MODEL PREDICTIVE CONTROL ON FED-BATCH PENICILLIN FERMENTATION PROCESS

CHEW LI MEI

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MODEL PREDICTIVE CONTROL ON FED-BATCH PENICILLIN FERMENTATION PROCESS

CHEW LI MEI

A thesis submitted in fulfillment of
the requirement of the award of the degree of
Bachelor of Chemical Engineering

Faculty of Chemical and Natural Resources Engineering
University Malaysia Pahang

APRIL 2009

I declared that this thesis entitled "*Model Predictive Control on Fed-Batch Penicillin Fermentation Process"* is the result of my own researched excepted as cited in the references. The thesis has not been accepted for any degree and is not concurrently submitted in candidature of any other degree.

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Date : 20 APRIL 2009

To my beloved mother and father

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ABSTRACT

In this research study the development of optimization strategies for a fed-batch penicillin fermentation process using model predictive controller was simulated using MATLAB 7.1 software. To facilitate the study, model predictive control (MPC) based on unstructured model for penicillin production in a fed-batch fermentor has been developed. A mathematical model of the system is derived based on published materials, the data is generated using PENSIM, dynamic response is analyzed, transfer function is developed and finally the MPC is implemented into the fermentation process. MPC offers an adaptive and optimizing control strategy which deals with multiple goals and constraints. The results of a study of the applicability of Model Predictive Control (MPC) in the process were obtainable. In order to obtain best optimization result for the fed-batch penicillin fermentation process, two optimization algorithms were selected. First, dynamic optimization using direct shooting method and second is implementation single step ahead Dynamic Matrix Control (DMC). Comparison of these two different approaches shows that DMC algorithm showed the best result with an optimization procedure.

ABSTRAK

Dalam projek kajian ini, pengembangan strategi untuk Proses Fermentasi Suapan Batch Penisilin mengunakan kawalan peramalan model (MPC) telah disimulasikan mengunakan MATLAB 7.1 software. Untuk memfasilitasi kajian ini, MPC berdasarkan model tidak berstruktur untuk penisilin produksi dalam fermentor suapan batch telah dikembangkan. Model matematik sistem diambil berdasarkan bahan yang dipublikasikan, data yang dihasilkan diambil daripada PENSIM, analisa dynamik respon dijalankan, fungsi pengalihan dikembangkan, dan akhirnya MPC diimplementasikan ke dalam proses fermentasi. MPC menawarkan kontrol adaptif dan mengoptimalkan strategi yang berkaitan dengan beberapa tujuan dan sekatan. Keputusan hasil kajian dari penerapan kawanlan peramalan model (MPC) dalam proses adalah memuaskan. Untuk memperoleh hasil optimasi terbaik untuk Proses Fermentasi Suapan Batch Penisilin, dua optimasi algoritma dipilih. Pertama, dinamis optimasi menggunakan *Direct Shooting Method* dan pelaksanaan kedua adalah menggunakan *Dynamic Matrix Control* (DMC). Perbandingan kedua-dua pendekatan yang berbeza menunjukkan bahawa algoritma DMC telah menunjukkan hasil terbaik dalam prosedur optimasi.

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LIST OF ABBREVIATIONS

MPC	-	Model Predictive Control
PID	-	Proportional Integral Derivatives
MV	-	Manipulated Variables
DV	-	Disturbance Variables
CV	-	Controlled Variables
FC	-	Flowrate Controller

LIST OF NOMENCLATURE

a	-Heat transfer coefficient of heating/cooling liquid (cal/h.°C)
$C_{a/b}$	-Acid or base concentration (molar)
C_L	-Dissolved oxygen concentration (= C_L^* at saturation) (g/l)
CO_2	-Carbon dioxide concentration (mmol/l)
c_p	-Heat capacity of medium (cal/g.°C)
c_{pc}	-Heat capacity of cooling liquid (cal/g.°C)
E_d	-Activation energy for cell death (cal/mol)
E_g	-Activation energy for growth (cal/mol)
f_g	-Oxygen flow rate (l/h)
F	-Feed flow rate of substrate (l/h)
F_a	-Acid flow rate (ml/h)
F_b	-Base flow rate (ml/h)
F_c	-Cooling water flow rate (l/h)
h	-Specific enthalpy
$[H^+]$	-Hydrogen ion concentration (mol/l)
k_d	-Arrhenius constant for cell death
k_g	-Arrhenius constant for growth
K	-Penicillin hydrolysis rate constant (h^{-1})
K_1	-Constant (mol/l)
K_2	-Constant (mol/l)
K_I	-Inhibition constant for product formation (g/l)
K_{OP}	-Oxygen limitation constant
K_{OX}	-Oxygen limitation constant
K_P	-Inhibition constant (g/h)
m_o	-Maintenance coefficient on oxygen (h^{-1})
m_X	-Maintenance coefficient on substrate (h^{-1})

P	-Penicillin concentration (g/l)
P_w	-Agitation power input (W)
q_s	-Specific rate of substrate
q_o	-Specific oxygen uptake rate
Q_o	-Rate of oxygen uptake per volume of broth
Q_{rxn}	-Heat generation due to microbial metabolism (KJ/kg)
Q_{ag}	-Heat generation due to mechanical agitation (KJ/kg)
Q_{gas}	-Heat generation due to aeration power input (KJ/kg)
Q_{exch}	-Heat generation due to the surroundings and/or heat exchanger (KJ/kg)
Q_{sen}	-Rate of sensible enthalpy
R	-Gas constant (1.987 cal/(mol.K)
r_{q1}	-Yield of heat generation (cal/g biomass)
r_{q2}	-Constant in heat generation (cal/g biomass.h)
s_f	-Feed substrate concentration (g/l)
S	-Substrate concentration (g/l)
T	-Temperature (K)
T_f	-Feed temperature of substrate (K)
V	-Culture volume (l)
X	-Biomass concentration (g/l)
$Y_{P/O}$	-Yield constant (g penicillin/g oxygen)
$Y_{P/S}$	-Yield constant (g penicillin/g glucose)
$Y_{X/O}$	-Yield constant (g biomass/g oxygen)
$Y_{X/S}$	-Yield constant (g biomass/g glucose)
α	-Constant in K_{la}
α_1	-Constant relating CO_2 to growth (mmol CO_2/g biomass)
α_2	-Constant relating CO_2 to maintenance energy (mmol CO_2/g -biomass.h)
α_3	-Constant relating CO_2 to penicillin production (mmol CO_2/l.h)
B	-Constant in K_{la}
γ	-Proportionality constant (mol $[H^+]$/g biomass)
μ_X	-Maximum specific growth rate (h^{-1})
μ_P	-Specific rate of penicillin production (h^{-1})
ρ	- Density of the culture medium (g/l)
ρ_c	-Density of the cooling liquid (g/l)

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Background Study

In recent years the performance requirements for processes in chemical and biotech processes have become increasingly difficult to satisfy. Modern plants have become more complicated to operate because of its trend toward complex and highly integrated processes. Therefore, dynamic model of the process was created with the intention that can be used in a computer simulation to evaluate alternative control strategies and to determine initial values of the controller settings.

There are many aspects that complicate the modeling of the bioprocesses. A fermentation process has both nonlinear and dynamic properties. The metabolic processes of the microorganisms are very complicated and cannot be modeled precisely. Because of these reasons, traditional modeling methods fail to model bioprocesses accurately. The modeling is further complicated because the fermentation runs are usually quite short and large differences exist between different runs.

Fermentations can be operated in batch, fed-batch or continuous reactors. In batch reactor all components, except gaseous substrates such as oxygen, pH-controlling substances and antifoaming agents, are placed in the reactor in the beginning of the fermentation. During process there is no input nor does output flow. In fed-batch process, nothing is removed from the reactor during the process, but one

substrate component is added in order to control the reaction rate by its concentration. There are both input and output flows in a continuous process, but the reaction volume is kept constant. As explained by Yuan *et al*. (1997), although continuous processes offer advantages such as higher productivity and ease of operation compared to batch processes, they retain certain disadvantages such as more severe impacts due to equipment failures, infection by other microorganisms, and spontaneous mutations in the strain. On the other hand, fed-batch modes are preferred since it provides better management of substrates and is able to avoid excessive substrate feed, which can inhibit microorganism growth. Since products are also withdrawn at the end of the batch, sterilized conditions can be maintained during process operation.

In this research study, penicillin production is considered due to its nonlinear dynamics and multistage nature as well as its industrial importance. The mechanistic model has been substantially improved by the inclusion of aeration rate, agitation power, feed flow rates of substrate and oxygen, carbon dioxide concentration, feed coolant and bioreactor temperatures, generated heat and the medium pH.

1.2 Problem Statement

Penicillin is produced by microorganism fermentation method. Until now, the production of penicillin still continues to attract research interest. This is because penicillin has significant benefit towards the commercial and therapeutic, and giving impact to the engineering field. Penicillin fermentation processes are complex bioprocesses of microorganism community growth, circulation and metabolism. Fermentation production involves high operating cost and energy consumption. Hence, in order to reduce penicillin production cost, increasing its yield and quality, penicillin fermentation production processes need to be optimized.

In fed batch fermentation penicillin process, inequality constraints do occur on input and output variable. Input constraints take place as a result of physical limitations on plant equipment such as pumps, control valves, and heat exchangers. Besides that, many output variables do not have set points. For these output, the control objectives is to maintain them between upper and lower limit instead of forcing them to set points. The inability to provide on-line measurement of fermentation variables such as biomass concentration has proved to be a significant obstacle for the implementation of advanced control and optimizations solutions in the fed batch fermentation penicillin process [Zhang and Lennox et al., 2004]. Therefore, Model Predictive Control (MPC) is used to solve the problem besides improving the simulation of penicillin production.

1.3 Objective

The main objective of this research study is to apply Model Predictive Control base on fed batch penicillin fermentation process using MATLAB 7.1 software.

1.4 Scope of Study

To achieve the objective, the following scope of research is proposed:

i. Identification of mathematical models for the fed-batch fermentation process
ii. Collecting data generation from fed batch fermentation process
iii. Analyzing the dynamic response of the fed batch fermentation process
iv. Development of transfer function based on dynamic response
v. Implementation of Model Predictive Control on fed batch fermentation process

1.5 Significant of Study

Model Predictive Control has given major impact on chemical industrial practice, with over 4500 applications worldwide. In these industries, MPC has become a method of choice for difficult multivariable control problem. MPC is an important advanced control technique for large multiple input-output with difference constraints on the inputs and/or output. If the model is accurate and representative of the process being considered, simulation studies will provide close guidance to what is supposed the optimum conditions for actual implementations. This will save not only time and efforts but also cost of operations.

CHAPTER 2

LITERATURE REVIEW

2.1 Penicillin

Penicillin is a group of Beta-lactam antibiotics used used to treat many different types of infections caused by a wide range of Gram-positive bacteria. “Penicillin” is also the informal name of a specific member of the penicillin group Penam Skeleton, which has the molecular formula R-$C_9H_{11}N_2O_4S$, where R is a variable side chain. Penicillin was the first naturally-occurring antibiotic discovered and the first to be used therapeutically. Its wide usage is a result of its lack of toxicity and irritancy. It works by interfering with the formation of the bacteria's cell wall while it is growing, weakening the wall and killing the bacteria. Below are the properties of penicillin:

Chemical Formula	: R-$C_9H_{11}N_2O_4S$
Melting Point	: 97 °C.
Density	: 1.41 g/ml
Molar mass	: 356.37g
Percent Composition by mass	: 57.4% C, 5.43% H, 8.38% N, 19.14% O, 9.59% S

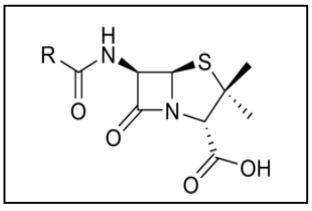

Figure 2.1: Molecular Structure of Penicillin

2.2 Fed Batch Fermentation Process

Fed-batch fermentation is a production technique in between batch and continuous fermentation. A proper feed rate, with the right component constitution is required during the process. Fed-batch fermentation offer few advantages such as:

a) Able to produce high cell densities due to addition of working time (particularly important in the production of growth-associated products)
b) Controlled conditions in the provision of substrates during the fermentation, particularly regarding the concentration of specific substrates as for ex. the carbon source
c) Control over the production of by-products or catabolite repression effects due to limited provision of substrates solely required for product formation
d) The mode of operation can overcome and control deviations in the organism's growth pattern as found in batch fermentation
e) Allows the replacement of water loss by evaporation
f) Alternative mode of operation for fermentations leading with toxic substrates (cells can only metabolize a certain quantity at a time) or low solubility compounds
g) Increase of antibiotic-marked plasmid stability by providing the correspondent antibiotic during the time span of the fermentation
h) No additional special piece of equipment is required as compared with the batch fermentation mode of operation

A complete model of the penicillin fermentation must include the following aspects of the process:

- Smooth transition between growth and production phases
- Substrate limitation of growth
- Induction of penicillin production in response to stress
- Degradation of penicillin
- Oxygen limitation effects on growth and penicillin production
- Mass transfer limitations to substrate and oxygen transfer

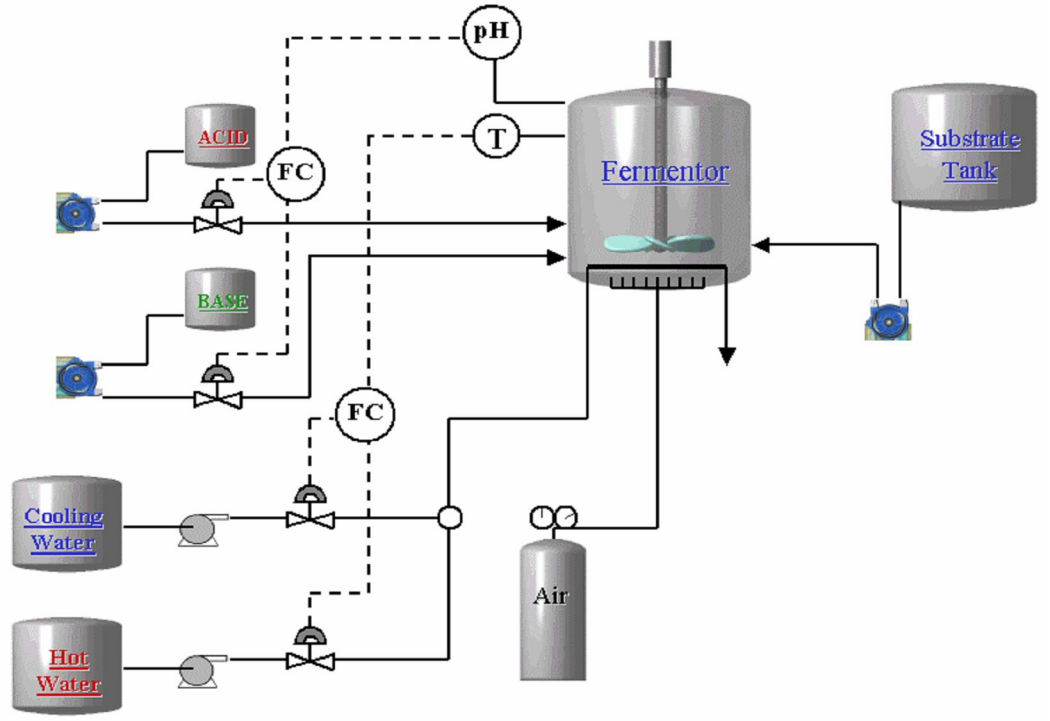

Figure 2.2: Fed-batch penicillin fermentation process (Birol *et al.*, 2002)

2.3 Unstructured Model of Fed-Batch Fermentation

Fermentation processes can be modeled either by 'structured' models or by 'unstructured' models. Structured models represent the individual organisms in detail, but are usually mathematically too complex to be useful for controller design. Simple unstructured models can be obtained by assuming that the fermenter culture consists of a single, homogeneously growing organism. These models are well suited to the design of the controllers, since the models are given by a few nonlinear ordinary differential equations. A variety of fermentations can be described by the unstructured model. In this research, we concentrate on product optimization of a Penicillin fermentation process. The mathematical model of the fed-batch Penicillin fermentation will be discussed in chapter 2.4.

2.4 Development Mathematical Model for Fed-batch Penicillin Fermentation

In this work, the unstructured model of fed-batch penicillin fermentation from Birol *et al.* (2002) works was chosen. This is because the form of these unstructured models fits well with any approach. They can be systematically identified and updated using data from experimental and production runs. In their work, the mechanistic model of Bajpai and Reuss (1980) was utilized as the starting point for model development. Additional input variables such as agitation power and aeration rate were included to extend the original model. The model is presented with better clarity in the next section.

2.4.1 Overall Mass Balance

The rate of change of mass in a fermenter can generally be represented by Equation (2.1).

$$\begin{bmatrix}\text{Rate of}\\ \text{mass}\\ \text{accumulated}\\ \text{in the system}\end{bmatrix} = \begin{bmatrix}\text{Rate of}\\ \text{mass in}\\ \text{by flow}\\ \text{in the system}\end{bmatrix} - \begin{bmatrix}\text{Rate of}\\ \text{mass out}\\ \text{by flow}\\ \text{in the system}\end{bmatrix} - \begin{bmatrix}\text{Rate of}\\ \text{mass}\\ \text{consumed}\\ \text{in the system}\end{bmatrix} + \begin{bmatrix}\text{Rate of}\\ \text{mass}\\ \text{generated}\\ \text{in the system}\end{bmatrix} \tag{2.1}$$

Letting F denotes the volumetric flow rate of the entering feed stream and F_{out} denotes the volumetric flow rate of the exiting product stream, the overall material balance takes the following form:

$$\frac{d(\rho V)}{dt} = \rho_{in} F - \rho_{out} F_{out} \tag{2.2}$$

However, since this is a fed-batch fermentation, there is no outlet flow until the batch cycle is completed thus $F_{out} = 0$. Thus the total material balance takes the following form:

$$\frac{d(\rho V)}{dt} = \rho_{in} F \tag{2.3}$$

In order to consider the effect of evaporative loss during fermentation, the term, F_{loss} is included. The loss in volume due to evaporation is significant in industrial fermentations because the air entering the fermenter is fairly dry and it is about 90-100% relative humidity after bubbling through the broth. Typically, 10-20% of the total broth can be lost due to evaporation in one week fermentation process, the actual amount depending on the temperature of the fermentation (Birol *et al.*, 2002). The effect of temperature and culture volume *V* on the evaporative loss can be represented by the following equation:

$$F_{loss} = V.\lambda(e^{5((T-To)/Tv-To)}-1) \tag{2.4}$$

Here T_o and T_v are the freezing and boiling temperatures of the culture medium respectively and are typically assumed to have same properties as water. Assuming that the evaporation rate can go to infinity at the boiling point, for engineering purposes the exponent 5 is considered large enough to represent this. Birol *et al.* (2002) suggested λ is arranged to give an evaporation rate of 2.5×10^{-4} l/h at the operation temperature (25 ºC).

In addition, the effect of acid/base addition on the total volume change of the culture broth, $F_{a/b}$ should also be included in Equation (2.3) as provided by Birol *et al.* (2002). The pH was kept constant at a value of 5.1 by adding highly concentrated (3 M) acid or base solution when necessary. By applying all these terms in Equation (2.3), the overall mass balance for a fermenter can be expressed as:

$$\frac{d\rho V}{dt} = \rho_{in} F + \rho_{a/b} F_{a/b} - \rho_{loss} F_{loss} \tag{2.5}$$

Assuming that densities of entering liquid stream, the culture fluid, acid/base addition and evaporation rate in liquid form are both equal to ρ , the overall mass balance for a fermenter can be reduced to:

$$\frac{dV}{dt} = F + F_{a/b} - F_{loss} \tag{2.6}$$

2.4.2 Mass Balance on Biomass

A similar mass balance approach based on Equation (2.1) can be performed for the biomass in a fermenter. In fed-batch operation, F_{out} = 0; mass of biomass is the product of biomass concentration, X multiplied by culture volume, V. Meanwhile the mass generated for certain time period is equal to μXV where μ is the specific growth rate of biomass, and the rate of biomass death is equal to $k_d XV$ where k_d is the specific death constant as explained by Bailey and Ollis (1986). Applying these terms in Equation (2.1) gives:

$$\frac{d(XV)}{dt} = FX_{in} + \mu XV - k_d XV \tag{2.7}$$

After expanding the differential and rearranging some terms in Equation (2.7), we obtain the following equation:

$$X\frac{dV}{dt} + V\frac{dX}{dt} = FX_{in} + (\mu - k_d)XV \tag{2.8}$$

Rearranging Equation (2.8) gives:

$$\frac{dX}{dt} = \frac{F}{V}X_{in} + \left(\mu - k_d - \frac{1}{V}\frac{dV}{dt}\right)X \tag{2.9}$$

Biomass in inlet flow, X_{in}, is equal to zero since the feed material is usually sterile. Meanwhile, the rate of biomass death is assumed to be negligible compared to growth so that $k_d << \mu$. Then Equation (2.9) becomes:

$$\frac{dX}{dt} = \mu X - \frac{X}{V}\frac{dV}{dt} \tag{2.10}$$

The specific growth rate μ can be described by Monod model as presented below, where the microorganisms' growth rate depends on the concentration of limiting nutrient (Bailey and Ollis, 1986).

$$\mu = \mu_X \frac{S}{(K_X + S)} \tag{2.11}$$

μ_X represents the maximum specific growth rate, and K_X is the substrate saturation constant. However, the Monod model is often not possible to describe the growth. It is only valid for balanced growth and should not be applied when growth conditions are changing rapidly. Therefore numerous modifications were made to Equation (2.11) to reduce the deviations of Monod model and measurements. One of the deviation forms of Equation (2.11) is Contois kinetics shown as Equation (2.12), which is used to represent the diffusion limitations that occur at high biomass concentrations.

$$\mu = \mu_X \frac{S}{(K_X X + S)} \tag{2.12}$$

In the Bajpai and Reuss model (1980), dissolved oxygen concentration C_L and oxygen limitation constant K_{OX} are included in Equation (2.12).

$$\mu = \mu_X \frac{S}{(K_X X + S)} \frac{C_L}{(K_{OX} X + C_L)} \tag{2.13}$$

According to Birol *et al*. (2002), effects of environmental variables such as pH and temperature should also be taken into account in the specific growth expression. These variables play an important role on the quality and quantity of the final product. By taking these variables into consideration, the specific growth rate can be expressed as:

$$\mu = \left[\frac{\mu_X}{1+\left[K_1/[H^+]\right]+\left[[H^+]/K_2\right]}\right]\frac{S}{(K_X X + S)}\frac{C_L}{(K_{OX} X + C_L)} \left\{\left[k_g \exp\left(-\frac{E_g}{RT}\right)\right]-\left[k_d \exp\left(-\frac{E_d}{RT}\right)\right]\right\} \quad (2.14)$$

2.4.2.1 Effect of Ph

The additional term in the specific growth rate expression Equation (2.14) is a typical inhibition term, which includes hydrogen ion concentration $[H^+]$ (Birol *et al.*, 2002).

$$\mu = f\left[\frac{\mu_X}{1+\left[K_1/[H^+]\right]+\left[[H^+]/K_2\right]}\right] \quad (2.15)$$

Here, the values of K_1 and K_2 are chosen to be in the range of their typical values in the literature (Nielsen and Villadsen, 1994). Since the pH of the culture medium tends to become acidic, as the concentration of biomass increases; the amount of NH_4OH added into the culture medium also increases, in order to keep the pH constant during the penicillin fermentation. Based on this observation, the hydrogen ion concentration is related to biomass formation as:

$$\frac{d[H^+]}{dt} = \gamma\left(\mu X - \frac{FX}{V}\right)+\left[\frac{-B+\sqrt{\left(B^2+4\times10^{-14}\right)}}{2}-[H^+]\right]\frac{1}{\Delta t} \quad (2.16)$$

Where B is given as:

$$B = \frac{\left[10^{-14}/[H^+] - [H^+]\right]V - C_{a/b}(F_a + F_b)\Delta t}{V + (F_a + F_b)\Delta t} \quad (2.17)$$

Here, F_a and F_b represent acid and base flow rates in l/h, respectively, where the concentration in both solutions, $C_{a/b}$ are equal to be 3 M (Birol *et al.*, 2002). Besides that, Birol *et al.* (2002) also suggested that under pH control, the hydrogen ion concentration can be calculated by taking the disassociation of water and acid/base into account as well as the hydrogen production. The proportionality constant, γ is estimated as 10^{-5} mol $[H^+]$/g biomass.

2.4.2.2 Effect of Temperature

Temperature causes positive changes on the specific growth rate of a microorganism. An increase in temperature up to a certain value might cause a rapid decrease in biomass concentration. Here, the effect of temperature on the specific growth rate is given by Birol *et al.* (2002) as an Arrhenius type of kinetics:

$$\mu = f\left\{\left[k_g \exp\left(-\frac{E_g}{RT}\right)\right] - \left[k_d \exp\left(-\frac{E_d}{RT}\right)\right]\right\} \quad (2.18)$$

Here, k_g and E_g are the constant and activation energy for growth, while k_d and E_d are the constant and activation energy for death, respectively. The gas constant, R is 1.987 cal/(mol.K).

2.4.3 Mass Balance on Penicillin

For fed-batch operation, F_{out} is equal to zero; penicillin concentration, $P_{in} = 0$ as there is no penicillin in the inlet flow to the fermenter. The mass of penicillin is equal to PV where P is the penicillin concentration and V is the culture volume, the mass generation term in Equation (2.1) can be described as $\mu_{PP}XV$ where the μ_{PP} is the specific penicillin production rate, and the KVP is the hydrolysis rate of penicillin where the K is the penicillin hydrolysis constant. Substituting these terms into Equation (2.1) gives:

$$\frac{d(PV)}{dt} = \mu_{PP} XV - KPV \tag{2.19}$$

Expanding the differential and rearranging Equation (2.19) gives:

$$\frac{dP}{dt} = \mu_{PP} X - KP - \frac{P}{V}\frac{dV}{dt} \tag{2.20}$$

The specific penicillin production rate, μ_{PP} can be defined as (Birol *et al.*, 2002):

$$\mu_{PP} = \mu_P \frac{S}{\left(K_P + S + S^2 / K_I\right)} \frac{C_L^{\ P}}{(K_{OP} X + C_L^{\ P})} \tag{2.21}$$

Here μ_P is the maximum specific penicillin production rate, K_P is the inhibition constant, K_I is the inhibition constant for product formation, K_{OP} is the oxygen limitation constant, and $C_L^{\ P}$ is the dissolved oxygen concentration.

2.4.4 Mass Balance on Substrate

Cells (biomass) consume substrate from external environment for growth and product synthesis requirements. The mass balance for the substrate can be represented by the following equation:

$$\frac{d(SV)}{dt} = Fs_f - q_s XV \tag{2.22}$$

Here, SV is the mass of substrate in the fermenter where S is the substrate concentration and V is the culture volume, F is the feed flow rate of substrate, s_f is the feed substrate concentration, q_s is the specific rate of substrate uptake, and X is the biomass concentration. By expanding the differential terms and some arrangements, Equation (2.22) can be rewritten as:

$$\frac{dS}{dt} = -q_s X + \frac{F}{V} s_f - \frac{S}{V}\frac{dV}{dt} \tag{2.23}$$

Patterns of substrate flow in cells synthesizing products depend on whether the product formation is directly linked to energy metabolism. When products are formed in energy-generating pathways such as in anaerobic culture, equation for rate of substrate consumption does not include a separate term for production; substrate requirements for product formation are already taken into account in terms of growth and maintenance-associated substrate uptake. In culture where product synthesis is only indirectly coupled to energy metabolism, rate of substrate consumption is a function of three factors: growth rate, product formation rate and substrate uptake rate for maintenance (Bailey and Ollis, 1986).

According to Bailey and Ollis (1986), a complete account of substrate uptake should include a maintenance component. Examples of maintenance functions are cell mobility, turnover of cellular components, and adjustment of membrane potential and internal pH. The specific rate of substrate uptake for maintenance activities is known as the maintenance coefficient, m_X. Incorporating this term into

the computation of the specific rate of substrate uptake q_s yields the following relationships:

$$-q_s = -\frac{\mu}{Y_{X/S}} - \frac{\mu_{PP}}{Y_{P/S}} - m_X \tag{2.24}$$

Substituting Equation (2.24) into Equation (2.23) yields:

$$\frac{dS}{dt} = -\frac{\mu}{Y_{X/S}} X - \frac{\mu_{PP}}{Y_{P/S}} X - m_X X + \frac{Fs_f}{V} - \frac{S}{V}\frac{dV}{dt} \tag{2.25}$$

$Y_{X/S}$ is the yield coefficient (g biomass/g substrate), $Y_{P/S}$ is the yield coefficient (g penicillin/g substrate), μ is the specific growth rate of biomass, μ_{PP} is the specific production rate of penicillin, and m_X is the maintenance coefficient.

2.4.5 Mass Balance on Dissolved Oxygen

In aerobic culture, cells take up oxygen from the liquid. The rate at which cells in a fermenter consume oxygen determines the rate at which it must be transferred from gas (bubbles) to liquid (culture broth). Among the most important factors that influence the oxygen demand are cell species, culture growth phase, and nature of the carbon source in the medium. In batch culture, rate of oxygen uptake per volume of broth, Q_o, varies with time. The reasons are: first, the concentration of cells increases during the course of batch culture and the total rate of oxygen uptake is proportional to the number of cells present. Secondly, the rate of oxygen consumption per cell, which is known as specific oxygen uptake rate, q_o also varies. The relationships between Q_o and q_o can be expressed as:

$$Q_o = q_o .X \tag{2.26}$$

The rate of oxygen transfer from the bubble to the cell is dominated by the rate of oxygen diffusing through the relatively stagnant liquid film surrounding the bubbles. The liquid film around the bubbles is regarded as a major resistance to oxygen transfer. In other words, the liquid-phase mass-transfer resistance dominates for cases involving solute that is poorly soluble in the liquid such as in the case of oxygen. The rate of change in dissolved-oxygen concentration C_L during fermentation is equal to the rate of oxygen transfer from gas to liquid, minus the rate of oxygen uptake by the cells, q_oXV as shown in Equation (2.27).

$$\frac{d(C_L V)}{dt} = k_L A\left(C_L^{\,*} - C_L\right) - q_o XV \tag{2.27}$$

Here, C_LV is the mass of oxygen in fermenter where C_L is the concentration of dissolved-oxygen and V is the culture volume, k_L is a transfer coefficient, and A is the transfer area over which transport occurs. The difference ($C_L^{\,*}$ - C_L) between the maximum possible and actual oxygen concentrations in the liquid culture represents the concentration-difference driving force for mass transfer. Equation (2.27) can then be simplified to:

$$\frac{dC_L}{dt} = k_L \frac{A}{V}\left(C_L^{\,*} - C_L\right) - q_o X - \frac{C_L}{V}\frac{dV}{dt} \tag{2.28}$$

The (k_LA/V) term can be represented by overall mass transfer coefficient K_{la}. By taking account for the effect of specific growth rate μ, specific production rate of penicillin μ_{PP}, and maintenance factor m_o in specific oxygen uptake rate q_o, Equation (2.28) can be written in the form:

$$\frac{dC_L}{dt} = K_{la}\left(C_L^{\,*} - C_L\right) - \left(\frac{\mu}{Y_{X/O}} + \frac{\mu_{PP}}{Y_{P/O}} + m_o\right)X - \frac{C_L}{V}\frac{dV}{dt} \tag{2.29}$$

Equation (2.29) is then rearranged to give:

$$\frac{dC_L}{dt} = -\frac{\mu}{Y_{X/O}} X - \frac{\mu_{PP}}{Y_{P/O}} X - m_o X + K_{la}\left(C_L{}^* - C_L\right) - \frac{C_L}{V}\frac{dV}{dt} \tag{2.30}$$

Where $Y_{X/O}$ is the yield constant with unit (g biomass/g oxygen), and $Y_{P/O}$ is the yield constant with unit (g penicillin/g oxygen). The overall mass transfer coefficient K_{la} is constant in the original model of Bajpai and Reuss. However, in this work, K_{la} is assumed to be a function of agitation power input P_w and flow rate of oxygen f_g as suggested by Birol *et al.* (2002). This is represented by Equation (2.31). Here, the values of α and β are constant for K_{la} so that the dependence of penicillin concentration on K_{la} showed a very similar behavior to the predictions of Bajpai and Reuss (Birol *et al.*, 2002).

$$K_{la} = \alpha\sqrt{f_g}\left(\frac{P_w}{V}\right)^{\beta} \tag{2.31}$$

2.4.6 Mass Balance on Carbon Dioxide (CO_2)

CO_2 evolution is assumed to be due to growth, penicillin biosynthesis and maintenance requirements. This can be expressed as:

$$\frac{dC_{co_2}}{dt} = \alpha_1 \frac{dX}{dt} + \alpha_2 X + \alpha_3 \tag{2.32}$$

Here, C_{CO_2} is carbon dioxide concentration, α_1 is the constant relating CO_2 to growth, α_2 is the constant relating CO_2 to maintenance energy, and α_3 is the constant relating CO_2 to penicillin production. The values of α_1, α_2 and α_3 are chosen to give CO_2 profiles similar to the prediction of Montague *et al.* work (Birol *et al.*, 2002).

2.4.7 Energy Balance

Based on conservation of energy principles, the overall energy balance equation can be written as:

$$\begin{bmatrix}\text{Rate}\\ \text{of}\\ \text{energy}\\ \text{accumulated}\end{bmatrix} = \begin{bmatrix}\text{Rate of}\\ \text{energy}\\ \text{in}\\ \text{by flow}\end{bmatrix} - \begin{bmatrix}\text{Rate of}\\ \text{energy}\\ \text{out}\\ \text{by flow}\end{bmatrix} - \begin{bmatrix}\text{Rate of}\\ \text{energy}\\ \text{consumed}\\ \text{in the system}\end{bmatrix} + \begin{bmatrix}\text{Rate of}\\ \text{energy}\\ \text{generated}\\ \text{in the system}\end{bmatrix} \quad (2.33)$$

For a fermenter during normal operation, Equation (2.33) can be simplified as Equation (2.34):

$$Q_{acc} = Q_{rxn} + Q_{ag} + Q_{gas} - Q_{exch} - Q_{sen} \quad (2.34)$$

Here Q_{acc} is the heat accumulation rate by the system, Q_{rxn} is the heat generation due to microbial metabolism, Q_{ag} is the heat generation due to mechanical agitation, Q_{gas} is the heat generation due to aeration power input, Q_{exch} is the heat generation due to the surroundings and/or heat exchanger and Q_{sen} is the rate of sensible enthalpy gain by the flow system streams (exit – inlet). In typical fermentation process, changes in heats of mixing of substrate and products with the broth are generally negligible since cell-culture media are usually dilute aqueous solutions with behavior close to ideal. The effect of heat generation due to mechanical agitation Q_{ag} and aeration power input Q_{gas} are assumed to be negligible compared to the heat generation caused by microbial metabolism Q_{rxn} and heat exchanger Q_{exch}. Therefore, Equation (2.34) can be written as:

$$Q_{acc} = Q_{rxn} - Q_{exch} - Q_{sen} \quad (2.35)$$

2.4.7.1 Rate of Accumulation

The accumulation term Q_{acc} can be written as:

$$Q_{acc} = \frac{dE}{dt} = \frac{d}{dt}\left[\rho V c_p (\Delta T)\right] \tag{2.36}$$

E represents the energy accumulated in the system. ρ is the density of culture volume, V is the culture volume, c_p is the heat capacity and ΔT is the temperature difference between the temperature in the system and the reference temperature, ($T - T_{ref}$). By assuming ρ, c_p and T_{ref} are constant with respect to time, Equation (2.36) can now be expanded and then simplified to give:

$$Q_{acc} = \frac{dE}{dt} = \rho c_p \left[V \frac{dT}{dt} + \left(T - T_{ref}\right)\frac{dV}{dt} \right] \tag{2.37}$$

2.4.7.2 Sensible Heat

For fed-batch operation Q_{sen} can be represented by Equation (2.38) where M_i is the mass flows into the system, c_p is the heat capacity, T_f is the feed temperature of the substrate, and T_{ref} is the reference temperature.

$$Q_{sen} = -M_i c_p (T_f - T_{ref}) \tag{2.38}$$

Substituting Equation (2.37) and Equation (2.38) into Equation (2.35) yields:

$$\rho c_p \left[V \frac{dT}{dt} + \left(T - T_{ref}\right)\frac{dV}{dt} \right] = Q_{rxn} - Q_{exch} - \left[- M_i c_p \left(T_f - T_{ref}\right) \right] \tag{2.39}$$

M_i can be defined as ρF where ρ is the density of the inlet (mass) flow and F is feed flow rate of the substrate. Here, the density ρ is assumed to be a constant. Equation (2.39) is then rearranged to give:

$$\frac{dT}{dt} = \frac{F}{V}\left(T_f - T_{ref}\right) - \frac{1}{V}\left(T - T_{ref}\right)\frac{dV}{dt} + \frac{1}{V\rho c_p}\left(Q_{rxn} - Q_{exch}\right) \tag{2.40}$$

(dV/dt) is assumed to be equal to F since the effect of $F_{a/b}$ and F_{loss} on heat generation is assumed to be negligible. Then, Equation (2.40) can be simplified to:

$$\frac{dT}{dt} = \frac{F}{V}\left(T_f - T\right) + \frac{1}{V\rho c_p}\left(Q_{rxn} - Q_{exch}\right) \tag{2.41}$$

2.4.7.3 Heat Input/Loss from Heat Exchanger

The energy balance model of a coiled type heat exchanger, which is suitable for a laboratory scale fermenter is given as follows (Birol *et al.*, 2002):

$$Q_{exch} = \frac{aF_c^{b+1}}{F_c + \left(aF_c^b / 2\rho_c c_{pc}\right)} \tag{2.42}$$

By substituting Equation (2.42) into Equation (2.41) yields:

$$\frac{dT}{dt} = \frac{F}{s_f}\left(T_f - T\right) + \frac{1}{V\rho c_p}\left[Q_{rxn} - \frac{aF_c^{b+1}}{F_c + \left(aF_c^b / 2\rho_c c_{pc}\right)}\right] \tag{2.43}$$

T_f is the feed temperature of substrate, F is the feed flow rate of substrate, F_c is the flow rate of the cooling liquid, ρ is the density of the culture medium, ρ_c is the density of the cooling liquid, c_p and c_{pc} represent the heat capacity of the culture medium and the cooling liquid respectively, Q_{rxn} is the heat of reaction while a and b are constants. For this particular equation, the unit of F is g/ (liter.hr).

2.4.7.4 Heat of Reaction

Reactions in bioprocesses occur as a result of enzyme activity and cell metabolism. During reaction, bonds between atoms are rearranged. This results in relatively large changes in internal energy and enthalpy. Heat of reaction ΔH_{rxn} is defined as the energy released or absorbed during reaction, and is equal to the difference in enthalpy of reactants and products:

$$\Delta H_{rxn} = \sum_{products} Mh - \sum_{reac\ tan\ ts} Mh \tag{2.44}$$

M is mass, and h is specific enthalpy. For heat generation caused by microbial reactions/metabolism, Birol *et al.* (2002) has suggested the following equation:

$$\frac{dQ_{rxn}}{dt} = r_{q_1} \frac{dX}{dt} V + r_{q_2} XV$$

(2.45)

(dQ_{rxn}/dt) is the volumetric heat production rate, r_{q1} is assumed to be constant and might be treated as a yield coefficient, and r_{q2} is a constant for heat production during maintenance. The second term in Equation (2.45) is important to consider since metabolic maintenance activities give a significant effect on the heat generation. According to Birol *et al.* (2002), the heat generation and CO_2 evolution show similar profiles. So, their production rate due to growth (dX/dt) and biomass (X) should have the same ratio as a first approximation. This observation has enabled the value of r_{q2} to be calculated.

2.4.8 Penicillin Fed-batch Process Model Equation

By substituting all the components of the total overall and energy balance into Equation (2.1) and (2.33), mathematical models for the penicillin fed-batch process can be summarized as:

$$\frac{dV}{dt} = F + F_{a/b} - F_{loss} \tag{2.46}$$

$$\frac{dX}{dt} = \mu X - \frac{X}{V}\frac{dV}{dt} \tag{2.47}$$

$$\frac{d[H^+]}{dt} = \gamma\left(\mu X - \frac{FX}{V}\right) + \left[\frac{-B + \sqrt{\left(B^2 + 4\times 10^{-14}\right)}}{2} - [H^+]\right]\frac{1}{\Delta t} \tag{2.48}$$

$$\frac{dP}{dt} = \mu_{PP} X - KP - \frac{P}{V}\frac{dV}{dt} \tag{2.49}$$

$$\frac{dS}{dt} = -\frac{\mu}{Y_{X/S}} X - \frac{\mu_{PP}}{Y_{P/S}} X - m_X X + \frac{Fs_f}{V} - \frac{S}{V}\frac{dV}{dt} \tag{2.50}$$

$$\frac{dC_L}{dt} = -\frac{\mu}{Y_{X/O}} X - \frac{\mu_{PP}}{Y_{P/O}} X - m_o X + K_{la}\left(C_L^{\ *} - C_L\right) - \frac{C_L}{V}\frac{dV}{dt} \tag{2.51}$$

$$\frac{dC_{co_2}}{dt} = \alpha_1 \frac{dX}{dt} + \alpha_2 X + \alpha_3 \tag{2.52}$$

$$\frac{dT}{dt} = \frac{F}{s_f}\left(T_f - T\right) + \frac{1}{V\rho c_p}\left[Q_{rxn} - \frac{aF_c^{b+1}}{F_c + \left(aF_c^b / 2\rho_c c_{pc}\right)}\right] \tag{2.53}$$

$$\frac{dQ_{rxn}}{dt} = r_{q_1}\frac{dX}{dt} V + r_{q_2} XV \tag{2.54}$$

$$F_{loss} = \mathrm{V}.\lambda(\mathrm{e}^{5((\mathrm{T\text{-}To})/\mathrm{Tv\text{-}To})} - 1) \tag{2.55}$$

$$\mu = \left[\frac{\mu_X}{1+\left[K_1/[H^+]\right]+\left[[H^+]/K_2\right]}\right]\frac{S}{(K_X X + S)}\frac{C_L}{(K_{OX} X + C_L)}$$
$$\left\{\left[k_g \exp\left(-\frac{E_g}{RT}\right)\right]-\left[k_d \exp\left(-\frac{E_d}{RT}\right)\right]\right\}$$

(2.56)

$$B = \frac{\left[10^{-14}/[H^+]-[H^+]\right]V - C_{a/b}(F_a + F_b)\Delta t}{V + (F_a + F_b)\Delta t} \tag{2.57}$$

$$\mu_{PP} = \mu_P \frac{S}{\left(K_P + S + S^2/K_I\right)}\frac{C_L{}^P}{(K_{OP} X + C_L{}^P)} \tag{2.58}$$

$$K_{la} = \alpha\sqrt{f_g}\left(\frac{P_w}{V}\right)^{\beta} \tag{2.59}$$

2.5 Model Predictive Control

MPC is widely adopted in industry as an effective means to deal with large multivariable constrained control problems. Model predictive control (MPC) has become a major research topic during the last few decades and unlike many other advanced techniques, it has also been successfully applied in industry. It is generally accepted that the reason for this success is the ability of MPC to optimally control multivariable system under various constraints. MPC is a method in which the current control action is obtained online by solving a finite horizon open-loop optimal control problem from the current system state or from its estimate based on output measurements.

MPC is a model-based control algorithm, where models of the process are derived from process testing where key MVs are perturbed to generate step response trends for the CVs. For an MPC system to function properly, it is imperative that controller models are representative of the process, and plant-model mismatch is minimal. To develop an effective MPC condition monitor, the process operating point should not be significantly different from that at the time when the MPC models were developed. MPC was chosen as it able to offer several important advantages toward the fed batch penicillin fermentation process such as:

a) The process model captures the dynamic and static interactions between input, output, and disturbance variables of the process
b) Disturbance on input and output are considered in a systematic manner
c) The control calculations can be coordinated with the calculation of optimum set points
d) Accurate model predictions can provide early warning of potential problems.

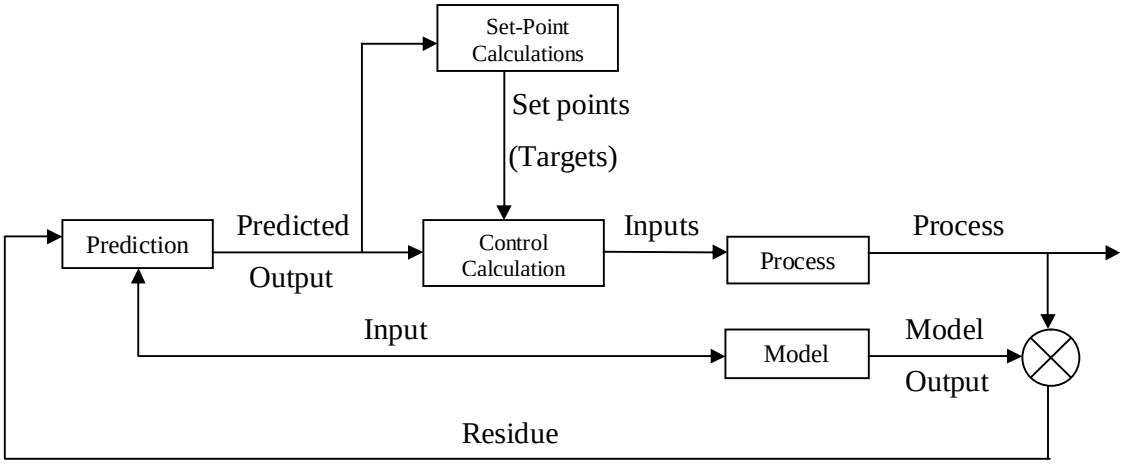

Figure 2.3: Block Diagram for MPC (Qin and Badwell, 2003)

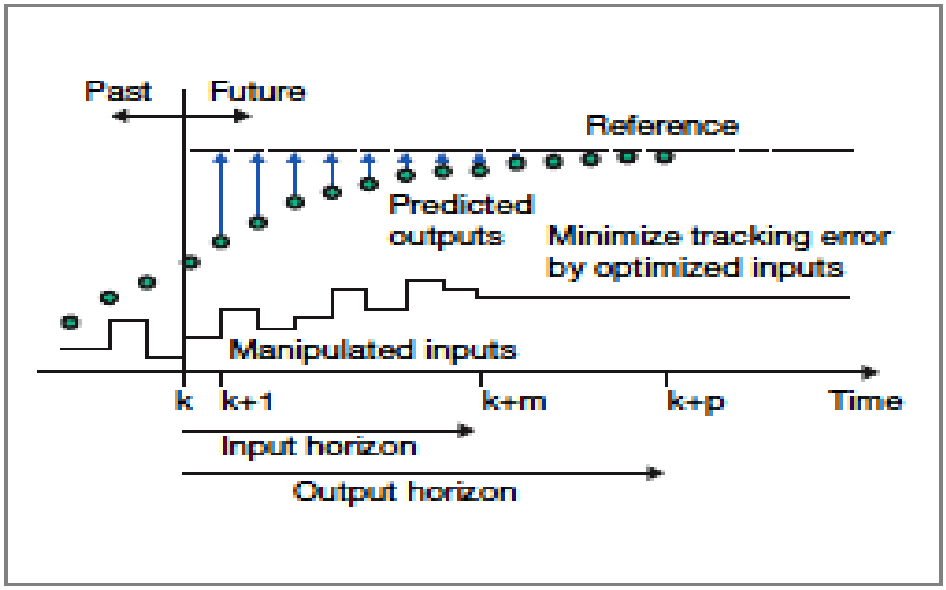

Figure 2.4: MPC Algorithm Schematic (Qin and Badwell, 2003)

2.5.1 Model Predictive Control Calculation

The flowchart in Figure 2.3 provides an overview of the MPC calculation. The steps are shown in the order they are performed at each execution time. For simplicity, the control execution time is assumed coincide with the measurement sampling instants. In MPC applications, the calculated input moves are usually implemented as set points for regulatory control loops has been disabled or placed in manual, the input variable is no longer available for control. In this situation, the control degree freedoms are reduced by one. Even though an input variable is unavailable for control, it can serve as disturbance variable if it is still measured.

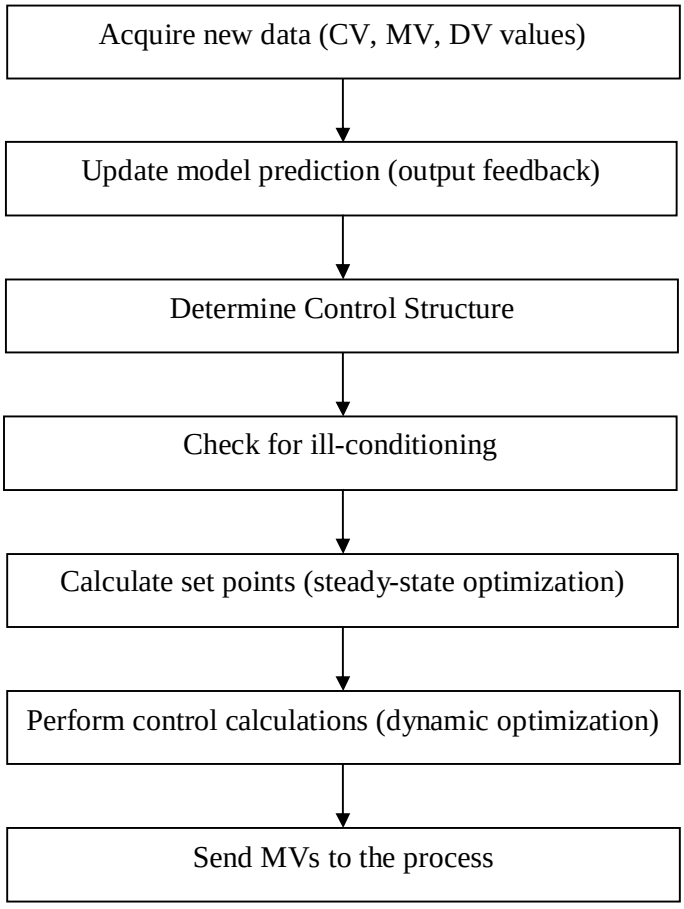

Figure 2.5: Flow chart for MPC calculation (modified form Qin and Badwell 2003)

2.5.2 Dynamic Matrix Control (DMC)

Dynamic matrix control (DMC) is the most popular MPC algorithm used in the chemical process today (Dougherty and Cooper,2001) . In this research, we want to implement this type of MPC algorithm. Cutler and Ramaker presented details of an unconstrained multivariable control algorithm which they named dynamic matrix control (DMC) at the 1979 National AIChE meeting (Cutler & Ramaker, 1980). Key features of the DMC control algorithm is:

1. linear step response model for the plant;
2. quadratic performance objective over a finite prediction horizon;
3. future plant output behavior specified by trying to follow the setpoint as closely as possible;
4. Optimal inputs computed as the solution to a least squares problem.

The linear step response model used by the DMC algorithm relates changes in a process output to a weighted sum of past input changes, referred to as input moves. For the SISO case the step response model looks like:

$$y_{k+j} = \sum_{i=1}^{n-1} s_i \Delta u_{k+j-i} + s_N u_{k+j-N} \tag{2.18}$$

The move weights s_i are the step response coefficients. Mathematically the step response can be defined as the integral of the impulse response; given one model form the other can be easily obtained. Multiple outputs were handled by superposition. By using the step response model one can write predicted future output changes as a linear combination of future input moves. The matrix that ties the two together is the so-called Dynamic Matrix. Using this representation allows the optimal move vector to be computed analytically as the solution to a least-squares problem. Feed forward control is readily included in this formulation by modifying the predicted future outputs. In practice the required matrix inverse can be computed off-line to save computation. Only the first row of the final controller gain matrix needs to be stored because only the first move needs to be computed.

Basically, DMC uses a linear finite step response model of the model of the process to predict the process variable profile, $\hat{y}(n+j)$ over j sampling instant ahead of the current time, n:

$$\hat{y}(n+j) = \underbrace{y_0 + \sum_{i=1}^{j} a_i \Delta u(n+j-i)}_{Effect\_of\_current\_and\_future\_moves} + \underbrace{\sum_{i=j+1}^{N-1} a_i \Delta u(n++j-i)}_{Effect\_of\_past\_moves} \qquad (2.19)$$

In Eq. (2.19), y_0 is the initial condition of the process variable, $\Delta u_i = u_i - u_{i-1}$ is the change in the controller output at the *i*th sampling instant, a_i is the *i*th unit step response coefficient of the process, and N is the model horizon and represents the number of sampling intervals of past controller output moves used by DMC to predict the future process variable profile. The current and future controller output moves have not been determined and cannot be used in the computation of the predicted process variable profile.

Therefore, Eq. (2.19) reduces to

$$\hat{y}(n+j) = y_0 + \sum_{i=j+1}^{N-1} (a_i \Delta u(n+j-i)) + d(n+j) \qquad (2.20)$$

where the term d (n+ j) combines the unmeasured disturbances and the inaccuracies due to plant-model mismatch. Since future values of the disturbances are not available, d(n+j) over future sampling instants is assumed to be equal to the current value of the disturbance, or

$$d(n+j) = d(n) = y(n) - y_0 - \sum_{i=1}^{N-1} (a_i \Delta u(n-i)) \qquad (2.21)$$

where y(n)is the current process variable measurement

The goal is to compute a series of controller output moves such that

$$y_{sp}(n+j) - \hat{y}(n+j) = 0 \qquad j = 1,2,.....,P, \qquad (2.22)$$

where P is the prediction horizon and represents the number of sampling intervals into the future over which DMC predicts the future process variable. Substituting Eq. (2.19) in Eq. (2.22) gives

$$\underbrace{y_{sp}(n+j) - y_0 - \sum_{i=j+1}^{N-1} a_i \Delta u(n+j-1) - d(n)}_{\text{Predicted error based on pased moves}} = e \quad \underbrace{\sum_{i=1}^{j} a_i \Delta u(n+j-i)\text{u}}_{\text{Effect of current and future move to be deterimined}} \tag{2.23}$$

J=1, 2, 3….. P.

Eq. (2.23) is a system of linear equations that can be represented as a matrix equation of the form

$$\begin{bmatrix} e(n+1) \\ e(n+2) \\ e(n+3) \\ : \\ e(n+N) \\ : \\ e(n+P) \end{bmatrix} = \begin{bmatrix} a_1 00.....0 \\ a_2 a_1 0.....0 \\ : \\ a_M a_{M-1} a_{M-2} .....a_1 \\ : \\ a_P a_{P-1} a_{P-2} ....a_{P-M+1} \end{bmatrix} \text{X} \begin{bmatrix} \Delta u(n) \\ \Delta u(n+1) \\ \Delta u(n+2) \\ \\ \Delta u(n+M-1) \end{bmatrix} \tag{2.24}$$

P x 1 P x M M x 1

or in a compact matrix notation as

$$\bar{e} = A\Delta\bar{u}, \tag{2.25}$$

where $\bar{e}$ is the vector of predicted errors over the next P sampling instants, A is the dynamic matrix, and $\Delta\bar{u}$ is the vector of controller output moves to be determined.

An exact solution to Eq. (2.25) is not possible since the number of equations exceeds the degrees of freedom (P > M). Hence, the control objective is posed as a least squares optimization problem with a quadratic performance objective function of the form.

The objective of a DMC controller is to drive the output as close to the set point as possible in a least squares sense with a penalty term on the MV moves. This result in smaller computed input moves and a less aggressive output response. As with the IDCOM reference trajectory, this technique provides a degree of robustness to model error. Move suppression factors also provide an important numerical benefit in that they can be used to directly improve the conditioning of the numerical solution.

$$\underset{\Delta \bar{u}}{Min}\ J = [\bar{e} - A\Delta \bar{u}]^T [\bar{e} - A\Delta \bar{u}] \tag{2.26}$$

In the unconstrained case, this minimization problem has a closed form solution, which represents he DMC control law:

$$\Delta \bar{u} = (A^T A + \lambda I)^{-1} A^T \bar{e} \tag{2.27}$$

Implementation of DMC with the control law in Eq. (2.27) results in excessive control action, especially when the control horizon is greater than one. Therefore, a quadratic penalty on the size of controller output moves is introduced into the DMC performance objective function. The modified objective function has the form

$$\underset{\Delta \bar{u}}{Min}\ J = [\bar{e} - A\Delta \bar{u}]^T [\bar{e} - A\Delta \bar{u}] + [\Delta \bar{u}]^T \lambda [\Delta \bar{u}] \tag{2.28}$$

where λ is the move suppression coefficient. In the unconstrained case, the modified objective function has a closed form solution of (e.g., Marchetti, Mellichamp, & Seborg, 1983)

$$\Delta \bar{u} = (A^T A + \lambda I)^{-1} A^T \bar{e} \tag{2.29}$$

Adding constraints to the classical formulation given in Eq. (2.15) produces the quadratic dynamic matrix control (QDMC) (Morshedi et al., 1985; Garc!ıa & Morshedi, 1985) algorithm.

CHAPTER 3

DATA GENERATION AND DYNAMIC RESPONSE

3.1 Introduction

In this research work, Model Predictive Controller is used to substitute Proportional Integral Derivatives (PID) controller in order to obtain a product optimization. In this chapter, we will be focusing on data generation and dynamic response where the sensitivity analysis for the process has been done to study the effect of the set point changed and disturbance rejection. The set point for biomass concentration and penicillin concentration has been changed in order to analyse the effect of the changes.

3.2 Data Generation

Data generation is obtained using PENSIM software which is the web base programme for dynamic simulation of fed batch penicillin production. The equation (2.46) – (2.54) which shown in Chapter 2 representing the mathematical model of the penicillin fermentation are solved simultaneously using software written within Matlab programming environment. The ordinary differential equations were solved using Fourth-Order Runge-Kutta algorithm with adaptive step size mechanism available in Matlab toolbox software. Sampling interval was fixed at 0.5hour. The work of Birol *et al.* (2002) was regarded as the benchmark for the simulation study

and as such, the kinetic parameters as well as the initial values were based on their work. These are tabulated in Table 3.1.

Table 3.1: Kinetic parameters for nominal condition

Parameters	Symbols	Value
Heat transfer coefficient of heating/cooling liquid (cal/h.°C)	a	1000
Acid or base concentration (molar)	$C_{a/b}$	3
Dissolved oxygen concentration (= C_L^* at saturation) (g/l)	C_L	1.16
Carbon dioxide concentration (mmol/l)	CO_2	0.5
Heat capacity of medium (cal/g.°C)	c_p	1/1500
Heat capacity of cooling liquid (cal/g.°C)	c_{pc}	1/2000
Activation energy for cell death (cal/mol)	E_d	50000
Activation energy for growth (cal/mol)	E_g	5100
Oxygen flow rate (l/h)	f_g	8.6
Feed flow rate of substrate (l/h)	F	0.0426
Acid flow rate (ml/h)	F_a	0.01
Base flow rate (ml/h)	F_b	100
Cooling water flow rate (l/h)	F_c	0
Hydrogen ion concentration (mol/l)	$[H^+]$	$10^{-5.1}$
Arrhenius constant for cell death	k_d	10^{33}
Arrhenius constant for growth	k_g	7000
Penicillin hydrolysis rate constant (h^{-1})	K	0.04
Constant (mol/l)	K_1	10^{-10}
Constant (mol/l)	K_2	$7x10^{-5}$
Inhibition constant for product formation (g/l)	K_I	0.1
Oxygen limitation constant	K_{OP}	0
Oxygen limitation constant	K_{OX}	0
Inhibition constant (g/h)	K_P	0.0002
Maintenance coefficient on oxygen (h^{-1})	m_o	0.467
Maintenance coefficient on substrate (h^{-1})	m_X	0.014
Penicillin concentration (g/l)	P	0

Agitation power input	P_w	29.9
Yield of heat generation (cal/g biomass)	r_{q1}	60
Constant in heat generation (cal/g biomass.h)	r_{q2}	0.00017
Feed substrate concentration (g/l)	s_f	600
Substrate concentration (g/l)	S	15
Temperature (K)	T	298
Feed temperature of substrate (K)	T_f	296
Culture volume (l)	V	100
Biomass concentration (g/l)	X	0.1
Yield constant (g penicillin/g oxygen)	$Y_{P/O}$	0.2
Yield constant (g penicillin/g glucose)	$Y_{P/S}$	0.9
Yield constant (g biomass/g oxygen)	$Y_{X/O}$	0.04
Yield constant (g biomass/g glucose)	$Y_{X/S}$	0.45
Constant in K_{la}	α	70
Constant relating CO_2 to growth (mmol CO_2/g biomass)	α_1	0.143
Constant relating CO_2 to maintenance energy (mmol CO_2/g biomass.h)	α_2	$4x10^{-7}$
Constant relating CO_2 to penicillin production (mmol CO_2/l.h)	α_3	10^{-4}
Constant in K_{la}	B	0.4
Proportionality constant (mol $[H^+]$/g biomass)	γ	10^{-5}
Maximum specific growth rate (h^{-1})	μ_X	0.092
Specific rate of penicillin production (h^{-1})	μ_P	0.005
Constant in F_{loss} (h^{-1})	λ	0.00025

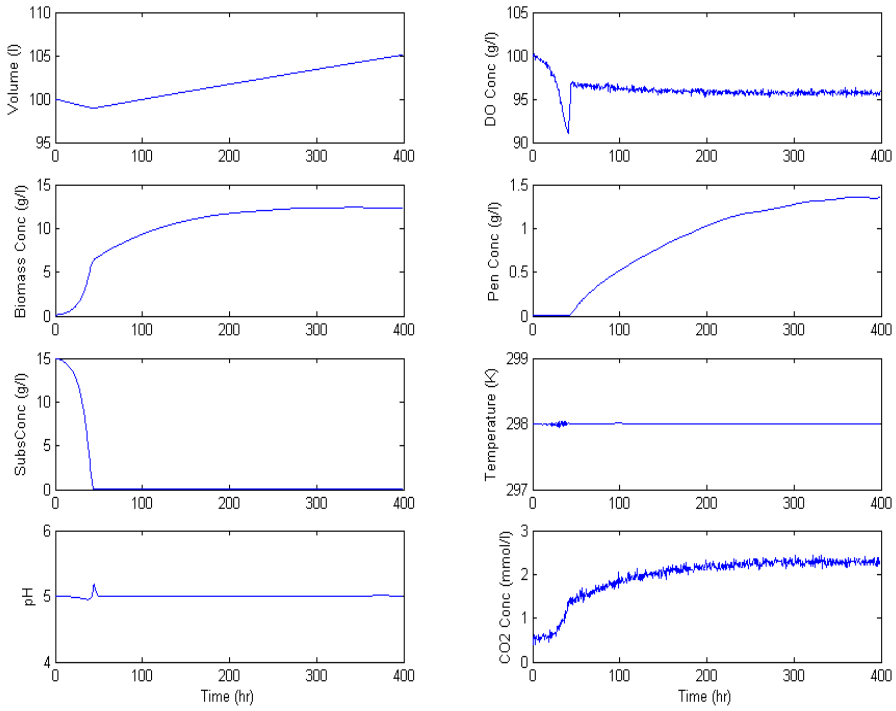

Figure 3.1: Dynamic simulations for penicillin fermentation process under nominal condition

3.3 Dynamic Response Analysis

A control system was necessary to control these values in order to improve the process quality. Before adding the MPC controllers into the system, dynamic response analysis was carried out to investigate the effects of some variables on the process. The dynamic response simulation was performed by manipulating input temperature values of ±5 % and ±10% from the initial condition which was illustrated in Figure 3.1. The simulation result shows that big fluctuation occurred in the eight output variables.

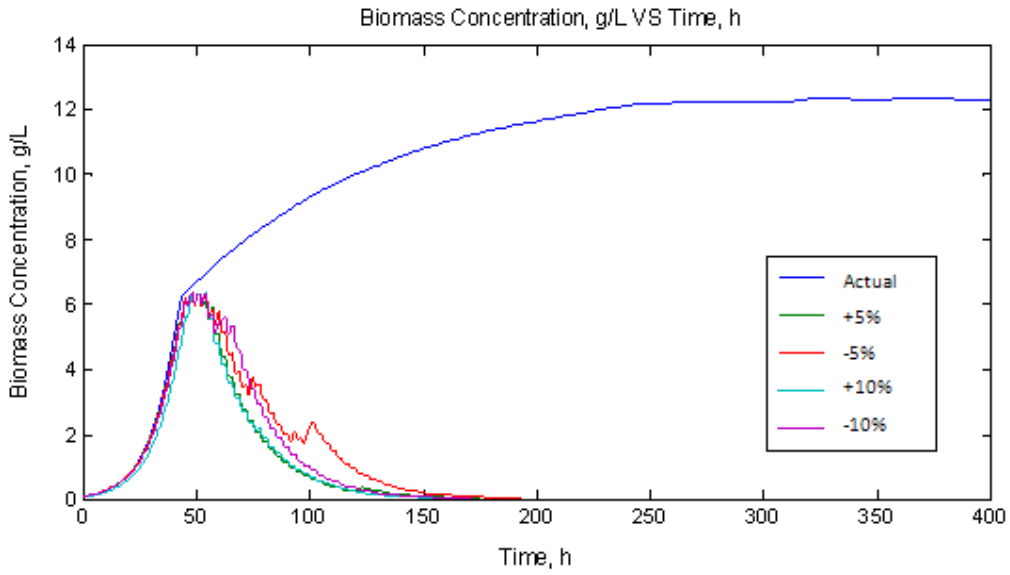

Figure 3.2: Dynamic response for biomass concentration, g/L

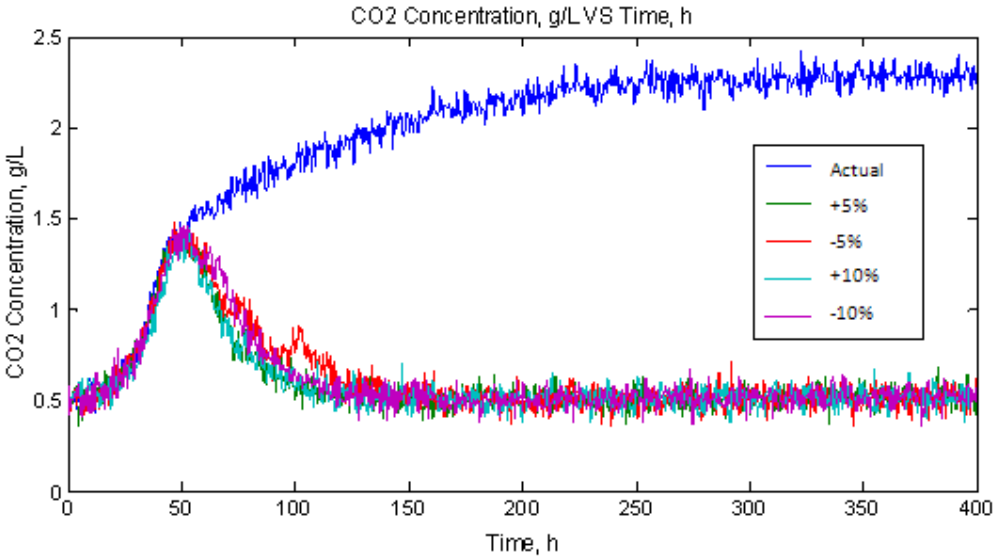

Figure 3.3: Dynamic response for carbon dioxide concentration, g/L

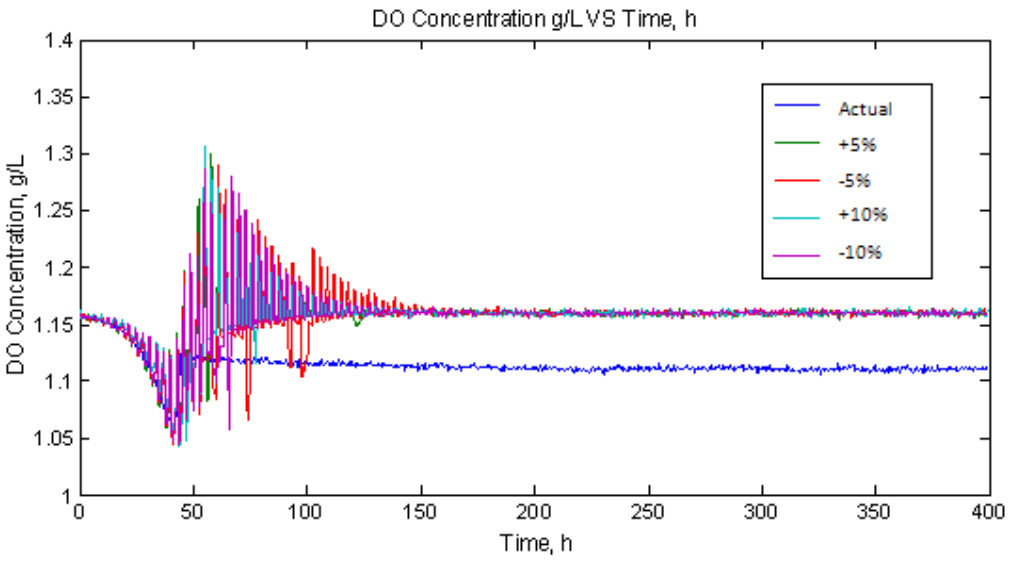

Figure 3.4: Dynamic response for dissolve oxygen concentration, g/L

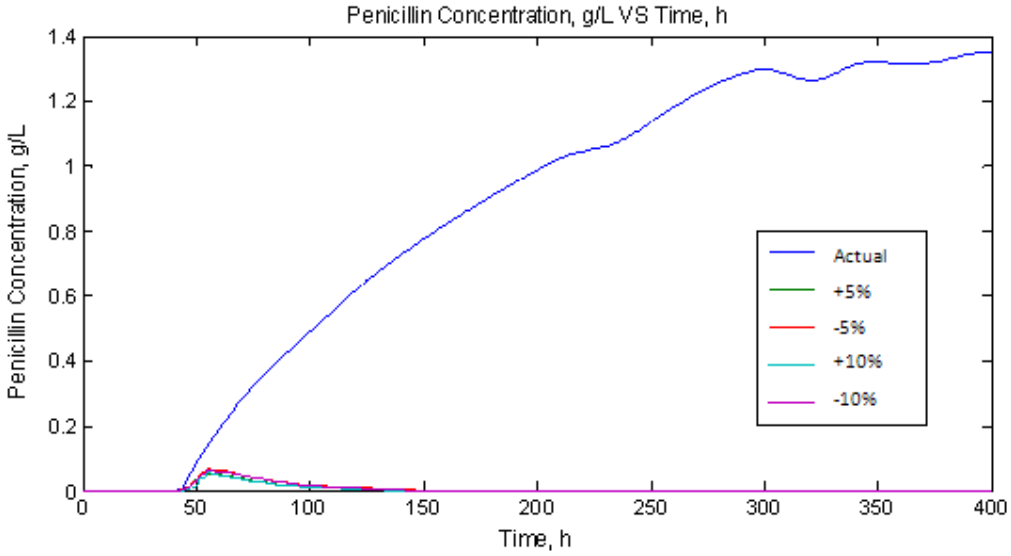

Figure 3.5: Dynamic response for penicillin concentration, g/L

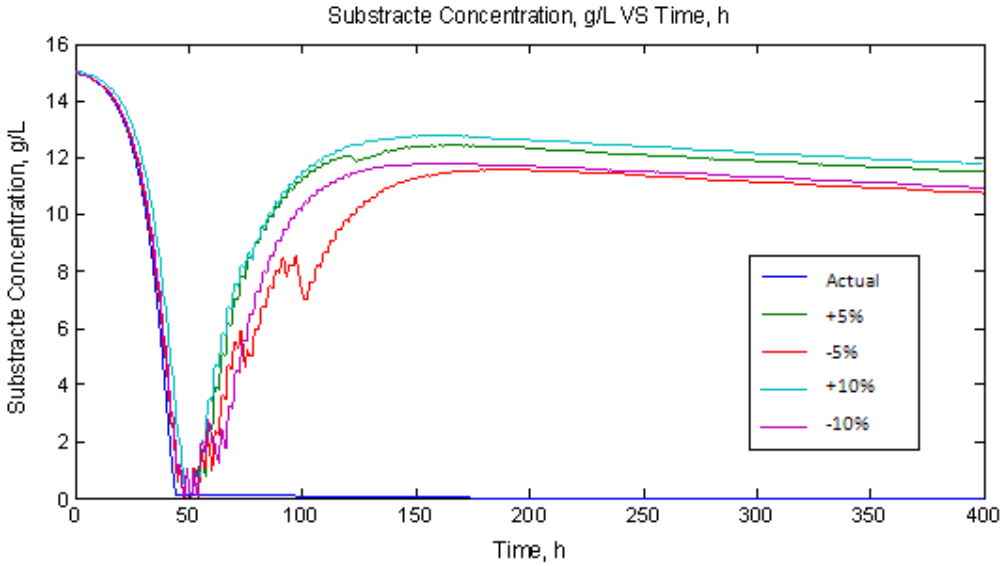

Figure 3.6: Dynamic response for substrate concentration, g/L

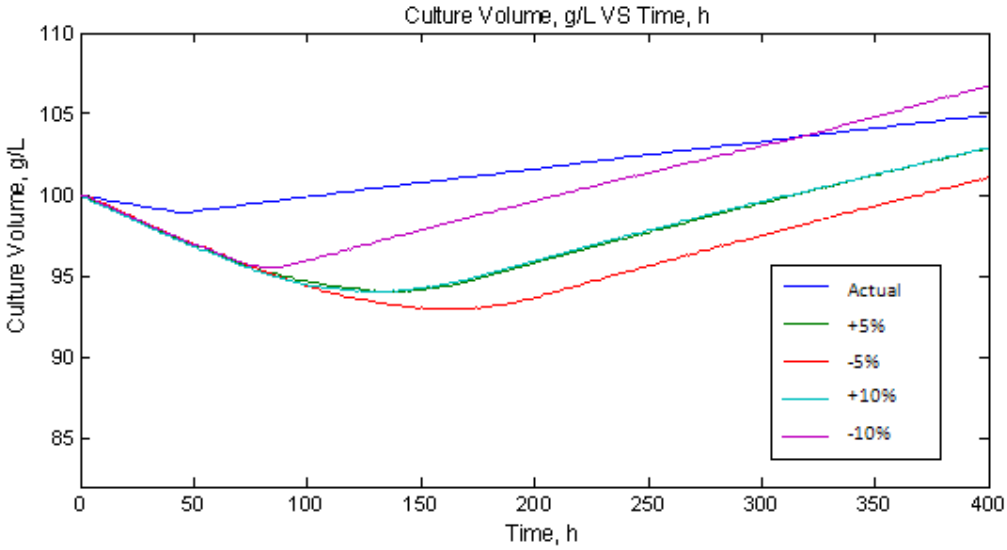

Figure 3.7: Dynamic response for culture volume, g/L

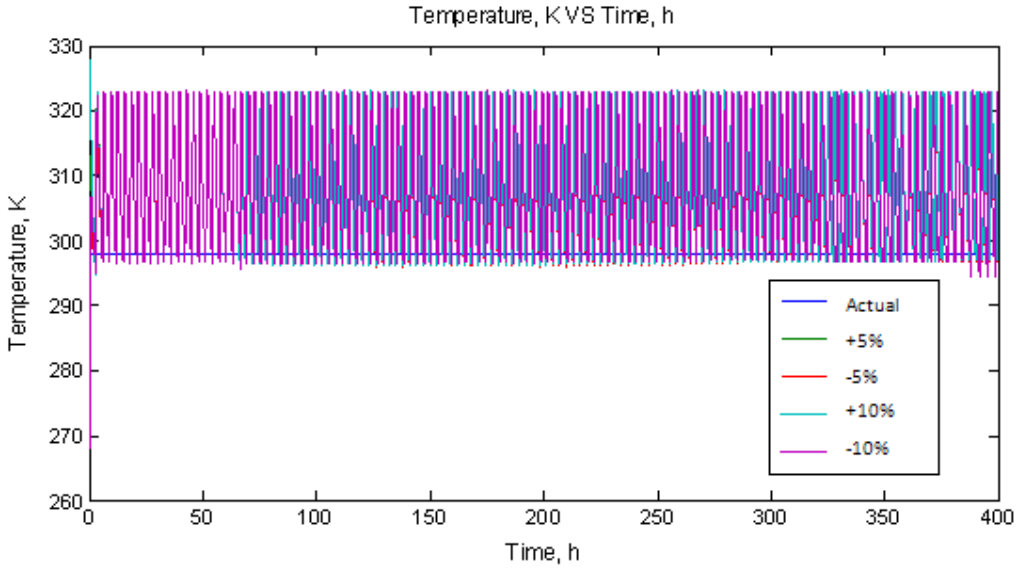

Figure 3.8: Dynamic response for temperature, K

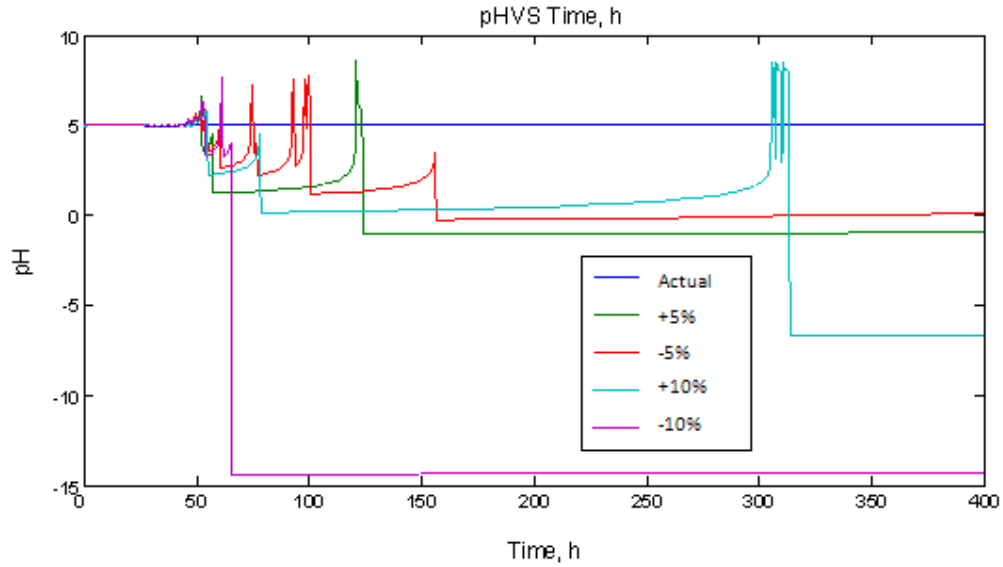

Figure 3.9: Dynamic response for pH

3.3.1 Discussion

As the input of the temperature was manipulated from 298K to 312.5K, the overall dynamic responses of the output variables which shown from Figure 3.2 until Figure 3.9 were undesirable due to the large deviation from the set point. This showed that a controller is needed in the process to cope with the changes of the input variable so that there the output variable will able to remain within the set point value. Among the eight output variables, 2 output variables which are the biomass concentration and penicillin concentration have been chosen to be applied in the MPC controller which enables the process variable to reach a set point by predicting future moves in a process using models of the controlled object's behaviour. Besides, the sensitivity studies to the process that involving the set point tracking and disturbance rejection will be done also.

CHAPTER 4

TRANSFER FUNCTION AND MPC IMPLEMENTATION

4.1 Introduction

Transfer function is an algebraic expression for the dynamic relation between a selected input and output of the process model. Many important characteristics of dynamic or control systems can be determined from the transfer function.

A transfer function can be derived only for a linear differential equation model because Laplace transforms can be applied only to linear equations. If the model is nonlinear, then it must be linearized first.

Next, model predictive control will be used to substitute the PID controller. The steps involved in the implementation of MPC can be summarized as follows (Qin and Badgwell, 2003);

1. Initial controller design
2. Pretest activity
3. Plant tests
4. Model development
5. Control system design and simulation

4.2 Transfer Function Development

The development of transfer function for the fed batch penicillin fermentation plays an important rule in this research as this transfer function will be use to apply in the MPC to obtain a desirable model in this process. The method to develop the transfer function is curve fitting step responses reference from R. Ramachandran *et al* (2005). The fed batch penicillin fermentation process is complete and non linear. In order to account for higher-order dynamics that is neglected in the first order model, a time delay is included. This modification can improve using First Order Plus Dead Time (FOPDT) which shown in Equation 4.1.

$$G(s) = \frac{Ke^{-\theta s}}{\tau s + 1} \qquad (4.1)$$

where , $\mathrm{K} = \mathrm{Gain} = \dfrac{\Delta \mathrm{y}}{\Delta \mathrm{x}} = \dfrac{\text{Output Changes}}{\text{Input Changes}}$

$\theta = \text{Dead time} = 1.3\mathrm{t}_1 - 0.29t_2$

$\tau = \text{Reset} = \text{Value of t which the response is 63.2\% complete}$

After considering the process, the temperature in the system will be taken as the input meanwhile the biomass concentration and the penicillin concentration will act as the output. Hence, the temperature inlet will be set to change in +5% from 298K to 312.9K. Figure 4.1, Figure 4.2 and Figure 4.3 below shows the result for the input and output changes.

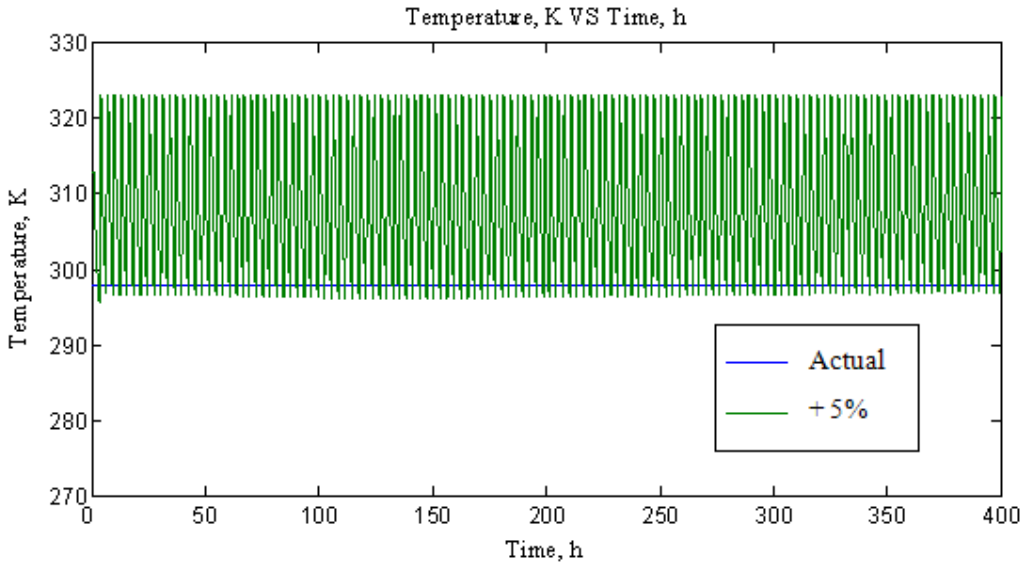

Figure 4.1: Input changes (Temperature, K, +5%)

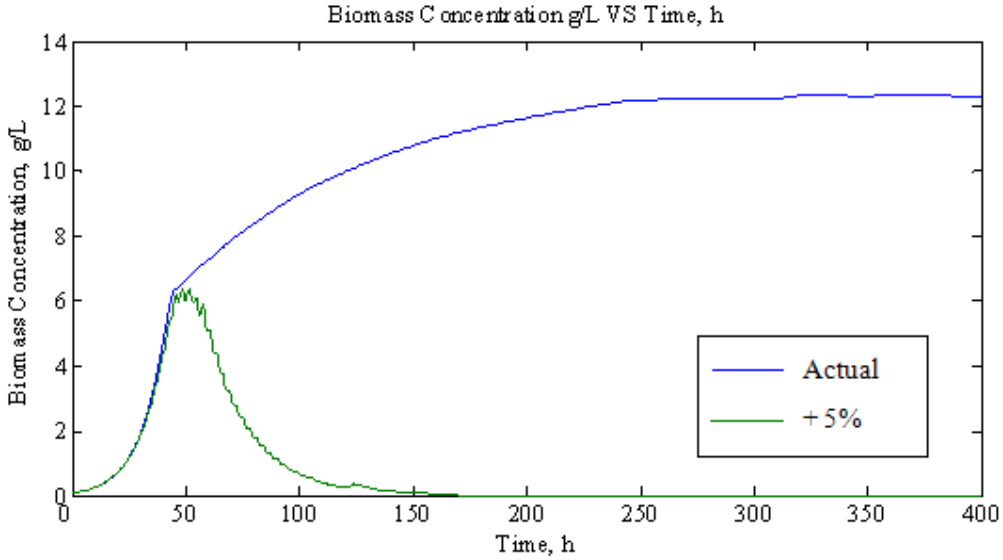

Figure 4.2: Output changes (Biomass Concentration, g/L, +5%)

For the vaporizer level,

$$K = \frac{\text{Output Changes}}{\text{Input Changes}} = \frac{6.326 - 0.1}{312.9 - 298} = 0.417$$

$\tau = 34.615$ min

$\theta = 15.385$ min

Hence, the transfer function is

$$G(s) = \frac{0.417e^{15.385s}}{34.615s + 1}$$

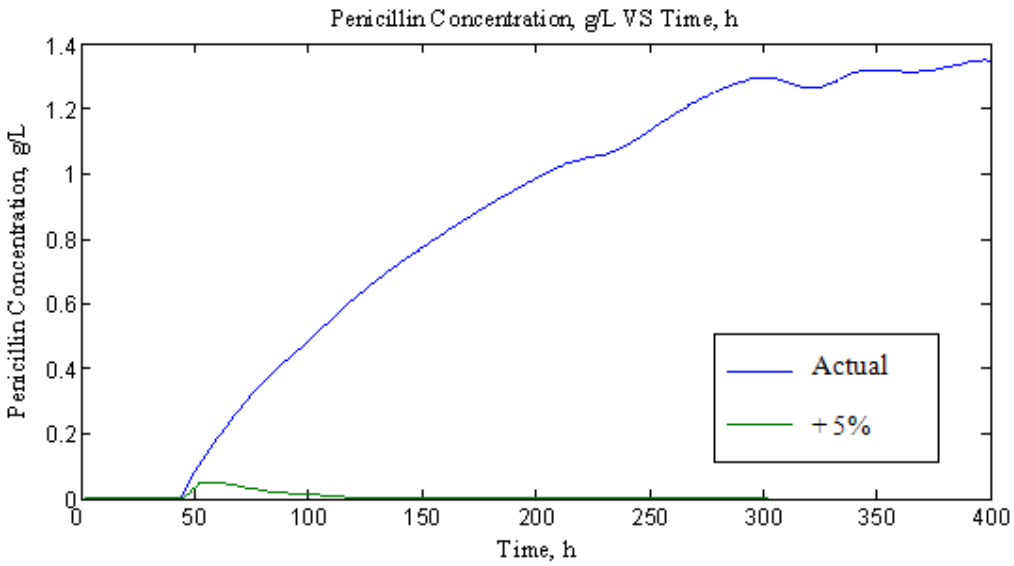

Figure 4.3: Output changes (Penicillin Concentration, g/L, +5%)

For the vaporizer level,

$$K = \frac{\text{Output Changes}}{\text{Input Changes}} = \frac{0.0462 - 0}{312.9 - 289} = 0.00308$$

$\tau = 50$ min

$\theta = 52$ min

Hence, the transfer function is

$$G(s) = \frac{0.00308e^{52s}}{52s + 1}$$

4.3 The Implementation of MPC

In order to implement the MPC to the fed-batch penicillin fermentation process, the dynamic models were created using Simulink® toolbox in the Matlab®. Dynamic models were constructed based on steady state models. In this research study, there are 3 types of model designation for the closed loop model;

a) The interacting process which both transfer function are implanted together
b) The biomass concentration closed loop
c) The penicillin concentration closed loop

The design begins with the model designation on Simulink as shown in Figure 4.5, where this model is known as closed loop model for the system. Then, the implementation of MPC would be complete by the designation of another 2 models which are;

a) Open loop for the system in Simulink as shown in figure 4.4
b) The m.files that compile both model that would be attached in Appendix A

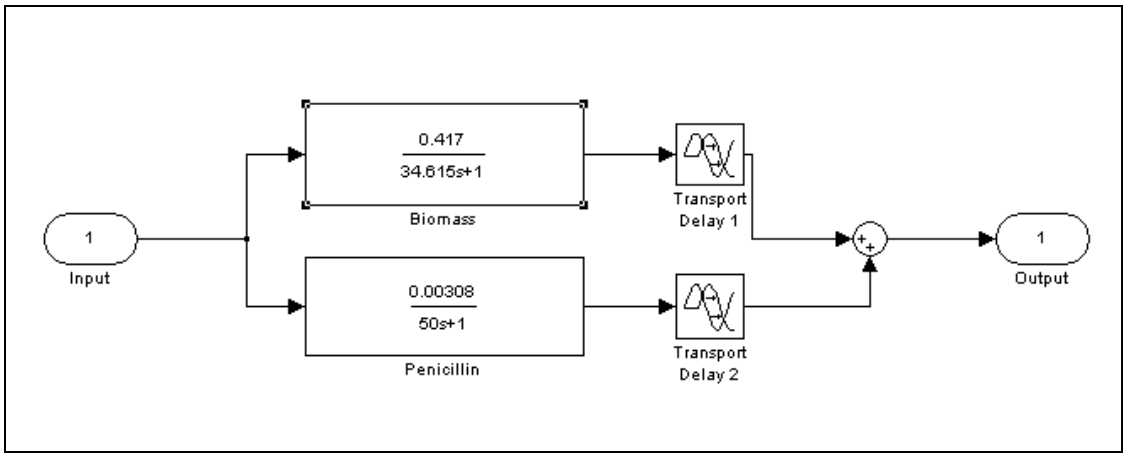

Figure 4.4: Simulink Open Loop model for the process

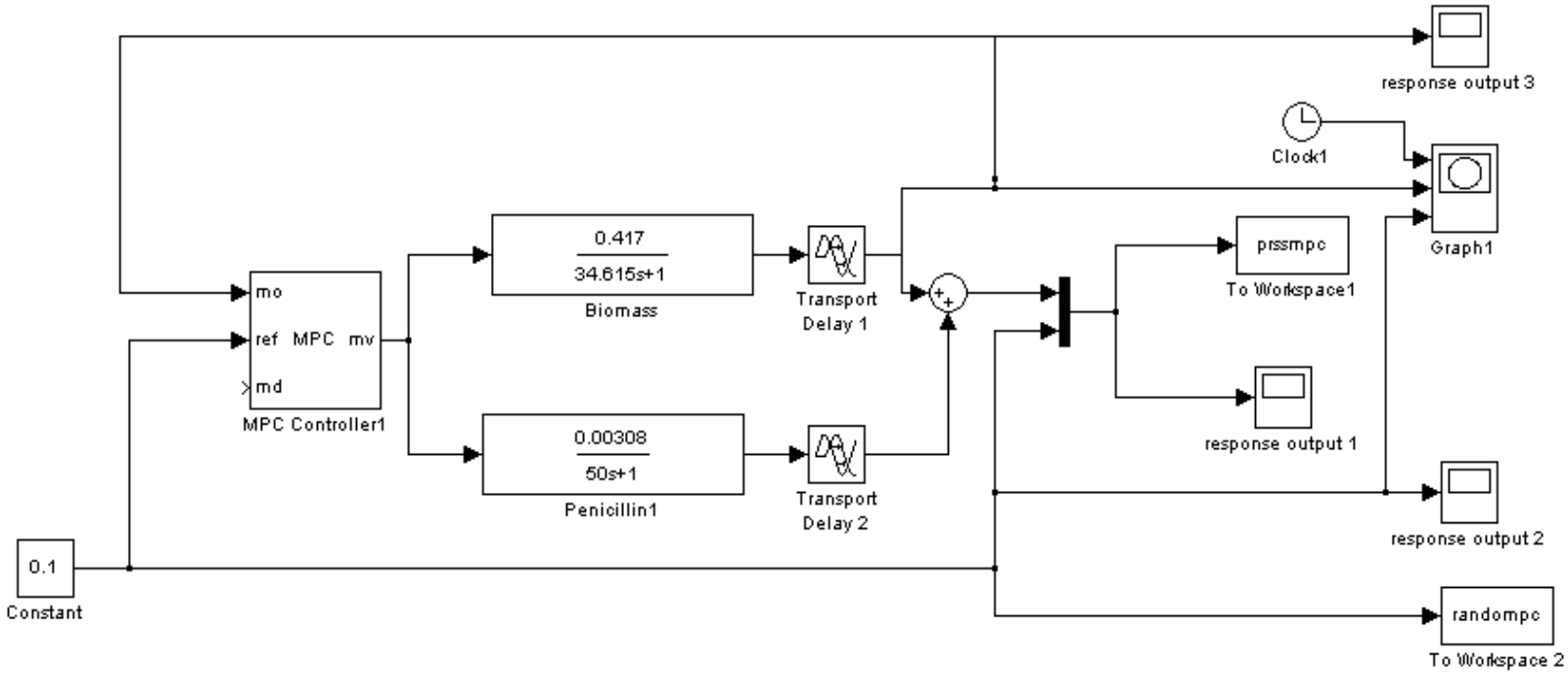

Figure 4.5: Simulink Closed Loop model for the process

4.4 MPC Tuning Process

The models used in the MPC have to be as simple as possible in order to minimize the response time. Therefore linearized models are used for prediction and optimization. The coefficients of the model are recalculated every time step to deal with the non linearity of the system. With this technique, called successive linearization, the actual work point is followed. In the tuning process, the time period for which the prediction is made is called "prediction horizon" and the time period for which the control inputs are optimized is called the "control horizon". The tuning is done by means of a Kalman filter, which corrects the state parameters of the process model. Based on this prediction, an objective function is optimized on-line with regard to the future control inputs to the process. Hence, the value of the control, M and Prediction, P horizon need to be tuned in order to obtain a better performance for the controller.

Theoretically, the non-adaptive DMC tuning strategy by Dougherty and Cooper (2002) have been implemented in this research. In applying MPC into the model, three different type of sources have been tested which are;

a) Constant number- The Constant block generates a real or complex constant value. The block generates a scalar, vector, or matrix output, depending on the dimensionality of the Constant value parameter and the setting of the Interpret vector parameters.

b) **Random number**- The Random Number block generates normally distributed random numbers. The seed is reset to the specified value each time a simulation starts.

c) **Band limited white noise**- The Band-Limited White Noise block generates normally distributed random numbers that are suitable for use in continuous or hybrid systems.

The primary difference between Band-Limited White Noise and the Random Number block is that the Band-Limited White Noise block produces output at a specific sample rate, which is related to the correlation time of the noise.

4.4.1 Tuning for Interacting Control Loop

For interacting control loop, the input, constant will be tuned first then followed by changing the constant to input disturbance which is the random number and band-limited white noise. For each of the input, there will be 5 different prediction horizon value used to run the simulation as trial to obtain the best result for the MPC controller. The control tuning strategy is shown in the Table 4.1.

Table 4.1: Interacting model tuning strategy

Input	**Tuning value**		**Condition**
	Prediction, P	**Control, M**	
Constant	15	1	Very Unstable
	25	1	Unstable
	50	1	To long to get desired output
	75	1	Stable
	100	1	Very Stable
Random Number	15	1	Very Unstable
	25	1	Unstable
	50	1	To long to get desired output
	75	1	Stable
	100	1	Very Stable
Band Limited White Noise	15	1	Very Unstable
	25	1	Unstable
	50	1	To long to get desired output
	75	1	Stable
	100	1	Very Stable

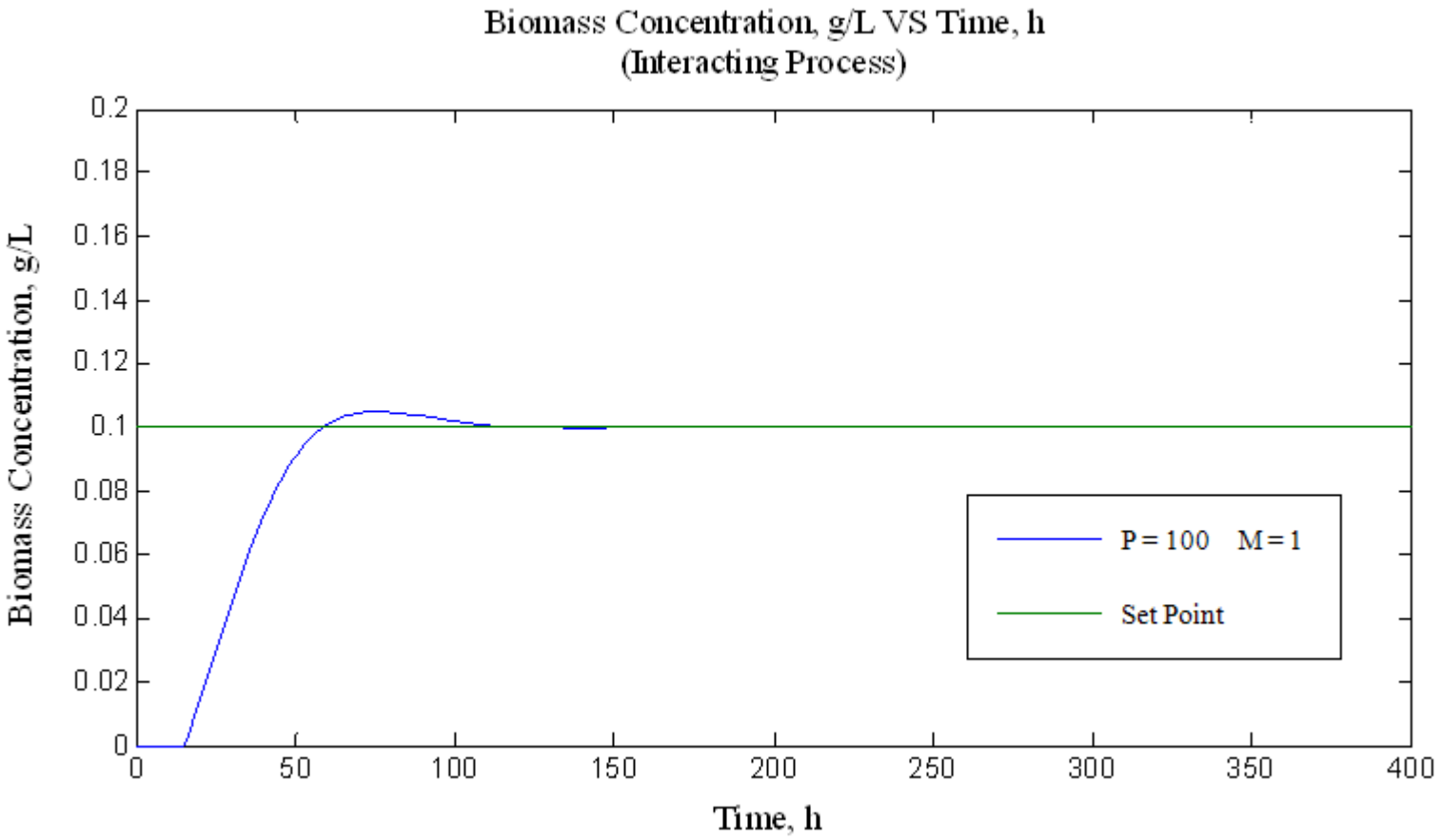

Figure 4.6: The optimum condition for interacting process control loop

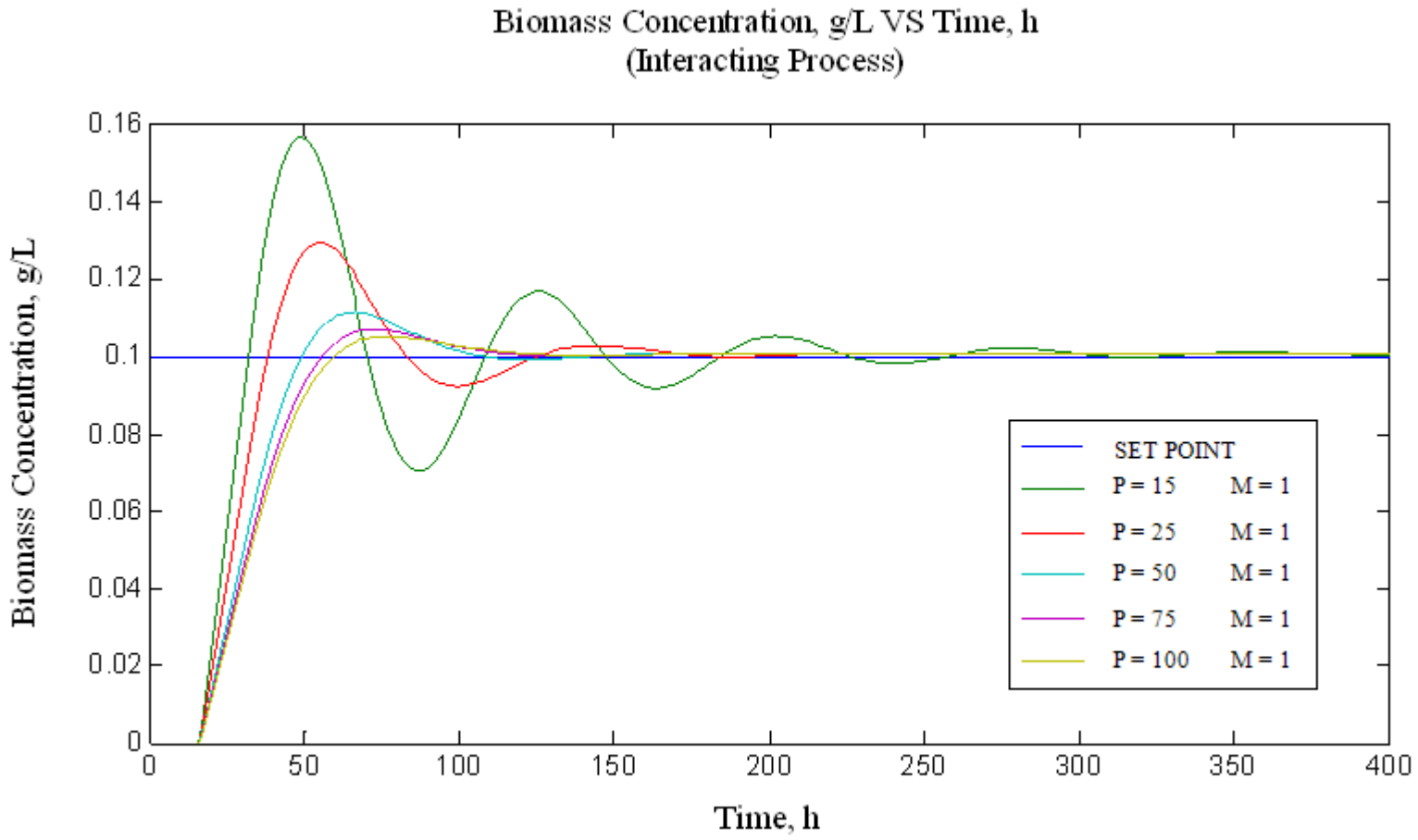

Figure 4.7: The tuning graph for interacting process using constant

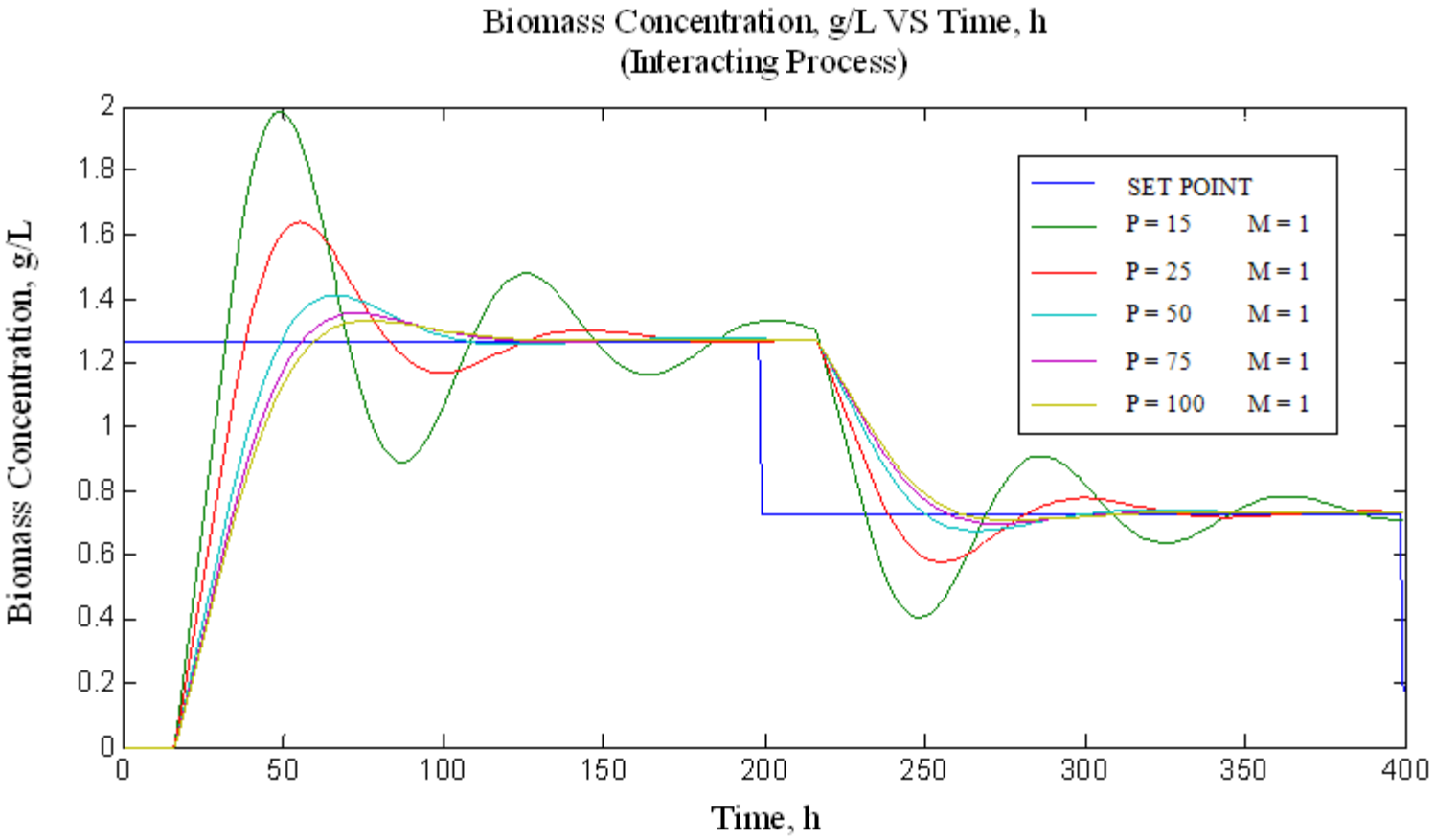

Figure 4.8: The tuning graph for interacting process using random number

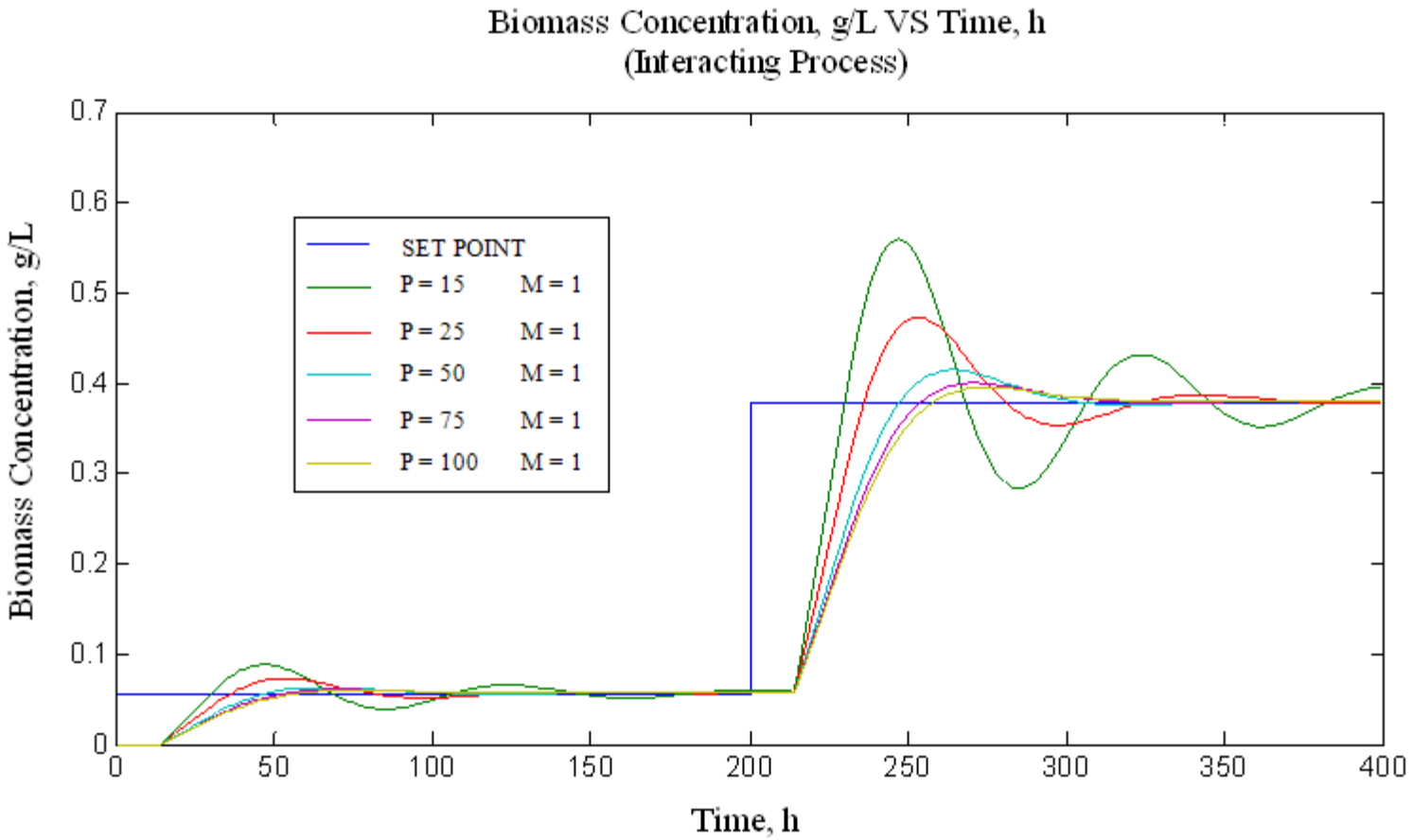

Figure 4.9: The tuning graph for interacting process using band limited white noise

4.4.2 Tuning for Biomass Concentration Control Loop

The same tuning process is to be repeated for the biomass concentration control loop. As the interacting process we are focusing on the biomass concentration, hence the loop input constant and input disturbance tuning strategy for the biomass concentration control will be the same as the table shown in Table 4.1. The control tuning strategy is shown in the Table 4.2.

Table 4.2: Biomass concentration model tuning strategy

Input	**Tuning value**		**Condition**
	Prediction, P	**Control, M**	
Constant	15	1	Very Unstable
	25	1	Unstable
	50	1	To long to get desired output
	75	1	Stable
	100	1	Very Stable
Random Number	15	1	Very Unstable
	25	1	Unstable
	50	1	To long to get desired output
	75	1	Stable
	100	1	Very Stable
Band Limited White Noise	15	1	Very Unstable
	25	1	Unstable
	50	1	To long to get desired output
	75	1	Stable
	100	1	Very Stable

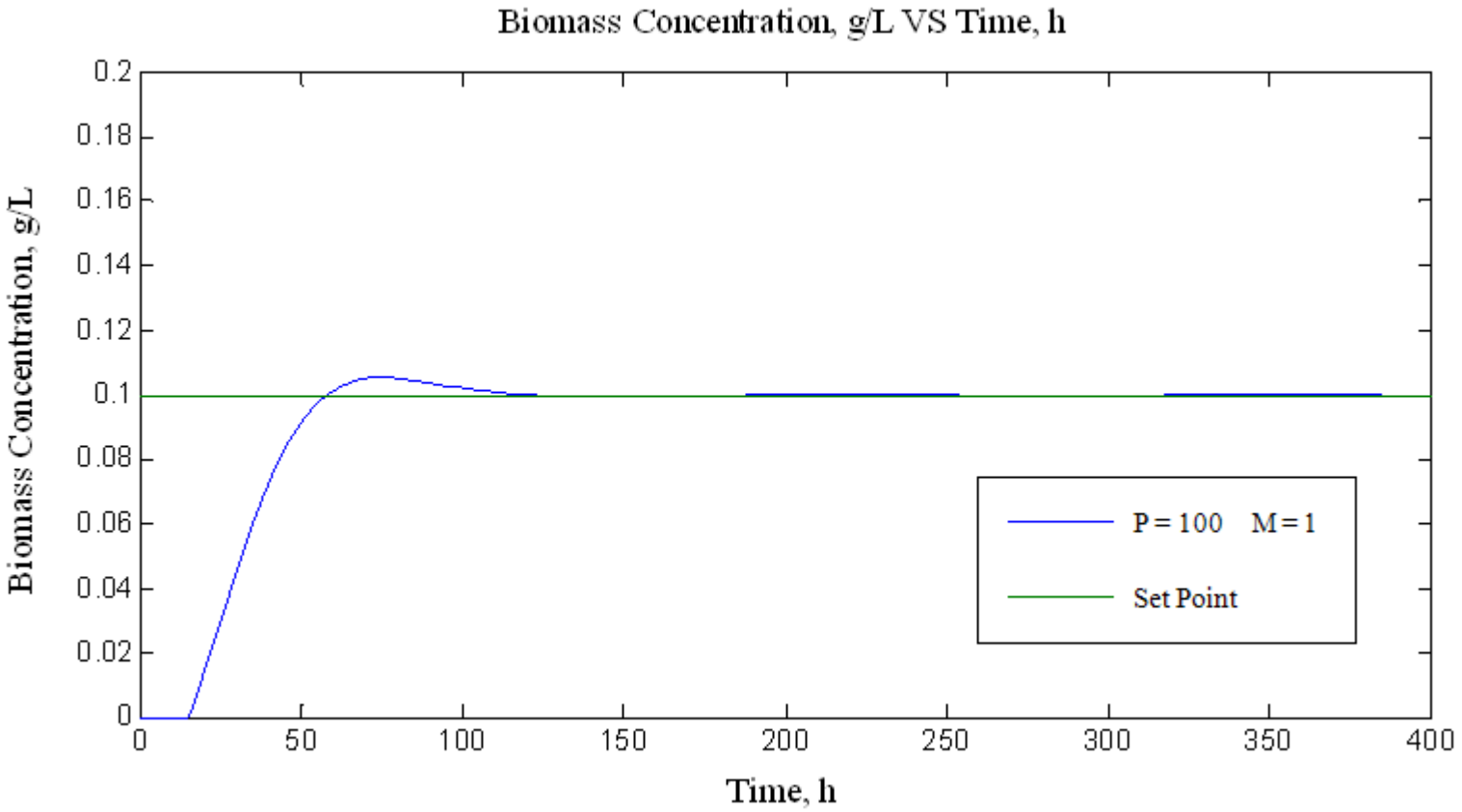

Figure 4.10: The optimum condition for biomass concentration process control loo

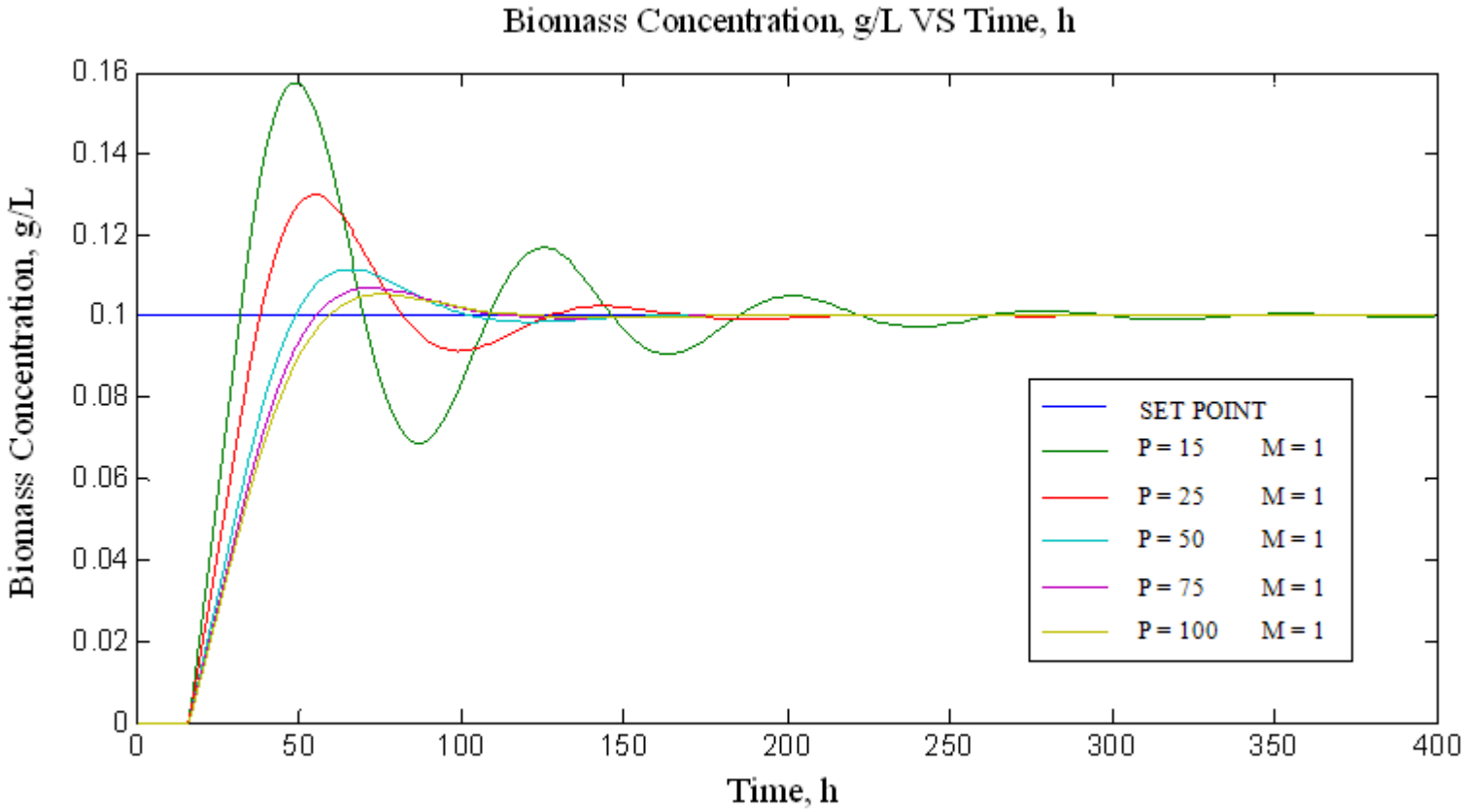

Figure 4.11: The tuning graph for biomass concentration using constant

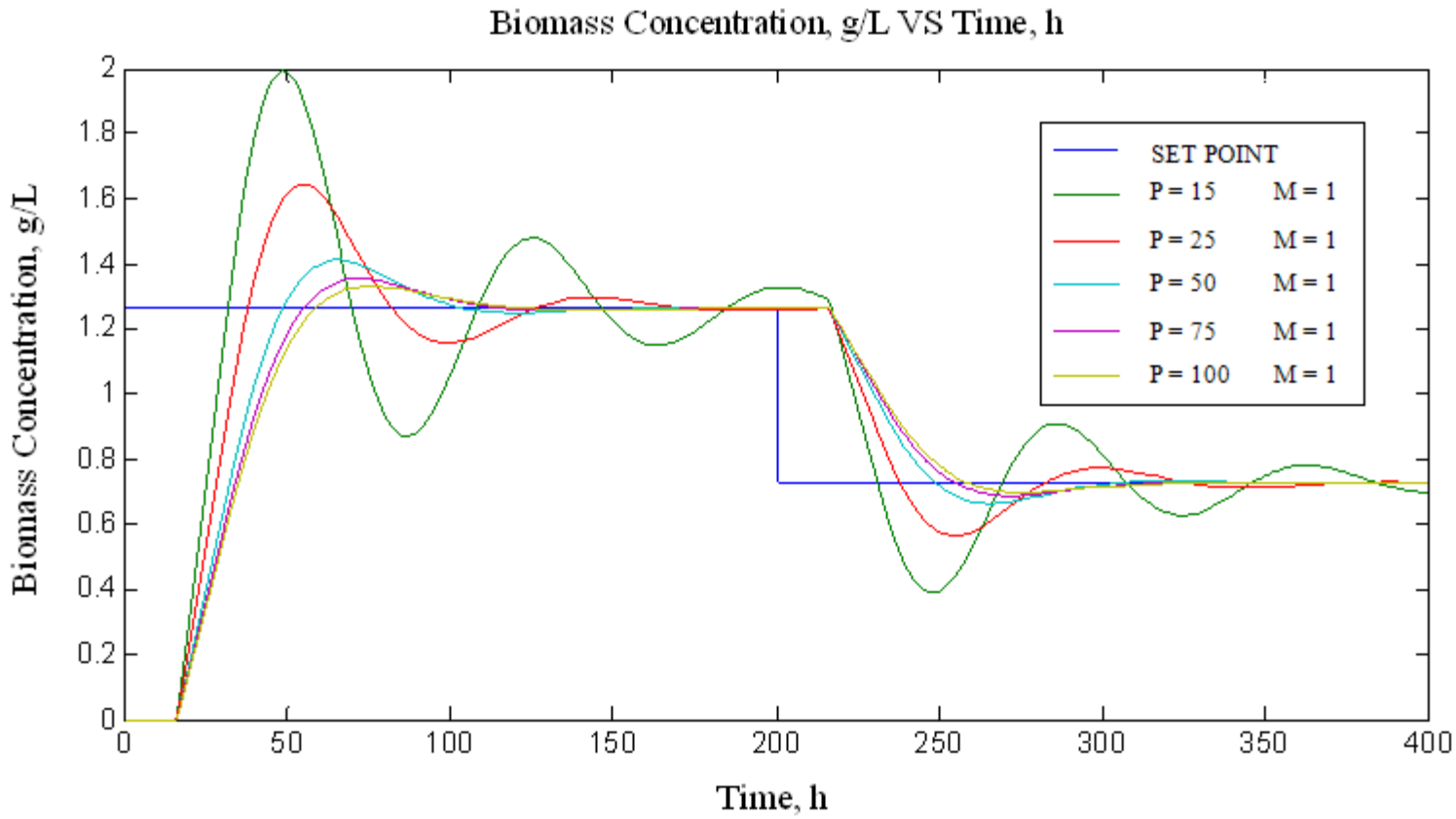

Figure 4.12: The tuning graph for biomass concentration using random number

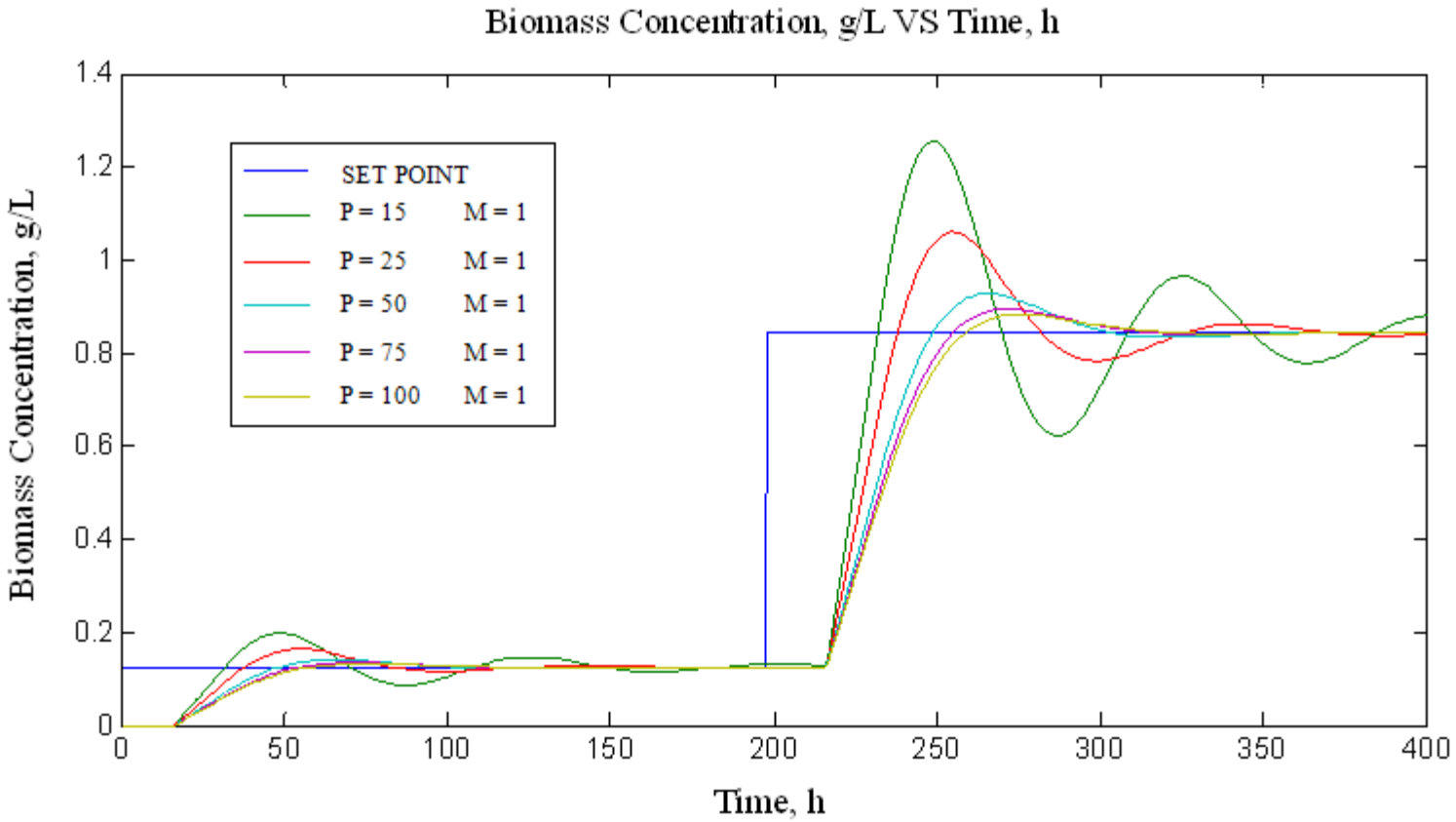

Figure 4.13: The tuning graph for biomass concentration using band limited white noise

4.4.3 Tuning for Penicillin Concentration Control Loop

Finally, tuning process is to be repeated for the penicillin concentration control loop. The control tuning strategy is shown in the Table 4.3.

Table 4.3: Penicillin concentration model tuning strategy

Input	**Tuning value**		**Condition**
	Prediction, P	**Control, M**	
Constant	24	1	Too long to get desired output
	26	1	Very stable
	28	1	Stable
	30	1	Unstable
	32	1	Very unstable
Random Number	24	1	Too long to get desired output
	26	1	Very stable
	28	1	Stable
	30	1	Unstable
	32	1	Very unstable
Band Limited White Noise	24	1	Too long to get desired output
	26	1	Very stable
	28	1	Stable
	30	1	Unstable
	32	1	Very unstable

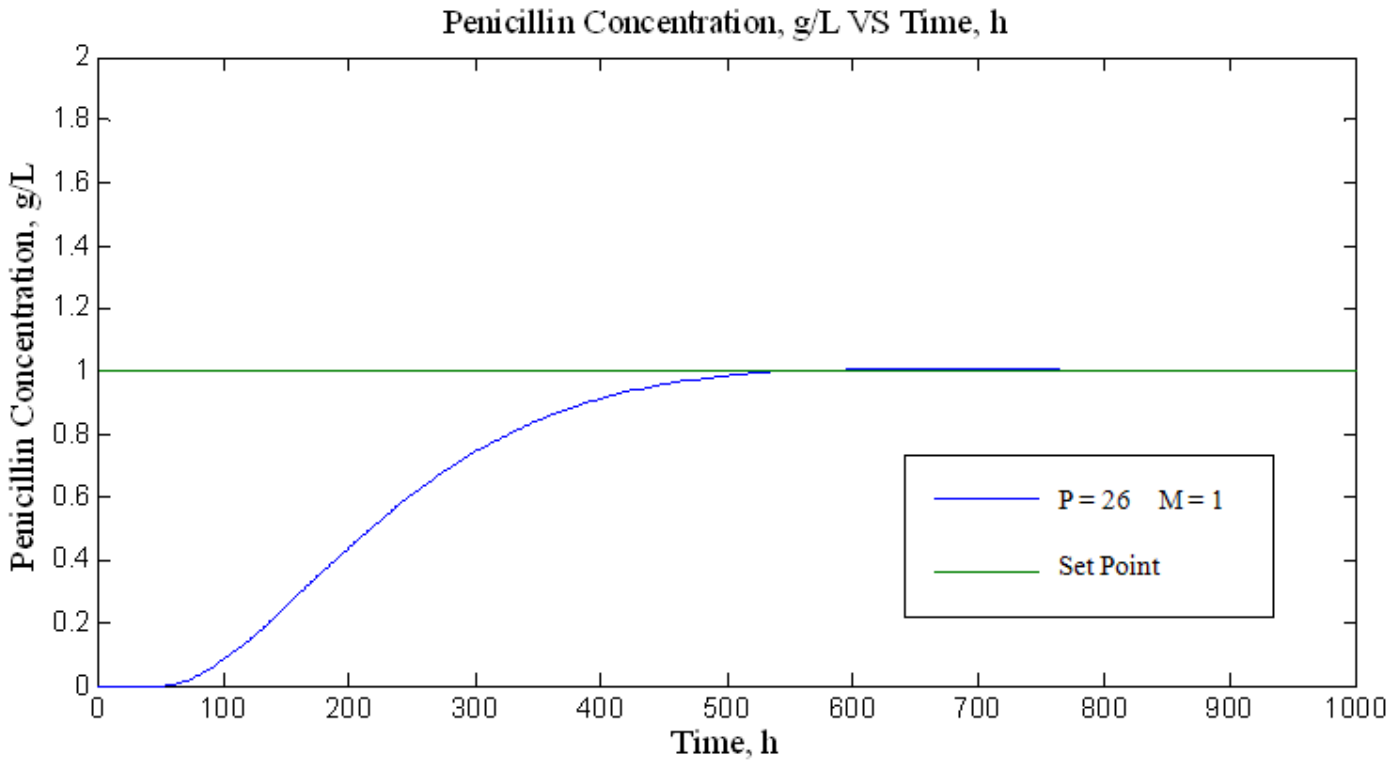

Figure 4.14: The optimum condition for penicillin concentration process control loop

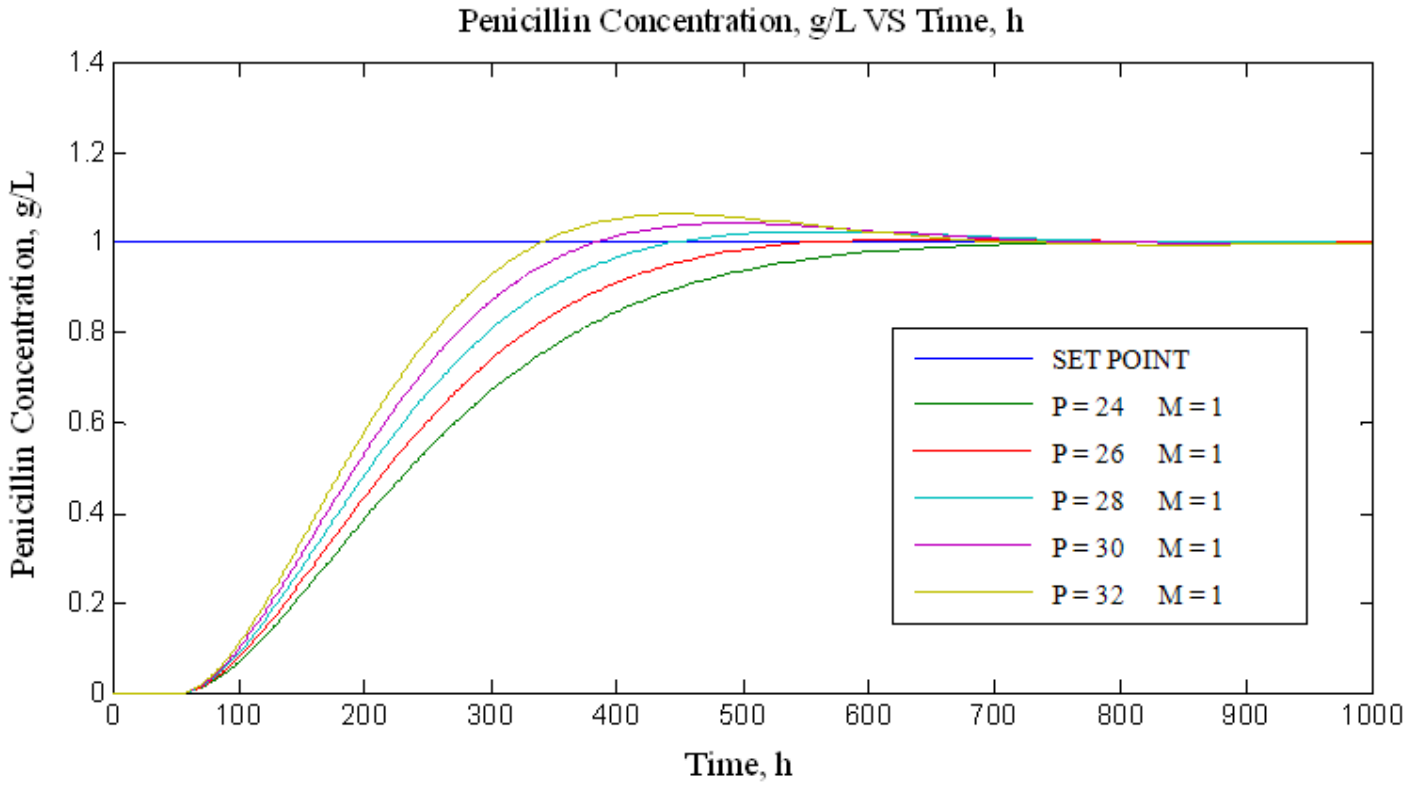

Figure 4.15: The tuning graph for penicillin concentration using constant

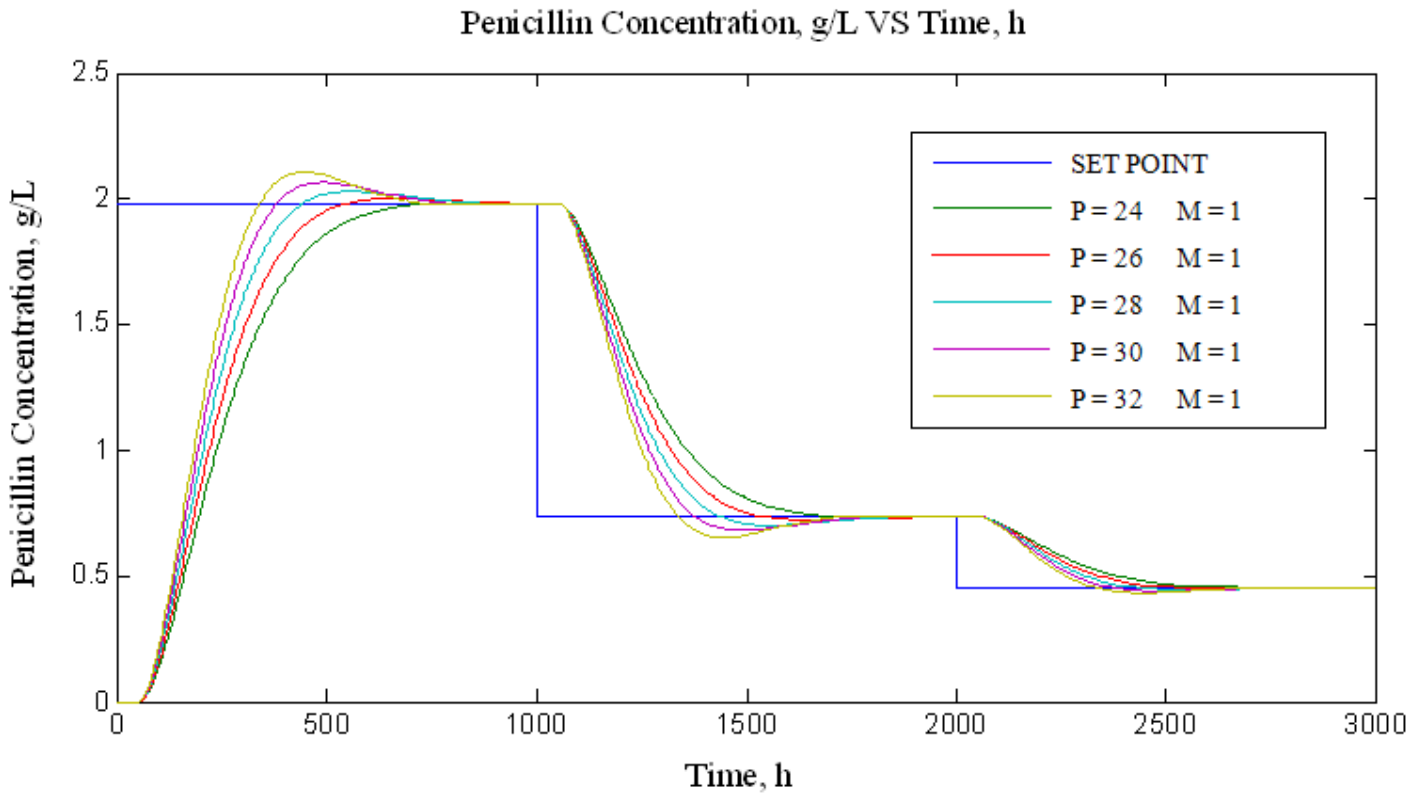

Figure 4.16: The tuning graph for penicillin concentration using random number

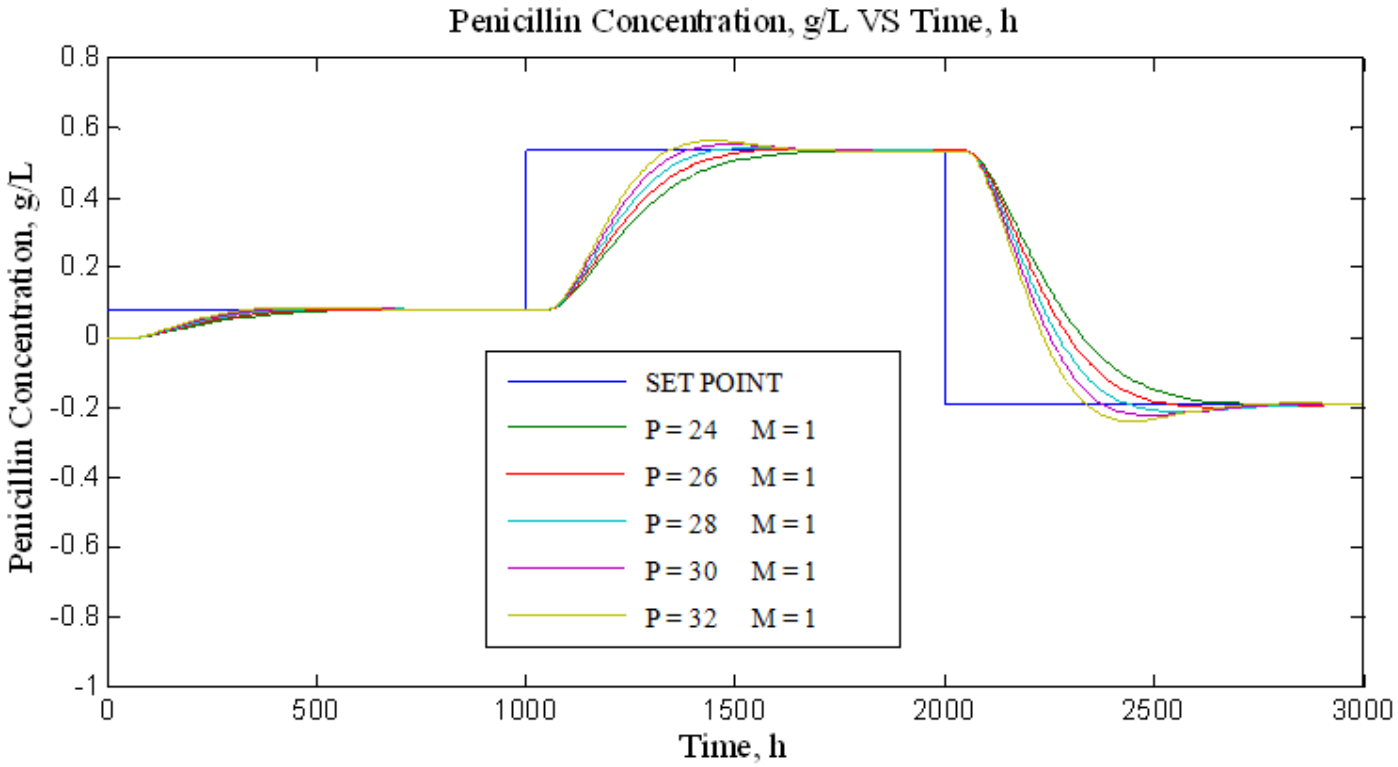

Figure 4.17: The tuning graph for penicillin concentration using band limited white noise

4.5 Discussion

The overall graphs result has shown that by having different tuning strategy, it able to affect the performance of a MPC controller. In Figure 4.7 and 4.11, the optimize value for the constant input in interacting control loop was p=100 and m=1. Meanwhile in Figure 4.15, the optimize value for the constant input in penicillin concentration control loop was p=26 and m=1. An important limitation of the process is the computation time required to do the optimization. Figure 4.6 and 4.10 shows that the optimization has been completed at time 100 hour and having the least deviation from its set point when using p=100 and m=1. Meanwhile, Figure 4.14 shows that the optimization has been completed at time 500 hour and having the least deviation from its set point when using p=26 and m=1.

In Figure 4.8 and Figure 4.12 the input constant will be replace by input disturbance which is the random number, then in Figure 4.9 and 4.13 the input constant will be replace by band limited white noise. Due to the disturbance that occurred, the controller will take action to minimize the deviation of the output from its set point or reference values. For example, in Figure 4.8, when time delay t = 34.156 hours, the controller is using a prediction horizon of 100 control intervals of 1, so it "sees" the impending disturbance at t = 100 and begins to prepare for it. The controller multiplies predicted deviation for the output to provide good set point tracking. Therefore, few prediction horizons are needed in order to obtain optimal performance for the MPC controller.

MPC consist of two major parts: 1) an optimization algorithm, which defines the best place to run the process at steady state, and 2) a dynamic control algorithm, which defines how to move the process to the steady state optimum in a smooth way, without violating any constraints. The controller algorithm runs at a set interval 0.5 hour and will use the current state of the process, as well as its predictive model, to determine if the control variables are predicted to remain within constraints over the prediction horizon. Therefore, for optimal performance of the MPC the prediction and control horizons, P and M, have to be selected carefully. If this can be achieved, then it will optimize the process according to the optimization algorithm, essentially

setting a new steady state target for each of the control variables. The dynamic control algorithm will then determine how to set the manipulated variable which is the temperature for this control iteration so as to move the process in a slow, steady fashion to the new operating target, minimizing the chance of a process upset due to rapid control changes.

CHAPTER 5

THE CAPABILITY OF MODEL PREDICTIVE CONTOLLER

5.1 Introduction

MPC directly addresses the limitations of Proportional Integral Derivatives (PID) applications. Fundamentally, MPC determines and drives current control moves which will cause a desired future behavior of the controlled variables. Stated another way, Model Predictive Control bases its actions not only on the observed past and present, but also on the predicted future. Achieving this control function requires several elements not present in traditional PID;

a) An accurate dynamic and state model of how the controlled variables respond to the manipulated and feed forward variables
b) An optimizing algorithm to compare and select the manipulated variable moves which will force
c) The “best” controlled variable trajectories. a second optimizing algorithm to determine the best steady state operating point for the process.

In this chapter, the capability of model predictive controller will be determine. A direct comparison with the PID would be complete in order to confirm the result of the MPC performance. Three types of the input have been choose in this project, that are constant value, random number and band limited white noise.

5.2 The MPC Performance on the Interacting Process

Figure 5.1 had shown the comparison between PID and MPC on interacting process which both transfer function were combined together using constant. The MPC shows that the process was able to reach the set point and stable at t=100 hours meanwhile the PID controller was unable remain stable when the process changes. The sudden change in the manipulated variable will cause the PID controller derivative term momentarily to become very large and thus provide a ‘derivative kick’ to the final control element. Then, the input constant is replaced by input disturbance and the result is shown in Figure 5.2 and 5.3. The PID controller in process has failed to settle to its set point when sustained disturbance occurs. On the other hand, the MPC has response well towards the changes of the process input which compromises between robustness and speed of response

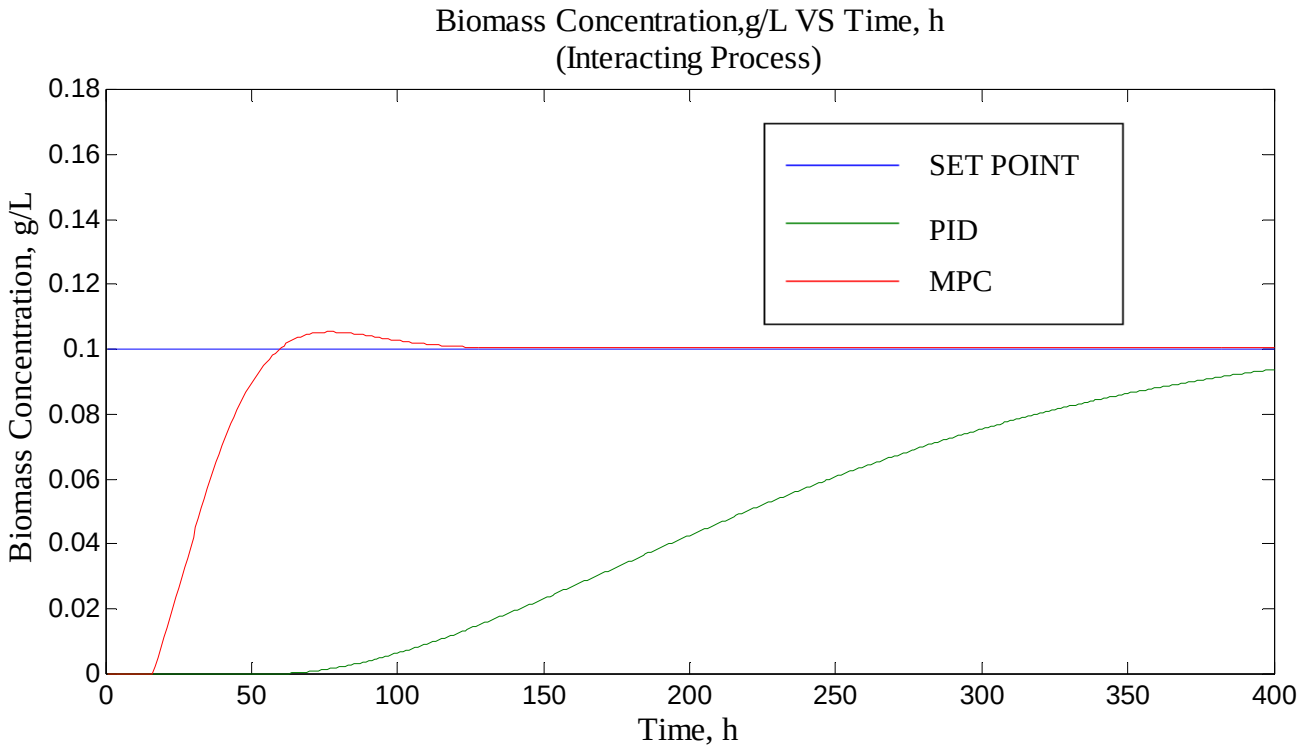

Figure 5.1: Comparison between PID and MPC on interacting process using constant

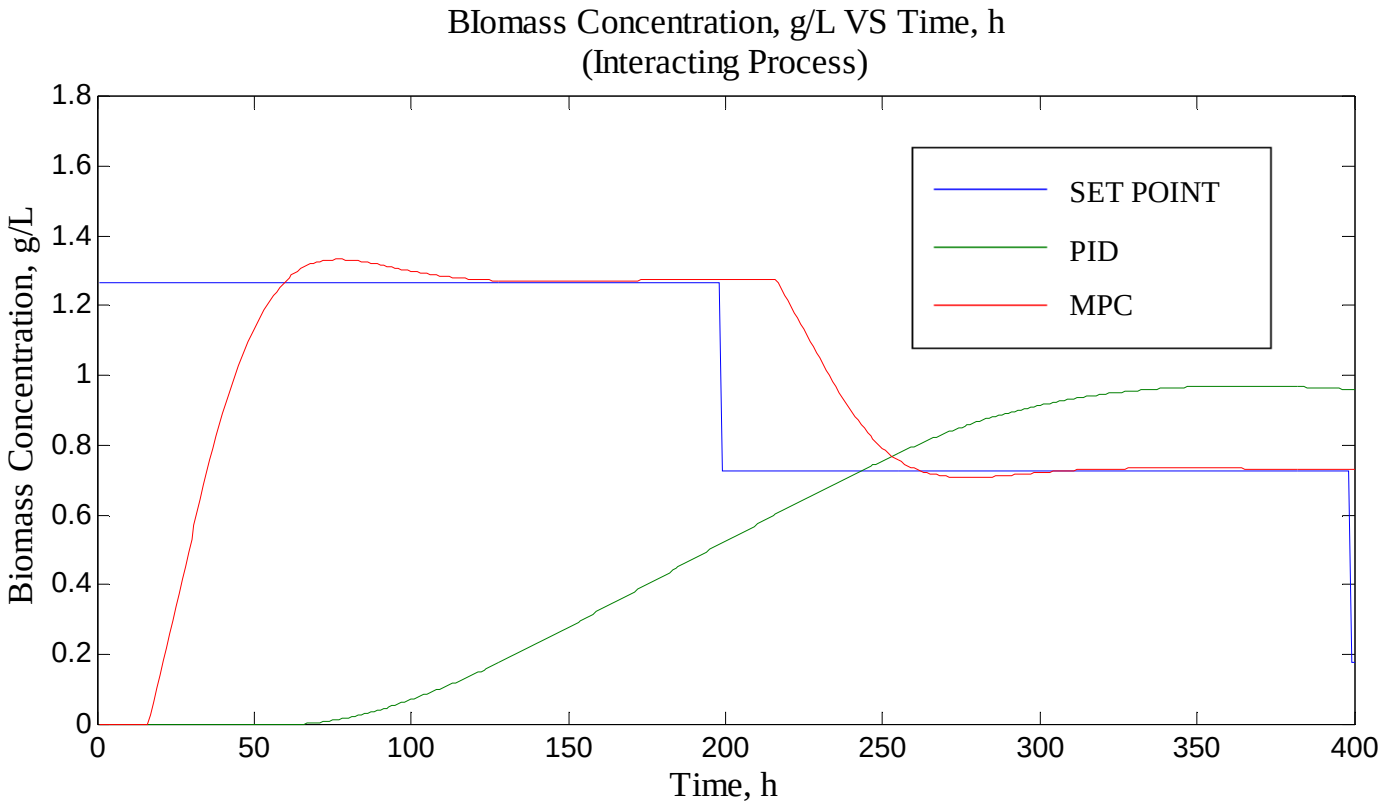

Figure 5.2: Comparison between PID and MPC on interacting process using random number

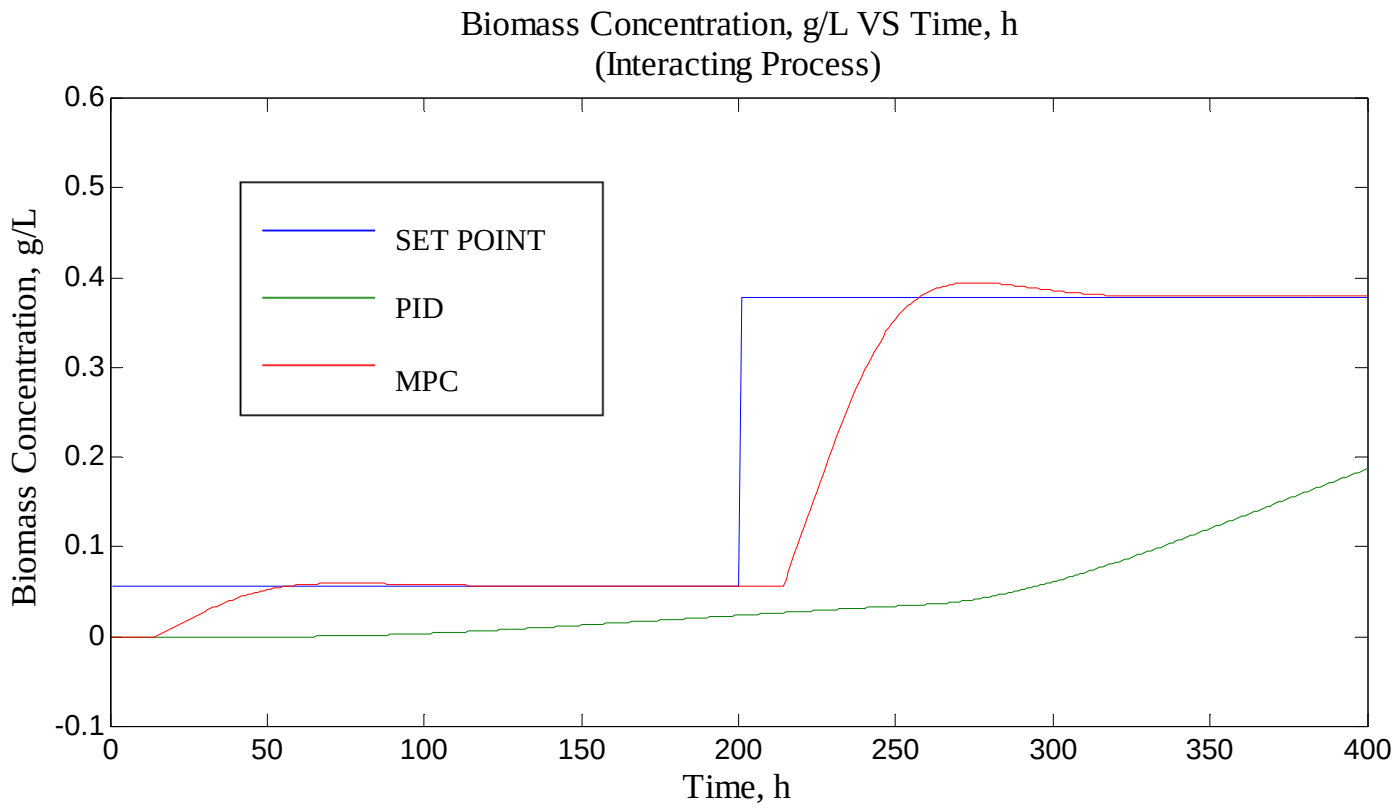

Figure 5.3: Comparison between PID and MPC on interacting process using band limited white noise

5.3 The MPC Performance on the Biomass Concentration

Comparison between PID and MPC on biomass concentration is also concluded. Figure 5.4 shows that the process was able to reach the set point and stable at t=100 hours by using MPC controller, meanwhile by using the PID controller, the process remain stable at t=225 hours when the temperature was manipulated. The time require for PID controller to settle to its set point is almost double compare to MPC controller. Then, the input constant is replaced by input disturbance and the result is shown in Figure 5.5 and 5.6. As the comparison is made, the graph showed that the recovery time after the disturbance is too long when the PID controller is used in the process. In fed batch penicillin fermentation process industry, the duration of time consumed is very crucial as it involve higher cost of maintenance. MPC has shown that its capabilities to handle the disturbance in the process well as it able to predict the process behavior.

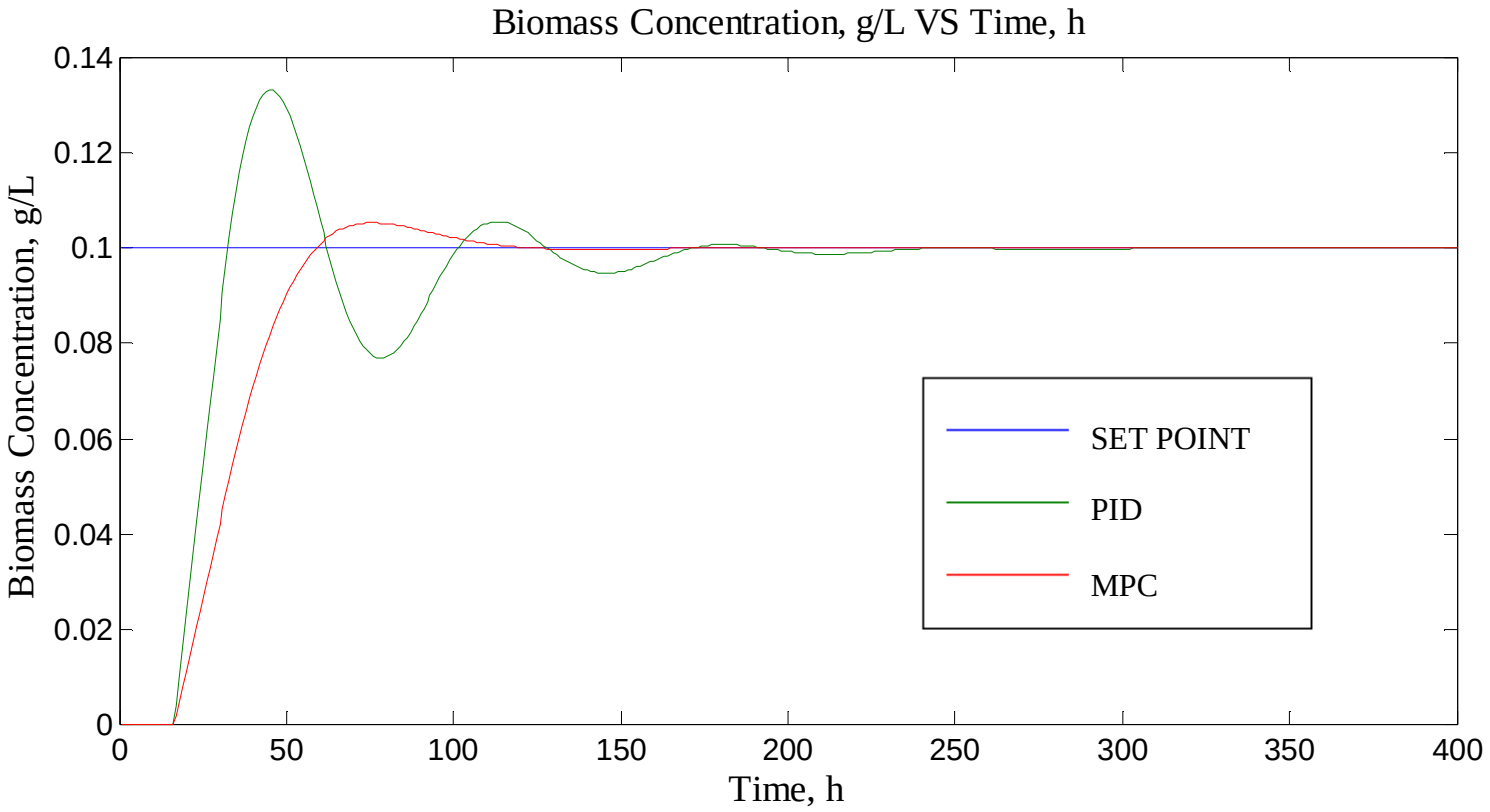

Figure 5.4: Comparison between PID and MPC on biomass concentration using constant

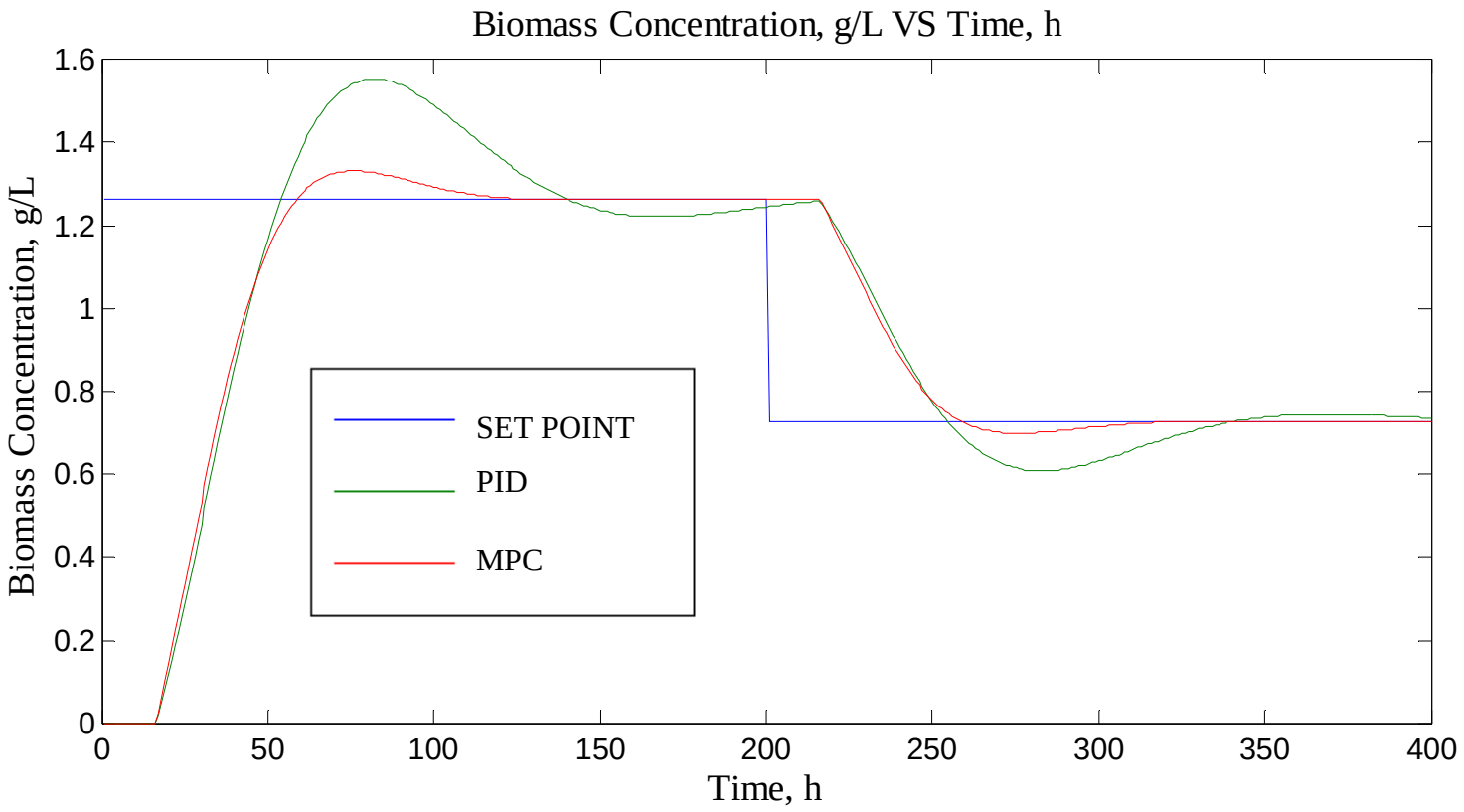

Figure 5.5: Comparison between PID and MPC on biomass concentration using random

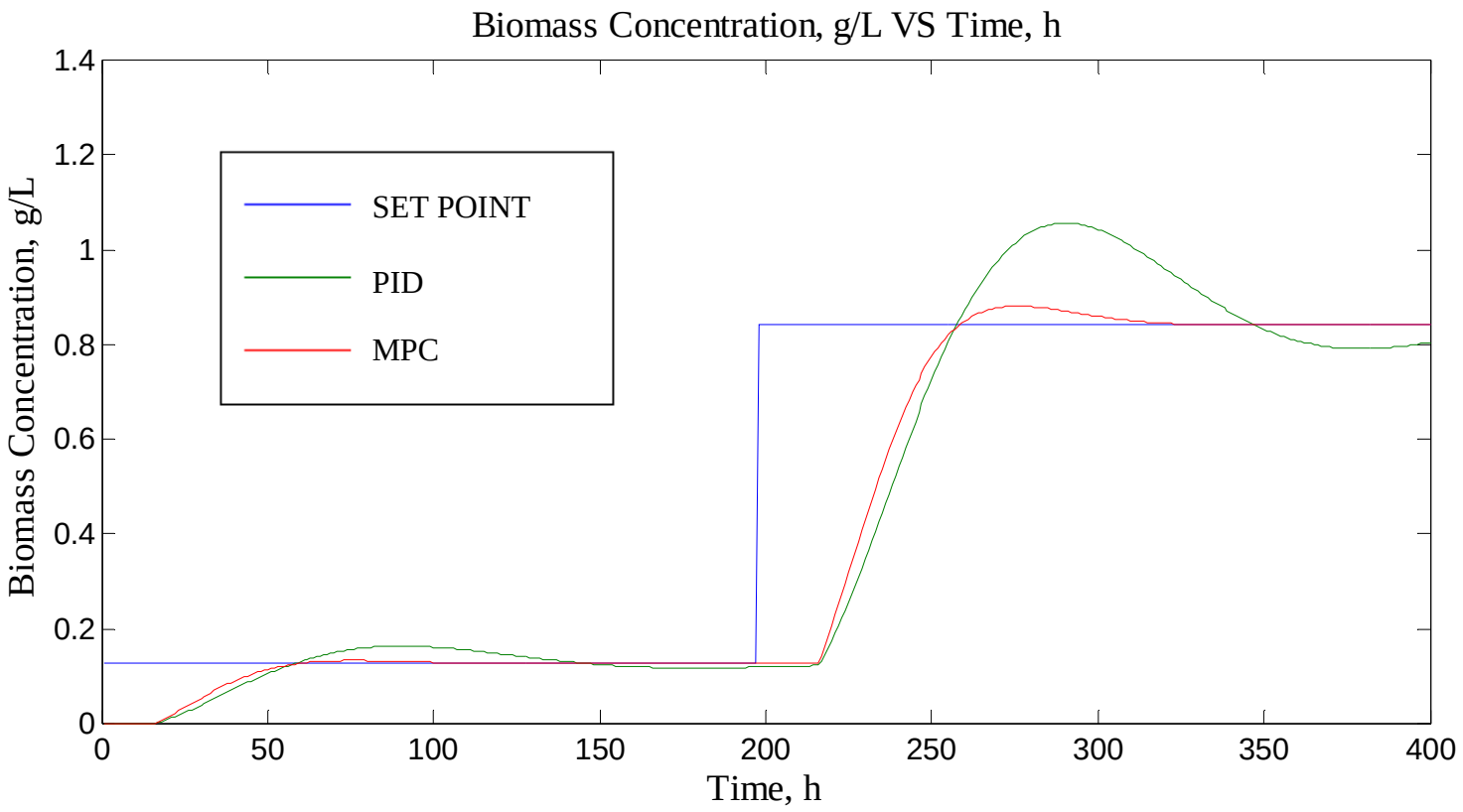

Figure 5.6: Comparison between PID and MPC on biomass concentration using band limited white noise

5.4 The MPC Performance on the Penicillin Concentration

Finally, the comparison is to be done the penicillin concentration. The result has also proven that the MPC controller plays a better performance compare to the PID controller in terms of input constant and input disturbance. This was shown in figure 5.7, Figure 5.8 and Figure 5.9. In figure 5.7, the MPC shows that the process was able to reach the set point and stable at t=500 hours meanwhile the PID controller was unable remain stable throughout the set point. The PID controller in process has once again failed to settle to its set point when sustained disturbance occurs. The penicillin production process, however, is known to be a strongly nonlinear process that depict a substantially time varying dynamics which causes PID hardly control the changes in the process. Hence, MPC is still a preferred controller to be use as it able to stabilize the disturbance that occurred in a short period of time.

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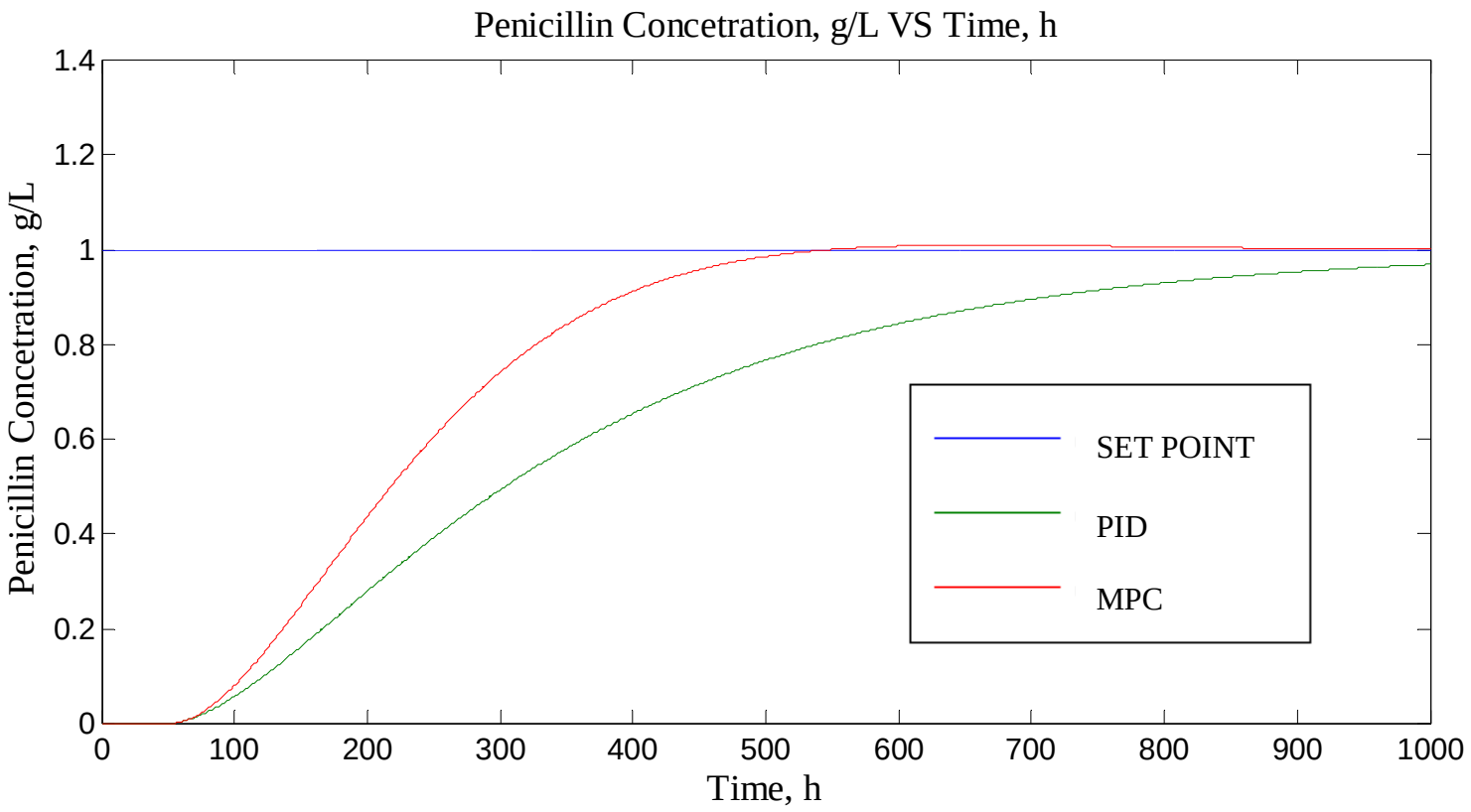

Figure 5.7: Comparison between PID and MPC on penicillin concentration using constant

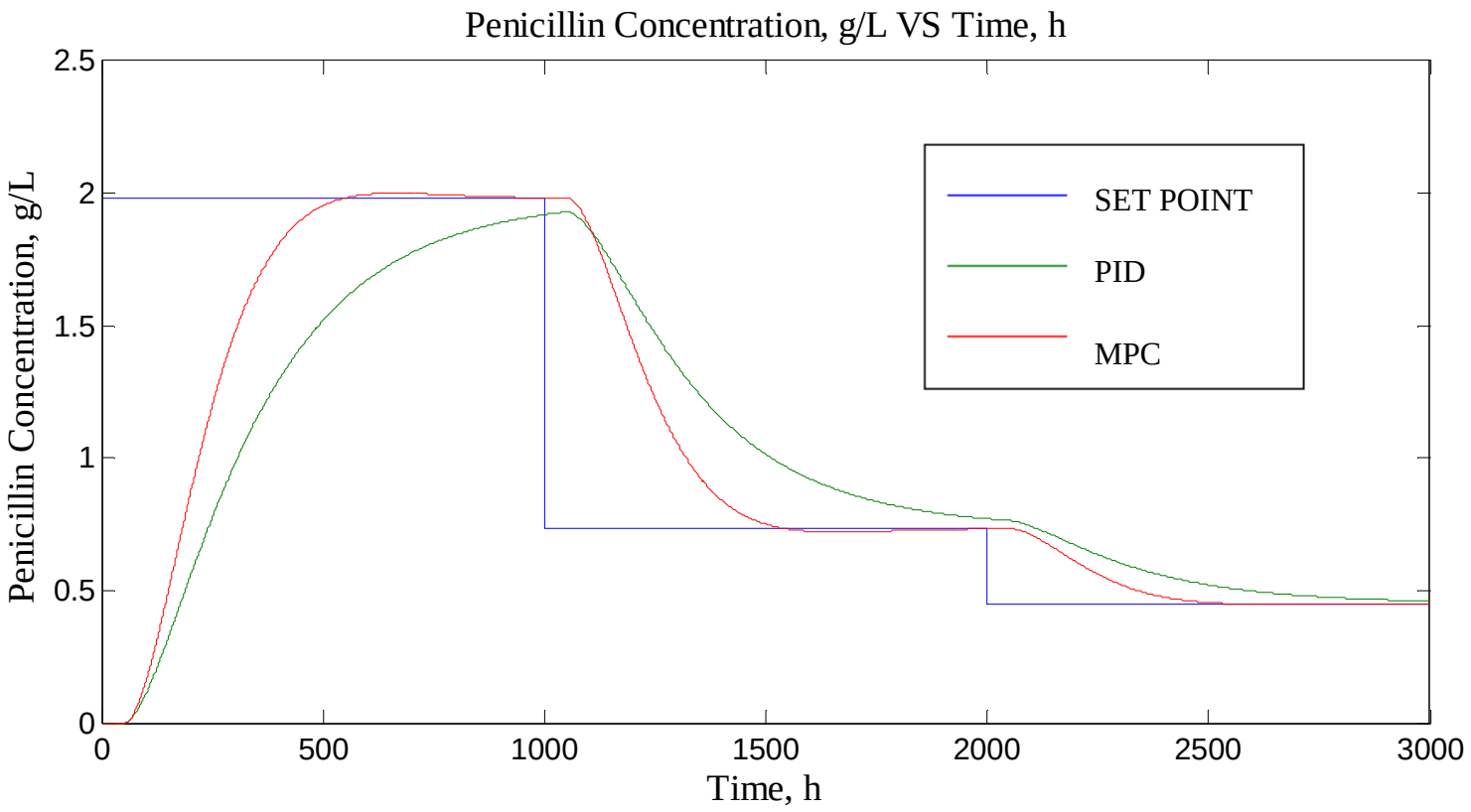

Figure 5.8: Comparison between PID and MPC on penicillin concentration using random number

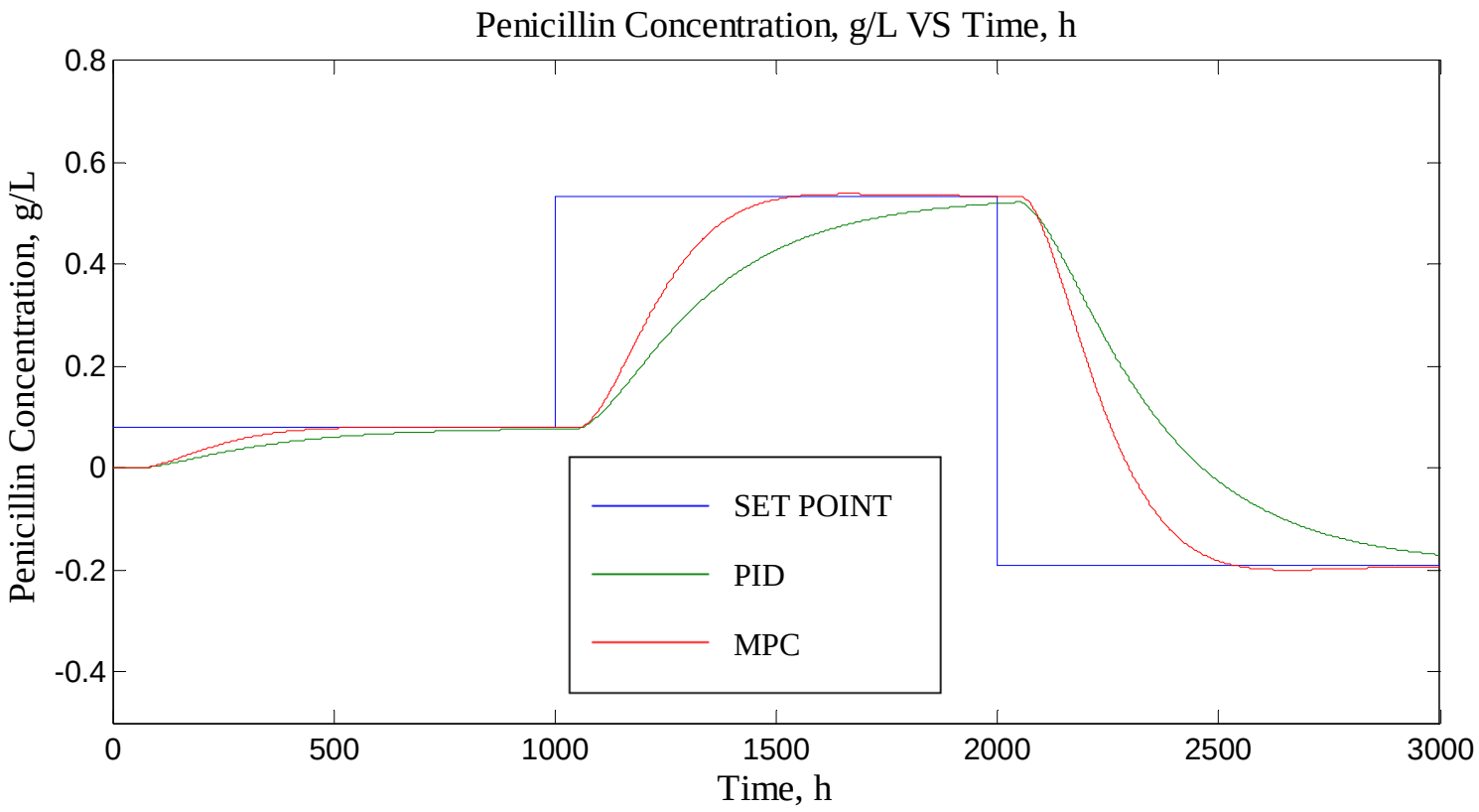

Figure 5.9: Comparison between PID and MPC on penicillin concentration using band limited white noise

5.5 Discussion

The MPC controller has proven that it provides a better performance towards the PID controller. From the simulation result, it has shown that there are two main reasons that speak against the PID controller. The most severe practical problem is that the control variables are usually measured off-line with a long sampling time increment, which is much larger than can be accepted for direct control. Hence, there is no measurement signal that can be used in the PID controller. The second reason is that PID controllers react on deviations in the actual value of the control variable from its corresponding set point in a predefined way specified by the controller parameters. The parameters of simple PID controllers are adjusted to the nominal process dynamics, which is assumed to be time-independent and known beforehand. The penicillin production process, however, is known to be a strongly nonlinear process that depict a substantially time varying dynamics.

On the other hand, the MPC controller has the ability to cope with these two problems. In MPC controllers, the information about the process state is determined indirectly by means of a model supported measurement. Hence, the direct measurement of the control variable, necessary in a simple controller, is replaced by using other measurement information and a sufficiently accurate relationship between the data and the control variables. In this way it is possible to cope with the long time increment mentioned before. When, the relationships connecting the measured variables with the control variables are dynamic relationships, the problem concerning the time-varying process dynamics is also solved. Moreover, MPC able to facilitates anticipation on future disturbances. This is useful when predictions can be made of the user behavior or when a switch in operating conditions is planned in advance.

CHAPTER 6

CONCLUSION AND RECOMMENDATION

6.1 Conclusion

Today, such fed batch penicillin fermentation process is being performed manually in most factories. But this way of controlling is expensive, since it binds considerable man-power, requires an extensive personnel training and the quality of control depends on the personal skills of the operator. The less expensive alternative is computer based process supervision and control. Hence, by substituting MPC controller will definitely reduce the time and cost of the process.

Model predictive control is a method of process control to determine a manipulated variable, which enables a process variable to reach a set point by predicting future moves in a process using models of the controlled object's behavior. The internal model is used to predict if any deviation from the set point will occur in the immediate future when process control is continued with the current manipulated variable. If a deviation is predicted, an adjusted manipulated variable is output and sent to the controlled object. Unlike PID control which implements a correction after a control deviation occurs, model predictive control predicts a deviation in advance using a model of the system's behaviour to enable stable process control while avoiding hunting (unstable movement).

The greatest advantages of model predictive control are process control stability, disturbance cancellation function, improved response to changes and improved set point following capability, as well as a high tolerance to the influence of changes in a process. Model predictive control can be applied to a process that is too difficult to control with general PID control. Its stable control enables improvement of maintenance productivity by minimizing energy waste and excess load on the driving part.

6.2 Recommendation

This project focused on designing the MPC controller for the fed-batch penicillin fermentation process. Thus, it does not involve any experimental or hardware work as the parameter needed was the derivation of the transfer function in the beginning of the project. Since the datasheet are available online, from the PENSIM official online resource hence, there is no cost involve. This project is considered an initial research, and it is recommended that any future project is based on this research, to apply it onto real observation. When applied onto really application, this project has a good potential to be commercialized in the future.

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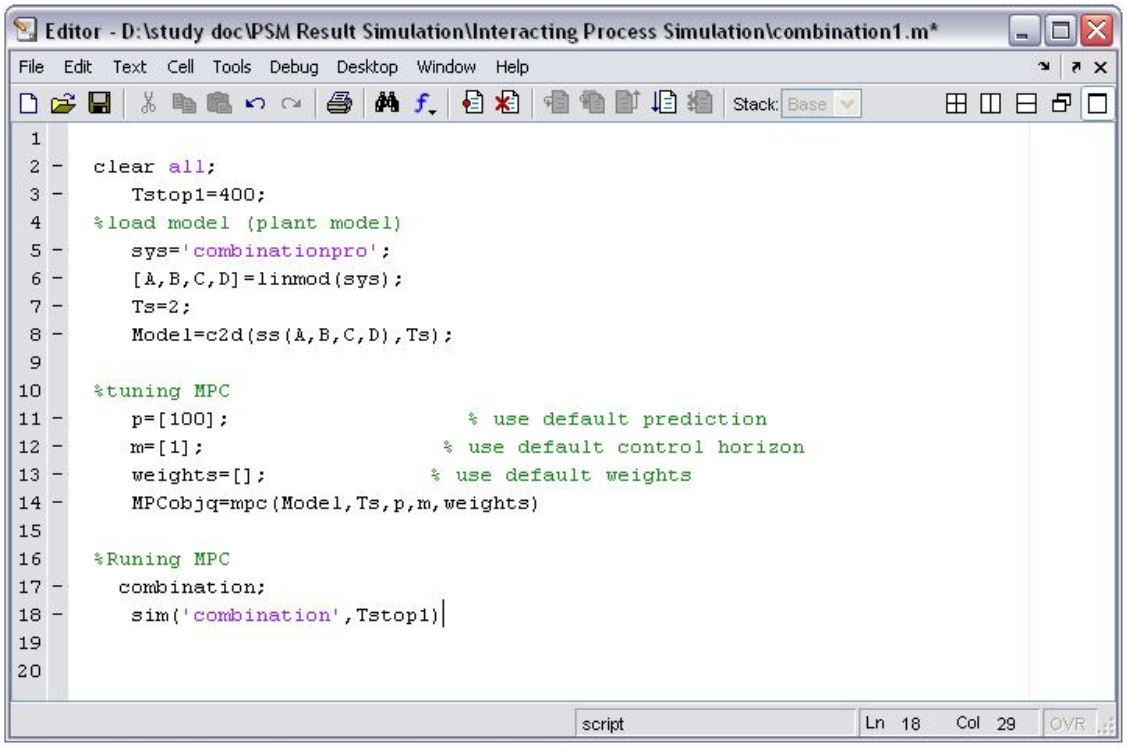
APPENDIX A

M.FILE FOR MPC PROGRAMMING



SIMULINK CLOSED LOOP MODEL USING PID