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RESEARCH ARTICLE

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A cellular automata model for simulating fed-batch penicillin fermentation process

Abstract A cellular automata model to simulate penicillin fed-batch fermentation process (CAPFM) was established in this study, based on a morphologically structured dynamic penicillin production model, that is in turn based on the growth mechanism of penicillin producing microorganisms and the characteristics of penicillin fed-batch fermentation. CAPFM uses the three-dimensional cellular automata as a growth space, and a Moore-type neighborhood as the cellular neighborhood. The transition rules of CAPFM are designed based on mechanical and structural kinetic models of penicillin batch-fed fermentation processes. Every cell of CAPFM represents a single or specific number of penicillin producing microorganisms, and has various state. The simulation experimental results show that CAPFM replicates the evolutionary behavior of penicillin batch-fed fermentation processes described by the structured penicillin production kinetic model accordingly.

Keywords penicillin fermentation process, fermentation dynamics, morphologically structured model, cellular automata model

1 Introduction

Penicillin is mainly produced via the microorganism fermentation method. High cost and energy consumption are the characteristics of fermentation production. Hence, optimizing penicillin fermentation production processes is very important for reducing penicillin production cost, and increasing penicillin yield and quality.

The basis for optimizing penicillin fermentation production processes is the use of models that reflect the mechanism of the penicillin fermentation processes. The dynamic models are often used (Cuthrell and Biegler 1989; Luus 1993; Zuo and Wu 2000; Mahadevan et al., 2001). which are derived from microbiological and fermentation mechanisms done under ideal conditions. Dynamic models are determinate models. Penicillin fermentation dynamic models can be classified into two kinds. One is the morphologically structured model, and the other is non-structured model (Qi and Wang 1999). The non-structured models view microorganism cells as a uniformly distributed substance, don't consider the difference between various hypha, and only consider the connection between various megascopic variables. Morphologically structured models divide penicillin production hypha into various configurations according to different characteristics, and consider the different conditions that they operate in during substrate consumption, hypha growth and product synthesis. These two models have inherent advantages and disadvantages. The non-structured model is simple, and has only a few parameters. Non-structured models can simulate fermentation results with macroscopic variables (such as biomass, substrate and product concentrations). However, non-structured models view the various segments of hypha as uniformly integral, which is inconsistent with the real growth conditions of hypha. Morphologically structured models consider the different effect of various hypha configurations in biomass growth and product synthesis processes. Because there are many affecting factors and modeling parameters, however, the models are very complex.

Penicillin fermentation processes are complex biochemical processes, in a manner of speaking, and microorganisms are their basic elements. Although a single microorganism's bioactivity is relatively simple, the behavior of the entire biochemical process is very complex. This is the collective effect performed by numerous microorganisms in the penicillin fermentation process. As live bodies, the growth and propagation of microorganisms in the penicillin fermentation process can be regarded as the

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development of a syngen. The development depends on the living conditions, such as glucose and oxygen levels, degree of acidity or basicity, and so on. The interaction process between micro-populations and their existing environment is the process by which micro-populations develop their organization or appearance, and in addition is a self-organizing process. The mechanism of the biochemical reactions in a microorganism fermentation process is complex, with a dynamic behavior that is constantly changing. The diversity of evolutionary patterns, stochastic behavior, indeterminacy and sensitivity to initialization reflect the characteristics of a penicillin fermentation processes.

Previous studies have not treated penicillin fermentation processes as complex systems. The above models are unable to show the complex evolutionary characteristics of penicillin fermentation systems. The optimum control strategies based on these models have huge limitations, and are quite far from the optimum demand for actual penicillin fermentation processes. Artificial life systems, such as artificial cellular automata, are complex systems, and can double as natural life systems. They provide ideal live computing models for simulating and controlling natural complex systems. Studies show that cellular automata (CA) have the ability for describing complex system behavior (Ray 1994). This ability makes it possible to model, simulate and control penicillin fermentation processes based on cellular automata.

Based on a morphologically structured dynamic penicillin production model proposed by Paul and Thomas (Paul and Thomas 1996), this paper proposes a cellular automata model for simulating penicillin batch-fed fermentation processes (CAPFM for short). This is in accordance with the growth mechanisms of penicillin producing microorganisms and the characteristics of penicillin batch-fed fermentation. The simulation experimental results show that the model not only replicates the evolving characteristics of a penicillin batch-fed fermentation process described by Paul's morphologically structured dynamic model, but also depicts the dynamic evolving behavior of penicillin batch-fed fermentation processes in more detail than in Paul's morphologically structured dynamic model.

2 Penicillium growth mechanism and the morphologically structured model

2.1 Penicillium growth mechanism

Penicillium chrysogenum is characterized as an olive modal blue mold. It is fit for submerged fermentation, and is widely used in the industrial production of penicillin (Yang 2001). There are membranes in the *Penicillium chrysogenum* hyphae. These are multicellular filamentous hyphae whose entire growth cycle includes spore germinating, hypha growth tip extension, branch formation, differentiation and conidiophore forming. Hyphal fermentation dynamic models only consider hyphal growth under fermentation conditions, so spore germinating and conidiophore forming need not be considered. The increase of hyphal quantity only affects the extension and increasing the number of growth tips. When establishing the morphologically structured dynamic model of a penicillin fermentation process, Paul et al. divide penicillin hyphae into five distinct regions (Paul et al., 1998), in which $A_0$is actively growing region, A_1 non-growing or penicillin producing region, A_2 vacuoles in the non-growing region, A_3 degenerated or metabolically inactive region, A_4 autolysis region. In fermentation liquor, the dry weight concentrations of A_i,(i=0,1,2,3,4) are denoted by a_i,(i=0,1,2,3,4). The dry weight concentrations of the contributions of vacuoles are considered negligible. Total biomass (represented by a_i,(i=0,1,2,3,4)) is obtained by a summation of the A_0, A_1 and A_3 regions (or cells). The schematic representation of the above five hyphal regions is shown in Fig.1. The overall reaction scheme is given in Fig.2.

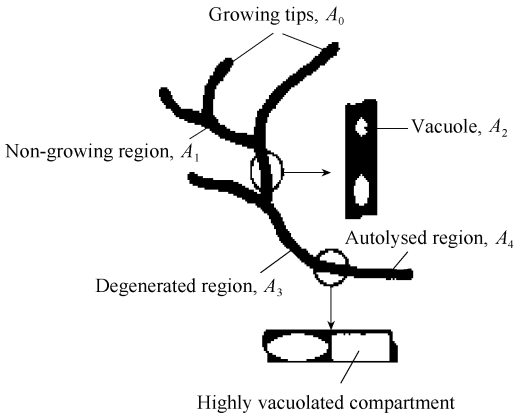

Fig. 1 Schematic representation of a *P. chrysogenum* mycelium in submerged fermentation

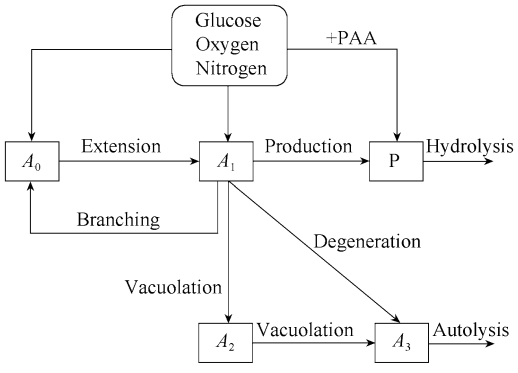

Fig. 2 Correlation scheme of various *P. chrysogenum* mycelium segments

2.2 Reductionistic morphologically structured fermentation process model

The aim for modeling penicillin fermentation processes is to

describe the dynamic characteristics of systems and provide computation models for system optimization and control. Active biomass concentration and penicillin final yield are the target variables in these models. Moreover, from the particular description of the dynamic of the penicillin fermentation process in literature(Yang 2001), we see that A_0 cells and A_1 cells affect the active biomass concentration of fermentation liquor, and A_1 cells directly affect the producing rate of penicillin. So, when using cellular automata to model penicillin fermentation processes, three processes (A_0 cell generation and differentiation, A_1 cell generation and degeneration, penicillin production) must be considered important. The reductionistic structured scheme of *Penicillium chrysogenum* hyphae is shown in Fig. 3, and various mycelium segments correlation scheme is shown in Fig. 4.

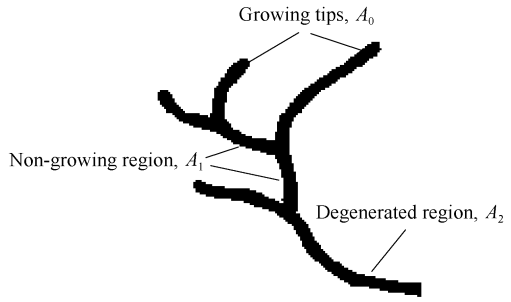

Fig.3 Schematic representation of P. chrysogenum simplified structure in submerged fermentation

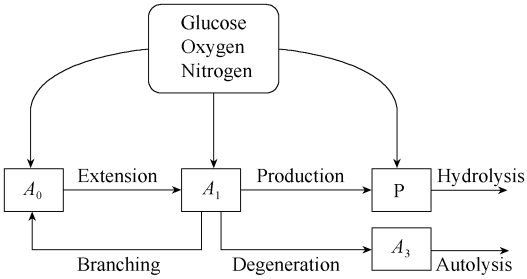

Fig. 4 Various mycelium segments correlation scheme

2.2.1 A_0 cell generation and differentiation

New growing regions (A_0 cells) are produced by the branches from A_1 cells. The process that A_1 cells produce branches is described by reaction (1)

$$A_1 + \alpha_0^{-1} S \rightarrow A_0 \tag{1}$$

α_0 is the stoichiometric coefficient [g • s • (g • A_0)$^{-1}$], S is the substrate in fermentation liquor. The rate [$r_{b.0}$, g • A_0 • h^{-1}] of formation of A_0 cells by branching is represented by Eq. (2), and the rate [$r_{s.0}$, g • s • h^{-1}] of substrate consumption in reaction (1) is represented by Eq. (3)

$$r_{b.0} = \frac{\mu_0 a_1 s}{K_0 + s} \tag{2}$$

$$r_{S.0} = \frac{\alpha_0 \mu_0 a_1 s}{K_0 + s} \tag{3}$$

s (g • L^{-1}) is the concentration of substrate, μ_0 is the rate constant (h^{-1}), K_0 is the saturation constant (g • L^{-1}), which is the substrate concentration supporting the reaction at half of its maximum rate.

The differentiation from A_0 cell to A_1 cell is affected by the substrate concentration in fermentation liquor, and the rate [$r_{d.1}$, g • A_1 • h^{-1}] of differentiation is represented by Eq. (4), and the rate [$r_{m.0}$, g • s • h^{-1}] of substrate consumption in differentiation process is represented by Eq. (5)

$$r_{d.1} = \frac{r_1 a_0}{K_1 + s} \tag{4}$$

$$r_{m.0} = \frac{m_0 a_0 s}{K_1 + s} \tag{5}$$

r_1 [g • s • h^{-1}] is the maximum rate of substrate utilization for the differentiation process from A_0 cell to A_1 cell, K_1 the saturation constant (g • L^{-1}), m_0 [g • s • (g A_0)$^{-1}$ • h^{-1}] the maintenance coefficient for A_0 cell. Eq. (4) implies that differentiation is inhibited by the presence of high concentration of substrate, but at very low substrate concentrations (e.g., during the production phase) the differentiation might be adequately described by first order kinetics in a_0 .

2.2.2 A_1 cell generation and degeneration

The growth of hypha is accomplished by the extension of the A_0 cell. This occurs when an A_0 cell grows and attains a certain length, and a septum is formed behind the tip. The tip is still the A_0 cell, but the hind part becomes the A_1 cell. The growth process is approximately represented by reaction Eq. (6).

$$A_0 + \alpha_e^{-1} S \rightarrow A_0 + A_1 \tag{6}$$

α_e is the stoichiometric coefficient [g • S • (g A_1)$^{-1}$].

The rate of reaction (6), $r_{e.1}$ [g • A_1 • h^{-1}], is represented by Eq. (7), and the rate [$r_{S.1}$, g • s • h^{-1}] of substrate consumption is represented by Eq. (8)

$$r_{e.1} = \frac{\mu_e a_0 s}{K_e + s} \tag{7}$$

$$r_{S.1} = \frac{\alpha_e \mu_e a_0 s}{K_e + s} \tag{8}$$

μ_e is the rate constant, and K_e is the saturation constant

($g \cdot L^{-1}$).

Because of the inhibition of substrate, vacuoles (A_2 cells) occur and grow in A_1 cells. When vacuoles increase in size under the condition of nutrient limitation in the medium, the cytoplasm left in A_1 cells decreases or disappears. Many A_1 cells with large vacuoles degenerate and transform into A_3 cells that do not contribute to penicillin biosynthesis. The rate ($r_{d.3}$) of A_1 cell degeneration is represented by Eq. (9). The rate ($r_{m.1}$, $g \cdot S \cdot h^{-1}$) of substrate consumption in this process is represented by Eq. (10)

$$r_{d.3} = \mu_3 a_1 \tag{9}$$

$$r_{m.1} = \frac{m_1 a_1 s}{K_2 + s} \tag{10}$$

μ_3 is the first order rate constant (h^{-1}), m_1 is the specific maintenance requirement for A_1 cells [$g \cdot S \cdot (g \cdot A_1)^{-1} \cdot h^{-1}$], and K_2 the substrate saturation constant (gL^{-1}).

When the vacuoles in A_3 cells become bigger and bigger, A_3 cells can either be autolyzed or fragmented by "shear" forces. The autolytic rate ($r_{d.4}$) of A_3 cells is represented by Eq. (11).

$$r_{d.4} = \mu_a a_3 \tag{11}$$

μ_a is the first order rate constant (h^{-1}).

2.2.3 Penicillin production and hydrolysis

Penicillin production is assumed to be relevant to A_1 cells only. When A_1 cells consume substrate, penicillin is synthesized simultaneously. But the excess substrate can inhibit penicillin production. The rate (r_P) of penicillin production is represented by Eq. (12). The rate ($r_{S.P}$) of substrate consumption in penicillin production process is represented by Eq. (13).

$$r_P = \frac{\mu_P a_1 s}{K_P + s(1 + s/K_I)} \tag{12}$$

$$r_{S.P} = \alpha_P r_P \tag{13}$$

μ_P is the specific penicillin production rate (h^{-1}). K_P is the saturation constant for substrate limitation for product formation ($g \cdot s \cdot L^{-1}$), K_I the saturation constant for substrate inhibition for product formation ($g \cdot S \cdot L^{-1}$), and α_P the stoichiometric coefficient.

Penicillin hydrolysis is considered to follow the first order kinetics in penicillin concentration in the broth. The penicillin hydrolysis rate （r_h）is represented by Eq. (14)

$$r_h = \mu_h p \tag{14}$$

μ_h is the first order penicillin hydrolysis constant (h^{-1}), and p is penicillin concentration.

2.2.4 Reductionistic morphologically structured model

According to the above discussion, the reductionistic morphologically structured dynamic model of penicillin fed-batch fermentation process is represented by Eq. (15)

$$\begin{cases} \dfrac{da_0}{dt} = r_{b.0} - r_{d.1} - \dfrac{Fa_0}{V} \\ \dfrac{da_1}{dt} = r_{e.1} - r_{b.0} + r_{d.1} - r_{d.3} - \dfrac{Fa_1}{V} \\ \dfrac{dp}{dt} = r_P - r_h - \dfrac{Fp}{V} \\ \dfrac{ds}{dt} = -\alpha_0 r_{b.0} - \alpha_e r_{e.1} - r_{m.0} - r_{m.1} - \alpha_P r_P - \dfrac{F(s_f - s)}{V} \\ \dfrac{dV}{dt} = F \end{cases} \tag{15}$$

V is the total fermenter volume (L), F is the rate of feed addition ($L \cdot h^{-1}$), and s_f is the concentration ($g \cdot L^{-1}$) of substrate in the feed.

Based on the experimental data presented in literature (Paul and Thomas 1996), the fitting values of various parameters in this reductionistic morphologically structured model are shown in table 1. This model can fit the experimental data of practical penicillin fermentation process well.

Table 1 Model parameters for fed-batch penicillin fermentation process

Parameters	Values
μ_0 (h^{-1})	0.105
μ_3 (h^{-1})	0.054
μ_e (h^{-1})	0.25
μ_P (h^{-1})	0.023
μ_h (h^{-1})	0.003
μ_a (h^{-1})	3.50E-3
γ_1 ($gSL^{-1}h^{-1}$)	5.36E-3
K_S ($cm\ h^{-1}$)	3.22E-5
m_0 ($g\ S(g\ A_0)^{-1}h^{-1}$)	0.029
m_1 ($g\ S(g\ A_1)^{-1}h^{-1}$)	0.029
α_0 ($g\ S(g\ A_0)^{-1}$)	2.10
α_e ($g\ S(g\ A_1)^{-1}$)	1.25
α_P ($g\ S(g\ P)^{-1}$)	1.00
K_0 ($g\ SL^{-1}$)	0.05
K_e ($g\ SL^{-1}$)	0.05
K_1 ($g\ SL^{-1}$)	0.05
K_2 ($g\ SL^{-1}$)	0.30
K_P ($g\ SL^{-1}$)	0.0002
K_I ($g\ SL^{-1}$)	0.002

3 CAPFM design

A three-dimensional cellular automaton is used as the growth space of a penicillin batch-fed fermentation process. Each cell of the model represents a specific number of penicillin production microorganisms, and has various state. In this cellular automaton, the growth evolvement process of *Penicillium chrysogenum* hyphae is the process where

every cell of the cellular automata model transforms their state values continuously. Thus, the cellular automata model of penicillin fermentation process is defined as a quintuple represented by Eq. (16)

$$\mathrm{CAPFM} = \langle t, \mathrm{Cells}, \mathrm{CellSpace}, \mathrm{Neighborhoods}, \mathrm{Rules} \rangle \quad (16)$$

t is discrete time, where each discrete time-step is represented by $t = kT_0$, where $k = \{0,1,2,...\}$ is the discrete time sequence, and T_0 the interval of discrete time. Cells are the primary elements (cells) of CAPFM. CellSpace is the set of all CAPFM cells. Neighborhoods are the neighbors of CAPFM cells (definition field of transition rules). Rules are the evolutionary rules that regulate the evolution of cell states.

3.1 Cell and cell space

Cells are the primary elements of CAPFM. Here, assuming that each CAPFM cell is a tiny cube, the edge length of each CAPFM cell is in millimeters. All CAPFM cells are linked in a regular crystal lattice, that compose the CAPFM CellSpace (Fig. 5). The CellSpace is located by a 3D coordinate system $O(i,j,k)$, where the cell located at (i,j,k) is denoted by $Cell(i,j,k)$, and the meridian cell located at the original point for the coordinate is denoted by $Cell(0,0,0)$. Thus, the CellSpace can be expressed by Eq. (17)

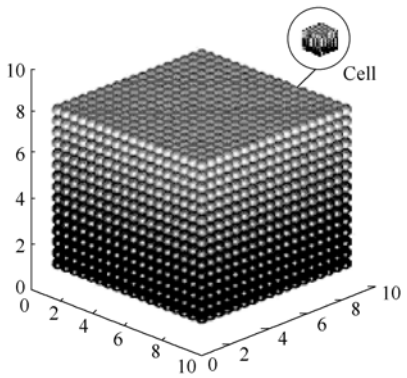

Fig. 5 The CellSpace of CAPFM

$$\mathrm{CellSpace} = \{Cell(i,j,k) \mid i,j,k \in \{0,1,2,\cdots,N\}\} \quad (17)$$

N is the cube root of biomass culture liquid volume, and $N \times N \times N$ is the total number of cells in CellSpace.

3.2 Neighborhood of CAPFM

The neighborhood of $Cell(i,j,k)$ is the evolutionary action range and the define area of CABGM transition rules is denoted by $V(Cell(i,j,k))$. Here, CAPFM adopts the Moore-neighborhood illustrated in Fig. 6 as its neighborhood. The neighborhood can also be expressed by Eq. (18)

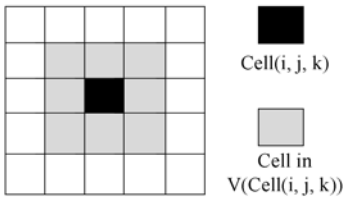

Fig.6 Two-dimensional Moore-neighborhood of CAPFM

$$V(Cell(i,j,k)) = \left\{ Cell(q,r,l) \middle| \begin{array}{l} q \in \{i-1,i,i+1\}, \\ r \in \{i-1,i,j+1\}, \\ I \in \{k-1,k,k+1\} \end{array} \right\} \setminus \{Cell(i,j,k)\} \quad (18)$$

3.3 Cell states of CAPFM

Each cell of CAPFM represents a specific number of penicillin-producing microorganisms, and has various state. If utilizing $S_{ijk}(t)$ to denote the state of $Cell(i,j,k)$ at time$t$, when simulating the evolution characteristics of penicillin fermentation process, $S_{ijk}(t)$ can take four different values expressed by Eq. (19), according to the reductionistic morphological structure of *Penicillium chrysogenum* hyphae described in section 1.2.4.

$$S_{ijk}(t) \in \{\mathrm{A}_0, \mathrm{A}_1, \mathrm{A}_3, \mathrm{O}\} \quad (19)$$

When $S_{ijk}(t)=A_0$, this means that $Cell(i,j,k)$ is the A_0 cell at time$t$. When $S_{ijk}(t)=A_1$, this means that $Cell(i,j,k)$ is the A_1 cell at time t. When $S_{ijk}(t)=A_3$, this means that $Cell(i,j,k)$ is A_3 cell at time t, and when $S_{ijk}(t)=O$ this means that $Cell(i,j,k)$ is empty or dead at time t. Thus, in CAPFM, the evolutionary process of biomass growth is the process where CAPFM cells change their state values among A_0, A_1, A_3 and O continuously.

3.4 Transition rules design of CAPFM

Transition rules of CAPFM have locality, which means that all CAPFM cells change their state depending only on the state of their adjacent cells. In other words, the cells' state at next time step is only relevant to the cells of their neighborhoods. CAPFM is synchronous, i.e. all CAPFM cells change their states simultaneously at any discrete time-steps according to transition rules.

Referring to the design method of cellular automata transition rules proposed in literature(Guinot 2002; Yu and Ruan 2004), on the reductionistic morphologically structured model proposed in section 1.2.4, and the dynamic mechanism of penicillin batch-fed fermentation processes, the transition rules f_ω are designed, where $\omega = 1,2,3$.

1）Rule f_1:

If $S_{ijk}(t) = O$, then $S_{ijk}(t+1) =$

$$\begin{cases} A_0 & \text{if } \exists\, q,r,l / Cell(q,r,l) \in V(Cell(i,j,k)) / S_{qrl}(t) = A_1 \\ & \quad \text{and } P_{O.A_0} > P_{O.A_0.Thr} \\ A_1 & \text{if } \exists\, q,r,l / Cell(q,r,l) \in V(Cell(i,j,k)) / S_{qrl}(t) = A_0 \\ & \quad \text{and } P_{O.A_1} > P_{O.A_1.Thr} \\ O & \text{else} \end{cases}$$

$P_{O.A_0}$ is the probability that A_1 cells produce A_0 cells by branching, its value is educed by Eq. (20). $P_{O.A_1}$ is the probability that A_0 cells produce A_1 cells by extending, its value is educed by Eq. (21). $P_{O.A_0.Thr}$ is the probability threshold that A_1 cells produce A_0 cells. $P_{O.A_1.Thr}$ is the probability threshold that A_0 cells produce A_1 cells. $P_{O.A_0.Thr}$ and $P_{O.A_1.Thr}$ should be determined according to specific fermentation conditions and mechanisms, and adjusted in simulation experiments.

$$P_{O.A_0} = \frac{\delta(A_1)}{26} \exp\left[\frac{r_{b.0}(KT_0) \times T_0}{a_0(KT_0)} \right] \tag{20}$$

$$P_{O.A_1} = \frac{\delta(A_0)}{26} \exp\left[\frac{r_{e.1}(KT_0) \times T_0}{a_1(KT_0)} \right] \tag{21}$$

$\delta(A_1)$ is the number of A_1 cells in the Moore neighborhood of the CAPFM $Cell(i,j,k)$. $\delta(A_0)$ is the number of A_0 cells in the Moore neighborhood of the CAPFM $Cell(i,j,k)$.

2）Rule f_2：

If $S_{ijk}(t) = A_0$ then $S_{ijk}(t+1) =$

$$\begin{cases} A_1 & \text{if } \exists\, q,r,l / Cell(q,r,l) \in V(Cell(i,j,k)) / S_{qrl}(t) = A_0 \\ & \quad \text{and } P_{A_0.A_1} > P_{A_0.A_1.Thr} \\ A_0 & \text{else} \end{cases}$$

$P_{A_0.A_1}$ is the differentiation probability from A_0 cells to A_1 cells, and its value is educed by Eq. (22). $P_{A_0.A_1.Thr}$ is the differentiation probability threshold from A_0 cells to A_1 cells. $P_{A_0.A_1.Thr}$ should be determined according to specific fermentation conditions and mechanisms, and adjusted in simulation experiments.

$$P_{A_0.A_1} = \frac{\delta(A_0)}{26} \exp\left[\frac{r_{d.1}(KT_0) \times T_0}{a_1(KT_0)} \right] \tag{22}$$

$\delta(A_0)$ is the number of A_0 cells in the Moore neighborhood of the CAPFM $Cell(i,j,k)$.

3）Rule f_3：

if $S_{ijk}(t) = A_1$ then $S_{ijk}(t+1) =$

$$\begin{cases} A_3 & \text{if } \exists\, q,r,l / Cell(q,r,l) \in V(Cell(i,j,k)) / S_{qrl}(t) = A_1 \\ & \quad \text{and } P_{A_1.A_3} > P_{A_1.A_3.Thr} \\ A_1 & \text{else} \end{cases}$$

$P_{A_1.A_3}$ is the transformation probability of A_1 cells to A_3 cells, and because of the form and growth of vacuoles, its value is educed by Eq. (23). $P_{A_1.A_3.Thr}$ is the transform probability threshold from A_1 cells to A_3 cells. $P_{A_1.A_3.Thr}$ should be determined according to specific fermentation conditions and mechanisms, and adjusted in simulation experiments.

$$P_{A_1.A_3} = \frac{\delta(A_1)}{26} \exp\left[\frac{r_{d3}(KT_0) \times T_0}{a_3(KT_0)} \right] \tag{23}$$

$\delta(A_1)$ is the number of A_1 cells in the Moore neighborhood of CAPFM $Cell(i,j,k)$.

4 Simulation experiment

4.1 Experimental method

Adopting the penicillin batch-fed fermentation process presented in literature (Paul and Thomas 1996) as the study object, we composed the simulation experimental program of CAPFM using the MATLAB language. The functions of this program include: 1) using the method introduced in section 2 to calculate the penicillin batch-fed fermentation process various components' concentration at every time kT_0; 2) implementing all transition rules, so as to make CAPFM evolve according to transition rules; 3) drawing the evolution configurations of CAPFM in two-dimensional state space automatically; 4) calculating the cell biomass concentrations a_0 and a_1 of CAPFM A_0 cells and A_1cells, and drawing evolution curves of cell biomass concentrations with time at every time kT_0; and 5) calculating the penicillin concentration at every corresponding time, based on the cell biomass concentrations a_0 and a_1 calculated in above step, using Eq. (15), and drawing evolutionary curves of penicillin concentration with time.

The statistical method of CAPFM determining the various A_2 cell biomass is used by regarding the quality of cell A_0, A_1 and A_3 as 1. Thus, when the number of A_0 cells is n_0, the number of A_1 cells is n_1, and the number of A_3 cells is n_3, with the total quality of CAPFM being $Q = n_0+n_1+n_3$. When β is defined as the transformation coefficient for CAPFM cells biomass concentration, the CAPFM cells biomass concentration a is expressed by Eq. (24).

$$a = \beta Q \tag{24}$$

β is determined by the initialization of CAPFM and the specific number of all penicillin-producing bacteria included in a single CAPFM cell.

4.2 Experimental results and discussion

Without losing generality, and assuming that CAPFM has

the initial configuration shown in Fig. 7, twenty-eight CAPFM cells are A_0 cells (denoted by green lattices), eighty-one CAPFM cells are A_1 cells (denoted by red lattices), and five CAPFM cells are A_3 cells (denoted by blue lattices) at starting time in two-dimensional state space, with all the other CAPFM cells at state O(denoted by yellow lattices).

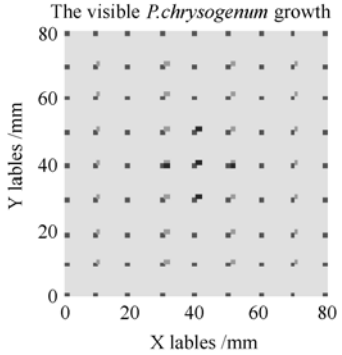

Fig. 7 The initial configuration of CAPFM

By analyzing the mechanism of practical penicillin batch-fed fermentation biomass growth dynamics and partial experimental verification, the discrete time interval of differential equation takes 0.1 h, the evolution time interval of CAPFM takes 1h. When CAPFM evolution program runs for one hundred and sixty hours, several evolution configurations of CAPFM in two-dimensional state space at different time steps are shown in Fig. 8. The evolution curves of the CAPFM A_0 and A_1 cell' biomass concentration with time are gained (Fig. 9). Taking the biomass concentrations of A_0 and A_1 cells into the reductionistic morphologically structured dynamic model of penicillin batch-fed fermentation process, the evolution curves of penicillin and substrate concentrations are gained (Fig. 10).

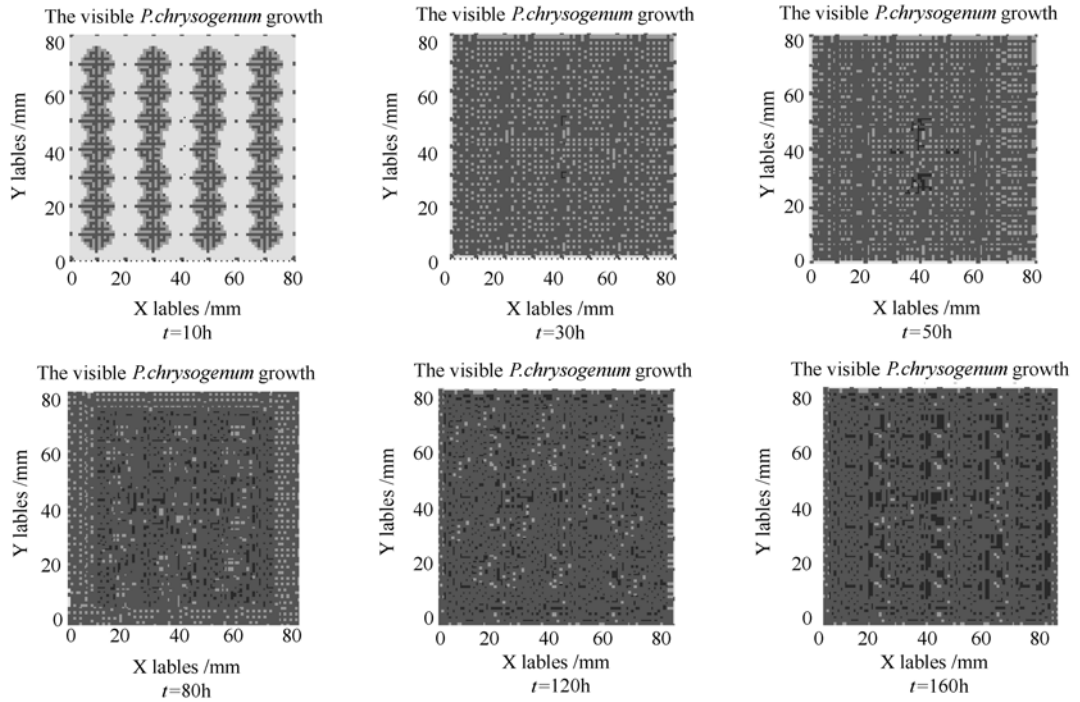

Fig. 8 Evolution configurations of CAPFM at different time steps

Figure 8 shows: 1) in thirty hours after CAPFM evolution started, the green and red areas grow rapidly, which shows that the *Penicillium chrysogenum* hyphae grow fast and no new A_3 cells are produced; 2) after CAPFM evolves for thirty hours, the red area continuously increases rapidly, the green area begins decreasing slowly, and the blue area begins increasing, which shows that the growth speed of *Penicillium chrysogenum* hyphae begins decreasing, and the A_3 cells begins appearing; 3) after CAPFM evolves for eighty hours, the green area continuously decreases, the blue area continuously increases, and red area does not change, which shows that cells in fermentation liquor stop growing, but are metabolically alive; 4) when CAPFM evolves up to one hundred and sixty hours, the green area almost disappears, the red area begins decreasing, and the blue area increases quickly, which shows that a plenty of A_3 cells begin appearing, and many cells begin autolyzing. It is obvious that the evolution configurations of CAPFM demonstrate the biomass growth evolutionary behavior of the penicillin batch-fed

fermentation process well.

The curves denoted by the small black and white squares in Fig. 9 clearly denote the evolution behavior of biomass

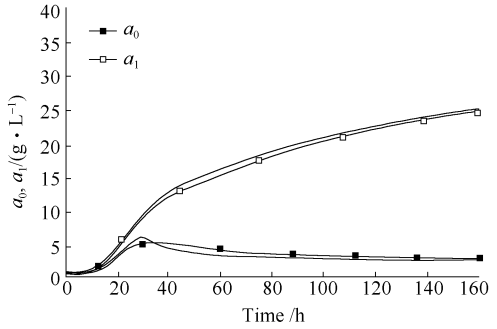

Fig.9 The evolution curves of various CAPFM cells' biomass concentrations

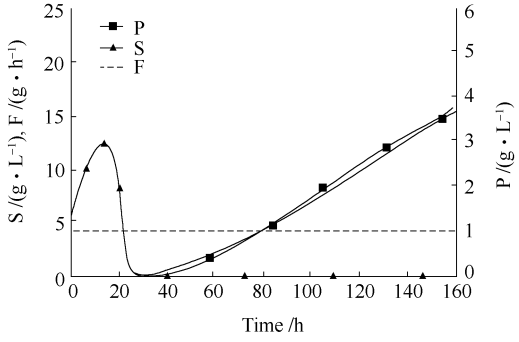

Fig.10 The evolution curves of CAPFM penicillin concentration and substrate concentration

concentrations a_0 and a_1 as confirmed by the penicillin batch-fed fermentation process reductionistic morphologically structured dynamic model. The other two curves clearly denote the evolution behaviour of biomass concentrations a_0 and a_1 as confirmed by CAPFM. The curves denoted by the small black triangles and diamonds in Fig. 10 clearly denote the evolution behavior of substrate concentration and penicillin concentration confirmed by the penicillin batch-fed fermentation process reductionistic morphologically structured dynamic model. The other two curves clearly denote the evolution behavior of substrate concentration and penicillin concentration confirmed by CAPFM. Fig.9 and Fig.10 show that the various component evolution curves of CAPFM demonstrate the various components' evolution behavior of the penicillin batch-fed fermentation process reductionistic morphologically structured dynamic model well. So, CAPFM can replicate the practical penicillin batch-fed fermentation process experimental data presented in literature (Paul and Thomas 1996) well.

5 Conclusion and foresight

Combining the producing microorganism growth mechanism and the Paul morphological structure dynamics model of a penicillin batch-fed fermentation process, this paper designs the random evolution rules of the penicillin batch-fed fermentation process CA model, and then establishes a visual probability CA model for simulating the penicillin fed-batch fermentation process, CAPFM for short. The results of simulation experiments show that CAPFM can replicate the penicillin batch-fed fermentation process described by the Paul morphological structure dynamics model accordingly. CAPFM establishes a foundation for studying the optimal control strategies of penicillin fermentation processes.

CAPFM is established based on the "Cellular Automata Model Simulating Penicillin Fermentation Process Biomass Growth" proposed by this paper's authors (Yu and Ruan 2004). CAPFM not only can be used to study the optimal feed problem of the penicillin batch-fed fermentation process, but also can be used to instruct operating crew to consider and adjust practical penicillin batch-fed fermentation processes.

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