STOCHASTIC MODELLING OF TIME DELAY FOR SOLVENT PRODUCTION BY CLOSTRIDIUM ACETOBUTYLICUM P262

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ABSTRACT

Ordinary differential equations (ODEs) and stochastic differential equations (SDEs) are widely used to model biological systems in the last decades. 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. For instance, a patient shows symptoms of an illness days or even weeks after the day in which they were infected. The dynamics of the systems differ 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 process is one of the systems which subject to the presence of uncontrolled fluctuation and delayed feedback. ODEs and SDEs are not capable to model uncontrolled fluctuation and delayed feedback in fermentation process. It is necessary to model this process via SDDEs. Thus, this research is carried out to propose a stochastic model with delay effect for cell growth and solvent production of acetone and butanol by *Clostridium Acetobutylicum* P262 in fermentation process. The kinetic parameters of the results model are estimated via maximum likelihood method. The analytical solutions of this model is hard to be found, hence numerical method of 4-stage stochastic Runge-Kutta (SRK4) provide a way to simulate the solutions of the model. The RK4 and SRK4 methods are translated into C languages to obtain the numerical solutions of mathematical model for the cell growth concentration and solvents production. The experimental data is used to validate the results. The results indicate that the most suitable model to explain the solvent production by *Clostridium Acetobutylicum* P262 in fermentation process is SDDEs.

ABSTRAK

Persamaan pembezaan biasa (ODEs) dan persamaan pembezaan stokastik (SDEs) digunakan secara meluas untuk memodelkan sistem biologi dalam beberapa dekad yang lalu. Dalam kedua-dua jenis persamaan fungsi yang tidak diketahui dan terbitannya dinilai pada masa yang sama, *t*. Walau bagaimanapun, kebanyakan fenomena semula jadi tidak mempunyai kesan segera pada kejadiannya. Sebagai contoh, seorang pesakit menunjukkan gejala penyakit satu hari atau beberapa minggu selepas hari dimana mereka telah dijangkiti. Sistem dinamik berbeza jika ciri persamaan yang sepadan melibatkan masa lengahan. Oleh itu, ODEs dan SDEs yang hanya bergantung kepada keadaan semasa tidak mencukupi untuk menerangkan proses ini. Fenomena seperti ini boleh dimodelkan melalui persamaan pembezaan stokastik dengan masa lengahan (SDDEs). Kelompok penapaian adalah salah satu sistem yang tertakluk kepada kehadiran turun naik yang tidak terkawal dan maklum balas lengahan. ODEs dan SDEs tidak boleh untuk memodelkan turun naik yang tidak terkawal dan maklum balas lenagahan dalam proses penapaian. Ia adalah perlu untuk memodelkan proses ini menggunakan SDDEs. Oleh itu, kajian ini dijalankan untuk mencadangkan satu model stokastik dengan kesan kelewatan untuk pertumbuhan sel dan penghasilan pelarut aceton dan butanol oleh *Clostridium Acetobutylicum* P262 dalam proses penapaian. Parameter kinetik model yang terhasil dianggarkan melalui kaedah kebolehjadian maksimum. Penyelesaian tepat model ini sukar untuk ditemui, maka kaedah berangka 4 peringkat stokastik Runge-Kutta (SRK4) menyediakan satu cara untuk mensimulasikan penyelesaian model. Kaedah SRK4 diterjemahkan kepada program C untuk mendapatkan penyelesaian berangka bagi model matematik kepekatan pertumbuhan sel dan penghasilan pelarut. Data eksperimen digunakan untuk mengesahkan keputusan. Keputusan menunjukkan model yang paling sesuai untuk menerangkan penghasilan pelarut oleh *Clostridium Acetobutylicum* P262 dalam proses penapaian adalah SDDEs.

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LIST OF SYMBOLS

a	Non-growth associated coefficient for acetone
b	Non-growth associated coefficient for butanol
A	Acetone
$A(t_0)$	Initial acetone concentration
B	Butanolc Concentration
$E(X)$	Expected value of X
N_r	Integer number
r	Time delay
R	Real set number
t	Time
T	Terminal time
var (X)	Variance of X
x	Concentration of cell mass
$x_{\max}$	Maximum cell concentration
X	Random variable or stochastic process
Δ	Size step
ΔW_k	Increment of Wiener process
Ω	Sample space
σ	Noise

$\exists$	Exist
$\forall$	For each
$\varphi(t)$	Initial function
μ_{max}	Maximum specific growth rate

LIST OF ABBREVIATIONS

Acetoacetytyl-CoA	Acetoacetytyl coenzyme A
Acetyl-CoA	Acetyl coenzyme A
ADP	Adenosine diphosphate
ATP	Adenorsine triphosphate
Butyryl-coA	Butyryl-coenzyme A
Crotonyl-CoA	Crotonyl-coenzyme A
DDEs	Delay differential equations
EM	Euler-Maruyama
NAD	Nicotinamide adenine dinucleotide
NAD+	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide + hydrogen
$NADH+H^+$	Nicotinamide Adenine Dinucleotide + Hydrogen+ Hydrogen
ODEs	Ordinary differential equations
RK	Runge-Kutta
SDEs	Stochastic differential equations
SDDEs	Stochastic delay differential equations
SRK	Stochastic Runge-Kutta
SRK4	4-Stage stochastic Runge-Kutta
YE1	Yeast extract

YE2	Yeast extract with ammonium chloride
YE3	Yeast extract with ammonium nitrate

CHAPTER 1

INTRODUCTION

1.1 RESEARCH BACKGROUND

Differential equations play a crucial role in formulation and analysis of many biological and physical systems (Jones et al., 2011). They relate the function of one or more variables with its derivative. The differential equations are called ordinary differential equations (ODEs) if the unknown function also known as dependent variable is a function of single independent variable t (Abell and Braselton, 2004). ODEs which explicitly allow the perturbation of random fluctuations are classified as stochastic differential equations (SDEs). In various range of applications SDEs have a richer mathematical framework compared with ODEs. SDEs incorporate the uncontrolled fluctuation into the biological and physical phenomenon, hence it provides a realistic mathematical model for the analysis of underlying systems than their deterministic counterpart do (Hale, 1993). However, ODEs and SDEs which are simply depending on the present state are unable to illustrate the physical processes which involve time delay. In both types of equations the unknown function and its derivative are evaluated at instant time t.

In most of natural phenomenon, a delayed-feedback is introduced when they are some hidden variables and processes which are not well understood but

are known to cause a time-lag (Bocharov and Rihan, 2000). A patient, for example, shows symptoms of an illness days or even weeks after the day in which she/he was infected. ODEs and SDEs can be improved by incorporating time delay into both equations. Deterministic differential equation with delayed-feedback is called delay differential equations (DDEs). However, DDEs are inadequate to model the process with the presence of both time delay and random effects. The process that involves the incorporation of both time delay and random effects can be modelled via stochastic delay differential equations (SDDEs). SDDEs are a generalization of DDEs and SDEs (Mohammed, 1984).

One of the most important systems that subject to the presence of noise and time delay is batch fermentation process. Fermentation is a process of converting sugar to solvents (acetone, butanol and ethanol) under anaerobic condition by using yeast undergoes (Madihah, 2002). 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 to 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. 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 are assumed to be in a lag phase. Obviously, at the end of lag phase the microorganism is well adjusted and cells multiply rapidly. Cell mass doubles regularly with time. This period is recognized as an exponential phase. As time evolves the intrinsic variability of competing within species occur and deviations from exponential growths arise. It happens as a result of the nutrient level and concentration of toxin reach as a value which is unable to sustain the maximum growth rate. This phase is the most frequently known as a stationary phase. The production of solvent occurs in two different phases which are acidogenic and solventogenic phases. Acetyl-CoA and butyryl-CoA function as the intermediates key for solvent production. Acetylaldehyde and butyraldehyde are produced in this stage. The production of solvents (acetone and butanol) happens in solventogenic phase. As

aforementioned, cell growth of *Clostridium Acetobutylicum* P262 is subjected to delayed-feedback and noise. The presence of these two features will influence the concentration of acetone and butanol that will be produced in batch fermentation process. To understand the behaviour of this physical system it is necessary to develop a mathematical model that incorporates both of the delayed-feedback and noisy environment. Thus, this research is carried out to model jointly time delay and stochasticity of the microbial growth and solvents production of acetone and butanol in batch fermentation process.

1.2 PROBLEM STATEMENTS

All biological and physical processes need time to complete. In batch fermentation process, time delay occurs due to the fact that initially cells are in the position of adapting themselves to the new environment. Hence, the biological regulatory reaction of the cell growth is not instantaneous. Cells only respond after some time lag, $r > 0$. The process indicates an intrinsic variability in the stationary phase. Cells compete with each other for space and food due to the exhausted of nutrient level and toxin concentration. Bearing in mind, all the phases involve in batch fermentation, it is necessary to model the process via SDDEs. Hence, the research problems were set as below;

(i) Will the stochastic model with time delay be an efficient model to describe the solvent production of acetone and buthanol by *Clostridium Acetobutylicum* P262 in batch fermentation process?

(ii) How to develop the algorithm to approximate the solutions of stochastic model in (i)?

(iii) How to estimate the kinetic parameter and simulate the solutions of stochastic model with delayed-feedback?

1.3 OBJECTIVES OF THE RESEARCH

Based on the above research problems, this research embarks on the following research objectives;

(i) To model jointly time delay and random effects of cell growth and solvents production (acetone and butanol) in batch fermentation.

(ii) To develop the algorithm of simulating the strong solutions of stochastic model in (i).

(iii) To estimate the kinetic parameter of mathematical model in (i) by using simulated maximum likelihood.

(iv) To simulate the solutions of stochastic logistic model with time delay via 4-stage stochastic Runge-Kutta method.

1.4 SCOPE OF THE RESEARCH

This research focuses on modelling delayed-feedback and uncontrolled fluctuation of batch fermentation process via SDDEs. Current study considers three phases namely lag, exponential and stationary phase in fermentation process. Solvent production of acetone and butanol are modelled by using stochastic Luedeking-Piret equations with delayed-feedback. Moreover, to investigate the performance of SDDE in explaining the behaviour of solvents production by *Clostridium Acetobutylicum* P262, mathematical models of ODEs, DDEs and SDEs are presented. This research had employed a 4-stage Runge-Kutta to simulate the solutions of DDEs, and 4-stage stochastic Runge-Kutta to approximate the solutions of SDEs and SDDEs. The data are obtained from the experiment done by Madihah (2002) for three different yeast cultures which are control medium (yeast extract only), YE1, yeast extract with ammonium chloride, YE2 and yeast extract with ammonium nitrate, YE3.

1.5 SIGNIFICANCE OF THE RESEARCH

This research provides significance contribution to the mathematics and its application in terms of;

(i) New findings: This research considers the important features previously neglected, which are time delay and random effect to describe the behaviour of batch fermentation process. The mathematical model developed in this research is more realistic since it considers all phases that involve in batch fermentation.

(ii) Specific or potential application: The newly developed mathematical model can be used by practitioners of biotechnology for better prediction of acetone and buthanol production in fermentation process. In biotechnology industries, for instance, our theoretical predictions and mathematical formulations will help to explain and verify experimental output.

(iii) The algorithms of simulating the numerical solutions of SDDEs can be applied in other related fields to simulate the solutions and analysis of the stochastic model with delayed-feedback.

1.6 THESIS ORGANIZATION

A brief description of the chapters contained in this thesis is now presented.

The first chapter provides the introduction to the whole thesis. It consists of the background of the research, statement of the problems, objectives of the research, scope of the research and their significance.

Chapter two contains the review of literature for fermentation process, progress of modelling in fermentation process, numerical methods and parameter estimation of SDDEs.

Chapter three concerns on the fundamental background of random variables, Brownian motion, DDEs, SDEs and SDDEs. This chapter also presents numerical methods for solving those differential equations.

Chapter four consist the main results of this research. A new mathematical model of SDDE for *Clostridium Acetobutylicum* P262 is developed. Moreover, solvent production of acetone and butanol are modelled by using stochastic Luedeking-Piret equation with delayed-feedback.

Chapter five demonstrate the numerical algorithm of SRK4 to simulate the solutions of stochastic model in Chapter four. The method of estimating kinetic parameter of stochastic models is also being presented in this chapter.

Chapter six presented the analyses of the result of solvent production by *Clostridium Acetobutylicum* P262. Based on the analysis, it is clear that stochastic logistic model with time delay for cell growth and stochastic Luedeking-Piret equations with delayed-feedback for solvents describe the experimental data more adequately compared to ODEs, DDEs and SDEs.

Chapter seven summarizes the report of this thesis. It provides conclusion to the entire research, as well as recommendations for the future studies.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

Modelling batch fermentation process via differential equations has been intensively researched over last few years. It has been developed under a framework of deterministic and stochastic modelling. Therefore, the main objective of this chapter is to review the previous works of deterministic and stochastic modelling of fermentation process which have been discovered in order to explore this area. Prior sections are discussed about physiological features of batch fermentation process. This chapter is divided into four parts which are fermentation process, mathematical model of fermentation process, parameter estimation and numerical methods for solving SDDEs. This chapter is concluded by remarks and motivation of this research.

2.2 FERMENTATION PROCESS

The term fermentation illustrates microbial cell propagation and generation of products under either aerobic or anaerobic conditions (Mosier and Ladisch, 2011). Aerobic refers to the condition where air is mixed with the medium. While anaerobic indicates a condition where oxygen is removed and excluded from media. It is due to the presence of this oxygen which is toxic to the cells (Alberts

et al., 1989). In a simple word, fermentation is a process of converting carbohydrates (sugar) to solvents by using bacterium or yeasts. This process occurs by the action of enzymes. It converts nutrients through (biochemical conversion) in food into valuable solvents and fuels due to the action of enzymes by the utilization of microorganism. This process will change the characteristics of food gradually.

Amongst of the bacterium that play an important role in a fermentation process is a class of Clostridium species. Clostridiums are the largest genera among the prokaryotes that can be classified into two main groups namely pathogenic and non-pathogenic. Pathogenic refers to the species that has an ability to cause disease. Meanwhile, non-pathogenic is a type of bacteria which cannot cause diseases. The non-pathogenic Clostridium has the capability to produce amylolytic and hydrolytic enzymes which then leads to the utilization of various substrates for solvents fermentation. Amongst these species that have a capability in producing solvents are *Clostridium Butyricum* (Andreesen et al., 1989), *Clostridium Butylicum* (Andel et al., 1985; Crabbendem et al., 1985), *Clostridium Acetobutylicum* (Gottschalk and Bahl 1981; Qureshi et al., 1992), *Clostridium Aurantibutyricum* (Somrultai et al., 1996), *Clostridium Tetanomorphom* (Gottwald et al., 1984) and *Clostridium Trobutyricum* (Sarin et al., 1990). It was reported by Gottschalk and Bahl (1981), Qureshi et al., (1992), Baut et al., (1994), Girbal and Soucaille (1998) and Madihah (2002) that *Clostridium Acetobutylicum* is an acetone, butanol and ethanol production species that has a great commercial values in industries such as for fuels, reagents and feed stocks.

Madihah (2002) introduced direct fermentation of gelatinized sago starch into solvent production of acetone, butanol and ethanol by *Clostridium Acetobutylicum* P262. This process is illustrated in Figure 2.1.

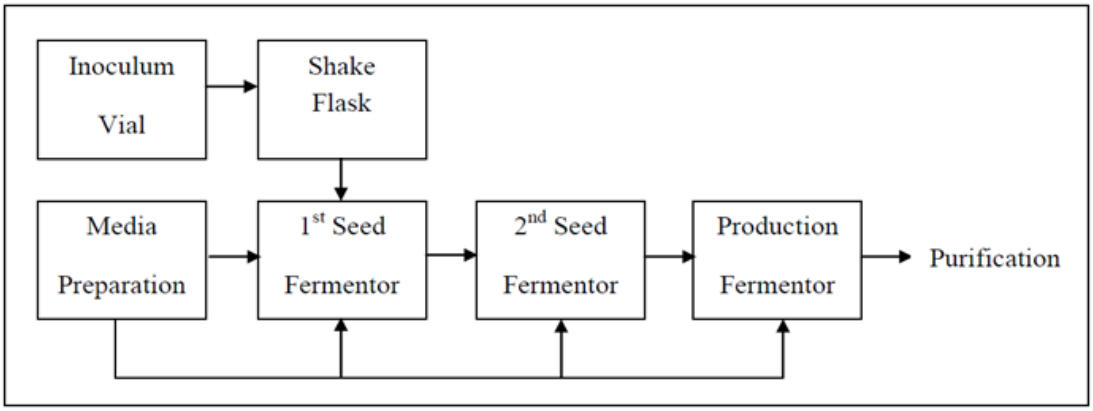

Figure 2.1: Flow diagram of batch fermentation

Source: Bazli (2010)

Figure 2.1 shows a flow diagram of batch fermentation process in a frozen vial. The frozen vial in the block contains a few millilitres of recombinant microbe which is taken out of from freezer and it strain thawed. This vial is referred as an inoculum vial and its content is known as an inoculum. The inoculum is then transferred to a shake flask via sterile procedure. The process of transferring this inoculum is called inoculation. The volume of media in the shake flask is usually on the order of magnitude of hundreds of millilitres. Cells can grow and reproduce after the inoculation. The shake flask is placed in an incubator shaker. The shaker operates under constant temperature. Media in the shake flask is shaking. The Shaking motion will keep the cells and the nutrients in the growth media in a homogeneous phase. Furthermore, this motion will increase the rate of oxygen uptake by the media. The cells then will grow to a particular density to inoculate the small fermenter known as seed fermenter.

Then, cells are transferred to a production fermenter after they reach their required volume and density. The density associated in which they are growing depends upon the desired product being growth or non-growth associated. Cells are grown to their mid at the end of exponential phase. At this position, chemical

is added that induces the cells to begin over expressing gene for a protein recombinant. Depletion of nutrients eventually happen. The cells enter their stationary growth phase. Cells are no longer capable to produce the amounts of the desired protein. As a result, the solvents of acetone and butanol will be produced.

Solvents of acetone and butanol have great commercial values in various industries such as in pharmaceutical, agriculture, cosmetic, chemical, rubbers, manufacturing, auto mobile lacquer, aircraft wing dopes and for manufacture of lacquers, resin, oil and gas industries (Krouwel et al., 1983). The next following subsection reports the applications of acetone and butanol in various industries.

2.2.1 Application of Solvent

Acetone and butanol have great commercial values in various industries such as pharmaceutical, agriculture, cosmetic, chemical, rubbers, manufacturing, auto mobile lacquer, aircraft wing dopes and for manufacture of lacquers, resin, oil and gas industries, fuel, reagents and feed stocks (Krouwel et al., 1983). The application of acetone and butanol are presented in Table 2.1.

Table 2.1: Application of acetone and butanol

Solvent	Field	Function	Reference
Acetone	Chemical industry	Solvent in auto mobile lacquer manufacture. Used in aircraft wing dopes. Solvent for manufacture of lacquers, resin, rubbers, fats and oil.	Krouwel et al., (1983)
	Coordinate manufacture	Weapons production	Jones and Wood (1986)

CHAPTER 1

INTRODUCTION

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CHAPTER 3

RESEARCH METHODOLOGY

3.1 INTRODUCTION

This chapter provides preliminaries concepts of this research. It consist of the probability theory background, stochastic processes, stochastic integrals, formulation of DDEs, SDEs and SDDEs, the numerical methods and parameter estimation of SDDEs.

3.2 PROBABILITY THEORY BACKGROUND

The fundamental background of probability theories which are required in this research is presented in this section. Those definitions, theorems, principles and basic relations associated with this research have been taken from Gardiner, (1989), Kloeden and Platen (1992), Mao (2008) and Mikosch (1998).

3.2.1 Basic Concept of Probability Theory

Random quantity in mathematics is interpreted as random variables, most frequently denoted as $X(\omega)$. Random variables are measured on its probability space (Ω, F, P). Ω corresponds to set of all possible outcomes, also known as a sample space. Each possible outcomes in a sample space is denoted as $\omega \in \Omega$.

A and A^c are two distinct outcomes of trial, A^c is complement of A, which are subset of Ω. Not all events in Ω are observable or interesting events. A collection of all observable or interesting events is denoted as *F*. An ordered pair (Ω, F) is a measurable space and the elements of *F* are called *F*-measurable sets. These interpretations are defined mathematically in the following definitions.

Definition 3.1: Random Variable (Kloeden and Platen, 1992)

A random variable is a real function $X(\omega)$, $\omega \in \Omega$ and measurable with respect to a probability measure *P*.

Definition 3.2: Probability Measure (Mao, 2008)

Probability measure P on sample space (Ω, F) is a function $P: F \to [0,1]$ such that

(i) $\forall A \in \Omega$, then $0 \le P(A) \le 1$

(ii) $P(\Omega) = 1$

(iii) $P(A) + P(A^c) = 1$

(iv) Assume that $A_1, A_2, A_3, ...A_n, ...$ are random events which are belonging to Ω. If

$$\{(A_i \cap B_j) = \phi, \text{ for } i \neq j\} \text{ then } P\left(\bigcup_{n=1}^{\infty} A_n\right) = \sum_{n=1}^{\infty} P(A_n) = 1$$

Definition 3.3: σ - algebra (Mao, 2008)

A family *F* is called σ - algebra which is subset of Ω. If the following properties hold

(i) $\phi \in F$, where ϕ illustrates empty set.

(ii) $A \in F \Rightarrow A^C \in A$, where $A^C = \Omega - A$ is complement of A in Ω.

(iii) For any sequence $A_n \subseteq F$, $\bigcup_{n=1}^{\infty} A_n \in F$.

Definition 3.4: Probability Space (Kloeden and Platen, 1992)

The triple (Ω, F, P) is a probability space which comprises of Ω (a set all of possible outcomes), a σ- algebra F of subsets Ω, called events and a probability measure is P on F.

The elementary events are grouped together in a set, Ω. σ- algebra is very important in studying a stochastic process because it aids as to communicate with the process situation (past, present and future). Modelling using SDEs and SDDEs involve continuous random variable. Hence, the following definition of continuous random variable and stochastic process are required.

Definition 3.5: Continuous Random variable (Mikosh, 1998)

$X(\omega)$ is a continuous random variable if there exist density function $f(x)$ such that

(i) $f(x) \geq 0$

(ii) $\int_{-\infty}^{\infty} f(x)\,dx = 1$

(iii) $F(x) = \int_{-\infty}^{x} f(u)\,du$

Definition 3.6: Stochastic Process (Kloeden and Platen, 1992)

A stochastic process is a family of random variable $X = X(t, \omega)$ of two variables $t \in T$ and $\omega \in \Omega$ on probability space (Ω, F, P) which assumes real values and is $P-$measurable as a function of ω for fixed t. the $X(t, \cdot)$ is a random variable on Ω. While $X(\cdot, t)$ indicates trajectory or sample path of stochastic process.