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A Kinetic Modelling of Enzyme Inhibitions in the Central Metabolism of Yeast Cells

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Abstract. Metabolic regulation plays an important role in the metabolic engineering of a cellular process. It is conducted to improve the productivity of a microbial process by identifying the important regulatory nodes of a metabolic pathway such as fermentation pathway. Regulation of enzymes involved in a particular pathway can be held to improve the productivity of the system. In the central metabolism of yeast cell, some enzymes are known as regulating enzymes that can be inhibited to increase the production of ethanol. In this research we study the kinetic modelling of the enzymes in the central pathway of yeast metabolism by taking into consideration the enzyme inhibition effects to the ethanol production. The existence of positive steady state solution and the stability of the system are also analysed to study the property and dynamical behaviour of the system. One stable steady state of the system is produced if some conditions are fulfilled. The conditions concern to the restriction of the maximum reactions of the enzymes in the pyruvate and acetaldehyde branch points. There exists a certain time of fermentation reaction at which a maximum and a minimum ethanol productions are attained after regulating the system. Optimal ethanol concentration is also produced for a certain initial concentration of inhibitor.

1. Introduction

Mostly genetic engineering used metabolic engineering as a powerful tool for optimization and introduction of a new cellular process [1-5]. Since it has been studied in a multidisciplinary approach, success researches keep accumulating [5-10]. Biochemical information which can be accessed freely was underlying the strategies for experimental design to find the manipulation targets, and today, increasing of yield and productivity were being the main objectives of metabolic engineering [11]. Many researchers gave some reviews about theoretical and practical aspects of metabolic engineering [12-17]. Information about metabolic networks or enzymes would be underlying the essential prerequisite of a successful metabolic regulation [14]. Internal regulation of a metabolic pathway is one of the best practical ways to improve the productivity of the cell. It refers to the metabolic regulation level by regulating the metabolic fluxes in a metabolic network.

In order to coordinate the metabolic fluxes, activity of the key enzymes can be engineered such that cellular activities involving multiple enzymes can be improved. Introducing a molecule of inhibitor is one of the engineering choices for internal regulation since it acts to reduce the velocity of an enzymatic reaction. It exists naturally or can be introduced experimentally by using synthetic molecules. For instance, various kinds of inhibitor have been studied for designing and optimization performance of microbial yeast cell factories [7, 18-21]. It becomes an interesting study since different

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inhibitor may has different mechanism. Furthermore the mechanism can be approximated mathematically by using kinetic modeling such that theoretical aspect of this regulation can be captured.

In this paper, modeling the metabolic process of a yeast cell is studied as a premise to capture an optimal fermentation design such that an optimal productivity of yeast cell can be achieved. It is an interesting metabolic system since it consists of a multiple branched metabolic pathway that interact biochemically and a multiple reaction that is catalyzed by different enzymes [19]. Our study is focused on the main metabolic pathways, at the pyruvate and acetaldehyde branch points, where the overflow metabolism was occurred. Since enzymes became a key point in the metabolic network, regulation can be taken place through controlling the enzyme activity. Based on the study results of Kasbawati et al. [22], the key regulating enzymes reside at the pyruvate and acetaldehyde branch points. These enzymes have a significant effect in reducing and increasing the flux of ethanol. Here, we carry out kinetic modeling of ethanol production by taking into consideration effects of inhibitor molecules to the regulating enzymes in the culture medium. We assume that the inhibitor is introduced experimentally to regulate the metabolic fluxes of yeast cell such that flux of ethanol can be maximized.

This paper is organized as follows: in Section 2 we formulate the kinetic model of fermentation system by taking into consideration the inhibition of regulating enzyme at the pyruvate and acetaldehyde branch points. In Section 3, analytical results are presented to study the steady state condition of the system. Numerical simulation and some discussions are presented in Section 4, and conclusions are presented in the last section.

Kinetic Formulation

In this paper we propose a mathematical model describing the chemical conversion of metabolites in the central metabolism of yeast cell. We assume that the continuous fermentation process occurred at the ideal conditions. Carbon metabolism on the yeast metabolic pathway is started with the uptake of glucose that be converted becomes pyruvate via glycolysis pathway (r_1). We assume the glycolytic pathway as a lumped reaction [19]. Chemical conversion of glucose into pyruvate as the last product of glycolytic pathway is modeled using Michaelis-Menten [23] that is

$$r_1 = v_1 \frac{s_1}{s_1 + k_1} \tag{1}$$

where s_1 is the concentration of glucose, v_1 is the maximum uptake reaction and k_1 is the affinity constant for the glucose uptake reaction. In the yeast Saccharomyces cerevisiae metabolic pathway, pyruvate as the end-product of glycolysis is a branch-point between fermentative and respiratory sugar metabolism (see figure 1). The key enzymes for regulation purposes are located at the pyruvate branch-point. Here, pyruvate (s_2) is converted into three intermediate metabolites, i.e. oxaloacetate (s_3) and acetyl-coa (s_4) which lead to the key part of aerobic respiration of the yeast (TCA cycle), and acetaldehyde (s_5) which leads to the fermentative metabolism of sugar by yeast cells. These chemical conversion processes involve enzymes to catalyze the reactions and the kinetics follow the Michaelis-Menten kinetic equation, i.e.

$$r_i = v_i \frac{s_2}{s_2 + k_i}, i = 2, \ldots, 4 \tag{2}$$

where v_i is the maximum velocity of reaction and k_i is the affinity constant for each reaction. At the fermentative metabolism, acetaldehyde is converted to become acetate (s_6) and ethanol (s_7) where the conversion reactions also follow the Michaelis-Menten kinetic for reversible and irreversible mechanisms, respectively, i.e.

$$r_5 = \frac{v_{5f} k_{5b} s_5 - v_{5b} k_{5f} s_7}{k_{5f} k_{5b} + k_{5b} s_5 + k_{5f} s_7} \tag{3}$$

$$r_6 = v_6 \frac{s_5}{s_5 + k_6}, \tag{4}$$

where v_i is the maximum velocity of the every reaction and k_i is the affinity constant for each reaction (reversible or irreversible reaction). Under some conditions, enzyme acetyl-CoA synthetase then converts the acetate to become acetyl-coa that is leading to TCA cycle for respiration process. The conversion process fullfills

$$r_7 = v_7 \frac{s_6}{s_6 + k_7}. \tag{5}$$

where v_i is the maximum velocity of enzyme acetyl-CoA synthetase and k_i is the affinity constant of the enzyme.

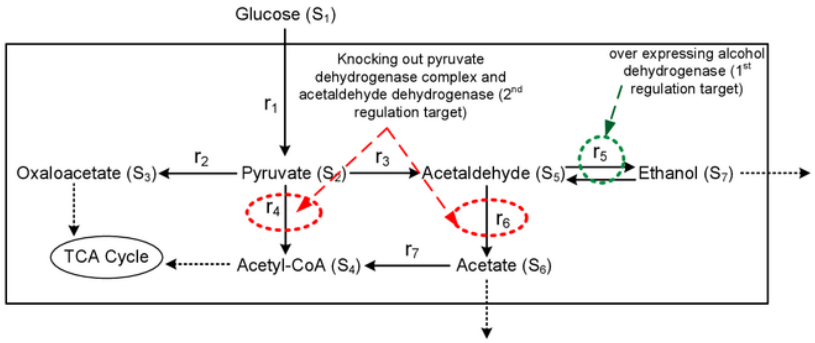

Figure 1. Central metabolism of *S. cerevisiae*. Reaction r_1 is a lumped process of glucose conversion to become pyruvate and reaction r_i, i=2, ..., 7 is a chemical conversion catalyzed by: (2) pyruvate carboxylase (3) pyruvate decarboxylase, (4) pyruvate dehydrogenase complex, (5) alcohol dehydrogenase, (6) acetaldehyde dehydrogenase, (7) acetyl-CoA synthetase. Reactions with cycle present enzymes for regulation target based on the sensitivity anaylisis results taken from [22].

In the previous study Kasbawati et al. [22] have showed that a fraction change of r_6 causes ethanol flux to decrease extremely. This reaction is catalyzed by acetaldehyde dehydrogenase and resides in the acetaldehyde branch point. Reducing the maximal rate of this reaction may lead the ethanol production to increases significantly. In fact, regulating r_6 leads also to regulate acetaldehyde branch point which involves r_4 and r_5. It is due to the stability condition for this branch, i.e. its maximum inflow should be less than its maximum outflow (see [22] for detail about the sensitivity results). Both reactions are respectively catalyzed by pyruvate decarboxylase and alcohol dehydrogenase which give positive control for ethanol flux. Therefore we have that enzymes in the acetaldehyde branch point are the key enzymes in the central metabolism of the yeast cell. An experimental observation showed that aspartate is an inhibitor for pyruvate dehydrogenase complex with inhibition constant, $k_i \approx 1.9$mM [19]. Some researchers also showed that furfural is another inhibitor for pyruvate dehydrogenase complex (r_4), alcohol dehydrogenase (r_5), and acetaldehyde dehydrogenase (r_6) with different inhibition pattern. It inhibits enzymes at the dehydrogenase classes. Activity of pyruvate dehydrogenase complex (PDH) and alcohol dehydrogenase (AlDH) decreased by more than 90% at a concentration of less than 2 mM furfural whereas the acetaldehyde dehydrogenase (ADH) activity decreased by less than 20% at the same concentration [20]. Mathematically, competitive inhibition model can be formulated to describe the inhibition effects of furfural to the ADH and AlDH activities

whereas noncompetitive inhibition model can be formulated to describe the inhibition effects of furfural to the PDH activity. By taking into consideration the furfural inhibition effects to the ADH, AlDH, and PDH, we then have the kinetic equations for these enzymes as follow

$$r_4 = v_4 \frac{s_2}{(s_2 + k_4) f(s_8)},\ r_5 = \frac{v_{5f} k_{5b} s_5 - v_{5b} k_{5f} s_7}{k_{5f} k_{5b} f(s_8) + k_{5b} s_5 + k_{5f} s_7},\ \text{and}\ r_6 = v_6 \frac{s_5}{s_5 + k_6 f(s_8)}$$

where $f(s_8) = 1 + s_8/(1+K)$ is an inhibition function that depends on the concentration of inhibitor s_8 with inhibition constant K. We assume that the concentration of inhibitor s_8 decreases with respect to the time t such that we have

$$\frac{ds_8(t)}{dt} = -\alpha s_8, \tag{6}$$

with the rate constant α. We assume that the inhibitor is only introduced to the system at the initial of reaction. There is no continuously inhibitor supply. If we assume that the initial concentration of inhibitor s_8 is $s_8(0) = p$ then from Equation (6) we get $s_8(t) = p\exp(-\delta t)$. For a long time of reaction, the inhibition function becomes $\lim_{t\to\infty} f(s_8) = \lim_{t\to\infty}\left(1 + \frac{pe^{-\delta t}}{1+K}\right) = 1$. Therefore by using the mass action rate law for the central metabolism of the yeast cell, we have the following nonlinear differential equation system,

$$\begin{aligned}
\dot{s}_1(t) &= \alpha G - v_1 \frac{s_1}{s_1 + k_1} = f_1,\\
\dot{s}_2(t) f_2 &= v_1 \frac{s_1}{s_1 + k_1} - \left(v_2 \frac{s_2}{s_2 + k_2} + v_3 \frac{s_2}{s_2 + k_3} + v_4 \frac{s_2}{(s_2 + k_4)\left(1 + \frac{s_8}{[1+K]}\right)} \right) = f_2,\\
\dot{s}_3(t) &= v_2 \frac{s_2}{s_2 + k_2} - \alpha s_3 = f_3,\\
\dot{s}_4(t) &= \left(v_4 \frac{s_2}{(s_2 + k_4)\left(1 + \frac{s_8}{[1+K]}\right)} + v_7 \frac{s_6}{s_6 + k_7} \right) - \alpha s_4 = f_4,\\
\dot{s}_5(t) &= v_3 \frac{s_2}{s_2 + k_3} - \left[\frac{v_{5f} k_{5b} s_5 - v_{5b} k_{5f} s_7}{k_{5f} k_{5b}\left(1 + \frac{s_8}{[1+K]}\right) + k_{5b} s_5 + k_{5f} s_7} + v_6 \frac{s_5}{s_5 + k_6\left(1 + \frac{s_8}{[1+K]}\right)} \right] = f_5,\\
\dot{s}_6(t) &= v_6 \frac{s_5}{s_5 + k_6\left(1 + \frac{s_8}{[1+K]}\right)} - v_7 \frac{s_6}{s_6 + k_7} - \alpha s_6 = f_6,\\
\dot{s}_7(t) &= \frac{v_{5f} k_{5b} s_5 - v_{5b} k_{5f} s_7}{k_{5f} k_{5b}\left(1 + \frac{s_8}{[1+K]}\right) + k_{5b} s_5 + k_{5f} s_7} - \alpha s_7 = f_7,\\
\dot{s}_8(t) &= -\delta s_8 = f_8,
\end{aligned} \tag{7}$$

with initial concentration for each metabolite: $s_1(0) = s_{1_0}, s_2(0) = s_{2_0}, s_3(0) = s_{3_0}, s_4(0) = s_{4_0}$, $s_5(0) = s_{5_0}, s_6(0) = s_{6_0}$, and $s_7(0) = s_{7_0}$. Since we model a continues fermentation system, the term αG in the model denotes the continues inflow of glucose supply and αs_i denotes the continuous outflow of products, $i = 3,4,6,7$, where α is a dilution rate that represents the volumetric flow rate of glucose supplied to the culture medium divided by the volume of the culture, i.e. $0<\alpha<1$ [24].

3. Mathematical Analysis

In this section we analyze the stability of the positive steady state solution of system (7) defined in the region $R_+^8 = \{(s_1, s_2, s_3, s_4, s_5, s_6, s_7, s_8) \in R^8 : s_i \geq 0, i = 1,...,8\}$. At the equilibrium condition we have $f_i = 0,\ i = 1,...,7$. Therefore from $f_1 = 0$ we have

$$s_1^* = \frac{\alpha G k_1}{v_1 - \alpha G}. \tag{8}$$

If $v_1 > \alpha G$ then we have $s_1^* > 0$ defined in R_+^8. Since $s_8^* = 0$ then for $f_2 = 0$ we get cubic polynomial in s_2 as follow,

$$a_1(s_2)^3 + a_2(s_2)^2 + a_3(s_2) + a_4 = 0 \tag{9}$$

with $a_1 = (v_2 + v_3 + v_4) - \alpha G$, $a_2 = (v_3 + v_4 - \alpha G)k_2 + (v_2 + v_4 - \alpha G)k_3 + (v_2 + v_3 - \alpha G)k_4$,
$a_3 = (v_2 - \alpha G)k_3 k_4 + (v_3 - \alpha G)k_2 k_4 + (v_4 - \alpha G)k_2 k_3$, $a_4 = -\alpha G k_2 k_3 k_4$.
If $v_i > \alpha G,\ i = 1,...,4$ then $a_i > 0,\ i = 1,2,3$. Since a_4 is negative then there exists one sign change of the coefficients of polynomial (9). Therefore based on Descartes' rule of sign, polynomial (9) has only one positive root. Furthermore consider $f_3 = 0$ and $f_4 = 0$. From these equations we get $s_3^* = \frac{v_2 s_2^*}{(s_2^* + k_2)\alpha}$ and $s_4^* = \frac{1}{\alpha}\left[\frac{v_3 s_2^*}{(s_2^* + k_3)} + \frac{v_7 s_6^*}{(s_6^* + k_7)}\right]$, which depend on s_2^* and s_6^*. Meanwhile from $f_7 = 0$ we have $s_5^* = \frac{k_{5f} s_7^* (v_{5b} + \alpha k_{5b} + \alpha s_7^*)}{k_{5b}(v_{5f} - \alpha s_7^*)}$ which depends on s_7^* that will be positive if it fulfils the condition $s_7^* < \frac{v_{5f}}{\alpha}$.
By substituting s_5^* to the equation $f_5 = 0$ we get a cubic polynomial in s_7 as follows

$$b_1(s_7)^3 + b_2(s_7)^2 + b_3(s_7) + b_4 = 0 \tag{10}$$

with $b_1 = -\alpha^2 k_{5f}$, $b_2 = k_{5b}\alpha^2(k_6 - k_{5f}) - k_{5f}\alpha\left(v_6 + v_{5b} - \frac{v_3 s_2^*}{s_2^* + k_3}\right)$, $b_3 = -\left(v_6 - \frac{v_3 s_2^*}{s_2^* + k_3}\right)(v_{5b} k_{5f} + \alpha k_{5b} k_{5f}) - \left(\frac{\alpha k_{5b} k_6 v_3 s_2^*}{s_2^* + k_3} + v_{5f}\alpha k_{5b} k_6\right)$
and $b_4 = \frac{v_3 s_2^*}{s_2^* + k_3} k_6 k_{5b} v_{5f}$. Since $b_1 < 0$ and $b_4 > 0$ then polynomial (14) will produce at least one positive root defined in R_+^8. This positive root fulfils the condition $0 < s_7^* < \frac{v_{5f}}{\alpha}$. Last equation is $f_6 = 0$. This equation generates a quadratic polynomial

$$c_1(s_6)^2 + c_2(s_6) + c_3 = 0 \tag{11}$$

with $c_1 = \alpha$, $c_2 = \alpha k_7 + v_7 - \left(\frac{v_6 s_5^*}{s_5^* + k_6}\right)$, $c_3 = -\left(\frac{v_6 s_5^* k_7}{s_5^* + k_6}\right)$. Since $c_1 > 0$ and $c_3 < 0$ then polynomial (15) will produce one positive root defined in R_+^8. Therefore in conclusion, system (11) has only one positive steady state solution defined in R_+^8 if it fulfils the conditions $v_i > \alpha G,\ i = 1,...,4$ and $0 < s_7^* < \frac{v_{5f}}{\alpha}$. We define the steady state solution as follows,

$$E = (s_1^*, \cdots, s_8^*) = \left(\frac{\alpha G k_1}{v_1 - \alpha G}, s_2^*, \frac{v_2 s_2^*}{(s_2^* + k_2)\alpha}, \frac{1}{\alpha}\left[\frac{v_3 s_2^*}{(s_2^* + k_3)} + \frac{v_7 s_6^*}{(s_6^* + k_7)}\right], \frac{k_{5f} s_7^* (v_{5b} + \alpha k_{5b} + \alpha s_7^*)}{k_{5b}(v_{5f} - \alpha s_7^*)}, s_6^*, s_7^*, 0\right)$$

where s_6^* and s_7^* are the solutions of polynomial (10) and (11). By linearizing system (7) arround the equilibrium point E, it gives a linearized system $\dot{\mathbf{s}}(t) = J\mathbf{s}(t)$ where $\mathbf{s}(t) = (s_1(t),...,s_8(t))$ and $J = \begin{bmatrix} J_1 & 0 \\ J_2 & J_3 \end{bmatrix}$ is a Jacobian matrix with

$$J_1 = \begin{bmatrix} -\frac{(v_1-\alpha G)^2}{v_1 k_1} & 0 & 0 \\ \frac{(v_1-\alpha G)^2}{v_1 k_1} & -\sum_{i=2}^{4}\frac{v_i k_i}{(s_2^*+k_i)^2} & 0 \\ 0 & \frac{v_2 k_2}{(s_2^*+k_2)^2} & -\alpha \end{bmatrix}, J_2 = \begin{bmatrix} 0 & \frac{v_3 k_3}{(s_2^*+k_3)^2} & 0 \\ 0 & \frac{v_4 k_4}{(s_2^*+k_4)^2} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, J_3 = \begin{bmatrix} -\alpha & 0 & \frac{v_7 k_7}{(s_6^*+k_7)^2} & 0 & 0 \\ 0 & -\left(\frac{v_6 k_6}{(s_5^*+k_6)^2}+\Delta_1\right) & 0 & \Delta_1 & 0 \\ 0 & \frac{v_6 k_6}{(s_5^*+k_6)^2} & -\frac{v_7 k_7}{(s_6^*+k_7)^2}-\alpha & 0 & 0 \\ 0 & \Delta_2 & 0 & -(\Delta_2+\alpha) & 0 \\ 0 & 0 & 0 & 0 & -\delta \end{bmatrix}$$

$\Delta_1 = \frac{k_{5f}k_{5b}(k_{5f}v_{5b}+s_5^*(v_{5f}+v_{5b}))}{(k_{5f}k_{5b}+k_{5b}s_5^*+k_{5f}s_7^*)^2}$, $\Delta_2 = \frac{k_{5f}k_{5b}(k_{5b}v_{5f}+s_7^*(v_{5f}+v_{5b}))}{(k_{5f}k_{5b}+k_{5b}s_5^*+k_{5f}s_7^*)^2}$. Jacobian matrix J generates a characteristic equation, $\det(\lambda I_3 - J_1) = 0$ or $\det(\lambda I_5 - J_3) = 0$. From $\det(\lambda I_3 - J_1) = 0$ we get

$$\lambda_1 = -\frac{(v_1-\alpha G)^2}{v_1 k_1},\ \lambda_2 = -\sum_{i=2}^{4}\frac{v_i k_i}{(s_2^*+k_i)^2},\ \lambda_3 = -\alpha, \text{ and } \left(\lambda+\frac{(v_1-\alpha G)^2}{v_1 k_1}\right)\left(\lambda+\sum_{i=2}^{4}\frac{v_i k_i}{(s_2^*+k_i)^2}\right)(\lambda+\alpha) = 0.$$

While from $\det(\lambda I_5 - J_3) = 0$ we get $\lambda_4 = -\left[\frac{v_7 k_7}{(s_6^*+k_7)^2}+\alpha\right]$, $\lambda_5 = -\alpha$, $\lambda_6 = -\delta$, and λ_7 and λ_8 which are the roots of polynomial $\lambda^2 + d_1\lambda + d_2 = 0$ with $d_1 = \left(\alpha+\Delta_1+\Delta_2+\frac{v_6 k_6}{(s_5^*+k_6)^2}\right)$, $d_2 = \frac{\Delta_1 v_6 k_6}{(s_5^*+k_6)^2}+\frac{\alpha v_6 k_6}{(s_5^*+k_6)^2}+\alpha\Delta_2$.

Since d_1>0 and d_2>0, then we get negative eigenvalues such that the equilibrium point E is locally asymptotically stable.

4. Numerical Results

In this section we present numerical simulation of the model using kinetic parameter values given in table 1. This simulation is generated to capture the dynamical behavior of the solutions of the model and to analyze the inhibition effect of furfural with respect to the ethanol production. In this simulation we assume that the initial concentrations of variables are $s_1(0)$=83 g/l, $s_8(0)$=10 g/l, and $s_i(0)$=0 for all i=2,...7. Figure 2 shows the comparison of the model with and without inhibition effects. We can observe that the existence of furfural in fermentation system has significantly affected the production of acetyl-coa, acetate and ethanol. As shown in figure 2, regulation of the enzymes at the pyruvate and acetaldehyde branch points decreases the concentration of acetyl-coa and acetate. In contrast, regulation of the fermentation system increases ethanol production as expected. Therefore this inhibitor has reduced the production of acetyl-coa as well as acetate. These simulation results are in agreement with the fact that furfural can inhibit the activity of pyruvate dehydrogenase complex in r_4, alcohol dehydrogenase in r_5, and acetaldehyde dehydrogenase in r_6. For ethanol observation, although both solutions converge to the same equilibrium solution, their transient behaviors are different (see figure 2). After regulating the fermentation system, ethanol concentration increases. However there exists a certain time at which the ethanol production decreases and goes to zero. It means that there exists a certain time at which the ethanol production reaches a maximum production and a minimum production (see figure 3).

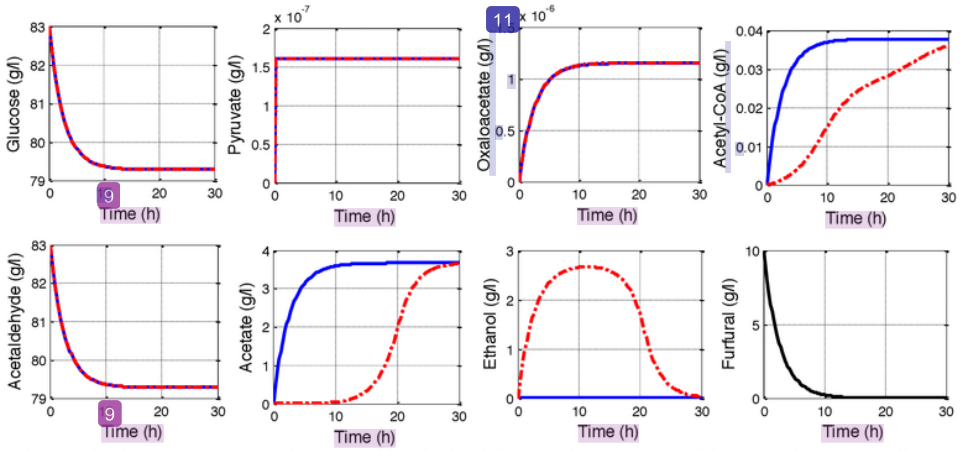

Figure 2. Comparison of solutions with (dashed line) and without (solid line) inhibition effects.

Table 1. Parameter value of parameter of the model.

Parameter	Value	Ref.	Parameter	Value	Ref.
α	0.38 1/h	[25]	vf	23 g/lh	[25]
v1	1.43 g/lh	[25]	kf	0.034 g/l	[25]
k1	0.94 g/l	[25]	vb	0.0125 g/lh	[25]
v2	648 g/lh	[26]	kb	0.057 g/l	[25]
k2	237.5 g/l	[26]	v6	4.8 g/lh	[25]
v3	5.81 g/lh	[25]	k6	2.64x10-4	[25]
k3	5x10-7 g/l	[25]	v7	0.0104 g/lh	[25]
v4	0.501 g/lh	[25]	k7	0.0102 g/l	[25]
k4	2x10-5 g/l	[25]	K	0.0019	[19]

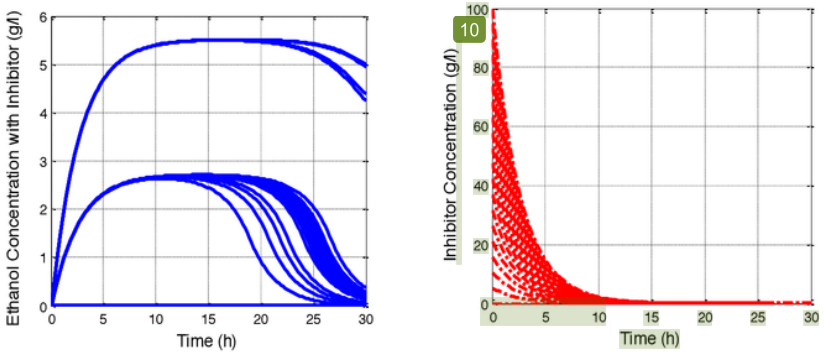

Figure 3. Simulations of ethanol concentration (left) and inhibitor concentration (right) for different initial concentration of inhibitor.

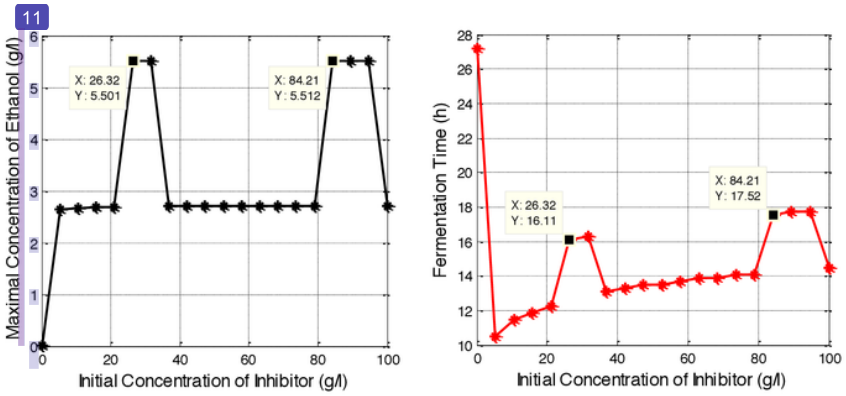

Figure 4. Graphs of maximal ethanol concentration (left) and fermentation time (right) with respect to the initial concentration of inhibitor. The fermentation time indicates the time span of fermentation required to produce a maximal ethanol concentration.

Furthermore, in figure 4, we present the simulation results for different initial concentration of inhibitor. We can observe that different initial concentration of inhibitor will produce different maximal concentration of ethanol (see the left picture in figure 4). Some initial concentrations of inhibitor produce almost similar maximal concentration of ethanol. While some other initial concentrations of inhibitor produce maximal concentration of ethanol which is higher than the previous one. For instance, by using 26 g/l initial concentration of inhibitor and by running the fermentation about 16 hours, it produces ethanol concentration about 5.5 g/l. Similar result is attained when we set the initial concentration of inhibitor becomes 84 g/l and run the fermentation reaction about 17.5 hours. Although the two schemes of fermentation system generate a similar result, the first scheme is more efficient than the second one since it only needs lower initial inhibitor concentration and shorter fermentation time to produce maximum ethanol concentration. Therefore experimentally, initial concentration of inhibitor and length of fermentation time should be set appropriately such that a maximum concentration of ethanol can be attained efficiently.

Conclusion

In this paper we formulated a mathematical model of the central metabolism of yeast cell by taking into consideration the inhibitions of some regulation enzymes at the pyruvate and acetaldehyde branch points. The inhibition mechanisms followed the competitive and noncompetitive inhibition mechanisms. Analytically the system produced one stable steady state if it fulfilled some existences and stability conditions that restricted the maximum reaction of enzymes at the pyruvate and acetaldehyde branch points. Numerically we found that inhibitions of the regulating enzymes affected the production of ethanol significantly. There existed a certain fermentation time at which ethanol production attained a minimum and a maximum concentration after regulating the system. There also existed a certain initial concentration of inhibitor that produced a maximum ethanol concentration in a short time of fermentation reaction.

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