การออฟติไมเซชันแบบพลวัตของเครื่องปฏิกรณ์แบบเฟดแบตช์ที่มีหลายสายป้อน

นางสาวทิพากร บวรเนาวรักษ์

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DYNAMIC OPTIMIZATION OF A FED-BATCH REACTOR WITH MULTIPLE FEEDS

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งานวิจัยนี้ศึกษาการออฟติไมเซชันแบบพลวัต (dynamic optimization) ของเครื่องปฏิกรณ์แบบเฟดแบตช์ที่มีหลายสายป้อน ทั้งนี้ได้เลือกการผลิตกรดแลคติกจากกระบวนการที่เกิดการย่อยและการหมักพร้อมกัน (simultaneous saccharification and fermentation, SSF) ของแป้งเป็นกรณีศึกษา การออฟติไมเซชันของกระบวนการเกี่ยวข้องกับการคำนวณหาอัตราการป้อนที่เหมาะสมของสารอาหารสองชนิดได้แก่แป้งและกลูโคส วิธีการหาคำตอบแบบจำลองพร้อมกับแก้ปัญหาออฟติไมเซชัน (simultaneous model solution and optimization) ถูกนำมาใช้ในการแก้ปัญหาออฟติไมเซชันแบบพลวัตโดยมีวัตถุประสงค์เพื่อให้ได้อัตราการผลิตกรดแลคติกสูงสุดเมื่อสิ้นสุดการดำเนินงาน ผลการจำลองพบว่าภายใต้การดำเนินงานที่เหมาะสมและกำหนดเวลาดำเนินงานของเครื่องปฏิกรณ์แบบเฟดแบตช์ กระบวนการที่เกิดการย่อยและการหมักพร้อมกันโดยมีการเติมแป้งและกลูโคสสามารถผลิตกรดแลคติกได้มากกว่าเมื่อเทียบกับกรณีที่มีการเติมแป้งอย่างเดียว นอกจากนี้ยังได้วิเคราะห์ผลของเวลาที่ใช้ในการดำเนินงานที่มีต่อการผลิตกรดแลคติกจากกระบวนการที่เกิดการย่อยและการหมักพร้อมกัน จากผลการศึกษาแสดงให้เห็นว่าสามารถคำนวณหาค่าเวลาต่ำสุดที่ใช้ดำเนินงานเพื่อให้ได้การผลิตกรดแลคติกสูงสุด

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In this research, the dynamic optimization of a fed-batch reactor with multiple feeds is studied. The production of lactic acid form the simultaneous saccharification and fermentation (SSF) process of starch is chosen as a case study. The optimization of a process involves the determination of the optimal feed rate of two substrates: starch and glucose. The simultaneous model solution and optimization approach is employed to solve the formulated dynamic optimization problem with an objective to maximize the production rate of lactic acid at the end of operation. Simulation results show that under the optimal operation and the fixed operating time of the fed-batch reactor, the lactic acid production through the SSF process with two feeds of starch and glucose is improved by comparison to that with single feed of starch. In addition, the effect of the operating time on the lactic acid production from the SSF process with two feeds of starch and glucose is analyzed. The result demonstrates that there is a minimum time for obtaining the maximum production of lactic acid.

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NOMENCLATURE

A	parameter for growth associated glucose consumption	(g/g)
b	parameter for non-growth associated glucose consumption	(g/g)
F	feed rate	(l/h)
G	glucose concentration	(g/l)
J	performance index in optimal control problem	(-)
K_G	glucose inhibition constant for saccharification	(g/l)
K_I	glucose inhibition constant for fermentation	(g/l)
K_L	lactate inhibition constant for fermentation	(g/l)
K_m	Michaelis-Menten constant	(g/l)
K_s	glucose saturation constant	(g/l)
n	exponential constant for inhibition on saccharifiation by fermentation product	(-)
P	product concentration	(g/l)
S	substrate concentration	(g/l)
t	time	(h)
V	bioreactor volume	(l)
X	biomass concentration	(g/l)

Greeks Letters

α	parameter for growth associated lactate production	(g/g)
β	parameter for non growth associated lactate production	(g/g)
μ_m	maximum specific cell growth rate	(l/h)

Subscripts

F	feed
f	final

G	glucose
S	starch
max	maximum
min	minimum
r	residual
0	initial

CHAPTER I

INTRODUCTION

1.1 Introduction

In recent years, the biotechnology industry is evolving rapidly, especially in manufacturing specialty chemicals, pharmaceuticals, bio-products, and polymers, for example. For the operation of bioprocesses, three basic modes of operation are possible: continuous, batch and fed-batch operation. Although continuous processes offer advantages such as higher productivity and ease of operation compared to batch processes, they have certain disadvantages associated with them such as equipment failures, infection by other microorganisms, and spontaneous mutations in the strain. On the other hand, batch and fed-batch modes are preferred as they have the advantage of avoiding excessive substrate feed which can inhibit microorganism growth. Since product is also withdrawn at the end of the batch, sterilized conditions can be maintained during process operation.

Control of fed-batch biochemical processes has become an active area of research. In the operation of a fed-batch reactor, it is necessary to determine the optimal feed rate of substrate that minimize or maximize the objective function subject to process model and specified constraints, i.e. safety, environmental and operating constraints for improved process performance. Proper control can lead to a reduced production cost and increased yield while maintaining the quality of the desired product at the same time (Rani and Rao, 1999). This requirement leads to a dynamic optimization problem that is difficult to solve.

The direct numerical methods used to find a deterministic solution of dynamic optimization problems can be grouped into two categories: sequential and simultaneous optimization approaches. In the former, also known as a control vector parameterization (CVP), only the control variables are discretized, leaving the state equations in the form of the original differential algebraic equation (DAE) system which is integrated using standard integration algorithm. On the other hands, for the latter, both the control and state variables are discretized using polynomials (e.g.,

Lagrange polynomials) of which the coefficients become the decision variables in a resulting nonlinear programming problem (NLP). Although the simultaneous approach requires an optimization algorithm for solving the large scale NLP, a constraint on state variables (path constraints) can be directly considered in the formulation of dynamic optimization problems.

There are many applications of such two approaches for determining feed profile in fed-batch fermentations (Cuthrell and Biegler, 1989; Chen and Hwang, 1990; Srinivasan *et al.*, 1995). However, a number of previous studies have been focused on a bioreactor system with a single substrate feed (one control variables). Typically a fed-batch bioreactor could have more than one control variable that needs to be optimized. This leads to the optimization of the fed-batch processes involving multiple singular control variables which is a numerically difficult problem.

There are various industrially important fermentation products for which fed-batch techniques are adopted. Among the various products, lactic acid (LA) is a very important commodity chemical, which finds major uses in food, drug, pharmaceutical, agro and cosmetic industries. Typical raw materials for LA production through fermentation are molasses (glucose) and whey (lactose). These sources are not abundantly found and are expensive. Recently, starch as a bioresource has been used as a raw material for LA production by coupling saccharification (of starch) and fermentation (of derived glucose) in a process termed as simultaneous saccharification and fermentation (SSF). This process is much more economical not only in terms of saving overall fermentation time but also in reducing reactor volume. Thus the SSF process uses starch as the primary raw material, which is cheap, abundant and present in variety of agricultural resources, e.g., potato tubers and pearl tapioca. As a case studied we consider the optimal control of simultaneous saccharification and fermentation (SSF) process that involves the addition of starch and glucose towards optimizing lactic acid product and improved productivity.

Therefore, the aim of this work is to study the control of a fed-batch bioreactor with multiple control variables. The SSF process for the production of LA is chosen as a control case study. The optimization of such a process involves the determination of the optimal feed rate of two substrates: starch and glucose. The simultaneous model solution and optimization approach is employed to solve the formulated dynamic

optimization problem with an objective to maximize the production rate of lactic acid at the end of operation.

1.2 Objective

The objective of this work is to apply an optimal control approach to the control of a fed-batch bioreactor with two feed of substrates.

1.3 Scope of research

- A fed-batch reactor where the simultaneous saccharification and fermentation (SSF) process for lactic acid product is carried out, is considered as a case study.
- A simultaneous model solution and optimization approach is used to solve dynamic optimization problems for determining an optimal feed policy to maximize the desired product with fixed final time of operation.
- An optimal control of a fed-batch bioreactor with single feed is carried out.
- An optimal control of a fed-batch bioreactor with two feeds is performed.
- All simulations of a fed-batch bioreactor and a control system are performed using Matlab.

CHAPTER II

LITERATURE REVIEW

In recent years, the biotechnology industry is evolving rapidly. Many biotechnology-based products such as pharmaceutical and health-care products, agricultural products, and chemicals have already been commercialized. Basically, the operation of bioprocesses can be divided into three modes, i.e. continuous, batch or fed-batch operation. However, there has been presently a growing interest in the fed-batch mode in which a substrate-associated growth inhibition can be avoided by controlling the substrate supply. During the course of the fed-batch cultivation, one or more feeds of substrate are slowly supplied to the fed-batch reactor while the product generated remains in the reactor until the end of operation.

In general, it is necessary to determine the optimal feed rate of substrate for improved process performance. Proper control leads to a reduced production cost and increased yield while maintaining the quality of the desired product at the same time (Rani and Rao, 1999). This chapter provides a review of the advance and development in fed-batch bioreactor (also known as a fermentor) control techniques. Emphasis is placed on the implementation of an optimal control approach.

2.1 Control of fed-batch fermentors

The most popular operation mode of bioreactors has been the fed-batch mode where the substrate is slowly fed to the reactor but no product is drawn until the end. A fed-batch culture has the advantage of avoiding substrate overfeeding which can inhibit the growth of micro-organisms.

The control approaches for fed-batch fermentation processes were classified as physiological model and dynamic optimization approaches (Johnson, 1987). While the former refers to the selection of a particular variable as the set point to be maintained constant on the basis of some theoretical reasoning without the use of

mathematical models, the latter refers to maximizing or minimizing an objective function to find the optimal trajectory for set points to be tracked. The second approach uses dynamic optimization involving iteration towards optimum by one of the four techniques based on Green's theorem, Pontryagin's maximum principle, Variational calculus, or Dynamic programming.

2.2 Control of fed-batch fermentors with single feed

For fed-batch fermentors with substrate inhibited kinetics, Cazzador (1988) presented an approach to generate optimal feed rate policy using Green's theorem for maximization of biomass production and also accounting for time. In the presence of substrate and product inhibition kinetics, Hong (1986) derived an optimal feeding policy analytically in terms of substrate and product concentrations and liquid volume by using Kelly's transformation to determine the conjunction point between nonsingular and singular arcs and applied to Lysine fermentation and alcohol fermentation. For the same fermentation system, Chen and Hwang (1990) proposed an optimal on-off control solution which was derived for a general process described by differential algebraic equations. A unified algorithm was derived for computing the gradients of the cost function and constraints, which facilitates the solution of parameter selection problem resulting from on-off control parametrization by gradient-based optimization methods. They claimed to have obtained better results than those reported by Hong (1986).

Renfro et al. (1987) proposed simultaneous optimization and solution procedure for systems described by differential/algebraic systems using piecewise constant functions for independent variables that combines technologies of quasi-Newton optimization algorithms and global spline collocation, and applied it to batch reactor control problems.

Cuthrell and Biegler (1989) proposed an alternative simultaneous optimization and solution strategy based on sequential quadratic program (SQP) using orthogonal collocation on finite elements to discretize the differential equations, and Lagrange polynomials to construct approximations to continuous profiles and applied it to the

fed-batch fermentation problem. The results obtained are reported to be better than the analytical solutions for biosynthesis of penicillin.

Banga et al. (1997) proposed the use of two stochastic dynamic optimization algorithms for batch and fed-batch processes. These algorithms are based on a sequential control parametrization strategy: the original dynamic optimization problem is transformed into a constrained nonlinear programming (NLP) problem using parametrization of the control function and the resulting constrained NLP is solved using stochastic algorithms such as Integrated Controlled Random Search for Dynamic Systems (ICRS/DS) and Adaptive Randomly Directed Search for Dynamic Systems (ARDS/DS). However, they have stressed the need for the development of tracking controllers for the implementation of the designed open-loop profiles as well as the need for on-line recalculation of the profiles in case of large disturbance.

Wang and Shyu (1997) developed an optimal feed policy for fed-batch fermentation of ethanol production by introducing additional inequality constraints in the optimization problem to assure optimal solution in a reality region. An updating rule of augmented Lagrange multipliers was introduced to handle inequality constraints so that Iterative Dynamic Programming could be used. The method was validated through experimental studies.

In addition, Riascos and Pinto (2002) developed mathematical programming strategies for simultaneous optimization of dynamic systems and evaluated their computational performance. Simultaneous optimization with orthogonal collocation is applied to a simplified model for biosynthesis of penicillin from glucose, which was studied by Cuthrell and Biegler (1989). The results show that discretization of differential equations systems (DAE) by orthogonal collocation in finite elements efficiently transforms dynamic optimization problems into nonlinear programming (NLP) problems, enabling to solve complex problems with several control variables and minimizing the approximation error. In additional, the same author (2004) develop and to evaluate a mathematical programming technique based on the method of orthogonal collocation with finite elements for the simultaneous optimization of dynamic processes, taking two fed-batch biochemical reactors as case studies. Initially, the methodology is applied to a simplified model for the biosynthesis of penicillin from glucose (from the previous work) and comparison of the methodology

performance was made with other approaches. Then, it is applied to a complex model for the fermentative production of polyhydroxyalkanoates (PHAs).

Moreover, Palanki et al. (1993) considered the problem of determining the optimal profile in feedback form. The authors analyzed the optimal control problem from a geometric perspective and introduced the concept of degree of singularity that allows a better characterization of the necessary conditions for optimality. Optimal feedback laws are then derived for the singular region of operation and results are presented for time-invariant systems and extended to include time-varying systems as well.

Hodge and Karim (2002) presented the development of an unstructured kinetic model incorporating the differing degrees of product, substrate, and pH inhibition on the kinetic rates of ethanol fermentation by recombinant *Zymomonas mobilis* CP4:pZB5 for growth on two substrates. The model was utilized in a nonlinear model predictive control (NMPC) algorithm to control the product concentration during fed-batch fermentation to offset the inhibitory effects of product inhibition. Using the optimal feeding policy determined online, the volumetric productivity of ethanol was improved 16.6% relative to the equivalent batch operation when the final ethanol concentration was reached.

Also, Soni and Parker (2004) applied a multi-scale model describing the growth of yeast in an aerobic fed-batch mode to address both the offline and online optimization and control issues for the fed-batch fermentation problem. Nonlinear optimization techniques are used offline to generate an optimal substrate feed profile for the nominal problem that maximizes the end of the batch ethanol concentration. Shrinking-horizon nonlinear quadratic dynamic matrix control is used online for closed-loop trajectory tracking and disturbance rejection.

Arndt et al. (2005) considered the feeding-phase of a batch/fed-batch cultivation of a recombinant *Escherichia coli* producing extracellular phytase. Based on the estimated process variables by a Kalman filter, a feedforward–feedback controller was implemented in order to maximize the phytase production and to minimize acetate production. Although the estimation of process variables was not accurate at the second half of the process, the control results are still satisfactory. It

seems that the adaptation of the maximum specific growth rate by the Kalman filter is able to compensate this model inadequacy.

2.3 Control of fed-batch fermentors with multiple feeds

A number of previous studies have been focused on a bioreactor system with a single substrate feed (one control variables). However, in many industrially important fermentation processes, microorganisms require more than one substrate for their growth and product formation (Modak & Lim, 1989). For examples, it has long been realized that the production of antibiotics and enzymes requires precise control of the nitrogen source in addition to the carbon source. The feed rate optimization of fed-batch bioreactors involving multiple singular control variables is a numerically difficult problem. The optimization of bioreactor performances by manipulating two control variables simultaneously by use of optimal control theory has been reported in literatures (Modak and Lim, 1989; Lee and Ramirez, 1994; Lee, Hong, and Lim, 1998; Rahman and Palanki, 1998). Also, there are some reports of use of direct search methods (adaptive stochastic algorithm, dynamic programming, genetic algorithms, simulated annealing etc.) that transform the optimal control problem into a nonlinear programming problem for solution of such problems.

There are various industrially important fermentation products for which fed-batch techniques are adopted. Among the various products, lactic acid (LA) is a very important commodity chemical, which finds major uses in food, drug, pharmaceutical, agro and cosmetic industries. Typical raw materials for LA production through fermentation are molasses (glucose) and whey (lactose). These sources are not abundantly found and are expensive. Recently, starch as a bioresource has been used to produce fermentative products. Glucose can also be enzymically derived from saccharification of starch but glucose (the product) inhibits the enzyme.

Anuradha et al. (1999) has shown experimentally that starch itself can be used as a raw material for LA production by coupling saccharification (of starch) and fermentation (of derived glucose) in a single process termed as simultaneous saccharification and fermentation (SSF). This process is much more economical not only in terms of saving overall fermentation time but also in reducing reactor volume.

Thus the SSF process uses starch as the primary raw material, which is cheap, abundant and present in variety of agricultural resources, e.g., potato tubers and pearl tapioca. A direct benefit of the SSF process is a decrease in inhibition caused by glucose accumulation leading to an increase in the LA productivity. Also, studied optimum operating conditions for the simultaneous saccharification and fermentation (SSF) of starch to lactic acid acid using *Lactobacillus delbrueckii* and developed a predictive model for SSF by combining the kinetics of saccharification and fermentation. Saccharification kinetics was determined through experiments on starch hydrolysis in which the effects of temperature, pH and different fermentation products as inhibitors are included. Fermentation kinetics was studied using glucose as substrate and effect of initial lactate on growth of *Lactobacillus delbrueckii* was also examined. The productivity and yields of lactic acid in SSF were always greater than in the two step process of saccharification followed by fermentation. Thus, the SSF process shows promise as a better alternative to the existent conventional process to obtain a high yield of lactic acid.

Consequently, Roy et al. (2001) performed the design and analysis of optimal control strategies for three types of inhibitory fed-batch bioprocesses. These are simple saccharification (SS) of starch to glucose, simple fermentation (SF) of derived glucose to lactic acid (LA) and simultaneous saccharification and fermentation (SSF) of starch to lactic acid (LA). Various optimal feeding strategies were investigated for the SSF process by manipulating starch addition rates. To avoid the complexity of solving a singular problem, the starch addition rates are expressed in terms of the broth volume, which is used as a control variable. The optimization strategy is thus solved in a nonsingular framework. The focus of all the optimization studies has been to improve the performance of the SSF process. Optimal control of starch additions in the fed-batch process gave improved performance of the process. Additional the performance of the SSF process can be improved substantially by operating in fed-batch mode rather than batch in term of final lactic acid concentration or productivity.

In additional, Mangesh et al. (2001) applied Differential Evolution (DE), an exceptionally simple and robust evolutionary algorithm with Lagrangian like method, to optimal control of fed-batch fermentation processes with state inequality constraints and bounds on feed rates. These infinite dimensional optimization problems were approximated into the finite dimensional optimization problems by

control vector parameterization (uniform/non-uniform). The proposed method was applied to decide optimal control policy in fed-batch fermentation for ethanol production and superior results were obtained using non-uniform control vector parameterization. The dynamic optimization of simultaneous saccharification and fermentation of starch to lactic acid was carried out using the proposed method. The performance of simultaneous saccharification and fermentation process was improved substantially in terms of end lactic acid concentration and productivity for single as well as multiple feed cases.

Moreover, Sarkar and Modak (2004) considered that determination of optimal feed rate profiles for fed-batch bioreactors with more than one feed rates is a numerically difficult problem involving multiple singular control variables. An optimization procedure based on genetic algorithm is developed for the determination of substrate feeding policies in fed-batch bioreactors with multiple control variables. The multiplier updating method is introduced in the proposed method to handle inequality constraints on state variables. The efficiency of the algorithm is demonstrated for two case studies on fed-batch bioreactors with two control variables taken from literature: production of foreign protein by recombinant bacteria, and the production of monoclonal antibody. The control policies obtained retain the characteristics of the profiles generated through rigorous application of control theory.

Khanna and Srivastava (2006) investigated the process improvements in terms of production of PHB by model-based fed-batch cultivation of *Ralstonia eutropha*. The model was then used to predict appropriate nitrogen and fructose feeding strategies which feature improved PHB productivity. Controlled fed-batch fermentations for production of PHB using two different nutrient feeding strategies were described. In one strategy, feeding of both nitrogen and fructose was carried out for a specified time continuously as and when their concentration(s) decreased. However, in another strategy, nitrogen and fructose were fed alternately such that the culture was maintained in the exponential growing phase till feeding was done and then finally nitrogen limitation was induced so that the remaining fructose could be consumed to produce PHB. Simulation demonstrated that this ensured a higher productivity in significantly lesser fermentation time. This was later confirmed by experimental studies.

CHAPTER III

THEORY

3.1 Bioprocess operations

In biotechnological processes, or bioprocesses, biological systems such as bacteria, yeast, fungi, algae or also animal cells, plant cells or isolated enzymes, are used to convert supplied substrates to a desired product. This product can be the organism itself or a chemical substance. The bioprocesses can generally be operated in batch, fed-batch, or continuous modes.

3.1.1 Batch processes

Batch fermentation refers to a partially closed system in which most of the materials required are loaded into a fermentor, decontaminated before the process starts and then, removed at the end. The only material added and removed during the course of batch fermentation is the gas exchange and pH control solutions. In this mode of operation, conditions are continuously changing with time, and the fermentor is an unsteady-state system, although in a well-mixed reactor, conditions are supposed to be uniform throughout the reactor at any instant time.

The principal disadvantage of batch processing is the high proportion of unproductive time (down-time) between batches, comprising the charge and discharge of the fermentor vessel, the cleaning and sterilization and re-start process.

3.1.2 Continuous processes

Continuous culture is a technique involving feeding the microorganism used for the fermentation with fresh nutrients and, at the same time, removing spent

medium plus cells from the system. A unique feature of the continuous culture is that a time-independent steady-state can be attained which enables one to determine the relations between microbial behavior (genetic and phenotypic expression) and the environmental conditions.

3.1.3 Fed-batch processes

The fed-batch technique was originally devised by yeast producers in the early 1900s to regulate the growth in batch culture of *Saccharomyces cerevisiae*. Yeast producers observed that in the presence of high concentrations of malt, a by-product ethanol was produced, while in low concentrations of malt, the yeast growth was restricted. The problem was then solved by a controlled feeding regime; so that yeast growth remained substrate limited. The concept was then extended to the production of other products, such as some enzymes, antibiotics, growth hormones, microbial cells, vitamins, amino acids and other organic acids. Basically, cells are grown under a batch regime for some time, usually until close to the end of the exponential growth phase. At this point, the reactor is fed with a solution of substrates, without the removal of culture fluid. This feed should be balanced enough to keep the growth of the microorganisms at a desired specific growth rate and simultaneously, reducing the production of by-products (that can be growth or product production inhibitory and make the system not as effective). These by-products may also affect the culture environment in such a way that might lead to early cell death even though sufficient nutrients are available or are still being provided.

A fed-batch is useful in achieving high concentration of products as a result of high concentration of cells for a relative large span of time. Moreover, fed-batch fermentations can be the best option for some systems in which the nutrients or any other substrates are only sparingly soluble or are too toxic to add the whole requirement for a batch process at the start.

3.2 Cell Growth

Stages of cell growth in a batch reactor are shown schematically in Fig. 3.1 and Fig. 3.2. Initially, a small number of cells is inoculated into (i.e., added to) the batch reactor containing the nutrients and the growth process begins as shown in Fig. 3.1. Fig. 3.2 shows the number of living cells as a function of time.

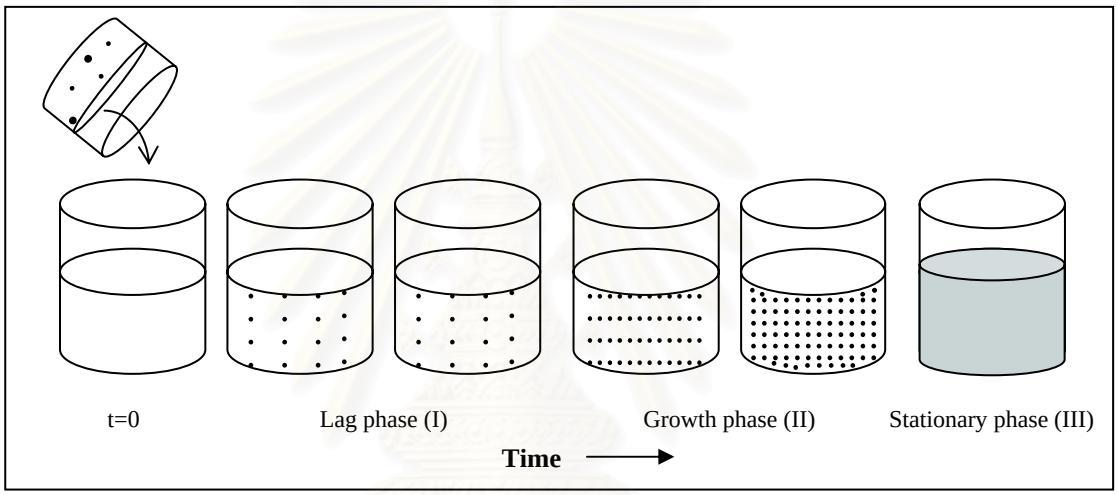

Fig. 3.1: Increase in cell concentration**.**

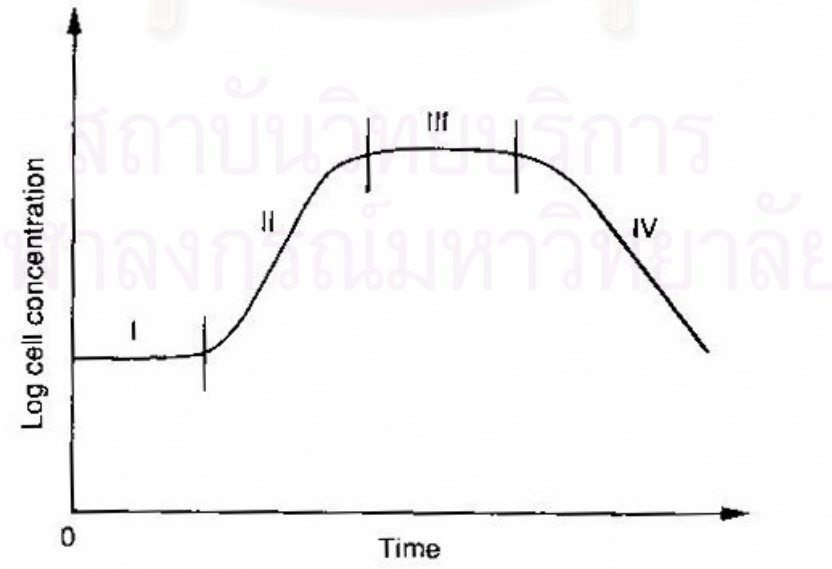

Fig. 3.2: Phase of bacteria cell growth**.**

In phase I, called the lag phase, there is little increase in cell concentration. During the lag phase, the cells are adjusting to their environment, synthesizing enzymes for utilizing the new substrate, and beginning the work for replicating the cells' genetic material. The duration of the lag phase depends upon the growth medium from which the inoculums was taken relative to the reaction medium in which it is placed. If the inoculums are similar to the medium of the batch reactor, the lag phase will be almost nonexistent. It, however, the inoculums were placed in a medium with a different nutrient or other contents, or if the inoculums culture were in the stationary phase, the cell would have to readjust their metabolic path to allow them to consume the nutrients most efficiently.

Phase II is called the exponential growth phase owing to the fact that the cell's growth rate is proportional to the cell concentration. In this phase the cells are dividing at the maximum rate because of the enzyme's pathways for metabolizing the substrate are in place (as a result of the lag phase) and the cells are able to use the nutrients most efficiently.

Phase III is the stationary phase, during which the cells reach a minimum biological space where the lag of one or more nutrients limits cell growth. During the stationary phase, the net growth rate is zero as a result of the depletion of nutrients and essential metabolites. Many important fermentation products, including most antibiotics, are produce in the stationary phase. For example, penicillin produced commercially using the fungus *Penicillium chrysogenumm* is formed only after cell growth has ceased. Cell growth is also slowed by the buildup of organic and toxic materials generated during the growth phase.

The final phase, Phase IV, is the death phase where a decrease in live cell concentration occurs. This decline is a result of the toxic by-products, harsh environments, and/or depletion of nutrient supply.

3.3 Formulation of dynamic optimization problems

In fed-batch process operations, the process variables undergo significant changes during the duration of fed-batch and there is no *steady state.* Unlike

continuous processes, the major objective is not to keep the system at a given set-point but to follow a trajectory that results in the optimization of an objective such as yield or product quality at the *end* of the batch cycle which is subject to specified constraints (i.e., safety, environmental and operating constraints) (Palanki *et al*., 1993). Such problems are called *dynamic optimization* problems. The dynamic optimization problems can be formulated mathematically as follows,

$$\min_{u(t)} G\left(x(t_f), t_f\right) \tag{3.1}$$

subject to

$$\dot{x}(t) = f(x(t), u(t), t) \tag{3.2}$$

$$x(t_0) = x_0 \tag{3.3}$$

$$h(t, x(t), u(t)) = 0 \tag{3.4}$$

$$g(t, x(t), u(t)) \le 0 \tag{3.5}$$

$$x(t)^L \le x(t) \le x(t)^U \tag{3.6}$$

$$u(t)^L \le u(t) \le u(t)^U \tag{3.7}$$

where h = equality design constraints vector,

g = inequality design constraints vector,

$x(t)^L, x(t)^U$ = lower and upper bounds of state profile,

$u(t)^L, u(t)^U$ = lower and upper bounds of control profile.

3.4 Solution methods of dynamic optimizations

Optimal control or dynamic optimization problem is solved to obtain an input profile that minimize or maximize the objective function subject to process model and specified constraints, i.e. safety, environmental and operating constraints. In general, the process model consisting of mass and energy balance equations is described by differential and algebraic equations (DAEs). The solution of dynamic optimization problems can be computed by two general approaches: direct and indirect optimization methods.

The indirect method is known as a variation approach solution, which is rely on Pontryagin's Maximum Principle and based on the solution of first order necessary condition to form the two point boundary value problem (TPBVP) whereas the direct method is based on the transformation of dynamic optimization problems to a nonlinear programming problem via discretization method. Depending on whether the dynamic model equations are integrated explicitly or implicitly, this method can be classified into two approaches: a sequential and a simultaneous approach, respectively.

3.4.1 Sequential approach

The optimization is carried out in the space of the input variables only. The differential equations are integrated using standard integration algorithms to evaluate the objective function. This corresponds to a "feasible path" approach since the differential equations are satisfied at each step of the optimization algorithm. Typically, a piecewise constant approximation over equally spaced time intervals is made for the inputs and the method is referred to as Control Vector Parameterization (CVP).

The advantage of the sequential approach is only the control input is discretized then, the optimization problem is a small scale NLP. However, it has disadvantage that is limited to handle a path constraints. This is because the state variables are not directly included in NLP.

3.4.2 Simultaneous approach

In the simultaneous strategy, often called total discretization method, the optimization is carried out in the full space of discretized inputs and states variables using polynomials (e.g., Lagrange polynomials) of which the coefficients become the decision variables in a much larger nonlinear programming (NLP) problem. The process dynamic models are transferred in form of algebraic equation system which is equality constrain in NLP. To solve this problem, optimization algorithms based on a sequential quadratic programming (SQP) technique are widely used in this approach. In this method, the process dynamic models and the optimization problem are solved

at the same time and therefore, the solution of differential and algebraic equations are solved only once at the optimal point. This method has advantages of dealing with path constraints through bounds or inequalities which are a natural part of the NLP.

It is noted that both the sequential and the simultaneous approaches converge to *local* optima. Determination of the global optimum is a non-trivial problem and from a practical perspective, one approach to overcome such a problem is to find the solution with different initial conditions. The global solution can be obtained by comparing the solution with the best objective function as the global optimum.

In the next section, a general NLP formulation for optimal control problems using orthogonal collocation on finite elements method is described.

3.5 NLP formulation

In order to derive the NLP problem, the differential equations are converted into algebraic equations using collocation on finite elements. Residual equations are then formed as a set of algebraic equations and included as equality constraints in NLP. These residuals are evaluated at the shifted roots of Legendre polynomials. The procedure is as follows.

Consider the initial value problem over the finite element i with time $t \in [\varsigma_i, \varsigma_{i+1}]$

$$\dot{x}(t) = f(t, x(t), u(t)) \quad t \in [t_0, t_f] \tag{3.8}$$

The solution is approximate by Lagrange polynomials over element i, $\varsigma_i \le t \le \varsigma_{i+1}$ as follows:

$$x_{K+1}(t) = \sum_{j=0}^{K} x_{ij}\phi_j(t); \quad \phi_j(t) = \prod_{k=0,j}^{K} \frac{(t - t_{ik})}{(t_{ij} - t_{ik})} \qquad i = 1,\ldots, NE \tag{3.9}$$

$$u_K(t) = \sum_{j=1}^{K} u_{ij}\theta_j(t); \quad \theta_j(t) = \prod_{k=1,j}^{K} \frac{(t - t_{ik})}{(t_{ij} - t_{ik})} \qquad i = 1,\ldots, NE \tag{3.10}$$

where $k = 0$, j means k starting form 0 and $k \neq$ j, NE is the number of elements. Also $x_{K+1}(t)$ is a $(K+1)^{th}$ degree of piecewise polynomial and $u_K(t)$ is piecewise polynomial of order K. The polynomial approximating the state x takes into account the initial conditions of $x(t)$ for each element i. Also, the Lagrange polynomial has the desirable property that (for $x_{K+1}(t)$, for example):

$$x_{K+1}(t_{ij}) = x_{ij} \tag{3.11}$$

which is due to the Lagrange condition $\phi_k(t_j) = \delta_{kj}$, where δ_{kj} is the Kronecker delta. This polynomial form allows the direct bounding of the states and controls, e.g., path constraints can be imposed on the problem formulation.

Using K point orthogonal collocation on finite elements as shown in Fig.3.3, and by defining the basis functions, so that they are normalized over the each element $\Delta\zeta_i(\tau \in [0,1])$, one can write the residual equation as follows:

$$\Delta\varsigma_i r(t_{ik}) = \sum_{j=0}^{K} x_{ij}\dot{\phi}_j(\tau_k) - \Delta\varsigma_i f(t_{ik}, x_{ik}, u_{ik})$$

$$i = 1,\ldots, NE \quad j = 0,\ldots, K \qquad k = 1,\ldots, K \tag{3.12}$$

where $\dot{\phi}_j(\tau_k) = d\phi_j/dt$, and together with $\phi_j(\tau), \theta_j(\tau)$ terms (basis functions), they are calculated beforehand, since they depend only on the Legendre root locations.

Note that $t_{ik} = \zeta_i + \Delta\zeta_i\tau_k$. This form is convenient to work with when the element lengths are included as decision variables. The element lengths are also used to find possible points of discontinuity for the control profiles and to insure that the integration accuracy is within a numerical tolerance. Additionally, the continuity of the states is enforced at element endpoints (interior knots ζ_i , i = 2,..., NE) as given in Eq. (3.13), but it is allowed that the control profiles to have discontinuities at these endpoints.

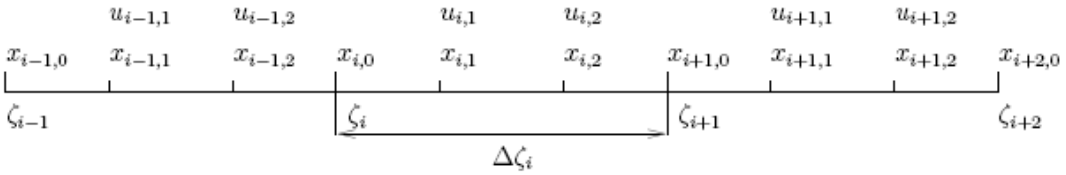

Figure 3.3: Collocation method on finite elements for state profiles, control profiles and element lengths ($K_x = K_u = 2$)

$$x^i_{K+1}(\varsigma_i) = x^{i-1}_{K+1}(\varsigma_i) \qquad i = 2,\ldots, NE \tag{3.13}$$

or

$$x_{i0} = \sum_{j=0}^{K} x_{i-1,j}\phi_j(\tau = 1) \qquad i = 2,\ldots, NE \quad j = 0,\ldots, K \tag{3.14}$$

These equations extrapolate the polynomial $x^{i-1}_{K+1}(t)$ to the end points of its element and provide an accurate initial conditions for the next element and polynomial $x^i_{K+1}(t)$.

At this point a few additional comments concerning construction of the control profile polynomials must be made. Note that these polynomials use only K coefficients per element and are of lower order than the state polynomials. As a result these profiles are constrained or bounded only at collocation points. The constraints of the control profile are carried out by bounding the values of each control polynomial at both ends of the element. This can be done by writing the equations:

$$u^L_i \le u^i_K(\varsigma_i) \le u^U_i \qquad i = 1,\ldots, NE \tag{3.15}$$

$$u^L_i \le u^i_K(\varsigma_{i-1}) \le u^U_i \qquad i = 1,\ldots, NE \tag{3.16}$$

Note that since the polynomial coefficients of the control exist only at collocation points, enforcement of these bounds can be done by extrapolating the polynomial to the endpoints of the element. This is easily done by using:

$$u_K^i(\varsigma_i) = \sum_{j=1}^{K} u_{ij}\theta_j(\tau = 0), \qquad i = 1,\ldots, NE \tag{3.17}$$

and

$$u_K^i(\varsigma_{i+1}) = \sum_{j=1}^{K} u_{ij}\theta_j(\tau = 1), \qquad i = 1,\ldots, NE \tag{3.18}$$

Adding these constraints affects the shape of the final control profile and the net effect of these constraints is to keep the endpoint values of the control profile from varying widely outside their ranges [u^L_i, u^U_i].

The NLP formulation consists of the ODE model discretized on finite elements, continuity equation for state variables, and any other equality and inequality constraints that may be required as given in the following equation.

$$\min_{x_{ij}, u_{ij}, \Delta\varsigma_i} G(x_f, t_f) \tag{3.19}$$

Such that

$$x_{10} - x_0 = 0$$

$$r(t_{ik}) = 0 \qquad i = 1,\ldots, NE \quad k = 1,\ldots, K$$

$$x_{i0} - x_{K+1}^{i-1}(\varsigma_i) = 0 \qquad i = 2,\ldots, NE$$

$$x_f - x_{K+1}^{NE}(\varsigma_{NE+1}) = 0$$

$$u_i^L \le u_K^i(\varsigma_i) \le u_i^U \qquad i = 1,\ldots, NE$$

$$u_i^L \le u_K^i(\varsigma_{i+1}) \le u_i^U \qquad i = 1,\ldots, NE$$

$$u_{ij}^L \le u_K(\tau_j) \le u_{ij}^U \qquad i = 1,\ldots, NE \quad j = 1,\ldots, K$$

$$x_{ij}^L \le x_{K+1}(\tau_j) \le x_{ij}^U \qquad i = 1,\ldots, NE \quad j = 0,\ldots, K$$

$$\Delta\varsigma_i^L \le \Delta\varsigma_i \le \Delta\varsigma_i^U \qquad i = 1,\ldots, NE$$

$$\sum_{i=1}^{NE} \Delta\varsigma_i = \varsigma_{total}$$

$$h(t_{ij}, x_{ij}, u_{ij}) = 0$$

$$g(t_{ij}, x_{ij}, u_{ij}) \leq 0$$

where *i* refers to the element, *j* and *k* refer to the collocation point, $\Delta\varsigma_i$ is finite-element lengths of each interval *i* = 1,…, *NE*, $x(t_f)$ is the value of the state of the final time $t = t_f$ and x_{ij}, u_{ij} are the collocation coefficients for the state and control profiles

Problem (3.19) can be now solved by any large-scale nonlinear programming solver. To solve this problem within MATLAB, the Optimization Toolbox in which several solvers for coping with optimization problems are included, was used. In this work, the function *fmincon* was chosen. This can minimize/maximize a given objective function with respect to nonlinear equality and inequality constraints.

CHAPTER IV

Simulation of Simultaneous Saccharification and Fermentation Process

This chapter describes the production of lactic acid through a simultaneous saccharification and fermentation (SSF) process in a fed–batch reactor. Independent kinetic models for saccharification and fermentation developed by Anuradha et al. (1999) were used in this study and integrated with the model equations of a fed-batch bioreactor to describe a simultaneous saccharification and fermentation (SSF) process. Detail of the models is discussed below.

4.1 Process model description

4.1.1 Saccharification

The kinetic model for the enzymic saccharification of starch with glucoamylase allowing for competitive inhibition can be given by:

$$\frac{dG}{dt} = \nu_m \frac{S}{K_m\left(1 + G/K_G\right) + S} \qquad (1)$$

Using the stoichiometric relation for the conversion of starch to glucose (1 g starch yields 1.1 g glucose on complete saccharification), the rate of glucose formation via starch saccharification can be given by the following expression.

$$\frac{dG}{dt} = \nu_m \frac{S_0 - G/1.11}{K_m\left(1 + G/K_G\right) + \left(S_0 - G/1.11\right)} \qquad (2)$$

The kinetic parameters in Eq. (2), i.e. V_m, K_m and K_G, are the functions of pH and temperature. In SSF process, Eq. (2) may also need a modification with respect to the possible inhibition by fermentation products.

4.1.2 Fermentation

For the growth kinetics of *L. delbrueckii*, a typical Monod's expression was modified to include substrate inhibition and lactate inhibition. The rate equation for biomass production can be given as:

$$R_X = \frac{dX}{dt} = \mu X \tag{3}$$

where the specific growth rate, μ, is given by

$$\mu = \mu_m \exp(-K_L P) \frac{G}{K_s + G + G^2/K_I}$$

The above expression includes both the substrate inhibition term K_s and product inhibition term K_L.

The model for lactic acid formation taking into account both growth associated and non-growth associated product formation developed originally by Leudeking and Piret (1993), was used:

$$R_P = \frac{dP}{dt} = \alpha \frac{dX}{dt} + bX \tag{4}$$

Similarly, the equation for glucose consumption rate incorporates both the growth associated and maintenance term can be given as:

$$R_G = \frac{dG}{dt} = -\left(a \frac{dX}{dt} + bX \right) \tag{5}$$

4.1.3 Simultaneous Saccharification and Fermentation (SSF)

The model equations developed in the previous sections for the saccharification and the fermentation processes were combined to develop the model equations to predict the dynamic behavior of a SSF process. The rate of saccharification, as given by Eq. (2), involves the substrate concentration expressed in terms of equivalent glucose obtained stoichiometrically (G^*). The actual glucose concentration (G) that accumulates in the system generally inhibits saccharification. Therefore, the rate of saccharification in the SSF process is given by:

$$R_{G^*} = \frac{dG^*}{dt} = \nu_m \frac{S_0 - G^*/1.11}{K_m\left(1 + G/K_G\right) + \left(S_0 - G^*/1.11\right)} \tag{6}$$

The rate of glucose accumulation is given by:

$$\begin{aligned} \frac{dG}{dt} &= R_{G^*} - R_G \\ &= \nu_m \frac{S_0 - G^*/1.11}{K_m\left(1 + G/K_G\right) + \left(S_0 - G^*/1.11\right)} - \left(a\frac{dX}{dt} + bX\right) \end{aligned} \tag{7}$$

The rates of biomass production (R_X) and lactic acid production (R_P) are given by Eqs. (3) and (4).

The model equations for a fed-batch bioreactor are combined with the kinetics of the saccharification and fermentation to describe a simultaneous saccharification and fermentation process (SSF). Fig. 4.1 shows schematic diagram of a fed-batch reactor consisting of two separate feeds of glucose and starch for the production of lactic acid from the SFF process. The dynamic model which comprise mass balance equations for SSF process is shown as follows,

$$\frac{dX}{dt} = -\left(\frac{F_g + F_s}{V}\right)X + \mu X \tag{8}$$

$$\frac{dS}{dt} = \frac{F_s}{V} S_F - \left(\frac{F_g + F_s}{V} \right) S - \frac{R_G}{1.11} \tag{9}$$

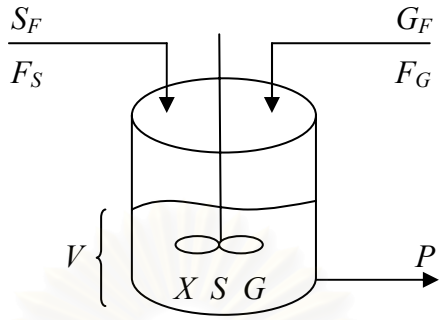

Fig. 4.1: Schematic diagram of the fed-batch reactor with two separate feed of glucose and starch.

$$\frac{dG}{dt} = \frac{F_g}{V} G_F - \left(\frac{F_g + F_s}{V} \right) G + \left[R_G - \left(a\mu X + bX \right) \right] \tag{10}$$

$$\frac{dP}{dt} = -\left(\frac{F_g + F_s}{V} \right) P + \left(\alpha\mu X + \beta X \right) \tag{11}$$

$$\frac{dV}{dt} = F_g + F_s \tag{12}$$

where X, S, G and P are the concentration of cell mass, starch, glucose and product (lactic acid), respectively, G_F and S_F are concentration of glucose and starch in the glucose feed rate, F_g and the starch feed rate, F_s, respectively. The kinetic model of the specific growth rate μ and the rate of saccharification R_G are given in Eqs. (13) and (14). The values of the process and kinetic parameters are shown in Table 4.1.

$$\mu = \mu_m e^{-K_L P} \left(\frac{G}{K_s + G + G^2 / K_I} \right) \tag{13}$$

$$R_G = V_m^0 e^{-kP^n} \frac{S}{K_m \left(1 + G/K_G \right) + S} \tag{14}$$

Table 4.1: Model parameters for lactic acid production by the simultaneous saccharification and fermentation process

Parameter	Value	Parameter	Value
a	6.9	b	0.023
k	0.02	n	0.4
K_m	95.6	K_G	33.0
Ks	6.65	K_L	0.0037
K_I	104.5	V^0_m	68.0
α	9.2	β	0.073
μ_m	0.25		

4.2 Preliminary studies of Simultaneous Saccharification and Fermentation process

In this section, preliminary studies of a simultaneous saccharification and fermentation (SSF) process are first addressed. Comparative evaluation of the production of lactic acid in batch and fed-batch operations is performed by simulations. As substrate feeding at different time during the course of fed-batch operation may play an important role on the reactor performance, two simulations of fed-batch reactor under the same feed profile introduced to the reactor at different time are preformed.

For all simulations, it is assumed that the fermentation time of both operation modes is fixed at 80 h and the reactor starts with 4.1 g/l glucose and 30 g/l starch, 0.5 g/l biomass, and 5 l of initial reactor volume.

4.2.1 Batch operation

The production of lactic acid through the SSF process operated in a batch mode is investigated. Fig. 4.2 shows the concentration of biomass, starch, glucose and lactic acid as a function of time.

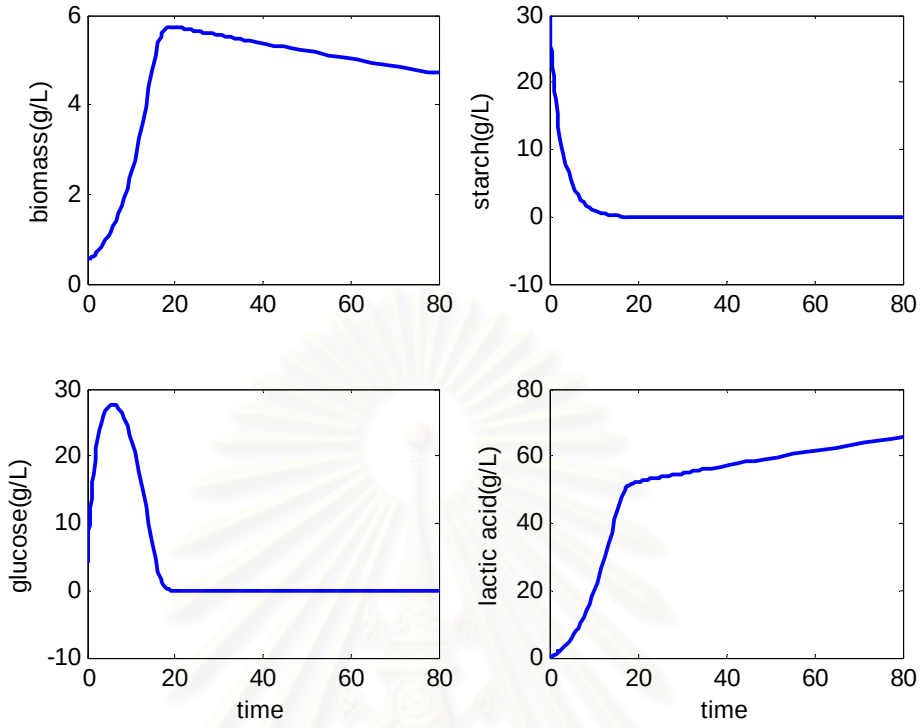

Fig.4.2: Concentration profiles in the SSF process under batch operation.

It is observed that initially, starch concentration decrease due to the saccharification process; starch is changed to glucose. This results in an increase in the concentration of glucose in the reactor. Once biomass starts to grow by consuming the glucose as substrate, glucose concentration is decreased. It can be seen that during the growth of the biomass, the lactic acid as product is increasingly generated. This process is still carried out until the operating time is about 20 h where the amount of starch is totally saccharified and at the same time, glucose is completely consumed by biomass. At this stage, the biomass is in the stationary phase and the biomass growth has a decreasing trend. As the specific growth rate for biomass decreases, the production of lactic acid decreases. Under the batch operation, the lactic acid concentration at the final time (= 80 h.) is 65.68 g/l.

4.2.2 Fed-batch operation

The production of lactic acid through the SSF process operated in a fed-batch mode is investigated. In this study, the feed stream consisting of starch with the

concentration (S_F) of 200 g/l is fed to the reactor at the constant flow rate (F_S) of 0.1 l/h. The initial conditions of the reactor are similar to the previous study. Fig. 4.3 show the change in the concentration of biomass, starch, glucose and lactic acid. As continuous feeding of starch during the operation, more glucose are produced via the saccharification process, leading to the increased cell concentration. This indicates the important effect of a amount of glucose on the biomass growth and the production of lactic acid. Under the fed-batch operation, the concentration of lactic acid of 257.45 g/l can be achieved at the end of run. Fig. 4.4 demonstrates the step change in feed flow rate and the corresponding profile of reactor volume. The final liquid volume within the reactor is 13 l.

It is noted that from Eq. 13, an increase in glucose as substrate normally inhibits the growth of biomass; however, the gradually increased concentration of glucose in the reactor by continuous feeding of starch reduces the inhibition effect on the biomass growth caused by glucose. This result indicates the advantage of the fed-batch operation and can be confirmed by simulation of the SSF process operating in the batch mode with high initial concentration of starch. Fig. 4.5 presents the result in case of the SSF process operated in the batch reactor staring with high starch concentration of 500 g/l. It can be seen that although glucose is more produced by the saccharification of starch, it has an inhibition effect of the growth of biomass. As a result, the concentration of the product, lactic acid, is decreased. Under the batch operation with high initial starch concentration, the concentration of lactic acid at the end of operation is 222.35 g/l which is lower that that obtained the SSF process operated in the fed-batch mode (P = 257.45 g/l). Thus, continuous feeding of starch during the simulataneous saccharification and fermentation process instead of adding all the starch at the start of a batch run can improves the performance of the process.

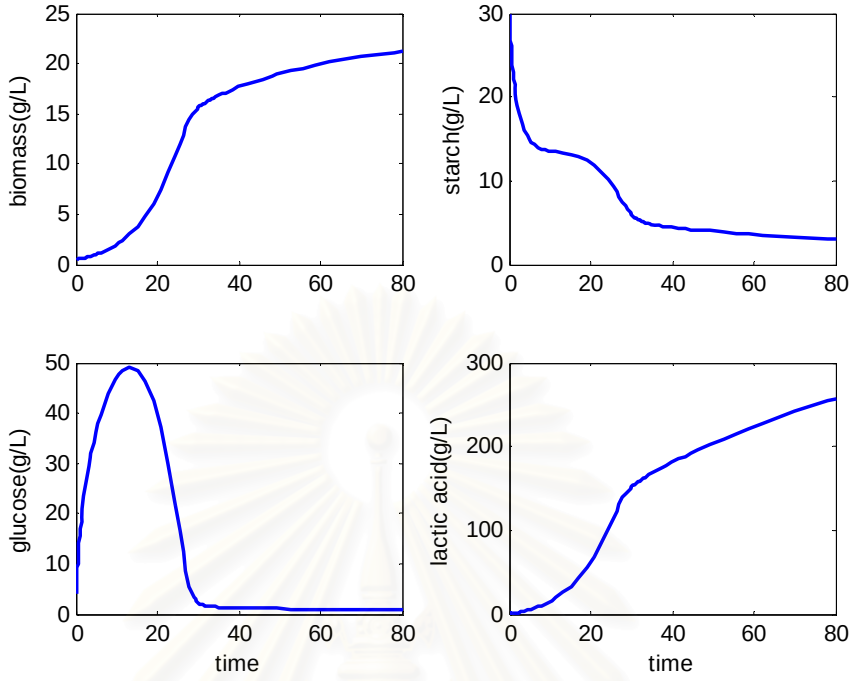

Fig.4.3: Concentration profiles in the SSF process under fed-batch operation.

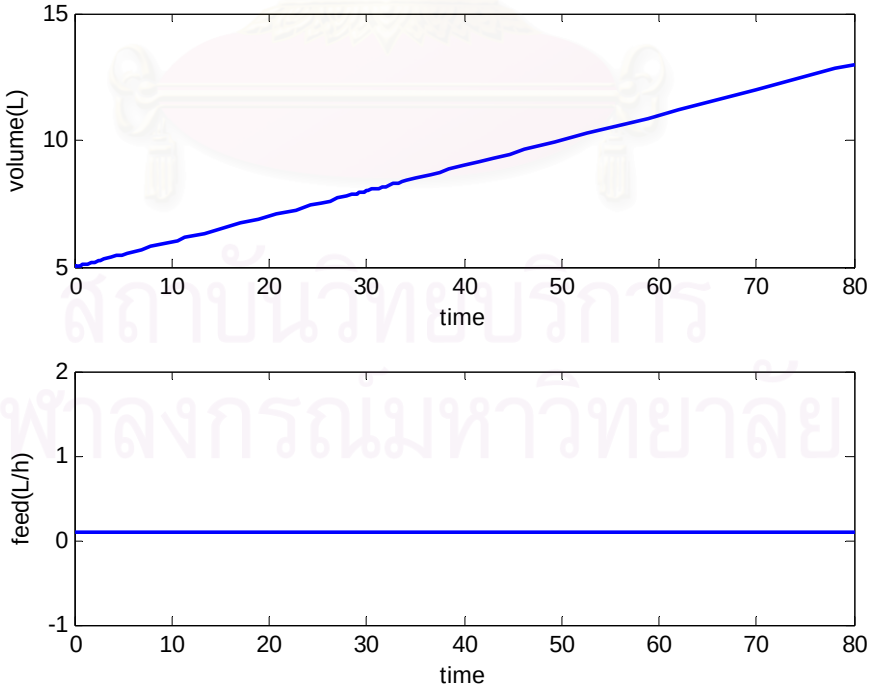

Fig.4.4: Change in reactor volume when starch is fed to the reactor at the flow rate of 0.1 l/h.

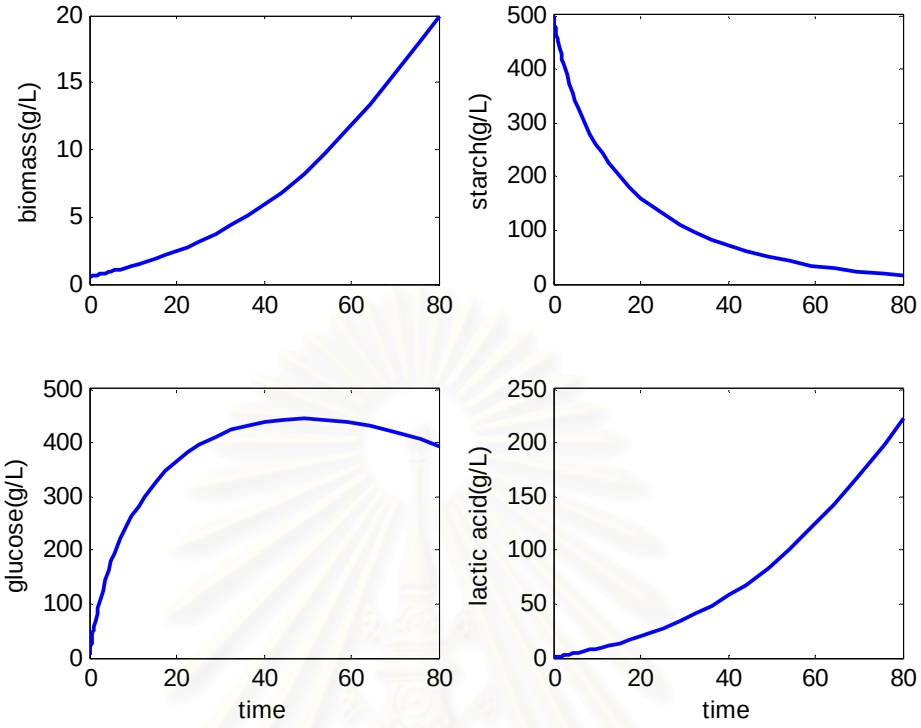

Fig.4.5: Concentration profiles in the SSF process under batch operation with the initial starch concentration of 500 g/l.

4.2.3 Comparison of fed-batch operations when feeding starch at the different operation time

In this section, the effect of feeding strategy of starch to the reactor on the production of lactic acid in the SSF process is studied. Two simulations of a fed-batch bioreactor with the same initial conditions and with the same total amount of feed are performed and the lactic acid concentration obtained at the end of the operation is used as the performance measure. The only difference between two case studies is the time at which the feed is introduced in the fed-batch reactor. Figs. 4.6 and 4.7 show the concentration and input profiles in case the starch feed is introduced in the reactor during the earlier stages of the operation whereas Figs. 4.8 and 4.8 provide the results when the feed is sent to the reactor during the latter part of the batch operation. From the figures, it is observed that feeding the starch at the earlier stages of the operation provides higher lactic acid product at the end of run than the other feeding strategy;

the obtained concentration of lactic acid is 291.36 g/l and 233.45 g/l, respectively. This result indicates the importance of feeding strategy for a fed-batch fermentation as it has a considerable impact on the productivity and yield of a desired product. Therefore, control of the feed at its optimal profile is required for operating fed-batch reactors efficiently.

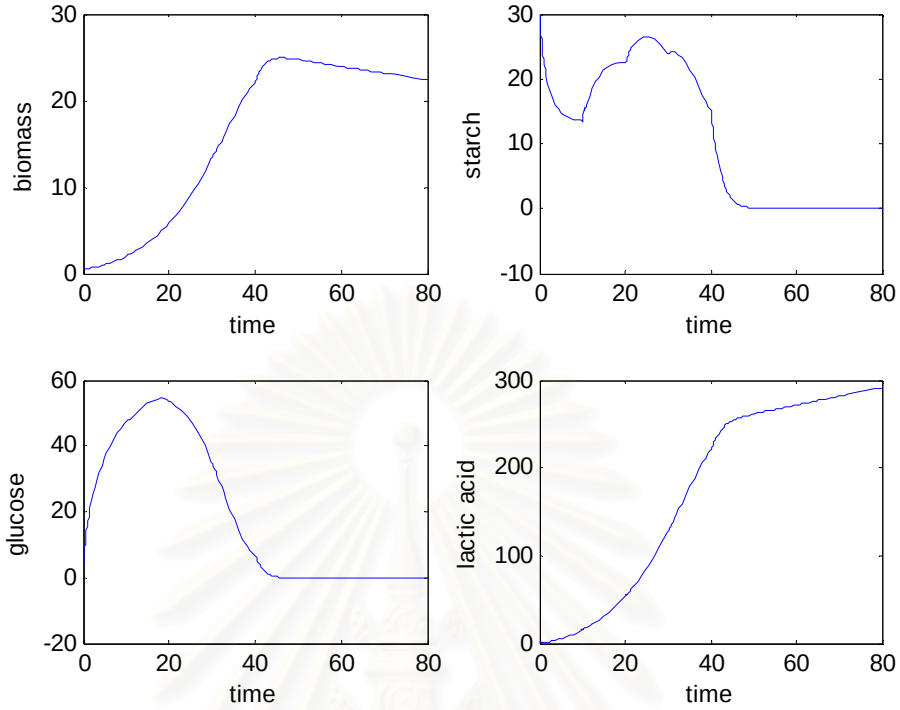

Fig. 4.6: Concentration profiles in the SSF process under fed-batch operation when starch is fed to the reactor during the earlier stages of the operation.

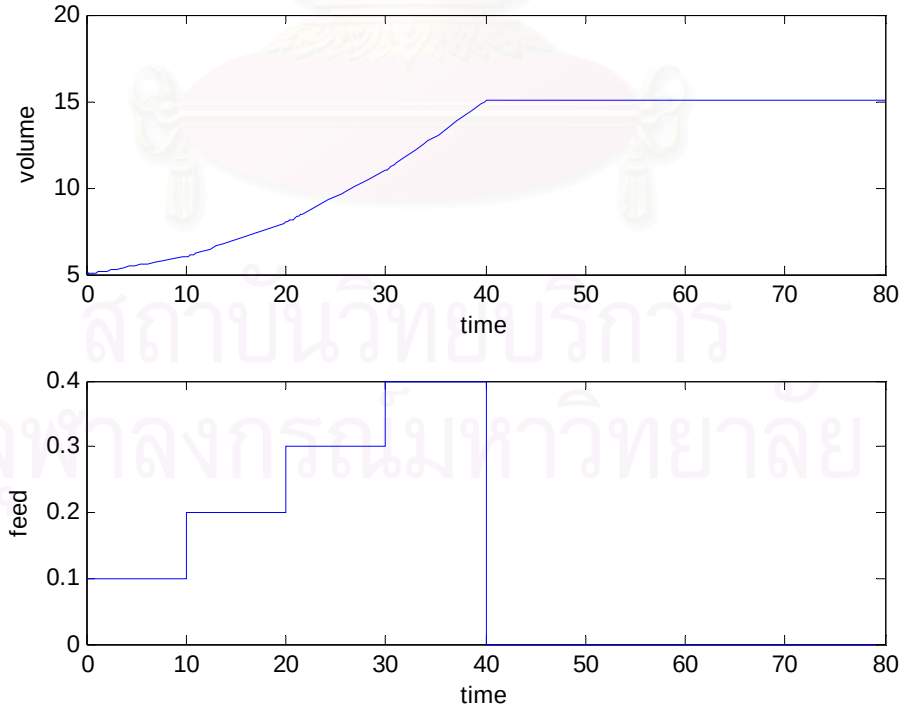

Fig.4.7: Reactor volume change and starch feed profile under fed-batch operation when starch is fed to the reactor during the earlier stages of the operation.

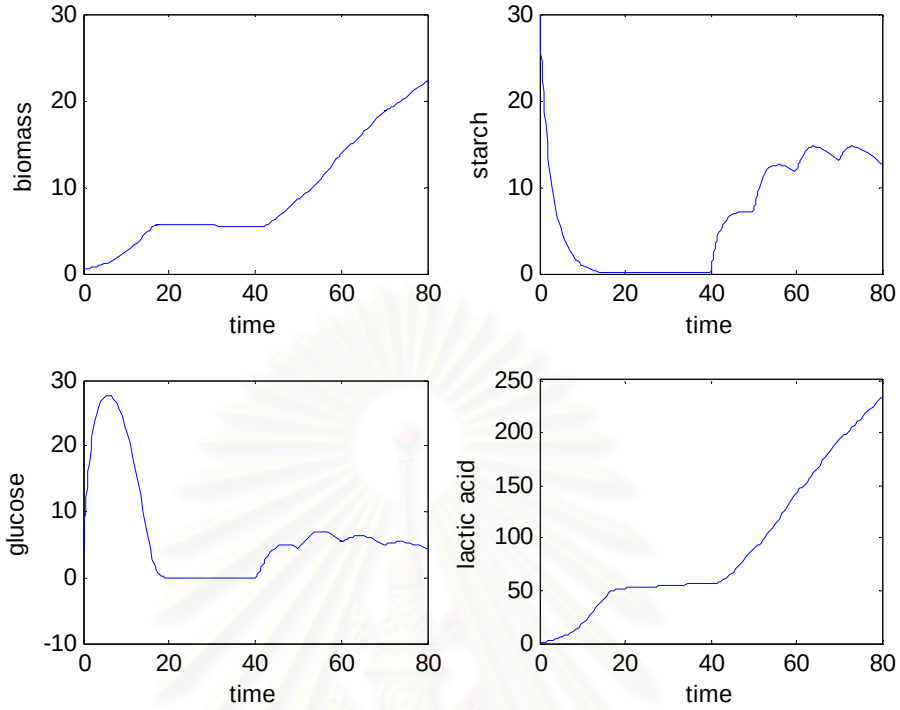

Fig. 4.8: Concentration profiles in the SSF process under fed-batch operation when starch is fed to the reactor during the later stages of the operation.

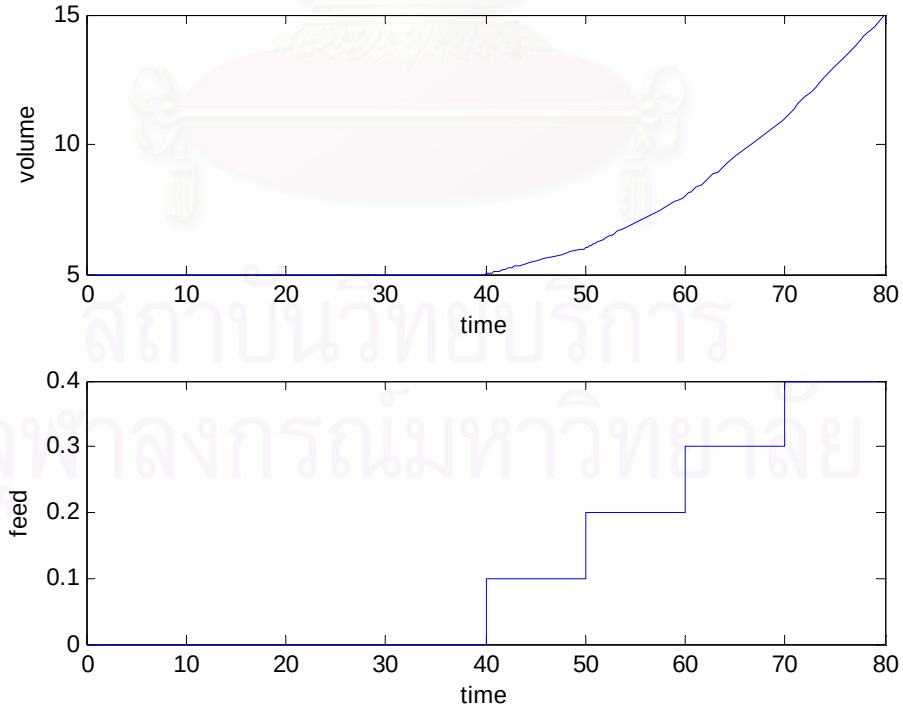

Fig 4.9: Reactor volume change and starch feed profile under fed-batch operation when starch is fed to the reactor during the earlier stages of the operation.

CHAPTER V

DYNAMIC OPTIMIZATION OF FED-BATCH REACTORS

In this chapter, the dynamic optimization of fed-batch reactors with single feed and multiple feeds is studied. The production of lactic acid from a simultaneous saccharification and fermentation (SSF) process is chosen as a case study. The detail of such a process can be seen in Chapter IV. The studies are divided into two parts; the first one focuses on the SSF process with a single feed containing both starch and glucose (a certain amount of glucose is produced during autoclaving of starch) whereas the second one deal with the SSF process with two separate feeds of starch and glucose (multiple feeds). In both parts of the study, the optimization is formulated to determine a optimal operation policy in terms of feed flow rate with an objective to maximize the production rate of the product, lactic acid, in a fixed operation time. The formulated optimization problem is solved by using a simultaneous model solution and optimization approach as described in Chapter III.

5.1 Fed-batch reactor with single feed

In this section, a fed-batch reactor where the simultaneous saccharification and fermentation is carried out, is considered. A single feed stream consisting of mainly starch is added to the reactor. Mathematic model of the fed-batch reactor for the SSF process can be described by the following equations:

$$\frac{dX}{dt} = -\frac{F}{V}X + \mu X \tag{1}$$

$$\frac{dS}{dt} = \frac{F}{V}(S_F - S) - \frac{R_G}{1.11} \tag{2}$$

$$\frac{dG}{dt} = \frac{F}{V}(G_F - G) + \left[R_G - \left(a\mu X + bX\right)\right] \tag{3}$$

$$\frac{dP}{dt} = -\frac{F}{V}P + \left(\alpha\mu X + \beta X\right) \tag{4}$$

$$\frac{dV}{dt} = F \tag{5}$$

where G_F and S_F are the concentration of glucose and starch in the feed, respectively. The kinetic model of the specific growth rate μ and the rate of saccharification R_G are given as in Eqs. (6) and (7).

$$\mu = \mu_m e^{-K_L P}\left(\frac{G}{K_s + G + G^2/K_I}\right) \tag{6}$$

$$R_G = V_m^0 e^{-kP^n}\frac{S}{K_m\left(1 + G/K_G\right) + S} \tag{7}$$

The objective of a dynamic optimization problem is to determine the optimal substrate feeding policies to maximize the production rate of lactic acid for a fixed final time (t_f = 80 h.) of fed-batch operation. The formulation of the dynamic optimization can be described mathematically as follows.

Find the feed flow rate, $F(t)$, which maximizes the following objective function:

$$\underset{F(t)}{Maximize}\, J = \frac{P\left(t_f\right)V\left(t_f\right)}{t_f} \tag{8}$$

where P is concentration of lactic acid and V is the reactor volume. In this work, it is assumed that the substrate feed rate value, F, is constrained as $F_{\min} \le F \le F_{\max}$. Since final volume is fixed at 100 l (V_f), the constraint on the volume of the reactor is as follows,

$$g_1 = V\left(t\right) - V_f \le 0 \tag{9}$$

The concentration of starch and glucose must be positive at all times (Eqs. (10)-(11).

$$g_2 = -S(t) \le 0 \tag{10}$$

$$g_3 = -G(t) \le 0 \tag{11}$$

Additionally, the final concentration of starch and glucose are constrained to ensure complete consumption and thus the following constraints are included to reduce the downstream processing of lactic acid.

$$g_4 = S(t_f) - S_r \le 0 \tag{12}$$

$$g_5 = G(t_f) - G_r \le 0 \tag{13}$$

In order to avoid large variation in control action, the flow rates are constrained as:

$$g_{5+l} = \left|F(l+1) - F(l)\right| \le 0.25F_{\max},\ l = 1,..., Nu-1 \tag{14}$$

The dynamic optimization problem as mentioned above is solved by the simultaneous method. This method is based on the transformation of dynamic optimization problems to a nonlinear programming problem via a discretization method; the process dynamic models are transferred in form of algebraic equation system which is posed as equality constraints in NLP.

In this study, the feed profile is discretized using a piecewise constant function. The number of time interval is set to be 40 (n = 40). The state variable vector $x(t)$ is expressed as $x = [X, S, G, P, V]^T$. The initial concentration of glucose and starch are taken as 4.1 and 30 g/l, respectively. The initial and final working volume is 5 and 100 l. The fermentation time is kept fixed as 80 h and initial biomass concentration is taken as 0.5 g/l. The upper limits on addition of starch sources ($F_{\max}$) are 2.0 l/h.

Figs.5.1 and 5.2 show the optimal concentration profiles for biomass, starch, glucose, lactic acid and volume and optimal feed flow rate, respectively. It is found that the maximum lactic acid concentration of 97.78 g/l, which is equivalent the production rate of 122.23 g/h, is obtained using the optimal starch feed strategy. From the feed rate profiles, it can be seen that at the beginning the optimizer predicts a starch addition; due to the saccharification of starch, glucose is produced and consumed for the growth of biomass. At t = 40 h. the optimizer predicts a decrease of feed rate to avoid the accumulation of glucose within the reactor, which leads to the inhibition of the biomass growth. However, the optimizer also suggests only smaller addition rates towards the end so as to prevent the glucose levels from falling to zero. This ensures that only those glucose levels that are necessary to maintain LA production and sustain the biomass growth are permitted.

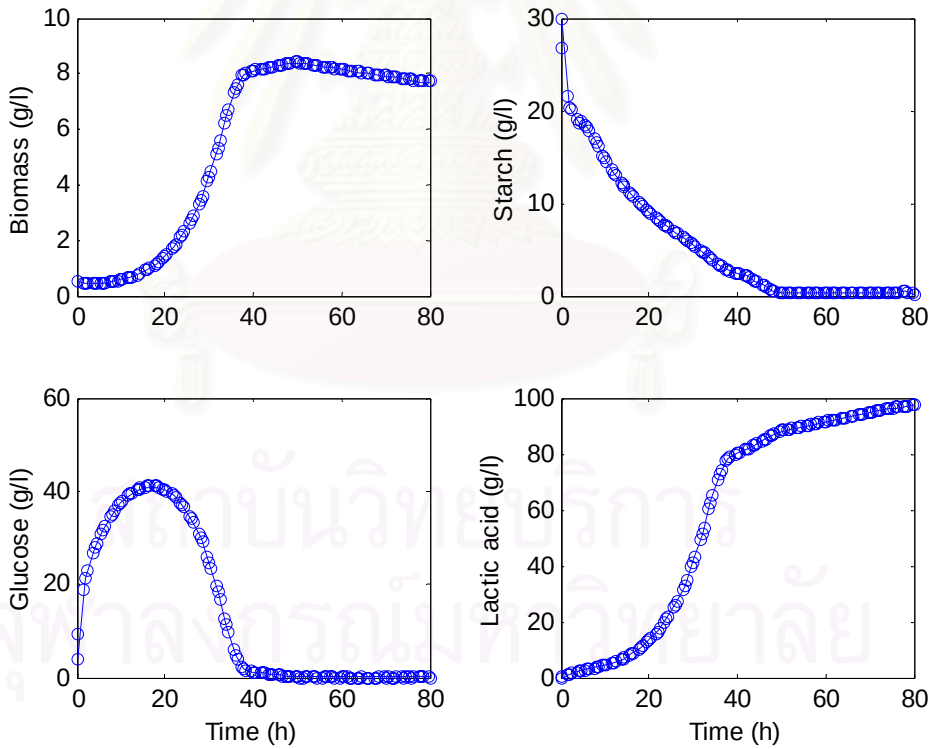

Fig. 5.1: The optimal concentration profiles for biomass, starch, glucose and lactic acid (in case of a fed-batch reactor with single feed).

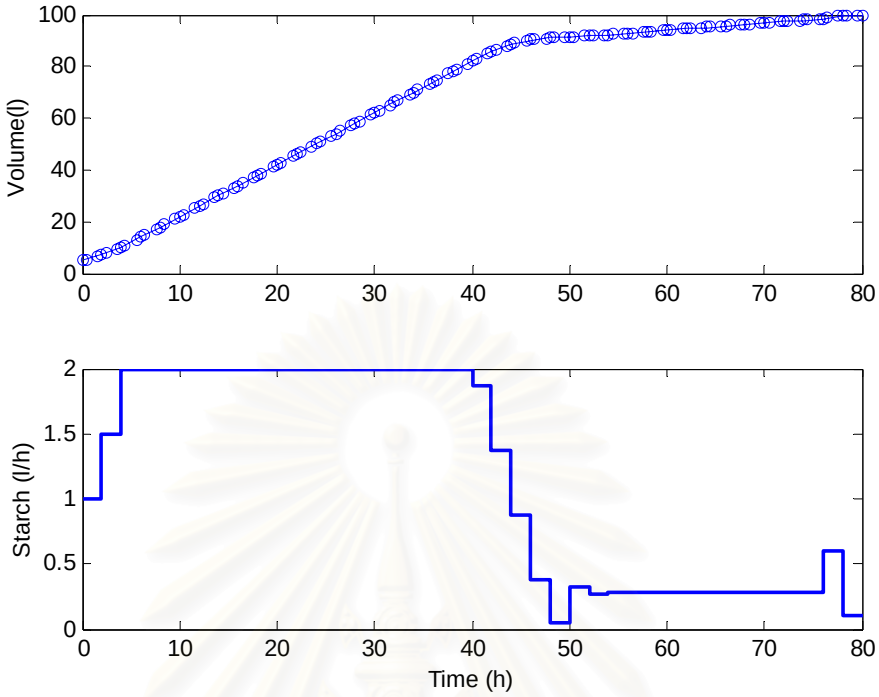

Fig 5.2: The optimal profile of reactor volume and feed rate (in case of a fed-batch reactor with single feed).

5.2 Fed-batch reactor with multiple feeds

In this section, we consider the fed-batch reactor for the SSF process with two separate feeds of starch and glucose. The reactor model is described by the following equations.

$$\frac{dX}{dt} = -\left(\frac{F_g + F_s}{V}\right)X + \mu X \tag{15}$$

$$\frac{dS}{dt} = \frac{F_s}{V}S_F - \left(\frac{F_g + F_s}{V}\right)S - \frac{R_G}{1.11} \tag{16}$$

$$\frac{dG}{dt} = \frac{F_g}{V}G_F - \left(\frac{F_g + F_s}{V}\right)G + \left[R_G - (a\mu X + bX)\right] \tag{17}$$

$$\frac{dP}{dt} = -\left(\frac{F_g + F_s}{V}\right)P + (\alpha\mu X + \beta X) \tag{18}$$

$$\frac{dV}{dt} = F_g + F_s \tag{19}$$

where F_s and F_g are the feeds which contain pure starch and pure glucose, respectively, S_F and G_F are the concentration of glucose and starch, respectively. The kinetic model of the specific growth rate μ and the rate of saccharification R_G are taken to be the same as given in Eqs. (6) and (7).

The dynamic optimization can be formulated as stated in Section 5.1. However, the difference is in the objective as two optimal feed profiles of starch and glucose are needed to determine; a number of control variables is two. For the process considered, the initial conditions and the parameters are the same as given in the previous section. The final volume fermentation is kept fixed as 100 l. The upper limits on addition of glucose and starch sources are 1.0 and 2.0 l/h, respectively. The concentrations of glucose (S_F) and starch (G_F) are 50 and 200 g/l, respectively.

Figs.5.3 and 5.4 present the optimal concentration profiles for biomass, starch, glucose, lactic acid and volume and the optimal feed flow rate, respectively. It can be seen from Fig. 5.4 that the calculated glucose feed profile starts at the upper limit and is kept almost constant during the process operation until at the end of run, the optimizer predicts a decrease in the glucose feed. This helps to keep the growth rate of biomass at high level while maintaining the rate of saccharification at low level. Since more glucose is generated, the fermentation rate of glucose to produce lactic acid product is more pronounced. The simulation shows that under the optimal feed policy of starch and glucose obtained from the solution of the dynamic optimization problem, the maximum lactic acid concentration at the end of operation is 248.55 g/l, which is equivalent the production rate of 310.69 g/h. This is higher than the case where the fed-batch reactor operated under optimal feed of starch (lactic concentration = 97.78 g/l and the production rate = 122.23 g/h). It can be further observed from Fig. 5.4 that the end point constraints on the starch and glucose concentration are met. This ensures that the substrate are completely consumed and this result demonstrates that separation cost would be low in the downstream processing.

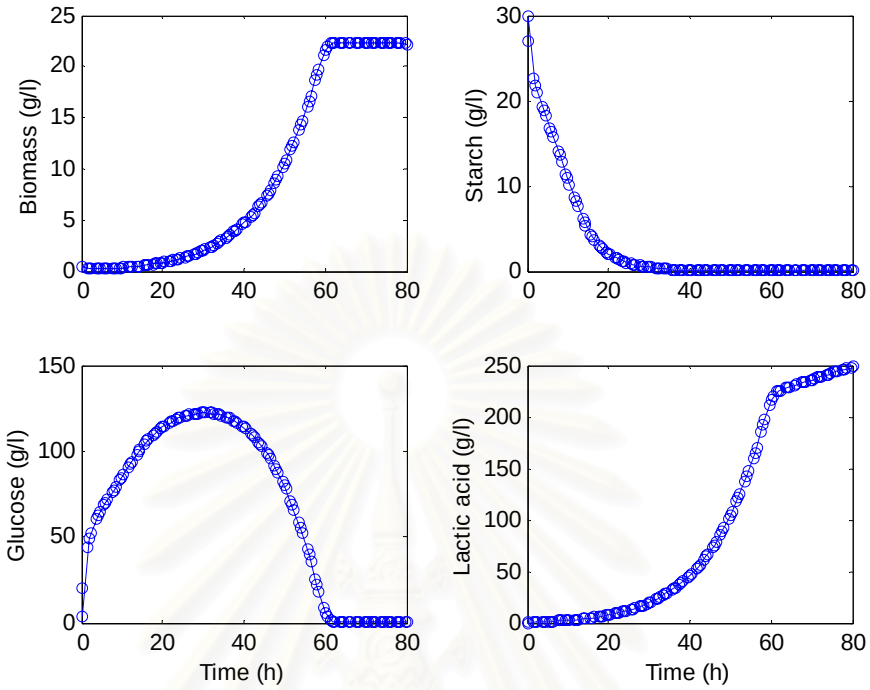

Fig. 5.3: The optimal concentration profiles for biomass, starch, glucose and lactic acid (in case of a fed-batch reactor with two feeds of starch and glucose).

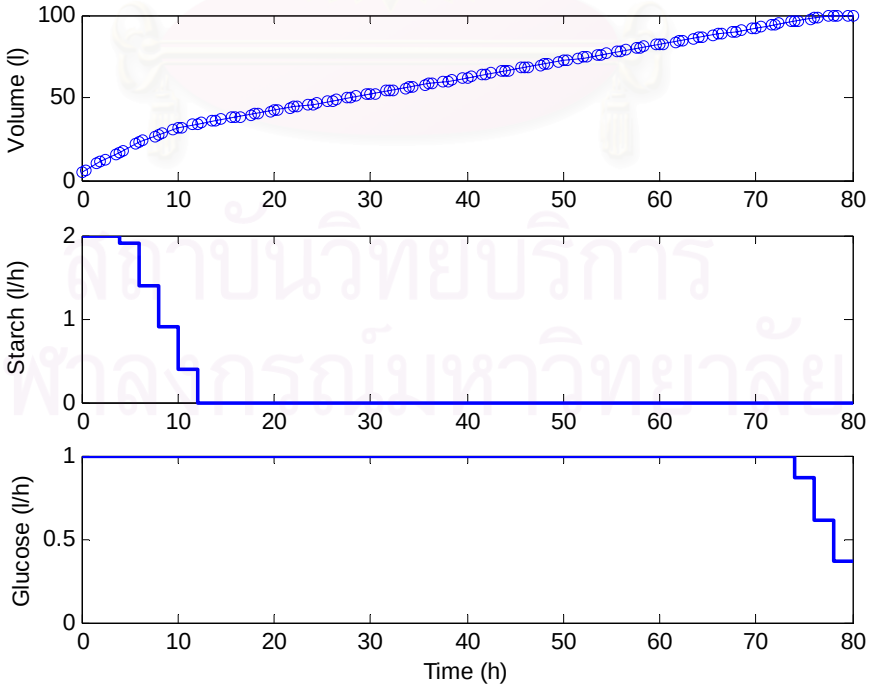

Fig. 5.4: The optimal profile of reactor volume and feed rate (in case of a fed-batch reactor with two feeds of starch and glucose)

5.2.1 Effect of the operating time: fed-batch reactor with multiple feeds

Previous studies demonstrate that if the reactor is continuously operated for a longer time, the product concentration of lactic acid would increase. This mean that a higher product concentration can be achieved; although, it may result in a lower production rate. Thus, in this section the effect of the operating time on the production rate under an optimal operation is investigated in order to improve the performance of a fed-batch reactor. The objective is to determine a minimum time of the operation of a fed-batch reactor for obtaining the maximum rate of production. The fed-batch reactor used in the production of lactic acid from the SSF process with two separate feeds of starch and glucose is considered.

The fed-batch reactor starts with the same initial operating condition as in previous section. The initial conditions of biomass, starch and glucose are 0.5, 30 4.1 g/l, respectively and the initial reactor volume is 5 l. The starch feed stream contains 50 g/l of starch and the glucose feed stream contains 200 g/l of glucose.

The dynamic optimization are formulated as in the previous section and solved to find an optimal profiles of starch and glucose feeds in order to maximize the production rate of lactic acid at a given operating time (t_f is varied). Table 5.1 summarizes the results in terms of production rate, product concentration and productivity of lactic acid obtained at the end of run when the fed-batch reactor is operated under the optimal starch and glucose feeds. From Table 5.1, it is clear that the optimal operating time of the fed-batch reactor for the SSF process with two separate feeds of starch and glucose is 56.5 h as the highest production rate and productivity of lactic acid are obtained; although, the concentration of lactic acid obtained is lower when compared with the result of the fed-batch reactor operated at 80 h. Figs. 5.5 and 5.6 show the optimal concentration profile and optimal feed flow rate when the operation time equals to 56.5 h (other simulation results are appeared in Appendix B.). Also, the end point constraints on the starch and glucose concentration are met ($S(t_f)$ = 0.0028 g/l and $G(t_f)$ = 0.1 g/l).

Table 5.1: Summary of the results of dynamic optimization at different operation time.

Operation time (h)	Production rate (g/h)	Product concentration (g/l)	Productivity (g/l h)
90	303.91	273.52	3.04
80	310.69	248.55	3.11
70	318.21	222.75	3.18
60	327.87	196.72	3.28
56.5	331.39	187.23	3.31
56	331.16	185.45	3.31
55	329.87	181.43	3.30
50	318.64	159.32	3.19
40	197.89	105.22	2.63

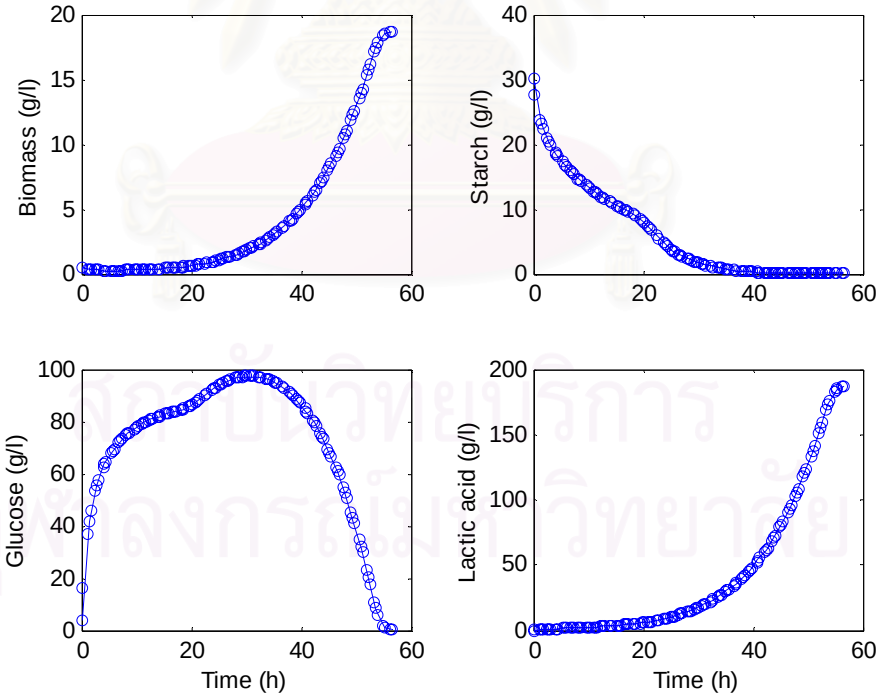

Fig. 5.5: The optimal concentration profiles for biomass, starch, glucose and lactic acid (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 56.5 h).

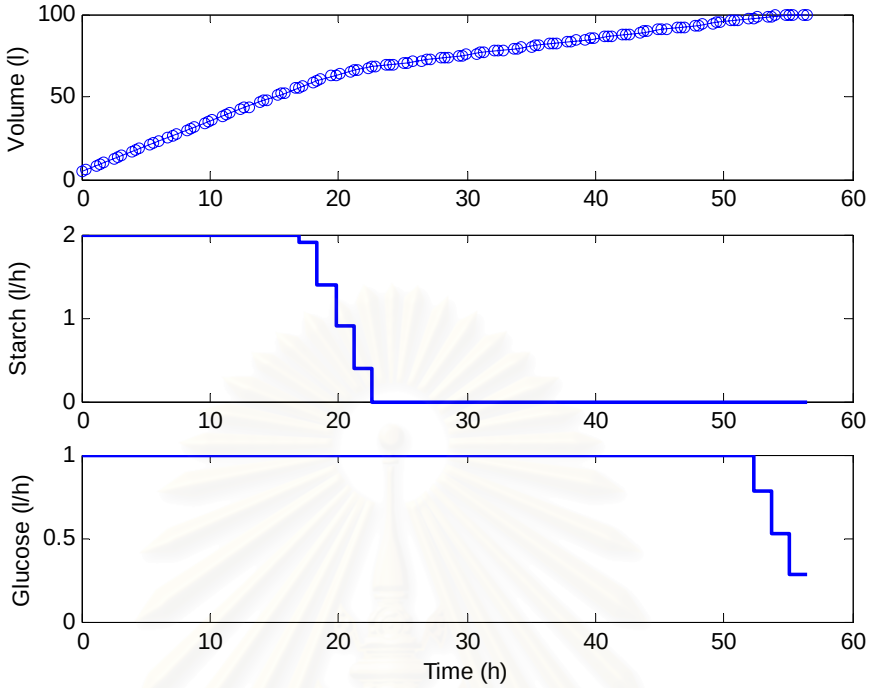

Fig. 5.6: The optimal profile of reactor volume and feed rate (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 56.5 h)

CHAPTER VI

CONCLUSIONS & RECOMMENDATIONS

6.1 Conclusions

The control of a fed-batch bioreactor with multiple control variables is studied in this work. The simultaneous saccharification and fermentation process for the production of lactic acid is chosen as a control case study. The aim is to determine an optimal feed profile of starch and glucose by solving a dynamic optimization problem with an objective to maximize the production rate of lactic acid. In this study, the formulated optimization problem is solved using a simultaneous model solution and optimization approach in which the dynamic optimization problem is transformed into a nonlinear programming problem by approximating state and control profiles. An orthogonal collocation method on finite elements is applied to discretize the state profile while a piecewise constant function is used to approximate the control profile.

Simulation of the SSF process operated under batch and fed-batch modes is first studied (Chapter IV). Comparative evaluation of the production of lactic acid in batch and fed-batch operations shows that the addition of starch during the process operation instead of adding all the starch at the start of a batch can improves the reactor performance in terms the obtained product concentration. In addition, it is found that substrate feeding at different time during the course of fed-batch operation play an important role on the reactor performance. Therefore, the control of the feed at its optimal profile is required for operating fed-batch reactors efficiently.

Next, the dynamic optimization of a fed-batch reactor for the SSF process is performed (Chapter V). The studies are divided into two parts; the first one focuses on the SSF process with a single feed containing both starch and glucose (a certain amount of glucose is produced during autoclaving of starch) whereas the second one deal with the SSF process with two separate feeds of starch and glucose (multiple feeds). The simultaneous model solution and optimization approach is successfully

applied to calculate the optimal feed rate profile for both case studies. The results show that under the optimal operation and the fixed operating time of the fed-batch reactor, the lactic acid production through the SSF process with two feeds of starch and glucose is improved by comparison to that with single feed of starch. Further, the investigation of the effect of the operating time on the production rate under an optimal operation has revealed that there is a minimum time for obtaining the maximum production of lactic acid.

6.2 Recommendations

For the future direction, the effect of initial condition and nature of objective functions on the optimal control profile should be studied. In addition, research on the implementation of an on-line dynamic optimization should be conducted as model mismatch and unknown disturbances may degrade the performance of fed-batch reactors.

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APPENDICES

APPENDIX A

COLLOCATION METHODS

These method are base on concept of interpolation of unequally spaced points; that is, choosing a function, usually a polynomial, that approximate the solution of a differential equation in the range of integration, $x_0 \le x \le x_f$, and determining the coefficients of that function from a set of base points.

Let us consider the set of two differential equations;

$$\frac{dy_1}{dx} = f_1(x, y_1, y_2)$$

$$\frac{dy_2}{dx} = f_2(x, y_1, y_2) \qquad \text{(A-1)}$$

with split boundary conditions;

$$y_1(x_0) = y_{1.0} \qquad \text{(A-2)}$$

$$y_2(x_f) = y_{2.f} \qquad \text{(A-3)}$$

Suppose that the solutions $y_1(x)$ and $y_2(x)$ of Eq. (A-1) can be approximated by the following polynomials, which we call *trial functions*:

$$y_1(x) \cong P_{1,n}(x) = c_{1,0} + c_{1,1}x + c_{1,2}x^2 + ... + c_{1,n}x^n \qquad \text{(A-4a)}$$

$$y_2(x) \cong P_{2,n}(x) = c_{2,0} + c_{2,1}x + c_{2,2}x^2 + ... + c_{2,n}x^n \qquad \text{(A-4b)}$$

We take the derivatives of both sides of Eq. (A-4) and substitute in Eq. (A-1):

$$P'_{m,n}(x) \cong f_m\left(x, P_{1,n}(x), P_{2,n}(x)\right) \qquad m = 1,2 \qquad \text{(A-5)}$$

We then form the residuals:

$$R_m(x) = P'_{m,n}(x) - f_m\left(x, P_{1,n}(x), P_{2,n}(x)\right) \; m = 1,2 \qquad \text{(A-6)}$$

The objective is to determine the coefficients $\left\{c_{m,i}, i = 0,1,...,n; m = 1,2\right\}$ of the polynomials $P_{m,n}(x)$ to make the residuals as small as possible over the range of integration of the differential equation. This is accomplished by making the following integral vanish:

$$\int_{x_0}^{x_f} W_k R_m(x) dx = 0 \qquad \text{(A-7)}$$

where W_k are weighting functions to be chosen. This technique is called the method of weighted residuals.

The collocation method chooses the weighting function to be the Dirac delta (unit impulse) function:

$$W_k = \delta(x - x_k) \qquad x_0 \le x_k \le x_f \qquad \text{(A-8)}$$

which has the property that

$$\int_{x_0}^{x_f} a(x)\delta(x - x_k) dx = a(x_k) \qquad \text{(A-9)}$$

Therefore, the integral (A-7) becomes

$$\int_{x_0}^{x_f} W_k R_m(x) dx = R_m(x_k) = 0 \qquad \text{(A-10)}$$

Combining Eqs. (A-6) and (A-10), we have

$$P'_{m,n}(x_k) - f_m\left(x_k, P_{1,n}(x_k), P_{2,n}(x_k)\right) = 0 \qquad m = 1,2 \qquad \text{(A-11)}$$

This implies that at a given number of collocation points, $\{x_k, k = 0,1,...,n\}$, the coefficients of the polynomials (A-4) are chosen so that Eqs.(A-11) is satisfied; that is, the polynomials are exact solutions of the differential equations at those collocation points (note that $x_n = x_f$). The larger the number of collocation points, the closer the trial function would resemble the true solution $y_m(x)$ of the differential equations.

Eq. (A-11) contains the $(2n+2)$ yet-to-be-determined coefficients of the polynomials $\{c_{m,i}, i = 0,1,...,n; m = 1,2\}$. These can be calculated by choosing $(2n+2)$ collocation points. Because it is necessary to satisfy the boundary condition of the problem, two collocation points are already fixed in this case of boundary-value problem.

At $x = x_0$:

$$y_1(x_0) = y_{1,0} = c_{1,0} + c_{1,1}x_0 + c_{1,2}{x_0}^2 + ... + c_{1,n}{x_0}^n = \sum_{i=0}^{n} c_{1,i}x_0^i \qquad \text{(A-12)}$$

And at $x = x_f$

$$y_2(x_f) = y_{2,0} = c_{2,0} + c_{2,1}x_f + c_{2,2}{x_f}^2 + ... + c_{2,n}{x_f}^n = \sum_{i=0}^{n} c_{2,i}x_f^i \qquad \text{(A-13)}$$

Therefore, we have the freedom to choose the remaining $(2n)$ internal collocation points and then write Eq. (A-11) for each of this point:

$$P'_{1,n}(x_1) - f_1\left(x_1, P_{1,n}(x_1), P_{2,n}(x_1)\right) = 0$$

.

.
.
. (A-14a)

$$P'_{1,n}(x_n) - f_1\left(x_n, P_{1,n}(x_n), P_{2,n}(x_n)\right) = 0$$

$$P'_{2,n}(x_0) - f_2\left(x_0, P_{1,n}(x_0), P_{2,n}(x_0)\right) = 0$$

.
. (A-14b)
.

$$P'_{2,n}(x_{n-1}) - f_2\left(x_{n-1}, P_{1,n}(x_{n-1}), P_{2,n}(x_{n-1})\right) = 0$$

Note that we have also written Eq. (A-11) for $x = x_f = x_n$ in Eq. (A-14a) and $x = x_0$ in Eq. (A-14b) because the values $y_{1,f}$ and $y_{2,0}$ are yet unknown. Eqs. (A-12) - (A-14) constitute a complete set of $(2n+2)$ simultaneous nonlinear equations in $(2n+2)$ unknowns. The solution of this problem requires the application of Newton's method for simultaneous nonlinear equations.

If the collocation points are chosen at equidistant intervals within the interval of integration, then the collocation method is equivalent to polynomial interpolation of equally spaced points and to the finite differences were all based on expanding the function in Taylor series. It is not necessary, however, to choose the collocation points at the roots of appropriate orthogonal polynomials, as the following discussion shows.

The orthogonal collocation method, which is an extension of the method just described, provides a mechanism for automatically picking the collocation points by making use of orthogonal polynomials. This method chooses the trial functions $y_1(x)$ and $y_2(x)$ to be the linear combination

$$y_m(x) = \sum_{i=0}^{n+1} a_{m,i} P_i(x) \qquad m = 1,2 \qquad \text{(A-15)}$$

of a series of orthogonal polynomials $P_i(x)$:

$$P_0(x) = c_{0,0}$$

$$P_1(x) = c_{1,0} + c_{1,1}x$$

$$P_2(x) = c_{2,0} + c_{2,1}x + c_{2,2}x^2 \qquad \text{(A-16)}$$

.

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$$P_i(x) = c_{i,0} + c_{i,1}x + c_{i,2}x^2 + ... + c_{i,n}x^i$$

This set of polynomials can be written in a condensed form:

$$P_i(x) = \sum_{k=0}^{i} c_{ik}x^k \qquad i = 0,1,...,n+1 \qquad \text{(A-17)}$$

The coefficients c_{ik} are chosen so that the polynomials obey the orthogonality condition:

$$\int_a^b w(x)P_i(x)P_j(x)dx = 0 \qquad i \neq j \qquad \text{(A-18)}$$

when $P_i(x)$ is chosen to be the *Legendre* set of orthogonal polynomials, the weight $w(x)$ is unity. The standard of interval of integration for *Legendre* polynomials is $[-1,1]$. The transformation equation is used to transform the *Legendre* polynomials to the interval $\lfloor x_0, x_f \rfloor$, which applies to our problem at hand:

$$x = \frac{(x_f - x_0)}{2}z + \frac{(x_f + x_0)}{2} \qquad \text{(A-19)}$$

Eq. (A-19) relates the variables x and z so that every value of x in the interval $\left\lfloor x_0, x_f \right\rfloor$corresponds to value of z in the interval $\left[-1,1\right]$ and vice versa. Therefore using x or z as independent variables is equivalent. Hereafter, we use z as the independent variables of the Legendre polynomials to stress that the domain under study is the interval $\left[-1,1\right]$. The derivatives with respect to x and z are related to each other by the following relation:

$$\frac{dy_m}{dx} = \frac{2}{\left(x_f - x_0\right)}\frac{dy_m}{dz} \qquad \text{(A-20)}$$

The two-point boundary-value problem given by Eqs. (A-1)- (A-3) has $\left(2n+2\right)$ collocation points, $\left\{z_j, j = 0,1,...,n+1\right\}$, including the two known boundary values $\left(z_0 = -1 \text{ and } z_{n+1} = 1\right)$. The location of the n internal collocation points $\left(z_1 \text{ to } z_n\right)$ are determined from the roots of polynomial $P_n\left(z\right) = 0$. The coefficients $a_{m,i}$ in Eq. (A-15) must be determined so that the boundary conditions are satisfied. Eq. (A-15) can be written for the $\left(n+2\right)$ points $\left(z_0 \text{ to } z_{n+1}\right)$ as

$$y_1\left(z_j\right) = \sum_{i=0}^{n+1} d_{1,i} z_j^i \qquad \text{(A-21a)}$$

$$y_2\left(z_j\right) = \sum_{i=0}^{n+1} d_{2,i} z_j^i \qquad \text{(A-21b)}$$

when the terms of the polynomials have been regrouped. Eqs. (A-21a) and (A-21b) may be represented in matrix notation as

$$y_1 = Qd_1 \qquad \text{(A-22a)}$$

$$y_2 = Qd_2 \qquad \text{(A-22b)}$$

where d_1 and d_2 are the matrices of coefficients and

$$Q_{j+1,i+1} = z_j^i \quad \begin{cases} i = 0,1,...,n+1 \\ j = 0,1,...,n+1 \end{cases} \tag{A.-23}$$

Solving Eqs. (A-22) for d_1 and d_2, we find

$$d_1 = Q^{-1} y_1 \tag{A-24a}$$

$$d_2 = Q^{-1} y_2 \tag{A-24b}$$

The derivatives of y are taken as

$$\frac{dy_1(z_j)}{dz} = \sum_{i=0}^{n-1} d_{1,i} i z_j^{i-1} \tag{A-25a}$$

$$\frac{dy_2(z_j)}{dz} = \sum_{i=0}^{n-1} d_{2,i} i z_j^{i-1} \tag{A-25b}$$

which in matrix form become

$$\frac{dy_1}{dz} = Cd_1 = CQ^{-1} y_1 = Ay_1 \tag{A-26a}$$

$$\frac{dy_2}{dz} = Cd_2 = CQ^{-1} y_2 = Ay_2 \tag{A-26b}$$

where

$$C_{j+1,i+1} = i z_j^{i-1} \quad \begin{cases} i = 0,1,...,n+1 \\ j = 0,1,...,n+1 \end{cases} \tag{A-27}$$

The two point boundary value problem of Eq. (A-1) can now be expressed in terms of the orthogonal collocation method as

$$Ay_1 = f_1(z, y_1, y_2) \tag{A-28a}$$

$$Ay_2 = f_2(z, y_1, y_2) \tag{A-28b}$$

or

$$\sum_{j=0}^{n+1} A_{ij} y_{1,j} = f_1(z_j, y_{1,j}, y_{2,j}) \tag{A-29a}$$

$$\sum_{j=0}^{n+1} A_{ij} y_{2,j} = f_2(z_j, y_{1,j}, y_{2,j}) \tag{A-29b}$$

with the boundary conditions:

$$y_1(z_0) = y_{1,0} \qquad \text{and} \qquad y_{2,n+1} = y_2(z_f) = y_{2,f} \tag{A-30}$$

Eqs. (A-29) and (A-30) constitute a set of $(2n+4)$ simultaneous nonlinear equations whose solution can be obtained using Newton's method for nonlinear equations. It is possible to combine Eqs. (A-29) and present them in matrix form:

$$A_2 Y = F \tag{A-31}$$

where

$$A_2 = \begin{bmatrix} A & 0 \\ 0 & A \end{bmatrix} \tag{A-32}$$

$$Y = \begin{bmatrix} y_1 \\ y_2 \end{bmatrix}$$

$$= \left[y_{1,0}, \ldots, y_{1,n+1}, y_{2,0}, \ldots, y_{2,n+1} \right]' \tag{A-33}$$

$$F = \begin{bmatrix} f_1 \\ f_2 \end{bmatrix} = \begin{bmatrix} f_1(z_0, y_{1,0}, y_{2,0}) \\ . \\ . \\ . \\ f_1(z_{n+1}, y_{1,n+1}, y_{2,n+1}) \\ f_2(z_0, y_{1,n+1}, y_{2,n+1}) \\ . \\ . \\ . \\ f_2(z_{n+1}, y_{1,n+1}, y_{2,n+1}) \end{bmatrix} \quad \text{(A-34)}$$

It should be noted that Eq. (A-31) is solved for the unknown collocation points which means that we should exclude the equations corresponding to the boundary conditions. In the problem described above, the first and the last equations in the set of Eq. (A-31) will not be used because the corresponding dependent values are determined by a boundary condition rather than by the collocation method.

The above formulation of solution for a two-equation boundary –value problem can be extended to the solution of m simultaneous first–order ordinary differential equations. For this purpose, we define the following matrices:

$$A_m = \begin{bmatrix} A & 0 & ... & 0 \\ 0 & A & ... & 0 \\ .. & .. & ... & .. \\ 0 & 0 & ... & A \end{bmatrix} \quad \text{(A-35)}$$

$$Y = [y_1, y_2, ..., y_m]' \quad \text{(A-36)}$$

$$F = [f_1, f_2, ..., f_m]' \quad \text{(A-37)}$$

Note that the matrix A in Eq. (A-35) is defined by Eq. (A-26) and appears m times on the diagonal of the matrix A_m. The values of the dependent variables $\{y_{ij}, i = 1,2,..., m;$

$j = 0,2,...,n+1\}$ are then evaluated from the simultaneous solution of the following set of nonlinear equations plus boundary conditions:

$$A_m Y - F = 0 \qquad \text{(A-38)}$$

The equation corresponding to the boundary conditions have been excluded from Eq. (A-38) at the time of solution.

If the problem to be solved is a second-order two-point boundary value problem in the form

$$y'' = f(x, y, y') \qquad \text{(A-39)}$$

with the boundary conditions

$$y(x_0) = y_0 \qquad \text{and} \qquad y(x_f) = x_f \qquad \text{(A-40)}$$

We may follow the similar approach as describes above and approximate the function $y(x)$ at $(n+2)$ points, after transforming the independent variable from x to z, as

$$y(z_j) = \sum_{i=0}^{n+1} d_i z_j^i \qquad \text{(A-41)}$$

The derivatives of y are then taken as

$$\frac{dy(z_j)}{dz} = \sum_{i=0}^{n+1} d_i i z_j^{i-1} \qquad \text{(A-42)}$$

$$\frac{d^2 y(z_j)}{dz^2} = \sum_{i=0}^{n+1} d_i i(i-1) z_j^{i-2} \qquad \text{(A-43)}$$

These equations can be written in matrix form:

$$\frac{dy}{dz} = CQ^{-1}y = Ay \tag{A-44}$$

$$\frac{d^2y}{dz^2} = DQ^{-1}y = By \tag{A-45}$$

where

$$D_{j+1,i+1} = i(i-1)z_j^{i-2} \qquad \begin{cases} i = 0,1,...,n+1 \\ j = 0,1,...,n+1 \end{cases} \tag{A-46}$$

APPENDIX B

Optimal Control Results

This appendix show optimal concentration profiles and optimal feed flow rate of starch and glucose obtained for the solution of a dynamic optimization problem of a fed-batch reactor with two separate feeds when the operating time is varied.

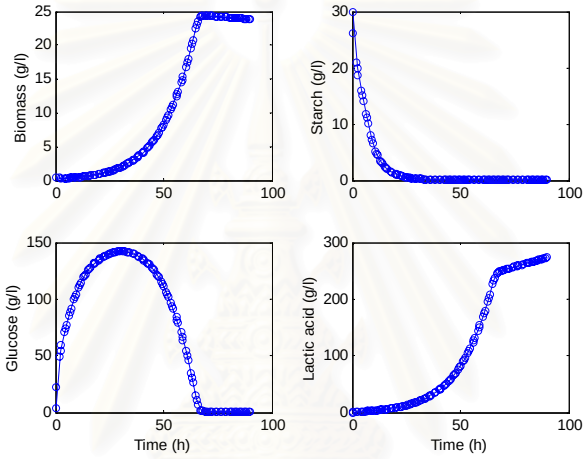

Fig.B-1.1: The optimal concentration profiles for biomass, starch, glucose and lactic acid (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 90 h).

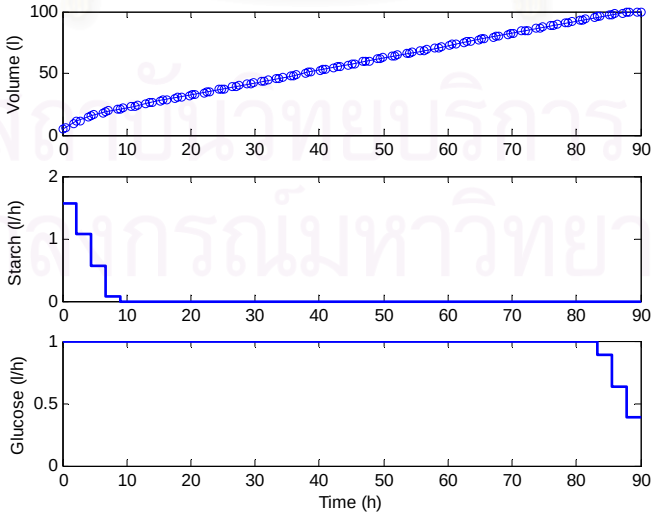

Fig.B-1.2: The optimal profile of reactor volume and feed rate (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 90 h)

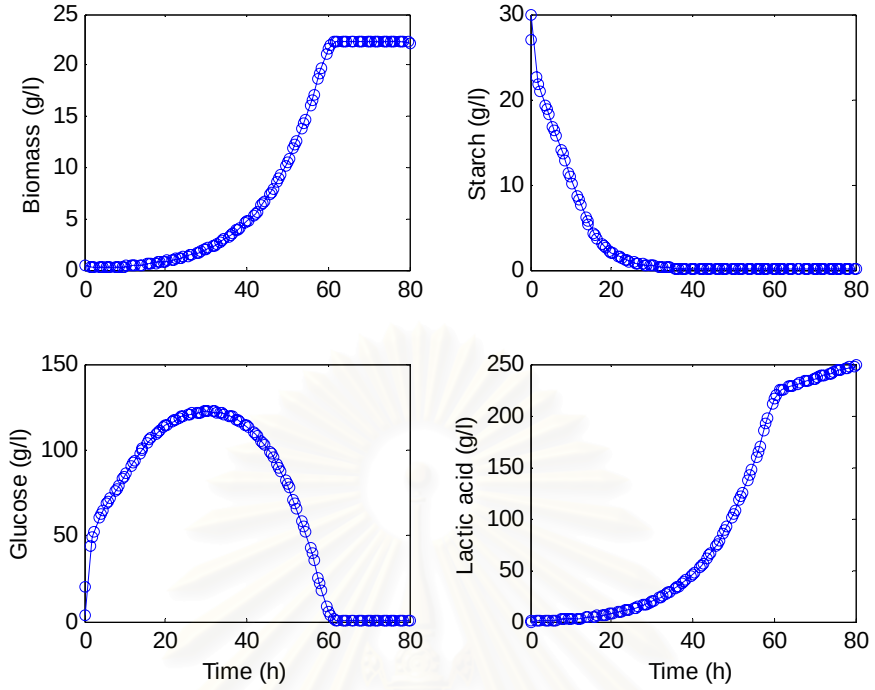

Fig.B-2.1: The optimal concentration profiles for biomass, starch, glucose and lactic acid (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 80 h).

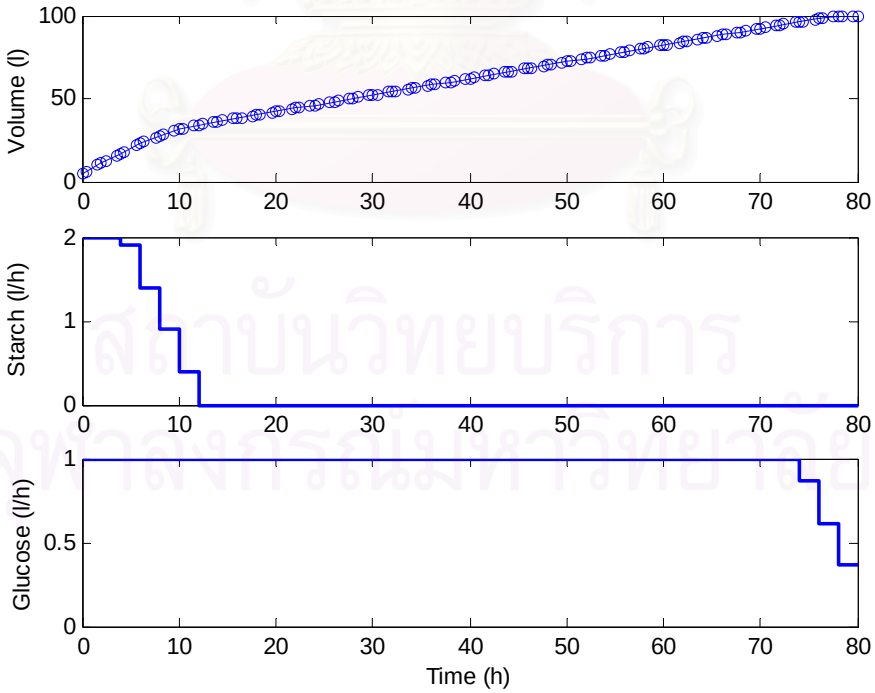

Fig.B-2.2: The optimal profile of reactor volume and feed rate (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 80 h)

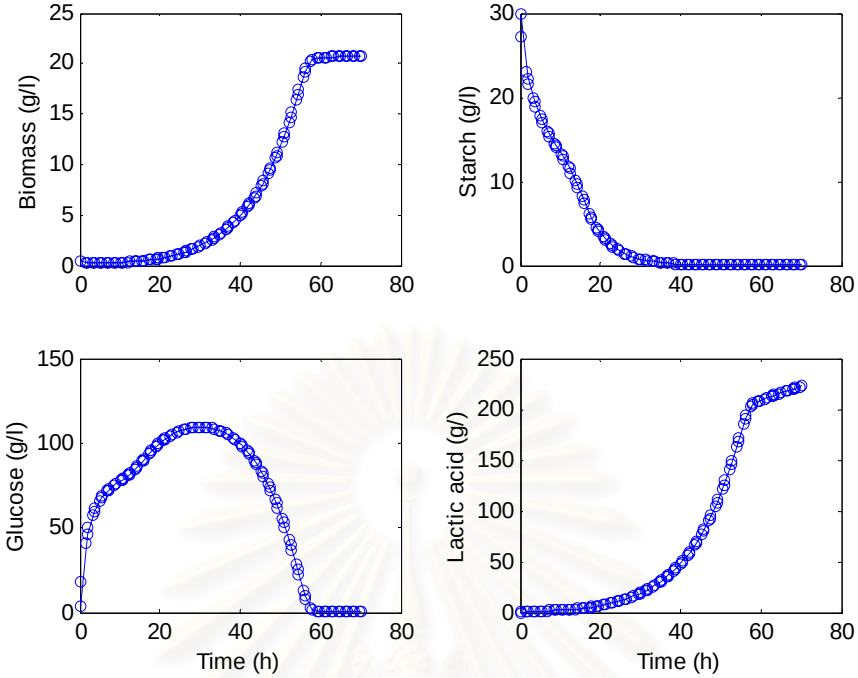

Fig.B-3.1: The optimal concentration profiles for biomass, starch, glucose and lactic acid (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 70 h).

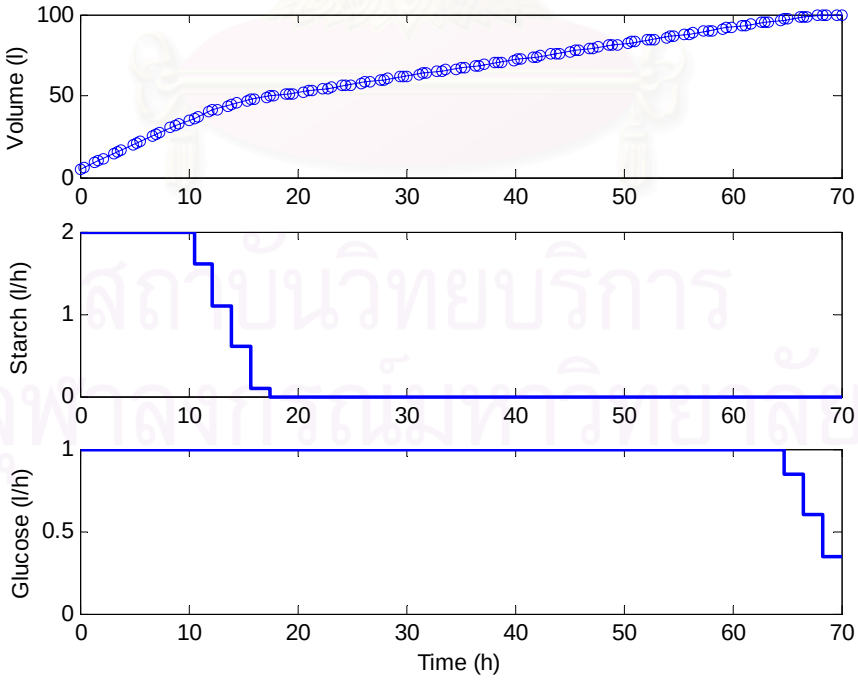

Fig.B-3.2: The optimal profile of reactor volume and feed rate (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 70 h)

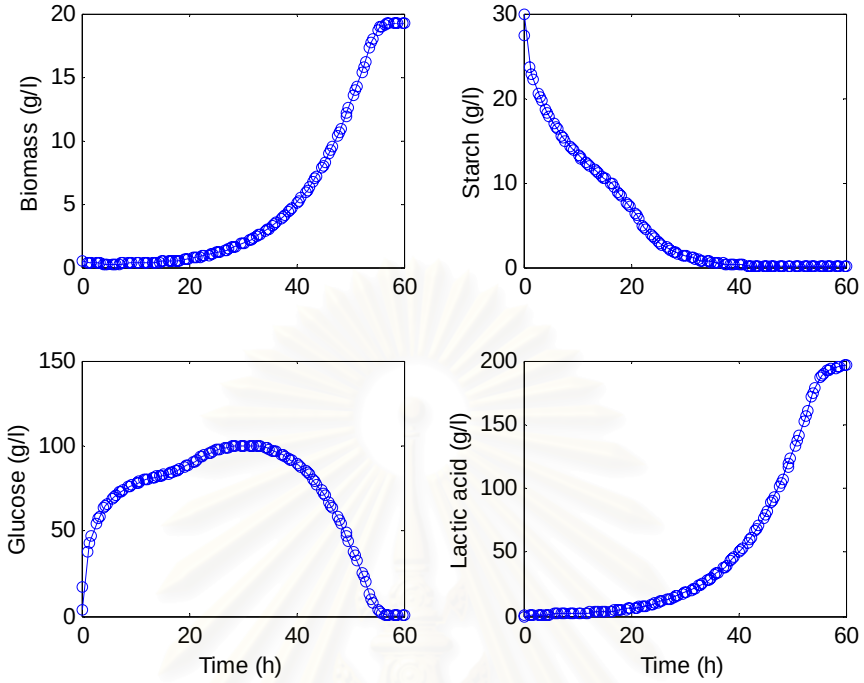

Fig.B-4.1: The optimal concentration profiles for biomass, starch, glucose and lactic acid (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 60 h).

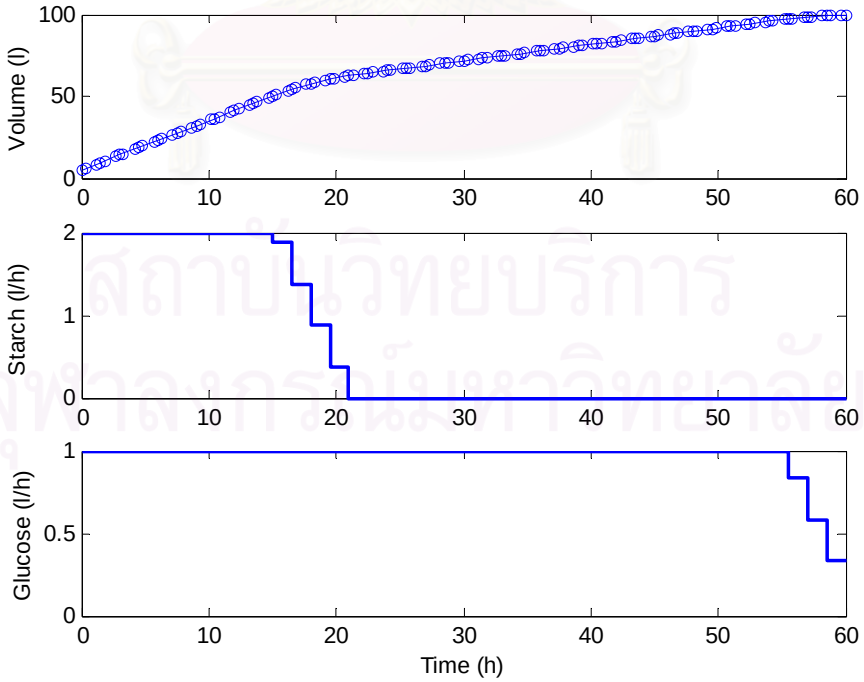

Fig.B-4.2: The optimal profile of reactor volume and feed rate (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 60 h)

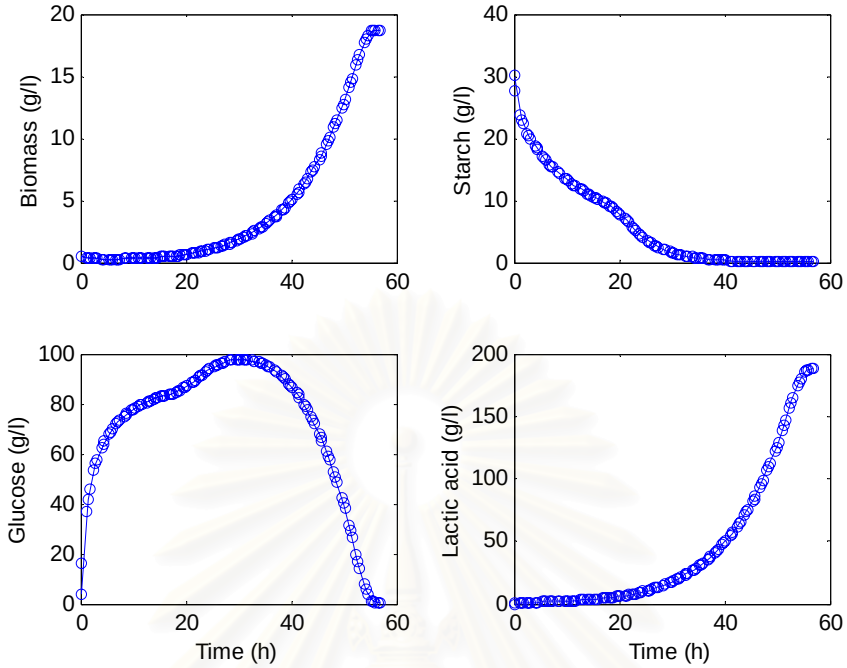

Fig.B-5.1: The optimal concentration profiles for biomass, starch, glucose and lactic acid (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 57 h).

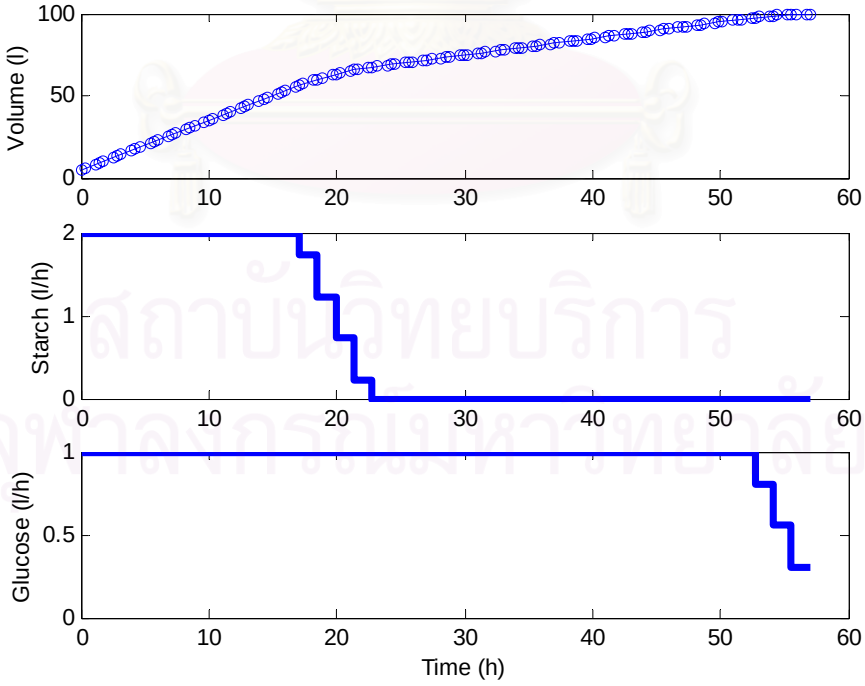

Fig.B-5.2: The optimal profile of reactor volume and feed rate (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 57 h)

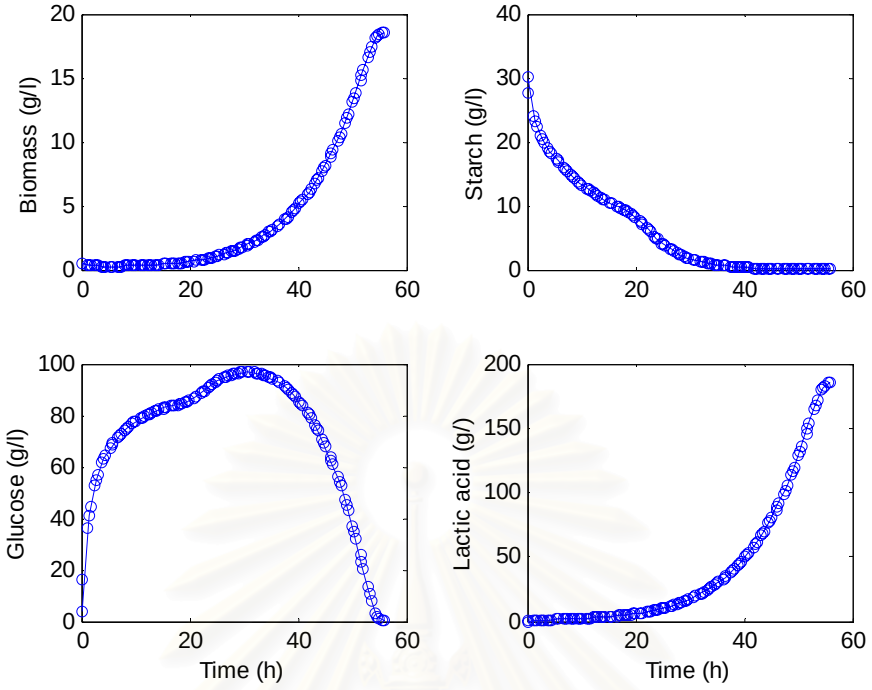

Fig.B-6.1: The optimal concentration profiles for biomass, starch, glucose and lactic acid (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 56 h).

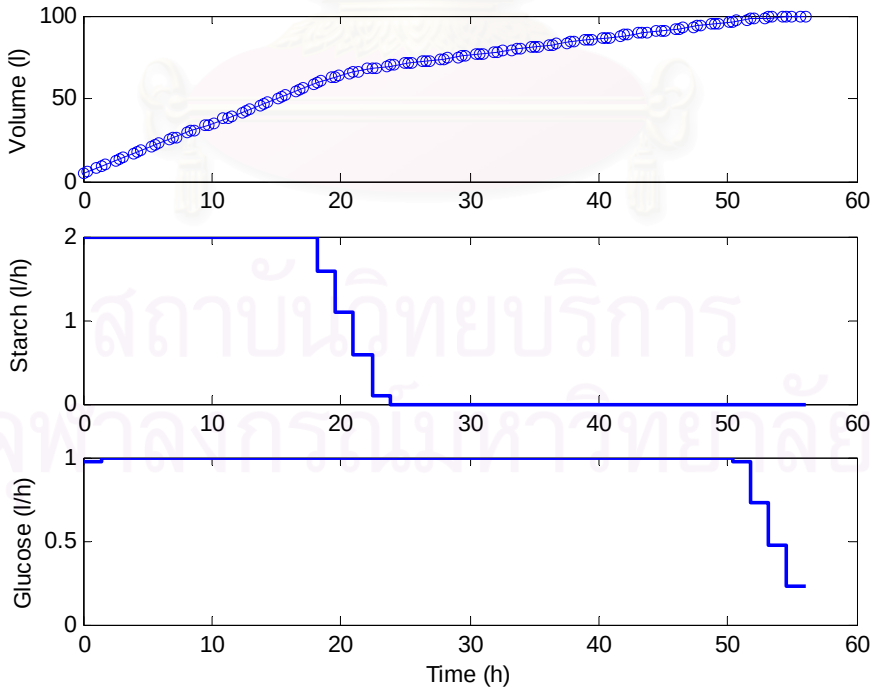

Fig.B-6.2: The optimal profile of reactor volume and feed rate (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 56 h)

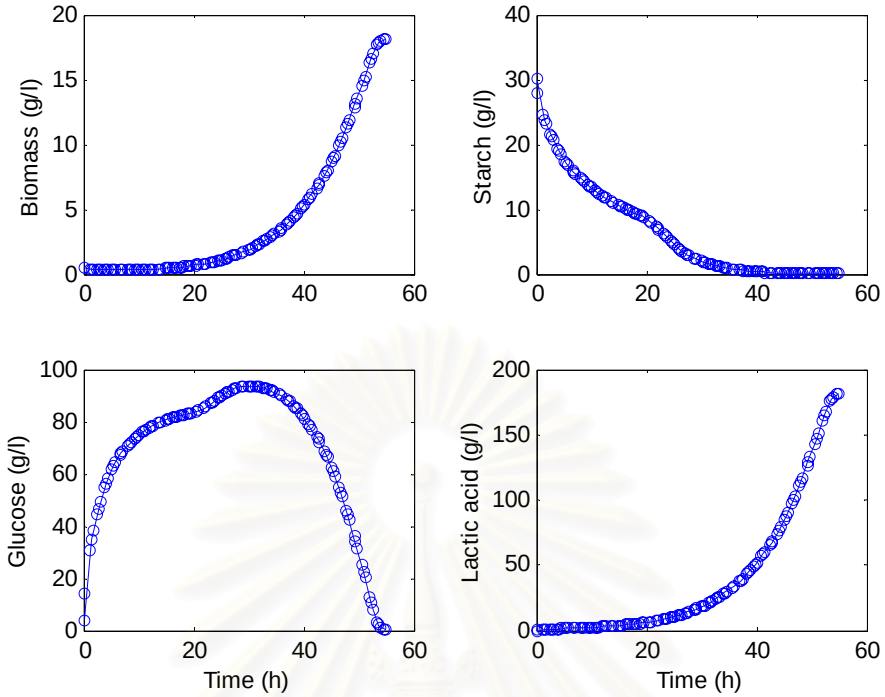

Fig.B-7.1: The optimal concentration profiles for biomass, starch, glucose and lactic acid (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 55 h).

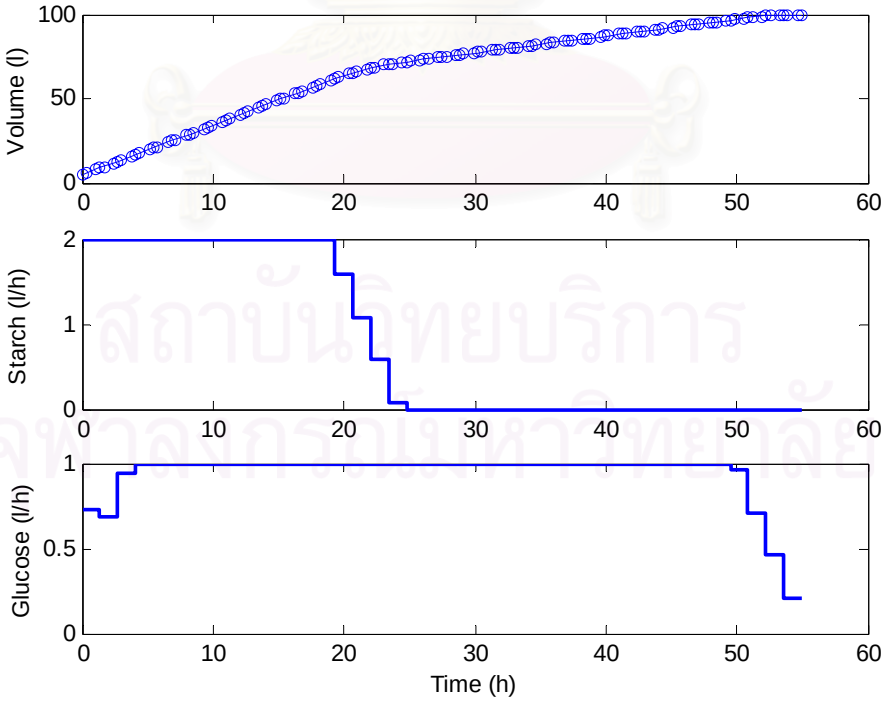

Fig.B-7.2: The optimal profile of reactor volume and feed rate (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 55 h)

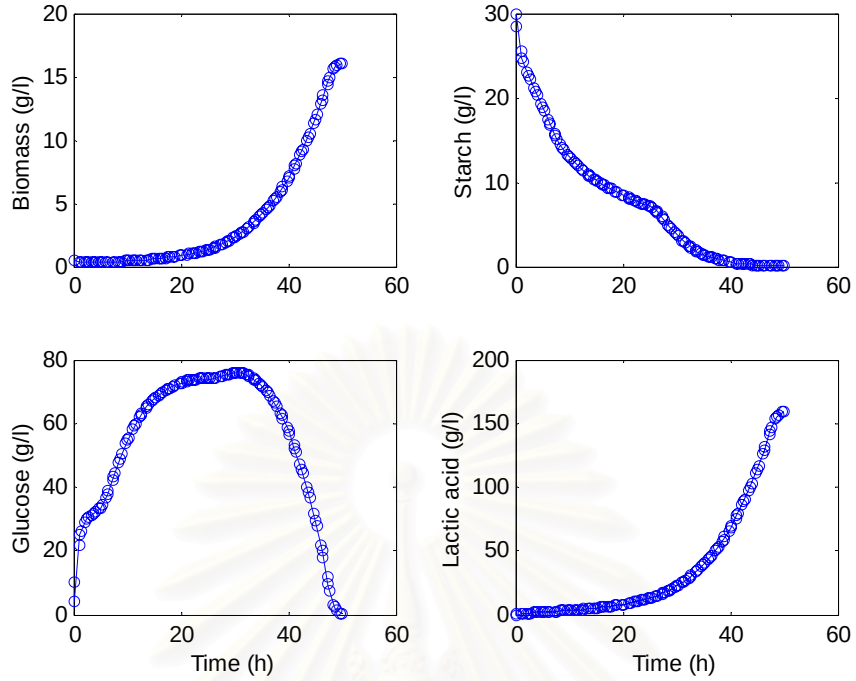

Fig.B-8.1: The optimal concentration profiles for biomass, starch, glucose and lactic acid (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 50 h).

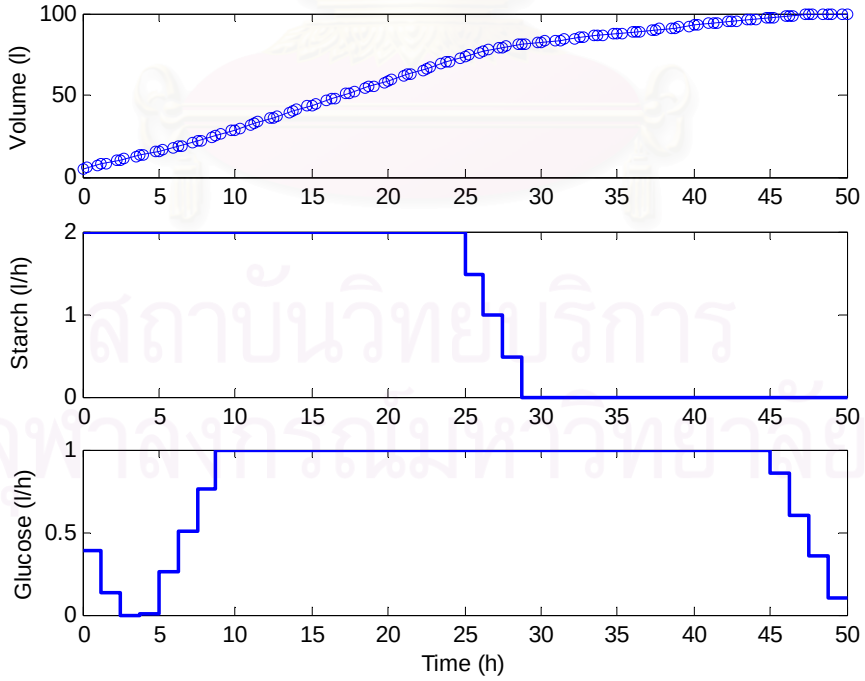

Fig.B-8.2: The optimal profile of reactor volume and feed rate (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 50 h)

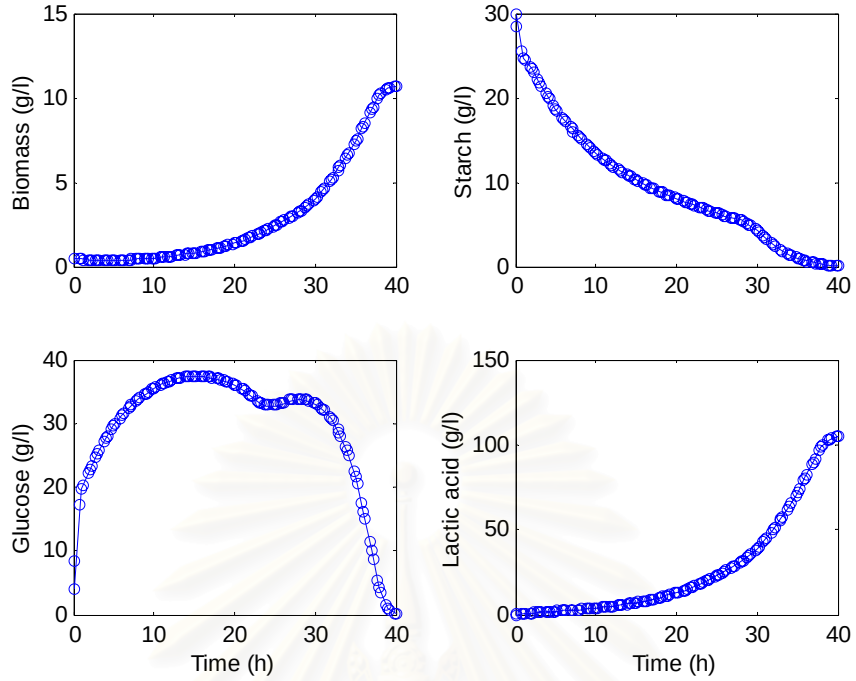

Fig.B-9.1: The optimal concentration profiles for biomass, starch, glucose and lactic acid (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 40 h).

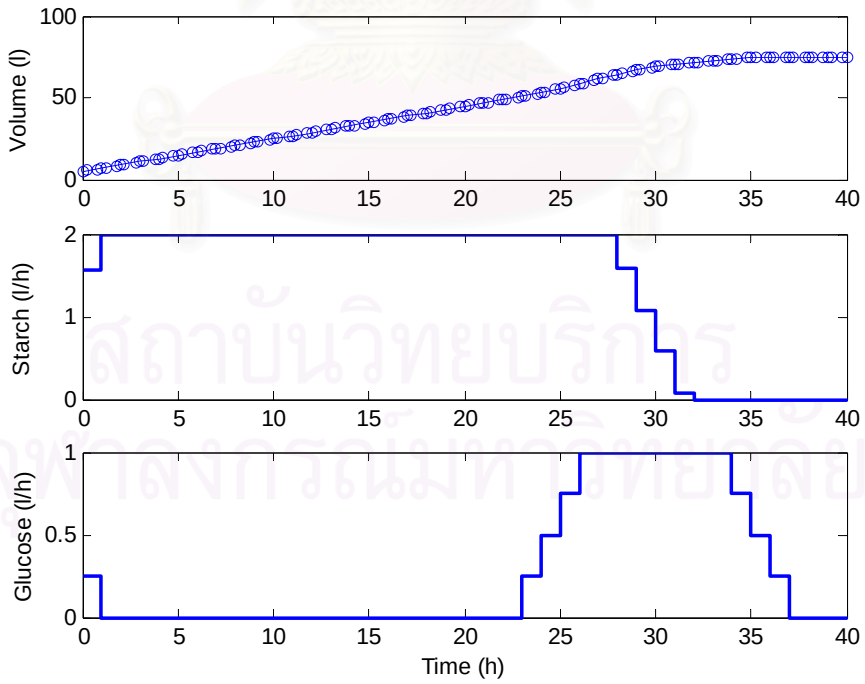

Fig.B-9.2: The optimal profile of reactor volume and feed rate (in case of a fed-batch reactor with two feeds of starch and glucose and t_f = 40 h)

VITA

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