Stochastic Model of Gelatinised Sago Starch to Solvent Production by C. *acetobutylicum* P262.

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ABSTRACT

Fluctuations are inherent property of many physical systems in biology, epidemiology, finance and chemical reactions. They are recognized as unknown disturbances or stochastic effects. In order to describe the system embedded with the above effect, the system is modelled using stochastic differential equations (SDEs). This work is carried out to model the growth of C. acetobutylicum P262 in batch fermentation and solvent production using SDE. Since, the analytical solutions of this SDE are complex, a numerical simulation is applied to approximate the strong solution of the SDE. This paper also discusses the use of three different numerical methods in modelling the growth of C. acetobutylicum P262 and solvent production.

Keywords: *Stochastic Differential Equations, batch fermentation, Euler-Maruyama (EM), 2-stage Stochastic Runge-Kutta (SRK2), 4-stage Stochastic Runge-Kutta (SRK4).*

Introduction

In a typical batch process the number of living cells varies with time. At zero time, the sterile nutrient solution in fermenter is inoculated with microorganism (C. *acetobutylicum* P262) and incubation is allowed to proceed under optimal physiological conditions. The microbial growth in gelatinized sago starch undergoes two distinct physiological stages (Madihah et al., 2008). The first stage is an acidogenic stage which involves an exponential growth phase. After a lag phase where no increase in cell numbers is evident, a period of rapid growth ensues and cell numbers increase exponentially with time. During exponential growth the pH culture decreases due to the production of acetic acid, butyric acid and hydrogen gas. The second phase has slow growth rate. This is a phase where the solvents (acetone and butanol) are produced. In this phase, both butyric acid and acetic acid are taken up by the bacterial cell to induce the transition to the solventogenic phase (Madihah, 2000). As time evolves, the system is subjected to an intrinsic variability of the competing within species and deviations from exponential growth arise (cell growth reach a stationary phase). It happens as a result of the nutrient level and toxin concentration achieves a value which can no longer support the maximum growth rate. These disturbances can be regarded as stochastic effects. Over last few decades, logistic and Luedeking-Piret equations had been used to model the solvent production by C. *acetobutylicum* P262. This model suffers several weaknesses. They lack of stochastic effect and give us no insight into the

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variables which influence the growth. Therefore, the mathematical models for this process should take into account of the uncertainty which can be formulated as SDE.

In many cases analytical solution of SDEs are not available and numerical method provide a suitable way to approximate them. It was Maruyama (1950s) who introduced the stochastic Euler scheme, which is Euler-Maruyama scheme. This scheme has strong order of convergence of 0.5 and weak order of convergence of 1.0 which are quite low, thus there is a need for higher order numerical schemes. One possible approach is to use the truncated Taylor series expansions. However, this approach needs more partial derivatives when more stochastic integrals terms are added. The method of derivative-free scheme was introduced to replace the derivatives in Taylor approximations by finite difference. Milstein scheme, a derivative-free method with strong order of 1.0 had been proposed in Milstein (1974). For multi-dimensional driving Wiener processes and non commutative case, the double stochastic integral in the Milstein scheme has to be approximated. This lead to the method with derivatives and it is difficult to implement. An improvement to this, a strong order of 1.5 has been introduced in Burrage and Burrage (1996). They presented a very general class of explicit stochastic Runge-Kutta with strong order of 1.5 and 2.0.

The present study introduces a stochastic model for direct fermentation of sago starch to solvent production by C. *acetobutylicum* P262. The prediction quality of the model is assessed by comparing the numerical simulation with the experimental data. This study is organized as followed; we introduced stochastic differential equations to describe the cell growth of C. *acetobutylicum* P262 and solvent production, followed by a description of numerical methods for solving SDEs namely EM, SRK2 and SRK4. Then, we numerically simulate the strong solution of SDE for C. *acetobutylicum* P262 and solvent production via SRK2. Root mean square error (RMSE) is computed in order to assess the adequacy of the stochastic model, whose prediction has been compared with the experimental data.

Stochastic Model of C. *acetobutylicum* P262

The deterministic model used to explain the cell growth of *C. acetobutylicum* P262 is given by logistic equation of

$$dx(t) = \mu_{\max}\left(1 - \frac{x(t)}{x_{\max}}\right)x(t)dt \qquad (1)$$
$$x(t_0) = x_0,\ t \in [0,T]$$

where x is the cell concentration, $\mu_{\max}$ and $x_{\max}$ correspond to the growth coefficient and maximum value of the cell growth respectively. The exact solution of (1) is given by

$$x(t) = \frac{x_{\max}\exp(\mu_{\max}t)}{\left(\frac{x_{\max}}{x_0}\right) - 1 + \exp(\mu_{\max}t)} \qquad (2)$$

The simply deterministic model does not accommodate random variations of metabolism. An alternative stochastic model would result from the hypothesis that the underlying mathematical process itself is not smooth. The cell growth of C. *acetobutylicum* P262 is in fact subject to a variety of internal and external influences, which change over time. We therefore define an SDE model by adding suitable system variability to the deterministic model (1). Arifah (2005) allows the parameter $\frac{\mu_{\max}}{x_{\max}}$ to vary randomly by introducing a white noise perturbation such that

$$b \to b + \sigma\frac{dW(t)}{dt} \qquad (3)$$

where $b = \frac{-\mu_{\max}}{x_{\max}}$, σ is a diffusion coefficient and $W(t)$ is a one dimensional stochastic process having scalar Wiener process components with increment $\Delta W(t) = W(t+\Delta t) - W(t)$ are independent Gaussian random variables $N(0, \Delta t)$. Model (1) with perturbation (3) is an Itô SDE of

$$dx(t) = \mu_{\max}\left(1 - \frac{x(t)}{x_{\max}}\right)x(t)dt + \sigma x^2(t)dW(t) \qquad (4)$$

or in the integral form it can be expressed as

$$x(t) = x_0 + \int_0^T \mu_{\max}\left(1 - \frac{x(s)}{x_{\max}}\right)x(s)ds + \int_0^T \sigma x^2(s)dW(s) \qquad (5)$$

The second integral in (5) is stochastic integral with respect to a Wiener process and it cannot be interpreted as Riemann-Stieltjes integral. The stochastic integrals can be interpreting as Itô or Stratonovich integral depending on the evaluation points of the integrand. SDE (4) has been presented in Mohd Khairul Bazli et al. (2009) and the strong solution of underlying model is approximated via EM. Though our model is in Itô form, it can be converted into Stratonovich form and vice-versa by means of the following formula

$$\bar{f}(t, x_t) = f(t, x_t) - \frac{1}{2}g(t, x_t)\frac{\delta g}{\delta x}(t, x_t) \qquad (6)$$

By employing (6) to drift coefficient in (4) we obtain stochastic model in Stratonovich form of

$$dx(t) = \left(\mu_{\max}\left(1 - \frac{x(t)}{x_{\max}}\right)x(t) - \sigma^2 x^3(t)\right)dt + \sigma x^2(t) \circ dW(t) \qquad (7)$$

or in the integral form

$$x(t) = x_0 + \int_0^T \left(\mu_{\max}\left(1 - \frac{x(s)}{x_{\max}}\right)x(s) - \sigma^2 x^3(s)\right)ds + \int_0^T \sigma x^2(s) \circ dW(s) \qquad (8)$$

The symbol $\circ$ is used to denote the Stratonovich form of SDE (i.e. $\circ\, dW(t)$). In this paper the numerical solution for SDE (7) is simulated via SRK2. Note that Runge-Kutta type schemes should not be used for Itô SDEs as they are generally not consistent with Itô calculus (Carletti, 2006). Throughout this paper we will consider stratonovich SDE of (7), so that numerical simulation can be approximated via SRK2. The equations (4) and (7) under different rules of calculus have the same solution. Luedeking-Piret equations for solvent production of acetone and butanol are given as follow

Acetone $$\frac{dA}{dt} = a\left(\frac{dx}{dt}\right) + b\,x \qquad (9)$$

Butanol $$\frac{dB}{dt} = c\left(\frac{dx}{dt}\right) + e\,x \qquad (10)$$

where
A = acetone concentration (g/L)
a = growth associated coefficient for acetone formation (g substrate/g cell)
b = non-growth associated coefficient for acetone formation (g substrate/g cell)
B = butanol concentration (g/L)
c = growth associated coefficient for butanol formation (g substrate/g cell)
e = non-growth associated coefficient for butanol formation (g substrate/g cell)

The equations (1), (9) and (10) are logistic and Luedeking-Piret equations which had been described elsewhere in Madihah (2000). However, the proposed model in Madihah (2000) was insufficient to describe the production of acetone and butanol. So, we formulate $x(t)$ as a stochastic process instead of in Madihah (2000), where $x(t)$ was considered as deterministic. Note that, the production of acetone and butanol was non-growth associated system as indicated by the non-zero values for the

non-growth associated coefficient for product formation, while the values of growth associated coefficient was zero (Madihah, 2000). Hence, the equations (9) and (10) in integral form are as follow

Acetone $$A(t) = A(t_0) + b\int_{t_0}^{t} x(s)ds \qquad (11)$$

Butanol $$B(t) = B(t_0) + e\int_{t_0}^{t} x(s)ds \qquad (12)$$

where *b* and *e* need to be estimated.

Numerical Methods for SDEs

The simplest numerical method for solving SDE is EM which can be represented by the following formula

$$x_{n+1} = x_n + f(x_n)\Delta t + g(x_n)\Delta W_n \qquad (13)$$

where *f* is a drift coefficient, *g* is a diffusion function, $\Delta t = t_{n+1} - t_n$ and $\Delta W_n = W(t_{n+1}) - W(t_n)$. ΔW_n is the increment of Wiener process and is generated numerically by using pseudo-random number generator which involves sampling from independent and normally distributed random variables with mean zero and variance, Δt. Then, Rumelin (1982) presented an *s*-stage explicit SRK for solving SDE numerically which was based on Wiener process. A simple generalisation of SRK methods to SDEs is

$$\begin{aligned} X_i &= x_n + h\sum_{j=1}^{s}\alpha_{ij} f(X_j) + J_1\sum_{j=1}^{s}\beta_{ij} g(X_j),\ i = 1,\ldots,s \\ x_{n+1} &= x_n + h\sum_{j=1}^{s}\eta_j f(X_j) + J_1\sum_{j=1}^{s}\gamma_j g(X_j) \end{aligned} \qquad (14)$$

where $\Lambda = (\alpha_{ij})_{s\times s}$ and $\Gamma = (\beta_{ij})_{s\times s}$ are matrices of real elements while $\eta^T = (\eta_1,\ldots,\eta_s)$ and $\gamma^T = (\gamma_1,\ldots,\gamma_s)$ are row vectors $\in \Re^s$. The stochastic component comes from J_1 integral, where $J_1 = \int_{t_n}^{t_{n+1}} \circ dW$. Burrage and Burrage (1996) refined the equation (14) by introducing other stochastic elements apart from J_1, there are arbitrary matrix $\mathbf{Z}$ and vector $\mathbf{z}^T$ were introduced whose elements themselves are random variables. Hence, the general family of *s*-stage SRK is formulated as follows

$$\begin{aligned} X_i &= x_n + h\sum_{j=1}^{s}\alpha_{ij} f(X_j) + \sum_{j=1}^{s} Z_{ij} g(X_j),\quad 1,\ldots,s \\ x_{n+1} &= x_n + h\sum_{j=1}^{s}\eta_j f(X_j) + \sum_{j=1}^{s} z_j g(X_j) \end{aligned} \qquad (15)$$

Z_{ij} and z_j can be written as a linear combination of *p* different random variables $\theta_1,\ldots,\theta_p$ as follows

$$Z_{ij} = \sum_{l=1}^{p}\beta_{ij}^{l}\theta_l, \quad i, j = 1,\ldots,s$$

$$z_j = \sum_{l=1}^{p}\gamma_j^{l}\theta_l, \quad j = 1,\ldots,s$$

An explicit SRK with strong order of 1.0 and 1.5 was developed by letting $p = 2$. For $p = 2$ we

have $\theta_1 = J_1$ and $\theta_2 = \frac{J_{10}}{h}$, where $J_1 = \int_{t_n}^{t_{n+1}} \circ\, dW(s)$ and $J_{10} = \int_{t_n}^{t_{n+1}} \int_{t_n}^{s} \circ\, dW(u)ds$. The random variable J_{10} has the following representation

$$\frac{J_{10}}{h} = \frac{\sqrt{h}}{2}\left(G_1 + \frac{G_2}{\sqrt{3}}\right)$$

where G_1 and G_2 are standard normal distribution. An *s*-stage SRK can be written as

$$\begin{aligned} X_i &= x_n + h\sum_{j=1}^{s}\alpha_{ij} f(X_j) + \sum_{j=1}^{s}\left(\beta_{ij}^{(1)} J_1 + \beta_{ij}^{(2)}\frac{J_{10}}{h}\right) g(X_j), \quad i = 1,\ldots,s \\ x_{n+1} &= x_n + h\sum_{j=1}^{s}\eta_j f(X_j) + \sum_{j=1}^{s}\left(\gamma_j^{(1)} J_1 + \gamma_j^{(2)}\frac{J_{10}}{h}\right) g(X_j) \end{aligned} \tag{16}$$

Burrage & Burrage scheme for 2-stage SRK with order of convergence 1.0 is formulated as below

$$\begin{aligned} X_1 &= x_n \\ X_2 &= X_1 + \frac{2}{3}h\, f(X_1) + \frac{2}{3}\Delta W_n g(X_1) \\ x_{n+1} &= X_1 + h\left(\frac{1}{4} f(X_1) + \frac{3}{4} f(X_2)\right) + \Delta W_n\left(\frac{1}{4} g(X_1) + \frac{3}{4} g(X_2)\right) \end{aligned} \tag{17}$$

while 4-stage SRK with strong order of 1.5 can be written in tableaus form as follows

$$\Lambda = \begin{pmatrix} 0 & & & \\ \frac{1}{2} & 0 & & \\ 0 & \frac{1}{2} & 0 & \\ 0 & 0 & 1 & 0 \end{pmatrix}, \quad \eta^T = \left(\frac{1}{6}, \frac{1}{3}, \frac{1}{3}, \frac{1}{6}\right)$$

$$\Gamma^{(1)} = \begin{pmatrix} 0 & & & \\ -0.72429163 & 0 & & \\ 0.42373534 & -0.19944370 & 0 & \\ -1.5784755 & 0.84010034 & 1.7383751 & 0 \end{pmatrix}$$

$$\Gamma^{(2)} = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 2.7002000410 & 0 & 0 & 0 \\ 1.757261649 & 0 & 0 & 0 \\ -2.918524118 & 0 & 0 & 0 \end{pmatrix}$$

$$\gamma^{(1)T} = (-0.78007, 0.073637, 1.4865, 0.21992)$$

$$\gamma^{(2)T} = (1.69395, 1.63610, -3.02400, -0.306049)$$

It had been shown in our previous paper Norhayati et al. (2010) that the performance of SRK4 is better than SRK2 and EM for modelling the growth of the microbe. SRK4 is *MS*-stable compared to other numerical methods and has order of convergence of 1.5 (Norhayati et al., 2009). However, in this paper we need to model the solvent production where SRK2 would be sufficient to be used.

Numerical Analysis & Discussion

Three data sets of cell growth of *C. acetobutylicum* P262 were observed in Madihah (2000) at $t \in [0,288]$, where *t* is time measured in hour. The experiment was carried out in order to investigate the effect of different inorganic nitrogen source to yeast extract, YE. YE1, YE2 and YE3 represent the medium exclude inorganic source (control), medium with inorganic source of YE + NH_4CL and medium of YE + NH_4NO_3 respectively. We estimated the value of $\mu_{\max}$ and σ using Levenberg Marquardt algorithm in Haliza et al. (2009), whereas *b* and *e* were approximated using Simplex method. The initial values of $x(t_0), A(t_0), B(t_0)$ and the maximum cell concentration, $x_{\max}$ are observed from the experimental data. The initial values of $x(t_0), A(t_0), B(t_0)$ are given in Table 1.

Table 1: Initial values of $x(t_0), A(t_0), B(t_0)$ for YE1, YE2 and YE3

Initial values	YE1	YE2	YE3
$x(t_0)$	0.0031	0.002	0.0025
$A(t_0)$	0.068	0.02096	0.02799
$B(t_0)$	0	0	0

The estimated values of kinetic parameter for YE1, YE2 and YE3 are presented below.

Table 2: Estimated values of kinetic parameter for YE1, YE2 and YE3

Kinetic Parameter	YE1	YE2	YE3
$\hat{\mu}_{\max}$	0.4848	0.5056	0.6354
$\hat{\sigma}$	0.0028	0.0127	0.0052
$\hat{x}_{\max}$	3.525	0.949	4.295
$\hat{b}$	0.1076	0.0414	0.0835
$\hat{e}$	0.2596	0.0072	0.2431

By using SDE (7), (11) and (12), the stochastic models for their respective YE1, YE2 and YE3 are as follows:

Cell growth for YE1,

$$dx_{YE1}(t) = \left(0.4848\left(1 - \frac{x_{YE1}(t)}{3.5250}\right)x_{YE1}(t) - 7.84\times10^{-6}x_{YE1}^3(t)\right)dt + 0.0028x_{YE1}^2(t) \circ dW(t) \qquad (18a)$$

acetone formation for YE1,

$$A(t) = 0.068 + 0.1076\int_{t_0}^{t} x(s)ds \qquad (18b)$$

butanol formation for YE1,

$$B(t) = 0.2596\int_{t_0}^{t} x(s)ds \qquad (18c)$$

cell growth for YE2;

$$dx_{YE2}(t) = \left(0.5056\left(1 - \frac{x_{YE2}(t)}{0.9490}\right)x_{YE2}(t) - 1.6129\times10^{-4}x_{YE2}^{3}(t)\right)dt + 0.0127x_{YE2}^{2}(t)\circ dW(t) \quad (19a)$$

acetone formation for YE2,

$$A(t) = 0.02096 + 0.0414\int_{t_0}^{t} x(s)ds \qquad (19b)$$

butanol formation for YE2,

$$B(t) = 0.0072\int_{t_0}^{t} x(s)ds \qquad (19c)$$

cell growth for YE3,

$$dx_{YE3}(t) = \left(0.6354\left(1 - \frac{x_{YE3}(t)}{4.2950}\right)x_{YE3}(t) - 2.704\times10^{-5}x_{YE3}^{3}(t)\right)dt + 0.0052x_{YE3}^{2}(t)\circ dW(t) \qquad (20a)$$

acetone formation for YE3 ,

$$A(t) = 0.02799 + 0.0835\int_{t_0}^{t} x(s)ds \qquad (20b)$$

butanol formation for YE3 ,

$$B(t) = 0.2431\int_{t_0}^{t} x(s)ds \qquad (20c)$$

SRK2 was applied to simulate the strong solution of SDEs. The results of (18a-20a), (18b-20b), (18c-20c) and their respective logistic equations (2), Luedeking-Piret equations (11-12) as well as experimental data for YE1, YE2 and YE3 were presented in Figure 1, Figure 2 and Figure 3 respectively.

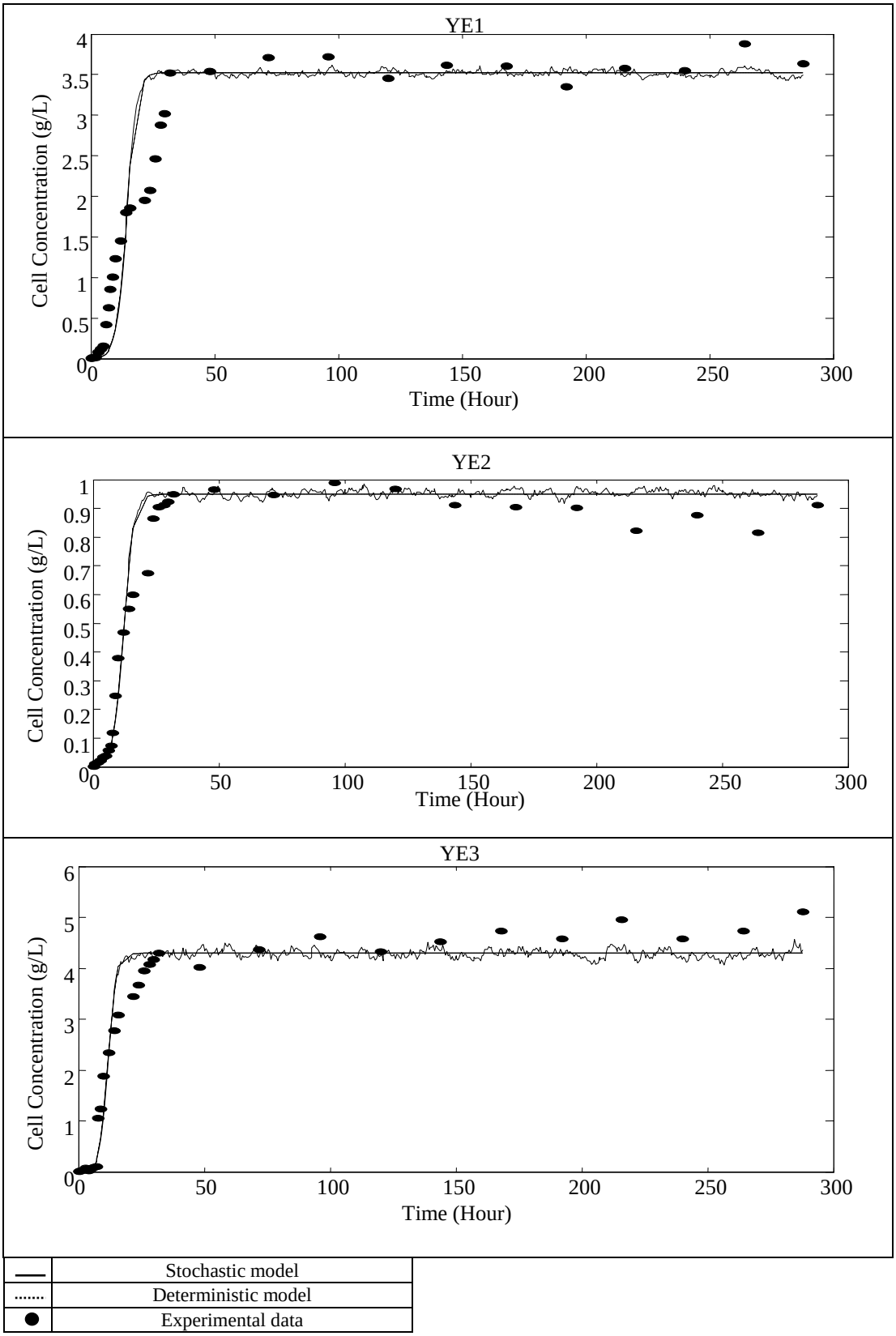

Figure 1: Results for cell concentration of YE1, YE2 and YE3

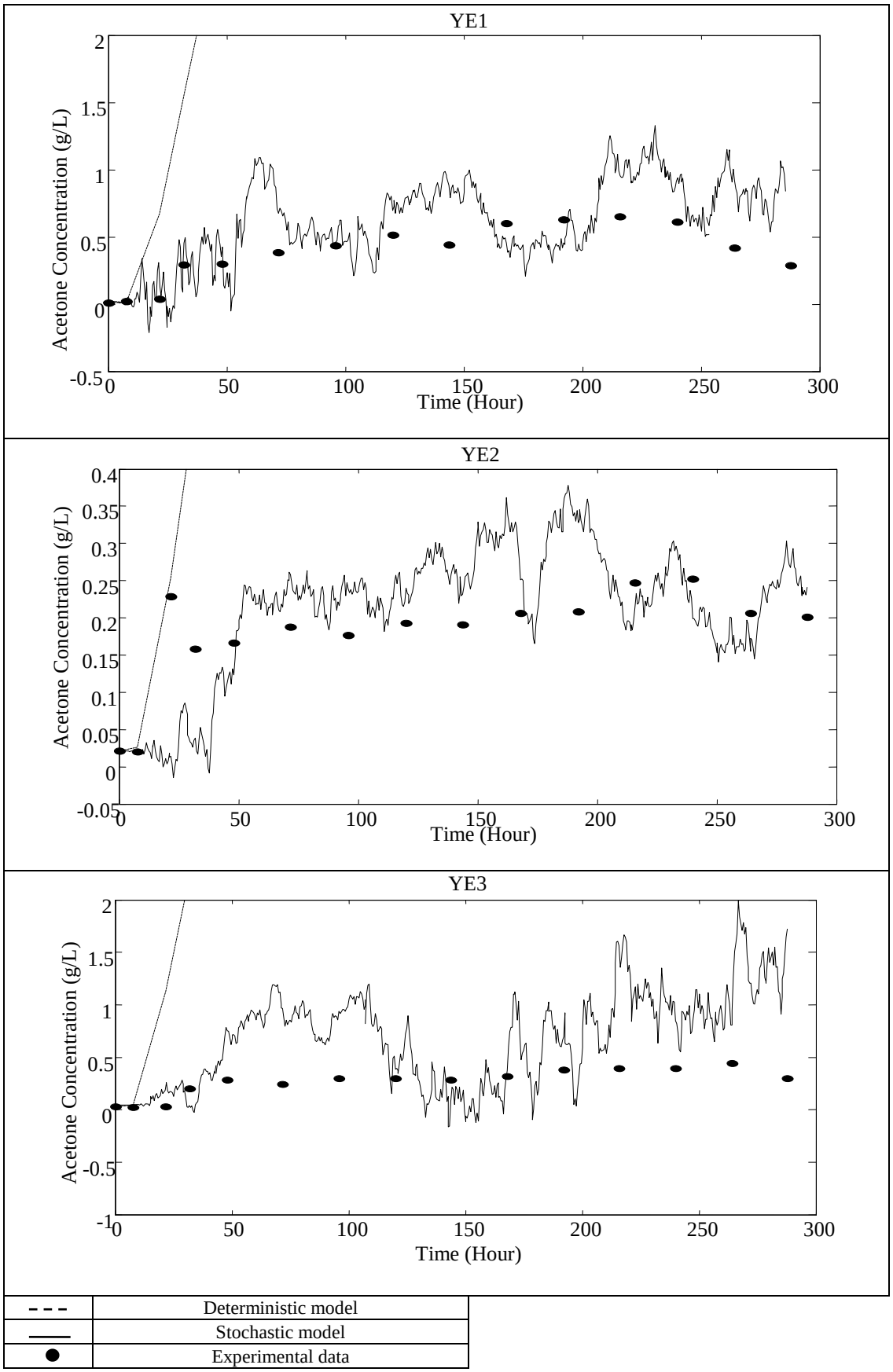

Figure 2: Results of acetone concentration using deterministic model, stochastic model and experimental data for YE1, YE2 and YE3

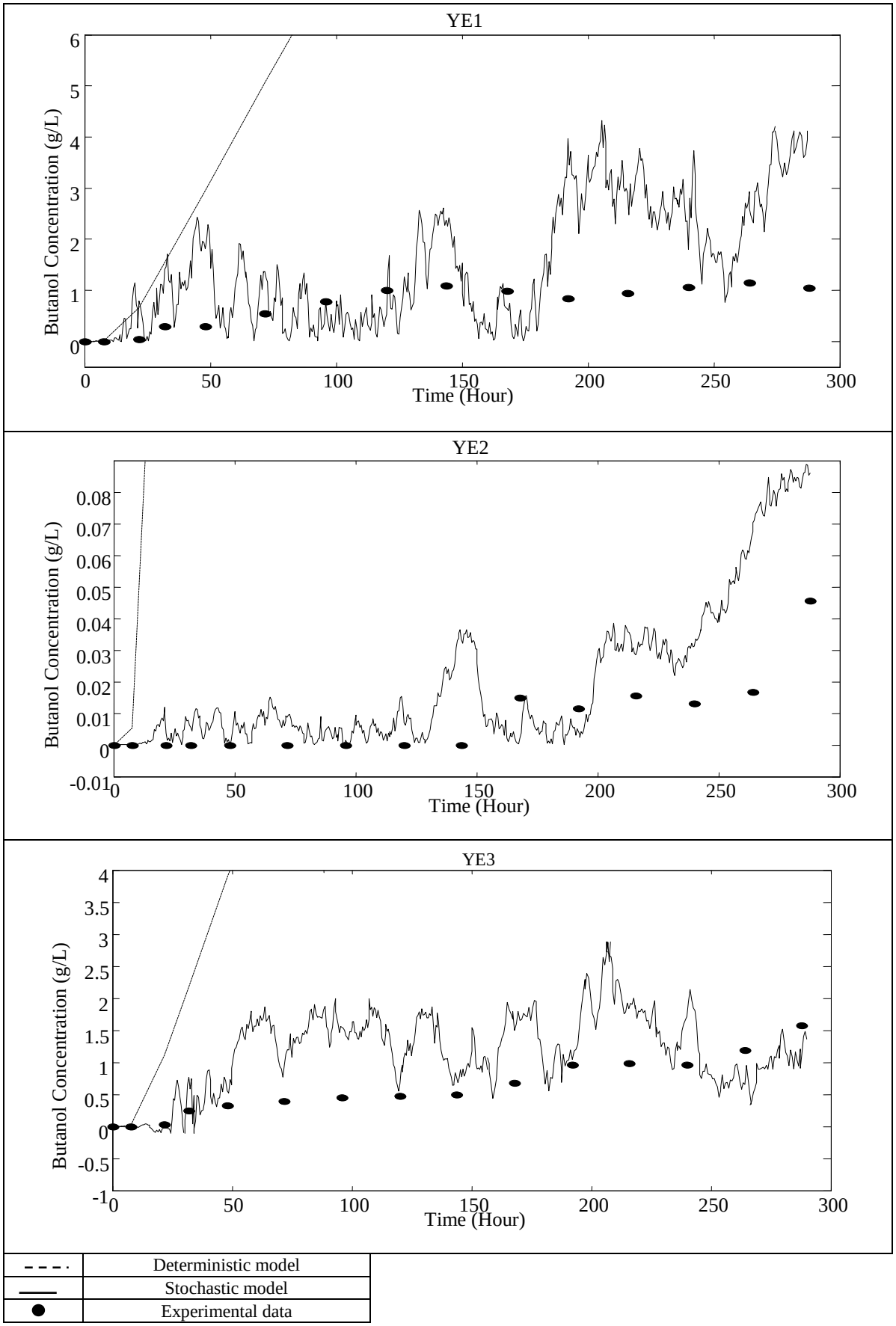

Figure 3: Results of butanol concentration using deterministic model, stochastic model and experimental data for YE1, YE2 and YE3

The prediction quality of the models can be assessed by using root mean square error (RMSE)

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(y_i - x_i)^2}{n}} \qquad (21)$$

where y_i is the experimental data and x_i is the predicted solution. The obtained RMSE for YE1, YE2, and YE3 are shown in Table 3.

Table 3: RMSE for YE1, YE2 and YE3

Model		RMSE ($n = 100$)		
		YE1	YE2	YE3
Stochastic logistic and Luedeking-Piret equation	Cell Growth	0.4451	0.0900	0.4263
	Acetone	0.2042	0.0666	0.2859
	Butanol	0.8401	0.0447	0.4540
Logistic and Luedeking-Piret equation	Cell Growth	0.5483	0.1058	0.5420
	Acetone	1.1262	0.6051	3.4364
	Butanol	3.4007	2.0022	9.4259

It can be seen that the numerical solution of stochastic logistic models describe the experimental data more adequacy as indicated by low values of RMSE for YE1, YE2 and YE3. The behaviour of cell proliferation of *C. acetobutylicum* P262 differs when stochastic logistic model is used. As time evolves, the system is subjected to an intrinsic variability of the competing within species and deviations from exponential growth arise. It happens as a result of the nutrient level and toxin concentration achieves a value which can no longer support the maximum growth rate. So, the stochastic fluctuations mainly affect the logistic growth of *C. acetobutylicum* P262 and we can conclude that cell growth in fermentation process can be modelled by using stochastic logistic model.

Since the cell growth of *C. acetobutylicum* P262 is no longer deterministic, the production of acetone and butanol shall be described by stochastic Luedeking-piret equations, indicating that $x(t)$ in (18b-20b) and (18c-20c) is a stochastic process. We can see that, the simulated data according to the models (18b-20b) and (18c-20c) fitted well to the experimental data as shown in Figure 2 and Figure 3. Furthermore, RMSE of product formation for acetone and butanol as presented in Table 3 are small, thus indicates that stochastic Luedeking-piret equation is also adequate to describe this process.

Conclusion

The models based on logistic and Luedeking-Piret equation were inadequate to describe direct fermentation of sago starch to solvent by *C. acetobutylicum* P262 (Mohd. Khairul Bazli et al., 2009). On the other hand, in this paper we found that stochastic logistic and Luedeking-Piret equation equipped with SRK2 describe the experimental data more adequate than its deterministic counterpart. The RMSE for YE1, YE2 and YE3 are all close to zero. We thus conclude that the behaviour of *C. acetobutylicum* P262 in gelatinised sago starch and solvent production of acetone and butanol can be modelled via stochastic logistic and Luedeking-Piret equations of (7), (11) and (12).

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