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Hybrid intelligent control of substrate feeding for industrial fed-batch chlortetracycline fermentation process

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ABSTRACT

The lack of accurate process models and reliable online sensors for substrate measurements poses significant challenges for controlling substrate feeding accurately, automatically and optimally in fed-batch fermentation industries. It is still a common practice to regulate the feeding rate based upon manual operations. To address this issue, a hybrid intelligent control method is proposed to enable automatic substrate feeding. The resulting control system consists of three modules: a presetting module for providing initial set-points; a predictive module for estimating substrate concentration online based on a new time interval-varying soft sensing algorithm; and a feedback compensator using expert rules. The effectiveness of the proposed approach is demonstrated through its successful applications to the industrial fed-batch chlortetracycline fermentation process.

1. Introduction

Fed-batch fermentation processes have been widely used to produce high value-added goods, including specialty chemicals, materials for microelectronics, agricultural products, food and pharmaceuticals [1]. In the fed-batch cultivation, substrate is continuously added to the fermentor while no withdrawal of cells and products takes place during the batch run. This operation offers a great opportunity to manipulate the feeding profile, thereby allowing tighter control of various cellular processes such as cell growth, nutrient uptake and formation of target metabolites. Thus, feeding operation can efficiently affect the productivity and the yield of the desired product. In this work, we focus on the feeding control of an industrial fed-batch chlortetracycline (CTC) fermentation process.

To reduce production costs and increase the yields while at the same time maintaining the quality of the target products, developing an economical and efficient control method is now of considerable interest to many fermentation industries. The task of bioprocess control consists in providing a near optimal environment for microorganisms to grow, multiply, and produce a desired product [2]. This includes keeping the right concentration of nutrients to the culture (e.g. carbon, oxygen), removing any toxic metabolic products (e.g. CO_2), and controlling important internal cellular parameters (e.g. temperature, pH). However, the control and optimization of fed-batch fermentation processes is still challenging mainly because [3–7]: (i) the inherent nonlinear and dynamic nature makes the processes extremely complex; (ii) accurate process models are rarely available to describe cell growth and product formation; (iii) responses of the processes are slow, and model parameters vary in an unpredictable manner; and (iv) the lack of reliable online sensors for key variables such as biomass or product concentration is a serious obstacle of controlling bioprocess accurately, automatically and optimally.

Over the past several decades, automatic control has been applied to maintain the operating temperature, pH and dissolved oxygen (DO) concentration at the desired level, whereas it is still a common practice to regulate the nutriment addition manually in industrial fed-batch cultivations. Substrate feeding is in fact a very sensitive process so that it is quite hard to be adjusted and has a deep impact on the final yield. The underfeeding can induce microorganism starvation while the overfeeding can promote the formation of undesirable products and lead to substrate inhibition. In practice, the difficulties encountered in feeding control arise mainly because the optimization of the feeding rate is a dynamic problem [5,7].

So far, various strategies have been proposed for improving feeding control of fed-batch bioprocesses [6]. The most straightforward methods for feeding operation are the predetermined feeding

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strategies. The earliest attempts at this type of methods used no model at all but tracked successful state trajectories from previous runs stored in the computer by using open-loop control [8]. Meanwhile, the constant, intermittent, and exponential feeding methods have been extensively used in various fed-batch cultivations [6,9]. Though the constant and intermittent approaches are simple and easy to operate, they are incapable of maintaining the residual substrate concentration at a relatively steady level due to the fact that the physiology status of biomass is changing and the substrate consumption rate would also alter with it. With regard to exponential feeding, it allows cells to grow at a constant specific growth rate given the underlying assumption of exponential growth of microorganisms. However, exponential feeding method is sensitive to process disturbances when cell growth does not match the predetermined profile. Furthermore, it is ill-suited for antibiotic production since formation of secondary metabolites is usually not associated with cell growth. In addition, a common drawback of the predetermined feeding methods is their essentially open-loop nature.

As alternative solutions, the simple indirect feedback methods have been proposed by coupling the nutrient feeding with easy-to-measure variable such as pH (pH-stat) or DO (DO-stat), thereby allowing manipulation of the nutrient feeding rate to maintain pH or DO at its set-point. When pH or DO is higher than its set-point, the on/off controller is activated to feed nutrients to the bioreactor at a predetermined rate. The pH-stat with high limit is based on the fact that pH rises due to excretion of ammonium ions when the principle carbon source is depleted [10]. Similarly, the DO-stat is based on the fact that DO increases sharply when a key substrate is depleted [11]. The pH-stat method, for example, has been widely applied to fed-batch fermentation processes. The common use of this method is to manipulate the substrate feeding by monitoring the pH change [12–14]. When pH or pH-increasing rate rose above an upper limit due to the depletion of substrate, the nutrient feeding was restarted until the pH reduced to the set-point. Through careful control of the feed solution pH, the quantity of substrate addition and the substrate concentration could be controlled well. A further automated feeding control scheme based on pH control was proposed by exploiting the relationship between the consumption of substrate and alkali [15–17]. The theory base for this method is that the amount of alkali consumed for neutralization should be proportional to the amount of carbon source converted to lactic acid. Following the quantitative relationship between consumption of alkali and substrate, the substrate addition is often performed by (i) continuously adding the proportionally mixed solution or (ii) periodically adding substrate according to the amount of alkali consumption and the built relationship, which aims to maintain the residual substrate concentration at an expected level by automatically adjusting pH. Though the indirect feedback feeding control is simple and readily to operate, it is impossible to achieve rigorous control because changes of pH or DO cannot thoroughly account for indicating substrate consumption.

Meanwhile, many efforts have been paid to advanced control algorithms for fed-batch fermentations. Numerous literature works have reported applications of advanced control in fermentation processes [2,3,7,8,18–23], involving dynamic programming, online adaptive control, nonlinear optimization, nonlinear control, optimal control, multivariable control, model reference control, fuzzy control, and model predictive control (MPC), etc. These types of methods have gained increasing popularity because of their strong capability in dealing with process nonlinearity, dynamics and optimization. MPC, for example, takes advantage of a dynamic model to predict the future behavior of a process to compute the optimal control actions with respect to a cost function while taking into account constraints imposed on process inputs and outputs or states. In practice, MPC has been recognized as the only one among advanced control techniques (defined as techniques more advanced than the PID method) which has been exceptionally successful in numerous practical applications [24]. By coupling real-time optimization (RTO) with nonlinear MPC (NMPC), the resulting paradigm of RTO-NMPC allows dealing with nonlinearities in process dynamics and solving effectively and simultaneously the quadratic problem and economic problem [25,26]. However, NMPC encounters a lot of limitations such as difficulties in building accurate dynamic models, the computational time that has to ensure real-time feasibility, the complexity of online implementation, and the insufficient accuracy of online solutions [2,27], which limits its applications to bioprocesses. Currently, many of the reported advanced control methods used in fed-batch bioprocesses are either simulations or implementations on small-scale fermentors, and they are rarely suitable for industrial processes. As a result, development of the advanced feeding control strategies remains challenging in practice.

Since those feeding strategies involving dynamic optimization or advanced control techniques require accurate mathematical models, which are often difficult to build, it is still the case that the control objective of substrate feeding in most industrial bioprocesses is often to maintain the substrate concentration within an expected range. Thus the direct feeding control according to substrate demand is appealing to achieve better control performance. The substrate concentration can be well controlled if it can be measured online. As prior requirements, substrate measurements play a crucial role in manipulation of feeding rate based on substrate consumption rate. However, how to determine the substrate concentration is always very difficult. Although much work has been done on sensor development, only a small portion of new sensors is available for use in fermentations [28]. Apart from the high costs associated with those available online analyzers, their reliability may be poor when applied to large-scale fermentors. This is mainly because bioprocesses are remarkably harsh environments for sensors so that the growing culture can infiltrate sensors and this invalidates their results. Consequently, the measurements on substrate concentration are usually based upon infrequent offline laboratory analysis.

Specific to the industrial CTC fed-batch fermentation processes under study, it is still the case that the feeding tuning only depends upon offline assay values, which are obtained at long time interval. The substrate concentration is usually analyzed once every 6–8 h in a laboratory. The main drawbacks of the current manual feeding control are (i) following the offline analysis results, operators would typically wait until the next laboratory analysis is made before taking any right action, which easily leads to overfeeding or underfeeding; (ii) the substrate concentration is only analyzed at a small number of sampling time instants, which results in a large blind zone of process monitoring; (iii) the regulation results often differ from person to person since the operators usually adjust the feeding rate manually according to their personal experience; and (iv) the manual operations will inevitably increase the production costs. Thus developing a suitable automatic feeding strategy is critical for industrial fed-batch CTC cultivation.

To tackle the above-mentioned problems, a hybrid intelligent control method, the main contribution of this work, is proposed to enable automatic substrate feeding for industrial fed-batch CTC cultivation process. The resulting control system consists of three modules: a presetting module built from previous successful runs by performing statistical analysis, serving as a feedforward component; a predictive module aimed to estimate substrate concentration online based on a novel time interval-varying soft sensing algorithm (TIVSS); and a feedback compensator using expert rules. Among these modules, the use of TIVSS soft sensors enables feedback correction to the presetting feeding rate. Unlike traditional one-step-ahead predictor which uses a single Nonlinear Auto-Regressive with eXogenous inputs (NARX) model, TIVSS approach requires to