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A STOCHASTIC MODEL FOR MICROBIAL FERMENTATION PROCESS UNDER GAUSSIAN WHITE NOISE ENVIRONMENT

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Abstract. In this paper, we propose a stochastic model for the microbial fermentation process under the framework of white noise analysis, where Gaussian white noises are used to model the environmental noises and the specific growth rate is driven by Gaussian white noises. In order to keep the regularity of the terminal time, the adjustment factors are added in the volatility coefficients of the stochastic model. Then we prove some fundamental properties of the stochastic model: the regularity of the terminal time, the existence and uniqueness of a solution and the continuous dependence of the solution on the initial values.

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1. **Introduction.**

In recent years there has been an increasing attention in microorganisms and their activities. This is due to their lower cost, higher production and no pollution in industrial applications [13, 14, 2]. In order to understand the exact mechanism of microbial fermentation, many works have been done to develop mathematical models simulating the actual microbial fermentation processes. We take the production of L-glutamic acid (LGA) by Corynebacterium glutamicum as an example, where LGA is produced commercially under aerobic fermentation conditions, the C. glutamicum undergo stresses, and the specific growth rate of C. glutamicum is continuously decreasing with the increase of product concentration (i.e. product inhibition occurs) and a low level of dissolved oxygen concentration ([5, 18, 4, 7, 8]). On the base of formal kinetic approach, Bona and Moser [3] proposed a mathematical model for L-glutamic acid production process, which included formal growth inhibition with product and production repression with substrate. Suresh et al. [16] developed the model in [3] by considering the growth-associated product formation conditions. Tian et al [17] presented a mathematical model of bioprocess with product inhibition and impulse effect. In these models, the microbial fermentation process are described by deterministic differential equations.

The deterministic microbial fermentation model requires that the parameters involved are completely known. However, in the real-world system, some parameters of the microbial fermentation model may fluctuate due to the environmental noises, which are usually random. Therefore stochastic influences are considered by many authors in the model to conform with the actual fermentation. For example, Soboleva et al [15] presented a stochastic model for calculating the time-dependent probability distribution of the microbial population size under arbitrary changes of temperature through time. Albert et al [1] gave a stochastic *Listeria monocytogenes* growth model in milk at the farm bulk tank stage. Kutalik et al [9] presented deterministic models of the lag and subsequent growth of a bacterial population and analyzed their connection with stochastic models for the lag and subsequent generation times of individual cells. Li and Mao considered a non-autonomous stochastic Lotka-Volterra competitive system in [10]. Wang et al [19, 20] formulated a stochastic model for the bioconversion of glycerol to 1,3-propanediol by Klebsiella pneumoniae in batch culture, where the microbial fermentation process is described by the stochastic differential equations driven by five-dimensional Brownian motion. Considering the actual microbial fermentation process, the stochastic models in [19, 20] may lose the regularity of the terminal time, for the initial value of the substrate concentration may be greater than the maximum concentrations of substrate and no product comes into being at the beginning of the microbial fermentation process. The regularity of the terminal time is an essential factor for the rationality of the stochastic system [11]. If the terminal time is irregular, it is possible that the terminal time → 0 occurs, which is irrational for a stochastic microbial fermentation model. Therefore, the stochastic models in [19, 20] require to be modified to ensure the regularity of the terminal time, which motivates our work.

In this paper we propose a stochastic microbial fermentation model under the framework of white noise analysis. Gaussian white noises are used to model the environmental noises and the specific growth rate is driven by Gaussian white noises. In order to ensure the regularity of the terminal time, we add two adjustment factors in the volatility coefficients of the stochastic model. Then, in the proposed stochastic model, we prove the regularity of the terminal time, the existence and uniqueness of a solution and the continuous dependence of the solution on the initial value, which are fundamental properties for the further analysis of the stochastic microbial fermentation model.

The paper is organized as follows: in Section 2 we formulate a stochastic model for the microbial fermentation process, where Gaussian white noise is used to model the environmental noises and the specific growth rate is driven by Gaussian white noise. Some properties of the stochastic microbial fermentation model are considered in Section 3, such as the regularity of the terminal time, the existence and uniqueness of a solution and the continuous dependence of the solution on the initial value. Finally we conclude this paper in Section 4.

Notations: Throughout this paper, Let $X_1(t)$ denote the biomass concentration (gl^{-1}); $X_2(t)$ the substrate concentration (gl^{-1}); $X_3(t)$ the product concentration (gl^{-1}); $\mu_{max} \in \mathbb{R}$ the maximal specific growth rate (h.1); $K_2 \in \mathbb{R}$ the substrate saturation constant (gl^{-1}); $K_3 \in \mathbb{R}$ growth inhibition constant by product (gl^{-1}); $q_{1,2} \in \mathbb{R}$ yield coefficient biomass from substrate (gg^{-1}); $q_{3,2} \in \mathbb{R}$ yield coefficient product from substrate (gg^{-1}); $q_{3,1} \in \mathbb{R}$ denotes the growth-associated constant (gg^{-1}); $W(t)$ denotes a 1−dimensional (1-parameter) Gaussian singular white noise process; $(\mathcal{S})^*$ denotes a Hida distribution space; $\{B_t\}_{t\geq 0}$ denotes a standard Brownian Motion defined on a probability space $(\Omega, \mathcal{F}, P)$.

2. A stochastic model for the microbial fermentation process under uncertainty.

A microbial fermentation model is composed of three equations: a growth equation, a substrate equation, and a product equation. Taking the production of L-glutamic acid (LGA) by Corynebacterium glutamicum as an example, they describe the kinetic behaviors of the concentration of bacteria $X_1(t)$, the sugar (glucose) $X_2(t)$, and LGA $X_3(t)$, respectively. In this paper, we use the microbial fermentation model developed by Bona and Moser (1997) [3] and Suresh et al.(2009) [16] as follows:

$$\frac{dX_1(t)}{dt} = \mu(X_2, X_3)X_1(t), \tag{1}$$

$$\frac{dX_2(t)}{dt} = -\frac{1}{q_{1,2}} \cdot \frac{dX_1(t)}{dt} - \frac{1}{q_{3,2}} \cdot \frac{dX_3(t)}{dt}, \tag{2}$$

$$\frac{dX_3(t)}{dt} = q_{3,1}\frac{dX_1(t)}{dt}, \tag{3}$$

where $\mu(X_2, X_3)$ is the specific growth rate and it is given by

$$\mu(X_2, X_3) = \frac{\mu_{max}X_2(t)}{X_2(t) + K_2(1 + X_3(t)/K_3)}.$$

$\mu_{max} \in \mathbb{R}$ is the maximal specific growth rate. $K_2 \in \mathbb{R}$ is the substrate saturation constant and $K_3 \in \mathbb{R}$ denotes growth inhibition constant by product. $q_{1,2}, q_{3,2}, q_{3,1} \in \mathbb{R}$ yield coefficient biomass from substrate, coefficient product from substrate and the growth-associated constant, respectively. The initial conditions are given by $X_1(0) = x_1 \in \mathbb{R}$, $X_2(0) = x_2 \in \mathbb{R}$ and $X_3(0) = x_3 \in \mathbb{R}$.

The modeling of the system (1)-(3) requires that the parameters involved are completely known. However, in the real-world system, the specific growth rate $\mu(X_2, X_3)$ may fluctuate due to some environmental noises, which are random.

This paper is designated to propose a realistic stochastic model for the microbial fermentation process. We use the Gaussian white noises to model the environmental noises. Let $W(t)$ be a 1−dimensional (1-parameter) Gaussian singular white noise process defined on a Hida distribution space $(\mathcal{S})^*$. Assume that the specific growth rate $\mu(X_2, X_3)$ is subject to the Gaussian white noises $W(t)$ as follows:

$$\mu(X_2, X_3) + W(t).$$

Then the deterministic microbial fermentation model (1)-(3) is improved as the stochastic model driven by Gaussian white noises:

$$\frac{dX_1(t)}{dt} = \mu(X_2, X_3)X_1(t) + X_1(t) \diamond W(t), \tag{4}$$

$$\frac{dX_2(t)}{dt} = -\left(\frac{1}{q_{1,2}} + \frac{q_{3,1}}{q_{3,2}}\right)\mu(X_2, X_3)X_1(t) - \left(\frac{1}{q_{1,2}} + \frac{q_{3,1}}{q_{3,2}}\right)X_1(t) \diamond W(t), \tag{5}$$

$$\frac{dX_3(t)}{dt} = q_{3,1} \cdot \mu(X_2, X_3)X_1(t) + q_{3,1} \cdot X_1(t) \diamond W(t), \tag{6}$$

where $X_1(t) \diamond W(t)$ is the Wick product of two elements $X_1(t), W(t) \in (\mathcal{S})^*$ and $\int X_1(t) \diamond W(t)dt$ is interpreted as an $(\mathcal{S})^*$-valued Pettis integral. (We refer to [6] for more information about the framework of Gaussian white noise.)

The stochastic model (4)-(6) can be transformed into the stochastic differential equations driven by Brownian motion under the framework of Gaussian white noise, for the full information of $X_1(t)$ is available at time t. Let $(\Omega, \mathcal{F}, P)$ be a probability space and let $\{B_t\}_{t\geq 0}$ be a standard Brownian Motion defined on it. $\mathcal{F}_t = \sigma(B_s; 0 \leq s \leq t)$ denotes the natural filtration generated by $\{B_t\}_{t\geq 0}$. Then we have

Theorem 2.1. *For $T > 0$, the stochastic model driven by Gaussian white noises (4)-(6) can be transformed into the SDEs on $[0, T]$ as follows*

$$dX_1(t) = \mu(X_2, X_3)X_1(t)dt + X_1(t)dB(t), \tag{7}$$

$$dX_2(t) = -\left(\frac{1}{q_{1,2}} + \frac{q_{3,1}}{q_{3,2}}\right)\mu(X_2, X_3)X_1(t)dt - \left(\frac{1}{q_{1,2}} + \frac{q_{3,1}}{q_{3,2}}\right)X_1(t)dB(t), \tag{8}$$

$$dX_3(t) = q_{3,1}\mu(X_2, X_3)X_1(t)dt + q_{3,1}X_1(t)dB(t) \tag{9}$$

with initial conditions $X_1(0) = x_1 \in \mathbb{R}$, $X_2(0) = x_2 \in \mathbb{R}$ and $X_3(0) = x_3 \in \mathbb{R}$.

Proof of Theorem 2.1. It suffices to prove Eq.(7), for the proofs of Eq.(8) and Eq.(9) are similar. Let $\int X_1(t)\delta B(t)$ be Skorohod integral of $X_1(t)$ (see Definition 2.5.1. in [6]). Then, by the relation of the Wick product to Skorohod integral (see Theorem 2.5.9 in [6]), Eq.(4) can be written as

$$dX_1(t) = \mu(X_2, X_3)X_1(t)dt + X_1(t)\delta B(t). \tag{10}$$

Since the full information of $X_1(t)$ is available at time t, $X_1(t)$ is $\mathcal{F}_t-$adapted processes such that

$$\int_0^T E\left[X_1^2(t)\right]dt < \infty \quad \text{for} \quad T > 0.$$

In view of the relation between Skorohod integral and Itô integral (see Proposition 2.5.4 in [6]), we can write Eq.(10) as Eq.(7) on $[0, T]$. □

For the sake of simplicity, we define the systemic state $X(t)$ of a microbial fermentation process as

$$X(t) = \begin{pmatrix} X_1(t) \\ X_2(t) \\ X_3(t) \end{pmatrix} \qquad \text{with} \qquad X(0) = x = \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix}.$$

Then, by the stochastic model (7)-(9), the systemic state $X(t)$ is of the following form

$$dX(t) = \begin{pmatrix} \mu(X_2, X_3)X_1(t) \\ -\left(\frac{1}{q_{1,2}} + \frac{q_{3,1}}{q_{3,2}}\right)\mu(X_2, X_3)X_1(t) \\ q_{3,1} \cdot \mu(X_2, X_3)X_1(t) \end{pmatrix} dt + \begin{pmatrix} X_1(t) \\ -\left(\frac{1}{q_{1,2}} + \frac{q_{3,1}}{q_{3,2}}\right)X_1(t) \\ q_{3,1} \cdot X_1(t) \end{pmatrix} dB(t). \tag{11}$$

Now we consider the terminal time of the stochastic system (11). The microbial fermentation process $X(t)$ is restricted on an interval $[0, T]$ and on a Borel set $\mathcal{G}$. In reality, $\mathcal{G}$ is of the following form

$$\mathcal{G} = \{x = (x_1, x_2, x_3) \in \mathbb{R}^3; 0 < x_1 < \rho_1, 0 < x_2 \le \rho_2, 0 \le x_3 < \rho_3\},$$

where the constants ρ_1, ρ_2 and ρ_3 denote the maximum concentrations of biomass, substrate and product in the bioreactor medium (gl^{-1}), respectively. Let $\tau_{\mathcal{G}}$ be the first exiting time of $\mathcal{G}$ for $X(t)$, i.e.,

$$\tau_{\mathcal{G}} = \inf\{t > 0; X(t) \notin \mathcal{G}\}.$$

Then the terminal time is $T \wedge \tau_{\mathcal{G}}$ for the stochastic system (11).

The regularity of the terminal time $T \wedge \tau_{\mathcal{G}}$ is an essential factor for the rationality of the stochastic system (11). If the terminal time $T \wedge \tau_{\mathcal{G}}$ is regular, it is impossible that the event $T \wedge \tau_{\mathcal{G}} \to 0$ occurs. In the following, we define the regularity of the terminal time.

Definition 2.2. [11] Let $T \in (0, \infty)$. The terminal time $T \wedge \tau_{\mathcal{G}}$ is called *regular* for the stochastic system (11) if there exists a constant $\delta > 0$ such that $\tau_{\mathcal{G}} > \delta$ almost surely for all initial values $x \in \mathcal{G}$.

Considering the actual microbial fermentation process, we find that the terminal time is possibly irregular in the stochastic system (11), which is due to two facts:

- It is possible that the initial value of the substrate concentration $X_2(t)$ is greater than ρ_2. Then, depending on (8), the probability of $X_2(\Delta t) > \rho_2$ is greater than 0 as $\Delta t \to 0$.
- It is usually assumed that $X_3(0) = x_3 = 0$, for no product comes into being at the beginning of the microbial fermentation process. According to (9), the probability $X_3(\Delta t) < 0$ is greater than 0 as $\Delta t \to 0$.

In both of the above cases, the terminal time $T \wedge \tau_{\mathcal{G}}$ loses the regularity in the stochastic system (11), for the probability of $\tau_{\mathcal{G}} \to 0$ is greater than 0. Consequently, It is indispensable that the stochastic system (11) is improved to ensure the regularity of the terminal time.

We make improvement on the stochastic system (11) by adding respectively adjustment factors

$$\frac{\chi_{\{X_2(t)<\rho_2\}}(X_2(t) - \rho_2)}{X_1(t)} \quad \text{and} \quad \frac{\chi_{\{X_3(t)>0\}}X_3(t)}{X_1(t)}$$

in the volatility coefficient of (8) and Eq.(9), where χ_E is the indicator function of an event E. As such, the stochastic system (11) is modified as

$$\begin{aligned} dX(t) &= b(X(t))dt + \sigma(X(t))dB(t), \\ X(0) &= x \in \mathcal{G}, \end{aligned} \tag{12}$$

where

$$b(X(t)) = \begin{pmatrix} \mu(X_2, X_3)X_1(t) \\ -\left(\frac{1}{q_{1,2}} + \frac{q_{3,1}}{q_{3,2}}\right)\mu(X_2, X_3)X_1(t) \\ q_{3,1}\mu(X_2, X_3)X_1(t) \end{pmatrix}$$

and

$$\sigma(X(t)) = \begin{pmatrix} X_1(t) \\ -\left(\frac{1}{q_{1,2}} + \frac{q_{3,1}}{q_{3,2}}\right)\chi_{\{X_2(t)<\rho_2\}}(X_2(t) - \rho_2) \\ q_{3,1}\chi_{\{X_3(t)>0\}}X_3(t) \end{pmatrix}.$$

Thus we propose the stochastic microbial fermentation model (12) described by the stochastic differential equation (12). It is obvious that the state $X(t)$ of the stochastic system (12) is an Itô diffusion.

3. The properties of the stochastic microbial fermentation model.

In this section, we discuss some properties of the stochastic model (12), such as the regularity of the terminal time, the existence and uniqueness of a solution and the continuous dependence of the solution on initial value. These properties are fundamental for the further analysis of the stochastic microbial fermentation model.

Firstly we consider the regularity of the terminal time for the stochastic system (12).

Theorem 3.1. *Let $T \in (0, \infty)$. The terminal time $T \wedge \tau_{\mathcal{G}}$ is regular in the stochastic system* (12).

Proof of Theorem 3.1. In the stochastic system (12), We get by Itô formula that

$$X_1(t) = x_1 \exp\{B(t) + (\mu(X_2, X_3) - 1/2)t\}.$$

$X_1(t)$ is a geometric Brownian motion. Therefore $X_1(t) > 0$ *a.s.* for all $X_1(0) = x_1 \in (0, \rho_1)$. Let

$$\tau_1 = \inf\{t > 0; X_1(t) \notin (0, \rho_1)\}.$$

Since the path of $X_1(t)$ is continuous *a.s.*, there exists a constant $\delta_1 > 0$ such that $\tau_1 > \delta_1$ holds *a.s.* for all $x_1 \in (0, \rho_1)$.

By adding regular factor $\frac{\chi_{\{X_2(t)<\rho_2\}}(X_2(t)-\rho_2)}{X_1(t)}$, it is obvious that $X_2(t) \leq \rho_2$ holds *a.s.* for all $X_2(0) = x_2 \in (0, \rho_2]$. Let

$$\tau_2 = \inf\{t > 0; X_2(t) \notin (0, \rho_2]\}.$$

Since the paths of $X_2(t)$ are continuous *a.s.*, there exists a constant $\delta_2 > 0$ such that $\tau_2 > \delta_2$ holds *a.s.* for all $x_2 \in (0, \rho_2]$.

Similarly, we have $X_3(t) > 0$ holds *a.s.* for all $X_3(0) = x_3 \in [0, \rho_3)$. Let

$$\tau_3 = \inf\{t > 0; X_3(t) \notin [0, \rho_3)\}.$$

Since the paths of $X_3(t)$ are continuous *a.s.*, there is a constant $\delta_3 > 0$ such that $\tau_3 > \delta_3$ holds *a.s.* for all $x_3 \in [0, \rho_3)$.

It is obvious that

$$\tau_{\mathcal{G}} = \tau_1 \wedge \tau_3 \wedge \tau_3.$$

Let $\delta := \delta_1 \wedge \delta_2 \wedge \delta_3$. Then there is a constant $\delta > 0$ such that $\tau_{\mathcal{G}} > \delta$ holds *a.s.* for all $x \in \mathcal{G}$. Therefore the terminal time $T \wedge \tau_{\mathcal{G}}$ is regular in the stochastic system (12). □

Next we discuss the existence and the uniqueness of a solution for the stochastic system (12) on $[0, T \wedge \tau_{\mathcal{G}}]$ in $\mathcal{G}$. In the theory of stochastic differential equations, Lipschitz continuity of the coefficients is typically required to ensure the existence and the uniqueness of a solution. Therefore, we begin by stating a lemma which shows the coefficients is Lipschtiz continuous in stochastic system (12). Note that we may extend, for technical reasons, the discussions on $[0, T]$ due to the fact that $[0, T \wedge \tau_{\mathcal{G}}] \subset [0, T]$.

Lemma 3.2. *Let $T > 0$. Then the drift coefficient $b(\cdot)$ and the volality coefficient $\sigma(.)$ of the stochastic system (12) are Lipschitz continuous on $[0, T]$, i.e.,*

$$|b(x) - b(y)| + |\sigma(x) - \sigma(y)| \le D|x - y|; \quad \text{for } x, y \in \mathbb{R}^3, \quad t \in [0, T] \tag{13}$$

for some constant D.

Proof of Lemma 3.2. Let $x = (x_1, x_2, x_3) \in \mathbb{R}^3$ and $y = (y_1, y_2, y_3) \in \mathbb{R}^3$. For notational simplicity, we define

$$\theta := 1/q_{1,2} + q_{3,1}/q_{3,2} \qquad \text{and} \qquad \kappa := \sqrt{1 + \theta^2 + q_{3,1}^2}.$$

We firstly consider

$$|\sigma(x) - \sigma(y)| = \Big((x_1 - y_1)^2 + \theta^2 \left(\chi_{\{x_2<\rho_2\}}(x_2 - \rho_2) - \chi_{\{y_2<\rho_2\}}(y_2 - \rho_2)\right)^2 + q_{3,1}^2 \left(\chi_{\{x_3>0\}}x_3 - \chi_{\{y_3>0\}}y_3\right)^2\Big)^{1/2}.$$

There are four cases of $\left(\chi_{\{x_3(t)>0\}}x_3(t) - \chi_{\{y_3(t)>0\}}y_3(t)\right)^2$ with respect to the values of x_3 and y_3.

1. If $x_3 \le 0$ and $y_3 \le 0$, we have $\left(\chi_{\{x_3>0\}}x_3 - \chi_{\{y_3>0\}}y_3\right)^2 = 0$;
2. If $x_3 > 0$ and $y_3 \le 0$, we have $\left(\chi_{\{x_3>0\}}x_3 - \chi_{\{y_3>0\}}y_3\right)^2 = x_3^2 \le (x_3 - y_3)^2$;
3. If $x_3 \le 0$ and $y_3 > 0$, we have $\left(\chi_{\{x_3>0\}}x_3 - \chi_{\{y_3>0\}}y_3\right)^2 = y_3^2 \le (x_3 - y_3)^2$;
4. If $x_3 > 0$ and $y_3 > 0$, we have $\left(\chi_{\{x_3>0\}}x_3 - \chi_{\{y_3>0\}}y_3\right)^2 = (x_3 - y_3)^2$.

Hence we conclude that

$$\left(\chi_{\{x_3>0\}}x_3 - \chi_{\{y_3>0\}}y_3\right)^2 \le (x_3 - y_3)^2. \tag{14}$$

Similarly we have

$$\left(\chi_{\{x_2<\rho_2\}}(x_2 - \rho_2) - \chi_{\{y_2<\rho_2\}}(y_2 - \rho_2)\right)^2 \le (x_2 - y_2)^2. \tag{15}$$

Let

$$\iota_1 = 1 \vee \theta^2 \vee q_{3,1}^2.$$

we get by combining (14) and (15)

$$|\sigma(x) - \sigma(y)| \le \sqrt{\iota_1}|x - y| \quad \text{for} \quad x, y \in \mathbb{R}^3 \tag{16}$$

Next we consider

$$\begin{aligned} |b(x) - b(y)| \le& \kappa\sqrt{(\mu(x_2, x_3)x_1 - \mu(y_2, y_3)y_1)^2} \\ =& \kappa\sqrt{2(\mu(x_2, x_3) - \mu(y_2, y_3))^2 x_1^2 + 2\mu(y_2, y_3)^2(x_1 - y_1)^2} \end{aligned} \tag{17}$$

Since $\mu(y_2, y_3)$ and x_1 are continuous on $[0, T]$, there exist $M_3 \in [0, \infty)$ and $M_4 \in [0, \infty)$ such that $|\mu(y_2, y_3)| \le M_3$ and $|x_1| \le M_4$. By the definition of $\mu(x_2, x_3)$, we have

$$\begin{aligned}&|\mu(x_2,x_3)-\mu(y_2,y_3)|\\ =&\mu_{max}\left|\frac{K_2(x_2-y_2)+(K_2/K_3)y_3(x_2-y_2)+(K_2/K_3)y_2(y_3-x_3)}{(x_2+K_2+(K_2/K_3)x_3)\,(y_2+K_2+(K_2/K_3)y_3)}\right|.\end{aligned}\tag{18}$$

Since y_2 and y_3 are continuous on $[0,T]$, there exist $M_1 \in [0,\infty)$ and $M_2 \in [0,\infty)$ such that $|y_2| \le M_1$ and $|y_3| \le M_2$. Moreover $K_2 \ge 0$ and $K_3 \ge 0$ hold. Thus (18) gives

$$\begin{aligned}&|\mu(x_2,x_3)-\mu(y_2,y_3)|\\ \le&\frac{\mu_{max}\left(K_2|x_2-y_2|+(K_2/K_3)|y_3||x_2-y_2|+(K_2/K_3)|y_2||x_3-y_3|\right)}{(|x_2|+K_2+(K_2/K_3)|x_3|)\,(|y_2|+K_2+(K_2/K_3)|y_3|)}\\ \le&(\mu_{max}/K_2^2)\left[(K_2+(K_2/K_3)M_2)\,|x_2-y_2|+(K_2/K_3)M_1|x_3-y_3|\right].\end{aligned}\tag{19}$$

Therefore, by combining (17) and (19), we get

$$\begin{aligned}|b(x)-b(y)| \le&\kappa\left[2M_4^2(\mu_x-\mu_y)^2+2M_3^2(x_1-y_1)^2\right]^{\frac{1}{2}}\\ \le&\kappa\left[\frac{4M_4\mu_{max}^2(1+M_2/K_3)^2}{K_2^2}(x_2-y_2)^2\right.\\ &\left.+\frac{4M_4\mu_{max}^2M_1^2}{K_2^2K_3^2}(x_3-y_3)^2+2M_3^2(x_1-y_1)^2\right]^{\frac{1}{2}}\end{aligned}$$

Let

$$\iota_2=\frac{4M_4\mu_{max}^2(1+M_2/K_3)^2}{K_2^2}\vee\frac{4M_4\mu_{max}^2M_1^2}{K_2^2K_3^2}\vee 2M_3^2.$$

Then we have

$$|b(x)-b(y)| \le \kappa\sqrt{\iota_2}|x-y|.\tag{20}$$

Combining (16) and (20), we get

$$|b(x)-b(y)|+|\sigma(x)-\sigma(y)| \le (\sqrt{\iota_1}+\kappa\sqrt{\iota_2})|x-y|, \quad \text{for} \quad x,y\in\mathbb{R}^3,$$

where κ, ι_1 and ι_2 are constants. Let $D=\sqrt{\iota_1}+\kappa\sqrt{\iota_2}$. Then we obtain (13), which completes the whole proof. □

We are now able to obtain the existence and the uniqueness of a solution for the stochastic system (12).

Theorem 3.3. *Let $T>0$. Then the stochastic system (12) has a unique $t-$continuous solution $X(t,\omega)$ on $[0,T]$ in $\mathcal{G}$, with the properties that*

$$X(t,\omega) \textit{ is adapted to the filtration } \mathcal{F}_t\tag{21}$$

and

$$E\left[\int_0^T |X(t)|^2dt\right]<\infty.\tag{22}$$

Proof of Theorem 3.3. We have obtained the drift coefficient $b(\cdot)$ and the volality coefficient $\sigma(.)$ of (12) are Lipschitz continuous on $[0,T]$ in Lemma 3.2. It is obvious that the stochastic system (12) is an Itô diffusion. In the case of Itô diffusion, Lipschitz continuity of $b(\cdot)$ and $\sigma(.)$ implies that $b(\cdot)$ and $\sigma(\cdot)$ are at most linear growth on $[0,T]$, *i.e.*

$$|b(x)|+|\sigma(x)| \le \alpha(1+|x|); \qquad x,y\in\mathbb{R}^3, \qquad t\in[0,T]$$

for some constant α. By the classical existence and uniqueness theorem for SDE (see Theorem 5.2.1 in [12]), we conclude that (12) has a unique $t-$continuous solution $X(t,\omega)$ on $[0,T]$ in $\mathcal{G}$, with the properties (21) and (22). $\square$

Remark 1. Here the uniqueness that we obtain is called strong or pathwise uniqueness. It means that if $X(t,\omega)$ and $Y(t,\omega)$ be two $t-$continuous stochastic processes satisfying (12), (21), and (22), then $X(t,\omega)=Y(t,\omega)$ for all $t\leq T$, a.s..

At the end of this section, we give the continuous dependence of the solution on the initial value in the stochastic system (12) on $[0,T]$.

Theorem 3.4. *For $T>0$, let $X(t;x)$ and $X(t;y)$ be solutions of Eq. (12) with initial values x and y on $[0,T]$, respectively. Then*

$$E\left[\sup_{0\leq t\leq T}|X(t;x)-X(t;y)|^{2p}\right]\leq C|x-y|^{2p} \tag{23}$$

holds for any fixed $2\leq p<\infty$, where C is a constant that depends only on T and p.

Proof of Theorem 3.4. Applying Itô formula to $|X(t;x)-X(t;y)|^2$, we have

$$\begin{aligned}d|X(t;x)-X(t;y)|^2 =&d\left(X(t;x)-X(t;y)\right)^2\\ =&2\left(X(t;x)-X(t;y)\right)\left(b(X(t;x))-b(X(t;y))\right)dt\\ &+2\left(X(t;x)-X(t;y)\right)\left(\sigma(X(t;x))-\sigma(X(t;y))\right)dB_t\\ &+\left(\sigma(X(t;x))-\sigma(X(t;y))\right)^2dt.\end{aligned} \tag{24}$$

Using the Cauchy-Schwarz inequality we obtain

$$\begin{aligned}&\left(X(t;x)-X(t;y)\right)\left(b(X(t;x))-b(X(t;y))\right)\\ \leq&|X(t;x)-X(t;y)||b(X(t;x))-b(X(t;y))|.\end{aligned}$$

Therefore, by Lipschitz continuity of b and Lipschitz continuity of σ, (24) gives

$$\begin{aligned}d|X(t;x)-X(t;y)|^2\leq&(2\kappa\sqrt{\iota_2}+\iota_1)|X(t;x)-X(t;y)|^2dt\\ &+2\left(X(t;x)-X(t;y)\right)\left(\sigma(X(t;x))-\sigma(X(t;y))\right)dB_t,\end{aligned} \tag{25}$$

where $\kappa\sqrt{\iota_2}$ is the Lipschitz constant of b and $\sqrt{\iota_1}$ is the Lipschitz constant of σ.

We write (25) as the corresponding stochastic integral equation of the following form

$$\begin{aligned}|X(t;x)-X(t;y)|^2\leq&|x-y|^2+(2\kappa\sqrt{\iota_2}+\iota_1)\int_0^t|X(s;x)-X(s;y)|^2ds\\ &+2\int_0^t\left(X(s;x)-X(s;y)\right)\left(\sigma(X(s;x))-\sigma(X(s;y))\right)dB_s.\end{aligned}$$

Then, for $p\geq 2$, there exists a constant c_p such that

$$\begin{aligned}&|X(t;x)-X(t;y)|^{2p}\\ \leq&c_p|x-y|^{2p}+c_p(2\kappa\sqrt{\iota_2}+\iota_1)^p\left[\int_0^t|X(s;x)-X(s;y)|^2ds\right]^p\\ &+2c_p\left(\int_0^t\left(X(s;x)-X(s;y)\right)\left(\sigma(X(s;x))-\sigma(X(s;y))\right)dB_s\right)^p.\end{aligned} \tag{26}$$

By Hölder's inequality, the following inequality holds for $p \geq 2$

$$\left[\int_0^t |X(s;x) - X(s;y)|^2 ds\right]^p \leq \int_0^t |X(s;x) - X(s;y)|^{2p} ds.$$

Therefore, (26) gives

$$\begin{aligned}
&E\left[\sup_{0\leq t\leq T} |X(t;x) - X(t;y)|^{2p}\right] \\
\leq& c_p|x-y|^{2p} + c_p(2\kappa\sqrt{\iota_2} + \iota_1)^p E\left[\sup_{0\leq t\leq T}\int_0^t |X(s;x) - X(s;y)|^{2p} ds\right] \\
&+ 2c_p E\left[\sup_{0\leq t\leq T}\left(\int_0^t (X(s;x) - X(s;y))\,(\sigma(X(s;x)) - \sigma(X(s;y)))\,dB_s\right)^p\right]
\end{aligned} \tag{27}$$

Since

$$E\left[\sup_{0\leq t\leq T}\left(\int_0^t (X(s;x) - X(s;y))\,(\sigma(X(s;x)) - \sigma(X(s;y)))\,dB_s\right)^p\right]$$

is a continuous local martingale with $2 \leq p < \infty$, we get by Burkhölder inequality

$$\begin{aligned}
&E\left[\sup_{0\leq t\leq T}\left(\int_0^t (X(s;x) - X(s;y))\,(\sigma(X(s;x)) - \sigma(X(s;y)))\,dB_s\right)^p\right] \\
\leq& E\left[\left\langle\int_0^{\cdot} (X(s;x) - X(s;y))\,(\sigma(X(s;x)) - \sigma(X(s;y)))\,dB_s\right\rangle_t^{\frac{p}{2}}\right] \\
=& E\left[2^{\frac{p}{2}}\left(\int_0^t (X(s;x) - X(s;y))^2\,(\sigma(X(s;x)) - \sigma(X(s;y)))^2\,dt\right)^{\frac{p}{2}}\right] \\
\leq& 2^{\frac{p}{2}}\kappa^p E\left[\left(\int_0^t |X(s;x) - X(s;y)|^4 ds\right)^{\frac{p}{2}}\right].
\end{aligned}$$

Therefore, we can write (27) as

$$\begin{aligned}
&E\left[\sup_{0\leq t\leq T} |X(t;x) - X(t;y)|^{2p}\right] \\
\leq& c_p|x-y|^{2p} + c_p(2\kappa\sqrt{\iota_2} + \iota_1)^p E\left[\int_0^T |X(s;x) - X(s;y)|^{2p} ds\right] \\
&+ 2^{\frac{p}{2}}\kappa^p c_p E\left[\left(\int_0^t |X(s;x) - X(s;y)|^4 ds\right)^{\frac{p}{2}}\right] \\
\leq& c_p|x-y|^{2p} + \left(c_p(2\kappa\sqrt{\iota_2} + \iota_1)^p + 2^{\frac{p}{2}}\kappa^p c_p\right) E\left[\int_0^T |X(s;x) - X(s;y)|^{2p} ds\right] \\
\leq& \left(c_p(2\kappa\sqrt{\iota_2} + \iota_1)^p + 2^{\frac{p}{2}}\kappa^p c_p\right) E\left[\int_0^T \sup_{0<r<s} |X(r;x) - X(r;y)|^{2p} ds\right] \\
&+ c_p|x-y|^{2p}.
\end{aligned} \tag{28}$$

Applying Fubini Theorem and Gronwall inequality to (28), we obtain

$$\begin{aligned}
&E\left[\sup_{0\le t\le T}|X(t;x)-X(t;y)|^{2p}\right]\\
\le&\left(c_p(2\kappa\sqrt{\iota_2}+\iota_1)^p+2^{p/2}\kappa^p c_p\right)\int_0^T E\left[\sup_{0<r<s}|X(r;x)-X(r;y)|^{2p}\right]ds\\
&+c_p|x-y|^{2p}\\
\le& c_p|x-y|^{2p}\exp\left\{\left(c_p(2\kappa\sqrt{\iota_2}+\iota_1)^p+2^{p/2}\kappa^p c_p\right)T\right\}.
\end{aligned}$$

Let

$$C=c_p\exp\left\{\left(c_p(2\kappa\sqrt{\iota_2}+\iota_1)^p+2^{p/2}\kappa^p c_p\right)T\right\}.$$

Then we have (23), which completes the proof. □

Remark 2. The indicator function in the modified stochastic microbial fermentation model (12) services several purposes: 1) keep the regularity of the terminal time; 2) guarantee the existence and uniqueness of a solution and the continuous dependence of the solutions on initial value; 3) make the expectation value of $X(t)$ still satisfy the deterministic model (1)-(3) which is an essential and necessary requirement when adding stochastic terms. There should be other ways of modifying the stochastic microbial fermentation model which service these purposes in similar manner, and will be part of our future work.

4. **Conclusion.**

In this paper, taking the production of LGA by Corynebacterium glutamicum as an example, we propose a continuous-time stochastic model for the microbial fermentation process under the framework of Gaussian white noise analysis. Then we prove the regularity of the terminal time, the existence and uniqueness of a solution and the continuous dependence of the solution on initial value. These properties are fundamental for the further analysis of the stochastic microbial fermentation model. Based on this stochastic model, the control problems of a microorganism culture process, such as feedback controls, are stochastic optimal control problems. Therefore it is a demanding task to deal with the stochastic optimal control problems in the stochastic microbial fermentation model. We leave this for future research.

REFERENCES

[1] I. Albert, R. Pouillot and J.-B. Denis, Stochastically modeling listeria monocytogenes growth in farm tank milk, *Risk Analysis*, **25** (2005), 1171–1185.

[2] H. Biebl, K. Menzel, A. P. Zeng and W. Deckwer, Microbial production of 1,3-propanediol, *Applied Microbiology and Biotechnology*, **52** (1999), 297–298.

[3] R. Bona and A. Moser, Modeling of l-glutamic acid production with Corynebacterium glutamicum under biotin limitation, *Bioprocess Engineering*, **17** (1997), 139–142.

[4] C. Hartmann and A. Delgado, Numerical simulation of the mechanics of a yeast cell under high hydrostatic pressure, *Journal of Biomechanics*, **37** (2004), 977–987.

[5] H. J. Henzler, Particle stress in bioreactors, *Advances in Biochemical Engineering*, **67** (2000), 35–82.

[6] H. Holden, B. Øksendal, J. Ubøe and T. S. Zhang, *Stochastic Partial Differential Equations-A Modeling, White Noise Functional Approach*, 2^{nd} edition, Springer-Verlag, New York, 2010.

[7] A. Kasperski, Modelling of cells bioenergetics, *Acta Biotheoretica*, **56** (2008), 233–247.

[8] A. Kasperski and T. Miskiewicz, Optimization of pulsed feeding in a Baker's yeast process with dissolved oxygen concentration as a control parameter, *Biochemical Engineering Journal*, **40** (2008), 321–327.

[9] Z. Kutalik, M. Razaz and J. Baranyi, Connection between stochastic and deterministic modelling of microbial growth, *Journal of Theoretical Biology*, **232** (2005), 285–299.

[10] X. Li and X. Mao, Population dynamical behavior of non-autonomous Lotka-Volterra competitive system with random perturbation, *Discrete and Continuous Dynamical Systems*, **24** (2009), 523–545.

[11] B. Øksendal and A. Sulem, *Applied Stochastic Control of Jump Diffusion*, 2^{nd} edition, Springer, Berlin, 2007.

[12] B. Øksendal, *Stochastic Differential Equations*, 6^{nd} edition, Springer, Berlin, Heidelberg, New York, 2005.

[13] H. J. Rehm and G. Reed, *Microbial Fundamentals*, Verlag Chemie, Weinheim, 1981.

[14] K. Schügerl, *Bioreaction Engineering: Reactions Involving Microorganisms and Cells: Fundamentals, Thermodynamics, Formal Kinetics, Idealized Reactor Types and Operation*, Wiley, Chichester, 1987.

[15] T. K. Soboleva, A. E. Filippov, A. B. Pleasants, R. J. Jones and G. A. Dykes, Stochastic modelling of the growth of a microbial population under changing temperature regimes, *International Journal of Food Microbiology*, **64** (2001), 317–323.

[16] S. Suresh, N. S. Khan, V. C. Srivastava and I. M. Mishra, Kinetic modeling and sensitivity analysis of kinetic parameters for l-glutamic acid production using Corynebacterium glutamicum, *International Journal of Chemical Reactor Engineering*, **7** (2009), Article A89.

[17] Y. Tian, A. Kasperski, K. Sun and Lansun Chen, Theoretical approach to modelling and analysis of the bioprocess with product inhibition and impulse effect, *BioSystems*, **104** (2011), 77–86.

[18] M. K. Toma, M. P. Rukilisha, J. J. Vanags, M. O. Zeltina, M. P. Leite, N. I. Galinina, U. E. Viesturs and R. P. Tengerdy, Inhibition of microbial growth and metabolism by excess turbulence, *Biotechnology and Bioengineering*, **38** (2000), 552–556.

[19] L. Wang, Z. Xiu and E. Feng, A stochastic model of microbial bioconversion process in batch culture, *International journal of Chemical reactor engineering*, **9** (2011), Article A82.

[20] L. Wang, Z. Xiu and E. Feng, Modeling nonlinear stochastic kinetic system and stochastic optimal control of microbial bioconversion process in batch culture, *Nonlinear Analysis: Modelling and Control*, **18** (2013), 99–111.

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