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Modelling batch bioreactions with continuous process simulators

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Abstract−Process models are increasingly becoming necessary for process understanding and optimizing. However, in the field of bioprocessing, modelling using a generic process simulator suffers from shortcomings given that many simulators cannot model batch mode bioreactors with varying reaction rates based on microbial metabolism. Bioprocesses, mostly batch, are difficult to model because most of the available unit operations in process simulators operate continuously. Our aim is to provide a general simulation platform to model these batch bioprocesses in commercial process simulators and explain how to transform batch processes with varying reaction rate into continuous unit operations for simulation purposes. Two typical fermentation processes, lactose fermentation and glucose/xylose co-fermentation, were simulated in steady state as case studies. The results are discussed as examples using the proposed approach. The potential of how to extend the simulation platform is also explained in detail.

Keywords: Process Simulation, Bioreactor, Batch Processing, Dairy Processing

INTRODUCTION

Process simulators play a critical role in the modelling and optimization of processes (chemical and bioprocess) at low risk, cost, and effort, due to their comprehensive thermodynamic databases, flexibility in unit operation combinations and extensive computational methods [1-3]. Most refineries and chemical processes are operated in continuous mode, and because typical process simulators such as *Aspen HYSYS*, and *VMGSim* were developed mainly for oil & gas and chemical plants, these conventional process simulators often only support continuous operation [4-7].

Since most bioprocesses and bioreactions depend heavily on the life cycle of microbes, they are usually operated in batch mode [8]. In each batch, a precultivated starter "cocktail" is inoculated to the reactor. The microorganisms start growing under a favorable environment, and then the reaction rate begins to speed up. At the final stage of the batch, the reaction rate drops as the reactant (food) for the microbes becomes exhausted and the concentrated reaction product will inhibit the bacteria from growing. This behavior of bioreaction kinetics significantly differs from chemical reactions. The major difference is that the varying bioreaction rates are due to biomass growth, temperature and reactant concentration [9].

There are several challenges in the application of commercial process simulators to bioprocess modelling: 1) uniqueness of specialized bioprocess unit operations such as homogenizers and fermenters, 2) under defined raw materials and products such as proteins and cells, and 3) batch operating and varying reaction rate nature of bioprocesses. Furthermore, bioprocess unit operations are often well characterized and work on physical and biological phenomena which are often not well described in commercial process simulators [10]. On the other hand, unit operations in most commercial process simulators are based on principles of phase equilibrium, so that they are unable to model bioprocesses while the raw materials and products of bioprocesses are mostly not well known or not pre-defined in the thermodynamic database. Additionally, the substrates fed to the bioprocess are mostly unknown or with varying compositions. The batch operating and varying reaction rate nature of bioprocesses raises significant challenges in modelling them in conventional process simulators [11].

The paradox is that conventional process simulators do not well support batch operations and bioreactions [12]. It is clearly evident from the recent literature that there is a substantial gap between traditional process simulators and current simulation methodologies used for modelling bioprocesses and batch biochemical reactions, especially when bioreactors are an important unit operation in chemical or food processes such as ethanol production from sugar/cellulose and cheese making in the dairy process.

Dedicated bioprocess simulators for bioprocess modelling are also not well established or developed. For example, the BioProcess Simulator (BPS) was developed to carry out material and energy balances of bioprocesses. This simulator had limited commercial success because it inherits steady state properties of continuously operated *Aspen Plus* (a commercial process simulator). Limited published information on dedicated bioprocess simulators is another obstacle in the way of their commercial success because, in the recent past, most of the practitioners from academics and industry have developed their classified models for their specific unit operations [13-15].

We aimed to mitigate this knowledge gap by introducing a new methodology for conventional process simulators. This method can help to use conventional process simulators as a general simulation platform to model batch bioprocesses or bioreactions with

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varying reaction rate. Furthermore, the strategy allows integrating batch bioprocesses with other unit operations in process simulators. The potential of the simulation platform was also explored to enable different modelling perspectives of bioreactions.

In this work, we adopted *VMGSim* (*VMGSim*; Virtual Materials Group Inc., Calgary, AB, Canada) process simulator ted. *VMGSim* was selected as the modelling environment or platform has user-friendly interface [16], the inclusion of the latest thermodynamic models integrated with National Institute of Standards and Technology thermodynamic database [17], flexibility regarding interfaces with other software and close integration with Microsoft Visio and Excel [18].

The manuscript is organized as follows. After this general introduction, the methods used in this work are discussed and explained in Section 2. Section 3 demonstrates two case studies and results. The potential of extending the simulation platform is considered in Section 4. Finally, the conclusions for this work are outlined in Section 5.

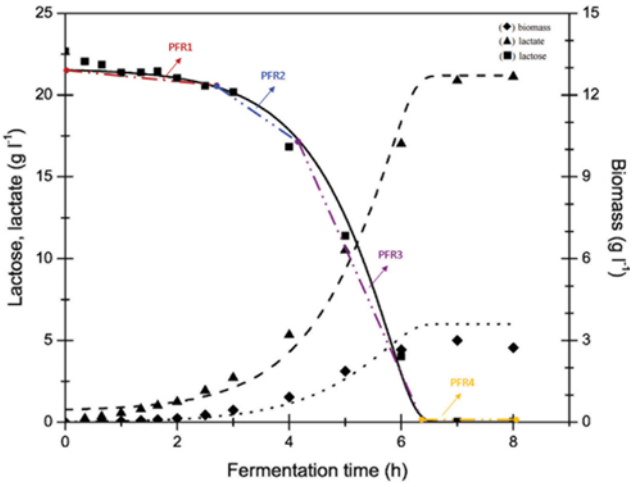

Fig. 1. Linearization of a lactose fermentation reaction curve [19] and correspondence to plug flow reactors (PFRs).

METHODS

1. Modelling Approaches Using Process Simulators

We considered different modelling approaches to model bioprocesses or bioreactions using commercial process simulators. First, it is possible to develop an interactive interface between conventional process simulators and those simulators dedicated for simulating batch bioprocesses such as *SuperPro* and *Aspen Batch* Process Developer. However, this approach was not adopted as it would include developing an interface between different software packages and the synchronized behavior (continuous vs. batch) of different simulators may raise extra complexities. In another modelling approach, the process simulator integrates with a model of the bioreactor in numerical tools such as MATLAB. However, in this approach, the bioreactor is still in batch mode.

Consequently, the methodology adopted in this research was to convert a batch biochemical reaction process into a continuous reaction process. Thus, it can be put into the conventional steady state/continuous simulator safely and avoid communicating with other potentially incompatible simulators.

2. Adopted Modelling Approach

To obtain a steady flow from a batch process in actual operations, multiple batch units (can be reactor or other batch unit operations) were used and they were scheduled to deliver the product one-by-one so as to form a semi-continuous feed or product flow. This methodology can be used to convert batch processes into continuous ones.

The first step of the conversion from batch to continuous was to consider each batch to share an identical reaction process, which was an average from multiple batches. This action indicated that each batch had the same reaction curve (defined as the percentage of reactant left and product produced after the reaction). Then, each batch was divided into some infinitely small batches, and each of these batches still shared the same reaction curve. These infinite batches can then be arbitrarily scheduled and "integrated" to form a continuous flow.

Once the batch reaction was "converted" to continuous operation, the reaction process can then be simulated using the reactor unit operations in the simulator. Typical reactor unit operations include a continuous stirred tank reactor (CSTR), plug-flow reactor (PFR), and equilibrium reactor (EQMR). A PFR was used to provide required holding effect and reaction time.

The second step was to address the problem that most biochemical reactions have a varying reaction rate. Since the reactions in a PFR are specified by a reaction constant A (Arrhenius constant) and activation energy E in the Arrhenius equation, one PFR can only express a reaction with a constant reaction rate.

For example, Fig. 1 shows a typical reaction curve for a biochemical reaction, which in this case is the lactose fermentation process [19]. The lactose (reactant) concentration can be observed to decrease throughout the process with a varying rate while the lactase (product) concentration rises accordingly.

The reaction curve was linearized into several segments with respect to time as shown in Fig. 1. Each of these segments was considered to have a constant reaction rate within their time region, and thus was expressed by a corresponding plug flow reactor. The linearization of the reaction curve was subjectively chosen depending on how accurate the simulation needs to be.

3. Generic Assumptions

The following generic assumptions were adopted after the following considerations:

a) The biomass inside the reactor was ignored as the primary focus is the reaction process and also for simplification purposes. This assumption may cause other deviations in the product prediction results due to the impact of biomass metabolism on the properties of broth as well as the reaction nature. Nevertheless, if the concentration of biomass reaches a level that it could significantly impact the thermodynamic properties of the broth, it should be taken into account by constructing hypothetical compounds in the process simulator database.

b) The flow rate and concentration of a reactant at inlet and outlet of respective PFRs should always be matched and guaranteed according to the reaction curve. At the end of the reaction, another optional PFR (i.e., PFR4 in Fig. 1) was placed so as to match

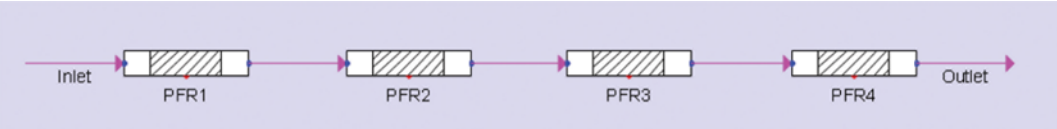

Fig. 2. Flow sheet layout of the lactose fermentation simulation case study.

Table 1. Key parameters of each PFR for the lactose fermentation process case study

	Lactose wt% at PFR inlet	Reaction time (hr)	Length (m)	Heat transfer coefficient ($W/m^2 \cdot K$)	A	E (kJ/kmol)
PFR1	4.2	3.5	11.14	1000	143	50000
PFR2	4.05	2	6.37	1000	1757	50000
PFR3	3	2	6.37	1000	4987	50000
PFR4	0.02	2.5	7.96	1000	0	50000

the remaining time after the major reaction process ends.

c) The *A* and *E* values in the Arrhenius equation for the reactions are specified using a trial and error method because the reaction curve is available. Otherwise, nature and the physical environment of the reaction estimate these values. Furthermore, there are many techniques available in the literature (e.g., Arrhenius plot, experimental data) to determine activation energy and pre-exponential factor of the Arrhenius equation. However, the simplest method (trial and error method) was employed in this study.

RESULTS AND DISCUSSION

Two fermentation processes, lactose fermentation in dairy production and glucose/xylose co-fermentation in bioethanol production, illustrate the methodology in an actual simulation environment.

1. Case Study 1: Simulation of Lactose Fermentation

Lactose fermentation is an important and well-studied process as it is one of the core reactions in yoghurt and cheese production processes. The reaction stoichiometry is shown in Eq. (1).

$$C_{12}H_{22}O_{11}+H_2O \rightarrow 4C_3H_6O_3 \qquad \Delta H_f = -1599.9\ \text{kJ} \qquad (1)$$

The reaction curve of lactose fermentation was selected from experimental data presented in Boonmee et al. [19]. A lactose concentration of 40 g/L in the starting mixture was adopted, and the reaction curve is shown in Fig. 1. The temperature of the fermentation process was maintained at 30 °C by a water bath. Along with generic assumptions (given in Section 2.3), the following specific assumptions were also adopted after the following considerations:

i) The biomass was not included in the simulation as it does not affect the reaction stoichiometry and thus can be considered as the catalyst.

ii) The density of the solution was assumed to be 1 kg/L throughout the reaction to convert the mass concentrations into weight percentages. This assumption should have limited impact on the result as fermentation processes usually take place in dilute water solutions.

iii) A mid-sized reactor was adopted and the inlet rate was assumed to be 100 kg/hr.

iv) The diameter of each PFR was assumed to be 20 cm to keep the length and the cross-section of the reactor at a reasonable ratio. The volume of the PFR was divided to obtain the length of each reactor.

The reaction curve as shown in Fig. 1 was linearized into three main segments, followed by another segment representing the extra time after the primary reactions are over. Four different PFRs were used and each of them corresponds to one of the segments. The concentration of lactose and reaction time at the start of each PFR were obtained from Fig. 1. The flow sheet layout of the simulation is shown in Fig. 2.

A systematic algorithm was adopted for the fine tuning of the reaction constant, Arrhenius constant A and activation energy E of the reaction. The value of the reaction constant for the forward direction was determined by setting E to a constant value, then manipulating A until the lactose concentration at the outlet of each PFR fit the reaction curve shown in Fig. 1. The A value for the reverse direction of the reaction was set to zero, indicating that the reaction is irreversible and non-equilibrium based. Table 1 and Fig. 3 show the basic parameters of each PFR. For parameter estimation, we employed literature and process simulation heuristics. Furthermore, a screenshot in Fig. 3 shows a general PFR information required for simulation.

The lactose fermentation model was simulated in steady state mode, and the lactic acid concentration at the outlet of each PFR was monitored and compared with literature data, which was obtained from Fig. 1 [19]. As a higher heat transfer coefficient was used and the reactor was maintained at 30 °C throughout the reaction process, the heat dissipated by the reactor was also recorded. The results are shown in Table 2.

Table 2 shows that the lactic acid weight percentage predicted by the model showed a close match with literature values, especially during the early stages of the reaction. The overestimation (deviation % of average relative error) of the value is due to the side reaction of the lactose fermentation causing less lactic acid production, or the lactic acid was further broken down by microbes into other compounds. The literature supports this claim in Fig. 1 that the total mass of lactic acid produced is less than the mass of lactose consumed, indicating hidden side reactions.

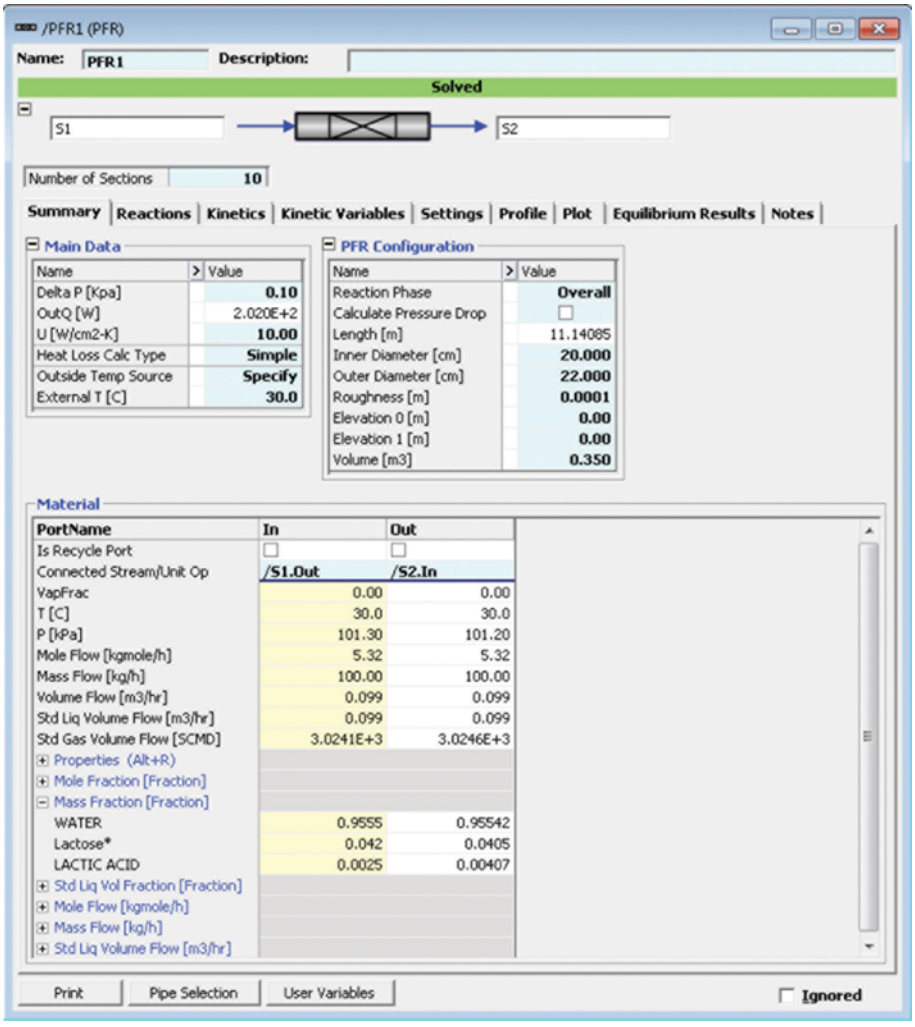

Fig. 3. Screen shot of one of the PFRs in the lactose fermentation simulation scenario.

Table 2. Simulation results and comparison to literature data for the lactose fermentation case study

	Lactic acid wt% at PFR outlet			Heat dissipation power (W)
	Literature	Model prediction	Deviation (%)	
PFR1	0.39	0.40	+2.56	202
PFR2	1.44	1.51	+4.86	1419
PFR3	4.07	4.65	+14.25	4032
PFR4	4.07	4.65	+14.25	1

Investigating the underlying cause of the mass balance problem can improve the accuracy of the model. The assumption of constant solution density could also cause additional deviations. The density of the solution throughout the reaction process can be used to address this issue; however, the related data was not reported in the literature [19].

2. Case Study 2: Simulation of Xylose and Glucose Co-fermentation

Another interesting scenario to look at is the sugar fermentation process, which is a very popular topic nowadays due to bioethanol production research. The case we picked was the simultaneous

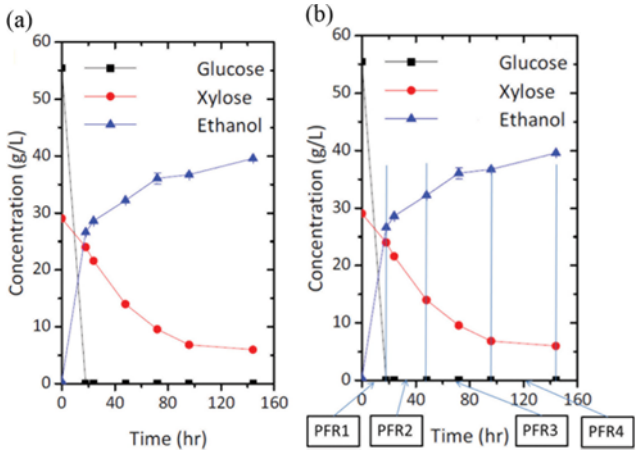

Fig. 4. Reaction curve of co-fermentation of xylose and glucose using Saccharomyces cerevisiae 424A. (a) Reaction curve Lau et al. [20], and (b) Linearization approach (present work).

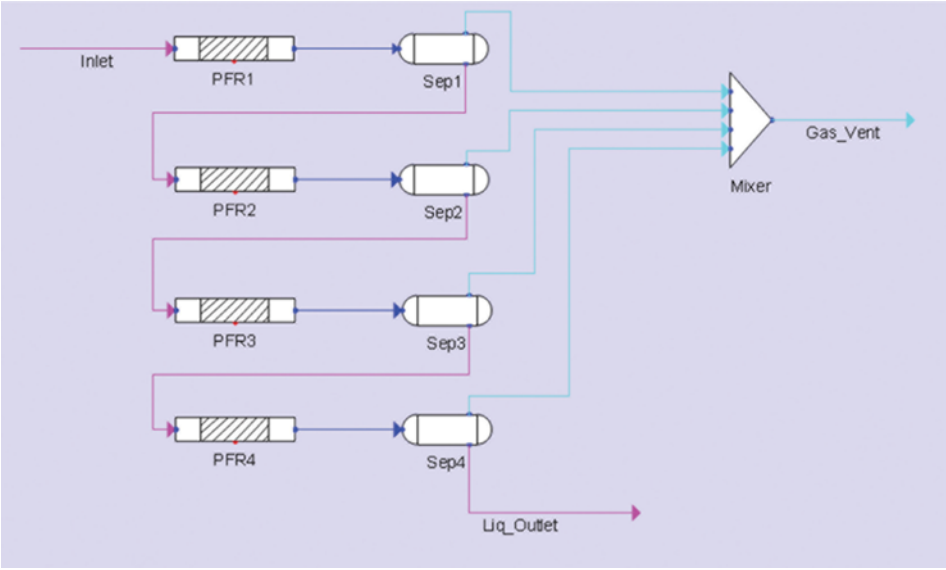

Fig. 5. Flowsheet layout in the simulation environment for glucose/xylose co-fermentation.

Table 3. Key parameters of each PFR for the glucose/xylose co-fermentation process case study

	Reaction time (hr)	PFR Length (m)	Glucose fermentation		Xylose fermentation		E for glucose & xylose fermentation (kJ/kmol)
			Glucose wt% at PFR inlet	A	Xylose wt% at PFR inlet	A	
PFR1	18	2.29	5.55	1958	2.85	74	50000
PFR2	29	3.69	0.01	0	2.40	86	50000
PFR3	49	6.24	0.01	0	1.40	35	50000
PFR4	49	6.24	0.01	0	0.70	5	50000

fermentation of xylose and glucose reported in Lau et al. [20]. In Lau et al. [20], xylose and glucose were co-fermented to obtain ethanol with relatively a high yield and a quick rate.

The potential value of simulating this particular bioreactor in conventional process simulators is that it allows integrating batch bioreactor with other upstream/downstream continuous unit operations in a single simulation environment, which includes pre-treatment, hydrolysis, distillation and purification. The reaction curve of the fermentation and linearization approach are shown in Fig. 4. The reaction stoichiometry is illustrated in Eqs. (2) and (3).

$$C_6H_{12}O_6 \rightarrow 2C_2H_6O + 2CO_2 \qquad \Delta H_f = -281.7\ \text{kJ} \tag{2}$$

$$3C_5H_{10}O_5 \rightarrow 5C_2H_6O + 5CO_2 \qquad \Delta H_f = -750.0\ \text{kJ} \tag{3}$$

The major difference in this scenario compared with lactose fermentation is that there are two simultaneous reactions taking place; thus, the linearization needs to take care of both reaction curves simultaneously. The curve with more linear segments required (xylose, in this case study) should be considered a priority rather than the other curve with fewer linear segments. Furthermore, the fermentation process produces CO_2 as a side product that requires separation after each reactor.

The same procedure as discussed in Section 3.1 was applied. All the PFRs were maintained at 30 °C as suggested by literature with a heat transfer coefficient of 1,000 W/m^{2}K to the environment. An inlet mass flow rate of 100 kg/hr was assumed. As the reaction takes a significantly longer time compared with lactose fermentation, all PFRs were set to have a 100 cm diameter, which aims to keep the dimension of each PFR at a reasonable ratio. The flow sheet layout in the simulation environment is shown in Fig. 5. Table 3 and Table 4 show the basic parameters for each PFR and the ethanol concentration prediction results, respectively.

Table 4. Simulation results and comparison to literature data for the glucose/xylose co-fermentation case study

	Ethanol wt% at PFR outlet			Heat dissipation power (W)
	Literature	Model prediction	Deviation (%)	
PFR1	2.70	2.86	+5.9	1662
PFR2	3.25	3.34	+2.8	336
PFR3	3.70	3.67	−0.8	231
PFR4	3.92	3.72	−5.1	3

Table 4 shows that the predicted ethanol concentration closely matches the experimental data throughout the reaction process. The possible causes for the deviations could come from the mass concentration conversion and the venting of ethanol from the reactor. Nevertheless, with minor variations, it is safe to say that the model showed a good performance in this scenario and was capa-

ble of simulating multiple reaction threads of bioreactions.

PLATFORM POTENTIAL

The simulation work carried out in this research aimed not only to mitigate the knowledge gap between current process simulators and simulation of bioreaction processes, but also to provide a common platform for further extension and exploration. Some potential directions for extending the simulation platform are listed here.

1. Modelling Bioreactors with Numerous Simultaneous Reactions

The glucose/xylose fermentation process included two reactions simultaneously, but the simulation platform is possibly capable of simulating many more simultaneous bioreactions. The additional work may come from further refining the linearization segments on each reaction curve, as well as defining the reaction clearly and adequately. However, the potential interference with different reactions should be considered and included when building the model.

2. Transformation to a Data-driven Model

As biochemical reactions have some degree of randomness among different batches and different cultures, building "hard models" using fundamental equations then obtaining definite results has its deficiencies. Alternatively, the problem can be compensated by "soft models" which purely depend on data. It would be interesting to find how temperature, reactant concentration and different microbes affect the reaction process, regarding building correlations between these manipulated variables with Arrhenius reaction constant A and activation energy E. If enough data could be fed to the model, the data-driven model would be more accurate in generating proper A and E values when given a particular reaction condition. Since traditional advanced process simulators such as *VMGSim* have an open interface with Excel and MATLAB, the model algorithm could be easily integrated.

3. Use of Physically Validated Reaction Parameters

The Arrhenius reaction constant A and activation energy E were determined from the reactant consumption rate in this work. Alternatively, A and E value could also be derived from the physical conditions of the reaction. This technique can further improve the prediction ability of the model regarding both the consumption rate of reactants as well as the formation rate of products.

4. Plant-wide Optimization and Control

With the presence of a data-driven model in the reactor and the reactor integration with other unit operations, plant-wide optimization becomes feasible. For example, the inlet flow rate of the reactor could be manipulated by measuring the reactant composition upstream or the product composition downstream. The heat dissipated from the reactor could also be used to heat cold streams to save energy. The key point is that these batch operated reactors will not be optimized and controlled individually anymore. Instead, they can be coupled with other continuous unit operations and optimized as a whole body; thus, the potential of optimization can be maximized.

CONCLUSIONS

We have proposed a new methodology to convert batch operated bioreactions into continuous ones. This method linearizes the experimental data based biochemical reaction curves into numerous smaller segments. Each segment expresses a reaction with a constant rate. Typical plug-flow reactor unit operation then separately models each segment of the reaction curve. This method integrates batch bioreactors with other continuous unit operations in modern commercial process simulators.

Two typical fermentation processes, lactose fermentation and glucose/xylose co-fermentation process, were simulated as case studies. The predicted product concentrations showed a close match with the experimental data.

This study proved that converting bioreactors from batch mode to continuous operation in the simulator using the proposed methodology has minor information loss and is also reliable in a continuous environment. The possible further development areas of the model applications were discussed regarding modelling numerous simultaneous biochemical reactions, using physically validated parameters for the reactions, transforming to a data-driven model and plant-wide optimization and control.

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REFERENCES

1. M. García, A. Gonzalo, J. L. Sánchez, J. Arauzo and J. Á. Peña, *Bioresour. Technol.*, **101**, 4431 (2010).
2. M. T. Munir, W. Yu and B. R. Young, *ISA Trans.*, **52**, 162 (2013).
3. Q. Qiu, G. Rangaiah and P. Krishnaswamy, *Comput. Chem. Eng.*, **27**, 73 (2003).
4. C. J. Arthur, M. T. Munir, B. R. Young and W. Yu, *Fuel*, **115**, 479 (2014).
5. M. T. Munir, W. Yu and B. R. Young, *Can. J. Chem. Eng.*, **91**, 1686 (2013).
6. M. T. Munir, Y. Zhang, W. Yu, D. I. Wilson and B. R. Young, *J. Dairy Sci.*, **99**, 3380 (2016).
7. Y. Zhang, M. T. Munir, W. Yu and B. R. Young, *J. Food Eng.*, **121**, 87 (2014).
8. E. Kougoulos, A. Jones and M. Wood-Kaczmar, *Org. Process Res. Dev.*, **10**, 739 (2006).
9. R. G. Harrison, P. Todd, D. P. Petrides and S. R. Rudge, *Bioseparations science and engineering*, Oxford University Press, U.S.A. (2015).
10. M. T. Munir, W. Yu, B. R. Young and D. I. Wilson, *Trends Food Sci. Technol.*, **43**, 205 (2015).
11. T. Shanklin, K. Roper, P. Yegneswaran and M. R. Marten, *Biotechnol. Bioeng.*, **72**, 483 (2001).
12. M. T. Munir, W. Yu and B. R. Young, *ISA Trans.*, **51**, 827 (2012).
13. A. Clarkson, M. Bulmer and N. Titchener-Hooker, *Bioprocess. Eng.*, **14**, 81 (1996).
14. D. P. Petrides, *Comput. Chem. Eng.*, **18**, S621 (1994).
15. Y. Zhou, I. Holwill and N. Titchener-Hooker, *Bioprocess. Eng.*, **16**,

367 (1997).
16. M. T. Munir, W. Yu and B. R. Young, *Plantwide control: Recent developments and applications*, **830447157** (2012).
17. M. T. Munir, W. Yu and B. R. Young, *Korean J. Chem. Eng.*, **30**, 997 (2013).
18. M. T. Munir, W. Yu and B. R. Young, *Chem. Eng. Res. Des.*, **90**, 110 (2012).
19. M. Boonmee, N. Leksawasdi, W. Bridge and P. L. Rogers, *Biochem. Eng. J.*, **14**, 127 (2003).
20. M. W. Lau, C. Gunawan, V. Balan and B. E. Dale, *Biotechnol. Biofuels*, **3**, 1 (2010).