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On Application of Computer Simulation Technologies in Chemical Fermentation – with Penicillin as an Example

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In this paper, we use the computer process simulation software UniSim Design R400 to simulate the operation of the penicillin fermentation device, apply the gravitation search algorithm to find the optimal parameters for the model, and take the forms of non-structural kenetic models for bacteria, products, substrate and volume into account, so as to determine the mathematical model to describe penicillin fermentation. We set up a process flow diagram (PFD) for penicillin fermentation, establish an initialization module, supplemented medium module and fermentation tank module. By changing the initial conditions, setting equipment failures and implementing different control strategies, we further study the working conditions for penicillin fermentation according to the established PFD to help people predict problems that they may encounter in the actual experiment or production.

1. Introduction

The computer process simulation technology is a technology where special software is used on the computer to describe unit equipment, unit processes and the entire processes in the process industries (Zlateva et al., 2014; Marek et al., 2010; Rodman et al., 2016). This technology, based on the mechanism model of a process, does material balance, heat balance, chemical balance, phase balance and other calculations according to the given process conditions through mathematical modeling, with software as the tool and applied computer as the auxiliary means, so as to simulate the industrial process as accurately as possible and describe all kinds of reactions involved in the process (Liu and Chang, 2012; Kazuo et al., 1990).

The optimization and scaling-up of the fermentation process are the focus of the research on fermentation system engineering. The main technical means to do such research is to establish a mathematical model which describes the characteristics of the fermentation process through the computer simulation technology and do the calculations so as to form a complete simulation system (Gebicke et al., 1993; Gebicke et al., 1993).

In this paper, we take the penicillin fermentation process as an example. We use the UniSim Design R400 process simulation platform and the liquid-phase activity coefficient model (NRTL) to predict the changes in liquid-gas equilibrium and build a kinetic model to simulate the actual operating conditions for penicillin fermentation.

2. Mathematical model for penicillin fermentation

We use the non-structural kinetic model to describe the penicillin fermentation process, which is accomplished with the process simulation software UniSim Design R400 (Chen et al., 2014). We use the gravitation search algorithm (GSA) (De et al., 2013; Geraili et al., 2014; Volesky, 2003) to estimate the model parameters for penicillin fermentation.

Let's assume that a group of N particles is flying in the D-dimensional search space. The state and location of the particle i at time t are defined as follows:

$$Xi = (x_i^1, x_i^{21}, \ldots, x_i^d, \ldots, x_i^D), i = 1,2,..d,\ldots,N \quad (1)$$

The acting force that the j-th particle has on the i-th one in the d-th dimension can be expressed as follows:

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$$F_{ij}^{d}(t) = G(t)\frac{M_i(t) \times M_j(t)}{Ri_j(t) + \varepsilon}(x_i^d(t) - x_j^d(t)) \tag{2}$$

Where, G(t) is the gravitational coefficient; Mi(t) and Mj(t) stand for the inertial mass of particles i and j, respectively; x_i^d and x_j^d stand for the locations of particles i and j in the d-th dimension at time t, respectively; R_{ij}(t) is the Euclidean distance between particles i and j at time t, which satisfies $R_{ij} = ||X_i(t), X_j(t)||_2$; ε represents a very small constant (Özel and Altan, 2000; Pantelides, 1998).
G(t) is a function of the initial value G0 and the number of iterations β:

$$G(t) = G(G_0, t) = G_0 * \exp(-\alpha * \frac{\beta}{T}) \tag{3}$$

The gravitational coefficient G will gradually decrease over time, thus controlling the search precision. Here, G0 is the initial value, which is set as 100; α is a constant, set as 20; β is the current number of iterations; T is the maximum number of iterations.
In the particle movement process, we need to keep updating the inertia mass of particles with the adaptive values (Sotoft et al., 2010; Schnepper and Stadtherr, 1996):

$$m_i(t) = \frac{fit_i(t) - worst(t)}{best(t) - worst(t)} \tag{4}$$

$$M_i(t) = \frac{m_i(t)}{\sum_{j=1}^{N} m_j(t)} \tag{5}$$

Where, mi(t) is the intermediate variable, fiti(t) is the fitness function value of particle i at time t, and best (t) and worst (t) represent the best and worst adaptive function values of the whole particle group at time t. Best (t) and worst (t) are defined as follows:

$$best(t) = \min_{j \in \{1,2,\ldots,N\}} fit_j(t) \quad worst(t) = \max_{j \in \{1,2,\ldots,N\}} fit_j(t)$$

The resultant force the i-th particle is under in the d-th dimension is defined as follows:

$$F_i^d(t) = \sum_{j \in kbest, j \neq i} randj \bullet F_{ij}^d(t) \tag{6}$$

Where, $rand_j$ is a random number between [0, 1], and kbest is a linear function that decreases over time. According to the formula for the force the particle is under, if the inertia mass of particle i is Mi(t), then the acceleration of particle i is (Imani et al., 1998):

$$a_i^t(t) = \frac{F_i^d(t)}{M_i(t)} \tag{7}$$

The evolved formulas for the velocity and location of particle i at the next moment are as follows:

$$v_i^d(t+1) = rand_i v_i^d + a_i^d(t) \tag{8}$$

$$x_i^d(t+1) = x_i^d(t) + v_i^d(t+1) \tag{9}$$

Where, randi is a number randomly generated between [0, 1].

3. Computer process simulation of the penicillin fermentation process

3.1 Definition of the basis for process simulation

Before simulating the fermentation process, we first need to define the main components involved in the fermentation and select a property package. The essence of fermentation is chemical reaction, so compositions are determined based on the stoichiometric equations in the fermentation reaction process. At the beginning of the fermentation, penicillium chrysogenum is cultured aerobically with glucose and ammonia as the substrate, where the elemental composition of penicillium chrysogenum is CH1.92O0.61N0.16:

$$C_6H_{12}O_6 + 0.55NH_3 + 2.39O_2 \rightarrow 3.42CH_{1.92}O_{0.61}N_{0.16} + 2.58CO_2 + 3.54H_2O \quad (10)$$

Glucose, as the substrate, continuously reacts with oxygen to produce carbon dioxide and water:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O \quad (11)$$

The three precursor amino acids - α-amino adipic acid, cysteine and valine, which are converted by glucose and ammonia, after tripeptide synthesis and cyclization, have acyl transfer reactions with precursor phenylacetic acid and produce penicillin G:

$$2.29C_6H_{12}O_6 + 2.46NH_3 + 1.05H_2SO_4 + C_8H_8O_2 + 1.6O_2 \rightarrow$$
$$C_{16}H_{18}O4N_2S + 0.36C_6H_9O_3N + 0.05C_8H_{12}O_3N_2S + 3.18CO_2 + 11.5H_2O \quad (12)$$

The components involved in the penicillin fermentation reactions are determined according to the above three main stoichiometric equations. The interface that sets the components are shown in Figure 1.

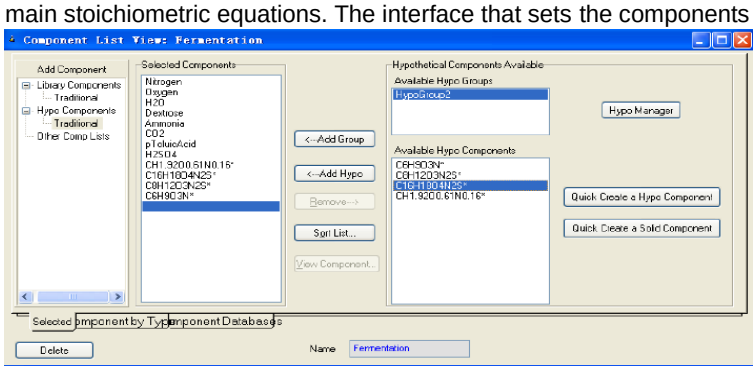

Figure 1: Interface setting of components

The NRTL equation is applicable to the gas-liquid phase calculations, so it can be chosen as the property package for penicillin fermentation. The interface that sets the property package is shown in Fig.2.

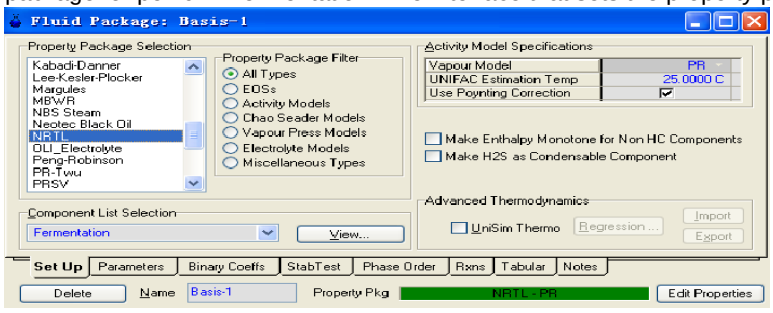

Figure 2: Interface setting of fluid package

3.2 Simulated flow chart for penicillin fermentation

We prepare the flow charts for the initialization, supplemented medium and fermentation tank modules respectively, and then obtain the general simulated flow chart for penicillin fermentation, as shown in Fig.3.
S_initial represents the feed inlet for the initial glucose solution, X_initial represents the feed inlet for the initial strain, and Water represents the inlet of the water solution. SControl, XControl, and WaterControl are used to control substrate concentration, bacterial concentration and water flow, respectively. MIX-initial acts as a pipe manifold. Supply is used to add material supplements in the fermentation process; FB-out is the outlet; the three PID controllers TIC-FB, FIC-FB and LIC-FB are used to control the temperature, flow and level of the fermentation broth, respectively; OS-FB is used to transfer data; TRF-FB is used to transfer materials; the vent gas is used to control the pressure inside the tank through PIC-gas; CW-in and CW-out are the inlet and outlet for the cooling water.

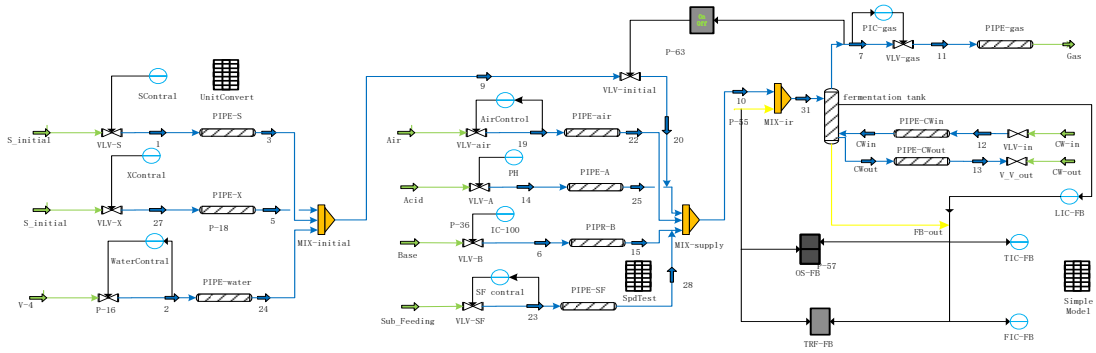

Figure 3: General simulated flow-chart for penicillin fermentation

4. Process simulation results and analysis

We use the UniSim Design R400 process simulation platform to study the specific conditions for the penicillin fermentation process so as to predict the potential problems in the production process and improve the ability to handle abnormal incidents.

4.1 Changing the initial conditions

With others remaining unchanged, we compare the product concentrations when the initial substrate concentrations are 15g/L, 25g/L and 30g/L, respectively. The simulated results are shown in Fig.4.

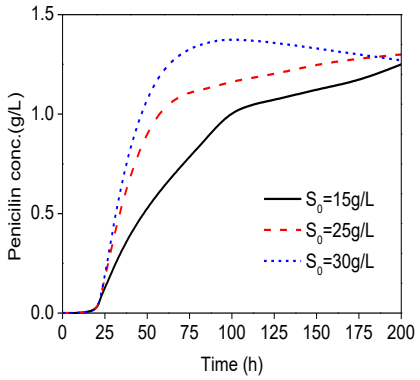

Figure 4: Diagram for process simulation under different initial conditions

It can be seen from the figure that the increase in the initial concentration of the substrate causes the penicillin production to rise over a certain period of time, but with the progress of fermentation, the penicillin production starts to decrease in the case where the initial substrate concentration is high. After 200h, the penicillin production at an initial substrate concentration of 30g/L is almost the same as that at an initial concentration of 15g/L, indicating that high concentration of substrate will inhibit the growth of bacteria. Therefore, before the actual production, we can apply the computer process simulation technology to simulate the fermentation process under different initial conditions, observe the product yields, and ultimately determine the most economical initial conditions.

4.2 Simulating equipment failures

During production, the equipment may encounter some failures, such as feeding valve blockage, which will result in the inability to supplement materials. So we simulate the blockage of the feeding valve - 95% of the valve is blocked and it continues throughout the entire fermentation process. The simulation results are shown in Fig.5.

As can be seen from the figure, when the feed pipe is blocked, after around 44 hours of fermentation, the bacteria will stop growing and penicillin will no longer be generated. If such situation occurs in actual production, we infer that the feed pipe is blocked.

In the production process, equipment or containers often leak. So we simulate a leakage of the pH control valve. We set the leakage to occur after 10 hours of fermentation, where 85% of the material is lost. Then we

compare the product concentration in the case of pH valve leakage and that under normal conditions, as shown in Fig.6.

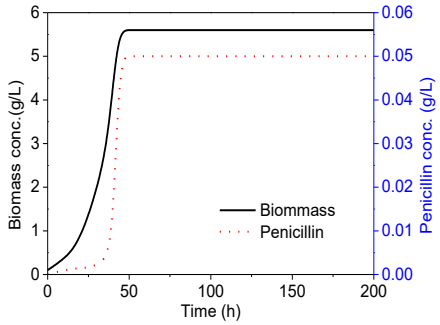

Figure 5: cell/product concentrations on conditions of feeding valve blocking

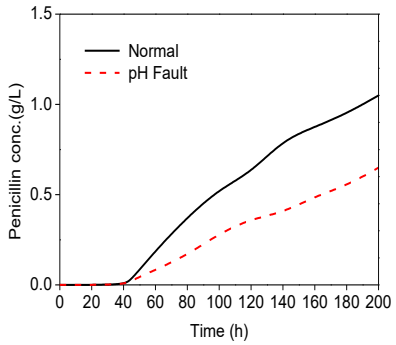

Figure 6: Comparison of product concentrations under normal and valve runaway condition

It can be seen from the figure that when the pH control line leaks, the pH value of the fermentation broth cannot be effectively controlled and the yield of penicillin is reduced. In the actual production process, if the trend of penicillin yield is similar to the curve shown in the figure, we should first consider whether there is any pipeline leakage.

4.3 Implementing different operating strategies

In the simulation process, we change some operating procedures or control strategies to study the variation trend of target production. According to the target requirements, we find the best operating procedure or appropriate control strategy. We carry out feeding at a constant speed. The solution is fed to the fermentation broth at a rate of 0.042L/h after 44 hours. Then we change the method to 0.042L/h after 62 hours and 0.03L/h after 63 hours. The simulated penicillin yield curves are compared in Fig.7.

It can be seen from the figure that the lower feed flow rate in the later stage of fermentation reduces the penicillin yield. Therefore, before the actual production, we can use the software to try different strategies first to select the most economical one, on the premises that the target can be met.

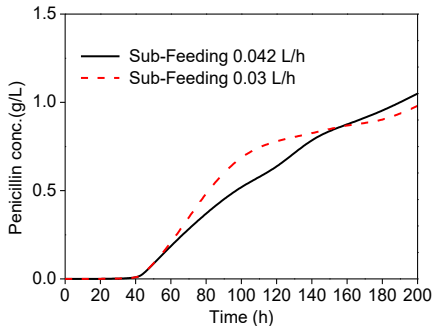

Figure 7: Comparison of penicillin yield at different feeding flows in process simulation

5. Conclusions

In this paper, we apply the computer process simulation technology to the fermentation process. We mainly use the flow simulation software UniSim Design R400 to study the penicillin fermentation process, and draw the following conclusions:

(1) We propose using the gravitation search algorithm to find the optimal parameters for the model and obtain the optimal kinetic equations for penicillin fermentation;

(2) We establish the initialization module, supplemented medium module and fermentation tank module for the penicillin fermentation process, complete the simulated operation of penicillin fermentation and validate the feasibility of the process simulation technology in fermentation processes.

(3) By changing the initial conditions, adjusting control strategies and setting equipment failures, we further study the working conditions for penicillin fermentation and get more familiar with the penicillin fermentation process.

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