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Development of a recursive time series model for fed-batch mammalian cell culture

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ABSTRACT

Recursive time series models are developed in this work for a fed-batch mammalian cell culture producing monoclonal antibodies, with key culture variables measured at different sampling frequencies. Glucose and glutamine feed rates are considered as inputs. A composite of an autoregressive moving average with exogenous input model and a dual rate-autoregressive with exogenous input model is used. Appropriate parameter constraints are imposed in parameter estimation algorithms and stability of these is examined and ensured. The data required for parameter estimation are generated from simulated fed-batch experiments using a well-tested first principles model. The predictions for glucose, glutamine, and viable cell concentrations track very well the data for these, with the errors for the high prediction horizons considered being limited to 10% or less. The prediction accuracy can be increased further if data from prior experiments with dynamic similarities are available. The models can be used reliably for model predictive control.

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1. Introduction

The demand for biopharmaceuticals produced from animal cell cultures has been on the rise due to their therapeutic and diagnostic applications (Butler, 2005; Lovrecz et al., 2014; Scott et al., 2012; Walsh, 2014; Wurm, 2004). Monoclonal antibodies (MAbs), produced by Chinese Hamster Ovary cells and hybridoma cells, account for nearly 40% of the sale of biologics in the U.S. (Aggarwal, 2014; De Jesus and Wurm, 2011). Cell growth is promoted by glucose and glutamine (Jang and Barford, 2000, 2002; Vriezen et al., 1997; Zeng and Deckwer, 1995) or glutamate (Berry et al., 2015; Capito et al., 2015; Gramer, 2014; Kyriakopoulos and Kontoravdi, 2014), and inhibited by waste products of glucose and glutamine metabolism, lactate and ammonia, which also influence MAb production (Miller et al., 1988a,b; Ozturk et al., 1992). Glutamate is now the nitrogen source of choice.

Design, optimization, scale-up and control of bioreactors used for MAb production requires reliable predictive first principles models (FPMs) or data-driven models (Butler, 2005; Frahm et al., 2002, 2003; Jang and Barford, 2002). The models used in prior studies have largely been FPMs and provide significant insight into functioning of the process and are useful in its design and optimization. Bulk of the FPMs are unstructured (Jang and Barford, 2000; Kontoravdi et al., 2007, 2008, 2010; Miller et al., 1988a,b; Ozturk and Palsson, 1991). The remaining FPMs, structured models (Bibila and Flickinger, 1991, 1992a,b; Gao et al., 2007; Gerdtzen, 2012; Kontoravdi et al., 2010; Sanderson et al., 1999; Zhou et al., 2006), provide additional insight into MAb synthesis and secretion.

Data-driven models have flexible structure, are not process-specific, and have applications in diverse fields (An et al., 2015; Shirmohammadi et al., 2013). The advantages and disadvantages of these models have been discussed by the two groups of authors, with the models being divided into two categories – neural network-based models (Bhutani et al., 2006; Cui et al., 2012; Shetty et al., 2008) and statistical models (Aumi and Mhaskar, 2012; Nucci et al., 2010; Zhaomin et al., 2014). The model parameters are estimated using prior process data, extensive knowledge of the process is not required, and the parameter values can vary in different portions of the same experiment and from one experiment to another. The simpler model structure facilitates frequent updating of model parameters and state of the process and prediction of process trajectories, features helpful in process control. With increasing information available about biological processes, data-driven models will have increasing utility in representation, monitoring and control of these processes. The data required for parameter estimation in data-driven models can be generated from (a) actual experiments by measuring important inputs and outputs at appropriate sampling rates and (b) from simulated experiments using a

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reliable, well-tested FPM (Huusom et al., 2012). Well-tested FPMs are usually based on extensive experimental database.

Time series models are popular statistical data-driven models with extensive applications (Box et al., 2015; Chaudhary and Raja, 2015; Dellana and West, 2009; Hill et al., 2012; Huusom et al., 2012; Rimaityté et al., 2012; Wang et al., 2012; Zhou et al., 2013). Estimation of model parameters for time series models is computationally less intensive due to their more flexible structure and linearity with respect to model parameters. Recursive time series models have been shown to be a powerful tool for describing a dynamic system with time varying characteristics (Ljung, 1999; Turksoy et al., 2014a,b).

In many processes, sampling frequencies for different inputs and outputs may not be the same. One may have to discard some of the measurements for the more frequently sampled variables, causing loss of important information, with the process being controlled at the slowest sampling rate. Instead of synchronizing the data acquired at different sampling rates to the slowest sampling rate, we can utilize a dual rate or multi-rate system to yield more accurate prediction (Ding and Chen, 2004, 2005; Ding and Ding, 2008; Kuure-Kinsey et al., 2006; Yu et al., 2008). Information on the less frequently measured variables is then inferred using past measurements of these and other more frequently measured variables.

Recursive time series models are developed in this work for a mammalian cell culture and their stability and predictive ability are assessed over an appropriate range of prediction horizon. An autoregressive moving average with exogenous input (ARMAX) model is used for the more frequently measured variables and a dual rate-autoregressive with exogenous input (ARX) model is used for the less frequently measured variables. The data required for parameter estimation have been generated for fed-batch cultures, with separate feed streams for glucose and glutamine, from simulated experiments using a well-tested FPM (Kontoravdi et al., 2010; Ozturk and Palsson, 1990).

2. First principles-based model (FPM)

Conservation equations are provided here for batch and fed-batch cultures, with the densities of feed streams and reaction mixture in the bioreactor being nearly the same. The total mass balance then is

$$\frac{dV}{dt} = F_0, \qquad V(0) = V_i, \tag{1}$$

with F_0 being the total volumetric feed rate, V the culture volume, and t the real time. Where applicable, the subscripts 0 and i refer to feed and initial conditions, respectively. The mammalian cell culture operation is considered not to be limited by dissolved oxygen, which therefore does not influence kinetics of key cellular processes. For brevity, we use the following notation: viable cells – X, glucose – S_1, glutamine – S_2, lactate – P_1, ammonium – P_2, monoclonal antibody (MAb) – P_3. The mass balances for viable cells and extracellular nutrients and metabolic products are

$$\frac{d(JV)}{dt} = F_{J0}J_0 + q_J XV + R_J V, \qquad J(0)V(0) = J_i V_i \tag{2}$$

In Eq. (2), J_0 and J denote concentrations of J in the bioreactor feed and the culture, respectively (J = X, S_1, S_2, P_1, P_2, P_3), F_{J0} the volumetric flow rate of feed stream containing J, q_J the cell-specific rate of generation of J in the biotic phase, and R_J the cell culture volume-specific rate of generation of J in the abiotic phase. Unless mentioned otherwise, R_J is zero. In fed-batch cultures, only glucose and glutamine are added to the culture via separate feed streams, the volumetric flow rates of these streams being F_1 and F_2. Therefore,

$$F_{S_1 0} = F_1, \quad F_{S_2 0} = F_2, \quad F_{J0} = 0, \quad J = X, P_1, P_2, P_3, \quad F_0 = (F_1 + F_2).$$

Substituting Eq. (1) into Eq. (2), the mass balance for J can be restated as

$$\frac{dJ}{dt} = \frac{(F_{J0}J_0 - F_0 J)}{V} + q_J X + R_J, \qquad J(0) = J_i. \tag{3}$$

We consider here the case of sterile feed and absence of cell recycle to the bioreactor (F_{X0} = 0, X_0 = 0). The forms of the rate expressions stated below are inspired by the work of Kontoravdi et al. (2010).

The net generation rate of viable cells (X), q_X, is expressed as

$$q_X = (\mu - \mu_d). \tag{4}$$

The specific cell growth rate, μ, and the specific cell death rate, μ_d, are expressed as

$$\begin{aligned} &\mu = \mu_0 f_1 f_2, \quad f_1 = \frac{S_1}{(K_{S_1} + S_1)}\frac{S_2}{(K_{S_2} + S_2)}, \\ &f_2 = \frac{K_{P_1}}{(K_{P_1} + P_1)}\frac{K_{P_2}}{(K_{P_2} + P_2)}, \mu_d = \frac{\mu_{d0}}{[1 + (K_{d,P_2}/P_2)^2]}. \end{aligned} \tag{5}$$

The kinetic parameters $\mu_0, \mu_{d0}, K_{S_i}, K_{P_i}$, and K_{d,P_2}, i = 1, 2, are considered to be constant. The rates of glucose and glutamine consumption and generation of lactate and ammonia are expressed as

$$\begin{aligned} &(-q_{S_1}) = \left(\frac{\mu}{Y_{X/S_1}} + m_1\right), \quad (-q_{S_2}) = \left(\frac{\mu}{Y_{X/S_2}} + m_2\right), \\ &m_2 = \frac{\alpha_1 S_2}{(\alpha_2 + S_2)}, q_{P_1} = Y_{P_1/S_1}(-q_{S_1}), \quad q_{P_2} = Y_{P_2/S_2}(-q_{S_2}). \end{aligned} \tag{6}$$

In Eq. (6), m_1 and m_2 represent utilization of glucose and glutamine, respectively, for cell maintenance. The binary yields in Eq. (6), Y_{X/S_1}, Y_{X/S_2}, Y_{P_1/S_1}, and Y_{P_2/S_2}, and the kinetic parameters m_1, α_1, and α_2 are considered to be constant. Glutamine degradation in the abiotic phase to generate ammonia is expressed as (Ozturk and Palsson, 1990)

$$(-R_{S_2}) = R_{P_2} = k_{d2} S_2. \tag{7}$$

k_{d2} being the kinetic coefficient for glutamine degradation. The specific antibody synthesis rate, q_{P_3}, is considered to be constant.

3. Data-driven models

We provide here background on multi-input, single output (MISO) data-driven models. For a fed-batch mammalian cell culture, the two inputs are $u_1 = F_1$ and $u_2 = F_2$ and an output y is one of the following: X, S_1, S_2, P_1, P_2, and P_3. Two of the outputs, S_1 and S_2, have lower sampling rate than that for u_1, u_2, X, P_1 and P_2. At the laboratory scale, the sampling rate for S_1 and S_2 is lower than that for X (Tatiraju et al., 1999). This may not be the case at the commercial scale. Another output, P_3 has a lower sampling rate than that for S_1 and S_2. For illustration, numerical results presented later pertain to X (higher sampling rate) and S_1 and S_2 (lower sampling rate). These outputs are strong determinants of mammalian cell metabolism and hence productivity of monoclonal antibody (MAb, P_3). Mammalian cell metabolism in a fed-batch culture can be regulated by the rates of supply of glucose (S_1) and glutamine (S_2). Varying volumetric rates of separate feeds containing fixed concentration of S_1 or S_2 is an experimentally convenient and cost-effective way of varying the rates of supply of these nutrients.

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