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Parameter Estimation of Stochastic Logistic Model: Levenberg-Marquardt Method

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Abstract In this paper, we estimate the drift and diffusion parameters of the stochastic logistic models for the growth of Clostridium Acetobutylicum P262 using Levenberg-Marquardt optimization method of non linear least squares. The parameters are estimated for five different substrates. The solution of the deterministic models has been approximated using Fourth Order Runge-Kutta and for the solution of the stochastic differential equations, Milstein numerical scheme has been used. Small values of Mean Square Errors (MSE) of stochastic models indicate good fits. Therefore the use of stochastic models are shown to be appropriate in modelling cell growth of Clostridium Acetobutylicum P262.

Keywords Ito differential equation; stochastic logistic model; Levenberg-Marquardt; Milstein scheme; fermentation.

1 Introduction

Many physical phenomena can be better presented and understood via mathematical modeling. Wide literatures on mathematical modeling of physical systems may be found with deterministic modeling particularly by deterministic differential equation whereby the element of noise is not considered. Deterministic differential equation describes a model of a physical system and is solved to explain how a system changes or evolves, when the change occurs and the effect of the starting point to the initial solution and so forth. It may present optimum situations and can be improved by introducing stochastic element since in reality many phenomena in nature are affected by stochastic noise therefore stochastic differential equations (SDE) may be required. Some of the fields which apply SDE are finance, population dynamics, hydrology, environmetric and biometry.

The perturbation or the white noise is included in the function and the stochastic modelling can be considered from the corresponding Ito or Stratonovich differential equations (SDEs) or from the associated Kolmogorov (Fokker-Planck and backward) differential equations (Gutierrez et al. [2]). All the above differential equations represent extrinsic stochasticity whereby the stochasticity is introduced by incorporating multiplicative or additive stochastic terms into the differential equation. Extrinsic stochasticity is due to random variation of one or more environmental or external factors such as temperature or concentration of reactant species whereas intrinsic stochasticity is inherent to the system, arising due to the relatively small number of reactant molecules. Intrinsic stochasticity can be

described by a chemical master equation developed by Gillespie in 1977 (Meng et al. [3]). The general form of the Ito SDE is as follows:

$$dx(t) = f(x,t)dt + g(x,t)dW(t) \tag{1}$$

where

$x(t)$ is the state of the physical system at time t
$f(x,t)$ is the deterministic or average drift term
$g(x,t)$ is the diffusive term
$dW(t)$ is the Brownian noise

Equation (1) is a one-dimensional stochastic process W perturbing x. In this paper we estimate the drift and diffusion parameters of the stochastic logistic models for the growth of Clostridium Acetobutylicum P262 in five substrates by employing one of the non linear least squares method Levernberg-Marquardt. The organization of the paper is as follows: section two describes the literature reviews on the parameter estimation methods of stochastic differential equations. Section three describes the deterministic logistic equation of cell growth, the perturbation of extrinsic stochasticity, the approximation of the stochastic logistic equation using Milstein and the minimization of the cost function using non linear least squares. Section four discusses the application of the parameter estimation method on fermentation data and the results obtained including the prediction quality of the model. Lastly we conclude in section five the findings of our study.

2 Literature Reviews

Most of the research in biotechnological areas employ deterministic modeling of systems. For example, in investigating the feasibility of sago starch as carbon source of Acetone-Buthanol Ethanol (ABE) fermentation, deterministic logistic differential equation was used to model the growth of strain Clostridium Acetobutylicum P262 (Madihah [4]). This however, is inadequate since stochastic model would offer a more realistic representation of systems compared to deterministic since system such as cell growth is subject to random fluctuation whether intrinsic or extrinsic. Bahar [5] incorporated stochasticity into power law logistic model and studied its properties. Here, we modeled cell growth of C.Acetobutylicum P262 using stochastic logistic model based on Bahar [5] but prior to that, the parameters had to be estimated from data. In SDEs, no method of parameter estimation had been specified, however in modeling stochasticity of biological process parameter estimation is a nontrivial task.

In this section, we will discuss some reviews of literature in estimating parameters of stochastic differential equations. Some previous works employed methods such as maximum likelihood method (Picchini et al. [1] and Gutierrez et al. [2]), methods of moment (Nielsen et al. [6]), filtering for example, extended Kalman filter based on Nielsen and Madsen [7] and non-linear least squares (Lo et al. [8]). In this paper we estimated the parameters of the logistic equation by applying the optimization method for non-linear least squares Levenberg-Marquardt method (LM method). The LM method had been widely used to estimate parameters in deterministic models since this method serves as a fast and convenient

method, however few literatures have been found in stochastic models. Milstein numerical scheme was used to approximate the solution of SDE since this scheme is considered more efficient that Euler Maruyama (Picchini et al. [1]). The LM method does not require the availability of the transition probability and has been applied to estimate the parameters of stochastic model in polymer rheology (Lo et al.[8]). It is the modified version of the Gauss-Newton method with the simplified form of the Hessian matrix (Taylan et al.[9]). Here we employed the method to estimate the parameters of stochastic logistic equation with the non-constant or multiplicative noise.

3 Parameter Estimation of Stochastic Differential Equation

3.1 Deterministic Logistic Equation of Cell Growth

Power law logistic differential equation was used to describe population dynamic has the following form

$$\frac{dN}{dt} = aN^{\xi} - bN^{\eta} \tag{2}$$

where

N is the population density
a is the growth coefficient
b is the crowding coefficient
a, b, ξ, η are constants

Letting

$$\xi = 1,\ a = \mu_{\max},\ b = \frac{\mu_{\max}}{x_{\max}},\ N = x(t),\ \frac{dN}{dt} = x(t) \text{ and } \eta = s + 1,$$

where s is an index of the inhibitory effect accounts for the deviation of growth from the exponential relationship, we obtain the model represents the rate of cell growth kinetic [4],

$$\frac{dx}{dt} = \mu_{\max} x(t) - \frac{\mu_{\max}}{x_{\max}} x^{s+1}(t). \tag{3}$$

For case when $s = 0$, it will be a complete inhibition of cell growth and for the case $s = 1$ it will be reduced to logistic model. If s ranges from 0 to 1 it describes a higher degree of inhibition compared to logistic growth (Muthuvelayudham and Viruthagiri, [10]). $\mu_{\max}$ is a constant represents the maximum specific growth rate $(h^{-1}), x$ is cell concentration $(g/L), x_{\max}$ is a maximum cell concentration (G/L). The logistic equation, for the case $s = 1$ was utilized to describe the kinetics of several fermentation systems.

3.2 Stochastic Perturbation to Logistic Cell Growth Equation

In this part, the deterministic logistic cell growth kinetic model, equation (3) will be perturbed by extrinsic Brownian white noise through its growth coefficient a. For simplicity, equation (3) is rewritten as

$$x'(t) = ax(t) + bx^{s+1}(t). \tag{4}$$

Every element of growth coefficient will be perturbed as $a \rightarrow a + \sigma x^s(t)dw(t)$. Since this is a one dimensional problem, equation (4) becomes

$$x^{'}(t) = x(t)\left(a + \sigma x^s(t)\frac{dw}{dt} + bx^s(t)\right).$$

Therefore,

$$dx(t) = x(t)\left(a + bx^s(t)\right)dt + \sigma x^{s+1}(t)dw(t).$$

For logistic model, setting

$$a = \mu_{\max} \text{ and } b = \frac{-\mu_{\max}}{x_{\max}},$$

the equation becomes

$$dx(t) = x(t)\left(\mu_{\max} - \frac{\mu_{\max}}{x_{\max}}x(t)\right)dt + \sigma x^2(t)dw(t) \tag{5}$$

which is the form of Ito stochastic differential equation with

$$f(x,t) = x(t)\left(\mu_{\max} - \frac{\mu_{\max}}{x_{\max}}x(t)\right)$$

is the average drift term and $g(x,t) = \sigma x^2(t)$ is the diffusion term. It is of interest to estimate the parameter $\mu_{\max}$ and σ.

3.3 Milstein Approximation

Many of SDE system do not have known analytical solution, thus solving these systems numerically is necessary. The usual approximation is the Euler-Maruyama and Milstein scheme. Euler-Maruyama method has strong order of convergence that is and weak order of convergence 1. Here we will only consider Milstein scheme since the scheme has a higher order, converges with strong order 1 and considered to be more precise than Euler-Maruyama (Picchini et al. [1]). Considering the Ito SDE in equation (1) on $[t_0, T]$ for a given discretisation $t_0 < t_1 < \cdots < t_n < \cdots < t_N = T$ a Milstein approximation is a continuous time stochastic process satisfying the iterative scheme given by

$$x_{i+1} = x_i + h_i f(x_i) + g(x_i)\Delta W_i + \frac{1}{2}g(x_i)g^{'}(x_i)((\Delta W_i)^2 - h_i) \tag{6}$$

with initial value x_0. The term $g'(x)$ represents the derivative of x. Based on Taylan et al. [9], in order to estimate the parameters, equation (6) has to be rearranged in a form of a difference quotient

$$\dot{\bar{x}}_i = f(x_i) + g(x_i)\frac{\Delta W_i}{h_i} + \frac{1}{2}g(x_i)g^{'}(x_i)\left(\frac{(\Delta W_i)^2}{h_i} - 1\right). \tag{7}$$

The value $\dot{\bar{x}}_i$ represents difference quotient based on the experimental data. Given $W \sim N(0,t)$ and $\Delta W = W_{t_{i+1}} - Wt_i, \Delta W \sim N(0, h_i)$, that is, $\Delta W \sim N(0, t_{i+1} - t_i)$ and

$\Delta t = t_{i+1} - t_i$ standardizing the normal distribution, $z = \frac{\Delta W - 0}{\sqrt{\Delta t}} = \frac{\Delta W}{\sqrt{\Delta t}}$ and $Z \sim N(0,1)$, equation (7) becomes

$$\dot{\tilde{x}}_i = f(x_i) + g(x_i)\frac{z_i}{h_i} + \frac{1}{2}g(x_i)g^{'}(x_i)\left(z_i^2 - 1\right). \tag{8}$$

From equation (5)

$$f(x,t) = x(t)\left(\mu_{\max} - \frac{\mu_{\max}}{x_{\max}}x(t)\right)$$

is the average drift term and $g(x,t) = \sigma x^2(t)$ is the diffusion term. Since σ is multiplicative with the x term, the stochastic model consists of nonlinear growth coefficient or the noise is non constant. Substituting the terms in equation (8), we obtain

$$\dot{\tilde{x}}_i = \mu_{\max}x_i\left(1 - \frac{x_i}{x_{\max}}\right) + \sigma x_i^2\frac{z_i}{\sqrt{h_i}} + \frac{1}{2}(\sigma x_i^2)(2\sigma x_i)\left(z_i^2 - 1\right).$$

Replacing $\mu_{\max}$ with θ for simplicity and rearranging the terms yields

$$\dot{\tilde{x}}_i = \theta x_i - \frac{\theta x_i^2}{x_{\max}} + \sigma x_i^2\frac{z_i}{\sqrt{h_i}} + \sigma^2 x_i^3(z_i^2 - 1). \tag{9}$$

3.4 Nonlinear Least Squares

The theoretical part of nonlinear least squares outlined next are adapted from Taylan et al. [9]. In general the difference quotient in equation (9) may be presented as a function of the parameters in the form of $\dot{\tilde{x}}_i = g(x_i, \theta, \sigma)$. The following optimization problem would be considered to determine values of θ and σ :

$$\text{minimize } f(\beta) := \sum_{i=1}^{N}\left(\dot{\tilde{x}}_i - g(x_i,\theta,\sigma)\right)^2 = \sum_{i=1}^{N} f_i^2(\beta) \tag{10}$$

where $\beta = (\theta, \sigma)^T$. In vector notation the equation becomes

$$\text{minimize } f(\beta) := \frac{1}{2}F^T(\beta)F(\beta) \tag{11}$$

where F is the vector-valued function given by

$$F(\beta) := (f_1(\beta), ..., f_N(\beta))^T$$

and $\frac{1}{2}$ serves for a more "optimal" normalization of the derivatives. By the chain rule,

$$\nabla f(\beta) := \nabla F(\beta)F(\beta) \tag{12}$$

where $\nabla F(\beta)$ is an $n \times n$-matrix-valued-function. Row wise differentiation of $\nabla f(\beta)$, the Hessian matrix of f will lead to

$$\nabla^2 f(\beta) := \nabla F(\beta)\nabla F^T(\beta) + \sum_{i=1}^{N} f_i(\beta)\nabla^2 f_i(\beta) \tag{13}$$

If β^* is the solution of equation (10) and if $f(\beta^*) = 0$, the model fits the data perfectly. Therefore, $F(\beta)^* = 0$ and $\nabla f(\beta^*) = 0$ in equation (12). As a result, the Hessian of f becomes $\nabla^2 f(\beta^*) := \nabla F(\beta^*)\nabla F^T(\beta^*)$ which is a positive semi-definite. Levernberg-Marquardt's method uses an approximation of the second additive form in equation (13) by taking $\sum_{i=1}^{N} f_i(\beta)\nabla^2 f_i(\beta) = \lambda I_N$ with some scalar $\lambda \geq 0$ and by replacing Hessian in the formula $\nabla^2 f(\beta)q = -\nabla f(\beta)$ of Gauss Newton Method. Hence from equation (13), the following linear system of equation is obtained:

$$-\nabla F(\beta)F(\beta) := (\nabla F(\beta)\nabla F^T(\beta) + \lambda I)q$$

where q is the Gauss-Newton increment $q = \beta_1 - \beta_2$.

4 Results and Discussions

Investigation of the feasibility of using sago starch as carbon source for solvent fermentation by Clostridium Acetobutylicum P262 had been carried out by Madihah [4]. Batch fermentation was carried out and one of the experiments involve the investigation of the effect of different inorganic nitrogen source to 5g/l yeast extract using 50 g sago starch/l as carbon source. Four different inorganic nitrogen such as ammonium nitrate (NH_4NO_3), ammonium sulfate $(NH_4)_2SO_4$, ammonium chloride (NH_4Cl) and ammonium hydrogen phosphate ($NH_4H_2PO_4$) were added to the substrate and the media was adjusted to pH 6 at 36° Celcius (Madihah et al. [11]). 22 experimental data of cell concentration from direct fermentation of sago starch using five different mixture of inorganic nitrogen source including the control (yeast only) mixture were observed at unequal time interval totaling of 72 hours. The simplified batch fermentation kinetic models for cell growth based on logistic equation were used to model growth of C.Acetobutylicum P262 and it is given by

$$\frac{dx}{dt} = \mu_{\max} x(t) - \frac{\mu_{\max}}{x_{\max}} x^2(t)$$

where $x(t)$ is cell concentration (g/L), $x_{\max}$ is the maximum cell concentration (g/L) and $\mu_{\max}$ is the maximum specific growth rate (h^{-1}).

The kinetic parameter of the above deterministic model was estimated first before proceeding to a stochastic model. The parameter of deterministic model was estimated by using fourth order Runge-Kutta approximation and Levenberg-Marquardt method was used to minimize the cost function since this would produce the value of parameter which does not depend on the initial value. Thus we minimize

$$\sum_{i=1}^{N} \left[\dot{\bar{x}}_i - \left(\frac{k_0}{6} + \frac{k_1}{3} + \frac{k_2}{3} + \frac{k_3}{6} \right) \right]^2$$

where

$$f(t,x) = \mu_{\max} x(t) - \frac{\mu_{\max}}{x_{\max}} x^2(t), \;\; \dot{\bar{x}}_i = \frac{x_{i+1} - x_i}{h_i}$$

and $k_0 = f(t, x_i)$, $k_1 = f(t+\frac{h}{2}k_0, x_i+\frac{h}{2}k_0)$, $k_2 = f(t+\frac{h}{2}k_1, x_i+\frac{h}{2}k_1)$, $k_3 = f(t+h, x_i+hk_2)$.

This method however did not produce a fix value of the parameter if different number of data (N) was used. To solve this problem, the parameter chosen was those with the least

Mean Square Error (MSE), that is, MSE $= \sum_{i=1}^{N}(x_i - f_i)^2/N$, where x_i is the observed values, f_i is the predicted values and N is the total observations. Figure 1 and Figure 2 show the plot of MSE for each value of N for all substrates.

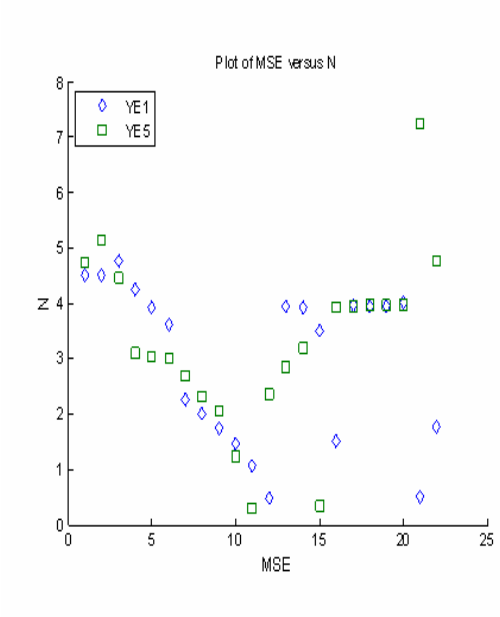

Figure 1: Plot of MSE Versus the Number of Observations (N) for YE1 and YE5.

Table 1 summarizes the estimated values of $\mu_{\max}$ obtained using Levenberg-Marquardt of the deterministic model. The corresponding values of the number of data are used to estimate the parameters for YE1, YE2, YE3, YE4 and YE5 are 15, 5, 13, 20 and 5 respectively. MSE at each value of N are 0.5110, 0.0175, 0.0124, 0.0081 and 0.2843. The parameters obtained for the deterministic model were later used to estimate the coefficient of the diffusive term of the stochastic models. The fitted plots of deterministic models shown in Figure 3 to Figure 7.

The values of parameter sigma in drift equation of logistic stochastic model (5) were determined by minimizing the cost function via the Levenberg-Marquardt method,

$$\sum_{i=1}^{N}\left[\dot{\bar{x}} - \left(\mu_{\max}x_i - \frac{\mu_{\max}x_i^2}{x_{\max}} + \sigma x_i^2\frac{z_i}{\sqrt{h_i}} + \sigma^2 x_i^3(z_i^2-1)\right)\right]^2.$$

The simulation of the Brownian noise were generated using the ziggurat method at 50, 100, 500 and 1000 times and the average of the parameter values were obtained. In order to reduce the variance of the simulated normal random numbers for calculating the predicted values, antithetic variates are employed when generating the numbers. The estimated mean parameters are listed in Table 2.

For modeling purposes only a single value of sigma will be chosen for each substrate therefore the MSE of the stochastic models were calculated using the value of sigma obtained

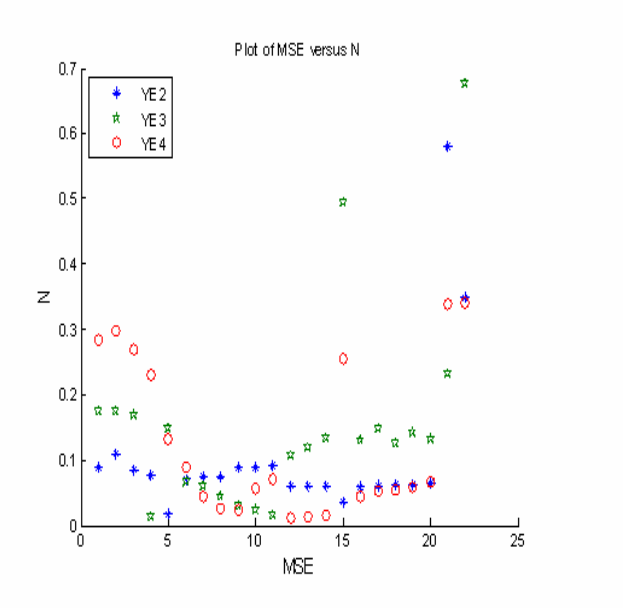

Figure 2: Plot of MSE Versus the Number of Observations (N) for YE2, YE3 and YE4.

Table 1: The Estimated Values of $\mu_{\max}$ Using Levenberg-Marquardt

Substrate	YE1	YE2	YE3	YE4	YE5
$\mu_{\max}$	0.4848	1.4429	0.9406	0.5056	0.6364

YE1 – Yeast only YE2 – Yeast + ammonium sulphate
YE3- Yeast + ammonium hydrogen YE4 – Yeast + ammonium chloride
YE5 – Yeast + ammonium nitrate

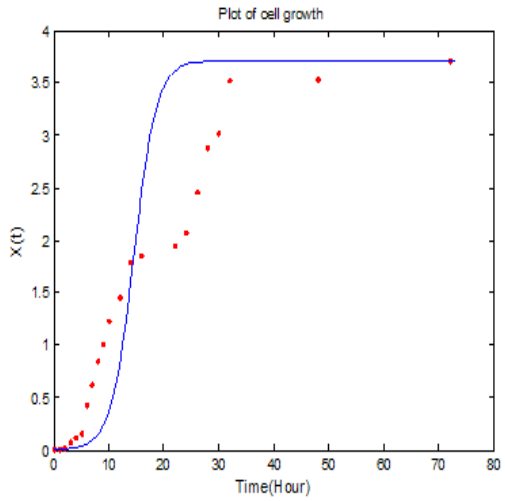

Figure 3: The Fitted Logistic Model of Cell Concentration (g/L) Versus Time (h) of Substrates YE1

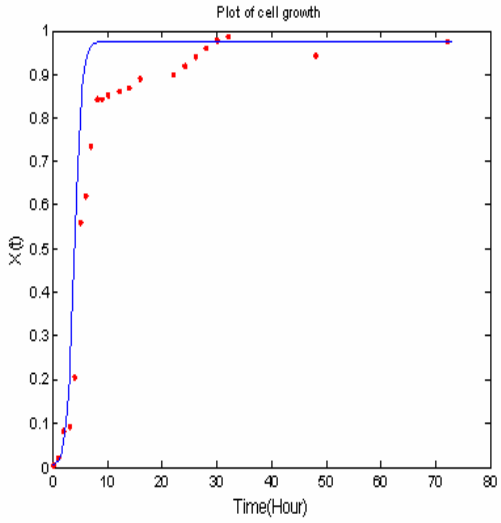

Figure 4: The Fitted Logistic Model of Cell Concentration (g/L) Versus Time (h) of Substrates YE2

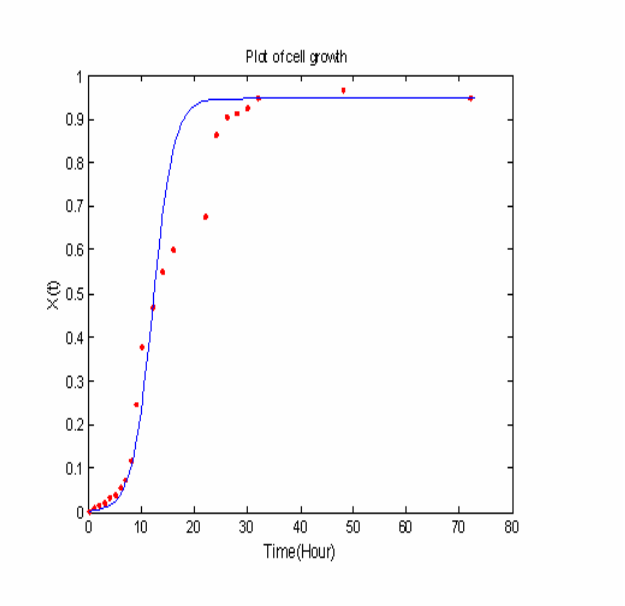

Figure 5: The Fitted Logistic Model of Cell Concentration (g/L) Versus Time (h) of Substrates YE3

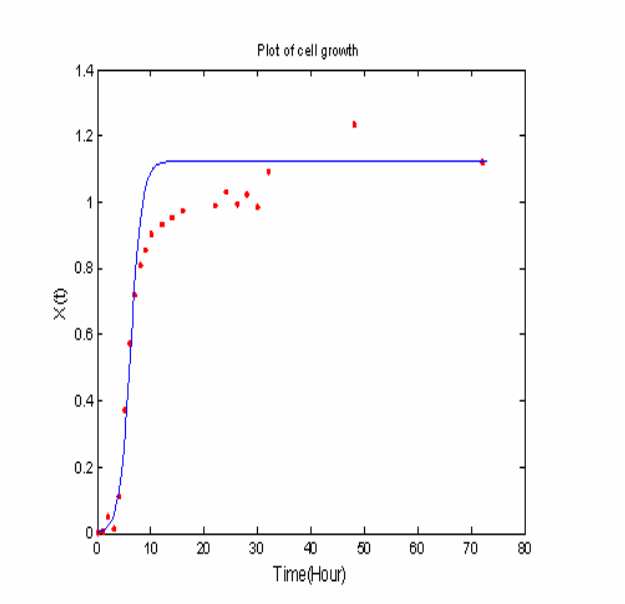

Figure 6: The Fitted Logistic Model of Cell Concentration (g/L) Versus Time (h) of Substrates YE4

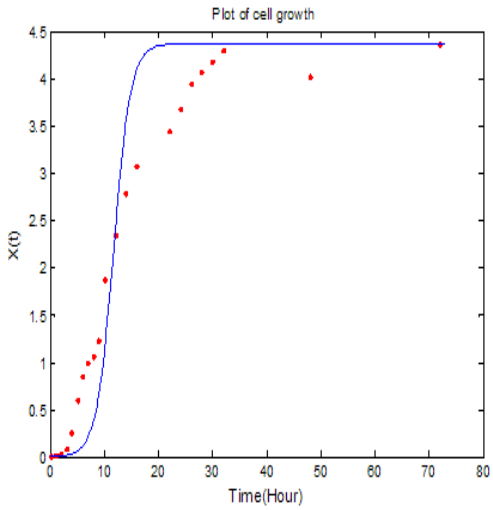

Figure 7: The Fitted Logistic Model of Cell Concentration (g/L) Versus Time (h) of Substrates YE5

Table 2: The Values of the Averaged Sigma for Different Number of Simulations

σ	YE1	YE2	YE3	YE4	YE5
N=50	0	0.3360	0.0009	0	0.0060
N=100	0.0028	0.2564	0.0144	0.0127	0.0052
N=500	0.0033	0.4808	0.0139	0	0.0059
N=1000	0.0018	0.5556	0.0038	0.0032	0.0047

at different number of simulations of the Brownian noise. The simulation of Brownian noise at N = 100 was chosen since it produces the least MSE of the stochastic model (5) for most substrates. Thus the value of sigma from 100 simulations of Brownian noise were chosen for the stochastic model. The parameter values obtained from the combination of parameter estimation of deterministic model and stochastic model are shown in Table 3.

Table 3: Parameters of Stochastic Models for $N = 100$

N=100	YE1	YE2	YE3	YE4	YE5
μ_{max}	0.4848	1.4429	0.9406	0.5056	0.6364
σ	0.0028	0.2564	0.0144	0.0127	0.0052

Figure 8 to Figure 12 depict the plot of stochastic models of cell concentration of C. Acetobutylicum P262.

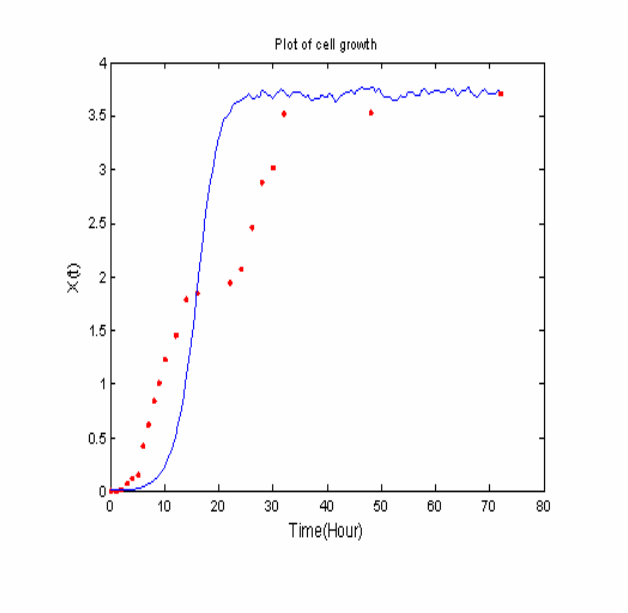

Figure 8: The Stochastic Logistic Model of Cell Concentration (g/L) Versus Time (h) of Substrates YE1

5 Prediction Quality of the Models

Table 4 below outlined the values of the MSE for the stochastic models.

From Table 4, it can be seen that the values of the MSE are small for all five models, thus indicating good fit. It can be concluded that it is appropriate to model cell growth of Clostridium Acetobutylicum P262 via stochastic logistic model.

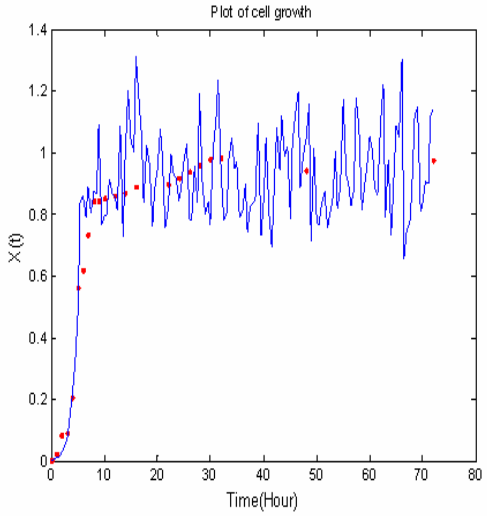

Figure 9: The Stochastic Logistic Model of Cell Concentration (g/L) Versus Time (h) of Substrates YE2

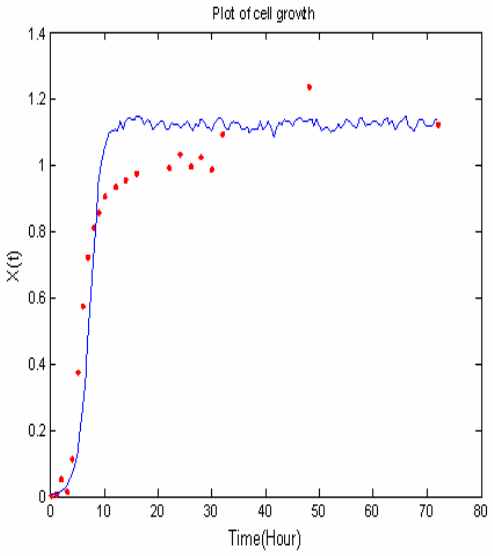

Figure 10: The Stochastic Logistic Model of Cell Concentration (g/L) Versus Time (h) of Substrates YE3

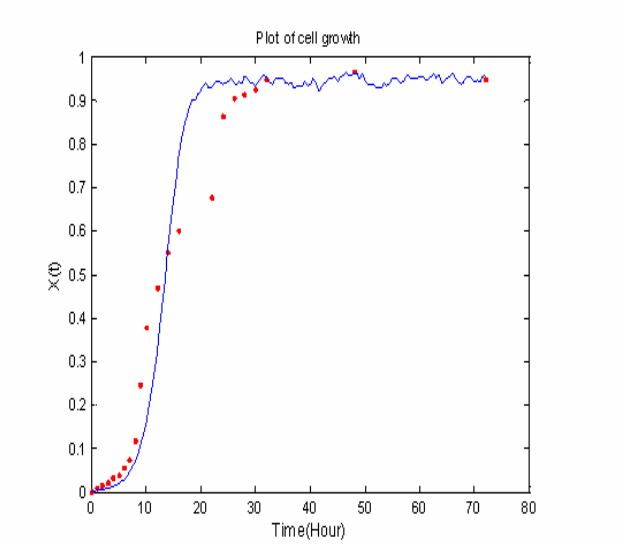

Figure 11: The Stochastic Logistic Model of Cell Concentration (g/L) Versus Time (h) of Substrates YE4

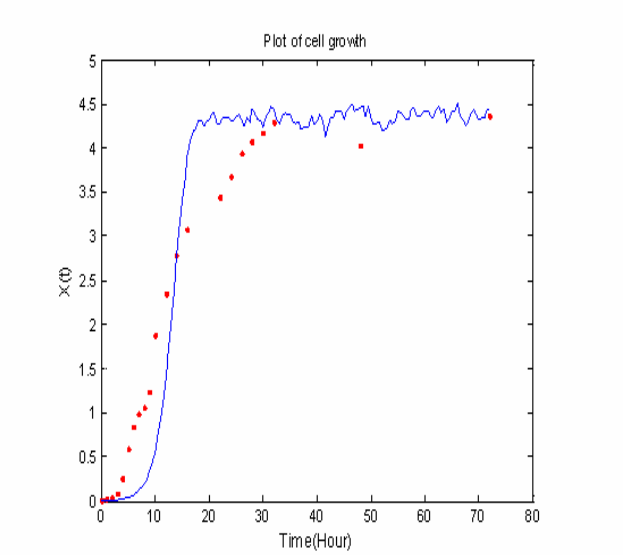

Figure 12: The Stochastic Logistic Model of Cell Concentration (g/L) Versus Time (h) of Substrates YE5

Table 4: Mean Square Error (MSE) of Deterministic Models and Stochastic Logistic Models Used to Characterize the Prediction Quality Based on the Experimental Data

Substrates	YE1	YE2	YE3	YE4	YE5
Stochastics	0.5418	0.0238	0.0194	0.0090	0.3693

6 Conclusions

We opted to estimate the drift and diffusion parameters separately by estimating the coefficient of the drift term first and the coefficient of the diffusive term next. The Levenberg-Marquardt had provided sufficient estimate of the diffusion parameters of the stochastic model by using difference quotient since the solutions obtained are independent of initial values of the parameters. The MSE for all five substrates the stochastic models are small thus indicates the adequacy of the stochastic logistic models in modeling of Clostridium Acetobutylicum P262.

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