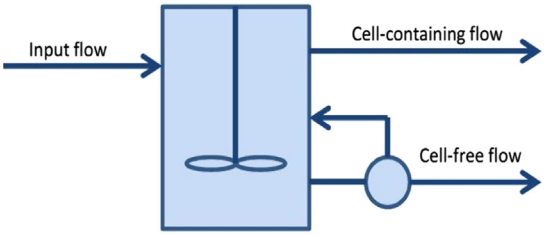

Fig. 1. Schematic representation of the perfusion culture.

substrate concentrations, to minimize the formation of toxic by-products and to avoid the waste of expensive nutrients via the effluent. Each approach has its own advantages and disadvantages. For example, the control of the growth rate, which has long been promoted by many researchers, seems to not have a great impact in the industrial practice. Gnoth et al. (2008) point out that this type of control is more affected by process disturbances and suggest the control of the cell concentration instead, which can be easily estimated in systems without this measurement. On the other hand, numerous (experimental) studies evidence that the control of glucose and glutamine, the two main nutrients, at low levels leads to reduced nutrient consumption as well as to reduced metabolite formation. Hence, the control of the nutrients at appropriate low levels is one of the most important criteria in cell cultures (Xu, Sun, Mathew, Jeevarajan, & Anderson, 2004).

In this study, a cascade control structure (Seborg, Edgar, & Mellichamp, 1989) is proposed to simultaneously control the cell and glucose concentrations in a perfused bioreactor. The control structure consists of an inner loop, which uses a feedback linearization control law (Henson & Seborg, 1997) to cancel, as much as possible, the nonlinearity involved in the reaction kinetics, and two outer loops, which employ simple adaptive PI controllers (Åström & Wittenmark, 1995). It is assumed that only the cell and glucose concentrations are measured, the other variables needed for the controller implementation are estimated from these measurements.

The feedback linearizing strategy is the basis of many works dedicated to the control of biological systems (see, for instance, Henson, 2006 and references therein). However, the feedback linearization heavily relies on the quality of available information (i.e., model accuracy and on-line measurements). To overcome these problems, several authors have employed some on-line adaptation schemes and nonlinear observers to deal respectively with model uncertainty and unpractical measurements (Smets, Claes, November, Bastin, & Van Impe, 2004). For instance, Coutinho and Vande Wouwer (2013) have proposed a robust approach for continuous bioreactors based on a cascaded-loop strategy. Zhu, Zamamiri, Henson, and Hjortso (2000) have proposed a linear model predictive control strategy based on a linear, discrete-time model for the stabilization of oscillating yeast cultures. Mjalli and Al-Asheh (2005) have compared two nonlinear neural networks (feedback linearizing and model predictive control) based algorithms for controlling an ethanol fermentation process. Farza, Nadri, and Hammouri (2000) have proposed nonlinear observers to estimate the specific growth rate which is the key parameter in bioreactor control. Here, two approaches are presented. The first approach assumes that some approximate knowledge on the process kinetics is available and the inner loop controller is tuned to minimize the effect of the unknown dynamics. An extended Kalman filter (EKF) (Jazwinski, 1970), which employs the approximate model of the inner loop, is designed to estimate the unknown process states required for the control law implementation. The second approach does not require any prior knowledge on the structure and parameters of the process kinetics and employs sliding mode observers (SMO) (Friedman, Moreno, & Iriarte, 2011) to estimate the needed rates to render the controlled dynamics linear. The outer loop can in principle make use of any kind of controller (Sbarciog, Coutinho, & Vande Wouwer, 2013b). Here, we have chosen the PI controller for its simplicity and wide use in controlling cultivation processes (Gnoth et al., 2008).

The novel contribution of this paper is twofold. On the one hand, the perfusion cell culture process is regarded as a multivariable system. Hence a multivariable control structure is proposed to simultaneously manipulate the two process inputs, i.e., the dilution rate and the bleed rate, which are equally important in the efficient operation of the process (presently, such studies are scarce). On the other hand, the potential complexity associated with the regulation of a nonlinear process is significantly reduced by combining principles and tools widely used in control engineering practice, such as the partial feedback linearization approach, and the cascade structure with a simple controller in the outer loop. In addition, state estimation schemes, either the classical EKF or the more fancy SMO, are showing excellent performance and robustness in combination with the proposed control scheme. Moreover, we propose a framework, which is not restricted to a specific process, but may be applied to a general class of cell culture systems.

The paper is organized as follows. The next section introduces the class of perfused cell culture systems to which the framework applies, and presents a realistic model that will be used as a case study. Section 3 details the control structure. Firstly, the kinetics-based feedback linearizing controller and the EKF are developed and the accuracy of the proposed estimation scheme is illustrated in the presence of parametric uncertainty and measurement noise. Secondly, the sliding mode observers based on the super-twisting algorithm are introduced and their accuracy is illustrated, and the kinetics-independent feedback linearizing controller is presented. Thirdly, the implementation of the PI controllers, including an anti-windup mechanism, and the receding horizon tuning algorithm are discussed. Section 4 illustrates the effectiveness and robustness of the proposed control scheme by means of simulation results for the two approaches. In the end conclusions are drawn.

2. System dynamics

The growth of animal cells is a complex process, which requires the supply of fresh medium rich in nutrients of which some components may be quite expensive. The dynamics of such systems have been modelled with different degrees of details, the existing models ranging from metabolic networks to macroscopic models. Independent of the cell line used, the components which play a crucial role in animal cell cultures are the cells, the two main nutrients glucose and glutamine and the two main by-products lactate and ammonia. All macroscopic models, built on mass balance principles, include the concentrations of these components as state variables. In perfusion operation (Fig. 1), fresh medium is fed to replenish the consumed nutrients, while an equal volume of spent medium is continuously withdrawn, allowing for the removal of inhibitory components. Cells are retained or recycled back to the reactor by some type of retention device (for instance an acoustic filter). Hence, a general model for perfusion animal cell cultures may be written as

$$\dot{\boldsymbol{\xi}} = D \cdot \boldsymbol{\xi}_{in} - D \cdot \mathbf{F} \cdot \boldsymbol{\xi} + \mathbf{K} \cdot \mathbf{r}(\xi) \tag{1}$$

where $\boldsymbol{\xi} \in \mathbb{R}^{+5}$ (the set of positive real vectors of dimension 5) represents the state vector which is composed of the concentrations of cells, glucose, glutamine, lactate and ammonia; $\boldsymbol{\xi}_{in} \in \mathbb{R}^{+5}$ is the vector of component concentrations in the influent, which