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# Advanced Process Control for Bioprocess

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## Editorial

Process control and real time optimization can be powerful system engineering tools to increase the productivity in bioprocesses. Recently, advanced process control technology such as model predictive control has gained increasingly attention in biotechnology industry. Comparing to the conventional control practice such as PID control, advanced process control technique usually employs real time optimization to optimize the reactor to increase the productivity and finance gain [1]. Considering the successful implantation of model predictive control in the chemical and petroleum industries, it holds great potential for increasing the productivity of bioprocesses [2]. Comparing with the pharmaceutical industry, the industrial biotechnology field such as fermentation for chemicals and small molecules is more adaptive for switching from conventional control to advance process control technique, due to federal regulation [3].

There have been several demonstrations of applying advanced process control method for microbial fermentation [3-5]. To apply the real time optimization for the reactor, certain key information, which is usually referred as 'state', needs to be obtained prior to the real-time optimization. A few examples of the process states for a fermentation/cell culture process include: cell density, concentration of target molecules, concentration of carbon and nitrogen source, concentration of toxic byproduct, concentration of metabolic, pH, dissolved oxygen, oxygen demand, and carbon dioxide generation. Not all of the above mentioned parameters need to be obtained, depending on the process characteristic. Some of the process information such as pH and dissolved oxygen can be easily measured online. There are other process parameters such as glucose or other intermediate metabolic cannot be measured in a real-time manner. For the process states that cannot be measured in a real time manner, technology referred as 'state estimation' has been developed to estimate the state information.

State estimation is a very important practice for process monitoring and controls [6-8]. Various state estimation technologies have been developed in academia and some of them have been applied in the industry. Applications of state estimation techniques in industry include performance evaluation, fault detection and diagnosis, and advanced process control [9]. One of the current challenges for state estimation is the existences of process disturbance, which can significant, reduce the estimation accuracy. The process disturbance may come from a variety of sources, such as errors from sensor and actuator [10]. The technology for state estimation under different process disturbances still needs improvement.

There are basically two types of state estimation techniques: first principle model-based and data-based state estimation. First principle model-based state estimation requires development of a first principle process model, either stoichiometry model or kinetic model, either continuous or discrete [11]. The process model is expected to be able to capture the main process states, preferably in a dynamic system. The development of first-principle model can be a challenge for processes with high variances and unknown disturbances. An ideal process model should be easy to implement and update. Model reduction methods can be applied if a process model is too complicated. There are many model-based state estimation techniques available, such as linear and nonlinear Kalman filter [12]. Linear and nonlinear Kalman filters were first designed to estimate the process states under noises with known covariance. The advantage for first principle model-based state estimation is that different disturbances can be simulated and studied individually. This advantage can help with fault diagnosis and isolation [13-15]. Linear and nonlinear observers have been one of the options for first principle model based state estimation. Recent research has demonstrated the capability for observer design and applications. The error or uncertainty from process model can lead to inaccurate state estimation. There are research dedicated to study the impact of modeling uncertainty on the state estimator [16,17]. Disturbances from multiple sources will be a challenge for some state estimators, if the multiple disturbances are not observable from the limited measurements.

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Another method for state estimation is the data-based method, which includes statistical data analysis such as principal component analysis and artificial intelligence such as machine learning [18]. Due to the difficulty of developing first principle model and availability of large volume of process data, data-based state estimation is more widely used in industry than the first principle model-based method. When large volume data is available in the industry, the data set can be trained to estimate the existing process, even under disturbances. For a new process without enough process data, the data training can be a challenge. A possible solution for this disadvantage is the hybrid model, which combines both data-based and model-based techniques [19]. It can overcome the extensive effort for model building and also require less data for the model training.

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