

***OPTIMAL CONTROL OF FERMENTATION  
PROCESSES***

by

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## ***ABSTRACT***

The modelling of fermentation processes is a basic part of any research in fermentation process control. Since all the optimisation work to be done is based on the reliability of the model equations, they are important for the right design. Alcoholic brewery fermentation is the main objective of this work.

This document is a compilation and discussion of previous mathematical models for fermentation processes that have been developed in recent years. Where possible, all the data has been added to show the model as it has been performed by its authors.

In the first chapter, an introduction of basic concepts and theory is pursued. This includes all the necessary knowledge in order to understand the purpose of the research.

In the second chapter, five items of published work are reviewed. They have been chosen because of their relevance to the development of the basic simulation done in the third chapter. Some of the papers show mathematical models of fermentation processes. The equations in each case are presented with their parameters so they could be employed in simulations. This is done to replicate the results shown by the authors and produce a helpful start for implementing the optimal control techniques of the Control Engineering Centre.

The third chapter includes simulation of the selected model using SIMULINK (called real process) and optimisation of the process with the help of the DISOPE algorithm. A brief explanation of the way that the System Identification Toolbox of MATLAB is used to reach the require matrices for implementation with the algorithm is also given.

## **CHAPTER I**

### ***INTRODUCTORY TERMINOLOGY AND BASIC CONCEPTS***

#### **1.1 MODELLING OF FERMENTATION PROCESSES**

The understanding and study of any process, requires a mathematical representation or model of the process. The process may have an input-output representation or a time series. The model is based on the prior physical or subjective knowledge about the process itself, the measured data on the inputs and the outputs, and the physical and engineering laws governing the working of the process.

If the model is a complete and exact representation of the process, it is called a deterministic model, and the process is called a deterministic process. The parameters of such a model are precisely known, and the model can be used to produce exact prediction of the process response from the past data. Most real life processes cannot be represented by this kind of model, because of the dynamic nature of the process and the lack of information and other uncertainties being associated with the available data. A model that incorporates noise or disturbance terms to account for such imprecision in the knowledge of the process is called a stochastic model.

The design of a control system is usually based upon a linear model of the plant to be controlled, for the good reason that the assumption of linearity makes the dynamical behaviour much easier to analyse. In practice, however, all systems are usually non-linear and, therefore, may exhibit forms of behaviour which are not at all apparent from the study of the linearised versions.

The model is not expected to be a reconstruction of the process, rather it is intended to serve as a set of operators on the identified set of inputs, producing similar output as expected from the process. The problem is that in real life the

process output is usually contaminated with noise and other disturbances, whereas ideally the model should follow the true output of the underlying representative process, which is unknown. There can be different models for the same process, although no model can be said to be the best.

The term “fermentation”, it is derived from the Latin verb *fervere*, to boil, thus describing the appearance of the action of yeast on extracts of fruit or malted grain.<sup>44</sup> Fermentation has come to have different meanings to biochemists and to industrial microbiologists. Its biochemical meaning relates to the generation of energy by the catabolism of organic compounds, whereas, its meaning in industrial microbiology tends to be much broader.

Brewing and the production of organic solvents may be described as fermentation in both senses of the word but the description of an aerobic process as fermentation is obviously using the term in the microbiological context.

In fermentation, an accurate mathematical model is a prerequisite for the control, optimisation and the simulation of a process. Models used for on-line control and those used for simulation will not generally be the same, even if they pertain to the same process, because they are used for different purposes.

In a quite general approach to modelling, a priori knowledge is the basis for a set of mathematical equations with unknown parameters.<sup>40</sup> Estimating algorithms, if properly chosen, yield the parameter values after processing of data coming from measurements on the system. Validation as a continuing exercise, could develop the best model equations.

An investigation into causes of the problems, associated with a system-theoretic approach to control of fermentation, has shown that it is not yet clear which mathematical framework is best fitted for modelling.

In batch or fed batch fermentation processes, there is no steady state. Growth and product formation rates vary with time due to a dependence on the present state of the batch as characterised by biomass, substrate and product concentrations, dissolved oxygen tension, nutrient feed rates and also on the condition of the culture.<sup>25</sup> These equations are generally non-linear. A batch fermentation process, such as on the beer fermentation process, is complex because of the biological phenomena taking place and the dynamic nature of the process itself.<sup>2</sup>

When formulating a model of a microbial process, feasibility is a guiding principle. A very frequent mistake committed is the creation of a very complex model including different approaches available in the literature, disregarding their relevance to the overall goal which should always be the simplest and yet adequately accurate way of describing the real process which would enable its simulation by calculations. Such a model can then be conveniently used for the prediction of optimal operating conditions of a technological process.

The formulation of mathematical fermentation process models, from the standpoint of system analysis, is usually realised in three stages:

- i. Qualitative analysis of the structure of a system, usually based on the knowledge of metabolic pathways and biogenesis of the desired product,
- ii. formulation of the model in a general mathematical form. This stage is sometimes called the structure synthesis of the process functional operator;
- iii. identification and determination of numerical values of model constants and/or parameters which are based on experimental or other operating data from a real process.

The process of creating the mathematical model of fermentation starts usually from a simplified scheme of reactions derived from knowledge of metabolic pathways involved. Each metabolic reaction step is characterised by the reaction stoichiometry on one hand and by the flux, represented by the reaction velocity or rate, on the other. Reactions are usually approximated by using one

of the relationships derived from the theory of enzymatic or chemical reactions. The most frequent relationships employed suitable for this purpose are summarised as:<sup>50</sup>

$$r_1 = kS$$

Linear relationship between the rate of the phenomenon and the reaction substrate concentration.

$$r_2 = kS^n$$

Derived from the Freundlich adsorption isotherm, characteristic for most hydrolytic reactions.

$$r_3 = \frac{kS}{K + S}$$

Most typical relationships used in fermentation, represents the rate of change of a phenomenon controlled by chemisorption of the substrate onto one active site such as the molecule of an enzyme.

$$r_4 = \frac{kS^n}{K + S^n}$$

Modification of the previous case where more than one active site is present on each biocatalytic molecule.

$$r_5 = k[1 - \exp^{(-S/K)}]$$

Unusual type of rate relationships suggested for describing the process dynamics, based on a purely physical interpretation derived from equations for movement of a mass point in an environment characterised by dissipation forces.

$$r_6 = k \exp^{(-S/K)}$$

The substance with concentration S is considered as directly participating in the dissipation of kinetic energy during the course of the reaction.

$$r_7 = \frac{kK}{K + S}$$

Based on the principle of hypothetical reversible blocking of the active reaction site by chemisorption of a substance with concentration S.

$$r_8 = \frac{kK}{K + S^n}$$

Derived from inhibition of a larger number of active reaction sites of a certain biochemical process bottleneck.

where:

$k$  is a constant rate value

$S$  is the substrate concentration value

$K$  is another constant value

$n$  is an exponential value

$r_n$  is the product formation rate

Very often, the use of these rate relationships is made by combinations between them based on superimposition of several phenomena in the given sub-system. Sometimes this aspect becomes relevant only when it comes to model identification. This is usually accomplished either by plotting the derived numerical relationships for rates against concentrations of the substrate or of the product. The plot and correlation of the rates against each other enables estimation of local yield coefficients or eventually of their mutual relationships.

The determination of numerical values of the mathematical model parameters based on an appropriate method is an important part of modelling. The methods can be divided into:<sup>50</sup> i) linear and non-linear regression (based on conventional methods of mathematical statistics), ii) momentum analysis of experimental data (using techniques derived from momentum analysis for expressing numerical values of model parameters) and iii) adaptive identification and estimation of model parameters (in which the computer continuously re-evaluates model parameters so that the behaviour of the process can be predicted and controlled).

In the simulation application, model equations are solved for different initial and boundary conditions according to a certain scenario based on the planning of simulation experiments. Simulation studies enable testing of novel or unconventional technological variants of the process such as the change from a batch to continuous-flow cultivation, or to the use of an immobilised-cell technology.

## 1.2 OPTIMAL CONTROL AND OPTIMISATION ALGORITHMS

Beer was first brewed by the ancient Egyptians, but the first true large-scale breweries date from the early 1700s when wooden vats of 1500 barrels capacity were introduced.<sup>42</sup> Even some process control was attempted in these early breweries, as indicated by the recorded use of thermometers in 1757 and the development of primitive heat exchangers in 1801. During the late 1800s Hansen started his pioneering work at the Carlsberg brewery and developed methods for isolating and propagating single yeast cells to produce pure cultures and established sophisticated techniques for the production of starter cultures.<sup>42</sup>

The heuristic method of trial and error, which is used to find an optimal or pseudo-optimal operating regime by manipulating the process technological parameters, is one of the oldest optimisation methods. Biotechnological processes, as the fermentation one, may be conveniently classified according to the mode chosen for process operation: either batch, fed-batch or continuous.<sup>25</sup> During batch operation of a process, no substrate is added to the initial charge nor is product removed until the end of the process. Nevertheless, continuous operation is more economic, where substrate is continually added and product continually removed. Fed-batch processes present the greatest challenge since the feed rate may be changed during the process but no product is removed until the end.

There are three reasons for process control: to ensure or enhance process stability, to suppress the influence of disturbances and finally to optimise the

process performance.<sup>45</sup> The formulation of an optimal control problem requires the following components:<sup>44</sup>

i) A model of the system to be controlled: this is the constitutive equation, together where applicable with end-state conditions and response transformation. It characterises the system and enables the effect of all iterative controls on the system to be predicted.

ii) The constraints upon the design: they limit the range of permissible solutions and fix many systems properties.

iii) The demands presented to the system as a design goal (objective, criterion or index): is derived from a design value statement. The problem is to decide the control that gives the least or greatest value of this index.

Many control design problems are based on two phases: choosing a control structure and choosing an optimal set of parameters given the control structure (a design process may pass repeatedly through these two phases).<sup>37</sup> The parameters are chosen to satisfy a set of inequalities specifying design objectives or to minimise a criterion subject to those inequalities.

The control of a fermentation process is based on the measurement of physical, chemical or biochemical properties of the fermentation broth and the manipulation of physical and chemical environmental parameters such as temperature, dissolved oxygen tension and nutrient concentrations.<sup>36</sup> The microorganisms or biomass concentrations are the central feature of fermentation affecting the rates of growth, substrate consumption and product formation.

Some known optimisation techniques used with the help of a known model are described briefly:<sup>50</sup>

*Analytical methods of optimisation:* are based on the mathematical theory of extremes of smooth continuous functions. The optimum given by an extreme of the object function is obtained upon derivation of this function by the technological parameter and the point is considered where the corresponding derivative is equal to zero. The resulting system of equations is subsequently solved and the solution represents the extreme of the function. From the sign of the second derivative it can be decided if there is a maximum, minimum or an inflection point. If there are some limitations of the function or parameters, the function extreme can be located by applying the method of Lagrange multipliers.<sup>23</sup>

*Numerical optimisation:* and corresponding methods involved were being established simultaneously with the relatively recent developments of systems theory. These methods have been applied particularly in cases where the analytical optimisation approach is especially difficult or outright impossible because of the complexity or discontinuity of the mathematics functions involved. For optimisation of static models (those with parameters not variable in time), the known techniques can be divided, according to the nature of the problem, into linear and non-linear ones.<sup>23,41</sup>

*Linear programming:* is a collection of methods used for optimisation of complex economic and transport problems where the function and constraints can be described by linear relationships. Since most models of fermentation processes are of a non-linear nature, the use of these techniques for process optimisation purposes is not very frequent.

*Non-linear programming:* is a general label for many different computer methods for solving optimisation problems concerning static models. One or more of these methods can solve most of the optimisation process problems. Some

certified methods and algorithms of these methods suitable for a computerised approach to the solution are MINIFUN, NELMIN, MINI, STEEP 1- STEEP 2, etc. All of them programmed in ALGOL 60 or FORTRAN IV in their first stages.<sup>29,41</sup>

*Dynamic programming:* is an optimisation technique that decomposes complex problems into simpler ones and is typical for the solution of optimal performance of multistage systems.<sup>18,29</sup> In the area of fermentation process optimisation, it seems that this technique has a potential for optimisation of the whole process including the fermentation stage.

*Optimisation using the maximum principle:* serves to locate the optimum performance of systems with dynamic characteristics. This method was originally proposed as a technique for optimal process control by a computer.<sup>18</sup> It can be applied, with certain modifications, in off-line process optimisation using a model, particularly for determination of the optimal temperature, pH profile or the substrate-feeding schedule.

The dynamic optimisation of batch processes attempts to find the best input profiles during a batch run. The methods for this optimisation can be classified in three categories:<sup>14</sup>

- i. One time-optimisation: an optimal control problem is formulated based on a dynamic model of the process. The solution provides the required input trajectories.
- ii. Batch-to-batch optimisation: the additional information available with the completion of each batch run is used to improve future operations. The calculations required by these methods are normally carried out in the intermediate period between two consecutive batch runs.
- iii. On-line optimisation: these methods try to compensate the fact that in the presence of modelling errors and disturbances for input profiles computed off-line become sub-optimal. It is accomplished by

repeating on-line model-based optimisation accompanied by system identification several times during a batch run using real time measurements, introducing feedback in the calculation of the input profiles.

### 1.3 SUMMARY

The basics concepts of mathematical modelling for an industrial process have been reviewed in this chapter. Emphasis was made on beer fermentation in batch processes and typical relationships are presented which are part of basic modelling approaches.

Optimal control techniques and optimisation methods are also subject of attention in this chapter. For a start, part of the history of beer control was considered, trying to notice how it is changing from time to time. After that, old and new optimisation algorithms have been presented with their main precursors and techniques.

## **CHAPTER II**

### ***REVIEW OF PREVIOUS WORK ON MODELLING AND CONTROL OF BREWERY FERMENTATION PROCESSES***

#### **2.1. FED-BATCH FERMENTATIONS: MATHEMATICAL MODELLING, PARAMETERS AND CONTROL**<sup>19</sup>

*Batch fermentation* refers to a partially closed system in which most of the materials required are loaded onto the fermentor, decontaminated before the process starts and then removed at the end. 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 of time.

*Continuous culture* is a technique involving feeding the micro-organism used for the fermentation with fresh nutrients and, at the same time, removing spent medium plus cells from the system. A time-independent steady state can be attained which enables one to determine the relations between microbial behaviour and the environmental conditions.

*Fed-batch processes* are commonly used in industrial fermentation. They improve control possibilities, such as computer based fermentation systems.

A fed batch is useful in achieving high concentrations of product because of high concentrations of cells for a relative large span of time. Two cases can be considered: the production of a growth associated product and the production of a non-growth-associated product. In the first case, it is desirable to extend the growth phase as much as possible, minimising the changes in the fermentor as far as specific growth rate, production of final product and avoiding the production of by-products. For non-growth associated products, the fed-batch would have two phases: a growth phase, in which the cells are grown to the required concentration, and then a production phase, in which carbon source and other requirements for production are fed to the fermentor.

Fed-batch fermentation can be the best option for some systems in which the nutrients or any other substrates are only sparingly soluble or are too toxic for adding the whole requirement for a batch process at the start. In the fixed volume fed-batch process, the limiting substrate is fed without diluting the culture. The culture volume can also be maintained practically constant by feeding the growth limiting substrate in undiluted form. A variable fed-batch is one in which the volume changes with the fermentation time due to the substrate feed. The way this volume changes is dependent on the requirements, limitations and objectives of the operator.

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. The production of by-products, which are generally related to the presence of high concentrations of substrate, can also be avoided by limiting its quantity to the amounts that are required solely for the production of the biochemical. When high concentrations of substrate are present, the cells become overloaded. In that, the oxidative capacity of the cells is exceeded and, due to the Crabtree effect, products other than the one of interest are produced, reducing the efficacy of the carbon flux. Moreover, these by-products prove to even contaminate the product of interest, such as ethanol production in baker's yeast production, and to impair the cell growth reducing the fermentation time and its related productivity.

*Adaptive control* is the name given to a control system in which the controller learns about the process by acquiring data from it and keeps on updating the controller parameters. A parameter estimator monitors the process and estimates the process dynamics in terms of the parameters of a previously defined mathematical model of the process. A control design algorithm is then used to generate controller coefficients from those estimates, and a controller sets up the required control signals to the devices controlling the process. An extremely important feature of an adaptive controller is the structure of the model used by the parameter estimator to analyse estimates of process dynamics. The process can be described by a set of mass balance equations, whose quantities can be measured directly or indirectly.

The optimal strategy for the fed-batch fermentation of most organisms is to feed the growth-limiting substrate at the same rate that the organism utilises the substrate; that is to match the feed rate with demand for the substrate. Regardless of the type of control, both mathematical model availability and measurement possibilities influence the design.

The mathematical development has the following assumptions: the feed is provided at a constant rate, the production of mass of biomass per mass of substrate is constant during the fermentation time; and a very concentrated feed is being provided to the fermentor in such a way that the change in volume is negligible (maintaining the level).

Parameter	Equation
Specific Growth Rate	$u = \frac{(FY_{x/s})}{X}$
Biomass (as a function of time)	$X_t = X_0 + FY_{x/s}t$
Product Concentration (non-growth associated)	$P = P_i + q_p X_0 t + \frac{q_p FY_{x/s} t^2}{2}$
Product Concentration (growth associated)	$P = P_i + r_p t$

where:

$X$  is the biomass (mass biomass/volume)

$X_0$  is the biomass at the beginning of the

$t$  is the time

$F$  is the substrate feed rate (mass substrate/(volume.time))

$Y_{x/s}$  is the yield factor (mass biomass/mass substrate)

$u$  is the specific growth rate (time<sup>-1</sup>)

$P$  is the product concentration (mass product/volume)

$q_p$  is the specific production rate of product

$r_p$  is the product formation rate (mass product/(volume . time))

In a variable fed-batch fermentation, an additional element should be considered: the feed. Consequently, the volume of the medium in the fermentor varies because there is an inflow and no outflow.

For the following mathematical development, the assumptions are: specific growth rate is uniquely dependent on the concentrations of the limiting substrate; the concentration of the limiting substrate in the feed is constant; the feed is sterile; and the yields are constant during the fermentation time.

Component	Mass Balance Equation
Overall	$F = \frac{dV}{dt}$
Biomass	$\frac{dX}{dt} = \frac{X(uV - K_d V - F)}{V}$
Substrate	$\frac{dS}{dt} = \frac{F(S_0 - S)}{V} - \frac{uX}{Y_{x/s}}$
Product	$\frac{dP}{dt} = q_p X - \frac{PF}{V}$

where:

$V$  is the volume of the fermentor

$X$  is the biomass concentration (mass biomass/volume)

$t$  is the time

$F$  is the feed rate (volume/time)

$u$  is the specific growth rate (time<sup>-1</sup>)

$K_d$  is the specific death rate (time<sup>-1</sup>)

$S$  is the substrate concentration in the fermentor (mass substrate/volume)

$S_0$  is the substrate concentration in the feed

$Y_{x/s}$  is the yield factor (mass biomass/mass substrate)

$P$  is the product concentration (mass product/volume)

$q_p$  is the specific production rate of product

List of growth models that can be found in biotransformations

Model	Form
Monod	$u = \frac{u_{max} S}{K_m + S}$
Constant yield	$Y_{x/s} = Y_0$

Substrate inhibition	$u = \frac{u_{max}S}{K_m + S + \frac{S^2}{K_i}}$
Constant yield	$Y_{x/s} = Y_0$
Substrate inhibition	$u = \frac{u_{max}S(1-TS)}{K_m + S + \frac{S^2}{K_i}}$
Variable yield	$Y_{x/s} = \frac{Y_0(1-TS)}{1+RS+GS^2}$
Substrate and product inhibition	$u = \frac{u_{max}S}{K_m + S + \frac{S^2}{K_i}}$
Inhibitions	$u = u_{max} \left( 1 - \frac{P}{P_m} \right)$
	$q_p = \alpha \cdot u + \beta$
Constant yields	$\alpha, \beta \text{ and } Y_{x/s}$

where:

$u$  is the specific growth rate (time<sup>-1</sup>)

$S$  is the substrate concentration in the fermentor (mass substrate/volume)

$K_m$  is the mass constant (mass of substrate/volume)

$Y_{x/s}$  is the yield factor (mass biomass/mass substrate)

$K_i$  refers to the inhibition constant (mass of substrate/volume)

$T$  is the time constant

$P$  is the product concentration (mass product/volume)

$\alpha$  and  $\beta$  are constants (volume/mass substrate)

$G$  is a kinetic constant value (volume/substrate)<sup>2</sup>

$q_p$  is the specific production rate of product

To design a feedback controller, a certain parameter to be maintained within certain limits is analysed as far as parameter requirements to keep its value within the desired range or level.

Because of some difficulties with measurement of some variables, some linear estimation of state can be used such as the Kalman filter. The *Kalman filter* uses past measurements for a weighted least square estimate of the current variable as reflected through the dynamic model. Another alternative is the use of a predictive controller<sup>4</sup>, which uses a linear dynamic mathematical model of the process and calculates the response resulting from initial conditions, disturbances, manipulated variable inputs and set-point changes.

*Calorimetry* is an excellent tool for monitoring and controlling microbial fermentations. Its main advantage is the generality of this parameter, since microbial growth is always accompanied by heat production, and the measurements are performed continuously on-line without introducing any disturbances to the culture.

For the production of a growth-associated product, the production of a certain product is related with the specific growth rate of the producing microorganism. Consequently, it is of interest to feed the fermentor in such a way that the specific growth rate remains constant.

*Substrate* is a particularly important parameter to control due to eventual associated growth inhibitions and to increase the effectiveness of the carbon flux, by reducing the amount of by-products formed and the amount of carbon dioxide evolved.

The production of by-products is undesirable because it reduces the efficacy of the carbon flux in fermentation. The production of these components take place whenever the substrate is provided in quantities that exceed the oxidative capacity of the cells. This approach has been used in the fermentation of *Saccharomyces cerevisiae*, in which acid production rate is used to provide on-line estimates of the specific growth rate.

*Respiratory quotient*, the ratio between the moles of carbon evolved per moles of oxygen consumed, has been a general method used to determine indirectly the lack of substrate in the growth medium. It is a fairly rapid method of measurement, which is useful because the gas analyses can be related to crucial process variables.

The feeding mode influences a fed-batch fermentation by defining the growth rate of the microorganisms and the effectiveness of the carbon cycle for product formation and minimisation of by-product formation. Inherently related with the concept of fed-batch, the feeding mode allows many variances in substrate or other components constitution and provision modes and consequently, better controls over inhibitory effects of the substrate and/or product.

An unusual method for controlling process parameters is the proton production, which estimates on-line the specific growth rates in a fed-batch culture and, indirectly, the substrate concentration. The measured amount of proton produced during the fermentation is calculated based on the volume of base added to the fermentor to control the pH at a pre-set value.

A linear relationship exists between the culture fluorescence and the dry cell weight concentration up to 30g dry cell weight/liter. Thus, fluorescence can be used to estimate on-line the biomass concentration and be a controlling parameter in the feed provision.

The control of a fed-batch fermentation process can implicate many difficulties: low accuracy of on-line measurements of substrate concentrations, limited validity of the feed schedule under a variety of conditions and prediction of variations due to strain modification or change in the quality of the nutrient medium. These aspects point to the need of a fed-batch fermentation strategy which is model independent, identifies the optimal state on-line, incorporates negative feedback control into the nutrient feeding system and contemplates a saturation kinetic model, a variable yield model, variation in feed substrate concentration and product inhibited fermentation.

In an open-loop operation system, a predetermined feed schedule is used. This approach considers that the system can be exactly translated into a set of mass balance equations which contains the specific growth rates. However, it is easy to assume that due to a non-identified physiological problem of the cells, the specific growth rate can be either higher or lower than the one that was previously established. The open-loop feed policy does not always result in an optimal operation.

A feedback control algorithm requires only a reliable on-line estimate of the specific growth rate. Since the objective of the algorithm is to optimise the cell-mass production by controlling the specific growth rate ( $\mu$ ) at an optimum value  $\mu_{opt}$ , the feedback law can be defined.

The use of fed-batch culture by the fermentation industry takes advantage of the fact that the concentration of the limiting substrate may be maintained at a very low level, thus: avoiding repressive effects of high substrate concentration, controlling the organism's growth rate and consequently controlling the oxygen demand of the fermentation.

*Saccharomyces cerevisiae* is industrially produced using the fed-batch technique to maintain the glucose at very low concentrations, maximising the biomass yield and minimising the production of ethanol, the chief by-product.

## 2.2 COMPUTER SIMULATION FOR THE ALCOHOLIC FERMENTATION PROCESS BASED ON A HETEROGENEOUS MODEL<sup>17</sup>

This model distinguishes the intracellular concentrations and the mass transfer resistance between the two phases. The model has been used to simulate successfully an industrial fed-batch fermentor and the superiority of the model over pseudohomogeneous models has been demonstrated.

The paper is concerned with the development of a more rigorous set of design equations for the fermentation process.

The design equations are based on a model that takes into account the mass transfer resistance between the intracellular and extracellular fluids, and is therefore expressed in terms of intracellular and extracellular concentrations of ethanol and sugar as well as the concentration of the micro-organism as state variables. The more classical approach of reducing the complex structure of the floc to an equivalent sphere is used.

Parameter	Description	Unit
$D_p$	Floc diameter	dm
$Kg_s$	Mass transfer coefficient for sugar	dm/h
$Kg_p$	Mass transfer coefficient for ethanol	dm/h
$K_s$	Saturation constant	g/L
$K_p$	Inhibition constant	g/L
$K_p'$	Rate constant	g/L
$n$	Toxic factor	dimensionless
$P$	Intracellular ethanol concentration	g/L
$P_b$	Extracellular ethanol concentration	g/L
$R_p$	Specific rate of ethanol production	$h^{-1}$
$R_s$	Specific rate of sugar consumption	$h^{-1}$
$R_x$	Specific growth rate	$h^{-1}$
$S$	Intracellular sugar concentration	g/L
$S_b$	Extracellular sugar concentration	g/L
$t$	Time	h
$V_b$	Liquid volume of the bulk solution	L
$X$	Biomass concentration	g/L
$X_m$	Maximum biomass concentration	g/L
$Y_c$	Yield factor for yeast	g yeast produced/g sugar
$Y_p$	Yield factor for ethanol	g ethanol produced/g sugar
$\mu_m$	Maximum specific growth rate	$h^{-1}$
$\rho$	Density of the floc	g/L

**Table 2.2.1: Nomenclature**

For batch fermentation, the equations for the intracellular substrate and ethanol are given by:

$$\frac{dS}{dt} = \frac{6Kg_s(S_b - S)}{D_p} - R_s\rho \quad (2.2.1)$$

$$\frac{dP}{dt} = \frac{-6Kg_p(P - P_b)}{D_p} + R_p\rho \quad (2.2.2)$$

The extracellular concentrations of substrate and ethanol are given by:

$$\frac{dS_b}{dt} = \frac{-6XKg_s(S_b - S)}{D_p(\rho - X)} \quad (2.2.3)$$

$$\frac{dP_b}{dt} = \frac{6XKg_p(P - P_b)}{D_p(\rho - X)} \quad (2.2.4)$$

The variation of the yeast concentration with time is given by:

$$\frac{dX}{dt} = R_x X \quad (2.2.5)$$

The kinetic rate equations, which were found to fit the experimental batch fermentor results for both intracellular and extracellular concentrations, are given by:

$$R_x = \frac{\mu_m K_p S \left(1 - \frac{X}{X_m}\right)^n}{(K_p + P)(K_s + S)} \quad (2.2.6)$$

$$R_s = \left(\frac{1}{Y_c}\right) \left[ R_x + \frac{\mu_m K_p'}{K_p' + P} \right] \quad (2.2.7)$$

$$R_p = R_s Y_p$$

The mass transfer coefficient of ethanol which best fits the experimental results was found to be a function in bulk substrate concentration in the following form:

$$Kg_p = a_0 + a_1 S_b + a_2 S_b^2 + a_3 S_b^3 \quad (2.2.8)$$

where,  $a_0 = 0.01071204$

$$a_1 = -3.6675^{-4}$$

$$a_2 = 0.43937^{-5}$$

$$a_3 = -1.79292^{-8}$$

The rest of the model parameters are given in **Table 2.2.2**

It was proposed that owing to an unbalance between the rate of production of ethanol and its net outflow there would be a net accumulation of ethanol inside the cells. The great value of experiments giving intracellular and extracellular concentrations is that they allow the development of such heterogeneous models

as the one developed here and also represent a critical test for fitting the model parameters to the concentration profiles in both phases.

	<i>Parameter</i>	<i>Values of the Parameter</i>
Kinetic Parameters	$\mu_m$	0.313
	$K_p$	35*
	$X_m$	1.5
	$n$	1.7
	$K_s$	0.22
	$K_p'$	3.0*
	$Y_c$	0.035
	$Y_p$	0.420
Physical Parameters	$D_p$	0.0005
	$Kg_s$	0.0504
	$P$	200
	$Kg_p$	Eq. (2.2.8)

**Table 2.2.2: Model Parameters (Units in Table 2.2.1)**

\* Empirical fitting using unsteady state experimental results

Its is important to notice that although the flocculation phenomenon has a negative effect on the rate of fermentation through the mass transfer resistance, it has a beneficial effect on the post fermentation stage of separating the micro-organism from the solution.

The model after introducing the necessary simple modification for fed-batch operation is used to simulate an industrial fed-batch fermentor. It operates under aerobic conditions for a period of 6-8 h in order to grow the necessary initial amount of yeast. Then it operates under anaerobic feed-batch conditions until the liquid volume of the fermentor reaches the working volume (65000 L). This last period lasts from 11 to 12 h, and after this period the fermentor operates under batch conditions for a period ranging from 6 to 8 h, until the fermentable sugar is consumed.

Initial conditions (data obtained from plant) of the anaerobic period are:

Biomass concentration	$X_0=1.09$ dry wt/L
Extracellular ethanol concentration	$P_{b0}=25$ g/L
Extracellular sugar concentration	$S_{b0}=59$ g/L

Intracellular ethanol concentration	$P_0=50$ g/L
Intracellular sugar concentration	$S_0=55$ g/L
Initial liquid volume	$V_0=36000$ L
Final total volume of the contents	$V_t=65000$ L
Volumetric feed flow rate	$Q=2500$ L/h
Sugar concentration in feed stream	$S_f=152$ g/L

The same parameters in Table 2.2.2 are used, except for the following values obtained from plant tests:

$Y_p=0.45$	$Y_c=0.01$
$X_m=2.5$	$D_p=0.0001$

The heterogeneous model developed for the fermentation process offers a better insight into the process and allows the understanding of the role played by the flocculation process.

### 2.3. OPTIMISATION OF A BATCH FERMENTATION PROCESS BY GENETIC ALGORITHMS<sup>3</sup>

The conventional way for beer fermentation is to add yeast to the wort and wait for some time, letting the yeast consume substrates and produce ethanol (without stirring). Fermentation can be accelerated with an increase of temperature but some contamination risks (*Lactobacillus*, etc.) and undesirable by-products yields (diacetyl, ethyl acetate, etc.) could appear.

With the data obtained experimenting in the laboratory, it has been possible to develop a new model of the fermentation dynamic behaviour based on the activity of suspended biomass. Thus, some equations of the model are devoted to the biomass behaviour: part of it settles slowly and is inactive, while the active biomass awakes from latency to start growing and producing ethanol, etc. An important effect of the temperature over the process acceleration was recorded: this influence is represented through variation laws of the coefficients of the model.

<b>Parameter</b>	<b>Description</b>	<b>Unit</b>
$x_{active}$	Suspended active biomass	g/l
$x_{lag}$	Suspended latent biomass	g/l
$x_{initial}$	Initial suspended biomass	g/l
$x_{bottom}$	Suspended dead biomass	g/l
$s_i$	Initial sugar	g/l
$s$	Concentration of sugar	g/l
$e$	Ethanol concentration	g/l
acet	Ethyl acetate concentration	ppm
diac	Diacetyl concentration	ppm
$\mu_x$	Specific rate of growth	
$\mu_D$	Specific settle down rate	
$\mu_s$	Specific substrate consumption	
$\mu_a$	Specific rate of ethanol production	
$f$	Fermentation inhibition factor	
$k_{dc}$	Appearance rate	
$k_{dm}$	Reduction or disappearance rate	

**Table 2.3.1: Nomenclature**

Biomass is segregated into three different types of cells: lag, active and dead. The whole process can be divided in two consecutive phases: a lag phase and a fermentation phase.

Here is the enunciation of the model:

$$\text{Lag Phase} \quad x_{active} + x_{lag} = constant = 0.48x_{initial} \quad (2.3.1)$$

$$\frac{dx_{lag}}{dt} = -\dot{x}_{active} = -\mu_{lag} x_{lag} \quad (2.3.2)$$

$$\text{Fermentation Phase} \quad \frac{dx_{active}}{dt} = \mu_x x_{active} - k_m x_{active} + \mu_{lag} x_{lag} \quad (2.3.3)$$

$$\frac{dx_{bottom}}{dt} = k_m x_{active} - \mu_D x_{bottom} \quad (2.3.4)$$

$$\mu_x = \frac{\mu_{x0} s}{0.5s_{initial} + e} \quad \mu_D = \frac{0.5s_{initial} \mu_{D0}}{0.5s_{initial} + e} \quad (2.3.5)$$

$$\frac{ds}{dt} = -\mu_s x_{active} \quad (2.3.6)$$

$$\frac{de}{dt} = \mu_a f x_{active} \quad (2.3.7)$$

$$f = 1 - \frac{e}{0.5s_{initial}} \quad \mu_s = \frac{\mu_{s0}S}{k_s + s} \quad \mu_a = \frac{\mu_{a0}S}{k_s + s} \quad (2.3.8)$$

To describe the evolution of the by-products that have a negative impact (ethyl acetate that contributes with bad odour and diacetyl that makes beer heavy and butter flavoured), the following equations are established:

$$\frac{d(acet)}{dt} = \mu_{eas} \frac{ds}{dt} = \mu_{eas} \mu_s x_{active} \quad (2.3.9)$$

$$\frac{d(diac)}{dt} = k_{dc} s x_{active} - k_{dm} (vdk) e \quad (2.3.10)$$

Since the process depends on temperature, we have the value of all parameters of the model calculated as Arrhenius functions of temperature:

$$\mu_{x0} = e^{108.31 - \frac{31934.09}{T+273.15}}$$

$$k_m = e^{130.16 - \frac{38313}{T+273.15}}$$

$$\mu_{eas} = e^{89.92 - \frac{26589}{T+273.15}}$$

$$\mu_{D0} = e^{33.82 - \frac{10033.28}{T+273.15}}$$

$$\mu_{s0} = e^{-41.92 + \frac{11654.64}{T+273.15}}$$

$$\mu_{a0} = e^{3.27 - \frac{1267.24}{T+273.15}}$$

$$\mu_{lag} = e^{30.72 - \frac{9501.54}{T+273.15}}$$

$$k_s = e^{-119.63 + \frac{34203.95}{T+273.15}}$$

$$k_{dc} = 0.000127672$$

$$k_{dm} = 0.00113864$$

An important new feature is the modelling of diacetyl without the inclusion of empirical delays.

The objective function used in order to accelerate the industrial fermentation reaching the required ethanol level in less time, without quality loss or contamination risks. The following terms were defined:

$$J_1 = +10 \cdot ethanol_{end} \quad \text{Measure the final ethanol production.}$$

$$J_2 = -5.73 \cdot e^{(95 \cdot diac - 11.51)} \quad \text{Limit diacetyl concentration at the end.}$$

$$J_3 = -1.16 \cdot e^{(46 \cdot acet - 66.77)} \quad \text{Limit level of ethyl acetate at the end.}$$

$$J_4 = - \int_0^t \mu_{LB} dt \quad \text{Temperature limit along the process.}$$

These terms combined to obtain a cost function of the process:

$$J = J_1 + J_2 + J_3 + J_4$$

We need to get a temperature profile that maximises this function in less time. As an initial reference, the same temperature profile used by industry was taken for a solution along 150 hours, with a value cost function of  $J=487.82$  to be improved.

The industry temperature profile along 200 hours is described from the graph used by the real industry and is presented in Chapter III as part of the modelling simulation, optimisation and results.

#### 2.4. OPTIMAL CONTROL OF A FED-BATCH FERMENTATION PROCESS<sup>48</sup>

Fermentation processes are used for producing many fine substances such as amino acids, antibiotics, baker's yeast, enzymes, etc. Among the modes of operation (batch, fed-batch and continuous), the fed-batch technique is often used in industry due to its ability to overcome the catabolic repression or glucose effect, which usually occurs during production of these fine chemicals.

The most used approach for process optimisation is to calculate an optimal feed-rate profile, that will optimise a given objective function. Since many state variables in fermentation processes, such as biomass, substrate and product concentration, are difficult to measure on-line, many methods have therefore been developed for on-line estimation of these state variables. The proposed method separates the optimisation problem of a fermentation process into two parts: firstly the optimal substrate concentration profile which has direct effect on the biochemical reaction rates in the fermentation process is derived; then a controller is designed to track the obtained optimal substrate concentration profile.

<b>Parameter</b>	<b>Description</b>	<b>Unit</b>
F	Substrate feed rate	L/h
F <sub>max</sub>	Maximum substrate feed rate	L/h
S	Substrate concentration	g/l
S <sub>opt</sub>	Optimal substrate concentration	g/l
S <sub>f</sub>	Substrate concentration in the feed	g/l
X	Biomass concentration	g/l
P	Product concentration	mg/l
V	Culture volume	L
V <sub>f</sub>	Maximum culture volume	L
D	Dilution rate	h <sup>-1</sup>
Y <sub>xs</sub>	Yield of biomass from substrate	g biomass/g
u	Control variable	
t	Time	h
t <sub>f</sub>	Final time	h
μ	Specific growth rate	h <sup>-1</sup>
μ <sub>max</sub>	Maximum specific growth rate	h <sup>-1</sup>
π	Specific product formation rate	h <sup>-1</sup>
π <sub>max</sub>	Maximum specific product formation	h <sup>-1</sup>
K <sub>S</sub> , K <sub>i</sub> , K <sub>πS</sub> , K <sub>πi</sub>	Kinetic constants	g/l

**Table 2.4.1: Nomenclature**

Mathematical models of fed-batch fermentation process can be written based on mass balance equations as:

$$\frac{dX}{dt} = \mu X - DX \quad (2.4.1)$$

$$\frac{dS}{dt} = -\frac{1}{Y_{XS}} \mu X + D(S_f - S) \quad (2.4.2)$$

$$\frac{dP}{dt} = \pi X - DP \quad (2.4.3)$$

$$\frac{dV}{dt} = F \quad (2.4.4)$$

$$D = \frac{F}{V} \quad (2.4.5)$$

Those equations represent a general model for a secondary metabolic production. For a primary metabolic process, since the primary metabolic depends directly on the biomass, and biomass can also be referred to as one of

the primary metabolic, eq. (2.4.3) can then be omitted. The remaining equations then constitute a model for the primary metabolic production in which biomass is the product.

Model predictive control is defined as a control scheme in which the controller determines a control variable profile that optimises some open-loop performance objective on a time interval extending from the current time to the current time plus a prediction horizon.

Non-linear model predictive control applied to a fed-batch fermentation process under the proposed control scheme can then be stated as follows, where the substrate feed rate ( $F$ ), which is the control variable, can be obtained:

$$\min_{F(k) \dots F(k+m-1)} \sum_{i=1}^p (\hat{S}(k+i/k) - S_{opt}(k+i))^2$$

where  $\hat{S}(k+i/k)$ : model predictive value of substrate concentration at time  $(k+i)$  based on information at time  $k$ .

$S_{opt}(k+i)$ : optimal substrate concentration at time  $(k+i)$ .

$p$ : prediction horizon

$m$ : control horizon:  $(F(k+1) = 0 \quad \forall \geq m; m < p)$

subject to:  $\frac{dX}{dt} = \mu X - DX; \quad X(0) = X_0$

$$\frac{dS}{dt} = -\frac{1}{Y_{XS}} \mu X + D(S_f - S); \quad S(0) = S_0$$

$$\frac{dP}{dt} = \pi X - DP; \quad P(0) = P_0$$

$$\frac{dV}{dt} = F; \quad V(0) = V_0$$

$$0 \leq F \leq F_{max}$$

$$V(t_f) \leq V_f$$

with:  $t \in [t_0, t_0 + T]$

The proposed closed-loop optimal control method is illustrated with application to primary and secondary metabolic production. In the primary metabolic production process, primary metabolites are synthesised directly from the primary metabolism. In the secondary metabolic production process, secondary metabolic production is associated with limited or sub-optimal growth, in which generally takes place two phases: growth phase and production phase. The specific growth rate ( $\mu$ ) and the specific product formation rate ( $\pi$ ) in the models are functions of substrate concentration and in the form of substrate inhibition kinetic, in the form:

$$\mu = \frac{\mu_{max} S}{\left( K_s + S + \frac{S^2}{K_i} \right)} \quad (2.4.6)$$

$$\pi = \frac{\pi_{max} S}{\left( K_{\pi s} + S + \frac{S^2}{K_{\pi i}} \right)} \quad (2.4.7)$$

The substrate inhibition kinetic is employed here because it can represent the catabolic repression effect, which in turn requires the operation of fermentation in the fed-batch mode. The parameters of the models are tabulated in Table 2.4.2 for the primary metabolic process and in Table 2.4.3 for the secondary metabolic process. They represent a general characteristic for a class of processes with the substrate inhibition type kinetic.

Parameter	Value	Unit
$\mu_{max}$	0.10	(g biomass/(g biomass*hr))
$K_s$	3.0	(g substrate/litre)
$K_I$	8.34	(g substrate/litre)
$Y_{xs}$	0.164	(g biomass/g substrate)
$X(0)$	1	(g biomass)
$S(0)$	20	(g substrate)
$V(0)$	20	(litre)
$V(t_f)$	50	(litre)
$S_f$	100	(g substrate/litre)

**Table 2.4.2: Model Parameters (Primary Metabolic)**

Parameter	Value	Unit
$\mu_{max}$	0.10	(g biomass/(g biomass*hr))
$K_s$	3.0	(g substrate/litre)
$K_i$	8.34	(g substrate/litre)
$Y_{xs}$	0.164	(g biomass/g substrate)
$\pi_{max}$	0.25	(mg product/g biomass*hr)
$K_{\pi s}$	0.4	(g substrate/litre)
$K_{\pi i}$	10	(g substrate/litre)
$X(0)$	1.0	(g biomass)
$S(0)$	4.6	(g substrate)
$V(0)$	20	(litre)
$V(t_f)$	50	(litre)
$S_f$	100	(g substrate/litre)

**Table 2.4.3: Model Parameters (Secondary Metabolic)**

## 2.5. APPLICATION OF A NOVEL OF A NOVEL OPTIMAL CONTROL ALGORITHM TO A BENCHMARK FED-BATCH FERMENTATION PROCESS<sup>7</sup>

The degrees of freedom for the determination of the optimum conditions in batch processes, maximum product with minimum cost and time, are often a combination of the initial conditions, the set-point profile and the time allowed for the transformation phase. The procedure used for determining an acceptable set-point profile is called dynamic optimisation, but the profile obtained with this method will only be optimal for the specific model and parameter values used in the optimisation.

The ISOPE algorithm (Integrated System Optimisation and Parameter Estimation) developed by Roberts<sup>34</sup> is capable of producing the true optimum regardless of model-reality difference. It takes account of the interaction between the two problems of system optimisation and parameter estimation by introducing a modifier into the model based optimisation problem. In further research, this principle was extended to develop an iterative technique for solving continuous time dynamic optimal control problems, this gave rise to the continuous time DISOPE algorithm (Dynamic Integrated System Optimisation and Parameter Estimation). There are also processes in the industrial practice which are discrete in nature and can only be controlled by using a discrete formulation of this algorithm, this has been developed, analysed and implemented by Becerra and Roberts<sup>10</sup>.

The formulation of the discrete-time DISOPE algorithm for batch processes is explained below:

Consider this real optimal control problem (ROP):

$$\begin{aligned}
 \min_{u(k)} J &= \varphi^*(x(N)) + \sum_{k=0}^{N-1} L^*(x(k), u(k), k) \\
 \text{s.t.} \quad x(k+1) &= f^*(x(k), u(k), k); & k \in [0, N-1] \\
 x(0) &= x_0 & (2.5.1)
 \end{aligned}$$

where  $u(k) \in \mathcal{U}^m$  and  $x(k) \in \mathcal{X}^n$  are the discrete control and state vectors, respectively,  $\varphi^*: \mathcal{X}^n \rightarrow \mathcal{R}$  is called the real terminal measure,  $L^*: \mathcal{X}^n \times \mathcal{U}^m \times \mathcal{K} \rightarrow \mathcal{R}$  is the real performance measure function and  $f^*: \mathcal{X}^n \times \mathcal{U}^m \times \mathcal{K} \rightarrow \mathcal{X}^n$  represents the real process dynamics.

Then, after expanding the optimal control problem (which is equivalent to the ROP), applying the theory of Lagrange multipliers and examining the resulting optimality conditions produces this modified model-based optimal control problem (MMOP):

$$\begin{aligned}
 \min_{u(k)} J &= \varphi(x(N), \gamma_1) - \Gamma_1^T x(N) + \sum_{k=0}^{N-1} \left[ L(x(k), u(k), \gamma_2(k)) - \lambda(k)^T u(k) \right. \\
 &\quad \left. - \beta(k)^T x(k) + \frac{1}{2} r_1 \|u(k) - v(k)\|^2 + \frac{1}{2} r_2 \|x(k) - z(k)\|^2 \right] \\
 \text{s.t.} \quad x(k+1) &= f(x(k), u(k), \alpha(k)); & k \in [0, N-1] \\
 x(0) &= x_0 & (2.5.2)
 \end{aligned}$$

where  $\varphi: \mathcal{X}^n \times \mathcal{R} \rightarrow \mathcal{R}$  is called the model terminal measure,  $L: \mathcal{X}^n \times \mathcal{U}^m \times \mathcal{R} \rightarrow \mathcal{R}$  is the model performance measure function and  $f: \mathcal{X}^n \times \mathcal{U}^m \times \mathcal{R} \rightarrow \mathcal{X}^n$  represents the dynamic model. The parameters  $\alpha(k) \in \mathcal{R}^r$ ,  $\gamma_2(k) \in \mathcal{R}$  and  $\gamma_1 \in \mathcal{R}$  are associated with the functions  $f$ ,  $L$  and  $\varphi$ , respectively;  $v(k) \in \mathcal{U}^m$  and  $z(k) \in \mathcal{X}^n$  are introduced to separate the control and state variables between the so-called optimisation

and parameter estimation problems. The sequence  $v(k) \in [0, N-1]$  represents the input profile to the batch process along every batch. The terms proportional to  $r_1$  and  $r_2$  are introduced to augment the performance index to provide convexification (improve convergence in difficult cases).

The solution of the MMOP is achieved under specified parameters:

$$\begin{aligned} f(z(k), v(k), \alpha(k)) &= f^*(z(k), v(k), k) \\ L(z(k), v(k), \gamma_2(k)) &= L^*(z(k), v(k), k) \\ k &\in [0, N-1] \end{aligned} \quad (2.5.3)$$

$$\begin{aligned} \gamma(k) &= \left[ \frac{\partial f}{\partial v(k)} - \frac{\partial f^*}{\partial v(k)} \right]^T \hat{p}(k+1) + \left[ \frac{\partial L}{\partial v(k)} - \frac{\partial L^*}{\partial v(k)} \right]^T \\ \beta(k) &= \left[ \frac{\partial f}{\partial z(k)} - \frac{\partial f^*}{\partial z(k)} \right]^T \hat{p}(k+1) + \left[ \frac{\partial L}{\partial z(k)} - \frac{\partial L^*}{\partial z(k)} \right]^T \\ k &\in [0, N-1] \end{aligned} \quad (2.5.4)$$

$$\varphi(z(N), \gamma_1) = \varphi^*(z(N)) \quad (2.5.5)$$

$$\Gamma_1 = \nabla_z \varphi(z(N), \gamma_1) - \nabla_z (\varphi^* z(N)) \quad (2.5.6)$$

$$\begin{aligned} v(k) &= u(k); \quad k \in [0, N-1] \\ z(k) &= x(k); \quad k \in [0, N] \\ \hat{p}(k) &= p(k); \quad k \in [0, N] \end{aligned} \quad (2.5.7)$$

with  $\hat{p}(k)$  introduced as a separation variable for the co-state  $p(k)$  obtained by solving MMOP.

Assuming convergence, the algorithm achieves the necessary optimality conditions of the ROP via repeated solutions of the MMOP. It is possible to integrate the iterations of DISOPE towards the dynamic optimum with the batchwise operation of the process. This is done by introducing a modification on the basic algorithm so that the control profile obtained at each iteration is

applied to the real process at every transformation phase. If the transformation time is fixed, the discrete-time algorithm is described:

- Data:**  $f, L, \varphi, x_0, N$  and means for calculating  $f^*, L^*$  and  $\varphi^*$ .
- Step 0:** Compute or choose a nominal solution  $v^0(k), k \in [0, N-1]$ , and  $\hat{p}^0(k), k \in [0, N]$ . Set  $i=0$ .
- Step 1:** During the transformation phase, apply the control profile  $v^i(k)$  to the batch plant. Obtain the corresponding state response  $z^i(k), k \in [0, N]$  and dynamic derivatives  $\partial f^*/\partial z(k)$  and  $\partial f^*/\partial v(k), k \in [0, N-1]$ .
- Step 2:** Compute the parameters  $\alpha^i(k), \gamma_2^i(k), k \in [0, N-1]$ , to satisfy (2.5.3) and  $\gamma_1$  to satisfy (2.5.5). This is called the parameter estimation step.
- Step 3:** Compute the multipliers  $\lambda^i(k)$  and  $\beta^i(k), k \in [0, N-1]$ , from (2.5.4) and  $\Gamma_1$  from (2.5.6).
- Step 4:** With the specified  $\alpha^i(k), \gamma_2^i(k), \lambda^i(k), \beta^i(k), k \in [0, N-1], \gamma_1(k)$  and  $\Gamma_1$  solve the discrete-time MMOP to obtain  $u^{i+1}(k), k \in [0, N-1], x^{i+1}(k)$  and  $p^{i+1}(k), k \in [0, N]$ . This is called the system optimisation step.
- Step 5:** This step tests convergence and updates the estimate for the optimal solution of ROP. To provide a mechanism for regulating convergence, a simple relaxation method is employed to satisfy (2.5.7). This is:

$$\begin{aligned} v^{i+1}(k) &= v^i(k) + k_v (u^{i+1}(k) - v^i(k)) \\ \hat{p}^{i+1}(k) &= \hat{p}^i(k) + k_p (p^{i+1}(k) - \hat{p}^i(k)) \end{aligned} \quad (2.5.8)$$

where  $k_v$  and  $k_p$  are scalar gains (usually  $\in [0, 1]$ ). If  $v^{i+1}(k) = v^i(k), k \in [0, N-1]$  within a given tolerance stop, else set  $i=i+1$  and continue from step 1.

For the estimation of the first derivatives matrices  $\partial f^*/\partial z$  and  $\partial f^*/\partial v$  required in the algorithm during the transformation phase, the method used is described below:

$$\text{Given} \quad x(k+1) = f^*(x(k), u(k)) \quad (2.5.9)$$

Define the augmented vector  $X = [x \ u]^T$ . As a consequence  $f^*(x, u) = f^*(X)$ . Given two different trajectories  $x^i(\cdot)$ ,  $x^{i+1}(\cdot)$ , and  $u^i(\cdot)$ ,  $u^{i+1}(\cdot)$ , define the change trajectory as:

$$\delta X^i(\cdot) = \begin{bmatrix} x^{i+1}(\cdot) - x^i(\cdot) \\ u^{i+1}(\cdot) - u^i(\cdot) \end{bmatrix} \quad (2.5.10)$$

The state and control trajectories denoted by the superindexes  $i$  and  $i+1$  may be interpreted as two successive iterates of the DISOPE algorithm.

For approximating the Jacobian a technique can be used based on Broyden's formula. A recursion is defined on the Jacobian trajectories, given two successive control and state trajectories:

$$D^{i+1}(\cdot) = D^i(\cdot) + \frac{[f^{*i+1}(\cdot) - f^{*i}(\cdot) - D^i(\cdot)\delta X^i(\cdot)]\delta X^i(\cdot)^T}{\|\delta X^i(\cdot)\|^2} \quad (2.5.11)$$

where  $D(\cdot)$  is the  $n \times (n + m)$  Jacobian matrix trajectory:

$$D(\cdot) = \frac{\partial f^*(X(\cdot))}{\partial X(\cdot)} = \begin{bmatrix} \frac{\partial f^*(x(\cdot), u(\cdot))}{\partial x(\cdot)} & \frac{\partial f^*(x(\cdot), u(\cdot))}{\partial u(\cdot)} \end{bmatrix} \quad (2.5.12)$$

Noting that  $x(k+1) = f^*(X(k)) = q x(k)$ , where  $q$  is the forward shift operator. Thus  $f^*(\cdot)$  in (2.5.11) is the state trajectory  $x(\cdot)$  shifted by one sample. It uses information of state and control trajectories along the transformation phase of the batch process.

For the same input profile, the response of the batch process can be different from batch to batch because of internal parameter variations and stochastic disturbances. It has been assumed that the process dynamics are unknown but fixed. To handle the random variations, the expected value of the objective function is minimised by working with the expected value of the state trajectory  $\{z^i(\cdot)\}$ . In step 1 the expected value of the response of the process  $E\{z^i(\cdot)\}$  for a given input profile  $\{v^i(\cdot)\}$  may be approximated by an average of the process response for a finite number of batches  $\{z_{11}^i(\cdot)\} \dots \{z_{Nb}^i(\cdot)\}$ :

$$\bar{z}^i(k) = \frac{1}{N_b} \sum_{j=1}^{N_b} z^i_j(k); \quad k \in [0, N] \quad (2.5.13)$$

Bound constraints on the decision variables  $u(k)$ :

$$u_l \leq u(k) \leq u_h \quad (2.5.14)$$

can easily be accommodated within the algorithm by using a variable transformation technique. The use of a saturation function both when evaluating the function  $L^*$ , and when applying the input profile  $\{v(\cdot)\}$  to the process, converts this type of constraint into a nonlinearity of the real problem, while the solution of MMOP remains unconstrained.

State constraints are handled within DISOPE by using a penalty relaxation approach, assuming that  $s$  state dependent inequality constraints are defined by:

$$\Psi(x(k)) \geq 0 \quad (2.5.15)$$

where  $\Psi: \mathcal{R}^n \rightarrow \mathcal{R}^s$  is the state constraint function. By using the penalty relaxation technique, the original state constrained problem is transformed into an unconstrained problem by adding a penalty term to the original performance weighting function  $L^*$ :

$$L^*_{\rho}(x(k), u(k)) = L^*(x(k), u(k)) + \rho \sum_{j=1}^s \left[ P_{\varepsilon}(\Psi_j(x(k))) \right]^2 \quad (2.5.16)$$

where  $\rho$  is a penalty factor and  $P_{\varepsilon}: \mathcal{R} \rightarrow \mathcal{R}$  is smoothed function given by:

$$P_{\varepsilon}(w) = \begin{cases} w & w \leq -\varepsilon \\ -\varepsilon(w + \varepsilon)^2 / 4\varepsilon & -\varepsilon < w < \varepsilon \\ 0 & w \geq \varepsilon \end{cases} \quad (2.5.17)$$

where  $w$  is a given scalar argument and  $\varepsilon$  is a small scalar value.

In order to define the model-based problem, a simple empirically calculated linear state space model of the process was used. The structure of the dynamic equation used in MMOP is as follows:

$$x(k+1) = f(x(k), u(k), \alpha(k)) = Ax(k) + Bu(k) + \alpha(k) \quad (2.5.18)$$

where  $A$  and  $B$  are known matrices which represent a linear approximation of the real and unknown dynamic mapping  $f^*$ .

Values of  $A$  and  $B$  can be identified from input/output data using the least squares method. The ARX model structure with first order matrix polynomials is assumed as follows:

$$A^*(q^{-1})y(k) = B^*(q^{-1})u(k) + \varepsilon(k)$$

$$A^*(q^{-1}) = I + A_1q^{-1}$$

$$B^*(q^{-1}) = B_1q^{-1}$$

Using Matlab's System Identification Toolbox, the state space model matrices are obtained. The relationships between the state space matrices and the ARX polynomial coefficients are:

$$A = -A_1$$

$$B = B_1$$

The MMOP was based on a linear dynamic model:

$$\min_{u(k)} J_m = -\Gamma_1^T x(N) + \sum_{k=0}^{N-1} \frac{1}{2} r_1 \|u(k) - v(k)\|^2 - \lambda(k)^T u(k) - \beta(k)^T x(k)$$

$$\text{s.t.} \quad x(k+1) = Ax(k) + Bu(k) + \alpha(k)$$

$$x(0) = x_0$$

where  $A$  and  $B$  are given above,  $r_1$  is adjusted along the iteration of the algorithm, and  $x_0$  is computed from the average initial value of the measured

variables at every iteration. Since the use of Broyden's method for computing the dynamic first derivatives along the trajectories, was seen to introduce sudden jumps in the resulting input profiles; the values of  $v(k)$  were filtered through a first-order filter before being applied to the process:

$$v(k)^{applied} = v(k-1)^{Algorithm} + k_f \left( v(k)^{Algorithm} - v(k-1)^{Algorithm} \right)$$

where the value of the constant  $k_f$  was 0.5.

The modified model-based problem (MMOP) was solved at each iteration of the algorithm by using LQ techniques.

## 2.6 SUMMARY

Different papers are reviewed in this chapter. All these works have relevant concepts that are important for the purposes of this research project.

The first work deals with general fermentation concepts, not just batch fermentation but fed-batch and continuous fermentation as well; this chapter is also used as an introduction of techniques been used to model this kind of processes. Basic models for fermentation are also included in order to notice how simple or complicated a fermentation could be.

The next three papers reviewed use mathematical models of real fermentation processes and they show different ways to be implemented. The most important one is perhaps the batch fermentation model developed by Andres-Toro et al<sup>3</sup>. This model is the one chosen among the others to become part of the simulation and optimisation research to be developed in the next chapter. Some parameters and equations have been taken from the original paper and some have been changed in order to obtain the expected results.

Finally, the DISOPE algorithm is presented with an application to a fed-batch fermentation process by Becerra et al<sup>7</sup>. The optimisation algorithm used in this work was used in the simulations presented in the next chapter.

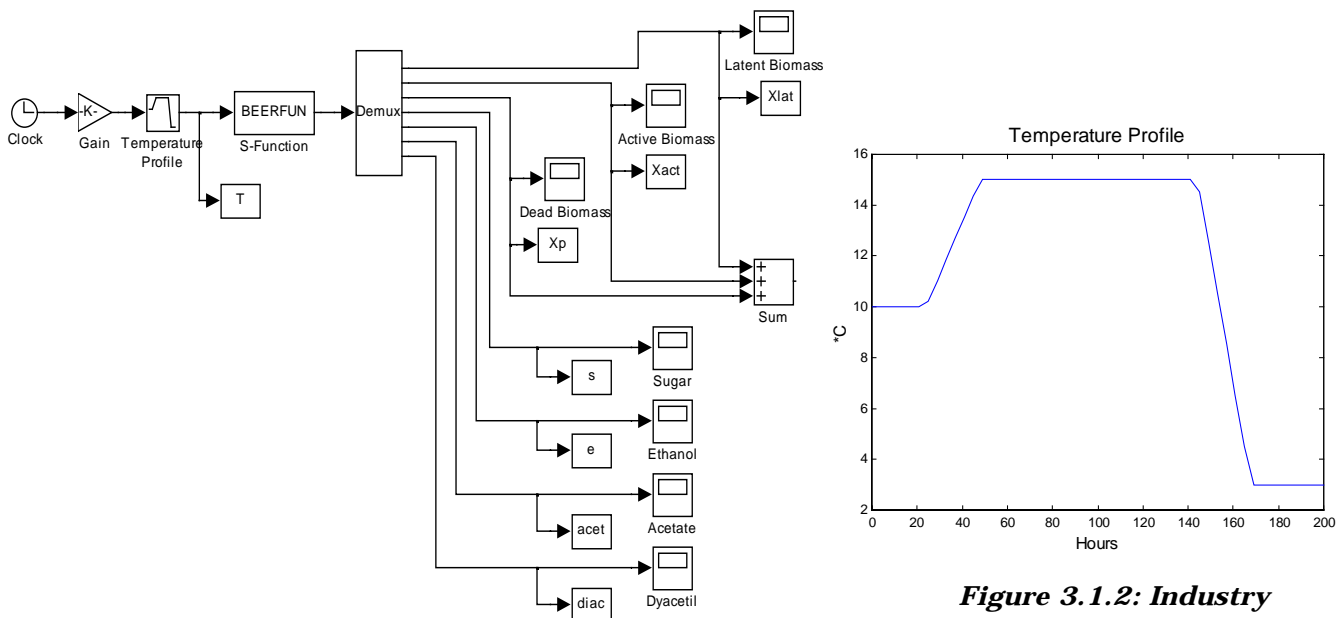
## CHAPTER III

### MODELLING, OPTIMISATION AND RESULTS

#### 3.1 INTRODUCTION

Mathematical models of beer fermentation processes have been reviewed in the previous chapter. For the purpose of this work, the kinetic model from Andres-Toro et al<sup>3</sup> has been chosen to be part of the simulation and optimisation. The model chosen had been obtained from many experimentally studies at laboratory scale showing good results taking into account realistic aspects of the process (as characteristics of the wort and yeast). It also takes into account two important by-products of the fermentation: ethyl acetate and diacetyl, both of them degrading beer quality in the production.

Figure 3.1.1 shows the SIMULINK model of this process using the Industry Temperature Profile (Figure 3.1.2) as the initial input. In this simulation, all the necessary differential equations are included in the S-Function of the process (see Appendix) as well as the initial values of the states.



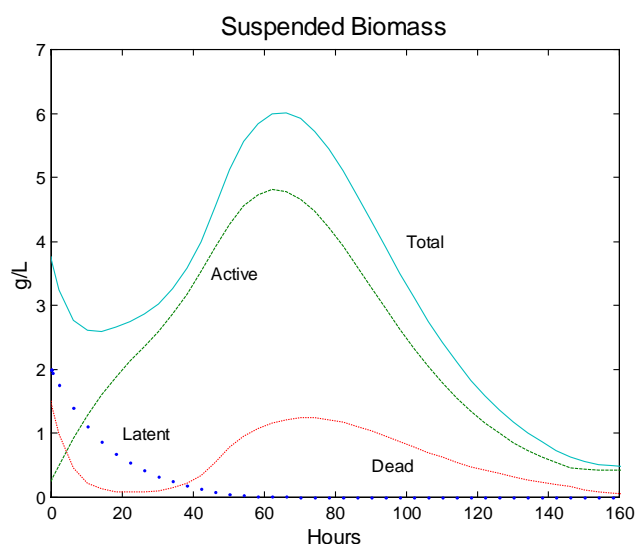
**Figure 3.1.2: Industry Temperature Profile**

**Figure 3.1.1: SIMULINK Model**

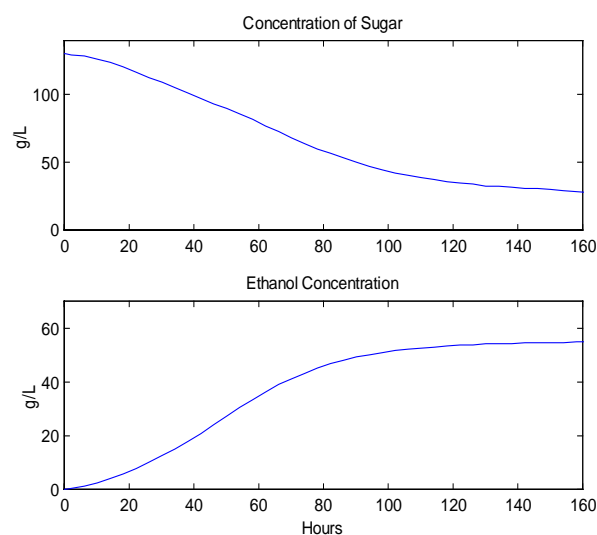
### 3.2 SIMULATION RESULTS

The simulation results obtained have been validated with the original results from the authors. The model seems to be adequate for testing with different optimisation techniques, trying to maximise the objective function (J) given also in the same work by the authors.

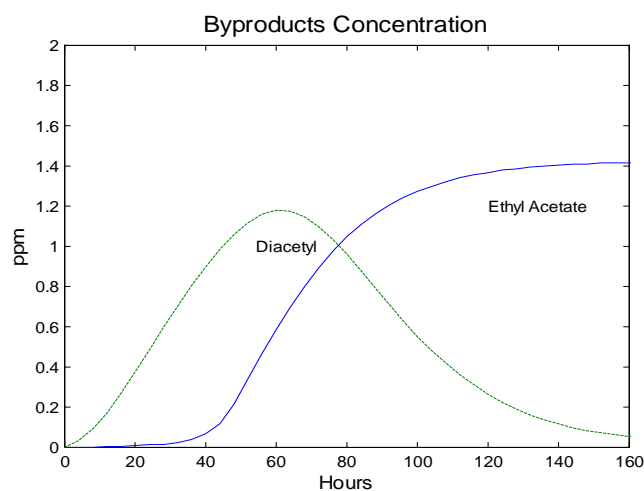
The purpose of the optimisation is to maximise the ethanol concentration without surpassing certain values of diacetyl and ethyl acetate at the end of the process and also avoiding the spoilage risk that depends on the temperature over 15°C along the whole period of time.



**Figure 3.2.1: Suspended Biomass**



**Figure 3.2.2: Sugar and Ethanol Concentration**



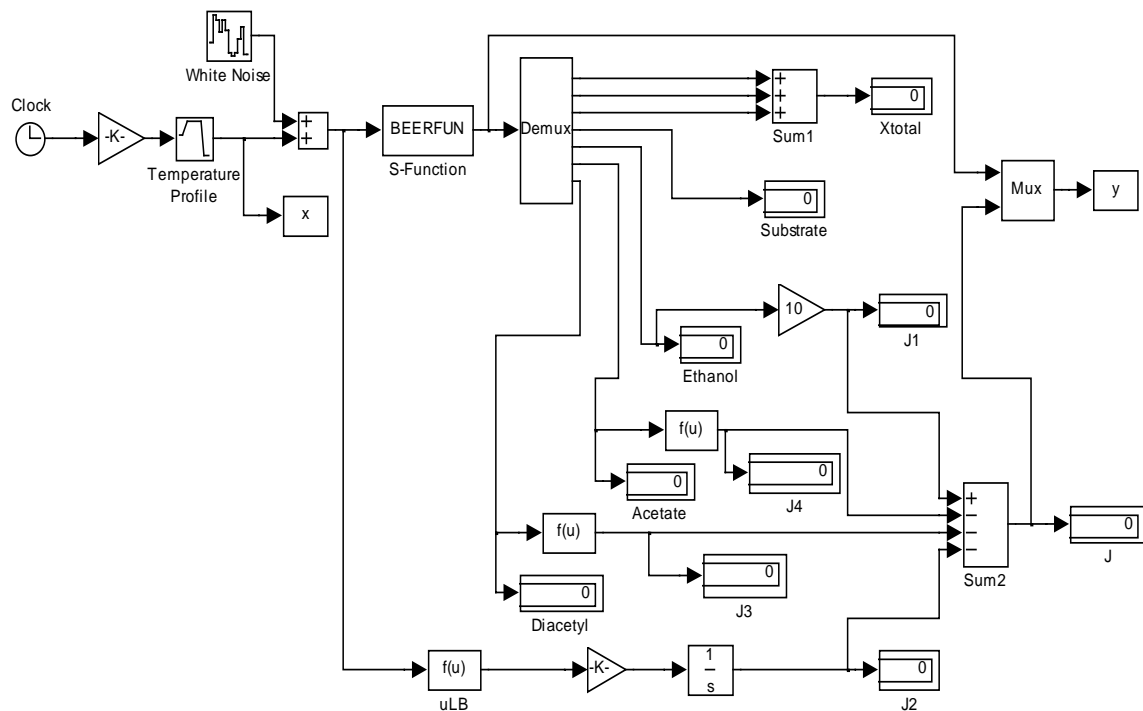
**Figure 3.2.3: By-products Concentration**

### 3.3 APPLICATION OF THE DISOPE ALGORITHM

In Figure 3.3.1, X and Y are the input and output vectors respectively. They are used as data in the system identification toolbox in order to obtain the state space model matrices with the help of the System Identification Toolbox from the MATLAB Software.

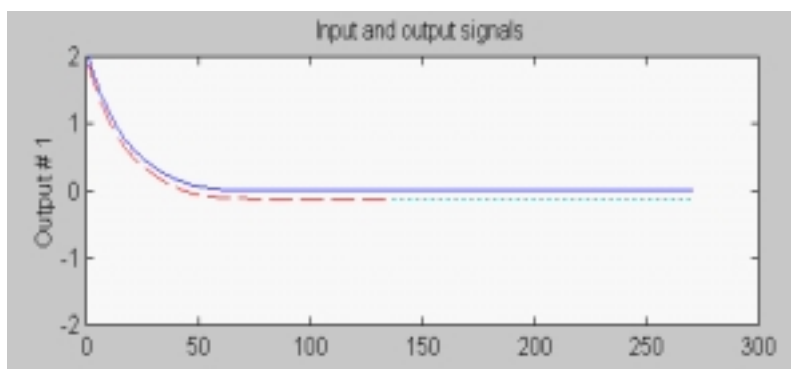
After importing the initial data to the toolbox, a “quick start” is done in the operations box in order to pre-process it. The estimation of the model is done choosing an ARX parametric model of order one (common poles, zeros and delay are one). In figures 3.3.2-11 we can see how similar are the plots of the states variables to the identification model pursued.

After the identification of the system, the step responses (Figs. 3.3.12-19) show how well the convergence of the model parameters (final states) is achieved.

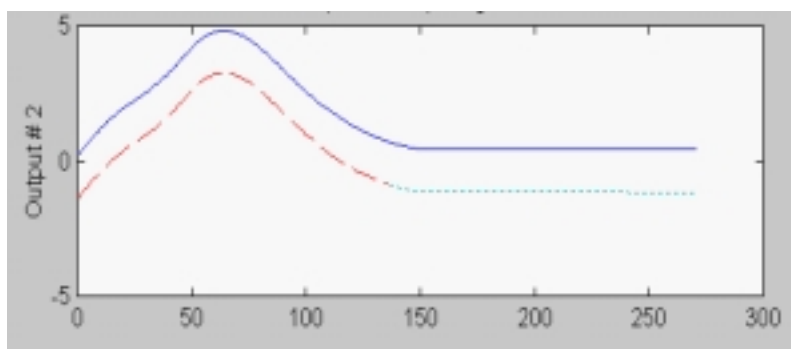


**Figure 3.3.1: Model Used for the System Identification**

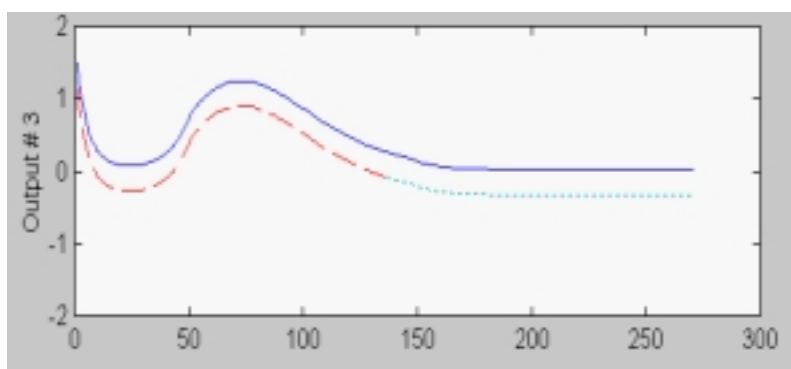
**Figure 3.3.2: Data Plot of Latent Biomass**



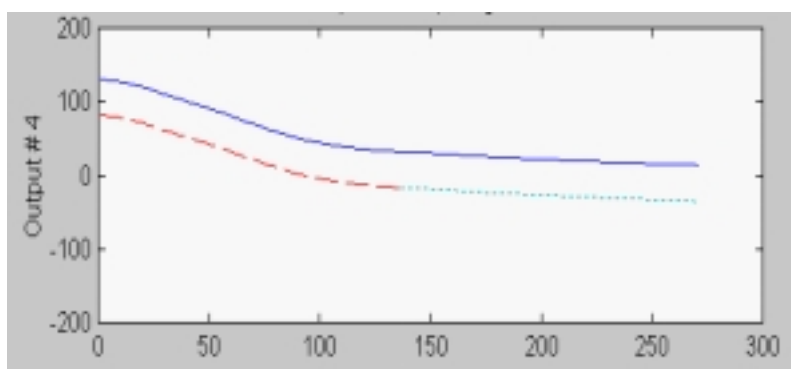
**Figure 3.3.3: Data Plot of Active Biomass**



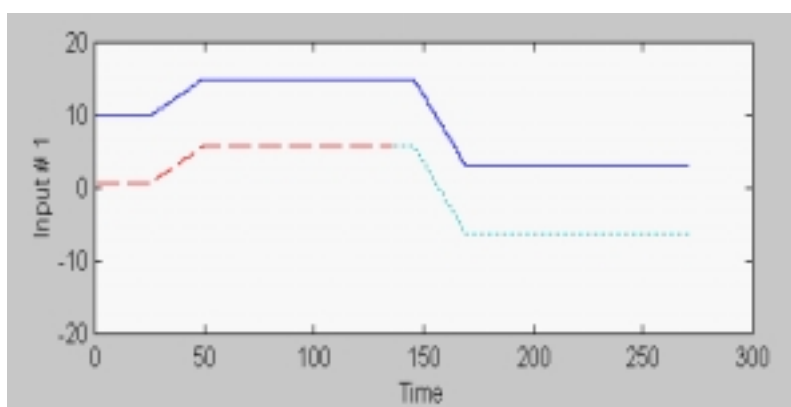
**Figure 3.3.4: Data Plot of Dead Biomass**



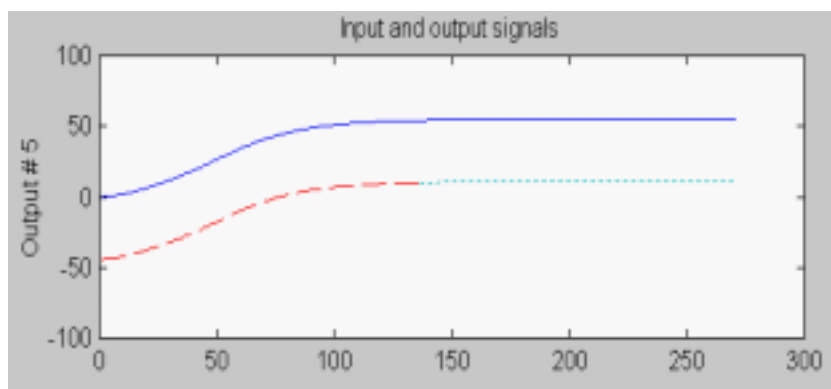
**Figure 3.3.5: Data Plot of Sugar Concentration**



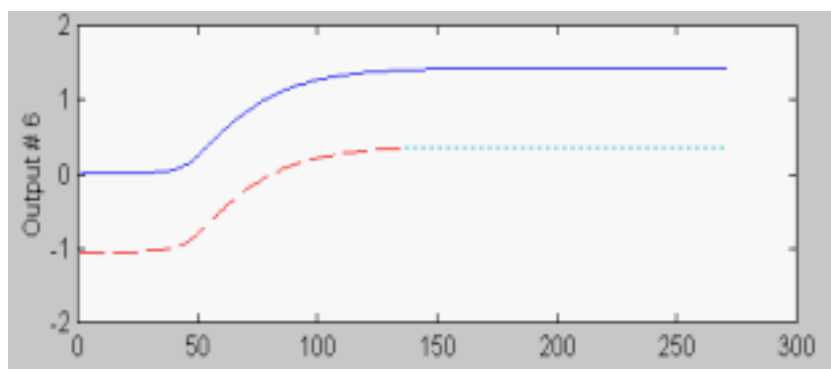
**Figure 3.3.6: Data Plot of Temperature Profile**



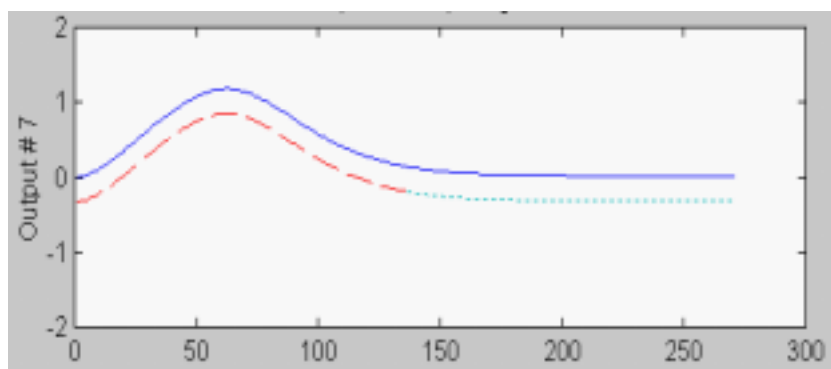
**Figure 3.3.7: Data Plot of Ethanol Concentration**



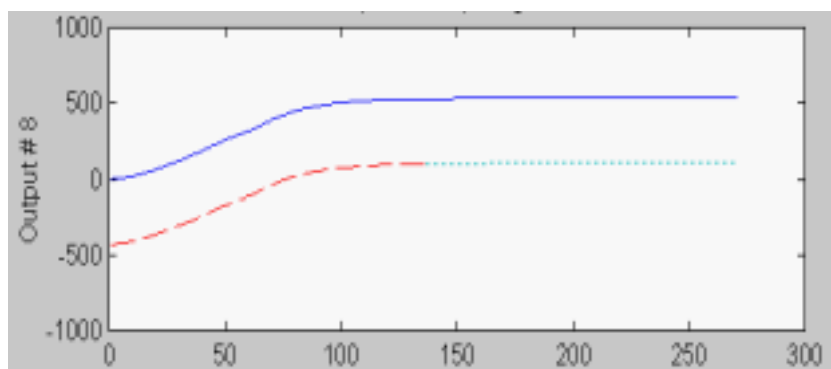
**Figure 3.3.8: Data Plot of Ethyl Acetate**



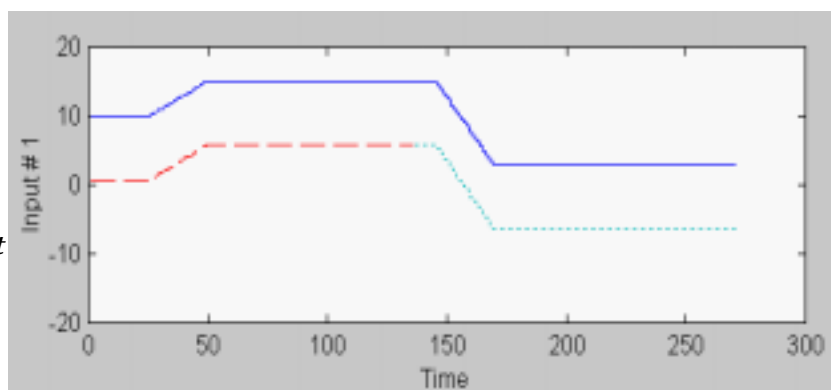
**Figure 3.3.9: Data Plot of Diacetyl**

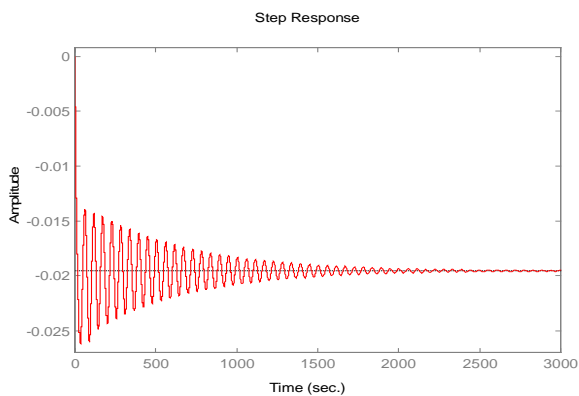


**Figure 3.3.9: Data Plot of Objective Function (J)**

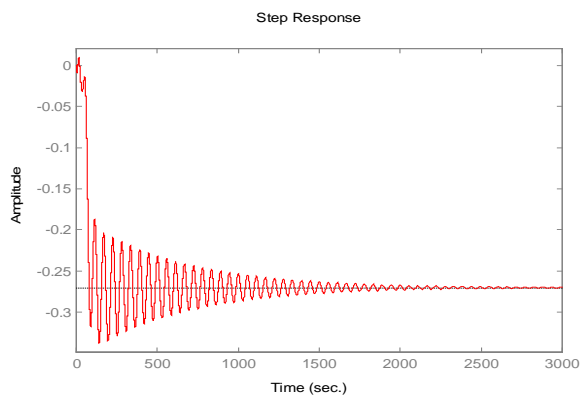


**Figure 3.3.10: Data Plot of Temperature Profile**

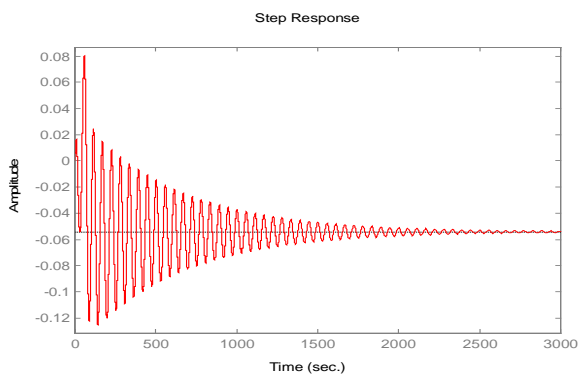




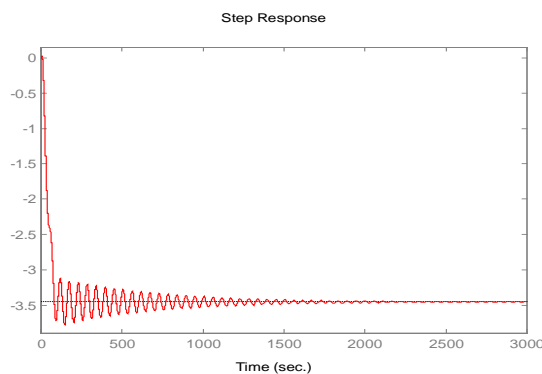
**Figure 3.3.12: Step Response of Latent Biomass**



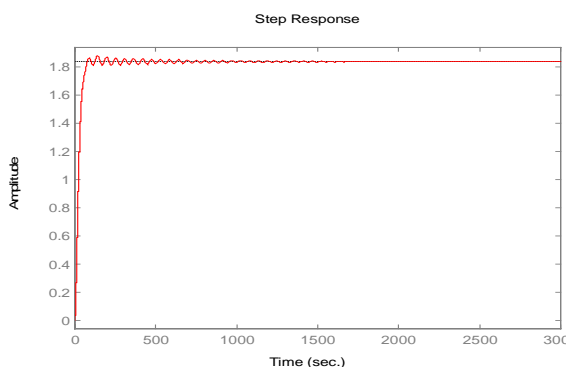
**Figure 3.3.13: Step Response of Active Biomass**



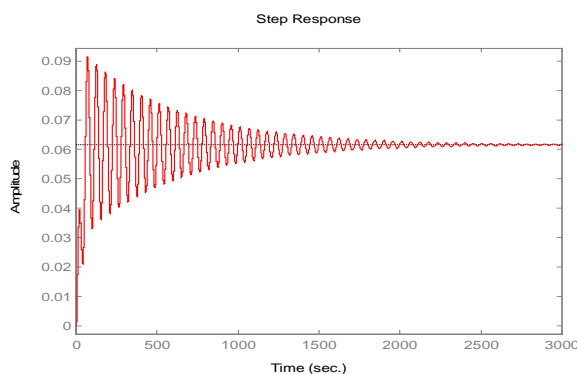
**Figure 3.3.14: Step Response of Dead Biomass**



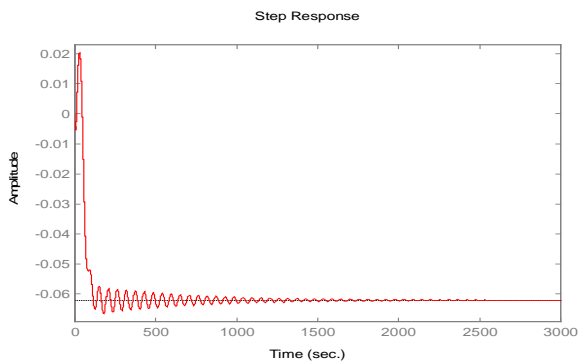
**Figure 3.3.15: Step Response of Sugar Concentration**



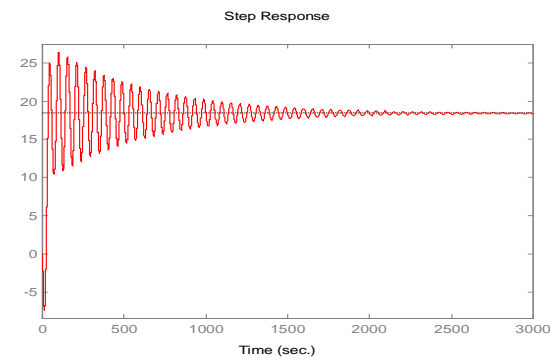
**Figure 3.3.16: Step Response of Ethanol Concentration**



**Figure 3.3.17: Step Response of Diacetyl**



**Figure 3.3.18: Step Response of Objective Function (J)**



**Figure 3.3.19: Step Response of Temperature Profile**

The state space model matrices (A and B) obtained from the System Identification are as follows:

$$\mathbf{A} = \begin{pmatrix} 0.9405 & 0.0017 & 0.0026 & 0.0015 & 0.0043 & -0.0401 & -0.0351 & -0.0000 \\ 0.0946 & 1.0299 & -0.0130 & 0.0088 & 0.0516 & -0.8107 & -0.3978 & -0.0013 \\ 0.0816 & 0.1637 & 0.8621 & -0.0002 & 0.0155 & -0.3975 & -0.5354 & -0.0001 \\ 1.4733 & 0.7454 & -0.1807 & 0.8915 & -0.0764 & -1.7931 & -2.0919 & -0.0026 \\ -0.4569 & -0.0665 & 0.0563 & 0.0360 & 1.0972 & -0.8743 & -0.1763 & -0.0027 \\ -0.0048 & 0.0266 & 0.0182 & 0.0015 & 0.0099 & 0.8451 & -0.1536 & -0.0003 \\ -0.0396 & -0.0118 & 0.0056 & 0.0033 & 0.0111 & -0.1127 & 0.9510 & -0.0003 \\ -1.0513 & -10.3621 & -6.7555 & 2.0997 & 4.0186 & -6.0051 & 24.8758 & 0.9877 \end{pmatrix}$$

$$\mathbf{B} = \begin{pmatrix} -0.0025 \\ -0.0056 \\ 0.0030 \\ 0.0150 \\ 0.0146 \\ 0.0004 \\ -0.0026 \\ -1.1793 \end{pmatrix}$$

The state and control vectors related for the are defined as:

$$x = [X_{act} \quad X_{lat} \quad X_p \quad s \quad e \quad acet \quad diac \quad J]^T \quad u = [T]$$

The performance index to be minimised, reflects the desire to maximise the final value of the objective function for a given time, it is given by:

$$J^* = -x_8(N)$$

where  $N = 159$  correspond with the transformation time of 160 units, given a sampling interval of one time unit, taking 0 as the initial time index of every batch or iteration.

$$\min_{u(k)} J_m = -\Gamma_1^T x(N) + \sum_{k=0}^{N-1} \left[ \frac{1}{2} (r_1 \|u(k) - v(k)\|^2 + r_2 \|x(k) - z(k)\|^2) - \lambda(k)^T u(k) - \beta(k)^T x(k) \right]$$

$$\text{subject to} \quad x(k+1) = Ax(k) + Bu(k) + \alpha(k) \quad x(0) = x_0$$

where A and B are given above,  $r_1$  and  $r_2$  are introduced to augment the performance index to provide convexification, and  $x_0$  is the initial value of measured variables.

$$\text{and } \Gamma_1 = \nabla_z \phi(z(N), \gamma_1) - \nabla_z \phi^*(z(N))$$

The parameters for the simplified performance index matrices used in the DISOPE algorithm are specified a priori in order to obtain proper results, and for this case are as follows:

$$\mathbf{Q} = \begin{pmatrix} 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \end{pmatrix}$$

$$\mathbf{R} = \begin{bmatrix} 0.0 \end{bmatrix}$$

$$\Phi = \begin{pmatrix} 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 \end{pmatrix}$$

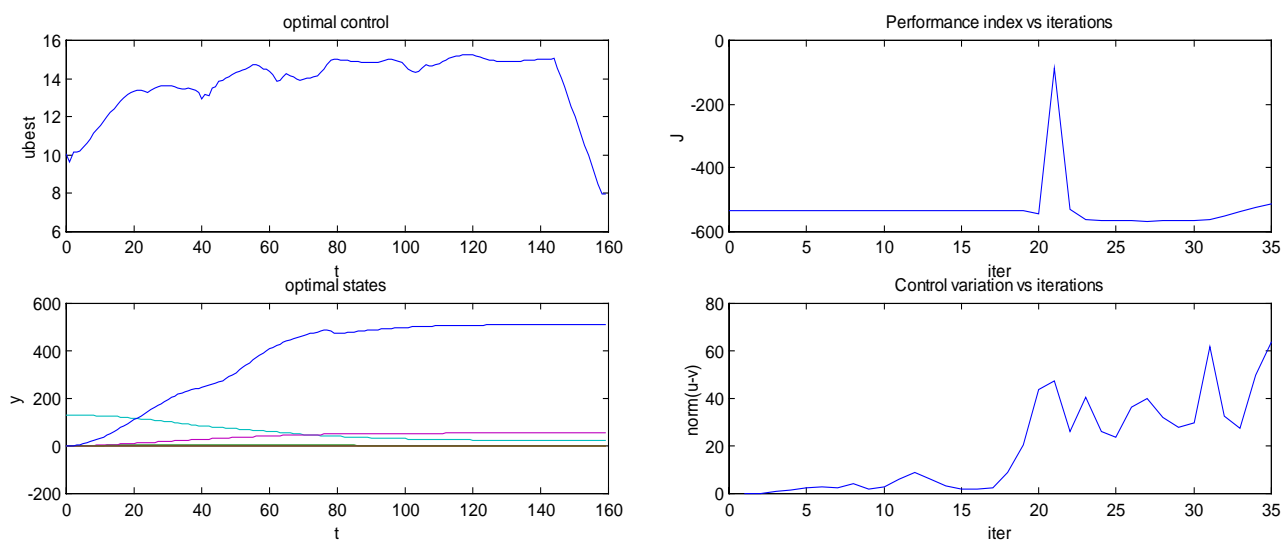
### 3.4 RESULTS OF THE OPTIMISATION

Table 3.4.1 shows the results obtained with the DISOPE algorithm for different parameters.

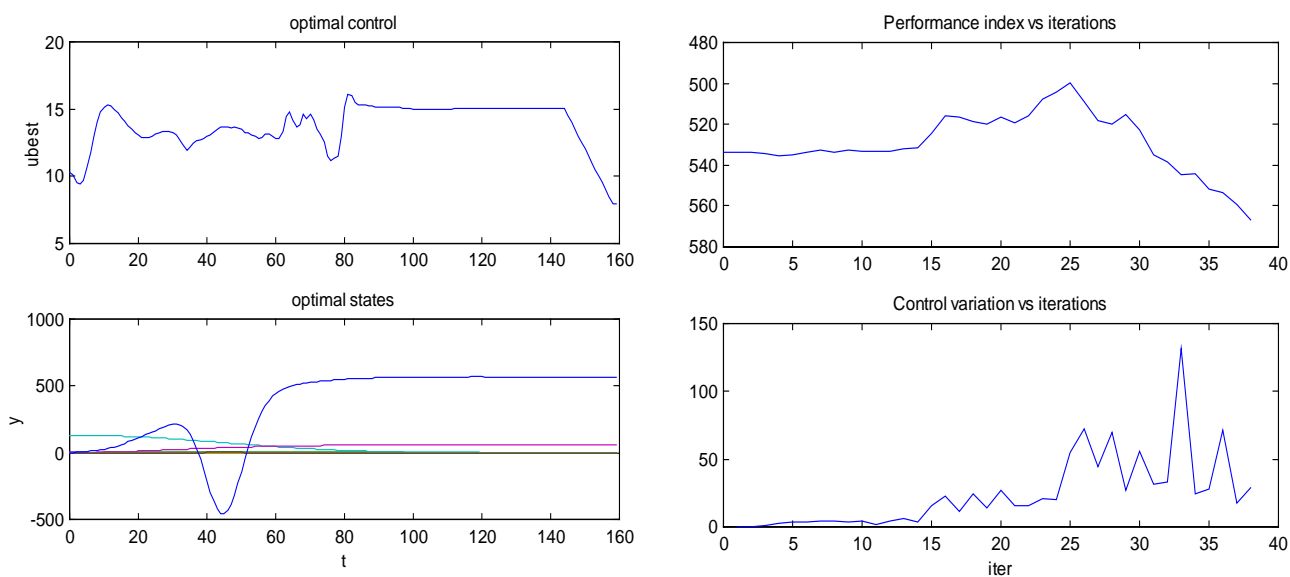
Parameters	$r_1$	$r_2$	Kr	Iter	J	Increase %	Figure #
1	81.0	0.0	0.11	35	568.3	6.44	3.4.1
2	82.0	0.0	0.13	40	566.3	6.07	3.4.2
3	99.0	0.0	0.11	35	541.7	1.46	3.4.3
Original Value					533.9		

**Table 3.4.1: DISOPE results**

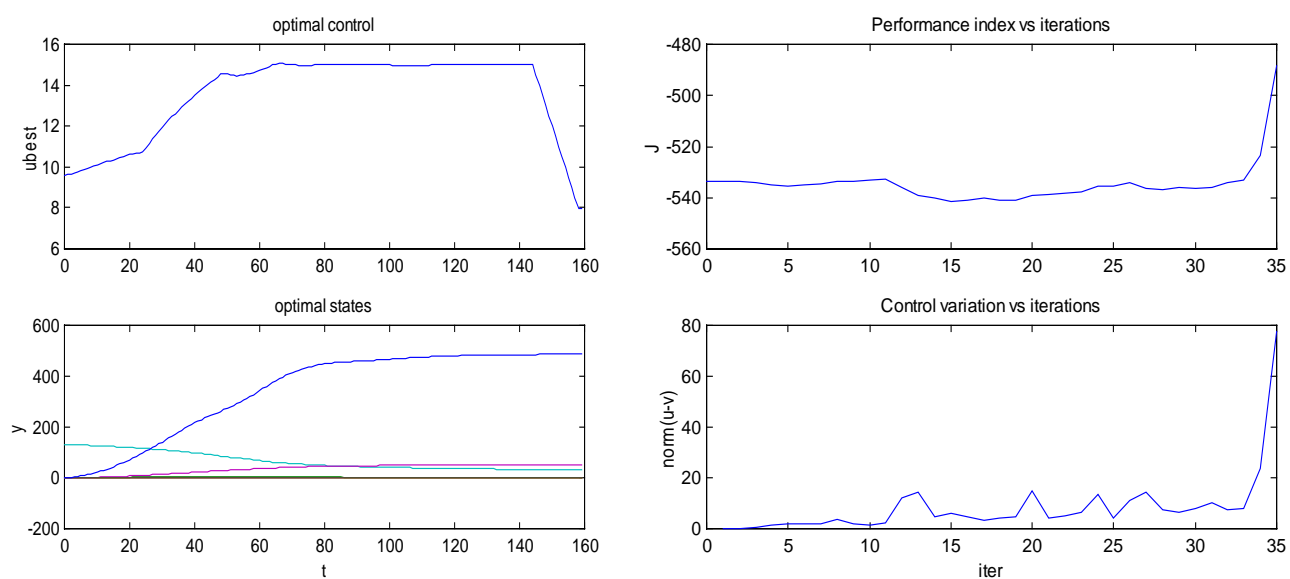
Plots of the results from the DISOPE algorithm are included (Figures 3.4.1-3). The first plot shows the optimal control profiles  $u$  vs. time (the best input profile for the whole period of time); the second one is the performance index ( $J$ ) vs. the number of iterations; the third plot shows the optimal states ( $y$ ) along the period of time; and finally the control variation (norm  $u-v$ ) vs. the number of iterations.



**Figure 3.4.1: Plots obtained with the algorithm (1)**

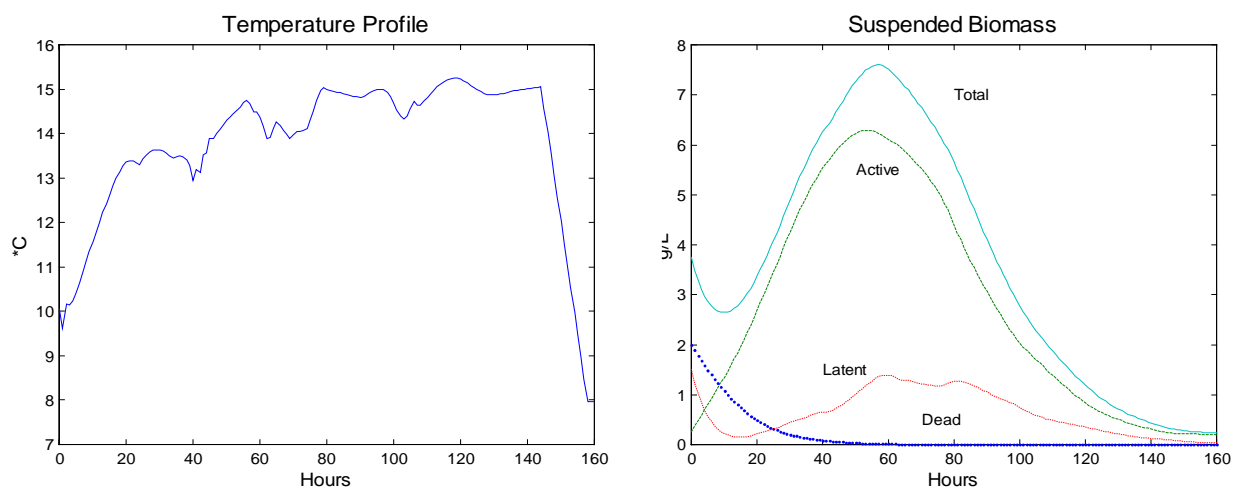


**Figure 3.4.2: Plots obtained with the algorithm (2)**

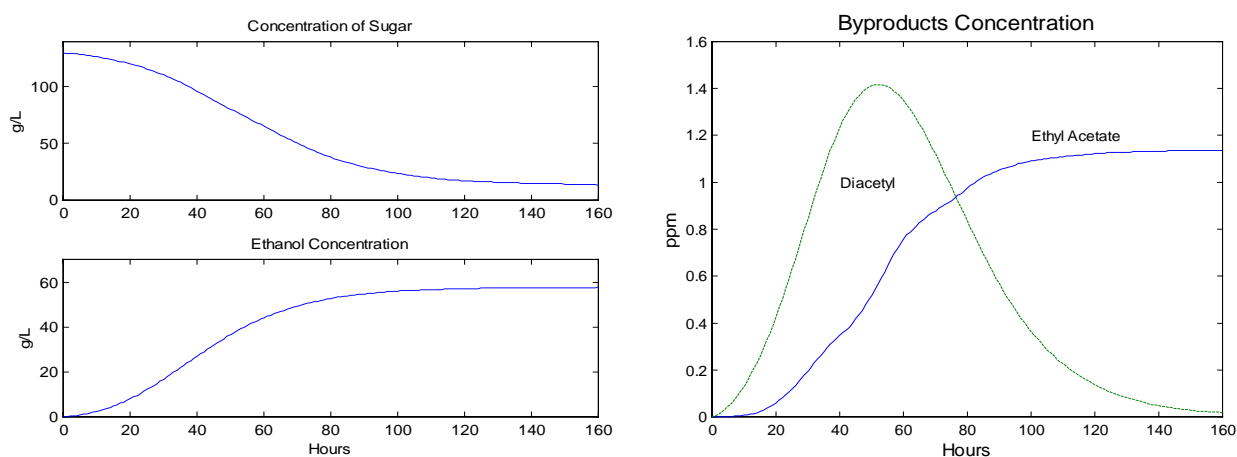


**Figure 3.4.3: Plots obtained with the algorithm (3)**

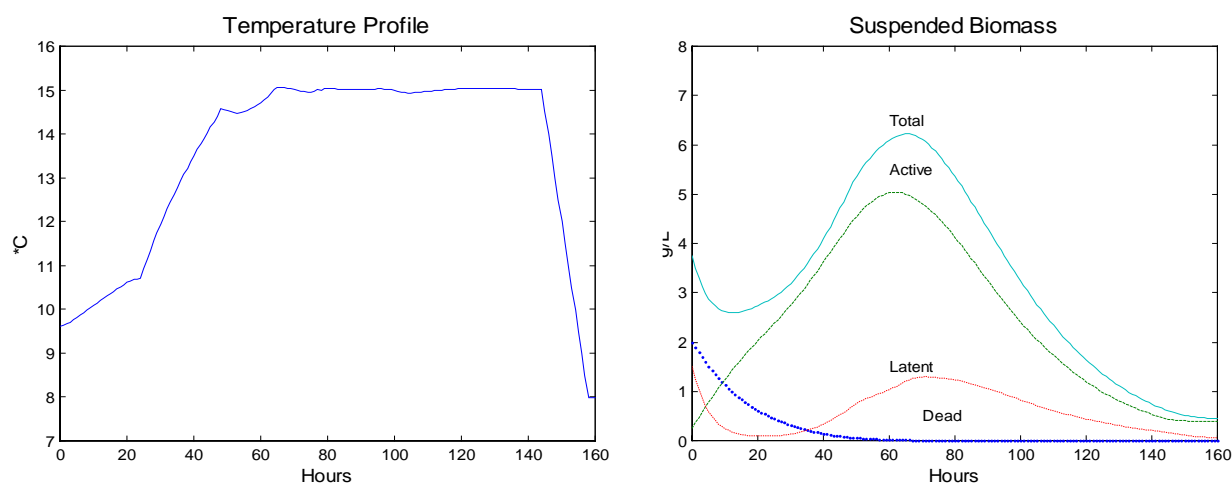
After obtaining the optimal temperature profile, they have been applied as the input of the original fermentation process; in order to have the resulting outputs (states) presented in Figures 3.4.4-6.



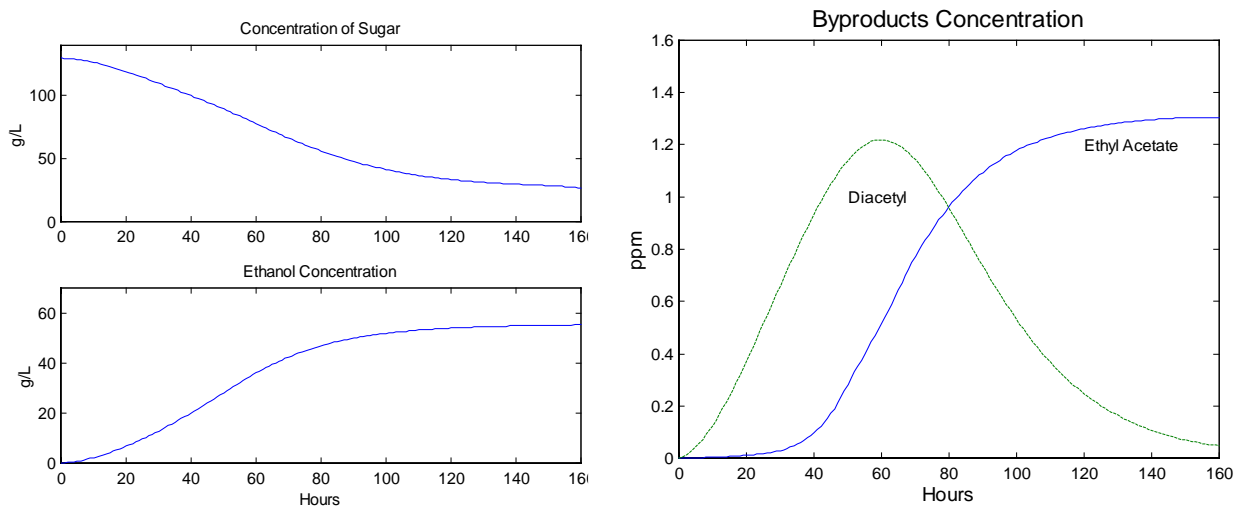
**Figure 3.4.4a: Optimised output variables of the process (1)**



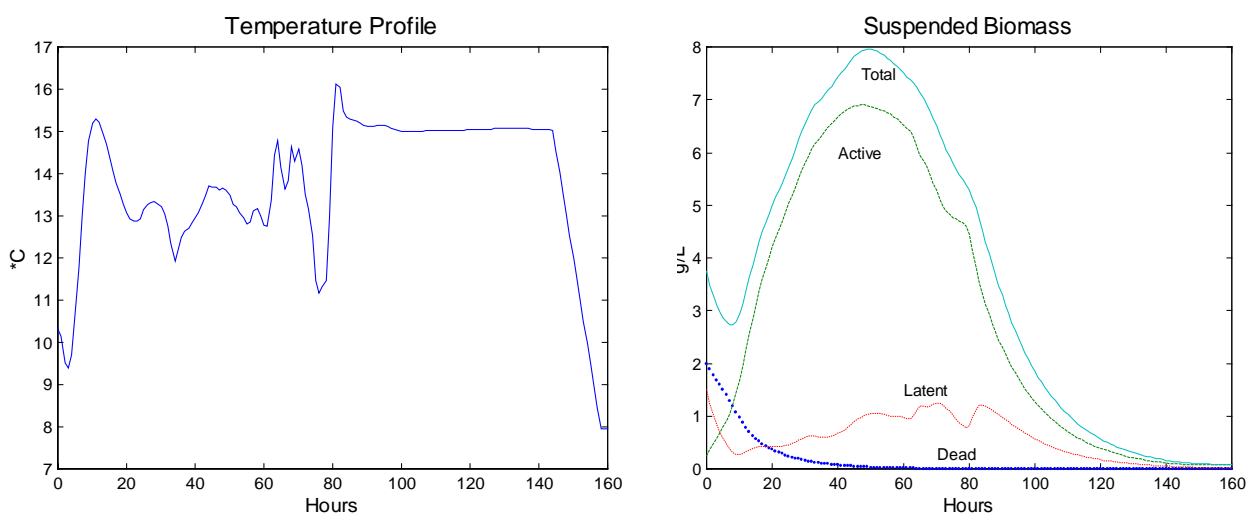
**Figure 3.4.4b: Optimised output variables of the process (1)**



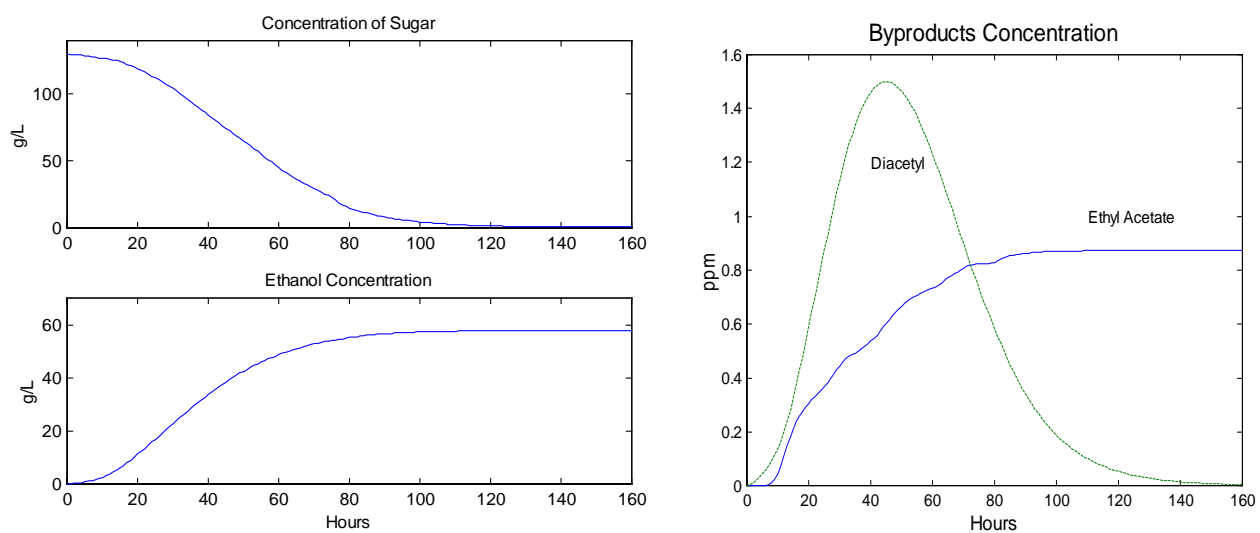
**Figure 3.4.5a: Optimised output variables of the process (2)**



**Figure 3.4.5b: Optimised output variables of the process (2)**



**Figure 3.4.6a: Optimised output variables of the process (3)**



**Figure 3.4.6b: Optimised output variables of the process (3)**

### 3.5 ANALYSIS OF RESULTS

The results obtained with the DISOPE algorithm are considered to be a good start for optimising the simulated model but further studies need to be carried out in order to see the viability of this algorithm with this kind of process. Convergence problems were noticed since large number of simulations had to be done in order to get the right parameters ( $r_1$ ,  $r_2$  and  $K_r$ ) for the optimal process. Furthermore, with all the tests carried out, an increment of just 6.44 % in the original objective function value (J) was obtained. All of these should be taken into account when other optimisation methods become part of the research.

Although the results obtained show some improvement in the objective function, industrial application is still not possible since all temperature profiles obtained were not suitable for practical implementation. Breweries normally use profiles with few temperature changes along the fermentation time. Obtaining implementable profiles is going to be an essential aspect of the future research to be carried out in this project.

### 3.6 SUMMARY

This chapter includes the simulation of the mathematical model selected from the work done by Andres-Toro et al.<sup>3</sup> and reviewed in the second chapter. In order to try to obtain similar results using the same model, some parameters have been changed and adapted. The SIMULINK version of the process is included as well as the necessary M-File (S-Function) in the appendix; it includes the model itself as differential equations and initial values.

The results obtained from the simulation were compared with the actual results of the previous work and showed how good the simulation was. The SIMULINK model itself was adapted to evaluate the objective function  $J$  in order to know the initial value to be optimised (for a 160 hours fermentation time); this was done taking into account the original objective function developed in the previous work<sup>3</sup>.

By adding white noise at the input and with the help of Matlab's System Identification Toolbox, the state space model matrices were obtained. The data views and step responses of the model parameters are included to show how the system tries to follow (in the best way possible) the real process. Notice that the quality of the model is not very good, as there is some ringing in identified model variables after the step. This is due to the fact that the model structure used was an ARX model with first order polynomials, as DISOPE requires the outputs to be equal to the states. The quality of the model could have been improved by increasing the order of the ARX polynomials, but the resulting model would not have been suitable for use with DISOPE.

With the help of the batch version of the DISOPE algorithm (modified by Becerra et al.<sup>7</sup>), and some other modifications made to adjust it to the simulated process; optimisation of the process has been pursued. The maximisation of the objective function achieved with three different combinations of the main parameters has been presented.

## **CHAPTER IV**

### **CONCLUSIONS AND FUTURE WORK**

After a literature review on mathematical modelling of fermentation processes and associated optimisation algorithms (Chapter I), a summary of main concepts is included in this work. The purpose of this information is to give a general view of the research reviewed and further work to be carried out in this project.

The mathematical modelling of beer fermentation processes has been the main topic of this report. Previous works have been discussed and included as reference for further studies. The simulated process used in this report was selected because of its relevance, the fact that it has been validated against a real process, and because it was possible, after some work, to reproduce the simulations that have been published.

Basic concepts of system identification have been presented as a helpful tool to implement the DISOPE algorithm for the optimisation of the process. This was done with the help of the System Identification Toolbox from the MATLAB Software. Then, the batch version of the DISOPE algorithm was interfaced to the model in order to use it to maximise the objective function associated with the process. Good results were obtained with this algorithm but more work has to be done to achieve an optimal input that could satisfy industry requirements (i.e. small changes or variations in the temperature). Convergence problems were noticed, since any small change in the initial parameters affected in great way the possible solution of the optimisation.

Future work has to be carried out trying to optimise the same simulated process with different techniques such as other versions of the DISOPE algorithm, Genetic Algorithms, Neural Networks, Fuzzy Logic and/or others. Comparisons among all of these will give a guide to choose the best optimisation technique to be used for such fermentation process. After doing this, other process model should be chosen and the same techniques applied to them, trying to test the reliability of the algorithms.

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## **APPENDIX**

### **A. S-FUNCTION OF THE PROCESS (BEERFUN.M)**

```

function [sys,x0,str,ts] = alsfun(t,x,u,flag)

%CSFUNC An example M-file S-function for defining a continuous system.

switch flag,
    %%%%%%%%%%%
    % Initialization %
    %%%%%%%%%%%
    case 0,
        [sys,x0,str,ts]=mdlInitializeSizes;
        %%%%%%%%%%%
    % Derivatives %
    %%%%%%%%%%%
    case 1,
        sys=mdlDerivatives(t,x,u);
        %%%%%%%%%%%
    % Outputs %
    %%%%%%%%%%%
    case 3,
        sys=mdlOutputs(t,x,u);
        %%%%%%%%%%%
    % Unhandled flags %
    %%%%%%%%%%%
    case { 2, 4, 9 },
        sys = [];
        %%%%%%%%%%%
    % Unexpected flags %
    %%%%%%%%%%%
    otherwise
        error(['Unhandled flag = ',num2str(flag)]);
end

% end csfunc
%=====
% mdlInitializeSizes
% Return the sizes, initial conditions, and sample times for the S-function
%=====

function [sys,x0,str,ts]=mdlInitializeSizes

sizes = simsizes;
sizes.NumContStates = 7;
sizes.NumDiscStates = 0;
sizes.NumOutputs = 7;
sizes.NumInputs = 1;
sizes.DirFeedthrough = 0;
sizes.NumSampleTimes = 1;
sys = simsizes(sizes);
x0 = [2,0.25,1.5,130,0,0,0]';
str = [];
ts = [0 0];

% end mdlInitializeSizes

```

```

%=====
% mdlDerivatives
% Return the derivatives for the continuous states.
%=====
function sys=mdlDerivatives(t,x,u)

Xlat = x(1);
Xact = x(2);
Xp = x(3);
s = x(4);
e = x(5);
acet = x(6);
diac = x(7);
T = u(1);

% Parameters as Arrhenius functions of temperature

si = 130;
kdc = 0.000127672;
kdm = 0.00113864;
ul = exp(30.72-9501.54/(T+273.15));
uxo = exp(108.31-31934.09/(T+273.15));
km = exp(130.16-38313/(T+273.15));
udo = exp(33.82-10033.28/(T+273.15));
uso = exp(-41.92+11654.64/(T+273.15));
ks = exp(-119.63+34203.95/(T+273.15));
uao = exp(3.27-1267.24/(T+273.15));
ueas = exp(89.92-26589/(T+273.15));

% Factor Equations

ux = uxo*s/(0.5*si+e);
ud = 0.5*si*udo/(0.5*si+e);
us = uso*s/(ks+s);
ua = uao*s/(ks+s);
f = 1-e/(0.5*si);

% Differential Equations

sys(1) = (-ul*Xlat)/3600;
sys(2) = (ux*Xact-km*Xact+ul*Xlat)/3600;
sys(3) = (km*Xact-ud*Xp)/3600;
sys(4) = (-us*Xact)/3600;
sys(5) = (ua*f*Xact)/3600;
sys(6) = (ueas*ux*Xact)/3600;
sys(7) = (kdc*s*Xact-kdm*diac*e)/3600;

% end mdlDerivatives
%
%=====
% mdlOutputs
% Return the block outputs.
%=====
%
function sys=mdlOutputs(t,x,u)

sys = x;

% end mdlOutput

```