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Application of Stochastic Delay Differential Equations on Cell Growth

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ABSTRACT: Modelling of biological system via ordinary differential equations (ODEs) and stochastic differential equations (SDEs) has become an intensive research over last few years. In both types of equations the unknown function and its derivatives are evaluated at the same instant time, *t*. However, many of the natural phenomena do not have an immediate effect from the moment of their occurrence. A patient, for example, shows symptoms of an illness days or even weeks after the day in which he was infected. The dynamics of the systems differ dramatically if the corresponding characteristic equations involve time delay. Therefore, ODEs and SDEs which are simply depending on the present state are insufficient to explain this process. Such phenomenon can be modelled via stochastic delay differential equations (SDDEs). Batch fermentation is one of the systems that subject to the presence of noise and delay effects. It is necessary to model this process via SDDEs. To the best of our knowledge, the mathematical model of this system takes the form of ODEs and SDEs.

Keywords: Stochastic Differential Equations, Delay Differential Equations, Lag phase Exponential phase, Stationary phase, Death phase, 4-Stage stochastic runge-kutta

1. INTRODUCTION

The relationship between independent variable and the function with derivative of function of dependent variable in different order derivative is called differential equation. Differential equations play a crucial role in formulation and analysis of many biological and physical systems in engineering, natural sciences and physics. The differential equation is called ordinary differential equations (ODEs) if one variable involves in that equation. (Ayuobi, 2012). ODEs which explicitly allow the perturbation of random fluctuations are classified as stochastic differential equations (SDEs). In various range of application SDEs show a great potential for modelling. SDEs incorporate the uncontrolled fluctuation into the biological and physical phenomenon; hence provide a realistic mathematical model of the underlying systems than their deterministic counterpart do, (Hale, 1993). However, ODEs and SDEs which are simply depending on the present state are insufficient to illustrate the physical processes which involve time delay. In both types of equation the unknown function and its derivative are evaluated at instant time *t*. Time delay is frequently occur in many biological and physical processes such as in population dynamics and infectious diseases. Moreover, the generalization of DDEs and SDEs lead to the stochastic delay differential equations (SDDEs) (Mohammad, 1984). Delay differential equations and stochastic delay differential equations incorporate time delay in the differential equations. However, DDEs are inadequate to model the process with the presence of random effect. The process that involves the incorporation of both time delay and random effect can be modelled via SDDEs. One of the important systems that involve the presence of noise and time delay is the batch fermentation.

Fermentation is a process that the conversion of sugar to alcohol under anaerobic condition by using yeast undergoes (Bazli, 2010). There are two important features that control the mechanism of this process, namely time delay and the system is continually subject to the effects of random which is referred as noise. The presence of time delay is a consequence of the simple fact that microbes are in the process of adapting themselves to the new environment (Norhayati, 2010). Thus, there is no growth occur. The microbes, synthesize the new enzymes in response to the changes in the availability of substrate. Microbes at this stage is said to be in a lag phase. Obviously, at the end of lag phase population of microorganism is well adjusted and cells multiply rapidly, cell mass doubles regularly with time. This period is called exponential phase. As time evolves an intrinsic variability of competing within species and deviations from exponential growths arise. It happens as a result of the nutrient level and concentration of toxin reach a value which is unable to maintain the maximum growth rate. Microbe is said to be at stationary phase. By considering all the phases involve, it is necessary to model the microbial growth in batch fermentation process via SDDEs (Norhayati, 2012).

2. FERMENTATION PROCESS

Fermentation process is conversion sugar to alcohol under anaerobic condition by using yeast (Bazli, 2010). In various industries such a fuel, reagents and feedstock, solvent (acetone, butanol and ethanol) have great commercial value. There are many applications of solvent such as in auto mobile lacquer, aircraft wing dopes and for manufacture of lacquers, resin, rubbers, fats and oil, (Krouwel, et al. 1983). Jones and Woods in 1986 stated that, acetone is widely used in production of munitions. Butanol is crucial for manufacture of lacquers, rayon, detergents, brake fluids and amine (Linden et al. 1985). In addition, Butanol also need in production of a synthetic rubber (Hasting, 1971) and (Compere and Griffith, 1979). In agriculture butanol is crucial for production chemical feedstock (Krouwel et al. 1983). Ethanol is a chemical ingredient that useful in various types of industry and it play a crucial role in production of industry especially for solvent fats and oil (Linden et al. 1985). In cosmetic, industry and medical pharmaceutical, ethanol is used in production of alcohol and has a role of anesthetic agent respectively (Klaus and Arpe, 1983). In addition, ethanol uses for sue and ester component and extraction solvent (Karl, 1994). It is evident that acetone, butanol and ethanol have beneficial commercial value of various industries. Those solvent productions are in batch fermentation process. This process can be understood by block flow diagram shown in the following figure.

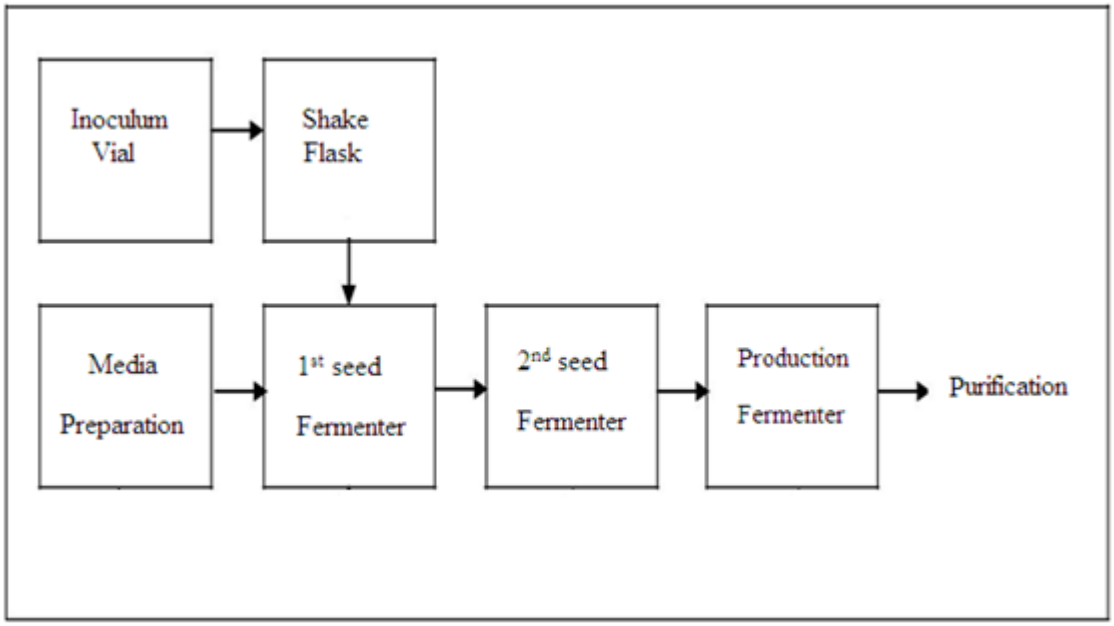

Figure 2.1: Block flow diagram of batch fermentation (Bazli, 2010).

Figure 2.1 represents a frozen vial containing a few millilitres of strain microbe recombine is taken out of freezers and strain thawed. Sometime vial and its contents are known as an inoculum. Inoculum is transferring in a sterile manner to shake flask containing growth media after thawing. This process called inoculum the volume of media in the shake flask is usually on the order of magnitude of hundreds of millilitres (Bazli, 2010). Cells can grow and be reproduced after inoculation. So, the shake flask is placed in an incubator shaker. In a constant temperature shaker is operating and it has two features which are;

(a) Homogeneous growth media keep the cells and nutrients.
(b) Media for the aerobic microbe cells increase the rate of oxygen uptake.

At the end of exponential phase cells are grown to a particular density and sued to inoculate a small fermenter known as a seed fermenter. Cells transfer to the production fermenter where they are grown to a particular density after cells reach their required volume and density. The density associated in which they are growing depend upon the desired product being growth or non-growth. Cells are grown to their mid to the end of exponential phase. At this position, a chemical is added that induces the cells being over denotes that gene is responsible to recombine protein. Depletion of nutrients eventually causes

the cells to enter their stationary growth phase. In addition, cells are no longer capable to produce the appreciable amounts of the desired protein (Bazli, 2010). There are two stages of batch fermentation which are;

(a) Growth stage
(b) Solvent production stage.

2.1 Growth Stage

In a growth stage cells are growing according to the four types of phases which are;

(a) Lag phase
(b) Exponential phase
(c) Stationary phase
(d) Death phase

Figure 2.2 depicts the cells growth curve for four phases in batch fermentation.

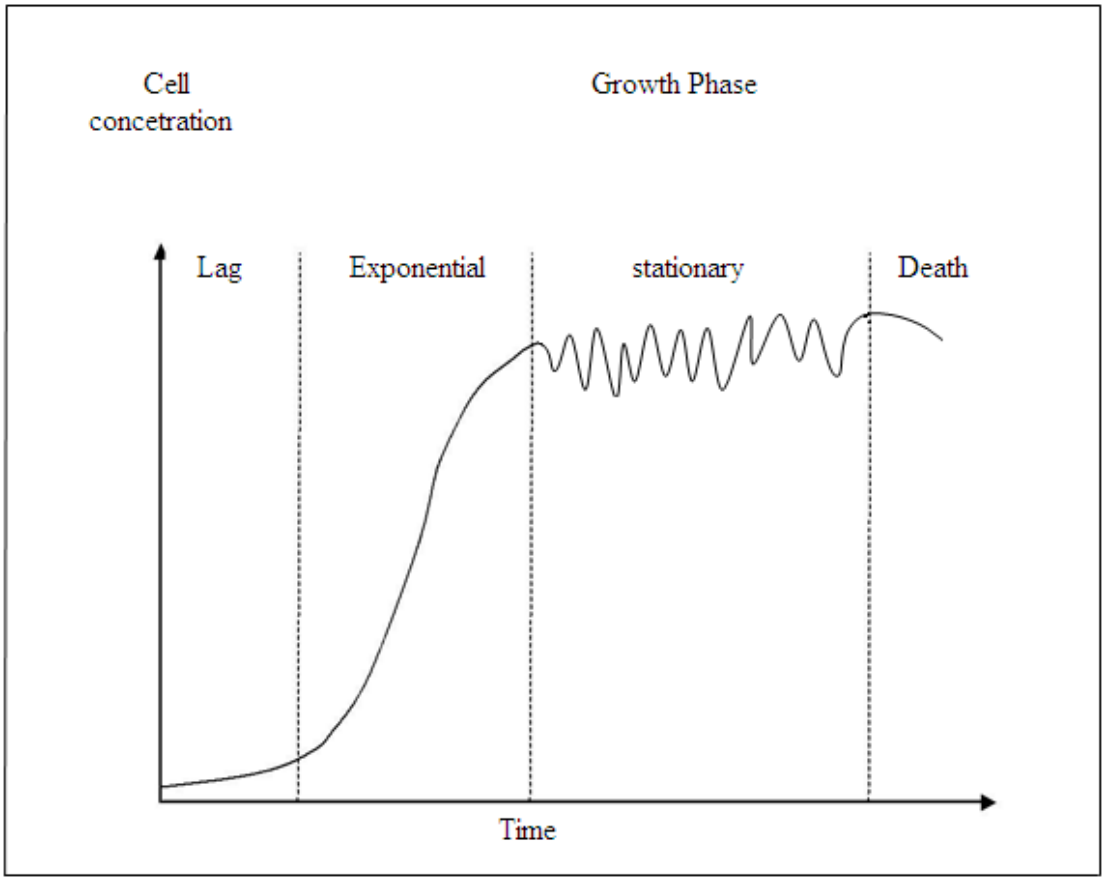

Figure 2.2: Growth phases of cells concentration in batch fermentation phase (Bazli, 2010).

Details regarding the mechanism of the cell growth in all phases are presented below.

A. Lag phase

(a) Cell in a period of adapting themselves to the new environment.
(b) Cells density minimal increase and in some causes no growth occur.
(c) Microbe subject to the time delay.

B. Exponential phase

(a) Also known as a logarithmic growth phase.
(b) The slope of the curve represents the specific growth rate of the organism which is measure the number of division per cell per unit time (Aziz,2010).

C. Stationary phase

(a) Rate dying and dividing numbers of cells are constant.
(b) Depletion of the essential growth nutrients.
(c) In production, accumulation of associated toxic growth.
(d) Microbe compete each other to survive due to the lack of nutrient and space. Hence, lead to the effect of stochasticity (Bazli, 2010).

D. Death phase

(a) Death phase is called decline phase.
(b) Rate of dividing less than rate of cell dying.
(c) Microbe run out of nutrients and die.

2.2.2 Solvent Production

The second stage of the batch fermentation process is solvent production. This stage has two different phases which are acidogenic and solventogenic phases. Acetate and butyrate are produced by acetyl-CoA and butyryl-CoA during acidogenic phase. Solvent production includes flow in the carbon which switch the acid producing ways to the solvent producing pathways, (Madihah, 2002). Acetyl-CoA and butyryl-CoA function as the intermediates key for butanol and ethanol producing during the solvent production. Acetylaldehyde and butyraldehyde are produced in this stage. Butanol produces under certain culture condition by Clostridium Acetobutylicum and ethanol can be produces independently from acetone (Madihah, 2002). Acetate, acetone and butanol are called secondary metabolite and butyrate and ethanol are called primary metabolite.

3. MATHEMATICAL MODEL OF FERMENTATION PROCESS

Modelling in mathematics illustrate how the world working as function and translate what we believes towards the phenomenon around us to the language of mathematics. Most of the physical systems in this world are subject to the random disturbances like whether that will affect the birth rate of the population under extreme weather condition. Despite, many actual systems take time to complete that is the systems in fact have the property of aftereffect. In the language of mathematics, the later means that the future states depend not only on the present states, but also on the past history. By taking into account the random disturbances and time delay, it is necessary to describe the real systems around us via SDDEs. One of the systems that involve the incorporation of both time delay and random disturbances is fermentation process. Therefore, it is necessary to model the batch fermentation via SDDEs. There has been quite abundance work on the modelling solvent production by microbial in the batch fermentation systems. The cell growth of C. *acetobutylicum* in batch system in the form of ODEs had been modelled by (Madihah, 2002). Then, Arifah in 2004 allows the parameter in population dynamics to vary randomly by introducing a white noise perturbation into ODEs to obtain general stochastic differential equations (SDEs) in population dynamics. In 2011, Bazli applied a general form of SDEs generated by (Arifah 2004) to a specific case of microbial growth for fermentation process. However under closer scrutiny, ODEs and SDEs are inadequate to describe the growth of the microbe. Cells initially are inactive and once it is activated the cell division is not instantaneous. 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 unable to sustain the maximum growth rate. Microbe at this phase is subjected to uncontrolled factors or stochasticity. Therefore, it is reasonable to

model jointly the lag phase and random disturbances in the fermentation process. An effort to model this system via SDDE have done by (Norhayati, 2012) by incorporating time delay into the deterministic function of SDEs provides by (Bazli, 2010). However, the perturbation considered in (Norhayati, 2012) lead to SDDEs with delay in diffusion. Stochasticity happen when the cells growth reach their maximum rate and at this position cells continuously grow, hence no delay occur.

4. PARAMETER ESTIMATION OF STOCHASTIC DELAY DIFFERENTIAL EQUATIONS

Stochastic delay differential equations (SDDEs) have been intensively research in the last few decades in various field of interest . Amongst of that research is development of the estimator for SDDEs. (Kuchler and Mensch 1992) introduced pseudo maximum likelihood estimation method to estimate the parameter of SDDEs. (Gushchin & Kuchler 1999) and (Kuchler and Kutoyants 2000) introduced non-standard asymptotic properties of maximum likelihood estimator. While, (Kuchler and Vasil'jev 2005) created successive manners with given percision in the L_2 -sense. Whereas, (ReiB, 2002a and ReiB, 2000b) investigated the non-parametric estimitors of SDDEs.

5. NUMERICAL METHOD FOR STOCHASTIC DELAY DIFFERENTIAL EQUATIONS

Most of SDDEs do not have an explicit solution. Hence, numerical methods provide a way to solve the problems. There are a few methods available for solving SDDEs numerically, namely Euler-Maruyama (EM), Milstein scheme and 4-stage stochastic Runge-Kutta (SRK4). It was (Baker, 2000) who proposed a numerical method of EM for SDDE. This method has 0.5 strong order of convergence. The derivation of Milstein scheme from stochastic Taylor expansion showed a strong order of convergence 1.0 was introduced by (Kuchler and Platen, 2004). Later work on numerical methods of SDDEs was conducted by (Norhayati, 2012) by introducing derivative-free method, that is 4-stage stochastic Runge-Kutta (SRK4) having 1.5 order of convergence, still it is the highest order method for solving SDDEs. Euler-Maruyama and Milstein scheme were developed by truncating the stochastic Taylor expansion of SDDEs. However, as the order increases the need for the computation of partial derivatives of drift and diffusion functions, contribute to the cost of computational. Thus, it is necessary to consider the derivative-free method SRK to simulate the strong solution of SDDEs.

6.1 MODELLING BATCH FERMENTATION PROCESS VIA SDDEs

SDDEs can be approached either as SDEs with added delay or DDEs with noise. In the acetone--butanol biosynthesis process by C. *Acetobutylicum* P262, a more sophisticated insight into physical phenomena may be achieved if the problems with time lags are considered and the observed biological system is assumed to operate in a noisy environment. In such a case, it is practical to model the cell division in batch culture via SDDE. It is also assumed no delay argument in diffusion function. This assumption is imposed due to the fact that as time evolves, microbial are competing within species for food and space. Hence no delay occur at this stage. Therefore, a general formulation of autonomous SDDE is in the form of

$$dx(t) = f\left(x(t), x(t-\tau)\right)dt + g(x(t), x(t-r))\,dW(t), t \in [-\tau, T]$$
$$x(t) = \Phi(t) \quad t \in [-\tau, t_0], \ \tau > 0$$

where σ corresponds to the diffusion coefficient and need to be estimated. In applied problems the initial function, $\Phi(t)$ is found experimentally and also may be determined from another equation without deviating argument. For our purpose $\Phi(t)$ is determined experimentally.

6.2 DATA COLLECTION

Three of sets data for cell growth of *C. acetobutylicum* P262 have been collected at $t \in [0, 288]$, by (Madihah, 2002) where *t* is a time measured in hour. The experiment is carried out to investigate the effect of different inorganic nitrogen source to yeast extract, YE. YE1, YE2 and YE3 represent the control medium (no inorganic source), medium with Ammonium Chloride (NH_4Cl) and medium with Ammonium Nitrate (NH_4NO_3) respectively.

6.3 PARAMETER ESTIMATION VIA PSEUDO MAXIMUM LIKELIHOOD ESTIMATOR

the estimator is obtained by discretizing the likelihood function for continuous time observation. The stochastic differential equations with delay are given by

$$dx(t) = \int_{-r}^{0} x(t+s)\,\alpha_\theta(ds) + \sigma dW(t)$$

where $\theta = [\mu_{\max}, \sigma]$ be a parameter to be estimated. α_θ is a measure on $[-r, 0]$ and is assumed to has a unique stationary solution. The measure α_θ is concentrated on the discrete points $-r_1, \ldots, r_N, 0 \le \ldots < r_N$. The distribution of the initial condition is stationary which always has the expectation zero. The data are observations at discrete time points and the autocovariance function, $K_\theta(t) = E_\theta(x(0)x(t)), \quad t \ge 0$ satisfies the differential equation

$$\partial_t K_\theta(t) = \int_{-r}^{0} K_\theta(t+s)\,\alpha_\theta(ds), \quad t \ge 0$$

When the process is observed continuously in time-interval $[0, t]$, the likelihood function is

$$L^c{}_t(\theta) = \exp\left(\theta^T A_t^c - \frac{1}{2}\theta^T I_t{}^c \theta\right)$$

where

$$A_t^c = \left(\int_0^t x(s-\tau_1)dx(s), \ldots, \int_0^t x(s-\tau_N)dx(s)\right)^T$$

T denotes transposition and $I_t^{\,c}$ is the observed information matrix,

$$I_t^{\,c} = \int_0^t x(s-\tau_i)x(s-\tau_j)ds$$

The maximum likelihood estimator of θ is

$$(I_t^{\,c})^{-1} A_t^c$$

When the data are discrete time observations, a simple estimator of θ is obtained by discretising the integrals in $A_t^{\,c}$ and $I_t^{\,c}$, that is

$$\hat{\theta}_n = I_n{}^{-1} A_n$$

6.4 NUMERICAL COMPUTATIONS VIA 4-STAGE STOCHASTIC RUNGE-KUTTA (SRK4)

4-stage stochastic Runge-Kutta (SRK4) method of order 1.5 with a fixed step size, h on the interval $[0, T]$, for $h = \frac{T}{N}$, $t_n = (n-1)\cdot h$, $n = 1, \ldots, N$ will be employed to simulate the solution of SDDEs. We assumed that, there is an integer number N_τ such that the delay can be expressed in terms of the step size $\tau = N_\tau \cdot h$.

6.4.1 Modelling Batch Fermentation via SDDEs

The classical growth logistic ordinary differential equation has been revealed by (Verhulst, 1838) which is;

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

to describe the cell growth of C. *acetobutylicum* P262 in batch fermentation process. The constant $x_{\max}$ denotes the maximum cell concentration (g/L), $\mu_{\max}$ corresponds to the maximum specific growth rate h^{-1} and T is the terminal point of time (h). In natural environment $x_{\max}$ is limiting population determined by carrying capacity of the environment. The production of acetone and butanol are formulated as

$$\frac{dA(t)}{dt} = ax \quad (2)$$

and

$$\frac{dB(t)}{dt} = bx \quad (3)$$

respectively, where A represents the acetone concentration (g/L), B is butanol concentration (g/L), a and b correspond to non-growth associated coefficient for acetone and butanol formation (g substrate/ g cell) respectively. Luedeking-Piret equations of (2) and (3) can be written in integral form as

$$A(t) = A(t_0) + a\int_{t_0}^{t} x(s)ds \quad (4)$$

and

$$B(t) = B(t_0) + b\int_{t_0}^{t} x(s)ds \quad (5)$$

where $A(t_0)$ and $B(t_0)$ correspond to the initial acetone and butanol concentration respectively. The cell growth of C. *acetobutylicum* P262 can better be described via delay differential equations (DDEs). The first effort to model the population growth using logistic DDE was done in (Hutchinson 1948), by assuming that the biological self-regulatory reaction represented by the factor $1-\frac{x(t)}{x_{\max}}$ in (1) is not instantaneous. The cell growth of the microbe responds after some time lag, $r>0$, due fact that initially the microbial are in the process of adapting themselves to the

changing environment. Thus, the corresponding classical growth logistic DDE is

$$\frac{dx(t)}{dt} = \mu_{\max}\left(1-\frac{x(t-r)}{x_{\max}}\right)x(t), t\in[-r,T] \quad (6)$$
$$x(t) = \Phi(t), t\in[-r,0]$$

where $t_0 = 0$. Time delay, r models the length of the time period between the initial time and maturing time wherein the division of the cell begins. One of the other factors that influence the mechanism of the microbial growth is the presence of external an internal noise in the batch system. The deterministic models of (1) and (6) do not accommodate random variations of metabolism. Stochastic model arising as a result of the hypothesis that the process itself is subjected to uncertainty. Therefore, it is necessary to add suitable system variability to the model (6). (Norhayati et. al 2011). had used stochastic delay differential equations (SDDEs) to model the solvent production by C. *acetobutylicum* P262. However, the perturbation considered in (Norhayati et. al 2011) lead to SDDEs with delay in diffusion. Stochasticity happen when the cells growth reach their maximum rate and at this position cells continuously grow, hence no delay occur. This research introduce a new perturbation through parameter $\rho = -\frac{\mu_{\max}}{x_{\max}}$ such that no delay in diffusion function. Therefore, the model derived in this section is in the form of (6) with random perturbation through ρ such that $\rho \to \rho + \frac{\sigma}{x(t-r)}\frac{dW(t)}{dt}$. Thus, a simplified batch fermentation kinetic model for cell growth of C. *acetobutylicum* P262 is

$$dx(t) = \mu_{\max}\left(1-\frac{x(t-r)}{x_{\max}}\right)x(t)dt + \sigma x(t)dW(t), \quad t\in[-r,T]$$
$$x(t) = \Phi(t), \quad t\in[-r,0]$$

The mathematical model of solvent production are represented by the equations (4) and (5), but $x(t)$ is subjected to time delay and no longer deterministic. The initial function, $\Phi(t)$ for $t\in[-r,0]$ is found experimentally, (Norhayati & Ayuobi, 2013).

6.4.2 Algorithm for Numerical Programming of 4-Stage Stochastic Runge-Kutta Method

We define a meshpoint with a uniform step size h on the interval $[0,T]$. Let $h = \frac{T}{N}$, for $t_n = n\cdot h$ and $n = 0,\ldots,N$. We assume that there is an integer m such that the time delay r can be expressed as $r = m\cdot h$. Let $X_k = \Phi(kh)$, where $k = -m,-m+1,\ldots,0,m,m+1,\ldots,N$. The initial values of $X_k = \Phi(kh)$ for $k = -m,-m+1,\ldots,0.$ The numerical scheme describes above was translated into C programs on a Core™ i5-computer to obtain the cell growth concentration and product formation at $t\in[0,288]$. ΔW_k is normally distributed with mean zero and variance, $h_k = t_{k+1} - t_k$. It can be generated in C programs using Box-Muller method. The numerical algorithm is presented below.

(a) Define the fix step size, $h_k = t_{(k+1)} - t_k$ and integer number N_τ such that delay can be expressed as $\tau = N_\tau \cdot h$. Define a step such that step is expressed as $\frac{T}{\tau}$.

(b) Do initial function, X_k evaluation for $k = -m,-m+1,\ldots,0.$

(c) Do drift function, $f(X_k) = \left[\mu_{\max}\left(1-\frac{X_{k-m+1}}{x_{\max}}\right)X_k\right]$ evaluation for $k = m,m+1,\ldots,N.$

(d) Do diffusion functions, $g(X_k) = \sigma X_k$ and $g(X_k)\frac{\partial}{\partial X_k} g(X_k) = \sigma^2 X_k$ evaluation for $k = m, m+1, \ldots, N$.

(e) Perform a random number generator.
(f) Perform an explicit 4-stage stochastic Runge-Kutta.

7. Conclusions

(a) The improved model can predict the production of acetone and butanol more accurately.

(b) The incorporation of stochasticity into the specific growth rate and the inclusion of the lag phase into the cell concentration in the fermentation process will reflect approximately real situation of fermentation process.

(c) The stochastic model of time lag is expected to be the generalisation in modeling cell growth.

(d) The development of numerical algorithm in estimating parameters and simulating the solution of stochastic model can be used by other researchers to simulate the solution and analyse the stochastic model with delay effect.

REFERENCES

1) Ayuobi, T. 2012. Differential Equations. Afghanistan: Kabul Education University.
2) Baker, C. T. H. 2000. Introduction to the Numerical Analysis of Stochastic Delay Differential Equations. Journal of Computational and Applied Mathematics, 125:297-307.
3) Bazli, M. K. 2010. Stochastic Modelling of the C. Acetobutylicum and Solvent Productions in Fermentation. Universiti Teknologi Malaysia: Master Thesis.
4) Buckwar, E. 2000. Introduction to the Numerical Analysis of Stochastic Delay Differential Equations. Journal of Computational and Applied Mathematics125:297-307.
5) Compere, A. L. and Griffith, W. L. 1979. Evaluation of Subtrate for Butanol Production Development Industrial Microbiology 20: 509-517
6) Gushchin, A.A. and Kuchler, U. 1999. Asymptotic inference for a linear Stochastic Differential Equation with time Delay. Bernoulli. 5: 1059-1098.
7) Hale, J. K. 1993. Introduction to Functional Differential Equations. Berlin: Springer.
8) Hastings, J. J. H. 1971. Development of the Fermentation Industries in Great Britain. Advance Applied Microbiology. 14:1-45
9) Jones, D. T. and Woods, D. R. 1986. Acetone-Butanol Fermentation Revisited. Microbiology Reviews 50: 484-524
10) Karl, S. 1994. Solvent Extraction in Biotechnology. Recovery of Primary and secondary Metabolites. Germany: Springer – Verlag Berlin, Heidelberg.
11) Klaus, W. and Arpe, H. J. 1983. Industrial Organic Chemistry. Second Revised and Extended Edition. Germany: VCH Publishers.
12) Krouwel, P. G.Groot, W. J. Kossen, N. W. F. and Van der Laan, W. F. M. 1983. Continuous Isopropanol-Butanol-Ethanol Fermentation by Immobilized Clostridium Beijerinkii Cell in a Packed Bed Fermenter. Journal of Enzyme Microbial Technology 5: 46-54
13) Kuchler, U. and Kutoyants, Y.A. 2000. Delay Estimation for Some Stationary Diffusion Type Processes. Scand. J. Statist, 27:405-414.
14) Kuchler, U. and Mensch, B. 1992. Langevin's Stochastic Differential Equation Extended by a Time-Delayed Term, Stochastic Reports, 40:23-42.
15) Kuchler, U. and Platen, E. 2000. Strong Discrete Time Approximation of Stochastic Differential Equations with Time Delay. Math. Computational Simulation, 54:189-205
16) Küchler, U.and Sørensen, M. 2013. Statistical Inference for Discrete Time Samples from Affine Stochastic Delay Differential Equations. Bernoulli, 19(2): 409-425.
17) Kuchler, U. and Vasiliev, V. 2005. Sequential Identification of Linear Dynamic Systems with Memory. Stat. Inference Stoch. Process, 8:1-24.

18) Linden, J. C. Moreira, A. R. and Lenz, T. G. 1985. Acetone and Butanol comprehensive Biotechnology. The Principles, Application and Regulations of Biotechnology in Industry, Agriculture and Medicine. England: Pergamon Press, 3:658-929
19) Madihah Md Salleh 2002. Direct Fermentation of Gelatinised Sago Starch to Solvent (Acetone-Butanol-Ethanol) by Clostridium Acetobutylicum P262. Universiti Putra Malaysia: PHD Thesis,
20) Mohammad. S. E. A. 1984. Stochastic Functional Differential Equations. 6th Edition England Wood Cliff, N.J: Pitman Advanced Publishing.
21) Norhayati, R. Arifah, B. Hoe, Y. S. and Haliza, A.R. 2010. Performance of Euler-Maruyama, 2-Stage SRK and 4-Stage SRK in approximating the strong solution of stochastic model. Journal Sains Malaysian, 39(5): 851-857.
22) Norhayati, R. Arifah, B. Haliza, A. R., Bazli, M.K. and Madihah, M.S. 2010. Stochastic Model of Gelatinised Sago Starch to Solvent Production by C. acetobutylicum P262, Proceedings of the Regional Conference on Statistical Sciences, June 13-14, Kelantan, Malaysia: RCSS'10. 9-20.
23) Norhayati, R. 2012. Stochastic Runge-Kutta Method for Stochastic Delay differential Equations, Universiti Teknologi Malaysia: PHD Thesis.
24) Norhayati, R., Ayuobi, T., Arifah, B., Haliza, A.R. and Madihah, M.S. 2013. Stochastic Growth Modeling with Aftereffect for Batch Fermentation Process, Third International Conference on Mathematical Sciences, Dec 17-19. PWTC Malaysia.
25) ReiB, M. 2002a. Minimax Rates for Nonparametric Drift Estimation in affine Stochastic Delay Differential Equations. Statistical Inference for Stochastic Process 5:131-152.
26) ReiB, M. 2002b. Nonparametric Estimation for Stochastic Delay Differential Equations. Berlin: Institut Für Mathimatik, Humboldt-Universität zu: PHD Thesis.